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Bioconjugation and synthetic approach towards enantioenriched *gem*-difluoromethylene compounds through carbenium ions

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Abstract

Bioconjugation of peptides and asymmetric synthesis of *gem*-difluoromethylene compounds are areas of the modern organic chemistry for which mild and selective methods continue to be developed. This thesis reports new methodologies for these two areas based on the use of stabilized carbenium ions.

The reaction that makes the bioconjugation of peptides possible takes place via the direct nucleophilic substitution of alcohols and is driven by the spontaneous formation of stabilized carbenium ions in water. By reacting with the thiol group of cysteine in very mild conditions and with a high selectivity, these carbenium ions allow the site-specific ligation of polypeptides containing cysteine and their covalent derivatization with functionalized probes. The ligation of the indole ring of tryptophan, an emerging target in bioconjugation, is also shown and takes place in the same conditions.

The second area investigated is the challenging access to optically active *gem*-difluoromethylene compounds. We describe a methodology relying on the synthesis of enantioenriched 1,3-benzodithioles intermediates that are shown to be precursors of the corresponding *gem*-difluoromethylene analogues by oxidative desulfurization-fluorination. This synthesis takes advantage of the highly enantioselective organocatalytic *α*-alkylation of aldehydes with the benzodithiolylium ion and of the wide possibilities of synthetic transformations offered by the 1,3-benzodithiole group. This approach allows the asymmetric access to complex *gem*-difluoromethylene compounds through a late-stage fluorination step, thus avoiding the use of fluorinated building blocks.

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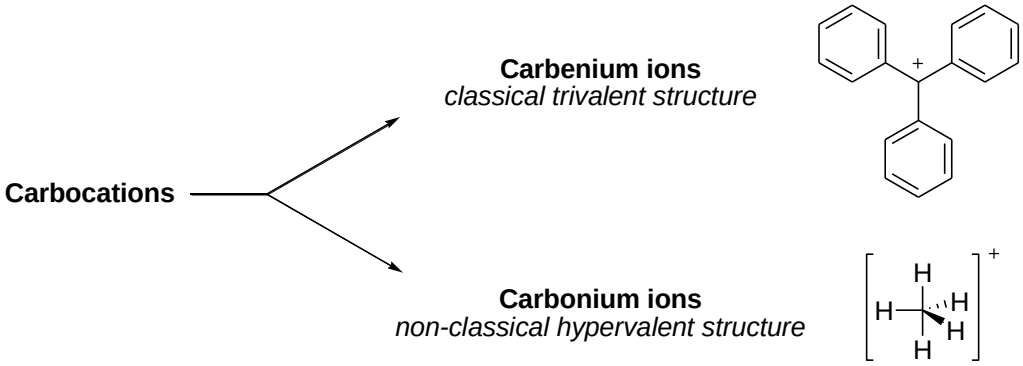
Chapter 1

Introduction

1.1. Stabilized carbenium ions and scales of reactivity.

On the occasion of the centennial of the discovery of the first carbocation, in 2001, George Olah wrote a review on the history of carbocation chemistry.[1] He reminded that, although highly reactive ionic hydrocarbon compounds were already thought to be involved in some organic transformations, the first carbocation discovered was in reality a persistent long-lived carbocation : the triphenylmethyl cation. With hindsight, this is not surprising since this carbocation benefits from resonance with three phenyl rings and a considerable protection by steric hindrance. Being a relative stable ion, the triphenylmethyl cation forms easily from the colourless triphenylmethanol, or from the analogous halide precursors, giving deep yellow solutions in mildly acidic conditions that can be easily observed.

The triphenylmethyl cation is a classical trivalent carbocation that contains an sp^2-hybridized electron-deficient carbon atom. Using Olah's convention,[2] this type of carbocations are called *carbenium ions* and they contrast with the non-classical penta-coordinate (or higher) *carbonium ions* (scheme 1). Carbonium ions differ from the trivalent carbenium ions by the need to use two-electrons three-centre bonding to describe their structure, hence the term "non-classical".

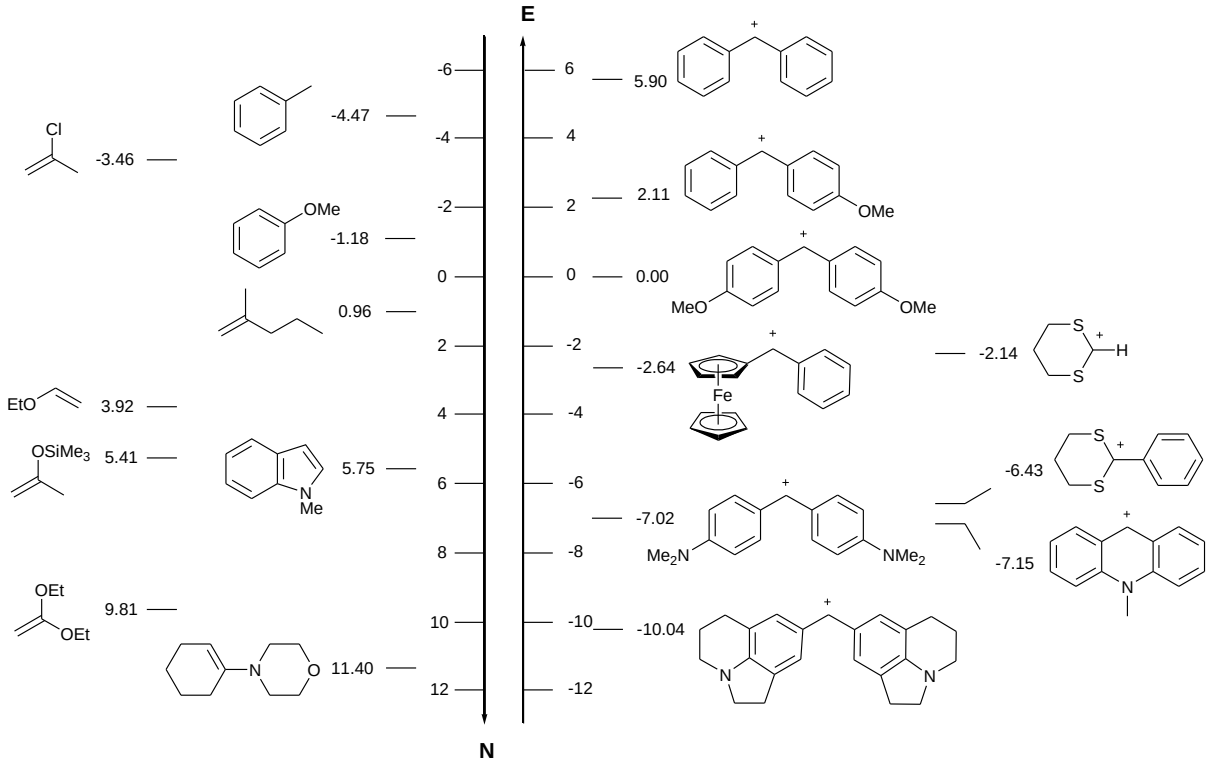


Scheme 1. The two different types of carbocations.

[1] G. A. Olah. 100 years of carbocations and their significance in chemistry. *J. Org. Chem.* **2001**, 5943 – 5957.

[2] G. A. Olah. The general concept and structure of carbocations based on differentiation of trivalent (classical) carbenium ions from three-center bound penta- or tetracoordinated (nonclassical) carbonium ions. Role of carbocations in electrophilic reactions. *J. Am. Chem. Soc.* **1972**, *94*, 808 – 820.

The use of highly acidic conditions with solvents of low nucleophilicity increase the lifetime of carbocations and this enables less stable carbenium ions to be observed by spectroscopy. The relative stability of carbocations is still a subject of study. Among the methods that have been developed to characterize the stability of carbenium ions, the Herbert Mayr's scales of electrophilicity and nucleophilicity are particularly useful.[3] These scales are constructed from the equation *log k = s (N + E)* that allows to calculate the reaction rate *k* of nucleophile-electrophile combinations from three parameter : the nucleophilicity and electrophilicity parameters of the reactants, respectively *N* and *E*, and the nucleophilic-dependent slope parameter *s*. By analysing the rate constants with various types of nucleophiles, the electrophilicity parameters *E* of many species have been established, including carbenium ions.[4] Now there is a correlation between these electrophilicity parameters and the relative stabilities of carbenium ions, as shown by Mayr himself.[5] The stability increases when the electrophilicity decrease. Thus, the carbenium ions at the bottom of the scale will be the more stables and the easier to form.



Scheme 2. The Mayr's scales of nucleophilicity (on the left) and electrophilicity (on the right) with selected *N* and *E* values.

[3] (a) H. Mayr, M. Patz. Scales of nucleophilicity and electrophilicity : a system for ordering polar organic and organometallic reactions. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938 – 957. (b) H. Mayr, B. Kempf, A. R. Ofial. π-nucleophilicity in carbon-carbon bond-forming reactions. *Acc. Chem. Res.* **2003,** *36*, 66 – 77.

[4] H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel. Reference scales for the characterization of cationic electrophiles and neutral nucleophiles. *J. Am. Chem. Soc.* **2001,** *123,* 9500 – 9512.

[5] C. Schindele, K. N. Houk, H. Mayr. Relationships between carbocation stabilities and electrophilic reactivity parameters, E : quantum mechanical studies of benzhydryl cation structures and stabilities. *J. Am. Chem. Soc.* **2002**, *124*, 11208 – 11214.

The Mayr's scales are principally employed to predict if a certain reaction can take place. As a rule of thumb, an electrophile can be expected to react with a nucleophile at room temperature when $N + E > -5$. This means that, on the representation on scheme 2, the nucleophiles at the bottom will react with the electrophiles at the top with diffusion control while nucleophiles and electrophiles located on similar levels require activation control to react at measurable rates. According to this, stabilized carbocations should react readily with good π-donor nucleophiles such as olefins, allyl silanes, enol silyl ethers and enamines. Since stabilized carbenium ions may be generated using mild reaction conditions, this has been the subject of an active area of research for use in synthetic methodologies.

1.2. Direct nucleophilic substitution through stabilized carbenium ions.

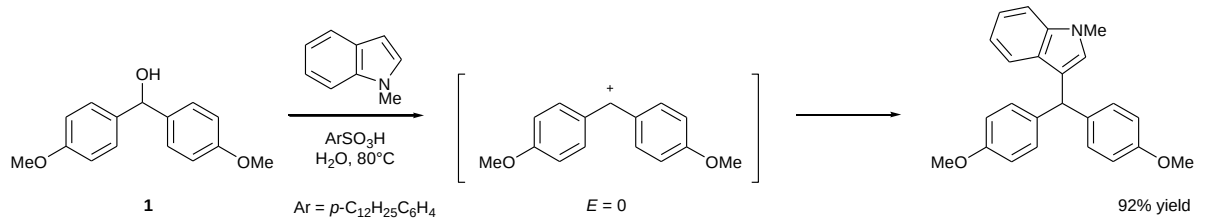
When the carbenium ion is generated from the corresponding alcohol, the overall process can be regarded as the *direct nucleophilic substitution* of the alcohol. This reaction is of great interest because the substitution of alcohols is part of the most frequently used approaches in organic synthesis but it often requires an additional and wasteful activation step.[6]

Kobayashi described in 2007 a series of such direct nucleophilic substitution reactions, done in water and catalyzed by a surfactant-type Brønsted acid.[7] Several suitable nucleophiles were described, such as thiols, enols, furans, and indoles as in scheme 3a. Later, our group went even further by describing similar reactions conducted in water but without the presence of acidic reagents (scheme 3b). The key was to use more stabilized carbenium ions so that water might become a Brønsted acid strong enough to catalyse their formation from the corresponding alcohols. For example, the alcohol **2** gives in water the substitution product with indole in good yield via formation of a more stable carbenium ion than for alcohol **1**. Other stabilized carbenium ions with similar electrophilicity parameters have given similar results but less stable cationic systems were unreactive under these conditions.

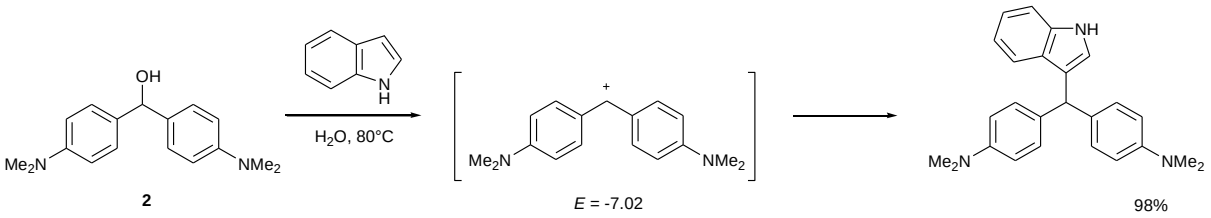
[6] The direct nucleophilic substitution of alcohols is indeed a key area in green chemistry. See : D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaksh, T. Y. Zhang. Key green chemistry research areas – a perspective from pharmaceutical manufacturers. *Green Chem.* **2007**, *9*, 411 – 420.

[7] S. Shirakawa, S. Kobayashi. Surfactant-type Brønsted acid catalyzed dehydrative nucleophilic substitutions of alcohols in water. *Org. Lett.* **2007**, *9*, 311 – 314.

a - Shirakawa, Kobayashi - 2007



b - Cozzi, Zoli - 2008



Scheme 3. Nucleophilic substitution of alcohols via stabilized carbenium ions.

The phenomenon that makes the formation of carbenium ions in water possible is called the *on water* effect. This term has been used by Karl Barry Sharpless[8] to describe the substantial rate acceleration that is observed when some insoluble organic reactants are stirred in aqueous suspension, as for example Diels-Alder cycloadditions or Claisen rearrangements. This effect is commonly explained by a simple acid-catalysis mechanism at the interface between water and the organic reactants.[9] The substrate is protonated by water and this is helped by the strong adsorption of the hydroxide ion by-product at the interface that tends to increase the acidity of water (1). Once activated, the substrate can react to give the reaction products (2).

$$S + H_2O \rightleftharpoons SH^+ + OH^-_{ads} \qquad (1)$$

$$SH^+ \longrightarrow \text{products} \qquad (2)$$

According to this mechanism, all the reactions that are subject to acid catalysis will be accelerated by the *on water* effect, including of course the direct nucleophilic substitution of alcohols. Since the protonation of the substrate is driven by adsorption of the hydroxide ion at the oil-water interface, this catalysis is clearly more effective in heterogeneous solutions of insoluble reactants in water.

1.3. Stabilized carbenium ions in asymmetric synthesis.

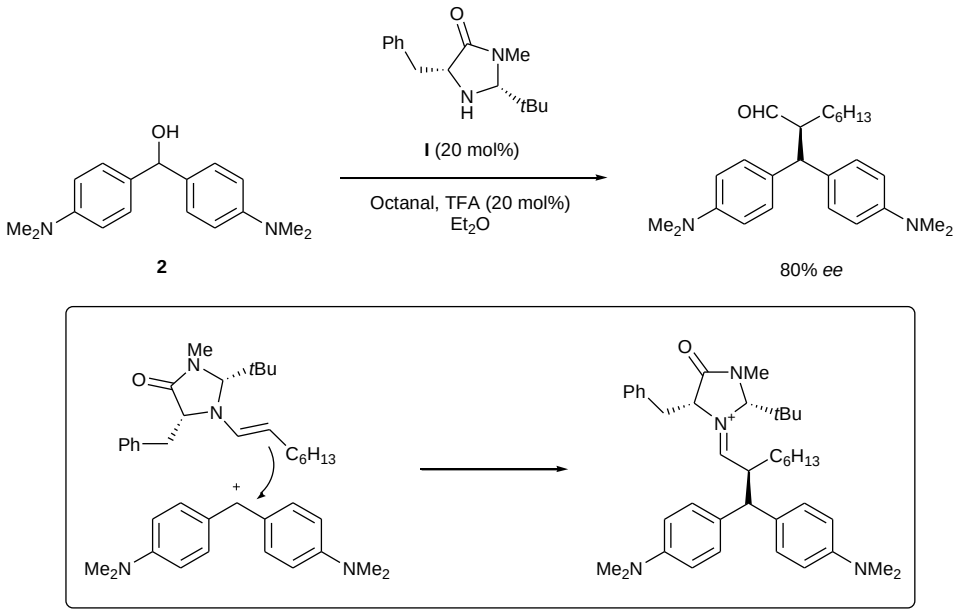
Among the suitable nucleophiles that have been described, enols are of particular interest since they lead to α-functionalized products from aldehyde compounds. The *α*-alkylation of aldehydes proceeds even better via enamine activation and, moreover, allows

[8] S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless. "On water" : unique reactivity of organic compounds in aqueous suspension. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275 – 3279.

[9] (a) J. K. Beattie, C. S. P. McErlean, C. B. W. Phippen. The mechanism of on-water catalysis. *Chem. Eur. J.* **2010**, *16*, 8972 – 8974 ; (b) Y. Jung, R. A. Marcus. On the theory of organic catalysis "on water". *J. Am. Chem. Soc.* **2007**, *129*, 5492 – 5502.

asymmetric induction when chiral catalyst systems are used. Many asymmetric synthetic methods have indeed been developed with the advent of proline, imidazolidinone and alkaloids as organocatalysts.[10] Because they are moderately strong nucleophiles with N parameters in the range 11-16 on the Mayr's scale[11], enamines should react readily with stabilized carbenium ions if suitables conditions can be developed wherein both the carbenium ion and the enamine are generated.

We have found that McMillan imidazolidinones are particularly effective in promoting the asymmetric α-alkylation of aldehydes with stabilized carbenium ions. By screening a series of pyrrolidine and imidazolidinone catalysts in a S_N1-type alkylation between octanal and the alcohol **2**, we found that the McMillan catalyst **I** had the highest activity.[12] This reaction involves the formation of a chiral enamine which reacts with the carbenium ion. We assume that the stereochemical outcome is determined by the carbenium ion approaching the least hindered side of the enamine. The resulting iminium complex is then hydrolyzed to generate both the product and the catalyst (scheme 4).



Scheme 4. Asymmetric α-alkylation of octanal with a stabilized carbenium ion via enamine activation.

The alkylation worked with other alcohols and stabilized carbenium ions as well and, depending on the substrates, the enantioselectivity was typically around 70–90% of enantiomeric excess (*ee*).[13] Among the different carbenium ions suitable for this alkylation,

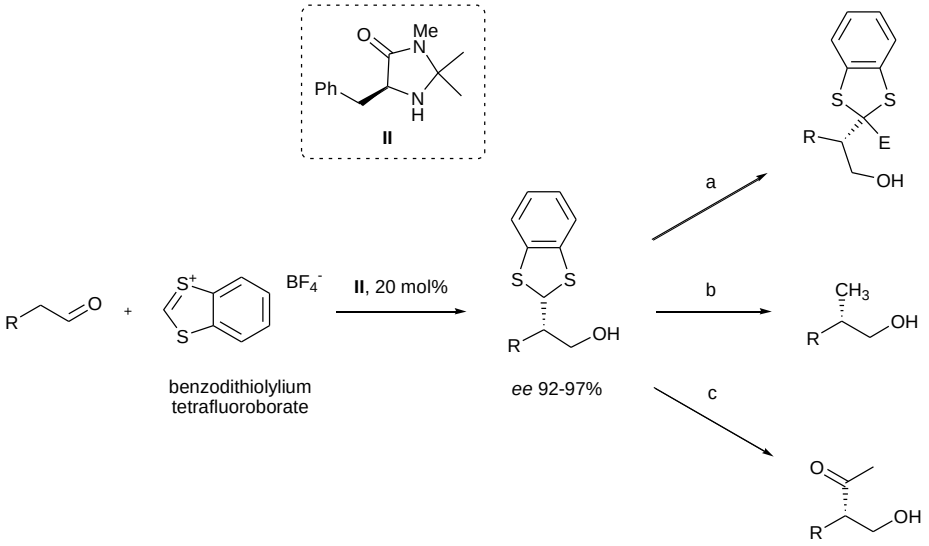
[10] (a) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli. Asymmetric aminocatalysis – gold rush in organic chemistry. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138 – 6171 ; (b) S. Bertelsen, K. A. Jorgensen. Organocatalysis – after the gold rush. *Chem. Soc. Rev.* **2009**, *38*, 2178 – 2189.

[11] B. Kempf, N. Hampel, A. R. Ofial, H. Mayr. Structure-nucleophilicity relationships for enamines. *Chem. Eur. J.* **2003**, *9*, 2209 – 2218.

[12] P. G. Cozzi, F. Benfatti, L. Zoli. Organocatalytic asymmetric alkylation of aldehydes by S_N1-type reaction of alcohols. *Angew. Chem. Int. Ed.* **2009**, *48*, 1313 – 1316.

[13] F. Benfatti, E. Benedetto, P. G. Cozzi. Organocatalytic stereoselective α-alkylation of aldehydes with stable carbocations. *Chem. Asian J.* **2010**, *5*, 2047 – 2052.

we have found that the benzodithiolylium ion could be particularly attractive because of the interest it has in synthesis.[14] Indeed, the benzodithiol group amounts to a 1,3-dithiane and is therefore useful as a versatile intermediate for further transformations.[15] Notably, it is an acyl anion equivalent that can easily react with electrophiles. It can also be hydrolysed or reductively removed, affording different types of chiral products that hold the enantiomeric excess induced in the *α*-alkylation step. Coupled with a reduction step, the alcohol products are formed in good yields and enantioselectivities from a large variety of aldehydes (scheme 5). Again, the best results have been obtained with McMillan catalysts, in particular with the catalyst **II**. We have outstandingly well demonstrated the interest of these benzodithiole products as chiral intermediates in synthesis by applications toward natural products syntheses. This shows also the utility of carbocation chemistry in asymmetric synthesis.



Scheme 5. Asymmetric *α*-alkylation of aldehydes by the benzodithiolylium ion and further transformations : a) alkylation with an electrophile E ; b) reduction to a methyl group ; c) alkylation and hydrolysis to a ketone.

The inherent reactivity of carbenium ions has been widely exploited in asymmetric synthesis.[16] Because they have a planar structure, carbenium ions may react with nucleophiles by the two faces. The key aspect is to control the facial selectivity of the nucleophilic attack and there are three basic strategies to do it. The first strategy involves the use of chiral nucleophiles in reaction with achiral carbenium ions, as in the examples of aminocatalysis above. Since stabilized carbenium ions may be generated under the same conditions in which organocatalysts are used, this strategy is particularly useful. The others strategies to induce enantioselectivity is to use chiral carbenium ions, in which an adjacent

[14] (a) A. Gualandi, E. Emer, M. G. Capdevila, P. G. Cozzi. Highly enantioselective *α* alkylation of aldehydes with 1,3-benzodithiolylium tetrafluoroborate : a formal organocatalytic *α* alkylation of aldehydes by the carbenium ion. *Angew. Chem. Int. Ed.* **2011**, *50*, 7842 – 7846 ; (b) A. Gualandi, L. Mengozzi, J. Giacoboni, S. Saulnier, M. Ciardi, P. G. Cozzi. A practical and stereoselective organocatalytic alkylation of aldehydes with benzodithiolylium tetrafluoroborate. *Chirality* **2014**, in press.

[15] M. Yus, C. Najera, F. Foubelo. The role of 1,3-dithianes in natural product synthesis. *Tetrahedron* **2003**, *59*, 6147 – 6212.

[16] R. Reddy Naredla, D. A. Klumpp. Contemporary carbocation chemistry : applications in organic synthesis. *Chem. Rev.* **2013**, *113*, 6905 – 6948.

stereocenter blocks either the *re* or the *si* face ; or to use a chiral counter-ion to form a tight ion pairing with the achiral carbenium ion. This last method is becoming increasingly useful with the development of new types of chiral Brønsted acids, as for example chiral phosphoric acids.

1.4. Objectives of the thesis.

The goal of this thesis is to use stabilized carbenium ions for the bioconjugation of amino acid and polypeptides firstly, and for the asymmetric synthesis of *gem*-difluoromethylene compounds, secondly.

Bioconjugation refers to the covalent derivatization of biomolecules. Because they react readily with soft nucleophiles, in particular with thiols and indoles, we think that stabilized carbenium ions will react with the side chains of cysteine (a thiol) and tryptophan (an indole) and, thus, with polypeptides. But the idea of using stabilized carbenium ions as potential substrates in bioconjugation comes mainly from the fact that they can be generated *on water* and in very mild conditions from the corresponding alcohols. This way, the ligation conditions will be very close to the physiological conditions, a feature difficult to achieve in bioconjugation.

The second objective concerns the use of the benzodithiolylium ion for the asymmetric synthesis of *gem*-difluoromethylene compounds. We have briefly discussed the use of the 1,3-benzodithiole group in synthesis as a 1,3 dithiane equivalent. A possibility that has never been taken into consideration is the possible transformation into a difluoromethylene group by a reaction called *oxidative desulfurization-fluorination*. This process is well known in the case of 1,3-dithianes and, with the right conditions, it can be applicable to benzodithioles. This reaction is to be considered of great interest because it allows the access to optically active *gem*-difluoromethylene compounds via a late-stage fluorination process, while the existing methods rely on earlier-stage asymmetric insertions of fluorinated building blocks.

Chapter 2

Bioconjugation through stabilized carbenium ions

2.1. Background.

2.1.1. Classic bioconjugation methods.

The goal of bioconjugation is to develop simple and efficient methods for the chemical bonding of biomolecules. For this purpose, a pre-required preceding modification of the bio-molecule using a bifunctional reagent with a high degree of selectivity or specificity is often necessary. These reagents are used as linkers and they might bring new functionalities into molecules. The main motivations for bio-conjugation include the discovery of biological interactions, biochemical assays, imaging *in vivo* and diagnostic applications. *PEG*ylation, that refers to the conjugation of *PolyEthyleneGlycol* molecules with proteins, and enzyme immobilization are others well-established applications.[17]

Classic polypeptide and protein bioconjugation primarily encompasses simple second-order reactions that selectively target the functionalities present in the side chains of amino acids.[18] Of those, cysteine and lysine are the most commonly modified residues for which methods continue to be developed and optimized.

The thiol group of cysteine can undergo disulfide exchange to form mixed disulfides as well as alkylation with alkyl halides or Michael addition to α,β-unsaturated carbonyl compounds to yield thioethers. Typical thiol-reactive functional groups include iodoacetamides (table 1, entry 1), maleimides (entry 2) and disulfides (entry 3). As cysteine is the second least common amino acid in natural proteins,[19] site-specific conjugation can often be performed at a unique cysteine residue. However, these classic methods have some disadvantages. The thiol-selectivity of iodoacetamides and maleimides is compromised at high concentrations of the reagents, resulting in alkylation of the side chains of other nucleophilic amino acid residues. In contrast, disulfide reagents react much more selectively with thiols but they are susceptible to reduction by biological reducing agents (*e.g.*

[17] For a review on bioconjugation and its applications, see : J. Kalia, R. T. Raines. Advances in bioconjugation. *Current Organic Chemistry* **2010***, 14,* 138 – 147.

[18] (a) G. T. Hermanson, *Bioconjugate Techniques, 2nd ed.*, Academic Press, San Diego, CA, **2008**. (b) M. Aslam, A. Dent. *Bioconjugation: Protein Coupling Techniques for the Biomedical Sciences*, Macmillan Reference Ltd., London, **1998**.

[19] P. McCaldon, P. Argos. Oligopeptide biases in protein sequences and their use in predicting protein coding regions in nucleotide sequences. *Proteins* **1988**, *4*, 99 – 122.

glutathione). Hence, the use of disulfides is limited to *in vitro* applications, such as crosslinking or immobilization.[20] Another problematic feature of maleimide conjugates is the susceptibility of their imido groups to undergo spontaneous hydrolysis, resulting in undesirable heterogeneity.[21]

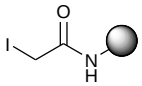
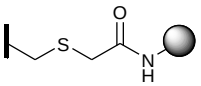
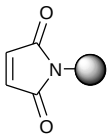
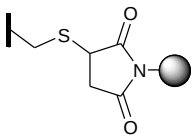
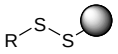
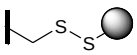
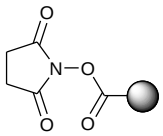
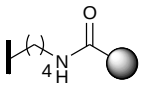
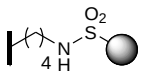
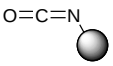
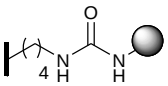
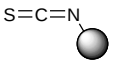
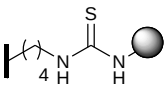
Although considerably more prevalent than cysteine, lysine residues are popular targets because of the abundance of methods to selectively modify primary amines. Lysine can react with activated esters (table 1, entry 4), sulfonyl chlorides (entry 5), isocyanate (entry 6) and isothiocyanates (entry 7) to afford amides, sulfonamides, ureas and thioureas, respectively. Lysine residues also undergo reductive amination reactions with aldehydes. Among these linkages, amide bonds are highly attractive for bio-conjugation due to their extraordinary stability : they have a half life of *ca*. 600 years in neutral solution[22]. However, it is to note that the reagents above for the lysine ligation can additionally modify the N terminus, making challenging the site-specific generation of amides. Native chemical ligation and the Staudinger ligation are two modern approaches for generating amide linkages at a specific site in a protein.

[20] (a) M. Li, K. Yamato, J. S. Ferguson, K. K. Singarapu, T. Szyperski, B. Gong. Sequence-specific, dynamic covalent crosslinking in aqueous media. *J. Am. Chem. Soc.* **2008**, *130*, 491 – 500 ; (b) D. S. Yeo, R. C. Panicker, L. P. Tan, S. Q. Yao. Strategies for immobilization of biomolecules in a microarray. *Comb. Chem. High. Throughput Screen.* **2004**, *7*, 213 – 221.

[21] J. Kalia, R. T. Raines. Catalysis of imido group hydrolysis in a maleimide conjugate. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6286 – 6289.

[22] A. Radzicka, R. Wolfenden. Rates of uncatalyzed peptide bond hydrolysis in neutral solution and the transition state affinities of proteases. *J. Am. Chem. Soc.* **1996**, *118*, 6105 – 6109.

Table 1. Classic bioconjugation reactions for the modification of cysteine and lysine residues.

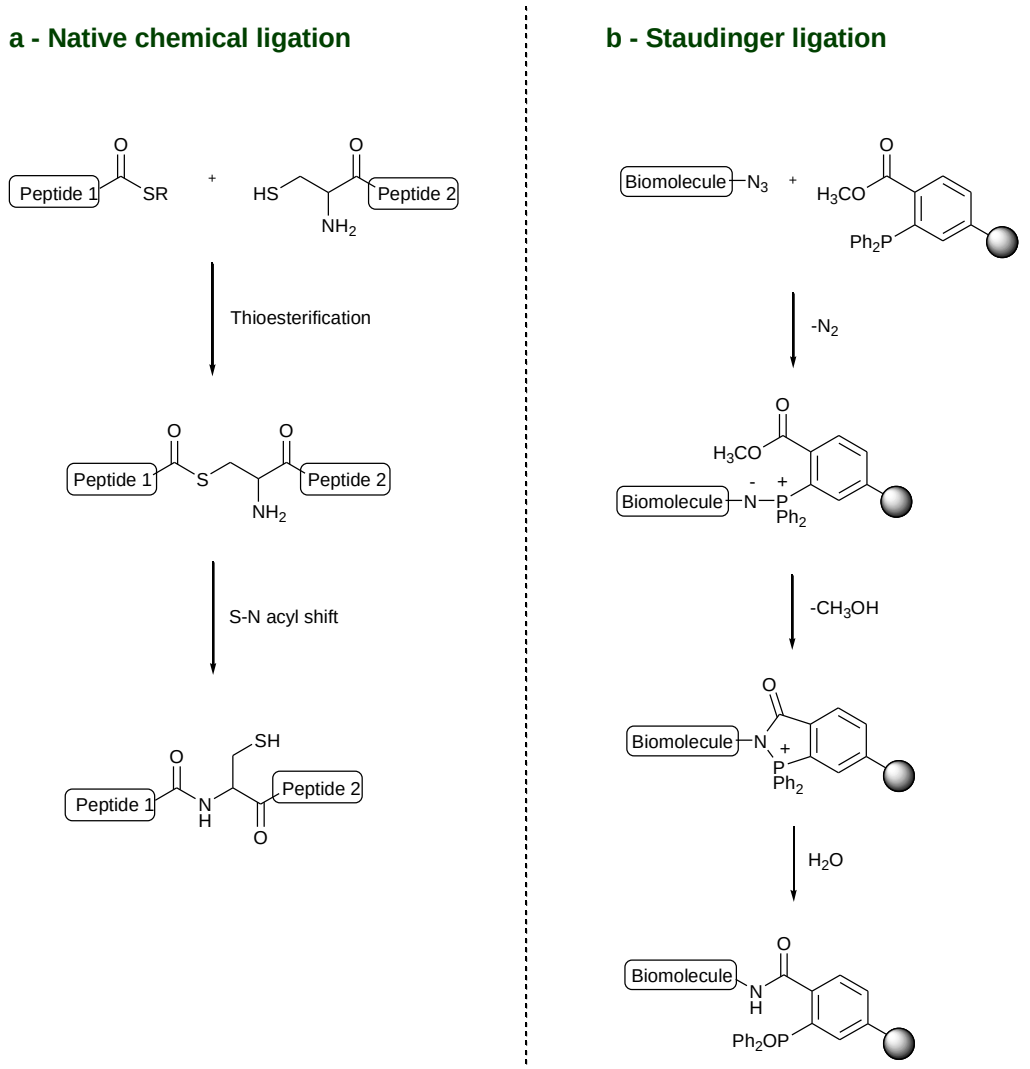
Entry	Residue	Reagent	Product
1	Cys		
2	Cys		
3	Cys		
4	Lys		
5	Lys		
6	Lys		
7	Lys		

In native chemical ligation,[23] an N-terminal cysteine residue reacts with a thioester to undergo a trans-thioesterification followed by a rapid S-N acyl transfer to form an amide (scheme 1a). This reaction is a powerful tool for peptide ligation and protein synthesis. An undesirable aspect of native chemical ligation is the introduction of a residual thiol at the site of bio-conjugation, which can be a focal point for side reactions. A solution to this limitation is provided by the Staudinger ligation.[24] This conjugation method is a modification of the classic Staudinger reduction of azides with triphenylphosphine where an ester group is situated in *ortho* position to the phosphorus : this way a covalent imide bond is generated prior to hydrolysis[25] (scheme 1b). With the development of the Staudinger ligation, azide made its debut as a particularly powerful chemical reporter group.

[23] (a) P. E. Dawson, T. W. Muir, I. Clarklewis, S. B. H. Kent. Synthesis of proteins by native chemical ligation. *Science* **1994**, *266*, 776 – 779 ; (b) P. E. Dawson, S. B. H. Kent. Synthesis of native proteins by chemical ligation. *Annu. Rev. Biochem.* **2000**, *69*, 923 – 960 ; (c) D. S. Y. Yeo, R. Srinivasan, G. Y. J. Chen, S. Q. Yao. Expanded utility of the native chemical ligation reaction. *Chem. Eur. J.* **2004**, *10*, 4664 – 4672.

[24] M. Köhn, R. Breinbauer. The Staudinger ligation - a gift to chemical biology. *Angew. Chem. Int. Ed.* **2004**, *43*, 3106 – 3116.

[25] F.L. Lin, H. M. Hoyt, H. van Halbeek, R. G. Bergman, C. R. Bertozzi. Mechanistic investigation of the Staudinger ligation. *J. Am. Chem. Soc.* **2005**, *127*, 2686 – 2695.



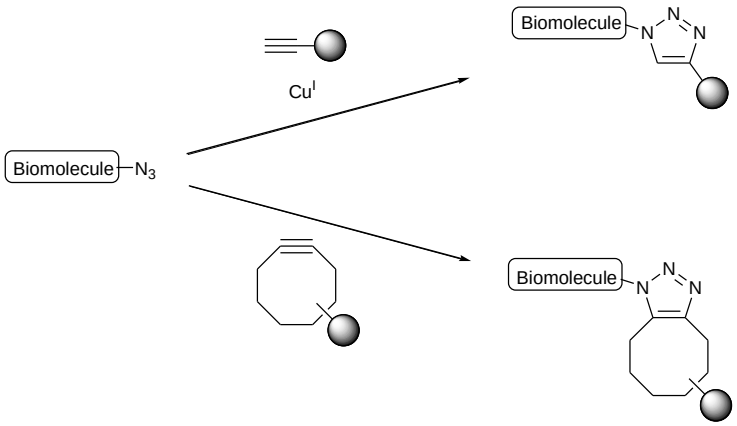
Scheme 1. a – Native chemical ligation of two peptides. b – The staudinger ligation of azides and triarylphosphines.

The Huisgen 1,3-dipolar azide–alkyne cycloadditions as alternate mode of reactivity for azide has become one of the most useful reactions for bioconjugation since the discovery of the rate acceleration availed by copper(I). This cycloaddition is often referred as *click reaction* and has been used in an extraordinary range of contexts, including protein labelling with small molecules, immobilization of proteins or carbohydrates, proteomics applications, functionalization of DNA, and the ligation of virus particles with fluorescent molecules.[26] However, the Cu(I)-catalyzed version of the Huisgen cycloaddition can cause cytotoxicity and protein precipitation due to the Cu(I) ion.[27] In addition, the reaction rates are slow and this precludes its use for studying cellular processes. To overcome these drawbacks, alkynes have been activated by a method other than metal catalysis : the ring strain of the cyclooctyne group. The bond angle of the sp-hybridized carbons in cyclooctynes is about 160°, which is

[26] For a review, see : C. W. Tornøe, M. Meldal. Cu-catalysed azide-alkyne cycloaddition. *Chem. Rev.* **2008**, *108*, 2952 – 3015.

[27] L. M. Gaetke and C. K. Chow. Copper toxicity, oxidative stress, and antioxidant nutrients. *Toxicology* **2003**, *189*, 147 – 163.

distorted toward the transition state of the cycloaddition reaction, resulting in a dramatic rate acceleration. This reaction has been named *copper-free click reaction*.[28]



Scheme 2. Copper-catalysed and strain-promoted [3+2] cycloadditions of azides and alkynes (*click reactions*).

By comparison with cysteine and lysine, the remaining eighteen amino acids have been minimally exploited for residue-selective modification. The phenol moiety of tyrosine has been modified through electrophilic aromatic substitution reactions with diazonium salts, iodine, or nitrous acid. Glutamate and aspartate residues have been targeted through coupling with amines via carbodiimides, although the potential cross-linking of proteins limits the utility of this technique. Pyrocarbonates have also been used to successfully modify histidine residues.

Much recent activity has focused on transition metal-mediated processes that are compatible with aqueous conditions,[29] especially for the modification of tyrosine and tryptophan residues that are relatively rare on protein surfaces and, thus, offer opportunities for controlled single-site modifications. Furthermore, the N terminus has emerged as a popular target for protein modification due to its unique pH-dependent reactivity that makes it an attractive target for single-site modification. Transamination reactions have been particularly successful for this purpose.[30] Other chemical methods rely on a specific residue at the N-terminus : for example, N-terminal serine and threonine residues undergo periodate oxidation to form glyoxylamides[31] and, of course, N-terminal cysteine permits native chemical ligation.

2.1.2. Water-driven ligations and S_N1 reactions of alcohols.

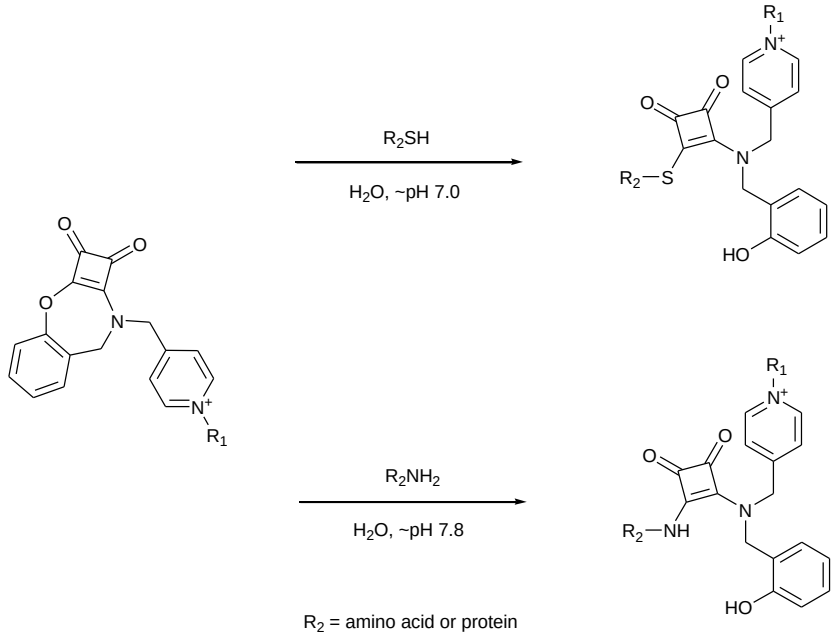
[28] For a review, see : J. C. Jewett, C. R. Bertozzi. Cu-free click cycloaddition reactions in chemical biology. *Chem. Soc. Rev.* **2010**, *39*, 1272 – 1279.

[29] J. M. Antos, M. B. Francis. Transition metal catalyzed methods for site selective protein modification. *Curr. Opin. Chem. Biol.* **2006**, *10*, 253 – 262.

[30] J. M. Gilmore, R. A. Scheck, A. P. Esser-Kahn, N. S. Joshi, M. B. Francis. N-Terminal protein modification through a biomimetic transamination reaction. *Angew. Chem. Int. Ed.* **2006**, *45*, 5307 – 5311.

[31] K. F. Geoghegan, J. G. Stroh. Site-directed conjugation of nonpeptide groups to peptides and proteins via periodate oxidation of a 2-amino alcohol. Application to modification at N-terminal serine. *Bioconjugate Chem.* **1992**, *3*, 138 – 146.

This overall look[32] has highlighted that the development of bioconjugation techniques has been motivated by the need for fast, selective and mild reactions. Bioconjugation reactions in water are the most attractive since they can be compatible with living systems. Recently, a new class of ligation reactions promoted by water via stabilization of the transition states has been developed and defined as *water-driven* ligations.[33] In these reactions, cyclic amino squarates ligate cysteine and lysine residues in entirely aqueous environment and without by-products in a similar way to S_N1 reactions (scheme 3). We know that this type of organic reactions promoted by water, either by stabilization of the transition states or by activation of the reactants, are feasible and often due to the *on water* effect discovered by Sharpless. In particular, this on water effect makes the S_N1 reactions of alcohols possible through highly stabilized carbenium ions.



Scheme 3. Water-driven ligations using cyclic amino squarates.

The direct substitution of alcohols on water without added Bronsted or Lewis acid is related to the stability of the corresponding carbenium ions. This direct substitution was first described for optically active ferrocenyl alcohols with indole, pyrrole, and thiophenols.[34] Later, it was showed that this reaction worked also with various benzylic alcohols, for which the corresponding carbenium ions had electrophilic parameters *E* in the range from -8.5 to -2.5 on the Mayr's scale of electrophilicity.[35] These carbenium ions react with soft C, N and S nucleophiles to give the substitution products (and water as the only by-product). In

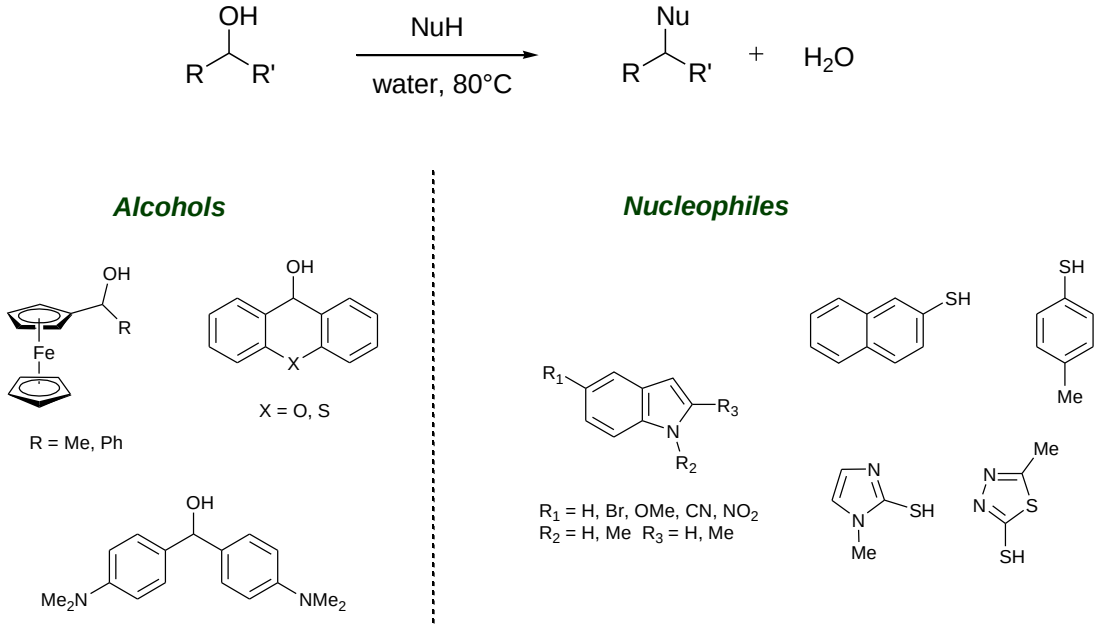
[32] For a more in-depth discussion of chemoselective protein modification methods, see : C. P. R. Hackenberger, D. Schwarzer. Chemoselective ligation and modification strategies for peptides and proteins. *Angew. Chem. Int. Ed.* **2008**, *47*, 10030 – 10074.

[33] D. Cui, D. Prashar, P. Sejwal, Y.-Y. Luk. Water-driven ligations using cyclic amino squarates: a class of useful S_N1-like reactions. *Chem. Commun.* **2011**, *47*, 1348 – 1350.

[34] P. G. Cozzi, L. Zoli. Nucleophilic substitution of ferrocenyl alcohols ''on water''. *Green Chem.* **2007**, *9*, 1292 – 1295.

[35] P. G. Cozzi, L. Zoli. A rational approach towards the nucleophilic substitutions of alcohols "on water". *Angew. Chem. Int. Ed.* **2008**, *47*, 4162 – 4166.

particular they react with thiol and indole derivatives (scheme 4). Because such nucleophiles are commonly present on polypeptides -through the amino acids cysteine and tryptophan- and because the nucleophilic substitution proceeds in very mild conditions, this reaction is suitable for peptide and protein ligation.

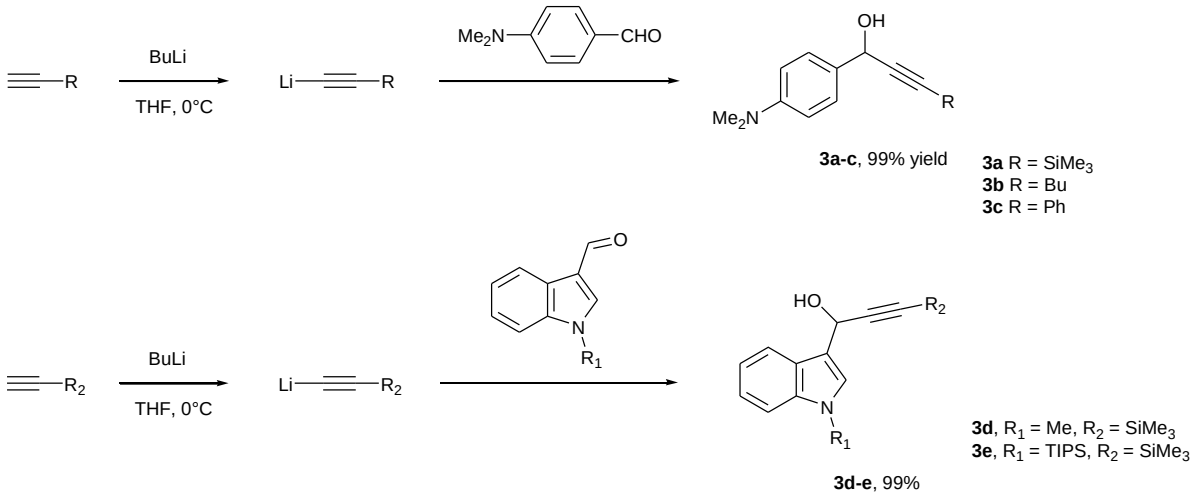


Scheme 4. Nucleophilic substitution of ferrocenyl and benzylic alcohols by indole and thiol derivatives.

2.2. Alcohols and carbenium ions substrates for the ligation.

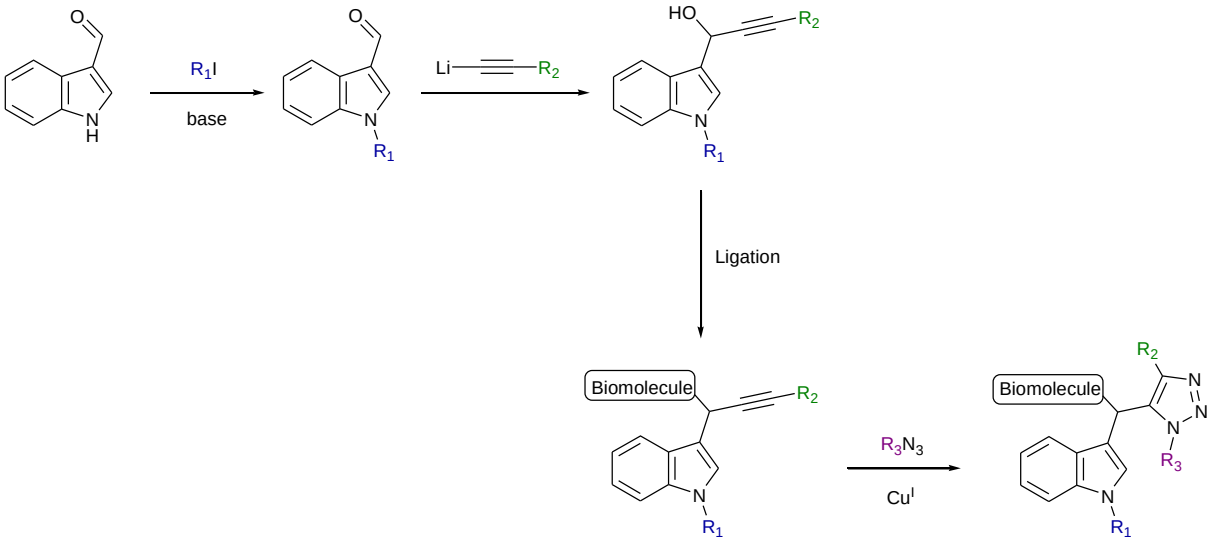
The alcohols shown on scheme 4 are reactive with indoles and thiols and should be reactive with cysteine and tryptophan, too. However, inserting a functional moiety on their structure without affecting the reactivity would be difficult. These alcohols cannot act as bifunctional linkers and, therefore, they are not suitable for bioconjugation.

In the search for structures that could give carbenium ions with similar stability, we have found that the propargylic alcohol **3a** below was reactive with thiols and indoles in the same mild conditions. This alcohol is prepared by the nucleophilic addition of a terminal alkyne to the corresponding benzaldehyde, as in scheme 5, and this way different functional moieties can be inserted. Slight differences of electrophilicity and stabilization of the corresponding carbenium ions have been obtained by substituting the TMS group of **3a** by an alkyl (**3b**) and a phenyl group (**3c**).



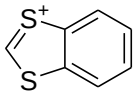
Scheme 5. Synthesis of propargylic alcohols **3a-e**.
(TIPS = triisopropylsilyl).

The alcohol **3a** has been chosen as model structure. The presence of the nitrogen atom on the *para* position of the aromatic ring is necessary for the stabilization of the carbenium ion. Actually, the absence of this nitrogen or its substitution by an oxygen atom make the alcohol non-reactive in water. Nevertheless, we assumed that the substitution of this aromatic ring by a pyrrole or an indole ring would give a similar stabilization of the carbenium ion. All the attempts to prepare pyrrole derivatives have been unsuccessful. On the other hand, the indolic alcohols **3d** and **3e** have been obtained from the corresponding indole-3-carboxaldehydes by the same process than for the benzylic alcohols **3a-c**. It is to note that the indole ring offers another possibility of functionalization on the indolic nitrogen. As for the triple bond, this functionalization must take place prior to the ligation. In addition, the triple bond should remain unchanged after the ligation and could be advantageously used for click chemistry. This feature is very attractive as it could allow to do multifunctional bioconjugation.

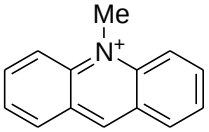


Scheme 6. Multifunctional bioconjugation.

The benzylic and indolic alcohols **3a-e** are structurally similar and, thus, the corresponding carbenium ions should show a similar reactivity with a given nucleophile. With the purpose to explore less electrophilic carbenium ions, we selected the benzodithiolylium ion **4** and the N-methylacridinium ion **5**. Both are structurally different, but in any case they show a higher stabilization of the positive charge resulting in a lower electrophilicity. The N-methylacridinium ion is characterized by an electrophilic parameter *E* = -7.14 on the Mayr's scale.[36] The benzodithiolylium ion should be slightly more electrophilic with an *E* parameter around -6, since structurally related compounds are situated in this range.



4
benzodithiolylium ion
E ~ -6



5
N-methylacridinium ion
E = -7.14

2.3. Reactivity with nucleophilic amino acids.

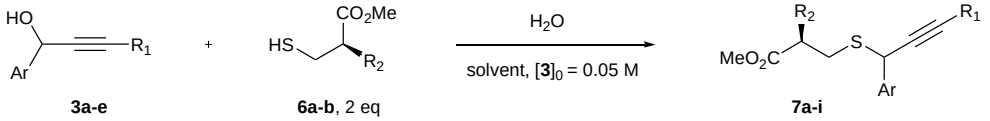
2.3.1. Reactivity with cysteine.

Alcohols **3a-e**, together with benzodithiolylium tetrafluoroborate and N-methylacridinium iodide, have been used as substrates to test the reactivity with several

[36] H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel. Reference scales for the characterization of cationic electrophiles and neutral nucleophiles. *J. Am. Chem. Soc.* **2001,** *123,* 9500 – 9512.

nucleophilic amino acids in aqueous media. First with cysteine and tryptophan, as we know that thiols and indoles are reactive, and then with tyrosine, threonine and lysine.

Alcohols **3a-e** have been used in a model reaction with N-acetyl and N-free cysteine methyl ester (**6a** and **6b**, scheme 7). Although the reactions were working in water, the yield of the substitution products have been improved by using acetonitrile as organic co-solvent. The same reaction conditions have been applied to Benzodithiolylium tetrafluoroborate and to N-methylacridinium iodide. It is to note that, in aqueous media, these carbenium ions must be considered in fast equilibrium with the corresponding alcohols.



3a : Ar = *p*-(NMe_2)-C_6H_4, R_1 = $SiMe_3$
3b : Ar = *p*-(NMe_2)-C_6H_4, R_1 = Bu
3c : Ar = *p*-(NMe_2)-C_6H_4, R_1 = Ph
3d : Ar = 1-Me-indol-3-yl, R_1 = $SiMe_3$
3e : Ar = 1-TIPS-indol-3-yl, R_1 = $SiMe_3$

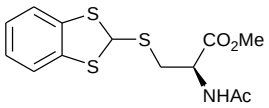
6a : R_2 = NHAc
6b : R_2 = NH_3Cl

7a : Ar = *p*-(NMe_2)-C_6H_4, R_1 = $SiMe_3$, R_2 = NHAc
7b : Ar = *p*-(NMe_2)-C_6H_4, R_1 = $SiMe_3$, R_2 = NH_2
7c : Ar = *p*-(NMe_2)-C_6H_4, R_1 = Bu, R_2 = NHAc
7d : Ar = *p*-(NMe_2)-C_6H_4, R_1 = Bu, R_2 = NH_2
7e : Ar = *p*-(NMe_2)-C_6H_4, R_1 = Ph, R_2 = NHAc
7f : Ar = 1-Me-indol-3-yl, R_1 = $SiMe_3$, R_2 = NHAc
7g : Ar = 1-TIPS-indol-3-yl, R_1 = $SiMe_3$, R_2 = NHAc
7h : Ar = indol-3-yl, R_1 = $SiMe_3$, R_2 = NHAc
7i : Ar = indol-3-yl, R_1 = $SiMe_3$, R_2 = NH_2

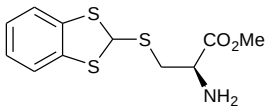
Scheme 7. Model reaction for the nucleophilic substitution with cysteine derivatives.

Despite the slight differences of stability for their corresponding carbenium ions, the results reported in table show a similar reactivity for the benzylic and indolic alcohols **3a-e**. They react at room temperature with both cysteine derivatives to give the substitution products. The addition takes place on the thiol group, even if the primary amine is not protected. We assumed that the amine is unreactive because protonated in these conditions. In the case of the alcohol **3e**, in which the indolic hydrogen is substituted by a triisopropylsilyl group (TIPS), the substitution product was first isolated as a mixture of N-protected and N-free indole because the hydrolysis of the TIPS group was relatively fast in these conditions. A basic aqueous work-up afforded only the hydrolysed products (entries 9-10).

No addition product have been observed in the case of the N-methylacridinium ion **5** (entries 14-15). This is probably due to its low electrophilicity because the more electrophilic benzodithiolylium cation is reactive under the same conditions and has given the addition products **8a-b** below (entries 12-13).



8a



8b

The on water effect is usually considered as more effective when water is used without co-solvent, even if the reactants are not soluble. But such heterogeneous reactions require a vigorous stirring to increase the reaction rate by increasing the total surface area of the reactants. This can be achieved by using ultrasounds and, this way, we have observed a

faster nucleophilic substitution with the alcohol **3a** (entries 2 and 4).[37] By comparison, the indolic alcohol **3e** has given the substitution product with a lower yield in the same conditions (entry 11) showing a lower reactivity. On the other hand, the hydrolysis of the TIPS protecting group does not take place as fast as in the acetonitrile-water mixture and, actually, the TIPS-protected adduct **7i** has been isolated as the main product.

Table 2. Ligation of cysteine derivatives (scheme 7).

Entry	Alcohol	Amino acid	Solvent	Time	Product	Yield[b] (%)
1	**3a**	**6a**	H_2O / CH_3CN	12h	**7a**	85
2[c]	**3a**	**6a**	H_2O	3h	**7a**	44
3	**3a**	**6b**	H_2O / CH_3CN	12h	**7b**	71
4[c]	**3a**	**6b**	H_2O	2h	**7b**	60
5	**3b**	**6a**	H_2O / CH_3CN	12h	**7c**	74
6	**3b**	**6b**	H_2O / CH_3CN	12h	**7d**	77
7	**3c**	**6a**	H_2O / CH_3CN	12h	**7e**	54
8	**3d**	**6a**	H_2O / CH_3CN	12h	**7f**	72
9[d]	**3e**	**6a**	H_2O / CH_3CN	12h	**7h**	52
10[d]	**3e**	**6b**	H_2O / CH_3CN	12h	**7i**	44
11[c]	**3e**	**6a**	H_2O	6h	**7g**	21
12[e]	**4**	**6a**	H_2O / CH_3CN	12h	**8a**	61
13[e]	**4**	**6b**	H_2O / CH_3CN	12h	**8b**	nd
14	**5**	**6a**	H_2O / CH_3CN	12h	**-**	-
15	**5**	**6b**	H_2O / CH_3CN	12h	**-**	-

[a] The reactions were carried out at room temperature with $[\mathbf{3}]_0$ = 0.05 M and 2 equiv of amino acid. [b] Yields of isolated products (1:1 mixtures of diastereoisomers). [c] Reaction carried out in an ultrasonic cleaning bath. [d] Reaction followed by the basic hydrolysis of the TIPS group. [e] Reaction carried out with $[\mathbf{4}]_0$ = 0.1 M.

2.3.2. Reactivity with tryptophan and other nucleophilic amino acids.

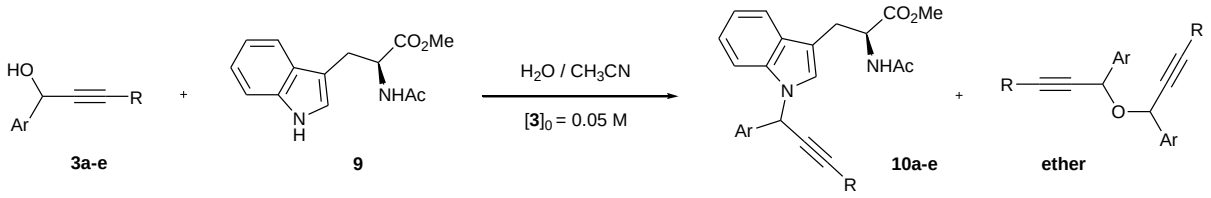
The reactivity with tryptophan has been explored in the same conditions and, among the differences observed in comparison with cysteine, the most important are the slower reaction rates and the regioselectivity that seems to depend on the substrate.

N-acetyl tryptophan methyl ester required higher temperatures to give the substitution product. Actually, only the indolic alcohol **3d** could react at room temperature (table 3). The substitution products were unstable and broke down during and after purification. NMR analysis have shown that the addition of the carbenium ions takes place on the indolic nitrogen of tryptophan (while usually on the 3-position of indoles when not substituted). The main product isolated was the ether formed by condensation of the

[37] The same reaction was quite slow when performed with a standard magnetic stirring.

alcohol (scheme 8). This ether is observed in the case of cysteine too, and is to be considered as the only by-product. Nevertheless, it is formed with a lower amount in the case of cysteine.

Scheme 8 and **table 3**. Nucleophilic substitution of benzylic and indolic alcohols with N-acetyl tryptophan methyl ester.[a]



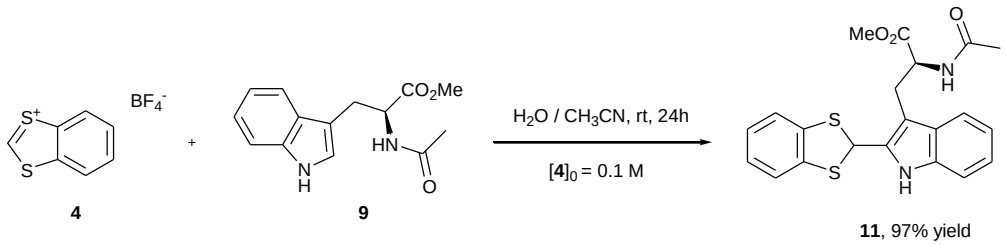
3a : Ar = *p*-(NMe_2)-C_6H_4, R = $SiMe_3$
3b : Ar = *p*-(NMe_2)-C_6H_4, R = Bu
3d : Ar = 1-Me-indol-3-yl, R = $SiMe_3$
3e : Ar = 1-TIPS-indol-3-yl, R = $SiMe_3$

10a : Ar = *p*-(NMe_2)-C_6H_4, R = $SiMe_3$
10b : Ar = *p*-(NMe_2)-C_6H_4, R = Bu
10c : Ar = 1-Me-indol-3-yl, R = $SiMe_3$
10d : Ar = 1-TIPS-indol-3-yl, R = $SiMe_3$
10e : Ar = indol-3-yl, R = $SiMe_3$

Entry	Alcohol	Conditions[a]	Product	Yield[b] (%)	Yield ether[b] (%)
1	**3a**	70°C – 12h	**10a**	33	30
2	**3b**	70°C – 18h	**10b**	15	72
3	**3d**	rt – 48h	**10c**	16	36
4	**3e**	70°C – 12h	**10d-e**	nd	68

[a] Reactions carried out at room temperature with $[\mathbf{3}]_0$ = 0.05 M and 2 equiv of N-acetyl tryptophan methyl ester. [b] Yields of isolated products.

Interestingly, a different regioselectivity has been observed with the benzodithiolylium ion (scheme 9). In this case the addition does not take place on the indolic nitrogen but on the 2-position, forming this time a stable carbon-carbon bond. The adduct is stable and has been isolated with a 97% yield at room temperature. Barring the possible influence of steric effects, this difference of regioselectivity can be interpreted as an example of the hard and soft acids and bases concept (i.e. electrophiles and nucleophiles). The benzodithiolylium ion, as a more stable electrophile, can be considered as a softer Lewis acid.

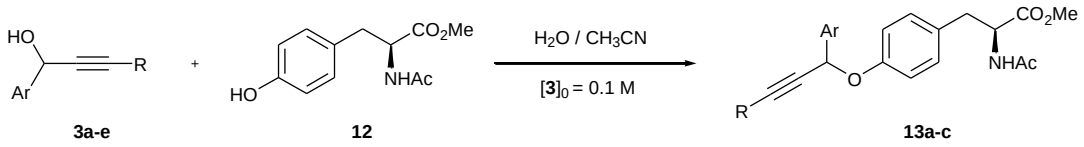


Scheme 9. Ligation of tryptophan by the benzodithiolylium ion.

Concerning the other nucleophilic amino acids, lysine and threonine are not reactive in these conditions whereas traces of substitution products have been observed with

tyrosine (except for the N-TIPS indolic alcohol **3e**, table 4). Although we could not isolate the products, we assume that the addition takes place on the phenol. Again, the N-methyl indolic alcohol **3d** reacts at room temperature while warmer temperatures are required for the other alcohols. The higher reactivity for **3d** compared with **3e** shows that the nature of the N-substituting group affects the electrophilicity of the indolic carbenium ions. The TIPS group gives indeed a higher inductive effect than the methyl group, resulting in a *lower stability* and a *higher electrophilicity* of the carbocation.

Table 4. Reaction of benzylic and indolic alcohols with N-acetyl tyrosine methyl ester.[a]



3a-e **12** **13a-c**

3a : Ar = *p*-(NMe_2)-C_6H_4, R = $SiMe_3$
3b : Ar = *p*-(NMe_2)-C_6H_4, R = Bu
3d : Ar = 1-Me-indol-3-yl, R = $SiMe_3$
3e : Ar = 1-TIPS-indol-3-yl, R = $SiMe_3$

13a : Ar = *p*-(NMe_2)-C_6H_4, R = $SiMe_3$
13b : Ar = *p*-(NMe_2)-C_6H_4, R = Bu
13c : Ar = 1-Me-indol-3-yl, R = $SiMe_3$

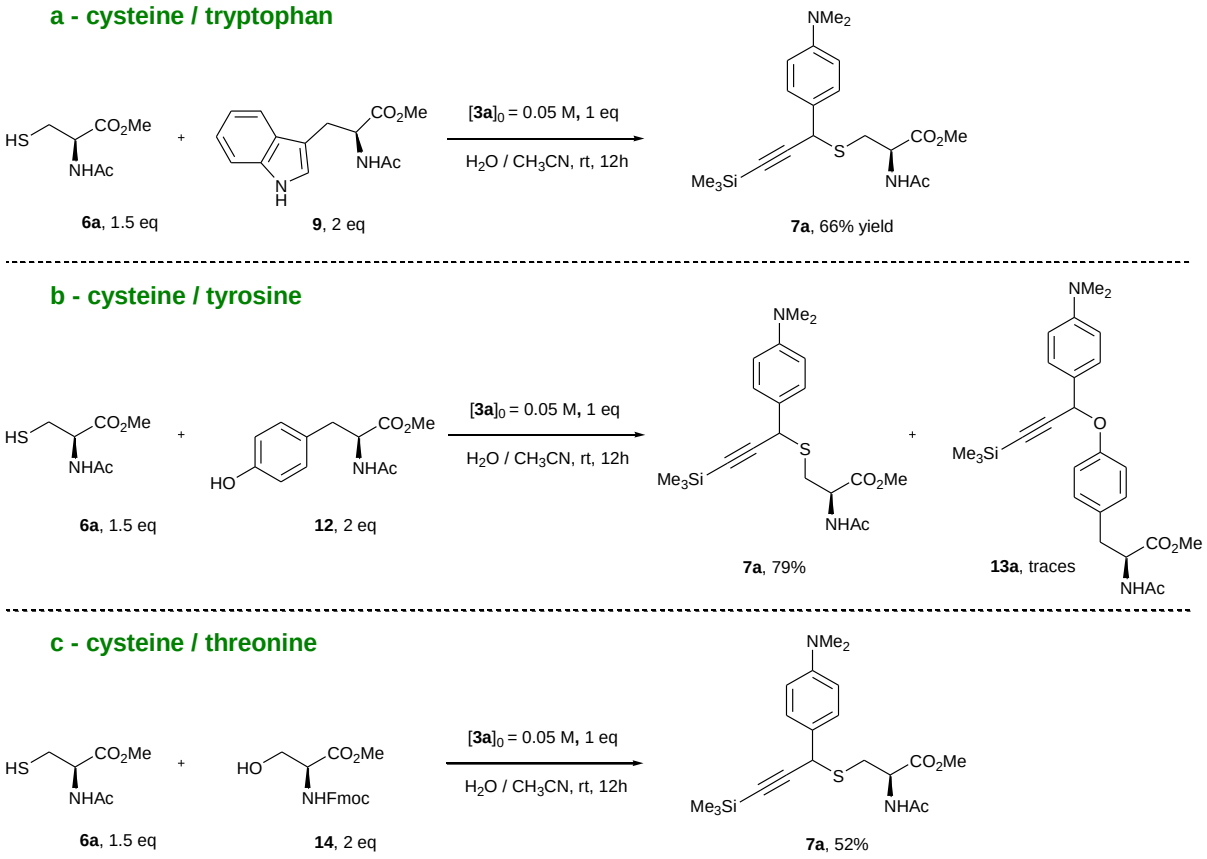
Entry	Alcohol	Conditions[a]	Product[b]	Yield
1	**3a**	70°C – 12h	**13a**	traces
2	**3b**	70°C – 18h	**13b**	traces
3	**3c**	rt – 48h	**13c**	traces
4	**3d**	70°C – 12h	-	-

[a] The reactions were carried out at room temperature with $[\mathbf{3}]_0$ = 0.1 M and 2 equiv of amino acid. [b] The products were detected by their molecular mass in HPLC – MS analysis.

The above observations are consistent with the higher nucleophilicity of the thiol group of cysteine among all the different amino acid side chains. Although indole derivatives are usually nucleophilic enough to react with stabilized carbenium ions, this is not the case for tryptophan because the indolic 3-position is not free leading to a more difficult addition. Phenols and alcohols are weaker nucleophiles and primary amines are protonated and, thus, not reactive in these conditions. Since only cysteine gives a stable substitution product at room temperature, we expect a selectivity for this amino acid.

2.3.3. Selective ligation of cysteine.

To illustrate the selectivity for the thiol group, reactions in which cysteine competes with an excess of another amino acid for the nucleophilic substitution have been performed with alcohol **3a** at room temperature (scheme 10). In each case, the ligation product to cysteine is the major product. Traces of the ligation product to the second amino acid have been observed only in the case of the competition reaction with tyrosine (scheme 10b) ; otherwise the ligation takes place on cysteine alone. This selectivity is a very interesting feature for the bioconjugation of natural polypeptides and proteins because of the low frequency of occurrence of cysteine residues.

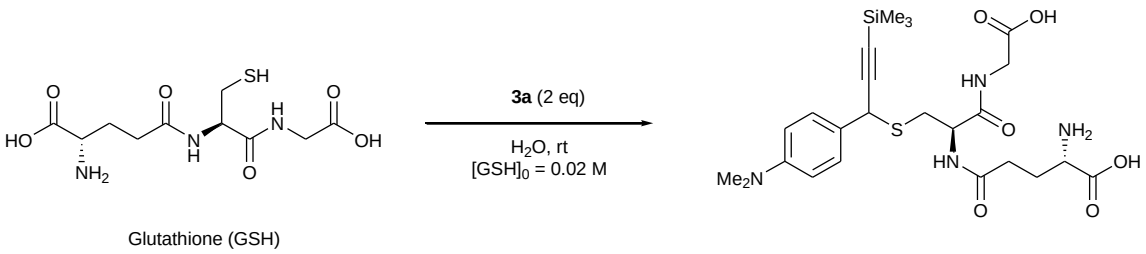


Scheme 10. Competition reactions showing the selectivity for cysteine

2.3.4. Ligation of glutathione.

The selectivity for the thiol group demonstrated, it was necessary to show the ligation with a natural polypeptide. We have chosen glutathione (GSH) for its high nucleophilicity and solubility in water. GSH is an endogenous tripeptide consisting of glycine, cysteine and glutamic acid (i.e. γ-L-glutamyl-L-cysteinylglycine) that participates in essential aspects of cellular homeostasis.[38] It is the major thiol compound of low molecular mass (307 $g.mol^{-1}$) in plants and animals, but it is also present in several additional forms : in particular glutathione disulfide, formed upon oxidation, and glutathione cysteinyl disulfides formed by oxidation of cysteine residues on proteins. Of course, only the reduced form GSH can be ligated by our method. This ligation has been successful with the alcohol **3a** in entirely aqueous solution (scheme 11). Only the mono-conjugated product has been observed by HPLC analysis, even with an excess of alcohol, showing again the absence of reactivity of primary amines and the selectivity for the thiol group.

[38] H. Sies. Glutathione and its role in cellular functions. *Free Radical Biology and Medicine* **1999**, *27*, 916 – 921.



Scheme 11. Ligation of reduced glutathione.
Ligation product detected by HPLC-MS analysis as the main product.

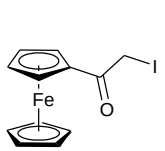
2.4. Bioconjugation of cysteine with ferrocenyl and pyrenyl moieties.

By reacting with a cysteine residue, the carbenium ion acts as a linker to attach on a polypeptide the functional moiety previously inserted on the triple bond. This functional moiety is often a synthetic small molecule that can function as probe for the discovery of biological interactions or for biochemical assays. We have studied the possibility to functionalize the alcohol **3a** with ferrocene and pyrene, two organic groups that have been widely used in bioconjugation since they give some particular properties to the target biomolecules.

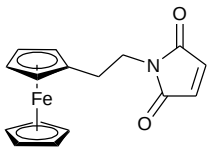
The stability of the ferrocenyl group in aqueous media, the accessibility of a large variety of derivatives, and its favourable electrochemical properties have made ferrocene and its derivatives very popular molecules for biological applications and for bioconjugation. In particular, the application of the redox chemistry of ferrocene in electrochemical sensor devices is an area that blossoms, with applications ranging from use in simple anion sensor to the monitoring of glucose levels in the blood of patients with diabetes and use in DNA sensors.

Chemical syntheses have been devised to create conjugates of ferrocene with all different kinds of biomolecules[39] : proteins, nucleic acids, carbohydrates and hormones. Conjugates of ferrocene with well-known drugs have also been reported, for example with antibiotics such as penicillins and cephalosporins. Ligation of ferrocene to amino acids and peptides usually takes place via amide or imide formation at the N-terminus, respectively with ferrocenecarboxylic acid derivatives or ferrocenecarbaldehyde. Unnatural amino acids containing a ferrocenyl side chain, such as ferrocenylalanine, have also been synthesized and incorporated into polypeptides. The selective labelling of cysteine uses the classic bioconjugation methods : glutathione, for example, has been labelled by both ferrocenylethyl maleimide and ferrocenyl iodoacetamide.

[39] For a review covering the bioconjugates of ferrocene, see : D. R. Van Staveren, N. Metzler-Nolte. Bioorganometallic chemistry of ferrocene. *Chem. Rev.* **2004,** *104*, 5931 – 5985.

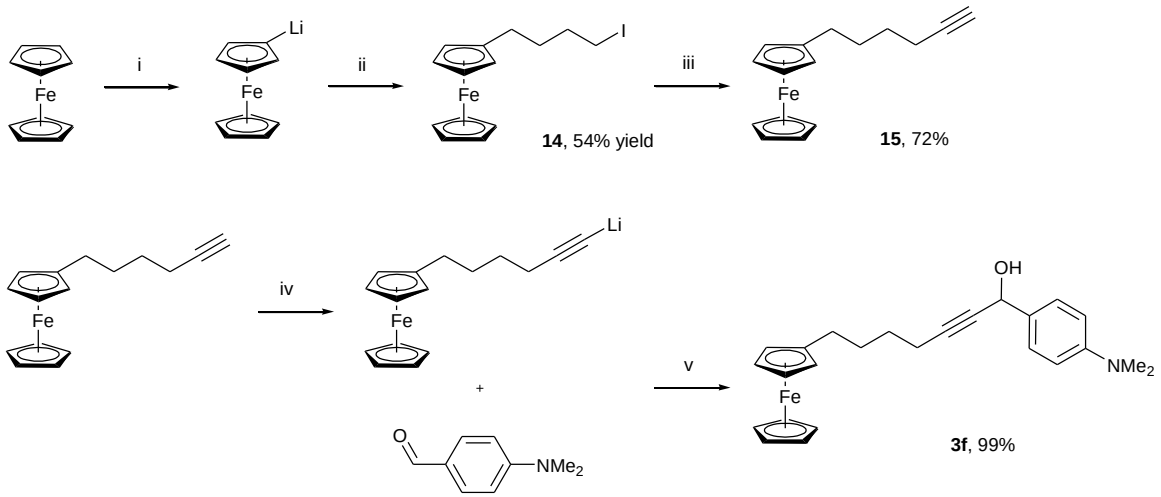


Ferrocenyl iodoacetamide



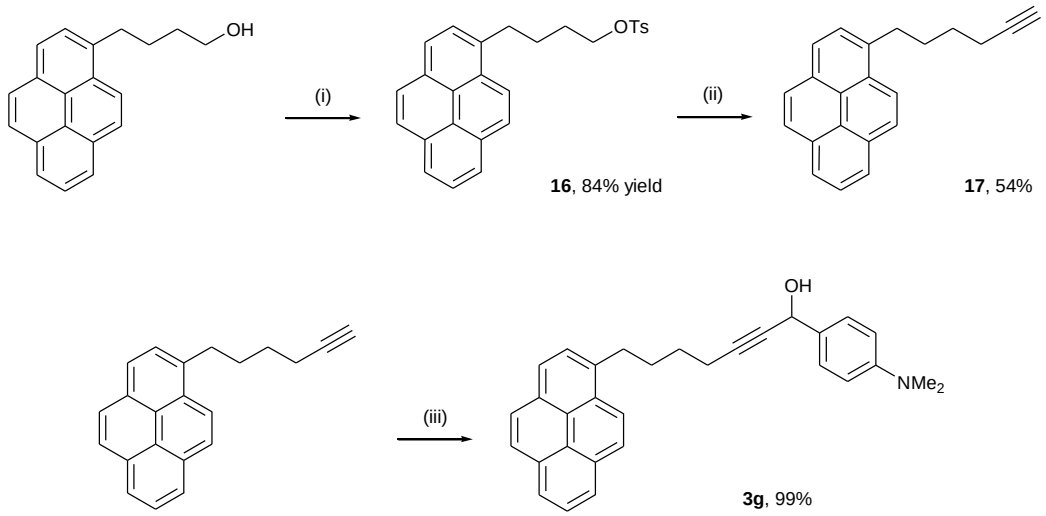
Ferrocenylethyl maleimide

The key to insert a ferrocenyl moiety on the triple bond of the propargylic alcohols **3a-e** is to prepare a ferrocene derivative containing a terminal acetylene. This have been done by alkylating ferrocene with a iodoalkyl chain. The iodide **14** is then converted to the terminal acetylene **15** by nucleophilic substitution with sodium acetylide. The terminal alkyne is easily deprotonated by butyllithium and reacts with N,N-dimethylaminobenzaldehyde to give the propargylic alcohol **3f** (scheme 12). This alcohol is substituted by cysteine methyl ester in the same conditions as for benzylic and indolic alcohols **3a-e**. This shows that the ferrocenyl moiety does not affect the reactivity.



Scheme 12. Synthesis of a propargylic alcohol containing a ferrocenyl moiety through the nucleophilic addition of a terminal alkyne. (i) *t*BuLi, THF, 0°C. (ii) 1,4-diiodobutane, THF/toluene, -78°C. (iii) Sodium acetylide, DMF, 0°C. (iv) BuLi, THF, 0°C. (v) THF, 0°C.

The same strategy has been used to insert a pyrenyl moiety on the model alcohol. The synthesis starts from the commercially available 4-pyrenyl-butanol and, this time, the terminal acetylene is introduced by nucleophilic substitution on the tosylate **16**. The pirene-containing alcohol **3g** is finally obtained by nucleophilic addition of the terminal alkyne **17** to N,N-dimethylaminobenzaldehyde, as for the ferrocene derivative **3f**.



Scheme 13. Synthesis of the pyrene-containing propargylic alcohol **3g**. (i) TsCl, DMAP, Et_3N, DCM, 0°C. (ii) sodium acetylide, DMF, 0°C. (iii) BuLi, THF, 0°C, then N,N-dimethylaminobenzaldehyde.

Pyrene is one of the oldest probes and has been employed to study a wide range of biomolecules. It is a fluorescent molecule with unique spectral features that can be used to investigate protein structures and conformations.[40] Proteins are typically conjugated with pyrene by labeling lysine or cysteine residues, using the classic bioconjugation techniques.[41] Pyrene has also been used for the immobilization of biomolecules on carbon nanotubes by non-covalent functionalization.[42] This is particularly interesting for the development of nanotube biosensors since the physical properties of the nanotubes are entirely preserved and the hydrophobic π-stacking interactions are stable in aqueous media.[43]

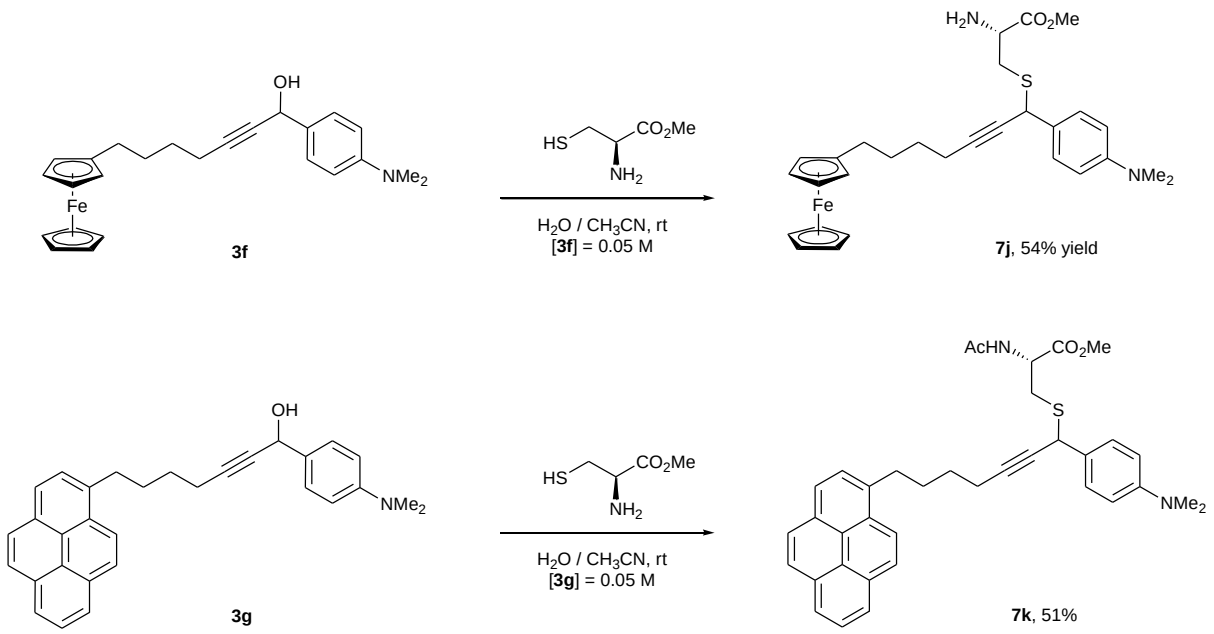
The ferrocene and pyrene-containing alcohols **3f** and **3g** react with cysteine methyl ester in the same conditions as previously, showing that the ferrocenyl and pyrenyl moieties do not affect the reactivity. These two examples illustrate the use of stabilized carbenium ions as bifunctional linkers for the bioconjugation of polypeptides through cysteine residues. The fluorescence properties of pyrene could be used to explore the possibility to ligate macromolecules.

[40] G. Bains, A. B. Patel, V. Narayanaswami. Pyrene : a probe to study protein conformation and conformational changes. *Molecules* **2011**, *16*, 7909 – 7935.

[41] R.P. Haugland, *The handbook : a guide to fluorescent probes and labeling technologies, 10th ed.* ; Molecular Probes ; Carlsbad, CA, USA, **2005**.

[42] R. Haddad, M. Holzinger, A. Maaref, S. Cosnier. Pyrene functionalized single-walled carbon nanotubes as precursors for high performance biosensors. *Electrochimica Acta* **2010**, *55*, 7800 – 7803.

[43] R.J. Chen, Y. Zhang, D. Wang, H. Dai. Noncovalent sidewall functionalization of single-walled carbon nanotubes for protein immobilization. *J. Am. Chem. Soc.* **2001,** *123,* 3838 – 3839.



Scheme 14. Ligation of cysteine by the ferrocene and pyrene-containing alcohols **3f** and **3g**.

2.5. Conclusion.

We have developed a simple and efficient method for the selective ligation of cysteine and cysteine-containing small polypeptides based on the S_N1 reaction of propargylic alcohols in aqueous media. This reaction does not need any catalyst and is actually driven by water in neutral conditions and at room temperature. The reactivity with high molecular weight polypeptides and proteins has not yet been shown but we have given tools to explore this possibility by derivatizing the alcohols with functional moieties that could be useful as probes for the physico-chemical detection. Another advantage of using propargylic alcohols is the presence of the triple bond that remains unchanged after the ligation and should allow multifunctional bioconjugation via click chemistry.

We have shown that the ligation of tryptophan on the indolic 2-position is also possible in the same mild conditions but with softer carbenium ions. This is very promising since the modern methods for the bioconjugation of tryptophan require acidic conditions or the use of transition metals that can affect the structure of the protein targets. The benzodithiolylium ion gives a stable conjugate with tryptophan and the resulting benzodithiole derivative might be a substrate for many types of transformations. The second part of this thesis research deals with one of these possible transformations : the oxidative desulfurization-fluorination into a *gem*-difluoromethylene group.

2.6. Experimental section.

2.6.1. General information and materials.

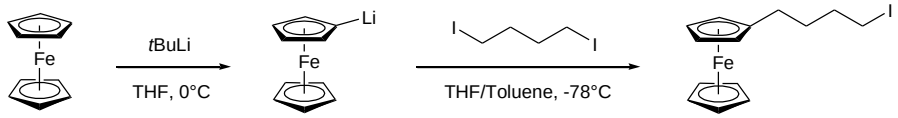
^1H and ^{13}C NMR spectra were recorded on Varian Gemini 200 and Varian Mercury 400 spectrometers. ^1H spectra are referenced relative to the residual $CDCl_3$ proton signal at δ

7.26 ppm and data are reported as follows : chemical shift (ppm), multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, b = broad, m = multiplet), coupling constants (Hz) and integration. ^{13}C spectra are referenced relative to the $CDCl_3$ carbon signal at δ 77.16 ppm and are reported in terms of chemical shifts. Chromatographic purifications were done with 240 - 400 mesh silica gel. Electrospray ionization (ESI) mass spectra were obtained on a Agilent Technologies MSD1100 single-quadrupole mass spectrometer.

Commercial grade reagents and solvents were used without further purification. Anhydrous solvents were supplied by Sigma-Aldrich in Sure/seal™ bottles. Amino acids were protected according to reported procedures[44] from commercially available sources.

2.6.2. Synthesis of (hex-5-ynyl)ferrocene 15.

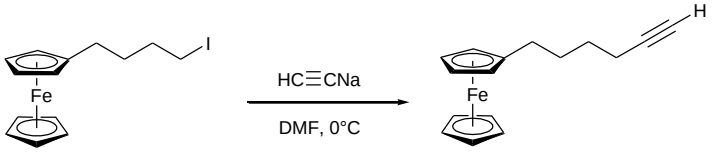
(4-iodobutyl)ferrocene (14).



14

Ferrocene (1.4 mmol, 1.1 eq.) is dissolved in 2 mL of anhydrous tetrahydrofuran (0.7 M) under inert atmosphere and the solution is cooled to 0°C. *Tert*-butyllithium (1.27 mmol, 1 eq.) is added dropwise and the reaction mixture is stirred for 15 minutes. 1 mL of anhydrous toluene is then added and the solution is cooled to −78°C. 1,4-diiodobutane (2.54 mmol, 2 eq.) is added dropwise and the mixture is stirred for 12 hours while warming to room temperature. After completion, the reaction mixture is poured into an excess volume of water, layers are separated, and the aqueous layer is extracted three times with cyclohexane. After drying the organic layers over $MgSO_4$, the crude product is concentrated under reduced pressure and purified by column chromatography (cyclohexane). The title compound has been obtained as an orange oil (54% yield).
^1H NMR (200 MHz, $CDCl_3$) δ = 4.11 (m, 9H), 3.20 (t, *J*=6.8, 2H), 2.34 (t, *J*=7.4, 2H), 1.86 (m, 2H), 1.60 (m, 2H).
ESI-MS (m/z) : 368 $[M]^+$.

(hex-5-ynyl)ferrocene (15).



14 **15**

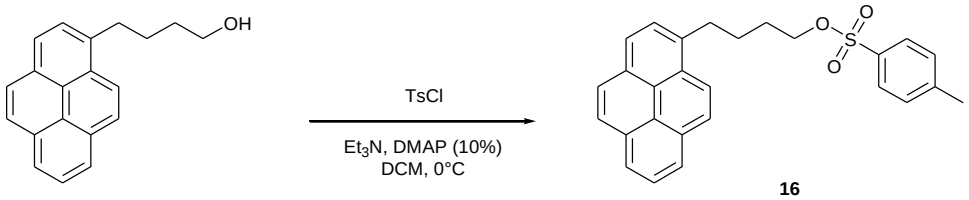
(4-bromobutyl)ferrocene **14** (0.7 mmol, 1 eq.) is dissolved in 1.4 mL of anhydrous dimethylformamide (0.5 M) and the solution is cooled to 0°C. Sodium acetylide (18 weight-% slurry in xylene, 1.05 mmol, 1.5 eq.) is slowly added and the mixture is stirred at 0°C until complete conversion (monitored by TLC, about 1 hour). 1 mL of water is then added and the solvent is removed under reduced pressure. The crude product is dissolved in water and cyclohexane, layers are separated, and the aqueous layer is extracted three times with

[44] A. Isidro-Llobet, M. Alvarez, F. Albericio. Amino acid protecting groups. *Chem. Rev.* **2009,** *109,* 2455 – 2504.

cyclohexane. After drying the organic layers over $MgSO_4$, the title compound is purified by column chromatography (cyclohexane) as an orange oil (72% yield).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 4.12 (s, 5H), 4.10 – 4.04 (m, 4H), 2.33 (t, *J*=7.4, 2H), 2.21 (td, *J*=6.7, 2.4, 2H), 1.95 (t, *J*=2.5, 1H), 1.70 – 1.48 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 89.3, 84.7, 68.8, 68.5, 68.3, 67.4, 30.1, 29.2, 28.5, 18.4.
ESI-MS (m/z) : 266 $[M]^+$.

2.6.3. Synthesis of 1-(hex-5-ynyl)pyrene 17.

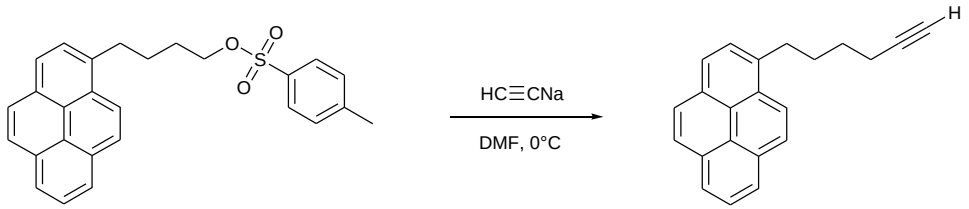
4-(pyren-3-yl)butyl 4-methylbenzenesulfonate (16).



16

4-(pyren-3-yl)butan-1-ol (1.5 mmol, 1 eq.) and triethylamine (1.8 mmol, 1.5 eq.) are dissolved in 2 mL of anhydrous dichloromethane (0.75 M) and the solution is cooled to 0°C. Tosyl chloride (1.8 mmol, 1.2 eq.) and dimethylaminopyridine (0.15 mmol, 0.1 eq.) are then added. The reaction mixture is stirred for 12 hours while warming to room temperature. After completion, the mixture is poured into an excess volume of water, layers are separated and the aqueous layer is extracted three times with dichloromethane. After drying the organic layers over $MgSO_4$, the title compound is purified by column chromatography (Cy/AcOEt 9:1, 84% yield).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 8.21 – 8.15 (m, 3H), 8.11 – 8.07 (m, 2H), 8.03 (s, 2H), 8.00 (t, *J*=7.6, 1H), 7.78 (d, *J*=7.8, 1H), 7.75 (d, *J*=8.3, 2H), 7.24 (d, *J*=8.1, 2H), 4.08 (t, *J*=6.2, 2H), 3.30 (t, *J*=7.5, 2H), 2.35 (s, 3H), 1.89 (m, 2H), 1.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.8, 135.9, 133.2, 131.5, 131.0, 130.0, 129.9, 128.7, 128.0, 127.6, 127.5, 127.3, 126.8, 126.0, 125.2, 125.11, 125.09, 124.9, 123.3, 70.5, 32.8, 28.9, 27.6, 21.7.

1-(hex-5-ynyl)pyrene (17).

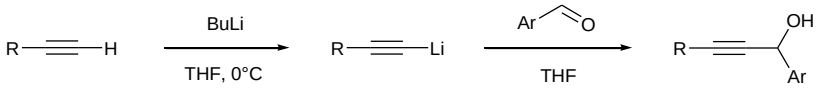


17

4-(pyren-3-yl)butyl 4-methylbenzenesulfonate **16** (1.2 mmol, 1 eq.) is dissolved in 2.4 mL of anhydrous dimethylformamide (0.5 M) and the solution is cooled to 0°C. Sodium acetylide (1.8 mmol, 1.5 eq.) is slowly added and the mixture is stirred at 0°C until complete conversion (monitored by TLC, about 3 hours). 1.8 mL of water are then added and the solvent is removed under reduced pressure. The crude product is dissolved in water and cyclohexane, layers are separated, and the aqueous layer is extracted three times with cyclohexane. After drying the organic layers over $MgSO_4$, the title compound is purified by column chromatography (cyclohexane, 54% yield).

^{1}H NMR (401 MHz, $CDCl_3$) δ = 8.29 (d, *J*=9.3, 1H), 8.18 (d, *J*=2.5, 1H), 8.16 (d, *J*=2.6, 1H), 8.12 (d, *J*=2.0, 1H), 8.10 (d, *J*=3.5, 1H), 8.03 (ABq, $\Delta\delta_{AB}$ = 0.02, *J*=8.9, 2H), 7.99 (t, *J*=7.6, 1H), 7.88 (d, *J*=7.8, 1H), 3.37 (t, *J*=7.8, 2H), 2.29 (td, *J*=7.1, 2.7, 2H), 2.05 – 1.96 (m, 3H), 1.77 – 1.69 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.5, 131.4, 130.9, 129.8, 128.6, 127.5, 127.18, 127.17, 126.6, 125.76, 125.07, 125.01, 124.81, 124.76, 124.6, 123.4, 84.3, 68.5, 33.0, 30.8, 28.4, 18.3.

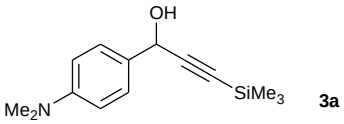
2.6.4. General procedure for the preparation of propargylic alcohols 3a-g.



3a-g

Alkyne (0.72 mmol, 1.44 eq.) is dissolved in 0.7 mL of anhydrous tetrahydrofuran (1 M) under inert atmosphere and the solution is cooled to 0°C. Butyllithium (0.6 mmol, 1.2 eq.) is then added. The reaction mixture is stirred at 0°C for 1 hour, which is enough for a complete metallation of the alkyne. Then, a solution of the aldehyde (0.5 mmol, 1 eq.) in 0.5 mL of anhydrous THF is added and the reaction mixture is stirred until complete conversion (monitored by TLC, generally about 4 hours) while warming to room temperature. After completion, an excess volume of water is added and the propargylic alcohol is extracted three times with Et_2O. The combined organic layers are washed with saturated $NaHCO_3$ aq. and dried over Na_2SO_4 ($MgSO_4$ should be avoided). Solvent is removed under reduced pressure at room temperature. The propargylic alcohol is obtained with a 99% yield and is used without further purification.

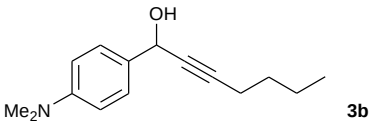
1-(4-(dimethylamino)phenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (3a).



3a

The reaction was carried out following the general procedure and using ethynyltrimethylsilane and 4-(dimethylamino)benzaldehyde as starting materials. The title compound has been obtained pure after concentration under vacuum at room temperature.
^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.47 – 7.36 (m, 2H), 6.79 – 6.67 (m, 2H), 5.37 (s, 1H), 2.96 (s, 6H), 2.05 (br s, 1H), 0.21 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 150.9, 128.5, 128.1, 112.5, 105.7, 90.9, 65.0, 40.7, 0.1.
ESI-MS (m/z) : 248 $[M+H]^+$, 270 $[M+Na]^+$.

1-(4-(dimethylamino)phenyl)hept-2-yn-1-ol (3b).

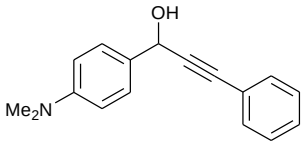


3b

The reaction was carried out following the general procedure and using hex-1-yne and 4-(dimethylamino)benzaldehyde as starting materials. The title compound has been obtained pure after concentration under vacuum at room temperature.

^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.46 – 7.36 (m, 2H), 6.77 – 6.67 (m, 2H), 5.37 (br s, 1H), 2.96 (s, 6H), 2.28 (td, *J*=6.9, 1.8, 2H), 2.02 (br s, 1H), 1.63 – 1.33 (m, 4H), 0.92 (t, *J*=7.0, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 150.8, 129.5, 127.9, 112.5, 87.1, 80.5, 64.8, 40.7, 30.9, 22.2, 18.7, 13.7.
ESI-MS (m/z) : 232 $[M+H]^+$, 254 $[M+Na]^+$, 485 $[2M+Na]^+$.

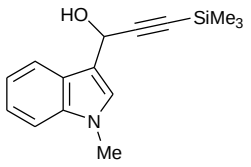
1-(4-(dimethylamino)phenyl)-3-phenylprop-2-yn-1-ol (3c).



3c

The reaction was carried out following the general procedure and using 1-ethynylbenzene and 4-(dimethylamino)benzaldehyde as starting materials. The title compound has been obtained pure after concentration under vacuum at room temperature.
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.51 – 7.46 (m, 4H), 7.34 – 7.29 (m, 3H), 6.77 – 6.73 (m, 2H), 5.61 (d, *J*=5.7, 1H), 2.97 (s, 6H), 2.15 (br d, *J*=5.8, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 150.9, 131.9, 128.8, 128.5, 128.4, 128.1, 122.9, 112.6, 89.5, 86.3, 65.1, 40.7.
ESI-MS (m/z) : 252 $[M+H]^+$, 274 $[M+Na]^+$, 290 $[M+K]^+$, 525 $[2M+Na]^+$.

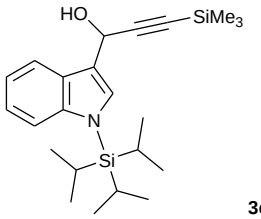
1-(1-methylindol-3-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (3d).



3d

The reaction was carried out following the general procedure and using ethynyltrimethylsilane and 1-methylindole-3-carbaldehyde as starting materials. The title compound has been obtained pure after concentration under vacuum at room temperature.
^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.83 (d, *J*=7.6, 1H), 7.33 – 7.22 (m, 2H), 7.22 – 7.09 (m, 2H), 5.71 (s, 1H), 3.69 (s, 3H), 2.37 (br s, 1H), 0.24 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 137.5, 127.7, 125.9, 122.2, 119.7, 119.6, 114.8, 109.5, 105.7, 89.4, 58.5, 32.8, 0.0.
ESI-MS (m/z) : 280 $[M+Na]^+$, 537 $[2M+Na]^+$.

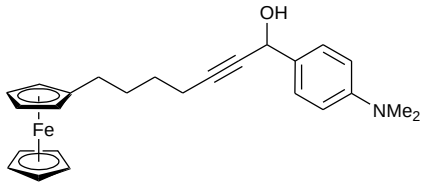
1-(1-(triisopropylsilyl)-indol-3-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (3e).



3e

The reaction was carried out following the general procedure and using ethynyltrimethylsilane and 1-(triisopropylsilyl)-indole-3-carbaldehyde as starting materials. The title compound has been obtained pure after concentration under vacuum at room temperature.
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.87 – 7.83 (m, 1H), 7.53 – 7.48 (m, 1H), 7.46 (s, 1H), 7.21 – 7.15 (m, 2H), 5.78 (s, 1H), 2.23 (br s, 1H), 1.78 – 1.65 (m, 3H), 1.20 – 1.16 (m, 18H), 0.27 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 141.9, 130.5, 129.0, 122.1, 120.2, 119.5, 118.2, 114.2, 105.8, 89.5, 58.8, 18.3, 12.9, 0.0.

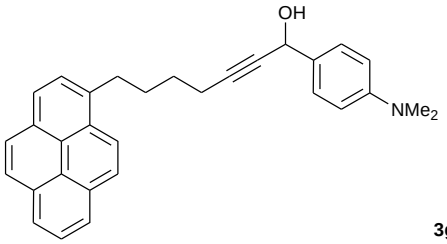
1-(4-(dimethylamino)phenyl)-7-ferrocenylhept-2-yn-1-ol (3f).



3f

The reaction was carried out following the general procedure and using (hex-5-ynyl)ferrocene **15** and 4-(dimethylamino)benzaldehyde as starting materials. The title compound has been obtained mixed with the unreacted starting alkyne (ratio propargylic alcohol **3f** / alkyne **15** = 7:3).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.44 – 7.39 (m, 2H), 6.74 – 6.70 (m, 2H), 5.38 (br s, 1H), 4.10 (s, 5H), 4.07 – 4.04 (m, 4H), 2.96 (s, 6H), 2.35 (m, 2H), 2.31 (td, *J*=6.9, 2.0, 2H), 2.03 (br s, 1H), 1.68 – 1.53 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 150.8, 129.5, 127.9, 112.6, 89.1, 86.8, 80.8, 68.6, 68.2, 67.2, 64.8, 40.7, 30.3, 29.2, 28.6, 18.9.
ESI-MS (m/z) : 415 $[M]^+$.

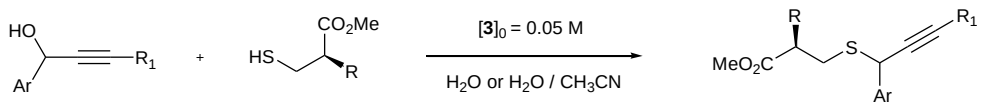
1-(4-(dimethylamino)phenyl)-7-(pyren-3-yl)hept-2-yn-1-ol (3g).



3g

The reaction was carried out following the general procedure and using 1-(hex-5-ynyl)pyrene **17** and 4-(dimethylamino)benzaldehyde as starting materials. The title compound has been obtained mixed with the unreacted starting alkyne (ratio propargylic alcohol **3g** / alkyne **17** = 7:3).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 8.29 (d, *J*=9.3, 1H), 8.18 – 8.14 (m, 2H), 8.13 – 7.96 (m, 5H), 7.87 (d, *J*=7.8, 1H), 7.40 – 7.36 (m, 2H), 6.66 – 6.61 (m, 2H), 5.37 (s, 1H), 3.40 – 3.34 (m, 2H), 2.89 (s, 6H), 2.39 (td, *J*=7.0, 2.0, 2H), 2.06 – 1.96 (m, 2H), 1.94 (br s, 1H), 1.80 – 1.70 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.8, 131.6, 131.0, 129.9, 128.8, 127.9, 127.7, 127.39, 127.37, 126.7, 125.9, 125.24, 125.19, 124.99, 124.95, 124.94, 124.8, 123.56, 123.53, 112.5, 86.7, 81.0, 64.9, 40.7, 33.2, 31.1, 28.7, 18.9.

2.6.5. General procedure for the ligation of cysteine via S_N1 reaction of propargylic alcohols.

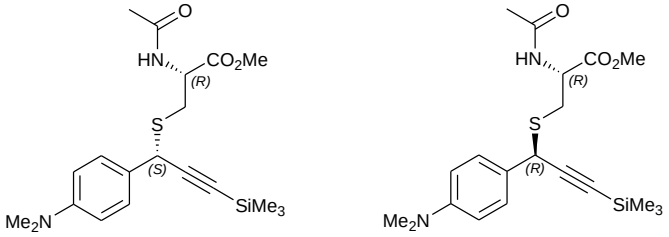


3a-g **6a-b**, 2 eq **7a-k**

Propargylic alcohol **3** (0.1 mmol, 1 eq.) and L-cysteine methyl ester **6** (0.2 mmol, 2 eq.) are placed in an ordinary vial equipped with a stir bar. The reaction starts by addition of either deionised water (2 mL, 0.05 M alcohol) or water/acetonitrile (1:1 volume, 2 mL). The reaction mixture is then vigorously stirred for 12 hours at room temperature. When water is

used without organic co-solvent, an ultrasonic cleaning bath may provide a better stirring and shorten the reaction time (temperature should be kept constant by cooling the bath). After completion, an excess volume of AcOEt is added and the organic layer is separated. The unreacted cysteine is eliminated by extraction with Na_2CO_3 aq. The organic layer is then washed with brine and dried over Na_2SO_4, and the solvent removed under reduced pressure. The ligation product **7** is purified by flash column chromatography and isolated as a 1:1 mixture of diastereoisomers.

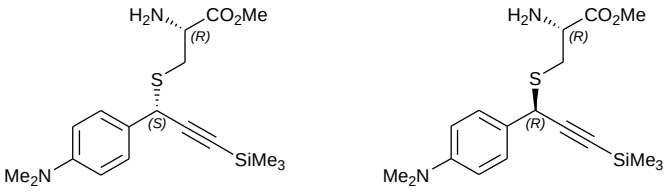
(R)-methyl 3-(1-(4-(dimethylamino)phenyl)-3-(trimethylsilyl)prop-2-ynylthio)-2-acetamidopropanoate (7a).



7a

The reaction was carried out following the general procedure and using the propargylic alcohol **3a** and N-acetyl L-cysteine methyl ester **6a** as starting materials. The ligation product has been isolated by flash column chromatography (Cy/AcOEt 1:1, 79% yield) and characterized as a 1:1 mixture of diastereoisomers *(R,S)* and *(R,R)*.
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.34 – 7.28 (m, 4H), 6.71 – 6.65 (m, 4H), 6.18 (d, *J*=7.9, 1H), 6.14 (d, *J*=7.8, 1H), 4.85 (s, 1H), 4.88 – 4.82 (m, 2H), 4.73 (s, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.28 (d, *J*=14.0, 1H), 3.27 (dd, *J*=13.8, 0.9, 1H), 3.03 (dd, *J*=14.1, 4.9, 1H), 2.94 (s, 6H), 2.94 (s, 6H), 2.88 (dd, *J*=13.8, 7.3, 1H), 2.02 (s, 3H), 1.96 (s, 3H), 0.22 (s, 9H), 0.21 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.54, 171.52, 170.0, 169.9, 150.4 (2C), 128.9, 128.8, 124.7, 124.5, 112.53, 112.51, 103.1 (2C), 91.29, 91.24, 52.73, 52.67, 51.67, 51.62, 40.62, 40.59, 39.5, 39.3, 34.1, 33.9, 23.25, 23.22, 0.1 (2C).
ESI-MS (m/z) : 429 $[M+Na]^+$, 445 $[M+K]^+$, 835 $[2M+Na]^+$.

(R)-methyl 3-(1-(4-(dimethylamino)phenyl)-3-(trimethylsilyl)prop-2-ynylthio)-2-aminopropanoate (7b).

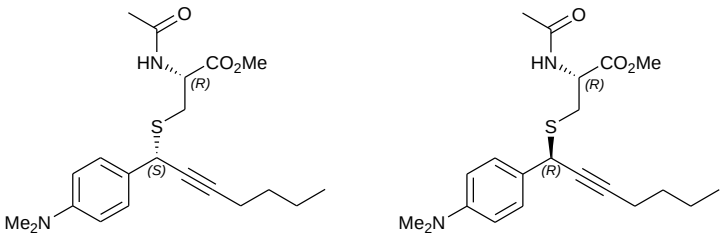


7b

The reaction was carried out following the general procedure and using the propargylic alcohol **3a** and L-cysteine methyl ester hydrochloride **6b** as starting materials. The ligation product has been isolated by flash column chromatography (Cy/AcOEt 1:2, 71% yield) and characterized as a 1:1 mixture of diastereoisomers *(R,S)* and *(R,R)*.
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.39 – 7.30 (m, 4H), 6.73 – 6.65 (m, 4H), 4.82 (s, 1H), 4.81 (s, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.75 – 3.69 (m, 2H), 3.17 (dd, *J*=13.6, 4.3, 1H), 3.03 (dd, *J*=13.8, 5.0, 1H), 2.96 (dd, *J*=13.8, 7.5, 1H), 2.71 (dd, *J*=13.6, 8.4, 1H), 1.78 (br s, 4H), 0.21 (s, 9H), 0.21 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.7, 174.5, 150.3 (2C), 128.84, 128.78, 125.0, 124.8,

112.5 (2C), 103.8, 103.6, 90.77, 90.74, 54.4, 54.1, 52.31, 52.27, 40.6 (2C), 39.6, 39.2, 37.3, 37.1, 0.1 (2C).

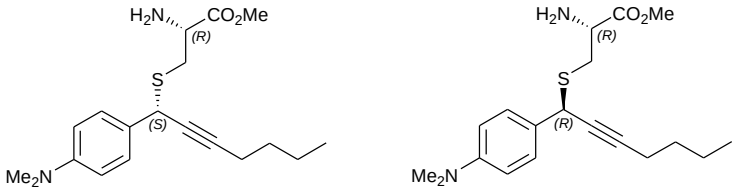
(R)-methyl 3-(1-(4-(dimethylamino)phenyl)hept-2-ynylthio)-2-acetamidopropanoate (7c)



7c

The reaction was carried out following the general procedure and using the propargylic alcohol **3b** and N-acetyl L-cysteine methyl ester **6a** as starting materials. The ligation product has been isolated by flash column chromatography (Cy/AcOEt 1:1, 54% yield) and characterized as a 1:1 mixture of diastereoisomers *(R,S)* and *(R,R)*.
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.34 – 7.29 (m, 4H), 6.70 – 6.65 (m, 4H), 6.15 (d, *J*=7.9, 1H), 6.12 (d, *J*=7.8, 1H), 4.86 – 4.78 (m, 2H), 4.79 (t, *J*=2.0, 1H), 4.71 (t, *J*=1.9, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.24 (dd, *J*=13.9, 5.1, 1H), 3.21 (dd, *J*=13.9, 4.3, 1H), 3.00 (dd, *J*=13.9, 4.8, 1H), 2.94 (s, 12H), 2.90 (dd, *J*=13.9, 6.8, 1H), 2.33 – 2.26 (m, 4H), 2.00 (s, 3H), 1.96 (s, 3H), 1.59 – 1.49 (m, 4H), 1.49 – 1.38 (m, 4H), 0.93 (t, *J*=7.3, 3H), 0.92 (t, *J*=7.2, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.57, 171.53, 170.0, 169.9, 150.3 (2C), 128.77, 128.74, 125.9, 125.8, 112.5 (2C), 87.15, 87.12, 77.8, 77.7, 52.74, 52.66, 51.8, 51.6, 40.66, 40.64, 39.3, 39.2, 33.80, 33.76, 31.03, 31.01, 23.24, 23.23, 22.2 (2C), 18.8 (2C), 13.8 (2C).

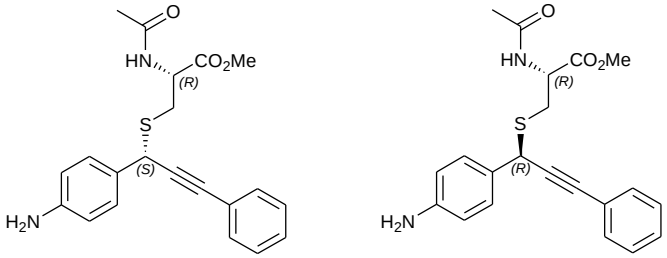
(R)-methyl 3-(1-(4-(dimethylamino)phenyl)hept-2-ynylthio)-2-aminopropanoate (7d).



7d

The reaction was carried out following the general procedure and using the propargylic alcohol **3b** and L-cysteine methyl ester hydrochloride **6b** as starting materials. The ligation product has been isolated by flash column chromatography (Cy/AcOEt 1:2, 77% yield) and characterized as a 1:1 mixture of diastereoisomers *(R,S)* and *(R,R)*.
^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.34 (d, *J*=8.6, 4H), 6.68 (d, *J*=8.7, 4H), 4.79 (t, *J*=2.0, 2H), 3.73 (s, 3H), 3.73 (s, 3H), 3.76 – 3.63 (m, 2H), 3.14 (dd, *J*=13.6, 4.3, 1H), 3.00 – 2.90 (m, 2H), 2.94 (s, 12H), 2.71 (dd, *J*=13.6, 8.3, 1H), 2.29 (td, *J*=6.7, 2.0, 4H), 1.72 (br s, 4H), 1.64 – 1.33 (m, 8H), 0.92 (t, *J*=7.0, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 174.8, 174.5, 151.1, 150.3, 128.76, 128.73, 126.2, 126.1, 112.5 (2C), 86.66, 86.63, 78.2 (2C), 54.4, 54.2, 52.31, 52.26, 40.7 (2C), 39.4, 39.1, 37.13, 37.05, 31.0 (2C), 22.1 (2C), 18.8 (2C), 13.8 (2C).
ESI-MS (m/z) : 371 $[M+Na]^+$, 719 $[2M+Na]^+$.

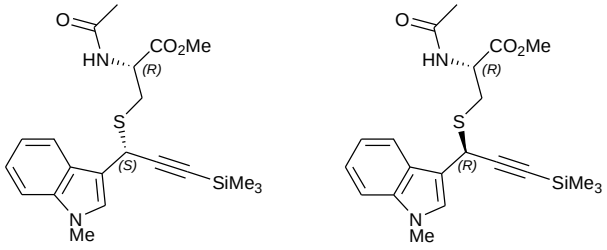
(R)-methyl 3-(1-(4-aminophenyl)-3-phenylprop-2-ynylthio)-2-acetamidopropanoate (7e).



7e

The reaction was carried out following the general procedure and using the propargylic alcohol **3c** and N-acetyl L-cysteine methyl ester **6a** as starting materials. The ligation product has been isolated by flash column chromatography (Cy/AcOEt 1:1, 54% yield) and characterized as a 1:1 mixture of diastereoisomers *(R,S)* and *(R,R)*.
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.52 – 7.46 (m, 4H), 7.40 (dd, *J*=8.9, 2.5, 4H), 7.35 – 7.30 (m, 6H), 6.71 (d, *J*=8.3, 4H), 6.24 (d, *J*=7.9, 1H), 6.20 (d, *J*=7.5, 1H), 5.06 (s, 1H), 4.96 (s, 1H), 4.92 – 4.86 (m, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.36 (dd, *J*=14.0, 4.8, 1H), 3.33 (dd, *J*=13.8, 4.2, 1H), 3.09 (dd, *J*=14.0, 4.9, 1H), 2.98 (dd, *J*=13.8, 6.7, 1H), 2.96 (s, 12H), 1.98 (s, 3H), 1.94 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.6, 171.5, 170.1, 170.0, 150.40, 150.37, 131.9, 131.87, 128.9 (2C), 128.8 (2C), 128.6, 128.51, 128.47, 128.43, 122.92, 122.85, 112.6 (2C), 87.2, 87.1, 86.4, 86.3, 52.82, 52.75, 51.9, 51.6, 40.7 (2C), 39.6, 39.4, 33.99, 33.96, 23.25, 23.23.
ESI-MS (m/z) : 433 $[M+Na]^+$, 449 $[M+K]^+$, 843 $[2M+Na]^+$.

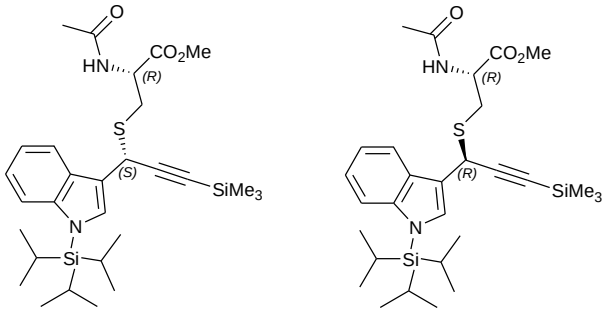
(R)-methyl 3-(1-(1-methylindol-3-yl)-3-(trimethylsilyl)prop-2-ynylthio)-2-acetamidopropanoate (7f).



7f

The reaction was carried out following the general procedure and using the propargylic alcohol **3d** and N-acetyl L-cysteine methyl ester **6a** as starting materials. The ligation product has been isolated by flash column chromatography (Cy/AcOEt 1:1, 72% yield) and characterized as a 1:1 mixture of diastereoisomers *(R,S)* and *(R,R)*.
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.79 (dd, *J*=7.6, 7.0, 2H), 7.32 – 7.21 (m, 4H), 7.19 – 7.12 (m, 4H), 6.06 (d, *J*=7.5, 1H), 6.00 (d, *J*=7.7, 1H), 5.21 (s, 1H), 5.09 (s, 1H), 4.86 – 4.77 (m, 2H), 3.77 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H), 3.65 (s, 3H), 3.31 (dd, *J*=14.0, 4.8, 1H), 3.27 (dd, *J*=13.8, 4.2, 1H), 3.00 (dd, *J*=14.0, 4.8, 1H), 2.89 (dd, *J*=13.8, 7.1, 1H), 1.92 (s, 3H), 1.66 (s, 3H), 0.24 (s, 9H), 0.23 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.5 (2C), 170.0, 169.8, 137.8, 137.7, 128.6, 128.4, 125.8, 125.7, 122.5, 122.4, 120.0, 119.8, 119.7, 119.6, 110.6, 110.3, 109.8, 109.7, 103.02, 103.00, 89.84, 89.80, 52.68, 52.66, 51.7, 51.4, 33.6, 33.2, 33.03, 33.02, 32.7, 32.4, 23.1, 22.8, 0.15, 0.14.
ESI-MS (m/z) : 439 $[M+Na]^+$, 455 $[M+K]^+$, 855 $[2M+Na]^+$.

(R)-methyl 3-(1-(1-(triisopropylsilyl)-indol-3-yl)-3-(trimethylsilyl)prop-2-ynylthio)-2-acetamidopropanoate (7g).



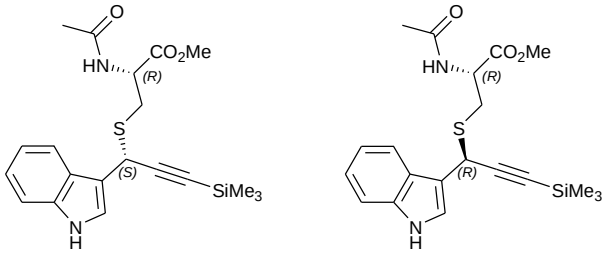
7g

The reaction was carried out following the general procedure and using the propargylic alcohol **3e** and N-acetyl L-cysteine methyl ester **6a** as starting materials and water as the reaction solvent. The ligation product has been isolated by flash column chromatography (Cy/AcOEt 7:3, 21% yield) and characterized as a 1:1 mixture of diastereoisomers *(R,S)* and *(R,R)*.

^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.83 – 7.71 (m, 2H), 7.55 – 7.42 (m, 2H), 7.36 (s, 2H), 7.23 – 7.09 (m, 4H), 6.07 – 5.91 (m, 2H), 5.16 (s, 1H), 5.07 (s, 1H), 4.83 – 4.68 (m, 2H), 3.72 (s, 3H), 3.53 (s, 3H), 3.32 (dd, *J*=13.8, 4.8, 1H), 3.25 (dd, *J*=13.5, 4.1, 1H), 2.90 (dd, *J*=13.8, 5.0, 1H), 2.80 (dd, *J*=13.5, 7.1, 1H), 1.89 (s, 3H), 1.78 – 1.59 (m, 6H), 1.64 (s, 3H), 1.22 – 1.09 (m, 36H), 0.24 (s, 9H), 0.23 (s, 9H).

ESI-MS (m/z) : 559 $[M+H]^+$, 581 $[M+Na]^+$, 597 $[M+K]^+$, 1139 $[2M+Na]^+$.

(R)-methyl 3-(1-(indol-3-yl)-3-(trimethylsilyl)prop-2-ynylthio)-2-acetamidopropanoate (7h).



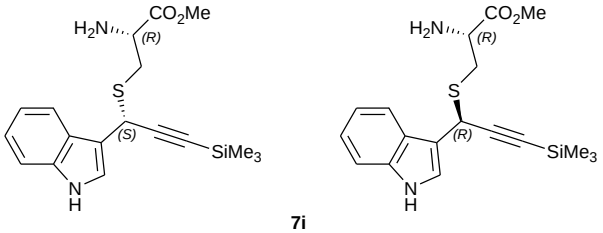
7h

The reaction was carried out following the general procedure and using the propargylic alcohol **3e** and N-acetyl L-cysteine methyl ester **6a** as starting materials. After completion, the reaction mixture was treated with aqueous $NaHCO_3$ for 1 hour to remove the TIPS protecting group. The ligation product has been then isolated by flash column chromatography (Cy/AcOEt 1:1, 52% yield) and characterized as a 1:1 mixture of diastereoisomers *(R,S)* and *(R,R)*.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 8.34 (br s, 2H), 7.83 – 7.76 (m, 2H), 7.36 (d, *J*=8.0, 2H), 7.28 (d, *J*=2.5, 2H), 7.21 (tdd, *J*=8.2, 2.8, 1.2, 2H), 7.18 – 7.12 (m, 2H), 6.06 (d, *J*=7.4, 1H), 5.98 (d, *J*=7.7, 1H), 5.19 (s, 1H), 5.09 (s, 1H), 4.82 – 4.74 (m, 2H), 3.72 (s, 3H), 3.62 (s, 3H), 3.28 (dd, *J*=13.9, 4.9, 1H), 3.24 (dd, *J*=14.0, 4.3, 1H), 2.99 (dd, *J*=14.0, 4.8, 1H), 2.88 (dd, *J*=13.8, 7.1, 1H), 1.88 (s, 3H), 1.61 (s, 3H), 0.23 (s, 9H), 0.22 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.5 (2C), 170.0, 169.9, 137.0, 136.9, 125.3, 125.2, 124.2, 124.0, 122.9, 122.8, 120.1, 120.0, 119.9, 119.7, 112.3, 112.0, 111.7, 111.6, 102.9, 102.8, 89.9 (2C), 52.69, 52.65, 51.7, 51.3, 33.3, 32.9, 32.7, 32.5, 23.1, 22.7, 0.13, 0.12.

ESI-MS (m/z) : 403 $[M+H]^+$, 425 $[M+Na]^+$, 441 $[M+K]^+$.

(R)-methyl 3-(1-(indol-3-yl)-3-(trimethylsilyl)prop-2-ynylthio)-2-aminopropanoate (7i).



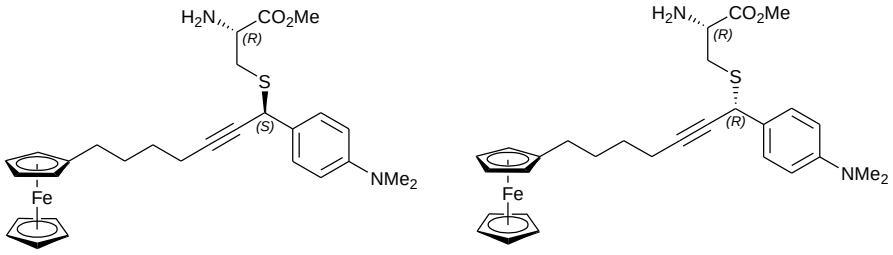
7i

The reaction was carried out following the general procedure and using the propargylic alcohol **3e** and L-cysteine methyl ester hydrochloride **6b** as starting materials. After completion, the reaction mixture was treated with aqueous $NaHCO_3$ for 1 hour to remove the TIPS protecting group. The ligation product has been then isolated by flash column chromatography (Cy/AcOEt 1:2, 44% yield) and characterized as a 1:1 mixture of diastereoisomers *(R,S)* and *(R,R)*.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 8.19 (br s, 2H), 7.82 (dd, *J*=7.8, 4.5, 2H), 7.39 – 7.33 (m, 2H), 7.30 (dd, *J*=5.3, 2.2, 2H), 7.21 (t, *J*=7.5, 2H), 7.18 – 7.12 (m, 2H), 5.19 (d, *J*=0.5, 1H), 5.18 (d, *J*=0.6, 1H), 3.79 – 3.74 (m, 1H), 3.72 (s, 3H), 3.74 – 3.68 (m, 1H), 3.66 (s, 3H), 3.16 (dd, *J*=13.6, 4.3, 1H), 3.06 (dd, *J*=13.8, 5.1, 1H), 3.00 (dd, *J*=13.8, 7.4, 1H), 2.72 (dd, *J*=13.6, 8.3, 1H), 1.68 (br s, 4H), 0.23 (s, 9H), 0.23 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.8, 174.4, 136.9, 136.8, 125.42, 125.41, 123.9, 123.6, 122.7 (2C), 119.97, 119.95, 119.89, 119.85, 112.7, 112.4, 111.50, 111.49, 103.71, 103.68, 89.5, 89.4, 54.5, 54.2, 52.30, 52.28, 36.9, 36.6, 32.7, 32.4, 0.14, 0.11.

ESI-MS (m/z) : 383 $[M+Na]^+$, 399 $[M+K]^+$.

(R)-methyl 3-(1-(4-(dimethylamino)phenyl)-7-ferrocenylhept-2-ynylthio)-2-acetamidopropanoate (7j).



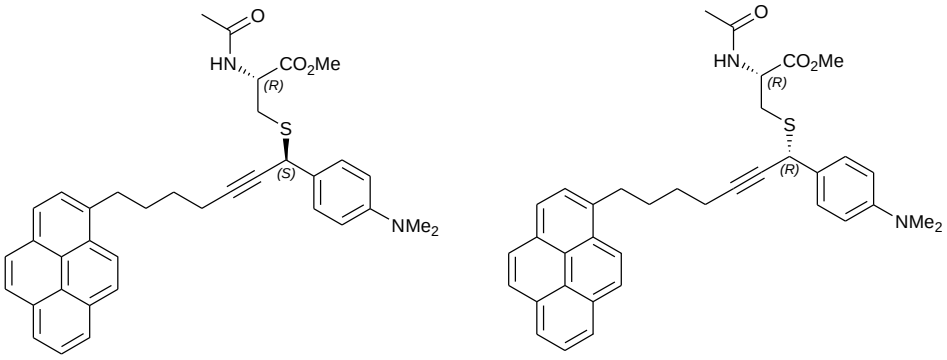
7j

The reaction was carried out following the general procedure and using the propargylic alcohol **3f** and L-cysteine methyl ester hydrochloride **6b** as starting materials. The ligation product has been isolated by flash column chromatography (Cy/AcOEt 3:2, 51% yield) and characterized as a 1:1 mixture of diastereoisomers *(R,S)* and *(R,R)*.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.34 (dd, *J*=8.7, 1.6, 4H), 6.68 (dd, *J*=8.7, 1.4, 4H), 4.79 (br s, 2H), 4.09 (s, 10H), 4.07 – 4.04 (m, 4H), 4.04 – 4.02 (m, 4H), 3.73 (s, 3H), 3.72 (s, 3H), 3.70 – 3.63 (m, 2H), 3.11 (dd, *J*=13.2, 4.6, 1H), 2.99 – 2.91 (m, 2H), 2.94 (s, 6H), 2.94 (s, 6H), 2.72 (dd, *J*=13.5, 8.2, 1H), 2.38 – 2.28 (m, 8H), 1.75 (br s, 4H), 1.69 – 1.54 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.7, 174.5, 150.2 (2C), 128.76, 128.73, 126.2, 126.1, 112.5 (2C), 89.1 (2C), 86.36, 86.34, 78.55, 78.54, 68.6 (2C), 68.2 (2C), 67.2 (2C), 54.4, 54.2, 52.32, 52.27, 40.7 (2C), 39.4, 39.2, 37.1, 37.0, 30.40, 30.38, 29.2 (2C), 28.78, 28.77, 19.0 (2C).

ESI-MS (m/z) : 532 $[M]^+$.

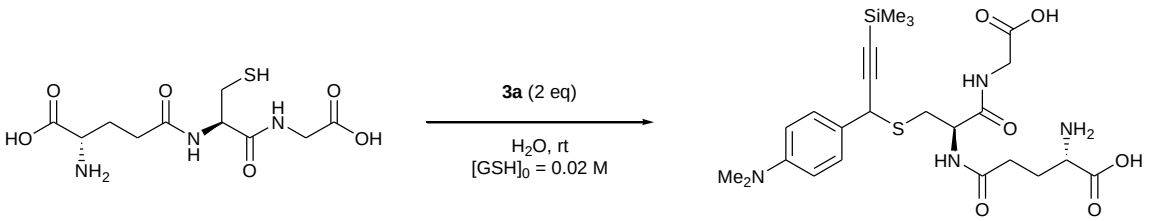
(R)-methyl 3-(1-(4-(dimethylamino)phenyl)-7-(pyren-3-yl)hept-2-ynylthio)-2-acetamidopropanoate (7k).



7k

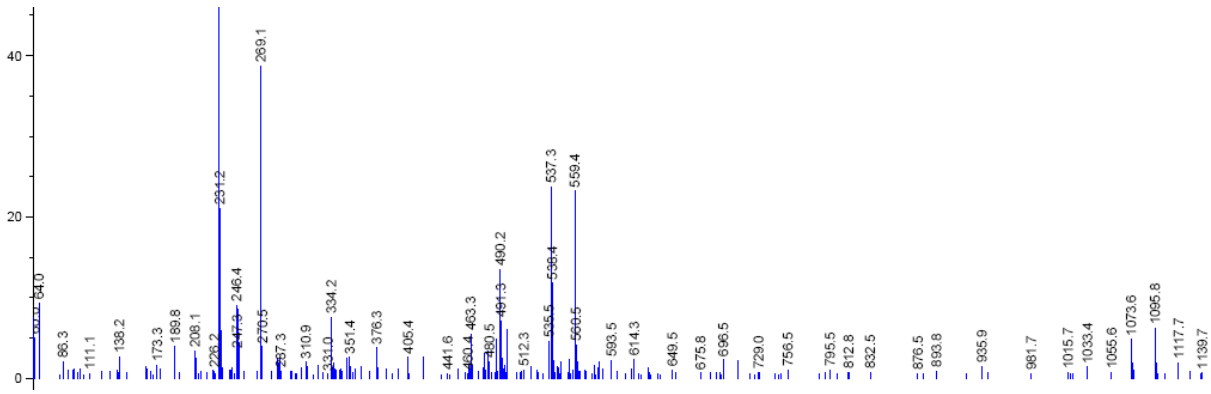
The reaction was carried out following the general procedure and using the propargylic alcohol **3c** and N-acetyl L-cysteine methyl ester **6a** as starting materials. The ligation product has been isolated by flash column chromatography (Cy/AcOEt 1:1, 54% yield) and characterized as a 1:1 mixture of diastereoisomers *(R,S)* and *(R,R)*.
^{1}H NMR (401 MHz, $CDCl_3$) δ = 8.29 (d, *J*=9.3, 2H), 8.16 (d, *J*=7.6, 4H), 8.11 (d, *J*=7.7, 2H), 8.07 (d, *J*=9.3, 2H), 8.02 (ABq, $\Delta\delta_{AB}$ = 0.02, *J*=9.1, 4H), 7.98 (t, *J*=7.6, 2H), 7.87 (d, *J*=7.8, 2H), 7.30 (dd, *J*=8.8, 2.7, 4H), 6.61 (d, *J*=8.6, 4H), 6.11 (d, *J*=8.2, 1H), 6.08 (d, *J*=7.9, 1H), 4.86 – 4.77 (m, 2H), 4.79 (s, 1H), 4.70 (s, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.41 – 3.34 (m, 4H), 3.21 (dd, *J*=14.0, 5.0, 1H), 3.19 (dd, *J*=13.8, 4.4, 1H), 2.99 (dd, *J*=14.0, 5.0, 1H), 2.89 (dd, *J*=13.8, 6.7, 1H), 2.88 (s, 12H), 2.41 (t, *J*=6.3, 4H), 2.07 – 1.98 (m, 4H), 1.96 (s, 3H), 1.92 (s, 3H), 1.81 – 1.72 (m, 4H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.4, 171.3, 169.8, 169.7, 136.64, 136.60, 131.4 (2C), 130.9 (2C), 129.77, 129.76, 128.62 (2C), 128.59, 128.58, 127.5 (2C), 127.23, 127.21, 126.54, 126.53, 125.76, 125.75, 125.05 (2C), 124.99 (2C), 124.80 (2C), 124.78 (2C), 124.67, 124.66, 123.38, 123.36, 112.4 (2C), 86.49, 86.44, 78.16, 78.10, 52.54, 52.47, 51.7, 51.5, 40.5 (2C), 39.14, 39.08, 33.66, 33.61, 33.0 (2C), 30.97, 30.94, 28.69, 28.66, 23.06, 23.04, 18.85, 18.83.
ESI-MS (m/z) : 613 $[M+Na]^+$.

2.6.6. Ligation of glutathione by S_N1 reaction of the propargylic alcohol 3a.

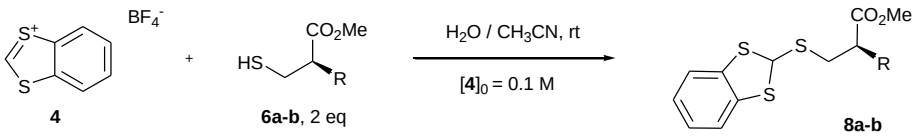


Glutathione (GSH) M_r = 536

The propargylic alcohol **3a** (0.1 mmol, 2 eq.) and the reduced L-glutathione (0.05 mmol, 1 eq.) are placed in an ordinary vial equipped with a stir bar. 2.5 mL of deionised water (0.02 M glutathione) are added and the reaction mixture is vigorously stirred for 12 hours at room temperature. After completion, an excess volume of Et_2O is added and the aqeous layer is separated and washed again with Et_2O. An HPLC-MS analysis of the aqueous layer shows the presence of the ligation product as the main product through its molecular mass (536 u).
ESI-MS (m/z) : 537 $[M+H]^+$, 559 $[M+Na]^+$, 1073 $[2M+H]^+$, 1095 $[2M+Na]^+$.

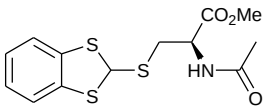


2.6.7. General procedures for the ligation of cysteine and tryptophan with the benzodithiolylium ion.



The reactions are carried out in an ordinary vial equipped with a stir bar. Benzodithiolylium tetrafluoroborate **4** (0.1 mmol, 1 eq.) and L-cysteine methyl ester **6** (0.2 mmol, 2 eq.) are dissolved in 1 mL water/acetonitrile (1:1 volume, 0.1 M). The reaction mixture is stirred for 12 hours at room temperature. After completion, an excess volume of AcOEt is added and the organic layer is separated. The unreacted cysteine is eliminated by extraction with Na_2CO_3 aq. The organic layer is then washed with brine and dried over Na_2SO_4 or $MgSO_4$, and the solvent removed under reduced pressure. The ligation product **8** is purified by flash column chromatography.

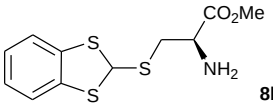
(R)-methyl 2-acetamido-3-(benzo-1,3-dithiol-2-ylthio)propanoate (8a).



8a

The reaction was carried out following the general procedure with N-acetyl L-cysteine methyl ester **6a** as starting material. The title compound has been isolated by flash column chromatography (Cy/AcOEt 1:1, 61% yield).
^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.33 – 7.22 (m, 2H), 7.16 – 7.05 (m, 2H), 6.28 (br d, *J*=7.3, 1H), 5.99 (s, 1H), 4.86 (dt, *J*=7.6, 5.0, 1H), 3.78 (s, 3H), 3.23 (dd, *J*=14.1, 4.9, 1H), 3.12 (dd, *J*=14.1, 5.2, 1H), 2.05 (s, 3H).
ESI-MS (m/z) : 352 $[M+Na]^+$, 681 $[2M+Na]^+$.

(R)-methyl 2-amino-3-(benzo-1,3-dithiol-2-ylthio)propanoate (8b).

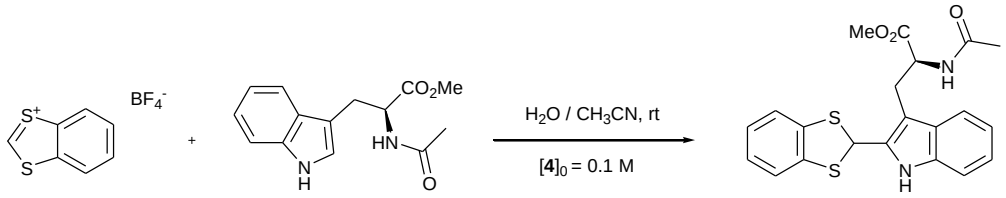


8b

The reaction was carried out following the general procedure with L-cysteine methyl ester hydrochloride **6b** as starting material. The title compound has been isolated by flash column chromatography (Cy/AcOEt 2:3, yield not determined).

^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.33 – 7.23 (m, 2H), 7.15 – 7.06 (m, 2H), 6.19 (s, 1H), 3.81 – 3.72 (m, 1H), 3.74 (s, 3H), 3.07 (dd, *J*=14.1, 4.9, 1H), 2.96 (dd, *J*=14.0, 7.1, 1H), 1.66 (br s, 2H).
ESI-MS (m/z) : 310 $[M+Na]^+$, 326 $[M+K]^+$.

(S)-methyl 2-acetamido-3-(2-(benzo-1,3-dithiol-2-yl)-indol-3-yl)propanoate (11).



4 **9**, 2 eq **11**

Benzodithiolylium tetrafluoroborate **4** (0.1 mmol, 1 eq.) and N-acetyl L-tryptophan methyl ester **9** (0.2 mmol, 2 eq.) are dissolved in 1 mL water/acetonitrile (1:1 volume, 0.1 M). The reaction mixture is stirred for 24 hours at room temperature. After completion, an excess volume of AcOEt is added and the organic layer is separated, washed with brine and dried over Na_2SO_4 or $MgSO_4$. The solvent is then removed under reduced pressure. The title compound has been isolated by flash column chromatography (Cy/AcOEt 1:1).
^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.56 (br s, 1H, *NH indole*), 7.46 (d, *J*=7.8, 1H), 7.34 – 7.03 (m, 7H), 6.56 (s, 1H), 6.10 (br d, *J*=7.7, 1H), 4.94 (dt, *J*=7.9, 5.2, 1H), 3.71 (s, 3H), 3.35 – 3.28 (m, 2H), 2.02 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 172.2, 170.0, 137.1, 136.9, 136.0, 132.3, 127.9, 126.39, 126.38, 123.7, 122.30, 122.27, 120.3, 119.2, 111.4, 108.7, 53.0, 52.9, 48.3, 26.8, 23.5.
ESI-MS (m/z) : 413 $[M+H]^+$, 435 $[M+Na]^+$, 825 $[2M+H]^+$, 847 $[2M+Na]^+$.

Chapter 3

Asymmetric synthesis of gem-difluoromethylene compounds through benzodithiole intermediates

3.1. Background.

3.1.1. Asymmetric insertion of *gem*-difluoromethylene building blocks.

The selective introduction of fluorine into organic molecules is mainly driven by the biological interest of organofluorine compounds. Although the greater proportion of this work has focused on monofluorination, *gem*-difluoromethylene compounds are of practical interest due to the unique electronic properties of the CF_2 group.[45] For example, when situated in the α-position of ketones, the CF_2 group allows the formation of stable hydrates by increasing the electrophilicity of the carbonyl. This feature has been exploited for proteases and esterases inhibition since it mimics the tetrahedral transition states involved in the hydrolytic action of these enzymes. Similarly, the difluoromethylene group can add stability to neighbouring glycosidic and acetal linkages. The difluoromethylene group is also considered as isoelectronic and isosteric of oxygen in phosphate analogues. This has given rise to the syntheses of several difluoromethylenephosphonate analogues of natural products since the resulting carbon-carbon bond confers hydrolytic stability and improved biological activity.

There are two approaches for the preparation of *gem*-difluoromethylene substituted molecules.[46] The first involves the use of fluorinating reagents for the direct difluorination of unsaturated functional groups, mainly aldehydes, ketones, alkenes or alkynes. The second approach is aimed at incorporating a CF_2 building block into a target molecule. Unlike the direct fluorination method, the building block method allows the asymmetric insertion of the *gem*-difluoromethylene group, most of the time through the use of a chiral auxiliary. All the methods described for the asymmetric synthesis of *gem*-difluoromethylene compounds depend indeed on this building block approach and they have been developed with the aim of preparing fluorinated analogues of molecules of biological interest.

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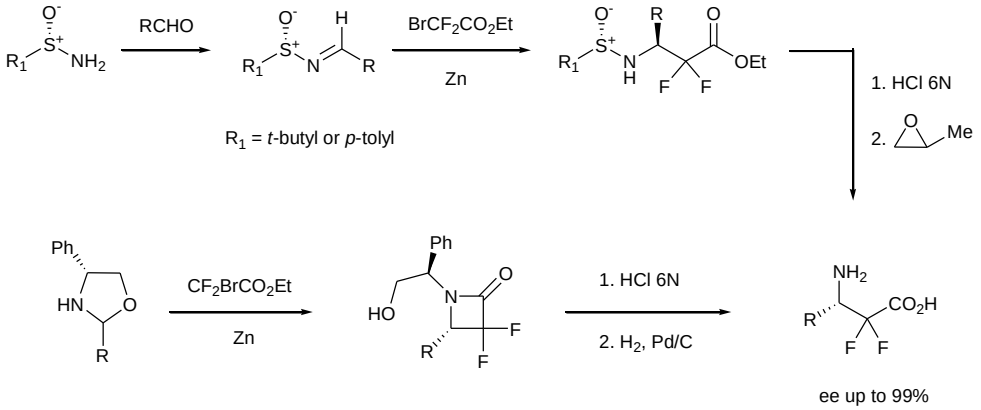
[45] R. E. Banks, B. E. Smart, J. C. Tatlow. *Organofluorine chemistry : principles and commercial applications*. Plenum Press: New York, **1994**.

[46] For reviews, see : (a) V. P. Reddy, M. Perambuduru, R. Alleti. Synthetic approaches to *gem*-difluoromethylene compounds. *Advances in Organic Synthesis, volume 2*, 327 – 351 ; (b) M. J. Tozer, T. F. Herpin. Methods for the synthesis of *gem*-difluoromethylene compounds. *Tetrahedron* **1996**, *52*, 8619 – 8683.

Among all the chemical transformations for the incorporation of a fluorinated building block, the Reformatsky reaction of halodifluoroacetates and halodifluoroketones is by far the most common. Reformatsky approaches have been used mainly to prepare difluoro analogues of amino acids for incorporation into peptides[47] and therefore have required asymmetric variations. In particular, there have been considerable interests in enantiomerically pure *α,α*-difluoro-β-amino acids. They have been obtained with high diastereoselectivities by Reformatsky reaction of ethylbromodifluoroacetate with optically pure 1,3-oxazolidines[48] and N-sulfinylimines[49] (scheme 1).



Scheme 1. Asymmetric synthesis of *α,α*-difluoro-β-amino acids with *N*-sulfinylimines and 1,3-oxazolidines as chiral auxiliaries.

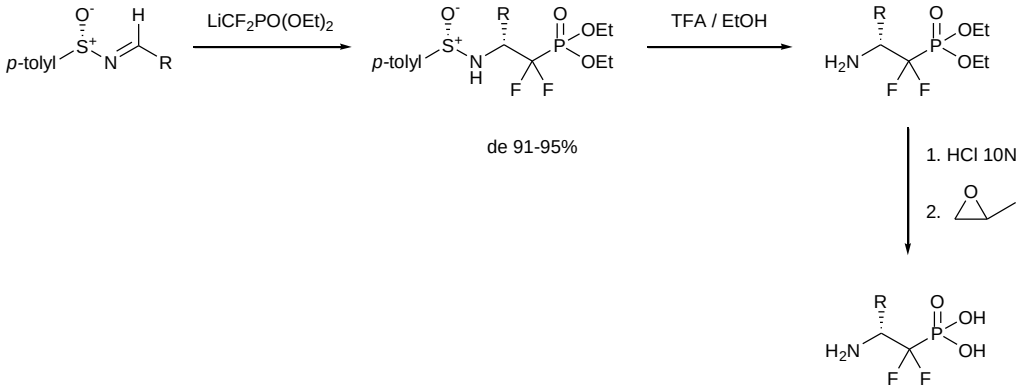
Similarly, the asymmetric synthesis of *α,α*-difluoro-β-amino phosphonic acids uses enantiopure sulfinimines in reaction with lithium difluoromethylene phosphonates or similar cadmium or zinc reagents[50] (scheme 2). As previously discussed, there is a wide interest in difluoromethylene phosphonates as hydrolytically stable analogues of phosphate esters.

[47] V. P. Kukhar, V. A. Soloshonok. *Fluorine-containing Amino Acids.* Eds. John Wiley & Sons: Chichester, **1995**.

[48] S. Marcotte, X. Pannecoucke, C. Feasson, J.-C. Quirion. Enantioselective synthesis of *α,α*-difluoro-β-amino acid and 3,3-difluoroazetidin-2-one via the Reformatsky-type reaction of ethyl bromodifluoroacetate with chiral 1,3-oxazolidines. *J. Org. Chem.* **1999**, *64*, 8461 – 8464.

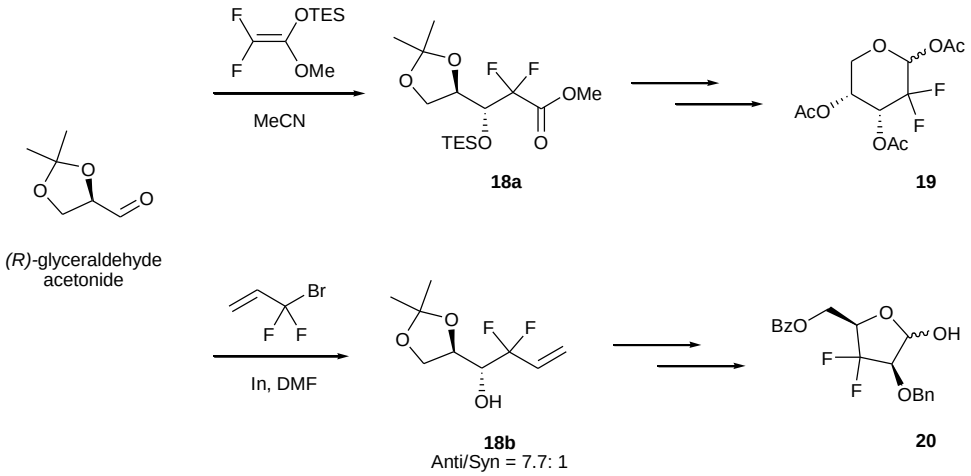
[49] (a) D. D. Staas, K. L. Savage, C. F. Homnick, N. N. Tsou, R. G. Ball. Asymmetric synthesis of *α,α*-difluoro-β-amino acid derivatives from enantiomerically pure *N-tert*-butylsulfinimines. *J. Org. Chem.* **2002**, *67*, 8276 – 8279 ; (b) A. Sorochinsky, N. Voloshin, A. Markovsky, M. Belik, N. Yasuda, H. Uekusa, T. Ono, D. O. Berbasov, V. A. Soloshonok. Convenient asymmetric synthesis of β-substituted *α,α*-difluoro-β-amino acids via Reformatsky reaction between Davis *N*-sulfinylimines and ethyl bromodifluoroacetate. *J. Org. Chem.* **2003**, *68*, 7448 – 7454.

[50] G.-V. Roeschenthaler, V Kukhar, J. Barten, N. Gvozdovska, M. Belik, A. Sorochinsky. Asymmetric synthesis of *α,α*-difluoro-β-amino phosphonic acids using sulfinimines. *Tetrahedron Lett.* **2004**, *45*, 6665 – 6667.



Scheme 2. A chiral sulfinimine as auxiliary in the asymmetric synthesis of α,α-difluoro-β-amino phosphonic acids.

Carbohydrate analogues in which fluorine substitutes an hydrogen or hydroxyl group are considered of considerable interest, in particular nucleosides analogues have a broad spectrum of antiviral and anticancer activities.[51] Their asymmetric synthesis often use *(R)*-glyceraldehyde acetonide as both starting material and chiral auxiliary in the CF_2 insertion step. An example is the preparation of the ribopyranose analogue **19** by reduction and deprotection of **18a**, which was obtained from the silylenol ether version of the Reformatsky reaction.[52] The arabinofuranose analogue **20** is prepared the same way from the indium mediated coupling of 3-bromo-3,3-difluoropropene with *(R)*-glyceraldehyde acetonide[53] (scheme 3).



Scheme 3. Examples of asymmetric syntheses of *gem*-difluorinated carbohydrates analogues from *(R)*-glyceraldehyde acetonide.

Beside these *nucleophilic* difluoromethylene synthons, there are two main types of reactions of *electrophilic* difluoromethylene units with nucleophiles : the apparent

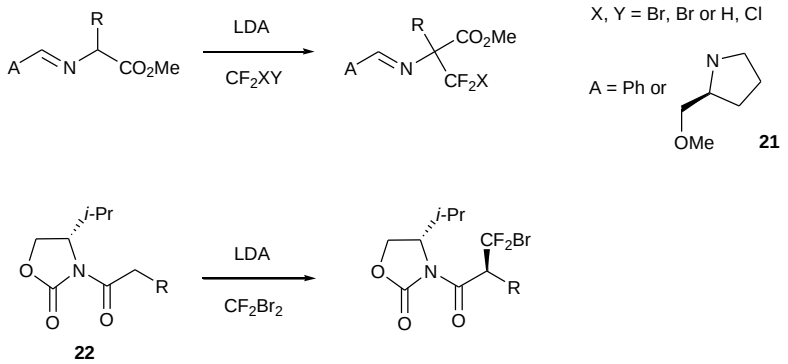
[51] K. W. Pankiewicz. Fluorinated nucleosides. *Carbohydr. Res*. **2000**, *327*, 87 – 105 ; and references therein.

[52] O. Kitagawa, T. Taguchi, Y. Kobayashi. Aldol reaction of iododifluoroacetate-Zn and 2,2-difluoroketene silyl acetal. *Tetrahedron Lett.* **1988**, *29*, 1803 – 1806.

[53] X. Zhang, H. Xia, X. Dong, J. Jin, W.-D. Meng, F.-L. Qing. 3-deoxy-3,3-difluoro-D-arabinofuranose : first stereoselective synthesis and application in preparation of *gem*-difluorinated sugar nucleosides. *J. Org. Chem.* **2003**, *68*, 9026 – 9033.

nucleophilic substitution of halodifluoromethanes, which involves in reality a radical or carbene mechanism, and the nucleophilic addition to difluoroalkenes and Michael acceptors. However, there are very few asymmetric versions.

Amino acid analogues, such as difluoroalanine, can be prepared by difluorocarbene insertion into enolates, and a general high yielding method involving imines has been developed for their synthesis.[54] An asymmetric version involving the chiral auxiliary **21** was already developed in 1983 but has met with limited success (scheme 4).[55] A similar diastereoselective bromodifluoromethylation has been described by Kobayashi and Iseki[56] and uses the chiral imide enolate **22**.



Scheme 4. Asymmetric insertions of fluorocarbenes into enolates.

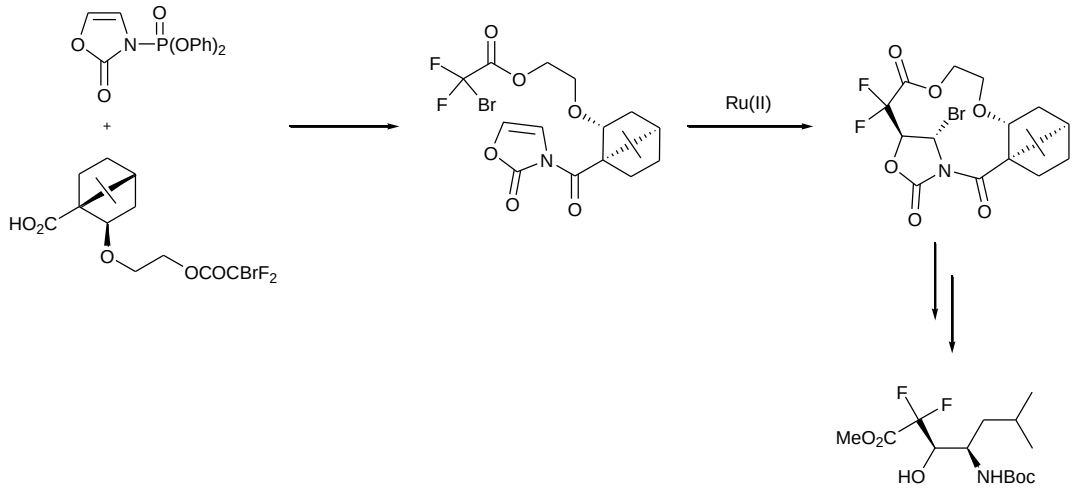
Difluoroalkyl radicals are usually more reactive than the corresponding non-fluorinated radicals in carbon-carbon bond forming reactions, because of their σ-nature and the increased strength of the bond formed. They are interesting intermediates for the preparation of complex fluorinated molecules under mild conditions, often via intramolecular radical cyclisations. For example, a key step in the preparation of 2,2-difluorostatine is the efficient ruthenium catalysed intramolecular addition of a difluoroacetyl radical to a 2-oxazolone derivative. With the aid of the chiral auxiliary 2-(hydroxyethoxy)-1-apocamphane carboxylic acid, the insertion of the difluoromethylene group takes place with a high diastereoselectivity[57] (scheme 5).

[54] T. Tsushima, K. Kawada, S. Ishihara, N. Uchida, O. Shiratori, J. Higaki, M. Hirata. Fluorine containing amino acids and their derivatives. Synthesis and antitumor activity of α- and γ-substituted methotrexate analogs. *Tetrahedron* **1988**, *44*, 5375 – 5387.

[55] M. Kolb, J. Barth. Asymmetric synthesis of α-substituted amino acids and amines by carbon-carbon bond formation in position α to the nitrogen. *Liebigs Ann. Chem.* **1983**, 1668 – 1688.

[56] K. Iseki, D. Asada, M. Takahashi, T. Nagai, Y. Kobayashi. Diastereoselective bromodifluoromethylation of chiral imide enolates via insertion of difluorocarbene. *Tetrahedron Lett*. **1995**, *36*, 3711 – 3714.

[57] T. Yamamoto, S. Ishibuchi, T. Ishizuka, M. Haratake, T. Kunieda. Stereoselective intramolecular radical addition of polyhaloacetyl functions to 2-oxazolones. A facile synthesis of statine and its 2,2-dichloro and 2,2-difluoro analogues. *J. Org. Chem.* **1993**, *58*, 1997 – 1998.



Scheme 5. Preparation of 2,2-difluorostatine via an asymmetric radical cyclisation.

The previous examples show that the asymmetric syntheses of *gem*-difluoromethylene compounds through the use of CF_2 building blocks are efficient and widely used. However the difluoromethylene group is often inserted at an early stage in the synthesis scheme, leading to a general difficulty associated with the preparation of complex fluorinated molecules : the changes in chemical reactivity brought about by fluorine often cause unexpected difficulties with reactions commonly used in organic synthesis. For example, a reversal of selectivity has been observed in aldol reactions involving Evans's[58] or Oppolzer's[59] chiral auxiliaries in the case of *α,α*-difluoro carbonyl compounds. Another example is the oxidation of the alcohol formed in the Reformatsky reaction, for which the Dess-Martin periodinane has become the method of choice since Swern, Collins or PDC procedures have been found to be problematic.[60] That tends to explain why direct fluorination is a so powerful technique when used at a late-stage in a synthetic scheme.

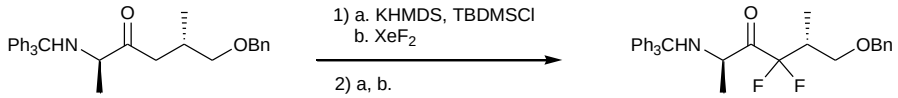
Direct *gem*-difluorinations bring two fluorine atoms on a sp^2 carbon and, therefore, do not allow any asymmetric induction. The only way to use these methods in asymmetric synthesis is when the chiral centre is already present in the substrate with a fixed configuration, as in the *α*-difluorination of the ketone below (scheme 6).[61] On the other hand, the substrate must be robust enough to withstand the often forcing conditions. This is probably the main reason why no general method has been described for the asymmetric synthesis of *gem*-difluorinated compounds involving a late-stage direct fluorination.

[58] About the reversal of stereoselectivity in the Evans aldol reaction of α,α-difluoro carbonyl compounds, see : (a) K. Iseki, S. Oishi, T. Taguchi, Y. Kobayashi, *Tetrahedron Lett.* **1993***, 34*, 8147 – 8150 ; (b) K. Iseki, S. Oishi, Y. Kobayashi, *Tetrahedron* **1996***, 52,* 71 – 84.

[59] K. Iseki, S. Oishi, Y. Kobayashi. Reversal of stereoselectivity in the aldol reaction of boron enolate derived from Oppolzer's sultam with *α,α*-difluoro and *α,α,α*-trifluoro carbonyl compounds. *Chem. Lett*. **1994**, *23*, 1135 – 1138.

[60] A. M. Doherty, I. Sircar, B. E. Kornberg, J. Quin III, R. T. Winters, J. S. Kaltenbronn, M. D. Taylor, B. L. Batley, S. R. Rapundalo, M. J. Ryan, C. A. Painchaud. Design and synthesis of potent, selective and orally active fluorine-containing renin inhibitors. *J. Med. Chem.* **1992**, *35*, 2 – 14.

[61] G. S. Garrett, T. J. Emge, S. C. Lee, E. M. Fischer, K. Dyehouse, J. M. McIver. Synthesis of the monofluoro ketone peptide isostere. *J. Org. Chem.* **1991**, *56*, 4823 – 4826.

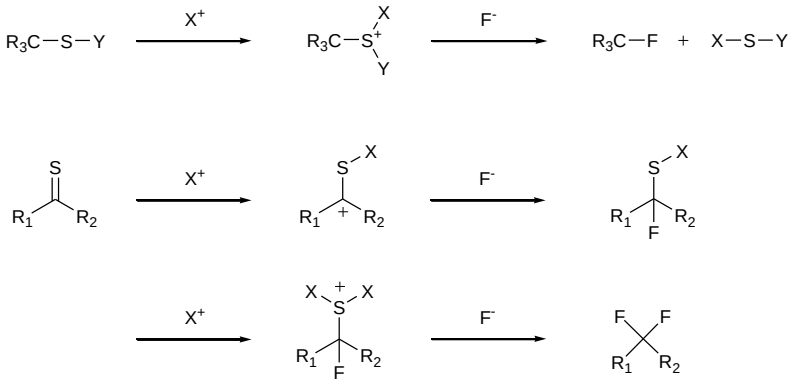


Scheme 6. A direct *gem*-difluorination on a chiral substrate without any loss of enantiomeric excess.

3.1.2. Direct *gem*-difluorination of aldehydes and ketones.

One of the most common and efficient strategy of direct *gem*-difluorination is the transformation of the carbonyl of aldehydes and ketones into the corresponding CF_2 group with several fluorinating reagents, in particular sulphur tetrafluoride (SF_4) and diethylaminosulfur trifluoride (DAST).[2,62] Other reagents may also be utilized for these conversions but their wider application has been limited by the hazards involved in their synthesis and use. In the search for more mild and selective reagents for the classic CO-CF_2 transformation, considerable efforts have been made to move away from the carbonyl group and exploit the various reactivities offered by carbonyl derivatives, notably hydrazones, oximes and dithioacetals.

Dithioacetals derived from aldehydes and ketones can be converted into the corresponding *gem*-difluoro compounds by a reaction called *oxidative desulfurization-fluorination*. This reaction was first explored by Kollonitsch and Marburg.[63] The basic concept is summarized in scheme 7. Sulfur is oxidized by an halonium species and becomes this way a good leaving group and, in the presence of a fluoride source, a nucleophilic substitution occurs to form the C-F bond. In the case of a substrate having a carbon-sulfur double bond, double desulfurization-fluorination takes place to give a *gem*-difluoromethylene compound.



X^+ : positive halogen; F^- : fluoride reagent

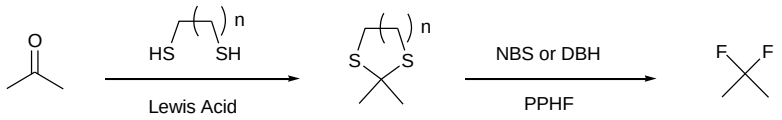
Scheme 7. The oxidative desulfurization-fluorination.

1,3-dithiolanes (n=1, scheme 8) and 1,3-dithianes (n=2) can be converted to the corresponding *gem*-difluoro compounds by a reagent system consisting of pyridiniumpolyhydrogen fluoride (PPHF) and an oxidant, usually 1,3-dibromo-5,5-

[62] R. P. Singh, J. M. Shreeve. Recent advances in nucleophilic fluorination reactions of organic compounds using Deoxofluor and DAST. *Synthesis* **2002**, 2561 – 2578.

[63] J. Kollonitsch, S. Marburg, L. M. Perkins. Fluorodesulfurization. A new reaction for the formation of carbon-fluorine bonds. *J. Org. Chem.* **1976**, *41*, 3107 – 3111.

dimethylhydantoin (DBH) or N-Bromosuccinimide (NBS).[64] Since the dithiolanes can be prepared readily from the corresponding aldehydes and ketones**,** the overall two-step process represents a convenient method to convert aldehydes and ketones to *gem*-difluoro compounds (scheme). Several alternatives of oxidant have been described.[65] For example, N-Iodosuccinimide (NIS) when electrophilic bromination presents a problem in the case of electron rich aromatic systems or $SOCl_2$ and SO_2ClF to facilitate the workup of the reaction (the only by-products are the volatile SO_2 and HCl). Nitrosonium tetrafluoroborate in PPHF also provides a convenient reagent for this transformation.



Scheme 8. Conversion of ketones to *gem*-difluoro compounds via dithioacetals intermediates.

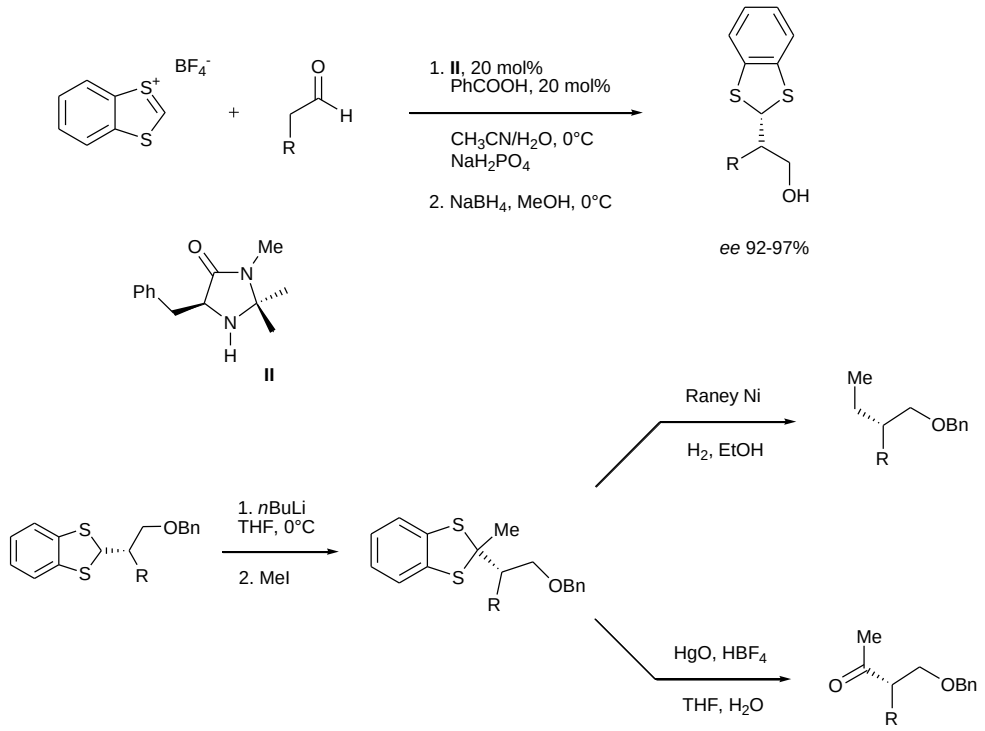
The 1,3-dithiane unit is not only precursor of a CF_2 group but a versatile system of great applicability in organic synthesis, both as an acyl anion synthetic equivalent and as a protecting group for carbonyl functionalities.[66] In 2011 we described the first organocatalytic enantioselective α-alkylation of aldehydes with 1,3-benzoditiolylium tetrafluoroborate[67] (scheme 9). This reaction gives access to optically active benzodithiole derivatives that have been shown to be synthetically equivalent to 1,3-dithianes and, thus, important intermediates in synthesis. For example, the benzodithiole group can be alkylated by electrophiles, reduced in methylene or transformed into the corresponding ketone (scheme 9). The possible transformation into a CF_2 group by means of an oxidative desulfurization-fluorination has never been taken into consideration, but there is no doubt that this reaction would be of great interest since it could give access to complex and optically active *gem*-difluoromethylene compounds.

[64] S. C. Sondej, J. A. Katzenellenbogen. *gem*-difluoro compounds : a convenient preparation from ketones and aldehydes by halogen fluoride treatment of 1,3-dithiolanes. *J. Org. Chem.* **1986**, *51*, 3508 – 3513.

[65] M. Kuroboshi, K. Kanie, T. Hiyama. Oxidative desulfurization-fluorination : a facile entry to a wide variety of organofluorine compounds leading to novel liquid-crystalline materials. *Adv. Synth. Catal.* **2001**, *343*, 235 – 250.

[66] For a review about the role of 1,3-dithiane in synthesis, see : M. Yus, C. Najera, F. Foubelo, *Tetrahedron* **2003**, *59*, 6147 – 6212.

[67] A. Gualandi, E. Emer, M. G. Capdevila, P. G. Cozzi. Highly enantioselective α alkylation of aldehydes with 1,3-benzodithiolylium tetrafluoroborate : a formal organocatalytic α alkylation of aldehydes by the carbenium ion. *Angew. Chem. Int. Ed.* **2011**, *50*, 7842 – 7846.

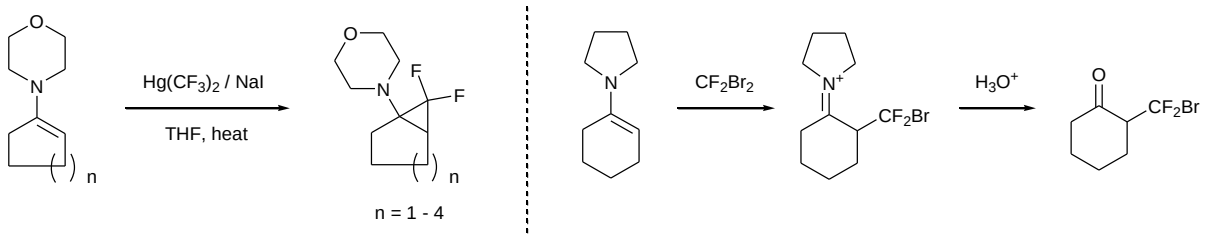


Scheme 9. Enantioselective α-alkylation of aldehydes with 1,3-benzodithiolylium tetrafluoroborate and use in organic synthesis.

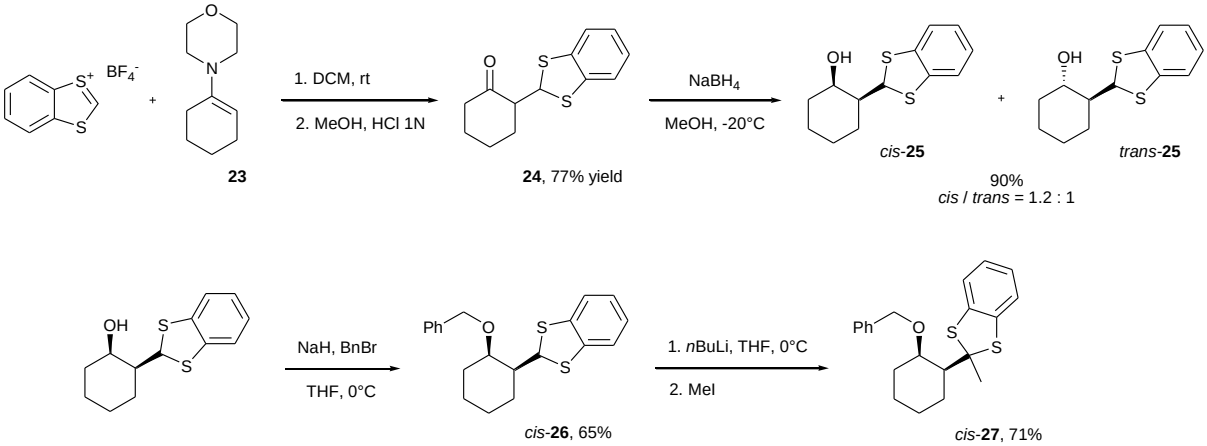
3.2. Oxidative desulfurization-fluorination of the benzodithiole group.

The benzodithiole derivative **27** has been chosen as substrate for the screening of the oxidative fluorination conditions. First because it is easily prepared by reaction of the benzodithiolylium ion with the enamine precursor **23** (scheme 11) ; and then because *gem*-difluorinated compounds have already been prepared from similar cyclic ketone-derived enamines (scheme 10).[68]

[68] (a) I. Nowak, J. F. Cannon, M. Robins. Synthesis and properties of *gem*-(difluorocyclopropyl)amine derivatives of bicyclo[*n*.1.0]alkanes. *J. Org. Lett.* **2004**, *6*, 4767 – 4770 ; (b) I. Rico, D. Cantacuzene, C. Wakselman. Condensation of CF_2Br_2, CF_2BrCl and $BrCF_2CF_2Br$ with enamines and ynamines. *Tetrahedron Lett.* **1981**, *22*, 3405 – 3408.



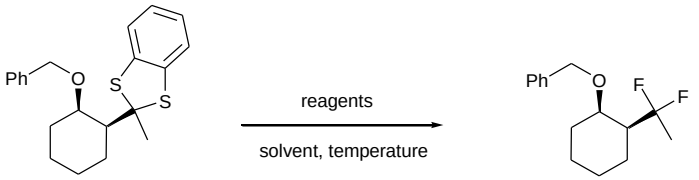
Scheme 10. Syntheses of *gem*-difluorinated compounds from cyclic ketone-derived enamines.



Scheme 11. Synthesis of the benzodithiole derivative *cis*-**27** from the cyclohexanone-derived enamine **23**.

After electrophilic addition of the benzodithiolylium ion and hydrolysis of the enamine product, the cyclic ketone **24** is reduced to the corresponding alcohol **25** (scheme 11). The synthesis of the substrate is achieved by protection of the alcohol as benzyl ether and alkylation of the benzodithiole group. Because the *cis* diastereoisomer has been obtained with a little excess and has given better results for the desulfurative fluorination, it has been chosen as substrate for the screening of the fluorination conditions (table 1).

Table 1. Screening of the oxidative desulfurization-fluorination conditions.



cis-**27** *cis*-**28**

Entry	Reagents	Equiv.[a]	Solvent	Temp. (°C)	Time	Yield[b]
1	NBS / PPHF	2:4	DCM	-40	10 min	traces[c]
2	DBH / $Et_3N.HF$	1:4	DCM	-70	30 min	.
3	DBH / PPHF	1:14	DCM	-70	1 h	52 %
4	**DBH / PPHF**	**1:40**	**DCM**	**-70**	**1 h**	**68 %**
5	DBH / PPHF	1:40	Hexane	-70	1 h	31 %
6	DBH / PPHF	1:40	Toluene	-70	1 h	12 %
7	DBH / PPHF	1:40	Et_2O	-70	1 h	traces[c]
8	DBH / PPHF	1:40	THF	-70	90 min	.

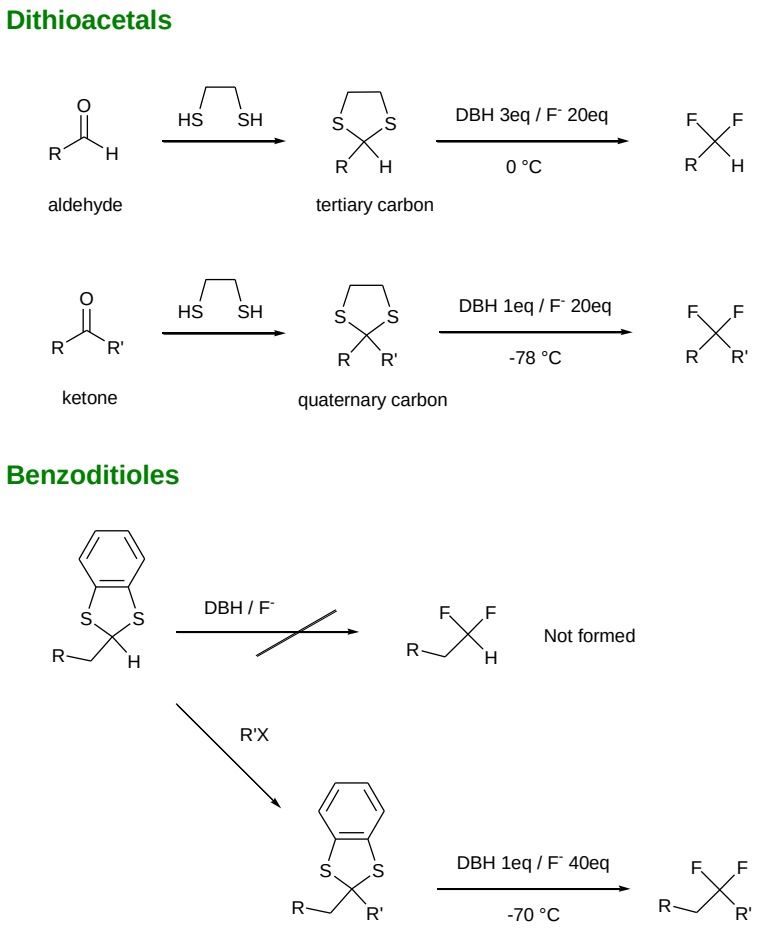
[a] Respective quantities of reagents for 1 eq of substrate *cis*-**27**. [b] Determined by ^1H NMR analysis of the crude mixture using 1,4-diacetylbenzene as internal standard. [c] Observed by GC-MS analysis of the crude mixture.

The best results for the desulfurative fluorination of dithioacetals are usually obtained using DBH or NBS with an excess of PPHF. Since the benzodithiole group can be regarded as a 1,3-dithiane equivalent, we decided to start the screening by using this reagent system. As expected, DBH and PPHF worked quite well with the substrate *cis*-**27** as long as the temperature was kept low. Temperature is indeed an important factor in this reaction : at -70°C, good yields of the difluoro product *cis*-**28** were obtained whereas several by-products were formed at warmer temperatures. The high excess of fluoride used is necessary, due to the low nucleophilicity of the fluoride anion and to the possible presence of better nucleophiles, especially traces of water that lead to the corresponding ketone product.

Among the possible solvents at such a low temperature, dichloromethane has given the best results, as already observed for dithioacetals. In the same conditions, non-polar solvents have given lower yield of the difluoro product and this is consistent with the proposed mechanism involving the formation of carbocation intermediates. Surprisingly, the reaction did not work in tetrahydrofuran and diethyl ether ; and yet tetrahydrofuran has ever been described as a possible solvent for the oxidative fluorination of 1,3-dithianes. Seemingly, oxygenated solvents prevent the reaction from taking place in the case of 1,3-benzodithioles. This difference of reactivity between the two substrates must imply different reaction mechanisms involving different types of intermediates.

There is another important difference of reactivity between the two substrates concerning the nature of the carbon atom at the reaction centre. Dithioacetals can derive

from aldehydes or ketones and the main difference rests on the formation of a tertiary or *quaternary* carbon atom. Although the oxidative fluorination takes place on both types, it requires more vigorous conditions in the case of aldehyde-derived dithioacetals because the tertiary carbon makes harder the formation of the carbocation intermediates (scheme 12). But in the case of the non-alkylated benzodithiole derivative *cis*-**26**, the fluorinated product has not been observed even at higher temperatures or using an excess of oxidant. Actually, only complex mixtures of elimination and rearranged products have been formed. This shows that non-alkylated benzodithioles are more sensible to the oxidative conditions than the corresponding dithioacetals and, thus, are not suitable for the oxidative fluorination. This limitation is actually of little significance since the benzodithiole unit is quite easy to alkylate and allows more molecular complexity in the target *gem*-difluoromethylene products.

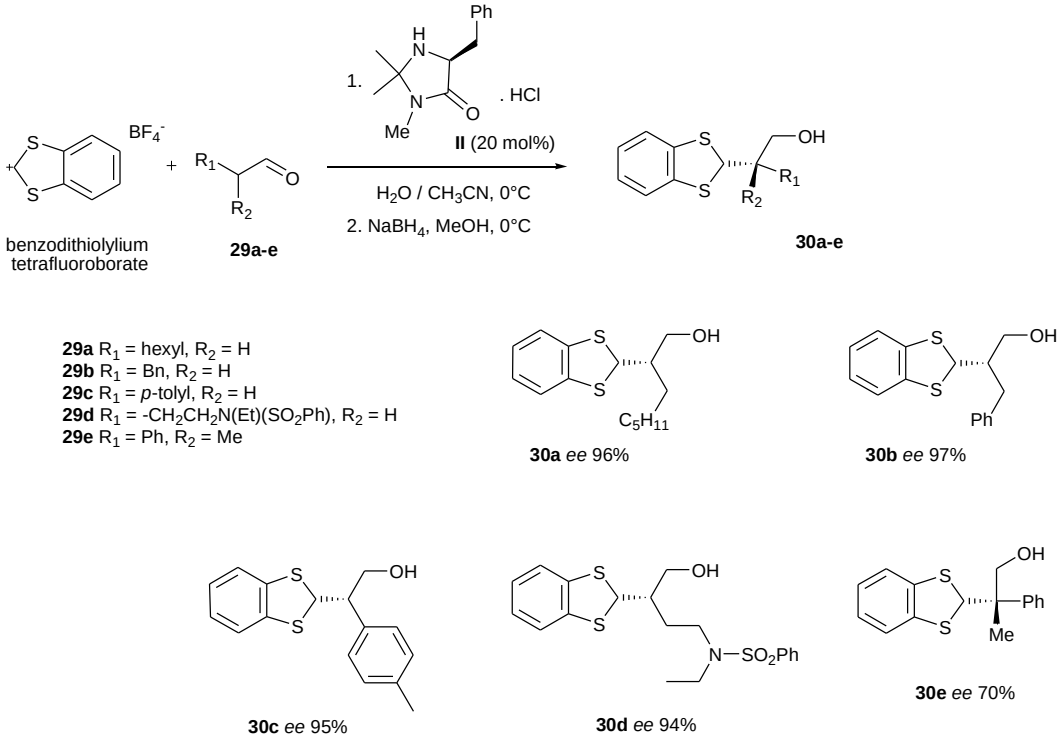


Scheme 12. Comparison of the oxidative desulfurization-fluorination between tertiary and quaternary dithioacetals and benzodithioles.

3.3. Synthesis of enantioenriched *gem*-difluoromethylene compounds.

3.3.1. Enantioselective *α*-alkylation of aldehydes.

The asymmetric α-alkylation of aldehydes takes place through chiral aminocatalysis. Cyclic secondary amines form iminium ions and enamine intermediates with non-hindered carbonyl compounds more readily than most other amines, a consequence of the increased nucleophilicity imparted by the cyclic strain.[69] Different proline derivatives and McMillan imidazolidinones[70] were tested in the work of 2011 and the best enantiocontrol was obtained with the commercially available McMillan catalyst **II** in the presence of water. The acidic conditions were necessary for the condensation of amines with carbonyls. Once alkylated, the aldehydes were reduced and the corresponding alcohols showed high enantiomeric excesses. According to this procedure, the alcohols **30a-d** have been prepared with high enantioselectivities (scheme 13).



Scheme 13. Asymmetric α-alkylation of aldehydes with the benzodithiolylium ion catalysed by the McMillan imidazolidinone **II**.

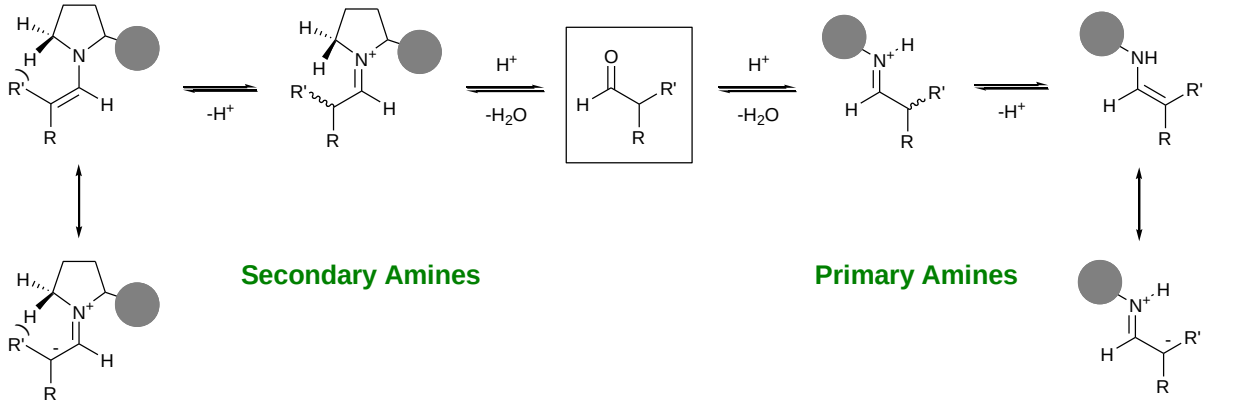
The alkylation of the α-substituted aldehyde **29e** has given the corresponding alcohol *(S)*-**30e** with a lower enantiomeric excess. This is due to steric factors that greatly affect the condensation between secondary amines and hindered carbonyl compounds. Primary amines are less influenced by these structural features and are more effective for the condensation with α-substituted aldehydes.[71] In addition, it has been demonstrated that secondary enamines (formed from primary amines) hydrolyze and react faster than the

[69] *Chemistry of Enamines* (Ed. Zvi Rappaport), Wiley, Chichester, **1994**.

[70] D. W. C. MacMillan. The advent and development of organocatalysis. *Nature* **2008**, *455*, 304 – 308.

[71] Studies on the iminium ion formation from primary amines: a) J. Hine, B. C. Menon, J. H. Jensen, J. Mulders, *J. Am. Chem. Soc.* **1966**, *88*, 3367 – 3373 ; b) J. Hine, F. A. Via, *J. Am. Chem. Soc.* **1972**, *94*, 190 – 194 ; c) F. Tanaka, R. Thayumanavan, N. Mase, C. F. Barbas III, *Tetrahedron Lett.* **2004**, *45*, 325 – 328. Studies on the iminium ion formation from secondary amines: d) J. Hine, J. Mulders, *J. Org. Chem.* **1967**, *32*, 2200 – 2205 ; e) J. Hine, R. C. Dempsey, R. A. Evangelista, E. T. Jarvi, J. M. Wilson, *J. Org. Chem.* **1977**, 42, 1593 – 1599.

corresponding tertiary enamines (from secondary amines).[72] This can be attributed again to steric factors since bulky substituents on the double bond and on the nitrogen atom make it difficult for the resulting enamine system to achieve a planar conformation. This geometry is required to maximize the overlap between the π orbital of the carbon–carbon double bond and the lone pair orbital on the nitrogen atom. The steric inhibition of the resonance structures is more pronounced for tertiary than for secondary enamines, since the secondary enamines always bear a small hydrogen substituent on the nitrogen atom that permits the π conjugation (scheme 14).



Scheme 14. Secondary versus primary amines in condensation with sterically hindered carbonyl compounds.

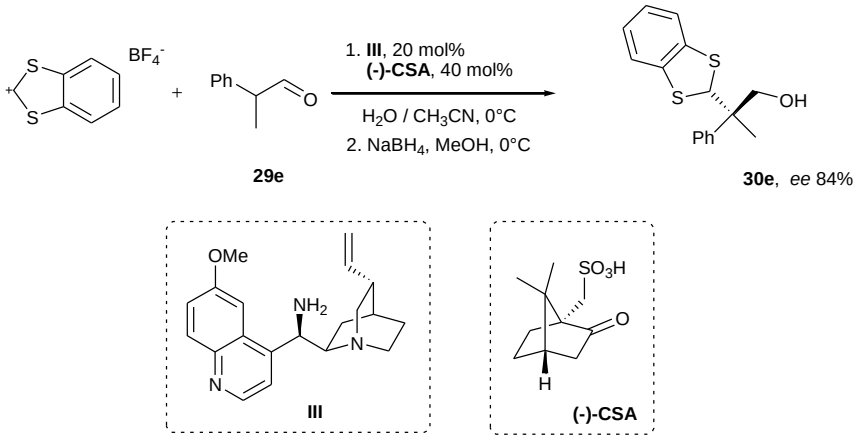
Among the different primary amines, 9-amino(9-deoxy)-*epi* cinchona alkaloids have enabled the stereoselective functionalization of a variety of sterically hindered carbonyl compounds via different activation modes and with consistently high levels of stereocontrol. This ability of cinchona primary amines to act as aminocatalysts is due to the flexibility and the multifunctional nature of the cinchona scaffold.[73] In a complementary work on the asymmetric addition of the benzodithiolylium ion, our group has shown that cinchona alkaloid derivatives were the most selective aminocatalyst for alkylation of *α*-substituted aldehydes.[74] In particular, the ion pair formed between cinchona alkaloid **III** and the chiral co-catalyst L(-)-camphorsulfonic acid (CSA)[75] has been found to be very effective in promoting the *α*-alkylation of aldehyde **29e** : alcohol *(R)*-**30e** has indeed been obtained with an enantiomeric excess of 84% (scheme 15).

[72] a) B. Capon, Z.-P. Wu, *J. Org. Chem.* **1990**, *55*, 2317 – 2324 ; b) F. Johnson, *Chem. Rev.* **1968**, *68*, 375 – 413, p. 392 ; c) J. E. Anderson, D. Casarini, L. Lunazzi, *Tetrahedron Lett.* **1988**, *29*, 3141 – 3144.

[73] P. Melchiorre. Cinchona-based primary amine catalysis in the asymmetric functionalization of carbonyl compounds. *Angew. Chem. Int. Ed.* **2012**, *51*, 9748 – 9770.

[74] A. Gualandi, D. Petruzziello, E. Emer, P. G. Cozzi. A general stereoselective enamine mediated alkylation of α-substituted aldehydes. *Chem. Commun.* **2012**, *48*, 3614 – 3616

[75] C. Liu, Q. Zhu, K. W. Huang, Y. Lu. Primary amine/CSA ion pair : a powerful catalytic system for the asymmetric enamine catalysis. *Org. Lett.* **2011**, *13*, 2638 – 2641.



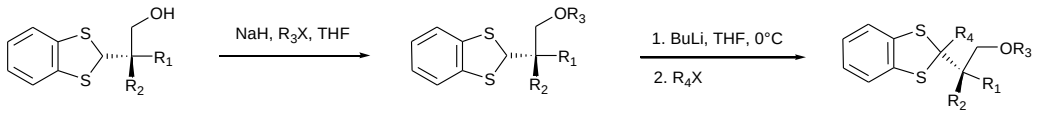
Scheme 15. Alkylation of the α-substituted aldehyde **29e** catalysed by the chiral cinchona alkaloid – CSA ion pair.

3.3.2. Synthesis of optically active benzodithiole derivatives.

Both the primary alcohol and the benzodithiole group make easy alkylations possible and, this way, complex benzodithiole derivatives can be obtained. Moreover, the alkylation of the benzodithiole group is necessary (as discussed before), as well as the protection of the primary alcohol. These derivatives hold the enantiomeric excess induced in the α-alkylation step and we have shown that they were precursors of the corresponding *gem*-difluoromethylene compounds. The alcohols **30a-e** have been used as starting materials for the preparation of more complex derivatives, according to the synthetic scheme shown below (scheme 16).[76] The alkylation of the benzodithiole group takes advantage of the stabilizing effect of sulfur atoms on adjacent carbanions. 2-lithio-1,3-benzodithiole derivatives are easily prepared by deprotonation with alkyllithiums at low temperatures and the anionic species obtained can react with many types of electrophiles.[77] Haloalcanes, acyl chlorides (**32c**), aldehydes (**32f**) and epoxides (**32g**) have been successfully used whereas aziridines are unreactive in these conditions. It is to note that the alkylation of the benzodithiole **31b** by benzaldehyde and by cyclohexene oxide has given two diastereoisomers of the products **32f** and **32g**, respectively. In the case of cyclohexene oxide, the two diastereoisomers have been separated. We assume that the epoxide opening gives the *trans* products, as in scheme 17. Conformational calculations and *Nuclear Overhauser Effect* experiments have been conducted on both diastereoisomers but have not allowed to attribute their absolute configurations. Therefore, the two diastereoisomers will be refered arbitrarily as **32g$_a$** and **32g$_b$** and drawn as in scheme 17 in order to be differentiated.

[76] The syntheses of **32f** and **32g** require an additional methylation step after alkylation of benzodithiole **b** with benzaldehyde and cyclohexene oxide.

[77] S. Ncube, A. Pelter, K. Smith, P. Blatcher, S. Warren. Generation and reactions of 2-lithio-2-substituted-1,3-benzodithioles ; new, convenient acyl carbanion equivalents. *Tetrahedron Lett.* **1978**, *19*, 2345 – 2348.

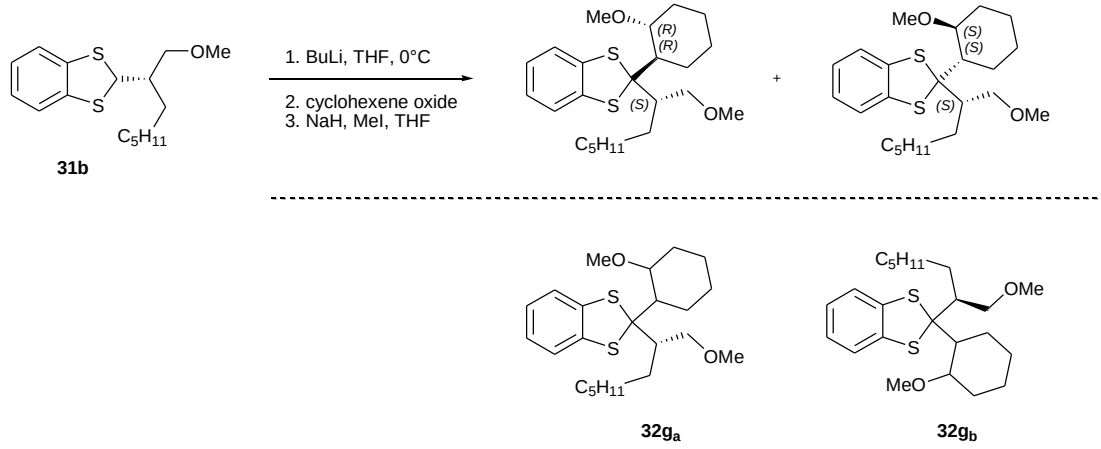


30a-e **31a-f** **32a-k**

31a R_1 = hexyl, R_2 = H, R_3 = Bn
31b R_1 = hexyl, R_2 = H, R_3 = Me
31c R_1 = Bn, R_2 = H, R_3 = Bn
31d R_1 = *p*-tolyl, R_2 = H, R_3 = Bn
31e R_1 = -$CH_2CH_2N(Et)(SO_2Ph)$, R_2 = H, R_3 = Me
31f R_1 = Ph, R_2 = Me, R_3 = Bn

32a R_1 = hexyl, R_2 = H, R_3 = Bn, R_4 = Me
32b R_1 = hexyl, R_2 = H, R_3 = Bn, R_4 = allyl
32c R_1 = hexyl, R_2 = H, R_3 = Bn, R_4 = -CO_2Et
32d R_1 = hexyl, R_2 = H, R_3 = Me, R_4 = Bn
32e R_1 = hexyl, R_2 = H, R_3 = Me, R_4 = 4-iodobutyl
32f R_1 = hexyl, R_2 = H, R_3 = Me, R_4 = -CH(OMe)Ph
32g R_1 = hexyl, R_2 = H, R_3 = Me, R_4 = 2-methoxycyclohexyl
32h R_1 = Bn, R_2 = H, R_3 = Bn, R_4 = Me
32i R_1 = *p*-tolyl, R_2 = H, R_3 = Bn, R_4 = Me
32j R_1 = -$CH_2CH_2N(Et)(SO_2Ph)$, R_2 = H, R_3 = Me, R_4 = Me
32k R_1 = Ph, R_2 = Me, R_3 = Bn, R_4 = Me

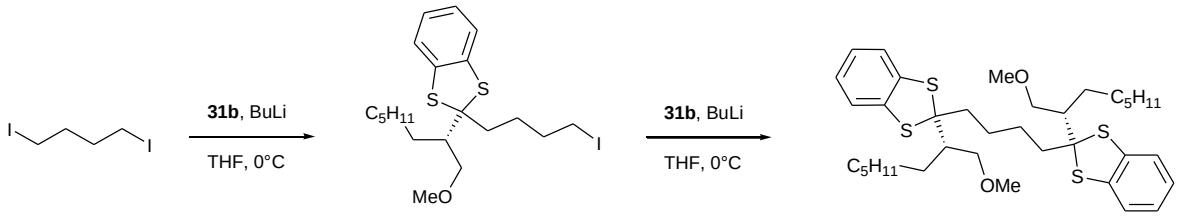
Scheme 16. Synthesis of complex optically active benzodithiole derivatives.



31b **32g$_a$** **32g$_b$**

Scheme 17. Alkylation of the benzodithiole **31b** by cyclohexene oxide. The theoretical configurations (*S,R,R*) and (*S,S,S*) could not be attributed to the products **32g$_a$** and **32g$_b$**.

The iodo derivative **32e** has been obtained by alkylation of 1,4-diiodobutane with the benzodithiole **31b**. A second alkylation has afforded the bis(benzodithiole) product **33** below with a raised optical purity.[78]



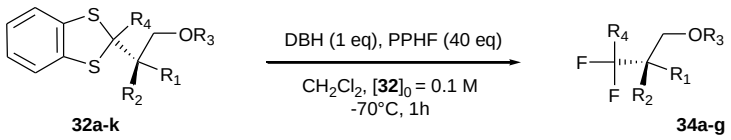
32e, *ee* 96% **33**, *ee* > 99%

Briefly stated, benzodithiole derivatives have been prepared by, first, inserting the benzodithiole unit in different aldehydes with an high enantiomeric excess and, then, by alkylating this unit with different electrophiles. This way, optically active compounds with a great structural diversity have been obtained. They are substrates for the oxidative desulfurization-fluorination.

[78] By eliminating the *meso* diastereoisomer, in accordance with the Horeau principle : J. P. Vigneron, M. Dhaenens, A. Horeau. Nouvelle méthode pour porter au maximum la pureté optique d'un produit partiellement dédoublé sans l'aide d'aucune substance chirale. *Tetrahedron* **1973**, *29*, 1055 – 1059.

3.3.3. Oxidative desulfurization-fluorination of optically active benzodithioles.

The optimized fluorination conditions found have been applied to the benzodithioles **32a-k** (scheme 18) and **33**. The large diversity of these compounds gives us the opportunity to screen the compatibility of several functional groups with the reaction conditions. The results are reported on table 2.



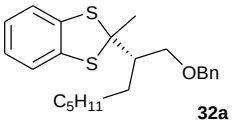
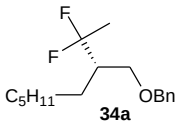
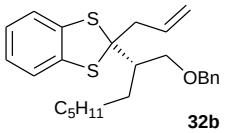
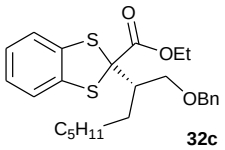
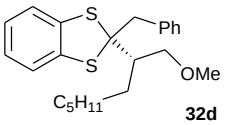
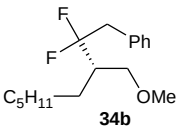
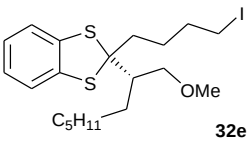
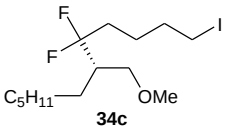
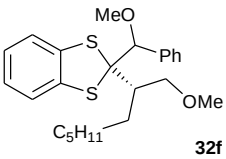
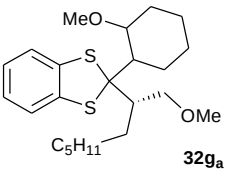
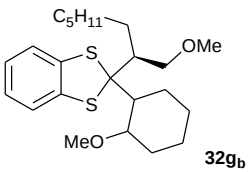
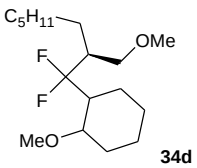
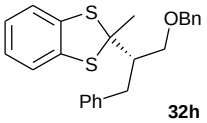
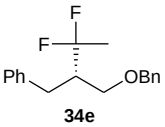
Scheme 18. Oxidative desulfurization-fluorination of optically active benzodithioles.

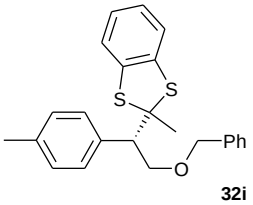
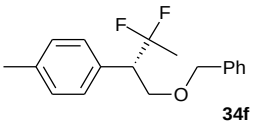
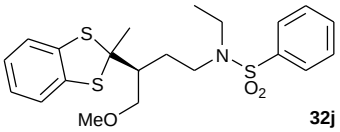
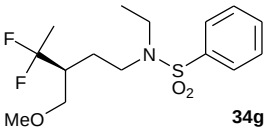
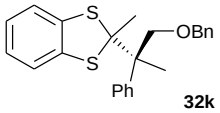
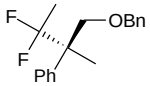
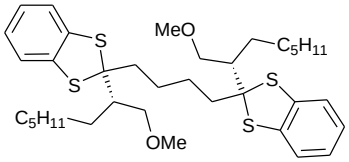
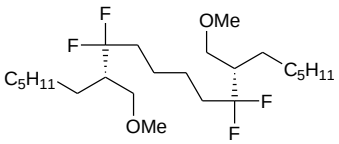
Electron-rich aromatic systems have been deliberately left out because they give ring-brominated by-products in the presence of bromonium reagents. For the same reason we assumed that the presence of double or triple bonds might be problematic and, indeed, the alkene **32b** did not give the fluorinated product (table 2, entry 2). The reaction does not work with substrates **32c** and **32f** in which electronegative substituents bind the adjacent carbon to the reactive centre (entries 3 and 6). This is explained by destabilization of the carbocation intermediates.

The two diastereoisomers $\mathbf{32g_a}$ and $\mathbf{32g_b}$ should have afforded the corresponding two diastereoisomers of the *gem*-difluoro product, but did not (entries 7 and 8). Actually the diastereoisomer $\mathbf{32g_a}$ gives a ketone which can be considered as the hydrolysis product. Since we could not assign the absolute configurations of the diastereoisomers or of the only *gem*-difluoro product **34d**, it is difficult to suggest an explanation for this difference of reactivity.

Apart from the examples above, the oxidative fluorination proceeds quite well with the majority of the substrates. We could separate the two enantiomers of the product **34e** by chiral HPLC analysis and we did not observe any loss of enantioselectivity in comparison with the alcohol **30b** precursor (entry 9). This shows definitively the synthetic equivalence between optically active benzodithioles and the corresponding *gem*-difluoromethylene compounds.

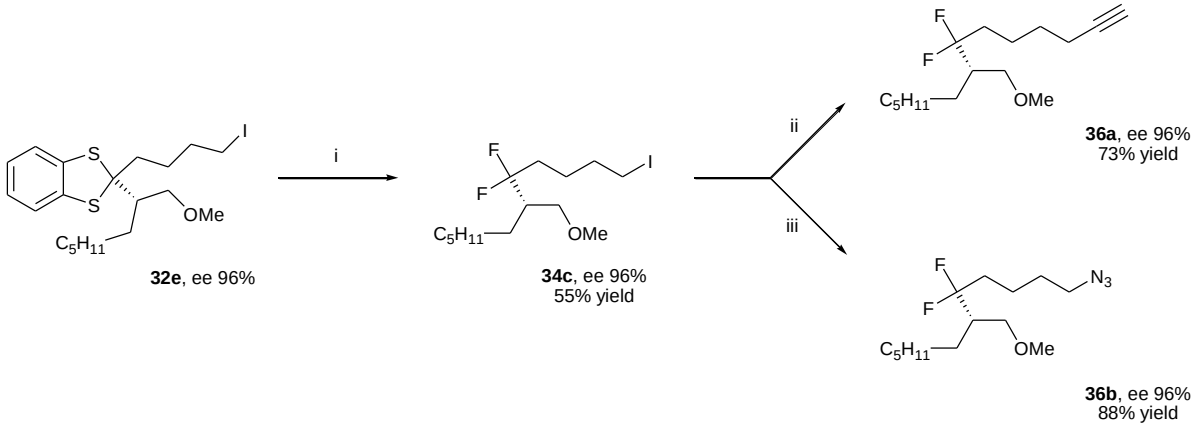
Table 2. Oxidative desulfurization-fluorination of optically active benzodithioles (scheme 18).[a]

Entry	Substrate	Product	Yield[b] (%)	*ee*[c] (%)
1	 **32a**	 **34a**	81	96
2	 **32b**	-	-	-
3	 **32c**	-	-	-
4	 **32d**	 **34b**	55	95
5	 **32e**	 **34c**	89	96
6	 **32f**	-	-	-
7	 **32g$_a$**	-	-	-
8	 **32g$_b$**	 **34d**	33[d]	96
9	 **32h**	 **34e**	62	97[e]

Entry	Substrate	Product	Yield[b] (%)	*ee*[c] (%)
10	 **32i**	 **34f**	73	95
11	 **32j**	 **34g**	37	94
12	 **32k**	 **34h**	74	84
13[f]	 **33**	 **35**	80	99

[a] Reaction conditions : 0.1 M in DCM, 1 equiv DBH, 40 equiv PPHF, -70°C, 1h. [b] Determined by ^{1}H NMR analysis of the crude mixture using 1,4-diacetylbenzene as internal standard. Yields of isolated products are given in the experimental section. [c] Determined by chiral HPLC analysis of the alcohol precursor **30x**. [d] Yield of the isolated product. [e] Determined by chiral HPLC analysis of the difluoro product. [f] Reaction carried out with 2 equiv of DBH.

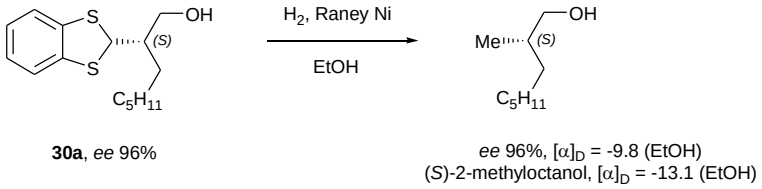
The compatibility of iodo derivatives (entry 5) is a very interesting point because they give the opportunity for further alkylations with functional groups that would not have been compatible with the oxidative fluorination conditions. For example, the *gem*-difluorinated iodo derivative **34c** is easily alkylated with sodium azide or acetylide (scheme 19).



Scheme 19. Alkylation of the iodo derivative **34c**.
(i) DBH, PPHF, DCM, -70°C. (ii) sodium acetylide, DMF, 0°C. (iii) NaN_3, MeCN/H_2O 9:1, reflux.

3.4. Determination of the absolute configuration.

So far, all the products derive from the (*S*)-McMillan catalyst **II** and have the (*S*) absolute configuration. This had been shown before by chemical correlation from the adduct **30a** after reduction and comparison of the specific rotation [α] with the reported value (scheme 20). Nevertheless, we set out to confirm the (*S*) absolute configuration of the difluoro products by preparing a reported compound with the 1,3-relation between the CF_2 and CO groups (which are quite scarce due to the lack of methods for their asymmetric synthesis).

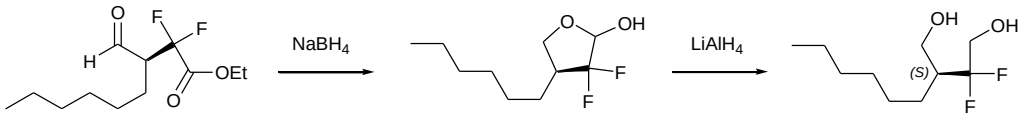


Scheme 20. Determination of the absolute configuration of the adduct **30a**.

In 2009, David W. C. McMillan reported an enantioselective *α*-trifluoromethylation and *α*-perfluoroalkylation of aldehydes via an organometallic photoredox catalysis.[79] In order to determine the enantiomeric excess of the difluoro aldehyde **37**, they had to reduce it to the corresponding diol **42** (reduction in two steps with the formation of a lactol intermediate, scheme 21). This diol was fully characterized and can be prepared by our methodology as shown in scheme 22.

Alkylation of the benzodithiole adduct **31a** with an acyl chloride followed by reduction of the ester gives the alcohol **38**. The oxygen atom binding the adjacent carbon to the benzodithiole unit has made the oxidative fluorination problematic. The choice of a protecting group for this OH has been crucial to complete successfully the synthesis. Both methoxymethyl and benzyl ethers have worked, but by using a benzyl group the *gem*-difluoro product **40b** is obtained with a better yield and only one additional step is necessary for the complete removal of the protecting groups (against two in the case of **40a**). A positive specific rotation has been found confirming the *(S)* absolute configuration for the diol **42** and, by correlation, for all the previous intermediates.

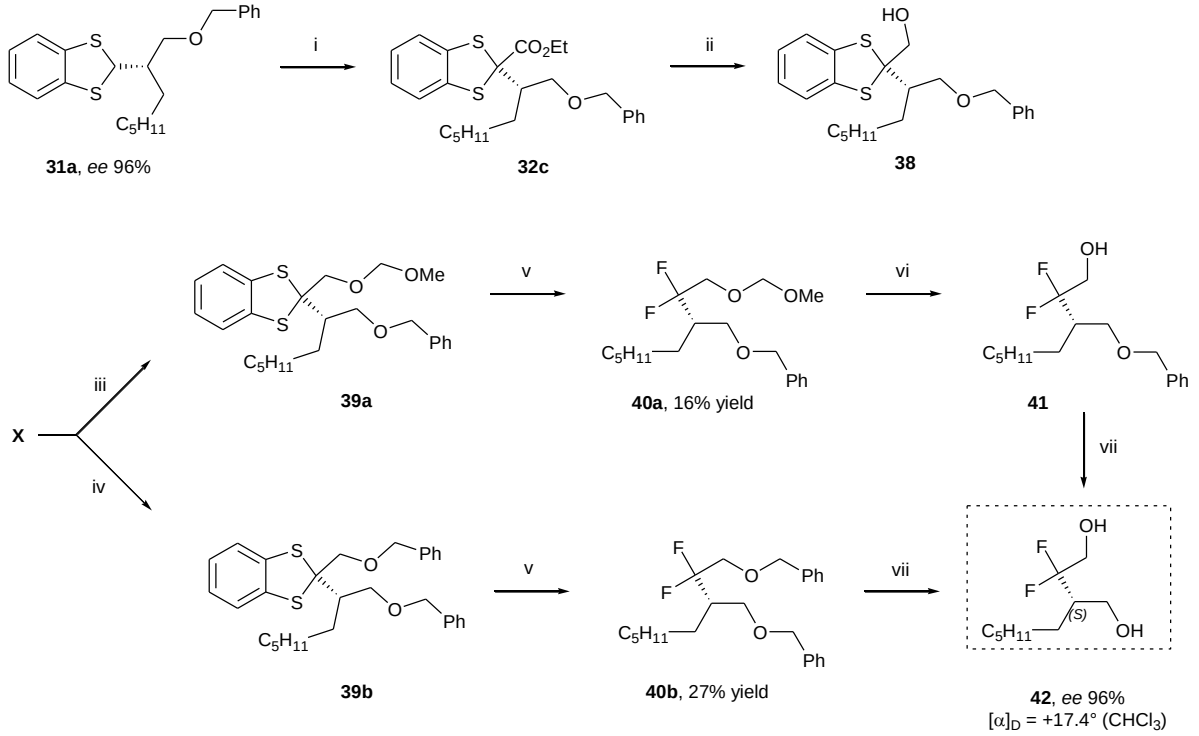
[79] D. A. Nagib, M. E. Scott, D. W. C. MacMillan. Enantioselective *α*-trifluoromethylation of aldehydes via photoredox organocatalysis. *J. Am. Chem. Soc.* **2009**, *131*, 10875 – 10877.



37

42, *ee* 99%
$[\alpha]_D$ = +20.4° ($CHCl_3$)

Scheme 21. Synthesis and optical rotation of *(S)*-2,2-difluoro-3-hexylbutane-1,4-diol. (McMillan, 2009)[70]



31a, *ee* 96%

32c

38

39a

40a, 16% yield

41

39b

40b, 27% yield

42, *ee* 96%
$[\alpha]_D$ = +17.4° ($CHCl_3$)

Scheme 22. Synthesis of the 2,2-difluoro-3-hexylbutane-1,4-diol **42** and attribution of the *(S)* absolute configuration from the specific rotation.
(i) BuLi, THF, 0°C, then $ClCO_2Et$. (ii) $LiAlH_4$, THF, 0°C. (iii) NaH, $ClCH_2OCH_3$, THF. (iv) NaH, BnBr, THF. (v) DBH, PPHF, DCM, -70°C. (vi) TFA, DCM. (vii) H_2, $Pd(OH)_2/C$, EtOAc.

3.5. Synthesis of a *gem*-difluoro analogue of arundic acid.

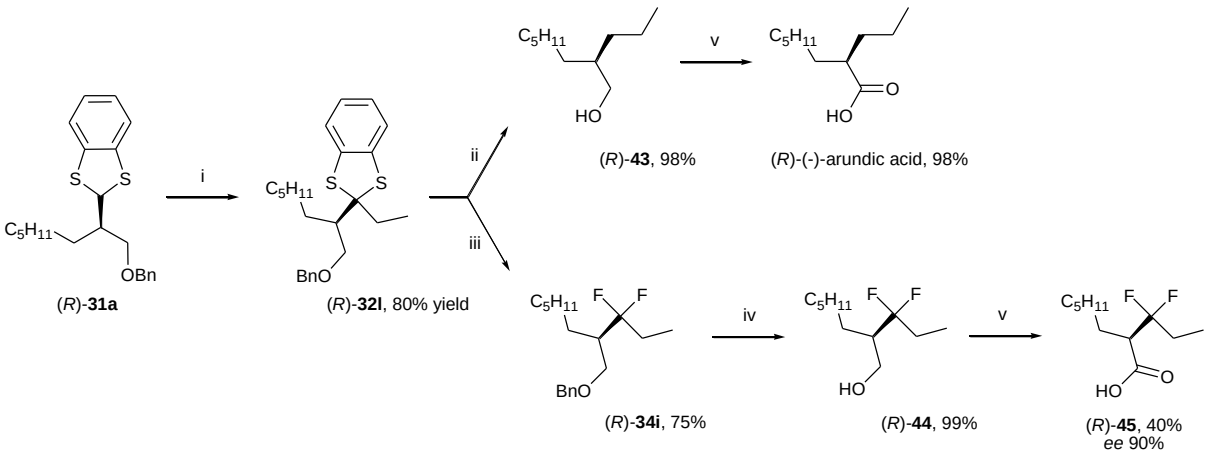
The non-natural compound *(R)*-(-)-arundic acid was discovered by the Minase Research Institute of Ono Pharmaceutical Co. Ltd. (Osaka, Japan) during a screening process[80] and has then emerged as a potential neuroprotective agent.[81] Arundic acid arrests the neurologic damages by modulating the enhanced astrocytic synthesis of *S*-100β protein.

[80] N. Tateishi, T. Mori, Y. Kagamiishi, S. Satoh, N. Katsube, E. Morikawa, T. Morimoto, T. Matsui, T. Asano. Astrocytic activation and delayed infarct expansion after permanent focal ischemia in rats. *J. Cereb. Blood Flow Metab.* **2002**, *22*, 723.

[81] For a review, see R. A. Fernandes, A. B. Ingle. Arundic acid, a potential neuroprotective agent: biological development and syntheses. *Current Medicinal Chemistry* **2013**, *20*, 2315 – 2329.

Phase II clinical trials for the treatment of acute ischemic stroke,[82] as well as clinical development in other neurodegenerative diseases including amytrophic lateral sclerosis, Alzheimer's disease[83] and Parkinson's disease[84] are now completed. A recent study has also found arundic acid as a potential therapeutic agent for liver fibrosis.[85] This may open a new area of research related to the treatment of liver diseases. Since arundic acid inhibits the synthesis of *S*-100β protein, it might become a viable therapeutic agent for treating *S*-100β protein over expression-related diseases (such as inflammatory bowl disease).

In 2011, our group described a straightforward synthesis of *(R)*-(-)-arundic acid from the *(R)* enantiomer of **31a**. The key step was the reduction of the benzodithiole group of *(R)*-**32l** to the corresponding methylene, which afforded the alcohol *(R)*-**43** and, upon oxidation, arundic acid (scheme 23). By submitting *(R)*-**32l** to the oxidative fluorination instead of the reduction, a *gem*-difluoro analogue of arundic acid has been obtained in both configurations *R* and *S*. Surprisingly, the removal of the benzyl ether protecting group was problematic due to the presence of fluorine atoms. Pd(0) did not afford the alcohol *(R)*-**44**, even at high pressures of hydrogen, and the use of Pd(II) has been essential. This provides another example of the unexpected difficulties that can be met with in the preparation of complex fluorinated molecules.



Scheme 23. Syntheses of arundic acid and of a *gem*-difluoro analogue.
(i) BuLi, THF, 0°C, then EtI ; (ii) H_2, Raney Ni, EtOH ; (iii) DBH, PPHF, DCM, -70°C ; (iv) H_2, $Pd(OH)_2/C$, EtOAc ; (v) $NaClO_2$, $NaClO_{(cat)}$, $TEMPO_{(cat)}$, MeCN, buffer pH 6.7.

3.6. Conclusion.

[82] Stroke is a neurodegenerative disease caused by depletion or deprivation of blood flow to the brain leading to rapid nerve cell death and dysfunction of the body part controlled by the affected nerve cells. It is responsible for serious long-term disabilities and can cause permanent neurological damages.

[83] Alzheimer's disease is a neurodegenerative disease that progresses and eventually leads to death. It is characterised by the deposition of amyloid β-plaques and the associated neuro-inflammation. The currently-approved drugs are only palliative and side-effects remain an important concern.

[84] Parkinson's disease is a degenerative disorder of the central nervous system. It results from the death of dopamine-generating cells in the substantia nigra, a region of the midbrain.

[85] W. Cui, M. Wang, H. Maegawa, Y. Teranishi, N. Kawada. Inhibition of the activation of hepatic stellate cells by arundic acid via the induction of cytoglobin. *Biochem. Biophy. Res. Commun*. **2012**, *425*, 642.

We have developed a methodology for the asymmetric synthesis of *gem*-difluoromethylene compounds. This methodology is based on the preparation of optically active benzodithiole derivatives and the further transformation of the benzodithiole unit into a *gem*-difluoromethylene group through an oxidative desulfurization-fluorination. We have found efficient conditions for this reaction and we have shown that they do not affect the configuration of the adjacent chiral centres.

Although the insertion of the CF_2 group is limited to the α-position of aldehydes, the use of cinchona alkaloids as catalysts allows to start from α-substituted aldehydes without loss of enantioselectivity and should allow the addition on hindered ketones, too. Furthermore, the easy alkylation of the benzodithiole group by many types of electrophiles makes possible the synthesis of more complex and varied structures. But the main advantage of this method is that the fluorine atoms are inserted in a late-stage during the synthesis, thereby avoiding the reactivity problems often met with in the syntheses of such complex molecules.

We hope that this methodology will motivate the development of new *gem*-difluoro analogues of molecules of biological interest, for which the syntheses may not be possible so far with the existing methods.

3.7. Experimental section.

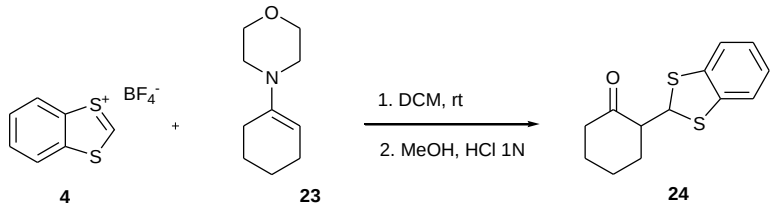
3.7.1. General information and materials.

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian Mercury 400 spectrometer. ^{1}H spectra are referenced relative to the residual $CDCl_3$ proton signal at δ 7.26 ppm and data are reported as follows : chemical shift (ppm), multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, b = broad, m = multiplet), coupling constants (Hz) and integration. ^{13}C spectra are referenced relative to the $CDCl_3$ carbon signal at δ 77.16 ppm and are reported as chemical shift and multiplicity when appropriate. ^{19}F spectra are referenced relative to the CF_3COOH fluorine signal at -76.55 ppm and are reported as chemical shift, multiplicity and coupling constants. Chromatographic purifications were done with 240 - 400 mesh silica gel. The determination of enantiomeric purities was performed on Agilent Technologies 1200 instrument equipped with a variable wave-length UV detector, using Daicel Chiralpak columns (4.6 mm internal diameter x 250 mm column length). HPLC-grade isopropanol and *n*-hexane were used as the eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 10 mm (sodium D line). Specific rotations are expressed in degrees and concentrations (c) in g/100 mL. Electrospray ionization (ESI) mass spectra were obtained on a Agilent Technologies MSD1100 single-quadrupole mass spectrometer.

Commercial grade reagents and solvents were used without further purification. Anhydrous solvents were supplied by Sigma-Aldrich in Sure/seal^{TM} bottles. When not commercially available, starting materials were prepared according to described procedures.

3.7.2. Preparation of alcohols *cis* and *trans*-25.

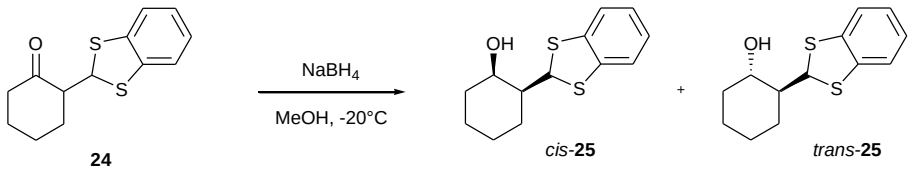
2-(benzo-1,3-dithiol-2-yl)cyclohexanone (24).



4 **23** **24**

Enamine **23** (2.25 mmol, 1.5 eq.) and benzodithiolylium tetrafluoroborate (1.5 mmol, 1 eq.) are dissolved in anhydrous dichloromethane (5 mL, 0.3 M) and the reaction mixture is stirred at room temperature for 1 hour. The solvent is removed under reduced pressure and the residue is dissolved in methanol (2 mL). HCl 1 N is added and the mixture is stirred at room temperature for 2 hours. An excess volume of Et_2O and water are then added and the organic layer is separated. The aqueous layer is extracted three times with Et_2O. The collected organic layers are washed with brine, dried over Na_2SO_4 and concentred under reduced pressure. The title compound is isolated by flash column chromatography (cyclohexane, 77% yield).

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.20 – 7.13 (m, 2H), 7.02 – 6.96 (m, 2H), 5.19 (d, *J*=7.0, 1H), 2.81 (dddd, *J*=12.5, 7.0, 5.4, 1.0, 1H), 2.51 – 2.40 (m, 2H), 2.29 (dddd, *J*=13.4, 12.3, 5.6, 1.1, 1H), 2.13 – 2.03 (m, 1H), 1.95 – 1.84 (m, 1H), 1.69 – 1.60 (m, 2H), 1.51 (dtd, *J*=25.4, 12.7, 3.6, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.7, 138.3, 137.7, 125.4, 125.3, 121.94, 121.90, 58.9, 52.1, 42.5, 29.7, 28.0, 25.0.

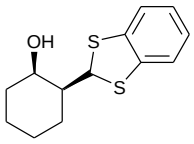


24 *cis*-**25** *trans*-**25**

cis / *trans* = 1.2 : 1

Ketone **24** (1.5 mmol, 1 eq.) is dissolved in Et_2O/MeOH (1:1 volume, 1.5 mL) without any particular precaution to exclude air and moisture. The solution is cooled to -20°C. $NaBH_4$ (0.75 mmol, 0.5 eq.) is then slowly added and the reaction mixture is stirred for 1 hour at -20°C. The reaction is quenched with water and extracted three times with Et_2O. The collected organic layers are washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Alcohols *cis* and *trans*-**25** are isolated by flash column chromatography (Cy/AcOEt 10:1) with a 90% yield and a diastereoisomeric ratio *cis*/*trans* = 1.2 : 1.

cis-2-(benzo-1,3-dithiol-2-yl)cyclohexanol (cis-25).

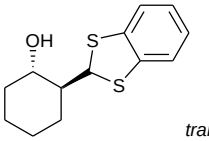


cis-**25**

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.24 – 7.18 (m, 2H), 7.03 – 6.98 (m, 2H), 4.95 (d, *J*=10.0, 1H), 4.34 (m, 1H), 1.93 – 1.73 (m, 4H), 1.55 – 1.39 (m, 3H), 1.38 – 1.30 (m, 2H), 1.21 (qt, *J*=12.8, 3.9, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.0, 137.7, 125.48, 125.45, 122.53, 122.50, 67.0, 58.3, 47.7, 33.6, 25.6, 24.8, 19.6.

ESI-MS (m/z) : 253 $[M+H]^+$, 270 $[M+NH_4]^+$, 275 $[M+Na]^+$.

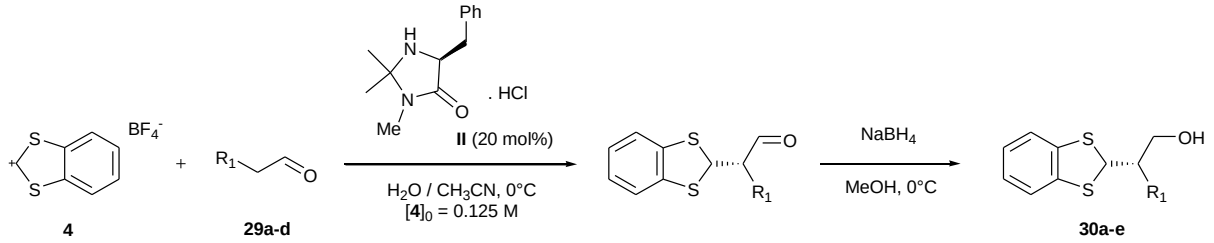
trans-2-(benzo-1,3-dithiol-2-yl)cyclohexanol (trans-25).



trans-**25**

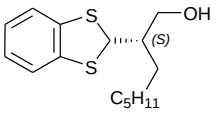
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.22 – 7.14 (m, 2H), 7.02 – 6.95 (m, 2H), 5.59 (d, *J*=3.5, 1H), 3.60 (td, *J*=9.8, 4.6, 1H), 1.99 (m, 1H), 1.89 (m, 1H), 1.70 (m, 1H), 1.66 – 1.55 (m, 3H), 1.33 – 1.08 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.0, 138.2, 125.38, 125.32, 121.8 (2C), 71.1, 54.7, 53.9, 36.1, 25.2, 24.7, 24.4.
ESI-MS (m/z) : 253 $[M+H]^+$, 270 $[M+NH_4]^+$, 275 $[M+Na]^+$.

3.7.3. General procedure for the enantioselective α-alkylation of aldehydes.



Aldehyde **29** (2.5 mmol, 2.5 eq.) and the catalyst **II** (0.2 mmol, 0.2 eq.) are dissolved in 8 mL of water/acetonitrile (1:1 volume). The mixture is cooled to 0°C and then 1,3-benzodithiolylium tetrafluoroborate **4** (1 mmol, 1 eq.) is added. The mixture is stirred overnight at 0°C. The reaction complete, an excess volume of Et_2O is added and the organic layer is separated. The aqueous layer is extracted 3 times with Et_2O. The collected organic layers are washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure and at room temperature. The residue is then diluted in MeOH (2.5 mL) and $NaBH_4$ (1.75 mmol, 1.75 eq) is slowly added at 0 °C. After 1 hour, the reaction is quenched with water and concentrated under reduced pressure. The residue is extracted with Et_2O, dried over Na_2SO_4 and concentrated.

(S)-2-(benzo-1,3-dithiol-2-yl)octan-1-ol (30a).

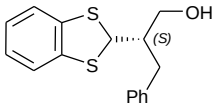


30a

90% yield, 96% *ee*.
Reaction carried out following the general procedure with octanal **29a** as starting material. The title compound has been isolated by flash column chromatography (Cy/Et_2O 85:15) and the enantiomeric excess determined by chiral HPLC analysis : Daicel Chiralcel IC column; Hex/iPrOH 95:5; flow rate 0.5 mL/min; 30°C; λ = 254, 262 nm; T_{min}=15 min, T_{maj}=16 min.
NMR data and specific rotation of both enantiomers have already been reported.[86]

(S)-2-(benzo-1,3-dithiol-2-yl)-3-phenylpropan-1-ol (30b)

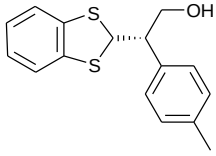
[86] A. Gualandi, E. Emer, M. G. Capdevila, P. G. Cozzi, *Angew. Chem. Int. Ed.* **2011**, *50*, 7842 – 7846.



30b

86% yield, 97% *ee*.
Reaction carried out following the general procedure with 3-phenylpropanal **29b** as starting material. The title compound has been isolated by flash column chromatography (Cy/AcOEt 9:1) and the enantiomeric excess determined by chiral HPLC analysis : Daicel Chiralcel IC column; Hex/iPrOH 95:5; flow rate 0.5 mL/min; 30°C; λ = 232, 254 nm; T_{min}=21 min, T_{maj}=24 min.
NMR data and specific rotation have already been reported.[86]

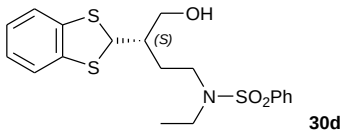
(S)-2-(benzo-1,3-dithiol-2-yl)-2-p-tolylethanol (30c).



30c

78% yield, 95% *ee*.
Reaction carried out following the general procedure with 2-*p*-tolylacetaldehyde **29c** as starting material. The title compound has been isolated by flash column chromatography (Cy/AcOEt 9:1) and the enantiomeric excess determined by chiral HPLC analysis : Daicel Chiralcel IB column; Hex/iPrOH 96:4; flow rate 0.5 mL/min; 30°C; λ = 254 nm; T_{min}=31 min, T_{maj}=40 min.
$[\alpha]_D^{20}$ = +84.6° (c 2, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.22 – 7.08 (m, 6H), 7.03 – 6.95 (m, 2H), 5.32 (d, *J*=9.7, 1H), 4.02 (dd, *J*=11.2, 6.3, 1H), 3.97 (dd, *J*=11.2, 4.9, 1H), 3.30 (ddd, *J*=9.7, 6.3, 4.9, 1H), 2.34 (s, 3H), 1.53 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.6, 137.43, 137.41, 136.2, 129.6, 128.5, 125.7, 125.5, 122.5, 122.4, 64.7, 56.6, 54.6, 21.2.
ESI-MS (m/z) : 306 $[M+NH_4]^+$, 311 $[M+Na]^+$, 327 $[M+K]^+$.

(S)-4-(N-ethyl-N-(phenylsulfonyl)amino)-2-(benzo-1,3-dithiol-2-yl)butan-1-ol (30d).



30d

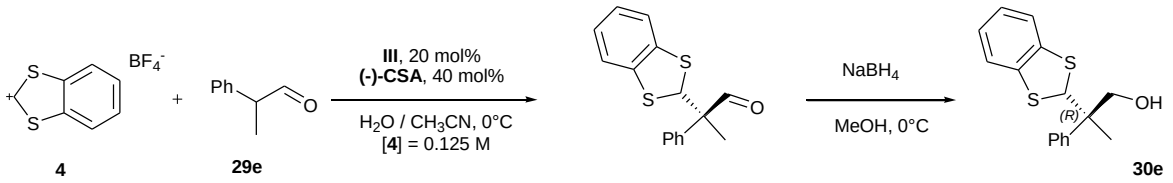
50% yield, 94% *ee*.
Reaction carried out following the general procedure with 4-(N-ethyl-N-(phenylsulfonyl)butanal **29d** (prepared by hydrolysis of the corresponding acetal[87]) as starting material. The title compound has been isolated by flash column chromatography (Cy/AcOEt 3:1) and the enantiomeric excess determined by chiral HPLC analysis : Daicel Chiralcel OD-H column; Hex/iPrOH 75:25; flow rate 0.5 mL/min; 30°C; λ = 254 nm; T_{min}=16 min, T_{maj}=20 min.
$[\alpha]_D^{20}$ = +19.0° (c 1.85, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.77 – 7.70 (m, 2H), 7.56 – 7.48 (m, 1H), 7.48 – 7.40 (m, 2H), 7.18 – 7.10 (m, 2H), 7.00 – 6.92 (m, 2H), 5.16 (d, *J*=6.1, 1H), 3.78 (dd, *J*=11.3, 4.4, 1H), 3.67

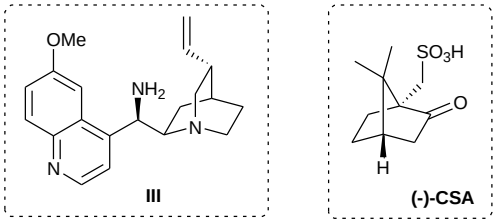
[87] M. Chiarucci, M. di Lillo, A. Romaniello, P. G. Cozzi, G. Cera, M. Bandini, *Chem. Sci.* **2012**, *3*, 2859 – 2863.

(dd, *J*=11.3, 5.7, 1H), 3.32 – 3.20 (m, 1H), 3.15 (q, *J*=7.2, 2H), 3.18 – 3.08 (m, 1H), 2.52 (bs s, 1H), 1.93 (m, 1H), 1.84 (dddd, *J*=13.7, 8.1, 3.7, 1H), 1.61 (dtd, *J*=13.7, 8.5, 4.9, 1H), 1.00 (t, *J*=7.2, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.7, 137.7, 137.5, 132.5, 129.1, 126.9, 125.45, 125.44, 122.03, 121.95, 61.7, 55.5, 45.62, 45.57, 42.6, 26.4, 13.8.
ESI-MS (m/z) : 410 $[M+H]^+$, 432 $[M+Na]^+$, 448 $[M+K]^+$, 841 $[2M+Na]^+$.

3.7.4. Enantioselective *α*-alkylation of *α*-substituted aldehydes.

(R)-2-(benzo-1,3-dithiol-2-yl)-2-phenylpropan-1-ol (30e).

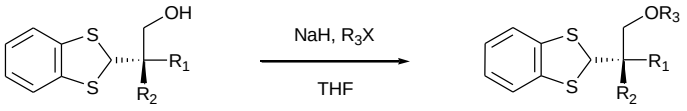




Aldehyde **29e** (2.5 mmol, 2.5 eq.), L-camphorsulfonic acid (0.4 mmol, 0.4 eq.) and the cinchona catalyst **III** (0.2 mmol, 0.2 eq., previously prepared according to the literature procedure[88]) are dissolved in 8 mL of water/acetonitrile (1:1 volume). The mixture is cooled to 0°C and then 1,3-benzodithiolylium tetrafluoroborate **4** (1 mmol, 1 eq.) is added. The reaction mixture is stirred overnight at 0°C. The reaction complete, a saturated solution of $NaHCO_3$ is added and the mixture is diluted with an excess volume of Et_2O. The organic layer is separated and the aqueous layer is extracted 3 times with Et_2O. The collected organic layers are washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure and at room temperature. The residue is then diluted in MeOH (2.5 mL) and $NaBH_4$ (1.75 mmol, 1.75 eq) is slowly added at 0 °C. After 1 hour, the reaction is quenched with water and concentrated under reduced pressure. The residue is extracted with Et_2O, dried over Na_2SO_4 and concentrated. The title compound has been isolated by flash column chromatography (Cy/AcOEt 9:1) and the enantiomeric excess has been determined by chiral HPLC analysis : Daicel Chiralcel OD-H column; Hex/iPrOH 90:10; flow rate 0.5 mL/min; 40°C; λ = 232, 254 nm; T_{maj}=23 min, T_{min}=26 min.
90% yield, 84% *ee*.
NMR data and specific rotation have already been reported.[89]

3.7.5. General procedure for the protection of OH groups.

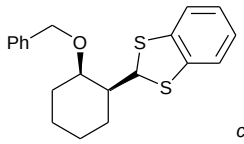
[88] S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367 – 6370.
[89] A. Gualandi, D. Petruzziello, E. Emer, P. G. Cozzi, *Chem. Commun.* **2012**, *48*, 3614 – 3616



30a-e **31a-f**

To a suspension of NaH (1,5 mmol, 2 eq.) in anhydrous THF (0.5 mL) at 0°C under inert atmosphere, a solution of alcohol **30** (0.75 mmol, 1 eq.) in anhydrous THF (0.75 mL) is slowly added. The reagent R_3X (1.5 mmol, 2 eq.) is then added and the mixture is stirred for 6 hours while warming to room temperature. The reaction complete, water is slowly added to quench the reaction and the mixture is diluted with an excess volume of Et_2O. The organic layer is separated and the aqueous layer is extracted with Et_2O. The collected organic layers are washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure.

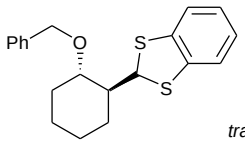
cis-2-(2-(benzyloxy)cyclohexyl)benzo-1,3-dithiole (cis-26).



cis-**26**

Reaction carried out following the general procedure with alcohol *cis*-**25** and benzyl bromide as starting materials. The title compound has been isolated by flash column chromatography (Cy/DCM 95:5, 65% yield).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.40 – 7.34 (m, 4H), 7.33 – 7.27 (m, 1H), 7.23 – 7.16 (m, 2H), 7.02 – 6.97 (m, 2H), 4.97 (d, *J*=10.5, 1H), 4.62 (d, *J*=11.4, 1H), 4.37 (d, *J*=11.4, 1H), 4.06 (q, *J*=3.0, 1H), 2.15 (ddt, *J*=14.3, 5.3, 3.3, 1H), 1.90 (dq, *J*=12.4, 3.7, 1H), 1.86 – 1.72 (m, 2H), 1.54 – 1.33 (m, 3H), 1.28 – 1.13 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.1, 138.0, 137.8, 128.5, 127.8, 127.6, 125.3 (2C), 122.5, 122.4, 73.9, 70.5, 58.1, 48.2, 28.2, 25.7, 25.6, 20.0.
ESI-MS (m/z) : 343 $[M+H]^+$, 365 $[M+Na]^+$.

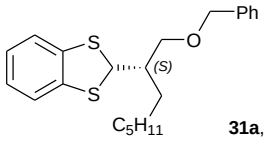
trans-2-(2-(benzyloxy)cyclohexyl)benzo-1,3-dithiole (trans-26).



trans-**26**

Reaction carried out following the general procedure with alcohol *trans*-**25** and benzyl bromide as starting materials. The title compound has been isolated by flash column chromatography (Cy/DCM 9:1, 79% yield).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.42 – 7.27 (m, 5H), 7.20 – 7.12 (m, 2H), 7.01 – 6.94 (m, 2H), 5.63 (d, *J*=3.3, 1H), 4.66 (d, *J*=11.4, 1H), 4.41 (d, *J*=11.4, 1H), 3.39 (td, *J*=9.9, 4.4, 1H), 2.25 (m, 1H), 1.91 (m, 1H), 1.78 – 1.68 (m, 2H), 1.61 (m, 1H), 1.29 – 1.11 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.2, 138.5, 138.4, 128.7, 128.2, 127.9, 125.26, 125.20, 121.64, 121.62, 77.6, 70.8, 54.0, 52.9, 31.0, 25.1, 24.6, 23.7.
ESI-MS (m/z) : 343 $[M+H]^+$, 365 $[M+Na]^+$.

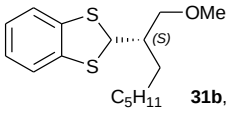
2-((S)-1-(benzyloxy)octan-2-yl)benzo-1,3-dithiole (31a).



31a, 96% *ee*

The reaction has been carried out following the general procedure with alcohol **30a** and benzyl bromide as starting materials. The title compound has been isolated by flash column chromatography (Cy/DCM 9:1, 89% yield).
NMR data and specific rotation have already been reported.[86]

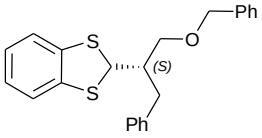
2-((S)-1-methoxyoctan-2-yl)benzo-1,3-dithiole (31b).



31b, 96% *ee*

Reaction carried out following the general procedure with alcohol **30a** and methyl iodide as starting materials. The title compound has been isolated by flash column chromatography (Cy/DCM 9:1, 85% yield).
$[\alpha]_D^{20}$ = +29.3° (c 0.9, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.21 – 7.15 (m, 2H), 7.01 – 6.96 (m, 2H), 5.18 (d, *J*=6.7, 1H), 3.50 (dd, *J*=9.7, 4.5, 1H), 3.42 (dd, *J*=9.7, 5.6, 1H), 3.30 (s, 3H), 1.95 (m, 1H), 1.57 (m, 1H), 1.46 – 1.18 (m, 9H), 0.87 (t, *J*=6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.3, 138, 125.4 (2C), 122.09, 122.04, 72.2, 59.1, 56.5, 46.4, 31.9, 29.5, 28.1, 27.4, 22.7, 14.2.
ESI-MS (m/z) : 335 $[M+K]^+$.

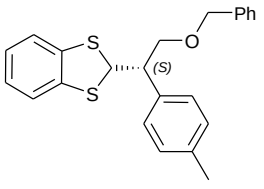
2-((S)-3-(benzyloxy)-1-phenylpropan-2-yl)benzo-1,3-dithiole (31c).



31c, 97% *ee*

Reaction carried out following the general procedure with alcohol **30b** and benzyl bromide as starting materials. The title compound has been isolated by flash column chromatography (Cy/DCM 9:1, 84% yield).
$[\alpha]_D^{20}$ = -4.9° (c 1, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.38 – 7.15 (m, 10H), 7.12 (d, *J*=7.4, 2H), 7.03 – 6.96 (m, 2H), 5.22 (d, *J*=6.6, 1H), 4.41 (ABq, Δδ=0.04, *J*=11.7, 2H), 3.50 (dd, *J*=9.5, 4.2, 1H), 3.42 (dd, *J*=9.5, 5.6, 1H), 3.02 (dd, *J*=13.5, 4.2, 1H), 2.67 (dd, *J*=13.4, 10.4, 1H), 2.32 – 2.22 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.7, 138.3, 138.1, 137.8, 129.3, 128.5, 127.8, 126.2, 125.5, 122.2, 122.1, 73.3, 68.4, 55.5, 49.2, 33.9.
ESI-MS (m/z) : 379 $[M+H]^+$, 401 $[M+Na]^+$.

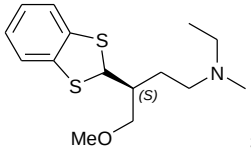
2-((S)-2-(benzyloxy)-1-p-tolylethyl)benzo-1,3-dithiole (31d).



31d, 95% *ee*

Reaction carried out following the general procedure with alcohol **30c** and benzyl bromide as starting materials. The title compound has been isolated by flash column chromatography (Cy/DCM 9:1, 72% yield).
$[\alpha]_D^{20}$ = +49.8° (c 1.5, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.42 – 7.27 (m, 5H), 7.22 – 7.05 (m, 6H), 7.00 – 6.92 (m, 2H), 5.47 (d, *J*=9.5, 1H), 4.51 (ABq, Δδ=0.02, *J*=11.8, 2H), 3.94 (dd, *J*=9.5, 5.2, 1H), 3.77 (dd, *J*=9.5, 4.8, 1H), 3.34 (dt, *J*=9.6, 5.0, 1H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.3, 138.0, 137.5, 137.2, 136.9, 129.1, 128.8, 128.5, 127.7 (2C), 125.4, 125.3, 122.3, 122.2, 73.5, 71.7, 57.0, 52.4, 21.2.
ESI-MS (m/z) : 379 $[M+H]^+$, 417 $[M+K]^+$.

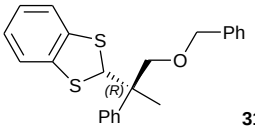
(S)-3-(benzo-1,3-dithiol-2-yl)-N-ethyl-4-methoxy-N-phenylsulfonylbutan-1-amine (31e).



31e, 94% *ee*

Reaction carried out following the general procedure with alcohol **30d** and methyl iodide as starting materials. The title compound has been isolated by flash column chromatography (Cy/AcOEt 7:1, 76% yield).
$[\alpha]_D^{20}$ = +22.5° (c 1.5, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.79 – 7.72 (m, 2H), 7.57 – 7.49 (m, 1H), 7.49 – 7.42 (m, 2H), 7.18 – 7.12 (m, 2H), 7.00 – 6.94 (m, 2H), 5.10 (d, *J*=6.5, 1H), 3.49 (dd, *J*=9.8, 4.5, 1H), 3.42 (dd, *J*=9.8, 5.5, 1H), 3.29 (s, 3H), 3.27 – 3.20 (m, 1H), 3.15 (q, *J*=7.1, 2H), 3.18 – 3.09 (m, 1H), 1.97 (m, 1H), 1.83 (m, 1H), 1.59 (dtd, *J*=13.8, 8.7, 5.0, 1H), 1.01 (t, *J*=7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.0, 137.8, 137.5, 132.4, 129.1, 127.0, 125.4 (2C), 122.1, 122.0, 71.5, 59.0, 55.6, 45.5, 43.9, 42.4, 26.6, 13.8.
ESI-MS (m/z) : 424 $[M+H]^+$, 446 $[M+Na]^+$, 869 $[2M+Na]^+$.

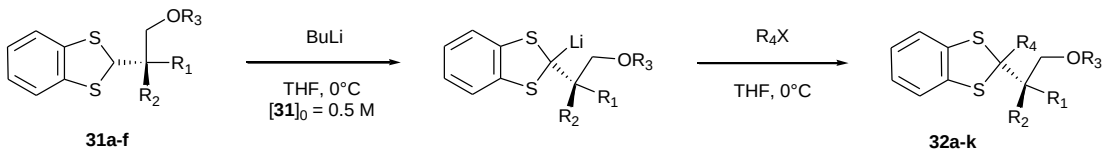
2-((R)-1-(benzyloxy)-2-phenylpropan-2-yl)benzo-1,3-dithiole (31f).



31f, 84% *ee*

Reaction carried out following the general procedure with alcohol **30e** and benzyl bromide as starting materials. The title compound has been isolated by flash column chromatography (Cy/EtOAc 9:1, 94% yield).
NMR data and specific rotation have already been reported.[89]

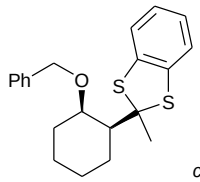
3.7.6. General procedure for the alkylation of 1,3-benzodithioles.



31a-f **32a-k**

Due to the sensibility of the substrates, butyllithium must be titrated with N-Pivaloyl-*o*-toluidine or N-pivaloyl-*o*-benzylaniline prior to use.[90]
Benzodithiole **31** (0.5 mmol, 1 eq.) is dissolved in anydrous THF (1 mL, 0.5 M) under inert atmosphere and the solution is cooled to 0°C. Then, BuLi (0.55 mmol, 1.1 eq.) is slowly added and the mixture turns to orange colour. After 15 minutes, the R_4X alkylation reagent is added and the reaction mixture in stirred at 0°C until completion (monitored by TLC, usually less than 1 hour). The reaction complete, water is added, the organic layer is separated and the aqueous layer is extracted with Et_2O. The collected organic layers are washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure.

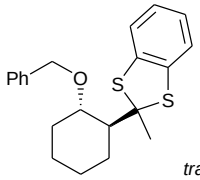
cis-2-(2-(benzyloxy)cyclohexyl)-2-methylbenzo-1,3-dithiole (cis-27).



cis-**27**

Reaction carried out following the general procedure and using benzodithiole *cis*-**26** and methyl iodide as starting materials. The title compound was isolated by flash column chromatography (Cy/DCM 95:5, 71% yield).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.44 – 7.39 (m, 2H), 7.39 – 7.33 (m, 2H), 7.31 – 7.28 (m, 1H), 7.19 – 7.14 (m, 2H), 7.01 – 6.96 (m, 2H), 4.61 (d, *J*=11.6, 1H), 4.43 (d, *J*=11.6, 1H), 4.06 (m, 1H), 2.21 – 2.06 (m, 2H), 1.89 (s, 3H), 1.96 – 1.81 (m, 3H), 1.58 (tt, *J*=13.4, 3.7, 1H), 1.50 – 1.41 (m, 1H), 1.39 – 1.18 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.2, 138.9, 137.2, 128.4, 127.9, 127.5, 125.3, 125.1, 122.6, 122.5, 74.7, 74.0, 70.3, 51.1, 29.5, 29.0, 26.4, 25.4, 20.0.
ESI-MS (m/z) : 357 $[M+H]^+$, 379 $[M+Na]^+$.

trans-2-(2-(benzyloxy)cyclohexyl)-2-methylbenzo-1,3-dithiole (trans-27).

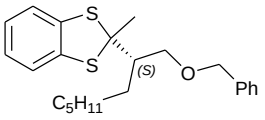


trans-**27**

Reaction carried out following the general procedure and using benzodithiole *trans*-**26** and methyl iodide as starting materials. The title compound was isolated by flash column chromatography (Cy/DCM 9:1, 64% yield).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.51 – 7.46 (m, 2H), 7.40 – 7.33 (m, 2H), 7.33 – 7.27 (m, 1H), 7.23 – 7.15 (m, 2H), 7.02 – 6.94 (m, 2H), 4.62 (ABq, Δδ=0.07, *J*=11.6, 2H), 3.29 (td, *J*=10.2, 4.0, 1H), 2.58 (td, *J*=11.6, 3.3, 1H), 2.27 (m, 1H), 1.96 (m, 1H), 1.73 (s, 3H), 1.85 – 1.70 (m, 2H), 1.37 – 1.19 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 141.4, 138.3, 135.3, 128.5, 128.4, 127.7, 125.3, 124.9, 122.37, 122.31, 78.8, 72.9, 70.5, 53.5, 31.3, 30.8, 27.1, 26.1, 24.9.
ESI-MS (m/z) : 357 $[M+H]^+$, 379 $[M+Na]^+$.

2-((S)-1-(benzyloxy)octan-2-yl)-2-methylbenzo-1,3-dithiole (32a).

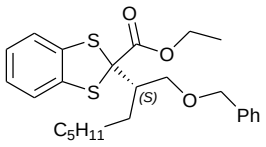
[90] J. Suffert. Simple direct titration of organolithium reagents using N-pivaloyl-*o*-toluidine and/or N-pivaloyl-*o*-benzylaniline. *J. Org. Chem.* **1989**, *54*, 509 – 510.



32a, 96% *ee*

Reaction carried out following the general procedure and using benzodithiole **31a** and methyl iodide as starting materials. The title compound has been isolated by flash column chromatography (Cy/DCM 95:5, 90% yield).
NMR data and specific rotation have already been reported.[86]

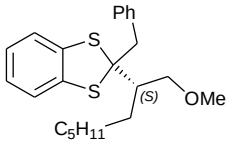
ethyl 2-((S)-1-(benzyloxy)octan-2-yl)benzo-1,3-dithiole-2-carboxylate (32c).



32c, 96% *ee*

Reaction carried out following the general procedure and using benzodithiole **31a** and ethyl chloroformate as starting materials. The title compound has been isolated by flash column chromatography (Cy/Et_2O 95:5, 69% yield).
$[\alpha]_D^{20}$ = +69.6° (c 1.7, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.40 – 7.24 (m, 5H), 7.16 – 7.08 (m, 2H), 7.02 – 6.95 (m, 2H), 4.43 (s, 2H), 4.12 (dq, *J*=10.7, 7.1, 1H), 4.06 (dq, *J*=10.7, 7.1, 1H), 3.67 (dd, *J*=10.1, 6.3, 1H), 3.58 (dd, *J*=10.1, 4.1, 1H), 2.57 (m, 1H), 1.81 (m, 1H), 1.60 – 1.35 (m, 2H), 1.35 – 1.15 (m, 7H), 1.18 (t, *J*=7.1, 3H), 0.86 (t, *J*=6.7, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.3, 138.2, 137.6, 136.9, 128.4, 127.9, 127.7, 125.57, 125.45, 121.7, 121.5, 76.0, 73.4, 70.5, 62.7, 47.4, 31.8, 29.4, 29.1, 28.1, 22.7, 14.2, 14.0.
ESI-MS (m/z) : 445 $[M+H]^+$, 467 $[M+Na]^+$.

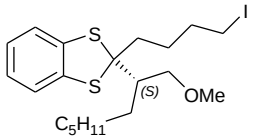
2-benzyl-2-((S)-1-methoxyoctan-2-yl)benzo-1,3-dithiole (32d).



32d, 95% *ee*

Reaction carried out following the general procedure and using benzodithiole **31b** and benzyl bromide as starting materials. The title compound has been isolated by flash column chromatography (Cy/DCM 95:5, 81% yield).
$[\alpha]_D^{20}$ = +14.4° (c 0.95, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.38 – 7.33 (m, 2H), 7.18 – 7.10 (m, 3H), 7.03 – 6.96 (m, 2H), 6.88 – 6.81 (m, 2H), 3.75 (dd, *J*=10.2, 5.3, 1H), 3.59 (dd, *J*=10.2, 3.9, 1H), 3.34 (ABq, Δδ=0.05, *J*=14.0, 2H), 3.34 (s, 3H), 2.33 – 2.24 (m, 1H), 1.86 – 1.75 (m, 1H), 1.62 – 1.41 (m, 2H), 1.40 – 1.21 (m, 7H), 0.90 (t, *J*=6.8, 3H). ^{13}C NMR (101 MHz, cdcl$_3$) δ = 138.3, 138.2, 136.4, 131.6, 127.4, 126.8, 125 (2C), 121.9, 78.2, 73.6, 58.9, 47.5, 46.4, 31.9, 30.8, 29.6, 28.6, 22.8, 14.2.
ESI-MS (m/z) : 387 $[M+H]^+$, 409 $[M+Na]^+$.

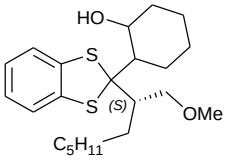
2-(4-iodobutyl)-2-((S)-1-methoxyoctan-2-yl)benzo-1,3-dithiole (32e).



32e, 96% *ee*

Reaction carried out following the general procedure and using benzodithiole **31b** and 1,4-diiodobutane (1.5 mmol, 3 eq.) as starting materials in 1.5 mL THF (0.33 M). The title compound has been isolated by flash column chromatography (Cy/DCM 95:5, 67% yield). The specific rotation could not be determined because of some starting benzodithiole mixed with the product.
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.15 – 7.08 (m, 2H), 7.02 – 6.93 (m, 2H), 3.65 (dd, *J*=10.1, 4.7, 1H), 3.51 (dd, *J*=10.1, 3.9, 1H), 3.33 (s, 3H), 3.15 (t, *J*=7.1, 2H), 2.21 – 2.13 (m, 1H), 2.10 – 2.01 (m, 2H), 1.89 – 1.73 (m, 3H), 1.73 – 1.62 (m, 2H), 1.59 – 1.40 (m, 2H), 1.39 – 1.20 (m, 7H), 0.86 (t, *J*=6.9, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.4, 138.1, 125.21, 125.15, 121.90, 121.87, 77.6, 73.1, 59, 47.7, 40.6, 33.7, 31.9, 30.4, 29.6, 28.5, 26.5, 22.8, 14.3, 6.5.

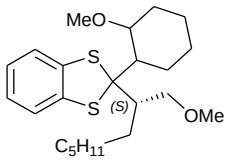
2-(2-((S)-1-methoxyoctan-2-yl)benzo-1,3-dithiol-2-yl)cyclohexanol (32g$_a$').



32g$_a$', 96% *ee*

Reaction carried out following the general procedure and using benzodithiole **31b** and cyclohexene oxide as starting materials. The title compound has been isolated by flash column chromatography (Cy/Et_2O 95:5). Diastereoisomeric ratio **32g$_a$'** / **32g$_b$'** = 1 : 1.5 ; 76% total yield.
$[\alpha]_D^{20}$ = +70.3° (c 1.3, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.08 – 7.01 (m, 2H), 6.95 – 6.89 (m, 2H), 3.80 (m, 1H), 3.54 (dd, *J*=10.3, 2.3, 1H), 3.47 (dd, *J*=10.3, 7.2, 1H), 3.33 (s, 3H), 2.87 (t, *J*=8.0, 1H), 2.42 (m, 1H), 2.11 – 1.94 (m, 3H), 1.67 (m, 2H), 1.41 – 1.16 (m, 14H), 0.85 (t, *J*=6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.2, 138.2, 124.8, 124.7, 121.0, 120.9, 82.9, 75.2, 72.9, 58.6, 53.9, 49.7, 38.3, 32.0, 29.6, 29.5, 28.5, 26.2, 25.2, 22.7, 14.2.
ESI-MS (m/z) : 417 $[M+Na]^+$, 433 $[M+K]^+$.

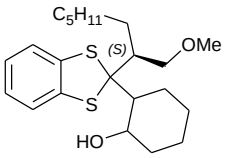
2-(2-methoxycyclohexyl)-2-((S)-1-methoxyoctan-2-yl)benzo-1,3-dithiole (32g$_a$).



32g$_a$, 96% *ee*

Reaction carried out following the general procedure for the protection of OH groups with benzodithiole **32g$_a$'** and methyl iodide as starting materials. The title compound has been isolated by flash column chromatography (Cy/DCM 4:1, 50% yield).
$[\alpha]_D^{20}$ = +98.5° (c 1.3, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.09 – 7.02 (m, 2H), 6.93 – 6.88 (m, 2H), 3.62 (d, *J*=3.4, 2H), 3.48 (m, 1H), 3.30 (s, 3H), 3.25 (s, 3H), 2.47 (m, 1H), 2.38 (m, 1H), 2.23 – 2.02 (m, 3H), 1.76 – 1.53 (m, 3H), 1.43 (m, 1H), 1.35 – 1.14 (m, 11H), 0.86 (t, *J*=6.7, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.5, 138.9, 124.7, 124.5, 120.8, 120.6, 82.0, 81.8, 73.4, 59.0, 55.7, 53.0, 48.5, 32.0, 31.5, 31.2, 29.6, 29.1, 29.0, 26.2, 24.6, 22.8, 14.3.

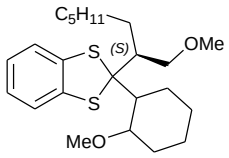
2-(2-((S)-1-methoxyoctan-2-yl)benzo-1,3-dithiol-2-yl)cyclohexanol (32g$_b$').



32g$_b$', 96% *ee*

Reaction carried out following the general procedure and using benzodithiole **31b** and cyclohexene oxide as starting materials. The title compound has been isolated by flash column chromatography (Cy/Et_2O 9:1). Diastereoisomeric ratio **32g$_a$'** / **32g$_b$'** = 1 : 1.5 ; 76% total yield.
$[\alpha]_D^{20}$ = +35.2° (c 0.65, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.12 – 7.05 (m, 2H), 7.00 – 6.91 (m, 2H), 4.10 (td, *J*=9.4, 4.6, 1H), 3.74 (dd, *J*=10.1, 4.5, 1H), 3.43 (dd, *J*=10.1, 3.3, 1H), 3.31 (s, 3H), 2.36 (m, 1H), 2.15 – 2.05 (m, 2H), 1.99 (m, 1H), 1.85 (m, 1H), 1.78 – 1.60 (m, 3H), 1.50 – 1.15 (m, 13H), 0.86 (t, *J*=6.4, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.4, 138.1, 125.3, 125.1, 121.4, 121.1, 81.3, 73.8, 72.2, 58.8, 53.0, 48.8, 36.1, 31.9, 30.2, 29.6, 28.54, 28.48, 26.1, 24.5, 22.7, 14.2.
ESI-MS (m/z) : 417 $[M+Na]^+$, 433 $[M+K]^+$.

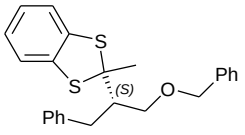
2-(2-methoxycyclohexyl)-2-((S)-1-methoxyoctan-2-yl)benzo-1,3-dithiole (32g$_b$).



32g$_b$, 96% *ee*

Reaction carried out following the general procedure for the protection of OH groups with benzodithiole **32g$_b$'** and methyl iodide as starting materials. The title compound has been isolated by flash column chromatography (Cy/DCM 4:1, 59% yield).
$[\alpha]_D^{20}$ = -54.3° (c 1.1, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.11 – 7.02 (m, 2H), 6.95 – 6.88 (m, 2H), 4.00 (dd, *J*=10.0, 3.7, 1H), 3.49 – 3.41 (m, 1H), 3.44 (dd, *J*=10.0, 4.9, 1H), 3.27 (s, 3H), 3.27 (s, 3H), 2.49 (m, 1H), 2.29 – 2.11 (m, 3H), 1.81 (m, 1H), 1.75 – 1.63 (m, 2H), 1.47 – 1.13 (m, 13H), 0.88 (t, *J*=6.7, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.7, 138.9, 124.8, 124.7, 120.91, 120.90, 81.7, 81.5, 75.7, 58.5, 55.7, 52.5, 48.9, 32.0, 31.2, 31.0, 29.7, 29.1, 28.3, 26.1, 24.4, 22.8, 14.3.

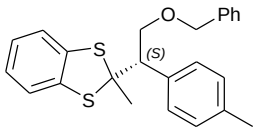
2-((S)-3-(benzyloxy)-1-phenylpropan-2-yl)-2-methylbenzo-1,3-dithiole (32h).



32h, 97% *ee*

Reaction carried out following the general procedure and using benzodithiole **31c** and methyl iodide as starting materials. The title compound has been isolated by flash column chromatography (Cy/DCM 9:1, 74% yield).
$[\alpha]_D^{20}$ = -12.7° (c 1.45, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.38 – 7.15 (m, 12H), 7.05 – 6.97 (m, 2H), 4.43 (ABq, Δδ=0.06, *J*=12.0, 2H), 3.65 (dd, *J*=10.3, 2.8, 1H), 3.40 (dd, *J*=10.3, 4.6, 1H), 3.18 (dd, *J*=13.4, 2.7, 1H), 2.87 (dd, *J*=13.4, 11.0, 1H), 2.55 (m, 1H), 1.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.6, 138.3, 138.16, 138.01, 129.4, 128.50, 128.45, 127.75, 127.67, 126.3, 125.45, 125.42, 122.63, 122.57, 73.5, 73.3, 68.6, 51.2, 35.7, 28.9.
ESI-MS (m/z) : 393 $[M+H]^+$, 415 $[M+Na]^+$, 807 $[2M+Na]^+$.

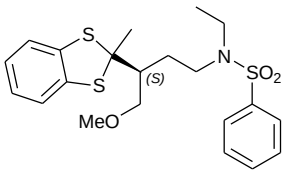
2-((S)-2-(benzyloxy)-1-p-tolylethyl)-2-methylbenzo-1,3-dithiole (32i).



32i, 95% *ee*

Reaction carried out following the general procedure and using benzodithiole **31d** and methyl iodide as starting materials. The title compound has been isolated by flash column chromatography (Cy/DCM 9:1, 52% yield).
$[\alpha]_D^{20}$ = -36.7° (c 1.1, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.34 – 7.21 (m, 7H), 7.19 – 7.11 (m, 4H), 7.01 – 6.96 (m, 2H), 4.52 (ABq, Δδ=0.03, *J*=12.3, 2H), 4.14 (dd, *J*=9.8, 6.0, 1H), 3.93 (dd, *J*=9.8, 7.5, 1H), 3.74 (dd, *J*=7.5, 6.0, 1H), 2.35 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.6, 138.2, 137.5, 137.3, 136.0, 129.3, 129.1, 128.4, 127.8, 127.7, 125.45, 125.42, 122.7, 122.5, 73.3, 71.9, 71.6, 54.8, 29.1, 21.3.
ESI-MS (m/z) : 393 $[M+H]^+$, 410 $[M+NH_4]^+$, 415 $[M+Na]^+$, 431 $[M+K]^+$.

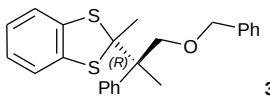
(S)-N-ethyl-4-methoxy-N-phenylsulfonyl-3-(2-methylbenzo-1,3-dithiol-2-yl)butan-1-amine (32j).



32j, 94% *ee*

Reaction carried out following the general procedure and using benzodithiole **31e** and methyl iodide as starting materials. The title compound has been isolated by flash column chromatography (Cy/AcOEt 95:5, 67% yield).
$[\alpha]_D^{20}$ = +6.1° (c 1.75, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.83 – 7.79 (m, 2H), 7.58 – 7.52 (m, 1H), 7.51 – 7.46 (m, 2H), 7.20 – 7.12 (m, 2H), 7.05 – 6.96 (m, 2H), 3.61 (dd, *J*=10.1, 4.3, 1H), 3.53 (dd, *J*=10.1, 4.8, 1H), 3.34 (s, 3H), 3.32 – 3.23 (m, 4H), 2.22 (m, 1H), 2.04 (m, 1H), 1.84 (s, 3H), 1.80 (m, 1H), 1.10 (t, *J*=7.2, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.3, 137.9, 137.8, 132.5, 129.2, 127.2, 125.55, 125.51, 122.59, 122.58, 73.0, 72.6, 59.1, 46.0, 45.9, 42.5, 29.1, 28.4, 13.7.
ESI-MS (m/z) : 438 $[M+H]^+$, 460 $[M+Na]^+$, 476 $[M+K]^+$, 897 $[2M+Na]^+$.

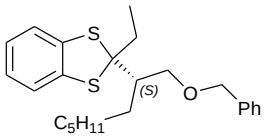
2-((R)-1-(benzyloxy)-2-phenylpropan-2-yl)-2-methylbenzo-1,3-dithiole (32k).



32k, 84% *ee*

Reaction carried out following the general procedure and using benzodithiole **31f** and methyl iodide as starting materials. The title compound has been isolated by flash column chromatography (Cy/AcOEt 9:1, 91% yield).
NMR data and specific rotation have already been reported.[89]

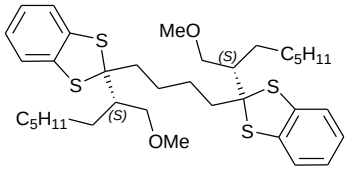
2-((S)-1-(benzyloxy)octan-2-yl)-2-ethylbenzo-1,3-dithiole (S)-32l.



(*S*)-**32l**, 96% *ee*

Reaction carried out following the general procedure and using benzodithiole **31a** and ethyl iodide as starting materials. The title compound has been isolated by flash column chromatography (Cy/DCM 95:5, 80% yield).
$[\alpha]_D^{20}$ = +21.7° (c 0.5, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.40 – 7.25 (m, 5H), 7.16 – 7.08 (m, 2H), 6.99 – 6.92 (m, 2H), 4.52 (ABq, Δδ=0.02, *J*=12.0, 2H), 3.76 (dd, *J*=10.0, 4.5, 1H), 3.61 (dd, *J*=10.0, 4.2, 1H), 2.25 (dtd, *J*=7.0, 4.3, 2.7, 1H), 2.11 (q, *J*=7.2, 2H), 1.86 – 1.75 (m, 1H), 1.64 – 1.50 (m, 1H), 1.50 – 1.38 (m, 1H), 1.38 – 1.20 (m, 7H), 1.07 (t, *J*=7.0, 3H), 0.89 (t, *J*=6.9, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.8, 138.5, 138.3, 128.4, 127.7, 127.6, 125.04, 124.98, 121.80, 121.76, 78.7, 73.3, 70.6, 47.5, 34.8, 31.9, 30.5, 29.6, 28.5, 22.8, 14.3, 10.1.
ESI-MS (m/z) : 401 $[M+H]^+$, 423 $[M+Na]^+$, 439 $[M+K]^+$.

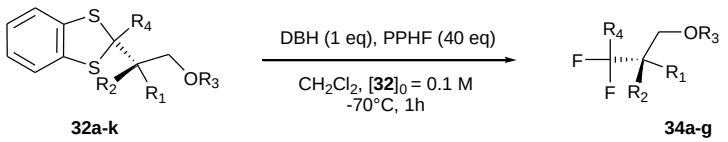
2-((S)-1-methoxyoctan-2-yl)-2-(4-(2-((S)-1-methoxyoctan-2-yl)benzo-1,3-dithiol-2-yl)butyl)benzo-1,3-dithiole (33).



33, 99% *ee*

Reaction carried out following the general procedure and using benzodithiole **31b** (0.5 mmol, 2 eq.) and 1,4-diiodobutane (0.25 mmol, 1 eq.) as starting materials. The title compound has been isolated by flash column chromatography (Cy/DCM 9:1, 61% yield).
$[\alpha]_D^{20}$ = +20.3° (c 1.15, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.13 – 7.06 (m, 2H), 6.97 – 6.91 (m, 2H), 3.62 (dd, *J*=10.1, 4.7, 1H), 3.46 (dd, *J*=10.1, 4.1, 1H), 3.30 (s, 3H), 2.20 – 2.11 (m, 1H), 2.09 – 1.93 (m, 2H), 1.80 – 1.69 (m, 1H), 1.60 – 1.38 (m, 4H), 1.36 – 1.19 (m, 7H), 0.88 (t, *J*=6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.5, 138.3, 125.09, 125.05, 121.77, 121.74, 77.7, 73.3, 58.9, 48, 41.7, 31.9, 30.5, 29.6, 28.6, 25.6, 22.8, 14.3.

3.7.7. General procedure for the oxidative desulfurization-fluorination.

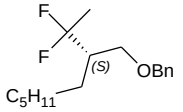


32a-k **34a-g**

Precautions must be taken to exclude moisture from the reaction media. 1,3-dibromo-5,5-dimethylhydantoin (0.1 mmol, 1 eq.) is dissolved in 1 mL of dry dichloromethane under inert atmosphere. The mixture is cooled to -70°C and then pyridinium polyhydrogen fluoride (4 mmol, 40 eq. HF) is added, followed by the dropwise addition of benzodithiole **32** (0.1 mmol, 1 eq.). The reaction mixture turns to a deep red colour and is stirred for 1 hour at -70°C. After completion, the mixture is diluted with dichloromethane and filtered through a short plug of basic alumina. The solvent is then removed under reduced pressure. The crude

mixture is analysed by ^{1}H NMR spectroscopy to determine the reaction yield using 1,4-diacetylbenzene (0.05 mmol) as internal standard.

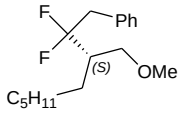
1-(((S)-2-(1,1-difluoroethyl)octyloxy)methyl)benzene (34a).



34a, 96% *ee*

Reaction carried out following the general procedure with benzodithiole **32a** as substrate. The title compound has been isolated by flash column chromatography (Cy/DCM 95:5, 67% yield).
$[\alpha]_D^{20}$ = +10.2° (c 0.9, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.38 – 7.27 (m, 5H), 4.50 (ABq, Δδ=0.03, *J*=12.1, 2H), 3.56 (dd, *J*=9.8, 5.2, 1H), 3.52 (dd, *J*=9.8, 4.1, 1H), 2.02 (m, 1H), 1.61 (t, *J*=19.4, 3H), 1.63 – 1.52 (m, 1H), 1.52 – 1.36 (m, 2H), 1.36 – 1.20 (m, 7H), 0.89 (t, *J*=6.6, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.4, 128.5, 127.74, 127.66, 126.5 (t, *J*=240.7), 73.3, 68.2 (dd, *J*=6.6, 5.3), 46.6 (t, *J*=23.0), 31.8, 29.6, 27.5, 26.1 (dd, *J*=5.2, 2.9), 22.8, 22.2 (t, *J*=27.8), 14.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ = -91.29 (dqd, *J*=242.6, 19.5, 10.7), -93.47 (dm, *J*=242.6).

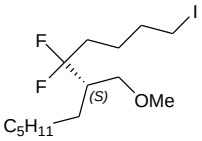
1-((S)-2,2-difluoro-3-(methoxymethyl)nonyl)benzene (34b).



34b, 95% *ee*

Reaction carried out following the general procedure with benzodithiole **32d** as substrate. The title compound has been isolated by flash column chromatography (Cy/DCM 9:1, 40% yield).
$[\alpha]_D^{20}$ = +3.8° (c 0.4, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.35 – 7.24 (m, 5H), 3.54 (dd, *J*=10.0, 5.7, 1H), 3.45 (dd, *J*=10.0, 4.2, 1H), 3.34 (s, 3H), 3.27 – 3.13 (m, 2H), 2.09 – 1.93 (m, 1H), 1.67 – 1.56 (m, 1H), 1.50 – 1.36 (m, 2H), 1.36 – 1.19 (m, 7H), 0.88 (t, *J*=6.7, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 133.6 (t, *J*=3.6), 130.8, 128.3, 127.2, 124.9 (t, *J*=245.3), 70.9 (t, *J*=5.6), 59, 45.2 (t, *J*=22.8), 41.6 (t, *J*=25.6), 31.8, 29.6, 27.5, 25.9 (dd, *J*=5.1, 3.1), 22.8, 14.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ = -99.47 (dm, *J*=246), -102.14 (dm, *J*=246).
ESI-MS (m/z) : 302 $[M+NH_4]^+$, 307 $[M+Na]^+$.

(S)-5,5-difluoro-1-iodo-6-(methoxymethyl)dodecane (34c).

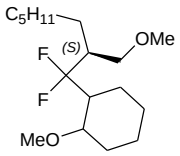


34c, 96% *ee*

Reaction carried out following the general procedure with benzodithiole **32d** as substrate. The title compound has been isolated by flash column chromatography (Cy/DCM 9:1, 55% yield).
$[\alpha]_D^{20}$ = +8.6° (c 0.5, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 3.46 (dd, *J*=10.0, 5.7, 1H), 3.38 (ddd, *J*=10.0, 4.1, 1.3, 1H), 3.31 (s, 3H), 3.19 (t, *J*=7.0, 2H), 2.06 – 1.79 (m, 5H), 1.69 – 1.51 (m, 3H), 1.48 – 1.21 (m, 9H), 0.88 (t, *J*=6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 126.1 (t, *J*=243.8), 70.8 (t, *J*=5.6), 59, 45.6 (t,

J=23.1), 33.9 (t, *J*=25.5), 33.4, 31.8, 29.6, 27.6, 25.8 (dd, *J*=4.8, 3.5), 23.1 (t, *J*=4.7), 22.8, 14.2, 6.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ = -101.42 (dm, *J*=244), -103.98 (dm, *J*=244).

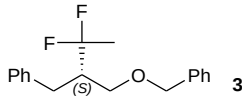
1-((S)-1,1-difluoro-2-(methoxymethyl)octyl)-2-methoxycyclohexane (34d).



34d, 96% *ee*

Reaction carried out following the general procedure with benzodithiole **32g$_b$** as substrate. The title compound has been isolated by flash column chromatography (Cy/DCM 3:1, 33% yield).
$[\alpha]_D^{20}$ = -23.5° (c 0.2, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 3.63 (dd, *J*=9.9, 5.0, 1H), 3.40 (dd, *J*=9.9, 5.3, 1H), 3.33 (s, 3H), 3.30 (s, 3H), 3.20 (td, *J*=9.3, 4.2, 1H), 2.41 (m, 1H), 2.16 (m, 1H), 2.10 – 1.91 (m, 2H), 1.77 – 1.66 (m, 2H), 1.64 – 1.54 (m, 1H), 1.42 – 1.12 (m, 13H), 0.88 (t, *J*=6.7, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 126.7 (dd, *J*=249.5, 247.7), 78.9 (dd, *J*=5.6, 2.9), 71.2 (t, *J*=5.6), 58.9, 56.1, 46.3 (t, *J*=22.9), 44.9 (dd, *J*=22.8, 21.9), 31.9, 30.8 (d, *J*=1.7), 29.8, 27.2, 27.0 (dd, *J*=6.3, 2.5), 24.9 (d, *J*=0.6), 24.1, 24.0 (dd, *J*=8.5, 3.8), 22.8, 14.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ = -107.36 (ddd, *J*=251.5, 25.4, 7.8), -110.16 (ddd, *J*=251.2, 20.4, 10.1).
ESI-MS (m/z) : 307 $[M+H]^+$, 329 $[M+Na]^+$.

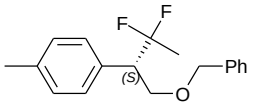
1-(((S)-2-benzyl-3,3-difluorobutoxy)methyl)benzene (34e).



34e, 97% *ee*

Reaction carried out following the general procedure with benzodithiole **32h** as substrate. The title compound has been isolated by flash column chromatography (Cy/DCM 9:1, 60% yield) and the enantiomeric excess determined by chiral HPLC analysis : Daicel Chiralcel OJ column, Hex/iPrOH 99:1, flow rate 0.6 mL/min, 30°C, λ = 214 nm, T_{min}=24 min, T_{maj}=29 min.
$[\alpha]_D^{20}$ = +40.7° (c 0.6, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.37 – 7.24 (m, 7H), 7.24 – 7.16 (m, 3H), 4.41 (ABq, Δδ=0.03, *J*=11.9, 2H), 3.51 (dd, *J*=10.1, 2.8, 1H), 3.38 (dd, *J*=10.1, 3.9, 1H), 2.96 (dd, *J*=13.6, 3.9, 1H), 2.76 (dd, *J*=13.6, 10.7, 1H), 2.31 (m, 1H), 1.69 (t, *J*=19.5, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.6, 138.2, 129.3, 128.6, 128.5, 127.73, 127.67, 126.4, 125.4 (t, *J*=240.9), 73.3, 66.8 (dd, *J*=6.1, 4.9), 48.8 (t, *J*=23.4), 31.6 (dd, *J*=5.8, 3.3), 22.4 (t, *J*=27.4). ^{19}F NMR (377 MHz, $CDCl_3$) δ = -90.83 (dqd, *J*=242.6, 19.6, 9.4), -93.48 (dm, *J*=242.6).
ESI-MS (m/z) : 308 $[M+NH_4]^+$.

1-((S)-1-(benzyloxy)-3,3-difluorobutan-2-yl)-4-methylbenzene (34f).

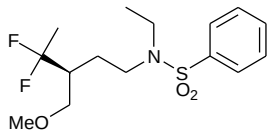


34f, 95% *ee*

Reaction carried out following the general procedure with benzodithiole **32i** as substrate. The title compound has been isolated by flash column chromatography (Cy/DCM 9:1, 65% yield)
$[\alpha]_D^{20}$ = -14.5° (c 1.1, $CHCl_3$).

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.35 – 7.25 (m, 3H), 7.24 – 7.12 (m, 6H), 4.49 (ABq, Δδ=0.04, *J*=12.2, 2H), 4.05 (dd, *J*=9.7, 5.4, 1H), 3.82 (ddd, *J*=9.7, 7.7, 1.0, 1H), 3.32 (dddd, *J*=19.8, 12.2, 7.7, 5.4, 1H), 2.35 (s, 3H), 1.51 (t, *J*=19.0, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.2, 137.4, 133.9 (dd, *J*=5.4, 1.7), 129.3, 129.2 (t, *J*=1.1), 128.5, 127.70, 127.68, 124.4 (t, *J*=242.7), 73.4, 69.3 (dd, *J*=5.4, 4.5), 53.3 (t, *J*=23.2), 23.2 (t, *J*=27.3), 21.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ = -92.51 (dqd, *J*=242.2, 19.0, 11.9), -95.90 (dp, *J*=242.2, 18.8).
ESI-MS (m/z) : 308 $[M+NH_4]^+$.

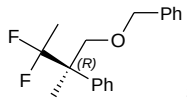
(S)-N-ethyl-4,4-difluoro-3-(methoxymethyl)-N-phenylsulfonylpentan-1-amine (34g).



34g, 94% *ee*

Reaction carried out following the general procedure with benzodithiole **32j** as substrate. The title compound has been isolated by flash column chromatography (Cy/AcOEt 9:1, 23% yield). Specific rotation not determined because of impurities mixed with the product.
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.84 – 7.78 (m, 2H), 7.60 – 7.54 (m, 1H), 7.54 – 7.47 (m, 2H), 3.52 (dd, *J*=9.7, 5.0, 1H), 3.40 (dd, *J*=9.9, 5.0, 1H), 3.33 (s, 3H), 3.31 – 3.19 (m, 2H), 3.25 (q, *J*=7.2, 2H), 2.06 (m, 1H), 1.85 (m, 1H), 1.72 (m, 1H), 1.59 (t, *J*=19.3, 3H), 1.10 (t, *J*=7.2, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.2, 132.5, 129.2, 127.2, 125.3 (t, *J*=241.0), 70.5 (t, *J*=5.9), 59.1, 45.7, 43.9 (t, *J*=23.5), 42.8, 25.5 (dd, *J*=4.7, 2.8), 22.0 (t, *J*=27.6), 13.9. ^{19}F NMR (377 MHz, $CDCl_3$) δ = -90.89 (dqd, *J*=244.0, 19.2, 10.0), -94.01 (dqd, *J*=244.0, 19.4, 16.3).

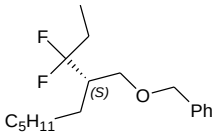
1-(((R)-3,3-difluoro-2-methyl-2-phenylbutoxy)methyl)benzene (34h).



34h, 84% *ee*

Reaction carried out following the general procedure with benzodithiole **32k** as substrate. The title compound has been isolated by flash column chromatography (Cy/AcOEt 95:5, 70% yield).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.47 (d, *J*=7.7, 2H), 7.36 – 7.23 (m, 8H), 4.53 (ABq, Δδ=0.04, *J*=12.2, 2H), 3.94 (d, *J*=9.4, 1H), 3.85 (d, *J*=9.4, 1H), 1.56 (s, 3H), 1.42 (t, *J*=19.5, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.5 (t, *J*=2.4), 138.3, 128.4, 128.2, 128.1 (t, *J*=1.7), 127.68, 127.66, 127.2, 126.1 (t, *J*=246.4), 73.7, 73.2 (dd, *J*=6.0, 4.1), 50.0 (t, *J*=21.1), 21.3 (t, *J*=27.8), 18.7 (dd, *J*=5.0, 3.9). ^{19}F NMR (377 MHz, $CDCl_3$) δ = -95.90 (dq, *J*=242.9, 19.6), -97.94 (dq, *J*=242.9, 19.4).

1-(((S)-2-(1,1-difluoropropyl)octyloxy)methyl)benzene (S)-34i.

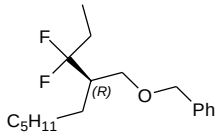


(S)-**34i**, 96% *ee*

Reaction carried out following the general procedure with benzodithiole *(S)*-**32l** as substrate. The title compound has been isolated by flash column chromatography (Cy/DCM 95:5, 75% yield).
$[\alpha]_D^{20}$ = +10.8° (c 0.85, $CHCl_3$).

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.40 – 7.25 (m, 5H), 4.50 (ABq, Δδ=0.02, *J*=12.1, 2H), 3.58 (dd, *J*=9.9, 5.4, 1H), 3.49 (ddd, *J*=9.9, 4.5, 1.1, 1H), 2.06 (m, 1H), 1.99 – 1.82 (m, 2H), 1.65 – 1.53 (m, 1H), 1.49 – 1.36 (m, 2H), 1.36 – 1.20 (m, 7H), 1.01 (t, *J*=7.5, 3H), 0.89 (t, *J*=6.9, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.4, 128.50, 127.7, 127.6, 126.5 (t, *J*=243.5), 73.3, 68.5 (t, *J*=5.7), 45.4 (t, *J*=23.2), 31.8, 29.6, 28.3 (t, *J*=26.1), 27.6, 26 (dd, *J*=4.6, 3.6), 22.8, 14.2, 6.2 (t, *J*=5.8). ^{19}F NMR (377 MHz, $CDCl_3$) δ = -103.76 (dm, *J*=242.6), -105.79 (dm, *J*=242.6).
ESI-MS (m/z) : 316 $[M+NH_4]^+$, 321 $[M+Na]^+$.

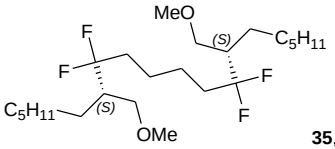
1-(((S)-2-(1,1-difluoropropyl)octyloxy)methyl)benzene (R)-34i.



(R)-**34i**, 90% *ee*

Reaction carried out following the general procedure with benzodithiole *(R)*-**32l** as substrate. The title compound has been isolated by flash column chromatography (Cy/DCM 95:5, 75% yield).
$[\alpha]_D^{20}$ = -11.35° (c 1.55, $CHCl_3$).
NMR spectra and ESI-MS analysis identical to those of *(S)*-**34i**.

(7S,14S)-8,8,13,13-tetrafluoro-7,14-bis(methoxymethyl)icosane (35).

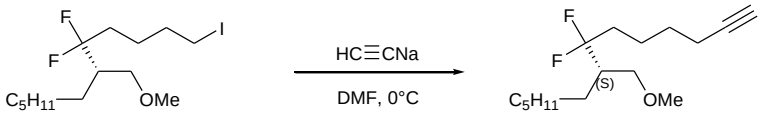


35, 99% *ee*

Reaction carried out following the general procedure with benzodithiole **33** as substrate and 2 eq. (0.2 mmol) of DBH. The title compound has been isolated by flash column chromatography (Cy/DCM 2:1, 68% yield).
$[\alpha]_D^{20}$ = +12.5° (c 0.75, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 3.47 (dd, *J*=10.0, 5.6, 1H), 3.38 (ddd, *J*=10.0, 4.3, 0.9, 1H), 3.31 (s, 3H), 2.06 – 1.94 (m, 1H), 1.94 – 1.76 (m, 2H), 1.62 – 1.49 (m, 3H), 1.46 – 1.20 (m, 9H), 0.89 (t, *J*=6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 126.2 (t, *J*=243.6), 71 (t, *J*=5.5), 59, 45.6 (t, *J*=23.1), 34.9 (t, *J*=25.3), 31.9, 29.6, 27.6, 26 (dd, *J*=4.5, 3.6), 22.8, 21.8 (t, *J*=4.7), 14.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ = -101.57 (dm, *J*=243.4), -103.92 (dm, *J*=243.4).
ESI-MS (m/z) : 460 $[M+NH_4]^+$, 465 $[M+Na]^+$.

3.7.8. Alkylation of the iodo derivative 34c.

(S)-7,7-difluoro-8-(methoxymethyl)tetradec-1-yne (36a).

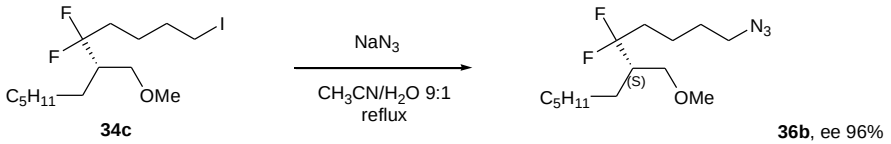


34c **36a**, ee 96%

The iodo derivative **34c** (0.1 mmol, 1 eq.) is dissolved in 0.4 mL of anhydrous DMF (0.25 M) under inert atmosphere and the solution is cooled to 0°C. Sodium acetylide (0.2 mmol, 2 eq.) is slowly added and the mixture is stirred at 0°C until complete conversion (monitored by TLC). 0.2 mL of water are then added and the solvent is removed under reduced pressure.

The crude product is dissolved in water and dichloromethane, layers are separated, and the aqueous layer is extracted with dichloromethane. The collected organic layers are washed with brine and dried over Na_2SO_4. The title compound is purified by flash column chromatography (Cy/DCM 9:1, 73% yield).
$[\alpha]_D^{20}$ = +4.2° (c 0.45, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 3.47 (dd, *J*=10.0, 5.6, 1H), 3.38 (ddd, *J*=10.0, 4.3, 1.2, 1H), 3.31 (s, 3H), 2.21 (td, *J*=6.7, 2.6, 2H), 1.99 (m, 1H), 1.95 (t, *J*=2.6, 1H), 1.94 – 1.79 (m, 2H), 1.67 – 1.50 (m, 5H), 1.46 – 1.22 (m, 9H), 0.89 (t, *J*=6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 126.18 (t, *J*=243.6), 84.29, 70.9 (t, *J*=5.6), 68.6, 59, 45.6 (t, *J*=23.1), 34.5 (t, *J*=25.4), 31.8, 29.6, 28.4, 27.6, 25.9 (dd, *J*=4.5, 3.6), 22.8, 21.1 (t, *J*=4.8), 18.5, 14.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ = -101.47 (ddd, *J*=243.6, 37.4, 11.4), -103.76 (ddd, *J*=243.6, 35.1, 16.5).

(***S*)-1-azido-5,5-difluoro-6-(methoxymethyl)dodecane (36b).**

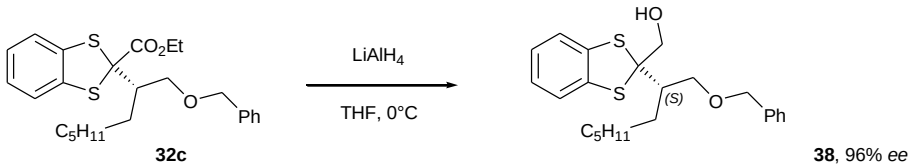


34c **36b**, ee 96%

The iodo derivative **34c** (0.1 mmol, 1 eq.) is dissolved in 225 µL of acetonitrile and 25 µL of water. NaN_3 is added and the reaction mixture is heated under reflux. After complete conversion (monitored by TLC), the solvent is removed under reduced pressure and the residue is extracted with dichloromethane. The collected organic layers are washed with brine and dried over Na_2SO_4. The title compound is purified by flash column chromatography (Cy/DCM 95:5, 88% yield).
$[\alpha]_D^{20}$ = +7.0° (c 0.6, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 3.46 (dd, *J*=9.9, 5.8, 1H), 3.38 (dd, *J*=9.9, 4.1, 1H), 3.31 (s, 3H), 3.29 (t, *J*=6.5, 2H), 2.06 – 1.80 (m, 3H), 1.69 – 1.50 (m, 5H), 1.47 – 1.20 (m, 9H), 0.89 (t, *J*=6.9, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 126.05 (t, *J*=243.6), 70.9 (t, *J*=5.6), 59, 51.4, 45.7 (t, *J*=23.1), 34.5 (t, *J*=25.4), 31.8, 29.6, 28.8, 27.6, 25.8 (dd, *J*=4.7, 3.5), 22.8, 19.3 (t, *J*=4.8), 14.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ = -101.49 (dm, *J*=244.1), -104.13 (dm, *J*=244.1).

3.7.9. Synthesis of *(S)*-2,2-difluoro-3-hexylbutane-1,4-diol.

(2-((S)-1-(benzyloxy)octan-2-yl)benzo-1,3-dithiol-2-yl)methanol (38).

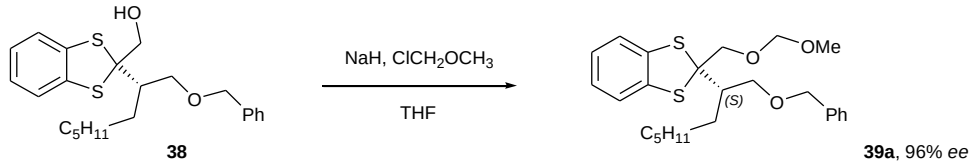


32c **38**, 96% *ee*

Benzodithiole **32c** (0.5 mmol, 1 eq.) is dissolved in anhydrous THF (1 mL, 0.5 M) under inert atmosphere and the solution is cooled to 0°C. Lithium aluminium hydride (0.5 mmol, 19 mg, 1 eq.) is then slowly added and the reaction mixture is stirred for 30 minutes at 0°C. The reaction complete, 19 µL of water are added (for 19 mg $LiAlH_4$) followed by 19 µL of $NaOH_{aq}$ 15% and the mixture is stirred for 5 minutes at 0°C. Then, 38 µL of water are added and the mixture is stirred for 5 minutes while allowed to warm to room temperature. The resulting heterogeneous mixture is filtered through celite and washed with Et_2O. The title compound is obtained after concentration under reduced pressure.

$[\alpha]_D^{20}$ = +56.3° (c 1.85, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.40 – 7.29 (m, 5H), 7.17 – 7.08 (m, 2H), 7.01 – 6.95 (m, 2H), 4.55 (ABq, Δδ=0.06, *J*=11.8, 2H), 3.96 – 3.86 (m, 2H), 3.68 (dd, *J*=10.2, 2.0, 1H), 3.64 (t, *J*=7.5, 1H), 3.59 (dd, *J*=10.2, 5.8, 1H), 2.39 (m, 1H), 1.78 (m, 1H), 1.58 (m, 1H), 1.40 – 1.18 (m, 8H), 0.88 (t, *J*=6.7, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.6, 137.27, 137.25, 128.7, 128.1, 128.0, 125.53, 125.48, 122.63, 122.56, 78.3, 73.6, 69.6, 67.3, 45.6, 31.8, 29.4, 29.3, 28.1, 22.7, 14.2.
ESI-MS (m/z) : 425 $[M+Na]^+$, 441 $[M+K]^+$.

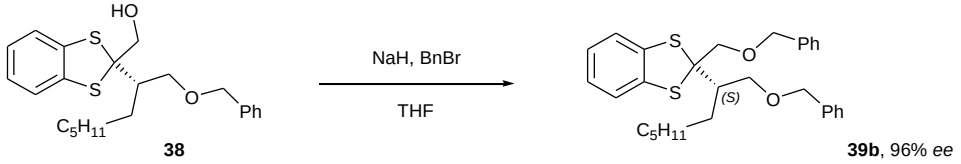
2-((S)-1-(benzyloxy)octan-2-yl)-2-((methoxymethoxy)methyl)benzo-1,3-dithiole (39a).



38 **39a**, 96% *ee*

The reaction is carried out following the general procedure for the protection of OH groups using alcohol **38** and chloromethyl methyl ether as starting materials. The title compound has been isolated by flash column chromatography (Cy/DCM 2:1, 80% yield).
$[\alpha]_D^{20}$ = +27.9° (c 1.8, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.41 – 7.25 (m, 5H), 7.15 – 7.08 (m, 2H), 7.01 – 6.93 (m, 2H), 4.60 (ABq, Δδ=0.03, *J*=6.5, 2H), 4.52 (ABq, Δδ=0.02, *J*=12.2, 2H), 3.92 (ABq, Δδ=0.04, *J*=10.7, 2H), 3.71 (dd, *J*=10.0, 4.1, 1H), 3.60 (dd, *J*=10.0, 3.8, 1H), 3.31 (s, 3H), 2.37 (m, 1H), 1.93 (m, 1H), 1.65 (m, 1H), 1.50 – 1.38 (m, 1H), 1.38 – 1.21 (m, 7H), 0.88 (t, *J*=6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.5, 138.3, 137.2, 128.4, 127.8, 127.7, 125.25, 125.20, 122.2, 122.1, 97.0, 75.4, 73.3, 72.9, 69.4, 55.6, 43.8, 31.9, 30.1, 29.5, 28.3, 22.8, 14.2.
ESI-MS (m/z) : 469 $[M+Na]^+$.

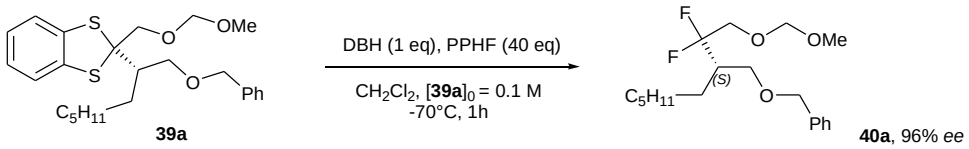
2-((benzyloxy)methyl)-2-((S)-1-(benzyloxy)octan-2-yl)benzo-1,3-dithiole (39b).



38 **39b**, 96% *ee*

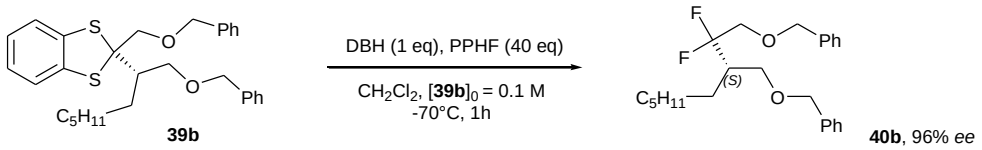
The reaction is carried out following the general procedure for the protection of OH groups using alcohol **38** and benzyl bromide as starting materials. The title compound has been isolated by flash column chromatography (Cy/DCM 4:1, 60% yield).
$[\alpha]_D^{20}$ = +23.5° (c 1.0, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.39 – 7.24 (m, 10H), 7.16 – 7.10 (m, 2H), 7.00 – 6.94 (m, 2H), 4.52 (ABq, Δδ=0.07, *J*=12.1, 2H), 4.44 (s, 2H), 3.85 (ABq, Δδ=0.04, *J*=10.2, 2H), 3.68 (dd, *J*=10.0, 4.0, 1H), 3.53 (dd, *J*=10.0, 3.9, 1H), 2.41 (m, 1H), 1.92 (m, 1H), 1.73 – 1.57 (m, 1H), 1.57 – 1.17 (m, 8H), 0.89 (t, *J*=6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.6, 138.4, 138.1, 137.4, 129.2, 128.42, 128.41, 127.8, 127.7, 127.6, 125.19, 125.15, 122.2, 122.1, 75.5, 75.4, 73.6, 73.2, 69.4, 43.8, 31.9, 30.2, 29.6, 28.3, 22.8, 14.3.
ESI-MS (m/z) : 510 $[M+NH_4]^+$, 515 $[M+Na]^+$, 531 $[M+K]^+$.

1-(((S)-2-(1,1-difluoro-2-(methoxymethoxy)ethyl)octyloxy)methyl)benzene (40a).



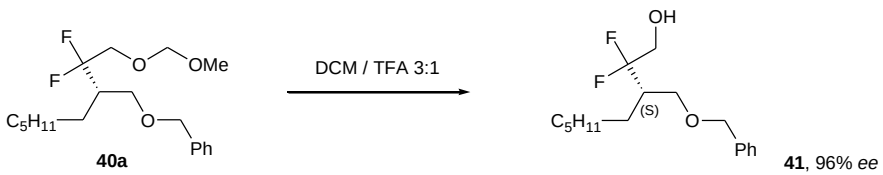
The reaction is carried out following the general procedure for the oxidative desulfurization-fluorination with benzodithiole **39a** as substrate. The title compound has been isolated by flash column chromatography (Cy/Et_2O 95:5, 16% yield).
$[\alpha]_D^{20}$ = +12.7° (c 0.9, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.39 – 7.25 (m, 5H), 4.64 (s, 2H), 4.50 (ABq, Δδ=0.02, *J*=12.1, 2H), 3.86 – 3.74 (m, 2H), 3.58 (dd, *J*=9.9, 5.8, 1H), 3.52 (dd, *J*=9.9, 4.0, 1H), 3.36 (s, 3H), 2.22 (m, 1H), 1.70 – 1.51 (m, 1H), 1.51 – 1.17 (m, 9H), 0.88 (t, *J*=6.9, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.2, 128.5, 127.81, 127.79, 123.7 (t, *J*=245.0), 96.9, 73.3, 67.8 (t, *J*=5.5), 67.4 (dd, *J*=31.0, 28.4), 55.6, 43.5 (t, *J*=21.8), 31.8, 29.6, 27.5, 25.3 (dd, *J*=4.7, 3.4), 22.8, 14.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ = -107.61 (dtd, *J*=253, 15.6, 10.9), -112.29 (dddd, *J*=253, 15.1, 14.3, 11.9).
ESI-MS (m/z) : 362 $[M+NH_4]^+$, 367 $[M+Na]^+$.

1-(((S)-3-((benzyloxy)methyl)-2,2-difluorononyloxy)methyl)benzene (40b).



The reaction is carried out following the general procedure for the oxidative desulfurization-fluorination with benzodithiole **39b** as substrate. The title compound has been isolated by flash column chromatography (Cy/DCM 4:1, 27% yield).
$[\alpha]_D^{20}$ = +16.8° (c 2.1, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.43 – 7.24 (m, 10H), 4.58 (s, 2H), 4.52 – 4.42 (m, 2H), 3.80 – 3.64 (m, 2H), 3.58 (dd, *J*=9.9, 5.7, 1H), 3.51 (dd, *J*=9.9, 4.5, 1H), 2.27 (m, 1H), 1.61 (m, 1H), 1.50 – 1.15 (m, 9H), 0.88 (t, *J*=6.9, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.3, 137.7, 128.6, 128.5, 128.0, 127.9, 127.7 (2C), 124.0 (t, *J*=245.4), 73.9, 73.3, 70.1 (dd, *J*=31.6, 29.3), 68.0 (t, *J*=5.5), 43.3 (t, *J*=21.8), 31.8, 29.6, 27.5, 25.3 (t, *J*=4.0), 22.8, 14.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ = -106.71 (ddd, *J*=254.6, 27.3, 15.3), -111.08 (ddt, *J*=254.6, 18.5, 12.3).
ESI-MS (m/z) : 391 $[M+H]^+$, 408 $[M+NH_4]^+$, 413 $[M+Na]^+$.

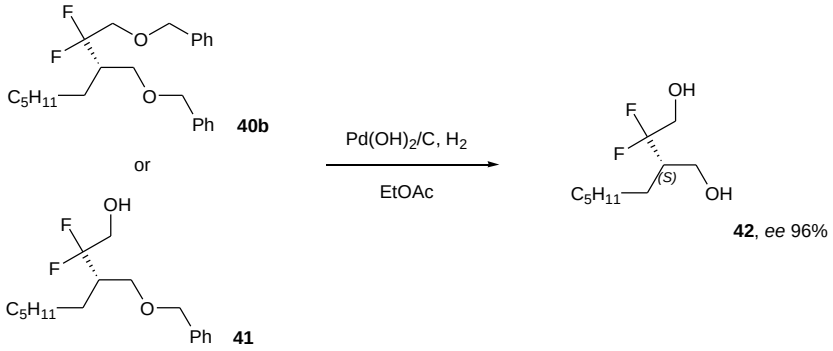
(S)-3-((benzyloxy)methyl)-2,2-difluorononan-1-ol (41).



Methoxymethyl ether **40a** is dissolved in dichloromethane without any precaution to exclude air and moisture. Trifluoroacetic acid is added and the solution is stirred for 1 hour at room temperature. The reaction complete, the solution is diluted with an excess volume of dichloromethane and a $NaHCO_3$ aqueous solution. The organic layer is separated and extracted three times with dichloromethane. The collected organic layers are washed with

brine and dried over Na_2SO_4. Concentration under reduced pressure affords the title compound in quantitative yield.
$[\alpha]_D^{20}$ = +10.3° (c 0.7, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.40 – 7.28 (m, 5H), 4.53 (ABq, Δδ=0.05, *J*=11.7, 2H), 3.82 (dd, *J*=12.8, 7.0, 1H), 3.72 (dd, *J*=12.8, 6.8, 1H), 3.57 (dt, *J*=10.1, 2.9, 1H), 3.52 (ddd, *J*=10.1, 8.0, 0.4, 1H), 3.22 (br s, 1H), 2.22 (m, 1H), 1.64 (m, 1H), 1.42 – 1.18 (m, 9H), 0.88 (t, *J*=6.7, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.0, 128.8, 128.4, 128.1, 124.0 (dd, *J*=246.9, 245.0), 73.9, 68.0 (dd, *J*=7.2, 3.7), 63.7 (dd, *J*=37.3, 29.5), 43.7 (t, *J*=23.3), 31.8, 29.4, 27.6, 24.4 (t, *J*=4.2), 22.7, 14.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ = -106.50 (ddddd, *J*=254.1, 24.2, 14.2, 7.5, 2.6), -116.11 (ddt, *J*=254.1, 14.1, 6.8).

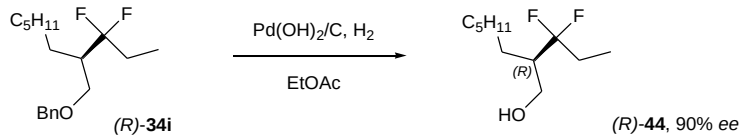
(S)-2,2-difluoro-3-hexylbutane-1,4-diol (42).



A catalytic quantity of $Pd(OH)_2/C$ is added to a solution of benzyl ether **40b** or **41** in ethyl acetate (0.1 M). The reaction mixture is placed under hydrogen at atmospheric pressure and room temperature and is stirred overnight. After completion, the mixture is filtered on celite and the filtrate is concentrated under reduced pressure to afford the diol **42** in quantitative yield. If necessary, the title compound can be purified by flash column chromatography (Cy/AcOEt 4:1).
$[\alpha]_D^{20}$ = +17.4° (c 0.4, $CHCl_3$) ; reported value : $[\alpha]_D^{20}$ = +20.4° (c 1, $CHCl_3$, 99% *ee*).[91]

3.7.10. Synthesis of *gem*-difluoro analogues of *(R)* and *(S)*-arundic acid.

(R)-2-(1,1-difluoropropyl)octan-1-ol (R)-44.

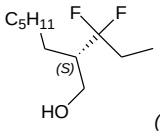


A catalytic quantity of $Pd(OH)_2/C$ is added to a solution of benzyl ether *(R)*-**34i** in ethyl acetate (0.1 M). The reaction mixture is placed under hydrogen at atmospheric pressure and room temperature and is stirred overnight. After completion, the mixture is filtered on celite and the filtrate is concentrated under reduced pressure to afford the alcohol *(R)*-**44** in quantitative yield. If necessary, the title compound can be purified by flash column chromatography (Cy/DCM 9:1).
$[\alpha]_D^{20}$ = -14.0° (c 0.55, $CHCl_3$).

[91] D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875 – 10877.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 3.78 (m, 2H), 2.02 – 1.80 (m, 3H), 1.62 (br s, 1H), 1.53 – 1.37 (m, 3H), 1.37 – 1.21 (m, 7H), 1.02 (t, *J*=7.5, 3H), 0.88 (t, *J*=6.6, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 127.5 (t, *J*=243.4), 60.7 (t, *J*=5.1), 46.6 (t, *J*=21.7), 31.8, 29.6, 28.1 (t, *J*=26.2), 27.6, 25.4 (t, *J*=4.1), 22.8, 14.2, 6.2 (t, *J*=5.9). ^{19}F NMR (377 MHz, $CDCl_3$) δ = -103.55 (dm, *J*=244.4), -104.96 (dm, *J*=244.4).
ESI-MS (m/z) : 226 $[M+NH_4]^+$, 231 $[M+Na]^+$.

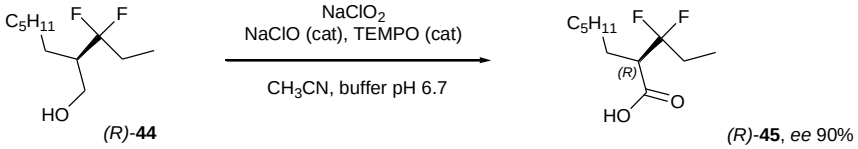
(S)-2-(1,1-difluoropropyl)octan-1-ol (S)-44.



(S)-**44**, 96% *ee*

$[\alpha]_D^{20}$ = +15.7° (c 0.7, $CHCl_3$).
NMR data and ESI-MS analysis identical to those of *(R)*-**44**.

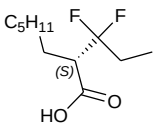
(R)-2-(1,1-difluoropropyl)octanoic acid (R)-45.



(R)-**44** *(R)*-**45**, *ee* 90%

Alcohol *(R)*-**44** (0.1 mmol) is dissolved in acetonitrile. A solution of $NaClO_2$ (0.2 mmol, 2 eq.) and TEMPO (0.025 mmol, 0.25 eq.) in 0.1 mL of water ; 0.2 mL of 0.67 M sodium phosphate buffer (pH 6.7) ; and a solution of diluted NaOCl (0.025 mmol, 0.25 eq.) are added. The mixture is stirred at room temperature for 5 hours and is then cooled to 0°C. Diluted $NaHCO_3$ aq. were added until pH 8. Na_2SO_3 (0.22 mmol) is added and the mixture is stirred for 30 minutes. The organic layer is separated and the aqueous layer is extracted with dichloromethane. HCl (0.1 M) is added to the aqueous phase until pH 2 and the aqueous layer is extracted again with dichloromethane. The collected organic layers are washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The *gem*-difluoro analogue *(R)*-**45** is isolated by flash column chromatography (Cy/EtOAc 2:1, 40% yield).
$[\alpha]_D^{20}$ = -10.3° (c 0.6, $CHCl_3$).
^{1}H NMR (401 MHz, $CDCl_3$) δ = 2.92 (dtd, *J*=14.3, 10.9, 3.7, 1H), 2.14 – 1.77 (m, 3H), 1.69 (m, 1H), 1.42 – 1.23 (m, 8H), 1.05 (t, *J*=7.4, 3H), 0.88 (t, *J*=6.8, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.5 (t, *J*=6.2), 123.3 (t, *J*=246.3), 52.6 (t, *J*=25.9), 31.6, 29.1, 27.9 (t, *J*=25.4), 27.5, 26.5 (t, *J*=3.8), 22.7, 14.2, 6.0 (t, *J*=5.5). ^{19}F NMR (377 MHz, $CDCl_3$) δ = -103.14 (dddd, *J*=245.9, 23.7, 12.7, 11.0), -104.02 (dddd, *J*=245.9, 24.2, 13.9, 12.0).
ESI-MS (m/z) : 240 $[M+NH_4]^+$, 245 $[M+Na]^+$, 261 $[M+K]^+$, 445 $[2M+H]^+$.

(R)-2-(1,1-difluoropropyl)octanoic acid (R)-45.



(S)-**45**, *ee* 96%

$[\alpha]_D^{20}$ = +8.2° (c 0.6, $CHCl_3$).
NMR data and ESI-MS analysis identical to those of *(R)*-**45**.