Synthesis and Reactivity of α-Trialkylsilyl α-Amino Acids

Von der Fakultät für Mathematik, Informatik und Naturwissenschaften
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vorgelegt von

Elisabetta Veri

aus Rom, Italien

Berichter: Universitätsprofessor Dr. C. Bolm
Universitätsprofessor Dr. D. Enders

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Ein Teil des Inhalts dieser Arbeit ist bereits veröffentlicht:

"*Enantiopure α-Silyl-Substituted α-Hydroxyacetic Acids Using O-H Insertion Methodology and Boron-Based Asymmetric Reductions"*, C. Bolm, S. Saladin, A. Claßen, A. Kasyan, E. Veri, G. Raabe, *Synlett* **2005**, 461-464.

To the persons I love.

Index

1. Introduction

The first reported synthesis of an α-diazo carbonyl compound was by Curtius in 1883.[1] It involved diazotisation of the natural α-amino acid glycine to give ethyl diazoacetate. Wolff discovered the well-known rearrangement that bears his name in 1912, but the availability of a wide range of diazo compounds came about as a result of the work of Arndt and Eistert[2,3] and Bradley and Robinson.[4]
Since then, the diazo moiety has become very popular and it is now used in a large range of transformations.[5] In particular, thermal, photochemical or catalytic extrusion of nitrogen generates a carbene (carbenoid) species which can undergo many reactions, depending on the nature of the partner present in the reaction mixture. For example, cyclopropanation, cyclopropenation, aromatic cycloaddition, intra and intermolecular C-H insertion, X-H insertion (where X = O-H, N-H, S-H or Si-H) and ylide-type transformations have been all reported in the literature.[6]
In this chapter, a description of the most common methods for preparing diazo compounds will be given followed by an introduction to chiral and achiral catalysts for carbenoid transformations. In addition, methods for the introduction of a triorganyl silyl group to an α-diazo carbonyl moiety and for the synthesis of α-triorganylsilyl α-amino acids will be reported.

1.1 Preparation of Diazo Compounds

This section introduces the simplest diazo compound, diazomethane, and covers the main synthetic strategies for the formation of the diazo compounds, including: acylation of diazoalkanes, diazo transfer reaction, diazo formation from tosylhydrazones or the use of nitrous acid and primary amines.

1.1.1 The Simplest Diazo Compound: Diazomethane

Diazomethane (**1**) is a widely used reagent, but unfortunately presents several safety hazards: it is extremely toxic and irritatant and, together with several of its precursors, is carcinogenic. It is also known to explode unaccountably (Figure 1). Since it is a moisture sensitive reagent, water must be

[1] a) T. Curtius, *Ber.* **1883**, *16*, 2230-31. b) T. Curtius, *J. Prakt. Chem.* **1888**, *38*, 396-440.
[2] F. Arndt, B. Eistert, W. Partale, *Ber.* **1927**, *60B*, 1364-1370.
[3] a) F. Arndt, J. Amende, *Ber.* **1928**, *61B*, 1122-1124. b) F. Arndt, B. Eistert, J. Amende, *Ber.* **1928**, *61B*, 1949-1953.
[4] W. Bradley, R. Robinson, *J. Chem. Soc.* **1928**, 1310-1318.
[5] M. P. Doyle, M. A. Mc Kervey, T. Ye in *Modern Catalytic Methods for Organic Synthesis for Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York, **1998**.
[6] a) T. Ye, M. A. Mc Kervey, *Chem Rev.* **1994**, *94*, 1091-1160. b) P. A. Evans in *Modern Rhodium-Catalysed Organic Reactions*, Wiley, Weinheim, **2005**.

removed from an ethereal solution using potassium hydroxide pellets. Drying agents such as calcium sulfate must be avoided as they can cause an explosion. Exposure to sunlight or artificial light must usually be avoided. However, the risks are minimized by using glassware with fire polished ground glass joints and handling the compound as a dilute solution at 0 °C. Despite the hazards of diazomethane and diazo compounds, their importance as reagents can be grasped from the fact that many are now from the commercially-available of many of these compounds.[5]

The most convenient method of preparing diazomethane is by the base-catalyzed decomposition of compounds with structure **2** (Figure 1), where R is carbonyl, sulfonyl or another electron-withdrawing substituent. For this, there are two different procedures described in *Organic Synthesis*[6,7]: Arndt[7] reported the potassium hyroxide mediated decomposition of nitrosomethylurea, De Boer and Backer[8] generated diazomethane from *N*-methyl-*N*-nitroso-*p*-toluensulfonamide (**3**) in the presence of potassium hydroxide and diethylene glycol monomethyl ether. The advantage of the latest method is the stability of the starting material and its solubility in many organic solvents. In fact, this precursor is commercially available and named Diazald™ (Figure 1). *N*-Methyl-*N*-nitro-*N*-nitrosoguanidine (**4**) (MNNG) is another commercially available precursor the use of which is recommended when less than one millimol of diazomethane is required. Trimethylsilyldiazomethane (**5**), a commercially available compound, is often employed as a safe alternative to diazomethane.[9]

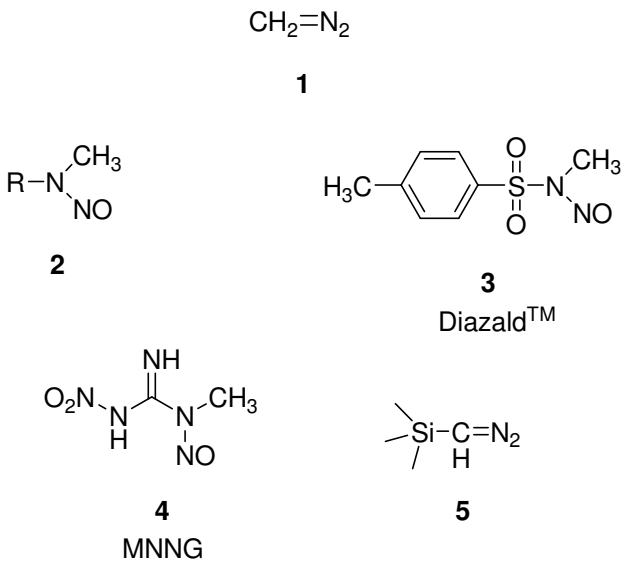
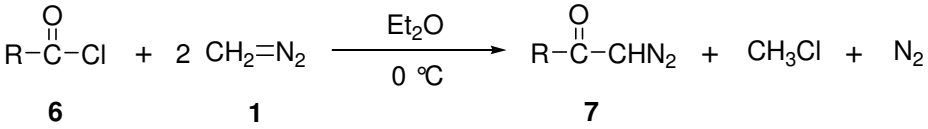


Figure 1. Diazomethane and some of its precursors.

[7] F. Arndt, *Org. Synth. Coll. Vol. 2*, (Ed.: A. H. Blatt), Wiley, New York, **1943**, 165-167.
[8] T. J. de Boer, H. J. Backer, *Org. Synth. Coll. Vol. 4*, (Ed.: N. Rabjohn), Wiley, New York, **1963**, 250-253.
[9] T. Ayoyama, T. Shioiri, *Tetrahedron Lett.* **1980**, *21*, 4461-4462.

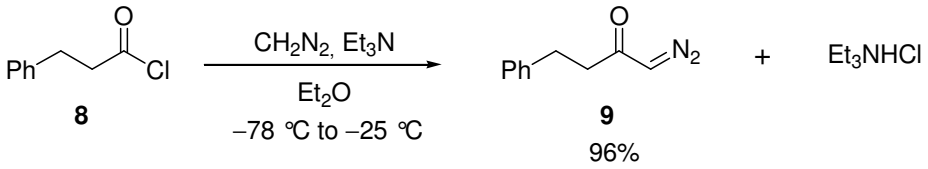
1.1.2 Acylation of Diazoalkanes

The Arndt-Eistert synthesis of diazo ketones (**7**) involves the addition of an acyl chloride (**6**) to 1-2 equiv. ethereal diazomethane (**1**) at 0 °C or below (Scheme 1).[2,3]



Scheme 1. Arndt-Eistert synthesis for diazoalkanes.

The use of an excess of diazomethane can be avoided by using non-enolizable precursors, such as aromatic acyl chlorides or adding triethylamine (1 equiv.) to the diazomethane solution.[10] Under such conditions, however, enolizable acyl chlorides give only low yields of impure diazo ketones. This approach is occasionally successful when lower temperatures are employed, as in the synthesis of compound **9** (Scheme 2).[11]



Scheme 2. Synthesis of a diazo ketone from an enolizable acyl chloride.

In the synthesis of the anticancer azotomycin (**10**) (Figure 2), Pettit and Nelson report the preparation of a bis-diazo ketone.[12] This involved treating the carboxylic acid in an ethereal solution with oxalyl chloride, triethylamine and catalytic amount of dimethyl formamide to furnish the acyl chloride. This was is then added to an ethereal solution of diazomethane at –78 °C.

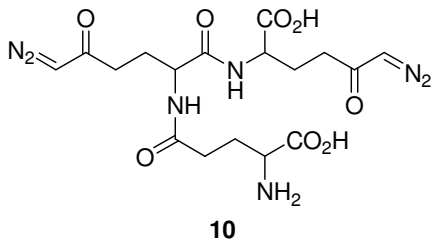


Figure 2. The anticancer *bis*-diazo ketone, azotomycin.

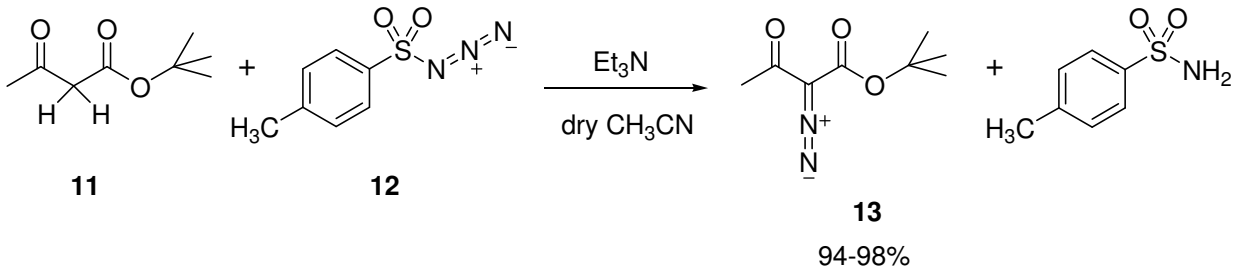
[10] M. S. Newmann, P. Beal, III, *J. Am. Chem. Soc.* **1949**, *71*, 1506-1507.
[11] L. T. Scott, M. A. Minton, *J. Org. Chem.* **1977**, *42*, 3757-3758.
[12] G. R. Pettit, P. S. Nelson, *J. Org. Chem.* **1983**, *48*, 741-744.

1.1.3 Diazo Transfer Route

The method reported in the previous paragraph has an obvious limitation: it can not be applied to cyclic α-diazo ketones. This is not the case with diazo group transfer, which was first described in 1910 by Dimroth.[13] Regitz and his collaborators showed that this is applicable to cyclic α-diazo ketones as well as many acyclic systems.[14] The method involves the transfer of a complete diazo group from a donor to an acceptor, where the diazo carbonyl group must be a acid or ketone derivative. The diazo donor is always a sulfonyl azide.

1.1.3.1 Simple Diazo Transfer Reactions

Diazo transfer requires the presence of an easily deprotonated α-methylene position. In some cases prior activation of the α position may be necessary but malonic esters, β-keto-esters **11**, β-keto amides and β-diketones are easily converted into 2-diazo-1,3-dicarbonyl products because the proton in the α-position is sufficiently acidic. Hence, direct exposure to tosyl azide (**12**) in dry acetonitrile or ethanol, using triethylamine as base, leads to the formation of the diazo derivative **13** (Scheme 3).[15]



11 **12** **13**

Scheme 3. Diazo transfer reaction on a β-keto-ester.

Diazo ester **14**[16], diazo amide **15**[17], diazo ketone **16**[18], diazo ketosulfonate **17**[19] and diazo ketophosphonate **18**[20] have all been prepared by this route (Figure 3).

[13] O. Dimroth, *Ann. Chem.* **1910**, *373*, 336-370.
[14] a) M. Regitz, *Angew. Chem.* **1967**, *79*, 786-801. *Angew. Chem. Int. Ed.* **1967**, *6*, 733-749. b) M. Regitz, *Synthesis,* **1972**, 351-373. c) M. Regitz, *Newer Methods of Preparative Organic Chemistry, Vol. 6,* (Ed.: W. Foerst), Academic Press, New York, **1971**. d) M. Regitz, G. Maas, *Diazo Compounds; Properties and Synthesis*, Academic Press, Orlando, **1986**.
[15] M. Regitz, J. Hocker, A. Liedhegener, *Org. Synth. Coll. Vol. 5*, (Ed.: H. E. Baumgarten), Wiley, New York, **1973**.
[16] M. Regitz, *Chem Ber.* **1966**, 99, 3128-3147.
[17] G. Lowe, H. W. Yeung, *J. Chem. Soc., Perkin Trans. 1* **1973**, 2907-2910.
[18] M. Oda, M. Kasai, Y. Kitahara, *Chem. Lett.* **1977**, 307-310.
[19] M. Kennedy, M. A. McKervey, A. R. Maguire, G. H. P. Roos, *J. Chem. Soc. Chem. Comm.* **1990**, 361-362.
[20] P. Callant, L. D' Haenes, M. Vandewalle, *Synth. Commun.* **1984**, *14*, 155-161.

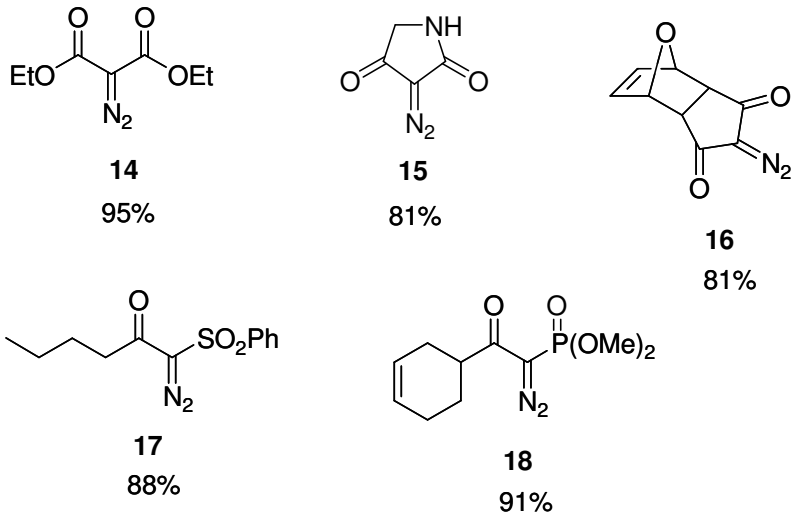
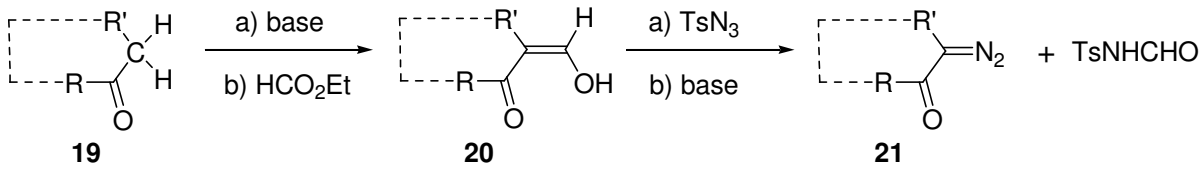


Figure 3. Various diazo compounds prepared by diazo transfer reaction.

1.1.3.2 Deformylating Diazo Transfer and Related Modifications

The diazo transfer reaction works very well for substrates in which the reaction site is activated by being in the α-position to two carbonyl groups. The Regitz's method, reported in the previous paragraph, usually fails when the methylene group is only activated by one carbonyl. A modification of this technique is also referred to as the Regitz deformylating diazo transfer and it involves, firstly, Claisen condensation of the ketone **19** with ethyl formate, to introduce a strongly activated formyl group, followed by reaction with tosyl azide and a base to form the diazo compound **21**.[14] Either the metal salt of **20**, or the neutral formyl compound, can be used as the activated intermediate and in many cases, isolation of the formyl derivative **20** is not required (Scheme 4).

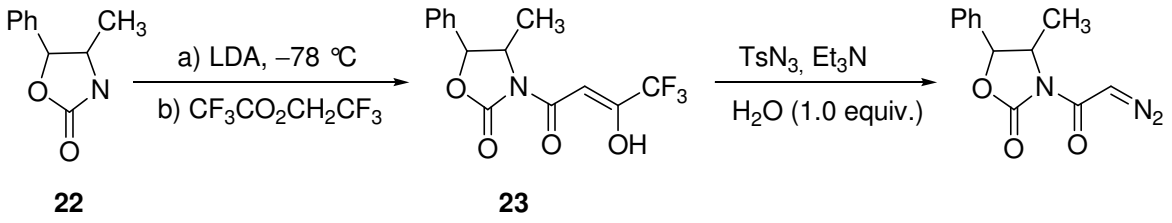


Scheme 4. Regitz's deformylating diazo transfer technique.

Another extension of Regitz's method was reported in 1985 by Doyle and co-workers.[21] He introduced a trifluoroacetyl substituent to improve the diazo transfer to a base sensitive system such as *N*-acetyloxazolidone **22**. This was successful because the enhanced reactivity of the

[21] M. P. Doyle, R. L. Dorow, J. W. Terpstra, R. A. Rodenhouse, *J. Org. Chem.* **1985**, *50*, 1663-1666.

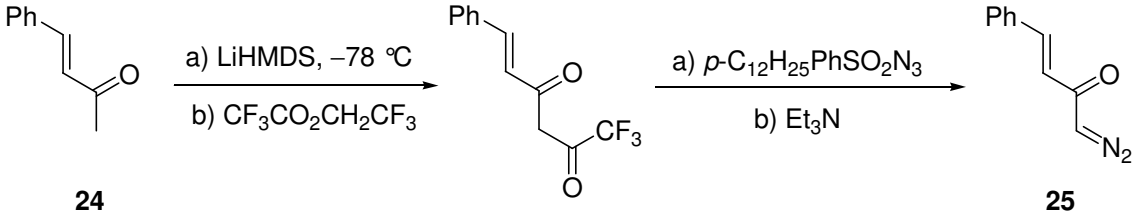
trifluoroacetyl group toward nucleophilic addition and the better leaving group ability of its hydroxyl derivative **23**, minimized competition with the hydrolytic cleavage of oxazolidone **22**, the major competing reaction in the deacylation (Scheme 5).



22 **23**

Scheme 5. Doyle's modification of the Regitz's diazo transfer technique.

Danheiser and co-workers found that the deformylating diazo transfer via the Claisen-type intermediate fails or gives low yields in some important cases, for example for α,β-enones.[22,23] The use of the Doyle-type method increases dramatically the yields of diazo derivatives of α,β-enones, as for compound **25** (Scheme 6).

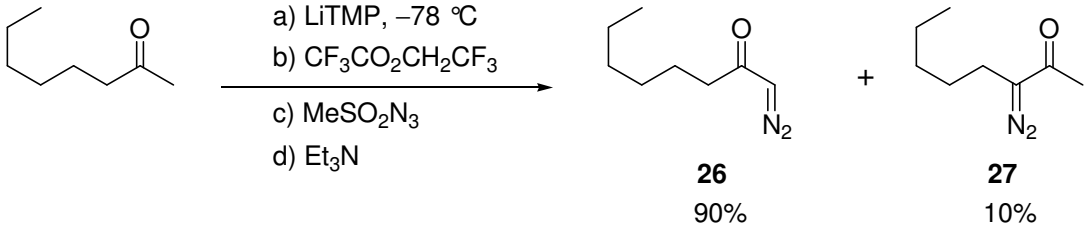


24 **25**
83%

Scheme 6. Doyle's modification of diazo transfer method applied to α,β-enones.

Doyle's detrifluoroacetylating diazo transfer procedure has the advantage of providing a good regiocontrol in diazo transfer to unsymmetrical diazo ketones, as depicted in Scheme 7. The use of lithium tetramethylpiperidide (LiTMP) achieves the generation of the kinetic enolate and thus the formation of the terminal diazo ketone **26**.[24]

[22] R. L. Danheiser, R. F. Miller, R. G. Brisbois, S. Z. Park, *J. Org. Chem.* **1990**, *55*, 1959-1964.
[23] R. L. Danheiser, R. F. Miller, R. G. Brisbois, *Org. Synth.* **1996**, *73*, 134-143.
[24] P. Datkins, N. McCarthy, M. A. McKervey, K. O'Donnel, T. Ye, B. Walter, *Tetrahedron: Asymmetry* **1994**, *5*, 195-198.



Scheme 7. Use of LiTMP for the generation of terminal diazo ketones.

In addition, this last procedure is also applicable to the synthesis of α-diazo esters, and four examples involving β-amino acids as in **28** and **29**, and peptides as in **30** and **31** are shown in Figure 4.[24]

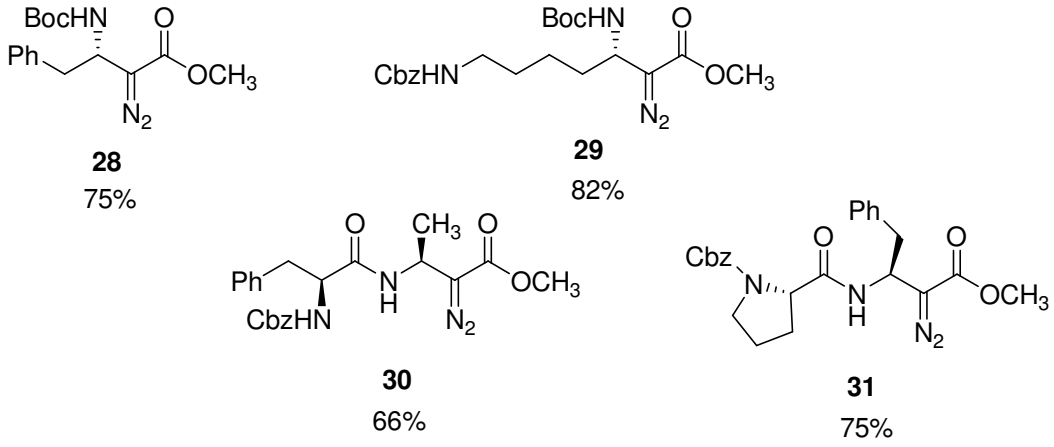
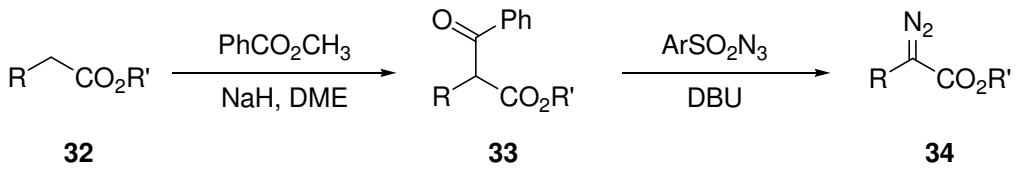


Figure 4. Some examples of α-diazo β-amino acids and diazo peptides.

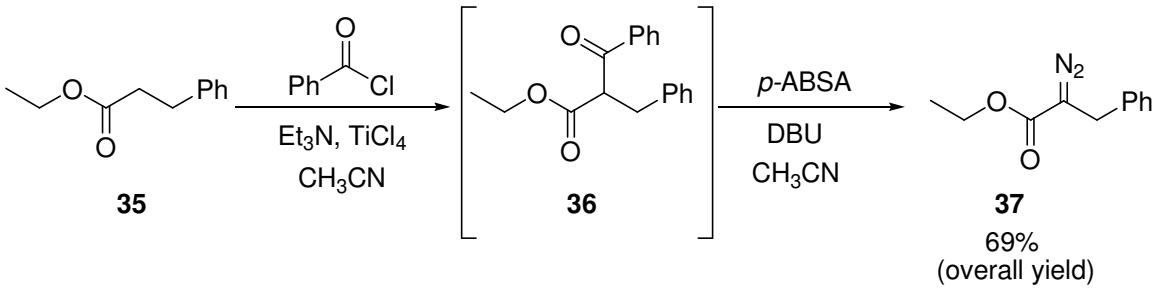
α-Diazo esters can additionally be synthesised by treating the anion of the ester **32,** depicted in Scheme 8, with methyl benzoate to obtain β-keto-ester **33** that react with the appropriate diazo transfer reagent and 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU). The diazo ester **34** comes out from the subsequent cleavage of the benzoyl group (Scheme 8).[25]



Scheme 8. Diazotisation of α-diazo esters *via* their benzoyl derivatives.

[25] D. F. Taber, K. You, Y. Song, *J. Org. Chem.* **1995**, *60*, 1093-1094.

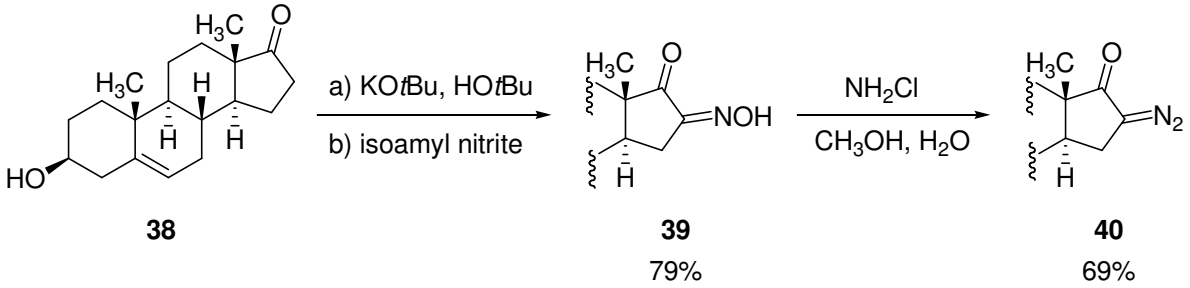
The method described in Scheme 8 was reported by Taber and co-workers in 1995, and recently improved by the same group.[25,26] They found that the combination of benzoyl chloride, triethylamine and titanium(IV) chloride, allowed the preparation of the diazo ester **37** without purification of its benzoylated precursor **36** (Scheme 9).



Scheme 9. Modification of Taber's synthesis of α-diazo esters.

1.1.4 Other Routes to Diazocarbonyl Compounds

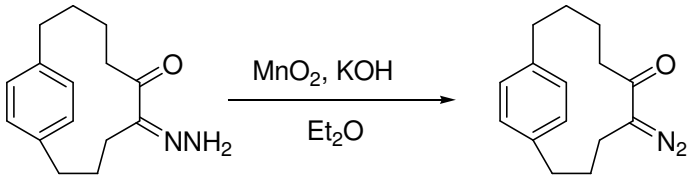
Complementary routes to α-diazo carbonyl compounds have diminished in importance since the introduction of the diazo transfer process. Anyway, classical methods as the Forster reaction,[27] dehydrogenation of hydrazones,[28] the Bamford-Stevens tosylhydrazone decomposition[29] and diazotisation of amines[1,30,31] have still a spread use in the synthesis of diazo carbonyl compounds.
In the Forster reaction,[27] the α-methylene position of a ketone, as in compound **38**, reacts with a nitrite to form an oxime **39**; the following reaction with a chloramine provides the α-diazo ketone as compound **40**, as in the example depicted in Scheme 10.



Scheme 10. Synthesis of a α-diazo ketone by Forster reaction of a ketone.

[26] D. F. Taber, R. B. Sheth, P. V. Joshi, *J. Org. Chem.* **2005**, *70*, 2851-2854.
[27] M. O. Forster, *J. Chem. Soc.* **1915**, *107*, 260-267.
[28] N. L. Arringer, L. A. Freiberg, *J. Org. Chem.* **1962**, *27*, 1490-1491.
[29] W. R. Bamford, T. S. Stevens, *J. Chem. Soc.* **1952**, 4735-4740.
[30] E. B. Womack, A. B. Nelson, *Org. Synth. Coll. Vol. 3*, (Ed.: E. C. Horning), Wiley, New York, **1955**, 392-393.
[31] N. E. Searle, *Org. Synth. Coll. Vol. 4*, (Ed.: N. Rabjohn), Wiley, New York, **1963**, 424-426.

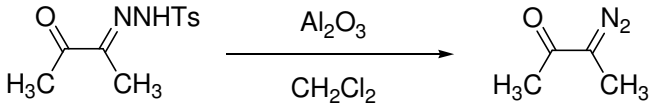
Dehydrogenation of hydrazones is one of the oldest reported methods for preparation of diazo compounds and various oxidation agents have been used to convert hydrazones into their diazo derivatives. An example for the synthesis of α-diazo ketone **42**, using manganese dioxide and potassium hydroxide, is reported in Scheme 11.[28]



41 **42**

Scheme 11. Example of dehydrogenation of hydrazones by oxidation.

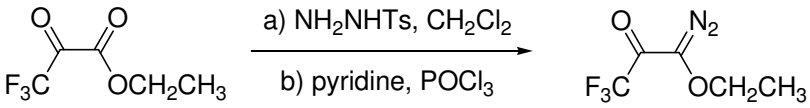
Closely related to the dehydrogenation discussed above is the Bamford-Stevens reaction to convert monohydrazones of dicarbonyl compounds such as **43** into the corresponding mono-diazo ester as in compound **44** (Scheme 12).[29]



43 **44**
86%

Scheme 12. Preparation of α-diazo ketones by Bamsford-Stevens reaction.

A one-pot modification for of the Bramford-Stevens reaction is reported by Shi and Xu for the synthesis of 3-trifluoro-2-diazo propionate **46**.[32] A mixture of ethyl trifluoropyruvate (**45**) and tosylhydrazide reacted with pyridine and phosphorus oxychloride to afford 3-trifluoro-2-diazopropionate (**46**) in 82% yield (Scheme 13).



45 **46**
82%

Scheme 13. Modification of Bamsford-Stevens reaction.

[32] G. Shi, Y. Xu, *J. Chem Soc. Chem Commun.* **1989**, 607-608.

When primary amines **47** are treated with nitrous acid (HONO), or more often with a nitrite salt,[33,34] such as $NaNO_2$ or an alkyl nitrite[35] in acid solution, a diazonium salt is formed. The first stage involves the formation of the reactive species NO^+ (**48**). This NO^+ cation then attacks the lone pair of the amine **47** and dehydratation occurs to form compound **49** (Figure 5).

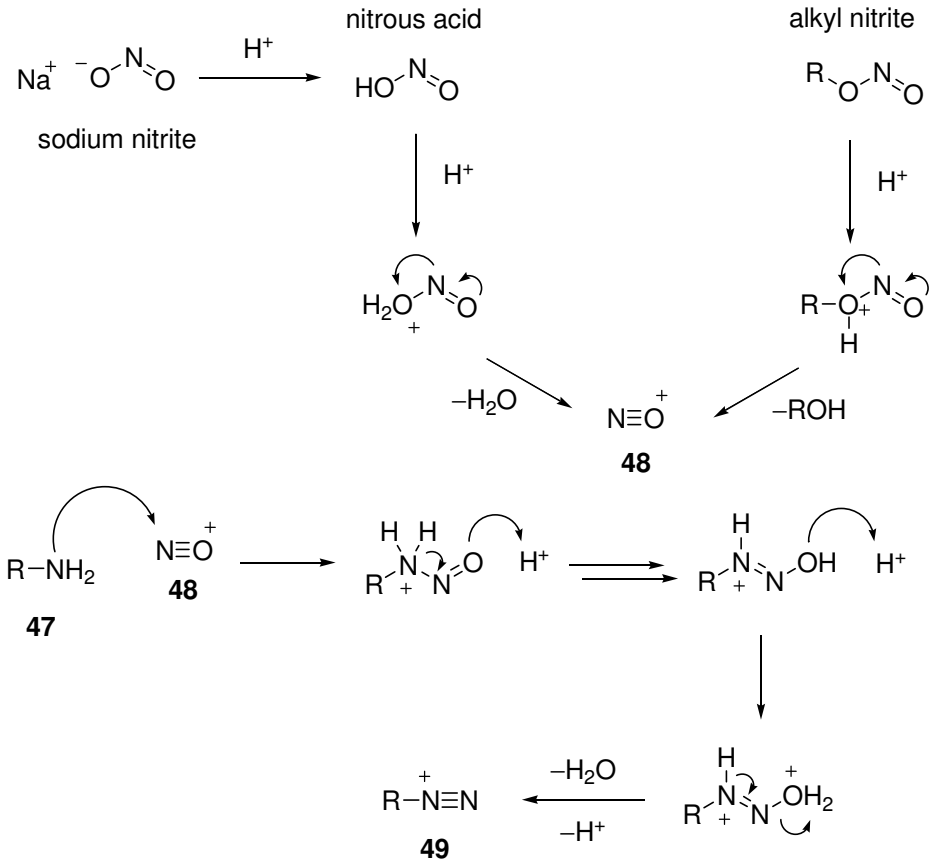
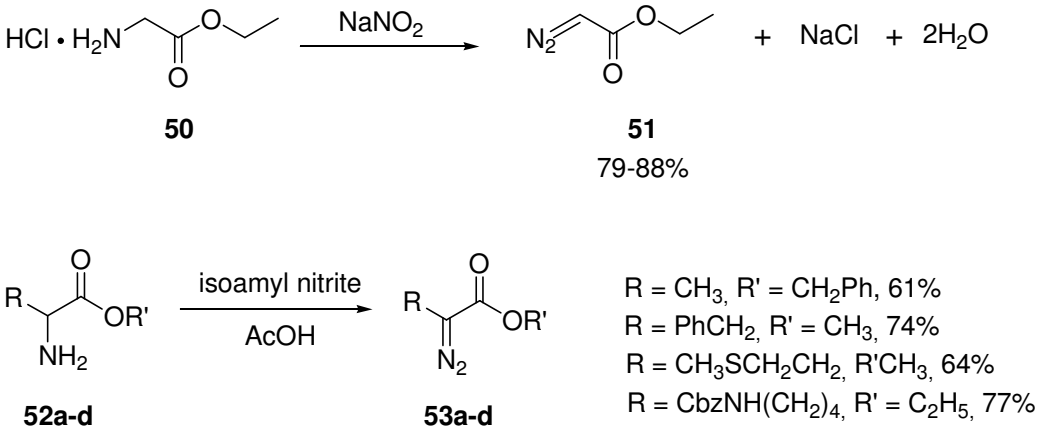


Figure 5. Mechanism of diazotisation of primary amines.

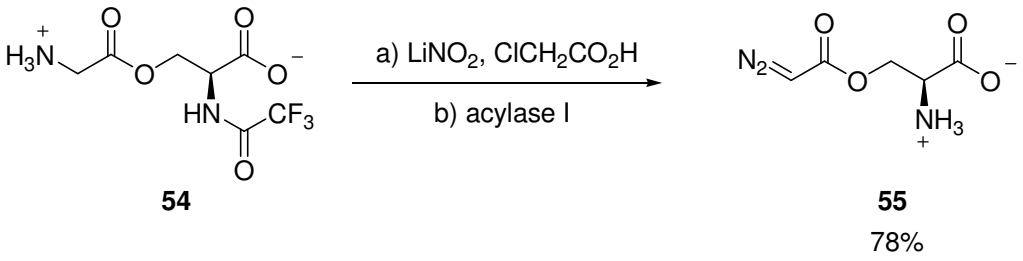
Diazo ethyl acetate (**51**) can be obtained by diazotisation of glycine ethyl ester **50** with sodium nitrite in aqueous acid, but in many cases the preferred diazotisation agent is isoamyl nitrite (Scheme 14).[31] This last methodology was applied successfully to other α-amino acids, such as alanine, phenylalanine, methionine and lysine (compounds **52a**-**d**).[36]

[33] W. Kirmse, H. Dietrich, *Chem. Ber.* **1965**, *98*, 4027-4030.
[34] B. J. Lam, B. L. Johnson, *Aust. J. Chem.* **1972**, *25*, 2269.
[35] H. Fritschi, U. Leutenegger, A. Pfaltz, *Helv. Chim. Acta* **1988**, *71*, 1553-1565.
[36] N. Takamura, T. Mizoguchi, K. Koga, S. Yamada, *Tetrahedron* **1975**, *31*, 227-230.



Scheme 14. Diazotisation of primary amines and α-amino acids.

The antibiotic azaserine (**55**), that shows also an anti-tumoral activity, was prepared by diazotisation of the corresponding *O*-(glycil)-*N*-(trifluroacetyl)-L-serine (**54**).[37] Treatment of **54** with lithium nitrate in the presence of chloroacetic acid, removal of the trifluoroacetyl protecting group with the enzyme acylase I affords the diazo ester **55** in 78% overall yield (Scheme 15).



Scheme 15. Synthesis of azaserine (**55**).

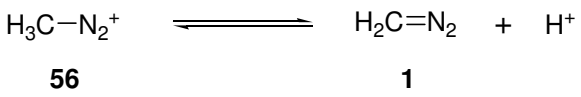
1.2 Catalysts for Metal Carbene Transformations

Diazo compounds are excellent sources of carbenoids or carbenes which are generated from the extrusion of nitrogen. A free carbene can be produced by thermal or photochemical methods, while carbenoids (metal-carbene complexes) are obtained in the reaction of the diazo precursor with a metal complex. Once formed, carbene and carbenoids can undergo to a large spectrum of transformations as, for example, C-H, O-H or N-H insertion, cyclopropanation or ylide formation.

[37] T. J. Curphey, *J. Org. Chem.* **1978**, *43*, 4666-4668.

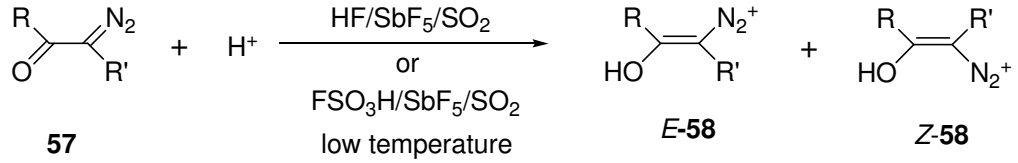
1.2.1 Electrophilic Addition to Diazo Compounds

Diazo compounds are unstable to acid-promoted decomposition, and it is this instability that promotes their effectiveness for catalytic reaction with transition metal complexes.
Diazomethane is the conjugate base of the methanediazonium ion (**56**) whose pK_a of 10 suggests to be the driving force for the high reactivity of diazomethane towards Lewis acids (Scheme 16).[38]



Scheme 16. Diazomethane and its conjugate acid methanediazonium ion.

pK_a values of diazonium ions derived from diazo esters and diazo ketones between −5 and –2 respectively, indicate an enhanced stability of these compounds to acid-promoted decomposition.[39] Diazo decomposition of diazomethane (**1**) results from *C*-protonation which is recognized to be thermodynamically more favourable than *N*-protonation, although the latter is kinetically more favourable but not productive.[40] In the case of diazo carbonyl compounds, *O*-protonation is observed only at low temperatures in super acids ($HF/SbF_5/SO_2$ or $FSO_3H/SbF_5/SO_2$), where the *E*- and *Z*-enol diazonium ions are formed (Scheme 17).[41]



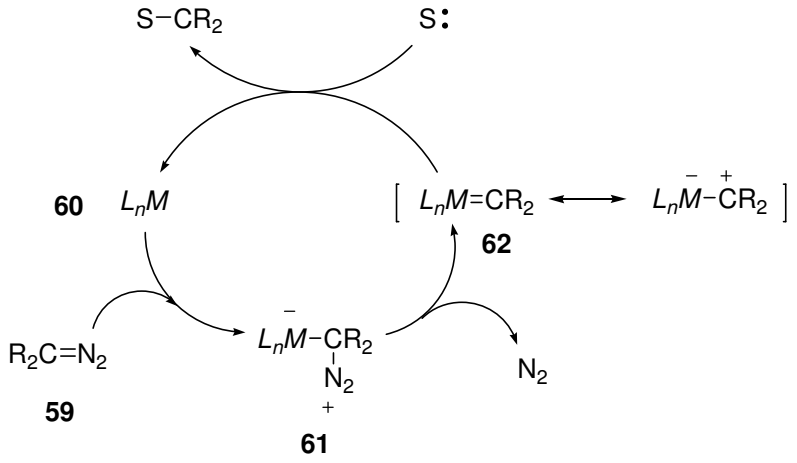
Scheme 17. Acid-catalysed decomposition of diazo carbonyl compounds.

1.2.2 Mechanism of Catalytic Diazo Decomposition

Transition metal complexes are Lewis acids and are responsible for catalytic decomposition of diazo compounds.[5] Their activity depends on the coordinative unsaturation at the metal center, that

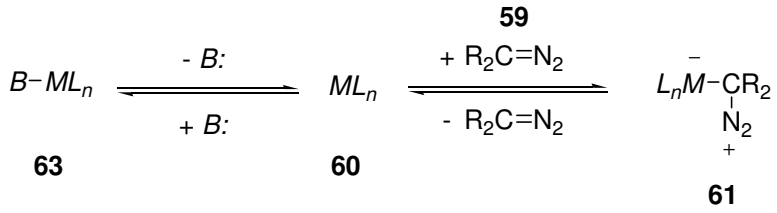
[38] J. F. McGarrity, T. Smith, *J. Am. Chem. Soc.* **1980**, *102*, 7303-7308.
[39] J. F. McGarrity in *The Chemistry of Diazonium and Diazo Groups* (Ed.: S. Patai), Wiley, New York, **1978**, Part 1.
[40] H. M. Niemeier, *Helv. Chim. Acta* **1976**, *59*, 1133-1139.
[41] a) M. Allard, J. Levisalles, J. M. Sommer, *J. Chem. Soc. Chem. Comm.* **1969**, 1515. b) C. Wentrup, H. Dahn, *Helv. Chim. Acta* **1970**, *53*, 1637-1645.

allows them to react as electrophile towards diazo compounds. The accepted mechanism, depicted in Scheme 18, was reported for the first time by Yates[42] and fully accepted by Doyle,[43] Padwa[44] and Davies:[45] the electrophilic addition of the metal complex (L_nM, **60**) to the diazo compound **59** produces the metal stabilized carbene species **62** and dinitrogen (Scheme 18). Transfer of the carbene part to the electrophilic substrates (S:) regenerates the metal complex and closes the catalytic cycle.



Scheme 18. Accepted mechanism for metal-catalysed decomposition of diazo compounds.

Furthermore, Lewis bases (*B:*) can inhibit transition-metal catalysed diazo decomposition because of their ability to coordinate the metal centre of the catalyst (Scheme 19).

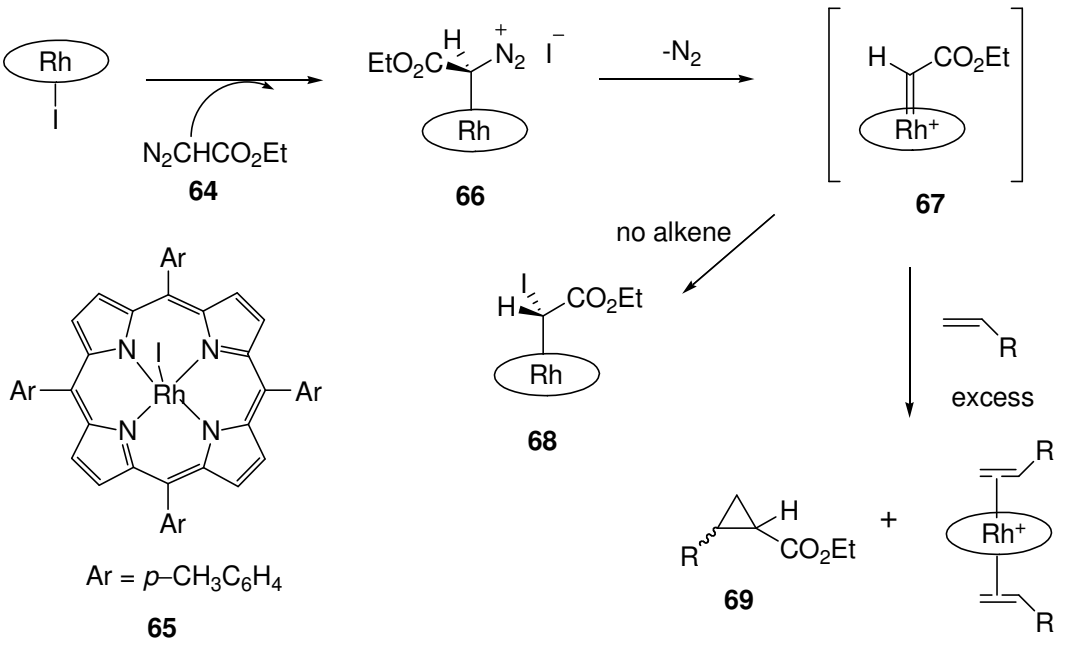


Scheme 19. Coordination of the metal centre of the catalyst by Lewis bases.

[42] P. Yates, *J. Am. Chem. Soc.* **1952**, *74*, 5376-5381.
[43] a) M. P. Doyle, *Chem. Rev.* **1986**, *86*, 919-939. b) M. P. Doyle in *Comprehensive Organometallic Chemistry II* (Ed.: L. S. Hegedus), Pergamon Press, New York, **1995**, Vo1. 12.
[44] a) A. Padwa, K. E. Krumpe, *Tetrahedron* **1992**, *48*, 5385-5453. b) A. Padwa, D. J. Austin, *Angew. Chem.* **1994**, *106*, 1881-1899. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1797-1815.
[45] H. M. L. Davies, *Tetrahedron* **1993**, *49*, 5203-5223.

The stability of the possible complex Lewis base-catalyst **63** restrict the ability of the diazo compound to decompose as in Scheme 18 and to form the adduct **61**; effective inhibitors are, in general, amines, sulfides[46] and nitriles.[47]

The two steps, the formation of the diazonium ion adduct **61** and the extrusion of dinitrogen which forms the metallocarbene **62**, have been considered as the rate limiting step of the cycle. Kinetic[48] and theoretical[49] studies indicate the second as the rate limiting step. Spectral evidences of the formation of the diazonium ion adduct **61** have been obtained when diazo ethyl acetate (**64**) and a iodorhodium(III) tetra-*p*-tolylporphyrin complex **65** were allowed to react; the diazonium ion **66** and then the iodorhodium complex **67** were formed. This latter complex could yield to the iodo acetate **68** when no alkene was present. Since the iodorhodium(III) complex **67** is an highly efficient catalyst for cyclopropanation, the cyclopropane derivative **69** was instead obtained when an alkene was present (Scheme 20).[50]



Scheme 20. Decomposition pathway of a rhodium-diazonium adduct.

Dichloromethane is the chosen solvent for diazo decomposition of diazo acetates and diazo ketones, but pentane and ethyl ether have also been used.[44a] When higher temperatures are necessary, as for

[46] An example of imination of sulfides in presence of a rhodium(II) catalyst has been reported: H. Okamura, C. Bolm, *Org. Lett.* **2004**, *6*, 1305-1307.
[47] R. G. Salomon, J. K. Kochi, *J. Am. Chem. Soc.* **1973**, *95*, 3300-3310.
[48] M. C. Pirrung, A. T. Morehead, Jr., *J. Am. Chem. Soc.* **1996**, *118*, 8162-8163.
[49] E. Nakamura, N. Yoshikai, M. Yamanaka, *J. Am. Chem. Soc.* **2001**, *124*, 7181-7192.
[50] J. L. Maxwell, K. C. Brown, D. W. Bartley, T. Kodadek, *Science* **1992**, *256*, 1544-1547.

decomposition of the less reactive diazo malonates and diazo acetoacetates, solvents as toluene, benzene and 1,2-dichloroethane are most often employed.[41b]

1.2.3 Copper Catalysts for Diazo Decomposition

Most of the early reports on metal-catalysed decomposition of diazo compounds used copper complexes as the catalysts.[43,51,52] In the 1960's, Moser[53] introduced a phosphine-legated copper(I) chloride and Nozaki[54] and co-workers copper(II) acetylacetonate [$Cu(acac)_2$]. Copper(I) triflate [$Cu(OSO_2CF_3)$ or Cu(OTf)] was used by Kochi[47,55] and his collaborator as a highly active catalyst in cyclopropanation reaction, as well as *N*-*tert*-butyl- and *N*-benzylsalicylaldimine copper complexes [$Cu(TBS)_2$] (**70a**) and [$Cu(BNS)_2$] (**70b**) reported by Corey and Myers[56] for diazo decomposition (Figure 6).

After the first reports of Aratani[57] and co-workers about copper-based chiral ligands as the salicylaldimine **71**, the major advance in this field was provided by Pfaltz[35,58] and co-workers, who described chiral semicorrin ligands **72** and **73**, suitable for coordination with copper(II) which were also used in cyclopropanation reactions (Figure 6). Since the active species was found to be copper(I), these catalyst were prepared as stable copper(II) complexes, which were activated by reduction with the diazo compound. Masamune,[59] Evans[60] and Pfaltz[61] also prepared a new series of C_2 asymmetric bis-oxazolines (**74**, **75**, **76**) generating the active copper(I) catalyst from CuOTf (Figure 6).

[51] M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, *98*, 911-935.
[52] H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861-2903.
[53] W. R. Moser, *J. Am. Chem. Soc.* **1969**, *91*, 1135-1140, 1141-1146.
[54] H. Nozaki, S. Moriuti, M. Yamabe, R. Noyori, *Tetrahedron Lett.* **1966**, *7*, 59-63.
[55] R. G. Salomon, J. K. Kochi, *J. Chem. Soc. Chem. Comm.* **1972**, 559-560.
[56] E. J. Corey, A. G. Myers *Tetrahedron Lett.* **1984**, *25*, 3559-3562.
[57] a) T. Aratani, Y. Yoneyoshi, T. Nagase, *Tetrahedron Lett.* **1975**, *16*, 1707-1710. b) T. Aratani, Y. Yoneyoshi, T. Nagase, *Tetrahedron Lett.* **1982**, *23*, 685-688.
[58] a) H. Fritschi, U. Leutenegger, A. Pfaltz, *Angew. Chem.* **1986**, *98*, 1028-1029. *Angew. Chem. Int. Ed*. **1986**, *25*, 1005-1006. b) H. Fritschi, U. Leutenegger, K. Siegmann, A. Pfaltz, W. Keller, C. Kratky, *Helv. Chim. Acta* **1988**, *71*, 1541-1552. c) U. Leutenegger, G. Umbricht, C. Fahrni, P. von Matt, A. Pfaltz, *Tetrahedron* **1992**, *48*, 2143-2156.
[59] a) R. E. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Lett.* **1990**, *31*, 6005-6008. b) R. E. Lowenthal, S. Masamune, *Tetrahedron Lett.* **1991**, *32*, 7373-7376.
[60] a) D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc*. **1991**, *113*, 726-728. b) D. A. Evans, K. A. Woerpel, M. Scott, *Angew. Chem.* **1992**, *104*, 439-441. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 430-432.
[61] D. Müller, G. Umbricht, B. Weber, A. Pfaltz, *Helv. Chim. Acta* **1991**, *74*, 232-240.

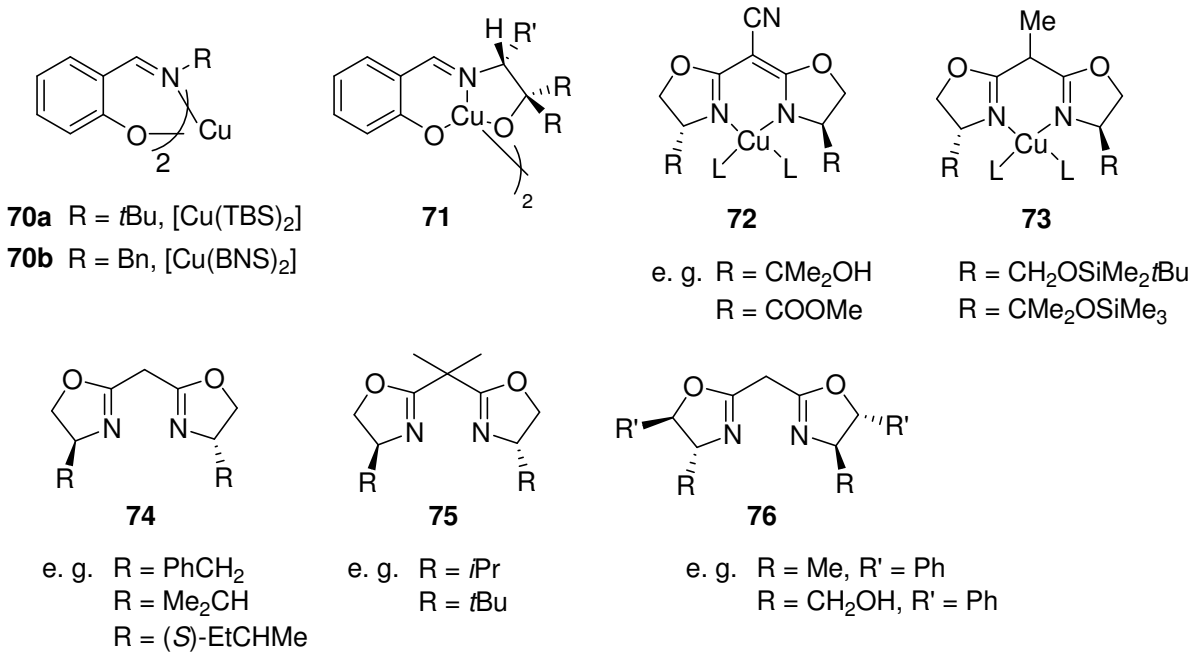


Figure 6. Various copper/ligand combinations for metal-carbene transformations.

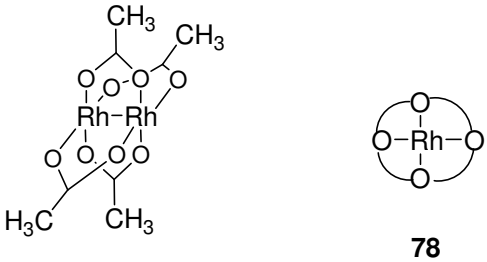
1.2.4 Rhodium Catalysts for Diazo Decomposition

1.2.4.1 Rhodium(II) Carboxylates Complexes and their Use in Catalysed-Decomposition Reaction of Diazo Compounds

Although the application of copper catalysts had expanded in diazo decomposition for cyclopropanation reactions, catalyst based on dirhodium(II) had been employed in a larger scope of reaction since the early report on the use of rhodium(II) carboxylate complexes by Reimlinger and co-workers.[62] Many reactions that showed low conversion with copper catalysts were found to proceed with an increased efficiency. Since then, rhodium(II) catalysts such as rhodium(II) tetraacetate [$Rh_2(OAc)_4$] (**77**) have become the most used catalysts in diazo decomposition.

The complex **77,** showed in Figure 7, possess a D_{4h} symmetry with four bridging acetate or derivative ligands and one vacant coordination site per rhodium atom. Its octahedral geometry resembles a "lantern": the atomic array (structure **78**) is near to that of a circular wall, whose circumference is electron rich and whose centre is electron deficient.

[62] R. Paulissen, H. Reimlinger, E. Hayez, A. J. Hibert, Ph. Tessyè, *Tetrahedron Lett*. **1973**, *14*, 2233-2236.



77 **78**

Figure 7. Rhodium(II) tetraacetate complex and its atomic array around one metal centre.

Doyle[63] and Padwa[44] established in their reports the effect of the modification of the bridging dirhodium(II) ligands on the selectivity. For example, the more electron-withdrawing substituent of rhodium(II) perfluorobutyrate $[Rh_2(pbf)_4]$ (**79**), shows an enhanced reactivity but a reduced stereoselectivity than $[Rh_2(OAc)_4]$ in the synthesis of γ-lactones from diazoacetoacetates.[63] On the contrary, dirhodium(II) carboxamidates, such as dirhodium(II) acetamide $[Rh_2(acam)_4]$ (**80**) and dirhodium(II) caprolactamate $[Rh_2(cap)_4]$ (**81**), exhibit lower reactivity but increased stereo and regioselectivity in the same system (Figure 8).[63]

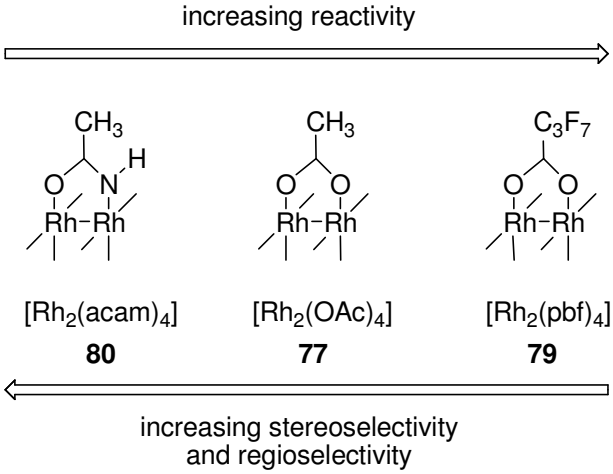
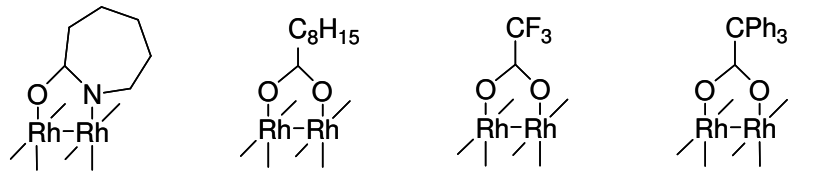


Figure 8. Ligand selectivity in metal-carbene transformations.

Other rhodium(II) carboxylates are rhodium(II) tetraoctanoate $[Rh_2(oct)_4]$ (**82**), which has a highly solubility in non polar solvents and a good reactivity in cyclopropanation of olefins through rhodium(II) vinylcarbenoids.[64] Rhodium(II) tetrafluoroacetate $[Rh_2(tfa)_4]$ (**83**) led to comparable results (Figure 9).

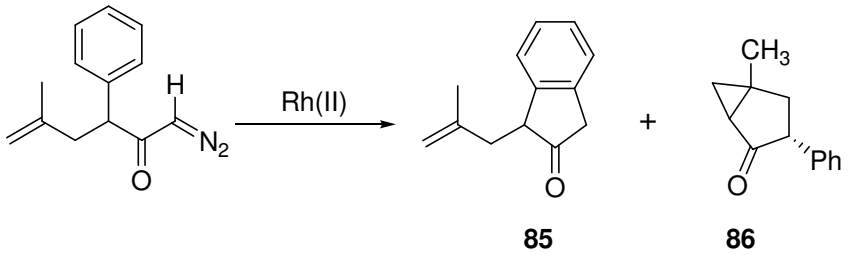
[63] M. P. Doyle, L. J. Westrum, W. N. E. Wendelmoed, M. M. See, W. P. Boone, V. Bagheri, M. M. Pearson, *J. Am. Chem. Soc.* **1993**, *115*, 958-964.
[64] H. M. L. Davies, N. J. S. Huby, W. R. Catrell, Jr., J. L. Olive, *J. Am. Chem. Soc.* **1993**, *115*, 9468-9479.



[Rh_2(cap)$_4$] **81** [Rh_2(oct)$_4$] **82** [Rh_2(tfa)$_4$] **83** [Rh_2(TPA)$_4$] **84**

Figure 9. Some examples of rhodium(II) catalysts.

Careful choice of the catalyst, the diazo precursor and the substrate allows control in the outcome of metal carbene transformations. Furthermore, slight electronic, steric and conformational changes can result in a large effect on the reaction pathway and enantioselectivity. For example, the high electrophilic [Rh_2(pbf)$_4$] (**79**), led exclusively the aryl C-H insertion product **85**, whereas the more electron rich [Rh_2(cap)$_4$] formed only the product of cyclopropanation **86**; [Rh_2(OAc)$_4$] (**77**) afforded a 1:1 mixture of products (Scheme 21).[43a]



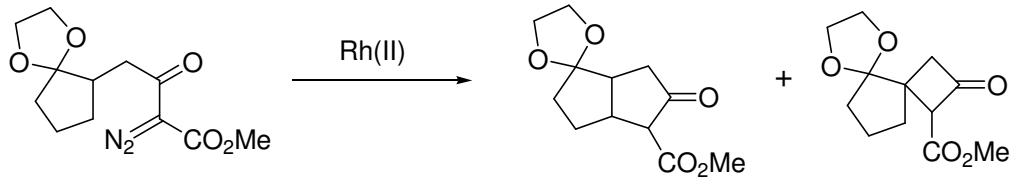
85 **86**

[Rh_2(pbf)$_4$] (**85**)/(**86**) = 100:0
[Rh_2(OAc)$_4$] (**85**)/(**86**) = 52:48
[Rh_2(cap)$_4$] (**85**)/(**86**) = 0:100

Scheme 21. Effects of rhodium(II) catalyst's electrophilicity to direct selectivity.

To Ikegami and co-workers is due the introduction of rhodium(II) tetratriphenylacetate [Rh_2(TPA)$_4$] (**84**) (Figure 9) featured by the steric bulk of the bridging ligand on the rhodium. In the study of the selectivity in the intramolecular C-H insertion of α-diazo-β-keto-esters (tethered to a cyclic system such as compound **87**), [Rh_2(TPA)$_4$] showed a high efficiency in insertion reactions into methylene over methine, better than other common catalysts (Scheme 22).[65]

[65] S. Hashimoto, N. Watanabe, S. Ikegami, *Tetrahedron Lett.* **1992**, *33*, 2709-2712.

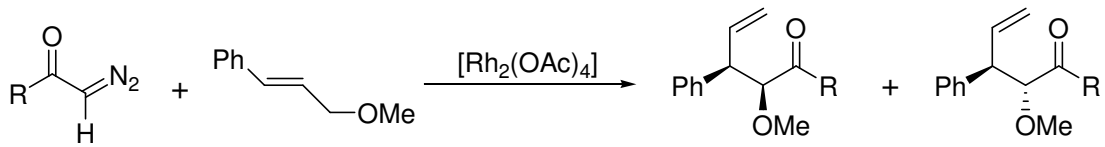


87 **88** **89**

$[Rh_2(OAc)_4]$	(**88**)/(**89**) = 37:63
$[Rh_2(tfa)_4]$	(**88**)/(**89**) = 56:44
$[Rh_2(O_2CPh)_4]$	(**88**)/(**89**) = 54:46
$[Rh_2(TPA)_4]$	(**88**)/(**89**) = 96:4

Scheme 22. Effects of the bridging ligands of rhodium(II) catalysts on site-selectivities.

The structure of the diazo compound also has a large influence on the chemoselectivity of rhodium(II) catalysed reactions. An example is showed in Scheme 23, where in the rhodium(II) catalysed reaction of diazo compounds **90a**-**c** with trans-cinnamyl methyl ether (**91**), the product of [2,3]-sigmatropic rearrangement was formed in preference (3:1) to olefine cyclopropanation.[66] The major product was formed as a 5:1 mixture of the *erythro* and *threo* isomers **92** and **93**, when diazo ethyl acetate (**90a**) was present. The ratio improved when aryl diazo ketones, **90b** and **90c**, were used instead diazo ethyl acetate (Scheme 23).



91 **92** **93**

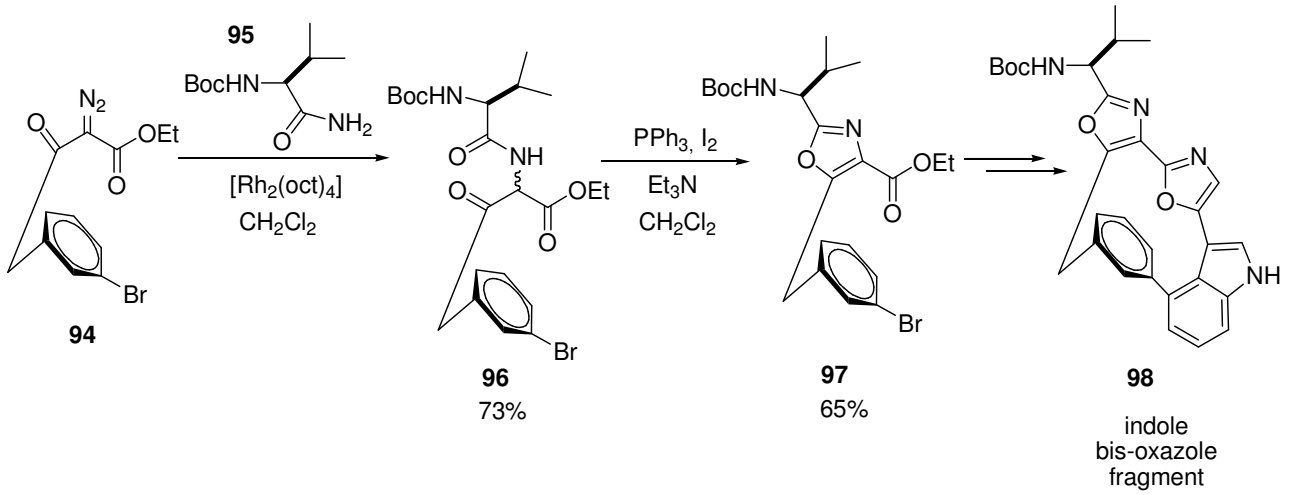
90a	R = OEt	69%	(**92**)/(**93**) = 80:20
90b	R = Ph	81%	(**92**)/(**93**) = 91:9
90c	R = *p*-$MeOC_6H_4$	82%	(**92**)/(**93**) = 91:9

Scheme 23. Effects of diazo substitution to direct selectivity.

Metal-carbene transformations find wide application in the synthesis of natural products. A recent example by Moody and co-workers on the synthesis of the indole bis-oxazole fragment of Diazonamide A, features as key step an intermolecular rhodium(II) catalysed N-H insertion (Scheme 24).[67] α-Diazo β-keto-ester **94** underwent chemoselective reaction with *N*-Boc valinamide (**95**) to give compound **96**, converted then in the oxazoles **97**, precursor of the indole bis-oxazole

[66] M. P. Doyle, V. Bagheri, N. K. Harn, *Tetrahedron Lett.* **1988**, *29*, 5119-5122.
[67] J. R. Davies, P. D. Kane, C. J. Moody, *J. Org. Chem.* **2005**, *70*, 7305-7316 and references cited therein.

fragment **98** of Diazonamide A.



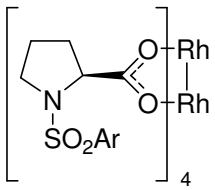
Scheme 24. Rhodium(II) catalysed N-H insertion reaction as key step in the synthesis of the indole bis-oxazole fragment **98** of Diazonamide A.

After the successful use of achiral rhodium(II) complexes in metal carbene transformations, the next step involves the replacement of the acetate by chiral carboxylate, which was reported by several groups. McKervey and co-workers developed a variety of *N*-protected-L-proline derivatives, such as the chiral *N*-benzensulfonyl-protected rhodium(II) catalyst [Rh_2(*S*-TBSP)$_4$] **99b** and [Rh_2(*S*-DOSP)$_4$] **99c** and [Rh_2(*S*-BSP)$_4$] **99a** which was the most successful, among the others, in enantioselective C-H activation reactions (Figure 10).[68] Davies showed examples of chiral decomposition of vinyl- and aryl- diazoacetates towards asymmetric cyclopranation with [Rh_2(*S*-TBSP)$_4$] and [Rh_2(*S*-DOSP)$_4$].[69] From Hashimoto and Ikegami is reported the modification of rhodium(II) carboxylate complexes with *N*-phthaloyl-(*S*)-amino acids as ligands (**100a**-**e**) and their application in the enantioselective intramolecular C-H insertion of α-diazo-β-keto-esters.[70] More recently a set of second generation catalysts has been reported with the introduction of an additional benzene ring (**101a**-**d**).[71] An example of Si-H insertion reaction is described by Hashimoto using *N*-phthaloyl-(*S*)-amino acids rhodium(II) complexes of first and second generation.[72]

[68] a) T. Ye, F. C. Garcia, M. A. McKervey, *J. Chem. Soc., Perkin Trans. I* **1995**, 1373-1379. b) T. Ye, M. A. McKervey, B. D. Brandes, M. P. Doyle, *Tetrahedron Lett.* **1994**, *35*, 7269-7272.
[69] H. M. L. Davies, *Eur. J. Org. Chem.* **1999**, 2459-2469 and references cited therein. b) H. M. L. Davies, T. Hansen, M. R. Churchill, *J. Am. Chem. Soc.* **2000**, *122*, 3063-3070.
[70] a) S. Hashimoto, N. Watanabe, S. Ikegami, *Tetrahedron Lett.* **1990**, *31*, 5173-5174. b) S. Hashimoto, N. Watanabe, K. Kawano, S. Ikegami, *Synth. Commun.* **1994**, *24*, 3277-3287.
[71] S. Kitagaki, M. Anada, O. Kataoka, K. Marsuno, C. Umeda, N. Watanabe, S. Hashimoto, *J. Am. Chem. Soc.* **1999**, *121*, 1417-1418.
[72] S. Kitagaki, M. Kinoshita, M. Takeba, M. Anada, S. Hashimoto, *Tetrahedron: Asymmetry* **2000**, *11*, 3855-3859.

L-proline based

Mc Kervey, Davies



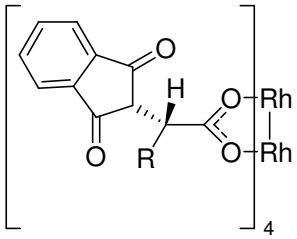
99a Ar = C_6H_5 $[Rh_2(S\text{-BSP})_4]$

99b Ar = *p*-*t*BuC_6H_4 $[Rh_2(S\text{-TBSP})_4]$

99c Ar = *p*-($C_{12}H_{25}$)C_6H_4 $[Rh_2(S\text{-DOSP})_4]$

Phthaloyl-protected amino acid-based

Ikegami/Hashimoto



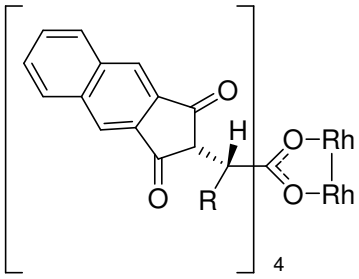
100a R = Bn $[Rh_2(S\text{-PTPA})_4]$

100b R = Me $[Rh_2(S\text{-PTA})_4]$

100c R = *i*Pr $[Rh_2(S\text{-PTV})_4]$

100d R = *t*Bu $[Rh_2(S\text{-PTTL})_4]$

100e R = Ph $[Rh_2(S\text{-PTPG})_4]$



101a R = Bn $[Rh_2(S\text{-BPTPA})_4]$

101b R = Me $[Rh_2(S\text{-BPTA})_4]$

101c R = *i*Pr $[Rh_2(S\text{-BPTV})_4]$

101d R = *t*Bu $[Rh_2(S\text{-BPTTL})_4]$

Figure 10. Chiral rhodium(II) carboxylates.

1.2.4.2 Rhodium(II) Carboxamidate Complexes

The general structure of the rhodium(II) carboxamidate catalysts involves four bridging amide ligands bound to the dirhodium(II) core, with two oxygen and two nitrogens bonded to each rhodium, such that the two nitrogen are adjacent to each other in a "*cis*-2-2" configuration (structures **102** and **103**). Commonly, it is overall more rigid than in rhodium(II) carboxylates. It is possible to synthesise ligands with "3-1" and "4-0" *cis*-configuration, but their selectivity is quite low while is not possible to obtain the "*trans*-2-2" (Figure 11). The stereogenic center of the ligand is the tetrahedral carbon α to the nitrogen, such that the chiral attachment, in the form of a carboxylate, is in a close proximity to the metal-catalysed carbene precursor, and can thus influence the regioselectivity and stereoselectivity of the reaction. Various examples of rhodium(II)

carboxamidate catalysts are reported in Figure 11, and are 2-oxopyrrolidines derivatives **104**,[73] 2-oxo-oxazolidine derivatives **105**,[74] *N*-acyl-2-oxoimidazolidine **106**,[75] and 2-oxo-azetidine **107**.[76]

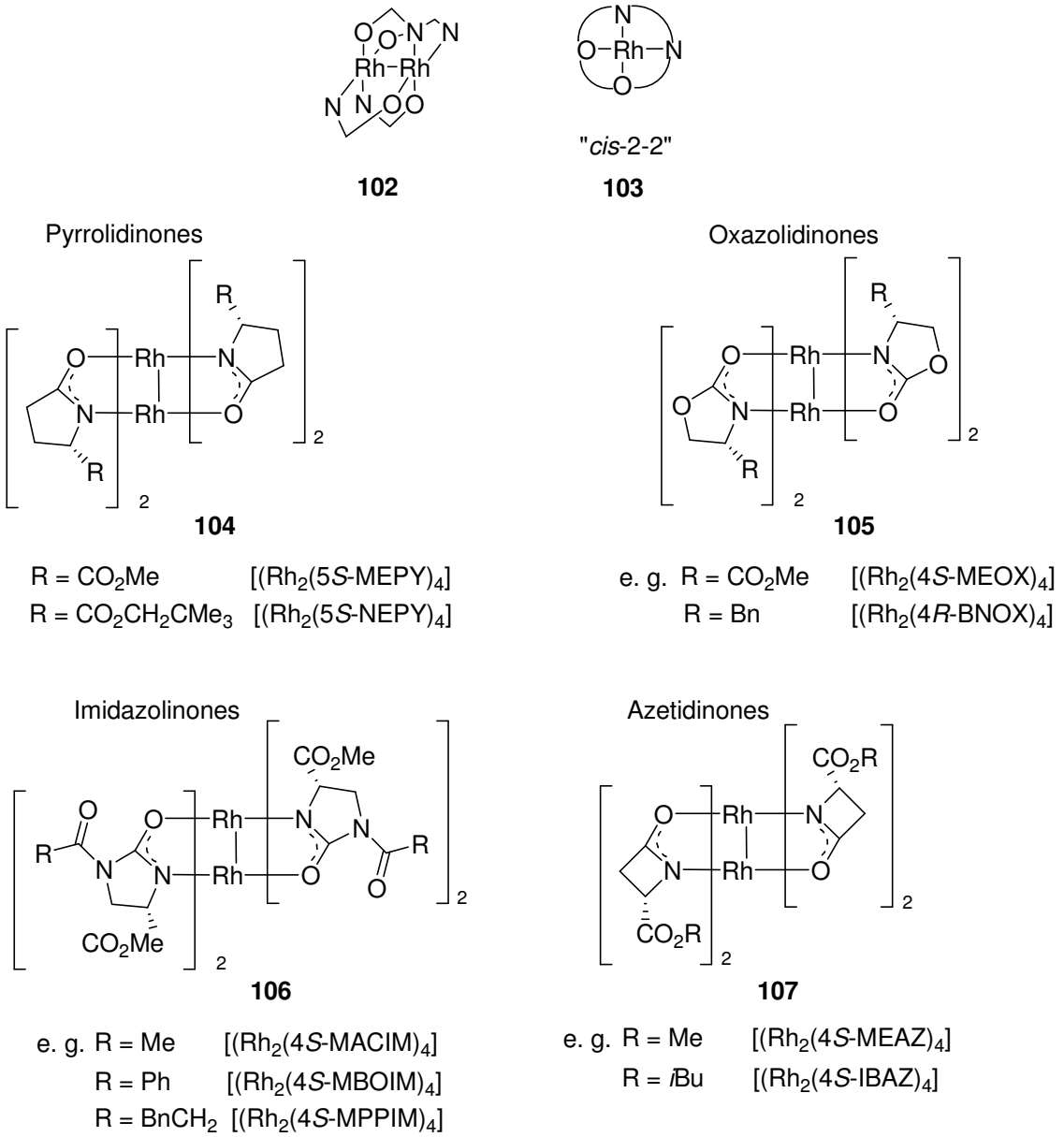


Figure 11. Chiral rhodium(II) carboxamidates.

[73] a) M. P. Doyle, W. R. Winchester, J. A. A. Horn, V. Linch, S. H. Simonsen, R. Ghosh, *J. Am. Chem Soc.* **1993**, *115*, 9968-9978. b) M. P. Doyle, W. R. Winchester, S. H. Simonsen, R. Ghosh, *Inorg. Chim. Acta* **1994**, *220*, 193-199.

[74] a) M. P. Doyle, W. R. Winchester, M. N. Protopopova, P. Müller, G. Bernardinelli, D. Ene, S. Motallebi, *Helv. Chim. Acta* **1993**, *76*, 2227-2235. b) M. P. Doyle, A. B. Dyatkin, M. N. Protopopova, C. I. Yang, C. S. Miertschin, W. R. Winchester, S. H. Simonsen, V. Lynch, R. Ghosh, *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 163-170.

[75] a) M. P. Doyle, R. E. Austin, A. S. Bailey, M. P. Dwyer, A. B. Dyatkin, A. V. Kalinin, M. M. Y Kwan, S. Liras, C. J. Oalmann, R. L. Pieters, M. N. Protopopova, C. E. Raab, G. H. P. Roos, Q. Zhou, S. F. Martin, *J. Am. Chem. Soc.* **1995**, *117*, 5763-5775. b) M. P. Doyle, C. E. Raab, G. H. P. Roos, V. Lynch, S. H. Simonsen, *Inorg. Chim. Acta* **1997**, *266*, 13-18.

[76] M. P. Doyle, Q.-L. Zhou, S. H. Simonsen, V. Lynch, *Synlett* **1996**, 697-698.

These complexes are usually prepared and stored as bis-acetonitrile complexes. The acetonitrile ligands occupy the axial-coordination site of each rhodium metal centre. Furthermore, by determining the equilibrium constant for acetonitrile association, it has been shown that oxazolidinone derivatives are generally more reactive than their pyrrolidinone counterparts, at the expense of lower enantiocontrol. The imidazolidinone-based catalysts, such as [(Rh_2(4*S*-MACIM)$_4$] and [(Rh_2(4*S*-MPPIM)$_4$], are more effective for decomposing less-sterically hindered diazoacetates, in cyclopropanation reactions, as well as in intramolecular aliphatic C-H insertions, in comparison to the pyrrolidinone derivative [(Rh_2(5*S*-MEPY)$_4$].

1.3 Silicon Modified Compounds

1.3.1 Introduction to Silicon Bonds

Silicon is the second most abundant element and one most similar to carbon. It belongs to the same periodic group as carbon and shares with it several properties, such as its tetracovalency, but, perhaps paradoxically, has found its greatest application and utility as a substitute of hydrogen.[77] In Table 1 are reported some examples of silicon bond strengths to other elements. Bonds to electronegative elements are generally stronger with silicon than with carbon: for example, the silicon fluorine bond is one of the strongest single-bonds known, while bonds to electropositive counterparts may be easily cleaved.

Table 1. Bond dissociation energies and bond lenghts.

Bond	***Dissociation energy (kJ mol^{-1})***	***Bond length (Å)***
Si-C	318	1.89
Si-O	531	1.63
Si-Cl	471	2.05
Si-F	808	1.60
C-C	334	1.54
C-O	340	1.41
C-Cl	335	1.78
C-F	452	1.39

[77] E. W. Colvin in *Silicon Reagents in Organic Synthesis* (Ed.: Academic Press), Harcourt Brace & Company Publishers, London, **1988**.

Under appropriate conditions, a silicon substituent can stabilize positive or negative charges and affect the π-system in various molecules. The electronic effects of a silyl substituent (R_3Si group) can be divided in four components: inductive effects, field effects, (p-d)-π-bonding and hyperconjugative effects. The total electronic effect of a R_3Si group in any silicon compound is usually a combination, to a greater or less degree, of each of these effects.[78]

Inductive effects are generally considered to act through the σ-framework of a molecule, and the electronegativity of an element is usually taken as a measure of its tendency to attracts σ-electrons. The values for carbon electronegativity (following Pauling)[79] are C 2.5, H 2.1, Si 1.8. The electronegativity of hydrogen falls between that of silicon and carbon. Eaborn[80] pointed out that the polaritry of bonds should be $Si^+ C^-$, $C^- H^+$, $Si^+ H^-$, which is consistent with the direction of bond cleveage. Silicon-carbon bonds usually cleave in the direction $Si^+ C^-$ by electrophilic attack at carbon or nucleophilic attack at silicon. Regarding the purely inductive effect, triorganylsilyl groups are electron-donating, however, this effect has a short-range character and a great influence only on atoms directly bonded to silicon.

The field effect is often confused with the inductive effect, but is quite distinct and more complex. It describes the response of a neighbouring π-system to the σ-dipole moment of the entire R_3Si group. A π-inductive effect, following the nomenclature of Topsom,[81] is one that modifies a π-system without charge transfer to or from that π-system. When a R_3Si group is present in the system, it is quite difficult to predict what the field effect may be, because, though the inductive polarization is $Si^+ C^-$, the R_3Si group can be electron withdrawing, with respect to the nature of R.

Although it is clear that the R_3Si group can act as a π-electron withdrawing group, the mechanism by which this electron withdrawal operates remaines questionable. The first explanation is that a relative low-lying, unoccupied silicon d-orbital can participate in (p-d)-π-bonding, as shown in Figure 12. In this way, electron density of the p-orbital on X can be partially transferred to the vacant 3d-orbital of the silicon through a donor-acceptor interaction. This conceptually simple (p-d)-π-bonding model has been applied to explain, for example, the enhanced acidity of R_3SiOH or the reduced basicity of $R_3SiNR'_2$, with respect to the corresponding carbon derivatives.[78]

[78] A. R. Bassindale, P G. Taylor in *The Chemistry of Organic Silicon Compounds: Part 2* (Eds.: S. Patai, Z. Rapoport), Wiley, Chicester, **1989**.
[79] L. Pauling in *The Nature of the Chemical Bond and the Structure of Molecules and Crystals* (3rd edn.), Cornell Univ. Press, Ithaca, N. Y., **1960**.
[80] C. Eaborn in *Organosilicon Compounds*, Butterworths, **1960**.
[81] R. P. Topsom in *Progress in Physical Organic Chemistry*, (Eds.: A. Streitweiser, R. W. Taft), Wiley, New York, **1976**, Vol. 12.

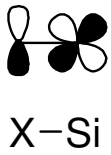


Figure 12. (p-d)-π-Bonding between a p-orbital of the halide X and a 3d-orbital of the silicium.

Hyperconjugation is also known as σ-π-conjugation and it has been considered as an alternative or complement to (p-d)-π-bonding.[82] If two adjacent molecular orbitals are close in energy and have an appropriate symmetry, they can undergo perturbation: the energy of one is lowered and the other is raised. In Figure 13 is shown the interaction σ∗-orbital with a π-orbital of a Si-C bond.

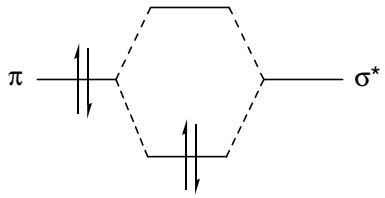


Figure 13. The hyperconjugative interaction of a π- and σ*-orbital.

In this example, the π-orbital is lowered in energy by hyperconjugation and this would be reflected, for example, in the ionisation potential.[82] The magnitude of the hyperconjugative effect depends more critically on the energy difference between the orbitals, and on the orbital coefficients. Furthermore, to evaluate fully the effect of the hyperconjugation it is necessary to consider σ*-π*-, σ-π- and σ-π*-interactions additionally to the discussed σ*-π.

1.3.2 Cleavage of Silicon-Carbon and Silicon-Oxygen Bonds

Starting from the theoretical background reported in the previous paragraph, some general remarks could be done about the reactivity of bonds involving a silicon atom. The silicon carbon-bond is quite stable towards homolytic fission but it is cleaved by ionic reagents, either by initial attack at Si or by electrophilic attack to the bonded C. Since a carbon-silicon bond dissociates in the same direction as a carbon-hydrogen ($C^- H^+$ *vs* $C^- Si^+$), the behaviour of a silicon-carbon bond in a chemical reaction could be predicted by consideration of an analogous hydrogen-carbon bond.[77] As a broad generalization, when a C-H bond can be cleaved by a particular ionic reagent, the corresponding C-$SiMe_3$ will be cleaved by the same reagent even more readily. Similar parallels

[82] C. G. Pitt, *J. Organomet. Chem.* **1973**, *61*, 49-70.

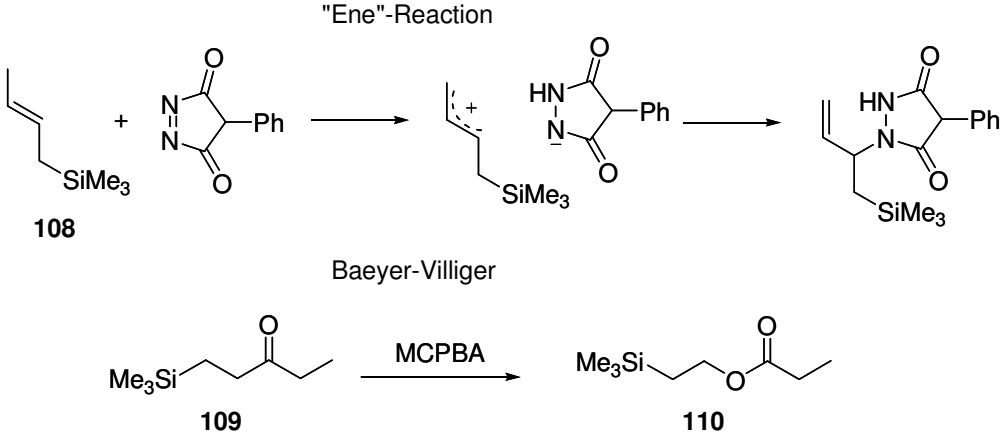
can be done also for O-H and O-Si bonds, although with the opposite reactivity, since O-H bonds can be cleaved more readily than the O-Si bonds. As a most useful general rule, Fleming has suggested that Si bonded to C should be considered as a "super proton", whereas, when it is bonded to an oxygen, it should be seen as an "enfeebled proton".[83]

In general, organosilicon compounds are stable and can be easily handled, although storage under argon or vacuum, even at room temperature, is preferable. The carbon-silicon bond can stand a variety of reaction conditions, and it possesses a latent lability, which can be revealed at the appropriate moment.

1.3.3 Some Examples of Reactivity of Organosilicon Compounds

Over the past decades, organosilicon compounds have reached considerable importance in synthetic organic chemistry, in particular for C-C bond formation reactions. The growing interest in silicon reagents is due to some simple effects, such as, for example, the stabilising effect of silyl groups on carbenium ions and anions and their utility as protecting groups.[84] In fact, introduction of organosilicon protecting groups on functional groups of various chemical nature changes the direction of the attack of the nucleophilic and electrophilic reagents and increases the selectivity of the reaction.

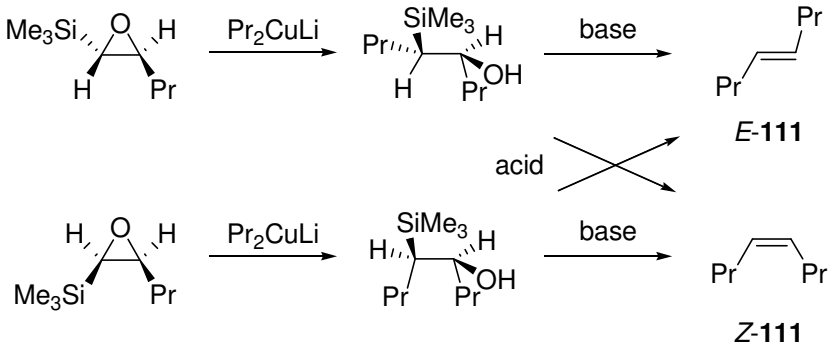
There are a number of reactions which are controlled by the formation of a β-silyl carbonium ion, such as the "ene"-reaction, involving compound **108**, and the Baeyer-Villiger reaction. In the latter, the presence of a trimethylsilyl group in β-position relative to a ketone (as in **109** in Scheme 25), stabilises the carbonium ion leading to the regioselective formation of ester **110**.



Scheme 25. Reactions controlled by the formation of a β-silyl carbonium ion.

[83] I. Fleming, *Chem. Soc. Rev.* **1981**, *10*, 83-111.
[84] G. G. Furin, O. A. Vyazankina, B. A. Gostevsky, N. S. Vyazankin, *Tetrahedron* **1988**, *44*, 2675-2749.

The activating and directive effects of silicon are also observed in carbanionic reactions as for the established alternative to the Wittig reaction, the Peterson olefination.[85] The carbonyl compound can be an aldehyde or a ketone and a range of carbanions have been employed. Unlike the Wittig reaction, the stereochemical outcome of the Peterson reaction is insensitive to counterions, added salts, solvents, and variations in temperature. The reaction may be also used to make single geometrical isomers of alkenes (as *E*-**111** and *Z*-**111**), where the geometry depends on the relative stereochemistry of the starting materials (Scheme 26).



Scheme 26. An example of the Peterson olefination.

1.4 α-Silyl-Substituted α-Diazo Esters

The silyl modification of a diazo compound, and more specific of a diazo ester, offers a number of possible transformation, mainly under the following aspects:

- silyl substituents can interact with the carbene (or carbenoid) centre in the same molecule
- silyl groups can be employed as substituents with modulating steric demand that can influence the selectivity of the reaction
- [3,4]-intramolecular reactions are possible, paving the way for the synthesis of various silaheterocycles, in addition to the already known 1,2-(Si-C) migration

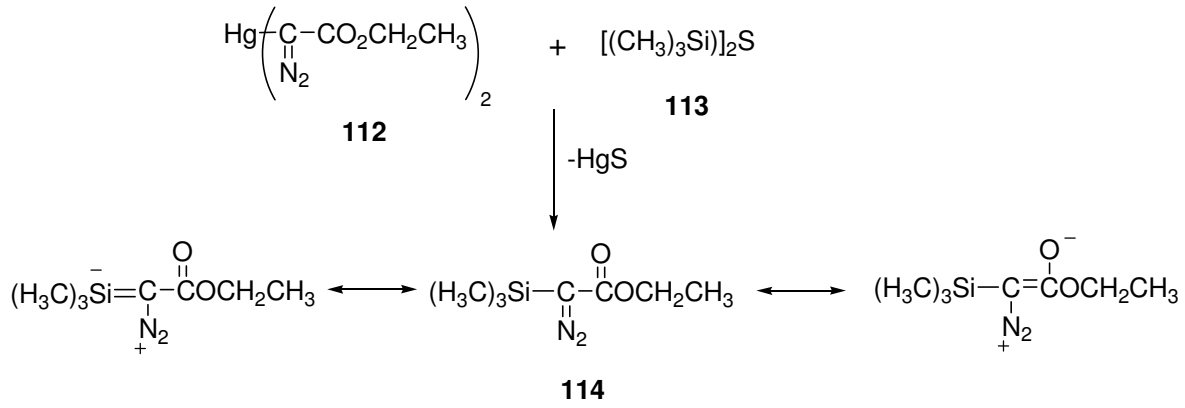
The *p*-acceptor character of trialkylsilyl groups has influence on the reactivity and the selectivity of the diazo compound, on the carbene (or carbenoid) and on other reactive intermediates.

The synthesis and the most important reaction features of α-silyl-substituted α-diazo esters will be discussed in this section.

[85] D. J. Ager, *Synthesis* **1984**, 384-398.

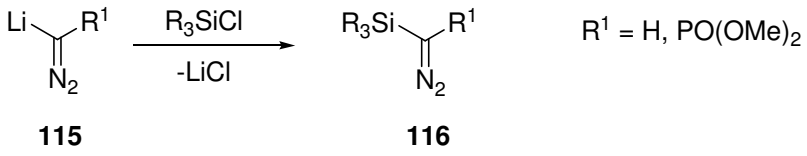
1.4.1 Preparation of α-Silyl-Substituted α-Diazo Esters.

The first synthesis of a α-silyl α-diazo ester was reported in 1969 by Schöllkopf and co-workers which carried out intensive studies about 2-trimethylsilyl-2-diazo ethyl acetate (**114**) and its reactivity towards activated olefines such as fumaric diethylester.[86] The synthetic pathway to the first substituted diazo ester deals about the ability of dimercurate-2-diazo ethyl acetate (**112**) to undergo reaction with bis-trimethylsilyl sulfide (**113**) to have access to 2-trimethylsilyl-2-diazo ethyl acetate (**114**) in 90% yield (Scheme 27).



Scheme 27. Synthesis of 2-trimethylsilyl-2-diazo ethyl acetate **114** from dimercurate-2-diazo ethyl acetate (**112**).

Lithium derivatives of diazo esters **115**, prepared *in situ*, could as well undergo silylation reaction in the presence of triorganylsilyl chloride as reported by Kostyuk co-workers (Scheme 28).[87]

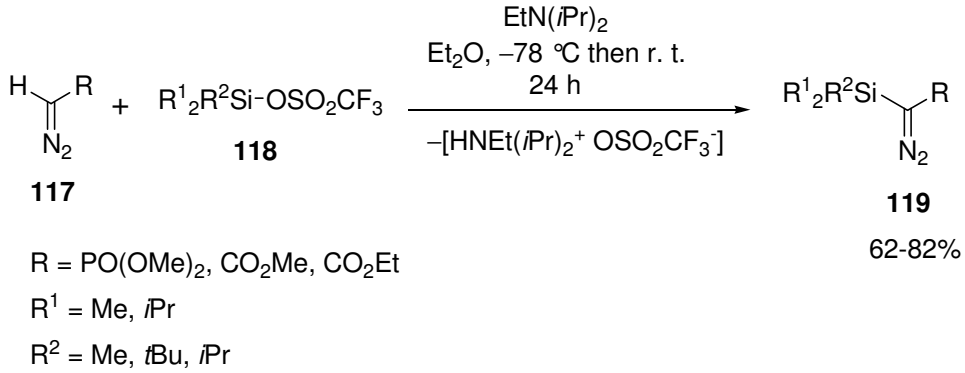


Scheme 28. Synthesis of triorganylsilyl diazo compounds **116** from their lithiated precursors **115**.

Other methods include the Bamsford-Stevens reaction, base catalysed removal of *N*-nitroso-*N*-silylmethyl acid amides and diazo transfer, which all involve introducing the diazo compound into silylated precursors.[88]

[86] U. Schöllkopf, D. Hoppe, N. Rieber, V. Jacobi, *Liebigs Ann. Chem*. **1969**, *730*, 1-15. See also: U. Schöllkopf, N. Rieber, *Angew. Chem.* **1967**, *5*, 238-239. *Angew. Chem. Int. Engl. Ed.* **1967**, *6*, 261-262.
[87] A. S. Kostyuk, I. B. Ruderfer, Y. I. Baukov, I. F. Lutsenko, *J. Gen. Chem. USSR (Engl. Transl.)* **1975**, *45*, 819-824.
[88] See sections 1.1.3 and 1.1.4.

Regitz and co-workers reported a general and versatile synthesis of trialkylsilyl diazo phosphon- and carboxy-esters **119**, which were prepared from diazo phosphonic- or carboxy-esters **117** and trialkylsilyl triflate **118**, in diethylether at –78 °C, in presence of Hünig's base [EtN(*i*Pr)$_2$] (Scheme 29).[89] Ethyldi*iso*propylamine triflate precipitates as salt from the solution and the purification of the crude reaction mixture by distillation affords trialkylsilyl-2-diazo esters **119** in up to 82% yield. The base deprotonates the carbon bearing the diazo group, and preserves the formed trialkylsilyl derivative **119** from any possible acid catalysed decomposition.

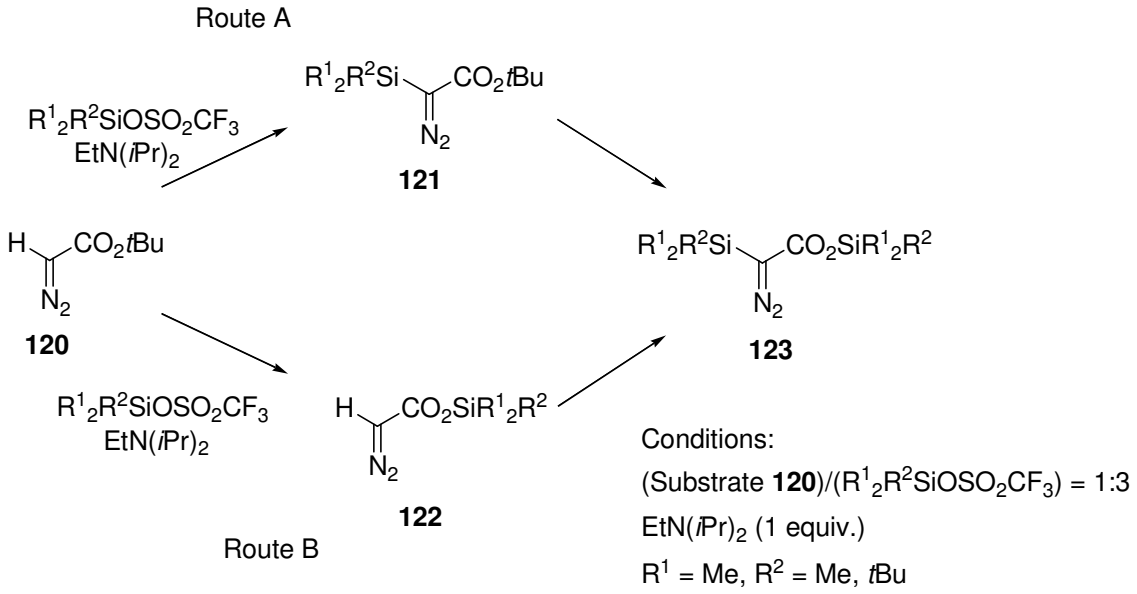


Scheme 29. Preparation of trialkylsilyl-2-diazo esters **119** from 2-diazo esters **117**.

α-Trialkylsilyl α-diazo esters show characteristic signals in their IR spectra, including the diazo absorption in the range 2090-2075 cm^{-1} and CO absorption between 1695-1680 cm^{-1}. In the ^{1}H NMR spectra methyl rests that are directly bonded to the silicon resonate at higher field.

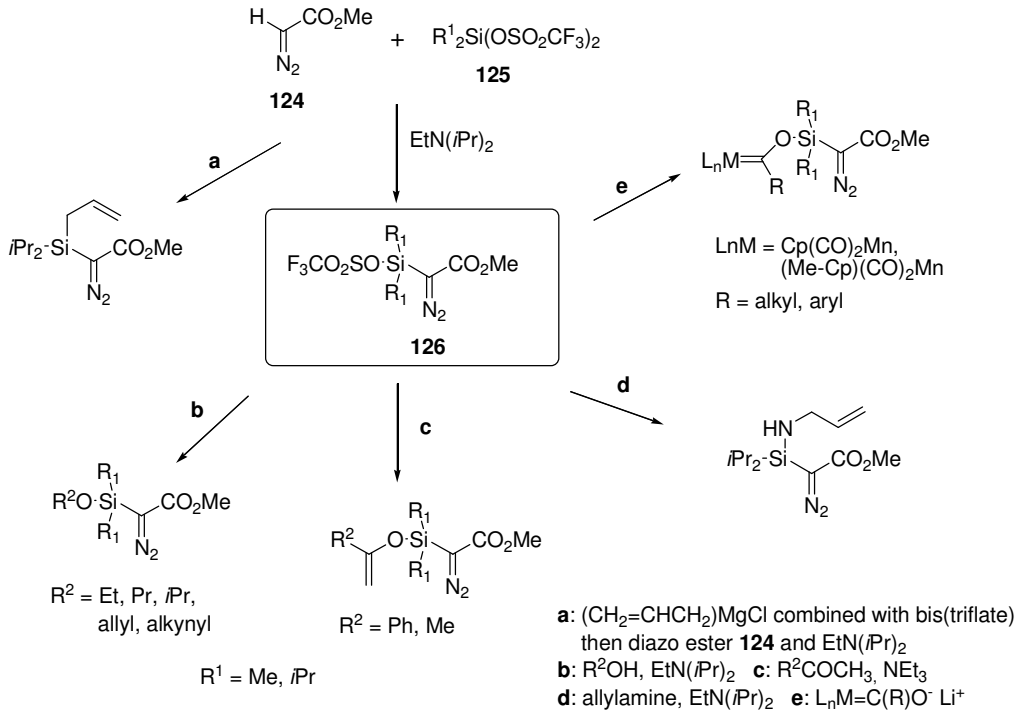
The increase of the ratio of trialkylsilyl triflate relative to the substrate 2-diazo *tert*-butyl acetate (**120**) led to interesting results. In fact, when 3 equivalents of trimethylsilyl or *tert*-butyldimethylsilyl triflate are added to compound **120**, the product of *C*-silylation **121** is formed together with a product of *C*- and *O*-silylation **123**, as depicted in Scheme 30. The formation of the *C*-silylated product **121** appears the fastest (Route A), although the *C*-silylation reaction of the early formed *O*-silylated product **122** can be possible (Route B).[89]

[89] T. Allspach, H. Gümbel, M. Regitz, *J. Organometal. Chem.* **1985**, *290*, 33-39.



Scheme 30. Synthesis of double-silylated diazo esters.

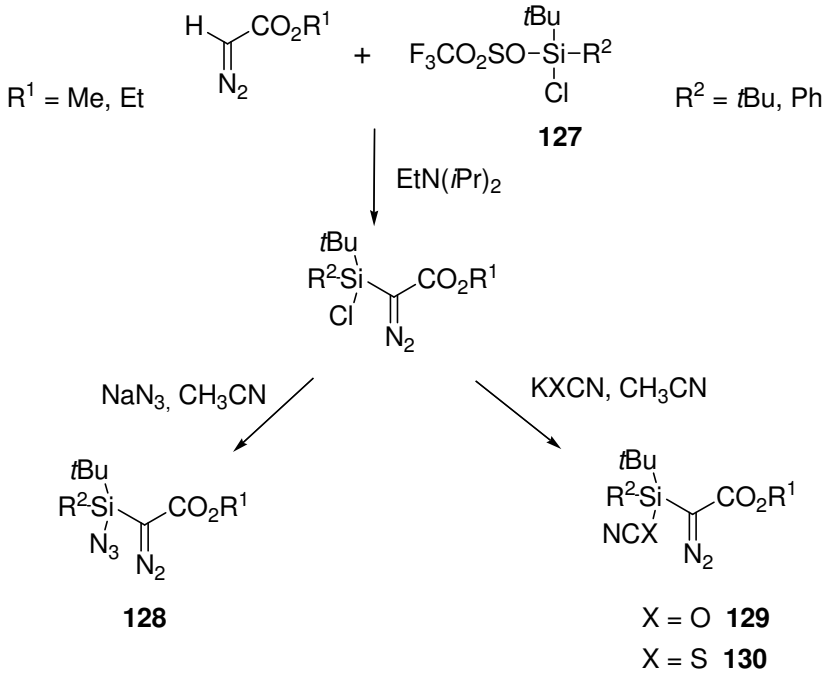
Various silicon-functionalised analogues of trialkylsilyl diazo acetates **119** are prepared in two steps by treating methyl-2-diazo acetate (**124**) first with one equivalent of silyl bis(triflate) **125** and then with an other carbon-, nitrogen- or oxygen-nucleophile. The results, depicted in Scheme 31, were summarised by Maas and Mayer.[90]



Scheme 31. Synthesis of silyl-functionalised diazo acetates.

[90] G. Maas, D. Mayer in *Organosilicon chemistry: From Molecules to Materials*, (Ed.: N. Auner, J. Weiss), Weinheim, **1996**, Vol. 2.

The same strategy of Scheme 31 has been used for the synthesis of azidosilyl diazo acetates **128**, *iso*-cyanatosilyl diazo acetates **129** and *iso*-thiocyanatosilyl diazo acetates **130**, with chlorosilyl triflates **127** as reactants (Scheme 32).[91]



Scheme 32. Synthesis of (azido-, *iso*-cyanato-, *iso*-thiocyanato-)silyl acetates.

1.5 α-Silyl α-Amino Acids

α-Amino acids have focused great interest in all areas of life sciences in the last 150 years. It is well known, that they are vital to life as itself, as building blocks of peptides and proteins and of many natural products.[92] Beyond this fundamental role, amino acids are widely used as pharmaceutical, agrochemical or food additives. In this context, a multitude of methods for their chiral preparation have been developed.[93]

Moreover, unnatural amino acids, non-genetically-coded amino acids either naturally occurring or chemical synthesised, are playing since years an important role in the area of peptide research. The incorporation of unnatural amino acids in peptide analogous, especially of α-amino acids, altering the conformational flexibility of these latter, improve the enzymatic stability and enhance the

[91] G. Maas, S. Bender, *Synthesis* **1999**, 1175-1180.
[92] a) H.-D. Jakubke, H. Jeschkeit in *Aminosäuren, Peptide, Proteine*, VHC, Weinheim, **1982**. b) H.-D. Jakubke in *Peptide: Chemie und Biologie*, Spektrum, Heidelberg, **1996**. c) *Peptides* (Ed.: B. Gutte), Academic Press, San Diego, **1995**. d) S. M. Hecht in *Bioorganic Chemistry: Peptides and Proteins*, Oxford University Press, New York, **1998**.
[93] a) R. M. Williams in *Synthesis of Optically Active α-Amino Acids*, Pergamon, Oxford, **1989**. b) R. M. Williams, J. A. Hendrix, *Chem. Rev.* **1992**, *92*, 889-917. b) R. O. Duthaler, *Tetrahedron* **1994**, *50*, 1539-1650.

pharmacodynamics and bioavailability.[94] Therefore a modification of an α-amino acids with the introduction of a silyl subsituent, goes towards the developing of new amino acids and peptides as potential tools in chemistry and biochemistry research.

Among the unnatural or non-proteinogenic amino acids, *tert*-leucine (**131**) has gained an important role, due to the presence of the hydrophobic and sterically hindered *tert*-butyl substituent, and it proved to be an effective building block for pharmacological targets. Furthermore, various reports describe the use of *tert*-leucine as intermediate in the synthesis of chiral auxiliaries.[95]

Early examples reported in the literature of organosilicon amino acids are depicted on Figure 14. After β-silyl alanine **133**[96] and substituted phenyl alanine **134**,[97] proline derivative **135** has been prepared and introduced in neurotensine analogues.[98] The trimethylsilyl derivative of compound **136** has been synthesised and characterised more recently (Figure 14).[99]

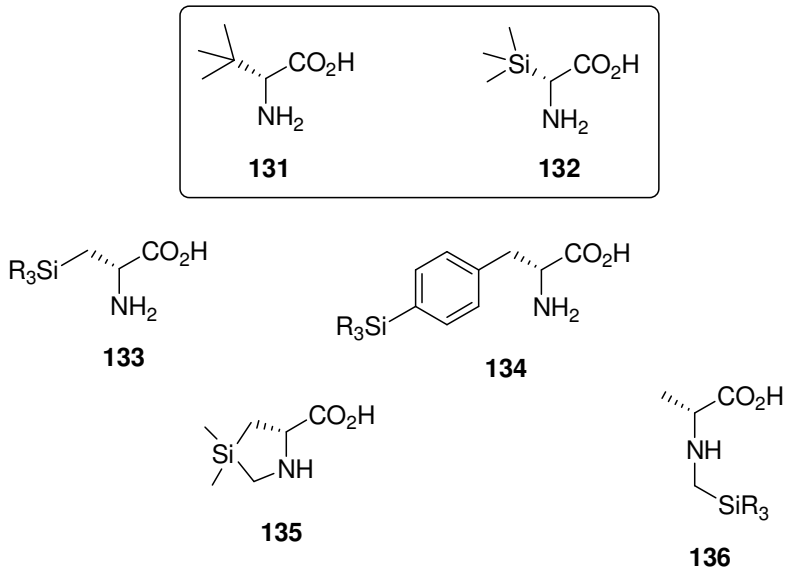


Figure 14. Unnatural amino acid *tert*-leucine **131** and silicon-substitued amino acids.

Along this line, in collaboration with the company Degussa, many efforts have been devoted to the

[94] F. A. Davis, B.-C. Chen, *Chem. Soc. Rev.* **1998**, *27*, 13-18. b) J. S. Ma, *Chimica Oggi (Chemistry Today)* **2003**, 65-68. c) M. Goodam, H Shao, *Pure Appl. Chem.* **1996**, *68*, 1303-1308. d) D. Seebach, A. Jeanguenant, J. Schmidt, T. Maetzke, *Chimia* **1989**, *43*, 314-317.

[95] See for example: a) A. Studer, *Synthesis* **1996**, 793-815. b) H. Waldmann, *Synlett* **1995**, 133-142. c) D. J. Hager, I. Prakash, D. R. Schaad, *Chem. Rev*. **1996**, *96*, 835-876. d) C. Bolm, K. Muniz-Fernandez, J. P. Hildebrand, *Org. Lett.* **1999**, *1*, 491-494.

[96] a) L. Birkofer, A. Ritter, *Angew. Chem.* **1956**, *68*, 461-462. b) R. Tacke, V. I. Handmann, *Organometallics* **2002**, *21*, 2619-2626.

[97] M. Frankel, A. Shenhar, D. Gertner, A. Zilkha, *Israel J. Chem*. **1968**, *6*, 921-926.

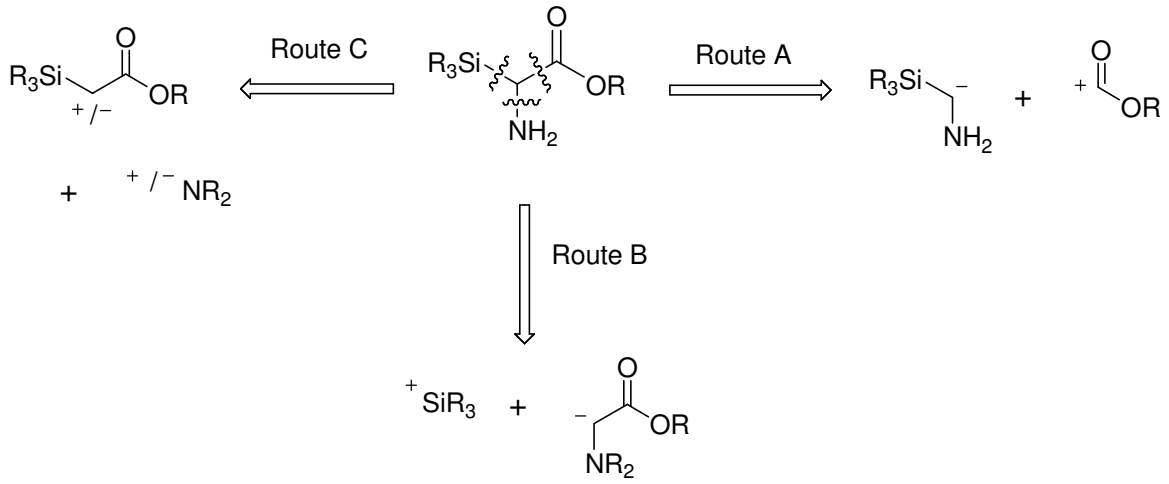
[98] F. Cavelier, B. Vivet, J. Martinez, A. Aubry, C. Didierjean, A. Vicherat, M. Marraud, *J. Am. Chem. Soc.* **2002**, *124*, 2917-2923.

[99] H. Sun, K. D. Moeller, *Org. Lett.* **2002**, *4*, 1547-1550.

synthesis and derivatisation of the α-silyl α-amino acid **132**.[100] As depicted in Figure 14, the analogy to *tert*-leucine is relevant. In fact, the *tert*-butyl group of the unnatural amino acid **131** has been replaced by a trimethylsilyl group, which should confer to the new structure different electronegativity on the carbon in α-position relative to the carboxylic group and, therefore, different properties in term of stability toward acidic and basic environments. The possibility to insert an α-silyl α-amino acid derivative in a oligopeptide structure or in a protein has been also considered since the early investigations in this field.[100,101]

1.5.1 Synthetical Approaches to α-Silyl α-Amino Acids

Routes to α-silyl α-amino acids can be classified according to three basic retro-synthetic disconnections: the carbon-carbon bond to the acid moiety (route A), the carbon-silicon bond (Route B) and the carbon-nitrogen bond (Route C). Examples of all three techniques are documented in the literature and involve the hypothetical synthons shown in the Scheme 33.



Scheme 33. Retro-synthetic disconnections for α-silyl α-amino acids.

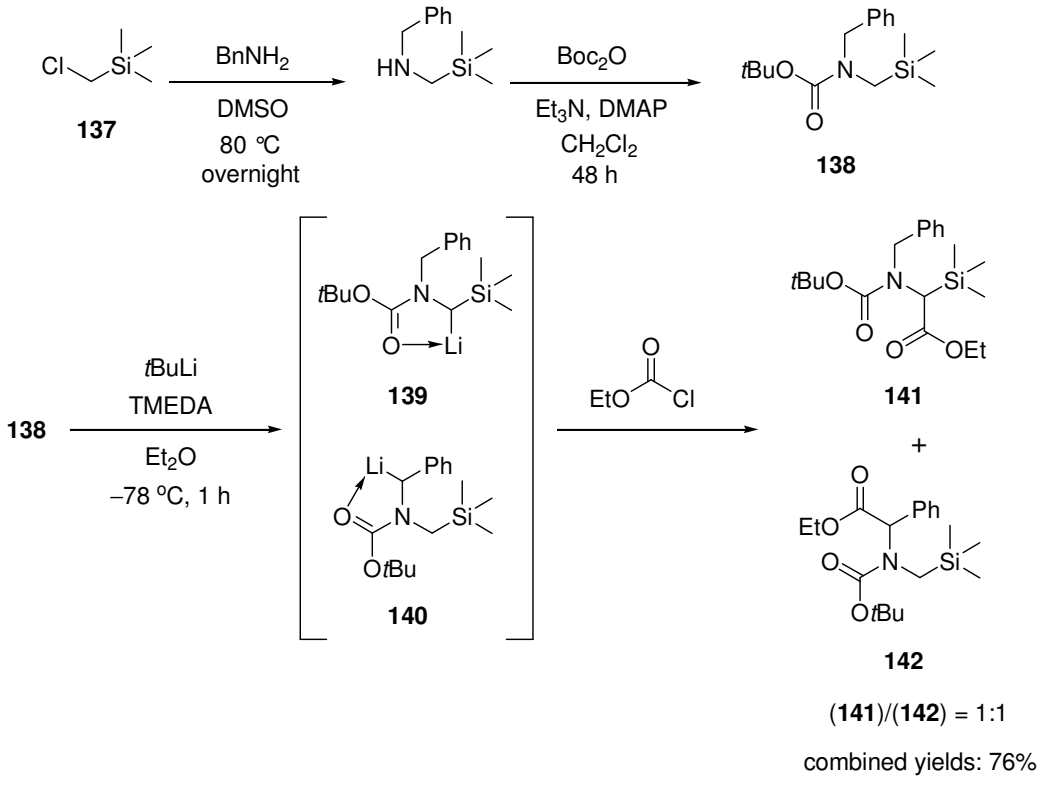
[100] C. Bolm, A. Kasyan, K. Drauz, K. Günther, G. Raabe, *Angew. Chem.* **2000**, *112*, 2374-2376. *Angew. Chem. Int. Ed.* **2000**, *39*, 2288-2290.
[101] G. Liu, S. McN. Sieburth, *Org. Lett.* **2003**, *5*, 4677-4679.

1.5.1.1 Route A: C-C Disconnection

There are two examples of this technique documented in the literature. The first investigation a) involves ordinary lithiation of α-alkyl-α-amino silanes whereas the second b) exploits zirconaziridines as the nucleophilic aminosilane source.

a) Lithiation of α-Alkyl α-Amino Silanes

Sieburth and co-workers took advantage of the ability of silicon to stabilise α-anions and that of nitrogen to direct proximal metalation, to lithiate α-alkyl α-amino silanes using alkyl lithium reagents.[102,103] It was found necessary to fully substitute the nitrogen atom to facilitate lithiation because formation of a dianion was unfavourable due to side reactions involving nucleophilic addition of the second equivalent of *s*BuLi. Furthermore, easily removable groups on the nitrogen atom were desired and Boc and benzyl were chosen, resulting in the use of **138** as starting material. This was synthesised from readily available chloromethyltrimethyl silane **137** as shown in Scheme 34. Deprotonation of **138** followed by reaction with an electrophile led to a mixture of products resulting from competitive metalation at the benzyl position **140** as well as the α-silyl position **139**. Several electrophiles were reacted with the anion, in particular aldehydes, but relevant was the use of ethyl chloroformate which gave the protected α-silyl α-amino acid **141** along with the benzyl substituted product **142**.

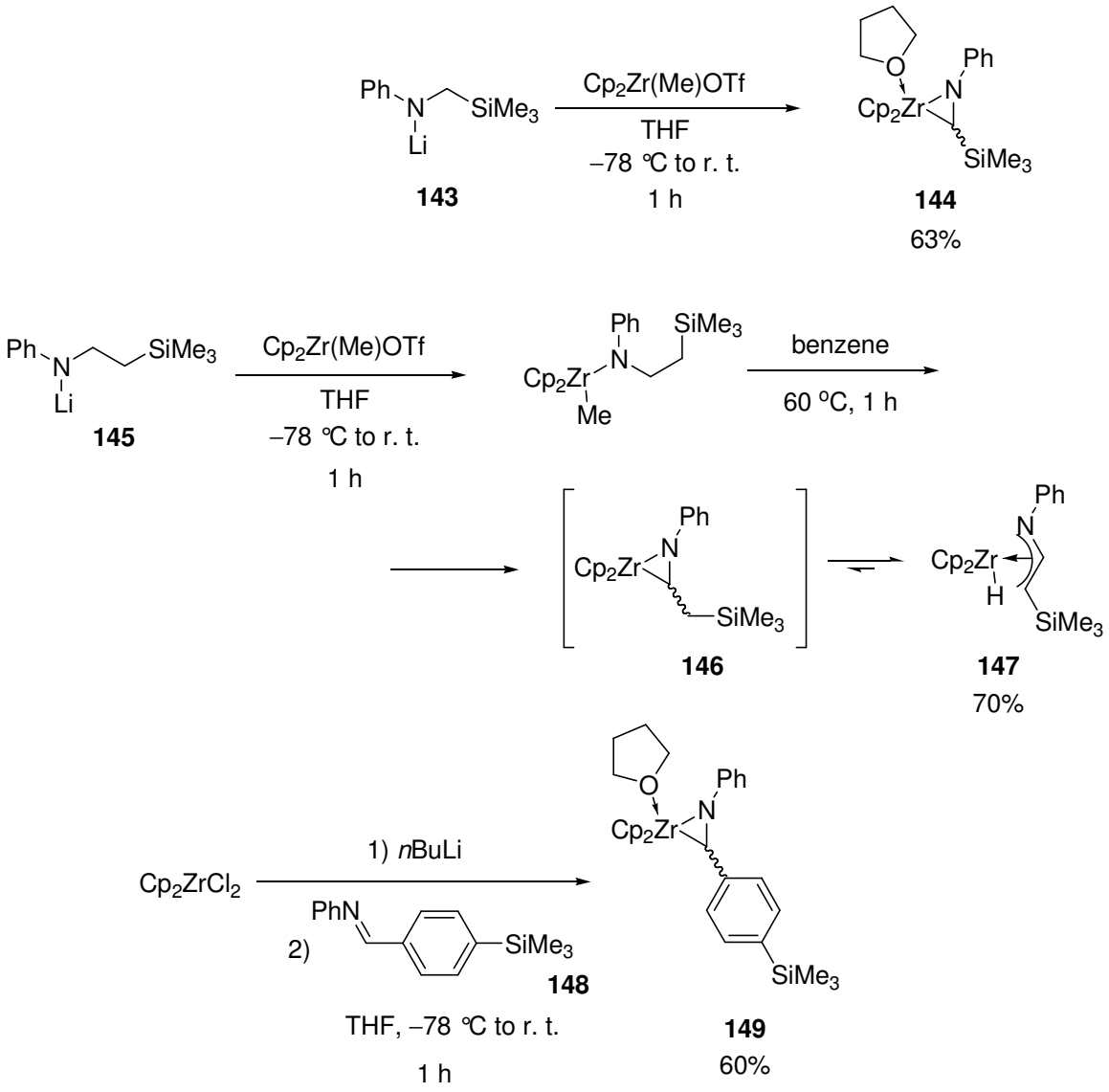


Scheme 34. Lithiation of α-amino silane **138**.

[102] S. McN. Sieburth, J. J. Somers, H. K. O'Hare, *Tetrahedron* **1996**, *52*, 5669-5682.
[103] S. McN. Sieburth, J. J. Somers, *Tetrahedron* **1996**, *52*, 5683-5690.

b) Via Zirconium-aziridines

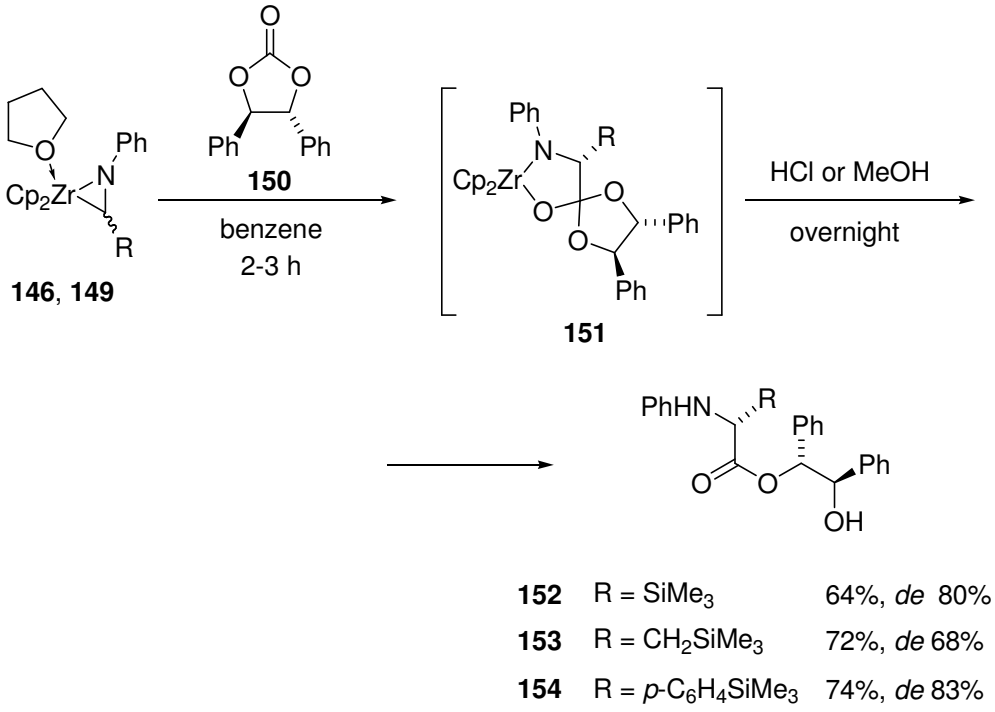
Norton and co-workers carried out much research into the α-carboxylation of amines by prior derivatisation to zirconium-aziridines and reaction with an optically active cyclic carbonate.[104] The group had also shown that the method was applicable to the synthesis of three types of silyl amino acids. Herein, the precursory silyl zirconium-aziridines **146** and **149** were synthesised from either the lithium amine **143** and **145** or the imine **148** (Scheme 35). Interestingly, the zirconium-aziridine **146** was found to be in equilibrium with the much more stable aza-allyl hydride **147**, but this behaved as the zirconium-aziridine in the subsequent reaction, perhaps due to the small amount of **146** present in the mixture.



Scheme 35. Synthesis of silyl derivatives of zirconium-aziridines.

[104] J.-X. Chen, J. A. Tunge, J. R. Norton, *J. Org. Chem.* **2002**, *67*, 4366-4369.

The zirconium-aziridines **146** and **149** were reacted with carbonate **150** to give the insertion products **151**. This reaction is actually a dynamic kinetic resolution, as the two enantiomers of **146** and of **149**, interconvert. The method resulted in good *de*'s of the products, as shown in the Scheme 36. Removal of the zirconacene moiety by addition of methanol or aqueous HCl gave the 2-hydroxyethyl esters **152**, **153**, **154**. Esters **153** and **154** could be transesterified with a mixture of methanol and sodium hydroxide, but **152** preferentially underwent desilylation.

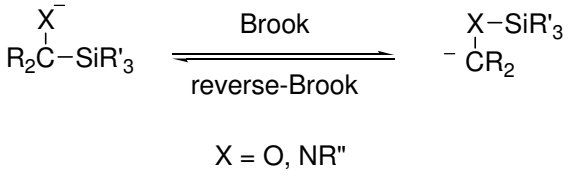


Scheme 36. Dynamic kinetic resolution of silyl derivatives of zirconium-aziridines.

1.5.1.2 Route B: C-Si Disconnection

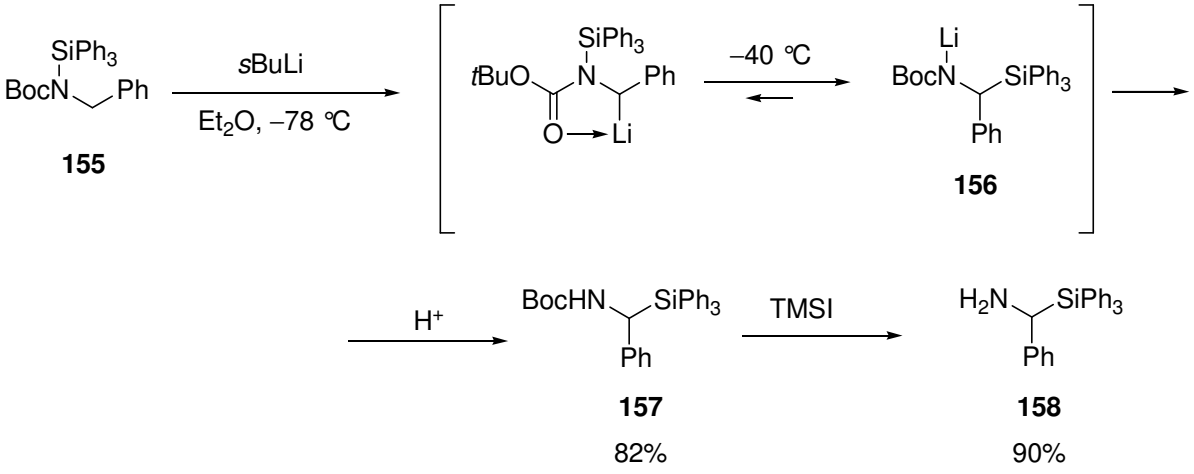
Over several years, Sieburth group's research into lithiation α to nitrogen (see section 1.5.1.1) led to an enantioselective synthesis of a protected α-silyl α-amino acid (see compound **141**), which was first obtained in a product mixture by reaction of the lithiated amino silane **139** or **140** (Scheme 34). Moreover, Sieburth[105] and co-workers had considered in their investigations that, deprotonation of an amine bearing a Boc and silyl group, could provide a driving force for an aza-reverse-Brook rearrangement (Scheme 37).[106]

[105] S. McN. Sieburth, H. K. O'Hare, J. Xu, Y. Chen, G. Liu, *Org. Lett.* **2003**, *5*, 1859-1861.
[106] See for example: A. G. Brook, *Acc. Chem. Res.*, **1974**, *7*, 77-84.



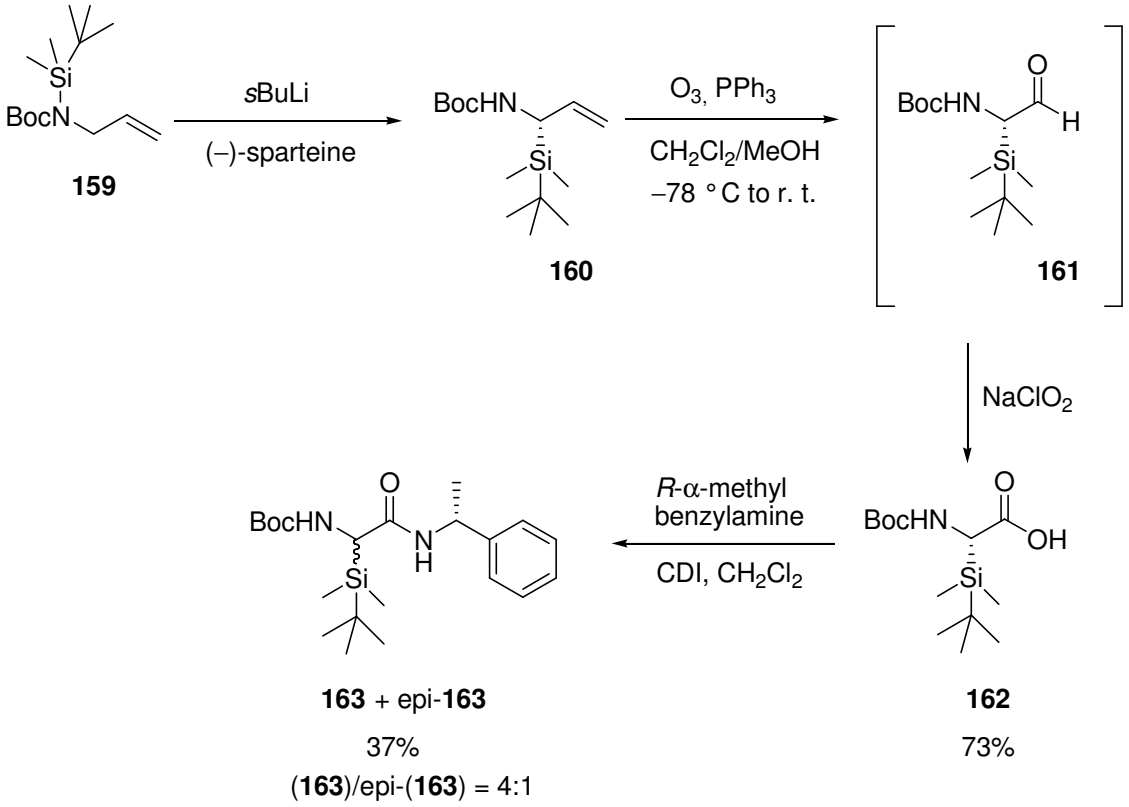
Scheme 37. Brook and reverse-Brook rearrangement.

Thus, treatment of *N,N'*-Boc-silyl amine **155** with *sec*-butyl lithium at low temperatures and acidic work-up, yielded to the amino silane **157**, derived from the product **156** of aza-Brook rearrangement, in good yields. Subsequent deprotection of the Boc group afforded the free amino silane **158** (Scheme 38).



Scheme 38. Aza-Brook rearrangement on the *N,N'*-Boc-silyl amine **155**.

The enantioselective version of the synthesis of amino silane **157** could be performed by deprotonation of *N,N'*-Boc-silyl amine **155** with a mixture of *sec*-buthyl lithium and (–)-sparteine.[105] This method was later applied by the same group as key step for the synthesis of α-silyl α-amino acid **160**.[101] Enantioselective aza-Brook rearrangement of *N-tert*-butyldimethylsilyl-*N'*-Boc allyl amine (**159**) afforded product **160** which then underwent ozonolytic cleavage of the alkene followed by Pinnick oxidation. The enantiopure *N*-Boc-protected α-*tert*-butyldimethlsilyl α-amino acid **162** was obtained in good yield (Scheme 39). Reaction of the formed amino acid **162** with the enantiopure (*R*)-(+)-α-methyl benzyl amine permitted to evaluate the stereochemical integrity of the whole transformation. The amide **163** was formed as 4:1 mixture of diastereomers, showing that the oxidation had proceeded with not complete epimerisation.



Scheme 39. Synthesis and derivatisation of *N*-Boc-protected α-*tert*-butyldimethylsilyl α-amino acid **162** *via* aza-Brook rearrangement and allyl silane oxidation.

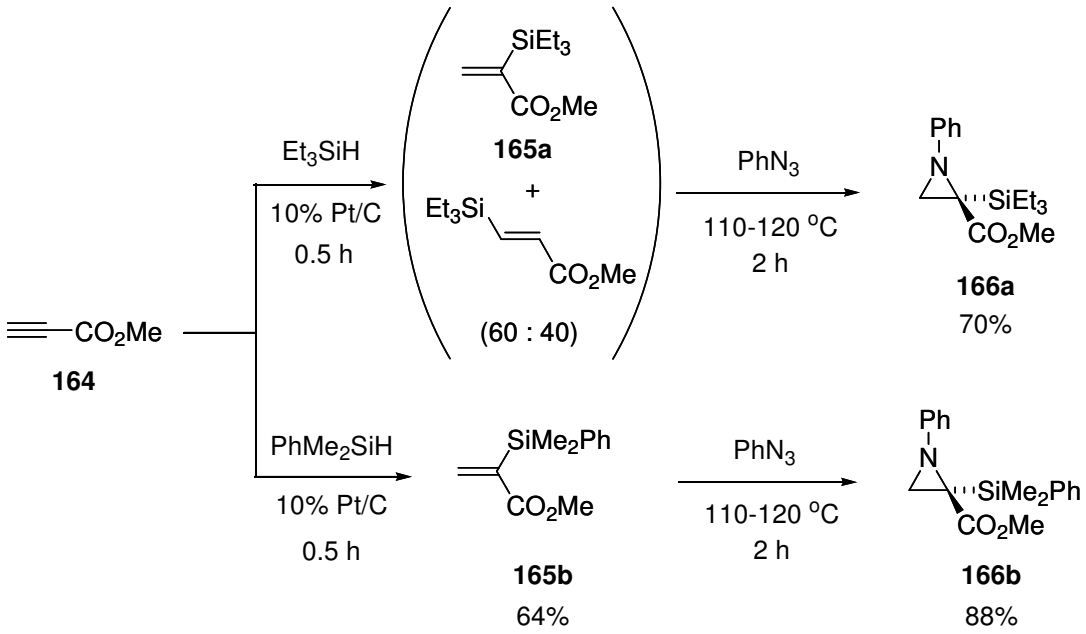
1.5.1.3 Route C: C-N Disconnection

a) Aziridines

2-Silyl-2-alkoxycarbonylaziridines **166a-b** satisfy the motif for α-silyl amino acids and can be thought of as α,α-disubstituted amino acids. Furthermore, if the ring could be opened at the C-C bond, in an analogous manner to epoxides, this would leave an ordinary *N*-substituted α-silyl α- or β-amino acid.

Bassindale, Taylor and co-workers developed three methods for the synthesis of 2-silyl-aziridines, depending on the desired substitution pattern.[107] That for 2-methoxycarbonyl-2-silylaziridines is reported in Scheme 40 and involves treatment of the alkene **165** (synthesised by hydrosilylation of the propyonate **164**) with phenylazide.

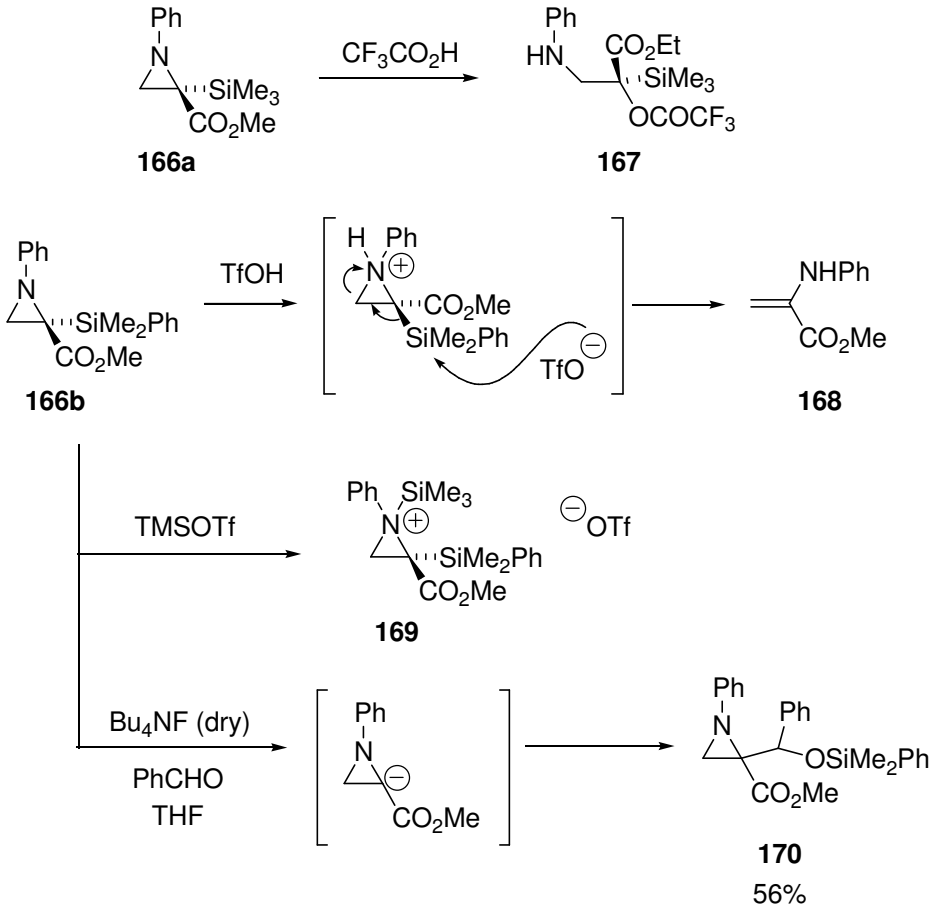
[107] A. R. Bassindale, P. A. Kyle, M.-C. Soobramanien, P. G. Taylor, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1173-1180.



Scheme 40. Synthesis of 2-silyl aziridines.

Bassindale and Taylor hypothesised that S_N1-type nucleophilic ring opening of 2-silylaziridines with a late transition state should favour attack β to silicon due to stabilisation involving the C-Si bond.[108] However, upon treatment with hydrogen halides, the aziridines were opened by nucleophilic attack α to silicon and in the case of 2-ethoxycarbonyl-1-phenyl-2-trimethylsilyl aziridine (**166a**), both C-N bonds were cleaved to give an aniline salt. Addition of trifluoroacetic acid to **166a** resulted in nucleophilic opening at the α-position to form compound **167**, whereas reaction of **166b** with trifluoromethanesulfonic acid resulted in desilylation to lead to enamine **168** (Scheme 41). Conversely, silylation of silylaziridine **166b** with trimethylsilyl triflate (TMSOTf) led not to a ring opened product, but to the silylated aziridine **168**. It was also found that, under rigorously dry conditions, aziridine **166b** could be desilylated with fluoride ion and the resulting anion could be trapped with benzaldehyde to give silyl ether **170**.

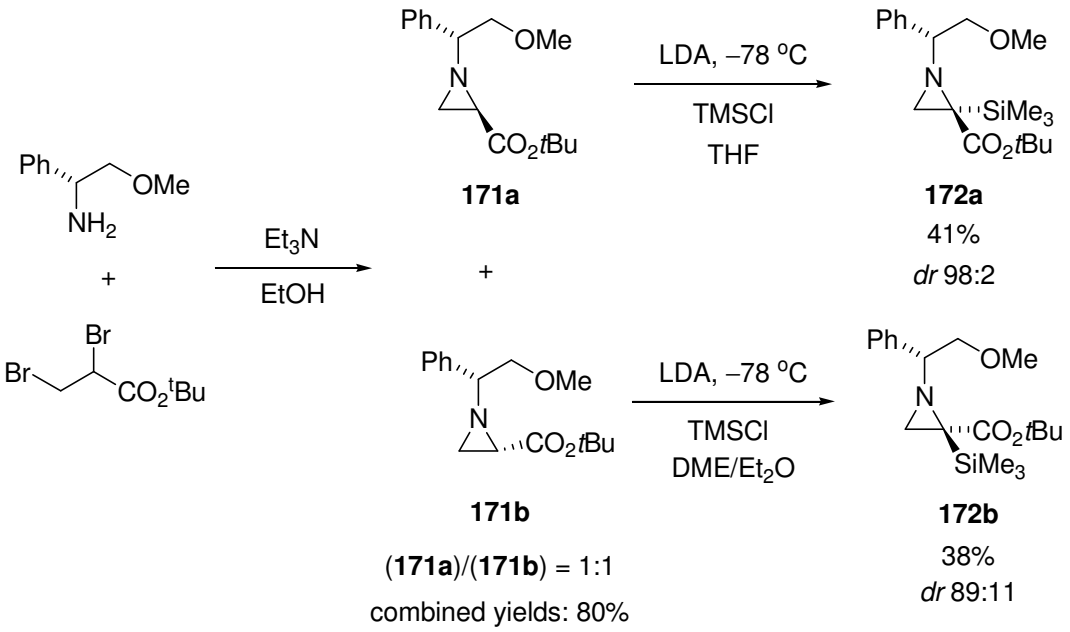
[108] A. R. Bassindale, P. A. Kyle, M.-C. Soobramanien, P. G. Taylor, *J. Chem. Soc., Perkin Trans. 1* **2000**, 439-448.



Scheme 41. Ring opening reactions of 2-silyl aziridines.

During research into the generation of aziridine carbanions, Husson and co-workers also synthesised 2-silyl-2-alkoxycarbonyl aziridines.[109,110] They deduced three requirements for the formation of configurationally and chemically stable *C*-lithiated aziridines as **172a-b** (Scheme 42): the presence of a *tert*-butyl ester, a tethered methoxy group on the nitrogen atom (derived from phenylglycinol) and the use of LDA as base. Interestingly, since the phenylglycinol unit is chiral, only the *R*,*S* diastereoisomer **171a** yielded to a stable carbanion. The other, **171b**, underwent intermolecular self condensation with the ester moiety, but this could be avoided if a 5:1 mixture DME/Et_2O was used as solvent. The carbanions were quenched with a range of electrophiles, including trimethylsilyl chloride (TMSCl) to give silylaziridines **172a-b** with good retention of configuration (Scheme 42).

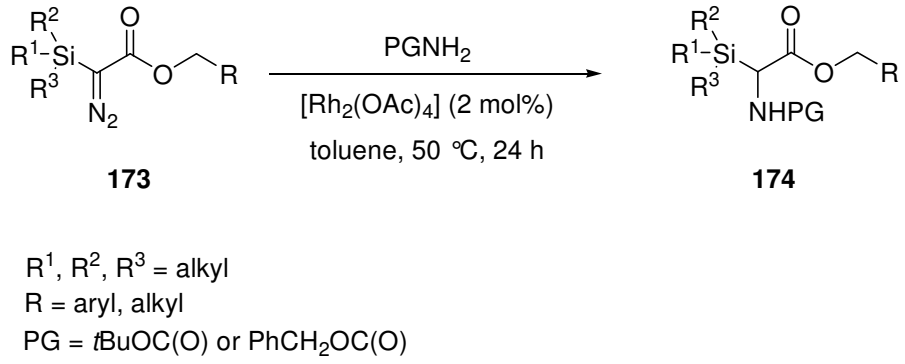
[109] V. Alezra, M. Bonin, L. Micouin, C. Policar, H.-P. Husson, *Eur. J. Org. Chem.* **2001**, 2589-2594
[110] V. Alezra, M. Bonin, L. Micouin, H.-P. Husson, *Tetrahedron Lett.* **2000**, *41*, 651-654.



Scheme 42. Synthesis of configurationally stable 2-silyl aziridines.

b) Diazo Compounds

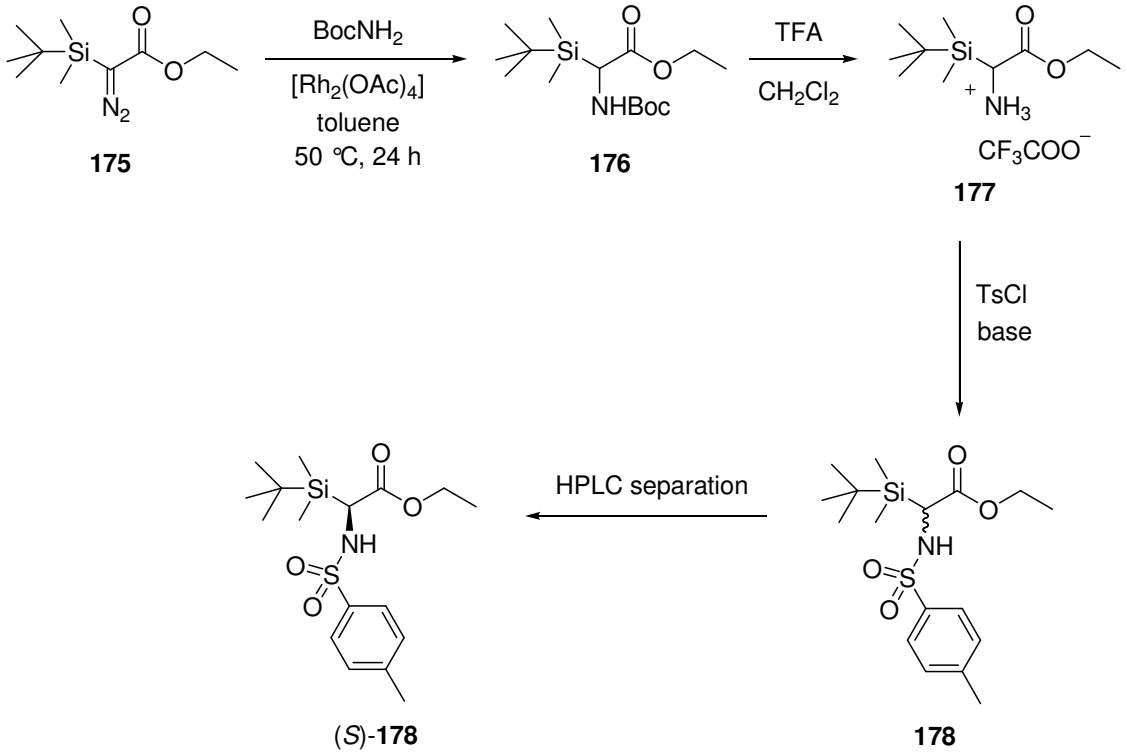
Synthesis of *N*-protected α-silyl α-amino esters has been reported from the group of Bolm in 2000.[100] Rhodium(II) catalysed cleavage of nitrogen of various α-trialkyl α-diazo acetates **173** and intermolecular carbenoid-type N-H insertion afforded the formation of the α-trialkylsilyl α-amino acid precursor **174** in up to 86% yield (Scheme 43).



Scheme 43. Synthesis of *N*-protected α-silyl α-amino esters by intermolecular N-H insertion reaction.

The synthesis of *N*-tosyl-protected 2-*tert*-butyldimethylsilyl-2-amino ethyl acetate (**178**) was not performed by direct intermolecular N-H insertion reaction of the corresponding 2-*tert*-butyldimethylsilyl-2-diazo ethyl acetate (**175**). First was prepared the intermediate *N*-Boc-protected amino ester **176**, which then underwent selective removal of the Boc group in the presence trifluoroacetic acid. Reaction of the formed trifluoroacetic salt **177** with tosylchloride and a base

afforded the racemic *N*-tosyl-protected 2-*tert*-butyldimethylsilyl-2-amino ethyl acetate (**178**) in 58% yield. An X-ray analysis of *rac*-**178** confirmed the constitution of the compound. The enantiomers of **178** were separated by means of chiral HPLC (Scheme 44).



Scheme 44. Synthesis of enantiopure *N*-tosyl-protected α-silyl α-amino ethyl ester **178**.

Further developments of the named methodology will be largely discussed in the following of this work (see section 3.3). In fact, the access to *N*-protected α-silyl α-amino acids derivatives by mean of rhodium catalysed intermolecular N-H insertion reaction, as reported in this paragraph, constituted a main topic of this research project.

2. Aim of the project

This project originates from the early results reported by Bolm and co-workers on the synthesis of racemic α-trialkylsilyl α-amino acids derivatives by intermolecular rhodium(II) catalysed N-H insertion reaction in the presence of achiral carbamates.[100]

Primary aim of this work is the development of synthetic strategies to obtain diasteromerically-enriched *N*-protected α-trialkylsilyl α-amino esters, precursors of enantiomerically-enriched free α-trialkylsilyl α-amino acids (section 3.1 to 3.5).

Furthermore, introduction of newly synthesised α-trialkylsilyl α-amino acid core in the structure of already-known molecules, could enlarge the range of possibilities in their application. An attempt of variation of a metallo-proteinase inhibitor structure is reported (section 3.6).

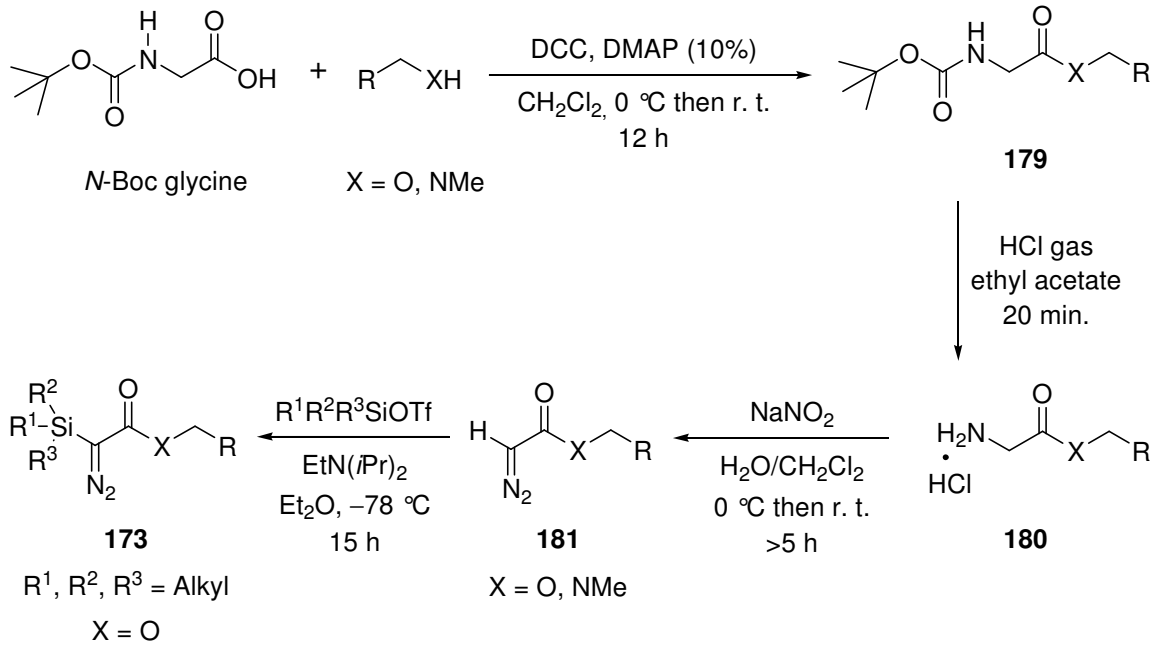
Finally, studies on microwave assisted synthesis of *N*-protected α-trialkylsilyl α-amino esters are described (section 3.7).

3. Results and Discussion

3.1 Synthesis of α-Trialkylsilyl α-Diazo Esters

Primary aim of this project was to study a possible rhodium(II) carboxylate-catalysed stereoselective N-H insertion reaction, starting from α-trialkylsilyl α-diazo esters which can be synthesized using an established protocol.[100]

Commercially-available, *N*-Boc-protected glycine reacts with an alcohol in the presence of *N*,*N'*-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-(*N*,*N*-dimethylamino)-pyridine as coupling reagents, to give *N*-Boc-protected glycine esters **179**. Removal of the Boc protecting group was performed by bubbling gaseous hydrogen chloride through a solution of **179** in ethyl acetate to obtain the pure HCl-salt of the corresponding glycine ester **180** without purification (Scheme 45).



Scheme 45. Synthesis of 2-trialkylsilyl-2-diazo acetates **173** from *N*-Boc-protected glycine.

Several *N*-Boc protected glycine esters were synthesized following the protocol given above (products **179a**-**d**, entries 1-4, Table 2); *N*-Boc protected *N*-methyl-benzyl glycinamide was also prepared in the same manner (**179e**, entry 5, Table 2). The formed products were then converted in their corresponding glycine esters HCl-salts (products **180a**-**e**, entries 1-5, Table 2).

FTable 2. *N*-Boc-protected glycine esters or amide **179** and their corresponding HCl-salts **180**.

Entry	*R*	*X*	*Condensation product*[111]	*Yield*	*HCl-salt*[111]	*Yield*
1	C_6H_5	O	**179a**	90%	**180a**	71%
2	*p*-$MeOC_6H_5$	O	**179b**	84%	**180b**	69%
3	*p*-$O_2NC_6H_5$	O	**179c**	92%	**180c**	63%
4	CCl_3	O	**179d**	91%	**180d**	62%
5	C_6H_5	NMe	**179e**	92%	**180e**	62%

Products **180a**-**d** were isolated as crystalline solids, while **180e** was a thick oil. They could all be stored at room temperature for months without decomposition. It is noteworthy that glycine benzyl ester hydrochloride **180a** is commercially available from Sigma-Aldrich, but was nevertheless synthesized following the previous procedure.

Diazotisation of the HCl-salts **180 a-e** were performed by portionwise addition of sodium nitrite to these substrates dissolved in a biphasic solvent system (H_2O/dichloromethane) at 0 °C, followed by stirring for at least 5 hours at room temperature. The crude products were purified by flash column chromatography on silica gel to obtain the products **181a-e** as a yellow oil. Diazotisation afforded the products **181a**-**e** in the reported yields (entries 1-5, Table 3). All 2-diazo acetates **181a**-**d** and **181e** were bright-yellow oils storable for weeks under vacuum or argon atmosphere, even at room temperature, with the exception of **181c** which was solid.[112] Characteristic of the presence of the diazo group was the peak at 2100-2200 cm^{-1} in the IR spectrum.

Table 3. 2-Diazo acetates **181**.

Entry	*R*	*X*	*Product*[113]	*Yield*
1	C_6H_5	O	**181a**	59%
2	*p*-$MeOC_6H_5$	O	**181b**	44%
3	*p*-$O_2NC_6H_5$	O	**181c**	55%
4	CCl_3	O	**181d**	42%
5	C_6H_5	NMe	**181e**	61%

2-Diazo acetates **181a**-**d** were then silylated using commercially-available silyl triflates ($R^1R^2R^3SiOTf$) in the presence of Hünig's [$EtN(iPr)_2$][89,114] in diethylether at –78 °C under an argon

[111] Most of these products (**179** and **180**) are described in the literature. For details see section 5.
[112] Decomposition was indicated by change of colour from yellow to orange.
[113] Products **181a**-**d** are all described in the literature. For details see section 5.

atmosphere. The 2-trialkylsilyl-2-diazo acetates thus formed, were then separated from unreacted starting material by flash column chromatography on silica gel (products **173a-i**, entries 1-9, Table 4). Several attempts were made to silylate *N*-benzyl-*N*-methyl 2-diazo acetamide (**181e**). Unfortunately, they remained unsuccessful. A detailed description of these attempts is given in section 3.6.6.

Table 4. 2-Trialkylsilyl-2-diazo acetates **173a-i** and **175**.

Entry	*X*	R_1	R_2	R_3	*Product*[115]	*Yield*
1	C_6H_5	Et	Et	Et	**173a**	89%
2	C_6H_5	*t*Bu	Me	Me	**173b**	51%
3	C_6H_5	Me	Me	Me	**173c**	72%
4	C_6H_5	*i*Pr	*i*Pr	*i*Pr	**173d**	38%
5	*p*-$MeOC_6H_5$	Et	Et	Et	**173e**	73%
6	*p*-$MeOC_6H_5$	*t*Bu	Me	Me	**173f**	22%
7	*p*-$MeOC_6H_5$	Me	Me	Me	**173g**	58%
8	*p*-$O_2NC_6H_5$	Et	Et	Et	**173h**	85%
9	CCl_3	Et	Et	Et	**173i**	49%
10	CH_3	*t*Bu	Me	Me	**175**	57%

Product **173i** (entry 9, Table 4) was synthesised following the procedure described above, but after purification *via* chromatography on silica gel, the fraction containing the desired product was also found to be contaminated with 20% of ethyldisiloxane ($Et_3SiOSiEt_3$) and triethylsilanol (Et_3SiOH). Product **175** (entry 10, Table 4) was synthesised starting from the commercially-available 2-diazo ethyl acetate. All the substituted 2-diazo acetates were yellow oils, with the exception of the solid **173h**. These are not sensitive to air and stable for days, although storage under argon or vacuum, even at room temperature, is preferable.

3.2 Synthesis of *N*-Protected α-Trialkylsilyl α-Amino Acids Precursors

In 2000 Bolm and co-workers reported the first synthesis of *N*-protected α-trialkylsilyl α-amino acids precursors, in which 2-trialkylsilyl-2-diazo acetates, in the presence of rhodium(II) tetraacetate as catalyst, were reacted with various carbamates, followed by deprotection, to form the named products in good yields.[100] These were the first examples of 2-diazo acetates bearing a

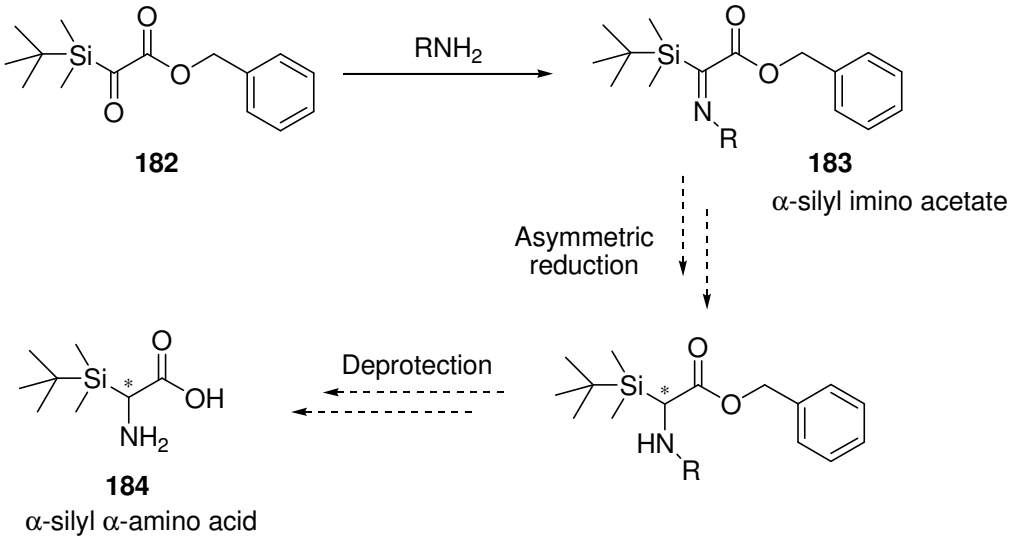
[114] a) R. Brückmann, K. Schneider, G. Maas, *Tetrahedron* **1989**, *45*, 5517-5530. b) S. P. Marsden, W. Ping, *Tetrahedron Lett.* **1998**, *39*, 6077-6080.
[115] Most of these products (**173a-i** and **175**) are described in the literature. For details see section 5.

trialkylsilyl group at the carbon bonded to the diazo group to undergo intermolecular carbenoid-type N-H insertion.

As an extension to this discovery, it was considered that a diastereoselective approach to *N*-protected α-trialkylsilyl α-amino acids precursors may lead, after deprotection, to the formation of enantiomerically-pure α-trialkylsilyl free α-amino acids. A variety of diastereoselective synthetic strategies were examined. These investigations involved the use of α-trialkylsilyl α-keto-esters as substrates, as well as various reactants such as amines, ureas, or chiral carbamates as sources of the chiral information.

3.2.1 An Approach to α-Trialkylsilyl Imino Acetates

2-*tert*-Butyldimethylsilyl-2-keto-benzyl acetate (**182**) was chosen as a suitable substrate for the formation of α-silyl imino acetate **183**, that could, in turn, undergo subsequent enantioselective reduction followed by deprotection to yield to the free, enantiomerically-enriched α-silyl α-amino acid **184** (Scheme 46).

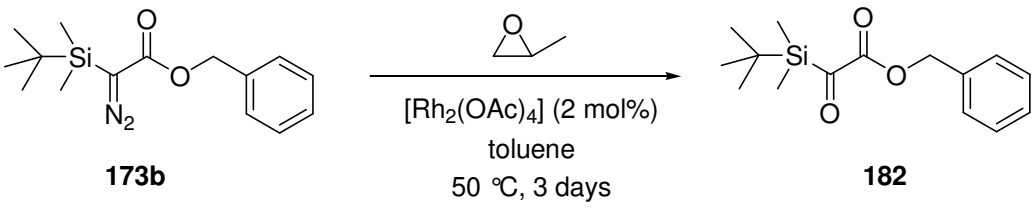


Scheme 46. α-Silyl imino acetates as intermediates in the synthesis of enantiomerically enriched α-silyl α-amino acids.

Initial efforts were directed toward the synthesis of 2-*tert*-butyldimethylsilyl-2-keto-benzyl acetate (**182**), using method previously reported in the literature.[116,117] To a solution of 2-*tert*-butyldimethylsilyl-2-diazo benzyl acetate (**173b**) and rhodium(II) tetraacetate (2 mol%) as catalyst in toluene, was added propylene oxide as an oxygen source in large excess under a stream of argon.

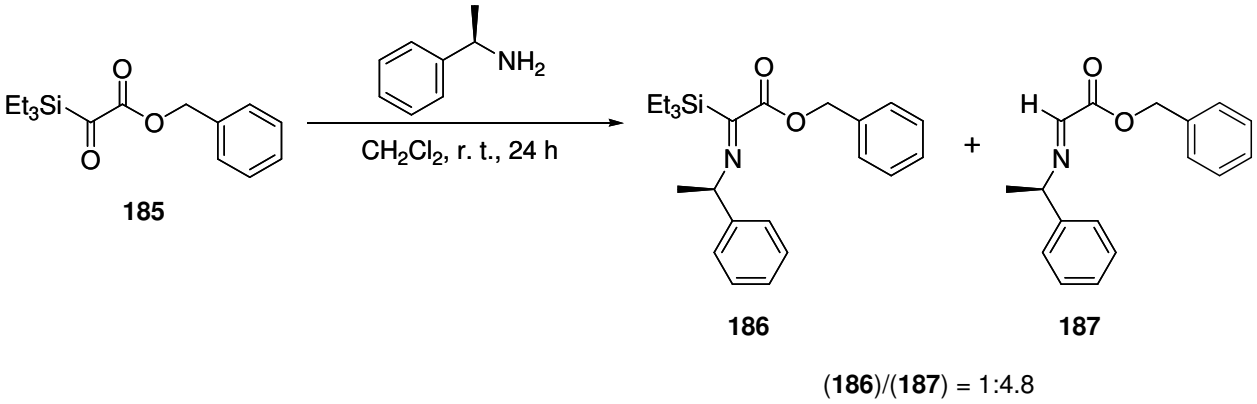
[116] M. Martin, *Synth. Commun*. **1983**, *13*, 809.
[117] C. Bolm, A. Kasyan, P. Heider, S. Saladin, K. Drauz, K Günther, C. Wagner, *Org. Lett.* **2002**, *4*, 2265-2267.

The reaction mixture was then heated at 50 °C for 3 days, after which the solvent was removed *in vacuo*. The crude reaction mixture, dissolved in pentane, was filtered through a plug of Florisil® to afford, after removing of the solvent, the desired product **182** in almost quantitative yield (Scheme 47).



Scheme 47. Preparation of 2-*tert*-butyldimethylsilyl-2-keto-benzyl acetate (**182**) from 2-*tert*-butyldimethylsilyl-2-diazo benzyl acetate (**173b**).

With the 2-keto-acetate **182** in the hand, *n*-butylamine was first considered as a suitable amine with which to form the corresponding imine (see Scheme 46) but this reaction with compound **182** did not proceed in dichloromethane, even in the presence of *p*-toluensulfonic acid. Only starting material was recovered. Conversion was, however, effected by reacting with (*R*)-(+)-1-phenylethyl amine which reacted with 2-triethylsilyl-2-keto-benzyl acetate (**185**) in dichloromethane.[118] The reaction was monitored *via* TLC analysis (eluent petroleum ether/ethyl acetate = 4:1) which suggested that a single product (R_f = 0.4) had formed. Flash chromatography allowed recovery of the starting material in 26% yield. Those fractions of R_f = 0.4 were found, by ^{1}H NMR analysis, to be composed of two compounds: the desired imine **186** and the corresponding desilylated product **187** in a ratio of 1 to 4.8 (Schema 48). It is assumed that the latter product formed by decomposition of the former material on contact with silica gel.



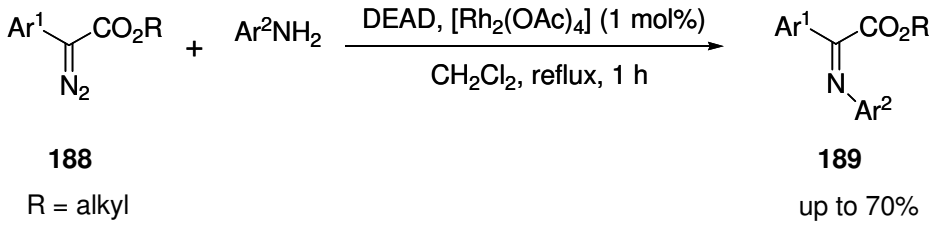
Scheme 48. Formation of the imine derivative **186** from 2-triethylsilyl-2-keto-benzyl acetate (**185**).

[118] The named product was synthesised from 2-triethylsilyl-2-diazo benzyl acetate (**173a**) (see Scheme 47).

Clear evidence that the product **187** had formed was provided by the singlet at δ 7.76 in the ^{1}H NMR spectrum, which was attributed to the proton bonded to the carbon bearing the nitrogen.

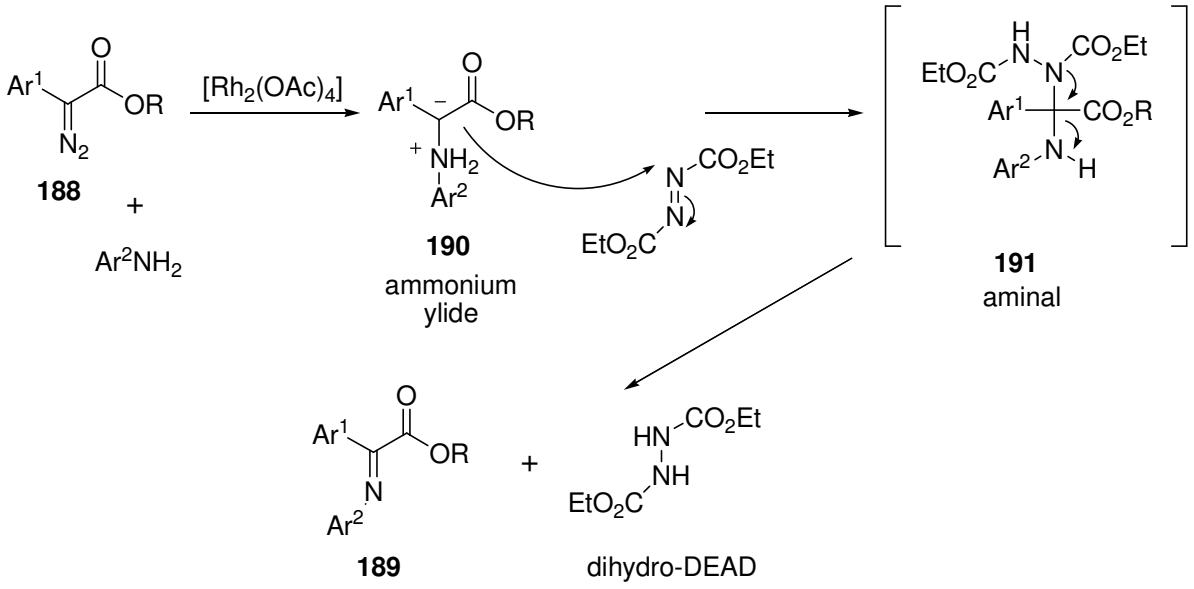
It is worth noting that the separation of the desilylated product from the desired, silylated product, remains problematic; silica gel is sufficiently acidic to hydrolize the carbon-silicon bond, while the use of the silicate-based, but less acidic solid support Florisil®, or the addition triethylamine to the solvent mixture used for the eluition, did not minimize the amount of **187** formed.

In 2005 Hu and co-workers reported a novel synthesis of aryl α-imino esters **189** from reaction of aryl diazo esters **188** and with various aryl amines (aniline or substituted anilines) in the presence of diethylazodicarboxylate (DEAD) and catalysed by $[Rh_2(OAc)_4]$ (Scheme 49).[119]



Scheme 49. Synthesis of aryl α-imino esters **189** from aryl diazo esters **188**.

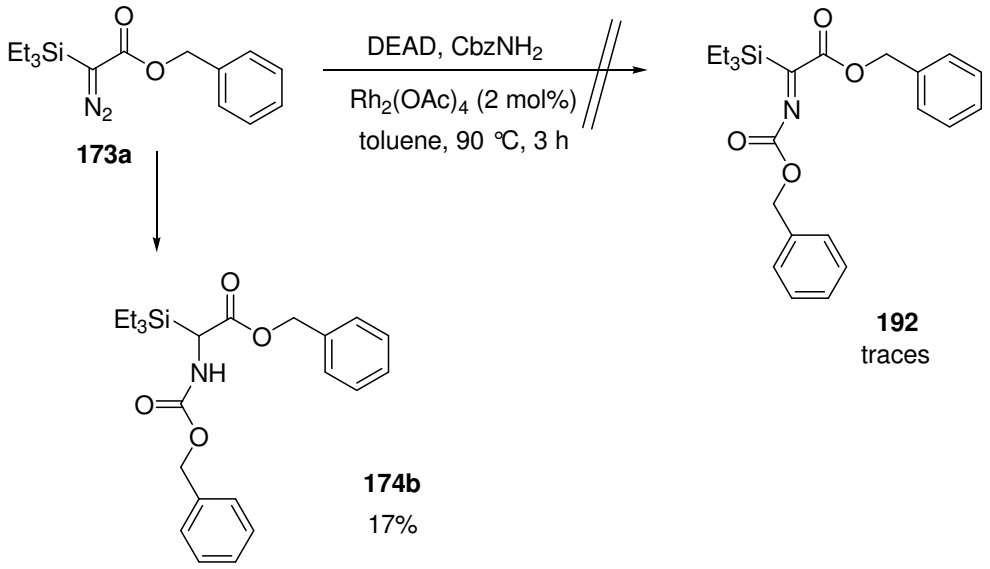
The mechanism by which this reaction is proposed to occur involves initial formation of an ammonium ylide **190** catalysed by the rhodium(II) complex. The ylide attacks then the DEAD to generate an aminal **191**, which subsequently fragments to the α-imino ester **189** and dihydro-DEAD (Scheme 50).



Scheme 50. Mechanism of formation of aryl α-imino esters **189**.

[119] H. Huang, Y. Wang, Z. Chen, W. H. Hu, *Synlett* **2005**, 2498-2500.

It was considered that this methodology could be applied here. As such, 2-triethylsilyl-2-diazo benzyl acetate (**173a**) and benzyl carbamate ($CbzNH_2$) (2.0 equiv.) were stirred in the presence of DEAD (1.1 equiv.) using rhodium(II) tetraacetate (2 mol%) as a catalyst in dichloromethane at room temperature for 20 hours, but no conversion was observed by ^1H NMR analysis. The same experiment was instead performed in toluene at 90 °C for 3 hours, after which time the *N*-Cbz protected 2-triethylsilyl-2-amino benzyl acetate (**174b**) had formed in 17% yield and only traces of the expected imine **192** were detected (Scheme 51). This compound **174b** is the product of rhodium(II) catalysed N-H insertion between **173a** and benzyl carbamate and it is usually isolated (in the absence of DEAD) in 56% yield.



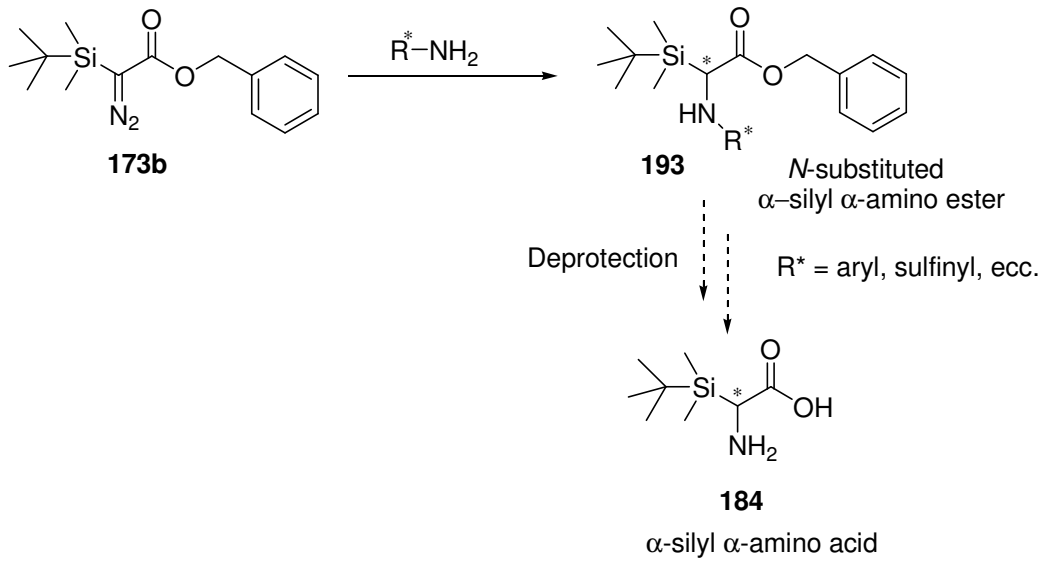
Scheme 51. Attempt to synthesise *N*-Cbz protected 2-triethylsilyl-2-imino benzyl acetate (**192**).

Reaction of 2-triethylsilyl-2-diazo benzyl acetate (**173a**) with aniline or derivatives in the presence of DEAD and [$Rh_2(OAc)_4$] remains unexplored, but even if formation of the α-imino ester could be performed, the difficulties with the following deprotection step would determine the success of this approach to chiral α-silyl α-amino acids.

3.2.2 Studies into the Use of Alternative N-H Sources

Further approaches to the formation of enantiomerically-enriched α-amino acids were developed in which various amines where chosen as alternative N-H sources for the reaction with 2-*tert*-butyldimethylsilyl-2-diazo benzyl acetate (**173b**) as test substrate. The reaction of a chiral amine with the named substrate **173b** could potentially yield a diasteromerically-enriched *N*-substituted α-

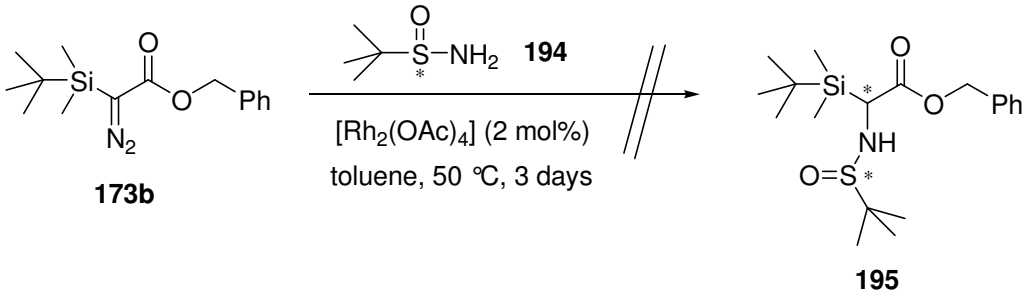
amino ester that could undergo deprotection to yield to the free, enantiomerically-enriched α-silyl α-amino acid (Scheme 52).



Scheme 52. *N*-substituted α-silyl α-amino esters **193** as intermediates in the synthesis of enantiomerically-enriched α-silyl α-amino acids **184**.

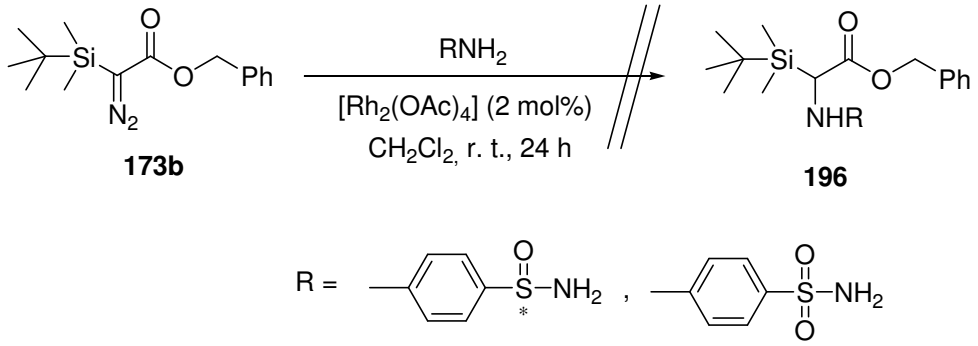
For this reason, an excess of (*R*)-(+)-1-phenylethyl amine was added in excess to a solution of *tert*-butyldimethylsilyl-2-diazo benzyl acetate (**173b**) and rhodium(II) tetraacetate (2 mol%) or rhodium(II) tetraoctanoate (2 mol%) in toluene. A ^{1}H NMR analysis of the crude reaction mixture obtained after heating at 50°C for 24 hours showed that the substrate remained unreacted: complete recovery of both starting materials was possible.

A similar approach using chiral sulfinamides, such as the commercially-available (*S*)-(−)-*tert*-butyl sulfinamide (**194**) was subsequently attempted. To a solution of compound **194** (1.5 equiv.) and 2-*tert*-butyldimethylsilyl-2-diazo benzyl acetate (**173b**) in anhydrous toluene, was added rhodium(II) tetraacetate (2 mol%) as catalyst. After heating at 50 °C for 24 hours, TLC analysis of the crude mixture showed no reaction to have occurred (Scheme 53). This was verified by ^{1}H NMR analysis which showed, after heating of the reaction mixture for further 2 days, only unreacted diazo compound **173b** and sulfinamide **194**, still be present in a ratio 1:1.5, respectively.



Scheme 53. Attempt to synthesise *N*-sulfinil 2-*tert*-butyldimethylsilyl-2-amino acetate (**195**), by rhodium(II) catalysed decomposition of 2-*tert*-butyldimethylsilyl-2-diazo benzyl acetate (**173b**).

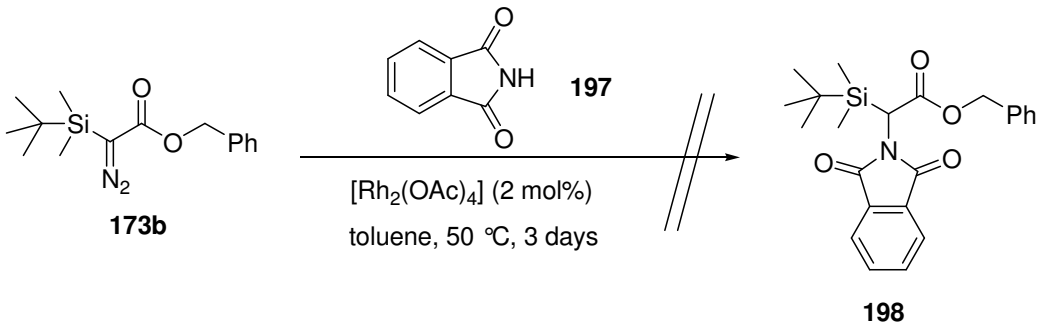
Another commercially-available sulfinamide, (*S*)-(+)-*p*-toluensulfinamide, failed to partecipate in a N-H insertion reaction of with diazo acetate **173b**. Furthermore, the synthesis of *N*-protected 2-*tert*-butyldimethylsilyl-2-amino acetate **196** by rhodium(II) catalysed decomposition of diazo acetate **173b** in presence of tosyl amide (2 equiv.), remained unsuccessful. (Scheme 54).[120]



Scheme 54. Attempt to synthesise *N*-protected 2-*tert*-butyldimethylsilyl-2-amino acetate **196**, by rhodium(II) catalysed decomposition of 2-*tert*-butyldimethylsilyl-2-diazo benzyl acetate (**173b**).

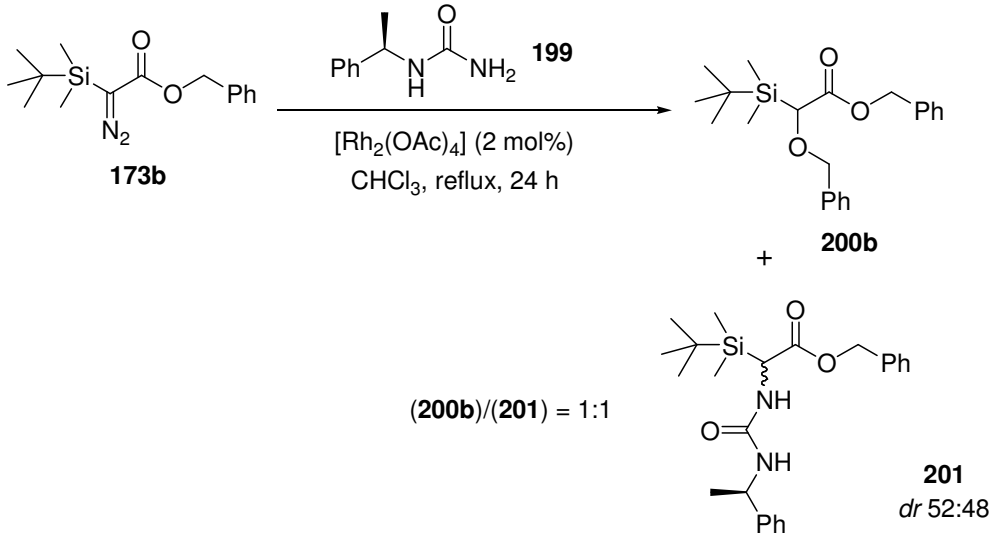
It was observed that the use of an amine with two electron-withdrawing groups may overcome the lack of reactivity noted in the previous examples. Thus, the diamide phtalimmide was chosen as a suitable substrate for the reaction of N-H insertion. However, phthalimide (**197**) did not undergo reaction with *tert*-butyldimethylsilyl-2-diazo benzyl acetate (**173b**) and rhodium(II) tetraacetate in toluene at 50 °C for 3 days, and only starting material was recovered (Scheme 55).

[120] An example of synthesis of a *N*-tosyl α-silyl α-amino ester (analogous to **196**) was already reported by Bolm and co-workers (see section 1.5.1.3 and ref. [100]).



Scheme 55. Compound **198** as possible product of N-H insertion in the reaction of 2-*tert*-butyldimethylsilyl-2-diazo benzyl acetate (**173b**) and phthalimide (**198**).

As final attempt to effect N-H insertion, a urea derivative, namely 1-((*R*)-(+)-1-phenylethyl)urea (**199**) was prepared.[121] ((*R*)-(+)-1-phenylethyl) amine reacted with potassium cyanate in a solution of hydrogen chloride and water to give the expected product up to 80% yield. The enantiopure urea derivative **199** reacted than with 2-*tert*-butyldimethylsilyl-2-diazo benzyl acetate (**173b**) in the presence of rhodium(II) tetraacetate in chloroform at reflux for 24 hours. GC-MS analysis of the crude product showed that urea **199** had partially reacted with the diazo acetate **173b** leading to the formation of two products. The analysis of the fragmentation patterns of every product permitted their identification as *O*-benzyl 2-*tert*-butyldimethylsilyl-2-hydroxy-benzyl acetate (**200b**)[122] and *N*-urea-substituted 2-*tert*-butyldimethylsilyl-2-amino benzyl acetate **201** (Scheme 56). The ^{1}H NMR analysis confirmed the presence of the two named products, formed in a ratio of close 1:1. Moreover, acetate **201** had formed as a mixture of diasteromers in a ratio of 52:48.



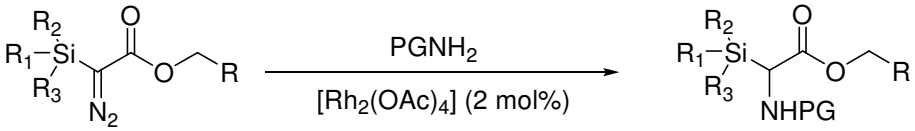
Scheme 56. Reaction of N-H insertion between 2-*tert*-butyldimethylsilyl 2-diazo benzyl acetate (**173b**) and an enantiopure urea derivative **199**.

[121] H. E. Baumgarten, P. Y.-N. Chen, H. W. Taylor, D. R. Wang, *J. Org. Chem.* **1976**, *41*, 3805-3811.
[122] *O*-benzyl 2-*tert*-butyldimethylsilyl-2-hydroxy-benzyl acetate (**200b**) was also formed as by-product in the reaction of N-H insertion between 2-*tert*-butyldimethylsilyl-2-diazo benzyl acetate (**173b**) and Boc- and benzyl-carbamate (see section 3.3).

3.3 Successful Examples of N-H Insertion Reactions: Carbamates

As reported in 2000 by Bolm and co-workers, 2-trialkylsilyl-2-diazo acetates can be converted into 2-trialkylsilyl-2-amino acid derivatives by treatment with *O*-substitued carbamates.[100] To investigate applications of these compounds and to test their reactivities we synthesised several 2-trialkylsilyl-2-amino acid derivatives.

According to the protocol reported in the cited paper, rhodium(II) tetraacetate was added to a solution of 2-trialkylsilyl-2-diazo acetates (**173**) and a carbamate. The solution was then heated at 50 °C usually for 24 hours, to achieve complete conversion of the substrate (Scheme to Table 5). The yield of the products **174a**-**f** are reported in Table 5.



173 **174**

R^1, R^2, R^3 = alkyl
R = aryl, alkyl
PG = *t*BuOC(O) or $PhCH_2OC(O)$

Table 5. *N*-protected 2-trialkylsilyl-2-amino acetates **174**.

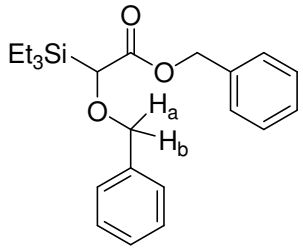
Entry	*R*	*R_1*	*R_2*	*R_3*	*PG*[a]	*Product*	*Yield*
1	C_6H_5	Et	Et	Et	Boc	**174a**	60%
2	C_6H_5	Et	Et	Et	Cbz	**174b**	56%
3	C_6H_5	*t*Bu	Me	Me	Boc	**174c**	22%
4	C_6H_5	*t*Bu	Me	Me	Cbz	**174d**	16%
5	*p*-$MeOC_6H_5$	Et	Et	Et	Cbz	**174e**	18%
6	Me	*t*Bu	Me	Me	Cbz	**174f**	42%

[a] Boc = *t*BuOC(O), Cbz = $PhCH_2OC(O)$

Characteristic of the ^{1}H NMR analysis of the products **174a**-**f** is a doublet at δ 4.20-4.00 (*J* approximately 9 Hz) which is attributed to the proton bonded to the carbon α to the carbonyl group. In some cases the signal of the NH group could be seen as a broad doublet at δ 4.90-4.80 (*J* approximately 9 Hz). *N*-protected 2-trialkylsilyl-2-amino acetates **174a**-**f** were all colourless oils which were stable for prolonged periods in air.

The formation of products **174a** and **174b**, was accompanied by a side-product, isolated in yields of 9% and 12% in the case of entry 1 and 2 (Table 5). The ^{1}H NMR spectrum of this compound **200a**

showed a singlet at δ 5.18 which corresponded to the two hydrogen atoms of the benzyl ester similar to those present in the substrate. It also showed two doublets (at δ 4.79 and 4.29 respectively, J = 11.5 Hz) representing the AB system, of the two diasterotopic benzylic hydrogen atoms (H_a and H_b in Figure 15). A singlet at δ 4.00 represented the hydrogen atom bonded to the carbon in α position to the carbonyl group.



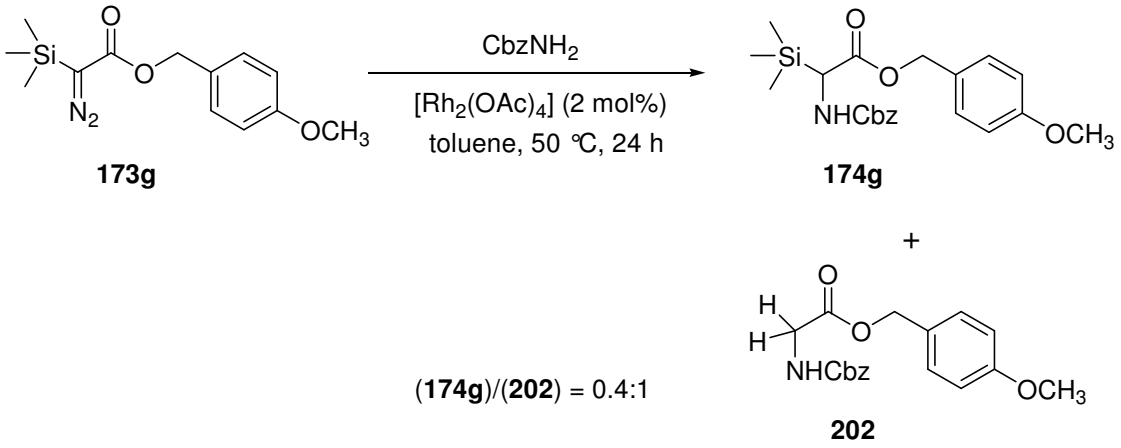
200a

Figure 15. *O*-benzyl 2-triethylsilyl-2-hydroxy-benzyl acetate (**200a**).

Full spectroscopic analysis (including *GCOSY*, *GHMQC*, *NOE*, mass spectroscopy, IR) confirmed the structure of this product as *O*-benzyl 2-triethylsilyl-2-hydroxy-benzyl acetate (**200a**) (Figure 15). Following the same procedure, *O*-benzyl 2-*tert*-butyldimethylsilyl-2-hydroxy-benzyl acetate (**200b**) was also obtained in 16% yield, for those reactions described in entries 3 and 4 (Table 5) respectively.

In contrast, in those reaction affording *N*-Cbz-protected 2-triethylsilyl-2-amino-(4-methoxybenzyl) acetate (**174e**) and *N*-Cbz-protected 2-*tert*-butyldimethylsilyl-2-amino ethyl acetate (**174f**) nor α-(4-methoxybenzyl)- or α-ethoxy ethyl acetate side-product, analogous to the discussed **200a** and **200b**, was detected.

In addition to the products reported in Table 5, *N*-Cbz-protected 2-trimethylsilyl-2-amino-(4-methoxybenzyl) acetate (**174g**) was synthesised from 2-trimethylsilyl-2-diazo-(4-methoxybenzyl) acetate (**173g**). The ^{1}H NMR analysis of the crude reaction mixture showed the presence of the expected product **174g** (doublet at δ 4.10, J = 8.7 Hz), but after purification by chromatography on silica gel, the ^{1}H NMR and GC-MS analysis clearly showed a large amount of the desilylated product **202** [ratio (**174g**)/(**202**) = 0.4:1] (Scheme 57).



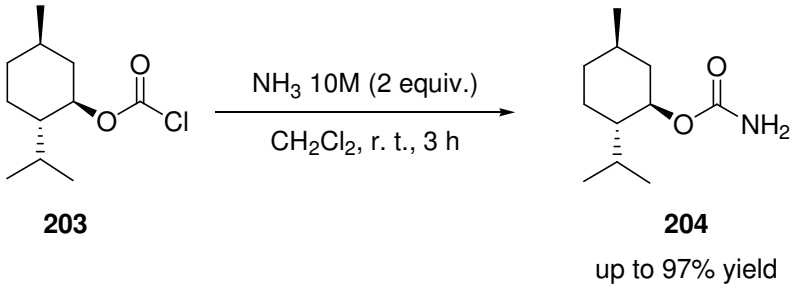
Scheme 57. Synthesis of *N*-Cbz-protected 2-trimethylsilyl-2-amino-(4-methoxybenzyl) acetate (**174g**).

The desilylated product **202** was identified by the presence of a doublet at δ 3.90 in the ^{1}H NMR spectrum representing the methylene group α to the carbonyl. Furthermore, no fragmentation ion at *m/z* 73, normally evidence of a trimethylsilyl group, was present in the GC-MS spectrum. It should be noted that the two products **174g** and **202** showed very similar physical-chemical properties as demonstrated by their similar retention times of the two peaks in GC-MS and essentially equal R_f values in the column chromatography (pentane/ethyl acetate = 9:1). This evidence showed clearly that the formed silyl amino acetate **174g** decomposes on silicate supports (GC-MS column is a silicon based polymer). This was verified when attempting to further purification of the mixture *via* chromatography on silica gel which led to the formation of at least 35% more of the desilylated amino acetate **202**.

All attempts to obtain the *tert*-butyldimethylsilyl analogous of product **174g** from the previous synthesized 2-*tert*-butyldimethylsilyl-2-diazo-(4-methoxybenzyl) acetate (**173f**) were not successful: *N*-Cbz-protected 2-*tert*-butyldimethylsilyl-2-amino-(4-methoxybenzyl) acetate was not formed under the standard conditions, or even after prolonged reaction times.

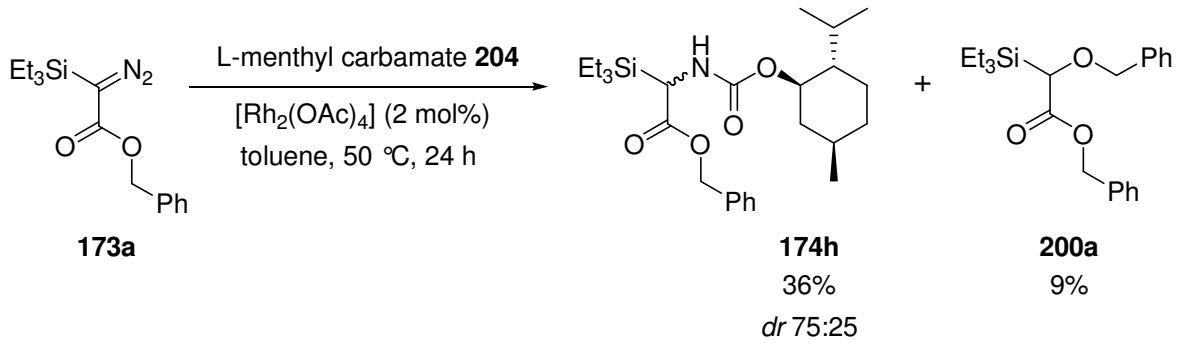
3.3.1 A Chiral Carbamate in a Diastereoselective N-H Insertion

Having demonstrated that is possible to effect N-H insertion reactions using carbamates, as reported in the previous section 3.3, this reaction was extended to the use of a *O*-substituted carbamate reagent with one or more stereogenic centres, in order to make the process stereoselective. For this purpose, (1*R*,2*S*,5*R*)-2-*iso*-propyl-5-methylcyclohexyl carbamate [L-(−)-menthyl carbamate] (**204**), easily synthesised from the commercially-available L-(−)-menthyl chloroformate **203** and aqueous ammonia, was chosen (Scheme 58).



Scheme 58. Preparation of L-(−)-menthyl carbamate (**204**) from L-(−)-menthyl chloroformate (**203**).

The white solid **204** was then added to a solution of 2-triethylsilyl-2-diazo benzyl acetate (**173a**) in toluene, to which was then added rhodium(II) tetraacetate and the mixture left react under the usual conditions. Purification on silica gel afforded one main product and a side-product, the latter of which identified as *O*-benzyl 2-triethylsilyl-2-hydroxy-benzyl acetate (**200a**) and recovered in 9% yield. The ^{1}H NMR analysis showed the presence of the characteristic doublet of *N*-protected silyl amino acetates **173**, (δ 4.29 , J = 9.06 Hz), representing the hydrogen atom bonded to the carbon in α-position to the ester group, which confirmed the formation of the desired *N*-menthyl-substituted 2-triethylsilyl-2-amino benzyl acetate (**174h**) as a mixture of diasteromers (36% yield) (Scheme 59).

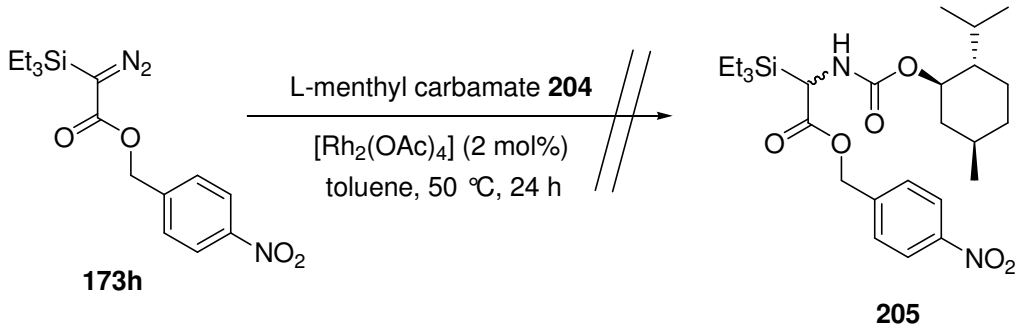


Scheme 59. Diastereoselective synthesis of *N*-menthyl-substituted 2-triethylsilyl-2-amino benzyl acetate (**174h**).

The diasteromeric ratio of 75:25 (50% *de*) was determined by ^{1}H NMR analysis; the two diasteromers were characterised by two singlets for the methylenic hydrogen atoms in benzylic position (δ 5.07 and 5.06, respectively for the minor and for the major diasteromer) and two very near doublets for the hydrogen atom bonded to the carbon in α-position relative to the nitrogen (Scheme 59).

An attempt to synthesise the tri*iso*propyl analogous of compound **174h** from the corresponding tri*iso*propylsilyl 2-diazo benzyl ester (**173d**) remained unsuccessful under the standard conditions, and only unreacted starting material was recovered.

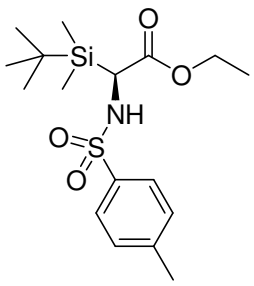
Furthermore, 2-triethylsilyl-2-diazo-(4-nitrobenzyl) acetate (**173h**) was allowed to react with L-menthyl carbamate **204** in presence of rhodium(II) tetraacetate, but no conversion of the starting material was observed under the standard conditions (Scheme 60).



Scheme 60. Unsuccessful example of N-H insertion reaction between 2-triethylsilyl-2-diazo-(4-nitrobenzyl) acetate (**173h**) and L-menthyl carbamate **204.**

3.4 Synthesis of Enantiomerically Pure α-Trialkylsilyl Protected Amino Acids: the Racemic Resolution Approach

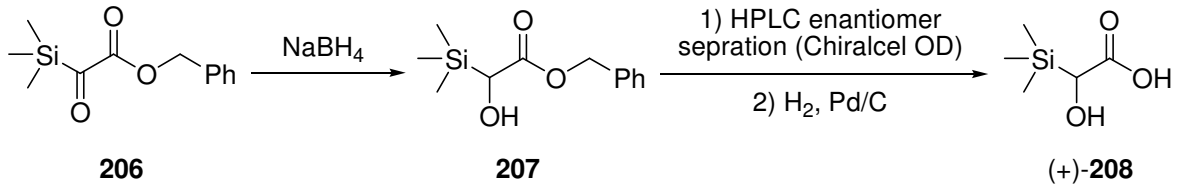
The resolution of a racemic mixture of two enantiomers of α-silyl α-amino acids was reported by Bolm and co-workers in 2000.[100] In this, the enantiomers of *N*-tosyl-protected 2-*tert*-butyldimethylsilyl-2-amino ethyl acetate (**178**) were separated by preparative HPLC using a chiral stationary phase. The enantiopure (+)-**178** was determined to be (*S*) by crystal structure analysis and resulted configurationally stable even after prolonged storage (Figure 16).



(*S*)-**178**

Figure 16. Enantiopure *N*-tosyl-protected 2-*tert*-butyldimethylsilyl-2-amino ethyl acetate (**178**).

The same approach was reported for racemic 2-trimethylsilyl-2-hydroxy-benzyl acetate (**207**), resolution of which by preparative HPLC on a chiral column gave access to optically active α-silyl α-hydroxy acids such as product (**+**)**-208** (Scheme 60).[123]



Scheme 60. Access to optically active α-silyl α-hydroxy acids.

Inspiration for resolution by chemical methods came from a procedure developed by the company Degussa: they resolved racemic *N*-Cbz-protected *tert*-leucine (**209**) using an enantiopure β-amino acid derivative. This substrate is analogous to a *N*-Cbz-protected 2-trimethylsilyl glycine (**210**) (Figure 17).

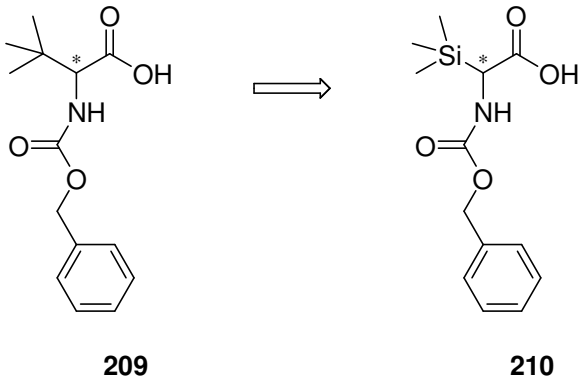
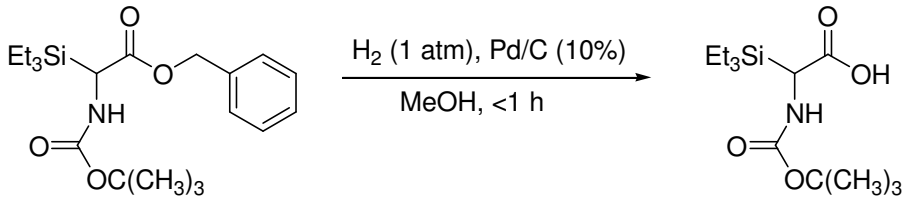


Figure 17. Enantiopure *N*-Cbz-protected 2-trimethylsilyl glycine (**210**) as analogous to enantiopure *N*-Cbz-protected *tert*-leucine (**209**)

It should be noted that access to racemic *N*-Boc-protected 2-triethylsilyl-2-amino acetic acid (**211**), a free acid analogous to compound **210**, could be performed by selective removal of the ester protecting group, since the reaction of *N*-Boc-protected 2-triethylsilyl-2-amino acetate (**174a**) with hydrogen gas over palladium(0) on charcoal afforded the free acid **211** after short time and with favourable yield (Scheme 61).[124] Attempted resolution of the racemic product **211** applying Degussa's procedure for *N*-Boc analogous resulted unsuccessful, since no salt of the β-amino acid derivative was formed and only starting material was recovered.

[123] See ref. [118]. See also C. Bolm, S. Saladin, A. Claßen, A. Kasyan, E. Veri, G. Raabe, *Synlett* **2005**, 461-464.



174a **211**

>60% yield

Scheme 61. Selective removal of the benzyl ester group by hydrogenolysis of *N*-Boc-protected 2-triethylsilyl-2-amino acetate (**174a**).

Considering these results, we investigated the possibility to obtain the free acid from selective deprotection of a corresponding ester moiety. Various esters protecting groups were considered, the removal of which could give access to the free carboxylic acids and thus, through resolution by chemical methods, to enantiopure α-silyl α-amino acids (Figure 18).[124]

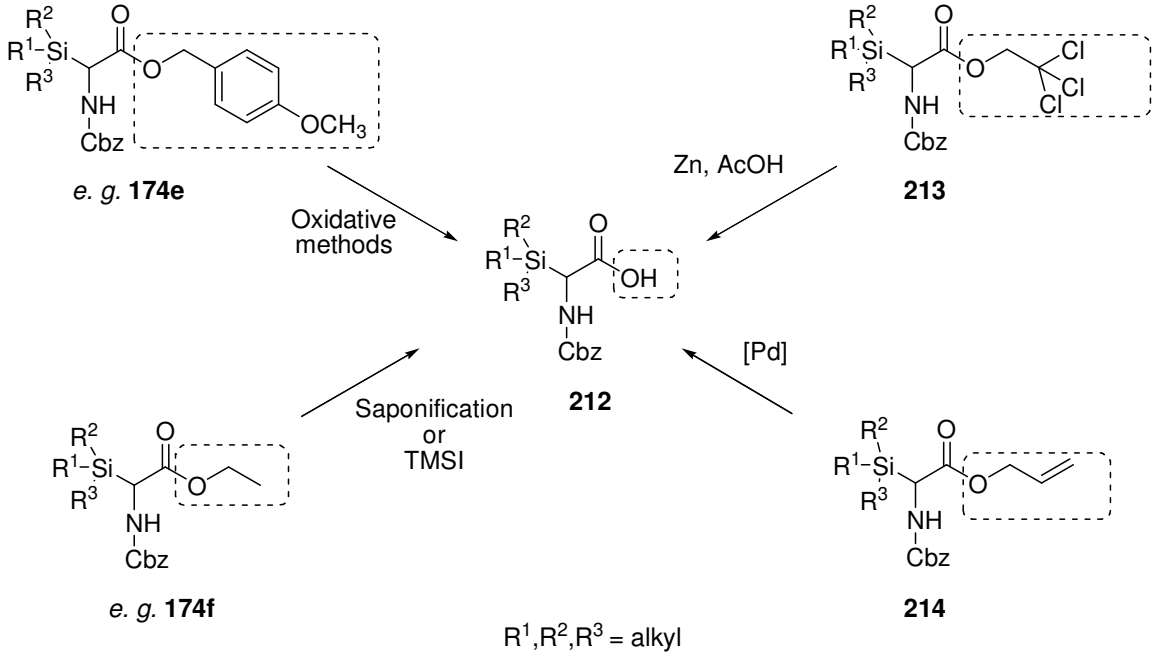
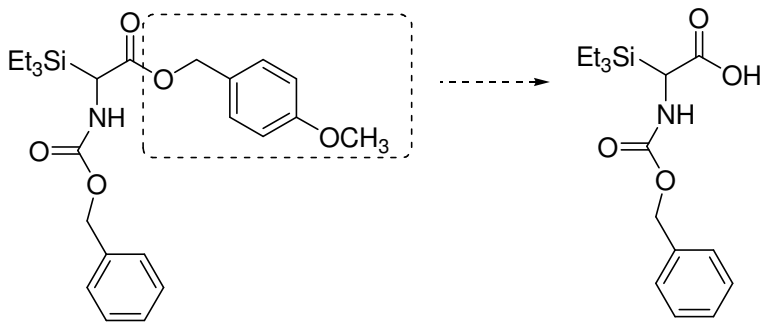


Figure 18. Synthetical pathway to *N*-Cbz-protected 2-trialkylsilyl-2-amino acid **212**.

[124] For a comprehensive report on methods of deprotection see: T. W. Greene, P. G. M Wuts in *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, **1999**.

3.4.1 Access to α-Silyl α-Amino Acids Derivatives from Selective Deprotection of α-Silyl α-Amino-(*p*-Methoxybenzyl) Esters

N-Cbz-protected 2-triethylsilyl-2-amino-(4-methoxybenzyl) acetate (**174e**) was considered as first substrate to attempt the removal of the ester moiety. The triethylsilyl group was considered as α-substituent in order to minimize the possibility of hydrolysis of the silyl group (Figure 19).



174e **215**

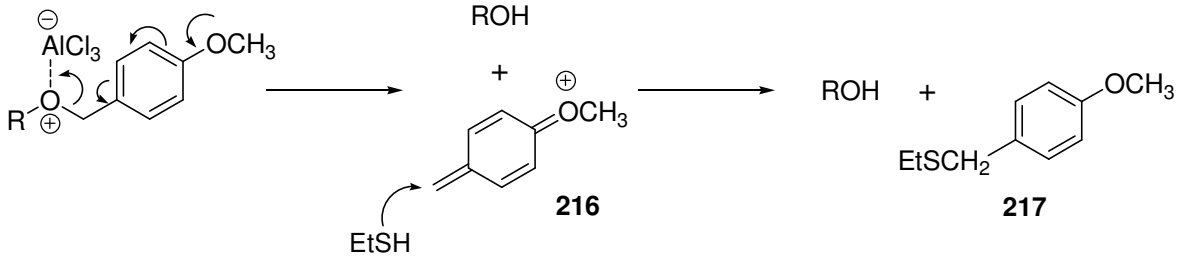
Figure 19. *N*-Cbz-protected 2-triethylsilyl-2-amino-(4-methoxybenzyl) acetate (**174e**) precursor of the free *N*-Cbz-protected 2-triethylsilyl-2-amino acetic acid (**215**).

Preliminary attempts at deprotection of the *p*-methoxybenzyl ester were performed on the inseparable mixture of *N*-Cbz-protected 2-trimethylsilyl-2-amino-(4-methoxybenzyl) acetate (1**74g**) and its desilylated derivative **202** as reported in the previous section 3.3. A paper by Torii and co-workers in 1991 describes the removal of the *p*-methoxy benzyl ester, using trifluoroacetic acid (TFA) and phenol as solvent, from an homologue of β-lactams.[125] The application of this method to our substrate resulted in the loss of the trimethylsilyl group which must be more reactive then the ester group.

The use of Lewis acids in combination with anisole or a thiol has been reported for *p*-methoxy benzyl esters,[126] although it is more often applied to *p*-methoxy benzyl ethers.[127,128] The impure *N*-Cbz-protected amino ester **174g**, was reacted with aluminum trichloride (2.5 equiv.) in a 4:1 mixture of anisole/dichloromethane, but only decomposition of the substrate was observed with no formation of the desired free acid.

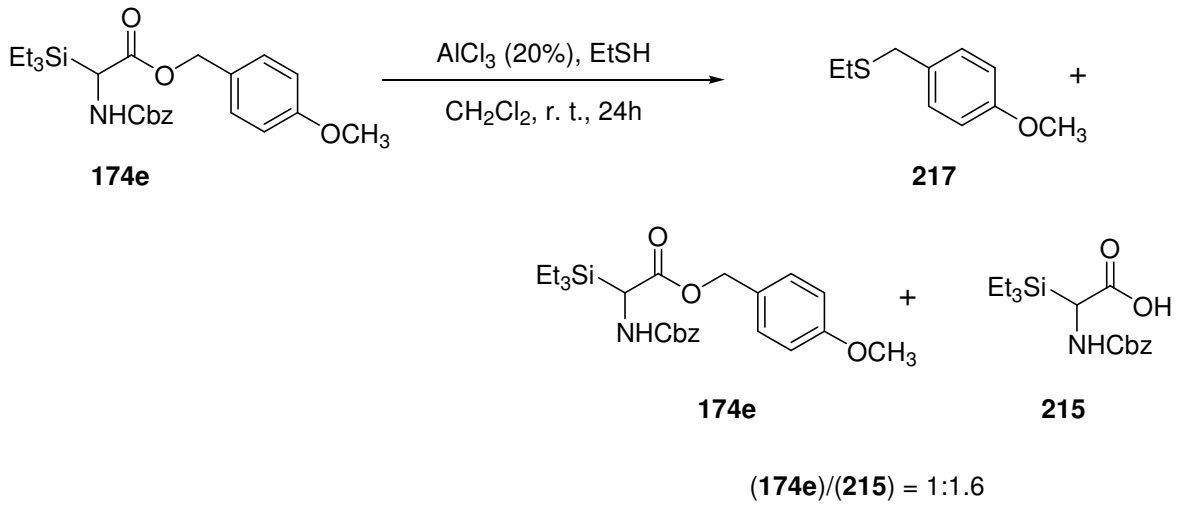
[125] S. Torii, H. Tanaka, M. Taniguchi, Y. Kameyama, *J. Org. Chem.* **1991**, *56*, 3633-3637.
[126] a) T. Tsuji, T. Kataoka, M. Yoshioka, Y. Sendo, Y. Nishitani, S.Hirai, T. Maeda, W. Nagata, *Tetrahedron Lett.* **1979**, *20*, 2793-2796. b) M. Node, K. Nishide, M. Sai, E. Fujita, *Tetrahedron Lett.* **1978**, *19*, 5211-5214.
[127] A. Bouzide, G. Sauvé, *Synlett* **1997**, 1153-1154.
[128] M. Ohtani, F. Watanabe, M. Narisada, *J. Org. Chem.* **1984**, *49*, 5271-5272.

In the case of *p*-methoxy benzyl protected (PMB) ethers, aluminum trichloride coordinates the ethereal oxygen, giving the protonated oxo-rest and the cation **216**, which is then attached from the nucleophilic ethanthiol to form *p*-methoxybenzyl ethylsulfide (**217**) (Scheme 62).



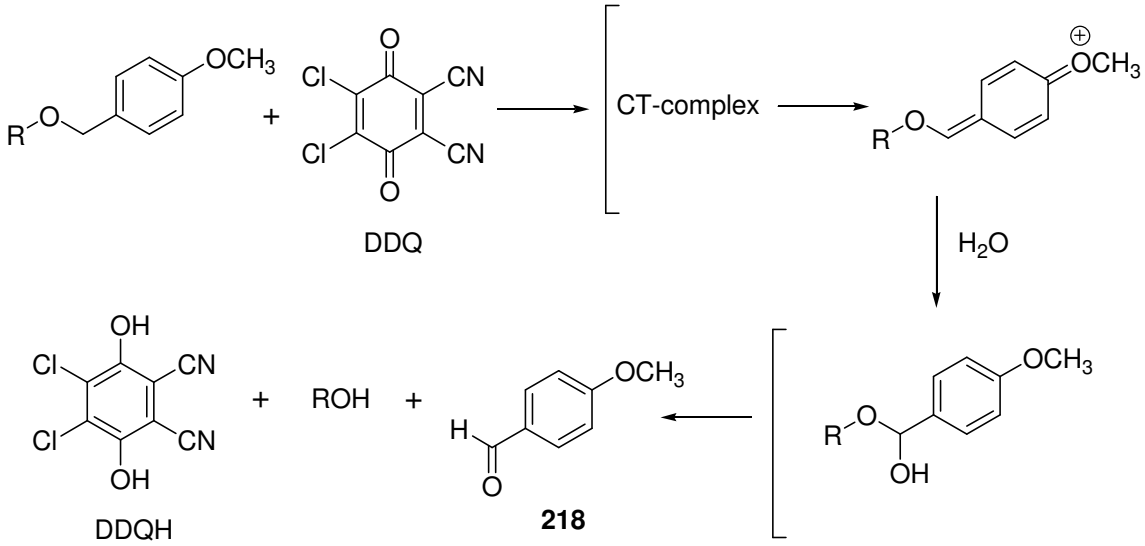
Scheme 62. Mechanism of deprotection of a *p*-methoxybenzyl (PMB) ethers.

The reaction of *N*-Cbz-protected 2-triethylsilyl-2-amino-(4-methoxybenzyl) acetate (**174e**) with a stoichiometric amount of aluminum trichloride in a mixture of ethanthiol/dichloromethane, yielded the *p*-methoxybenzyl ethylsulfide (**217**), clearly identified by ^{1}H NMR and GC-MS analysis, and to an unknown product, while unreacted substrate remained. The ^{1}H NMR analysis presented a doublet at δ 4.04 (J = 8.9 Hz), while in the ^{13}C NMR spectrum a signal at δ 178.0 was observed. These two characteristic signals, together with the GC-MS fragmentation pattern, allowed us to identify the product as the desired *N*-Cbz-protected 2-triethylsilyl-2-amino acetic acid (**215**), in a ratio 1.6 to 1 respect to the substrate **174e** (Scheme 63). In order to isolate and completely characterise the acid **215**, the reaction should be optimised and repeated on a large scale.



Scheme 63. Synthesis of the free *N*-Cbz-protected 2-triethylsilyl-2-amino acetic acid (**215**).

Selective removal of the PMP group is usually reported for ethers and can be achieved by oxidation with 2,3-dichloro-5,6-dyciano-1,4-benzoquinone (DDQ)[129] or cerium(IV) ammonium nitrate.[130]
The mechanism of benzylic oxidation using DDQ has been extensively studied: the PMB ether reacts with the oxidating agent by the initial formation of a charge-transfer (CT-complex) between an electron donating aromatic ring and the electron accepting ring of DDQ. This is followed by benzylic dehydrogenation caused by water (Scheme 64).[129]

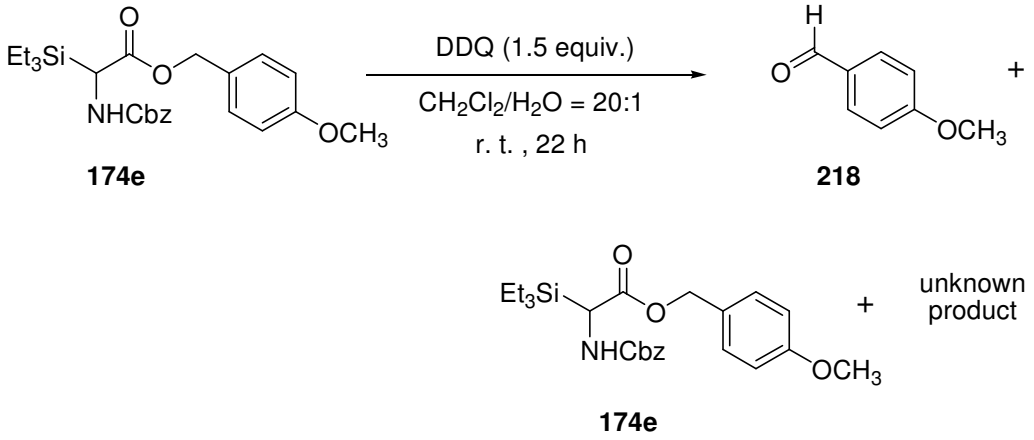


Scheme 64. Mechanism of oxidation of PMB ether using DDQ.

The oxidation then results in the formation of an alcohol and of *p*-methoxy benzyl aldehyde (**218**). It was then decided to try the oxidating agent DDQ for deprotection of the PMB ester moiety of the previously synthesised *N*-Cbz-protected 2-triethylsilyl-2-amino-(4-methoxybenzyl) acetate (**174e**). To a solution of the amino ester **174e** in dichloromethane/water = 20:1 was added DDQ (1.5 equiv.) and the mixture stirred at room temperature (Scheme 65). After two hours, TLC analysis (pentane/ethyl acetate = 4:1) showed the presence of a large amount of unreacted substrate. This was still the case after further 20 hours. The ^{1}H NMR analysis of the crude product mixture showed the presence of *p*-methoxy benzaldehyde (**218**) (singlet at δ 9.81 ppm), of an unknown product, while unreacted substrate **174e** remained. The GC-MS of the crude mixture confirmed the presence of large amount of unreacted substrate **174e** and of the unknown product, the fragmentation pattern of which was not compatible with the desired *N*-Cbz-protected 2-triethylsilyl-2-amino acetic acid

[129] K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa, O. Yonemitsu, *Tetrahedron* **1986**, *42*, 3021-3028 and references cited therein.
[130] R. Johansson, B. Samuelsson, *J. Chem. Soc. Perkin Trans 1* **1984**, 2371-2374.

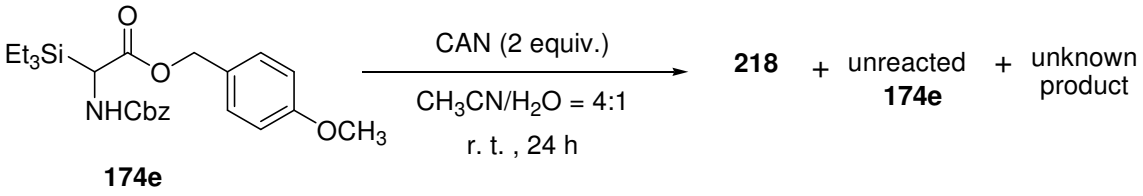
(**215**), since no fragmentation peaks with *m/z* 115 or similar corresponding to triethylsilyl group were present.



Scheme 65. Reaction of selective deprotection of *N*-Cbz-protected -2-triethylsilyl-2-amino-(4-methoxybenzyl) acetate (**174e**) using DDQ.

A further attempt was performed using an increased amount of water (dichloromethane/water = 10:1) but no different product distribution pattern was observed.

Cerium (IV) ammonium nitrate (CAN) was then tried as oxidating agent for removal of the PMB group. *N*-Cbz-protected 2-triethylsilyl-2-amino-(4-methoxybenzyl) acetate (**174e**) and CAN (2 equiv.) were added to a solution of acetonitrile/water = 4:1 and stirred at room temperature for 24 hours. The ^{1}H NMR analysis of the crude reaction mixture showed the presence unreacted substrate, *p*-methoxy benzaldehyde (**218**) and the product already obtained by oxidation reaction in presence of DDQ (Scheme 66).



Scheme 66. Reaction of selective deprotection of *N*-Cbz-protected 2-triethylsilyl-2-amino-(4-methoxybenzyl) acetate (**174e**) using CAN.

3.4.2 Attempts of Selective Deprotection of Various α-Silyl α-Amino Esters.

The previously discussed idea and reported attempts of selective removal of the *p*-methoxybenzyl ester, had opened the possibility of using various protective groups for the ester moiety. Therefore the synthesis of *N*-Cbz-protected α-silyl α-amino esters derived from ethanol (compound **174f**),

from 2,2,2-trichloroethanol (compound **213**) and from allylic alcohol (compound **214**) was investigated (Figure 20).

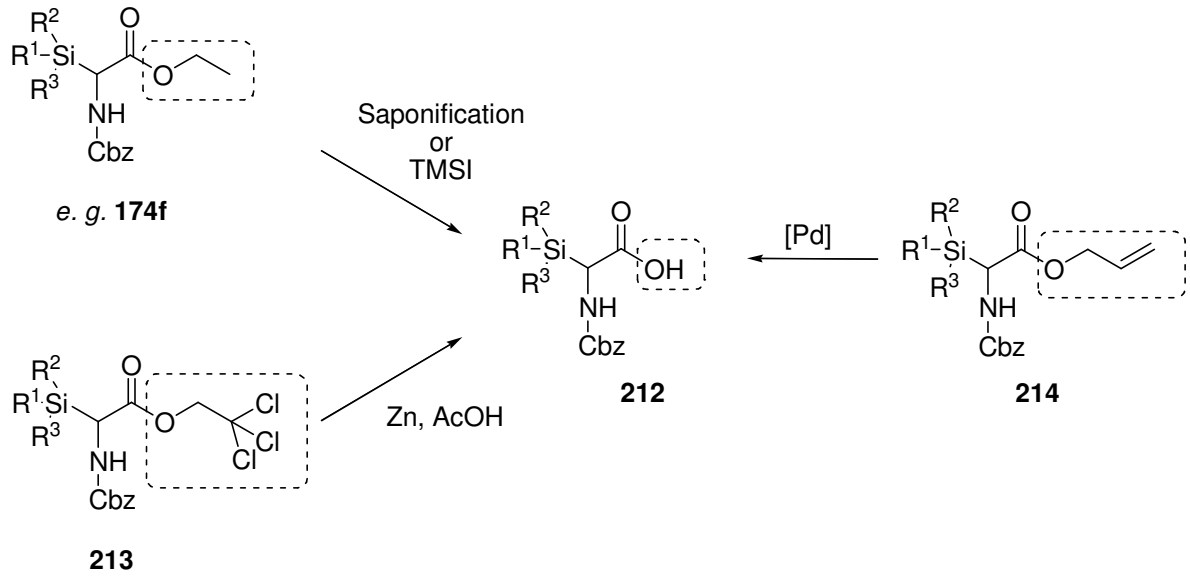
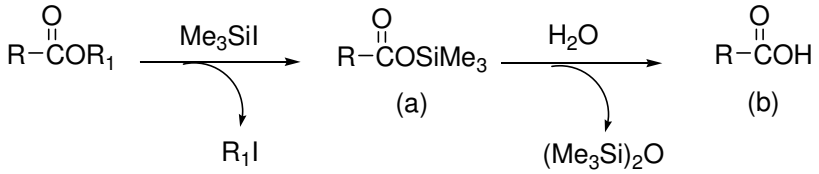


Figure 20. *N*-Cbz-protected α-silyl α-amino esters as precursors of *N*-Cbz-protected α-silyl α-amino acid **209**.

Thus, *N*-Cbz-protected 2-*tert*-butyldimethylsilyl-2-amino ethyl acetate (**174f**) was synthesised as reported in section 3.3, in 42% yield. Preliminary considerations pointed out that a selective removal of the ethyl group through classical saponification (using an aqueous solution of NaOH) would result in hydrolysis of the carbon-silicon bond with consequent loss of the silyl group. As such, a milder method of saponification was attempted by addition of lithium hydroxide monohydrate (3 equiv.) to a solution of the compound **174f** in methanol. TLC analysis (pentane/ethyl acetate = 4:1), performed after two hours, showed only unreacted substrate and this was still the case after a further 22 hours.

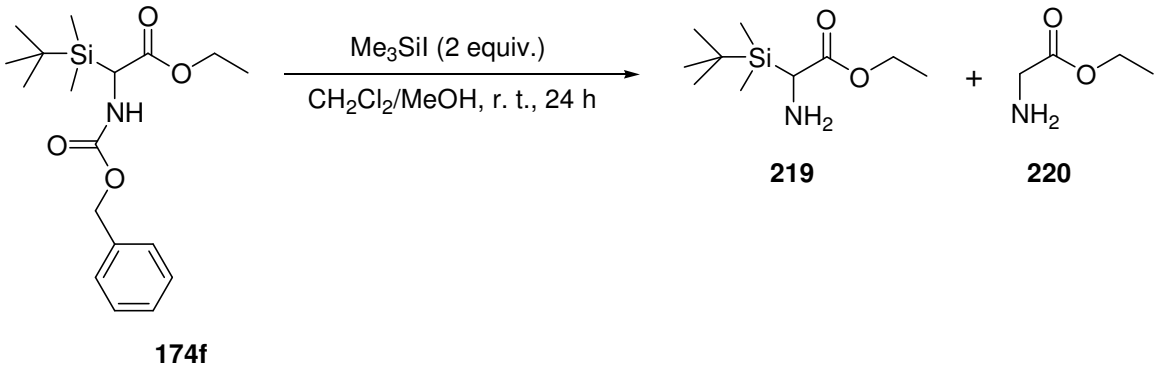
A protocol for selective dealkylation of ethyl esters using trimethylsilyl iodide and water was reported from Jung and Lyster in 1977, whereby the ester first reacts with trimethylsilyl iodide to give the silyl ester (a) which, after hydrolysis, yields to free carboxylic acid (b) (Scheme 67).[131]

[131] M. E. Jung, M. A. Lyster, *J. Am. Chem. Soc.* **1977**, *99*, 968-969.



Scheme 67. Removal of an ester group by treatment with trimethylsilyliodide.

Using this methodology, the substrate *N*-Cbz-protected 2-*tert*-butyldimethylsilyl-2-amino ethyl acetate (**174f**) was dissolved in dichloromethane and to the mixture was added trimethylsilyl iodide (2 equiv.). After 15 hours TLC analysis (pentane/ethyl acetate = 10:1) indicated two compounds. After 24 hours methanol was added to the reaction mixture as a milder alternative to water and the solvents mixture was then removed. The ^{1}H NMR analysis of the crude reaction mixture confirmed the complete conversion of the substrate into a mixture of products. Which were identified as the mono-deprotected 2-*tert*-butyldimethylsilyl-2-amino ethyl acetate (**219**) and its desilylated derivative (**220**) (Scheme 68).



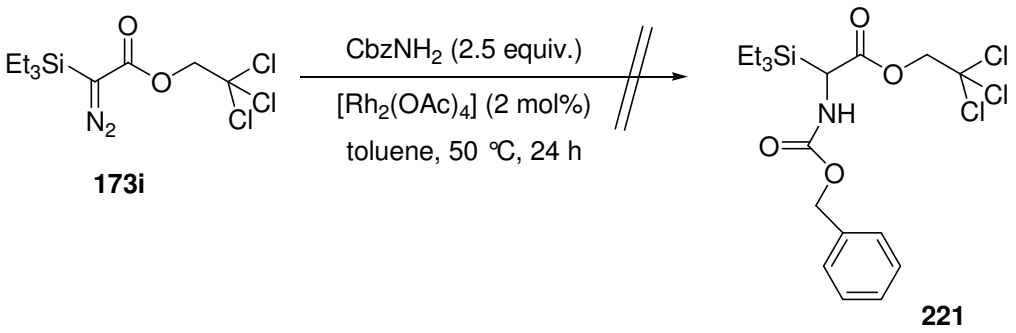
Scheme 68. Reaction of *N*-Cbz-protected 2-*tert*-butyldimethylsilyl-2-amino ethyl acetate (**174f**) with trimethylsilyl iodide.

An evidence of hydrolysis of the nitrogen-carbon bond of the carbamate moiety of compound **174f** was the absence of any residual characteristic signal of this functional group. Indeed, the ^{1}H spectrum showed no more signal at δ 5.11 representive of the methylene protons of the benzyl group, while no signal at δ 156.5 was present in the ^{13}C NMR spectrum. This last analysis, instead, showed the presence of two carbonyl signals at δ 170.8 and δ 167.2, which are consistent with the values expected for the carbonyl group of product **219** and product **220**, respectively. Cleavage of the carbamate probably results in the formation of benzyl alcohol, since aromatic signals were present between δ 7.5-7.0, the integral of which matches that of a singlet at δ 4.38, which could arise from methylene protons of this by-product.

Since the reported attempt did not selective the ester moiety, an ester derived from a 2,2,2-

trichloroethyl (Tce) group was employed.[132,133] Tce protecting group has found a moderate use in the chemistry of peptides. In 1998, Shioiri reported the selective removal of Tce in a linear depsiheptapeptide without interference with other protective groups present (*e.g.* Boc, benzyl, TBDMS), using zinc powder in acetic acid to obtain the corresponding free acid of the depsiheptapeptide in 96% yield.[133]

This deprotective methodology was applied 2-triethylsilylacetate-2-diazo-(2,2,2-trichloroethyl) acetate (**173i**), which was synthesised following the general procedure described in section 3.2. To our surprise, compound **173i** did not react at all with benzyl carbamate (2.5 equiv.) in the presence of rhodium(II) tetraacetate after heating the reaction mixture at 50 °C for 24 hours. *N*-Cbz-protected 2-triethylsilyl-2-amino-(2,2,2-trichloroethyl) acetate (**221**) did not form and starting materials were completely recovered (Scheme 69).



Scheme 69. Attempt to synthesise *N*-Cbz-protected 2-triethylsilyl-2-amino-(2,2,2-trichloroethyl) acetate (**221**) from 2-triethylsilyl-2-diazo-(2,2,2-trichloroethyl) acetate (**173i**)

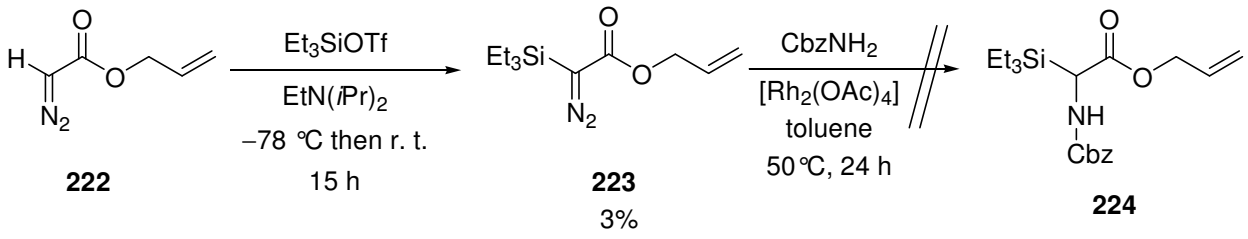
The use of microwave heating was considered as alternative to the conventional methods of heating used above.[134] Thus, the reaction mixture was heated at 100 °C for 30 minutes at 200 W output power, but still, no conversion of the substrate **173i** was observed.

Although the more reactive catalyst rhodium(II) perfluorobutyrate [$Rh_2(pbf)_4$] was used as an alternative to rhodium(II) tetraacetate, no desired *N*-Cbz-protected 2-triethylsilyl-2-amino-(2,2,2-trichloroethyl) acetate (**221**) was formed. Instead, 2-triethylsilyl-2-diazo-(2,2,2-trichloroethyl) acetate (**173i**) reacted with benzyl carbamate in the presence of [$Rh_2(pbf)_4$] under microwave irradiation at 100 °C at 200 W for 45 minutes, to afford a complex mixture of decomposition products, probably result of reaction of self-condensation of the substrate **173i**.

The synthesis of a *N*-Cbz-protected α-silyl α-amino ester derived from 2,2,2-trichloroethanol proved impossible using the discussed synthetic strategies. No less problematic was the synthesis of

[132] M. Namikoshi, B. Kundu, K. L. Rinehart, *J. Org. Chem.* **1991**, *56*, 5464-5466.
[133] J. Deng, Y. Hamada, T. Shioiri, *Synthesis* **1998**, 627-638.
[134] For a detailed discussion on microwave irradiation, see section 3.7.

N-Cbz-protected α-silyl α-amino ester derived from an allyl alcohol (see compound **214**). In fact, its precursor 2-triethylsilyl-2-diazo allyl acetate (**223**) was obtained only in 3% yield from the silylation reaction of 2-diazo allyl acetate (**222**).[135] An attempt to synthesise *N*-Cbz-protected 2-triethylsilyl-2-amino allyl acetate (**224**) from compound **223** and benzyl carbamate in presence rhodium(II) tetraacetate at 50 °C for 24 hours, resulted unsuccessful and only starting material was recovered (Scheme 70).



Scheme 70. Attempt to synthesise *N*-Cbz-protected 2-triethylsilyl-2-amino allyl acetate (**224**).

3.5 Deprotection by Selective Hydrogenation of *N*-Cbz-Protected α-Silyl α-Amino Benzyl Esters

The idea of selective removal of an ester moiety, from a compound were also a carboxybenzyl (Cbz) function was present, was further exploited considering, in this case, *N*-Cbz-protected 2-triethylsilyl-2-amino benzyl acetate (**174b**), which could give access to *N*-Cbz-protected 2-triethylsilyl-2-amino acetic acid (**215**). In fact, it can be seen that two different benzyl substituents are present in the α-triethylsilyl α-amino ester **174b** depicted in Figure 21: the benzyl ester, which protects the carboxylic acid functionality and the carbobenzyloxy moiety which protects the amino moiety. The two groups should, in principle, behave similarly in, for example, a reducing environment, but it was considered that we could take advantage of the differences between the ester and carbamate chemical environments to obtain information about their relative reactivities.

[135] W. Kirmse, H. Dietrich, *Chem. Ber.* **1965**, 4027-4032.

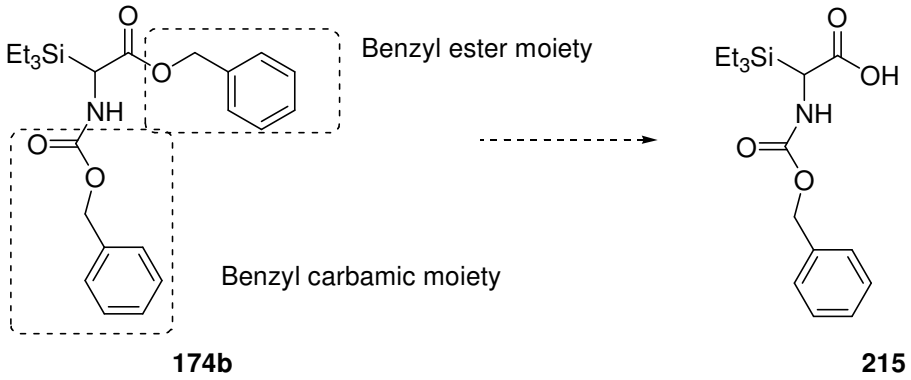
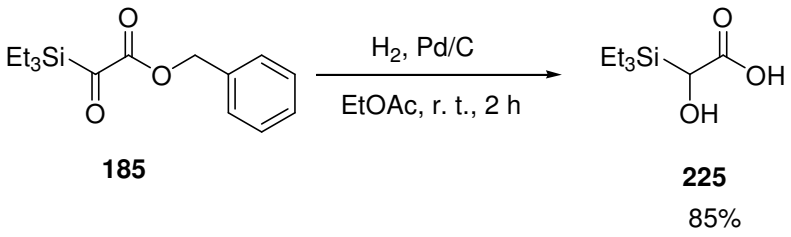


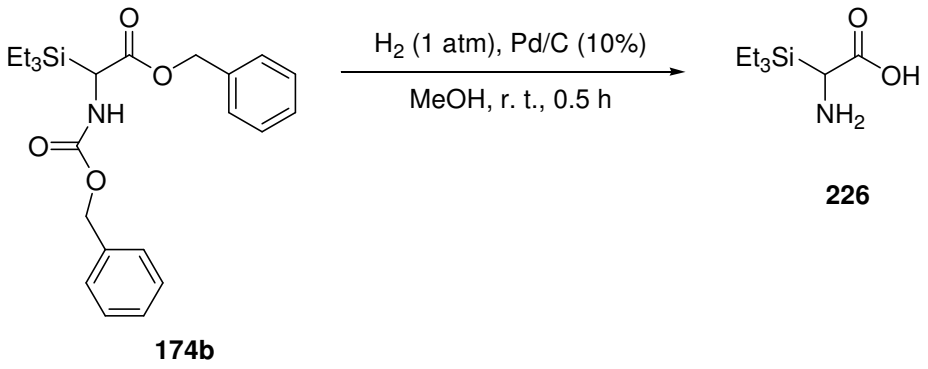
Figure 21. *N*-Cbz-protected 2-triethylsilyl-2-amino benzyl acetate (**174b**) and the free *N*-Cbz-protected 2-triethylsilyl-2-amino acetic acid (**215**).

The removal of a benzylic group under mild and neutral condition is usually performed using palladium(0) on charcoal and molecular hydrogen.[124] This protocol was already applied by Bolm and co-workers for the reduction, for example, of 2-triethylsilyl-2-keto-benzyl acetate (**185**) to 2-triethylsilyl-2-hydroxy acetic acid (**225**) as depicted in Scheme 71.[117]



Scheme 71. Synthesis of 2-triethylsilyl-2-hydroxy acetic acid (**225**) from 2-triethylsilyl-2-keto-benzyl acetate (**185**).

In keeping with this methodology, *N*-Cbz-protected 2-triethylsilyl-2-amino benzyl acetate (**174b**) reacted with hydrogen gas (1 atmosphere) in the presence of a suspension of palladium(0) on charcoal (10% Pd, 100 mg per mmol of substrate) in methanol. After 0.5 hours, the conversion of the substrate was complete, affording a white, crystalline solid, compound **226**, after filtration and removal of the solvent under reduced pressure (Scheme 72).



Scheme 72. Synthesis of 2-triethylsilyl-2-amino acid (**226**) from *N*-Cbz-protected 2-triethylsilyl 2-amino benzyl acetate (**174b**).

A characteristic feature of the ^{1}H NMR spectrum of the substrate *N*-Cbz-protected 2-triethylsilyl-2-amino benzyl acetate (**174b**) in $CDCl_3$ was a multiplet between δ 5.19 and 5.07, which is attributed to the resonance of five hydrogen atoms and, in particular, to both methylenes of the benzylic and carbobenzyloxy group and to the proton bonded to the nitrogen. In contrast, the ^{1}H NMR spectrum of the product exhibited no such signal representive of benzylic methylene protons and, additionally, no resonances attributable to the protons of aromatic groups were observed.

The ^{1}H NMR spectrum of the free amino acid **226**, performed in CD_3OD, showed additionally signals corresponding to the triethylsilyl group (triplet at δ 0.96 and quartet at δ 0.61) and a singlet at δ 3.80 attributed to the proton bonded to the carbon in the α position relative to the silyl group. Although the signal did not correctly integrate for one proton, this could presumably be solved if the spectrum was performed in a less protic solvent such as dimethyl sulfoxide or if a longer relaxation delay was used in the NMR experiment. It has, of course, to be considered that the highly protic solvent (CD_3OD) used to perform the NMR experiment did not allow signals corresponding to the highly exchangeable protons of the carboxylic and/or amine moieties to be observed.

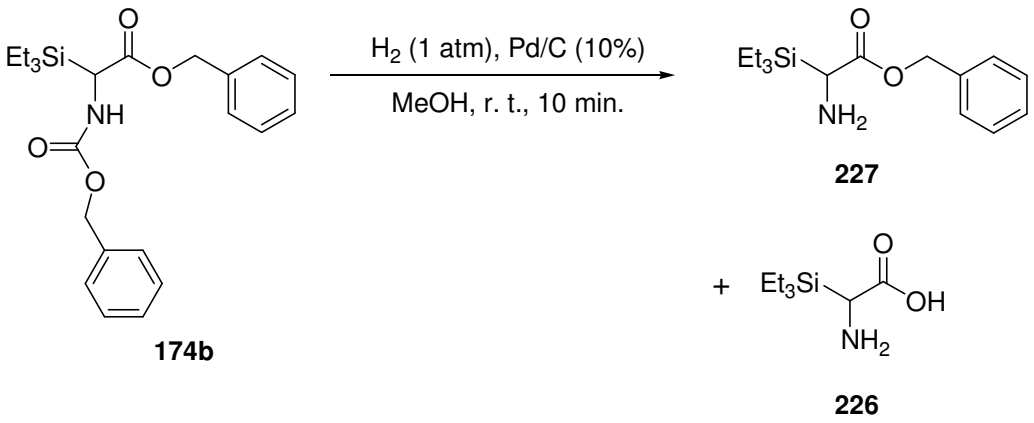
In the ^{13}C NMR spectrum two signals corresponding to the methylene and methyl carbons of the silyl group was observed at δ 4.9 and at δ 7.0, respectively. A signal at δ 40.2 was considered to arise from the carbon in the α position relative to the silyl group since its chemical shift corresponds to the chemical shift (δ 45.1) of the corresponding carbon in the substrate **174b**.

The infrared spectrum was comparable to an amino acid structure with the strong absorption maximum at 1598 cm^{-1} corresponding to the asymmetric carbonyl stretching of the carboxylic group and the broad bands at 3200-2800 and 3600-3300 cm^{-1}, corresponding to the N-H and O-H stretching, respectively. The electron impact (EI) mass spectral analysis featured a molecular ion at *m/z* 189 and fragment ions peaks at *m/z* 161 and *m/z* 131, representing loss of one and two ethyl

groups from the molecular ion, respectively. The presence of a fragment at *m/z* 115 corresponded to the triethylsilyl group.

Although the use of molecular hydrogen in presence of Pd(0)/C caused the removal of both benzylic and benzyloxy groups resulting in the formation of the amino acid **226**, it was still desired to determine which of the reductive deprotection processes was faster.

Thus, the experiment described in Scheme 72 was repeated, performing ^{1}H and a ^{13}C NMR spectra of the reaction mixture after only 10 minutes. The ^{1}H NMR spectrum showed the presence of one main product and of the compound **226** as a minor product. Noteworthy, the multiplet at δ 5.19-5.07 was corresponding to the two benzylic hydrogens which suggested a removal of a single benzylic group (the signal of NH_2 group could not be detected since the experiment was performed in the highly exchangeable solvent CD_3OD) (Scheme 73).



174b **227** **226**

Scheme 73. Hydrogenolysis of *N*-Cbz-protected 2-triethylsilyl-2-amino benzyl acetate (**174b**) for 10 minutes.

The ^{13}C NMR spectrum of the substrate *N*-Cbz-protected 2-triethylsilyl-2-amino benzyl acetate (**174b**) in $CDCl_3$ showed one peak at δ 173.1 which was compatible with an ester carbonyl, and an other peak at δ 156.6 compatible with a carbamic carbonyl (for comparison, refer to the signal at δ 156.8 attributed to the benzyl carbamate **228** in Figure 22). In contrast, the ^{13}C NMR spectrum of the crude mixture in CD_3OD (Scheme 73) featured one carbonyl signal at δ 176.5 which corresponded to the ester moiety of compound **227**.

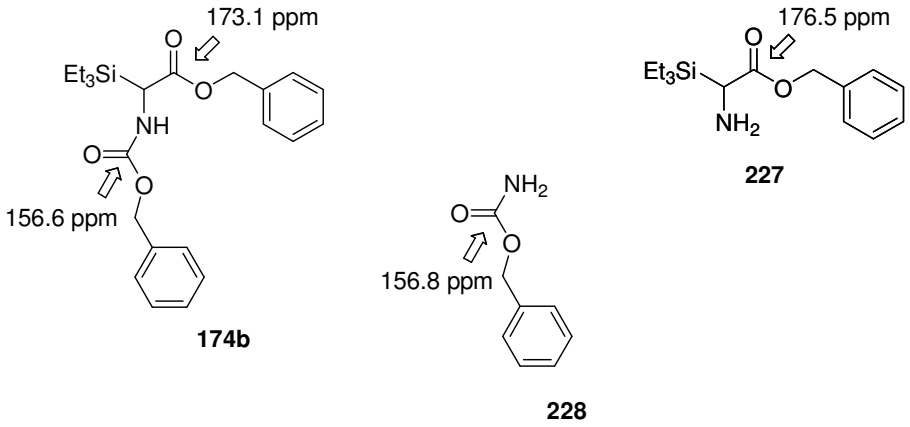


Figure 22. Comparison of chemical shifts of *N*-Cbz-protected 2-triethylsilyl-2-amino benzyl acetate (**174b**), *N*-free 2-triethylsilyl-2-amino benzyl acetate (**227**) and benzyl carbamate (**228**).

It was thus evident that the product formed was the *N*-free 2-triethylsilyl-2-amino benzyl acetate (**227**) and not the expected *N*-Cbz-protected 2-triethylsilyl-2-amino acetic acid (**215**). From this result, a difference in reactivity between the benzyl and carbobenzyloxy groups towards reduction had been demonstrated, but in seeking to selectively form the *N*-protected α-silyl α-amino acid **215**, it was considered that different catalyst could serve to modulate the chemoselectivity for reductive hydrogenolysis of the ester.

Initial investigation involved the use of Lindlar's catalyst, usually composed of Pd(0) (5%) on a mixture of $CaCO_3$/$Pb(OAc)_2$, and subsequent studies involved reduction using platinum oxide (PtO_2) or rhodium(0) on alumina. The results are summarized in Table 6.

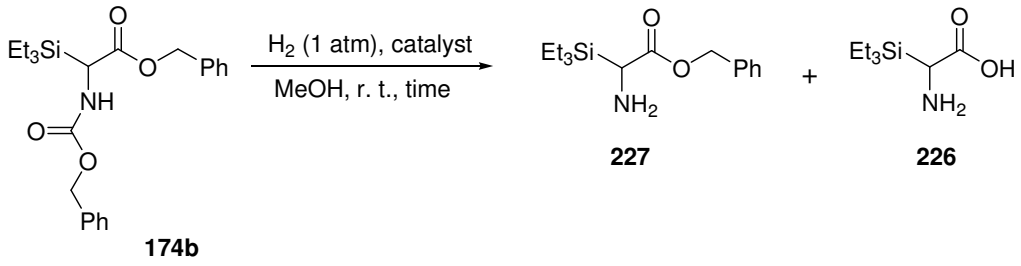


Table 6. Use of different catalysts in the hydrogenolysis reaction of *N*-Cbz-protected 2-triethylsilyl-2-amino benzyl acetate (**174b**).

Entry	***Catalyst***[a]	***% of substrate (after 0.5 h)***	***% of substrate (after 24 h)***	***Product***
1	Lindlar's[b]	0%	--	**226**
2	PtO_2	100%	0%	**227**
3	Rh/Al_2O_3	100%	0%	**226**

[a] Amount of catalyst used: 100 mg per mmol of substrate **174b.**
[b] Lindlar's catalyst: 5% Pd(0) on $CaCO_3$/$Pb(OAc)_2$.

The use of Lindlar's catalyst resulted in complete conversion of the substrate **174b** to 2-triethylsilyl-2-amino acetic acid (**226**) after 0.5 hour (entry 1, Table 6) even though the catalyst contained a lower percentage amount of Pd compared to that contained in the Pd on charcoal.

N-Cbz-protected 2-triethylsilyl-2-amino benzyl acetate (**174b**) failed to react with hydrogen gas on PtO_2 (see entry 2, Table 6), after 0.5 hours. The ^{1}H NMR spectrum of the reaction mixture ater 24 hours showed slight formation of the mono-deprotected 2-triethylsilyl-2-amino benzyl acetate (**227**).

The same substrate **174b**, when treated under reductive conditions using rhodium(0) on aluminum oxide (Al_2O_3) as the catalyst, failed to effect reaction. Increasing the amount of metal to 200 mg per mmol of substrate did not enhance the reactivity since, after 2 hours, the conversion remained near to 0%. Indeed, after 24 hours, the ^{1}H NMR spectrum showed formation of the bi-deprotected amino acid **226** (entry 3, Table 6).

As discussed, palladium showed the best reactivity toward the reductive hydrogenolysis: the use of the less reactive platinum oxide and rhodium increased the reaction times but did not yield more information concerning the chemoselectivity of the reaction.

Catalytic transfer hydrogenation has been reported in the literature not only by means of molecular hydrogen as a proton donor but also through the use of other donor compounds.[136] The donor can, in principle, be any organic compound whose oxidation potential is sufficiently low for the hydrogen transfer to occur under mild condition and in the presence of a catalyst. Sasson and Blum reported the reduction of the double bond of an α,β-unsaturated carbonyl compound in 1971 using a benzyl alcohol as a donor and dichloro*tris*(triphenylphosphine)ruthenium(II) [$RuCl_2(PPh_3)_3$] as a catalyst at high temperature.[137] However, when *N*-Cbz-protected 2-triethylsilyl-2-amino benzyl acetate (**174b**) was reacted using the same catalytic hydrogenation system (without employing any solvent) at 100 °C for 4 hours, no reaction was observed.

3.6 An example of Application of *N*-Protected α-Trialkylsilyl-α-Amino Acids: Studies towards an Analogue of a Matrix Metalloproteinase Inhibitor

The discussed developments of various synthetic strategies yielding enantiomerically enriched α-silyl α-amino acids, was only one of the two major guidelines of this research project. The second part of this work started pointing out that the α-silyl α-amino acid core could become a substructure of a more complicated structure, as already considered by Bolm and co-workers[100] and by Sieburth and co-worker.[101]

[136] G. Brieger, T. J. Nestrick, *Chem. Rev.* **1974**, *74*, 567-580.
[137] Y. Sasson, J. Blum, *Tetrahedron Lett.* **1971**, *24*, 2167-2170.

Matrix metalloproteinase (MMP) inhibitors are considered a relevant synthetic target in the modern synthetic and medicinal chemistry. The modification of a MMP structure with the insertion of an α-silyl α-amino acid functionality, could confer to the so modified structure a different reactivity and a better bio-availability, thus paving the way to a variety of most interesting and new applications.

3.6.1 Introduction to MMP Inhibitors and Choice of a Sila Analogue of a MMP Inhibitor

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that are capable of collectively degrading all kinds of extracellular matrix proteins including a number of biologically-active molecules. MMPs play an important role in tissue remodelling associated with various physiological and pathological processes such as morphogenesis, angiogenesis, tissue repair, arthritis and tumor invasion.[138] The inhibition of various MMPs has been considered as a target for therapeutic intervention against such pathologies. Although it is not the purpose of this thesis to provide detailed explanation of such effects, some simple remarks concerning structure-activity relationship and retrosynthesis will be discussed.

For a molecule to be an effective inhibitor of the MMP class of enzymes it must embody a functional group *(e.g.*, hydroxamic acid, carboxylic acid, sulfidryl) that can coordinate to the zinc(II) ion at the active site of the enzyme.[139] Additionally it is necessary that a functional group which can provide a hydrogen bond interaction with the enzyme backbone, and one or more side chains which can interact with the enzyme subsites *via* van der Waals interactions, are present. These requirements could be satisfied from a number of different classes of MMP inhibitor, which have been extensively studied through structural-based design[140] and combinatorial chemistry.[141]

Early studies conducted by Johnson and co-workers demonstrated that succinyl hydroxamic derivatives are more potent inhibitors of MMP-1 (fibroblast collagenase, a subclass of MMP, which act on fibrillar and nonfibrillar collagens) than the corresponding malonyl or glutaryl derivatives.[141] Later studies showed that a wide range of MMPs are inhibited by succinyl hydroxamates, the structure-activity relationships of which are schematised in Figure 23.

[138] A C. Buisson, J. M. Zahm, M. Polette, D. Pierrot, G. Bellon, E. Puchelle, P. Birembaut, J. M. Tournier, *J. Cell. Physiol.* **1996**, *166*, 413-426.
[139] M. Whittaker, C. D. Floyd, P. Brown, A. J. H. Gearing, *Chem. Rev.* **1999**, *99*, 2735-2776.
[140] R. E. Babine, S. L. Bender, *Chem. Rev.* **1997**, *97*, 1359-1472.
[141] W. H. Johnson, N. A. Roberts, N. Borkakoti, *J. Enz. Inhib.* **1987**, *2*, 1-22.

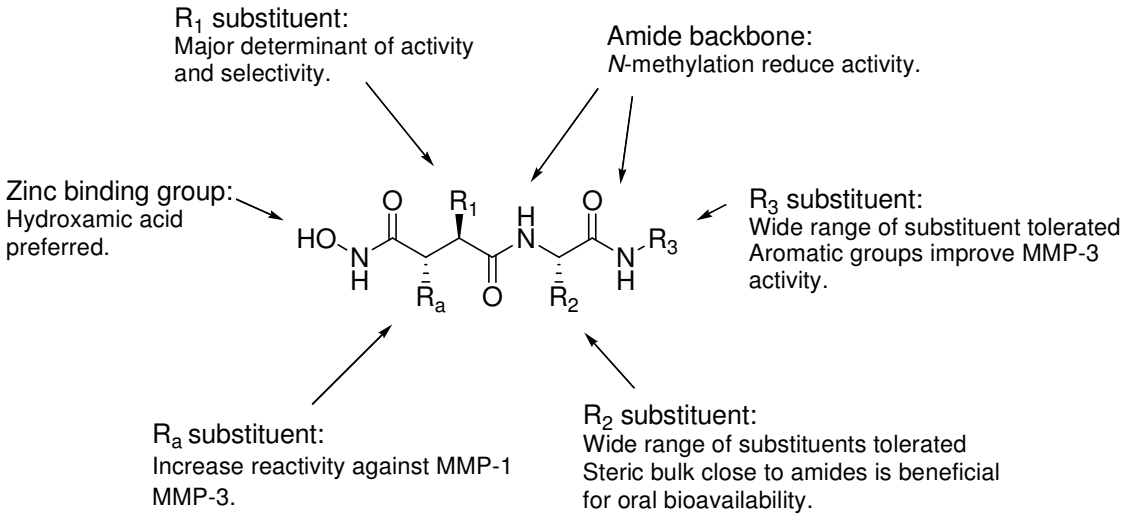
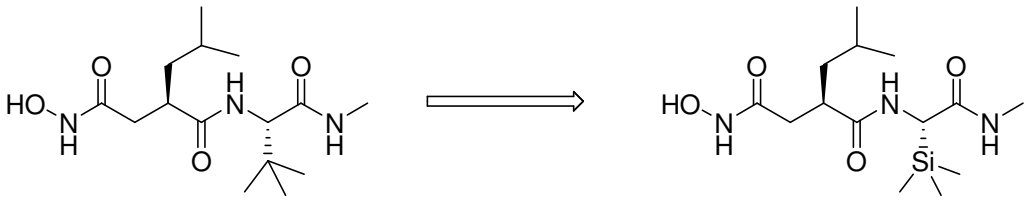


Figure 23. Structure-activity relationship of succinyl hydroxamates based MMPs inhibitors.

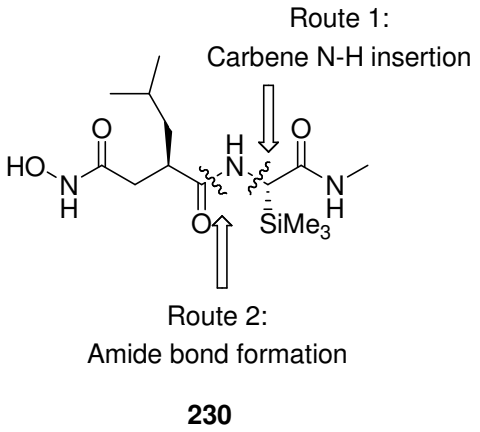
In fact in 1999, Whittaker and co-workers collected a list of more than one hundred molecules of similar structure, that showed inhibition of various subclasses of MMPs.[139] Between them, we focused our attention on a succinyl hydroxamic structure (**229**, Figure 24) that inhibits a range of MMPs and embodies a *tert*-leucine residue in the backbone.



229 **230**

Figure 24. Structure comparison between a succinyl hydroxamic based MMPs inhibitor and its silyl modified analogue.

It was considered that the *tert*-butyl moiety of *tert*-leucine could, through the appropriate modification, be replaced with a trimethylsilyl group, thereby generating the sila analogue **230** of compound **229**, which may possess improved bioavailability. This potential application of a *N*-protected α-trialkylsilyl α-amino acid leads itself to two retrosynthetic approaches, each described in Figure 25.

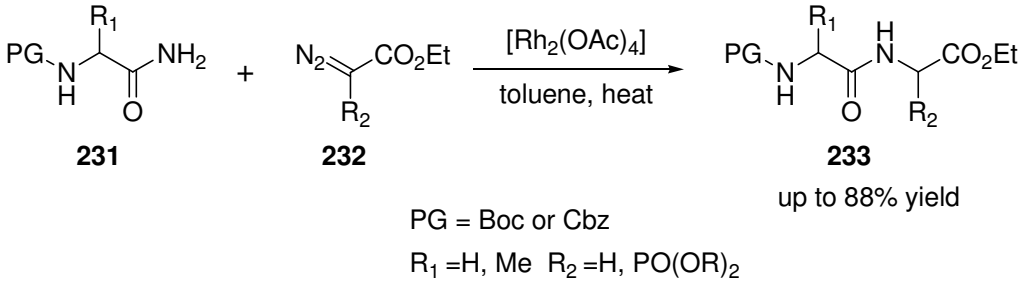


230

Figure 25. Retrosynthetic approaches to sila modified succinyl hydroxamic based MMPs inhbitor **230.**

3.6.1.1 Route 1: Carbene N-H Insertion Approach

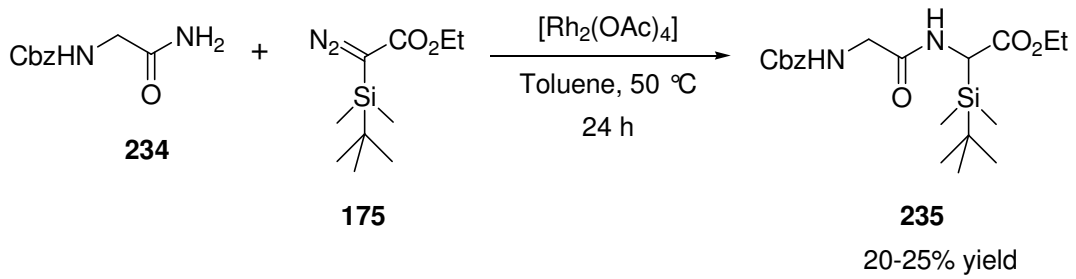
The use of carbene N-H insertion methodology for the formation of a peptide bond was first reported by Moody and co-workers in 1997 and applied to the coupling of the amide **231** with the diazo ester **232** in the presence of rhodium(II) tetracetate (Scheme 74).[142]



Scheme 74. Formation of a peptide bond from the amide **231** and the diazo ester **232**.

Following similar methodology, Bolm and co-workers later reported the reaction between *N*-Cbz-protected glycine amide (**234**) and 2-*tert*-butyldimethylsilyl-2-diazo ethyl acetate (**175**) in the presence of rhodium(II) tetraacetate, from which the dipeptide **235** was afforded in ca. 20% yield (Scheme 75).[100]

[142] C. J. Moody, L. Ferris, D. Haigh, E. Swann, *Chem. Commun*. **1997**, 2391-2392.



Scheme 75. Synthesis of the dipeptide **235** from the amide **234** and the diazo ester **175**.

The application of these synthetic strategies to the formation of our target molecule **227** required the synthesis of the building blocks reported in Figure 26, namely the succinyl hydroxy-amide **236** and the 2-trimethylsilyl-2-diazo-*N*-methyl amide (**237**). Attempts to synthesise an analoge of the diazo amide **237**, are reported in details in section 3.6.5.

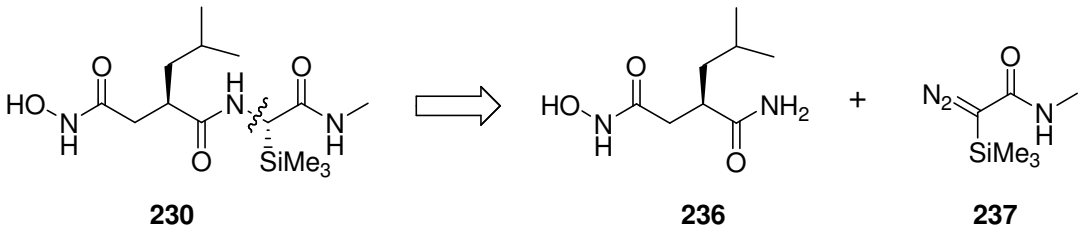
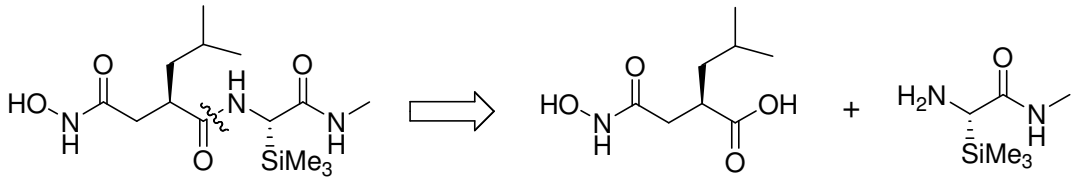


Figure 26. Carbene N-H insertion retro-synthetic approach to sila modified succinyl hydroxy-amide based MMPs inhbitor **230**.

Since the chemoselectivity of the possible reaction of an N-H insertion between a primary amide such as in **236** and a 2-trialkylsilyl-2-diazo-*N*-methyl amide as **237** had never been studied, it was unknown what electronic properties an amide moiety in the α position relative to the diazo group would confer on the molecule with respect to the insertion process. For this reason, an alternative route to compound **230** was chosen, in which the key step in the proposed synthesis involved amide-bond formation.

3.6.1.2 Route 2: Amide-Bond Formation Approach

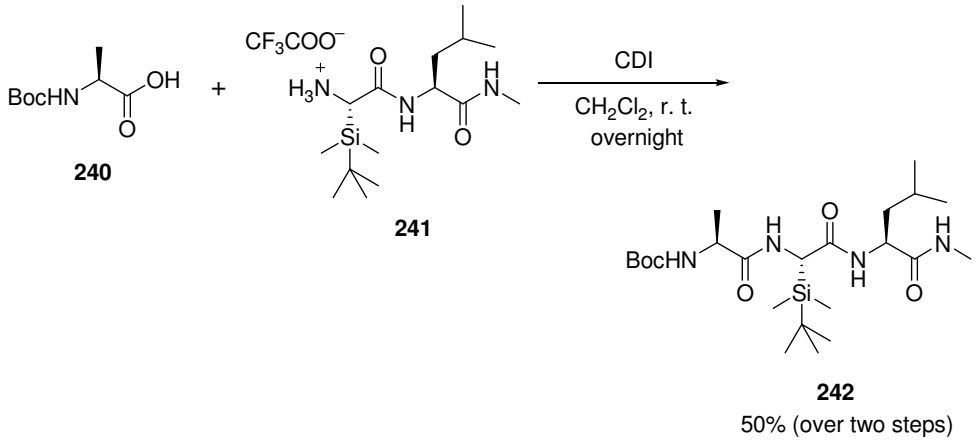
For the amide-bond formation approach, two building blocks were required, the succinyl hydroxamic acid **238** and the 2-trimethylsilyl-2-amino-*N*-methyl amide (**239**) (Figure 27).



230 **238** **239**

Figure 27. Amide-bond formation approach to sila modified succinyl hydroxy-amide based MMPs inhbitor **230**.

The coupling of a free carboxylic acid function to the amino group of an α-trialkylsilyl α-amino acid derivative was reported by Sieburth and co-worker in which the tripeptide **242** was synthesised from the trifluoroacetic salt of the silyl dipeptide **241** and *N*-Boc-alanine **240** in the presence of carbonyldiimidazol (CDI) as a coupling reagent (Scheme 76).[101,143]



240 **241** **242**

50% (over two steps)

Scheme 76. Coupling between the amino group of the dipeptide **241** and the acid function of *N*-Boc alanine **240**.

The amide-bond formation approach to compound **230** was initially studied without considering the chirality of the two coupling partners, in the hope to extend the chemistry to the asymmetric version of the system. For this reason, the synthesis of the racemic β-*iso*-butyl-succinyl hydroxamic acid **238** and of the racemic 2-trialkylsilyl-2-amino-*N*-methyl amide (**239**) were considered.

3.6.2 Synthetical Approach to the Succinyl Hydroxamic Acid Building Block

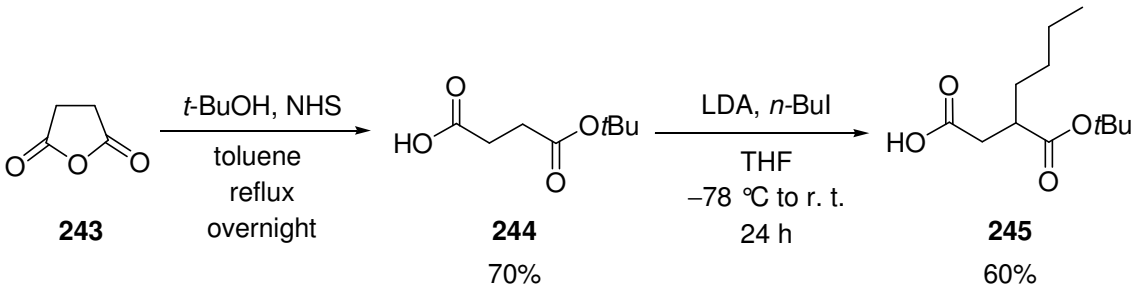
Several examples in the literature deal with the synthesis of succinyl hydroxamic acid precursors from the ring-opening reaction of succinic anhydride or derivatives with a nucleophile.[144] Our aim

[143] A previous research by Bolm and co-workers dealt with a coupling of the free carboxylic acid function of a α-silyl α-amino acid and the terminal amino moiety of a simple amino acid: see ref. [100].

[144] a) M. Akiyama, K. Shimizu, S. Aiba, F. Banba, *J. Chem Soc., Perkin Trans 1* **1980**, 2122-2125. b) P. R. Guzzo, M. J. Miller, *J. Org. Chem.* **1994**, *59*, 4869-4867. c) R. Stephani, V. Cesare, I. Sadarangani, I. Lengyel, *Synthesis* **2002**, 47-52. d) S. C. Bergmeier, K. A. Ismail, *Synthesis* **2000**, 1369-1371. e) J. P. Devlin, J. E. Thorpe, R. J. Wood, B. J.

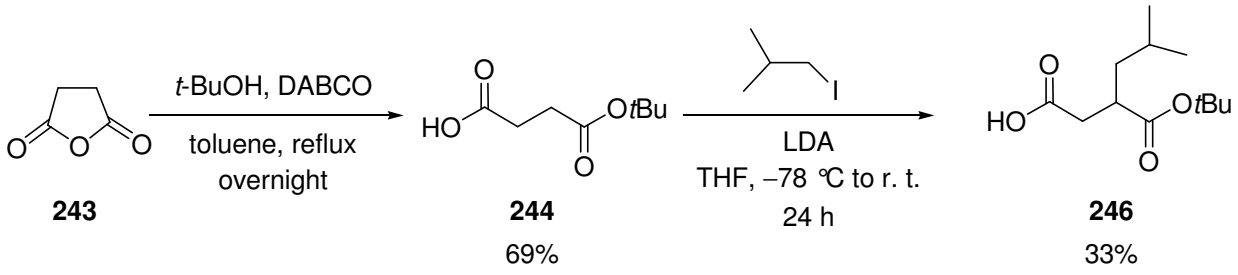
was then to synthesise a racemic α-*iso*-butyl-succinyl hydroxamic acid and to use it as test substrate in the coupling reaction with sila amino acid derivatives.

Bergmeier and co-workers reported a simple strategy to obtain various alkyl-succinate derivatives employing ring-opening reaction of succinic anhydride (**243**) with *tert*-butanol followed by alkylation of the opened product **244** with an alkyl halide in the presence of lithium di*iso*propyl amine, to afford the corresponding β-alkylated-succinic acid **245** (Scheme 77).[144b,144d]



Scheme 77. Synthesis of β-*n*-butyl-succinic acid **245** from ring-opening reaction of succinic anhydride **243**.

Using the same procedure, although slightly modified, β-*iso*-butyl-succinic acid **246** was synthesised. Succinic anhydride (**243**) and *tert*-butanol were reacted together with 1,4-diazabicyclo[2.2.2]octane (DABCO), as a catalyst, to give the opened product **244** in 69% yield. This latter compound reacted then with LDA and *iso*-butyl iodide to yield to the β-*iso*-butyl-succinic acid **246**, which was then isolated *via* chromatography on silica gel in 33% yield (Scheme 78).

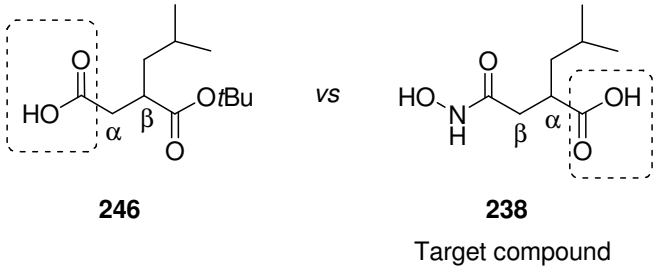


Scheme 78. Synthesis of β-*iso*-butyl-succinic acid **246** from ring-opening reaction of succinic anhydride (**243**).

The comparison of β-*iso*-butyl-succinic acid **246**, with the target compound **238**, features the alkyl substituent bonded to the carbon in β position relative to the carboxylic acid moiety, while the latter

Broughton, P. J. Warren, K. R. H. Wooldridge, D. E. Wright, *J. Chem Soc., Perkin Trans 1* **1975,** 830-841. f) B. J. Broughton, P. J. Warren, K. R. H. Wooldridge, D. E. Wright, W. D. Ollis, R. J. Wood, *J. Chem Soc., Perkin Trans I* **1975,** 842-846.

features an α-alkylated system (Figure 28). The synthetical pathway to the target **238** should now involve the carboxylic acid moiety of compound **246** to be converted into an hydroxy amide rest. The thus formed α-*iso*-butyl-succinyl hydroxamic ester could then undergo de-esterification to form the target α-*iso*-butyl-succinyl hydroxamic acid **238**.

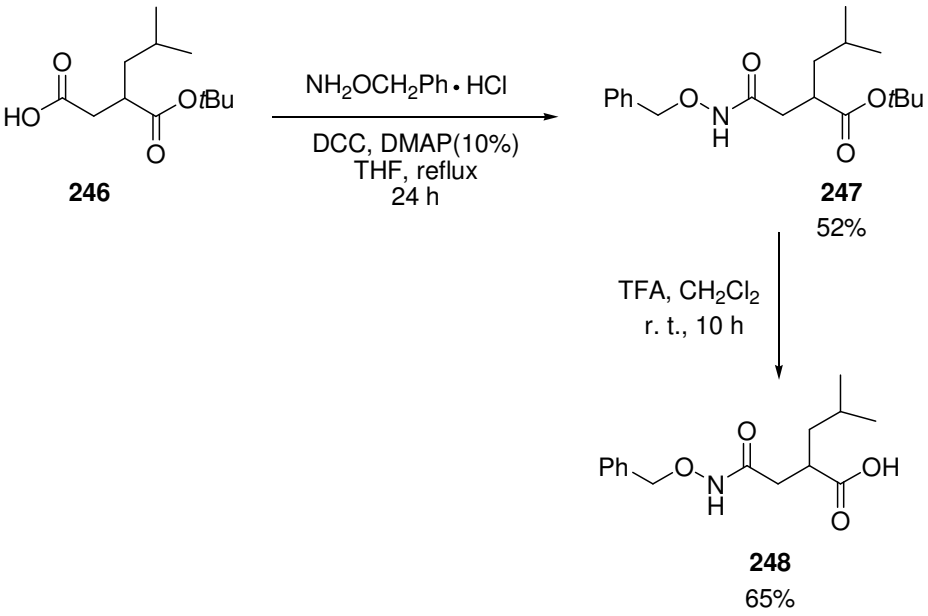


246 **238**

Target compound

Figure 28. Comparison between the structure of the already synthesised **246** and the structure of the target molecule **238**.

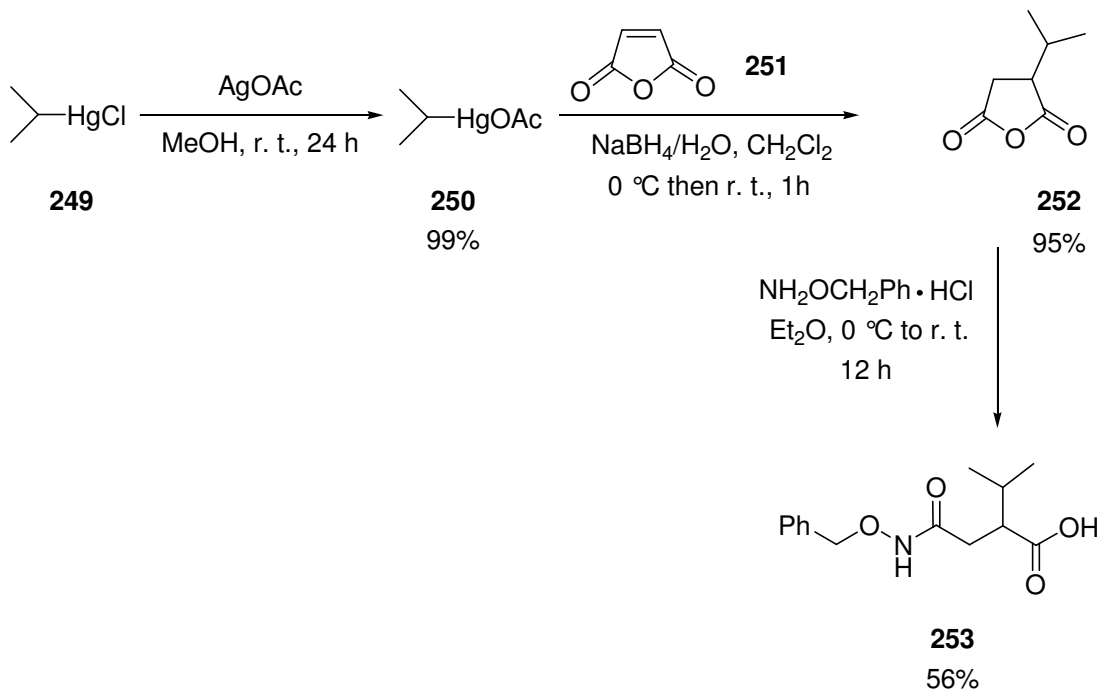
Therefore, β-*iso*-butyl-succinic acid **246** was dissolved in tetrahydrofurane and to the mixture was added benzyl hydroxyl amine (derived from the corresponding hydrochloride), DCC and DMAP (10 mol%). The reaction mixture was heated to reflux for 24 hours and then the amide **247** was afforded in 52% yield. The removal of the *tert*-butoxy group protecting the ester was provided dissolving the formed compound **247** in dichloromethane and treating it with trifluoroacetic acid (TFA) to yield to *N*-benzyl-protected α-*iso*-butyl-succinyl hydroxamic acid **248** in 65% yield (Scheme 79).



Scheme 79. Preparation of *N*-benzyl-protected α-*iso*-butyl-succinyl hydroxamic acid **248** from β-*iso*-butyl-succinic acid **246**.

Protection of the hydroxyl group could prevent this moiety from taking part to the subsequent coupling with the silyl amino acid derivative. The removal of the benzyl group could be effected in a later stage under reductive mild condition, as hydrogenation.

Furthermore, an analogue of compound **248** was synthesised, which could be used as test-substrate in the coupling reaction with the silyl amino acid derivative. For this purpose, *iso*-propyl mercury chloride (**249**) underwent reaction with silver acetate to yield *iso*-propyl mercury acetate (**250**) in quantitative yield.[145] This latter compound reacted then with maleic anhydride (**251**) in dichloromethane at 0 °C. To the solution was then added sodiumborohydride ($NaBH_4$) and the mixture was warmed at room temperature 2 hours to afford *iso*-propyl-succinic anhydride (**252**) in 95% yield. The alkylated anhydride **252** reacted then with benzyl hydroxyl amine (derived from the corresponding hydrochloride) to afford *N*-benzyl-protected α-*iso*-propyl-succinyl hydroxamic acid **253** in 56% yield (Scheme 80).

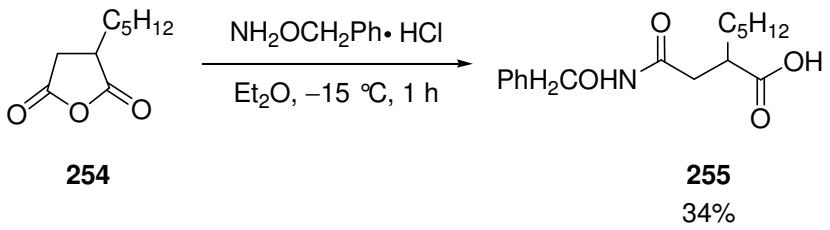


Scheme 80. Preparation of *N*-benzyl-protected α-*iso*-propyl-succinyl hydroxamic acid **253**.

The ^{1}H NMR spectrum of compound **253** was compatible with the formation of only one regioisomer from the ring-opening reaction of anhydride **252**. The product could be identified as *N*-benzyl-protected α-*iso*-propyl-succinyl hydroxamic acid **253** and not the corresponding β-*iso*-propyl isomer by comparison with ^{1}H NMR data already reported in literature. In fact, a similar anhydride-opening reaction was discussed by Ollis and co-workers, in which α-*n*-pentyl-succinyl

[145] E. Veri thanks Arno Claßen for the generous gift of *iso*-propyl chloride.

hydroxamic acid (**255**) was synthesised regioselectively from *n*-pentyl-succinic anhydride (**254**) (Scheme 81).[144b]

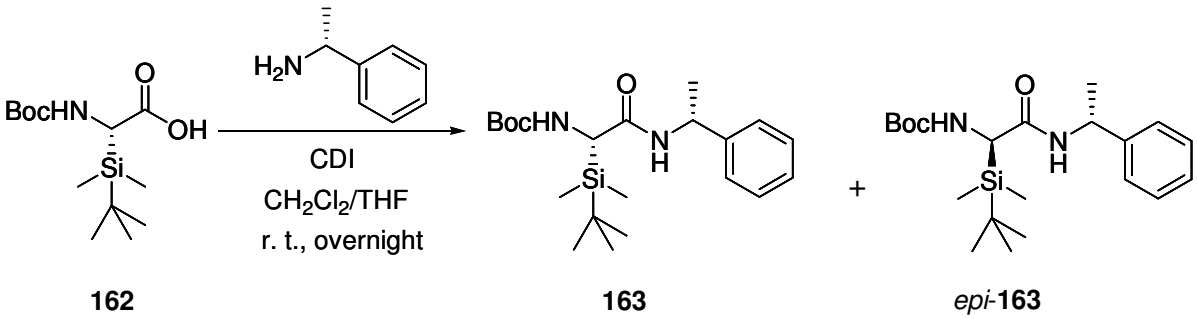


Scheme 81. Regioselective synthesis of α-*n*-pentyl-succinyl hydroxamic acid **255** from *n*-pentyl succinic anhydride (**254**).

3.6.3 Synthetical Approach to the α-Silyl α-Amino Acid Building Block

With the α-*iso*-butyl-succinyl hydroxamic acid **248** in the hand, the synthesis of the α-silyl α-amino acid core, the other building block of the silyl modified MMP inhibitor, was considered. In this section, an attempt to synthesise an α-silyl α-amino amide (analogous to compound **239**, section 3.6.1.2) will be discussed

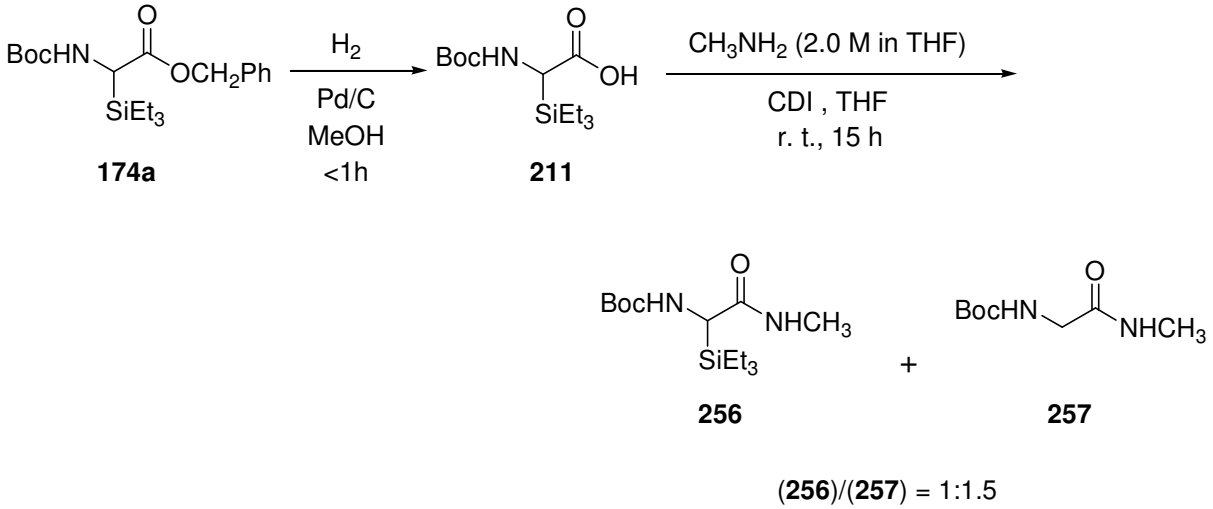
A literature example of synthesis of an α-silyl α-amino amide, had been reported by Sieburth and co-worker, coupling *N*-Boc-protected 2-*tert*-butyldimethylsilyl-2-amino acetic acid (**162**) with the primary amine (*R*)-(+)-α-methyl benzyl amine in the presence of carbonyldiimidazol (CDI).[101] *N*-Boc-protected 2-*tert*-butyldimethylsilyl-2-amino acetamide (**163**) was obtained as an inseparable mixture with its epimer, *epi*-**163** [ratio (**163**):(*epi*-**163**) = 4:1] (Scheme 82).



Scheme 82. Synthesis of *N*-Boc-protected 2-*tert*-butyldimethylsilyl-2-amino acetamide (**163**) from *N*-Boc-protected 2-*tert*-butyldimethylsilyl-2-amino acetic acid (**162**)

The reported protocol was then applied to *N*-Boc-protected 2-triethylsilyl-2-amino acetic acid substrate (**211**) (previously synthesised from the corresponding ester **174a**), which underwent reaction with methyl amine in the presence of CDI, for 15 hours. The ^{13}C NMR analysis of the crude reaction mixture featured one carbonyl signal at δ 170.5, that matches the chemical shift of an

amidic carbonyl, while the signal attributed to the substrate **211** at δ 179.4 was no more present. The ^{1}H NMR spectrum of the crude mixture confirmed the presence of the *N*-Boc-protected 2-triethylsilyl-2-amino-*N*-methyl acetamide (**256**) but pointed out the contemporary formation of its desilylated derivative **257**, whose characteristic was a doublet at δ 3.73, representing the methylene group in the α position relative to the amidic carbonyl. The calculated ^{1}H NMR ratio [(**256**)/(**257**) = 1:1.5] resulted favourable to the desilylated product (Scheme 83).

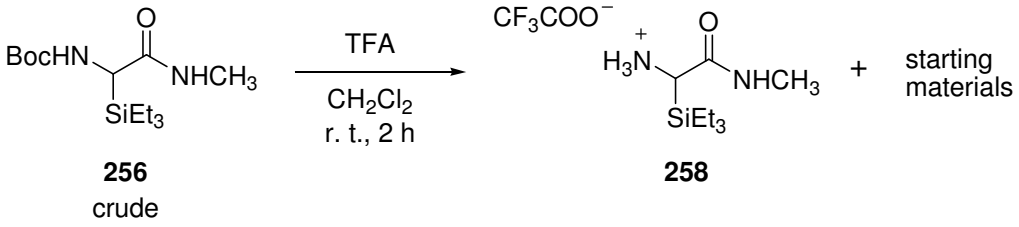


Scheme 83. Synthesis *N*-Boc-protected 2-triethylsilyl-2-amino-*N*-methyl acetamide (**256**) and of its desilylated derivative **257**.

Any effort to isolate the desired acetamide **256**, either by purification via chromatography on silica gel and filtration on Florisil®, remained unsuccessful, since only desilylated amide **257** and *tert*-butyl silanol as by-products could be recovered.

The removal of the Boc-protecting group of the acetamide **256** could be afforded by reaction with trifluoroacetic acid.[146] A try in this direction was performed on a crude reaction mixture of *N*-Boc-protected 2-triethylsilyl-2-amino-*N*-methyl acetamide (**256**) and its desilylated derivative **257**, the ratio of which was similar to the depicted in Scheme 83, in presence of TFA for 2 hours. ^{1}H NMR analysis of the crude mixture featured the partial removal of the Boc group from the lower intensity of the signal attributable to the *tert*-butyl group of this latter, but a quantitative result could not be reported, since the mixed composition of the starting materials (Scheme 84). This last result indicates, though, the possibility of hydrolysis of a Boc group of an α-silyl α-amino acetamide with TFA and the subsequent formation of its trifluoroacetic salt derivative **258** (Scheme 84).

[146] A first example of Boc removal of a *N*-Boc protected α-silyl α-amino acetamide was reported by Sieburth and co-worker (see ref. [101]).

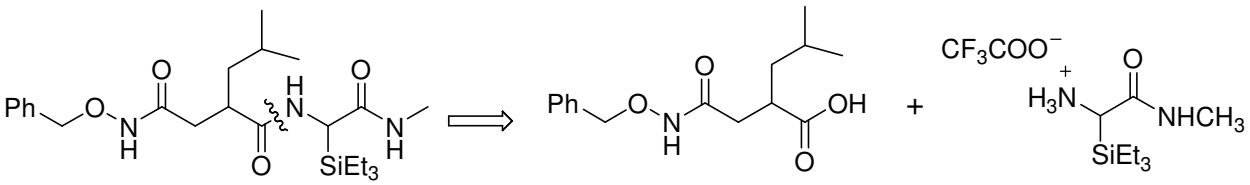


256 crude **258**

Scheme 84. Attempt of removal of a Boc group from a *N*-Boc-protected α-silyl α-amino acetamide.

3.6.4 Strategies of Coupling of the Two Building Blocks, Succinyl Hydroxamic Acid Derivative and α-Silyl α-Amino Acid Derivative

As discussed in a previous section 3.6.1.2, the amide-bond formation approach to the silyl modified MMP inhibitor involved the synthesis of two building blocks, the succinyl hydroxamic acid and the α-silyl α-amino acid derivative part. A precursor of α-*iso*-butyl-succinyl-hydroxamic acid, compound **248**, could be prepared. More difficult proved the synthesis of the α-silyl α-amino acid derivative, as the trifluoroacetic salt of 2-triethylsilyl-2-amino-*N*-methyl acetamide **258** (Figure 29).



259 **248** **258**

Figure 29. Disconnection approach to the silyl modified MMP inhibitor derivative **259**.

It appeared necessary, at this point, to investigate an alternative synthetic strategy that could yield the silyl modified MMP inhibitor derivative **259**. The option thus considered involved a first disconnection of the amidic bond of the terminal silyl amide of compound **259**, and a subsequent disconnection of the amidic bond between the succinyl hydroxamic and the α-silyl α-amino acid core of compound **261**. Therefore *N*-benzyl-protected α-*iso*-butyl-succinyl hydroxamic acid (**248**) and 2-triethylsilyl-2-amino benzyl acetate (**260**) arose to be the two desired building blocks in the new synthesis (Figure 30).

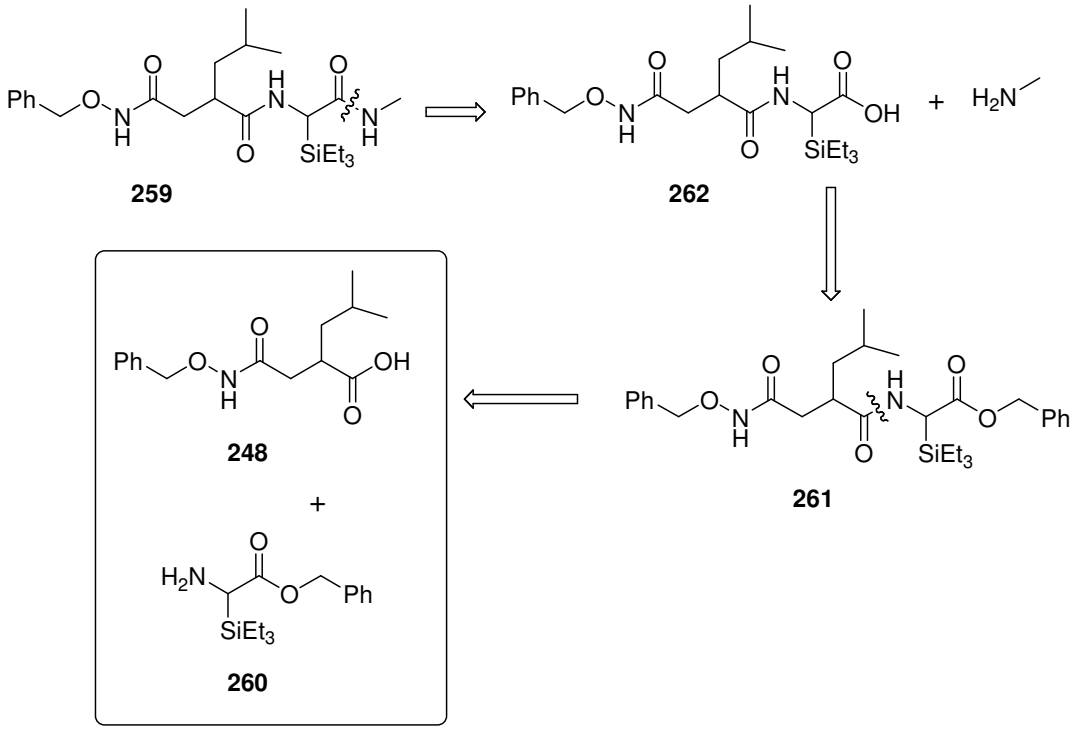
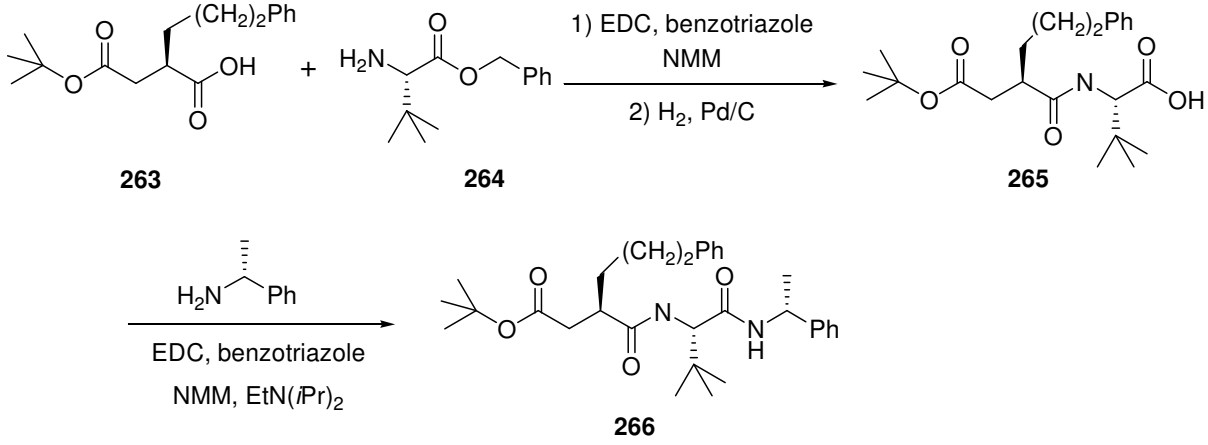


Figure 30. Retro-synthetic approach to the silyl modified MMP inhibitor derivative **259**.

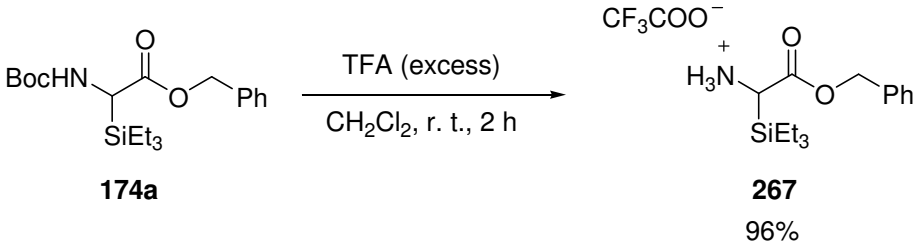
The discussed retro-synthetic approach had been supported by a work of Fray and Ellis in 1998.[147] In their investigations, an α-alkyl-succinic acid **263** was coupled with *L-tert*-leucine benzyl ester (**264**) in the presence of *N*-dimethylamino-propyl-*N*'-dimethyl carbodiimide (EDC), hydroxybenzotriazole and *N*-methyl morpholine (NMM), and de-esterificated to afford the adduct **265**. This latter was then coupled with (*R*)-(+)-α-methyl benzyl amine in the presence of the previous coupling reagents and Hünig's base to yield to the MMP inhibitor intermediate analoge **266** in almost quantitative yields (Scheme 85).



Scheme 85. Synthesis of the MMP inhibitor intermediate **266**.

[147] M. J. Fray, D. Ellis, *Tetrahedron* **1998**, *54*, 13825-13832.

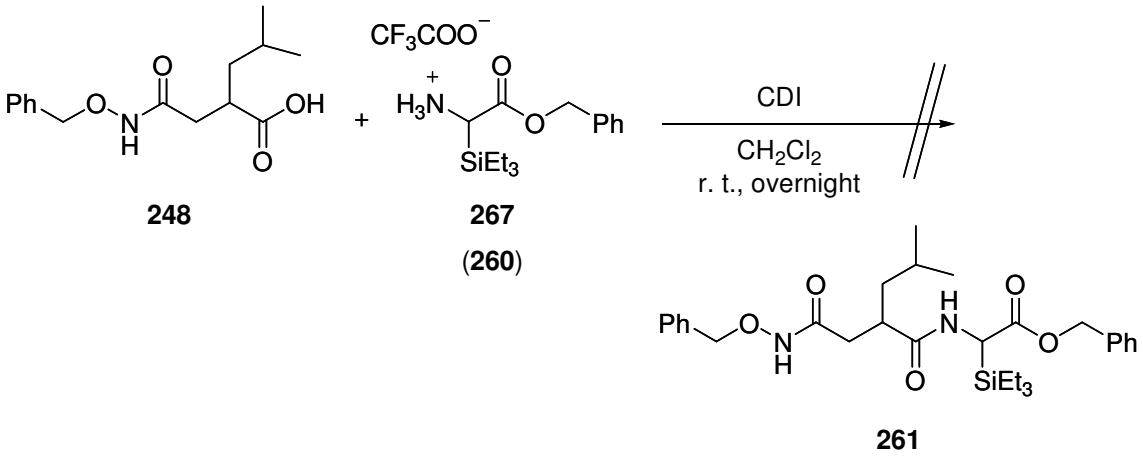
An analogous strategy was then applied to the synthesis of our silyl modified MMP inhibitor derivative **259**. Thus, the trifluoroacetic salt of 2-triethylsilyl-2-amino benzyl acetate (**267**) (salt of compound **260**, see Figure 30) was prepared from *N*-Boc-protected 2-triethylsilyl-2-amino benzyl ester (**174a**) and obtained in almost quantitative yields (Scheme 86).



174a **267** 96%

Scheme 86. Removal of the Boc group from *N*-Boc-protected 2-triethylsilyl-2-amino benzyl acetate (1**74a**).

The formed trifluoroacetic salt **267** was then added to a solution of succinyl hydroxamic acid **248** (1 equiv.) and carbonyldiimidazol (1.1 equiv.) in dichloromethane and stirred at room temperature overnight.[101] The GC-MS analysis of the crude reaction mixture showed clearly the presence of two peaks, whose fragmentation patterns were fitting to the both starting material of the reaction, compound **248** and compound **267** (in the form of neutral compound **260**) (Scheme 87).

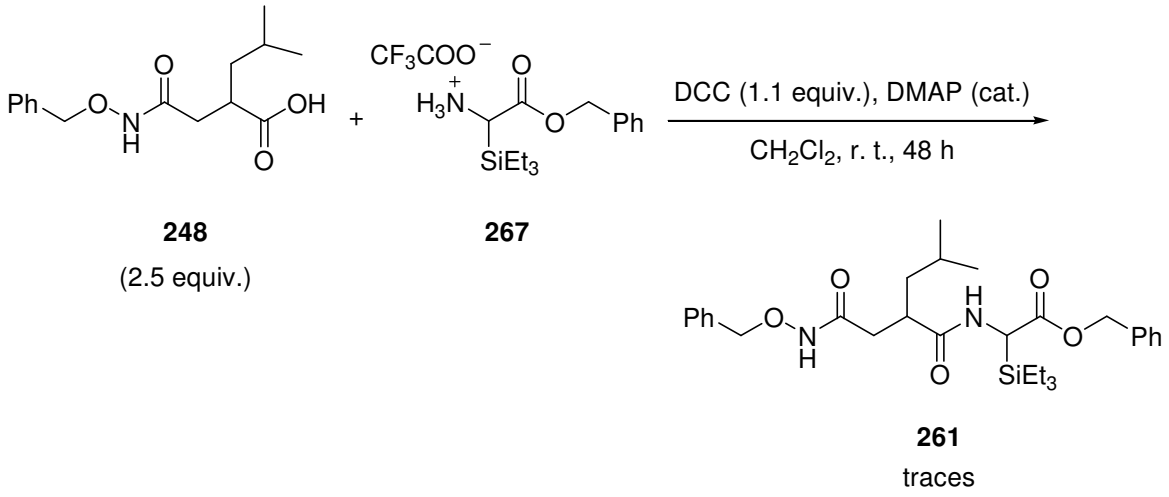


248 **267** (**260**) **261**

Scheme 87. Attempt of coupling between the α-*iso*-butyl-succinyl hydroxamic acid **248** and the silyl amino acetate **267** in the presence of CDI.

A further attempt was performed adding compound **267** to an excess of the succinyl hydroxamic acid **248** (2.5 equiv.) in the presence of *N*,*N'*-dicyclohexylcarbodiimide (DCC) (1.1 equiv.) and catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine as coupling reagents instead of

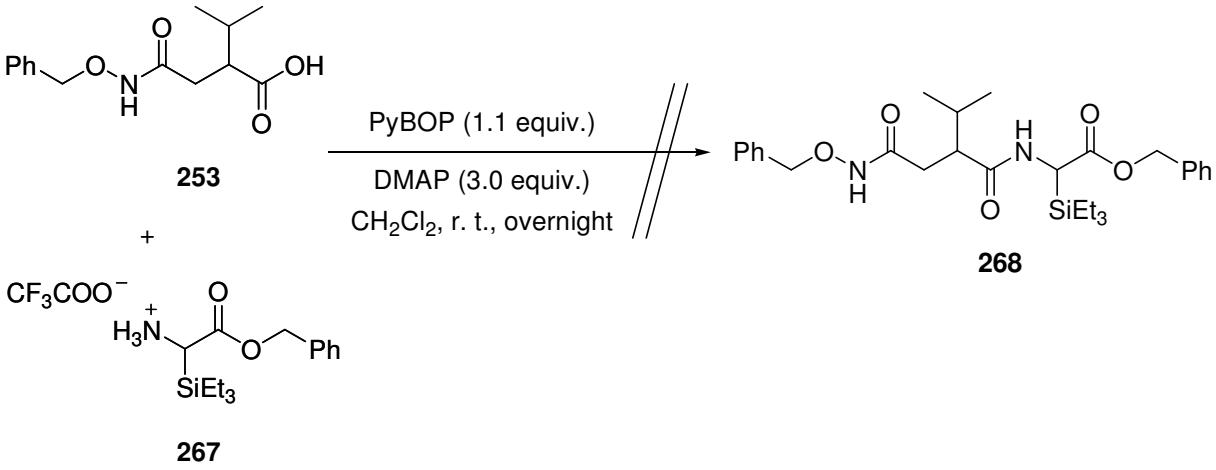
carbonyldiimidazol.[148] After 48 hours, the conversion of the reaction partners **248** and **267**, monitored by ^{1}H NMR analysis, was barely noticeable (Scheme 88).



Scheme 88. Attempt of coupling between the α-*iso*-butyl-succinyl hydroxamic acid **248** and the silyl amino acetate **267** in the presence of DCC/DMAP.

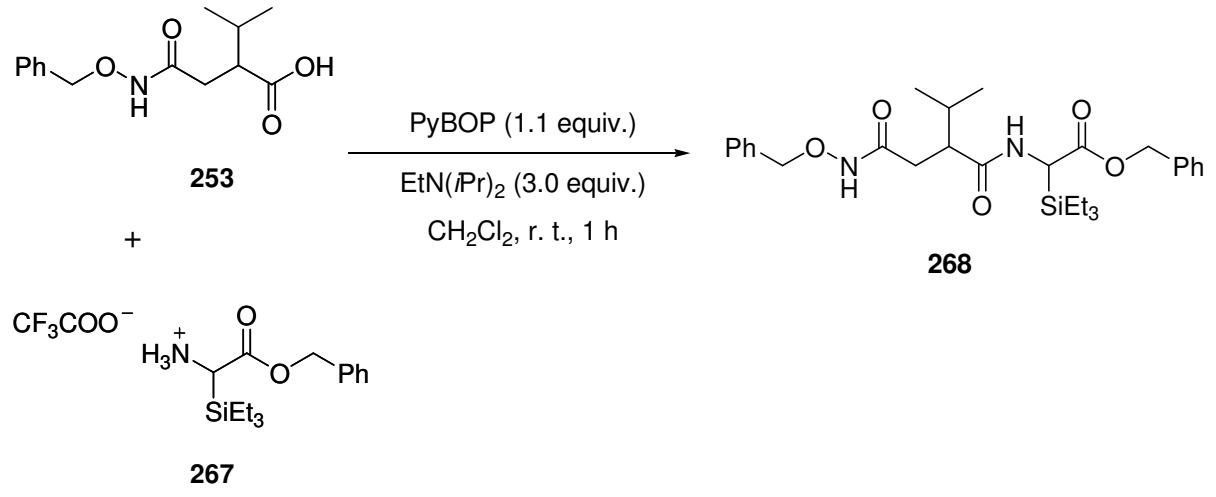
In the wide field of coupling reagents for modified peptides, PyBOP® [(1H-1,2,3,-benzotriazol-1-yloxy)-tris(pyrrolidino)-phosponium hexafluorophosphate] appears as one of the most famous.[149] The named reagent (1.1 equiv.) and DMAP (3.0 equiv.) were added to a solution of the trifluoroacetic salt of the 2-triethylsilyl-2-amino benzyl acetate (**267**) and *N*-benzyl-protected α-*iso*-propyl-succinyl hydroxamic acid **253** (1 equiv.), analogous of compound **248**, and stirred overnight. After that time, the TLC analysis (pentane/ethyl acetate = 9:1) showed the presence of the starting materials and of the PyBOP®, without formation of the desired adduct **268** (Scheme 89).

[148] About the use of DCC as coupling reagent in peptide chemistry, see for example: S. Han, Y. Kim, *Tetrahedron* **2004**, *60*, 2447-2467 and references cited therein.
[149] See for example: E. Frèrot, J. Coste, A. Pantaloni, M. -N. Dufour, P. Jouin, *Tetrahdron* **1991**, *47*, 259-270 and references cited therein. See also C. Najera, *Synlett* **2002**, 1388-1403.



Scheme 89. Attempt of coupling between the α-*iso*-propyl-succinyl hydroxamic acid **253** and the silyl amino acetate **267** in the presence of PyBOP/DMAP.

Last essay in this field was performed in the presence of PyBOP®/EtN(*i*Pr)$_2$ to assist the formation of the adduct **268**. A mixture of *N*-benzyl-protected α-*iso*-propyl-succinyl hydroxamic acid **253** and PyBOP® was combined to a solution of the silyl amino acetate **267** and ethyldi*iso*propylamine (3.0 equiv.) in dichloromethane. The reaction mixture was then stirred for 1 hour. The TLC analysis of the crude mixture (pentane/ethyl acetate = 9:1) evidenced the complete absence of the substrates. The ^{1}H NMR analysis of the crude reaction mixture featured also the absence of the starting materials and the presence of a product, which was consistent to the desired silyl modified MMP inhibitor derivative **268** (Scheme 90).



Scheme 90. Product of coupling between α-*iso*-propyl-succinyl hydroxamic acid **253** and the silyl amino acetate **267**.

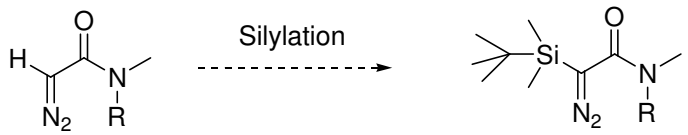
3.6.5 Studies towards an Analogue of a Matrix Metalloproteinase Inhibitor: Conclusions

Various synthetic strategies were considered and attempted towards the synthesis of the two building blocks of a silyl modified succinyl hydroxamic acid based MMPs inhibitor such as **230**. The amide-bond formation approach to compound **230** (discussed in section 3.6.1.2) remained unsuccessful. In fact, α-*iso*-butyl-succinyl hydroxamic acid **248**, precursor of the succinyl hydroxamic acid building block **238**, was synthesised in 65% yield, while the attempted synthesis of the silyl amino acid derivative core, the trifluoroacetic salt of 2-triethylsilyl-2-amino-*N*-methyl acetamide (**258**), analogous to compound **239**, failed.

An alternative approach to compound **230** was attempted through the coupling of succinyl hydroxamic acid **248** (or the corresponding *iso*-propyl analoge **253**) and the trifluoroacetic salt of 2-triethylsilyl-2-amino benzyl acetate (**267**) using various coupling reagents. Between them, PyBOP® combined with ethyldi*iso*propylamine, appeared the most promising.

3.6.6 Attempts to Synthesise α-Silyl α-Diazo Acetamides

Together with the investigations aimed to the formation of a silyl modified MMPs inhibitor, the synthesis of silylated diazo amides was attempted, as shortly reported in section 3.6.1.1. In this section we will discuss the attempts to prepare 2-*tert*-butyldimethylsilyl-2-diazo *N*-methyl acetamide (**270**) and 2-*tert*-butyldimethylsilyl-2-diazo *N*-benzyl-*N'*-methyl acetamide (**271**) from direct silylation of the corresponding 2-diazo *N*-methyl acetamide (**269**) and 2-diazo *N*-methyl-*N'*-benzyl acetamide (**181e**) (Figure 31).

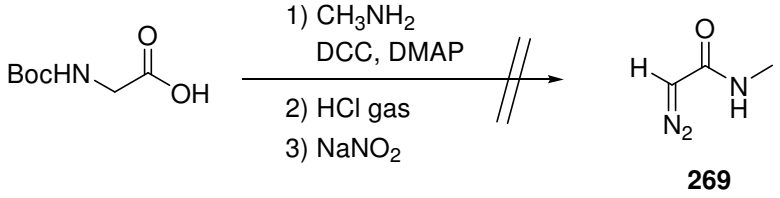


269 R = H
181e R = CH_2Ph

270 R = H
271 R = CH_2Ph

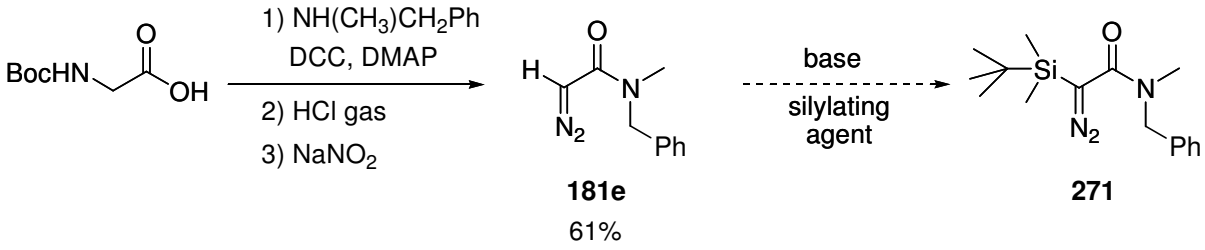
Figure 31. Silyl acetamides **270** and **271** and their precursors acetamides **269** and **181e**.

The preparation of 2-diazo *N*-methyl acetamide (**269**) was performed following the procedure described in section 3.1. *N*-Boc glycine reacted with methyl amine and the formed condensation product underwent removal of the Boc protecting group with hydrochloride gas. Subsequently diazotisation with sodium nitrite afforded the formation of a mixture of products, and between them the expected amide **269** was formed only in a little amount. After the purification *via* chromatography on silica gel no more desired product **269** could be detected (Scheme 91).



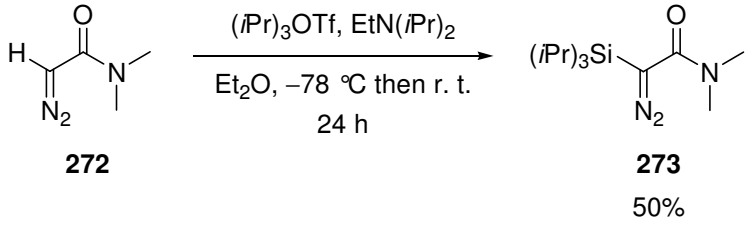
Scheme 91. Attempt of synthesis of 2-diazo *N*-methyl acetamide (**269**).

Moreover, 2-diazo *N*-benzyl-*N'*-methyl acetamide (**271**) was prepared following the procedure depicted in Scheme 91 in 61% yield and largely explained in section 3.1 (Scheme 92).



Scheme 92. Synthesis of 2-diazo *N*-benzyl-*N'*-methyl acetamide (**181e**) and its possible derivatisation.

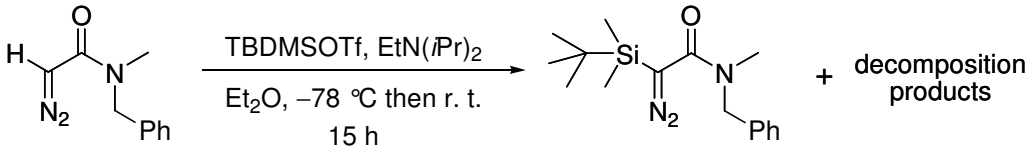
The only report in the literature about direct silylation of a diazo amide is by Maas and co-workers, which discussed the reaction 2-diazo *N,N'*-dimethyl acetamide (**272**) and tri*iso*propylsilyl trifluoromethanesulfonate in the presence of Hünig's base: 2-tri*iso*propylsilyl-2-diazo *N,N'*-dimethyl acetamide (**273**) was afforded in 50% yield (Scheme 93).[114a]



Scheme 93. Synthesis of 2-tri*iso*propylsilyl-2-diazo *N,N'*-dimethyl acetamide (**273**) from 2-diazo *N,N'*-dimethyl acetamide (**272**).

Therefore, to a solution of 2-diazo *N*-benzyl-*N'*-methyl acetamide (**181e**) and EtN(*i*Pr)$_2$ in diethylether was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) at –78 °C. The reaction mixture was stirred then for 15 hours, till it reached the temperature of *ca.* 10 °C. The ^{1}H NMR analysis of the crude product showed the absence of the starting material diazo acetamide **181e**, since no singlet was anymore present at δ 5.09, consistent chemical shift to the hydrogen

bonded to the carbon in α-position relative to the diazo group. The ^{1}H NMR spectrum pointed out the possible presence of the expected 2-*tert*-butyldimethylsilyl-2-diazo *N*-benzyl-*N'*-methyl acetamide (**271**), the characteristic of which was a singlet at δ 0.1 and 1.1 for the methyl and *tert*-butyl of the *tert*-butyldimethylsilyl group, respectively, and a singlet at δ 2.90 and δ 4.82 for the methyl and the benzylic methylene in the amide moiety (Scheme 94).



181e **271**

Scheme 94. Possible products of silylation of 2-diazo *N*-benzyl-*N'*-methyl acetamide (**181e**)

Furthermore the ^{1}H NMR analysis of the crude showed the presence of a by-product, which was supposed to originate by decomposition of the substrate **181e**, since was already present in little quantity in the starting material. The following purification *via* chromatography on silica gel did not allow to isolate the formed amide **271**, which decomposed on silica gel. A different purification method, such as distillation, could probably afford better results on the way to obtain the expected 2-*tert*-butyldimethylsilyl-2-diazo *N*-benzyl-*N'*-methyl acetamide (**271**).

3.7 Microwave Assisted Synthesis of α-Trialkylsilyl α-Diazo Ester Derivatives

In this section, a brief introduction on the main features that characterize a microwave assisted organic synthesis will be reported, followed by the discussion on the results of microwave assisted synthesis of α-trialkylsilyl α-diazo ester in the presence of rhodium(II) catalysts.

3.7.1 Microwave Radiation

Microwave chemistry has gained in the last years a wide attention, since the groups of Gedye[150] and Giguere and Majetich[151] published in 1986 early reports on acceleration of organic reactions through microwave heating. In recent years, the field of microwave assisted organic synthesis (MAOS), has gained a considerably increasing interest in modern chemistry.[152,153]

Microwave radiation is an electromagnetic irradiation in the frequencies range between 0.3 and 300 GHz, corresponding to wavelengths to 1 cm to 1m.[154] The microwave region of the electromagnetic spectrum lies between the IR and the radio frequencies. All the domestic microwave ovens, as well as the dedicated reactors for microwave synthesis, work at a frequency of 2.45 GHz, in order not to interfere with telecommunications frequencies. The energy associated with a microwave photon is 0.0016 eV which is too low to cleave molecular bonds, such as for example, the strong carbon-hydrogen bond that is expressed by an energy of 4.28 eV. Also, the weak hydrogen bond, that correspond to an energy of 0.04-0.44 eV, or even the Brownian motion can not be affected by microwave radiation. Therefore, in contrast to UV radiation and radiation of the visible spectrum, microwaves can not induce chemical reactions by direct absorption of energy. An acceleration of a chemical reaction by microwave irradiation is based on the "microwave dielectric heating" effect, which expresses the ability of a material or a reaction mixture to absorb microwave energy and to convert it into heat. Microwaves are electromagnetic waves composed by a magnetic and an electric field component, which is responsible of the wave-material interactions, and causes heating by two main mechanisms, the dipolar polarization and ionic conduction.[155,156]

[150] R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge, J. Rousell, *Tetrahedron Lett.* **1986**, *27*, 279-282.
[151] R. J. Giguere, T. L. Bray, S. M. Duncan, G. Majetich, *Tetrahedron Lett.* **1986**, *27*, 4945-4958.
[152] a) C. O. Kappe, *Angew. Chem.* **2004**, *116*, 6408-6443. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250-6284. b) *Tetrahedron* **2006**, *62* (19) (Dedicated Issue).
[153] a) J. Tierney, P. Lindström in *Microwave Assisted Organic Synthesis*, Backwell, Oxford, **2005**. b) P. Lindström, J. Tierney, B. Wathey, J. Westman, *Tetrahedron* **2001**, *57*, 9225-9283.
[154] C. O. Kappe, A. Stadler in *Microwaves in Organic and Medicinal Chemistry* (Eds.: R. Mannhold, H. Kubinyi, G. Folkers), Wiley, Weinheim, **2005**.
[155] D. R. Baghurst, D. M. P. Mingos, *Chem. Soc. Rev.* **1991**, *20*, 1-47.
[156] C. Gabriel, S. Gabriel, E. H. Grant, B. S. Halstead, D. M. P. Mingos, *Chem. Soc. Rev.* **1998**, *27*, 213-223.

3.7.2 Dielectric Properties of a Medium

The ability of a medium, for example a solvent, to conduce heat is dependant on the dielectric properties of the material.[154] The ability of a solvent to convert electromagnetic energy into heat is quantified from the so-called loss tangent, tan δ, which is expressed as the quotient tan δ = ε"/ε'.
ε" represents the dielectric loss, which is an indication of the efficiency with which energy is converted into heat, and ε' is the dielectric constant of the solvent which refers to the polarizability of the molecules in the electric field. In Table 7 are summarized tan δ, ε" and ε' values of some common solvents; high tan δ is required for efficient absorption, then for rapid heating. To a medium with a high dielectric constant ε', such as water (ε' = 80.4), may correspond a low tan δ value which does affect the ability of the solvent of efficient absorption of microwave radiations. In general, solvents can be classified as high (tan δ > 0.5), medium (0.1 < tan δ < 0.5), or low microwave-absorbing (tan δ < 0.1). Other common solvents without a permanent dipole, such as carbon tetrachloride, dioxane or benzene are considered microwave-transparent.

Table 7. Physical properties of common solvents.[157]

Solvent	*Boiling point (°C)*	*ε"*	*ε'*	*tan δ= ε"/ε'*	*Microwave absorbance*
Ethylene Glycol	197	49.950	37.0	1.350	very good
Ethanol	78	22.866	24.3	0.941	good
Water	100	9.889	80.4	0.123	medium
Dichloromethane	40	0.382	9.1	0.042	low
Toluene	110	0.096	2.4	0.040	low

It has to be pointed out that a low tan δ does not preclude the solvent to be used in a microwave assisted reaction; many reagents/reactants or catalysts possess a permanent dipolar moment that can confer to the reaction mixture the ability to interact with the microwave radiation, even in the presence of low absorbing solvents.

3.7.3 Microwave Effects

Despite the relative large amount of publications on microwave assisted chemistry, the exact reason why microwaves enhance chemical processes is still not fully understood. Some groups have hypothesized the existence of the so-called "microwave effect", which could be the consequence of a specific wave-matter interaction that leads to a decrease in activation energy or an increase in the pre-exponential factor in the Arrhenius equation, due to orientation of polar species in an

[157] B. L. Hayes in *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing, Matthews, NC, **2002**.

electromagnetic field.[158] Other researchers profile also the existence of specific effects of the microwave irradiation but rationalize them in terms of rapid heating and high temperatures that are reached in a microwave heated reaction, formation of microscopic or macroscopic hotspots, or selective heating of a specific component in the reaction mixture.[159]

Rate enhancement in a microwave assisted chemical reaction can be rationalized considering the following three possibilities:[152]

Thermal effects (kinetics)

Specific microwave effects

Non-thermal (athermal) microwave effects

The majority of the scientific community explains the observed rate enhancement only in terms of a thermal/kinetic effect, as a consequence of the high reaction temperature that can be rapidly obtained by irradiating a polar material in a microwave. In addition, microwave effects could be also caused by the unique nature of the microwave dielectric heating mechanism. These can be defined as accelerations of chemical transformations in a microwave field which can not be achieved or imitated by conventional heating, but which are still thermal effects. The scientific world agrees less when dealing with non-thermal (or athermal microwave) effects. These can be classified as accelerations of chemical transformations under microwave irradition that can not be rationalised in terms of kinetic effects. Essentially, it has been argued that non-thermal effects of microwave are due to the presence of the electric field, that leads to orientation effects of dipolar molecules and thus changes the pre-exponencial factor A or the activation energy (in term of entropy) in the Arrhenius equation.

3.7.4 Equipment in Microwave Chemistry

In the mid-1980s, at the beginning of microwave chemistry, the experiments were carried out using conventional multimode domestic microwave ovens.[154] They present some advantages, as their availability and the low price. The main drawback of these household instruments is the lack of control systems: it is difficult to monitor the temperature and the pressure and a reaction mixture can not be stirred easily. Furthermore, the pulsed irradiation (on-off duty cycles of the magnetron), and the resulting inhomogeneity of the microwave field leads to problems of reproducibility, since the irradiation occurs in the cavity and not directly in the reaction vessel (Figure 32).

[158] a) L. Perreux, A. Loupy, *Tetrahedron* **2001**, *57*, 9199-9223. b) A. de la Hoz, A. Dìaz-Ortiz, A. Moreno, *Chem. Soc. Rev.* **2005**, *34*, 164-178.

[159] a) N. Kuhnert, *Angew. Chem.* **2002**, *114*, 1943-1946. *Angew. Chem. Int. Ed.* **2002**, *41*, 1863-1866. b) C. R. Strauss, *Angew. Chem.* **2002**, *114*, 3741-3743. *Angew. Chem. Int. Ed.* **2002**, *41*, 3589-3590.

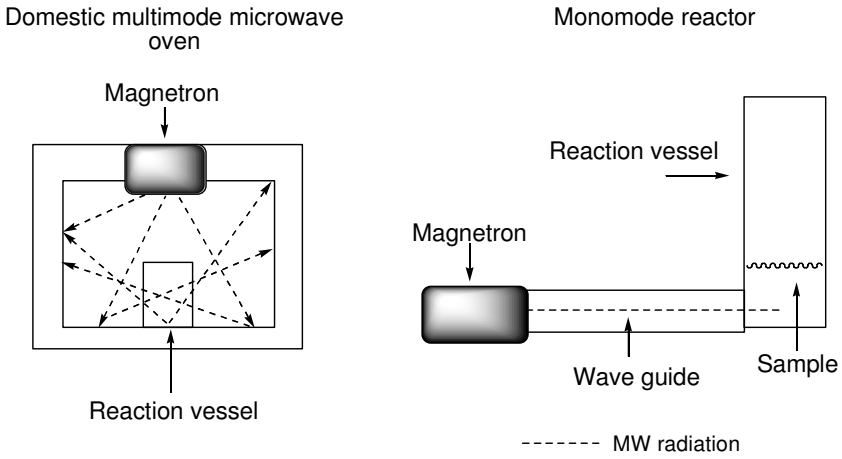


Figure 32. Domestic multimode microwave oven *vs* monomode microwave reactor.

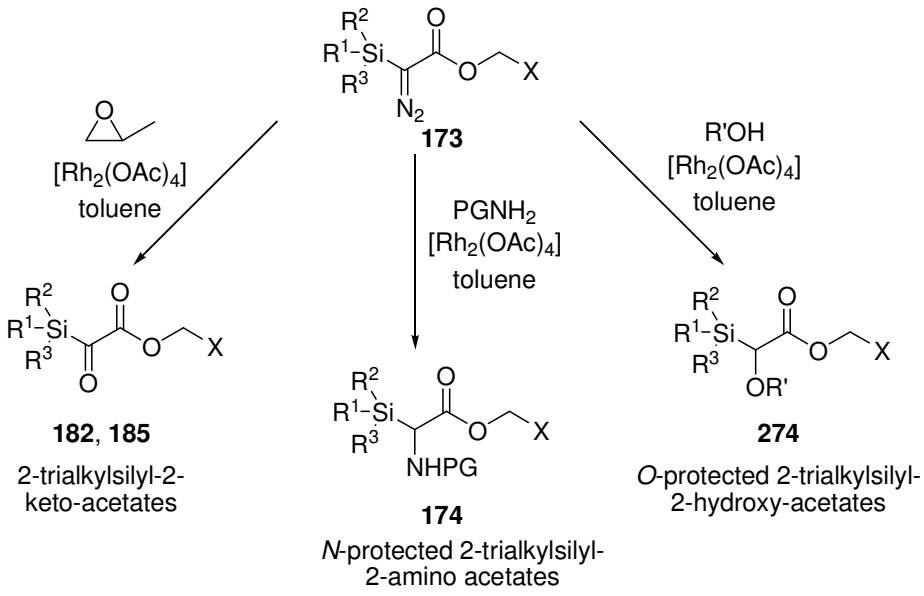
In contrast, most of the microwave reactors produced today are equipped with a built-in magnetic stirrer, a direct control of the temperature with a IR sensor or a fiber-optic thermometer, and software that enables the control and the direct on line monitoring of the temperature/pressure system by regulation of the output power. Modern microwave instruments are today designed following two different guidelines: in multimode reactors the microwaves that enter the cavity are reflected by the walls in the large volume (similar in this to a domestic microwave oven), while in monomode cavities only one mode is present and the wave is directed through a designed wave guide to the reaction vessel mounted at a fixed distance from the magnetron, which is the radiation source (see Figure 32).

3.7.5 Studies on Microwave Assisted Synthesis of 2-Trialkylsilyl-2-Diazo Acetates

Microwave heating is often applied to known conventional thermal reactions in order to have a rate acceleration of the reaction and reducing the overall process time. The aim of this research was therefore to apply microwave heating to several of the described synthetic methods, for which the reactivity pattern under conventional heating were already completely known. Interesting appeared the fact that the microwave irradiation could shorten the reaction time and have influence on the selectivity.

As already discussed from section 3.1 to 3.4, this project had been focused on derivatisation of 2-trialkylsilyl-2-diazo acetates **173** (Scheme 95). The named substrates can react with propylene oxide in the presence of rhodium(II) tetraacetate, yielding to 2-trialkylsilyl-2-keto-acetates as **182** or **185** (see section 3.2.1), or undergo rhodium(II) catalysed reaction with carbamates to form *N*-protected 2-trialkylsilyl-2-amino acetates **174** (see section 3.3). 2-Trialkylsilyl-2-diazo acetates can also react with alcohols in the presence of rhodium(II) tetraacetate to form *O*-protected 2-

trialkylsilyl-2-hydroxy-acetates **271**.[160] The named synthetic methods, usually performed under conventional heating, were repeated and performed under microwave irradiation.



X=aryl or alkyl, R^1=R^2=R^3= alkyl, R'=aryl or alkyl, PG=Boc or Cbz

Scheme 95. Derivatisation of 2-trialkylsilyl-2-diazo acetates **173**.

3.7.5.1 "Translating" Conventional Heating Methods

The first item of these investigations was to translate reaction parameters, as time and temperature, in parameters suitable for microwave heating. The reactions depicted in Scheme 95 were all performed in anhydrous toluene, usually at 50 °C in a reaction time comprised between 12 and 72 hours.

A "microwave translation" of these conditions needed a preliminary consideration about the solvent: as discussed in section 3.7.2, toluene is not a good solvent for microwave irradiation, since its low loss tangent value (tan δ = 0.040) permits only a very low absorbance of the microwave radiation. However, the real microwave absorbance of a reaction mixture could be different from the neat solvent, since the species participating to the reaction could posses a dipole moment and therefore interact with the microwave radiation.

Moreover, a recent trend in microwave assisted organic chemistry is to perform reaction in sealed vessels in single mode-microwave reactors with high power density. Under this autoclave-type conditions, microwave absorbing solvents with low boiling point for example methanol, can be superheated to temperatures 100 °C higher than their boiling points under microwave irradiation.

[160] S. Saladin, PhD Thesis, Aachen **2004**.

All commercially-available industrial microwave reactors are controlled by software packages which commonly are programmed for a temperature-controlled program.[161] Using this program, the system generally tries to reach the set temperature as fast as possible by applying the maximum microwave output power. The same software calculates, for every solvent, the conversion of the temperature and time necessary for the "classical" reaction into temperature and time associated to a microwave reaction. Some softwares offer the possibility to work at constant microwave power or constant pressure inside the sealed vessel, but since the reaction temperature is the most crucial parameter in the ongoing of a reaction, these program variations are used rarely.

3.7.5.2 From Conventional to Microwave Heating : a Practical Example

The microwave reactor used in the present study was the Discover® Labmate™ single-mode reactor commercialised by CEM corporation.[162] It can be used between –80 °C to +300 °C, monitoring the temperatures by a standard IR thermometer.

As discussed before, the standard conditions for the reaction reported in Scheme 95 included the use of toluene as solvent, 50 °C temperature and reaction times between 12 and 72 hours.

The software of the instrument suggested a conversion of 50 °C in toluene in three possible temperature: 75, 100 or 150 °C, which could correspond to reaction times of 5 to 30 minutes (Table 8). The pressure inside the sealed vessel could be set at circa 4 atmospheres and usually remained constant during the irradiation. The first set parameters were the starting points for preliminary investigations in the field of microwave assisted derivatisation of α-trialkylsilyl-α-diazo acetates.

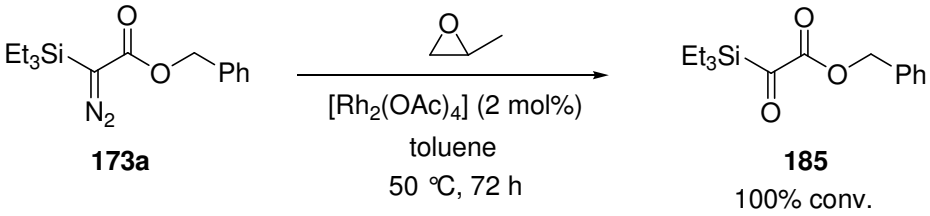
Table 8. Conventional heating *vs* microwave heating conditions.

Conventional heating	***Microwave heating***
toluene	toluene
50 °C	75, 100, 150 °C
12 to 72 h	5 to 30 min.

[161] C. O. Kappe, A. Stadler in *Microwaves in Organic and Medicinal Chemistry* (Eds.: R. Mannhold, H. Kubinyi, G. Folkers), Wiley, Weinheim, **2005**.
[162] http://www.cem.com/synthesis/discover.asp

3.7.5.3 Microwave Assisted Synthesis of 2-Trialkylsilyl-2-Keto-Acetates

As already discussed in section 3.2.1, 2-trialkylsilyl-2-keto-acetates **182** and **185** could be synthesised following an established protocol.[116] The synthesis of 2-triethylsilyl-2-keto-benzyl acetate (**185**) starting from 2-triethylsilyl-2-diazo acetate (**173a**) was considered. The latter compound was dissolved in anhydrous toluene and after addition of rhodium(II) tetraacetate as catalyst and propylene oxide underwent to complete conversion after heating in an oil-bath for 72 hours (as detected by ^{1}H NMR analysis) (entry 1, Table 8). Characteristic of the product **182** was a singlet at δ 5.26 in the ^{1}H NMR spectrum representing the benzylic methylene (singlet at δ 5.19 for the substrate) (Scheme 96).



Scheme 96. Synthesis of 2-triethylsilyl-2-keto-benzyl acetate **185** under conventional heating.

The synthesis of compound **185** was then attempted under microwave irradiation, starting from the substrate **173a** first at 75 °C for 30 minutes. The ^{1}H NMR analysis of the crude mixture showed still the presence of 50% of the substrate, and the formation of 38% of the expected product **185** (entry 2, Table 9). Furthermore, the ^{1}H NMR analysis indicated the formation of triethylsiloxane **275**, characterised from a quartet at δ 0.45, corresponding to the methylene protons of the silyl substituent group. The increase of the output power to 200 W enhanced slightly the formation of the keto-acetate **185** to 44% in the products mixture (entry 3, Table 9). The complete conversion of the substrate, the formation of 75% of the desired keto-acetate **185** and of 25% of triethylsiloxane **275** were obtained by microwave irradiation at 100 °C after 30 minutes at 200 W (entry 4). The same reaction was then performed under conventional heating in a preheated oil-bath at 100 °C for 30 minutes and the ^{1}H NMR analysis indicated clearly the absence of unreacted substrate (entry 5). The ratio of the products distribution could not be determined because of the presence between δ 1 and 0 of a complex signal system belonging to the triethylsiloxane and to additional side-products. The GC-MS confirmed the absence of the substrate, the presence of 23% of the keto-acetate **185** and of a large quantity of the other side-product, the fragmentation pattern of which allowed to identify it as a triethylsiloxane derivative; 4% of the simple triethylsiloxane **275** was also present.

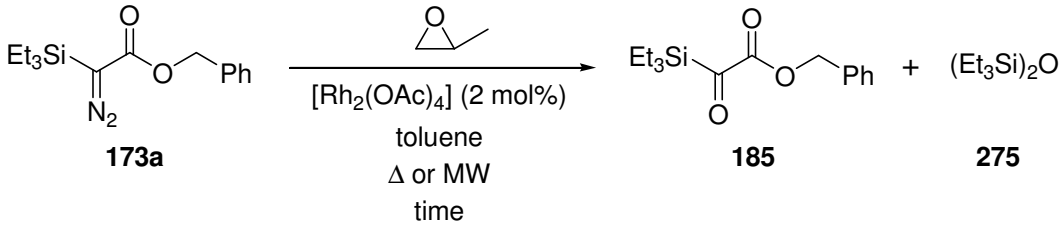


Table 9. Synthesis of 2-triethylsilyl-2-keto-benzyl acetate **185** under conventional heating and microwave irradiation.

Entry	*Heating*	*Temperature (°C)*	*Rxt. time*	*Power (W)*	*Unreacted Substrate (173a) (% NMR)*	*Product (185) (% NMR)*	*Side-product (275) (% NMR)*
1	Δ[a]	50	72 h	--	0	100	0
2	MW[a]	75	30 min.	100	50	38	12
3	MW[a]	75	30 min.	200	44	44	12
4	MW[a]	100	30 min.	200	0	75	25
5	Δ[a]	100	30 min.	--	0[b]	23[b]	4[b,c]
6	MW	150	20 min.	200	32[b]	5[b]	11[b,c]
7	MW	150	30 min.	200	0[b]	29[b]	7[b,c]

[a] 0.17 mmol of substrate **173a** in 1.0 mL toluene. [b] GC-MS ratio. [c] Presence of a further decomposition product.

The other two attempts reported in entry 6 and 7 (Table 9) (150 °C, 20 or 30 minutes, 200 W) confirmed the formation of relevant amounts of side-product.

It is worth to note that, transformation involving diazo carbonyl derivatives are usually performed at temperatures between 50-70 °C.[163] due to presumed instability of the latter substrates at higher temperatures. Thus, the substrate **180a** was heated in toluene in the microwave reactor at 100 °C for 30 minutes at 200 W outlet power. The ^{1}H NMR analysis of the reaction mixture evidenced no decomposition of the diazo acetate **173a**, showing its stability under irradiation at this temperature.

In summary, the enhancement of the temperature in the conversion of 2-triethylsilyl-2-diazo benzyl acetate (**173a**) into 2-triethylsilyl-2-keto-benzyl acetate (**185**) allowed the shortening of the reaction time, but increased the quantity of side-products under either microwave irradiation and conventional heating.

[163] See for example ref. [100]

3.7.5.4 Microwave Assisted Synthesis of *N*-Protected 2-Trialkylsilyl-2-Amino Acetates

N-Boc-protected 2-triethylsilyl-2-amino benzyl acetate (**174a**) was synthesised under conventional heating starting from 2-triethylsilyl-2-diazo benzyl acetate (**173a**) in presence of rhodium(II) tetraacetate as catalyst and *tert*-butyl carbamate ($BocNH_2$) in toluene (entry 1, Table 10). The reaction mixture was stirred at 50 °C for 24 hours, and *O*-benzyl-protected 2-triethylsilyl-2-hydroxy-benzyl acetate (**200a**) was found as a side-product. The first microwave experiment of the reaction at 75 °C for 5 minutes at 100 W (conditions suggested by the software of the microwave reactor) did not yield to any conversion of the substrate **173a** (entry 2). Meanwhile, the enhanced temperature to 100 °C and the prolonged reaction time to 30 minutes (entry 4, Table 10), showed the formation of 83% the product **174a** and 17% of the side-product **200a** (^{1}H NMR yield). Similar results were reported for the conventional heated system in entry 1 (Table 2), which, however needed a considerably longer reaction time.

An unexpected result appeared when the usual reaction mixture was microwave irradiated at 75 °C for 30 minutes (entry 3, Table 10): the desired amino acetate **174a** and the hydroxy-acetate **200a** were formed in similar quantities (respective 56% and 44%).

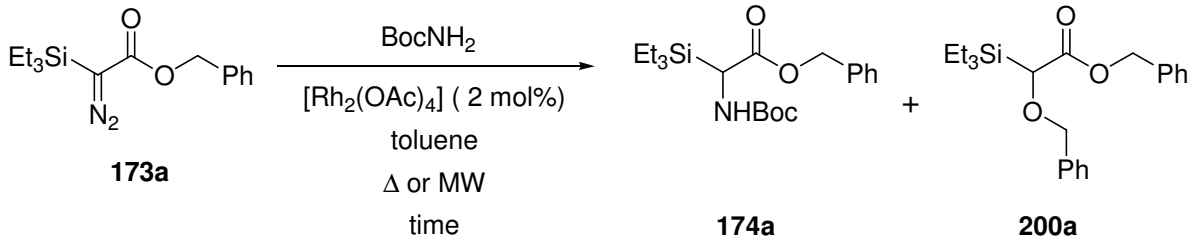


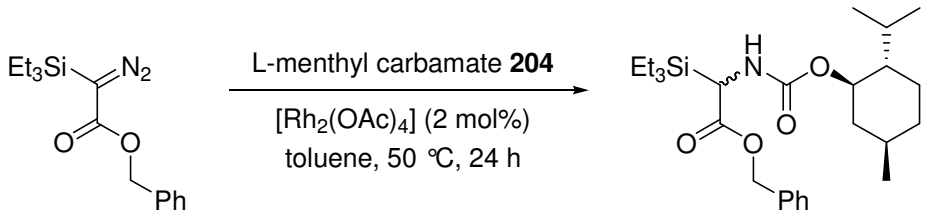
Table 10. Synthesis of *N*-Boc-protected 2-triethylsilyl-2-amino benzyl acetate **174a** under conventional heating and microwave irradiation.

Entry	*Heating*	*Temperature (°C)*	*Rxt. time*	*Power (W)*	*Product (174a) (% NMR)*	*Side-product (200a) (% NMR)*
1	Δ[a]	50	24 h	--	82	18
2	MW[a]	75	5 min.	100	0	0
3	MW[a]	75	30 min.	200	56	44
4	MW[a]	100	30 min.	200	83	17

[a] 0.17 mmol of substrate **173a** in 1.0 mL toluene.

In summary, the use of microwave did not enhance the chemoselectivity of the reaction, since the amount of the synthesised product was comparable to the result obtained under conventional heating (entry 1 and 4, Table 4), but the application of microwave radiation enables a nearly instant access to the *N*-Boc-protected amino benzyl acetate **174a**. Due to the shortened reaction time, the new protocol seems to open the possibility to perform the synthesis of sila amino esters in increased temperatures of up to 100 °C, without loss in chemoselectivity.

A diastereoselective synthesis of α-silyl α-amino esters derivatives was performed under microwave irradiation starting from the standard substrate **173a**, which reacted with L-menthyl carbamate (**204**) in presence of rhodium(II) tetraacetate at 100 °C for 30 minutes, 200 W power. The ^{1}H NMR analysis evidenced the diasteroselective formation of *N*-menthyl-substitued 2-triethylsilyl-2-amino benzyl acetate (**174h**) and a 69:31 diastereomeric ratio (entry 1, Table 11). The same reaction performed under conventional heating at 50 °C for 24 hours, resulted in a mixture of diastereomers of compound **174h** in a ratio 75:25 (entry 2, Table 11). It is comprehensible that a higher diastereoselectivity can be obtained at lower temperature, but the drastically enhanced reactivity under microwave irradiation had only a minor influence on the stereochemical outcome of the reaction.



173a **174h**

Table 11. Synthesis of *N*-menthyl-substitued 2-triethylsilyl-2-amino benzyl acetate (**174h**) under conventional heating and microwave irradiation.

Entry	***Heating***	***Temperature (°C)***	***Rxt. time***	***Power (W)***	***dr (174h) (NMR ratio)***
1	MW	100	30 min.	200	69:31
2	Δ	50	24 h	--	75:25

[a] 0.17 mmol of substrate **173a** in 1.0 mL toluene.

3.7.5.5 Microwave Assisted Synthesis of *O*-Substitued 2-Trialkylsilyl-2-Hydroxy-Acetates

The rhodium(II) catalysed decomposition of 2-triethylsilyl-2-diazo benzyl acetate (**173a**) in presence of 4-methoxy-benzyl alcohol was originally performed at 50 °C and needed 12 hours to obtain fully conversion to *O*-benzyl-protected 2-triethylsilyl-2-hydroxy-benzyl acetate (**276**), as detected by ^{1}H NMR analysis.

The optimisation of this reaction under microwave irradiation, allowed to obtain 100% of the desired product **274** at 150 °C after only 5 minutes (entry 4, Table 6). This last result exemplified an advantage in using a microwave reactor: in fact, a temperature higher than the boiling point of toluene could be reached without the use of an autoclave as in classical condition of heating.

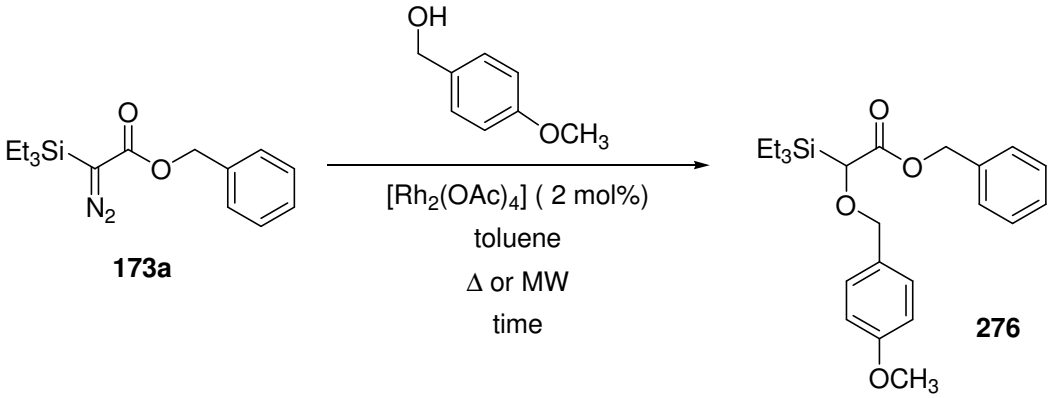


Table 12. Synthesis of *O*-benzyl-protected 2-triethylsilyl-2-hydroxy-benzyl acetate (**276**) under conventional heating and microwave irradiation.

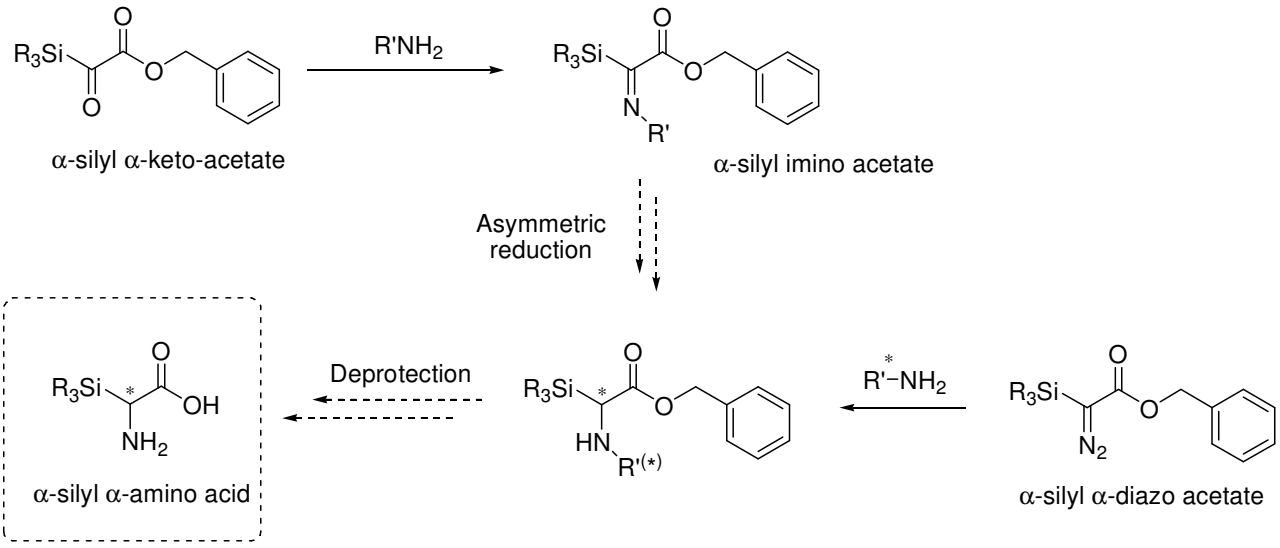
Entry	***Heating***	***Temperature (°C)***	***Rxt. time***	***Power (W)***	***Product (276) (% NMR)***
1	Δ	50	12 h	--	100
2	MW	150	20 min.	200	100
3	MW	150	10 min.	200	100
4	MW	150	5 min.	200	100

[a] 0.17 mmol of substrate **173a** in 1.0 mL toluene.

4. Summary

In 2000, Bolm and co-workers reported the first synthesis of *N*-protected α-trialkylsilyl α-amino acids precursors, in which 2-trialkylsilyl-2-diazo acetates, in the presence of rhodium(II) tetraacetate as catalyst, were reacted with various carbamates, followed by deprotection, to form the named products in good yields.[100] These were the first examples 2-diazo acetates bearing a trialkylsilyl group at the carbon bonded to the diazo group to undergo intermolecular carbenoid-type N-H insertion.

As an extension to this discovery, it was accounted that a diastereoselective approach to *N*-protected α-trialkylsilyl α-amino acids precursors may lead, after deprotection, to the formation of enantiomerically-pure α-trialkylsilyl free α-amino acids. A variety of diastereoselective synthetic strategies were examinated. These investigations involved the use of α-trialkylsilyl α-keto-acetates as substrates, as well as various reactants such as amines, ureas, or chiral carbamates as sources of the chiral information (Scheme 97).

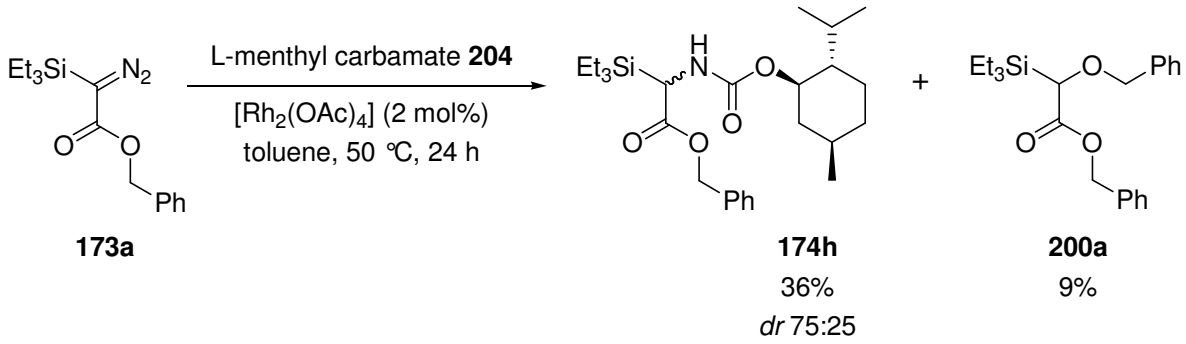


Scheme 97. Synthetic pathways to enantiomerically-enriched α-silyl α-amino acids.

Neither of the two synthetic pathways depicted in Scheme 97 to access to enatiomerically-enriched α-silyl α-amino acids resulted was entirely successful. Promising results were exclusively provided by the rhodium(II) catalysed N-H insertion reaction between 2-*tert*-butyl-dimethylsilyl-2-diazo benzyl acetate (**173b**) and 1-((*R*)-1-phenylethyl)urea (**199**) as N-H source, which yielded to the formation of *N*-urea-substituted 2-*tert*-butyldimethylsilyl-2-amino benzyl acetate **201**.

Carbamates were confirmed as the mostly efficient N-H sources for rhodium(II)-catalysed reaction.

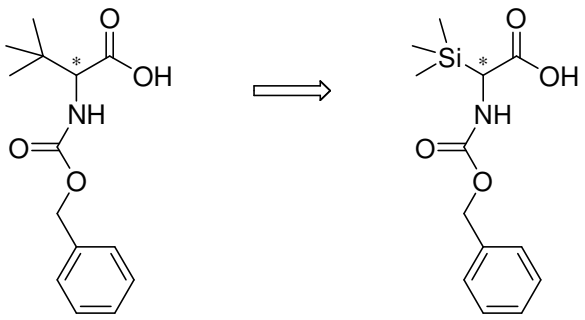
A diastereoselective N-H insertion reaction was attempted between the silyl diazo acetate **173a** and L-menthyl carbamate **204**. The reaction proceeded in a diastereoselective formation of compound **174h**, in a diastereomeric ratio of 75 to 25 (Scheme 59).



173a **174h** 36% *dr* 75:25 **200a** 9%

Scheme 59. Diastereoselective synthesis of *N*-menthyl-substituted 2-triethylsilyl-2-amino benzyl acetate (**174h**).

The resolution of a racemic mixture of two enantiomers of α-silyl α-amino acids was reported by Bolm and co-workers in 2000.[100] A part of this project was devoted to the synthesis of the racemic *N*-Cbz-protected 2-trimethylsilyl glycine, the enantiopure derivative of which (compound **210**) is depicted in Figure 17.



209 **210**

Figure 17. Enantiopure *N*-Cbz-protected 2-trimethylsilyl glycine (**207**) as analoge to enantiopure *N*-Cbz-protected *tert*-leucine (**206**)

The possibility to obtain the free carboxylic functional group as in compound **209** from selective deprotection of a corresponding ester moiety was investigated. Various ester protecting groups were considered, the removal of which could give access to the free carboxylic acids and thus to enantiopure α-silyl α-amino acids through resolution by chemical methods (Figure 18).

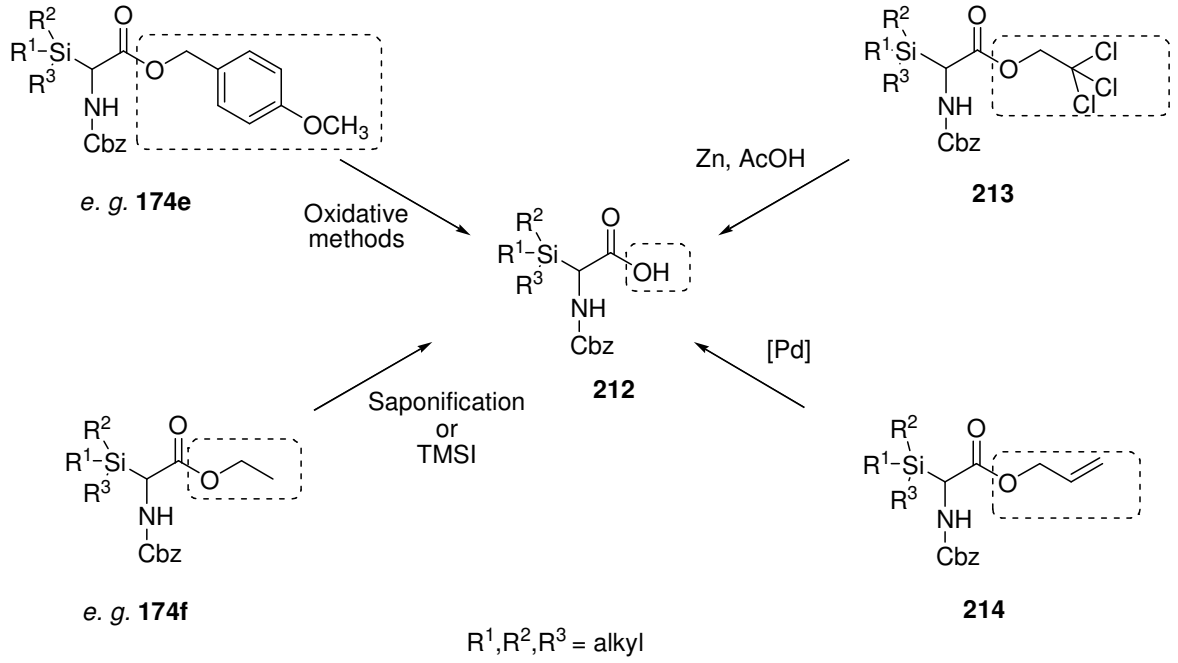
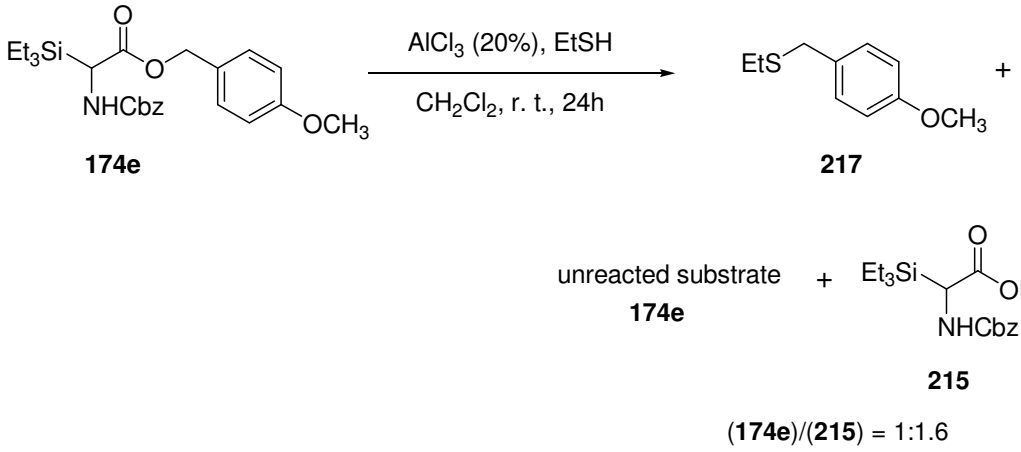


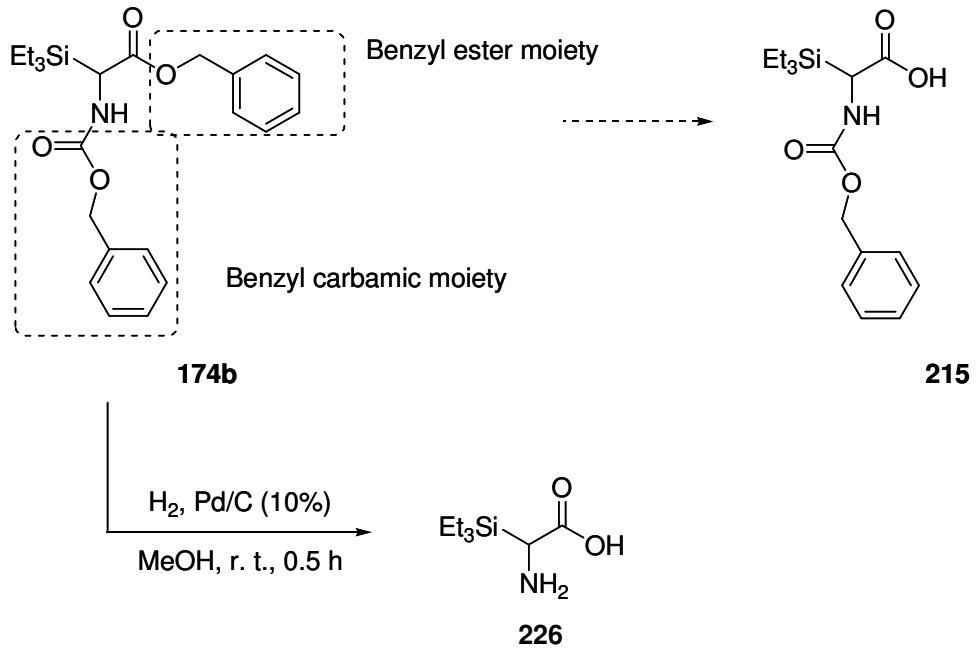
Figure 18. Synthetical pathway to *N*-Cbz-protected 2-trialkylsilyl-2-amino acetic acid (**212**).

The most promising result was obtained when the 4-methoxybenzyl acetate **174e** underwent reaction with $AlCl_3$/EtSH to yield to the free acid **215** in a ^1H NMR ratio 1.6 to 1 respect to the substrate **174e** (Scheme 63).



Scheme 63. Synthesis of the free *N*-Cbz-protected 2-triethylsilyl-2-amino acetic acid (**215**).

Attempts to selective removal of the benzyl ester moiety of *N*-Cbz-protected α-silyl α-amino benzyl acetate **174b** through selective hydrogenation remained unsuccessful. Hydrogenation over palladium(0) allowed exclusively the formation of the free α-silyl α-amino acetic acid **226** (Scheme 98).



Scheme 98. Deprotection of *N*-Cbz-protected α-silyl α-amino benzyl acetate **174b**.

As already considered by Bolm and co-workers[100] and by Sieburth and co-worker,[101] the α-silyl α-amino acid core could become a substructure of a more complicated structure. Matrix metalloproteinase (MMP) inhibitors are considered relevant synthetic targets in the modern synthetic and medicinal chemistry. The modification of a MMP structure with the insertion of an α-silyl α-amino acid functionality, could confer to the so modified structure a different reactivity and a better bio-availability, thus paving the way to a variety of most interesting and new applications (Figure 24).

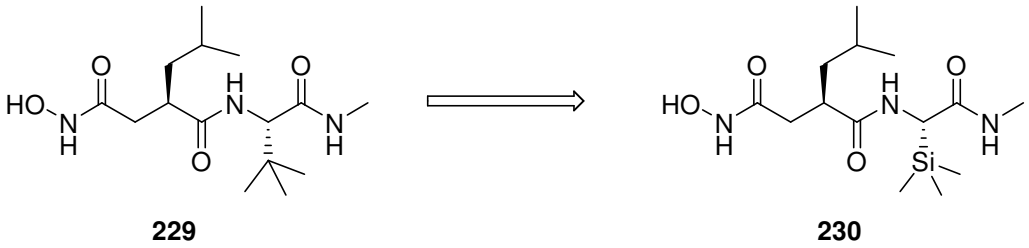
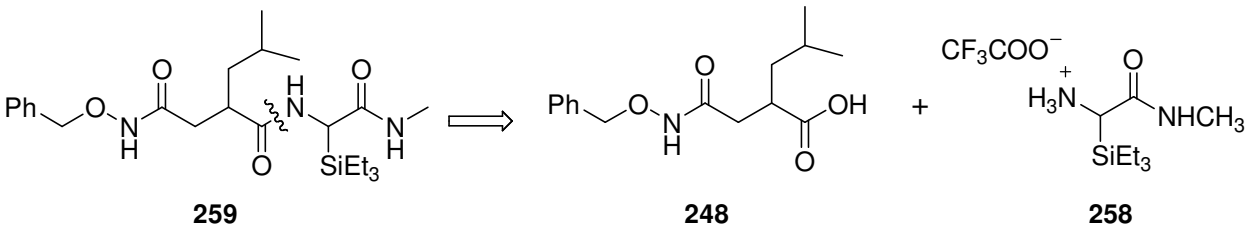


Figure 24. Structure comparison between a succinyl hydroxamic based MMPs inhibitor **229** and its silyl modified analogue **230**.

Various synthetic strategies were considered and attempted towards the synthesis of the two building blocks of a silyl modified succinyl hydroxamic acid based MMPs inhibitor, such as **230**. The amide-bond formation approach to compound **259**, an analogue of **230**, remained unsuccessful.

In fact, α-*iso*-butyl-succinyl hydroxamic acid **248**, derivative of the succinyl hydroxamic acid building block, was synthesised in 65% yield, while the attempted synthesis of the silyl amino acid derivative core, the trifluoroacetic salt of 2-triethylsilyl-2-amino-*N*-methyl acetamide (**258**), failed to succeed (Figure 29).



259 **248** **258**

Figure 29. Disconnection approach to the silyl modified MMP inhibitor derivative **259**.

An alternative approach to compound **259** was attempted through the coupling of succinyl hydroxamic acid **248** (or the corresponding *iso*-propyl analogue **253**) and the trifluoroacetic salt of 2-triethylsilyl-2-amino benzyl acetate (**267**) using various coupling reagents, between them, PyBOP®, combined with ethyldi*iso*propylamine, appeared the most promising.

Finally, studies on microwave assisted synthesis of *N*-protected α-trialkylsilyl α-amino esters were described. A final summary of the several examples reported indicated a shortening of the reaction times under microwave irradiation in comparison to the same transformations performed under standard conditions and conventional heating. To this result, although, did not correspond a sensible enhancement of the chemo- and the stereoselectivity of the discussed reactions.

5. Experimental Section

5.1 General Information

Reactions with air or moisture sensitive reagents were carried out under argon atmosphere using conventional Schlenk techniques. The addition of all the reagents as well as pre-dried solvents were carried out by using plastic syringes under an argon stream.
All α-diazo esters and α-trialkylsilyl α-diazo esters were stored under argon.

5.1.1 Purification and Drying of Solvents and Reagents

Dichloromethane:	purchased in analytical pure form from Merck or Fisher Scientific, refluxed over CaH_2 and then distilled.
Diethylether:	pre-dried over KOH, refluxed over sodium/benzophenone ketyl radical and then distilled.
Ethyl acetate:	refluxed and then distilled.
Ethyldiisopropylamine:	distilled over CaH_2.
Methanol:	purchased in analytical pure form from Merck or Aldrich.
Pentane:	refluxed and then distilled.
Toluene:	refluxed over Na/benzophenone ketyl radical and then distilled.

5.1.2 Commercially-Available Reagents

The most common used reagents were purchased from the companies Acros, Aldrich, Fluka, Lancaster, Merck. Palladium on charcoal (5% and 10%) and rhodium on alumina (5%) were kindly provided by Degussa.

5.1.3 Determination of the Physical Data

^{1}H NMR

^{1}H NMR spectra were recorded on a Varian VXR 300 (300 MHz), a Varian Gemini 300 (300 MHz), a Varian Inova 400 (400 MHz) or a Varian Unity 500 (500 MHz) spectrometer. Chemical shifts are given in ppm based on deuterated solvent peak (chloroform δ = 7.26 ppm, methanol δ = 3.34 ppm). In order to describe the signals, the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), dd (double doublet), m (multiplet), br s (broad singlet), br d (broad doublet). The coupling constants *J* are given in Hz. Diastereomerer ratios are determined by analysis of the ^{1}H NMR spectrum of their mixture.

^{13}C NMR

^{13}C were ^{1}H broad band-decoupled and measured with a Varian VXR 300 (75 MHz), a Varian Gemini 300 (75 MHz), a Varian Inova 400 MHz (100 MHz) or a Varian Unity 500 (125 MHz) spectrometer. Chemical shifts are given in ppm based on deuterated solvent peak (chloroform δ = 77.1 ppm, methanol δ = 49.0 ppm).

All spectra (^{1}H and ^{13}C) were recorded at room temperature.

Mass Spectrometry

Mass spectra were recorded on a Varian MAT 212 and a Finnigan Mat 95 spectrometer. All the entries are given atomic unit of mass per elemental charge (*m/z*). The mass of the biggest fragment is given when the peaks (M^+) or ($M^+–H^+$) are not visible. The number in brackets are the intensities of *m/z* as percentage of the basis peak.

Infrared Spectrometry

Infrared spectra were recorded on a Perkin-Elmer PE-1760 FT. All bands are given in cm^{-1}. Only the strongest bands (60%-100% intensity) are reported.

Elemental Analysis

Elemental analyses were recorded using a CHNO-Rapid machine from the company Heraus. All values are given as mass percentage.

GC-MS Analysis

GC-MS analysis were recorded using: GC (HP 6890 Series) with MSD 5973, column: HP-5 MS (30 m x 0.25 m x 0.25 m), He as carrier gas at 200 °C.

5.1.4 Chromatograpic Methods

Thin Layer Chromatography

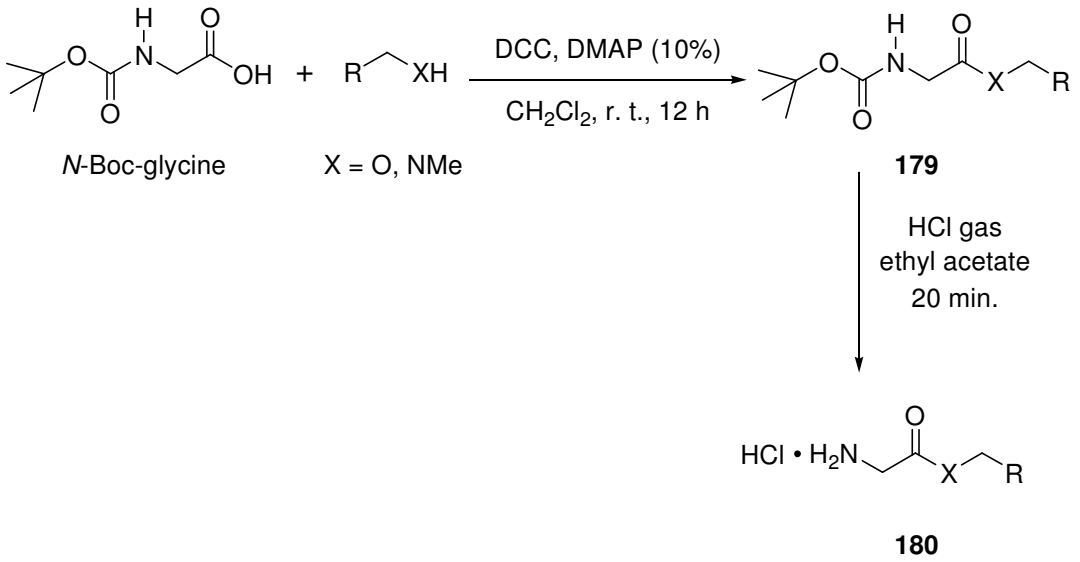
Thin layer chromatography were performed on aluminium backed plates 0.25 mm (Kiesegel 60 F_{254}) from Merck. Compounds were detected using UV-light (ν = 253 nm) and/or with the aid of a staining reagent synthesized from 2.5 g of cerium sulfate, 6.3 g of molybdatophosphoric acid, 15 mL of conc. sulfuric acid and 230 mL of H_2O. An other staining reagent used was made from 3.0 g of vanillin, 50 mL of 95% ethanol solution, 15 mL of 2M sulphuric acid.

Flash–Chromatography

Flash column chromatography were carried out using silica gel (Kieselgel 60, 43-60 m) from Merck. In the case of compounds sensitive to desilylation, Florisil® 100-200 mesh was used, purchased from the company Acros.

5.2 Synthesis of Glycine Derivatives

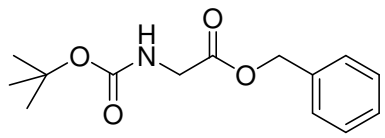
5.2.1 General Procedure



To a stirred solution of *N*-Boc-glycine (10 g, 13 mmol) in dichloromethane, was added the corresponding alcohol or amine (13 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (0.16 g, 1.3 mmol) and the mixture was cooled to 0 °C. A 1 M solution of *N*,*N*'-dicyclohexylcarbodiimide (DCC) (13.6 mL, 13.6 mmol) in dichloromethane was then added. After addition, the reaction mixture was left stirring at room temperature for 12 hours. The precipitated urea was filtered off and the filtrate was washed with 5% NaOH and 5% HCl. The organic phase was then dried over $MgSO_4$ and filtered. The removal of the solvent under reduced pressure afforded the crude products **179a**-**e** without further purification. The corresponding glycine ester **179a**-**d** or glycine amide **179e** was dissolved in ethyl acetate and hydrogen chloride gas was bubbled inside the flask for 30 minutes. The precipitate was filtered off and washed with ethyl acetate to afford the corresponding HCl-salt of the corresponding glycine ester **180a**-**d** and the HCl-salt of the glycine amide **180e**.

5.2.2 *N*-Boc-Protected Glycine Derivatives

5.2.2.1 *Tert*-butyl ((benzyloxy)carbonyl)methylcarbamate (179a)[164]



3.2 g, 12 mmol; 90% yield; white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34-7.29 (m, 5H, arom. C*H*), 5.35 (br s, 1H, N*H*), 5.11 (s, 2H, CH_2Ph), 3.87 (m, 2H, NCH_2), 1.40 (s, 9H, C(CH_3)$_3$).

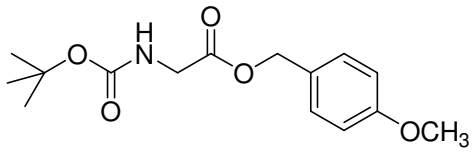
^{13}C NMR (75 MHz, $CDCl_3$): 170.2, 155.7, 135.2, 128.4, 128.1, 127.9, 79.6, 66.7, 42.3, 28.1.

IR (KBr): 3394, 2934, 1753, 1541, 1457, 1386, 959, 753, 702.

CI-MS (methane): *m/z* = 266 (M^++1, 2), 256 (3), 211 (3), 210 (31), 209 (13), 166 (43), 92 (7), 91 (100).

Anal. Calcd. for $C_{14}H_{19}NO_4$: C 63.38; H 7.22; N 5.28. **Found:** C 63.67; H 7.21; N 5.17.

5.2.2.2 *Tert*-butyl ((4-methoxybenzyloxy)carbonyl)methylcarbamate (179b)[165]



3.2 g, 11 mmol; 84% yield; pale-yellow oil.

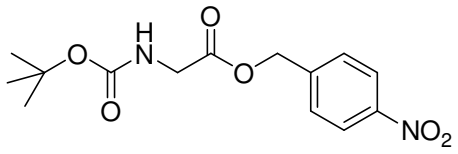
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.8 Hz, 2H, arom. C*H*), 6.88 (d, *J* = 8.8 Hz, 2H, arom C*H*), 5.11 (s, 2H, CH_2Ph), 5.03 (br s, 1H, N*H*), 3.91 (m, 2H, NCH_2), 3.80 (s, 3H OCH_3), 1.44 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 170.2, 159.7, 130.3, 128.6, 127.3, 114.0, 80.0, 67.0, 55.4, 46.6, 28.4.

[164] The title compound was already reported in the literature but synthesised following a different methodology, see for example C. A. M. Afonso, *Tetrahedron Lett.* **1995**, *36*, 8857-8858.

[165] The title compound is known and synthesised according to literature method: S. Saladin, PhD Thesis, Aachen **2004**.

5.2.2.3 *Tert*-butyl ((4-nitrobenzyloxy)carbonyl)methylcarbamate (179c)[165]

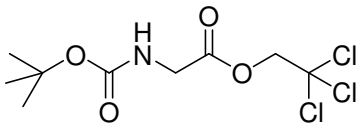


3.5 g, 12 mmol; 92% yield; clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.8 Hz, 2H, arom. C*H*), 7.51 (d, *J* = 8.8 Hz, 2H, arom C*H*), 5.27 (s, 2H, CH_2Ph), 5.06 (br s, 1H, N*H*), 3.98 (d, *J* = 5.8 Hz, 2H, NCH_2), 1.44 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 170.2, 142.7, 128.7, 124.0, 80.5, 65.7, 42.8, 28.6.

5.2.2.4 *Tert*-butyl ((2,2,2-trichloroethoxy)carbonyl)methylcarbamate (179d)[166]

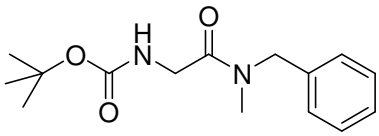


3.7 g, 12 mmol; 91% yield; white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.18 (br s, 1H, N*H*), 4.75 (s, 2H, OCH_2), 4.02 (s, 2H, NCH_2), 1.41, (s, 9H, C(CH_3)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): 169.1, 155.7, 94.5, 80.2, 74.3, 42.2, 28.3.

5.2.2.5 *Tert*-butyl (*N*-benzyl-*N*-methylcarbamoyl)methylcarbamate (179e)



3.3 g, 12 mmol; 92% yield; yellow-orange oil.

[166] The title compound is known and synthesised according to literature method: J. Deng, Y. Hamada, T. Shioiri, *Synthesis* **1998**, 627-638. See also: K: E. Pryor, J. Rebek, Jr., *Org. Lett.* **1999**, *1*, 39-42.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33-7.92 (m, 5H, arom. C*H*), 5.68 (m, 1H, N*H*), 4.42 (d, 2H, CH_2Ph), 3.98 (d, *J* = 5.6 Hz, 2H, NHCH_2), 2.88 (d, 3H, NCH_3), 1.40 (s, 9H, C(CH_3)$_3$).

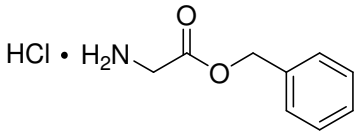
^{13}C NMR (100 MHz, $CDCl_3$): 168.6, 155.8, 136.4, 128.8, 128.5, 127.9, 127.4, 126.3, 79.6, 52.2, 51.2, 42.4, 42.2, 34.1, 33.5, 28.3.

IR (neat): 1712, 1655, 1492, 1455, 1411, 1368, 1252, 1168.

CI-MS (methane): *m/z* = 279 (M^++1, 7), 251 (17), 237 (9), 224 (13), 223 (100), 222 (11), 205 (11), 180 (7), 179 (60).

5.2.3 Hydrochloride Salts of Glycine Derivatives

5.2.3.1 Benzyl glycine hydrochloride salt (180a)[167]



1.7 g, 8.5 mmol; 71% yield; white solid.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.52-7.35 (m, 5H, arom C*H*), 5.31 (s, 2H, CH_2Ph), 3.93 (s, 2H, NCH_2).

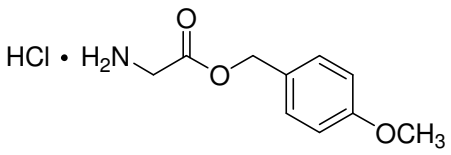
^{13}C NMR (100 MHz, CD_3OD): 168.2, 136.3, 129.6, 129.5, 68.8, 41.1.

IR (KBr): 2997, 2622, 1754, 1562, 1499, 1404, 1241, 1144, 1052, 912, 732.

CI-MS (methane): *m/z* = 166 (10), 119 (5), 92 (7), 91 (100).

Anal. Calcd. for $C_9H_{12}NO_2Cl$: C 53.61; H 6.00; N 6.95. **Found:** C 52.86; H 6.13; N 7.12.

5.2.3.2 4-Methoxybenzyl glycine hydrochloride salt (180b)[168]



1.8 g, 7.6 mmol; 69% yield; white solid.

[167] The title compound is commercially-available. It is already known in the literature and was synthesised with a similar methodology from *N*-Boc benzyl glycine (4M HCl in dioxane, 20 °C, 30 min.): J. W. Perich, R. B. Johns, *J. Org. Chem.* **1989**, *54*, 1750-1752.

[168] The title compound was already reported in the literature without a fully characterization: J. A. Mc Laren, *Aust. J. Chem.* **1972**, *25*, 1293-1299.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.38 (d, *J* = 8.8 Hz, 2H, arom C*H*), 6.94 (d, *J* = 8.8 Hz, 2H, arom C*H*), 5.24 (s, 2H, CH_2Ph), 3.90 (s, 2H, NCH_2), 3.81 (s, 3H, OCH_3).

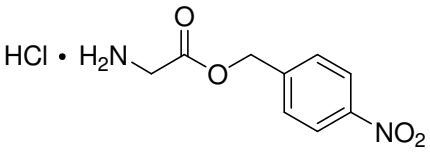
^{13}C NMR (100 MHz, CD_3OD): 165.7, 158.8, 128.9, 125.7, 112.3, 66.2, 53.2, 38.6.

IR (KBr): 2969, 2884, 1741, 1609, 1481, 1423, 1251, 1038, 913, 821.

CI-MS (methane): *m/z* = 195 (2), 149 (3), 122 (9), 121 (100), 78 (1).

Anal. Calcd. for $C_{10}H_{14}NO_3Cl + H_2O$: C 48.10; H 6.46; N 5.61. **Found:** C 47.89; H 5.60; N 6.94.

5.2.3.3 4-Nitrobenzyl glycine hydrochloride salt (180c)[169]



1.9 g, 7.6 mmol; 63% yield; white solid.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.28 (d, *J* = 8.8 Hz, 2H, arom C*H*), 7.70 (d, *J* = 8.8 Hz, 2H, arom C*H*), 5.45 (s, 2H, PhCH_2), 4.01 (s, 2H, NCH_2).

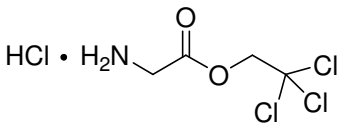
^{13}C NMR (100 MHz, $CDCl_3$): 168.2, 149.1, 143.7, 129.8, 124.6, 67.3, 41.1.

IR (KBr): 2999, 2919, 1743, 1603, 1522, 1495, 1418, 1347, 1243, 849.

CI-MS (methane): *m/z* = 212 (10), 211 (100), 165 (17), 136 (50).

Anal. Calcd. for $C_9H_{11}N_2O_4Cl$: C 43.83; H 4.50; N 11.36. **Found:** C 43.98; H 4.82; N 11.29.

5.2.3.4 2,2,2-Trichloroethyl glycine hydrochloride salt (180d)[170]



1.8 g, 7.4 mmol; 62% yield; white solid.

^{1}H NMR (300 MHz, CD_3OD): δ = 4.95 (s, 2H, OCH_2), 4.11 (s, 2H, NCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): 166.5, 95.5, 75.7, 40.9.

IR (KBr): 3444, 3106, 3005, 2962, 2905, 1772, 1508, 1423, 1397, 1202, 1123, 1052, 897.

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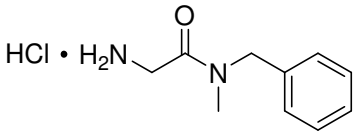
[169] The title compound was already reported in the literature without a fully characterization: J. A. Mc Laren, *Aust. J. Chem.* **1971**, *24*, 1695-1702.

[170] The title compound was already reported in the literature without a fully characterization: B. Marinier, C. Y. Kim, J. M. Navarre, *Can. J. Chem.* **1973**, *51*, 208-214. See also J. Deng, Y. Hamada, T. Shioiri, *Synthesis* **1998**, 627-638.

CI-MS (methane): *m/z* = 210 (30), 208 (100), 206 (98), 172 (37), 170 (59), 144 (10), 143 (18), 142 (17), 141 (27), 106 (18).

Anal. Calcd. for $C_4H_8NO_2Cl_4$: C 19.70; H 3.31; N 5.74. **Found:** C 19.41; H 3.63; N 5.68.

5.2.3.5 Hydrochloride salt of *N*-benzyl-*N*-methyl glycine amide (180e)



1.3 g, 7.4 mmol; 62% yield; thick orange oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46-7.28 (m, 5H, arom. C*H*), 4.64 (d, 2H, CH_2Ph), 3.98 (d, NH_2CH_2), 3.38 (d, 3H, NCH_3).

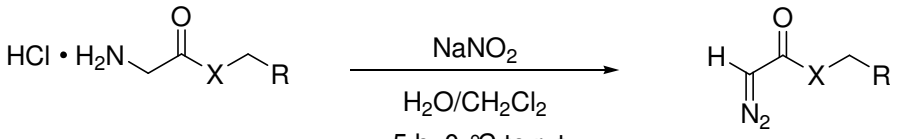
^{13}C NMR (75 MHz, $CDCl_3$): 164.5, 137.8, 130.2, 128.8, 129.1, 128.8, 127.9, 53.3, 52.1, 41.3, 34.3.

IR (neat): 2937, 1718, 1661, 1497, 1453, 1240, 746.

CI-MS (methane): *m/z* = 180 (12), 179 (M^++1, 100), 122 (16), 120 (12), 91 (22).

Anal. Calcd. for $C_{10}H_{15}N_2OCl$: C 55.94; H 7.04; N 13.05. **Found:** C 54.81; H 7.51; N 12.66.

5.3 Synthesis of 2-Diazo Acetates Derivatives



180a-e

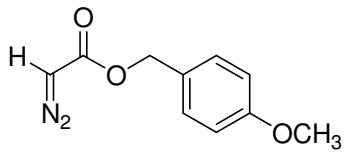
X = O, NMe

181a-e

Sodium nitrite ($NaNO_2$) (0.72 g, 10.5 mmol) was added portion wise to an ice-cooled mixture of the HCl salt of the corresponding glycine derivative **180a-e** (7.0 mmol) in water (60 mL) and dichloromethane (80 mL). After a minimun reaction time of 5 hours, the mixture was warmed to room temperature. The lower organic phase was separated and the aqueous phase was washed twice with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and the removal of the solvent under reduced pressure afforded the corresponding crude 2-diazo acetate **181a-d** or 2-diazo acetamide **181e**. The product was purified *via* flash chromatrography on silica

gel and eluted with pentane/ethyl acetate in various gradients (ratio in brackets). Benzyl 2-diazo acetate (**181a**) is known and synthesised according to the literature method.[171]

5.3.1 4-Methoxybenzyl 2-diazo acetate (181b)[165]



618 mg, 3.1 mmol; 44% yield; yellow oil; (10:1).

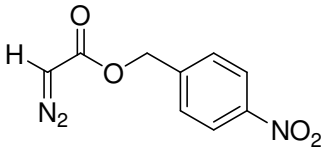
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.8 Hz, 2H, arom. C*H*), 6.89 (d, *J* = 8.8 Hz, 2H, arom. C*H*), 5.13 (s, 2H, CH_2), 4.76 (br s, 1H, C*H*N_2), 3.79 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 159.6, 130.0, 127.9, 113.9, 66.3, 55.3, 46.3.

IR (capillary): 2112, 1692, 1515, 1389, 1352, 1246, 1173, 1033.

CI-MS (methane): *m/z* **=** 207 (M^++1, 3), 121 (M^+, 100).

5.3.2 4-Nitrobenzyl 2-diazo acetate (181c)[165]



866 mg, 3.9 mmol; 55% yield; yellow solid; (8:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.7 Hz, 2H, arom. C*H*), 7.50 (d, *J* = 8.7 Hz, 2H, arom. C*H*), 5.27 (s, 2H, CH_2), 4.87 (br s, 1H, C*H*N_2).

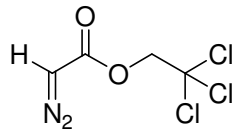
^{13}C NMR (100 MHz, $CDCl_3$): 186.4, 147.5, 143.2, 128.2, 123.7, 64.9, 46.5.

IR (KBr): 3108, 2361, 2123, 1690, 1605, 1524, 1401, 1347, 1198, 842, 823, 737, 502.

CI-MS (*iso*butane): *m/z* **=** 223 (10), 222 (M^+, 100).

[171] S. R. Angle, D. S. Bernier, N. A. El-Said, D. E. Jones, S. Z. Shaw, *Tetrahedron Lett.* **1998**, *39*, 3919-3922.

5.3.3 2,2,2-Trichloroethyl 2-diazo acetate (181d)[172]



632 mg, 2.9 mmol; 42% yield; yellow oil; (10:1).

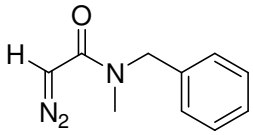
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.93 (br s, 1H, C*H*N_2), 4.79 (s, 2H, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): 165.5, 95.1, 73.8, 46.6.

IR (neat): 2121, 1711.

CI-MS (methane): *m/z* **=** 221 (34), 219 (100), 218 (M^+, 13), 217 (98), 183 (43), 181 (61), 87 (28), 69 (31).

5.3.4 *N*-benzyl-*N'*-methyl 2-diazo acetamide (181e)[173]



813 mg, 4.3 mmol; 61% yield; yellow oil; (3:7 then 4:6).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.30 (m, 5H, arom. C*H*), 5.09 (s, 1H, C*H*N_2), 4.54 (br s, 2H, CH_2Ph), 2.89 (br s, 3H, NCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): 166.1, 136.9, 128.7, 127.5, 127.1, 60.3, 46.5, 34.3.

IR ($CDCl_3$): 2107, 1609, 1477, 1448, 1409, 731.

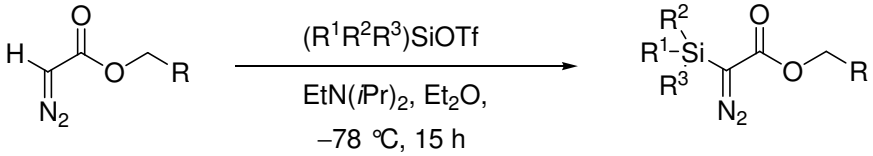
CI-MS (methane): *m/z* **=** 191 (12), 190 (M^++1, 100), 162 (13), 161 (23), 160 (14), 118 (13), 105 (15), 104 (36), 91 (39).

Anal. Calcd. for $C_{10}H_{11}N_3O$: C 63.48; H 5.86; N 22.21. **Found:** C 62.91; H 5.27; N 22.07.

[172] The title compound was already reported in the literature: W. L. Mock, M. E. Hartman, *J. Org. Chem.* **1977**, *42*, 459-465.

[173] The title compound was already reported in the literature but synthesised following a different methodology: M. P. Doyle, S. M. Shanklin, H. Q. Pho, *Tetrahedron Lett.* **1988**, *29*, 2639-2642.

5.4 Synthesis of 2-Diazo-2-Trialkylsilyl Acetates

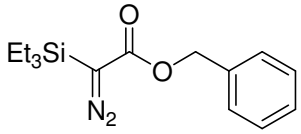


181a-d **173a-i, 175**

The reaction was performed following the procedure reported by Regitz.[89] To a solution of the corresponding substituted 2-diazo acetate **181a-d** (3.0 mmol) and fresh distilled ethyldi*iso*propylamine (0.57 mL, 3.3 mmol) in diethylether (10 mL) under an argon atmosphere, was added drop wise at –78 °C a solution of the corresponding silyl triflate (3.15 mmol) in diethylether (5 mL). The reaction was then stirred overnight and allowed to warm at room temperature. The precipate ammonium salt was filtered off and the solvent was removed under reduced pressure to afford an oily residue. The crude 2-diazo-2-trialkylsilyl acetate **173a-i** and **175** was then purified *via* flash chromatrography on silica gel (pentane/ethyl acetate, various gradients, tatios in brackets).

Ethyl 2-Diazo-2-*Tert*-butyldimethylsilyl acetate (**175**) was synthesised starting from the commercially-available 2-diazo ethyl acetate and following the reported procedure.

5.4.1 Benzyl 2-diazo-2-triethylsilyl acetate (173a)[165]



784 mg, 2.7 mmol; 89% yield; yellow oil; (20:1).

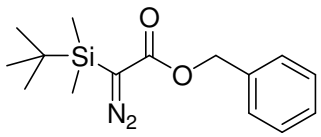
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36-7.28 (m, 5H, arom. C*H*), 5.19 (s, 2H, PhCH_2), 0.97 (t, *J* = 8.3 Hz, 9H, CH_2CH_3), 0.74 (q, *J* = 8.0 Hz, 6H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 169.0, 136.1, 128.4, 128.1, 128.0, 66.4, 45.1, 7.2, 3.3.

IR (neat): 2956, 2089, 1689, 1263, 1206, 743.

CI-MS (methane): *m/z* = 292 (20), 291 (M^++1, 100), 261 (27), 233 (22), 182 (22), 130 (40), 115 (21), 91 (49).

5.4.2 Benzyl 2-diazo-2-*tert*-butyl-dimethylsilyl acetate (173b)[165]



436 mg, 1.5 mmol; 51% yield; yellow oil; (20:1).

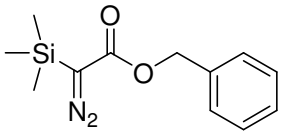
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.31 (m, 5H, arom. C*H*), 5.18 (s, 2H, PhCH_2), 0.95 (s, 9H, SiC(CH_3)$_3$), 0.23 (s, 6H, SiCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 169.0, 136.1, 128.5, 128.2, 128.1, 66.5, 26.5, 18.9, -6.1.

IR (neat): 2090, 1690, 1259, 1200.

CI-MS (*iso*butane): *m/z* = 292 (22), 291 (M^++1, 100).

5.4.3 Benzyl 2-diazo-2-trimethylsilyl acetate (173c)[165]



546 mg, 2.2 mmol; 72% yield; yellow oil; (20:1).

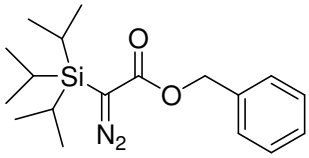
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36-7.07 (m, 5H, arom. C*H*), 5.15 (s, 2H, CH_2), 0.23 (s, 9H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 168.6, 136.1, 128.4, 128.1, 128.0, 66.4, -1.4.

IR (neat): 2092, 1688, 1267, 1210, 846.

CI-MS (*iso*butane): *m/z* = 250 (19), 249 (M^++1, 100), 131 (10).

5.4.4 Benzyl 2-diazo-2-tri*iso*propylsilyl acetate(173d)[165]



333 mg, 1.1 mmol; 38% yield; yellow oil; (20:1).

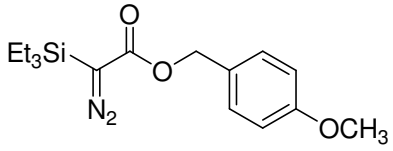
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25-7.17 (m, 5H, arom. C*H*), 5.08 (s, 2H, PhCH_2), 1.26-1.13 (m, 3H, C*H*(CH_3)$_2$), 0.96 (d, *J* = 7.7 Hz, 18H, CH(CH_3)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): 169.1, 136.2, 128.4, 128.2, 128.1, 66.3, 42.3, 18.2, 11.4.

IR (neat): 2947, 2868, 2087, 1690, 1257, 1198.

EI-MS: *m/z* = 289 (63), 221 (77), 91 (100).

5.4.5 4-Methoxybenzyl 2-diazo-2-triethylsilyl acetate (173e)



704 mg, 2.2 mmol; 73% yield; yellow oil; (20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.8 Hz, 2H, arom. C*H*), 6.88 (d, *J* = 8.8 Hz, 2H, arom. C*H*), 5.10 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 0.96 (t, *J* = 8.0 Hz, 9H, CH_2CH_3) 0.73 (q, *J* = 7.9 Hz, 6H, C$H_2$$CH_3$).

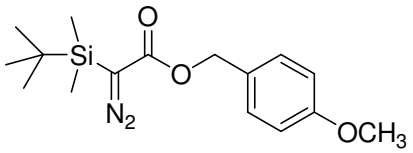
^{13}C NMR (100 MHz, $CDCl_3$): 168.8, 159.5, 129.9, 128.3, 113.9, 66.3, 55.3, 7.2, 3.3.

IR (neat): 2953, 2090, 1686, 1258, 1178, 737.

CI-MS (methane): *m/z* = 263 (5), 183 (3), 136 (8), 122 (8), 121 (100).

Anal. Calcd. for $C_{16}H_{24}N_2O_3Si$: C 60.00; H 7.55; N 8.74 . **Found:** C 59.94; H 7.06; N 8.74.

5.4.6 4-Methoxybenzyl 2-diazo-2-*tert*-butyldimethylsilyl acetate (173f)



211 mg, 0.66 mmol; 22% yield; yellow oil; (20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.8 Hz, 2H, arom. C*H*), 6.88 (d, *J* = 8.8 Hz, 2H, arom. C*H*), 5.10 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 0.92 (s, 9H, C(CH_3)$_3$) 0.20 (s, 6H, Si(CH_3)$_2$).

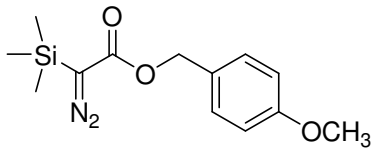
^{13}C NMR (100 MHz, $CDCl_3$): 168.6, 159.5, 130.1, 128.3, 113.8, 66.3, 55.3, 26.5, 25.8, 18.9, -6.6.

IR (neat): 2089, 1687, 1254, 824.

CI-MS (*iso*butane): *m/z* = 294 (7), 293 (34), 277 (7), 171 (7), 122 (9), 121 (100).

Anal. Calcd. for $C_{16}H_{24}N_2O_3Si$: C 59.97; H 7.55; N 8.74 . **Found:** C 60.46; H 7.86; N 7.80.

5.4.7 4-Methoxybenzyl 2-diazo-2-trimethylsilyl acetate (173g)[165]



474 mg, 1.7 mmol; 58% yield, yellow oil; (20:1).

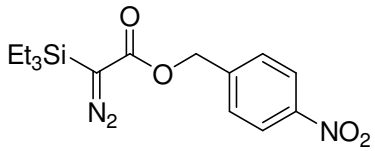
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.5 Hz, 2H, arom. C*H*), 6.88 (d, *J* = 8.5 Hz, 2H, arom. C*H*), 5.11 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 0.24 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 168.5, 159.4, 129.0, 128.3, 113.8, 66.2, 55.3, -1.4.

IR (neat): 2092, 1685, 1515, 1265, 1211, 1176, 1079, 1038, 846.

CI-MS (methane): *m/z* = 279 (M^+, 1), 250 (3), 161 (3), 149 (5), 141 (3), 137 (5), 136 (6), 121 (100).

5.4.8 4-Nitro 2-diazo-2-trimethylsilyl acetate (173h)



871 mg, 2.6 mmol; 85% yield; yellow solid; (20:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.9 Hz, 2H, arom. C*H*), 7.48 (d, *J* = 8.9 Hz, 2H, arom. C*H*), 5.24 (s, 2H, $PhCH_2$), 0.94 (t, *J* = 8.4 Hz, 9H, CH_2CH_3), 0.72 (q, *J* = 7.9 Hz, 6H, CH_2CH_3).

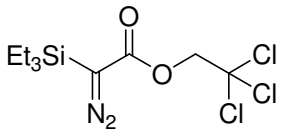
^{13}C NMR (75 MHz, $CDCl_3$): 168.8, 147.6, 143.6, 128.2, 123.7, 42.2, 64.8, 6.9, 3.0.

IR (KBr): 2948, 2089, 1685, 1524, 1347, 838, 736, 701.

CI-MS (*iso*butane): *m/z* = 337 (M^++2, 21), 336 (M^++1, 100).

Anal. Calcd. for $C_{15}H_{21}N_3O_4Si$: C 53.71; H 6.31; N 12.53 . **Found:** C 53.78; H 6.52; N 12.45.

5.4.9 2,2,2-Trichloroethanol 2-diazo-2-triethylsilyl acetate (173i)[a]



49% yield;[a] yellow oil; (20:1)

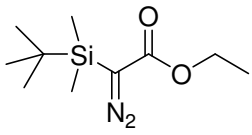
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.80 (s, 2H, OCH_2), 0.99 (t, *J* = 7.8 Hz, 9H, CH_3CH_2), 0.77 (q, *J* = 7.8 Hz, 6H, CH_3CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): 186.6, 95.3, 74.1, 7.2, 3.2.

CI-MS (metan): *m/z* = 304 (7), 302 (7), 275 (9), 273 (9), 269 (19), 267 (27), 241 (9), 239 (15), 209 (10), 207 (22), 205 (29), 203 (12), 201 (11), 199 (16), 199 (52), 197 (87), 191 (10), 181 (8), 179 (27), 177 (25), 161 (14), 156 (12), 155 (100), 129 (8), 127 (12), 123 (19), 121 (59), 111 (18), 71 (11).

[a]*Note: the title compound was purified via flash chromatrography on silica gel, though contained 20% of $Et_3SiOSiEt_3$ and possible traces of Et_3SiOH.*

5.4.10 Ethyl 2-diazo-2-*tert*-butyldimethylsilyl acetate (175)[165]



388 mg, 1.7 mmol; 57% yield; yellow oil; (20:1).

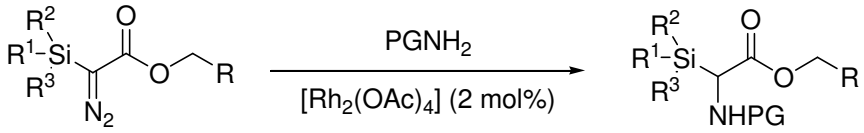
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.17 (q, *J* = 7.14 Hz, 2H, CH_2CH_3), 1.25 (t, *J* = 7.14 Hz, 3H, CH_2CH_3), 0.94 (s, 9H, $C(CH_3)_3$), 0.21 (s, 6H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 168.6, 60.7, 26.5, 18.9, 14.6, -6.1.

IR (neat): 2945, 2090, 1692, 1262, 1201, 833.

CI-MS (methane): *m/z* = 201 (19), 200 (74), 185 (88), 173 (89), 171 (17), 145 (37), 143 (28), 117 (20), 115 (38), 103 (100), 75 (48), 73 (23).

5.5 Synthesis of *N*-Protected 2-Trialkylsilyl-2-Amino Acetates

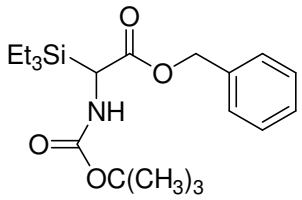


173, **175** **174a-f**

PG = *t*BuOC(O) or $PhCH_2OC(O)$

Rhodium(II) tetracetate [$Rh_2(OAc)_4$] (17.7 mg, 0.04 mmol, 2 mol%) was added to a stirring solution of benzyl 2-diazo-2-triethylsilyl acetate (**173a**) (2.0 mmol) or benzyl 2-diazo-2-*tert*-butyl-dimethylsilyl acetate (**173b**) (2.0 mmol) and the corresponding carbamate (5.0 mmol) in anhydrous toluene (10 mL). The reaction mixture was heated to 45-50 °C for 24 hours. The solvent was then removed under reduced pressure and the crude were then purified *via* flash chromatrography on silica gel (pentane/ethyl acetate = 10:1) to afford the pure **173a** or **173b**. The corresponding benzyl 2-(benzyloxy)-2-(triethylsilyl) acetate (**200a**) or benzyl 2-(benzyloxy)-2-(*tert*-butyldimethylsilyl) acetate (**200b**) were isolated as side products.

5.5.1 *Tert*-butyl [(benzyloxy)carbonyl](triethylsilyl) methylcarbamate (174a)[174]



Tert-butyl carbamate (293 mg, 5.0 mmol) was used as reagent for the insertion reaction.
455 mg, 1.2 mmol; 60% yield; colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34-7.28 (m, 5H, arom. C*H*), 5.17-5.13 (m, 1H, C*H*HPh, AX system), 5.09-5.05 (m, 1H, CH*H*Ph, AX system), 4.89 (br d, *J* = 9.2 Hz, 1H, N*H*), 4.21 (d, *J* = 9.2 Hz, 1H, C*H*N), 1.42 (s, 9H, $C(CH_3)_3$), 0.94 (t, *J* = 7.9 Hz, 9H, CH_2CH_3), 0.59 (q, *J* = 7.8 Hz, 6H, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): 173.3, 155.9, 135.6, 128.6, 128.4, 128.2, 79.7, 66.5, 44.5, 28.3, 7.0, 2.2.

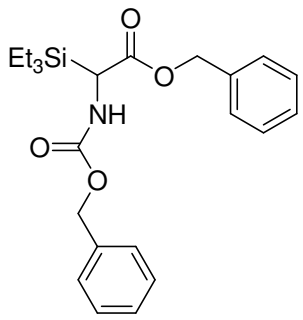
[174] This compound was already reported in the literature without a fully characterization: see ref. [100].

IR (neat): 2957, 2879, 1711, 1496, 1311, 1170, 1015, 739.

CI-MS (*iso*butane): *m/z* = 381 (M^++2, 13), 380 (M^++1, 49), 325 (23), 324 (100) 210 (81).

Anal. Calcd. for $C_{20}H_{33}NO_4Si$: C 63.29; H 8.76; N 3.69. **Found:** C 62.80; H 8.01; N 4.39.

5.5.2 Benzyl [(benzyloxy)carbonyl](triethylsilyl) methylcarbamate (174b)[174]



Benzyl carbamate (756 mg, 5.0 mmol) was used as reagent for the insertion reaction.

454 mg, 1.1 mmol; 56% yield; colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35-7.33 (m, 10H, arom. C*H*), 5.19-5.07 (m, 5H, N*H*, CH_2Ph), 4.28 (d, *J* = 9.2 Hz, 1H, C*H*N), 0.92 (t, *J* = 7.9 Hz, 9H, CH_2CH_3), 0.61 (q, *J* = 7.8 Hz, 6H, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): 173.1, 156.6, 136.4, 135.6, 128.7, 128.6, 128.4, 128.2, 67.2, 66.8, 45.1, 7.0, 2.2.

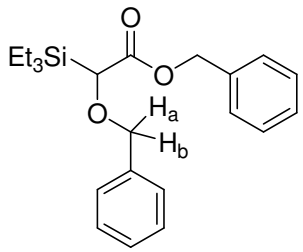
IR (neat): 2955, 2878, 1720, 1505, 1188, 739, 699.

CI-MS (*iso*butane): *m/z* = 416 (8), 415 (29), 414 (M^++1, 100), 300 (9).

EI-MS: *m/z* = 193 (10), 150 (10), 115 (14), 108 (11), 107 (13), 92 (15), 91 (100), 87 (12).

Anal. Calcd. for $C_{23}H_{31}NO_4Si$: C 66.79; H 7.55; N 3.39. **Found:** C 65.95; H 7.52; N 3.92.

5.5.3 Benzyl 2-(benzyloxy)-2-(triethylsilyl) acetate (200a)[175]



89 mg, 0.24 mmol; 12% yield; pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.27 (m, 10H, arom. C*H*), 5.18 (s, 2H, CH_2Ph), 4.80-4.76 (m, 1H, OCH_aH$_b$, AB system), 4.30-4.26 (m, 1H, OCH$_a$$H_b$, AB system), 4.00 (s, 1H, C*H*O), 0.91 (t, *J* = 7.9 Hz, 9H, CH_2CH_3), 0.62 (q, *J* = 7.9 Hz, 6H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 173.7, 138.1, 136.0, 128.7, 128.6, 128.3, 128.3, 128.2, 127.7, 74.8, 72.3, 66.1, 7.2, 2.1.

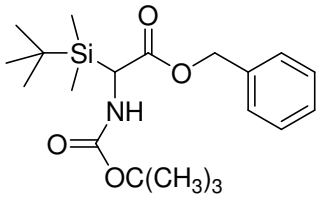
IR (neat): 2953, 2880, 1732, 1417, 1245, 1174, 1091, 1009, 736, 702.

CI-MS (*iso*buthane): *m/z* = 372 (M^++2, 28), 371 (M^++1, 100).

CI-MS (methane): *m/z* = 372 (M^++2, 19), 371 (M^++1, 71), 313 (28), 279 (17), 236 (21), 235 (100), 193 (15), 181 (80), 133 (13), 119 (16), 115 (11), 91 (99).

Anal. Calcd. for $C_{22}H_{30}O_3Si$: C 71.31; H 8.16. **Found:** C 71.12; H 8.50.

5.5.4 *Tert*-butyl [(benzyloxy)carbonyl] (*tert*-butyldimethylsilyl) methylcarbamate (174c)[174]



T*ert*-butyl carbamate (293 mg, 5.0 mmol) was used as reagent for the insertion reaction.

167 mg; 0.44 mmol; 22% yield; colourless oil.

[175] The title compound was already reported in literature but synthesised following a different procedure: see S. Saladin, PhD Thesis, Aachen **2004**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.30 (m, 5H, arom. C*H*), 5.12 (s, 2H, CH_2Ph), 4.87 (br d, *J* = 9.1 Hz, 1H, N*H*), 4.22 (d, *J* = 9.1 Hz, 1H, C*H*N), 1.43 (s, 9H, C(CH_3)$_3$), 0.91 (s, 9H, C(CH_3)$_3$), 0.08 (s, 3H, CH_3), 0.01 (s, 3H, CH_3).

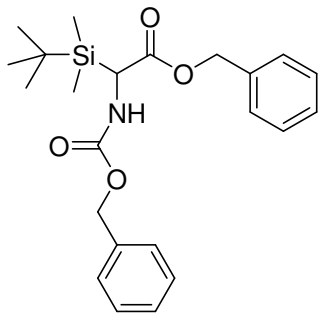
^{13}C NMR (100 MHz, $CDCl_3$): 173.2, 155.7, 135.5, 128.5, 128.4, 128.2, 79.8, 66.6, 45.1, 28.4, 26.6, 17.5, -6.7, -7.16.

IR (neat): 3346, 2952, 2890, 2859, 1727, 1527, 1465, 1319, 1257, 1172, 1017, 846, 751.

CI-MS (methane): *m/z* = 380 (M^++1, 13), 325 (24), 324 (100), 308 (34), 306 (17), 281 (13), 280 (59), 266 (26), 216 (12), 91 (12).

Anal. Calcd. for $C_{20}H_{33}NO_4Si$: C 63.29; H 8.76; N 3.69. **Found:** C 63.22; H 8.77; N 3.25.

5.5.6 Benzyl [(benzyloxy)carbonyl] (*tert*-butyldimethylsilyl) methylcarbamate (174d)[174]



Benzyl carbamate (756 mg, 5.0 mmol) was used as reagent for the insertion reaction.

132 mmol, 0.32 mmol; 16% yield; colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38-7.31 (m, 10H, arom. C*H*), 5.11-5.08 (m, 5H, N*H*, CH_2Ph), 4.28 (d, *J* = 9.4 Hz, 1H, C*H*N), 0.90 (s, 9H, C(CH_3)$_3$), 0.08 (s, 3H, CH_3), 0.00 (s, 3H, CH_3).

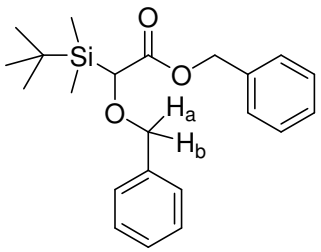
^{13}C NMR (100 MHz, $CDCl_3$): 173.0, 156.4, 135.4, 128.7, 128.5, 128.3, 128.1, 67.3, 66.8, 45.7, 26.6, 17.6, -6.6, -7.3.

IR (neat): 2936, 1721, 1504, 1311, 1252, 1189, 844.

CI-MS (*iso*butane): *m/z* = 415 (30), 414 (M^++1, 100), 370 (12), 181 (10).

Anal. Calcd. For $C_{23}H_{31}NO_4Si$: C 66.79; H 7.56; N 3.39. **Found:** C 66.09; H 6.75; N 3.65

5.5.7 Benzyl 2-(*tert*- butyldimethylsilyl)-2-(benzyloxy) acetate (200b)[175]



118 mg, 0.32 mmol; 16% yield; pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.27 (m, 10H, arom. C*H*), 5.18 (q, *J* = 12.5 Hz, 2H, CH_2Ph), 4.75-4.72 (m, OCH_aH$_b$, AB system), 4.31-4.28 (m, 1H, OCH$_a$$H_b$, AB system), 4.01 (s, 1H, C*H*O), 0.90 (s, 9H, C(CH_3)$_3$), 0.07 (s, 3H, CH_3), 0.01 (s, 3H, CH_3).

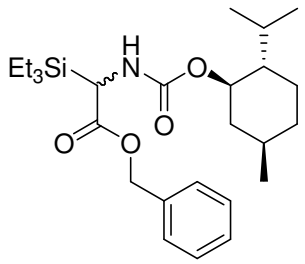
^{13}C NMR (100 MHz, $CDCl_3$): 173.4, 137.5, 135.9, 128.7, 128.5, 128.3, 128.2, 128.2 127.8, 74.8, 73.3, 66.2, 26.7, 17.4, -6.7, -7.6.

IR (neat): 2936, 2859, 1731, 1461, 1252, 1174, 1137, 1093, 838, 744, 699.

CI-MS (*iso*butane): *m/z* = 372 (M^++2, 30), 371 (M^++1, 100), 181 (11).

Anal. Calcd. for $C_{22}H_{30}O_3Si$: C 71.31; H 8.16. **Found:** C 70.84; H 8.67.

5.5.8 (1*R*,2*S*,5*R*)-2-*iso*-Propyl-5-methylcyclohexyl [(benzyloxy)carbonyl)] (triethylsilyl) methylcarbamate (174h)



The title compound was synthesised following the reported procedure (section 5.5) starting from benzyl 2-diazo-2-triethylsilyl acetate (**173a**) (581 mg, 2.0 mmol) and (1*R*,2*S*,5*R*)-2-*iso*-propyl-5-methylcyclohexyl carbamate (**204**) (997 mg, 5.0 mmol).

Mixture of diasteromers, *dr*: 75:25; 332 mg, 0.72 mmol; 36% yield; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36-7.31 (m, 5H, arom. C*H*), 5.14 (s, 2H, CH_2Ph), 5.13 (s, 2H, CH_2Ph), 4.89 (d, *J* = 9.4 Hz, 1H, CHN*H*), 4.56-4.53 (m, 1H, OC*H*), 4.29 (d, *J* = 9.1 Hz, 1H, C*H*NH), 2.02 (m, 1H, CH menthyl), 1.71-1.61 (m, 3H menthyl), 1.50-1.38 (m, 2H menthyl), 1.35-

1.23 (m, 3H menthyl), 1.00-0.86 (m, 9H, CH_3 menthyl), 0.77 (t, J = 8.1 Hz, CH_3CH$_2$Si), 0.59 (q, J = 8.1 Hz, CH$_3$CH_2Si).

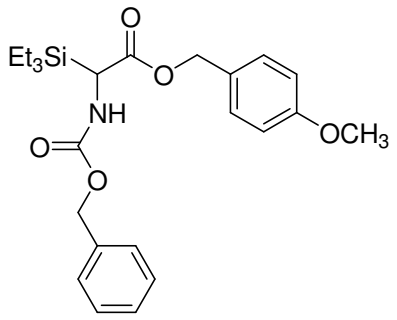
^{13}C NMR (100 MHz, $CDCl_3$): 173.0, 156.4, 135.5, 128.5, 128.5, 128.4, 128.3, 75.2, 75.1, 66.7, 47.5, 47.4, 45.0, 41.6, 41.4, 34.4, 31.5, 31.4, 26.6, 26.2, 23.8, 23.6, 22.1, 20.9, 20.8, 16.7, 16.5, 7.1, 2.4.

IR (neat): 3364, 2953, 1716, 1501, 1460, 1310, 1183, 1030, 738, 701.

CI-MS (methane): *m/z* = 463 (M^++2, 28), 462 (M^++1, 100), 325 (21), 324 (96), 306 (15), 294 (32), 280 (33), 210 (17).

Anal. Calcd. for $C_{26}H_{43}NO_4Si$: C 67.64; H 9.39; N 3.03. **Found:** C 67.75; H 8.94; N 3.37.

5.5.9 Benzyl [(4-methoxybenzyloxy)carbonyl] (triethylsilyl) methylcarbamate (174e)



The title compound was synthesised following the reported procedure (section 5.5) starting from 4-methoxybenzyl 2-diazo-2-triethylsilyl acetate (**173a**) (348 mg, 1.06 mmol) and benzyl carbamate (401 mg, 2.65 mmol).

84 mg, 0.19 mmol; 18% yield; colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37-7.25 (m, 7H, arom. CH), 6.88 (d, J = 8.4 Hz, 2H, arom. CH), 5.18-5.03 (m, 5H,CH_2Ph, NH), 4.27 (d, J = 9.2 Hz, 1H, CHN), 3.80 (s, 3H, OCH_3), 0.92 (t, J = 7.9 Hz, 9H, CH$_2$CH_3), 0.59 (q, J = 7.9 Hz, 6H, CH_2CH$_3$).

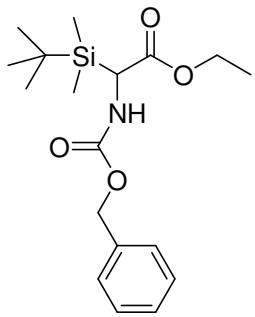
^{13}C NMR (75 MHz, $CDCl_3$): 173.1, 159.7, 156.6, 136.4, 132.1, 130.5, 128.5, 128.2, 127.8, 113.9, 67.2, 66.5, 55.3, 45.1, 7.0, 1.3.

IR (neat): 2955, 2912, 2879, 1718, 1515, 1307, 1251, 1178, 1034, 823, 741, 701.

CI-MS (*iso*butane): *m/z* = 414 (6), 263 (5), 211 (7), 122 (9), 121 (100).

Anal. Calcd. for $C_{24}H_{33}NO_5Si$: C 64.98; H 7.50; N 3.16. **Found:** C 64.62; H 7.77; N 3.11.

5.5.10 Benzyl (ethoxycarbonyl) (*tert*-butyldimethylsilyl) methylcarbamate (174f)[174]



The title compound was synthesised following the reported procedure (section 5.5) starting from ethyl 2-diazo-2-*tert*-butyldimethylsilyl acetate (**175**) (278 mg, 1.22 mmol) and benzyl carbamate (461 mg, 3.05 mmol).

179 mg, 0.51 mmol; 42% yield; colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.29 (m, 5H, arom. C*H*), 5.11 (s, 3H, N*H*, CH_2Ph), 4.23 (d, *J* = 9.4 Hz, 1H, C*H*N), 4.22-4.09 (m, 2H, CH_2CH$_3$), 1.26 (t, *J* = 7.2 Hz, 3H, CH$_2$CH_3), 0.95 (s, 9H, SiC(CH_3)$_3$), 0.12 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3).

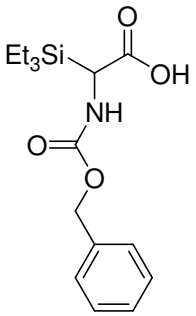
^{13}C NMR (75 MHz, $CDCl_3$): 173.3, 156.5, 128.6, 128.3, 128.2, 67.2, 60.8, 45.5, 26.5, 17.5, 14.3, -6.8, -7.3.

IR (neat): 2934, 2897, 2860, 1717, 1507, 1467, 1313, 1254, 1198, 1041, 846, 777.

EI-MS: *m/z* = 351 (M^+, 18), 216 (20), 91 (100), 73 (60).

Anal. Calcd. for $C_{18}H_{35}NO_4Si$: C 61.50; H 8.32; N 3.98. **Found:** C 61.19; H 8.14; N 4.40.

5.6 *N*-Cbz-substituted 2-triethylsilyl-2-amino acetic acid (215)[176]



Aluminum thrichloride (1 mg, 0.01 mmol) was added to a mixture of benzyl [(4-methoxybenzyloxy)carbonyl] (triethylsilyl) methylcarbamate (**174e**) (15 mg, 0.03 mmol) and

[176] For a detailed discussion on the named compound see section 3.4.1.

ethanthiol (0.1 mL, 0.12 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at room temperature for 24 hours and then washed with brine. The organic phase was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. ^{1}H NMR, ^{13}C NMR and GC-MS analysis refer to the compound **215** in mixture with substrate **174e** [ratio (**215**)/(**174e**) = 1.6:1] and with *p*-methoxybenzyl ethylsulfide.

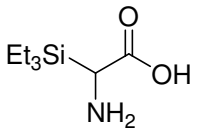
^{1}H NMR (400 MHz, $CDCl_3$): 7.37-7.32 (m, 5H, arom. C*H*), 5.12 (s, 2H, CH_2Ph), 5.05 (br d, *J* = 8.6 Hz, 1H, CHN*H*), 4.04 (d, *J* = 8.9 Hz, 1H, C*H*NH), 0.99 (t, *J* = 7.8 Hz, 9H, CH_2CH_3), 0.64 (q, *J* = 8.9 Hz, 6H, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): 178.0, 156.6, 140,8, 130.6, 128.2, 128.1, 67.4, 45.0, 7.20, 2.36.

GC-MS: *t* = 43.21 min. (Run time 64.00 min.; initial temp. 40 °C for 3 min.; ramp 1, 5 °C/min. up to 200 °C; ramp 2, 20 °C/min. up to 280 °C; pressure in precolumn: 0.63 bar; flow 1.2 mL/min.).

m/z = 294 (M^+–29, 5), 250 (4), 186 (95), 158 (10), 144 (4), 128 (13), 115 (64), 91 (100), 79 (38), 70 (3), 59 (18), 45 (12).

5.7 2-Triethylsilyl-2-amino acetic acid (226)[177]



To a stirring solution of benzyl [(benzyloxy)carbonyl](triethylsilyl)methylcarbamate (**174b**) (300 mg, 0.73 mmol) in methanol (7 mL) was added 10% palladium on charcoal (73 mg, 0.069 mmol). A balloon containing molecular hydrogen was attached, and the mixture was stirred at room temperature for 0.5 hour. The palladium was then filtered off using paper filters and the solvent was removed under reduced pressure affording the pure compound **226**.

114 mg, 0.60 mmol; 81% yield; white solid.

^{1}H NMR (400 MHz, CD_3OD): δ = 3.80 (s, 1H, C*H*NH), 0.96 (t, *J* = 7.8 Hz, 9H, CH_2CH_3), 0.61 (q, *J* = 7.8 Hz, 6H, CH_2CH_3).

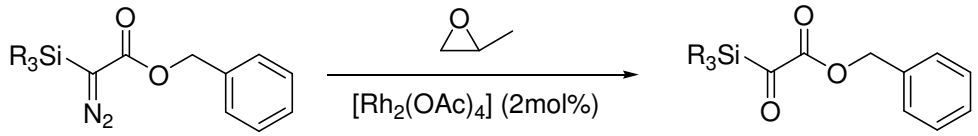
^{13}C NMR (100 MHz, CD_3OD): 175.8, 40.2, 7.0, 4.9.

IR (KBr): 3183, 3111, 2918, 1598, 1500, 1401, 1334, 1120, 925, 892.

EI-MS: *m/z* = 189 (M^+, 9), 161 (9), 131 (8), 116 (9), 115 (72), 107 (14), 105 (16), 103 (23), 92 (22), 58 (19).

[177] For a detailed discussion on the characterisation of the named compound see section 3.5.

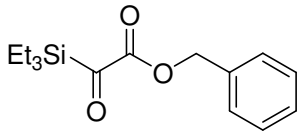
5.8 Synthesis of Benzyl 2-Trialkylsilyl-2-Oxoacetates



173a, **173b** **185**, **182**

Rhodium(II) tetracetate [$Rh_2(OAc)_4$] (17.7 mg, 0.04 mmol, 2 mol%) and propylene oxide (2.1 mL, 30 mmol), were added to a stirring solution of benzyl 2-diazo-2-triethylsilyl acetate (**173a**) (2.0 mmol) or benzyl 2-diazo-2-*tert*-butyl-dimethylsilyl acetate (**173b**) (2.0 mmol) in anhydrous toluene (10 mL). The reaction mixture was heated to 50 °C and left stirring at this temperature for 72 hours. The solvent was then removed under reduced pressure and the crude reaction mixture was dissolved in pentane and eluited through a small column containing Florisil® to afford benzyl 2-triethylsilyl-2-oxoacetate (**185**) or benzyl 2-*tert*-butyldimethylsilyl-2-oxoacetate (**182**).

5.8.1 Benzyl 2-triethylsilyl-2-oxoacetate (185)[165]



512 mg, 1.8 mmol; 92% yield; bright yellow oil.

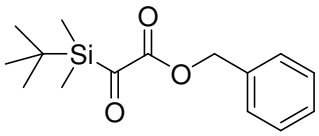
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.33 (m, 5H, arom. C*H*), 5.26 (s, 2H, PhCH_2), 0.94 (t, *J* = 8.5 Hz, 9H, CH_2CH_3), 0.80 (q, *J* = 8.5 Hz, 6H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 232.3, 162.4, 134.7, 128.9, 128.9, 67.6, 7.5, 2.5.

IR (neat): 2957, 2913, 2877, 1743, 1720, 1661, 1459, 1262, 1241, 1216, 1003, 972, 745, 698.

EI-MS: *m/z* = 278 (M^+, 13), 221 (11), 193 (25), 163 (20), 143 (21), 115 (100), 91 (52), 87 (88).

5.8.2 Benzyl 2-*tert*-butyldimethylsilyl-2-oxoacetate (182)[165]



519 mg, 1.9 mmol; 93% yield; bright yellow oil.

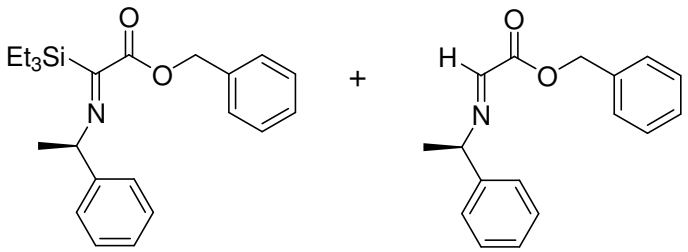
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41-7.30 (m, 5H, arom. C*H*), 5.25 (s, 2H, PhCH_2), 0.93 (s, 9H, SiC(CH_3)$_3$), 0.24 (s, 6H, SiCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 162.5, 134.8, 128.8, 128.8, 128.7, 67.4, 26.5, 19.1, -6.8.

IR (neat): 2954, 2933, 2889, 2859, 1741, 1463, 1257, 1172, 841.

EI-MS: *m/z* = 165 (8), 149 (6), 133 (15), 115 (20), 91 (100), 73 (32).

5.9 Benzyl 2-((*R*)-1-phenylethylimino)-2-triethylsilyl acetate (186)[178]



186 **187**

(*R*)-(+)-1-phenylethyl amine (0.04 mL, 0.34 mmol) was added to a stirring solution of benzyl 2-triethylsilyl-2-oxoacetate (**185**) (95 mg, 0.34 mmol) in anhydrous dichloromethane (5 mL) and the reaxtion mixture was stirred at room temperature for 24 hours. The solvent was then removed under reduced pressure. The crude reaction mixture was then purified *via* flash chromatrography on silica gel (petroleum ether/ethyl acetate = 4:1) to afford an inseparable mixture (34 mg) of imine **186** and of its desilylated derivative, imine **187** [ratio (**186**)/(**187**) = 1:4.8].

Analytical data for imine **186**:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43-7.26 (m, 5H, arom. C*H*), 5.31 (s, 2H, CH_2Ph), 4.33 (q, *J* = 6.8 Hz, 1H, C*H*CH_3), 1.61 (s, 3H, CHCH_3), 0.98 (t, *J* = 7.9 Hz, 9H, CH_2CH_3), 0.60 (q, *J* = 7.9 Hz, 6H, C$H_2$$CH_3$).

Analytical data for imine **187**:

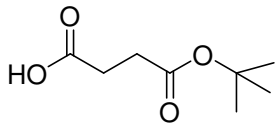
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (s, 1H, C*H*N), 7.43-7.26 (m, 5H, arom. C*H*), 5.31 (s, 2H, CH_2Ph), 4.61 (q, *J* = 6.8 Hz, 1H, C*H*CH_3), 1.63 (s, 3H, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): 168.0, 162.5, 152.1, 128.7, 127.6, 126.9, 69.8, 67.4, 23.8.

[178] For a detailed discussion on the named compound see section 3.2.1.

5.10 Toward the Syhthesis of a Sila Analogue of a MMP Inhibitor: the Succinyl Hydroxamic Acid Building Block

5.10.1 2-(*Tert*-butoxycarbonyl) propanoic acid (244)[179]



Tert-butanol (2.8 mL, 30 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.45 g, 4 mmol) were added to a stirring solution of succinic anhydride (1.0 g, 10 mmol) in anhydrous toluene (10 mL) and the reaction mixture was heated to reflux and stirred overnight. After cooling to room temperature, ethyl acetate (5 mL) was added and the organic layer was washed three times with HCl 5% and once with brine, then dried over $MgSO_4$ and filtered. The solvent was then removed under reduced pressure and the crude product was recrystallized from diethylether to afford the pure product **244**.

1.2 g, 6.9 mmol; 69% yield; brown solid.

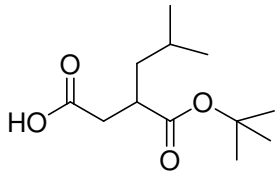
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.91 (br s, 1H, COOH), 2.64-2.57 (m, 2H, CH_2COOH), 2.55-2.50 (m, 2H, CH_2COC(CH_3)$_3$), 1.43 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): 178.6, 171.5, 81.1, 30.2, 29.1, 28.1.

IR (KBr): 1721, 1440, 1373, 1252, 1155, 936, 843.

CI-MS (methane): *m/z* = 175 (M^++1, 4), 159 (5), 147 (4), 129 (19), 120 (5), 119 (100), 101 (51).

5.10.2 3-(*Tert*-butoxycarbonyl)-5-methylhexanoic acid (246)



A solution of *n*-butyl lithium (7.9 mL, 12.5 mmol) was added to *iso*-propylamine (1.8 mL, 12.5 mmol) in THF (10 mL) at 0 °C. The mixture was stirred for 10 minutes at 0 °C and then cooled to –78 ° C. A solution of 2-(*tert*-butoxycarbonyl) propanoic acid (**244**) (1.0 g, 5.7 mmol) in THF (5 mL) was then added and the solution was stirred at that temperature for 0.5 hours. 1-Iodo-1-

[179] The named compound was synthesised through a modification of a reported procedure: see ref. [144b]

methylpropane (0.93 mL, 8.0 mmol) was added drop wise. The reaction was allowed to warm at room temperature, stirred for 24 hours and then quenched with water (3 mL) and concentrated. To the residue was then added ethyl acetate (30 mL) and the mixture was washed with HCl 5% (20 mL), dried on $MgSO_4$ and filtered. The solvent was then removed under reduced pressure and the crude product was then purified *via* flash chromatrography on silica gel (petroleum ether/ethyl acetate = 7:3) to afford the pure product **246**.

433 mg, 1.88 mmol; 33 % yield; colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.79-2.72 (m, 1H), 2.69-2.63 (m, 1H), 2.41 (dd, *J* = 16.5, 4.7 Hz, 1H), 1.65-1.52 (m, 2H), 1.44 (s, 9H, $C(CH_3)_3$), 1.26 (quin, *J* = 6.8 Hz, 1H, $CH_2CH(CH_3)_2$), 0.91 (dd, *J* = 15.8, 6.5 Hz, 6H, $CH_2CH(CH_3)_2$).

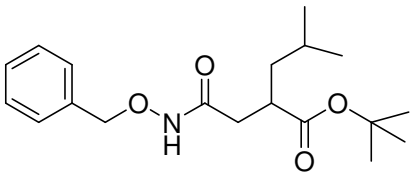
^{13}C NMR (75 MHz, $CDCl_3$): 174.4, 80.9, 41.3, 40.3, 36.5, 28.1, 25.9, 22.8, 22.3.

IR (neat): 2961, 1717, 1156.

CI-MS (methane): *m/z* = 231 (M^++1, 3), 185 (5), 176 (9), 175 (100), 158 (5), 157 (62), 61 (9).

Anal. Calcd. for $C_{12}H_{22}O_4$: C 62.58; H 9.63. **Found:** C 62.85; H 9.77.

5.10.3 *Tert*-butyl 2-((benzyloxycarbamoyl)methyl)-4-methylpentanoate (247)



To a stirred solution of 3-(*tert*-butoxycarbonyl)-5-methylhexanoic acid (**246**) (433 mg, 1.88 mmol) in THF (10 mL), was added benzyl hydroxyl amine (231 mg, 1.88 mmol) (formed from the corresponding hydrochloride salt) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (23 mg, 0.19 mmol) and the mixture was cooled to 0 °C. A 1 M solution of *N*,*N*'-dicyclohexylcarbodiimide (DCC) (1.88 mL, 1.88 mmol) in dichloromethane was then added. After addition, the reaction mixture was heated to reflux for 12 hours. The precipitated urea was filtered off and the filtrate was washed with 5% NaOH and 5% HCl. The organic phase was then dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to afford the crude product which was then purified *via* flash chromatrography on silica gel (petroleum ether/ethyl acetate = 3:2) to afford the pure product **247**.

329 mg , 0.98 mmol; 52% yield; colourless oil.

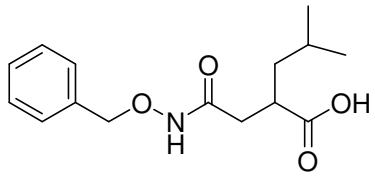
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.5 (br s, 1H, N*H*), 7.37-7.26 (m, 5H, arom. C*H*), 4.87 (s, 2H CH_2Ph), 2.79-2.63 (m, 1H), 2.36-1.72 (m, 2H), 1.61-1.38 (m, 2H), 1.39 (s, 9H, C(CH_3)$_3$), 1.26-1.18 (m, 1H, CH_2C*H*(CH_3)$_2$), 0.89 (dd, *J* = 11.3, 6.4 Hz, 6H, CH_2CH(CH_3)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): 175.1, 169.7, 129.2, 128.8, 128.6, 81.0, 78.2, 41.6, 40.6, 39.1, 28.1, 25.9, 22.8, 22.2.

IR ($CHCl_3$): 3191, 2960, 2873, 1726, 1662, 1368, 1155, 753.

CI-MS (methane): *m/z* = 336 (M^++1, 6), 308 (7), 281 (16), 280 (100), 262 (7), 174 (16), 107 (9).

5.10.4 2-((Benzyloxycarbamoyl)methyl)-4-methylpentanoic acid (248)



To a stirring solution of *tert*-butyl 2-((benzyloxycarbamoyl)methyl)-4-methylpentanoate (**247**) (329 mg , 0.98 mmol) in dichloromethane (10 mL), was added trifluoroacetic acid (0.23 mL, 2.94 mmol) and the mixture was then stirred at room temperature for 15 hours. The reaction mixture was then washed with brine. The organic phase was then dried over $MgSO_4$ and filtered. The removal of the solvent afforded the crude product, which was then purified by recrystallization in diethylether to afford the pure product **248**.

179 mg, 0.64 mmol; 65% yield; white solid.

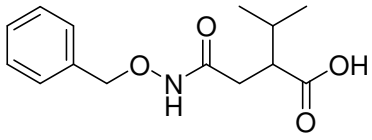
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47-7.35 (m, 5H, arom. C*H*), 5.10 (s, 2H CH_2Ph), 2.76-2.66 (m, 2H), 2.26-2.19 (m, 1H), 1.72-1.62 (m, 2H), 1.24-1.17 (m, 1H, CH_2C*H*(CH_3)$_2$), 0.90 (dd, *J* = 17.4, 6.2 Hz, 6H, CH_2CH(CH_3)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): 174.3, 170.6, 133.2, 130.0, 129.3, 78.4, 40.6, 35.5, 32.3, 25.8, 23.0, 21.6.

IR (KBr): 1722, 1224.

EI-MS: *m/z* = 262 (69), 119 (7), 92 (8), 91 (100).

5.10.5 2-((Benzyloxycarbamoyl)methyl)-3-methylbutanoic acid (253)



Silver acetate (1.2 g, 7.2 mmol) was added to a stirring solution of *iso*-propyl mercury chloride (**249**) (2.0 g, 7.2 mmol) in methanol (15 mL). The resulting mixture was stirred at room temperature in the dark for 16 hours. The formed precipitate silver chloride was filtered off on a glass filter and washed with methanol. The filtrate was then evaporated under reduced pressure to afford the pure *iso*-propyl mercury acetate (**250**) (2.1 g, 6.9 mmol) in 96% yield. Compound **250** was added to a stirring solution of maleic anhydride (0,48 g, 4.9 mmol) in dichloromethane (20 mL) and the reaction mixture was cooled to 0 °C. A solution of sodium borohydride (0.38 g, 10 mmol) in water (1 mL) was then added one pot and the reaction mixture was allowed to warm at room temperature and stirred for 2 hours. The organic phase was then dried over $MgSO_4$ and filtered. The removal of the solvent under reduced pressure afforded the pure *iso*-propyl-succinic anhydride (**252**) (0.68 g, 4.7 mmol) in 95% yield. To a stirring solution of compound **252** in diethyl ether (10 mL) was then added benzyl hydroxyl amine (579 mg, 4.7 mmol) (formed from the corresponding hydrochloride salt) and the reaction mixture was stirred at room temperature for 24 hours. After this time a white precipitate was formed, which was filtered off. The removal of the solvent from the filtrate afforded the pure compound **253**.

0.7 g, 2.6 mmol; 56% yield; white solid.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.46-7.34 (m, 5H, arom. C*H*), 4.85 (s, 2H CH_2Ph), 2.79-2.74 (m, 1H), 2.41 (dd, *J* = 14.8, 10.0 Hz, 1H), 2.23 (dd, *J* = 14.8, 4.7 Hz, 1H), 2.04-1.96 (m, 1H, C*H*$(CH_3)_2$), 0.98 (dd, *J* = 6.7, 4.8 Hz, 6H, CH(C$H_3)_2$).

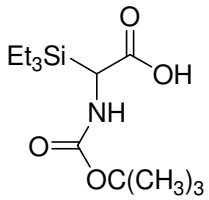
^{13}C NMR (100 MHz, CD_3OD): 177.6, 171.4, 136.9, 130.3, 129.6, 129.4, 79.0, 32.5, 31.3, 20.4, 20.1.

IR (KBr): 3236, 2960, 1714, 1650, 1520, 1237, 751.

CI-MS (methane): *m/z* = 266 (M^++1, 24), 248 (23), 171 (7), 144 (7), 143 (100), 142 (35), 124 (21), 115 (26), 107 (52), 97 (13), 91 (53), 79 (14).

5.11 Toward the Syhthesis of a Sila Analogue of a MMP Inhibitor: the α-Silyl α-Amino Acid Building Block

5.12.1 *N*-Boc-substituted 2-triethylsilyl-2-amino acetic acid (211)



To a stirring solution of *tert*-butyl [(benzyloxy)carbonyl](triethylsilyl)methylcarbamate (**174a**) (200 mg, 0.7 mmol) in methanol (5 mL) was added 10% palladium on charcoal (70 mg). A balloon containing molecular hydrogen was attached, and the mixture was stirred at room temperature for ca. 1 hour. The palladium was then filtered off using paper filters and the solvent was removed under reduced pressure affording the pure compound **211**.

139 mg, 0.48 mmol; 68% yield; white solid, m. p. 89-90 °C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.28 (br s, 1H, COO*H*), 4.87 (d, *J* = 8.9 Hz, 1H, CHN*H*), 4.18 (d, *J* = 8.9 Hz, 1H, C*H*NH), 1.41 (s, 9H, $C(CH_3)_3$), 0.96 (t, *J* = 7.9 Hz, 9H, CH_2CH_3), 0.68 (q, *J* = 7.9 Hz, 6H, CH_2CH_3).

^{1}H NMR (300 MHz, CD_3OD): δ = 3.97 (s, 1H, CHN*H*), 3.27-3.26 (m, 1H, C*H*NH), 1.40 (s, 9H, $C(CH_3)_3$), 0.96 (t, *J* = 7.9 Hz, 9H, CH_2CH_3), 0.71 (q, *J* = 7.9 Hz, 6H, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): 179.4, 157.4, 79.9, 44.5, 28.3, 7.0, 2.2.

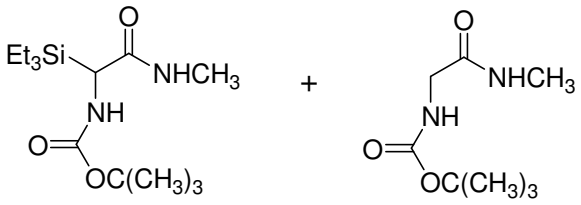
IR (KBr): 2957, 2361, 1673, 1400, 1311, 1171, 1017, 737.

CI-MS (*iso*butane): *m/z* = 290 (M^++1, 5), 262 (5), 236 (5), 235 (16), 234 (100), 233 (16).

EI-MS: *m/z* = 290 (M^++1, 4), 274 (6), 263 (5), 235 (25), 234 (100), 218 (4), 216 (6), 205 (9), 204 (37), 191 (9), 190 (35), 160 (5).

Anal. Calcd. for $C_{13}H_{27}NO_4Si$: C 53.95; H 9.40; N 4.84. **Found:** C 52.69; H 9.37; N 4.84.

5.11.2 *Tert*-butyl (methylcarbamoyl)(triethylsilyl) methylcarbamate (256)



256 **257**

Carbonyl diimidazol (156 mg, 0.96 mmol) was added to a solution of *N*-Boc-substituted 2-triethylsilyl-2-amino acetic acid (**211**) (139 mg, 0.48 mmol) in THF (4 mL) and stirred at room temperature for 1 hour. Methyl amine (2.0M in THF) (0.72 mL, 1.44 mmol) was added to the reaction mixture and stirred for further 14 hours. The solvent was then removed under reduced pressure to afford an inseparable mixture of amide **256** and of its desilylated derivative, amide **257** [ratio (**256**)/(**257**) = 1:1.5].

Analytical data for amide **256**:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.6 (br s, 1H, N*H*CH_3), 5.16 (br d, *J* = 8.9 Hz, 1H, CHN*H*), 3.79 (d, *J* = 8.9 Hz, 1H, C*H*NH), 2.78 (s, 3H, NHC*H*$_3$), 1.41 (s, C(C*H*$_3$)$_3$), 0.91 (t, *J* = 8.0 Hz, 9H, CH_2CH_3), 0.50 (q, *J* = 8.0 Hz, 6H, CH_2CH_3).

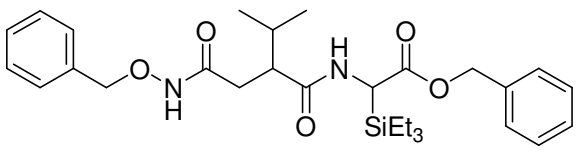
^{13}C NMR (100 MHz, $CDCl_3$): 170.5, 160.6, 79.9, 43.9 (?), 28.4, 26.2, 7.4, 2.5.

Analytical data for amide **257**:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.6 (br s, 1H, N*H*CH_3), 5.86 (br s, 1H, N*H*CH_3), 3.74 (d, *J* = 5.5 Hz, 2H, CH_2NH), 2.81 (s, 3H, NHC*H*$_3$), 1.44 (s, C(C*H*$_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 170.5, 160.6, 79.5, 43.9, 28.4, 27.1.

5.11.3 Silyl modified MMP inhibitor derivative (268)

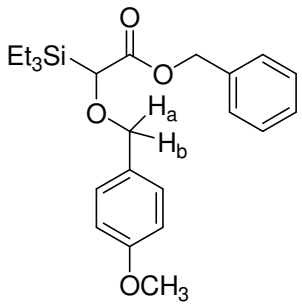


To a stirring solution of *tert*-butyl [(benzyloxy)carbonyl](triethylsilyl) methylcarbamate (**174a**) (50 mg, 0.14 mmol) in anhydrous dichloromethane (4 mL) was added trifluoroacetic acid (0.1 mL, 1.4 mmol) and mixture was stirred at room temperature for 2 hours. The solvent was then removed

under reduced pressure to eliminate the excess of trifluoroacetic acid. The residue was dissolved in a little amount of anhydrous dichloromethane and added to a stirring solution of 2-((benzyloxycarbamoyl)methyl)-3-methylbutanoic acid (**253**) (36 mg, 0.14 mmol) and PyBOP (80 mg, 0.15 mmol) in anhydrous dichloromethane (4 mL). Ethyldi*iso*propylamine (0.07 mL, 0.42 mmol) was added and the reaction mixture was stirred at room temperature for further 1 hour. After this time, a 1M solution of potassium bisulfate ($KHSO_4$) was added. The organic phase was then dried over $MgSO_4$ and filtered. The removal of the solvent under reduced pressure afforded the crude compound **268**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.29 (m, 10H, arom. C*H*), 5.14 (s, 1H, N*H*), 5.10 (s, 2H, CH_2Ph), 5.09 (s, 2H, CH_2Ph), 3.76 (br s, 1H, N*H*), 3.64 (m, 1H, C*H*NH), 2.70-2.55 (m, 2H), 2.34 (dd, *J* = 17.9, 4.1 Hz, 1H), 2.21-2.17 (m, 1H), 0.92 (t, *J* = 7.8 Hz, 9H, $SiCH_2CH_3$), 0.91 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 0.78 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 0.52 (q, *J* = 7.8 Hz, 9H, $SiCH_2CH_3$).

5.12 Benzyl 2-(4-methoxybenzyloxy)-2-(triethylsilyl) acetate (276)



Rhodium(II) tetracetate [$Rh_2(OAc)_4$] (4 mg, 0.01 mmol, 2 mol%) was added to a stirring solution of benzyl 2-diazo-2-triethylsilyl acetate (**173a**) (120 mg, 0.4 mmol) and 4-methoxybenzyl alcohol (276 mg, 2.0 mmol) in anhydrous toluene (1-2 mL). The reaction mixture was then heated to 45-50 °C for 12 hours. The solvent was then removed under reduced pressure to afford the crude compound. This was then purified *via* flash chromatrography on silica gel (pentane/ethyl acetate = 10:1) to afford the pure **276**.

101 mg, 0.25 mmol; 63%yield; colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.33 (m, 7H, arom. C*H*), 7.22 (d, *J* = 8.5 Hz, 2H, arom. C*H*), 6.85 (d, *J* = 8.5 Hz, 2H, arom. C*H*), 5.18 (d, *J* = 1.9 Hz, 2H, CH_2Ph), 4.72-4.69 (m, 1H, OCH_aH$_b$, AB system), 4.25-4.22 (m, 1H, OCH$_a$$H_b$, AB system), 3.80 (s, 1H, C*H*O), 0.90 (t, *J* = 8.0 Hz, 9H, CH_2CH_3), 0.61 (q, *J* = 8.0 Hz, 6H, C$H_2$$CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 173.6, 159.1, 135.9, 130.0, 129.7, 128.6, 128.5, 128.2, 113.6, 74.3, 71.7, 66.1, 55.3, 7.3, 2.2.

IR (neat): 2953, 2878, 1733, 1612, 1513, 1460, 1249, 1173, 1086, 1009, 821, 734.

CI-MS (*iso*butane): *m/z* = 399 (M^+−1, 3), 211 (4), 193 (3), 149 (4), 122 (9), 121 (100), 91 (12).

Anal. Calcd. for $C_{23}H_{32}O_4Si$: C 68.96; H 8.05. **Found:** C 68.25; H 8.54.

6. Appendix: Common Abbreviations

Å	angstrom(s)
alkyl	aliphatic substituent
aryl	aromatic subsubstituent/group
br	broad signal
Boc	*tert*-butoxycarbonyl
*n*Bu	normal (primary) butyl
*t*Bu	*tert*-butyl
BuLi	butyl lithium
°C	degree Celsius
CAN	cerium ammonium nitrate
cat.	catalyst
C-H	carbon-hydrogen
CI	chemical ionisation in mass spectrometry
cm^{-1}	wavenumber(s)
δ	ppm
d	doublet
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublets
DMAP	4-(*N,N*-dimethylamino)pyridine
dr	diasteromeric ratio
EI	electron impact ionisation in mass spectrometry
equiv.	equivalent(s)
Et	ethyl
GC	gas chromatography
h	hour(s)
IR	infrared
J	coupling constant
M	molar
M^+	parent molecular ion in mass spectrometry
m	multiplet
Me	methyl
MHz	megahertz
min.	minute(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
MS	mass spectrometry
m/z	mass-to-charge ratio in mass spectrometry
N-H	nitrogen-hydrogen
NMR	nuclear magnetic resonance
OAc	acetate
O-H	oxygen-hydrogen
OMe	methoxy
oct	octanoate
pfb	perfluorbutyrate
Ph	phenyl
ppm	parts per million

Pr	propyl
*i*Pr	*iso*-propyl
PyBOP	benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
q	quartet
quin.	quintet
R	substituent
R_f	retention factor in chromatography
rac	racemic
r. t.	room temperature
Rxt.	reaction
s	singlet
t	triplet
TFA	trifluoroacetic acid
Tf	triflate, trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tos	4-tolylsulfonyl
t	retention time

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8. Curriculum Vitae

Name: Elisabetta Veri

Date and place of birth: 12th May 1975, Rome, Italy

Nationality: Italian

Marital status: Single

EDUCATION

December 2002-July 2006

PhD student in the group of Prof. C. Bolm, Institute of Organic Chemistry, RWTH Aachen University, Aachen, Germany. Thesis title: "*Synthesis and Reactivity of α-Trialkylsilyl α-Amino Acids*".

Date of final examination: 31th July 2006.

October 1994-May 2002

Laurea in Chemistry (five year Italian degree) from the University "La Sapienza", Rome. Thesis title: "*Amination of α,β-Unsaturated γ-Lactones*". Supervisors: Prof. M. A. Loreto, Prof. P. A. Tardella.

Date of final examination: 16th May 2002.

July 1994

Maturità scientifica (high school degree) at Liceo "B. Russell", Rome.