SCUOLA DI DOTTORATO "VITO VOLTERRA"

PhD in Chemical Sciences- XXXII Cycle

Development of new *green* strategies based on Brønsted and Lewis acid catalysis in organic synthesis

Achille Antenucci
Matriculation number 1398379

Thesis Advisor: Dr. Riccardo Salvio

Ph.D. Program Coordinator: Prof. Osvaldo Lanzalunga
Academic year 2018-2019

Research carried out with the contribution of CNR Institute for Biological Systems
Istituto per i Sistemi Biologici CNR-ISB - Sede di Roma - Meccanismi di Reazione

Summary

"Don't depend too much
on anyone in this world,
because even your own shadow
leaves you when you are
in the darkness"

Ibn Taymiyyah

To my grandpa Achille

Chapter 1

Introduction

1.1 Green chemistry: a mindset of chemists

Environmental protection is one of the greatest themes of the XXI century. For several decades, starting from the first industrial revolution, humanity did not take into consideration the impact that technological innovations could have on global climate, atmosphere, flora and fauna, to the point that many side aspects are being considered just very recently. For what concerns chemistry, its contribution has been not negligible, from massive consumption of fossil fuel and relative consequences, to different environmental disasters, many of which were depicted by the american author and biologist Rachel Carson, in her influential masterpiece *Silent Spring*.[1,2] After all, the term "green chemistry" starts to appear in the literature only in the early 1990's,[3] even before its current formal and exhaustive definition, given by Paul T. Anastas and John C. Warner in 1998.[4] Anastas and Warner formulated a list of 12 principles, that constitute the most complete definition of green chemistry. In fact, it cannot be exhaustively described in a few words, although a suitable way to shortly depict it is probably as a mindset of people doing chemistry. Among the various areas of modern chemistry, organic chemistry is perhaps the one which shall take into account this aspect the most: synthesis of organic compounds leads a chemist to think about efficiency (*e. g.* yield of a reaction, minor number of steps as possible), possibility of employing non destructive analytical techniques in order to recover the sample, risk prevention in handling hazardous reactants and waste disposal. The relevance assumed from some of these points, in particular those connected to safety measures for the operator and for the environment, is constantly growing, also thanks to the progress that mankind has made in other areas of science, such as biology and medicine, so that nowadays even the law is stricter about what can be done or not under certain conditions in a chemical laboratory as well as in an industrial plant. Green chemistry concerns all these items, and every researcher should try to think to the consequences of the chemistry he is planning and performing. In practice, this means to try to respect the 12 principles of green chemistry as much as possible. It is worth mentioning that not all the 12 principles concern specifically organic synthesis and that chemistry developed in the past cannot be neglected at all; this means that sometimes is not possible to fully respect all the principles and a compromise is needed. For instance, real time analysis for prevention of pollution (11th principle) expects one to develop a protocol in which an integrated system for the analysis of waste products is included, which is more or less specifically referred to industrial and analytical chemists and to chemical engineers rather than to synthetic organic chemists, who will perhaps not strictly respect this principle while doing their job. On the other side, willing to realize a cross coupling reaction in the laboratory, for instance, employment of toxic transition metals is unavoidable, and some of the 12 principles will not be followed. To summarize and conclude, green chemistry concerns the constant attempt to reduce any risk from chemistry, both for the environment and for those who have to run the operations. In any case, the best way to deeply understand is to familiarize with some fundamental concepts and with the principles themselves, including practical examples of their application from the literature.

1.2 Useful concepts

In order to give chemists some practical instruments to evaluate a chemical process with respect to green chemistry, a couple of metrics have been defined over the last decades. We are dealing with numeric parameters, whose function is to to quantify the efficiency or environmental performance of a given chemical process, so that further upgrades can be precisely evaluated. Not less important is the will, through green chemistry metrics, to spread adoption of green chemistry technologies in industrial plants. Numerous metrics have been formulated over the years, engendering discussions about clearness, simplicity, objectivity and general applicability.[5] In spite of everything, these items are very helpful in understanding problems and issues of a green mindset.

a) Effective mass yield (EMY)

Effective mass yield is the mass of useful products relative to the mass of non-benign reagents employed in the synthesis, expressed in percentage. It was defined by Hudlicky in 1999,[6] and it can be expressed in the form of equation 1.1.

$$EMY(\%) = \frac{mass\ of\ products}{mass\ of\ non{-}benign\ reactants}\ x\ 100 \qquad (1.1)$$

Since the definition of benign substances is somehow subjective, thus giving possibilities of criticism, the definition given by Hudlicky is here reported: benign are "those by-products, reagents or solvents that have no environmental risk associated with them, for example, water, low-concentration saline, dilute ethanol, autoclaved cell mass, etc.".

b) Sheldon Environmental Factor (E-factor)

E-factor was the very first general green chemistry metric. It was defined by Roger A. Sheldon in 1994 and is the simple ratio between the total mass of waste produced by a given chemical process and the mass of the desired products (equation 1.2).[7]

$$E\text{-}factor = \frac{total\ mass\ of\ waste}{mass\ of\ desired\ products} \qquad (1.2)$$

According to this simple definition, formalized in equation 2, E-factor is extremely straightforward to apply to any reaction or process. In fact, it is still nowadays one of the most popular and employed metrics: higher E-factor corresponds to higher environmental

impact, that means major possibility of intervention to improve the protocol by reducing waste or enhancing reaction yield and/or selectivity. Nevertheless, to a deeper analysis, this simplicity makes it extremely flexible and incomplete at the same time. Features of the system shall be clearly defined before making any estimation or calculation of total mass waste, whose results could profoundly change upon different boundary conditions. For instance, recycling of solvents and catalyst reduce the total waste amount, and a proper way to take into account these factors should be considered a priori. However, once yield, stoichiometry, catalyst and solvent recycle have been incorporated in the calculation, E-factor is an excellent metric. As a matter of fact, Sheldon himself calculated E-factors for various industries and, according to this parameter, pharmaceutical industry (E-factor = 25-100) has an environmental impact up to 1000 times higher than oil refining industry (E-factor = 0.1), for instance. The reason is that, despite a higher amount of waste (10^5-10^7 against 2.5 × 10^2-10^5 tons per year), oil refining has also a higher global yield in useful products (10^6-10^8 against 10–10^3 tons per year).[8] This is due to the possibility of oil refining industry to recover and reuse byproducts which would normally be discharged, while pharmaceutical sector is more focused on obtaining products in compliance with standard quality parameters.

c) Carbon Efficiency (CE)

Carbon efficiency is the percentage of carbon that ends up in the useful products, according to equation 1.3.

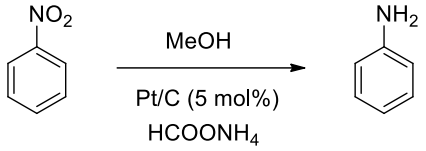
$$CE(\%) = \frac{C\ amount\ in\ products}{total\ C\ amount\ in\ reactants}\ x\ 100 \qquad (1.3)$$

This metric takes into account the stoichiometry of reactants and products, thus being simple enough for application in the pharmaceutical industry, where the key target is the construction of carbon skeletons of biologically active molecules.

d) EcoScale

The EcoScale metric was proposed by Van Aken in 2006 for the numeric evaluation of the effectiveness of a synthetic reaction.[9] Like the yield-based scale, the EcoScale gives a score from 0 to 100, taking into account several items, like yield, cost, safety, technical set-up, energy required and purification techniques employed. It is obtained by assigning a value of 100 to an ideal reaction defined as "Compound A (substrate) undergoes a reaction with (or in the presence of) inexpensive compound(s) B to give the desired compound C in 100% yield at room temperature with a minimal risk for the operator and a minimal impact on

the environment", and then subtracting penalty points for non-ideal conditions. These penalty points take into account both the advantages and disadvantages of all the items considered by the EcoScale. At the end, penalty points are subtracted from 100 and the result serves to classify the reaction as inadequate (< 50), acceptable (from 50 to 75) or excellent (> 75). To give a practical example, the reduction of nitrobenzene to aniline is taken into consideration (scheme 1.1).[10]



Scheme 1.1 *Reduction of nitrobenzene to aniline by Gowda and Mahesh*

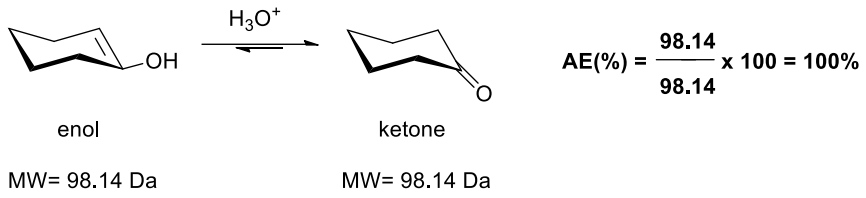
In relation to this synthetic protocol and according to a precise classification, penalty points are assigned to the employment of methanol (toxic and flammable, -10), nitrobenzene (toxic and dangerous for the environment, -10), Pt on carbon (flammable and costly, -8), yield of 90% (-5) and washing with brine (waste, -3). The total amount of penalty points is 36, which means that reaction is classified as acceptable (64 points), according to the EcoScale.

e) Atom economy (AE)

Atom economy is a numerical parameter, expressed in percentage, whose significance is the degree of atom retain from reagents to desired products, a sort of Lavoisier conservation of mass law on atomic scale. In this, it is different from other green chemistry metrics, most of which were designed to measure process improvements. It was introduced by Barry Trost in 1995.[11] It can be resumed in equation 1.4.

$$AE(\%) = \frac{\Sigma\ MW\ of\ desired\ products}{\Sigma\ MW\ of\ reactants}\ x\ 100 \qquad (1.4)$$

Reagents that do not end up in the final product (*e.g.* catalysts, reagents used for the work-up of the reaction, solvents) must not be taken into account in this calculation. The atom economy percentage is a synthetic measure of reaction intrinsical "green-ness", and it can be useful in the early stage design of an industrial synthetic process or of a multi-step total synthesis. An example of reaction having atom economy of 100% is a generic isomerization, like keto-enol tautomerization (scheme 1.2).



Scheme 1.2 *A keto-enol tautomerization, a reaction intrinsically having atom economy of 100%*

f) Reaction mass efficiency (RME)

Reaction mass efficiency (RME) is a green chemistry metric that includes atom economy, chemical yield and stoichiometry. For a generic reaction A + B → C, RME is calculated (in percentage) as follows:

$$RME(\%) = \frac{MW\ of\ C}{MW\ of\ A + (MW\ of\ B\ x\ molar\ ratio\ \frac{B}{A})}\ x\ 100 \quad (1.5)$$

Or, more simply:

$$RME(\%) = \frac{Mass\ of\ C}{Mass\ of\ A + Mass\ of\ B}\ x\ 100 \quad (1.6)$$

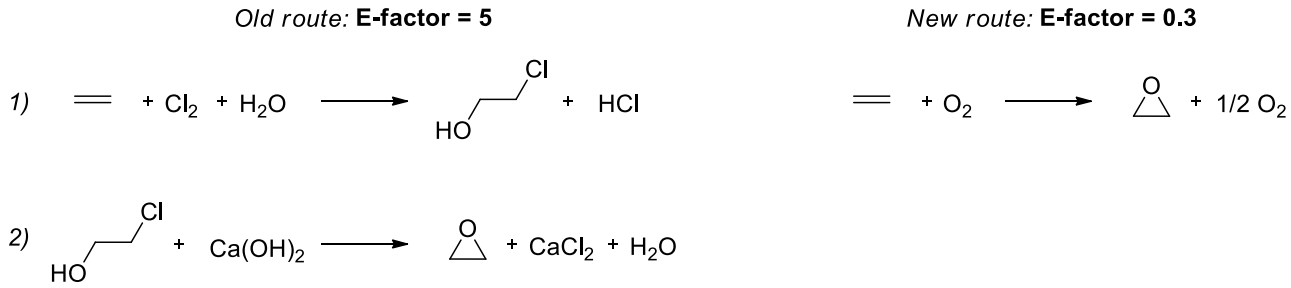
This metric is very similar to carbon efficiency in measuring how much a reaction is clean. Nevertheless, process parameters are not taken into account, so RME alone (and even more so atom economy) is not an exhaustive green chemistry metric. For instance, atom economic reactions carried out in non-green solvents, with hazardous reagents or at very low/ very high temperature (with consequential energy comsumption) make the process less attractive in a green perspective.

1.3 The twelve principles of green chemistry

The twelve principles of Green chemistry, introduced by Paul T. Anastas and John C. Warner in 1998,[4,12] represent not only a guiding framework for the design of new chemicals and reactions or processes, but also the best definition of green chemistry. They were recently summarized by Poliakoff into the memorable acronym PRODUCTIVELY.[13] In succession, there is the principles list, with an explanation related to their application in organic synthesis and practical examples for each of them.

1) Prevention

The first principle could better be resumed in the sentence: it is better to prevent the production of waste than to clean up or treat it after it has been produced. It is interesting to notice how both the first principle and the first green chemistry metric concern prevention and disposal of waste; in fact, Sheldon E-factor is nothing but the numerical measure of respect of a given reaction or process towards the first principle. The lower is the E-factor value, the lower is the environmental impact, and thus lowering the E-factor of a chemical process can be considered an improvement of its green-ness. An example is the synthesis of ethylene oxide, originally prepared through a chlorohydrin intermediate with E-factor = 5 (5 kg of waste produced for each kg of product, not taking into consideration chlorine-containing wastewater).[8,14] The development of a new synthetic route based on the employment of molecular oxygen dropped the E-factor down to 0.3, eliminating at the same time the dangerous use of chlorine and its wastewater as well (scheme 1.3).[15]



Scheme 1.3 *Route improvement for the synthesis of ethylene oxide*

However, waste can have many forms having different impact on the environment, depending on toxicity, amount and release,[14b] and it can even be recycled in order to transform waste material into differently useful products and decrease the E-factor, like in the processes for the production of biofuel.[16]

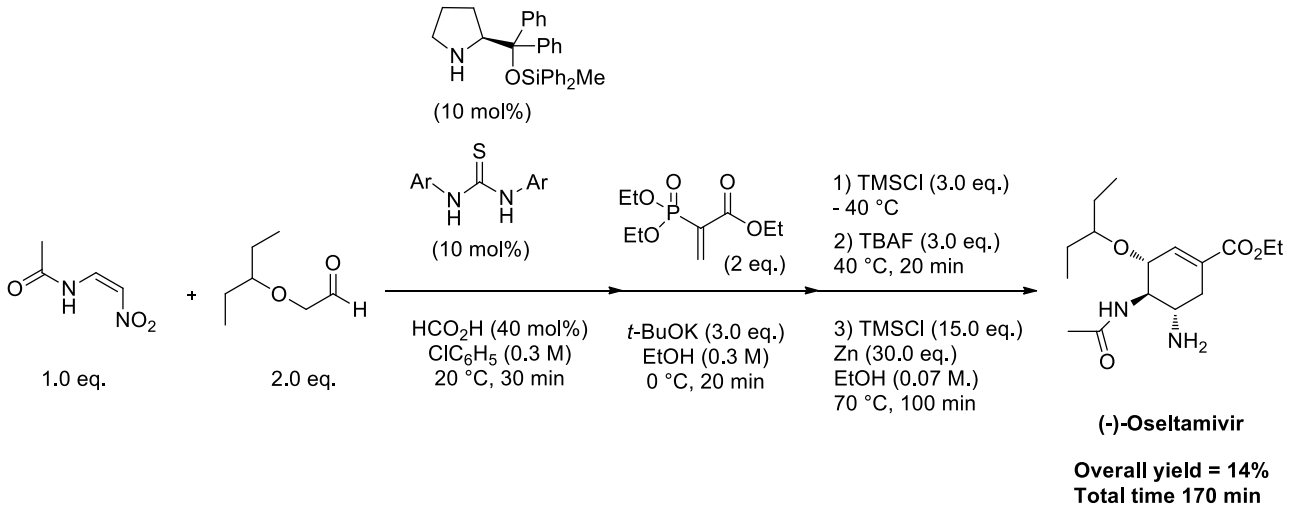
2) Atom Economy

Also in the case of the second principle, a corresponding green chemistry metric, even having the same name, can be found. Based on the definition of Atom Economy given by Barry Trost, the ideal reaction is that in which all the atoms of the reactants are incorporated in the products. For chemical reactions, this is an intrinsical feature, so certain reaction mechanisms lend themselves to green applications, while others do not. Once other details concerning work-up, solvents and other safety measures have been properly fixed, these reactions can truly lead to perfectly green protocols. Some examples of reactions having an

atom economy of 100% are isomerizations, cycloadditions, hydration or alkoxylation of alkenes and alkynes (see chapter 2).

3) Less hazardous chemical synthesis

A non hazardous chemical synthesis is that in which the use or generation of substances which pose concerns for the environment or human health is minimized. This includes the production of significative amounts of waste. To respect the third principle, multi-step synthetic routes should be designed employing atom-economic reactions, when possible, and avoiding the use of dangerous reagents, toxic solvents or catalysts, etc. One-pot, cascade and tandem reactions can minimize the generation of undesired waste and manipulation of potentially dangerous crudes,[17] while novel strategies like C-H direct activation are conceived with the aim of reducing number of steps or byproducts (in particular halogen derivatives) deriving from nucleophilic substitutions.[18] In scheme 1.4, pot and time economy multigram scale synthesis of (-)-Oseltamivir by Hayashi is reported.[19] This synthetic route could obviously be improved (overall yield = 14%); nevertheless, it represents a significative step forward, with respect to the over 60 procedures previously reported.



Scheme 1.4 *Hayashi's one-pot improved route for the synthesis of (-)-Oseltamivir on a gram scale*

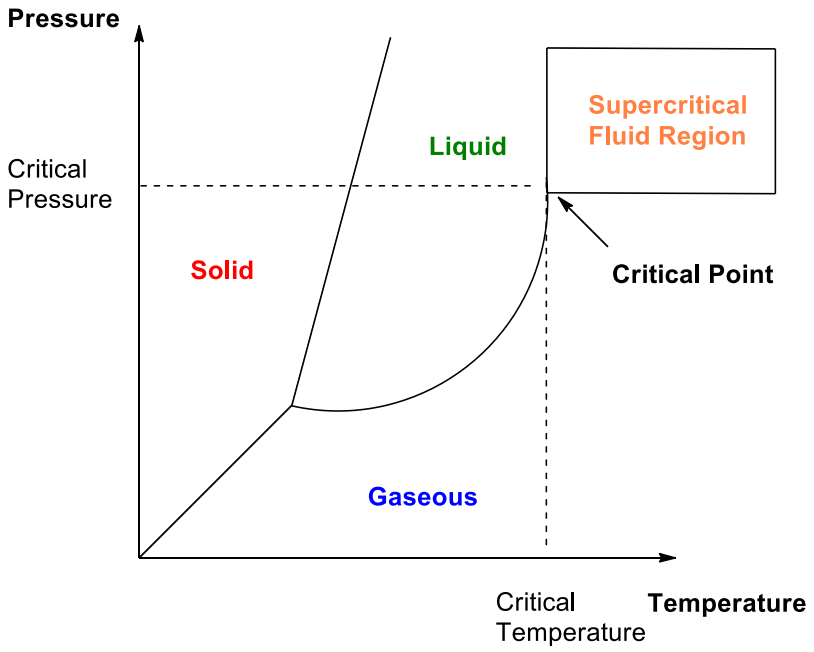
4) Designing safer chemicals

Chemical products should be designed to preserve efficacy of the function while reducing toxicity. Pioneeristic work by Ariëns in 1984[20] and by Garrett and DeVito in 1996 showed that designing safer molecules is not utopistic.[21] Nowadays, toxicologic and clinical studies have made the elaboration of design strategies possible, so, for instance, there are computational models which can relate structure to function, while designing new drugs;

to this purpose, one of the most challenging technologies, in our century, is protein computational design.[22]

5) Safer solvents and auxiliaries

Auxiliary substance is a term that may refer to various chemicals whose use is often required in a chemical process: protecting groups, solvents, separation agents, etc. According to the 5th principle, their use should be made unnecessary, whenever possible and, when not, innocuous. Apart from protecting groups, whose introduction and removal goes against the principle of atom economy, and separation agents, whose possible toxicity has already been discussed, this principle mainly focuses the attention on solvents, which represent the majority of waste material.[23] For this reason, most of green chemistry research is currently concentrated on the problem of eliminating solvents or choosing more benign and safer ones, being non toxic, non flammable and/or non corrosive.[24] Green alternatives to classical solvents refer to neat reactions,[25] or to reaction carried out in water,[26] Super Critical fluids (SCFs)[27] or ionic liquids.[28] The ideal situation would be to have a solventless system, since energy, efforts and other chemicals are often required for the work up and may produce additional waste. When this is not possible, water can be used as a "universal solvent", being non toxic, non flammable and ideal for biocatalytic reactions; however, in this case a little weakness is due to its high boiling boint, which requires a considerable amount of energy for solvent removal. From this perspective, a very good alternative is represented by SCFs, which exist as liquid just over certain conditions of pressure and temperature (scheme 1.5).

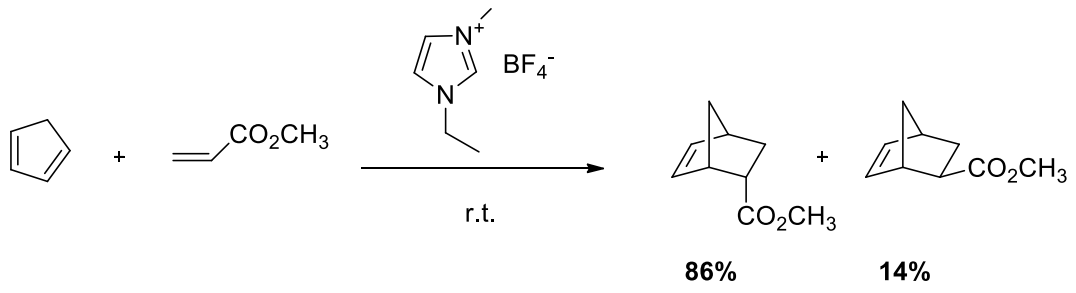


Scheme 1.5 *Pressure vs Temperature phase diagram showing the supercritical region*

Common SCFs are generated by acetone, methane, methanol, ethanol and even water; however, the most commonly occurring SCF is supercritical carbon dioxide (sCO_2). The reason for preference towards CO_2, among all the substances that can generate SCF, is due to its natural occurrence, its low cost and the easiness of removal: in fact, simple reduction of pressure and temperature to atmospheric conditions turns CO_2 newly into a gaseous phase, which does not require any energetic effort nor produces waste. Apart from applications in organic synthesis,[29] sCO_2 has also being used to replace chlorinated solvents in coffee grains decaffeination and in dry cleaning.[30] Finally, ionic liquids are simply ionic salts, whose natural phase at ambient temperature and atmospheric pressure is liquid. Moreover, they are non flammable and have no vapor pressure, but can sometimes be particularly expensive and unconvenient.

6) Design for energy efficiency

Coherently with the aim of green chemistry, excessive energetic expenses can be considered waste as well as undesired byproducts and discharge material deriving from reaction work-up, for example. In fact, the rapid depletion of petroleum and other fossil fuels feedstocks, prompted scientists (engineers and chemists in particular) to find renewable, more environmental-friendly and less expensive forms of energy.[31] Accordingly, in a broad sense, design for energy efficiency may refer to chemical processes for generating electricity: solar cells, hydrogen fuel cells, wind power, hydro power, derivation of biofuels and geothermal energy. In organic synthesis, this simply means that reactions requiring heating or continuous cooling (cryostat) are not preferable, and ideal reactions should run at room temperature, if possible. A practical example of green reaction which, among the others, respects also this principle, is the Diels-Alder cycloaddition between cyclopentadiene and methyl acrylate, which has been investigated in ionic liquids by Welton and co-workers in 1997.[32] Different ionic liquids were tested by the authors, but the stereoselective protocol proved to be particularly efficient in 1-ethyl-3-methylimidazolium tetrafluoroborate, a ionic iquid often employed in cellulose processing (scheme 1.6).



Scheme 1.6 *Stereoselective Diels-Alder cycloaddition in 1-ethyl-3-methylimidazolium tetrafluoroborate at room temperature*

7) Use of renewable feedstocks

Along the line of what has already been said about energy efficiency, even in the case of starting materials, it is important to prefer bio-mass, derived from natural organisms, which includes agricultural residues, crops, food, etc., in order not to exhaust natural gas and petroleum feedstocks.[33] Examples of renewable bio-mass used in organic synthesis is represented by chitosan, cellulose, glycerol, lactic acid, sugars, alkaloids. In particular, an important class of naturally occurring compounds is those of chiral natural organic molecules, generally known as "chiral pool", and its role in asymmetric synthesis has become very important, in particular in the last 20 years (see chapter 3).

8) Reduce derivatives

The use of protecting groups is ubiquitarious in organic synthesis.[34] Covalent derivatization occurs very often for various reasons: if the derivative is more easily detectable with an analytical technique (*e.g.* derivatization of a non UV-vis active scaffold with a cromophore), to introduce chirality on a target molecule (3rd generation asymmetric synthesis) or to reduce its volatility (introduction of high-weight protecting groups), etc. Nevertheless, this approach inevitably increases the total amount of waste of the overall process. To this purpose, a notable example of an innovative alternative to covalent derivatization has been given by John C. Warner, one of the pioneers of green chemistry. While Warner was a researcher at Polaroid, he was trying to release hydroquinones (developer for instant photographies) at high pH values. Rather than proposing the derivatization with a base-labile covalent protecting group, he devised a new co-crystallization process of hydroquinones with bis-(N,N-dialkyl)terephthalamides, which yielded a complex product having enhanced solubility in water, with respect to hydroquinones themselves.[35] Nowadays, non-covalent derivatization (NCD) is a well known technique that has been also extended to industry to reduce energy and waste.[36]

9) Catalysis

In the optical of pursuing green processes, organic synthesis benefits from the employment of a catalyst for different reasons. The first reason is that the catalyst lowers the activation barrier of the reaction, which will then require less energy to occur, in its presence. The second reason is that, in the presence of good catalysts, reactions run selectively, minimizing the formation of undesired byproducts. Furthermore, the employment of a catalyst avoids the use of stoichiometric reagents, which not only decreases the total amount of waste, but also reduces the risk, in the case of hazardous reagents (*e. g.* catalytic hydrogenation). Two approaches to catalysis that often naturally cover more than one requirement from the 12 principles are biocatalysis[37] and organocatalysis (see chapter 3).

10) Design for degradation

Talking about organic synthesis, the 10th principle expresses the necessity of designing synthetic routes in which products and possibly formed byproducts do not persist in the environment, but biodegradate instead into innocuous species. This is the reason why branches of organic synthesis like organocatalysis and biocatalysis could gain some success, since, differently from what often happens in organometallic chemistry, reactions are promoted by perfectly ecosustainable molecules.

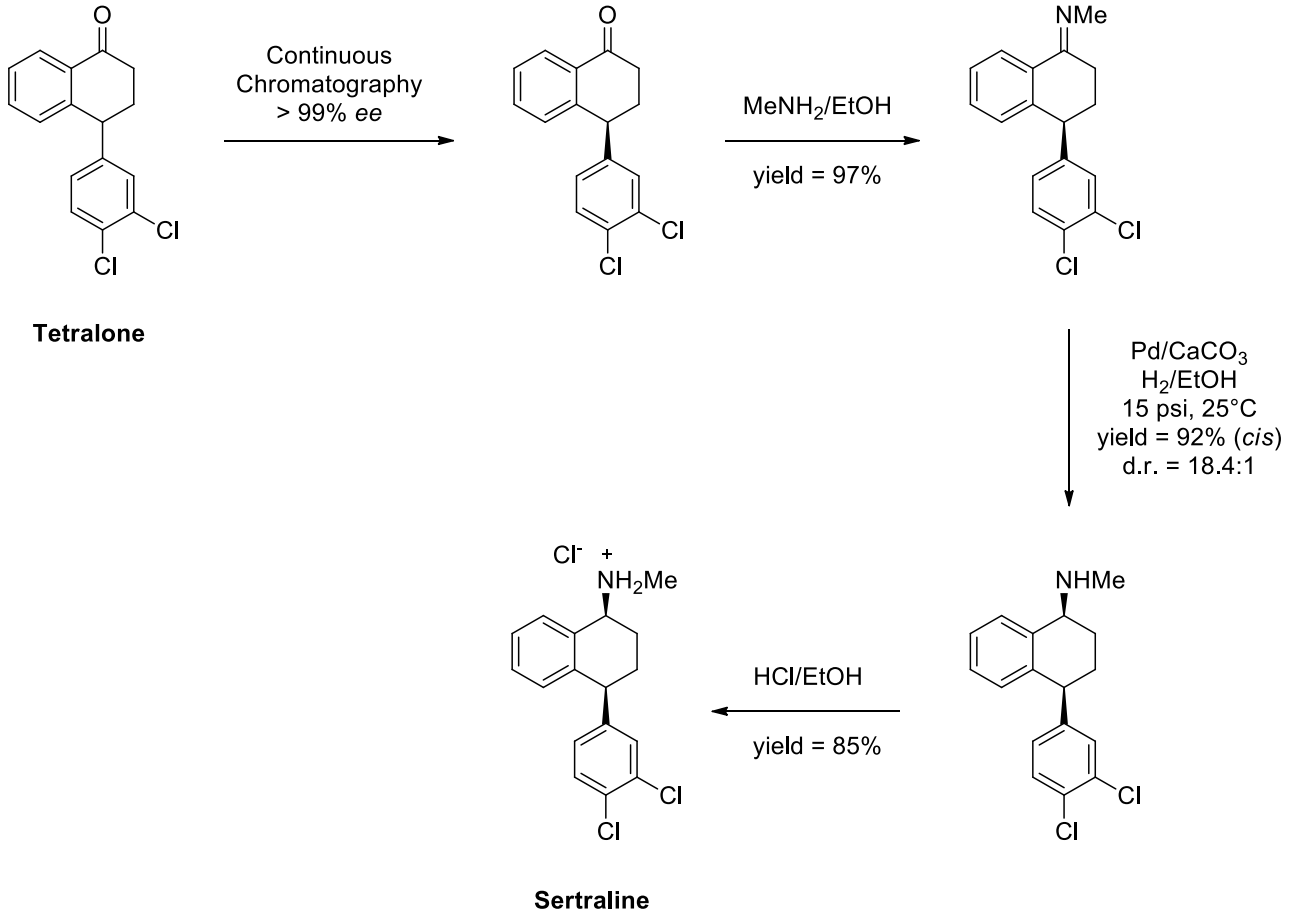
11) Real-time analysis for pollution prevention

This principle is more related to in-line analytical technologies used to monitor the possible formation of hazardous substances and the reaction conditions, as part of industrial plants. For synthetic organic chemistry, with some forcing to the original definition of the 11th principle, a good real time analysis may refer to the preferential employment of non-destructive techniques to monitor the reaction, in order to reduce waste. Actually, every standard procedure control allows recovery of the sample after the analysis (NMR, HPLC/UV-vis spectroscopy, IR spectroscopy) or, if destructive, is performed on so exiguous amounts of sample that talking about waste production would truly be an exaggeration (MS).

12) Inherently safer chemistry for accident prevention

Talking about atom economy, some examples of reactions intrinsically being respectful towards the 3rd principle have been given. The opposite way, there are certain protocol intrinsically not respectful towards not only the 3rd principle, but towards the green chemistry aim in general and so, in particular, towards the 11th principle. When possible, alternative reactions or even alternative routes should be taken into account, in order to avoid to run some risks, in compliance with the conditions of the laboratory or the industrial plant in which the reactions are carried out, and to avoid generation of waste and pollution in general. In 1994, the "Chemical accident prevention and the clean air act amendments of 1990" were promulgated, stating that identifying and assessing hazards is the first form of risk prevention.[38] Two examples will be mentioned, the first concerning replacement of a reaction, and the second regarding the design of a more benign synthetic route. The Wittig reaction[39] and related variations (Horner-Wadsworth-Emmons, [40] Still-Gennari[41]) are useful protocols for the synthesis of alkenes, in which electrophilic carbonylic compounds (aldehydes or ketones) react with nucleophilic phosphorous ylides or phosphonate carbanions, giving the desired alkene, but inevitably generating at the same time a phosphine oxide (toxic for humans and for the environment) as byproduct. On the contrary, olefin methatesis between two carbonylic compounds does not produce a large amount of

waste, nor toxic byproducts, and thus it can be considered a greener alternative.[42] In 2002, Pfizer developed a green synthetic route for antidepressive sertraline, avoiding the use and the manipulation of DCM, tetrahydrofuran, toluene and hexane, with respect to the previous industrial procedure.[43] Furthermore, the new protocol avoided all the work-up steps, except for the last, by carrying out the reaction one-pot in ethanol (scheme 1.7).



Scheme 1.7 *Pfizer one-pot synthetic route for sertraline*

1.4 Bibliography

[1] [a] Paull, J. *SAGE Open* **2013**, *3*, 1; [b] Glausiusz, J. *Discover Magazine* **2007**, 34.

[2] Carson, R. *Silent Spring*, Houghton Mifflin Company, **1962**.

[3] Linthorst, J. A. *Found. Chem.* **2010**, *12*, 55.

[4] Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*, Oxford University Press, New York, **1998**.

[5] Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.* **2002**, *4*, 521.

[6] Hudlicky, T.; Frey, D. A.; Koroniak, L.; Claeboe, C. D.; Brammer, L. E. Jr. *Green Chem.* **1999**, *1*, 57.

[7] Sheldon, R. A. *Chemtech* **1994**, 38.

[8] Sheldon, R. A. *Green Chem.* **2007**, *9*, 1273.

[9] Van Aken, K.; Strekowski, L.; Patiny, L. *Beilstein J. Org. Chem.* **2006**, *2*, 3.

[10] Gowda, D. C.; Mahesh, B. *Synth. Commun.* **2000**, *30*, 3639.

[11] Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259.

[12] Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301.

[13] [a] Tang, S. L. Y.; Smith, R. L.; Poliakoff, M. *Green Chem.* **2005**, *7*, 761; [b] Tang, S.; Bourne, R.; Smith, R.; Poliakoff, M. *Green Chem.* **2008**, *10*, 268.

[14] [a] McClellan, P. P. *Ind. Eng. Chem*. **1950**, *42*, 2402; [b] Sheldon, R. A. *Chem. Commun*. **2008**, 3352.

[15] Kilty, P. A.; Sachtler, W. M. H. *Catal. Rev.* **1974**, *10*, 1.

[16] [a] Pasquon, I.; Zanderighi, L. in *La Chimica Verde, Le utilizzazioni dei prodotti vegetali e le biotecnologie*, Ulrico Hoepli Ed., Milano, **1987**; [b] Centi, G.; Van Santen, R. A. in *Catalysis for Renewables, From Feedstocks to Energy Production*, Wiley-VCH Verlag GmbH & Co., KGaA, Weinheim, **2007**; [c] Khanal, S. K.; Rasmussen, M.; Shrestha, P.; Leeuwen, H. V.; Visvanathan, C.; Liu, H. *Water Environ. Res.* **2008**, *80*, 1625; [d] Cavani, F.; Centi, G.; Perathoner, S.; Trifirò, F. in *Sustainable Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co., KGaA, Weinheim, **2009**.

[17] [a] Nicolau, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Comm.* **2003**, 551; [b] Nicolau, K. C. Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; [c] Parsons, P. J.; Pelkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195; [d] Padwa, A. *Pure Appl. Chem.* **2004**, *76*, 1933; [e] Hayashi, Y. *Chem. Sci.* **2016**, *7*, 866; [f] Hayashi, Y.; Koshino, S.; Ojima, K.; Kwon, E. *Angew. Chem. Int. Ed.* **2017**, *56*, 11812.

[18] [a] Murai, S. *Activation of Unreactive Bonds and Organic Synthesis* in *Topics in Organometallic Chemistry*, Springer-Verlag, Berlin Heidelberg, **1999**, vol. 3; [b] Goldberg, K.; Goldberg, A. S. *Activation and Functionalization of C-H Bonds*, ACS Symposium Series, Oxford University Press, **2004**; [c] Herrerias, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546; [d] Yu, J.-Q.; Shi, Z. *C-H Activation* in *Topics of Current Chemistry*, Springer Ed., New York, **2010**.

[19] Hayashi, Y.; Ogasawara, S. *Org. Lett.* **2016**, *18*, 3426.

[20] Ariëns, E. J. *Drug Metab. Rev.* **1984**, *15*, 425.

[21] DeVito, S. C.; Garrett, R. L. in *Designing Safer Chemicals: Green Chemistry for Pollution Prevention*, ACS Symposium Series, Washington DC, **1996**, vol. 640.

[22] Kuhlman, B.; Dantas, G.; Ireton, G. C.; Varani, G.; Stoddard, B. L.; Baker, D. *Science* **2003**, *302*, 1364.

[23 a] Curzons, A. D.; Constable, D. J. C.; Mortimer, D. N.; Cunningham, V. L. *Green Chem.* **2001**, *3*, 1; [b] Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.* **2002**, *4*, 521.

[24 a] Anastas, P. T. in *Clean Solvent Alternative Media for Chemical Reactions and Processing*, ACS Symposium series 819, Washington DC, **2002**, ch. 1; [b] DeSimone, J. M. *Science*, **2002**, *297*, 799; [c] Sheldon, R. A. *Green Chem.* **2005**, *7*, 267; [d] Li, C.-J.; Trost, B. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 13197.

[25 a] Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159; [b] Tanaka, K. in *Solvent-free Organic Synthesis*, Wiley-VCH Verlag GmbH & Co KGaA, Weinheim, Germany, **2003**; [c] Varma, R. S.; Ju, Y. in *Green Separation Processes*, Wiley-VCH Verlag GmbH & Co KGaA, Weinheim, Germany, **2005**, pp. 53–87; [d] Kerton, F. M. in *Alternative Solvents for Green Chemistry*, RSC Green Chemistry Book Series, Royal Society of Chemistry, **2009**, ch. 2, p. 23.

[26 a] Breslow, R. *Green Chem.* **1998**, 225; [b] Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095; [c] Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68; [d] Li, C.-J.; Chan, T.-H. in *Comprehensive Organic Reactions in Aqueous Media*, ed. John Wiley & Sons, Inc., Hoboken, New Jersey, 2nd edn, **2007**; [e] Kerton, F. M. in *Alternative Solvents for Green Chemistry*, RSC Green Chemistry Book Series, Royal Society of Chemistry, **2009**, ch.3, p.44.

[27 a] Hyde, J. R.; Licence, P.; Carter, D.; Poliakoff, M. *Appl. Catal., A* **2001**, *222*, 119; [b] Arai, Y.; Sako, T.; Takebayashi, Y. in *Supercritical Fluids, Springer series in material processing*, Springer, New York, **2002**; [c] Gordon, C. M.; Leitner, W. in *Catalyst Separation, Recovery and Recycling*, Springer, Netherlands, **2006**, ch.8, p.215; [d] Kerton, F. M. in *Alternative Solvents for Green Chemistry*, RSC Green Chemistry Book Series, Royal Society of Chemistry, **2009**, ch.8, p.68.

[28 a] Welton, T. *Chem. Rev.* **1999**, *99*, 2071; [b] Earle, M. J.; Seddon, K. R. *Pure Appl. Chem.* **2000**, *72*, 1391; [c] Earle, M. J.; Seddon, K. R. in *Clean Solvents: Alternative Media for Chemical Reactions and Processing—Ionic liquids: green solvents for the future*, ACS Symposium Series, American Chemical Society, **2002**, vol. 819, pp. 10–25; [d] Rogers, R. D.; Seddon, K. R.; Volkov, S. in *Green Industrial Applications of Ionic Liquids*, Kluwer Academic Publishers, Dordrecht, **2002**; [e] Seddon, K. R. *Nat. Mater.* **2003**, *2*, 363; [f] Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Willauer, H. D.; Huddleston, J. G.; Rogers, R. D. *NATO Science Series: II, Mathematics Physics and Chemistry* **2003**, *92*, 137; [g] Rogers, K. R.; Seddon, K. R. in *Ionic Liquids as Green Solvents*, ACS Symposium Series, American Chemical Society, **2003**, p. 856; [h] W. L. Hough and R. D. Rogers, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 2262; [i] Wasserscheid, P.; Welton, T. in *Ionic Liquids in Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2007**; [j] Plechkova, N. V.; Seddon, K. R. in *Methods and Reagents for Green Chemistry-Ionic liquids: ''designer'' solvents for green chemistry*, John Wiley & Sons Inc, Hoboken, **2007**, pp. 105–130.

[29] [a] Mistele, C. D.; DeSimone, J. M. in *Green Chemistry*, Oxford University Press, Oxford, UK, **1998,** pp. 286–311; [b] Leitner, W. in *Modern Solvents in Organic Synthesis, Reactions in Supercritical Carbon Dioxide*, Springer-Verlag, Berlin Heidelberg, **1999**, vol. 206, p. 107; W. Leitner, Acc. Chem. Res., 2002, 35, 746; [c] Young, J. L.; DeSimone, J. M. *Pure Appl. Chem.* **2000**, *72*, 1357; [d] Franck, F.; Peter, L.; Howdle, V.; Steven, M.; Martyn, P. *Actualite Chimique* **2003**, *4–5*, 62; [e] Jessop, P. G.; Subramaniam, B. *Chem. Rev.* **2007**, *107*, 2666;

[30] DeSimone, J. M.; Tumas, W. in *Green Chemistry Using Liquid and Supercritical Carbon Dioxide*, Green Chemistry Series, Oxford University Press, Inc., **2003**.

[31] [a] Laughton, M. A. in *Renewable Energy Sources, Watt Committee report 22*, Elsevier Applied Science, **1990**; [b] Johansson, T. B.; Kelly, H.; Reddy, A. K. N.; Williams, R. H. in *Renewable Energy, Sources for Fuels and Electricity*, Island Press, **1993**; [c] Turner, W. C. in *Energy Management Handbook*, The Fairmont Press, Inc., Lilburn, USA, 5th edn, **2005**; [d] Kreith, F.; Goswami, D. Y. in *Handbook of Energy Efficiency and Renewable Energy*, CRC Press, Taylor & Francis Group, LLC, Boca Raton, USA, **2007**.

[32] Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1997**, *40*, 793.

[33] [a] P. Gallezot, *Green Chem.* **2007**, *9*, 295; [b] Bozell, J. J.; Patel, M. K. in *Feedstocks for the Future*, ACS Symposium Series 921, Oxford University Press, **2006**; [c] Kamm, B.; Gruber, P. R.; Kamm, M.in *Biorefineries-Industrial Processes and Products, Status Quo and Future Directions*, Wiley-VCH Verlag GmbH, Weinheim, **2006**, vol. 1; [d] Graziani, M.; Fornasiero, P. in *Renewable Resources and Renewable Energy, A Global Challenge*, CRC Press Taylor & Francis Group LLC, Boca Raton, **2007**;

[34] [a] Knapp, D. R. in *Handbook of Analytical Derivatization Reactions*, John Wiley & Sons, Inc., **1979**; [b] Carey, F. A.; Sundberg, R. J. in *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, Springer, New York, **2007**, 5th ed.

[35] Cannon, A. S.; Warner, J. C. *Crystal Growth & Design* **2002**, *2*, 255.

[36] Warner, J. C.; Stole, E. in *Green Techniques for Organic Synthesis and Medicinal Chemistry*, Wiley, **2018**, 2nd ed.

[37] [a] Silverman, R. B. *The Organic Chemistry of Enzyme-Catalyzed Reactions*, Academic Press, New York, **2002**; [b] Bommarius, A. S.; Riebel-Bommarius, B. R. *Biocatalysis, Fundamentals and Applications*, Wiley-VCH Verlag GbmH, Weinheim, 1st edn, **2004**; [c] Hobbs, H. R.; Thomas, N. R. *Chem. Rev.* **2007**, *107*, 2786; [d] Sheldon, R. A.; Arends, I.; Hanefeld, U. in *Green Chemistry and Catalysis*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2007**, ch. 1, p. 29; [e] van Rantwijk, F.; Sheldon, R. A. *Chem. Rev.* **2007**, *107*, 2757; [f] Anastas, P.; Crabtree, R. in *Handbook of Green Chemistry- Green Catalysis: Biocatalysis*, Wiley-VCH Verlag GmbH, New York, **2009**, vol.3.

[38] Solid Waste and Emergency response CEPPO, Chemical accident prevention and the clean air act amendments of 1990, US Environmental Protection Agency, Washington DC EPA, 550K94001, **1994**.

[39] [a] Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318; [b] Wittig, G.; Haag, W. *Chem. Ber.* **1955**, *88*, 1654.

[40] [a] Horner, L.; Hoffmann, H. M. R.; Wippel, H. G. *Ber.* **1958**, *91*, 61; [b] Horner, L.; Hoffmann, H. M. R.; Wippel, H. G.; Klahre, G. *Ber.* **1959**, *92*, 2499; [c] Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733; [d] Wadsworth, W. S., Jr.; Emmons, W. D. *Org. Synth.* **1965**, *45*, 44.

[41] Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

[42] Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117.

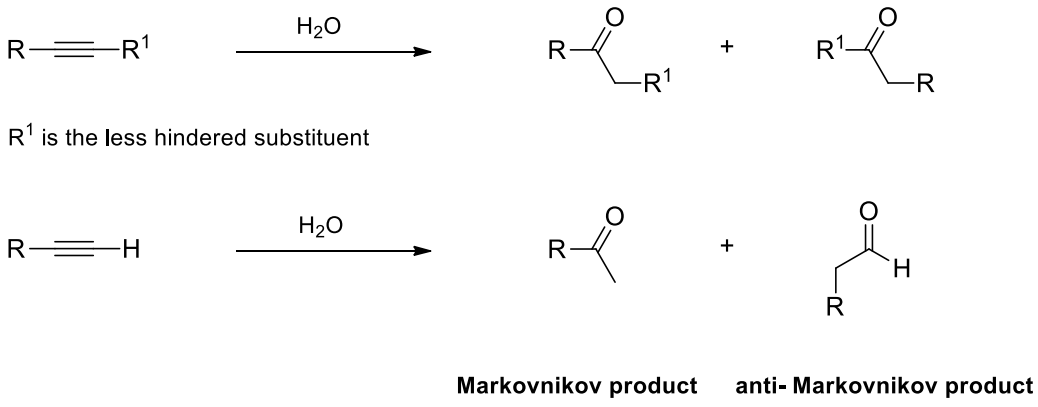
[43] Ritter, S. K. *Chem. Eng. News* **2002**, *80*, 26.

Chapter 2

Green hydration of internal alkynes under Lewis acid-assisted Brønsted acid catalysis

2.1 The white canvas of chemical synthesis

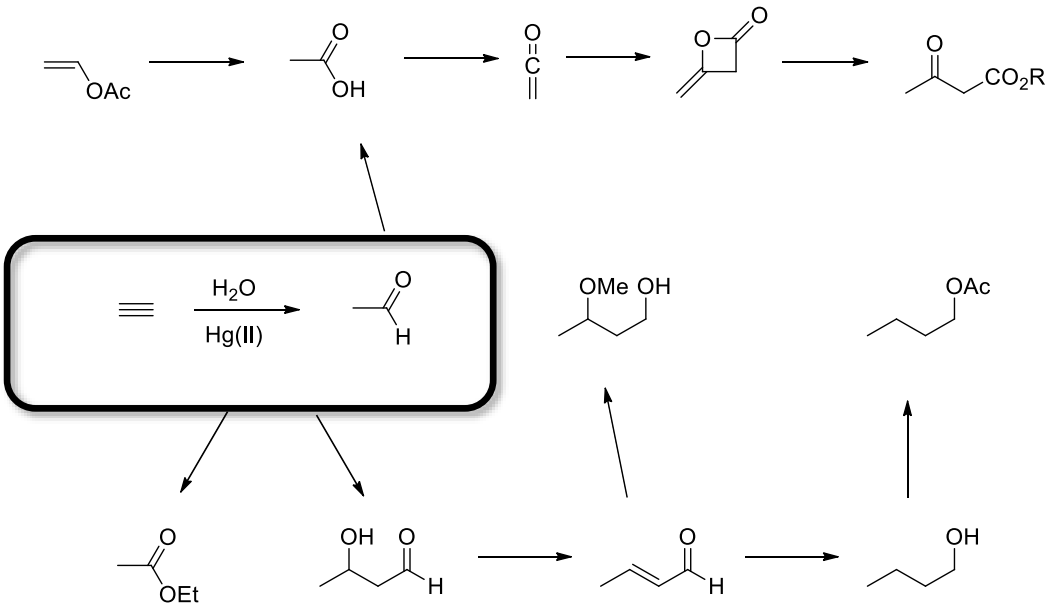
Among all of the substrates which have been used over the decades as starting material for chemical transformations, a special role has been played by alkynes, the white canvas of chemical synthesis.[1] The general interest towards these compounds is both due to the possibility of transformation of the triple bond C-C, because of its electron-richness, and to the acidity of the proton of an *sp*-hybridized carbon (pKa~ 25),[2] to consequently disfruit the conjugate base of the alkyne (acetylide) as a powerful chemical tool. Talking about reactions involving acetylides, it is worth to mention coupling reactions (Sonogashira, Negishi, Cadiot-Chodkiewicz, Glaser, Castro-Stephens),[3] which proceed *via* an acetylide intermediate, metallation and alkynylations involving organometallic reagents (Grignard, organo-Cu, organo-Li, mixed organo-metal, organo-Ag, etc.).[4] All of these reactions are central in chemical synthesis because they lead to the formation of a new C-C bond, thus providing an important way to build the carbon skeleton of a target molecule. Reactivity of the triple bond, apart from the great diversity of metal complexes formation, mainly refers instead to a plethora of addition reactions, which include: hydration,[5] hydroalogenation,[6] [3+2] dipolar additions, and in particular click reaction,[7] oxidations[8] and reductions.[9] Alkyne hydration, in particular, is a straightforward method to obtain carbonyl compounds. This reaction may theoretically lead to a mixture of Markovnikov and anti-Markovnikov products, but several procedures have been developed for the regioselective synthesis of both of them.[5b] Thus, nowadays it is possible to select among a wide variety of procedures to obtain either the only Markovnikov or just the anti-Markovnikov product from the hydration of an alkyne (Scheme 2.1).



Scheme 2.1 *Possible reaction pathways in alkyne hydration, which is the formal water addition to the C-C triple bond, for internal and terminal alkynes*

2.2 Early examples: Hg(II)-catalyzed hydration of alkynes

Acetylene (IUPAC name: ethyne), the simplest alkyne, was discovered in 1836 by Edmund Davy, professor of chemistry to the Royal Dublin Society.[10] It is an extremely dangerous gas, since a minimum trigger can cause its combustion reaction with oxygen in the air, so it is often stored in acetone solution.[11] When the french chemist Marcellin Berthelot in 1860 performed for the first time acetylene hydration in sulphuric acid, he misunderstood the product of the reaction, identifying it as the vinyl alcohol.[12] Later, in 1877, Lagermack and Eltekoff could instead verify that the crude product was actually a mixture of acetaldehyde and crotonaldehyde.[13] Meanwhile, similarly, hydration of propyne to acetone had already been performed in 1875.[14] Finally, Kucherov (Kutscheroff, in German transliteration) described catalysis from mercury salts for alkyne hydration in 1881, and further papers were published by the same author in the following years, in which he demonstrated the effectiveness of diverse Hg(II) species in promoting the reaction.[15] The discovery that alkyne hydration can be catalyzed by metal salts was very important for the development of chemical synthesis in industry: from that moment, acetylene became the starting material for several industrial preparation. Among these, one of the most important is acetic acid synthesis from acetylene, which was hydrated to acetaldehyde by Hg(II)-catalysis, and then oxidized in air to the final product with a Mn-based catalyst.[16] This kind of process was commonly employed on industrial scale in Germany from 1916, before being later replaced by Wacker process (ethylene + O_2) and Monsanto process of methanol carbonylation.[17] Hg(II)-catalyzed acetylene hydration gave then access to many interesting and useful synthetic chemical compounds (Scheme 2.2),[17-19] while hydration of higher alkynes remained unexplored until 1938.[20]



Scheme 2.2 *Base chemicals from acetylene, around 1950* [5b,19]

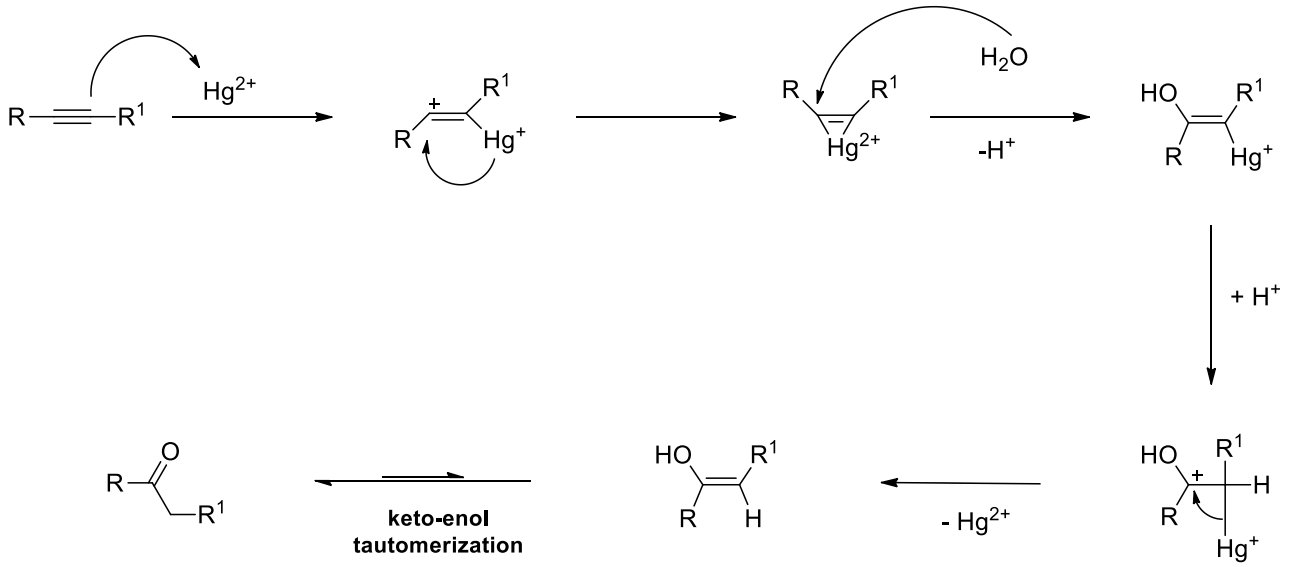
In the meanwhile new procedures for general hydration of both internal and terminal alkynes, based on Hg(II), continued to appear in the literature (Table 2.1).[21, 15a]

Catalyst	Amount (mol%)	Conditions	Substrates
HgO-H_2SO_4 [15a, 21a]	0.5 - 250	H_2O, r.t. – 100 °C	RC≡CH RC≡CR
HgO-H_2SO_4 [21b]	0.7	ROH (Me_2CO, AcOH)-H_2O, 60-80 °C, 4 h	RC≡CH RC≡CR
$Hg(OTf)_2$ – tetramethylurea [21c]	1 - 5	MeCN-DCM-H_2O r.t., 6-48 h	RC≡CH
Hg(II)-Ion-Exchange Resin [21d]	-	AcOH (EtOH)-H_2O r.t. to 100 °C	AlkC≡CH RC≡CR
HgO-BF_3 [21e, f]	1 - 4	CCl_3CO_2H, MeOH/ROH * r.t. to 60 °C	RC≡CH RC≡CR

* The reaction generates acetals, which are hydrolized in acidic workup conditions

Table 2.1 *Some of the most important procedures for alkyne hydration employing Hg(II) species as the catalyst*

The mechanism of Hg(II)-catalyzed hydration of alkynes has been deeply investigated, also in recent literature.[21] It proceeds *via* an electrophilic addition of the triple bond to a mercuric ion, followed by the formation of a 3-membered ring which includes the Hg atom. The subsequent nucleophilic attack by water occurs at the most substituted carbon. Markovnikov rule is respected, since conjugative/hyperconjugative effects can stabilize the positive charge, resulting in a deprotonation/reprotonation cycle on the most substituted carbon. The final stage includes the lysis of the C-Hg bond and keto-enol tautomerization, which leads to the keton (acetaldehyde, in the case of acetylene) from the enol, as the final reaction product (Scheme 2.3).



Scheme 2.3 *Mechanism of Hg(II)-catalyzed hydration of alkynes*

The most critical issue with the employment of mercury is its toxicity. In the Victorian England, the inauspicious effects of handling mercury salts were evident in hatters, probably the professional category to be mostly exposed to this metal. Felt for top hats was commonly obtained by immersion of animal skin in a $Hg(NO_3)_2$ aqueous solution, to separate hair from skin, while reinforcing the last. Since hatters used to shape their hats by wearing them during the manufacturing process, they constantly assimilated a certain amount of mercury, little by little. At a certain point, the assimilation of mercury led the poor hatter's hair to turn bright orange, his eyes sprayed, his mood bipolar. The expression "mad like a hatter", very popular in England during XVIII and XIX century, was certainly inspiring for the character of the "mad hatter" in Lewis Carroll's masterpiece *Alice in Wonderland*. After all, in that period, mercury poisoning was commonly known as "mad hatter disease".[23] In modern era, it is well known both in theory and in practice what mercury pollution can cause to the environment, the fauna and the people. In 1956, in the area of Minamata Bay (Kumamoto Prefecture, Japan) were firstly described the symptoms of a neurological disease, from that moment generally referred to as "Minamata disease": ataxia (muscular control loss), paresthesia (limbs sensitivity and tact loss), sight and hearing loss, speaking disorders, mental disorders. It was caused by the disposal of mercurial waste in the wastewater by Chisso Corporation, a local chemical factory which produced acetaldehyde.[24] By the end of March 2001, 2265 victims (including 1784 dead after poisoning) have been certified on the Yatsushiro Sea coast and other 690 in the Agano River basin.[25] Inorganic mercurial waste combustion or release in water produces methylmercury salts, having the general chemical formula $CH_3Hg^+ X^-$. Since methylmercury has a prolonged biological half-life (around 80 days for humand and around 72 days in sea species (especially tilefish, swordfish, king mackerel, shark, bigeye tuna),[26] it goes towards biomagnification,[27] starting from fitoplancton, zooplancton and krill.

2.3 Transition metal-catalyzed Markovnikov alkyne hydration: ruthenium

Since hazardousness of mercury handling has been recognized, scientific community readily prompted for the research of more eco-friendly catalysts. One of the first metals to be found suitable for alkyne hydration was ruthenium (table 2.2). In 1961, ruthenium chloride in 5M HCl at 50-80 °C was shown to be effective for acetylene and propionic acid hydration (entry 1).[28] Unfortunately, no synthetic applications have been performed due to the formation of the catalytically inactive complexes $[Ru^{II}Cl_4(CO)_2]^{2-}$ and $[Ru^{II}Cl_4(CO)(H_2O)]^{2-}$, the deactivation of the catalyst being faster for higher alkynes.[28b] More elaborated catalysts, such as complexes $[RuCl_2(PR_3)(\eta^6\text{-arene})]$ and $[RuCl(PR_3)_2(\eta^6\text{-arene})]Cl$, can activate terminal aliphatic alkyne and also, with opportune variations in the arene and phosphane ligands, terminal aryl alkynes, with high Markovnikov selectivity (entry 2).[29-31] The catalyst $[Ru(\eta^5\text{-indenyl})Cl(\eta^4\text{-COD})]$ too hydrates both aliphatic and aryl terminal alkynes giving preferentially the Markovnikov product (entry 4).[32] Terminal aryl alkynes (not aliphatic alkynes) can be also hydrated in presence of Ru-based catalyst with diphosphane ligands, after pre-treatment with silver hexafluoroantimonate(IV). The general structure of these catalysts is $[RuCl(P\text{-}P)_2(arene)]Cl$, P-P being a diphosphane or 2 Bu_3P (entry 3). In this case, a large amount of water inhibites the catalysis.[33] Among all of the catalysts above mentioned, no one is broadly used on a large variety of substrates. In the case of ruthenium, this can be due to the tendency of ruthenium to form ruthenium-acyl adducts, which result from the interaction of the catalyst with the hydration product, which later decarboxylates (CO affinity for ruthenium is higher than those of acyl compound themselves). This explanation has been given by the Bianchini group, which deeply investigated the mechanisms of Ru-catalyst deactivation.[34]

Catalyst	Amount (mol%)	Conditions	Substrates
$RuCl_3$-HCl (aq.) [28]	-	[Ru] = 0.1 M, 5M HCl 50-80 °C	AlkC≡CH ArC≡CH HC≡CH
$RuCl_2(PR_3)(arene)$ [29-31]	2.5 - 5	iPrOH-H_2O 80-100 °C, 24-48 h	AlkC≡CH ArC≡CR
[RuCl(P-P)]Cl-2 $AgSbF_6$ [33]	5	Me_2CO-H_2O r.t., 10-36 h	ArC≡CH
[(Ind)(RuCl)(COD)*] [32]	5	iPrOH-H_2O 90-100 °C, 12-48 h	AlkC≡CH ArC≡CR

* Ind= indenyl (η^5-C_9H_7); COD= η^4-1,5-cyclooctadiene

Table 2.2 *Ruthenium catalysts for Markovnikov alkyne hydration*

2.4 Transition metal-catalyzed Markovnikov alkyne hydration: rhodium and iridium

Some documented literature regarding alkyne hydration in the presence of rhodium and iridium catalysts has also to be taken into account. Kinetic measurements carried out on acetylene and 3-phenylpropiolic acid allowed to demonstrate that, in aqueous acidic solution, hydration of the triple bond occurs three times faster in the presence of ruthenium chloride with respect to rhodium choride, the deactivation of the metal catalyst still remaining a critical issue (table 2.3, entry 1).[35] Apart from mechanistic studies, the activity of rhodium complexes has also been reported, even if the results were not properly encouraging for synthetic use. A catalytic system composed by rhodium chloride and a quaternary ammonium salt was used by Blum and co-workers to regioselectively hydrate terminal alkynes in low yields (entry 2). This system was found to be effective in the hydration of internal alkynes too; however, in the latter case, the transformation is not regioselective, and the formation of a regioisomeric mixture of the Markovnikov and anti-Markovnikov products is observed. The results can be slightly improved (yield up to 40%) employing higher temperatures, longer reaction times and $IrCl_3$ instead of $RhCl_3$ (entry 3).[36] A certain efficiency for terminal arylalkynes was finally exhibited by $[RhCl_4(H_2O)_2]^-$.[37] A water-soluble Ir(I) complex $[IrCl(TPPTS)_2(CO)]$ [TPPTS = $(m\text{-}NaOSO_2C_6H_4)_3P$] was a performing catalyst (mild reaction conditions, yields over 90%) for the hydration of acetylene and terminal alkynes. Organic solvents containing 10% of water were found to be better solvents than water alone, because of competition between water and the substrate in coordinating the metal center. In the presence of methanol, the formation of acetals was also observed but at a lower rate with respect to hydration itself, in which the catalyst turnover number is around 900 (entry 4).[38] In any case, acetal byproducts can be hydrolyzed to afford the corresponding carbonyl compounds. The precursor of the above mentioned complex, $[Ir(COD)_2]BF_4$, was itself effective in very low amount (0.02 equivalents) in the hydration of terminal alkynes (yields in the range 70-80%), if employed together with triisopropylphosphite and $ZrCl_4$ or other Lewis acidic chloride metal salts (entry 5). If triethylphosphite and $AlCl_3$ were used as co-catalysts in the presence of methanol or higher alcohols, direct addition of the alcohol to the terminal triple bond was observed, thus affording acetals.[39] Also in this case, the desired carbonyl compound can be lately obtained by deprotection from acetal protecting group. All of the above mentioned protocols concerning the employment of catalytic systems based on rhodium and iridium for the Markovnikov hydration of alkynes are summarized in table 2.3, as follows.

Catalyst	Amount (mol%)	Conditions	Substrates
$RhCl_3$ [35]	-	[Rh]= 0.0125 M, HCl (aq.) 3M 50-65 °C	HC≡CH PhC≡CCO$_2$H
$RhCl_3$ – NR_4Cl [36]	20	NR_4Cl (0.3 eq.), THF - H_2O, r.t.-80 °C, 3-25 h	AlkC≡CH Ar≡CH (20%)
$IrCl_3$ – NR_4Cl [36]	20	NR_4Cl (0.3 eq.) 104 °C, 230 h	RC≡CR' (20 – 40%)
$IrCl(CO)(PR_3)_2$ *[38]	33	MeOH-H_2O 25 °C, 4-24 h	PhC≡CH HC≡CH (> 90%)
$[Ir(COD)^*_2]BF_4$ [39]	1	$P(OiPR)_3$ (0.02 eq.), $ZrCl_4$ (0.1 eq.) n-BuOH-H_2O, 70 °C, 15 h	AlkC≡CH ArC≡CH

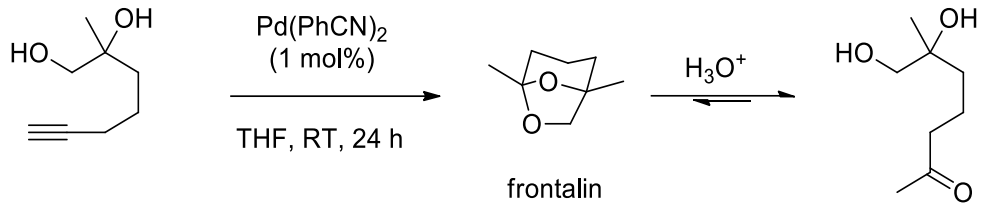
* R= (*m*-$NaOSO_2C_6H_4$); COD= η^4-1,5-cyclooctadiene

Table 2.3 *Rhodium and iridium catalysts for Markovnikov alkyne hydration*

2.5 Transition metal-catalyzed Markovnikov alkyne hydration: palladium and platinum

Catalytic activity of metals from the 10th group leads to take into consideration palladium and platinum, since nickel has never been shown to perform as a catalyst in alkyne hydration. Palladium(II) chloride is highly specific for hydration with anchimeric assistance, so acetylene does not undergo the reaction because of its lack of neighbouring groups. Ultrasound irradiation has occasionally been used to speed up the reaction, but its employment seems to be nothing more than an optional.[40] $PdCl_2$ has furthermore been used in biphasic dichlorometane/ aqueous HCl systems, together with tetrabutylammonium chloride acting as a phase transfer catalyst.[41] Acetylene hydration was possible if the complex $[Pd(NH_3)_4Cl_2]$ was used instead of $PdCl_2$ itself: in fact, no neighbouring groups were required, but the reaction had to be performed with $Fe_2(SO_4)_3$ and H_2SO_4 as co-catalysts.[42] Despite they do not refer to direct hydration of the triple bond, Utimoto studies on the rearrangements of alkynols or alkynyl ketones catalyzed by $PdCl_2$ (or its acetonitrile-solvated form $[Pd(CH_3CN)Cl_2]$) shall not be neglected.[43] In fact, oxygen heterocycles obtained after the rearrangement can be conveniently hydrolyzed to afford carbonyl compounds, thus obtaining a formal hydration after 2 steps. The same argument

may be applied to spiro acetals obtained after Pd(II)-catalyzed isomerization of alkynyl diols with hydroxyl groups at proper distance to conveniently attack the triple bond. This is the case of frontalin (scheme 2.4).[43,44]



Scheme 2.4 *Pd(II)-catalyzed cyloisomerization of an alkynyl diol to give spiro-acetal frontalin. Acetal hydrolysis can afford the product of formal direct hydration of the substrate*

All the above mentioned procedures are summarized in table 4, entry 1. Apart from these, other two interesting applications involving palladium as the catalyst should be remembered. A species generated in situ from *cis*-[Pd(PhPMe$_2$)Cl$_2$] and silver trifluoroborate catalyzes water addition to dimethyl acetylene dicarboxylate in refluxing acetone.[45] Finally, a Pd(II)-Nafion resin has been employed for the hydration of propargylic alcohol.[46] Regarding catalysis from platinum, hydration of both terminal and internal alkynes (including unfunctionalized asymmetric internal alkynes) can be performed with a relatively low loading of platinum chloride (or other halides) as well as of Zeise's dimer [{Pt(C$_2$H$_4$)Cl$_2$}$_2$] (table 4, entry 2).[47] The regioselectivity of these kind of systems has been compared to those obtained in aqueous media with mercuric ion acting as the catalyst,[48] which had been previously investigated.[49] Tipically, hydration of unfunctionalized asymmetric internal alkynes is not performed in complete regioselectivity, neither with mercuric, nor with other metal ions. Despite this, it can be verified that the degree of regioselectivity obtained with Zeise's dimer and platinum halides is generally higher than that obtained with mercury.[48] Precoordination of the substrate to the catalyst seems to play a certain role in the case of ethers/thioethers bearing a triple bond in the molecular scaffold, in order to place the metal center preferentially close to one of the alkyne carbon centers (regioselectivity up to 95%).[48] In its higher oxidation state IV, as in PtCl$_4$, platinum can furthermore catalyze hydration reactions either in H$_2$O/THF or in biphasic mixture under phase transfer catalysis (PTC) conditions (with quaternary ammonium chlorides as PTCs). The reaction is carried out under carbon monoxide atmosphere: first, the active species [PtH(CO)Cl(L)] (L being CO, H$_2$O or THF) is generated under high pressure of gaseous CO (14 bar), then the pressure is reduced by a factor 10 (1.4 bar). The substrate scope is quite large, including alkynones, terminal and internal alkynes, which can be hydrated in moderate to good yields (table 2.4, entry 3).[50] It is worth mentioning that platinum does not suffer from the presence of large amount of alcohols, giving selective hydration. Nevertheless, with a catalytic amount of a non nuclephilic base (2,6-tetramethylpyridine, Na$_2$SO$_4$, MgSO$_4$) the formation of acetals can be observed.[51] In the case of Zeise's dimer,

acetals or spiro-acetals are directly obtained from the cyclization of alkynols without any co-catalyst support.[44] To conclude, *cis*-$(TPPTS)_2PtCl_2$ has been employed for the conversion of pent-4-yn-1-ol and pent-3-yn-1-ol. The mechanistic pathway seems to be compatible with anchimeric assistance, since starting from either of the substrates, 5-hydroxy-2-pentanone is obtained.[52] The same activity is observed if the sulfonated chelating ligand DPPETS ($[\{m\text{-}NaO_3SC_6H_4\}_2)PCH_2CH_2P\{m\text{-}C_6H_4SO_3Na\}_2]$) is used instead of TPPTS.[53]

Catalyst	Amount (mol%)	Conditions	Substrates
$PdCl_2$ o $PdCl_2(RCN)_2$ [40-45]	1-5	MeCN-H_2O r.t., 80 °C, 0.5-40 h ultrasound (optional)	AlkC≡CH * RC≡CR *
$Pt_2Cl_4(C_2H_4)_2$ or $PtCl_2$ [47-48]	0.7	THF-H_2O 70 °C, 24 h	AlkC≡CH RC≡CR
$PtCl_4/CO$ [50]	2	CO (1.4 bar) i) H_2O-THF/glyme 80 – 100 °C *or* ii) NR_4Cl (0.04 eq.) $C_2H_2Cl_4$, 110 °C (i) and (ii) 1.5-9 h	AlkC≡CH (46%) ArC≡CH (74 %) RC≡CR (80%)

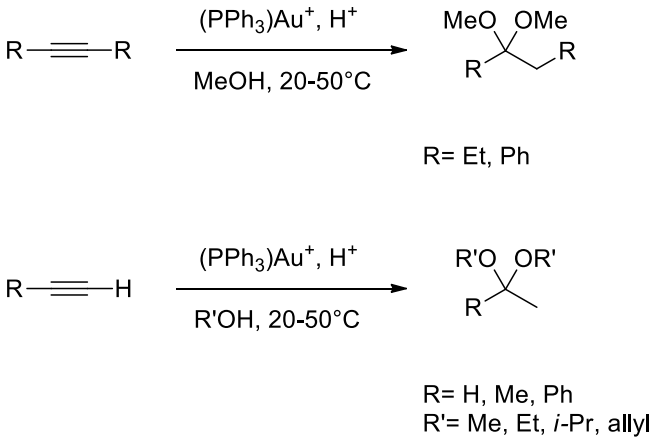
* Anchimeric assistance required

Table 2.4 *Palladium and Platinum catalysts for Markovnikov alkyne hydration*

2.6 Transition metal-catalyzed Markovnikov alkyne hydration: copper and gold

The second element of the 11th group, silver, is a singular case among the *d*-block metals. Despite the high affinity of this metal for triple bonds, its employment in alkyne hydration (in the form of triflate or $AgPF_6$) is scarcely documented in the literature.[5b] The few available examples concern cyclizations,[54] hydration of N-propargylamides[55] and direct acetalization of π-acceptors alkynes.[56] Copper catalysis has instead been a little more explored for both the possible oxidation states of this transition metal. The employment of different sources of Cu(I) has been studied for industrial scale hydration of acetylene and propyne.[57] A crucial role, in this case, seems to be played by hydrogen sulfide, inorganic sulfides[58] or thiols[59] added as co-catalysts. The very first application of this type was the hydration of acetylene at 80-85 °C with copper(I) chloride, a small amount (0.4-3%) of a sulfide source, NH_4Cl and a mineral acid as additives.[58a] The same catalytic system leads to a mixture of Markovnikov

and anti-Markovnikov product in the hydration of propyne, with a ratio decreasing from 21:2 to 8:5 in favour of the Markovnikov product upon increasing the amount of the sulfide source.[58b] The direct proportionality between the amount of anti-Markovnikov product and sulfide source has been explained as the formation and subsequent hydrolysis of a vinyl sulfide. In case the sulfur source was an organic thiol, not negligible effects were observed on regioselectivity in dependence of the size of its carbon chain.[59b] All these applications are summarized in table 2.5, entry 1. The active catalyst is supposed to be formed in situ by sulfide-promoted clusterization of CuCl.[60] Copper(II) is also an active catalyst, despite attention shall be paid in choosing its counteranion. In fact, while $Cu(OTf)_2$ and $Cu(BF_4)_2$ hydrate methylbut-3-yn-2-ol,[61,46a] $Cu(OAc)_2$ is ineffective even on simple alkynes because of the coordinating effect of the acetate anion.[46a,61] Because of the possibility of giving anchimeric assistance, $Cu(OAc)_2$ is however active in the case of N-propargylamides.[55] The action of Cu(II) on simple alkynes has instead proven to be effective, despite long reaction times, on a Cu(II)-Nafion resin.[46a] Talking about gold catalysis, much more references can be found in the literature. For long time gold has been considered unsufficiently reactive for catalytic applications, until in 1976 $HAuCl_4$ was used to hydrate alkynes,[62] paving the way for further achievementes with its sodium salt (table 2.5, entry 2), which allows to obtain in excellent yields (around 90%) hydration products of both terminal and internal alkynes in mild acidic conditions[40b,63] and dimethyl acetals in dry methanol.[63] Sodium tetrachloroaurate was furthermore employed for the catalytic hydration of terminal propargyl ethers to β-keto ethers and the catalytic Meyer-Schuster reaction of internal propargyl ethers to α,β-unsaturated ketones.[64] Another important milestone was reached at BASF in 1998, when an in-situ generated active Au(I) cationic complex [L-Au^+] (L= PR_3, AsR_3, RPO_3^{2-}) was demonstrated to be a good catalyst for the addition of alcohols to triple bonds in mild reaction conditions (20-50 °C) and in the presence of an acidic co-catalyst like methansulfonic acid (scheme 2.5).[65]



Scheme 2.5 *Teles procedure for Au(I)-catalyzed direct alcohol addition to terminal and internal alkynes*

Direct hydration of triple bonds was then a consequence, replacing dry alcohol with aqueous methanol as the solvent (entry 3).[66] One of the methods for the generation of the active species in-situ is protonolysis of Au-C bond of [AuMe(PPh_3)] with a strong mineral acid containing a non-nucleophilic counteranion (H_2SO_4, HBF_4, $MeSO_3H$). In combination with etherate boron trifluoride, complexes AuX(PPh_3) (X=RSO_3, ROCO) hydrate a broad alkyne scope, the catalyst with X= $OCOC_2F_5$ being the most efficient one, also upon recovery and recycle (entry 4).[67] Finally, heterocyclic ligands have been employed to stabilize Au(I) complexes. In particular, hex-3-yne undergoes water addition with catalytic amounts of a gold(I) complex bearing an N-heterocyclic carbene[68] and phenylacetylene does the same in the presence of [Au(TPP)Cl] (TPP= tetraphenylporphirine) catalyst.[69] A similar result was accomplished on phenylacetylene and hept-1-yne using a variety of gold(III) containing organometallic compounds, among which $[Au(C_6F_5)_2Cl_2]^-$. The best results were obtained with negatively charged ligands and in acidic media (entry 5).[70]

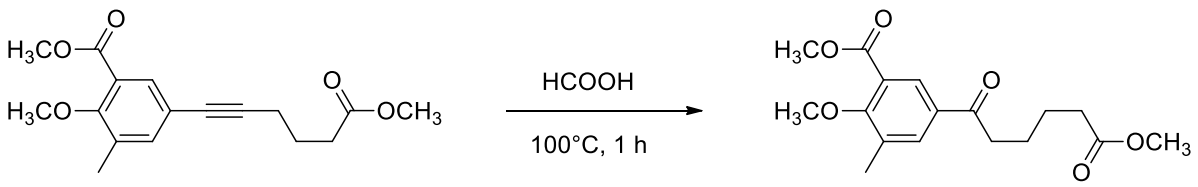
Catalyst	Amount (mol%)	Conditions	Substrates
CuCl [58-60]	-	NH_4Cl, HCl, H_2O, H_2S (or Na_2S, M_nS_m or RSH) 80-85 °C	HC≡CH MeC≡CH *
$NaAuCl_4$ [63]	2	MeOH-H_2O 70 °C, 1-5 h	RC≡CH RC≡CR (90%)
AuMe(PPh_3) [66]	0.1-1	H_2SO_4 (0.5 eq.) MeOH-H_2O 70 °C, 2 h	RC≡CH RC≡CR (50 - 99%)
AuX(PPh_3) [67]	0.1-5	$BF_3 \cdot Et_2O$ (0.05 eq.) MeOH-H_2O X= *p*-OTs or $OCOC_2F_5$, 45 °C	AlkC≡CH RC≡CR
$[Au(C_6F_5)_2Cl_2]^-$ [70]	2-4.5	H_2SO_4 (optional), MeOH-H_2O, 70 °C, 1.5 h	PhC≡CH AlkC≡CH (90-98%)

* Generates propanal and propanone in various ratios.

Table 2.5 *Copper and gold catalysts for Markovnikov alkyne hydration*

2.7 Brønsted acid-catalyzed Markovnikov hydration of alkynes

Being hydration a formal addition of water to the triple bond, one of the truly first attempts to realize this transformation in the laboratory was, in 1894, to run the reaction in pure water as the solvent.[71] However, this kind of procedure suffers from several disadvantages, like scarce solubility of apolar higher alkynes and necessity of high temperatures for the conversion of the substrates. In recent examples, microwave irradiation has been employed to replace heating (table 2.6, entry 1).[72] The substrate scope is limited, since while electron rich arylalkynes react rapidly, aliphatic alkynes hydration suffers from some difficulties. Despite water addition occurs even without any catalyst in aqueous media under harsch reaction conditions,[71-72] a certain amount of H_3O^+ ion is however present due to water autoprotolysis. Increasing its amount by adding a proton source like a mineral acid (e.g. H_2SO_4) a valuable improvement of the reaction rate can be observed (entry 2).[73] Reaction rate in water seems to benefit also from the presence of Lewis acids like $AuBr_3$.[72b] Catalytic (20 mol%) *p*-toluenesulfonic acid can hydrate in refluxing alcohols (reflux can be replaced by m.w. irradiation) terminal, internal and π-donors heteroaryl alkynes (entry 3),[74] while trifluoromethanesulfonic acid (or trifluoromethanesulfonimide) hydrates alkynes in refluxing dioxane (entry 4).[75] Brønsted acids have not only been added in catalytic amount in alkyne hydration reactions; a plethora of application can be found in the literature where the Brønsted acid itself is the solvent of the reaction or it is present in stoichiometric amount. Some examples are the use of more than 1 eq. of Na_2S/diluted HCl in methanol for activated heteroarylalkynes[76] or the employment of TFA containing 5% of water as the solvent for the hydration of activated terminal aryl and heteroaryl alkynes (entry 6).[77] All of the above examples refer to strong Brønsted acids, with high values of the dielectric constant ε and the acidic constant K_a in aqueous solution. The only example of alkyne hydration promoted by a weak Brønsted acid, HCO_2H has been given by Shvo and co-workers;[78] the substrate scope has not been broadly explored, but both internal and terminal alkynes react relatively rapidly (0.5-10 h) at 100 °C (entry 5). Interestingly, formic acid seems to auto-catalyze its own addition to the triple bond, with further decarbonylation on the resulting formyl enol (scheme 2.6).[79]



Scheme 2.6 *Formic acid-catalyzed Markovnikov hydration of an internal arylalkyne*

Other notable examples of Brønsted acid-promoted alkyne hydration are: vapor phase (150- 350 °C) hydration catalyzed by phosphoric acid over a solid support,[80] water addition

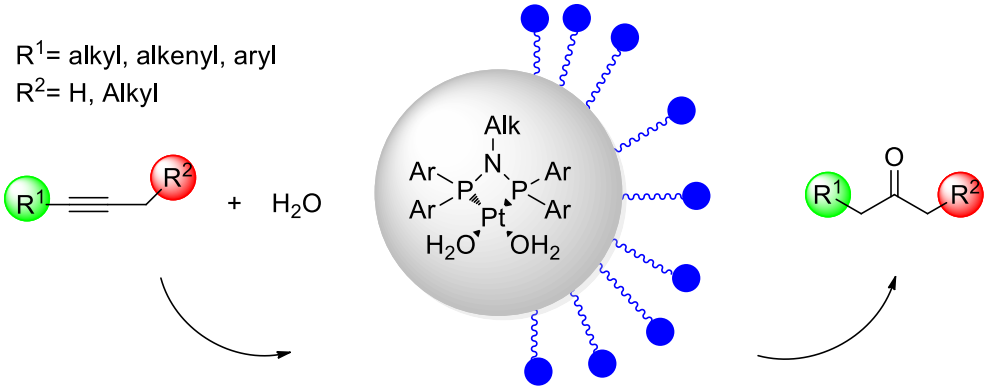
to triple bond catalyzed by acidic ion-exchange resin at high temperatures (60 to 100 °C)[81] and photo-catalyzed hydration of arylalkynes with UV-light having λ= 254 nm, in dilute acid.[82] In the latter case, the photoexcited state is more basic with respect to the ground state, so it is easily protonated to a vinyl cation. The enol which results from water addition has been observed by UV-spectroscopy. Regarding the mechanistic pathway of acid-catalyzed hydration, it seems to be correlated to the basicity of the alkyne. The first step is, in fact, protonation of the triple bond to form a strongly electrophilic vinyl cation, to which water can fastly add. Keto-enol tautomerization of the resulting enol affords the final carbonyl compound, thus completing the catalytic cycle. The fact that protonation is the rate-determining step has been confirmed by two experimental evidences. The first one is a measured kinetic isotopic effect of ~2, replacing H_2SO_4 with D_2SO_4; the second one is a strong dependence of the reaction rate from the ability of the substituent (aryl or alkyl) directly connected to the triple bond to stabilize the vinyl cation. Hence, electron withdrawing group-substituted triple bonds result in a slower reaction, while a higher reaction rate can be observed with electron donating group-substituted triple bonds.[83]

Catalyst	Amount (mol%)	Conditions	Substrates
H_2O [71-72]	-	H_2O 200-350 °C (or mw irradiation) 0.5-3 h	RC≡CH RC≡CR
H_2SO_4 [73]	-	H_2O, 280 °C, 1 h	RC≡CH
p-TsOH [74]	20	ROH-H_2O 80-170 °C, 6-144 h	ArC≡CH HetarC≡CH RC≡CR
HOTf [75]	10-20	Dioxane, H_2O 100 °C, 50 h	RC≡CH RC≡CR
HCO_2H [h - i]	100	100 °C, 0.5-10 h	RC≡CH RC≡CR
CF_3CO_2H [77]	> 100	H_2O, r.t. to 60 °C, 50 h	HetarC≡CH ArC≡CH (only π-donors activated aryls)

Table 2.6 *Brønsted acid catalysts for Markovnikov alkyne hydration*

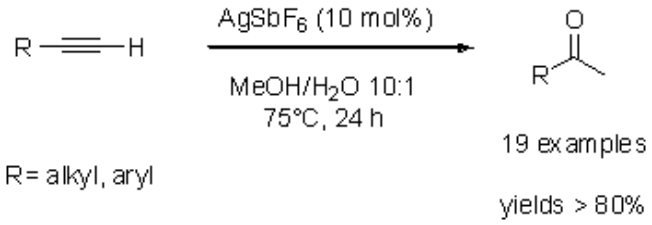
2.8 Acid-free catalytic hydration of alkynes

A few procedures have been reported to carry on alkyne hydration in acid-free conditions. In 2012 active momeric Pt(II) catalysts complexed with small bite angle N,N-bis(diarylphosphino)amine ligands were used to realize Markovnikov hydration of terminal and internal alkynes in water containing a surfactant (SDS sodium dodecylsulfate, SDSU sodium dodecylsulfonate, zwitterionic N-dodecyl-N,N-dimethyl-3-ammonium-1-propanesulfonate, Triton X-100 Polyoxyethylene(10)isooctyl phenyl ether). Ion pairing with anionic micelles made possible the dissolution of apolar alkynes in the aqueous media, promoting the intimate contact between reagents and catalyst. After 4 cycles of the catalyst, recovered from the aqueous phase, no loss of catalytic activity was observed (scheme 2.7).[84]



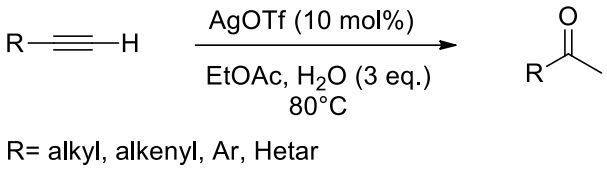
Scheme 2.7 *Pt-catalyzed acid-free Markovnikov alkyne hydration in aqueous media*

In the same period, two procedures employing a silver catalyst were reported. The first one disfruits a catalytic amount of silver hexafluoroantimoniate to realize the chemoselective hydration of a broad range of terminal alkynes in hydroalcoholic environment and in mild reaction conditions (scheme 2.8).[85a]



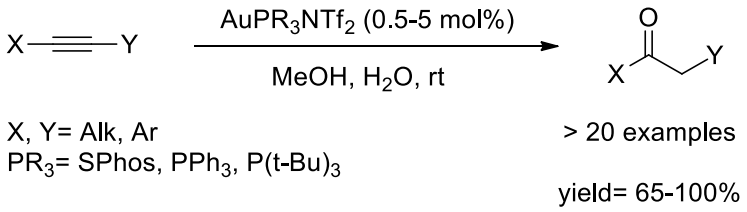
Scheme 2.8 *$AgSbF_6$-catalyzed acid-free Markovnikov hydration of terminal alkynes in hydroalcoholic medium and in mild reaction conditions*

The second one, by Das and Chakraborty, describes the silver triflate-catalyzed hydration of terminal alkynes in excellent yields. The reactions have been performed in mild reaction conditions but in organic media, with 3 equivalents of water acting as the hydrating agent (scheme 2.9).[85b]



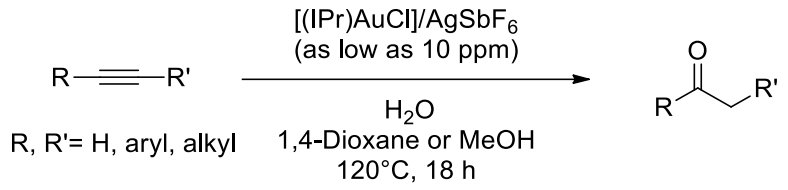
Scheme 2.9 *AgOTf-catalyzed acid-free Markovnikov hydration of terminal alkynes reported by Das and Chakraborty*

Other interesting examples are consistent with the use of more or less expensive transition metal-based catalysts like tin-tungsten mixed oxides,[86] water-soluble cobalt-porphyrin complexes,[87] indium (III) and hafnium (IV) triflate in liquid SO_2.[88] However, the most abundant literature concerns gold catalysts.[89] In 2009, Leyva and Corma reported the application of gold-phosphine complexes for the acid-free hydration of internal alkynes to the corresponding ketones in nearly quantitative yields. Good functional group tolerance on the substrates is obtained due to the absence of proton sources and, apart from alkyl and aryl internal alkynes, the system is compatible also with propargylic alcohols, enynes and enantiopure scaffolds (scheme 2.10).[89a]



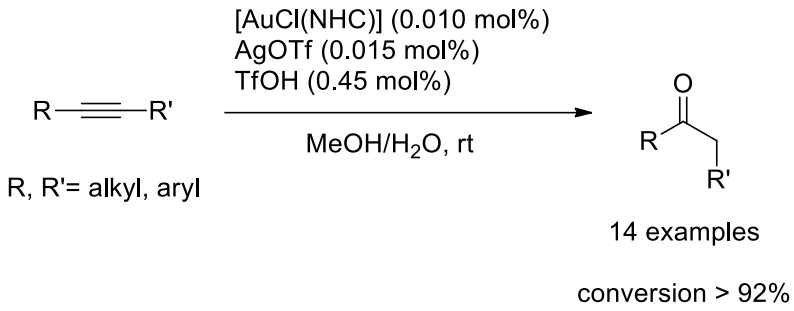
Scheme 2.10 *Leyva and Corma Markovnikov hydration of internal alkynes catalyzed by gold-phosphine complexes under acid-free conditions*

In the same year, a highly efficient [AuI(NHC)]-based (NHC= N-heterocyclic carbene) catalytic system for the hydration of an array of alkynes that operates under acid-free conditions and at very low catalyst loadings (typically 50-100 ppm and as low as 10 ppm) was reported. Terminal and internal alkynes possessing any combination of alkyl and aryl substituents were found to react in the above described conditions (scheme 2.11).[89b]



Scheme 2.11 *Gold-NHC complexes for the acid-free hydration of a broad range of internal and terminal alkynes*

Very similar to the last, despite not properly acid-free, one of the most recent applications is those of minimum amounts (0.01-0.05% mol) of a bispentiptycenyl-NHC gold complex having the general formula [AuCl(NHC)] activated with 1.5 equivalents of silver triflate and 45 equivalents of triflic acid. The conversion is virtually quantitative at room temperature in hydroalcoholic medium, the catalyst having a turnover number of around $3 \cdot 10^5$ (scheme 2.12).[89c]

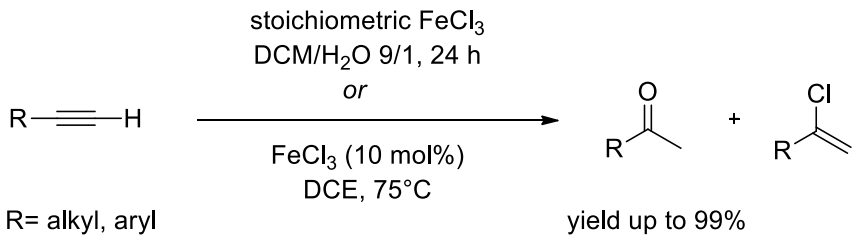


Scheme 2.12 *Recent example Markovnikov hydration of alkyl and aryl alkynes catalyzed by gold-NHC complexes in mild reaction conditions*

2.9 Aim of the work

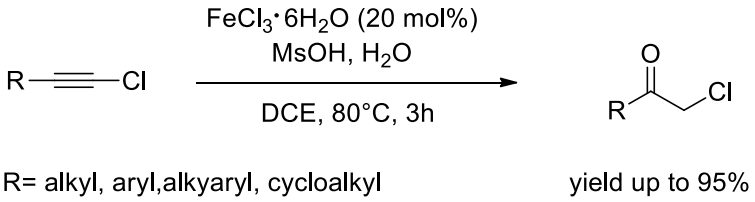
In the current scenario, the addition reaction of heteroatom (oxygen in particular) nucleophiles to the triple bond, including hydration, has been intensively studied.[5] Despite this kind of transformation is exoergonic, half-life times of the uncatalyzed process make it practically unfeasible without the presence of a catalyst.[90] Across the years, several catalytic systems and procedures based on Brønsted or Lewis acidic species have been developed, most of which being efficient for a limited range of substrates (e.g. terminal aliphatic alkynes, activated heteroarylalkynes, etc.). Moreover, currently available catalysts for alkyne hydration require the presence of strong Brønsted acids, in combination with expensive and sometime toxic Lewis acids, if necessary. For this reason, sustainability of the catalyst in terms of cost, eco and bio-compatibility, safety and handableness still remains a tantalizing challenge.[47a,66] Recently, the employment of the catalytic system constituted by hydrate iron(III) sulfate $Fe_2(SO_4)_3 \cdot nH_2O$ in neat acetic acid as the solvent and as the proton

donor for the hydration of terminal arylalkynes, has been reported by our group.[91] The iron salt is inexpensive, non-toxic and easily handable; furthermore, alogenated solvents are not involved in the protocol and the reactions are chemoselective. Furthermore, the proton donor is a truly weak acidic medium, due to the value of its dielectric constant (ε),[92] about 9 times lower than that of formic acid,[93] the only weak acid previously employed for the hydration of alkynes in absence of any co-catalyst.[78] Since the substrate scope has not been extensively investigated in the case of alkyne hydration in weak acidic medium (formic acid) and no chemoselective and halogen free procedures involving an iron-based catalytic system have been reported, the aim of this work was to extend the field of applicability of the catalytic system $Fe_2(SO_4)_3 \cdot nH_2O$/acetic acid. For this reason, its usefulness in the hydration of a wide variety of internal arylalkynes has been studied. Moreover, a mechanistic proposal was formulated to explain the course of the reaction on the basis of both experimental data and theoretical calculations.[94] The use of first period transition metals in catalytic alkyne hydration, iron in particular, is preferable due to generally lower cost and toxicity, but largely unexplored due to their generally lower efficiency as catalysts. This can be explained through Lewis HSAB (Hard and Soft Acid and Bases) theory.[95] A "soft" nucleophile like the π bond of an alkyne will react preferentially with a "soft" electrophile, like a transition metal with fully occupied *d*-orbitals. A few exceptions are represented by copper[46a,58a] and zinc catalysts,[96] which not casually possess fully occupied *d*-orbitals, so being "soft" Lewis acids. In addition to these, inexpensive iron trichloride has been used in stoichiometric amount in a pioneeristic work by Damiano and Postel.[97] Dry $FeCl_3$, in fact, can promote transformation of phenylacetylene into acetophenone in mild reaction conditions and in 24 hours, using dichloromethane/ water 9/1 as the solvent system. Despite the full conversion of the substrate, the yield in the desired product is not quantitative, due to the parallel formation of a not negligible amount of α-chlorostyrene. The procedure was extended to other aromatic and aliphatic terminal alkynes, the latest requiring higher reaction temperatures for the conversion into the corresponding methyl ketone, isolated in yields around 50%. Furthermore, in 2009, the first iron-catalyzed Markovnikov hydration of terminal alkynes with 10 mol% of $FeCl_3$ has been reported by the Darcel group.[98] Apart from the fact that even in this case traces of undesired α-chlorovinyl products are observed, both the procedures are suitable for aliphatic and aromatic terminal alkynes, but not for internal alkynes, which result inhert under any circumstances (scheme 2.13).



Scheme 2.13 *The earliest examples of Fe(III)-promoted Markovnikov hydration of terminal alkynes in stoichiometric (Damiano and Postel[97]) or catalytic amount (Darcel et al.[98])*

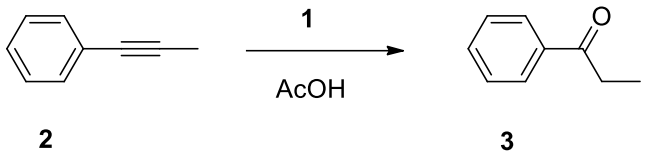
The hydration of internal alkynes poses additional concerns, due to their inherently lower reactivity which makes them either unreactive[85a,87,99] or reactive under harscher reaction conditions.[78a,100] For this reason, following from these seminal works, iron catalysis has further been extended to the hydration of internal alkynes, although in a limited number of cases. The triflimide iron(III) salt [$Fe(NTf_2)_3$] (generated in situ from $FeCl_3$ and $AgNTf_2$) promotes the direct hydration of terminal and internal alkynes in high yield with Markovnikov regioselectivity. The weakly-coordinating triflimide anion seems in this case to be crucial for the catalytic activity. Moreover, the catalyst can be recycled upon complexation with triphenylphosphineoxide, which exhibits similar activity and selectivity. However, spectroscopic and kinetic studies show that [$Fe(NTf_2)_3$] hydrolyzes under the reaction conditions, forming less active Brønsted species, which suggests a Lewis/Brønsted co-catalysis.[101] The only example of use of an iron(II) species is the employment of 5 mol% $FeCl_2 \cdot 4H_2O$ together with methanesulfonic acid (110 mol%) in 1,2-dichloroethane at 60 °C.[102] Despite the use of an alogenated solvent still remains a critical issue, no traces of α-chlorovinyl byproducts were detected and good to excellent yields were obtained in short reaction times (as long as 1 hour) for both terminal and internal alkynes, including internal arylalkynes deactivated by electron withdrawing substituents. Finally, alkynyl chlorides can be converted into α-chloromethyl ketones by using $FeCl_3 \cdot 6H_2O$ (20 mol%) alongside with water and MsOH for 3 hours in 1,2-dichloroethane at 80 °C (scheme 2.14).[103]



Scheme 2.14 *Conversion of alkynyl chlorides into α-chloromethyl ketones with $Fe_2Cl_3 \cdot 6H_2O$, MsOH and water*

2.10 Results and discussion

The study of the activity of the catalytic system $Fe_2(SO_4)_3 \cdot nH_2O$ (**1**)/ acetic acid follows from previous results obtained for terminal arylalkynes,[91] in which amounts in the range 4-9 mol% of the iron salt have been used to promote the hydration of the triple bond. The substrate scope included electron donating group-substituted (*p*-OMe, *p*-NMe_2, *o*-OMe, 3,4,5-$(OMe)_3$, *p*-vinyl) and electron withdrawing group-substituted (*p*-Br, *p*-CF_3) terminal arylalkynes, so that the substituent effect had been evaluated. Experimental evidences showed that the reaction is favoured (higher yields, shorter times) in case the substituent is an electron donor, confirming that the basicity of the substrate is a key point of the reactivity. Moreover, structural effects of the metal co-catalyst, like the nature of counteranion and the water amount had been taken into account. For what concerns the anion effect, a dramatic decrease of both the yield and the chemoselectivity (formation of α-chlorovinyl byproducts) was observed upon switching from sulfate to chlorine counteranion. The most plausible reason for that is the non-nucleophilic and soft low-coordinating nature of sulfate anion, which makes the metal center more accessible while modulating its Lewis acid character, in terms of HSAB theory.[95] A "soft" ligand like sulfate favours the formation of "soft" Lewis acid low-spin complexes of the iron center, so that their affinity for "soft" Lewis basic π triple bond is enhanced. In the meanwhile, thermogravimetric analysis on the iron salt (**1**) batch had clarified that its chemical formula can be correctly written in the form $Fe_2(SO_4)_3 \cdot 9H_2O$. Finally, some recovering-recycling tests on the metal co-catalyst had been performed, showing a net decrease of its performances. The results of the first run on the hydration of model substrate phenylacetylene, which afforded benzophenone in 99% yield, could not be replicated in the following cycles, whose average yield dropped to around 10%. Presumably, due to its partial solubility in the reaction medium, the iron salt was not fully recovered after filtration, so that the effective catalyst loading was lower in the subsequent cycles. With these premises, hydration of 1-phenylpropyne (**2**) to 1-phenylpropanone (**3**) was chosen as the model reaction of hydration for internal arylalkynes, to optimize reaction parameters like the catalyst loading, its water content and the temperature. The results, reported in table 2.7, refer to GC peak areas, which were normalized with respect to 1,2- diphenylethane as internal standard. All the reactions (if not differently indicated) have been performed in air for 24 hours on 1.0 mmol of the substrate in 2.0 mL of AcOH (0.5 M). The iron salt is undeniably a catalyst for the reaction, together with acetic acid, and its role cannot be neglected. In fact, with acetic acid alone, the amount of the desired product (**3**) is minimum (table 2.7, entry 1), and increasing the loading of (**1**) from 0 to 10 mol% has a beneficial role on the yield (entries 1, 2 and 4). On the contrary, increasing the alkyne initial concentration from 0.5 M to 1.0 M has no positive effect on the reaction rate (entry 3) and running the reaction at 95 °C instead of 120 °C affords the product in a lower yield at the same reaction time (entry 5). The employment of d_4-acetic acid as the solvent has a detrimental effect on the transformation (entry 8) as well as those of a dehydrate form of the iron salt as the co-catalyst (entry 6), while the corresponding iron(II) salt is practically ineffective (entry 7).



2 3

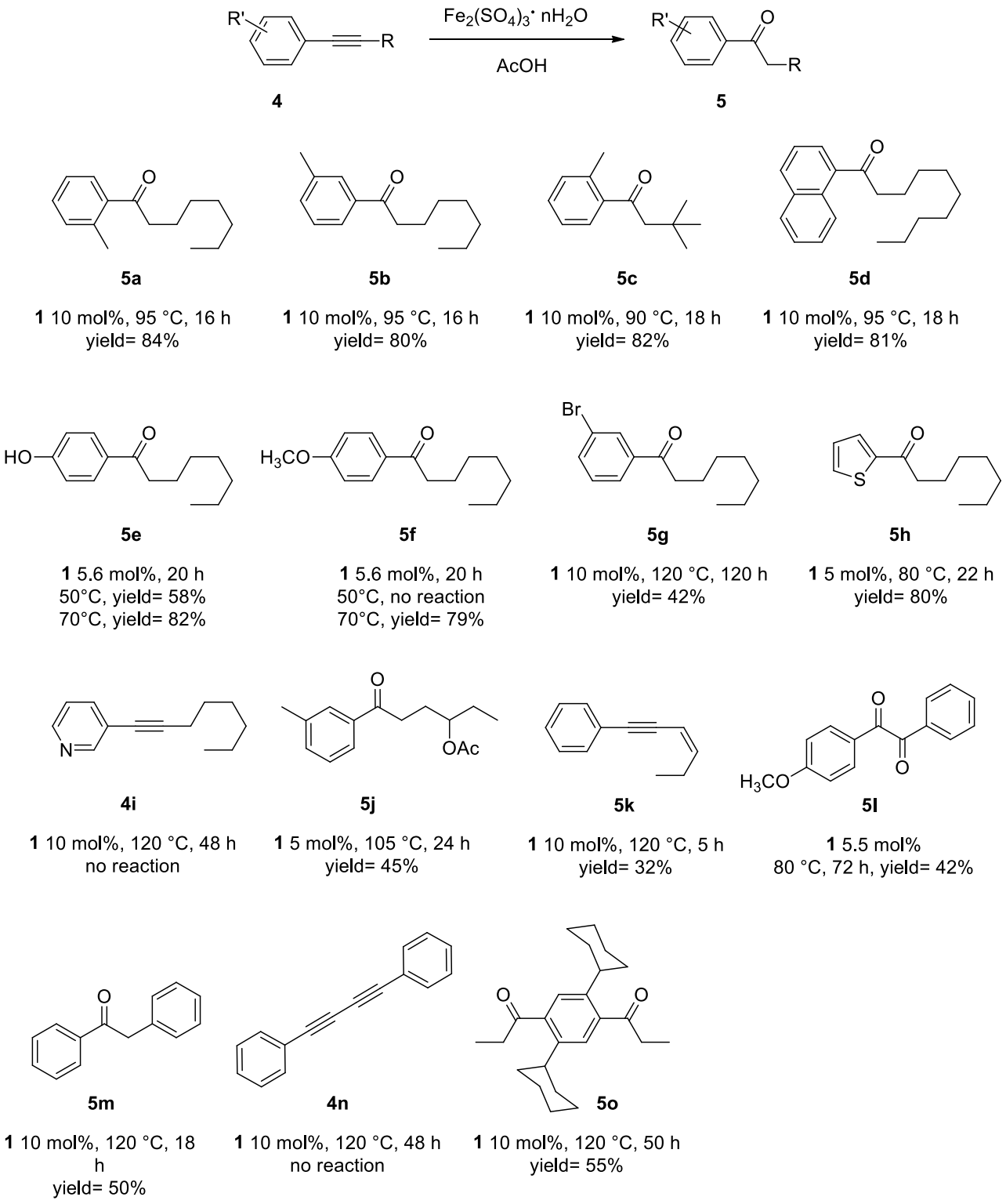
Entry	Iron salt (mol%)	T (°C)	2 [a]	3 [a]
1	-	120	96	1
2	**1** (10)	120	2	78
3[b]	**1** (10)	120	25	58
4	**1** (5)	120	36	43
5	**1** (10)	95	66	18
6	$Fe_2(SO_4)_3 \cdot 3H_2O$	120	81	15
7	$FeSO_4 \cdot 7H_2O$	120	98	< 1
8	**1** (10) in CD_3CO_2D	120	68	16 [c]

[a] GC percentages of **2** and **3**
[b] The initial concentration of **2** is 1.0 M
[c] $PhCOCD_2CH_3$ (*m*/*z* = 136)

Table 2.7 *Reaction optimization and control experiments*

The reaction was then repeated in the optimal conditions (10 mol% of (**1**) as the catalyst, (**2**) 0.5 M in AcOH, 120 °C for 24 hours) on a larger scale (3.4 mmol of 1-phenylpropyne) and pure (**3**) was isolated after column chromatography in 61% yield. Even if the observed yield was not encouraging, the excellent Markovnikov regioselectivity was a valid reason to expand the scope of the reaction to other internal alkynes. To this aim, a series of compounds having the general formula ArC≡CR was prepared using the general protocol developed by Sonogashira and Hagihara.[104] The substrate scope is further reported in scheme 2.15. Starting from +I electron donating group-substituted internal arylalkynes, excellent yields (over 80%) were obtained for the hydration of 1-methyl-2-(oct-1-ynyl)-benzene (**4a**), 1-methyl-3-(oct-1-ynyl)-benzene (**4b**), or *o*-tolyl-*t*-butylacetylene (**4c**). In these cases, even at 70 °C it was possible to observe the formation of traces of the desired ketone (TLC, GC-MS); however, full conversion was obtained at 90-95 °C. The fact that the reaction conditions are comparable to those used for generally more reactive terminal alkynes[91] is remarkable. Furthermore, the insensitivity of the triple bond towards the steric hindrance of the *ortho*-methyl group and the congested *t*-butyl in the alkyl chain shall be highlighted. The increasing degree of conversion upon increasing the lenght of the alkyl chain is instead not a novelty, having already been observed under catalysis of $FeCl_3/3{\cdot}AgNTf_2$.[97] 1-Dec-1-ynylnaphthalene (**4d**) also reacted smoothly at 95 °C to afford the corresponding

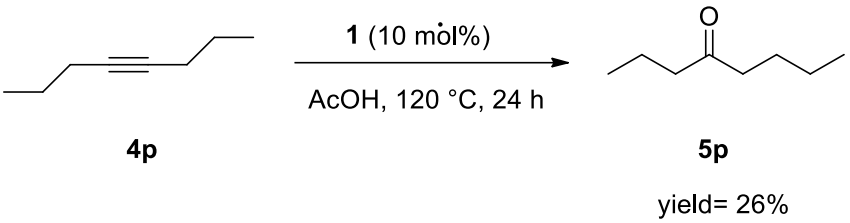
ketone (**5d**) in 81% yield. For what concerns stronger +R electron donating group-substituted internal arylalkynes (*p*-OCH_3 σ_p= -0.27 or *p*-OH σ_p= -0.37), milder conditions (lower catalyst loading, lower temperatures) were sufficient to afford the desired products in high yields (around 80%). In the case of substrate **4e**, the degree of conversion into ketone **5e** was remarkably good even at 50 °C, while in the absence of the iron salt only traces of the product were detected. Switching to deactivated electron withdrawing- substituted alkynes, 1-bromo-3-(oct-1-ynyl)-benzene (**4g**, σ_m = +0.39 for bromine) required 120 °C and five days for a modest conversion, affording the pure ketone **5g** in 42% yield after work-up and column chromatography. Instead, heteroaromatic 3-(oct-1-yn-1-yl)pyridine (**4i**) gave no conversion after 48 hours at 120 °C. It is not clear if this is due to the strong electron withdrawing effect of the heteroaromatic nitrogen, which is comparable to those of a nitro substituent, or to a protonation of the same nitrogen atom under the reaction conditions, that deactivates the triple bond. In fact, *p*-NMe_2 ethynyl benzene did not suffer from any problem of this type, as described in the previous work focused on terminal arylalkynes.[91] On the contrary, 1-(thiophen-2-yl)-1-octyne (**4h**) smoothly reacts at 80 °C, affording product **5h** in 80% yield as evidence of compatibility of the catalytic system with sulfur donor atoms. Since the hydration of propargylic alcohols is often known to be a challenging goal,[5b] the procedure was then extended to homopropargylic 1-(*m*-tolyl)oct-1-yn-3-ol (**4j**) and 1-phenylhex-1-yn-3-ol (**4k**). In the first case, the O-acetylated ketone **5j** was obtained in 45% yield, while in the latter the substrate easily dehydrated to the conjugated *cis*-enyne **5k**, which was not possible to further convert into the corresponding conjugated enol/ ketone, despite harscher reaction conditions have been adopted. The hydration of the activated diaryl alkyne 1-methoxy-4-(phenylethynyl)benzene (**4l**) proceeded easily, though affording a regioisomeric mixture of both the possible products. Only after prolonged reaction time at 80 °C, pure diketone **5l** could be isolated in 42% yield. Transition metal-catalyzed direct oxidation of internal alkynes is a known process, and it can be applied to the synthesis of 1,2-diketones, in presence of oxygen.[105] In this case, the course of the reaction can be rationalized since it is performed in the air. In the case of symmetric diphenylethylene **4m**, the reaction did not efficiently proceed under catalysis of **1** (10 mol%) in AcOH, so that ketone **5m** was isolated in 50% yield after 18 hours at 120 °C. The conjugated diyne **4n** was totally inert toward any transformation under the reaction conditions. Finally, the reaction was performed on symmetric bifunctional (2,5-di(prop-1-yn-1-yl)-1,4-phenylene)dicyclohexane **4o**, affording a mixture of the mono and the di-hydrated product, which were not separable by column chromatography. However, after 2 consecutive crystallyzation with the slow vapour diffusion method,[106] pure diketone **5o** was isolated as yellow needle-shaped crystals in 55% yield. It is worth noticing that the long reaction time (50 hours) is due to the high steric congestion of the substrate, while the moderate yield reflects the lower reactivity of a short propynyl group, with respect to longer alkynyl chains.



Scheme 2.15 *Substrate scope for the hydration of internal arylalkynes with the catalytic system* $Fe_2(SO_4)_3 \cdot nH_2O$ */ acetic acid*

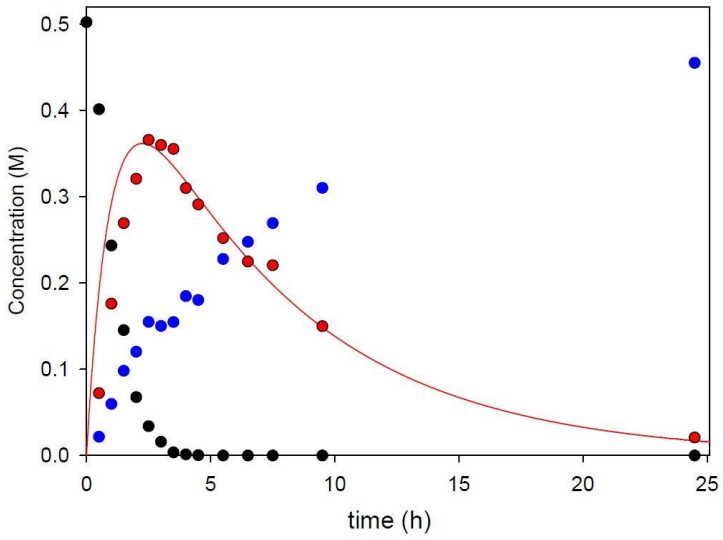
Despite the catalytic system was proven to be useful on a wide variety of internal arylalkynes, its weakness is the hydration of internal aliphatic alkynes. As a matter of fact,

hydration of 4-octyne (**4p**) resulted in a low conversion into 4-octanone (**5p**), even at 120 °C (scheme 2.16).



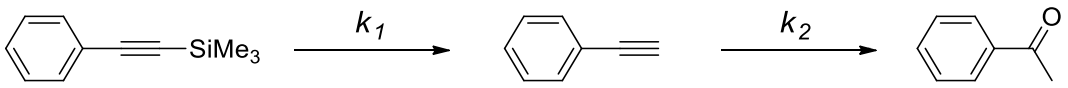
Scheme 2.16 *Hydration of 4-octyne promoted by $Fe_2(SO_4)_3 \cdot nH_2O$ in acetic acid*

To further show the practical usefulness of iron sulfate in acetic acid to promote alkyne hydration under mild reaction conditions, the substrate scope was then extended to some aryltrimethylsilylalkynes. The TMS group is a protective group for the ethynyl function and silylated alkynes are more stable and easily handable materials with respect to unprotected terminal alkynes.[107] It is well known that TMS, as well as other trialkylsilyl protecting groups (*e.g.* TBDMS, TES, etc.), can be easily removed upon treatment with a fluoride ion source (tipically TBAF) or with OH^- ions, while hydrolysis in acidic enviroment requires more vigorous conditions. However, no procedure had been reported so far for the hydrolysis of the C_{sp}-Si bond, as well as for the one-pot desilylation/ hydration process, under the action of a weak acid. This kind of process is highly desirable in terms of atom economy, safety and environmental sustainability. Direct transformation of aryltrimethylsilylacetylenes into the corresponding acetyl derivatives had instead already been described under polynuclear aromatic resin catalysis,[108] strong acidic conditions[100a,109] and gold catalysis.[89c] First of all, phenyltrimethylsilylacetylene (**6a**) was treated with the iron catalyst in acetic acid and, after 16 hours at 90 °C, GC-MS analysis revealed the nearly quantitative formation of acetophenone (**8a**) in 98% yield. This encouraging result required a deeper investigation of the overall process, so the reaction of compound **6a** was repeated at 85 °C and monitored as a function of the time by sequential GC-MS analysis. Collection of 15 experimental points was followed by nonlinear least-squares fitting, so to obtain a graph describing the gradual disappearance of the substrate, the formation of the acetyl derivative and, in the meanwhile, formation and consumption of phenylacetylene (**7a**) as a reaction intermediate (scheme 2.17).



Scheme 2.17 *Transformation of PhC≡CSiMe₃ (•, 1 mmol) into PhCOMe (•) in presence of $Fe_2(SO_4)_3 \cdot nH_2O$ (10 mol%) in AcOH (2.2 mL), 85 °C; concentration of the species was determined by GC-MS using 1,2-diphenylethane as internal standard; best line fitting of PhC≡CH (•) with equation 2.2*

An assessment of the rate constants for the separate processes of desilylation (k_1) and hydration (k_2) can be made with the assumption that those reactions are consecutive and irreversible first order transformations (equation 2.1).

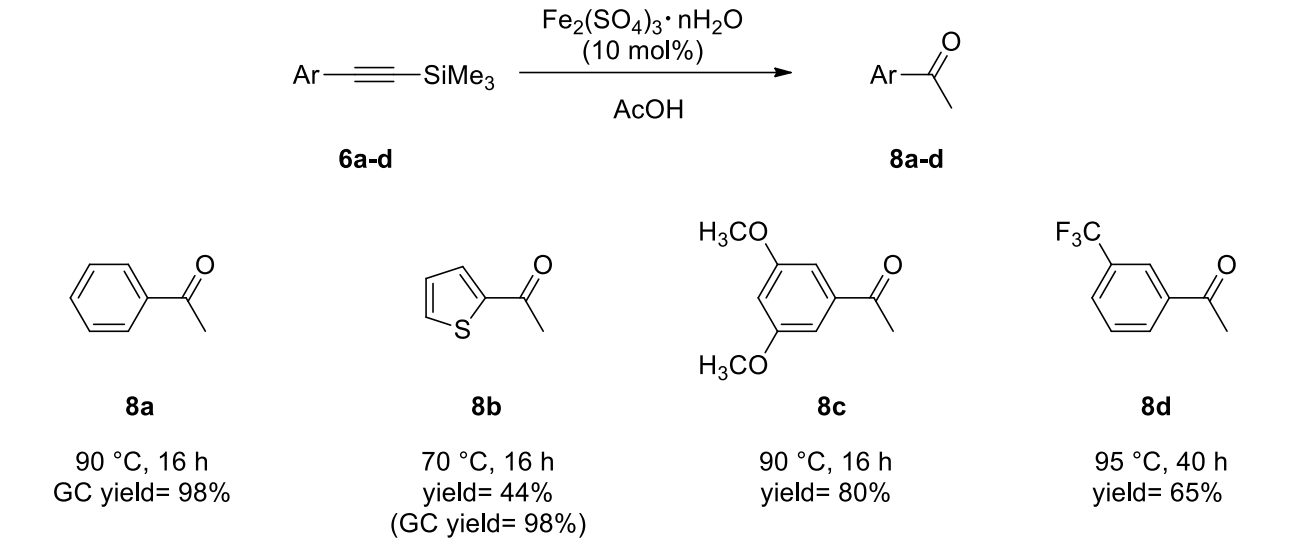


6a **7a** **8a** (2.1)

From standard integrated equations, properly adapted to the present case, equation 2.2 follows for the time concentration of **7a**.

$$[\mathbf{7a}] = \frac{k_1 \text{ x } [\mathbf{6a}]}{k_2 - k_1} \left(e^{-k_1 t} - e^{-k_2 t}\right) \qquad (2.2)$$

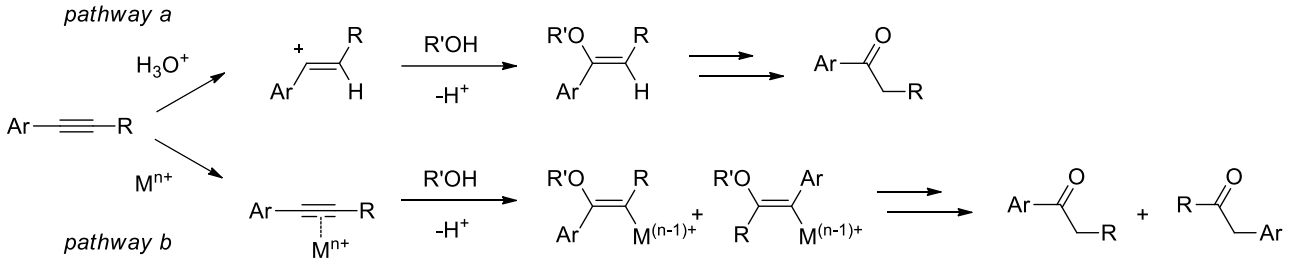
A nonlinear least squares experimental fit of equation 2.2 gives the following values of best fit parameters: k_1 = 2.8 (±0.9) × 10^{-4} s^{-1} and k_2 = 4.0 (± 1.5) × 10^{-5} s^{-1}. These data indicate that desilylation process is significantly faster than alkyne hydration. The same reaction performed in absence of the iron catalyst showed the presence of unreacted silyl substrate **6a** and only traces (0.2%) of phenylacetylene **7a**, pointing out that acetic acid alone cannot perform the desilylation step. This one-pot procedure can be extended to other trimethylsilyl-protected arylalkynes including heteroaryl, electron donating and electron withdrawing aryl substituents (scheme 2.18).



Scheme 2.18 *Substrate scope for the one-pot desilylation-hydration of aryltrimethylsilylacetylenes promoted by $Fe_2(SO_4)_3 \cdot nH_2O$/acetic acid*

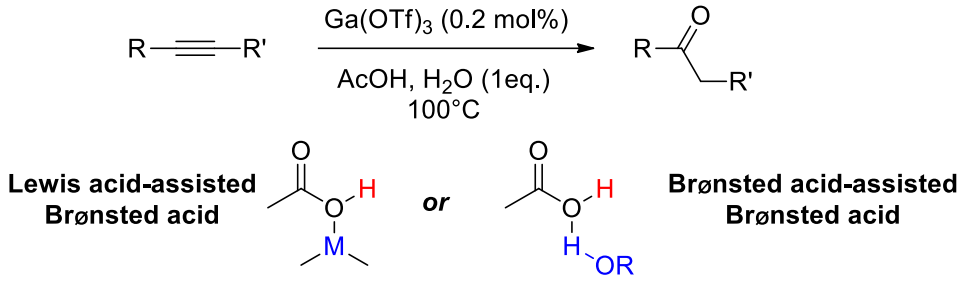
2.11 Investigation on reaction mechanism

Since the advent of iron catalysis for alkyne hydration is rather recent, the reaction mechanism has been carefully evaluated in the course of this thesis, by taking into account the general paths followed in the case of alkyne hydration, represented by two limited cases: activation by Brønsted acid or transition metal catalyst (scheme 2.19).[97,110]



Scheme 2.19 *General mechanistic pathways for heteroatom addition to internal arylalkynes*

Since acetic acid alone does not add to the triple bond to a considerable extent (table 2.7, entry 1), a Lewis acid-assisted Brønsted acid catalysis (LBA)[111] mechanism has been hypotesized for the reaction course, in agreement with general pathway a (scheme 2.23). One of the first documented examples of this approach to acid catalysis is a study on superacidity and superelectrophilicity of carbonyl-BF_3 complexes, in which Lewis acidic boron trifluoride is shown to decrease the pK_a of an α-proton of acetaldehyde from 17 to -7, upon complexation of the carbonyl oxygen atom.[112] A more recent example of LBA catalysis, specifically regarding alkyne hydration, is that of the catalytic system constitued by gallium(III) triflate in aqueous acetic acid, developed by Hammond and Xu (scheme 2.20).[113]



Scheme 2.20 *Acid-assisted Brønsted acid catalysis for alkyne hydration with Ga(OTf)₃/ AcOH*

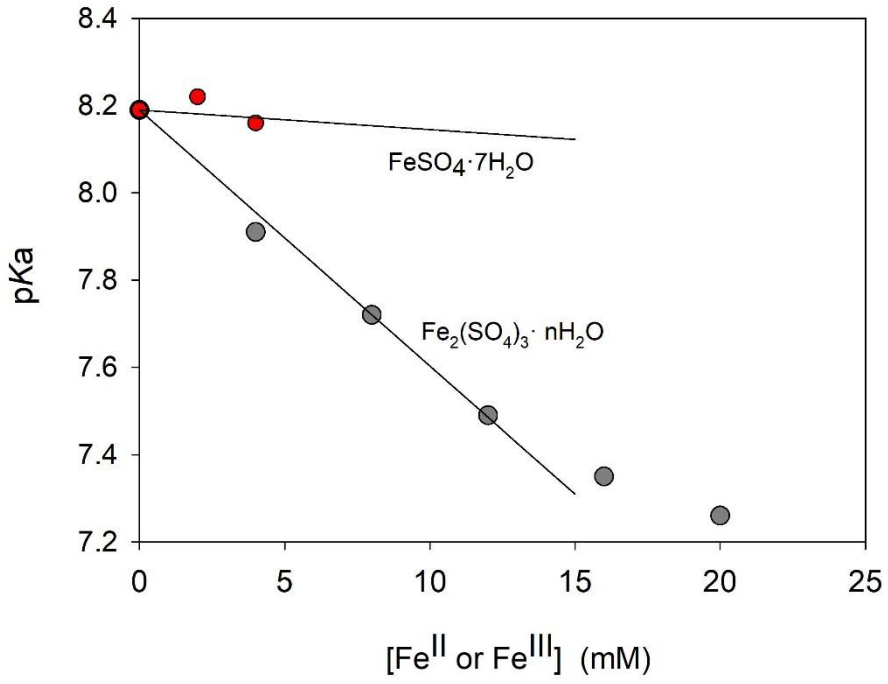
In order to confirm this hypothesis, the acidity constant of acetic acid was measured in the presence of different amounts of **1**, using a mixture of DMSO/H_2O 80:20 (v/v) (80% DMSO),[114] in which the salt is soluble enough to carry out potentiometric measurements. In this medium the pK_w for water autoprotolysis rises to 18.4 and the pK values of neutral acids rise too, with respect to those measured in pure water (pK_a). This acidity inhibition results in more evident effects of an interacting additive on the dissociation of acid species.[115] Apparent acidity constants of acetic acid in the presence of hydrate iron(III) sulfate at different concentrations were determined by potentiometric titrations, carried out on 1.0 mM solutions of acetic acid, using tetramethylammonium hydroxide as base and tetraethylammonium perchlorate (5.0 mM) as ionic strength buffer Analogous measurements were carried out in the presence of $FeSO_4 \cdot 7H_2O$, for comparison (table 2.8).

Entry	Iron salt	(mM) [b]	p*K* [c]
1	–	0.0	8.19
2	$Fe_2(SO_4)_3 \cdot nH_2O$	4.0	7.91
3	$Fe_2(SO_4)_3 \cdot nH_2O$	8.0	7.72
4	$Fe_2(SO_4)_3 \cdot nH_2O$	12.0	7.49
5	$Fe_2(SO_4)_3 \cdot nH_2O$	16.0	7.35
6[d]	$Fe_2(SO_4)_3 \cdot nH_2O$	20.0	7.26
7	$FeSO_4 \cdot 7H_2O$	2.0	8.22
8[e]	$FeSO_4 \cdot 7H_2O$	4.0	8.16

[a] [AcOH]= 1.0mM, 25 °C, 5 mM Et_4NClO_4; [b] Concentration of the iron ions; [c] Experimental uncertainty = ±0.04 pK units; [d] At this salt concentration, a faint precipitation occurs; [e] $FeSO_4 \cdot nH_2O$ is not soluble in this mixture at concentration higher than 4 mM.

Table 2.8 *Determination of apparent acidity constants of acetic acid alone and in the presence of various amounts of different iron salts by potentiometric titrations*

The acidity of the medium is evidently affected by the presence of iron salt **1**, since its apparent pK decreases from 8.19 down to 7.35 upon addition of increasing amount of the salt (table 2.8, entries 1-5) up to 20 mM, which is the solubility limit of the salt. At this concentration value, the pK rises to 7.26, due to the limited solubility of the species (entry 6). On the other hand, the addition of $FeSO_4 \cdot 7H_2O$, which did not catalyze the reaction of **2** (entry 7), gave no appreciable change of the measured acidity. The effect of adding increasing amount of an iron salt can be more effectively explained in terms of slope of the straight lines obtained from least squares fitting of experimental points 1-5 (effect of **1**) and 1 + 6-7 (effect of $FeSO_4 \cdot 7H_2O$). The plot of pKa values against the amount of iron is depicted in scheme 2.21.



Scheme 2.21 *Apparent pK values of AcOH versus the concentration of iron ions in 80% DMSO at 20 °C. The higher is the slope value, the higher is the effect of iron ions in increasing the acidity of AcOH*

The observed enhanced acidity can thus be explained in terms of interaction of acetic acid with Fe(III) centre, so as to generate free hydronium and acetate complexes. This can be written down in the form of equation 2.3, in which sulfate ions have been omitted for clarity.

$$(AcOH)Fe^{3+}(H_2O)_x + H_2O \rightleftharpoons (AcOFe)^{2+}(H_2O)_x + H_3O^+ \qquad (2.3)$$

The equilibrium is driven by the affinity of the acetate ligand for the ferric ion, while the low coordinating and non-basic sulfate ions may assist both coordination and protonic

release of acetic acid. Iron salts with more basic counteranions were indeed found to be poor catalysts.[91]

Furthermore, the assumption that the first step of the reaction is the protonation of the triple bond is reflected in the strong dependence of the substrate reactivity on the electronic effect of the aryl substituents (see scheme 2.15 and relative discussion). In the search of a parameter that may reflect the wide difference in the reactivity of the substrates, the relative proton affinity (PA_R, proton affinity determined with respect to a model compound) was calculated for a series of internal alkynes, including or *o*-tolyl-*t*-butylacetylene (**4c**), 1-phenylpropyne (**2**), 1,2-diphenylacetylene (**4m**) and 1,4-diphenylbuta-1,3-diyne (**4n**). The reactive terminal alkyne phenylacetylene (**7a**) was taken as a reference for the calculation of relative proton affinities (PA_R). The PA_R values were obtained by ab-initio calculations performed at the HF/6-311G(d,p) level in vacuum and in acetic acid, and are expressed as the negative of the ΔE value of the isodesmic reaction shown in equation 4.[116]

$$Ph^{(+)}C{=}CH_2 + RC{\equiv}CR' \rightleftharpoons PhC{\equiv}CH + R^{(+)}C{=}CHR' \qquad (4)$$

The obtained value for a substrate should be a measure of its tendency to undergo a reactive process *via* initial protonation, with respect to phenylacetylene (**7a**): a positive PA_R indicates that the alkyne is more basic than **7a**, and vice versa. The calculated values show opposite trends in vacuum and in the solvent, a common case for proton affinities of organic compounds (table 2.9).[116b]

Entry	RC≡CR′	PA_R (kcal/ mol) (vacuum)	PA_R (kcal/ mol) (AcOH)
1	*o*-tolylC≡C*t*-Bu (**4c**)	6.35	1.46
2	PhC≡CH (**7a**)	0	0
3	PhC≡CMe (**2**)	0.48	– 1.35
4	PhC≡CPh (**4m**)	0.61	– 3.82
5	PhC≡CC≡CPh (**4n**)	0.98	– 7.13

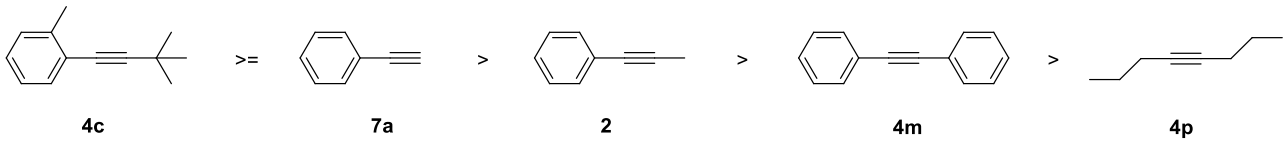
Table 2.9 *Relative Proton affinity (PA_R) of internal alkynes versus phenylacetylene* (**7a**)

In vacuum all the PA_R values are positive, thus indicating a higher basicity of the internal alkynes compared to **7a**, due to charge stabilization of the corresponding carbocation by increased molecular dimensions. In acetic acid, the opposite trend can be rationalized by taking into account another structural feature, apart from molecular size. When the triple bond is protonated, it partially loses its conjugation, and this effect increases at increasing extension of the π-system in the alkyne. In acetic acid, the solvent provides the stabilization of the positive charge of the carbocation, so the partial conjugation loss becomes the prevalent factor and a trend inversion is observed with respect to the situation in the vacuum, where carbocation stabilization by molecular dimension slightly prevails. Accordingly, **4c** is the most basic alkyne, both in vacuum and acetic acid, because of its greater molecular dimension, the degree of conjugation being similar to that of phenylacetylene (table 2.9, entry 1). Alkynes with more extended π-system (**4m** and **4n**) become instead less basic due to conjugation loss upon protonation (entries 4-5). Alongside proton affinity calculation, the reactivity of compounds **2**, **7a**, **4c**, **4m** and **4n** was experimentally investigated by performing competition reactions between couples of alkynes. The reactions were performed with 5 mol% of the iron catalyst **1**, two alkynes (1.0 M in AcOH) at 120 °C, in order to observe conversion for all the compounds in the series. The experimental value of the molar ratio of the hydration products (P_1 and P_2) deriving from each alkyne couple, measured upon integration of the proper signals in the ^{1}H NMR spectrum of the reaction mixture after work-up, was taken as an experimental measure of the relative reactivity of the substrates (table 2.10).

Entry	Alkyne 1	Alkyne 2	$[P_1]/[P_2]$	Time (h)
1	PhC≡CH (**7a**)	*o*-tolylC≡C*t*-Bu (**4c**)	1≅1	4.0
2	*o*-tolylC≡C*t*-Bu (**4c**)	PhC≡CMe (**2**)	25:1	5.5
3	PhC≡CH (**7a**)	PhC≡CMe (**2**)	20:1	5.0
4	PhC≡CMe (**2**)	PhC≡CPh (**4m**)	100:1	8.0
5	PhC≡CPh (**4m**)	PrC≡CPr (**4p**)	2:1	19.0

Table 2.10 *Competition experiments for the hydration of internal arylalkynes catalyzed by **1** in acetic acid*

These results are in agreement with the trend shown by theoretical calculation of the proton affinity, so that it is possible to draw a basicity scale, which also reflects reactivity, with the assumption that protonation of the triple bond is the rate-determining step of the overall hydration process (scheme 2.22).

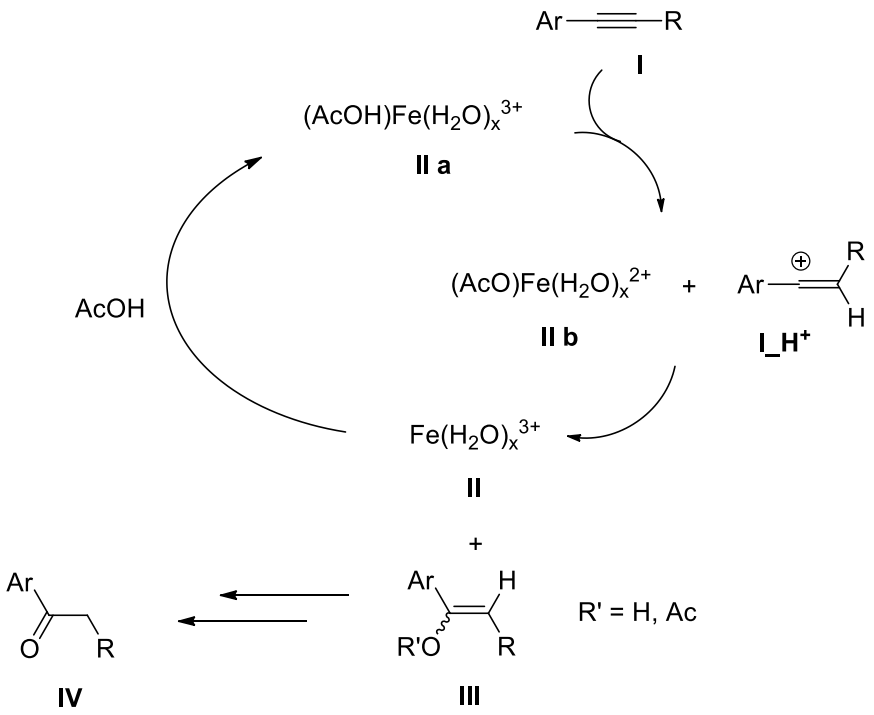


Scheme 2.22 *Reactivity scale based on competitive hydration experiments and theoretical calculations (PA_R)*

2.12 Conclusions and future perspectives

The catalytic system constituted by $Fe_2(SO_4)_3 \cdot nH_2O$ in acetic acid, which had previously been found to be suitable for the hydration of terminal arylalkynes, was proven to be effective also to hydrate alkylaryl alkynes to the corresponding aryl ketones. Interaction of the iron salt with acetic acid provides a stronger Brønsted acidic species under catalytic conditions, suitable for either simple hydration or sequential protodesilylation/hydration of internal alkynes. The complete regioselectivity exhibited by the process on a broad substrate scope, together with the high yields obtained in many cases, make this catalytic system ideal for transformations both on a small laboratory scale and for scale-up applications. Moreover, expensive or toxic transition metals, harsch conditions due to the employment of strong mineral acids, halogenated materials and solvents are not involved in the procedure. All these features of the reaction protocol make it intrinsically respectful towards the principles of green chemistry.[117] Prevention (1st and 12th principle) and employment of safer solvents and chemicals (5th principle) result from the use of a combination of weak acidic medium and a non toxic and easily available transition metal salt (7th principle), which lays the groundwork for future applications of this catalytic system (9th principle) in less hazardous chemical multi-step synthesis (3rd principle).[118] Both the regioselectivity and the application in the one-pot deprotection-hydration of aryltrimethylsilylalkynes are a clear index of atom-economic feasibility of chemical transformations under the relatively mild reaction conditions (2nd and 8th principle), and so with less energetic demand as possible (6th principle). In a narrow sense, nine of the twelve principles of green chemistry are fully respected. However, it is worth pointing out that no chemical has been designed in the development of this catalyic system (4th principle concerns the design of safer chemicals) and that the reactions have been performed just on a small laboratory scale, so without taking into account the possibility of integrating a real time system for analysis, degradation and possible recycling of waste products (10th and 11th principle), which is typically done in industrial plants. For what concerns mechanistic aspects of the protocol, after a careful examination of relative proton affinity calculations in the vacuum and in acetic acid and of

experimental relative reactivities, a catalytic cycle has been proposed to explain the mechanism of the reaction (scheme 2.23).



Scheme 2.23 *Proposed catalytic cycle for the mechanism of the reaction under LBA conditions*

First, the alkyne **I** is protonated by acetic acid to the corresponding arylvinyl carbocation **I_H**$^{+}$, whose stability accounts for the observed complete regioselectivity of the procedure, unattainable by the most active catalytic systems. The acidity of acetic acid is enhanced by coordination to the metal center in the complex **II a**, that turns to complex **II b** upon protonation of the substrate. Subsequent addition of an acetate ion or of a water molecule affords acetyl enol ether **III** and the hydrated iron salt **II**, which can coordinate acetic acid again for a new catalytic cycle. Further deprotection of **III** and tautomerization of the enol to the final carbonyl compound **IV** complete the cycle. The nature of the mechanism of LBA catalysis explains both the advantages (*e.g.* insensitivity to steric hindrance in the substrate) as well as the limitations in the substrate scope. It is worth mentioning that the role of protons has also been specifically discussed in the context of homogeneous gold catalysis.[119] All the reactions here described proceeded under heterogeneous conditions due to the low solubility of the iron salt in acetic acid. Various attempts to obtain homogeneous solutions by adding more polar solvents corresponded to drastic reduction of activity. Moreover, the solid material recovered by filtration at the end of reaction exhibited poor activity in subsequent runs.

Future perspectives include a deeper investigation on the chemoselectivity exhibited by the catalytic system in the simultaneous presence of different kinds of triple bond within the

same molecular skeleton likely to undergo hydration (*e. g.* terminal and internal alkynes, electron rich and electron poor triple bonds of the same type). Other interesting issues to face in order to demonstrate that hydrated iron(III) sulfate can be employed on industrial scale are: the compatibility with various basic nitrogen-containing molecules in the reaction environment and, obviously, the employment alongside the total synthesis of natural compounds and active pharmaceutical ingredients on a large scale. It is worth mentioning that the present catalytic system has already been proved compatible with complex molecular scaffolds, since it was succefully employed along the synthesis of (+)-Dalesconol A and B, for the formation of seven membered cyclic ketone rings.[118]

2.13 Experimental section

2.12.1 General information, instruments and materials

Chemicals and solvents were obtained from commercial sources (Carlo Erba, Sigma Aldrich, Alfa Aesar) and used as received, including glacial acetic acid, unless noted otherwise. The iron salt $Fe_2(SO_4) \cdot nH_2O$ was a Carlo Erba (RPE grade) product, with iron content 20 ± 1%. The thermogravimetric analysis of the salt exhibited an overall weight loss of 26.2% in the temperature range 120 – 265 °C, in agreement with the specified iron content corresponding to a material composed essentially by ferric sulfate nonahydrate. Tetrahydrofuran was distilled under argon over Na/K alloy. Triethylamine or diisopropylamine were distilled under nitrogen atmosphere over calcium hydride. Petroleum ether (40-70 °C) was distilled on a rotavapor at atmospheric pressure. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300Avance II spectrometer operating at 300 MHz and 75 MHz, respectively, and referenced to the residual solvent signal ($C\underline{H}Cl_3$, δ= 7.26 ppm; $\underline{C}DCl3$, δ= 77.0 ppm). GC-MS analyses were performed on an Agilent Technologies 6890N Network GC System equipped with a 5973 Network Mass Selective Detector. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 pre-coated glass plates, and preparative flash chromatography was performed using silica gel 60 (0.040-0.063 mm), following Still technique[120] and adapting an aquarium bubbling pump as an air compressor.[121] High-resolution mass spectra were obtained on an ESI-Q-Tof Micro Mass instrument. The substrates 1-phenylpropyne (**2**), diphenylacetylene (**4m**), 2,5-dicyclohexyl-1,4-di-1-propynylbenzene (**4o**) and 4-octyne (**4p**) were commercially available and used as received. The substrates 1-methyl-2-(oct-1-yn-1-yl)benzene (**4a**),[122] 1-methyl-3-(oct-1-yn-1-yl)benzene (**4b**), 1-t-butylacetylenyl-2-methylbenzene (**4c**),[123] 1-dec-1-ynylnaphtalene (**4d**),[124] 1-methoxy-4-(oct-1-ynyl)benzene (**4f**),[125] 1-(thiophen-2-yl)-1-octyne (**4h**),[126] (3-oct-1-ynyl)pyridine (**4i**)[127] and 4-(phenylethynyl)anisole (**4l**)[128] were synthesized by cross-coupling reactions with the Sonogashira-Hagihara protocol.[105] The substrate 4-(oct-1-yn-1-yl)phenol (**4e**) was prepared as described in the literature.[129] The substrates 1-phenylhex-1-yn-3-ol (**4k**), 1,4-phenylhex-1-yn-3-ol (**4n**), 1-Phenyl-2-(trimethylsilyl)acetylene (**6a**),

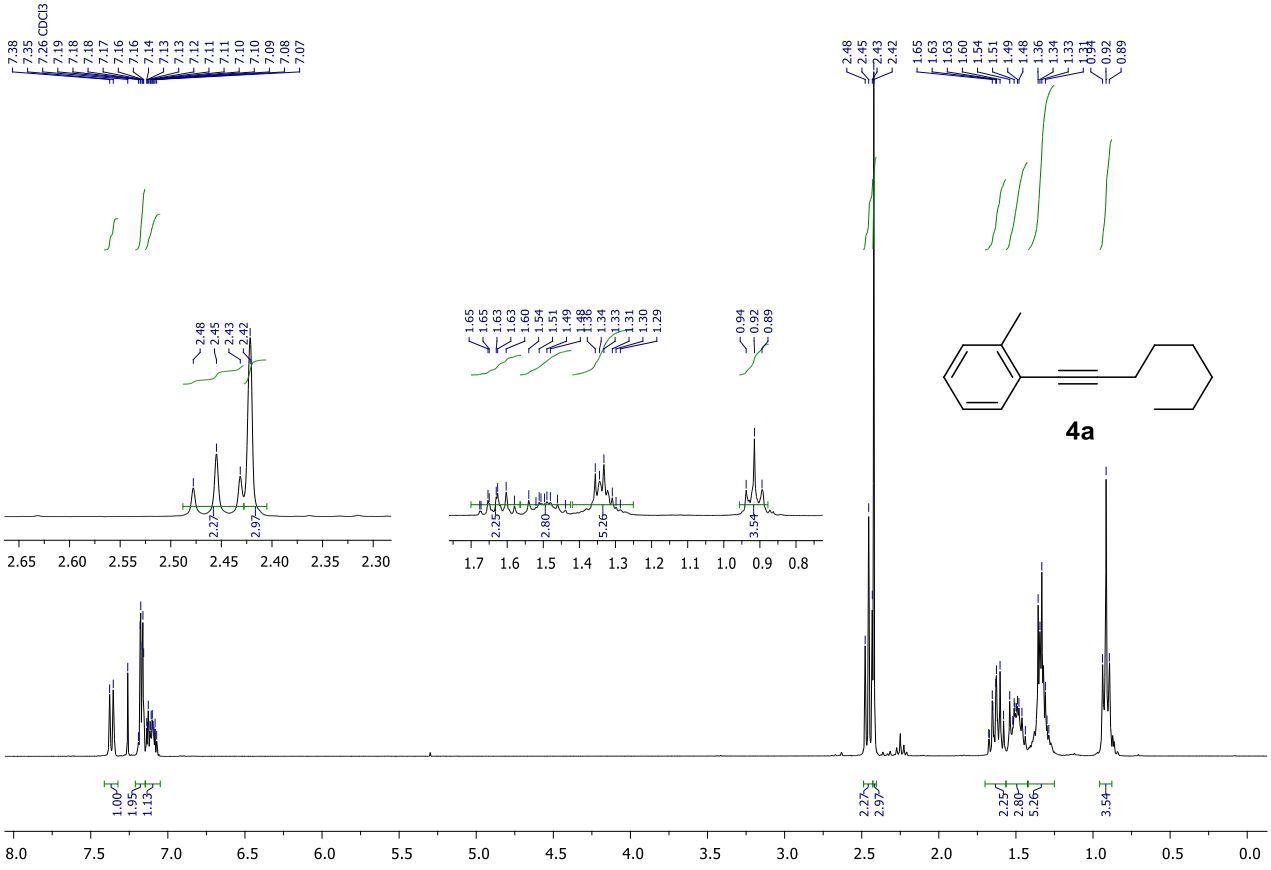
trimethyl(thiophen-3-ylethynyl)silane (**6b**), (3,5-dimethoxyphenyl)ethynyl)trimethylsilane (**6c**) and trimethyl((3-(trifluoromethyl)phenyl)ethynyl)silane (**6d**) had previously been prepared in the laboratory under Sonogashira-Hagihara reaction conditions. The substrate 1,4-diphenyl-1,3-butadiyne (**4n**) had previously been prepared in the laboratory following a literature procedure.[130] Experimental data relative to NMR signals of 1-(4-hydroxylphenyl)-octan-1-one (**5e**),[131] 1-(4-methoxylphenyl)-octan-1-one (**5f**),[132] 1-(thiophen-2-yl)octan-1-one (**5h**),[133] (Z)-1-phenyl-1-yn-hex-3-ene (**5k**),[134] 1-(4-methoxylphenyl)-2-phenylethane-1,2-dione (**5m**),[135] 1-(thiophen-3-yl)-ethanone (**8b**),[86b] 1-(3,5-dimethoxyphenyl)ethanone (**8c**),[85] and 3-(trifluoromethyl)acetophenone (**8d**)[136] were found in agreement with those reported in the literature.

2.12.2 Substrates synthesis and characterization

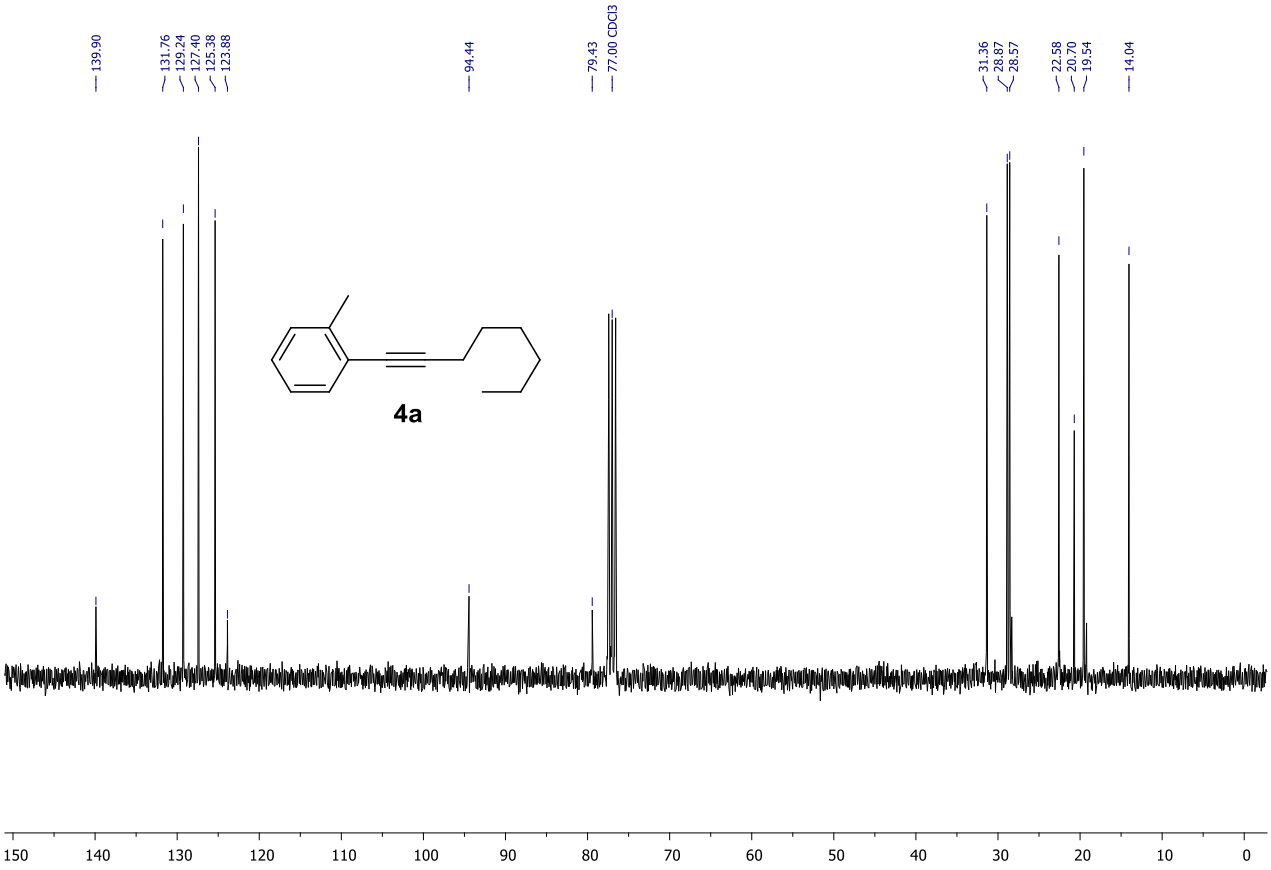
The synthesis of the substrates was performed following a general procedure, on the basis of Sonogashira-Hagihara protocol.[105] In a flame dried Schlenk tube, $[PdCl_2(PPh_3)_2]$ (5 mol%) and CuI (10 mol%) were added under nitrogen atmosphere. Following three nitrogen/ vacuum cycles, triethylamine (or triisopropylamine), the aryl halide (1 eq., 0.6-1 M in the amine) and the terminal alkyne (1.2 eq.) were added by syringe. The tube was sealed with a rubber septum, immersed in an oil bath, and the mixture kept under magnetic stirring at the set temperature. At the end of reaction, as checked by TLC and/ or by GC-MS, the heterogeneous mixture was filtered over Celite on a glass filter and washed with diethyl ether. The organic phase was treated with a saturated solution of ammonium chloride and with brine, dried over sodium sulfate and evaporated off under vacuum. The brown oily residue was purified by column chromatography on silica gel (eluent petroleum ether, petroleum ether/chloroform or petroleum ether/ethyl acetate) to afford the desired product.

1-methyl-2-(oct-1-yn-1-yl)benzene (4a)

Prepared from 2-iodotoluene (9.2 mmol) and 1-octyne (11.0 mmol) in triethylamine (13 mL) at 50 °C for 18 hours. Yield= 95%



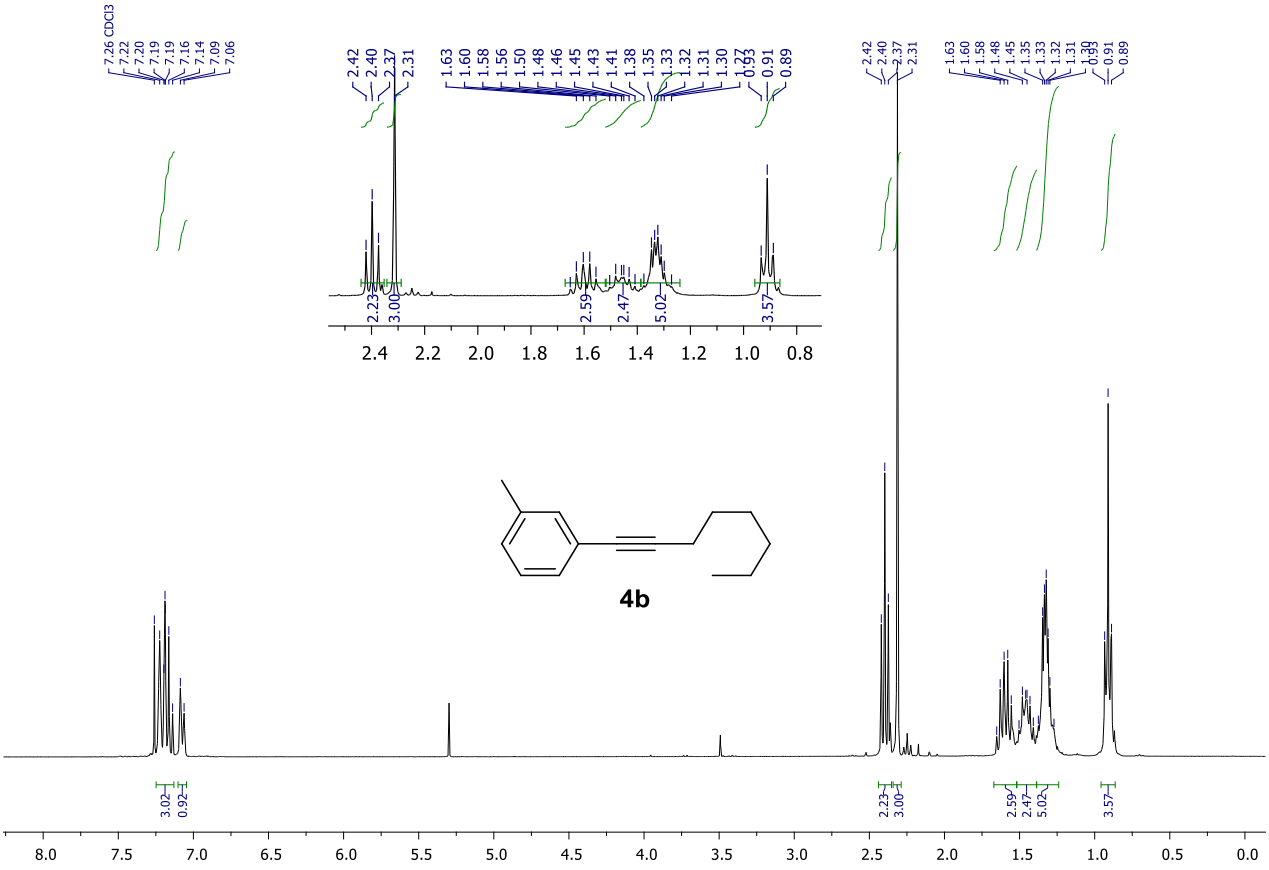
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 7.1 Hz, 1H), 7.20 – 7.15 (m, 2H), 7.15 – 7.06 (m, 1H), 2.45 (t, J = 7.0 Hz, 2H), 2.42 (s, 3H), 1.69 – 1.56 (m, 2H), 1.57 – 1.43 (m, 2H), 1.43 – 1.25 (m, 4H), 0.92 (t, J = 6.6 Hz, 3H).



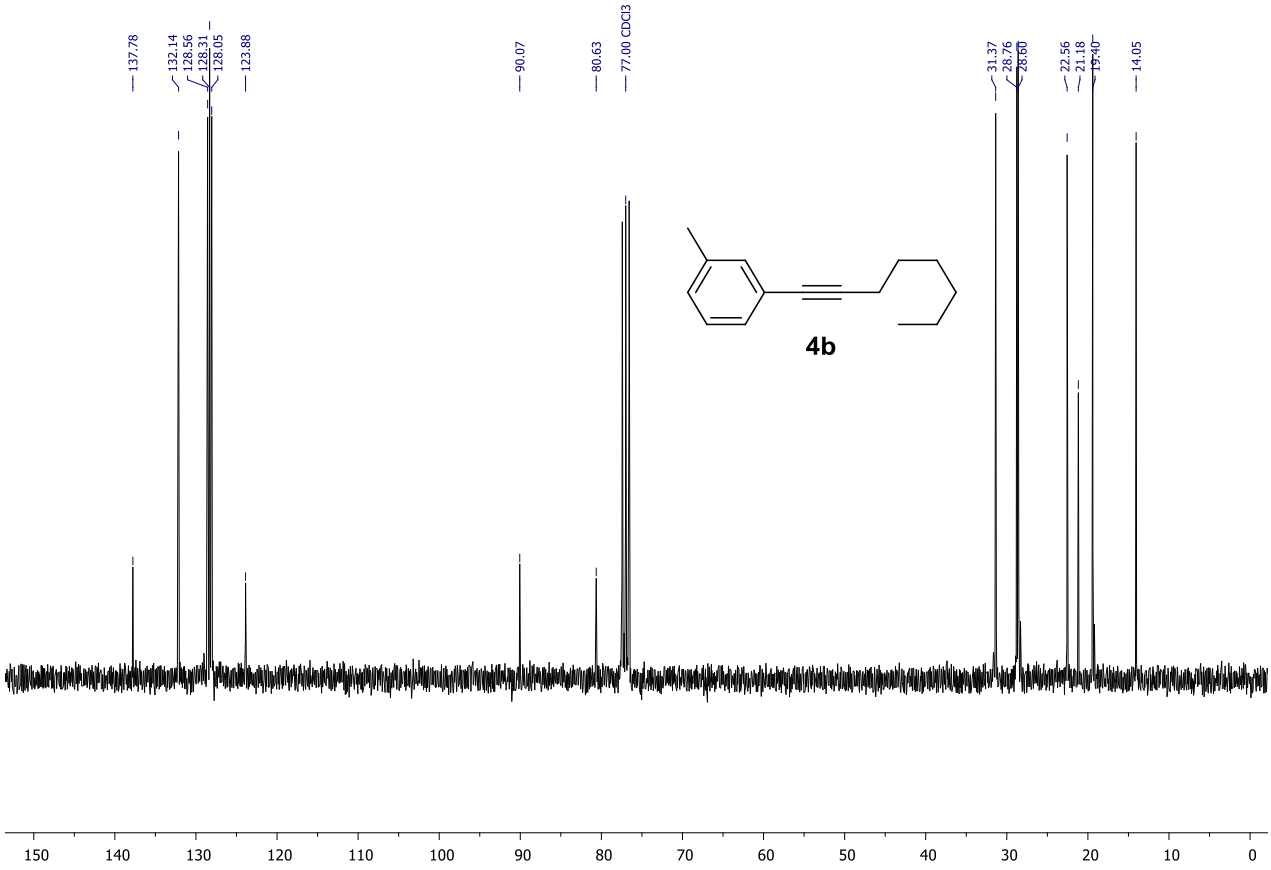
^{13}C NMR (75 MHz, $CDCl_3$) δ 139.90, 131.76, 129.24, 127.40, 125.38, 123.88, 94.44, 79.43, 31.36, 28.87, 28.57, 22.58, 20.70, 19.54, 14.04.

1-methyl-3-(oct-1-yn-1-yl)benzene (4b)

Prepared from 3-iodotoluene (6.8 mmol) and 1-octyne (8.2 mmol) in triethylamine (11 mL) at 50 °C for 4 hours. Yield= 93%



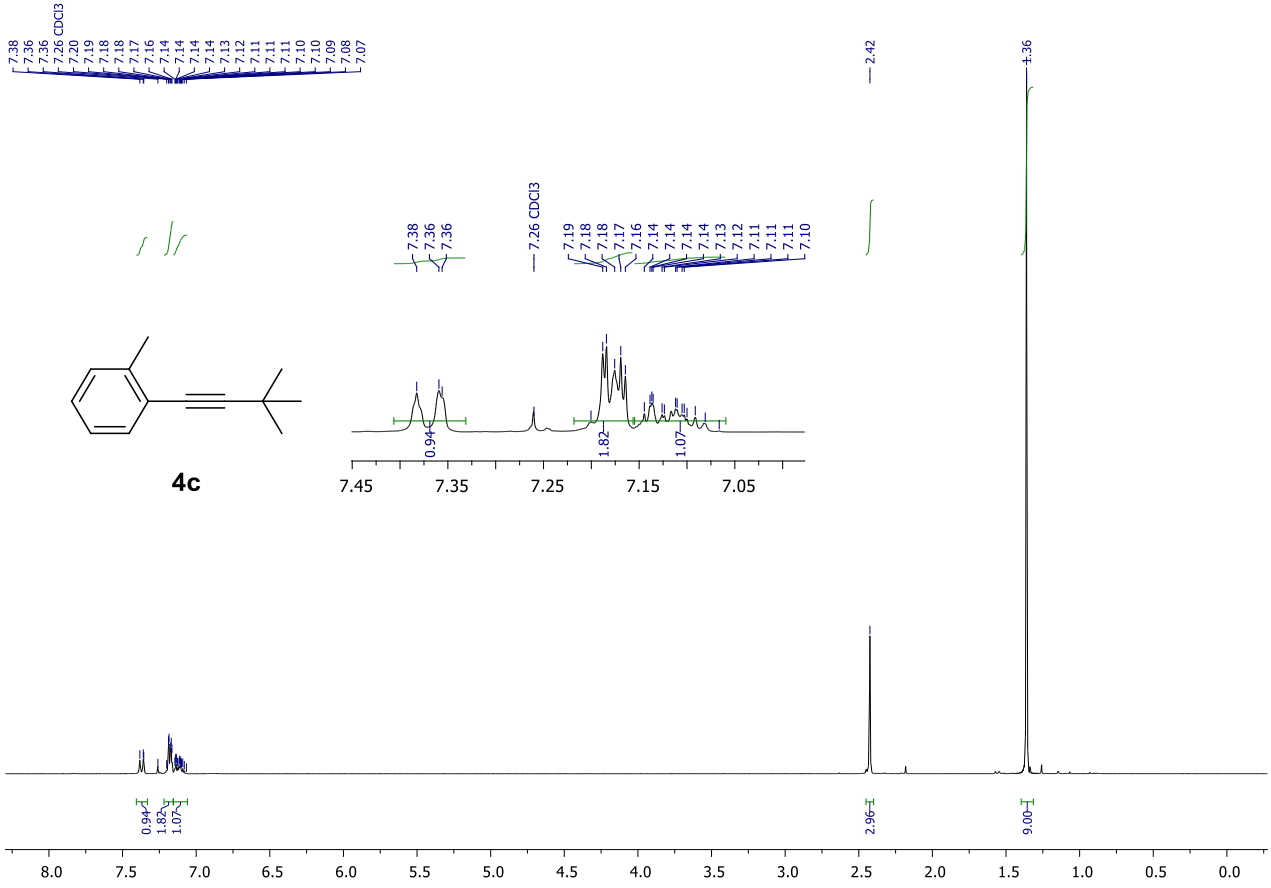
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.12 (m, 3H), 7.07 (m, 1H), 2.40 (t, J = 7.0 Hz, 2H), 2.31 (s, 3H), 1.60 (dt, J = 14.3, 7.0 Hz, 2H), 1.46 (m, 2H), 1.38 – 1.24 (m, 4H), 0.91 (t, J = 6.9 Hz, 3H).



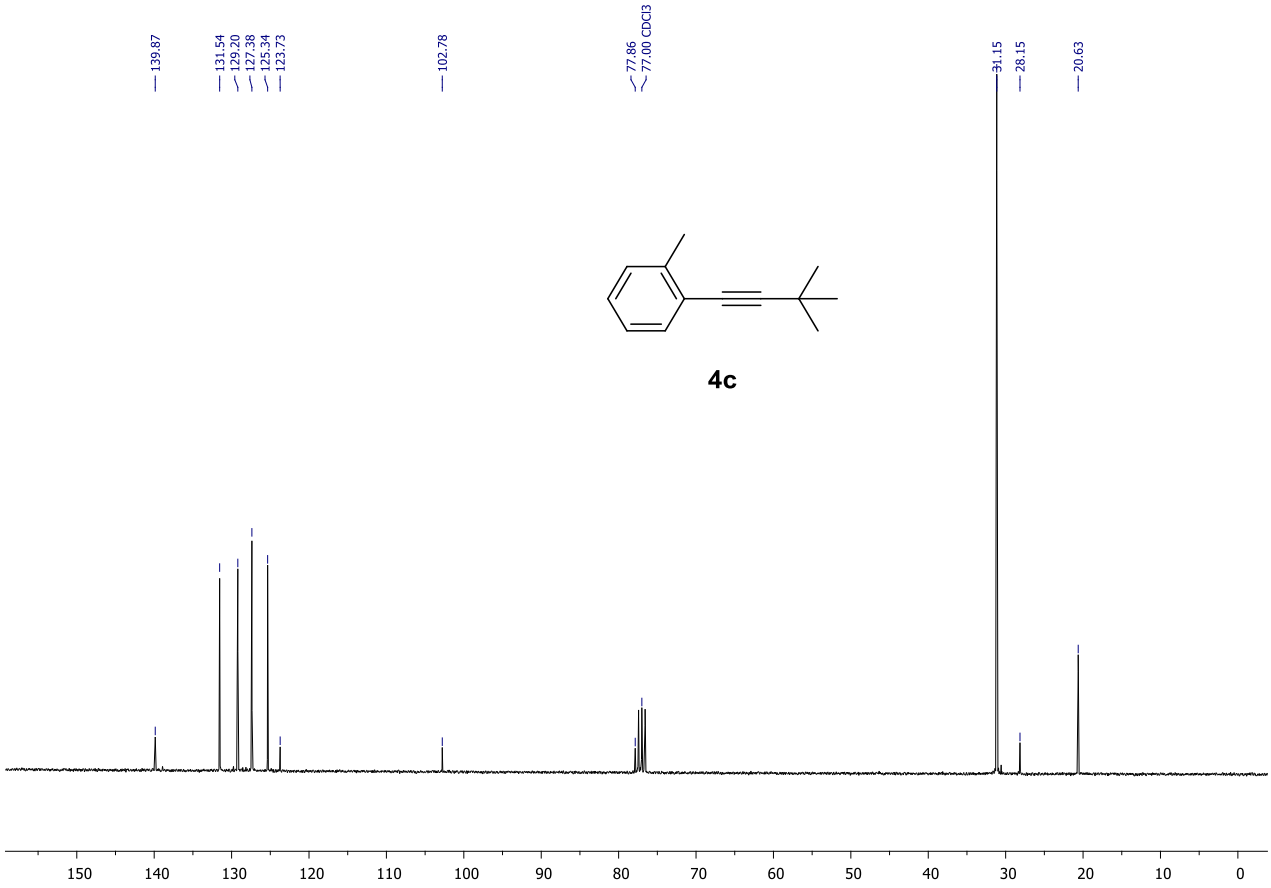
^{13}C NMR (75 MHz, $CDCl_3$) δ 137.78, 132.14, 128.56, 128.31, 128.05, 123.88, 90.07, 80.63, 31.37, 28.76, 28.60, 22.56, 21.18, 19.40, 14.05.

1-*t*-butylacetylenyl-2-methylbenzene (4c)

Prepared from 2-iotoluene (9.2 mmol) and t-butylacetylene (11 mmol) in triethylamine (16 mL) at 35 °C for 22 hours. Yield= 95%.



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 1H), 7.18 (m, 2H), 7.15 – 7.06 (m, 1H), 2.42 (s, 3H), 1.36 (s, 9H).

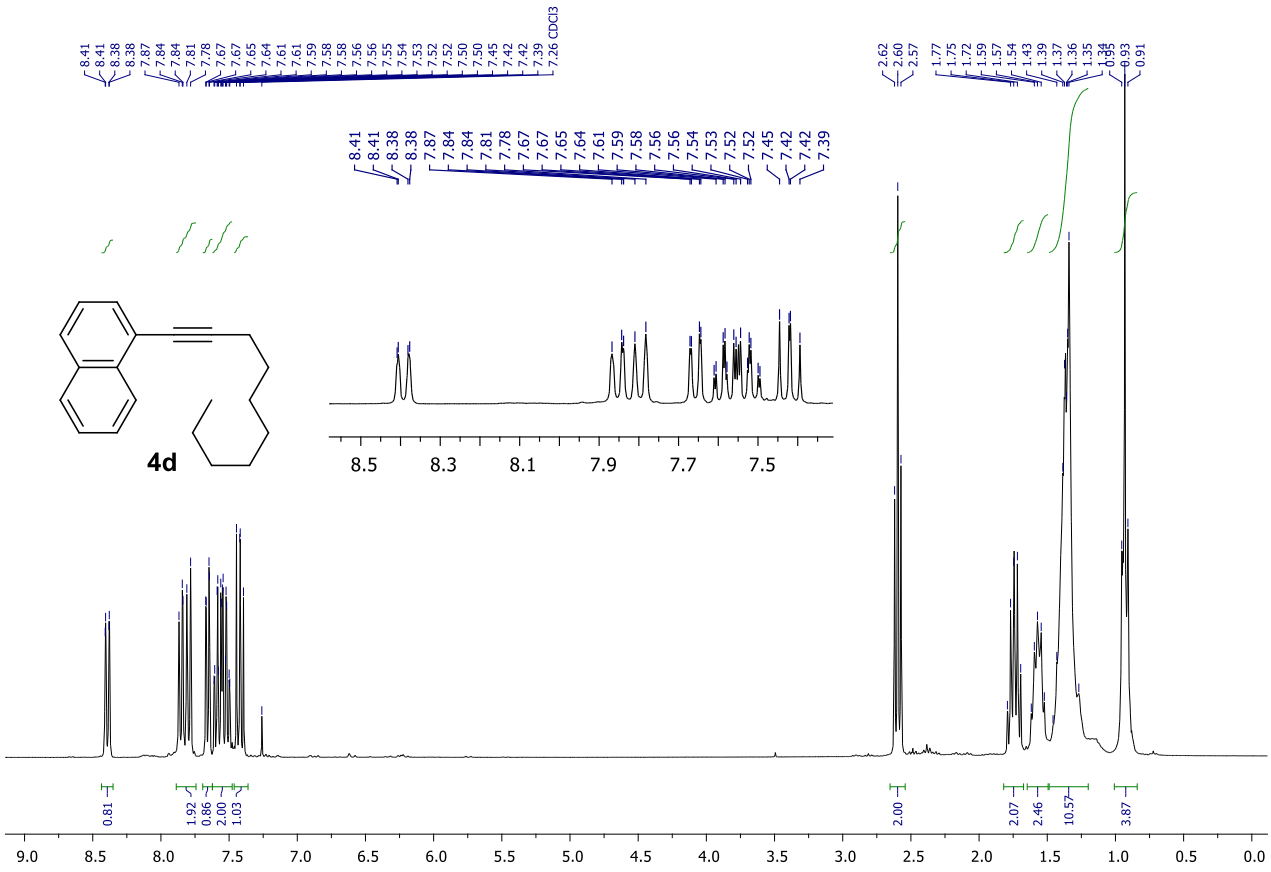


^{13}C NMR (75 MHz, $CDCl_3$) δ 139.87, 131.54, 129.20, 127.38, 125.34, 123.73, 102.78, 77.86, 31.15, 28.15, 20.63.

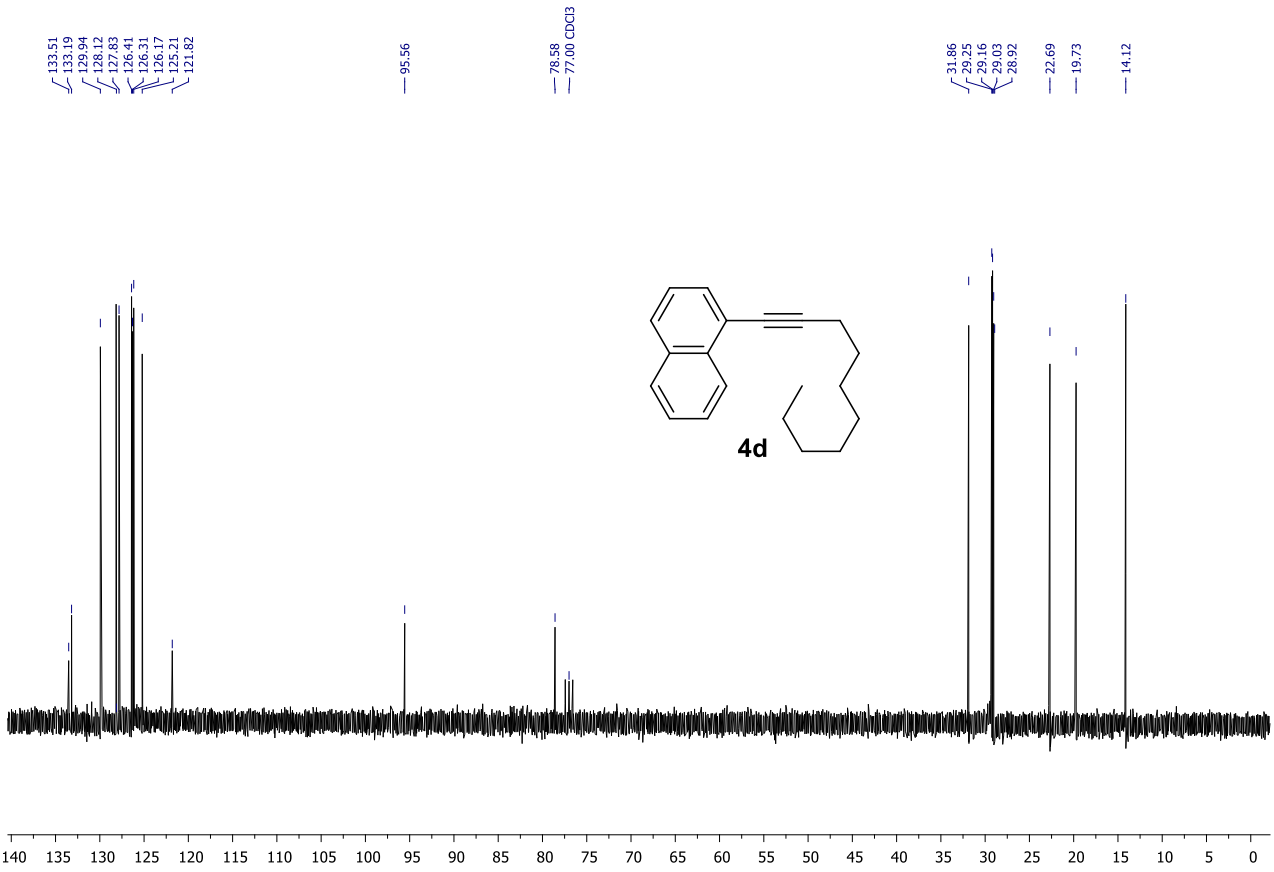
HRMS (ESI-TOF) m/z for ($C_{13}H_{18}O + Na^+$) calculated 213.1255, found 213.1208.

1-dec-1-ynylnaphtalene (4d)

Prepared from 1-bromonaphtalene (4.8 mmol) and 1-decyne (8.8 mmol) in triethylamine (5 mL) at 90 °C for 24 hours. In this case $[PdCl_2(PPh_3)_2]$ 3 mol% and CuI 6 mol% were used. Yield= 25%.



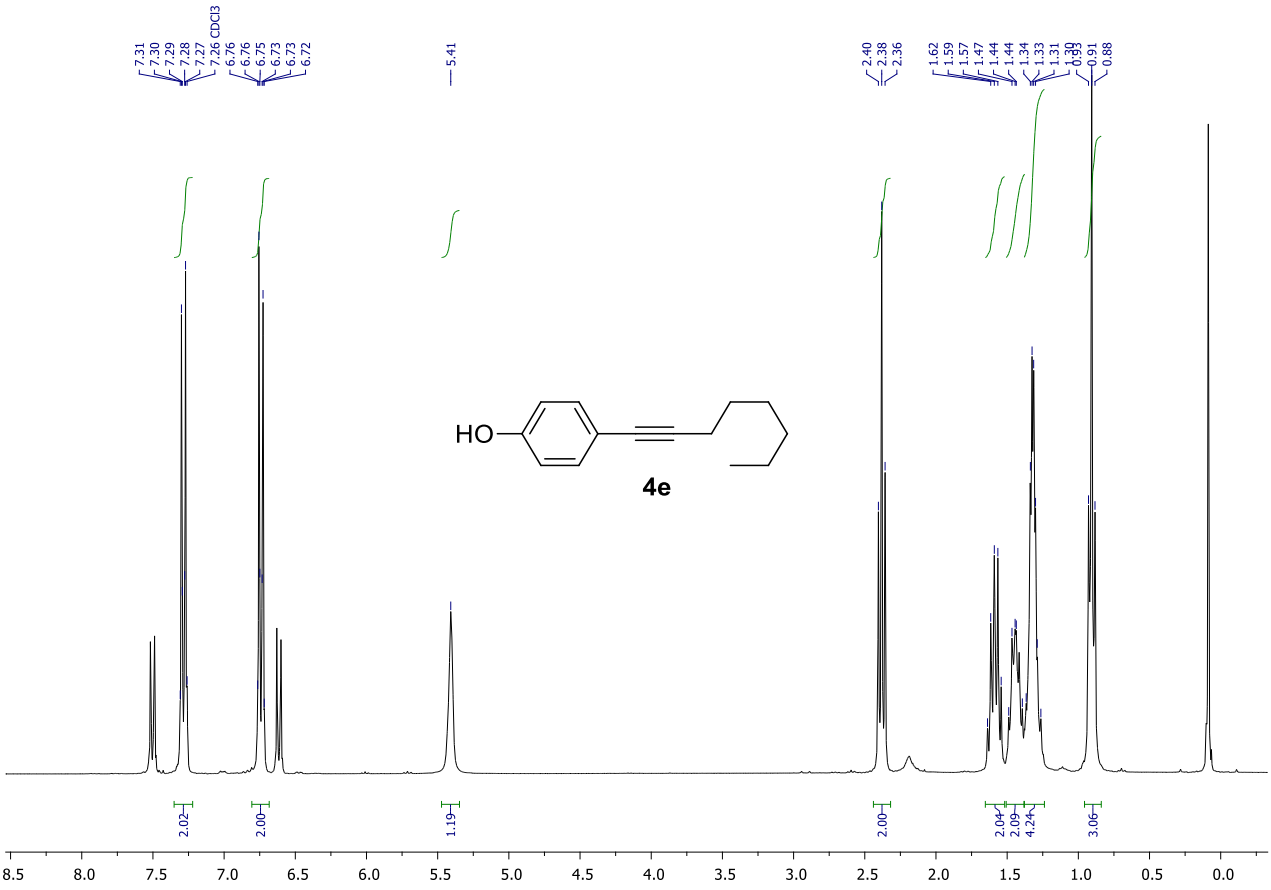
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (dd, J = 8.2, 0.8 Hz, 1H), 7.90 – 7.75 (m, 2H), 7.66 (dd, J = 7.1, 1.0 Hz, 1H), 7.62 – 7.48 (m, 2H), 7.42 (dd, J = 8.2, 7.2 Hz, 1H), 2.60 (t, J = 7.0 Hz, 2H), 1.81 – 1.66 (m, 3H), 1.64 – 1.50 (m, 3H), 1.49 – 1.21 (m, 6H), 0.93 (t, J = 6.8 Hz, 3H).



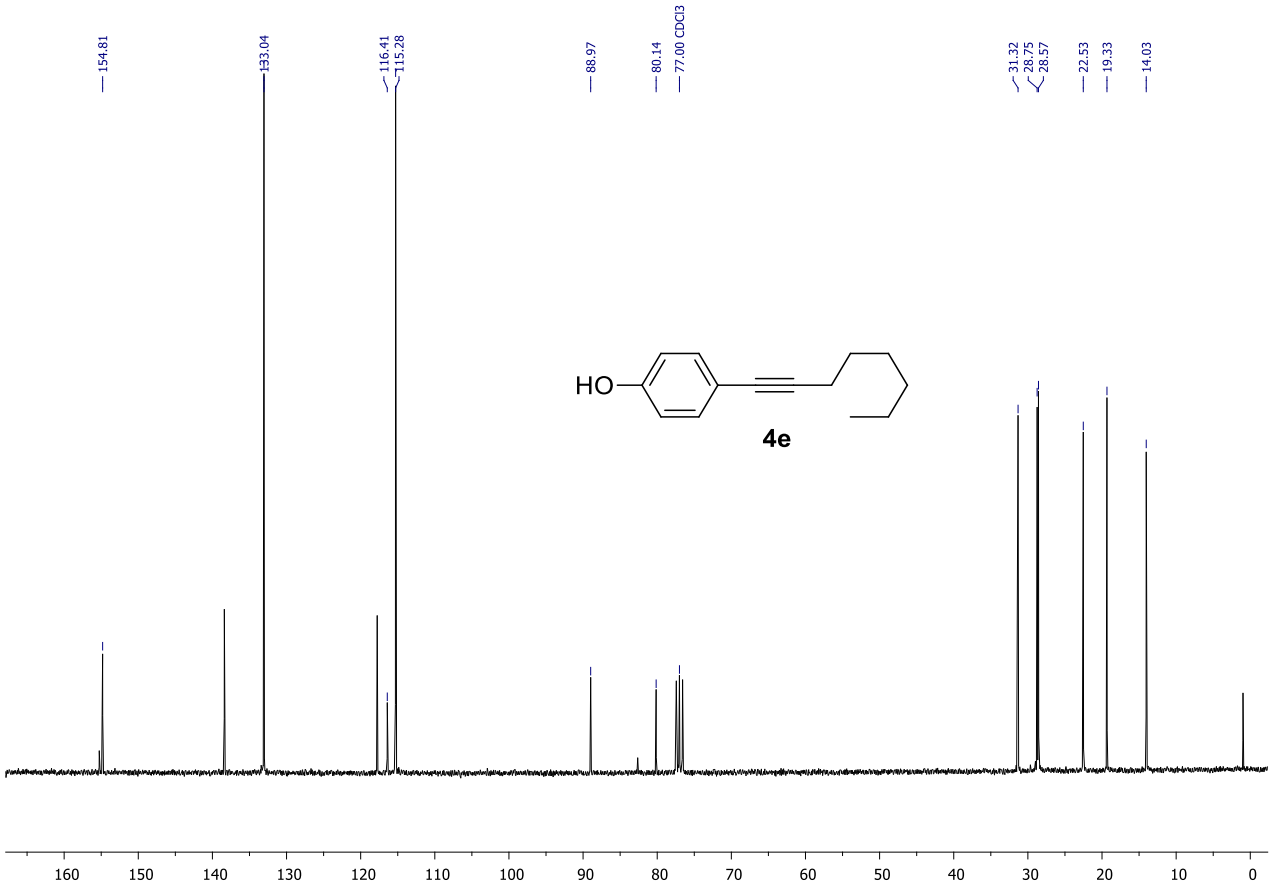
^{13}C NMR (75 MHz, $CDCl_3$) δ 133.51, 133.19, 129.94, 128.12, 127.83, 126.41, 126.31, 126.17, 125.21, 121.82, 95.56, 78.58, 31.86, 29.25, 29.16, 29.03, 28.92, 22.69, 19.73, 14.12.

4-(oct-1-yn-1-yl)phenol (4e)

Prepared from 4-iodophenol (9.0 mmol) and 1-octyne (10.8 mmol) in 30% aqueous ammonia (25 mL) and THF (50 mL) at room temperature for 24 hours. In this case $[PdCl_2(PPh_3)_2]$ 1,3 mol% and CuI 2,6 mol% were used. Yield= 51%.



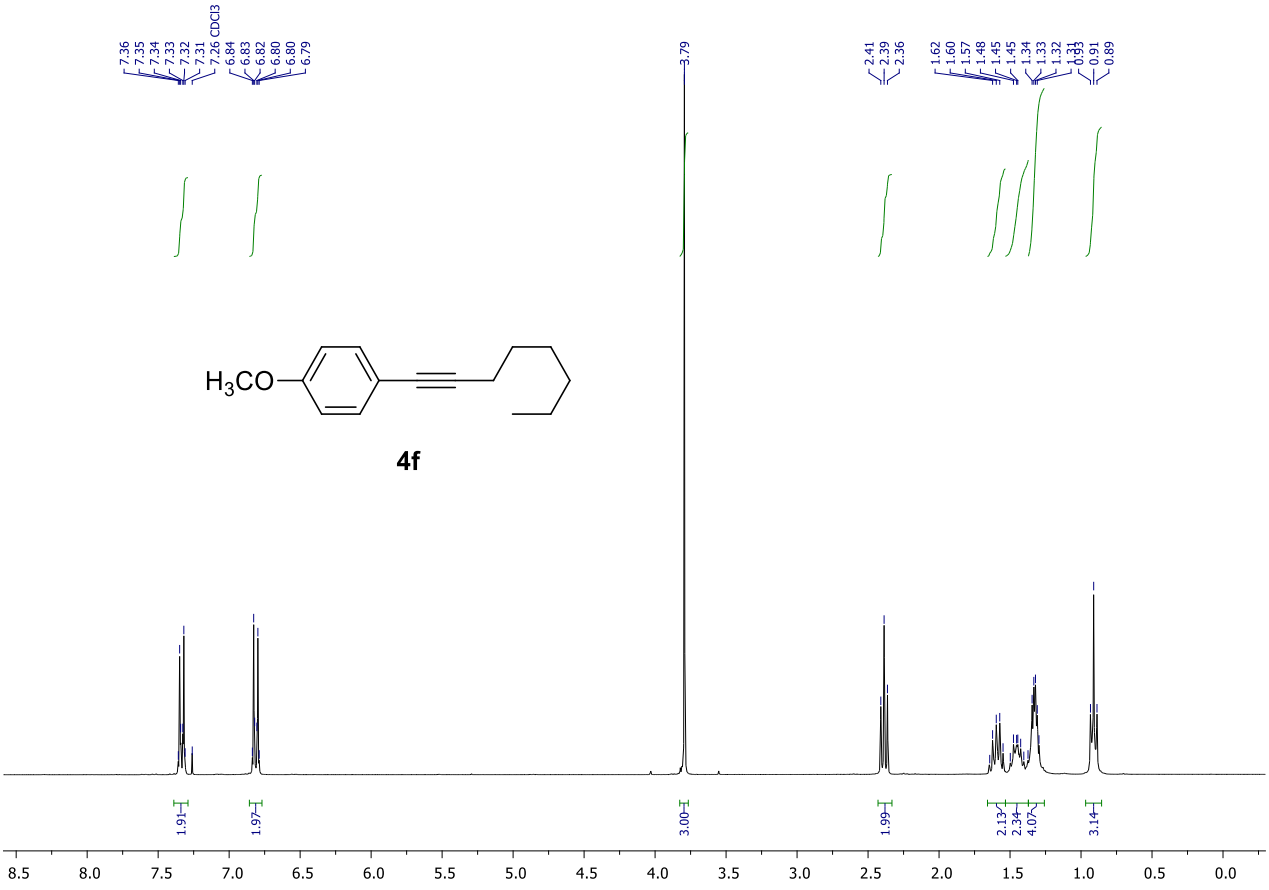
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 2H), 6.79 – 6.68 (m, 2H), 5.41 (br s, 1H), 2.38 (t, *J* = 7.0 Hz, 2H), 1.68 – 1.52 (m, 2H), 1.52 – 1.38 (m, 2H), 1.38 – 1.23 (m, 4H), 0.91 (t, *J* = 6.8 Hz, 3H).



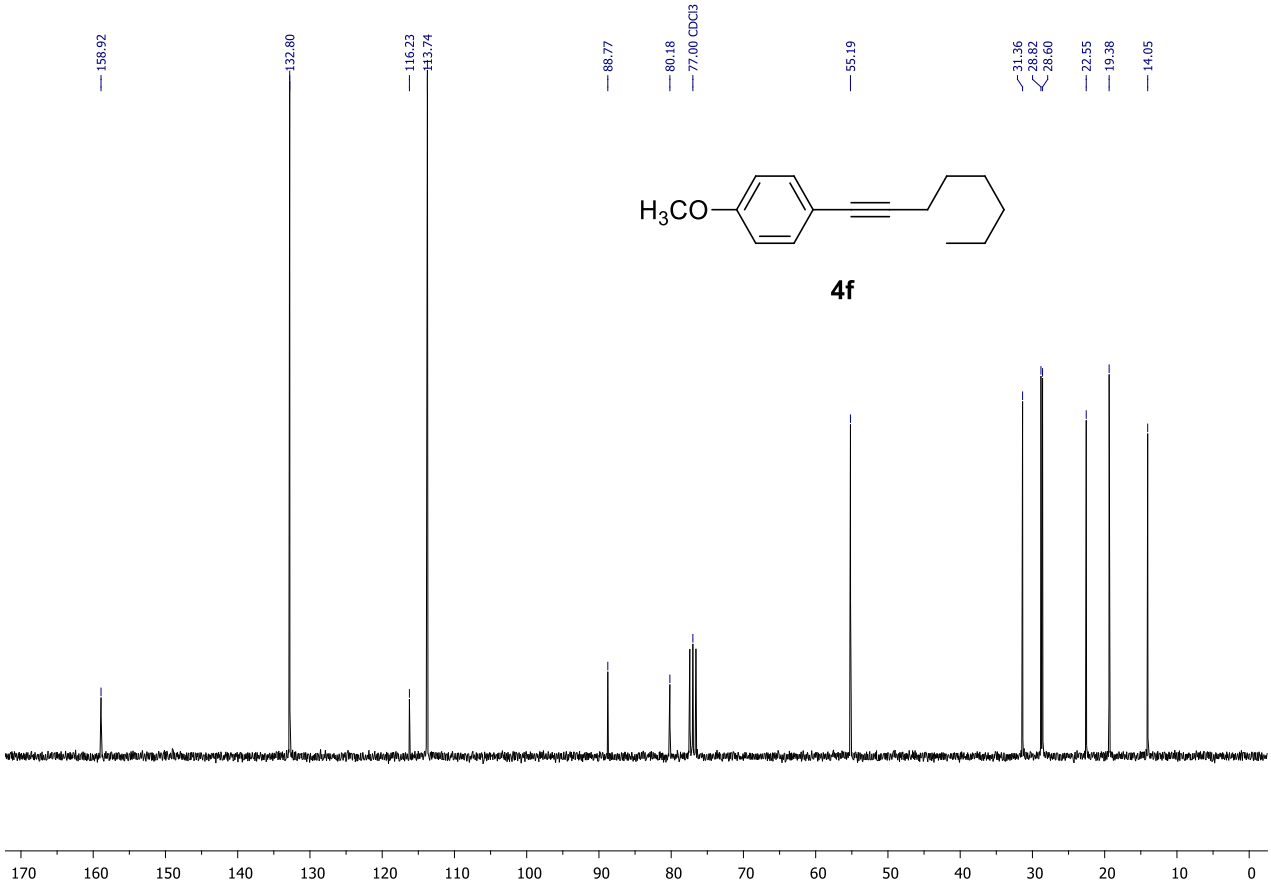
^{13}C NMR (75 MHz, $CDCl_3$) δ 154.81, 133.04, 116.41, 115.42, 88.97, 80.14, 31.32, 28.75, 28.57, 22.53, 19.33, 14.03.

1-methoxy-4-(oct-1-ynyl)benzene (4f)

Prepared from 4-iodoanisole (4.3 mmol) and 1-octyne (4.7 mmol) in triethylamine (7 mL) at room temperature for 4 hours. Yield= 63%.



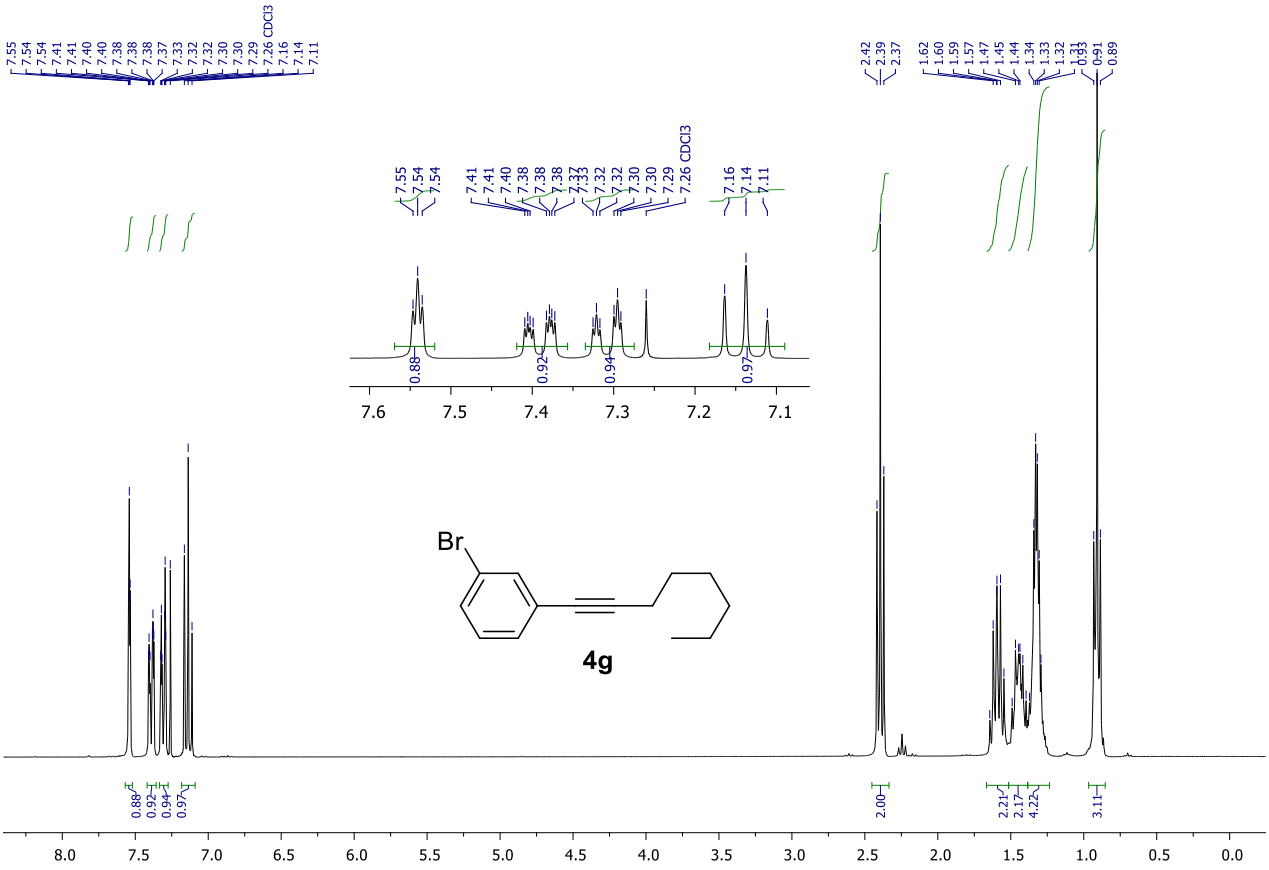
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 2H), 6.85 – 6.77 (m, 2H), 3.79 (s, 3H), 2.39 (t, *J* = 7.0 Hz, 2H), 1.66 – 1.53 (m, 2H), 1.52 – 1.37 (m, 2H), 1.37 – 1.26 (m, 4H), 0.91 (t, *J* = 6.9 Hz, 3H).



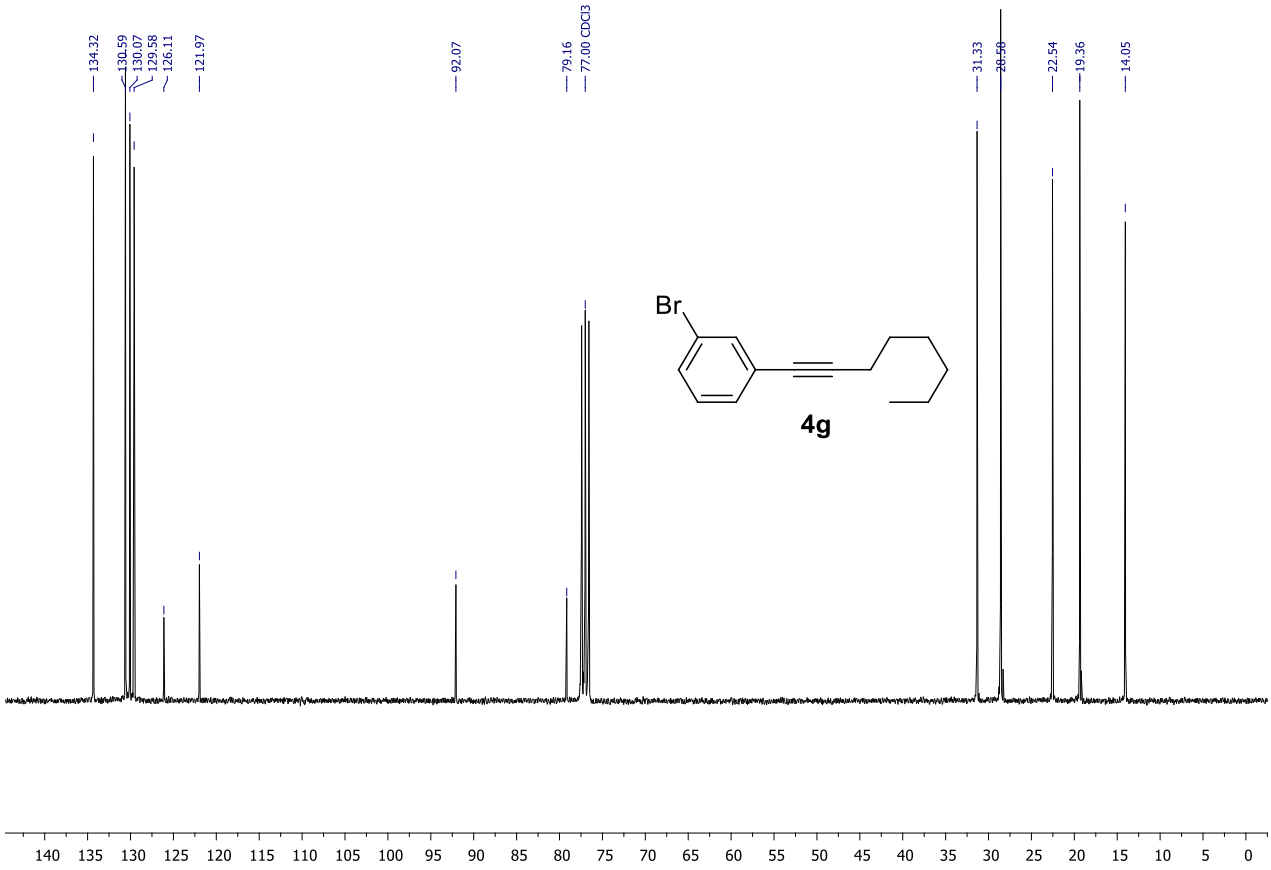
^{13}C NMR (75 MHz, $CDCl_3$) δ 158.92, 132.80, 116.23, 113.74, 88.77, 80.18, 55.19, 31.36, 28.82, 28.60, 22.55, 19.38, 14.05.

1-bromo-3-(oct-1-yn-1-yl)benzene (4g)

Prepared from 1-bromo-3-iodobenzene (5.3 mmol) and 1-octyne (6.3 mmol) in diisopropylamine (11 mL) at 50 °C for 21 hours. In this case [$PdCl_2(PPh_3)_2$] 3 mol% and CuI 6 mol% were used. Yield= 74%.



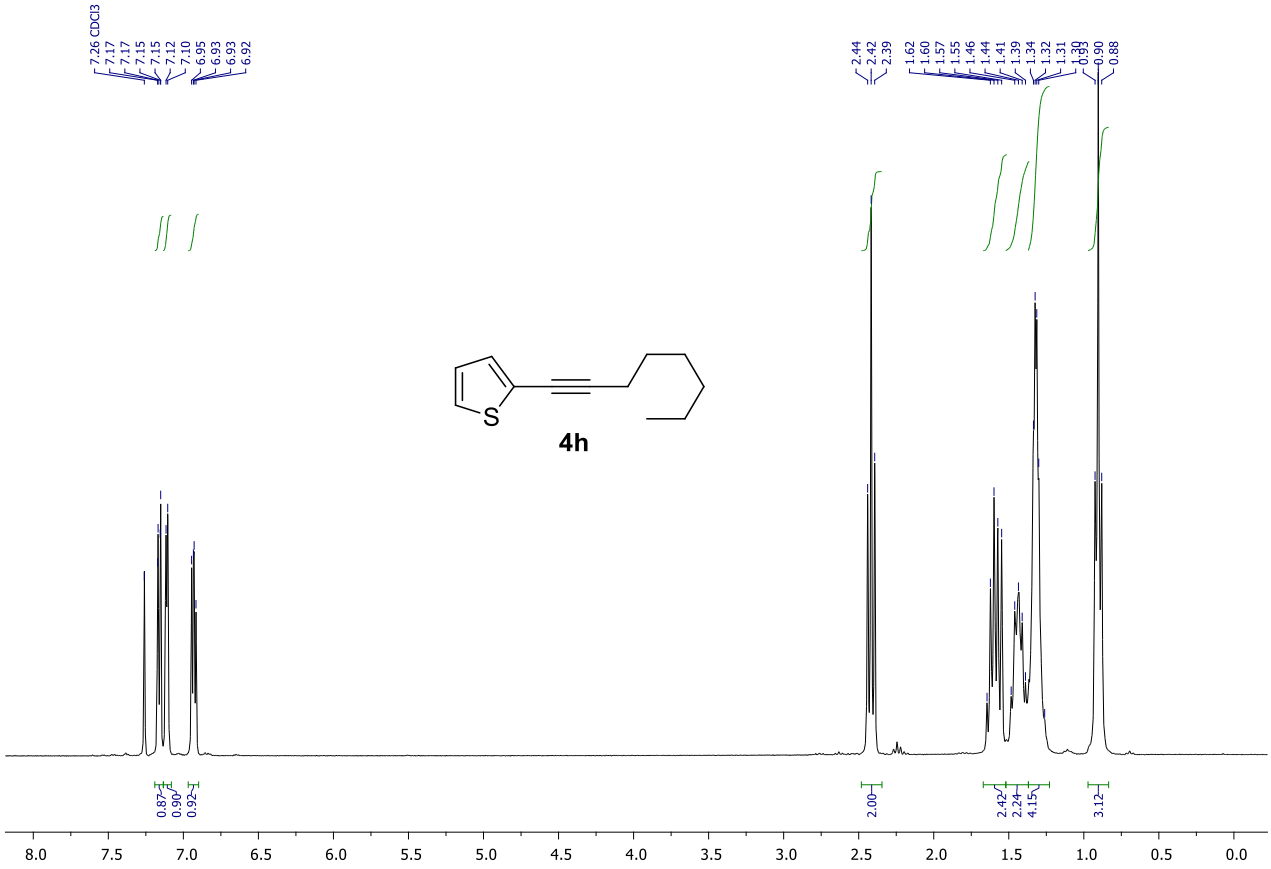
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (t, *J* = 1.7 Hz, 1H), 7.39 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H), 7.31 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.14 (t, *J* = 7.9 Hz, 1H), 2.39 (t, *J* = 7.0 Hz, 2H), 1.60 (dq, *J* = 14.3, 7.0 Hz, 2H), 1.44 (m, 2H), 1.38 – 1.24 (m, 4H), 0.91 (t, *J* = 6.9 Hz, 3H).



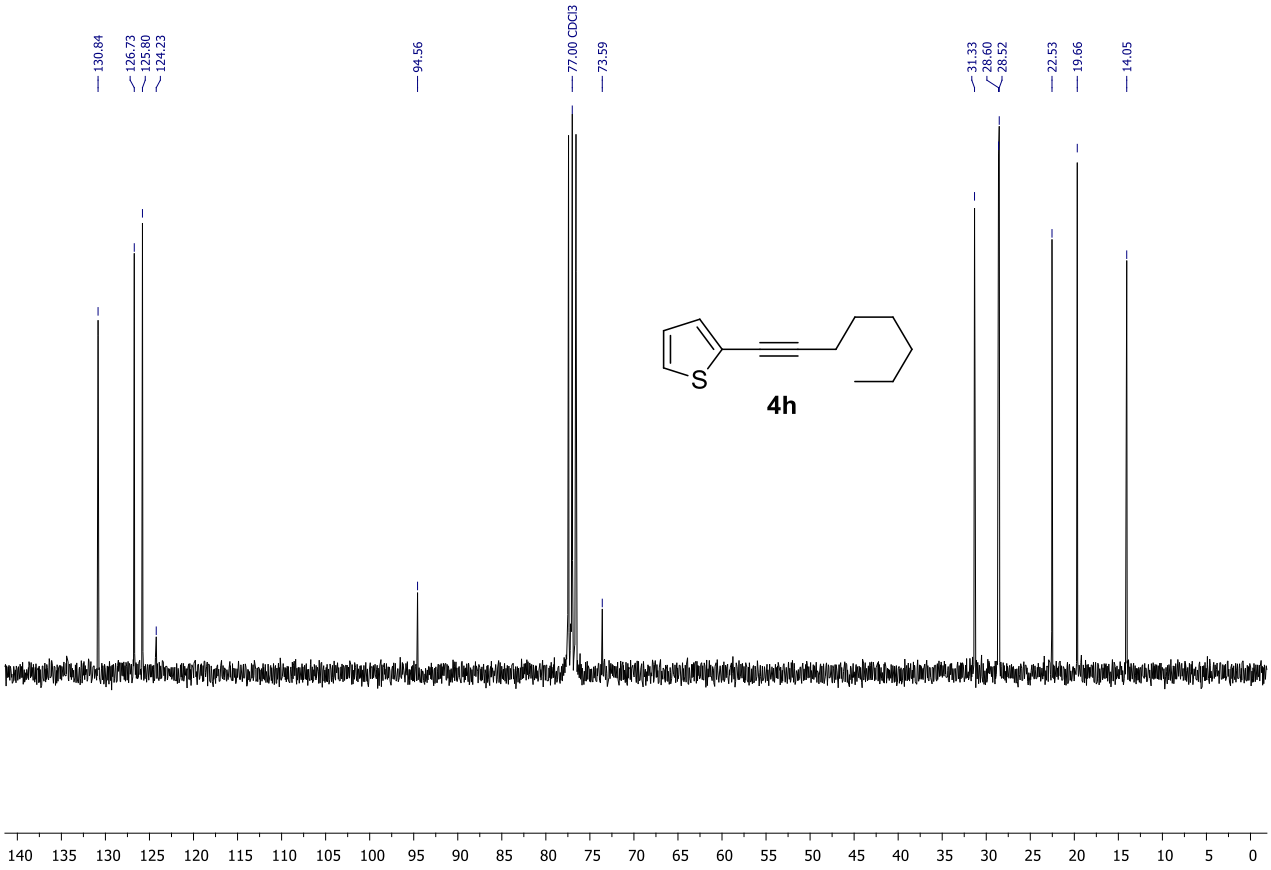
^{13}C NMR (75 MHz, $CDCl_3$) δ 134.32, 130.59, 130.07, 129.58, 126.11, 121.97, 92.07, 79.16, 31.33, 28.58, 22.54, 19.36, 14.05.

1-(thiophen-2-yl)-1-octyne (4h)

Prepared from 2-iodotiophene (7.0 mmol) and 1-octyne (8.4 mmol) in triethylamine (10 mL) and THF (3 mL) at 35 °C for 23 hours. Yield= 20%



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (dd, J = 5.2, 0.9 Hz, 1H), 7.11 (d, J = 3.3 Hz, 1H), 6.93 (dd, J = 5.1, 3.7 Hz, 1H), 2.42 (t, J = 7.1 Hz, 2H), 1.66 – 1.52 (m, 3H), 1.44 (m, 2H), 1.37 – 1.23 (m, 3H), 0.90 (t, J = 6.7 Hz, 3H).

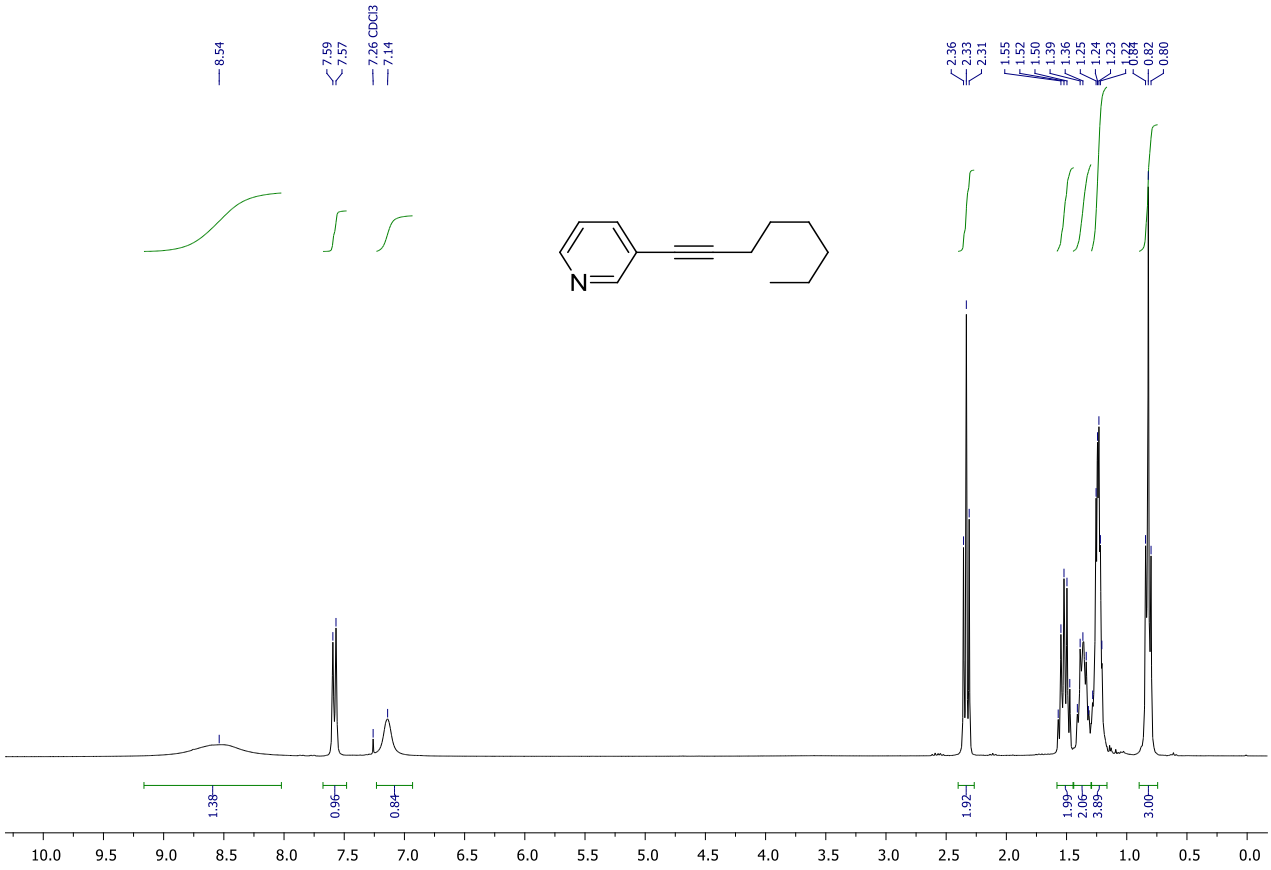


^{13}C NMR (75 MHz, $CDCl_3$) δ 130.84, 126.73, 125.80, 124.23, 94.56, 73.59, 31.33, 28.60, 28.52, 22.53, 19.66, 14.05.

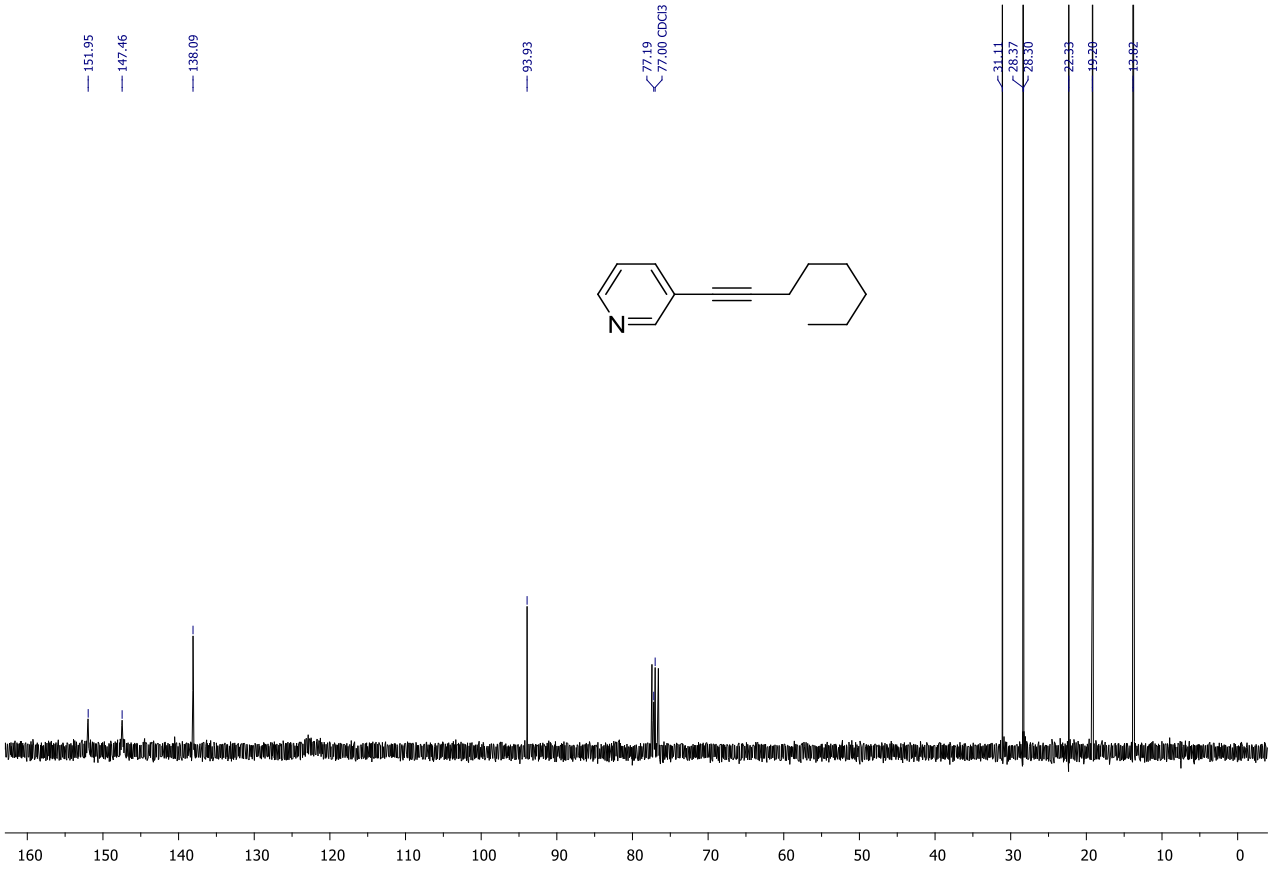
3-(oct-1-yn-1-yl)pyridine (4i)

Prepared from 3-bromopyridine (6.3 mmol) and 1-octyne (7.6 mmol) in triethylamine (8 mL) at 90 °C for 30 hours. In this case $[PdCl_2(PPh_3)_2]$ 3 mol% and CuI 6 mol% were used.

Yield= 91%.



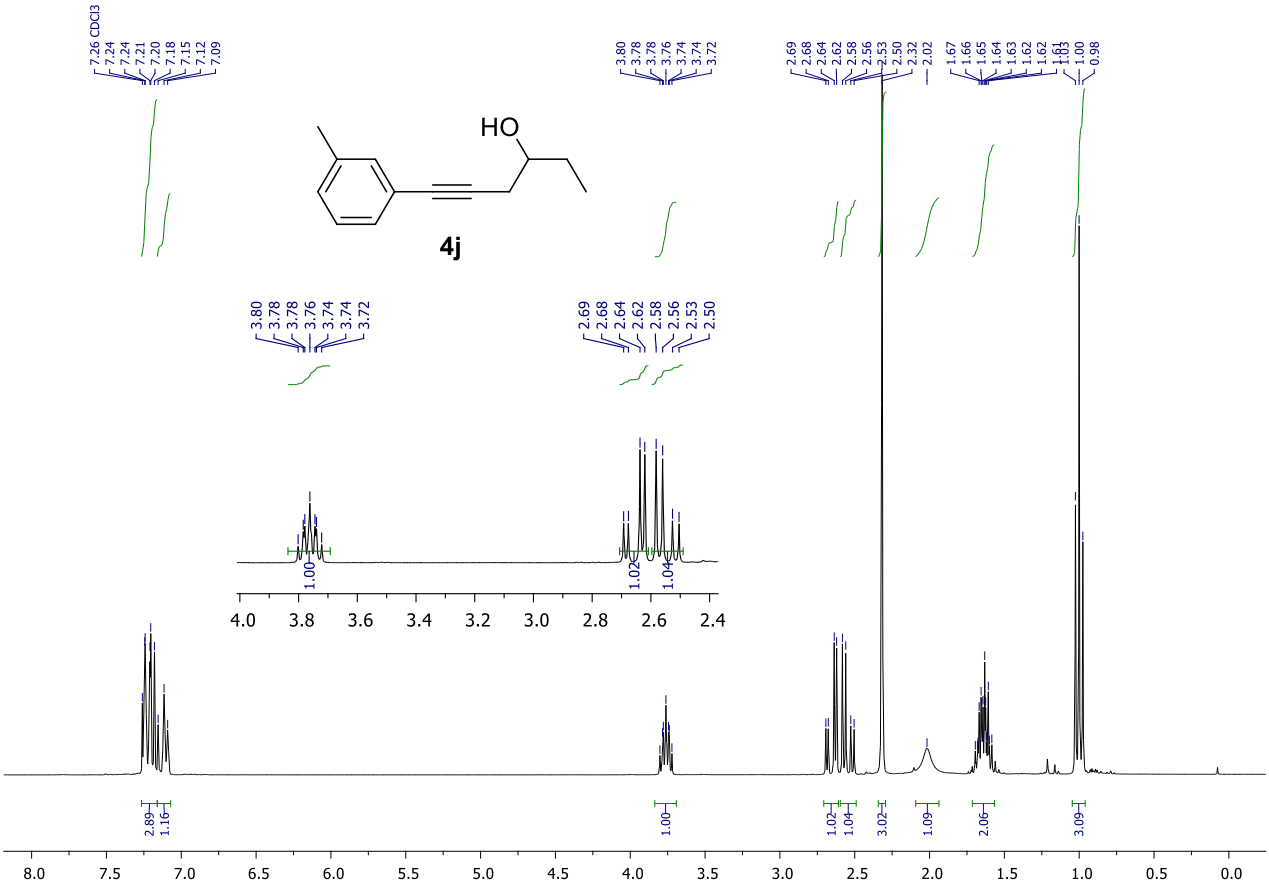
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (br m, 2H), δ 7.58 (d, *J* = 7.8 Hz, 1H), δ 7.14 (br s, 1H), δ 2.33 (t, *J* = 7.0 Hz, 1H), 1.60 – 1.45 (m, 1H), 1.45 – 1.30 (m, 1H), 1.30 – 1.17 (m, 2H), 0.82 (t, *J* = 6.8 Hz, 2H).



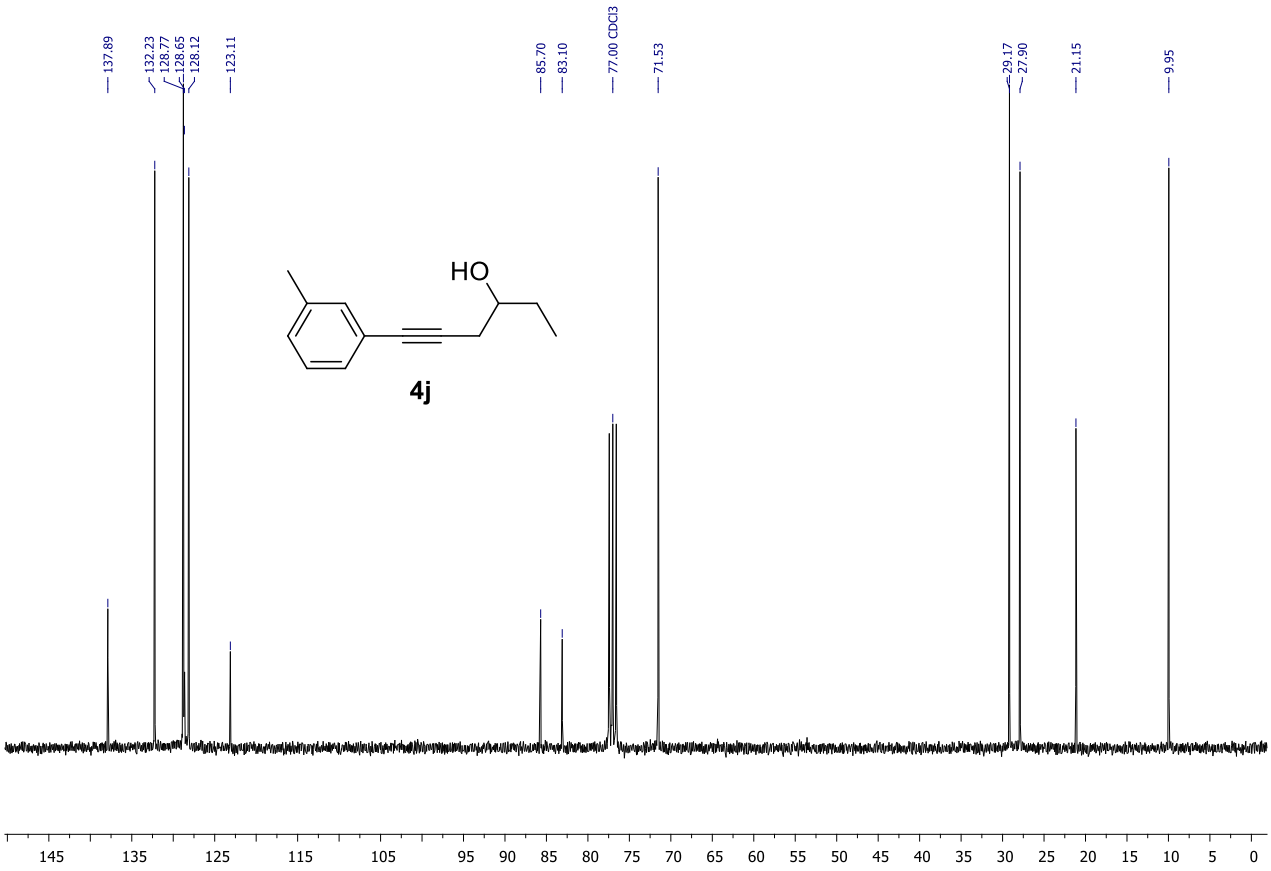
^{13}C NMR (75 MHz, $CDCl_3$) δ 151.95, 147.46, 138.09, 93.93, 77.19, 31.11, 28.37, 28.30, 22.33, 19.20, 13.82.

1-(*m*-tolyl)hex-1-yn-4-ol (4j)

Prepared from 3-iodotoluene (6.8 mmol) and 5-hexyn-3-ol (8.2 mmol) in diisopropylamine (11 mL) at 50 °C for 6 hours. Yield= 66%



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.16 (m, 3H), 7.17 – 7.06 (m, 1H), 3.76 (tt, *J* = 6.8, 5.3 Hz, 1H), 2.66 (dd, *J* = 16.7, 4.9 Hz, 2H), 2.54 (dd, *J* = 16.7, 6.7 Hz, 2H), 2.32 (s, 3H), 2.02 (br s, 1H), 1.74 – 1.53 (m, 2H), 1.00 (t, *J* = 7.5 Hz, 3H).

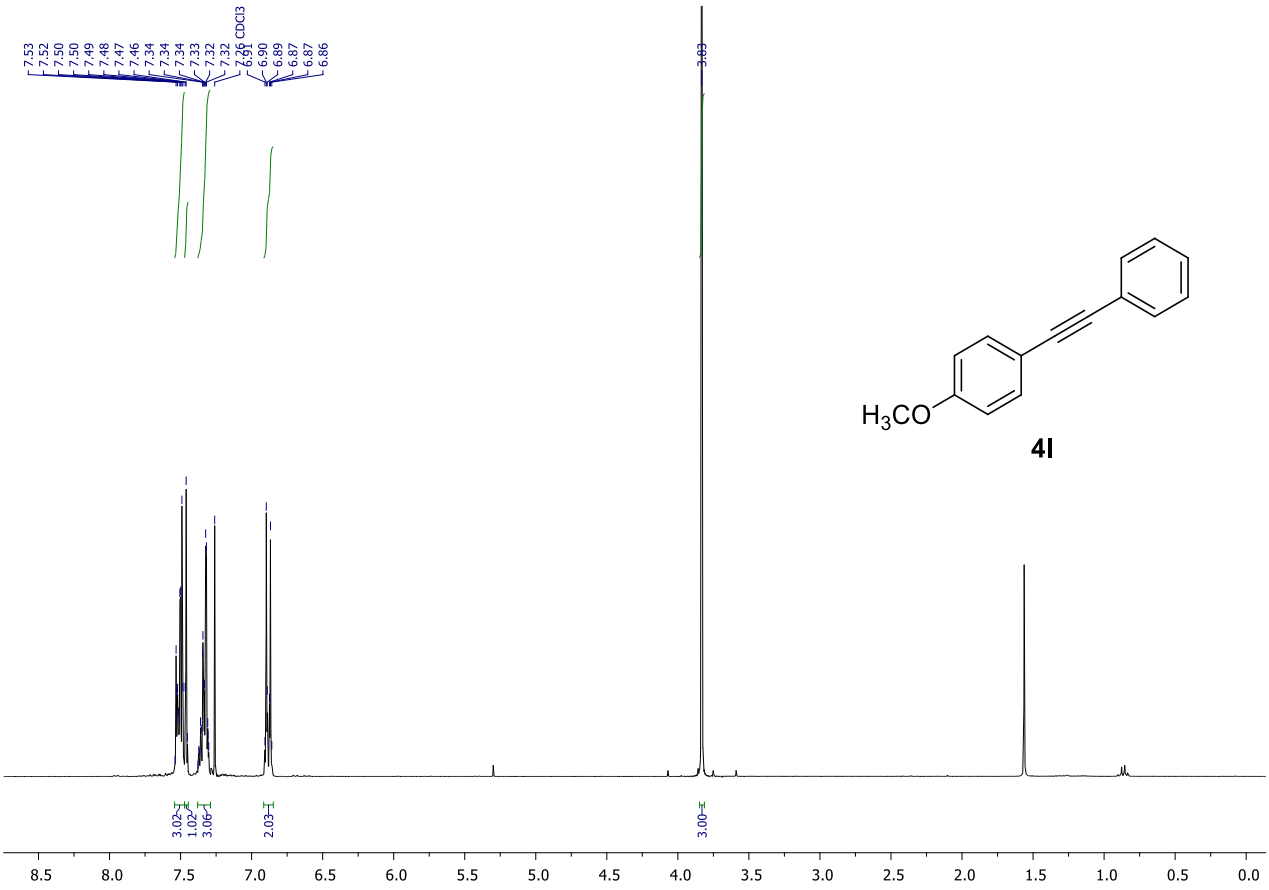


^{13}C NMR (75 MHz, $CDCl_3$) δ 137.89, 132.23, 128.77, 128.65, 128.12, 123.11, 85.70, 83.10, 71.53, 29.17, 27.90, 21.15, 9.95.

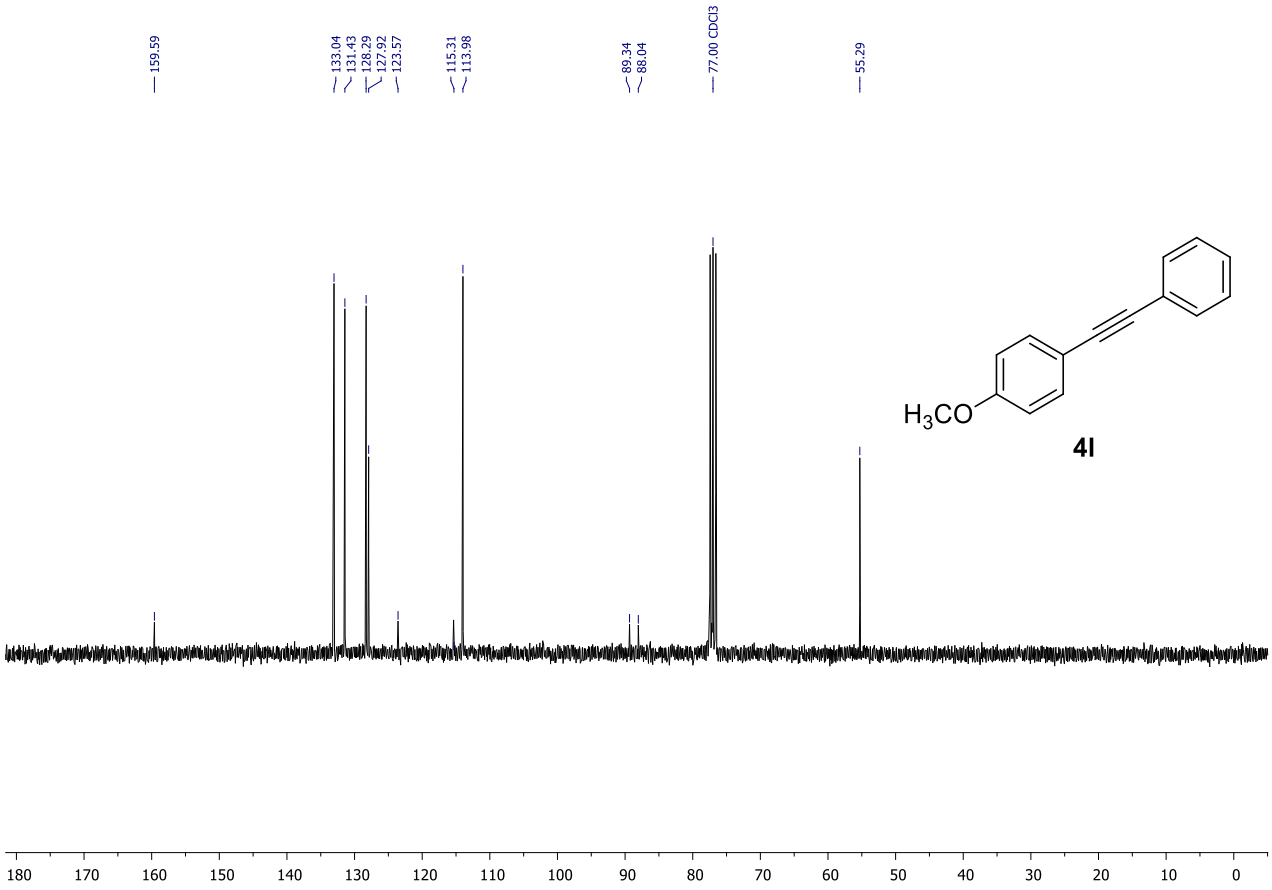
HRMS (ESI-TOF) m/z for ($C_{13}H_{16}O + H^+$) calculated 189.1279, found 189.1219.

1-methoxy-4-(phenylethynyl)benzene (4l)

Prepared from 4-iodoanisole (4.3 mmol) and phenylacetylene (5.2 mmol) in triethylamine (7 mL) at 50 °C for 18 hours. Yield= 81%.



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 3H), 7.47 – 7.44 (m, 1H), 7.38 – 7.29 (m, 3H), 6.92 – 6.85 (m, 2H), 3.83 (s, 3H).

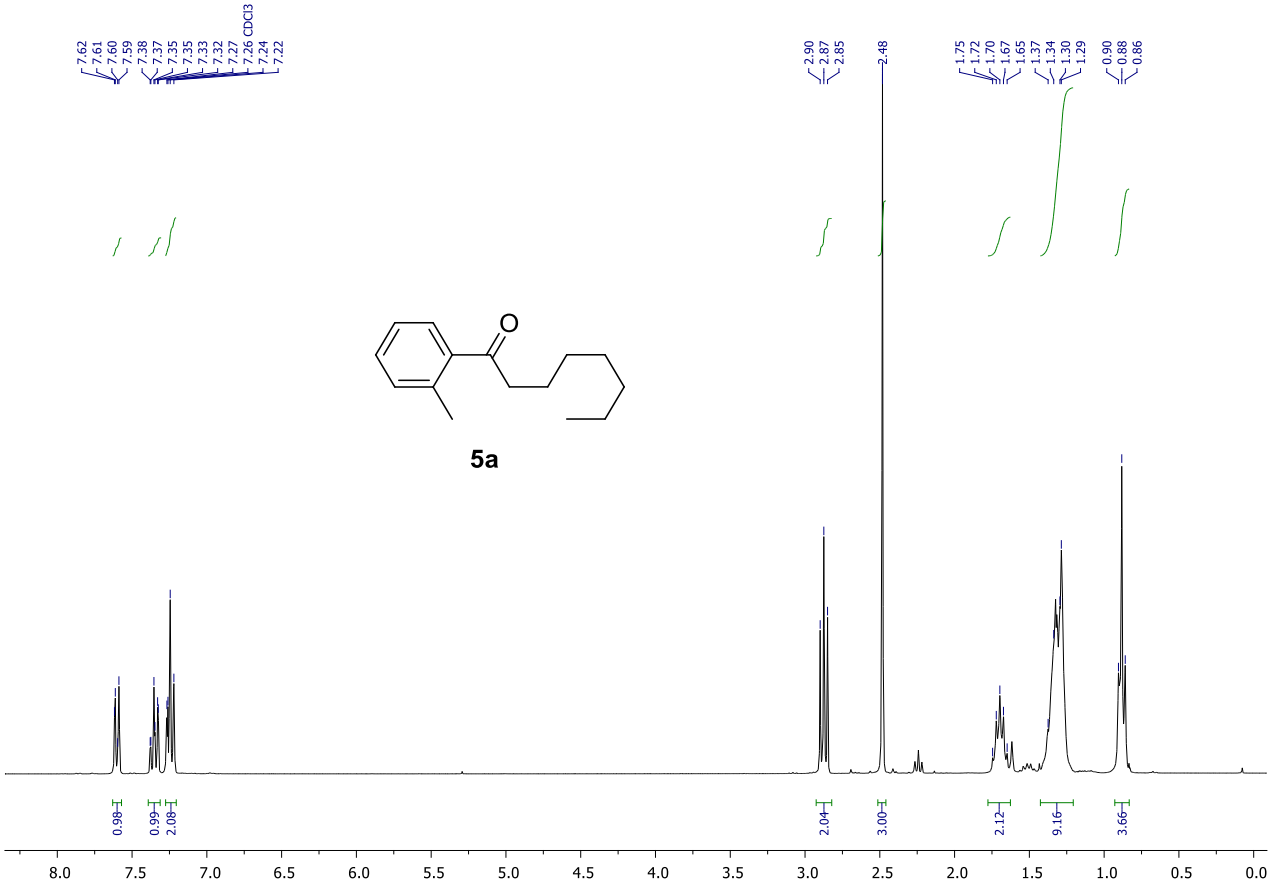


^{13}C NMR (75 MHz, $CDCl_3$) δ 159.59, 133.04, 131.43, 128.29, 127.92, 123.57, 115.31, 113.98, 89.34, 88.04, 55.29.

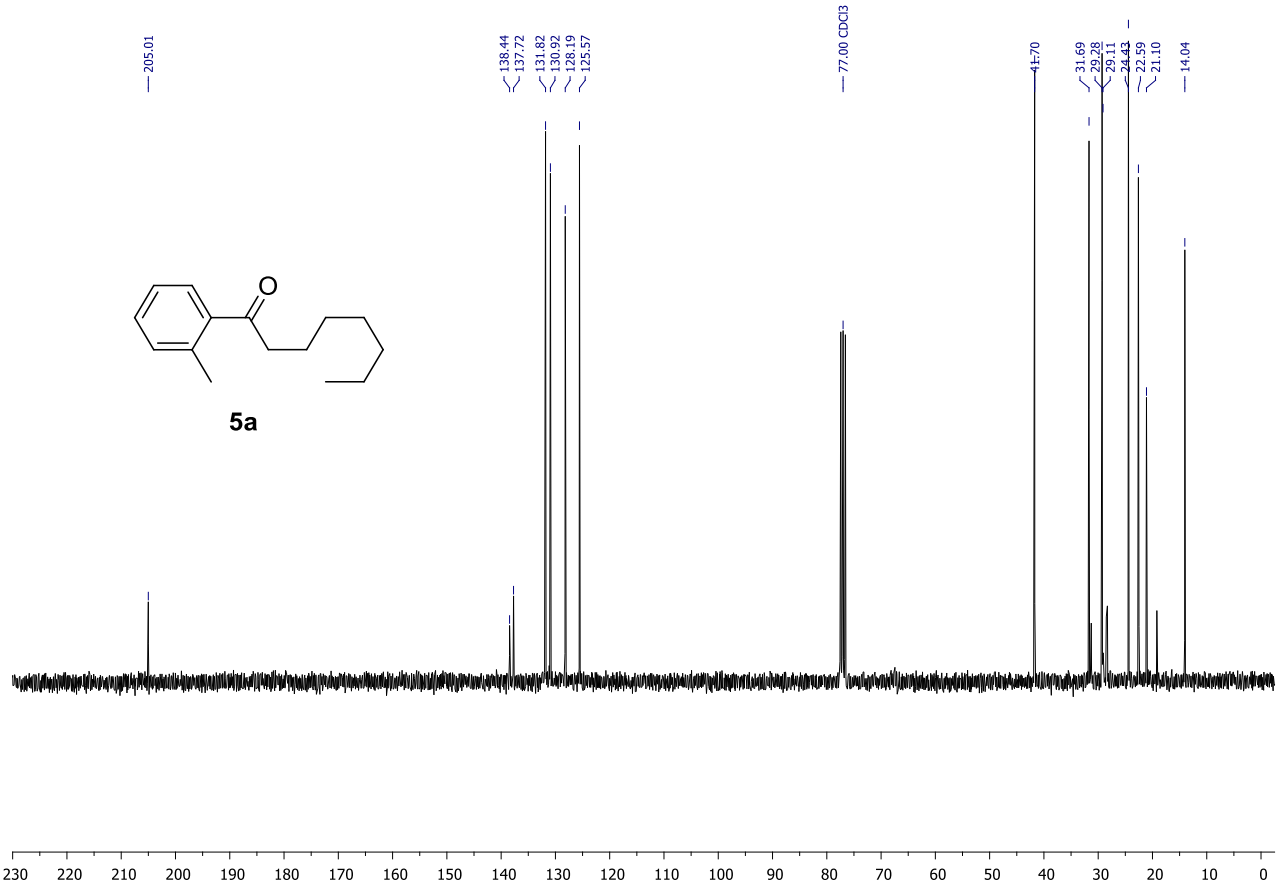
2.12.3 Hydration products synthesis and characterization

The reactions were carried out on a 1–2 mmol scale of alkyne, following a general procedure. Hydrate ferric sulfate (**1**, 5-10 mol%), glacial acetic acid and the alkyne **4a-p** (1 eq., 0.5 M in acetic acid) were introduced (not necessarily in this order) into a 25 mL round bottom flask, equipped with a magnetic bar and a water condenser. The flask was immersed into an oil bath set at the proper temperature. The reaction mixture was left under stirring until consumption of the substrate was evidenced by TLC and/or GC-MS. Upon cooling, the heterogeneous mixture was filtered through a Celite pad and washed with diethyl ether. The organic phase was washed twice with a saturated aqueous solution of $NaHCO_3$, then with water and dried over sodium sulfate. After filtration and removal of solvent under vacuum, the oily residue was filtered through a short chromatographic column (using petroleum ether, petroleum ether/chloroform or petroleum ether/ethyl acetate) as eluent to afford the corresponding ketone **5a-p**.

2-methylphenyl-1-octanone (5a)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 6.8, 2.1 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.29 – 7.17 (m, 2H), 2.87 (t, *J* = 7.4 Hz, 2H), 2.48 (s, 3H), 1.75 – 1.64 (m, 2H), 1.32 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H).



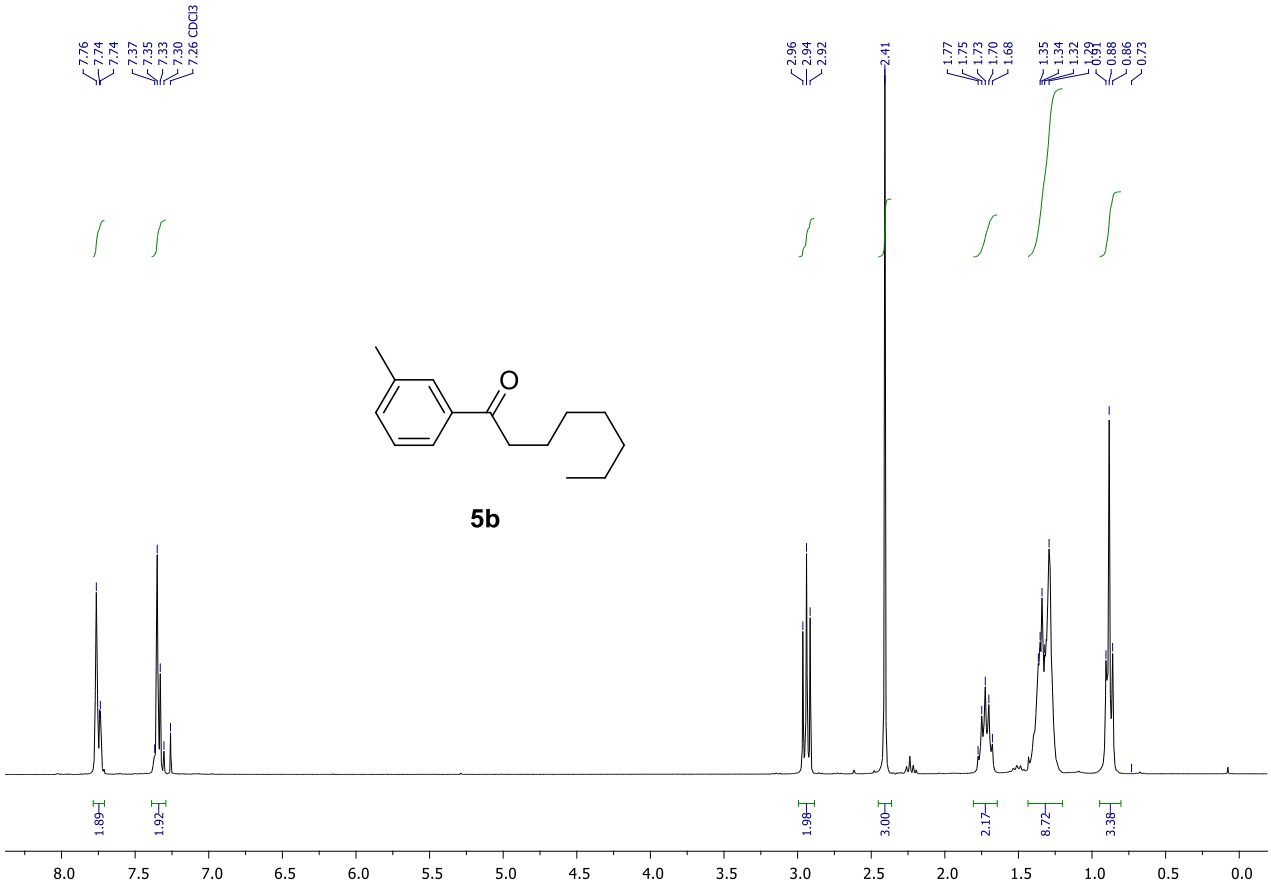
^{13}C NMR (75 MHz, $CDCl_3$) δ 205.01, 138.44, 137.72, 131.82, 130.92, 128.19, 125.57, 41.70, 31.69, 29.28, 29.11, 24.43, 22.59, 21.10, 14.04.

Clear oil, eluent petroleum ether

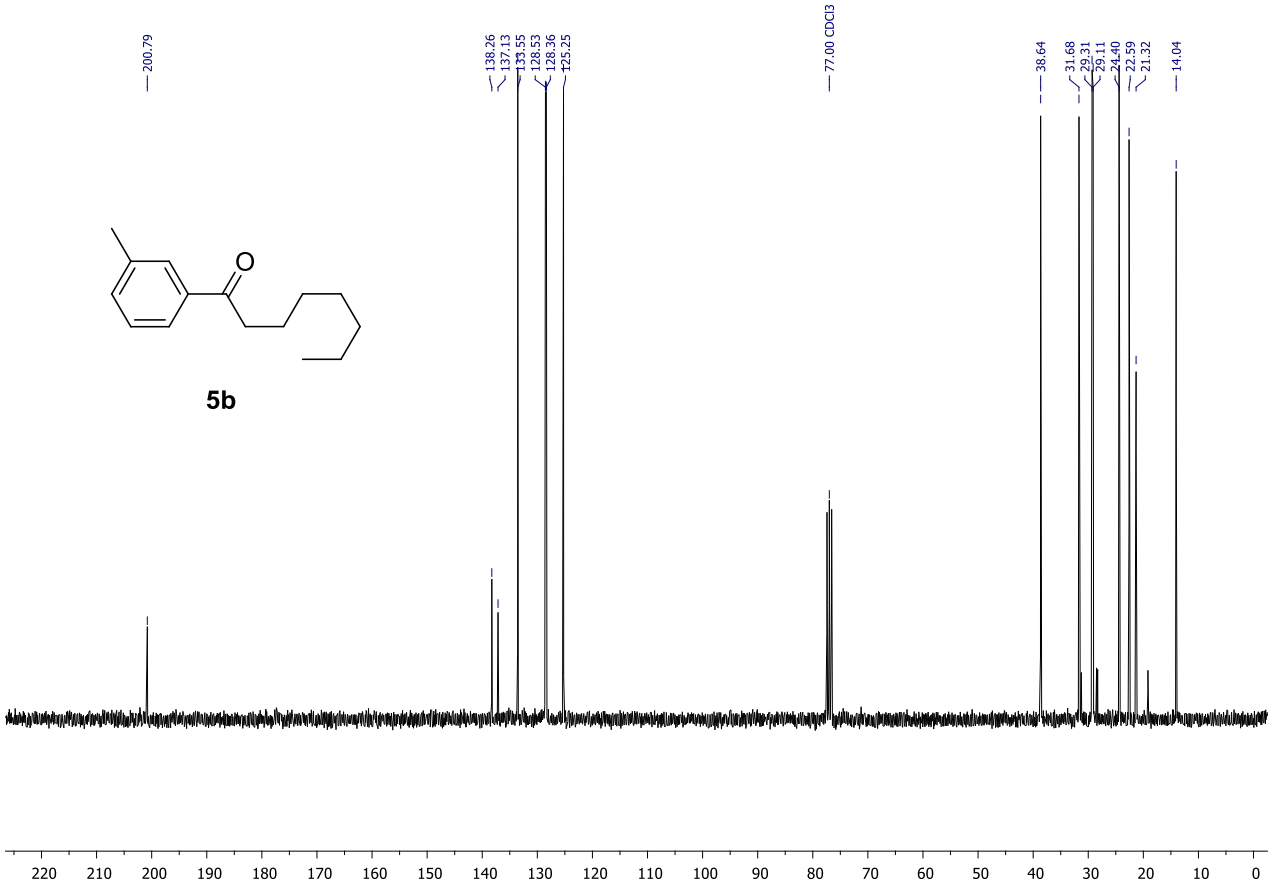
Yield = 84%

GC-MS: (*m*/*z*, M^+ = 218.0): 218 (5%), 203 (8%), 134 (15%), 119 (100%), 91 (23%), 65(7%).

3-methylphenyl-1-octanone (5b)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.69 (m, 2H), 7.39 – 7.30 (m, 2H), 2.98 – 2.89 (t, *J* = 7.2 Hz, 1H), 2.41 (s, 3H), 1.81 – 1.64 (m, 2H), 1.45 – 1.20 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H).



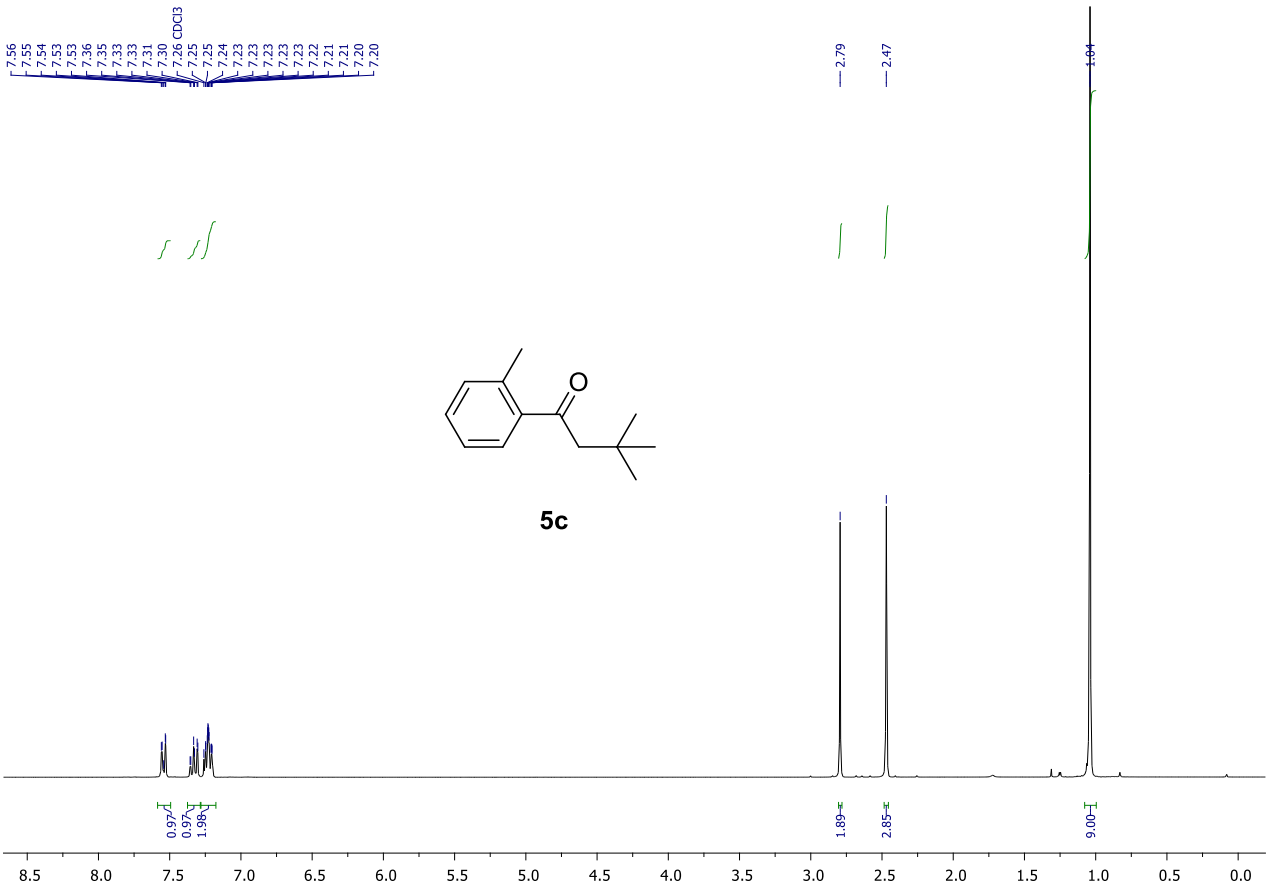
^{13}C NMR (75 MHz, $CDCl_3$) δ 200.79, 138.26, 137.13, 133.55, 128.53, 128.36, 125.25, 38.64, 31.68, 29.31, 29.11, 24.40, 22.59, 21.32, 14.04.

Clear oil, eluent petroleum ether

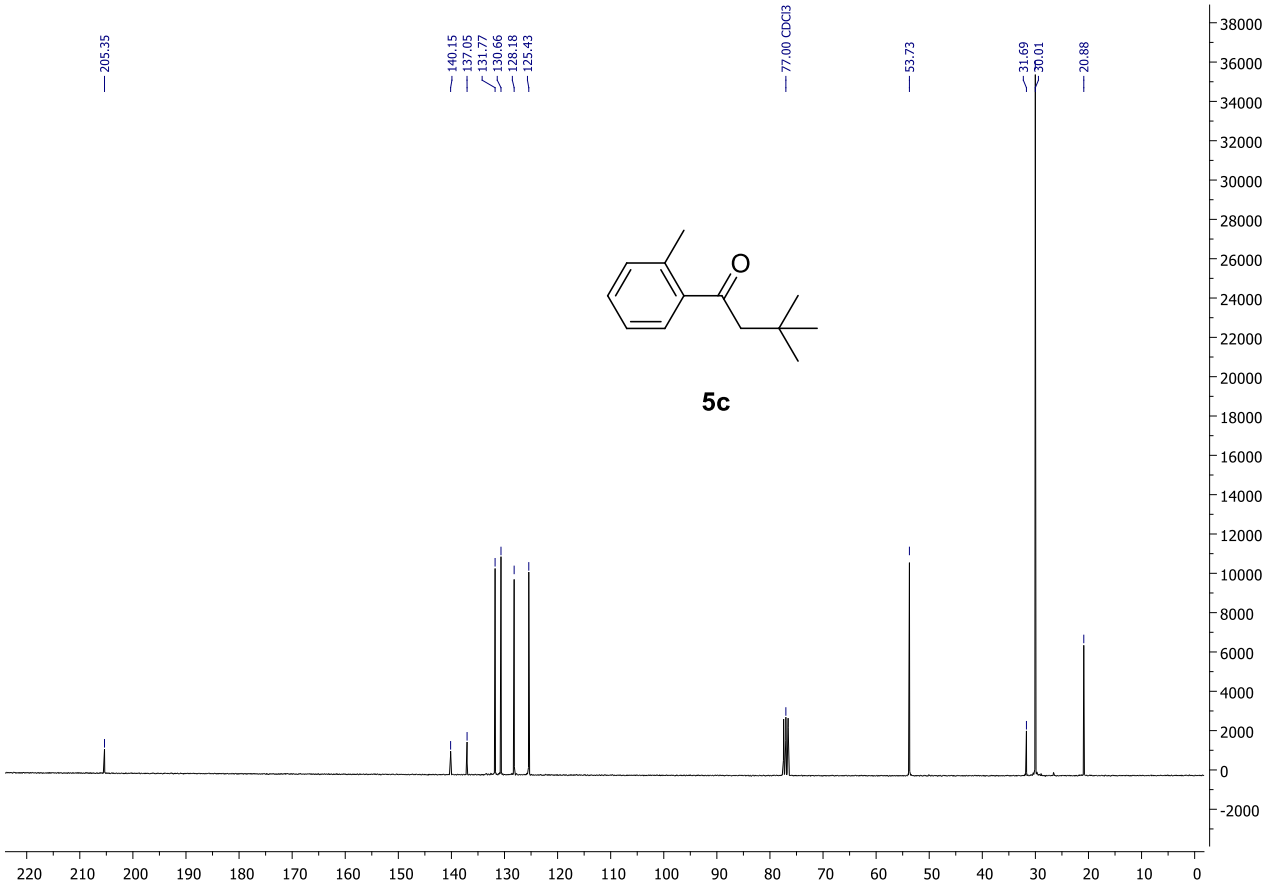
Yield = 80%

GC-MS: (m/z, M^+ = 218.0): 218 (19%), 147 (12%), 134 (93%), 119 (100%), 91 (12%), 65 (9%).

3,3-dimethyl-1-(2-methylphenyl)butan-1-one (5c)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.51 (m, 1H), 7.38 – 7.28 (m, 1H), 7.28 – 7.18 (m, 2H), 2.79 (s, 2H), 2.47 (s, 3H), 1.04 (s, 9H).



^{13}C NMR (75 MHz, $CDCl_3$) δ 205.35, 140.15, 137.05, 131.77, 130.66, 128.18, 125.43, 53.73, 31.69, 30.01, 20.88.

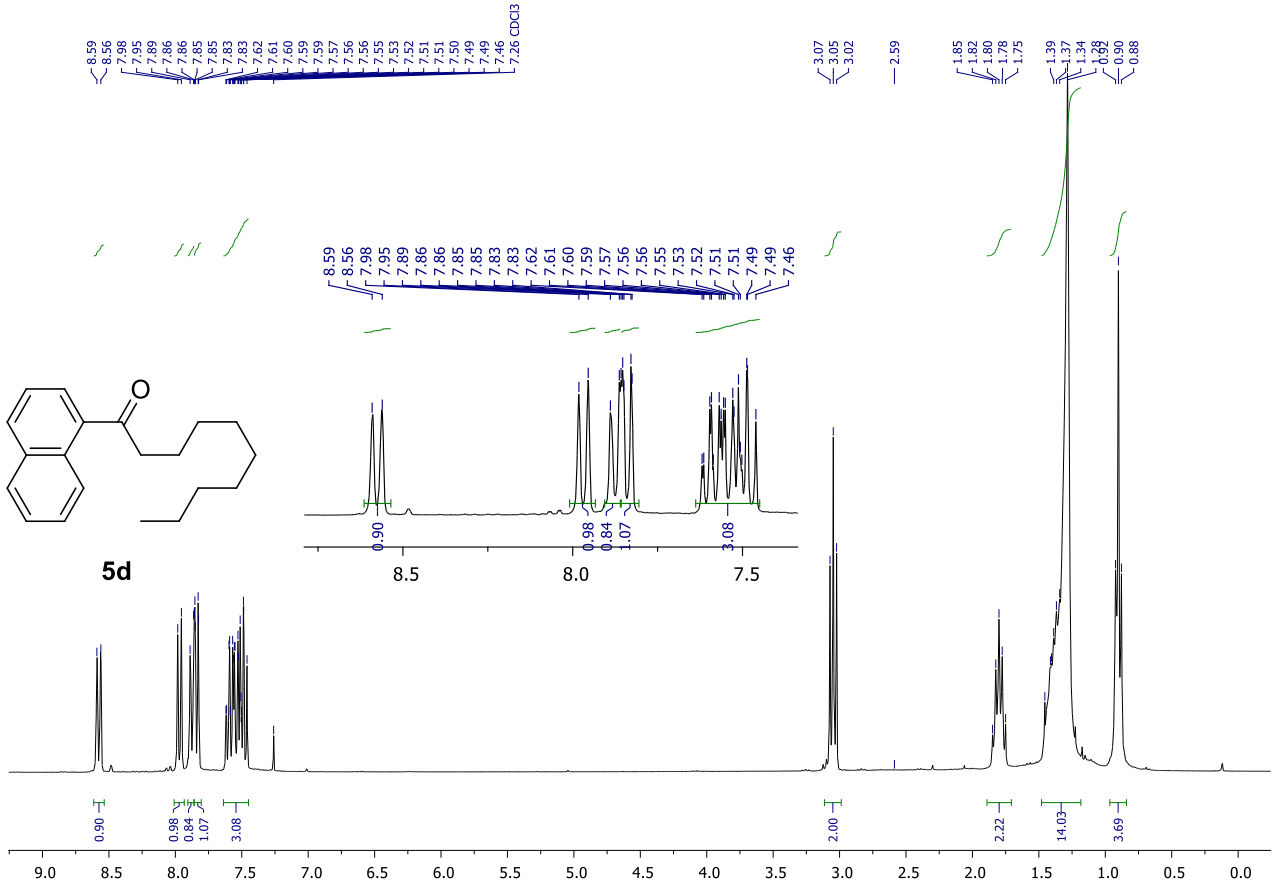
Clear oil, eluent petroleum ether

Yield = 82%

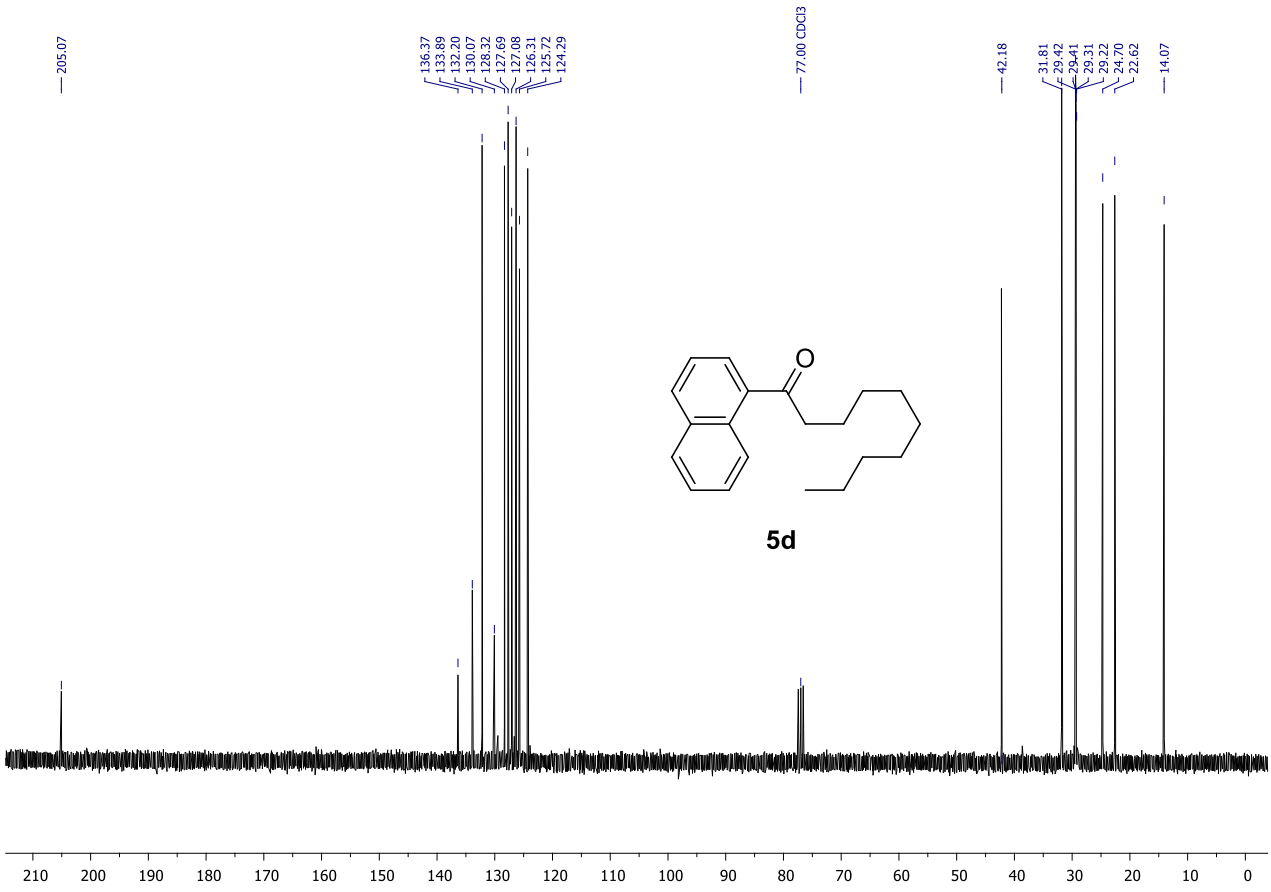
GC-MS: (m/z, M^+ =190.0): 190 (7%), 175 (14%), 134 (9%), 119 (100%), 91 (28%), 65 (10%).

HRMS (ESI-TOF) m/z for ($C_{13}H_{18}O + Na^+$) calculated 213.1255, found 213.1208.

1-(1)naphthyldecan-1-one (5d)



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, *J* = 9.0 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.84 (dd, *J* = 7.2, 1.0 Hz, 1H), 3.05 (t, *J* = 7.4 Hz, 2H), 1.88 – 1.71 (m, 2H), 1.49 – 1.20 (m, 8H), 0.90 (t, *J* = 6.7 Hz, 3H).



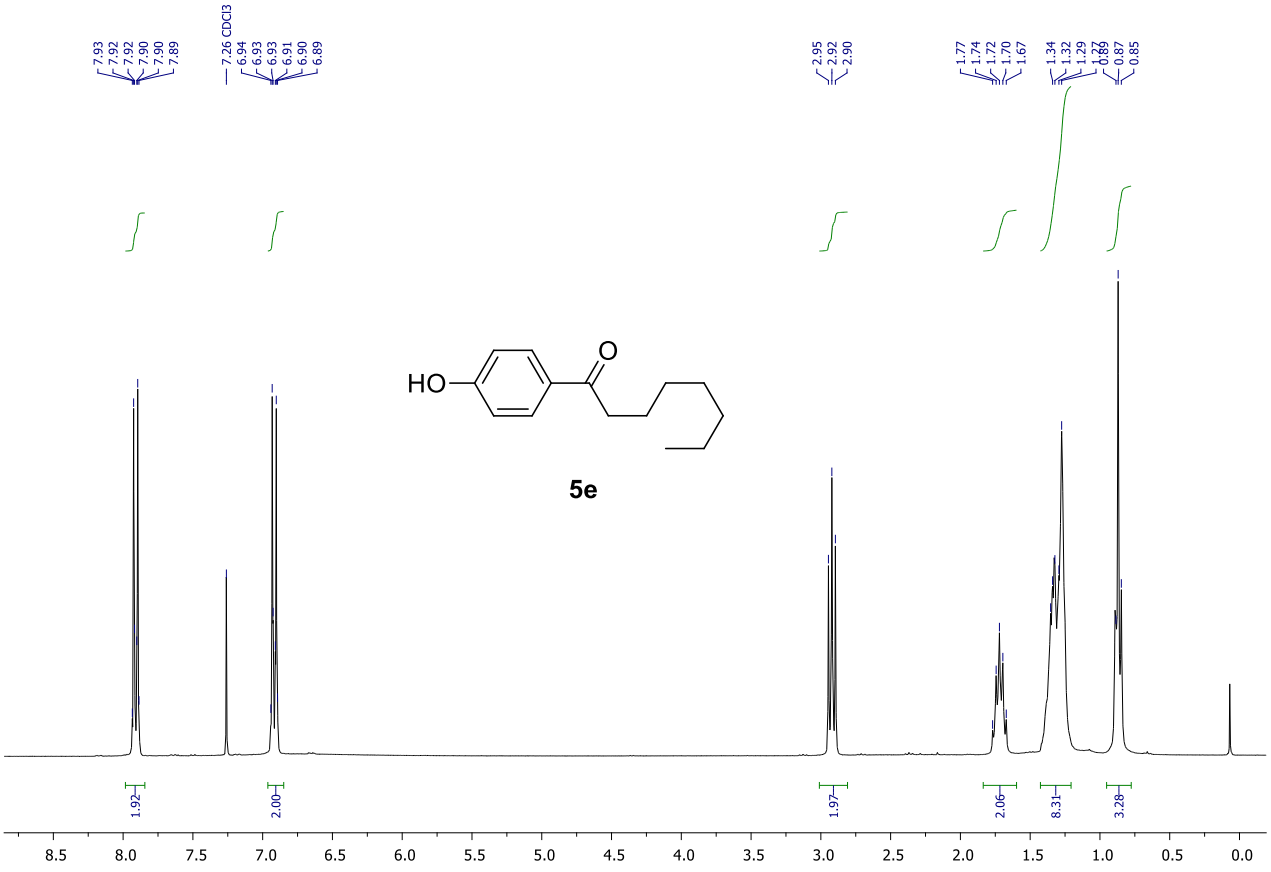
^{13}C NMR (75 MHz, $CDCl_3$) δ 205.07, 136.37, 133.89, 132.20, 130.07, 128.32, 127.69, 127.08, 126.31, 125.72, 124.29, 42.18, 31.81, 29.42, 29.41, 29.31, 29.22, 24.70, 22.62, 14.07.

Clear oil, eluent petroleum ether

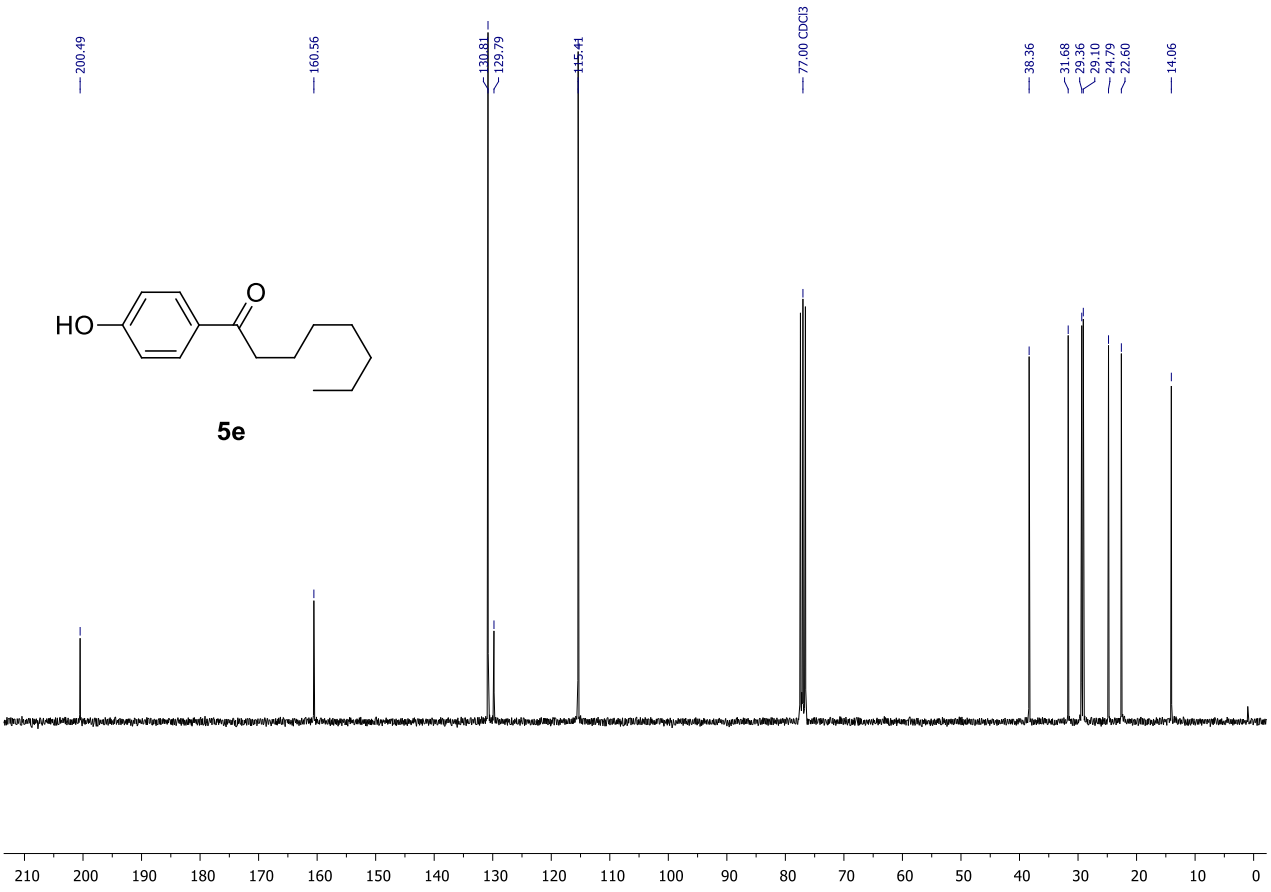
Yield = 81%

HRMS (ESI-TOF) m/z for ($C_{20}H_{26}O + Na^+$) calculated 305.1881, found 305.1908.

4-hydroxyphenyl-1-octanone (5e)



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 – 7.82 (m, 2H), 7.00 – 6.85 (m, 2H), 2.99 – 2.85 (t, *J* = 7.5 Hz 2H), 1.82 – 1.61 (m, 2H), 1.48 – 1.15 (m, 8H), 0.87 (t, *J* = 5.8 Hz, 3H).

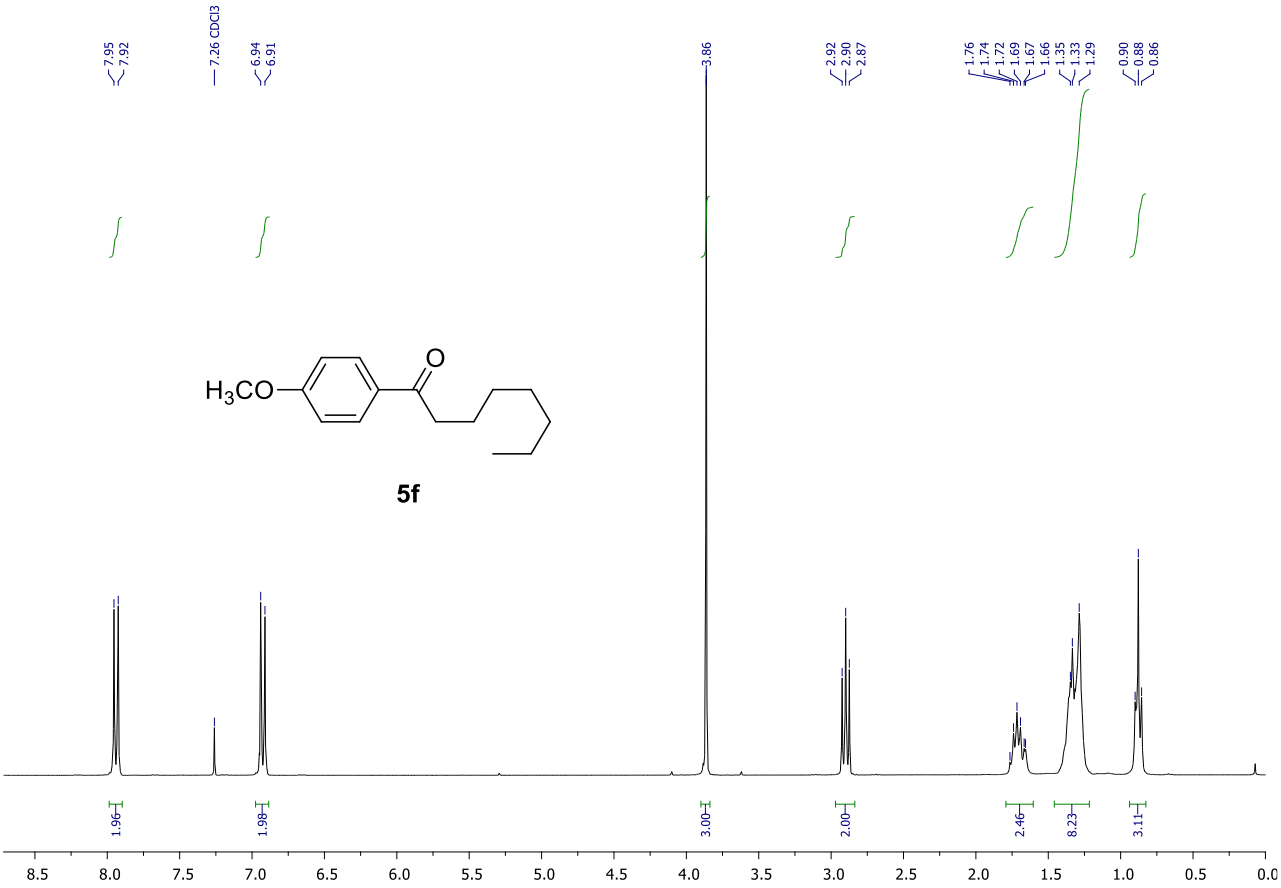


^{13}C NMR (75 MHz, $CDCl_3$) δ 200.49, 160.56, 130.81, 129.79, 115.41, 38.36, 31.68, 29.36, 29.10, 24.79, 22.60, 14.06.

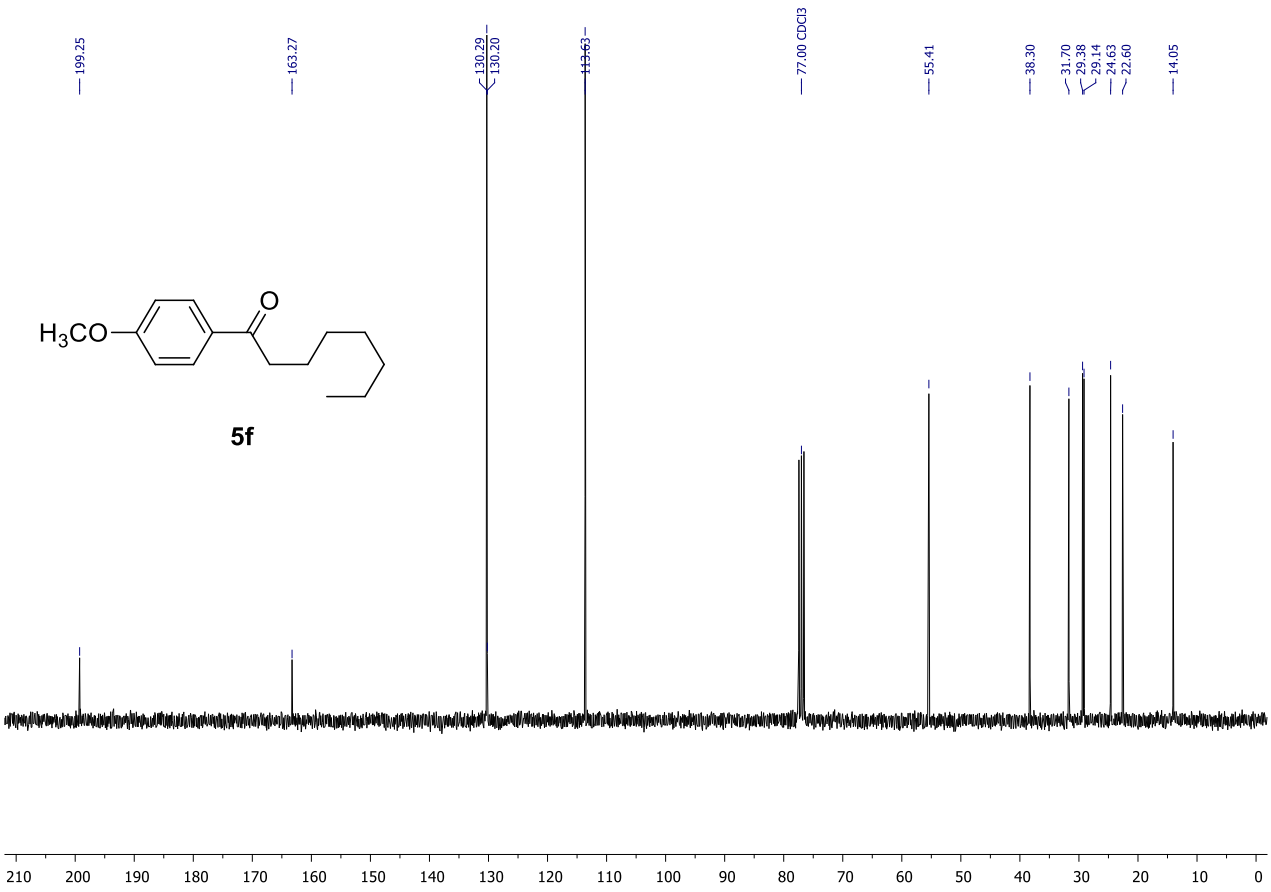
Oil, eluent chloroform

Yield = 82%

4-methoxyphenyl-1-octanone (5f)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 2.90 (t, *J* = 7.4 Hz, 2H), 1.79 – 1.62 (m, 2H), 1.48 – 1.17 (m, 8H), 0.88 (t, *J* = 6.7 Hz, 3H).



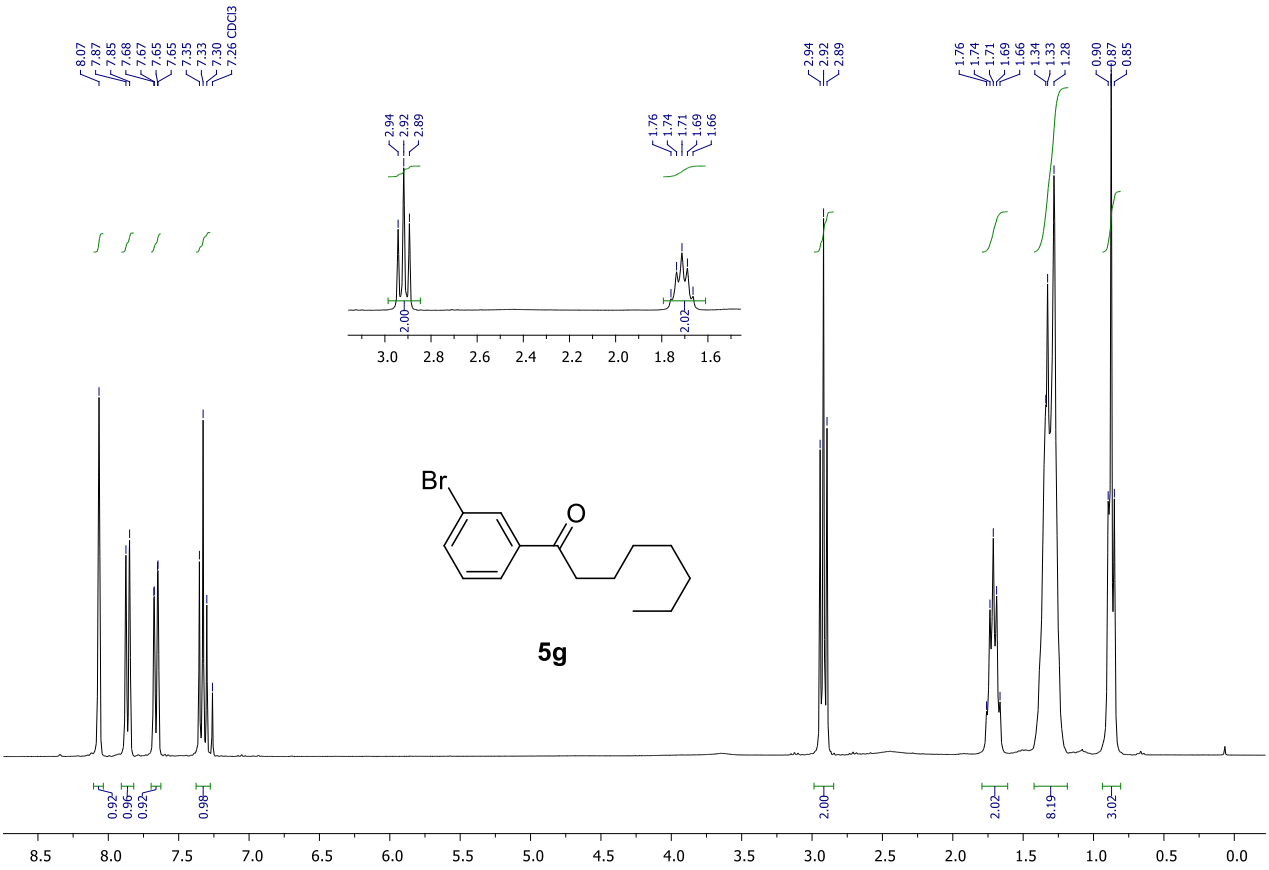
^{13}C NMR (75 MHz, $CDCl_3$) δ 199.25, 163.27, 130.29, 130.20, 113.63, 55.41, 38.30, 31.70, 29.38, 29.14, 24.63, 22.60, 14.05.

Oil, eluent petroleum ether/ethyl acetate

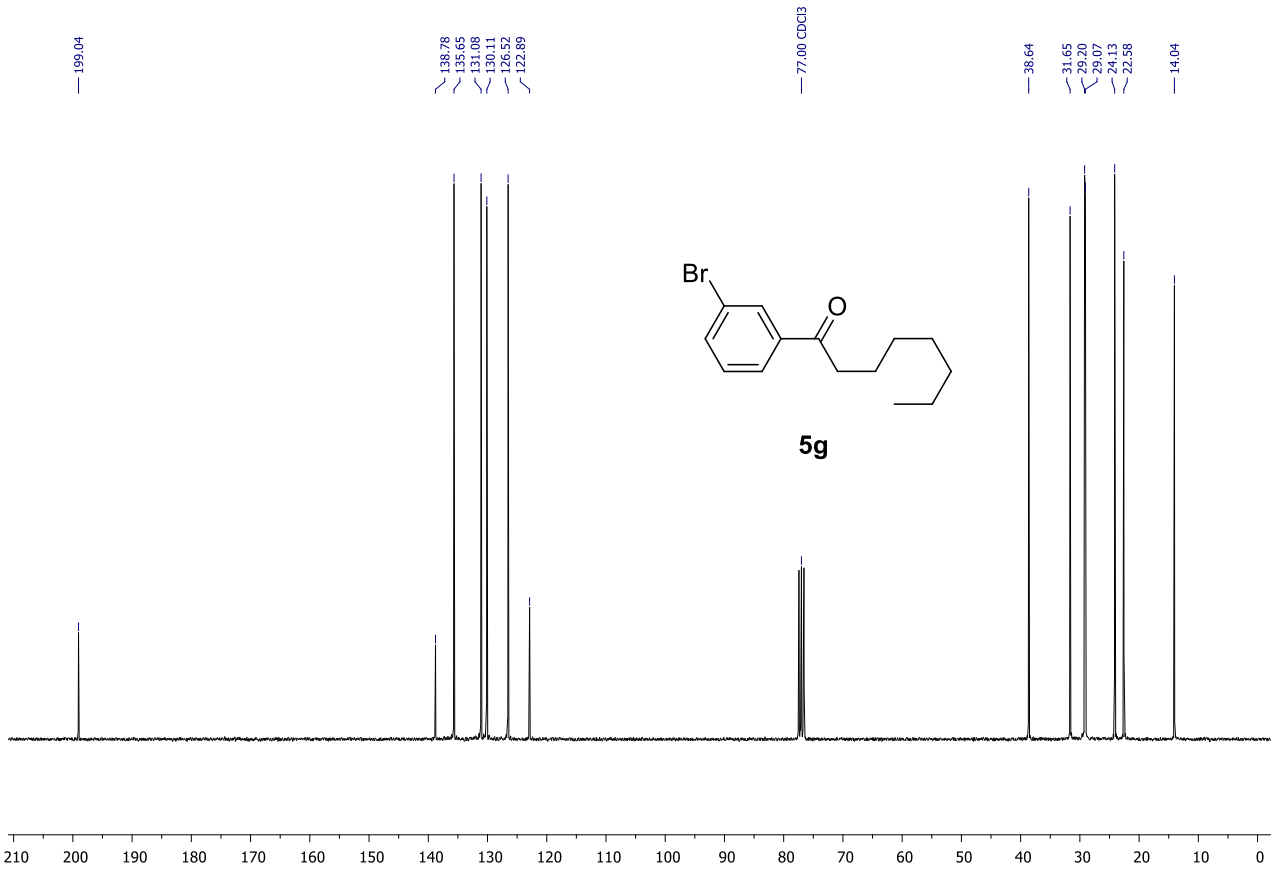
Yield = 79%

GC-MS: (m/z, $M^{+\cdot}$ = 234.0): 234 (7%), 163 (12%), 150 (87%), 135 (100%), 107 (8%), 92 (7%), 77 (10%), 64 (6%).

3-bromophenyl-1-octanone (5g)



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.66 (dd, J = 8.0, 0.9 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 2.92 (t, J = 7.4 Hz, 2H), 1.78 – 1.63 (m, 2H), 1.42 – 1.20 (m, 8H), 0.87 (t, J = 6.6 Hz, 3H).



^{13}C NMR (75 MHz, $CDCl_3$) δ 199.04, 138.78, 135.65, 131.08, 130.11, 126.52, 122.89, 38.64, 31.65, 29.20, 29.07, 24.13, 22.58, 14.04.

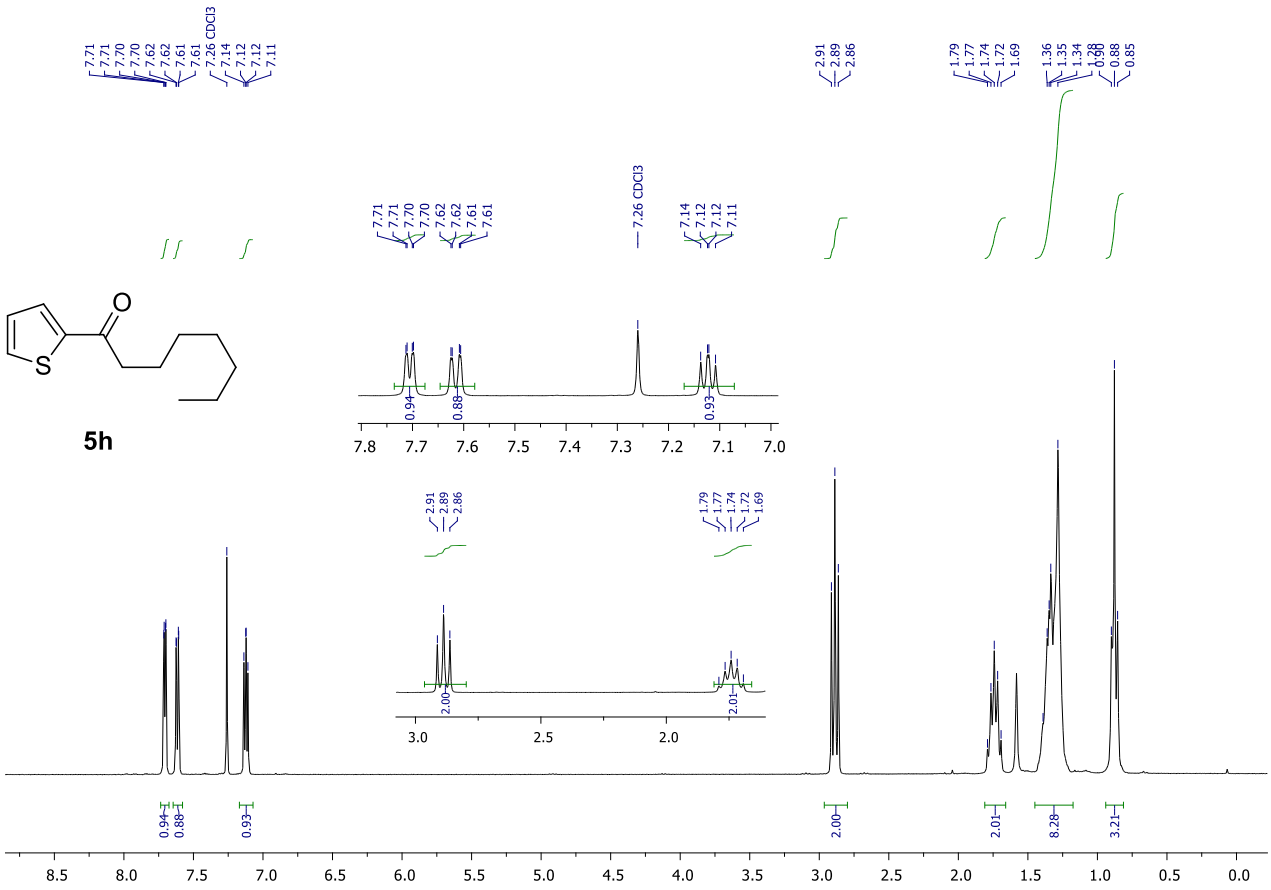
Oil, eluent petroleum ether/chloroform (1:2)

Yield = 42%

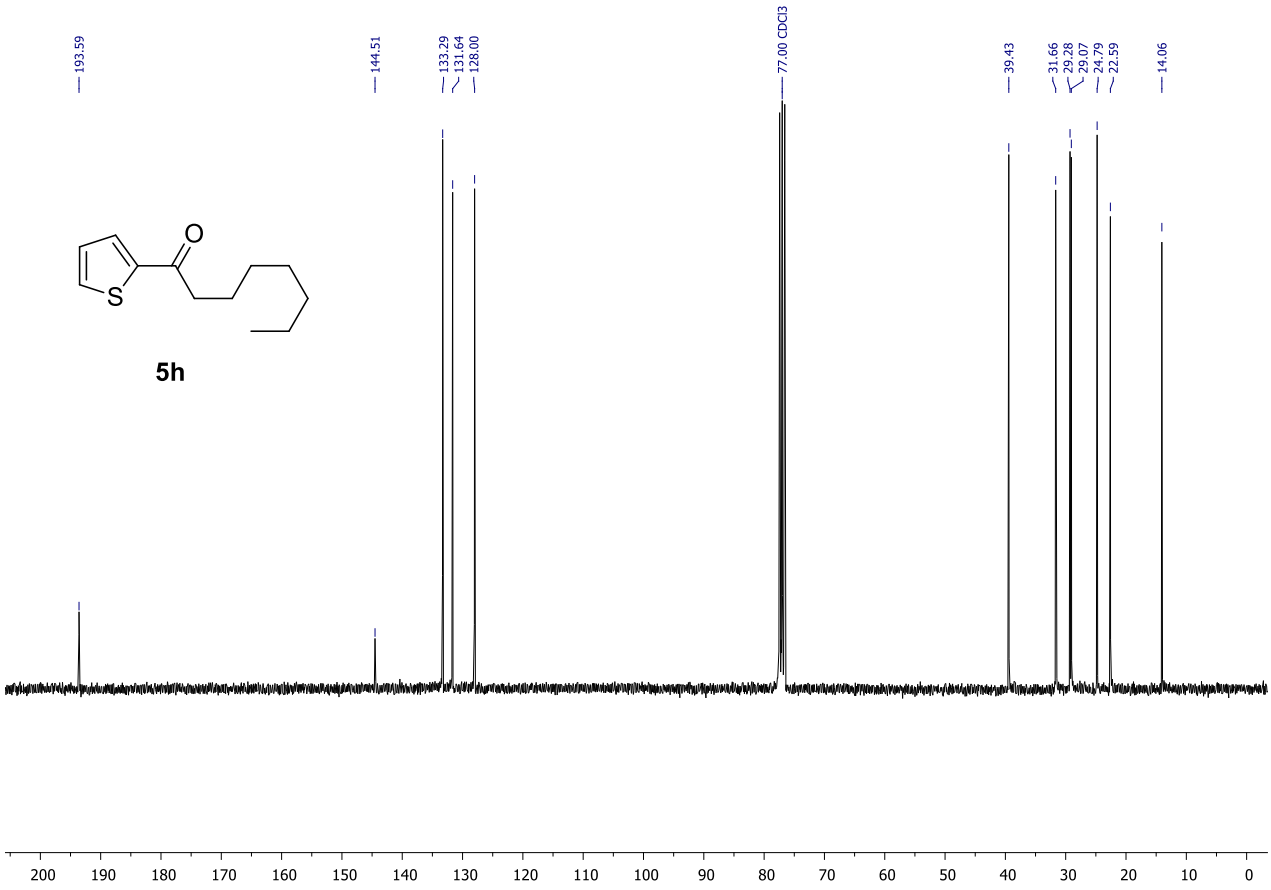
GC-MS: (m/z, $M^{+\cdot}$=282.06): 282–284 (9%), 198–200 (100%), 183–185 (83%), 157, 159 (27%), 132 (11%), 76 (13%).

HRMS (ESI-TOF) m/z for ($C_{14}H_{19}BrO + K^+$) calculated 321.0256, found 321.0261.

1-(thiophen-2-yl)octan-1-one (5h)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 3.7, 0.7 Hz, 1H), 7.62 (dd, *J* = 4.9, 0.7 Hz, 1H), 7.12 (dd, *J* = 4.7, 4.0 Hz, 1H), 2.89 (t, *J* = 7.5 Hz, 2H), 1.82 – 1.67 (m, 2H), 1.43 – 1.18 (m, 8H), 0.88 (t, *J* = 6.7 Hz, 3H).

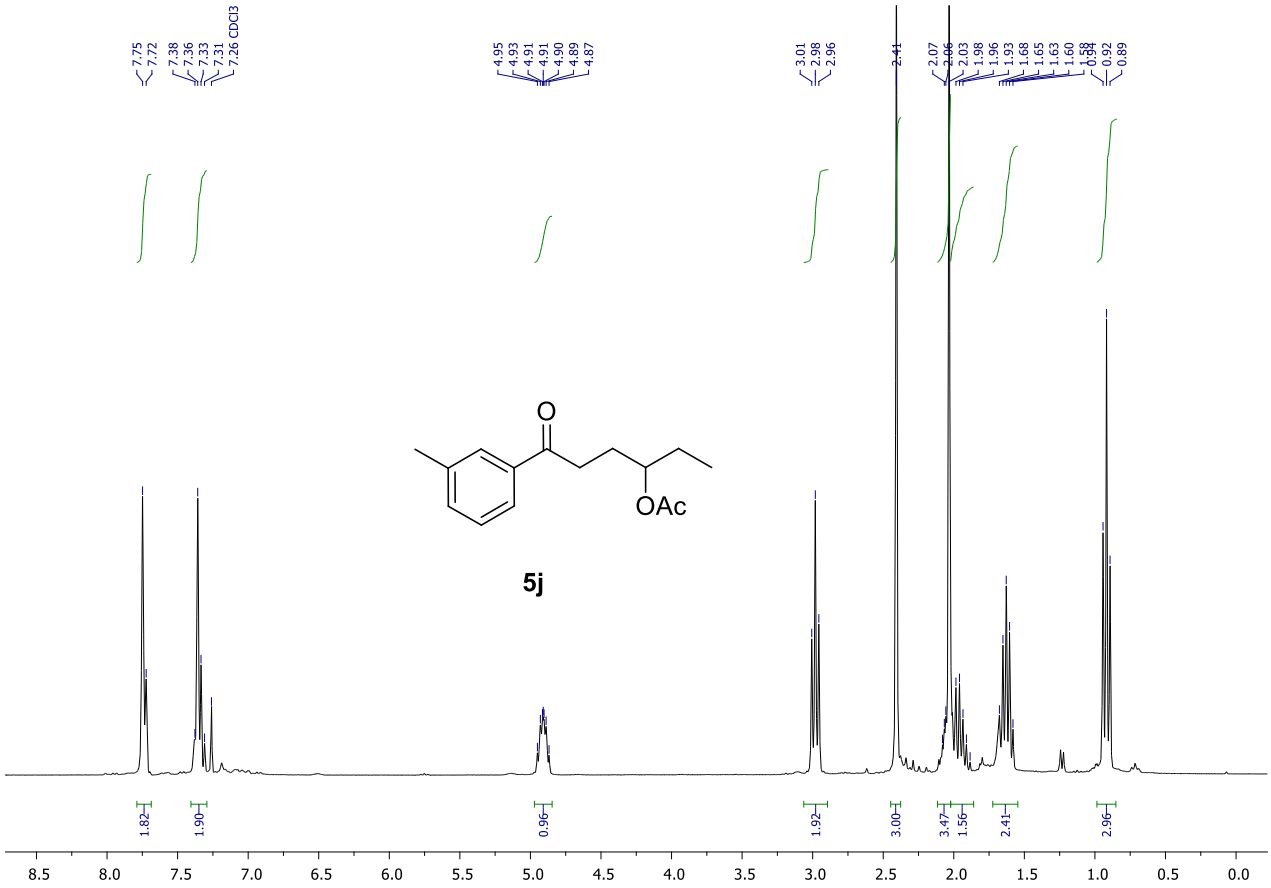


^{13}C NMR (75 MHz, $CDCl_3$) δ 193.59, 144.51, 133.29, 131.64, 128.00, 39.43, 31.66, 29.28, 29.07, 24.79, 22.59, 14.06.

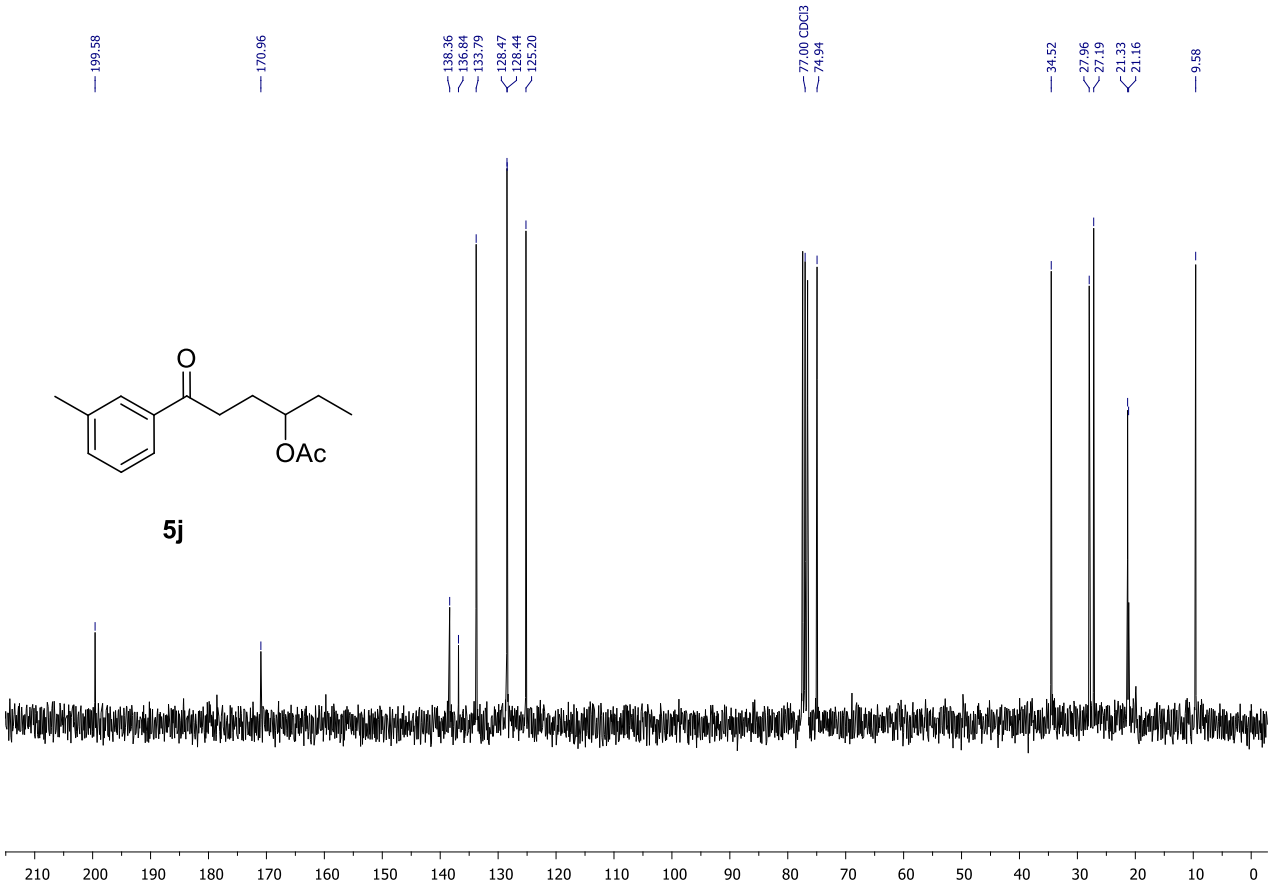
Oil, eluent petroleum ether/chloroform (3:2)

Yield = 45%

4-acetyloxy-1-(*m*-tolyl)hexan-1-one (5j)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (m, 2H), 7.41 – 7.29 (m, 2H), 4.97 – 4.85 (m, 1H), 2.98 (t, *J* = 7.6 Hz, 2H), 2.41 (s, 3H), 2.03 (s, 3H), 2.12 – 1.87 (m, 3H), 1.71 – 1.55 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H)



^{13}C NMR (75 MHz, $CDCl_3$) δ 199.58, 170.96, 138.36, 136.84, 133.79, 128.47, 128.44, 125.20, 74.94, 34.52, 27.96, 27.19, 21.33, 21.16, 9.58.

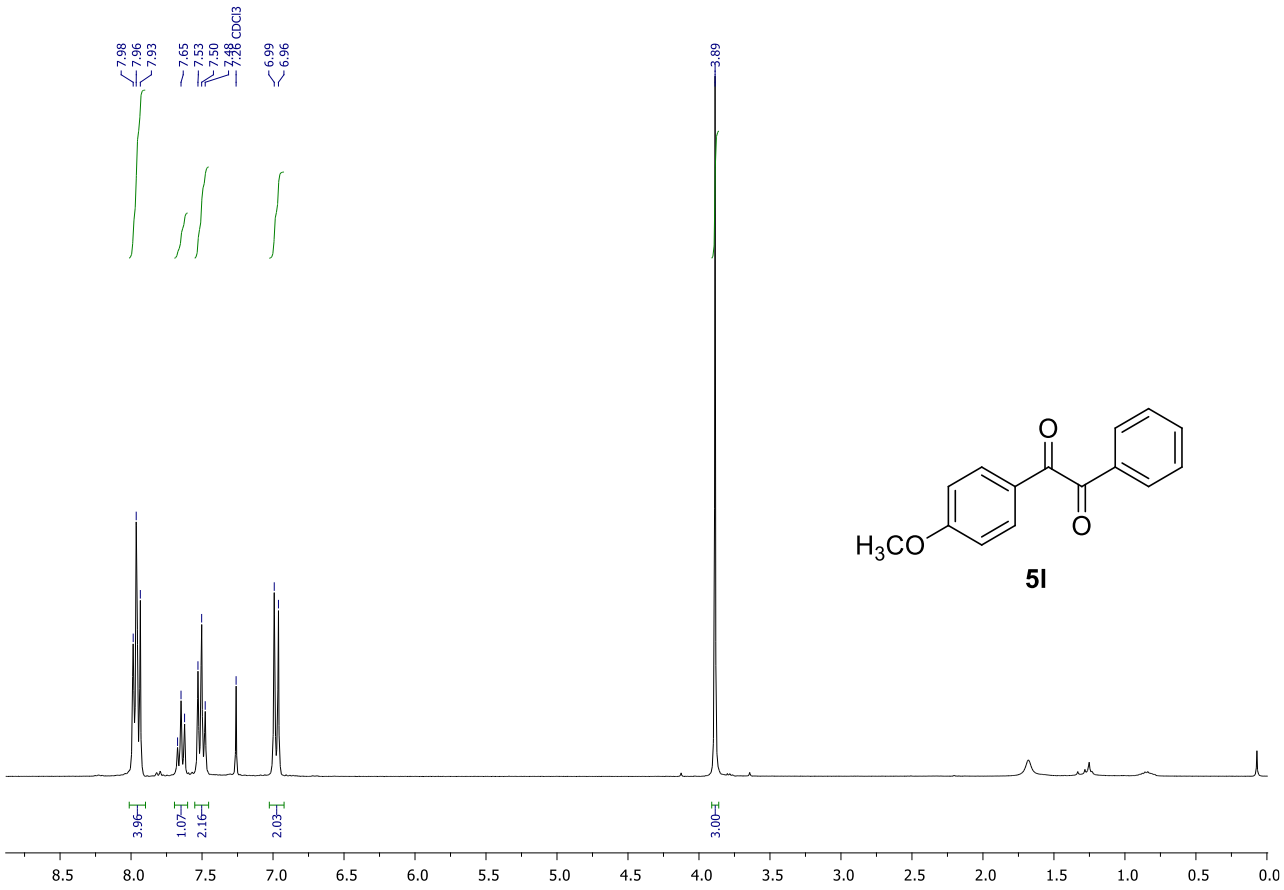
Red oil, eluent chloroform

Yield = 45%

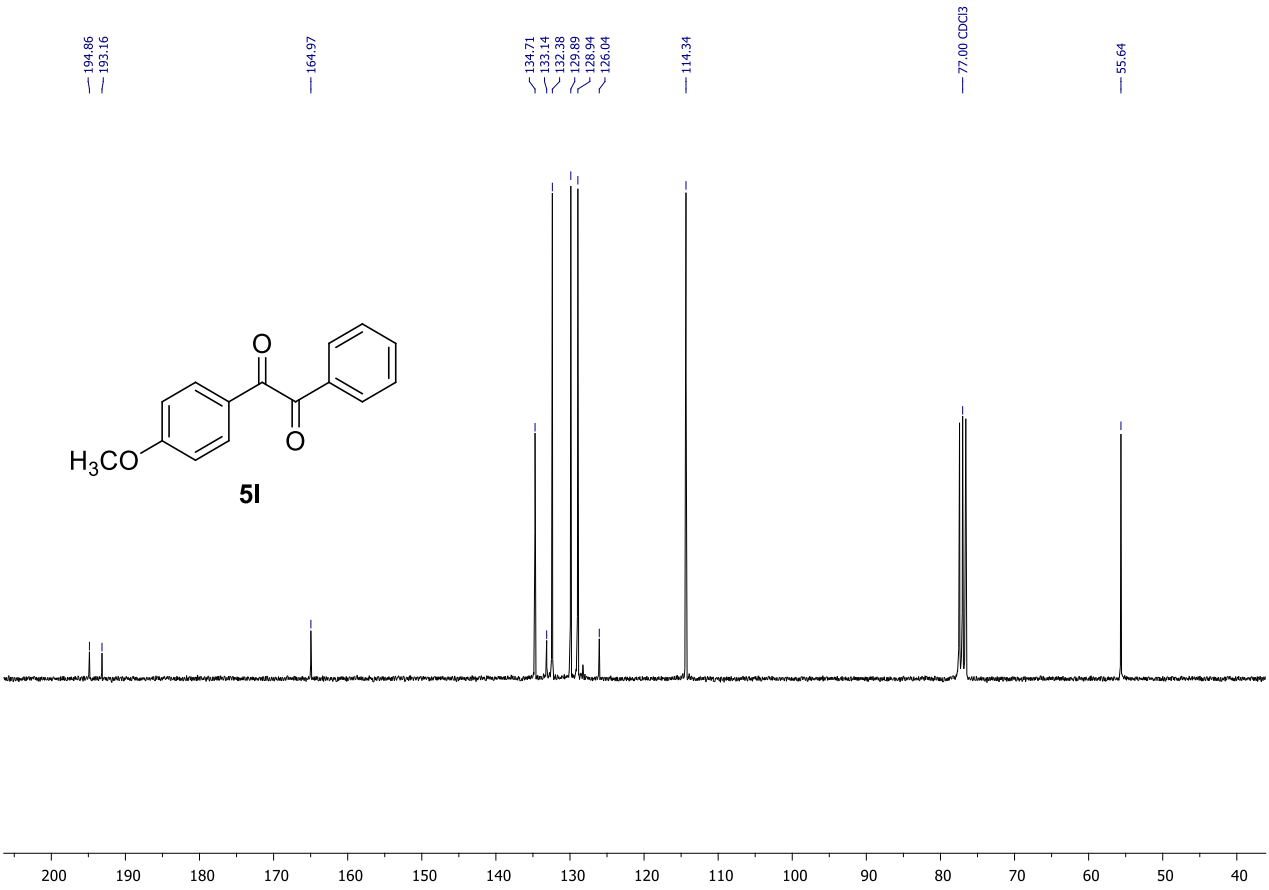
GC-MS: (m/z, M+ =248.14): 205 (M^{+-} Ac, 30%), 188 (28%), 134 (35%), 119 (100%), 91 (32%), 65 (10%).

HRMS (ESI-TOF) m/z for ($C_{15}H_{20}O_3$ + Na^+) calculated 271.1310, found 271.1266.

1-(4-methoxylphenyl)-2-phenylethane-1,2-dione (5l)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (m, 4H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 31H).

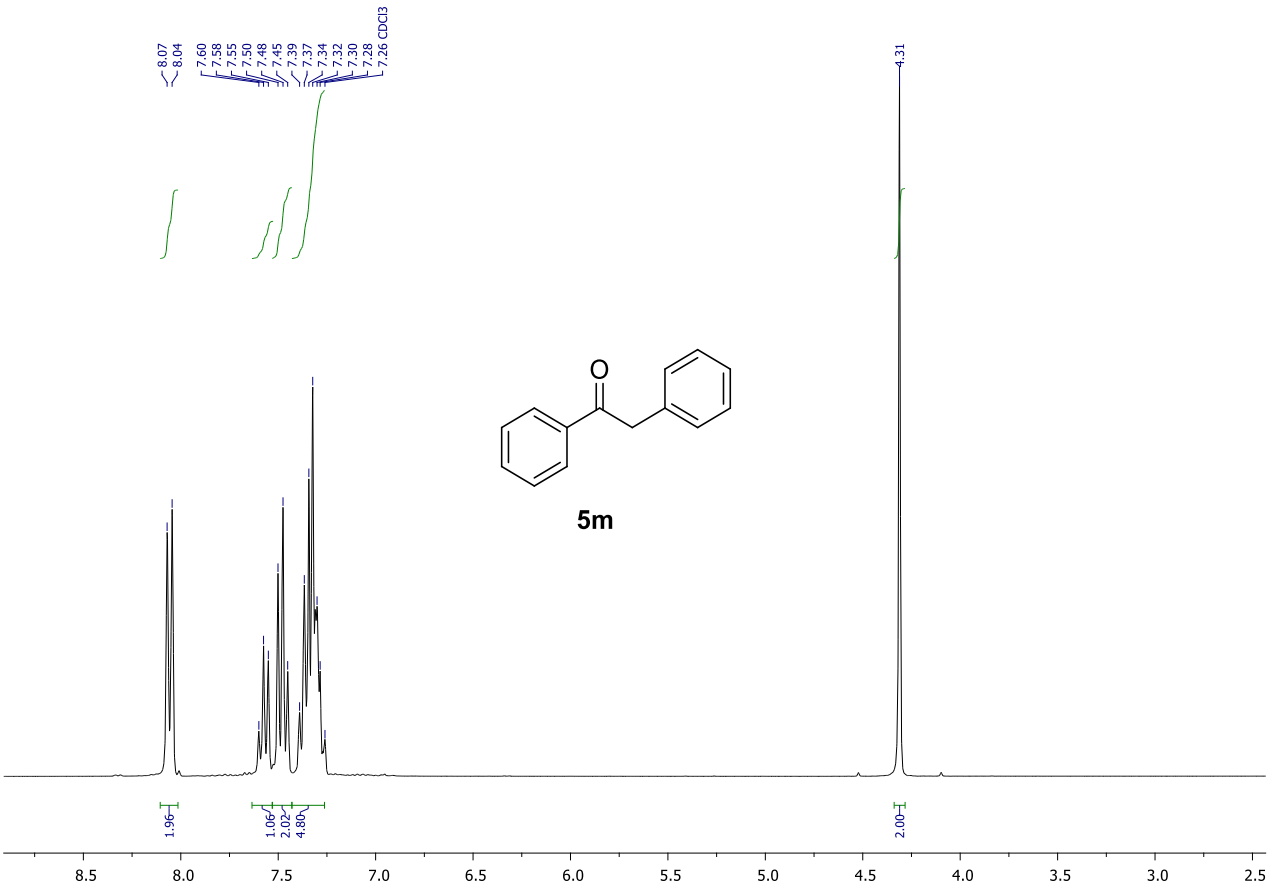


^{13}C NMR (75 MHz, $CDCl_3$) δ 194.86, 193.16, 164.97, 134.71, 133.14, 132.38, 129.89, 128.94, 126.04, 114.34, 55.64.

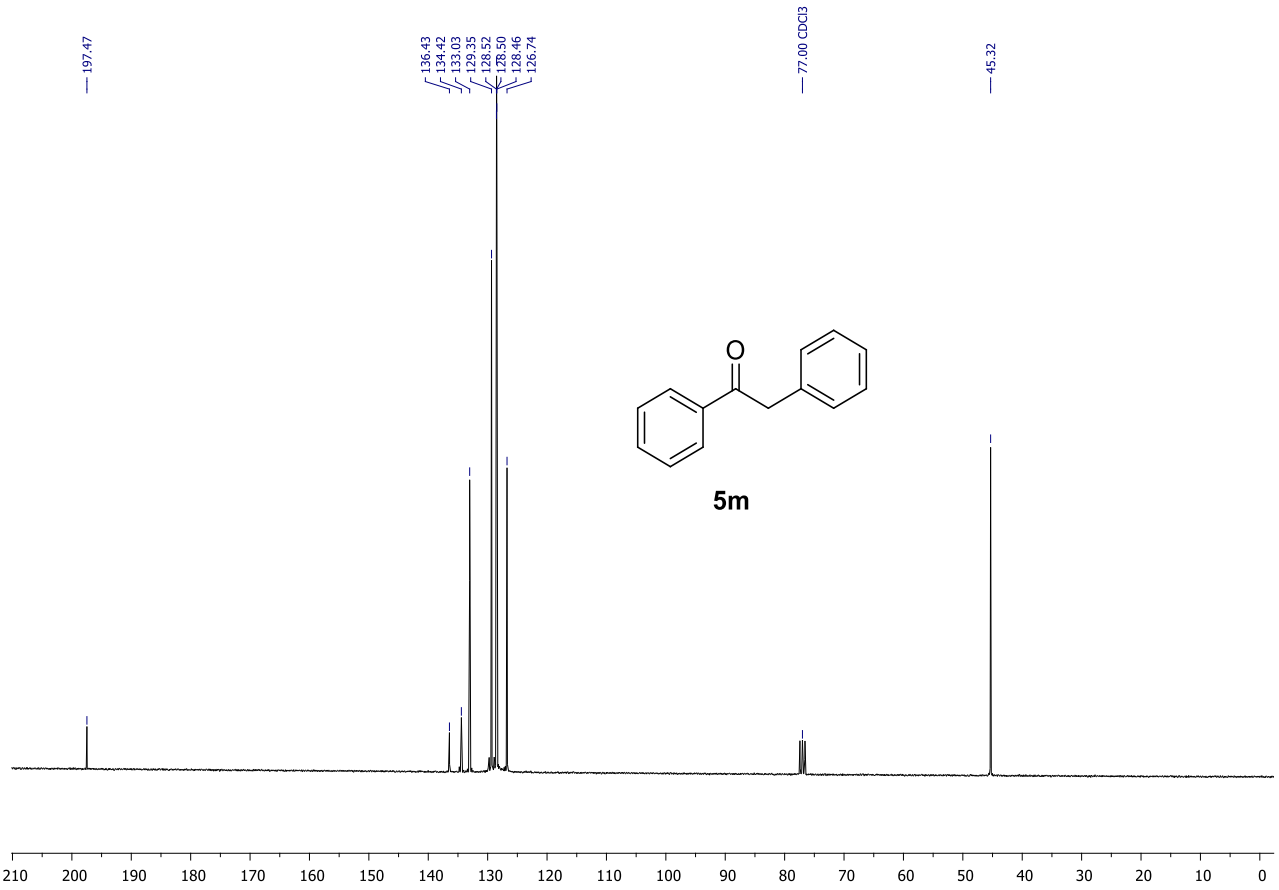
Red oil, eluent petroleum ether/ethyl acetate

Yield = 42%

1,2-diphenylethanone (5m)



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.7 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.42 – 7.26 (m, 5H), 4.31 (s, 2H).



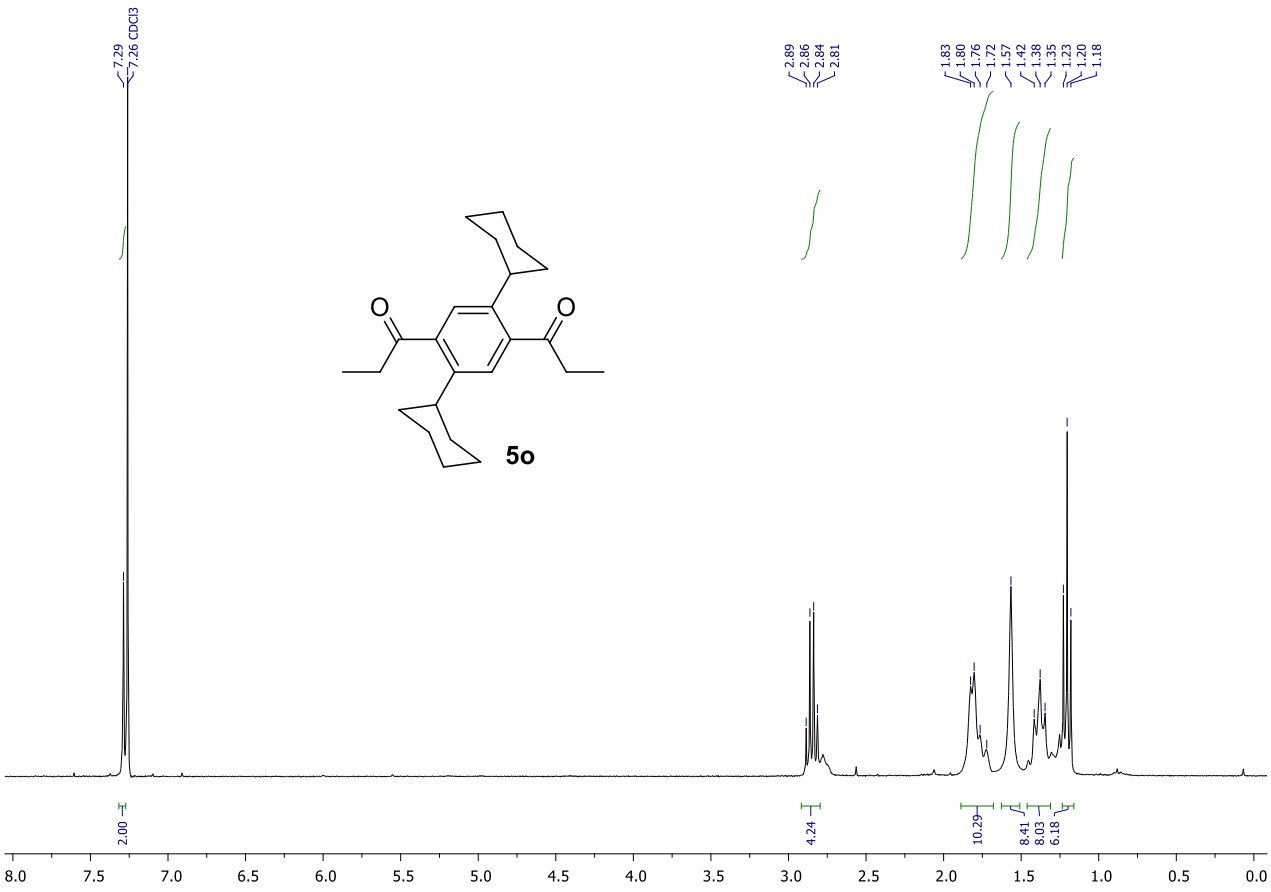
^{13}C NMR (75 MHz, $CDCl_3$) δ 197.47, 136.43, 134.42, 133.03, 129.35, 128.52, 128.50, 128.46, 126.74, 45.32.

Red oil, eluent petroleum ether/ethyl acetate (9:1)

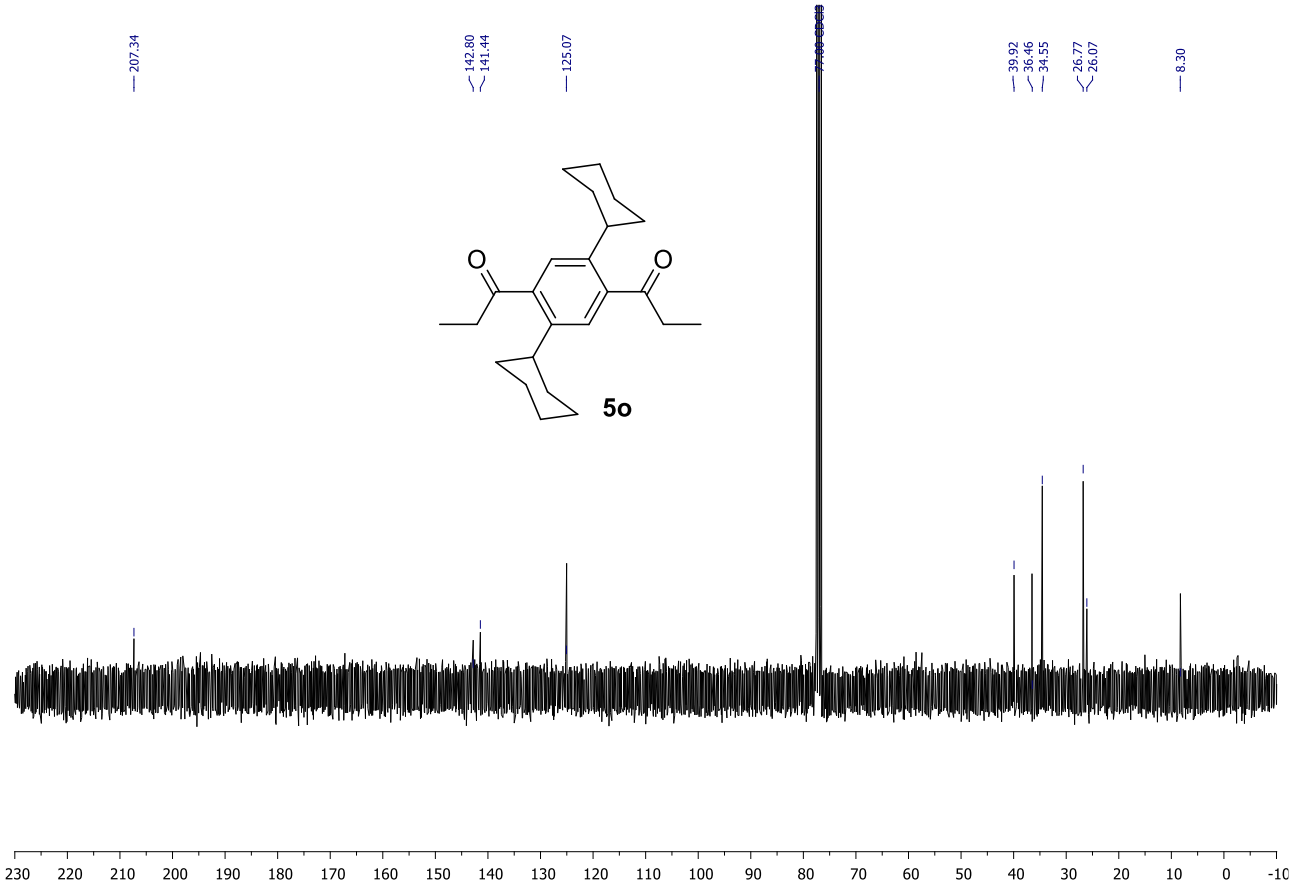
Yield = 50%

GC-MS: (m/z, $M^{+\cdot}$ = 196.0): 196 (7%), 105 (100%), 91 (8%), 77 (21%), 65 (5%).

2,5-dicyclohexyl-1,4-di-(1-propanone)benzene (5o)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 2H), 2.85 (q, *J* = 7.3 Hz, 4H), 1.89 – 1.65 (m, 6H), 1.64 – 1.49 (m, 5H), 1.48 – 1. 25 (m, 4H), 1.20 (t, *J* = 7.3 Hz, 6H).



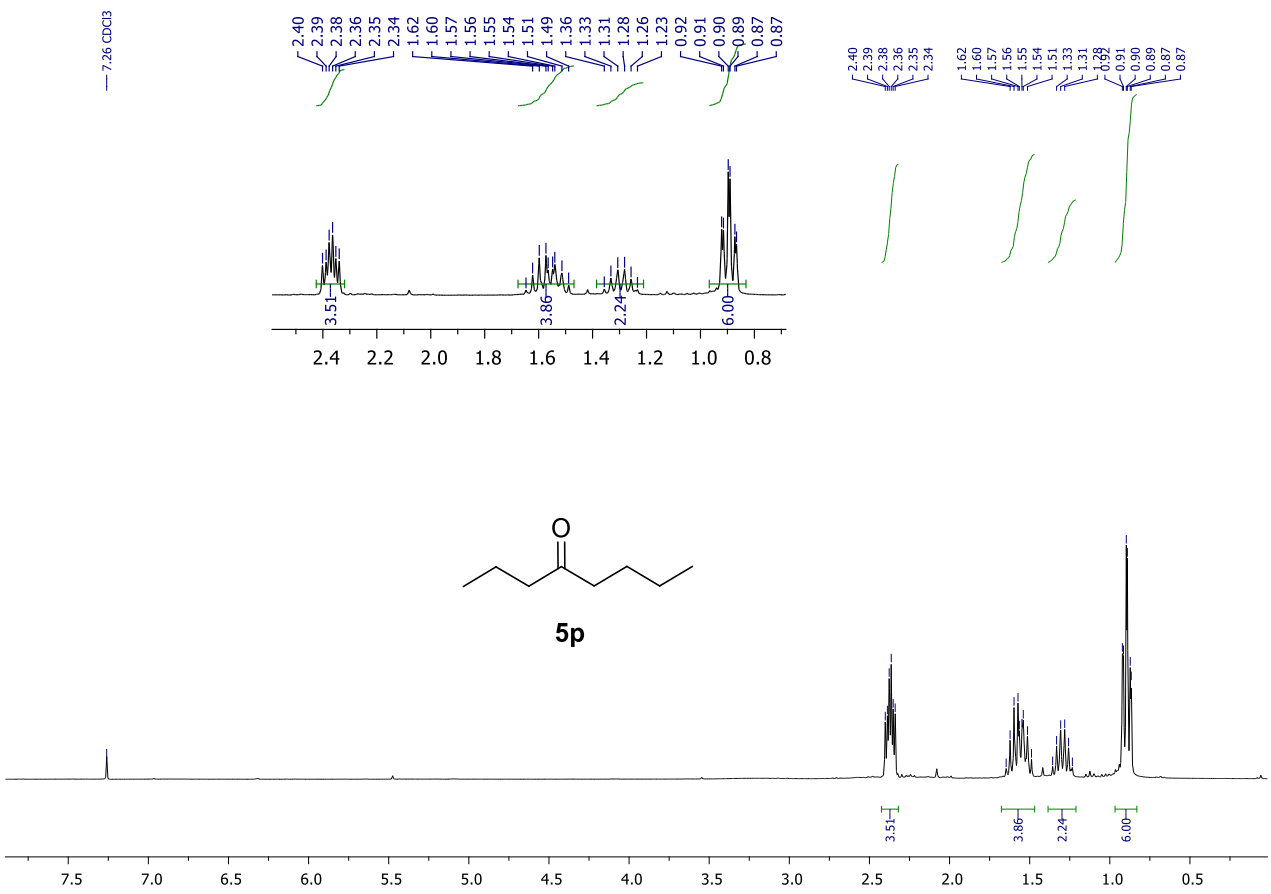
^{13}C NMR (75 MHz, $CDCl_3$) δ 207.34, 142.80, 141.44, 125.07, 39.92, 36.46, 34.55, 26.77, 26.07, 8.30.

Needle-shaped yellow solid, eluent chloroform, crystallized from chloroform/hexane with slow vapour diffusion method, mp=156-162 °C.

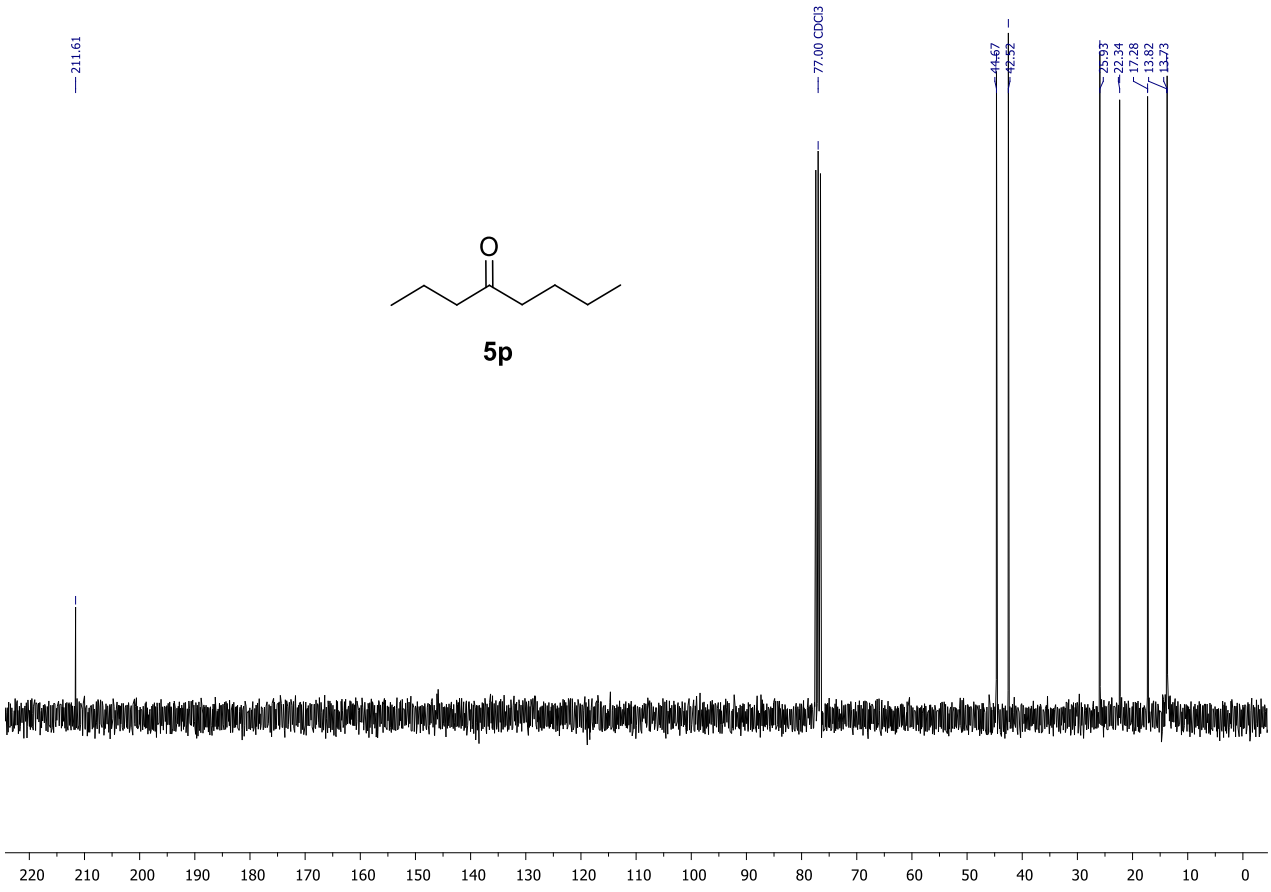
Yield = 55%

HRMS (ESI-TOF) m/z for ($C_{24}H_{34}O_2 + Na^+$) calculated 377.2457, found 377.2449.

4-octanone (5p)

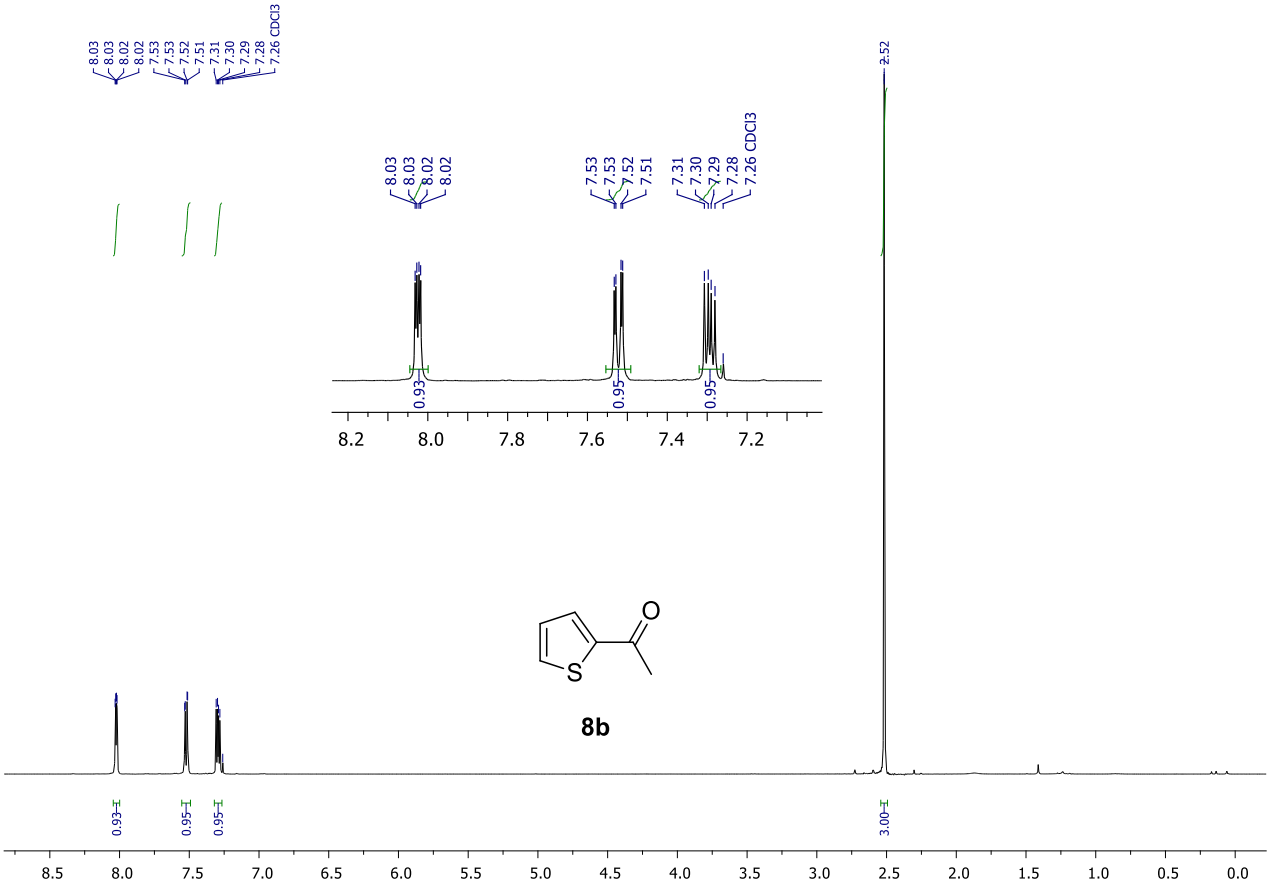


^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (t, J = 7.4 Hz, 2H), 2.36 (t, J = 7.3 Hz, 2H), 1.66 – 1.47 (m, 4H), 1.32 (q, J =7.5 Hz, 1H), 1.27 (q, J = 7.4 Hz, 1H), 0.89 (t, J = 7.3 Hz, 3H).0.90 (t, J = 7.4 Hz, 3H).

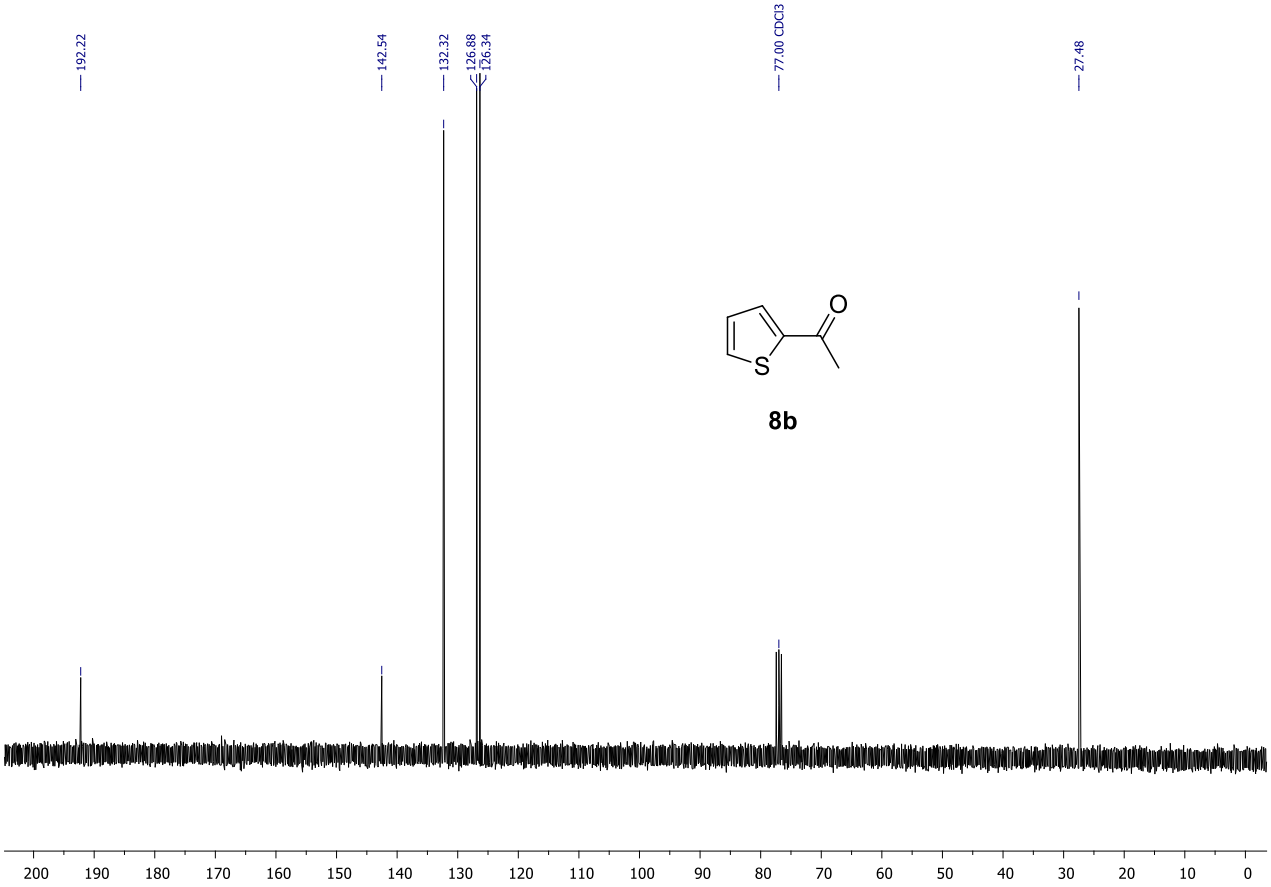


^{13}C NMR (75 MHz, $CDCl_3$) δ 211.61, 44.67, 42.52, 25.93, 22.34, 17.28, 13.82, 13.73.

1-(thiophen-3-yl)-ethanone (8b)



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 2.9, 1.2 Hz, 1H), 7.52 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.29 (dd, *J* = 5.1, 2.9 Hz, 1H), 2.52 (s, 3H).

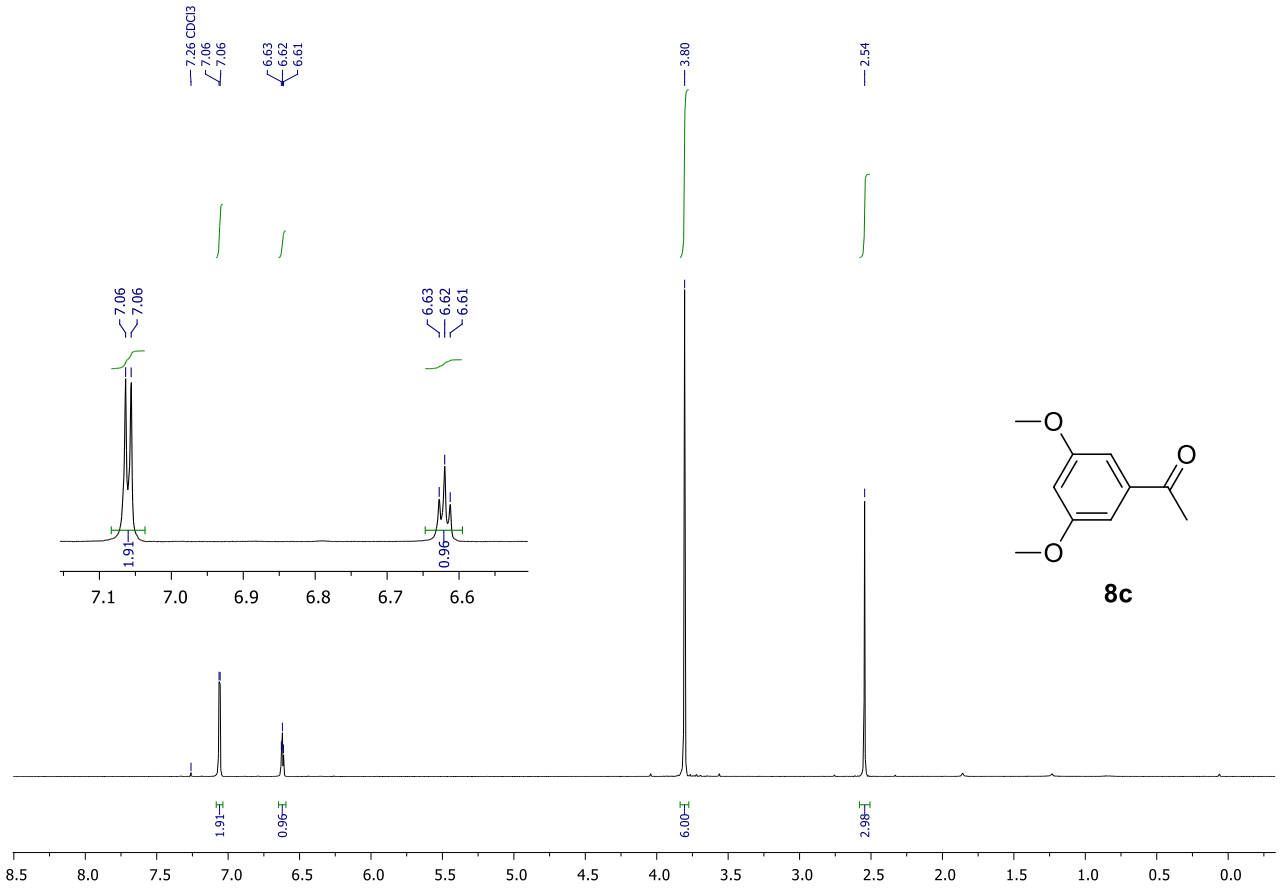


^{13}C NMR (75 MHz, $CDCl_3$) δ 192.22, 142.54, 132.32, 126.88, 126.34, 27.48.

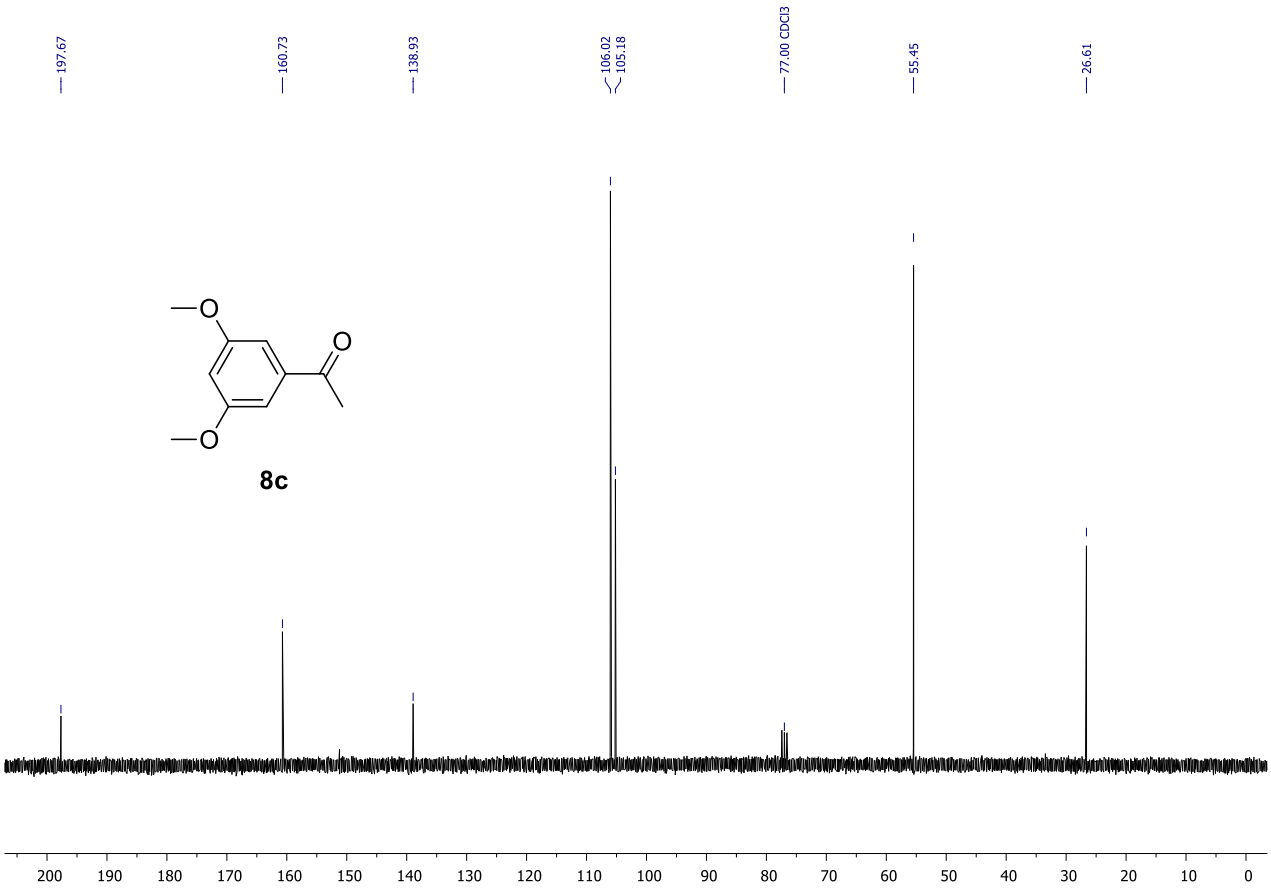
Clear oil, no column

GC yield = 98%, isolated yield = 44%

1-(3,5-dimethoxyphenyl)ethanone (8c)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, *J* = 2.3 Hz, 2H), 6.62 (t, *J* = 2.3 Hz, 1H), 3.80 (s, 6H), 2.54 (s, 3H)

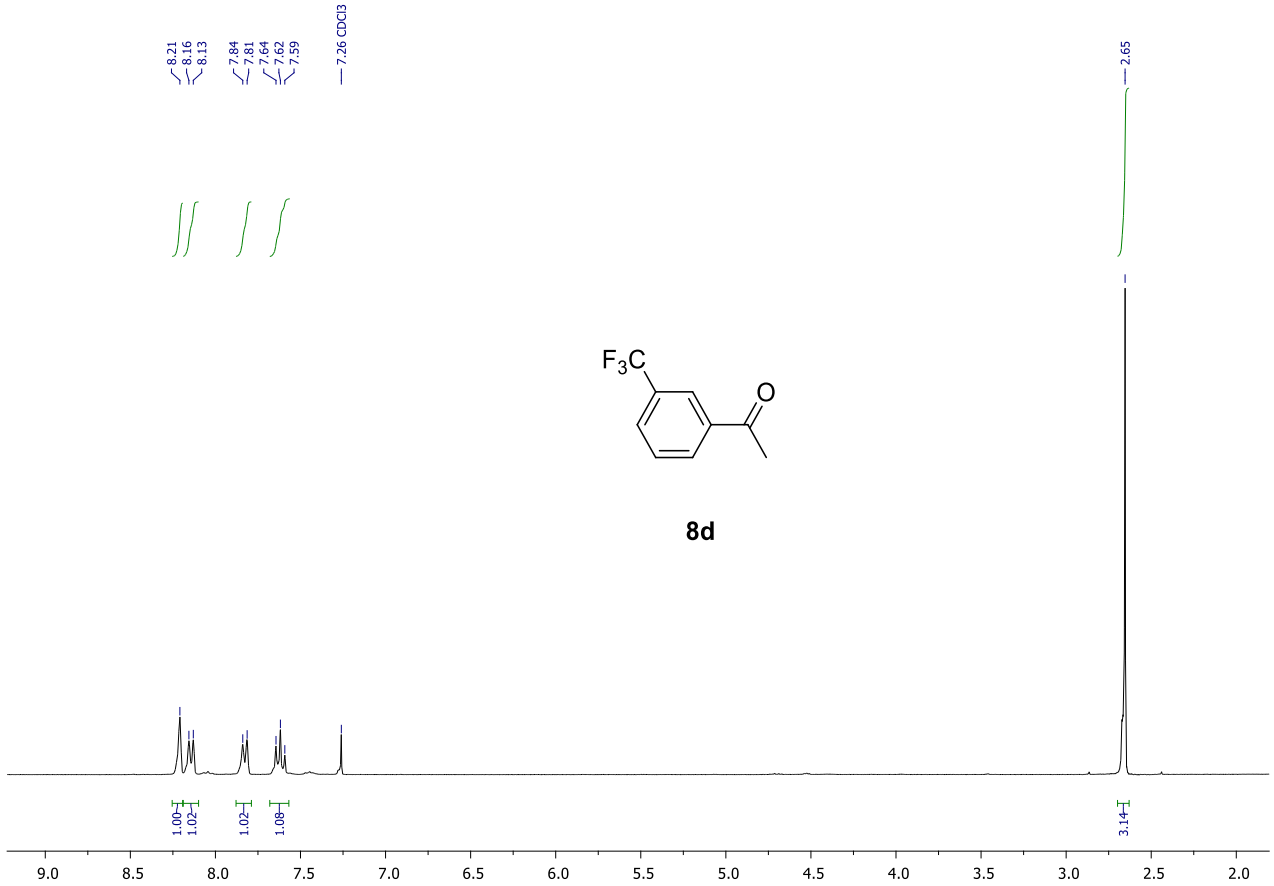


^{13}C NMR (75 MHz, $CDCl_3$) δ 197.67, 160.73, 138.93, 106.02, 105.18, 55.45, 26.61.

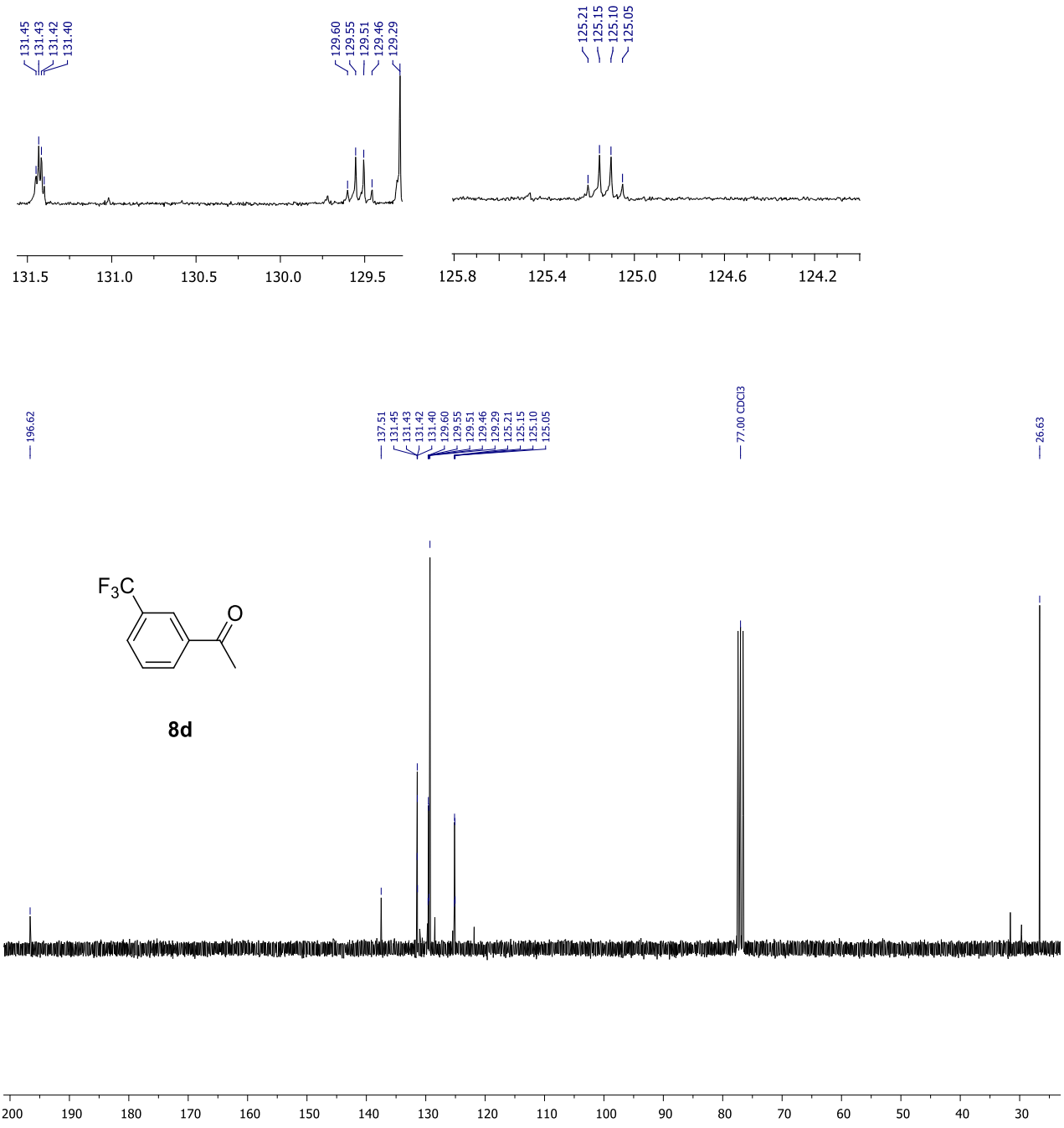
Clear oil, no column

Yield = 80%

3-(trifluoromethyl)acetophenone (8d)



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 2.65 (s, 3H).



^{13}C NMR (75 MHz, $CDCl_3$) δ 196.62, 137.51, 131.42 (q, $J_{C\text{-}F}$ = 1.2 Hz), 129.53 (q, $J_{C\text{-}F}$ = 3.7 Hz), 125.13 (q, $J_{C\text{-}F}$ = 3.9 Hz), 26.63.

Clear oil, eluent hexane/chloroform

Yield = 65%

2.12.4 Kinetic measurements

For the determination of the kinetic constants in the one-pot protodesylylation-hydration process (par. 2.8, scheme 22,), the amounts of reagent, product and intermediate were measured by a GC/MS analysis on solutions prepared from the reaction mixture quenched at different time interval. The 1,2-diphenylethane was used as internal standard. A 100 µl sample of reaction mixture, was collected at the indicated time and diluted in in 0.5 mL of petroleum ether. After extraction with a saturated water solution $NaHCO_3$, 1-2 µl of the organic phase were injected in the GC-MS. A nonlinear least-squares fit of experimental data was carried out with equations 5, 6 and 7.

$$[R] = [R]_0 \, e^{-k_1 t} \qquad (5)$$

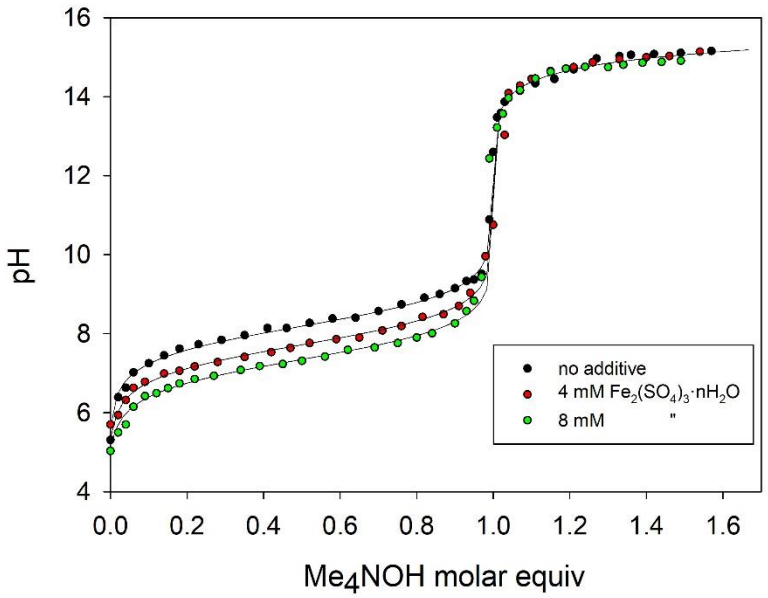
$$[I] = [R]_0 \frac{k_1}{(k_2 - k_1)(e^{-k_1 t} - e^{-k_2 t})} \qquad (6)$$

$$[P] = [R]_0 \frac{(1 - k_2)}{(k_2 - k_1)(\frac{e^{-k_1 t} + k_1}{(k_2 - k_1)e^{-k_2 t}})} \qquad (7)$$

R, I and P are the reagent, the intermediate and the product, respectively. The nonlinear least-squares fitting was carried out with the software SigmaPlot 12.0 (Systat Software, Inc.).

2.12.5 Potentiometric titrations

Potentiometric titrations were performed under a nitrogen atmosphere by an automatic titrator Mettler Toledo DL50, provided with a pH microelectrode. The electrode was calibrated for DMSO: H_2O using standard solutions, at different concentration, of perchloric acid and tetramethylammonium hydroxide. The ionic strength was buffered with tetraethylammonium perchlorate, I = 5.0 mM. The measurements of the pH of the standard solution were taken after wating 10 minutes, in order to obtain a stable value. The calibration plot of calculated −log cH^+ values vs experimental pH readings, obtained by following a tested procedure,[137] was linear in the range 2–17. The pK_w values determined in several titrations coincided within experimental error with that reported in the literature.[138] A 6 mL solution of tetramethylammonium hydroxide in 80% DMSO (50-100 mM) was added to the titration vessel in small increments. Analysis of titration plots was carried out by the programs HySS vers. 4.031 and HYPERQUAD 2000 (scheme 29).[139]

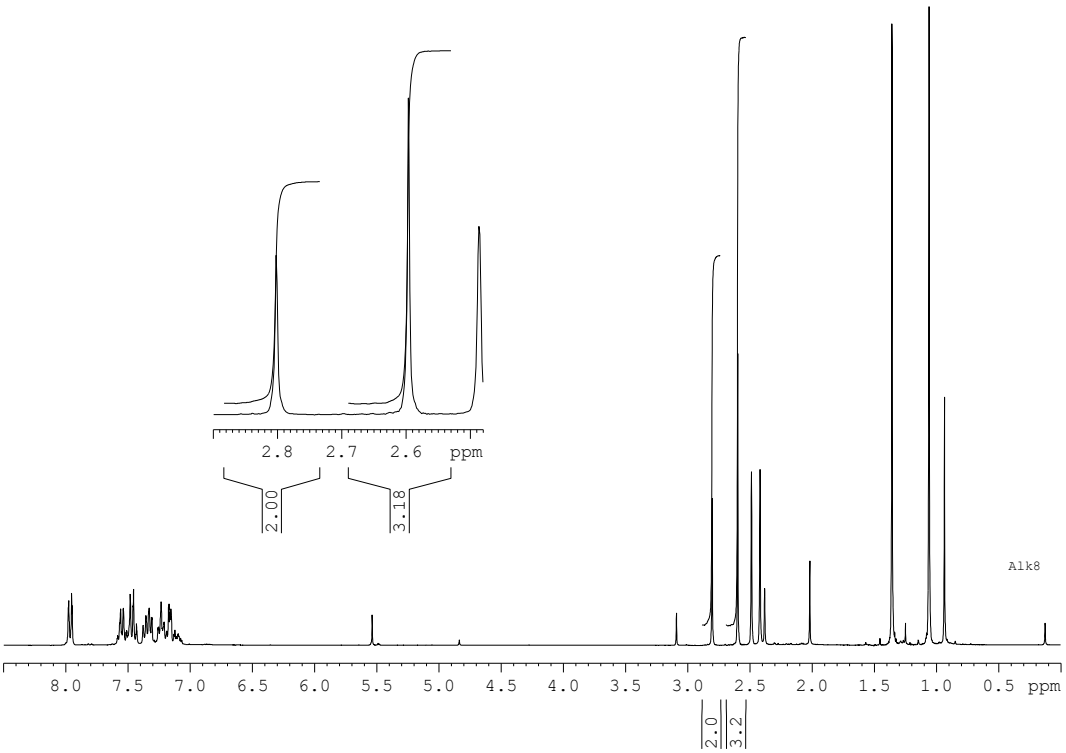


Scheme 29 *Titration of AcOH (1.0 mM) with Me_4NOH in the presence of the indicated amount of $Fe_2(SO_4)_3 \cdot nH_2O$. Conditions: 25 °C, 80% DMSO, 5 mM Et_4NClO_4 as ionic strength buffer*

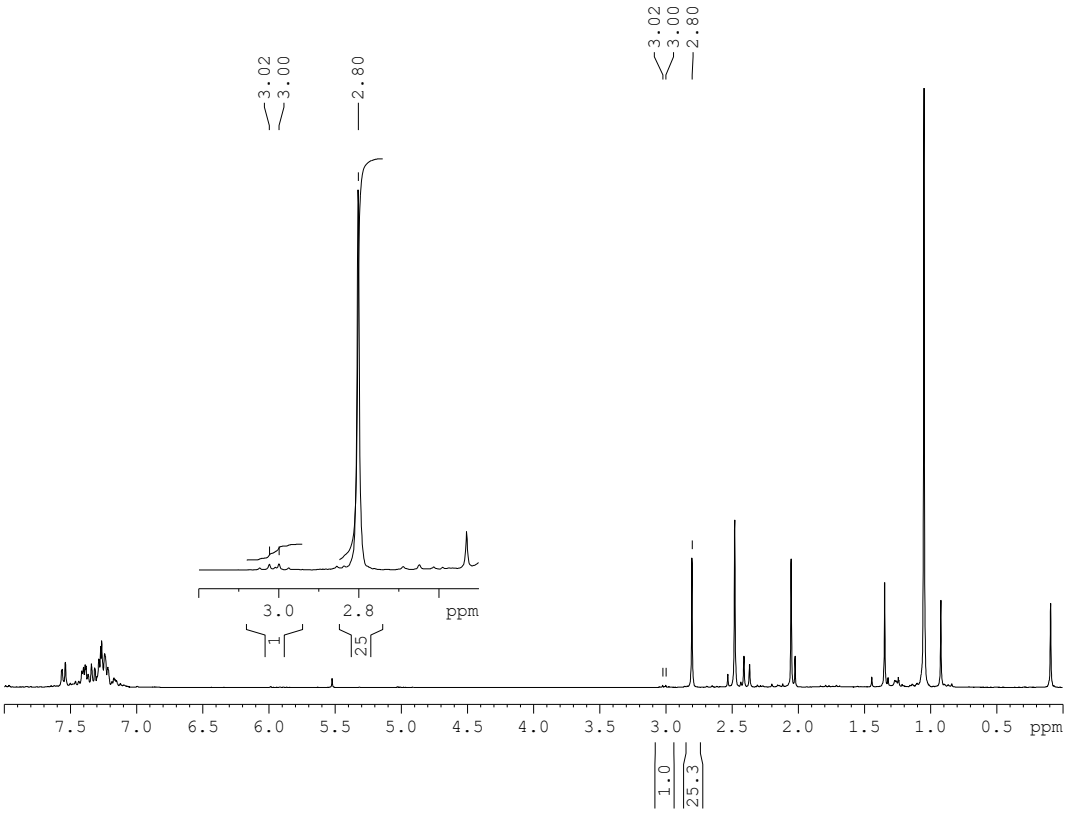
2.12.6 Computational details

The calculations were carried out by prof. Paolo Mencarelli at the HF/6-311G(d,p) level of theory by using the Gaussian 09 D1 package with keyword scf= tight.[140] Harmonic vibrational frequencies were calculated at the HF/6-311G(d,p) level of theory to confirm that the stationary points found correspond to local minima and to obtain the zero-point vibrational energy (ZPVE) corrections. The solvent effect was taken into consideration through the use of the Polarizable Continuum (PCM) model.[141] The keyword SCRF= (PCM, SOLVENT= AceticAcid) was used. The most stable carbocation, among the two possibly formed upon protonation of the alkyne, was considered for the calculation of the relative proton affinity (PAR).

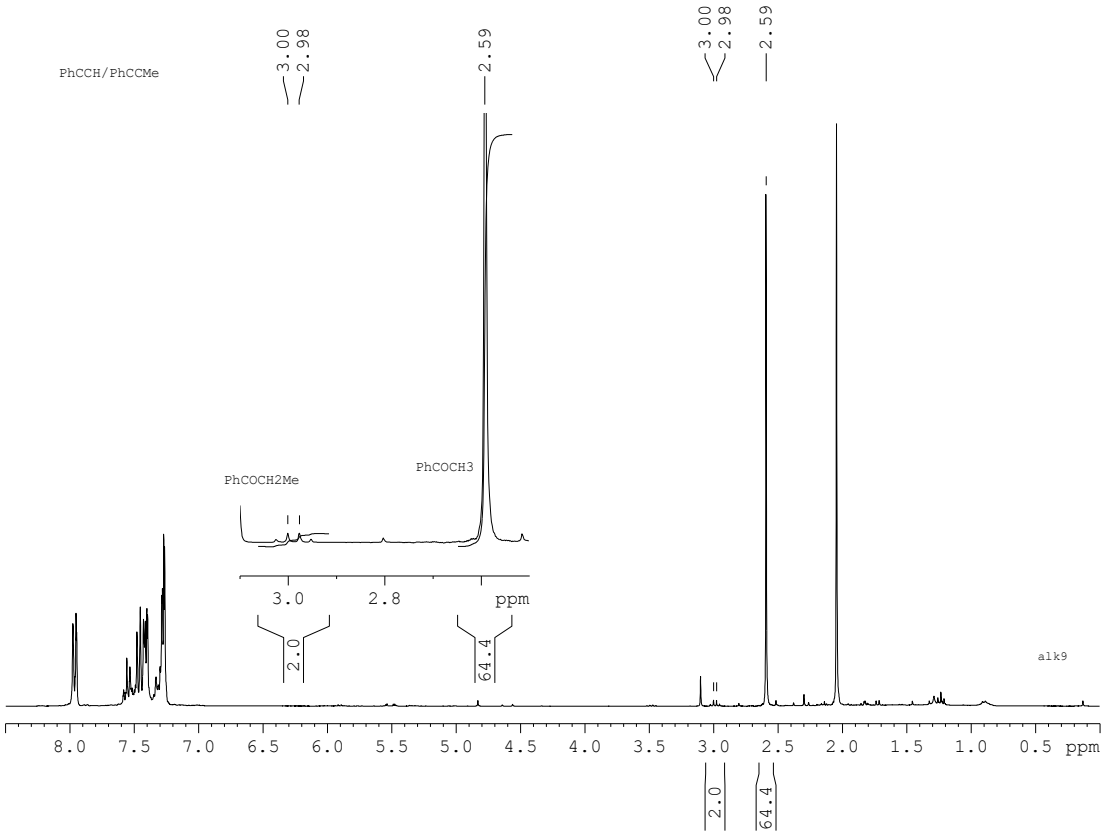
2.12.7 Competitive experiments of alkyne hydrations



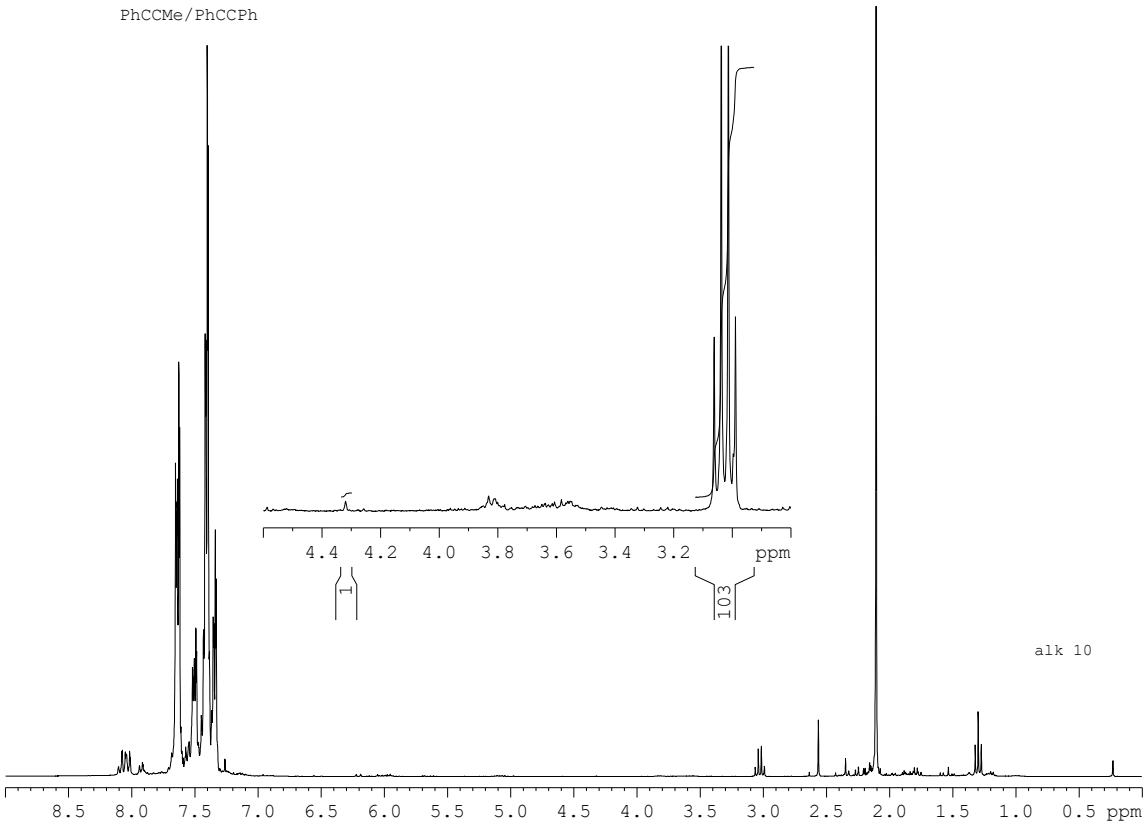
^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the crude extract from the reaction of phenylacetylene (**7a**) and o-tolyl-t-butylacetylene (**4c**) [$Fe_2(SO_4)_3 \cdot n H_2O$ (5 mol%) in acetic acid, 120 °C, 4 h].



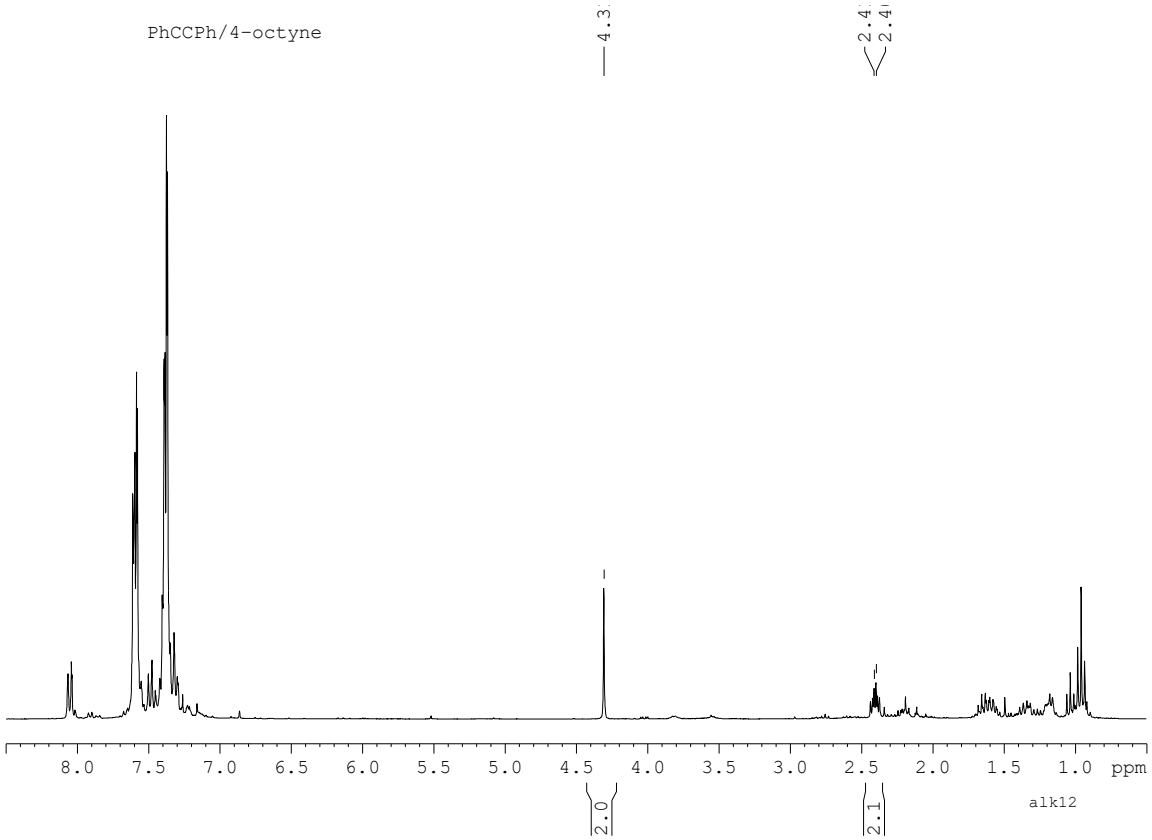
^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the crude extract from the reaction of 1-phenylpropyne (**2**) and o-tolyl-*t*-butylacetylene (**4c**) [$Fe_2(SO_4)_3 \cdot n H_2O$ (5 mol%) in acetic acid, 120 °C, 5 h].



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the crude extract from the reaction of phenylacetylene (**7a**) and 1-phenylpropyne (**2**) [$Fe_2(SO_4)_3 \cdot nH_2O$ (5 mol%) in acetic acid, 120 °C, 5 h].



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the crude extract from the reaction of 1-phenylpropyne (**7a**) and diphenylacetylene (**4m**) [$Fe_2(SO_4)_3 \cdot nH_2O$ (5 mol%) in acetic acid, 120 °C, 8 h].



^{1}H NMR (300 MHz, $CDCl_3$) of the crude extract from the reaction of 4-octyne (**4p**) and diphenylacetylene (**4m**) ($Fe_2(SO_4)_3 \cdot nH_2O$ 5 mol% in acetic acid, 120 °C, 19 h).

2.14 Bibliography

[1] https://www.masterorganicchemistry.com/2013/06/24/alkynes-are-a-blank-canvas/ , 16-09-2019.

[2] Viehe, H. G. *Chemistry of Acetylenes (1st ed.)* **1969**, New York: Marcel Dekker, inc. pp. 170-179 & 225-241.

[3] [a] Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46; [b] King, A. O.; Okukado, N.; [c] Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683; [d] Chodkiewicz, W. *Ann. Chim. Paris* **1957**, *2*, 819; [e] Cadiot, P.; Chodkiewicz, W. in *Chemistry of Acetylenes (1st ed.)* **1969**, Viehe, H.G. Ed., New York: Marcel Dekker, inc. pp. 597–647; [f] Glaser, C. *Ann. Chem. Pharm.* **1870**, *154*, 137; [g] Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422; [h] Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313; [i] Owsley, D. C.; Castro, C. E. *Org. Synth.* **1972**, *52*, 128.

[4] [a] Grignard, V. *Compt. Rend.* **1900**, *130*, 1322; [b] House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 3893; [c] Corey, E. J., Floyd, D.; Lipshutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418; [d] Carey, F.; Sundberg, R. J. *Advanced Organic Synthesis. Part B: Reactions and Synthesis (5th ed.)* **2007**, Springer ed.

[5] [a] Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079; [b] Hintermann, L.; Labonde, A. *Synthesis* **2007**, *8*, 1121; [c] Zuccaccia, D.; Del Zotto, A.; Baratta, W. *Coord. Chem. Rev.* **2019**, *396*, 103.

[6] [a] Kropp, P. J.; Crawford, S. D. *J. Org. Chem.* **1994**, *59*, 3102; [b] Xi-Yan, L..; Sheng-Ming, M. *Chin. J. Chem.* **1998**, *16*, 388.

[7] [a] Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720; [b] Fürstner, A.; Stimson, C. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 8845; [c] Tron, G. C.; Pirali, T.; Billington, R. A.; Canonica, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008**, *28*, 278; [d] Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952.

[8] [a] Ballistreri, F.P.; Failla, S.; Spina, E.; Tomaselli, G. A. *J. Org. Chem.* **1989**, *54*, 947; [b] Ren, W.; Liu, J.; Chen, L.; Wan, X. *Adv. Synth. Catal.* **2010**, *352*, 1424.

[9] [a] Bianchini, C.; Meli, A.; Peruzzini, M.; Vizza, F.; Zanobini, F.; Frediani, P. *Organometallics* **1989**, *8*, 2080; [b] Chandrasekhar, S.; Narsihmulu, C.; Chandrashekar, G.; Shyamsunder, T. *Tetrahedron Lett.* **2004**, *45*, 2421; [c] Ashby, E. C.; Lin, J. J. *J. Org. Chem.* **1978**, *43*, 2567; [d] Daeuble, J. F.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 2397; [e] Trost, B. M.; Ball, Z. T.; Jöge, T. *J. Am. Chem. Soc.* **2002**, *124*, 7922; [f] Brown, C. A.; Ahuja, V. *J. Chem. Soc., Chem. Commun.* **1973**, 553.

[10] Davy, E. *Report of the Sixth Meeting of the British Association for the Advancement of Science* **1836**, *5*, 62.

[11] Weissermel, K.; Arpe, H.-J.; R. Lindley, C. R. *Industrial organic chemistry (4th ed.)* **2003**, Wiley-VCH, pp. 91-106.

[12] Berthelot, M. *Ann. Chim. Phys.* **1863**, *67*, 52.

[13] Lagermack, H.; Eltekoff, A. *Chem. Ber.* **1877**, *10*, 637.

[14] Fittis, R.; Schroher, A. *Chem. Ber.* **1875**, *8*, 367.

[15] [a] Kutscheroff, M. G. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1540; [b] Kutscheroff, M. G. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 13.

[16] Neumann, B.; Schneider, H. *Angew. Chem.* **1920**, *33*, 189.

[17] *Acetaldehyde*, in *Ullmann's Encyclopedia of Industrial Chemistry*, 7th ed.; Wiley-VCH, Weinheim, **2006**.

[18] *Acetylene*, in *Ullmann's Encyclopedia of Industrial Chemistry*, 7th ed.; Wiley-VCH, Weinheim, **2006**.

[19] Hester, A. S.; Himmler, K. *Ind. Eng. Chem.* **1959**, *51*, 1424.

[20] Thomas, R. J.; Campbell, K. N.; Hennion, G. F. *J. Am. Chem. Soc.* **1938**, *60*, 718.

[21] [a] Stacy, G. W.; Mikulee, R. A. *Org. Snth Coll. Vol. IV* **1963**, 13; [b] Thomas, R. J.; Campbell, K. N.; Hennion, G. F. J. Am. Chem. Soc. **1938**, *60*, 718; [c] Nishizawa, M.; Skwarezynski, M.; Imagawa, H.; Sugihara, T. Chem. Lett. **2002**, 12; [d] Nieuwland, J. A.; Vogt, R. R.; Foohey, W. L. *J. Am. Chem. Soc.* **1930**, *52*, 1018; [e] Newman, M. S. *J. Am. Chem. Soc.* **1953**, *75*, 4740; [f] Olah, G. A.; Meidar, D. *Synthesis* **1978**, 671.

[22] Velegraki, G.; Stratakis, M. *J. Org. Chem.* **2013**, *78*, 8880.

[23] Weeden, R. P. *Am. J. Ind. Med.* **1989**, *16*, 225.

[24] Ishimure, M. *Paradise in the Sea of Sorrow: Our Minamata Disease*, Yamaguchi: Kyoto **1990**.

[25] http://www.env.go.jp/en/chemi/hs/minamata2002/ch2.html , 16-09-2019.

[26] [a] Jo, S.; Woo, H. D.; Kwon, H.-J.; Oh, S.-Y.; Park, J.-D.; Hong, Y.-S.; Pyo, H.; Park, K. S.; Lee, S.-A.; Eom, S.-Y.; Kim, B.-G.; Lee, K.-M.; Lee, J.-H.; Hwang, M.S.; Kim, J. *Int. J. Environ. Res. Public Health* **2015**, 12, 9054; [b] https://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm115644.htm , 16-09-2019.

[27] Gray, J. S. *Mar. Poll. Bull.* **2002**, *45*, 46.

[28] [a] Halpern, J.; James, B. R.; Kemp, A. L. W. *J. Am. Chem. Soc.* **1961**, *83*, 4097; [b] Halpern, J.; James, B. R.; Kemp, A. L. W. *J. Am. Chem. Soc.* **1966**, *88*, 5142.

[29] Tokunaga, M.; Wakatsuki, Y. *Angew. Chem. Int. Ed.* **1998**, *37*, 2867.

[30] [a] Hansen, H. D.; Nelson, J. H. *Organometallics* **2000**, *29*, 4640; [b] Ghebreyessus, K. Y.; Nelson, J.H. *Inorg. Chim. Acta* **2003**, *350*, 12.

[31] Cadierno, V.; Crochet, P.; Garcìa-Garrido, S. E.; Gimeno, J. *Dalton Trans.* **2004**, 3635.

[32] Alvarez, P.; Gimeno, J.; Lastra, E.; García-Granda, S.; Van der Maelen, J. F.; Bassetti, M. *Organometallics* **2001**, *20*, 3762.

[33] Chen, Y.; Valentini, M.; Pregosin, P. S.; Albinati, A. *Inorg. Chim. Acta* **2002**, *327*, 4.

[34] Bianchini, C.; Casares, J. A.; Peruzzini, M.; Romerosa, A.; Zanobini, F. *J. Am. Chem. Soc.* **1996**, *118*, 4585.

[35] James, B. R.; Rempel, G. L. *J. Am. Chem. Soc.* **1969**, *91*, 863.

[36] Blum, J.; Huminer, H.; Alper, H. *J. Mol. Catal.* **1992**, *75*, 153.

[37] Setty-Fichman, M.; Sasson, Y.; Blum, J. *J. Mol. Catal.* **1997**, *126*, 27.

[38] Chin, C. S.; Chang, W.-T.; Yang, S.; Joo, K.-S. *Bull. Korean Chem. Soc.* **1997**, *18*, 324.

[39] Hirabayashi, T.; Okimoto, Y.; Saito, A.; Morita, M.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2006**, *62*, 2231.

[40 a] Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816; [b] Imi, K.; Imai, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 3127.

[41] Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron* **1993**, *49*, 4955.

[42 a] Sokol'skii, D. V.; Dorfman, Y. A.; Segizbaeva, S. S. US Patent 398270, **1973**; [b] Sokol'skii, D. V.; Dorfman, Y. A.; Segizbaeva, S. S. *Chem. Abstr.* **1974**, *81*, 49251.

[43] Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845.

[44] Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907.

[45 a] Avshu, A.; O' Sullivan, R. D.; Parkins, A. W.; Alcock, N. W.; Countryman, R. M. *J. Chem. Soc., Dalton Trans.* **1983**, 1619; [b] Kataoka, Y.; Matsumoto, O.; Ohashi, M.; Yamagata, T.; Tani, K. *Chem. Lett.* **1994**, 1283.

[46 a] Meier, I. K.; Marsella, J. A. *J. Mol. Catal.* **1993**, *78*, 31; [b] Saimoto, H.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3078.

[47 a] Hiscox, W.; Jennings, P. W. *Organometallics* **1990**, *9*, 1997; [b] Hartman, J. W.; Hiscox, W. C.; Jennings, P. W. *J. Org. Chem.* **1993**, *58*, 7613.

[48] Jennings, P. W.; Hartman, J. W.; Hiscox, W. C. *Inorg. Chim. Acta* **1994**, *222*, 317.

[49] Petron, A. A.; Kupin, B. S. *Zh. Obshch. Khim.* **1929**, *59*, 3153.

[50 a] Baidossi, W; Lahav, M.; Blum, J. *J. Org. Chem.* **1997**, *62*, 669; [b] Israelsohn, O.; Vollhardt, K. P. C.; Blum, J. *J. Mol. Catal.* **2002**, *184*, 1.

[51] Hartman, J. W.; Sperry, L. *Tetrahedron Lett.* **2004**, *45*, 3787.

[52] Francisco, L. W.; Moreno, D. A.; Atwood, J. D. *Organometallics* **2001**, *20*, 4237.

[53] Lucey, D. W.; Atwood, J. D. *Organometallics* **2002**, *21*, 2481.

[54] Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, 1019.

[55] Easton, N. R.; Cassady, D. R.; Dillard, R. D. *J. Org. Chem.* **1965**, *30*, 3084.

[56] Kataoka, Y.; Matsumoto, O.; Tani, K. *Chem. Lett.* **1996**, 727.

[57] Sokol'skii, D. V.; Dorfman, Y. A.; Karazhanova, N. A.; Nogerbekov, B. Y. *Zh. Org. Khim.* **1971**, 7, 1581.

[58] [a] Vartanyan, S. A.; Pirenyan, S. K.; Manasyan, N. G. *Zh. Obshch. Khim.* **1961**, *31*, 2436; [b] Shestakov, G. K.; Vsevsvyatskaya, N. Y.; Stepanov, A. M.; Temkin, O. N. *Kinet. Catal.* **1976**, *17*, 815.

[59] [a] Shestakov, G. K.; Temkin, O. N.; Vsevsvyatskaya, N. Y.; Stepanov, A. M. *Zh. Org. Khim.* **1979**, *15*, 248; [b] Vsevsvyatskaya, N. Y.; Shestakov, G. K.; Temkin, O. N. *Kinet. Catal.* **1986**, *27*, 1330; [c] Vsevsvyatskaya, N. Y.; Tsyganov, D. V.; Bykov, A. M.; Shestakov, G. K.; Temkin, O. N. *Zh. Org. Khim.* **1985**, *21*, 2041.

[60] Vsevsvyatskaya, N. Y.; Shestakov, G. K.; Temkin, O. N. *Kinet. Catal.* **1988**, *29*, 965.

[61] Bassetti, M.; Floris, B. *Gazz. Chim. Ital.* **1986**, *116*, 595.

[62] Norman, R. O. C.; Parr, W. G. E.; Thomas, C. B. *J. Chem. Soc., Perkin Trans.* **1976**, 1983.

[63] Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729.

[64] Fukuda, Y.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013.

[65] Teles, S.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415; [b] Schulz, M., Teles, J. H. *Chem. Abstr.* **1997**, *127*, 121499; [c] Schulz, M., Teles, J. H. US Patent 6037482, **2000**.

[66] Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4563.

[67] Roembke, P.; Schmidbaur, H.; Cronje, S.; Raubenheimer, H. *J. Mol. Catal.* **2004**, *212*, 35.

[68] Schneider, S. K.; Herrmann, W. A.; Herdtweck, E. Z. *Anorg. Allg. Chem.* **2003**, *629*, 2363.

[69] Zhou, C.; Chan, P. W. H.; Che, C. *Org. Lett.* **2006**, *8*, 325.

[70] Casado, R.; Contel, M.; Laguna, M.; Romero, P.; Sanz, S. *J. Am. Chem. Soc.* **2003**, *125*, 11925.

[71] Desgrez, A. *Ann. Chem.* **1894**, *3*, 209.

[72] [a] Vasudevan, A.; Verzal, M. K. *Synlett* **2004**, 631; [b] Kremsner, J. M.; Kappe, C. O. *Eur. J. Org. Chem.* **2005**, 3672.

[73] An, G.; Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1997**, *62*, 2505.

[74] [a] Olivi, N.; Thomas, E.; Peyrat, J.; Alami, M.; Brion, J. *Synlett* **2004**, 2175; [b] Le Bras, G.; Provot, L.; Peyrat, J.; Alami, M.; Brion, J. *Tetrahedron Lett.* **2006**, *47*, 5497.

[75] Tsuchimoto, T.; Joya, T.; Shirakawa, E.; Kawakami, Y. *Synlett* **2000**, 1777.

[76] Chapdelaine, M. J.; Warwick, P. J.; Shaw, A. *J. Org. Chem.* **1989**, *54*, 1218.

[77] [a] Meseguer, B.; Alonso-Díaz, D.; Griebenow, N.; Herget, T.; Waldmann, H. *Angew. Chem. Int. Ed.* **1999**, *38*, 2902; [b] Duclos, S.; Stoeckli-Evans, H.; Ward, T. R. *Helv. Chim. Acta* **2001**, *84*, 3148.

[78] [a] Menashe, N.; Reshef, D.; Shvo, Y. *J. Org. Chem.* **1991**, *56*, 2912; [b] Menashe, N.; Shvo, Y. *J. Org. Chem.* **1993**, *58*, 7434.

[79] Xu, G.; Hartman, T. L.; Wargo, H.; Turpin, J. A.; Buckheit, R. W.; Cushman, M. *Bioorg. Med. Chem.* **2002**, *10*, 283.

[80] Schaad, R. E.; Ipatieff, V. N. *J. Am. Chem. Soc.* **1940**, *62*, 178.

[81] [a] Kupin, B. S. *Zh. Org. Khim.* **1965**, *1*, 1206; [b] Iimura, S.; Manabe, K.; Kobayashi, S. *Org. Biomol. Chem.* **2003**, *1*, 2416.

[82] [a] Woolridge, T.; Roberts, T. D. *Tetrahedron Lett.* **1973**, *41*, 4007; [b] Wan, P.; Culshaw, S.; Yates, K. *J. Am. Chem. Soc.* **1982**, *104*, 2509; [c] Chiang, Y.; Kresge, A. J.; Capponi, M.; Wirz, J. *Helv. Chim. Acta* **1986**, *69*, 1331.

[83] [a] Noyce, D. S.; Matesich, M. A.; Peterson, P. E. *J. Am. Chem. Soc.* **1967**, *89*, 6225; [b] Noyce, D. S.; Schiavelli, M. D. *J. Am. Chem. Soc.* **1968**, *90*, 1020; [c] Schmid, G. H. In *Chemistry of the Carbon-Carbon Triple Bond*; Patai, S., Ed.; John Wiley: Chichester, **1978**, 275; [d] Allen, A. D.; Chiang, Y.; Kresge, J. A.; Tidwell, T. T. *J. Org. Chem.* **1982**, *47*, 775; [e] Lucchini, V.; Modenan, G. *J. Am. Chem. Soc.* **1990**, *112*, 6291.

[84] Trentin, F.; Chapman, A. M.; Scarso, A.; Sgarbossa, P.; Michelin, R. A.; Strukul, G.; Wass, D. F. *Adv. Synth. Catal.* **2012**, *354*, 1095.

[85] [a] Thuong, M. B. T.; Mann, A.; Wagner, A. *Chem. Commun.* **2012**, *48*, 434; [b] Das, R.; Chakraborty, D. *Appl. Organomet. Chem.* **2012**, *26*, 722.

[86] Jin, X.; Oishi, K.; Yamaguchi, K.; Mizuno, N. *Chem. Eur. J.* **2011**, *17*, 1261.

[87] Tachinami, T.; Nishimura, T.; Ushimaru, R.; Noyori, R.; Naka, H. *J. Am. Chem. Soc.* **2013**, *135*, 50.

[88] Suta, K.; Turks, M. *ACS Omega* **2018**, *3*, 18065.

[89] [a] Leyva, A.; Corma, A. *J. Org. Chem.* **2009**, *74*, 2067; [b] Marion, N.; Ramón, R. S.; Nolan, S. P. *J. Am. Chem. Soc.* **2009**, *131*, 448; [c] Heidrich, M.; Bergmann, M.; Müller-Borges, D.; Plenio, H. *Adv. Synth. Catal.* **2018**, *360*, 3572; [d] Schreyer, M.; Milzarek, T. M.; Wegmann, M.; Brunner, A.; Hintermann, L. *ChemCatChem* **2019**, *11*, in press.

[90] Grotjahn, D. B.; Lev, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 12232.

[91] Bassetti, M.; Ciceri, S.; Lancia, F.; Pasquini, C. *Tetrahedron Lett.* **2014**, *55*, 1608.

[92] Parthipan, G.; Thenappan, T. *J. Solution Chem.* **2007**, *36*, 1231.

[93] Putintsev, N. M.; Stepanova, N. V.; Putintsev, D. N.; Zinov'eva, A. B. *Russ. J. Phys. Chem. A* **2010**, *84*, 624.

[94] Antenucci, A.; Flamini, P.; Fornaiolo, M. V.; Di Silvio, S.; Mazzetti, S.; Mencarelli, P.; Salvio, R.; Bassetti, M. *Adv. Synth. Catal.* **2019**, *361*, 4517.

[95] Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533

[96] [a] Ban, M.; Ida, F. *Chem. Abstr.* **1957**, *51*, 85804; [b] Ban, M.; Ida, F. US Patent 2791614, **1957**.

[97] Damiano, J. P.; Postel, M. J. *J. Organomet. Chem.* **1996**, *522*, 303.

[98] Wu, X.; Bezier, D.; Darcel, D. *Adv. Synth. Catal.* **2009**, *351*, 367.

[99] Niu, T.-F.; Jiang, D.-Y.; Li, S.-Y.; Shu, X.-G.; Li, H.; Zhang, A.-L.; Xu, J.-Y.; Ni, B.-Q. *Tetrahedron Lett.* **2017**, *58*, 1156.

[100] [a] Jacubert, M.; Provot, O.; Peyrat, J.-F.; Hamze, A.; Brion, J.-D.; Alami, M. *Tetrahedron* **2010**, *66*, 3775; [b] Wong, W.-L.; Ho, K.-P.; Lee, L. Y. S.; Lam, K.-M.; Zhou, Z.-Y.; Chan, T. H.; Wong, K.-Y. *ACS Catal.* **2011**, *1*, 116.

[101] Cabrero-Antonino, J. R.; Levya-Pérez, A.; Corma, A. *Chem. Eur. J.* **2012**, *18*, 11107.

[102] Park, J.; Yeon, J.; Lee, P. H.; Lee, K. *Tetrahedron Lett.* **2013,** *54*, 4414.

[103] Yi, W.; Yan, D.; Wu, C.; Lan, L. *Chem. J. Chin. Univ.* **2014**, *35*, 2563.

[104] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

[105] [a] Ren, W.; Xia, Y.; Wan, X.; Zhao, J. *Org. Lett.* **2009**, *11*, 1841; [b] Xue, J.-W.; Zeng, M.; Hou, Chen, Z.; Yin, G. *Asian J. Org. Chem.* **2018**, *7*, 212.

[106] Baldock, P.; Mills, V.; Stewart, P. S. *J. Cryst. Growth* **1996**, *168*, 170.

[107] Larson, G. L. *Synthesis*, **2018**, *50*, 2433.

[108] Tanemura, K.; Suzuki, T. *Tetrahedron Lett.* **2017**, *58*, 955.

[109] [a] Klumpp, D. A.; Rendy, R.; Zhang, Y.; McElrea, A.; Gomez, A.; Dang, H. *J. Org. Chem.* **2004**, *69*, 8108; [b] Wang, Y.; Peng, C.; Liu, L; Zhao, J; Su, L.; Zhu, Q.*Tetrahedron Lett.* **2009**, *50*, 2261; [c] Birault, V.; Campbell, A. J.; Harrison, S.; Le, J.; Shukla, L. WO2013/160418, **2013**, A1; [d] Politanskaya, L.; Tretyakov, E. *Synthesis* **2018**, *50*, 555.

[110] Velegraki, G.; Stratakis, M. *J. Org. Chem.* **2013**, *78*, 8880.

[111] Yamamoto, H.; Futatsugi, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 1924.

[112] Ren, J.; Cramer, C. J.; Squires, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 2633.

[113] Liang, S.; Hammond, G. B.; Xu, B. *Chem. Commun.* **2015**, *51*, 903

[114] [a] Georgieva, M. *Anal. Chim. Acta* **1977**, *90*, 83; [b] Wróbel, R.; Chmurzyński, L. *Anal. Chim. Acta* **2000**, *405*, 303.

[115] [a] Kreevoy, M. M.; Baughman, E. H. *J. Phys. Chem.* **1974**, *78*, 421; [b] Pawlak, Z.; Bates, R. G. *J. Solution Chem.* **1975**, *4*, 817.

[116] [a] M. J. S. Dewar, M. J. S.; Dieter, K. M. *J. Am. Chem. Soc.* **1986**, *108*, 8075; [b] Maksic', Z. B.; Kovacčvic', B.; Vianello, R. *Chem. Rev.* **2012**, *112*, 5240.

[117] [a] Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*, Oxford University Press, New York, **1998**; [b] Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301.

[118] Zao, G.; Xu, G.; Qian, C.; Tang, W. *J. Am. Chem. Soc.* **2017**, *139*, 3360.

[119] Hashmi, A. S. K. *Catal. Today* **2007**, *122*, 211.

[120] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[121] Jacobson, B. M. *J. Chem. Educ.* **1988**, *65*, 459.

[122] Hernández Torres, G.; Choppin, S.; Colobert, F. *Eur. J. Org. Chem.* **2006**, 1450.

[123] Lei, C.; Jin, X.; Zhou, J. *ACS Catal.* **2016**, *6*, 1635.

[124] Feuerstein, M.; Berthiol, F.; Doucet, H.; Santelli, M. *Synthesis* **2004**, 1281.

[125] Rasolofonjatovo, E.; Tréguier, E.; Provot, O.; Hamze, A.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem.* **2012**, 1603.

[126] Ma, Y.; Song, C.; Jiang, W.; Wu, Q.; Wang, Y.; Liu, X.; Andrus, M. B. *Org. Lett.* **2003**, 3317.

[127] Colobert, F.; Castanet, A.-S.; Abillard, O. *Eur. J. Org. Chem.* **2005**, 3334.

[128] Lu, L.; Chellan, P.; Smith, G. S.; Zhang, X.; Yan, H.; Mao, J. *Tetrahedron* **2014**, *70*, 5980.

[129] San Jose, B. A.; Matsushita, S.; Akagi, K. *J. Am. Chem. Soc.* **2012**, *134*, 19795.

[130] Campbell, I. D.; Eglinton, G.; Groves, J.; Boekelheide, V. *Org. Synth.* **1965**, 45, 39.

[131] Krzyanowska, E.; Olszanowski, A.; Juskowiak, M. *J. Praktische Chemie* **1989**, *331*, 617.

[132] Liu, Y.; Yao, B.; Deng, C. L.; Tang, R. Y.; Zhang, X. G.; Li, J. H. *Org. Lett.* **2011**, *13*, 9.

[133] Adak, L.; Bhadra, S.; Ranu, B. C. *Tetrahedron Lett.* **2010**, *51*, 3811.

[134] Sartori, G.; Pastorio, A.; Maggi, R.; Bigi, F. *Tetrahedron* **1996**, *52*, 8287.

[135] Huang, L.; Cheng, K.; Yao, B.; Xie, Y.; Zhang, Y. *J. Org. Chem.* **2011**, *76*, 5732.

[136] Schaaf, P.; Gojic, V.; Bayer, T.; Rudroff, F.; Schnürch, M.; Mihovilivic, M. D. *ChemCatChem* **2018**, *10*, 920.

[137 a] Salvio, R.; Moliterno, M.; Caramelli, D.; Pisciottani, L.; Antenucci, A.; D'Amico, M.; Bella, M. *Catal. Sci. Technol.* **2016**, *6*, 2280; [b] Salvio, R.; Cacciapaglia, R.; Mandolini, L.; Sansone, F.; Casnati, A. *RSC Adv.* **2014**, *4*, 34412.

[138 a] Savelli, C.; Salvio, R. *Chem. Eur. J.* **2015**, *21*, 5856; [b] Salvio, R.; Cincotti, A. *RSC Adv.* **2014**, *4*, 28678.

[139 a] Gans, P.; Sabatini, A.; Vacca, A. *Talanta* **1996**, *43*, 1739; [b] Alderighi, L.; Gans, P.; Ienco, A.; Peters, D.; A. Sabatini, A.; Vacca, A. *Coord. Chem. Rev.* **1999**, *184*, 311.

[140] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; J. Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT, **2013**.

[141] Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999.

Chapter 3

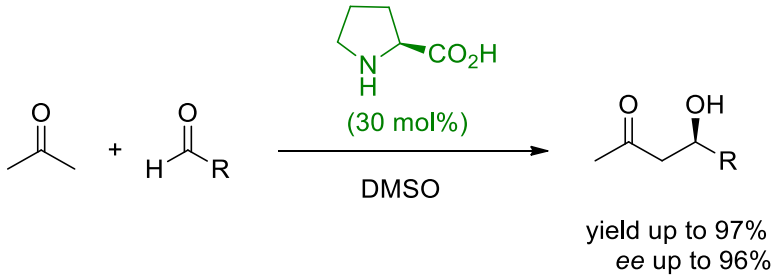
Towards new green phosphoric acid organocatalysts

3.1 Organocatalysis and green chemistry

Organocatalysis is the catalysis from small organic molecules, where metals are not part of the active principles, which function either donating or removing protons or electrons. According to this definition, four distinct areas can be identified: Brønsted acid and base organocatalysis, and Lewis acid and base organocatalysis.[1] Despite the first example of organocalytic reaction dates back to 1860[2] and sporadic reactions following one of these general schemes can be found in the literature over the decades,[3] this field acquired great fortune starting from the beginning of the 21st century, when three pioneeristic papers by Maruoka,[4] List[5] and MacMillan[6] were published. Actually, definition of organocatalysis is even more recent[7] and the general interest towards it is nowadays mainly due to its applications in asymmetric synthesis. With respect to green chemistry, organocatalysis often naturally encounters the necessities expressed in the twelve principles: mild reaction conditions, naturally-occurring substrates and catalysts, no particular safety measures required, user-friendly equipments. However, sometimes chemical transformations are carried out in the full respect of the definition of organocatalytic reaction, but not of green chemistry concepts, thus not disfruiting the potential of the two combined approaches. This happens, for instance, when reactions are performed in halogenated solvents or at very low temperatures (below -20 °C), unsuitable both for safety and possibility of large scale application. These requirements are not rare in asymmetric organocatalysis, since dichlorometane and chloroform are privileged solvents due to their low dielectric constant, which favours the formation of tight chiral ion pairs, while low temperatures help in enhancing enantioselectivity, in agreement with Eyring equation (equation 3.1).

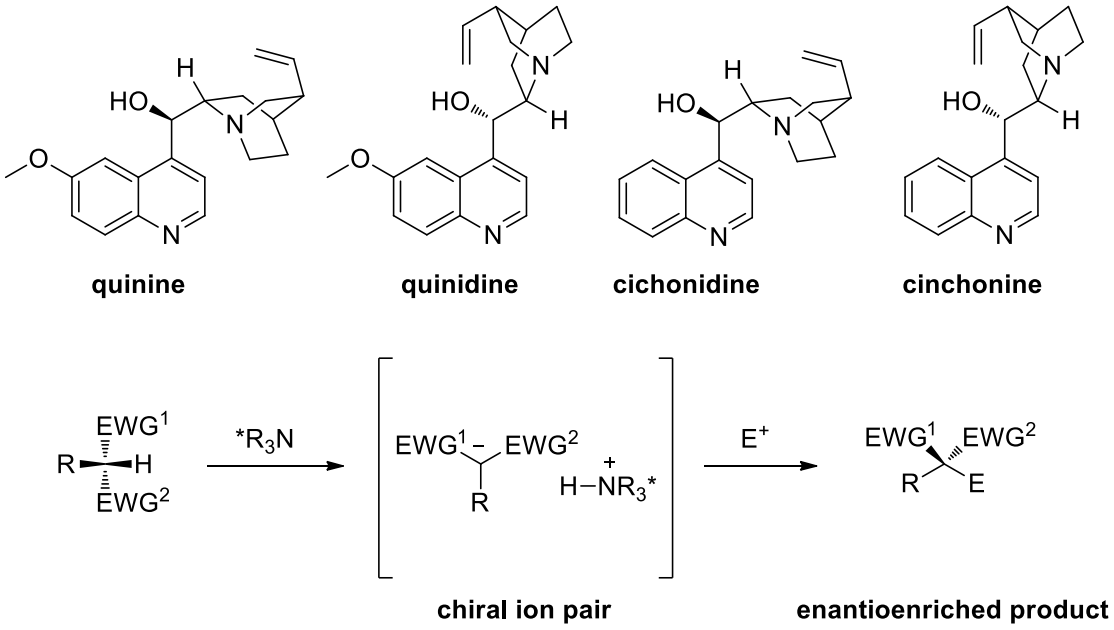
$$k = \frac{k_B T}{\hbar} e^{\frac{-\Delta G^{\ddagger}}{RT}} \qquad (3.1)$$

Another issue, deserving separate discussion, is the structure of the organocatalyst. Organocatalysts derived from the chiral pool are available, inexpensive and eco-compatible. For instance, List described the employment of natural amino acid (L)-proline to promote aldol reaction of various aldehydes in excellent yields and enantioselectivities (scheme 3.1).[5]



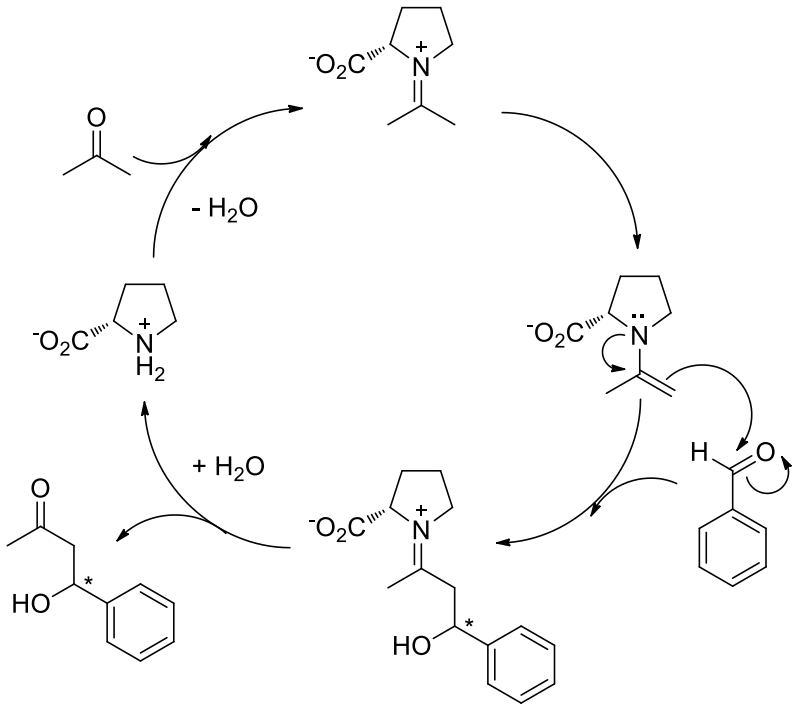
Scheme 3.1 *Proline-catalyzed direct asymmetric aldol reaction by List, a pioneeristic example of asymmetric organocatalysis*

Other notable examples of compounds from the chiral pool, whose employment as organocatalysts has led to important results, are *Cinchona* alkaloids[8] and other natural amino acids.[9] Both *Cinchona* alkaloids and amino acids act as general Brønsted bases, whilst following different mechanisms. *Cinchona* alkaloids are extracted from the bark of *Cinchona Officinalis* and include two couples of pseudoenantiomers: quinine and quinidine, cinchonine and cinchonidine. Their tertiary amino function on quinuclidine moiety can deprotonate the substrate, thus affording a chiral ion pair in which one of the enantiotopic faces of the anion is more acessible for the attack of an electrophile (scheme 3.2).



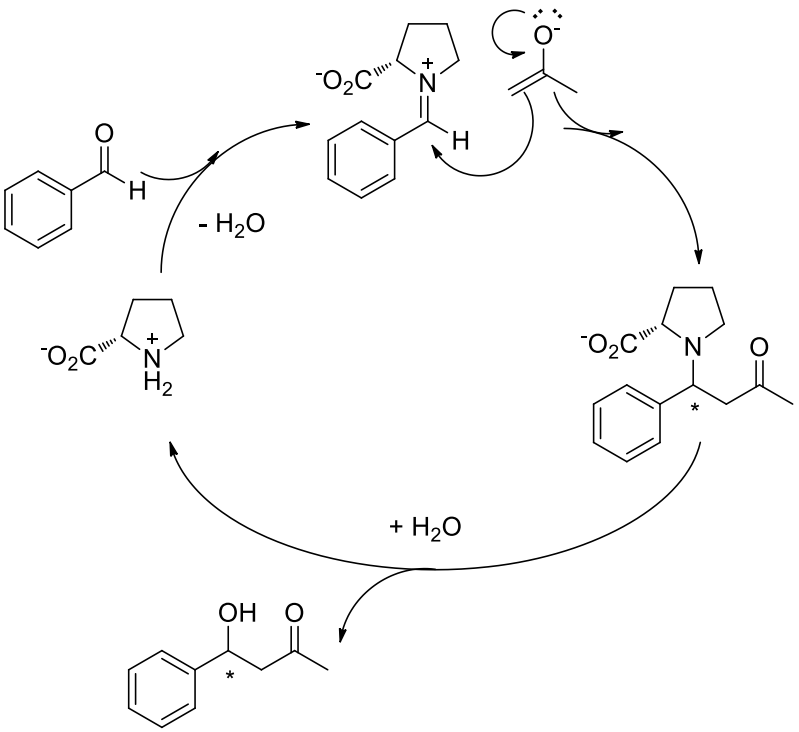
Scheme 3.2 *Naturally occurring Cinchona akaloids, extracted from the bark of Cinchona Officinalis, and their mechanism as asymmetric organocatalysts*

On the other side, amino acids follow two general mechanisms: activation *via* enamine and *via* iminium ion. In the first case the catalyst is a secondary amine, whose iminium ion with the carbonylic compound can be deprotonated in the α position, thus forming a chiral enamine, which undergoes an asymmetric Stork reaction,[10] acting as a nucleophile (scheme 3.3). The stereochemical outcome of the reaction can be predicted on the basis of the enamine geometry through the construction of a Zimmerman-Traxler transition state model[11] and the absolute stereochemistry of the electrophilic carbonyl compound backbone, using Cram rule.[12]



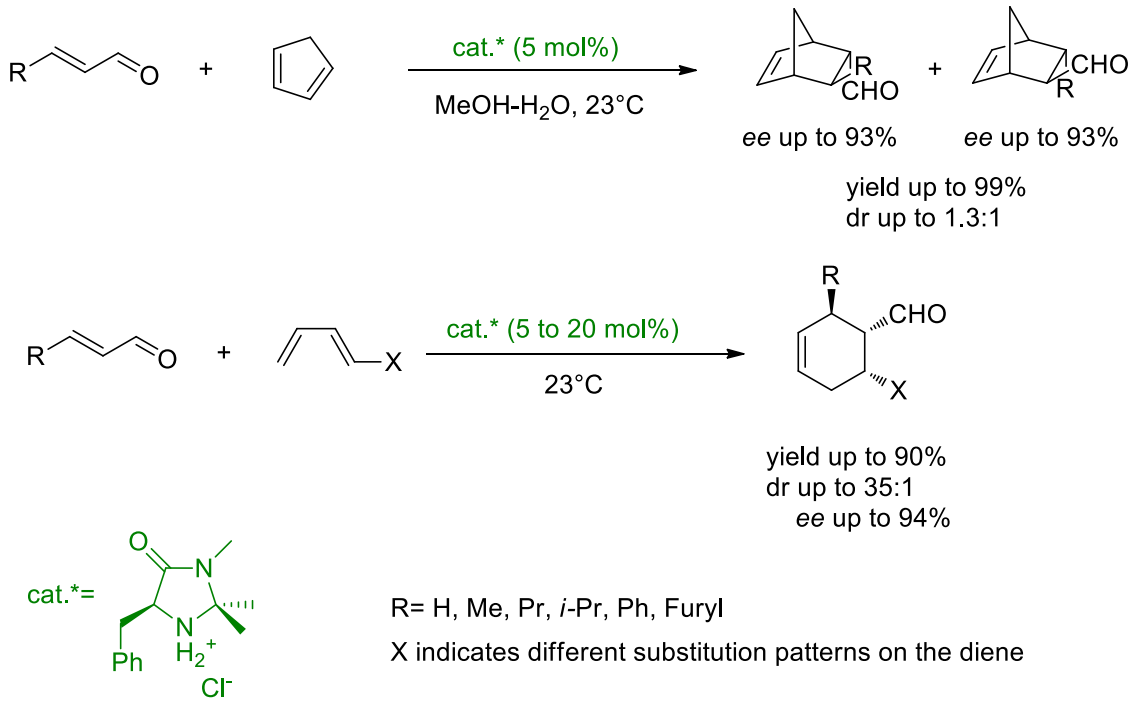
Scheme 3.3 *Activation via enamine in asymmetric organocatalysis with (L)-proline*

In the second case the catalyst is a primary or secondary amine and the chiral iminium ion intermediate is the electrophile of an aldol condensation; upon hydrolysis of the formal condensation product in the last irreversible step, the final product aldol (or enone) can be obtained (scheme 3.4).



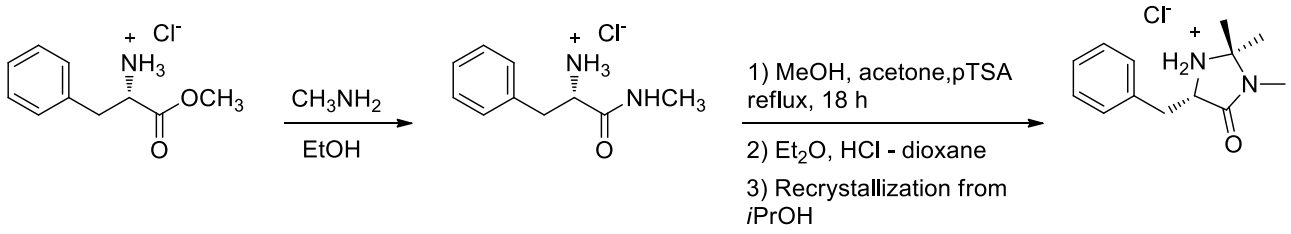
Scheme 3.4 *Activation via iminium ion in asymmetric organocatalysis with (L)-proline*

Coincidentally, the other two milestones of asymmetric organocatalysis describe two complementary approaches, relatively to the catalyst scaffold. A few months later with respect proline-catalyzed aldol reaction protocol by List, the MacMillan group reported the first example of highly efficient diastereoselective and enantioselective organocatalytic Diels-Alder reaction (scheme 3.5).[6]



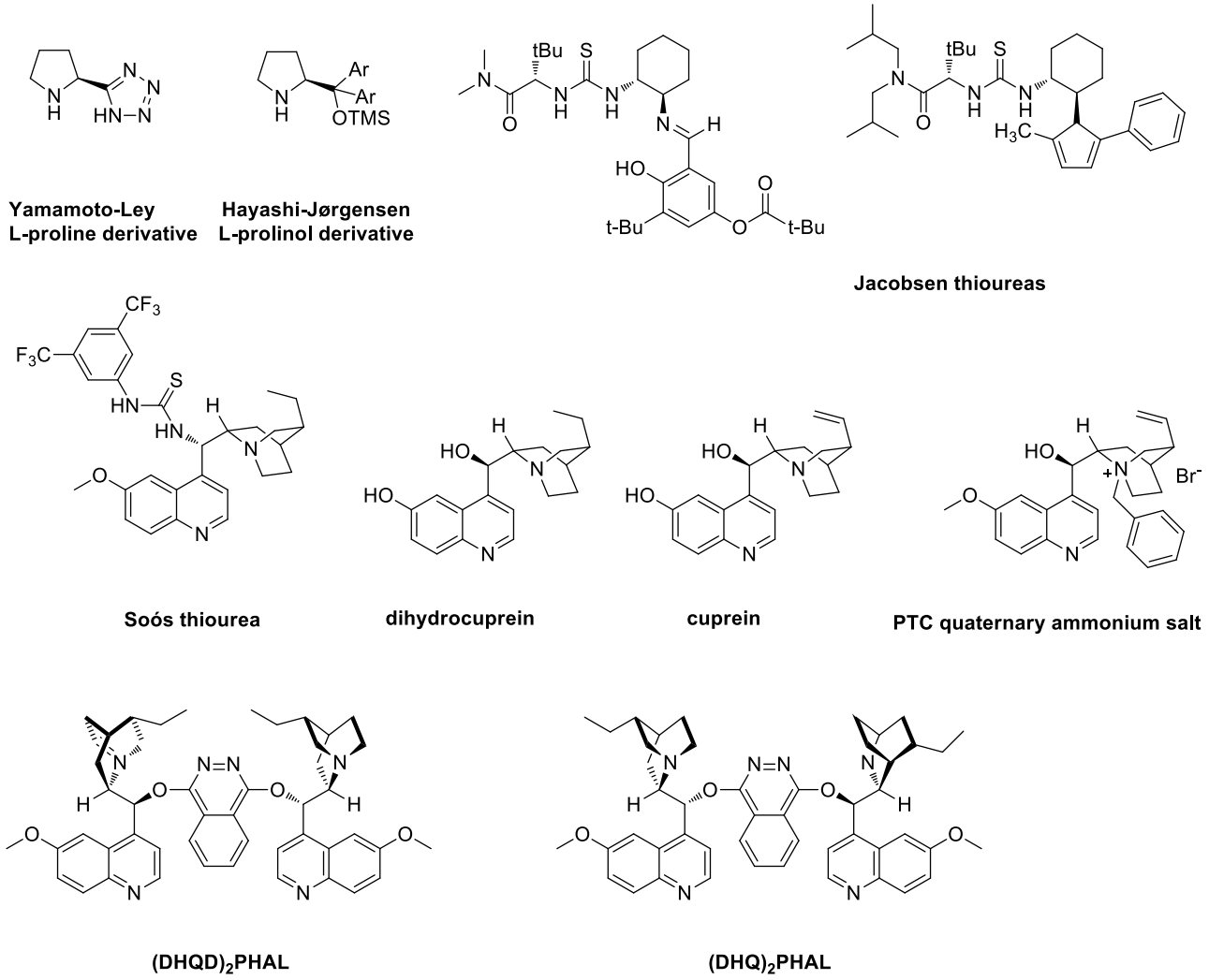
Scheme 3.5 *Organocatalytic diastereo and enantioselective Diels-Alder reaction by MacMillan, a pioneeristic example of asymmetric organocatalysis*

In the latter case, the catalyst is not naturally occurring, but prepared in the laboratory. Nevertheless, no dangerous reactions and reagents or toxic and expensive transition metals are involved in its synthetic plan. Coherently, MacMillan catalyst can be defined a *green* scaffold and a fully organocatalytic approach (no transition metal involved in the active principle) is pursued from the catalyst preparation to its employment in further applications (scheme 3.6).



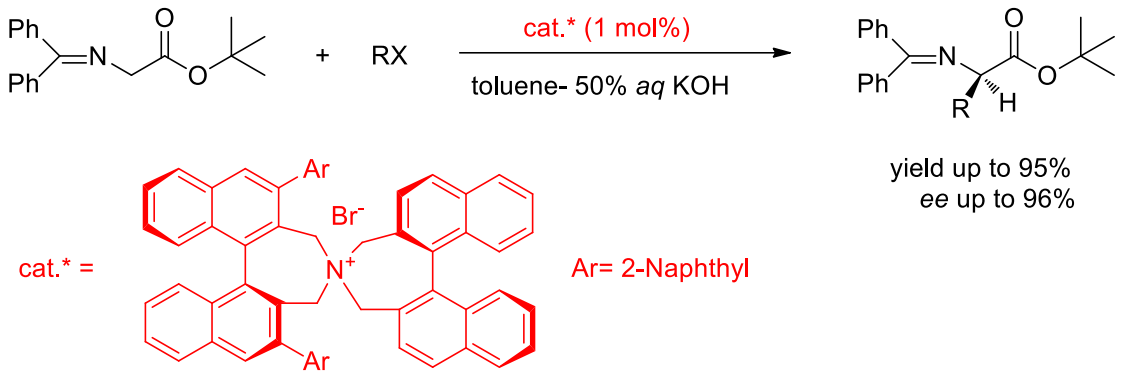
Scheme 3.6 *Synthetic plan for(S)-5-benzyl-2,2,3-trimethyl-4-oxoimidazolidin-1-ium chloride (MacMillan catalyst)*

The list of chiral organic scaffolds developed from simple reagents with easy, short and safe synthetic procedures for catalytic purposes, along the lines of MacMillan catalyst, is very long. Of all, it is worth mentioning proline derivatives proposed by Yamamoto and Ley[13] and by Hayashi and Jørgensen;[14] thioureas by Jacobsen[15] and Soós;[16] *Cinchona* alkaloid derivatives, including modified scaffolds and dimers[17] as well as quaternary ammonium salts for PTC (scheme 3.7).[3e-g,18]



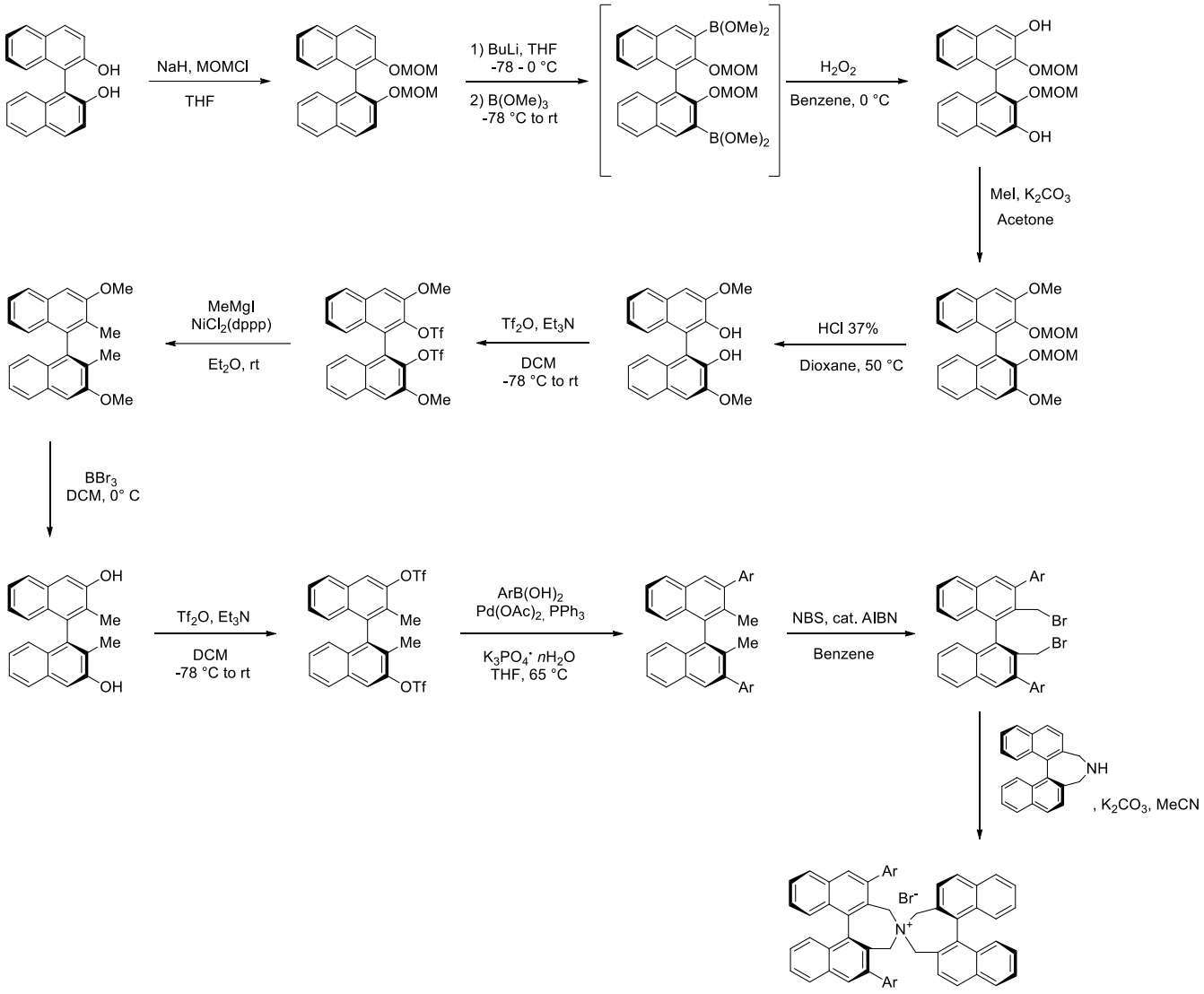
Scheme 3.7 *Some non naturally occurring ecosustainable organocatalysts*

The very first modern paper concerning asymmetric organocatalysis is Maruoka asymmetric α-alkylation of amino acid derivatives under phase transfer catalysis (PTC) conditions. Excellent yields and enantioselectivities are obtained for non naturally occurring (R)-amino acids but, in order to achieve this result, an engineered bis-biaryl quaternary ammonium salt is employed as the phase transfer catalyst (scheme 3.8).[4]



Scheme 3.8 *The very first modern asymmetric organocatalytic procedure by Maruoka: enantioselective α-alkylation of amino acid derivatives under PTC conditions*

An engineered organocatalyst is an organic molecule whose molecular scaffold has been properly designed and synthetized in the laboratory with the only aim to efficiently catalyze a given reaction. The term organocatalysis implicitly suggests a series of advantages of employing an organic molecule rather than metal salts or coordination compounds. However, this advantage is dramatically reduced whenever the organic molecule is particularly expensive, difficult to synthetize or when the use of costly or toxic transition metal species is required in order to synthetize that molecule. In particular, Maruoka catalyst is obtained through a multi-step synthesis, which is not conform to the principle of atom economy. Moreover, critical steps involving transition metal species are included within the synthetic route (scheme 3.9).[4,19] The critical steps are: boronylation at -78 °C, ether hydrolysis in concentrate hydrochloric acid, methylation of the biaryl scaffold in the positions 2 and 2' and, mostly, Suzuki-Miyaura coupling[20] to introduce aryl groups on the biaryl scaffold in the positions 3 and 3'. Boronylation and ether hydrolysis are critical transformations because of their harsch reaction conditions. On the contrary, methylation and Suzuki-Miyaura biaryl coupling take place in mild reaction conditions, but transition metals (Ni and Pd) are involved. Moreover, it is worth mentioning that, while methylation leads to the product in a very good yield (88%), biaryl coupling on BINOL backbone is intrinsically characterized by low yields, generally lower than 50%, dramatically contributing to reduce the overall yield and atom economy.[21] Other examples of engineered catalysts will be examined more in detail in the following paragraph.

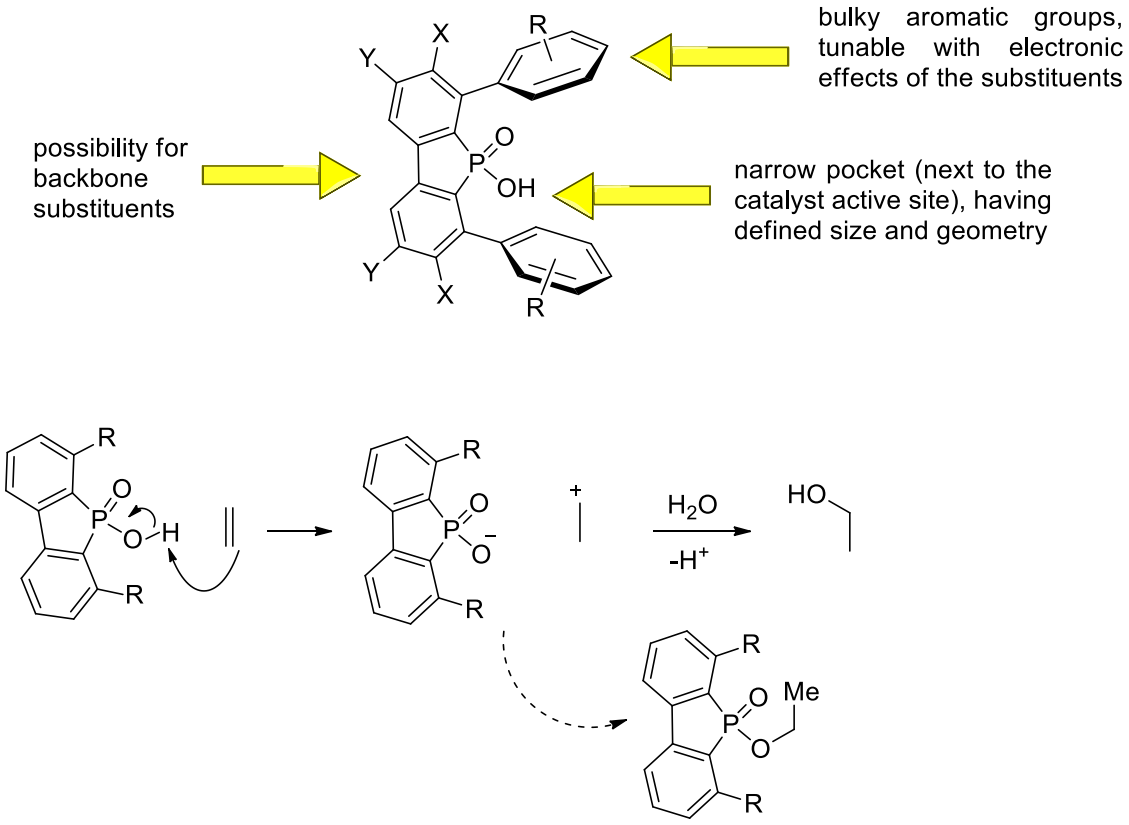


Scheme 3.9 *Multi-step synthetic plan for Maruoka phase transfer bis-biaryl catalyst*

3.2 Phosphoric acids in organocatalysis

The employment of organic chiral Brønsted bases has state-of-the-art mostly been exploited.[22] The complementary approach of employing chiral Brønsted acids[23] gives access both to alternative strategies to carry out the same chemical transformations (*e.g.* activation *via* iminium ion with chiral amine and achiral acid/ with achiral amine and chiral acid, C-C bond formation *via* enolate/ enol nucleophilic attack) as well as to the asymmetric version of those reactions that requiring an acidic catalyst (*e.g.* acetalization, alkene hydration). Beyond good hydrogen bond-donor thioureas,[15,16] literature concerning strong Brønsted acids is largely dominated by phosphoric acids and their derivatives.[23,24] The employment of chiral phosphorous-containing Brønsted acids takes the moves from the work on phosphinic acids by Sir John Cornforth, which dates back to 1978.[25] Cornforth, who got the

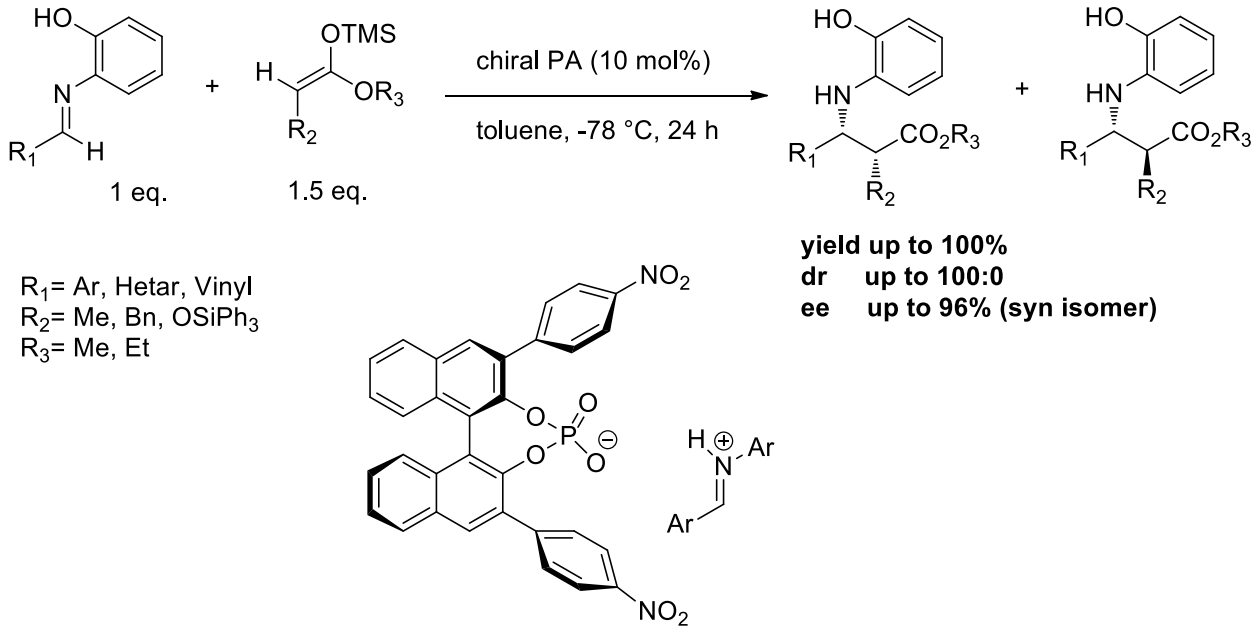
Nobel Prize for Chemistry in 1975 for his contributions to the stereochemistry of enzyme-catalyzed reactions, tried to apply this know-how in designing the structure of a catalyst for alkene hydration. In particular, he guessed the potential of introducing bulky aromatic groups in appropriate positions of the phosphinic acid scaffold, in order to create a narrow pocket for substrates, on the model of the active site of enzymes. Moreover, electron-donating or withdrawing substituted aryl groups can modulate the pocket size and geometry and the acidity of the compound (scheme 3.10).



Scheme 3.10 *General structure of Cornforth phosphinic acids and proposed mechanism for phosphinic acid-catalyzed alkene hydration*

Phosphinic acids were efficiently employed in alkene hydration, resulting more active with respect to other species such as *p*-toluenesulphonic acid. Reaction mechanism proposed by Cornforth includes protonation of the double bond and formation of a tight ion pair. The resulting carbocation can undergo water addition to afford the corresponding alcohol or deactivate the catalyst by forming a phosphinic ester with its conjugated base. Furthermore, the bulkiness of the substituents X on the acid backbone and R on the phenyl rings would potentially introduce stereogenic axes in the position 3 and 3′ of the biaryl scaffold and provide a chiral source for an eventual application in an asymmetric version of the reaction. Unfortunately, Cornforth did not report any result of the studies carried out on enantioselectivity in this process; nevertheless, he can be considered a fully-fledged

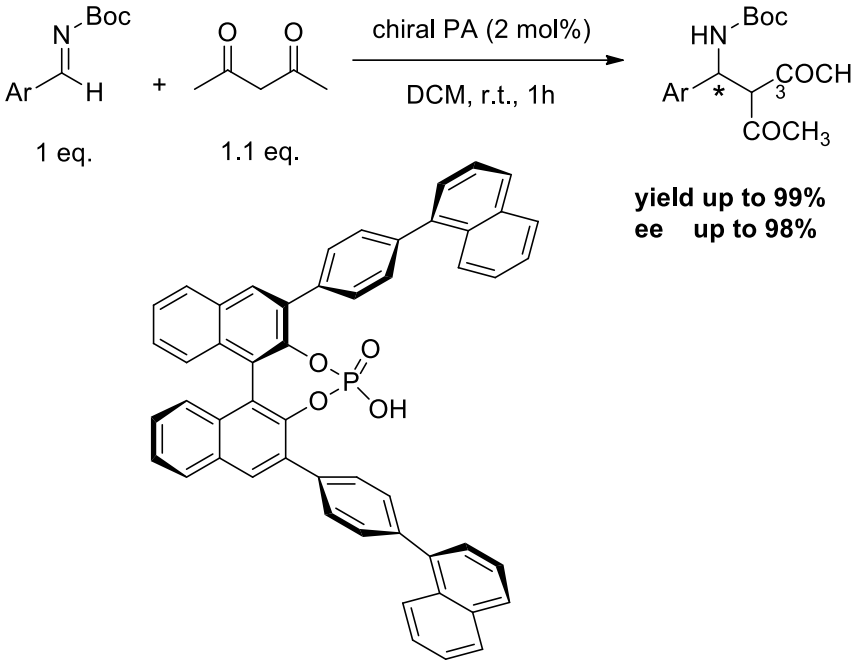
precursor of catalysis from chiral phosphoric acids, considering the influence that his work had on the pioneeristic publications of this field. In 2004, Akiyama and co-workers developed a diastereoselective and enatioselective acid-catalyzed Mannich-type reaction between silyl ketene acetals and N-aryl aldimines.[26] All the products were obtained in excellent yields with good to high degree of stereoselectivity. The presence of an *ortho*-hydroxyl group on the phenyl ring of aldimine seemed to be crucial for the enantioselectivity (scheme 3.11).



Scheme 3.11 *Akiyama protocol for phosporic acid-catalyzed Mannich-type reaction between silyl ketene acetals and N-aryl aldimines*

For the first time, an axially chiral BINOL-based seven-membered cyclic phosphoric acid diester was used as an organocatalyst. BINOL has always been attractive to synthetic organic chemists, in particular for the design of chiral ligands for transition metals. The employment of chiral catalysts with BINOL-based ligands was so successful in different and non related areas that Jacobsen coined the definition of "privileged chiral catalysts" for them.[27] In the case of Akiyama catalyst, BINOL is substituted in the positions 3 and 3' with *p*-nitrophenyl rings. The proposed mechanism includes protonation of the aldimine nitrogen atom, to form a tight ion pair in the catalyst pocket, whose shape and size are defined by the 3,3'-substituents. The formation of a chiral ion pair in a tight space shields one of the enantiotopic faces of protonated aldimine, thus driving the nucleophilic attack of silyl ketene acetal on the other side. Just one month later, a highly efficient enatioselective protocol for Mannich reaction by Terada appeared in the literature. In this work, direct addition of acetylacetone to N-Boc protected arylaldimines is promoted by a small amount (2 mol%) of a BINOL-phosphoric acid with 3,3'-biaryl substituents. Conversion of the

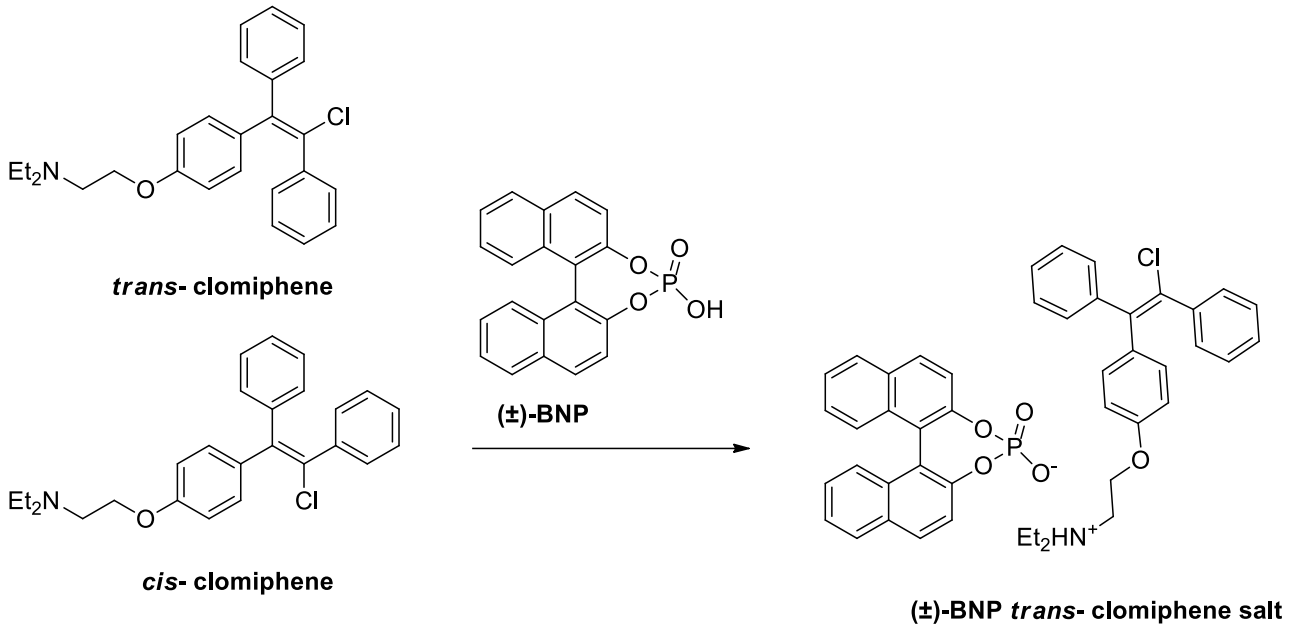
reagents occurs in short times, extremely mild reaction conditions, excellent yields and enantioselectivities (scheme 3.12).[28]



Scheme 3.12 *Terada protocol for phosporic acid-catalyzed Mannich-type reaction between acetylacetone and N-Boc protected arylaldimines*

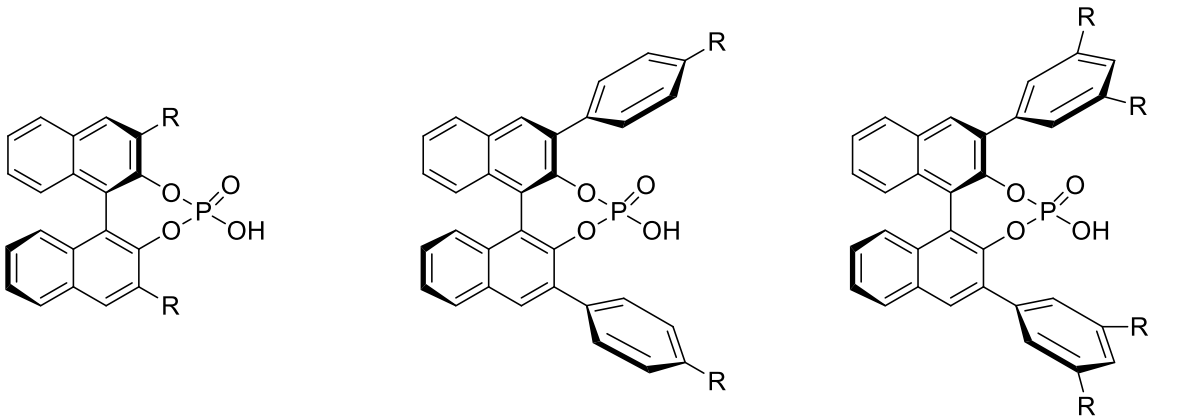
The influence of pioneeristic work by Cornforth is evident in the confined architecture of both the chiral catalysts by Akiyama and Terada. In fact, the synthesis of BINOL-based chiral phosphoric acids was not a novelty, at the time; nevertheless, up till that moment, their employment had been limited to the resolution of racemic mixtures of chiral amines. One of the earliest reports dates back to 1971: (±)-propetamide could be reacted with BINOL-phosphoric acid (BNP) to form a salt which, upon crystallization and acid−base wash, provides the enantiopure (+)-propetamide. The application was then extended to a range of other amines and found to be quite general. [29] In the late 1980s and early 1990s, other research groups were also able to employ enantiopure BNP as a resolving agent for chiral amines.[30] In 2006, Feringa showed that BINOL-derived phosphoric acids are able to induce conformational changes in receptors by recognition of chiral amines.[31] A very recent example of employment of (±)-BNP as a resolving agent was given by the italian pharmaceutical company F.I.S., which patented a protocol that includes the isolation of the selective estrogen receptor modulator *trans*-clomiphene from the mixture with its geometrical isomer *cis*-clomiphene. In this case, chirality is not involved; the *trans* isomer salt with BNP can be filtered and washed to afford the active pharmaceutical ingredient (*trans*: *cis* ratio from 90:10 to 98:2), while the *cis* isomer remains in the mother liquor (scheme 3.13).[32] It shall be highlighted that, in all the above examples, simple BNP is succesfully

employed as the resolving agent, therefore not requiring any sterical hindrance in the positions 3 and 3′.



Scheme 3.13 *Protocol for the isolation of trans-clomiphene BNP salt by italian company F.I.S.*

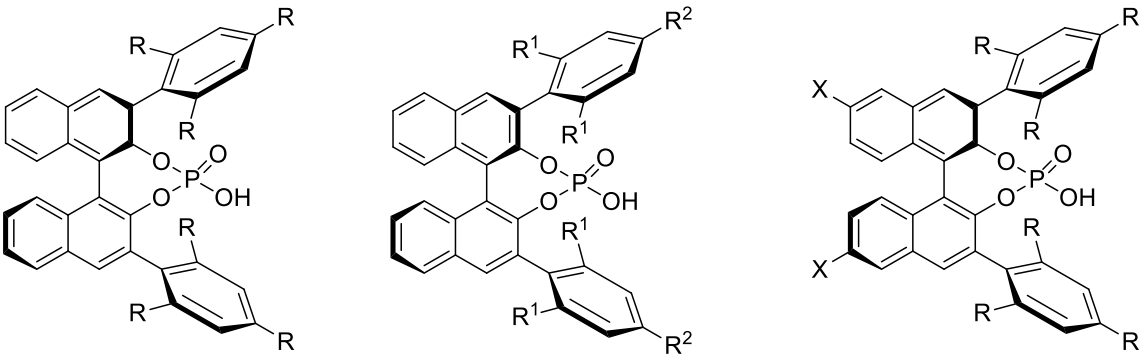
Coming back to BINOL-based phosphoric acids for catalytic employment, several 3,3′-substitution patterns have been developed; some of them are depicted in scheme 3.14.



PA 1, R = H
PA 2, R = $SiPh_3$
PA 3, R = Si(4-*t*Bu$C_6H_4)_3$
PA 4, R = adamanthyl
PA 5, R = 1-naphthyl
PA 6, R = 2-naphthyl
PA 7, R = 9-anthracenyl
PA 8, R = 9-phenanthryl
PA 9, R = 1-pyrenyl

PA 10, R = H
PA 11, R = tBu
PA 12, R = F
PA 13, R = Cl
PA 14, R = OMe
PA 15, R = NO_2
PA 16, R = Ph
PA 17, R = 3,5-$(CF_3)_2C_6H_3$
PA 18, R = 2,3,4,5,6-F_5C_6
PA 19, R = 2-naphthyl

PA 20, R = CF_3
PA 21, R = SF_5
PA 22, R = Ph
PA 23, R = 2,4,6-$(Me)_3C_6H_2$



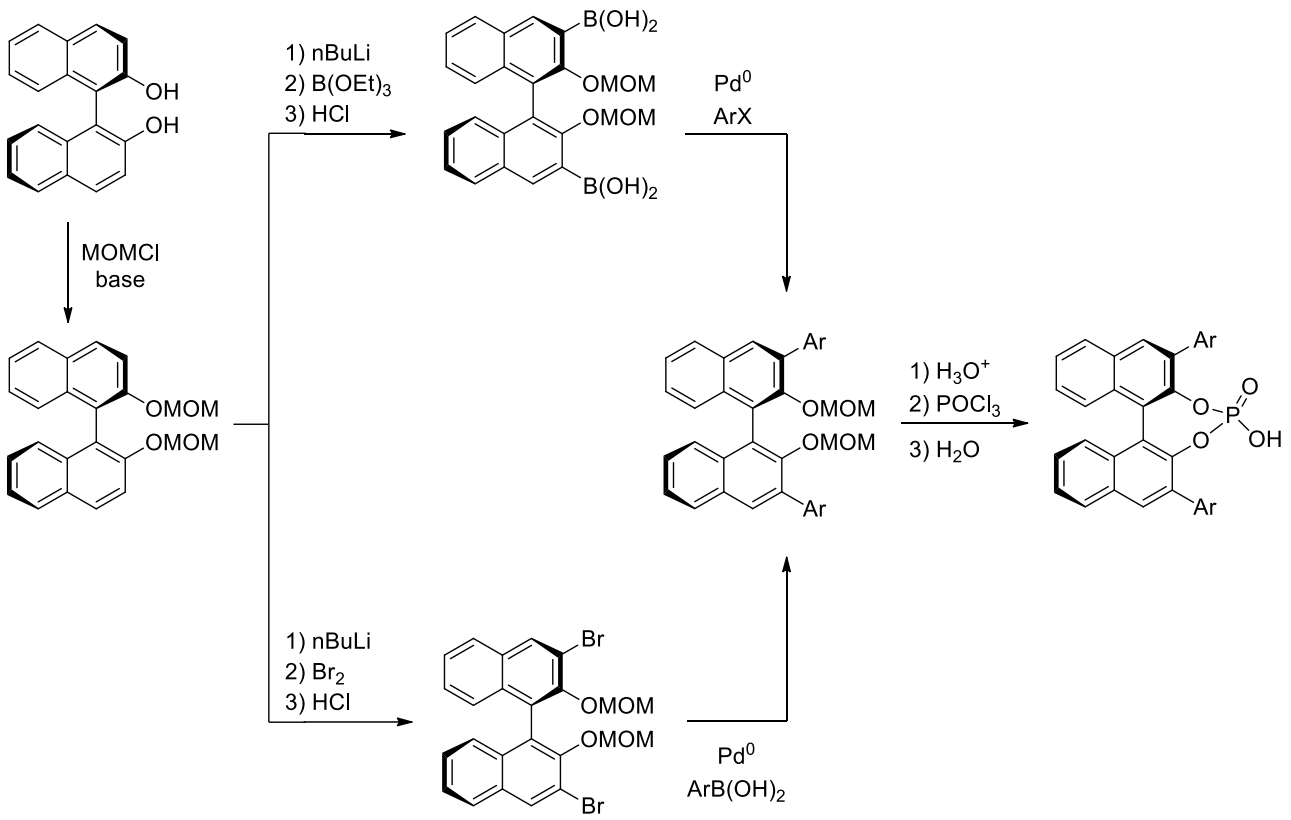
PA 24, R = Me
PA 25, R = *i*Pr

PA 26, R^1 = Me, R^2 = OMe
PA 27, R^1 = *i*Pr, R^2 = *t*Bu
PA 28, R^1 = *i*Pr, R^2 = 4-*t*BuC_6H_4
PA 29, R^1 = *i*Pr, R^2 = 9-anthracenyl

PA 30, R = *i*Pr, X = I
PA 31, R = *i*Pr, X = NO_2
PA 32, R = *i*Pr, X = Si(*i*Pr)$_3$
PA 33, R = *i*Pr, X = C_8H_{17}

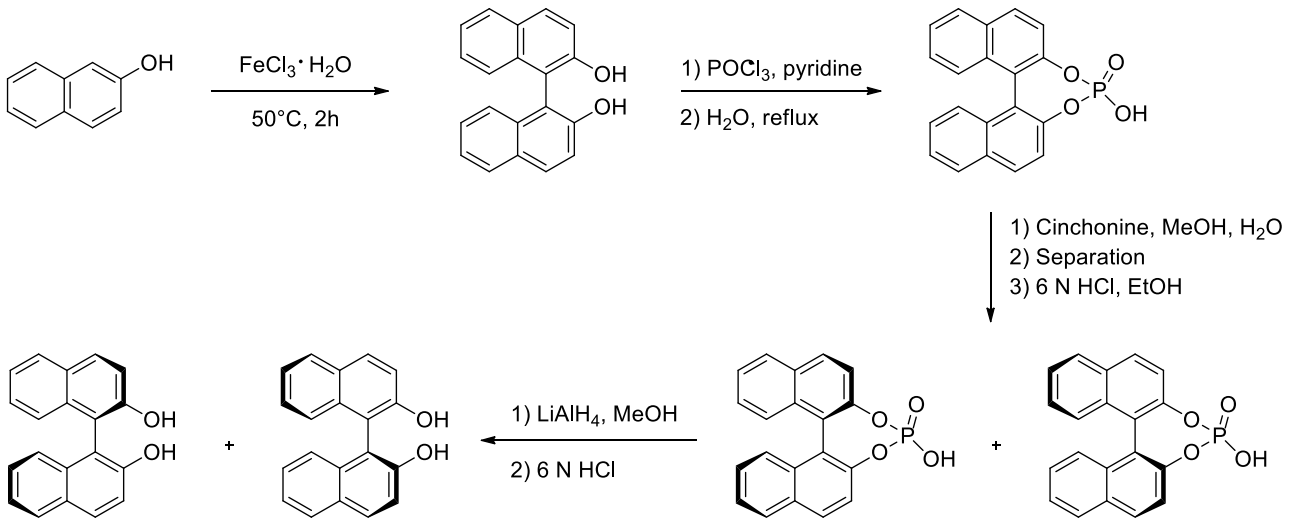
Scheme 3.14 *Structures of some 3,3′-substituted phosphoric acid organocatalysts among the most frequently appearing in the literature*

Acid **PA 1** is the simplest and less used organocatalyst and it is obtained from direct phosphorylation of BINOL. However, just 3,3′-substituted confined BINOL-derived phosphoric acids found successful applications by far. Usually, Suzuki-Miyaura reaction is disfruited to introduce bulky aryl groups (**PA 4-9**). Sterically hindered silyl groups have also been used to functionalize biaryl scaffolds (**PA 2-3**); in this case, palladium can be avoided, but the use of hazardous butyllithium is required.[33] Para-substituted aryl groups, including *p*-nitrophenyl used by Akiyama (**PA 15**), have the double effect of bulkiness and tuning the acidity of the catalyst with their electronic effet (**PA 11-19**). Despite less frequently, 3,5-disubstitution of the benzene rings has also been reported (**PA 20-23**), while 2,4,6-trisubstitution can be much more often encountered (**PA 24-33**). In particular, **PA 25**, namely 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl phosphoric acid, also known as TRIP, has been designed by List and is the most utilized catalyst of this type by far.[34] Substitution on BINOL backbone (**PA 30-33**) helps in modulating solubility, beyond electronics. What makes these molecules engineered catalyst is their multi-step synthetic route, whose problematics are more or less the same as those of Maruoka catalysts: low overall yield and atom economy, non-naturally-occurring substrates, employment of hazardous reagents and difficult reaction conditions, including Pd-catalyzed Suzuki-Miyaura coupling (scheme 3.15).[24a]



Scheme 3.15 *General scheme of synthetic route for BINOL-derived phosphoric acid organocatalysts*

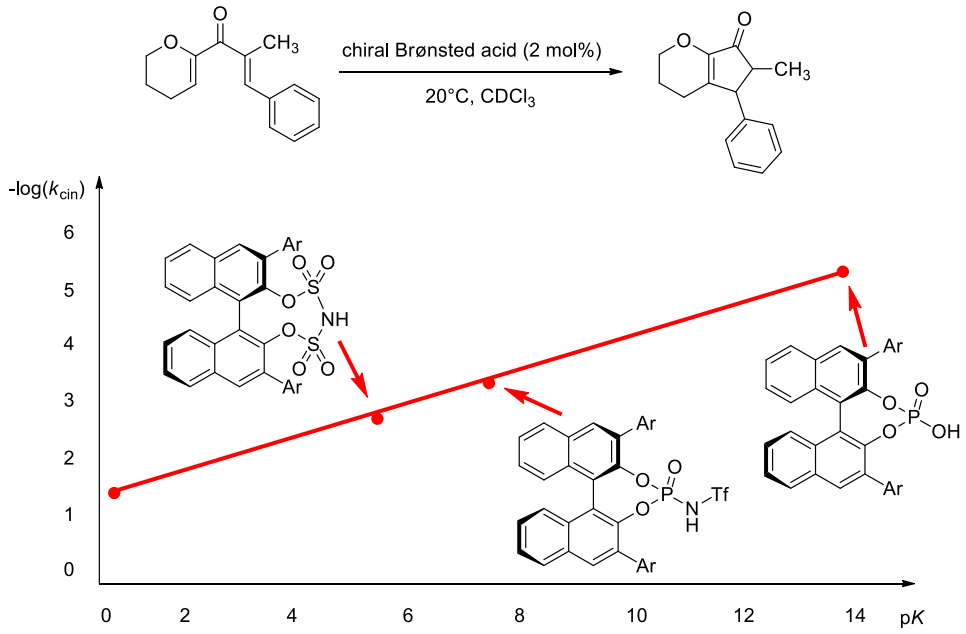
Moreover, BINOL itself is an engineered scaffold. It can be prepared from β-naphthol through Fe(III)-catalyzed omocoupling.[35] However, since enantiopure BINOL is needed in order to prepare a chiral phosphoric acid organocatalyst, additional steps for racemate resolution are required (scheme 3.16).[36]



Scheme 3.16 *Synthetic route for enantiopure (R) and (S)-BINOL*

3.3 General activation modes and models for stereoselectivity

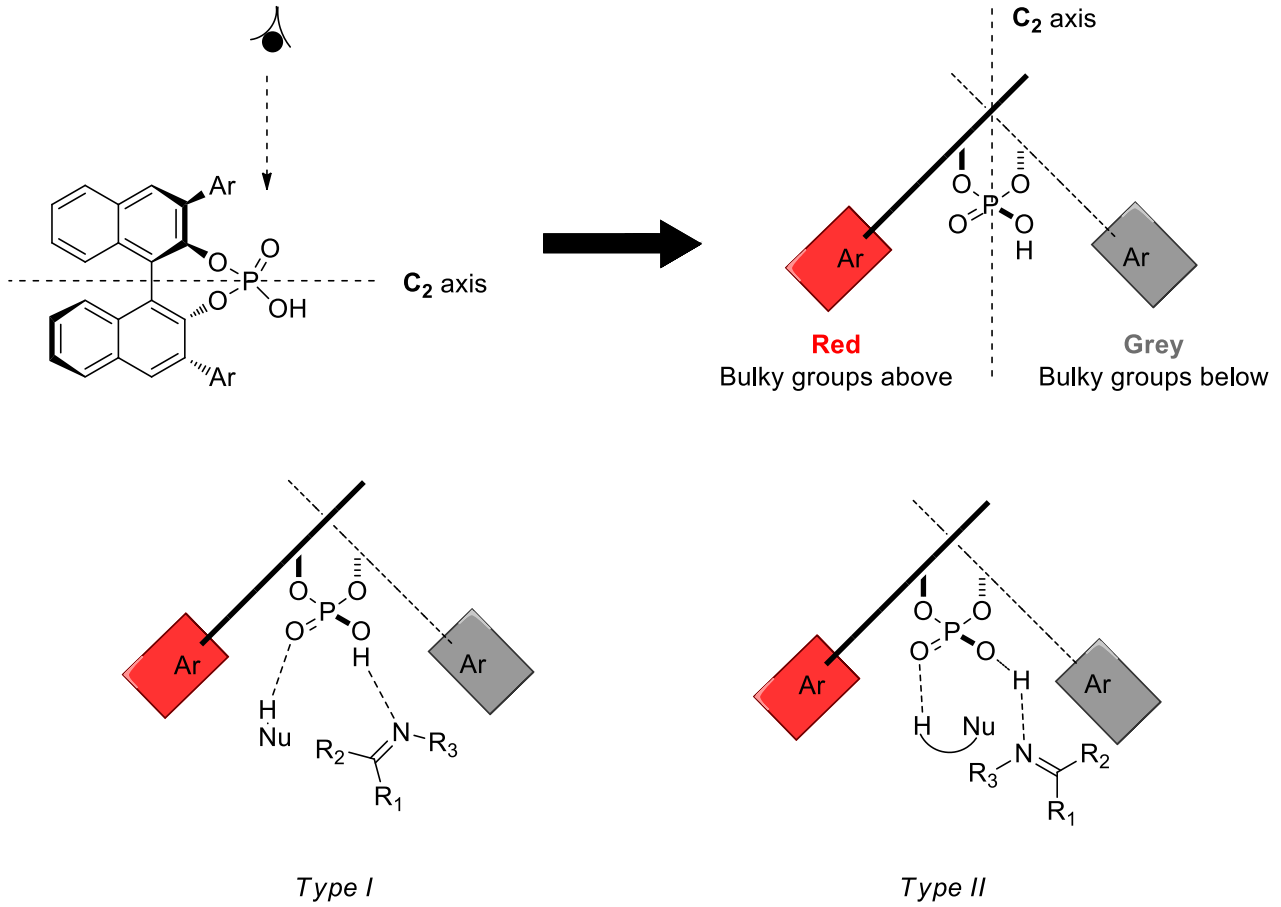
From a mechanistic point of view, the versatility of Brønsted acidic catalysts is due to their ability to activate an electrophile towards reaction with a nucleophile by protonation, thus lowering the energy of its LUMO. Complementarily, Brønsted basic catalysts raise the energy of the HOMO of the nucleophile by deprotonation. Based on the above, the degree of protonation of the electrophile is crucial for a quantitative transformation: to a first approximation, the catalytic activity of a Brønsted acid is directly proportional to its acidity. In fact, from an experimental point of view, the nature of the phosphoric acid used as the catalyst of a given reaction was found to be crucial to determine its succesful outcome. Despite these arguments, literature data concerning pK_a of BINOL-phosphoric acids are relatively scarce. The pK_a values of a range of chiral Brønsted acids in DMSO were published by O'Donoghue and Berkessel[37] and, more recently, pK_a values of BINOL-phosphoric acids, including more acidic thiophosphoric acids, were reported in a theoretical study by Cheng and Li.[38] In 2013, an acidity scale for commonly occurring BINOL-Brønsted acid catalysts was drawn up by Rueping and Leito. On the basis of UV-vis spectrophotometric measurements carried out in acetonitrile, it was measured a pK_a in the range 12-14 for phosphoric acids (PA), 6-7 for N-sulfonyl phosphoramides, and around 5 for disulfonyl imides (DSI). For comparison, in the same conditions, hydrobromic acid has $pK_a = 5.5$, *p*-nitrophenylsulphonic acid 6.7, *p*-toluenesulphonic acid 8.5, hydrochloric acid 10.3, picric acid (2,4,6-trinitrophenol) 11, saccharin 14.6. The study also investigated the correlation between acidity and reactivity, with a Nazarov cyclization as a model reaction (no product inhibition occurs in this transformation). Using different catalysts and plotting $-\log(k_1)$ against the pK_a of the catalyst in a graph, linearity between the observed rate constant and the acidity of the catalyst was observed (scheme 3.17).[39]



Scheme 3.17 *A plot of the rate of a Nazarov cyclization reaction versus acidity of the catalyst*

Moreover, phosphoric acids and their derivatives benefit from the presence of two structural motifs which can act as coordination sites: in fact, while the acidic proton of the phosphate diester can protonate or donate an H-bond to the electrophile (Brønsted/Lewis acidic site, respectively), the oxygen of the double bond P=O is an electron rich heteroatom, which can donate a lone pair (Lewis basic site). Therefore, two coordination sites may be involved in the mechanism of reactions catalyzed by phosphoric acids and, disfruiting both of them, a bifunctional activation mode is possible. To this purpose, elucidating the exact mechanisms involved in chiral phosphoric acid-catalyzed reactions is not a straightforward procedure, due to the fact that, varying the catalyst scaffold and the substrate, a large number of their mutual interactions is possible. Mechanistic studies by Rueping and Gschwind have revealed that proton transfer from the catalyst to the substrate is not evident as it was suggested by early studies on this topic.[41] Using detailed NMR experiments, Rueping and Gschwind tried to determine the factors affecting the preference for proton transfer or hydrogen bonding. Unsurprisingly, what came out was that more electron-rich imines were prone to proceed *via* protonation and ion-pairing with phosphate anion, while electron-deficient imines had more tendency to establish hydrogen-bonding interactions.[42] Other factors such as the pK_a and the solvent also played an important role. In any case, the general aim in studying reactions catalyzed by chiral phosphoric acids, is not those to distinguish between ion-pairing and hydrogen bonding; nevertheless, it must be noticed that both these types of interactions are likely to occur side by side. For what concerns the enantioselectivity, it is directly connected to the shape and size of the catalyst pocket, thus to the architecture of the catalyst scaffold. Along the line of the Felkin-Anh model for stereoselective reduction of carbonyl compounds[40] or the Zimmerman-Traxler model for stereoselective aldol reaction,[11] immediately after the publication of pioneeristic works by Akiyama and Terada, several studies have been done to formulate a general transition state pattern, in order to justify the stereochemical outcome of reactions promoted by confined BINOL-derived acids. Naturally, it would be too pretentious to expect a theory to be general enough to predict the activated complex geometry for all the substrates and reactants that undergo a reaction under these conditions. Nevertheless, reactions of imines with various nucleophiles under acid catalysis have intensively been investigated, and the absolute configuration of the resulting product is nowadays often fully predictable. However, more frequently, the stereochemical aspect of each specific reaction is rationalized *a posteriori*, with the proposal of a reaction mechanism which is suitable exclusively for that case. In 2011, Simón and Goodman, after analyzing more than 40 stereoselective reactions catalyzed by BINOL-phosporic acids and comparing literature data with computational calculations, postulated a transition state model to predict the stereochemistry of bifunctional phosphoric acid-catalyzed reactions of imines,[43] which was further improved in the following years.[44] The model is suitable just considering a bifunctional activation mode, since a classical three point interaction model,[45] often used in supramolecular chemistry and chiral recognition,[46] has been selected by the authors for molecular computings. In fact, for chiral discrimination between a host and a guest, the presence of at least three interactions is required. A planar representation of the catalyst pocket is obtained by imaging to look at the system from the

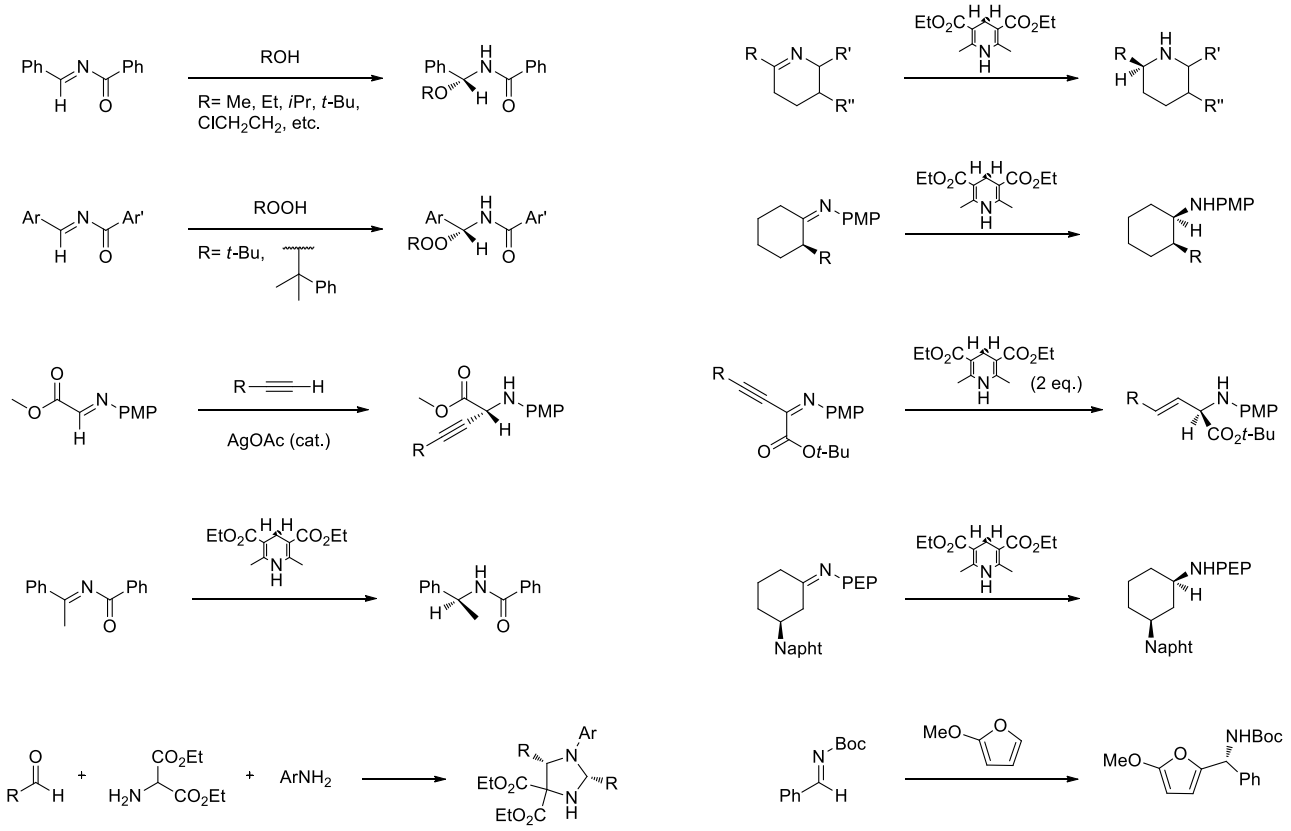
top of the catalyst, the observer laying in the sheet plane, with the symmetry C_2 axis dividing his view in the middle (scheme 3.18).



Scheme 3.18 *Planar representation of the transition state model by Simón and Goodman for stereoselectivity prediction*

An alternative planar representation of the system had been previously adopted by Himo and Marcelli[47] and by Gridnev and Terada.[48] For the lowest energy transition state of reactions with many nucleophiles, the nitrogen substituent of the imine (empty side of the catalyst pocket)is directed toward the opposite side with respect to the oxygen to which it is H bonded (Type I). The transition state in which the imine substituent is directed towards the above bulky catalyst group (depicted in red) has usually higher energy, as a consequence of additional steric interactions (Type II). Generally, because of its lower energy, Type I framework is preferably adopted, and this model explains the enantioselectivity obtained for many reactions of imines: addition of alcohols,[49] peroxides,[50] metal acetylides,[51] reduction with Hantzsch ester,[52] Mannich type reaction,[28] aza Friedel Crafts,[53] 1,3-dipolar cycloaddition,[54] just to give some examples (scheme 3.19). Two phenomena can account for anomalous results: the first one is E/Z isomerism of the imine, when R_1 and R_2 are different (further explanations highly depend on the structure of the imine), while the second one is

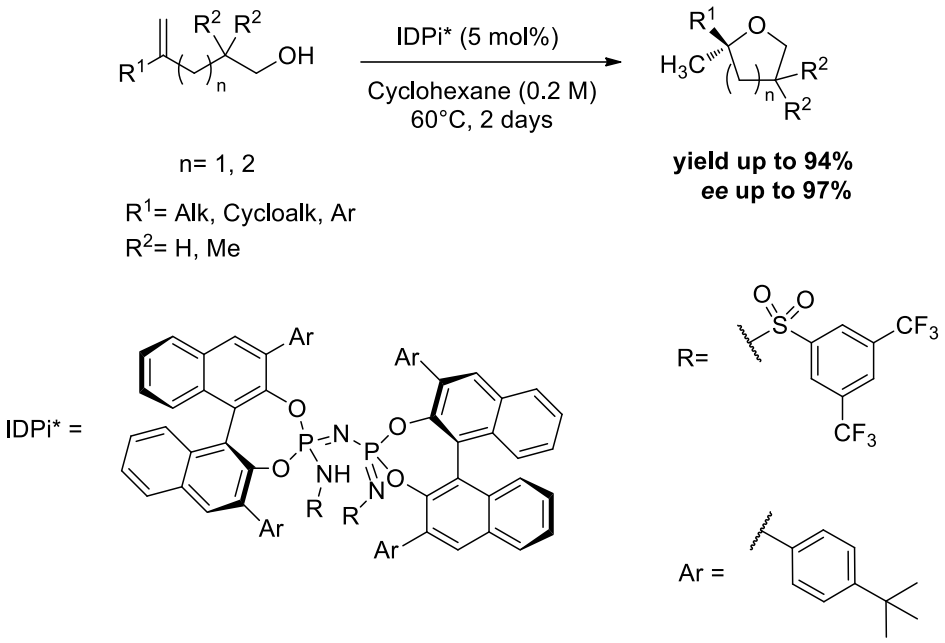
the case in which transition state of Type II has lower energy than Type I, and this happens when the nucleophile is not in line with the H bond and when R_2 needs more space on the right side than R_3.



Scheme 3.19 *Some reactions of imines for which Simón and Goodman transition state model for enantioselectivity proved to be suitable*

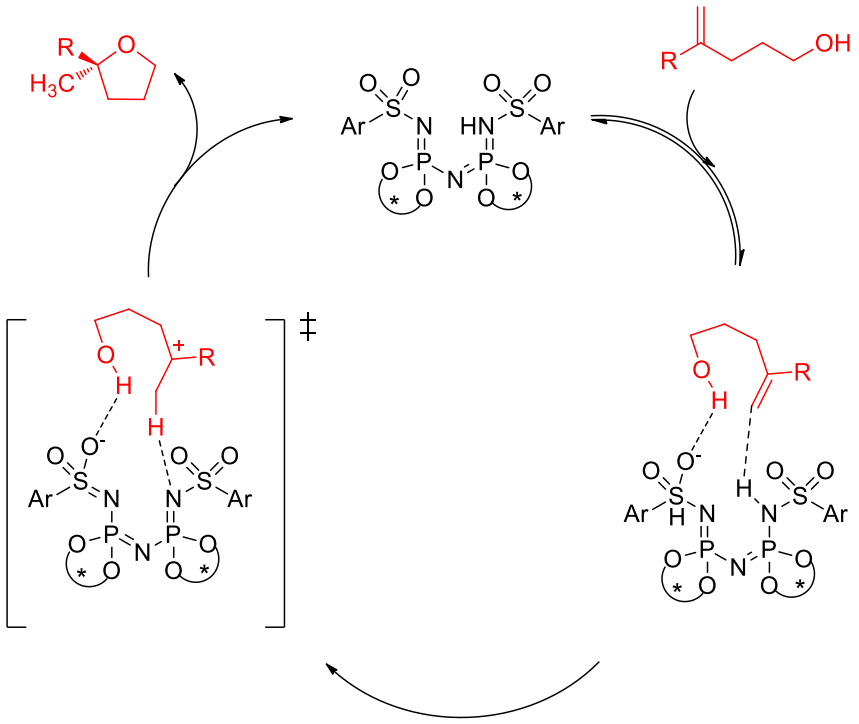
3.4 Selected examples of reactions catalyzed by phosphoric acids

BINOL-phosphoric acids are extremely versatile catalysts, whose employment since 2004 has provided not only an alternative strategy to base-catalyzed reactions, but also an innovative route to acid-promoted transformations. Moreover, the possibility to obtain more complex and acidic derivatives (*e. g.* dimers, phosphoramides) allowed the activation of generally unreactive or inhert substrates under mild reaction conditions. A notable recent example is the enantioselective intramolecular hydroalkoxylation of sterically and electronically unbiased alkenes, to afford 1,1-disubstituted tetrahydrofurans by List.[55] This stereoselctive transformation, generally relying on biocatalysis[56] and otherwise unfeasible, even by transition metal catalysis (due to the phenomenon of "hidden acid catalysis"[57]), was instead carried out in mild reaction conditions with a chiral imidophosphorimidate (IDPi), a BINOL-phosphoric acid dimer having enhanced acidity and confinement (scheme 3.20).



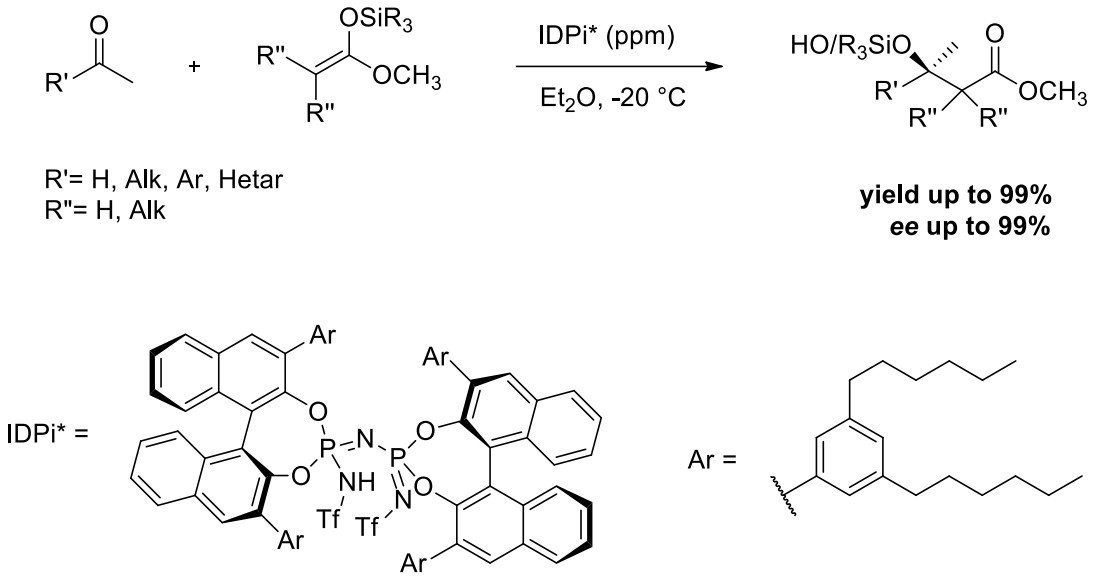
Scheme 3.20 *Enantioselective intramolecular hydroalkoxylation of unbiased alkenes by List*

Studies on the reaction mechanisms confirmed that the reaction proceeds *via* protonation of the double bond, followed by enantioselective ring closure. The acidity of the catalyst is crucial, since less acidic phosphoric acids (PA) were completely ineffective. Transition state depicted in scheme 3.21, accounts for the absolute configuration of the product.



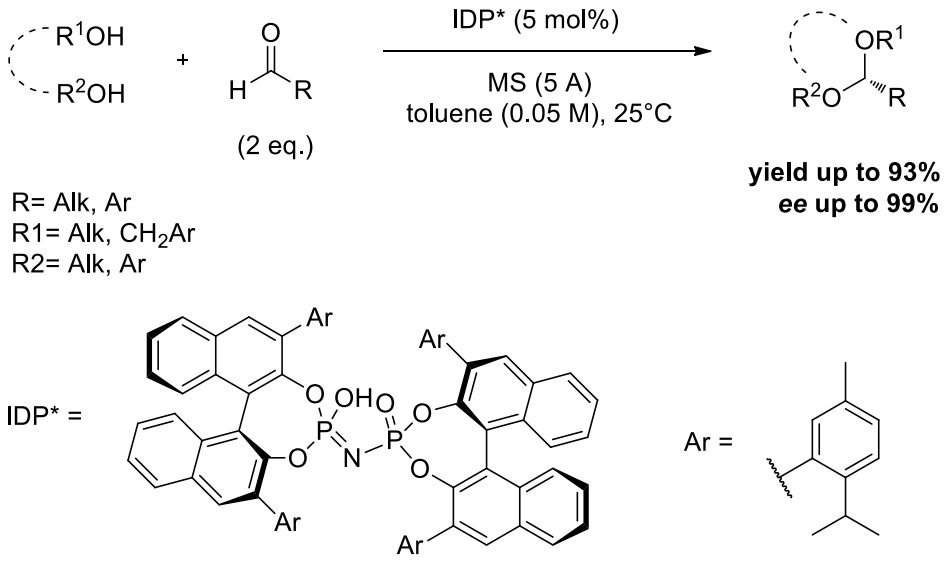
Scheme 3.21 *Reaction mechanism of intramolecular hydroalkoxylation of unbiased alkenes by List*

It is worth mentioning that, with this kind of phosphoric acid derivatives, the List group could also develop a sub-ppm-level organocatalytic asymmetric Mukaiyama aldol reaction of silyl ketene acetals with ketones as electrophiles. Apart from the challenging ketols (tertiary aldols) which can be afforded in high yields and in enantiopure form, the great novelty of this work was the demonstration that parts per million of highly active organic molecules, as well as transition metal species, can efficiently promote scalable carbon-carbon forming reactions (scheme 3.22).[58]



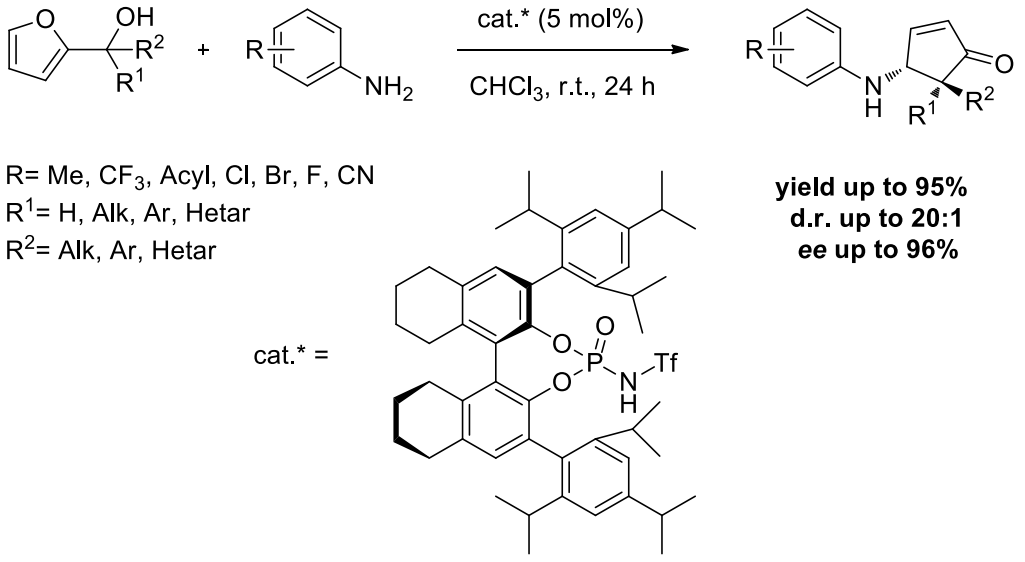
Scheme 3.22 *Sub-ppm-level organocatalytic asymmetric Mukayama aldol reaction by List, with a highly confined and acidic IDPi as the catalyst*

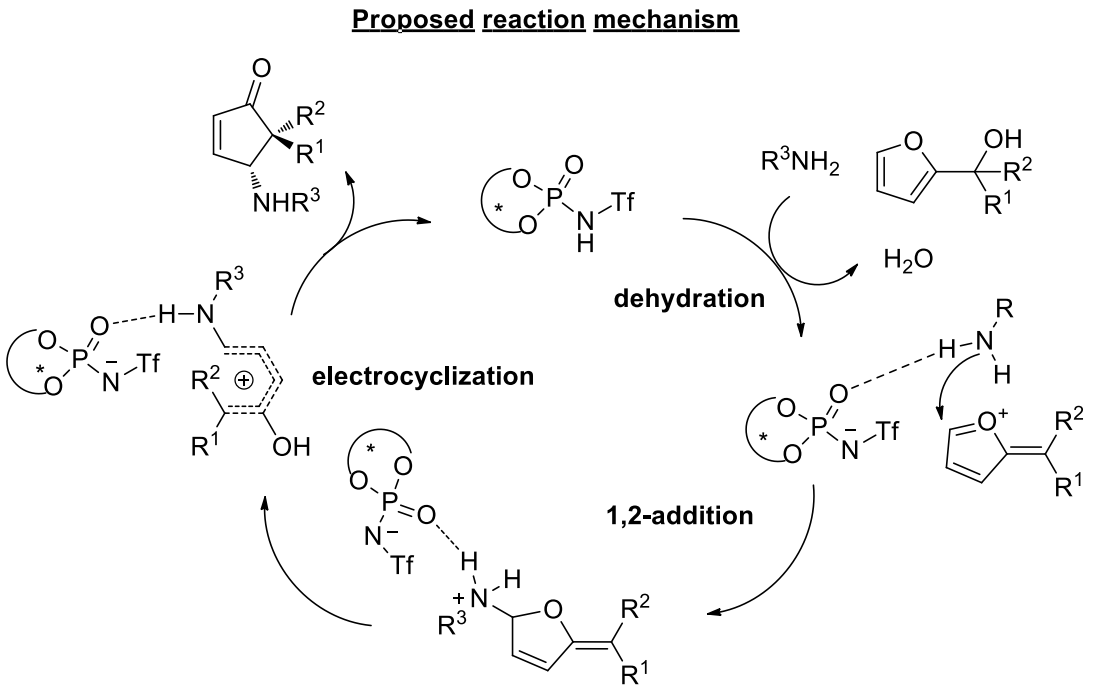
Lastly, another interesting application of IDPi catalysts concerns the synthesis of tetrahydrofurans and tetrahydropyrans bearing tetrasubstituted stereogenic centers *via* catalytic chemo and enantioselective nucleophilic addition of silyl ketene acetals to ketoaldehydes, in which, under the reaction conditions imposed by the use of the IDPi, an umpolung is observed and ketone reacts preferentially over the aldehyde.[59] Other biaryl phosphoric acid dimers, developed also in this case by the List group, are imidodiphosphoric acids (IDP). Remarkably, pK of these compounds in acetonitrile is around 11.5, thus they are much less acidic than IDPis (pK≈ 4.5 in acetonitrile). However, their slightly improved acidity and their more confined structure, with respect to simple phosphoric acids (pK≈ 13-14 in acetonitrile), made them good catalysts for reactions that classical PAs could not succesfully promote. For instance, in 2013 the first report of an organocatalytic asymmetric O,O-acetalization was succesfully carried out under IDP-catalysis (scheme 3.23),[60] where TRIP was a poor catalyst (pK = 13.6 in acetonitrile, conversion = 66%, *ee* = 33%).[61] More easily accessible enantiopure N,N-, N,S- and N,O- acetals could instead be obtained under chiral PA catalysis.[62]



Scheme 3.23 *Organocatalytic asymmetric acetalization by List, with a highly confined IDP as the catalyst*

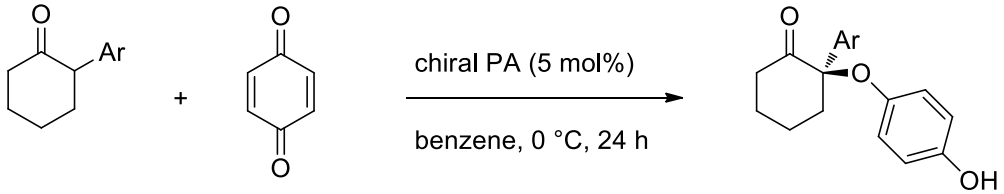
Looking at other phosphoric acid derivatives, the first organocatalytic asymmetric protocol for the aza-Piancatelli rearrangement was recently reported by the Rueping group under phosphoramide catalysis.[63] This is a variation of Piancatelli protonation-dehydration of furyl carbinols,[64] with an amine replacing water as the nucleophile. The catalyst shall be acidic enough to dehydrate the target furylcarbinol to an oxocarbenium ion, but also control the regioselectivity of 1,2-addition of the amine and the stereochemistry during the enantiodetermining step (4π-electrocyclization) to afford trans-substituted 4-hydroxy-5-aryl(alkyl)-cyclopentenones in high degree of stereoselectivity (scheme 3.24).



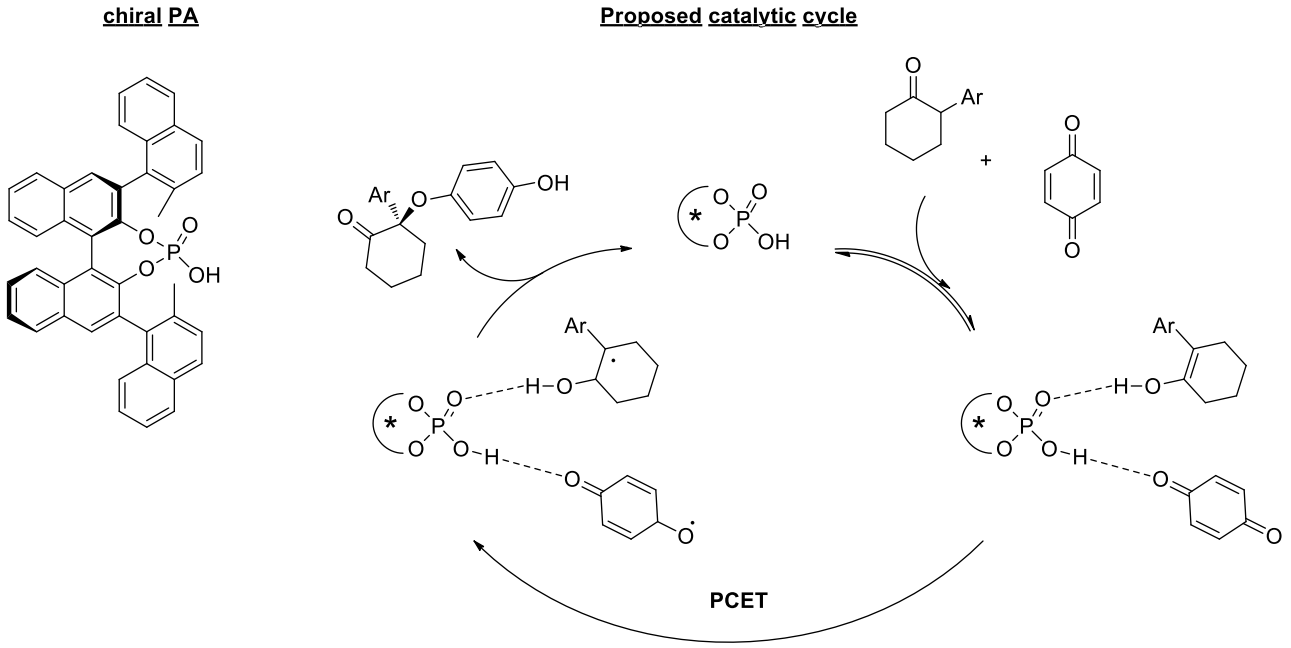


Scheme 3.24 *Organocatalytic asymmetric aza-Piancatelli rearrangement by Rueping*

Talking about simple PAs, apart from the above mentioned protocols concerning imines as substrates,[49-54] which include mannich-type reactions,[26,28] their applications range from pericyclic reactions,[65] including 1,3-dipolar cycloadditions[66] and Diels Alder reactions,[67] to multicomponent reactions,[68] Friedel-Crafts reactions,[69] Michael additions[70] and even oxidations.[71] Naturally, these examples do not cover the plethora of reactions that can be promoted by chiral PAs; however, the current trend in organocatalysis is to activate even more inhert substrate towards reaction and, for this reason, more acidic derivatives like phosphoramides, IDPs and IDPis are privileged chiral Brønsted organocatalysts. Nevertheless, some important reactions catalyzed by chiral PAs were also reported in very recent times. One of the latest applications of PA catalysts concerns asymmetric α-oxidation of 2-aryl substituted cyclohexenones with *p*-benzoquinone.[72] Direct 1,6-addition to the quinone is observed rather than expected 1,4-Michael type addition, and a Proton Coupled Electron Transfer mechanism has been hypothesized on the basis of Hammett plot, O-H dissociation energy calculations and previous kinetic studies by Mayr (scheme 3.25).[73]



yield up to 73%
***ee* up to 92%**



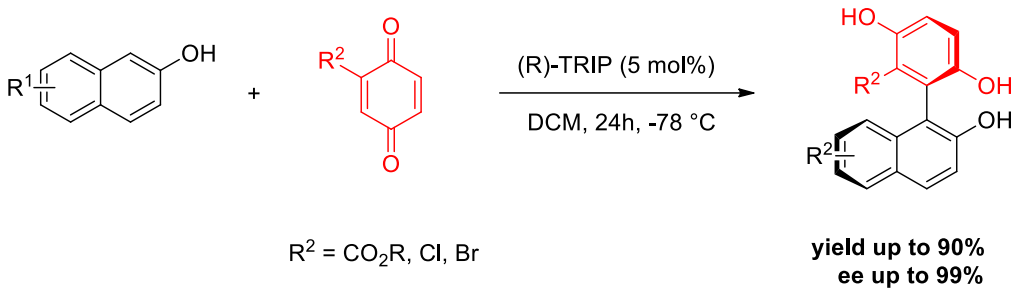
Scheme 3.25 *Organocatalytic asymmetric α-oxidation of 2-aryl substituted cyclohexenones with p-benzoquinone by List*

3.5 Aim of the work

In the current scenario, extensive literature exists regarding the design and employment of BINOL-derived phosphoric acids, including dimers and other derivatives (phosphoramides, IDPs, IDPis). Nowadays, organocatalysis has achieved a milestone thanks to the chemistry developed with these powerful catalysts in hand. Consequently, room for improvement is very narrow in this field, unless one has access to important resources to buy or at least to prepare these catalysts. Only 500 mg of TRIP cost 1340 €,[74] while IDPs and IDPis are not accessible from the market, and their preparation requires specific equipments to work under inhert atmosphere. The challenging aim of this work is to develop new phosphoric acid scaffolds for catalytic purposes, having lower environmental impact and cost with respect to BINOL-phosphoric acids. In this context, following from previous works developed by our group, two main strategies were adopted. The first strategy was the development of a synthetic route for non-C_2 symmetrical biaryl phosphoric acids, disfruiting enantiopure BINOL-type biaryl compounds as starting material. The second strategy was the synthesis of punctually chiral phosphoric acids from a waste byproduct of soy lecithin processing and from inexpensive natural product derivatives. It is worth mentioning that both the types of scaffolds were not reported in the literature.

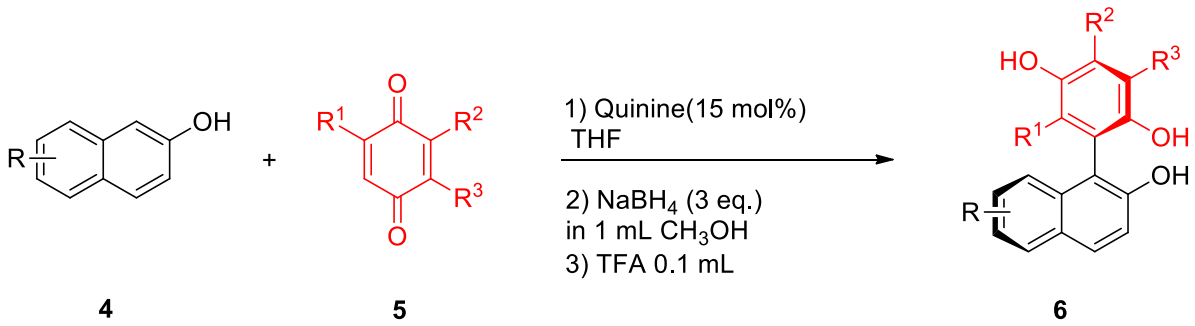
3.5.1 Premises concerning non-C_2 symmetrical biaryl phosphoric acids

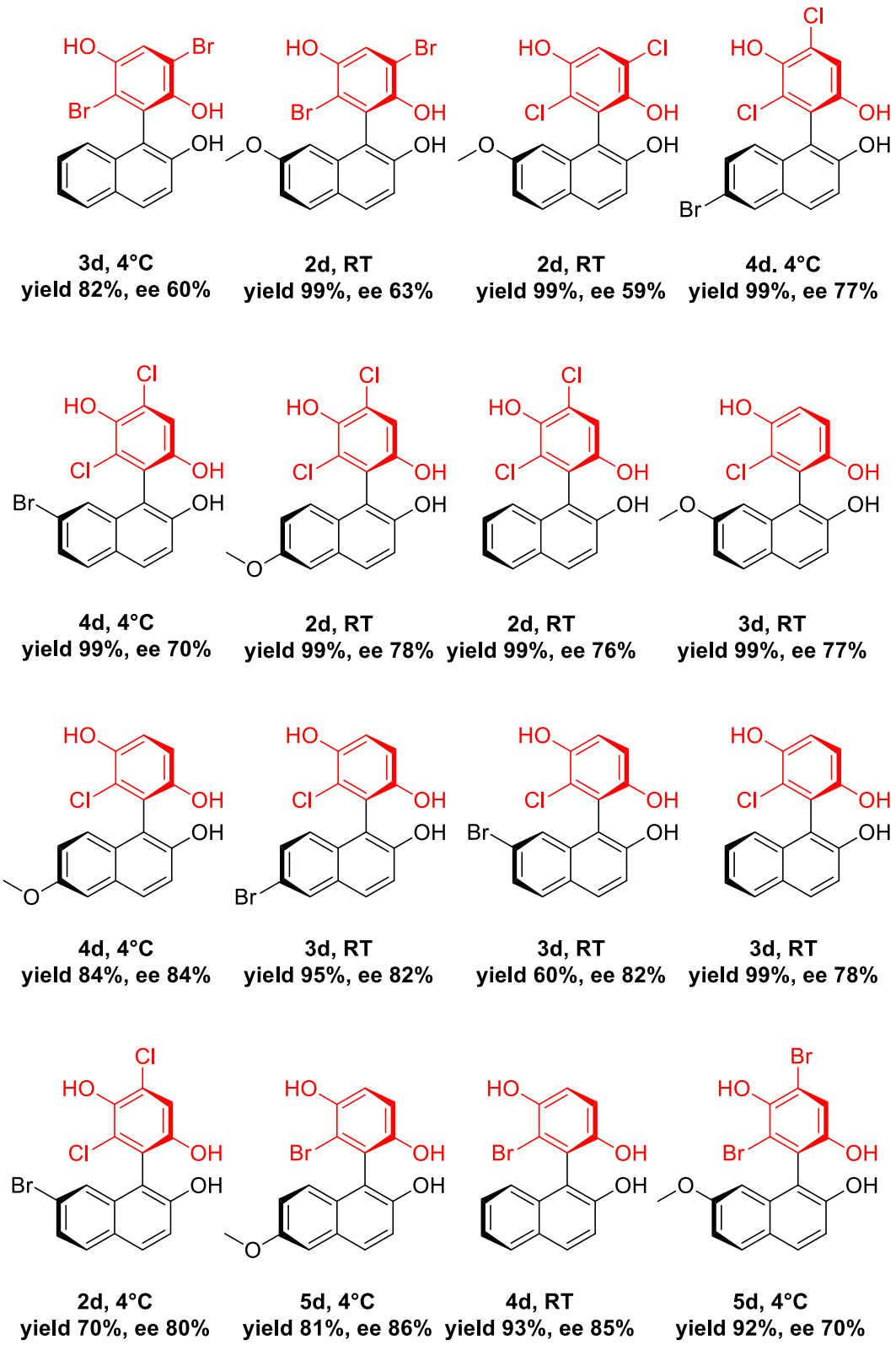
Until 2015, no general organocatalytic protocol to obtain non-C_2 symmetrical BINOL-like biaryls was available in the literature.[75-77] This kind of scaffolds was obtained for the first time in an enantioselective way by the Tan group.[75] The synthetic strategy relies on a Michael-type addition of naphthols to 1,4-benzoquinones. The use of an engineered phosphoric acid like (R)-TRIP allows the transformation to take place over 24 hours in high degree of stereoselectivity and in excellent yield with various naphtols and quinones. The best results were obtained in dichloromethane at -78 °C (scheme 3.26).



Scheme 3.26 *TRIP-catalyzed enantioselective synthesis of non-C_2 symmetric biaryls by Tan*

A complementary strategy was reported by our group a few months later with respect to Tan protocol.[76] In this case, various β-naphthols were added to mono- or di-halogen substituted 1,4-benzoquinones under Brønsted base-catalysis from naturally occurring *Cinchona* alkaloid quinine (scheme 3.27).





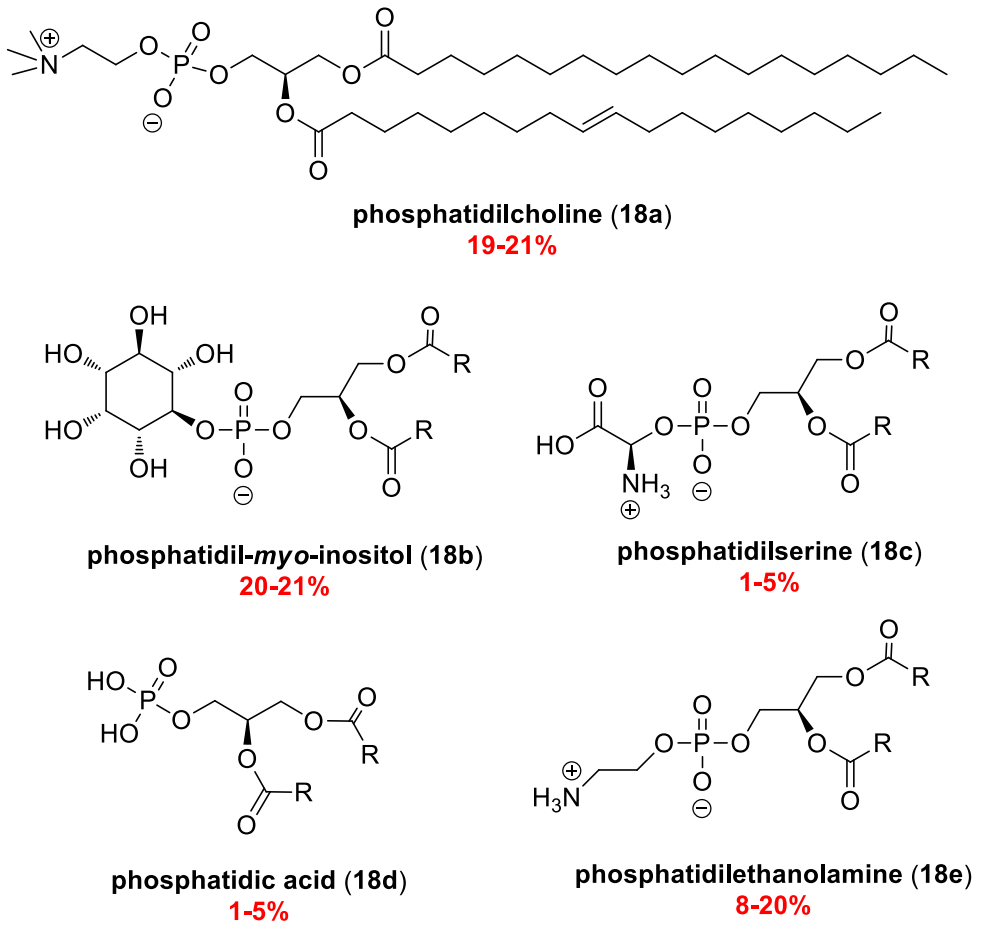
Scheme 3.27 *Quinine-catalzed enantioselective synthesis of non-C_2 symmetric biaryls*

Both the procedures are theoretically valuable to obtain the starting material for the synthesis of phosphoric acids. In fact, in both cases a single step is required to afford

enantiopure biaryls on a gram scale, eventually after recrystallization, and transition metals are not involved.[75,76] However, the quinine-catalyzed coupling was selected as the privileged protocol due to the absence of alogenated solvents, the major availability and lower cost of the catalyst and the milder reaction conditions, in compliance with the principles of green chemistry.

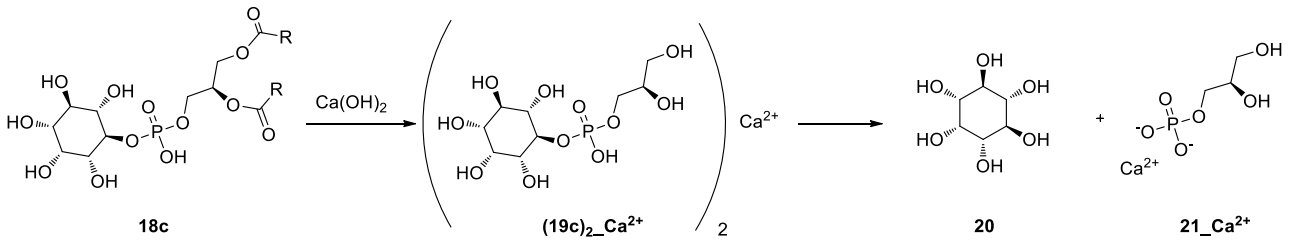
3.5.2 Premises concerning punctually chiral phosphatidic acids

Soy lecithin is a natural matrix,[78] isolated for the first time by Gobley from egg yolk and,[79] in 1874, he finally identified its composition. Nowadays the major source of lecithin are soy seeds, and the amount, the exact structure and the stereochemistry of its components is well known.[80] The major constituent of soy lecithin is soy oil (33-35%), while lower percentages of carbohydrates (5-11%), sterols (2-5%) and residual water (1%) represent the minor constituents. However, the most important part of soy lecithin is constituted by phosphatides (scheme 3.28)



Scheme 3.28 *Phosphatides of soy lecithin with relative abundance percentages*

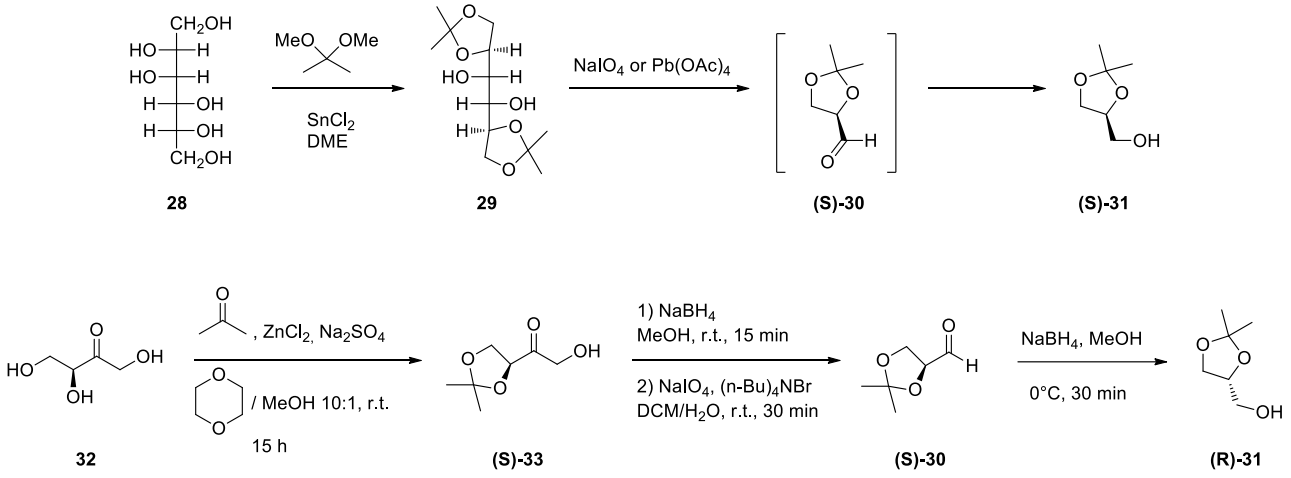
Phosphatides are substantially phospholipids provided with a hydrophilic head (amino alcohol, amino acid, phosphoric acid, amino group, hydroxyl group) esterified to phosphate group and a lipophilic tail, constituted by fatty acids (long chain saturated or unsaturated carboxylic acids) esterified to glycerol backbone. Their peculiar structure allows soy lecithin to place itself at the interface between two immiscible liquids, thus being capable of working as emulsifying or solubilizing agent. Its industrial employments also include those of crystallization control agent (food industry), anti binder (paints and coatings industry) and drug carrier (pharmaceutical industry).[81] Recently, our group worked on the isolation of a pure component of soy lecithin, glycerophospho-*myo*-inosithol. In order to satisfy the request of a local chemical company, glycerophospho-*myo*-inositol had to be isolated as a calcium salt, in order to handle it in a solid form. However, while optimizing the amount of calcium hydroxide necessary to precipitate the calcium salt, upon hydrolysis with an excess of $Ca(OH)_2$, hydrolysis of the phosphoesteric bond was observed, thus affording *myo*-inositol (**20**) and the calcium salt of glycerophosphoric acid (**21_Ca^{2+}**) instead of the desired glycerophospho-*myo*-inositol calcium salt (scheme 3.29).



Scheme 3.29 *Final step of isolation of glycerophosphate calcium salt from soy lecithin*

In the literature, the use of engineered axially chiral phosphoric acid is well documented, while no examples of efficient punctually chiral phosphoric acids have been reported, except for spiro phosphoric acids derived from SPINOL, which are indeed engineered catalysts (scheme 58).[24a,82] Glycerophosphoric acid, derived from enantiopure phosphatides, is enantiopure; moreover the use of a natural, inexpensive and readily available feedstock like soy lecithin is compliant to the 7th principle of green chemistry. This unexpected byproduct of soy lecithin processing became then the substrate for the synthesis of a novel punctually chiral non-engineered phosphoric acid organocatalyst. In order to ensure a good degree of asymmetric induction, promoted by proximity effects of the stereogenic unit to the catalyst active site, a cyclization reaction of compound **21_Ca^{2+}** was carried out. Several glycerophosphoric acid cyclization procedures have already been reported in theliterature,[83] despite resulting phosphatidic acids have never been devoted to catalytic purposes. Since the protocol relying on the cyclization of glycerophosphoric acid (**21**) gives access just to the corresponding cyclic phosphate diester, having a free hydroxyl group and being particularly unstable under acidic conditions, a complementary synthetic strategy was taken under consideration to obtain diverse and more stable phosphatidic acids. Moreover,

the functionalization offers the possibility of incrementing the degree of asymmetric induction, which is promoted by orientation and proximity to the catalytic site (phosphoric acid): in fact, appropriate substituents can be choosen because of their steric hindrance, chirality or presence of further binding sites for substrates. The key point of the synthetic route is the possibility of selectively protect two hydroxyl groups of glycerol (**27**), which, like soy lecithin, is a renewable feedstock.[84] The remaining free hydroxyl group of glycerol acetonide, commercially known as solketal,[85] can be then disfruited for functionalization. The last approach appears to be promising also because both the enantiomers of the final catalyst would be easily accessible in this way. In fact, (S)-solketal (**31**) can be obtained from inexpensive D-mannitol (**28**),[86] while the (R) enantiomer can be prepared from L-erythrulose, a ketose sugar largely employed in the formulation of suntan lotions.[87] Both **(R)-31** and **(S)-31** are commercially available and inexpensive reagents (scheme 3.30).



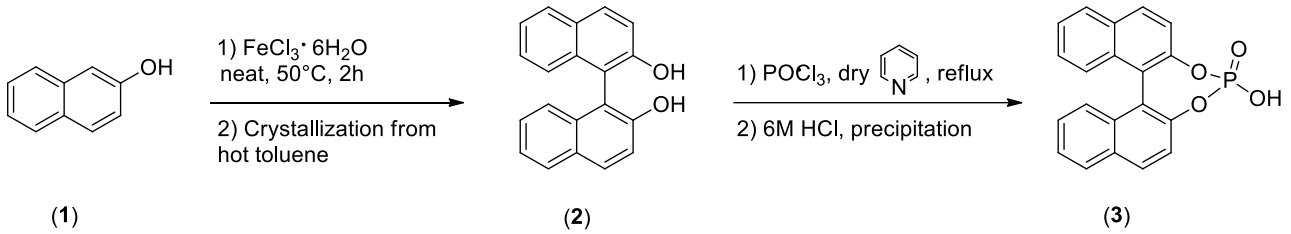
Scheme 3.30 *Synthetic routes for (S) and (R)-solketal from natural chiral products*

3.6 Results and discussion

3.6.1 Synthesis of non-C_2 symmetrical biaryl phosphoric acids

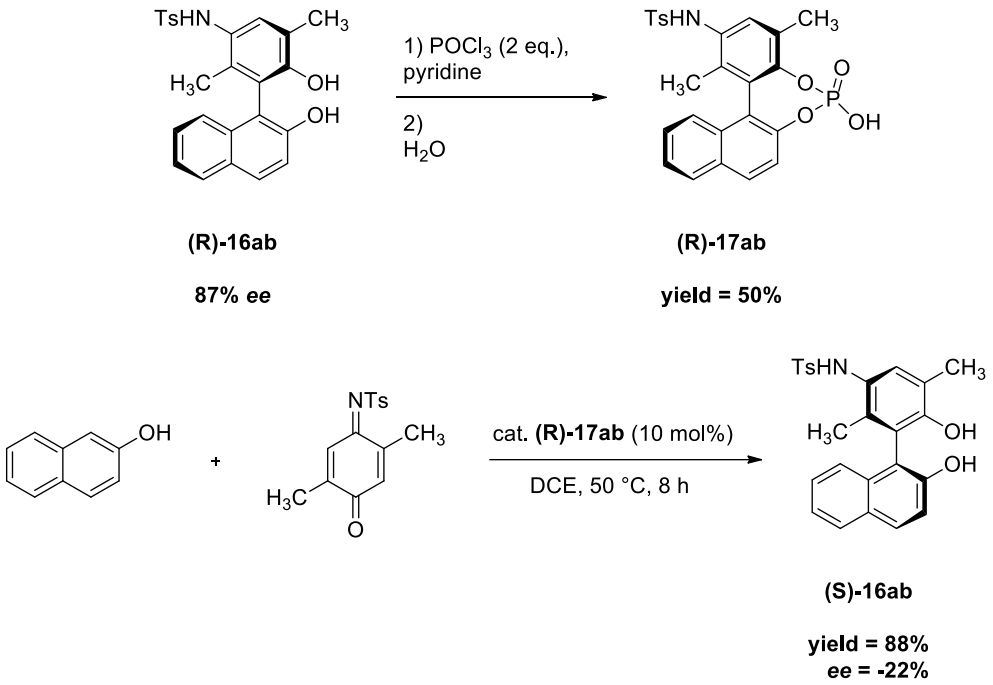
The preliminary result of phosphorylation of a non-C_2 symmetric biaryl had been acquired immediately after the recrystallization of some target biaryls. Unfortunately, this first attempt of phosphorylation following the literature procedure by Koy et al.[88] was not succesful, since neither the desired product or byproducts, nor the unconverted substrate could be isolated. In order to avoid waste of time and precious resources, a step back was taken, and racemic 2,2'-bi-2-naphthol (**2**) was choosen as the model substrate to test any kind of reaction conditions before transferring it to non-C_2 biaryls. In fact, BINOL can be easily obtained through a simple and inexpensive Fe(III)-catalyzed omocoupling of

β-naphthol (**1**) and its purification does not require chromatographic column, but just a crystallization from hot toluene.[89] Experimental data from ^{1}H NMR and ^{13}C NMR spectra of (**2**) were in agreement with those reported in the literature, so the Koy protocol, originally conceived for BINOL derivatives, was tested on BINOL itself. Even in this case, the procedure was ineffective and no considerable amount of material was yielded. In order to identify the problem, the original phosphorylation procedure by Jacques and Fouquey was tested.[29,36] In this case, the simple BINOL phosphoric acid diester 2,2-bi-2-naphthylmonohydrogenphosphate (**3**), more commonly known as BNP or BNHP (binaphthyl phosphate or binaphthyl monohydrogen phosphate, respectively) was isolated and the signals from ^{1}H NMR, ^{13} NMR and ^{31}P NMR were perfectly in agreement with literature data. In the overall process that leads to BNP, it is remarkable the complete absence of any chromatographic purification (scheme 3.31).



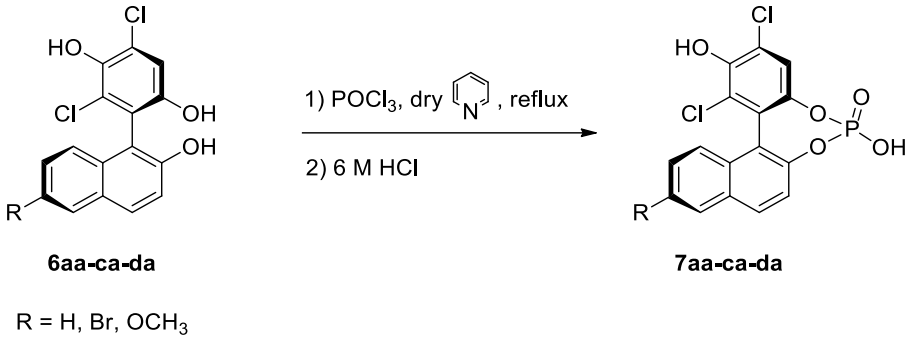
Scheme 3.31 *Synthetic scheme for (±)-BNP starting from β-naphthol*

The phosphorylation step, according to Jacques and Fouquey protocol, was carried out under inhert atmosphere, in dry pyridine under reflux. Pyridine has the double role to act as the solvent and the base, deprotonating the phenol functional groups, thus favouring nucleophilic attack on phosphorous oxychloride. Further dropwise addition of 6M hydrochloric acid serves both to hydrolize the biaryl phosphoric acid chloride and to supersaturate the solution, in order to cause precipitation of the desired phosphoric acid, which was washed again with hydrochloric acid and finally filtered and dried under high vacuum. Once a suitable procedure was identified for BINOL phosphorylation, its comparison with the failure one allowed to formulate a hypotesis for the unsuccesful outcome of the previous attempts, which was ascribed to a probably unuseful filtration on mineral coal, retaining organic material (impurities and useful material, in our case). Then, some target non C_2-biaryls were synthetized and recrystallized in near enantiopurity, so to make an attempt of direct phosphorylation (scheme 3.32).



Scheme 3.32 *Synthesis of non-C_2 biaryls choosen as model substrates*

Biaryl **6bb**, which was not included in the substrate scope of the biaryl coupling, should have been the privileged model compound, since it bears two bromine atoms in the positions 3 and 3', the right ones to introduce sterically hindered aryl groups. Unfortunately, quinone **5b** is not commercial, while naphthol **4b** is particularly expensive and it was not available in the laboratory. In order to obtain a good amount of both the reagents, **5b** was prepared according to a literature procedure[90] and a naphthol bromination protocol from the XIX century[91] was readapted, affording in this case a regioisomeric mixture of various brominated β-naphthols, not separable by column chromatography. Consequently, due to the unavailability of **4b**, compound **6bb** was set aside, while biaryls **6aa**, **6ca** and **6da** were prepared on a multigram scale. It is worth noticing that, according to previous experiments, it is known that large scale reaction is not straightforward for all the biaryls, even though the reaction is easily feasible on a small laboratory scale; moreover, in many cases, even with the pure biaryl in hands after chromatography, crystallization did not yield any crystal or products in low degree of enantioselectivity were afforded. So, while biaryls **6ca** and **6da** had already been prepared on a gram scale and recrystallized, the protocol was succesfully extended to **6aa** for the first time. Biaryls **6aa**, **6ca** and **6da** were selected because the corresponding naphthols and quinones were inexpensive and immediately available in the laboratory. Non-C_2 model compounds were then reacted with $POCl_3$ in pyridine, according to Jacques and Fouquey procedure (scheme 3.33).



6aa-ca-da

R = H, Br, OCH_3

7aa-ca-da

Scheme 3.33 *Scheme of direct non-C_2 biaryl phosphorylation*

After reaction with phosphorous oxychloride, water was added and the mixture was left under reflux for other three hours. The reaction mixture was then transferred into a dropping funnel and added dropwise to a 6 M HCl solution. Differently from what happened in the case of BINOL, no precipitation occurred in these cases. Moreover, NMR spectra of samples from the respective reaction mixtures, conveniently evaporated and dried under vacuum, could allow us to identify exclusively the signals relative to pyridine ring. The most likely hypotesis was that pyridinium hydrochloride signals were hiding the signals of products and reagent. The crude was then evaporated and dissolved in water, then the aqueous phase was extracted with different organic solvents (ethyl acetate, toluene, chloroform). Results of ^{1}H NMR analysis on the aqueous and the organic phase were very similar for the the crude of phosphorylation reactions carried out on **6aa**, **6ca** and **6da**: ^{1}H NMR of the aqueous phase exhibited signals from pyridinium hydrochloride and lower unidentifiable peaks, while pyridinium chloride was found to constitute the organic phase. Despite no product was clearly identified by NMR spectrometry, it seemed that the tested organic phase did not have any affinity with the material contained in the reaction mixture. A 10 M solution of sodium hydroxide was added to the aqueous phase, in order to deprotonate pyridinium ion and distill pyridine away from the reaction mixture. Distillation under vacuum (rotative pump, 115 °C) afforded a pale brown solid, which was analyzed by ^{1}H NMR spectroscopy in CD_3OD and D_2O. In both cases, an intense signals due to the presence of water could be observed, but signals ascribable to the product were lacking. At this point, reactions were repeated and, avoiding treatment with hydrochloric acid, the crude was evaporated and purified by flash column chromatography on silica gel with hexane/ethyl acetate 5:1 as the eluent. TLC analysis of the crude showed the presence of phosphorous oxychloride, pyridine and a lower spot. The latter spot was different from the substrate and turned yellow upon spotting with $KMnO_4$. This spot was isolated, but its ^{31}P NMR spectrum showed the presence of different phosphorous containing species (figure 3.1).

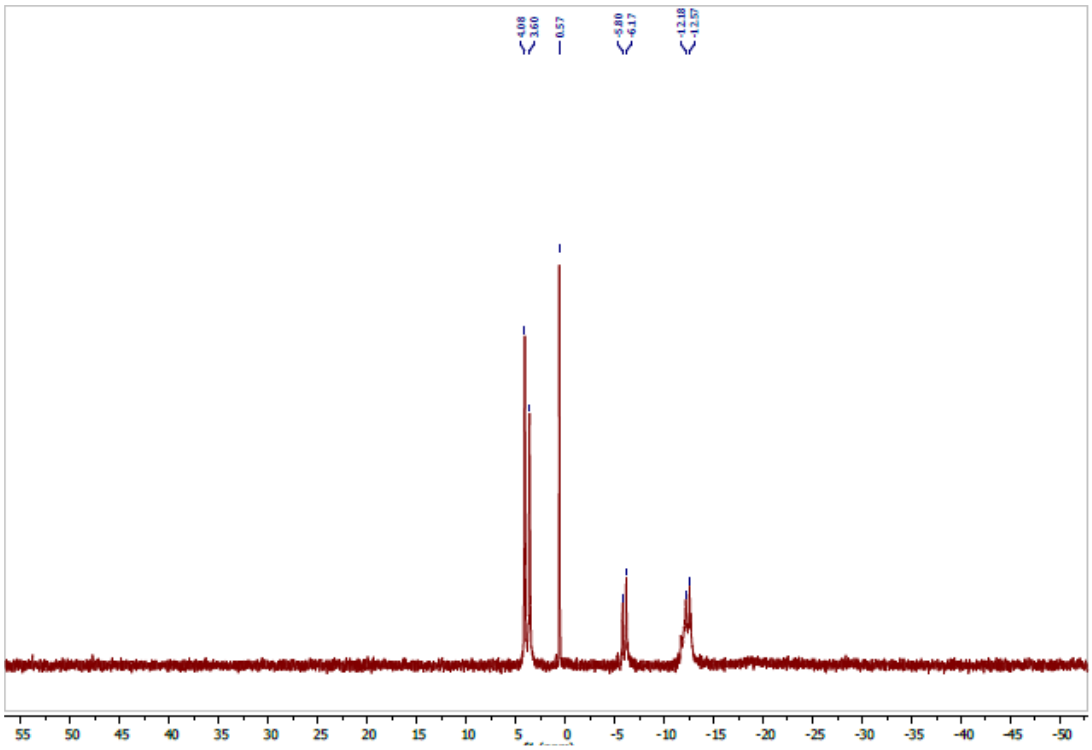


Figure 3.1 *^{31}P NMR (161 MHz) analysis of the supposed product **7ca** after column chromatogtraphy*

The isolated fractions containing the spot of concern were purified again with eluent mixtures $CHCl_3$/MeOH, DCM/MeOH, DCM/Et_2O and Et_2O/MeOH. However, in all the cases, major difficulties resided in getting rid of pyridine. For this reason, the phosphorylation reaction of compound **6aa** was repeated again in toluene with 10 equivalents of pyridine as the base. After adding of a small amount water for the hydrolysis step, the precipitation of a pale brown solid was observed, whose ^{1}H NMR signals exhibited the presence of pyridine signals and lower peaks between 7 and 8 ppm. The solid was the dissolved in methanol to try to perform a solid/liquid extraction of the product, and the precipitation of a white grainy solid of a pyridinium salt (^{1}H NMR) was observed. The organic phase was dried and the resulting solid was crystallized again from a small amount of hot methanol. The mother liquor was dried under vacuum, but its ^{1}H NMR spectrum revealed that pyridine was again a major constituent of the crude (figure 3.2).

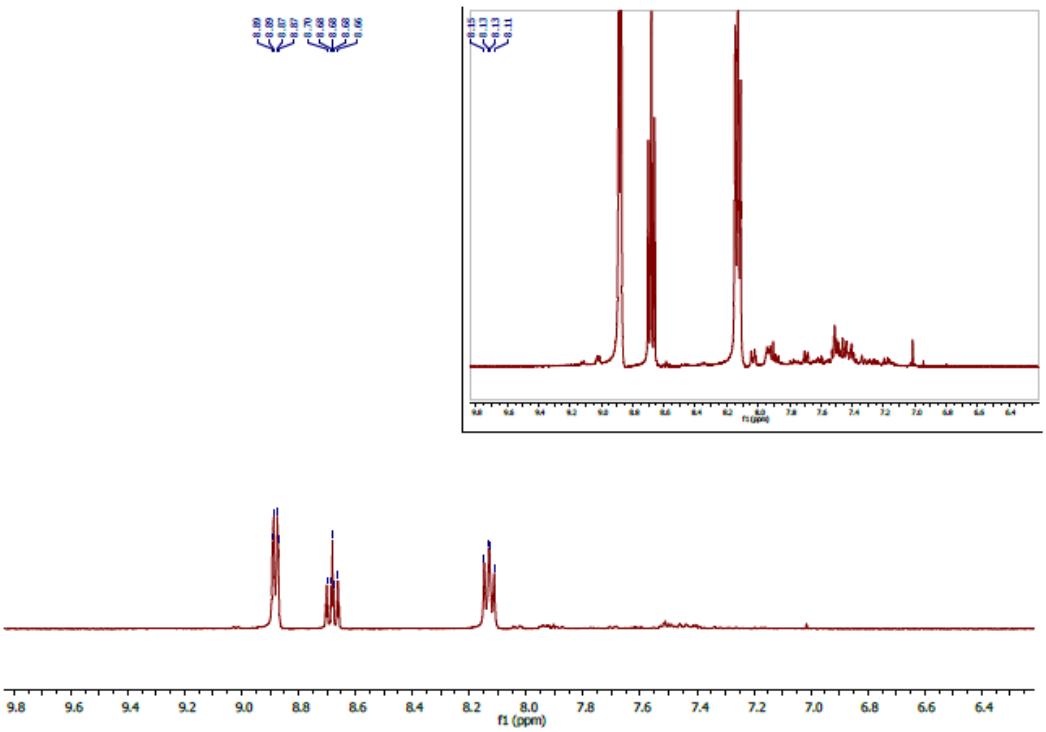


Figure 3.2 *^{1}H NMR (400 MHz) analysis of the mother liquor from crystallization of the phosphorylation crude of compound **6aa** in toluene and pyridine (10 eq.)*

In order to try to get rid of pyridine, taking into account its Brønsted basic nature, an attempt of filtration of the crude on a different stationary phase was made. Basic and neutral alumina were the selected stationary phases, while AcOEt/MeOH and pure MeOH were the eluent. No improvement was observed in any case, spectra being very similar to those depicted in figures 3.1 and 3.2. The reaction of compound **6aa** was then repeated again, reducing the amount of pyridine to 3 equivalents and paying attention to reduce as much as possible its employment, replacing it with water for work-up operations after hydrolysis (*e. g.* to recover crude residuals after transfer into the dropping funnel). The larger amount of water, with respect to the previous experiments, determined a turbidity of the solution and the further precipitation of a solid. The reaction work-up was then developed as in the case of BNP (**3**), transferring the crude in a dropping funnel and adding it dropwise to a 6 M hydrochlric acid solution; in these conditions, the precipitation of a pink solid was observed. The solid was filtered and washed in hot 6 M hydrochloric acid, then filtered again and dried. Signals from ^{31}P NMR showed the presence of a major peak at 3.02 ppm, together with other peaks indicating the presence of other phosphorous containing species (figure 3.3). Unfortunately, neither ^{1}H NMR and ^{13}C NMR peaks, nor data from ESI-MS spectrometry gave any advice in the identification of the desired compound.

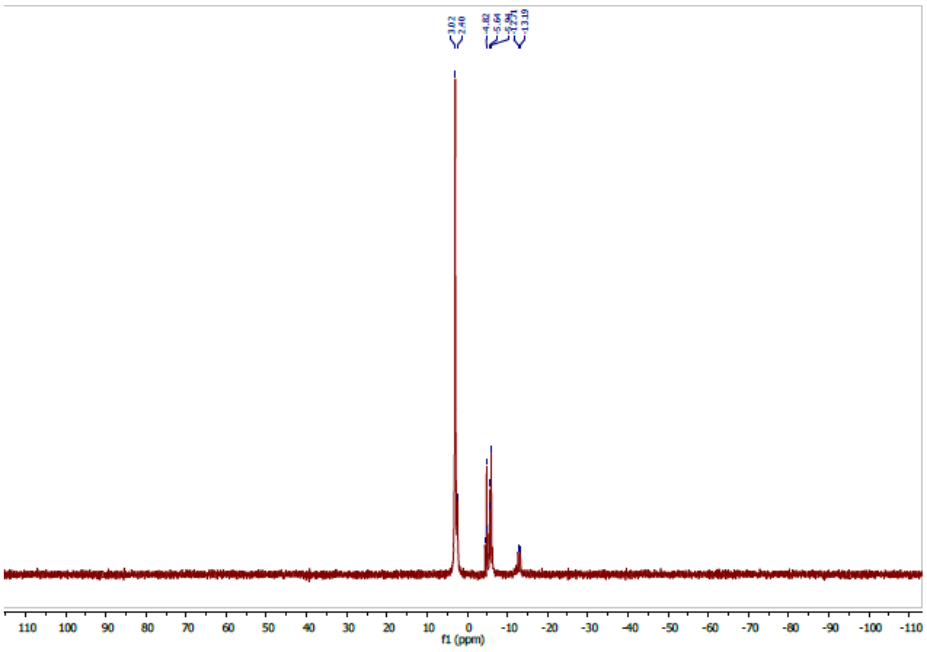


Figure 3.3 *^{31}P NMR (161 MHz) of the pink solid obtained upon phosphorylation of **6aa** in toluene*

Because of the small amount of material collected, the reaction was repeated on a larger scale, and the solid separated from hydrochloric acid by centrifugation after washing, so to collect as much material as possible; however, NMR data did not differ from the previous case. The hypotesis that the signals in ^{31}P NMR spectrum could belong to degradation products of $POCl_3$ prompted to repeat the reaction with a new batch of this reagent. A pink solid was isolated, exhibiting a single ^{31}P NMR signal at 150.86 ppm (figure 3.4).

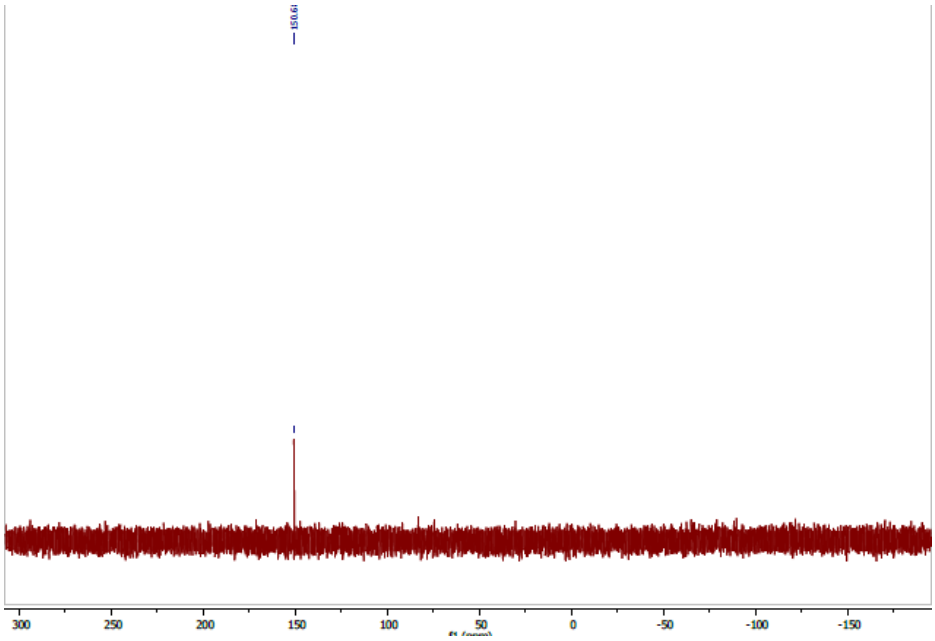
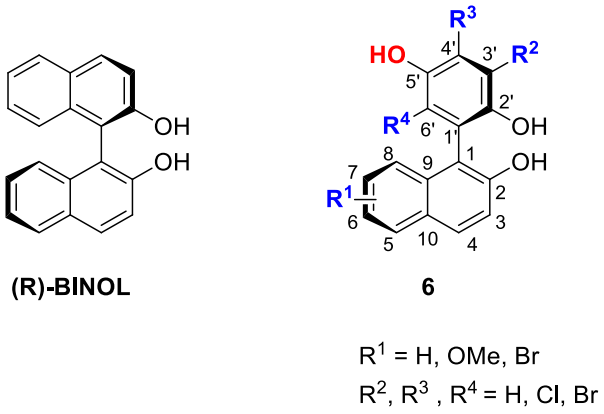


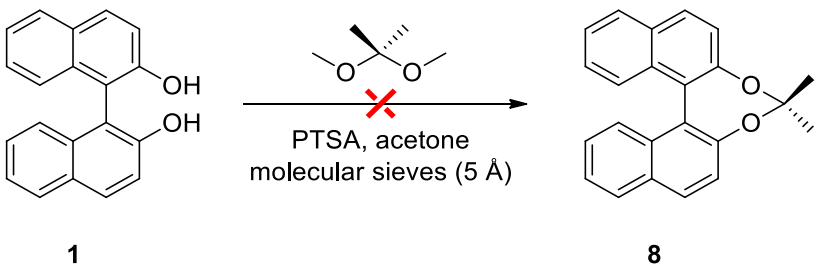
Figure 3.4 *^{31}P NMR (161 MHz) spectrum of the pink solid obtained upon work-up of phosphorylation of compound **6aa** in toluene, using a new batch of $POCl_3$*

Despite the presence of a singlet peak in the ^{31}P NMR spectrum, $^{1}HNMR$ signals of the pink solid revealed a mixture of different compounds, so it was purified by flash column chromatography on silica gel with a mixture chloroform/ethanol in gradient to pure ethanol as the eluent. Unfortunately, neither in this case it was possible to isolate fraction ascribable to the desired product. At this stage, it is important to highight the structural differences between BINOL and non-C_2 symmetric biaryls used as substrates (scheme 3.34).



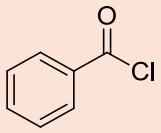
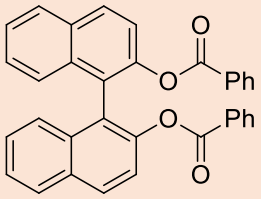
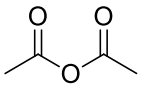
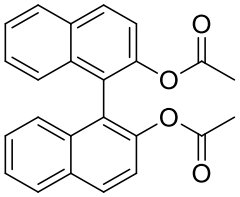
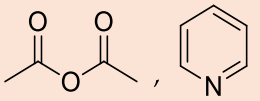
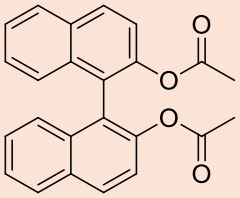
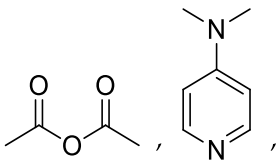
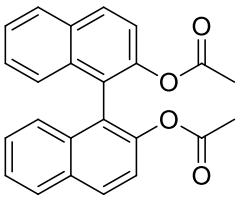
Scheme 3.34 *Structural differences between BINOL and non-C_2 symmetric biaryls*

Apart from the upper ring (naphtyl in the case of BINOL, phenyl in the case of non-C_2 biaryls) major differences reside in the susbstituents, which (especially those from the upper ring) make our biaryl more polar than BINOL. In particular, the hydroxyl group in the position 5′ can interfere in the phosphorylation reaction. The aim of direct phosphorylation of non C_2 biaryls was then replaced with selective monoprotection of 5′-hydroxyl group before going on. Since hydroxyl groups in the positions 2, 2′ and 5′ are expected to have a similar reactivity, some strategies were carried out to identify and disfruit possible differences in the reactivity selectively protect 5′-OH group: acetalization of the vicinal diol, monoprotection of 5′-OH group and acetal hydrolysis; direct selective monoprotection; non selective tri-protection and further selective di-deprotection. The first strategy was based on a literature protocol,[92] uneffective when the reaction was repeated in our laboratory on BINOL (**1**) as the model substrate. Accordingly, this strategy was discharged (scheme 3.35).



Scheme 3.35 *Unsuccessful attempt of BINOL acetalization*

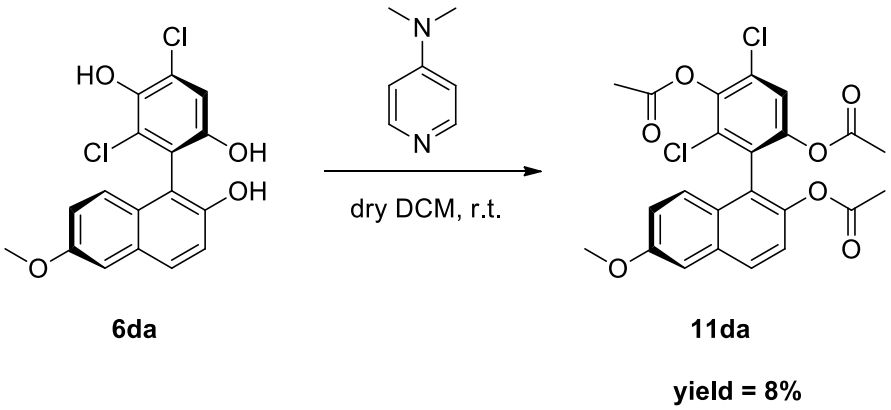
Talking about the second and the third strategy, there was the necessity of a straightforward procedure to protect a phenol hydroxyl function in high yield and that could be removed, if necessary. For this reason, esterification reaction was selected and different reaction conditions were tested, on the basis of literature procedures, with BINOL as the model substrate (table 3.1).

Entry	Reaction conditions	Ref.	Product	Yield (%)
1	 , $AlCl_3$ in toluene	[93]	 **9**	n.d.
2	 , NaOH 2.5 M, 0-5 °C DCM, recrystallyzation from MeOH	[94]	 **10**	55[a]
3	 , DCM, r.t.	[95]	 **10**	63
4	 , dry DCM, r.t.	[96]	 **10**	93

[a] NMR yield

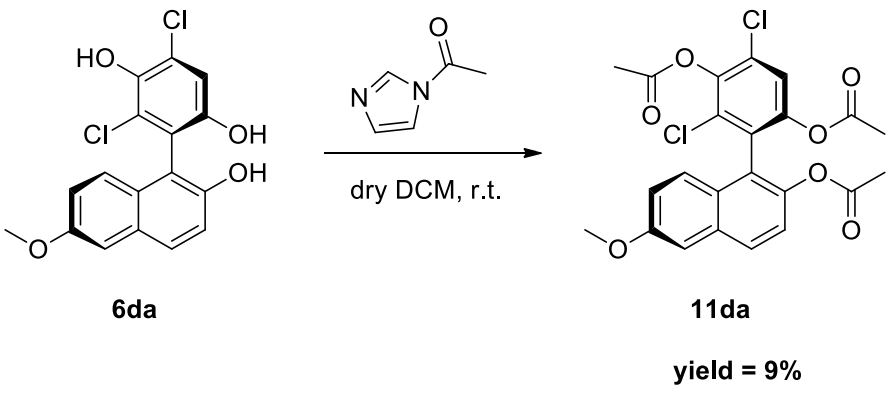
Table 3.1 *Reaction conditions screening for the best hydroxyl protection protocol on BINOL as the model substrate*

Acylation in the presence of benzoyl chloride afforded many sideproducts, probably due to impurities contained in the reagent, so the procedure[93] was discharged and the yield was not determined (table 2, entry 1). Then, acetic anhydride was employed as the acylating agent, but in this case of the first literature protocol[94] (table 2, entry 2) purification was not carried out due to low conversion. However, acylpyridinium ions generated in situ from the corresponding anhydrides in the presence of pyridine or,[97] even better, DMAP,[98] are better acylating agent than anhydrides themeselves. This reactivity trend was confirmed by experimental data (table 2, entries 3 and 4),[95,96] so acetylpirydinium ion resulting from the employment of DMAP and acetic anhydride was selected as the acylating agent to test on non-C_2 biaryls. Biaryl **6da** was choosen as the model compound, but using 1.1 equivalent of the acylating agent a mixture of three compounds having similar RF was obtained. The major compound (8% yield) was the triprotected biaryl. Further attempts at lower temperature (4 °C, -20 °C) did not improve the chemoselectivty, but reduced the reaction rate (scheme 3.36).



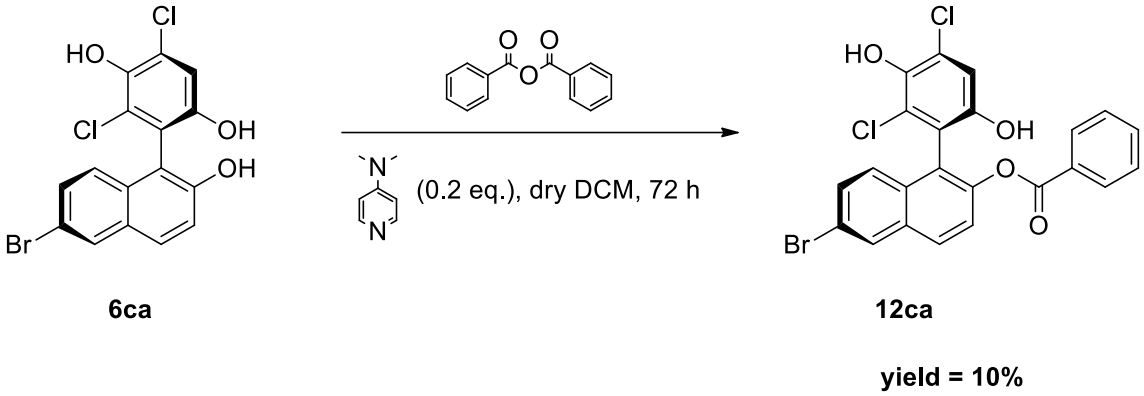
Scheme 3.36 *Monoacetylation of a non-C_2 biaryl model compound with DMAP and Ac_2O*

Since imidazolides (N-acyl imidazoles) are known to be milder acylating agents than N-acylpyridynium ions,[99] acetyl imidazolide was synthetized according to a literature procedure[100] and used in the same reaction. Even then, a mixture of three products was obtained, and only compound **11da** could be again isolated pure in 9% yield (scheme 3.37).



Scheme 3.37 *Monoacetylation on a non-C_2 biaryl model compound with acetyl imidazolide*

Since it was not possible to selectively introduce a single acetyl group, it was hypothesized that a bulkier group could better discriminate among the three hydroxyl functions, thanks to additional steric hindrance. For this reason, attempts of selective monobenzoylation with 1.5 equivalents of benzoic anhydride were carried out on compound **6ca**, modifying a literature procedure (scheme 3.38).[101]



Scheme 3.38 *Monobenzoylation on a biaryl model compound with benzoic anhydride and DMAP*

The formation of 3 new spots was observed by TLC. The spot having higher RF was isolated upon washing the crude with sodium bicarbonate and brine, and chromatographic purification. ^{1}H NMR and ^{13}C NMR spectra confirmed the formation of a monoacetylated product, despite undesired impurities of benzoic acid. Comparing 1D spectra of **12ca** (product) and **6ca** (substrate), it is possible to notice the lack of an hydroxyl proton in ^{1}H NMR spectrum of **12ca** (figure 3.5) and the shift from 153.7 to 147.3 ppm of a ^{13}C NMR signal belonging to a quaternary carbon bearing an hydroxyl function (figure 3.6).

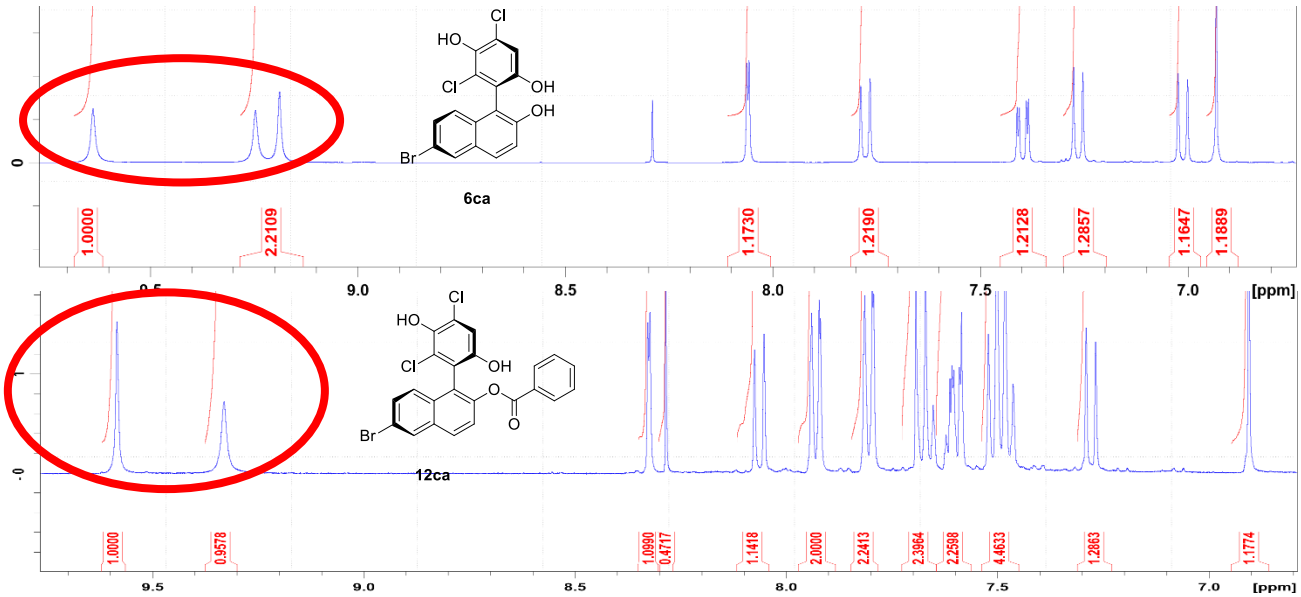


Figure 3.5 *Comparison between ^{1}H NMR (400 MHz) spectra of* ***6ca*** *and* ***12ca***

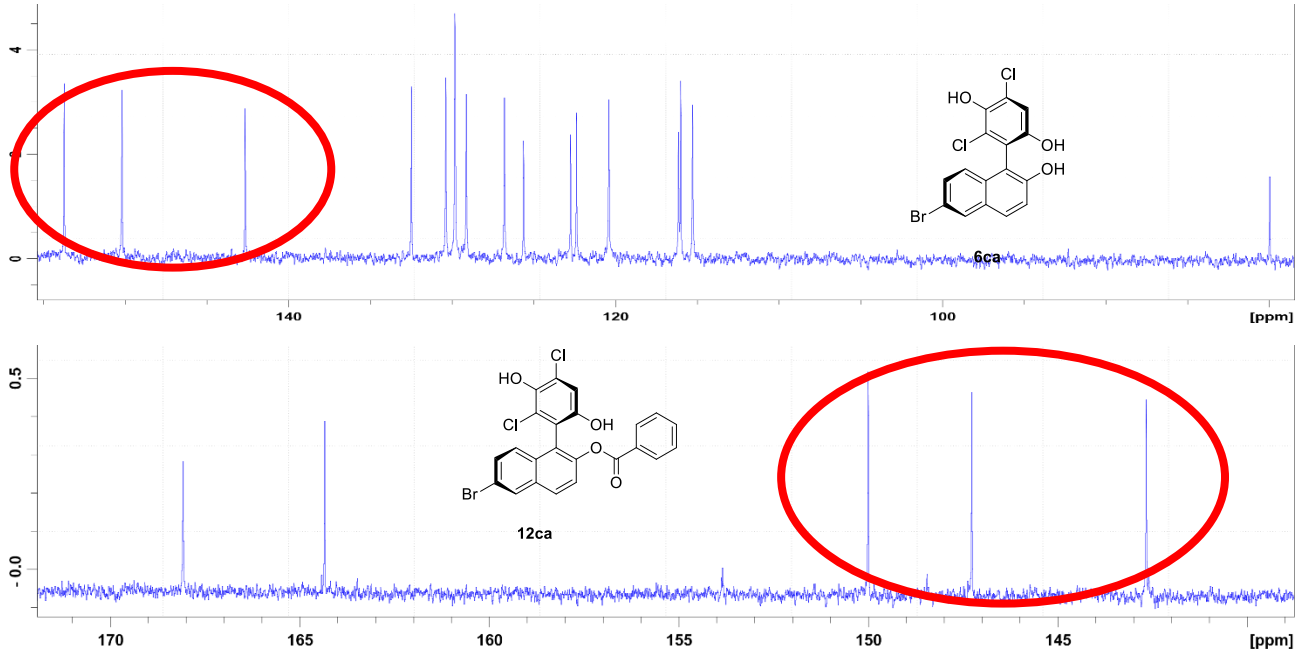


Figure 3.6 *Comparison between ^{13}C NMR (100 MHz) spectra of* ***6ca*** *and* ***12ca***

To exactly determine the position of the benzoylated hydroxyl group, bidimensional NMR spectra (HSQC, HMBC, ^{1}H-^{1}H COSY, NOESY) were acquired for **12ca** and **6ca**. First of all, in HSQC spectrum it can be seen that three proton signals do not correlate with any carbon signal; furthermore, there are three deshielded carbon signals between 142 and 153 ppm, which have been assigned to the three carbons bearing an hydroxyl function (figure 3.7).

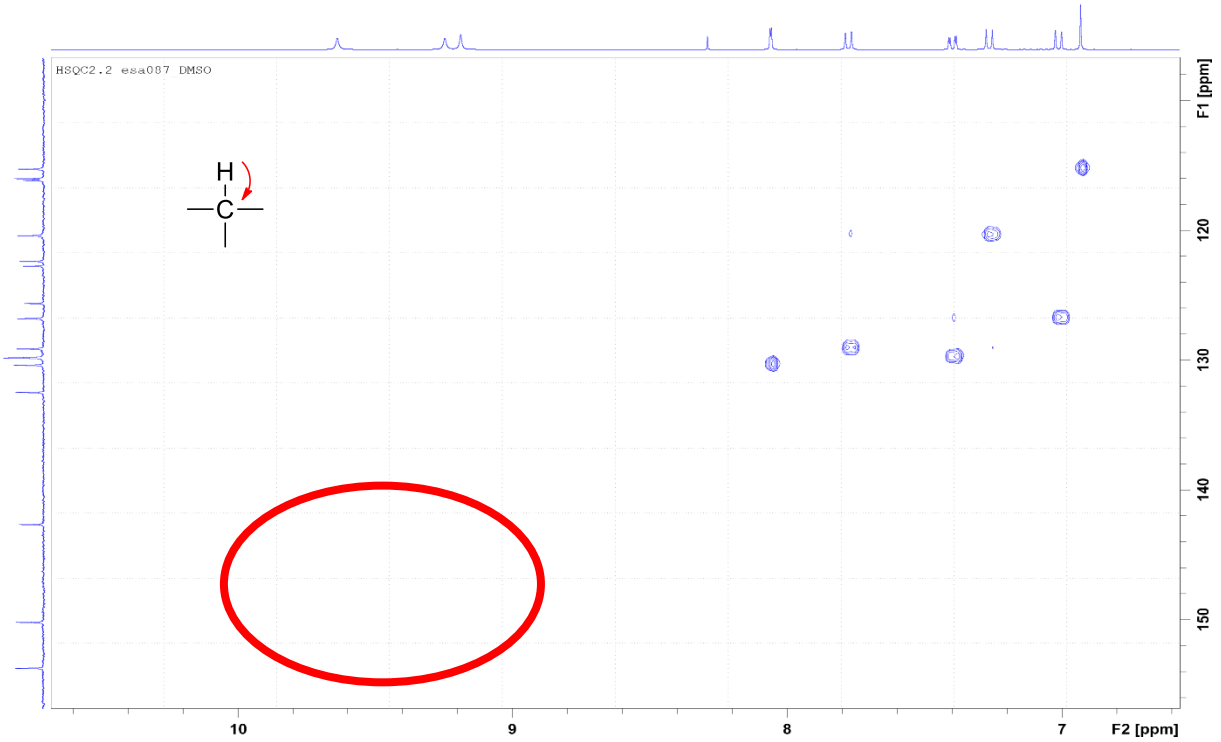


Figure 3.7 *HSQC (400 MHz) spectrum of compound* ***6ca*** *acquired in d⁶-DMSO*

Analyzing HMBC spectrum of **6ca**, the three hydroxyl functions have been assigned to the corresponding carbons. Since the singlet at 6.90 ppm (belonging to the only proton of the upper ring, $H_{3'}$) correlates with carbons at 150.2 and 142.6 ppm, it can be assumed that these two carbons bear hydroxyl groups and that the carbon having chemical shift 153.7 ppm belongs to naphtol ring. Consequently, proton singlets at 9.25 and 9.20 ppm belong to hydroxyl functions of the upper ring, while the remaining broad singlet at 9.60 ppm belong to the hydroxyl group of naphtol lower ring. These data were then compared with those from HMBC spectrum of product **12ca**, remembering that carbon having 153.7 ppm in ^{13}C NMR spectrum of **6ca** shifts at 147.3 ppm in ^{13}C NMR spectrum of **6ca**. This carbon is the only one which does not correlate with any hydroxyl proton (figure 3.8).

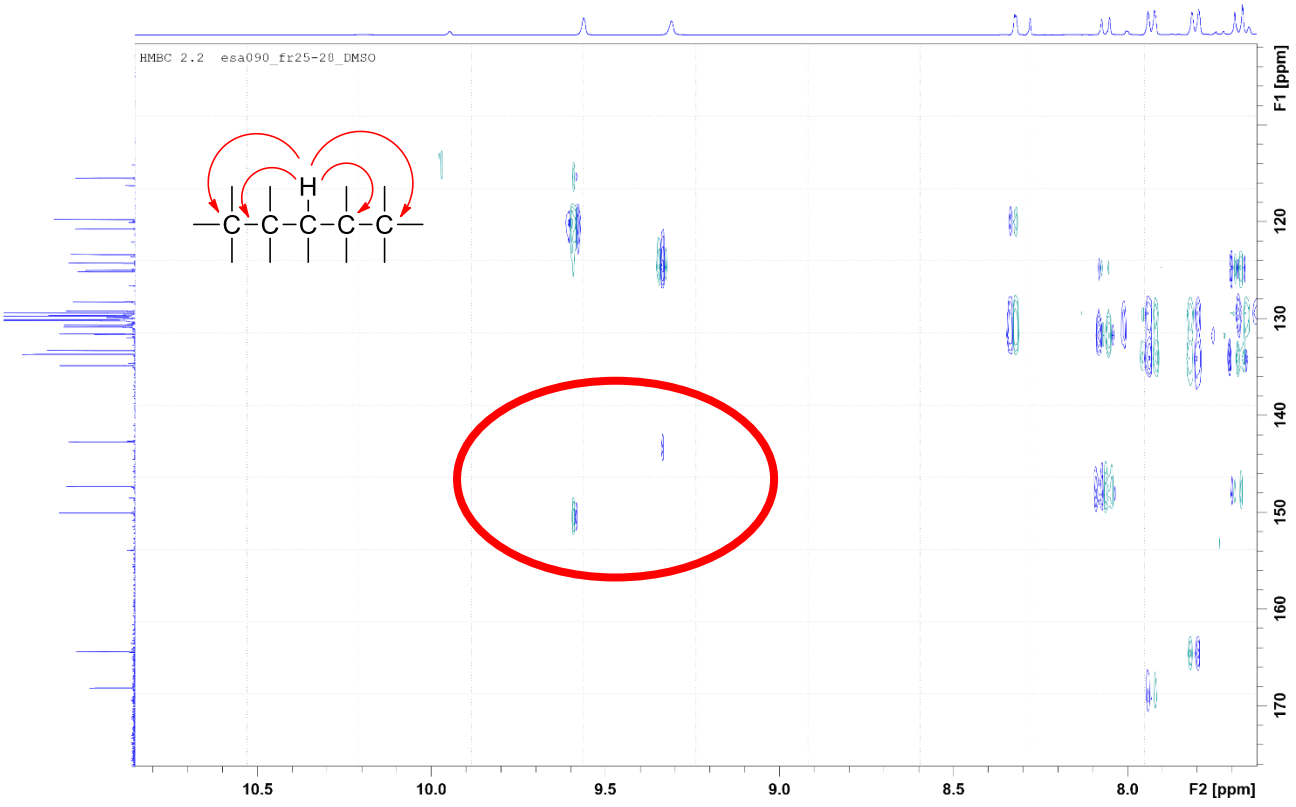
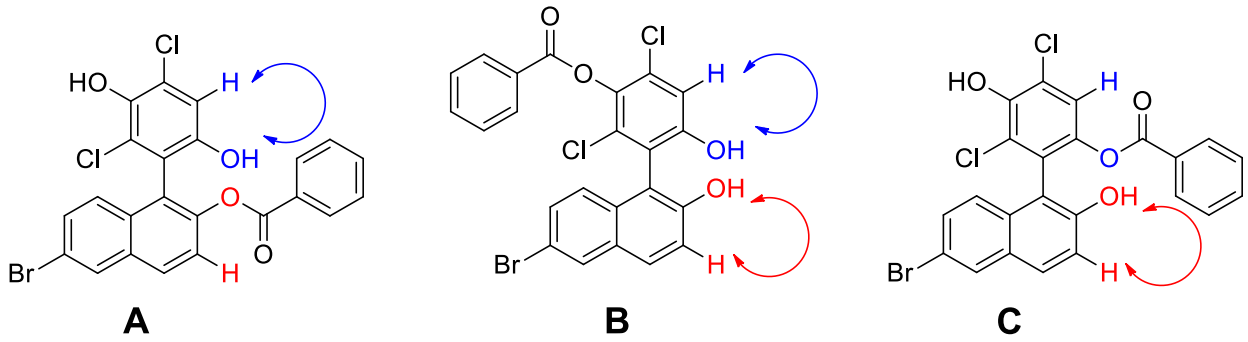


Figure 3.8 *HMBC (400 MHz) spectrum of compound* ***12ca*** *acquired in d⁶-DMSO*

Upper ring singlet at 6.90 ppm correlates with carbon having chemical shifts 142.7 and 150.0 ppm, which consequently bear hydroxyl groups. The remaining signal at 147.3 ppm is then relative to naphthol carbon bearing the OH group, since it does not correlate with hydroxyl protons, nor with singlet aromatic proton of the upper ring. As a further evidence, NOESY spectrum of the product **12ca** was acquired and analyzed. Taking into consideration the 3 possible structures of a monobenzoylated product, they would lead to different number of NOESY correlations or NOESY correlations among different protons (scheme 3.39).



Scheme 3.39 *NOESY correlations in each possible monobenzoylated product*

Looking at NOESY spectrum (figure 3.9), there is just a single correleation, and this leads to discharge structure B, which contemplates instead 2 correlations. Since the only evident correlation is the one between the broad singlet at 9.58 ppm and the singlet at 6.90 ppm, belonging to quinone moiety, the correct structure of compound **12ca** is those indicated as A in scheme 3.39. In the case of structure C, in fact, the NOESY correlation would concern a broad singlet and the doublet belonging to H_3 proton of the naphthol moiety.

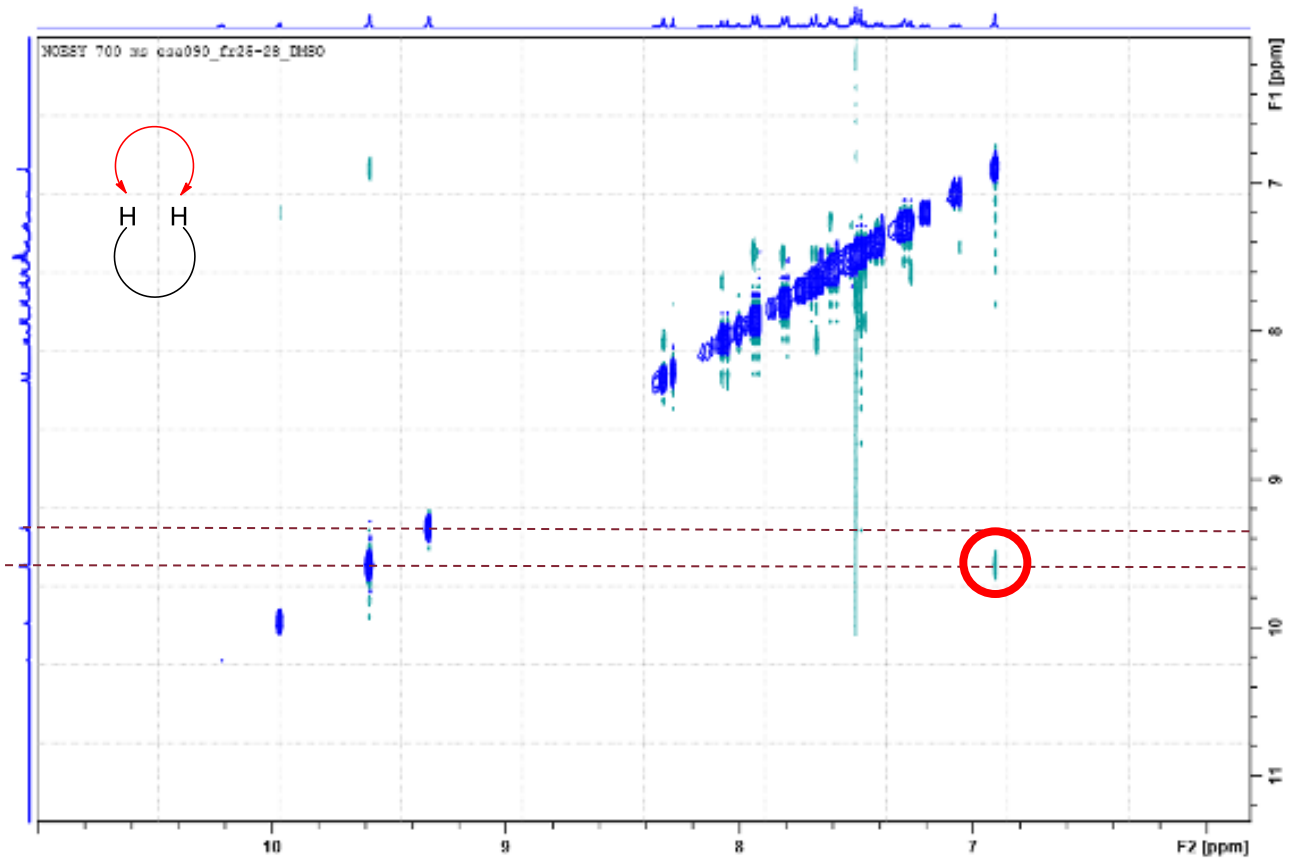


Figure 3.9 *NOESY (400 MHz) spectrum of compound* ***12ca*** *in* d^6*-DMSO*

Moreover, after two weeks from the acquisition of 1D and 2D spectra, ^{1}H NMR of the same sample shows the formation of a scrambling product, whose ratio was 1: 2.4, with respect to **12ca** (figure 3.10).

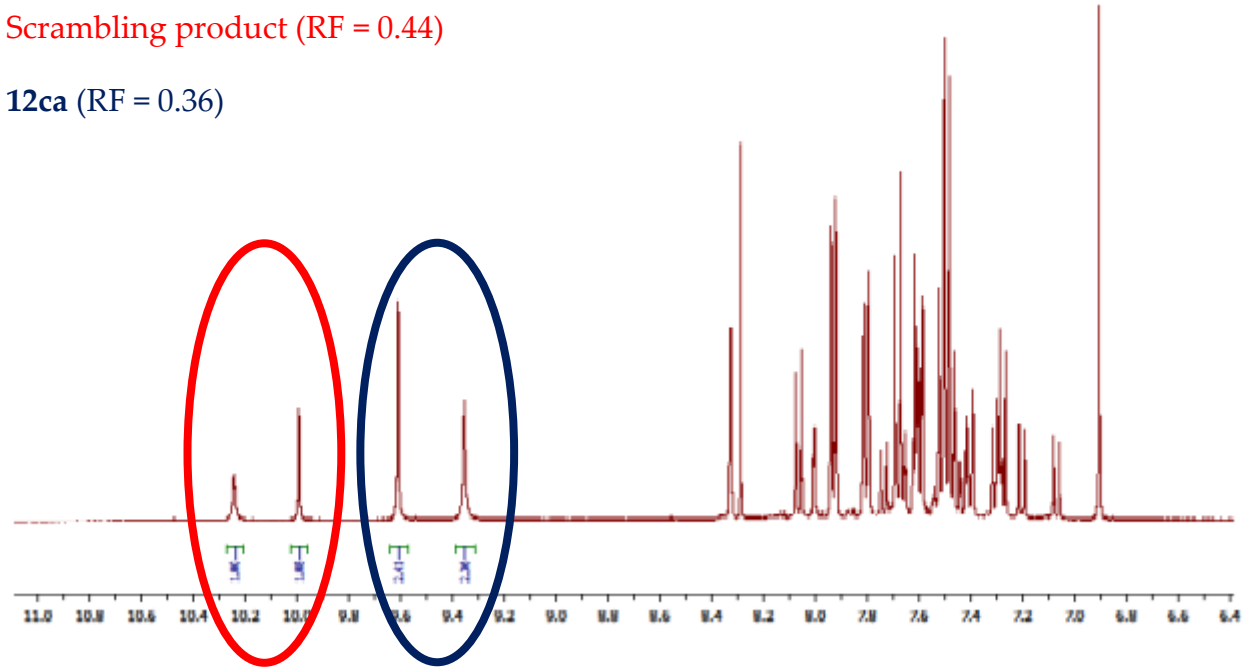
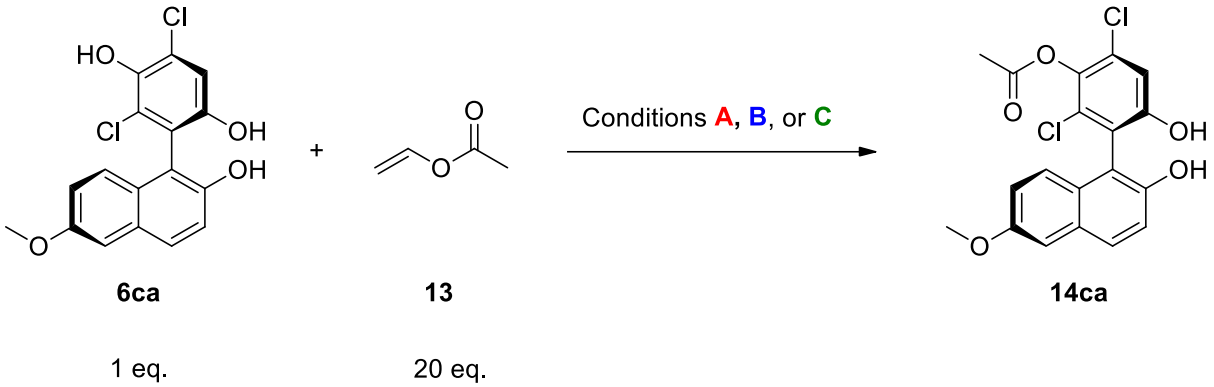


Figure 3.10 *^{1}H NMR (400 MHz) spectrum of sample originally containing **12ca** in d^{6}-DMSO after two weeks from the first NMR analysis*

The benzoylation reaction was then repeated at lower temperature (4 °C) and this time the middle spot was isolated as the major compound, although in low yield (10%). Despite NMR spectra were slightly different from those of **12ca**, also in this case collected data suggested the formation of a monobenzoylation product. However, 2D NMR spectra (COSY, HSQC, HMBC, NOESY) could not give any further useful information to clarify its structure. However, TLC and ^{1}H NMR comparisons suggested that it may be the previously observed scrambling product. In the meanwhile, a different strategy based on enzymatic transacetyation was carried out (scheme 3.40). Since just two lipases were immediately available in the laboratory (Amano Lipase PS from *Burkholderia Cepacia* and Lipase from porcine pancreas), literature procedures were slightly modified. At first, two literature procedures were followed, changing the enzyme and the substrate (biaryl instead of BINOL-derivatives).[102,103] Since no conversion was observed in any case, the opposite approach was followed and a literature procedure was selected on the basis of the enzyme (Amano Lipase PS from *Burkholderia Cepacia*), the substrates being aliphatic or benzylic alcohols.[104] In fact, no procedure was found in the literature for BINOL derivatives with available enzymes in the laboratory. Unfortunately, despite a little screening of solvents and acetyl donors (table 3.3), neither in these case it was possible to react substrate **6ca**.



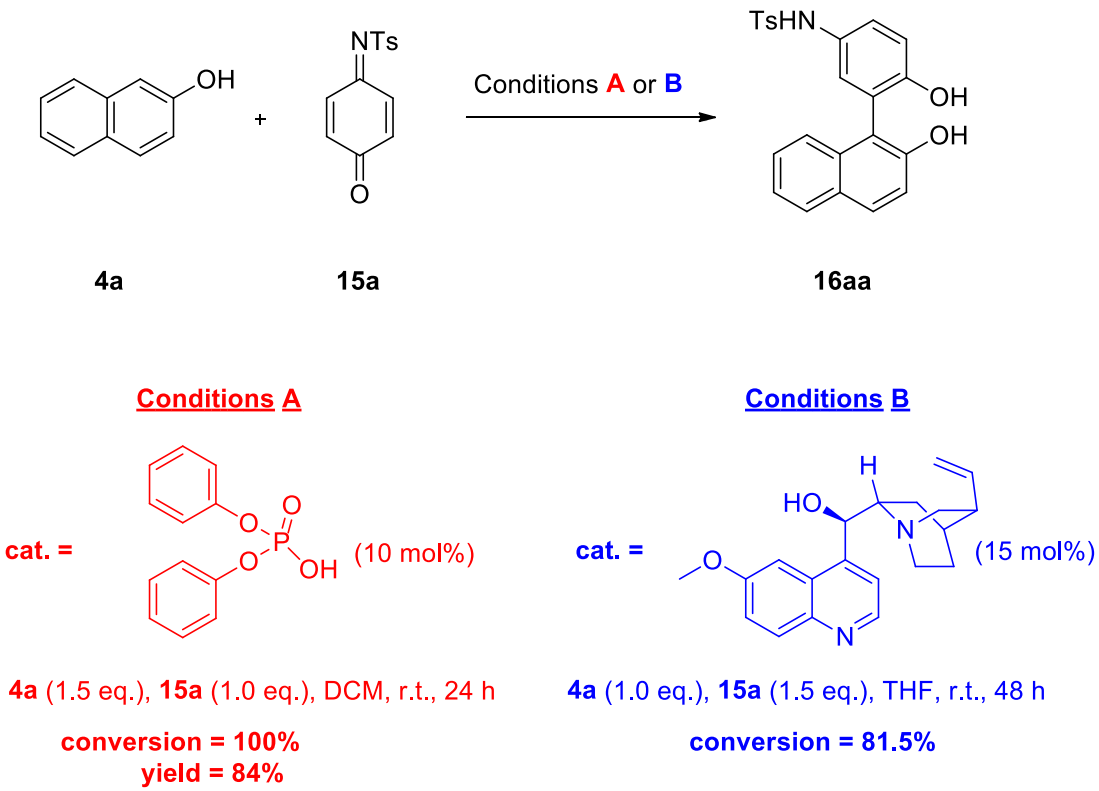
Scheme 3.40 *Attempts of enzymatic selective monoacetylation of biaryl* ***6ca***

Solvent [a]	Acyl donor	Time (d)
Vinyl acetate	Vinyl acetate	10
Chloroform	Vinyl acetate	10
Ethyl acetate	Ethyl acetate	10
TBME	Vinyl acetate	11
DMSO	Vinyl acetate	10
DMF	Vinyl acetate	10

[a] The solvent was pre-equilbrated in a sealed container over a saturated $MgCl_2$ aqueous solution (a_w= 0.32)

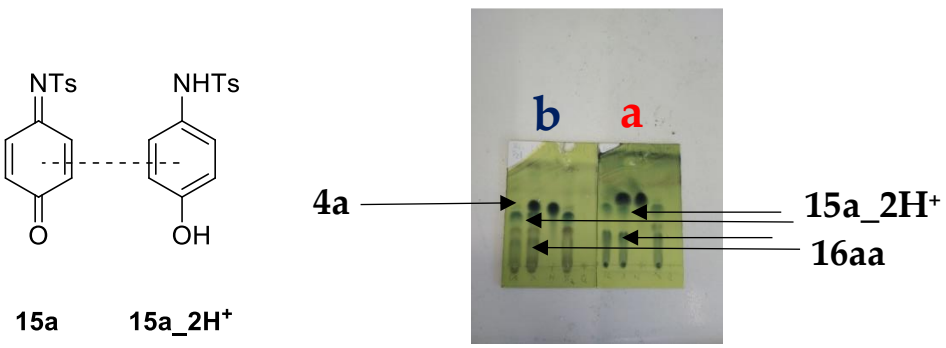
Table 3.3 *Solvent and acetyl donor screening on reaction conditions C*[94] *for biaryl* ***6ac***

In order to avoid additional protection steps, the possibility of employing N-tosyl monoiminoquinones **15** was taken under consideration and a comparative synthesis of simple biaryl **16aa** under basic (quinine) and acid (diphenylphosphoric acid, DPPA) was performed (scheme 3.41).



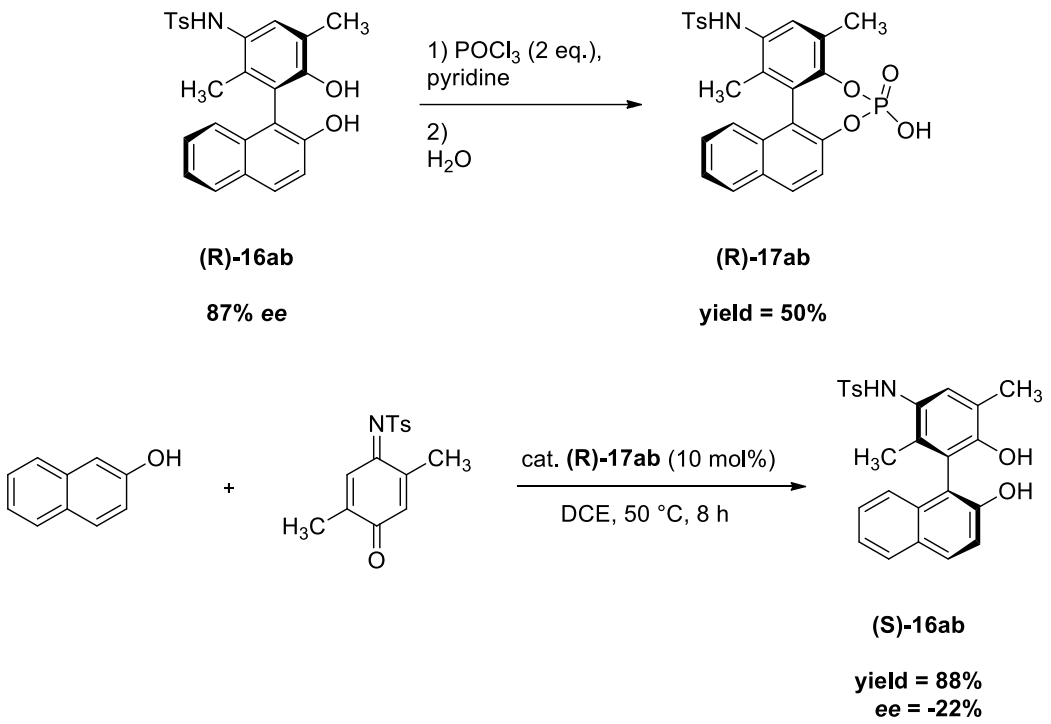
Scheme 3.41 *Comparative synthesis of biaryl **16aa** under acid and basic catalysis*

Acid-catalyzed coupling afforded the product in 84% yield, while from the crude of the base-catalyzed coupling it was possible to estimate a conversion of 81.5%, on the basis of recovered naphthol (**4a**), after column chromatography. In the latter case, **16aa** was isolated in mixture with N-tosyl p-aminophenol (**15a_2H**$^+$), the reduced form of iminoquinone **15a**. In fact, benzoquinones and their derivatives spontaneously reduce to hydroquinones and the two redox partners cohexist in a π-adduct.[105] This behavior of iminoquinones accounts for incomplete conversion of **4a**, following procedure A. Looking at TLC of the crude in the reaction conditions A and B is reported, protocol A appears more convenient (scheme 3.42).



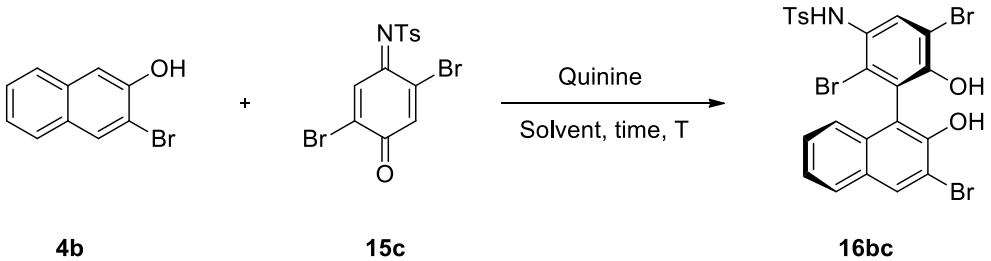
Scheme 3.42 *TLC of the crude in conditions A and B, and π-redox pair adduct of iminoquinone **15a***

At this stage, a patent application from Gao and Kürti was found in the literature, reporting, among other things, the proof of concept of non-C_2 symmetric chiral phosphoric acids as organocatalysts.[106] The synthetic approach to the scaffold is based on (R)-TRIP-catalyzed atroposelective coupling of β-naphthols with N-tosyl iminoquinones; the same biaryl coupling was used as a test reaction for the phosphoric acid obtained this way (scheme 3.43).



Scheme 3.43 *Proof of concept of synthesis and application of non-C_2 axially chiral phosphoric acids as organocatalysts*

Despite the enantioselectivity of the reaction catalyzed by **(R)-17ab** is not good and significative improvements could be done on the scaffold, in order to obtain performing phosphoric acid catalysts, the innovation of disfruiting a non-C_2 symmetric BINOL-like substrate was now lacking and room for improvement was very limited. The most challenging way to make a step forward would be to perform the quinine-catalyzed synthesis of biaryl **16bc** in high degree of enantioselectivity (scheme 3.44).

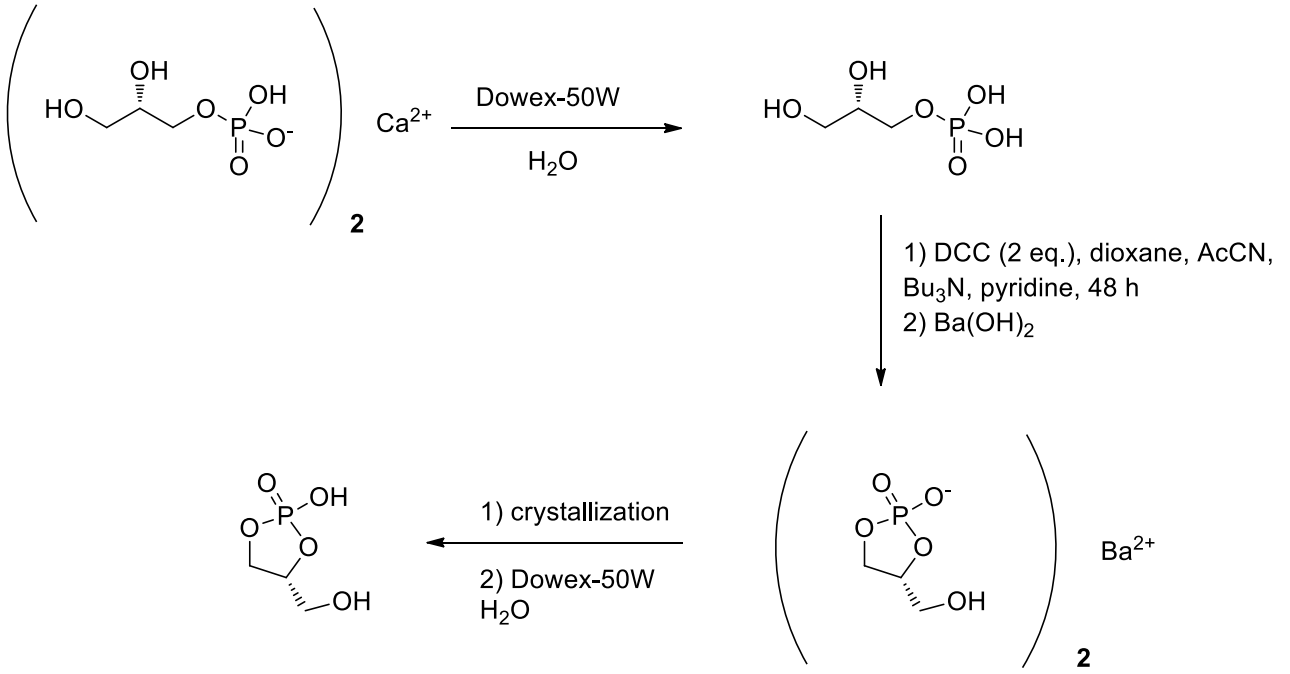


Scheme 3.44 *Ideal atroposelective synthesis of biaryl **16bc***

Biaryl **16bc** is provided with 3,3'-bromine substituents, which could be further disfruited to introduce bulky groups. However, the reaction conditions should be re-optimized, biaryl **16bc** could be not recrystallizable and quinine could be not the best catalyst. Moreover, iminoquinone **15c** is not commercially available and, like other iminoquinones, could be not air-stable. All of these issues were discouraging in pursuing this aim, so this project was set aside.

3.6.2 Synthesis of punctually chiral phosphatidic acids

Reutilisation of calcium 1-glycerophosphate isolated as a byproduct of soy lecithin processing was interesting in the perspective of the 7th principle of green chemistry (use of renewable feedstocks). Moreover, phosphatidic (cycloglycerophosphoric) acids were never employed in organocatalysis, despite the availability of literature procedures for the cyclization of 1-glycerophosphoric acid[83] and for the phosphorylation of glycerol-derived diols. Following Fordham and Wang protocol,[83d] compound **21_Ca^{2+}** was passed over a pad of Dowex-50W cationic exchange resin, to afford the corresponding glycerol-1-phosphoric acid (**21**). Compound **21** was then lyophilized and treated with DCC in a mixture of dry solvents constituted by dioxane, acetonitrile, pyridine and tri-*n*-butylamine in ratio 1.0:1.0:0.1:0.2. DCC-promoted dehydration leads to cyclization of compound **21**; then cycloglycerophosphoric acid **22** should have been precipitated with $Ba(OH)_2$ in the form of its barium salt, and finally passed over Dowex-50W resin to recover pure **22** (scheme 3.45).



Scheme 3.45 *Literature protocol for the cyclization of glycerol-1-phosphoric acid*

However, upon treating with $Ba(OH)_2$, precipitation did not occur. After bubbling CO_2 in the solution to precipitate the excess of barium as $BaCO_3$, the aqueous phase was lyophilized. On the basis of ^1H NMR analysis of the resulting white solid, the formation of a mixed salt, having Ba^{2+} and tri-*n*-butylammonium as counteranions, was hypothesized. In fact, two multiplets in the regions 1.75–1.62 ppm and 1.28-1.42 ppm and a triplet at 0.95 ppm, belonging to tri-*n*-butylamine, could be observed (figure 3.11).

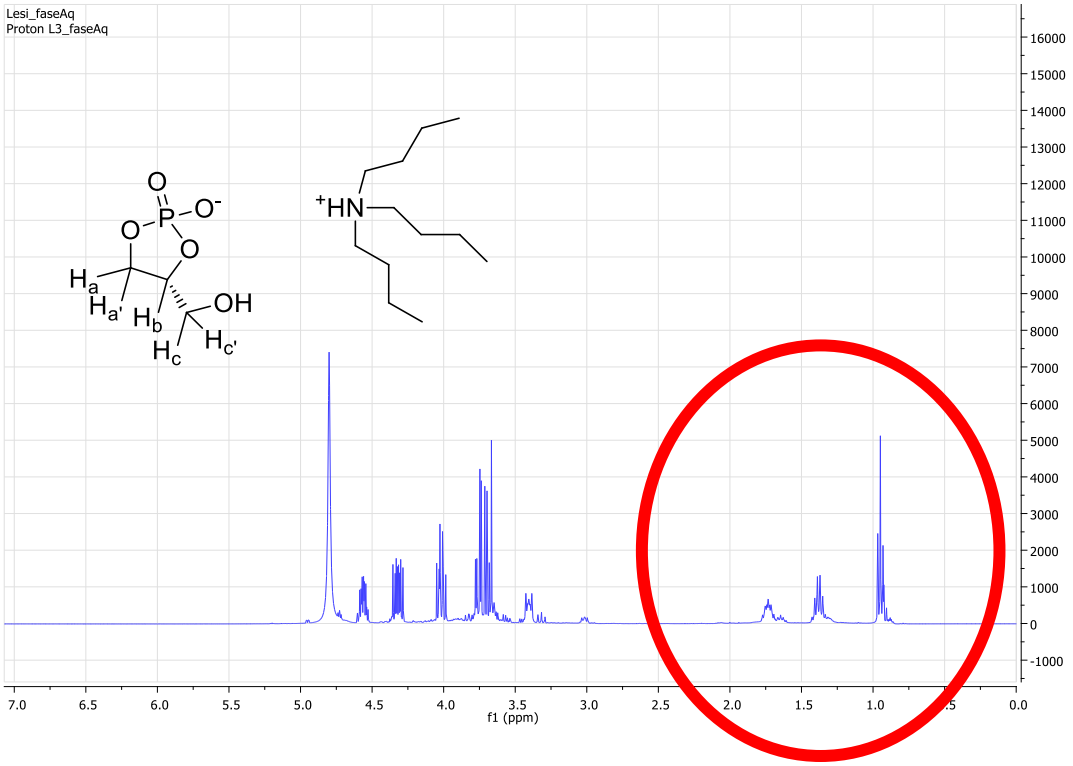


Figure 3.11 *^1H NMR (400 MHz) in D_2O of mixed salt of compound* **22**. *Signals from tri-n-butylammonium are highlighted in red*

Looking at the region between 3.50 ppm and 4.79 ppm (figure 3.12), characteristic signals of the protons belonging to the phosphoric diester ring can be identified:

- The multiplet belonging to the proton on the stereogenic center (H_b), due to coupling with diastereotopic protons H_a, $H_{a'}$, H_c, $H_{c'}$ and P in the region 4.62 – 4.51 ppm. Deconvolution of the multiplet reveals it is a qdq;
- Two AA'BC systems at 4.32 ppm and 4.03 ppm, due to the diastereotopic protons H_a and $H_{a'}$;
- Two double doublets with roof effect in the region 3.77 – 3.66 ppm, due to mutual coupling of diastereotopic protons H_c and $H_{c'}$ and their coupling with proton H_b.

Moreover, relative integral ratio 1:1.39 between the multiplet relative to proton H_b and the triplet at 0.95 ppm, relative to 9 protons of terminal methyl groups from the alkyl chains of tri-*n*-butylamine, allows to estimate that about 15.5% of the phosphate anion is present as

tri-*n*-butylammonium salt. Finally, ^{31}P NMR analysis shows one major signal at 18.03 ppm, which is another good index of the formation of a five-membered phosphoric diester ring. In fact, ^{31}P NMR signal prediction is not straightforward as well as for ^{1}H and ^{13}C NMR. Indeed, chemical shift values from ^{31}P NMR spectra of new compounds are generally compared to those of similar known compounds, taken from proper databases. By relying on this general methodology, chemical shifts of phosphorous atoms in a five-membered phosphoric diester ring are in the range 15-20 ppm.[107]

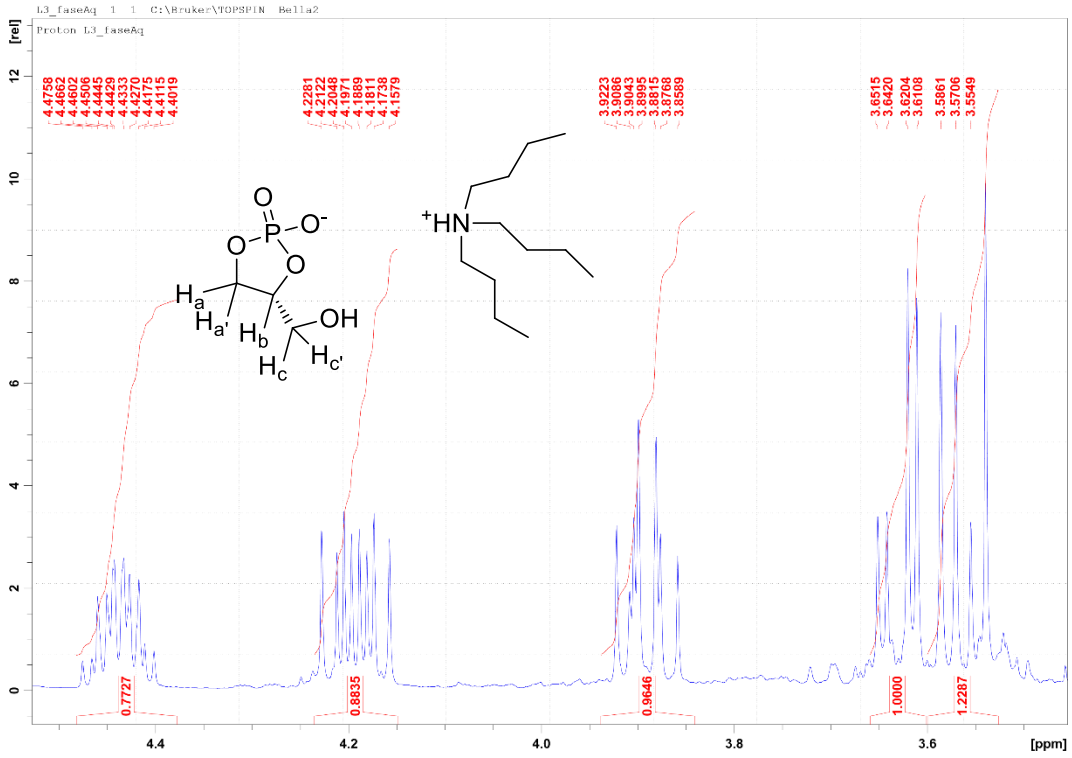


Figure 3.12 *Zoom on the ^{1}H NMR (400 MHz) signals (in D_2O) of mixed salt of compound* **22**

Crystallization of the mixed salt was not successful, so ionic exchange on Dowex-50W resin was directly performed, avoiding the previous step. Even in this case, the procedure was not successful, since ^{1}H NMR and ^{13}C NMR spectrum of the sample after ionic exchange were very different from those expected from phosphoric acid diester **22**. In particular, a region of ^{1}H NMR spectrum of the sample after ionic exchange can be perfectly overlapped to ^{1}H NMR spectrum of glycero-1-phosphoric acid **21** (figure 3.13). Moreover, in ^{13}C NMR spectrum of compound 22 after ionic exchange it was evident the presence of more than 3 carbon signals, as expected.

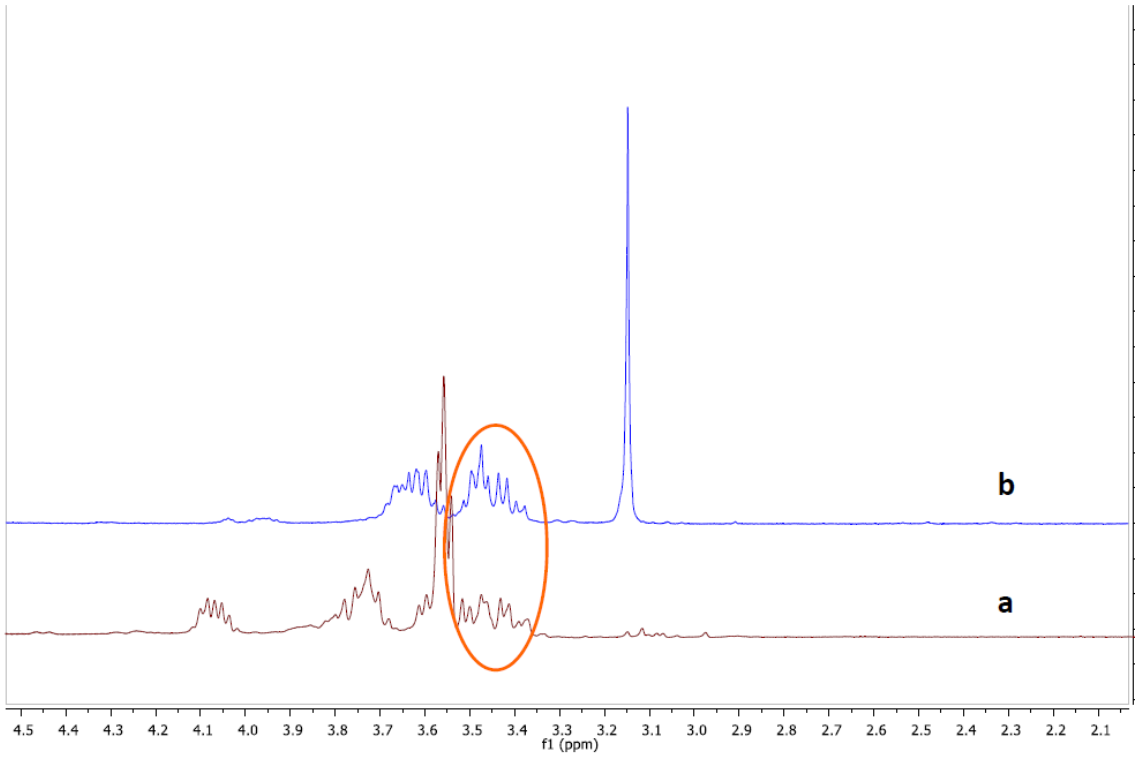
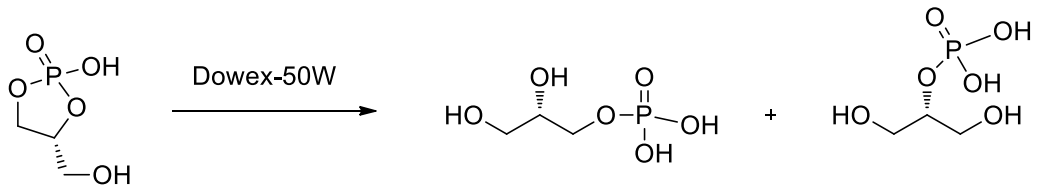


Figure 3.13 *Overlapping of ^{1}H NMR (400 MHz) spectra of **21** (b) and **22** after ionic exchange (a)*

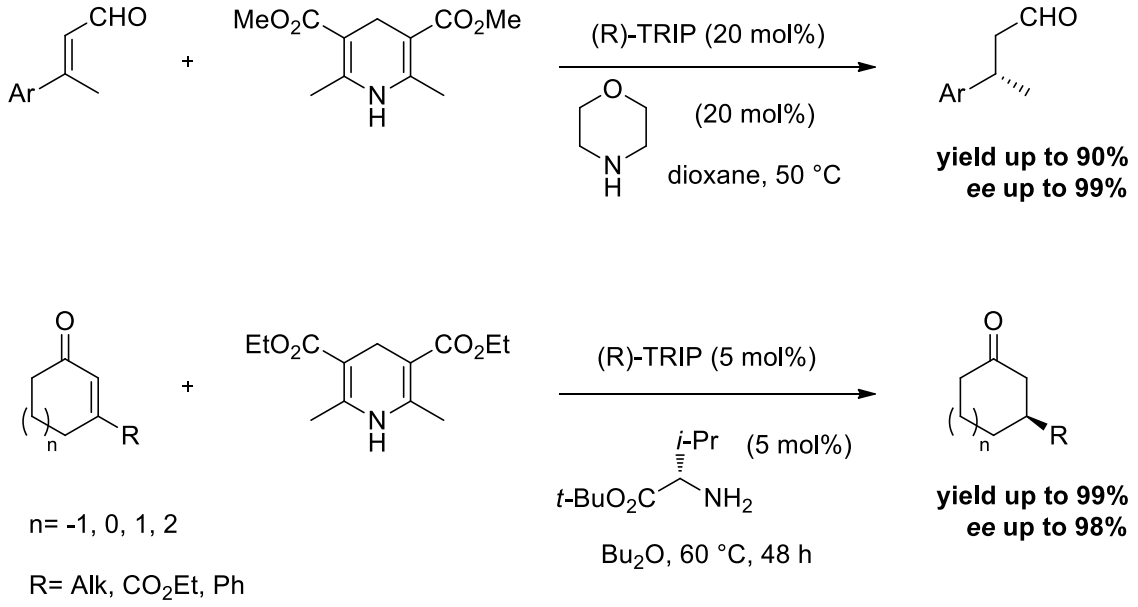
The most likely hypothesis was the acid hydrolysis of phosphoric acid diester, which is known to occur below pH = 3,[108] to give compounds **21** and **23** (scheme 3.46).



Scheme 3.46 *Hypotesis of effective outcome of the ionic exchange step*

Since the preparation of tri-*n*-butylammonium salt was straightforward, while it was not possible to obtain pure barium salts, nor to convert the mixed salt into the acidic form, the possibility of modifying Fordham and Wang protocol by replacing tri-*n*-butylamine with other amines was taken into consideration. In this case, the aim was to obtain a salt that could be used itself as a catalyst following one among two general: Chiral Multiple Catalysis (CMC) or Asymmetric Counteranion Directed Catalysis (ACDC). CMC is catalysis by two (or more than two) nonracemic chiral subunits brought together by noncovalent bonds.[109]

Salts constituted by enantiopure cation and anion fall into this category, whose general advantage is that chemical synthesis is not required, so that several new catalytic systems are easily available simply by differently combining libraries of chiral acids and chiral amines. In the case of chiral salts from soy lecithin processing, a few steps are required for isolation of calcium gycero-1-phosphate (**21_Ca**$^{2+}$), acidification by ion exchange resin and cyclization in the presence of the amine, although the overall process requires enough time because of reaction duration and solvent removal (*e. g.* lyophilization). Indeed, ACDC requires the presence of ion pairing between two subunits, in which just the anion is the chiral nonracemic species. The concept of ACDC was first introduced by Arndtsen in 2000,[110] and then formalized by List,[111] who applied it in asymmetric organocatalysis disfruiting BINOL-phosphoric acids. In the case of ACDC, the salt of a primary or secondary amine is required, in order to ensure activation *via* iminium ion: the racemic or achiral amine serves to form the imine, while the chiral acid provides both the chiral environment and the acidic proton which catalyzes imine formation. An example is asymmetric reduction of α,β-unsaturated carbonyl compounds with Hantschz esters (NADH synthetic analogues) catalyzed by (R)-TRIP salts with morpholine or L-valine *t*-butyl ester (scheme 3.47).[112,113]



Scheme 3.47 *Two examples of ACDC organocatalytic asymmetric reduction of α,β-unsaturated carbonyl compounds*

Morpholine (**24**), quinine (**25**) and 2,2,6,6-tetramethylpiperidine (**26**) were selected among the amines immediately available in the laboratory. The cyclization reaction was performed on the commercially available racemic magnesium salt of compound **21**, after cationic exchange on Dowex-50W resin, in a mixture of dry solvents constituted by dioxane and acetonitrile and with 3 equivalents of amine (in the case of 2,2,6,6-tetramethylpiperidine **26**, separation of unreacted amine from the products was easier employing 1.1 equivalents of

26 in the cyclization step of the selected amine). Reaction with morpholine (**24**) did not afford any cyclic product, since the only signals exhibited by ^{1}H NMR were those from compounds **21** and **24**, while a singlet belonging to the phosphorous atom of compound **21** constituted ^{31}P NMR spectrum. On the contrary, cyclization reactions in the presence of amine **25** or **26** leads to cyclic phosphate salts, despite in low purity. Upon treating the reaction crude with $Ba(OH)_2$ and CO_2, precipitation of barium salt of **21** and $BaCO_3$ did not occur, but ^{1}H NMR spectrum of the lyophilized aqueous phase exhibited two characteristic multiplets at 4.51/4.52 ppm and 4.27/4.28 ppm, belonging to the cyclic phosphate **22**. Other signals of **22** were hidden by impurities, which gave rise to peaks having non-resolved fine structure between 3.45 and 4.10 ppm. The most likely hypothesis was that the sample was constituted from a mixture of salts of **21** and **22**, due to uncomplete cyclization of **21**. Overlapping ^{1}H NMR spectrum of the lyophilized aqueous phases to ^{1}H NMR spectrum of the corresponding amine with glycero-1-phosphoric acid **21** was consistent with this scenario (figure 3.14). Moreover, the hypothesis was also supported by ^{13}C NMR and ^{31}P NMR spectra; in particular, the presence of two appropriate ^{31}P NMR peaks (δ 16.48, 1.79 ppm for quinine salt in D_2O; δ 16.88, 0.46 ppm for 2,2,6,6-tetramethylpiperidine salt in DMSO) was considered a good experimental evidence.

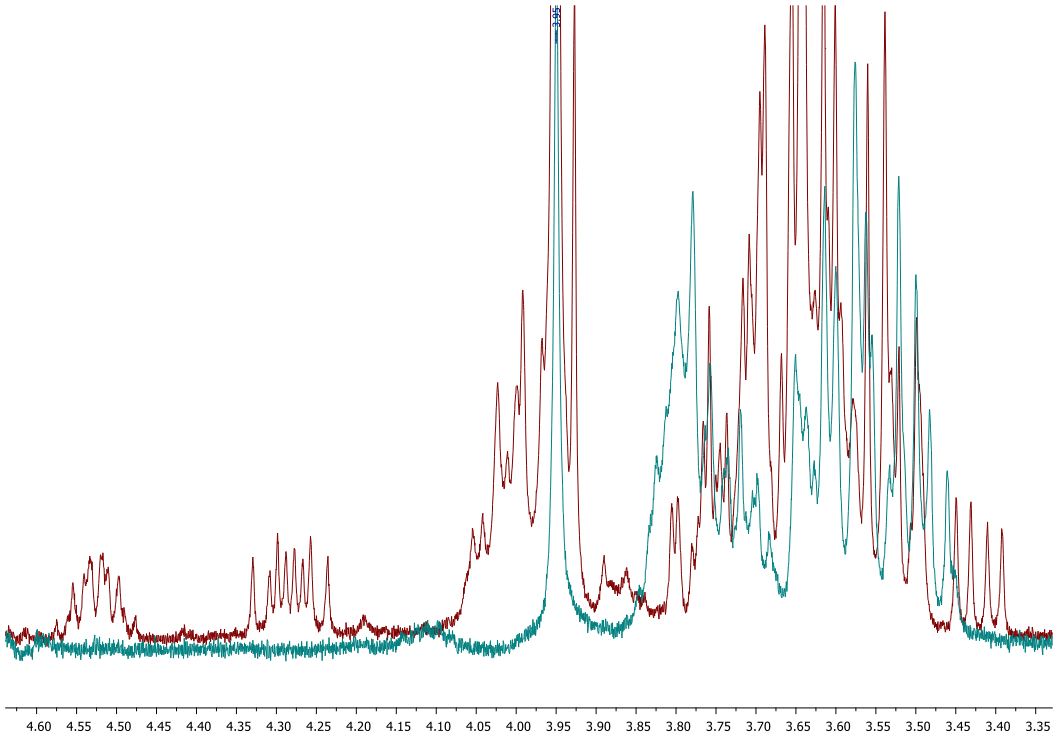
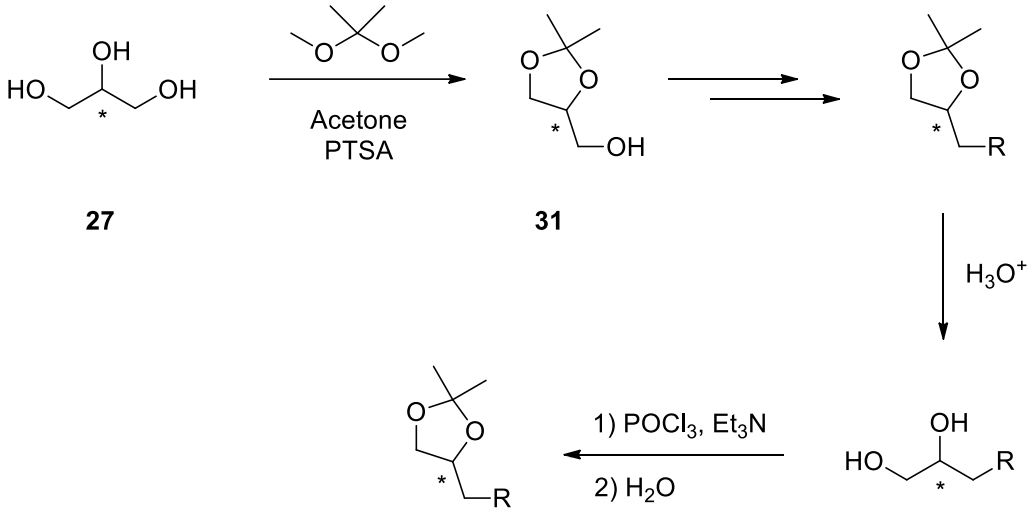


Figure 3.14 *Overlapping of ^{1}H NMR (300 MHz) spectra of lyophilized aqueous phase of cyclization in the presence of* **25** *(red) and salt* **21**+**25** *(blue) in the region 3.35-4.60 ppm*

Chromatographic separation of cyclic (**22**) and linear (**21**) glycerophosphate was historically performed by paper chromatography with a mixture of 2-propanol, water and aqueous

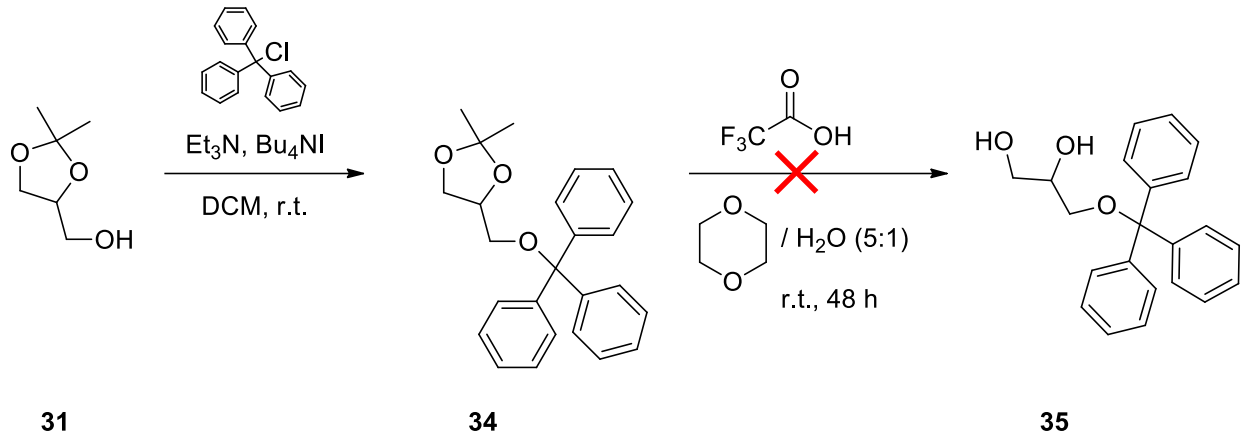
ammonia (30%) in ratio 7:2:1, as the eluent.[83] Phosphate species were then stained, following Hanes and Isherwood method[114] or modified protocols.[115] However, despite two spots having similar RF could be observed by TLC, using plates coated with either silica gel or cellulose, it was not possible to obtain the separation of the compounds by column chromatography on cellulose. Other stationary phases were not taken into consideration, due to the incompatibility with high polar eluents. Moreover, at this stage, it is worth mentioning that the stability of cycloglycerophosphoric acid (**22**) depends not only on the acidity of the aqueous phase,[83a] but also from the temperature. In fact, upon treating compound **22** above 36 °C, a ^{1}H NMR spectrum similar to those obtained after ionic exchange on Dowex-50W resin was observed (see figure 3.13). Since the presence of a free hydroxyl group in the scaffold of compound **22** can potentially give anchimeric assistance to phosphate cyclic diester hydrolysis, thus contributing to its instability, a different strategy for the synthesis of punctually chiral glycerophosphoric acid derivatives was carried out (scheme 3.48).



Scheme 3.48 *General synthetic route for glycerophosphoric acid derivatives*

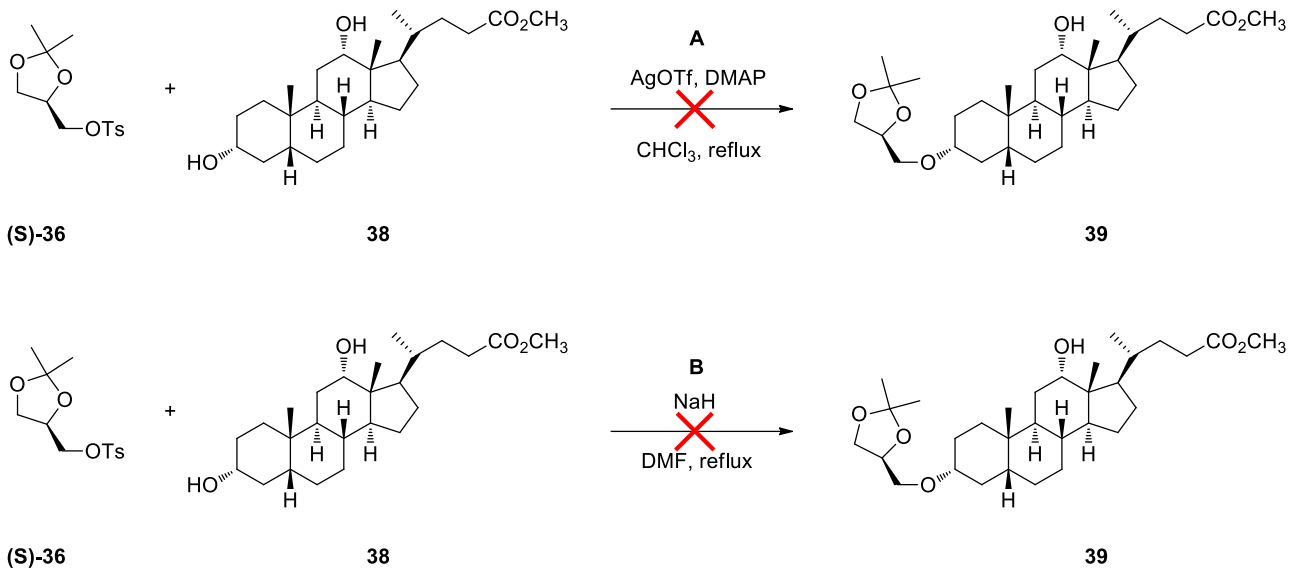
The aim of the new strategy was to obtain more stable glycerophosphoric acid derivatives. Moreover, the functionalization offers the possibility of incrementing the degree of asymmetric induction, which is promoted by orientation and proximity to the catalytic site (phosphoric acid): in fact, appropriate substituents can be choosen because of their steric hindrance, chirality or presence of further binding sites for substrates. Compound **(±)-31** was employed as the model substrate during the protecting group screening for free hydroxyl group, because of its lower cost. Protecting agents were choosen on the basis of cost, availability in the laboratory, straightforwardness of functionalization reactions in mild reaction conditions, steric bulk and presence of possible binding sites for substrates. Trityl chloride was the first reagent to be employed because of its bulk; following a literature procedure[116] it was possible to isolate trityl solketal (**34**) in 71% yield. Different procedures

were available in the literature[117] for selective ketal hydrolysis on compound **34**, based on lithium tetrafluoroborate,[117d] lanthanum nitrate,[117f] oxone and microwave irradiation[117e] or highly diluted trichloroacetic acid in a 5:1 mixture dioxane/water.[117a-c] Despite the latter protocol was the most outdated, it was selected because of its feasibility with low efforts and avoiding the employment of rare-earth species, replacing unavailable trichloroacetic acid (pK_a= 0.7) with slightly more acidic trifluoroacetic acid (pK_a= -0.25). Compound **35** could not be isolated (scheme 3.49), but glycerol **27** and aromatic peaks belonging to trityl group (probably due to the formation of trityl alcohol) were observed in ^{1}H NMR spectra of different chromatographic fractions. The most likely hypothesis was the simultaneous hydrolysis of ketal and trityl ether, whose lability can be ascribed to the formation of a highly stabilized trityl carbocation under acidic conditions. Consequently this protecting group was set aside, in order to avoid further issues connected to trityl ether fragility in the presence of an acidic phosphoric acid group on the same scaffold.



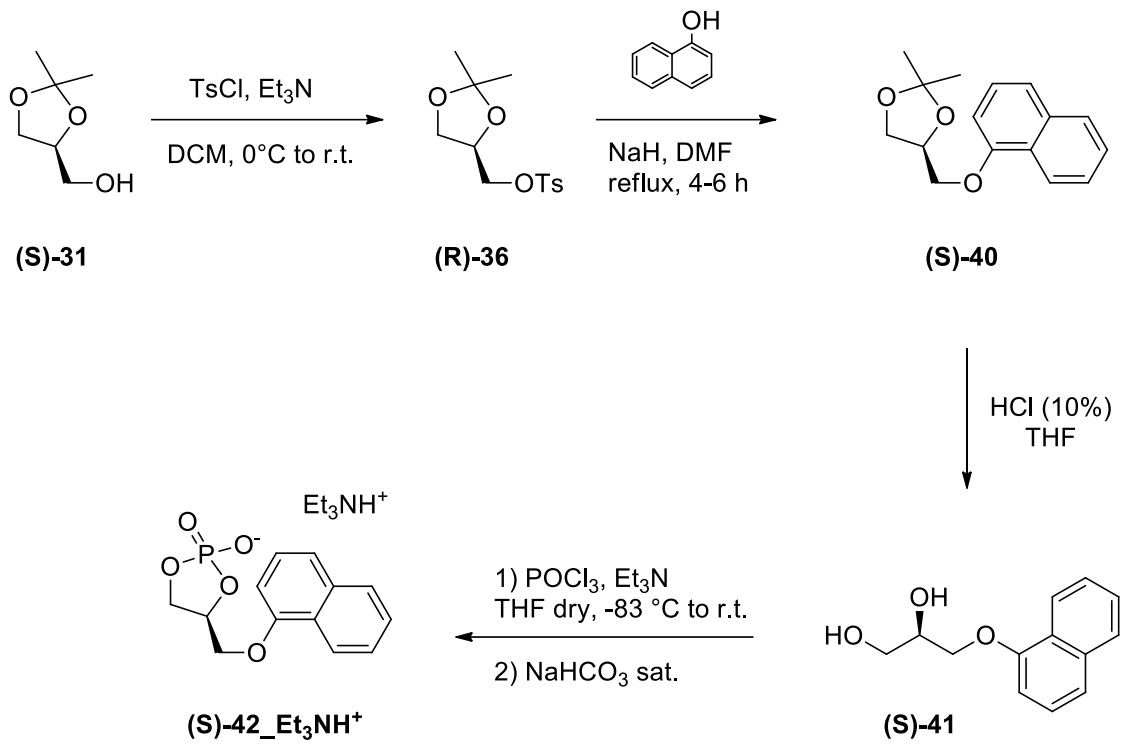
Scheme 3.49 *Synthetic route for O-trityl glycerol **35***

Another interesting protecting group is represented by bile acids. Apart from steric bulk, their properties include the presence of an extended chiral backbone, whose amphiphility could be disfruited to create chiral organocatalysts capable of working in water. Unfortunately, attempts of etherification on (S)-tosyl solketal (**36**) with methyl ester of deoxycholic acid (**38**) were not successful (scheme 3.50). However, Williamson reaction for the synthesis of ethers is particularly difficult for bile acids derivatives, and just a single procedure was found in the literature.[118] Nevertheless, different linkers could be introduced, in order to obtain phosphoric acid functionalized with bile acids, for a new confinement strategy in organocatalysis.



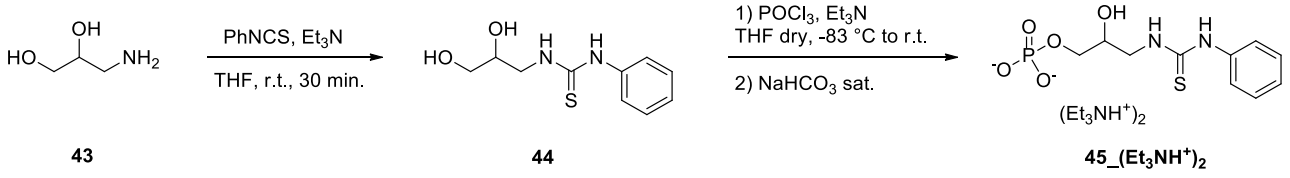
Scheme 3.50 *Attempts to functionalize (S)-solketal (**31**) with deoxycholic acid methyl ester through ether formation*

In the meanwhile, two protecting groups were found to be suitable to resist until phosphorylation step. The first protecting group was 1-naphtyloxy ether, which could be introduced in high yield on compound **31** over 2 steps. On the contrary, ketal hydrolysis was not completely selective, and compound **41** was isolated in low yield (45%). Final phosphorylation step was performed at -83 °C in dry THF with 10 equivalents of $POCl_3$ and 10 equivalents of triethylamine as the base. It is worth mentioning that previous phosphorylation attempts carried out at room temperature were not selective (formation of several phosphorylated species was observed by TLC and ^{31}P NMR) and the definitive phosphorylation protocol was optimized taking inspiration from a literature procedure.[119] In particular, pyridine was replaced by triethylamine and the temperature was set to -83 °C. Pure triethylammonium salt of phosphoric acid **42** was afforded by column chromatography on silica gel with ethyl acetate/methanol 3:1 as the eluent. ^{31}P NMR spectrum consisted of a peak at 15.33 ppm, in compliance with the formation of a cyclic phosphoric acid diester. Once the synthetic route was proven to be successful on **(±)-31**, it was carried out again on pure **(S)-31** as the substrate (scheme 3.51).



Scheme 3.51 *Synthetic route to triethylammonium salt of phosphoric acid* ***42***

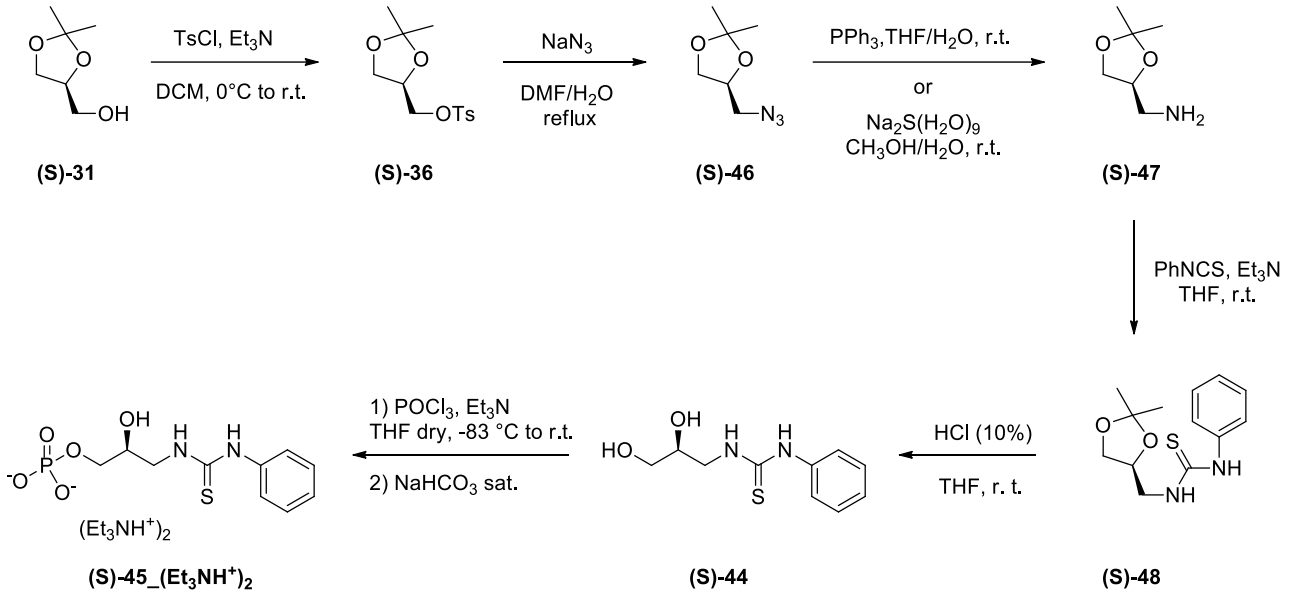
The second protecting group was N-phenylthiourea, which was choosen because thiourea structural motif is known to be a good binding site for substrates, both as acceptor or donor of hydrogen bonding. Racemic chiral glycerol derivative 3-amino-1,2-propanediol (**43**) is cheap and commercially available. Its conversion into thiourea **44**, which proceeded *via* reaction with phenylisotiocianate, in the presence of catalytic amounts of triethylamine at room temperature, was complete over 20 minutes. Phosphorylation step, carried out in the same conditions of diol **41**, afforded pure triethylammonium salt of compound **45** as the major compound after column chromatography on silica gel with methanol/ethyl acetate 2:1 as the eluent (scheme 3.52).



Scheme 3.52 *Synthetic route to triethylammonium salt of phosphoric acid* ***45***

In the case of the enantiopure substrate, it was necessary to perform a 5-steps one-pot conversion of compound **(S)-31** into thioureidic derivative **(S)-48**. Solketal tosylation,

followed by nucleophilic substitution with sodium azide and reduction to amine **(S)-47** was performed following a literature procedure.[120] Thiourea **(S)-48** was easily prepared in the same conditions. Selective ketal hydrolysis was also in this case a critical point, and product **(S)-44** was isolated in 31% yield. The overall process is depicted in scheme 3.53.



Scheme 3.53 *Synthetic route to triethylammonium salt of enantiopure phosphoric acid* ***(S)-45***

The salt of compound **(S)-45** was not the target product, while the corresponding cyclic phosphoric diester scaffold was expected. However, the observed chemical shift of 1.44 ppm was consistent with the formation of a linear phosphoric ester. Moreover, compound **45** was obtained upon dropwise acidification with 1 M HCl and superimposition of ^{1}H NMR spectra before and after acidification showed a compatibility of the signals, while triethylamine peaks disappeared (figure 3.15).

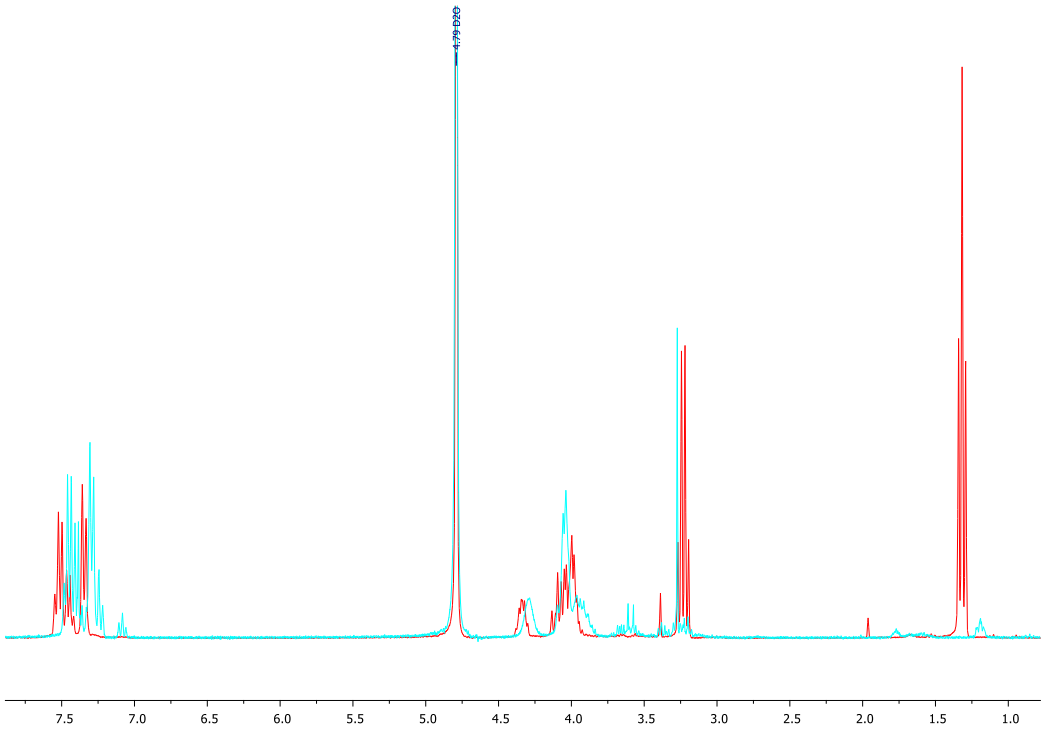


Figure 3.15 *Superimposition of ^{1}H NMR (300 MHz) spectra of compounds* ***45_(Et$_3$NH$^+$)$_2$*** *and* ***45***

Finally, the acquisition of ^{31}P NMR spectrum in the presence of ^{31}P-^{1}H coupling confirmed the structure of compound **45**. In fact, the observed triplet with coupling constant $J_{P\text{-}H}$ = 6.2 Hz (figure 3.16) is consistent with the above proposed structure, with a free hydroxyl on carbon C_2 and phosphate on carbon C_1; in the case of a free hydroxyl on carbon C_1 and phosphate on carbon C_2, a doublet would have been observed.

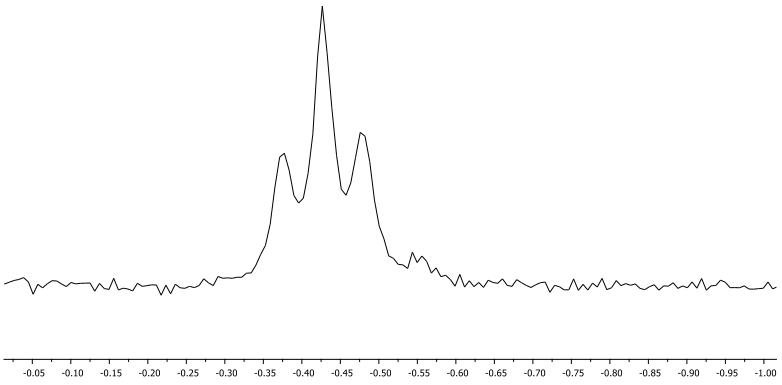


Figure 3.16 *^{31}P NMR (121 MHz) spectrum of compound* ***45*** *in the presence of coupling ^{31}P-^{1}H*

3.7 Conclusions and future perspectives

In the course of this thesis, strategies for the synthesis of new chiral phosphoric acid diester scaffolds have been carried out, looking forward for organocatalytic applications in asymmetric reactions of carbon-carbon bond formation. Since modern organocatalysis mainly relies on the design of engineered catalyst scaffolds for the activation of generally unreactive substrates, the constant demanding for more eco-friendly and less costly catalytic systems was inspiring in the design of more accessible organocatalysts. Particular attention was devoted to avoid, whenever possible, the use of engineered substrates, transition metal species and dangerous reaction conditions, in order to comply with green chemistry principles. Because of the sudden discovery of a patent application, including the structure of the first non-C_2 symmetric axially chiral phosphoric acid, the strategy relying of non-C_2 symmetric biaryls as substrates remained unaccomplished. However, on a different front, the approach to the synthesis of unexplored punctually chiral organocatalyst from natural feedstocks (soy lecithin, glycerol, D-mannitol and L-erythrulose) was engaged. Cyclization reaction carried out on soy lecithin derivative gycero-1-phosphoric acid led to a labile tetrabutylammonium salt of cycloglycerophosphoric acid (**22**). Modification of literature procedures, based on the employment of different amines, resulted in uncomplete cyclization reactions, whose products were not separable by column chromatography on cellulose. Furthermore, glycerophosphate cyclic diester ring was proven to be labile under certain conditions of acidity and temperature. In order to avoid chromatographic separation, cyclization yield should be improved in order to obtain pure cycloglycerophosphoric acid (**22**) salts to employ under CMC or ACDC conditions. The most promising strategy is actually synthesis of phosphoric acid derivatives from solketal. This protocol can give access to both the enantiomer of the final product, employing natural and inexpensive natural products derivatives as the substrates; moreover, the strategy based on the introduction of diverse protecting groups on solketal free hydroxyl group allows to explore different substitution patterns of the chiral backbone. State-of-the-art, enantiopure triethylammonium salts of phosphoric acids **42** and **45** have been isolated. Acidification to the corresponding acids and their application as catalysts of model reactions are currently under investigation.

Future perspectives include the introduction of other protecting groups on solketal, in order to obtain other promising phosphoric acid derivatives; moreover, phosphorylation protocol modifications, based on the replacement of trimethylamine with other amines, have been taken into consideration. The final aim of this work is to isolate phosphoric acid derivatives to employ as organocatalysts in asymmetric synthesis, either with acid catalysis, CMC or ACDC mechanism.

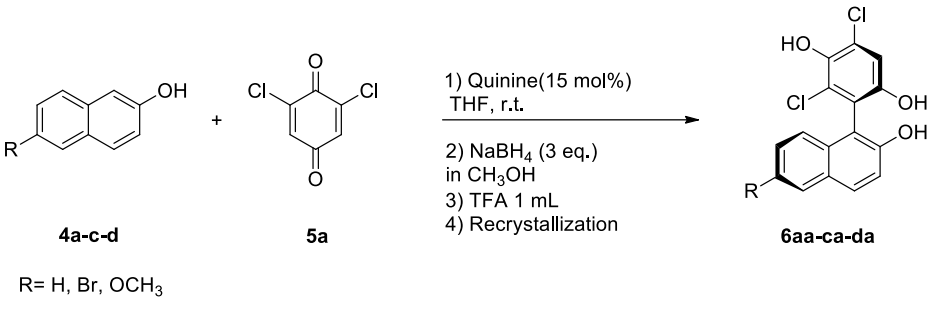
3.8 Experimental section

3.8.1 General information, instruments and materials

Chemicals and solvents were obtained from commercial sources (Sigma Aldrich, Alfa Aesar, Fluorochem, AlaR Normapur) and used as received, unless noted otherwise. Tetrahydrofuran was distilled under argon over Na/K alloy. An IKA® EUROSTAR 200 digital mechanical stirrer was used for soy lecithin processing. An ALC-4237 mechanical centrifuge was used for centrifugation of soy lecithin derivatives and small-scale biaryl phosphorylation crudes. An Analitica De Mori® Heto Dry Winner lyophilizer was used for lyophilization of aqueous samples. ^{1}H, ^{13}C NMR and ^{31}P NMR spectra were recorded on a Bruker 300Avance II spectrometer operating at 300 MHz, 75 MHz and 121 MHz, respectively, or on a Bruker Ultrashield 400 spectrometer operating at 400 MHz, 100 MHz and 161 MHz, respectively, and referenced to the residual solvent signal ($C\underline{H}Cl_3$, δ= 7.26 ppm; $\underline{C}DCl3$, δ= 77.16 ppm; $C\underline{H}_3OH$, δ= 3.31 ppm; $\underline{C}HD_2OD$, δ= 49.00 ppm; $C\underline{H}D_2(SO)C\underline{H}D_2$, δ= 2.50 ppm; $\underline{C}D_3(SO)\underline{C}D_3$ δ= 39.52 ppm; $\underline{H}_2O$, δ= 4.79 ppm). In the case of phosphorous-containing compounds, H_3PO_4 was used as internal standard for ^{31}P NMR spectra ($H_3\underline{P}O_4$ δ= 0.00 ppm). Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 pre-coated glass plates, and preparative flash chromatography was performed using silica gel 60 (0.040-0.063 mm), following Still technique[121] and adapting an aquarium bubbling pump as an air compressor.[122] High-resolution mass spectra were obtained on an ESI-Q-Tof Micro Mass instrument. Enantiomeric excess of chiral compounds was determined by HPLC on chiral stationary phase using CHIRALPAK columns IA, IB, IC, ID, IF with UV spectrofotometer (PDA or single UV) as the detector. Polarimetric measurements were carried out on a Jasco DIP-370 polarimeter, operating at λ= 589 nm; samples were dissolved in chloroform or methanol.

3.8.2 Experimental procedures, ^{1}H, ^{13}C and ^{31}P NMR spectra

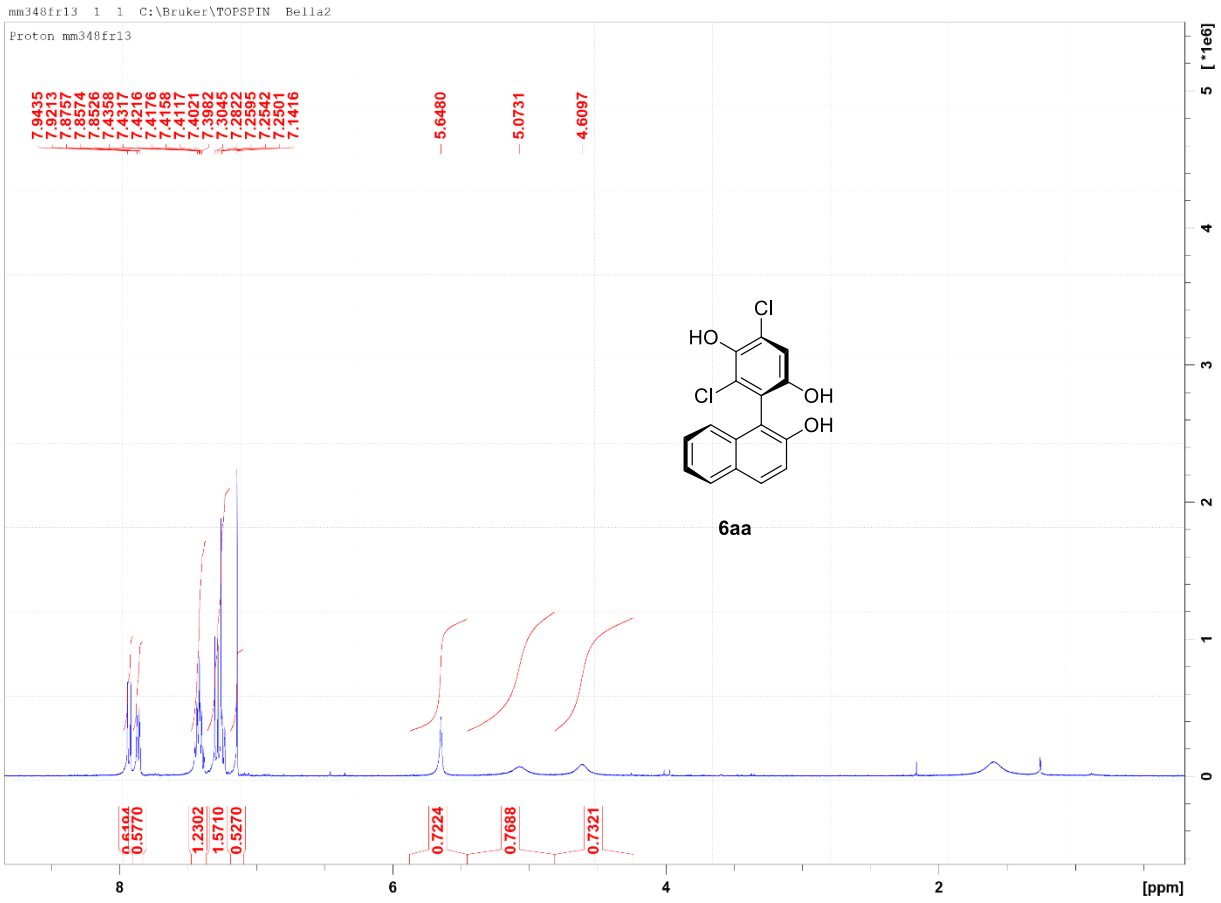
Biaryls 6aa, 6ca and 6da



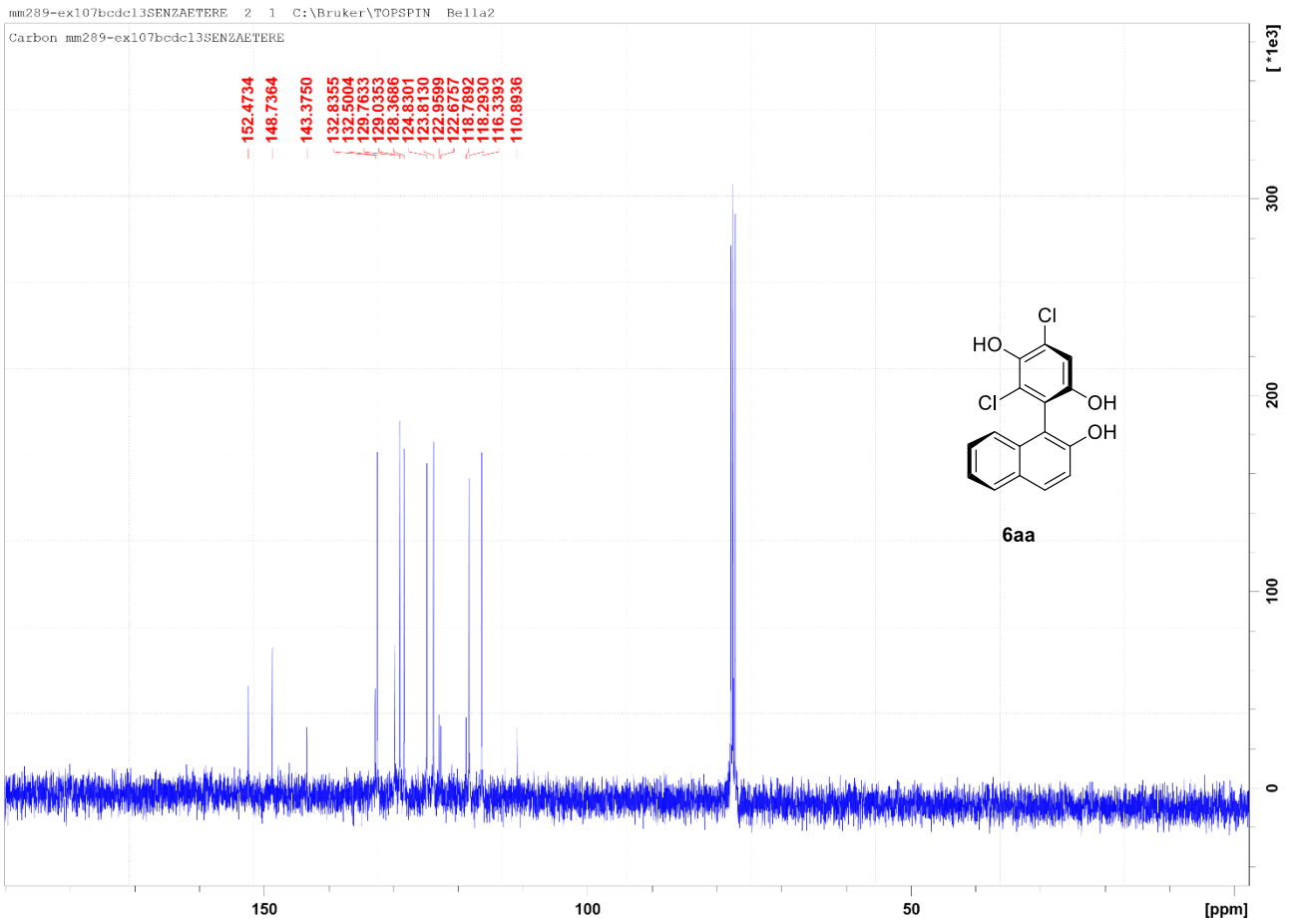
4a-c-d **5a** **6aa-ca-da**

R= H, Br, OCH_3

In a round bottom flask, quinone **5a** (1.5 equivalents) and quinine (0.15 equivalents) were added and dissolved in THF. A solution of β-naphthol **4a**, **4c** or **4d** in THF was added and the reaction was left under stirring until disappearance of the naphthol was observed by TLC. At this stage, 3 equivalents of sodium borohydride were added, followed by dropwise addition of methanol. After the end of development of gaseous hydrogen, 1 mL of trifluoroacetic acid and silica gel were added, the solvent was evaporated under reduced pressure and the crude, immobilized on silica gel, was purified by column chromatography with dichloromethane/diethyl ether as the eluent. The final products could be recrystallized from hot toluene.



^{1}H NMR (400 MHz, $CDCl_3$) 4.64 (br, 1H), 5.12 (br, 1H), 5.66 (br, 1H), 7.13 (s, 1H), 7.26-7.28 (m, 2H), 7.41-7.43 (m, 2H), 7.84-7.87 (m, 1H), 7.91 (d, 1H; J = 8.9 Hz).



^{13}C NMR (100 MHz, $CDCl_3$) δ 110.9, 116.3, 118.3, 118.8, 122.7, 123.0, 123.8, 124.8, 128.4, 129.0, 129.8, 132.5, 132.8, 143.4 148.7, 152.5.

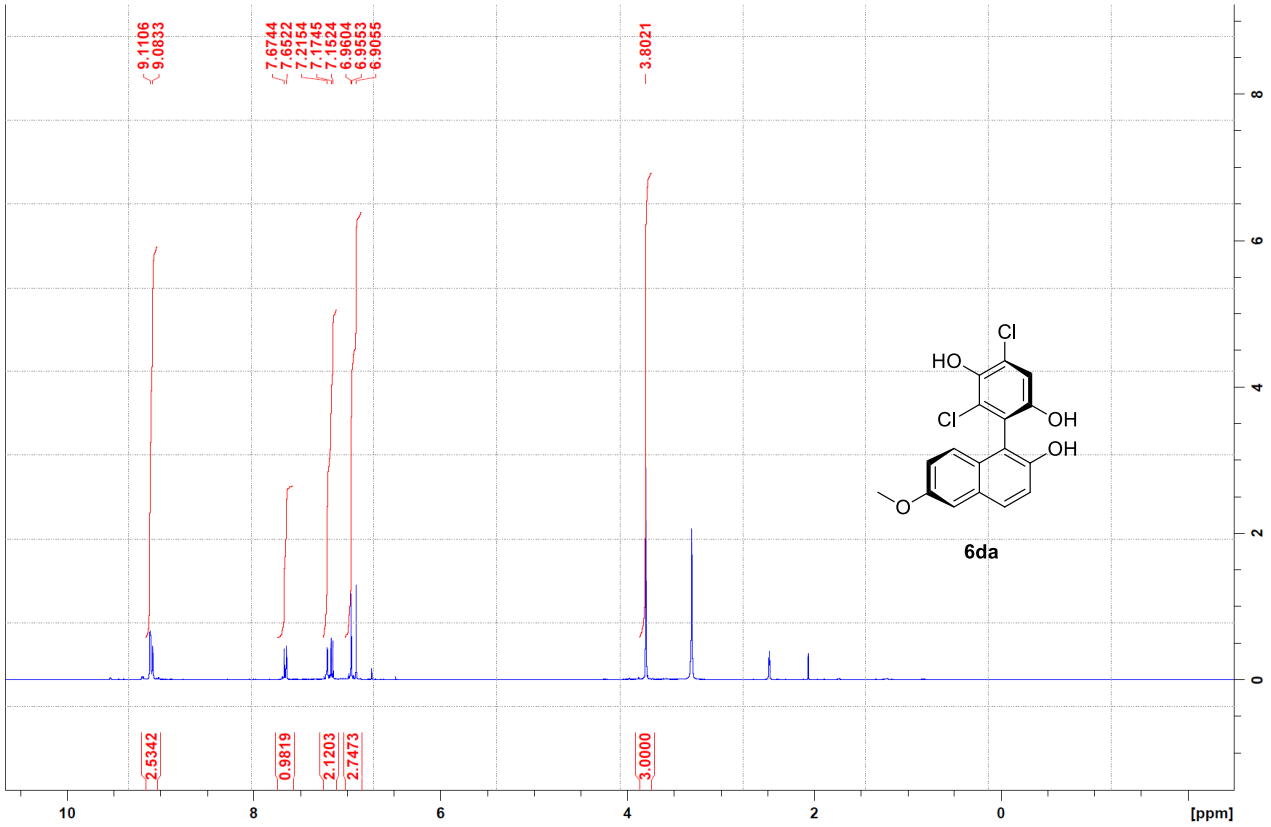
Yield = 91%

R_f = 0.30 (DCM/Et_2O 10:1)

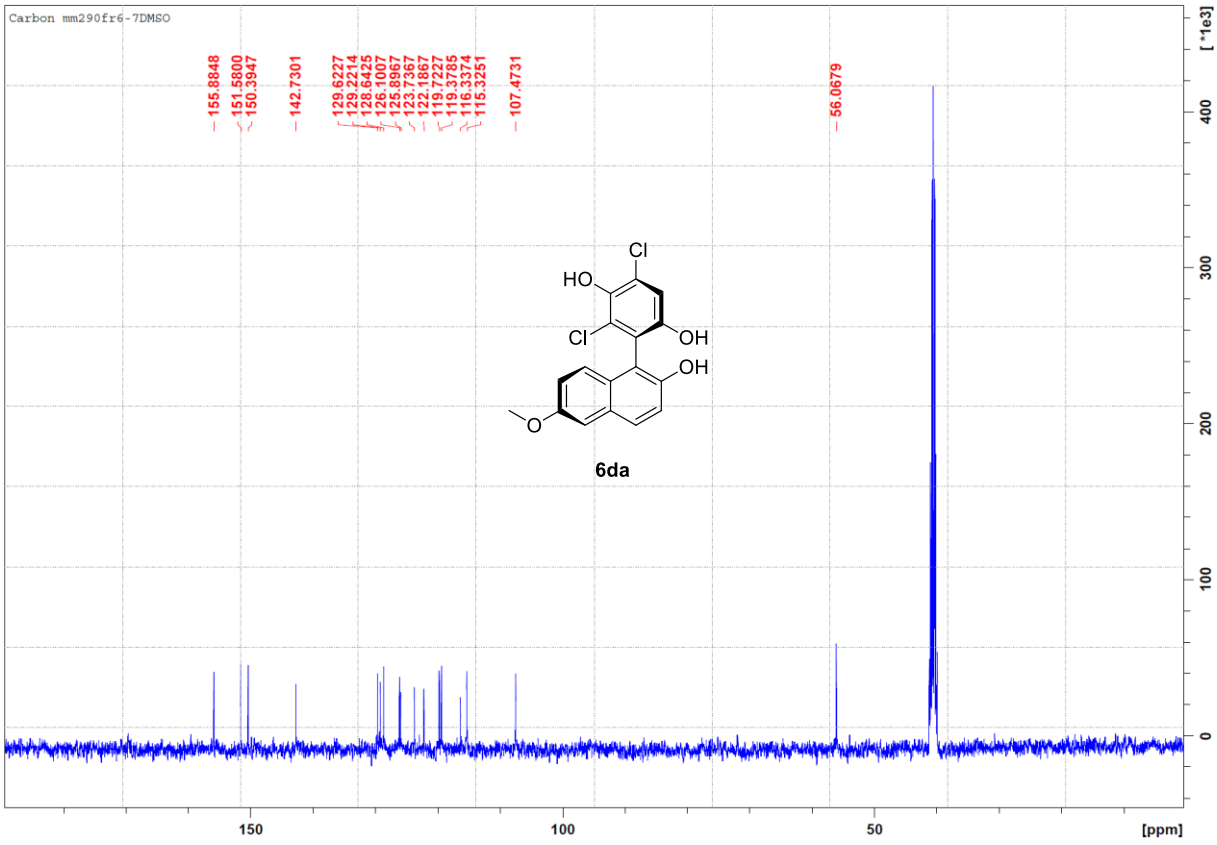
HPLC on CHIRALPAK ID column, eluent n-hexane/2-propanol 88:12, flux rate 0.9 mL/min, τ_1 (minor)= 14,8 min, τ_2 (major)= 17,5 min, ee 76%

POLARIMETRY $[\alpha]_D$ = -2.5° (c 3.4, $CDCl_3$,, ee 76%)

HRMS (ESI-TOF) m/z for $C_{16}H_9Cl_2O_3^-$ $[M-H]^-$ calculated 318.9934, found 318.9931.



^{1}H NMR (400 MHz, DMSO-d$_6$) δ 3.80 (s, 3H), 6.91 (s, 1H), 6.95-6.96 (m, 2H), 7.16 (d, 1H; *J* = 8.8 Hz), 7.22 (s, 1H), 7.66 (d, 1H, *J* = 8.9 Hz), 9.08-9.11 (m, 3H).



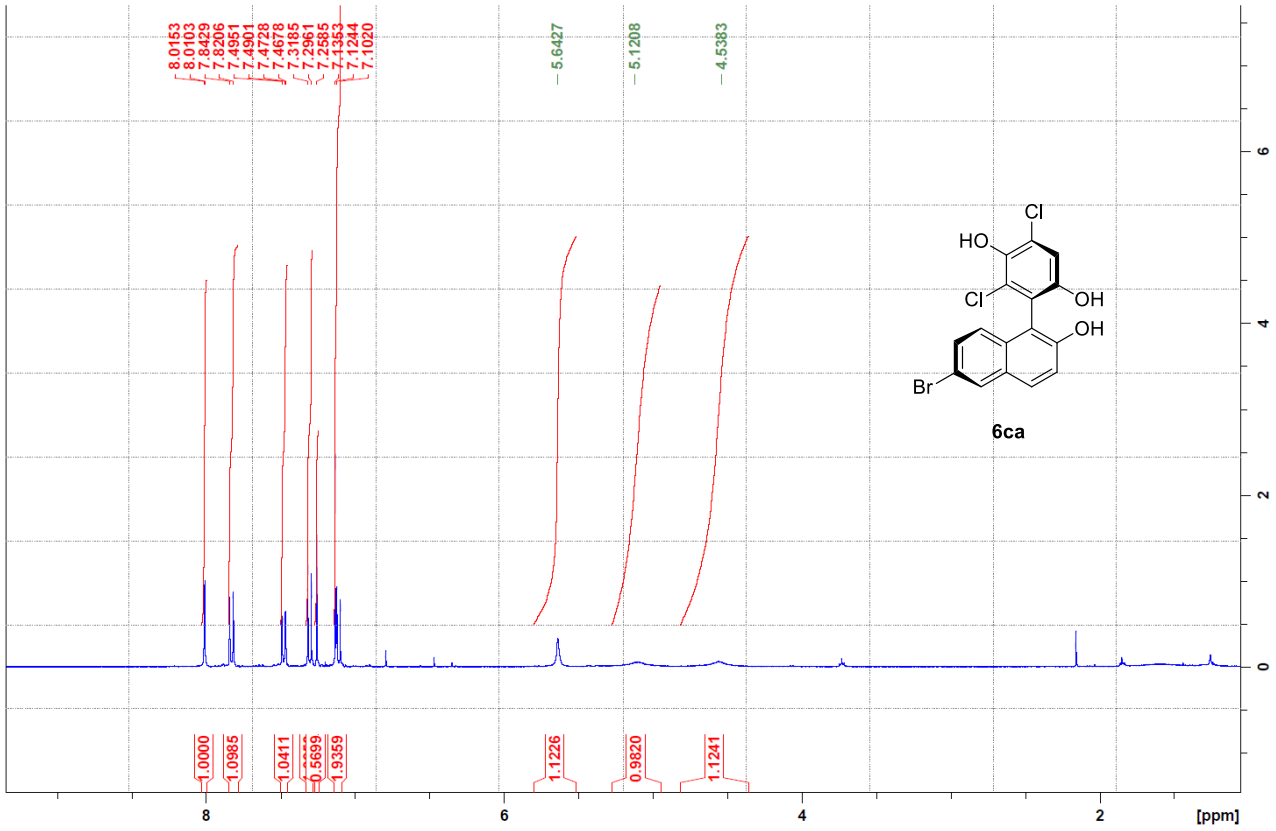
^{13}C NMR (100 MHz, DMSO-d$_6$) δ 56.1, 107.5, 115.3, 116.3, 119.4, 119.7, 122.2, 123.7, 125.9, 126.1, 128.6, 129.2, 129.6, 142.7, 150.4, 151.6, 155.9.

Yield = 43%

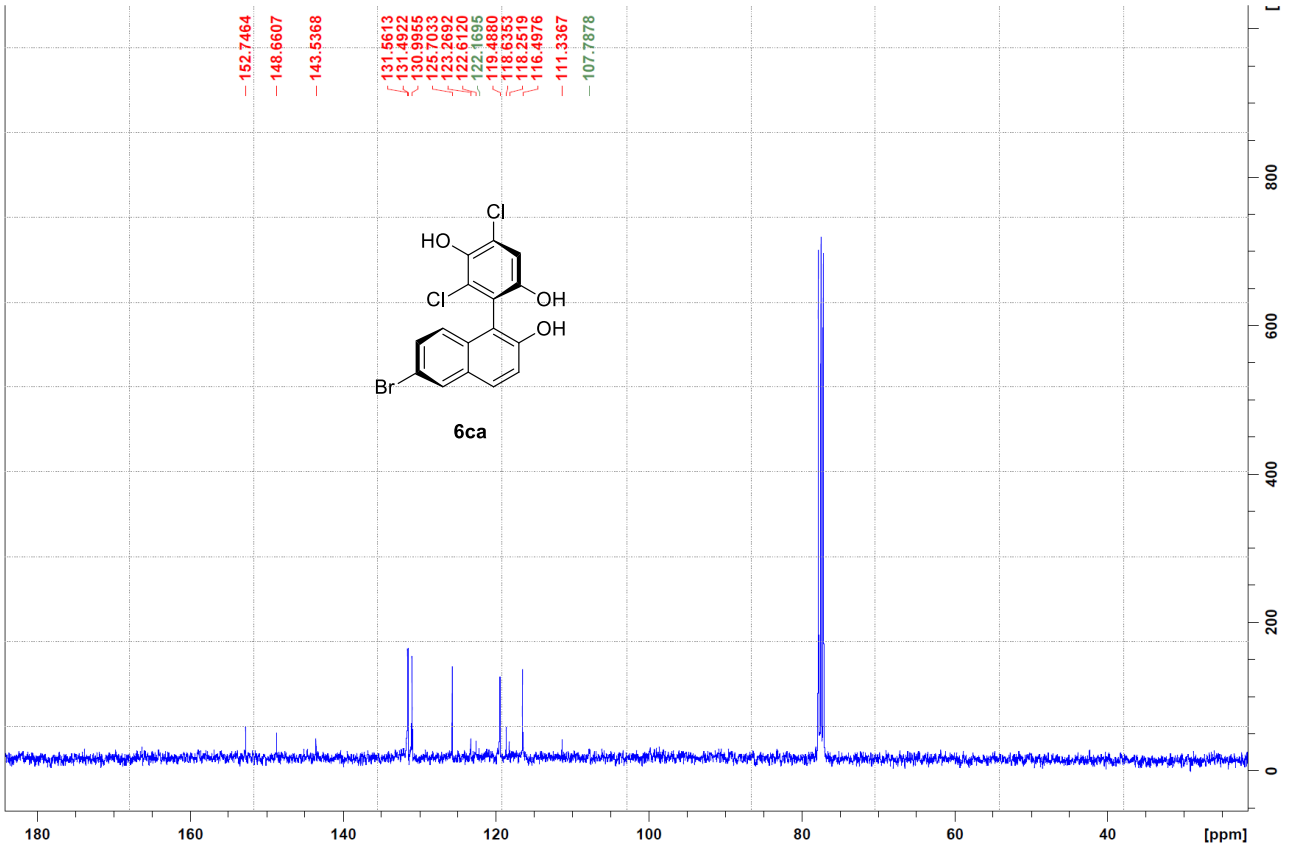
HPLC on CHIRALPAK IF column, eluent n-hexane/2-propanol 88:12, flux rate 0.9 mL/min, τ_1 (minor)= 23,7 min, τ_2 (major)= 30,2 min, *ee* 78%

POLARIMETRY [α]D = +15.8° (c 4.2, CH_3OH, *ee* 94%)

HRMS (ESI-TOF) m/z for $C_{17}H_{11}Cl_2O_4$ $[M-H]^-$ calculated 349.0034, found 349.0020



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (br, 1H), 5.12 (br, 1H), 5.64 (br, 1H), 7.10-7.14 (m, 2H), 7.31 (d, 1H; *J* = 9.0 Hz), 7.48 (dd, 1H; *J* = 2.0, 8.9 Hz), 7.83 (d, 1H; *J* = 8.9 Hz), 8.01 (d, 1H; *J* = 2.0 Hz).



^{13}C NMR (100 MHz, $CDCl_3$) δ 107.8, 111.3, 116.5, 118.3, 118.6, 119.5, 122.2, 122.6, 123.3, 125.7, 131.0, 131.5, 131.6, 143.5, 148.7, 152.7.

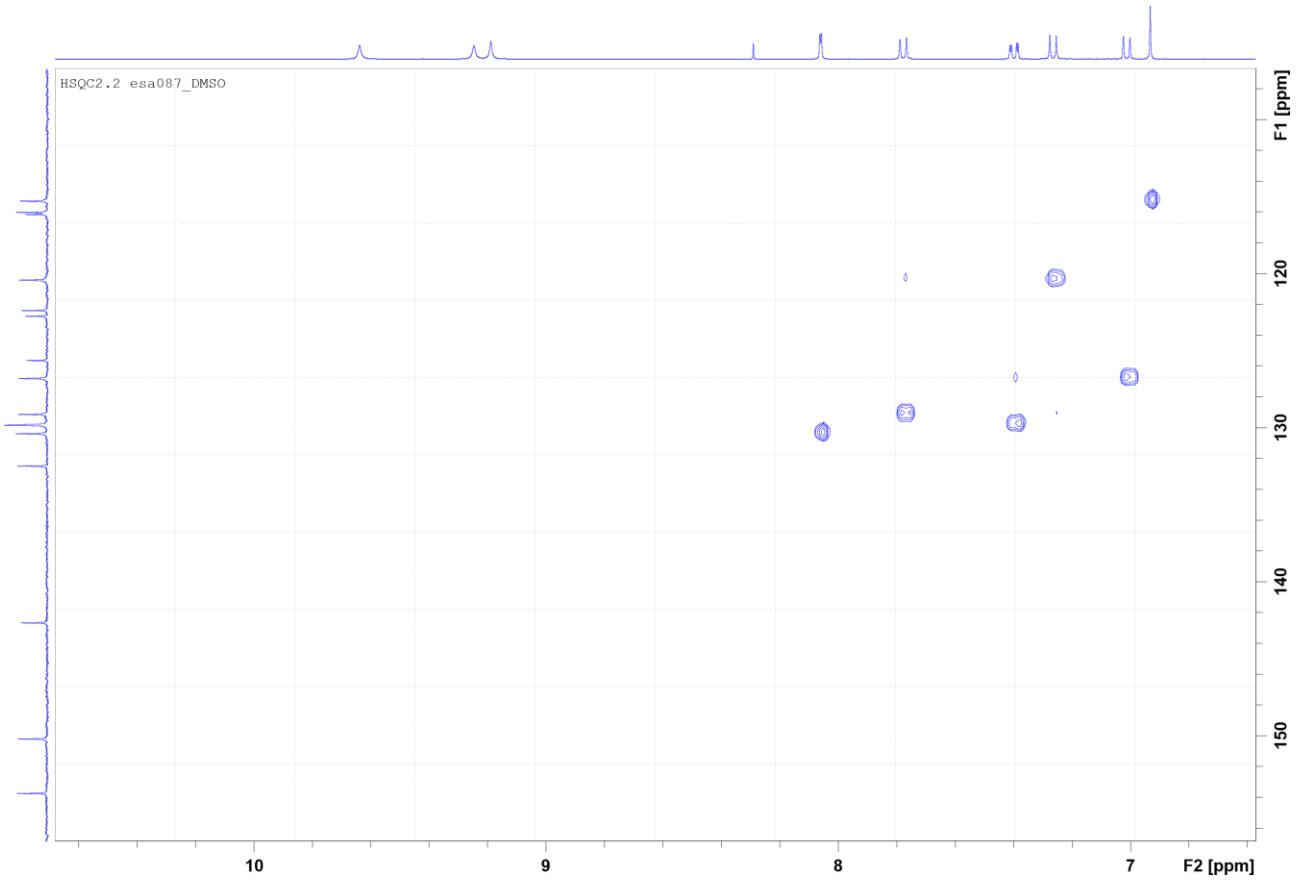
Yield = 57%

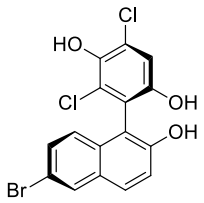
R_f = 0.23 (DCM:Et_2O 10:1)

HPLC on CHIRALPAK IF column, eluent n-hexane/2-propanol 90:10, flux rate 0.9 mL/min, τ_1 (minor)= 19,2 min, τ_2 (major)= 24,4 min, *ee* 77%

POLARIMETRY $[\alpha]_D$ = +20.7° (c 12.8, CH_3OH, *ee* 98%)

HRMS (ESI-TOF) m/z for $C_{16}H_8BrCl_2O_3$ [M-H]- calculated 396.9034, found 396.9052

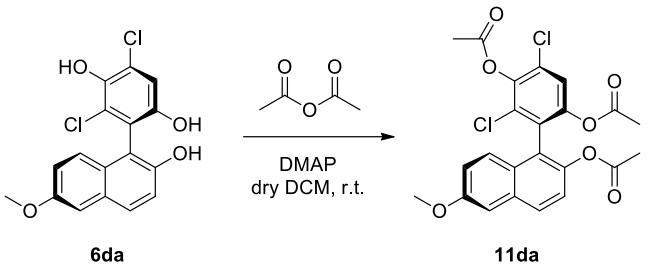




6ca

HSQC (400 MHz, DMSO-d_6)

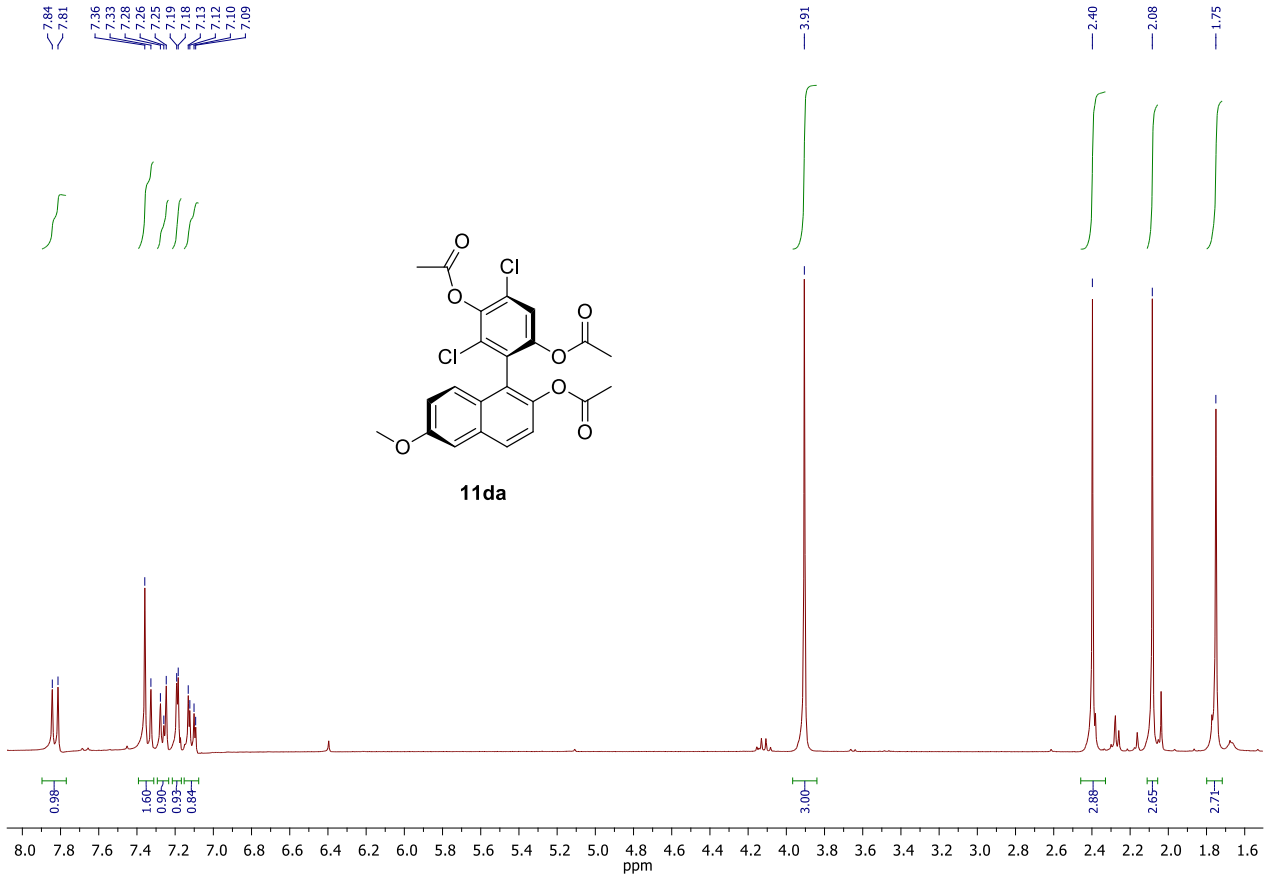
Biaryl 11da



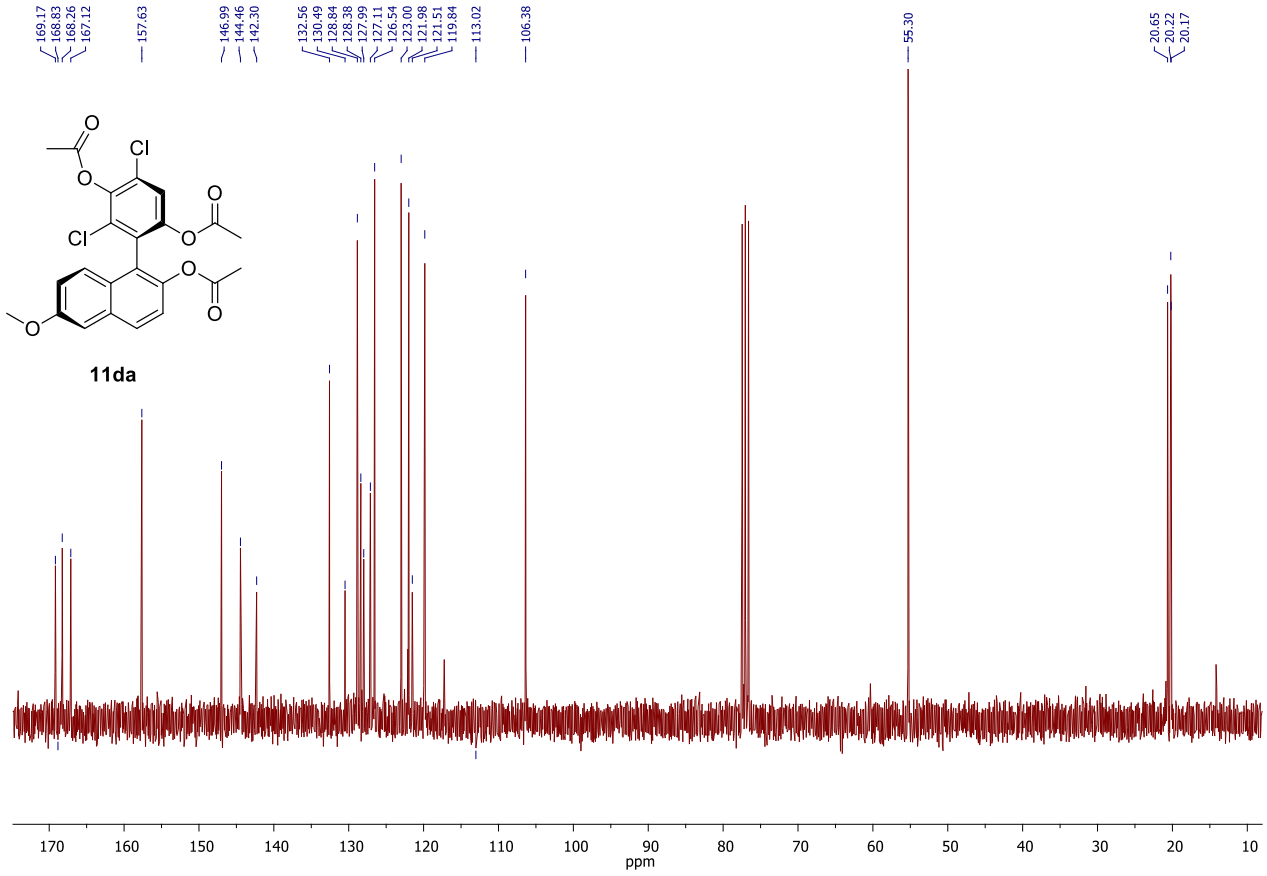
6da **11da**

Biaryl **6da** was dissolved in dry DCM a flame-dried vial, then 1.2 equivalents of acetic anhydride and 0.2 equivalents of DMAP were added (final concentration of **6da** in DCM 1.4 M). The reaction was stirred for 72 hours, until consumption of substrate **6da** was observed by TLC (hexane/ethyl acetate 2:1). The crude was diluted with dichloromethane and washed with three portions of a saturated aqueous solution of $NaHCO_3$ and a portion of water. The organic phase was dried over Na_2SO_4, filtered, evaporated under reduced pressure and dired under high vacuum. After flash chromatography purification on column (hexane/ethyl acetate), product **11da** was isolated as a colourless solid in 53% yield. Further attempts at lower temperature (0 °C, -20 °C), with portionwise addition of acetic anhydride or using different acylation catalysts (pyridine, acyl imidazolide) resulted in lower reactivities and isolated yields (below 10%).

Yield = 53%

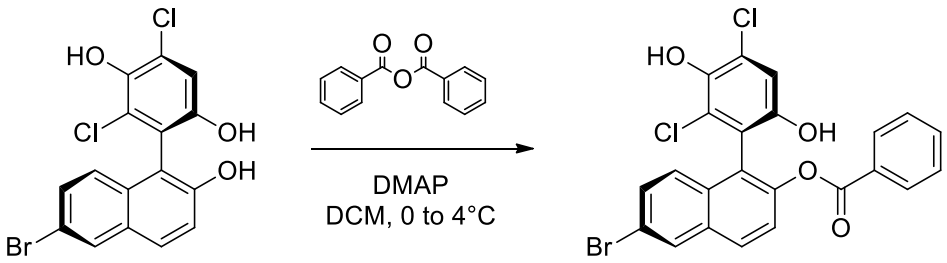


^{1}H NMR (300 MHz, CDCl3) δ 7.83 (d, *J* = 9 Hz, 1H), 7.36-7.09 (m, 5H), 3.91 (s, 3H), 2.40 (s, 3H), 2.08 (s, 3H), 1.75 (s, 3H).



^{13}C NMR (300 MHz, $CDCl_3$) δ 169.17, 168.83, 168.26, 167.12, 157.63, 146.99, 144.46, 142.30, 132.56, 130.49, 128.84, 128.38, 127.99, 127.11, 126.54, 123.0, 121.98, 121.51, 119.84, 113.02, 106.38, 55.30, 20.65, 20.22.

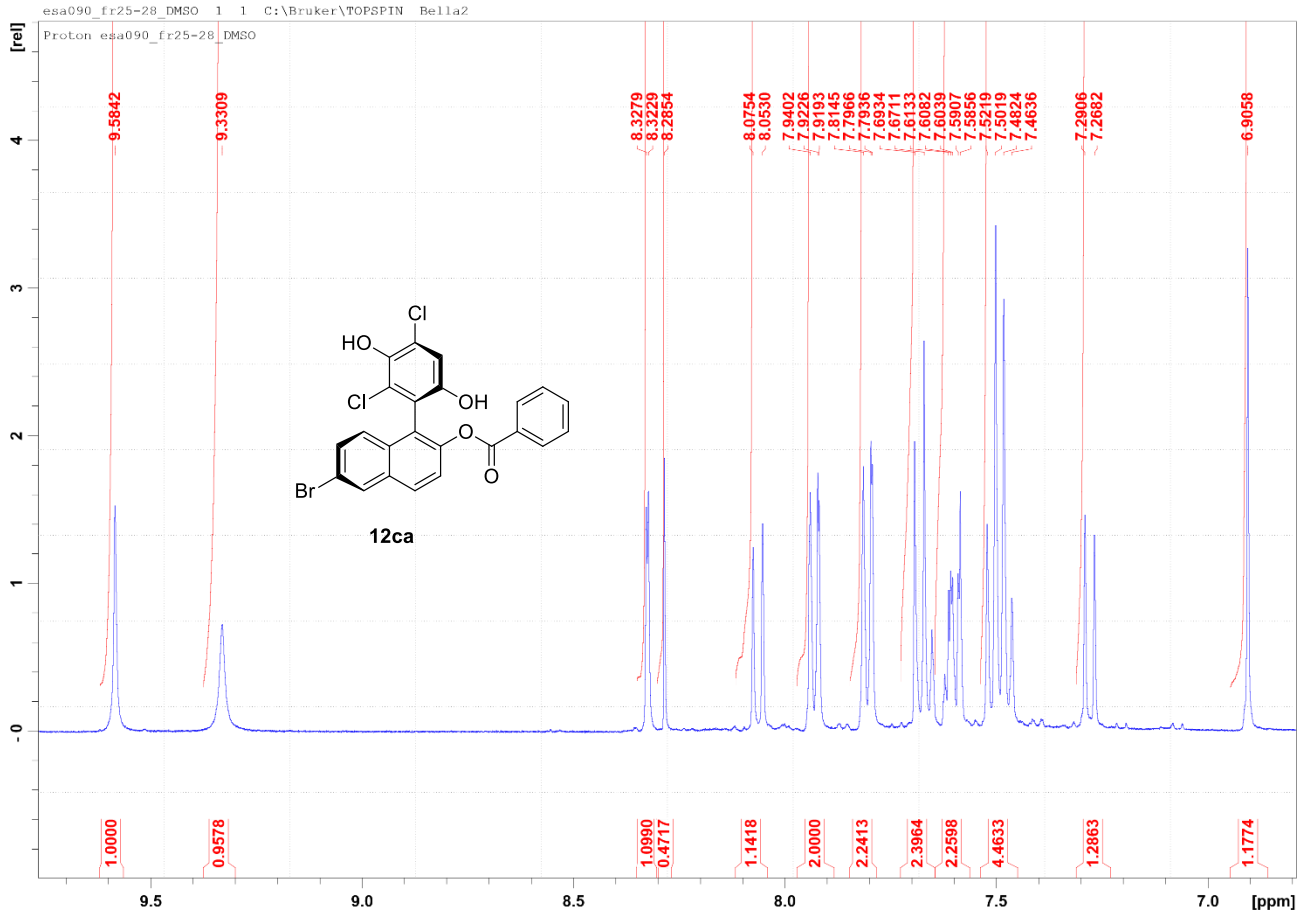
Biaryl 12ca



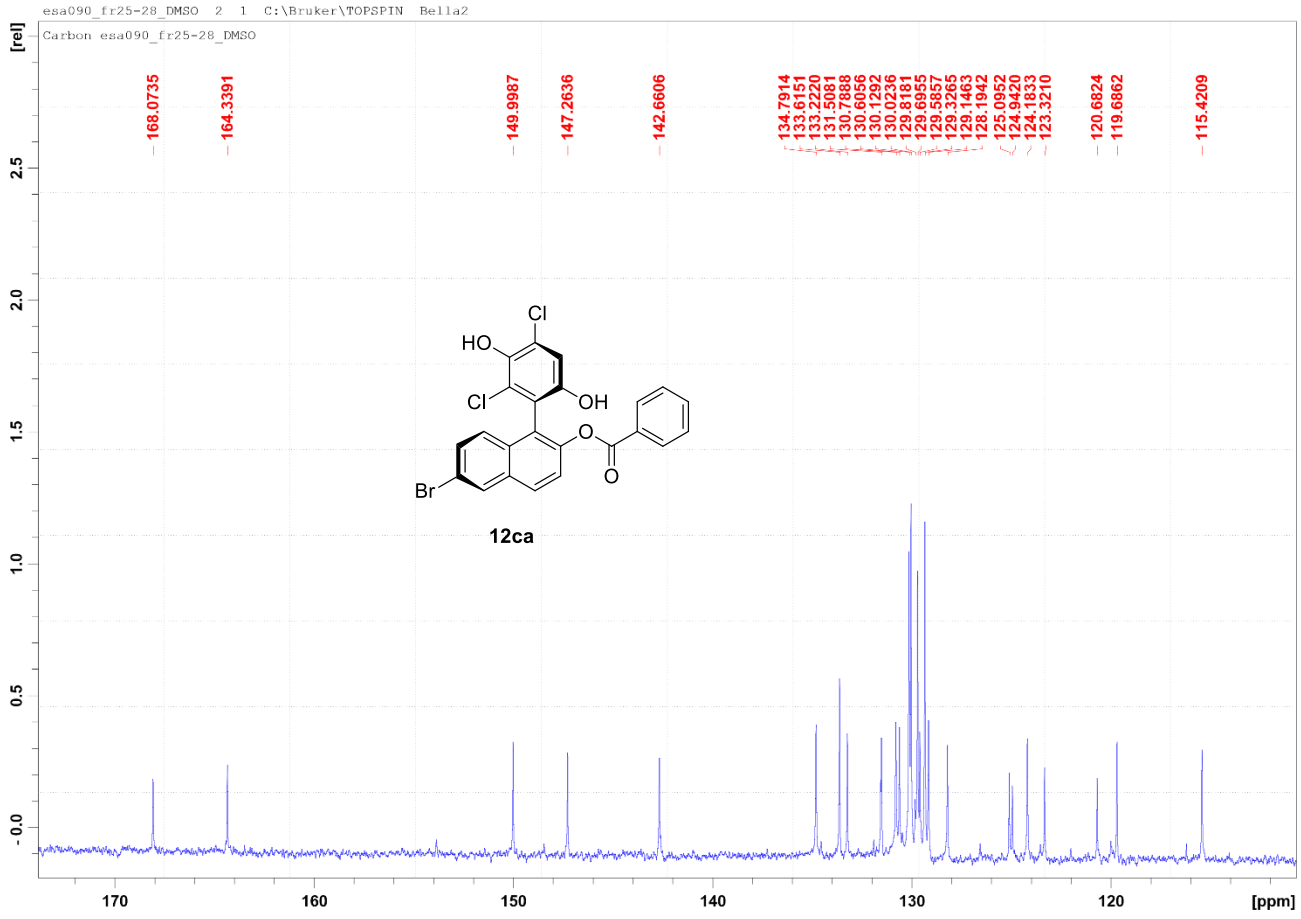
6ca **12ca**

Biaryl **6ca** and DMAP (0.2 equivalents) were dissolved in degased dichloromethane in a vial (final concentration of **6ca** in DCM 0.07 M) and mixture was kept under stirring at 4 °C. A 0.07 M solution of benzoic anhydride in degased dichloromethane was added portionwise to the first solution at 0 °C. Benzoic anhydride solution portions were added upon disappearance of the previous amount of reagent by TLC (hexane/ethyl acetate 2:1). The crude was diluted with dichloromethane and washed with three portions of a saturated aqueous solution of $NaHCO_3$ and a portion of water. The organic phase was dried over Na_2SO_4, filtered, evaporated under reduced pressure and dired under high vacuum. After flash chromatography purification on column (hexane/ethyl acetate), product **12ca** was isolated as a pink solid.

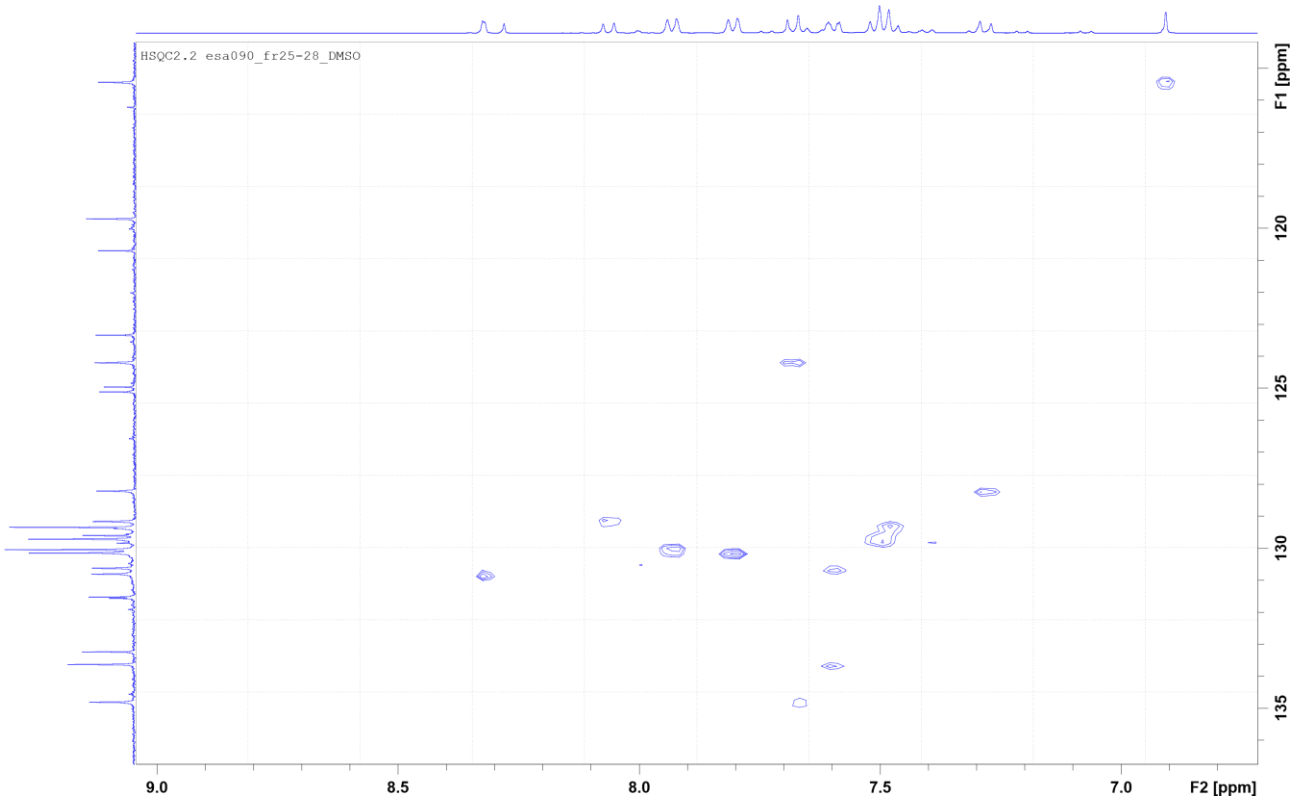
Yield = 10%

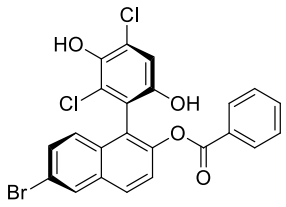


^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.58 (br s, 1H), 9.33 (br s, 1H), 8.33 (d, *J* = 2.0 Hz, 1H), 8.06 (d, *J* = 9 Hz, 1H), 7.80 (d, *J* = 9.0 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 1H), 6.91 (s, 1H).



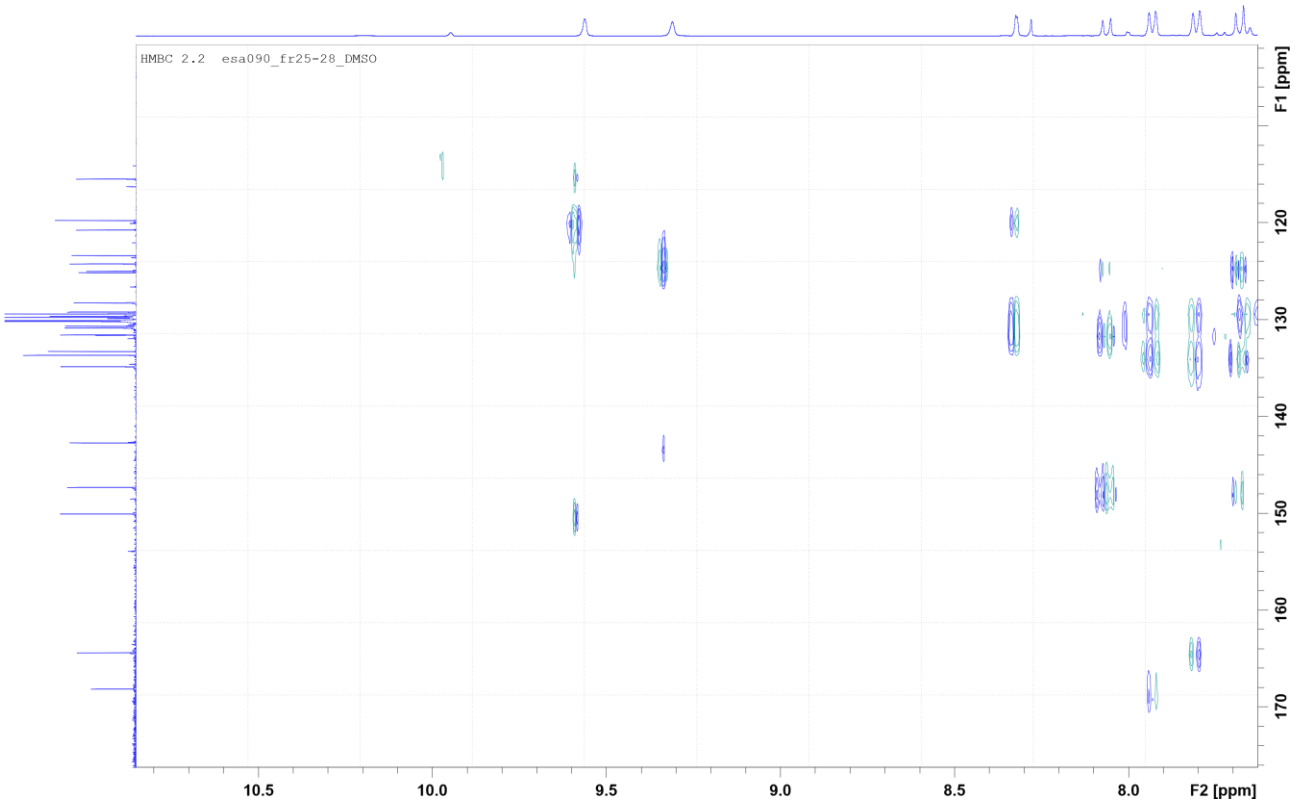
^{13}C NMR (400 MHz, DMSO-d$_6$) δ 164.34, 150.0, 147.26, 142.66, 133.62, 133.22, 131.51, 130.61, 130.02, 129.7, 129.59, 129.33, 129.15, 128.19, 125.1, 124.94, 124.18, 123.32, 120.68, 119.69, 115.42.

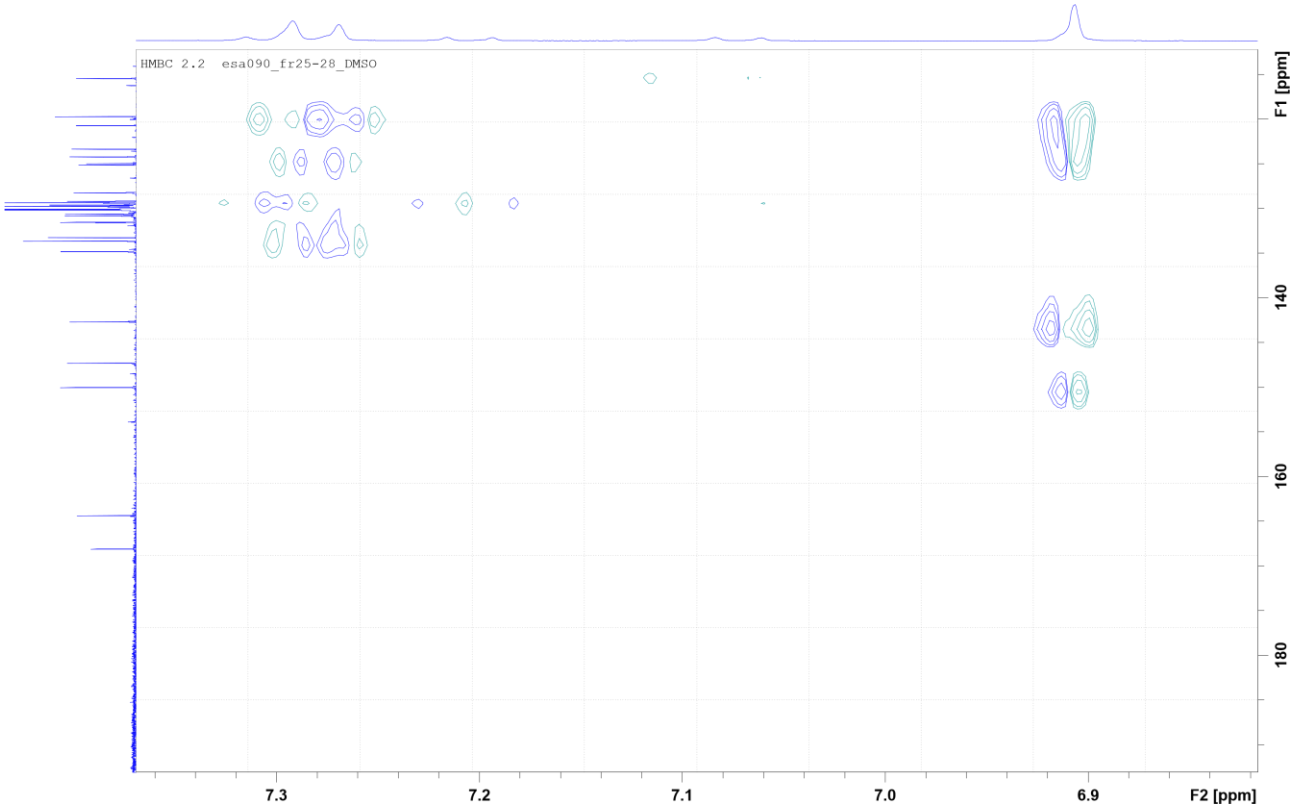


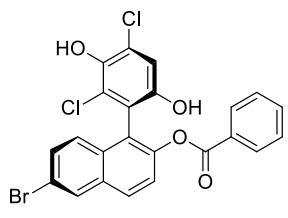


12ca

HSQC (400 MHz, DMSO-d_6)

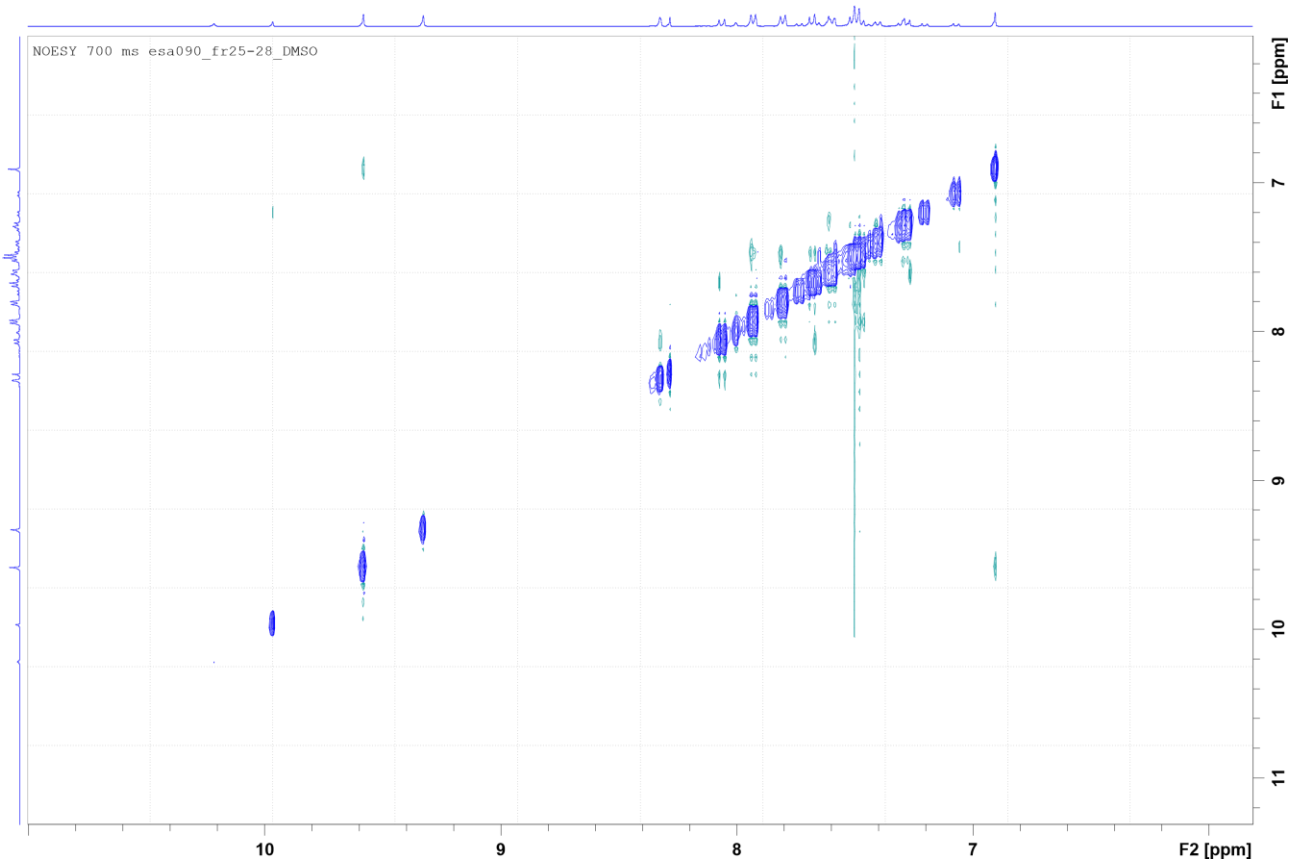


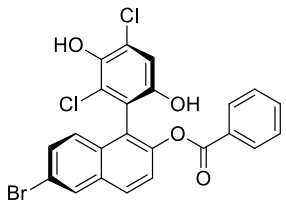




12ca

HMBC (400 MHz, DMSO-d_6)

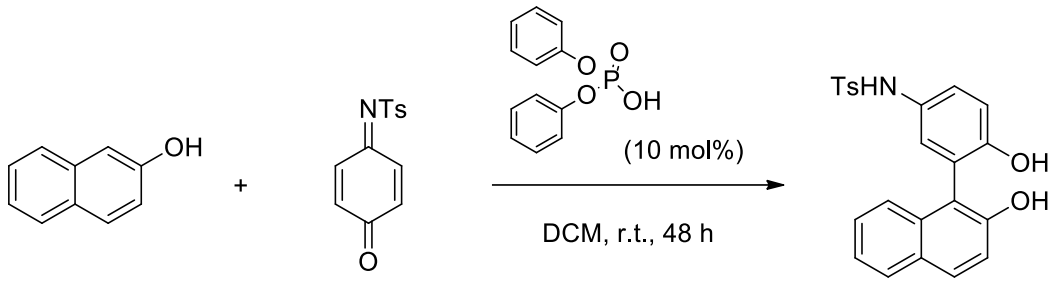




12ca

NOESY (400 MHz, DMSO-d_6)

Biaryl 16aa



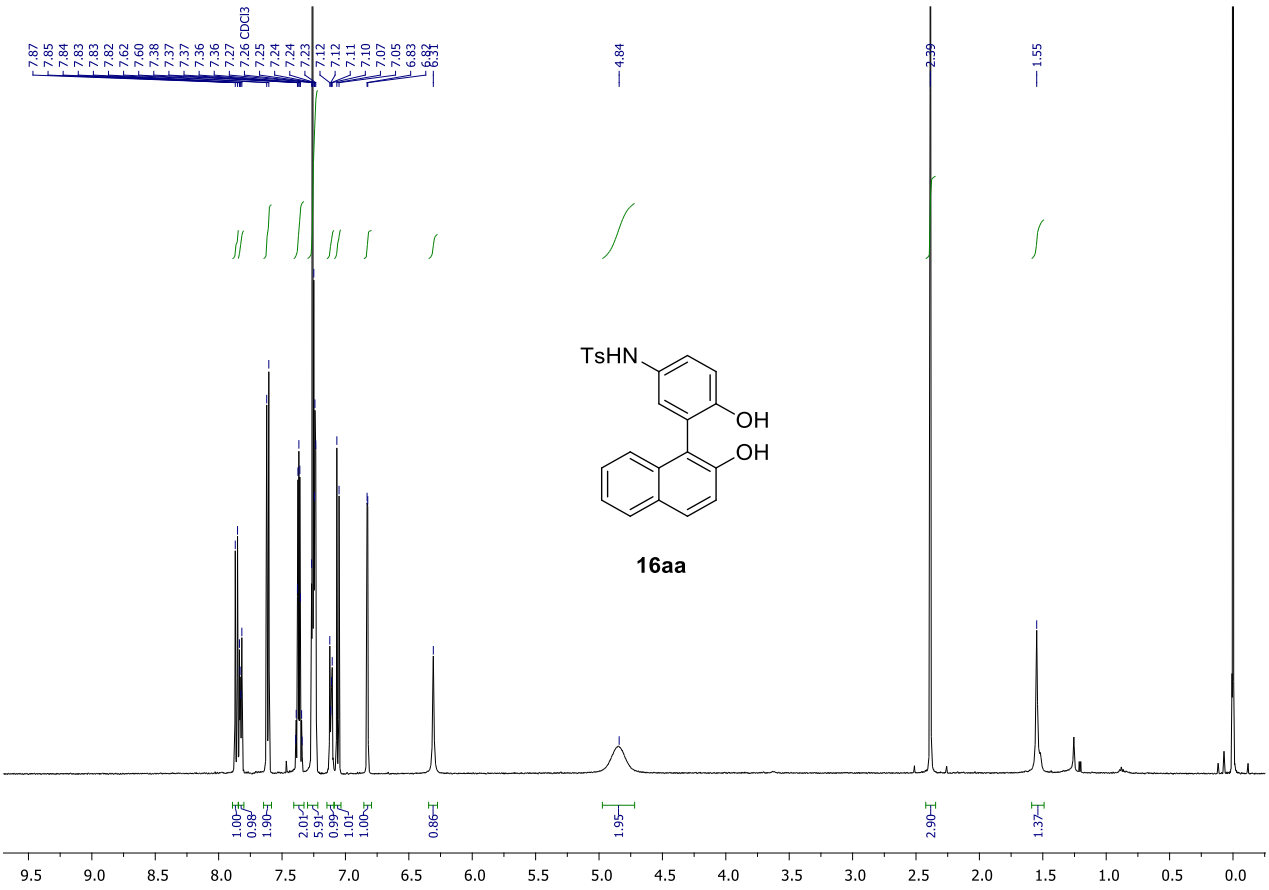
4a **15a** **16aa**

In an oven dried Schlenk tube diphenyl phosphate (10 mol%), naphthol **4a** and iminoquinone **15a** were dissolved in anhydrous DCM (4 mL) under argon atmosphere. The pale yellow-orange reaction mixture was stirred at room temperature and monitored by TLC (eluant DCM:Et_2O:AcOH 99:1:1) for 48 hours, until consumption of **15a**. At the endo of this period, the solvent was evaporated under vacuum and the crude was purified by flash chromatographic column (eluent DCM/AcOEt 10:1) and monitored by TLC (eluent DCM:AcOEt 10:1 + 1% AcOH). A 2 cm diameter chromatographic column filled with 5-6 inches of silica gel was used under 0.3 bar Argon flow pressure. The product was isolated as a pale brown solid.

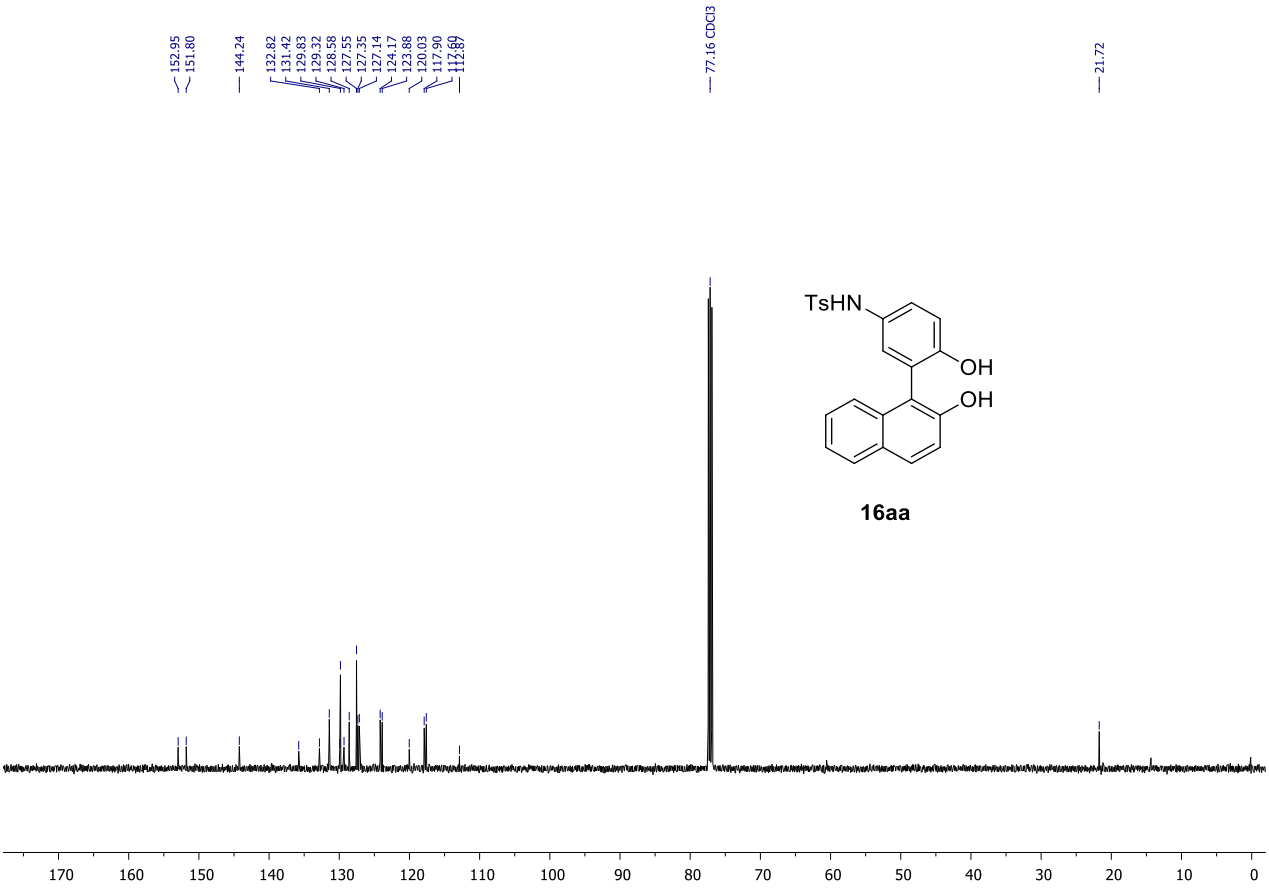
Yield = 84%

HPLC on DAICEL AS-R column, eluent acetonitrile/water 60:40, flux rate 1.0 mL/min, τ_1 (minor)= 3,08 min, τ_2 (major)= 3,47 min

HRMS (ESI-TOF) m/z for $C_{23}H_{18}NO_4S^-$ $[M-H]^-$ calculated 404.0962, found 404.0951.



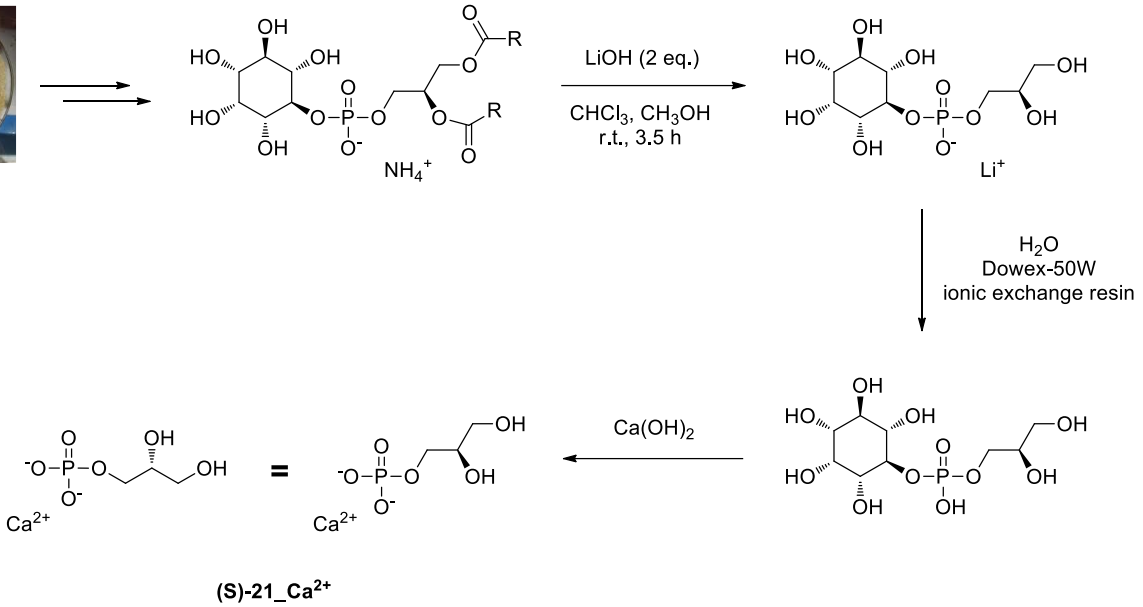
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.9 Hz, 1H), 7.83 (dd, *J* = 6.0, 3.4 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.33 (m, 2H), 7.28 – 7.21 (m, 3H), 7.11 (dd, *J* = 6.2, 3.3 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 6.31 (s, 1H), 4.84 (br s, 2H), 2.39 (s, 3H), 1.55 (s, 1H).



^{13}C NMR (126 MHz, $CDCl_3$) δ 152.95, 151.80, 144.24, 135.78, 132.82, 131.42, 129.93, 129.83, 129.32, 128.58, 127.55, 127.35, 127.14, 124.17, 123.88, 120.03, 117.90, 117.60, 112.87, 77.16, 21.72.

Glycerol-1-phosphate (21)

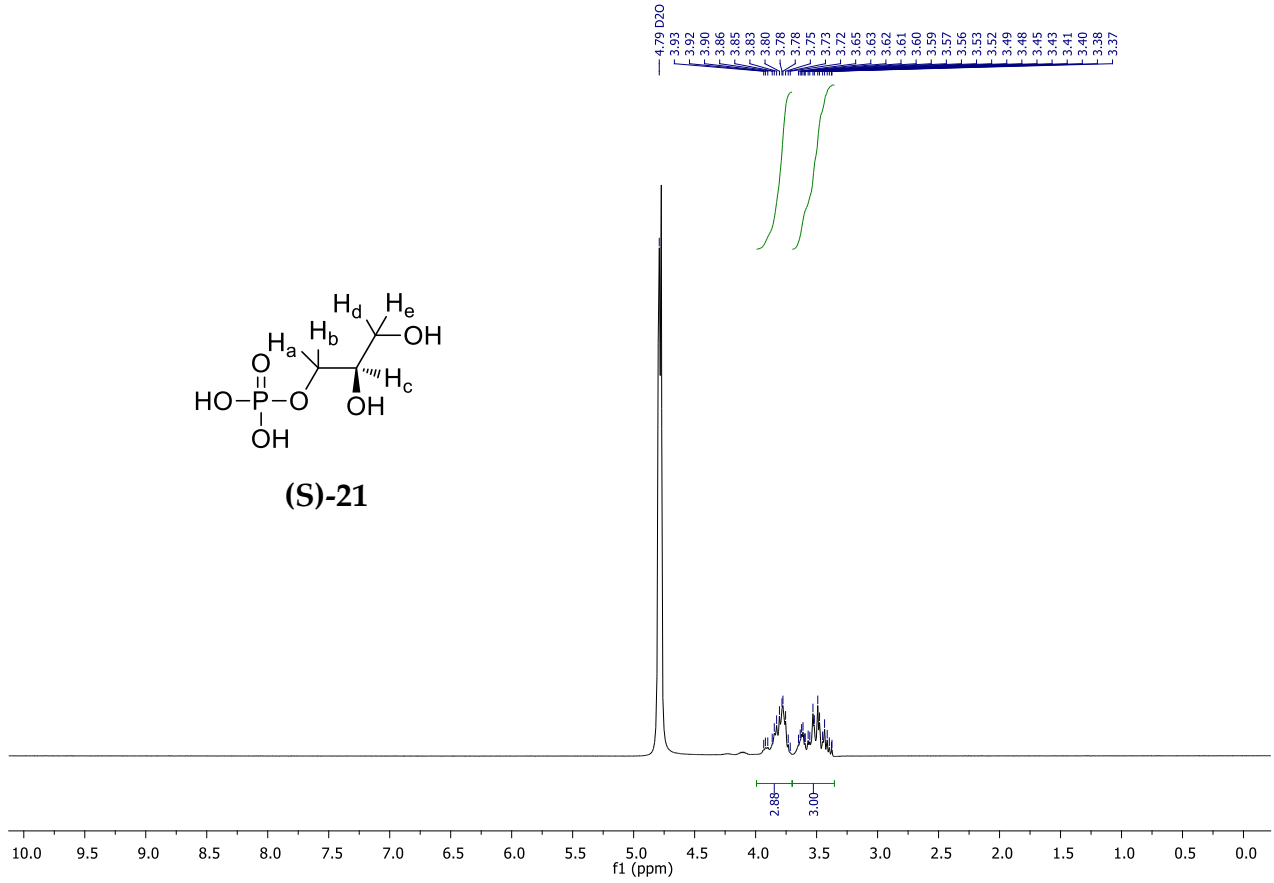
Soy lecithin



(S)-21_Ca^{2+}

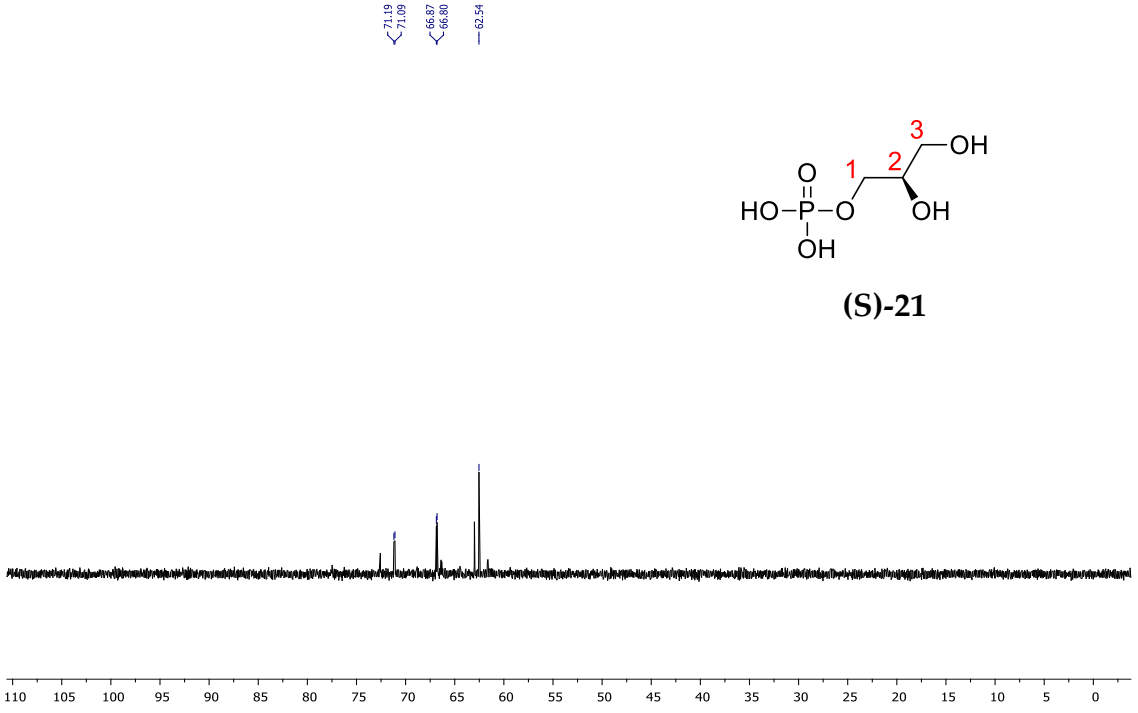
In a three-neck round bottom flask, soy lecithin (100 g), chloroform (350 mL) and methanol (350 mL) were added, and the mixture was put under mechanical stirring. Then, aluminium oxide Al_2O_3 (30 g) was added and the mixture was kept under stirring for 1 hour. At the end of this period, the solid phase was separated from mother liquor and washed with chloroform (50 mL) and methanol (50 mL). Solid phase was then redissolved in fresh chloroform (100 mL) and methanol (100 mL), hydroxylammonium acetate was added (30 mL of 30% aqueous solution), and the resulting heterogeneous mixture was kept under stirring for 40 minutes. After isolation of the organic phase, the flask was refilled with chloroform, methanol and hydroxylammonium acetate, then stirred for 30 minutes. Collected organic phases were diluted with chloroform (100 mL) and washed with brine (100 ml), then evaporated under vacuum to afford phosphatidyl-*myo*-inositol in 20-30% w/w yield. This product was put in a three-neck round bottom flask, chloroform (90 ml) was added and the mixture was put under mechanical stirring. Methanol (360 ml) and lithium hydroxide (1.1 g) were added, and the mixture was kept under stirring for 3.5 hours. At the end of this period, water (300 mL), ethanol (200 mL) and chloroform (300 mL) were added and aqueous phase was isolated after extraction and passed through a glass column (diameter Ø= 5 cm) filled with a small pad of Dowex-50W ionic exchange resin (pH of eluted aqueous phase controlled by litmus test). Aqueous phase was then divided in 50 mL portions. Each portion was treated with calcium hydroxide (>50 mg) and put under magnetic stirring for 20 minutes. At the end of this period, the solvent was removed under reduced pressure, 2 mL of water were added and, upon addition of 25 mL of methanol, precipitation of a white solid occurred. The mixture was centrifugated to isolate the solid, which was washed with 20 mL of methanol and centrifugated again. The white solid was collected, washed with three 15 mL portions of methanol to eliminate residuals of *myo*-inositol, evaporated under reduced pressure and dried under high vacuum to afford

the calcium salt of compound **21** as a white solid, which could be acidified through passage on Dowex-50W resin.



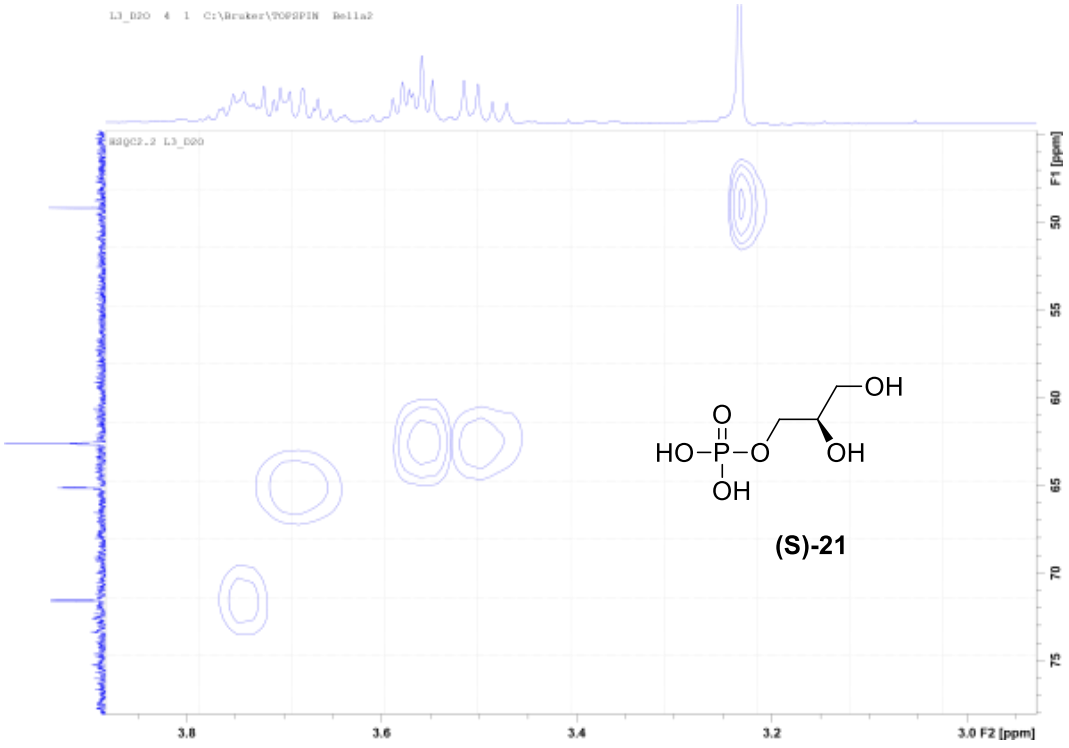
(S)-21

^{1}H NMR (300 MHz, D_2O) δ 4.00 - 3.70 (m, 3H, H_a, H_b, H_c), 3.69 - 3.50 (m, 1H, H_d), 3.49 - 3.35 (m, 1H, H_e).



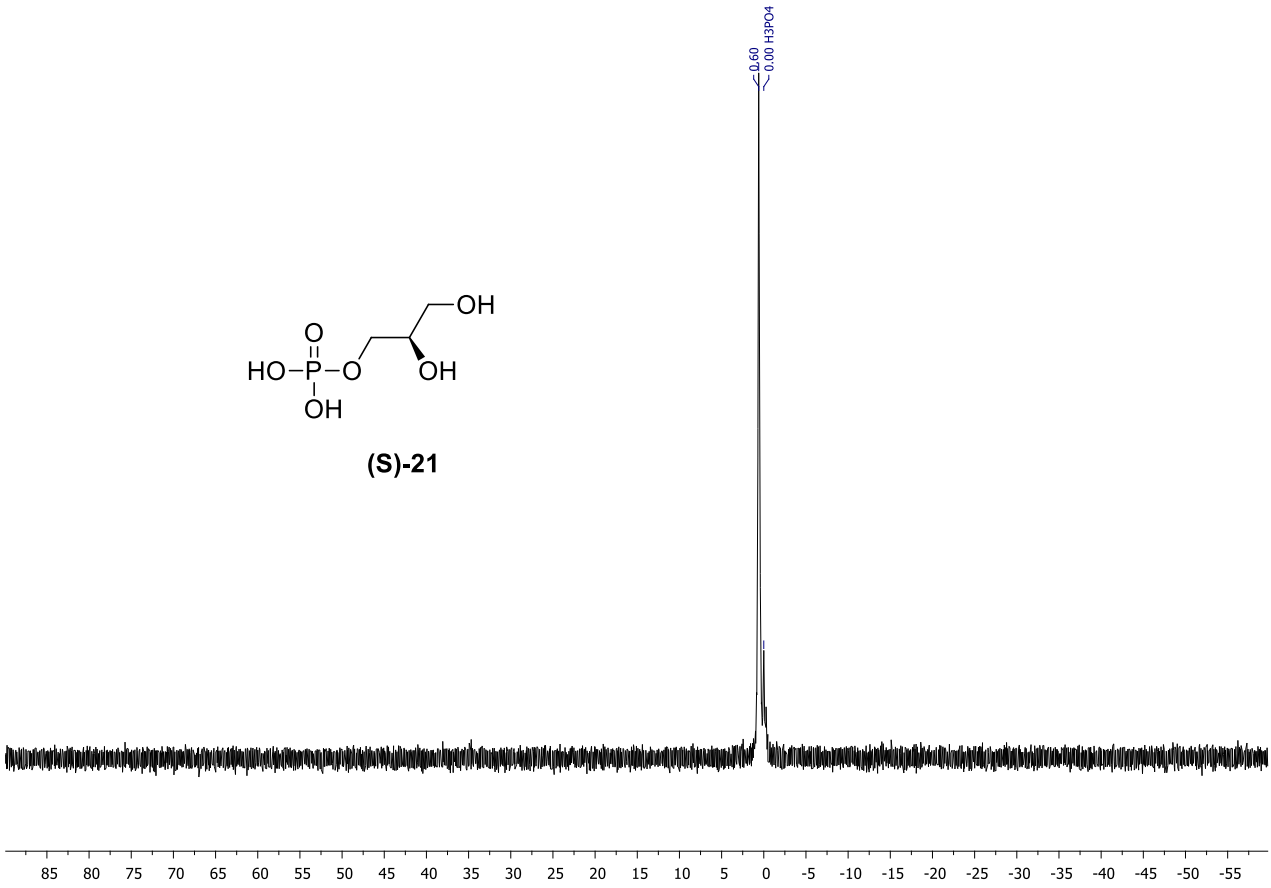
(S)-21

^{13}C NMR (75 MHz, D_2O) δ 71.14 (d, *J* = 7.9 Hz, C_2), 66.83 (d, *J* = 5.2 Hz, C_1), 62.54 (s, C_3).



(S)-21

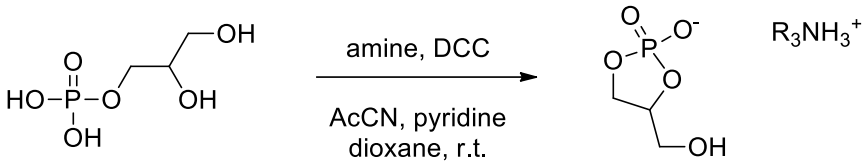
HSQC (400 MHz, D_2O)



(S)-21

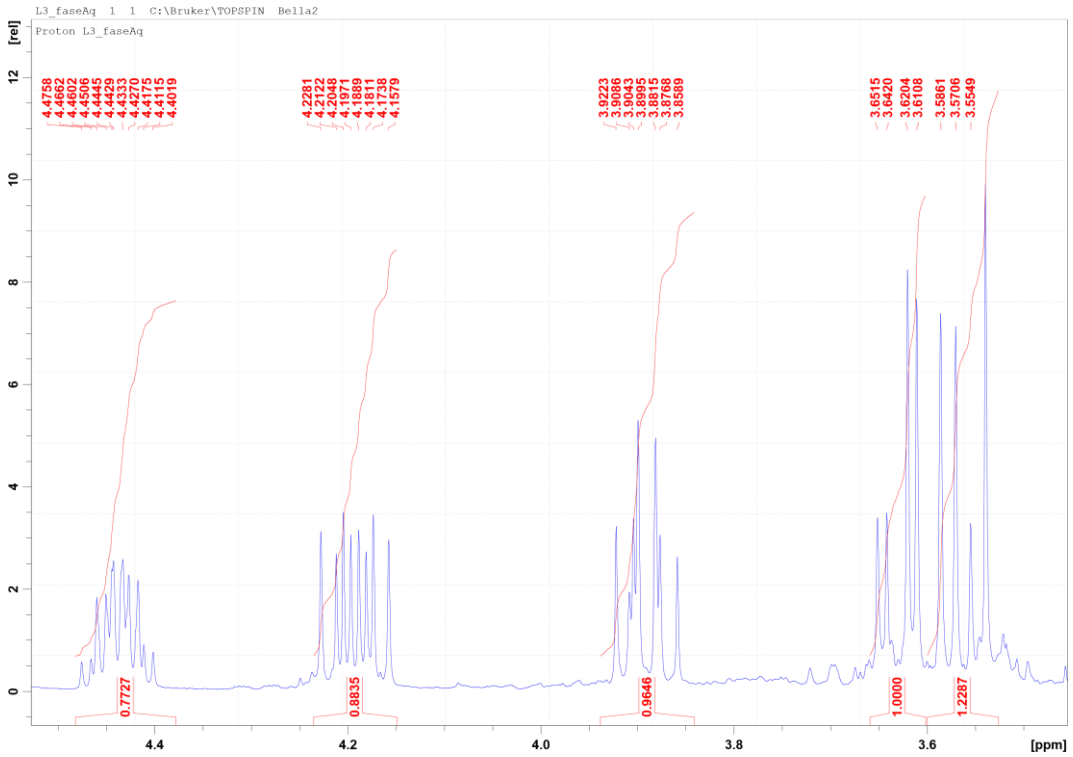
^{31}P NMR (121 MHz, D_2O) δ 0.60 ppm

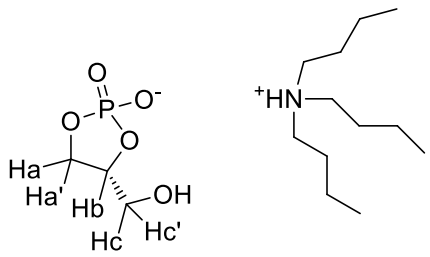
Glycerol cyclic phosphate (22) salts



21 **22_R_3NH^+**

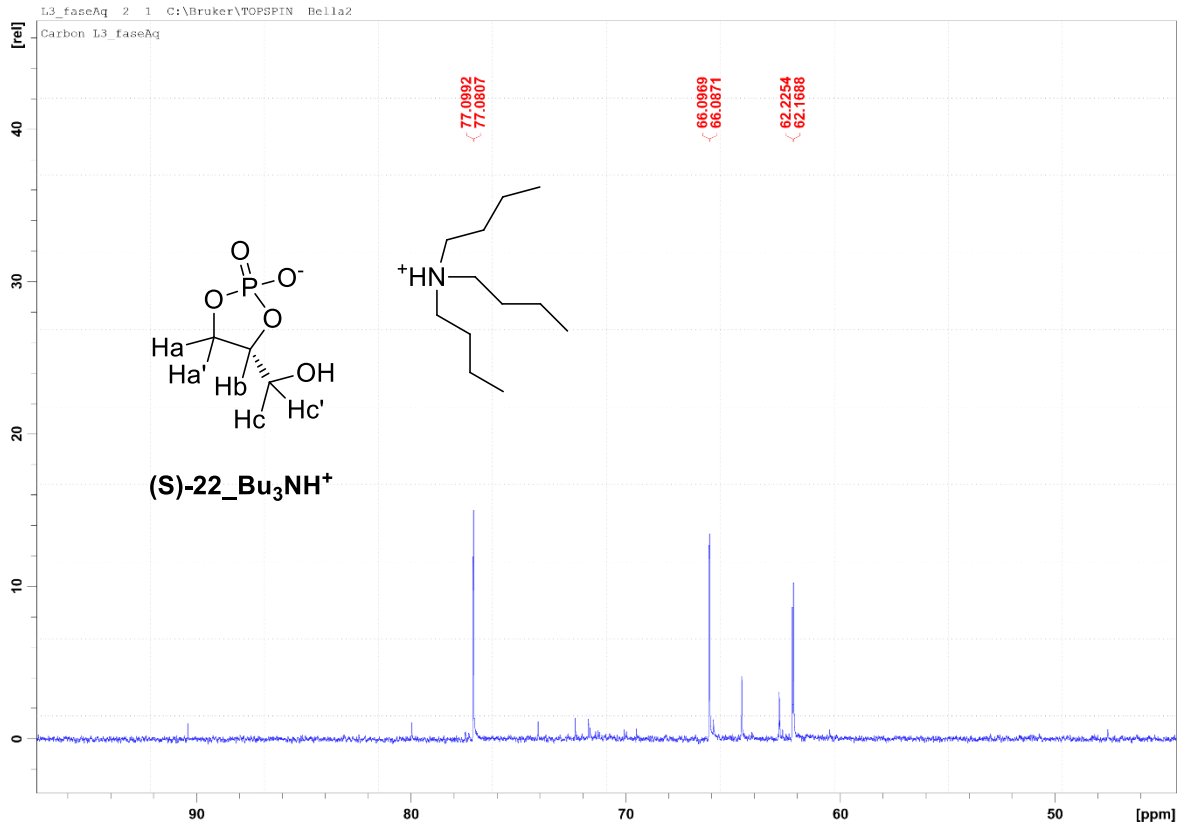
Compound **21** (500 mg, 2.9 mmol), obtained after treatment of the corresponding calcium salt (isolated from soy lecithin or obtained by commercial sources) and lyophilization, was dissolved in a mixture of acetonitrile (5 mL), pyridine (0.5 mL), dioxane (5 mL), and the selected amine (1-4 equivalents, pure if liquid or dissolved in the minimum amount of acetonitrile if solid). To this mixture, 2 equivalents of DCC were added and the reaction was left under stirring for 48 hours. At the end of this period, 15 mL of water were added to precipitate dicyclohexylurea, which was filtered away from the solution. Barium hydroxide was added until pH= 9 and, if a precipitate was present (**21_Ba^{2+}**), it was eliminated by centrifugation and filtration. Supernatant solution was saturated with gaseous CO_2 to precipitate the excess of Ba^{2+} as $BaCO_3$. The solution was centrifugated, filtered, concentrated under reduced pressure and lyophilized. The products were isolated as light yellow gelatinous oils.



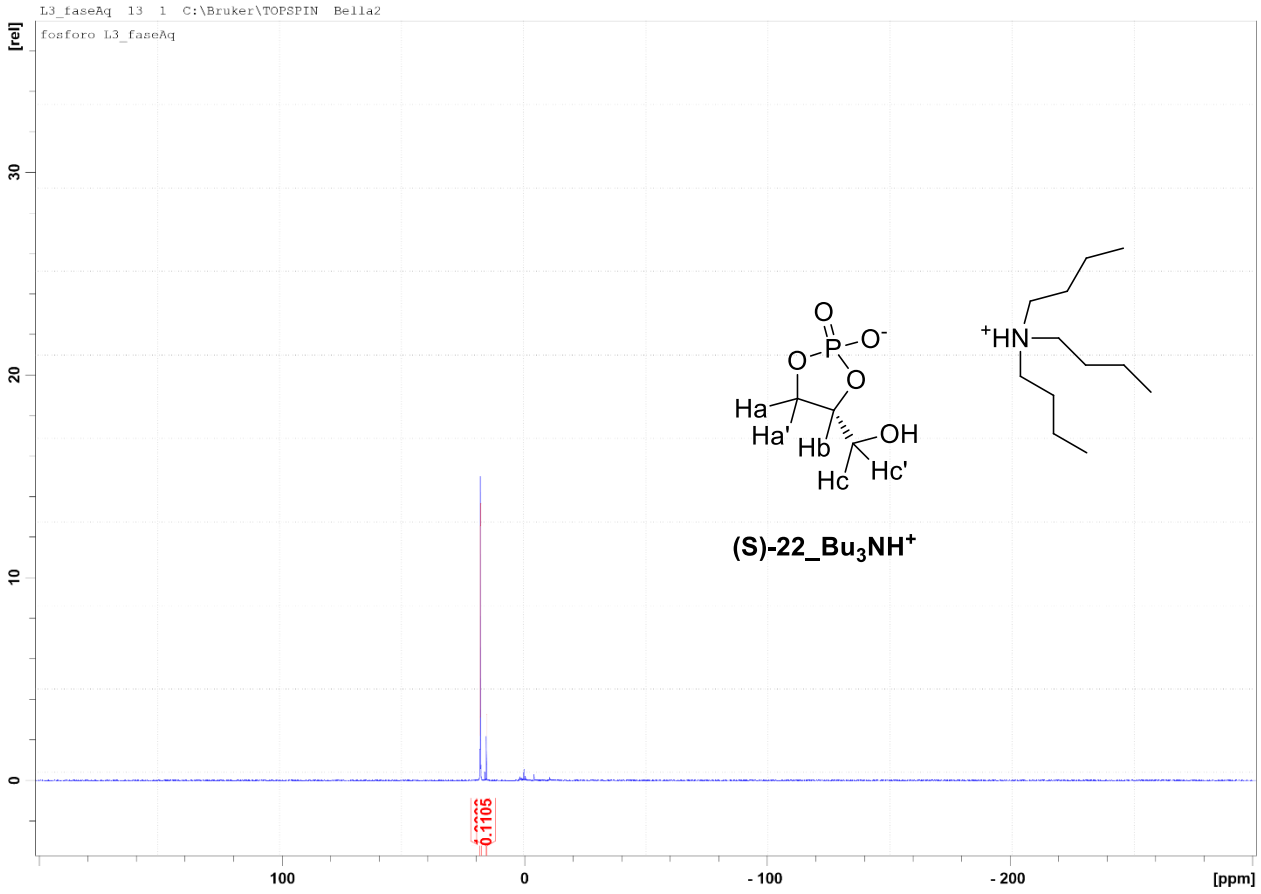


(S)-22_Bu_3NH^+

^{1}H NMR (400 MHz, D_2O) δ 4.43 (dqd, $J_{H\text{-}P}$= 11.1 Hz, $J_{H\text{-}H}$= 6.2, 3.8 Hz, H_b), 4.18 (ddd, $J_{H\text{-}P}$= 12.4 Hz, $J_{H\text{-}H}$= 9.3, 6.3 Hz, H_a), 3.82 (td, $J_{H\text{-}P}$= 12.0 Hz, $J_{H\text{-}H}$= 5.0 Hz, $H_{a'}$), 3.63 (dd, J= 8.1, 3.8 Hz, H_c), 3.56 (dd, J= 9.3, 3.8 Hz, $H_{c'}$)

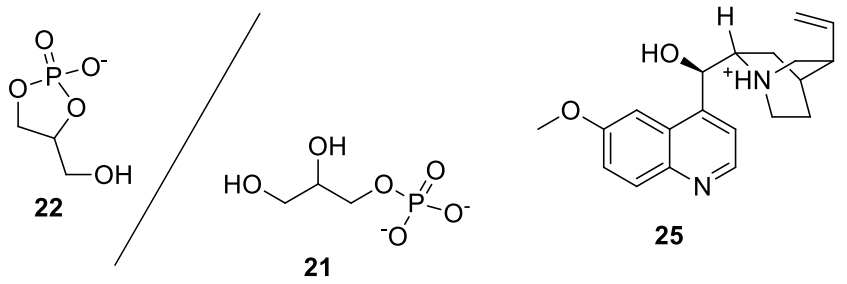


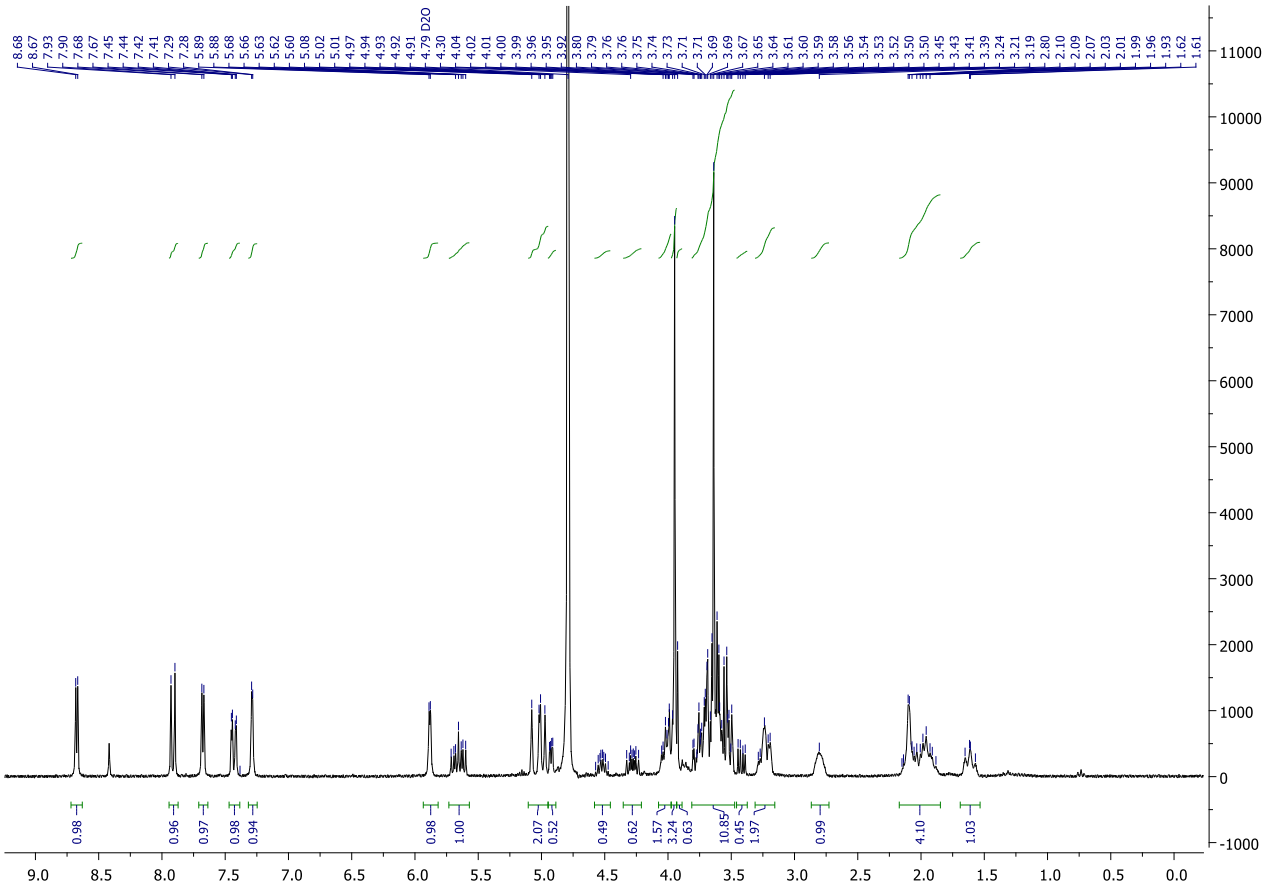
^{13}C NMR (100 MHz, D_2O) δ 62.4 (d, $J_{C\text{-}P}$= 6.4 Hz), 66.2 (d, $J_{C\text{-}P}$= 1.3 Hz), 77.1 (d, $J_{C\text{-}P}$= 2.3 Hz)



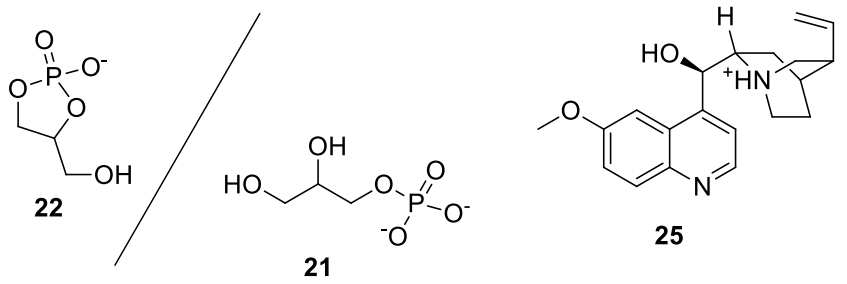
^{31}P NMR (161 MHz, D_2O) δ 18.3 (s)

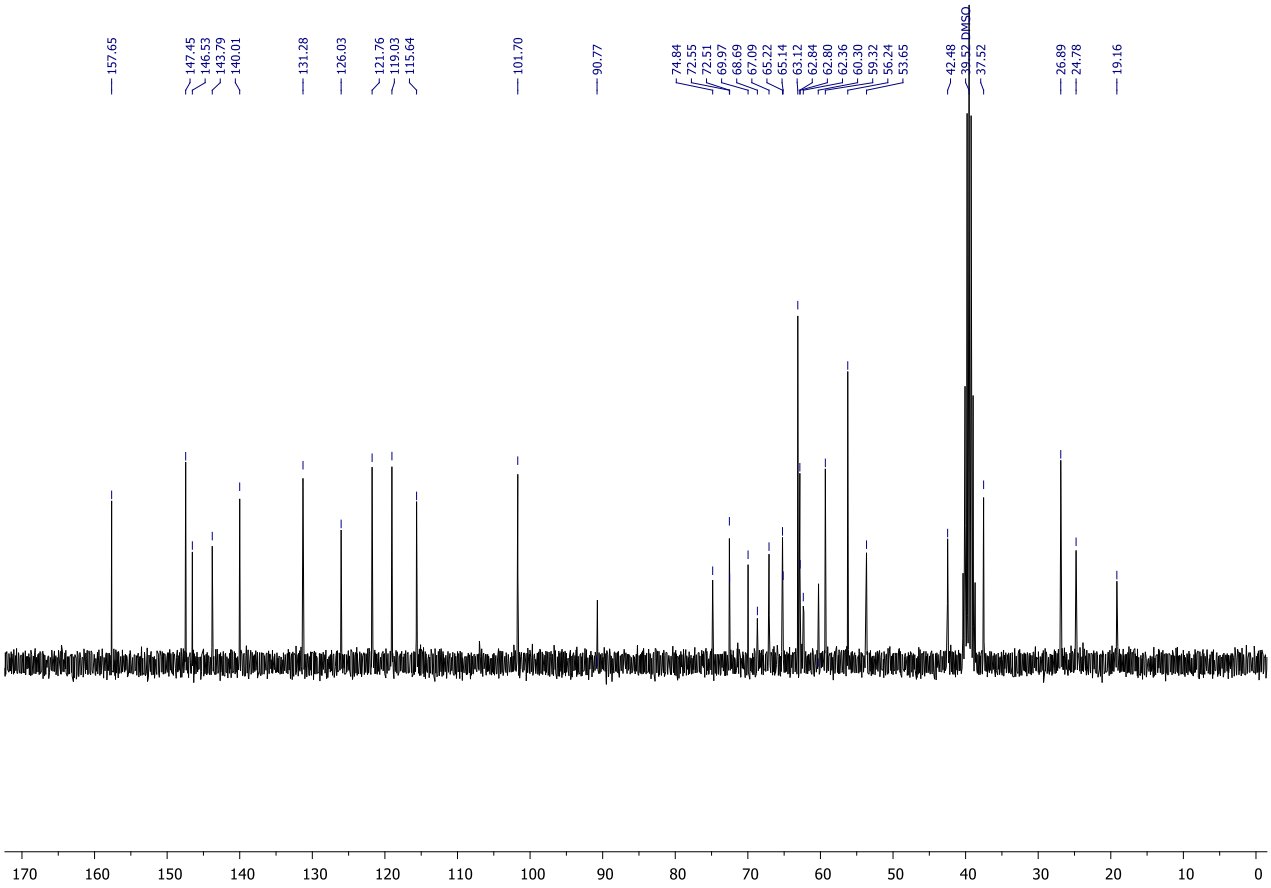
Yield = 54%



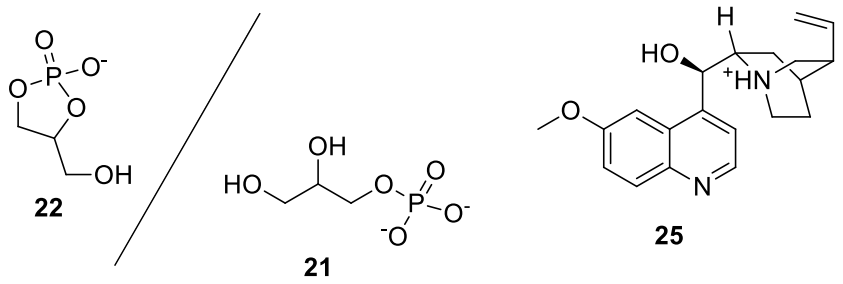


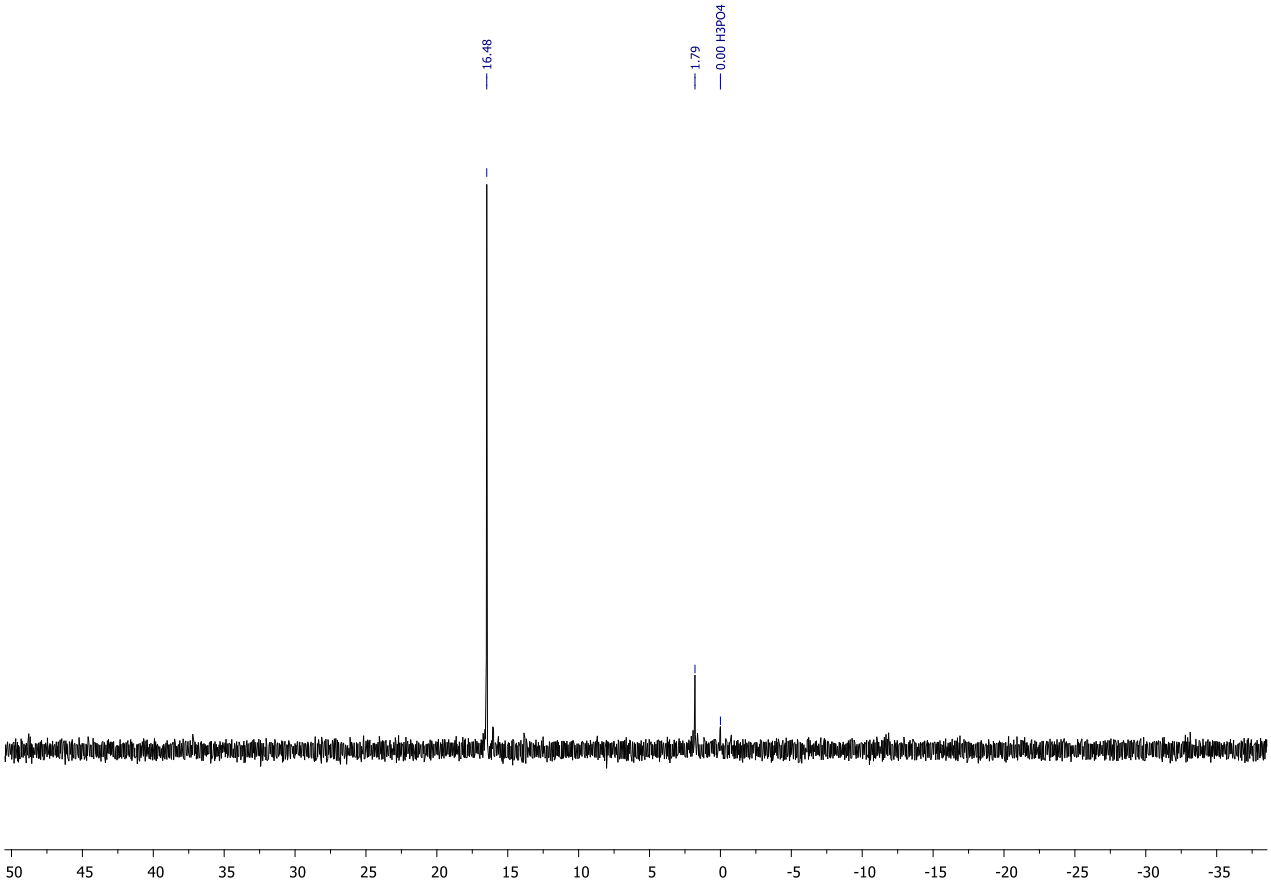
^{1}H NMR (300 MHz, D_2O) δ 8.67 (d, *J* = 4.8 Hz, 1H), 7.91 (d, *J* = 9.4 Hz, 1H), 7.68 (d, *J* = 4.8 Hz, 1H), 7.43 (dd, *J* = 9.3, 2.5 Hz, 1H), 7.29 (d, *J* = 2.6 Hz, 1H), 5.88 (d, *J* = 3.2 Hz, 1H), 5.66 (ddd, *J* = 17.1, 10.5, 6.5 Hz, 1H), 5.02 (dd, *J* = 17.4, 13.8 Hz, 2H), 4.92 (dd, *J* = 5.2, 2.5 Hz, 1H), 4.52 (qd, *J* = 10.3, 6.2 Hz, 0.5H), 4.28 (ddd, *J* = 12.6, 9.4, 6.3 Hz, 0.5H), 4.08 – 3.89 (m, 2H), 3.95 (s, 3H), 3.82 – 3.47 (m, 11H), 3.42 (dd, *J* = 11.5, 5.4 Hz, 0.5H), 3.32 – 3.15 (m, 2H), 2.80 (s, 1H), 2.18 – 1.84 (m, 4H), 1.61 (dd, *J* = 13.3, 11.3 Hz, 1H).





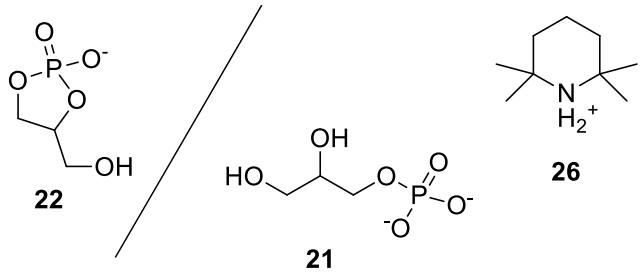
^{13}C NMR (75 MHz, DMSO) δ 157.65, 147.45, 146.53, 143.79, 140.01, 131.28, 126.03, 121.76, 119.03, 115.64, 101.70, 90.77, 74.84, 72.55, 72.51, 69.97, 68.69, 67.09, 65.18 (d, $J_{C\text{-}P}$ = 9.7 Hz), 63.12, 62.82 (d, $J_{C\text{-}P}$ = 4.8 Hz), 62.32 (d, $J_{C\text{-}P}$ = 9.7 Hz), 60.30, 59.32, 56.24, 53.65, 42.48, 37.52, 26.89, 24.78, 19.16.

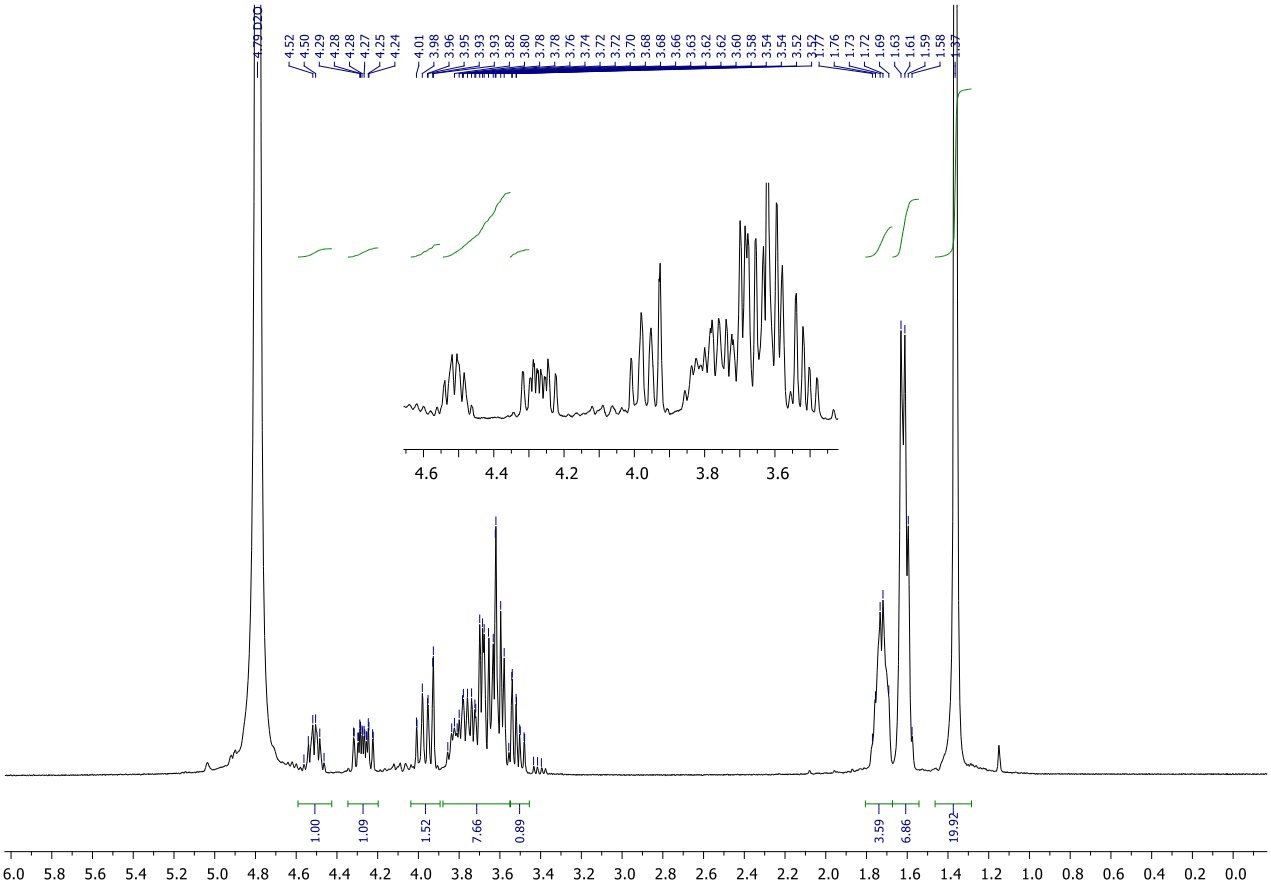




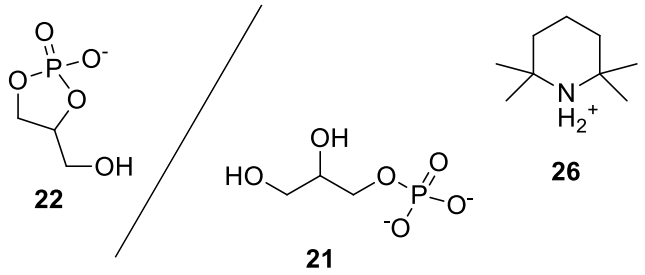
^{31}P NMR (121 MHz, DMSO) δ 16.48, 1.79.

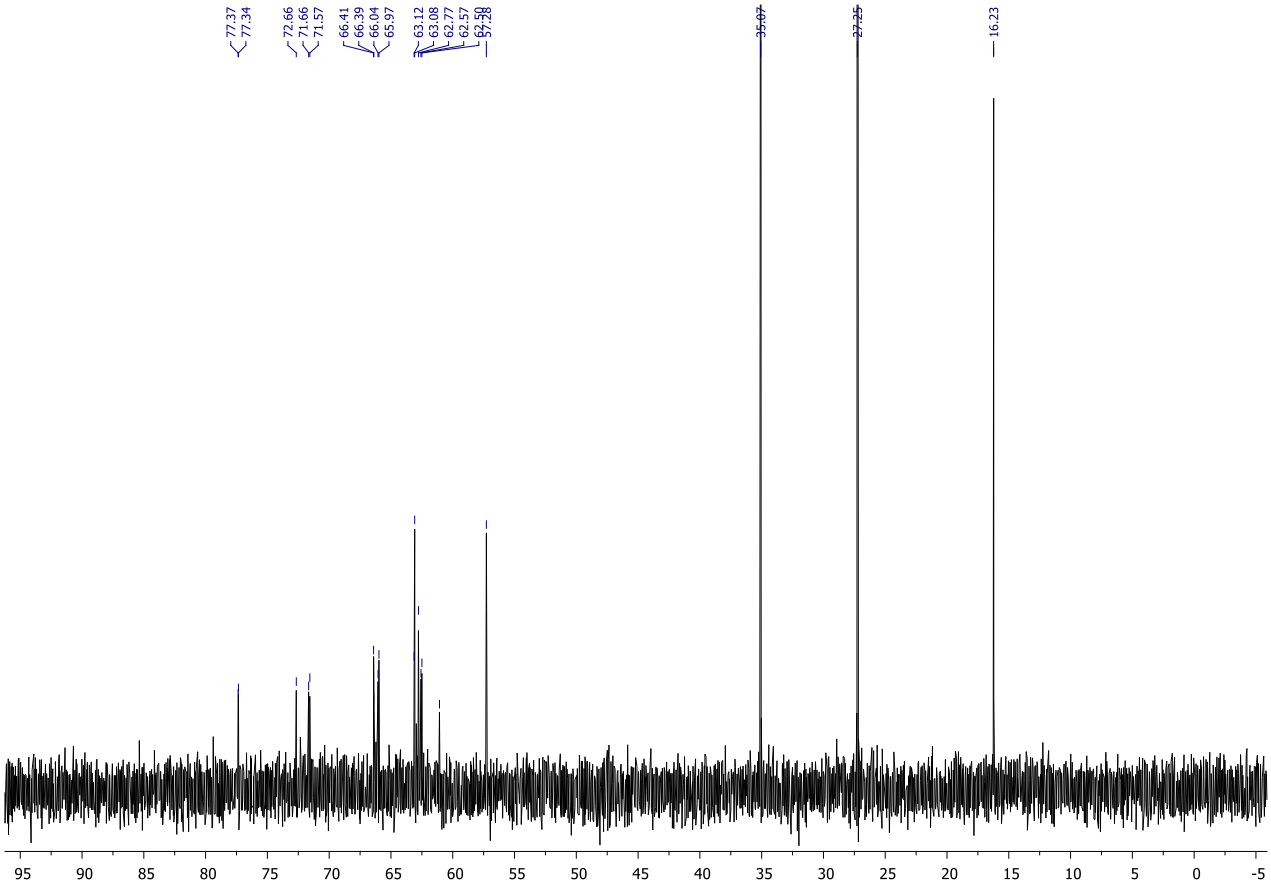
Yield = n.d.



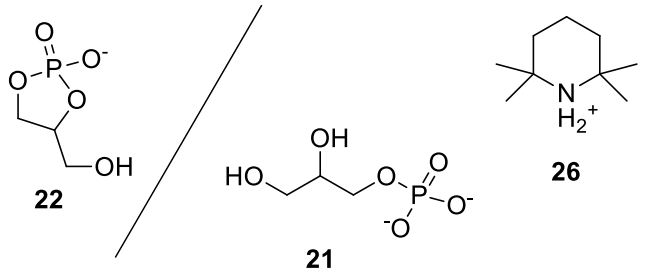


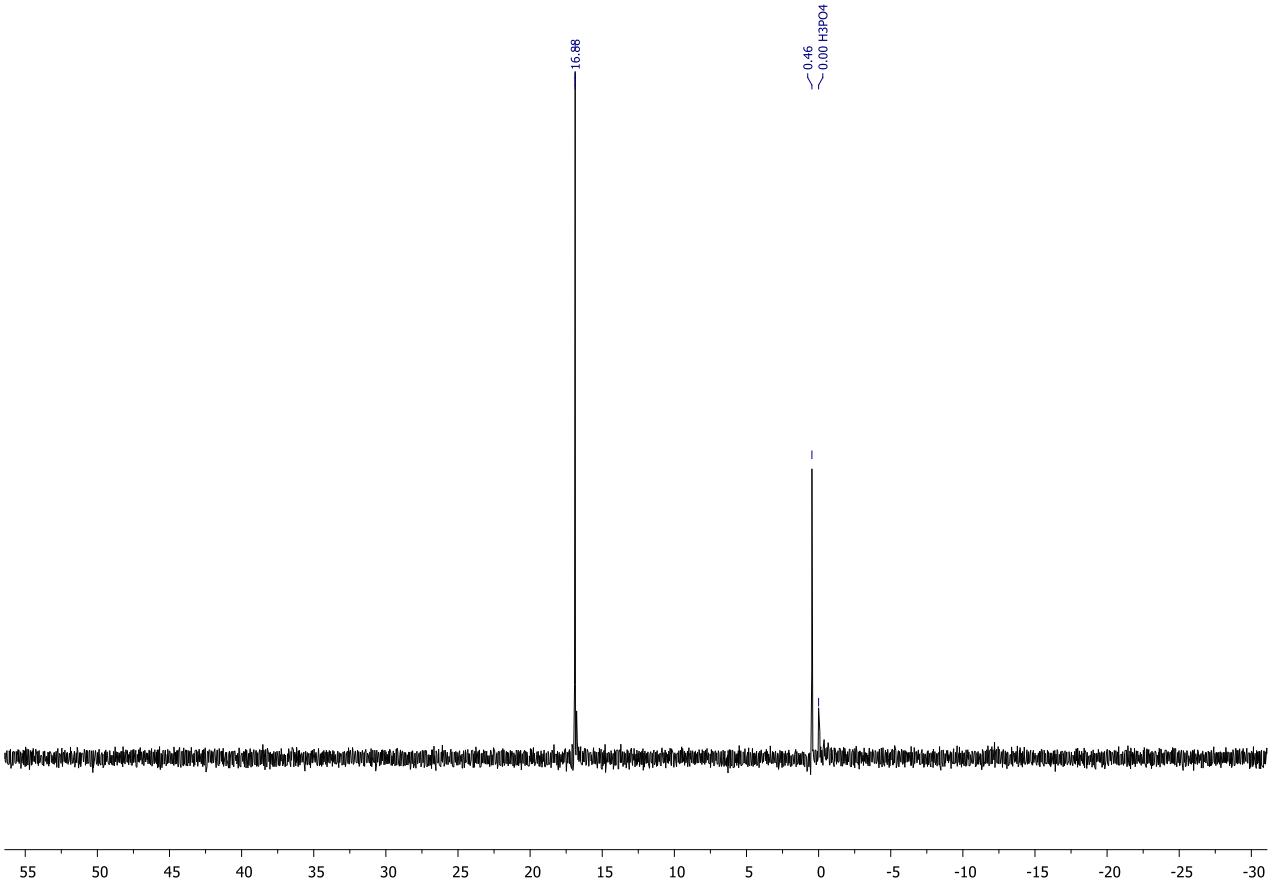
^{1}H NMR (300 MHz, D_2O) δ 4.51 (dq, *J* = 12.4, 6.4 Hz, 1H), 4.27 (dddd, *J* = 12.5, 9.3, 6.3, 0.9 Hz, 1H), 3.97 (ddd, *J* = 16.7, 8.2 Hz, 0.9 Hz, 1H), 3.87 – 3.56 (m, 8H), 3.51 (ddd, *J* = 12.0, 6.4, 0.8 Hz, 1H), 1.73 (dt, *J* = 12.8, 6.5 Hz, 4H), 1.60 (dd, *J* = 10.7, 5.6 Hz, 7H), 1.37 (s, 20H).





^{13}C NMR (75 MHz, D_2O) δ 77.36 (d, *J* = 2.1 Hz), 72.66, 71.61 (d, *J* = 7.2 Hz), 66.41, 66.01 (d, *J* = 5.4 Hz), 63.10 (d, *J* = 3.4 Hz), 62.77, 62.53 (d, *J* = 5.7 Hz), 35.07, 27.25, 16.23.

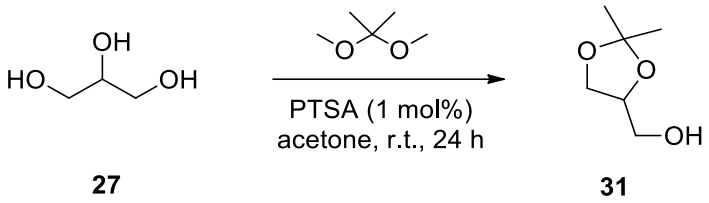




^{31}P NMR (121 MHz, D_2O) δ 16.88, 0.46.

Yield = n.d.

Solketal *or* (2,2-dimethyl-1,3-dioxolan-4-yl)methanol (31)



27 **31**

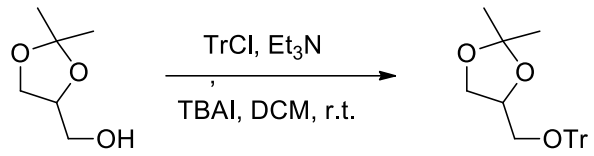
In a round bottom flask containing glycerol (**27**), 2,2-dimethoxypropane (2.0 eq.), acetone (final concentration of glycerol 1.0 M) and a catalytic amount of *p*-toluenesulphonic acid (0.01 eq.) were added in this order. The mixture was stirred at room temperature for 24 hours. At the end of this period, the crude was diluted with DCM or ethyl acetate and washed with three portions of an aqueous saturated solution of $NaHCO_3$. The organic phase was dried over Na_2SO_4, evaporated under reduced pressure and then dried under high vacuum to give the desired product as a colourless oil. NMR spectra were in agreement with literature data.[113]

Yield = 70%

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 – 4.00 (m, 1H), 3.88 (dd, *J* = 7.9, 6.8 Hz, 1H), 3.60 (dd, *J* = 8.0, 6.6 Hz, 1H), 3.47 (qd, *J* = 11.5, 4.9 Hz, 2H), 3.34 (s, 1H), 2.01 (s, 1H), 1.27 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 108.77, 75.88, 65.56, 62.49, 26.15, 24.75.

O-Trityl solketal *or* 2,2-dimethyl-4-((trityloxy)methyl)-1,3-dioxolane (34)



31 **34**

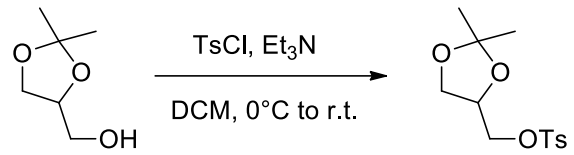
In a round bottom flask containing a solution of solketal (**31**) in DCM (final concentration of **31** in DCM 0.3 M) triethylamine (1.1 eq.) and *t*-butylammonium iodide (0.1 eq.) were added. The mixture was stirred at room temperature for 18-48 h. After this period, the crude (orange/amber colored turbid solution) was quenched with 1.5 mL of 1M HCl and suddenly turned limpid. Then, DCM was added and the organic phase was washed with three portions of an aqueous saturated solution of $NaHCO_3$ and a portion of brine. The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude was finally purified by flash chromatography on silca gel with hexane/ethyl acetate 20:1-15:1-10:1-5:1 to afford the desired product as yellowish oil. NMR spectra were in agreement with literature data.[116]

Yield = 71%

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.2 Hz, 5H), 7.40 – 7.25 (m, 10H), 4.36 (m, 1H), 4.11 (dd, *J* = 8.2, 6.5 Hz, 1H), 3.83 (dd, *J* = 8.2, 6.2 Hz, 1H), 3.37 (dd, *J* = 9.5, 5.4 Hz, 1H), 3.18 (dd, *J* = 9.5, 5.6 Hz, 1H), 1.49 (s, 3H), 1.45 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.90, 128.74, 127.86, 127.07, 109.32, 86.63, 75.00, 67.03, 64.96, 26.75, 25.54.

O-Tosyl solketal *or* (2,2-Dimethyl-1,3-dioxolan-4-yl)methyl 4-tolylsulfonate (36)



31 **36**

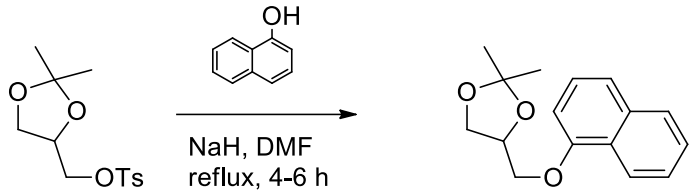
In a round bottom flask, solketal (**31**) and triethylamine (1.2 eq.) were dissolved in DCM (final concentration of **31** in DCM 1.0 M) and the reaction was put in an ice bath. After thermal equilibration, tosyl chloride (1.2 eq.) was added portionwise over 1 h under vigorous stirring. The mixture was then left under stirring overnight at room temperature. At the end of this period, the crude was washed with three portions of an aqueous saturated solution of $NaHCO_3$, a portion of water and a portion of brine, then the organic phase was dried over Na_2SO_4, filtered, evaporated under reduced pressure and dried under high vacuum. Quantitative conversion of the substrate **31** was verified by TLC and ^{1}H NMR spectroscopy. The crude was then purified by column chromatography on silica gel with hexane/ethyl acetate 15:1 as the eluent or used without further purification. NMR spectra were in agreement with literature data.[120a]

Yield = 85%

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (m, 2H), 7.33 (m, 2H), 4.31 – 4.19 (m, 1H), 4.07 – 3.88 (m, 3H), 3.74 (dd, *J* = 8.8, 5.1 Hz, 1H), 2.43 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 145.16, 132.65, 129.99, 128.04, 110.09, 72.96, 69.58, 66.22, 26.68, 25.19, 21.71.

O-(1-naphthyloxy)-solketal *or* 2,2-dimethyl-4-((naphthalen-1-yloxy)methyl)-1,3-dioxolane (40)



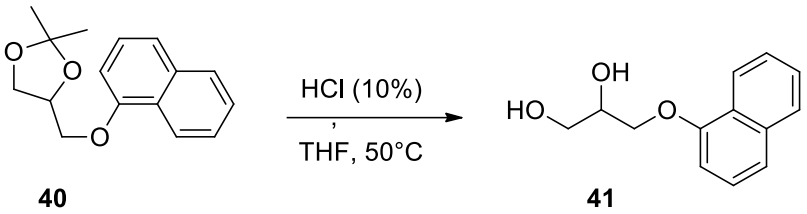
36 **40**

In a round bottom three neck flask containing O-tosyl solketal (**36**) and α-naphthol (1.5 eq.), dry DMF was added under inert atmosphere and the mixture was put under stirring. Then, a solution of sodium hydride in dry DMF was added (final concentration of **36** in DMF 0.63 M) under inhert atmosphere and the mixture was refluxed under stirring for 4 to 6 h. At the end of this period, the reaction had turned dark purple. Then, hexane and methanol were added to quench the excess of sodium hydride in safety conditions. The crude was evaporated under reduced pressure, then chloroform was added and the organic phase was washed with 7 portions of brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude was finally purified by flash chromatography on silica gel with petroleum ether/ ethyl acetate 40:1 -35:1-30:1-25:1-20:1, to yield the desired product as a dark brown oil or used without further purification in the following ketal hydrolysis step. ^{1}H NMR spectrum was in agreement with literature data.[123]

Yield = 51%

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 5.7, 3.8 Hz, 1H), 7.80 (dd, *J* = 5.9, 3.3 Hz, 1H), 7.48 (td, *J* = 10.3, 6.4 Hz, 3H), 7.37 (t, *J* = 7.9 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 4.69 – 4.58 (m, 1H), 4.32 – 4.22 (m, 2H), 4.14 (dd, *J* = 9.6, 6.3 Hz, 1H), 4.07 (dd, *J* = 8.5, 5.7 Hz, 1H), 1.52 (s, 3H), 1.45 (s, 3H).

1-O-(1-Naphthyloxy)-glycerol *or* 3-(naphthalen-1-yloxy)propane-1,2-diol (41)



40 **41**

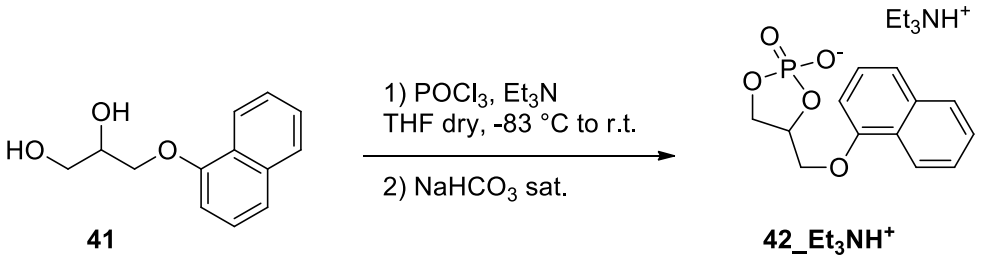
In a round bottom flask containing a 0.3 M solution of O-(1-naphthoxy) solketal (**40**) in THF, HCl (10%) was added (4 mL for 12.23 mmol of naphthoxy solketal) and the mixture was left to stir at 50°C under vigorous stirring, until consumption of the substrate **40** was complete. The crude was then diluted in diethyl ether or ethyl acetate and rine, washed with three portions of a saturated aqueous solution of $NaHCO_3$ and a portion of brine. The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude was finally purified by flash chromatography on silica gel with petroleum ether-petroleum ether/ethyl acetate 20:1-10:1, affording the desired product in form of an orange-brown solid. NMR spectra were in agreement with literature data.[123]

Yield = 68%

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 6.5, 3.2 Hz, 1H), 7.81 (dd, *J* = 6.1, 3.3 Hz, 1H), 7.55 – 7.41 (m, 3H), 7.37 (t, *J* = 7.9 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 4.32 – 4.18 (m, 3H), 3.94 (dd, *J* = 11.5, 3.5 Hz, 1H), 3.85 (dd, *J* = 11.4, 5.3 Hz, 1H), 2.36 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.16, 134.63, 127.76, 126.66, 125.93, 125.54, 121.72, 121.07, 105.15, 77.16, 70.70, 69.37, 63.96.

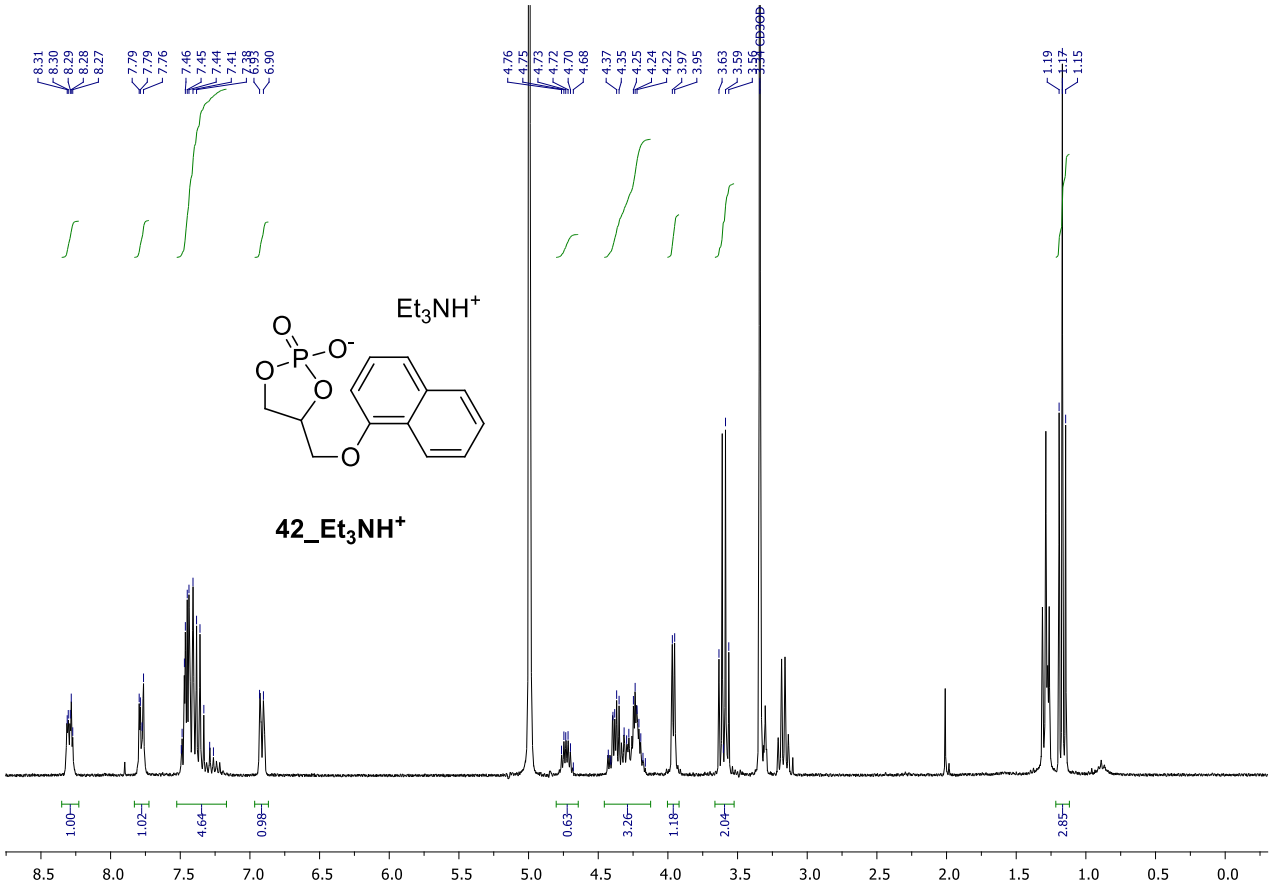
2-hydroxy-4-((naphthalen-1-yloxy)methyl)-1,3,2-dioxaphospholane 2-oxide (42) triethylammonium salt



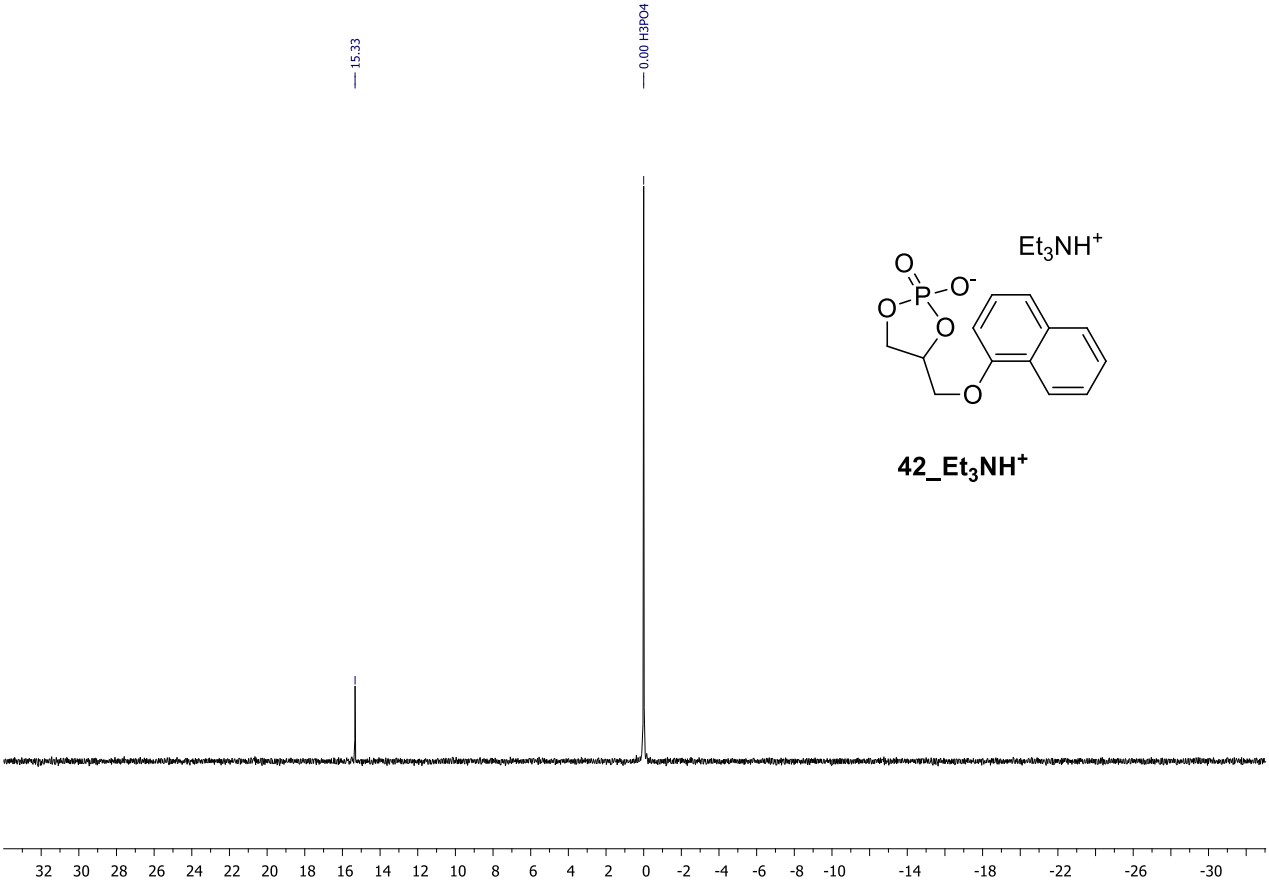
41 **42_Et_3NH^+**

To a solution of $POCl_3$ (10 eq.) in dry THF, triethylamine (10.0 eq.) was added under inert atmosphere at -83°C and the mixture was left to stir for 5 minutes. Keeping the temperature to -83°C, a 0.1 M solution of the diol **41** (303 mg, 1.4 mmol, 1.0 eq.) in dry THF was added over 5 minutes under inert atmosphere (final concentration of **41** in THF 0.1 M). The reaction was left to stir at -83 °C for 1 hour, then other 2 hours at room temperature. The reaction was then poured into an Erlenmeyer flask containing an aqueous saturated solution of $NaHCO_3$ and concentrated under reduced pressure to obtain a semisolid residue. Methanol was then added and the formation of a white insoluble solid was observed. After filtration of the white solid, the organic phase was concentrated again under reduced pressure, and filtered after the precipitation of the white solid. The operations of concentration and filtration were repeated until no more formation of white solid was observed. The crude, dissolved in methanol, was immobilized on celite and the main product was isolated by flash chromatography on silica gel with AcOEt/MeOH 3:1 as the eluent. It is soluble in water, methanol and DMSO.

Yield = n.d.

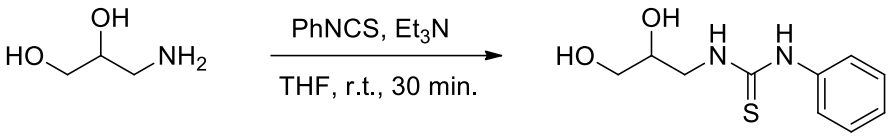


^{1}H NMR (300 MHz, CD_3OD) δ 8.30 (dd, *J* = 6.5, 2.9 Hz, 1H), 7.78 (dd, *J* = 6.5, 2.9 Hz, 1H), 7.51 – 7.19 (m, 4H), 6.92 (d, *J* = 8.3 Hz, 1H), 4.80 – 4.67 (m, 1H), 4.45 – 4.14 (m, 3H), 3.96 (d, *J* = 5.0 Hz, 1H), 3.60 (dd, *J* = 12.9, 8.3 Hz, 2H), 1.17 (t, *J* = 7.0 Hz, 3H).



^{31}P NMR (121 MHz, DMSO) δ 15.33.

1-(2,3-dihydroxypropyl)-3-phenylthiourea (44)

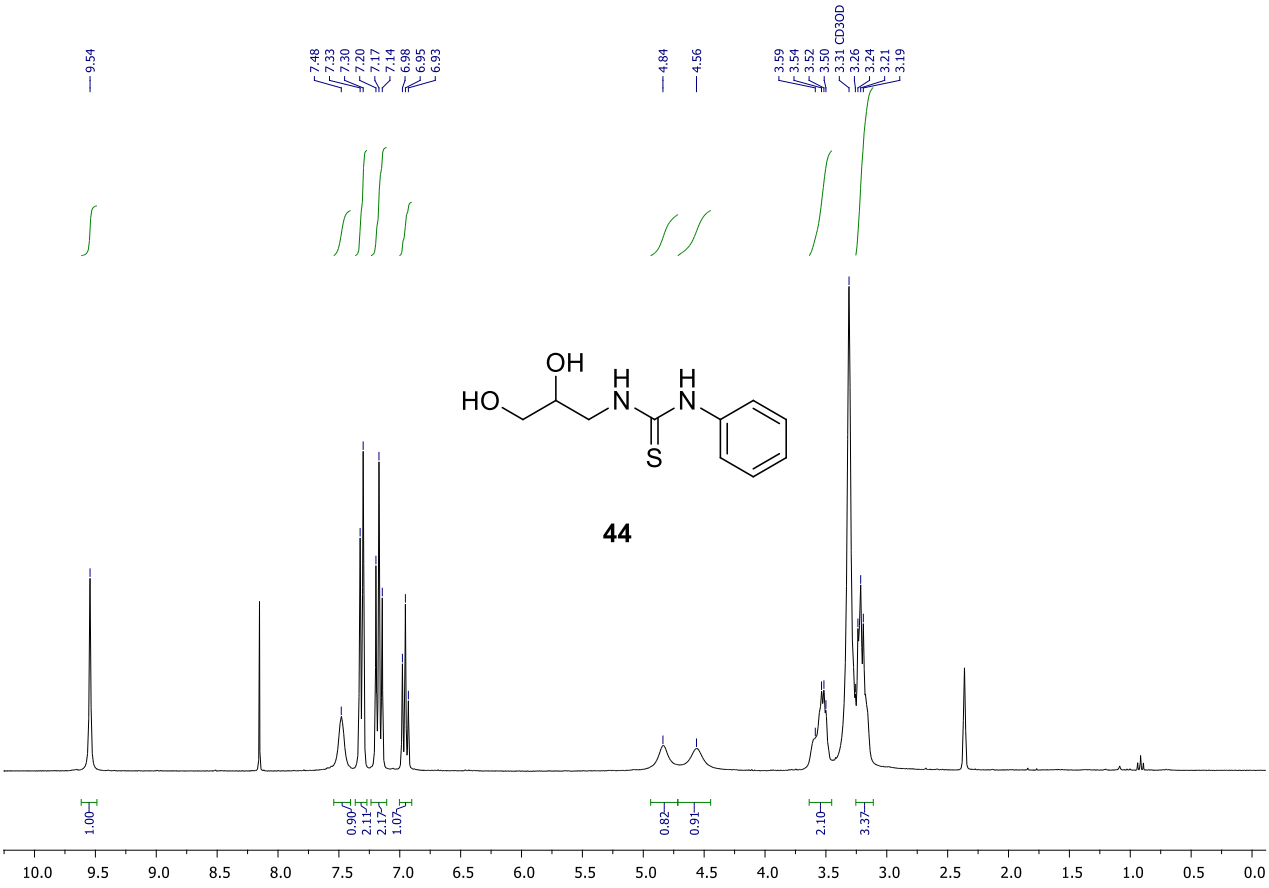


43 **44**

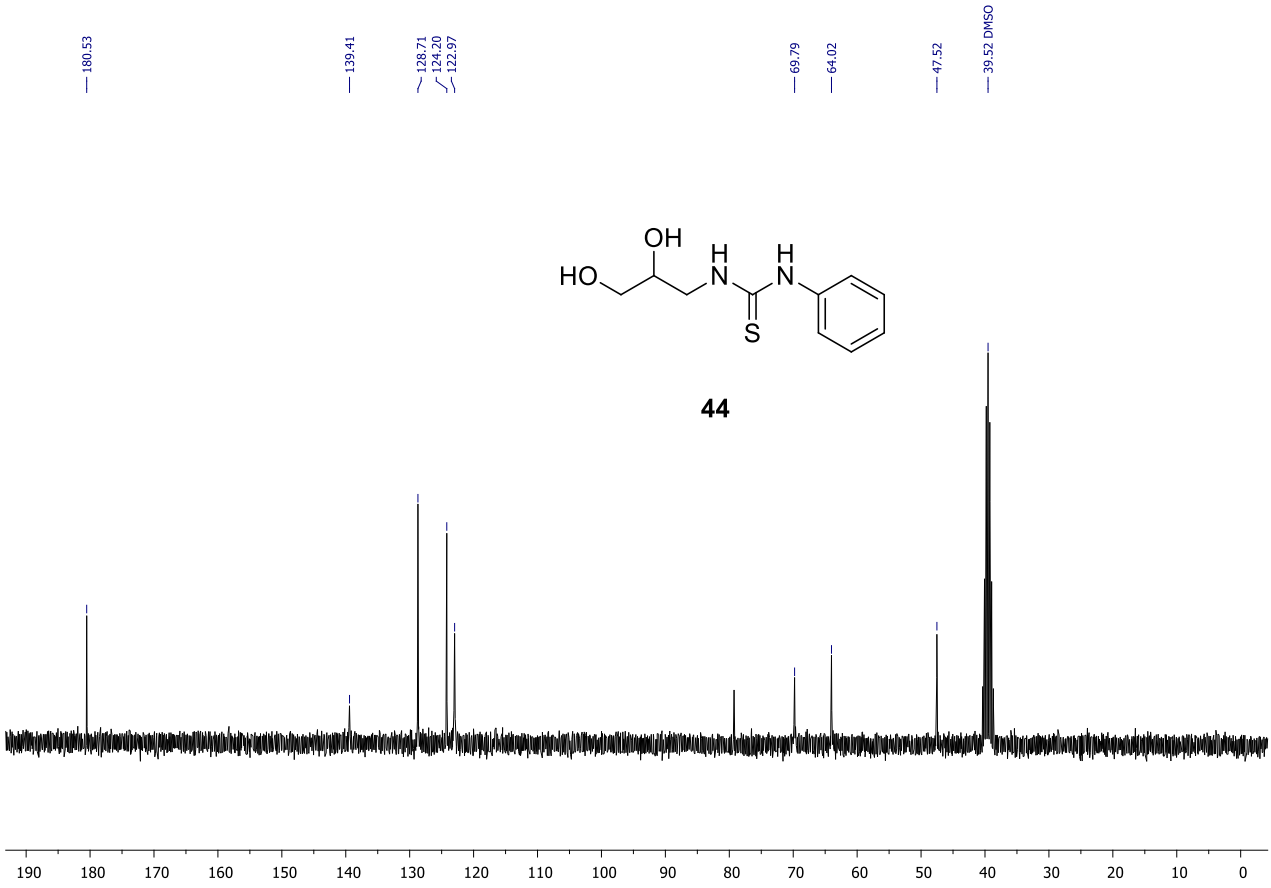
In a round bottom flask, 3-amino-1,2-propanediol (**43**) was dissolved in THF (final concentration of **43** in THF 0.24 M), triethylamine was added and the mixture was put under stirring. Phenyl isotiocianate was then added and the reaction was kept under stirring for 30 minutes. The solvent was removed under reduced pressure and the crude was purified by flash chromatography on silica gel with ethyl acetate as eluent. The product was isolated as a light-yellow glue with sulfur smell.

Yield = 92%

R_f = 0.41 (AcOEt)

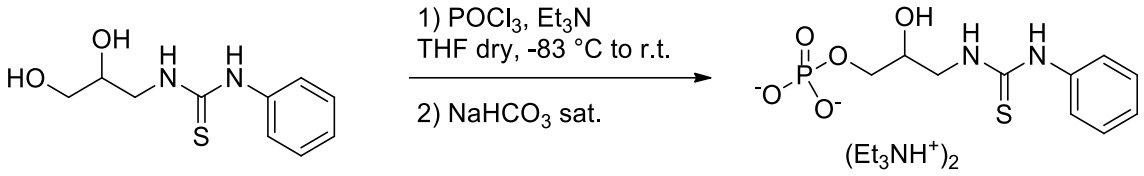


^{1}H NMR (300 MHz, DMSO) δ 9.68 (s, 1H), 7.62 (br s, 1H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 4.98 (br s, 1H), 4.70 (br s, 1H), 3.86 – 3.43 (m, 2H), 3.47 – 3.24 (m, 3H).



^{13}C NMR (75 MHz, DMSO) δ 180.53, 139.41, 128.71, 124.20, 122.97, 69.79, 64.02, 47.52.

2-Hydroxy-3-(3-phenylthioureido)propyl phosphate (45) triethylammonium salt

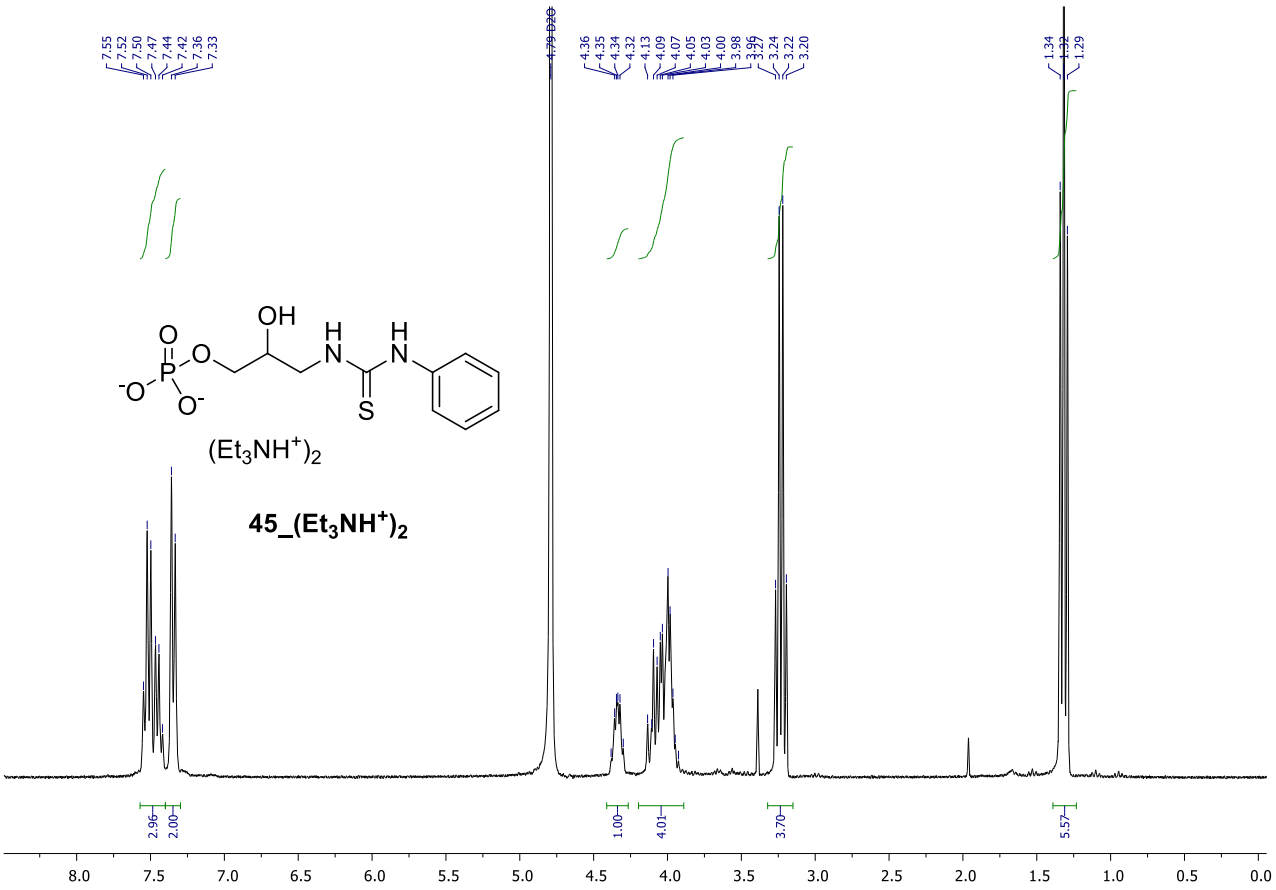


44 **45_$(Et_3NH^+)_2$**

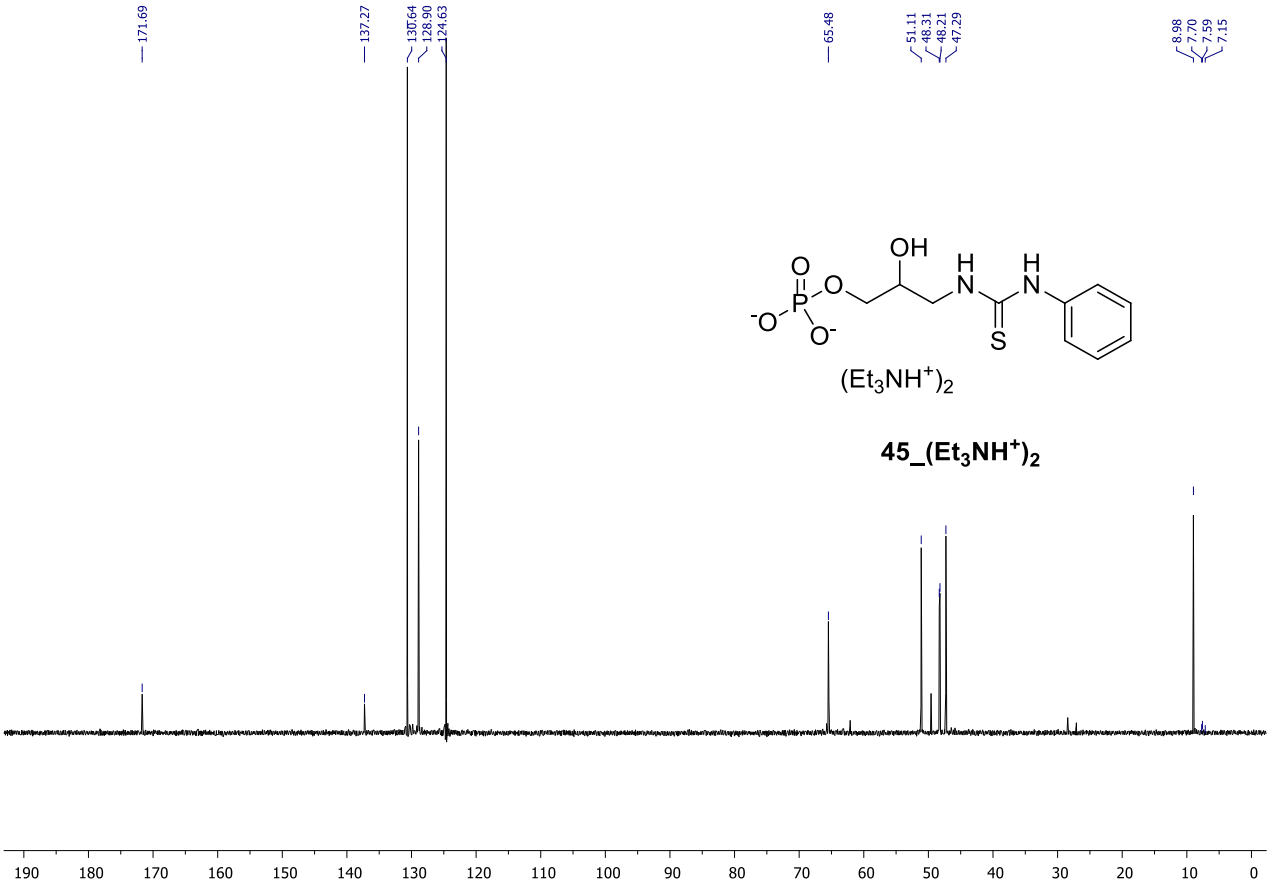
To a solution of $POCl_3$ (10 eq.) in dry THF, triethylamine (10.0 eq.) was added under inert atmosphere at -83°C and the mixture was left to stir for 5 minutes. Keeping the temperature to -83°C, a 0.2 M solution of the diol **44** (250 mg, 1.1 mmol, 1.0 eq.) in dry THF was added over 5 minutes under inert atmosphere (final concentration of **44** in THF 0.1 M). The reaction was left under stirring at -83 °C for 1/ 2.5 hours, then another 2 hours at room temperature. During the period at -83°C, the reaction had assumed a white milky colour, which later turned into cream yellow; during the period at room temperature, the reaction finally assumed a brown colour. The reaction was then poured into an Erlenmeyer flask containing 125 mL of an aqueous saturated solution of $NaHCO_3$ and concentrated under reduced pressure to obtain a semisolid residue. Methanol was added and the formation of a white insoluble solid was observed. After filtration of the white solid, the organic phase was concentrated again under reduced pressure, and filtered after the precipitation of the white solid. The operations of concentration and filtration were repeated until no more formation of white solid was observed. The crude, dissolved in the organic phase, was immobilized on celite and the main product was isolated by flash chromatography on silica gel with MeOH/AcOEt 2:1 as the eluent, as a yellow/orange oil. It is soluble in water, methanol and DMSO.

Yield (%) = n.d.

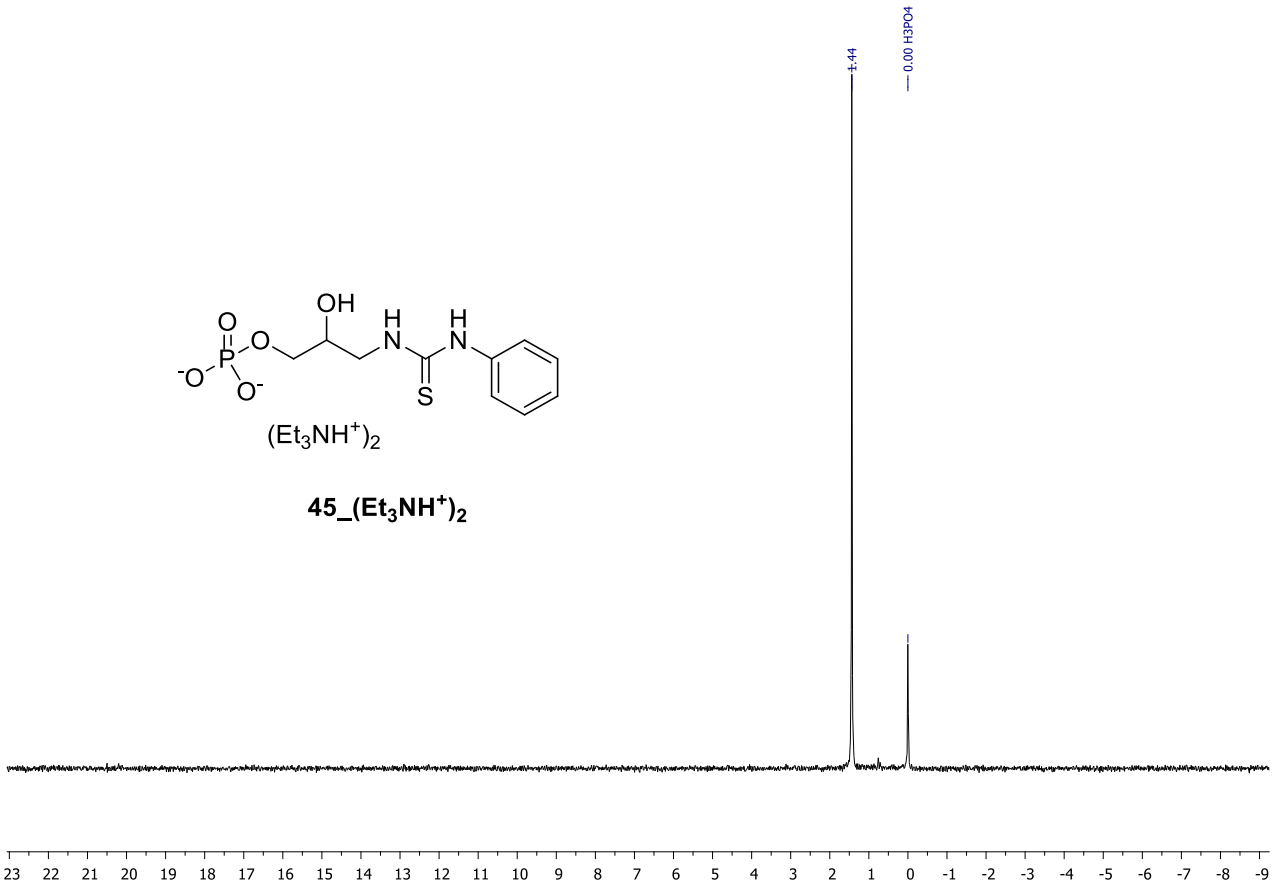
R_f = 0.1 on silica gel plates with MeOH/AcOEt 2:1 or *i*-PrOH/H_2O/NH_3(30%) 7:2:1



^{1}H NMR (300 MHz, D_2O) δ 7.58 – 7.40 (m, 3H), 7.35 (d, *J* = 7.7 Hz, 2H), 4.41 – 4.27 (m, 1H), 4.18 – 3.91 (m, 4H), 3.23 (q, *J* = 7.3 Hz, 4H), 1.32 (t, *J* = 7.3 Hz, 6H).

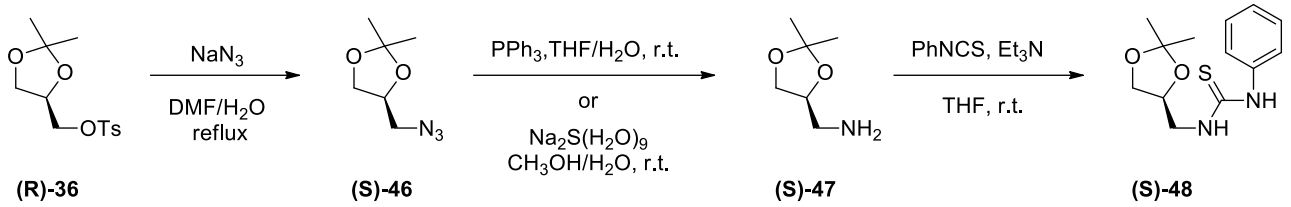


^{13}C NMR (75 MHz, D_2O) δ 171.69, 137.27, 130.64, 128.90, 124.63, 65.48, 51.11, 48.26 (d, *J* = 8.0 Hz), 47.29, 8.98.



^{31}P NMR (121 MHz, D_2O) δ 1.44

(S)-1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-3-phenylthiourea (48)

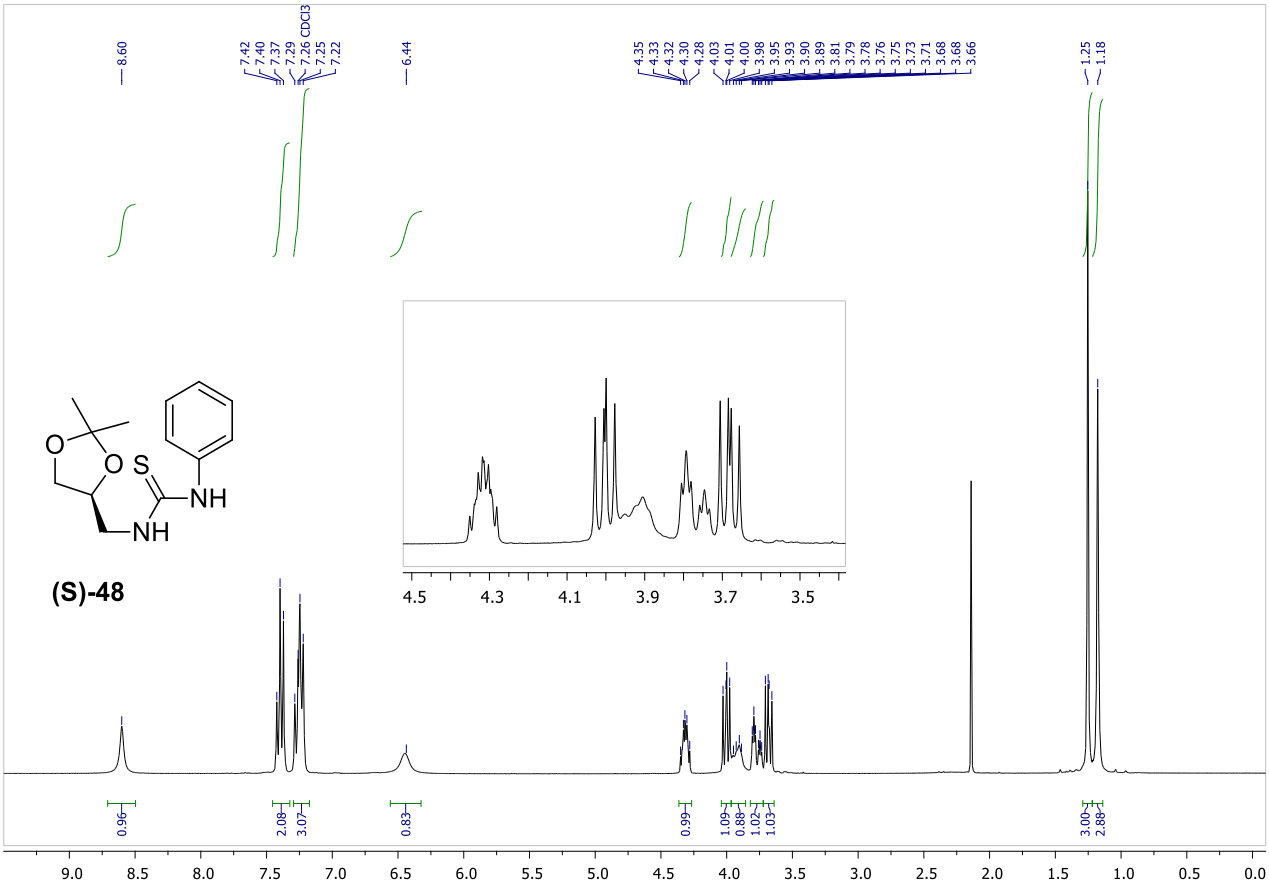


(R)-36 (S)-46 (S)-47 (S)-48

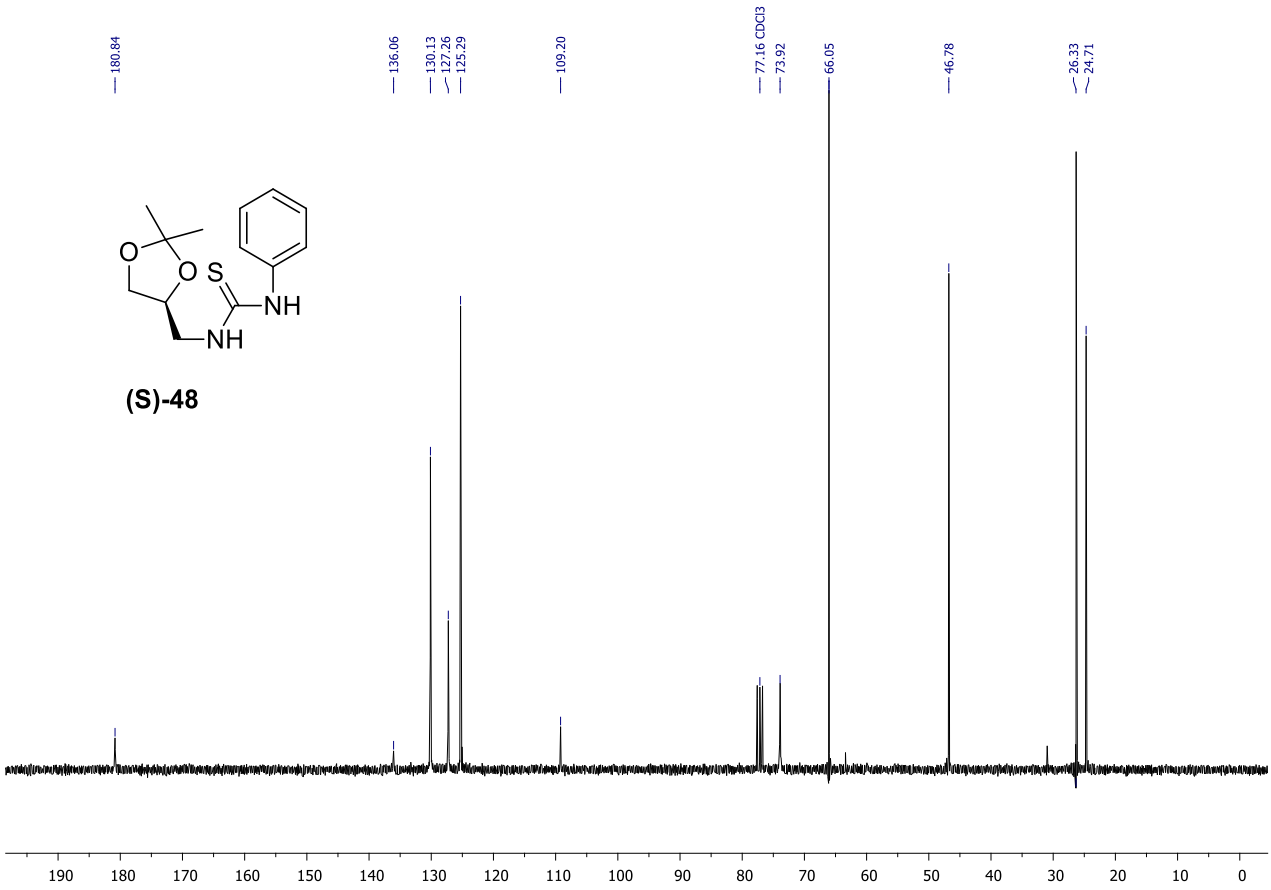
In a round bottom flask, (R)-solketal tosylate (**36**) was dissolved in DMF/water 1:1 (final concentration of **(R)-36** 0.5 M), sodium azide was added portionwise over 5 minutes and the reaction was kept under reflux and vigorous stirring overnight. At the end of this period, 50 mL of brine were added to the reaction and the crude was extracted in diethyl ether. The product was analyzed by ^{1}HNMR spectroscopy to verify the agreement with literature data and used without further purification in the following step. Methanol was added in the reaction flask containing the crude. An aqueous solution of sodium sulfide nonahydrate (1.9 eq.) was added (the concentration of each of the 2 solutions in 1 M in its own component). The biphasic mixture that was obtained was left at 55°C under stirring for 24 hours. At the end of this period, the solution had turned homogeneous, limpid and orange. Sodium chloride was added up to a saturated solution, then the crude was extracted 5 times with diethyl ether. The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. After drying the crude under high vacuum, a yellowish oil was isolated, whose ^{1}H NMR signals were in agreement with an impure sample of the desired product, which was used in the following step without further purifications. The crude was dissolved in THF (final concentration of **(S)-47** in THF 0.37 M), triethylamine (0.1 eq.) was added and the mixture was kept under stirring at room temperature until complete dissolution of the substrate. Phenyl isotiocianate was added and the reaction was kept under stirring for other 5 hours. The solvent was evaporated under reduced pressure and the crude was purified by flash chromatography on silica gel with a hexane/ethyl acetate 3:1 as eluent. The desired product was isolated as a white solid.

Yield = 20% over 4 steps (including quantitative tosylation of **(S)-31** to **(R)-36**)

R_f = 0.24 (Hex: AcOEt 3:1)



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (br s, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.25 (m, 3H), 6.44 (br s, 1H), 4.37 – 4.27 (m, 1H), 4.00 (dd, *J* = 8.5, 6.7 Hz, 1H), 3.92 (dd, *J* = 12.7, 5.5 Hz, 1H), 3.77 (dt, *J* = 14.1, 3.7 Hz, 1H), 3.68 (dd, *J* = 8.5, 6.3 Hz, 1H), 1.25 (s, 3H), 1.18 (s, 3H).



^{13}C NMR (75 MHz, $CDCl_3$) δ 180.84, 136.06, 130.13, 127.26, 125.29, 109.20, 73.92, 66.05, 46.78, 26.33, 24.71.

3.9 Bibliography

[1] List, B.; Maruoka, K. *Asymmetric Organocatalysis*, Thieme Chemistry, **2012**.

[2] Von Liebig, J. *Ann. Chem. Pharm.* **1860**, *113*, 246.

[3] [a] Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496; [b] Eder, U.; Wiechert, R.; Sauer, G. German Offenlegungsschrift (DOS) 2 014 757, **1970**; [c] Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615; [d] Hajos, Z. G.; Parrish, D. R. German Offenlegungsschrift (DOS) 2 102 623, **1970**; [e] Dolling, U.-H.; Davis, P.; Gabrowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446; [f] O'Donnel, M. J.; Wu, S.; Hoffmann, J. C. *Tetrahedron Lett.* **1994**, *50*, 450; [g] Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595.

[4] Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519.

[5] List, B.; Lerner, R.; Barbas, C. F. III *J. Am. Chem. Soc*. **2000**, *122*, 2395.

[6] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

[7] MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

[8] Wynberg, H. *Asymmetric catalysis by alkaloids* in *Topics of Stereochemistry*, vol.16, Wiley Ed., **1986.**

[9] Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481.

[10] Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178.

[11] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

[12] Cram, D. J. *J. Am. Chem. Soc.* **1952**, *74*, 5828.

[13] [a] Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2004**, 43, 1983; [b] Cobb, A J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558.

[14] [a] Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.; [b] Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 794.

[15] [a] Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, 124, 10012; [b] Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, 124, 12964.

[16] Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.

[17a] Giemsa, G.; Halberkann, J. *Ber. Dtsch. Chem. Ges*. **1918**, *51*, 1325; [b] Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, 57, 2768.

[18] [a] Lygo, B.; Crosby, J.; Lowdon, T. R.; Peterson, J. A.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2403; [b] Lygo, B.; Andrews, B. I.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **2002**, *43*, 8015; [c] Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222.

[19] [a] Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, 122, 5228; [b] Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139.

[20] [a] Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, 3437; [b] Miyaura, N.; Suzuki, A. *Chem. Commun.* **1979**, 866.

[21] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

[22] [a] Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632; [b] Ting, A.; Goss, J. M.; McDougal, N. T.; Schaus, S. E. *Top. Curr. Chem.* **2010**, *291*, 145.

[23] Rueping, M.; Parmar, D.; Sugiono, E. *Asymmetric Brønsted Acid Catalysis*, Wiley-VCH Ed., **2016**.

[24] [a] Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047; [b] Liao, S.; Čorić, I.; Wang, Q.; List, B. *J. Am. Chem. Soc.* **2012**, *134*, 10765; [c] Kim, J. H.; Čorić, I.; Vellalath, S.; List, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 4474; [d] Schreyer, L.; Properzi, R.; List, B. *Angew. Chem. Int. Ed.* **2019**, *58*, 12761.

[25] [a] Cornforth, J. *Proc. R. Soc. London, Ser. B.* **1978**, *203*, 101; [b] Cornforth, J.; Cornforth, R. H.; Gray, R. T. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2289; [c] Cornforth, J.; Sierakowski, A. F.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2299; [d] Cornforth, J.; Ridley, D. D.; Sierakowski, A. F.; Uguen, D.; Wallace, T. W.; Hitchcock, P. B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2317; [e] Cornforth, J.; Ridley, D. D.; Sierakowski, A. F.; Uguen, D.; Wallace, T. W. *J. Chem. Soc., Perkin Trans.* 1 **1982**, 2333; [f] Cornforth, J.; Robertson, A. D. *J. Chem. Soc., Perkin Trans. 1* **1987**, 867; [g] Cornforth, J.; Huguenin, L. M.; Wilson, J. R. H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 871; [h] Cornforth, J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2889.

[26] Akiyama, T.; Itoh, J; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566.

[27] Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*, Springer, New York, **2004**.

[28] Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5326.

[29] Jacques, J.; Fouquey, C.; Viterbo, R. *Tetrahedron Lett.* **1971**, 4617.

[30] [a] Arnold, W.; Daly, J. J.; Imhof, R.; Kyburz, E. *Tetrahedron Lett.* **1983**, *24*, 343; [b] Wilen, S. H.; Qi, J. Z.; Williard, P. G. *J. Org. Chem.* **1991**, *56*, 485.

[31] Eelkema, R.; Feringa, B. L. *Org. Lett.* **2006**, *8*, 1331.

[32] Serafini, S.; Padovan, P. US Patent 9428442, **2016**.

[33] [a] Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 8834; [b] Simonin, C.; Awale, M.; Brand, M.; Van Deursen, R.; Schwartz, J.; Fine, M.; Kovacs, G.; Häfliger, P.; Gyimesi, G.; Sithampari, A.; Charles, R.-P.; Hediger, M. A.; Reymond, J.-L. *Angew. Chem. Int. Ed.* **2015**, *54*, 14748; [c] Wang, P.; Ma, G.-R.; Yu, S.-L.; Da, C.-S. *Chirality* **2019**, *31*, 79.

[34] Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424.

[35] Toda, F.; Tanaka, K.; Iwata, S. *J. Org. Chem.* **1989**, *54*, 3007.

[36] Jacques, J.; Fouquey, C. *Org. Synth.* **1988**, *67*, 1.

[37] Christ, P.; Lindsay, A. G.; Vormittag, S. S.; Neudoerfl, J.-M.; Berkessel, A.; O'Donoghue, A. C. *Chem. Eur. J.* **2011**, *17*, 8524.

[38] Yang, C.; Xue, X.-S.; Jin, J.-L.; Li, X.; Cheng, J.-P. *J. Org. Chem.* **2013**, *78*, 7076.

[39] Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 11569.

[40] [a] Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199; [b] Anh, N. T.; Eisenstein, *O. Nouv. J. Chim.* **1977**, *1*, 61; [c] Anh, N. T.; Eisenstein, O.; Lefour, J-M.; Dau, M-E. *J. Am. Chem. Soc.* **1973**, *95*, 6146.

[41] Fleischmann, M.; Drettwan, D.; Sugiono, E.; Rueping, M.; Gschwind, R. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 6364.

[42] Appel, R.; Chelli, S.; Tokuyasu, T.; Troshin, K.; Mayr, H. *J. Am. Chem. Soc.* **2013**, *135*, 6579.

[43] Simón, L.; Goodman, J. M. *J. Org. Chem.* **2011**, *76*, 1775.

[44] Reid, J. P.; Simón, L.; Goodman, J. M. *Acc. Chem. Res.* **2016**, *49*, 1029.

[45] Easson, L. H.; Stedman, E. *J. Biochem.* **1933**, *27*, 1257.

[46] Vadim, A. D. *Chirality* **1997**, *9*, 99.

[47] Marcelli, T.; Hammar, P.; Himo, F. *Chem. Eur. J.* **2008**, *14*, 8562.

[48] Gridnev, I. D.; Kouchi, M.; Sorimachi, K.; Terada, M. *Tetrahedron Lett.* **2007**, *48*, 497.

[49] Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216.

[50] Zheng, W.; Wojtas, L.; Antilla, J. C. *Angew. Chem. Int. Ed.* **2010**, *49*, 6589.

[51] Rueping, M.; Antonchick, A. P.; Brinkmann, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 6903.

[52] [a] Kang, Q.; Zhao, Z.-A.; You, S.-L. *Org. Lett.* **2008**, *10*, 2031; [b] Zhou, J.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 7498; [c] Antilla, J. C. *Org. Lett.* **2009**, *11*, 1075; [d] Wakchaure, V. N.; Zhou, J.; Hoffmann, S.; List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 4612; [e] Rueping, M.; Antonchick, A. P. *Angew. Chem. Int. Ed.* **2008**, *47*, 5836; [f] Schrader, W.; Handayani, P. P.; Zhou, J.; List, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 1463.

[53] Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804.

[54] Liu, W.-J.; Chen, X.-H.; Gong, L.-Z. *Org. Lett.* **2008**, *10*, 5357.

[55] Tsuji, N.; Kennemur, J.; Buyck, T.; Lee, S.; Prévost, S.; Kaib, P. S.; Bykov, D.; Farès, C.; List, B. *Science* **2018**, 359, 1501.

[56] [a] Wendt, K. U.; Poralla, K.; Schulz, G. E. *Science* **1997**, *277*, 1811; [b] Gao, S.-S.; Garcia-Borràs, M.; Barber, J. S.; Hai, Y.; Duan, A.; Garg, N. K.; Houk, K. N.; Tang, Y. *J. Am. Chem. Soc.* **2017**, *139*, 3639.

[57] [a] Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179; [b] Dang, T. T.; Boeck, F.; Hintermann, L. *J. Org. Chem.* **2011**, *76*, 9353.

[58] Bae, H. Y.; Höfler, D.; Kaib, P. S.; Kasaplar, P.; De, C. K.; Döhring, A.; Lee, S.; Kaupmees, K.; Leito, I.; List, B. *Nat. Chem.* **2018**, *10*, 888.

[59] Lee, S.; Bae, H. Y.; List, B. *Angew. Chem. Int. Ed*. **2018**, *57*, 12162.

[60] [a] Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198; [b] Terada, M.; Tanaka, H.; Sorimachi, K. *J. Am. Chem. Soc.* **2009**, *131*, 3430; [c] Zhang, Q.-W.; Fan, C.-A.; Zhang, H.-J.; Tu, Y.-Q.; Zhao, Y.-M.; Gu, P.; Chen, Z.-M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8572.

[61] Kim, J. H.; Čorić, I.; Vellalath, S.; List, B. *Angew. Chem. Int. Ed*. **2013**, *52*, 4474.

[62] [a] Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696; [b] Liang, Y.; Rowland, E. B.; Rowland, G. B.; Perman, J. A.; Antilla, J. C. *Chem. Commun.* **2007**, 4477; [c] Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216; [d] Ingle, G. K.; Mormino, M. G.; Wojtas, L.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 4822; [e] Cheng, X.; Vellalath, S.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786; [f] Vellalath, S.; Čorić, I.; List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 9749; [g] Rueping, M.; Antonchick, A. P.; Sugiono, E.; Grenader, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 908; [h] Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744; [i] Terada, M. *Synthesis* **2010**, 1929.

[63] Cai, Y.; Tang, Y.; Atodiresei, I.; Rueping, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 14126.

[64] Piancatelli, G.; Scettri, A.; Barbadoro, S. *Tetrahedron Lett.* **1976**, *17*, 3555.

[65] [a] Mueller, S.; List, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 9975; [b] Rueping, M.; Antonchick, A. P. *Angew. Chem. Int. Ed.* **2008**, *47*, 10090.

[66] [a] Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 2411; [b] Zamfir, A.; Tsogoeva, S. B. *Synthesis* **2011**, 1988; [c] Serdyuk, O. V.; Zamfir, A.; Hampel, F.; Tsogoeva, S. B. *Adv. Synth. Catal.* **2012**, *354*, 3115; [d] Rueping, M.; Maji, M. S.; Küçük, H. B.; Atodiresei, I. *Angew. Chem. Int. Ed.* **2012**, *51*, 12864; [e] Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652; [f] He, L.; Chen, X.-H.; Wang, D.-N.; Luo, S.-W.; Zhang, W.-Q.; Yu, J.; Ren, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2011**, *133*, 13504; [g] Yu, J.; He, L.; Chen, X.-H.; Song, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2009**, *11*, 4946; [h] Wang, C.; Chen, X.-H.; Zhou, S.-M.; Gong, L.-Z. *Chem. Commun.* **2010,** *46*, 1275; [i] Shi, F.; Luo, S.-W.; Tao, Z.-L.; He, L.; Yu, J.; Tu, S.-J.; Gong, L.-Z. *Org. Lett.* **2011**, *13*, 4680; [j] Cheng, M.-N.; Wang, H.; Gong, L.-Z. *Org. Lett.* **2011**, *13*, 2418; [k] Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819; [l] Shi, F.; Tao, Z.-L.; Luo, S.-W.; Tu, S.-J.; Gong, L.-Z. *Chem. Eur. J.* **2012**, *18*, 6885; Shi, F.; Zhu, R.-Y.; Liang, X.; Tu, S.-J. *Adv. Synth. Catal.* **2013**, *355*, 2447; [m] Guo, C.; Song, J.; Gong, L.-Z. *Org. Lett.* **2013**, *15*, 2676.

[67] [a] Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4796; [b] Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141; [c] Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070; [d] Momiyama, N.; Tabuse, H.; Terada, M. *J. Am. Chem. Soc.* **2009**, *131*, 12882.

[68] [a] Gong, L.-Z.; Chen, X. H.; Xu, X. Y. *Chem. Eur. J.* **2007**, *13*, 8920; [b] Gong, L.-Z.; Chen, X.-H.; Xu, X.-Y. *Chem. Eur. J.* **2007**, *13*, 8920; [c] Li, X.; Deng, H.; Luo, S.; Cheng, J. P. *Eur. J. Org. Chem.* **2008**, 4350; [d] Yue, T.; Wang, M.-X.; Wang, D.-X.; Masson, G.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6717; [e] Jiang, J.; Yu, J.; Sun, X.-X.; Rao, Q.-Q.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2008**, *47*, 2458; [f] Jiang, J.; Qing, J.; Gong, L.-Z. *Chem. Eur. J.* **2009**, *15*, 7031; [g] Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156; [h] Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156; [i] Su, Y.; Bouma, M. J.; Alcaraz, L.; Stocks, M.; Furber, M.; Masson, G.; Zhu, J. *Chem. Eur. J.*

2012, *18*, 12624; [j] An, D.; Fan, Y.-S.; Gao, Y.; Zhu, Z.-Q.; Zheng, L.-Y.; Zhang, S.-Q. *Eur. J. Org. Chem.* **2014**, 301; [k] Wang, Y.; Tu, M.-S.; Shi, F.; Tu, S.-J. *Adv. Synth. Catal.* **2014**, *356*, 2009.

[69] [a] Terada, M.; Yokoyama, S.; Sorimachi, K.; Uraguchi, D. *Adv. Synth. Catal.* **2007**, *349*, 1863; [b] Li, G.; Rowland, G. B.; Rowland, E. B.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 4065; [c] Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5661; [d] He, Y.; Lin, M.; Li, Z.; Liang, X.; Li, G.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 4490.

[70] [a] Cai, Q.; Zheng, C.; You, S.-L. *Angew. Chem. Int. Ed.* **2010**, *49*, 8666; [b] Gu, Q.; Rong, Z.-Q.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4056; [c] Rubush, D. M.; Morges, M. A.; Rose, B. J.; Thamm, D. H.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 13554.

[71] [a] Lu, M.; Zhu, D.; Lu, Y.; Zeng, X.; Tan, B.; Xu, Z.; Zhong, G. *J. Am. Chem. Soc.* **2009**, *131*, 4562; [b] Lu, M.; Lu, Y.; Zhu, D.; Zeng, X.; Li, X.; Zhong, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 8588.

[72] Schevchenko, G. A.; Oppelaar, B.; List, B. *Angew. Chem. Int. Ed.* **2018**, *57*, 10756.

[73] Guo, X.; Mayr, H. *J. Am. Chem. Soc.* **2013**, *135*, 12377.

[74] https://www.sigmaaldrich.com/catalog/product/aldrich/689890?lang=it&region=IT , 16-09-2019.

[75] Chen, Y.; Cheng, D.; Zhang, J.; Wang, Y.; Liu, X.; Tan, B. *J. Am. Chem. Soc.* **2015**, *137*, 15062.

[76] Moliterno, M.; Cari, R.; Puglisi, A.; Antenucci, A.; Sperandio, C.; Moretti, E.; Di Sabato, A.; Salvio, R.; Bella, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6525.

[77] [a] Gao, H.; Xu, Q.-L.; Keene, C.; Yousufuddin, M.; Ess, D. H.; Kürti, L. *Angew. Chem. Int. Ed.* **2016**, *55*, 566; [b] Wang, J.-Z.; Zhou, J.; Xu, C.; Sun, H., Kürti, L.; Xu, Q.-L. *J. Am. Chem. Soc.* **2016**, *138*, 5202.

[78] Gobley, T. *J. Pharm. Chim.* **1850**, *17*, 411.

[79] Gobley, T. *J. Pharm. Chim.* **1846**, *9*, 81.

[80] Scholfield, C. R. *J. Am. Oil Chem.' Soc.* **1981**, *58*, 889.

[81] Schneider, M. P. in *Chemical Probes in Biology*, Springer Science & Business Media, Berlin, **2003**, p.39.

[82] Birman, V. B.; Rheingold, A. L.; Lam, K.-C. *Tetrahedron Asymmetry* **1999**, *10*, 125.

[83] [a] Ukita, T.; Nagasawa, K. *Pharm. Bull.* **1959**, *7*, 401; [b] Kugel, L.; Halmann, M. *J. Am. Chem. Soc.* **1967**, *89*, 4125; [c] Fordham, W. D.; Wang, J. H. *J. Am. Chem. Soc.* **1967**, *89*, 4198; [d] Clarke, M.; Dawson, R. M. C. *Biochem. J.* **1976**, *153*, 745; [e] Patel, B. H.; Percivalle, C.; Ritson, D. J.; Duffy, C. D.; Sutherland, J. D. *Nat. Chem.* **2015**, *7*, 301.

[84] [a] Hunt, J. A. *Pharm. J.*, **1999**, *263*, 985; [b] Bonnardeaux, J. *Glycerin Overview*, Report for the Western Australia Department of Agriculture and Food, **2006**; [c] Pagliaro, M; Ciriminna, R.; Kimura, H.; Rossi, M.; Della Pina, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 4434.

[85] Karmee, S. K. *Synth. Comm.* **2013**, *43*, 450

[86] Thomas, B. N.; Christopher M. Lindemann, C. M.; Corcoran, R. C.; Cotant, C. L.; Janet E. Kirsch, J. E.; Persichini, P. J. *J. Am. Chem. Soc.* **2001**, *124*, 1227.
[87] De Wilde, H; De Clercq, P.; Vandewalle, M. *Tetrahedron Lett.* **1987**, *28*, 4757.

[88] Koy, C.; Michalik, M.; Oehme, G.; Fischer, C.; Tillack, A.; Baudisch, H.; Kempe, R. *Phosphorus Sulfur* **1999**, *152*, 203.

[89] Dolsophon, K.; Ruangsupapichat, N.; Soponpong, J.; Sungsuwan, S.; Prabpai, S.; Kongsaeree, P.; Thongpanchang, T. *Tetrahedron Asymmetry* **2016**, *27*, 1113.

[90] Lopez-Alvarado, P.; Avendano, C.; Menendez, J. C. *Synth. Commun.* **2002**, *32*, 3233.

[91] Fries; S. *Liebig. Ann. Chem.* **1930**, *484*, 245.

[92] Yasuda M.; Kojima, R.; Tsutsui, H.; Watanabe L. A.; Hobo, J.; Yamashita, T.; Shiragami, T.; Shima, K. *Chem. Lett.* **1999**, *28*, 1269.

[93] Azad, S. M.; Bennett, S. M. W.; Brown, S. M.; Green, J.; Sinn, E.; Topping, C. M.; Woodward, S. *J. Chem. Soc. - Perkin Trans. 1* **1997**, 687.

[94] Adroja, P. P.; Gami, S. P.; Patel, J. P.; Parsania, P. H. *Eur. J. Org. Chem.* **2011**, *8*, 762.

[95] Yang, L.; Yang, F.; Lan, J.; Gao, G.; You, J.; Su, X. *Org. Biomol. Chem.* **2011**, *9*, 2618.

[96] Gupta, P.; Rouf, A.; Shah, A.; Mahajan, N.; Chaubey, S. C.; Taneja, S. C. *J. Mol. Catal. B: Enzymatic* **2014**, *101*, 35.

[97] Fersht, A. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1970**, *92*, 5432.

[98 a] Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 562; [b] Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129.

[99] Staab, H. A.; Rohr, W. *Newer Methods Prep. Org. Chem.* **1968**, *5*, 61.

[100] Temperini, A.; Terlizzi, R.; Testaferri, L.; Tiecco, M. *Synth. Commun.* **2009**, *40*, 295.

[101] Qu, S.; Greenhalgh, M. D.; Smith, A. D. Chem. Eur. J. **2019**, *25*, 2816.

[102] Juárez-Hernandez, M; Johnson, D.V.; Holland, H. L.; McNulty, J.; Capretta, A. *Tetrahedron Asymmetry* **2003**, *14*, 289.

[103] Gupta, P.; Rouf, A.; Ali Shah, B.; Mahajan, N.; Chaubey, A.; Taneja, S. C. *J. Mol. Catal., B Enzym.* **2014**, *101*, 35.

[104] Nordin, O; Nguyen, B.-V..; Vörde, C.; Hedenström, E.; Hödberg, H.-E. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 367.

[105] Huynh, M. H. V.; Meyer, T. J. *Chem. Rev.* **2007**, *107*, 5014.

[106] Gao, H.; Kürti, L. *Transition Metal Free Synthesis of Biaryl Compounds*, WO 2017/083719 A1.

[107] Kühl, O. *Phosphorus-31 NMR Spectroscopy*, Springer, Berlin, **2008**.

[108] Ukita, T.; Nagasawa, K.; Irie, M. *Pharm. Bull.* **1957**, *5*, 121

[109] Piovesana, S.; Scarpino Schietroma, D. M.; Bella, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 6216.

[110] Llewellyn, D. B.; Adamson, D.; Arndtsen, B. A. *Org. Lett.* **2000**, *2*, 4165.

[111] Mahlau, M.; List, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 518.

[112] Mayer, S.; List, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 4193.

[113] Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368.

[114] Hanes, C. S.; Isherwood, F. A. *Nature* **1949**, *164*, 1107.

[115] [a] Bandurski, R. S.; Axelrod, B. *J. Biol. Chem.* **1951**, *193*, 405; [b] Burrows, S.; Grylls, F. S. M.; Harrison, J. S. *Nature* **1952**, *167*, 800.

[116] Mallik, S.; Prasad, R.; Bhattacharya, A.; Sen, P. *ACS Med. Chem. Lett.* **2018**, 9, 434.

[117] [a] Molotkovskii, Y. G.; Bergel'son, L. D. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, *4*, 925; [b] Molotkovskii, Y. G.; Mikulina, L. F.; Bergel'son, L. D. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, *4*, 927; [c] Molotkovskii, Y. G.; Bergel'son, L. D. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, *10*, 2321; [d] Lipshutz, B. H.; Harvey, D. F. *Synth. Comm.* **1982**, *12*, 267; [e] Subhas Bose, D.; Jayalakshmi, B.; Venkat Narsaiah, A. *Synthesis* **2000**, *1*, 67; [f] Malla Reddy, S.; Venkat Reddy, Y.; Venkateswarlu, Y. *Tetrahedron Lett.* **2005**, *46*, 7439.

[118] Ghosh, S.; Maitra, U. *Org. Lett.* **2006**, *8*, 399.

[119] Timmer, M. S. M.; Sauvageau, J.; Foster, A. J.; Ryan, J.; Lagutin, K.; Shaw, O.; Harper, J. L.; Sims, I. M.; Stocker, B. L. *J. Org. Chem.* **2014**, *79*, 7332.

[120] [a] Gibson, F. S.; Park, M. S.; Rapoport, H. *J. Org. Chem.* **1994**, 59, 7503; [b] Dobozewski, B.; Groaz, E.; Herdewijn, P. *Eur. J. Org. Chem.* **2013**, 4804.

[121] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[122] Jacobson, B. M. *J. Chem. Educ.* **1988**, *65*, 459.

[123] Ogg, G. D.; Neilson, D. G.; Stevenson, I. H.; Lyles, G. A. *J. Pharm. Pharmacol.* **1987**, *39*, 378.