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Acceleration of Diels-Alder Reactions in Batch in HFIP for Continuous Flow Applications

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ACCELERATION OF DIELS-ALDER REACTIONS IN BATCH IN HFIP FOR CONTINUOUS FLOW APPLICATIONS

Mémoire présenté pour l'obtention

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Accélération de Réactions de Diels-Alder en Réactions Discontinues dans le HFIP pour des Applications en Chimie en Flux Continu

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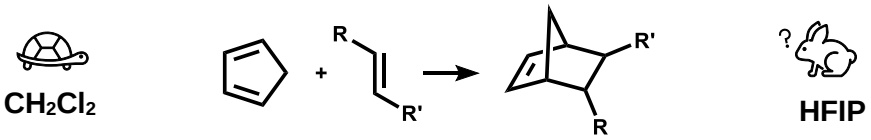
Résumé

L'amélioration des vitesses et sélectivités des réactions de Diels-Alder réalisées dans des solvants non traditionnels est connue depuis le début des années 80. Suite à l'intérêt croissant pour l'eau comme solvant efficace en chimie organique, Breslow *et al.* ont rapporté en 1980 des accélérations des réactions de Diels-Alder dans des mélanges aqueux. Plus tard, les alcools fluorés ont été décrits comme une nouvelle classe de solvants hautement efficaces pour ces cycloadditions. De telles conditions ont été utilisées avec grand succès par Loïc Jeanmart du laboratoire du COS pour des cycloadditions de quinones. Ces accélérations nous ont inspirés à aborder l'une des principales limitations de la chimie en flux continu : la nécessité de temps de réaction courts. En effet, le flux offre plusieurs avantages qu'il serait intéressant d'appliquer aux réactions de Diels-Alder, étant donné leur omniprésence en synthèse organique.



L'objectif de ce projet est d'élargir le champ des réactions de Diels-Alder décrites dans le HFIP et, par la suite, de discuter leur faisabilité dans un système de flux continu. Dans ce travail, nous présentons les résultats d'un *screening* de diénophiles, au cours duquel nous avons observé plusieurs accélérations remarquables pour une variété de composés courants tels que des esters ou des nitro-alcènes.

Mémoire de master en Sciences Chimiques à Finalité Spécialisée

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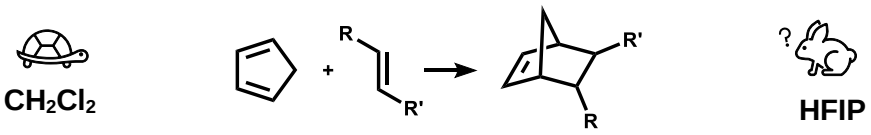
Acceleration of Diels-Alder Reactions in Batch in HFIP for Continuous Flow Applications

MARÉCHAL Nathan

Abstract

The enhancement of reaction rates and selectivities in Diels-Alder reactions conducted in non-traditional solvents has been recognized since the early 1980s. Following the growing interest in water as an effective solvent for organic chemistry, Breslow *et al.* reported accelerations of Diels-Alder reactions in aqueous mixtures in 1980. Fluorinated alcohols were later described as a new class of highly effective solvents for these cycloadditions. Such conditions have been used with great success by Loïc Jeanmart from the COS laboratory for cycloadditions of quinones. These accelerations inspired us to tackle one of the main limitations of continuous flow chemistry: the need for short reaction times. In fact, flow offers several advantages that would be interesting to apply to Diels-Alder reactions, given their ubiquity in organic synthesis.



The goal of this project is to broaden the scope of Diels-Alder reactions described in HFIP and later, discuss their feasibility in a continuous flow system. Herein, we report the results of a screening of dienophiles during which we observed several impressive accelerations for a variety of common compounds such as esters, or nitro-alkenes.

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Ce mémoire symbolise pour moi la clôture de mon parcours universitaire, et il serait impossible de citer et remercier ici toutes les personnes qui y ont contribué, de près ou de loin. Elles restent cependant dans mon esprit comme tant de bons moments ou de précieux conseils et j'en suis infiniment reconnaissant.

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Je suis ensuite extrememement reconnaissant envers toutes les amitiés que j'ai eu la chance de nouer tout au long de mon cursus. Que ce soient les chimistes rencontrés en cours ou les physiciens découverts à la Revue, merci à tous pour votre soutien et les bons moments partagés, puissent-ils être encore nombreux.

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Table of Contents

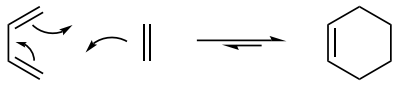
List of Abbreviations

Ac	Acetyl
Bu	Butyl
cat.	Catalytic
COSY	Correlated Spectroscopy
cHex	Cyclohexane
CPD	Cyclopentadiene
DEPT	Distortionless Enhancement by Polarisation Transfer
DCPD	Dicyclopentadiene
DA	Diels-Alder
DFT	Density Functional Theory
Et	Ethyl
EWG	Electron Withdrawing Group
GC-MS	Gas Chromatography - Mass Spectrometry
HBD	Hydrogen Bond Donor
HBA	Hydrogen Bond Acceptor
HDA	Hetero-Diels-Alder
HFIP	1,1,1,3,3,3-hexafluoropropan-2-ol
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple-Quantum Correlation
IEDDA	Inverse Electronic Demand Diels-Alder
***i*Pr**	*iso*-propyl
Me	Methyl
NMR	Nuclear Magnetic Resonance
PFC	Poly- or Perfluorinated Compounds
PG	Protecting Group
PMT	Persistent Mobile and Toxic
Ph	Phenyl
***p*Tol**	*para*-tolyl
REACH	Registration, Evaluation and Authorisation of Chemicals
THF	Tetrahydrofurane
TFE	2,2,2-trifluoroethanol
TLC	Thin Layer Chromatography
UV	Ultra-Violet

1 Introduction

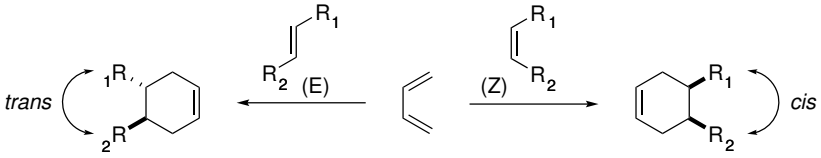
1.1 The Diels-Alder Reaction

Ever since its description by Otto Diels and Kurt Alder[1] in a series of publications in 1928, the eponymous reaction has seen a growing interest from chemists, quickly becoming one of the most powerful tools for organic synthesis. Its major strength is the formation in one step, of up to four stereocenters in a predictable manner. To fully grasp the power of this reaction, it is worth discussing its features briefly.



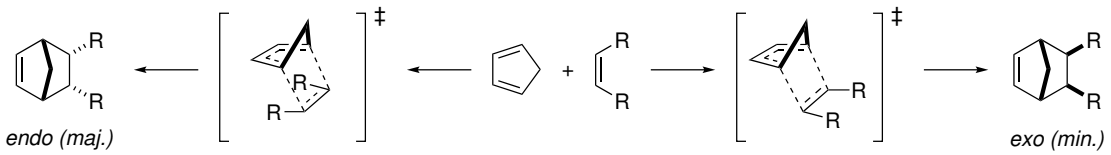
Scheme 1: Illustration of the mechanism of the Diels-Alder reaction.

The Diels-Alder reaction is a [4+2] cycloaddition between a dienophile and a conjugated diene in which two C–C bonds are formed through the sharing of electrons: three π bonds are broken and a new one is formed alongside two new σ bonds, resulting in the formation of a six-membered ring (**Scheme 1**). During this concerted mechanism, the diene has to adopt a s-*cis* conformation for the reaction to take place. Since this reaction is stereospecific, the relative conformation of the reactants is reflected in the final product (**Scheme 2**). From reagents differing only by configuration, two diastereoisomers are produced.



Scheme 2: Illustration of the stereospecificity of the Diels-Alder reaction.

In cases where the diene also bears substituents, a second type of selectivity is observed. Let us consider a similar reaction but using cyclopentadiene instead of butadiene. **Scheme 3** illustrates the transition states and adducts corresponding to two different approaches of the reaction partners. Experimentally, one can see that the *endo* adduct is formed in higher quantity. This specific behaviour, coined the "*endo*-rule" by Diels, has been and still is the subject of intensive study. To date, no general model has been established, and justifications still have to be provided on an almost case-by-case basis.[2] What is certain however, is that this *endo* product, being the more sterically hindered, must be the result of a kinetic control. In fact, the Diels-Alder is a reversible reaction and it is possible to obtain a majority of the thermodynamically favoured *exo* product by heating the *endo* adduct over a long period of time.[3]



Scheme 3: Illustration of the *endo-exo* selectivity of the Diels-Alder reaction.

Before discussing this behaviour, it is necessary to look at the reaction from an orbital point of view through the frontier molecular orbitals (FMO) theory developed by Fukui.[4] In a typical Diels-Alder reaction, the electronic demand is called *standard* and the reaction takes place between an electron rich diene and an electron poor dienophile. In terms of orbitals, this means that the most favourable orbital overlap (or smallest HOMO-LUMO gap) is between the $HOMO_{diene}$ and the $LUMO_{dienophile}$ (**Figure 1**). In the opposite case, when the smallest gap is between the $HOMO_{dienophile}$ and the $LUMO_{diene}$, the electronic demand is described as *inverse*.[5] These inverse electronic demand Diels-Alder (IEDDA) reactions occur between electron poor dienes and electron rich dienophiles, and often involve heteroatoms. However, they are less commonly encountered.

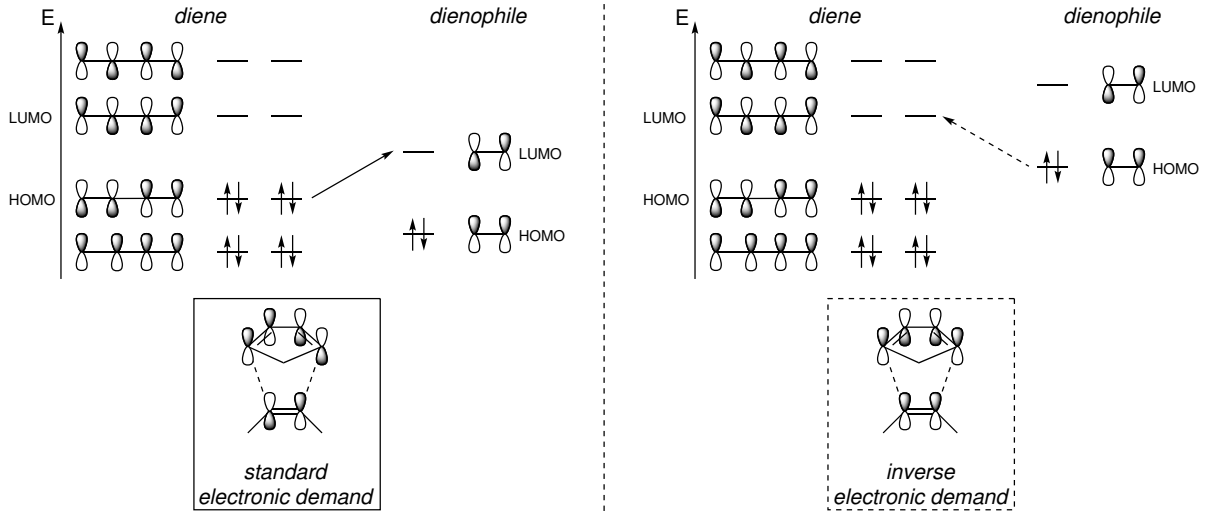


Figure 1: Theoretical molecular orbitals diagram of a Diels-Alder reaction with a standard or inverse electronic demand.

The substituents on the reaction partners influence their electron density and often dictates the type of electronic demand. For example, the standard Diels-Alder is favoured when electron withdrawing groups (EWG) are present on the dienophile, lowering its LUMO. Conversely, well positioned electron donating groups (EDG) on the diene can enrich its electron density on the double bonds, raise the level of its HOMO and once again, favour the reaction. In both cases, the activation energy is lowered by the effect of the substituents.

If we look back at the example of **Scheme 3** and consider unsymmetrical dienophiles (R $\neq$ R'), we can see that several isomers could be formed. However, the distribution of those isomers would not be statistical because the Diels-Alder reaction is regioselective. **Figure 2** shows an example of this

selectivity where the adduct with the groups in *ortho* is the only obtained. This figure also illustrates how the frontier molecular orbitals and more specifically their LCAO coefficients can be used to explain it. Higher coefficients correspond to a higher probability of atomic orbitals interaction, which leads to preferential bonding positions. The influence of the substituents on the orbitals coefficients (lobes sizes) mentioned previously, explains this result. The same reasoning can also be applied to explain the site selectivity in the case of polyunsaturated dienophiles.[3]

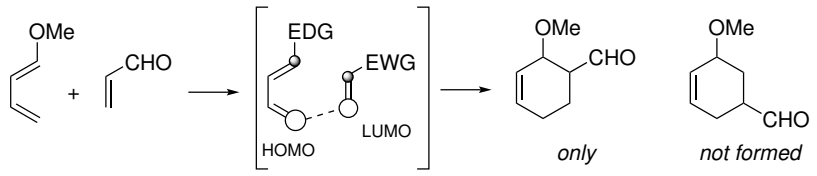


Figure 2: Example of regioselectivity for the Diels-Alder reaction of 1-methoxybutadiene and acrolein[3]

Finally, one last observation from **Figure 1** is that, since the reaction takes place *via* the overlap of *p* orbitals, the reaction partners approach one another in a very specific fashion. Such an approach can lead to facial selectivity if one face is more sterically hindered than the other. This effect can be exploited to control the outcome of the reaction (**Figure 3**).[6]

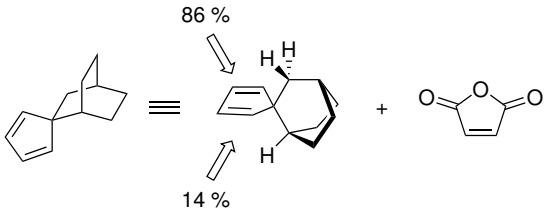


Figure 3: Example of facial selectivity for the Diels-Alder reaction of maleic anhydride and spiro[bicyclo[2.2.2]octane-2,1'-[2,4]cyclopentadiene].[6]

We can now conclude with the diastereoselectivity of the Diels-Alder. The argument often used to explain the *endo* selectivity is that, as shown in **Figure 4**, this approach allows additional orbital overlap. These non-bonding interactions are called *secondary orbital interactions*. They typically occur between π orbitals or lone pairs of the substituents, that are not involved in the primary bonding. Such interactions are believed to lower the activation energy and stabilise the transition state, explaining the formation of a major product. Even though they are the most often invoked justification, the secondary orbital interactions theory has been mainly constructed to justify experimental results based on feeble evidence and the success of the orbital symmetry rules of Woodward-Hoffman. Recently, a growing number of counterexamples and computational studies cast doubt on the veracity of this theory, invoking instead a combination of other known factors (solvent interactions, hydrogen bonding, steric hindrance, ...)[2]

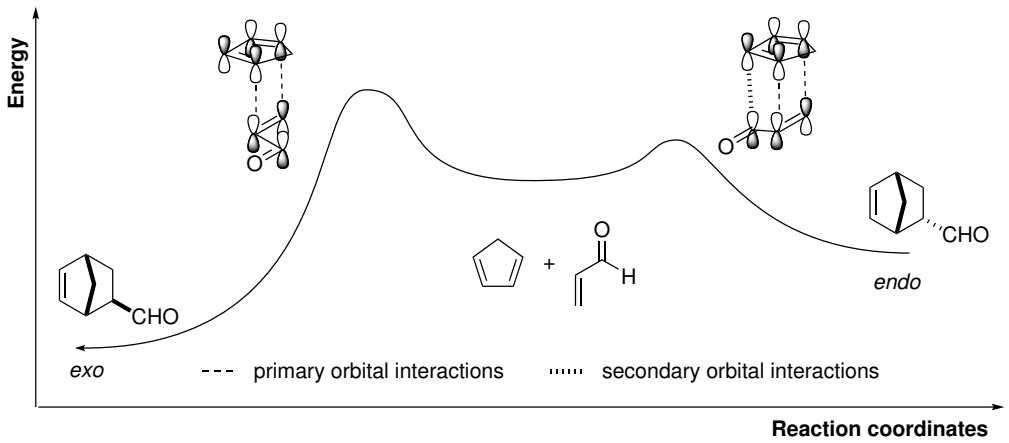
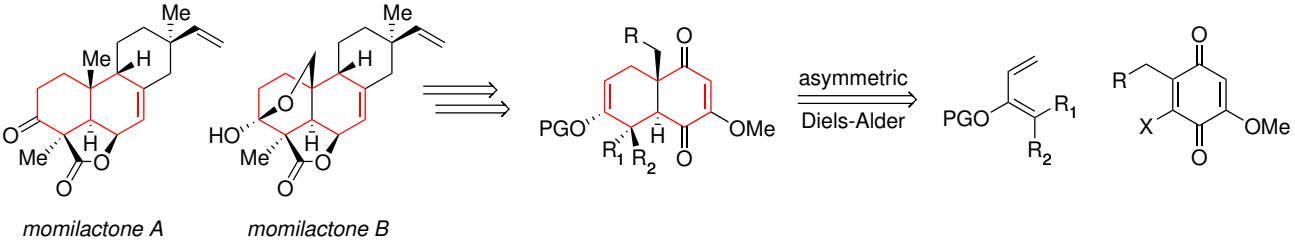


Figure 4: Difference in activation energies for the *endo* and *exo* approaches in the Diels-Alder reaction of cyclopentadiene and acrolein.

Despite these impressing feats, the Diels-Alder reaction also has limitations: in most cases, the reactions are slow in standard conditions. The rates can be improved with increased temperature but at the loss of kinetic control, therefore leading to more of the *exo* product as explained previously. More often, catalysts are used to obtain satisfying yields while conserving or even improving the selectivities. The catalysts employed are usually Lewis acids and historically, the Diels-Alder is the first reaction where such catalysts were used.[7] By increasing the coefficients of the LUMO of the dienophile, they reduce the activation energy while also favouring certain orientations, leading to improved regio- and stereoselectivities as well as higher rates. Unfortunately, such catalysts often come with disadvantages: high costs, limited elements availability, contamination of crude with trace metals, formation of hazardous wastes... Therefore, there is an interest in finding other means of intensification.

An interesting illustration of the potential of the Diels-Alder reaction is given in the work of Dr Loïc Jeanmart[8] from the COS laboratory. The goal of his thesis was to propose an innovative enantioselective synthetic pathway for the production of momilactones A an B, potential anti-cancer candidates (**Scheme 4**). In the approach he envisioned, the formation of the decaline moiety was to be conducted in a highly stereoselective fashion thanks to an asymmetric Diels-Alder reaction. To achieve such selectivity, the main strategy was the use of sulfinyl quinones as chiral auxiliaries. By using the steric hindrance of the sulfinyl groups, the facial diastereoselectivity would be controlled.



Scheme 4: Excerpt of the retrosynthesis of momilactones A and B suggested by Jeanmart highlighting the decaline moeity formed through a Diels-Alder reaction.

1.2 Solvent Effect on Diels-Alder Reactions

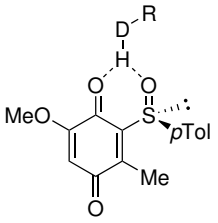


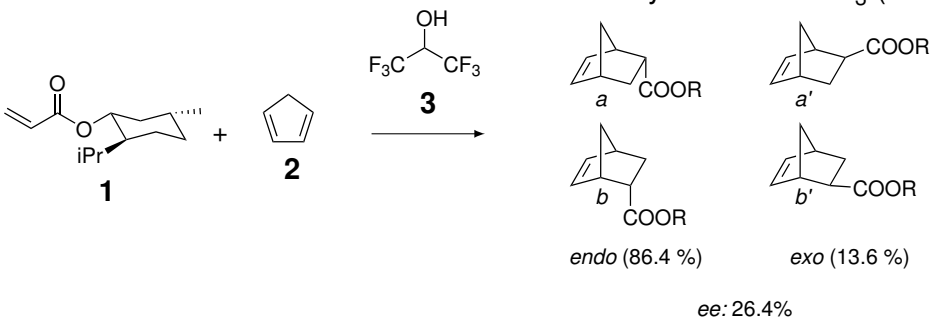
Figure 5: Proposed interactions between sulfinyl quinones and protic solvents.[8]

In order to thoroughly analyse the Diels-Alder reaction of dienes with sulfinylquinones and develop a model to predict the selectivities, Dr Jeanmart decided to study the influence of the solvent on those reactions. With the help of Kalina Mambourg,[9] a master student, they highlighted that protic solvents lead to increased facial diastereoselectivities for their system. The hypothesis of a six-membered ring formation through hydrogen bonding allowed them to explain these observations (**Figure 5**). The sulfoxide constrained with the *para*-tolyl (*p*Tol) group pointing upwards hinders the top face, preventing the approach of the diene. In the search of good hydrogen bond donors (HBD) that also are poor acceptors (HBA), one particular solvent stood out. When running reactions in hexafluoroisopropanol (HFIP, **3**), not only were the stereoselectivities enhanced, the reaction rates were also drastically improved. Reaction times were sometimes shifted from days to minutes and total conversions were even reached for reactions that would otherwise exhibit no or very low conversions. These results highlight the importance of solvents for organic reactions and their potential as a source of intensification.[10]

The earliest mention of a solvent-influenced Diels-Alder cycloaddition dates back to 1980, when Breslow and Rideout[11] published their discovery of up to 200-fold accelerations and improved selectivities for reactions in aqueous solutions. Nowadays, the term "on-water" is preferred since it best describes the ideal process: insoluble reactants are stirred vigorously to form aqueous suspensions, resulting in increased rates. However, the term "in-water" has also been historically used but is now reserved for totally or partially homogeneous systems. In these, improved rates can also be observed, albeit at lower levels, hinting at the complexity of the mechanism involved.[12] In their publication, Breslow *et al.* used the now deprecated concept of solvophobic effect to justify their observations. They suggested that reactants, brought closer together within the organic phase, interact more easily and react faster.[11] Currently, the mechanism is better understood and several combined effects explain these accelerations. The droplets formed in the aqueous suspension indeed provide a favourable space for chemical reactions due to higher pressure, larger surface of contact and increased effective concentrations. Furthermore, the arrangement of insoluble molecules within the droplets allows for multiple interactions with the solvent, such as hydrogen bonding, charge stabilisation, or dipolar effects, which, when combined, lead to the observed accelerations.[13] These effects are also partially present in "in-water" reactions, explaining the accelerations mentioned above.

Following this seminal work, other groups decided to focus on the impact of the solvent on the stereoselectivity of the Diels-Alder reaction. In the early 90's, the solvent polarity was frequently invoked alongside solvophobic effects to justify these accelerations. However, the intrinsic correla-

tion of these two parameters prevented the elaboration of a model to predict behaviours in a general way.[14] In 1992, while studying these effects in the case of asymmetric Diels-Alder reactions, Cativiela and co-workers decided for the first time to include two fluorinated alcohols (trifluoroethanol (TFE) and hexafluoroisopropanol) in the list of solvents tested. These two compounds having a very high polarity but low solvophobicity, allowed them to discuss the colinearity of these two parameters. For the reaction of (–)menthyl acrylate (**1**) and cyclopentadiene (**2**) in HFIP, their results led to a diastereomeric excess similar to the one obtained with a Lewis acid catalyst such as $AlCl_3$ (**Scheme 5**).



Scheme 5: Results obtained by Cativiela *et al.* for the reaction of (–)menthyl acrylate (**1**) and cyclopentadiene (**2**) in HFIP.[15]

To better understand these results, they conducted a computational study using different and quasi-independent parameters. The conclusion of their work was that, while solvophobicity plays a major role in rate enhancements, it does not account for improved *endo/exo* selectivities and enantiomeric excesses. These variations seemed to be resulting from a combination of electrostatic and hydrogen-bonding interactions that stabilise preferentially one of the transition states. These effects are similar to those observed in aqueous media but with the added benefit of not being limited to the interfacial area.[15]

Following these results, the group continued to explore the potential of those solvents for Diels-Alder reactions. They reported asymmetric induction akin to that of Lewis acids, good performances at low temperatures,[16] but also some limitations. By conducting cycloadditions of cyclopentadiene (**2**) with acrolein, it was shown that, as opposed to TFE, HFIP is a well suited solvent for Lewis-acid-sensitive reagents thanks to its lower nucleophilicity. However, its rather high acidity (pK_a = 9.4[17]) compared to *iso*-propanol (pK_a = 17.1) makes it less suitable for Brønsted-acid-sensitive reagents.[18] Furthermore, they also remarked upon two main advantages

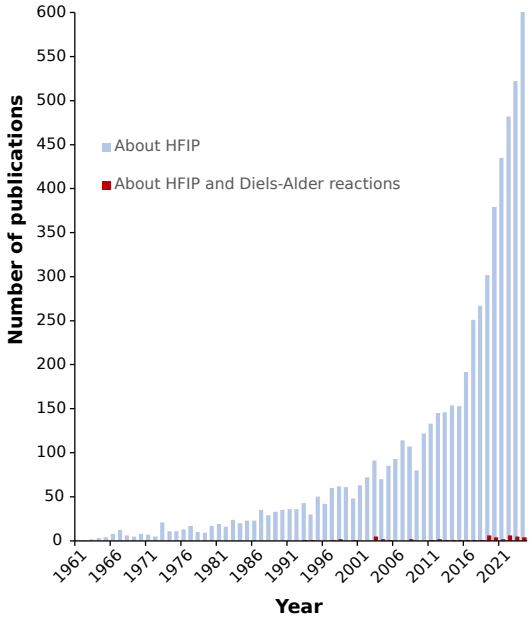


Figure 6: Publications listed in the SciFinder® database mentioning HFIP and Diels-Alder reactions.

of HFIP: its ease of recovery (*b.p.* = 56.8 °C) and outstanding solubilising properties.

In fact, ever since its simultaneous invention by Soviet Union chemists J. L. Knunyants and M.P. Krasuskaya (1960)[19] and Dupont de Nemours workers (1964),[20] HFIP has been used to solubilise tenacious polymers[21] and proteins or even as an azeotroping agent for hydrocarbon separation.[22]

Since then, HFIP has grown in popularity as its versatile properties are beneficial to many other chemical processes. Some recent reviews describe the range of possible applications of this uncommon medium.[23–25] In them, Diels-Alder reactions are seldom mentioned (**Figure 6**).

1.3 Continuous Flow Chemistry

One particular field that could benefit from the improved rates aforementioned is continuous flow chemistry. Moving from flasks and batch reactors to tubing and chip reactors offers many advantages but also suffers from a major drawback: the reaction times are translated to reactor lengths. Long lasting reactions mean that the efficiency and compactness of a flow system cannot be maintained.[26] Diels-Alder reactions typically fall under this category but can thankfully be intensified in a number of ways.

The main advantage of flow chemistry is the use of small diameter tubes. The high surface area to volume ratio (specific surface) leads to improved reaction rates for bimolecular reactions.[27] Furthermore, this large specific surface also means that the temperature of the system can be finely and quickly tuned since heat transfers are rapid. Then, flow setups require pressure to function properly and are also well-suited for the use of high pressures. These can improve reactions rates on their own but they also allow the use of new chemical windows. By working at high temperatures and pressures, one can conduct reactions far above the boiling point of solvents. These kind of conditions are typically used for Diels-Alder reactions in continuous flow setups.[2]

Flow chemistry also allows the use of heterogeneous catalysts, with one added benefit. Since these catalysts are typically employed in a packed-bed reactor (**Figure 7**), the apparent catalyst concentration is extremely high, further decreasing reaction times.[26] Moreover, since the catalyst is contained in a cartridge, no subsequent separation is required. However, leaching of the catalyst frequently occurs.[28]

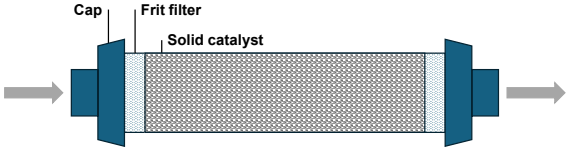


Figure 7: Illustration of a typical packed-bed reactor for continuous flow setups.[26]

Finally, other activation techniques such as sonication or UV irradiation are easily applicable to such setups.[29] Notably, reports of Diels-Alder reactions facilitated by microwave heating have been made by several groups.[30,31] Finally, *in situ* preparation of highly reactive reagents is also quite suitable. For example, hydrogenation reactions have been successfully conducted in flow by producing hydrogen gas on demand with an electrolysis cell, greatly reducing the risks of the process.[32] Similarly, Orrego-Hernández and co-workers conducted Diels-Alder reactions between cyclopentadiene and acetylene derivatives in flow *via in situ* cracking of dicyclopentadiene, lowering the preliminary work required and preventing the re-dimerisation of the diene.[33]

Overall, when applicable, continuous flow chemistry offers an appealing work environment. Since reactions are scaled over time rather than volumes, the total amount of chemicals involved is always low, reducing risks and to some extent, waste generation. Furthermore, the great energy efficiency of the processes can reduce the environmental impact of the reactions. These conditions are attractive for effective production of chemicals and since the Diels-Alder reaction is involved in numerous synthetic pathways,[34] there is a great interest in trying to merge these areas further. More specifically, the solvent accelerations discussed previously could serve as an additional intensification techniques for Diels-Alder reactions.

2 Objectives and Strategies

The primary objective of this work is to evaluate the feasibility and scope of conducting Diels-Alder in continuous flow using HFIP as a non-conventional solvent. This study differs from the condition typically reported in the literature for these cycloadditions: whereas they usually require elevated temperature, our goal is to evaluate their performance in mild conditions but in an alternative solvent. Doing so, we seek to assess the benefits and limits of the singular polarity and hydrogen bonding properties of HFIP.

Additionally, while the use of fluorinated alcohols to accelerate Diels-Alder reactions is well known, examples are still short in the scientific literature. The approach we propose would allow to broaden our knowledge in this area as well as the range of reactions described.

To achieve these objectives, our strategy is to conduct a screening during which we would compare HFIP with other solvents in fixed conditions. The solvents considered are: dichloromethane for the classically used apolar solvents, *iso*-propanol to illustrate its difference with HFIP and water, as an other non-conventional medium. The comparisons will be based on key parameters such as reaction rate, conversion, yield and whenever applicable, selectivities.

By initially focussing on the dienophile and keeping the diene constant, several observations could already be made, depending on the compounds studied. A judicious selection of dienophiles will enable us to explore the following categories, among others:

- Poly-functional dienophiles such as maleic anhydride or dimethyl fumarate since they are highly reactive, largely studied and could serve as a benchmark for the comparisons.

- Electron deficient dienophiles, since they are highly reactive and are often used to discuss the regioselectivity of the Diels-Alder. At the same time, they also provide access to valuable intermediates (electron poor alkynes, acrylate, ...).

- Cyclic dienophiles are invaluable intermediates for constructing polycyclic molecules, making them a logical choice. They also exhibit specific regio- and stereoselectivities on which the influence of HFIP would be interesting to study.

- Facially hindered dienophiles, such as menthyl or phenylmenthyl acrylates, that were studied by Cativiela in 1993.[16] These substrates are particularly intriguing for continuous flow applications, as investigating them would provide valuable insights and further enrich the conclusions drawn in Cativiela's work.

- Challenging dienophiles that would include substrates with inherently low reactivities or prone to side-reactions.

- Functionalised dienophiles, including nitroalkenes, fluorinated alkenes, and α,β-unsaturated amides, offer additional complexity due to their diverse electronic and steric profiles. For example, nitroalkenes present a dual challenge of high electrophilicity and potential side reactions.

Finally, by frequent comparisons with the literature, we hope to highlight the divergences between conventional conditions and the ones proposed here.

3 Results and Discussions

3.1 Methodology

In order to compare the solvents, the method employed was to run the reactions in parallel with a 15 min offset in the same pressure and temperature conditions (ambient). The stoichiometric ratio used was kept the same (1:2.2 equivalents) and the amount of solvent proportional (10 mL/mmol).

The completeness of the reactions was monitored by TLC as it is easy to setup, flexible and suited for long reaction times. Spots were applied on the plates every minute for the first ten minutes and then every quarter of an hour until the starting material spot was no longer observable. This method enable a good balance between precision and workload. In cases of uncertainty, NMR monitorings were conducted. A sufficient amount of crude was collected and worked-up in order to have approximatively 20 mg of product in the sample. After seven days, the reactions were stopped as the cyclopentadiene had theoretically reacted or dimerised after this time.

In the absence of reactivity, higher temperatures were used (50 °C) but the optimisation of reaction temperature was not performed at this stage of the project.

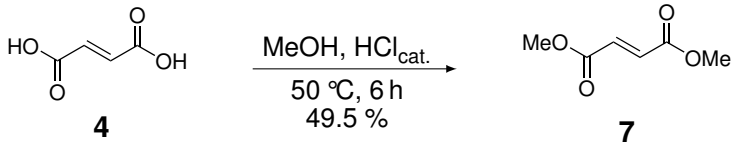
The molecules investigated were common reagents, either commercially available or synthesised as needed based on described protocols.

3.2 Screening of Dienophiles in Batch

As a starting point for the screening, we decided to investigate the model reaction of maleic anhydride (**5**) with cyclopentadiene in HFIP. This compound is a highly reactive dienophile since two strong EWG substituents lower its LUMO level. Furthermore, the molecule being planar and strained, the reactive site is readily accessible to the diene. The reaction time of 1.5 h obtained for the cycloaddition in CH_2Cl_2 is indicative of this high reactivity (**Table 1**). Even shorter reactions times were obtained when the solvent was changed to HFIP, with total conversion reached in less than a minute. The added purification step imposed by the polymerisation of the diene led to a slightly lower isolated yield when HFIP was used. As is the case throughout most of the screening, only the *endo* adduct was observed in the crude mixture.

Encouraged by these first results, we decided to investigate dienophiles with increasingly lower reactivities in order to assess the limits of this solvent-based acceleration. Therefore, dimethyl fumarate (**7**) was prepared by esterification of fumaric acid (**4**) in methanol (**Scheme 6**). With similar EWG but the absence of strain, a lower reactivity was expected in comparison to maleic anhydride. This has indeed been observed as shown by the results of **Table 1**. A less intense acceleration (around two-fold) was observed and comparable yields were obtained.

Next, an ester with only one electron withdrawing group was used. Ethyl acrylate (**9**) was reacted



Scheme 6: Fischer esterification of fumaric acid (**4**) in methanol, catalysed by hydrochloric acid to produce dimethyl fumarate (**7**).

with cyclopentadiene but its volatility prevented us from monitoring the reaction *via* TLC. Even when using a mixture of pentane and ether as eluant, the spots observed were too broad and overlapped with those of the cycloadducts. In order to verify that the reaction could indeed take place at ambient temperature and pressure, a ^{1}H NMR monitoring was conducted. Formation of the adduct was observed in deuterated chloroform, as can be seen from the peaks of **Figure 8**. Over time, signals corresponding to a mixture of *endo* and *exo* isomers can be observed in the spectrum. Simultaneously, the peaks of cyclopentadiene decrease in intensity due to the cycloaddition, dimerisation and evaporation of the diene. This experiment confirmed the feasibility of this reaction but above all, the relevance of accelerating it. Indeed, total conversion was not reached before consumption of all the diene, as is evident by the remaining signals of the dienophile. This reaction has already been successfully conducted in a continuous flow micro-reactor by Bai-cheng and co-workers,[35] who achieved a reaction time of 335 s at 80 °C. Furthermore, an acceleration caused by HFIP has been reported by the group of Cativiela[18] for a similar compound (methyl acrylate) using gas chromatography (GC). But to the best of our knowledge, a combination of these two conditions has never been reported. Due to material and time limitations, we could not conduct these reactions in a GC system or using quantitative ^{1}H NMR and we therefore could not report any conversion data.

Instead, it was decided to react methyl propiolate (**11**) with cyclopentadiene, hoping that this higher-boiling compound would allow TLC monitoring. Unfortunately, the same issues arose. Similarly, ^{1}H NMR indicated the formation of some cycloadduct (**12**) in CH_2Cl_2 at room temperature after 24 h. But given the impossibility of evaluating the reaction time with our method, the reaction was not attempted in HFIP. This cycloaddition has been reported with appreciable yields on several occasions *via* photocatalysis[36–38] or simple Lewis acid catalysis[39] but to the best of our knowledge was never described in HFIP nor in flow. Since the Diels-Alder reaction can take place twice on this kind of dienophile, as was reported under Lewis acid catalysis by Lasne and Ripoll,[40] it would be interesting to see if the use of HFIP can lead to this phenomenon. In dichloromethane, no traces of this double cycloaddition product were observed in the crude mixture.

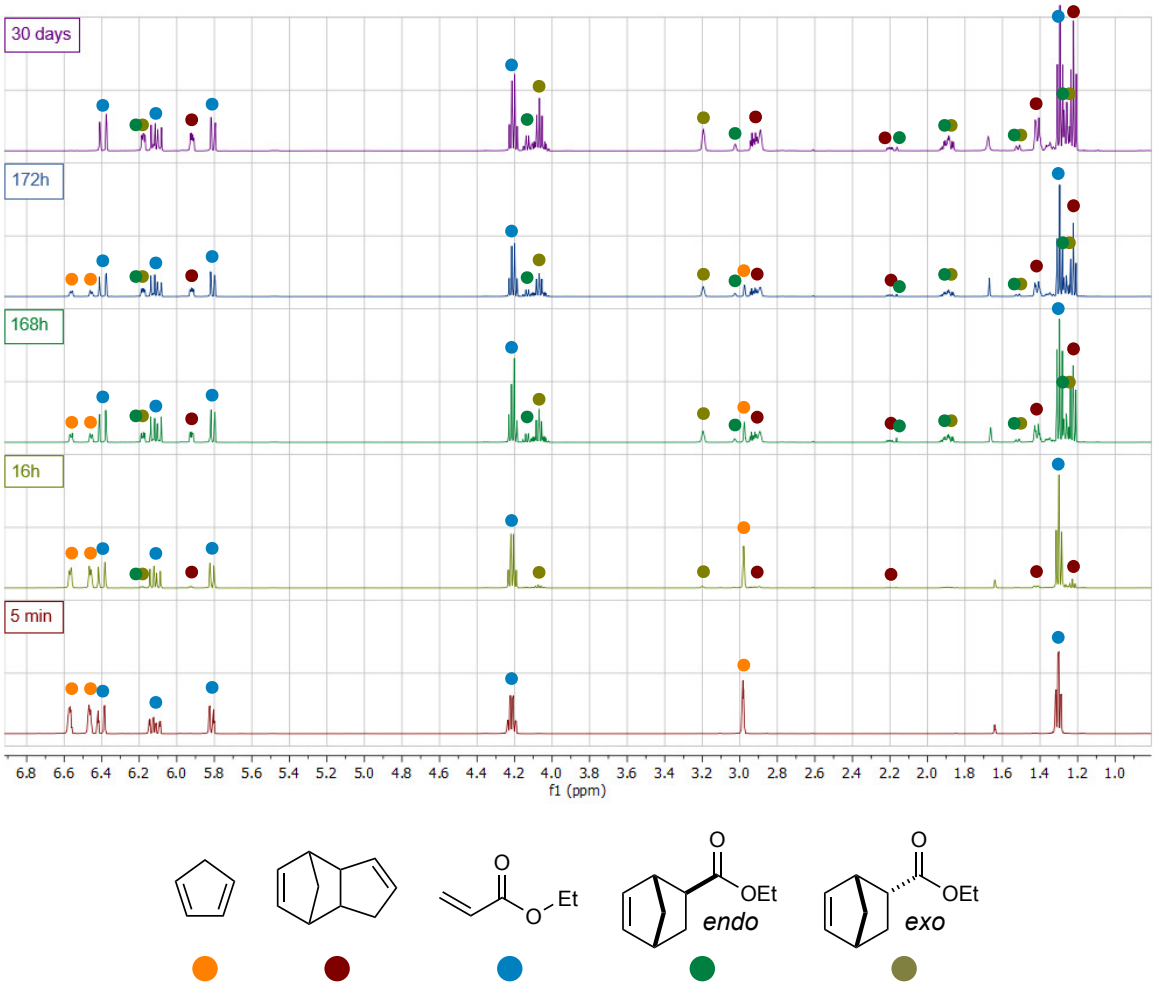
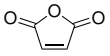
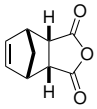
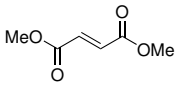
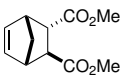
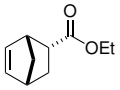
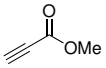
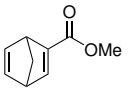


Figure 8: ^{1}H NMR monitoring of the reaction between cyclopentadiene (**2**) and ethyl acrylate (**9**) in $CDCl_3$. The peaks attribution is based on values from Fringuelli *et al.*[41] for the *endo* and Sterk *et al.*[42] for the *exo*.

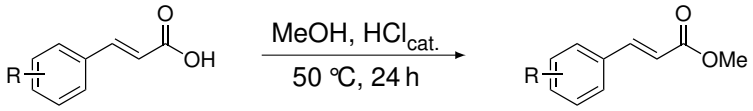
Table 1: Structures of the expected products, reaction times, conversions and isolated yields for the cycloadditions of maleic anhydride (**5**), dimethyl fumarate (**7**), ethyl acrylate (**9**) and methyl propiolate (**11**).

Dienophile		Adduct		Solvent	Time	Conversion[a] (%)	Isolated yield (%)
5		**6**		CH_2Cl_2	1.25 h	quant.	>99
				HFIP	<1 min	quant.	87
7		**8**		CH_2Cl_2	3.5 h	quant.	97
				HFIP	1.25 h	quant.	97
9		**10**		CH_2Cl_2	—	n.d.	—
				HFIP	—	n.d.	—
11		**12**		CH_2Cl_2	—	n.d.	—

n.d.=non determined. [a] Based on the ^{1}H NMR spectra of the crude mixtures.

Afterwards, the reactivity of the dienophile was lowered even more by use of electron donating substituents such as a phenyl group. Methyl cinnamate (**19**) was firstly tested but no reaction was observed, neither in CH_2Cl_2 nor HFIP (**Table 2**). These results are consistent with the literature, where the only references to this reaction describe it as sluggish,[43] requiring Lewis acid catalysis[44,45] or high temperatures over long periods of time (e.g.: 76 % yield after 288 h in refluxing toluene).[46,47] It is probably necessary to work at higher temperatures in order to start noticing the impact of HFIP on this cycloaddition. Since the optimisation of reaction temperature is much easier in a flow setup, this dienophile could be further explored in future studies stemming from the present work.

To explore these outcomes in more depths using more reactive dienophiles, several methyl cinnamates bearing fluorine or trifluoromethyl substituents were synthesised (**Scheme 7**). To ensure thoroughness, all positions (2,3 and 4) of the phenyl group were investigated. However, since none of these compounds led to the formation of a cycloadduct, this impact could not be discussed. It would appear that the electronegativity of these substituents is not sufficient to bring the reactivity in a convenient window. Similarly to methyl cinnamate (**19**), studies at higher temperatures could be conducted in flow. In addition, increasing the number of substituents could prove beneficial, provided that steric hindrance does not impose itself as a new issue. One of the few mentions of the Diels-Alder reaction of these substituted cinnamates has been made by the List group[48] during an extensive study of the performance of an innovative silylium Lewis acid catalyst on α,β-unsaturated esters.

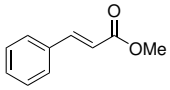
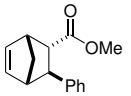
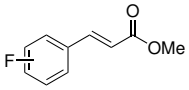
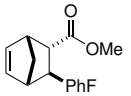
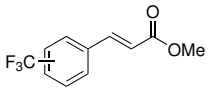
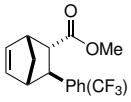


13o: R=2-F		**15o**: R=2-F	94 %
13m: R=3-F		**15m**: R=3-F	88 %
13p: R=4-F		**15p**: R=4-F	95 %
14o: R=2-CF_3		**16o**: R=2-CF_3	94 %
14m: R=3-CF_3		**16m**: R=3-CF_3	97 %
14p: R=4-CF_3		**16p**: R=4-CF_3	66 %

Scheme 7: Fischer esterification of cinnamic acids (**13o**, **13m**, **13p**, **14o**, **14m**, **14p**) in methanol, catalysed by hydrochloric acid to produce the corresponding methyl cinnamates (**15o**, **15m**, **15p**, **16o**, **16m**, **16p**).

In order to explore other functional groups and further increase the reactivity in comparison to cinnamates, we then turned our attention to nitro-alkenes. The nitro group is of utmost importance in organic synthesis since it can readily be converted in a large variety of groups.[49] An ever increasing number of publications is proof of this utility.[50] However, when it comes to Diels-Alder reactions, there are fewer examples. While conjugated nitro-alkenes are good dienophiles due to the electronic

Table 2: Structures of the dienophiles and expected products, reaction times, conversions and isolated yields for the cycloadditions of the cinnamates derivatives studied.

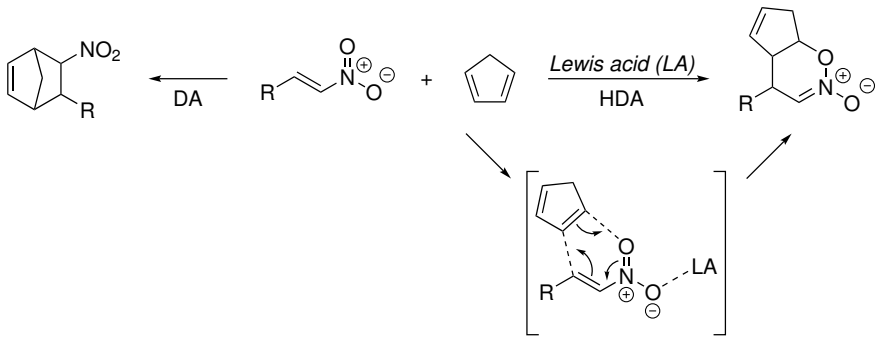
Dienophile		Adduct		Solvent	Time	Conversion[a] (%)	Isolated yield (%)
19		**20**		CH_2Cl_2	7 d	0	—
				HFIP	7 d	0	—
15o **15m** **15p**		**17o** **17m** **17p**		CH_2Cl_2	7 d	0	—
				HFIP	7 d	0	—
16o **16m** **16p**		**18o** **18m** **18p**		CH_2Cl_2	7 d	0	—
				HFIP	7 d	0	—

n.d.=non determined. [a] Based on the ^{1}H NMR spectra of the crude mixtures.

effect of the NO_2 group,[51] they are usually only suited for reactions that can be achieved in mild conditions.[52]

In fact, conjugated nitro-alkenes are prone to side reactions such as polymerisation[52] or Michael additions.[49] But more specifically, in cases where a Lewis catalyst is used to increase the rate of the cycloaddition, another product is often formed. Denmark *et al.*[53] has demonstrated that by coordinating one of the two oxygen atoms of the nitro group, the Lewis acid can increase the double bond character of the second, altering the energy level of its orbitals. Therefore, the inverse electronic demand mechanism becomes favourable, the dienophile behaves as an heterodiene and a product of hetero-Diels-Alder is obtained (**Scheme 8**). In an effort to better understand this phenomenon, Hook and co-workers[54] have studied the transition structures of these cycloadditions. In their work, a comparison between DFT calculations and experimental data has been made. One point of particular interest is the mention of improved yields and selectivities when the reactions were run in trifluoroethanol. Computational implicit solvation methods allowed them to confirm that this was the results of a lowered activation energy through H-bonding, regardless of the reaction pathway. These results align with the work of Takenaka *et al.* who reported for the first time the H-bond catalysis of the cycloaddition of cyclopentadiene and nitro-alkenes.[55] The catalysts they used were double H-bond donors such as thioureas or azaindole derivatives. With the hypothesis that this double interaction leads to an even dispersion of the charge in the nitro group, preventing an hetero-diene behaviour. In their work, they reported improved rate and *endo* selectivity, achieving at most a yield of 49 % in 8 h for the reaction of cyclopentadiene with β-nitrostyrene (**21**) at room temperature without any hetero-Diels-Alder adduct.

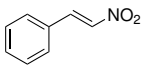
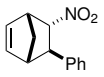
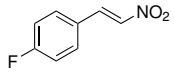
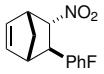
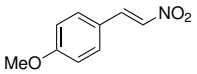
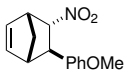
When we conducted the same reaction in HFIP, outstanding results were obtained, since total conversion of the dienophile was reached in 1.5 h and no side product could be detected (**Table 3**).



Scheme 8: Diels-Alder (DA) and Hetero-Diels-Alder (HDA) products for the reaction of cyclopentadiene with a conjugated nitro-alkene.

In comparison, the same reaction run in CH_2Cl_2 only allowed partial conversion before consumption of the diene in other transformations. One remarkable aspect of these experiments is that we obtained results seemingly superior to those reported in the literature but using a single H-bond donor. This outcome is counter-intuitive to what would be expected on the basis of mechanistic considerations and further study would be beneficial. Separation of the cycloadduct and nitrostyrene proved challenging and could only be partially accomplished by column chromatography or Kugelrohr distillation. We therefore relied on quantitative ^{1}H NMR for the determination of conversions and yields.

Table 3: Structures of the dienophiles and expected products, reaction times, conversions and isolated yields for the cycloadditions of the nitrostyrenes derivatives studied.

Dienophile		Adduct		Solvent	Time	Conversion[a] (%)	Isolated yield (%)
21		**22**		CH_2Cl_2	7 d	83	55
				HFIP	5.5 h	quant.	90
				H_2O	7 d	21	10
				*i*Pro	7 d	39	4
23		**24**		CH_2Cl_2	7 d	19	13
				HFIP	5.25 h	quant.	77
25		**26**		CH_2Cl_2	7 d	34	3
				HFIP	6 h	96	85

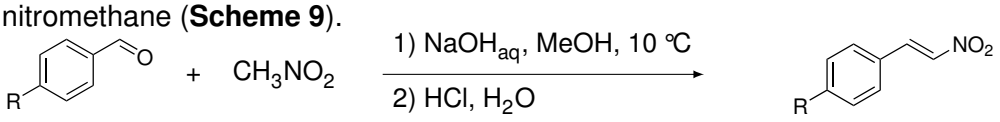
n.d.=non determined. [a] Based on the ^{1}H NMR spectra of the crude mixtures.

In order to have better points of comparison and since it had never been reported, we decided to compare our results with the reaction conducted in water and isopropanol. The benefits of HFIP over its non fluorinated equivalent are self-evident when it comes to yield since only a meagre amount of adduct was obtained. The low conversion observed in iso-propanol could result from a bad solubil-

isation of the cyclopentadiene, since it is a polar protic solvent. However, this improvement comes at a price since the former costs around 100 × more than the latter.[56] On the other hand, if HFIP proves capable of replacing catalysts, it could become an economically interesting alternative.

For the reaction on water, only a small quantity of cycloadduct was formed. Usually, these reactions use liquid reagents. However, one reagent can be solid, provided that it is accompanied by a liquid partner in which it is readily solubilised.[12] Since nitrostyrene is solid at room temperature and given its difference in polarity with cyclopentadiene ($\mu_{nitrostyrene}$ = 3.85 D,[57] μ_{CPD} = 0 D), a low solubility is to be expected, which would explain the extremely low yield obtained. Moreover, one of the main benefits of using water is the easy product isolation by decanting.[12] On the very small scale we used, this was not possible and a liquid-liquid extraction had to be performed, possibly lowering the isolated yield. To overcome this mixing issue, a small quantity of organic solvent could be added, thus trading a bit of reaction speed for feasibility. Another approach would be the use of additives, as is reported in one of the few mentions of this reaction in water.[58]

Motivated by the results obtained with nitrostyrene, we decided to study other nitro-alkenes compounds. With the help of master students (C. R. De Haes and N. Pierard), 4-fluoro– and 4-methoxynitrostyrenes were synthesised by through Henry reaction between the corresponding aldehydes with nitromethane (**Scheme 9**).

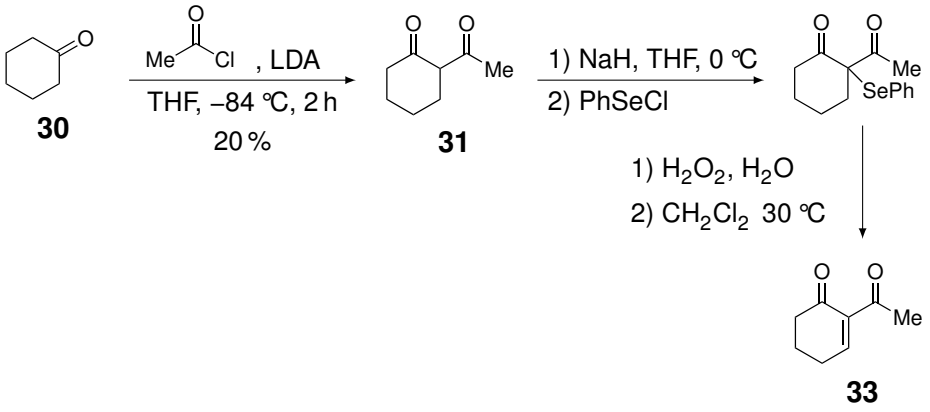


27: R=H		**21**: R=H	36.3 %
28: R=F		**23**: R=F	58.9 %
29: R=OMe		**25**: R=OMe	38.4 %

Scheme 9: Henry reaction between benzaldehydes (**27**, **28**, **29**) and nitromethane yielding the corresponding nitrostyrenes (**21**, **23**, **25**).

A smaller reaction rate was expected with the additional methoxy group, since its electron donating character should raise the level of the LUMO. A longer reaction time was indeed observed to reach full conversion of the dienophile, compared to nitrostyrene. Unexpectedly, the opposite trend was not observed for the electron withdrawing fluorinated group, and only a small difference was witnessed. A good correlation between the substituents on the phenyl ring and the cycloaddition rate has been described by Larkovich and co-workers.[59] In their work, they detail how the presence of a methoxy group results in slower reaction rates. In contrast, the fluorine atom accelerates the reaction although its effect is less pronounced than that of the methoxy group. The hypothesis we proposed to justify our results is that the variations stem mostly from disparities in ambient temperature. Indeed, the initial tests were conducted during the summer, while the final ones took place in late autumn, with an approximate temperature variation of 10 °C. To confirm this idea, the reaction was conducted again in HFIP shortly after the two other compounds were tested. The new reaction time of 5.5 h

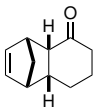
confirms our theory. This new experiment is also coherent with the expected reactivity scale, however, seeing the large variations observed, this conclusion is to be treated with caution. Our method was not sensitive enough to detect those variations rigorously and would be better suited in a more controlled environment such as a thermostated flask or a in our case, a flow reactor. Nevertheless, HFIP was shown to be an appropriate medium for the acceleration of Diels-Alder cycloadditions for all three nitrostyrenes tested.



Scheme 10: Synthesis of 2-acetyl-cyclohexenone (**33**) by acetylation of cyclohexenone (**34**) followed by a selenoxide elimination of 2-acetyl-cyclohexanone (**31**).

Finally, the last motif studied was a cyclic enone. Cyclohexenone (**34**) is notoriously unreactive in Diels-Alder reaction[60,61] but is of great interest as it can lead to methylene-bridged decaline, an important route towards the synthesis of many natural products.[10] When we tried reacting cyclohexenone with cyclopentadiene, no adduct could be detected in CH_2Cl_2. In HFIP however, traces amounts could be observed *via* ^{1}H NMR after 7 days (**Table 4**). It appears that this change of solvent leads to an improved rate but the reaction still requires further intensification to achieve appreciable yields. As a starting point, an optimisation of the reaction temperature could be conducted to further investigate these new conditions. In the meantime, we decided to prepare another cyclic enone with an expected higher reactivity. 2-acetyl-cyclohexenone (**33**) was synthesised by selenoxide elimination of 2-acetyl-cyclohexanone (**31**, **Scheme 10**). However purification and storage of this highly reactive compound turned out to be complex and we could not prepare enough to test the cycloadditions in a timely manner.

Table 4: Structures of the dienophiles and expected products, reaction times, conversions and isolated yields for the cycloadditions of the nitrostyrenes derivatives studied.

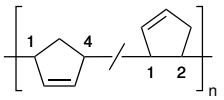
Dienophile		Adduct		Solvent	Time	Conversion[a] (%)	Isolated yield (%)
34		**35**		CH_2Cl_2	7 d	0	—
				HFIP	7 d	n.d.	traces[b]

n.d.=non determined. [a] Based on the ^{1}H NMR spectra of the crude mixtures. [b] Isolation not achieved.

3.3 General Observations

One of the first observations made during this work was the systematic formation of a precipitate when cyclopentadiene (**2**) was used in HFIP. The acidic character of hexafluoroisopropanol makes it capable of catalysing the cationic polymerisation of the diene, forming poly-(cyclopentadiene) (**Figure 9**, **36**). This behaviour had already been described by Cativiela *et al.* when they first used HFIP for a Diels-Alder reaction, an effect which "[...] *precluded the calculation of accurate rate constant values.*"[16] Consequently, using this highly reactive diene allowed us to focus only on the dienophiles but introduced new challenges, as the diene is now subject to two side reactions. Precise control of the stoichiometric ratios could mitigate this polymerisation since it is not of the same kinetic order as the cycloaddition. However, fine tuning of these ratios is more easily done in flow and could be addressed at a later stage in this project. For now, flash chromatography columns allowed us to discard this compound with ease.

This polymer is formed through chain polymerisation and two polymeric units can be obtained depending on the charge delocalisation:[62] 1,2 and 1,4 structures (**Figure 9**). When we verified the nature of our precipitate by ^{1}H NMR, we applied a method proposed by Aso and co-workers[63] to estimate the ratio of 1,2 to 1,4 structure in the material. The method relies on dimethylcyclopentenes as model molecules to assign NMR signals corresponding to the moieties of the 1,2 or 1,4 additions. The spectra of the polymer is then split in four regions (**Figure 9**): *A* corresponding to the β-methylene found in 1,4-structures, *B, C* corresponding to α-methylenes and α, β-methines found in both structures and *D* around 5.6 ppm for olefinic protons. Region *A* being unique to 1,4-structures, the ratio can then be calculated as follows:



36

$$\frac{[1,4-structure]}{[1,2-structure]}(\%) = \frac{(B+C)-A}{A+(B+C)} \times 100$$

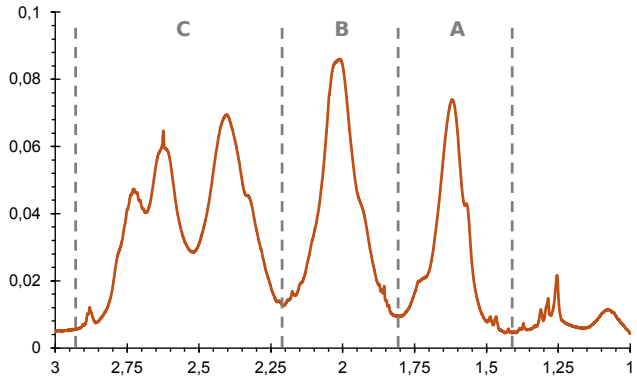


Figure 9: General structure of poly(cyclopentadiene) (**36**) and excerpt of an experimental ^{1}H NMR spectra.

In our case, a ratio of approximately 60 % was determined. This could be explained by the HFIP that leads to a higher charge delocalisation. Therefore, a looser ion pair is formed and results in more 1,2 addition.[63] Control of the molecular weight distribution and 1,2 to 1,4 ratio has been the subject

of a number of publications.[64] One of the lead for this control is living cationic polymerisation but few systems have been described.[65] Our results suggest that HFIP might be an applicable candidate.

4 Conclusions

So far, we have studied a considerable panel of Diels-Alder cycloadditions in HFIP. In all cases where reaction already took place at room temperature and ambient pressure in dichloromethane, striking accelerations were observed when using HFIP. This situation was observed for maleic anhydride (**5**), dimethyl fumarate (**7**) and three different nitro-alkenes (**21**, **23** & **25**). On the other hand, for dienophiles such as methyl cinnamate (**19**) and its fluorinated (**15**) of trifluoromethylated (**16**) analogues, no reaction was observed in CH_2Cl_2 and switching to HFIP did not yield noticeable improvements, even when mildly heated (50 °C). Similar behaviour was observed for the reaction of cyclohexenone (**34**) for which the acceleration only produced traces amount of cycloadduct.

For more volatiles compounds such as ethyl acrylate (**9**) and methyl propiolate (**11**), positive results were expected since similar studies have been conducted by other groups[18] and the reaction readily takes place in dichloromethane. However, the small difference in polarity between the dienophiles and their cycloadducts prevented us from monitoring the reaction *via* TLC and no conclusions regarding the impact of HFIP could be drawn.

The most striking example of acceleration reported in this work is the one involving nitrostyrenes. In all three cases studied, the use of HFIP led to total conversion in appreciable times, without noticeable formation of side products. This is particularly appealing since Diels-Alder reactions of nitroalkenes are notoriously complex to catalyse due to the hetero-Diels-Alder mechanism that take place when Lewis acids are used. H-bond catalysis has been proposed and used by several groups[48] but to the best of our knowledge, such pronounced improvements have never been reported.

Furthermore, these compounds allowed us to highlight the extreme sensitivity of the Diels-Alder to temperature. More specifically for nitrostyrene (**21**), reaction time dropped from 1.5 h to 5.5 h with only a minor change in ambient temperature. Additionally, we tried to assess the impact of the substitution of the aromatic ring on the reactivity by using 4-fluoronitrostyrene (**23**) and 4-methoxynitrostyrene (**25**). The expected trend was observed: slower reaction with the methoxy-substituted compound and faster with the fluorinated one. However, in view of the high variability of our results in regards to temperature, this conclusion is to be treated with caution and requires further investigations.

Finally, we compared our results for nitrostyrene with two other solvents: *iso*-propanol and water. In both cases, the high solubilising power of HFIP makes it a superior medium. For the former, poor solubilisation of cyclopentadiene is probably responsible for the low yield observed. In the latter, the lack of solubility of nitrostyrene in cyclopentadiene did not allow us to benefit from the advantages of on-water reactions and led to poor yields.

In conclusion, we reported the acceleration in HFIP of Diels-Alder reactions that can, fully or not, take place at room temperature in CH_2Cl_2. In all cases, these accelerations made it possible to achieve total conversion of the starting materials, most notably in the case of nitrostyrene derivatives, where it was otherwise not observed. This last observation is of particular interest since, to the best of our knowledge, such mild and efficient conditions were never reported.

5 Perspectives

To continue this work, several perspectives in two different areas, batch and flow, could be explored. Regarding batch reactions, if further tests were to be carried out, it is clear that better comparisons could be achieved by working in a temperature-controlled setup.

Then, the scope of molecules tested could be broadened. Whether it be other dienes or other dienophiles with EWG capable of accepting hydrogen bonds such as nitriles, cyanates and isocyanates. For the former, it would be interesting to see if polymerisation is a general issue.[16] Additionally, it might be worth considering other nitro-alkenes, as they have led to the most interesting results. Finally, developing a method to monitor these reactions in GC-MS would allow the study of more volatile compounds. Moreover, our efforts to synthesise and isolate 2-acetylcyclohexenone could be continued to investigate one more dienophile.

Additionally, one of the main drawbacks of HFIP is its high price compared with traditional solvents. It would therefore be profitable to minimise the quantity required for the best outcome possible. One way of doing this would be to use mixtures of HFIP and other solvents. Similar studies have already been done by other groups[18,66] but not for all systems considered herein. Furthermore, HFIP has been classified as persistent, mobile and toxic (PMT) under the REACH Regulation and is therefore a potential treat to the environment.[67] As is the case with most poly- or perfluorinated compounds (PFC), hexafluoroisopropanol is not readily metabolised and therefore bioaccumulates and bioamplifies leading to long-term health issues.[68] Added to its inherent dangers (respiratory irritation, skin burns and reproductive toxicity[69]), it seems responsible to try and use the least amount possible.

For the nitro-alkenes, additional work concerning the hydrogen bonding mechanism involving HFIP, and its influence on the hetero-Diels-Alder would be worthwhile. The surprising observations made during this study could be supported by computational studies such as transition stated modelling. Paying greater attention to the presence of hetero-Diels-Alder cycloadduct when conducting further reactions could also be advisable, in order to confirm the conclusions drawn here.

Regarding the continuous flow applications, the accelerations observed, once coupled with the inherent intensifications of flow, make the beginning of a screening relevant. Furthermore, precise control of the reaction temperature in flow would allow us to properly understand and quantify its

impact. Working at higher temperature and under pressure could also allow the use of dienophiles unreactive in standard conditions such as cinnamates or cyclohexenone. The effect of heat on the selectivities of the cycloadditions could also be investigated in such a study.

Secondly, precise control over the quantity of reagents in flow would help overcome limitations such as diene polymerisation or potential double reaction on compounds such as methyl propiolate.

Finally, one last limitation of our work in batch was the pyrolysis of dicyclopentadiene to produce our diene. This tedious preliminary step could be improved, as it requires a certain amount of time and has a rather poor yield due to the formation of higher-order polymers caused by heating. In our case, using chemical generators could be useful since continuous flow cracking of cyclopentadiene and its use in synthesis have already been described, allowing increased energy efficiency among other benefits.[33,70]

To go even further, a multistep synthesis could be devised in flow as a proof of concept. For example, the synthesis of fencamfamin, an amphetaminic stimulant, would allow us to put forward our results on the Diels-Alder reaction of conjugated nitro-alkenes (**Figure 10**). Additionally, the hydrogenation step would highlight one benefit of flow chemistry as explained previously.[32] And lastly, this could be an all-encompassing approach since Henry reactions have been successfully reported in flow setups, allowing safer handling of potentially explosive species.[71]

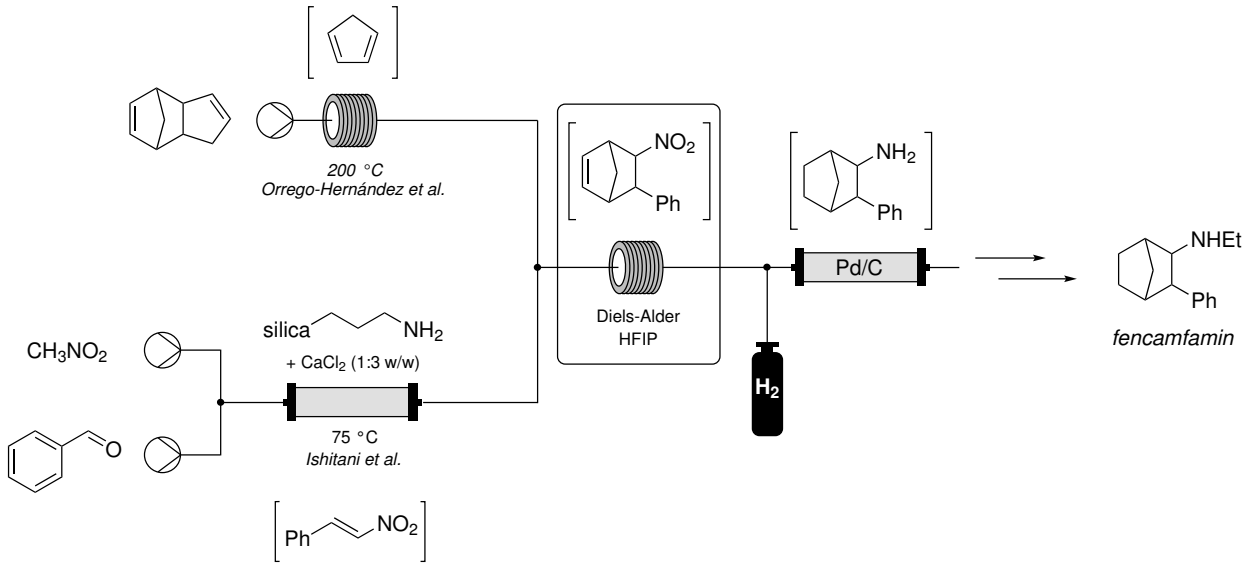


Figure 10: Flow diagram for the first steps of a synthetic pathway of fencamfamin.[33,71]

6 Experimental Section

6.1 General Indications

NMR Spectroscopy

The NMR spectra were recorded on JEOL JNM instruments (EX-400 and ECZ-500R) at 400 or 500 MHz for ^{1}H-NMR and 101 or 126 MHz for ^{13}C-NMR respectively. The samples were prepared in standard 5 mm quartz tubes at ambient temperature using deuterated solvents. The spectra were processed using the Delta software from JEOL. Chemical shifts (δ) are reported in ppm and calibrated on the residual peak of the solvent. All ^{13}C spectra are decoupled from the protons. The signals are reported as follows: (multiplicity, total number of protons, coupling constant(s), assignment of the signal) and the multiplicity was coded as: d = doublet, t = triplet, q = quarter, m = multiplet. Assignment of the signals was made using ^{1}H-^{1}H correlations (COSY, NOESY), DEPT analysis, and ^{13}C correlations (HMBC, HMQC). For the quantitative ^{1}H-NMR, the internal reference used was pentamethylbenzene with signals at 7.00, 2.41, 2.38, 2.34 ppm in $CDCl_3$ at 500 MHz.[72]

Thin Layer Chromatography

The thin layer chromatography (TLC) plates used were aluminium sheets coated with silica gel 60 F254 from Merck. The eluents used for TLC are indicated between parentheses with the volume/volume ratios. TLC plates were revealed using UV light (254 nm) followed by chemical staining and heat. The solution used was composed of $KMnO_4$ (3 g), K_2CO_4 (20 g) and 5 mL of aqueous NaOH (5 % in 300 mL of water).

Column Chromatography

Flash column chromatography was performed under pressure of compressed air with silica gel 60 Roth (0.04-0.063 mm). The solvents quantities are expressed in volume/volume ratios.

Reagents and Solvents

Reagents were purchased from Merck (previously Sigma-Aldrich), Doug Discovery, Tokyo Chemical Industries, abcr GmbH, Fisher Scientific or BLD Pharmatech Ltd. and used without further purification, unless indicated below.

- Dicyclopentadiene (DCPD) was cracked (±150 °C) and cyclopentadiene (CPD) distilled (±45 °C at atmospheric pressure) shortly before use.[73]

All solvents used were analytical grade. Cyclohexane, ethyl acetate and dichloromethane were purified with a MBraun SPS Compact solvent purification system. Deuterated solvents were purchased from Eurisotop.

General Method A – Fischer Esterifications

The esters were synthesised from the corresponding carboxylic acids according to the following procedure: In a 25 mL flask equipped with a condenser and filled with 10 mL of alcohol (methanol or ethanol), was added the carboxylic acid ($\sim$ 1 g) and 3 mL of concentrated HCl. The mixture was heated to 50 °C for 24 h under stirring. The reaction mixture was then quenched with 5 mL of a saturated solution of $NaHCO_3$ and 20 mL of CH_2Cl_2 were added to the crude mixture. The phases were separated and the aqueous phase was extracted 3 times with 50 mL of CH_2Cl_2. The organic phases were gathered, washed 1 times with 15 mL of brine, dried over $MgSO_4$ and the solvent was evaporated.

General Method B – Henry Reactions

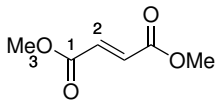
The nitrostyrenes were synthesised from the corresponding aldehydes according to the procedure of Worrall *et al.*:[74] In a cooled 25 mL two-neck flask, filled with 3.5 mL of methanol was added the aldehyde ($\sim$ 1 g, 1.0 eq) and nitromethane (1.0 eq). Under stirring, an aqueous solution of sodium hydroxide (1.25 eq , 3.8 M) was added drop-wise, a white precipitate formed upon addition. If the crude became too thick, additional solvent was added. After 30 min of stirring, the pasty solution was rendered clear by addition of 4 mL of distilled water. The crude mixture was then added drop-wise to a cooled solution of concentrated HCl ($\sim$ 4.8 M, 2.4 eq), a yellow precipitate immediately formed. The solid was filtered and rinsed with water until the pH of the filtrate reached 7. The solid was then dissolved in CH_2Cl_2. The phases were separated and the aqueous phase was extracted three times with 10 mL of CH_2Cl_2. The organic phases were gathered, dried over $MgSO_4$ and the solvent was evaporated.

General Method C – Diels-Alder Reactions

The Diels-Alder cycloadditions were conducted by firstly introducing 1.0 eq. of dienophile in a 5 or 10 mL round flask in an appropriate amount of solvent (10 mL/mmol) and secondly adding 2.2 eq. (unless noted) of freshly distilled cyclopentadiene, under magnetic stirring. Whenever HFIP was used, after evaporation of the solvent, the crude mixture was solubilised in CH_2Cl_2 and purified by column chromatography.

6.2 Preparation of the Dienophiles

Dimethyl (2E)-but-2-enedioate (7)



$C_6H_8O_4$

$M_W = 144.126\,g\,mol^{-1}$

This compound was synthesised according to the procedure of Sathe *et al.*:[75] In a heated 25 mL round-bottom flask (50±5 °C), fumaric acid (**4**) (1.096 g, 8.70 mmol, 1.0 eq.) was added to 10.0 mL of methanol with 1.0 mL of HCl, under stirring. After 3 h, a precipitate was observed suspended in the flask and a white crust was formed above the surface, which was detached with a spatula. After 24 h of reaction, the heating was stopped and the crude was cooled to 0 °C under agitation. The precipitate was filtered off and washed with 50 mL of chilled methanol. The product collected (**7**, 620.6 mg) required no further purification.

Aspect: fluffy white powder

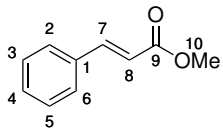
TLC: $R_f \approx 0.78$ (cHex/AcOEt: 9:1), visualised by $KMnO_4$

Yield: 49%

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) **6.87** (s, 2H, 2 × C^2H), **3.81** (s, 6H, 2 × C^3H_3)

^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) **52.54** (2×C^3H_3), **133.60** (2×C^2H), **165.58** (2×C^1_q)

Methyl (2E)-3-phenylprop-2-enoate (19)



$C_{10}H_{10}O_2$

$M_W = 162.188\,g\,mol^{-1}$

This compound was synthesised according to the following procedure: in a cooled (ice bath) 25 mL flask filled with 15 mL of CH_2Cl_2, is added cinnamoyl chloride (1027.7 g, 6.17 mmol, 1.0 eq.) and methanol (0.60 mL, 15.17 mmol, 2.5 eq.) under stirring. The solution is initially salmon pink. After 48h, a solution of 10 % $NaHCO_3$is added step-wise until the pH of the medium reaches 7. A white precipitate forms immediately upon addition. The phases were separated and the aqueous phase was extracted three times with 10 mL of CH_2Cl_2. The organic phases were gathered, washed three times with 10 mL of brine, dried over $MgSO_4$ and the solvent was evaporated. The product (**19**) is obtained as a yellow solid (945.7 mg) and no further purification was necessary.

Aspect: yellow crystals

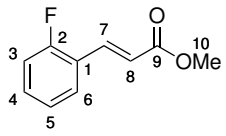
TLC: $R_f \approx 0.59$ (cHex/AcOEt: 7:3), visualised by $KMnO_4$

Yield: 94%

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) **7.70** (d, 1H, J = 16.0 Hz, C^7H), **7.54-7.51** (m, 2H, $C^{2,6}H$), **7.39**

(t, 3H, J = 3.2 Hz, $C^{3,4,5}H$), **6.45** (d, 1H, J = 16.0 Hz, $C^{8}H$), **3.81** (s, 3H, $C^{10}H_3$)

Methyl (2E)-3-(2-fluorophenyl)prop-2-enoate (15o)



$C_{10}H_9FO_2$

M_W = 180.18 g mol^{-1}

This compound was synthesised according to the general procedure A: 2-fluorocinnamic acid (**13o**) (1.028 g, 6.19 mmol, 1.0 eq.) was reacted in methanol, yielding 1.053 mg of product **15o**.

Aspect: yellow oil

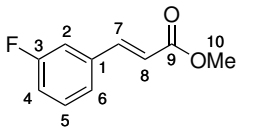
TLC: $R_f \approx 0.73$ (cHex/AcOEt: 8:2), visualised by $KMnO_4$

Yield: 94%

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) **7.82** (d, 1H, $C^{5}H$), **7.52-7.55** (td, 1H, J = 1.72; 7.45 Hz, $C^{7}H$), **7.34-7.38** (m, 1H, $C^{3}H$), **7.15-7.18** (td, 1H, J = 1.15; 7.45 Hz, $C^{4}H$), **7.08-7.12** (ddd, 1H, J = 1.15; 8.60; 19.47 Hz, $C^{2}H$), **6.55** (d, 1H, J = 16.61 Hz, $C^{8}H$), **3.82** (s, 3H, $C^{10}H_3$)

Spectral data are in good agreement with published data.[48]

Methyl (2E)-3-(3-fluorophenyl)prop-2-enoate (15m)



$C_{10}H_9FO_2$

M_W = 180.18 g mol^{-1}

This compound was synthesised according to the general procedure A: 3-fluorocinnamic acid (**13m**) (1.022 g, 6.15 mmol, 1.0 eq.) was reacted in methanol, yielding 976.5 mg of product **15m**.

Aspect: yellow oil

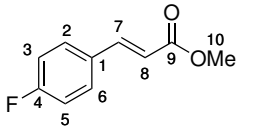
TLC: $R_f \approx 0.73$ (cHex/AcOEt: 8:2), visualised by $KMnO_4$

Yield: 88%

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) **7.64** (d, 1H, J = 16.04 Hz, $C^{7}H$), **7.35** (td, 1H, J = 2.29; 5.73 Hz, $C^{6}H$), **7.28-7.29** (m, 1H, $C^{5}H$), **7.20-7.23** (dt, 1H, $C^{2}H$), **7.06-7.10** (tdd, 1H, J = 1.15; 2.29; 8.02 Hz, $C^{4}H$), **6.43** (d, 1H, J = 16.04 Hz, $C^{8}H$), **3.81** (s, 3H, $C^{10}H_3$)

Spectral data are in good agreement with published data.[48]

Methyl (2E)-3-(4-fluorophenyl)prop-2-enoate (15p)



$C_{10}H_9FO_2$

M_W = 180.18 g mol^{-1}

This compound was synthesised according to the general procedure A: 4-fluorocinnamic acid (**13p**) (1.004 g, 6.04 mmol, 1.0 eq.) was reacted in methanol, yielding 1.037 g of product **15p**.

Aspect: white crystals

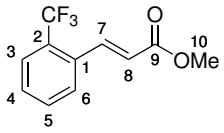
TLC: $R_f \approx 0.66$ (cHex/AcOEt: 8:2), visualised by $KMnO_4$

Yield: 95%

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) **7.65** (d, 1H, J = 16.04 Hz, C^7H), **7.49-7.25** (m, 2H, $C^{2,6}H$), **7.07** (tt, 2H, J = 2.86; 8.59 Hz, $C^{3,5}H$), **6.36** (d, 1H, J = 16.04 Hz, C^8H), **3.80** (s, 3H, $C^{10}H_3$)

Spectral data are in good agreement with published data.[48]

Methyl (2E)-3-[2-(trifluoromethyl)phenyl]prop-2-enoate (16o)



$C_{11}H_9F_3O_2$

M_W = 230.18 g mol^{-1}

This compound was synthesised according to the general procedure A: 2-(trifluoromethyl)cinnamic acid (**14o**) (1.092 g, 5.05 mmol, 1.0 eq.) was reacted in methanol, yielding 1.091 g of product **16o**.

Aspect: white oil

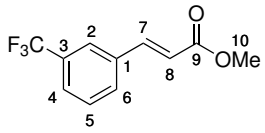
TLC: $R_f \approx 0.73$ (cHex/AcOEt: 8:2), visualised by $KMnO_4$

Yield: 94%

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) **8.06** (m, 1H, C^3H), **7.70** (m, 2H, $C^{7,4}H$), **7.57** (t, 1H, J = 7.45 Hz, C^6H), **7.48** (t, 1H, J = 7.45 Hz, C^5H), **6.41** (d, 1H, J = 15.46 Hz, C^8H), **3.83** (s, 3H, $C^{10}H_3$)

Spectral data are in good agreement with published data.[48]

Methyl (2E)-3-[3-(trifluoromethyl)phenyl]prop-2-enoate (16m)



$C_{11}H_9F_3O_2$

$M_W = 230.18\,g\,mol^{-1}$

This compound was synthesised according to the general procedure A: 3-(trifluoromethyl)cinnamic acid (**14m**) (1.002 g, 4.63 mmol, 1.0 eq.) was reacted in methanol, yielding 1.003 g of product **16m**.

Aspect: white powder

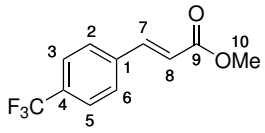
TLC: $R_f \approx 0.73$ (cHex/AcOEt: 8:2), visualised by $KMnO_4$

Yield: 97%

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) **7.74** (s, 1H, C^2H), **7.69** (d, 1H, J = 16.04 Hz, C^7H), **7.67** (d, 1H, J = 7.45 Hz, C^5H), **7.62** (d, 1H, J = 8.02 Hz, C^4H), **7.50** (t, 1H, J = 8.02 Hz, C^6H), **6.49** (d, 1H, J = 16.04 Hz, C^8H), **3.80** (s, 3H, $C^{10}H_3$)

Spectral data are in good agreement with published data.[48]

Methyl (2E)-3-[4-(trifluoromethyl)phenyl]prop-2-enoate (16p)



$C_{11}H_9F_3O_2$

$M_W = 230.18\,g\,mol^{-1}$

This compound was synthesised according to the general procedure A: 4-(trifluoromethyl)cinnamic acid (**14p**) (1038.2 g, 4.80 mmol, 1.0 eq.) was reacted in methanol, yielding 728.2 mg of product **16p**.

Aspect: white powder

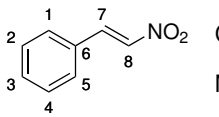
TLC: $R_f \approx 0.73$ (cHex/AcOEt: 8:2), visualised by $KMnO_4$

Yield: 66%

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) **7.69** (d, 1H, J = 16.04 Hz, C^7H), **7.62** (dd, 4H, J = 4.58; 8.59 Hz, $C^{2,3,5,6}H$), **6.49** (d, 1H, J = 16.04 Hz, C^8H), **3.81** (s, 3H, $C^{10}H_3$)

Spectral data are in good agreement with published data.[48]

[(E)-2-Nitroethenyl]benzene (21)



$C_8H_7NO_2$

$M_W = 149.149\,g\,mol^{-1}$

This compound was synthesised according to the general procedure B: benzaldehyde (**27**) (0.68 mL, 7.09 mmol, 1.06 eq.) was reacted with nitromethane (0.36 mL, 6.70 mmol, 1.00 eq.) in methanol, yielding 603.7 mg of product **21**.

Aspect: lime yellow needle crystals

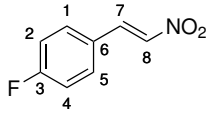
Yield: 61%

TLC: $R_f \approx 0.42$ (cHex/AcOEt: 9:1), visualised by $KMnO_4$

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) **8.00** (d, 1H, *J* = 13.75 Hz, C^8H), **7.58** (d, 1H, *J* = 13.75 Hz, C^7H), **7.54-7.42** (m, 5H,$C^{1-6}H$)

^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) **139.3** (C^8H), **137.3** (C^7H), **132.3** (C^6_q), **129.6** ($2\times C^{1,5}$H), **129.3** ($3\times C^{2,3,4}$H)

[1-Fluoro-4-[(1E)-2-nitroethenyl]benzene (23)



$C_8H_6FNO_2$

M_W = 167.14 g mol^{-1}

This compound was synthesised according to the general procedure B: 4-fluorobenzaldehyde (**28**) (0.85 mL, 8.07 mmol, 1.01 eq.) was reacted with nitromethane (0.43 mL, 8.01 mmol, 1.00 eq.) in methanol, yielding 805.6 mg of product **23**.

Aspect: pale yellow needle crystals

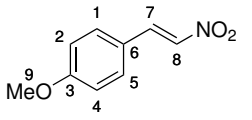
TLC: $R_f \approx 0.38$ (cHex/AcOEt: 9:1), visualised by $KMnO_4$

Yield: 60%

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) **8.00** (dd, 1H, *J* = 5.15; 13.75 Hz, C^8H), **7.57-7.52** (m, 3H, $C^2_{47}H$), **7.19-7.14** (m, 2H, C^1_5H),

Spectral data are in good agreement with published data (Zhao A. *et al.*, *Tetrahedron Lett.* **2016**, *57*(1), 80-84.).

[1-Methoxy-4-[(1E)-2-nitroethenyl]benzene (25)



$C_9H_9NO_3$

M_W = 179.17 g mol^{-1}

This compound was synthesised according to the general procedure B: 4-methoxybenzaldehyde (**29**) (0.89 mL, 7.30 mmol, 1.01 eq.) was reacted with nitromethane (0.39 mL, 7.26 mmol, 1.00 eq.) in methanol, yielding 810.2 mg of product **25**.

Aspect: bright yellow needle crystals

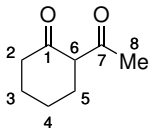
Yield: 62%

TLC: $R_f \approx 0.25$ (cHex/AcOEt: 9:1), visualised by $KMnO_4$

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) **7.99** (d, 1H, *J* = 13.51 Hz, C^8H), **7.55-7.50** (m, 3H, $C^2_{47}H$), **6.97-6.96** (m, 2H, C^1_5H),

Spectral data are in good agreement with published data (Liu J. *et al.*, *Synlett* **2013**, *24*(20), 2740-2742.).

2-Acetyl-1-cyclohexanone (31)



$C_8H_{12}O_2$

$M_W = 140.18\,g\,mol^{-1}$

This compound was synthesised according to the procedure of Kopp *et al.*:[76] In a dry 25 mL two-neck flask under argon atmosphere, diisopropyl amide (0.24 mL, 1.68 mmol, 1.12 eq.) was dissolved in 10 mL of anhydrous THF. The system was cooled down to –84 °C and n-hexyllithium (0.77 mL, 1.65 mmol, 1.10 eq.) was added drop-wise. The solution was kept at –84 °C and stirred 40 minutes. Then, cyclohexanone (0.15 mL, 1.45 mmol, 1.00 eq.) was added and the solution was stirred at –84 °C for 1 hour. Then, acetyl chloride (0.13 mL, 1.80 mmol, 1.20 eq.) was added and the solution was stirred at –84 °C for 1 hour. The reaction mixture was then quenched with 10 mL of a saturated solution of NH_4Cl. The phases were separated and the aqueous phase was extracted 3 times with 15 mL of ethyl acetate. The organic phases were gathered, dried over $MgSO_4$and the solvent was evaporated. was purified by flash column chromatography on silica gel (cHex/diethyl ether: 7:3) yielding 146 mg of product **31**.

Aspect: yellow oil

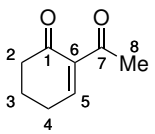
TLC: $R_f \approx 0.61$ (cHex/AcOEt: 7:3), visualised by $KMnO_4$

Yield: 72%

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) **2.33-2.29** (dd, 4H, J = 5.15 ; 6.30 Hz,$C^{2,5}H_2$), **2.11** (s, 3H, C^8H_3), **1.67** (m, 4H,$C^{3,4}H_2$) (enol form)

^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) **199.2** (C^1_q), **182.2** (C^7_q), **107.3** (C^6_q), **31.3** (C^2H_2), **25.1** (C^5H_2), **24.5** (C^3H_2), **23.0** (C^4H_2), **21.9** (C^8H_3) (enol form)

2-Acetyl-2-cyclohexenone (33)



$C_8H_{10}O_2$

$M_W = 138.16\,g\,mol^{-1}$

This compound was synthesised according to the procedure of Renga *et al.*:[77] In a dry 100 mL two-neck flask under argon atmosphere, NaH (60 % in oil) (82.9 mg, 2.07 mmol, 1.43 eq.) was added and rinsed three times with pentane. Then, 25 mL of anhydrous THF were added and the system was cooled to 0 °C. Under stirring, 2-acetyl-cyclohexanone (**31**) (0.20 mL, 1.45 mmol, 1.0 eq.) was added drop-wise. The crude mixture takes a milky aspect. After 20 min, a solution of phenylselenenyl

chloride[a] (7.2 mL, 1.52 mmol, 1.05 eq.) was quickly added. The mixture becomes translucent and yellowish. After 30 min, the crude mixture was poured in a beaker filled with a solution of pentane/ether (1:1, 6 mL), $NaHCO_3$ (7 %, 5 mL) and ice (7 mL). The phases were separated and the aqueous phase was extracted 3 times with 50 mL of pentane/ether. The organic phases were gathered, washed 1 times with 25 mL of brine, dried over Na_2SO_4 and the solvent was evaporated.

The yellow oil obtained was transferred in a 50 mL three-neck flask equipped with a condenser, a septum and a thermometer filled with 20 mL of $CHCl_3$. An aqueous solution of H_2O_2 (30 %) (0.31 mL, 3.04 mmol, 2.1 eq.) in 0.30 mL of water was then added drop-wise, keeping the temperature below 35 °C. After 20 min, the crude mixture was heated to 30 °C, the solution then becomes translucent. Upon completion, the crude mixture was washed with $NaHCO_3$ and $Na_2S_2O_3$. The organic phases were gathered, dried over Na_2SO_4 and the solvent was evaporated. Product **33** was obtained as an impure yellow oil and degraded upon purification (was purified by flash column chromatography on silica gel (cHex/AcOEt: 6:4) or Kugelrohr distillation).

Aspect: yellow oil

Yield: n.d.

TLC: $R_f \approx 0.13$ (cHex/ether (7:3)), visualised by $KMnO_4$

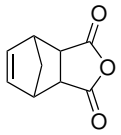
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) **7.64-7.06** (dd, 1H, J = 0.57; 4.01 Hz, C^5H), **2.52-2.46** (m, 4H, $C^{2,4}H_2$), **2.42** (s, 3H, C^8H_3), **2.03-1.98** (m, 2H, C^3H_2)

^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) **198.7** (C_q^7), **197.1** (C_q^1), **156.7** (C^5H), **140.0** (C^6H), **39.1** (C^2H_2), **30.9** (C^8H_3), **26.6** (C^4H_2), **22.4** (C^3H_2)

[a] Prepared by mixing equal amounts of diphenyl selenide and sulfuryle chloride in chloroform.

6.3 Diels-Alder Cycloadditions in Batch

5-norbornene-2,3-dicarboxylic anhydride (6)



$C_9H_8O_3$

M_W = 164.160 g mol^{-1}

Maleic anhydride (**5**) (CH_2Cl_2: 89.9 mg, 0.92 mmol, 1.0 eq.; HFIP: 211.5 mg, 2.16 mmol, 1.0 eq.) and cyclopentadiene (**2**) (CH_2Cl_2: 0.15 mL, 1.82 mmol, 2.0 eq.; HFIP: 0.35 mL, 4.25 mmol, 2.0 eq.) were reacted following the general procedure C to give product **6** (CH_2Cl_2: 150.5 mg; HFIP: 309.9 mg).

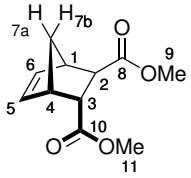
Aspect: White powder

Yield: CH_2Cl_2: >99.9; HFIP: 87.5

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) **6.29** (t, 2H, 2×C^1*H*), **3.56** (m, 2H, 2×C^3*H*), **3.49** (m, 2H, 2×C^2*H*), **1.75,1.77** (d, 1H, C^{5b}*H*), **1.54,1.56** (d, 1H, C^{5a}*H*)

^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) **171.44** (2×C_q^4), **135.66** (2×*C*^{1}H), **52.88** (*C*^{5}H$_2$), **47.19** (2×*C*^{3}H), **46.24** (2×*C*^{2}H)

dimethyl (1R,2S,3S,4S)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (8)



$C_{11}H_{14}O_4$

M_W = 210.23 g mol^{-1}

Dimethyl fumarate (**7**) (CH_2Cl_2: 144.2 mg, 1.0 mmol, 1.0 eq.; HFIP: 144.6 mg, 1.0 mmol, 1.0 eq.) and cyclopentadiene (**2**) (CH_2Cl_2: 0.18 mL, 2.2 mmol, 2.2 eq.; HFIP: 0.18 mL, 2.2 mmol, 2.2 eq.) were reacted following the general procedure C to give product **8** (CH_2Cl_2: 204.9 mg; HFIP: 203.5 mg).

Aspect: colourless oil

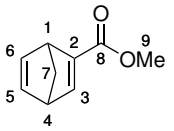
Yield: CH_2Cl_2: 97; HFIP: 97

TLC: $R_f \approx 0.48$ (cHex/AcOEt: 8:2), visualised by $KMnO_4$

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) **6.24** (dd, 1H, *J* = 2.86; 5.73 Hz, C^5*H*), **6.04** (dd, 1H, *J* = 2.86; 5.73 Hz, C^6*H*), **3.68** (s, 3H, C^{11}*H*$_3$), **3.61** (s, 3H, C^9*H*$_3$), **3.34** (t, 1H, *J* = 4.01 Hz, C^3*H*), **3.23** (br s, 1H, C^1*H*), **3.09** (br s, 1H, C^4*H*), **2.65** (dd, 1H, *J* = 2.29; 4.58 Hz, C^2*H*), **1.58** (dd, 1H, *J* = 1.72; 9.16 Hz, C^{7b}*H*), **1.47** (dd, 1H, *J* = 1.72; 9.16 Hz, C^{7a}*H*)

^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) **174.8** (C_q^8), **137.68** (C_q^{10}), **137.5** (*C*^{5}H), **135.1** (*C*^{6}H), **52.0** (*C*^{11}H$_3$), **51.8** (*C*^{9}H$_3$), **47.8** (*C*^{3}H), **47.6** (*C*^{1}H), **47.3** (*C*^{4}H), **47.0** (*C*^{2}H), **45.55** (*C*^{7}H$_2$)

methyl bicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (12)



$C_9H_{10}O_2$

$M_W = 150.17\,g\,mol^{-1}$

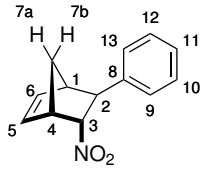
Methyl propiolate (**11**) (CH_2Cl_2: 0.09 mL, 1.01 mmol, 1.0 eq.) and cyclopentadiene (**2**) (CH_2Cl_2: 0.09 mL, 1.10 mmol, 1.09 eq.) were reacted following the general procedure C to give product **12** (23.8 mg).

Aspect: white oil

Yield: 14%

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) **7.64** (d, 1H, *J* = 2.86 Hz, C^3H), **6.91** (dd, 1H, *J* = 1.72; 2.86 Hz, C^5H), **6.73** (dd, 1H, *J* = 1.72; 2.86 Hz, C^6H), **3.90** (br s, 1H, C^2H), **3.80** (s, 3H, C^9H_3), **3.73** (s, 1H, C^1H), **2.12** (m, 2H, C^7H_2)

endo-2-nitro-exo-3-phenylbicyclo[2.2.1]hept-5-ene (22)



$C_{13}H_{13}NO_2$

$M_W = 215.25\,g\,mol^{-1}$

β-nitrostyrene (**21**) (CH_2Cl_2: 76.0 mg, 0.51 mmol, 1.0 eq.; HFIP: 74.2 mg, 0.50 mmol, 1.0 eq.; *i*PrOH: 75.3 mg, 0.50 mmol, 1.0 eq.; H_2O: 76.5 mg, 0.51 mmol, 1.0 eq.) and cyclopentadiene (**2**) (0.09 mL, 1.09 mmol, 2.2 eq.) were reacted following the general procedure C to give product **22** (CH_2Cl_2: 60.39 mg; HFIP: 96.63 mg; *i*PrOH: 4.63 mg; H_2O: 11.21 mg).

Aspect: Pale yellow oil

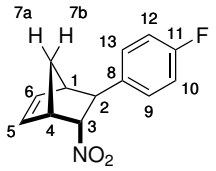
^{1}H NMR yields: CH_2Cl_2: 83.5 %; HFIP: 90.2 %; *i*PrOH: 4.3 %; H_2O: 10.2 %

TLC: $R_f \approx 0.59$ (cHex/AcOEt: 9:1), visualised by $KMnO_4$

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) **7.38-7.32** (m, 4H, $C^{9-13}H$), **6.61** (dd, 1H, *J* = 3.44; 5.73 Hz, C^5H), **6.14** (q, 1H, *J* = 2.86 Hz, C^6H), **5.02** (dd, 1H, *J* = 3.44; 5.74 Hz, C^2H), **3.62** (br s, 1H, C^1H), **3.47-3.45** (m, 1H, C^3H), **3.19** (br s, 1H, C^2H), **1.90** (d, 1H, *J* = 9.74 Hz, $C^{7a}H$), **1.75** (ddd, 1H, *J* = 2.29; 4.01; 9.16 Hz, $C^{7b}H$)

^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) **141.5** (C^8_q), **140.9** (C^5H), **133.2** (C^6H), **129.0** ($2\times C^{9,13}$H), **127.5** ($2\times C^{10,12}$H), **127.0** (C^{11}H), **92.4** (C^2H), **49.1** (C^3H), **48.2** (C^4H), **48.0** (C^1H), **46.2** (C^7H)

endo-2-nitro-exo-3-fluorophenylbicyclo[2.2.1]hept-5-ene (24)



$C_{13}H_{12}FNO_2$

$M_W = 233.24\,g\,mol^{-1}$

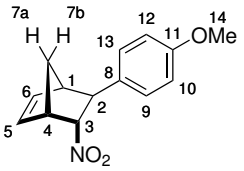
4-fluoronitrostyrene (**23**) (CH_2Cl_2: 78.2 mg, 0.47 mmol, 1.0 eq.; HFIP: 78.2 mg, 0.47 mmol, 1.0 eq.) and cyclopentadiene (**2**) (0.08 mL, 0.97 mmol, 2.1 eq.) were reacted following the general procedure C to give product **24** (CH_2Cl_2: 12.85 mg; HFIP: 78.65 mg).

Aspect: dark yellow oil

^{1}H NMR yields: CH_2Cl_2: 12.8 %; HFIP: 77.1 % **TLC**: $R_f \approx 0.50$ (cHex/AcOEt: 9:1), visualised by $KMnO_4$

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) **7.32** (dd, 2H, J = 2.86 ; 8.59 Hz,$C^{9,13}H$), **7.06** (t, 2H, J = 8.59 Hz,$C^{10,12}H$), **6.62** (dd, 1H, J = 2.29; 5.73 Hz, C^5H), **6.16** (q, 1H, J = 2.89 Hz, C^6H), **4.93** (t, 1H, J = 4.01 Hz, C^2H), **3.63** (br s, 1H, C^1H), **3.43** (br s, 1H, C^3H), **3.16** (br s, 1H, C^2H), **1.88** (d, 1H, J = 9.16 Hz, $C^{7a}H$), **1.79-1.77** (m, 1H, $C^{7b}H$)

endo-2-nitro-exo-3-methoxyphenylbicyclo[2.2.1]hept-5-ene (26)



$C_{14}H_{15}NO_3$

$M_W = 245.28\,g\,mol^{-1}$

4-methoxynitrostyrene (**25**) (CH_2Cl_2: 78.5 mg, 0.44 mmol, 1.0 eq.; HFIP: 74.8 mg, 0.42 mmol, 1.0 eq.) and cyclopentadiene (**2**) (CH_2Cl_2: 0.08 mL, 0.97 mmol, 2.2 eq.; HFIP: 0.08 mL, 0.97 mmol, 2.3 eq.) were reacted following the general procedure C to give product **26** (CH_2Cl_2: 3.17 mg; HFIP: 76.61 mg).

Aspect: yellow oil

^{1}H NMR yields: CH_2Cl_2: 3.4 %; HFIP: 85.3 % **TLC**: $R_f \approx 0.45$ (cHex/AcOEt: 9:1), visualised by $KMnO_4$

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) **7.27** (d, 2H, J = 8.59 Hz,$C^{10,12}H$), **6.90** (m, 2H, $C^{9,13}H$), **6.61** (dd, 1H, J = 3.44; 5.73 Hz, C^5H), **6.14** (dd, 1H, J = 2.29; 5.73 Hz, C^6H), **3.82** (s, 3H, $C^{14}H_3$), **3.60** (br s, 1H, C^1H), **3.40** (br s, 1H, C^3H), **3.14** (br s, 1H, C^2H), **1.89** (d, 1H, J = 9.74 Hz, $C^{7a}H$), (m, 1H, $C^{7b}H$)

References

[1] Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1928**, *460*, 98–122.

[2] García, J. I.; Mayoral, J. A.; Salvatella, L. *Acc. Chem. Res.* **2000**, *33*, 658–664.

[3] Fleming, I. *Molecular Orbitals and Organic Chemical Reactions*, student ed.; Wiley: Chichester, 2011.

[4] Fukui, K.; Yonezawa, T.; Shingu, H. *J. Chem. Phys.* **1952**, *20*, 722–725.

[5] Fleischhauer, J.; Asaad, A. N.; Schleker, W.; Scharf, H.-D. *Liebigs Ann. Chem.* **1981**, *1981*, 306–311.

[6] Burnell, D. J.; Goodbrand, H. B.; Kaiser, S. M.; Valenta, Z. *Can. J. Chem.* **1987**, *65*, 154–165.

[7] Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436–4437.

[8] Jeanmart, L. Asymmetric Diels-Alder Reactions of Quinones and Sulfinylquinones for the Synthesis of Terpenes. Doctorate in Sciences, University of Namur, Namur, 2021.

[9] Mambourg, K. Étude de La Réaction de Diels-Alder Utilisant Une Sulfinylquinone Chirale Comme Diénophile et Développement d'un Modèle Expliquant La Stéréosélectivité. Master of Science, University of Namur, Namur, 2018.

[10] Jeanmart, L.; Mambourg, K.; Hanquet, G.; Lanners, S. *Arkivoc* **2024**, *5*.

[11] Breslow, R.; Rideout, D. C. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817.

[12] Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275–3279.

[13] Rodgman, A.; Wright, G. F. *J. Org. Chem.* **1953**, *18*, 465–484.

[14] Cativiela, C.; García, J. I.; Mayoral, J. A.; Avenoza, A.; Peregrina, J. M.; Roy, M. A. *J. Phys. Org. Chem.* **1991**, *4*, 48–52.

[15] Cativiela, C.; García, J. I.; Mayoral, J. A.; Royo, A. J.; Salvatella, L.; Assfeld, X.; Ruiz-Lopez, M. F. *J. Phys. Org. Chem.* **1992**, *5*, 230–238.

[16] Cativiela, C.; García, J. I.; Mayoral, J. A. *Tetrahedron-Asymmetr* **1993**, *4*, 1616–1618.

[17] Eberson, L.; Hartshorn, M. P.; Persson, O. *J. Chem. Soc. Perk. T. 2* **1995**, 1735–1744.

[18] Cativiela, C.; García, J. I.; Mayoral, J. A.; Salvatella, L. *Can. J. Chem.* **1994**, *72*, 308–311.

[19] Knunyants, I. L.; Krasuskaya, M. P. Method for Producing Hexafluoroisopropyl Alcohol. 1960.

[20] Middleton, W. J. Hexafluoro-2-Propanol and Its Complex with Tetrahydrofuran. 1968.

[21] Middleton, W. J. *J. Fluorine Chem.* **1999**, 207–216.

[22] Hutton, D. G. Azeotropic Distillation of Hydrocarbons with Hexafluoroisopropyl Alcohol. 1966.

[23] Khaksar, S. *J. Fluorine Chem.* **2015**, *172*, 51–61.

[24] Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. *Nat. Rev. Chem.* **2017**, *1*, 0088.

[25] Motiwala, H. F.; Armaly, A. M.; Cacioppo, J. G.; Coombs, T. C.; Koehn, K. R. K.; Norwood, V. M.; Aubé, J. *Chem. Rev.* **2022**, *122*, 12544–12747.

[26] Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. *Chem. Rev.* **2017**, *117*, 11796–11893.

[27] Hartman, R. L.; McMullen, J. P.; Jensen, K. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 7502–7519.

[28] Smith, C. D.; Baxendale, I. R.; Lanners, S.; Hayward, J. J.; Smith, S. C.; Ley, S. V. *Org. Biomol. Chem.* **2007**, *5*, 1559.

[29] García-Lacuna, J.; Domínguez, G.; Pérez-Castells, J. *ChemSusChem* **2020**, *13*, 5138–5163.

[30] Shore, G.; Organ, M. G. *Chem. Commun.* **2008**, 838–840.

[31] Yokozawa, S.; Ohneda, N.; Muramatsu, K.; Okamoto, T.; Odajima, H.; Ikawa, T.; Sugiyama, J.-I.; Fujita, M.; Sawairi, T.; Egami, H.; Hamashima, Y.; Egi, M.; Akai, S. *RSC Adv.* **2015**, *5*, 10204–10210.

[32] Irfan, M.; Glasnov, T. N.; Kappe, C. O. *ChemSusChem* **2011**, *4*, 300–316.

[33] Orrego-Hernández, J.; Hölzel, H.; Quant, M.; Wang, Z.; Moth-Poulsen, K. *Eur. J. Org. Chem.* **2021**, *2021*, 5337–5342.

[34] Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698.

[35] Bai-cheng, F.; Xi-chao, H.; Tie-lin, W.; Jian-qiang, L.; Yan, J. *ChemistrySelect* **2020**, *5*, 952–956.

[36] Nishino, H.; Nakamura, A.; Inoue, Y. *J. Chem. Soc. Perk. T. 2* **2001**, 1693–1700.

[37] Ihara, E.; Ishii, S.; Yokoyama, K.; Fujiwara, Y.; Ueda, T.; Inoue, K.; Itoh, T.; Momose, H.; Nodono, M. *Polym. J.* **2013**, *45*, 606–613.

[38] Valiulin, R. A.; Arisco, T. M.; Kutateladze, A. G. *J. Org. Chem.* **2013**, *78*, 2012–2025.

[39] Trost, B. M.; Balkovec, J. M.; Angle, S. R. *Tetrahedron Lett.* **1986**, *27*, 1445–1448.

[40] Lasne, M.-C.; Ripoll, J.-L. *Bull. Soc. Chim. Fr.* **1986**, *5*, 766–770.

[41] Fringuelli, F.; Girotti, R.; Pizzo, F.; Vaccaro, L. *Org. Lett.* **2006**, *8*, 2487–2489.

[42] Sterk, M.; Bannwarth, W. *Helv. Chim. Acta* **2015**, *98*, 287–307.

[43] Rondestvedt, C. S.; Ver Nooy, C. D. *J. Am. Chem. Soc.* **1955**, *77*, 4878–4883.

[44] Camilo, F. F.; Gruber, J. *Quím. Nova* **1999**, *22*, 382–395.

[45] Alves, C.; Camilo, F.; Gruber, J.; Da Silva, A. *Tetrahedron* **2001**, *57*, 6877–6883.

[46] Nicolas, L.; Beugelmans-Verrier, M.; Guilhem, J. *Tetrahedron* **1981**, *37*, 3847–3860.

[47] Mamaghani, M. *Tetrahedron* **2002**, *58*, 147–151.

[48] Gatzenmeier, T.; Turberg, M.; Yepes, D.; Xie, Y.; Neese, F.; Bistoni, G.; List, B. *J. Am. Chem. Soc.* **2018**, *140*, 12671–12676.

[49] Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, 1–18.

[50] Sukhorukov, A. Y. *Front. Chem.* **2020**, *8*, 595246.

[51] *Science of Synthesis* **2010**, *47*, 579.

[52] Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, A. K.; Iyengar, R. *J. Org. Chem.* **1980**, *45*, 1185–1189.

[53] Denmark, S. E.; Kesler, B. S.; Moon, Y. C. *J. Org. Chem.* **1992**, *57*, 4912–4924.

[54] Paton, R. S.; Mackey, J. L.; Kim, W. H.; Lee, J. H.; Danishefsky, S. J.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 9335–9340.

[55] Takenaka, N.; Sarangthem, R. S.; Seerla, S. K. *Org. Lett.* **2007**, *9*, 2819–2822.

[56] 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) , 100 Ml, CAS No. 920-66-1 | Reagents for Peptide Synthesis for Washing/Deprotection/Splitting | Peptide Synthesis | Organic & Bioorganic Chemicals | Chemicals | Carl Roth - International. https://www.carlroth.com/com/en/reagents-for-peptide-synthesis-for-washing-deprotection-splitting/111333-hexafluoro-2-propanol-%28hfip%29/p/2473.3.

[57] Kraus, K. W.; Schilte, G. N.; Dolter, R. J.; Buenker, R. J.; Plamandon, J. P.; Koopman, D. *Proc. Iowa Acad. Sci.* **1964**, *71*, 208–211.

[58] Xu, D.-Q.; Xia, A.-B.; Luo, S.-P.; Tang, J.; Zhang, S.; Jiang, J.-R.; Xu, Z.-Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 3821–3824.

[59] Larkovich, R. V.; Ponomarev, S. A.; Aldoshin, A. S.; Tabolin, A. A.; Ioffe, S. L.; Nenajdenko, V. G. *Eur. J. Org. Chem.* **2020**, *2020*, 2479–2492.

[60] Fringuelli, F.; Minuti, L.; Pizzo, F.; Taticchi, A.; Consiglio, G.; Chanon, M.; Striley, C.; Weidlein, J.; Nasiri, A.; Okada, Y. *Acta Chem. Scand.* **1993**, *47*, 255–263.

[61] Constantino, M.; Júnior, V.; Da Silva, G. *Molecules* **2002**, *7*, 456–464.

[62] Zhang, D.; Sun, W.-H.; Hou, J.; Jie, S.; Chang, F. *J. Polym. Sci. A Polym. Chem.* **2006**, *44*, 264–272.

[63] Aso, C.; Kunitake, T.; Ito, K.; Ishimoto, Y. *J. Polym. Sci. B Polym. Lett.* **1966**, *4*, 701–706.

[64] Radchenko, A. V.; Kostjuk, S. V.; Gaponik, L. V. *Polym. Bull.* **2011**, *67*, 1413–1424.

[65] Ouchi, M.; Kamigaito, M.; Sawamoto, M. *Macromolecules* **2001**, *34*, 3176–3181.

[66] Tzouma, E.; Mavridis, I.; Vidali, V. P.; Pitsinos, E. N. *Tetrahedron Lett.* **2016**, *57*, 3643–3647.

[67] Arp, H. P.; Hale, S. *REACH: Improvement of Guidance and Methods for the Identification and Assessment of PMT/vPvM Substances*; 2019; p 131.

[68] Savoca, D.; Pace, A. *Int. J. Mol. Sci.* **2021**, *22*, 6276.

[69] Pozhydaiev, V.; Power, M.; Gandon, V.; Moran, J.; Lebœuf, D. *Chem. Commun.* **2020**, *56*, 11548–11564.

[70] Baumann, M. *React. Chem. Eng.* **2019**, *4*, 368–371.

[71] Ishitani, H.; Saito, Y.; Tsubogo, T.; Kobayashi, S. *Org. Lett.* **2016**, *18*, 1346–1349.

[72] Smith, L. B.; Armstrong, R. J.; Matheau-Raven, D.; Donohoe, T. J. *J. Am. Chem. Soc.* **2020**, *142*, 2514–2523.

[73] Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 7th ed.; Elsevier/Butterworth-Heinemann: Amsterdam : London, 2013.

[74] Worrall, D. E. *Org. Synth.* **1929**, *9*, 66.

[75] Sathe, D.; Das, A.; Bhagwatkar, R. A.; Raikar, S.; Ahire, R.; Surve, Y. Improved Process for the Preparation of Dimethyl Fumarate. 2017.

[76] Kopp, F.; Stratton, C. F.; Akella, L. B.; Tan, D. S. *Nat. Chem. Biol.* **2012**, *8*, 358–365.

[77] Renga, J. M.; Reich, H. J. *Org. Synth.* **1979**, *59*, 58.