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***New designs in organocatalysis to unlock novel
catalytic systems and complex chemical spaces***

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*"Organic chemists are like masons...
They differ only because the dimensions
of the bricks are different."*

-A. Brusa

*"It is necessary to think about on the already seen to
understand it better."*

-Anonymous

*"...(Because) There is nothing worse than bitterness and
vengeance... Always keep your dignity and be true to yourself."*

-M. Satrapi, "Persepolis"

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Abstract

In Chapter 1, a general introduction to catalysis and its branches that will be encountered in this manuscript has been given.

In Chapter 2, an application of a novel class of aminocatalysts for the asymmetric Michael addition of masked acetaldehyde as dimethyl acetal to β -nitrostyrenes to produce key intermediates for the synthesis of a class of APIs (Active Pharmaceutical Ingredients) will be shown. These catalysts are specifically designed to work in water acting like micelles, thus avoiding the use of polluting organic solvents, while the acetaldehyde is released using catalytic amount of Amberlyst-15, an acidic heterogeneous resin. Critical to the success is the use of chemometrics-assisted 'Design of Experiments' (DoE) optimization during the development, which allowed to investigate the chemical space in a rational way.

An application of Asymmetric Counteranion Directed Catalysis merged with nanomaterials application will be described in Chapter 3. Indeed, a specifically designed type of Carbon Dots (a novel class of nanomaterials) functionalised with primary amine moieties has been used to perform asymmetric aminocatalysis via iminium ion recurring to a chiral phosphoric acid to transfer the chiral information in the 1,4-reduction of α,β -unsaturated- β,β -disubstituted aldehydes using dihydropyridines as reductants. A correlation between the features of the CDs' surfaces and their catalytic performance was shown, and the catalytic activity of the employed CDs proved to be higher than simple molecular primary amines.

In Chapter 4, a new route towards the synthesis of silyl-heterocycles via catalytic 1,1-carboboration is reported. Due to the shortage of methods to synthesise this scaffold, four- and five-membered silyl-heterocycles are a challenge: however, the use of catalytic carboboration reaction shows how these heterocyclic

cores can be easily prepared recurring to the use of [H-B-9-BBN]₂ as catalyst and pinacolborane in stoichiometric amount to regenerate the catalyst and functionalise the product, opening the path for downstream derivatisations. Mechanistic studies, including ¹³C-labelling, computational studies, and single-turnover experiments, suggest a reaction pathway proceeding by 1,2-hydroboration, 1,1-carboboration, and transborylation to release the alkenyl boronic ester product and regenerate the borane catalyst.

In Chapter 5, a feasible synthesis of a primary metabolite of Cannabidiol (CBD), 7-hydroxy Cannabidiol, is described. Due to the wide interest the CBD had gathered in recent years, the study of its metabolites is of primary importance to understand its biological action for future clinical trials. However, the synthesis of this metabolites, is a challenge due to the many synthetic steps required and the consequent low yields they lead. In this chapter, an eight-step synthesis of 7-hydroxy Cannabidiol from CBD is described, recurring to easy reaction condition and to a final Piers–Rubinsztajn reaction as the key to enable a mild deprotection, affording the desired product in 31% overall yield.

In Chapter 6, an overview of the other projects I have contributed to will be given. The first one is a review on the alkali and alkali-earth metals salts of chiral phosphoric acids to which I have contributed as main author. In this review, the developments achieved in this field since its beginning are exposed in a critical perspective, focusing on their reaction mechanism and the potential future developments. The second project, to which I have contributed as secondary author, presents the development of a new and greener synthetic method of Dibenzosuberone (DBS), an important intermediate for the preparation of active pharmaceutical ingredients (API), born from a collaboration with the pharmaceutical company Dipharma Francis.

1. Introduction

1.1 General Overview

Even though the topics investigated in this PhD can appear very different from each other, a common leitmotif can be highlighted: the development of new catalytic approaches. For this reason, a general description of the concept of catalysis, and its versions explored in this manuscript as well, has to be reminded.

A catalyst can be defined as *a compound that takes part in a reaction increasing the rate of the process without modifying the overall standard Gibbs energy change and, since it is not consumed during the reaction, but rather regenerated at each cycle, it can be employed in sub-stoichiometric amounts.*¹

The catalyst then gives turnover, *defined as the ability to act upon more than one reactant and the turnover number can be defined as the average number of reactants that a catalyst acts upon before the catalyst loses its activity. Because the catalyst affects the rate of the reaction, it is involved in the rate law for the reaction, but because it is regenerated, its concentration never changes.*¹

A little depiction of how a catalysed reaction works is given in Figure 1: a catalysed path is shown as lower in energy compared to an uncatalyzed one, since the catalyst is able to bind to the transition state of the reaction and therefore lowering its energy (**1a** and **1b**). However, being a transition state a mixture of substrate and product structures, it is reasonable to think that the catalyst can bind also the substrate and the product during the reaction. So, it is more correct to say that an equilibrium is established between the substrate and the catalyst, subsequently

¹ V. E. Anslyn, D. A. Dougherty *Modern Physical Organic Chemistry* **2006**, Chapter 9: Catalysis, p. 489.

this activated intermediate is able to overcome the activation barrier towards the transition state and finally there is the dissociation of the catalyst from the product (**1c**).

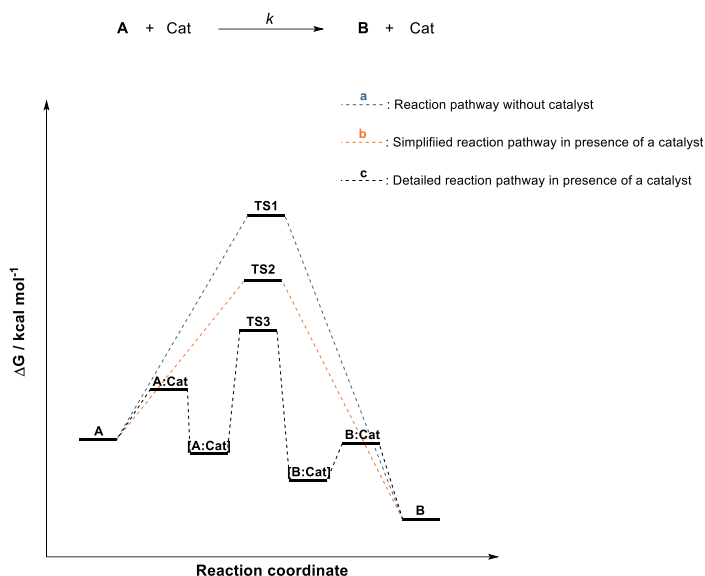


Figure 1: a) uncatalysed pathway; b) catalysed pathway (simplified): the catalyst binds to the reactants and facilitates the desired reactivity; c) catalysed pathway (detailed): the catalyst lowers the activation energy of the transition state but it passes through an adduct with the reagent ($[A:Cat]$) before and with the product ($[B:Cat]$) after.

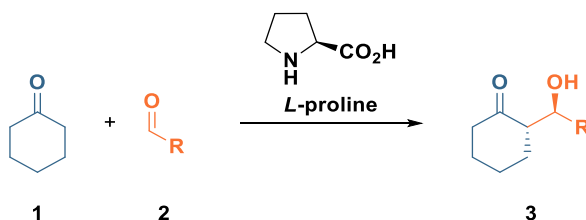
All these features opened new perspectives about recycling and improving enormously the sustainability of chemical processes, making catalysts the main actors in unlocking new and more sustainable synthetic pathways of organic molecules such as drugs, natural products and agrochemicals. Moreover, the fact that a catalyst can be used in a sub-stoichiometric amount and can be recovered at the end of the process, helps the cost-effectiveness of the process itself, enhancing the atom economy of the reaction.

Even though transition metals,^{2,3} and especially Palladium among them, have been the main actors in this field for over 40 years

² J. F. Hartwig *Organotransition Metal Chemistry: from Bonding to Catalysis* **2010**, University Science Books.

³ R. Jana, T. P. Pathak, M. S. Sigman *Chem. Rev.* **2011**, 111, 3, 1417-1492.

thanks to the wide applicability and reliability even on industrial scale, their use is now attracting concern due to their toxicity and high cost, making an alternative highly desirable. In this scenario, organocatalysis emerged as a possible solution: although known for over a century, the use of small chiral organic molecules as catalysts started attracting interest by the chemistry community in the early 2000s thanks to the seminal works of David W. C. MacMillan and Benjamin List, who laid the foundations of and conceptualised the field of asymmetric organocatalysis.^{4,5}



Scheme 1: Proline-catalysed aldol reaction of cyclic ketones **1** with aldehydes non-bearing α -acidic protons **2**.

Indeed, the possibility to use inexpensive organic molecules, such as proline (Scheme 1), alongside with the easy setup of the reactions being air- and moisture-stable, attracted a wide approval and is more and more increasing its notoriety, even though some limitations are still persisting, like the lower catalytic turnover observed compared to metal-based catalysts.⁶

1.2 Aminocatalysis

The most common and widely explored strategies in asymmetric organocatalysis are grouped under the definition of aminocatalysis.

⁴ K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan "New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels-Alder Reaction" *J. Am. Chem. Soc.* **2000**, 122, 4243.

⁵ B. List, R. A. Lerner, C. F. Barbas III "Proline-Catalyzed Direct Asymmetric Aldol Reactions" *J. Am. Chem. Soc.* **2000**, 122, 2395.

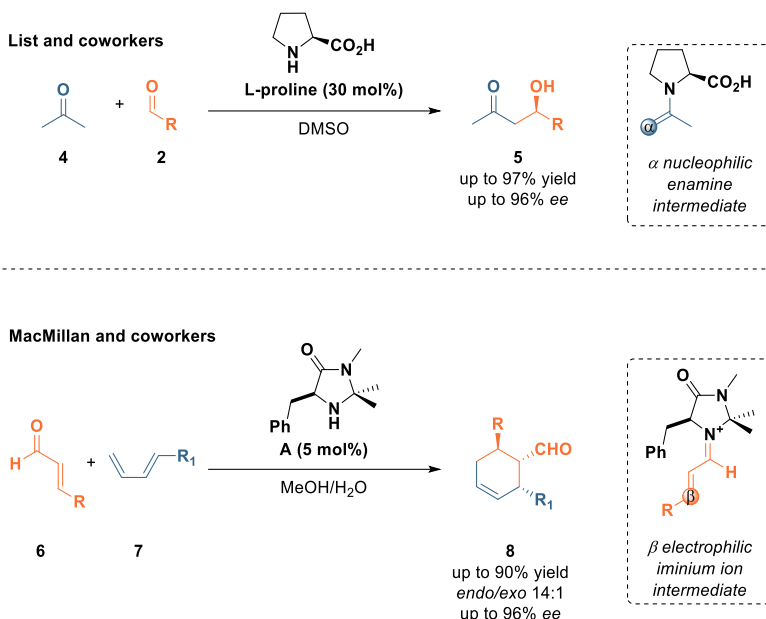
⁶ D. W. C. MacMillan "The Advent and Development of Organocatalysis" *Nature* **2020**, 455, 304.

These strategies are based on the generation of active covalent intermediates (enamines and iminium ions) obtained from the condensation of chiral amines with carbonyl compounds, a kind of reactivity that shares many analogies with the activity of several enzymes, such as aldolase, that catalyses the retro-aldol reaction.^{7,8} Although in the early sixties (Stork's group) and middle seventies (Baum's group) of the XX Century the formation of enamines and iminium ions was widely explored for its application in organic synthesis,^{9,10} it was only thirty years later that its application to perform catalysed asymmetric reactions took place, thanks to two pioneering works: the asymmetric enamine-mediated aldol reaction catalysed by *L*-proline, from the group of List,* Lerner and Barbas III, and the iminium ion-mediated Diels-Alder reaction promoted by a *L*-phenylglycine-derived imidazolidinone (**A**), proposed by MacMillan (Scheme 2).^{4,5}

In enamine-mediated reactions, an aminocatalyst quickly condenses with carbonyl compounds, generating ions carrying highly acidic α -protons (I). The deprotonation of such species generates enamines (II), nucleophilic synthetic equivalents of enols with increased HOMO energies that can stereoselectively react with a wide variety of electrophiles providing α -functionalised carbonyl compounds (9) after the release of the catalyst.

⁷ P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli "Asymmetric Aminocatalysis – Gold Rush in Organic Chemistry" *Angew. Chem. Int. Ed.* **2008**, 47, 6138.

⁸ D. Voet, J. G. Voet *Biochemistry 4th Edition* **2011**, Chapter 17: Glycolysis, p. 602, Wiley.



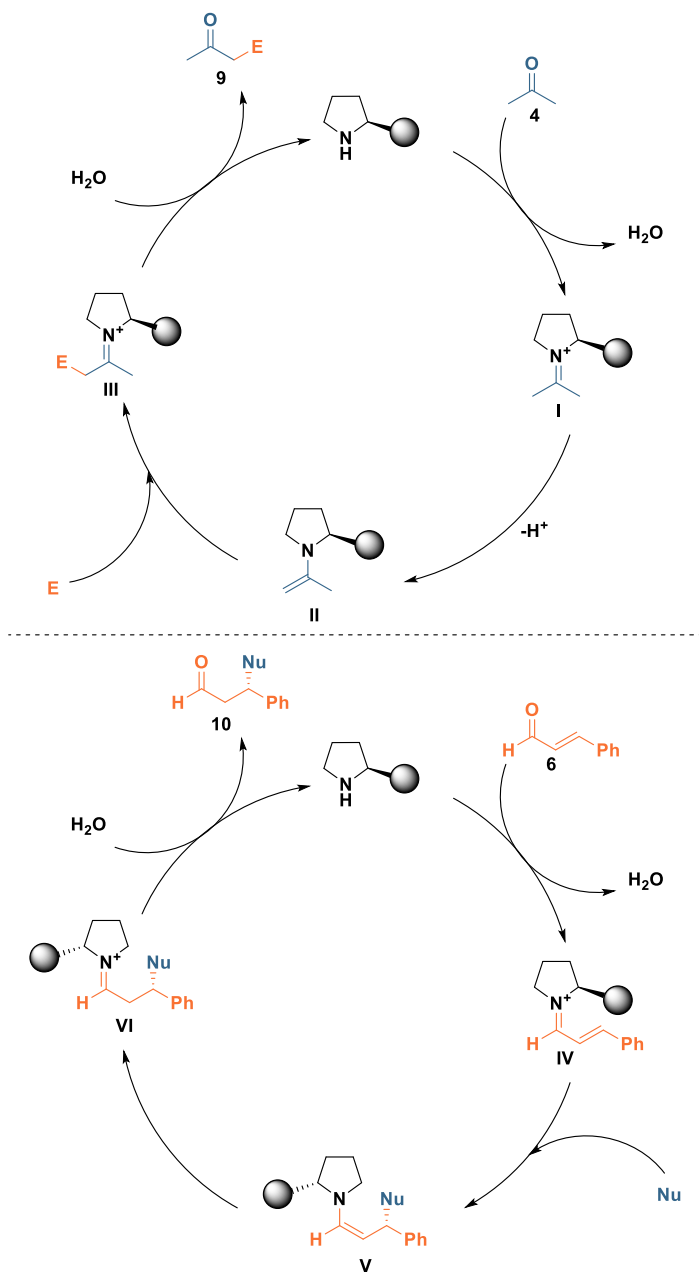
Scheme 2: L-proline asymmetric enamine-mediated aldol reaction by List and coworkers (above) and iminium ion-mediated Diels-Alder reaction promoted by a L-phenylglycine-derived imidazolidinone by MacMillan's group (below).

In iminium ion-mediated reactions, on the other hand, the condensation of amines takes place with α,β -unsaturated carbonyl compounds instead, affording an cationic electrophilic intermediate (IV), with a lowered LUMO orbital energy that can facilitate nucleophilic additions or pericyclic reactions, affording β -functionalised products stereoselectively (see Scheme 3).^{9,10,11}

⁹ S. Mukherjee, J. W. Yang, S. Hoffmann, B. List "Asymmetric Enamine Catalysis" *Chem. Rev.* **2007**, 107, 5471.

¹⁰ A. Erkkilä, I. Majander, P. M. Pihko "Iminium Catalysis" *Chem. Rev.* **2007**, 107, 5416.

¹¹ I. Fleming *Molecular Orbitals and organic Chemical Reactions Reference Edition* **2010**, Chapter 6: *The Effect of Lewis Acids on Diels-Alder Reactions*, p. 318, Wiley.



Scheme 3: Catalytic cycle for the asymmetric enamine-mediated addition to an electrophile (left); catalytic cycle for the asymmetric iminium ion-mediated addition of a nucleophile (right).

Usually, the high stereoselectivity obtained in aminocatalysis lies in the fact that the reaction passes through a covalently bound adduct

whose effectiveness can be improved modifying the catalyst structure. For those reactions that pass through an enamine intermediate, it has been observed that the catalyst scaffold can direct the electrophile approach preferentially towards one of the two prochiral faces through hydrogen bonding or steric hindrance, while for the iminium ion-mediated reactions, the approach of the nucleophile is usually directed by steric effects (Figure 2).^{12,13}

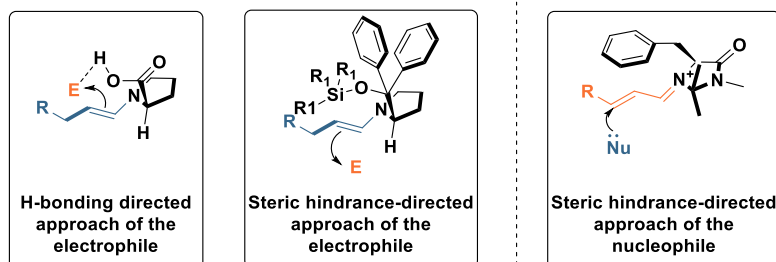


Figure 2: Role of electronic and/or steric effects in the transmission of the steric information.

The applicability of aminocatalysis is extremely wide and several aminocatalysts have been employed to carry out asymmetric transformation even in industry. Easy to synthesise from cheap, safer starting materials, they represent a useful tool and their application to unlock a new design of the Michael reaction in water will be shown in Chapter 2.

1.3 ACDC

Within the framework of asymmetric organocatalysis, phosphoric acid is a term commonly referred to phosphoric acid diesters having the general molecular formula R_2HPO_4 , the two R groups belonging to the same scaffold, which is usually a C_2 -symmetric

¹² A. Kawara, T. Taguchi "An Enantioselective Michael Addition of Soft Nucleophiles to Prochiral Enone Catalyzed by (2-Pyrrolidyl) Alkyl Ammonium Hydroxide" *Tetrahedron Lett.* **1994**, 35, 8805.

¹³ R. K. Kunz, D. W. C. MacMillan "Enantioselective Organocatalytic Cyclopropanations. The Identification of a New Class of Iminium Catalyst Based upon Directed Electrostatic Activation" *J. Am. Chem. Soc.* **2005**, 127, 3240.

structure. The design of the very first chiral phosphoric acids from BINOL (acronym BPA, BINOL-based Phosphoric Acid), was accomplished in order to access a resolution agent for chiral amines.¹⁴

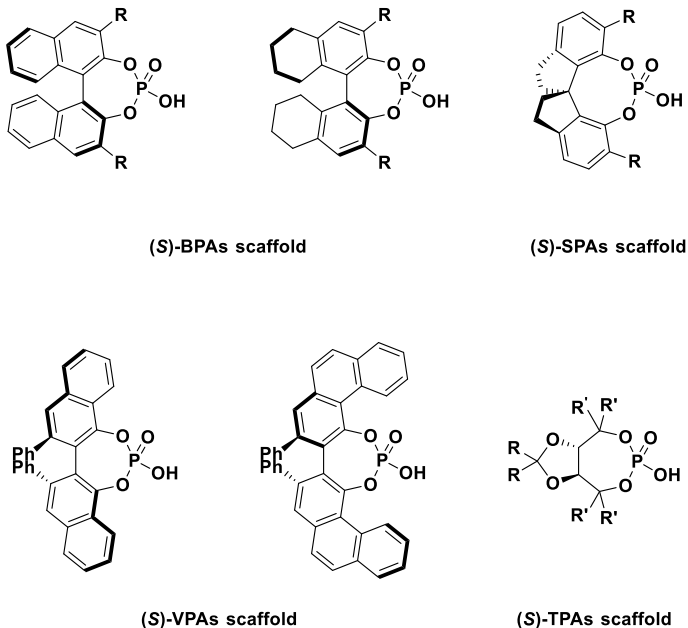


Figure 3: The most used chiral phosphoric acid scaffolds.

The possibility of functionalization of BINOL in the 3,3' positions in a robust fashion paved the way to the successful synthesis and application BPAs libraries in asymmetric catalysis.¹⁵ Later on, the phosphorylation of other C_2 -symmetric diols, such as vaulted biaryls, namely VANOL and VAPOL,¹⁶ and derivatives of

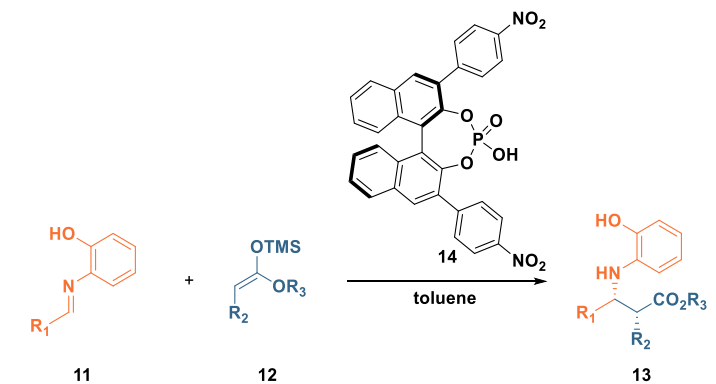
¹⁴ a) J. Jacques, C. Fouquey, R. Viterbo *Tetrahedron Lett.* **1971**, 12, 4617-4620; b) J. Jacques, C. Fouquey, *Org. Synth.* **1989**, 67, 1.

¹⁵ a) D. Parmar, E. Sugiono, S. Raja, M. Rueping *Chem. Rev.* **2014**, 114, 9047-9153; b) M. Rueping, D. Parmar, E. Sugiono, *Asymmetric Brønsted Acid Catalysis*, Wiley, **2016**.

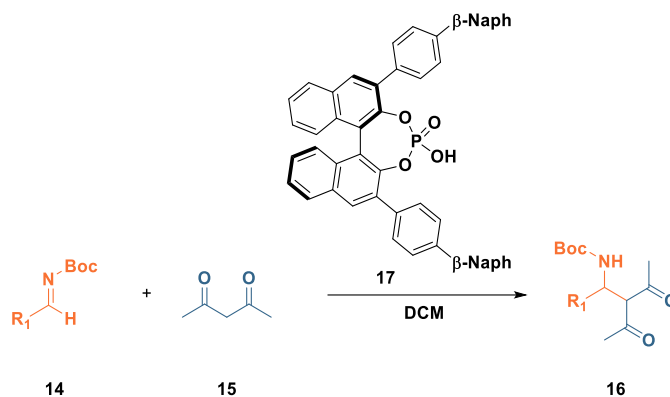
¹⁶ a) J. Bao, W. D. Wulff, J. B. Dominy, M. J. Fumo, E. B. Grant, A. C. Rob, M. C. Whitcomb, S.-M. Yeung, R. L. Ostrander, A. L. Rheingold *J. Am. Chem. Soc.* **1996**, 118, 3392-3405; b) Z. Ding, W. E. G. Osminski, H. Ren, W. D. Wulff *Org. Process Res. Dev.* **2011**, 15, 1089-1107.

TADDOL¹⁷ and SPINOL¹⁸ also afforded efficient chiral organocatalysts (VPAs, TPAs and SPAs, respectively) for different asymmetric synthetic methodologies (Figure 3).¹⁹

Akiyama et al.



Terada et al.



Scheme 4: Asymmetric Mannich reactions using chiral phosphoric acids performed by the groups of Akiyama (up) and Terada (bottom).

¹⁷ T. Akiyama, Y. Saitoh, H. Morita, K. Fuchibe *Adv. Synth. Catal.* **2005**, 347, 1523-1526.

¹⁸ a) F. Xu, D. Huang, C. Han, W. Shen, X. Lin, Y. Wang *J. Org. Chem.* **2010**, 75, 8677-8680;
b) I. Čorić, S. Müller, B. List *J. Am. Chem. Soc.* **2010**, 132, 17370-17373.

¹⁹ E. Cocco, A. Antenucci, A. Carlone, P. Manini, F. Pesciaioli, S. Dughera *ChemCatChem* **2024**, e202400328.

The first application of a phosphoric acid in asymmetric Brønsted acid catalysis was disclosed by Yamamoto's group,²⁰ but their extensive study came up in 2004 only, when the groups of Akiyama and Terada used them to perform asymmetric Mannich reactions as reported in Scheme 4.^{21,22}

These discoveries made a huge impact on the organocatalysis field and, even though it was later discovered that the catalyst used by Terada's group was a calcium phosphate salt,²³ this class of organocatalyst is still one of the most studied, having the capacity to unlock a wide variety of transformations. Being the chiral counteranion of the phosphoric acid responsible for the introduction of the chiral information, in 2006 the group of Benjamin List developed a new form of organocatalysis, namely *Asymmetric Counteranion Directed Catalysis* (ACDC), that can be defined as follows: *the induction of enantioselectivity in a reaction proceeding through a cationic intermediate by means of ion pairing with a chiral, enantiomerically pure anion provided by the catalyst.*²⁴

Due to its broadness, the definition of Asymmetric Counteranion Directed Catalysis embraces many reactions, being the formation

²⁰ H. Ishibashi, K. Ishihara, H. Yamamoto *Chem. Rec.* **2002**, 2, 177 – 188.

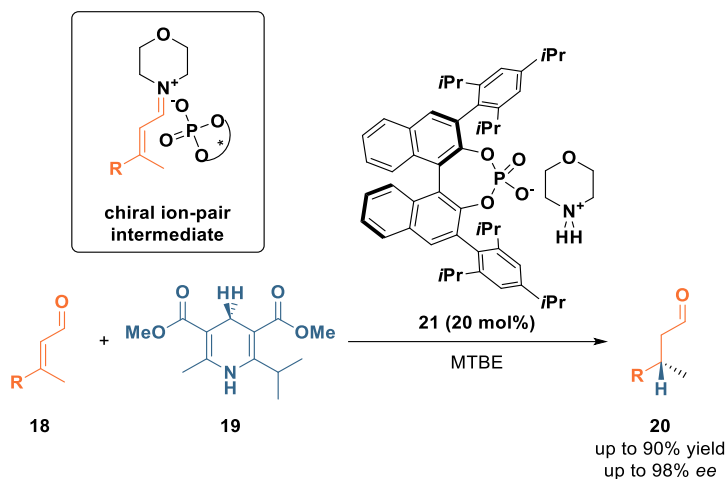
²¹ a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe *Angew. Chem.* **2004**, 116, 1592 – 1594; b) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe *Angew. Chem. Int. Ed.* 2004, 43, 1566 – 1568.

²² D. Uraguchi, M. Terada *J. Am. Chem. Soc.* **2004**, 126, 5356 – 5357.

²³ a) M. Hatano, K. Moriyama, T. Maki, K. Ishihara *Angew. Chem.* **2010**, 122, 3911 – 3914; b) M. Hatano, K. Moriyama, T. Maki, K. Ishihara *Angew. Chem. Int. Ed.* **2010**, 49, 3823 – 3826.

²⁴ M. Mahlau, B. List *Angew. Chem. Int. Ed.* **2013**, 52, 518 – 533.

of an ion pair with a chiral anion the main feature.^{25,26,27,28} Even the Brønsted Acid Catalysis can be seen as a specific form of ACDC, considering that the ion pairs are often stabilized by hydrogen bonds and that the Coulombic attraction within the ion pairs in ACDC can be accompanied by further stabilizing interactions such as hydrogen binding itself, as long as the ionic character of the intermediate does not become negligible.^{24,29}



Scheme 5: Asymmetric Counteranion Directed Catalysis (ACDC) for the β -reduction of unsaturated aldehydes by List and coworkers.

However, in this section only the “exact” form of ACDC will be analysed, being useful to understand the concepts exposed in the third chapter of this manuscript. With the term “exact” it is indicated the ACDC without any strong stabilising effect and it usually refers to those reactions in which the chiral phosphate interacts with iminium ions obtained by the condensation of achiral amines with α,β -unsaturated aldehydes.

²⁵ I. D. Gridnev, M. Kouchi, K. Sorimachi, M. Terada *Tetrahedron Lett.* **2007**, 48, 497 – 500.

²⁶ N. J. A. Martin, B. List *J. Am. Chem. Soc.* **2006**, 128, 13368 – 13369.

²⁷ G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste *Science* **2007**, 317, 496 – 499.

²⁸ S. Liao, B. List *Angew. Chem.* **2010**, 122, 638 – 641; S. Liao, B. List *Angew. Chem. Int. Ed.* **2010**, 49, 628 – 631.

²⁹ M. Yamanaka, J. Itoh, K. Fuchibe, T. Akiyama *J. Am. Chem. Soc.* **2007**, 129, 6756 – 6764.

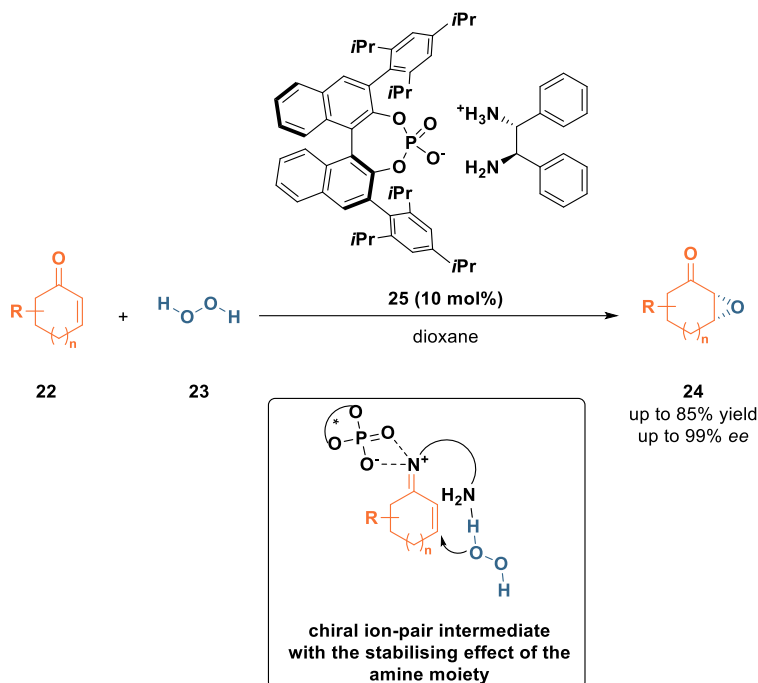
The 1,4-reduction of β -disubstituted enals **18** with dihydropyridines is one of the most famous examples of this class of catalysis: indeed, the achiral secondary amine generates an achiral iminium ion with the α,β -unsaturated aldehydes, thus able to coordinate with the chiral phosphate anion generating a chiral ion pair. The hydride source **19** is then able to reduce the double bond and an enantioselectively saturated aldehyde **20** is generated, as depicted in Scheme 5.^{24,30}

A similar protocol was reported for the enantioselective epoxidation of ketones, still by List and coworkers.³¹ Here, using a phosphate ammonium salt derived from primary chiral amines and (S)-TRIP, the epoxidation with dihydrogen peroxide afforded the desired product with high yield and enantioselectivities (see Scheme 6). Remarkably, the presence of a second amine group provided to be crucial due to its ability to organize the transition state helping to direct the attack of the dihydrogen peroxide towards one of the two faces of the double bond.

On the basis of the several outcomes reported (only few of which are shown in this introduction), ACDC proved to be a powerful tool in catalysis, useful to design several organocatalytic reactions showing better or at least complementary results compared to more traditional methods.

³⁰ a) J.W. Yang, M. T. F. Hechavarria, B. List *Angew. Chem.* **2004**, 116, 6829 – 6832; J.W. Yang, M. T. F. Hechavarria, B. List *Angew. Chem. Int. Ed.* **2004**, 43, 6660 – 6662; b) J. W. Yang, M. T. F. Hechavarria, N. Vignola, B. List *Angew. Chem.* **2005**, 117, 110 – 112; J. W. Yang, M. T. F. Hechavarria, N. Vignola, B. List *Angew. Chem. Int. Ed.* **2005**, 44, 108 – 110; c) S. G. Ouellet, J. B. Tuttle, D.W. C. MacMillan *J. Am. Chem. Soc.* **2005**, 127, 32 – 33.

³¹ X. Wang, C. M. Reisinger, B. List *J. Am. Chem. Soc.* **2008**, 130, 6070 – 6071.



Scheme 6: ACDC applied to the enantioselective epoxidation of cyclic enones by List's group.

Moreover, its reliability and capacity to be coupled with transition metal catalyst, widened its application field, increasing the value of this tool. Its application alongside with the use of Carbon Dots, a class of nanomaterials, in order to develop a new system to perform asymmetric 1,4-reductions will be shown and discussed in detail in Chapter 3.

1.4 Boron Catalysis

Over the past several decades, the chemistry of organoboron compounds has experienced a huge growth, owing to its diverse utility, not only as a stoichiometric reagent for organic transformation reactions, but also as catalysts. A plethora of organoboranes relevant to organic synthesis have been developed thus far thanks to the unique electronic and steric features of the Lewis acidic boron center, whose derivatization allows to unlock

complex reactivity and chemical spaces. Many boranes have been synthesised and employed over the years, including trialkyl-, triaryl- and trihalo-boranes.³² As the field of boron chemistry was growing, the variety of boron reagents grew along and over the years a series of boron-based catalysts of tunable acidity and increasing structural complexity arose. Tris(pentafluorophenyl)borane, trichloroborane, trifluoroborane and the Corey-Bakshi-Shibata catalyst (Figure 4) are some famous members of a wide family of compounds that has been summarised basing on various aspects and applications, from the formation of frustrated Lewis pairs (FLP) for the activation of small molecules³³ to

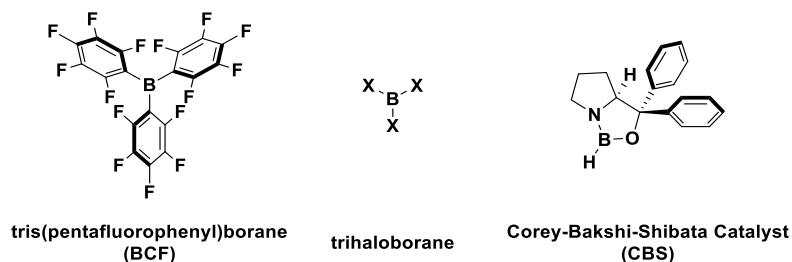


Figure 4: Common Boron-based catalyst scaffolds.

the synthesis of aromatic and heterocyclic compounds³⁴ or the activation of carboxylic acids and alcohols,³⁵ just to cite some examples.

Another extremely useful application of electron-withdrawing organoboranes is their use as deprotecting agents: in particular, they can be used in dealkylation reaction of ethers. Even though strong bases or highly reactive acids (such as HBr or AlCl_3) in

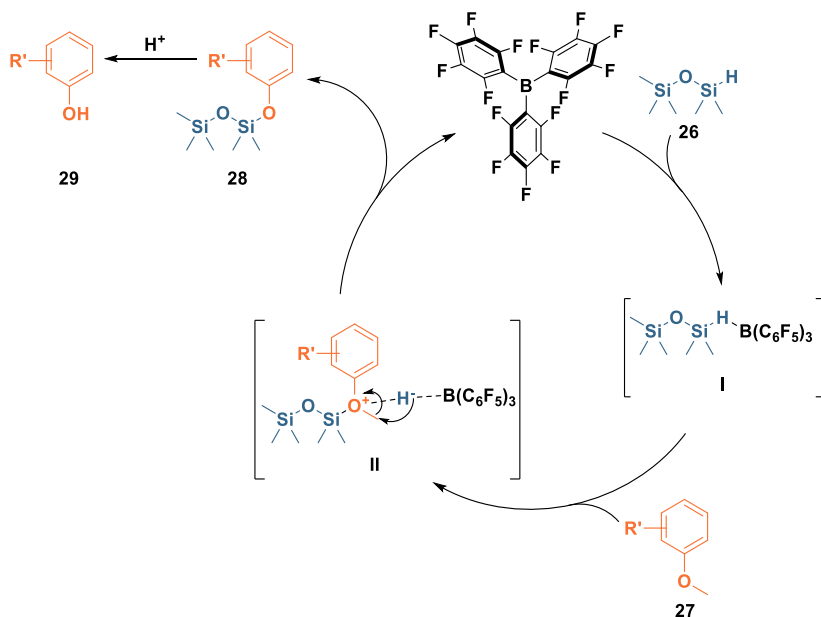
³² V. Nori, F. Pesciaoli, A. Sinibaldi, G. Giorgianni, A. Carlone *Catalysts* **2022**, 12, 5.

³³ a) G. Erker *Dalton Trans.* **2005**, 1883–1890; b) X. Feng, H. Du *Tetrahedron Lett.* **2014**, 55, 6959–6964; c) M. Oestreich, J. Hermeke, J. Mohr *Chem. Soc. Rev.* **2015**, 44, 2202–2220; d) D. W. Stephan, G. Erker *Angew. Chem. Int. Ed.* **2015**, 54, 6400–6441.

³⁴ R. L. Melen *Chem. Commun.* **2014**, 50, 1161–1174.

³⁵ H. Zheng, D. G. Hall, *Aldrichimica Acta* **2014**, 47, 41–51.

stoichiometric amount are often reported as the most reliable solution,³⁶ they do not match well with acid-sensitive scaffold, that can be easily decomposed in strong acidic conditions. Thanks to their modulable reactivity, organoboranes provided a useful alternative, allowing milder reaction conditions and to be used in catalytic amount (Scheme 7).³⁷



Scheme 7: BCF-catalysed demethylation of aryl methyl ethers: activation of the Si-H bond to generate a hydride specie (**I**); “silylation” of the ether oxygen and nucleophilic attack of the hydride to the methyl group generating a silyl phenyl ether (**II**); acid-mediated deprotection of the silyl phenyl ether.

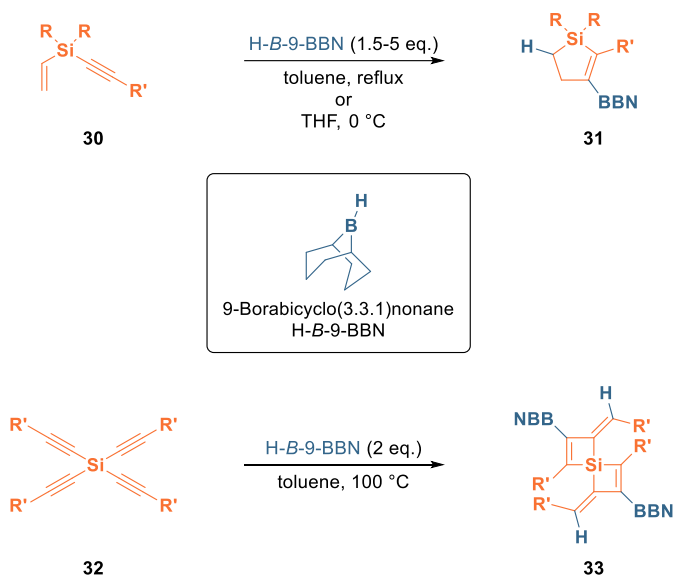
In Chapter 5 of this thesis, an interesting application of an O-demethylation reaction of phenols using a catalytic amount of tris(pentafluorophenyl)borane (BCF) will be shown applied to the synthesis of a primary metabolite of Cannabidiol (CBD).³⁸

³⁶ P. G. M. Wuts, T. W. Greene *Greene's Protecting Groups in Organic Synthesis* **2006**, Chapter 2: Protection for the Hydroxyl Groups, Including 1,2- and 1,3- Diols, pag. 16.

³⁷ A. A. Torrens, A. L. Ly, D. Fong, A. Adronov *Eur. J. Org. Chem.* **2022**, e202200570.

³⁸ E. Cocco, D. Iapadre, A. Brusa, P. Allegrini, S. P. Thomas, F. Pesciaoli, A. Carlone *RSC Adv.* **2024**, 14, 2741.

Additionally, in recent years, a novel application of organoboron compounds has been found in the construction of silyl-heterocycles through 1,1- and 1,2- carboboration reaction. As reported by Wrackmeyer and coworkers, the use of 9-borabicyclo(3.3.1)nonane (BBN) unlocked the feasible formation of this otherwise difficult to access chemical space (Scheme 8,^{39,40,41,42} without recurring to organometallics,⁴³ transition metals or highly reactive and unstable reagents.⁴⁴



Scheme 8: carboboration reactions designed by Wrackmeyer and coworkers.

On the other hand, the limitation of this approach lies in the fact that the use of the BBN has to be stoichiometric. For these reasons, Thomas and coworkers, building upon the outcomes reported by Gellreich's group,⁴⁵ designed a novel approach in which the BBN

³⁹ B. Wrackmeyer, O. L. Tok, R. Kempe *Inorganica Chimica Acta* **2005**, 358, 14, 4183-4190.

⁴⁰ B. Wrackmeyer *Athens Journal of Sciences* **2015**, 2, 4, 241-256.

⁴¹ E. Khan, S. Bayer, R. Kempe, B. Wrackmeyer *Eur. J. Inorg. Chem.* **2009**, 4416-4424.

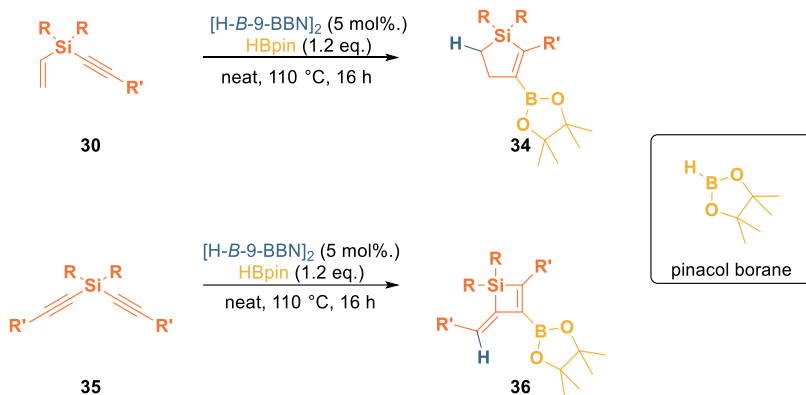
⁴² B. Wrackmeyer, E. Khan, R. Kempe *Appl. Organometal. Chem.* **2008**, 22, 383-388.

⁴³ I. Sasaki, T. Ohmura, M. Suginome *Org. Lett.* **2020**, 22, 2961-2966.

⁴⁴ W. Lu, Y. Zhao, F. Meng *J. Am. Chem. Soc.* **2022**, 144, 5233-5240.

⁴⁵ R. S. Phatake, A. Averdunk, C. Würtele, U. Gellrich, *ACS Catal.* **2022**, 12, 13961-13968.

can be used in catalytic amount being regenerated through a transborylation process employing the more acidic pinacol borane (Scheme 9).⁴⁶ A deeper and more detailed analysis of this new approach will be given in Chapter 4.

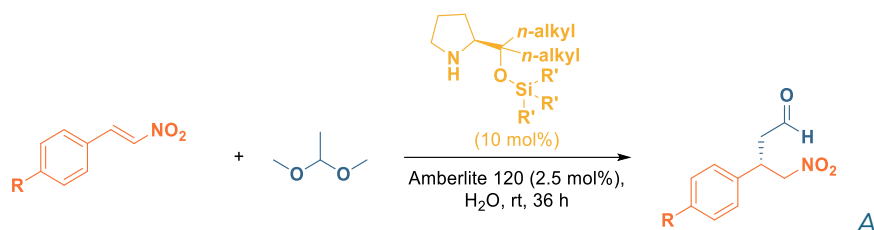


Scheme 9: Transborylation-enabled diastereoselective catalytic carboboration reactions designed by Thomas and coworkers.

⁴⁶ D. R. Willcox, E. Cocco, G. S. Nichol, A. Carlone, S. P. Thomas *Angew. Chem. Int. Ed.* **2024**, 63, e202401737.

2. DoE-Driven Development of an Organocatalytic Enantioselective Addition of Acetaldehyde to Nitrostyrenes in Water

Part of this chapter has been published as: V. Nori, A. Sinibaldi, G. Giorgianni, F. Pesciaoli, F. Di Donato, E. Cocco, A. Biancolillo, A. Landa, A. Carlone *Chemistry-A European Journal* 2022, 28, e202104524.



novel and safe protocol to perform enantioselective addition of masked acetaldehyde to (E)-nitroalkenes in water via enamine intermediate has been developed recurring to a chemometric approach. Moreover, the use of water as solvent improves the industrial relevance of this protocol to access important pharmaceutical precursors.

2.1 Introduction

In the last two and a half decades, since it was discovered, aminocatalysis made its way as a powerful tool to perform an impressive number of reactions. Since the first seminal works of MacMillan and List,^{4,5} more and more aminocatalyst were developed, increasing the applicability of this field.^{47, 48} The feasible and robust synthesis of these aminocatalysts, alongside their selective and reliable reactivity, with the potential to mimic

⁴⁷ a) S. H. Xiang, B. Tan *Nat. Commun.* **2020**, 11, 3786–3790. b) A. Carlone, L. Bernardi *Phys. Sci. Rev.* **2019**, 4, 20180097–20180117.

⁴⁸ D. Wallace, S. Challenger, Z. D. Ding, W. E. G. Osminski, H. Ren, W. D. Wulff, A. A. Desai, M. Munmun, J. P. Scott, M. Alam et al. *Org. Process Res. Dev.* **2011**, 15, 1088–1211.

enzymes,^{7,8} made them a solid alternative to transition-metal catalysts, with the additional aspect of being greener, less polluting and easy to prepare from cheap starting materials,⁴⁹ thus appealing for industrial applications.

As mentioned before, the high selectivity of this class of catalysts comes from the fact the reaction passes through a covalently bound intermediate (enamine or iminium ion) generated from the achiral substrate and the catalyst: this intermediate carries then the chiral information when it reacts with the coregent, transmitting it to the product before the release of the catalyst.^{9,10,11} The stereocentre is usually generated through steric hindrance, when the bulky group on the catalyst hinders one of the two prochiral faces when the intermediate is formed (Figure 5).^{12,13}

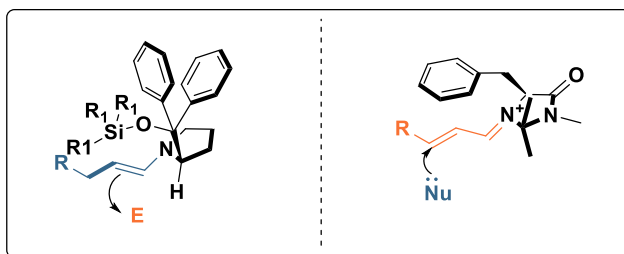
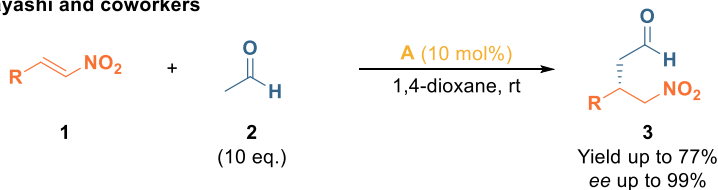
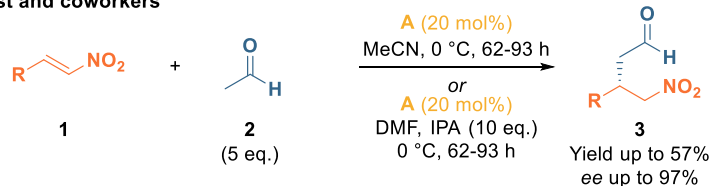
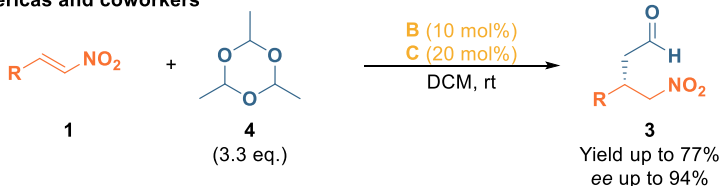
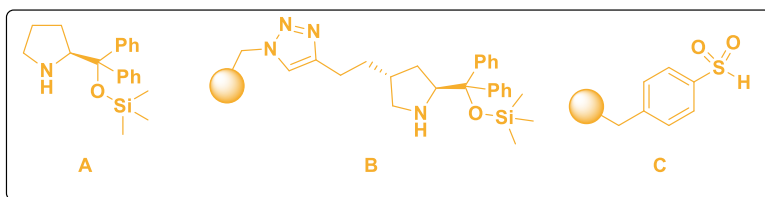
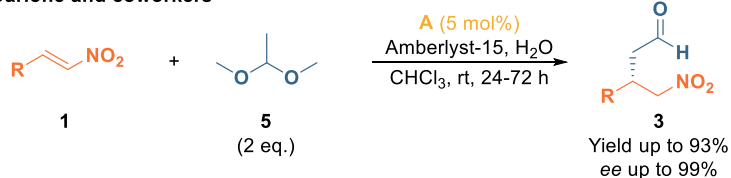


Figure 5: Role of electronic and/or steric effects in the transmission of the steric information.

A well-known application of proline-based aminocatalysts is the enamine-catalysed addition of acetaldehyde to β -nitrostyrenes to generate γ -aminoacids precursors, as depicted. Though conceptually simple, this reaction is not without challenges that several groups tried to tackle during years.

⁴⁹ a) *Green Chemistry: Theory and Practice* (Eds.: P. T. Anastas, J. C. Warner), Oxford University Press, New York, 1998; b) P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, 39, 301–312; c) A. Antenucci, S. Dughera, P. Renzi, *ChemSusChem* **2021**, 14, 2785–2853.

a: Hayashi and coworkers**b: List and coworkers****c: Pericàs and coworkers****d: Carlone and coworkers**

Scheme 10: Evolution of the enantioselective enamine-mediated addition of acetaldehyde to nitroalkenes.

Indeed, acetaldehyde tends to form oligomers, is highly reactive, toxic, and flammable. It is not surprising that it took several years to develop protocols for this reaction: seminal works by Hayashi⁵⁰

⁵⁰ a) Y. Hayashi, T. Itoh, S. Aratake, H. Ishikawa *Angew. Chem. Int. Ed.* **2008**, 47, 2082–2084; *Angew. Chem.* **2008**, 120, 2112–2114; b) Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa *Angew. Chem. Int. Ed.* **2008**, 47, 4722–4724; *Angew. Chem.* **2008**, 120, 4800–4802.

and List ⁵¹ demonstrated the possibility of an efficient enantioselective addition of the acetaldehyde is possible, despite high catalyst loading and large amounts of acetaldehyde are required (**Scheme 10 a and b**) in order to counterbalance the high reactivity of the aldehyde towards self-aldol reactions.

Another approach proposed by Pericàs and coworkers suggested the use of paraldehyde to generate acetaldehyde *in situ*, ⁵² however, counting that one equivalent of paraldehyde corresponds to three equivalents of free acetaldehyde, ten effective equivalents of aldehyde were required, as well as relatively high catalyst loading of two supported organocatalysts (**Scheme 10 c**). Recently, Carlone and coworkers proposed a method to overcome the issues related to the overloading of both acetaldehyde and the catalyst through the use of acetaldehyde dimethyl acetal and the acidic resin Amberlyst-15 to generate the aldehyde *in situ*, ⁵³ allowing to reduce the amount of the aldehyde to two equivalents only. However, the main limitation was then related to the use of chloroform, a class 2 solvent (**Scheme 10 d**).

Building upon these outcomes, this project aimed to solve the issues of both the aldehyde loading and the solvent, resolving to perform the reaction in water, the ideal solvent to use, being completely harmless and cheap. However, to perform the reaction in water several parameters like catalyst type and loading, cosolvent, molarity and additives had to be reassessed. Then, instead of proceeding through the classic OVAT (One Variable At Time) method, it has been decided to explore the chemical space in

⁵¹ P. Garcia-Garcia, A. Ladepeche, R. Halder, B. List *Angew. Chem. Int. Ed.* **2008**, *47*, 4719–4721; *Angew. Chem.* **2008**, *120*, 4797–4799.

⁵² X. Fan, C. Rodriguez-Escrich, S. Sayalero, M. A. Pericàs *Chem. Eur. J.* **2013**, *19*, 10814–10817.

⁵³ G. Giorgianni, V. Nori, A. Baschieri, L. Palombi, A. Carlone *Catalysts* **2020**, *10*, 1296–1300.

(DoE) and its application in organocatalysis

a rational way using Design of Experiments (DoE):⁵⁴ basing on the fact that variables can influence each other, this method allowed to change some of them simultaneously, reducing the total amount of experiments required to find the optimised reaction conditions.

2.1.1 Design of Experiments (DoE) and its application in organocatalysis

Design of Experiments (DoE) is a powerful tool that allows the systematic examination of different types of chemical problems affected by numerous experimental and/or instrumental variables. Conceived in 1935 by Ronald Fisher in order to optimise the ratio between the quality of the data obtained and the experimental efforts,⁵⁵ the chemometric approach is nowadays widely used in industry to optimise the processes: cost- and time-effective are its keywords indeed.⁵⁶ In the last decades, this method proved its effectiveness in academia too, where synthetic chemists preferred it to the classic trial and error approach that proceeds changing one variable at time (OVAT). However, DoE still remains scarcely used in academia,⁵⁷ probably due to the benefits it provides are not fully appreciated yet.

The core of the chemometric approach states that the variables influencing a reaction interact with each other, so they need to be changed simultaneously to find the real optimum conditions for the

⁵⁴ a) T. Lundstedt, E. Seifert, L. Abramo, B. Thelin, A. Nystrom, J. Pettersen, R. Bergman *Chemometr. Intell. Lab.* **1998**, 42, 3–40; b) R. Carlson *Chemometr. Intell. Lab.* **2004**, 73, 151–166; c) C. Jamieson, M. S. Congreve, D. F. Emiabata-Smith, S. V. Ley *Synlett* **2000**, 603–1607; d) C. Jamieson, M. S. Congreve, D. F. Emiabata-Smith, S. V. Ley, J. J. Scicsinski *Org. Process Res. Dev.* **2002**, 6, 823–825.

⁵⁵ R. A. Fisher “The Design of Experiments”, *Hafner Publishing Company, Inc.*: New York, **1935**.

⁵⁶ a) S. Stone, T. Wang, J. Liang, J. Cochran, J. Green, W. Gu *Org. Biomol. Chem.* **2015**, 13, 10471; b) S. A. Weissman, N. G. Anderson *Process Res. Dev.* **2015**, 19, 1605.

⁵⁷ V. Nori, A. Sinibaldi, F. Pesciaioli, A. Carlone *Synthesis* **2022**, 54, 4246–4256.

(DoE) and its application in organocatalysis

process. However, the whole theory behind the DoE will not be deepened further, focusing on some selected examples in organocatalysis only.

One of the most remarkable applications of DoE to organocatalysis has been provided by Bella and coworkers in 2013. In this work they have applied the DoE to overcome two critical issues of the organocatalysed enantioselective aza-Michael addition of imides to enones (Scheme 11):⁵⁸

- the poor reactivity related to the scarce nucleophilicity of the imide and the weak electron-pull exerted by the cyclic enones;
- the low stereoselectivity and configurational stability of the reaction intermediate, arisen from a retro-Michael reaction.

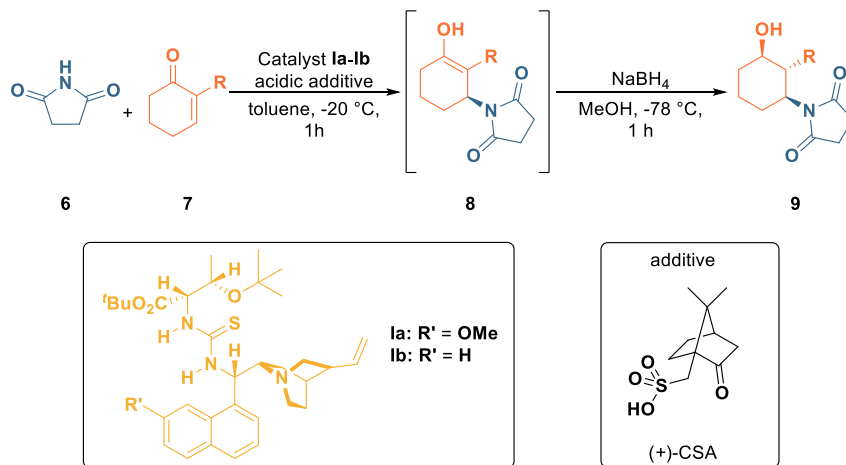
Changing the catalyst from quinidine to bifunctional thioureas they managed to observe an increase in both yield and ee, a result that was further improved recurring to tunable catalysts obtained derivatising the quinidine and cinchonidine moieties with thioureas in C9 stereocenter.

Basing on these preliminary results, they moved forward recurring to chemometrics to investigate the effect of the use of acid co-catalysts in the enantioselection of the reaction, therefore finding the best partner in (+)-CSA in 10 mol% while a racemisation of the intermediate was also observed increasing the reaction time. The multidimensional chemical domain was explored through D-Optimal design, finding a good approximation of the description of the experimental domain in the second-degree polynomial function, assuming the binary interaction effect between the variables is negligible. As a result, the enantiomeric excess was

⁵⁸ M. Silvi, P. Renzi, D. Rosato, C. Margarita, A. Vecchioni, I. Bordacchini, D. Morra, A. Nicolosi, R. Cari, F. Sciubba, D. M. Scarpino Schietroma, M. Bella *Chem. Eur. J.* **2013**, 19, 9973.

(DoE) and its application in organocatalysis

raised from 85% to 95% and the number of experiments required was lowered sensitively from 144 to 19, proving the effectiveness of DoE as optimisation tool.



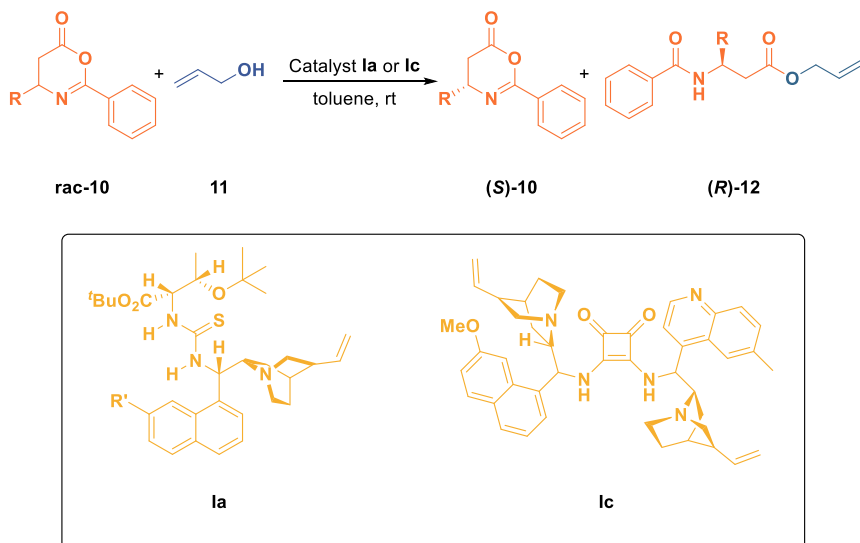
Scheme 11: DoE-optimised enantioselective addition of imines to enones by Bella's group.

Always from Bella and coworkers is the second example here reported, an organocatalytic kinetic resolution of 4-substituted oxazinones (Scheme 12).⁵⁹ The first step of their approach provided some experiments to determine the variable ranges to choose during the DoE. During these experiments, the most promising catalysts and their loadings, as well as the reaction concentration values, were determined.

After performing the DoE, a significant interaction between the solution concentration and the catalyst type and loading was found; the first one, as the type of solvent as well, affecting the conversion and the ee of the starting material while the second ones influence the enantiomeric excess of the product. This way the two catalysts and the two solvents as the best reaction

⁵⁹ P. Renzi, C. Kronig, A. Carlone, S. Eröksüz, A. Berkessel, M. Bella *Chem. Eur. J.* **2014**, *20*, 11768.

conditions to yield both the enantiopure starting material and the allyl ester product were identified.



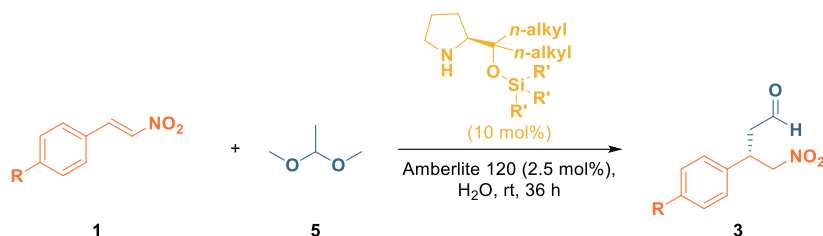
Scheme 12: DoE-optimised kinetic resolution of 4-substituted oxazinones by Bella and coworkers.

However, a second DoE had to be performed in order to improve the selectivity factor. In the end, performing the reaction in toluene for 5 h and using catalyst **la** in 12.5 mol%, the starting material **(S)-10** and the product **(R)-12** were obtained with 99% and 82% ee respectively, with a conversion of 55%, while using catalyst **lc** in 5 mol%, the ee obtained were 94% and 89% respectively, alongside a conversion of 51%. These results proved the effectiveness of DoE as a powerful tool to perform and improve asymmetric reactions, allowing to change more variables at once thus reducing the overall number of experiments to carry out.

2.2 Aim of the Project

The limitations related to the asymmetric Michael addition of acetaldehyde to β -nitrostyrenes (Scheme 10a-c) were overcome by our group recurring to the use of acetaldehyde dimethylacetal (Scheme 10d),⁵⁴ however, as mentioned before, the main restriction

was the use of chloroform as solvent. In order to solve this problem, the proposal to perform the reaction in water, the most appealing of the solvents to be used, being cheap and, of course, non-toxic. The use of water as solvent, however, led to the necessity to assess several parameters to perform the reaction and for this reason it was chosen to explore the chemical space in a rational way using the DoE.



Scheme 13: DoE-optimised enantioselective addition of masked acetaldehyde to nitroalkenes in water (this work).

Here a new protocol to perform the asymmetric organocatalysed addition of acetaldehyde protected as dimethyl acetal to β -nitrostyrenes using water as solvent is successfully reported (Scheme 13): the DoE played a pivotal role allowing the simultaneous change of different parameters at once and reducing the total amounts of experiments required.

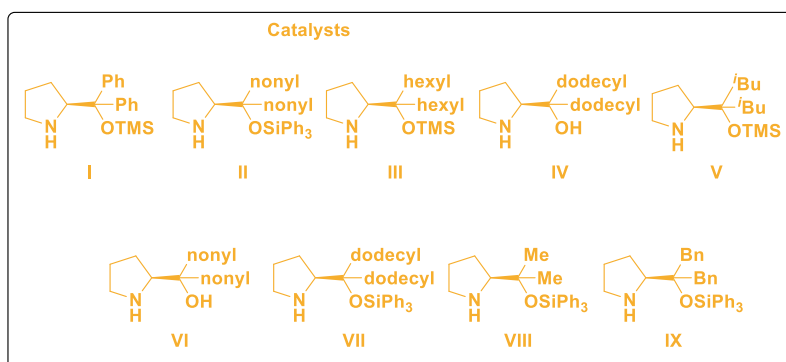
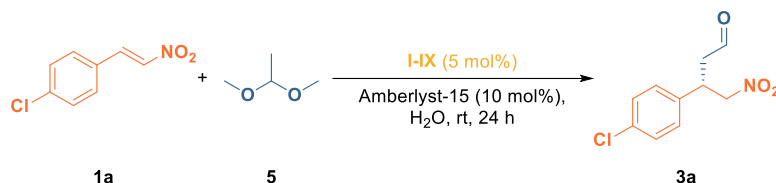
2.3 Development and Outcomes

Here the development of a novel approach for the enantioselective catalytic addition of acetaldehyde dimethyl acetal (5) to β -nitrostyrenes (1) in water is reported. The project started with a preliminary screening of proline-derived catalysts that can catalyse reactions in aqueous medium.

The substrate chosen was the β -nitrostyrenes **1a**, bearing a chlorine atom in *para* position and leading to the baclofen precursor **3a**, while the tested acid co-catalyst to deprotect the acetaldehyde *in situ* was Amberlyst-15 (Table 1).

Table 1: preliminary data for the addition of acetaldehyde dimethyl acetal to **1a** in water. [a] Reactions performed on 0.4 mmol scale; catalyst (0.02 mmol, 5 mol%), 4-chloro- β -nitrostyrene **1a** (60 mg, 0.4 mmol, 1 equiv.), acetaldehyde dimethyl acetal **5** (85 μ L, 0.8 mmol, 2 equiv.), Amberlyst-15 (14 mg, 10 mol%) and water as solvent at room temperature. [b] Measured by ^1H NMR spectroscopy. [c] Determined by chiral HPLC analysis after conversion of the aldehyde into the corresponding alcohol by reduction with NaBH_4 .

60



Entry ^a	Catalyst	M [mol/l]	Conv. [%] ^b	ee [%] ^c
1	I	1.6	27	62
2	II	1.6	<5	nd
3	III	1.6	6	79
4	IV	1.6	<5	nd
5	V	1.6	<5	nd
6	VI	1.6	<5	nd
7	VII	1.6	20	79
8	VIII	1.6	12	72
9	IX	1.6	17	61
10	VII	0.8	19	80
11	VII	0.4	18	79

⁶⁰ C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, A. Puente, S. Vera *Angew. Chem. Int. Ed.* **2007**, 46, 8431–8435.

The results of this preliminary screening are summarised in Table 1 and proved the effectiveness of the catalyst bearing the longer aliphatic chain (Entry 7), while the others showed lesser or not appreciable conversions, alongside lower enantiomeric excesses, while decreasing the reaction concentration did not seem to interfere in the reactivity (Entries 10 and 11).

After this preliminary screening, the first rational Design of Experiment was carried out to determine how the variables affect the reaction and influence each other: the quantitative variables were investigated using the usual coding for the levels (-1 for low and +1 for high level) whereas the implicit level was used to evaluate the qualitative ones. For the first optimisation, a full factorial design would have required 43200 experiments, whereas a D-optimal design drastically reduced the number of experiments to 34. The variables investigated were: a) type of organocatalyst (**I-VII**), b) catalyst loading (2.5 mol%-10 mol% range), c) equivalents of **5** (1.5-3 equivalents range), d) reaction time (24-72 h range), e) reaction concentration (0.2-1.2 M range), f) cosolvents (EtOAc, MeOH, THF, IPA or none), g) acidic co-catalyst (5 acidic resins and 5 organic acids), h) acidic co-catalyst loading (2.5 mol%-20 mol% range), i) ionic strength of water (NaCl, CaCl₂ or none); while the qualitative variables were: 1) **I** for the catalyst loading, 2) absence of cosolvent, 3) Amberlite 2900 as acidic co-catalyst, 4) absence of salt in water (see ionic strength of water). All the responses were analysed in terms of conversion and enantiomeric excess of **3a** and it was found that nine factors (four qualitative and the remaining ones quantitative) were believed to affect the conversion (Y_{NMR}) and the enantiomeric excess (ee) of product **3a** (Figure 6).

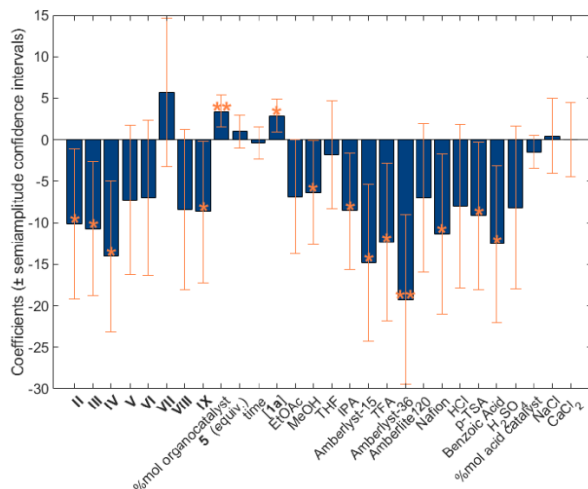


Figure 6: Plot of the coefficients of the mathematical model of the response YNMR for the first preliminary screening via D-Optimal Design. The significance of the coefficients is labelled with the same convention for asterisks in all the figures: *p-value<0.05, **p-value<0.01, ***p-value<0.001.

The best catalysts were found to be **I** and **VII**, being also catalyst loading and reaction concentration determinant factors, while cosolvents and salts have shown no effects. Moreover, parameters regarding the equivalents of **5**, reaction time and the amount of acidic co-catalyst were found to be not significant, even though they have been included in the following screening, alongside catalyst **II** (similar in structure to **VII**), to see if any contribution may arise. In terms of the acidic catalyst, the resin Amberlite 2900 gave the best results; Amberlyst-15, Amberlite 1200 and HCl, cost effective catalysts, were, however, also included in the next screening.

With these informations in hand, a second design of experiments (D-optimal) was performed (see Figure 7).

This time, the parameters analysed were: 1) organocatalysts (**I**, **II** and **VII**); 2) catalyst loading; 3) equivalents of **5**; 4) reaction time; 5) reaction concentration; 6) acidic catalysts; 7) acidic catalyst loading, allowing to drastically reduce the number of experiments from 288 to 42 only, where 6 of them are replicates.

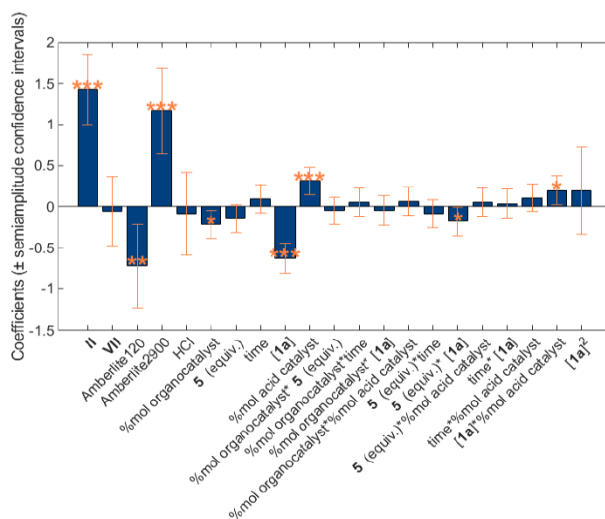


Figure 7: Plot of the coefficients of the mathematical model of the response scores on PC2 (to be minimised in order to maximise YNMR and ee) for the second screening via D-Optimal Design.

From this analysis the following informations were obtained:

- the best catalysts were **I** and **VII** (attending to the model the choice is arbitrary);
- the best acidic co-catalyst is Amberlite-120;
- 10 mol% is the best compromise for the catalyst loading (its coefficient is significant and negative);
- the coefficient related to the time reaction is non-significant and positive (its variations do not affect the final responses to be optimized, so it can be chosen arbitrarily and independently from the other variables);
- the acid co-catalyst loading, the reaction concentration and the acetaldehyde dimethyl acetal **5** loading have correlated each other, and the highest response was found for 2.5 equivalents of **5**, **1a** 1.2 M in the aqueous medium and acidic resin in 5 mol%;

- the catalyst loading and the reaction concentration were significant parameters, contributing to the response positively;
- equivalents of **5**, time and amount of acidic co-catalyst were not significant, not affecting the final responses.

The outcomes of the 42 experiments were analysed through the scores plot and the loading plot obtained from PCA (Principal Component Analysis) on the experimental data matrix. The scores plot showed agreement between the replicates which are close in the space of the main components PC1 and PC2; the trend showed by the samples justifies the choice of the scores on PC2 as response (to be minimised in order to maximise Y_{NMR} and ee) (Figure 8). To further optimise the reaction conditions for all the responses under study, a third DoE (full factorial design with two variables and two levels) was performed, one for each remaining organocatalysts (**I** and **VII**). The variable investigated were: 1) reaction time and 2) loading of the acidic catalyst.

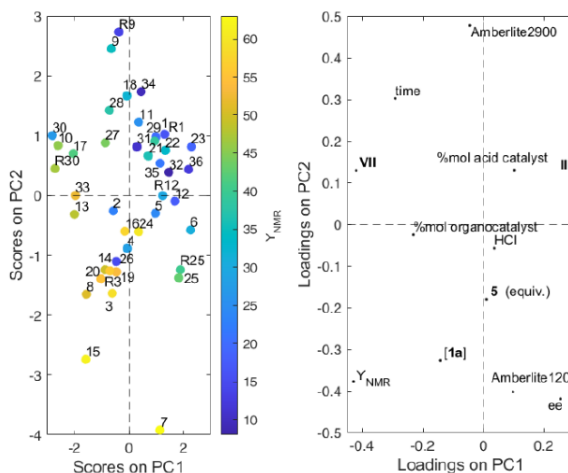


Figure 8: Scores (left) and loadings (right) plots of the Principal Component Analysis (PCA) on the experimental data matrix. The colorbar shows the improving of the yield with the decreasing of the PC2-scores.

The final choice between the two catalysts remained was **VII**: indeed, for **I** the resulting chemometric model was not significant

given that none of the coefficients associated to the investigated variables is significant, while the model generated to optimize yield and ee showed that **VII** was a better choice to improve the yield, even though in the investigated domain no significative improvements in ee occurred.

About the yield it was observed that it could be further optimized attending to other coefficients: indeed, the coefficient related to the reaction time was positive and the related response reached its maximum when time was set at 36 h, while the coefficient related to the percentage of the acidic co-catalyst was not significative, thus the loading was set at its lowest level (2.5 mol%) as depicted in Figure 9. Being these two variables non-correlated each other, the resulted model was linear (Eq. 1).

$$\text{(Eq. 1) } Y_{\text{NMR}} (\%) = 43 + 15.5 \cdot \text{time} + 0.5 \cdot \% \text{mol acid catalyst} - 5 \cdot \text{time} \cdot \% \text{mol acid catalyst}$$

Basing on the results obtained by the optimisation through DoE, the generality of the reaction was started (Scheme 14).

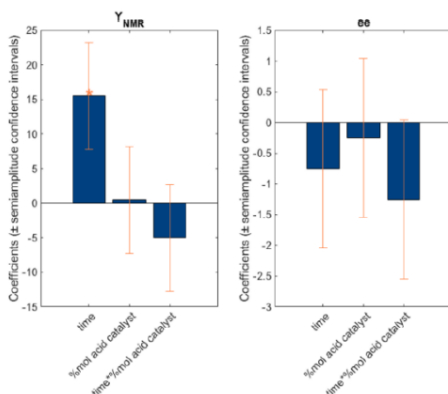
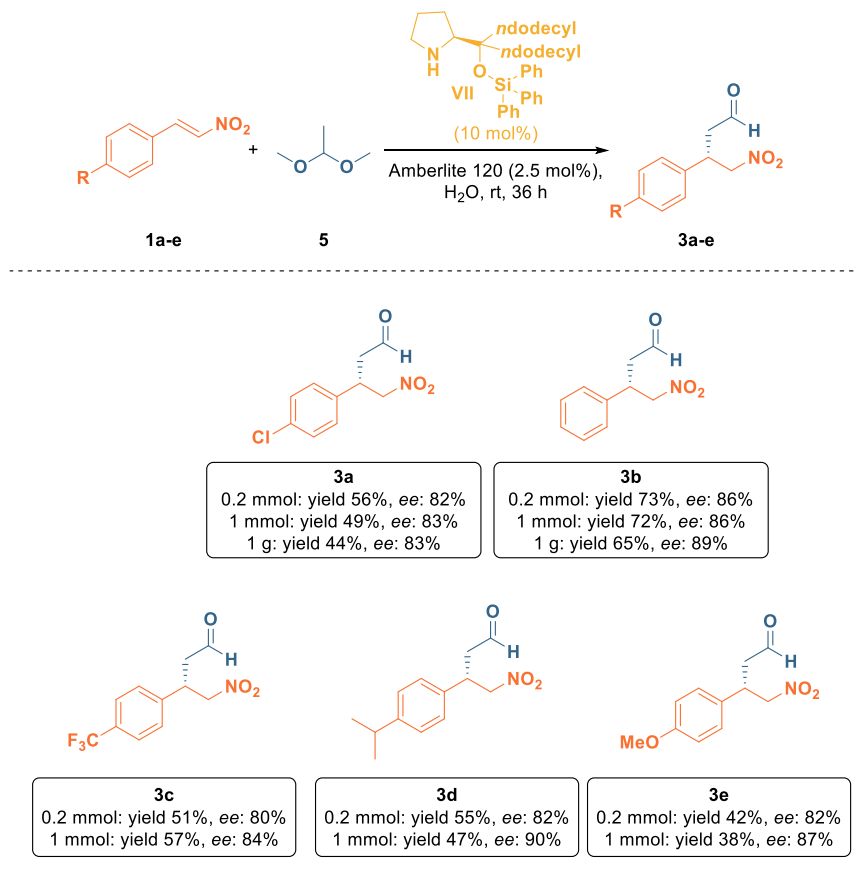


Figure 9: Plot of the coefficients of the mathematical model of the response YNMR and the ee for the third screening via Full Factorial Design using **VII** as catalyst.

As shown in the scheme below and as expected basing on literature, the best results were obtained in the case of β -nitrostyrene **1b**. Both electron donor and electron withdrawing

substituents in *para* position were well tolerated, with a slightly better enantiomeric excess for the former ones.



Unsuccessful Substrates



Scheme 14: Scope of the organocatalysed Michael addition in water with various aromatic nitroalkenes **1a-e**.

Intriguingly, this method proved to solid and reliable, affording comparable yields when the scale of the reaction was increased to 1 mmol and 1 g: indeed, usually biphasic systems can lead to mixing and stirring problems when the scale is increased, but in our case, those issues did not arise. Unfortunately, very low yields,

alongside the formation of several byproducts related to self-aldol phenomena, were observed when aliphatic nitroalkenes (**1f-i**) were used, in contrast to the outcomes obtained when the reaction was run in chloroform.⁵⁴ Then, focusing on **1f**, it was tried to optimise the reaction condition for the aliphatic substrates: two factors (at two different levels), acidic co-catalyst loading (10 mol% and 20 mol%) and acetaldehyde dimethyl acetal **5** (5 equiv and 10 equiv.), were taken into account into a further full-factorial design, resulting in 7 experiments (3 of which were replicates) carried out. However, the fact that the coefficients resulted as non-significant (Figure 10) meant that the yield could not be improved modifying the selected variables and the general outcome of the analysis indicated the not complete suitability of this strategy for the intended purpose.

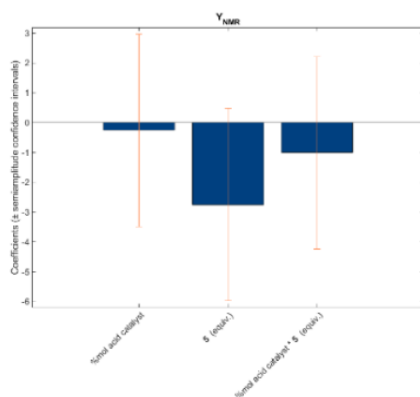
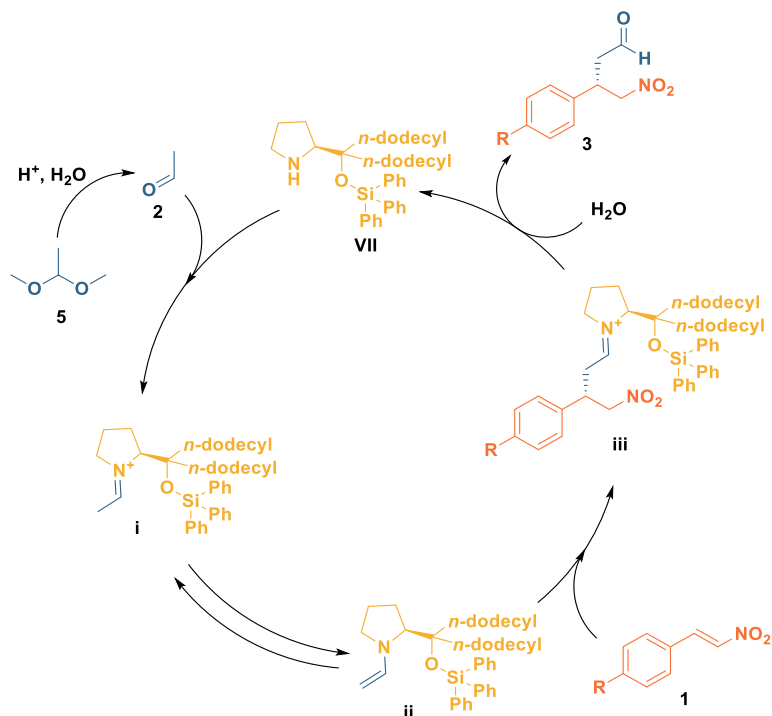


Figure 10: Plot of the coefficients of the mathematical model of the response Y_{NMR} for the full factorial design applied on aliphatic substrates.

According to previous reports,⁵⁴ here is reported the proposed catalytic cycle (see Scheme 15): after the release of the free acetaldehyde **2** from the acetal **5** operated from the acidic co-catalyst, an iminium intermediate (**i**) with aminocatalyst **VII** is formed, in equilibrium with the enamine intermediate **ii**. **ii** is then able to give Michael addition to the β -nitrostyrene **1** enantioselectively, leading to the intermediate **iii** that is then

hydrolysed releasing the product **3** and regenerating the aminocatalyst **VII**.



Scheme 15: Proposed catalytic cycle.

2.4 Conclusions

In conclusion, a new protocol to perform asymmetric Michael addition of acetaldehyde to nitroalkenes in water has been developed. This approach avoids the side reactions related to the reactivity of acetaldehyde introducing it as dimethyl acetal and deprotecting it *in situ*. More important, it made use of the Design of Experiment to avoid the use of polluting solvents (such as chloroform) in favor of water and to reduce sensitively the total amount of experiments required to find the optimal reaction conditions. Even though still some limitations remains when aliphatic nitroalkenes are used, the reaction performs well with β -nitrostyrenes, leading to good yield and ees.

2.5 Experimental Section

General Information. ^1H -NMR spectra were recorded in CDCl_3 at 400 MHz on Bruker Avance 400 instrument. Chemical shifts (in ppm) are referenced to tetramethylsilane ($\delta = 0$ ppm) as an internal standard and are relative to residual signals of the solvent 7.26 ppm. ^{13}C NMR spectra were recorded in CDCl_3 at 100.6 MHz and were calibrated with CDCl_3 ($\delta = 77.36$ ppm) or tetramethylsilane ($\delta = 0$ ppm). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad signal. ^1H -NMR yields were measured by analysing the reaction mixture using 1,2,4,5-Tetramethylbenzene (durene) as an internal standard. HPLC analyses were acquired using an Agilent 1220 Infinity II liquid chromatographer equipped with a Phenomenex column Lux 3 μm i-Cellulose-5 or Lux 3 μm Cellulose-1.

Racemic samples were prepared using a racemic mixture of (R,S)-diphenyltrimethylsiloxymethylpyrrolidine (**I**) as a catalyst at room temperature in chloroform (CHCl_3) overnight. Optical rotations were measured on a ZUZI 412 Digital Polarimeter (tube length: 100 mm). The high-resolution mass spectra (HRMS) were obtained with an ESI-QTOF (Agilent Technologies, model G6520A) instrument, and the m/z values are referred to the mono isotopic mass.

General procedures. Chromatographic purifications of products were performed using automated BÜCHI - Reveleris® X2-UV System on silica gel (35-70 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used, using UV light as the visualising agent or basic aqueous potassium permanganate (KMnO_4), and heat as developing agents. Organic solutions were

concentrated under reduced pressure on a Büchi rotary evaporator (in vacuo at 40 °C, ~5 mbar).

Assignment of absolute configuration. Absolute configurations of compounds **3a-3e** were assigned by comparing their absolute optical rotations with the values reported in the literature. The absolute configuration of all other products was assigned by analogy, considering a uniform mechanism of stereoinduction.

Materials. Acetaldehyde dimethyl acetal **5**, β -nitrostyrene **1b**, **1**, 1,2,4,5-Tetramethylbenzene, p-Toluensulfonic acid monohydrate (p-TSA), Trifluoroacetic acid TFA), Hydrochloric acid (HCl), Amberlyst®15 hydrogen form (Amberlyst 15), Amberlite® IRC120 H hydrogen form (Amberlite 120), Amberlyst® 36 (Amberlyst 36), Dowex® Marathon™ MSC hydrogen form (Amberlite 2900), Nafion™ NR50 (Nafion) were purchased by Merck and used as received unless otherwise stated. Silica Gel 60A (35-70 μ), HPLC solvents and analytical grade solvents were purchased by Merck. Nitroalkenes **1a** and **1c - e** were prepared as previously reported.⁵⁴ Catalysts **II - IX** were previously reported.⁶¹

2.5.1 Reaction conditions optimisation via DoE

DoEs were carried out to determine which variables had the greatest impact on the two responses (yield and enantiomeric excess of the compound **3a**), and in order to maximise them.

General procedure for DoE. The reactions were carried out following the general procedure in accordance with the parameters investigated with Design of Experiment (see the tables below): acetaldehyde dimethyl acetal **5** was added to a suspension of organocatalyst (**I-IX**), nitroalkene **1a** (36.6 mg, 0.2 mmol, 1 equiv), co-solvent (10% v/v), additive (0.11 M in water), and acid catalyst

⁶¹ C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, Á Puente, S. Vera *Angew. Chem. Int. Ed.* **2007**, 46, 8431–8435.

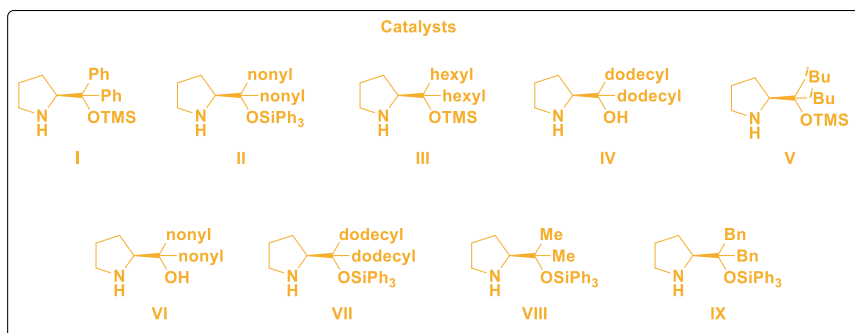
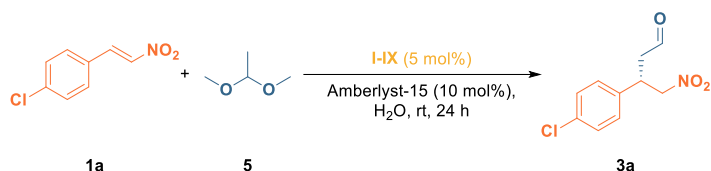
in water. The reaction mixture was left under stirring at 25 °C for the required time. The reaction was quenched with 2 mL of HCl(aq) 1M, and the aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* after filtration. The crude was purified by using automated BÜCHI - Reveleris® X2-UV System (silica gel, mixture of petroleum ether/ethyl acetate 9:1 v/v) to afford the desired compound. NMR spectra of previously reported compounds were in agreement with those of the authentic samples and/or available literature data. NMR yield was measured by analysing the reaction mixture using 1,2,4,5-Tetramethylbenzene (durene) as an internal standard. The spectrum was recorded using a higher than usual pulse delay (D1=10). The enantiomeric excess (ee) was determined by chiral-enantiopure-stationary-phase HPLC analysis after conversion of the aldehyde into the corresponding alcohol by reduction with NaBH₄ in MeOH by comparison with the authentic racemic material.

First Design of Experiment – Preliminary screening via D-Optimal Design

In the first DoE the variables reported below were investigated:

1. Organocatalysts (discrete variable with 9 levels (Catalysts I - IX)).
2. Catalyst loading (continuous variable in the range 2.5 mol% – 10 mol%).
3. Equivalents of acetaldehyde dimethyl acetal **5** (continuous variable in the range 1.5 – 3 equiv).
4. Reaction time (continuous variable in the range 24 h – 72 h).
5. Solution concentration (continuous variable in the range 0.2 M – 1.2 M).

6. Cosolvents (discrete variable with 5 levels (EtOAc, MeOH, THF, IPA, none)).
7. Acidic catalysts to deprotect masked acetaldehyde (discrete variable with 10 levels: 5 acidic resins and 5 organic acids).
8. Acidic catalysts to deprotect masked acetaldehyde (discrete variable with 10 levels: 5 acidic resins and 5 organic acids).
9. Ionic strength of water (discrete variable with 3 levels of additive (NaCl, CaCl₂, none)).

Table 2: Experimental Conditions for the first D-Optimal.

Entry	Catalyst (mol%)	5 (equiv.)	Time (h)	[1a] (M)	Co-solv	Acidic Co-cat. (mol%)	Additive	Y _{NMR} (%)	ee (%)
1	I (10 mol%)	1.5	24	1.2 M	EtOAc	Benzoic acid 20 mol%	CaCl ₂	12	85
2	IV (2.5 mol%)	3	24	0.2 M	-	Amberlite 120 20 mol%	NaCl	0	n.d.
3	VIII (10 mol%)	3	24	0.2 M	THF	H ₂ SO ₄ 5 mol%	-	12	74
4	II (2.5 mol%)	1.5	24	0.2 M	IPA	Amberlite 2900 20 mol%	CaCl ₂	0	n.d.
5	V (2.5 mol%)	1.5	24	1.2 M	-	Amberlyst 36 5 mol%	CaCl ₂	1	n.d.

6	V (2.5 mol%)	3	72	1.2 M	MeOH	Benzoic acid 20 mol%	NaCl	0	n.d.
7	VII (10 mol%)	1.5	72	1.2 M	-	Nafion-H 20 mol%	-	25	82
8	II (2.5 mol%)	1.5	72	1.2 M	THF	Amberlyst 15 20 mol%	-	0	n.d.
9	VI (10 mol%)	3	72	1.2 M	MeOH	Amberlyst 36 20 mol%	-	0	n.d.
10	VII (10 mol%)	3	24	0.2 M	MeOH	Amberlyst 15 5%	CaCl ₂	15	82
11	III (10 mol%)	1.5	24	1.2 M	THF	Nafion 20 mol%	NaCl	8	72
12	IX 2.5 mol%	3	24	0.2 M	EtOAc	HCl 5 mol%	-	0	n.d.
13	II 10 mol%	3	72	0.2 M	EtOAc	<i>p</i> -TSA 5 mol%	NaCl	8	82
14	IX 10 mol%	3	72	0.2 M	THF	TFA 20 mol%	CaCl ₂	4	n.d.
15	VII 2.5 mol%	1.5	72	0.2 M	THF	Amberlyst 36 20 mol%	NaCl	3	n.d.
16	VIII 10 mol%	1.5	72	0.2 M	-	Amberlyst 15 20 mol%	NaCl	2	n.d.
17	IV 10 mol%	1.5	72	1.2 M	IPA	HCl 20 mol%	CaCl ₂	0	n.d.
18	I 2.5 mol%	3	72	0.2 M	IPA	Nafion 5 mol%	CaCl ₂	3	n.d.
19	III 10 mol%	1.5	72	0.2 M	-	Benzoic acid 5 mol%	-	9	65.
20	III 2.5 mol%	3	72	1.2 M	EtOAc	H ₂ SO ₄ 20 mol%	CaCl ₂	0	n.d.
21	IV 2.5 mol%	1.5	72	0.2 M	EtOAc	Amberlite 2900 5 mol%	-	0	n.d.
22	II 10 mol%	3	72	0.2 M	EtOAc	<i>p</i> -TSA 5 mol%	NaCl	0	n.d.
23	VI 2.5 mol%	1.5	72	0.2 M	THF	<i>p</i> -TSA 20 mol%	CaCl ₂	0	n.d.
24	III 10 mol%	1.5	72	0.2 M	-	Benzoic acid 5 mol%	-	0	n.d.
25	III 2.5 mol%	3	72	1.2 M	EtOAc	H ₂ SO ₄ 20 mol%	CaCl ₂	0	n.d.
26	IX 10 mol%	1.5	72	0.2 M	MeOH	H ₂ SO ₄ 5 mol%	NaCl	5	84
27	I 10 mol%	3	72	1.2 M	-	Amberlite 2900 5 mol%	NaCl	36	88
28	V	1.5	72	0.2 M	IPA	Amberlite 120	-	2	n.d.

	10 mol%	20 mol%							
29	IV 10 mol%	1.5	72	1.2 M	IPA	HCl 20 mol%	CaCl ₂	0	n.d.
30	VIII 2.5 mol%	1.5	72	1.2 M	MeOH	Amberlite 120 5 mol%	CaCl ₂	5	83
31	VI 2.5 mol%	1.5	24	1.2 M	IPA	TFA 5 mol%	NaCl	0	n.d.
32	IV 2.5 mol%	3	24	0.2 M	-	Amberlite 120 20 mol%	NaCl	0	n.d.
33	IX 2.5 mol%	3	24	1.2 M	IPA	p-TSA 20 mol%	-	0	n.d.
34	I 2.5 mol%	1.5	24	0.2 M	MeOH	TFA 20 mol%	-	0	n.d.

Based on previous knowledge and preliminary experiments results, nine factors (four qualitative and the remaining ones quantitative) were believed to affect the conversion (Y_{NMR}) and the enantiomeric excess (ee) of product **3a**. The assumed mathematical model, containing only one constant and 28 linear terms, is the following:

$$\begin{aligned}
 1) \quad Y \text{ (both } Y_{\text{NMR}} \text{ and ee)} = & b_0 + b_{1\text{II}} X_{1\text{II}} + b_{1\text{III}} X_{1\text{III}} + b_{1\text{IV}} X_{1\text{IV}} + \\
 & b_{1\text{V}} X_{1\text{V}} + b_{1\text{VI}} X_{1\text{VI}} + b_{1\text{VII}} X_{1\text{VII}} + b_{1\text{VIII}} X_{1\text{VIII}} + b_{1\text{IX}} X_{1\text{IX}} + b_2 X_2 + \\
 & b_3 X_3 + b_4 X_4 + b_5 X_5 + b_{6\text{EtOAc}} X_{6\text{EtOAc}} + b_{6\text{MeOH}} X_{6\text{MeOH}} + b_{6\text{IPA}} \\
 & X_{6\text{IPA}} + b_{6\text{THF}} X_{6\text{THF}} + b_{7\text{Amberlyst-15}} X_{7\text{Amberlyst-15}} + b_{7\text{TFA}} X_{7\text{TFA}} + \\
 & b_{7\text{Amberlyst-36}} X_{7\text{Amberlyst-36}} + b_{7\text{Amberlite120}} X_{7\text{Amberlite120}} + b_{7\text{Nafion}} \\
 & X_{7\text{Nafion}} + b_{7\text{HCl}} X_{7\text{HCl}} + b_{7\text{p-TSA}} X_{7\text{p-TSA}} + b_{7\text{BenzoicAcid}} X_{7\text{BenzoicAcid}} + \\
 & b_{7\text{H2SO4}} X_{7\text{H2SO4}} + b_8 X_8 + b_{9\text{NaCl}} X_{9\text{NaCl}} + b_{9\text{CaCl2}} X_{9\text{CaCl2}}
 \end{aligned}$$

Where terms X_i are the reaction variables:

- X_1 : type of organocatalysts;
- X_2 : catalyst loading;
- X_3 : equivalents of **5**;
- X_4 : reaction time;
- X_5 : reaction concentration;
- X_6 : cosolvents;
- X_7 : acidic catalysts to deprotect;

X₈: acidic catalyst loading;

X₉: ionic strength of water.

The quantitative variables were investigated using two levels, respectively coded as -1 and +1; whereas the implicit level was used to evaluate the qualitative ones (I for X₁, absence of cosolvent for X₆, Amberlite2900 for X₇, absence of salt for X₉), i.e. each coefficient is to be considered with respect to the implicit level performances. Different combinations of implicit levels were tested without changes in the results. The levels were chosen on the basis of organic expertise:

X₁: I, II, III, IV, V, VI, VII, VIII, IX;

X₂: 2.5, 10 mol%;

X₃: 1.5, 3 equivalents;

X₄: 24, 72 h;

X₅: 0.2, 1.2 M;

X₆: absence of cosolvent, EtOAc, MeOH, IPA, THF;

X₇: Amberlyst-15, Amberlyst-36, Amberlite 120, Amberlite 2900, Nafion, HCl, p-TSA, Benzoic Acid, H₂SO₄, TFA;

X₈: 5, 20 mol%;

X₉: absence of salt, NaCl, CaCl₂.

D-optimal design was performed to identify, among all the possible experiments, the subset leading to the best possible compromise between experimental effort and quality of information by maximising the normalised determinant of the information matrix. The solution with 31 experiments was selected and 3 replicates were added, according to the experimental matrix in Table 2.

The coefficients of the mathematical model in equation (1) were computed by Multiple Linear Regression only for the response Y_{NMR}, since, without its improvement, the exploration of the ee response

would be meaningless. The mathematical model for Y_{NMR} (to be maximised) is:

$$\begin{aligned} (2) Y_{\text{NMR}} = & 27.1 (***) - 10.1X_{1\text{II}} (*) - 10.7X_{1\text{III}} (*) - 14.1X_{1\text{IV}} (*) - \\ & 7.3X_{1\text{V}} - 7.0X_{1\text{VI}} + 5.7X_{1\text{VII}} - 8.4X_{1\text{VIII}} - 8.7X_{1\text{IX}} (*) + 3.4X_2 (**) + \\ & 1.0X_3 - 0.4X_4 + 3.0X_5 (*) - 6.8X_{6\text{EtOAc}} - 6.3X_{6\text{MeOH}} (*) - 1.8X_{6\text{IPA}} (*) \\ & - 8.6X_{6\text{THF}} - 14.8X_{7\text{Amberlyst-15}} (*) - 12.3X_{7\text{TFA}} (*) - 19.3X_{7\text{Amberlyst-36}} \\ & (**) - 7.0X_{7\text{Amberlite120}} - 11.3X_{7\text{Nafion}} (*) - 8.1X_{7\text{HCl}} - 9.2X_{7\text{p-TSA}} (*) - \\ & 12.6X_{7\text{BenzoicAcid}} (*) - 8.2X_{7\text{H}_2\text{SO}_4} - 1.5X_8 + 0.4X_{9\text{NaCl}} + 0.04X_{9\text{CaCl}_2} \end{aligned}$$

Concerning the variable X_1 , b_{1i} are always negative, except for the coefficient of organocatalyst **VII** that is positive, even though slightly not significant. Therefore, organocatalysts **I** and **VII** seem to be the ones cause an improvement of the Y_{NMR} . Organocatalyst **II** is retained for its structural similarity with **VII**, despite of its negative $b_{1\text{II}}$. Moreover, we were also interested to investigate the effects related to the possible hydrophobic interaction by considering the different alkyl side chains. As expected, the increase of the catalyst causes an increase of Y_{NMR} , nevertheless exceed the 10%mol is not convenient so it is maintained as upper limit for X_2 . Similar considerations can be done for X_5 , because its increase leads to an improvement of the response, but [**1a**] higher than 1.2 M is not experimentally feasible. Against expectation, instead, b_3 and b_4 are not significant. This outcome could be biased by the bad results obtained; therefore, we decide to further investigate the equivalents of **5** and the reaction time in the next designs. The coefficients of all the cosolvents are negative since their introduction in the reaction environment decreases Y_{NMR} . On the contrary, the presence of salts does not contribute in any way to the response since all the coefficients are not significant. Therefore, it is reasonable to exclude variables X_6 and X_9 in the further investigation (no additive and salts will be used in the reaction). Respect to the variable X_7 the performances of all the acidic catalysts are worse (negative coefficients) than those of the

implicit level. Nevertheless, Amberlyst-15, Amberlyst-36 and HCl are further investigated in addition to Amberlite2900 because of their performances previously investigated. The loading of the acidic catalyst has a negative coefficient, even though slightly not-significant, so we decided to keep the variable X8 changing the levels. This first DoE was used as exploratory screening to decide the further approaches, for this reason no model validation was performed.

Second Design of Experiment - screening via D-Optimal Design

In the second DoE the reported variable were investigated:

- Organocatalysts (discrete variable with 3 levels (catalysts **I**, **II**, and **VII**)).
- Catalyst loading (continuous variable in the range 5 mol% – 10 mol%).
- Equivalents of acetaldehyde dimethyl acetal (continuous variable in the range 1.5 – 2.5 equiv).
- Reaction time (continuous variable in the range 24 h – 72 h).
- Solution concentration (discrete variable with 3 levels 0.8 M, 1 M and 1.2 M).
- Acidic catalysts (a discrete variable with 4 levels).
- Acidic catalyst loading (continuous variable in the range 5 mol% – 10 mol%).

Table 3: Experimental conditions for the second D-Optimal.

	1a (1 equiv.)	5 (1.5-2.5 equiv.)					3a
Catalysts 							
Entry	Catalyst (mol%)	Acid co-catalyst (mol%)	5 (equiv.)	Time (h)	[1a]	Y _{NMR} (%)	ee (%)
1	II 10%	Amberlyst 15 5%	2.5	24	0,8	13	80
2	VII 5%	Amberlyst 15 5%	2.5	24	1	15	77
3	I 10%	Amberlyst 15 5%	1.5	72	1,2	41	83
4	VII 10%	Amberlite 120 5%	1.5	24	0,8	16	81
5	I 5%	Amberlite 120 5%	2.5	72	0,8	15	82
6	II 5%	Amberlite 120 5%	2.5	24	1,2	17	81
7	I 10%	Amberlite 120 5%	2.5	24	1,2	63	86
8	VII 5%	Amberlite 120 5%	1.5	72	1,2	32	76
9	II 5%	Amberlite 2900 5%	1.5	72	0,8	19	77
10	VII 10%	Amberlite 2900 5%	2.5	72	0,8	24	76
11	II 10%	Amberlite 2900 5%	1.5	24	1,2	15	80
12	I 5%	HCl 5%	1.5	24	0,8	13	87
13	VII 10%	HCl 5%	1.5	72	0,8	26	78
14	VII 5%	HCl 5%	1.5	24	1,2	27	78
15	VII 5%	HCl 5%	2.5	72	1,2	57	81
16	II 10%	HCl 5%	2.5	72	1,2	37	78
17	VII 5%	Amberlyst 15 10%	1.5	72	0,8	22	75
18	II 10%	Amberlyst 15 10%	2.5	72	0,8	18	76
19	VII 10%	Amberlyst 15	1.5	24	1	35	83

		10%					
20	VII 10%	Amberlyst 15 10%	2.5	24	1.2	34	78
21	II 5%	Amberlyst 15 10%	2.5	72	1.2	19	80
22	II 10%	Amberlite 120 10%	1.5	24	0.8	18	78
23	II 5%	Amberlite 120 10%	2.5	24	0.8	13	80
24	II 10%	Amberlite 120 10%	2.5	72	1	41	78
25	I 5%	Amberlite 120 10%	1.5	24	1.2	22	85
26	VII 10%	Amberlite 120 10%	2.5	72	1.2	12	81
27	VII 5%	Amberlite 2900 10%	1.5	24	0.8	22	82
28	I 10%	Amberlite 2900 10%	1.5	72	0.8	19	83
29	I 5%	Amberlite 2900 10%	2.5	24	1	13	84
30	VII 10%	Amberlite 2900 10%	1.5	72	1.2	15	75
31	I 5%	Amberlite 2900 10%	2.5	72	1.2	11	85
32	I 10%	HCl 10%	2.5	24	0.8	8	84
33	VII 5%	HCl 10%	2.5	72	0.8	33	74
34	II 5%	HCl 10%	1.5	72	1	8	78
35	II 10%	HCl 10%	1.5	24	1.2	14	80
36	II 5%	HCl 10%	2.5	24	1.2	11	83
R1	II 10%	Amberlyst 15 5%	2.5	24	0.8	19	78
R3	I 10%	Amberlyst 15 5%	1.5	72	1.2	33	83
R9	II 5%	Amberlite 2900 5%	1.5	72	0.8	11	78
R12	I 5%	HCl 5%	1.5	24	0.8	16%	84
R25	I 5%	Amberlite 120 10%	1.5	24	1.2	19%	85
R30	VII 10%	Amberlite 2900 10%	1.5	72	1.2	24%	77

By taking into account the results of the first DoE, we retained 7 factors (two qualitative and five quantitative) reducing and/or changing the correspondent levels. At this step, a mathematical model contained one constant, 10 linear terms, 10 interaction terms and one quadratic term was considered:

$$\begin{aligned}
 (1) \ Y \text{ (both } Y_{\text{NMR}} \text{ and ee)} &= b_0 + b_{1\text{II}} X_{1\text{II}} + b_{1\text{VI}} X_{1\text{VI}} + b_{1\text{VII}} X_{1\text{VII}} \\
 &+ b_{2\text{Amberlite120}} X_{2\text{Amberlite120}} + b_{2\text{Amberlite2900}} X_{2\text{Amberlite2900}} + b_{2\text{HCl}} \\
 &X_{2\text{HCl}} + b_3 X_3 + b_4 X_4 + b_5 X_5 + b_6 X_6 + b_7 X_7 + b_{34} X_3 X_4 + b_{35} \\
 &X_3 X_5 + b_{36} X_3 X_6 + b_{37} X_3 X_7 + b_{45} X_4 X_5 + b_{46} X_4 X_6 + b_{47} X_4 X_7 \\
 &+ b_{56} X_5 X_6 + b_{57} X_5 X_7 + b_{67} X_6 X_7 + b_{66} X_{62}
 \end{aligned}$$

Where terms X_i are the reaction variables:

X_1 : type of organocatalysts;

X_2 : acidic catalysts to deprotect;

X_3 : organocatalyst loading;

X_4 : equivalents of **5**;

X_5 : reaction time;

X_6 : reaction concentration;

X_7 : acidic catalyst loading.

As for the first DoE, the quantitative variables were investigated using two or three levels, coded as -1 (low-level), 0 (mid-level) and +1 (high-level); whereas the implicit level was used to evaluate the qualitative ones (I for X_1 and Amberlyst-15 for X_2). The levels are the following:

X_1 : I, II, VII;

X_2 : Amberlyst-15, Amberlite120, Amberlite2900, HCl;

X_3 : 5, 10 mol%;

X_4 : 1.5, 2.5 equivalents;

X_5 : 24, 72 h;

X_6 : 0.8, 1, 1.2 M;

X_7 : 5, 10 mol%.

A second D-optimal design was performed and the solution with 36 experiments came out. Six replicates were further selected from the latter sub-set exploiting again a D-optimal design. The experimental matrix is showed in Table 3. Principal Component Analysis (PCA) was then performed on the experimental matrix.

PCA is an exploratory analysis method which lays on the bilinear decomposition of the data matrix into a set of scores (called principal components) and a set of loadings (which “weight” the relationship between original and latent variables). From the geometrical point of view, it can be seen as the projection of the observations onto the directions of maximum variance (i.e., the PCs). This, among the others, provides a number of benefits; in particular, the realisation of graphical representations (as the scores and loadings plots discussed below) suitable for the interpretation of the system under study. The scores and loadings plot of the PCA performed on the experimental matrix, the Y_{NMR} and the ee values were used to take a decision about how to deal with the two-responses problem. As it can be seen from Figure 8, a trend of the experiment points (colored according to the increasing of the responses) can be highlighted in the scores plot: the highest is Y_{NMR} , the lowest is the scores on PC2, as for ee. Both the responses, indeed, have high and negative loadings on PC2. Driven by these considerations, the *Scores on PC2* was selected as compromise-response.

The coefficients of the mathematical model in equation (3) were again computed by Multiple Linear Regression for the response *Scores on PC2* (to be minimised):

$$\begin{aligned} (2) \text{ Scores on PC2} = & -0.7 (*) + 1.4X_{1\text{II}} (***) - 0.06X_{1\text{VII}} - \\ & 0.7X_{2\text{Amberlite120}} (**) + 1.2X_{2\text{Amberlite2900}} (***) - 0.09X_{2\text{HCl}} - 0.2X_3 (*) - \\ & 0.1X_4 + 0.09X_5 - 0.6X_6 (***) + 0.3X_7 (***) - 0.05X_3X_4 + 0.05X_3X_5 - \\ & 0.05X_3X_6 + 0.06X_3X_7 - 0.09X_4X_5 - 0.2X_4X_6 (*) + 0.05X_4X_7 + 0.03X_5X_6 \\ & + 0.1X_5X_7 + 0.2X_6X_7 (*) + 0.2X_{62} \end{aligned}$$

In the scenario of *Scores on PC2* minimisation (maximisation of Y_{NMR} and ee), the considerations of the first-DoE about the organocatalysts are confirmed. Indeed, the positive coefficient of organocatalyst I suggests, as expected, a decrease of the original

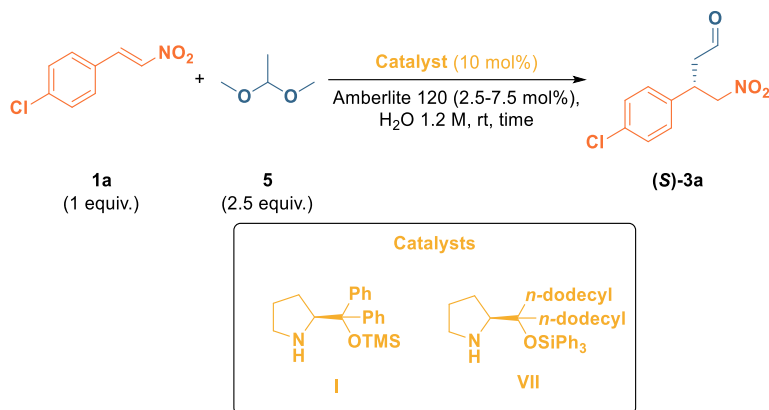
responses when it is employed. At the same time, the performances of **II** and **VII** can be considered good and comparable. Taken Amberlyst-15 as implicit level, Amberlite120 (negative and significative coefficient) results to be the best acidic catalyst, instead of Amberlite 2900 (b2Amberlite2900 is positive and significative) suggested by the previously design, in the improvement of Y_{NMR} and ee. The coefficient of the organocatalyst loading is negative and significative and no interaction terms are, so its increase would lead to an increase of the responses (decrease of Scores on PC2). Nevertheless, exceed the actual loading is not experimentally convenient. Conversely, time's linear coefficient is positive even though slightly not-significant, so it would be convenient to decrease the level of this variable on the basis of a time-saving criterion. The variable X_4 shows a not significant linear term (negative) and a significative interaction term (negative) X_4X_6 . The reaction concentration's coefficients are negative and significant for both the linear and the interaction term (X_4X_6). The variable X_7 shows positive and significant coefficients for linear and interaction term with variable X_6 . Therefore, these variables should be considered simultaneously. Y_{NMR} and ee would improve when, at the same time, X_4 (equivalents of **5**) and X_6 (reaction concentration) are at the highest-level and X_7 (acidic catalyst loading) is at its lowest level. The experimental conditions were suggested as optimal for the improving of the conversion and the enantiomeric excess of the product **3a** results to be the one already investigated in the point 7 of the design. This second DoE was not validated for the same reason as the first-one.

Third Design of Experiment - Full Factorial Design

To further optimise the reaction conditions for all the responses under study, the third Design of Experiments was performed. The variables investigated were:

- Organocatalysts (discrete variable with 2 levels (catalysts I and VII));
- Reaction time (discrete variable with 3 levels 24 h, 36 h, and 72 h);
- Acidic catalyst loading (discrete variable with 3 levels 2.5 mol%, 5 mol%, and 7,5 mol%).

Table 4: Experimental conditions for the third DoE – Full Factorial.



Entry	Catalyst	Amberlite 120 (mol%)	Time (h)	Y _{NMR} (%)	ee (%)
1	I	2,5%	16	35	85
2	I	2,5%	36	31	86
3	I	7,5%	16	19	90
4	I	7,5%	36	38	85
5	I	5%	24	46	87
6	I	5%	24	55	84
7	I	5%	24	51	87
8	VII	2,5%	16	22	81
9	VII	2,5%	36	63	82
10	VII	7,5%	16	33	83
11	VII	7,5%	36	54	79
12	VII	5%	24	43	80
13	VII	5%	24	41	81
14	VII	5%	24	36	80

The last D-optimal Design suggested aims at exploring the surrounding domain of the experimental point 7; for this reason, the

latter was taken as central point of two Full Factorial Designs with two variables (the only ones on which we can further act) and two levels, one for each of the organocatalysts (**I** and **VII**) resulting the most suitable. The mathematical models were assumed to be:

$$(1) Y_{\text{organocatalyst I (both } Y_{\text{NMR}} \text{ and ee)}} = b_{I0} + b_{I1} X_1 + b_{I2} X_2 + b_{I12} X_{12}$$

$$(2) Y_{\text{organocatalyst VII (both } Y_{\text{NMR}} \text{ and ee)}} = b_{VII0} + b_{VII1} X_1 + b_{VII2} X_2 + b_{VII12} X_{12}$$

Where terms X_i and respective levels are:

- X_1 : reaction time, levels 16, 36 h;
- X_2 : acidic catalyst loading, levels 2.5, 7.5 %mol.

and all the other factors are maintained as in the point 7 (see **Table 5**) because is not convenient to change them. The two experimental matrices in Table 5 showed the experiments (entries 1-4) used to compute the models and the ones (entries 5-7) for the validation of the DoE using the **VII** organocatalyst.

The coefficients, showed in Figure 6, of the mathematical model in equation (5) were computed by Multiple Linear Regression both for Y_{NMR} and ee:

$$(7a) Y_{\text{NMR-I}} = 30.8 (***) + 3.8X_1 - 2.3X_2 + 5.8X_{12}$$

$$(7b) Y_{\text{ee-I}} = 86.5 (**) - 1.0X_1 + 1.0X_2 - 1.5X_{12}$$

All the coefficients in both the models result not significant, i.e. it is not possible to improve Y_{NMR} and ee changing the selected variables in the investigated domain. For this reason, organocatalyst **I** was rejected; however, as it stands, it allows to obtain product **3a** with 31% of conversion and 87% of enantiomeric excess.

The coefficients of the mathematical model in equation (6), showed in the Figure 8, were as usual computed by Multiple Linear Regression both for Y_{NMR} and ee:

$$(8a) Y_{\text{NMR-VII}} = 43.0 (***) + 15.5X_1 (*) - 0.5X_2 - 5.0X_{12}$$

$$(8b) Y_{ee-VII} = 81.3 (***) - 0.75X_1 - 0.25X_2 - 1.3X_{12}$$

Concerning the conversion modeling in equation (8a), it can be highlighted that only an increase of reaction time would lead to an increase of the yield and, therefore, it would be advisable to use the acidic catalyst at its lowest loading in a perspective of reaction-economy. This is also suggested looking at the response surface (Figure 7) calculated on the model. It can be represented by a plane with a maximum in the point (36h, 2.5%mol of acidic catalyst). In the equation (8b) only the constant term is significant, so further improving of the enantiomeric excess is not possible in the explored domain. This is confirmed by the very low slope of the plane representing the ee response surface in Figure 7. Looking more deeply at the shape of ee-surface we can note a slightly distortion of the plane due to which ee can be improved both with experimental conditions (36h, 2.5 mol% of acidic catalyst) and (24 h, 7.5 mol% of acidic catalyst), and mostly in this last point. Nevertheless, with the aim of find the best compromise between the two responses, we selected as optimal the solution (36h, 2.5 mol% of acidic catalyst), highlighted in yellow in both the planes.

It is also interesting to note, comparing equation (7b) and (8b), that the enantiomeric excess is higher with the organocatalyst **I**, but it is worth losing around 6% of ee to gain around 12% and more of conversion with the organocatalyst **VII**.

The final models (8a-b) were validated using 3 replicates of the central point as test set (entries 5-7) and the Student's T-distribution at 5% as level of significance. Concerning the yield, the predicted value with its semiamplitude of confidence interval is $(43.0 \pm 7.7)\%$ and the experimental one is $(45.3 \pm 7.5)\%$; whereas, the predicted value of ee is $(81.3 \pm 1.3)\%$ and the experimental is $(80.3 \pm 1.4)\%$.

Table 5: Full Factorial Design experimental matrices and responses Y_{NMR} (%) and ee (%) with the organocatalyst **I** (on the right) and **VII** (on the left). The entries 1-4 were considered for the model computation whereas the entries 5-7 were performed in the central point of the design and used for its validation.

Entry	X_1	X_2	Y_{NMR} (%)	ee (%)	Entry	X_1	X_2	Y_{NMR} (%)	ee (%)
1	-1	-1	35	85	1	-1	-1	22	81
2	1	-1	31	86	2	1	-1	63	82
3	-1	1	19	90	3	-1	1	33	83
4	1	1	38	85	4	1	1	54	79
					5	0	0	43	80
					6	0	0	41	81
					7	0	0	52	80

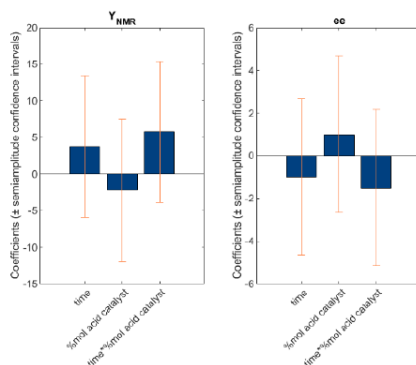


Figure 11: Plot of the coefficients of the mathematical models of the responses Y_{NMR} and ee (both to be maximised) in the third Full Factorial Design using the organocatalyst **I**.

Fourth DoE on aliphatic substrates - Full Factorial Design

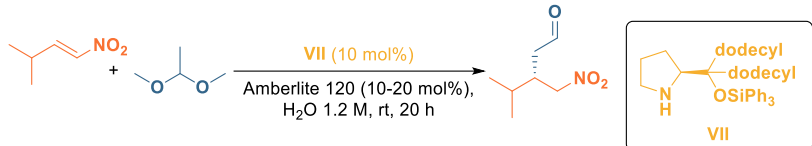
In this case we decided to evaluate the following variables using (*E*)-3-methyl-1-nitrobut-1-ene **1f**:

- acidic catalyst loading (continuous variable with two levels 10 mol% and 20 mol%).

- equivalents of acetaldehyde dimethyl acetal (continuous variable in the range 5 - 10 equiv).

We chose to investigate only these variables as we considered that a more similar approach to the conditions found in the literature would probably have led to the best results from an organic perspective. We therefore increased the loading of acid catalyst and the equivalents of masked reagent in order to raise the local concentration of free acetaldehyde and have a higher probability of forming the Michael addition product.

Table 6: Experimental conditions for the aliphatic starting materials.

			
1f (1 equiv.)	5 (5-10 equiv.)	(S)-3f	
Entry	5 (equiv.)	Amberlite 120 (mol%)	Y _{NMR} (%)
1	10	20	14
2	5	10	20
3	5	20	22
4	10	10	17
5	7.5	15	27
6	7.5	15	25
7	7.5	15	24

The last design of experiment aims at exploring the generality of the reaction and the applicability of the previously optimised conditions on some selected aliphatic substrates. A full factorial design with two factors (acidic catalyst loading and equivalents of acetaldehyde dimethyl acetal) and two levels was conceived and computed, resulting in seven experiments, (4 + 3 replicates at the central point). The assumed mathematical model is:

$$(9) Y_{\text{NMR}} = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_{12}$$

Where terms X_i and respective levels are:

X_1 : acidic catalyst loading, levels: 10 mol%, 20 mol%

X_2 : acetaldehyde dimethyl acetal, levels: 5 equiv, 10 equiv

Table 7 showed the experiments used to compute the model.

The coefficients of the mathematical model in equation (9) were computed by Multiple Linear Regression:

$$(10) Y_{\text{NMR}} = 18.5(***) - 0.25X_1 - 2.75X_2 - 1.00 X_{12}$$

All the coefficients (except for b_0) result not significant, i.e. it is not possible to significantly improve Y_{NMR} modifying the selected variables in the investigated domain. For this reason, the application of the investigated conditions on aliphatic substrates could not represent the most suitable solution.

Table 7: Experimental conditions for the aliphatic starting materials

Entry	Amberlite 120 (mol%)	5 (equiv.)	Y_{NMR} (%)
1	1	1	14
2	-1	-1	20
3	1	-1	22
4	-1	1	17
5	0	0	27
6	0	0	25
7	0	0	24

2.5.2 Substrates synthesis

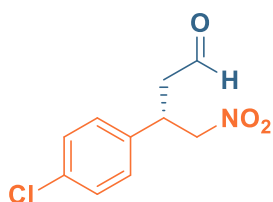
Synthesis of γ -nitroaldehydes 3a-e.

General procedure A for the asymmetric Michael addition of acetaldehyde dimethyl acetal to nitroalkenes. Acetaldehyde dimethyl acetal **5** (53 μL , 0.5 mmol, 2.5 equiv) was added to a suspension of catalyst **VII** (10 mol%), nitroalkene **1a - e** (1 equiv), and Amberlite® IR-120 (2.35 mg, 2.5 mol%) in water (167 μL , 1.2 M) at 25 °C. The reaction was quenched after 36 h with 2 mL of HCl(aq) 1M, and the aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried over MgSO_4 and concentrated *in vacuo* after filtration. The crude was purified by using automated BÜCHI - Reveleris® X2-UV System (silica gel,

mixture of petroleum ether/ethyl acetate 9:1 v/v) to afford the desired compound. NMR spectra of previously reported compounds were in agreement with those of the authentic samples and/or available literature data.

2.5.3 Products characterization

(S)-3-(4-chlorophenyl)-4-nitrobutanal (**3a**)



Prepared following **General Procedure A** using (*E*)-1-chloro-4-(2-nitrovinyl)benzene **1a** (1 equiv, 0.2 mmol, 36.6 mg). Isolated yield: 25.6 mg, 0.11 mmol, 56%; ¹H NMR yield 63%. 82% ee.

¹H NMR (400 MHz, CDCl₃, 298 K) δ = 9.70 (s, 1H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 4.67 (dd, *J* = 12.6, 6.9 Hz, 1H), 4.59 (dd, *J* = 12.6, 7.8 Hz, 1H), 4.06 (m, 1H), 2.94 (d, *J* = 7.1 Hz, 2H).

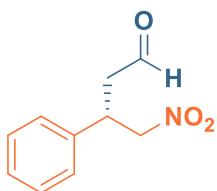
¹³C NMR (101 MHz, CDCl₃, 298 K) δ = 198.3 (CO), 136.7 (Car), 134.0 (Car), 129.4 (2xCHar), 128.8 (2xCHar), 79.1 (CH₂), 46.3 (CH₂), 37.3 (CH).

$[\alpha]_D^{25} = -0.55$ (*c* = 0.22 in CHCl₃, 82% ee).

HPLC (Lux 3 μ m i-Cellulose-5, Hexane/*i*-Propanol 90:10, flow: 0.5 mL/min., λ =210 nm) t_{major} : 17.2 min; t_{minor} : 15.6 min.

The same reaction was carried out according to the **General Procedure A** using (*E*)-1-chloro-4-(2-nitrovinyl)benzene **1a** (1 equiv, 1 mmol). Isolated yield: 49%; 83% ee.

The same reaction was carried out according to the **General Procedure A** using (*E*)-1-chloro-4-(2-nitrovinyl)benzene **1a** (1 equiv, 1 g, 5.5 mmol). Isolated yield: 44%; 83% ee.

(S)-4-nitro-3-phenylbutanal (3b).

Prepared following **General Procedure A** using β -nitrostyrene **1b** (1 equiv, 0.2 mmol, 30 mg). Isolated yield: 28 mg, 0.14 mmol, 73%; ^1H NMR yield 77%. 86% ee.

^1H NMR (400 MHz, CDCl_3 , 298 K) δ = 9.71 (s, 1H), 7.38 – 7.28 (m, 3H), 7.23 (d, J = 7.6 Hz, 2H), 4.68 (dd, J = 12.5, 7.2 Hz, 1H), 4.62 (dd, J = 12.5, 7.5 Hz, 1H), 4.08 (m, 1H), 2.95 (d, J = 7.0 Hz, 2H).

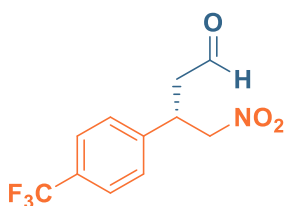
^{13}C NMR (101 MHz, CDCl_3 , 298 K) δ = 198.7 (CO), 138.1 (Car), 129.2 (2xCHar), 128.2 (CHar), 127.4 (2xCHar), 79.4 (CH₂), 46.4 (CH₂), 38.0 (CH).

$[\alpha]_D^{25}$ = – 0.58 (c = 0.24 in CHCl_3 , 86% ee).

HPLC (Lux $3\mu\text{m}$ Cellulose-1, Hexane/*i*-Propanol 90:10, flow: 0.5 mL/min., λ =210 nm) t_{major} : 24.8 min; t_{minor} : 19.6 min.

The same reaction was carried out according to the **General Procedure A** using β - nitrostyrene **1b** (1 equiv, 1 mmol). Isolated yield: 72%; 86% ee.

The same reaction was carried out according to the **General Procedure A** using β -nitrostyrene **1b** (1 equiv, 1 g, 6.7 mmol). Isolated yield: 65%; 89% ee.

(S)-4-nitro-3-(4-(trifluoromethyl)phenyl)butanal (3c).

Prepared following **General Procedure A** using (E)-1-(2-nitrovinyl)-4-(trifluoromethyl)benzene **1c** (1 equiv, 0.2 mmol, 43 mg). Isolated yield: 27 mg, 0.10 mmol, 51%; ^1H NMR yield 53%. 80% ee.

^1H NMR (400 MHz, CDCl_3 , 298 K) δ = 9.72 (s, 1H), 7.61 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 4.72 (dd, J = 12.8, 6.8 Hz, 1H), 4.64 (dd, J = 12.8, 7.9 Hz, 1H), 4.16 (m, 1H), 2.99 (d, J = 6.9 Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3 , 298 K) δ = 198.0 (CO), 142.3 (Car), 130.4 (q, $2J_{\text{C-F}}$ = 32.7 Hz; Car), 127.9 (2xCHar), 126.2 (q, $3J_{\text{C-F}}$ = 3.7 Hz, 2xCHar), 123.8 (q, $1J_{\text{C-F}}$ = 272.2 Hz), 78.7 (CH_2), 46.2 (CH_2), 37.5 (CH).

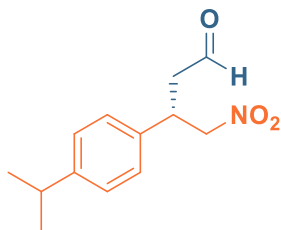
^{19}F NMR (376 MHz, CDCl_3 , 298 K) δ = -62.7.

$[\alpha]_{\text{D}}^{25}$ = - 0.94 (c = 0.23 in CHCl_3 , 80% ee).

HPLC (Lux 3 μm i-Cellulose-5, Hexane/*i*-Propanol 95:5, flow: 0.5 mL/min., λ =210 nm) t_{major} : 22.8 min; t_{minor} : 21.6 min.

The same reaction was carried out according to the **General Procedure A** using (E)-1-(2-nitrovinyl)-4-(trifluoromethyl)benzene **1c** (1 equiv, 1 mmol). Isolated yield: 57%; 84% ee.

(S)-3-(4-isopropylphenyl)-4-nitrobutanal (3d).



Prepared following **General Procedure A** using (E)-1-isopropyl-4-(2-nitrovinyl)benzene **1d** (1 equiv, 0.2 mmol, 38 mg). Isolated yield: 26 mg, 0.11 mmol, 55%; ^1H NMR yield 77%. 82% ee.

^1H NMR (400 MHz, CDCl_3 , 298 K) δ = 9.70 (s, 1H), 7.20 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H), 4.66 (dd, J = 12.5, 7.5 Hz, 1H), 4.60 (dd, J = 12.5, 7.4 Hz, 1H), 4.05 (m, 1H), 2.95 – 2.83 (m, 3H), 1.22 (d, J = 6.9 Hz, 6H).

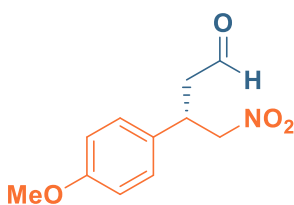
^{13}C NMR (101 MHz, CDCl_3 , 298 K) δ = 199.0 (CO), 148.8 (Car), 135.3 (Car), 127.3 (2xCHar), 127.3 (2xCHar), 79.5 (CH_2), 46.5 (CH_2), 37.7 (CH), 33.7 (CH), 23.8 (2xCH₃).

$[\alpha]_{\text{D}}^{25}$ = - 1.07 (c = 0.22 in CHCl_3 , 82% ee).

HPLC (Lux 3 μm i-Cellulose-5, Hexane/*i*-Propanol 95:5, flow: 0.4 mL/min., $\lambda=210$ nm) t_{major} : 47.9 min; t_{minor} : 43.3 min.

The same reaction was carried out according to the **General Procedure A** using (E)-1- isopropyl-4- (2-nitrovinyl)benzene **1d** (1 equiv, 1 mmol). Isolated yield: 47%; 90% ee.

(S)-3-(4-methoxyphenyl)-4-nitrobutanal (3e).



Prepared following **General Procedure A** using (E)-1-methoxy-4-(2-nitrovinyl)benzene **1e** (1 equiv, 0.2 mmol 36 mg). Isolated yield: 19 mg, 0.08 mmol, 42%; ^1H NMR yield 48%. 82% ee.

^1H NMR (400 MHz, CDCl_3 , 298 K) δ = 9.63 (s, 1H), 7.08 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 4.58 (dd, J = 12.4, 7.2 Hz, 1H), 4.50 (dd, J = 12.3, 7.6 Hz, 1H), 3.96 (m, 1H), 3.72 (s, 3H), 2.84 (d, J = 7.1 Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3 , 298 K) δ = 198.9 (CO), 159.3 (Car), 129.9 (Car), 128.5 (2xCHar), 114.6 (2xCHar), 79.7 (CH₂), 55.3 (CH₃), 46.5 (CH₂), 37.4 (CH).

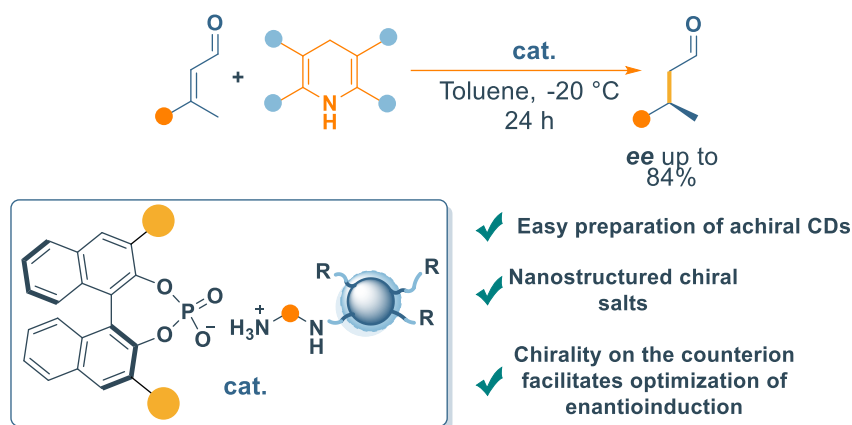
$[\alpha]_{\text{D}}^{25} = -0.83$ (c = 0.16 in CHCl_3 , 82% ee).

HPLC (Lux 3 μm Cellulose-1, Hexane/*i*-Propanol 90:10, flow: 0.5 mL/min., $\lambda=210$ nm) t_{major} : 25.8 min; t_{minor} : 23.3 min.

The same reaction was carried out according to the **General Procedure A** using (E)-1-methoxy-4-(2-nitrovinyl)benzene **1e** (1 equiv, 1 mmol). Isolated yield: 38%; 87% ee.

3. Nitrogen-Rich Carbon Dots as Effective Catalysts in the 1,4-Reduction of α,β -Unsaturated Aldehydes via Ion pair Asymmetric Nano-Organocatalysis

Part of this chapter has been published as: A. Carioscia,* E. Cocco,* M. E. Casacchia, G. Gentile, M. Mamone, E. Incerto, M. Prato, F. Pescioli, G. Filippini, A. Carlone ACS Catal. **2024**, 14, 13429-13438.



The development of a new nanostructured catalyst, consisting of a chiral phosphoric acid and achiral primary amines-doped Carbon Dots, has been successfully employed in the enantioselective 1,4-reduction of α,β -unsaturated aldehydes, with high yields and enantiomeric excesses.

3.1 Introduction

3.1.1 Carbon Dots: an overview

Carbon Dots are a class of carbon-based fluorescent nanomaterials constituted by nanoparticles having dimensions equal or inferior to 10 nm⁶² and, basing on the operation conditions and the syntheses

⁶² C. Rosso, G. Filippini, M. Prato ACS Catal. **2020**, 10, 15, 8090–8105.

precursor, they can show one or more functional groups: carboxylic acids, alcohols and amines are just some examples of the external derivatizations of the carbon nucleus of this new class of nanomaterials. These functional groups are responsible for bio-compatible properties, solubility and the low toxicity towards the environment these nanomaterials show.⁶³

Another important feature at the base of the increasing popularity of these materials is the rapid and easy preparation on large scale from cheap feedstocks.⁶⁴

The two main approaches, the *top-down approach* and the *bottom-up approach*, in which the carbon dots are obtained from graphite materials and molecular precursor respectively, are described below:

- the top-down approach: carbon dots are obtained starting from the decomposition of higher carbon-based structures such as graphite or carbon nanotubes through chemical or electrochemical oxidation, arc discharge, laser ablation, acid exfoliation or ultrasonic procedures. Important drawbacks on the large-scale application of this method of this approach are the long reaction times and the high prices of the starting materials;⁶²
- the cheaper bottom-up approach: carbon dots are prepared through carbonization, pyrolysis or hydrothermal treatment of small organic molecules or through incomplete combustion of biomasses.⁶⁵

The “bottom-up” approach is more ecological, simple and economical than “top-down” method. Furthermore, “bottom-up”

⁶³ F. Arcudi, L. Đorđević, M. Prato *Acc. Chem. Res.* **2019**, 52, 2070–2079.

⁶⁴ M. Bortolami, I. I. Bogles, C. Bombelli, F. Pandolfi, M. Feroci, F. Vetica *Molecules* **2022**, 27, 5150–5166.

⁶⁵ Y. Wang, A. Hu *J. Mater. Chem. C.* **2014**, 2, 6921–6939.

synthetic paths lead to production of CDs with well-defined dimensions and shapes. This level of control, combined with the ability to easily introduce doping with different heteroatoms, allows the modulation of the properties of these systems. In particular, heteroatoms such as oxygen, nitrogen, sulfur, phosphorus, boron, etc., can be easily incorporated into CDs structures using appropriate precursors such as amino acids, amines, thiols, phosphonates or borates.⁶² The features of CDs can be easily varied then, obtaining different structures depending on the application they will be employed to, making this class of compounds a rising star in several fields such as:

- *Biomedicine*: Since CDs are fluorescent, biocompatible, soluble nanomaterials water and characterized by high cellular permeability, can prove useful in some techniques used in biomedicine (fluorescent bioimaging for cells and tissues; biosensors for the monitoring of glucose, copper, iron, potassium, phosphates and nucleic acids; drug delivery for the distribution of drugs in the body and monitoring their effects)⁶⁶.
- *Optoelectronics*: Being eco-compatible and fluorescent materials, carbon dots can be used in this field in the construction of dyes-sensitised solar cells (DSC), organic solar cells (OSC) and LED.⁶⁵
- *Catalysis*: TiO₂-derived carbon dots have been employed in photo electrochemistry to perform Hydrogen Evolution Reactions (HER), while nitrogen-doped have shown good catalytic performances in the Oxygen Reduction Reactions (ORR).⁶⁵
- *Biosensors*: By monitoring changes in their fluorescence intensity under external physical or chemical stimuli, CDs

⁶⁶ A. Sharma; J. Das *J. Nanobiotechnology* **2019**, 17, 92-116.

have been used for qualitative and quantitative studies on substances and ions such as: DNA, phosphates, nitrites, glucose, biethiol, Fe^{3+} , Cu^{2+} , Ag^+ , Hg^{2+} .⁶⁵

Since the CDs family is quite large, it may be useful to remind the classification and nomenclature of these nanoparticles. Specifically, CDs can be divided into different subgroups depending on the nature of the nanostructures:

- *Graphene Quantum Dots* (GQD): bidimensional nanoparticles composed by one or more graphene sheets, obtained from exfoliation processes of graphite materials.
- *Carbon Quantum Dots* (CQD): quasi-spherical nanoparticles with a crystalline core, obtained by high-temperature heat treatment ($T > 300\text{ }^{\circ}\text{C}$) of suitable precursors.
- *Carbon Nano Dots* (CND): quasi-spherical amorphous nanoparticles obtained at lower temperatures than CQDs. Compared to them, they do not show a quantum confinement effect but possess excited states like molecular ones.
- *Polymer-like Dots* (PD): aggregated or cross-linked polymeric materials prepared from linear polymers or monomers.

In general, due to determining the precise structure and excited state of this class of materials is extremely difficult, it is common to use the term “Carbon Dots” to describe all those quasi-spherical carbon nanoparticles that have a behavior that extends between CNDs and CQDs.⁶²

In terms of application in chemistry, knowledge of the external composition of CDs, *i.e.* the extent of the terminal functional groups, is of fundamental importance. The surface properties of these systems play an important role in determining the chemical behavior of the entire nanoparticle in terms of reactivity, solvation

and redox properties. The exact chemical structure of most CDs remains unclear due to the unknown nature of their formation mechanisms and their difficult structural analysis. However, there are useful analysis methods for studying the physical and structural properties of CDs which concern the "core" and external functional groups. Below a list of the techniques used in determining the characteristics of the "core":

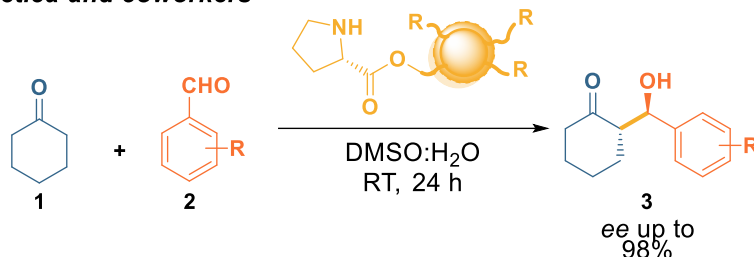
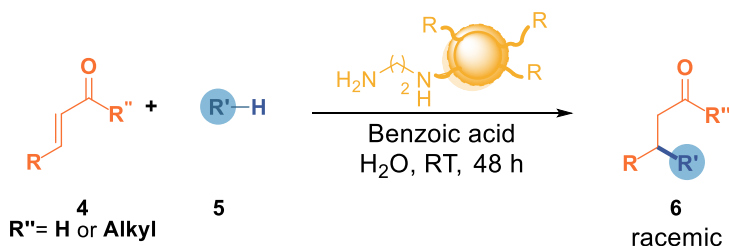
- The internal crystal structure of CQDs can be distinguished from (amorphous) CNDs using transmission electron microscopy (TEM) or Raman spectroscopy;⁶³
- The size of carbon nanoparticles can be determined by atomic force microscopy (AFM), dynamic light scattering (DLS), or by TEM;⁶³
- Electronic properties can be identified via optical spectroscopy through UV-Vis absorption or photoluminescence (PL): most CDs show strong absorption centered in the UV region extending into the visible region (π - π^* or n - π^* transitions) and which varies depending on the nature and preparation of the CDs.⁶²

While the following techniques are used to investigate the terminal functional groups on the surface:

- Amine groups can be detected by X-ray photoelectron spectroscopy (XPS) and quantified by Kaiser test (KT) or by nuclear magnetic resonance (NMR) on the formation of covalent adducts;
- Carboxyl and alcohol groups can be recognized by infrared spectroscopy (FT-IR) and quantified by acid-base or conductometric titrations;⁶⁷

⁶⁷ G. Filippini, F. Amato, C. Rosso, G. Ragazzon, A. Vega-Penaloza, X. Companyo, L. Dell'Amico, M. Bonchio, M. Prato *Chem* **2020**, 6,3022–3037.

- On the surface, group density and pyrolytic behavior of CDs at high temperatures can be approximately evaluated by thermogravimetric analysis (TGA).⁶²

Vetica and coworkers**Prato and coworkers**

Scheme 16: selected examples of aminocatalysis using amine-enriched CDs as catalyst. Enantioselective aldol reaction through enamine intermediate (HOMO-raising) by Vetica and coworkers (above) and racemic 1,4-addition of nucleophiles (LUMO-lowering) by Prato's group (below).

In this chapter, the application of a novel class of Quantum Nano Dots (QND), functionalized with primary amino groups on the surface, to ACDC type catalysis will be discussed. Indeed, this class of carbon dots showed to be a promising alternative to molecular amines, being completely non-toxic and easy to handle, and, as reported by Prato's group⁶⁷ and Vetica and coworkers (Scheme 16),⁶⁸ they were efficiently employed in aminocatalysis.

Basing on these outcomes, our group proposed their first application in LUMO-lowering catalysis when used alongside

⁶⁸ M. Bortolami, D. Rocco, B. Simonis, M. Feroci, F. Vetica *Synth. Commun.* **2023**, 53, 1647–1663.

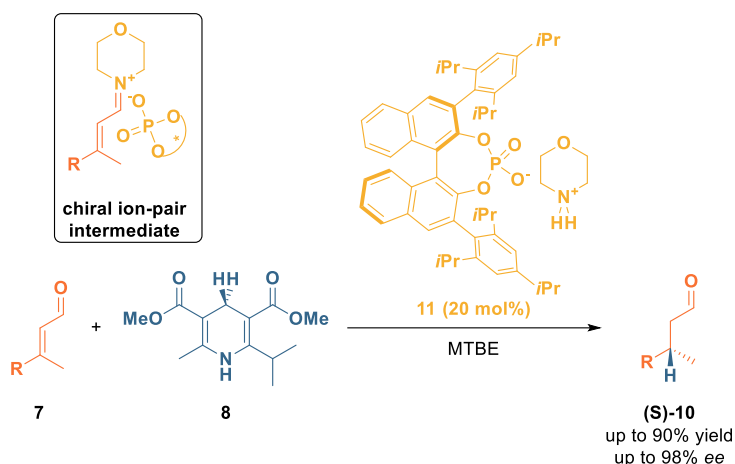
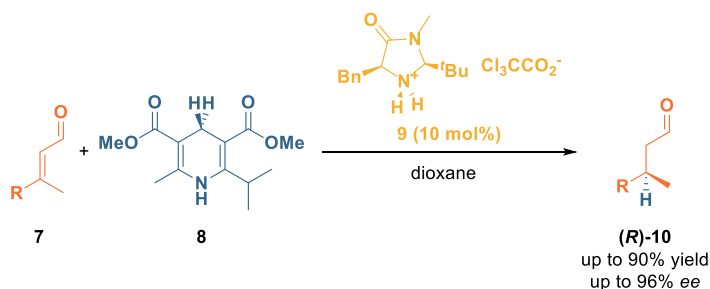
Chiral Phosphoric Acids (CPA) in the 1,4-enantioselective reduction of α,β -unsaturated aldehydes.

3.1.2 1,4-enantioselective reduction of aldehydes through ACDC

As already mentioned in Chapter 1, Asymmetric Counteranion Directed Catalysis (ACDC) emerged in the last decade as a powerful tool to unlock the asymmetric synthesis of a vast number of different reactions, in which the catalytic species is formed by an ionic couple in which the steric information is induced by the chiral counteranion.^{25,26,27,28} Even the Brønsted Acid Catalysis can be seen as a specific form of ACDC, considering that the ion pairs are often stabilized by hydrogen bonds and that the Coulombic attraction within the ion pairs in ACDC can be accompanied by further stabilizing interactions such as hydrogen binding itself, as long as the ionic character of the intermediate does not become negligible.²⁹

Among all the existing variants of ACDC, the most known is the enantioselective 1,4-reduction of α,β -unsaturated aldehydes, developed by List and coworkers and that makes use of dihydropyridines as reducing agents (Scheme 17).^{24,30}

Initially, they investigated the reactivity recurring to a catalytic salt from MacMillan's imidazolidinone, therefore inserting the chiral information through classical iminium ion intermediate. However, even though it required a higher catalyst loading, it was observed that an even higher ee could be obtained using an achiral amine (morpholine) in presence of the chiral phosphoric acid (S)-TRIP, therefore forming an ionic couple in which the chiral information is transmitted by the chiral counteranion.

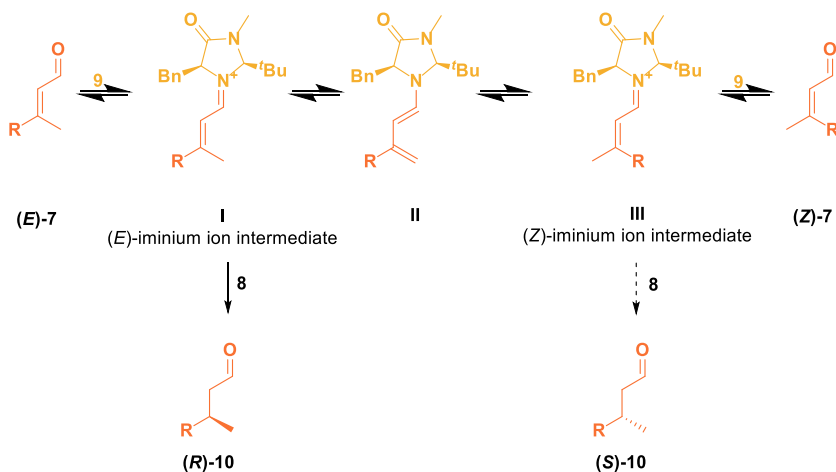


Scheme 17: the first example of ACDC 1,4-reduction of unsaturated aldehydes (below) reported by List and coworkers compared to the same reaction carried out through classical chiral iminium ion intermediate (above).

Indeed, after the iminium ion from the aldehyde **7** and morpholine is formed, it interacts with chiral phosphate forming a chiral-ion pair intermediate. Therefore, the interaction between this chiral intermediate and the dihydropyridine **8** can occur on the non-shielded face only, affording an enantioenriched product (**10**).

It can be useful to highlight that the chiral iminium ion intermediate (mainly *E*) is in equilibrium with its *Z* conformer through dienamine formation, a fact that can lead to a lower enantiomeric excess. However, it has been demonstrated that, assuming the hydride transfer as the rate-determining step, the nucleophilic attack of the hydride on the *E*-isomer is faster compared to that one on the *Z*-

isomer, therefore affording the desired product **10** with high ee (Scheme 18).



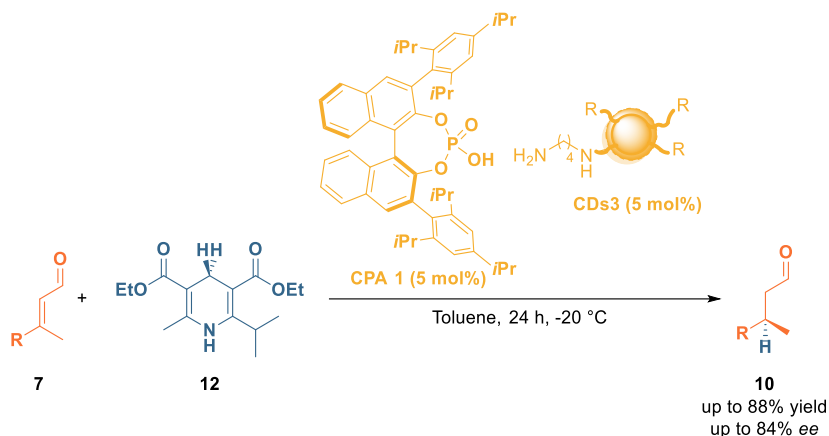
Scheme 18: equilibrium between the two iminiums ion I and III isomers through enamine intermediate II.

These approach towards the enantioselective 1,4-reduction of α,β -unsaturated aldehydes proved to be solid and efficient, being able to catalyse the reduction of both aromatic and aliphatic aldehydes such as citral.

On the bases of these outcomes, it has been decided to use this reaction to investigate the applicability of achiral primary amines-enriched CDs in organocatalysis.

3.2 Aim of the project

In the last decade, the development of nanostructured organocatalysts is emerging as a prominent field in materials science. To this purpose, nitrogen doped carbon dots (CDs) have been effectively employed in enantioselective enamine organocatalysis.⁶⁹ On the other hand, enantioselective iminium ion nano-organocatalysis (LUMO lowering) was much less explored, given the complexity of the composition of the nanomaterial and up to now non-enantioselective reactions only have been performed.



Scheme 19: This work.

With this work, the possibility of performing an asymmetric reaction through iminium ion intermediate using Carbon Dots via asymmetric counteranion-directed catalysis (ACDC) has been proven (Scheme 19).

Indeed, using the chiral phosphoric acid (S)-TRIP **12** and CDs whose surface has been functionalized with non-chiral, primary amine moieties, it has been possible to carry out a 1,4-reduction of α,β -unsaturated aldehydes employing dihydropyridine **13** as hydride source. The catalytic system proved to be extremely reactive, working with a catalyst loading of 5 mol% and affording up to 88% yield and up to 84% ee.

3.3 Development and Outcomes

3.3.1 Amino-enriched Carbon Dots (CDs) design and synthesis

The amine-functionalised Carbon Dots (namely **CDs** in this manuscript) have been prepared from L-Arginine and different primary alkyl amines as starting materials, following a reported

procedure.⁶⁹ 1,4-diamino butane and 1,2-diamino ethane were used for the synthesis of **CDs3** and **CDs4** respectively, while the chiral diamines (*R,R*)-1,2-cyclohexanediamine and (*S,S*)-1,2-cyclohexanediamine were employed for the preparation of the chiral nanoparticles **CDs1** and **CDs2**. The first step of the preparation has been the hydrothermal treatment of the molecular precursors at 240 °C for 180 s, followed by the filtration to remove large carbon particles and insoluble organic compounds. Then, dialysis vs water allowed the removal of soluble molecular species, and finally, through freeze-drying, the purified **CDs** have been afforded as yellowish solid materials (further details reported in SI).⁷⁰

In order to apply this **CDs** in aminocatalysis, the density of amine moieties on the surface had to be determined, therefore a Kaiser Test (KT) has been carried out to perform this quantification: in this analysis, Ruhemann's purple dye, which can be identified and measured by UV-vis spectroscopy, is generated when ninhydrin reacts with aliphatic primary amines on the surface of nanomaterials.⁷¹ From this test, all the **CDs** emerged positive on the surface to the presence of primary amines, as demonstrated by the characteristic purple colour.

⁶⁹ a) L. Đorđević, F. Arcudi, A. D'Urso, M. Cacioppo, N. Micali, T. Bürgi, R. Purrello, M. Prato, *Nat. Commun.* **2018**, 9, 3442; b) L. Đorđević, F. Arcudi, M. Prato, *Nat. Protoc.* **2019**, 14, 2931–2953.

⁷⁰ G. Gentile, M. Mamone, C. Rosso, F. Amato, C. Lanfrit, G. Filippini, M. Prato, *ChemSusChem* **2023**, 16, e202202399.

⁷¹ a) E. Kaiser, R. L. Colescott, C. D. Bossinger, P. I. Cook, *Anal. Biochem.* **1970**, 34, 595–598; b) M. Garrido, L. Gualandi, S. Di Noja, G. Filippini, S. Bosi, M. Prato, *Chem. Commun.* **2020**, 56, 12698–12716.

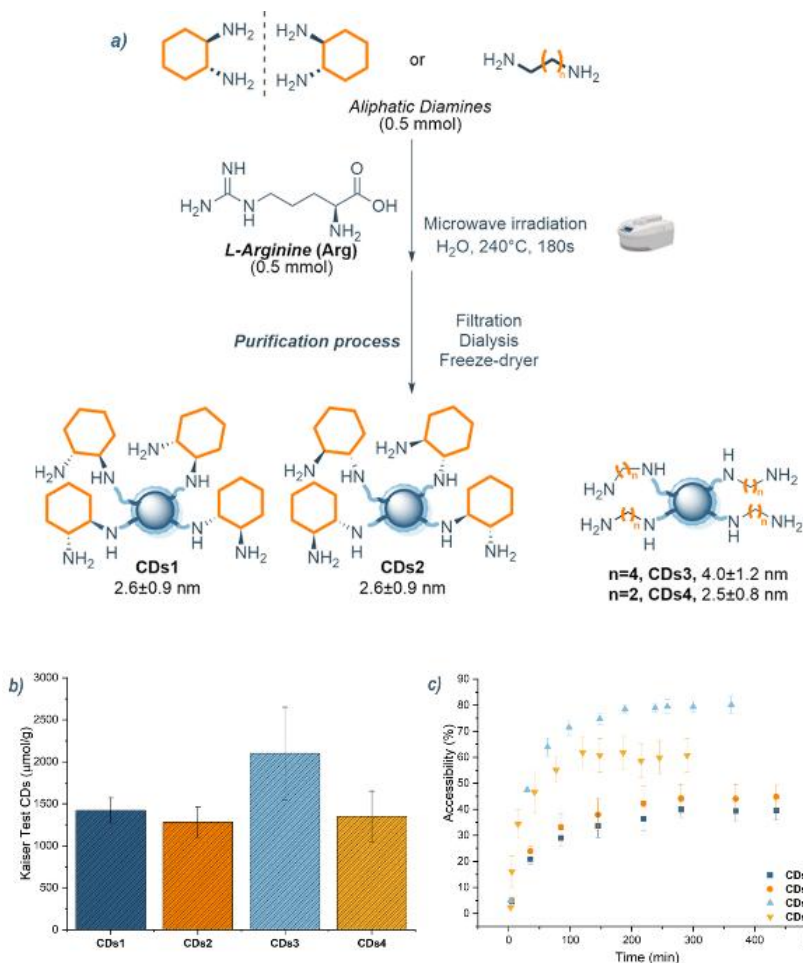


Figure 12: (a) Synthetic scheme for the production of **CDs1-4** starting from L-Arginine (Arg) and different alkyl diamines; (b) Kaiser Test (KT) of **CDs1-4** carried out at 120 °C; (c) Accessibility curves for **CDs1-4** at 25 °C - 100% of accessibility is set as KT value at 120 °C.

Both **CDs1** and **CDs2** showed a comparable number of amines at $1420 \pm 150 \mu\text{mol/g}$ and $1280 \pm 180 \mu\text{mol/g}$, respectively. Interestingly, **CDs3** had a higher number of amines at $2100 \pm 550 \mu\text{mol/g}$, whereas **CDs4** bear approximately $1350 \pm 300 \mu\text{mol/g}$ of primary amino groups (Figure 12). The fact the test is carried out at high temperatures (120 °C) ensured the complete reaction of all the amine moieties with the ninhydrin. Additionally, through a time-dependant Kaiser Test at room temperature, it has been

possible to determine the reactivity of primary aliphatic amines allowing the time-dependent accessibility to be reported as a percentage of the value measured at 120 °C. In accordance with the data previously obtained, the highest accessibility value was found for **CDs3** (80±5%), while lower values were obtained for **CDs4** (61±6%), **CDs1** (40±4%) and **CDs2** (45±5%).

3.3.2 Reaction design and optimization

In order to test the applicability of the **CDs** as aminocatalysts in ACDC, two selected reactions from the literature were investigated: the 1,4-reduction of α,β -unsaturated aldehydes with dihydropyridines and the epoxidation of α,β -unsaturated carbonyl compounds, both reported by List and coworkers.⁷²

The preliminary screenings for the 1,4-reduction of aldehyde **7a**, carried out using dihydropyridine **13** (the simplest Hantzsch' ester, see Figure 14), (S)-TRIP **CPA 1** 20 mol% and **CDs3** 20 mol% in toluene ($c = 0.1$ M), afforded interesting results after 24 h, with an almost complete conversions but low yields (47%) and ee (56%), however leaving space for further improvements. The first part of the optimisation regarded then the **CDs** screening (Entries 1-4, **Table 8**), and **CDs3** proved to be the best choice, as supported by the higher accessibility of their surface amino groups. Interestingly, when using the opposite enantiomer of the nanocatalyst (**CDs1** and **CDs2**) no effect on the stereoinduction of the reaction was observed (entries 1-2), in contrast with previous report of homogeneous ACDC employing chiral primary amines where a match/mismatch effect was reported and could affect the ee sensitively.⁷³

⁷² M. Mahlau, B. List *Isr. J. Chem.* **2012**, 52, 630–638.

⁷³ N. J. A. Martin, B. List *J. Am. Chem. Soc.* **2006**, 128, 13368–13369.

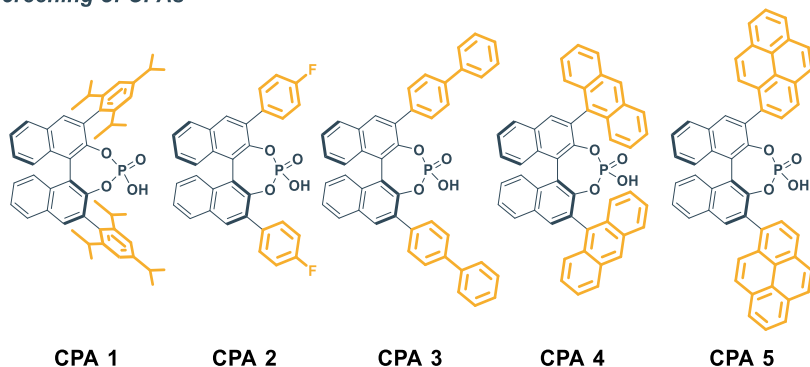
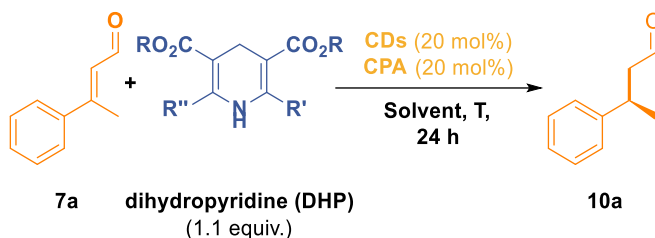
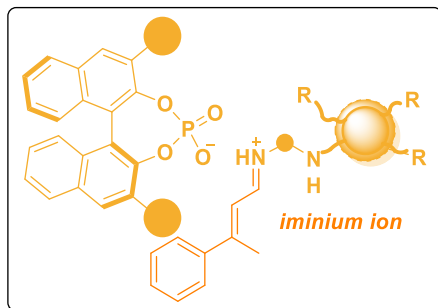
Screening of CPAs

Figure 13: Screening of CPAs.

Once found the most efficient **CDs** type, the chiral phosphoric acids were screened (see Figure 13). The most efficient was confirmed to be the (S)-TRIP **CPA 1**, while the others, even though with almost total conversion, afforded mediocre yields and ee. Among different solvents tested, toluene proved to be the best option (entries 9-12, see SI for additional experiments). Finally, a screening of different Hantzsch esters was performed (Figure 14). An increased steric hindrance at C-3 and C-5 (**14**) led to a reduction of the reaction rate with significant loss of stereinduction (entry 15).

Table 8: Under the starting conditions, the reactions were performed with **1a** (14.6 mg, 0.1 mmol, 1 equiv.), **CDs3** (9.6 mg, 0.02 mmol, 0.2 equiv.), **CPA1** (15 mg, 0.02 mmol, 0.2 equiv.), **13** (27.9 mg, 0.11 mmol, 1.1 equiv.) in toluene (1 mL, 0.1 M) for 24 hours at RT. [a] Reaction performed on a 0.25 mmol scale. [b] Isolated yield. [c] 5 mol% of benzylamine used instead of **CDs3**. [d] 5 mol% of butylamine used instead of **CDs3**. [e] 20 mol% of piperidine used instead of **CDs3**. [f] substrate **7h** used instead of the model substrate **7a**.



Entry	Solvent	CDs	CPA	DHP	T (°C)	NMR Conv. (%)	Y _{NMR} (%)	ee (%)
1	Toluene	CDs1	CPA1	13	rt	98	12	33
2	Toluene	CDs2	CPA1	13	rt	94	33	35
3	Toluene	CDs3	CPA1	13	rt	99	47	56
4	Toluene	CDs4	CPA1	13	rt	99	25	55
5	Toluene	CDs3	CPA2	13	rt	83	16	9
6	Toluene	CDs3	CPA3	13	rt	90	30	12
7	Toluene	CDs3	CPA4	13	rt	95	28	8
8	Toluene	CDs3	CPA5	13	rt	92	25	rac.
9	Chloroform	CDs3	CPA1	13	rt	99	41	54
10	Dioxane	CDs3	CPA1	13	rt	92	47	30
11	EtOAc	CDs3	CPA1	13	rt	99	27	37
12	THF	CDs3	CPA1	13	rt	93	21	48
13	Toluene	CDs3	CPA1	8	rt	99	66	70
14	Toluene	CDs3	CPA1	12	rt	99	59	78
15	Toluene	CDs3	CPA1	14	rt	82	48	8

16	Toluene	CDs3	CPA1	15	rt	82	<5	-
17	Toluene	CDs3	CPA1	18	rt			-50
18	Toluene	CDs3	CPA1	-	rt	74	<5	-
19	Toluene	CDs3	-	13	rt	43	<5	-
20	Toluene	-	CPA1	13	rt	90	62	rac.
21	Toluene	-	-	13	rt	<5	<5	-
22	Toluene	CDs3	CPA1	12	10	99	70	78
23	Toluene	CDs3	CPA1	12	-20	99	74	83
24^a	Toluene	CDs3 (5 mol%)	CPA1 (5 mol%)	12	-20	92	86 ^b	82
25^c	Toluene	-	CPA1	12	-20	84	41	81
26^d	Toluene	-	CPA1	12	-20	86	40	81
27	Toluene	CDs3	CPA1	16	rt	>95	27	21
28^e	Toluene	-	CPA1	16	rt	69	10	21
29^e	Toluene	-	CPA1	12	rt	69	10	82
30	Toluene	CDs3	CPA1	18	rt	>95	48	-55
31^f	Toluene	CDs3	CPA1	18	rt	94	56	-58
32	Toluene	CDs3	CPA1	17	rt	>95	28	15
33^e	Toluene	-	CPA1	18	rt	61	19	37
34^{e,f}	Toluene	-	CPA1	18	rt	70	18	16

On the other hand, moving two encumbered isopropyl substituents at C-2 and C-6 (**15**) led to complete loss of reactivity (entry 16). A striking balance was obtained with non-symmetric dihydropyridine **12** that showed a great positive effect on the enantioinduction (entry 14). Further variations on the ester moiety (dihydropyridine **8**) did not lead to any improvements in the ee (entry 13), while the presence of two ethyl moieties at C-2 and C-6 respectively (dihydropyridine **18**, entry 17) led to an inversion in the enantioselectivity of the reaction. Lowering the reaction temperature allowed to better control the reactivity, resulting in increased yield and ee (Entry 22 and 23). Moreover, lowering the catalyst loading did not affect negatively the reactivity but increased the yield of the reaction (Entry 24).

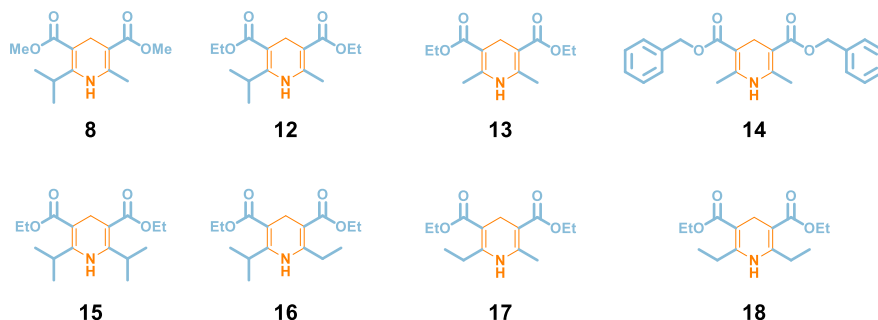
Screening of Hantzsch esters

Figure 14: Screening of dihydropyridines.

A common feature observed is the discrepancy between the conversion and the yield of the reaction, a feature that can be explained by aza-Michael additions of free amino groups on the surface of **CDs** to the formed iminium ion,⁷⁴ resulting in a loss of product. Even though analysing the recovered **CDs** did not provide any useful information, this hypothesis has been supported by some control experiments. Indeed, when the reaction was performed in absence of dihydropyridine (Entry 18), a conversion of 74% with less than 5% yield have been observed, supporting the outcome obtained in Entry 16, where compound **7a** has been consumed without reacting with dihydropyridine **15**. A similar behavior has been observed when the reaction was performed in absence of the **CPA** (Entry 19). Moreover, as shown in Entry 20, the formation of the iminium ion intermediate is the key to transmitting the chiral information: indeed, performing the reaction in absence of **CDs**, almost complete conversion and a high yield were obtained, but a racemic product has been isolated, demonstrating that in absence of **CDs** the reaction proceeds via Brønsted-acid catalysis. Furthermore, **7a** was fully recovered in the absence of

⁷⁴ D. Enders, C. Wang, J. X. Liebich *Chem. Eur. J.* **2009**, *15*, 11058–11076.

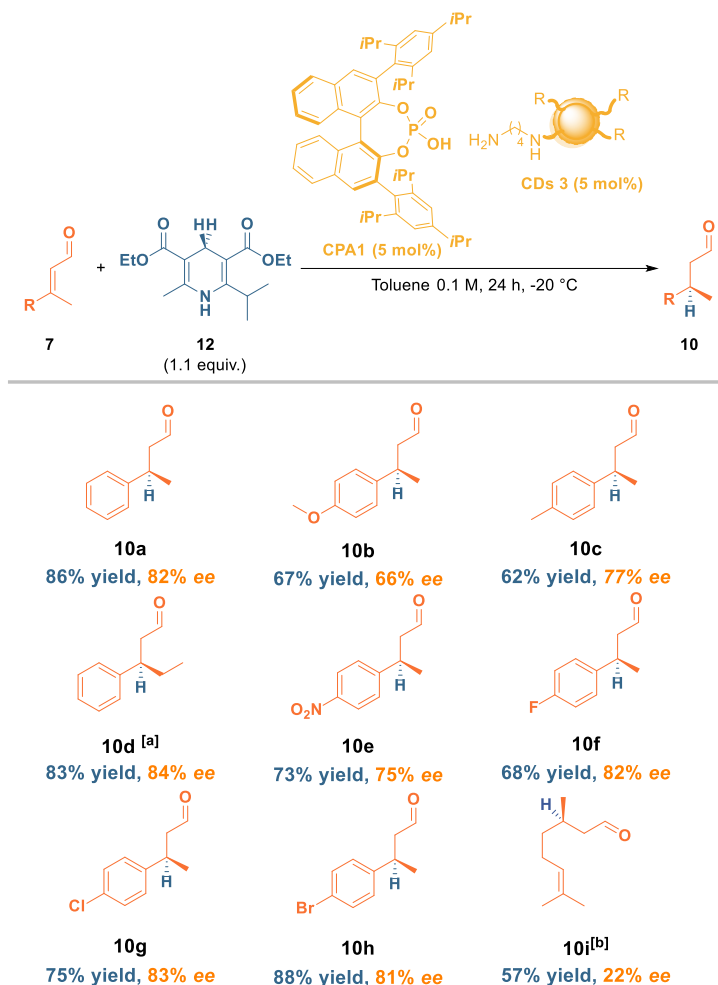
both **CDs** and **CPA** (entry 21), suggesting that the retention of the reagent on the **CDs** could be the major side reaction.

Finally, to prove the reliability of the system, the same reaction was tested in presence of primary molecular amines that could emulate the moieties in the **CDs** surface, such as benzylamine and butylamine (Entry 25 and 26): even though the *ee* gave similar values, the yield dropped drastically, demonstrating the efficiency of the use of the **CDs** employed.

Additionally, in parallel with the substrate scope described ahead, an investigation on the role of dihydropyridines bearing different substituents in position 2 and 6 and it has been carried out (highlighted in yellow in the optimisation table): indeed, it has been found that an inversion of the stereocenter occurs both on **10h** and in the model substrate **10a** when dihydropyridine **18** has been employed (Entry 30 and 31), while only reduced yields and *ees* have been observed in presence of dihydropyridines **16** and **17** (Entry 27 and 32 respectively). Even more surprising was the fact that this inversion in the enantioselectivity has been observed when the carbon dots **CDs3** have been employed for the preparation of the catalytic ammonium phosphate while, using a molecular amine such as piperidine, no inversion has been found (Entry 33 and 34).

With the optimized conditions in hand (Entry 24), the generalities of the reaction were investigated (Scheme 20). The reaction proved to perform well on aromatic substrates bearing electron-donor substituents (**10b-10c**), and electron-withdrawing groups as well (**10e-10h**). A good result was also obtained when the steric hindrance on the reacting carbon was increased (**10d**). Moreover, an interesting behavior arose when the pure *Z* isomer of **7a** was used in the reaction: interestingly, but not unexpectedly, the *Z* isomer of **7a** did not react to provide **10a**, suggesting that the *Z* isomer is less reactive, and its isomerization does not occur in our

conditions, in contrast with previous reports that show isomerization at higher temperatures.⁷⁵



Scheme 20: Scope of the reaction. Reactions performed with **7** (0.25 mmol, 1 equiv.), CD3 3 (0.0125 mmol, 0.05 equiv.), CPA1 (0.0125 mmol, 0.05 equiv.), **12** (0.275 mmol, 1.1 equiv.) in toluene (2.5 mL, 0.1 M) for 24 hours at -20 °C. Yields of isolated compounds are reported. Enantiomeric excess (ee) determined by chiral HPLC analysis. [a] **7d** was produced as an inseparable *E/Z* mixture (4:1) and used as such; isolated yield corrected with respect to *E* content. [b] **7i** used as 1:1 *E/Z* mixture; reaction carried out on a 0.5 mmol scale.

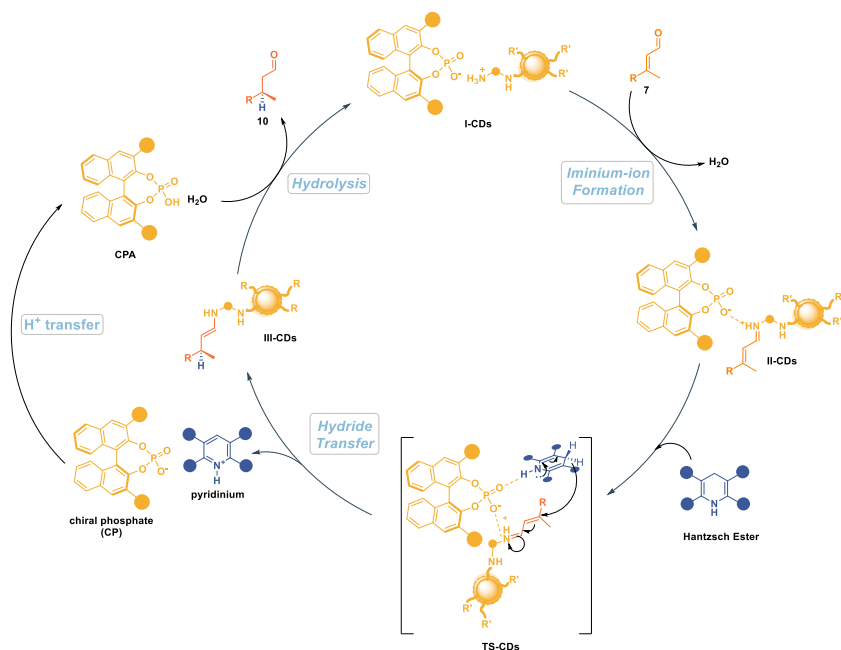
However, the system was not efficient in reducing aliphatic substrates, as demonstrated when citral (1:1 *E/Z* mixture) **7i** was

⁷⁵ S. G. Ouellet, J. B. Tuttle, D. W. C. *J. Am. Chem. Soc.* **2005**, 127, 32–33.

used: even though the yield was in line with the ones obtained with aromatic substrates, the ee obtained was dramatically lower.

Basing on the outcomes obtained from the reaction optimisation, control experiments and the substrate scope, a proposed mechanism is reported in Scheme 21.

Once the catalytic specie **I-CDs** is formed (from the amine-doped **CDs** and the corresponding **CPA**), it reacts with the α,β -unsaturated aldehyde **7**, forming the iminium ion intermediate that forms a ionic couple (**II-CDs**) with the chiral phosphate.



Scheme 21: Proposed reaction mechanism.

At this point, the phosphate is able to direct the approach of dihydropyridine through hydrogen bonding, leading to the transition state (**TS-CDs**) in which the specific coordination of both the iminium ion and the dihydropyridine to the phosphate allows the hydride transfer enantioselectively and releasing the chiral neutral enamine intermediate **III-CDs**.

The enamine intermediate is then hydrolysed, and the **CDs** is able to be form again the catalytic specie **I-CDs** with the regenerated chiral phosphoric acid **CPA**.

To confirm the formation of the iminium ion intermediate on **CDs** and the reliability of this approach, ^{19}F -nuclear magnetic resonance (NMR) spectroscopy was exploited. Indeed, using the fluorinated aldehyde **7f** as a probe enabled to display the ^{19}F -NMR signals that can be ascribed to in situ formation of the covalent fluorinated intermediates (Figure 15).⁷⁶

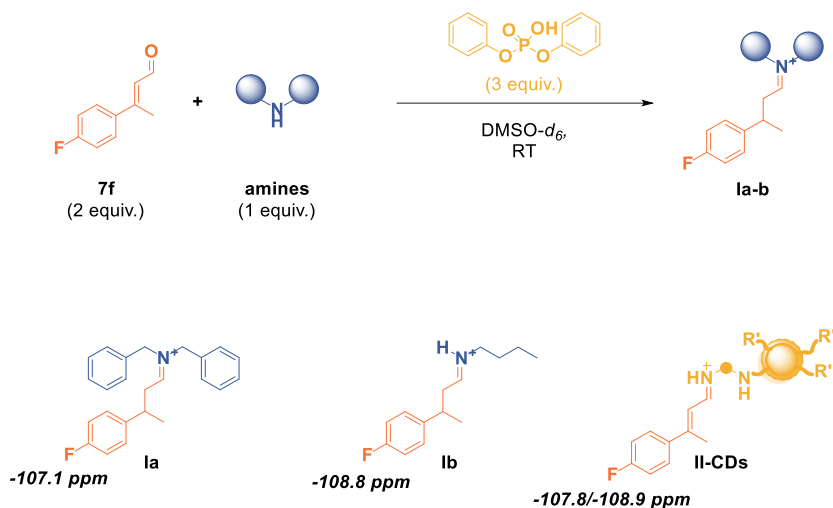


Figure 15: Reaction scheme for the formation of iminium ion intermediates with model amines and compound **7f**. DMSO- d_6 was chosen given the high solubility of CDs in this solvent.

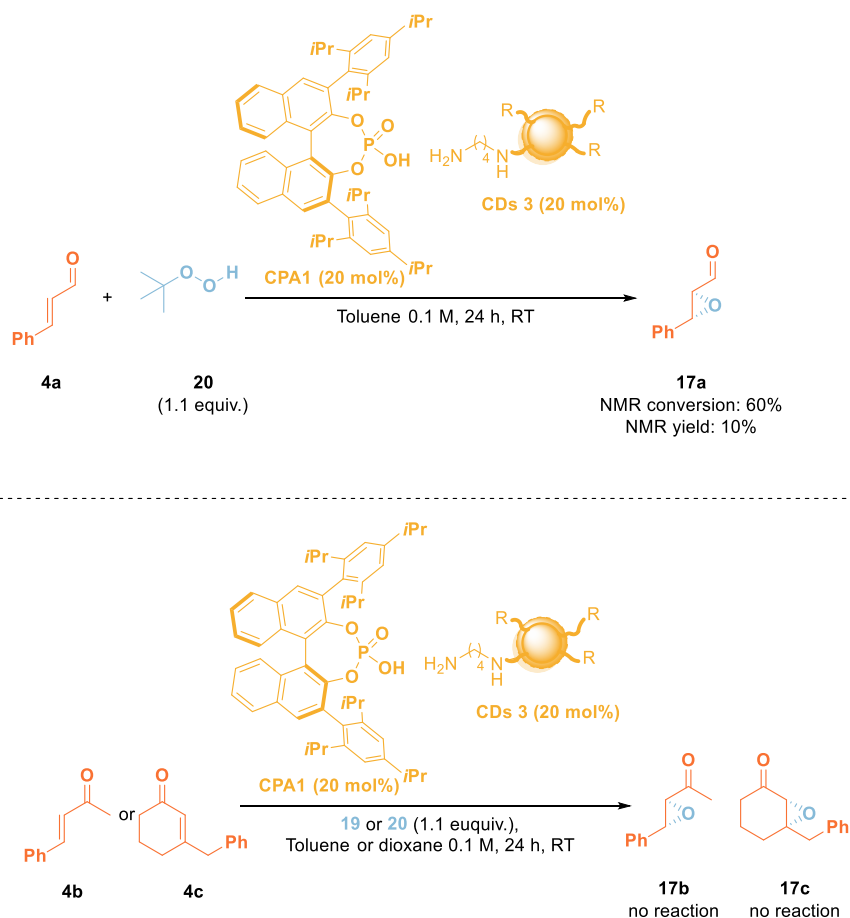
The chemical shifts of the iminium ions were identified by comparison of the iminium ions formed by reaction with dibenzylamine and butylamine, respectively **la** and **lb**. Remarkably, the formation of iminium ions on the **CDs3** (**I-CDs3**) showed broad signals between -108.0 and -107.7 ppm, similarly to **la** and **lb**, thus

⁷⁶A. Dandia, P. Saini, M. Sethi, K. Kumar, S. Saini, S. Meena, S. Meena, V. Parewa, *Cataly. Rev.* **2023**, 65, 874–928.

confirming the formation of various iminium ions on the surface of CDs3.

3.3.3 Reactions under discovery

As mentioned above, other reactions alongside the 1,4-reduction of α,β -unsaturated aldehydes have been investigated. The first examples regarded the epoxidation of α,β -unsaturated carbonyl compounds.



Scheme 22: Preliminary epoxidation reactions tested.

Using the same catalytic system used for the previous optimization (**CDs3** and **CPA1** 20 mol% in toluene 0.1 M), the epoxidation of cinnamaldehyde **4a** and cinnamyl methyl ketone (**4b**) was

investigated (Scheme 22). Basing on the reports of List and coworkers,³¹ the oxidation reagents chosen to be investigated were dihydrogen peroxide (35% in water) **19** and *tert*-butyl peroxide (5.5 M in methanol) **20**. Unfortunately, the epoxidation of ketone **4b** did not lead to any reactivity. Even after several days or solvent change or heating, no reaction was observed. A similar outcome has been observed on the cyclic ketone **4c**.

On the other hand, after several failed efforts, a very small reactivity was observed on cinnamaldehyde **4a**: after 96 h at room temperature, using toluene as solvent and *tert*-butyl peroxide (**20**) 5.5 M in methanol as oxidant, a small 10% NMR yield, alongside a far higher 60% NMR conversion, was observed. This outcome opens new possibility for the application of **CDs** in ACDC-type and will be further investigated.

3.4 Conclusions

In conclusion, the first example of asymmetric iminium ion-mediated 1,4-reduction of α,β -unsaturated aldehydes using amine-doped Carbon Dots via ACDC has been developed. Several **CPAs**, **CDs** and dihydropyridines have been screened in order to have a reliable system that afforded good yields and ee's. **CDs3** outperformed the other **CDs** tested and their different reactivity is in accordance with the different accessibility of amino groups on their surface. The catalytic performance of **CDs3** was also compared with those of simple molecular amines, namely benzylamine and butylamine, and outperformed them, as demonstrated by the control experiments and the ¹⁹F NMR spectrometry. Additional value can also be found in the fact **CDs** can show an unique reactivity in presence of specific dihydropyridines, leading to an inversion of the stereoselectivity of the reaction that does not occur when molecular amines are employed, a singular behaviour that is currently under investigation

in our group. The only flaw of this approach lies in its scarce reactivity towards aldehydes bearing aliphatic substituents in β -positions, as demonstrated by the low ee obtained when citral **7i** was used.

Moreover, even though under study yet, the system showed some reactivity in the epoxidation of α,β -unsaturated aldehydes, opening new horizons that can widen the application of this class of nano-materials in asymmetric organocatalysis.

3.5 Experimental Section

Instrumentation

Nuclear magnetic resonance analyses (^1H -, ^{19}F - and ^{13}C -NMR spectra) were acquired using a Bruker Advance III 400 MHz spectrophotometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^1H - and ^{13}C -NMR (^1H -NMR: 7.26 ppm for CDCl_3 ; ^{13}C -NMR: 77.16 ppm for CDCl_3). Both ^{13}C -NMR and ^{19}F -NMR spectra were acquired with ^1H broadband decoupled mode. Coupling constants are given in Hz. ^1H -NMR yields were measured by analysing the reaction mixture using Triphenylmethane as internal standard. Chromatographic purifications of compounds **7a-h**, **10a-h**, **21a-h**, **22a-h**, **23a-h** and the dihydropyridines were performed using automated Biotage® Isolera LS Systems.

Materials and methods

Chiral phosphoric acids (CPAs) were purchased from BLDPharm, compounds **21a-i** were purchased from Merck and used as received unless otherwise stated. Silica Gel 60A (35-70 μm), HPLC solvents and analytical grade solvents were purchased from Merck. Compounds **7a-h**, **10a-h**, **21a-h**, **22a-h**, **23a-h** and the dihydropyridines were prepared as shown below. The Carbon Dots loading has been evaluated by KT analysis at 120 $^\circ\text{C}$.

Determination of enantiomeric purity

Chiral HPLC analyses were acquired using an Agilent 1220 Infinity II liquid chromatographer equipped with Phenomenex columns (100 × 4.6 mm): Lux 3 µm i-Cellulose 1, Lux 3 µm i-Cellulose 2, Lux 3 µm i-Cellulose 3, and Lux 3µm-Amylose 2. HPLC analyses of **10a-h** were performed on the corresponding alcohols obtained by reduction of the aldehydes using NaBH₄ in methanol. HPLC analysis of **10i** was performed on the compound obtained via reductive amination with benzylamine followed by tosylation of the secondary amine (N-benzyl-N-(3,7-dimethyloct-6-en-1-yl)-4-methylbenzenesulfonamide). HPLC traces were compared to racemic samples prepared using diphenyl phosphate (CAS Number: 838-85-7) and piperidine as catalysts, in toluene at 50 °C for 2 h. Optical rotations were measured on a ZUZI 412 Digital Polarimeter (tube length: 100 mm).

Determination of absolute configuration

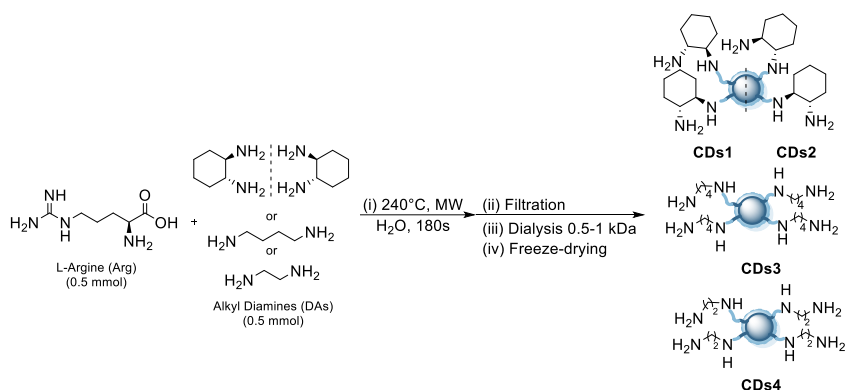
The absolute configurations of the optically active compounds **10a-b** were determined on the basis of the measured optical rotations that were compared with literature values. All other absolute configurations were assigned by analogy based on a uniform reaction mechanism and the uniform elution order observed in the HPLC chromatograms.

3.5.1 Preparation of Carbon Dots and Characterisation of Superficial Amines

CDs1-4 Synthesis

Arg (87.0 mg, 0.5 mmol, 1 equiv.), Milli-Q water (100.0 mL), along with one of the alkyl diamines (0.5 mmol, 1 equiv.), were introduced in a sealable microwave reaction vessel and heated in a microwave reactor (200 W) at 240 °C for 180 seconds. After this, the color of the reaction mixture turns from transparent to brown. The solution was then diluted with water and filtered through a 0.1 µm PTFE

microporous membrane. The crude obtained was dialyzed against Milli-Q water through a dialysis membrane (0.5-1 kDa Cut-Off) Float-A-Lyzer® for 48 hours. After the CDs were lyophilized from their aqueous solution, they were obtained as a yellow foamy solid. Due to high hygroscopicity, the samples were stored in a desiccator. Figure S1 summarizes the synthetic workflow.



Scheme 23: Synthesis of the CDs.

CDs1 - synthesized according to a reported procedure.⁷⁰



L-Arginine (87.0 mg, 0.5 mmol, 1 equiv.), (R,R)-1,2-cyclohexanediamine (57.0 mg, 1 equiv.) and Milli-Q water (100.0 mL) were irradiated into a microwave

reactor (200 W) at 240 °C for 180 seconds. The aqueous solution of **CDs1** was lyophilized resulting in a yellow solid (**CDs1**: 21.3 mg, 15% mass yield). Analytical data in accordance with literature report.

CDs2 - synthesized according to a reported procedure.⁷⁰



L-Arginine (87.0 mg, 0.5 mmol, 1 equiv.), (S,S)-1,2-cyclohexanediamine (57.0 mg, 1 equiv.) and Milli-Q water (100.0 mL) were irradiated into a microwave

reactor (200 W) at 240 °C for 180 seconds. The aqueous solution of **CDs2** was lyophilized resulting in a yellow solid (**CDs2**: 20.8 mg, 14% mass yield). Analytical data in accordance with literature report.

CDs3 - synthesized by following the literature.⁷¹



L-Arginine (87.0 mg, 0.5 mmol, 1 equiv.), 1,4-Diaminobutane (BDA) (50 mL, 0.5 mmol, 1 equiv.) and Milli-Q water (100.0 mL) were irradiated into a microwave reactor (200 W) at

240 °C for 180 seconds. The aqueous solution of **CDs3** was lyophilized resulting in a yellow solid (**CDs3**: 15.6 mg, 17% mass yield). Analytical data in accordance with literature report.

CDs4 - synthesized accordingly to the literature.⁷⁷



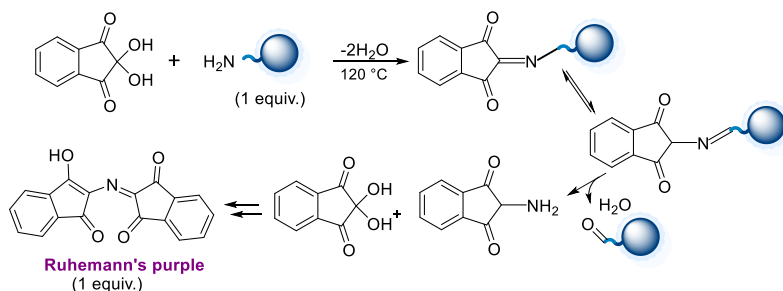
L-Arginine (87.0 mg, 0.5 mmol, 1 equiv.), 1,2-Diaminoethane (EDA) (32 mL, 0.5 mmol, 1 equiv.) and Milli-Q water (100.0 mL) were irradiated into a microwave reactor (200 W) at

240 °C for 180 seconds. The aqueous solution of **CDs4** was lyophilized resulting in a yellow solid (**CDs4**: 29.4 mg, 25% mass yield). Analytical data in accordance with literature report.

⁷⁷ L. Đorđević, F. Arcudi, M. Prato, *Nat. Protoc.* **2019**, *14*, 2931–2953.

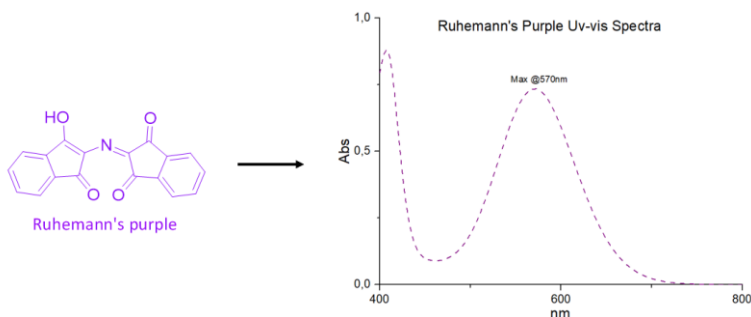
Kaiser test Procedure

Kaiser tests (KTs) were performed according to a modified protocol by employing a commercially available kit provided by Merck.⁷⁸ Generally, a test tube was filled with 1 mg of CDs. Next, 100 μ L of a KCN solution in pyridine/water (Sol B), 75 μ L of a ninhydrin solution in ethanol (Sol C), and 75 μ L of a phenolic solution in ethanol (Sol A) were added. A rapid formation of the purple pigment is observed. The tube was sealed and the so obtained mixture was heated at 120 $^{\circ}$ C for 10 minutes. The resulting solution was diluted with ethanol in water (60% v/v, 1:18 dilution) and its absorption spectrum was recorded. For reference, a blank solution was also executed. At least three separate analyses were carried out for every sample. Primary amines on the carbon dots surface were thus quantified from the absorbance value recorded at 570 nm, considering a molar absorption coefficient for the ninhydrin derivative of 15000 $\text{M}^{-1} \text{cm}^{-1}$ (Ruhemann's purple). Equation 11 was used to determine the KT value.



Scheme 24: Schematization of Kaiser test molecular mechanism.

⁷⁸ D. Iannazzo, A. Piperno, A. Ferlazzo, A. Pistone, C. Milone, M. Lanza, F. Cimino, A. Speciale, D. Trombetta, A. Saija, S. Galvagno, *Org. Biomol. Chem.* **2012**, 10, 1025-1031.



Scheme 25: Visible spectra of Ruhemann's purple dye.

$$KT (\mu\text{mol}/g) = \frac{[Abs@570nm \times dil \times 10^6]}{\varepsilon \times Weight (mg)}$$

Equation 11: Calculation of primary amines on **CDs1-4**.

Room temperature Kaiser test Procedure (Accessibility %)

In the accessibility experiments, the reaction mixture was kept at room temperature (25 °C) throughout the experiment. Therefore, to a known of **CDs** (about 1 mg), the Kaiser test solutions (Sol A, B and C) were added as previously described. An aliquot (20 mL) was collected, diluted, and analyzed. The experiment was repeated in triplicate for each **CDs** material. Equation 12 was used to determine the accessibility values.

$$Accessibility (\%) = \frac{KT (r. t)}{KT (120^\circ C)} \times dil \times 100$$

Equation 12: Determination of the accessibility of the examined amines into the corresponding ninhydrin derivative.

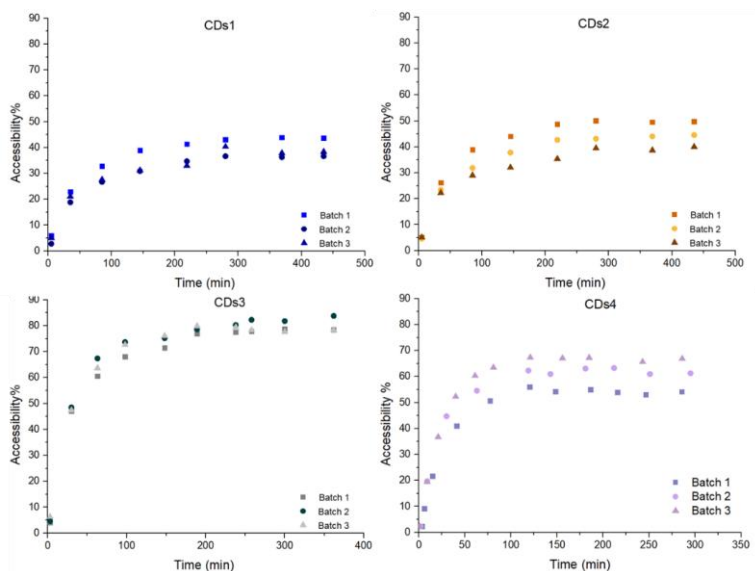


Figure 16: Time-dependent Kaiser test performed at 25°C for **CDs1-4**.

^1H and ^{19}F -NMR studies

First, the formation and stability of the iminium ions **la-b** derived from different representative amines (namely dibenzylamine and butylamine) have been studied with the fluorine aldehyde (**7f**) in DMSO- d_6 . Then, the formation of iminium ions **I-CDs3** on the surface of the **CDs3** using the aldehyde **7f** have been performed. Therefore, the amine was added in a vial containing aldehyde in DMSO- d_6 . After five minutes, the achiral phosphoric acid (3 equiv.) was added to the solution and immediately analysed through ^1H - and ^{19}F -NMR.

^{19}F -NMR (Figure 17) and ^1H -NMR (Figure 18) spectra have been used to characterize the so-formed iminium ion derivatives.

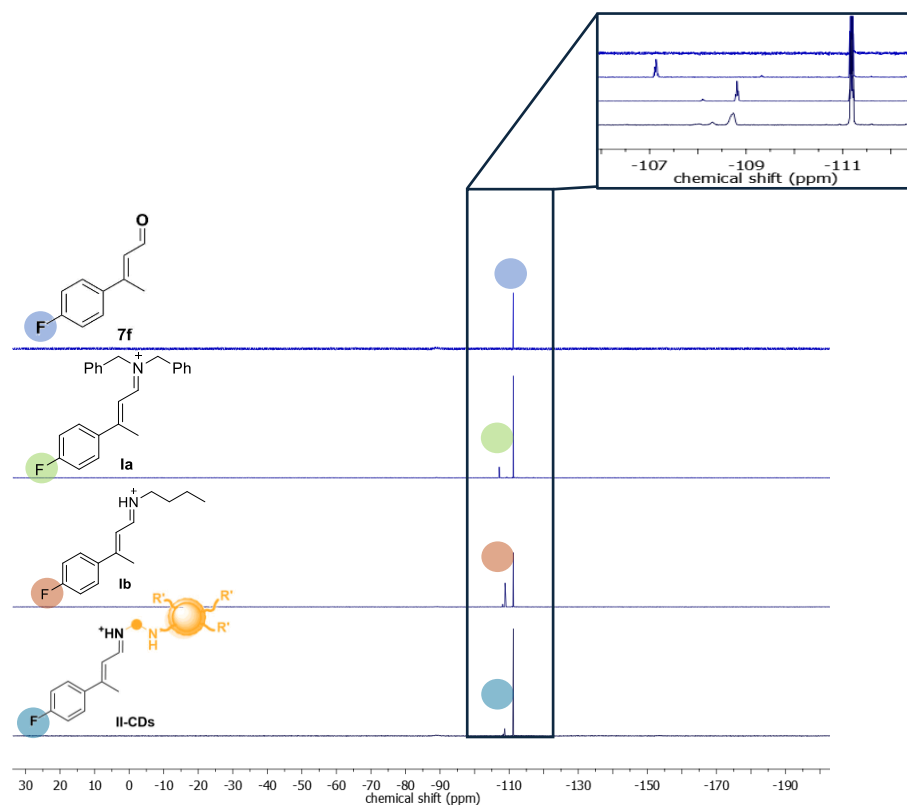


Figure 17: ^{19}F -NMR spectra of the in-situ formation of the iminium ions **Ia-b** and **I-CDs3** derived from aldehyde (**1f**) and respectively dibenzylamine (50 mol%), butylamine (50 mol%) or **CDs3** (50 mol%) in DMSO-d_6 . Comparison between ^{19}F -NMR spectra of **7f**, and iminium ions **Ia-b** and **II-CDs3**.

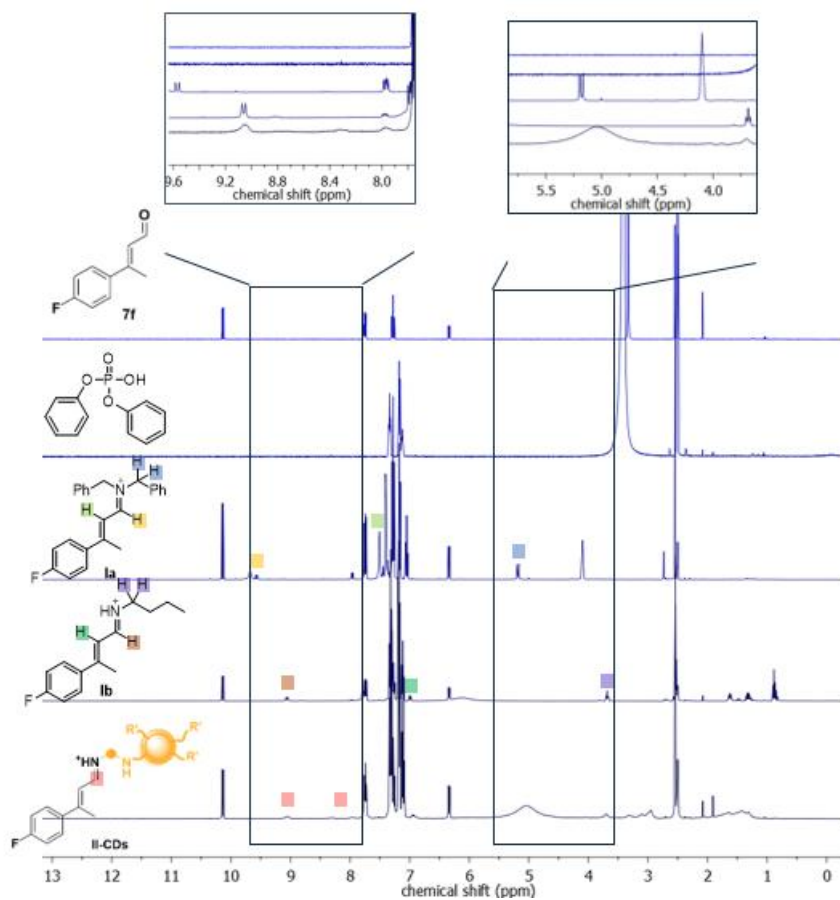
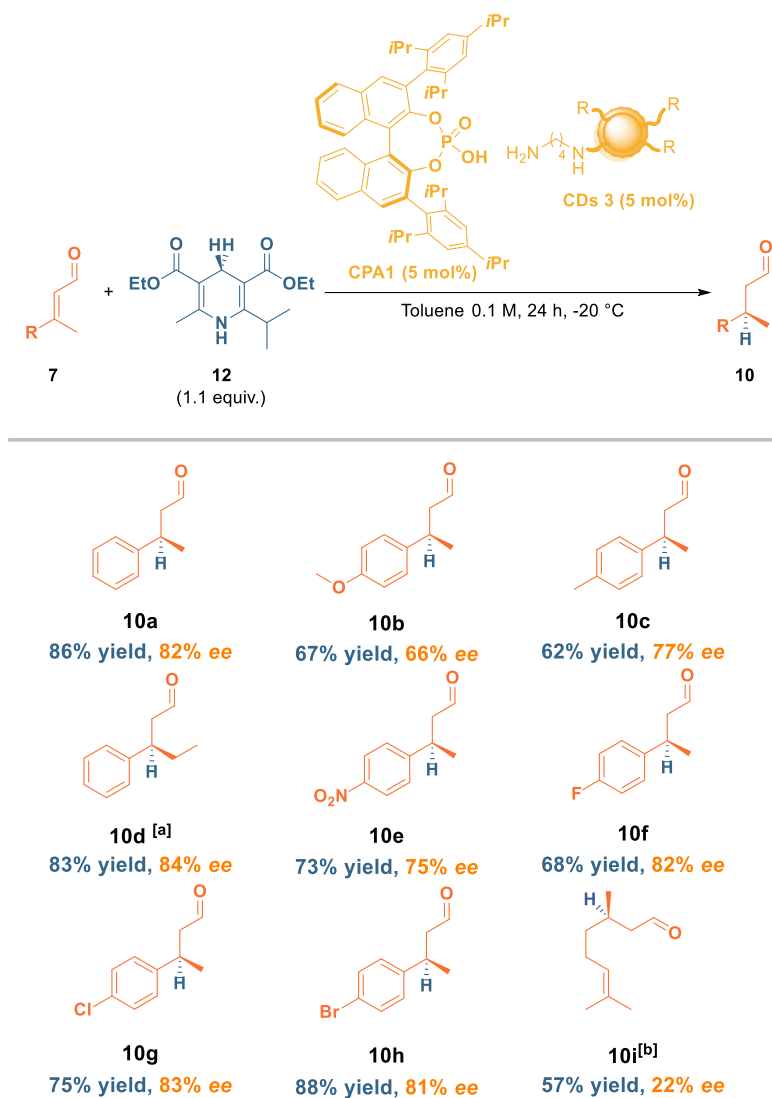


Figure 18: ^1H -NMR spectra of the in-situ formation of the iminium ions **la-b** and **II-CDs3** derived from aldehyde (**7f**) and respectively dibenzylamine (50 mol%), butylamine (50 mol%) or **CDs3** (50 mol%) in DMSO-d_6 . Comparison between ^1H -NMR spectra of **7f**, and iminium ions **la-b** and **II-CDs3**.

3.5.2 Experimental Procedures

General Procedure for the nano-organocatalysed reactions



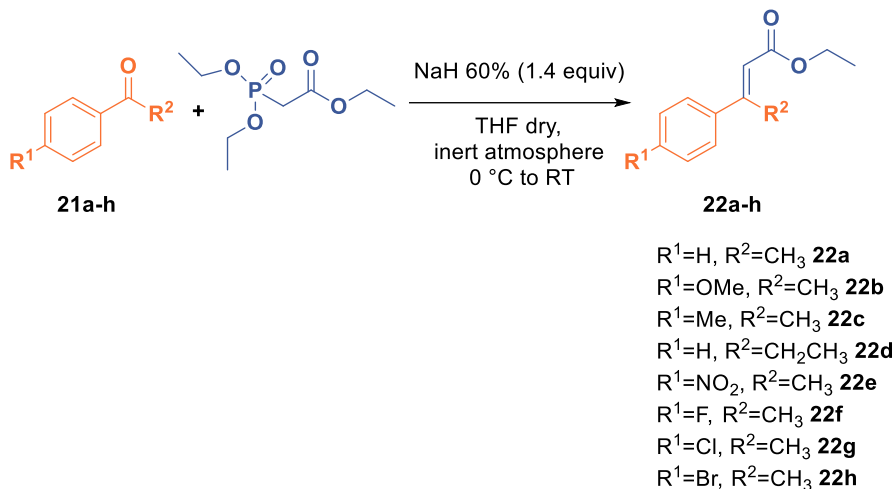
Scheme 26

CDs (loading based on KT analysis at 120°C) were suspended in the solvent. Then the **CPA** was added, and the suspension was left to stir for 10 min. Then, the aldehyde was added, and the mixture

was left to stir for 10 min. The Hantzsch's ester (dihydropyridine) was added afterwards, and the suspension was left to stir until the completion of reaction, monitored through TLC analysis. The reaction was quenched with a saturated solution of NH_4Cl , the phases were separated, and the aqueous phase was extracted with DCM (3x5 mL). The organic phases were combined, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification over silica gel afforded the pure product.

Synthesis of substrates

General Procedure for the Synthesis of ethyl (*E*)-3-phenylbut-2-enoate derivatives (**22a-h**)⁷⁹



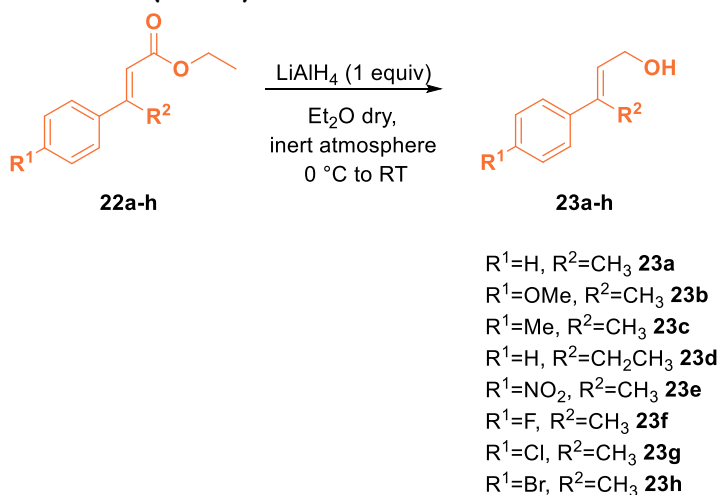
Scheme 27

NaH 60% dispersion in mineral oil (1.4 equiv.) was dissolved in anhydrous THF (0.2 M) at RT under inert atmosphere. The solution was then cooled down to 0°C and triethyl phosphonoacetate (1.5 equiv.) was added dropwise. The reaction was left to stir for 30 min at 0 °C, and subsequently compound **21a-h** (1 equiv.) was slowly

⁷⁹ Y. Kanazawa, Y. Tsuchiya, K. Kobayashi, T. Shiomi, J. Itoh, M. Kikuchi, Y. Yamamoto, H. Nishiyama, *Chem. Eur. J.* **2006**, 12, 63-71.

added. The reaction was then warmed up to room temperature and left to stir for 48-72 hours. After this time, the reaction was cooled down to 0 °C and quenched with a saturated solution of ammonium chloride, the phases were separated, and the water phase was extracted with ethyl acetate. The organic phases were then combined, washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification over silica gel eluting in Petroleum/Ethyl Acetate 98:2 afforded the pure product.

General Procedure for the synthesis of (*E*)-3-phenylbut-2-en-1-ol derivatives (23a-h**)⁸⁰**



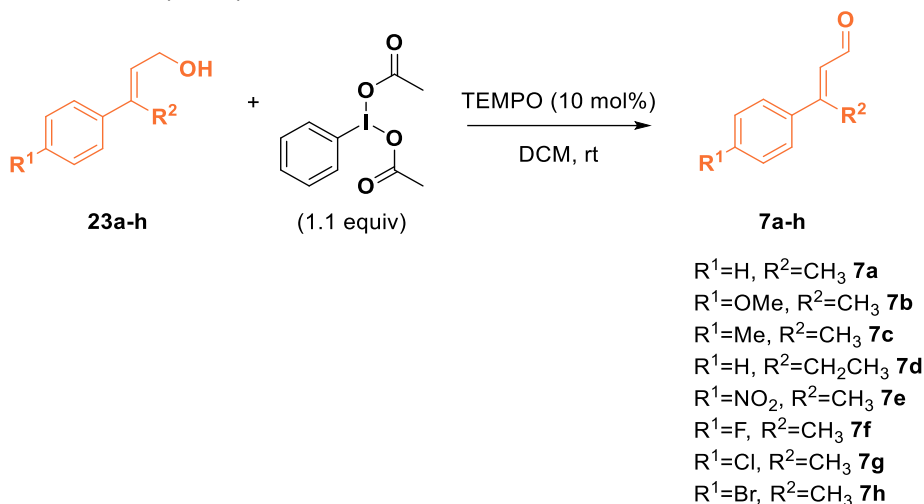
Scheme 28

Compound **22a-h** (1 equiv.) was dissolved in anhydrous diethyl ether (0.8 M) under inert atmosphere. The solution was cooled down at 0 °C and a 1M solution of LiAlH_4 in diethyl ether (1 equiv.) was added dropwise. The reaction was allowed to warm to RT and left to stir at this temperature until completion (monitored through TLC analysis, Petroleum Ether/Ethyl Acetate 9:1, roughly 10 minutes). The reaction mixture was quenched with a saturated solution of NaHCO_3 , the two phases were separated, and the

⁸⁰ X. Liu, J.-M. Pons, V. Monnier, L. Charles, A. Quintard, C. Bressy *Eur. J. Org. Chem.* **2022** e202101475.

aqueous phase was extracted with diethyl ether. The organic phases were combined, washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. The product was used with no further purifications. (Exception for **22d**: the reaction was conducted at $-20\text{ }^\circ\text{C}$ to avoid the reduction of the nitro group, the final product was purified over silica gel eluting in Petroleum Ether/Ethyl Acetate 9:1).

General Procedure for the synthesis of (*E*)-3-phenylbut-2-enal derivatives (7a-h**)⁸¹**



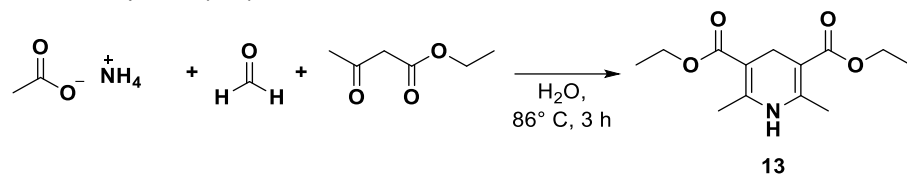
Scheme 29

Diacetoxyiodo(benzene) (1.1 equiv.) and compound **23a-h** (1 equiv.) were dissolved in DCM (0.5 M) and TEMPO (10 mol%) was then added. The reaction was stirred at RT until completion (monitored through TLC analysis, Petroleum Ether/Ethyl Acetate 8:2, roughly 2 hours). The mixture was diluted with dichloromethane and washed with a saturated solution of sodium thiosulfate. The two phases were separated and the aqueous phase was extracted with dichloromethane. The organic phases were then combined, washed with a saturated solution of sodium

⁸¹ R. De Mico, L. Margarita, A. Parlanti, G. Vescovi, A. Piancatelli, *J. Org. Chem.* **1997**, 62, 6974-6977.

bicarbonate and then with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Purification over silica gel eluting in Petroleum Ether/Ethyl Acetate 100:0 to 9:1 afforded the pure product.

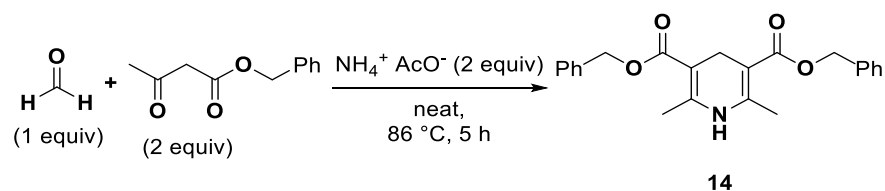
Synthesis of diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**13**)⁸²



Scheme 30

Formaldehyde solution in water 37% (2.44 g, 30.1 mmol), ethyl acetoacetate (15.2 mL, 120 mmol) and ammonium acetate (4.64 g, 60.2 mmol) were dissolved in water (55 mL). The reaction mixture was warmed at 86°C and vigorously stirred for 3 h. The mixture was filtered and washed with water and cold diethyl ether. The solid was dried under vacuum to afford the Hantzsch ester **13**. The product was used with no further purifications. Analytical data in accordance with literature reports.

Synthesis of dibenzyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**14**)⁸³



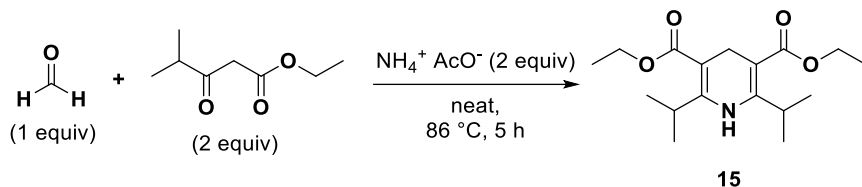
Scheme 31

Formaldehyde solution in water 37% (0.97 mL, 13 mmol), benzyl acetoacetate (4.5 mL, 26 mmol), ammonium acetate (1.5 g, 19.5 mmol) were mixed, and the reaction was warmed at 60°C and

⁸² E. Tatunashvili, B. Chan, P.E. Nashar, C. S. McErlan *Org. Biomol. Chem.* **2020**, *18*, 1812-1819.

vigorously stirred for 3 h. A yellow precipitate was formed. The suspension was filtered, and the yellow solid washed with water and then dried to afford the desired Hantzsch ester **14**. The product was used with no further purifications. Analytical data in accordance with literature reports.

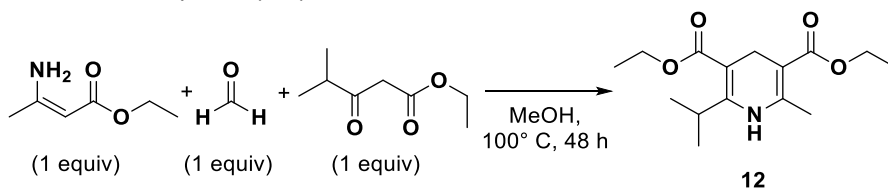
Synthesis of diethyl 2,6-diisopropyl-1,4-dihydropyridine-3,5-dicarboxylate (15**)**⁸³



Scheme 32

Formaldehyde solution in water 37% (746 mg, 9.2 mmol), ethyl 4,4-dimethylacetoacetate (3 g, 18.4 mmol) and ammonium acetate (1.48 g, 18.4 mmol) were mixed, and the reaction was warmed at 60°C and vigorously stirred for 5 h. The mixture was extracted with DCM, the organic phases were combined, dried over MgSO_4 , filtered and concentrated in vacuo. Purification over silica gel eluting from pure Petroleum Ether to Petroleum Ether/Ethyl Acetate 8:2 afforded the pure product. Analytical data in accordance with literature reports.

Synthesis of diethyl 2-isopropyl-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (12**)**

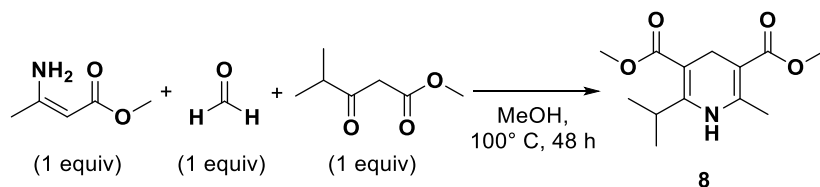


Scheme 33

2.25 g (17.4 mmol) of ethyl 3-amino butanoate was dissolved in 120 mL of absolute ethanol under inert atmosphere. Then formaldehyde solution in water 37% (523 mg, 17.4 mmol) and ethyl isobutyrylacetate (2.81 mL, 17.4 mmol) were added. The

solution was then heated to 100 °C until completion (48 h, monitored by ^1H -NMR analysis). The solvent was removed in vacuo and the crude was purified over silica gel eluting from pure Petroleum Ether to Petroleum Ether/Ethyl Acetate 95:5.

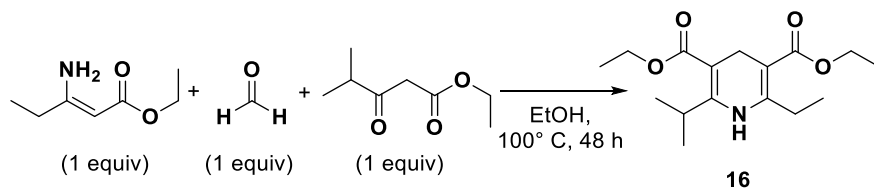
Synthesis of dimethyl 2-isopropyl-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (8)^{83,84}



Scheme 34

1.1g (9.55 mmol) of methyl 3-amino butanoate was dissolved in 100 mL of methanol under inert atmosphere. Then formaldehyde solution in water 37% (1.38 g, 9.55 mmol) and methyl isobutyrylacetate (287 mg, 9.55 mmol) were added. The solution was then heated to 60 °C until completion (48 h, monitored by ^1H -NMR analysis). The mixture was cooled down and the solvent evaporated under vacuum. The crude was purified over silica gel eluting in Petroleum Ether/Ethyl Acetate 8:2. Analytical data in accordance with literature reports.

Synthesis of dimethyl 2-isopropyl-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (16)

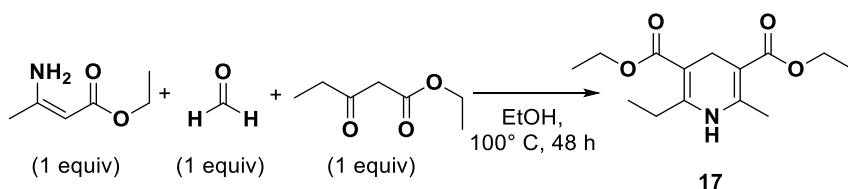


⁸³ M. van Rhee, J. Jiang, N. Melman, M. E. Olah, G. L. Stiles, K. A. Jacobson *J. Med. Chem.* **1996**, 39, 2980-2989.

⁸⁴ B. List, S. Mayer, N. Martin, X. Wang (Evonik Industries AG), US 2009/0030216 A1, **2009**.

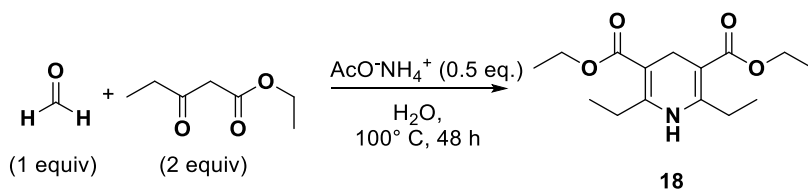
1.1 g (7.02 mmol) of ethyl 3-amino-4-methylpent-2-enoate was dissolved in 60 mL of ethanol under inert atmosphere. Then formaldehyde solution in water 37% (211 mg, 7.02 mmol) and ethyl 3-oxopentanoate (1.01 g, 7.02 mmol) were added. The solution was then heated to 100 °C until completion (48 h, monitored by ^1H -NMR analysis). The mixture was cooled down and the solvent evaporated under vacuum. The crude was purified over silica gel eluting in Petroleum Ether/Ethyl Acetate 8:2.

Synthesis of dimethyl 2-isopropyl-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (17)



907 mg (7.02 mmol) of ethyl-3-amino butanoate was dissolved in 60 mL of ethanol under inert atmosphere. Then formaldehyde solution in water 37% (211 mg, 7.02 mmol) and ethyl 3-oxopentanoate (1.01 g, 7.02 mmol) were added. The solution was then heated to 100 °C until completion (48 h, monitored by ^1H -NMR analysis). The mixture was cooled down and the solvent evaporated under vacuum. The crude was purified over silica gel eluting in Petroleum Ether/Ethyl Acetate 8:2.

Synthesis of diethyl 2,6-diethyl-1,4-dihydropyridine-3,5-dicarboxylate (18)⁸²



2.8 g (20 mmol) of ethyl propionil acetate, 406 mg (5 mmol) of NH_4OAc , and formaldehyde solution in water 37% (771 mg, 10 mmol) were suspended in 10 mL of H_2O . The solution was then heated to 100 °C until completion (3 h, monitored by ^1H -NMR analysis). Then, 10 mL of cold H_2O were added and the mixture was left to cool at 0 °C. The mixture was extracted with DCM (x4) and the organic layer dried over MgSO_4 and concentrated in vacuo. The crude was suspended in hexane and the supernatant was removed. The yellow solid was washed 3 times with cold hexane and then dried. Analytical data in accordance with literature reports.

3.5.3 Additional Experiments

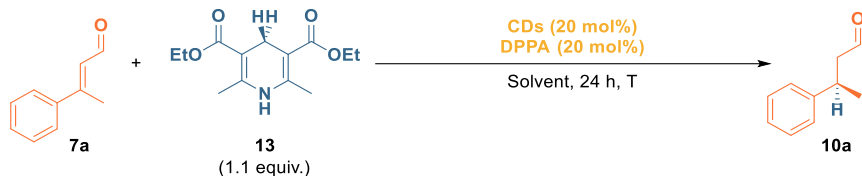
Table 9: Additional control experiments. a: abbreviation for diphenyl phosphate.

Entry	Solvent	Acid	CDs	Conv. (%)	Y _{NMR} (%)	ee (%)
1	Toluene	CPA1	-	84	64	rac.
2	Toluene	-	-	-	-	-
3	Toluene	-	CDs3	-	-	-
4	Mesitylene/pentane 1:1	CPA1	-	89	64	rac.
5	Toluene	DPPA ^a	-	37	16	rac.
6	Toluene	CPA1	-	90	62	rac.

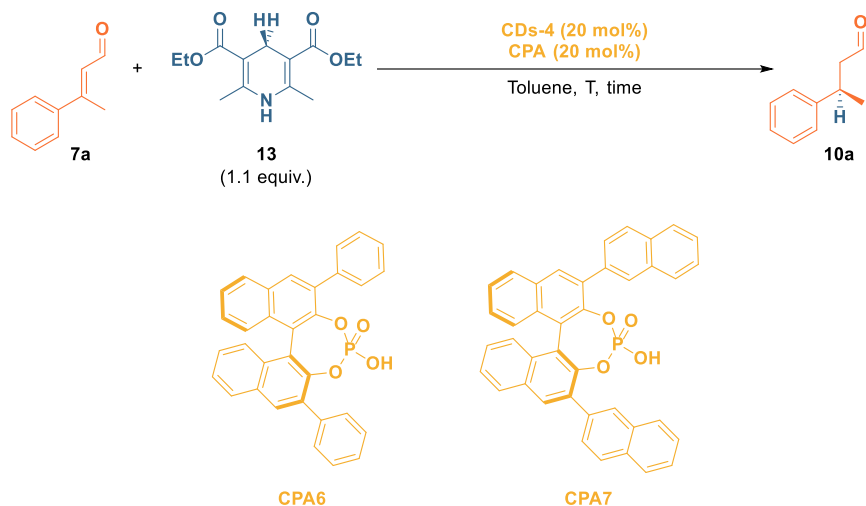
Table 10: Additional Experiments. a: 0.2 equiv. of HCl in dioxane were added in the reaction mixture; b: performed in absence of Hantzsch's ester; c: 2 equivalents of **13** used; d: **CDs/CPA** ratio different from 1:1, 8.5 mg (instead of 9.5 mg) of **CDs Type 2** used for 15 mg of (S)-TRIP; e: concentration of the system 0.05 M; f: concentration of the system 0.15 M; g: Toluene dry.

Entry	Dihydropyridine	T (°C)	Conv. (%)	Y _{NMR} (%)	ee (%)
1	13	25	99	47	56
2 ^a	13	25	96	53	26
3 ^b	13	25	74	-	-
4 ^c	13	25	99	32	58
5 ^d	13	25	99	53	57
6 ^e	13	10	63	25	70
7 ^f	13	10	42	7	-
8	13	25	99	45	58
9	12	10	99	70	79
10 ^g	12	-40	83	50	80
11	12	-40	53	34	65

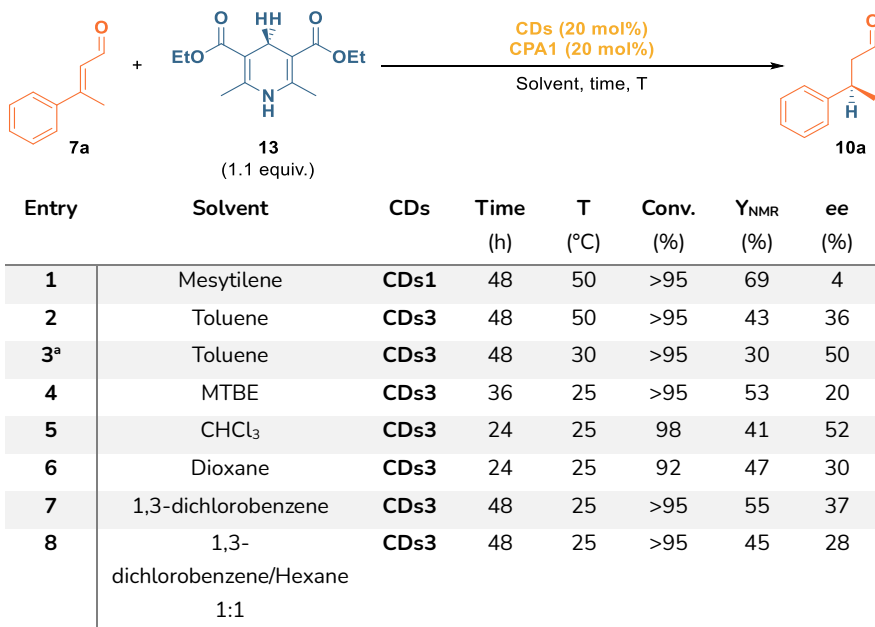
Table 11: Additional Experiments using DPPA as Phosphoric Acid. a: Internal standard: trimethoxybenzene (0.1 mmol); b: work-up: plug on silica gel; c: 1 equiv. of DPPA.



Entry ^a	Solvent	CDs	Time (h)	T (°C)	Conv. (%)	Y _{NMR} (%)
1 ^b	DCM	CDs4	48	RT to 40	93	15
2 ^b	Dioxane	CDs4	48	RT to 50	-	5
3 ^b	Toluene	CDs4	48	RT to 50	94	13
4	CHCl ₃	CDs4	48	RT to 40	85	10
5	Toluene	CDs4	48	50	>95	35
6	Toluene	CDs4	48	50	90	18
7	Toluene	CDs4	48	50	>95	37
8	Toluene	CDs4	6	50	80	16
9	Toluene	CDs4	12	50	85	23
10	Toluene	CDs4	18	50	85	34
11	Toluene	CDs4	24	50	98	35
12	Toluene	CDs4	24	50	83	19
13	Toluene	CDs4	48	50	>95	30
14	Benzene- <i>d</i> ₆	CDs4	24	50	59	10
15	Benzene- <i>d</i> ₆	CDs4	48	50	>95	12
16 ^c	Toluene	CDs4	48	50	92	8
17	Toluene	CDs3	24	50	64	20
18	Toluene	CDs3	48	50	>95	30

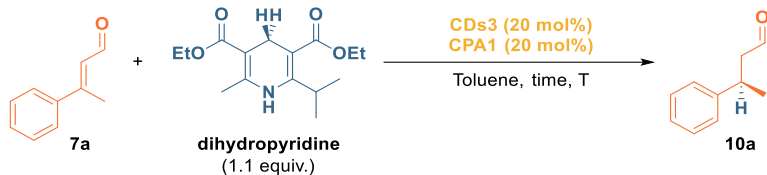
Table 12: Additional Experiments of CPAs screening.

Entry	CPA	Time (h)	T (°C)	Conv. (%)	Y _{NMR} (%)	ee (%)
1	CPA6	24	25	77	21	6
2	CPA7	24	25	71	36	3

Table 13: Additional Solvent Screening Experiments. a: addition in situ of NaBH₄.

9	Toluene	CDs3	48	30	>95	35	37
10	Mesitylene/Pentane 1:2	CDs3	24	25	95	47	29
11	Mesitylene/Pentane 2:1	CDs3	24	25	95	54	9
12	Mesitylene/Pentane 1:3	CDs3	24	25	95	52	2
13	Mesitylene	CDs3	24	25	92	68	20
14	Mesitylene/Pentane 1:1	CDs3	24	25	95	51	rac.
15	Toluene	CDs3	24	25	96	60	40
16	MTBE	CDs3	24	25	99	43	18
17	CHCl ₃	CDs3	16	25	97	33	52
18	CHCl ₃	CDs3	6	25	81	39	46
19	Anisole	CDs3	24	25	95	40	54

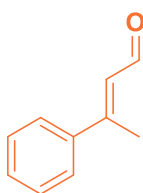
Table 14: Additional Screening Experiments. a: Reaction performed in dry toluene; b: 100 mg of MS 4 Å were added to the reaction mixture; c: 100 mg of MS 13X were added to the reaction mixture; d: 100 mg of MS 5 Å were added to the reaction mixture.



Entry	Acid	CDs	Time (h)	T (°C)	Conv. (%)	Y _{NMR} (%)	ee (%)
1	CPA1	CDs3	18	-40	92	72	82
2	CPA1	CDs3	24	-40	96	74	83
3 ^a	CPA1	CDs3	24	-40	82	50	80
4 ^a	CPA1	CDs3	24	-20	91	78	81
5 ^b	CPA1	CDs3	24	-20	99	72	79
6 ^c	CPA1	CDs3	24	-20	99	57	79
7 ^d	CPA1	CDs3	24	-20	96	72	80
8	CPA1	CDs3	24	-20	23	11	76
	2.5 mol%	2.5 mol%					

3.5.4 Characterisation of Compounds

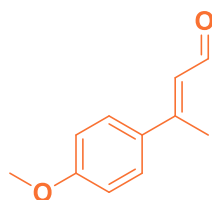
(*E*)-3-phenylbut-2-enal (7a)



Synthesized in accordance with general procedure for (*E*)-3-phenylbut-2-enal derivatives using diacetoxyiodo(benzene) (2.54 g, 7.64 mmol), TEMPO (109 mg, 0.69 mmol) and (*E*)-3-phenylbut-2-en-1-ol **23a** (1.03, 6.95 mmol) dissolved in 7.5 mL of DCM.

Chromatography on silica gel (Petroleum Ether/Ethyl Acetate 100:0 to 90:10). The desired product was obtained as a yellowish oil (606 mg, 4.15 mmol, yield = 60 %). **¹H-NMR** (400 MHz, CDCl₃, 303 K) δ 9.48 (d, *J* = 8.2 Hz, 1H), 7.49 - 7.37 (m, 2H), 7.35 - 7.26 (m, 3H), 6.14 (dt, *J* = 8.2, 1.4 Hz, 1H), 2.32 (d, *J* = 1.4 Hz, 3H). **¹³C-NMR** (101 MHz, CDCl₃, 303 K) δ 193.6, 162.2, 138.6, 129.3, 129.3, 128.5, 128.5, 26.6. Analytical data in accordance with literature reports.

(*E*)-3-(4-methoxyphenyl)but-2-enal (7b)

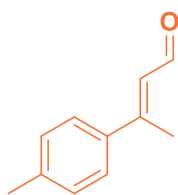


Synthesized in accordance with general procedure for (*E*)-3-phenylbut-2-enal derivatives using diacetoxyiodo(benzene) (451 mg, 1.4 mmol), TEMPO (20.7 mg, 0.13 mmol) and (*E*)-3-(4-methoxyphenyl)but-2-en-1-ol

23b (226 mg, 1.27 mmol) dissolved in 2 mL of DCM. Chromatography on silica gel (Petroleum Ether/Ethyl Acetate 100:0 to 90:10). The desired product was obtained as a waxy yellow solid (148 mg, 0.842 mmol, yield = 66 %). **¹H-NMR** (400 MHz, CDCl₃) δ 10.15 (d, *J* = 7.9 Hz, 1H), 7.54 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 6.39 (d, *J* = 9.2 Hz, 1H), 3.85 (s, 3H), 2.54 (s, 3H). **¹³C-NMR** (101 MHz, CDCl₃, 303 K) δ 191.4, 161.5, 157.1,

132.5, 127.9, 125.7, 114.2, 55.5, 16.2. Analytical data in accordance with literature reports.

(E)-3-(p-tolyl)but-2-enal (7c)

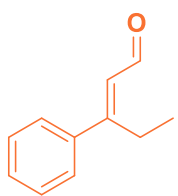


Synthesized in accordance with general procedure for (E)-3-phenylbut-2-enal derivatives using diacetoxyiodo(benzene) (632 mg, 1.95 mmol), TEMPO (29 mg, 0.19 mmol) and (E)-3-(p-tolyl)but-2-en-1-ol **23c** (289 mg, 1.78 mmol)

dissolved in 2 mL of DCM. Chromatography on silica gel (Petroleum Ether/Ethyl Acetate 100:0 to 90:10). The desired product was obtained as a yellow oil (209 mg, 1.3 mmol, yield = 73 %).

¹H-NMR (400 MHz, CDCl₃, 303 K) δ 10.17 (d, J = 7.9 Hz, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 6.40 (d, J = 7.95 Hz, 1H), 2.56 (s, 3H), 2.39 (s, 3H). ¹³C-NMR (101 MHz, CDCl₃, 303 K) δ 191.4, 157.7, 140.7, 137.7, 129.6, 126.7, 126.4, 21.4, 16.4. Analytical data in accordance with literature reports.

(E)-3-phenylpent-2-enal (7d)

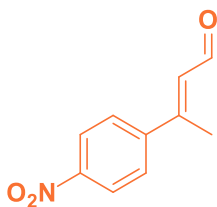


Synthesized in accordance with general procedure for (E)-3-phenylbut-2-enal derivatives using diacetoxyiodo(benzene) (707 mg, 2.13 mmol), TEMPO (30.2 mg, 0.194 mmol) and (E)-3-phenylpent-2-en-1-ol **23d** (314 mg, 1.94 mmol)

dissolved in 10 mL of DCM. Chromatography on silica gel (Petroleum Ether/Ethyl Acetate 100:0 to 90:10). The desired product was obtained as an inseparable mixture E/Z 4:1, as an orange oil (200 mg, 1.25 mmol, yield = 64 %). Major isomer (E): ¹H-NMR (400 MHz, CDCl₃, 303 K) δ 10.01 (d, J = 8.0 Hz, 1H), 7.34 - 7.24 (m, 5H), 6.11 (d, J = 7.9 Hz, 1H), 2.97 - 2.86 (m, 2H), 1.03 (t, J

= 7.53 Hz, 3H). **¹³C-NMR** (101 MHz, CDCl₃, 303 K) δ 190.2, 163.84, 138.8, 129.2, 128.2, 126.2, 125.9, 22.6, 14.3. Analytical data in accordance with literature reports.

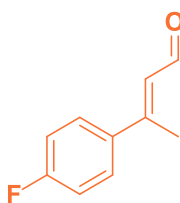
(E)-3-(4-nitrophenyl)but-2-enal (7e)



Synthesized in accordance with general procedure for (E)-3-phenylbut-2-enal derivatives using diacetoxyiodo(benzene) (345 mg, 1.07 mmol), TEMPO (15.2 mg, 0.097 mmol) and (E)-3-(4-nitrophenyl)but-2-en-1-ol **23e** (188 mg, 0.97 mmol) dissolved in 2 mL of DCM.

Chromatography on silica gel (Petroleum Ether/Ethyl Acetate 100:0 to 90:10). The desired product was obtained as a yellow solid (125 mg, 0.65 mmol, yield = 67 %). **¹H-NMR** (400 MHz, CDCl₃, 303 K) δ 10.21 (d, J = 7.5 Hz, 1H), 8.28 (d, J = 9.0 Hz, 2H), 7.68 (d, J = 9.2 Hz, 2H), 6.40 (d, J = 8.9 Hz, 1H), 2.61 (d, J = 1.4 Hz, 3H). **¹³C-NMR** (101 MHz, CDCl₃, 303 K) δ 190.8, 154.6, 148.5, 147.2, 129.5, 127.4, 124.1, 16.7. Analytical data in accordance with literature report.

(E)-3-(4-fluorophenyl)but-2-enal (7f)

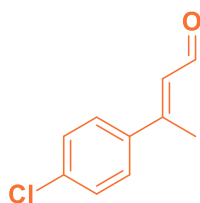


Synthesized in accordance with general procedure for (E)-3-phenylbut-2-enal derivatives using diacetoxyiodo(benzene) (4.64 g, 14.40 mmol), TEMPO (187 mg, 1.20 mmol) and (E)-3-(4-fluorophenyl)but-2-en-1-ol **23f** (2 g, 12 mmol)

dissolved in 24 mL of DCM. Chromatography on silica gel (Petroleum Ether/Ethyl Acetate 100:0 to 90:10). The desired product was obtained a pale yellow solid (1.05 g, 6.39 mmol, yield = 53 %). **¹H-NMR** (400 MHz, CDCl₃, 303 K) δ 10.17 (d, J = 7.8 Hz, 1H), 7.54 (dd, J = 8.9, 5.3 Hz, 2H), 7.10 (t, J = 8.7 Hz, 2H), 6.35

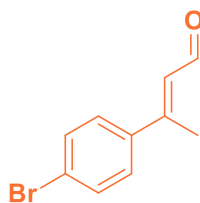
(dd, $J = 7.7, 1.3$ Hz, 1H), 2.56 (d, $J = 1.4$ Hz, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3 , 303 K) δ 191.1, 165.1, 162.6, 156.3, 136.6, 128.3, 128.3, 127.1, 127.1, 115.9, 115.7, 16.5. $^{19}\text{F NMR}$ (376 MHz, CDCl_3 , 303 K) δ -110.50. Analytical data in accordance with literature report.

(E)-3-(4-chlorophenyl)but-2-enal (7g)



Synthesized in accordance with general procedure for (E)-3-phenylbut-2-enal derivatives using diacetoxyiodo(benzene) (2.1 g, 6.38 mmol), TEMPO (90.7 mg, 0.58 mmol) and (E)-3-(4-chlorophenyl)but-2-en-1-ol **23g** (1.06 g, 5.8 mmol) dissolved in 6 mL of DCM. Chromatography on silica gel (Petroleum Ether/Ethyl Acetate 100:0 to 90:10). The desired product was obtained as a yellowish solid (643 mg, 3.56 mmol, yield = 61 %). $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 303 K) δ 10.17 (d, $J = 7.8$ Hz, 1H), 7.48 (d, $J = 8.8$ Hz, 2H), 7.39 (d, $J = 8.8$ Hz, 2H), 6.36 (d, $J = 7.8$ Hz, 1H), 2.55 (d, $J = 1.4$ Hz, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3 , 303 K) δ 191.2, 156.1, 139.0, 136.3, 129.1, 127.7, 127.5, 16.4. Analytical data in accordance with literature report.

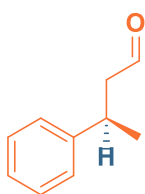
(E)-3-(4-bromophenyl)but-2-enal (7h)



Synthesized in accordance with general procedure for (E)-3-phenylbut-2-enal derivatives using diacetoxyiodo(benzene) (1.77 g, 4.84 mmol), TEMPO (75.7 mg, 0.48 mmol) and (E)-3-(4-bromophenyl)but-2-en-1-ol **23h** (1.10 g, 4.84 mmol) dissolved in 5 mL of DCM. Chromatography on silica gel (Petroleum Ether/Ethyl Acetate 100:0 to 90:10). The desired product was obtained as a yellow solid (820 mg, 3.64 mmol, yield = 75 %). $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 303 K) δ 10.17 (d, $J = 7.7$ Hz,

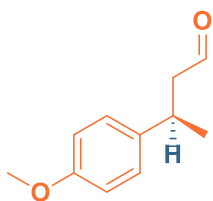
1H), 7.55 (d, $J = 8.8$ Hz, 2H), 7.41 (d, $J = 8.7$ Hz, 2H), 6.36 (d, $J = 7.7$ Hz, 1H), 2.54 (s, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3 , 303 K) δ 191.2, 156.2, 139.6, 132.1, 130.0, 127.9, 127.6, 124.6, 16.4. Analytical data in accordance with literature report.

(R)-3-phenylbutanal (10a)



Synthesized in accordance with General Procedure for nano-organocatalysed reaction using (*E*)-3-phenylbut-2-enal **7a** (0.25 mmol, 14.6 mg), Hantzsch's ester **12** (0.11 mmol, 30.9 mg), **CDs-3** (0.05 eq, loading 2100 $\mu\text{mol/g}$, 5.95 mg), (*S*)-TRIP (5 mol%, 3.76 mg) dissolved in 2.5 mL of toluene. Chromatography on silica gel (Petroleum ether/DCM 3:2) The desired product was obtained as a colourless oil (31 mg, 0.209 mmol, yield = 84 %). $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 303 K) δ 9.71 (t, $J = 2.1$ Hz, 1H), 7.35 - 7.27 (m, 1H), 7.22 (d, $J = 7.8$ Hz, 2H), 3.37 (h, $J = 7.0$ Hz, 1H), 2.82 - 2.60 (m, 2H), 1.33 (d, $J = 7.0$ Hz, 4H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3 , 303 K) δ 201.9, 145.6, 128.8, 126.9, 126.7, 51.8, 34.4, 22.3. HPLC (Lux 3 μm -Cellulose 1, Hexane/*i*-Propanol 95:5, flow: 0.5 mL/min, $\lambda = 210$ nm), t_{minor} : 10.8 min; t_{major} : 9.5 min. $[\alpha]_{\text{D}}^{25} = -27.37$ ($c = 0.0019$ g/mL, CHCl_3). Analytical data in accordance with literature report.

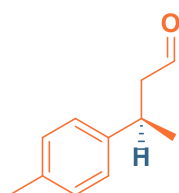
(R)-3-(4-methoxyphenyl)butanal (10b)



Synthesized in accordance with General Procedure for nano-organocatalysed reaction using (*E*)-3-(4-methoxyphenyl)but-2-enal **7b** (0.25 mmol, 44.1 mg), Hantzsch's ester **12** (0.275 mmol, 86.9 mg), **CDs-3** (0.05 eq, loading 2100 $\mu\text{mol/g}$, 5.95 mg), (*S*)-TRIP (5 mol%, 9.41 mg) dissolved in 2.5 mL of toluene. Chromatography on silica gel (Petroleum Ether/Ethyl Acetate 95:5). The desired product was obtained as a

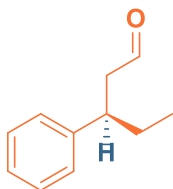
yellowish oil (30 mg, 0.168 mmol, yield = 67 %). **¹H-NMR** (400 MHz, CDCl₃, 303 K) δ 9.70 (t, J = 2.1 Hz, 1H), 7.14 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 3.32 (m, 1H), 2.77 - 2.57 (m, 2H), 1.30 (d, J = 7.0 Hz, 3H). **¹³C-NMR** (101 MHz, CDCl₃, 303 K) δ 202.1, 158.4, 137.7, 127.9, 114.2, 55.4, 52.1, 33.7, 22.5. HPLC (Lux 3 μ m-Amylose 2, Hexane/*i*-Propanol 98:2, flow: 0.3 mL/min, λ = 225 nm), t_{minor} : 55.7 min; t_{major} : 48.7 min. $[\alpha]_{\text{D}}^{25}$ = -27.84 (c = 0.0027 g/mL, CHCl₃). Analytical data in accordance with literature report.

(*R*)-3-(*p*-tolyl)butanal (10c)

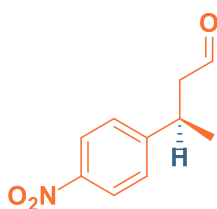


Synthesized in accordance with *General Procedure for nano-organocatalysed reaction* using (*E*)-3-(*p*-tolyl)but-2-enal **7c** (0.25 mmol, 40.1 mg), Hantzsch's ester **12** (0.275 mmol, 86.9 mg), **CDs-3** (0.05 eq, loading 2100 μ mol/g, 5.95 mg), (*S*)-TRIP (5 mol%, 9.41 mg) dissolved in 2.5 mL of toluene.

Chromatography on silica gel (Petroleum ether/DCM 3:2). The desired product was obtained as a colourless oil (25 mg, 0.154 mmol, yield = 62 %). **¹H-NMR** (400 MHz, CDCl₃, 303 K) δ 9.70 (s, 1H), 7.11 (s, 4H), 3.33 (q, J = 7.0 Hz, 1H), 2.79 - 2.58 (m, 2H), 2.32 (s, 3H), 1.30 (d, J = 7.0 Hz, 3H). **¹³C-NMR** (101 MHz, CDCl₃, 303 K) δ 202.2, 142.6, 136.2, 129.5, 126.8, 51.9, 34.1, 22.4, 21.1. HPLC (Lux 3 μ m-Cellulose 3, Hexane/*i*-Propanol 95:5, flow: 0.5 mL/min, λ = 210 nm), t_{minor} : 8.3 min; t_{major} : 9.1 min. $[\alpha]_{\text{D}}^{25}$ = +34.09 (c = 0.0008 g/mL, CHCl₃). Interestingly, the direction of the optical rotation is opposite to the other compounds; this entry was repeated twice to confirm the measurement of the optical rotation. Analytical data in accordance with literature report.

(R)-3-phenylpentanal (10d)

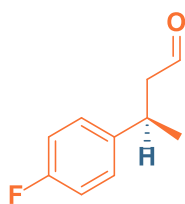
Synthesized in accordance with *General Procedure for nano-organocatalysed reaction* using (*E*)-3-phenylpent-2-enal **7d** (0.25 mmol, 40.1 mg), Hantzsch's ester **13** (0.275 mmol, 86.9 mg), **CDs-3** (0.05 eq, loading 2100 $\mu\text{mol/g}$, 5.95 mg), (*S*)-TRIP (5 mol%, 9.41 mg) dissolved in 2.5 mL of toluene. Chromatography on silica gel (Petroleum ether/DCM 3:2). The desired product was obtained as a colourless oil (26.5 mg, 0.166 mmol, yield = 66 %). $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 303 K) δ 9.67 (t, J = 2.1 Hz, 1H), 7.35 – 7.26 (m, 2H), 7.26 – 7.11 (m, 2H), 3.14 – 2.96 (m, 1H), 2.72 (dd, J = 7.3, 2.1 Hz, 2H), 1.80 – 1.56 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3) δ 190.2, 163.8, 138.8, 129.2, 128.8, 126.2, 125.9, 22.6, 14.3. HPLC (Lux 3 μm -Cellulose 3, Hexane/*i*-Propanol 95:5, flow: 0.5 mL/min, λ = 210 nm), t_{minor} : 20.8 min; t_{major} : 17.0 min. $[\alpha]_{\text{D}}^{25}$ = -23.31 (c = 0.0016 g/mL, CHCl_3). Analytical data in accordance with literature report.

(R)-3-(4-nitrophenyl)butanal (10e)

Synthesized in accordance with *General Procedure for nano-organocatalysed reaction* using (*E*)-3-(4-nitrophenyl)but-2-enal **7e** (0.25 mmol, 47.8 mg), Hantzsch's ester **12** (0.275 mmol, 86.9 mg), **CDs-3** (0.05 eq, loading 2100 $\mu\text{mol/g}$, 5.95 mg), (*S*)-TRIP (5 mol%, 9.41 mg) dissolved in 2.5 mL of toluene. Chromatography on silica gel (Petroleum Ether/Ethyl Acetate 95:5). The desired product was obtained as a pale yellowish oil (35 mg, 0.181 mmol, yield = 73 %). $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 303 K) δ 9.73 (t, J = 1.5 Hz, 1H), 8.18 (d, J = 8.9 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 3.50 (m, 1H), 2.87 – 2.70 (m, 2H), 1.35 (d, J = 6.9 Hz, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3 , 303 K) δ 200.1,

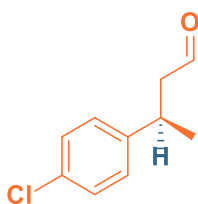
153.2, 146.7, 127.7, 124.0, 51.3, 33.9, 21.8. HPLC (Lux 3 μ m-Cellulose 2, Hexane/*i*-Propanol 95:5, flow: 0.5 mL/min, λ = 250 nm), t_{minor} : 27.0 min; t_{major} : 31.4 min. $[\alpha]_{\text{D}}^{25}$ = +20.80 (c = 0.0025 g/mL, CHCl_3). Interestingly, the direction of the optical rotation is opposite to the other compounds; this entry was repeated twice to confirm the measurement of the optical rotation. Analytical data in accordance with literature report.

(*R*)-3-(4-fluorophenyl)butanal (10f)

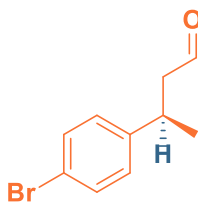


Synthesized in accordance with *General Procedure for nano-organocatalysed reaction* using (*E*)-3-(4-fluorophenyl)but-2-enal **7f** (0.25 mmol, 47.8 mg), Hantzsch's ester **12** (0.275 mmol, 86.9 mg), **CDs-3** (0.05 equiv, loading 2100 μ mol/g, 5.95 mg), (*S*)-TRIP (5 mol%, 9.41 mg) dissolved in 2.5 mL of

toluene. Chromatography on silica gel (Petroleum ether/DCM 3:2). The desired product was obtained as a colourless oil (35 mg, 0.181 mmol, yield = 73 %). **¹H-NMR** (400 MHz, CDCl_3 , 303 K) δ 9.70 (t, J = 1.9 Hz, 1H), 7.23 – 7.13 (m, 2H), 7.04 – 6.93 (m, 2H), 3.36 (m, 1H), 2.78 – 2.58 (m, 2H), 1.30 (d, J = 7.0 Hz, 3H). **¹³C-NMR** (101 MHz, CDCl_3 , 303 K) δ 201.6, 162.8, 160.4, 141.3, 128.4, 115.5, 52.0, 33.7, 22.4. **¹⁹F-NMR** (376 MHz, CDCl_3 , 303 K) δ -116.64. HPLC (Lux 3 μ m-Cellulose 3, Hexane/*i*-Propanol 98:2, flow: 0.5 mL/min, λ = 210 nm), t_{minor} : 11.9 min; t_{major} : 13.2 min. $[\alpha]_{\text{D}}^{25}$ = -22.41 (c = 0.0012 g/mL, CHCl_3). Analytical data in accordance with literature report.

(R)-3-(4-chlorophenyl)butanal (10g)

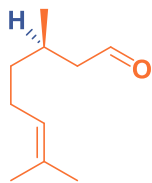
Synthesized in accordance with *General Procedure for nano-organocatalysed reaction* using (*E*)-3-(4-chlorophenyl)but-2-enal **7g** (0.25 mmol, 45.2 mg), Hantzsch's ester **12** (0.275 mmol, 86.9 mg), **CDs-3** (0.05 equiv, loading 2100 $\mu\text{mol/g}$, 5.95 mg), (*S*)-TRIP (5 mol%, 9.41 mg) dissolved in 2.5 mL of toluene. Chromatography on silica gel (Petroleum ether/DCM 3:2). The desired product was obtained as a colourless oil (34.2 mg, 0.187 mmol, yield = 75 %). $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 303 K) δ 9.71 (t, J = 1.9 Hz, 1H), 7.33 - 7.24 (m, 2H), 7.21 - 7.11 (m, 2H), 3.35 (h, J = 7.0 Hz, 1H), 2.79 - 2.60 (m, 2H), 1.30 (d, J = 7.0 Hz, 4H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3 , 303 K) δ 201.3, 144.1, 132.3, 128.9, 128.3, 51.8, 33.8, 22.2. HPLC (Lux 3 μm -Cellulose 2, Hexane/*i*-Propanol 99:1, flow: 0.5 mL/min, λ = 210 nm), t_{minor} : 11.6 min; t_{major} : 13.3 min. $[\alpha]_{\text{D}}^{25}$ = -41.48 (c = 0.0031 g/mL, CHCl_3). Analytical data in accordance with literature report.

(R)-3-(4-bromophenyl)butanal (10h)

Synthesized in accordance with *General Procedure for nano-organocatalysed reaction* using (*E*)-3-(4-bromophenyl)but-2-enal **7h** (0.25 mmol, 56.3 mg), Hantzsch's ester **12** (0.275 mmol, 86.9 mg), **CDs-3** (0.05 equiv, loading 2100 $\mu\text{mol/g}$, 5.95 mg), (*S*)-TRIP (5 mol%, 9.41 mg) dissolved in 2.5 mL of toluene. Chromatography on silica gel (Petroleum ether/DCM 3:2). The desired product was obtained as a colourless oil (50.2 mg, 0.221 mmol, yield = 88 %). $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 303 K) δ 9.70 (s, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 3.33 (m, 1H), 2.78 - 2.53 (m, 2H), 1.29 (d, J = 7.0 Hz, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3 , 303 K) δ 201.3,

144.5, 131.9, 128.7, 120.4, 51.7, 33.9, 22.2. HPLC (Lux 3 μ m-Cellulose 2, Hexane/*i*-Propanol 95:5, flow: 0.5 mL/min, λ =210 nm), t_{minor} : 14.1 min; t_{major} : 16.4 min. $[\alpha]_{\text{D}}^{25} = -12.73$ ($c=0.0022$ g/mL, CHCl_3). Analytical data in accordance with literature report.

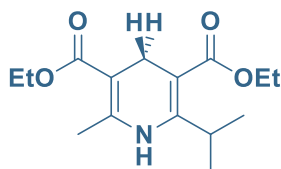
(*R*)-3,7-dimethyloct-6-enal (10i)



Synthesized in accordance with *General Procedure for nano-organocatalysed reaction* using (*E*)-3,7-dimethylocta-2,6-dienal (0.5 mmol, 76.1 mg), Hantzsch's ester **12** (0.55 mmol, 155 mg), **CDs-3** (0.05 equiv, loading 2100 μ mol/g, 11.9 mg), (*S*)-TRIP

(5 mol%, 18.8 mg) dissolved in 5 mL of toluene. Chromatography on silica gel (Petroleum ether/DCM 9:1). The desired product was obtained as a colourless oil (44 mg, 0.285 mmol, yield = 57 %). **¹H-NMR** (CDCl_3 , 400 MHz, 303 K) δ : 9.74 (t, J = 4 Hz, 1H), 5.10-5.05 (m, 1H), 2.39 (ddd, J = 16.1, 5.6, 2.1 Hz, 1H), 2.22 (ddd, J = 15.9, 7.9, 2.6 Hz, 1H), 2.11-1.92 (m, 3H), 1.67 (s, 3H), 1.59 (s, 3H), 1.40-1.22 (m, 2H), 0.96 (d, J = 8 Hz, 3 H). **¹³C-NMR** (CDCl_3 , 101 MHz, 303 K) δ : 203.04, 131.87, 124.18, 51.13, 37.08, 27.93, 25.80, 25.53, 19.99, 17.77. HPLC (Lux 3 μ m-Cellulose 1, Hexane/*i*-Propanol 95:5, flow: 0.5 mL/min, λ =210 nm), t_{minor} : 10.99 min; t_{major} : 10.19 min. $[\alpha]_{\text{D}}^{25} = +10.43$ ($c=0.0023$ g/mL, CHCl_3).

Diethyl 2-isopropyl-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (12)

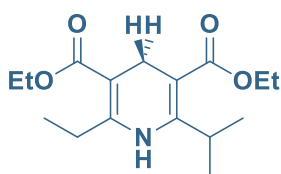


Synthesized in accordance with *synthesis of diethyl 2-isopropyl-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate* procedure using 2.5 g (19.4 mmol) of ethyl

3-amino butanoate, paraformaldehyde solution in water 37% (581 mg, 19.4 mmol), and ethyl isobutyrylacetate (3.12 mL, 19.4 mmol) dissolved in 190 mL of

absolute ethanol. The desired product was obtained as a yellow oil (2.75 g, 9.77 mmol, yield = 50 %). $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 303 K) δ 4.14 (m, 4H), 4.10 - 4.02 (m, 1H), 3.25 (s, 2H), 2.19 (s, 3H), 1.26 (t, $J = 7.1$ Hz, 6H), 1.07 (d, $J = 7.0$ Hz, 6H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3 , 303 K) δ 168.1, 167.8, 153.2, 145.2, 99.2, 98.2, 59.7, 59.7, 27.2, 25.2, 20.2, 19.3, 14.6, 14.5.

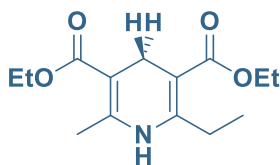
Diethyl 2-ethyl-6-isopropyl-1,4-dihydropyridine-3,5-dicarboxylate (16)



Synthesized in accordance with synthesis of diethyl 2-ethyl-6-isopropyl-1,4-dihydropyridine-3,5-dicarboxylate procedure using 1.1 g (7.02 mmol) of ethyl 3-amino-4-methylpent-2-enoate,

paraformaldehyde solution in water 37% (211 mg, 7.02 mmol), and ethyl 3-oxopentanoate (1.01 g, 7.02 mmol) dissolved in 60 mL of absolute ethanol. The desired product was obtained as a yellow sticky oil (623 mg, 2.11 mmol, yield = 30 %). $^1\text{H NMR}$ (400 MHz, CDCl_3 , 303 K) δ 4.16 (m, 4H), 4.09 (m, 1H), 3.26 (s, 2H), 2.63 (q, $J = 7.5$ Hz, 2H), 1.28 (t, $J = 7.1$, 6H), 1.20 - 1.09 (m, 3H), 1.09 (d, $J = 1.1$ Hz, 6H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3 , 303 K) δ 167.8, 167.7, 153.5, 150.7, 98.4, 98.0, 59.8, 59.8, 27.3, 25.9, 25.1, 20.3, 14.6, 14.6, 12.7.

Diethyl 2-ethyl-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (17)



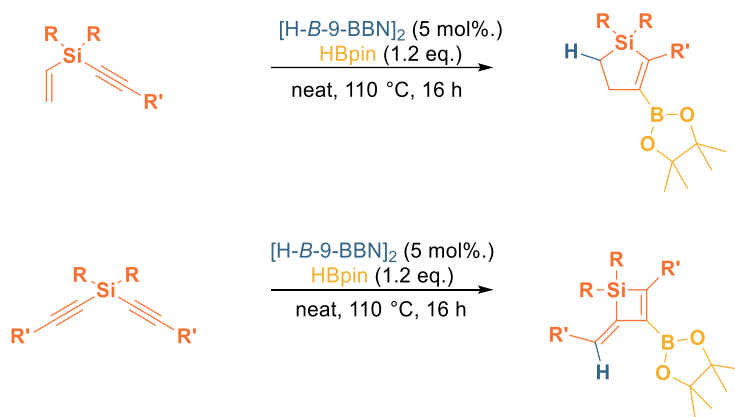
Synthesized in accordance with synthesis of diethyl 2-ethyl-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate procedure using 907 mg (7.02 mmol) of ethyl-3-amino butanoate,

paraformaldehyde solution in water 37% (211 mg, 7.02 mmol), and ethyl 3-oxopentanoate (1.01 g, 7.02 mmol) dissolved in 60 mL of absolute ethanol. The desired product was obtained as a yellow

solid (891.6 mg, 3.01 mmol, yield = 43%). **¹H NMR** (400 MHz, CDCl₃, 303 K) δ 4.16 (q, J = 7.1 Hz, 4H), 3.26 (s, 2H), 2.58 (q, J = 7.5 Hz, 2H), 1.27 (t, J = 7.1 Hz, 6H), 1.14 (t, J = 7.5 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃, 303 K) δ 168.2, 167.8, 150.5, 145.2, 99.5, 98.8, 59.8, 25.9, 25.0, 19.3, 14.6, 14.6, 12.7.

4. Catalytic Access to Diastereometrically Pure Four- and Five-Membered Silyl-Heterocycles Using Transborylation

Part of this chapter has been published as: D. R. Willcox, E. Cocco, G. S. Nichol, A. Carlone, S. P. Thomas *Angew. Chem. Int. Ed.* **2024**, e202401737.



A novel borane-catalyzed intramolecular 1,1-carboboration of silyl-alkynes has been developed for the synthesis of 2,3-dihydrosilolyl and silylcyclobut-2-enyl boronic esters. Successful, catalytic carboboration has been achieved on a variety of functionally diverse silyl-alkynes, using a borane catalyst and transborylation enabled turnover.

4.1 Introduction

4.1.1 Silicon-containing heterocycles: properties and challenges

At the center of the interest of organic and inorganic chemists for over half a century,⁸⁵ silicon-containing heterocycles have been

⁸⁵ R. A. Benkeser, Y. Nagai, J. L. Noe, R. F. Cunico, P. H. Gund *J. Am. Chem. Soc.* **1964**, 86, 2446–2451.

initially seen just as a synthetic challenge but, with the emergence of their potential applications in both medicinal and material chemistry, their synthesis has now become a consolidated research field.⁸⁶

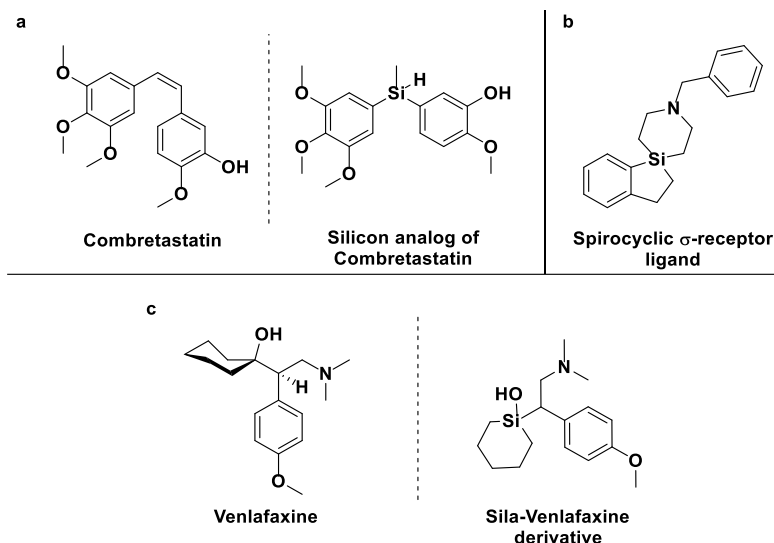


Figure 19: Selected examples of organosilanes in medicinal chemistry.

Silicon-containing active pharmaceutical ingredients have been of particular interest to medicinal chemists due to their unique properties, which provides an alternative pathway for drug optimization: indeed, the increased bond length ($1.87 \text{ \AA}$ for the Si-C bond compared to the $1.54 \text{ \AA}$ for the C-C bond) and the lower electronegativity ($\chi_{\text{C}} = 2.50$; $\chi_{\text{Si}} = 1.75$) allow the exploration and design of novel chemical spaces, altering the size and the shape of the molecule, alongside a greater lipophilicity that can lead to improved uptake through cell membranes,⁸⁷ defining the so-called concept of “silicon switch”, used in drug discovery to identify those

⁸⁶ G. A. Showell, J. S. Mills *Drug Discov. Today* **2003**, 8, 551–556. b) H. Murata, Z. H. Kafafi, M. Uchida *Appl. Phys. Lett.* **2002**, 80, 189–191. c) L. C. Palilis, H. Murata, M. Uchida, Z. H. Kafafi *Org. Electron.* **2003**, 4, 113–121.

⁸⁷ a) R. Ramesh, D. S. Reddy *J. Med. Chem.* **2018**, 61, 3779–3798. b) A. K. Franz, S. O. Wilson, *J. Med. Chem.* **2013**, 56, 388–405.

biologically active compounds in which one or more carbon atoms are substituted with silicon atoms.⁸⁸

An interesting report by Nakamura and coworkers in 2013 demonstrated how organosilanes can work as bioisosters of *cis*-alkenes, preparing silicon analogs of combretastin (see Figure 19a),⁸⁹ a molecule active in the inhibition of microtubule activity by binding to tubulin at the colchicine site, thereby interfering with cell growth and proliferation. Other promising application of organosilane as silylheterocycles in medicinal chemistry have been found as σ -receptor ligands (Figure 19b) or as homologues of venlafaxine, belonging to the serotonin and norepinephrine reuptake inhibitors (SNRI) class, derivatives (Figure 19c).⁹⁰

Beyond biological applications, silyl-heterocycles, such as silole, have found use in materials applications as organic light-emitting materials and dyes. One example has been reported by Tang and coworkers, designing new siloles consisting of 2,3,4,5-tetraphenylsiloles unit and 1-phenyl-1H-benzo[d]imidazole (**PBI**) or 1-phenyl-1Hphenanthro[9,10-d]imidazole (**PPI**) groups:⁹¹ these compounds show aggregation-induced emission (AIE) effects, alongside good thermal stabilities and low LUMO energy levels, and are noteworthy highly emissive in solid films. However, wider exploitation of silylheterocycles is limited by the lack of preparative methods, and the scope of these methods to give structurally

⁸⁸ J. O. Daiss, C. Burschka, J. S. Mills, J. G. Montana, G. A. Showell, J. B. H. Warneck, R. Tacke *Organometallics* **2006**, 25, 1188–1198.

⁸⁹ M. Nakamura, D. Kajita, Y. Matsumoto, Y. Hashimoto, *Bioorg. Med. Chem.* **2013**, 21, 7381–7391.

⁹⁰ a) R. Ramesh, D. S. Reddy, *J. Med. Chem.* **2018**, 61, 3779–3798. b) A. K. Franz, S. O. Wilson, *J. Med. Chem.* **2013**, 56, 388–405.

⁹¹ H. Nie, B. Chen, J. Zeng, Y. Xiong, Z. Zhao, B. Z. Tang *J. Mater. Chem. C* **2018**, 6, 3690–3698.

diverse silyl-heterocycles which are essential for wider applications.

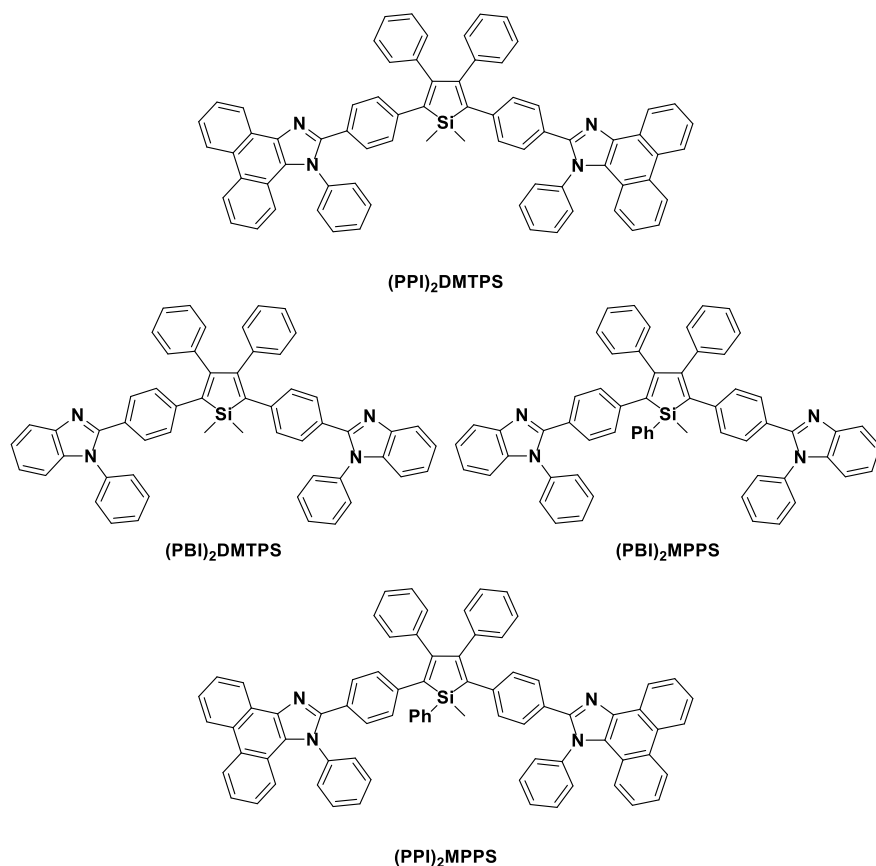


Figure 20: Cyclic siloles as AIE studies designed by Tang and coworkers.

The main approach to the preparation of silylheterocycles require an extensive use of organometallics in stoichiometric amount,⁹² therefore limiting the variation of the core scaffold, while, where the use transition-metal catalysis has emerged as a tool towards their synthesis, the main restraints are highly pre-functionalized starting materials, including specifically designed silanes and

⁹² a) R. Tacke, V. I. Handmann, R. Bertermann, C. Burschka, M. Penka, C. Seyfried *Organometallics* **2003**, 22, 916–924. b) J. O. Daiss, C. Burschka, J. S. Mills, J. G. Montana, G. A. Showell, J. B. H. Warneck, R. Tacke *Organometallics* **2006**, 25, 1188–1198.

synthetically challenging reagents,⁹³ and where readily available starting materials have been used, substitution about the silyl-heterocycle ring has been limited in functionality (see Figure 21).⁹⁴

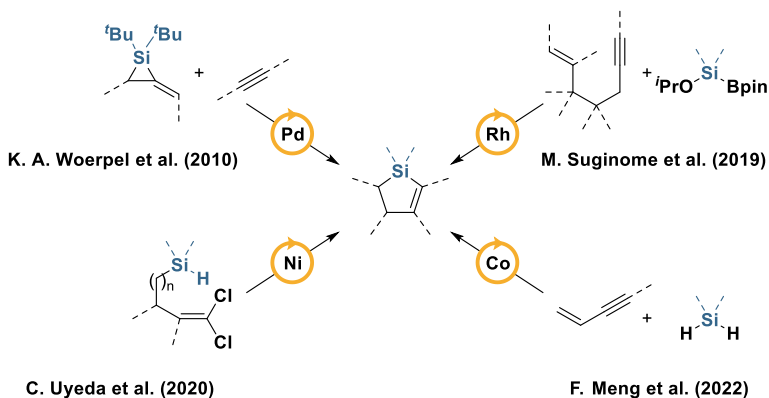


Figure 21: Selected examples of transition metals applied to the catalytic synthesis of silylheterocycles.

4.1.2 Organoboron reagents to access complex silyl-heterocycles through carboboration reactions

In the last decades, in order to access to the complex chemical spaces represented by the four-, five- and six-membered ring silyl-heterocycle moieties, carboboration reactions were investigated, unlocking new pathways that do not require to recur to organometallics nor transition metal catalysts.

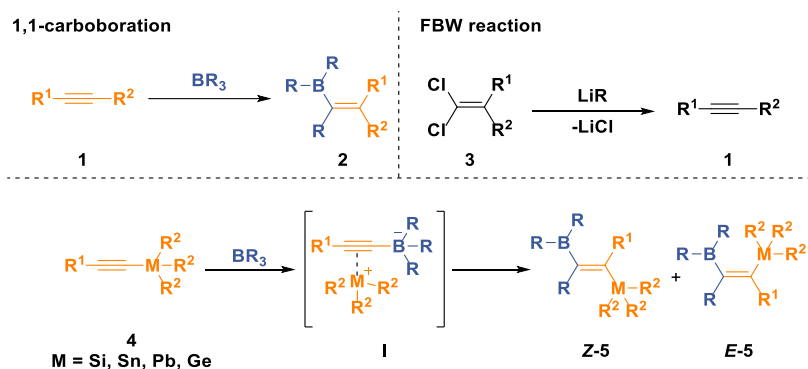
Indeed, in boranes the trigonal-planar surrounded boron atom in boranes is an electrophilic centre, that makes them able to act as

⁹³ a) T. Ohmura, I. Sasaki, M. Suginome *Org. Lett.* **2019**, *21*, 1649–1653. b) I. Sasaki, T. Ohmura, M. Suginome, *Org. Lett.* **2020**, *22*, 2961–2966. c) S. Biswas, S. Pal, C. Uyeda *Chem. Commun.* **2020**, *56*, 14175–14178. d) H. Fang, W. Hou, G. Liu, Z. Huang *J. Am. Chem. Soc.* **2017**, *139*, 11601–11609. e) M. Gimferrer, Y. Minami, Y. Noguchi, T. Hiyama, A. Poater *Organometallics* **2018**, *37*, 1456–1461. f) K. M. Buchner, K. A. Woerpel *Organometallics* **2010**, *29*, 1661–1669.

⁹⁴ a) W. Wang, S. Zhou, L. Li, Y. He, X. Dong, L. Gao, Q. Wang, Z. Song *J. Am. Chem. Soc.* **2021**, *143*, 11141–11151. b) W. Lu, Y. Zhao, F. Meng *J. Am. Chem. Soc.* **2022**, *144*, 5233–5240. c) H. Chen, Y. Chen, X. Tang, S. Liu, R. Wang, T. Hu, L. Gao, Z. Song *Angew. Chem. Int. Ed.* **2019**, *58*, 4695–4699.

Lewis acids. This Lewis acid behaviour depends also on the electronegativity (as in the case of haloboranes) and size (bulky organic, usually alkyl, groups) of substituents on the boron atom, as their abilities to be engaged in π - π interactions (like the case of the nitrogen lone-pair in aminoboranes) as well.

When it comes to talk about triorganoboranes with general structure BR_3 (with R an alkyl or aryl group), they are usually classified as weak Lewis acids, unless R refers to polyhalogenated aromatics, as in the case of BCF $B(C_6F_5)_3$.⁹⁵ This fact, alongside with the characteristics mentioned above, allows triorganoboranes to show interesting weak interactions that can take place in interesting reactivities such in the case of frustrated Lewis pairs (FLP).⁹⁶



Scheme 35: Comparison between 1,1-carboboration reaction and FBW reaction (above). Mechanism of 1,1-carboboration reaction (below).

To this class of reactivities belongs 1,1-carboboration: this reaction resembles an insertion of a vinylidene isomer of an alkyne into a B–C bond of a borane, a sort of reversal Fritsch–Buttenberg–Wiechell (FBW) reaction, although mechanistically the reaction of suitable

⁹⁵ a) W. E. Piers, T. Chivers *Chem. Soc. Rev.* **1997**, 26, 345–354. b) J. R. Lawson, R. Melen *Inorg. Chem.* **2017**, 56, 15, 8627–8643.

⁹⁶ a) G. Kehr, S. Schwendemann, G. Erker *Topics Curr. Chem.* **2013**, 332, 45–84. b) D. Stephan, W. Erker *Chem. Sci* **2014**, 6, 2625–2640.

alkynes with boranes takes a very different mechanistic course to arrive at the 1,1-carboboration products (see Scheme 35).⁹⁷

Even though long known, the 1,1-carboboration reaction presented the main limitation of requiring activated alkynes in which R^1 or R^2 are silyl, stannyl, germyl or plumbyl groups⁹⁸ or substituents containing a transition metal, having these functionalities the propension to undergo the the required 1,2-migration along the alkynyl backbone. Indeed, the first step is an alkynyl abstraction from **4** operated by the trialkylborane BR_3 , leading to the formation of the trialkyl(alkynyl)boronate **I** in which the electrophilic $[M(R^2)_3]^+$ moiety remains coordinated to the triple bond, followed by a rearrangement in which one of the alkyl groups on the boron rapidly shifts on the same carbon atom of the alkynyl moiety where the BR_2 group is attached, leading to the formation of an *E/Z* mixture of **5**, as demonstrated by Wrackmeyer and coworkers studying extensively a great number of activated alkynes in which the typical migrating $-M(R^2)_3$ groups are main group metal centered substituents such as $-Si(R^2)_3$, $-Sn(R^2)_3$, $-Ge(R^2)_3$, $-Pb(R^2)_3$ or even few selected transition metals containing groups $-PtL_n$ or $-TiL_n$.^{97,98} Of course, the reaction conditions are strictly dependant from the substituents on the acetylene unit.⁹⁹

⁹⁷ G. Kehr, G. Erker *Chem. Commun.* **2012**, 48, 1839–1850.

⁹⁸ a) B. Wrackmeyer, W. Milius, O. L. Tok *Chem.–Eur. J.* **2003**, 9, 4732–4738. b) B. Wrackmeyer, E. V. Klimkina, Y. N. Bubnov *J. Organomet. Chem.* **2001**, 620, 51–59. c) B. Wrackmeyer, B. H. Kenner-Hofmann, W. Milius, P. Thoma, O. L. Tok, M. Herberhold *Eur. J. Inorg. Chem.* **2006**, 101–108. d) B. Wrackmeyer, A. Pedall, J. Weidinger *J. Organomet. Chem.* **2002**, 649, 225–231.

⁹⁹ a) R. Köster, G. Seidel, B. Wrackmeyer *Chem. Ber.* **1989**, 122, 1825–1850. b) Y. N. Bubnov, M. E. Gruskii, S. Y. Erdyakov, O. A. Kizas, G. D. Kolomnikova, N. Y. Kuznetsov, T. V. Potapova, O. A. Varzatskii, Y. Z. Voloshim *J. Organomet. Chem.* **2009**, 694, 1754–1763. c) B. Wrackmeyer, A. Pedall, W. Milius, O. L. Tok, Y. N. Bubnov *J. Organomet. Chem.* **2002**, 649, 232–245.

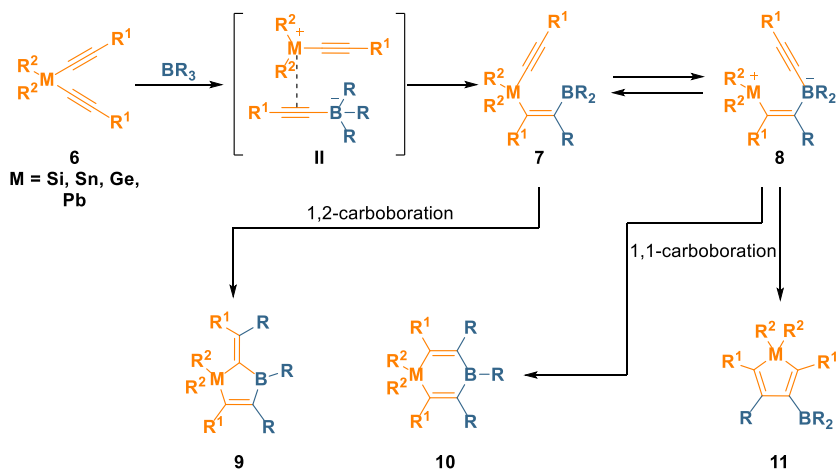
Focusing on the reactivity of dialkynyl group metal 14 substrates, and more in detail to the dialkynyl silyl derivatives, some of the most interesting results were obtained, proving to be a solid way to access to cyclic siloles and metals (Sn, Ge, Pb) containing heterocycles more in general.

The proposed mechanism is briefly reported on dialkynylmetal compound **6** in Scheme 36: the borane proceeds to give alkynyl abstraction on compound **6**, leading to the transition state **II** followed by a rearrangement giving the intermediate **7** as in the classical 1,1-carboboration. At this point, three competing pathways are possible to occur: a) 1,2-carboboration, that leads to the 1-bora-3-metallacyclopent-4-ene **9**;¹⁰⁰ b) an intramolecular alkynyl abstraction leads to an equilibrium between compounds **7** and **8** and this last one can then react through another 1,1-carboboration (1,1-alkylboration) to give the 1-bora-4-metallacyclohexa-2,5-diene **10**;¹⁰¹ c) after the alkynyl abstraction that forms **8**, this compound can react through a 1,1-carboboration (1,1-alkenylboration) to give boryl-substituted metallacyclopenta-2,4-diene **11**.¹⁰²

¹⁰⁰ B. Wrackmeyer, M. H. Bhatti, S. Ali, O. L. Tok, Y. N. Bubnov *J. Organomet. Chem.* **2002**, 657, 146–154.

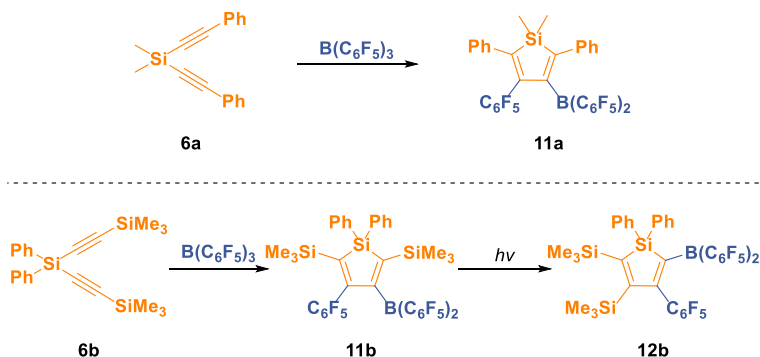
¹⁰¹ B. Wrackmeyer, K. Horchler, R. Boese *Angew. Chem. Int. Ed.* **1989**, 28, 1500–1502.

¹⁰² E. Khan, S. Bayer, R. Kempe, B. Wrackmeyer *Eur. J. Inorg. Chem.* **2009**, 4416–4424.



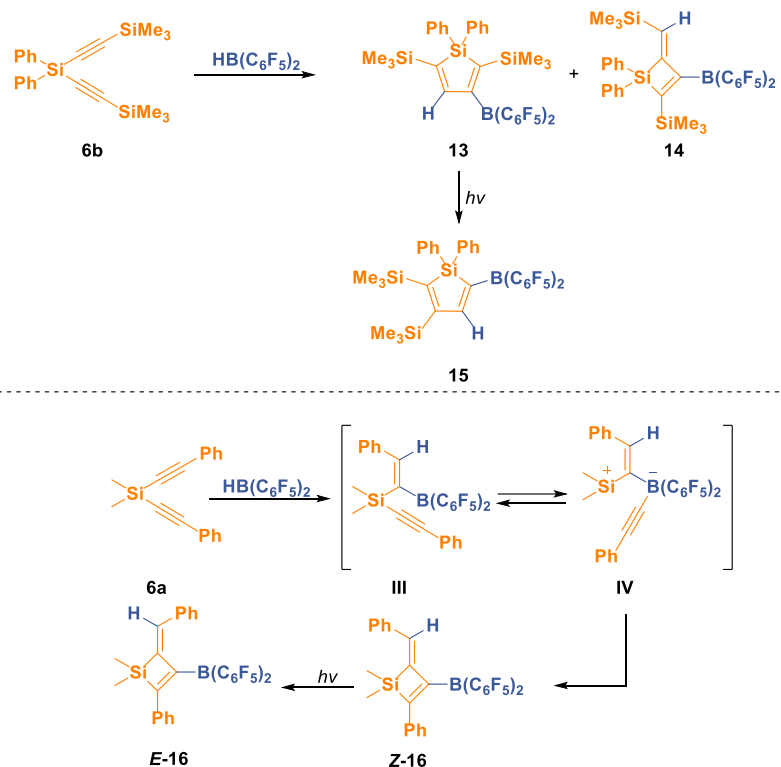
Scheme 36: Competing reaction mechanisms in the carboboration of dialkynyl metal 14 compounds.

When $\text{B}(\text{C}_6\text{F}_5)_3$ was employed, it proved to be extremely effective in undergoing 1,1-carbaboration on activated alkynes, obtaining the desired products in mild conditions (Scheme 37).¹⁰³



Scheme 37: 1,1-carbaboration carried out using $\text{B}(\text{C}_6\text{F}_5)_3$ as borane.

¹⁰³ G. Dierker, J. Ugolotti, G. Kehr, R. Fröhlich, G. Erker *Adv. Synth. Catal.* **2009**, 351, 1080–1088.



Scheme 38: Employment of Piers's Borane in the reactivity of dialkynylsilanes and proposed mechanism to the formation of the four-membered ring silole.

Employing Piers' Borane¹⁰⁴ $\text{HB}(\text{C}_6\text{F}_5)_2$ in place of $\text{B}(\text{C}_6\text{F}_5)_3$ the reaction afforded the expected silole **13** that isomerizes photolitically (the photochemical rearrangement of these silole derivatives can formally be regarded as di- π -rearrangements)¹⁰⁵ to **15** as expected but also a new product, the stable Z four-membered silole **14** (Scheme 38).¹⁰⁶ For the formation of compound **13**, a sequence of alkynyl abstraction/rearrangement can be assumed to take place, with the addition of an initial 1,1-hydroboration on the triple bond.

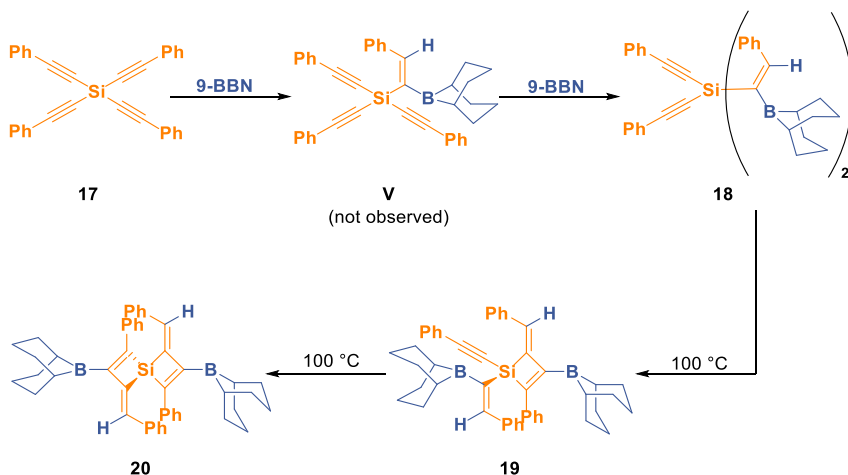
¹⁰⁴ D. J. Parks, W. E. Piers, G. P. A. Yap *Organometallics* **1998**, 17, 5492–5503.

¹⁰⁵ H. E. Zimmerman *Pure Appl. Chem.* **2006**, 78, 2193–2203.

¹⁰⁶ J. Ugoletti, G. Dierker, R. Fröhlich, G. Kehr, G. Erker *J. Organomet. Chem.* **2011**, 696, 1184–1188.

To explain the formation of the four-membered siloles **14** and **Z-16**, a 1,2-hydroboration followed by a 1,1-carboboration are the reason of the outcome. The silole **Z-16** can then rearranges photolitically to its *E* isomer.¹⁰⁷

As can be observed, the 1,2-hydroboration of dialkynyl(dialkyl)silanes is highly regiospecific if a group different from the hydrogen is present on the alkyne moiety.



Scheme 39: highly regiospecific synthesis of spirosilanes combining 1,2-hydroboration and 1,1-carboboration using 9-BBN.

Even more interesting is the fact that the presence of a bulky group on the alkyne,¹⁰⁸ such as *tert*-butyl or phenyl, can induce complete regiospecificity if 9-borabicyclo[3.3.1]nonane (9-BBN) is used as hydroborating reagent, as reported by Wrackmeyer and coworkers (Scheme 39). It is important to note that using the tetraalkynyl silane **17**, the product of the first hydroboration **V** is not observed through ²⁹Si NMR, but immediately affords a second hydroboration to give the product **18**. Under heating, two intramolecular 1,1-

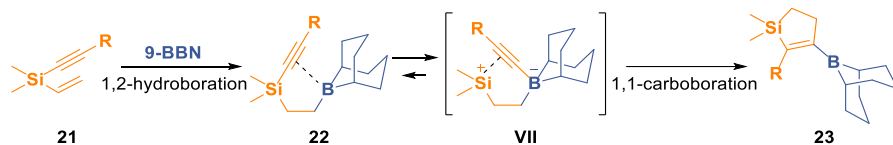
¹⁰⁷ B. Wrackmeyer, O. L. Tok, W. Milius, A. Khan, A. Badshah *Appl. Organomet. Chem.* **2006**, 20, 99–105.

¹⁰⁸ a) B. Wrackmeyer, A. Badshah, E. Molla, A. Mottalib, *J. Organomet. Chem.* **1999**, 584, 98.

b) B. Wrackmeyer, W. Milius, M. H. Bhatti, S. Ali, *J. Organomet. Chem.* **2003**, 669, 72.

carboboration reactions take place step wisely, showing first the formation of **19** and then of final product **20**.⁴²

As mentioned above, usually harsh reaction conditions are required to perform intermolecular 1,1-carboboration reactions on dialkynylsilanes, therefore limiting the applications. However, it has been observed that some organoboranes such as $B(C_6F_5)_3$, Piers' borane or 9-BBN are able to perform intramolecular 1,1-carboboration reactions in milder conditions. Specifically, Piers' borane and 9-BBN are able to introduce the $-BR_2$ moiety in the respective silane prior to the 1,1-carboboration taking place through 1,2-hydroboration phenomena.¹⁰⁹ All these elements allowed to set up the stage for the design of a selective 1,2-hydroboration-1,1-carboboration sequence in which an efficient regioselectivity is displayed, exploiting the better affinity of 9-BBN for vinyl groups in comparison to alkynyl groups.¹¹⁰



Scheme 40: Scheme for the selective 1,2-hydroboration-1,1-carboboration sequence on alkynyl(dialkyl)vinyl silanes.

Indeed, employing an alkynyl(dimethyl)vinyl silane (**21**) as substrate, it has been observed that the hydroborating 9-BBN reacted selectively with the vinyl moiety, placing the boryl unit at the terminal carbon atom. At this point the stereochemistry is set for the intramolecular Si-C triple bond activation (**VII**) followed by the 1,1-carboboration leading to the 1-silacyclopent-2-ene derivative **23** (Scheme 40).⁴⁰

¹⁰⁹ a) H. C. Brown, E. F. Knights, C. G. Scouten *J. Am. Chem. Soc.* **1974**, 96, 7765–7770. b) H. C. Brown *Organic Syntheses via Boranes*, Wiley **1975**.

¹¹⁰ a) B. Wrackmeyer, O. L. Tok, E. V. Klimkina, W. Milius *Eur. J. Inorg. Chem.* **2010**, 2276–2282. b) B. Wrackmeyer, E. V. Klimkina, W. Milius, C. Butterhof, K. Z. Inzenhofer *Naturforsch. Teil B.* **2014**, 1269–1289.

As can be seen, 1,1-carboboration has proven to be a solid approach for the preparation of silaheterocycles, allowing the construction of rings with different sizes and in presence of several substituents, being the only requirement the presence of two unsaturated moieties on the silicon atom. It was even possible to perform the 1,1-carboboration reaction on non-silylated alkynes when strongly acidic boranes were employed.¹¹¹ However, the main limitation of this approach is the necessity to use stoichiometric amounts of boranes and the resulting products are air- and moisture-sensitive,¹¹² therefore limiting its application and no examples of main-group-catalyzed 1,1-carboboration of alkynes have been reported to date and only a single metal-catalyzed example is known, which required a diazo coupling partner.¹¹³

4.1.3 Transborylation reactions: rendering classic organoborane reactions catalytic

To propose an answer to the issues mentioned above, it has been proposed to recur to transborylation reactions.

The transborylation reaction concept is based on the controlled redistribution of substituents by σ -bond metathesis about two boron centers and has gathered increasing attention over the years thanks to the possibility of employing it as a turnover step in catalysis, through a combination of stoichiometric borane reactivity and stoichiometric redistribution¹¹⁴ and, among the boranes, the

¹¹¹ A. Bismuto, G. S. Nichol, F. Duarte, M. J. Cowley, S. P. Thomas *Angew. Chem. Int. Ed.* **2020**, 59, 12731–12735.

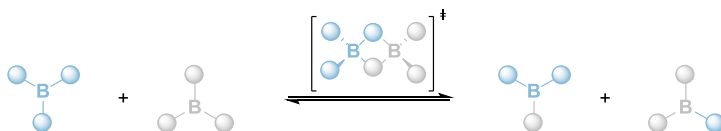
¹¹² J. R. Lawson, V. Fasano, J. Cid, I. Vitorica-Yrezabal, M. J. Ingleson *Dalton Trans.* **2016**, 45, 6060–6070.

¹¹³ Z. Li, J. Sun *Org. Lett.* **2021** 23, 3706–3711.

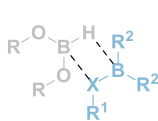
¹¹⁴ A. D. Bage, K. Nicholson, T. A. Hunt, T. Langer, S. P. Thomas *Synthesis* **2023**, 55 (01), 62–74.

most employed as stoichiometric turnover reagents are usually catecholborane (HBcat) and pinacolborane (HBpin). More in detail, the broadest application of σ -metathesis in the p-block is in the exchange between two boron atoms and transborylation can be defined as an *isodesmic σ -bond metathesis between two boron-containing species, where the group of interest is exchanged from one boron to another boron atom*, therefore making this process far different from ligand exchange or transesterification and more similar to a transmetalation process (Scheme 41).

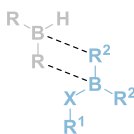
a) Stoichiometric Redistribution of Boranes



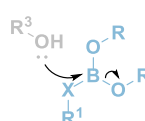
b) Mechanisms Comparison of B/B σ -bond Metathesis and Transesterification



Transborylation
B-X bond broken



Ligand Redistribution
B-X bond maintained

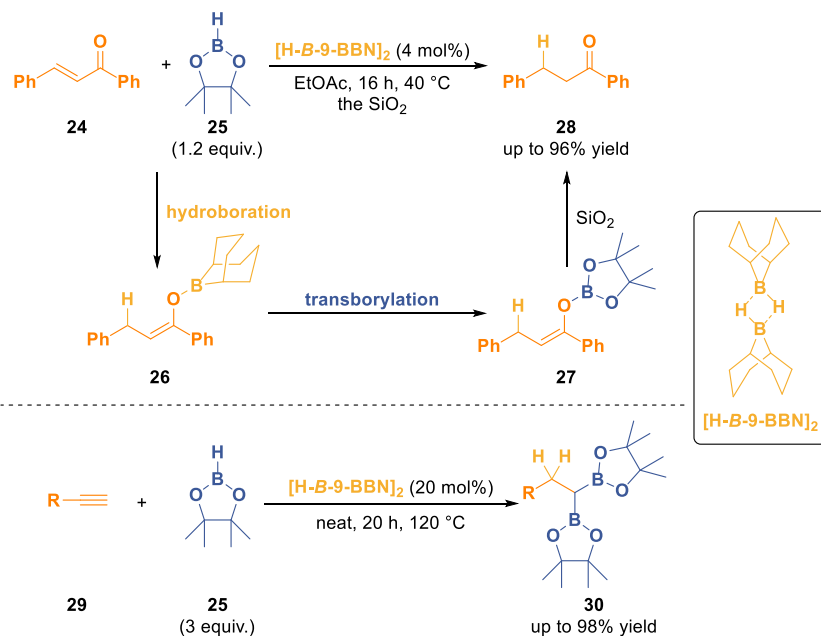


Transesterification
No B-B bond exchange

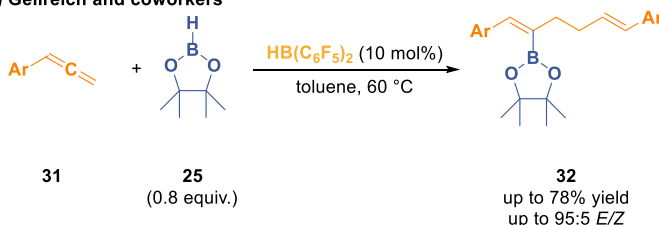
Scheme 41: a) Stoichiometric borane redistribution; b) Mechanisms of boron-boron σ -bond metathesis and transesterification.

As shown by Thomas and coworkers, through this method it is possible to employ dioxaborolane derivatives such as pinacolborane **25** as reagents to perform hydroboration reactions using $[\text{H-B-9-BBN}]_2$ as catalyst, when normally dioxaborolane compounds are not able to carry out this kind of reduction. In the case of chalcone **24**, the first step is carried out by $[\text{H-B-9-BBN}]_2$ that performs the hydroboration reaction forming the intermediate **26**. At this point, the more acidic pinacolborane performs the transborylation producing **27** and regenerating the $[\text{H-B-9-BBN}]_2$.

a) Thomas and coworkers



b) Gellreich and coworkers

**Scheme 42:** Selected examples of transborylation reactions.

The reaction work-up with silica allows the removal of the pinacol borane and the isolation of the saturated ketone **28** (Scheme 42a).¹¹⁵ This reduction approach proved to be effective on alkynyl moieties too, leading to an easy formation of gem-diboryl alkanes (**30**).¹¹⁶

Therefore, transborylation has proven to be a solid way to render classic organoborane reactions catalytic (Scheme 42a-b) and it was

¹¹⁵ K. Nicholson, T. Langer, S. P. Thomas *Org. Lett.* **2021**, 23, 2498–2504.

¹¹⁶ J. H. Docherty, K. Nicholson, A. P. Dominey, S. P. Thomas *ACS Catal.* **2020**, 10, 4686–4691.

even applied for C–C bond forming reactions, however, Gellrich's borane-catalyzed reductive dimerization of allenes is the only example where a C–C bond is formed, and the turnover reagent (pinacolborane) is maintained in the isolated product (Scheme 42b), allowing eventual down-stream transformations and functionalisations.⁴⁵

4.2 Aim of the project

This project aimed to propose as reliable approach toward the synthesis of four- and five-membered silaheterocycles through merging the 1,2-hydroboration-1,1-carboboration carried out in presence of [H-B-9-BBN]₂ with the use of pinacol borane as transborylating reagent. Indeed, successful, catalytic carboboration has been achieved on a variety of functionally diverse silyl-alkynes, using [H-B-9-BBN]₂ in catalytic amount and a transborylation enabled turnover. Mechanistic studies, including ¹³C-labelling, computational studies, and single-turnover experiments, suggest a reaction pathway proceeding by 1,2-hydroboration, 1,1-carboboration, and transborylation to release the alkenyl boronic ester product and regenerate the borane catalyst.

4.3 Development and Outcomes

4.3.1 Reaction development and optimisation

The exploration of the reactivity was conducted on the phenylacetynyl(dimethyl)vinyl silane **21a** and it was found that it rapidly reacts with stoichiometric 9-borabicyclo[3.3.1]nonane dimer [H-B-9-BBN]₂ at room temperature to give the air- and moisture sensitive 1,1-carboboration product **23a**.³⁹ On the basis of this outcome, it has then been thought that the transborylation step would be rate-limiting, so a highly Lewis acidic dioxaborolane

would be required to effect turnover, at a rate comparable to 1,1-carboboration.¹¹⁷

Table 15: Optimisation of reaction conditions.

	21a			33a			34a	
Entry	Solvent	B-catal.	B-catal. loading	HB(OR) ₂	HB(OR) ₂ eq.	T (°C)	33a (%)	34a (%)
1	THF	[H-B-9-BBN] ₂	10 mol%	HBcat	1.2	80	11	9
2	THF	H-BCy ₂	10 mol%	HBcat	1.2	80	traces	17
3	THF	BCl ₃	10 mol%	HBcat	1.2	80	traces	16
4	THF	[H-B-9-BBN] ₂	10 mol%	HBpin	1.2	80	traces	0
5	THF	[H-B-9-BBN] ₂	5 mol%	HBpin	2	80	21	0
6	neat	[H-B-9-BBN] ₂	5 mol%	HBpin	1	80	3	0
7	neat	[H-B-9-BBN] ₂	5 mol%	HBpin	2	80	14	0
8	neat	[H-B-9-BBN] ₂	5 mol%	HBpin	3	80	17	0
9	neat	[H-B-9-BBN] ₂	5 mol%	HBpin	5	80	21	0

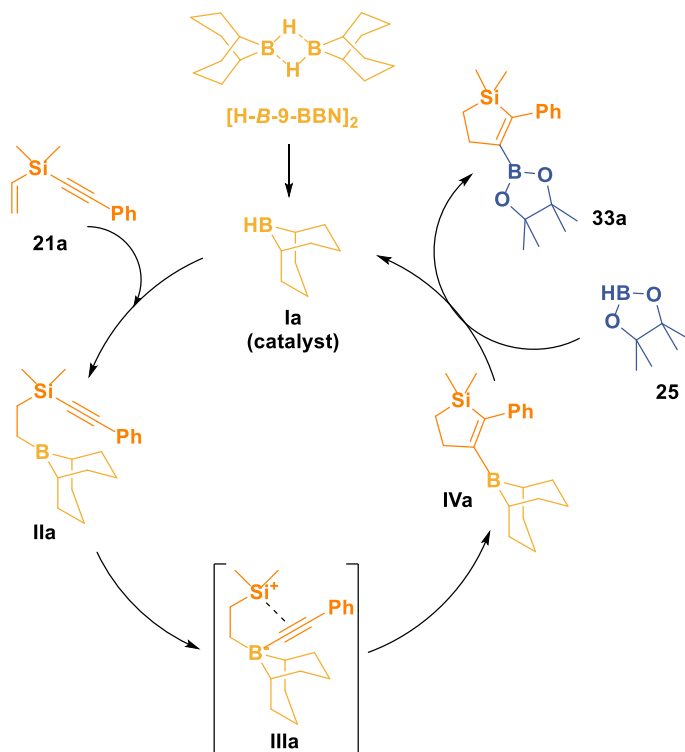
¹¹⁷ a) Y. Suseela, A. S. B. Prasad, M. Periasamy *J. Chem. Soc. Chem. Commun.* **1990**, 446–447. b) Y. Suseela, M. Periasamy *J. Organomet. Chem.* **1993**, 450, 47–52. c) A. Arase, M. Hoshi, A. Mijin, K. Nishi *Synth. Commun.* **1995**, 25, 1957–1962.

10	neat	[H-B-9- BBN] ₂	5 mol%	HBpin	5	100	70	0
11	neat	[H-B-9- BBN] ₂	5 mol%	HBpin	5	110	80	traces
12	neat	[H-B-9- BBN] ₂	5 mol%	HBpin	1.2	110	80	traces

However, when catecholborane (HBcat) was trailed using [H-B-9-BBN]₂ as catalyst, the yield of the desired product **33a** was low and the presence of an alkyl boronic ester (**34a**) was detected, meaning that, instead of cyclization, alkene hydroboration was followed immediately by transborylation, therefore ruining the reactivity of the system (Table 15, Entry 1).

When alternative boron reagents as catalysts have been used, only trace amounts of cyclization were obtained, observing predominantly the alkene hydroboration-transborylation product **34a** (Entries 2-3). It was then clear that the problem was the too fast transborylation and, to slow down the transborylation on the intermediate trialkylborane **34a'** (precursor of the boronic ester **34a**), in order to increase the selectivity towards the cyclisation, the less acidic pinacol borane (HBpin) **25** was tested. As shown in Entry 4, using HBpin, the formation of the linear alkyl boronic ester **34a** was suppressed: the reason can be explained by the fact that the slower rate of transborylation using HBpin, compared to HBcat, enabled an increased amount of cyclization to proceed and thus transborylation now occurred at the cyclized alkenyl borane.

With these useful informations in hand, an optimisation was carried out: increasing the amount of HBpin to 2 equivalents allowed to obtain **33a** in 21% yield even using lesser amount of catalyst (Entry 5) in THF.



Scheme 43: Proposed reaction mechanism.

Interesting results were obtained performing the reaction in neat conditions: keeping the catalyst loading to 5 mol% the desired product was detected, even though in very few amounts (Entry 6). Gradually changing pinacol borane amount and temperature (Entries 7-11) it has been possible to increase the yield to a good yield, reaching the 80% and the best conditions, were found to be in absence of solvent, with 1.2 equivalents of pinacol borane at 110 °C and with a catalyst loading of 5 mol%, affording the desired product **33a** in 80% yield with full control of chemo- and regioselectivity (Entry 12). Basing on the previous finding and the outcomes obtained, the proposed mechanism is reported in Scheme 43: once the 9-BBN catalyst **1a** is generated from the corresponding dimer, it undergoes 1,2-hydroboration on the vinyl group on **21a**, generating the intermediate **IIa**. **IIa** is then able to

rearrange, passing through the activated specie **IIIa**, and forming the intermediate **IVa** through 1,1-carboboration. At this point, **IVa** can undergo transborylation with pinacol borane **25**, releasing the desired dihydrosilolyl boronic ester product **33a** and regenerating the catalyst.

4.3.2 Substrate Scope

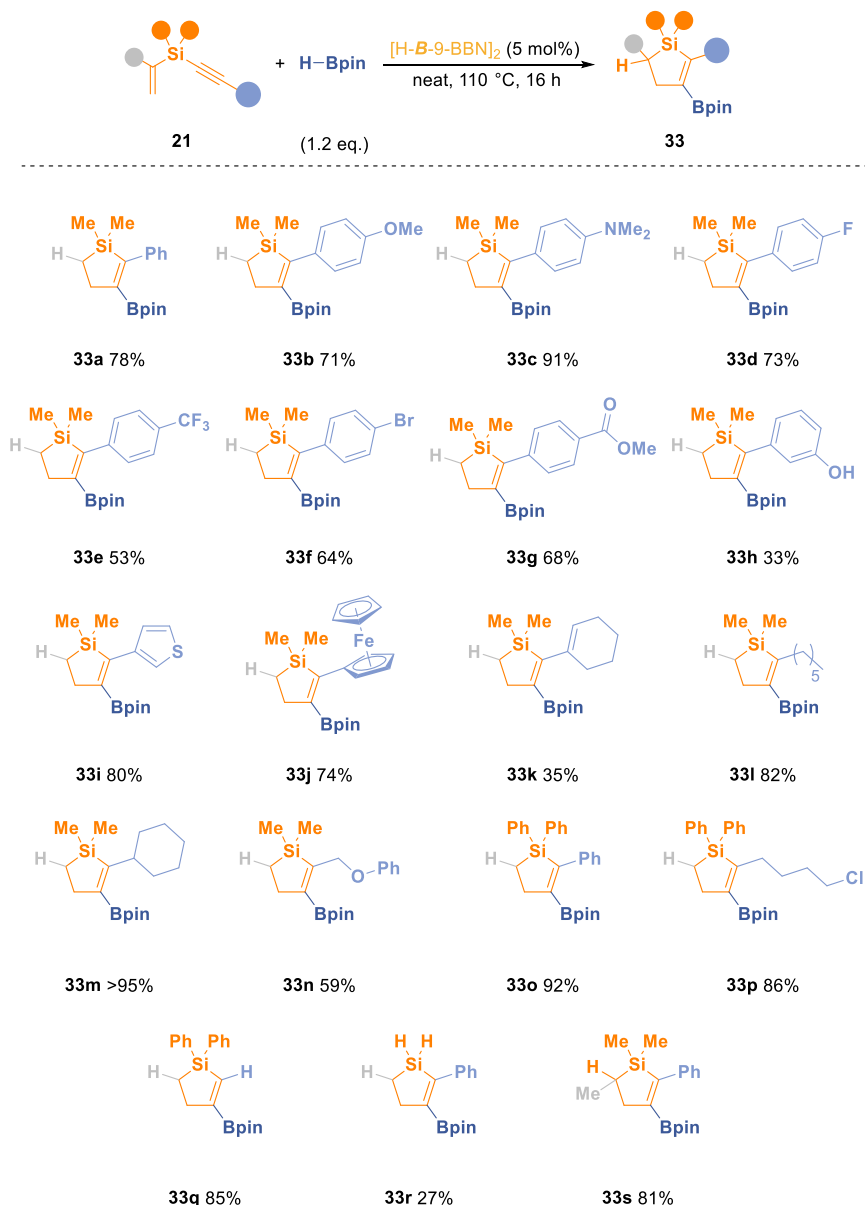
With the optimised conditions in hand, the generalities of the reaction were investigated (Scheme 44): aromatic substituents on the alkyne were well tolerated, with Lewis basic, electron-donating substituents such as anisole **33b** and aniline derivatives **33c** giving excellent yields of the corresponding 2,3-dihydrosilolyl boronic ester as a single regioisomer. Complete control of stereoselectivity and good yields were observed also in presence of halogenated aromatic substituents **33d-f** and in presence of an ester moiety as well, with a complete control on the chemoselectivity, as shown when the substrate **21g** was employed.¹¹⁸ Phenol-substituted alkyne **21h** gave a fair yield, requiring an extra equivalent of HBpin to act as a traceless protecting group.¹¹⁹

Other heterocycles, such as thiophene **33i** and ferrocene **33j** gave high yields, the latter being characterized by X-ray crystallography, validating the assumed substitution pattern. When the 1,3-enyne **21k** was employed, it underwent selective cyclization in a fair yield and good chemoselectivity for reaction at the alkyne. Moreover, where cyclization was observed to be slow, due to competition of the alkene hydroboration, the selectivity for cyclization of could be

¹¹⁸ A. Moreno González, K. Nicholson, N. Llopis, G. S. Nichol, T. Langer, A. Baeza, S. P. Thomas *Angew. Chem. Int. Ed.* **2022**, 61, e202209584.

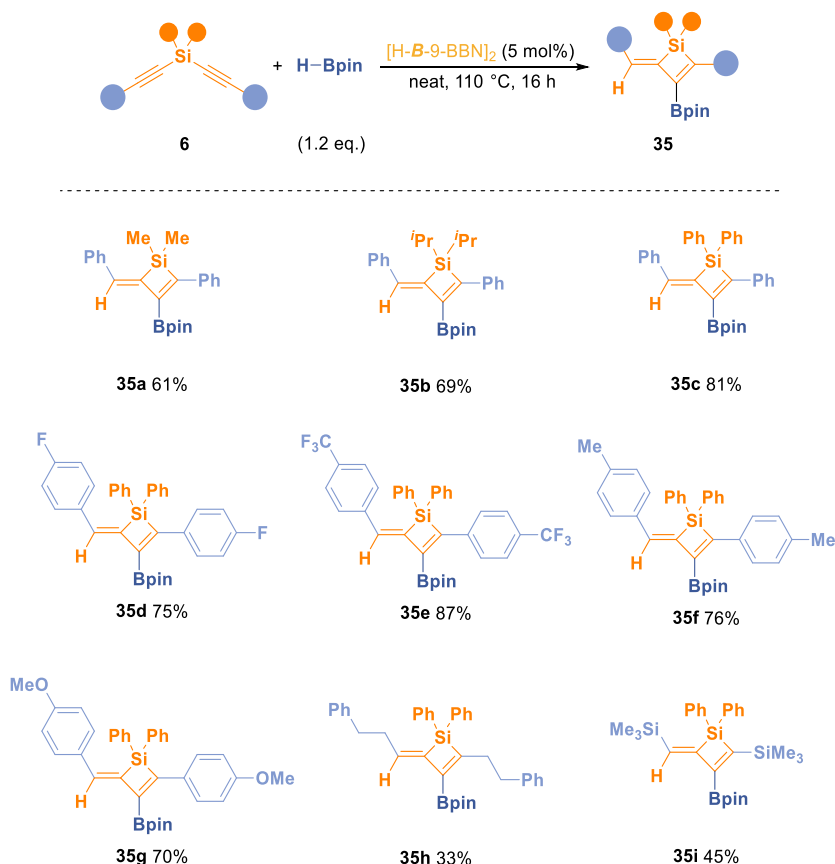
¹¹⁹ a) S. M. Preshlock, D. L. Plattner, P. E. Maligres, S. W. Krska, R. E. Maleczka Jr., M. R. Smith III *Angew. Chem. Int. Ed.* **2013**, 52, 12915–12919. b) Y.-M. Tian, X.-N. Guo, Z. Wu, A. Friedrich, S. A. Westcott, H. Braunschweig, U. Radius, T. B. Marder *J. Am. Chem. Soc.* **2020**, 142, 13136–13144.

controlled by slow addition of HBpin; primary **21l** and secondary **21m** alkyl-alkynes gave excellent yields of the corresponding silylheterocycles **33l-m** using this method, while in case of an ether-substituted alkyl group, such as in **33n**, the slow addition was not necessary.



Scheme 44: Generalities of the reaction on alkynylvinyl silanes.

Change of the substitution on the silane to diphenyl **33o** afforded improved yields, showing that the reaction in this case can tolerate the presence of an alkyl chloride **33p** and terminal alkyne **33q** under standard conditions. The dihydride **33r** gave a reduced yield, showing that substitution on the silane promoted the reaction. Using a 1,1-disubstitued alkene such as **21s** gave an excellent yield of a highly substituted 2,3- dihydrosilolyl boronic ester **33s**. Unluckily, attempts to increase the size of the ring using a 4-sila-1,5-enyne were unsuccessful, resulting in a too strong competitive transborylation over the 1,1-carboboration, therefore affording mainly the alkene boronic ester.



Scheme 45: Generalities of the reaction on dialkynyl silanes.

At this point the attention was turned on the intramolecular 1,1-carboboration of *bisalkynylsilanes* (Scheme 45), a class of substrates already demonstrated to be suitable from the reports of Wrackmeyer and Tok. Dimethyl-di(phenylethynyl)silane **6a** reacted to give a good yield of the corresponding air- and moisture-stable, 4-membered silylcyclobut-2-enyl boronic ester **35a**, a class of compounds previously unreported in catalysis. The diisopropyl product **35b** was obtained gave a better yield compared to **35a**, presumably due to increased stability of an intermediate silicon cation: this theory appears to be confirmed by the further increase in yield obtained when the di(phenylacetynyl)diphenyl silane substrate **6c** has been used. An aryl fluoride **6d** gave an excellent yield of the corresponding boronic ester **5d** and exhibited the same tolerance as the ene-yne reaction. For the aryl trifluoromethyl substituted substrate **6e**, the catalyst loading was doubled to give an excellent yield of the corresponding boronic ester **35e**. Electron donating groups, such as the methyl- **6f** and methoxy-substituted arenes **6g** gave good yields of the corresponding boronic esters

35f-g. Compared to the alkynyl-arene-containing substrates, the alkyl-alkynyl substrate **6h** gave a reduced yield, while the silylcyclobut-2-enyl boronic ester **35i** has been afforded in a mediocre yield probably due to competing carboboration on the trimethylsilyl groups.

4.3.3 Database Analysis and Downstream Reactivity

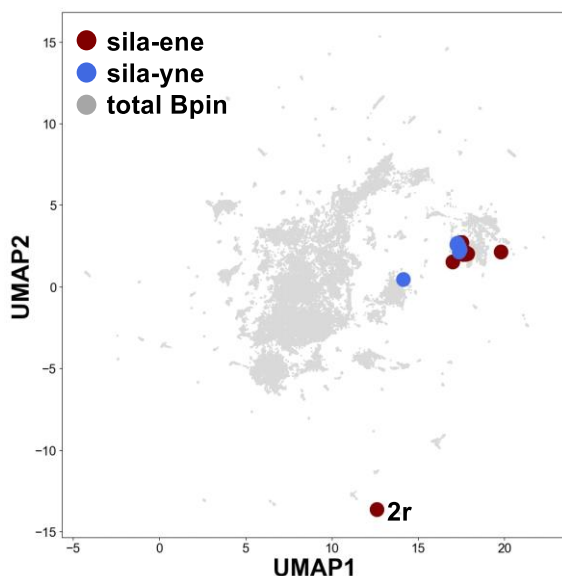


Figure 22: Uniform Manifold Approximation (UMAP).

To assess the novelty of these 2,3-dihydrosilolyl and silylcyclobut-2-enyl boronic esters, an assessment of the chemical space covered by existing pinacol boronic esters was carried out and, using the Reaxys® database,¹²⁰ every compound containing a pinacol boronic ester, which had been characterized by NMR spectroscopy was obtained as simplified molecular-input line-entry system (SMILES) strings. These strings have been then corrected in order to remove duplicates and compounds with incorrect SMILES, affording a total space of 51325 pinacol boronic esters. Two-dimensional descriptors were calculated using Mordred¹²¹ and filtered (see Section 4.5 - Experimental section) to give a total of 1420 descriptors for the Reaxys compounds and the substrates synthesized here. These descriptors were reduced to a

¹²⁰ "Reaxys," can be found under <https://www.reaxys.com/>.

¹²¹ H. Moriwaki, Y.-S. Tian, N. Kawashita, T. Takagi *J. Cheminform.* **2018**, 10, 4.

two-dimensional space using the Uniform Manifold Approximation (UMAP, see Figure 22),¹²²

which showed that the 2,3-dihydrosilolyl and silylcyclobut-2-enyl boronic esters clustered away from the majority of pinacol boronic esters, into less explored chemical space. The dihydride substrate **33r**, sat in an empty region of chemical space, representing a motif for further exploration.

Being these dihydrosilolyl and silylcyclobut-2-enyl boronic esters a completely new class of compounds, to gain insight for their possible application, their downstream reactivity has been investigated (Scheme 46).

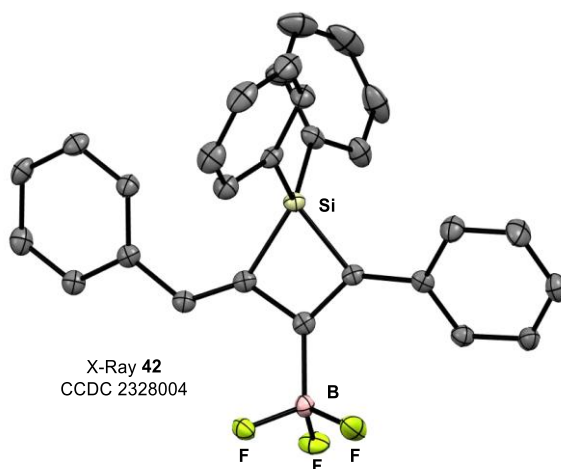


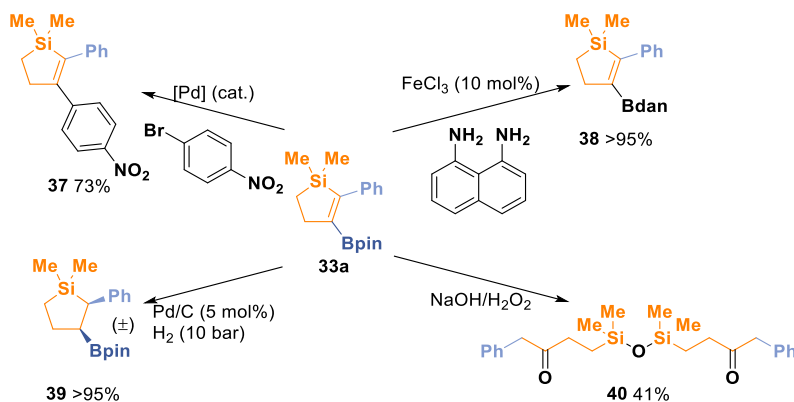
Figure 23: Crystal structure of potassium trifluoroborate salt **42**. Thermal ellipsoids shown at 50 % probability level. Hydrogen and potassium atoms, and solvent omitted for clarity. Two molecules were present in the unit cell, one omitted for clarity.

The dihydrosilolyl boronic ester **33a** underwent a Suzuki-Miyaura coupling successfully to give the 2,3-dihydrosilolyl arene **37** and tranesterification of the Bpin group to 1,8-diaminonaphthalene (Bdan) **38** proceeded with good yields.¹²³

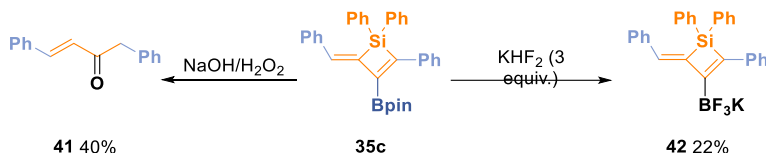
¹²² L. McInnes, J. Healy, J. Melville *arXiv* **2020**, DOI 10.48550/arXiv.1802.03426.

¹²³ a) S. S. Chissick, M. J. S. Dewar, P. M. Maitlis *J. Am. Chem. Soc.* **1961**, 83, 2708–2711. b) H. Noguchi, K. Hojo, M. Sugimoto *J. Am. Chem. Soc.* **2007**, 129, 758–759.

5 mem. derivatization



4-mem. derivatization



Scheme 46: Downstream reactivity explored.

Similarly, an excellent yield has been obtained in the reduction of the alkene also to give the *cis*-boryl-silolane **39**,¹²⁴ while oxidation of the silolyl boronic ester **33a** under basic conditions ($NaOH/H_2O_2$) gave an unusual ringopened β -silyl-ketone dimer **40**. On the other hand, silylcyclobut-2-enyl boronic ester **35c** was converted to the potassium trifluoroborate salt **42** in a low yield but allowed for characterization by X-ray diffraction to confirm the structure and its substitution pattern and that the (*Z*)-alkene was obtained (Figure 23). Oxidation of the silylcyclobut-2-enyl boronic ester **5c** under standard conditions ($NaOH/H_2O_2$) gave a ringopened enone **41** in moderate yield (40%).

¹²⁴ S. Nishimura, *Handbook of Heterogeneous Catalytic Hydrogenation For Organic Synthesis*, Wiley, New York, 2001.

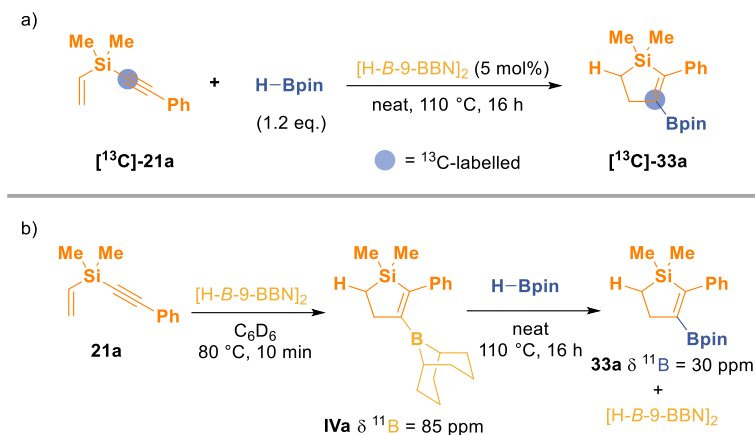
4.3.4 Mechanism Studies: Isotope Labeling

The mechanism of 1,1-carboboration of group 14 alkynes was proposed to occur by donation of the R_3E-C alkynyl group to the empty p-orbital of the trialkylborane, to give a zwitterionic tetracoordinate boronate specie and an alkyne-coordinated cation, $[R_3M]^+$. This ion pair was proposed to undergo a 1,2-metallate rearrangement to give the 1,1-carboboration product. Intriguingly, the zwitterionic intermediates have been isolated and characterized where $M = Sn$ and Pb ,¹⁰³ but there has been no such intermediate characterized where $M = Si$. In the case of non-activated alkyne 1,1-carboboration, a zwitterionic intermediate has been isolated and characterized between ferrocenylacetylene and $B(C_6F_5)_3$.¹¹²

Therefore, in order to gain insights on the proposed mechanism (see Scheme 43), ^{13}C -labelling experiments have been carried out: dimethyl(phenyl(1- ^{13}C ethynyl))(vinyl)silane [^{13}C]-**21a** was synthesized and reacted under standard conditions to track any carbon migration (Scheme 47a). The ^{13}C -labelled product [^{13}C]-**33a** was analyzed by ^{13}C NMR spectroscopy and found to be exclusively enriched in the 3-position, alpha to the boron, suggesting that after hydroboration of the alkene, exchange of the alkynyl group between boron and silicon is regiospecific and therefore supporting Wrackmeyer and co-workers' original hypothesis.

It was then decided to proceed to determine if transborylation occurred before or after cyclization (Scheme 47b) and therefore single-turnover experiments were carried out: exposure of $[H-B-9-BBN]_2$ to an excess of dimethyl(phenylethynyl)(vinyl)silane **21a** in C_6D_6 at 80 °C gave complete conversion to the *B*-9-BBN-substituted 2,3-dihydrosilole **IVa**, by ^1H and ^{11}B NMR spectroscopy within 10 minutes and, after removal of solvent, adding an equivalent of HBpin and heating to 110 °C for 16 h, it has been

observed the presence of the Bpin-substituted 2,3-dihydrosilole **33a** by ^1H and ^{11}B NMR spectroscopy.



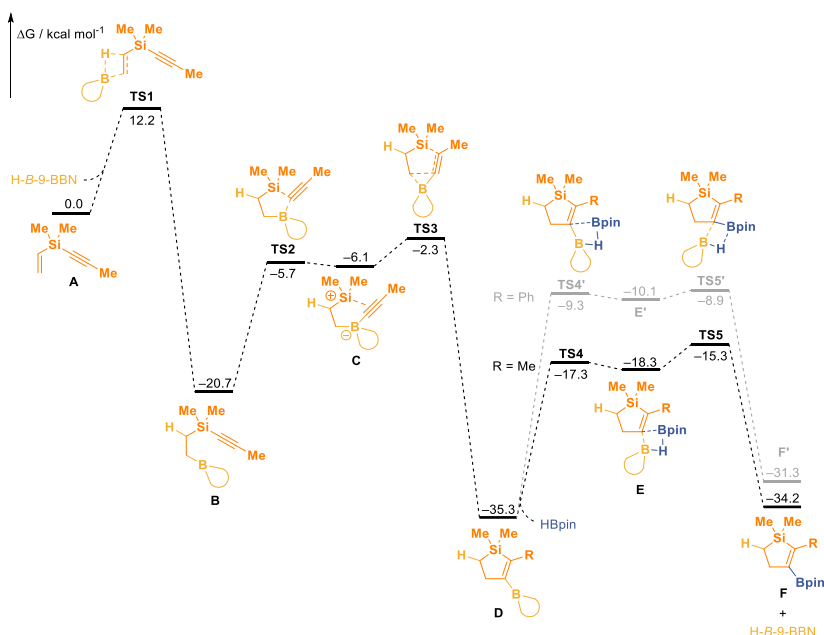
Scheme 47: Mechanism studies on 1-Ph-acetynyl(dimethyl)vinylsilane **21a**.

4.3.5 Mechanism Studies: DFT Calculations

The mechanism was probed further using gas-phase density functional theory (DFT) calculations (M06-2X(D3)/Def2-TZVP//M06-2X(D3)/6-31G(d,p)).

Starting from the dimethyl(1-propynyl)(vinyl)silane **A**, hydroboration from H-B-9-BBN monomer proceeded with a small free energy barrier (**TS1** 12.2 kcal mol⁻¹) giving the alkylborane **B** (Scheme 48) that then undergoes 1,1-carboboration as predicted by Wrackmeyer, donating the alkynyl group and generating a highly zwitterionic intermediate **C**. This intermediate is then able to undergo cyclization with migration of the silicon with a moderate overall barrier (**TS3** 18.4 kcal mol⁻¹), consistent with the rapid observed reactivity (<10 minutes at 80 °C), therefore generating the 2,3-dihydrosilolyl borane **D**. As with previous examples, transborylation with HBpin was found to occur through a highly three-center-two-electron-bound intermediate **E** in an endergonic process and giving a relatively small overall barrier

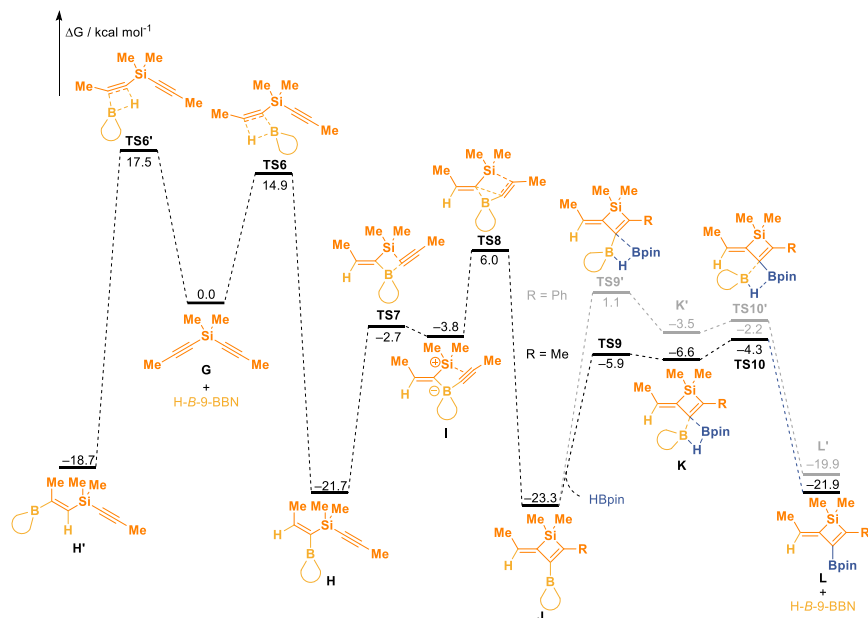
(**TS5** 20.0 kcal mol⁻¹),¹²⁵ inconsistent with the need for elevated reaction temperatures (110 °C).



Scheme 48: DFT-computed free energy values (M06-2X(D3)/Def2-TZVP//M06-2X(D3)/6-31G(d,p)) for 1,1-carbaboration of alkenyl(alkynyl)silanes.

However, when the barrier has been calculated for the phenyl-substituted 2,3-dihydrosilolyl borane **D'-F**, consistency with the observed experimental reactivity has been observed (**TS5'** 26.6 kcal mol⁻¹), indicating a strong steric-dependence on the rate of transborylation. Moreover, the overall free-energy path was also calculated for dimethyl-di(1-propynyl)silane **G** (Scheme 49). A relatively small barrier was observed for the 1,2-hydroborylation **TS6** 14.9 kcal mol⁻¹) to give the *gem*-boryl-silylalkene **H**. Interesting, but not unexpected, the calculated barrier for the opposed regioselectivity was found to be larger (**TS6'** 17.5 kcal mol⁻¹), consistent with the experimental observations.

¹²⁵ a) F. Meger, A. C. W. Kwok, F. Gilch, D. R. Willcox, A. J. Hendy, K. Nicholson, A. D. Bage, T. Langer, T. A. Hunt, S. P. Thomas *Beilstein J. Org. Chem.* **2022**, *18*, 1332–1337.



Scheme 49: DFT-computed free energy values (M06-2X(D3)/Def2-TZVP//M06-2X(D3)/6-31G(d,p)) for 1,1-carboboration of bis-alkynylsilanes.

1,1-Carboboration to the silylcyclobut-2-enyl borane **J** proceeded through a similar path as before, even though through a much higher free energy barrier (**TS8** 27.7 kcal mol⁻¹), but anyway as expected and consistent with the findings of Wrackmeyer.¹²⁶ As in the case of intermediate **D**, the transborylation with HBpin has been found dependent on the steric bulk of the β -substituent: from the methyl-substituted silylcyclobut-2-enyl borane **J**, the barrier was low (**TS10** 19.0 kcal mol⁻¹), and elevated for the phenyl-substituted silylcyclobut-2-enyl borane **J'** (**TS9'** 24.4 kcal mol⁻¹). However, differing from the formation of the five-membered silyl-hetrocycle, in this process the rate-determining step has been found to be the 1,1-carboboration step, independently from the substituents.

¹²⁶ B. Wrackmeyer, E. Khan, S. Bayer, K. Shahid *Zeitschrift für Naturforsch. B* **2007**, 62, 1174–1182.

4.4 Conclusions

In conclusion, a novel use of boron in catalysis has been developed to mimic transition metal reactivity,¹²⁷ reshaping stoichiometric reactions in a catalytic fashion and proving to have unique reactivities.¹²⁸ Here, it has been demonstrated how transborylation catalysis can be used to synthesize building blocks with novel reactivity, and that occupy unexplored regions of chemical space.

These complex chemical spaces, such as four- and five-membered silole boronic esters, were synthesized from easy-to-prepare dialkynyl- and alkynylvinyl-silanes with high yields and complete control on the chemo- and regio-selectivity. Moreover, the new products obtained were fully characterised and proved to be air- and moisture-stable, suitable for undergoing further transformations as shown by the downstream reactions carried out.

The findings given here also represent the first step in turning the wide array of stoichiometric 1,1-carboboration reactions into usable catalytic systems, opening new perspectives towards new catalytic systems.

4.5 Experimental Section

General Information

Reaction setup: All reactions were performed in oven (185 °C) and/or flame dried glassware. All glassware was cleaned using base (KOH, *i*PrOH) and acid (HCl(aq)) baths. All reported reaction temperatures correspond to ambient room temperature, which was approximately 20 °C.

¹²⁷ a) P. P. Power, *Nature* **2010**, 463, 171–177. b) A. D. Bage, K. Nicholson, T. A. Hunt, T. Langer, S. P. Thomas, *Synthesis* **2022**, 55, 62–74. c) D. R. Willcox, S. P. Thomas, *Beilstein J. Org. Chem.* **2023**, 19, 325–348.

¹²⁸ a) C. Weetman, S. Inoue, *ChemCatChem* **2018**, 10, 4213–4228. b) L. C. Wilkins, R. L. Melen, *Coord. Chem. Rev.* **2016**, 324, 123–139.

NMR spectroscopy: ^1H , ^2D , ^{13}C , ^{19}F , ^{29}Si , and ^{11}B spectra were recorded on Bruker Avance III 400 and 500 MHz; Bruker PRO 500 MHz; Bruker Avance I 600 MHz spectrometers. Chemical shifts are reported in parts per million (ppm). ^1H and ^{13}C NMR spectra were referenced to the residual solvent peak (CDCl_3 : 7.26 ppm). Multiplicities are indicated by app. (apparent), br. (broad), s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), sext. (sextet), sept. (septet), non. (nonet). Coupling constants, J , are reported in Hertz and rounded to the nearest 0.1 Hz. Integration is provided. ^{13}C NMR spectra are decoupled from the proton channel.

Chromatography: Column chromatography was carried out on a Teledyne ISCO CombiFlash NextGen 300+ using RediSep Rf normal phase silica flash columns (12,

25, 40, or 80 g; 20–40 microns). Substrates were purified using 40/60 petroleum ether

and EtOAc on a gradient of 100:0 to 0:100 with flow rates of 10–110 mL min⁻¹ depending on the size of column and ΔR_f .

Mass Spectrometry: Mass spectrometry (MS) was performed by the University of Edinburgh, School of Chemistry, Mass Spectrometry Laboratory. High resolution mass spectra were recorded on a VG autospec, or Thermo/Finnigan MAT 900, mass spectrometer. Electron Impact (EI+) spectra were performed at 70 eV using methane as the carrier gas, with either a double focusing sector field (DFSf) or time-of-flight (TOF) mass analyzer. Chemical ionization (CI+) spectra were performed with methane reagent gas, with either a double focusing sector field (DFSf) or time-of-flight (TOF) mass analyzer. Electrospray ionization (ESI+) spectra were performed using a time-of-flight (TOF) mass analyzer. Data are reported in the form of m/z (intensity relative to the base peak = 100).

Chemicals: All reagents were purchased from Sigma Aldrich, Alfa Aesar, Acros organics, Tokyo Chemical Industries UK, Fluorochem and Apollo Scientific without further purification. The compounds dimethylbis(phenylethynyl)silane **6a**, diisopropylbis(phenylethynyl)silane **6b**, diphenylbis(phenylethynyl)silane **6c**, and diphenylbis(trimethylsilylethynyl)silane **6i** were prepared according to literature procedure and data were in accordance with those previously reported.¹²⁹

4.5.1 Reaction Optimisation: Additional Experiments

Dimethyl(phenylethynyl)(vinyl)silane (0.250 mmol, 47.0 mg), H-B-9-BBN dimer (0.013 mmol, 3.2 mg, 5 mol%), and HBpin were dissolved in solvent (if applicable) and the reaction was stirred at temperature for 16 hours. All volatiles were removed *in vacuo* and the yield determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

Table 16: Reaction optimisation: additional experiments.

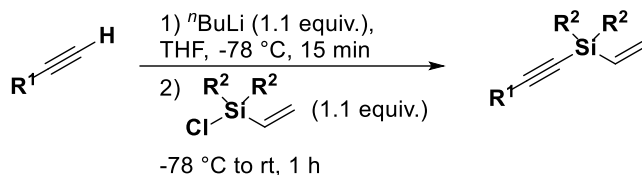
21a $\xrightarrow[\text{solvent, T, 16 h}]{\text{H-Bpin (X eq.)}, [\text{H-B-9-BBN}]_2 (5 \text{ mol\%})}$ 33a

Entry	T (°C)	Solvent (5 M)	HBpin eq.	NMR conv. (%)	Y _{NMR} (%)
1	40	Neat	2	10	3
2	60	Neat	2	20	6
3	80	THF	2	38	21
4	80	DCM	2	50	28
5	80	Hexane	2	35	16
6	80	Toluene	2	35	12

¹²⁹ Y. Cho, Y. M. Jung, Y. T. Park, *Bull. Korean Chem. Soc.* **2021**, 42, 380–387. c) Y. T. Park, *Bull. Korean Chem. Soc.* **2014**, 35, 1825–1831.

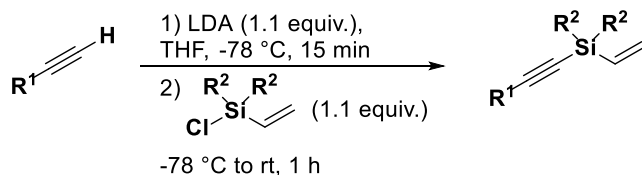
4.5.2 Substrate Synthesis

General Procedure A

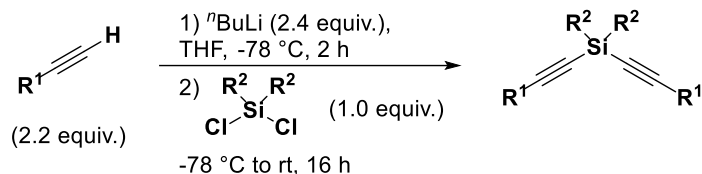


By modification of the method of Wrackmeyer,³⁹ *n*-butyl lithium (5.50 mmol, 2.5 M in hexanes, 2.20 mL) was added dropwise to a stirred solution of alkyne (5.00 mmol) in THF (5.00 mL) at -78°C . After 15 minutes, the chloro-vinyl-silane (5.50 mmol) was added dropwise and the mixture was allowed to warm to room temperature over 1 hour. All volatiles were removed *in vacuo*, the solution diluted with Et₂O (20.0 mL), filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂).

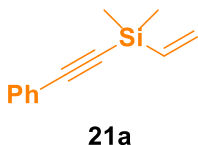
General Procedure B



By modification of the method of Wrackmeyer,³⁹ freshly prepared lithium diisopropyl amide (5.50 mmol, 1.0 M in THF, 5.50 mL) was added dropwise to a stirred solution of alkyne (5.00 mmol) in THF (5.00 mL) at -78°C . After 15 minutes, the chloro-vinyl-silane (5.50 mmol) was added dropwise and the mixture was allowed to warm to room temperature over 1 hour. All volatiles were removed *in vacuo*, the solution diluted with Et₂O (20.0 mL), filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂).

General Procedure C

By modification of the method of Erker,¹³⁰ *n*-butyl lithium (12.0 mmol, 2.5 M in hexanes, 4.80 mL) was added dropwise to a stirred solution of alkyne (11.0 mmol) in THF (5.00 mL) at -78°C . After two hours, the dichlorosilane (5.00 mmol) was added dropwise and the mixture was allowed to warm to room temperature and stirred for 16 hours. All volatiles were removed *in vacuo*, the solution diluted with Et₂O (20.0 mL), filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂).

Dimethyl(phenylethynyl)(vinyl)silane 21a

According to general procedure A, phenylacetylene (40.0 mmol, 4.40 mL), *n*-butyl lithium (44.0 mmol, 2.5 M in hexanes, 17.6 mL), and chloro(dimethyl)vinylsilane (44.0 mmol, 6.10 mL) were reacted in THF (40.0 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 80 g SiO₂, 50 mm Ø, 40/60 petroleum ether) to give dimethyl(phenylethynyl)(vinyl)silane **21a** (6.59 g, 35.4 mmol, 88%) as a colourless oil.

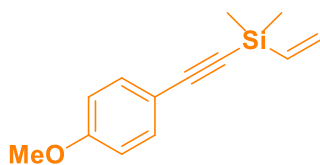
¹H NMR (500 MHz, CDCl₃) δ: 7.52 – 7.47 (m, 2H), 7.36 – 7.28 (m, 3H), 6.22 (dd, *J* = 19.9, 14.5 Hz, 1H), 6.07 (dd, *J* = 14.5, 3.9 Hz, 1H), 5.93 (dd, *J* = 19.9, 3.9 Hz, 1H), 0.34 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ : 136.7, 133.3, 132.2, 128.8, 128.3, 123.1, 106.4, 92.1, -1.3 .

^{29}Si NMR (99 MHz, CDCl_3) δ : -24.7 .

Data were in accordance with those previously reported.³⁹

Dimethyl(4-methoxyphenylethynyl)(vinyl)silane 21b



21b

According to general procedure A, 4-methoxyphenylacetylene (5.00 mmol, 661 mg), *n*-butyl lithium (5.50 mmol, 2.5 M in hexanes, 2.20 mL), and chloro(dimethyl)vinylsilane (5.50 mmol, 759 μL) were reacted in THF (5.00 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO_2 , 50 mm $\varnothing$, 40/60 petroleum ether) to give *dimethyl(4-methoxyphenylethynyl)(vinyl)silane 21b* (503 mg, 2.32 mmol, 46%) as a colourless oil.

^1H NMR (500 MHz, CDCl_3) δ : 7.42 (d, $J = 8.9$ Hz, 2H), 6.82 (d, $J = 8.9$ Hz, 2H), 6.21 (dd, $J = 20.0, 14.5$ Hz, 1H), 6.05 (dd, $J = 14.5, 3.8$ Hz, 1H), 5.91 (dd, $J = 20.0, 3.8$ Hz, 1H), 3.80 (s, 3H), 0.31 (s, 6H).

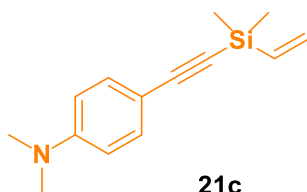
^{13}C NMR (126 MHz, CDCl_3) δ : 160.0, 136.9, 133.7, 133.1, 115.3, 114.0, 106.5, 90.5, 55.4, -1.2 .

^{29}Si NMR (99 MHz, CDCl_3) δ : -25.0 .

IR ν_{max} (film) 2155 (w), 1605 (s), 1507 (s), 1254 (s).

MS (HRMS – EI^+) Found 216.096792 ($\text{C}_{13}\text{H}_{16}\text{OSi}$) requires 216.09649.

Dimethyl(4-*N,N*-dimethylaminophenylethynyl)(vinyl)silane 21c



According to general procedure A, 4-ethynyl-*N,N*-dimethylaniline (3.92 mmol, 571 mg), *n*-butyl lithium (4.31 mmol, 2.5 M in hexanes, 1.73 mL), and chloro(dimethyl)vinylsilane (4.31 mmol, 596 μ L) were reacted in THF (4.00 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give *dimethyl(4-(N,N-dimethylaminophenylethynyl)(vinyl)silane* **21c** (813 mg, 3.54 mmol, 90%) as a pale yellow amorphous solid.

¹H NMR (500 MHz, CDCl₃) δ : 7.35 (d, *J* = 8.9 Hz, 2H), 6.59 (d, *J* = 9.0 Hz, 2H), 6.21 (dd, *J* = 20.1, 14.5 Hz, 1H), 6.03 (dd, *J* = 14.5, 3.7 Hz, 1H), 5.90 (dd, *J* = 20.1, 3.7 Hz, 1H), 2.97 (s, 6H), 0.30 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ : 150.4, 137.3, 133.4, 132.8, 111.7, 109.9, 107.9, 89.2, 40.3, -1.1.

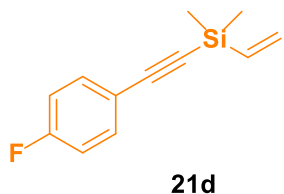
²⁹Si NMR (99 MHz, CDCl₃) δ : -25.5.

IR $\nu_{\max}$ (film) 2139 (w), 1607 (s), 1519 (s), 1359 (br).

MS (HRMS - EI⁺) Found 229.127647 (C₁₄H₁₉NSi) requires 229.12813.

MP (40/60 petroleum ether) 55 – 57 °C.

Dimethyl(4-fluorophenylethynyl)(vinyl)silane **21d**



According to general procedure A, 4-fluorophenylacetylene (5.00 mmol, 601 mg), *n*-butyl lithium (5.50 mmol, 2.5 M in hexanes, 2.20 mL), and chloro(dimethyl)vinylsilane (5.50 mmol, 759 μ L) were reacted in THF (5.00 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether) to give *dimethyl(4-*

fluorophenylethynyl)(*vinyl*)silane **21d** (750 mg, 3.67 mmol, 73%) as a colourless oil.

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ : 7.49 – 7.41 (m, 2H), 6.99 (t, J = 8.7 Hz, 2H), 6.20 (dd, J = 20.0, 14.5 Hz, 1H), 6.06 (dd, J = 14.5, 3.8 Hz, 1H), 5.91 (dd, J = 20.0, 3.8 Hz, 1H), 0.32 (s, 6H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ : 162.8 (d, J = 250 Hz), 136.6, 134.1 (d, J = 8.4 Hz), 133.3, 119.3 (d, J = 3.6 Hz), 115.7, 105.2, 91.9 (d, J = 1.0 Hz), –1.4.

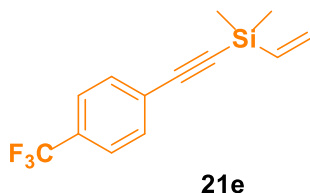
$^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ : –110 (m).

$^{29}\text{Si NMR}$ (99 MHz, CDCl_3) δ : –24.7.

IR ν_{max} (film) 2161 (w), 1600 (w), 1505 (s).

MS (HRMS – EI^+) Found 204.076830 ($\text{C}_{12}\text{H}_{13}\text{FSi}$) requires 204.07651.

Dimethyl(4-trifluoromethylphenylethynyl)(vinyl)silane **21e**



According to general procedure A, 4-trifluoromethylphenylacetylene (5.00 mmol, 816 μL), *n*-butyl lithium (5.50 mmol, 2.5 M in hexanes, 2.20 mL), and chloro(dimethyl)vinylsilane (5.50 mmol,

759 μL) were reacted in THF (5.00 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO_2 , 50 mm $\varnothing$, 40/60 petroleum ether) to give *dimethyl*(4-*trifluoromethylphenylethynyl*)(*vinyl*)silane **21e** (1140 mg, 4.49 mmol, 90%) as a colourless oil.

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ : 7.60 – 7.54 (m, 4H), 6.20 (dd, J = 20.0, 14.5 Hz, 1H), 6.08 (dd, J = 14.5, 3.8 Hz, 1H), 5.92 (dd, J = 20.0, 3.8 Hz, 1H), 0.34 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ : 136.2, 133.6, 132.4, 130.5 (q, J = 32.7 Hz), 126.9 (q, J = 1.4 Hz), 125.3 (q, J = 3.9 Hz), 124.0 (q, J = 272 Hz), 104.6, 95.3, -1.5.

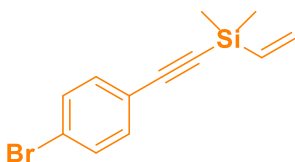
^{19}F NMR (471 MHz, CDCl_3) δ : -62.9 (s).

^{29}Si NMR (99 MHz, CDCl_3) δ : -24.2.

IR ν_{max} (film) 2164 (w), 1615 (w), 1405 (w), 1321 (s).

MS (HRMS - EI^+) Found 254.073712 ($\text{C}_{13}\text{H}_{13}\text{F}_3\text{Si}$) requires 254.07331.

Dimethyl(4-bromophenylethynyl)(vinyl)silane 21f



21f

According to general procedure B, 4-bromophenylacetylene (5.00 mmol, 905 mg), lithium diisopropyl amine (5.50 mmol, 1.0 M in THF, 5.50 mL), and chloro(dimethyl)vinylsilane (5.50 mmol,

759 μL) were reacted in THF (5.00 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO_2 , 50 mm $\varnothing$, 40/60 petroleum ether) to give *dimethyl(4-bromophenylethynyl)(vinyl)silane 21f* (693 mg, 2.61 mmol, 52%) as a pale yellow oil.

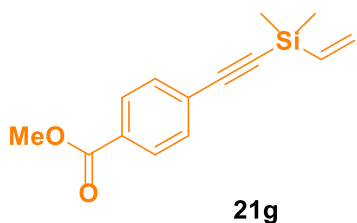
^1H NMR (500 MHz, CDCl_3) δ : 7.44 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 6.20 (dd, J = 20.0, 14.4 Hz, 1H), 6.06 (dd, J = 14.5, 3.8 Hz, 1H), 5.91 (dd, J = 19.9, 3.8 Hz, 1H), 0.32 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ : 136.4, 133.6, 133.4, 131.6, 123.1, 122.1, 105.1, 93.7, -1.4.

^{29}Si NMR (99 MHz, CDCl_3) δ : -24.5.

IR ν_{max} (film) 2159 (w), 1484 (w), 1249 (s).

MS (HRMS - EI^+) Found 263.997489 ($\text{C}_{12}\text{H}_{13}\text{BrSi}$) requires 263.99644.

Methyl 4-((dimethylvinylsilyl)ethynyl)benzoate 21g

According to general procedure B, methyl 4-(ethynyl)benzoate (5.00 mmol, 801 mg), lithium diisopropyl amine (5.50 mmol, 1.0 M in THF, 5.50 mL), and chloro(dimethyl)vinylsilane (5.50 mmol, 759 μ L) were reacted in

THF (5.00 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give methyl 4-((dimethylvinylsilyl)ethynyl)benzoate **21g** (804 mg, 3.29 mmol, 66%) as a colourless oil.

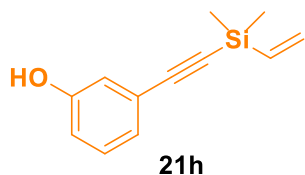
¹H NMR (500 MHz, CDCl₃) δ : 7.96 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 6.19 (dd, J = 20.0, 14.5 Hz, 1H), 6.06 (dd, J = 14.5, 3.8 Hz, 1H), 5.91 (dd, J = 20.0, 3.8 Hz, 1H), 3.90 (d, J = 0.9 Hz, 3H), 0.32 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ : 166.6, 136.2, 133.6, 132.0, 130.0, 129.5, 127.7, 105.2, 95.7, 52.3, -1.5.

²⁹Si NMR (99 MHz, CDCl₃) δ : -24.3.

IR ν_{max} (film) 2159 (w), 1724 (s), 1605 (w), 1272 (s).

MS (HRMS – EI⁺) Found 244.091136 (C₁₄H₁₆O₂Si) requires 244.09141.

Dimethyl(3-hydroxyphenylethynyl)(vinyl)silane 21h

n-Butyl lithium (11.0 mmol, 2.5 M in hexanes, 4.40 mL) was added dropwise to a stirred solution of 3-hydroxyphenylacetylene (5.00 mmol,

545 μ L) in THF (20.0 mL) at -78 ° C. After 30 minutes,

chloro(dimethyl)vinylsilane (11.0 mmol, 1520 μ L) was added dropwise and the mixture was allowed to warm to room temperature over 1 hour. All volatiles were removed *in vacuo*, and the solution was diluted with methanol (10.0 mL) and dichloromethane (10.0 mL). *p*-Toluenesulfonic acid monohydrate (5.50 mmol, 1050 mg) was added and the solution was stirred for 1 hour. The solution was diluted with water (50 mL), extracted with dichloromethane (3×50 mL), dried (MgSO_4), and filtered. The solution was concentrated *in vacuo* and purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO_2 , 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give dimethyl(3-hydroxyphenylethynyl)(vinyl)silane **21h** (825 mg, 4.08 mmol, 82%) as a colourless viscous oil.

^1H NMR (500 MHz, CDCl_3) δ : 7.16 (t, $J = 7.9$ Hz, 1H), 7.05 (dt, $J = 7.6, 1.2$ Hz, 1H), 6.96 (dd, $J = 2.7, 1.4$ Hz, 1H), 6.82 (ddd, $J = 8.2, 2.7, 1.0$ Hz, 1H), 6.20 (dd, $J = 20.0, 14.5$ Hz, 1H), 6.05 (dd, $J = 14.5, 3.8$ Hz, 1H), 5.91 (dd, $J = 20.0, 3.8$ Hz, 1H), 5.65 (br s, 1H), 0.31 (s, 6H).

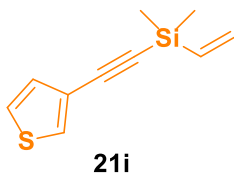
^{13}C NMR (126 MHz, CDCl_3) δ : 155.5, 136.6, 133.3, 129.7, 124.7, 124.2, 118.8, 116.4, 106.0, 92.2, -1.4 .

^{29}Si NMR (99 MHz, CDCl_3) δ : -24.6 .

IR ν_{max} (film) 3480 (br), 2156 (w), 1577 (w), 1478 (w), 1154 (s).

MS (HRMS – EI^+) Found 202.080163 ($\text{C}_{12}\text{H}_{14}\text{OSi}$) requires 202.08084.

Dimethyl(3-thiophenylethynyl)(vinyl)silane **21i**



According to general procedure A, 3-ethynylthiophene (5.00 mmol, 493 μ L), *n*-butyl lithium (5.50 mmol, 2.5 M in hexanes, 2.20 mL), and chloro(dimethyl)vinylsilane (5.50 mmol, 759 μ L) were reacted in THF (5.00 mL). The product

was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO₂, 50 mm Ø, 40/60 petroleum ether) to give *dimethyl(3-thiophenylethynyl)(vinyl)silane* **21i** (654 mg, 3.40 mmol, 68%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ: 7.50 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.24 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.13 (dd, *J* = 5.0, 1.2 Hz, 1H), 6.19 (dd, *J* = 20.0, 14.5 Hz, 1H), 6.05 (dd, *J* = 14.5, 3.7 Hz, 1H), 5.90 (dd, *J* = 20.0, 3.8 Hz, 1H), 0.31 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ: 136.6, 133.3, 130.3, 130.0, 125.3, 122.4, 101.1, 91.9, -1.4.

²⁹Si NMR (99 MHz, CDCl₃) δ: -24.7.

IR $\nu_{\max}$ (film) 2152 (w), 1403 (w), 1249 (w).

MS (HRMS – EI⁺) Found 192.042344 (C₁₀H₁₂SSi) requires 192.04235.

Dimethyl(ferrocenylethynyl)(vinyl)silane **21j**



21j

According to general procedure A, ethynylferrocene (2.50 mmol, 525 mg), *n*-butyl lithium (2.75 mmol, 2.5 M in hexanes, 1.10 mL), and chloro(dimethyl)vinylsilane (2.75 mmol, 370 μ L) were reacted in THF

(2.50 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO₂, 50 mm Ø, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give *dimethyl(ferrocenylethynyl)(vinyl)silane* **21j** (378 mg, 1.29 mmol, 51%) as an amorphous orange solid.

¹H NMR (500 MHz, CDCl₃) δ: 6.19 (dd, *J* = 20.0, 14.5 Hz, 1H), 6.04 (dd, *J* = 14.5, 3.9 Hz, 1H), 5.90 (dd, *J* = 20.0, 3.9 Hz, 1H), 4.45 – 4.44 (m, 2H), 4.20 (s, 5H), 4.19 – 4.18 (m, 2H), 0.28 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ : 137.2, 132.9, 105.6, 88.5, 72.0, 70.3, 68.9, 64.8, -1.1 .

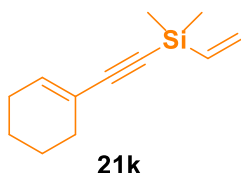
^{29}Si NMR (99 MHz, CDCl_3) δ : -25.3 .

IR ν_{max} (film) 2145 (w), 1411 (w), 1248 (w), 1003 (w).

MS (HRMS – EI^+) Found 294.051926 ($\text{C}_{16}\text{H}_{18}\text{FeSi}$) requires 294.05217.

MP (40/60 Petroleum ether) 63 – 65 $^{\circ}\text{C}$.

Dimethyl(1-cyclohexenylethynyl)(vinyl)silane **21k**



According to general procedure A, 1-ethynylcyclohexene (5.00 mmol, 588 μL), *n*-butyl lithium (5.50 mmol, 2.5 M in hexanes, 2.20 mL), and chloro(dimethyl)vinylsilane (5.50 mmol, 759 μL) were reacted in THF

(5.00 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO_2 , 50 mm $\varnothing$, 40/60 petroleum ether) to give *dimethyl(1-cyclohexenylethynyl)(vinyl)silane* **21k** (599 mg, 3.15 mmol, 63%) as a colourless oil.

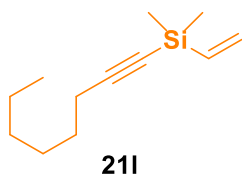
^1H NMR (500 MHz, CDCl_3) δ : 6.20 (tt, $J = 4.0, 1.8$ Hz, 1H), 6.14 (dd, $J = 20.0, 14.5$ Hz, 1H), 6.00 (dd, $J = 14.5, 3.8$ Hz, 1H), 5.84 (dd, $J = 20.0, 3.9$ Hz, 1H), 2.16 – 2.06 (m, 4H), 1.65 – 1.54 (m, 4H), 0.24 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ : 137.1, 136.7, 132.9, 120.8, 108.6, 88.8, 29.2, 25.8, 22.3, 21.6, -1.2 .

^{29}Si NMR (99 MHz, CDCl_3) δ : -25.4 .

IR ν_{max} (film) 2147 (w), 1436 (w), 1402 (w), 1247 (w).

MS (HRMS – EI^+) Found 190.117810 ($\text{C}_{12}\text{H}_{18}\text{Si}$) requires 190.11723.

Dimethyl(1-octynyl)(vinyl)silane **21l**

According to general procedure A, 1-octyne (5.00 mmol, 738 μ L), *n*-butyl lithium (5.50 mmol, 2.5 M in hexanes, 2.20 mL), and chloro(dimethyl)vinylsilane (5.50 mmol, 759 μ L) were reacted in THF (5.00 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether) to give *dimethyl(1-octynyl)(vinyl)silane* **21l** (424 mg, 2.18 mmol, 44%) as a colourless oil.

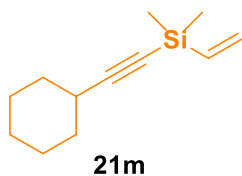
¹H NMR (500 MHz, CDCl₃) δ : 6.13 (dd, *J* = 20.0, 14.5 Hz, 1H), 5.99 (dd, *J* = 14.5, 3.8 Hz, 1H), 5.83 (dd, *J* = 20.1, 3.9 Hz, 1H), 2.23 (t, *J* = 7.2 Hz, 2H), 1.52 (p, *J* = 7.2 Hz, 2H), 1.41 – 1.35 (m, 2H), 1.35 – 1.24 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.21 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ : 137.4, 132.7, 109.2, 82.3, 31.4, 28.7, 28.6, 22.7, 20.1, 14.2, –1.1.

²⁹Si NMR (99 MHz, CDCl₃) δ : –26.0.

IR ν_{max} (film) 2175 (w), 1401 (w), 1249 (w).

MS (HRMS – EI⁺) Molecular ion not detected. For C₁₂H₂₂Si – CH₃: Found 179.125085 (C₁₁H₁₉Si) requires 179.12505.

Dimethyl(cyclohexylethynyl)(vinyl)silane **21m**

According to general procedure A, 1-ethynylcyclohexane (5.00 mmol, 653 μ L), *n*-butyl lithium (5.50 mmol, 2.5 M in hexanes, 2.20 mL), and chloro(dimethyl)vinylsilane (5.50 mmol, 759 μ L) were reacted in THF (5.00 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether) to give

dimethyl(cyclohexylethynyl)(vinyl)silane **21m** (417 mg, 2.16 mmol, 43%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ : 6.13 (dd, J = 20.0, 14.4 Hz, 1H), 5.98 (dd, J = 14.5, 3.9 Hz, 1H), 5.84 (dd, J = 20.0, 4.0 Hz, 1H), 2.41 (tt, J = 9.1, 3.7 Hz, 1H), 1.84 – 1.76 (m, 2H), 1.74 – 1.66 (m, 2H), 1.54 – 1.40 (m, 3H), 1.34 – 1.23 (m, 3H), 0.21 (s, 6H).

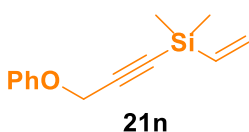
¹³C NMR (126 MHz, CDCl₃) δ : 137.5, 132.6, 113.3, 81.7, 32.7, 30.2, 26.0, 24.9, –1.0.

²⁹Si NMR (99 MHz, CDCl₃) δ : –25.9.

IR $\nu_{\max}$ (film) 2172 (w), 1449 (w), 1248 (w).

MS (HRMS – EI⁺) Found 192.132888 (C₁₂H₂₀Si) requires 192.13288.

Dimethyl(3-phenoxy-prop-1-ynyl)(vinyl)silane 21n



According to general procedure A, phenyl propargyl ether (5.00 mmol, 642 μ L), *n*-butyl lithium (5.50 mmol, 2.5 M in hexanes, 2.20 mL), and chloro(dimethyl)vinylsilane (5.50 mmol, 759 μ L) were reacted in THF (5.00 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether) to give *dimethyl(3-phenoxy-prop-1-ynyl)(vinyl)silane* **21n** (730 mg, 3.37 mmol, 67%) as an orange oil.

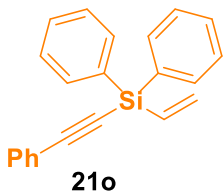
¹H NMR (500 MHz, CDCl₃) δ : 7.33 – 7.28 (m, 2H), 7.01 – 6.97 (m, 3H), 6.12 (dd, J = 19.8, 14.5 Hz, 1H), 6.01 (dd, J = 14.5, 3.8 Hz, 1H), 5.83 (dd, J = 19.9, 3.9 Hz, 1H), 4.70 (s, 2H), 0.25 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ : 157.9, 136.1, 133.6, 129.5, 121.6, 115.2, 101.4, 90.8, 56.9, –1.6.

²⁹Si NMR (99 MHz, CDCl₃) δ : –24.4.

IR $\nu_{\max}$ (film) 2173 (w), 1597 (w), 1495 (s), 1212 (s).

MS (HRMS – EI⁺) Found 216.096978 (C₁₃H₁₆OSi) requires 216.09649.

Diphenyl(phenylethynyl)(vinyl)silane 21o

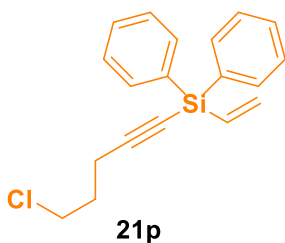
According to general procedure A, phenylacetylene (5.00 mmol, 549 μ L), *n*-butyl lithium (5.50 mmol, 2.5 M in hexanes, 2.20 mL), and chloro(diphenyl)vinylsilane (5.50 mmol, 1220 μ L) were reacted in THF (5.00 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether) to give diphenyl(phenylethynyl)(vinyl)silane **21o** (917 mg, 2.95 mmol, 59%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ : 7.77 (dt, *J* = 7.8, 1.8 Hz, 4H), 7.62 (dt, *J* = 7.8, 1.7 Hz, 2H), 7.52 – 7.34 (m, 9H), 6.56 (dd, *J* = 20.0, 14.4, 1H), 6.35 (dd, *J* = 14.4, 3.5 Hz, 1H), 6.16 – 6.07 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ : 137.0, 135.3, 133.6, 133.1, 132.4, 130.0, 129.2, 128.4, 128.1, 122.9, 109.5, 88.6.

²⁹Si NMR (99 MHz, CDCl₃) δ : –31.9.

Data were in accordance with those previously reported.

Diphenyl(6-chlorohex-1-ynyl)(vinyl)silane 21p

According to general procedure B, 6-chlorohex-1-yne (5.00 mmol, 606 μ L), lithium diisopropyl amide (5.50 mmol, 1.0 M in THF, 5.50 mL), and chloro(diphenyl)vinylsilane (5.50 mmol, 1220 μ L) were reacted in THF (5.00 mL).

The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether) to give diphenyl(6-chlorohex-1-ynyl)(vinyl)silane **21p** (365 mg, 1.12 mmol, 22%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ : 7.77 – 7.65 (m, 4H), 7.46 – 7.37 (m, 6H), 6.47 (dd, J = 19.9, 14.4, 1H), 6.28 (dd, J = 14.4, 3.7, 1H), 6.00 (dtd, J = 20.0, 3.7, 1.5 Hz, 1H), 3.60 (t, J = 5.5 Hz, 2H), 2.44 (t, J = 6.8 Hz, 2H), 1.97 (p, J = 7.3 Hz, 2H), 1.79 (p, J = 6.9, 2H).

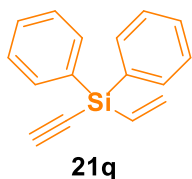
¹³C NMR (126 MHz, CDCl₃) δ : 136.6, 135.2, 134.0, 133.5, 129.9, 128.1, 111.4, 79.9, 44.6, 31.7, 25.8, 19.6.

²⁹Si NMR (99 MHz, CDCl₃) δ : –32.7.

IR $\nu_{\max}$ (film) 2173 (w), 1429 (w), 1114 (w).

MS (HRMS – EI⁺) Found 324.110161 (C₂₀H₂₁ClSi) requires 324.10956.

Diphenyl(ethynyl)(vinyl)silane **21q**



By modification of the method of Wrackmeyer, ethynyl magnesium bromide (5.50 mmol, 1.00 M in diethyl ether, 5.50 mL) was added dropwise to a stirred solution of chloro(diphenyl)vinylsilane (5.00 mmol, 1110 μ L) in THF (5.00 mL) at –78 °

C. The solution was allowed to warm to room temperature and stirred for 16 hours. All volatiles were removed *in vacuo*, the solution diluted with pentane (20.0 mL), filtered, and concentrated *in vacuo*. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether) to give diphenyl(ethynyl)(vinyl)silane **21q** (349 mg, 1.50 mmol, 30%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ : 7.70 – 7.65 (m, 4H), 7.47 – 7.38 (m, 6H), 6.47 (dd, J = 20.0, 14.4 Hz, 1H), 6.31 (dd, J = 14.5, 3.6 Hz, 1H), 6.04 (dd, J = 20.0, 3.6 Hz, 1H), 2.74 (s, 1H).

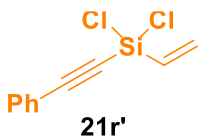
¹³C NMR (126 MHz, CDCl₃) δ : 137.4, 135.2, 132.8, 132.4, 130.2, 128.2, 97.6, 84.9.

^{29}Si NMR (99 MHz, CDCl_3) δ : -31.8.

IR ν_{max} (film) 2036 (w), 1429 (w), 1032 (w).

MS (HRMS – EI^+) Found 234.085338 ($\text{C}_{16}\text{H}_{14}\text{Si}$) requires 234.08593.

Dichloro(phenylethynyl)(vinyl)silane **21r'**



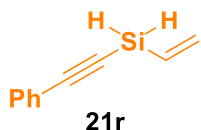
By modification of the method of Wrackmeyer, *n*-butyl lithium (40.0 mmol, 2.5 M in hexanes, 16.0 mL) was added dropwise to a stirred solution of phenylacetylene (40.0 mmol, 4.39 mL) in THF (40.0 mL) at -78°C . After 15 minutes, the solution was allowed to warm to 0°C , then added dropwise via cannula to a separate solution of trichlorovinylsilane (120 mmol, 15.0 mL) in THF (40.0 mL) at -78°C . The mixture was allowed to warm to room temperature over 1 hour. The mixture was concentrated *in vacuo*, diluted with pentane (40 mL), filtered, and all volatiles removed *in vacuo*. The crude oil was distilled (62°C , 6.4×10^{-2} mbar) to give dichloro(phenylethynyl)(vinyl)silane **21r'** (1.62 g, 7.14 mmol, 18%) as a colourless oil.

^1H NMR (500 MHz, C_6D_6) δ : 7.23 – 7.19 (m, 2H), 6.90 – 6.86 (m, 1H), 6.82 – 6.77 (m, 2H), 6.10 (dd, $J = 19.9, 2.9$ Hz, 1H), 6.00 (dd, $J = 19.9, 13.9$ Hz, 1H), 5.78 (dd, $J = 13.9, 2.9$ Hz, 1H).

^{13}C NMR (126 MHz, C_6D_6) δ : 138.4, 132.7, 131.7, 130.3, 128.6, 120.8, 109.8, 86.1.

^{29}Si NMR (99 MHz, C_6D_6) δ : -21.1.

Data were in accordance with those previously reported.¹²⁷

Phenylethynyl(vinyl)silane 21r

Dichloro(phenylethynyl)(vinyl)silane (2.50 mmol, 568 mg) was added dropwise to a stirred solution of LiAlH_4 (5.00 mmol, 190 mg) in THF (10.0 mL) at 0 °C. After stirring at this temperature for 30

minutes, isopropanol (1.00 mL) was added dropwise (*caution: hydrogen evolution!*), and the solution was diluted with cold water (10.0 mL). The mixture was extracted with diethyl ether (3 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO_2 , 50 mm Ø, 40/60 petroleum ether) to give phenylethynyl(vinyl)silane **1r** (294 mg, 1.86 mmol, 74%) as a colourless oil.

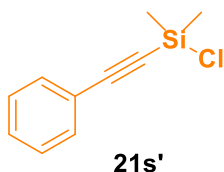
^1H NMR (500 MHz, CDCl_3) δ : 7.52 – 7.49 (m, 2H), 7.38 – 7.30 (m, 3H), 6.23 – 6.09 (m, 3H), 4.38 – 4.37 (m, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ : 137.7, 132.2, 129.3, 128.7, 128.5, 122.6, 109.1, 84.6.

^{29}Si NMR (99 MHz, CDCl_3) δ : –63.1.

IR ν_{max} (film) 2152 (s), 1593 (w), 1488 (w).

MS (HRMS – EI^+) Found 158.054176 ($\text{C}_{10}\text{H}_{10}\text{Si}$) requires 158.05463.

Chlorodimethyl(phenylethynyl)silane 21s'

By modification of the method of Wrackmeyer, *n*-butyl lithium (55.0 mmol, 2.5 M in hexanes, 22.0 mL) was added dropwise to a stirred solution of phenylacetylene (50.0 mmol, 5.50

mL) in hexane (50.0 mL) at –78 °C. After 15 minutes, the suspension was allowed to warm to room temperature, then added

dropwise *via* cannula to dichlorodimethylsilane (150 mmol, 18.0 mL) at room temperature. The mixture was refluxed at 90 °C for 5 hours, then cooled to room temperature. The mixture was filtered and all volatiles removed *in vacuo*. The crude oil was distilled (51 °C, 1.2×10^{-1} mbar) to give chlorodimethyl(phenylethynyl)silane **21s'** (3.73 g, 19.1 mmol, 38%) as a colourless oil.

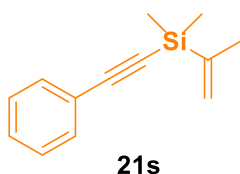
¹H NMR (500 MHz, C₆D₆) δ : 7.49 – 7.44 (m, 2H), 7.05 – 6.94 (m, 3H), 0.54 (s, 6H).

¹³C NMR (126 MHz, C₆D₆) δ : 132.4, 129.5, 128.6, 122.3, 107.6, 90.4, 3.6.

²⁹Si NMR (99 MHz, C₆D₆) δ : 0.1.

Data were in accordance with those previously reported.

Dimethyl(phenylethynyl)(2-propenyl)silane **21s**



By modification of the method of Wrackmeyer, 2-propenyl magnesium bromide (5.50 mmol, 0.50 M in diethyl ether, 11.0 mL) was added dropwise to a stirred solution of chlorodimethyl(phenylethynyl)silane (5.00 mmol, 974 mg) in diethyl ether (5.00 mL) at 0 °C. The solution was allowed to warm to room temperature and stirred for 16 hours. All volatiles were removed *in vacuo*, the solution diluted with pentane (20.0 mL), filtered, and concentrated *in vacuo*. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO₂, 50 mm Ø, 40/60 petroleum ether) to give dimethyl(phenylethynyl)(2-propenyl)silane **21s** (635 mg, 3.17 mmol, 63%) as a colourless oil.

^1H NMR (500 MHz, CDCl_3) δ : 7.50 – 7.46 (m, 2H), 7.35 – 7.28 (m, 3H), 5.69 – 5.66 (m, 1H), 5.50 – 5.58 (m, 1H), 1.96 – 1.94 (m, 3H), 0.33 – 0.32 (m, 6H).

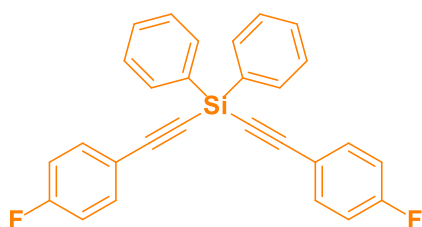
^{13}C NMR (126 MHz, CDCl_3) δ : 144.9, 132.2, 128.7, 128.3, 126.6, 123.2, 106.3, 92.2, 22.2, –1.9.

^{29}Si NMR (99 MHz, CDCl_3) δ : –22.6.

IR ν_{max} (film) 2157 (s), 1489 (s), 1248 (w).

MS (HRMS – EI^+) Found 200.101436 ($\text{C}_{13}\text{H}_{16}\text{Si}$) requires 200.10158.

Diphenylbis(4-fluorophenylethynyl)silane 6d



6d

According to general procedure C, 4-fluorophenylacetylene (11.0 mmol, 1.32 g), *n*-butyl lithium (12.0 mmol, 2.5 M in hexanes, 4.80 mL), and dichloro(diphenyl)silane (5.00 mmol, 1.06 g) were reacted in

THF (4.80 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO_2 , 50 mm $\varnothing$, 40/60 petroleum ether) to give *diphenylbis(4-fluorophenylethynyl)silane* **6d** (791 mg, 1.90 mmol, 38%) as a colourless oil.

^1H NMR (500 MHz, CDCl_3) δ : 7.85 – 7.83 (m, 4H), 7.59 – 7.55 (m, 4H), 7.47 – 7.41 (m, 6H), 7.05 – 7.01 (m, 4H).

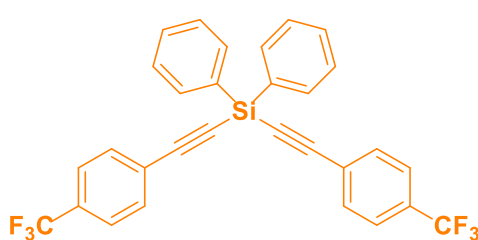
^{13}C NMR (126 MHz, CDCl_3) δ : 164.0, 162.1, 134.9, 134.4, 134.4, 132.8, 130.3, 128.1, 118.5, 118.5, 115.7, 115.6, 107.6, 87.4, 65.8, 15.3.

^{19}F NMR (471 MHz, CDCl_3) δ : –109.0 (m).

^{29}Si NMR (99 MHz, CDCl_3) δ : -48.1.

MS (HRMS – ESI $^+$) Found 421.1218 ($\text{C}_{28}\text{H}_{19}\text{F}_2\text{Si}$) requires 421.1219.

Diphenylbis(4-trifluoromethylphenylethynyl)silane 6e



6e

According to general procedure C, 4-

trifluoromethylphenylacetylene (11.0 mmol, 1.80 mL), *n*-butyl lithium (12.0 mmol, 2.5 M in hexanes, 4.80 mL), and dichloro(diphenyl)silane (5.00 mmol, 1.06 mL) were reacted in THF (4.80 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO_2 , 50 mm $\varnothing$, 40/60 petroleum ether) to give *diphenylbis(4-trifluoromethylphenylethynyl)silane 6e* (947 mg, 1.90 mmol, 38%) as a colourless oil.

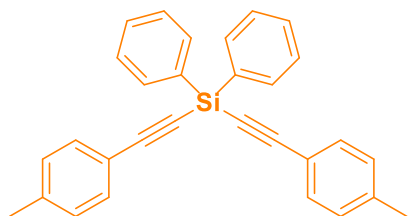
^1H NMR (500 MHz, CDCl_3) δ : 7.86 – 7.85 (m, 4H), 7.70 (d, J = 7.7 Hz, 4H), 7.61 (d, J = 7.6 Hz, 4H), 7.52 – 7.44 (m, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ : 134.9, 134.5, 132.6, 132.4, 132.0, 131.4, 131.1, 130.9, 130.6, 128.3, 127.9, 127.0, 126.0, 125.3 (q, J = 125 Hz), 124.8, 122.7, 107.1, 90.2, 79.6.

^{19}F NMR (471 MHz, CDCl_3) δ : -63.0 (s).

^{29}Si NMR (99 MHz, CDCl_3) δ : -47.8.

MS (HRMS – ESI $^+$) Found 520.9084 ($\text{C}_{30}\text{H}_{18}\text{F}_6\text{Si}$) requires 520.5494.

Diphenylbis(4-methylphenylethynyl)silane 6f**6f**

According to general procedure C, 4-methylphenylacetylene (11.0 mmol, 1.40 mL), *n*-butyl lithium (12.0 mmol, 2.5 M in hexanes, 4.80 mL), and dichloro(diphenyl)silane (5.00 mmol, 1.06 mL) were reacted in

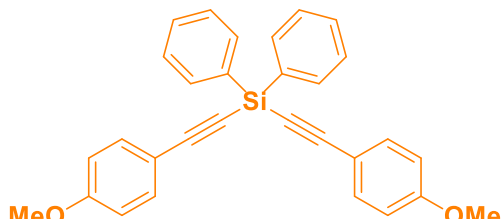
THF (4.80 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO₂, 50 mm Ø, 40/60 petroleum ether) to give *diphenylbis(4-methylphenylethynyl)silane 6f* (1.30 g, 3.15 mmol, 63%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ: 7.88 – 7.86 (m, 4H), 7.49 – 7.47 (m, 4H), 7.45 – 7.40 (m, 6H), 7.14 (d, *J* = 7.1 Hz, 4H), 2.36 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ: 139.5, 134.9, 133.4, 132.3, 130.1, 129.0, 128.0, 119.4, 109.0, 86.9, 21.6.

²⁹Si NMR (99 MHz, CDCl₃) δ: –48.2.

MS (HRMS – ESI⁺) Found 413.1713 (C₃₀H₂₅Si) requires 413.1720.

Diphenylbis(4-methoxyphenylethynyl)silane 6g**6g**

According to general procedure C, 4-methoxyphenylacetylene (11.0 mmol, 1.43 mL), *n*-butyl lithium (12.0 mmol, 2.5 M in hexanes, 4.80 mL), and

dichloro(diphenyl)silane (5.00 mmol, 1.06 mL) were reacted in THF

(4.80 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO₂, 50 mm Ø, 40/60 petroleum ether) to give *diphenylbis(4-methoxyphenylethynyl)silane* **6g** (1.29 g, 2.90 mmol, 58%) as a colourless oil.

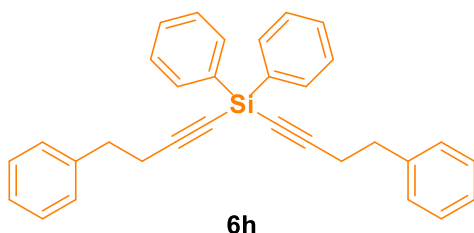
¹H NMR (500 MHz, CDCl₃) δ: 7.88 – 7.85 (m, 4H), 7.54 – 7.51 (m, 4H), 7.46 – 7.40 (m, 6H), 6.86 (d, *J* = 6.9 Hz, 4H), 3.82 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ: 160.3, 134.9, 133.9, 133.5, 130.1, 128.0, 114.6, 113.9, 108.9, 86.3, 55.3.

²⁹Si NMR (99 MHz, CDCl₃) δ: –48.3.

MS (HRMS – ESI⁺) Found 445.1605 (C₃₀H₂₅O₂Si) requires 445.1618.

Diphenylbis(4-phenyl-but-1-ynyl)silane **6h**



According to general procedure C, 4-phenyl-but-1-yne (9.60 mmol, 1.35 mL), *n*-butyl lithium (10.5 mmol, 2.5 M in hexanes, 4.20 mL), and

dichloro(diphenyl)silane (4.36 mmol, 0.920 mL) were reacted in THF (4.80 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 40 g SiO₂, 50 mm Ø, 40/60 petroleum ether) to give *diphenylbis(4-phenyl-but-1-ynyl)silane* **6h** (1.30 g, 2.96 mmol, 68%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ: 7.65 – 7.63 (m, 4H), 7.42 – 7.39 (m, 2H), 7.37 – 7.33 (m, 4H), 7.30 – 7.27 (m, 4H), 7.25 – 7.21 (m, 6H), 2.92 (t, *J* = 2.9 Hz, 4H), 2.65 (t, *J* = 2.7 Hz, 4H).

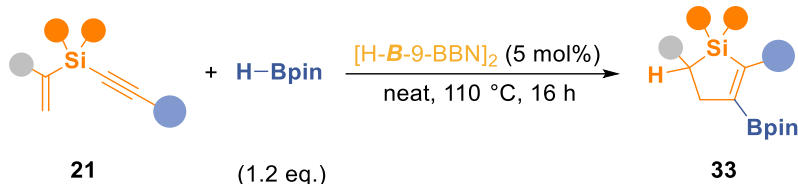
¹³C NMR (126 MHz, CDCl₃) δ: 140.3, 134.7, 133.7, 133.7, 129.9, 128.5, 128.4, 127.9, 126.3, 110.6, 79.5, 65.8, 34.6, 22.4.

^{29}Si NMR (99 MHz, CDCl_3) δ : -49.7.

MS (HRMS – ESI⁺) Found 441.2020 ($\text{C}_{32}\text{H}_{29}\text{Si}$) requires 441.2033.

4.5.3 Substrate Scope

General Procedure D



To a mixture of H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%) and the substrate (0.500 mmol), was added HBpin (0.600 mmol, 87.0 μL). The stirred mixture was heated in a sealed container at 110 $^\circ\text{C}$ for 16 hours. After cooling to room temperature, the mixture was diluted with dichloromethane (1.00 mL), silica (ca. 50 mg) was added and left stirring for 10 minutes (or until gas evolution ceased). The product was purified by flash column chromatography (SiO_2).

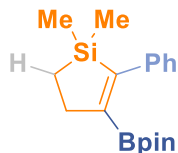
General Procedure E

A mixture of H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%) and the substrate (0.500 mmol) was stirred in a sealed container at 110 $^\circ\text{C}$. To this, HBpin (0.600 mmol, 87 μL , 4.4 $\mu\text{L h}^{-1}$) was slowly added by syringe pump. After 36 hours, the mixture was cooled to room temperature, diluted with dichloromethane (1.00 mL), silica (ca. 50 mg) was added and left stirring for 10 minutes (or until gas evolution ceased). The product was purified by flash column chromatography (SiO_2).

Note: the ^{13}C NMR spectroscopy signal associated with the C-B bond was not always observed.

Where applicable, NMR yields are reported from the crude ^1H NMR spectrum using mesitylene as an internal standard.

1,1-Dimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33a**



33a

According to general procedure D, dimethyl(phenylethynyl)(vinyl)silane **21a** (0.500 mmol, 93.2 mg), H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μL) were reacted. The product was purified by flash

column chromatography (CombiFlash Isco NextGen300+, 12 g SiO_2 , 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,1-dimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33a** (123 mg, 0.390 mmol, 78%) as a colourless oil.

^1H NMR (500 MHz, CDCl_3) δ : 7.26 – 7.21 (m, 2H), 7.17 – 7.12 (m, 3H), 2.75 – 2.71 (m, 2H), 1.15 (s, 12H), 0.89 – 0.85 (m, 2H), 0.19 (s, 6H).

^{11}B NMR (160 MHz, CDCl_3) δ : 30.5.

^{13}C NMR (126 MHz, CDCl_3) δ : 157.2, 152.8 (br), 142.7, 127.9, 127.2, 125.8, 83.5, 34.6, 24.7, 10.7, –1.3.

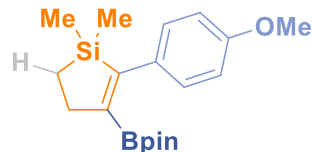
^{29}Si NMR (99 MHz, CDCl_3) δ : 20.4.

IR ν_{max} (film) 1477 (w), 1303 (w), 1142 (w).

MS (HRMS – EI^+) Found 314.186604 ($\text{C}_{18}\text{H}_{27}\text{BO}_2\text{Si}$) requires 314.18679.

1,1-Dimethyl-5-(4-methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole 33b

According to general procedure D, dimethyl(4-methoxyphenylethynyl)(vinyl)silane **21b**



33b

(0.500 mmol, 108 mg), H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography

(CombiFlash Isco NextGen300+, 12 g SiO_2 , 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,1-dimethyl-5-(4-methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33b** (123 mg, 0.355 mmol, 71%) as a colourless amorphous solid.

^1H NMR (500 MHz, CDCl_3) δ : 7.12 – 7.08 (m, 2H), 6.82 – 6.78 (m, 2H), 3.80 (s, 3H), 2.73 – 2.69 (m, 2H), 1.18 (s, 12H), 0.89 – 0.81 (m, 2H), 0.19 (s, 6H).

^{11}B NMR (160 MHz, CDCl_3) δ : 30.7.

^{13}C NMR (126 MHz, CDCl_3) δ : 158.1, 156.4, 135.1, 128.4, 113.4, 83.5, 55.4, 34.6, 24.8, 10.7, – 1.3.

^{29}Si NMR (99 MHz, CDCl_3) δ : 19.8.

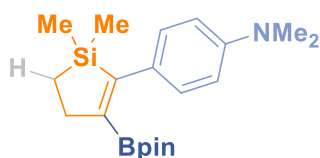
IR ν_{max} (film) 1605 (w), 1506 (w), 1341 (w), 1287 (w).

MS (HRMS – EI^+) Found 344.197315 ($\text{C}_{19}\text{H}_{29}\text{BO}_3\text{Si}$) requires 344.19735.

MP (40/60 petroleum ether) 48 – 49 $^{\circ}\text{C}$.

1,1-Dimethyl-5-(4-*N,N*-dimethylaminophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33c**

According to general procedure D, dimethyl(4-*N,N*-dimethylaminophenylethynyl)(vinyl)silane **21c** (0.500 mmol, 115



33c

mg), H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$,

40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,1-dimethyl-5-(4-*N,N*-dimethylaminophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33c** (163 mg, 0.455 mmol, 91%) as a yellow oil.

¹H NMR (500 MHz, CDCl₃) δ : 7.12 – 7.08 (m, 2H), 6.67 – 6.63 (m, 2H), 2.93 (s, 6H), 2.73 – 2.68 (m, 2H), 1.22 (s, 12H), 0.86 – 0.81 (m, 2H), 0.20 (s, 6H).

¹¹B NMR (160 MHz, CDCl₃) δ : 31.0.

¹³C NMR (126 MHz, CDCl₃) δ : 156.2, 149.3, 131.1, 128.3, 112.5, 83.4, 41.0, 34.6, 24.9, 10.8, – 1.1.

²⁹Si NMR (99 MHz, CDCl₃) δ : 19.4.

IR ν_{max} (film) 1607 (w), 1593 (w), 1514 (w), 1344 (w), 1142 (w).

MS (HRMS – EI⁺) Found 357.229714 (C₂₀H₃₂BNO₂Si) requires 357.22899.

1,1-Dimethyl-5-(4-fluorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33d**

According to general procedure D, dimethyl(4-fluorophenylethynyl)(vinyl)silane **21d** (0.500 mmol, 102 mg), H-*B*-



33d

9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to

0:100) to give 1,1-dimethyl-5-(4-fluorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33d** (121 mg, 0.365 mmol, 73%) as a colourless amorphous solid.

¹H NMR (500 MHz, CDCl₃) δ : 7.11 – 7.06 (m, 2H), 6.96 – 6.91 (m, 2H), 2.74 – 2.69 (m, 2H), 1.16 (s, 12H), 0.89 – 0.84 (m, 2H), 0.18 (s, 6H).

¹¹B NMR (160 MHz, CDCl₃) δ : 30.4.

¹³C NMR (126 MHz, CDCl₃) 161.6 (d, *J* = 243 Hz), 156.4, 138.7 (d, *J* = 3.1 Hz), 128.6 (d, *J* = 7.8 Hz), 114.6 (d, *J* = 21.0 Hz), 83.6, 34.6, 24.8, 10.6, –1.4.

¹⁹F NMR (471 MHz, CDCl₃) δ : –118 (m).

²⁹Si NMR (99 MHz, CDCl₃) δ : 20.4.

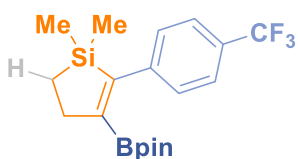
IR ν_{max} (film) 1503 (w), 1338 (w).

MS (HRMS – EI⁺) Found 332.176816 (C₁₈H₂₆BFO₂Si) requires 332.17737.

MP (40/60 petroleum ether) 58 – 60 °C.

1,1-Dimethyl-5-(4-trifluoromethylphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole 33e

According to general procedure D, dimethyl(4-trifluoromethylphenylethynyl)(vinyl)silane **21e** (0.500 mmol, 127



33e

mg), H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60

petroleum ether/EtOAc 100:0 to 0:100) to give 1,1-dimethyl-5-(4-trifluoromethylphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33e** (102 mg, 0.265 mmol, 53%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ : 7.51 – 7.48 (m, 2H), 7.22 – 7.19 (m, 2H), 2.77 – 2.72 (m, 2H), 1.13 (s, 12H), 0.92 – 0.87 (m, 2H), 0.19 (s, 6H).

¹¹B NMR (160 MHz, CDCl₃) δ : 30.3.

¹³C NMR (126 MHz, CDCl₃) δ : 156.8, 127.4, 126.9 (q, J = 270 Hz), 124.8 (q, J = 3.9 Hz), 83.7, 34.7, 24.7, 10.6, –1.5.

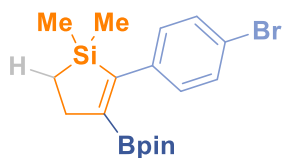
¹⁹F NMR (471 MHz, CDCl₃) δ : –62.2.

²⁹Si NMR (99 MHz, CDCl₃) δ : 21.5.

IR ν_{max} (film) 1615 (w), 1308 (s), 1122 (w).

MS (HRMS – EI⁺) Found 382.174010 (C₁₉H₂₆BF₃O₂Si) requires 382.17417.

1,1-Dimethyl-5-(4-bromophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole 33f

**33f**

According to general procedure D, dimethyl(4-bromophenylethynyl)(vinyl)silane **21f** (0.500 mmol, 133 mg), H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted.

The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,1-dimethyl-5-(4-bromophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33f** (127 mg, 0.320 mmol, 64%) as a pale yellow oil.

¹H NMR (500 MHz, CDCl₃) δ : 7.37 – 7.34 (m, 2H), 7.02 – 6.99 (m, 2H), 2.74 – 2.69 (m, 2H), 1.16 (s, 12H), 0.89 – 0.84 (m, 2H), 0.17 (s, 6H).

¹¹B NMR (160 MHz, CDCl₃) δ : 30.4.

¹³C NMR (126 MHz, CDCl₃) δ : 156.3, 141.8, 130.9, 129.0, 119.6, 83.7, 34.7, 24.8, 10.6, –1.4.

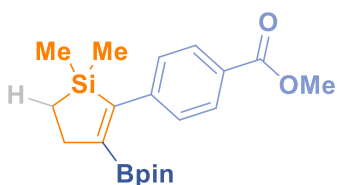
²⁹Si NMR (99 MHz, CDCl₃) δ : 20.8.

IR $\nu_{\max}$ (film) 1483 (w), 1345 (w), 1303 (w), 1142 (s).

MS (HRMS – EI⁺) Found 392.097868 (C₁₈H₂₆BBrO₂Si) requires 392.09730.

1,1-Dimethyl-5-(4-methoxycarbonyl-phenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole 33g

According to general procedure D, methyl 4-((dimethylvinylsilyl)ethynyl)benzoate **21g** (0.500 mmol, 122 mg),



33g

H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to

0:100) to give 1,1-dimethyl-5-(4-methoxycarbonyl-phenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33g** (127 mg, 0.340 mmol, 68%) as a pale yellow oil.

¹H NMR (500 MHz, CDCl₃) δ : 7.92 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.3 Hz, 2H), 3.90 (s, 3H), 2.78 – 2.71 (m, 2H), 1.14 (s, 12H), 0.91 – 0.85 (m, 2H), 0.19 (s, 6H).

¹¹B NMR (160 MHz, CDCl₃) δ : 30.4.

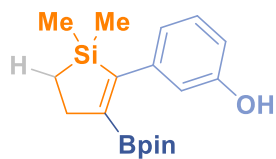
¹³C NMR (126 MHz, CDCl₃) δ : 167.5, 157.0, 154.3 (br), 148.3, 129.3, 127.5, 127.2, 83.7, 52.0, 34.8, 24.8, 10.6, –1.4.

²⁹Si NMR (99 MHz, CDCl₃) δ : 21.6.

IR ν_{max} (film) 1716 (s), 1604 (w), 1436 (w), 1274 (s).

MS (HRMS – EI⁺) Found 372.192603 (C₂₀H₂₉BO₄Si) requires 372.19227.

1,1-Dimethyl-5-(3-hydroxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33h**



33h

To a mixture of H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%) and dimethyl(3-hydroxyphenylethynyl)(vinyl)silane **21h** (0.500 mmol, 122 mg), was added HBpin (1.10 mmol, 160 μ L). The stirred mixture was heated in a sealed container at 110 $^{\circ}$ C

for 16 hours. After cooling to room temperature, the mixture was diluted with dichloromethane (1.00 mL) and methanol (1.00 mL), silica (ca. 50 mg) was added and left stirring for 30 minutes. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,1-dimethyl-5-(3-hydroxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33h** (33.5 mg, 0.165 mmol, 33%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ : 7.10 (t, J = 7.8 Hz, 1H), 6.70 (ddd, J = 7.6, 1.6, 1.0 Hz, 1H), 6.63 (ddd, J = 8.0, 2.6, 1.0 Hz, 1H), 6.59 (dd, J = 2.5, 1.5 Hz, 1H), 4.81 (br s, 1H), 2.74 – 2.68 (m, 2H), 1.17 (s, 12H), 0.88 – 0.83 (m, 2H), 0.18 (s, 6H).

¹¹B NMR (160 MHz, CDCl₃) δ : 30.6.

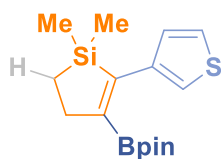
¹³C NMR (126 MHz, CDCl₃) δ : 156.8, 155.2, 144.6, 129.1, 119.9, 114.1, 112.8, 83.6, 34.5, 24.8, 10.7, –1.3.

²⁹Si NMR (99 MHz, CDCl₃) δ : 20.4.

IR ν_{max} (film) 3510 (br), 1577 (w), 1347 (w), 1141 (s).

MS (HRMS – EI⁺) Found 330.181233 (C₁₈H₂₇BO₃Si) requires 330.18170.

1,1-Dimethyl-5-(3-thiophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33i**



33i

According to general procedure D, dimethyl(3-thiophenylethynyl)(vinyl)silane **21i** (0.500 mmol, 96.2 mg), H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give *1,1-dimethyl-5-(4-thiophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole 33i* (128 mg, 0.400 mmol, 80%) as a pale yellow oil.

¹H NMR (500 MHz, CDCl₃) δ : 7.21 (dd, J = 4.8, 3.1 Hz, 1H), 7.05 – 7.03 (m, 2H), 2.75 – 2.68 (m, 2H), 1.23 (s, 12H), 0.88 – 0.81 (m, 2H), 0.21 (s, 6H).

¹¹B NMR (160 MHz, CDCl₃) δ : 30.6.

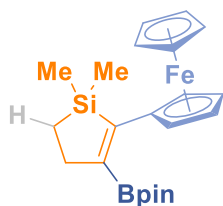
¹³C NMR (126 MHz, CDCl₃) δ : 150.4, 142.7, 128.1, 124.5, 119.8, 83.6, 34.7, 24.9, 10.4, –1.4.

²⁹Si NMR (99 MHz, CDCl₃) δ : 20.4.

IR ν_{max} (film) 1458 (w), 1298 (w).

MS (HRMS – MALDI⁺) Found 343.13220 (C₁₆H₂₅BO₂SSiNa) requires 343.13331.

1,1-Dimethyl-5-(ferrocenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole 33j



33j

According to general procedure D, dimethyl(ferrocenylethynyl)(vinyl)silane **21j** (0.360 mmol, 106 mg), H-B-9-BBN dimer (0.0180 mmol, 4.40 mg, 5 mol%), and HBpin (0.432 mmol, 63.0 μ L) were reacted. The product was purified by flash column chromatography (CombiFlash Isco

NextGen300+, 12 g SiO_2 , 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,1-dimethyl-5-(ferrocenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33j** (113 mg, 0.266 mmol, 74%) as an amorphous orange solid. Recrystallization from 40/60 petroleum

ether gave crystals suitable for X-ray diffraction (CCDC 2328005).

^1H NMR (500 MHz, CDCl_3) δ : 4.47 (t, J = 1.9 Hz, 2H), 4.19 (t, J = 1.9 Hz, 2H), 4.08 (s, 5H), 2.63 – 2.57 (m, 2H), 1.36 (s, 12H), 0.81 – 0.75 (m, 2H), 0.34 (s, 6H).

^{11}B NMR (160 MHz, CDCl_3) δ : 31.2.

^{13}C NMR (126 MHz, CDCl_3) δ : 152.6, 83.6, 69.3, 68.3, 68.2, 64.2, 35.5, 25.1, 10.4, –0.3.

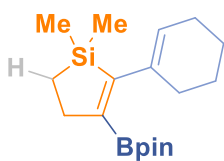
^{29}Si NMR (99 MHz, CDCl_3) δ : 19.8.

IR ν_{max} (film) 1477 (w), 1454 (w), 1346 (w), 1012 (w).

MS (HRMS – EI^+) Found 422.153126 ($\text{C}_{22}\text{H}_{31}\text{BFeO}_2\text{Si}$) requires 422.15303.

MP (40/60 petroleum ether) 45 – 46 $^{\circ}\text{C}$.

1,1-Dimethyl-5-(1-cyclohexenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33k**



33k

According to general procedure E, dimethyl(1-cyclohexenylethynyl)(vinyl)silane **21k** (0.500 mmol, 95.0 mg), H-*B*-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50

mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,1-dimethyl-5-(1-cyclohexenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33k** (55.8 mg, 0.175 mmol, 35%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ : 5.40 (tt, J = 3.8, 1.7 Hz, 1H), 2.60 – 2.55 (m, 2H), 2.14 – 2.01 (m, 4H), 1.68 – 1.53 (m, 4H), 1.26 (s, 12H), 0.76 – 0.69 (m, 2H), 0.15 (s, 6H).

¹¹B NMR (160 MHz, CDCl₃) δ : 30.9.

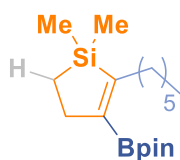
¹³C NMR (126 MHz, CDCl₃) δ : 158.6, 139.6, 122.1, 83.4, 34.1, 29.6, 25.8, 24.9, 23.2, 22.4, 10.6, –1.0.

²⁹Si NMR (99 MHz, CDCl₃) δ : 18.8.

IR ν_{max} (film) 1454 (w), 1346 (w), 1013 (w).

MS (HRMS – EI⁺) Found 318.217793 (C₁₈H₃₁BO₂Si) requires 318.21809.

1,1-Dimethyl-5-(1-hexyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33l**



33l

According to general procedure E, dimethyl(1-octynyl)(vinyl)silane **21l** (0.500 mmol, 97.0 mg), HB-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc

100:0 to 0:100) to give 1,1-dimethyl-5-(1-hexyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33l** (132 mg, 0.420 mmol, 82%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ : 2.56 (ddt, J = 8.4, 5.6, 1.5 Hz, 2H), 2.49 (ddt, J = 9.4, 6.2, 1.5 Hz, 2H), 1.38 – 1.22 (m, 20H), 0.90 – 0.86 (m, 3H), 0.70 – 0.66 (m, 2H), 0.13 (s, 6H).

¹¹B NMR (160 MHz, CDCl₃) δ : 29.8.

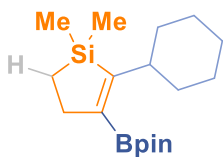
¹³C NMR (126 MHz, CDCl₃) δ : 161.6, 83.0, 33.9, 32.2, 31.9, 30.9, 29.7, 25.0, 22.8, 14.3, 10.3, – 1.2.

²⁹Si NMR (99 MHz, CDCl₃) δ : 18.6.

IR ν_{max} (film) 1497 (w), 1471 (w), 1341 (w).

MS (HRMS – EI⁺) Found 322.248940 (C₁₈H₃₅BO₂Si) requires 322.24939.

1,1-Dimethyl-5-(cyclohexyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33m**

**33m**

According to general procedure E, dimethyl(cyclohexylethynyl)(vinyl)silane **21m** (0.500 mmol, 99.0 mg), H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,1-dimethyl-5-(cyclohexyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33m** (162 mg, 0.490 mmol, 98%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ : 2.80 (tt, J = 11.6, 3.5 Hz, 1H), 2.55 – 2.51 (m, 2H), 1.74 – 1.61 (m, 6H), 1.29 – 1.18 (m, 16H), 0.68 – 0.63 (m, 2H), 0.17 (s, 6H).

¹¹B NMR (160 MHz, CDCl₃) δ : 30.1.

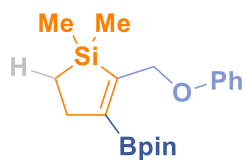
¹³C NMR (126 MHz, CDCl₃) δ : 165.5, 83.1, 43.1, 35.1, 33.5, 26.8, 26.4, 25.0, 10.5, 0.5.

²⁹Si NMR (99 MHz, CDCl₃) δ : 17.9.

IR ν_{max} (film) 1447 (w), 1370 (w), 1343 (w), 1291 (w).

MS (HRMS – EI⁺) Found 320.232742 (C₁₈H₃₃BO₂Si) requires 320.23374.

1,1-Dimethyl-5-((phenoxy)methyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33n**



33n

According to general procedure D, dimethyl(3-phenoxy-prop-1-ynyl)(vinyl)silane **21n** (0.500 mmol, 108 mg), H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,1-dimethyl-5-((phenoxy)methyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33n** (102 mg, 0.295 mmol, 59%) as a pale yellow oil.

¹H NMR (500 MHz, CDCl₃) δ : 7.29 – 7.25 (m, 2H), 6.93 – 6.89 (m, 3H), 5.06 (t, J = 2.4 Hz, 2H), 2.68 – 2.62 (m, 2H), 1.29 (s, 12H), 0.74 – 0.69 (m, 2H), 0.20 (s, 6H).

¹¹B NMR (160 MHz, CDCl₃) δ : 29.2.

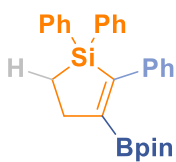
¹³C NMR (126 MHz, CDCl₃) δ : 159.5, 137.9, 129.4, 120.3, 114.7, 83.4, 70.1, 34.3, 25.1, 10.0, –1.1.

²⁹Si NMR (99 MHz, CDCl₃) δ : 21.3.

IR ν_{max} (film) 1585 (w), 1496 (w), 1300 (w), 1141 (s).

MS (HRMS – EI⁺) Found 344.197206 (C₁₉H₂₉BO₃Si) requires 344.19735.

1,1,5-Triphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33o**



33o

According to general procedure D, diphenyl(phenylethynyl)(vinyl)silane **21o** (0.500 mmol, 155 mg), H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,1,5-triphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33o** (202 mg, 0.460 mmol, 92%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ : 7.53 – 7.50 (m, 4H), 7.40 – 7.30 (m, 6H), 7.16 – 7.06 (m, 5H), 2.96 – 2.92 (m, 2H), 1.43 – 1.39 (m, 2H), 1.20 (s, 12H).

¹¹B NMR (160 MHz, CDCl₃) δ : 30.7.

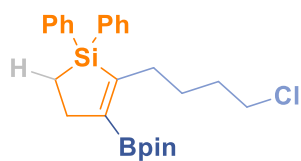
¹³C NMR (126 MHz, CDCl₃) δ : 156.5 (br), 153.4, 142.4, 135.6, 135.4, 129.6, 128.0, 127.8, 127.8, 126.1, 83.7, 34.9, 24.8, 10.1.

²⁹Si NMR (99 MHz, CDCl₃) δ : 9.6.

IR ν_{max} (film) 1427 (w), 1370 (w), 1343 (w), 1142 (s).

MS (HRMS – MALDI⁺) Found 461.20643 (C₂₈H₃₁BO₂SiNa) requires 461.20839.

1,1-Diphenyl-5-(4-chlorobutyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33p**



33p

According to general procedure D, diphenyl(6-chlorohex-1-ynyl)(vinyl)silane **21p** (0.500 mmol, 162 mg), H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product

was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,1-diphenyl-5-(4-chlorobutyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33p** (194 mg, 0.460 mmol, 86%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ : 7.59 – 7.56 (m, 4H), 7.42 – 7.35 (m, 6H), 3.24 (t, J = 6.9 Hz, 2H), 2.80 (tt, J = 6.9, 1.5 Hz, 2H), 2.66 (tt, J = 7.5, 1.4 Hz, 2H), 1.56 (dq, J = 8.7, 7.0 Hz, 2H), 1.36 – 1.28 (m, 14H), 1.27 – 1.23 (m, 2H).

¹¹B NMR (160 MHz, CDCl₃) δ : 29.6.

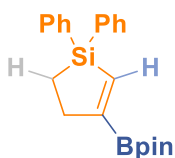
¹³C NMR (126 MHz, CDCl₃) δ : 157.7, 152.9 (br), 135.9, 135.2, 129.5, 128.0, 83.3, 45.0, 34.4, 32.5, 31.5, 27.9, 25.1, 9.5.

²⁹Si NMR (99 MHz, CDCl₃) δ : 9.6.

IR $\nu_{\max}$ (film) 1427 (w), 1344 (s), 1300 (w), 1142 (w), 1111 (w).

MS (HRMS – EI⁺) Found 452.211857 (C₂₆H₃₄BClO₂Si) requires 452.21042.

1,1-Diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33q**



According to general procedure D, diphenyl(ethynyl)(vinyl)silane **21q** (0.500 mmol, 117 mg), HB-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,1-diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33q** (154 mg, 0.425 mmol, 85%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ : 7.56 – 7.50 (m, 4H), 7.39 – 7.30 (m, 6H), 7.15 (t, J = 2.2 Hz, 1H), 2.86 – 2.80 (m, 2H), 1.29 (s, 12H), 1.28 – 1.27 (m, 2H).

¹¹B NMR (160 MHz, CDCl₃) δ : 29.2.

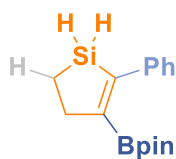
¹³C NMR (126 MHz, CDCl₃) δ : 143.9, 136.3, 135.1, 129.5, 128.0, 83.7, 34.7, 25.0, 9.2.

²⁹Si NMR (99 MHz, CDCl₃) δ : 12.3.

IR ν_{max} (film) 1558 (w), 1454 (w), 1347 (w), 1141 (w), 1055 (s).

MS (HRMS – MALDI⁺) Found 385.17534 (C₂₂H₂₇BO₂SiNa) requires 385.17699.

5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33r**



33r

According to general procedure D, (phenylethynyl)(vinyl)silane **21r** (0.500 mmol, 79.0 mg), H-*B*-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+,

12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33r** (38.0 mg, 0.135 mmol, 27%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ : 7.29 – 7.24 (m, 5H), 4.44 (tt, *J* = 4.0, 1.7 Hz, 2H), 2.89 (ddt, *J* = 8.7, 5.4, 1.7 Hz, 2H), 1.20 (s, 12H), 1.14 – 1.09 (m, 2H).

¹¹B NMR (160 MHz, CDCl₃) δ : 30.5.

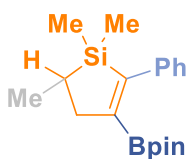
¹³C NMR (126 MHz, CDCl₃) δ : 150.2, 129.1, 128.0, 127.8, 126.5, 83.8, 37.4, 24.8, 4.1.

²⁹Si NMR (99 MHz, CDCl₃) δ : –21.2.

IR ν_{max} (film) 1472 (w), 1054 (w), 1033 (s).

MS (HRMS – EI⁺) Found 286.154715 (C₁₆H₂₃BO₂Si) requires 286.15549.

1,1,2-Trimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33s**



33s

According to a modified general procedure D, dimethyl(phenylethynyl)(2-propenyl)silane **21s** (0.500 mmol, 100 mg), H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted at 120 $^{\circ}$ C for 24 hours. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+,

12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,1,2-trimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33s** (134 mg, 0.405 mmol, 81%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ : 7.25 – 7.21 (m, 2H), 7.17 – 7.12 (m, 3H), 2.98 (dd, J = 17.7, 8.5 Hz, 1H), 2.26 (dd, J = 17.7, 6.0 Hz, 1H), 1.31 – 1.21 (m, 1H), 1.16 (s, 12H), 1.09 (d, J = 7.6 Hz, 3H), 0.17 (s, 3H), 0.12 (s, 3H).

¹¹B NMR (160 MHz, CDCl₃) δ : 30.4.

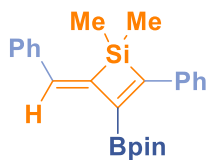
¹³C NMR (126 MHz, CDCl₃) δ : 57.1, 142.8, 127.9, 127.2, 125.8, 83.5, 44.5, 24.8, 24.7, 18.7, 15.8, –1.9, –4.8.

²⁹Si NMR (99 MHz, CDCl₃) δ : 19.6.

IR ν_{max} (film) 1388 (w), 1301 (w), 1143 (w) 1057 (s).

MS (HRMS – EI⁺) Found 328.201273 (C₁₉H₂₉BO₂Si) requires 328.20244.

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-phenyl-4-(Z)-benzylidene-1,1-dimethylsilacyclobut-2-ene 35a



35a

According to a modified general procedure D, dimethylbis(phenylethynyl)silane **6a** (0.500 mmol, 130 mg), H-B-9-BBN dimer (0.0500 mmol, 12.2 mg, 10 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography

(CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-phenyl-4-(Z)-benzylidene-1,1-dimethylsilacyclobut-2-ene **35a** (NMR: 61%; isolated: 56.1 mg, 0.150 mmol, 30%) as a yellow oil.

¹H NMR (500 MHz, CDCl₃) δ : 8.11 (s, 1H), 7.50 – 7.47 (m, 2H), 7.35 – 7.30 (m, 4H), 7.29 – 7.22 (m, 4H), 1.32 (s, 12H), 0.29 (s, 6H).

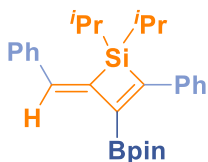
¹¹B NMR (160 MHz, CDCl₃) δ : 31.6.

¹³C NMR (126 MHz, CDCl₃) δ : 159.0, 140.4, 131.9, 128.9, 128.2, 128.0, 127.7, 123.5, 105.8, 94.4, 83.4, 24.8, 0.8.

²⁹Si NMR (99 MHz, CDCl₃) δ : -27.4.

MS (HRMS – ESI⁺) Found 389.2102 (C₂₄H₃₀BO₂Si) requires 389.2103.

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-phenyl-4-(Z)-benzylidene-1,1-diisopropylsilacyclobut-2-ene 35b



35b

According to a modified general procedure D, diisopropylbis(phenylethynyl)silane **6b** (0.500 mmol, 158 mg), H-B-9-BBN dimer (0.0500 mmol, 12.2 mg, 10 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography

(CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-phenyl-4-(Z)-benzylidene-1,1-diisopropylsilacyclobut-2-ene **35b** (NMR: 69%; isolated: 100 mg, 0.230 mmol, 46%) as a yellow oil.

¹H NMR (500 MHz, CDCl₃) δ : 7.47 – 7.46 (m, 2H), 7.33 – 7.28 (m, 6H), 7.24 – 7.21 (m, 1H), 7.19 – 7.16 (m, 1H), 7.04 (s, 1H), 1.48 (p, J = 7.5 Hz, 2H), 1.17 (d, J = 7.4 Hz, 6H), 1.11 (d, J = 7.4 Hz, 6H).

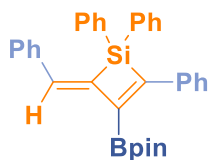
¹¹B NMR (160 MHz, CDCl₃) δ : 29.0.

¹³C NMR (126 MHz, CDCl₃) δ : 166.1, 139.9, 139.3120, 129.5, 128.3, 128.2, 128.1, 127.3, 126.5, 126.3501, 83.9, 25.0, 18.2, 18.2, 13.2.

²⁹Si NMR (99 MHz, CDCl₃) δ : 28.8.

MS (HRMS – ESI⁺) Found 445.2730 (C₂₈H₃₈BO₂Si) requires 445.2729.

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-phenyl-4-(Z)-benzylidene-1,1-diphenylsilacyclobut-2-ene 35c



35c

According to general procedure D, diphenylpropylbis(phenylethynyl)silane **6c** (0.500 mmol, 192 mg), H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product

was purified by flash column chromatography

(CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-phenyl-4-(Z)-benzylidene-1,1-diphenylsilacyclobut-2-ene **35c** (NMR: 81%; isolated: 154 mg, 0.300 mmol, 70%) as a yellow foam.

¹H NMR (500 MHz, CDCl₃) δ : 7.74 – 7.72 (m, 4H), 7.53 – 7.52 (m, 2H), 7.44 – 7.40 (m, 2H), 7.37 – 7.34 (m, 4H), 7.32 – 7.30 (m, 2H), 7.28 – 7.25 (m, 2H, overlapping with solvent), 7.22 – 7.19 (m, 2H), 7.16 – 7.13 (m, 2H), 7.10 – 7.06 (m, 1H), 1.45 (s, 12H).

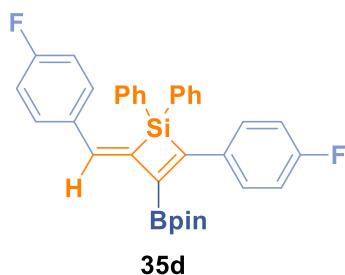
¹¹B NMR (160 MHz, CDCl₃) δ : 29.1.

¹³C NMR (126 MHz, CDCl₃) δ : 167.7, 147.1, 139.2, 138.1, 135.7, 132.9, 130.4, 129.8, 128.4, 128.3, 128.2, 127.9, 126.8, 126.7, 84.2, 25.0.

²⁹Si NMR (99 MHz, CDCl₃) δ : 1.3.

MS (HRMS – ESI⁺) Found 513.2423 (C₃₄H₃₄BO₂Si) requires 513.2416.

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4-fluorophenyl)-4-(Z)-(4-fluorobenzylidene)-1,1-diphenylsilacyclobut-2-ene 35d



According to general procedure D, diphenylpropylbis(4-fluorophenylethynyl)silane **6d** (0.500 mmol, 210 mg), H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by

flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4-fluorophenyl)-4-(Z)-(4-fluorobenzylidene)-1,1-diphenylsilacyclobut-2-ene **35d** (NMR: 75%; isolated: 152 mg, 0.280 mmol, 56%) as a yellow foam.

¹H NMR (500 MHz, CDCl₃) δ : 7.81 – 7.76 (m, 5H), 7.60 – 7.58 (m, 2H), 7.50 – 7.47 (m, 2H), 7.44 – 7.40 (m, 4H), 7.34 – 7.31 (m, 2H), 7.03 – 7.00 (m, 2H), 6.91 – 6.88 (m, 2H), 1.49 (s, 12H).

¹¹B NMR (160 MHz, CDCl₃) δ : 29.2.

¹³C NMR (126 MHz, CDCl₃) δ : 166.8, 163.3, 162.7, 161.7, 161.0, 158.9, 146.5, 135.6, 135.5 (d, J = 3.6 Hz), 134.3 (d, J = 3.6 Hz), 133.9, 133.8, 130.6, 130.2 (d, J = 7.7 Hz), 129.4, 128.6, 128.3, 128.1 (d, J = 7.7 Hz), 127.7, 115.2 (dd, J = 21.5, 3.0 Hz), 114.3, 114.2, 84.2, 83.5, 25.0, 24.4.

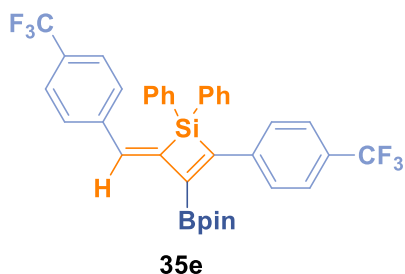
¹⁹F NMR (471 MHz, CDCl₃) δ : –113.3, –115.4.

²⁹Si NMR (99 MHz, CDCl₃) δ : 1.3.

MS (HRMS – ESI⁺) Found 549.2227 (C₃₄H₃₂BF₂O₂Si) requires 549.2227.

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4-trifluoromethylphenyl)-4-(Z)-(4-trifluoromethylbenzylidene)-1,1-diphenylsilacyclobut-2-ene 35e

According to a modified general procedure D, diphenylpropylbis(4-trifluoromethylphenylethynyl)silane **6e** (0.500 mmol, 260 mg), H-



B-9-BBN dimer (0.0500 mmol, 12.2 mg, 10 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO_2 , 50 mm $\varnothing$, 40/60

petroleum ether/EtOAc 100:0 to 0:100) to give 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4-trifluoromethyl)-4-(Z)-(4-trifluoromethylbenzylidene)-1,1-diphenylsilacyclobut-2-ene **35e** (NMR: 87%; isolated: 90.0 mg, 0.140 mmol, 28%) as a yellow foam.

^1H NMR (500 MHz, CDCl_3) δ : 7.71 – 7.69 (m, 4H), 7.63 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 7.5 Hz, 2H), 7.49 – 7.45 (m, 2H), 7.42 – 7.38 (m, 8H), 7.29 (s, 1H), 1.45 (s, 12H).

^{11}B NMR (160 MHz, CDCl_3) δ : 28.9.

^{13}C NMR (126 MHz, CDCl_3) δ : 168.2, 149.8, 142.4, 141.2, 135.6, 135.4, 135.4, 134.9, 132.6, 131.7, 130.9, 129.7, 129.5, 128.5, 128.5, 128.3, 127.9, 126.9, 125.3 (m), 84.5, 29.7, 25.2.

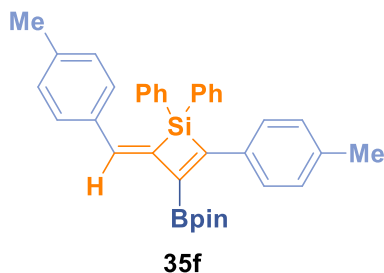
^{19}F NMR (471 MHz, CDCl_3) δ : –62.4, –62.6.

^{29}Si NMR (99 MHz, CDCl_3) δ : 1.7.

MS (HRMS – ESI^+) Found 649.2164 ($\text{C}_{36}\text{H}_{32}\text{BF}_6\text{O}_2\text{Si}$) requires 649.2163.

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4-methylphenyl)-4-(Z)-(4-methylbenzylidene)-1,1-diphenylsilacyclobut-2-ene 35f

According to general procedure D, diphenylpropylbis(4-methylphenylethynyl)silane **6f** (0.500 mmol, 206 mg), H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was purified by flash column chromatography



(CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm Ø, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4-methylphenyl)-4-(Z)-(4-methylbenzylidene)-1,1-diphenylsilacyclobut-2-ene **35f** (NMR: 76%; isolated: 100 mg, 0.185 mmol, 37%) as a yellow foam.

¹H NMR (500 MHz, CDCl₃) δ : 7.76 – 7.74 (m, 4H), 7.46 – 7.44 (m, 2H), 7.44 – 7.40 (m, 2H), 7.38 – 7.35 (m, 4H), 7.24 – 7.22 (m, 2H), 7.16 (s, 1H), 7.09 (d, *J* = 7.9 Hz, 2H), 6.97 (d, *J* = 7.9 Hz, 2H), 2.32 (s, 3H), 2.26 (s, 3H), 1.46 (s, 12H).

¹¹B NMR (160 MHz, CDCl₃) δ : 29.4.

¹³C NMR (126 MHz, CDCl₃) δ : 166.9, 146.0, 137.8, 136.5, 136.3, 135.7, 135.5, 135.4, 133.1, 130.2, 129.3, 129.0, 128.4, 128.1, 126.7, 84.1, 25.0, 21.3, 21.1.

²⁹Si NMR (99 MHz, CDCl₃) δ : 1.2.

MS (HRMS – ESI⁺) Found 541.2725 (C₃₆H₃₈BO₂Si) requires 541.2729.

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4-methoxyphenyl)-4-(Z)-(4-methoxybenzylidene)-1,1-diphenylsilacyclobut-2-ene 35g

According to general procedure D, diphenylpropylbis(4-methoxyphenylethynyl)silane **6g** (0.500 mmol, 222 mg), H-B-9-

BBN dimer (0.0250 mmol, 6.10

mg, 5 mol%), and HBpin (0.600

mmol, 87.0 μ L) were reacted.

The product was purified by

flash column chromatography

(CombiFlash Isco

NextGen300+, 12 g SiO₂, 50

mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 3-

(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4-

methoxyphenyl)-4-(Z)-(4-methoxybenzylidene)-1,1-

diphenylsilacyclobut-2-ene **35g** (NMR: 70%; isolated: 188 mg,

0.330 mmol, 66%) as a yellow foam.

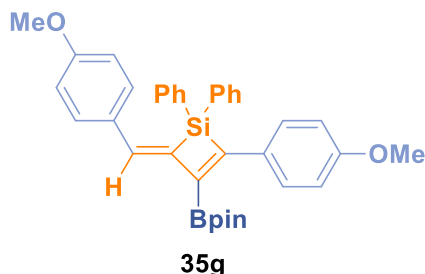
¹H NMR (500 MHz, CDCl₃) δ : 7.77 – 7.75 (m, 4H), 7.56 – 7.53 (m, 2H), 7.45 – 7.42 (m, 2H), 7.40 – 7.36 (m, 4H), 7.29 – 7.26 (m, 2H), 7.17 (s, 1H), 6.84 – 6.81 (m, 2H), 6.73 – 6.70 (m, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 1.47 (s, 12H).

¹¹B NMR (160 MHz, CDCl₃) δ : 29.2.

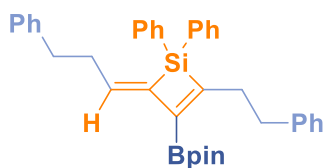
¹³C NMR (126 MHz, CDCl₃) δ : 166.0, 159.4, 158.5, 144.7, 135.7, 133.2, 132.4, 131.1, 130.2, 130.0, 128.4, 128.2, 127.8, 113.7, 113.7, 84.0, 55.2, 55.1, 25.0.

²⁹Si NMR (99 MHz, CDCl₃) δ : 1.1.

MS (HRMS – ESI⁺) Found 573.2636 (C₃₆H₃₈BO₄Si) requires 573.2627.



3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2-phenylethyl)-4-(Z)-(4-phenylbutylidene)-1,1-diphenylsilacyclobut-2-ene 35h



35h

According to general procedure D, diphenylpropylbis(4-phenylbut-1-ynyl)silane **6h** (0.500 mmol, 220 mg), H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were reacted. The product was

purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2-phenylethyl)-4-(Z)-(4-phenylbutylidene)-1,1-diphenylsilacyclobut-2-ene **35h** (NMR: 33%; isolated: 94.0 mg, 0.150 mmol, 30%) as a yellow foam.

¹H NMR (500 MHz, CDCl₃) δ : 7.64 – 7.61 (m, 4H), 7.45 – 7.41 (m, 2H), 7.38 – 7.35 (m, 4H), 7.20 – 7.15 (m, 4H), 7.13 – 7.09 (m, 2H), 7.04 – 6.99 (m, 4H), 6.26 (t, J = 6.9 Hz, 1H), 2.99 – 2.96 (m, 2H), 2.71 – 2.67 (m, 2H), 2.61 – 2.58 (m, 2H), 2.36 – 2.31 (m, 2H), 1.31 (s, 12H).

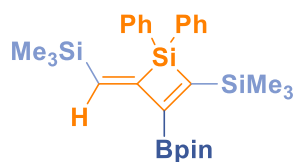
¹¹B NMR (160 MHz, CDCl₃) δ : 27.8.

¹³C NMR (126 MHz, CDCl₃) δ : 174.7, 144.9, 142.4, 142.1, 135.3, 134.2, 129.9, 128.4, 128.1, 128.1, 128.0, 127.9, 125.6, 125.5, 83.2, 36.9, 36.4, 36.4, 34.3, 25.0.

²⁹Si NMR (99 MHz, CDCl₃) δ : 1.2.

MS (HRMS – ESI⁺) Found 569.3022 (C₃₈H₄₂BO₂Si) requires 569.3042.

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-trimethylsilyl-4-(Z)-(2-trimethylsilyl-ethylidene)-1,1-diphenylsilacyclobut-2-ene 35i

**35i**

According to general procedure D, diphenylpropylbis(2-trimethylsilyl-ethylidene)silane **6i** (0.500 mmol, 188 mg), H-B-9-BBN dimer (0.0250 mmol, 6.10 mg, 5 mol%), and HBpin (0.600 mmol, 87.0 μ L) were

reacted. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO₂, 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-trimethylsilyl-4-(Z)-(2-trimethylsilyl-ethylidene)-1,1-diphenylsilacyclobut-2-ene **35i** (NMR: 45%; isolated: 89.0 mg, 0.175 mmol, 35%) as a yellow foam.

¹H NMR (500 MHz, CDCl₃) δ : 7.72 – 7.70 (m, 4H), 7.45 – 7.37 (m, 6H), 6.48 (s, 1H), 1.37 (s, 12H), 0.07 (s, 9H), –0.08 (s, 9H).

¹¹B NMR (160 MHz, CDCl₃) δ : 27.4.

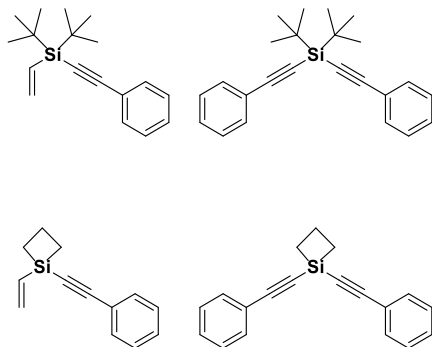
¹³C NMR (126 MHz, CDCl₃) δ : 179.9, 165.3, 135.6, 134.3, 131.1, 129.9, 127.8, 83.7, 25.1, 0.0, –0.5.

²⁹Si NMR (99 MHz, CDCl₃) δ : 8.0, –7.4, –11.1.

MS (HRMS – ESI⁺) Found 505.2564 (C₂₈H₄₂BO₂Si₃) requires 505.2580.

Failed Substrates

Unsuccessful substrates synthesis



Unsuccessful carboboration reaction

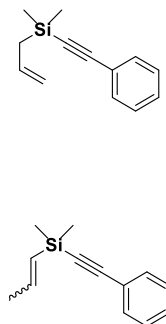
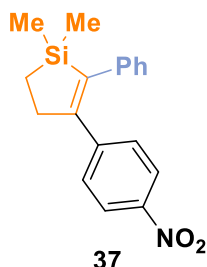


Figure 24: Failed substrates.

4.5.4 Downstream derivatisation

1,1-Dimethyl-5-phenyl-4-(4-nitrophenyl)-2,3-dihydrosilole **37**

1,1-Dimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33a** (0.250 mmol, 79.0 mg), 4-nitro-bromobenzene (0.250 mmol, 51.0 mg), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.0125 mmol, 9.0 mg, 5 mol%), PPh_3 (0.0190 mmol, 5.0 mg, 7.5 mol%), and K_2CO_3 (0.375 mmol, 52.0 mg) were suspended in toluene (1.00 mL). Water

(0.500 mmol, 9.0 μL) was added and the mixture was stirred at 100 $^\circ\text{C}$ for 16 hours. The mixture was cooled to room temperature and water (10.0 mL) was added. The mixture was extracted with diethyl ether (3×10.0 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO_2 , 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,1-dimethyl-5-phenyl-4-(4-nitrophenyl)-2,3-dihydrosilole **37** (56.1 mg, 0.365 mmol, 73%) as a pale yellow amorphous solid.

^1H NMR (500 MHz, CDCl_3) δ : 8.01 – 7.98 (m, 2H), 7.24 – 7.20 (m, 2H), 7.19 – 7.15 (m, 2H), 7.12 – 7.08 (m, 1H), 6.88 – 6.85 (m, 2H), 3.01 – 2.95 (m, 2H), 1.07 – 1.01 (m, 2H), 0.28 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ : 152.8, 147.9, 146.4, 145.6, 140.6, 129.3, 128.5, 127.9, 125.8, 123.3, 36.2, 9.4, –1.2.

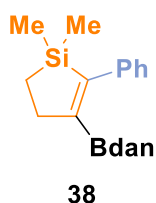
^{29}Si NMR (99 MHz, CDCl_3) δ : 23.5.

IR ν_{max} (film) 1593 (w), 1576 (w), 1509 (s), 1342 (s), 1249 (w).

MS (HRMS – MALDI $^+$) Found 310.12494 ($\text{C}_{18}\text{H}_{20}\text{NO}_2\text{Si}$) requires 310.12578.

MP (40/60 petroleum ether) 108 – 110 $^{\circ}\text{C}$.

1,1-Dimethyl-5-phenyl-4-(2,3-dihydro-1*H*-naphtho[1,8-de][1,3,2]-diazaborinyl)-2,3-dihydrosilole **38**



By modification of the method of Watson,¹³⁰ 1,1-dimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33a** (0.440 mmol, 139 mg), 1,8-diaminonaphthalene (0.750 mmol, 119 mg), FeCl_3 (0.0500 mmol, 8.0 mg, 10 mol%), and imidazole (1.50 mmol, 102 mg) were dissolved in acetonitrile (0.800 mL) and water (0.200 mL). The mixture was stirred at room temperature for 24 hours. The mixture was concentrated *in vacuo* and the product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 4 g SiO_2 , 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,1-dimethyl-5-phenyl-4-(2,3-dihydro-1*H*naphtho[1,8-de][1,3,2]-diazaborinyl)-2,3-dihydrosilole **38** (150 mg, 0.422 mmol, 96%) as a pale yellow amorphous solid.

¹³⁰ D. L. Cain, C. McLaughlin, J. J. Molloy, C. Carpenter-Warren, N. A. Anderson, A. J. B. Watson *Synlett* **2019**, 30, 787–791.

^1H NMR (500 MHz, CDCl_3) δ : 7.35 – 7.31 (m, 2H), 7.27 – 7.24 (m, 1H), 7.14 – 7.10 (m, 2H), 7.00 (dd, J = 8.3, 7.3 Hz, 2H), 6.92 (dd, J = 8.3, 0.9 Hz, 2H), 5.99 (dd, J = 7.3, 1.0 Hz, 2H), 5.34 (br s, 2H), 2.83 – 2.76 (m, 2H), 0.96 – 0.89 (m, 2H), 0.21 (s, 6H).

^{11}B NMR (160 MHz, CDCl_3) δ : 27.4.

^{13}C NMR (126 MHz, CDCl_3) δ : 158.8, 143.1, 141.2, 136.4, 128.6, 127.6, 126.8, 126.1, 119.8, 117.4, 105.7, 34.4, 10.0, –1.6.

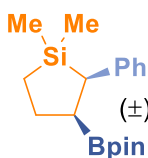
^{29}Si NMR (99 MHz, CDCl_3) 22.0.

IR ν_{max} (film) 3409 (s), 1625 (w), 1591 (s), 1500 (s), 1406 (w), 1032 (w).

MS (HRMS – MALDI⁺) Found 354.17077 ($\text{C}_{22}\text{H}_{23}\text{BN}_2\text{Si}$) requires 354.17224.

MP (40/60 petroleum ether) 82 – 84 °C.

($\pm$)-*cis*-1,1-Dimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-silolane **39**



39

1,1-Dimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33a** (0.160 mmol, 50.3 mg) and palladium on activated charcoal (0.0125 mmol, 1.3 mg, 5 mol%, 10% Pd) were dissolved in methanol (2.00 mL) in an autoclave. The vessel was purged pressurised with hydrogen (10 bar) and left stirring for 16 hours. The mixture was concentrated and diluted with diethyl ether (1.00 mL). The mixture was passed through a celite plug and all volatiles removed *in vacuo* to give ($\pm$)-*cis*-1,1-dimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) silolane **39** (49.7 mg, 0.157 mmol, 98%) as a colourless oil.

^1H NMR (500 MHz, CDCl_3) δ : 7.16 – 7.12 (m, 2H), 7.06 – 7.03 (m, 2H), 7.02 – 6.97 (m, 1H), 2.57 (d, $J = 7.9$ Hz, 1H), 2.11 – 2.05 (m, 1H), 2.01 – 1.90 (m, 1H), 1.61 (ddd, $J = 12.7, 7.9, 6.0$ Hz, 1H), 1.02 (s, 6H), 0.95 (s, 6H), 0.90 (ddd, $J = 14.7, 7.9, 2.9$ Hz, 1H), 0.62 (ddd, $J = 14.6, 10.3, 8.8$ Hz, 1H), 0.18 (s, 3H), –0.20 (s, 3H).

^{11}B NMR (160 MHz, CDCl_3) δ : 33.9.

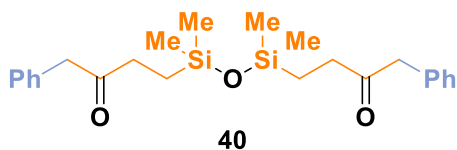
^{13}C NMR (126 MHz, CDCl_3) δ : 146.0, 128.0, 127.9, 123.9, 83.0, 36.8, 30.8 (br), 27.9, 24.9, 24.7, 13.8, –0.8, –3.2.

^{29}Si NMR (99 MHz, CDCl_3) δ : 23.1.

IR ν_{max} (film) 1319 (w), 1143 (w).

MS (HRMS – MALDI⁺) Found 339.19127 ($\text{C}_{18}\text{H}_{29}\text{BO}_2\text{SiNa}$) requires 339.19221.

1,11-Diphenyl-5,5,7,7-tetramethyl-5,7-disila-6-oxa-2,10-undecanedione **40**



A mixture of H_2O_2 (30% in water, 0.330 mL) and aqueous NaOH (2 M, 0.660 mL) was added to a stirred

solution of 1,1-dimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole **33a** (0.440 mmol, 137 mg) in THF (1.00 mL) at 0 °C. After 30 minutes the mixture was diluted with water (10.0 mL), extracted with diethyl ether (3×10.0 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO_2 , 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,11-diphenyl-5,5,7,7-tetramethyl-5,7-disila-6-oxa-2,10-undecanedione **40** (39.2 mg, 0.180 mmol, 41%) as a colourless oil.

^1H NMR (500 MHz, CDCl_3) δ : 7.34 – 7.30 (m, 4H), 7.27 – 7.23 (m, 2H), 7.22 – 7.19 (m, 4H), 3.69 (s, 4H), 2.45 – 2.36 (m, 4H), 0.75 – 0.68 (m, 4H), –0.02 (s, 12H).

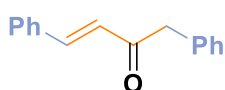
^{13}C NMR (126 MHz, CDCl_3) δ : 209.1, 134.6, 129.5, 128.8, 127.1, 49.6, 36.0, 11.8, 0.3.

^{29}Si NMR (99 MHz, CDCl_3) δ : 8.1.

IR ν_{max} (film) 1713 (s), 1265 (w), 1255 (w), 1032 (w).

MS (HRMS – EI^+) Found 425.194176 ($\text{C}_{24}\text{H}_{33}\text{O}_3\text{Si}$) requires 425.19627.

(E)-1,4-Diphenylbut-1-en-3-one **41**



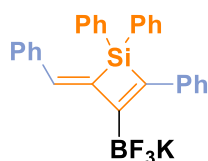
A mixture of H_2O_2 (30% in water, 0.330 mL) and aqueous NaOH (2 M, 0.660 mL) was added to a stirred solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-phenyl-4-(Z)-benzylidene-1,1-diphenylsilacyclobut-2-ene **35c** (0.100 mmol, 51.0 mg) in THF (1.00 mL) at 0 °C. After 30 minutes the mixture was diluted with water (10.0 mL), extracted with diethyl ether (3 $\times$ 10.0 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 12 g SiO_2 , 50 mm $\varnothing$, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give (E)-1,4-diphenylbut-1-en-3-one **41** (9.0 mg, 40 μmol , 40%) as a pale yellow amorphous solid.

^1H NMR (500 MHz, CDCl_3) δ : 7.63 (d, J = 16.1 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.41 – 7.32 (m, 5H), 7.30 – 7.20 (m, 3H), 6.78 (d, J = 16.1 Hz, 1H), 3.95 (s, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ : 197.4, 143.6, 134.6, 130.7, 129.6, 129.1, 128.9, 128.5, 127.2, 125.4, 48.6.

Data were in accordance with those previously reported.¹³¹

Potassium 3-(trifluoroborate)-2-phenyl-4-(Z)-benzylidene-1,1-diphenylsilacyclobut-2-ene 42



42

A solution of saturated aqueous KHF_2 (ca. 4.5 M, 500 μL) was added dropwise to a stirred solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-phenyl-4-(Z)-benzylidene-1,1-diphenylsilacyclobut-2-ene **35c** (0.740 mmol, 381 mg) in acetonitrile (2.30 mL) at 0 °C. After 4

hours, the mixture was concentrated *in vacuo* and the water removed by azeotrope with toluene and then acetone. The resulting solid was triturated with hot acetone (5 $\times$ 5.00 mL), filtered, and concentrated *in vacuo*. The resulting solid was dissolved in minimum hot acetone, layered with minimum hot 40/60 petroleum ether and slowly cooled to room temperature. The resulting crystals were washed with cold 40/60 petroleum ether and dried *in vacuo* to give *potassium 3-(trifluoroborate)-2-phenyl-4-(Z)-benzylidene-1,1-diphenylsilacyclobut-2-ene 42* (72.0 mg, 0.163 mmol, 22%) as colourless needles (CCDC 2328004).

^1H NMR (500 MHz, CDCl_3) δ : 7.68 – 7.67 (m, 4H), 7.37 – 7.31 (m, 9H), 7.24 – 7.23 (m, 2H), 7.09 – 7.01 (m, 5H), 6.80 (s, 1H).

^{11}B NMR (160 MHz, CDCl_3) δ : 2.4.

^{13}C NMR (126 MHz, CDCl_3) δ : 162.7, 148.2, 141.0, 139.6, 135.4, 134.2, 130.2, 129.0, 128.3 (t, J = 128 Hz), 127.6, 126.8, 126.6, 126.3, 124.8, 30.9.

^{19}F NMR (471 MHz, CDCl_3) δ : –134.2.

^{29}Si NMR (99 MHz, CDCl_3) δ : –0.6.

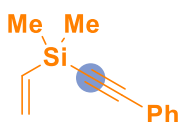
¹³¹ B. D. Mokar, R.-S. Liu, *Chem. Commun.* **2014**, 50, 8966–8969.

MS (HRMS – ESI⁺) Found 453.1454 (C₂₈H₂₁BF₃Si) requires 453.1463.

4.5.5 Mechanistic Studies

¹³C-Labelelling

Dimethyl(phenyl-1-¹³C-ethynyl)(vinyl)silane [¹³C]-21a



According to general procedure A, phenylacetylene-2-¹³C (0.400 mmol, 45.0 μL), *n*-butyl lithium (0.440 mmol, 2.5 M in hexanes, 176 μL), and chloro(dimethyl)vinylsilane (0.440 mmol,

[¹³C]-21a 60.0 μL) were reacted in THF (0.500 mL). The product was purified by flash column chromatography (CombiFlash Isco NextGen300+, 4 g SiO₂, 50 mm Ø, 40/60 petroleum ether) to give *dimethyl(phenyl-1-¹³C-ethynyl)(vinyl)silane* [**¹³C**]-21a (70.8 mg, 0.380 mmol, 95%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ: 7.50 – 7.46 (m, 2H), 7.34 – 7.27 (m, 3H), 6.20 (ddd, *J* = 20.0, 14.5, 1.8 Hz, 1H), 6.05 (dd, *J* = 14.5, 3.7 Hz, 1H), 5.91 (dd, *J* = 20.0, 3.8 Hz, 1H), 0.32 (d, *J* = 2.7 Hz, 6H).

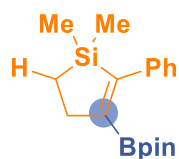
¹³C NMR (126 MHz, CDCl₃) δ: 136.7 (d, *J* = 5.2 Hz), 133.3 (d, *J* = 2.0 Hz), 132.2 (d, *J* = 2.2 Hz), 128.8, 128.3, 123.1 (d, *J* = 9.5 Hz), 106.3 (d, *J* = 137 Hz), 92.1 (satellites: d, *J*_{C-Si} = 87 Hz; d, *J*_{C-C} = 137 Hz), –1.3 (d, *J* = 5.5 Hz).

²⁹Si NMR (99 MHz, CDCl₃) δ: –24.7 (d, *J* = 87 Hz).

Data were in accordance with the unlabelled compound. *J*_{C-C} values are consistent with those previously reported.¹³²

¹³² R. M. Lynden-Bell, N. Sheppard, A. R. Todd *Proc. R. Soc. London. Ser. A. Math. Phys. Sci.* **1962**, 269, 385–403.

1,1-Dimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-4-¹³Csilole [¹³C]-33a



[¹³C]-33a

According to general procedure D, dimethyl(phenyl-1-¹³C-ethynyl)(vinyl)silane [¹³C]-**21a** (0.100 mmol, 18.6 mg), H-*B*-9-BBN dimer (5.0 μmol, 1.2 mg, 5 mol%), and HBpin (0.120 mmol, 18.0 μL) were reacted. The product was purified by

flash column chromatography (CombiFlash Isco NextGen300+, 4 g SiO₂, 50 mm Ø, 40/60 petroleum ether/EtOAc 100:0 to 0:100) to give 1,1-dimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-4-¹³C-silole [¹³C]-**33a** (30.9 mg, 0.0980 mmol, 98%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ: 7.25 – 7.21 (m, 2H), 7.17 – 7.12 (m, 3H), 2.76 – 2.69 (m, 2H), 1.15 (s, 12H), 0.90 – 0.84 (m, 2H), 0.19 (s, 6H).

¹¹B NMR (160 MHz, CDCl₃) δ: 30.6.

¹³C NMR (126 MHz, CDCl₃) δ: 157.2 (d, *J* = 56.6), 152.7 (br), 142.8, 127.9, 127.2 (d, *J* = 3.5 Hz), 125.8, 83.5 (d, *J* = 1.5 Hz), 34.6 (d, *J* = 35 Hz), 24.8, 10.7, –1.3 (d, *J* = 1.2 Hz).

²⁹Si NMR (99 MHz, CDCl₃) δ: 20.4 (d, *J* = 7.5 Hz).

Data were in accordance with the unlabelled compound. *J*_{C-C} values are consistent with those previously reported.¹³³

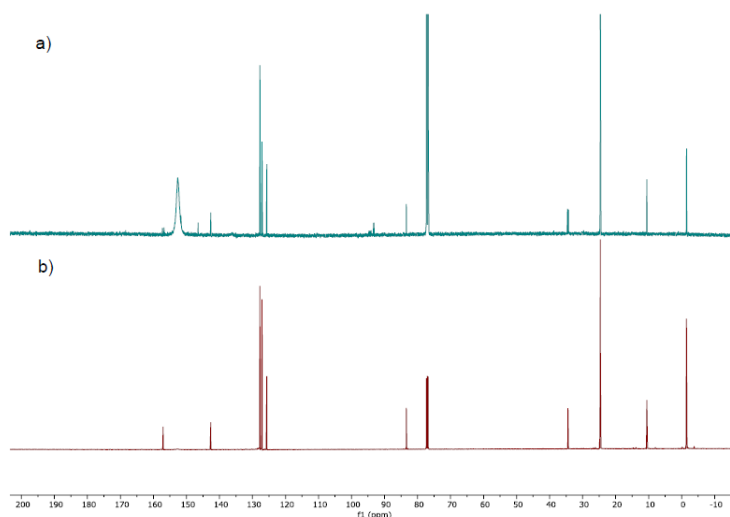
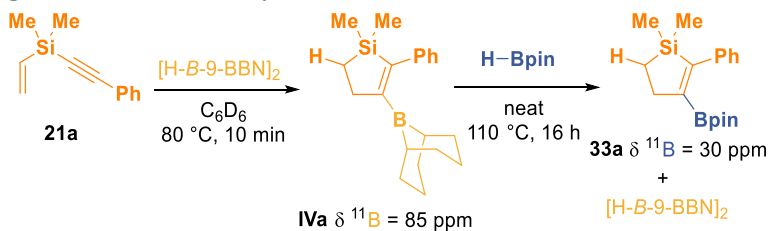


Figure 25: Overlaid ^{13}C NMR (126 MHz, CDCl_3) spectra of labelled (a) and unlabelled (b) 1,1-dimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrosilole.

Single-Turnover Experiment



In a J-Young tap NMR tube, H-B-9-BBN dimer (0.0500 mmol, 12.2 mg) and dimethyl(phenylethynyl)(vinyl)silane (0.200 mmol, 38.0 mg) were dissolved in C_6D_6 (0.500 mL), heated for 10 minutes at 80°C , and then analysed by ^1H and ^{11}B NMR spectroscopy. Volatiles were removed *in vacuo*, HBpin (0.100 mmol, 13.0 μL) was added and the tube was heated at 110°C for 16 hours. After cooling to room temperature, C_6D_6 (0.500 mL) was added and the mixture analysed by ^1H and ^{11}B NMR spectroscopy.

By the ^1H and ^{11}B NMR spectra of the first reaction, the silolenyl borane **IVa** was observed as the major product (^1H NMR (500 MHz, C_6D_6) 7.17 – 7.12 (m, 2H), 7.07 – 7.01 (m, 3H), 2.89 – 2.82 (m, 2H), 1.93 – 1.81 (m, 6H), 1.80 – 1.70 (m, 4H), 1.66 – 1.61 (m,

2H), 1.35 (ddt, $J = 12.4, 6.0, 3.1$ Hz, 2H), 0.97 – 0.92 (m, 2H), 0.25 (s, 6H). **¹¹B NMR** (160 MHz, C₆D₆) 84.6. Data were in accordance with those previously reported).³⁹ After reaction with HBpin, conversion to the silolenyl boronic ester was observed (in accordance with previous characterisation).

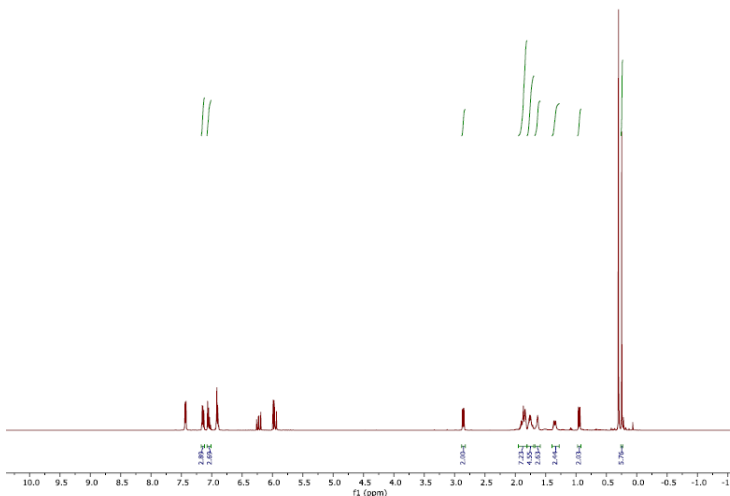


Figure 26: ^1H NMR (500 MHz, C_6D_6) spectrum of crude 1,1-dimethyl-5-phenyl-4-(9-borabicyclo[3.3.1]nonanyl)-2,3-dihydrosilole.

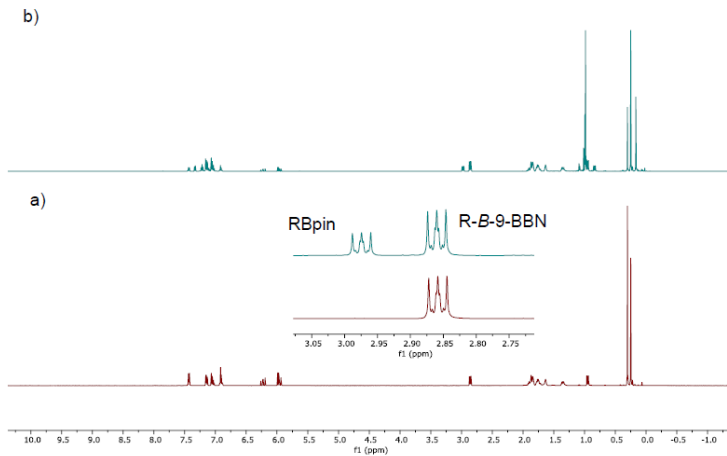


Figure 27: Overlaid ^1H NMR (500 MHz, C_6D_6) spectra of before (a) and after (b) reaction of 1,1-dimethyl-5-phenyl-4-(9-borabicyclo[3.3.1]nonanyl)-2,3-dihydrosilole with HBpin.

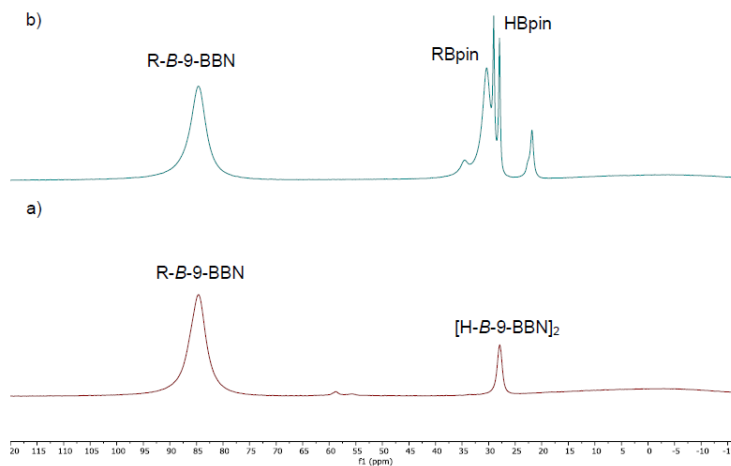
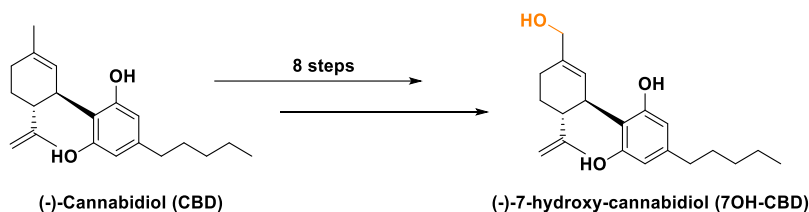


Figure 28: Overlaid ^{11}B NMR (160 MHz, C_6D_6) spectra of before (a) and after (b) reaction of 1,1-dimethyl-5-phenyl-4-(9-borabicyclo[3.3.1]nonanyl)-2,3-dihydrosilole with HBpin.

For more informations about the experimental data, such as cartesian coordinates, chemical spaces analyses, crystal data and NMR spectra, please check the following link: [anie202401737-sup-0001-misc_information.pdf](#).

5. Piers–Rubinsztajn reaction to unlock an 8-step synthesis of 7-hydroxy cannabidiol

Part of this chapter has been published as: E. Cocco, D. Iapadre, A. Brusa, P. Allegrini, S. P. Thomas, F. Pesciaoli, A. Carlone *RSC Adv.* **2024**, *14*, 2741–2744.



A novel 7-Hydroxy-cannabidiol (7-OH CBD) is a primary metabolite of cannabidiol (CBD) generated during the first stages of metabolism and for this reason is highly requested as analytical standard to study the mechanism by which CBD exerts its therapeutic efficacy. Moreover, interest in 7-OH CBD has significantly grown due to several effects that were observed in preclinical studies. Here we report a 8-step synthesis of 7-OH CBD from (-)-CBD featuring two telescoped transformations, that avoids harsh deprotection conditions. Piers–Rubinsztajn reaction has been successfully employed to unlock the final demethylation of the cannabidiol metabolite in acid-free fashion and mild conditions.

5.1 Introduction

5.1.1 Cannabis Sativa and natural cannabinoids

Cannabis Sativa, one of the three subspecies of the *Cannabis* family (alongside *Cannabis Indica* and *Cannabis Ruderalis*) and commonly known as hemp, has been cultivated for over 6000 years and employed widely in manufacturing, being an important resource to produce textile fibers (renown for being highly resistant), paper,

industrial oils and building materials.¹³³ Compared to the other two subspecies, *Cannabis Sativa* is a tall, thin-leaved plant that can grow 1.5 to 5.5 meters tall, often branchless,¹³⁴ and that is widely known for its versatility: indeed, *Cannabis Sativa* exploitation is not limited to the production of materials of great economic interest, but it extends to the extraction of substances for medical use and their therapeutic properties have been known since ancient times.

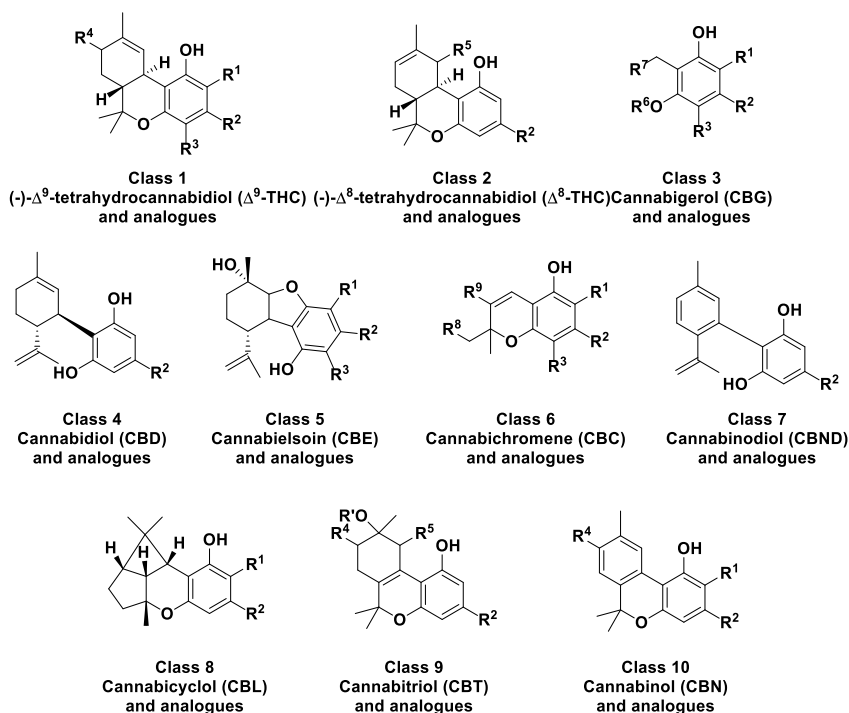


Figure 29: Phytocannabinoids main classes and their structures.

Up to now, between the more than 500 different compounds isolated from *Cannabis Sativa*, 120 have been identified as natural cannabinoids or derivatives, united by one specific structural characteristic: a typical terpenophenolic skeleton made up of 21

¹³³ E.B. Russo *Journal of Cannabis Therapeutics* **2001**, 1, 103-132.

¹³⁴ K.W. Hillig *Genetic Resources & Crop Evolution* **2005**, 52, 161-180.

carbon atoms, not found in any other botanical species.¹³⁵ The definition *cannabinoids*, or more precisely *phytocannabinoids*, is used to highlight their vegetal origin, therefore distinguishing them from endogenous cannabinoids (endocannabinoids) or synthetic cannabinoids. Depending on the structure, eleven different classes of cannabinoids have been found, and among them ten have relatively fixed substituents or structural modifications on their terpenophenolic skeletons (Figure 29).

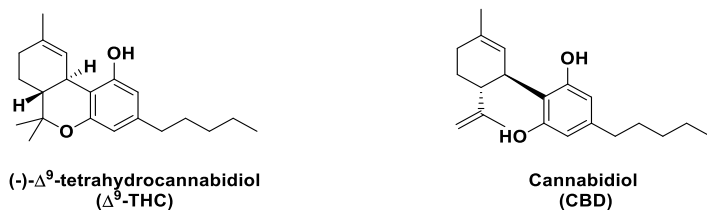


Figure 30: Comparison of the structures of Δ^9 -tetrahydrocannabinidiol (Δ^9 -THC) and Cannabidiol (CBD).

However, two among the phytocannabinoids have gathered the main interest, both in academy and industry, due to the pharmacological activity they showed: Δ^9 -tetrahydrocannabinidiol (Δ^9 -THC) and Cannabidiol (CBD). On a structural level it is possible to see THC as the cyclized form of CBD (Figure 30) and the difference arises from the fact that THC is characterized by a tricyclic skeleton condensed, making it more stable and less polar than cannabidiol. Both they have the same brute formula $C_{21}H_{30}O_2$ and therefore constitute a pair of isomers constitutional.

Indeed, when in presence of Lewis acids or strong Brønsted acids, cannabidiol undergoes a cyclisation to THC easily, resulting in substantial change in the biological activities.¹³⁶ While CBD does not exhibits any psychotropic activity, Δ^9 -tetrahydrocannabinidiol is

¹³⁵ M.A. Elsohly, M.M. Radwan, W. Gul, S. Chandra, A. Galal *Springer International Publishing*, **2017**.

¹³⁶ R. K. Razdan, in *The Total Synthesis of Natural Products*, Wiley, **2007**, vol. 4, pp. 185–262.

known to be a psychotropic and hallucinogenic substance, actually being the main psychoactive constituent present in preparations obtained from Cannabis.¹³⁷ For this reason, compounds obtained from Cannabis have been labelled as narcotics and subjected to restrictions and strict control, making their production and trade illegal in many countries. These restrictions have limited the scientific research on the potential pharmaceutical properties of cannabidiol and its derivatives, research which has been resumed and has continued intensified following the recent easing of restrictions in most countries until, since the end of 2017, the World Health Organization (WHO) has declared that Cannabidiol is no longer classified as a controlled substance.¹³⁸ Indeed, cannabidiol is non-psychoactive and has shown some analgesic, anticonvulsant, and anti-inflammatory activities: differently from THC, it does not appear to act at the level of central nervous system as it has low affinity for cannabinoid receptors called CB1 and CB2. The first is present mainly in the central nervous system and in non-neuronal tissues (glands, heart, lungs, gastrointestinal tract), while the second is present mainly in the cells of the immune system and in general in lymphoid tissues. These receptors can bind both endocannabinoids and cannabinoids, that constitute the physiological substrate, both Δ^9 -tetrahydrocannabidiol, which explains its strong action at the level of the central nervous system as a psychoactive substance. On the other hand, instead, cannabidiol appears to interact with the CB1 and CB2 receptors indirectly.¹³⁹

¹³⁷ S. Tchilibon, R. Mechoulam *Organic Letters* **2000**, 2, 21, 3301-3303.

¹³⁸ Drugs (psychoactive): Cannabidiol (compound of cannabis), WHO, **2017**.

¹³⁹ H. Li, Y. Liu, D. Tian, L. Tian, X. Ju, L. Qi, Y. Wang, C. Liang *Eur. J. Med. Chem.* **2020**, 192, 112163.

5.1.2 Cannabidiol and its properties

Cannabidiol was first isolated from Cannabis by Adams and coworkers¹⁴⁰ in 1940 and it is not naturally present in *Cannabis Sativa*, but an artifact obtained from the decarboxylation of the corresponding Cannabidiolic acid (CBDA) during the desiccation process (Figure 31).¹⁴¹

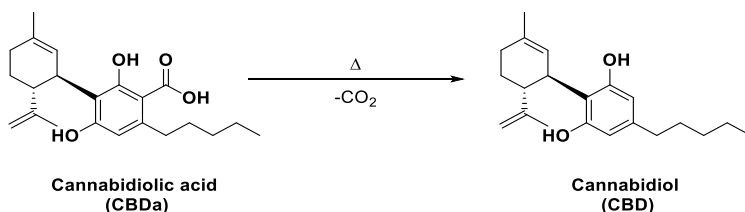


Figure 31: Decarboxylation process of the cannabidiolic acid (CBDA) to obtain cannabidiol (CBD).

Through absorption spectra and catalytic hydrogenation reduction reactions, the main functional groups on the molecules have been identified since the beginning, however, the proposed structure was not correct and the correct structure has been unfold twenty-three years later only, after an accurate NMR analysis carried out by Mechoulam and coworkers.¹⁴² Next, in 1977, thanks to the efforts of Jones and coworkers, the crystalline structure of cannabidiol has been determined, as well as its two optical isomers (Figure 32).

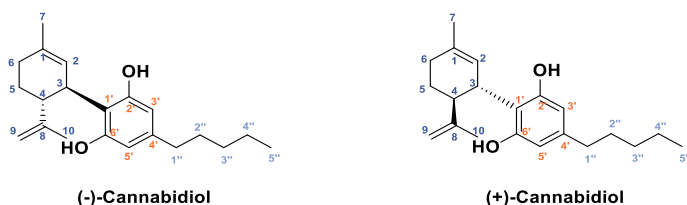


Figure 32: the two optical isomers of cannabidiol.

¹⁴⁰ R. Adams, M. Hunt, J.H. Clark *J. Am. Chem. Soc.* **1940**, 62, 735-737.

¹⁴¹ L. Hanus, Z. Krejci, *Acta Univ. Palacki. Olomuc.* **1986**, 114, 11-29.

¹⁴² R. Mechoulam, Y. Shvo *Tetrahedron* **1963**, 19, 2073-2078.

Considering the three-dimensional structure of cannabidiol, it has been hypothesised and proved that the terpene ring, in the most stable chair conformation, and the aromatic ring are arranged perpendicular to each other to minimize the tension related to the steric hindrance. The main difference between these two configurations is the stereochemistry of the connection between the resorcinol moiety and the terpene core. (-)-CBD exists in natural *Cannabis* plants, while (+)-CBD can only be obtained by organic synthesis: all the naturally occurring CBD-type cannabinoids have a (-)-trans-(1*R*,6*R*) absolute configuration, presumably corresponding to negative optical rotation.¹⁴³ Research on the determination of structure, stereochemistry and total synthesis of cannabidiol were stimulated by the potential that this molecule showed at the time of its discovery already. Its properties as potential antiepileptic have along unofficial story and were so well known that the determination of its structure was undertaken mainly to study possible structural correlations with anticonvulsant drugs already on the market.

Currently, there are several properties attributed to cannabidiol: analgesic, anti-inflammatory, antihypertensive, anticonvulsant and anti-allergic activity, in addition to the fact that it seems able to attenuate the effects generated by Δ^9 -tetrahydrocannabidiol, as it shows an anxiolytic activity. However, many of these properties have not been recognised officially yet due to limitations in clinical trials imposed by different countries and are currently being studied in various academic fields. Studies on the neuroprotective activity of cannabidiol are still in a pre-clinical stage despite their potential huge impact on the treatment of neurodegenerative diseases such as Alzheimer's disease, as well as studies on the potential activity of cannabidiol as an antioxidant.

¹⁴³ L. Vollner, D. Bieniek, F. Korte *Tetrahedron Lett.* **1969**, 3, 145-147.

On the other hand, the anticonvulsant activity of cannabidiol has been confirmed: in 2018 FDA (*Food and Drug Administration*) and EMA (*European Medicines Agency*) have approved the use of a cannabidiol-based drug to for the treatment of severe forms of childhood epilepsy resistant to common drugs already on the market.

The use of CBD has been shown to be safe as it appears to present limited side effects and low toxicity, without inducing addiction even with a prolonged administration. However, the main limitations to the exploitation of cannabidiol as a drug arise from its scarce solubility and its chemical instability. For this reason, several research groups have begun to focus on compounds or metabolites of cannabidiol, both natural and synthetic, even speculating that some of the biological effects attributed to cannabidiol could be related to its primary metabolites instead.

So far, cannabidiol has shown a wide range of opportunities in the field of pharmacology, both as an absolute drug and in combination with other drugs, setting the starting point for the design and the development of future drugs.

5.1.3 CBD and its metabolites

Nowadays, the metabolism of cannabidiol has been defined, as well as the structures of the metabolites found in major concentration: up to one hundred different metabolites have been isolated from different organisms.¹⁴⁴ Intriguingly, it has been observed that the most of the cannabidiol administered has been excreted intact; however, its pharmacokinetics are strongly dependent on the mode of administration, resulting in a significant

¹⁴⁴ DJ. Harvey, *Biochemistry and physiology of substance abuse* (Watson RR, ed.) 279–365, 1991.

variation of the amount of metabolites that can be found in the body fluids or in the secretions.

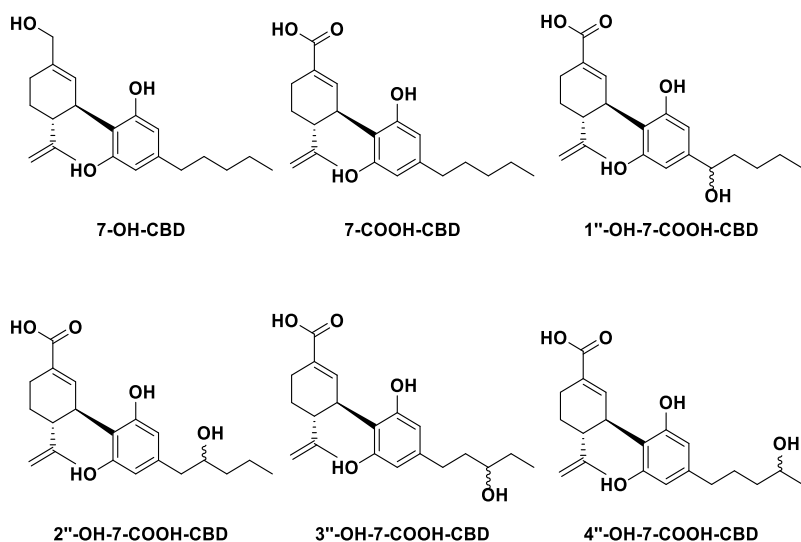


Figure 33: Metabolites observed during the first phase of cannabidiol metabolism.

Attending to the findings (Figure 33), the first step of the metabolism of cannabidiol is its hydroxylation at the C7, leading to the formation of 7-hydroxy cannabidiol (7OH-CBD), which is then further oxidized at the same position to its acid counterpart, 7-carboxy-cannabidiol (7COOH-CBD). At this point, different hydroxylations can take place at the pentyl chain, leading to the formation of different hydroxy-alkyl carboxyl acids, that can be further oxidated on the terpene moiety.¹⁴⁵ After being isolated, many of the primary metabolites have been synthesised to verify the chemical structure and obtain a detailed characterisation. *In vivo* studies are limited to the analysis of composition of the metabolic pattern of cannabidiol, however the majority of these metabolites lack of a systematic study to describe their biological activity in the human body, even though it has been thought they could show therapeutic effects if used in relevant concentrations.¹⁴⁵

¹⁴⁵ I. Ujvary, L. Hanus, *Cannabis and Cannabinoid Research*, 1.1, 2016.

Nowadays, *in vitro* studies on 7-hydroxy cannabidiol and 7-carboxyl cannabidiol are the only ones that have been conducted, stating their anti-inflammatory activity and their capacity to act as free-radical generation inhibitors.¹⁴⁶

In this chapter, however, the attention will be focused on one only of these metabolites, the 7-hydroxy cannabidiol, therefore some key features of this compound have to be highlighted.

5.1.4 7-hydroxy cannabidiol: origin, structure and importance

As already mentioned, 7-hydroxy cannabidiol (7OH-CBD) is a terpene-phenolic molecule, coming from the metabolism of cannabidiol and, as cannabidiol itself, its structure can be divided in three sections, common to several compounds belonging to this family: a) terpene portion, b) aromatic portion and c) *n*-pentyl portion.

On the terpen portion, two unsaturations, one endocyclic while the other one is exocyclic, and a hydroxyl group are present, while the aromatic moiety consists of a *para* disubstituted 2',6'-resorcinol, bearing a bond with the terpene moiety in position 1' and a *n*-pentyl chain in position 4'. If compared to cannabidiol, the only difference is the presence of a hydroxyl group on the terpene moiety, specifically on C7, and, as in all cannabidiol-related molecules, two stereocenters are present, on C3 and C4 of the terpene moiety respectively.

As already mentioned, 7-hydroxy cannabidiol is obtained from the first step of the CBD metabolism in mammals as result of the oxidation process carried out in the liver by two microsomal enzymes, CYP2C19 and CYP2C9. The latter belong to the P460

¹⁴⁶ R. Mechoulam, S. Tchilibon, E. Fride Pharmaceutical compositions comprising cannabidiol derivatives. US Patent 7759526, **2010**.

cytochrome family, a class of enzymes in which an EME group is present and able to function as monooxygenases in the oxidation of different types of compounds.

Given the increasing interest cannabidiol and its related compounds are gathering in the scientific community, 7-hydroxy cannabidiol is playing a significant role among the metabolites studied.

Indeed, the progressive growth of this research field is related to the understanding of pharmacodynamics and pharmacokinetics of cannabidiol and its analogues, therefore requiring a deep and accurate knowledge of processes that CBD undergoes from the administration to the excretion: it is essential to shed light on how cannabidiol is distributed in the body or where it tends to accumulate, by evaluating its levels in different matrices such as blood, urine or hair.

Thus, standard control samples of both cannabidiol and its major metabolites are required and 7-hydroxy cannabidiol, being a primary metabolite, can be an excellent analyte to use as reference, which is why it is required to be produced in significant quantities and used as a standard for the validation of analytical methods.^{147,148}

On the other hand, 7-hydroxy cannabidiol is being studied for its potential pharmaceutical activity: indeed, since the first pure cannabidiol-based anticonvulsant drug was released, several research groups have speculated that the products of its metabolism could also have the same kind of pharmacological activity. In one study in particular, patented in 2017, researchers

¹⁴⁷ S. Malaca, M. Gottardi, F. Pigliasco, S. Barco, A. Cafaro, E. Amadori, A. Riva, M. Marcenaro, P. Striano, G. Cangemi, R. Pacifici, S. Pichini, F. P. Busardò *Pharmaceuticals* **2021**, 7, 14.

¹⁴⁸ A. F. Lo Faro, B. Venanzi, G. Pilli, U. Ripani, G. Basile, S. Pichini, F. P. Busardò *Journal of Pharmaceutical and Biomedical Analysis* **2022**, 217, 114841.

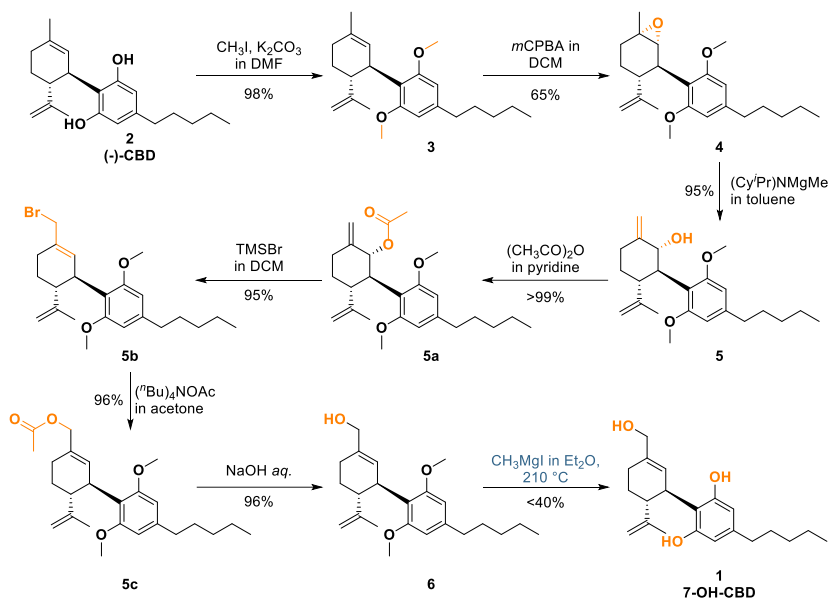
focused on the potential of 7-hydroxy cannabidiol as an anti-epileptic for treating the same severe forms of childhood epilepsy for which the use of cannabidiol has been authorised.¹⁴⁹ More in details, the use of 7-hydroxy cannabidiol in pure form or in combination with another hydroxylated cannabinoid has shown positive effects as antiepileptic on animals, proving to be more effective than cannabidiol itself for the regulation and control of spasms, however no test on the human body has been carried out yet.

Basing on these outcomes, the research on this metabolite of cannabidiol is proving to be promising, even though it is still far from being well explored: 7-hydroxy cannabidiol and the other metabolites are indeed difficult to be isolated, being easily metabolised further and further by the organism.

However, to deepen the study on this metabolite, reliable and scalable methods of preparation are highly requested and one of them is of course their artificial synthesis.

The development of a robust synthesis is, therefore, critical in enabling any future prospect of targeted clinical trials. Of significant note, and inhibiting many synthetic efforts, is that in the presence of acid CBD, and its metabolites, cyclize to form Δ^9 -tetrahydrocannabinol (Δ^9 -THC), and derivatives, it is therefore imperative to plan a feasible synthesis that avoids such acidic reaction conditions.¹³⁷

¹⁴⁹ C. Stott, N. Jones, B. Whalley, G. Stephens, C. Williams, "7-hydroxy-cannabidiol (7-OH-CBD) and/or 7-oh-cannabidivarin (7-OH-CBDV) for use in the treatment of epilepsy.", Gran Bretagna, US 2017/0209390, **2017**.



Scheme 50: 8-step synthesis of 7-hydroxy cannabidiol from CBD reported by Mechoulam and coworkers.

The directed oxidation of cannabinoids to obtain hydroxy-derivatives is a reported strategy which involves the use of selenium dioxide (SeO_2) as an oxidizing agent,¹⁵⁰ however, even though used in the oxidation of limonene, it lacks of regioselectivity, leading to the formation of a mixture of different hydroxylated products.¹⁵¹

Unlike other metabolites of cannabidiol, there is a synthetic procedure of 7-hydroxy cannabidiol, developed in 2000 by R. Mechoulam and S. Tchilibon (Scheme 50): up to now it is the only synthetic process to get this metabolite reported and consists of a multi-step synthesis to obtain the desired product **1** with eight reaction steps from the cannabidiol **2**. The synthetic process is straightforward, starting with a rapid succession of methylation of

¹⁵⁰ A. Breuer, C. G. Haj, M. V. Fogaça, F. V. Gomes, N. R. Silva, J. F. Pedrazzi, E. A. D. Bel, J. C. Hallak, J. A. Crippa, A. W. Zuardi, R. Mechoulam, F. S. Guimarães *PLoS One* **2016**, *11*, e0158779.

¹⁵¹ S. Yoshitsugu *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3348–3349.

phenol groups, regioselective epoxidation of the endocyclic alkene and base-promoted epoxide opening allowed to obtain the secondary alcohol intermediate **5**. Attending to the authors report, the use of the methyl group as protecting agent for the phenol moieties was forced by the fact that bulkier protecting groups prevented the epoxide opening step leading to **5**. At this point, acetylation converted the hydroxy group in a good leaving group, allowing the next allylic bromination to happen, leading to compound **5b**. Compound **5b** was then acetoxylated on C7 and the ester was then hydrolysed to get compound **6**, that was deprotected in the next step, with a key limitation being the demethylation of the protected aryl OH groups requiring the use of methyl magnesium iodide in neat conditions at 210 °C.¹³⁸

Indeed, the main challenge lied in the impossibility to use different protecting groups from the methyl groups; moreover, the usual Lewis acidic conditions for the deprotection of methyl ethers could not be employed due to the intrinsic nature of CBD-like structure to undergo cyclisation in acidic environment to give THC-like scaffolds. Therefore, the use of strong basic conditions to pull the double nucleophilic deprotection on an extremely electron-rich system such as the aromatic moiety of the CBD. However, the use of extreme deprotection conditions, such as methyl magnesium iodide at 210 °C, lowers drastically the applicability of the system, being not only difficult to replicate, but also extremely dangerous to perform, especially in higher scale. The harsh conditions involved in this deprotection concisely highlights the challenge that lies in the final demethylation, where acidic conditions are to be avoided and hard-to-perform basic conditions lead to mediocre yields (usually lower than 40%) and difficult, dangerous for the operator set ups.

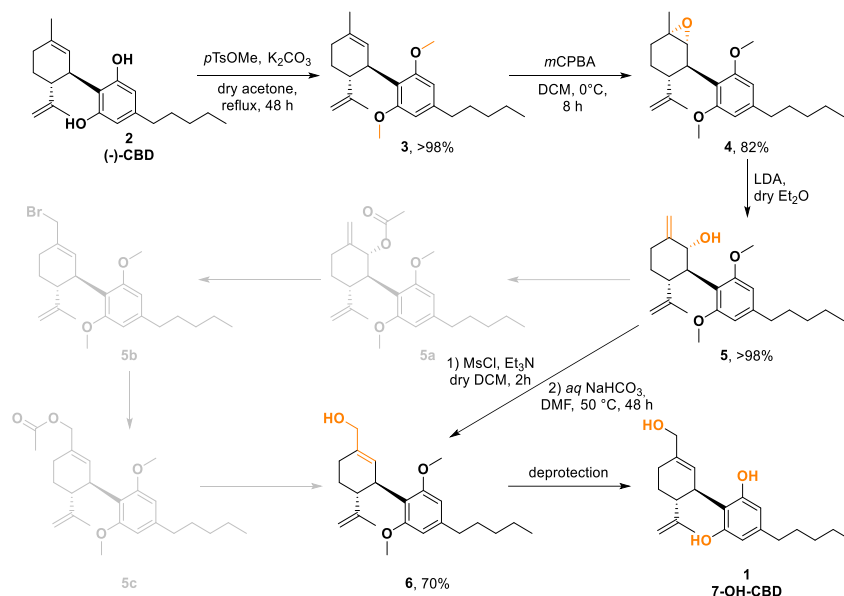
5.2 Aim of the project

The aim of the project has been to design and perform synthesis of 7-OH CBD **1** that could be of industrial interest and generate enough material to undertake preclinical studies. Therefore, in collaboration with Indena S.p.a (our industrial partner in this work), the previous work of Mechoulam and coworkers has been kept as starting point with the goal to overcome the critical passages and develop a new approach to obtain 7-hydroxy cannabidiol (**1**) from cannabidiol (**2**). Since from the outset, it has been decided to avoid the forcing conditions for the final deprotection, aiming to lower the operation risks for the operator, redesigning the synthesis to be shorter at the same time. A successful and reliable mild deprotection method has been found making use of BCF as catalyst in presence of pentamethyldisiloxane and, even though the overall number of synthetic steps could not be lowered, they have been redesigned to be performed in milder and safer conditions, therefore enabling the synthesis of 7-hydroxy cannabidiol **2** in higher yields and in a greener fashion.

5.3 Development and Outcomes

5.3.1 Synthesis Design

The approach proposed has been designed following two guidelines: to reduce the overall amount of synthetic steps and to avoid potentially harmful reagents and reaction conditions (Scheme 51). The synthetic pathway starts in a way similar to that one proposed by Mechoulam and coworkers, with a sequence of methylation, epoxidation and base-promoted epoxide opening to get the secondary alcohol **5**.

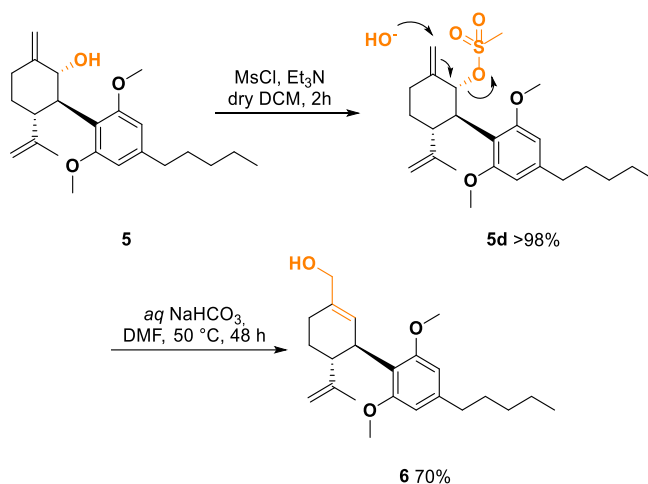


Scheme 51: Our synthetic pathway toward 7-hydroxy cannabidiol from CBD.

As already mentioned, the methyl protecting groups were the only ones that did not interfere with the subsequent epoxide opening in this case it has been proceeded using methyl paratoluensulfonate as methyl source,¹⁵² being less harmful and easier to handle (being a solid) compared to methyl iodide, and compound **3** has been obtained in an almost quantitative yield. The regioselective epoxidation leading to compound **4** afforded a slightly better yield (82%) when conducted under temperature control, while, about the following base-promoted epoxide opening, LDA proved to be efficient and cost effective for the purpose,¹⁵³ providing allylic alcohol **5** in quantitative yield, without any purification needed. All these steps afforded the same yields when the reaction scale was increased from 200 mg to a multigram scale.

¹⁵² M. A. Arai, Y. Yamaguchi M. Ishibashi Org. *Biomol. Chem.* **2017**, *15*, 5025–5032.

¹⁵³ A. Yasuda, S. Tanaka, K. Oshima, H. Yamamoto H. Nozaki *J. Am. Chem. Soc.* **1974**, *96*, 6513–6514.



Scheme 52: Telescoped secondary alcohol activation followed by allylic rearrangement leading to intermediate **6**.

At this point, an allylic rearrangement of **5**, that would represent an important shortcut in the synthesis and directly afford primary alcohol **6**, was envisaged; if successful, this would indeed provide an advanced intermediate to 7-OH CBD **1**. The approach was designed with a sequence of alcohol activation enabling the following and $\text{Sn}2'$ reaction: indeed, basing on the report of McAulay and Clark on perillyl alcohol,¹⁵⁴ the secondary alcohol **5** has been mesylated and then, after a solvent exchange, it underwent the allylic rearrangement using hydroxide as a nucleophile in aqueous conditions, leading to compound **6** with yields up to 70% (Scheme 52).

About the $\text{Sn}2'$ reaction on intermediate **5d** it should be noted that, given the multiple steps, complex, biphasic solvent and reagent mixture, the yield of the reaction is scale dependent.

Indeed, when the scale of the reaction was increased to a multigram scale, the yield of the reaction dropped from 70% to a maximum of 50%.

¹⁵⁴ K. McAulay, J. S. Clark *Chem.–Eur. J.* **2017**, 23, 9761–9765.

However, to our delight, the remaining mass balance was the diastereomer of the allylic alcohol **5**, obtained from competitive the nucleophilic substitution carried out by the hydroxide on the intermediate **5d**, that could be recovered to be mesylated and subjected to the allylic rearrangement again. Interestingly, after some outcomes recently obtained in our group, it has been observed that if the biphasic $\text{Sn}2'$ reaction on **5d** is carried producing mechanical collision in the reaction vessel (performed introducing two glass sticks in the flask during the stirring) the reaction conversion towards the desired compound **9** increases.

5.3.2 Deprotection Trials

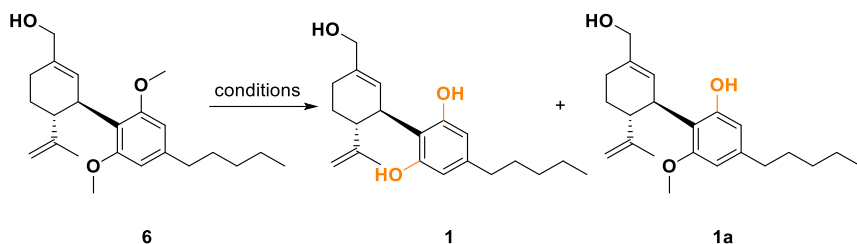
With a solid and somehow scalable approach towards compound **6** in hand, the demethylation reaction to afford 7-hydroxy cannabidiol **1** has been investigated, but the removal of the methoxy-protecting groups on the phenolic moieties posed a stimulating challenge.

Indeed, as already stated, strong acids or acidic conditions induce a tertiary carbocation formation on the isopropenyl substituent resulting in a cyclization to give the THC skeleton, while strong bases in oxidizing conditions give hydroxy-1,4-benzoquinone derivatives as byproducts, therefore posing strict limitations to the deprotection step. In order to overcome these issues, different deprotecting agents have been tested.¹⁵⁵ When mild Lewis acids, such as FeCl_3 , AlCl_3 or AcCl , alone or in combination with other reagents, were employed (entries 1-4), complete recovery of the starting material **6** or decomposition have been observed.

Table 17: Unsuccessful deprotection conditions. Unless otherwise stated all the reactions were carried out on a 0.1 mmol scale. a) on 0.2 mmol scale, NaSEt 20 eq., dry DMF 140 °C, 24 h, then NaSEt 30 eq., dry DMF, 145 °C, 20 h; b) isolated yield; c) on 2 mmol scale, NaSEt

¹⁵⁵ P. G. M. Wuts, T. W. Greene "Greenes's Protecting Groups in Organic Synthesis" 4th edition 2007, chapter 3, page 370, Wiley.

20 eq., dry DMF, 140 °C, 24 h, then Ac₂O, TEA, DMAP, dry DCM, rt, 12 h, then NaSEt 30 eq., dry DMF, 145 °C, 20 h; d) on 0.1 mmol scale, NaSEt 20 eq., dry DMF, 140 °C, 24 h, then MeCOOH 10.5 eq., 24 h, then NaSEt 30 eq., dry DMF, 145 °C, 20 h.



Entry	Solvent	Reag. 1	Coreag.	T (°C)	Time (h)	Conv (%)	1 Y _{NMR} (%)	1a Y _{NMR} (%)
1	DCM	AlCl ₃ (1 eq.)	Et ₃ N (2.85 eq.)	0 °C to reflux	3 h	0%	-	-
2	CH ₃ CN/THF 1:1	AcCl (5 eq.)	Nal (6 eq.)	0 °C to rt	21 h	0%	-	-
3	Ac ₂ O	FeCl ₃ (1 eq.)	-	80 °C	24 h	>95%	-	-
4	DCM	AlCl ₃ (3.5 eq.)	-	rt	3 h	>95%	-	-
5	Dry DMF	HPPPh ₂ (4 eq.)	^t BuOK (4 eq.)	80 °C	15 h	87%	-	85
6	Dry DMF	EtSNa (6 eq.)	-	150 °C	24 h	75%	Traces at MS	70
7^a	Dry DMF	EtSNa (50 eq.)	-	145 °C	44 h	>95%	5 ^b	30 ^b
8^c	Dry DMF	EtSNa (50 eq.)	-	145 °C	56 h	90%	-	90
9^d	Dry DMF	EtSNa (50 eq.)	-	145 °C	68 h	85%	-	80

Attention was then turned to the use of nucleophilic deprotecting reagent obtained from the combination of HPPPh₂ and ^tBuOK (entry 5), which has been exploited in mild deprotection protocols of aryl methyl/benzyl/allyl ethers.¹⁵⁶ However, a single phenolic oxygen has been deprotected only, even under forcing conditions or when subjecting the mono-deprotected product **1a** to a second round of the deprotection reaction.

¹⁵⁶ W. Pan, C. Li, H. Zhu, F. Li, T. Li, W. Zhao *Org. Biomol. Chem.* **2021**, 19, 7633–7640.

An additional nucleophilic deprotecting reagent tested was the sodium ethanthiolate: despite a successful deprotection of CBD dimethyl ether **3** has been reported using 4 equivalents NaSEt at 150 °C for 5 hours leading to CBD **2**,¹⁵⁷ when this approach has been tested on 7-hydroxy cannabidiol precursor **6** (entry 6, two more equivalents of NaSEt were used due to the presence of the free hydroxy group), it proved to be unsuccessful, yielding to the mono protected compound **1a** and the desired 7OH-CBD **1** in traces visible at the mass analysis only. This issue suggests that in the presence of nucleophiles such as HPPPh₂ or NaSEt the first demethylation provides a methoxy phenolate that increases the electron density of the aromatic ring, rendering the second deprotection more difficult.

Always making use of sodium ethanethiolate, an approach recently reported by Passerella and coworkers has been tested: indeed, they managed to successfully deprotect the CBD dimethyl ether in small scale using a large excess of NaSEt, in two sequential steps, isolating the monodeprotected intermediate.¹⁵⁸ However, this method failed when it has been tested on our precursor **6** (entry 7): 7-OH CBD **1** was obtained in very low yield, barely visible through the NMR spectroscopy and mass analysis despite the extremely pushing reaction conditions. Eventual monodemethylation followed by derivatisation of phenolate **1a** with an easily removable electron withdrawing group to possibly enable the second deprotection were attempted, along with adjusting the pH, but no traces of the desired 7-hydroxy cannabidiol **1** have been observed (entries 8-9).

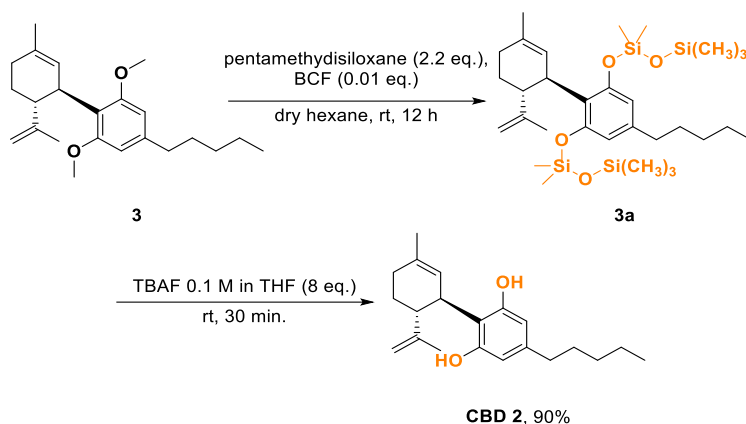
¹⁵⁷ K. Abdur-Rashid, W. Jia, K. Abdur-Rashid WO 2020/232545A1, 2020.

¹⁵⁸ P. Marzullo, A. Maiocchi, G. Paladino, U. Ciriello, L. Lo Presti, D. Passarella *Eur. J. Org. Chem.* **2022**, 22, e202200392.

After these unsuccessful attempts to deprotect compound **6**, it has been thought to recur to the use of boron chemistry, more in detail to the Piers-Rubinsztajn reaction, although it had not been reported for the purpose in the context of cannabinoids.¹⁵⁹ Indeed, in paper recently published by Adronov and coworkers, the use of tris(pentafluorophenyl) borane (BCF) as a catalyst in the presence of silyl hydrides constitutes a mild and scalable deprotection methodology for aryl ethers (Scheme 7).³⁷ As shown, Lewis basic oxygen species, such as methyl ethers, perform a nucleophilic attack on the activated Si-center of the Lewis complex formed between BCF and a siloxane, then a reductive cleavage of both O-methyl groups on the phenolic oxygens take place releasing methane and leading to the formation of Ar–O–Si bonds in their place: at this point, the silicon protecting group can be easily removed with TBAF in acid-free conditions.

More importantly for the case of deprotecting dimethoxy derivative **6**, this approach allows to avoid the formation of the electron-rich phenolate intermediate, capping the negative charge with the silane and therefore allowing a second nucleophilic attack leading to the formation of the disilylated product.

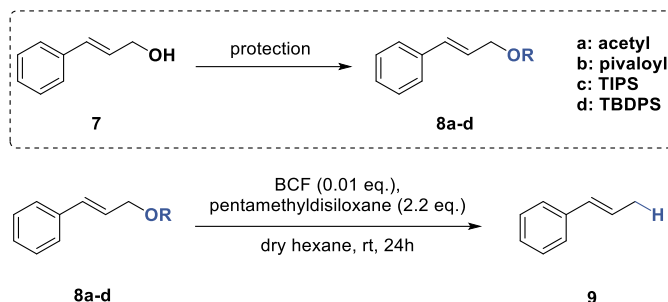
¹⁵⁹ a) S. Rubinsztajn, J. A. Cella *Macromolecules* **2005**, 38, 1061–1063. b) J. M. Blackwell, E. R. Sonmor, T. Scoccitti, W. E. Piers *Org. Lett.* **2000**, 2, 3921–3923.



Scheme 53: Piers-Rubinsztajn reaction trial to deprotect CBD dimethyl ether **3**.

Initial tests using CBD dimethylether **3** as a model substrate were very encouraging: ^1H NMR analysis showed the complete formation of CBD **2** as the main product (Scheme 53), confirmed by the complete disappearance of the methoxy singlet at 3.71 ppm and the appearance of the broad doublet corresponding to the aromatic protons of **CBD 2** at 6.22 ppm. However, when the 7-hydroxy cannabidiol precursor **6** was trialed, the only product observed by NMR analysis was the **CBD 2**: indeed, as demonstrated by Yamamoto, primary and allylic alcohols can be reduced to alkanes using BCF and $\text{HSi}(\text{Et})_3$,¹⁶⁰ therefore, under the reductive cleavage of methoxy group, an undesired deoxygenation occurred. In order to provide a solution to this issue, it has been thought to insert a protecting group on the allylic alcohol: cinnamyl alcohol **7** has been selected as model for the trials, being cheaper than the 7-hydroxy cannabidiol precursor **6** by far, while the protecting groups selected were acetyl-, pivaloyl-, triisopropylsilyl- and *tert*-butyl(diphenyl)silyl-moieties (Table 18).

¹⁶⁰ V. Gevorgyan, M. Rubin, S. Benson, J. X. Liu, Y. Yamamoto *J. Org. Chem.* **2000**, 65, 6179–6186.

Table 18: Protecting groups tested to prevent the allylic alcohol moiety deoxygenation.

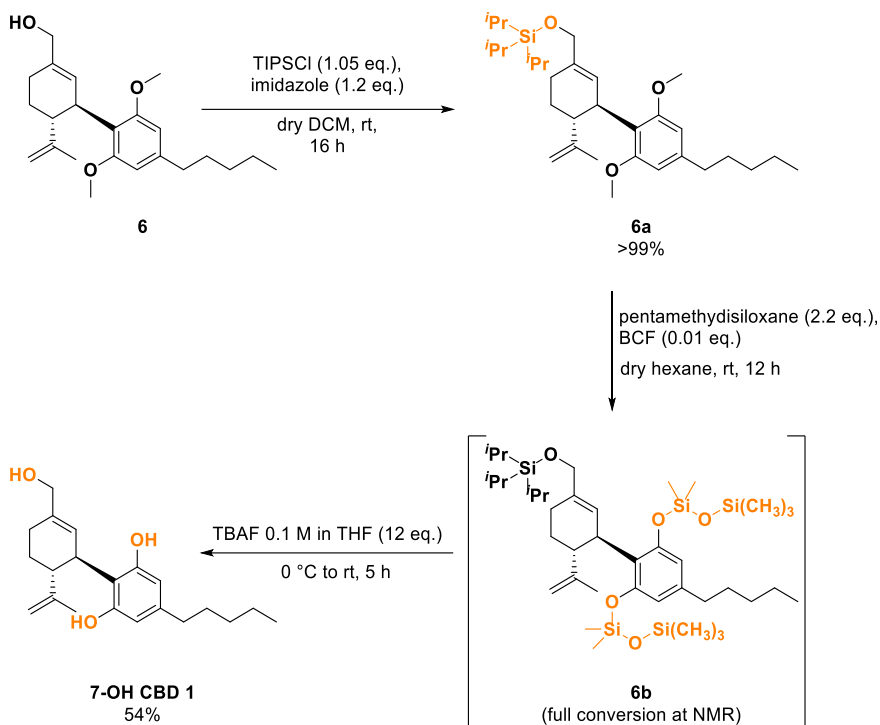
Entry	R	NMR Conversion	11 recovered
1	Acetyl	100%	-
2	Pivaloyl	100%	-
3	TIPS	-	75%
4	TBDPS	-	80%

The protecting groups selected have been chosen to be then easily removed alongside with the siloxanes on the phenol moieties in one step. Both the ester acetyl and pivaloyl protecting groups failed in presence BCF and pentamethyldisiloxane, leading to complete reductive deoxygenation of **8** to **9**, probably due to the fact they made the oxygen a better leaving group (Entries 1 and 2). On the other hand, bulky silyl protecting groups, such as TIPS and TBDPS, proved to be resistant to the action of the BCF and the siloxane, allowing a good recovery of the protected cinnamyl alcohol (Entries 3 and 4): even though they afforded a similar recovery, TIPS has been preferred over the TBDPS, being cheaper compared to the latter.

With these results in hand, it has been proceeded with the modification of the synthesis of **1** (Scheme 54).

TIPS-protection of compound **6** with triisopropyl chloride and imidazole allowed to obtain compound **6a** with a quantitative yield and it has been used for the next steps without further purifications. BCF-catalysed demethylation of the phenolic of **6a**

groups with pentamethyldisiloxane proceeded smoothly without any side reactivity, allowing the complete formation of compound **6b** at the NMR and the complete disappearance of the methoxy singlet at 3.71 ppm (Figure 34).



Scheme 54: Modification of the deprotection step towards 7-hydroxy cannabidiol **1** from **9**.

Finally, using an excess of TBAF in order to cleave all the silyl ether moieties, 7-hydroxy cannabidiol has been obtained in 54% yield over three steps from the precursor **6**. All the peaks of the isolated product **1** (third spectrum) are in accordance with the expected ones. Moreover, the peak at 2.24 ppm present in our spectrum of **1** can be found in the spectra of **6** (2.20 ppm) and **6a** (2.19 ppm) and in all the three cases it shows the same integral (two protons). Both proton and carbon NMR spectra and MS spectra showed interesting results that are in accordance with the desired molecule **1**.

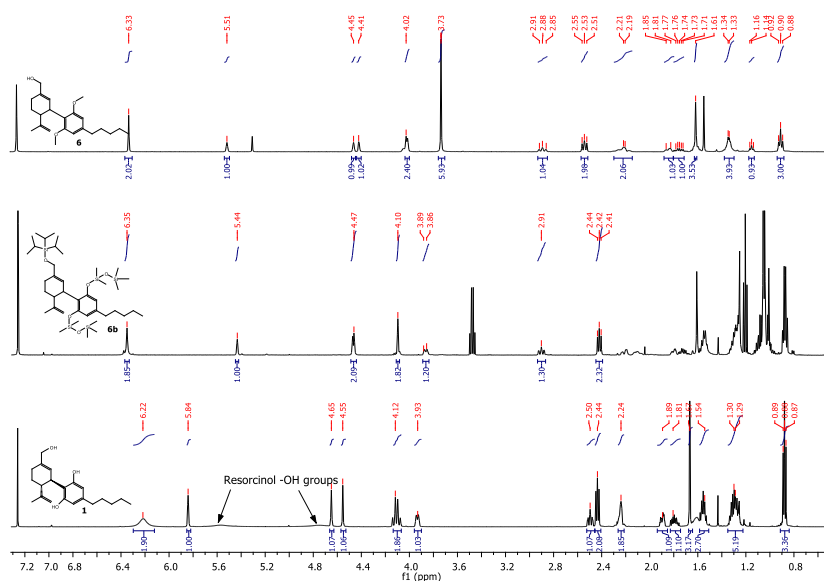


Figure 34: Comparison of the ¹H NMR spectra of compounds **6** (up), **6b** (middle) and **7OH-CBD 1** (bottom).

The successful deprotection procedure, consisting of three consequential steps, enabled indeed a reliable and easily replicable synthesis of 7-hydroxy cannabidiol **1** avoiding harsh reaction conditions in eight steps with an overall yield of 31%.

5.4 Conclusions

In conclusion, we report the development of an 8-step synthesis, with two telescoped transformations, of 7-hydroxy-cannabidiol **1** in 31% overall yield. The synthesis features an allylic rearrangement and a Piers–Rubinsztajn reaction as key steps: the development of the final removal of the O-methyl groups was indeed critical to efficiently perform the deprotection reaction under milder and safer conditions. Interestingly, this type of deprotection of cannabidiol derivatives has been applied for the first time, proving to be an efficient method with high potential in the synthesis of molecules belonging to the cannabinoid family. Further work is underway in our labs to access similar derivatives

and undertake research for clinical studies on the pharmacological activity of 7-hydroxy-cannabidiol.

5.5 Experimental Section

General Informations

Instrumentations: Nuclear magnetic resonance analyses (^1H -NMR, ^{13}C -NMR, COSY, HSQC, HMBC and TOCSY spectra) were acquired using a Bruker Advance III 400 MHz spectrophotometer (400 MHz for ^1H and 101 MHz for ^{13}C) or Bruker ava600 (600 MHz for ^1H and 151 MHz for ^{13}C). Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^1H NMR (^1H -NMR: 7.26 ppm for CDCl_3) and ^{13}C NMR (^{13}C -NMR: 77.0 ppm for CDCl_3). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sept, septet; m, multiplet; br s, broad signal. Chromatographic purifications of compound were performed using automated Biotage® Isolera LS Systems. For extremely sensitive reactions, an IT inert atmosphere glovebox was used. Exact masses were measured on hybrid quadrupole-TOF high resolution (HRMS) mass spectrometer (Xevo G2 QTOF, Waters, Manchester, UK) using a Z-spray-ESI interface operating in positive ionization mode with resolution of the TOF mass spectrometer about 20,000 at full width half maximum (FWHM). High resolution mass spectra were recorded on a VG autospec, or Thermo/Finnigan MAT 900, mass spectrometer. Electrospray Ionization (ESI⁺) spectra were performed using a time-of-flight (TOF) mass analyser. Data are reported in the form of m/z (intensity relative to the base peak = 100).

General Procedures: All reactions requiring inert atmosphere were set up under a nitrogen atmosphere in oven-dried glassware using standard Schlenk techniques, unless otherwise stated. Synthesis grade solvents were used as purchased. Anhydrous solvents were

purchased from Merck, VWR or taken from a commercial SPS solvent dispenser. Chromatographic purification of products was accomplished using flash column chromatography (FC) on silica gel (35-70 mesh). Thin layer chromatography (TLC) analysis was performed using company precoated TLC plates (insert model), UV light as the visualizing method and either cerium ammonium molybdate (Hanessian stain) or basic aqueous potassium permanganate (KMnO_4), and heat as developing agents. Organic solutions were concentrated under reduced pressure on a rotary evaporator (in vacuo at 40 °C, ~5 mbar).

Materials: All the starting materials were commercially available. Commercial grade reagents and solvents were purchased at the highest commercial quality from Merck, TCI, Fluorochem and Carlo Erba and used as received, unless otherwise stated. Cannabidiol was provided pure by Indena S.p.A. and used as received.

5.5.1 7-OH CBD 1: 2D spectra analysis

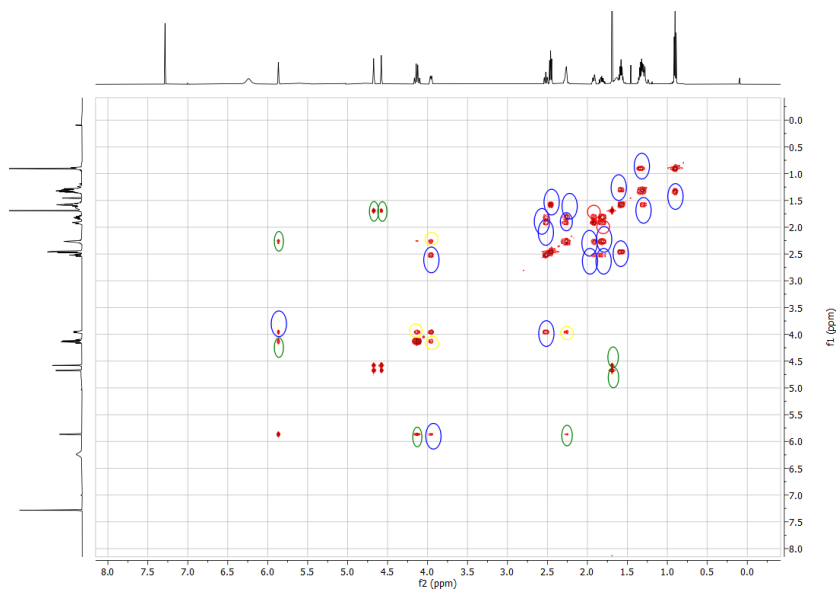


Figure 35: COSY spectrum of 7-hydroxy cannabidiol (1); (the different colours are related to the entity of the crosspeak, red for J2, blue for J3, green for J4 and yellow for J5) Note: due to the broadness of the peak itself, no crosspeaks can be seen for the aromatic protons at 6.21 ppm.

The singlet at 5.84 ppm (1H on the C2) couples with three different sets: the quartet at 4.11 (2H on the C7) and the multiplet at 2.29-2.21 (2H on the C6) with a J4 and the doublet at 3.93 ppm (1H, probably the benzylic proton on the C3) with a J3. The presence of the J4 is explained by the fact that it is an allylic system, and it is confirmed by the respective specular crosspeaks. The two singlets at 4.65 and 4.55 ppm belonging to the alkenyl CH₂ on C9 both couple with the methyl group in C10 with a J4 being this an allylic system too. A J5 coupling can be observed between the quartet at 4.11 ppm (protons on the C7) and the doublet at 3.93 ppm, confirming this last one as the proton on C3 (the J5 coupling can be explained by the presence of the unsaturation between the C1 and C2).

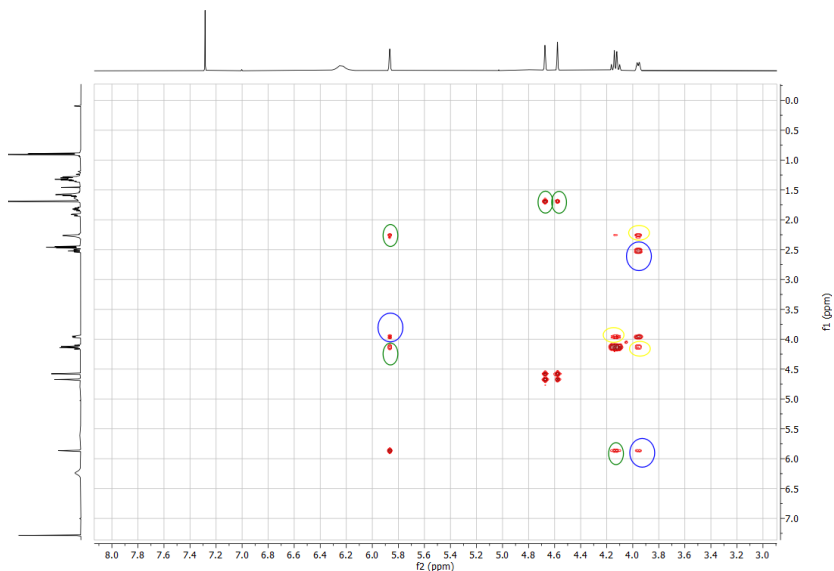


Figure 36: COSY spectrum of compound 1 (from 8.00 ppm to 3.00 ppm range).

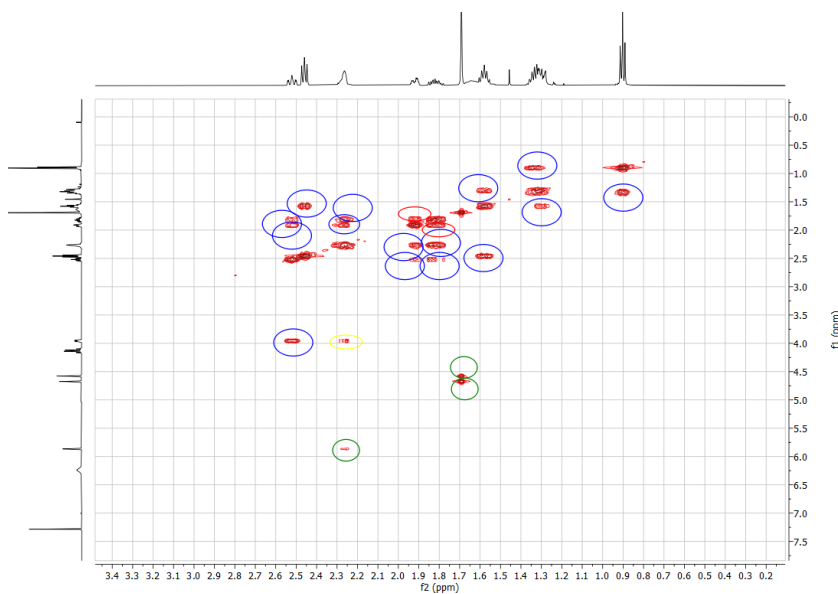


Figure 37: COSY spectrum of compound 1 (from 3.00 ppm to 0.00 ppm range).

The multiplet at 2.52 - 2.48 ppm (1H) shows three J3 crosspeaks that let us suppose it is the proton on the C4: indeed, it couples with the proton on the C3 and with the two multiplets at 1.91 - 1.88 ppm and 1.83 - 1.76 (both integrating for 1H and that can be identified with the two protons on the C5). Meanwhile, the triplet

at 2.44 ppm (integrating for 2H) can be identified as the two benzylic protons on the C17, showing a crosspeak (J3) with the dt at 1.55 ppm (2H) only. Then, the dt at 1.55 ppm refers to the two protons on the C18 due to its two J3 coupling with both the benzylic protons on C17 and the multiplet at 1.35 - 1.26 ppm that can be identified with the four aliphatic protons on C19 and C20. As expected, the triplet at 0.88 ppm (integrating for 3H) can be confirmed as the methyl group C21 due to its J3 coupling with the four protons on C19 and C20 only.

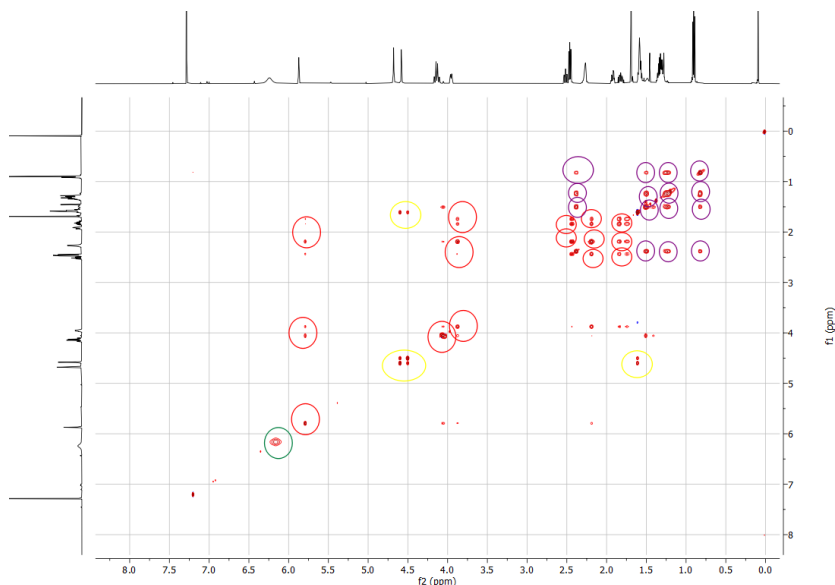
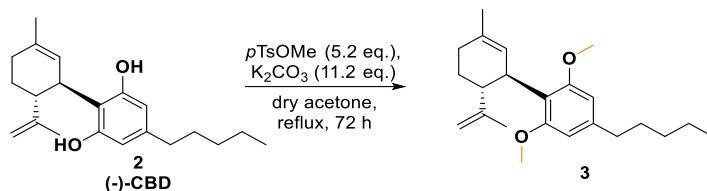


Figure 38: TOCSY spectrum of compound **1** (the different colours refer to the different moieties coupling; green for aromatics, red for the cyclic terpene, yellow for the isopropylene and violet for the *n*-pentyl moiety).

The TOCSY spectrum confirms the assignment obtained from the COSY. Indeed, all the protons belonging to a specific region of the molecule couple each other with clear crosspeaks.

5.5.2 Procedures

Synthesis of compound 3



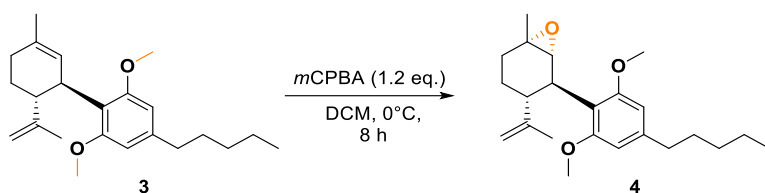
In a flame dried two-necked flask equipped with a condenser, to a solution of (-) - CBD **2** (3 g, 9.54 mmol) in dry acetone (48 mL), potassium carbonate (11.2 eq., 14.8 g, 107 mmol) was added under a nitrogen atmosphere. After 30 minutes, methyl *p*-toluensulfonate (5.2 eq., 9.24 g, 49.6 mmol) was added and the system was let to reflux under nitrogen atmosphere for 72 hours. Upon completion of the reaction, as indicated by TLC analysis, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate and the two layers were separated. The aqueous layer was extracted with diethyl ether (20 mL x 3 times), then the organic layers were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography over silica gel (10% of diethyl ether in petroleum ether) afforded compound **3** as a yellow oil in quantitative yield (3.3 g).

^1H NMR (400 MHz, CDCl_3) δ 6.33 (s, 2H), 5.20 (s, 1H), 4.43 (d, J = 6.7 Hz, 2H), 3.99 (d, J = 10.7 Hz, 1H), 3.73 (s, 6H), 2.89 (td, J = 10.8, 4.1 Hz, 1H), 2.53 (t, J = 7.8 Hz, 2H), 2.23 – 2.17 (m, 1H), 2.0 – 1.96 (m, 1H), 1.77 – 1.74 (m, 2H), 1.66 (s, 3H), 1.60 (s, 5H), 1.34 – 1.33 (m, 5H), 0.90 (t, J = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 149.7, 142.0, 131.3, 126.1, 119.2, 109.7, 105.2, 56.1, 45.4, 36.6, 36.2, 31.9, 31.1, 30.9, 29.9, 23.6, 22.7, 19.2, 14.2.

Analytical data are in agreement with those reported in literature.¹³⁹

Synthesis of compound 4



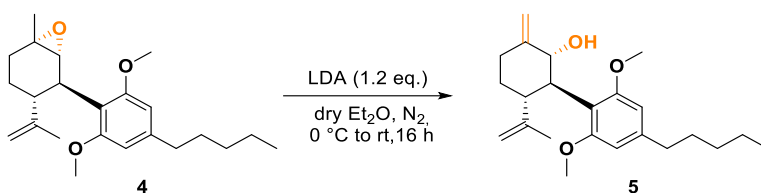
Following a literature reported procedure:¹⁶¹ 3-chloro-perbenzoic acid (1.2 eq., 0.92 g, 5.31 mmol) was dissolved in 45 mL of CH_2Cl_2 and then cooled to 0 °C. A solution of compound **3** (1.49 g, 4.35 mmol) in 15 mL of CH_2Cl_2 was added dropwise to the system. The starting material disappeared after 8 h, as indicated by TLC analysis. The reaction was quenched with a saturated solution of sodium bicarbonate, then the two layers were separated, and the aqueous layer was extracted with diethyl ether (15 mL x 3 times). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography over silica gel (7% of diethyl ether in petroleum ether) afforded compound **4** as a colorless oil in 82% yield (1.3 g).

^1H NMR (400 MHz, CDCl_3) δ 6.34 (d, J = 11.1 Hz, 2H), 4.38 (s, 1H), 4.18 (s, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.59 (d, J = 10.8 Hz, 1H), 2.91 (s, 1H), 2.55 (t, J = 8 Hz, 2H), 2.29 – 2.23 (m, 1H), 2.06 – 2.03 (m, 1H), 1.87 – 1.79 (m, 1H), 1.70 – 1.61 (m, 6H), 1.36 – 1.26 (m, 8H), 0.90 (t, J = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 158.2, 148.6, 142.7, 117.5, 110.3, 104.4, 65.6, 58.7, 55.9, 55.6, 53.5, 46.4, 36.6, 34.8, 31.8, 31.2, 30.7, 24.9, 23.4, 22.7, 18.5, 15.4, 14.2. Analytical data are in agreement with those reported in literature.¹³⁹

¹⁶¹ M. R. Arms, C. S. Wilcox *J. Am. Chem. Soc.* **2006**, 128, 250-256.

Synthesis of compound 5

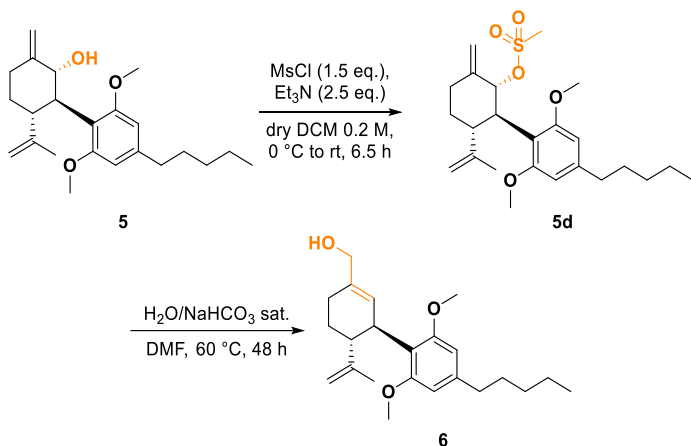


The procedure for the preparation of **5** was a slight modification from a literature procedure:¹⁶¹ To a flame dried two-necked flask with 8 mL of dry diethyl ether, 1.06 mL (1.2 eq., 2.64 mmol) of *n*BuLi 2.5 M in hexane were added and the system was cooled to 0 °C. At this point, freshly distilled diisopropyl amine (1.2 eq., 2.64 mmol, 0.371 mL) was added under nitrogen atmosphere and the system was stirred for 1 hour at room temperature. Afterwards, the solution was cooled to 0 °C and compound **4** (2.2 mmol, 790 mg) was added to the reaction mixture; the system was stirred at room temperature for 12 h. Upon the completion of the reaction, as indicated by TLC analysis, the system was cooled to 0 °C and the reaction was quenched with water. The organic and aqueous layers were then separated, the aqueous layer was extracted with diethyl ether (15 mL x 2), the combined organic layers were washed with HCl 2 M (10 mL) and brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography over silica gel (25% of diethyl ether in petroleum ether) afforded compound **5** as pale-yellow oil in quantitative yield (0.788 g). The reaction was repeated on a 1.64 g scale and **5** was obtained in 91% yield (1.49g).

¹H NMR (400 MHz, CDCl₃) δ 6.34 (s, 2H), 5.09 (s, 1H), 4.82 (s, 1H), 4.62 (d, *J* = 14.6 Hz, 1H), 4.49 (s, 1H), 4.39 (s, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.34 – 3.27 (m, 1H), 3.20 (td, *J* = 11.7, 3.3 Hz, 1H), 2.56 – 2.53 (m, 2H), 2.53 – 2.50 (m, 1H), 2.46 (td, *J* = 13.4, 4.1 Hz, 1H), 1.6274 (ddd, *J* = 12.5, 7.4, 3.2 Hz, 1H), 1.66 – 1.57 (m, 2H), 1.49 (s, 3H), 1.38 – 1.28 (qd, *J* = 6.3, 3.3 Hz, 4H), 0.91 (t, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 159.2, 159.0, 150.9, 148.0, 143.0, 113.3, 110.0, 104.5, 104.2, 72.8, 55.9, 55.0, 47.4, 47.1, 36.5, 34.1, 33.5, 31.7, 30.8, 22.5, 18.6, 14.0. Analytical data are in agreement with those reported in literature.¹³⁹

Synthesis of compound 6



Synthesis of 5d: The procedure for the preparation of **5d** was a slight modification from a literature procedure:¹⁵⁵ In a flame dried two-neck flask, **5** (5.86 mmol, 2.1 g) was dissolved in 20 mL of dry CH_2Cl_2 and the solution was cooled to $0\text{ }^\circ\text{C}$. At this point dry triethylamine (2.5 eq., 14.6 mmol, 2.04 mL) was added, and methanesulfonyl chloride (1.5 eq., 8.79 mmol, 0.682 mL) was added after 30 minutes. The system was stirred for 6 h at room temperature until complete disappearance of the starting material, as indicated by TLC analysis. The reaction was then cooled to $0\text{ }^\circ\text{C}$ and quenched with water. The layers were then separated, and the aqueous phase extracted with CH_2Cl_2 (20 mL x 3 times), the organic layers were combined, washed with sat. ammonium chloride and brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The product was used without purification in the next step. (The formation of **5d** was confirmed by crude ^1H NMR).

¹H NMR (400 MHz, CDCl₃) δ 6.32 (s, 2H), 4.42 (d, J = 26.6 Hz, 2H), 4.04 (s, 2H), 3.72 (s, 6H), 2.82 (t, J = 11.2 Hz, 1H), 2.55 – 2.51 (m, 2H), 2.35 – 2.19 (m, 2H), 1.86 – 1.72 (m, 2H), 1.61 (s, 3H), 1.54 (s, 2H), 1.33 – 1.25 (m, 5H), 0.98 – 0.81 (m, 3H).

Synthesis of compound 6: The procedure for the preparation of **6** was a slight modification from a literature procedure:¹⁵⁵ Crude compound **5d** (50 mg, 0.115 mmol) was dissolved in 0.5 mL of DMF, then 0.15 mL of water and 0.15 mL of a sat. solution of NaHCO₃ were added. The reaction was heated to 60 °C and stirred for 48 h. Upon disappearance of the starting material, as indicated by TLC analysis, the reaction was diluted with water and extracted with diethyl ether (2 mL x 3 times), then the organic layers were combined, washed with water and brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography over silica gel eluting in petroleum ether/diethyl ether 8:2 afforded compound **6** as a colorless sticky oil in 70% yield over two steps (30 mg).

Preparation on 2.5g scale: Crude compound **5d** (2.5 g, 5.73 mmol) was dissolved in 25 mL of DMF, then 7.5 mL of water and 7.5 mL of sat. NaHCO₃ were added. At this point the temperature is set to 60 °C and the reaction is let to stir for 48 h. When the starting material disappeared on TLC, the reaction was diluted with water and extracted with diethyl ether (10 mL x 3 times), then the organic layer was washed with water, brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography over silica gel (20% of diethyl ether in petroleum ether) afforded 1.04 g of product **6** as a colorless sticky oil. Yield = 50% (over two steps).

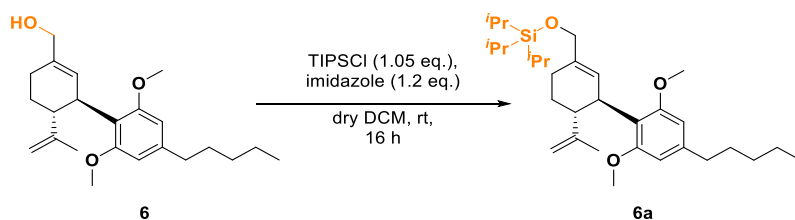
¹H NMR (400 MHz, CDCl₃) δ 6.33 (s, 2H), 5.51 (s, 1H), 4.44 (d, J = 17.0 Hz, 2H), 4.04 – 4.01 (m, 3H), 3.73 (s, 6H), 2.92 – 2.85 (m, 1H), 2.54 (t, J = 8 Hz, 2H), 2.27 – 2.15 (m, 2H), 1.86 – 1.82 (m, 1H), 1.79 – 1.71 (m, 1H), 1.64 – 1.57 (m, 5H), 1.39 – 1.23 (m, 5H), 0.90 (t, J = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 149.0, 142.2, 135.0, 128.6, 118.0, 109.9, 104.8, 67.7, 55.8, 45.5, 36.4, 35.9, 31.7, 31.0, 29.3, 26.4, 22.5, 19.0, 14.0.

MS-ESI: 359.2581 (calculated mass of $\text{C}_{23}\text{H}_{35}\text{O}_3$, $[\text{M}+\text{H}^+]$), found: 359.2574; 381.2400 (calculated mass of $\text{C}_{23}\text{H}_{34}\text{O}_3\text{Na}$ 1, $[\text{M}+\text{Na}^+]$), found: 381.2397.

Analytical data are in agreement with those reported in literature.¹³⁹

Synthesis of compound 1 (7OH-CBD)

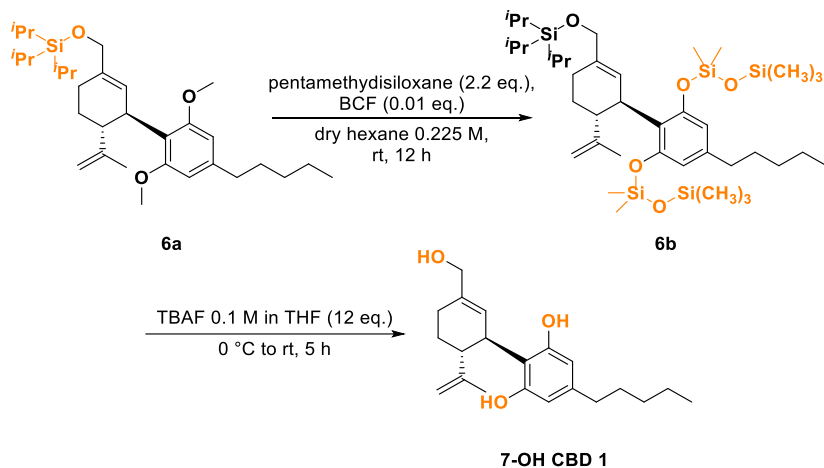


Synthesis of 6a: The procedure for the preparation of **6a** was a slight modification from a literature procedure:¹⁶¹ a Schlenk flask containing 0.5 mL of dry CH_2Cl_2 , 24 mg of imidazole (0.34 mmol, 1.2 eq.) and 100 mg of **6** (0.28 mmol) was cooled to 0 °C. 62.2 μL of triisopropylsilyl chloride (0.30 mmol, 1.05 eq.) was added dropwise and the reaction mixture stirred at room temperature overnight. Upon the completion of the reaction as indicated by ^1H NMR analysis, water was added, the organic layer separated, and the aqueous layer extracted with diethyl ether (3 mL x 3 times). The combined organic layers were dried over MgSO_4 , filtered and the solvent removed in vacuo. Without any purification, the crude (171.4 mg, quantitative yield) was used for the next step.

^1H NMR (601 MHz, CDCl_3) δ : 6.31 (s, 2H), 5.45 (s, 1H), 4.44 (s, 1H), 4.40 (s, 1H), 4.11 (s, 2H), 4.03 – 4.01 (d, J = 4.9 Hz, 1H), 3.71 (s, 6H), 2.91 – 2.85 (m, 1H), 2.55 – 2.50 (m, 2H), 2.19 (d, J = 2.6 Hz, 2H), 1.83 – 1.78 (m, 1H), 1.73 (ddd, J = 16.0, 11.3, 6.0 Hz, 1H), 1.61

– 1.60 (m, 4H), 1.33 (dd, $J = 14.5, 7.6$ Hz, 4H), 1.09 – 1.03 (m, 21H), 0.90 (t, $J = 7.0$ Hz, 3H).

MS-ESI: 515.3915 (calculated mass of C₃₂ H₅₅ O₃ Si₁, [M+H⁺]), found: 515.3919; 537.3733 (calculated mass of C₃₂ H₅₄ O₃ Si₁ Na 1, [M+Na⁺]), found: 537.3718.



Synthesis of compound 6b:³⁷ in glovebox under Argon atmosphere, the aryl ether substrate **6a** (50 mg, 0.097 mmol) dissolved in 0.44 mL of dry n-hexane (0.225 M) was added in a reaction tube equipped with a magnetic stirring bar. Pentamethyldisiloxane (1.10 eq. per aryl ether functionality, 41.8 μ L, 0.22 mmol) was added and the solution stirred for 1 minute. B(C₆F₅)₃ (0.01 eq., 0.5 mg, 0.001 mmol) was added and the reaction was stirred in the glovebox at room temperature for 12 h. Afterwards the reaction was carried out of the glovebox, quenched with water (1 mL), extracted with diethyl ether (2 mL x 3 times), dried over magnesium sulfate, filtered and concentrated in vacuo. ¹H NMR analysis on the crude mixture showed a clean deprotection of the methoxy groups on the aromatic ring (the peak at 3.71 ppm disappeared completely, see crude spectrum **6b** below in the Spectra Section, the presence of the desired intermediate was

confirmed by ESI analysis) and used for the next step without any further purification.

MS-ESI: 779.4768 (calculated mass of C₄₀ H₇₉ O₅ Si₅, [M+H⁺]), found: 779.4766; 801.4588 (calculated mass of C₄₀ H₇₈ O₅ Si₅ Na⁺, [M+Na⁺]), found: 801.4565.

Synthesis of 7-OH CBD 1: In a two necked flame dried flask crude **6b** was diluted in 1 mL of dry THF, under nitrogen atmosphere, and 1.2 mL of TBAF 1M in THF (12.0 eq.) was added dropwise at 0 °C. The reaction was then allowed to warm to room temperature and stirred for 5 hours. The reaction was then quenched with a saturated aqueous solution of ammonium chloride, extracted with diethyl ether (2 mL x 3 times), dried over magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography over silica gel eluting with petroleum ether ethyl acetate solvent mixture from 100% petroleum ether to 100% ethyl acetate afforded product **1** as a yellow sticky oil in 54% yield over three steps (18 mg).

¹H NMR (601 MHz, CDCl₃) δ : 6.22 (s, 2H), 5.84 (s, 1H), 4.65 (s, 1H), 4.55 (s, 1H), 4.11 (q, J = 13.3 Hz, 2H), 3.95 – 3.92 (m, 1H), 2.52 – 2.47 (m, 1H), 2.44 (t, J = 7.6 Hz, 2H), 2.27 – 2.24 (m, 2H), 1.91 – 1.88 (m, 1H), 1.83 – 1.76 (m, 1H), 1.67 (s, 3H), 1.55 (dt, J = 15.0, 7.6 Hz, 2H), 1.34 – 1.25 (m, 4H), 0.88 (t, J = 7.1 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ : 148.8, 143.2, 142.0, 125.3, 113.4, 111.0, 66.5, 46.4, 36.7, 35.5, 31.5, 30.6, 28.2, 26.0, 22.5, 20.2, 14.0.

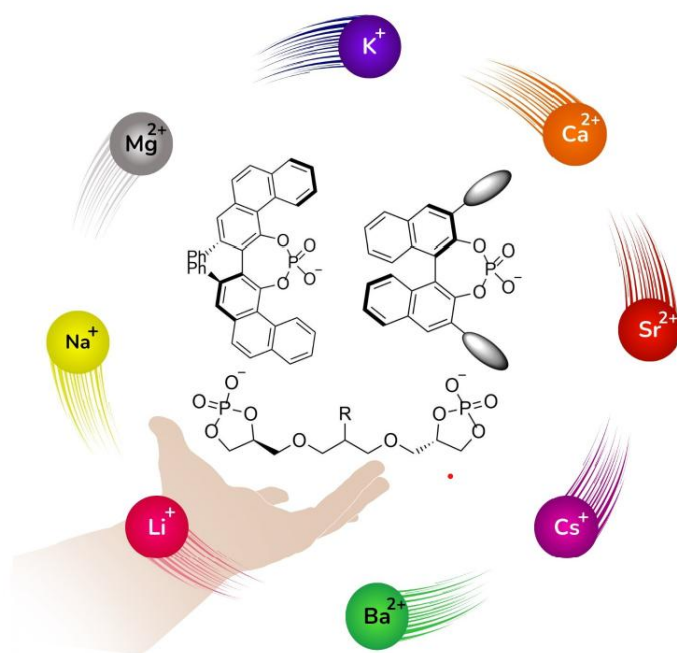
MS-ESI: 331.2268 (calculated mass of C₂₁H₃₁O₃, [M+H⁺]), found: 331.2265; 353.2087 (calculated mass of C₂₁H₃₀O₃Na, [M+Na⁺]), found: 352.2085.

$[\alpha]_D^{25}$ = – 115.5 (c = 8.26 · 10⁻³ g/mL, CHCl₃).

6. Other Projects

6.1 “Stereoselective Reactions Promoted by Alkali Metal Salts of Phosphoric Acid Organocatalysts”

Part of this chapter has been published as: E. Cocco, A. Antenucci, A. Carlone, P. Manini, F. Pesciaioli, S. Dughera *ChemCatChem* **2024**, e202400328.



As already mentioned in Chapter 1, chiral phosphoric acids are a milestone within the framework in asymmetric organocatalysis: since their first application as asymmetric Brønsted acid catalyst by Yamamoto and the extensive study done by the groups of Akiyama and Terada, they have been widely employed in organocatalysis being able to unlock a wide variety of transformations. Indeed, being the first phosphoric acids designed from the BINOL moiety (namely BPA, BINOL-based Phosphoric Acids) and thanks to the

Chapter 6 6.1 “Stereoselective Reactions Promoted by Alkali Metal Salts of Phosphoric Acid Organocatalysts”

possibility of wide functionalization of BINOL in the 3,3'-positions, it has been possible to access to a wide range of different asymmetric transformations dependent on the bulky groups inserted in those positions. Later on, even more asymmetric procedures have been unlocked recurring to the phosphorylation of other C₂-symmetric diols such as VANOL and VAPOL and vaulted biaryls as TADDOL and SPINOL, leading to those classes of chiral phosphoric acids named VPAs, TPAs and SPAs respectively.

In general, chiral phosphoric acids featuring 8- and 7-membered rings are the most used, given their stability and, in addition, their isolation in the form of free acids after the synthesis and purification is the preferred protocol.

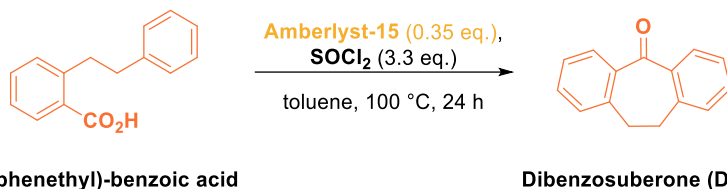
In the last twenty years the chemistry of chiral phosphoric acids scaffolds was studied deeply, especially in the field of asymmetric counteranion directed catalysis (ACDC), where the chiral phosphate is responsible for the generation of the stereocentre. Even though the most known examples of ACDC are constituted by an ionic couple formed by an iminium ion and a chiral phosphate, also salts obtained from chiral phosphoric acids with alkali, alkali-earth and transition metals can be ascribed to this class of catalysis. The main difference with classical examples of ACDC relies on the presence of the metal cation that is, in some cases, crucial in order to achieve outstanding catalytic activity by stabilizing the reaction intermediates via secondary interactions (i. e. cation / π interactions) and sometimes, depending on the metal cation used, it is even possible to directly affect the formation of the stereocentre thanks to its capacity to coordinate more than one phosphate anion at time, as in the case of bivalent metals such as magnesium or calcium. Within this background, I have contributed to the writing of a review presenting the asymmetric reactions catalysed by alkali and alkali-earth metals salts of chiral phosphoric acids. This review

Dibenzosuberone

shows all the developments achieved in this field, with a focus on the reaction mechanisms to highlight the effects of the several metal cations and their role in the activation of the substrate and the enantioselectivity.

6.2 A Sustainable and Catalytic Synthesis of Dibenzosuberone

Part of this chapter has been published as: V. Nori, F. Della Penna, E. Cocco, S. Mantegazza, G. Razzetti, G. Quattrocchi, F. Pesciaioli, A. Carlone *ChemCatChem* **2023**, 15, e202300642.



Dibenzosuberone (DBS) is an important precursor in the synthesis of several API's (Active Pharmaceutical Ingredients) such as Amitriptyline, Nortriptyline, Noxiptiline or Cyproheptadine, which synthesis is valuable due to their anti-depressant and anti-cancer (as in the case of suberenyl chloride) activities: indeed, DBS belongs to the family of tricyclic antidepressant drugs (namely TCA), widely employed in the treatment of migraines, tension headaches, anxiety attacks and schizophrenia. Therefore, DBS represents a valuable synthetic target, with a plenty of different synthetic methodologies to unlock it. However, the methodologies commonly employed make use of harsh reaction conditions, such as the intramolecular Friedel-Craft of 2-(phenethyl)-benzoic acid with stoichiometric amount of Lewis acids in presence of halogenating reagents, making more sustainable and greener approaches highly desirable. Additionally, milder approaches designed, such as the ring closing of 2-(phenethyl)-benzoic acid through photocatalysis or the use of safer Lewis acids like

Dibenzosuberone

polyphosphoric acid (PPA), ended up giving significant drawbacks regarding the waste disposal, therefore affecting negatively the greenness of the processes.

With this project, to which I have participated as third author, in collaboration with the pharmaceutical company Dipharma Francis S.r.l., a new catalytic approach towards the synthesis of DBS has been unlocked. This methodology makes use of a sulfonated styrene-divinylbenzene copolymer ion exchange resin used as immobilised catalyst to perform the Friedel-Craft reaction on 2-(phenethyl)-benzoic acid in presence of thionyl chloride in toluene, with high yields in mild reaction conditions. The use of the immobilised catalyst has shown impactful advantages as improved stability, reusability, and localization of the catalyst itself arising from the easy separation of the catalyst from the reaction medium and its simple regeneration *via* acidic rinsing.

In conclusion, this synthetic process of DBS proved to be a significant improvement in terms of sustainability and industrial applicability by abating the large and unsustainable waste produced and providing feasible and milder reaction conditions.

7. General Conclusions

7.1 Conclusions

During this PhD, my research has been focused on the design of new organocatalytic systems and the synthesis of bioactive compounds with potential pharmacological value.

In **Chapter 2**, the development of an enantioselective organocatalysed enamine-mediated addition of acetaldehyde dimethyl acetal to *trans*-nitroalkenes *via* rational approach helped to move away from the use of chloroform. The use of water as reaction medium represents a great improvement in the sustainability of the protocol, therefore increasing its relevance towards its potential industrial exploitation for the synthesis of pharmaceutically relevant intermediates. Critical to the success is the use of chemometrics-assisted ‘Design of Experiments’ (DoE) optimization during the development of the presented new synthetic approach, which allows to investigate the chemical space in a rational way.

In **Chapter 3**, the first exploration of nitrogen-rich Carbon Dots in asymmetric organocatalysis *via* ACDC is reported. Making use of chiral phosphoric acids and Carbon Dots functionalised with 1,4-butanediamine on the surface, a new organocatalysed system has been designed and employed successfully in the enantioselective 1,4-reduction of α,β -unsaturated β -disubstituted aldehydes with dihydropyridines as hydride source, affording good yields and ees, with low catalytic loading. Moreover, a correlation between the features of the CDs’ surfaces and their catalytic performance was shown, and the catalytic activity of the employed CDs proved to be higher than simple molecular amines.

Chapter 4 shows a new approach towards the synthesis of silyl-heterocycles through the use of [H-B-9-BBN]₂ as catalyst. Indeed,

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the use of catalytic amount of BBN dimer alongside a stoichiometric amount of pinacol borane unlocked a threefold reaction system in which 1,1-carboboration, cyclisation and transborylation reactions take place in turn, affording moisture-, air-stable four- and five-membered sila-heterocycles with high yields in solventless conditions from dialkynyl silanes and vinyl-alkynyl silanes respectively. The reaction mechanism has been cleared through isotopic labelling, DFT and NMR studies and downstream derivatisations have been performed to test the synthetic potential relevance of this protocol.

A novel protocol towards the synthesis of 7-hydroxy cannabidiol is reported in **Chapter 5**. The designed approach is composed of eight steps, with two telescoped transformations, leading to 7-hydroxy-cannabidiol in 31% overall yield. The synthesis features an allylic rearrangement and a Piers–Rubinsztajn reaction as key steps; in particular, the development of the final removal of the O-methyl groups was critical to efficiently effect the deprotection reaction under more mild and safer conditions. Interestingly, this type of deprotection of cannabidiol derivatives is reported for the first time. Finally, in **Chapter 6** a small resume of two projects I had the opportunity to work to is reported. The first one is a review on the reaction promoted by chiral phosphates of alkaline- and alkali-earth metals, to which I had the opportunity to work as first author. The second one is a novel and greener approach towards the preparation of Dibenzosuberone (DBS), a key intermediate in the synthesis of compounds of pharmaceutical relevance.

7.2 List of Publications

- “DoE-driven development of an organocatalytic enantioselective addition of acetaldehyde to nitrostyrenes in water” V. Nori, A. Sinibaldi, G. Giorgianni, F. Pesciaioli, F. Di Donato, E. Cocco, A. Biancolillo, A. Landa, A. Carlone, *Chem. – Eur. J.* **2022**, 28, e202104524.
- “A Sustainable and Catalytic Synthesis of Dibenzosuberone” V. Nori, F. Della Penna, E. Cocco, S. Mantegazza, G. Razzetti, G. Quattrocchi, F. Pesciaioli, A. Carlone *ChemCatChem* **2023**, e202300642.
- “Piers–Rubinsztajn reaction to unlock an 8-step synthesis of 7-hydroxy cannabidiol” E. Cocco, D. Iapadre, A. Brusa, P. Allegrini, S. P. Thomas, F. Pesciaioli, A. Carlone *RSC Adv.* **2024**, 14, 2741-2744.
- “Catalytic Access to Diastereometrically Pure Four- and Five-Membered Silyl-Heterocycles Using Transborylation” D. R. Willcox, E. Cocco, G. S. Nichol, A. Carlone, S. Thomas *Angew. Chem. Int. Ed.* **2024**, e202401737.
- “Stereoselective reactions promoted by alkali metal salts of phosphoric acid organocatalysts” E. Cocco, A. Antenucci, A. Carlone, P. Manini, F. Pesciaioli, S. Dughera *ChemCatChem* **2024**, e202400328.
- “Nitrogen-Rich Carbon Dots as Effective Catalysts in the 1,4-Reduction of α,β -Unsaturated Aldehydes via Ion Pair Asymmetric Nano-Organocatalysis ” A. Carioscia, E. Cocco, M. E. Casacchia, G. Gentile, M. Mamone, G. Giorgianni, E. Incerto, M. Prato, F. Pesciaioli, G. Filippini, A. Carlone *ACS Catalysis* **2024**, 14, 13429–13438.

7.3 List of Conferences and Schools Attended

- “Congresso Interregionale TUMA 2022”: Perugia, 1st and 2nd September 2022.

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- “XLI Convegno Nazionale della Divisione di Chimica Organica, CDCO Roma 2023”: Rome, 10th-14th September 2023.
- “CINMPIS 2024”: Bari, 7th-9th February 2024.
- “c³-Day 2024”: Bologna, 4th June 2024.
- “XLVIII ISOS Corbella Summer School 2024”: Gargnano (BS), 16th-21st June 2024.

7.4 Oral Presentations

- “A feasible synthesis of 7-hydroxy cannabidiol”; *XLI Convegno Nazionale della Divisione di Chimica Organica, CDCO Roma 2023*.
- “Piers–Rubinsztajn reaction to unlock an 8-step synthesis of 7-hydroxy cannabidiol”; *CINMPIS 2024*.
- “Catalytic Access to Diastereometrically Pure Four- and Five-Membered Silyl-Heterocycles Using Transborylation”; *XLVIII ISOS Corbella Summer School 2024*.

7.5 Poster Sessions

- “A novel five-step synthesis of 7-hydroxy cannabidiol”; *Congresso Interregionale TUMA 2022*.
- “A new and feasible approach approach towards the synthesis of 7-hydroxy cannabidiol”; *RSC Twitter Conference 2023*.
- “Catalytic Access to Diastereometrically Pure Four- and Five-Membered Silyl-Heterocycles Using Transborylation”; *c³-Day 2024*.

8. Acknowledgements

This long journey as a PhD student is close to an end and, looking back to the pathway crossed, all the successes achieved would not have been possible without the help and support of many people that I would like to thank in this section.

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