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# Dearomatization of electron-poor arenes by (4+2) cycloaddition reactions

Batoul Rkein

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Normandie Université

# THÈSE

Pour obtenir le diplôme de doctorat

Spécialité CHIMIE

Préparée au sein de l'Université de Rouen Normandie

## Dearomatization of Electron-Poor Arenes by (4+2) Cycloaddition Reactions

Présentée et soutenue par  
**Batoul RKEIN**

Thèse soutenue publiquement le 28 Novembre 2019  
devant le jury composé de

|                           |   |                        |
|---------------------------|---|------------------------|
| Dr. Laurence GRIMAUD      | Directrice de Recherche CNRS<br>Ecole Nationale Supérieure de Paris | Rapporteur             |
| Prof. Cyrille KOUKLOVSKY  | Professeur des universités<br>Université Paris-Sud                  | Rapporteur             |
| Dr. Françoise DUMAS       | Directrice de recherche<br>Université Paris-Sud                     | Examinatrice           |
| Dr. Sami LAKHDAR          | Chargé de Recherche CNRS<br>Université de Caen                      | Examineur              |
| Prof. Isabelle CHATAIGNER | Professeur des universités<br>Université de Rouen Normandie         | Directrice de thèse    |
| Dr. Muriel DURANDETTI     | Maître de Conférence<br>Université de Rouen Normandie               | Co-directrice de thèse |

Thèse dirigée par Prof. Isabelle CHATAIGNER et co-dirigée par Dr. Muriel DURANDETTI,  
laboratoire COBRA UMR CNRS 6014







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Normande de Chimie





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A la douce mémoire de ma chère grand-mère,





## List of Abbreviations

$\Delta E$  : HOMO-LUMO gap  
1D : one-dimensional  
2D : two-dimensional  
3D : three-dimensional  
Å : angstrom  
ACN : acetonitrile  
AP : affinity purification  
ASE : aromatic stabilization energy  
atm : atmospheric  
CA : cycloadduct  
Cat : catalyst  
conc : concentrated  
DABCO : 1,4-diazabicyclo[2.2.2]octane  
DBU : 1,8-diazabicyclo[5.4.0]undec-7-ene  
DCM : dichloromethane  
DiPA : diisopropylamine  
DMAD : dimethyl acetylenedicarboxylate  
DMAP : 4-dimethylaminopyridine  
DME : dimethoxyethane  
DMF : dimethylformamide  
DMPU : N,N'-dimethylpropyleneurea  
DMSO : dimethyl sulfoxide  
*E* : electrophilicity parameter  
 $E^+$  : electrophiles  
EDA : electron donor-acceptor  
*ee* : enantiomeric excess  
equiv : equivalent  
*er* : enantiomeric ratio  
ESI : electron spray ionisation  
EtOAc : ethylacetate  
EtOH : ethanol  
*FMO* : frontier molecular orbital  
 $h\nu$  : light  
HDA : hetero-Diels-Alder  
HFIP : hexafluoro-2-propanol  
HIV : human immunodeficiency virus  
HMPA : hexamethylphosphoramide  
HOMA : harmonic oscillator model of aromaticity  
*HOMO* : highest occupied molecular orbital

HP : *high pressures*  
HPLC : *high performance liquid chromatography*  
HRMS : *high resolution mass spectrometry*  
i.e. : *that is*  
IED : *inverse electron demand*  
iPr : *isopropyl*  
IUPAC : *international union of pure and applied chemistry*  
kbar : *kilobar*  
LA : *Lewis acid*  
LDA : *lithium diisopropylamide*  
LiHMDS : *lithium bis(trimethylsilyl)amide*  
LUMO : *lowest unoccupied molecular orbital*  
min : *minutes*  
MVK : *methyl vinyl ketone*  
MW : *microwave*  
N : *nucleophilicity parameter*  
NED : *normal electron demand*  
NICS : *nucleus independent chemical shift*  
NMR : *nuclear magnetic resonance*  
oa-TOF : *orthogonal acceleration time-of-flight*  
P : *pressure*  
PA : *primary adduct*  
pKa : *acid dissociation constant*  
p-TSA : *p-toluenesulfonic acid*  
r.t. : *room temperature*  
RE : *resonance energy*  
T : *temperature*  
TADDOL :  *$\alpha, \alpha, \alpha', \alpha'$ -tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol*  
TFA : *trifluoroacetic acid*  
THF : *tetrahydrofuran*  
TLC : *thin-layer chromatography*  
TMEDA : *tetramethylethylenediamine*  
TS : *transition state*  
US : *ultrasound*  
 $\Delta V^\ddagger$  : *activation volume*  
 $\eta$  : *viscosity*

## Introduction

Aromatic compounds are common substrates, obtained either from petrochemical industry through catalytic reforming of petroleum or from natural products. Number of methods, and among them dearomatizations play an important role to convert these simple and easily available molecules into tridimensional (3D) complex structures. Dearomatization is, thermodynamically, a difficult process because it requires the breaking of the aromaticity of the starting material, and thus loss of the resonance energy. Moreover, rearomatization of the obtained adduct has to be avoided in many cases.

In this context, cycloaddition reactions, and more specifically the (4+2) Diels-Alder reactions, remain a method of choice widely used in organic synthesis. They represent an efficient and reliable approach to construct poly(cyclic) compounds in a single step.

In these reactions, aromatics are mainly used as dienes due to their electron-richness.<sup>1,2</sup> However, the dienophilic behavior of electron-depleted aromatics is more scarcely described.<sup>3,4</sup>

Therefore, in this work we aimed at studying the dienophilic/electrophilic character of different electron-poor aromatics, in particular indole derivatives, in dearomatizing normal electron demand (4+2) cycloaddition/annulation reactions.

In the first chapter, some bibliographic references concerning the dearomatization strategies, more specifically involving the Diels-Alder reaction, will be presented.

The second chapter will describe the involvement of various electron-deficient aromatics in (4+2) Diels-Alder reactions as dienophiles in reaction with silyloxydienes (Scheme 1).

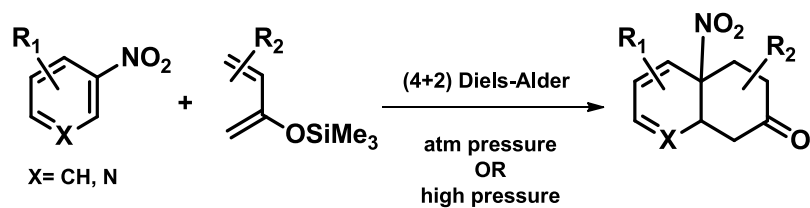
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<sup>1</sup>Atherton, J. C. C.; Jones, S. *Tetrahedron* **2003**, *59*, 9039-9057.

<sup>2</sup>Liebov, B. K.; Harman, W. D. *Chem. Rev.* **2017**, *117*, 13721-13755.

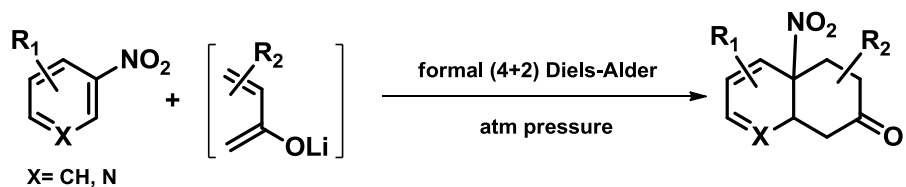
<sup>3</sup>Chrétien, A.; Chataigner, I.; L'Hélias, N.; Piettre, S. R. *J. Org. Chem.* **2003**, *68*, 7990-8002.

<sup>4</sup>Kil'met'ev, A. S.; Shul'ts, E. E.; Shakirov, M. M.; Rybalova, T. V.; Tolstikov, G. A. *Russ. J. Org. Chem.* **2013**, *49*, 872-885.



**Scheme 1: (4+2) dearomatizing cycloaddition reactions between electron-poor aromatics and silyloxydienes.**

The third chapter will discuss our results obtained from the condensation of lithium enolates on electron-poor arenes via formal (4+2) dearomatizing cycloaddition reactions (Scheme 2).



**Scheme 2: Dearomatization of electron-deficient aromatics via lithium enolates.**

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## **Chapter I. Literature Review**



*«The more I learn, the more I realize how much I don't know»  
Albert Einstein*



# 1 Aromaticity

## 1.1 Introduction

Before examining the process of dearomatization and its own characteristic features, it is important to discuss briefly the concept of aromaticity.

The earliest use of the term aromatic was launched on a class of benzenic compounds because of their pronounced odors (aromas), unlike pure saturated hydrocarbons.

The term aromaticity goes back to the work of Kekulé in 1865 who was the first to suggest the cyclic structure of the benzene ring, isolated by Faraday in 1825 (Figure 1).<sup>5,6</sup>

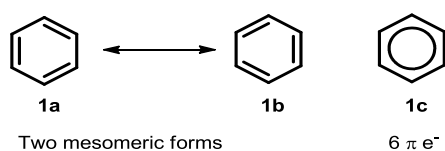


Figure 1: Some benzene structures suggested by Kekulé.

In 1931, Hückel explained the unique stability of benzene and defined the Hückel's rule<sup>7</sup> to determine if a planar ring molecule has aromatic properties. This rule states that if a cyclic, planar, fully conjugated molecule has  $(4n+2)$  electrons involved in the conjugation, with  $n$  being zero or positive integer, it is considered aromatic (Table 1).


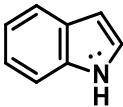
| Molecule  | Cyclic | Conjugated | $\pi$ bonds | Lone pair (Total) $\pi$ electrons | $4n+2$ | Aromatic |
|---|--------|------------|-------------|-----------------------------------|--------|----------|
|  | Yes    | Yes        | 3           | 0 (6)                             | Yes    | Yes      |
|  | Yes    | Yes        | 4           | 2 (10)                            | Yes    | Yes      |

Table 1: Aromatic molecules and Hückel's rule.

The concept of aromaticity is very important in organic chemistry since many organic compounds possess an aromatic system in their structure. The frequent use of different terms

<sup>5</sup> Faraday, M. *Phil. Trans. R. Soc. London*. **1825**, 115, 440-466.

<sup>6</sup> Kekulé, A. *Bull. Soc. Chim. Fr.* **1865**, 3, 98-110.

<sup>7</sup> Hückel, E. *Z. Physik*. **1931**, 70, 204-286.

associated with aromaticity/aromatic character underlines the importance of a proper definition. By the 1960s, most chemists agreed that aromatic compounds are:

- Planar, cyclic with delocalized  $\pi$ -electron systems.
- More stable than their linear analogs.
- Their bond lengths are between those of typical single and double bonds.
- Their  $\pi$  electron ring current induces a magnetic field and low field chemical shifts are observed for aromatic protons in the  $^1\text{H}$  NMR spectra.
- Aromatic compounds generally undergo substitution reactions (by addition/rearomatization processes most of the time) rather than addition reactions.

All these criteria are non-measurable, thus the definition remained somehow inaccurate. For this reason, chemists have set new criteria to quantify the aromaticity:<sup>8,9</sup> geometric, energetic and magnetic.

### 1.1.1 Geometrical criteria

Krygowski and Cyrański<sup>10</sup> developed a structural-based method for assigning aromaticity, known as the harmonic oscillator model of aromaticity (HOMA). An essential built-in assumption of HOMA is that the more symmetric the molecule is, the more aromatic it is. It is defined according to the following simplified equation:

$$\text{HOMA} = 1 - \text{ENergetic} - \text{GEOmetric}$$

Where EN describes the loss of aromaticity due to lengthening of bonds over the mean length. The second term, GEO, describes the degree of bond length alternation; the greater GEO, the greater the loss of the aromatic character due to an increase of alternation.

### 1.1.2 Energetic criteria

The first quantitative description of aromaticity was proposed in 1933 by the introduction of a thermodynamic term called resonance energy (RE) i.e. the energy by which the aromatic compound is more stable than its virtual olefinic analogue. Later, the term RE was replaced by

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<sup>8</sup> Krygowski, T. M.; Szatyłowicz, H. *ChemTexts*, **2015**, *1*, 1-10.

<sup>9</sup> Krygowski, T. M.; Cyrański, M. K. *Chem. Rev.* **2001**, *101*, 1385-1419.

<sup>10</sup> Krygowski, T. M.; Cyrański, M. K. *Tetrahedron* **1999**, *55*, 11143-11148.

more precisely defined aromatic stabilization energy (ASE)<sup>11</sup> which is estimated by the use of either isodesmic or more precise homodesmotic reactions. The latter is defined as a virtual reaction leading to products with the same number of CH bonds and the same number of atoms in the appropriate hybridization states. If ASE value is strongly positive, the molecule is aromatic. However, if it is strongly negative, then the molecule is anti-aromatic.

It is important to note that the ASE values depend dramatically on the choice of the computation method and the selected reference system.

### 1.1.3 Magnetic criteria

This can be quantified through a computational method known as nucleus independent chemical shift (NICS).<sup>11,12</sup> It is defined as the negative of the absolute magnetic shielding computed at the center of the ring [NICS(0)] or at 1 Å above the ring [NICS(1)]. In this method, negative NICS values indicate aromaticity and positive values, anti-aromaticity. In addition, the more negative the NICS value is, the more aromatic the compound is.

The definition of aromaticity is still debated among the chemists' community. Despite many efforts, it is impossible to delineate it precisely. Each method has its own defaults and has led to wrong conclusions for various systems.

## 2 Heteroaromatic Compounds

### 2.1 Introduction

Heteroaromatics are compounds which contain heteroatoms (i.e. O, N and S) as part of their cyclic conjugated  $\pi$  system. These compounds obey Hückel's rule and thus they are aromatic.

Of the existing heteroaromatics, indole **2a** plays a special role since the indolyl core is represented in many alkaloid derivatives (Figure 2) by its tautomeric form (i.e. indolenine **2b**), reduced analogs (i.e. indoline **2c**), oxidized derivatives (i.e. oxindole **2d**) or even isomeric forms (i.e. isoindole **2e**). Also, it possesses biological activities such as anti-HIV, anticancer, antimicrobial, analgesic, anti-inflammatory and cardiovascular for instance,<sup>13</sup> which makes it a valuable heterocycle.

<sup>11</sup> Stanger, A. *Chem. Commun.* **2009**, 1939-1947.

<sup>12</sup> Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. V. R. *Chem. Rev.* **2005**, *105*, 3842-3888.

<sup>13</sup> Sravanthi, T. V.; Manju, S. L. *Eur. J. Pharm. Sci.* **2016**, *91*, 1-10.



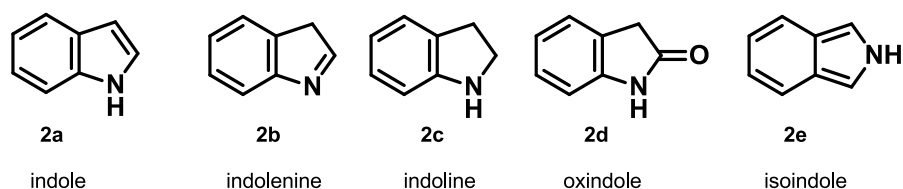


Figure 2: Indole and its tautomeric forms.

Indole derivatives are common substrates used in this work. Their general characteristics and chemistry are described in the forthcoming pages.

## 2.2 Generalities

Indole **2a** is a benzopyrrole in which the benzene and pyrrole rings are fused to each other (Figure 2). It was first prepared in 1866 by Adolf von Baeyer from oxindole **2d**, a degradation product of indigo (a blue dye imported from India). It is in the form of a white solid with a melting point of 52 °C and an intense characteristic odor.

The pKa of indole in water is 16.97, very close to that of pyrrole (pKa = 17.51). This relative acidity of hydrogen for a secondary amine is related to the engagement of the non-binding lone pair electrons of the nitrogen atom in the aromaticity.

As for the aromaticity, a classification for bicyclic heterocycles reveals an order similar to that observed with monocyclic heterocycles (Figure 3).<sup>14</sup>

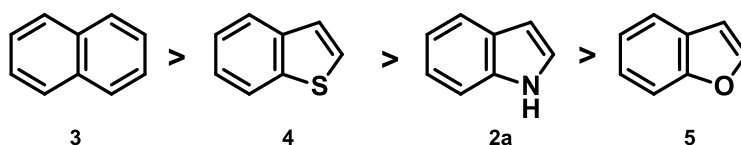


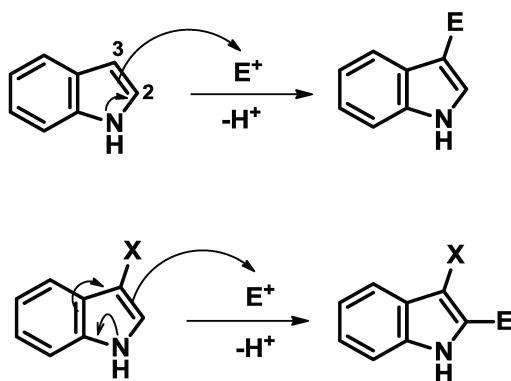
Figure 3: Order of aromaticity of bicyclic aromatics.

Most commonly, indoles are electron-rich heteroaromatics and undergo electrophilic substitution reactions such as nitration, halogenation, sulfonation and Mannich reactions.<sup>15,16</sup> These reactions take place mainly at position 3 of the nucleus (Scheme 3). Only if position 3 is blocked, the indole nucleus may then react towards electrophiles (E<sup>+</sup>) at position 2 before undergoing rearomatization to deliver 2,3-disubstituted indoles (Scheme 3). When positions 2 and 3 are occupied, the electrophile reacts on the benzene ring.

<sup>14</sup> Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles: Structure, Reactions Synthesis and Applications (second edition)*; Wiley-VCH: Weinheim, 2003.

<sup>15</sup> Gribble, G. W. *Pure Appl. Chem.* **2003**, *75*, 1417-1432.

<sup>16</sup> Bandini, M. *Org. Biomol. Chem.* **2013**, *11*, 5206-5212.



Scheme 3: Electrophilic substitution in indole.

### 3 Dearomatization Strategies

#### 3.1 Introduction

The number of reports on the development and application of dearomatization processes has steadily increased in the recent decades (Figure 4), and will likely continue to grow in the future.

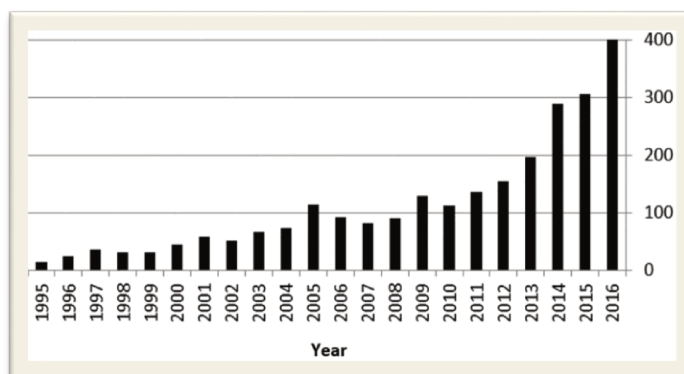


Figure 4: The number of titles publications using the term “dearomatization” since the year 1995.

In principle, every aromatic compound can undergo a dearomatization reaction. However, due to their reduced resonance stabilization energies, heteroaromatics, such as furan, pyrrole or pyridine derivatives for instance, are more prone to dearomative transformations than all-carbon arenes such as benzenic ones (Figure 5).

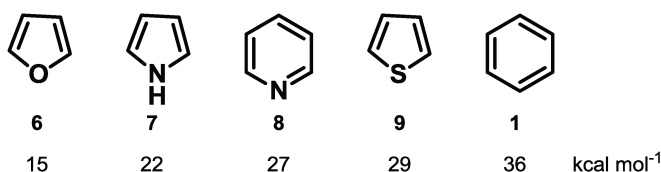


Figure 5: Resonance stabilization energy for some aromatic compounds.

In the context of dearomatizations, different methodologies have been developed. We will just mention them rapidly to focus, then, on the methodologies related to this work. These include for instance:

- Hydrogenation using homogeneous<sup>17,18</sup> or heterogeneous catalysts.<sup>19,20</sup>
- Microbial oxidation<sup>21</sup> and oxidation of phenols and aniline.<sup>22</sup>
- Radical dearomatization.<sup>23,24,25,26,27</sup>
- Transition metal mediated dearomatization using  $\eta^2$  and  $\eta^6$ -aryl metals (Cr, Mn, Mo, Ru, Re and W).<sup>28,29,30</sup>
- Transition metal catalyzed dearomatization using Pd and Cr catalysts.<sup>31,32,33</sup>
- Photochemical dearomative para cycloaddition between arenes and small molecules termed arenophiles (i.e. N-methyl-1,2,4-triazoline-3,5-dione).<sup>34,35,36</sup>

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<sup>17</sup> Wei, Y.; Zeng, X. *Synlett* **2016**, 27, 650-655.

<sup>18</sup> Melaimi, M.; Jazzar, R.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem. Int. Ed.* **2017**, 56, 10046-10068.

<sup>19</sup> Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. *J. Org. Chem.* **2008**, 73, 4895-4902.

<sup>20</sup> Heitbaum, M.; Fröhlich, R.; Glorius, F. *Adv. Synth. Catal.* **2010**, 352, 357-362.

<sup>21</sup> Bugg, T. D. H.; Lin, G. *Chem. Commun.* **2001**, 941-952.

<sup>22</sup> Wu, W.-T.; Zhang, L.; You, S.-L. *Chem. Soc. Rev.* **2016**, 45, 1570-1580.

<sup>23</sup> Birch, A. J. *J. Chem. Soc.* **1944**, 430-436.

<sup>24</sup> Lebeuf, R.; Dunet, J.; Beniazza, R.; Ibrahim, D.; Bose, G.; Berlande, M.; Robert, F.; Landais, Y. *J. Org. Chem.* **2009**, 74, 6469-6478.

<sup>25</sup> Wefelscheid, U. K.; Berndt, M.; Reißig, H.-U. *Eur. J. Org. Chem.* **2008**, 3635-3646.

<sup>26</sup> Ohno, H.; Okumura, M.; Maeda, S.-I.; Iwasaki, H.; Wakayama, R.; Tanaka, T. *J. Org. Chem.* **2003**, 68, 7722-7732.

<sup>27</sup> Crich, D.; Sannigrahi, M. *Tetrahedron* **2002**, 58, 3319-3322.

<sup>28</sup> Myers, J. T.; Shivokevich, P. J.; Pienkos, J. A.; Sabat, M.; Myers, W. H.; Harman, W. D. *Organometallics* **2015**, 34, 3648-3657.

<sup>29</sup> Wilson, K. B.; Myers, J. T.; Nedzbala, H. S.; Combee, L. A.; Sabat, M.; Harman, W. D. *J. Am. Chem. Soc.* **2017**, 139, 11401-11412.

<sup>30</sup> Pigge, F. C.; Dhanya, R.; Hoefgen, E. R. *Angew. Chem. Int. Ed.* **2007**, 46, 2887-2890.

<sup>31</sup> Bao, M.; Nakamura, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, 123, 759-760.

<sup>32</sup> Zhang, S.; Ullah, A.; Yamamoto, Y.; Bao, M. *Adv. Synth. Catal.* **2017**, 359, 2723-2728.

<sup>33</sup> Chen, W.; Bai, J.; Zhang, G. *Adv. Synth. Catal.* **2017**, 359, 1227-1231.

<sup>34</sup> Southgate, E. H.; Pospech, J.; Fu, J.; Holycross, D. R.; Sarlah, D. *Nat. Chem.* **2016**, 8, 922-928.

<sup>35</sup> Hernandez, L. W.; Klöckner, U.; Pospech, J.; Hauss, L.; Sarlah, D. *J. Am. Chem. Soc.* **2018**, 140, 4503-4507.

<sup>36</sup> Okumura, M.; Shved, A. S.; Sarlah, D. *J. Am. Chem. Soc.* **2017**, 139, 17787-17790.

- Nucleophilic addition of reactive species (i.e. organolithium,<sup>37,38,39</sup> organomagnesium<sup>40,41</sup> and enamine<sup>42</sup>) to arenes activated by electron-withdrawing groups (carbonyls, esters, amides, nitriles, nitro, etc....).
- Cycloaddition/Annulation reactions.

Cycloaddition/Annulation reactions, which are the bases of our work, will be discussed in the coming paragraph.

## 3.2 Diels-Alder reaction

### 3.2.1 Generalities

The Diels-Alder reaction is one of the most useful synthetic transformation in organic synthesis. This latter allows the creation of new bonds, in one step, to generate cyclic compounds with, generally, good controls over the regio- and stereochemical outcomes.

Discovered by Otto Diels and Kurt Alder in 1928,<sup>43</sup> [ $\pi 4s + \pi 2s$ ] cycloaddition reaction proceeds through the suprafacial/suprafacial interaction of a  $4\pi$  electrons 1,3-conjugated diene and a  $2\pi$  electrons dienophile. This transformation can be carried out in an inter- or intramolecular fashion under various conditions.

The Diels-Alder reaction is a pericyclic reaction which involves a six-centered transition state in which the formation and the breaking of the bonds is concerted. However, depending on the experimental conditions and/or the nature of the reagents, a synchronous<sup>44</sup> or asynchronous transition state<sup>45</sup> (involving the formation of both new bonds simultaneously but not at the same speed) is possible.<sup>46,47</sup> In general, a synchronous concerted mechanism only occurs in the case of symmetrical reagents, whereas the cycloaddition of non-symmetrical diene and/or dienophile leads to distorted transition state (TS) and therefore to a concerted asynchronous reaction.

<sup>37</sup> López Ortiz, F.; Iglesias, M. J.; Fernández, I.; Sánchez, C. M. A.; Gómez, G. R. *Chem. Rev.* **2007**, *107*, 1580-1691.

<sup>38</sup> Lemièrre, G.; Sedehizadeh, S.; Toueg, J.; Fleary-Roberts, N.; Clayden, J. *Chem. Commun.* **2011**, *47*, 3745-3747.

<sup>39</sup> Alford, P. E.; Kishbaugh, T. L. S.; Gribble, G. W. *Heterocycles* **2010**, *80*, 831-840.

<sup>40</sup> Bartoli, G. *Acc. Chem. Res.* **1984**, *17*, 109-115.

<sup>41</sup> Bartoli, G.; Bosco, M.; Cantagalli, G.; Dalpozzo, R. *Tetrahedron* **1984**, *40*, 3437-3442.

<sup>42</sup> Andreini, M.; Chapellas, F.; Diab, S.; Pasturaud, K.; Piettre, S. R.; Legros, J.; Chataigner, I. *Org. Biomol. Chem.* **2016**, *14*, 2833-2839.

<sup>43</sup> Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1928**, *460*, 98-122.

<sup>44</sup> Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1986**, *108*, 5771-5779.

<sup>45</sup> Dewar, M. J. S.; Pierini, A. B. *J. Am. Chem. Soc.* **1984**, *106*, 203-208.

<sup>46</sup> Beno, B. R.; Houk, K. N.; Singleton, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 9984-9985.

<sup>47</sup> Singleton, D. A.; Schulmeier, B. E.; Hang, C.; Thomas, A. A.; Leung, S.-W.; Merrigan, S. R. *Tetrahedron* **2001**, *57*, 5149-5160.

However, a stepwise mechanism is also possible where the bonds are not formed simultaneously, but through diradical or zwitterionic intermediates (Figure 6).

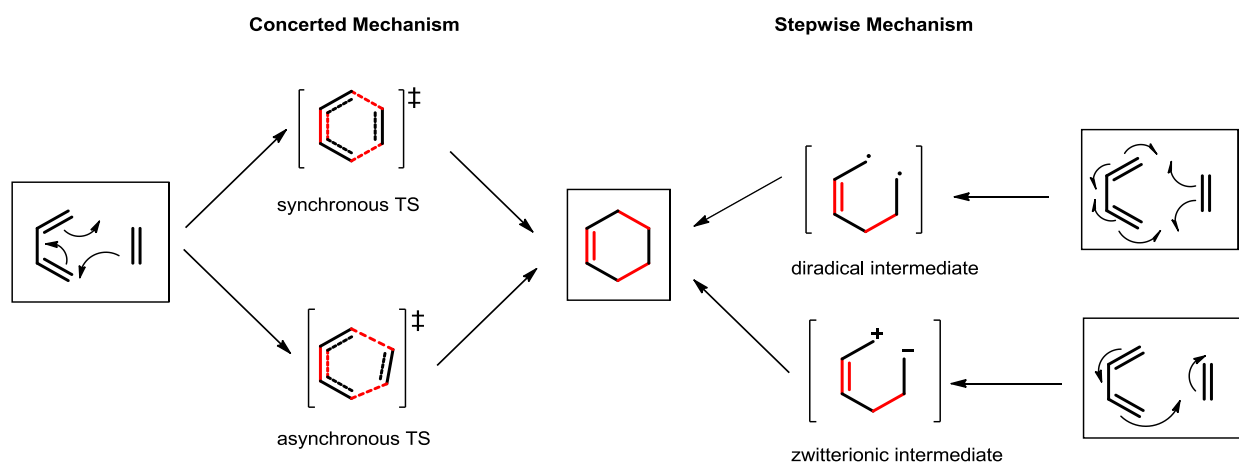


Figure 6: Plausible mechanisms of Diels-Alder cycloaddition.

### 3.2.1.1 Frontier molecular orbital theory

Frontier Molecular Orbital (FMO) theory permits the prediction and the rationalization of the regio- and the stereoselectivities of the Diels-Alder reaction. According to this theory, the energetically favored interaction, between the Highest Occupied Molecular Orbital (HOMO) of one partner and the Lowest Unoccupied Molecular Orbital (LUMO) of the other allows to define three different types of cycloadditions: normal, reverse and neutral electron demand (Figure 7). So, the reaction is said to be of the Normal Electron Demand (NED) type when the interactions involve the HOMO of the diene and the LUMO of the dienophile. When the favored interaction involves the LUMO of the diene and the HOMO of the dienophile, the cycloaddition is said to be of the Inverse Electron Demand (IED) type. In the case of a neutral electron demand (dimerization for instance), no orbital interaction is dominant.

The feasibility of a Diels-Alder reaction depends directly on the difference in energy between the HOMO and LUMO of the reagents ( $\Delta E$ ), and the reaction is more favored if this difference is smaller. The presence of electron-withdrawing groups on a reagent reduces the energies of its HOMO and LUMO orbitals, while electron-donating ones increase their energy levels (Figure 7). In a NED (4+2) cycloaddition, the use of an electron-poor dienophile (with a low-lying LUMO) and an electron-rich diene (with a high-lying HOMO) favors the reaction. In contrary, an IED (4+2) cycloaddition involves an enriched-dienophile (with a high-lying HOMO) and an electron-depleted diene (with a low-lying LUMO).

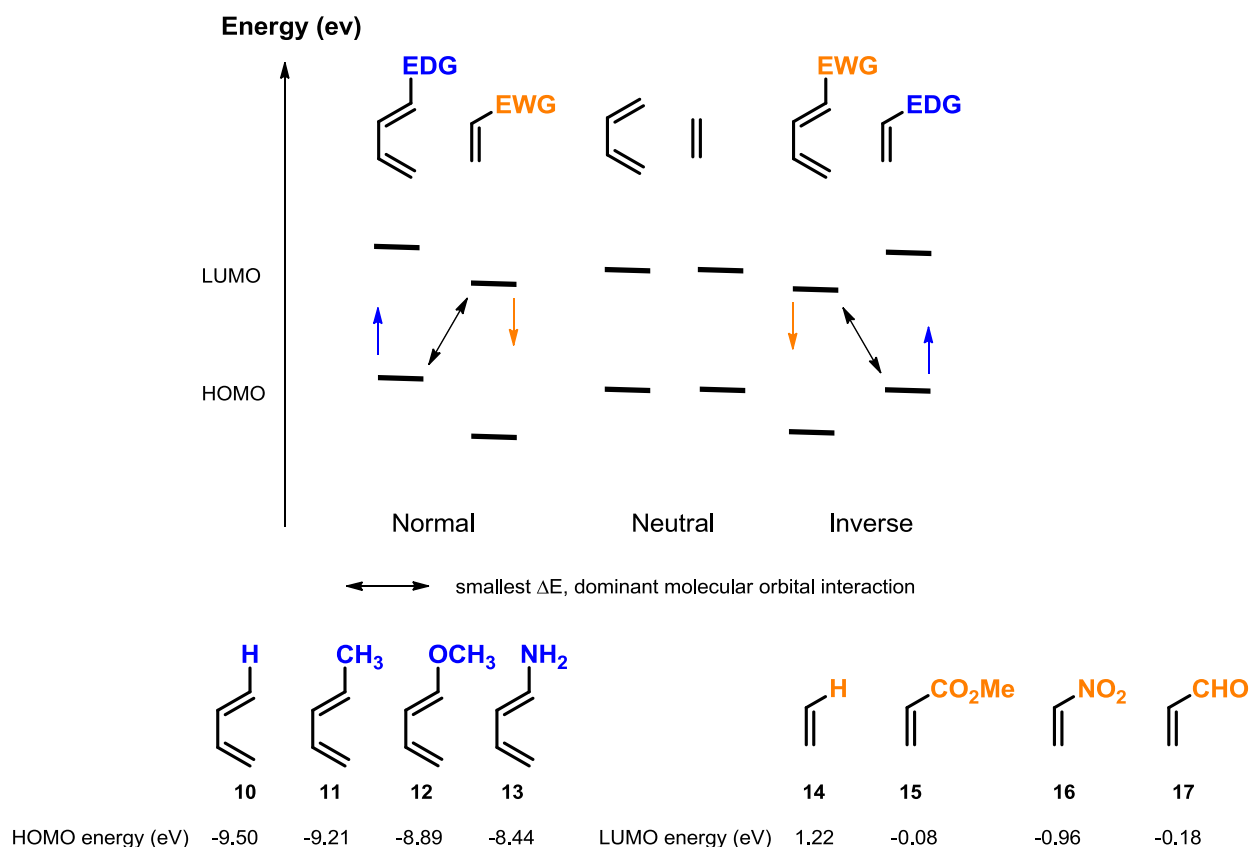


Figure 7: Different types of (4+2) cycloaddition and the substitution effects.

### 3.2.1.2 Regioselectivity

The usefulness of the Diels-Alder reaction arises from its versatility and from its remarkable selectivities. The interaction between unsymmetrical dienes and dienophiles can give two isomeric cycloadducts, depending upon the relative position of the substituents in the cycloadducts: head-to-head or head-to-tail (Figure 8). The selectivity for the formation of one adduct over the other is called regioselectivity, and usually the formation of one regioisomer is predominant if not unique. According to the FMO theory, the favored interaction involves the reaction sites having the most important orbital coefficients in absolute value (i.e. the relative sizes of the p orbitals in the LUMO and HOMO involved). The regioselectivity in Diels-Alder reaction is often high, yet it is rather well established that the more powerful the electron-donating and electron-withdrawing substituents on the diene/dienophile pair are, the more regioselective the reaction is.

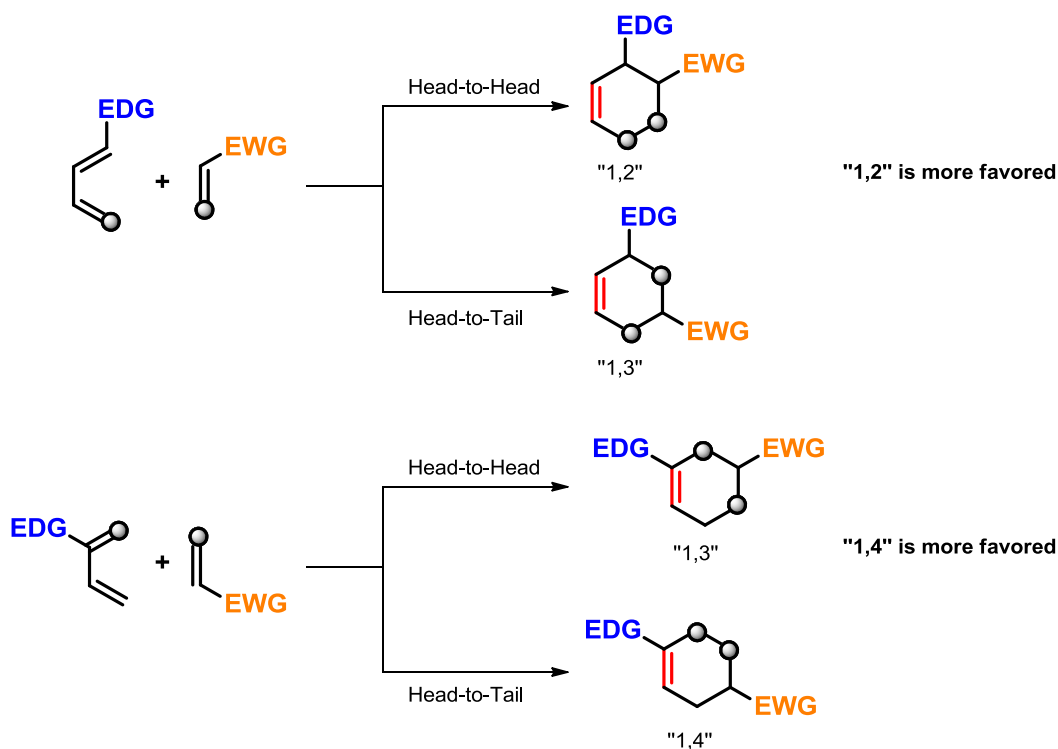


Figure 8: Regioselectivity of Diels-Alder cycloaddition.

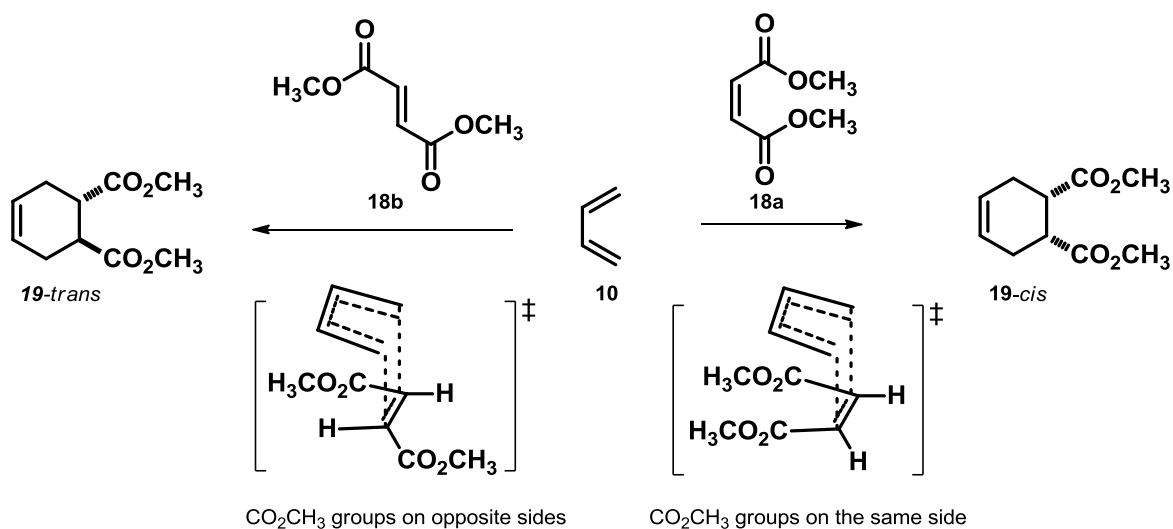
It is important to note that, the number and the nature of the substituents should be taken into account to successfully predict the regioselectivity of the reaction. Also, the operating conditions such as solvent, temperature and the presence of a catalyst can have dramatic effects on the regioselectivity of the process.<sup>48</sup>

### 3.2.1.3 Stereospecificity

Another characteristic of the Diels-Alder reaction is its high stereoselectivity, in general. Up to four new chiral centers are created during the reaction between the diene and the dienophile but as mentioned before one diastereomer often predominates. The stereochemistry of the major product can usually be predicted on the basis of two rules: the retention of the stereochemistry of the substrates and the *endo* rule.

First of all, a suprafacial approach of the diene and dienophile results in the retention of the relative configuration of these reagents within the product. The reaction is thus stereospecific (Scheme 4).

<sup>48</sup> Guner, O. F.; Ottenbrite, R. M.; Shilladay, D. D.; Alston, P. V. *J. Org. Chem.* **1987**, *52*, 391-394.



Scheme 4: Stereospecificity of Diels-Alder cycloaddition.

### 3.2.1.4 *Endo* versus *Exo* approach

As for the *endo* addition, it can be defined as “the *endo* mode of attack is the spatial arrangement of the reactants in which the bulkier sides of the diene and dienophile lie one above the other”.<sup>49</sup>

In other words, the approach of the diene and the dienophile implies two different possible transition states, which are often called the *endo* and *exo* transition states, potentially leading to adducts of different stereochemistry (Scheme 5). In the *endo* transition state, the substituents on the dienophile are oriented towards the diene  $\pi$  system, while in the *exo* they are oriented away from it. According to Alder’s rule<sup>50</sup> the major stereoisomer in Diels-Alder reactions is the one that is formed by maximum accumulation of double bonds in the transition state (through-space) i.e. the *endo* transition state is typically preferred, despite often being more sterically congested. The most widely accepted explanation for the origin of this effect is a favorable interaction between the dienophile substituent’s  $\pi$  system and that of the diene termed “secondary orbital effects”<sup>51,52</sup> proposed by Woodward and Hoffmann in 1965.<sup>53</sup> Dipolar and van der Waals attractions may also play a role.<sup>54,55</sup>

<sup>49</sup> Fringuelli, F.; Tattichi, A. *The Diels-Alder Reaction: Selected Practical Methods*; Wiley: Chichester, UK, 2002.

<sup>50</sup> Alder, K.; Stein, G. *Angew. Chem.* **1937**, *50*, 510-519.

<sup>51</sup> Arrieta, A.; Cossio, F. P. *J. Org. Chem.* **2001**, *66*, 6178-6180.

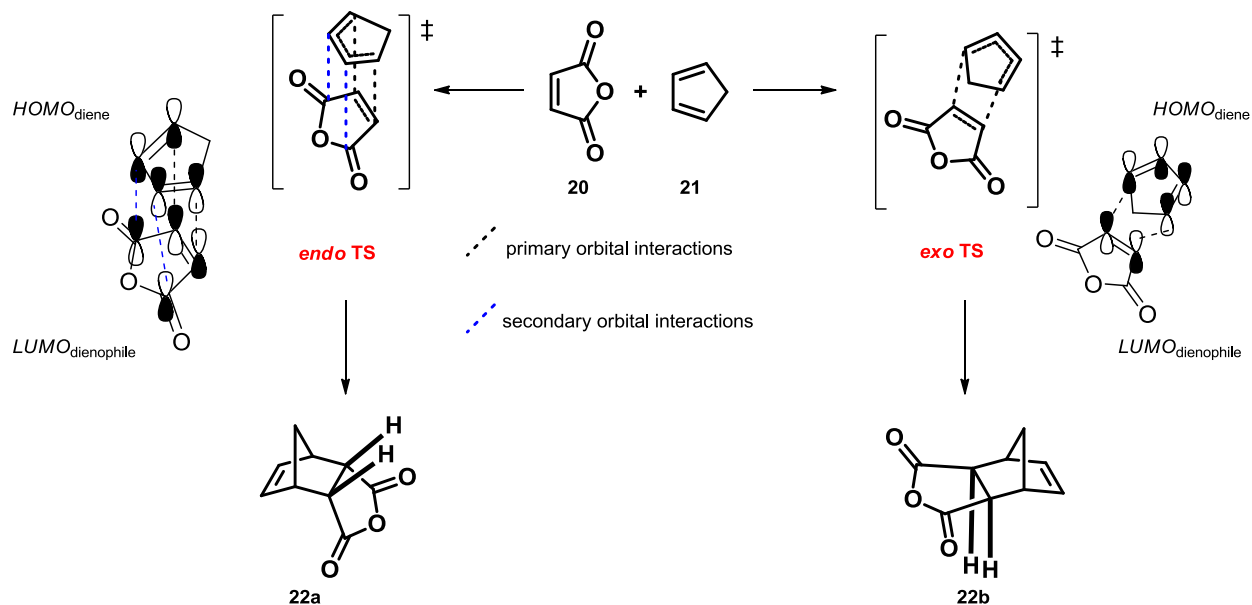
<sup>52</sup> Wannere, C. S.; Paul, A.; Herges, R.; Houk, K. N.; Schaefer III, H. F.; Schleyer, P. V. R. *J. Comput. Chem.* **2007**, *28*, 344-361.

<sup>53</sup> Hoffmann, R.; Woodward, R. B. *J. Am. Chem. Soc.* **1965**, *87*, 4388-4389.

<sup>54</sup> Kobuke, Y.; Sugimoto, T.; Furukawa, J.; Fueno, T. *J. Am. Chem. Soc.* **1972**, *94*, 3633-3635.

<sup>55</sup> Williamson, K. L.; Hsu, Y.-F. L. *J. Am. Chem. Soc.* **1970**, *92*, 7385-7389.





**Scheme 5: Diels-Alder reaction between cyclopentadiene and maleic anhydride.**

Oftentimes, as with highly substituted dienes or very bulky dienophiles, steric effects can greatly influence *endo/exo* selectivity. Dienes with bulky terminal substituents (C1 or C4) decrease the rate of reaction, presumably by impeding the approach of the diene and dienophile;<sup>56</sup> however, bulky substituents at the C2 or C3 position actually increase reaction rate by destabilizing the *s-trans* conformation and forcing the diene into the reactive *s-cis* conformation.<sup>57</sup>

### 3.2.1.5 Diastereoselectivity

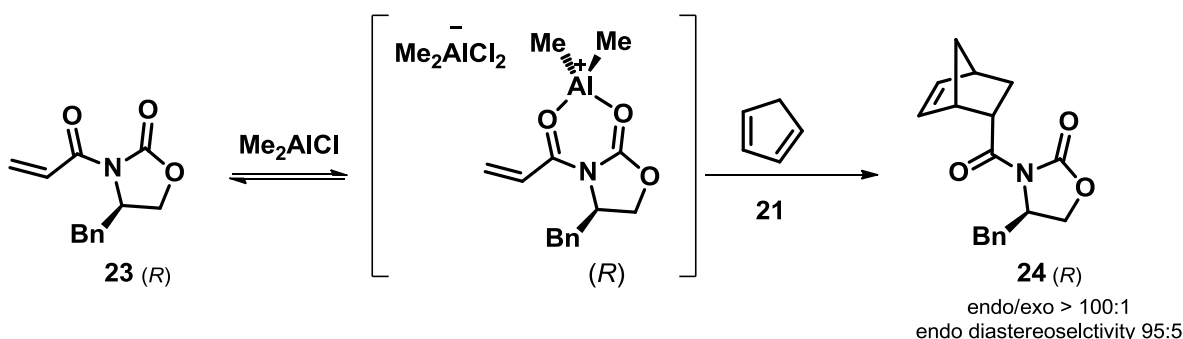
The diastereoselectivity inherent to the Diels-Alder reaction is apparent in several reported examples. However, the reaction is not inherently enantioselective since, when the substrates are achiral, there is no facial control to bias approach of the dienophile to the diene from a single face leading to the formation of racemic mixtures in this case.

The key to enantioselectivity is to provide facial control by the presence of stereogenic centers in the molecule that usually make one face more sterically hindered than the other. This can be performed in the presence of chiral substrates, using a chiral auxiliary covalently attached to the diene or dienophile (more used) leading to enhanced selectivity in the obtained

<sup>56</sup> Craig, D.; Shimpman, J. J.; Flower, R. B. *J. Am. Chem. Soc.* **1960**, *83*, 2885-2891.

<sup>57</sup> Backer, H. L. *Recueil des Travaux Chimiques des Pays-Bas* **1939**, *58*, 643-661.

diastereomers.<sup>58,59</sup> For instance, the Diels-Alder reaction of chiral  $\alpha,\beta$ -unsaturated-*N*-acyloxazolidinone **23** and cyclopentadiene **21** has been reported. In presence of dimethyl aluminum chloride the reaction proceeded to give **24** with high *endo* selectivity (Scheme 6).<sup>60</sup>



**Scheme 6: Dimethyl aluminum chloride promoted highly diastereoselective Diels-Alder cycloaddition.**

Another, nowadays more common, approach uses a chiral catalyst (chiral Lewis/Brønsted acid or organocatalysts). This will be detailed in the coming paragraphs.

### 3.2.2 Activation methods

In many cases, Diels-Alder reactions give poor yields and/or require excessively harsh reaction conditions and long reaction times. The development of “chemical” and “physical” activation methods for the purpose of improving the rate and/or the selectivity of (4+2) cycloaddition reaction was and is still an interest of many researchers. A short presentation of these methods with some examples is presented below.

#### 3.2.2.1 Physical activation methods

Physical activation methods of the Diels-Alder reaction have been developed and they have the advantage of avoiding the separation step of all the additives which are required in the chemical activation methods.

<sup>58</sup> Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876-889.

<sup>59</sup> Fang, L.-C.; Hsung, R. P.; Ma, Z.-X.; Presser, W. R. *Org. Lett.* **2013**, *15*, 4842-4845.

<sup>60</sup> Evans, D. A.; Chapman, K. T.; Bisaha, J. J. *Am. Chem. Soc.* **1988**, *110*, 1238-1256.

### 3.2.2.1.1 Thermal activation

From the moment of its discovery in 1928 until the discovery of Lewis acid activation methods in 1960, heating was almost the only activation method used to carry out the inter-<sup>61,62</sup> and intramolecular<sup>63,64,65,66,67</sup> (4+2) Diels-Alder reactions. Thermal activation is very useful and remains until now the first and the easiest to be investigated. Although so many products have been obtained using this simple technique, the application of high temperatures for a long time may cause the degradation and/or the polymerization of the reactants. It also favors the retro-cycloadditions in some cases. Considering the case of dearomatizing Diels-Alder cycloadditions, it may also lead to the rearomatization of the obtained adducts.

### 3.2.2.1.2 Ultrasound

The use of ultrasound (US) to promote chemical reactions, including Diels-Alder reactions,<sup>68,69,70,71</sup> is called sonochemistry. The "hot spot" theory explains the effects of ultrasound observed during organic reactions ascribed to the phenomenon of cavitation. The latter is a physical process that creates, enlarges, and collapses gaseous and vaporous cavities in an irradiated liquid. Cavitation induces very high local temperatures and pressures inside the bubbles, thereby activating the cycloaddition reaction.

Li et al. showed that furan derivatives can react as electron-rich aromatic dienes in Diels-Alder reactions under US irradiation (Scheme 7).<sup>72</sup> When a mixture of furans **26b** and dimethyl acetylenedicarboxylate (DMAD) **25** was subjected to US irradiation in the absence of solvent, the respective oxabicyclic compounds **27b** were obtained in good to excellent yields. Interestingly, when 2-vinyl furans **26a** were used as dienes in the cycloaddition reaction with DMAD **25** under US irradiation, only cyclic furan diene cycloadducts **27a** were obtained. However, under thermal

<sup>61</sup> Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, *110*, 7188-7194.

<sup>62</sup> Kishbaugh, T. L. S.; Gribble, G. W. *Tetrahedron Lett.* **2001**, *42*, 4783-4785.

<sup>63</sup> Kraus, G. A.; Raggon, J.; Thomas, P. J.; Bougie, D. *Tetrahedron Lett.* **1988**, *29*, 5605-5608.

<sup>64</sup> Stork, G.; Yamashita, A.; Adams, J.; Schulte, G. R.; Chesworth, R.; Miyazaki, Y.; Farmer, J. J. *J. Am. Chem. Soc.* **2009**, *131*, 11402-11406.

<sup>65</sup> Padwa, A.; Brodney, M. A.; Lynch, S. M.; Rashatasakhon, P.; Wang, Q.; Zhang, H. *J. Org. Chem.* **2004**, *69*, 3735-3745.

<sup>66</sup> Zhang, H.; Boonsombat, J.; Padwa, A. *Org. Lett.* **2007**, *9*, 279-282.

<sup>67</sup> France, S.; Boonsombat, J.; Leverett, C. A.; Padwa, A. *J. Org. Chem.* **2008**, *73*, 8120-8123.

<sup>68</sup> Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741-761.

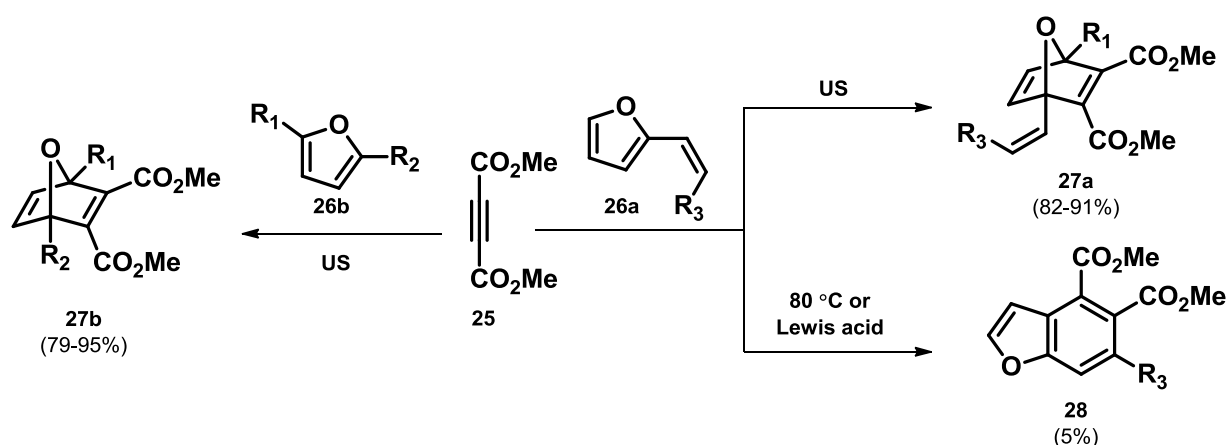
<sup>69</sup> Avalos, M.; Babiano, R.; Cabello, N.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; Palacios, J. C. *J. Org. Chem.* **2003**, *68*, 7193-7203.

<sup>70</sup> Cabello, N.; Cintas, P.; Luche, J.-L. *Ultrason. Sonochem.* **2003**, *10*, 25-31.

<sup>71</sup> Villacampa, M.; Pérez, J. M.; Avendano, C.; Menéndez, J. C. *Tetrahedron* **1994**, *50*, 10047-10054.

<sup>72</sup> Wei, K.; Gao, H.-T.; Li, W.-D. *J. Org. Chem.* **2004**, *69*, 5763-5765.

conditions or in the presence of Lewis acid the only product formed in a low yield was the exocyclic diene **28**, thus demonstrating the contribution of sonication to selectivity.



Scheme 7: Diels-Alder reaction of furan derivatives under US irradiation.

### 3.2.2.1.3 Microwaves

The region of the microwave (MW) radiation is located between the infrared and radio waves. MW accelerates some organic reactions and increases the yields, especially when polar substrates or intermediates are involved. Also, the reaction times can be reduced (even to minutes) and the further formation of by-products is avoided in some cases. It is sometimes more advantageous when compared to thermally activated Diels-Alder reactions which generally require harsher conditions (high temperatures and longer reaction times). Compared to ultrasound activation mode, microwave irradiation is much more often used to activate (4+2) Diels-Alder cycloaddition reactions.<sup>73,74,75,76</sup>

Different hypotheses have been proposed to explain the activation phenomenon by microwaves.<sup>77,78,79,80,81,82,83</sup> Some people suggested that the MW lowers the activation Gibbs energy and thus accelerates the reaction. Others demonstrated that MW is a more efficient way

<sup>73</sup> Kneeteman, M. N.; López Baena, A. F.; Della Rosa, C.; Mancini, P. M. E. *IRJPAC* **2015**, *8*, 229-235.

<sup>74</sup> De La Hoza, A.; Díaz-Ortiz, A.; Fraile, J. M.; Gómez, M. V.; Mayoral, J. A.; Moreno, A.; Saiz, A.; Vázquez, E. *Synlett* **2001**, 753-756.

<sup>75</sup> Loupy, A.; Maurel, F.; Sabatié-Gogová, A. *Tetrahedron* **2004**, *60*, 1683-1691.

<sup>76</sup> Zaimoku, H.; Nishide, H.; Nishibata, A.; Goto, N.; Taniguchi, T.; Ishibashi, H. *Org. Lett.* **2013**, *15*, 2140-2143.

<sup>77</sup> Baghurst, D. R.; Mingos, M. P. *J. Chem. Soc., Chem. Commun.* **1992**, 674-677.

<sup>78</sup> Panunzio, M.; Campana, E.; Martelli, G.; Vicennali, P.; Tamanini, E. *Mater. Res. Innov.* **2004**, *8*, 27-31.

<sup>79</sup> Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199-9223.

<sup>80</sup> Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225-9283.

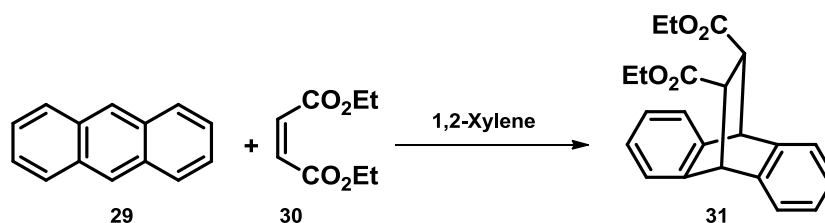
<sup>81</sup> Laurent, R.; Laporterie, A.; Dubac, J.; Bernal, J.; Lefeuvre, S.; Audhuy, M. *J. Org. Chem.* **1992**, *57*, 7099-7102.

<sup>82</sup> Raner, K. D.; Strauss, C. R.; Vyskoc, F.; Mokbel, L. *J. Org. Chem.* **1993**, *58*, 950-953.

<sup>83</sup> Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233-238.

of heating and it does not affect the thermodynamics of the reaction when careful temperature control is guaranteed.

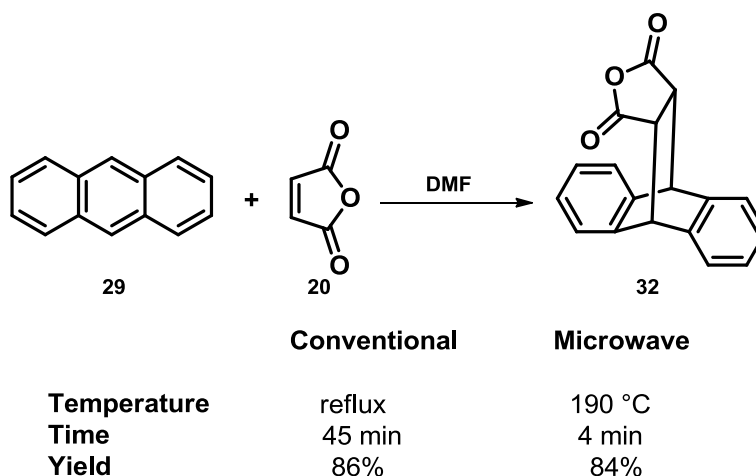
For example, Bernal et al. demonstrated that the Diels-Alder cycloaddition of anthracene **29** and diethyl maleate **30** is more rapid under MW irradiation than under conventional conditions.<sup>84</sup> However, Raner et al. showed that there is no acceleration in the rate of this reaction, within experimental error, under either mode of heating at the same temperature (Table 2).<sup>82</sup>



| Temperature (°C) | Microwave $k$ ( $M^{-1} s^{-1}$ ) | Oil bath $k$ ( $M^{-1} s^{-1}$ ) |
|------------------|-----------------------------------|----------------------------------|
| 140              | $1.0 \times 10^{-5}$              | $9.6 \times 10^{-6}$             |
| 150              | $1.5 \times 10^{-5}$              | $1.3 \times 10^{-5}$             |
| 160              | $3.5 \times 10^{-5}$              | $2.9 \times 10^{-5}$             |
| 170              | $4.7 \times 10^{-5}$              | $4.4 \times 10^{-5}$             |

Table 2: Heat and MW second-order rate constants.

When compared to conventional heating, MW decreases dramatically the reaction times for variety of Diels-Alder reactions.<sup>85,86</sup> For example, the reaction between anthracene **29** and maleic anhydride **20** requires 4 min under MW instead of 45 min under conventional heating (Scheme 8).<sup>85</sup>



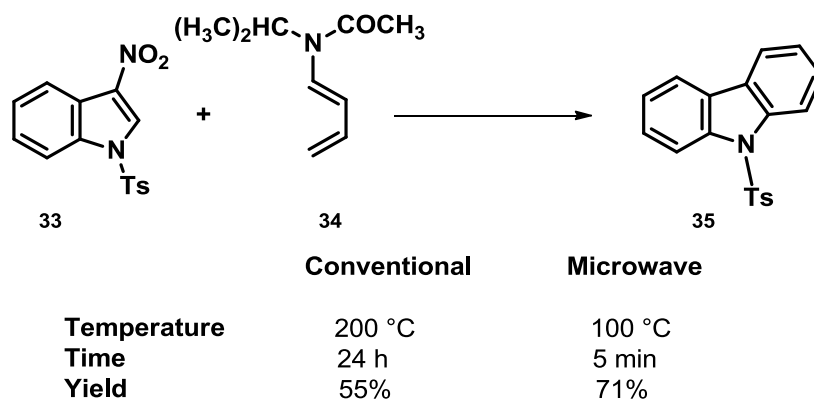
<sup>84</sup> Bernal, J.; Giboreau, P.; Lefeuvre, S.; Marchand, C. *Tetrahedron Lett.* **1991**, 32, 2363-2366.

<sup>85</sup> Majetich, G.; Hicks, R. *Radiat. Phys. Chem.* **1995**, 45, 567-579.

<sup>86</sup> Teyssot, M.-L.; Lormier, A.-T.; Chataigner, I.; Piettre, S. R. *J. Org. Chem.* **2007**, 72, 2364-2373.

## Scheme 8: Comparison between conventional heat and MW assisted Diels-Alder reaction.

Gómez et al. also showed that MW could be advantageous over conventional heating in the Diels-Alder reaction between indole derivative **33** and diene **34** (Scheme 9).<sup>87</sup> The yield was improved to 71% and the required time was decreased to 5 min.

Scheme 9: Heat versus MW activated Diels-Alder between **33** and **34**.

Like any activation method involving a thermal effect, the microwave irradiation can induce the degradation of the reagents and/or the products if the reaction lasts for a long time. It can also allow the retro-Diels-Alder and/or the aromatization processes to take place.

### 3.2.2.1.4 Photochemistry

The photochemical activation of the Diels-Alder reaction can be carried out by two ways, either by the direct activation of the diene and the dienophile, or by the use of a photosensitizer (such as rose bengal, methylene blue and tetraphenylporphyrin) that interacts with the reaction partners. Upon irradiation, a new species is formed (electronically excited reagent, radical cation or radical) that is trapped by the other reagent.<sup>49</sup> Different examples were reported in the literature<sup>88,89,90</sup> however, up to now, it is still limited.

Steckhan et al. reported in 1991 the photo-induced Diels-Alder of indole **2a** and substituted cyclohexa-1,3-dienes **36** in the presence of catalytic amounts of triarylpyrylium tetrafluoroborates **38**.<sup>91</sup> By irradiating the indole partner, the diene and the photosensitizer in

<sup>87</sup> Gómez, M. V.; Aranda, A. I.; Moreno, A.; Cossío, F. P.; De Cózar, A.; Díaz-Ortiz, A.; De La Hoz, A.; Prieto, P. *Tetrahedron* **2009**, *65*, 5328-5336.

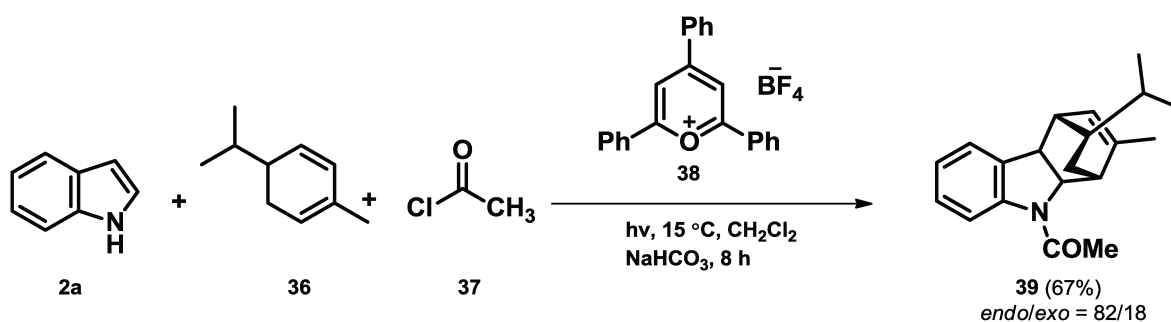
<sup>88</sup> Cornelisse, J. *Chem. Rev.* **1993**, *93*, 615-669.

<sup>89</sup> Hoffmann, N. *Synthesis* **2004**, 481-495.

<sup>90</sup> Mattay, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 663-665.

<sup>91</sup> Gieseler, A.; Steckhan, E.; Wiest, O.; Knoch, F. *J. Org. Chem.* **1991**, *56*, 1405-1411.

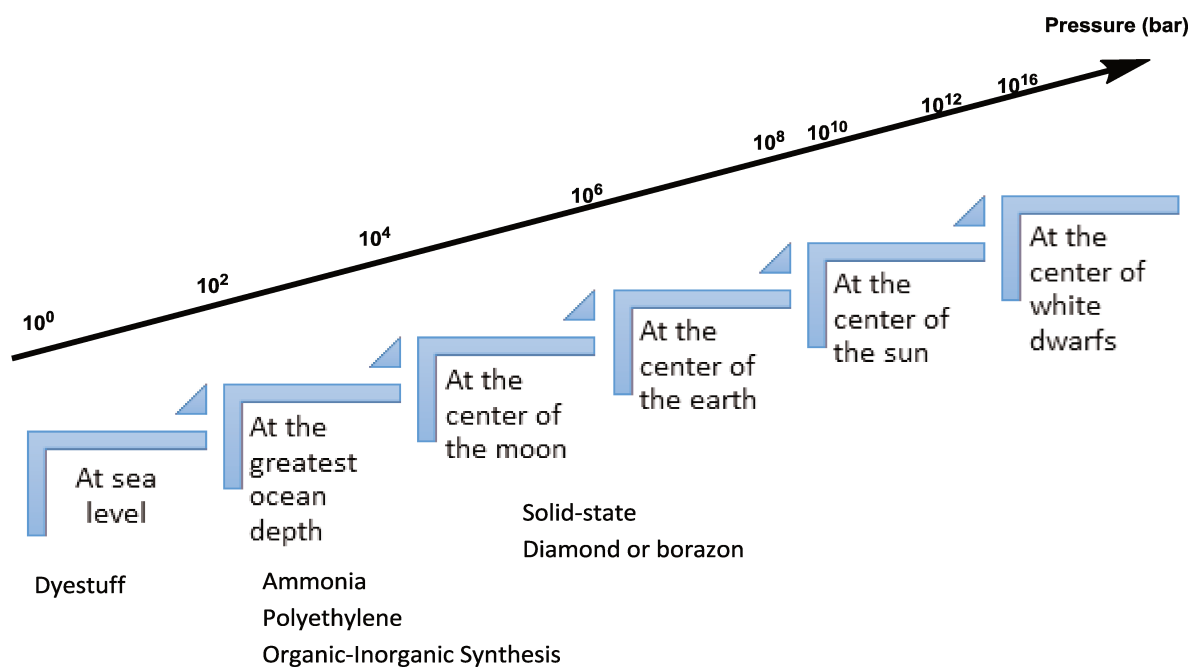
the presence of acetyl chloride **37**, the dearomatized cycloadduct **39** was isolated after 8 h in a 67% yield (Scheme 10).



Scheme 10: Photo-induced Diels-Alder reaction of indole.

### 3.2.2.1.5 High pressure

When we talk about high pressure, we talk about a fixed phenomenon taking place around us in the deep sea, inside the Earth and on other planets.<sup>92</sup> The application of pressures between 1 and 20 kbar has led to many applications (Figure 9). One of the interesting uses is the preparation of synthetic diamond, ruby and borazon developed in the 1950s.<sup>93,94</sup>



<sup>92</sup> Matsumoto, K.; Hamana, H.; Iida, H. *Helv. Chim. Acta* **2005**, *88*, 2033-2234.

<sup>93</sup> Bridgman, P. W. *The Physics of High Pressure*; G. Bell and Sons: London, UK, 1952.

<sup>94</sup> Hammann, S. D. *Physico-Chemical Effects of Pressure*; Butterworth: London, UK, 1987.

Figure 9: Pressure scale and applications of high pressure.

The positive effect of high pressure in organic chemistry has been known since 1940 with the dimerization of cyclopentadiene under hyperbaric conditions.<sup>95</sup> The role as well as the importance of high pressure in synthesis was reported by Jenner in 2002 (Table 3).<sup>96</sup>

| Activation mode   | Advantages  | Drawbacks   |
|-------------------|---|---|
| <b>Ultrasound</b> | Simple method<br>Large volume reactions<br>No or little work-up<br>Adaptable to heterogeneous reactions | No generality<br>Cost of equipment<br>Hazardous temperature control   |
| <b>Microwaves</b> | Large volume reactions<br>Fast reactions  | Hazardous temperature control<br>Safety problems<br>No reproducibility<br>Thermal stability of the products |
| <b>Photons</b>    | Flexible, selective method<br>Method based only on the reactivity of the excited state                  | Energy cost<br>Low volume reactions<br>Parallel reactions   |
| <b>Pressure</b>   | Simple non-destructive method<br>No or little work-up<br>Excellent reproducibility                      | Low volume reactions<br>Cost of equipment<br>Limited to homogeneous reactions                               |

Table 3: Advantages and drawbacks of different activation modes.

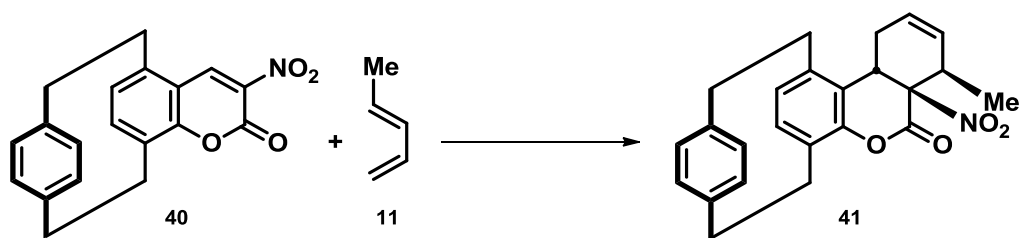
Although the application of this activation mode has allowed some difficult and/or impossible reactions to proceed, its use remains limited due to its technical constraints (equipment and cost, in particular). For example, the Diels-Alder reaction between nitrocoumarin **40** and (*E*)-piperylene **11** did not proceed under atmospheric pressure in toluene at 110 °C (Scheme 11). However, under HP (8 kbar), cycloadduct **41** was isolated in a 53% yield.<sup>97</sup> Thus, high pressures make possible reactions prohibited at atmospheric pressure.

<sup>95</sup> Weale, K. E. *Chemical Reactions at High Pressure*; E. And F. N. Spon: London, 1967.

<sup>96</sup> Jenner, G. *Tetrahedron* **2002**, *58*, 5185-5202.

<sup>97</sup> Minuti, L.; Marrocchi, A.; Landi, S.; Seri, M.; Gacs-Baitz, E. *Tetrahedron* **2007**, *63*, 5477-5481.



**Conditions:**

Toluene, 110 °C, 39 h  
 CH<sub>2</sub>Cl<sub>2</sub>, 8 kbar, 50 °C, 20 h

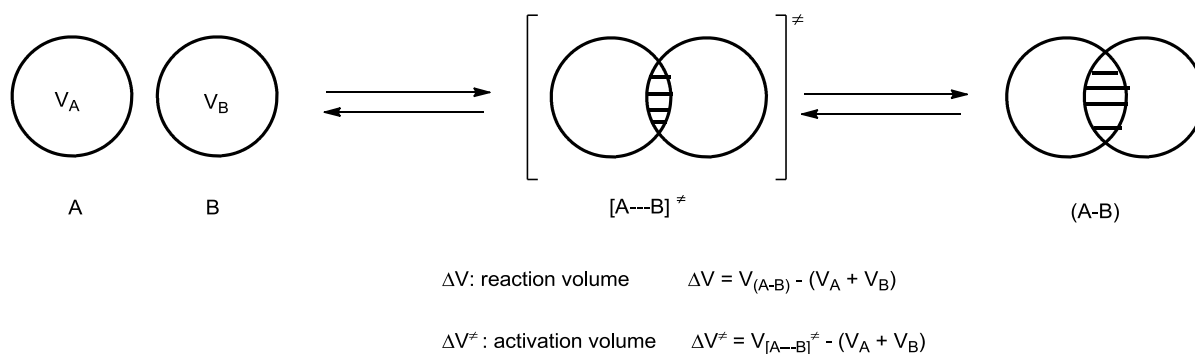
No reaction  
 53%

**Scheme 11: Reactivity of nitrocoumarin under high pressure.**

Taking advantage of the largely negative volume of activation characterizing the Diels-Alder reaction (about -25 to -45 cm<sup>3</sup>.mol<sup>-1</sup>), these processes are generally highly accelerated under high pressure. To understand this mode of activation, some aspects should be defined and discussed.

### 3.2.2.1.5.1 General principles

A chemical reaction is characterized by an activation volume  $\Delta V^\ddagger$  (Figure 10).<sup>98</sup> The latter is defined as the difference between the volume of the transition state and the initial volumes of the reactants measured at constant pressure (P) and temperature (T).



**Figure 10: Definition and representation of the activation volume.**

The application of pressure in the range of 1-20 kbar influences the rate and the equilibrium of many organic reactions. This effect can be described using thermodynamic principles.<sup>99,100</sup> The activation volume  $\Delta V^\ddagger$  is related to the activation free energy and to the speed constant  $k_p$  as a function of the pressure according to the equation below. The latter was deduced by Evans and

<sup>98</sup> Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1-26.

<sup>99</sup> Benito-López, F.; Egberink, R. J. M.; Reinhoudt, D. N.; Verboom, W. *Tetrahedron* **2008**, *64*, 10023-10040.

<sup>100</sup> Jurczak, J. *Physica* **1986**, 709-716.

Polanyi based on transition-state theory. Accordingly, when the pressure increases, the reaction is accelerated if  $\Delta V^\ddagger$  is negative.

$$\Delta V^\ddagger = \left( \frac{\partial \Delta G^\ddagger}{\partial p} \right)_T = \left( \frac{-\partial \ln Kp}{\partial p} \right)_T \cdot RT$$

In other words, and over simplistically, the reactions accompanied by a decrease in volume (often also characterized by  $\Delta V^\ddagger < 0$ ) are accelerated by a pressure increase. Here we can mention any reaction with bond formation (addition or cycloaddition reactions for instance), concentration of charge and ionization in the transition state. However, if the reaction is accompanied by an increase in the activation volume ( $\Delta V^\ddagger > 0$ ) it is retarded. In this category, we can state any reaction with bond cleavage, charge dispersal and neutralization in the transition state.

Le Noble et al. and Matsumoto et al. have reported the activation volumes of several reactions.<sup>92,101,102,103</sup> Table 4 shows some of these data.

| Chemical Reaction                  | $\Delta V^\ddagger$ (cm <sup>3</sup> . mol <sup>-1</sup> ) |
|------------------------------------|--|
| Homolytic bond cleavage            | +10  |
| Bond formation                     | -10  |
| Bond deformation                   | ≈0   |
| Ionization                         | -20  |
| Neutralization of charges          | +20  |
| Cyclization                        | ≈0   |
| (4+2) Cycloaddition                | -25 to -50   |
| Intramolecular (4+2) Cycloaddition | -10 to -15   |
| (3+2) Cycloaddition                | -20 to -25   |
| (2+2) Cycloaddition                | -20 to -50   |

Table 4: Activation volumes of different reactions.

### 3.2.2.1.5.2 Influence of high pressure on physical properties

The implementation of reactions under pressure requires a judicious choice of the solvent(s). The application of pressure affects the physical properties of the solvent such as the freezing temperature, viscosity, solubility, density and others. For example, an increase in pressure results in an increase in the freezing temperature of the solvents, except for water.<sup>98,104</sup> Unfortunately,

<sup>101</sup> Asano, T.; Le Noble, W. J. *Chem. Rev.* **1978**, *78*, 407-489.

<sup>102</sup> Van Eldik, R.; Asano, T.; Le Noble, W. J. *Chem. Rev.* **1989**, *89*, 549-688.

<sup>103</sup> Drljaca, A.; Hubbard, C. D.; Van Eldik, R.; Asano, T.; Basilevsky, M. V.; Le Noble, W. J. *Chem. Rev.* **1998**, *98*, 2167-2289.

<sup>104</sup> Jenner, G. *Mini-Reviews in Organic Chemistry* **2004**, *1*, 9-26.

sufficient data on all these properties are often unavailable. However, Simon and Glatzel equation can be used to estimate the freezing temperature of solvents as a function of temperature and pressure.<sup>105</sup>

$$\frac{P}{\alpha} = \left(\frac{T_p}{T_c}\right)^\beta - 1$$

$\alpha, \beta$  = constants;  $T_c$  = critical temperature

Based on this equation as well as on experimental results, the freezing temperatures of some solvents are now available (Table 5).<sup>92,98</sup>

| Solvent         | Freezing Temperature (°C) |                         |
|-----------------|---------------------------|-------------------------|
|                 | at 1 bar                  | at high pressure (kbar) |
| Acetone         | -94.8                     | 20(8)                   |
| Benzene         | 5.5                       | 33.4(1)                 |
| Chloroform      | -61.0                     | -45.2(1)                |
| Cyclohexane     | 6.5                       | 58.9(1)                 |
| Dichloromethane | -96.7                     | -85.8(1)                |
| Diethyl ether   | -116.3                    | 35(12)                  |
| Ethyl acetate   | -83.6                     | 25(12.1)                |
| Methanol        | -97.7                     | 25(30)                  |
| Toluene         | -95.1                     | 30(9.6)                 |
| Water           | 0.0                       | -9.0(1)                 |

**Table 5: Fusion points of different solvents with and without pressure.**

Moreover, during the compression, the viscosity ( $\eta$ ) of the reaction medium increases exponentially with the pressure ( $\eta = \eta_0 \cdot \exp(\gamma P)$ ;  $\gamma$  is the pressure coefficient). Also, the solubility of solids in liquids decreases, and thus the reagents tend to crystallize. Therefore, when conducting a reaction under high pressure it is not only necessary to choose a solvent that allows the solubilization of the reactants but also to ensure its fluidity under high pressure. Alcohols, dichloromethane and acetonitrile are considered as good solvents usually used under HP.

### 3.2.2.1.5.3 Application of hyperbaric conditions to Diels-Alder reaction

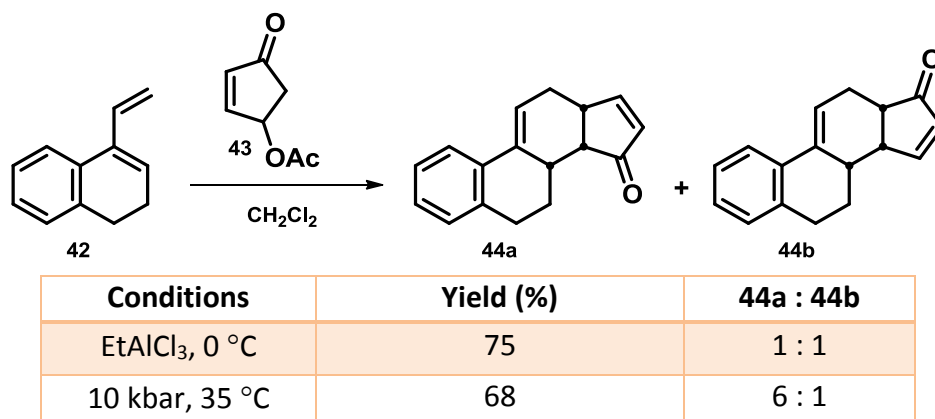
High pressures (HP) constitute an activation mode particularly suitable for Diels-Alder reactions and many groups including ours have been interested in this mode of

<sup>105</sup> Babb, S. E. *Rev. Mod. Phys.* **1963**, 35, 400-413.

activation.<sup>3,86,106,107,108,109,110</sup> Indeed, these processes are characterized by largely negative activation volumes, between  $-20$  and  $-45$   $\text{cm}^3\cdot\text{mol}^{-1}$  for intermolecular reactions and  $-15$  to  $-30$   $\text{cm}^3\cdot\text{mol}^{-1}$  for intramolecular ones.<sup>101,102,103</sup>

From a mechanistic point of view, hyperbaric conditions tend to favor pericyclic mechanisms over stepwise mechanisms. Indeed, a pericyclic transition state is generally more compact, leading to a more negative activation volume which further favors this reaction path.<sup>111</sup> For the same reason, HP generally favor the endo approach (see below). Complementarily, they also disfavor the side reactions such as degradation, elimination reactions, retro-Diels-Alder or rearomatization (in case of dearomatization reactions).

As discussed before the application of pressure influences the rate of the Diels-Alder reaction. It can also affect the regioselectivities in some cases (Table 6).<sup>112</sup> For example, the cycloaddition reaction of the diene **42** with the acetate **43** has led, in the presence of a Lewis acid, to cycloadducts **44a** and **44b** without any regioselectivity. Whereas at 10 kbar, the regioselectivity increases to 6 : 1, in favor of compound **44a**.



**Table 6: Influence of high pressure on the regioselectivity of Diels-Alder reactions.**

HP have often an effect on the diastereoselectivity of the Diels-Alder reaction. Indeed, the *endo* transition state is generally more compact ( $1$  to  $3$   $\text{cm}^3\cdot\text{mol}^{-1}$ ) and is therefore favored under

<sup>106</sup> Lomberget, T.; Chataigner, I.; Bouyssi, D.; Maddaluno, J.; Balme, G. *Tetrahedron Lett.* **2004**, 45, 3437-3441.

<sup>107</sup> Maingot, L.; Leconte, S.; Chataigner, I.; Martel, A.; Dujardin, G. *Org. Lett.* **2009**, 11, 1619-1622.

<sup>108</sup> Biolatto, B.; Kneeteman, M.; Paredes, E.; Mancini, M. E. *J. Org. Chem.* **2001**, 66, 3906-3912.

<sup>109</sup> Chrétien, A.; Chataigner, I.; Piettre, S. R. *Tetrahedron* **2005**, 61, 7907-7915.

<sup>110</sup> Andreini, M.; De Paolis, M.; Chataigner, I. *Catal. Commun.* **2015**, 63, 15-20.

<sup>111</sup> Klärner, F.-G.; Wurche, F. J. *Prakt. Chem.* **2000**, 342, 609-636.

<sup>112</sup> Gacs-Baitz, E.; Minuti, L.; Taticchi, A. *Tetrahedron* **1994**, 50, 10359-10366.

hyperbaric conditions.<sup>113,114,115,116</sup> Maddaluno et al. showed that diphenylisobenzofuran **45** can react with pyrroline derivative **46** in (4+2) cycloaddition reaction (Table 7).<sup>117</sup> The *endo/exo* selectivity observed in the product depends on the activation conditions: thermal conditions tend to favor the *endo* isomer **47b**, while HP favors the *exo* isomer **47a**. This would be due to the more compactness of the corresponding transition state with respect to the one leading to the *endo* isomer.

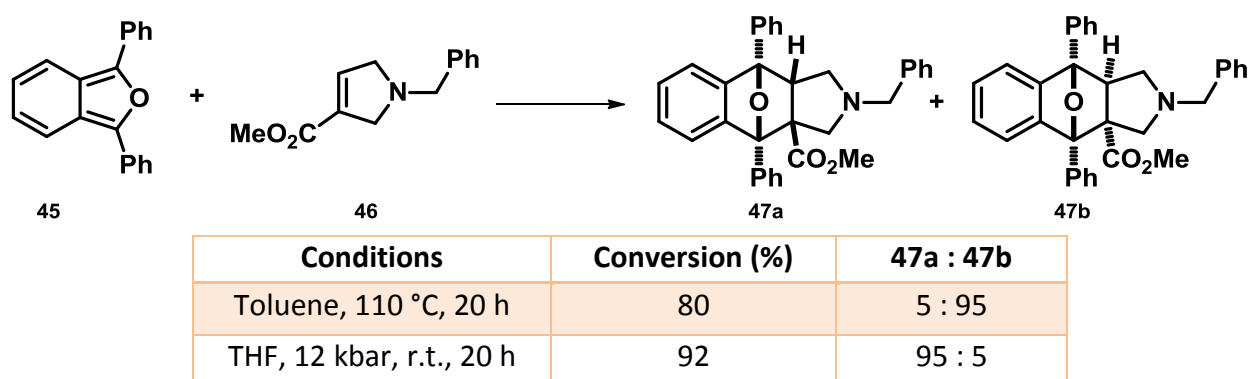


Table 7: Influence of HP on diastereoselectivity.

The combination of high pressure and organocatalysis is also possible but it is not well developed.<sup>118,119</sup> Kwiatkowski et al. described recently the asymmetric organocatalytic hydroxyalkylation of indoles **48** with trifluoromethyl ketones **49** (Scheme 12).<sup>120</sup> A combination of pressure (8.5-9 kbar) and catalytic amount of cinchonidine **50**, gave chiral tertiary alcohols **51** in good yields and enantioselectivities (up to 95%, 89% *ee*).

<sup>113</sup> Kinsman, A. C.; Kerr, M. A. *Org. Lett.* **2000**, *2*, 3517-3520.

<sup>114</sup> Jenner, G. *Tetrahedron* **1997**, *53*, 2669-2695.

<sup>115</sup> Chopin, N.; Gérard, H.; Chataigner, I.; Piettre, S. R. *J. Org. Chem.* **2009**, *74*, 1237-1246.

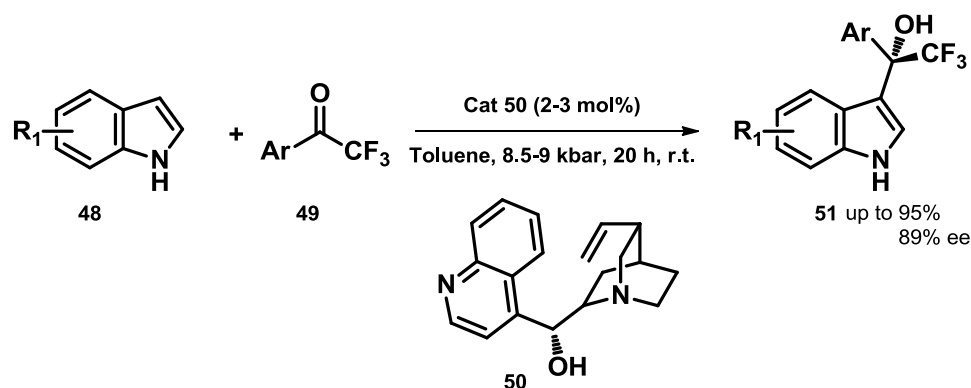
<sup>116</sup> Chataigner, I.; Hess, E.; Toupet, L.; Piettre, S. R. *Org. Lett.* **2001**, *3*, 515-518.

<sup>117</sup> Pichon, N.; Harrison-Marchand, A.; Mailliet, P.; Maddaluno, J. *J. Org. Chem.* **2004**, *69*, 7220-7227.

<sup>118</sup> Kwiatkowski, P.; Cholewiak, A.; Kasztela, A. *Org. Lett.* **2014**, *16*, 5930-5933.

<sup>119</sup> Biedrzycki, M.; Kasztela, A.; Kwiatkowski, P. *ChemCatChem* **2017**, *9*, 2453-2456.

<sup>120</sup> Kasztela, A.; Biedrzycki, M.; Kwiatkowski, P. *Adv. Synth. Catal.* **2016**, *358*, 2962-2969.



Scheme 12: Organocatalytic Diels-Alder reaction under high pressure.

### 3.2.2.2 Chemical activation

#### 3.2.2.2.1 Acid catalysis

Historically, the Brønsted acids were the first acids used to activate the (4+2) cycloaddition reactions. This method has shown a broad applicability.

The Diels-Alder reaction can be activated by a Lewis acid<sup>121</sup> such as  $\text{AlCl}_3$ ,  $\text{BF}_3$  or  $\text{TiCl}_4$  for instance.

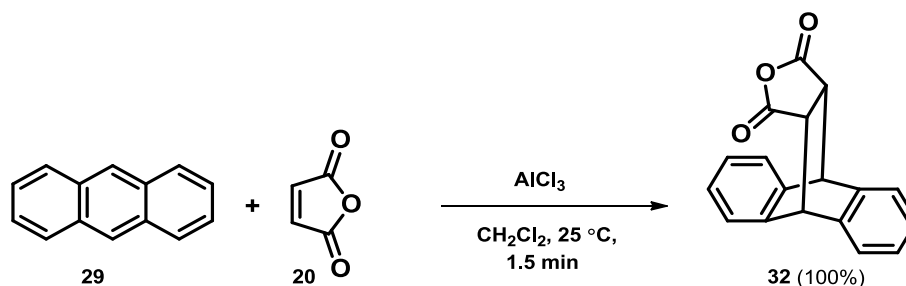
Wasserman was the first to observe the acceleration of the Diels-Alder reaction in acidic medium in 1942.<sup>122,123</sup> After 20 years of this observation, Yates and Eaton<sup>124</sup> demonstrated the value of using a Lewis acid ( $\text{AlCl}_3$ ) in this reaction. They studied the reaction between maleic anhydride **20** and anthracene **29** in the presence of aluminum chloride, which was completed in 1.5 minutes (Scheme 13), whereas they estimated the required reaction time under the same conditions in the absence of the catalyst to be approximately 4800 hours!

<sup>121</sup> Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650-1667.

<sup>122</sup> Wassermann, A. *J. Chem. Soc.* **1942**, 618-621.

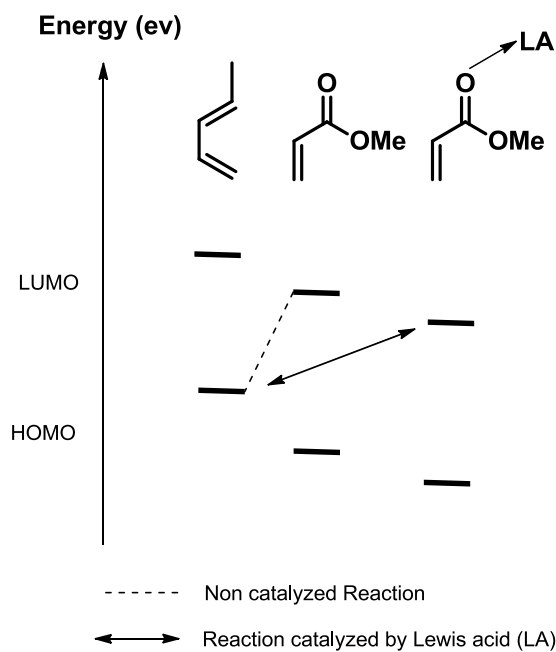
<sup>123</sup> Wassermann, A. *J. Chem. Soc.* **1942**, 623-626.

<sup>124</sup> Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436-4437.



**Scheme 13: Lewis acid catalyzed Diels-Alder reaction.**

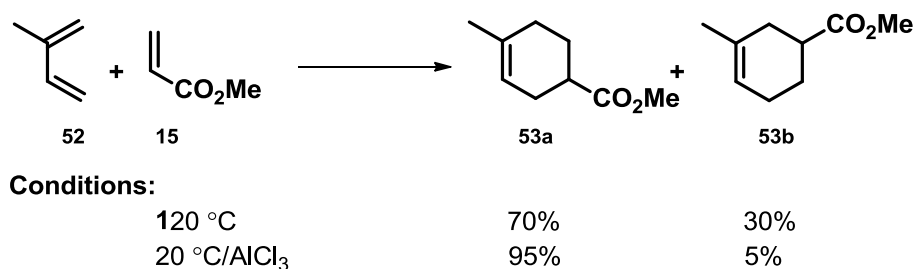
The mechanism of activation by acids can be understood with the aid of the FMO theory. Formation of the complex dienophile-acid lowers the energy of its LUMO compared to the one of the uncomplexed dienophile, resulting in a decrease in the HOMO-LUMO energy difference and, in turn, the rate of the Diels-Alder reaction is increased (Figure 11).



**Figure 11: Effect of acid catalyst on the HOMO-LUMO gap.**

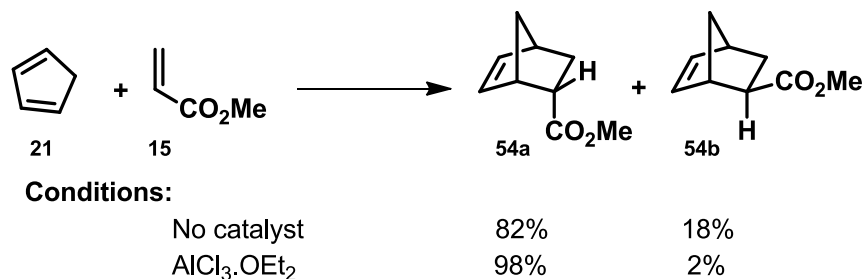
The use of Lewis acid (LA) influences the regioselectivity of the reaction because of their impact on the orbital coefficients of the reaction atoms (Scheme 14).<sup>125</sup>

<sup>125</sup> Inukai, T.; Kojima, T. *J. Org. Chem.* **1971**, *36*, 924-928.



Scheme 14: Impact of Lewis acid on regioselectivity.

Sauer and Kredel also demonstrated the effect of Lewis acids on the stereoselectivity.<sup>126</sup> Upon addition of  $\text{AlCl}_3 \cdot \text{OEt}_2$  the *endo/exo* selectivity of the reaction between cyclopentadiene **21** and methyl acrylate **15** improved from 82% to 98% (Scheme 15). This improvement is due to the enhanced orbital coefficients of the methyl acrylate **15** which lead to more effective secondary orbital interactions favoring the *endo* approach.



Scheme 15: Influence of Lewis acid on selectivity.

Enantioselective Diels-Alder reactions using Lewis acid bearing a chiral ligand was also reported.<sup>127,128</sup> Evans et al. reported the use of  $\text{C}_2$ -symmetry copper complex bearing chiral bisoxazoline chiral ligands **56** to activate the Diels-Alder reaction between cyclopentadiene **21** and  $\alpha,\beta$ -unsaturated carbonyl compounds **55** (Scheme 16).<sup>129</sup> The desired cycloadduct **57** was obtained in a good yield and enantiomeric excess.

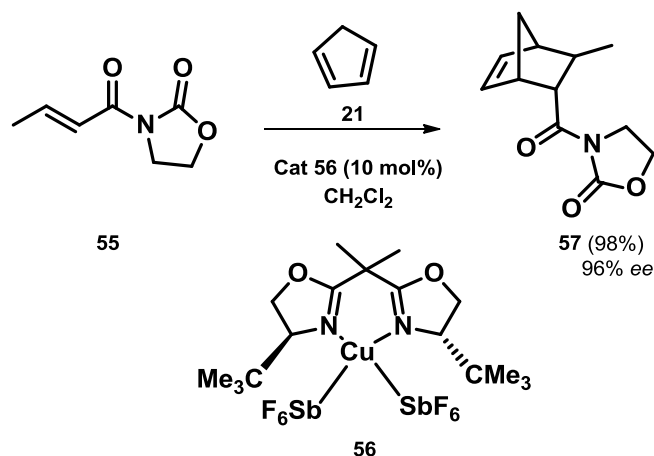
<sup>126</sup> Sauer, J.; Kredel, J. *Tetrahedron Lett.* **1966**, 7, 731-736.

<sup>127</sup> Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, 115, 6460-6461.

<sup>128</sup> Evans, D. A.; Miller, S. J.; Lectka, T.; Von Matt, P. *J. Am. Chem. Soc.* **1999**, 121, 7559-7573.

<sup>129</sup> Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, 33, 325-335.





**Scheme 16: Chiral Lewis acid catalyzed enantioselective Diels-Alder reaction.**

Lewis acids therefore favor the Diels-Alder reaction and thus make it possible to take place under much milder conditions. They generally improve the regio- and stereoselectivity of the reaction. Nevertheless, some limitations should be taken into consideration. Indeed, catalysis by a Lewis acid is not applicable in the cases where the diene and/or the dienophile are acid sensitive. In addition, the diene polymerization can be favored under these conditions, especially in case of electron-rich molecule.

### 3.2.2.2.2 Organocatalysts

The use of organic molecules to catalyze Diels-Alder reactions is increasing nowadays. These metal-free organic catalysts are generally non-toxic, often readily available and stable. These properties allow most reactions to be performed in wet solvent and under air, which increases the reproducibility and operational simplicity.

Organocatalysts activate Diels-Alder reactions mainly by two different ways: either by activating the dienophilic partner by lowering its LUMO energy through hydrogen bonding or iminium ion formation, or by raising the HOMO energy of the dienic partner through (poly)enamine formation.<sup>130,131</sup>

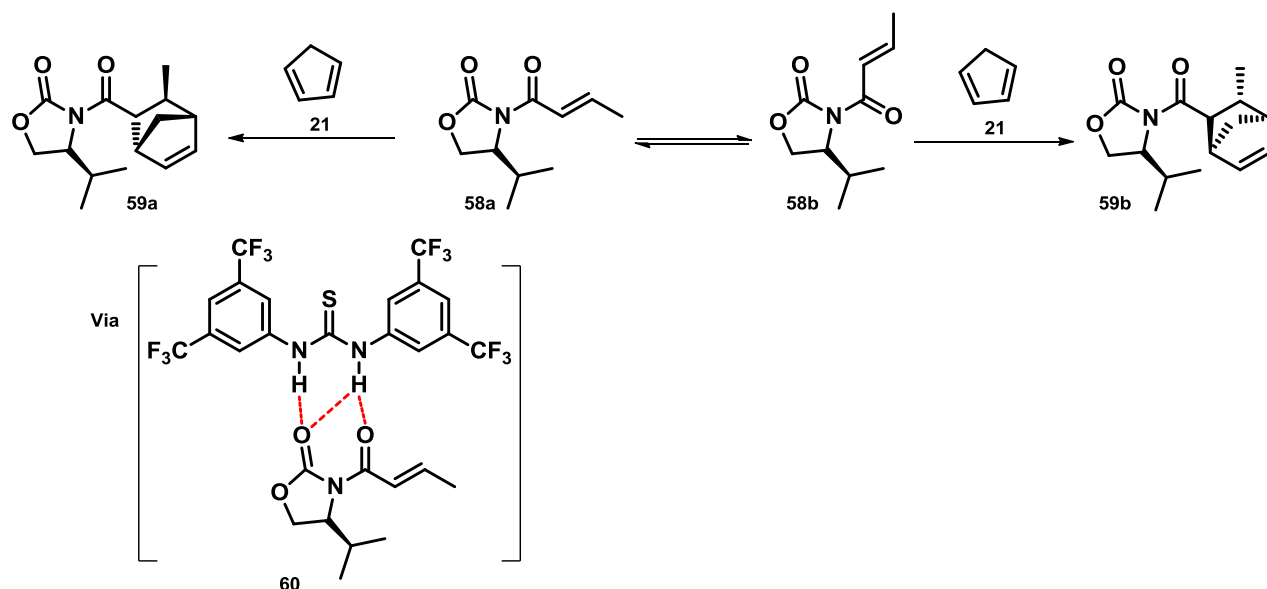
Small organic molecules that are able to form hydrogen bonds with carbonyl groups such as diols, biphenols, ureas, thioureas, squaramides and others<sup>132</sup> have been used to catalyze the Diels-Alder reactions. Similarly to Lewis acids, activation of the dienophilic partner occurs in this case by the formation of hydrogen bond(s), this lowers the LUMO energy of the complex and facilitates the whole process. For instance, Schreiner and Wittkopp have demonstrated that

<sup>130</sup> Arceo, E.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 5290-5292.

<sup>131</sup> Kumar, I.; Ramaraju, P.; Mir, N. A. *Org. Biomol. Chem.* **2013**, *11*, 709-716.

<sup>132</sup> Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520-1543.

diarylthioureas **60** can catalyze the prototypical Diels-Alder reaction between cyclopentadiene **21** and  $\alpha,\beta$ -unsaturated carbonyl compounds **58** (Scheme 17).<sup>133,134</sup>



**Scheme 17: Thiourea catalyzed Diels-Alder reaction.**

The uncatalyzed reaction did not occur at 23 °C (Table 8, entry 1). Yet, when prolonged heating was carried out, the cycloadducts **59a** and **59b** were obtained in a 36 : 64 ratio, respectively (entry 2). In the presence of a catalytic amount of thiourea **60**, the reaction could be carried out efficiently at 23 °C (entry 3). The diastereomeric ratio was reversed and enhanced for product **59a**. These results can be explained by the conformation of the activated reactive complex. Indeed, the uncomplexed species adopts preferentially the conformation **58b** (Scheme 17) and thus leads to **59b** as the major product. In contrast, the complexed activated dienophile adopts preferably conformation **58a** (Scheme 17) in the presence of thiourea catalyst, leading to **59a** as a major product. Note that, the same effect had been noticed with Lewis acids (bidentate complexation for instance with copper salts as seen in the previous paragraph).

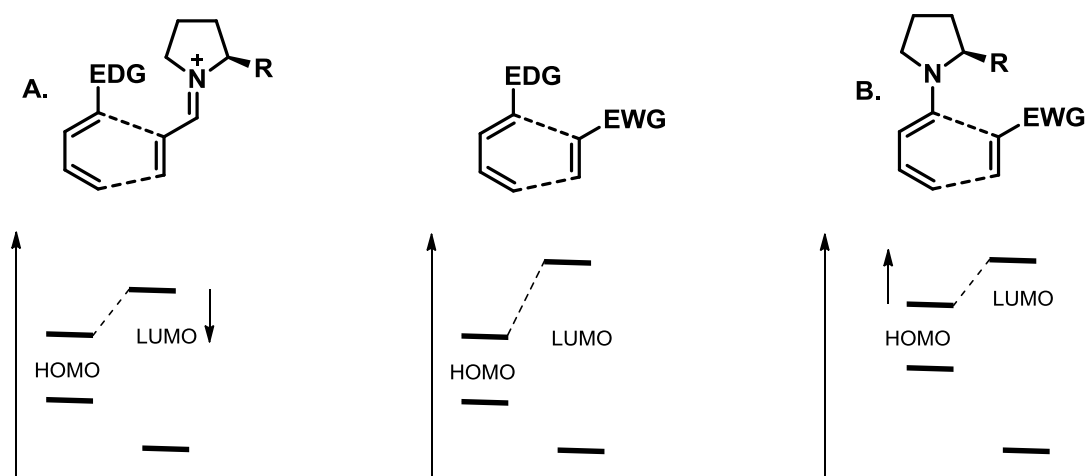
<sup>133</sup> Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217-220.

<sup>134</sup> Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407-414.

| Entry | Conditions   | Yield (%) | 59a : 59b |
|-------|--|-----------|-----------|
| 1     | Benzene, r.t.  | 0         | -         |
| 2     | Benzene, 130 °C                                      | 55        | 36 : 64   |
| 3     | Cat <b>60</b> (25 mol%),<br>CHCl <sub>3</sub> , r.t. | 78        | 81 : 19   |

**Table 8: Effect of diarylthioureas on stereoselectivity of Diels-Alder reaction.**

Considering the use of chiral amines as organocatalysts in NED Diels-Alder reaction, the activation of the carbonyl functional group can be performed either through LUMO-lowering via iminium ion intermediates (Figure 12, A) or HOMO-raising via dienamine, trienamine or tetraemanine formation (Figure 12, B).



**Figure 12: FMO model of NED Diels-Alder reaction.**

Göbel<sup>135,136,137,138</sup> and MacMillan<sup>139,140</sup> were pioneers in the use of organocatalysts to accelerate Diels-Alder reaction.

MacMillan et al. described the first amine-catalyzed asymmetric Diels-Alder reaction, and demonstrated the effectiveness of the imidazolidinone catalyst **62** in the activation of the  $\alpha,\beta$ -unsaturated ketone **61** (Scheme 18).

<sup>135</sup> Schuster, T.; Kurz, M.; Göbel, M. W. *J. Org. Chem.* **2000**, *65*, 1697-1701.

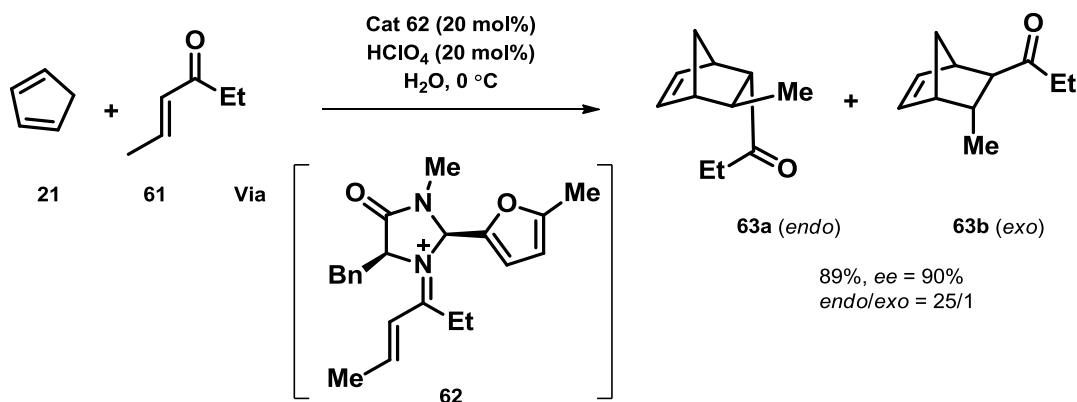
<sup>136</sup> Schuster, T.; Bauch, M.; Dürner, G.; Göbel, M. W. *Org. Lett.* **2000**, *2*, 179-181.

<sup>137</sup> Tsogoeva, S. B.; Dürner, G.; Bolte, M.; Göbel, M. W. *Eur. J. Org. Chem.* **2003**, 1661-1664.

<sup>138</sup> Weimar, M.; Dürner, G.; Bats, J. W.; Göbel, M. W. *J. Org. Chem.* **2010**, *75*, 2718-2721.

<sup>139</sup> Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.

<sup>140</sup> Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458-2460.

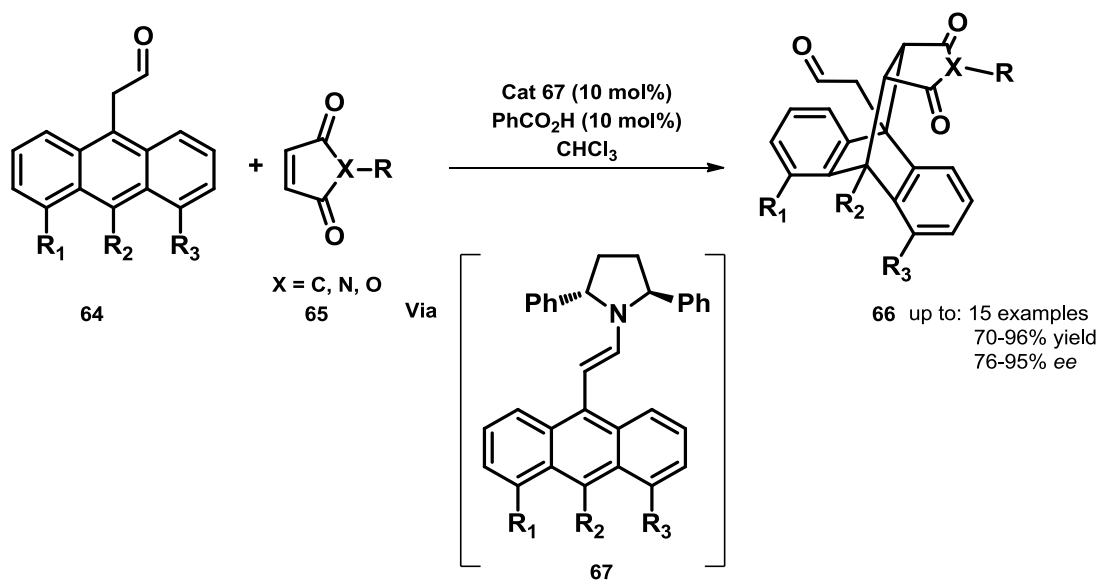


**Scheme 18: Imidazolidinone catalyzed asymmetric Diels-Alder reaction.**

This activation mode is based on the formation of covalently bonded active intermediate generated by the condensation of the chiral cyclic amine on the carbonyl group of the dienophile. The reversible formation of a positively charged iminium ion intermediates mimics the electronic situation of the  $\pi$  orbitals in Lewis acid catalysis. Thus, the energy of the LUMO of the system is efficiently lowered, the iminium is much more reactive than its carbonyl precursor. The two faces of the activated dienophile are well differentiated and the enantioselectivity is efficiently controlled by the engagement of the diene substrate with the *si*-face of the *cis*-iminium isomer.

In 2013, Jørgensen et al. reported the asymmetric cycloaddition of anthracene derivatives **64**.<sup>141</sup> This cycloaddition takes place using a  $C_2$ -symmetric aminocatalyst **67** to afford **66** with excellent yields and stereoselectivities (Scheme 19). Here, the activation mode is different, in contrast to the previous example, proceeds through a nucleophilic activation of the dienic partner through the formation of enamine.

<sup>141</sup> Rodriguez-Esrich, C.; Davis, R. L.; Jiang, H.; Stiller, J.; Johansen, T. K.; Jørgensen, K. A. *Chem. Eur. J.* **2013**, *19*, 2932-2936.



Scheme 19: Asymmetric cycloaddition of anthracene.

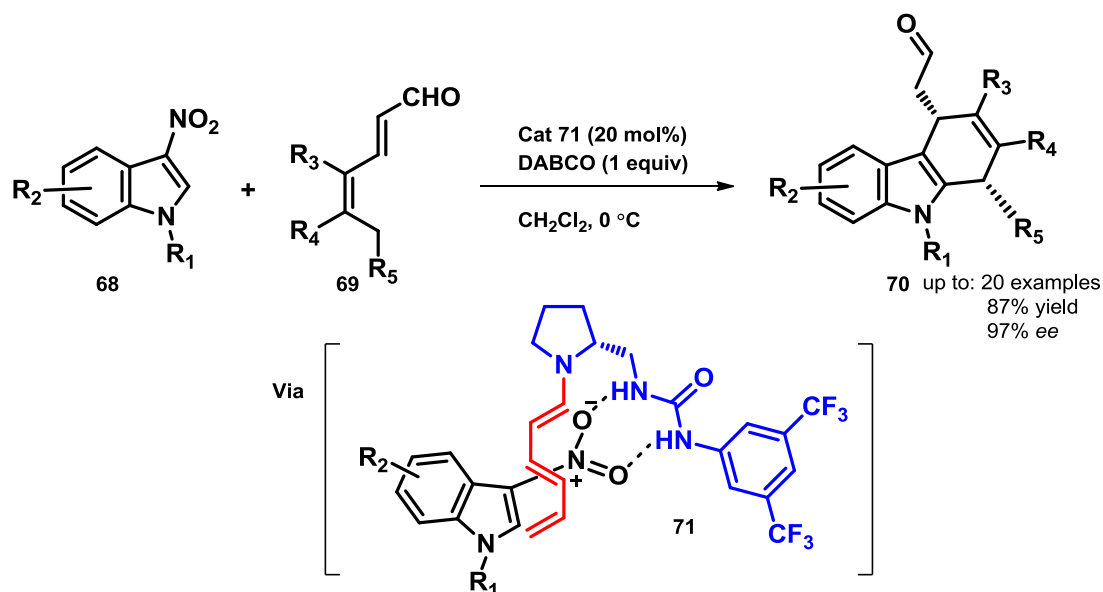
Many other examples were reported in the literature,<sup>142,143,144</sup> however in 2016, Jørgensen et al.<sup>145</sup> reported the first enantioselective dearomatizing (4+2) reaction of 3-nitroindole derivatives **68** by trienamine catalysis to yield chiral dihydrocarbazole scaffolds **70** (Scheme 20). The trienamine pathway showed to be efficient in dearomatizing various nitroindole derivatives at low temperature. The elimination of nitrous acid by heating under basic conditions was needed for the proper isolation of the products.

<sup>142</sup> Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 15212-15218.

<sup>143</sup> Bertuzzi, G.; Sinisi, A.; Pecorari, D.; Caruana, L.; Mazzanti, A.; Bernardi, L.; Fochi, G. *Org. Lett.* **2017**, *19*, 834-837.

<sup>144</sup> Donlund, B. S.; Monleón, A.; Palazzo, T. A.; Christensen, M. L.; Dahlggaard, A.; Erickson, J. D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2018**, *57*, 1246-1250.

<sup>145</sup> Li, Y.; Tur, F.; Nielsen, R. P.; Jiang, H.; Jensen, F.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 1020-1024.



Scheme 20: Enantioselective (4+2) reaction of 3-nitroindole derivatives.

### 3.2.2.2.3 Solvent effects

For a long time, solvent polarity was believed to have little or no effect on the course of a Diels-Alder reaction. However, solvents exert their influence on organic reactions through a complicated mixture of all possible types of non-covalent interactions. Many textbooks, when discussing this subject, now refer to the Diels-Alder cycloaddition as a typical example.

The solvent has an effect not only on the rate of the Diels-Alder reaction but also on the selectivity and the mechanism.<sup>146</sup> Normally, for these reactions, diene and/or dienophile should be activated by electron donating or withdrawing substituent(s). These almost invariably contain heteroatoms, which, in turn interact efficiently with the solvent, resulting in an amplification of the solvent effect on the reaction. A multitude of these processes have been studied. The first correlation of the rate of Diels-Alder reactions with solvent parameters was published in 1974.<sup>147</sup>

Water was long considered as a detrimental solvent for organic reactions. However, the “Big Bang” was achieved by the work of Breslow<sup>148,149,150</sup> and Grieco<sup>151,152</sup> in the 1980s who showed the positive effect of water on the rates and selectivities of Diels-Alder reactions between

<sup>146</sup> Ruiz-López, M. F.; Assfeld, X.; Gracia, J. I.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1993**, *115*, 8780-8787.

<sup>147</sup> Von Blankenburg, B.; Fiedler, H.; Hampel, M.; Hauthal, H. G.; Just, G.; Kahlert, K.; Korn, J.; Müller, K. H.; Pritzkow, W.; Reinhold, Y.; Röllig, M.; Sauer, E.; Schunurpfeil, D.; Zimmermann, G. *J. Prakt. Chem.* **1974**, *316*, 804-816.

<sup>148</sup> Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816-7817.

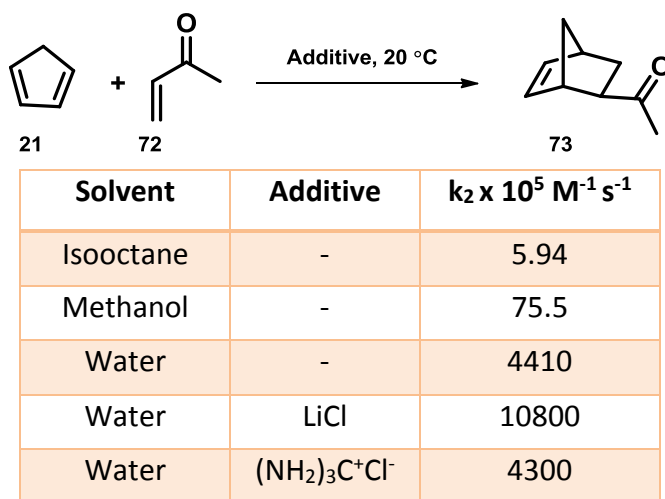
<sup>149</sup> Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901-1904.

<sup>150</sup> Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984**, *25*, 1239-1240.

<sup>151</sup> Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897-1900.

<sup>152</sup> Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983**, *48*, 3137-3139.

cyclopenta-1,3-diene **21** and methyl vinyl ketone (MVK) **72** where a hydrophobic acceleration was observed. When non polar compounds are suspended in water, their relative insolubility causes them to associate, diminishing the hydrophobic effect. This association brings the reactive partners into a close proximity which results in a contraction effect and thus increases the rate of the reaction. For that reason, any additive that increases the hydrophobic effect will increase the rate of the reaction. Table 9 summarizes the preparation of **73** in aqueous media, with or without additives. As this table shows, the reaction in water is largely accelerated (more than 700 folds) compared to hydrocarbon solvent. The rate in methanol is intermediate but closer to isooctane. LiCl is a salt that increases the hydrophobic effect i.e. “salts out” non-polar material dissolved in water, and its use dramatically increases the reaction rate, while guanidinium chloride ((NH<sub>2</sub>)<sub>3</sub>C<sup>+</sup>Cl<sup>-</sup>) decreases these interactions (“salts in”).



**Table 9: Hydrophobic effect on the rate of Diels-Alder reaction.**

Water is considered a green solvent, inexpensive, inflammable and non-toxic solvent. However, the main reason that limits its use is the lack of solubility of organic reagents in aqueous solutions. To overcome this problem, new organic polar reaction media have been developed by many groups such as the use of lithium perchlorate in diethyl ether<sup>153,154,155,156,157,158</sup> and lithium trifluoromethane-sulfonate in ether or acetonitrile.<sup>159</sup>

<sup>153</sup> Grieco, P. A.; Dai, Y. *J. Am. Chem. Soc.* **1998**, *120*, 5128-5129.

<sup>154</sup> Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595-4596.

<sup>155</sup> Grieco, P. A.; Pineiro-Nunez, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 7606-7615.

<sup>156</sup> Grieco, P. A.; Kaufman, M. D. *Tetrahedron Lett.* **1999**, *40*, 1265-1268.

<sup>157</sup> Kim, A. I.; Rychnovsky, S. D. *Angew. Chem. Int. Ed.* **2003**, *42*, 1267-1270.

<sup>158</sup> Deshpande, S. S.; Kuram, A. *Advances in Organic Synthesis* **2005**, *1*, 215-232.

<sup>159</sup> Augé, J.; Gil, R.; Kalsey, S.; Lubin-Germain, N. *Synlett* **2000**, 877-879.

As an example, in 1990, Grieco observed the influence of a solution of lithium perchlorate (5.0 M) in diethyl ether on the kinetics and stereoselectivity of the Diels-Alder reaction (Table 10).<sup>154</sup>

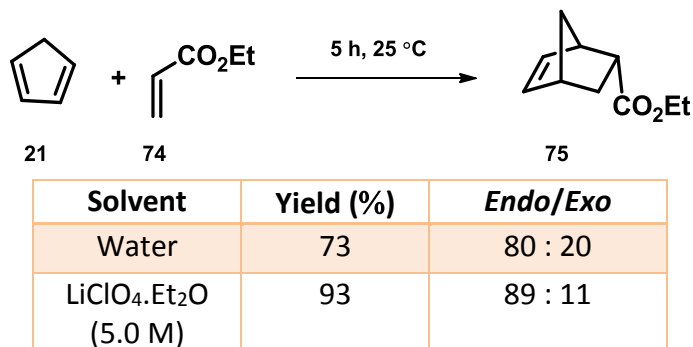


Table 10: Effect of polar media on the stereoselectivity of Diels-Alder reaction.

Initially, this acceleration of the reaction was explained by the high internal pressure generated by the solvent. Another explanation has also been invoked, relying on the Lewis acidic character of lithium cation. For the moment, the contribution of these two factors in activating the Diels-Alder reaction in LiClO<sub>4</sub>.Et<sub>2</sub>O medium has not been clearly established.<sup>160,161</sup>

In my opinion, whether perchlorates accelerate or not Diels-Alder reactions, they are toxic and their use should be avoided.<sup>162,163</sup>

## 4 Dearomatizing Cycloaddition/Annulation Reactions of Electron-Poor Arenes

The following bibliographical section will focus on the dearomatizing (4+2) and (3+2) cycloaddition and annulation reactions involving electron-depleted arenes as partners with two  $\pi$  electrons.

### 4.1 Indoles

As mentioned previously, indole derivatives are the basic substrates used in this work and thus their involvement in cycloaddition and annulation reactions will be discussed.

<sup>160</sup> Kumar, A.; Pawar, S. S. *J. Org. Chem.* **2001**, *66*, 7646-7652.

<sup>161</sup> Heydari, A. *Tetrahedron* **2002**, *58*, 6777-6793.

<sup>162</sup> Sijimola, M. R.; Jyothy, S.; Pradeepkumar, A. P.; Chandran, M. S. S.; Ghose, S. S.; Mohan, M. *Environmental Forensics* **2015**, *16*, 125-134.

<sup>163</sup> Yu, J.; Dong, H.-W.; Shi, L.-T.; Tang, X.-Y.; Liu, J.-R.; Shi, J.-H. *Food and Chemical Toxicology* **2019**, *128*, 212-222.



### 4.1.1 (4+2) dearomatizing cycloadditions and annulations

Various strategies have been developed to dearomatize indole derivatives.<sup>164,165,166</sup> The dearomatization of the latter by Diels-Alder reaction is known since the end of the 1950s.<sup>167</sup> The reactivity of indoles, substituted in position 2 or 3 by a vinyl group, as dienes in NED Diels-Alder reactions has been studied by many groups.<sup>168,169,170,171,172,173,174,175</sup> This reactivity makes it possible to achieve interesting polycyclic structures that are often found in natural products.

On the other hand, a complementary strategy which uses indole as a dienophile has been developed. Yet, this strategy has been much less studied, and up to now has been mainly studied in IED Diels-Alder reactions where C2=C3 indolic double bond reacts as an enriched dienophile.<sup>176</sup>

The reactivity of electron-poor indole derivatives as electron-poor dienophiles in NED Diels-Alder reaction was first reported in 1988 by Wenkert.<sup>61</sup> He showed the requirement for an electron-withdrawing groups in positions 1 and 3 of the indole **76** in order to obtain the cycloadducts **77** in good yields but with modest regioselectivity (Scheme 21).<sup>177</sup> Rigorous thermal conditions (typically at 195 °C for 72 h) were needed to carry out these cycloadditions.

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<sup>164</sup> Roche, S. P.; Tendoung, J.-J. Y.; Tréguier, B. *Tetrahedron* **2014**, *71*, 3549-3591.

<sup>165</sup> Ramachandran, G.; Sathiyarayanan, K. I. *Current Organocatalysis* **2015**, *2*, 14-26.

<sup>166</sup> Denizot, N.; Tomakinian, T.; Beaud, R.; Kouklovsky, C.; Vincent, G. *Tetrahedron Lett.* **2015**, *56*, 4413-4429.

<sup>167</sup> Noland, W. E.; Kuryla, W. C.; Lange, R. F. *J. Am. Chem. Soc.* **1959**, *81*, 6010-6017.

<sup>168</sup> Alonso, M. A.; López-Alvarado, P.; Avendano, C.; Menéndez, C. J. *Tetrahedron* **2003**, *59*, 2821-2830.

<sup>169</sup> Pindur, U.; Kim, M.-H.; Rogge, M.; Massa, W.; Molinier, M. *J. Org. Chem.* **1992**, *57*, 910-915.

<sup>170</sup> Diker, K.; De Maindreville, M. D.; Royer, D.; Le Provost, F.; Levy, J. *Tetrahedron Lett.* **1999**, *40*, 7463-7467.

<sup>171</sup> Laronze, M.; Sapi, J. *Tetrahedron Lett.* **2002**, *43*, 7925-7928.

<sup>172</sup> Eitel, M.; Pindur, U. *J. Org. Chem.* **1990**, *55*, 5368-5374.

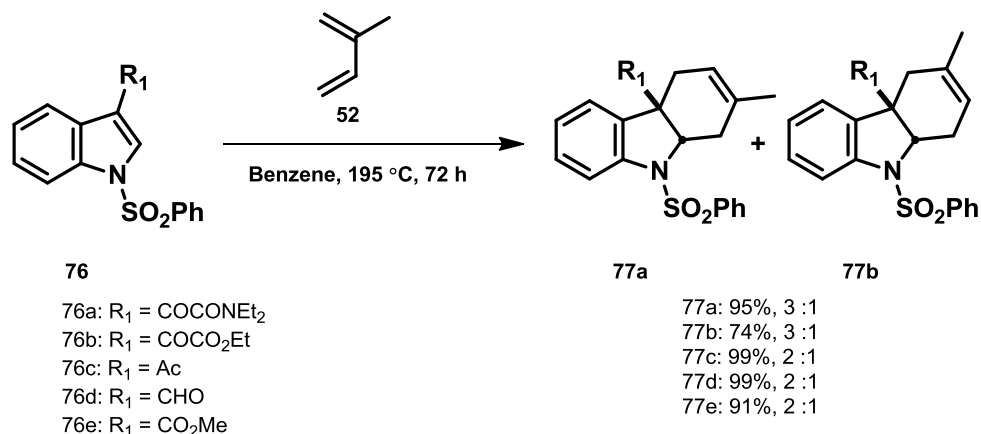
<sup>173</sup> Bai, Y.; Yuan, J.; Hu, X.; Antilla, J. C. *Org. Lett.* **2019**, *21*, 4549-4553.

<sup>174</sup> Rossi, E.; Abbiati, G.; Pirovano, V. *Eur. J. Org. Chem.* **2017**, 4512-4529.

<sup>175</sup> Cowell, J.; Abualnaja, M.; Morton, S.; Linder, R.; Buckingham, F.; Waddell, P. G.; Probert, M. R.; Hal, M. J. *RSC Adv.* **2015**, *5*, 16125-16152.

<sup>176</sup> Lily, L.; Snyder, J. K. *Advances in Cycloaddition* **1999**, *6*, 119-171.

<sup>177</sup> Reported yields are based on the recovery of the starting material.



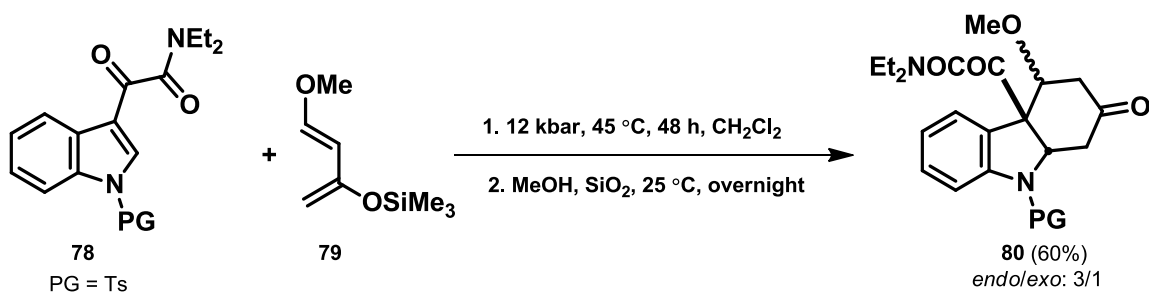
**Scheme 21: Indole derivatives as dienophiles in NED Diels-Alder reaction.**

In this article, Wenkert also showed that the addition of 0.3 equiv of AlCl<sub>3</sub> to the reaction between **76c** and isoprene **52** is beneficial, by lowering the temperature (70 °C) and increasing the regioselectivity (24 : 1).

Gribble et al. also reported the reactivity of 2- and 3-nitroindole derivatives towards various dienes, however in this case the aromatized cycloadducts were obtained in good yields.<sup>62</sup>

Yet, in order to achieve these (4+2) cycloadditions under milder conditions, high pressure activation has been considered in our laboratory.

We have reported the reaction between indole **78**, featuring a ketoamide group at position 3, and Danishefsky's diene **79** (Scheme 22).<sup>3,116</sup> The reaction took place under 12 kbar and at 45 °C and the cycloadducts **80** were obtained as a single regioisomer, in 3 : 1 mixture of *endo/exo* diastereomers in a 60% yield.



**Scheme 22: Cycloaddition between indole derivative 78 and diene 79.**

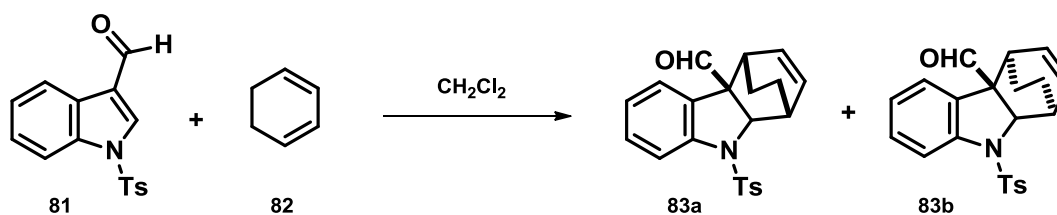
The protecting group can influence this reaction (Table 11) by which the carbamate protected indole (entry 3) showed to be more reactive than the ones protected by tosyl or triflyl (entries 1

and 2).<sup>178</sup> This is explained by the unexpected ability of the Boc group to achieve more efficient delocalization of the nitrogen lone pair and thus to decrease the aromaticity of the indole.

| Entry | Protecting group | Time (h) | Conversion (%) | Endo/Exo | Yield (%) |
|-------|------------------|----------|----------------|----------|-----------|
| 1     | Ts               | 8        | 31             | 75 : 25  | -         |
| 2     | Tf               | 8        | 66             | 90 : 10  | 60        |
| 3     | Boc              | 8        | 87             | 90 : 10  | 75        |

Table 11: Effect of protecting groups on the reaction between **78** and **79**.

HP can also activate the reaction between indole derivative **81** and 1,3-cyclohexadiene **82** (Table 12).<sup>116</sup> A 4 : 1 mixture of *endo* **83a** and *exo* **83b** cycloadducts were obtained under thermal conditions (entry 1). However, this ratio increased to 96 : 4 (entry 2) under a pressure of 16 kbar. The same ratios were observed when the reaction was activated by zinc chloride alone at 70 °C (entry 3). Bi-activation by pressure and the same Lewis acid gave the best result in term of reactivity and selectivity (> 98 : 2, entry 4).<sup>179</sup>



| Entry | Conditions                               | Yield (%) | Endo : Exo |
|-------|--|-----------|------------|
| 1     | 72 h, 195 °C                             | 25        | 80 : 20    |
| 2     | 16 kbar, 48 h, 50 °C                     | 50        | 96 : 4     |
| 3     | ZnCl <sub>2</sub> , 120 h, 70 °C         | 48        | 96 : 4     |
| 4     | 16 kbar, ZnCl <sub>2</sub> , 48 h, 25 °C | 62        | > 98 : 2   |

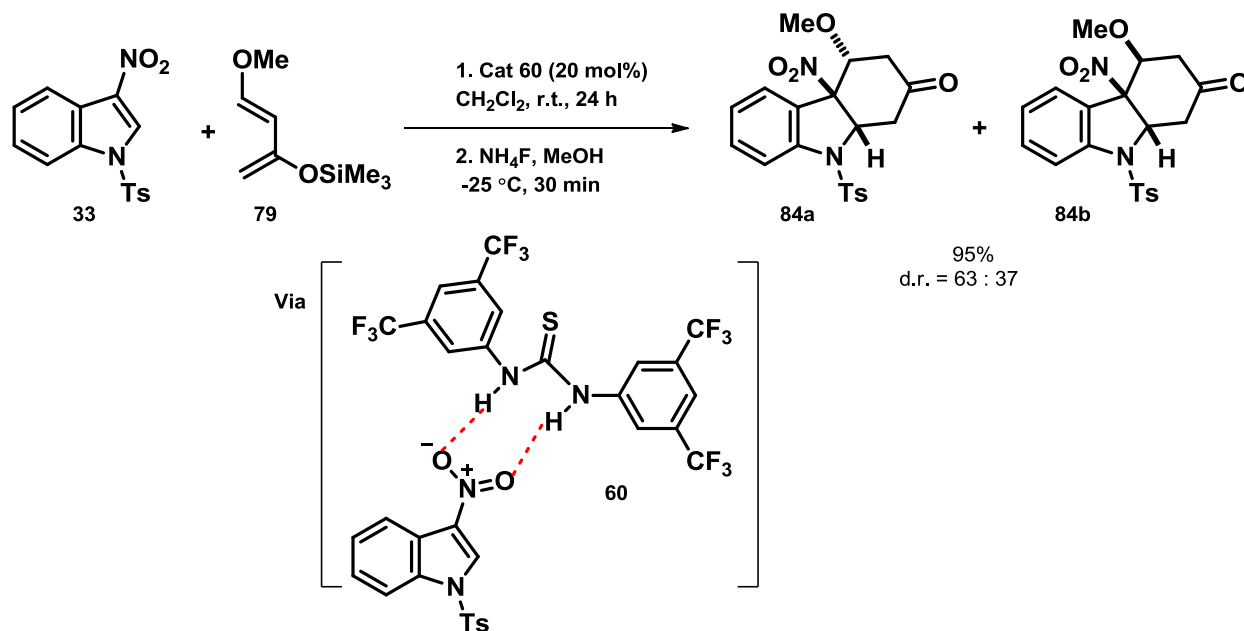
Table 12: High pressure activated Diels-Alder reaction of indole **81**.

Our group has also reported in 2015 the thiourea-catalyzed dearomatizing (4+2) cycloaddition of 3-nitroindole **33** (Scheme 23).<sup>110</sup> Performing NED cycloaddition of 3-nitroindole and Danishefsky's diene **79** in presence of various organocatalysts at room temperature was possible. As shown in Scheme 23 the reaction proceeds in presence of 20 mol% of the achiral Schreiner's thiourea catalyst **60** to give the corresponding cycloadduct **84** in a 95% yield and 63 : 37 diastereomeric ratio. In attempts to perform this reaction in an enantioselective manner, the

<sup>178</sup> Chataigner, I.; Panel, C.; Gérard, H.; Piettre, S. R. *Chem. Commun.* **2007**, 3288-3290.

<sup>179</sup> The *exo* stereoisomer being undetectable by <sup>1</sup>H NMR spectrometry analysis.

reaction was tested in presence of different chiral catalysts. However, the facial discrimination of the catalyst was not efficient and the enantioselectivities remained low until now.



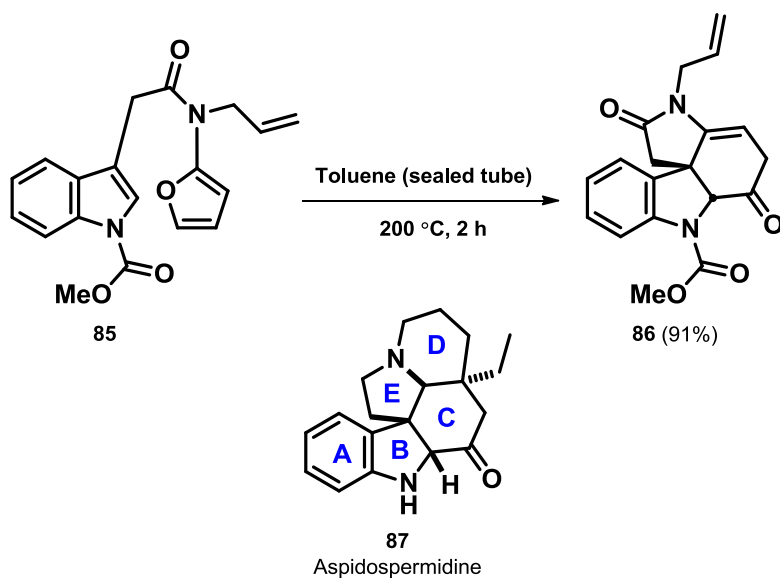
**Scheme 23: Thiourea-catalyzed reaction between 3-nitroindole and Danishefsky's diene.**

The dienophilic behavior of the indole in Diels-Alder reaction was also an interest of many other groups.<sup>62,108,180,181</sup> An intramolecular reaction involving the indole core allowed the synthesis of advanced tetracyclic indolines, and indole alkaloids could then be obtained in an elegant way.<sup>63,65,66,67</sup> Padwa used this strategy in attempt to construct the *ABCE* tetracyclic core found in both the *Strychnos* and *Aspidosperma* families **87** (Scheme 24).<sup>182</sup> In this case, probably because the higher reactivity due to the intramolecular character of this reaction, no electron-withdrawing group in position 3 of the indole nucleus was required. The reaction still needed high temperatures but for shorter times.

<sup>180</sup> Biolatto, B.; Kneeteman, M.; Mancini, P. *Tetrahedron Lett.* **1999**, *40*, 3343-3346.

<sup>181</sup> Biolatto, B.; Kneeteman, M.; Mancini, P. M. *Molecules* **2000**, *5*, 393-395.

<sup>182</sup> Lynch, S. M.; Bur, S. K.; Padwa, A. *Org. Lett.* **2002**, *4*, 4643-4645.

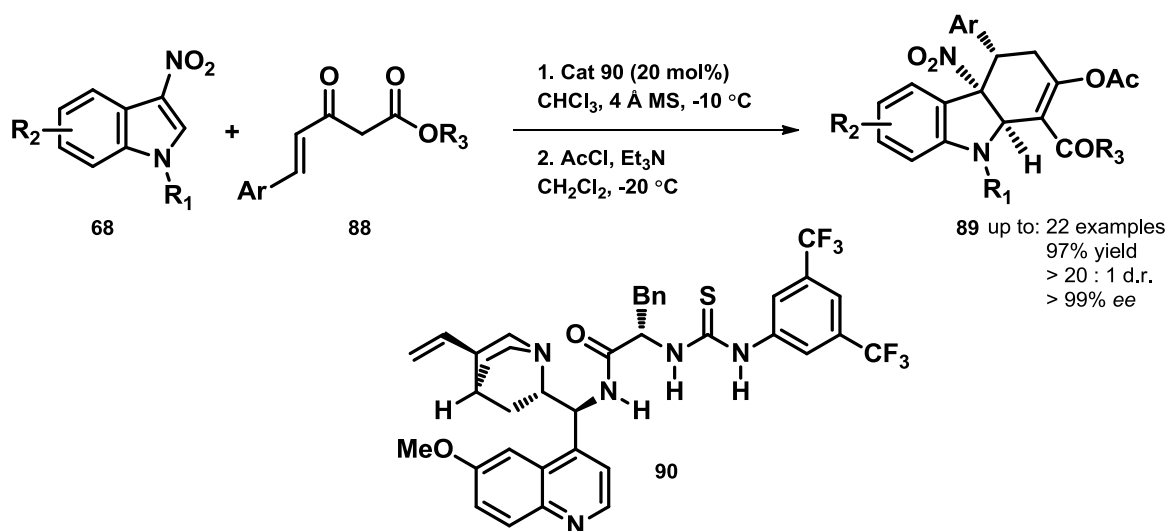


**Scheme 24:** Example on intramolecular Diels-Alder reaction by Padwa.

Indole derivatives can also undergo (4+2) annulation reactions, which are based on vinylogous Michael addition/cyclization steps. The application of this strategy to indole derivatives is still limited, but it will obviously develop in the coming years.

In 2017, Yuan et al. reported the dearomatizing (4+2) annulation of 3-nitroindoles **68** with Nazarov reagents **88** in presence of the hydrogen-bonding bifunctional thiourea catalyst **90** (Scheme 25).<sup>183</sup> The bifunctional nature of the catalyst allows the activation of 3-nitroindole by the formation of hydrogen-bonding and the simultaneous activation of the Nazarov reagent. This dual activation is crucial for the reactivity and the stereocontrol. The chiral hydrocarbazole derivatives **89** were obtained in good to excellent yields with excellent diastereo- and enantioselectivities.

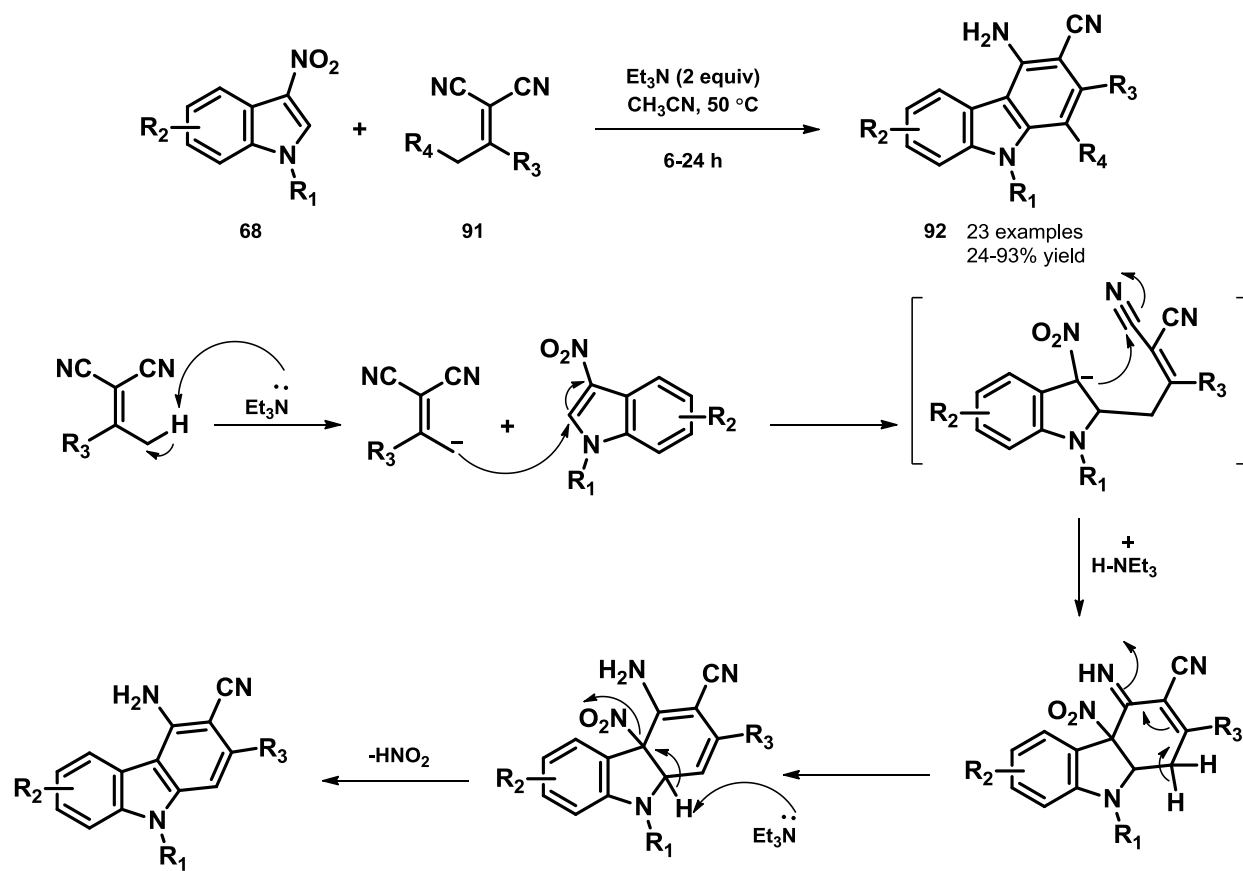
<sup>183</sup> Yue, D.-F.; Zhao, J.-Q.; Chen, X.-Z.; Zhou, Y.; Zhang, X.-M.; Xu, X.-Y.; Yuan, W.-C. *Org. Lett.* **2017**, *19*, 4508-4511.



Scheme 25: Asymmetric dearomative (4+2) annulation of 3-nitroindoles.

More recently, Yang et al. reported the (4+2) annulation of 3-nitroindoles **68** with alkylidene malononitriles **91**.<sup>184</sup> Carbazol-4-amine derivatives **92** were obtained via four-steps: vinylogous Michael addition, cyclization, isomerization and elimination of HNO<sub>2</sub> (Scheme 26).

<sup>184</sup> Cao, D.; Ying, A.; Mo, H.; Chen, D.; Chen, G.; Wang, Z.; Yang, J. *J. Org. Chem.* **2018**, *83*, 12568-12574.



Scheme 26: (4+2) annulation of 3-nitroindole by alkylidene malononitriles and the plausible mechanism.

#### 4.1.2 (3+2) dearomatizing cycloadditions and annulations

(3+2) cycloaddition/annulation reactions are reactions between a 1,3-dipole and a dipolarophile to form a five-membered ring. These reactions are activated via similar activation modes used in (4+2) Diels-Alder cycloaddition/annulation reactions.

(3+2) cycloaddition/annulation reactions of 3-nitroindoles (acting as dipolarophiles) and 1,3-dipoles have been successfully reported in the literature. 1,3-dipoles include azomethine ylides, azomethine imines, trimethylenemethanes, vinyl-cyclopropanes, -azirines, -epoxides, isothiocyanato oxindoles, thiol and 2,3-dienoate derivatives.

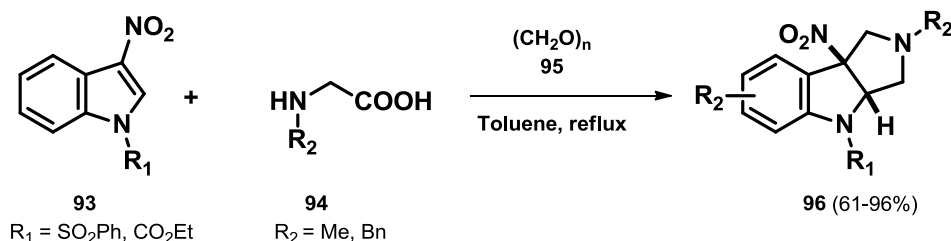
Many groups including ours were interested in the reactivity of 3-nitroindole derivatives towards the unstabilized azomethine ylides<sup>185,186</sup> and azomethine imines.<sup>187</sup>

<sup>185</sup> Lee, S.; Diab, S.; Queval, P.; Sebban, M.; Chataigner, I.; Piettre, S. R. *Chem. Eur. J.* **2013**, *19*, 7181-7192.

<sup>186</sup> Awata, A.; Arai, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 10462-10465.

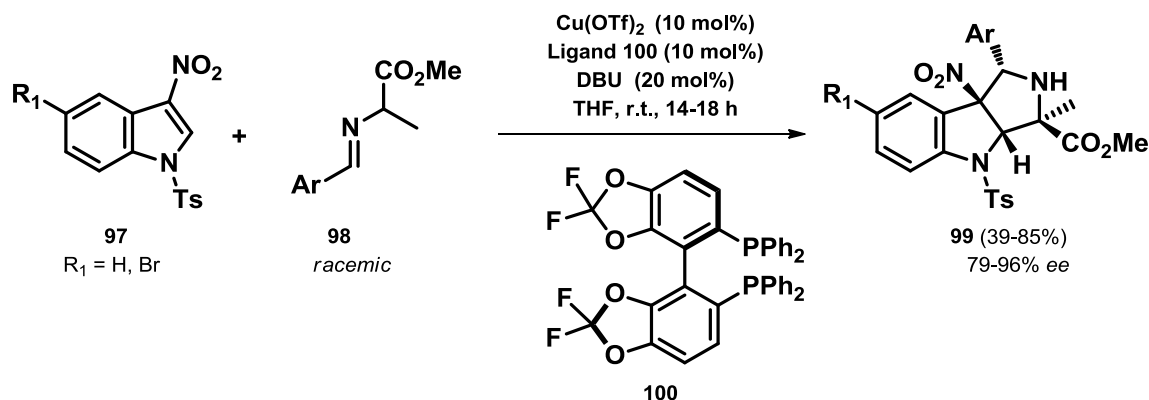
<sup>187</sup> Liu, X.; Wang, K.; Zhang, J.; Wang, R. *Green Chem.* **2017**, *19*, 82-87.

Gribble et al. initially reported the cycloaddition reaction of unstabilized azomethine ylides with 2- and 3-nitroindoles **93** to form racemic pyrroloindolines **96** in good to excellent yields (Scheme 27).<sup>188</sup> The unstabilized azomethine ylides, in this case, were generated *in situ* from the corresponding  $\alpha$ -amino acids **94** and paraformaldehyde **95** in refluxing toluene.



Scheme 27: Reactivity of azomethine ylides with nitroindole derivatives.

More recently, Stanley et al. reported the diastereo- and enantioselective (3+2) dearomative cycloadditions of alanine derived azomethine ylides **98** with 3-nitroindoles **97**.<sup>189</sup> These reactions gave pyrroloindolines **99** with four contiguous stereogenic centers thanks to a catalyst generated from  $\text{Cu}(\text{OTf})_2$  and (*R*)-fluorophos ligand **100** (Scheme 28).



Scheme 28: Enantioselective (3+2) dearomative cycloadditions of 3-nitroindole derivatives.

(3+2) cycloadditions and annulations of indole derivatives using trimethylenemethanes,<sup>190</sup> isothiocyanato oxindoles<sup>191</sup> and thiol<sup>192</sup> derivatives have been also reported.

For example, Yuan et al. described the organocatalytic asymmetric (3+2) annulation reaction of 3-isothiocyanato oxindoles **101** and 3-nitroindoles **102** in the presence of amino-

<sup>188</sup> Roy, S.; Kishbaugh, T. L. S.; Jasinski, J. P.; Gribble, G. W. *Tetrahedron Lett.* **2007**, *48*, 1313-1316.

<sup>189</sup> Gerten, A. L.; Stanley, L. M. *Org. Chem. Front.* **2016**, *3*, 339-343.

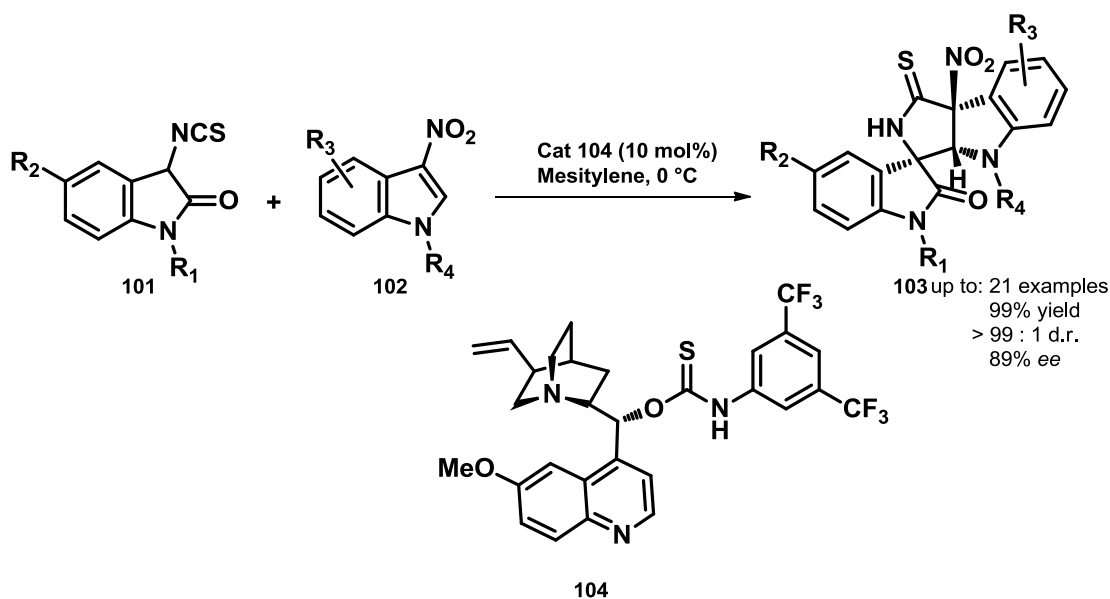
<sup>190</sup> Trost, B. M.; Ehmke, V.; O'Keefe, B. M.; Bringley, D. A. *J. Am. Chem. Soc.* **2014**, *136*, 8213-8216.

<sup>191</sup> Zhao, J.-Q.; Wu, Z.-J.; Zhou, M.-Q.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2015**, *17*, 2050-5023.

<sup>192</sup> Chen, X.-M.; Lei, C.-W.; Yue, D.-F.; Zhao, J.-Q.; Wang, Z.-H.; Zhang, X.-M.; Xu, X.-Y.; Yuan, W.-C. *Org. Lett.* **2019**, *21*, 5452-5456.



thiocarbamate catalyst **104**.<sup>193</sup> Polycyclic spirooxindoles **103** were obtained with good yields and enantioselectivities (Scheme 29).



**Scheme 29: (3+2) annulation reaction between 101 and 102.**

Vinyl-cyclopropanes,<sup>194,195,196</sup> -aziridines,<sup>197,198</sup> -epoxides<sup>199</sup> can also dearomatize 3-nitroindole derivatives via (3+2) annulations under palladium catalysis.

By way of example, Shi et al. reported the catalytic asymmetric dearomative (3+2) cycloaddition reaction of 3-nitroindoles **68** with vinylcyclopropanes **105**.<sup>200</sup> The chiral indoline scaffolds **106** were generated in good yields and high enantioselectivities (Scheme 30).

<sup>193</sup> Zhao, J.-Q.; Zhou, M.-Q.; Wu, Z.-J.; Wang, Z.-H.; Yue, D.-F.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2015**, *17*, 2238-2241.

<sup>194</sup> Laugeois, M.; Ling, J.; Féraud, C.; Michelet, V.; Ratovelomanana-Vidal, V.; Vitale, M. R. *Org. Lett.* **2017**, *19*, 2266-2269.

<sup>195</sup> Gee, Y. S.; Rivinoja, D. J.; Wales, S. M.; Gardiner, M. G.; Ryan, J. H.; Hyland, C. J. T. *J. Org. Chem.* **2017**, *82*, 13517-13529.

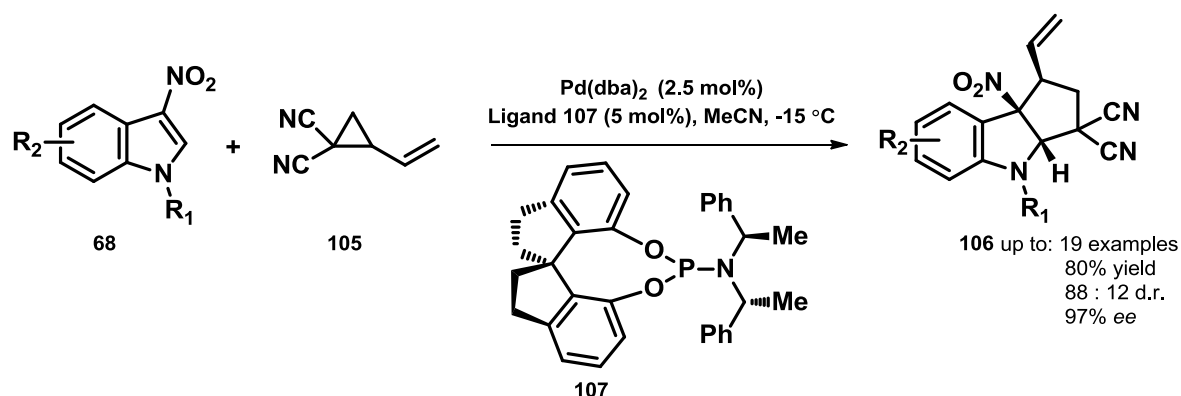
<sup>196</sup> Zhang, J.-Q.; Tong, F.; Sun, B.-B.; Fan, W.-T.; Chen, J.-B.; Hu, D.; Wang, X.-W. *J. Org. Chem.* **2018**, *83*, 2882-2891.

<sup>197</sup> Rivinoja, D. J.; Gee, Y. S.; Gardiner, M. G.; Ryan, J. H.; Hyland, C. J. T. *ACS Catal.* **2017**, *7*, 1053-1056.

<sup>198</sup> Suo, J.-J.; Liu, W.; Du, J.; Ding, C.-H.; Hou, X.-L. *Chem. Asian J.* **2018**, *13*, 959-963.

<sup>199</sup> Cheng, Q.; Zhang, F.; Cai, Y.; Guo, Y.-L.; You, S.-L. *Angew. Chem. Int. Ed.* **2018**, *57*, 2134-2138.

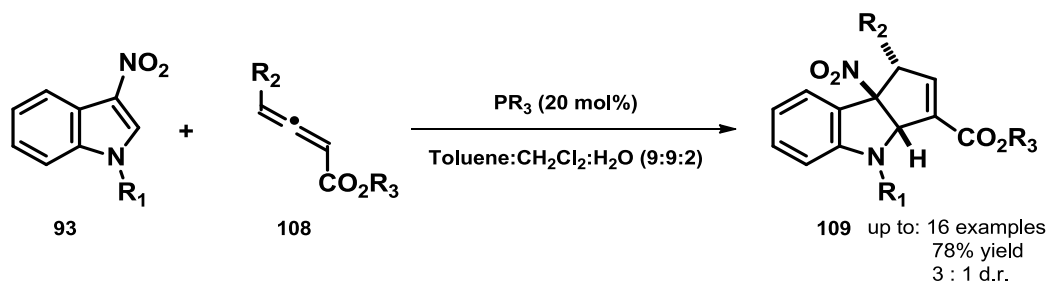
<sup>200</sup> Sun, M.; Zhu, Z.-Q.; Gu, L.; Wan, X.; Mei, G.-J.; Shi, F. *J. Org. Chem.* **2018**, *83*, 2341-2348.



Scheme 30: (3+2) cycloaddition reaction of 3-nitroindoles with vinylcyclopropanes.

Very recently, many groups reported the reactivity of 3-nitroindoles towards allenates in presence of chiral or non-chiral phosphine catalysts in (3+2) dearomatizing annulation processes.<sup>201,202,203,204,205</sup>

In this context, our group reported the dearomatization of 3-nitroindoles **93** with highly  $\gamma$ -functionalized allenates **108** in formal (3+2) cycloadditions.<sup>206</sup> The functionalized  $\alpha$ -cycloadducts **109** were exclusively obtained in good yields with *cis/trans* diastereoselectivities up to 3 : 1 (Scheme 31).



Scheme 31: Formal (3+2) cycloadditions involving 3-nitroindole derivatives.

<sup>201</sup> Wang, H.; Zhang, J.; Tu, Y.; Zhang, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 5422-5426.

<sup>202</sup> Jin, L.-W.; Jiang, F.; Chen, K.-W.; Du, B.-X.; Mei, G.-J.; Shi, F. *Org. Biomol. Chem.* **2019**, *17*, 3894-3901.

<sup>203</sup> Cerveri, A.; Faza, O. N.; López, C. S.; Grilli, S.; Monari, M.; Bandini, M. *J. Org. Chem.* **2019**, *84*, 6347-6355.

<sup>204</sup> Liu, K.; Wang, G.; Cheng, S.-J.; Jiang, W.-F.; He, C.; Ye, Z.-S. *Tetrahedron Lett.* **2019**, *60*, 1885-1890.

<sup>205</sup> Li, K.; Gonçalves, T. P.; Huang, K.-W.; Lu, Y. *Angew. Chem. Int. Ed.* **2019**, *58*, 5427-5431.

<sup>206</sup> Birbaum, L.; Gillard, L.; Gerard, H.; Oulyadi, H.; Vincent, G.; Moreau, X.; De Paolis, M.; Chataigner, I. *Chem. Eur. J.* **2019**, *25*, 1-7.

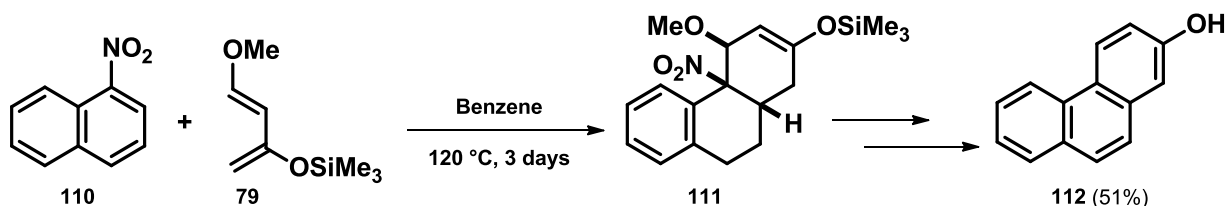
## 4.2 Aromatic compounds

The dearomatization of most arenes takes place via NED Diels-Alder cycloadditions where they act as dienes because of their electron-richness.<sup>1</sup> The reactivity of electron-depleted arenes as dienophiles in these reactions is more scarcely described in the literature.

### 4.2.1 (4+2) cycloadditions and annulations

The first use of nitronaphthalene in cycloaddition reaction goes back to 1955, where Hurd proved that 1-nitronaphthalene can react with anthracene at 300 °C.<sup>207</sup>

Well after this work, Mancini et al. published a short publication on the use of nitronaphthalene as dienophile in Diels-Alder reaction.<sup>208</sup> For instance, the reaction between 1-nitronaphthalene **110** and Danishefsky's diene **79** could be performed under thermal activation conditions (120 °C). The aromatized cycloadduct **112** was obtained in 51% yield, after a cycloaddition/rearomatization processes (Scheme 32).



Scheme 32: 1-nitronaphthalene as dienophile in NED Diels-Alder reaction.

After this publication, Mancini reported a full work on the reactivity of nitronaphthalene derivatives towards various dienes under thermal conditions.<sup>209,210,211</sup> From the series of dinitronaphthalenes, 1,3-dinitronaphthalene **113** gave a mixture of aromatized cycloadducts (**114**, **115**) when reacting with Danishefsky's diene **79** (Scheme 33). The presence of the two nitro groups in a 1,3 relation favors the cycloaddition at C3-C4 bond over C1-C2 bond and thus **114** is obtained as the major product. Noteworthy, even if an excess of diene was employed, only the products resulting from a mono-cycloaddition were isolated.

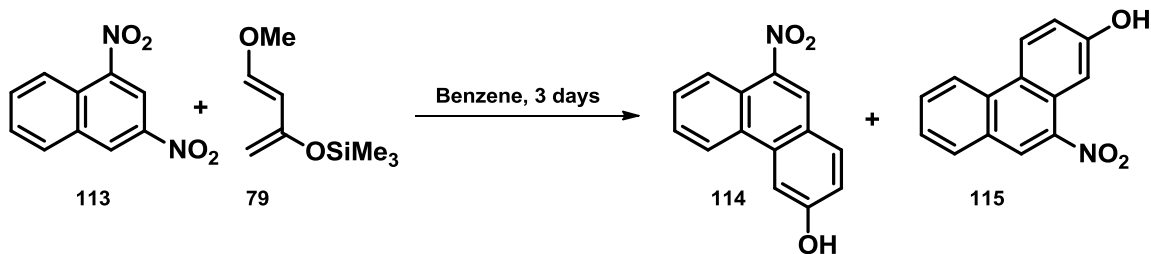
<sup>207</sup> Hurd, C. D.; Juel, L. H. *J. Am. Chem. Soc.* **1955**, *77*, 601-606.

<sup>208</sup> Paredes, E.; Biolatto, B.; Kneeteman, M.; Mancini, P. M. *Tetrahedron Lett.* **2000**, *41*, 8079-8082.

<sup>209</sup> Paredes, E.; Biolatto, B.; Kneeteman, M.; Mancini, P. *Tetrahedron Lett.* **2002**, *43*, 4601-4603.

<sup>210</sup> Paredes, E.; Brasca, R.; Kneeteman, M.; Mancini, P. M. E. *Tetrahedron* **2007**, *63*, 3790-3799.

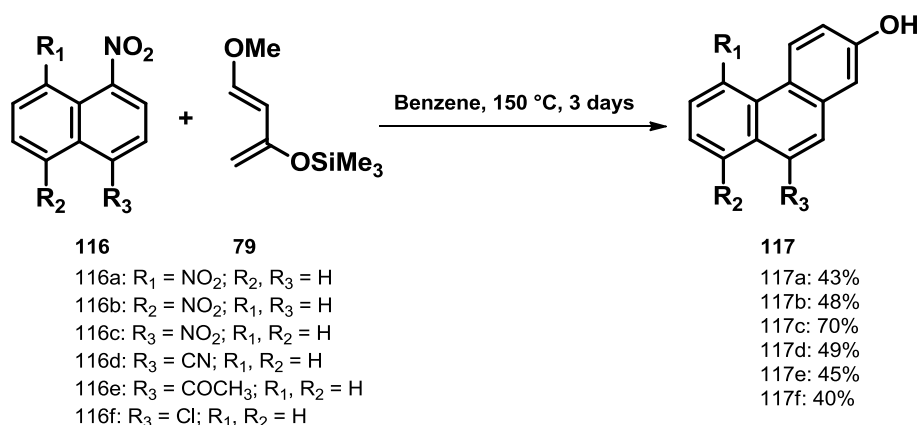
<sup>211</sup> Domingo, L. R.; Aurell, M. J.; Kneeteman, M. N.; Mancini, P. M. *Journal of Molecular Structure: THEOCHEM* **2008**, *853*, 68-76.

**Conditions:**

|        |     |     |
|--------|-----|-----|
| 120 °C | 57% | 12% |
| 150 °C | 80% | 5%  |

**Scheme 33: Dearomatization of 1,3-dinitronaphthalene by Mancini.**

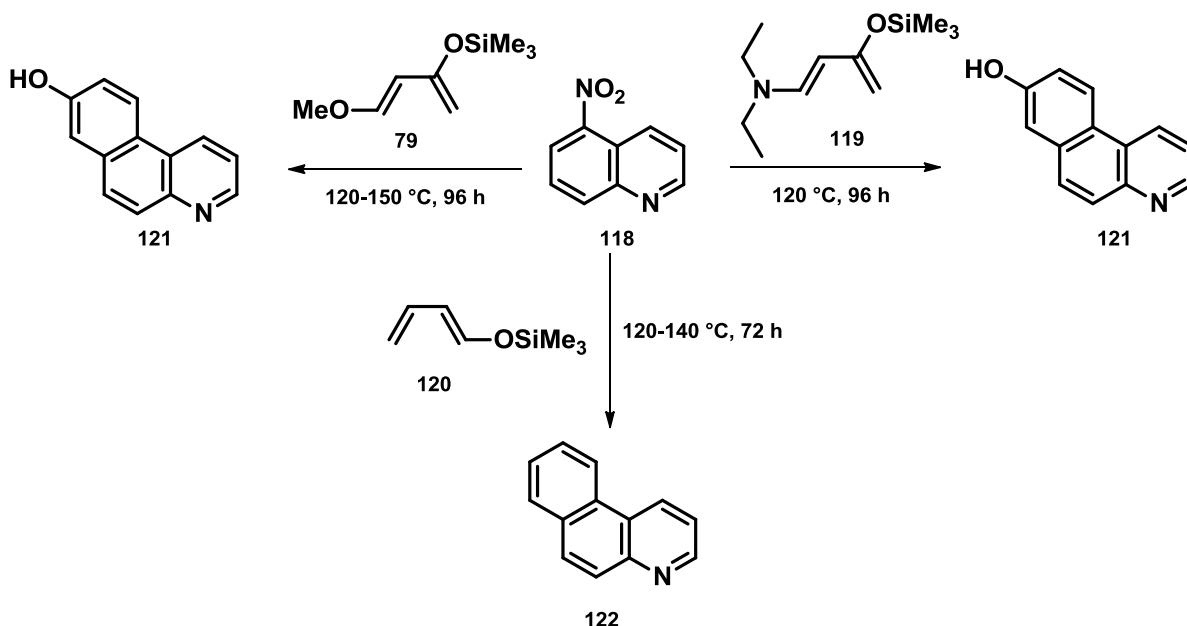
Other nitronaphthalenes **116** were also tested (Scheme 34).

**Scheme 34: Reaction of nitronaphthalenes with Danishefsky's diene.**

The reactions of 1,8- (**116a**), 1,5- (**116b**) and 1,4-dinitronaphthalene (**116c**) yielded the corresponding phenanthrene derivatives (**117a**, **117b**, and **117c**). The lower yields in case of 1,8-dinitronaphthalene **116a** could be explained by the steric effects derived from the proximity of the nitro groups, which caused considerable overcrowding in the molecule. Here again, in these reactions the regioselectivity is complete and mono-cycloaddition is observed.

Under similar conditions, nitronaphthalenes bearing electron-withdrawing groups such as cyano (**116d**), acetyl (**116e**) and chloro (**116f**) in the para-position also produced the expected phenanthrenes (**117d-f**). Nitronaphthalenes having an additional electron-withdrawing group, of different nature, react as dienophiles in these reactions and the selectivity is governed by the more electron-withdrawing nitro substituent.

The same group then reported the use of nitroquinoline as dienophiles in Diels-Alder reaction (Scheme 35).<sup>212</sup> 5- and 8-nitroquinolines showed to react as dienophiles in Diels-Alder reaction to give the corresponding aromatized product. The isolation of the intermediate cycloadduct was never achieved under these conditions. These reactions are initialized by a Diels-Alder reaction followed by hydrolysis and elimination of nitrous acid/elimination of methanol or amine or oxidation depending on the cycloadduct.



Scheme 35: Reactivity of 5-nitroquinoline towards different dienes.

Terrier et al. reported the use of the “super-electrophilic” nitrobenzofurazans and benzofuroxans (10  $\pi$  electron heteroatomic substrates which exhibit an extremely high electrophilic character) in dearomatizing Diels-Alder annulation reaction.<sup>213,214,215,216</sup> As illustrated in the example below, the reaction involving 4,6-dinitrobenzofuroxan **123** and the 1-trimethylsilyloxybuta-1,3-diene **120** is a stepwise mechanism (Scheme 36).

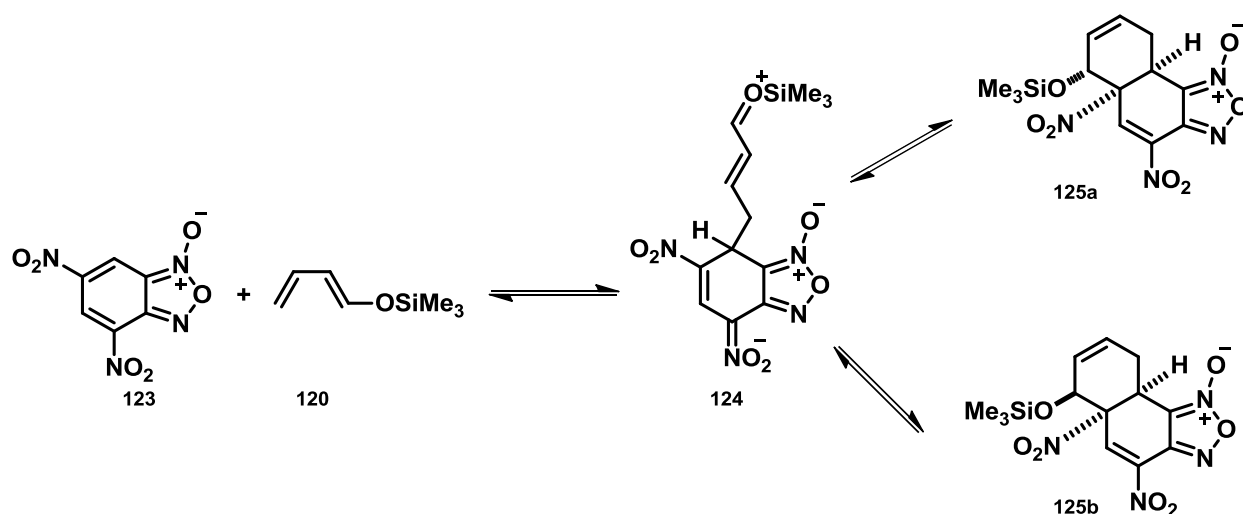
<sup>212</sup> Cancian, S.; Kneeteman, M. N.; Mancini, P. M. E. *International Electronic Conference on Synthetic Organic Chemistry*, **2010**, MDPI AG, Basel, Switz.

<sup>213</sup> Vichard, D.; Alvey, L. J.; Terrier, F. *Tetrahedron Lett.* **2001**, *42*, 7571-7574.

<sup>214</sup> Lakhdar, S.; Terrier, F.; Vichard, D.; Berionni, G.; El Guesmi, N.; Goumont, R.; Boubaker, T. *Chem. Eur. J.* **2010**, *16*, 5681-5690.

<sup>215</sup> Steglenko, D. V.; Kletsky, M. E.; Kurbatov, S. V.; Tatarov, A. V.; Minkin, V. I.; Goumont, R.; Terrier, F. *Chem. Eur. J.* **2011**, *17*, 7592-7604.

<sup>216</sup> Terrier, F.; Dust, J. M.; Buncel, E. *Tetrahedron* **2012**, *68*, 1829-1843.

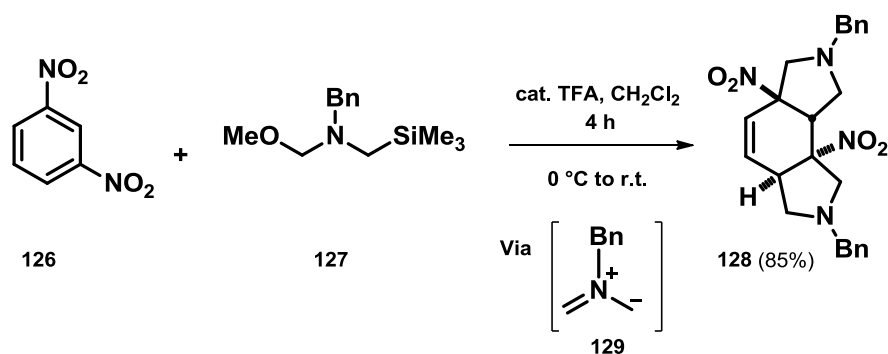


Scheme 36: Dearomatizing Diels-Alder reaction of 4,6-dinitrobenzofuroxan.

#### 4.2.2 (3+2) dearomatizing cycloadditions and annulations

The energy barrier linked to the aromaticity of benzenic compounds proved to be a constraint in using them in (3+2) cycloaddition/annulation reactions. To our knowledge, only two examples were reported in the literature.

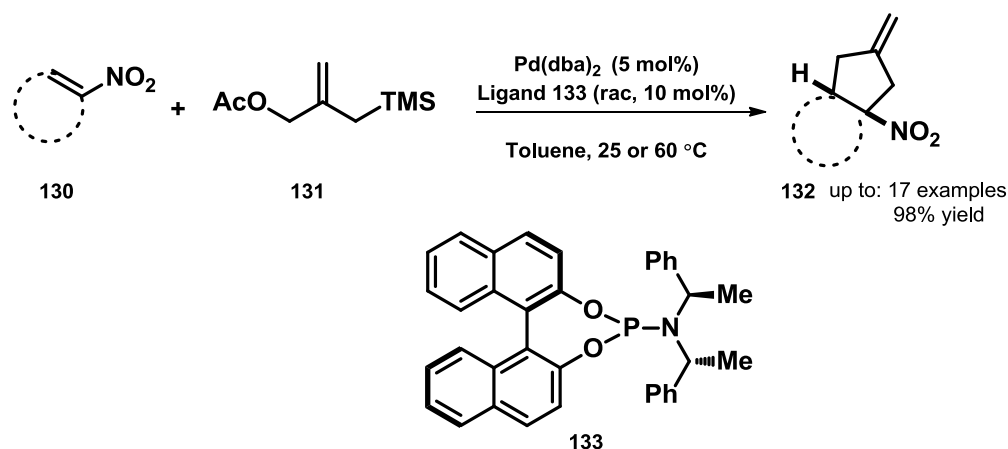
The first example was reported by our group using the non-stabilized azomethine ylides **129** (Scheme 37).<sup>185,217</sup> Different electron-poor aromatics were dearomatized using this way and the polycyclic structures that contain pyrrolidinyl ring(s) were isolated in good yields.

Scheme 37: Dearomatization reaction of 1,3-dinitrobenzene with *N*-benzyl azomethine ylide.

The other one was reported by Trost et al. using palladium catalysis.<sup>190</sup> Trost et al. achieved the dearomative formal (3+2) cycloaddition reaction of various nitroarenes **130** with

<sup>217</sup> Lee, S.; Chataigner, I.; Piettre, S. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 472-476.

trimethylenemethane **131** and the dearomatized polycyclic products **132** were isolated without subsequent rearomatization (Scheme 38).



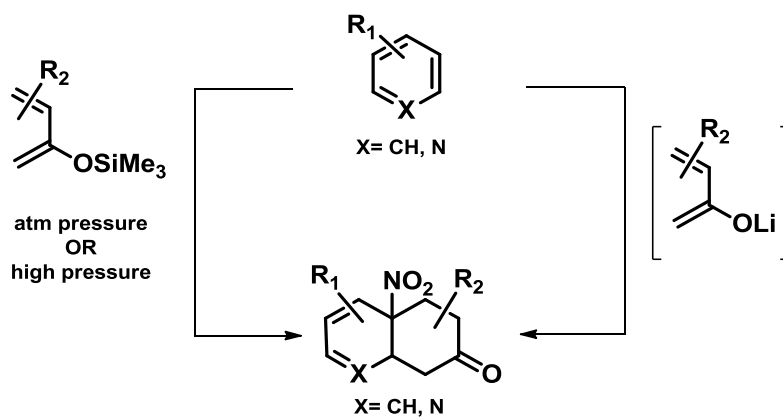
Scheme 38: Dearomative (3+2) cycloaddition reaction of nitroarenes.

## 5 Conclusion

As we have seen in this introductory part, the dearomatization strategies are important and allow access to complex 3D structures useful in the synthesis of natural and pharmaceutical products. These strategies have grown in the recent decades and will likely continue to develop in the future. Among these strategies, the Diels-Alder reactions are one of the most interesting strategies.

As for the Diels-Alder reactions and as we have discussed, several activation methods exist (chemical or physical). However, the sensitivity of the starting materials and/or the obtained cycloadducts restricted their use and thus limited the scope of these reactions. Recent developments in the Diels-Alder reaction allow alternative activation modes to be considered to achieve these cycloadditions under milder conditions.

In this manuscript, we will focus on the NED Diels-Alder reactions where electron poor aromatics are used as dienophiles. Firstly, their reactivity towards different silyloxydienes will be studied under atmospheric or high pressure. Then, in a separate chapter the nucleophilic activation of the diene, through the formation of its lithium enolate, as well as the results obtained from its reactivity towards these aromatics will be discussed (Scheme 39).



Scheme 39: Dearomatization of electron-poor aromatics.





## **Chapter II. Reactivity of Silyoxylated Dienes towards Electron-Poor Aromatics**



*«If somebody tells you a rule, break it.  
That's the only thing to move things forward »  
Hans Zimmer*



## 1 Introduction

The electrophilic character of aromatics increases in the presence of electron-withdrawing groups. Such a substitution renders possible the reaction of C=C aromatic double bonds as electron-poor dienophiles in NED Diels-Alder cycloaddition reactions leading to their dearomatization. In this context, the reaction of electron-rich dienes such as silyloxydienes and in particular Danishefsky's diene with electron-poor arenes has been studied. Whenever the classical activation methods (heat, acid) are not sufficient to activate the Diels-Alder reaction, the use of HP can become effective.

In this chapter, the reactivities of different silyloxydienes toward various electron-poor aromatics will be discussed.

### 1.1 Danishefsky's diene

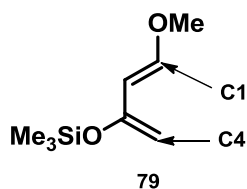
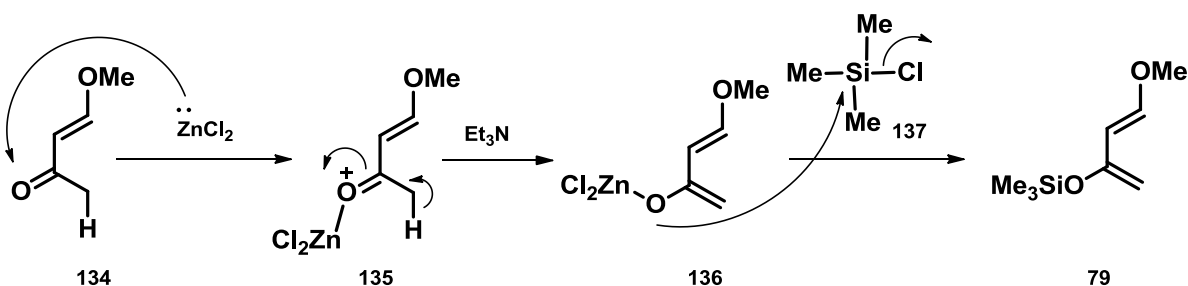


Figure 13: Structure of Danishefsky's diene.

In 1974, Danishefsky et al. developed an electron-rich diene bearing two oxygenated substituents. Due to its significance, it has become the so-called "Danishefsky's diene" **79** (Figure 13). It was first synthesized by the reaction of trimethylsilyl chloride **137** with 4-methoxy-2-buten-1-one **134** in the presence of zinc chloride (Scheme 40).<sup>218</sup>



Scheme 40: Synthesis of Danishefsky's diene.

<sup>218</sup> Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807-7808.

Danishefsky's diene or *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene **79** (IUPAC name) is an organosilicon compound. The structure of this functional diene, the double enol ether function placed in a 1,3-position, explains its exceptional use in particular in total synthesis of natural products, because it increases its reactivity while allowing the introduction of interesting functionalities.<sup>219,220</sup> The combined effects of the two oxygenated substituents indeed operate in a synergetic way, enhancing the reactivity and allowing a totally regioselective cycloadditions in most cases.

Noticeably, there are variants on Danishefsky's diene which have been reported in the literature (Figure 14).<sup>221</sup>

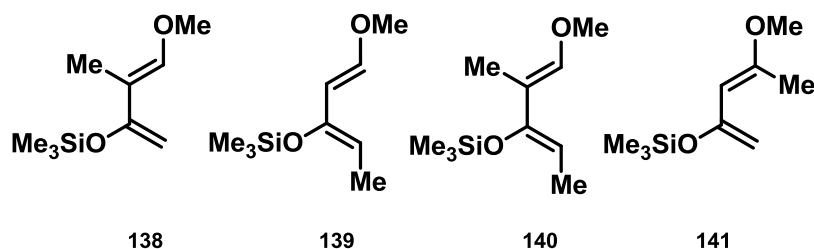


Figure 14: Structures of various modified Danishefsky's dienes.

The reactivity of a diene in NED Diels-Alder reaction is known to be increased by the presence of electron-donating groups, planarity of the system and its ability to adopt a *s-cis* conformation. In this context, the Danishefsky's diene is considered a reactive diene when compared to other dienes<sup>222</sup> (Figure 15) and it is a good candidate for Diels-Alder<sup>216,223,224</sup> and hetero-Diels-Alder reactions.<sup>225</sup>

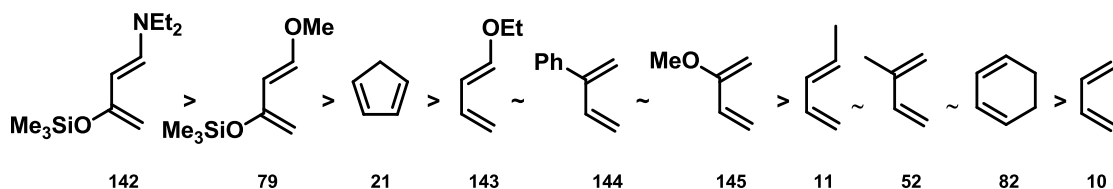


Figure 15: Relative reactivities of dienes with maleic anhydride.

<sup>219</sup> Kumamoto, T.; Kitani, Y.; Tsuchiya, H.; Yamaguchi, K.; Seki, H.; Ishikawa, T. *Tetrahedron* **2007**, *63*, 5189-5199.

<sup>220</sup> Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1380-1419.

<sup>221</sup> Taheri Kal Koshvandi, A.; Heravi, M. M. *Tetrahedron: Asymmetry* **2017**, *28*, 1506-1556.

<sup>222</sup> Huisgen, R. *Chemistry of the Alkenes*; Wiley: New York, 1976.

<sup>223</sup> Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. J. *Am. Chem. Soc.* **1979**, *101*, 6996-7000.

<sup>224</sup> Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668-1698.

<sup>225</sup> Takeda, Y.; Hisakuni, D.; Lin, C.-H.; Minakata, S. *Org. Lett.* **2015**, *17*, 318-321.

## 1.2 Mayr's database

The concepts of electrophilicity and nucleophilicity have an enormous impact on understanding and predicting a wide range of organic reactions. From these we can mention, nucleophilic and electrophilic substitution reactions, Michael additions, acylation and Diels-Alder reactions.

Quantitative scales of electrophilicity and nucleophilicity are useful resources for both the rationalization of chemical reactivity and the prediction of new reactions. In 1994, Mayr et al. proposed a scale to find these parameters and thus to explain diverse types of reactions.<sup>226,227</sup> It was demonstrated that the kinetic rate constants of reactions for series of electrophile-nucleophile combinations can fit the following linear relationship:

$$\log k_{20^{\circ}\text{C}} = s_N (N + E)$$

Where  $N$  and  $E$  are respectively the nucleophilicity and electrophilicity parameters and  $s$  is the nucleophile-dependent slope parameter.

Until now, Mayr's Database of Reactivity Parameters comprises information for 1177 nucleophiles and 311 electrophiles spanning a nucleophilicity range:  $-8.80 \leq N \leq 30.82$  and an electrophilicity range:  $-24.69 \leq E \leq 8.02$ .<sup>228</sup>

Using this database, the nucleophilicity of various 1,3-dienes and silylated enol ethers were reported.<sup>227,229</sup> The results are summarized in Figure 16.

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<sup>226</sup> Mayr, H.; Patz, M. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 938-957.

<sup>227</sup> Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500-9512.

<sup>228</sup> Mayr's Database website. <http://www.cup.lmu.de/oc/mayr/reaktionsdatenbank/>.

<sup>229</sup> Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66-77.



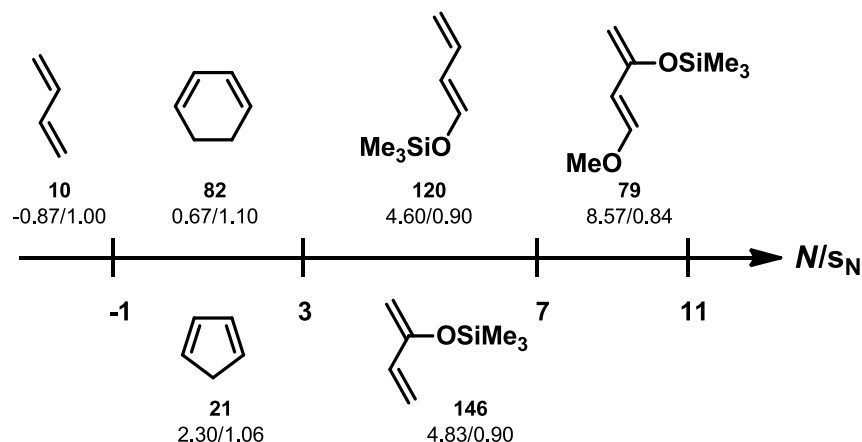


Figure 16: Mayr's scale for some nucleophiles.

From this figure, in the series of 1,3-dienes; cyclopentadiene **21** is the most reactive with  $N = 2.30$ . Passing to the silylated dienes, 1-(trimethylsilyloxy)-1,3-butadiene **120** and 2-(trimethylsilyloxy)-1,3-butadiene **146** have similar reactivities. These in turn are much more reactive than 1,3-butadiene **10**. Danishefsky's diene **79** has the highest nucleophilicity value with  $N = 8.57$ . This is due to the presence of the additional donating methoxy group at position 1. This nucleophilic character makes it a good candidate for the Diels-Alder reaction.

Based on these parameters, wide range of electrophiles and nucleophiles can be expected to react at room temperature just if  $(E + N) \geq -5$ .

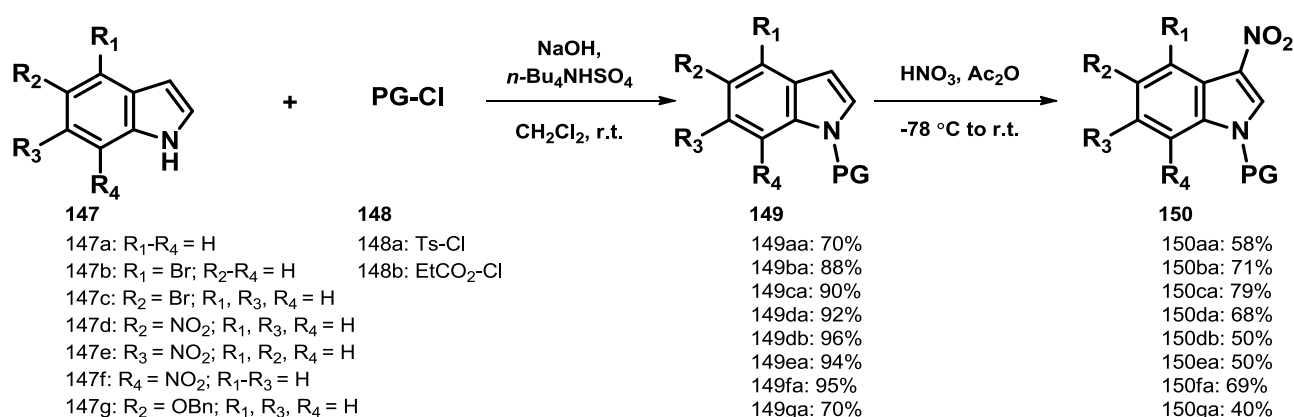
For example, in the example shown in Scheme 36, the  $E$  value for 4,6-dinitrobenzofuroxan **123** is  $-5.06$ , and the  $N$  value for the nucleophile 1-(trimethylsilyloxy)buta-1,3-diene **120** is  $N = 4.60$ . By applying  $(E + N) \geq -5$  we find  $-0.46$ ; thus, if the reaction is of the first order, it should take place at room temperature, which is indeed the case.

## 2 Results and Discussion

### 2.1 3-nitroindole derivatives and Danishefsky's diene

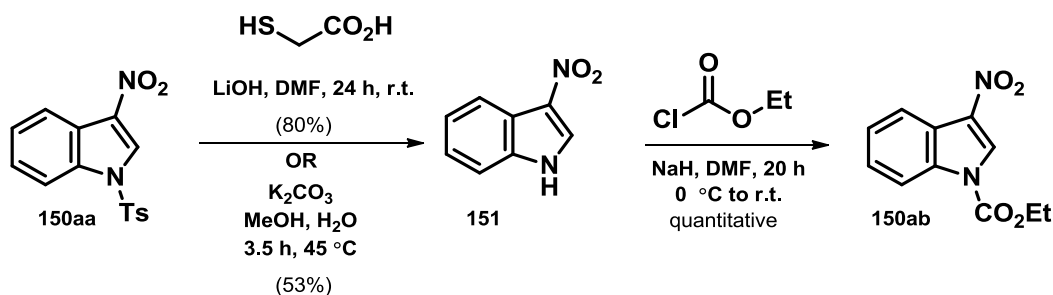
As discussed in this brief introduction, the Danishefsky's diene is considered a reactive ( $N = 8.57$ ) and interesting diene to be used in Diels-Alder reactions. On the other hand, most cycloadducts obtained from the reaction of nitroarenes and this diene tend to aromatize after cycloaddition when thermal activation is employed.<sup>62,208,209,210,211,212</sup> The use of smoother reaction conditions should disfavor the aromatization process and allow the isolation of the dearomatized cycloadducts. We thus wondered whether nitroindole derivatives were sufficiently electrophilic to react at room temperature, in the absence of any activator, with weak nucleophiles such as Danishefsky's diene.

Before starting this work, nitroindole derivatives were synthesized from the corresponding commercial indoles according to a procedure reported in the literature, in 2 steps.<sup>197</sup> Following the protection of the nitrogen atom, nitration was carried out using nitronium acetate as nitrating agent (Scheme 41).



**Scheme 41: General procedure for indole derivatives preparation.**

Ethyl-3-nitro-1*H*-1-carboxylate **150ab** was synthesized from 3-nitro-1-tosyl-1*H*-indole **150aa** by a deprotection<sup>230,231</sup>/protection sequence since the classical conditions have led to a mixture of products and low yields in this case (Scheme 42).

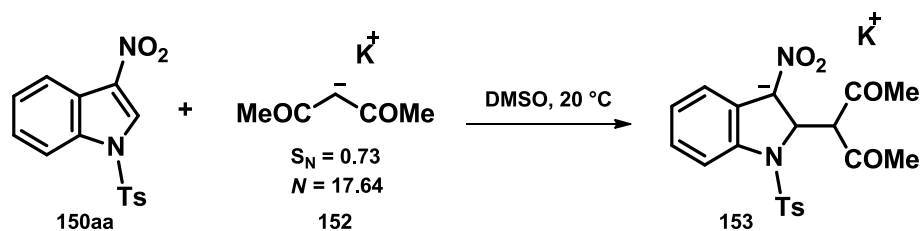


**Scheme 42: Synthesis of ethyl-3-nitro-1*H*-1-carboxylate.**

A physicochemical study, in collaboration with Dr. Sami Lakhdar at the LCMT laboratory in Caen, was then envisaged to evaluate the electrophilicity of 3-nitroindoles. The kinetic investigations were performed by Dr. Ludovik Noël-Duchesneau by studying the reaction of 3-nitro-1-tosyl-1*H*-indole **150aa** with carbanion **152** in DMSO at 20 °C (Scheme 43).

<sup>230</sup> Haskins, M. C.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 599-601.

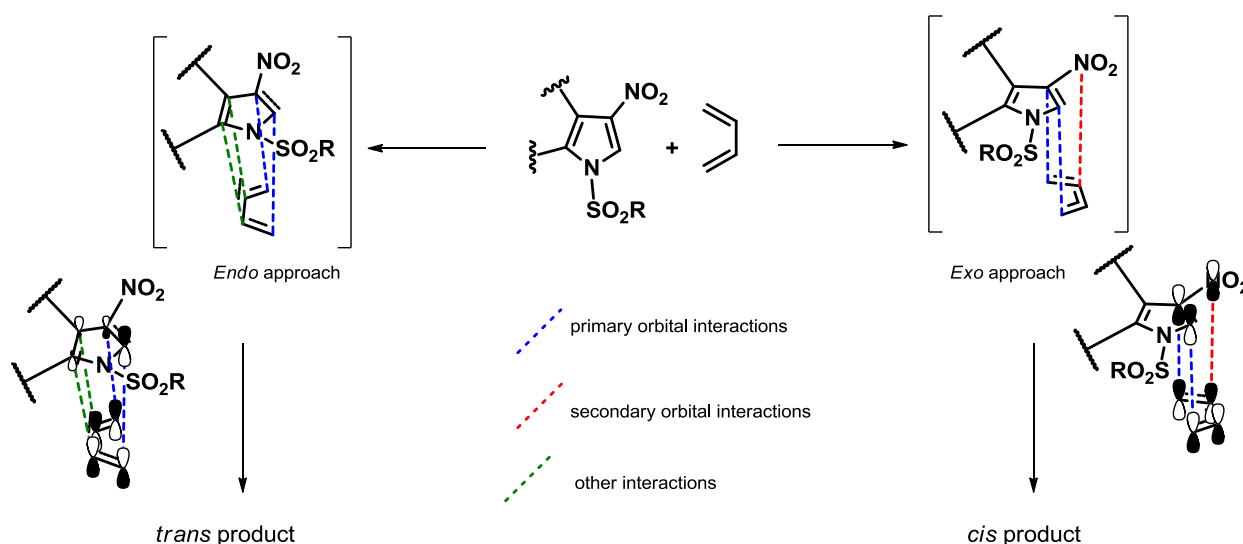
<sup>231</sup> The other procedure was developed in our laboratory.



Scheme 43: Reaction of 3-nitroindole with carbanion 152.

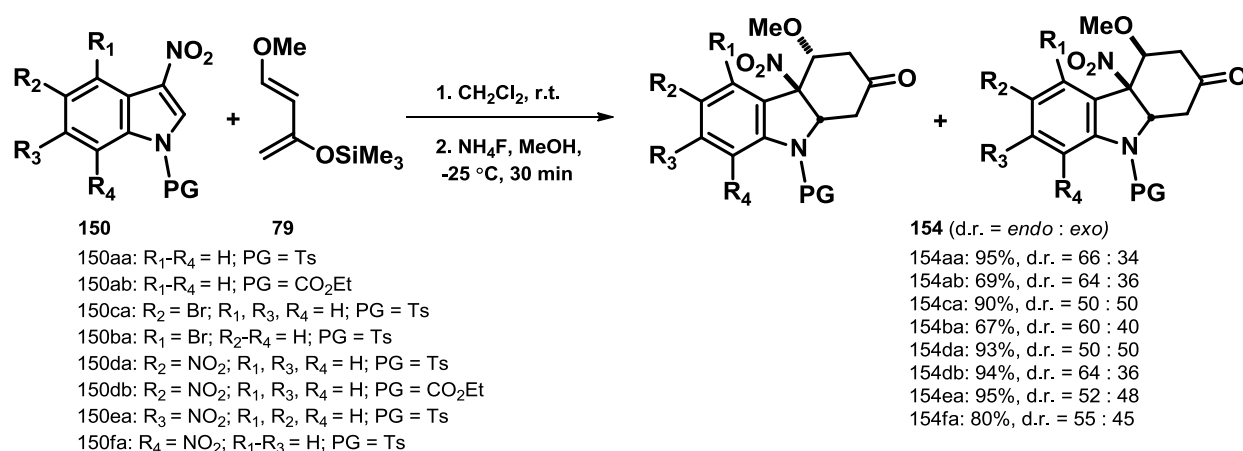
The electrophilicity value was estimated to be  $-13.30$  for **150aa**, meaning that the electrophilicity of this aromatic compound was unexpectedly high, in between the one of the non-aromatic 4-methoxy-beta-nitrostyrene ( $E = -14.70$ ) and 4-nitro-beta-nitrostyrene ( $E = -12.37$ ). In light of these investigations and by using Mayr's rule of thumb ( $E + N \geq -5$ ), one can anticipate **150aa** to react with nucleophiles characterized by a  $N \geq 8.8$ . If we consider a first order reaction, the reactivity limit of **150aa**, at room temperature, is thus expected with mild nucleophiles such as silyoxydienes and for instance Danishefsky's diene ( $N = 8.57$ ,  $s_N = 0.84$ ). It should be noted that Mayr's rule could be applicable in this case since DFT calculations indeed showed that the reaction is a stepwise reaction (see end of this part).

Regardless the mechanism that takes place in this case, the reaction between nitroheteroaromatic compound and any diene could proceed via two approaches (*endo/exo*) leading to a mixture of diastereoisomers (Figure 17).


 Figure 17: *Endo/Exo* approaches of a model 3-nitroheteroaromatic and diene.

The *endo* approach could be rationalized by the favored secondary orbital interactions between the CH of the diene and the aromatic part of the heteroaromatics leading to the *trans* diastereomer. While the *exo* approach could be favored thanks to the interactions between the

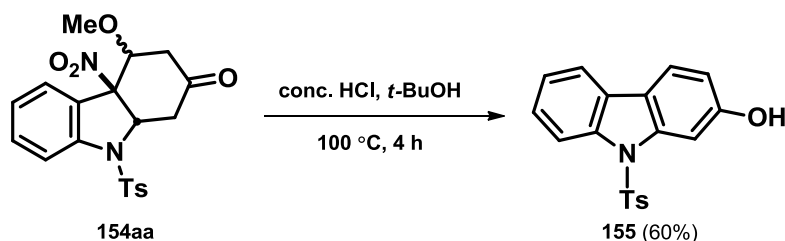
CH of the diene and the nitrogen of the nitro group yielding the *cis* diastereomer. So, in this case no preference for one approach over the other.



**Scheme 44: Reactivity of 3-nitroindoles with Danishefsky's diene.**

With this in mind, we first reacted **150aa** with a slight excess of **79** (1.2 equiv in dichloromethane at room temperature). After 24 hours, we were pleased to observe the total conversion of the starting aromatic substrate. After a smooth hydrolysis of the silylated enol ether using NH<sub>4</sub>F at -25 °C, the expected dearomatized cycloadduct **154aa** was isolated as a 66 : 34 mixture of diastereomers (*endo/exo*) in a global 95% yield (Scheme 44). This result confirmed the high electrophilicity of 3-nitroindole derivative **150aa**. The diastereoselectivity of the process is however low, revealing a poor control of the *endo* vs the *exo* approaches.

Removal of the methoxy group of β-methoxycyclohexanone part of **154aa** was then tried in the presence of conc. HCl in *t*-BuOH according to a procedure developed in our laboratory. In our case, it led to the completely aromatized product **155**, isolated in a 60% yield, and confirmed the sensitivity of these cycloadducts (Scheme 45).



**Scheme 45: Aromatization of cycloadduct 154aa.**

It is important to mention that, the reactivity of 3-nitroindole **150aa** towards Danishefsky's diene **79** was already reported under thermal conditions<sup>62</sup> to give mainly the aromatized cycloadduct. This reaction could also take place under hyperbaric conditions<sup>108</sup> or in presence of

a thiourea organocatalyst<sup>110</sup> to give the corresponding dearomatized cycloadduct. However, the results obtained here show the possibility of performing this reaction at ambient temperature and atmospheric pressure, in reagentless conditions, without any additives or activation.

With this result in hand, we then tested ethyl-3-nitro-1*H*-1-carboxylate **150ab**. Under the same conditions (1.2 equiv of **79**), only 62% of the starting indole was converted into the expected cycloadduct **154ab** after 3 days. However, in presence of 2.4 equiv of **79** the conversion increased to 92% within 2 days and the cycloadduct **154ab** was isolated in a 69% yield and a 64 : 36 diastereomeric ratio (Scheme 44). The isolated adduct kept the tetrasubstituted carbon atom at the ring junction and all the functionalities brought by the diene and the formation of the rearomatized product, similar to the one isolated by Gribble et al.,<sup>62</sup> was never observed.

5-bromo-3-nitro-1-tosyl-1*H*-indole **150ca** was then examined. In the presence of 1.2 equiv of **79**, 70% conversion can be achieved after 3 days. However, when doubling the diene quantity, a total conversion was observed within 2 days. The cycloadduct **154ca** was isolated in a 90% yield and a 50 : 50 diastereomeric ratio (Scheme 44).

When reacting the more hindered 4-bromo-3-nitro-1-tosyl-1*H*-indole **150ba** under the same conditions, no reaction was observed and only starting materials were recovered (Table 13, entries 1 and 2). Gratifyingly, under thermal conditions (entries 3 and 4) the expected cycloadduct **154ba** was obtained in a 67% yield as a 60 : 40 mixture of diastereomers.

| Entry    | Diene (equiv) | Conditions  | Conversion (%) | d.r.    | Yield (%) |
|----------|---------------|-------------|----------------|---------|-----------|
| <b>1</b> | 1.2           | 48 h, r.t.  | -              | -       | -         |
| <b>2</b> | 2.4           | 24 h, r.t.  | -              | -       | -         |
| <b>3</b> | 1.2           | 24 h, 42 °C | 90             | 50 : 50 | 67        |
| <b>4</b> | 2.4           | 24 h, 42 °C | 100            | 60 : 40 | 67        |

Table 13: Conditions for the reaction between **150ba** and diene **79**.

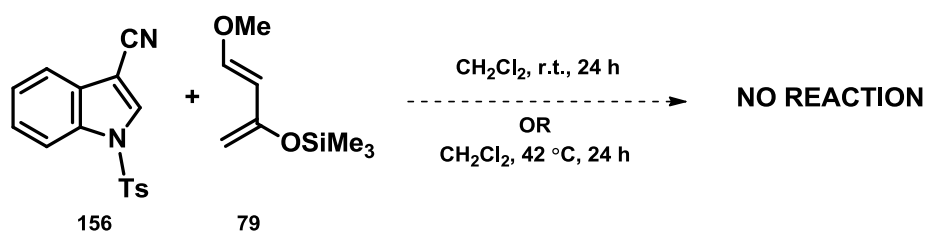
Indoles bearing additional nitro group on the 6-membered ring (**150da**, **150db**, **150ea** and **150fa**) were then tested. The reactivity/selectivity of the process was not altered involving regioselectively the C2=C3 moiety of the 5-membered heteroaromatic part as the dienophilic part. Expectedly, **150db** and **150fa** appeared to be more reactive than **150da**, leading to nearly complete conversions within 24 h while **150ea** was only slightly less reactive (Table 14, compare entries 3, 6 and 2, 5).

The cycloadducts **154da**, **154db**, **154ea** and **154fa** were isolated in a 93%, 94%, 95% and 80% yield respectively as nearly 50 : 50 diastereomeric mixtures (Scheme 44, Table 14).

| Entry | Indole | Diene (equiv) | Conditions | Conversion (%) | d.r.    | Yield (%) |
|-------|--------|---------------|------------|----------------|---------|-----------|
| 1     | 150da  | 1.2           | 24 h       | 50             | 45 : 55 | -         |
| 2     | 150da  | 1.2           | 48 h       | 95             | 50 : 50 | 93        |
| 3     | 150db  | 1.2           | 24 h       | 100            | 64 : 36 | 94        |
| 4     | 150ea  | 1.2           | 24 h       | 68             | 57 : 43 | -         |
| 5     | 150ea  | 2.4           | 48 h       | 100            | 52 : 48 | 95        |
| 6     | 150fa  | 1.2           | 24 h       | 95             | 55 : 45 | 80        |

Table 14: Results obtained from the reaction of indole derivatives 150da-150fa and diene 79.

Going to indole derivative **156** with a less electron-withdrawing cyano group at position 3, no reaction took place at room temperature. Upon heating at 42 °C for 24 hours, starting materials were also recovered (Scheme 46). This shows that a strong electron-withdrawing group such as the nitro group is needed to perform the Diels-Alder reaction in absence of any other activation.



Scheme 46: Reactivity of 1-tosyl-1H-indole-3-carbonitrile towards Danishefsky's diene.

## 2.2 Benzo-furans and -thiophenes and Danishefsky's diene

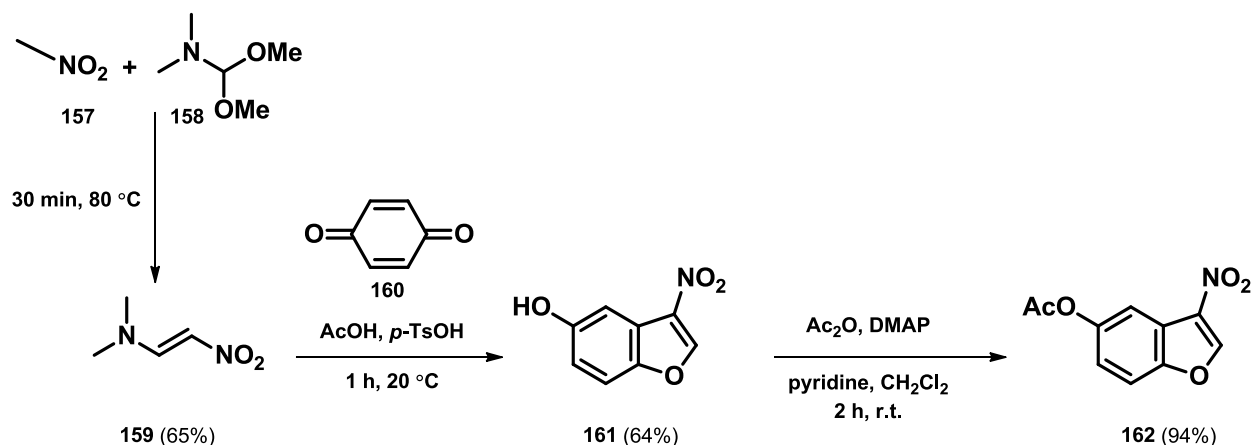
Away from indole derivatives, we wondered if other heteroaromatics, more precisely benzofuran and benzothiophene derivatives, could react to give the corresponding dearomatized cycloadducts. These heterocycles have great potential in pharmaceutical research and serve as versatile scaffolds in drug design.<sup>232,233</sup>

3-nitrobenzofuran-5-yl-acetate **162** can be obtained directly from the commercially available 3-nitrobenzofuran-5-ol **161** by protection of the aromatic hydroxyl group. It can also be obtained from the reaction between 1,4-benzoquinone **160** and dimethylamino nitroethylene **159**,

<sup>232</sup> Li, W.; Li, J.; Wu, Y.; Rancati, F.; Vallese, S.; Raveglia, L.; Wu, J.; Hotchandani, R.; Fuller, N.; Cunningham, K.; Morgan, P.; Fish, S.; Krykbaev, R.; Xu, X.; Tam, S.; Goldman, S. J.; Abraham, W.; Williams, C.; Sypek, J.; Mansour, T. S. *J. Med. Chem.* **2009**, *52*, 5408-5419.

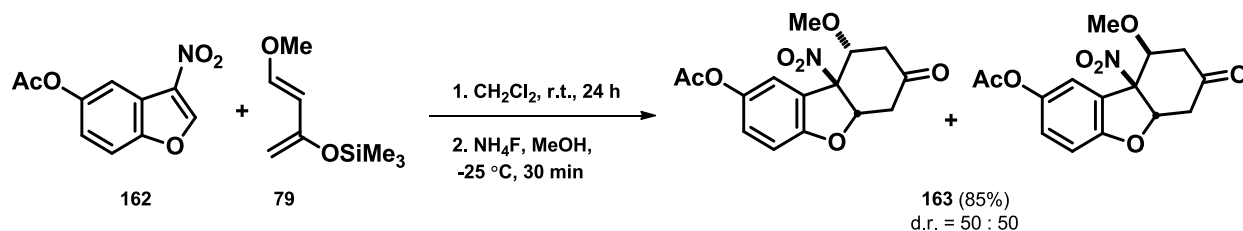
<sup>233</sup> Patpi, S. R.; Pulipati, L.; Yogeewari, P.; Sriram, D.; Jain, N.; Sridhar, B.; Murthy, R.; Devi T, A.; Kanlivendi, S. V.; Kantevari, S. *J. Med. Chem.* **2012**, *55*, 3911-3922.

obtained from nitromethane **157** and the acetal of dimethylacetamide **158**, followed by the same protection (39% overall yield) (Scheme 47).<sup>234,235</sup>



Scheme 47: Synthesis of 3-nitrobenzofuran-5-yl-acetate.

Compound **162** reacted with 1.2 equiv of Danishefsky's diene **79** under the same conditions and gave, after hydrolysis, the cycloadduct **163** in a 85% yield and a 50 : 50 diastereomeric ratio (Scheme 48). The aromaticity of benzofurans is known to be less important than the one of indoles and, in this respect, this result is perfectly in line with the ones described above. It is however worth mentioning that the dienophilic behavior of 3-nitrobenzofuran towards Danishefsky's diene was already reported by Mancini et al.<sup>236,237</sup> at 140 °C, and that the corresponding aromatized cycloadduct was isolated.



Scheme 48: Outcomes of the reaction between benzofuran derivative and diene **79**.

We then envisaged the reaction with benzothiophene derivatives bearing less electron-withdrawing group at position 3 and an additional nitro group on the 6-membered ring. These

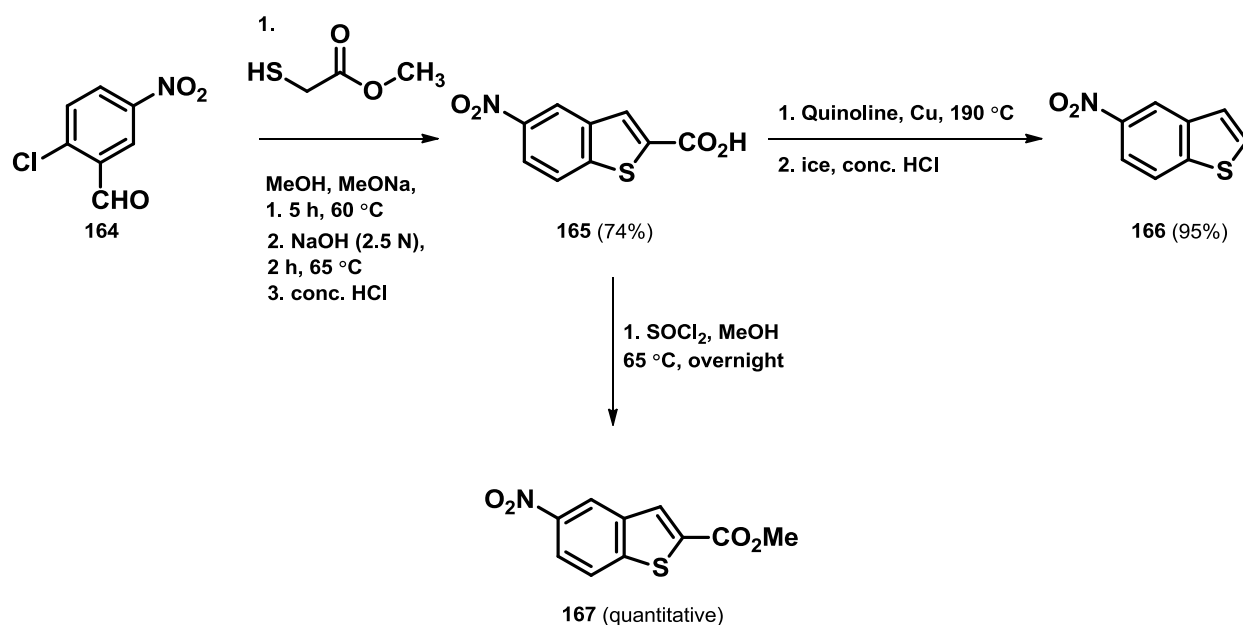
<sup>234</sup> Nicolaou, K. C.; Snyder, S. A.; Huang, X.; Simonsen, K. B.; Koumbis, A. E.; Bigot, A. *J. Am. Chem. Soc.* **2004**, *126*, 10162-10173.

<sup>235</sup> Lyubchanskaya, V. M.; Granik, V. G. *Khimiya Geterotsiklicheskikh Soedinenii* **1990**, *5*, 597-600.

<sup>236</sup> Della Rosa, C. D.; Sanchez, J. P.; Kneeteman, M. N.; Mancini, P. M. E. *Tetrahedron Lett.* **2011**, *52*, 2316-2319.

<sup>237</sup> Della Rosa, C. D.; Mancini, P. M. E.; Kneeteman, M. N.; Lopez Baena, A. F.; Suligov, M. A.; Domingo, L. R. *J. Mol. Struct.* **2015**, *1079*, 47-53.

substrates are indeed easily available, according to a reported procedure as described in Scheme 49.<sup>238</sup>



**Scheme 49: Syntheses of benzothiophene derivatives.**

Upon reacting **166** and **167** with **79** under normal or thermal conditions (42 °C, DCM reflux), expectedly, no reaction was observed. 3-nitrobenzothiophene was also tested, but the reaction failed under the same conditions. This weak reactivity of benzothiophene derivatives, even when bearing a nitro group at position 3, could be explained by their higher aromatic character in comparison to indole and benzofuran derivatives, leading to a much lower reactivity.

To sum-up this part, various 3-nitroindole derivatives were shown to be reactive towards Danishefsky's diene in a NED Diels-Alder reactions. The corresponding cycloadducts were isolated in good yields as a mixture of *endo/exo* diastereoisomers. In this case, the reactivities can be predicted and supported by finding their electrophilicity values (*E*) since this reaction is a stepwise mechanism as found by DFT calculations done by Prof. Isabelle Chataigner on slightly simpler model compounds at the M062X/6-31+G(d,p) level, considering a polarized continuum (SMD:DCM) to mimic the solvent effects (Figure 18). A two-step mechanism is computed by which the first step is the rate determining step and leads to the formation of the primary adduct (PA) which then cyclizes intramolecularly to give the cycloadduct (CA) in the second step. The

<sup>238</sup> Jeanguenat, A.; Durieux, P.; Edmunds, A. J. F.; Hall, R. G.; Hughes, D.; Loiseleur, O.; Pabba, J.; Stoller, A.; Trah, S.; Wenger, J.; Dutton, A.; Crossthaite, A. *Bioorg. Med. Chem.* **2016**, *24*, 403-427.



small energy difference ( $\Delta\Delta G^\ddagger = 0.9$  kcal.mol<sup>-1</sup>) between the *endo/exo* transition states can explain the obtained low diastereomeric ratios.

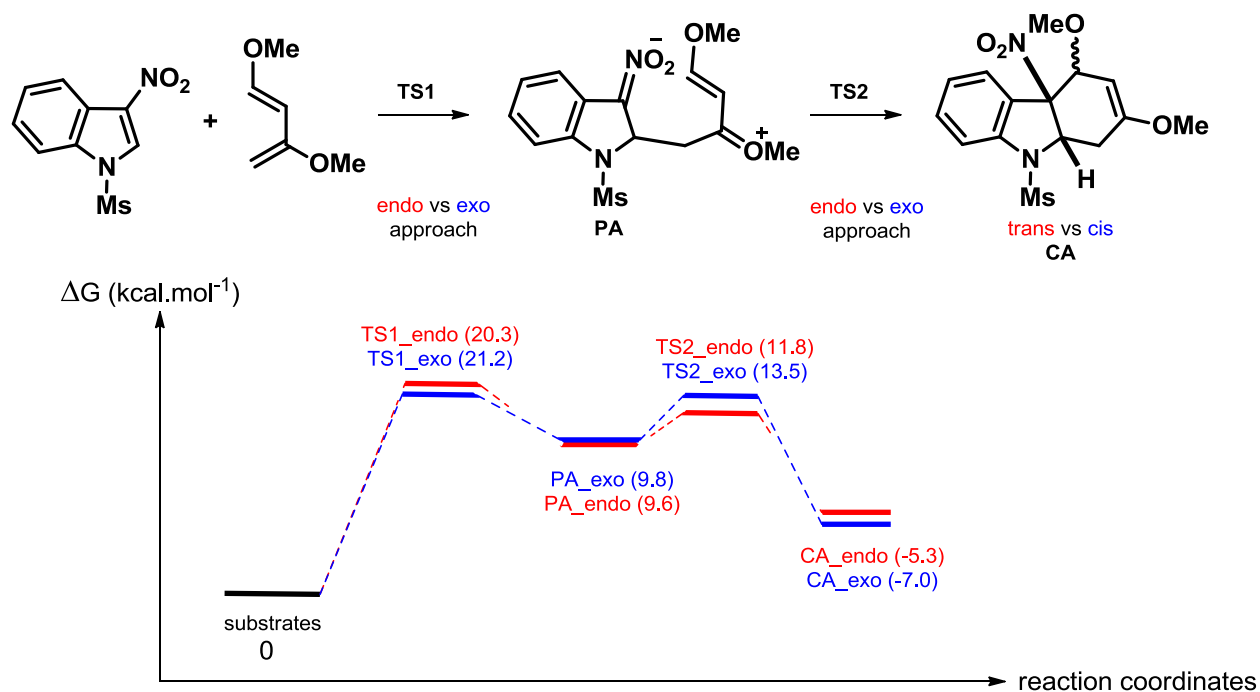


Figure 18: DFT calculations on the (4+2) cycloaddition reaction involving model substrates.

### 2.3 3-nitroindole derivatives and other dienes

We next investigated the reactivity of 3-nitro-1-tosyl-1*H*-indole **150aa** with other dienes, known for their relatively high reactivity (Figure 19).

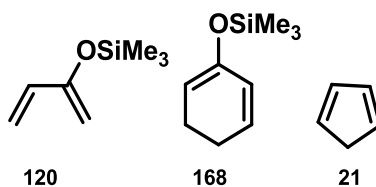
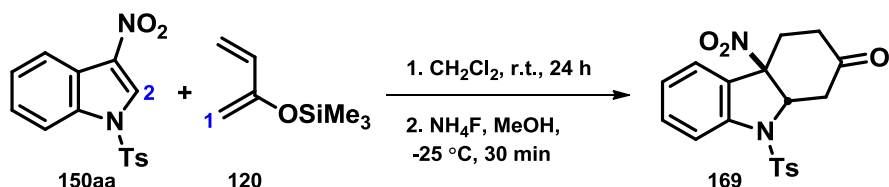


Figure 19: Structures of different dienes to be investigated.

When performing the reaction under the conditions described above (r.t.) using these three dienes, no reaction took place, unfortunately. Even under thermal conditions (DCM or Toluene reflux), 3-nitro-1-tosyl-1*H*-indole remained intact.

The ability of high pressure to allow reactions that do not take place under atmospheric pressure especially with sensitive substrates, drew our attention to use it as an activation mode in these reactions.

We first tested the reaction between 3-nitroindole derivative **150aa** and diene **120** under hyperbaric conditions (Table 15).

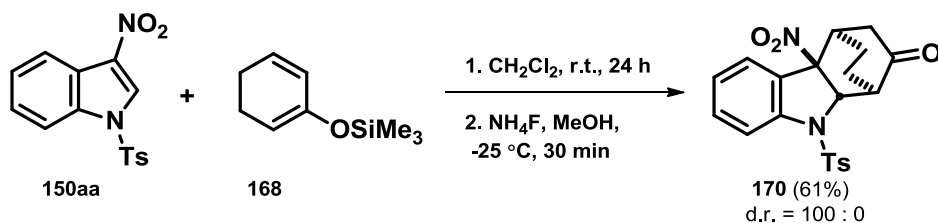


| Entry | Equiv of <b>120</b> | Conditions | Conversion (%) | Yield (%) |
|-------|---------------------|------------|----------------|-----------|
| 1     | 6                   | 16 kbar    | 100            | 55        |
| 2     | 3                   | 16 kbar    | 100            | 55        |
| 3     | 3                   | 12 kbar    | -              | -         |

Table 15: Reaction of 3-nitroindole and **120** under various conditions.

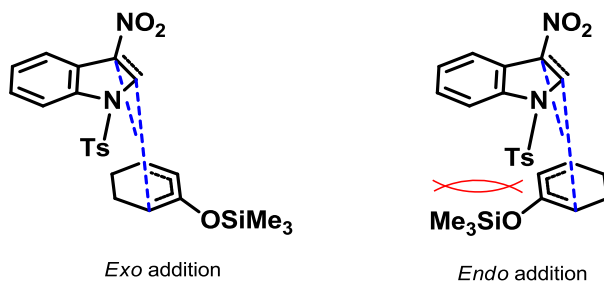
Under 16 kbar and using large excess of diene **120**, we were pleased to observe full conversion of **150aa** within 24 hours (entry 1). Same conversion was obtained when performing this reaction with 3 equiv of diene **120** under the same pressure (entry 2) and the product **169** was obtained in a 55% yield. Yet, decreasing the pressure to 12 kbar was not sufficient to allow the reaction to proceed (entry 3). The product **169** was expectedly obtained as single regioisomer, governed by the biggest HOMO/LUMO orbital coefficients on the diene/dienophile (position 1 for the HOMO of the diene and position 2 for the LUMO of the indole, respectively).

With this result, we then tested the reactivity of 3-nitro-1-tosyl-1*H*-indole **150aa** towards 2-(trimethylsiloxy)-1,3-cyclohexadiene **168**. In the presence of 1.2 equiv of **168** at 16 kbar, the desired cycloadduct was not observed after 24 hours. However, when doubling the quantity of the diene, a total conversion was observed (Scheme 50) and the cycloadduct **170** was obtained in a 61% yield as a single *trans* isomer. The higher reactivity observed with this diene can be explained by its electron-richness, due to the presence of trimethylsiloxy group, associated to its imposed *s-cis* reactive conformation due to its cyclic nature.



**Scheme 50: Reaction of 150aa and diene 168 under high pressure.**

This reaction showed complete regio- and stereoselectivity, leading to one of four possible adducts. Here again, the regiochemistry is probably well controlled and governed by the favored interactions between the biggest HOMO/LUMO orbital coefficients on the diene/dienophile. The stereoisomer obtained constitutes an *exo* selectivity of the Diels-Alder reaction presumably for steric reasons (Figure 20a).<sup>239</sup> The high diastereoselectivity observed here could be due to a concerted mechanism rather than a stepwise one, as shown for Danishefsky's diene.



**Figure 20: *Endo* and *Exo* approaches of 3-nitro-1-tosyl-1*H*-indole and diene 168.**

Regarding cyclopentadiene **21**, it showed to be inert under high pressure since it tends to polymerize rapidly under these conditions.

To conclude, less nucleophilic silyloxyated dienes can react with 3-nitro-1-tosyl-1*H*-indole only under hyperbaric conditions (16 kbar). The corresponding reactions showed the positive effect of HP and have led to new adducts unreachable under thermal conditions.

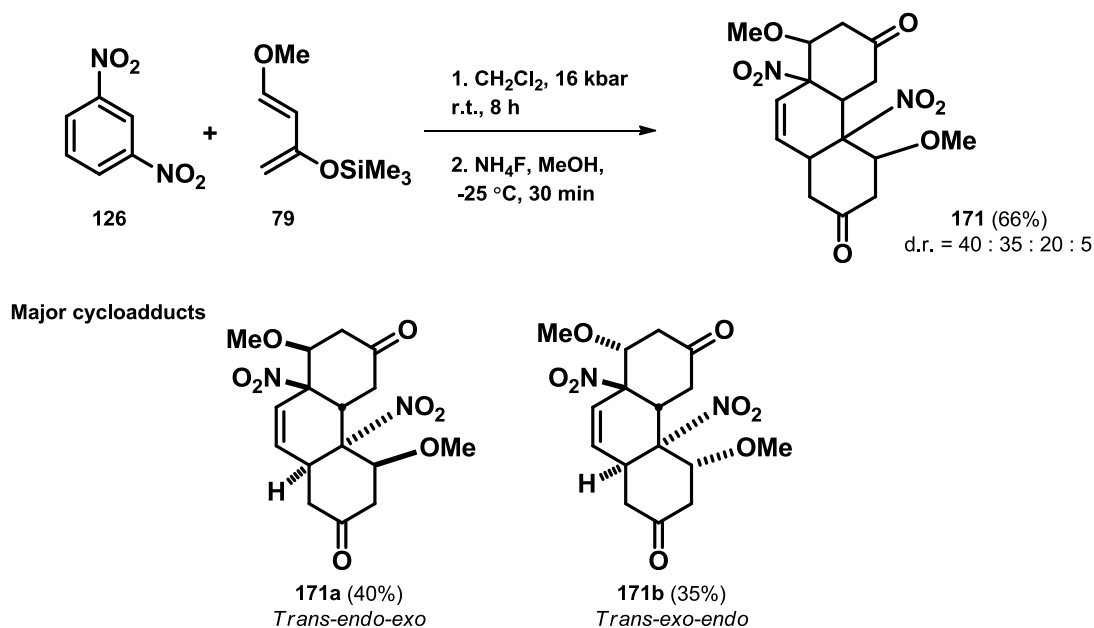
## 2.4 Other nitroaromatics and Danishefsky's diene

With these results in hand, another question came up: would it be possible to enlarge the scope of this reaction by moving to more aromatic nitroarenes? If so, could high pressure permits the formation and isolation of the corresponding dearomatized cycloadducts?

Switching to more aromatic compounds such as naphthalene or quinoline compounds, the reactivity is expectedly much lower because of their high stabilization energies. Mostly, using these aromatics as dienophiles in NED Diels-Alder reactions requires high temperature and prolonged heating. As discussed in the introduction, nitro-naphthalene and -quinoline derivatives can react with silyloxyated dienes under high temperature. All the reported examples led to the aromatized products.

<sup>239</sup> Reference 49; *Endo* addition can be defined as “the particular arrangement of reactants in which the more bulky sides of the diene is under the more bulky side of the dienophile”.

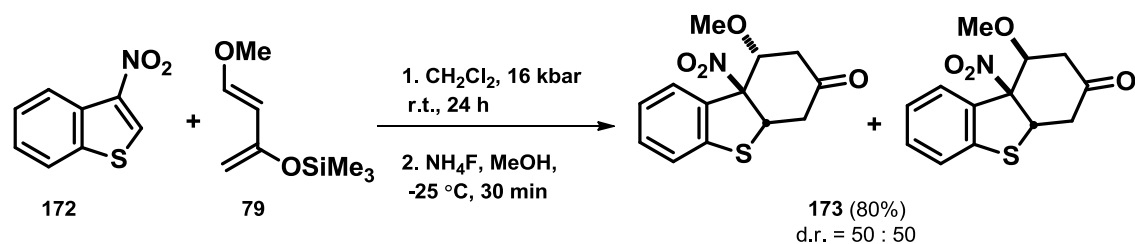
This study started with Dr. Sunnyoung Lee, a former post-doctoral fellow in our group, who discovered the reactivity of 1,3-dinitrobenzene **126** towards Danishefsky's diene **79**. Thanks to high pressure, the dearomatization of the latter could take place at ambient temperature and in the absence of any catalyst. The tricyclic compound **171**, obtained through double Diels-Alder reaction on the double bonds bearing the nitro groups, was isolated, after a smooth hydrolysis, in an overall 66% yield as a mixture of four diastereoisomers in 40 : 35 : 20 : 5 ratio (Scheme 51). The stereochemistry of the two major cycloadducts is shown in Scheme 51.<sup>240</sup> These conditions thus allowed avoiding the rearomatization of the cycloadducts.



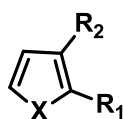
Scheme 51: Dearomatizing Diels-Alder reaction of 1,3-dinitrobenzene.

With this result in hand, we were motivated to study the reactivity of other aromatic compounds. As discussed in the previous paragraph, 3-nitrobenzothiophene **172** did not react under atmospheric pressure and ambient temperature with diene **79**. For that, we firstly tried to react it with 6 equiv of diene **79**, under the same conditions used with the dinitrobenzene **126**. After 24 hours, we were pleased to see a total conversion of the aromatic compound **172** into the corresponding dearomatized cycloadduct **173**. The tricyclic compound was isolated in a 80% yield as a 50 : 50 diastereomeric mixture (Scheme 52).

<sup>240</sup> Unpublished results.


 Scheme 52: High pressure activated Diels-Alder reaction between **172** and diene **79**.

In the series of heterocycles, we then tried the reaction with 2-nitrofuran **174**, 2-nitrothiophene **175** and 3-nitro-1-tosyl-1*H*-pyrrole **176** (Figure 21) under the same conditions ( $\text{CH}_2\text{Cl}_2$ , 16 kbar, 24 h, r.t.). The results are summarized in Table 16.



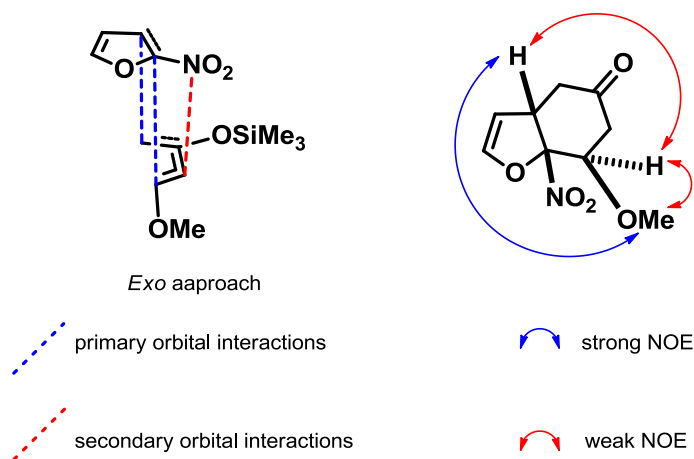
- 174**: X = O, R<sub>1</sub> = NO<sub>2</sub>, R<sub>2</sub> = H  
**175**: X = S, R<sub>1</sub> = NO<sub>2</sub>, R<sub>2</sub> = H  
**176**: X = N-Ts, R<sub>1</sub> = H, R<sub>2</sub> = NO<sub>2</sub>

Figure 21: Structures of heteroaromatics to be investigated.

| Substrate  | Conversion (%) | Product | d.r.    | Yield (%) |
|------------|----------------|---------|---------|-----------|
| <b>174</b> | 100            |         | 100 : 0 | 90        |
| <b>175</b> | 78             |         | 50 : 50 | 46        |
| <b>176</b> | 100            |         | -       | 79        |

 Table 16: Results of the reactions between heteroaromatics **174-176** and diene **79**.

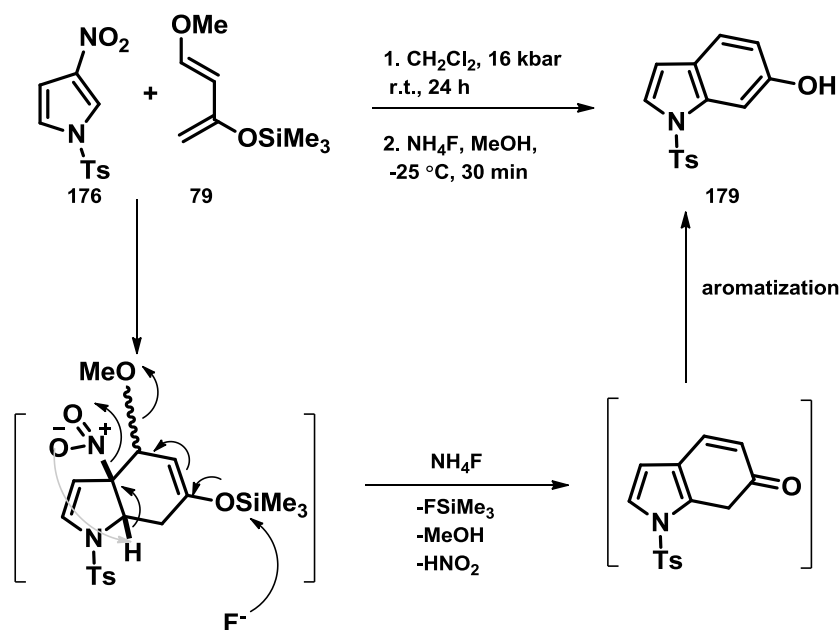
As depicted in Table 16, 2-nitrofuran **174** reacts efficiently with Danishefsky's diene **79** under high pressure to give the cycloadduct **177** as a single diastereoisomer. Its relative stereochemistry was assigned thanks to NOESY experiments. A preferred *exo* transition state can explain this result (Figure 22).



**Figure 22:** *Exo* approach of diene **79** to 2-nitrofuran.

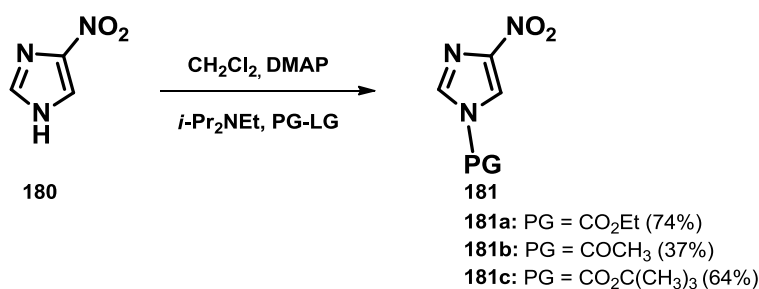
Two diastereoisomers **178** (d.r. = 50 : 50) were isolated in the case of 2-nitrothiophene **175** in 46% yield (78% conversion). In attempt to obtain total conversion, we performed this reaction for 72 hours, however with no success. It is important to mention here that the cycloadduct **178** proved unstable once isolated, turning from brown to black within few hours, indicating its degradation. Compared to the furan case, the diastereoselectivity is here quite different and this disparity remains difficult to rationalize.

3-nitro-1-tosyl-1*H*-pyrrole **176** reacted in a similar manner however the isolated product proved to be the aromatized one **179** in this case (79% yield). This is probably due to the higher tendency of the indolines thereby generated to rearomatize (Scheme 53).



Scheme 53: Proposed mechanism for the formation of 179.

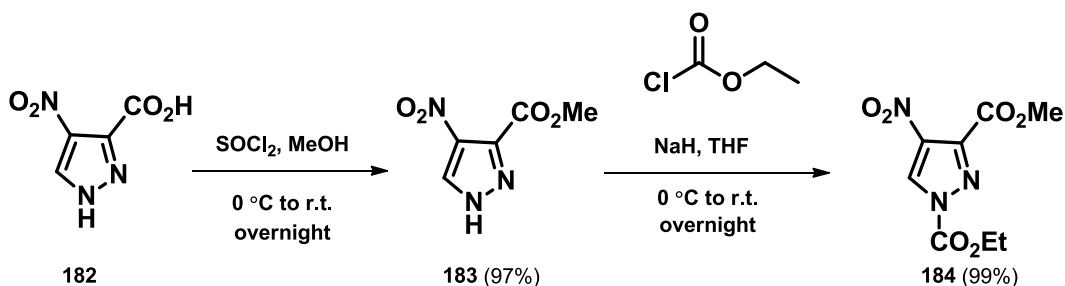
With this final result, we were interested to try other nitrogen containing heteroaromatics. We have thus synthesized differently protected imidazole derivatives **181a-c** (Scheme 54).



Scheme 54: Synthesis of imidazole derivatives.

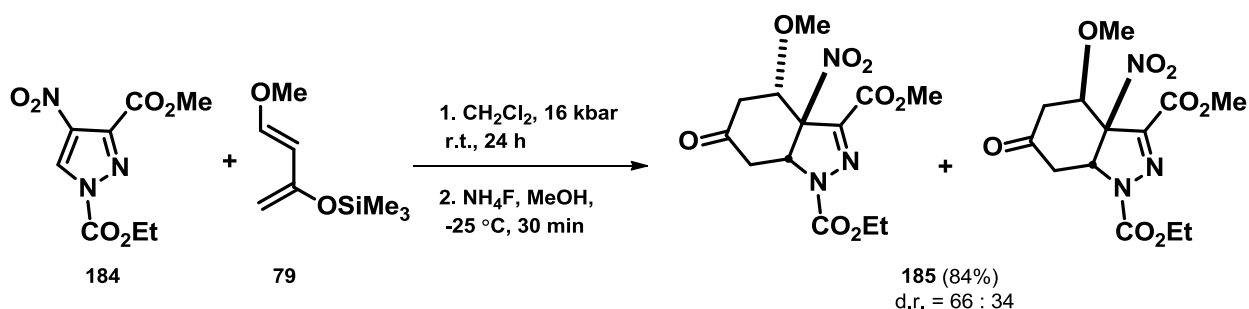
When testing the reactivity of these imidazole derivatives **181a-c** at room temperature or at reflux of DCM for 24 hours, no reaction was observed and only starting materials were recovered in all cases. The same reactions were then conducted with compounds **181a** and **181c** under 16 kbar. No reaction was observed and the starting materials were also recovered. This might be due to their poor solubility, when placed under pressure. The poor solubility of compound **181b**, even at atmospheric pressure, prevented us from testing it under high pressure.

We then investigated the reactivity of 4-nitropyrazole derivative **184** bearing three electron-withdrawing groups in positions 1, 3 and 4, which was easily obtained from the commercially available pyrazole **182** (Scheme 55).<sup>241</sup>



Scheme 55: Synthesis of 1-ethyl-3-methyl-4-nitro-1*H*-pyrazole-1,3-dicarboxylate.

The reaction between diene **79** and 4-nitropyrazole derivative **184** under 16 kbar yielded the expected cycloadduct **185** in a 84% yield as a 66 : 34 diastereomeric mixture (Scheme 56). To our knowledge, this is the first example which uses the dienophilic character of pyrazole in NED Diels-Alder reaction.

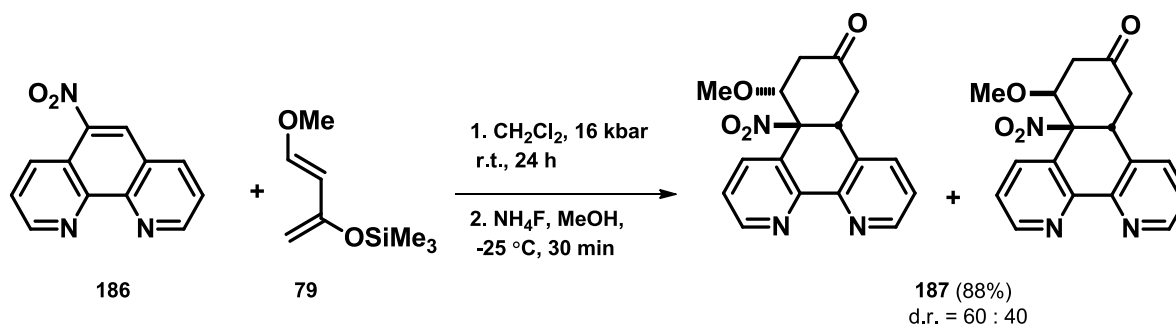


Scheme 56: Reaction between pyrazole derivative and Danishefsky's diene under 16 kbar.

5-nitro-1,10-phenanthroline **186** was next tested as an example of nitroaromatic compound bearing 6-membered all-carbon reactive ring. It underwent a fast and easy transformation to deliver the tetracyclic compound **187** in a 88% yield and a 60 : 40 diastereomeric ratio (Scheme 57). Similar to the ratios observed with most of 5-membered nitroheteroaromatics, the low *endo/exo* ratio obtained in this case, with a 6-membered aromatic ring, is probably due to the same favorable/unfavorable interactions in both *endo/exo* approaches.

<sup>241</sup> La Rosa, S.; Benicchi, T.; Bettinetti, L.; Ceccarelli, I.; Diodato, E.; Federico, C.; Fiengo, P.; Franceschini, D.; Gokce, O.; Heitz, F.; Lazzeroni, G.; Luthi-Carter, R.; Magnoni, L.; Miragliotta, V.; Scali, C.; Valacchi, M. *ACS Med. Chem. Lett.* **2013**, *4*, 979-984.





Scheme 57: Reactivity of 186 and 79 under high pressure.

We then tried to perform this reaction with the more challenging nitro-quinoline and -isoquinoline derivatives (Figure 23, **188a-188d** and **189**). The importance and relevance of such studies is dictated by the presence of a significant number of quinoline compounds that have useful biological activities. The quinoline moiety is indeed found in numerous alkaloids, pharmaceuticals and cyanine dyes.<sup>242,243</sup>

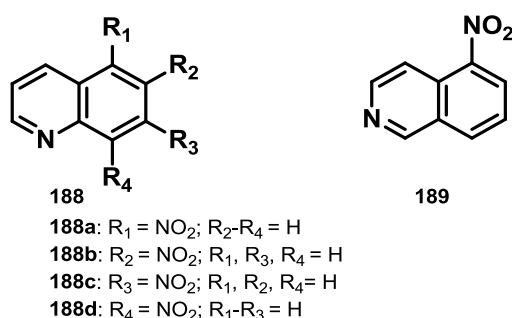
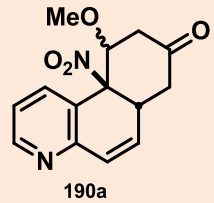
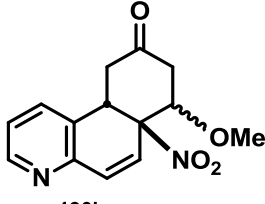
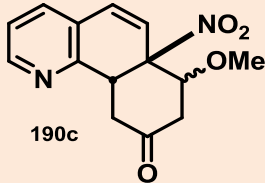
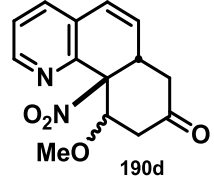
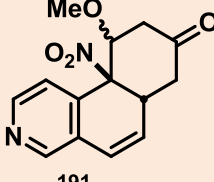


Figure 23: Structures of 3-nitroquinoline derivatives.

5-, 6-, 7-, 8-nitroquinoline (**188a-188d**) and 5-nitroisoquinoline (**189**) were thus reacted with Danishefsky's diene under a 16 kbar pressure. The results are summarized in Table 17.

<sup>242</sup> Foley, M.; Tilley, L. *Pharmacol. Ther.* **1998**, 79, 55-87.

<sup>243</sup> Fu, Y. L.; Zhang, B. R.; Wang, S.; Gao, X. X.; Wang, L. Y. *Bull. Korean Chem. Soc.* **2013**, 34, 489-494.

| Substrate | Time (h) | Conversion (%) | Product   | d.r.    | Yield (%) |
|-----------|----------|----------------|---|---------|-----------|
| 188a      | 24       | 100            | <br>190a  | 55 : 45 | 92        |
| 188b      | 72       | 75             | <br>190b  | 50 : 50 | 73        |
| 188c      | 24       | 100            | <br>190c  | 53 : 47 | 89        |
| 188d      | 72       | 84             | <br>190d | 62 : 38 | 78        |
| 189       | 24       | 100            | <br>191 | 53 : 47 | 99        |

**Table 17: Tricyclic products obtained from the reaction of nitroquinoline derivatives and diene 79.**

Quinolines **188a-188d** as well as isoquinoline **189**, which contained a nitro group on the benzene ring, displayed complete ring selectivity in favor of the all-carbon nitrosubstituted cycle and no reaction was observed on the nitrogenated electron-poor heterocycle. The azacycle acts here as an electron-withdrawing substituent and allow the C=C nitrated double bond to behave as an electron-poor dienophile to generate the dearomatized tricyclic compounds **190a-190d** and **191** respectively, in good to excellent yields. The d.r. are however modest, in line with the previous results.

The extension of this reaction to compounds having a particular stability such as nitronaphthalene derivatives is also interesting. The importance of studying their reactivity as dienophiles is due to two reasons. Firstly, they are not exhaustively explored and mainly lead to rearomatized cycloadducts up to now. Secondly, the thereby generated tricyclic compound could

constitute the base skeleton of diterpenes such as pisiferic acid **192** and carnosic acid **193** (Figure 24).<sup>244</sup>

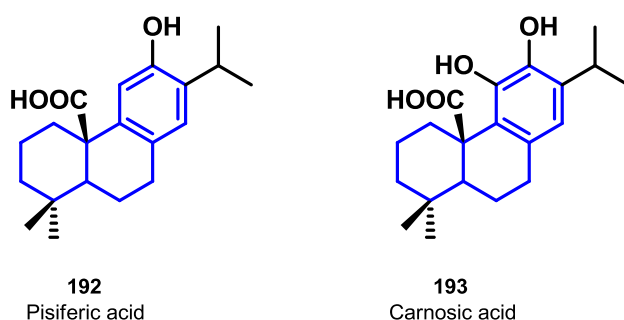
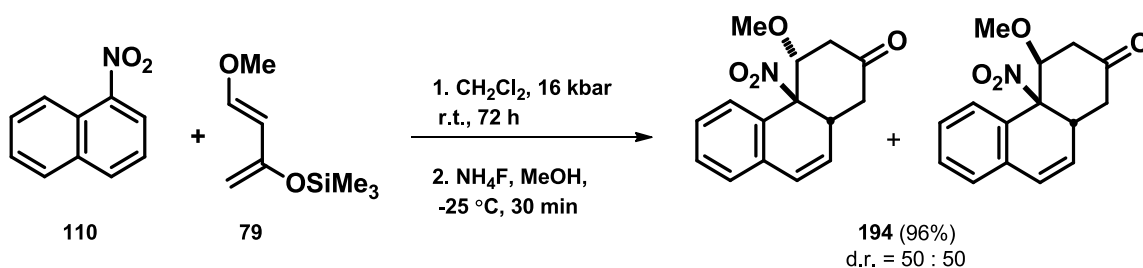


Figure 24: Diterpenes structures.

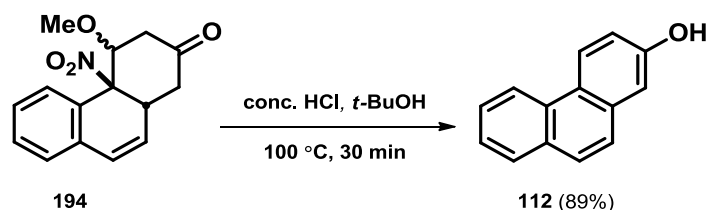
The dienophilic character that 1-nitronaphthalene **110** exhibits in the reaction with the Danishefsky's diene **79** is demonstrated under high pressure and it led, after smooth hydrolysis, to the expected dearomatized cycloadduct **194**, isolated in a good yield albeit no diastereoselectivity (Scheme 58). Conversion of the aromatic starting material into the product decreased from 100% to 50% when the reaction time was decreased from 72 to 24 hours.



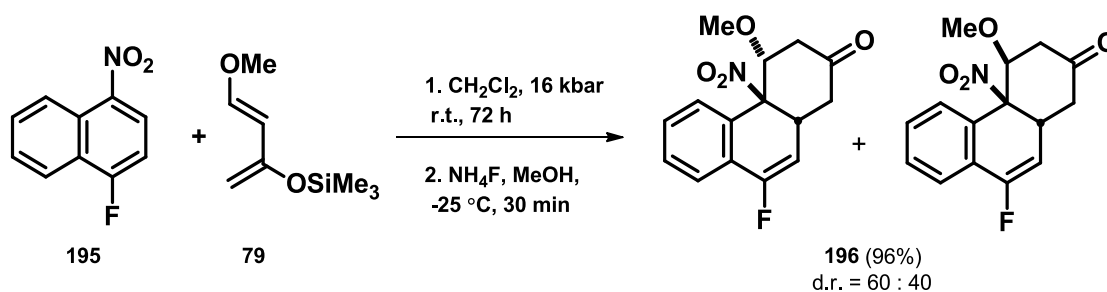
Scheme 58: Reaction of nitronaphthalene and diene **79**.

In attempt to remove the methoxy group of **194**, we noticed its complete conversion to phenanthren-2-ol **112** when heated at 100 °C in presence of *t*-BuOH and concentrated HCl (Scheme 59).

<sup>244</sup> González, M. A. *Tetrahedron* **2015**, *71*, 1883-1908.

Scheme 59: Aromatization of product **194**.

The more activated 1-fluoro-4-nitronaphthalene **195** behaved similarly and led to the tricyclic adduct **196**. The reaction was expectedly faster and reached 70% conversion after 24 hours (Scheme 60).<sup>245</sup> Noteworthy, even if an excess of diene was used in the process, no subsequent cycloaddition was observed on the remaining fluorinated C=C bond.

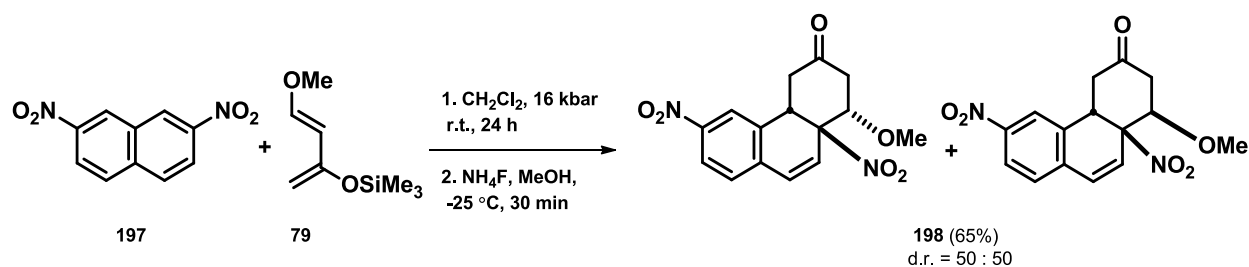
Scheme 60: Reaction of 1-fluoro-4-nitronaphthalene and diene **79**.

With these results, we then moved to dinitronaphthalene derivatives, which were expected to be more reactive. In this series, we started with 1,5-dinitronaphthalene **116b**, but due to its low solubility in different solvents, we were not able to run the reaction under high pressure.

The solubility of 2,7-dinitronaphthalene **197** in dichloromethane allowed us to perform the reaction under high pressure (16 kbar) and we were glad to observe the total conversion after 24 hours (Scheme 61).<sup>246</sup> Analysis of the NMR data revealed that a mono-cycloaddition had taken place, involving one of the two double bonds bearing a nitro group. The other double bond remained intact even when doubling the amount of the diene.

<sup>245</sup> We did not run the reaction for 48 hours; which may be sufficient to complete this reaction.

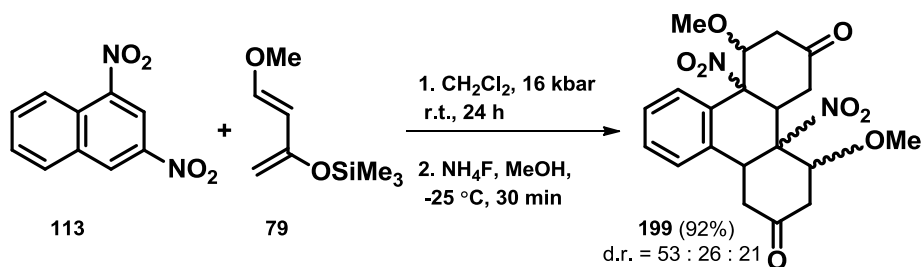
<sup>246</sup> The crude was purified via reverse phase HPLC.



Scheme 61: Cycloadducts obtained from the reaction of 197 and diene 79.

We then tried the reaction with 1,8-dinitronaphthalene **116a**. Although the crude <sup>1</sup>H NMR of the reaction showed the absence of the starting material, we were unable to isolate or identify any of the products formed in this reaction. The Diels-Alder reaction is probably more difficult in this case, for steric reasons.

1,3-dinitronaphthalene **113** was the last to be tested in this series and we were pleased to find that the reaction could occur under the same conditions (Scheme 62). This time, however, the crude <sup>1</sup>H NMR showed the presence of three diastereoisomers **199** in a 53 : 26 : 21 ratio.<sup>247</sup> Two consecutive cycloaddition reactions took place in this case and the reactivity of 1,3-dinitronaphthalene appears to be similar to that of 1,3-dinitrobenzene (see beginning of this section).



Scheme 62: Dearomatization of 1,3-dinitronaphthalene under high pressure.

This reaction allows the formation of 6 stereogenic centers in one step, and out of a total of 2<sup>6</sup> stereoisomers (32 couples of diastereoisomers) only three of them were observed and isolated (53 : 26 : 21 ratio). If the Diels-Alder reaction is a concerted process, each cycloaddition reaction imposes the stereochemistry at the ring junction, and this would reduce the number of possibilities and the formation of 8 couples is then possible. According to the *endo* or *exo* approaches and the *cis* or *trans* relative stereochemistry between the two new cycles we can draw these structures (Figure 25).

<sup>247</sup> Reverse phase HPLC was also performed in this case to separate the diastereoisomers.

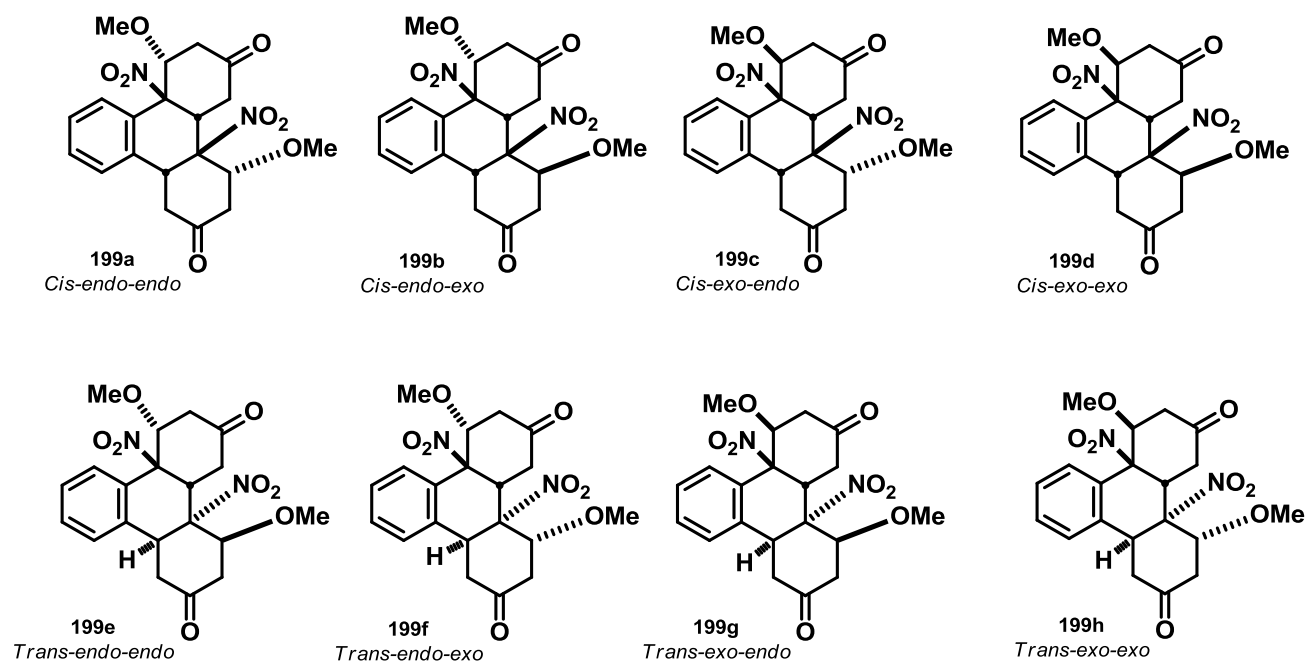


Figure 25: Structure of the 8 diastereomers.

Analysis of the 1D and 2D NMR spectra of the two major diastereoisomers, done by Dr. Ghanem Hamdoun and Prof. Hassan Oulyadi, at the COBRA lab in Rouen, revealed that the “*Trans-endo-exo*” **199f** “*Trans-exo-endo*” **199g** are most probably the major ones (Figure 26). This resembles the results obtained with 1,3-dinitrobenzene **126**.

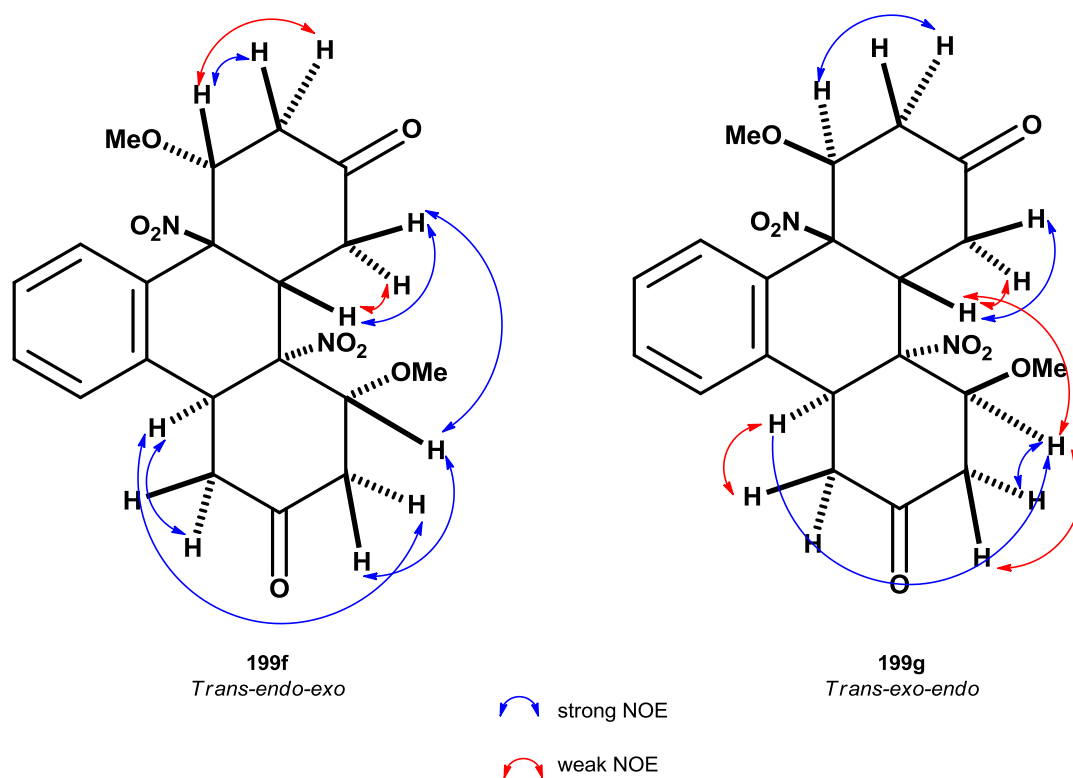


Figure 26: Significant NOE effects for the major diastereoisomers.

## 2.5 Extending the reaction to enantioselective version

Since the pioneering work by Rawal et al. in 2003,<sup>248</sup> the enantioselective hetero-Diels-Alder (HDA) reaction promoted by a hydrogen bond using diol compounds has become a topic of interest in asymmetric organocatalysis.<sup>249,250,251</sup> In these catalytic systems, the hydrogen-bonding interaction between the hydroxyl group of the diol catalyst and the carbonyl group of the substrate is considered to be the main driving force of the catalysis.

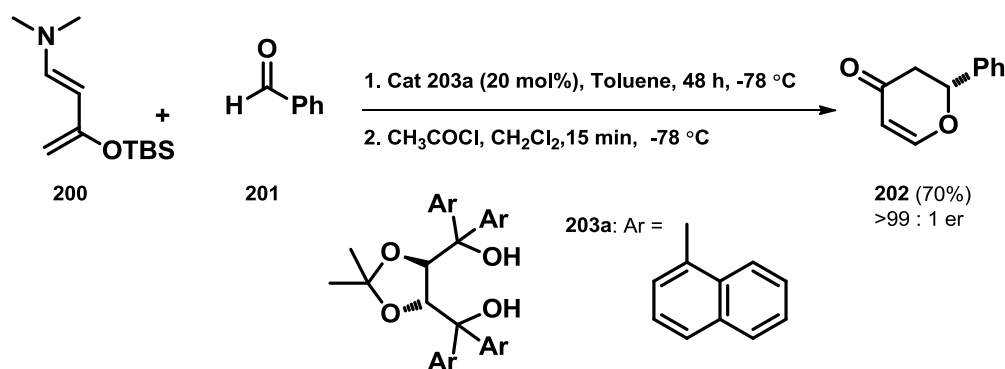
For example, Rawal demonstrated that TADDOL **203a** is the best catalyst for the HDA reaction between diene **200** and benzaldehyde **201**, affording the product **202** in a 70% yield and > 99 : 1 er (Scheme 63).<sup>248</sup>

<sup>248</sup> Huang, Y.; Unni, A. K.; Thandani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146.

<sup>249</sup> Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289-296.

<sup>250</sup> Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080-1081.

<sup>251</sup> Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5755-5760.



Scheme 63: TADDOL catalyzed HAD reaction.

An interesting phenomenon is that naphth-1-yl-TADDOL **203a** exhibits remarkably superior performance compared to that of its phenyl analogues **203b-c**, in several HDA or Diels-Alder reactions in terms of both activity and enantioselectivity (Figure 27).<sup>248,252</sup>

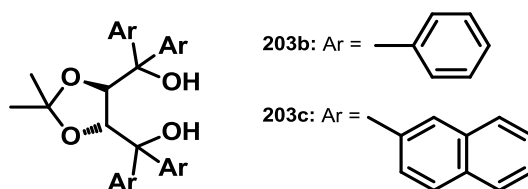


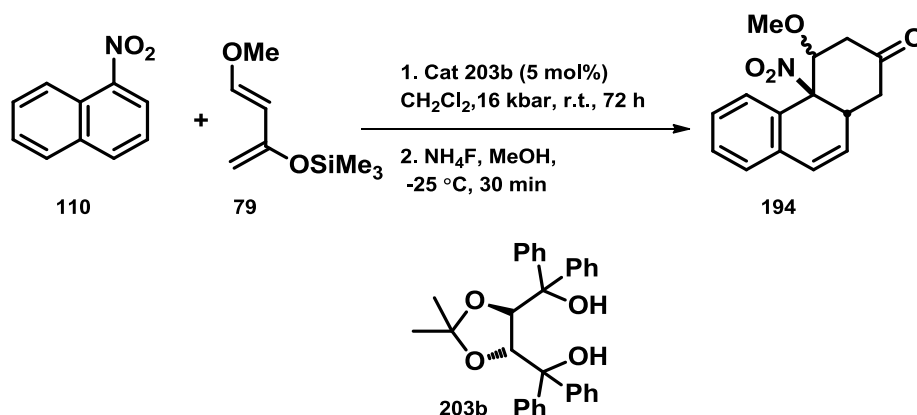
Figure 27: Structures of other TADDOL derivatives.

According to this, we wondered if H-bonding TADDOL derivatives can permit us to perform our dearomative reaction using nitroaromatics in an enantioselective way.

Firstly, the reaction of 1-nitronaphthalene **110** and diene **79** was conducted under high pressure in presence of 5 %mol of the commercially available TADDOL **203b** (Scheme 64).

<sup>252</sup> Thandani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5846-5850.

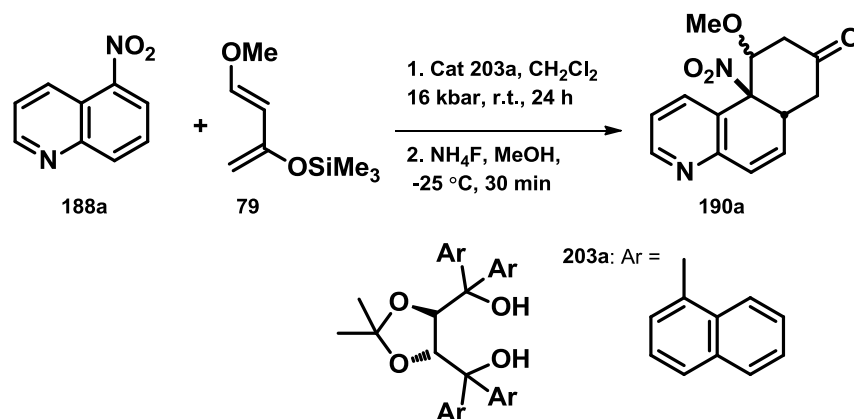




Scheme 64: TADDOL **203b** catalyzed reaction between **110** and **79**.

Chiral HPLC, performed by Emilie Petit and L etitia Bailly, showed that the reaction proceeds but no enantiomeric excess was observed.

We then tried another TADDOL derivative **203a** with the reaction of 5-nitroquinoline **188a** and **79** (Scheme 65). Performing the reaction in presence of 5 %mol and 0.5 equiv of TADDOL derivative **203a**, did not show any enantioselectivity.

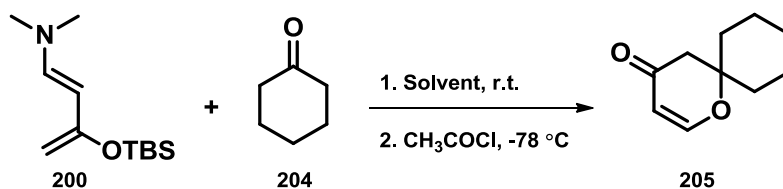


Scheme 65: TADDOL **203a** catalyzed reaction of **188a**.

## 2.6 Study of the influence of H-bonding solvents

In 2002, Rawal et al.<sup>253</sup> showed that the reaction between diene **200** and cyclohexanone **204** was also highly accelerated using H-bonding solvents. He also found that although better hydrogen-bonding alcohols (methanol and ethanol in this case) promote faster reactions, they also solvolyze the diene (Table 18).

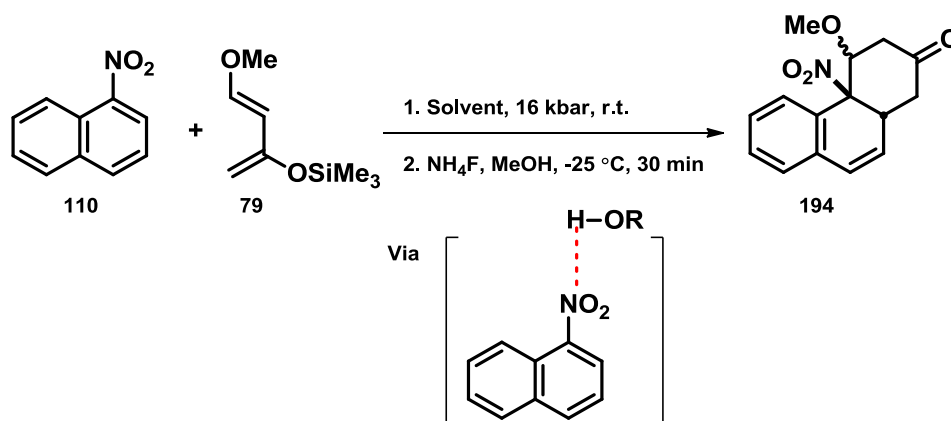
<sup>253</sup> Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662-9663.



| Solvent    | Time (h) | Solvolysis (%) | Yield (%) |
|------------|----------|----------------|-----------|
| Chloroform | 48       | 20-25          | 45        |
| Methanol   | 0.5      | ~ 40           | 0         |
| Ethanol    | 0.5      | ~ 50           | 30        |
| 2-butanol  | 5        | <5             | 78        |

Table 18: Reaction between cyclohexanone and diene **200** in H-bonding solvents.

In order to evaluate the efficiency of activating the nitro group by alcohols, in our case, we studied the solvent effect on the Diels-Alder reaction between 1-nitronaphthalene **110** and Danishefsky's diene **79** which required 72 hours under 16 kbar (Scheme 66).



Scheme 66: Diels-Alder reaction between **110** and **79** in H-bonding solvents.

It is known that the cycloadditions are accelerated to a much greater extent in protic solvents, where the OH group can perform stronger H-bonds. With this in mind, we studied the impact of adding catalytic amount of H-bonding solvents (more precisely 5 mol% of 2-butanol or HFIP in  $\text{CH}_2\text{Cl}_2$ ) on this reaction (Scheme 66).

To see the solvent effect, the reaction mixtures underwent three successive compressions/decompressions steps at intervals of time 24 hours. After each decompression, the conversion of the starting material was determined by  $^1\text{H}$  NMR (Figure 28).

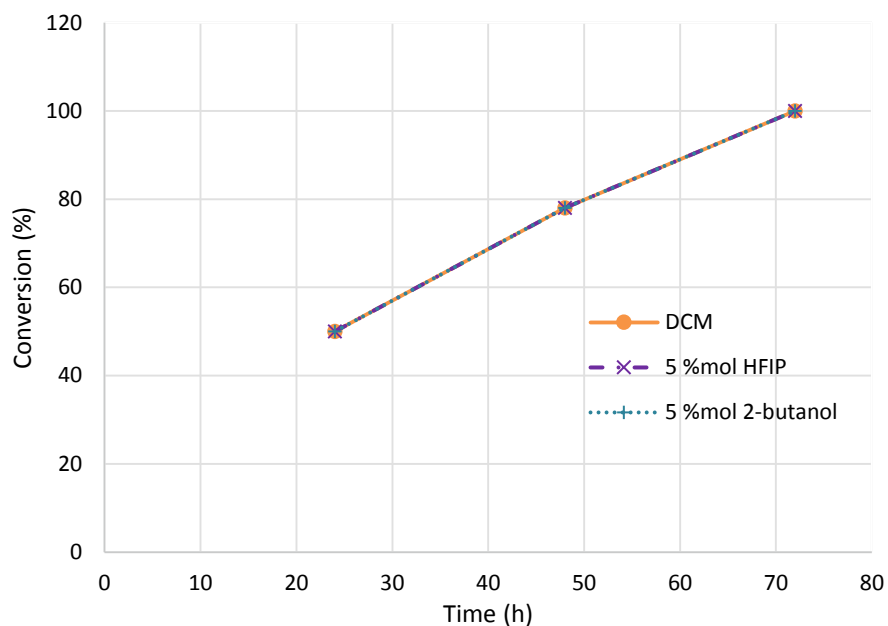


Figure 28: Evolution of the reaction every 24 hours under high pressure.

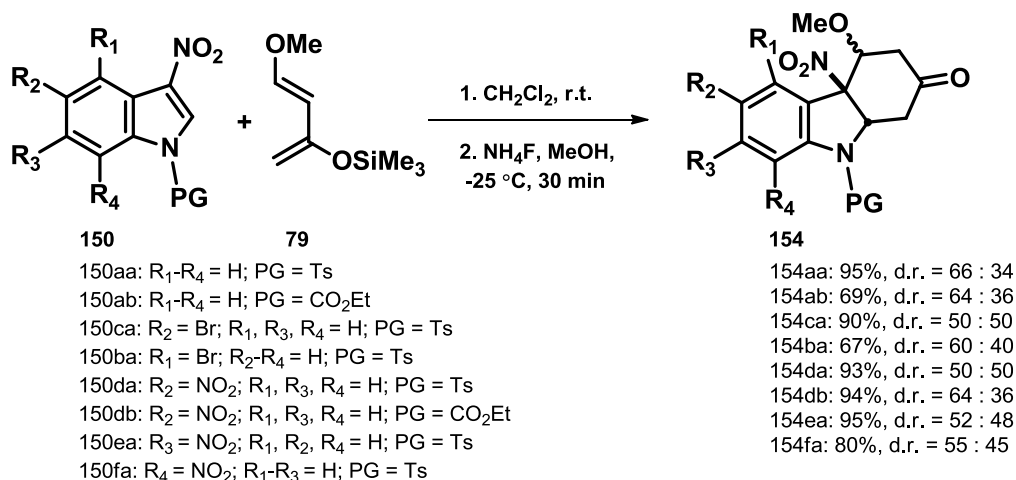
As shown in this graph, the three solvents showed no difference in the % conversion over 72 hours. Within 24 hours, 50% conversion was obtained. This value increased to 78% after the second compression, and the reaction was complete after 3 days. This shows that, the H-bonding solvents have no impact on the rate of this reaction. But, it is interesting to note that no degradation or solvolysis of the diene took place.

To conclude, high pressure proved to be an efficient activation method for Diels-Alder reactions of highly stable compounds such as nitro-phenanthroline **186**, -quinoline (**188a-d** and **189**) and -naphthalene (**110**, **195**, **197** and **113**) derivatives for instance. The ability to isolate the dearomatized cycloadducts has been successful in most cases, although we were not able to perform these reactions enantioselectively using H-bonding catalysis.

### 3 Conclusion

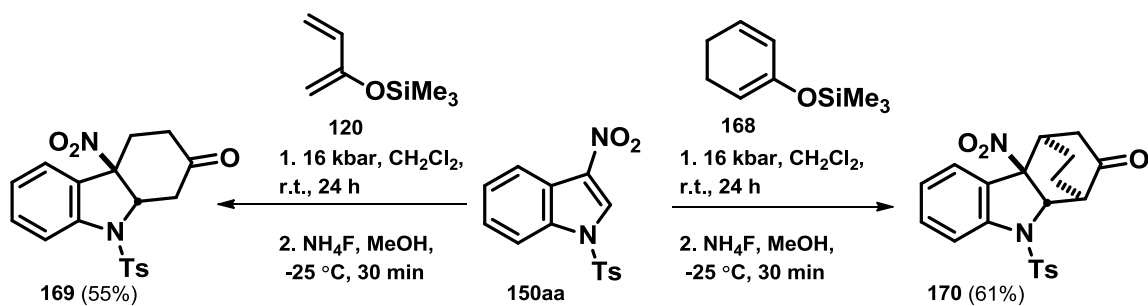
In this chapter, we have discussed the reactivity of Danishefsky's diene towards nitroindole derivatives and nitroaromatics.

We have shown that 3-nitroindole derivatives **150aa-150fa** react readily with Danishefsky's diene **79** at atmospheric pressure. The dearomatized cycloadducts can be isolated in good yields as a mixture of two diastereoisomers with a modest d.r. (Scheme 67).



Scheme 67: Reactivity of indole derivatives and Danishefsky's diene.

Contrary to Danishefsky's diene, 2-trimethylsiloxy-1,3-butadiene **120** and 2-(trimethylsiloxy)-1,3-cyclohexadiene **168** showed to be less reactive toward 3-nitro-1-tosyl-1*H*-indole **150aa** and required HP conditions (Scheme 68).

Scheme 68: Reactivity of **150aa** and other silyloxydienes.

The positive effect of high pressure on this reaction promoted the dearomatization of several nitroaromatics by NED Diels-Alder reaction with Danishefsky's diene **79**. The obtained cycloadducts proved to be the dearomatized ones in most cases, contrary to the results reported under thermal activation.<sup>208,209,210,211,212</sup>

Unreactive heterocycles at room temperature and atmospheric pressure, showed to be reactive under high pressure. Single or mixture of diastereoisomers, depending on the substrate and on the preferred transition state, were isolated in good yields (Figure 29).

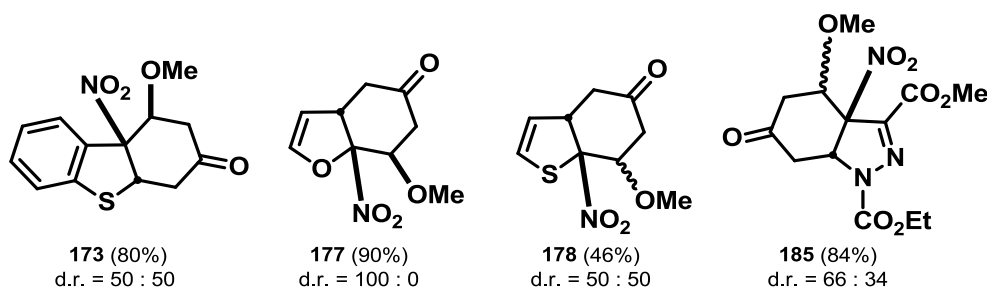
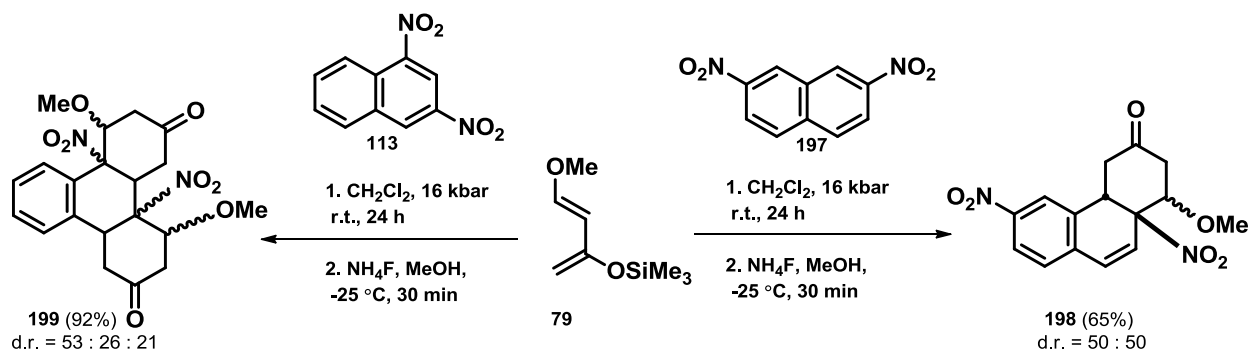


Figure 29: Structures of the obtained cycloadducts under high pressure.

5-nitro-1,10-phenanthroline (**186**), nitroquinoline (**188a-d** and **189**) and nitronaphthalene derivatives (**110** and **195**) proved also reactive under high pressure. In all cases, the regioselectivity of the cycloaddition reaction was controlled by the nitro group.

The more challenging dinitronaphthalene derivatives could also be involved in these processes. 2,7-dinitronaphthalene **187** underwent mono-cycloaddition reaction with diene **79**, while 1,3-dinitronaphthalene **113** behaved differently and two cycloadditions occurred on the two double bonds bearing the nitro groups in this case (Scheme 69). In both processes, the dearomatized polycyclic adducts were isolated in good overall yields.


 Scheme 69: Reaction between dinitronaphthalene derivatives and **79** under high pressure.

## **Chapter III. Reactivity of Lithium Enolates towards Electron-Poor Aromatics**



*«Do not ask yourself whether you are good enough to tackle a new problem:*

*JUST DO IT»*

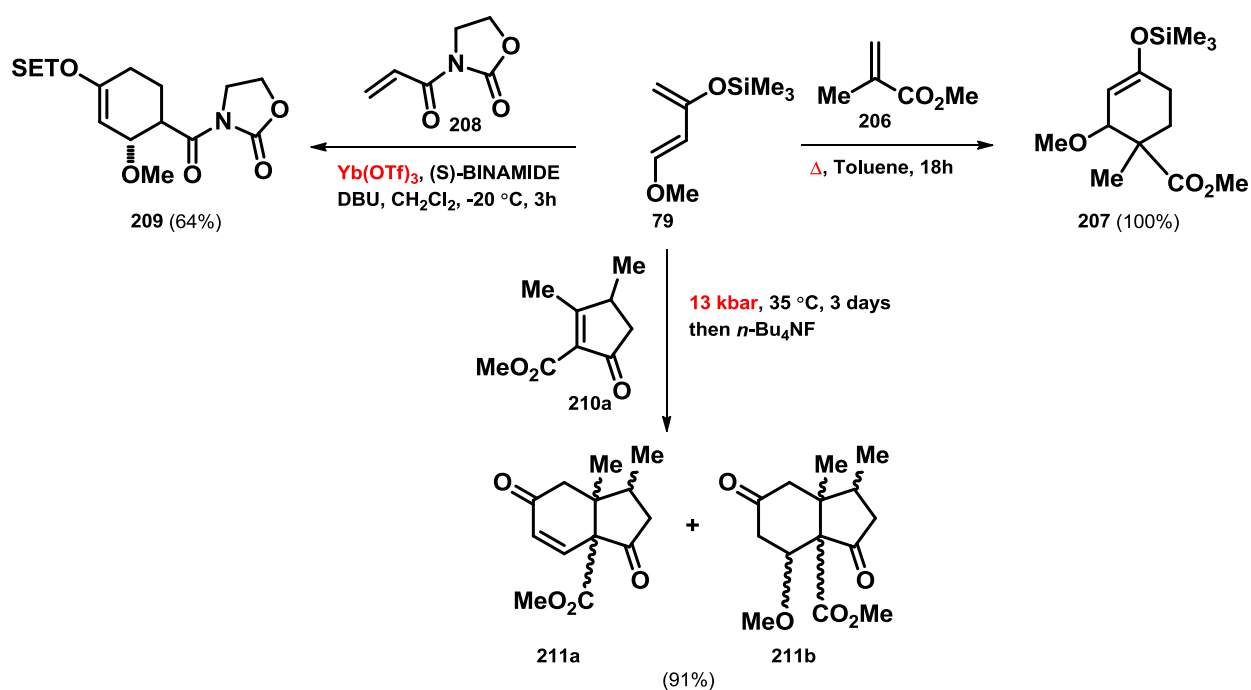
*Jean-Pierre Sauvage*





## 1 Activation of Danishefsky's diene

As discussed in the previous chapters, Danishefsky's diene is a good candidate for Diels-Alder reactions. However, its use may be limited when the dienophiles used are inert and/or sensitive. Different activation methods are conventionally used (Scheme 70). The thermal activation of cycloadditions using Danishefsky's diene is the most used.<sup>254</sup> The electrophilic activation of the dienophile by acid catalysis (Lewis or Brønsted) is also possible at low temperatures.<sup>255</sup> Although this mode of activation is very effective, the acid sensitivity of Danishefsky's diene prevents its use in many cases. As a solution, high pressure was used, instead, to activate these reactions (Scheme 70).<sup>256,257</sup>



Scheme 70: Diels-Alder reaction involving Danishefsky's diene.<sup>254,255,256</sup>

But, due to the lack of hyperbaric equipment in most synthetic organic laboratories and the poor reactivity of some benzenic substrates under HP, an alternative method was needed. In this

<sup>254</sup> Zheng, S.; Laxmi, Y. R. S.; David, E.; Dinkova-Kostova, A. T.; Shiavoni, K. H.; Ren, Y.; Zheng, Y.; Trevino, I.; Bumeister, R.; Ojima, I.; Wigley, W. C.; Blishka, J. B.; Mierke, D. F.; Honda, T. *J. Med. Chem.* **2012**, *55*, 4837-4846.

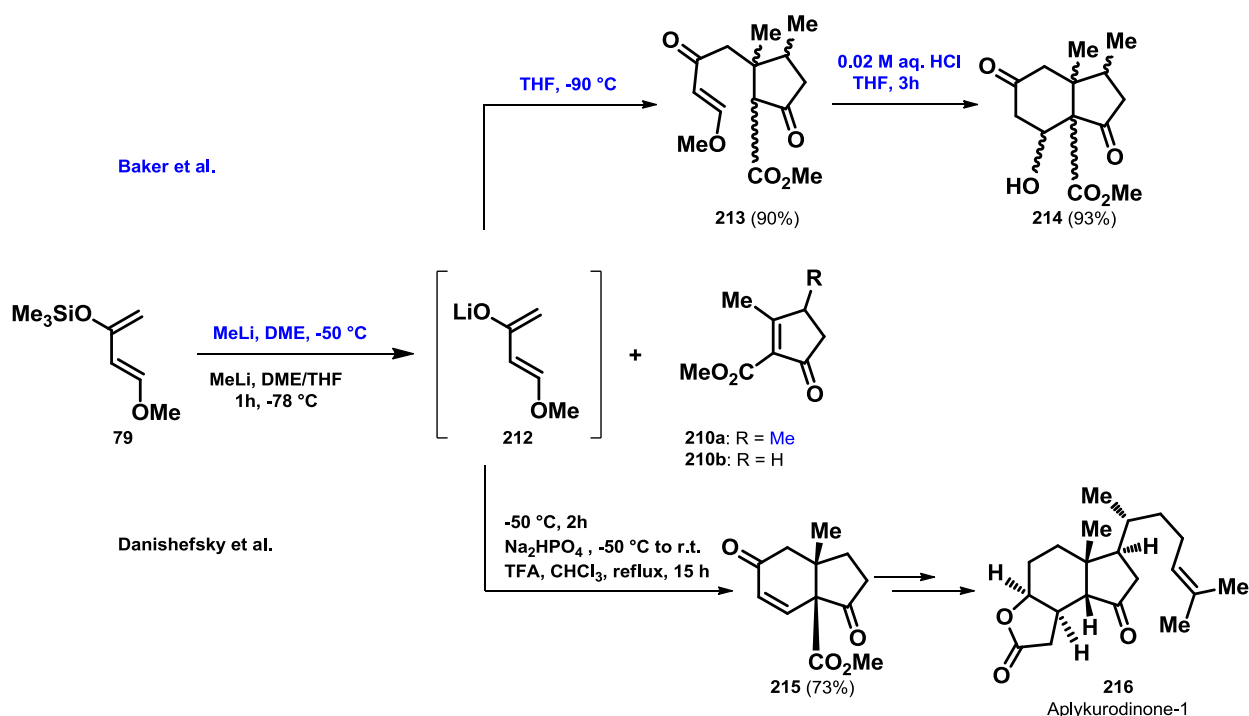
<sup>255</sup> Hiraoka, S.; Harada, S.; Nishida, A. *J. Org. Chem.* **2010**, *75*, 3871-3874.

<sup>256</sup> Baker, R.; Selwood, D. L.; Swain, C. J.; Webster, N. M. H. *J. Chem. Soc., Perkin Trans 1* **1988**, 471-480.

<sup>257</sup> Ortuno, R. M.; Ibarzo, J.; D'Angelo, J.; Dumas, F.; Alvarez-Larena, A.; Piniella, J. F. *Tetrahedron: Asymmetry* **1996**, *7*, 127-138.

context, activation of the diene by raising the energy of its HOMO appeared as an attractive and alternative option.

The idea of the nucleophilic activation of Danishefsky's diene goes back to 1988. As a part of a sesquiterpene synthesis, Baker et al. developed a methodology to activate Danishefsky's diene **79**<sup>256</sup> (Scheme 71), by converting it into its lithium enolate **212** counterpart in the presence of methyllithium in dimethoxyethane (DME) at  $-50\text{ }^{\circ}\text{C}$ . The more nucleophilic enolate intermediate **212** can then react with an inert tetrasubstituted dienophile **210a** to give the Michael adduct **213** at  $-90\text{ }^{\circ}\text{C}$  in THF. The latter was further cyclized under acidic conditions to afford the corresponding cycloadduct **214** isolated as a mixture of four diastereoisomers in a good yield. Later on, Danishefsky et al. reported a very similar activation method in the context of the total synthesis of ( $\pm$ )-aplykurodinone **216** (Scheme 71).<sup>258</sup> In this case, the intermediates were not isolated and the cyclohexenone **215** was isolated after a stronger acidic treatment.



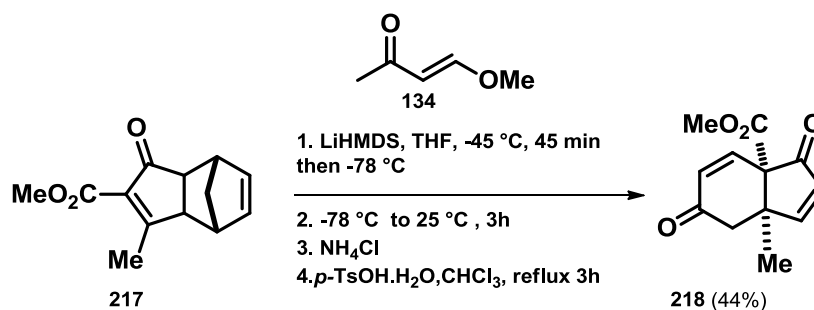
**Scheme 71: Activation of Danishefsky's diene using MeLi.**

More recently, Snyder et al. performed a similar nucleophilic activation to access Hajos-Parrish ketone isomers (Scheme 72).<sup>259</sup> In this case, the nucleophilic activation of *trans*-4-methoxy-3-buten-2-one **134**, rather than the Danishefsky's diene **79** was performed by the action of LiHMDS. This successful activation led to the formal cycloadduct **218** after the reaction with

<sup>258</sup> Zhang, Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 9567-9569.

<sup>259</sup> Egan, J. M.; Hori, M.; Wu, J.; Kanyiva, K. S.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 1-6.

the sterically hindered tetrasubstituted dienophile **217**. The cycloadduct **218** was obtained in a three-steps mechanism including Michael addition, followed by cyclization in the presence of *p*-toluenesulfonic acid and then a final retro-Diels-Alder step. The isomer **218** was obtained in a 44% overall yield.

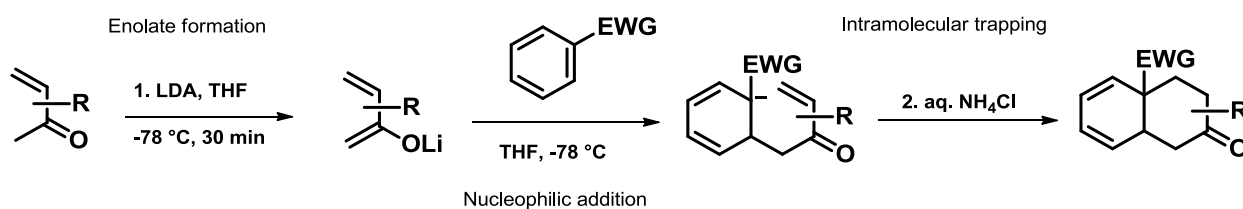


Scheme 72: Activation of *trans*-4-methoxy-3-buten-2-one by LiHMDS.

Based on these works, we wondered if this nucleophilic activation path could be effective in dearomatizing electron-poor aromatics, used as Michael acceptors in formal (4+2) cycloadditions.

## 2 Development of Methodology

This idea was confirmed by a former PhD student, Dr. Karine Pastraud, who developed a methodology to dearomatize nitroaromatics in a formal (4+2) cycloadditions using lithium enolates (Scheme 73).

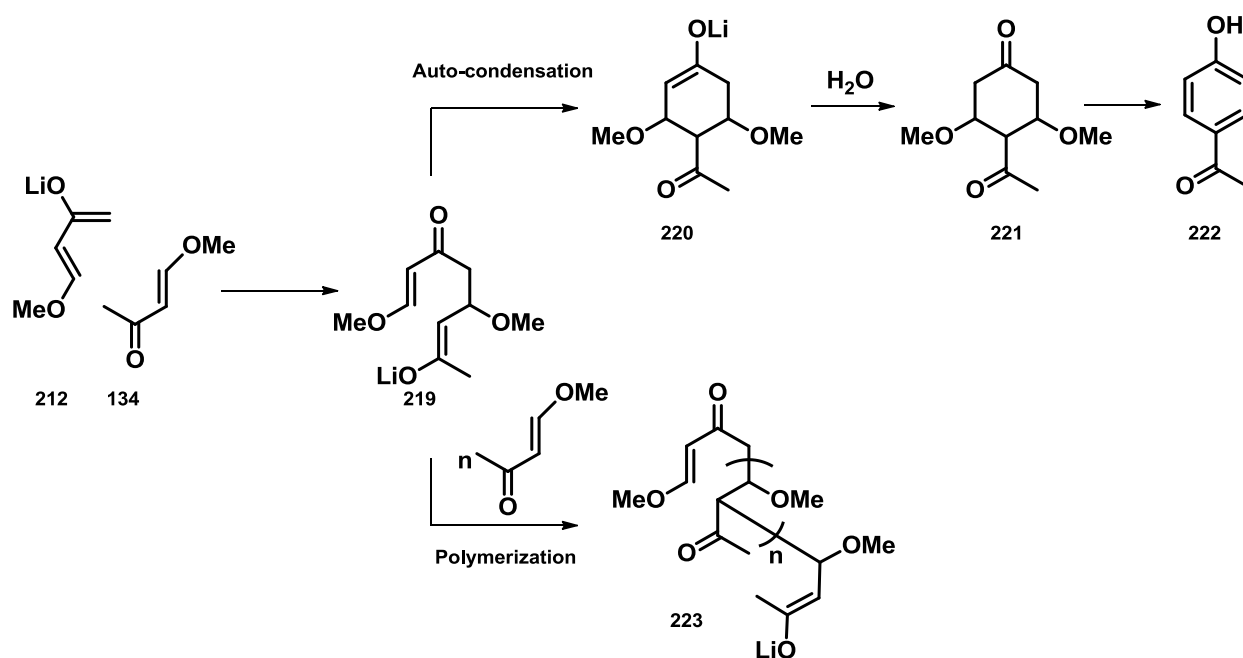


Scheme 73: Strategy for dearomatizing nitroarenes via lithium enolate.

This methodology was based on the enolate formation from *trans*-4-methoxy-3-buten-2-one **134**. This was performed in THF at -78 °C using LDA which was prepared at the same temperature from diisopropylamine and *n*-BuLi.

The main problem in this case could have been the auto-condensation of lithium enolate **212** on its precursor **134**, which is a good Michael acceptor. Polymerization is also possible (Scheme 74). However, the use of LDA, a strong and slightly nucleophilic base, associated with the slow

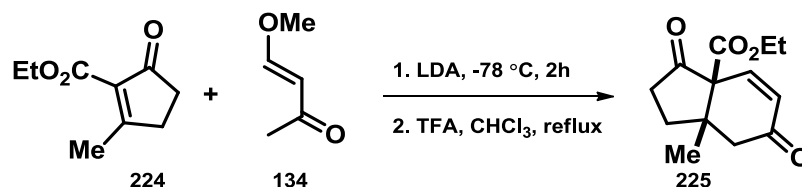
addition of the enone precursor at low temperature, limited these side-reactions and allowed the formation of the enolate in a quantitative manner at low temperature.



Scheme 74: Side reactions between **212** and **134**.

Dr. Karine Pastraud also showed that the *in situ* generated enolate **212** is stable at  $-78\text{ }^\circ\text{C}$ . Upon going to  $-40\text{ }^\circ\text{C}$ , the degradation of the enolate reached 65% within 24 hours. However, at  $-20\text{ }^\circ\text{C}$ , this was faster (60% within 2 hours). For that, the best conditions to perform this reaction were at  $-78\text{ }^\circ\text{C}$  in THF.

To confirm that this enolate **212** can react in a similar manner as the one generated from Danishefsky's diene, she reacted it with a model tetrasubstituted ketone **224** (Scheme 75).



| Entry | Solvent              | Conversion (%)   | d.r.    | Yield (%) |
|-------|----------------------|------------------|---------|-----------|
| 1     | DME/THF <sup>a</sup> | 100 <sup>a</sup> | 100 : 0 | 55        |
| 2     | DME                  | 0                | -       | -         |
| 3     | THF                  | 100 <sup>a</sup> | 100 : 0 | -         |

a: similar to the conditions used by Danishefsky et al.<sup>258</sup>

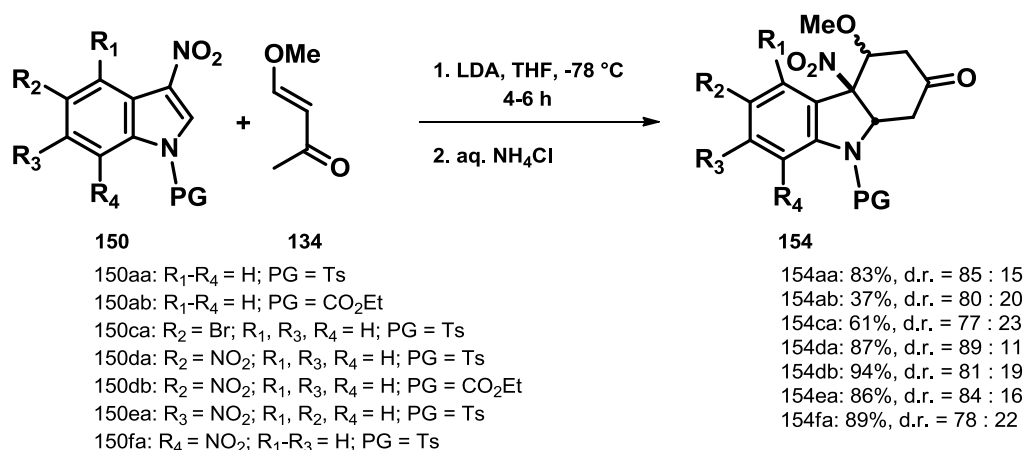
Scheme 75: Reaction between 134 and 224.

Gratifyingly, as shown in the table, the enolate generated in our way led to the same results as those obtained from the Danishefsky's diene.

This led us to use the *trans*-4-methoxy-3-buten-2-one **134** as an enolate precursor for the dearomatization study of various nitroarenes.<sup>260</sup>

### 3 Results and Discussion

#### 3.1 3-nitroindole derivatives and *trans*-4-methoxy-3-buten-2-one enolate



Scheme 76: Dearomatization of 3-nitroindoles 150aa-150fa with 134.

We first demonstrated that 3-nitro-1-tosyl-1*H*-indole **150aa** can act as a Michael acceptor and react with the enolate generated from *trans*-4-methoxy-3-buten-2-one **134** (Scheme 76). The

<sup>260</sup> Pasturaud, K.; Rkein, B.; Sanselme, M.; Sebban, M.; Lakhdar, S.; Durandetti, M.; Legros, J.; Chataigner, I. *Chem. Commun.* **2019**, 55, 7494-7497.

reaction proceeds with a slight excess of enolate **212**. After 4 hours, the reaction mixture was hydrolyzed and we were pleased to observe the complete conversion of the starting aromatic substrate into the expected cycloadduct **154aa**, obtained as a 85 : 15 diastereomeric mixture and isolated in a global 83% yield.

Thus, it is possible to dearomatize 3-nitroindole **150aa** by formal cycloaddition through the nucleophilic activation of the diene partner. Rearomatization of the generated indoline **154aa** by elimination of nitrous acid was not observed under the basic conditions of the reaction. In addition, no strong acidic treatment was required after the conjugate addition to trigger the cyclization step. The higher diastereomeric ratio obtained here compared to the one observed from the Danishefsky's diene (d.r. = 66 : 34) could be due the difference in the mechanism. By which the higher ratio of the obtained *trans* cycloadduct is due to the arrangement of the 1,4-Michael adduct in the more reactive conformation (Figure 30).

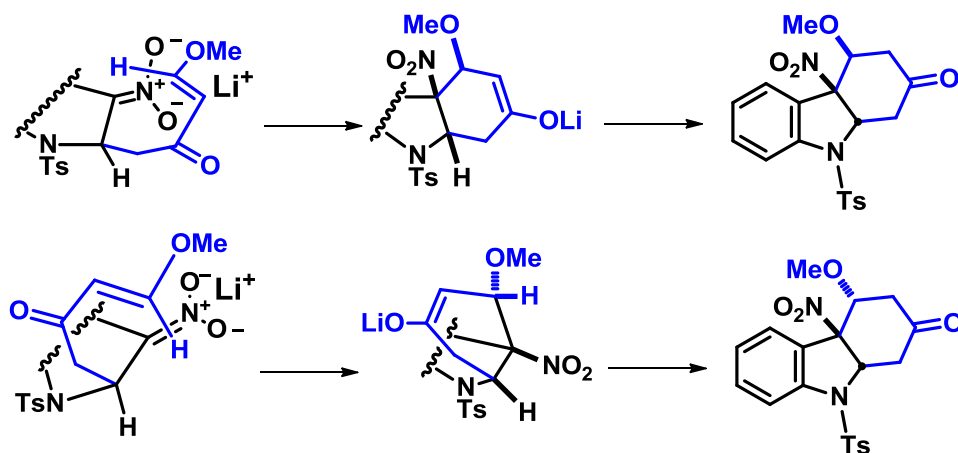


Figure 30: Plausible arrangements of 1,4-Michael adduct to give **154aa**.

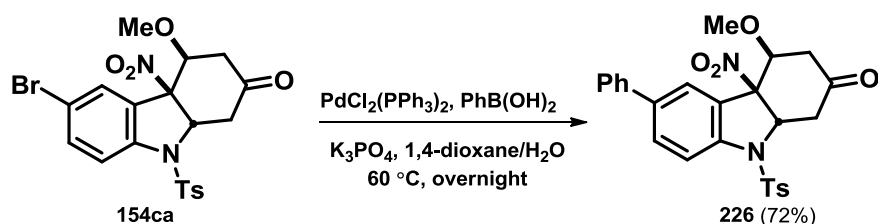
With this result in hand, we then extended this methodology to other nitroindoles. Ethyl-3-nitro-1*H*-indole-1-carboxylate **150ab** was chosen because its supposedly higher reactivity compared to *N*-tosyl indole.<sup>178</sup> In the presence of 1.2 equiv of the same enolate **212**, no starting materials were observed after 5 hours. The purification on silica gel or neutralized silica, afforded the corresponding cycloadduct **154ab** in a low 37% yield and a 80 : 20 diastereomeric ratio along with the deprotected starting indole (Scheme 76). This side reaction thus dramatically limits the desired process.

The indole derivative **150ca** bearing a bromine substituent in position 5, reacted in an analogous way and led to **154ca** isolated in a 61% yield and a 77 : 23 diastereomeric ratio. However, it required 2.4 equiv of the enolate **212** to achieve a complete reaction (Table 19).

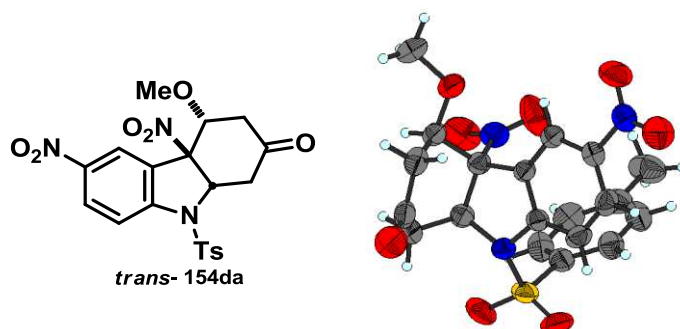
| Enolate quantity (equiv) | Conversion (%) | d.r.    |
|--------------------------|----------------|---------|
| 1.2                      | 62             | 77 : 23 |
| 2.4                      | 100            | 77 : 23 |

Table 19: Reaction of **150ca** and **134** under different conditions.

Notably, a Suzuki coupling was performed with the *cis* brominated tricyclic compound **154ca** and phenylboronic acid, under classical conditions, showing the possible derivatization of this compound (Scheme 77).<sup>261</sup>

Scheme 77: Suzuki coupling of **154ca**.

With an additional nitro substituent on the 6-membered ring of the indole, **150da** reacted similarly, involving regioselectively the C2=C3 moiety of the 5-membered heteroaromatic part as the Michael acceptor. It furnished **154da** in a 87% yield as a 89 : 11 mixture of diastereomers (Scheme 76). The *trans* relative stereochemistry between the nitro and the methoxy groups in the major diastereomer could be confirmed by an X-ray diffraction study on monocrystals of **154da** (Figure 31).

Figure 31: X-ray structure of the major cycloadduct **154da**.

Dinitroindoles **150db**, **150ea** and **150fa** also reacted and gave the corresponding cycloadducts **154db**, **154ea** and **154fa** in 94, 86 and 89% yields respectively, in similar diastereoselectivities (Scheme 76). Noteworthy here, the competitive deprotection of the starting indole carbamate

<sup>261</sup> Düfert, M. A.; Billingsley, K. L.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 12877-12885.



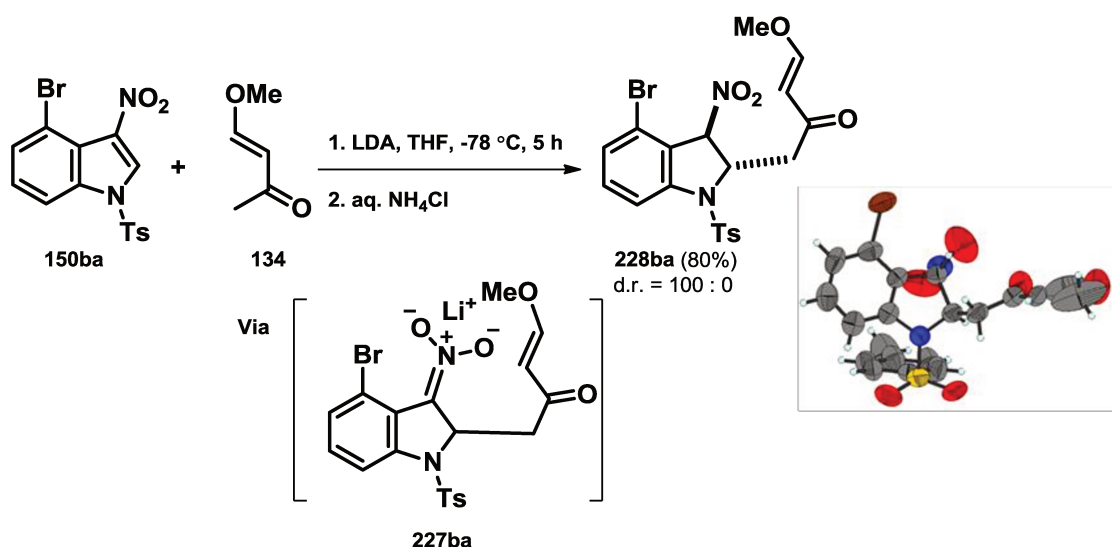
**150db** is not occurring and the tricyclic compound **154db** is obtained in a good yield. This suggests a much faster reaction of the lithium enolate on the more electron-depleted nitroindole derivative **150db**.

Indole derivative bearing a bromine atom in position 4, **150ba**, behaved in a different way (Table 20).

| Enolate quantity (equiv) | Conversion (%) |
|--------------------------|----------------|
| 1.2                      | 56             |
| 1.6                      | 72             |
| 2.4                      | 100            |

Table 20: Conversion of **150ba** in presence of different enolate quantity.

With 1.2 equiv of the enolate **212**, 56% conversion was observed by  $^1\text{H}$  NMR analysis of the crude mixture after 4 hours. Increasing the number of equivalent to 1.6, led to a 72% conversion within the same time. Yet, a 2.4 equiv of the enolate was necessary to get a complete transformation. After hydrolysis, the dearomatized Michael adduct **228ba**, which was expected to be unstable and give back the starting materials, proved stable and was isolated as a single *trans* diastereomer in a 80% yield (Scheme 78). The nitronate intermediate **227ba** did not spontaneously cyclize in this case, and this might be due to the steric hindrance generated by the bromine atom in position 4, close to the potentially reactive center. This result is in line with the more difficult reaction observed with 4-substituted nitroindoles in (3+2) dearomative cycloadditions.<sup>202,204</sup> An X-ray diffraction study on monocrystals of **228ba** confirmed the *trans* stereochemistry between the nitro and the methoxy groups.



Scheme 78: X-ray structure of **228ba** obtained from the reaction between **150ba** and **134**.

In attempt to obtain the cycloadduct, several tests were carried out (Table 21).

As seen in the previous chapter, the reaction of **150ba** with Danishefsky's diene **79** proceeded under thermal conditions (dichloromethane, 42 °C) to give the corresponding cycloadducts **154ba**. For that, we first tested the cyclization under similar conditions (entry 1). However, the Michael adduct **228ba** showed to be stable under such conditions and no change was observed.

Mild acidic conditions were then considered (entry 2). Michael adduct **228ba** was stirred at room temperature on silica. However, it was recovered and no cyclic product was formed. Similar results were obtained when heating **228ba** and silica in dichloromethane at 42 °C overnight (entry 3), showing its stability.

Snyder et al. used 2 equiv of *p*-toluenesulfonic acid (*p*-TSA) for promoting the cyclization during the synthesis of Hajos-Parrish ketone isomer. Considering similar conditions, in our case, did not allow the cyclization and only products of degradation were observed (entry 4).

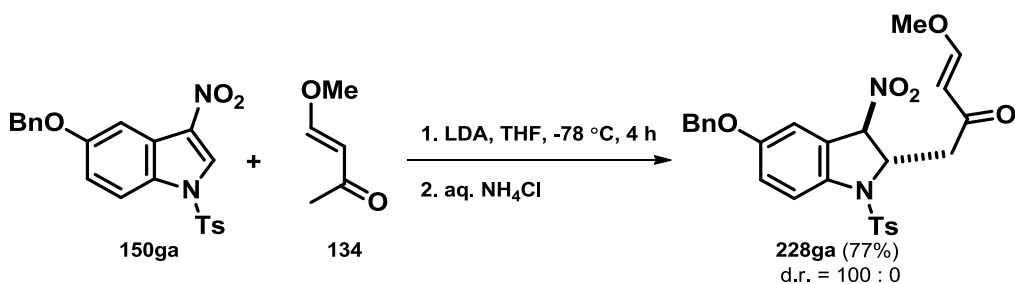
We also tested the conditions reported by Danishefsky et al. Degradation products were also obtained when refluxing **228ba** in presence of trifluoroacetic acid (TFA) in dichloromethane (entry 5).

Basic conditions were also tested (entry 6). However, in presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the only recovered product was the Michael adduct **228ba**.

| Entry | Conditions             | Temperature (°C) | Time (h)  | Product      |
|-------|------------------------|------------------|-----------|--------------|
| 1     | DCM                    | reflux           | overnight | <b>228ba</b> |
| 2     | SiO <sub>2</sub> , DCM | r.t.             | overnight | <b>228ba</b> |
| 3     | SiO <sub>2</sub> , DCM | reflux           | overnight | <b>228ba</b> |
| 4     | <i>p</i> -TSA, DCM     | reflux           | overnight | degradation  |
| 5     | TFA, DCM               | reflux           | overnight | degradation  |
| 6     | DBU, ACN               | -40              | 4         | <b>228ba</b> |

Table 21: Cyclization conditions of **228ba**.

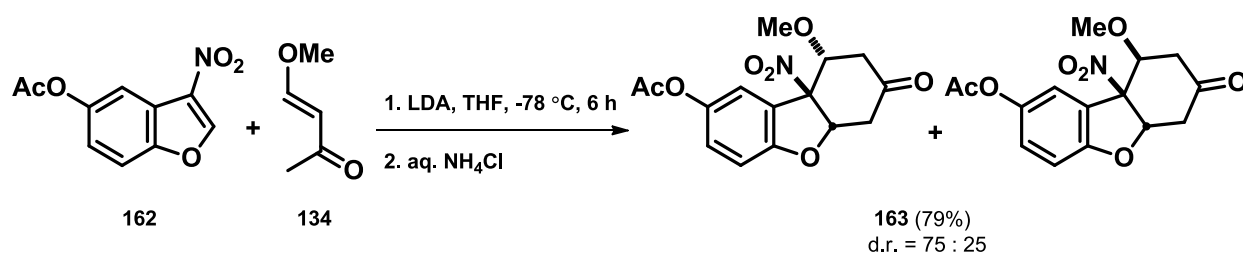
A similar behavior was observed with the 5-benzyloxyindole derivative **150ga**, which afforded the *trans* Michael adduct **228ga** in a 77% yield (Scheme 79). 1.2 equiv of the enolate **212** was sufficient to give a 56% conversion in 2 hours and a total conversion in 4 hours. Cyclization tests could not be performed of this adduct due to its sensitivity to silica or heat or any other conditions, where a retro-Michael addition reaction took place in this case.



Scheme 79: Dearomatization of 5-benzyloxyindole derivative.

The outcome of the last two indole derivatives **150ba** and **150ga** suggests that the cyclic adducts obtained before were, as expected, formal cycloadducts, formed through a two-step sequence.

Benzofuran derivative **162**, also reacted with 1.2 equiv of the enolate **212** to yield the corresponding cycloadduct **163** in a 79% yield and a 75 : 25 diastereomeric ratio (Scheme 80).



Scheme 80: Dearomatizing formal (4+2) cycloaddition reaction of **162**.

Switching from the nitro substituted indoles to derivatives bearing less electron-withdrawing groups such as acetyl **229**, ester **230** or cyano **156** groups unfortunately failed to react under these conditions (Figure 32). Only starting materials and side products were recovered. This shows that a strong electron-withdrawing group more precisely the nitro group is required for the reaction to take place.

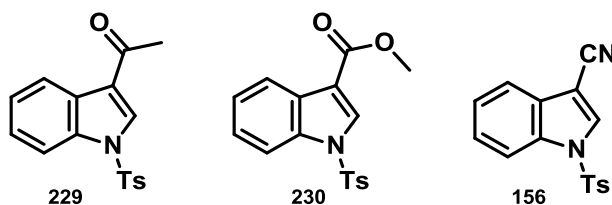
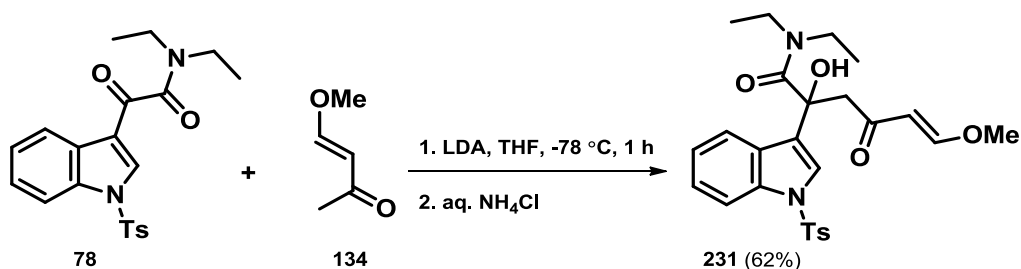


Figure 32: Non-reactive indole derivatives.

*N,N*-diethyl-2-oxo-2-(1-tosyl-1*H*-indole-3-yl)acetamide **78** was also tested under the same conditions. 50% conversion was obtained after 1 hour in the presence of 1.2 equiv of **134**. However, 2.4 equiv led to complete conversion of the starting indole within the same time. Yet, the obtained product **231** was neither the 1,4-Michael adduct nor the formal cycloadduct. It proved to be the product resulting from the direct nucleophilic addition of the lithium enolate on the carbonyl group (Scheme 81). This contrasts with the result observed previously in our laboratory with these indoles when reacted with Danishefsky's diene under high pressure, which led to the dearomatized cycloadducts.<sup>3,116</sup>



Scheme 81: Reactivity of **134** towards **78**.

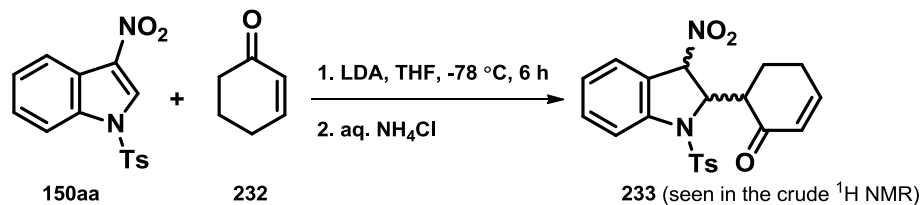
To sum up this part, 3-nitroindole derivatives can be dearomatized at a low temperature using the highly nucleophilic lithium enolate derived from *trans*-4-methoxy-3-buten-2-one. *Trans* 1,4-adducts can be isolated in some cases, or these adducts can undergo one-step beyond and cyclize to furnish the corresponding formal cycloadducts in other cases, in d.r. that are generally a little higher than the ones obtained under the more classical (4+2) cycloaddition reactions, in the presence of Danishefsky's diene.

### 3.2 3-nitro-1-tosyl-1*H*-indole and other enolates

In order to extend the methodology, we next examined other differently substituted enolates.

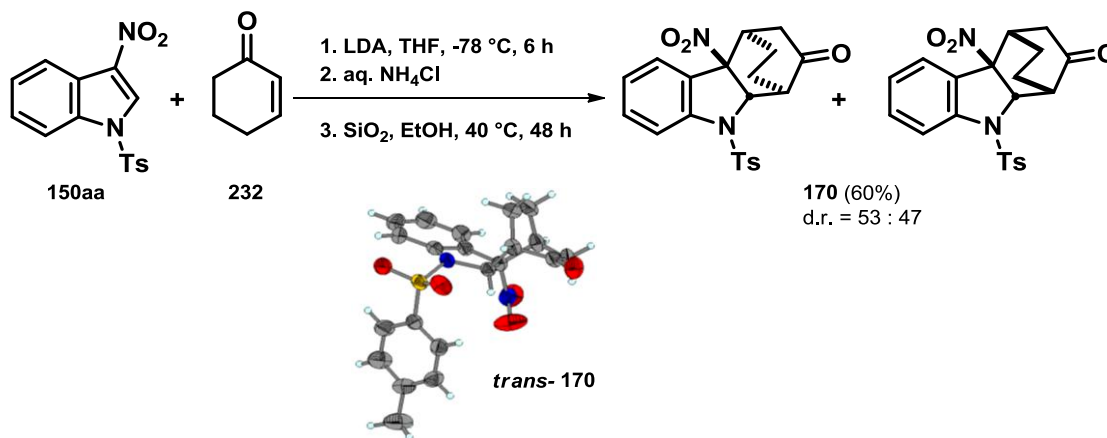
We first selected cyclohexenone **232** as a precursor for the enolate in the reaction towards 3-nitro-1-tosyl-1*H*-indole **150aa**. Under the same operating conditions, a full conversion of the substrate **150aa** was observed within 6 hours (Scheme 82). The resulting 1,4-adduct **233** proved, in this case, to be unstable on silica. Its isolation was difficult since it tends to cyclize during the purification step.<sup>262</sup>

<sup>262</sup> On silica gel, we obtained unclear fractions containing the Michael adduct as well as the cycloadducts.



Scheme 82: 1,4-Michael adduct obtained from the reaction of 150aa and 232.

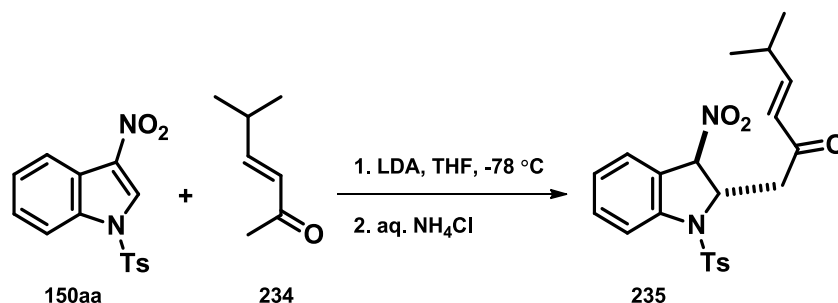
In order to solve the problem of reproducibility, we tried to obtain only the cyclized product. For that, we heated the crude mixture with silica at 40 °C in ethanol. After 48 hours, the disappearance of the 1,4-Michael **233** adduct was confirmed by  $^1\text{H NMR}$  spectroscopy. Purification on silica gel gave the formal cycloadduct **170** in an overall 60% yield as a 53 : 47 mixture of diastereomers (Scheme 83). An X-ray diffraction study on the major diastereomer allowed the assignment of the relative stereochemistry (Scheme 83).



Scheme 83: Formal cycloadduct obtained from 233.

Noteworthy, as seen in the previous chapter, 2-(trimethylsiloxy)-1,3-cyclohexadiene **168** remained inert towards **150aa** at ambient temperature and pressure. The reaction was only possible under high pressure.

With this result, we then tested the isopropyl substituted enolate, generated from 5-methylhex-3-en-2-one **234** (Scheme 84).



Scheme 84: Reaction between 150aa and 234.

This was a more challenging case, the hindrance imposed by the *i*-Pr group being expected to slow down the cyclization step. A 59% conversion was observed after 3 hours at  $-78^\circ\text{C}$  when 1.2 equiv of **234** were used and the *trans* Michael adduct **235** was formed. Increasing the reaction time to 24 hours and using a larger 1.8 equiv excess of **234** led to a 95% conversion.

The purification of this adduct on silica gel proved to be difficult and non-reproducible. Fractions containing starting material, Michael adduct, *cis* cycloadduct and aromatized cycloadduct were obtained in variable ratios.

In attempts to have reproducible results, several tests were performed (Table 22).

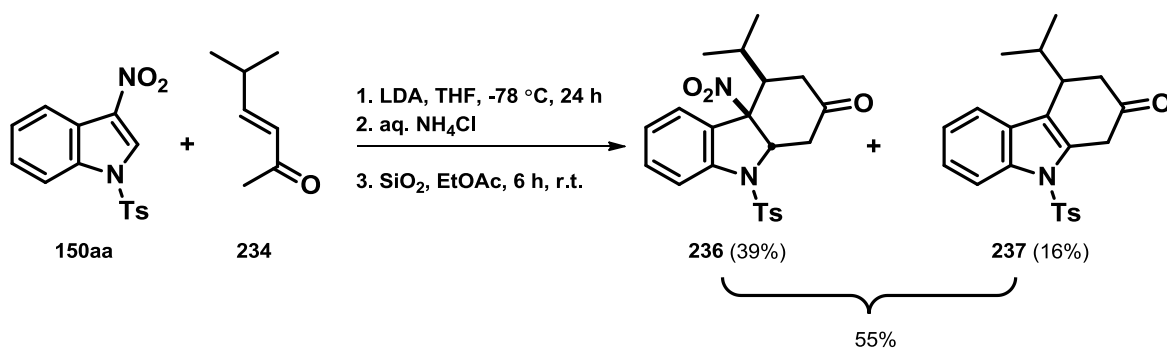
Heating the Michael adduct **235** in dichloromethane only or in ethanol in presence of silica, led to degradation (entries 1 and 2).

Using Snyder or Danishefsky's conditions also failed and only products resulting from degradation were observed (entries 3 and 4). Similar results were obtained under basic conditions using DBU (entry 5).

By noticing that this cyclization was taking place during the purification on silica gel, we thought of stirring the crude mixture with silica in ethyl acetate. Monitoring this test by TLC, showed the disappearance of the 1,4-Michael adduct **235** after 6 hours (entry 6). Successfully, this time, **235** easily cyclized to furnish the corresponding formal cycloadducts. The compound **236** featuring a *cis* relationship between the nitro and *i*-Pr groups was isolated in a 39% yield, while the rearomatized cycloadduct **237** was obtained in a 16% yield (Scheme 85).

| Entry | Conditions               | Temperature (°C) | Time      | Product                   |
|-------|--------------------------|------------------|-----------|---------------------------|
| 1     | DCM                      | reflux           | overnight | degradation               |
| 2     | SiO <sub>2</sub> , EtOH  | 42               | overnight | degradation               |
| 3     | <i>p</i> -TSA, DCM       | reflux           | overnight | degradation               |
| 4     | TFA, DCM                 | reflux           | overnight | degradation               |
| 5     | DBU, ACN                 | r.t.             | 30 min    | degradation               |
| 6     | SiO <sub>2</sub> , EtOAc | r.t.             | 6 h       | <b>236</b> and <b>237</b> |

Table 22: Cyclization tests performed on 235.



Scheme 85: Reactivity of 150aa under the best conditions.

The aromatized product can be explained by an easier elimination of HNO<sub>2</sub> from the *trans* cycloadduct. The structures of **236** and **237** could be firmly assigned thanks to X-ray analyses (Figure 33).

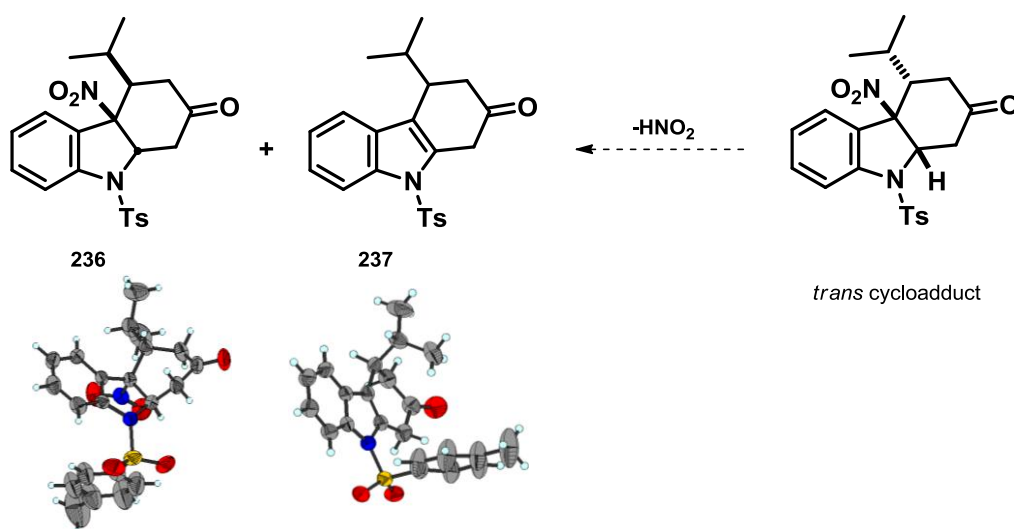
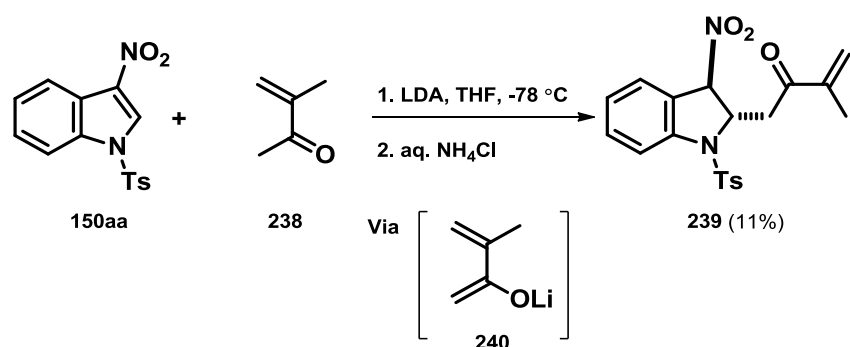


Figure 33: X-ray structures of 236 and 237.

We then tried to perform the reaction with the enolate generated from 3-methyl-3-buten-2-one **238** (Table 23).



| Entry | Number of enolate equivalent | Time (h) | Conversion (%) |
|-------|------------------------------|----------|----------------|
| 1     | 1.2                          | 4        | -              |
| 2     | 1.2                          | 21       | 67             |
| 3     | 1.2                          | 48       | 61             |

Table 23: Reaction of **150aa** and **238** under various conditions.

When 1.2 equiv of **238** were used, no reaction was observed after 4 hours (entry 1). In contrast, when performing the reaction for 21 hours, the starting indole **150aa** was consumed (67% conversion) (entry 2). No better result was observed when leaving the reaction for 48 hours (entry 3). The resulting *trans* dearomatized Michael adduct **239** was formed but proved, in this case, highly unstable on silica and was isolated in a poor 11% yield.

However, it should be mentioned that neither the conditions nor the yields were optimized in this case. The low conversion and yields obtained could be either due to the conditions used (the solvent or the temperature are not adapted for the enolate obtained from **238**) or due to the favored backward reaction. Attempts to cyclize the intermediate Michael adduct should now be performed to try to promote a smooth cyclization reaction on the resulting  $\beta$ -unsubstituted enone.

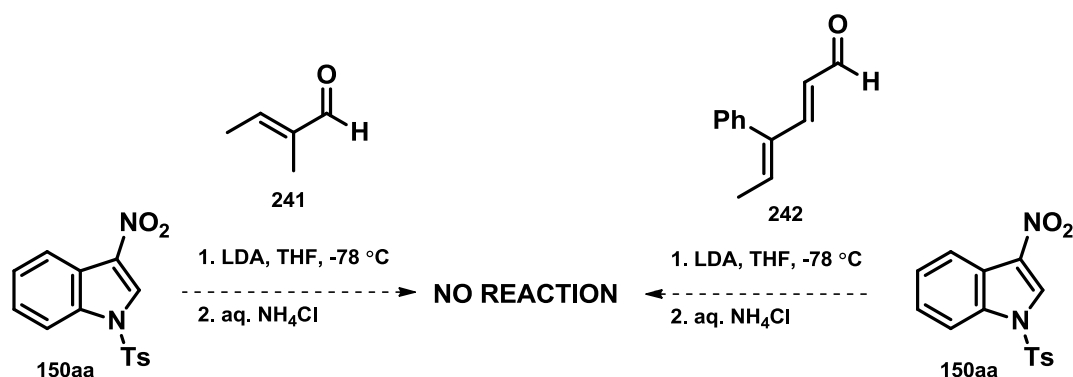
We then tested the reactivity of lithium enolates obtained from aldehydes rather than from ketones, towards 3-nitroindole **150aa**. The reaction between **150aa** and *trans*-2-methyl-2-butenal **241** or with 4-phenylhexa-2,4-dienal **242**<sup>263,264</sup> was performed under the same conditions. Keeping the reaction mixture for 24 hours at -78 °C did not show any change in both

<sup>263</sup> Deagostino, A.; Prandi, C.; Toppino, A.; Venturello, P. *Tetrahedron* **2008**, *64*, 10344-10349.

<sup>264</sup> Zhou, J.-H.; Jiang, B.; Meng, F.-F.; Xu, Y.-H.; Loh, T.-P. *Org. Lett.* **2015**, *17*, 4432-4435.



cases (Scheme 86). Even when the temperature was increased to room temperature, only starting materials were recovered.



Scheme 86: Testing the reactivity of **150aa** with **241** and **242**.

To conclude, extending the methodology to other enolate precursors is possible. The reactivity of both enolates generated from cyclohexenone **232** and 5-methylhex-3-en-2-one **234** gave the corresponding 1,4-Michael adducts. The case was different when using aldehydes (**241** and **242**), their lithium enolate showed to be inert towards 3-nitroindole **150aa**.

### 3.3 Other nitroaromatics and enolates

The application of this methodology was then extended to more demanding nitroarenes. Dr. Karine Pasturaud had demonstrated that the addition of deaggregating agent was required to perform these reactions. Lithium enolates indeed form aggregates in solution (generally tetrameric ones)<sup>265,266</sup> and their reactivity is notably influenced by the size of these clusters. The addition of deaggregating agents favor the formation of smaller and more reactive species.<sup>267,268</sup>

Dr. Karine Pasturaud first examined the influence of various deaggregating agents (Figure 34) in the reaction of 1,5-dinitronaphthalene **116b** and *trans*-4-methoxy-3-buten-2-one **134** (Table 24).

<sup>265</sup> Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2459-2463.

<sup>266</sup> Guang, J.; Liu, Q. P.; Hopson, R.; Williard, P. G. *J. Am. Chem. Soc.* **2015**, *137*, 7347-7356.

<sup>267</sup> Houghton, M. J.; Collum, D. B. *J. Org. Chem.* **2016**, *81*, 11057-11064.

<sup>268</sup> Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028-2038.

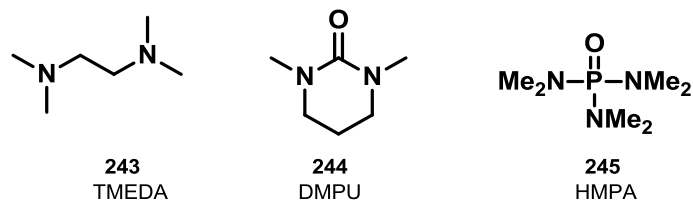
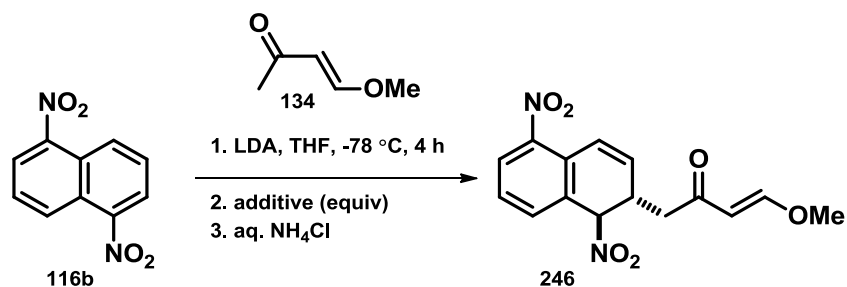


Figure 34: Structure of various deaggregating agents.

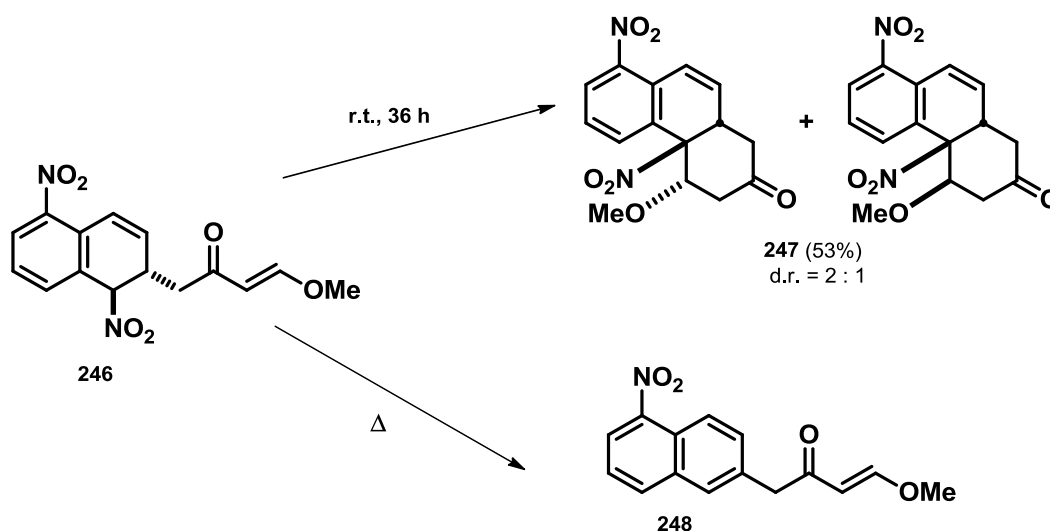


| Entry | Additive (equiv)       | Conversion (%) | Yield (%) |
|-------|------------------------|----------------|-----------|
| 1     | None                   | -              | -         |
| 2     | TMEDA <b>243</b> (1.2) | Traces         | -         |
| 3     | DMPU <b>244</b> (1.2)  | 28             | -         |
| 4     | HMPA <b>245</b> (1.2)  | 97             | 79        |
| 5     | HMPA <b>245</b> (4.8)  | 100            | 82        |

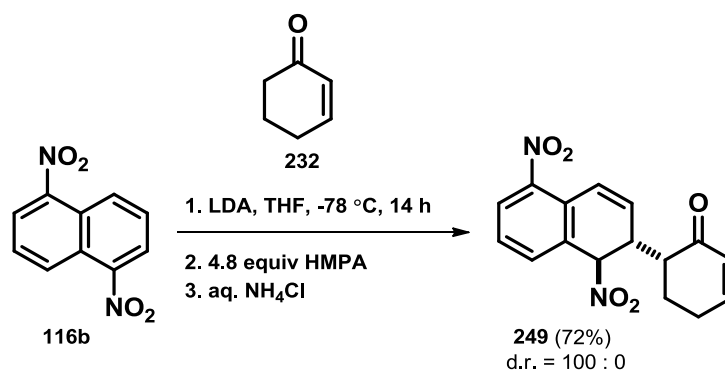
Table 24: The effect of deaggregating agents on the reaction between **116b** and **134**.

As shown in Table 24, under conditions similar to the ones used for nitroindole derivatives; no reaction was observed (entry 1). However, traces of the expected adduct were formed in the presence of 1.2 equiv of TMEDA **243** (entry 2). Switching from TMEDA to DMPU **244** improved the conversion to 28% (entry 3). The best results were obtained with HMPA **245** which allowed nearly complete conversion of the 1,5-dinitronaphthalene **116b** into its Michael adduct **246** (entry 4). Increasing the amount of HMPA to 4.8 equiv led to complete conversion and slightly increased the isolated yield (entry 5). The 1,4-adduct **246** was stable enough to be purified on column chromatography and could be isolated as a single *trans* diastereomer in a 82% yield.

The obtained 1,4-Michael adduct **246** gave the corresponding cycloadduct **247** when maintained at room temperature for 36 hours in a 53% yield (over the two steps). The cyclization took place under smooth conditions and the rearomatization **248** was not observed unless heating was performed (Scheme 87).


 Scheme 87: Transformations of 1,4-Michael adduct **246**.

The dearomatization of 1,5-dinitronaphthalene **116b** could be also performed in the presence of the enolate generated from cyclohexenone **232** and 4.8 equiv of HMPA **245**. The corresponding 1,4-Michael adduct **249** was obtained as a single *trans* diastereomer in a 72% yield (Scheme 88).


 Scheme 88: Reactivity of **116b** with the enolate generated from **232**.

The same strategy also allowed to dearomatize 3-nitropyridine. The enolate generated from *trans*-4-methoxy-3-buten-2-one **134** can add onto the pyridine core, giving the 1,4-dihydropyridine **250** in a 71% yield (Figure 35). The regioselectivity of the addition is in line with the reported data involving the nucleophilic addition reactions on 3-substituted pyridines.<sup>37,143</sup>

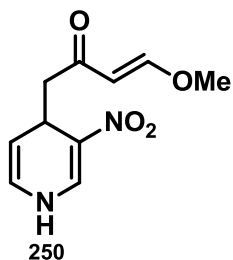


Figure 35: Structure of 1,4-dihydropyridine.

### 3.4 Extending the reaction to enantioselective version

In an attempt to perform this reaction in an enantioselective manner, the reaction was conducted in the presence of different chiral amines through the formation of chiral mixed aggregates (Figure 36).

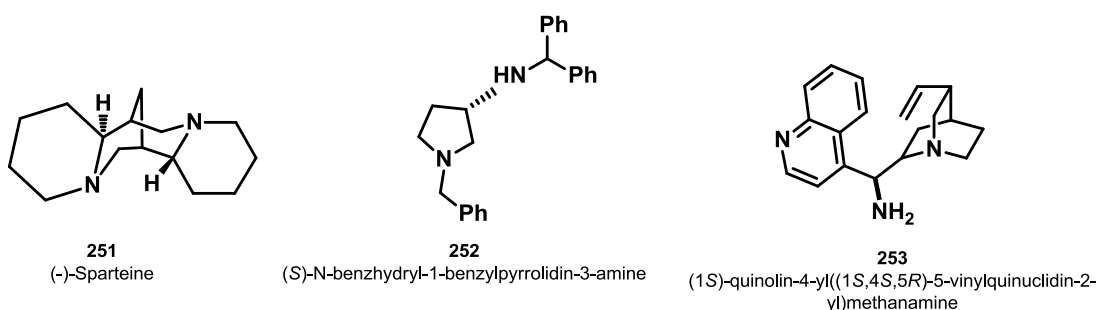
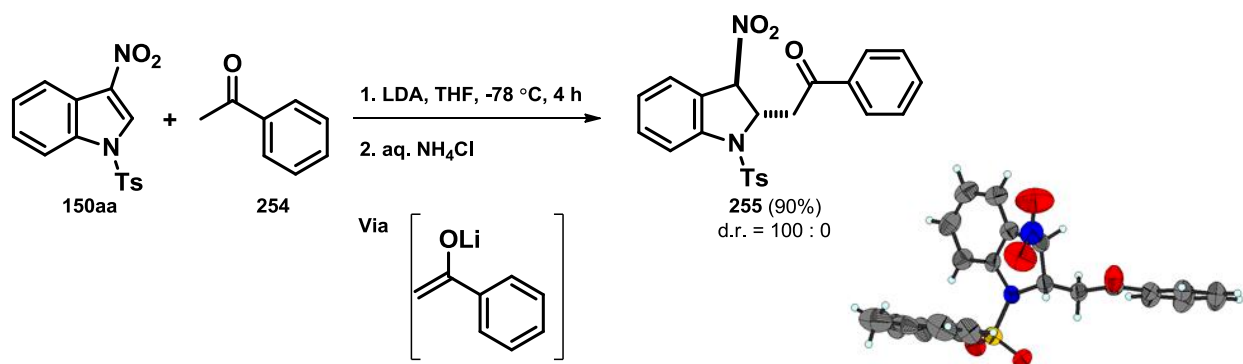


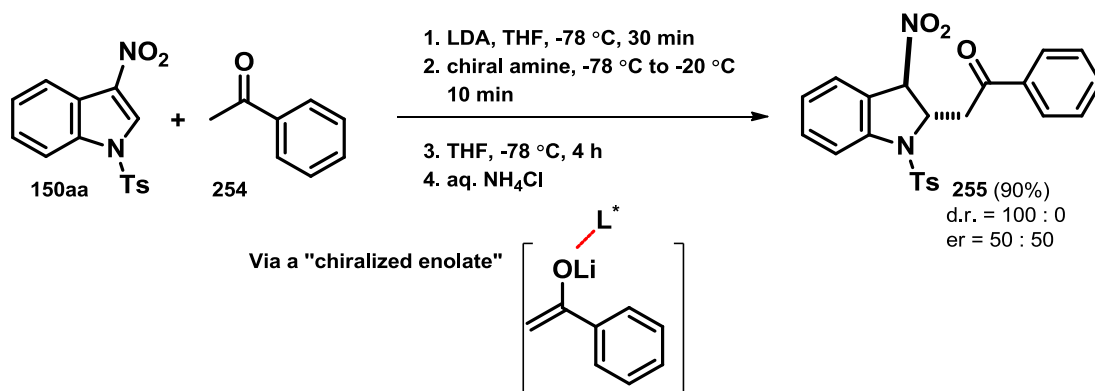
Figure 36: Structures of chiral amines.

For this, we first performed a reaction between **150aa** and acetophenone **254** under similar conditions without the use of any chiral amine (Scheme 89). The reaction was complete within 4 hours and the *trans* 1,4-Michael adduct **255** was isolated in a 90% yield. An X-ray diffraction study on monocrystals of **255** confirmed the *trans* stereochemistry between the nitro and the ketonic groups.



Scheme 89: Reaction between 150aa and 254.

The same reaction was then repeated but in the presence of chiral amines **251**, **252** and **253**. The operating conditions were the same until the generation of the enolate. After which we added the chiral amine (1.2 equiv) and the reaction mixture was transferred to a  $-20\text{ }^{\circ}\text{C}$  bath. This step was essential to allow the exchange between the diisopropoyl amine and the chiral amine.<sup>269</sup> After 10 minutes, the reaction was cooled to  $-78\text{ }^{\circ}\text{C}$  and stirred for 4 hours (Scheme 90).



Scheme 90: Reaction between **150aa** and **254** in presence of different chiral amines.

The same *trans* adduct **255** was isolated in the three cases in a 90% yield. Chiral HPLC revealed the absence of any enantiomeric excess in the reactions with amines **251** and **252**. However, gratifyingly, with the cinchona based amine **253**, an encouraging 22% excess was measured by chiral HPLC. Due to time constraints, other chiral amines have not been tested yet.

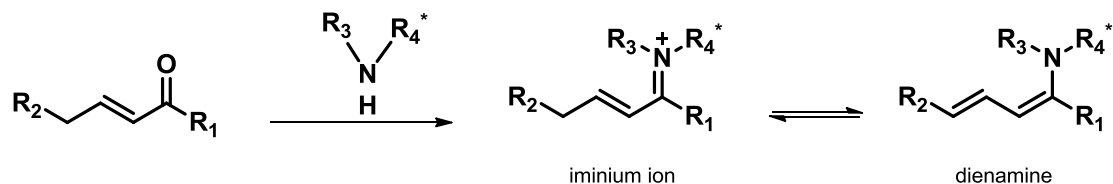
In conclusion, cinchona-based amine **253** showed that it can induce an enantioselective process, and other tests (amines, conditions) will have to be done to optimize this preliminary result.

### 3.5 Extending the reaction to dienamine derived process

The first use of dienamines in Diels-Alder reaction was reported in 1939 by H. R. Snyder.<sup>270</sup> The process is based on a unique activation mode which exploits the condensation of a chiral secondary amine catalyst on a  $\alpha,\beta$ -unsaturated aldehyde or ketone. This condensation leads to the formation of the expected electrophilic iminium ion intermediate, which is in equilibrium with an electron-rich dienamine intermediate (Scheme 91).

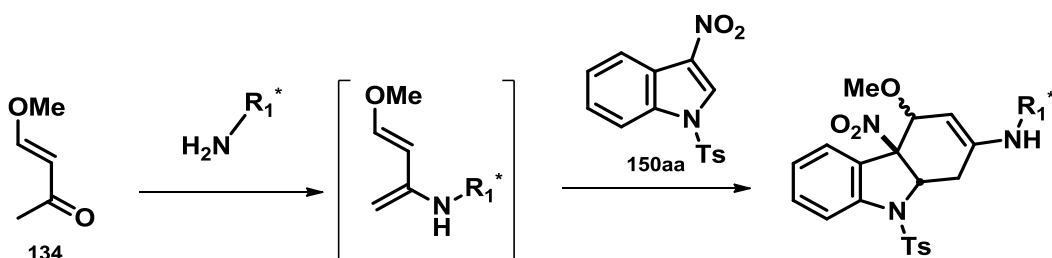
<sup>269</sup> Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1995**, *117*, 891-900.

<sup>270</sup> Snyder, H. R.; Hasbrouck, R. B.; Richardson, J. F. *J. Am. Chem. Soc.* **1939**, *61*, 3558-3560.



Scheme 91: Dienamine catalysis.

The use of this HOMO raising strategy in Diels-Alder reaction was reported by many groups.<sup>271,272,273,274</sup> For that, we tested if this strategy could work in our case (Scheme 92).



Scheme 92: Dienamine strategy for dearomatizing 3-nitroindole 150aa.

Urea-based amino catalyst **71** and cinchona-based primary amine **256** were selected for this study (Figure 37).

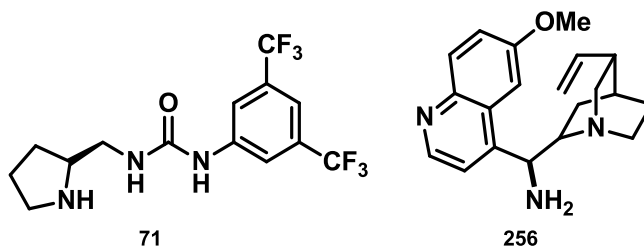


Figure 37: Structures of the organocatalysts.

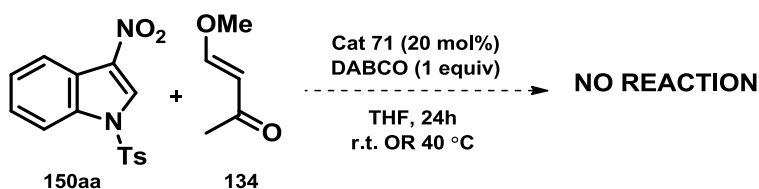
We first considered the urea based amino catalyst **71** used by Jørgensen et al.<sup>145</sup> in the enantioselective dearomatizing (4+2) reaction of 3-nitroindoles by trienamine catalysis. The use of a ketonic precursor in our case was not optimal and, when performing the reaction in the presence of DABCO, at room temperature or at 40 °C, only starting materials were recovered after 24 hours (Scheme 93).

<sup>271</sup> Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865-887.

<sup>272</sup> Ren, Q.; Wang, J. *Asian J. Org. Chem.* **2013**, 2, 542-557.

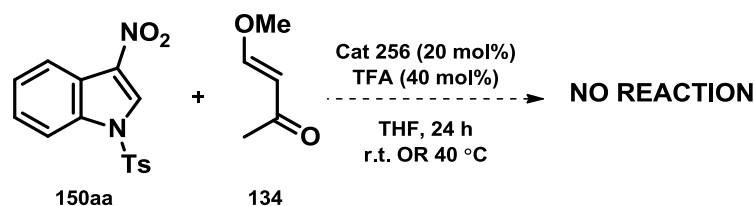
<sup>273</sup> Liu, K.; Chougnet, A.; Woggon, W.-D. *Angew. Chem. Int. Ed.* **2008**, 47, 5827-5829.

<sup>274</sup> He, X.-L.; Zhao, H.-R.; Duan, C.-Q.; Han, X.; Du, W.; Chen, Y.-C. *Chem. Eur. J.* **2018**, 24, 6277-6281.



Scheme 93: Reaction between 150aa and 134 in presence of catalyst 71.

Similarly, when considering the reaction with the cinchona-based primary amine **256**, for a more favorable ketone activation,<sup>275</sup> unfortunately no reaction was observed in the presence of an acid co-catalyst (Scheme 94).



Scheme 94: Cinchona-based primary amine catalyzed reaction between 150aa and 134.

The dienamine activation with a ketonic precursor thus seems less promoting than the nucleophilic activation.

## 4 Conclusion

In this chapter, we have described the dearomatization of nitroaromatic derivatives at low temperature via formal (4+2) cycloaddition reactions. This takes place using the highly nucleophilic lithium enolates which are obtained directly from the corresponding methyl vinyl ketone derivatives by the action of LDA.

This methodology has been developed previously in our laboratory, and is considered a method that is easy to implement and to reproduce. It is advantageous over the methodologies developed by Baker and Danishefsky. Firstly, it does not use the rather expensive Danishefsky's diene. Secondly, our methodology is easier to implement: no need for a mixture of solvents, modification of the temperature or cannulation. Finally, the cycloadducts can be obtained without strong acidic treatments.

Differently substituted enolates reacted with 3-nitroindole derivatives in a dearomatizing formal (4+2) cycloaddition to give the polycyclic indoline structures in good yields (Figure 38). In

<sup>275</sup> Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 2-25.

these reactions, the nitro group is essential for the reaction to occur, as indoles with less-electron withdrawing groups showed to be inert, showing the limitation of this methodology.

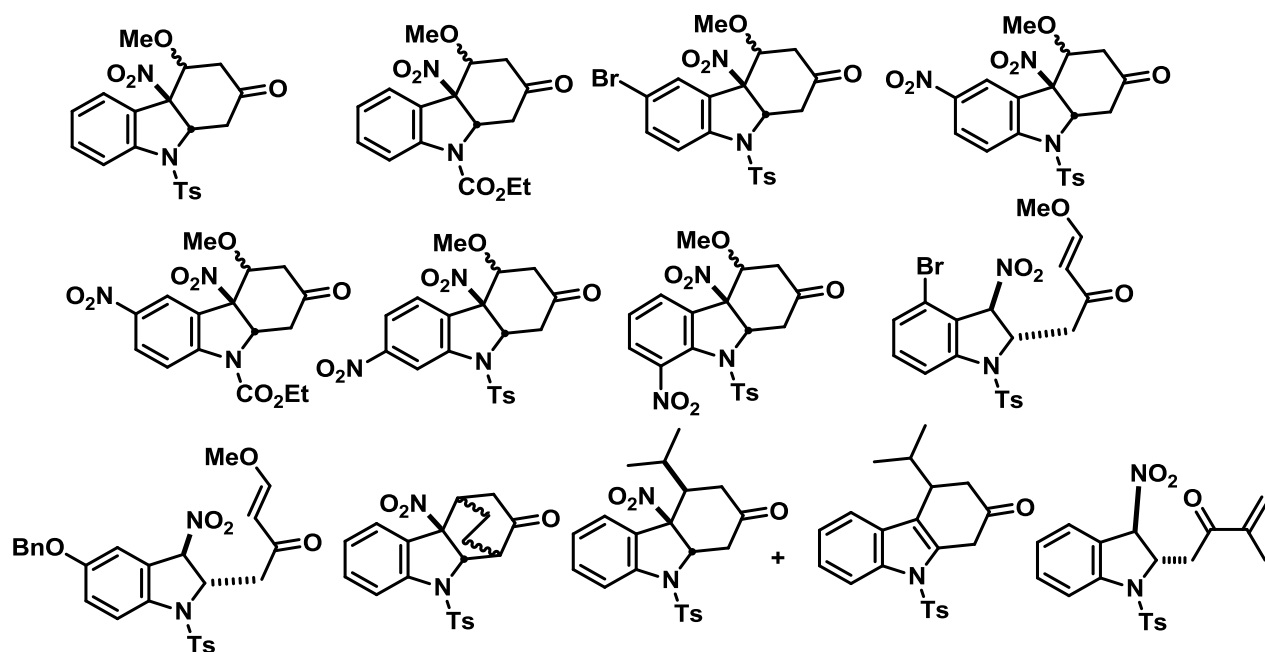
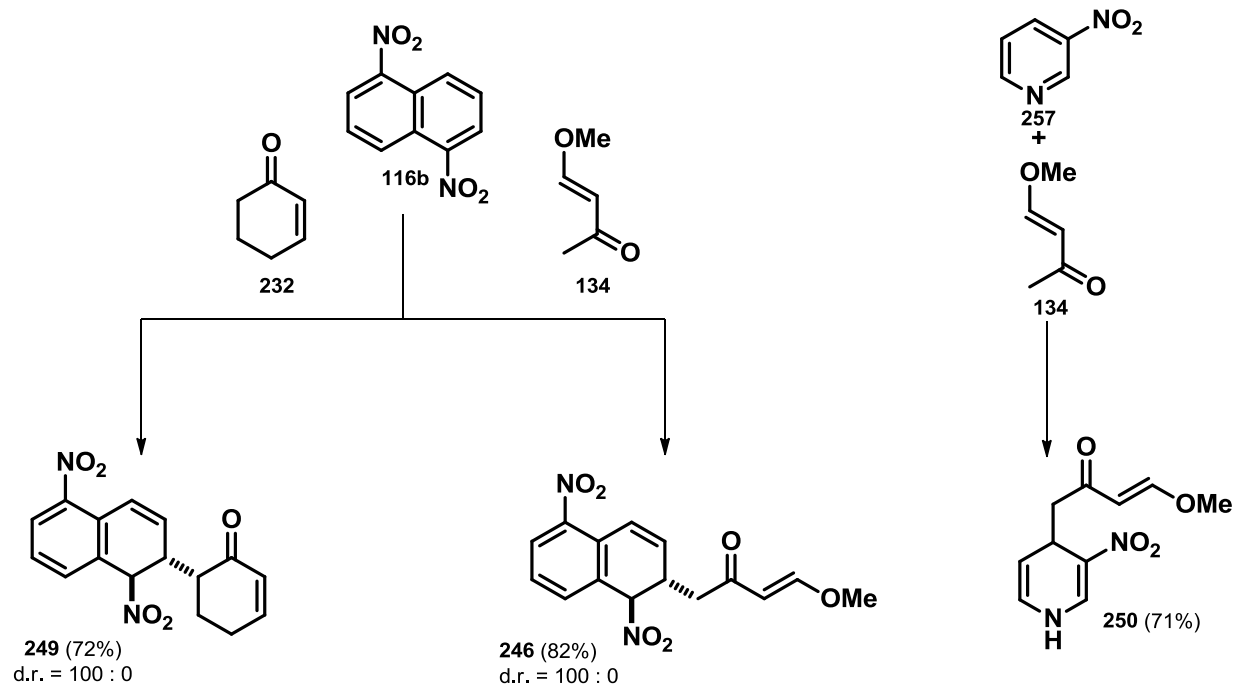


Figure 38: Indoline structures obtained from the dearomatization of nitroindole derivatives.

More challenging nitroaromatics (1,5-dinitronaphthalene **116b** and 3-nitropyridine **257**) can also undergo dearomatization reactions using this methodology but in the presence of HMPA **245** (Scheme 95).





Scheme 95: Dearomatization of nitroarenes.

## **Chapter IV. Conclusion & Perspectives**



*«Imagination is more important than knowledge»*

Albert Einstein



## 1 General Conclusion

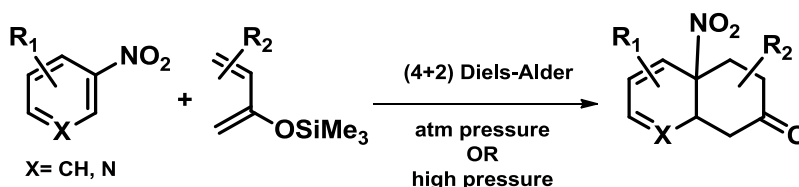
The use of dearomatization strategies to generate 3D scaffolds from commercially available aromatics has steadily increased in the recent decades and will likely continue to grow in the future. Even if several efficient dearomatizing methods have been reported, the development of complementary methodologies is still needed.

In this context, cycloaddition reactions, and more specifically the (4+2) Diels-Alder reactions, remain a method of choice widely used in organic synthesis. They represent an efficient and reliable approach to construct poly(cyclic) compounds in a single step.

In these reactions, aromatics are mainly used as dienes due to their electron-richness. However, the dienophilic behavior of electron-depleted aromatics is more scarcely described.

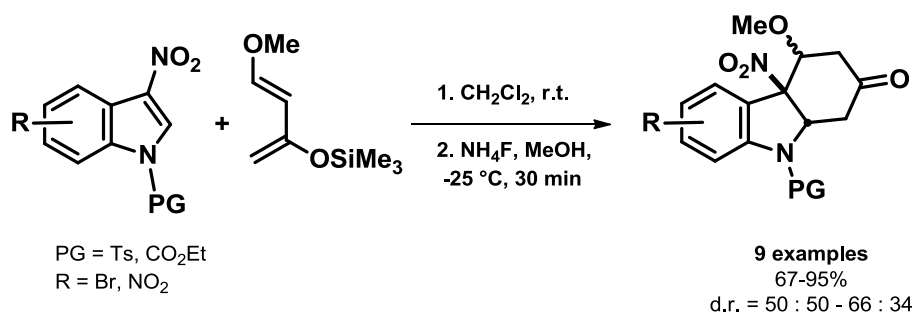
Therefore, in this work we aimed at studying the dienophilic/electrophilic character of different electron-poor aromatics in dearomatizing NED (4+2) cycloaddition/annulation reactions.

Firstly, we have studied the involvement of the dienophilic character of various nitroaromatics in (4+2) Diels-Alder reactions towards mild silyloxydienes. Such reactions can proceed either at atmospheric (atm) or high pressure depending on the substrate (Scheme 96).



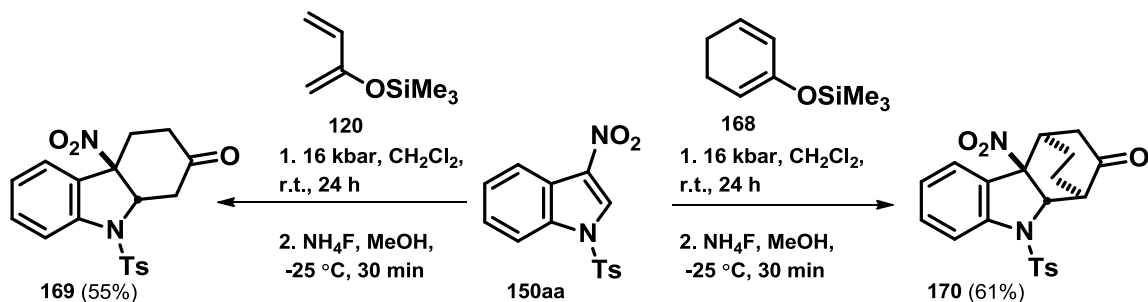
**Scheme 96: Dearomatizing (4+2) Diels-Alder reactions of nitroaromatics with silyloxydienes.**

All indole derivatives reacted efficiently with Danishefsky's diene in NED Diels-Alder reaction at ambient temperature and atmospheric pressure. The dearomatized cycloadducts can be isolated as a mixture of diastereomers in good yields (Scheme 97).



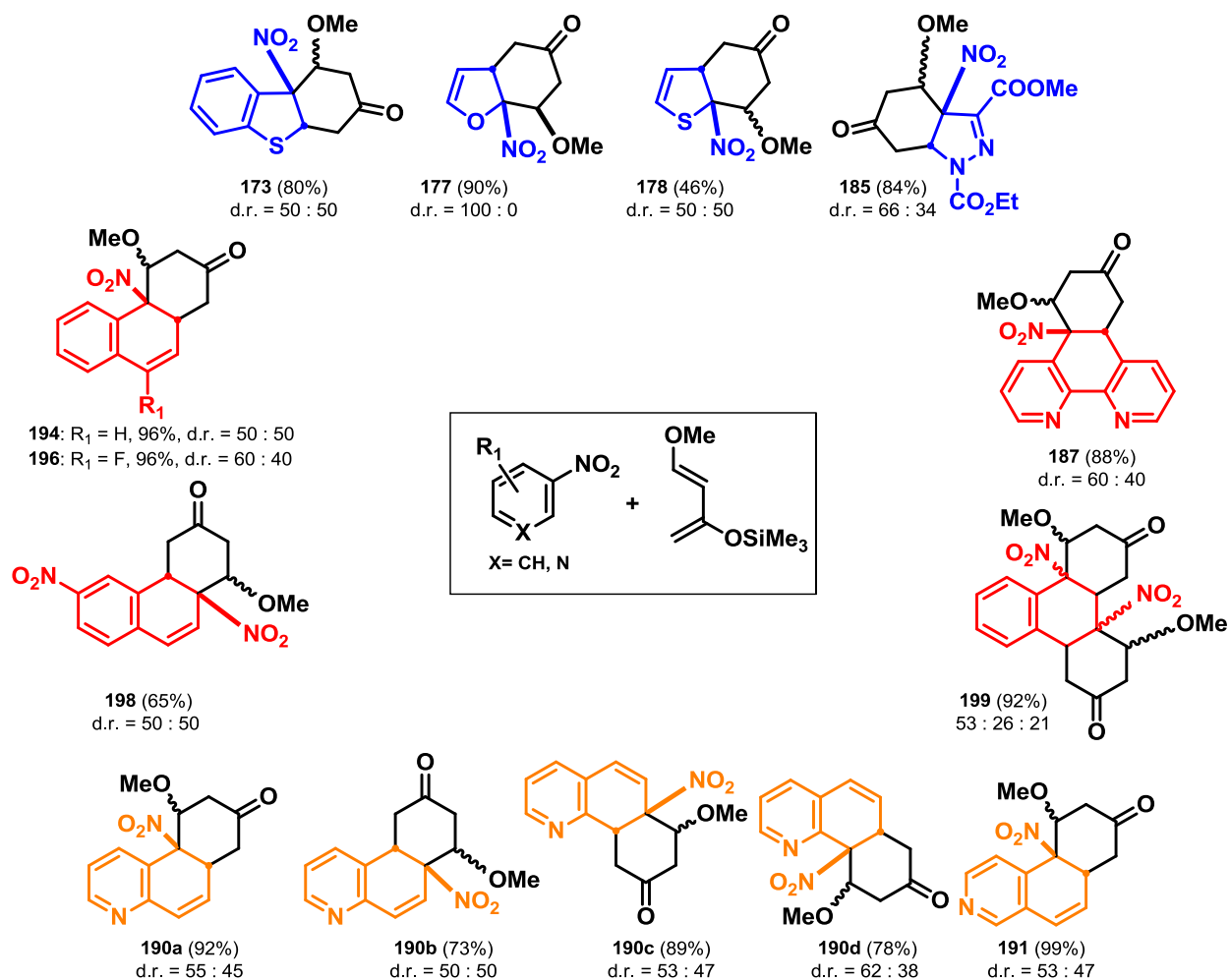
Scheme 97: Reactivity of nitroindole derivatives towards Danishefsky's diene.

With silyloxydienes **120** and **168**, the (4+2) cycloaddition reaction required a pressure of 16 kbar to proceed (Scheme 98).



Scheme 98: Reactivity of 3-nitro-1-tosyl-1H-indole towards silyloxydienes **120** and **168**.

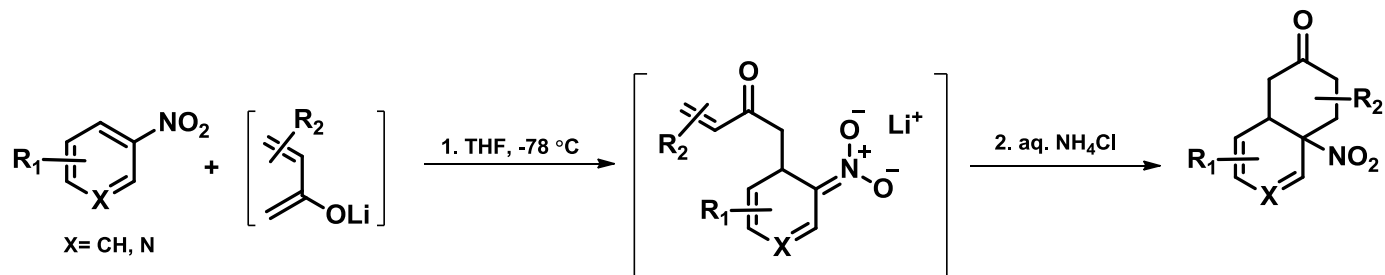
The application of high pressure also allowed us to obtain the dearomatized cycloadducts from more demanding nitroaromatics thus enlarging the scope of this reaction (Scheme 99).



**Scheme 99: Cycloadducts obtained from the reactivity of nitroarenes and Danishefsky's diene.**

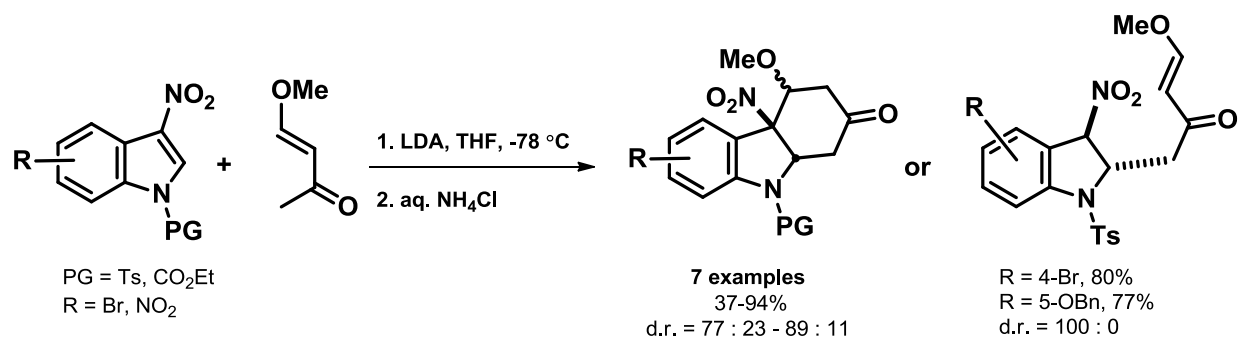
Secondly, we have developed a methodology to dearomatize electron-poor aromatics without the use of the expensive Danishefsky's diene. This was based on the nucleophilic activation of methyl vinyl ketones using LDA at  $-78\text{ }^{\circ}\text{C}$ . The condensation of lithium enolates on nitroaromatics gave directly the formal cycloadducts without strong acidic treatments (Scheme 100). In this case, the mechanism is most probably stepwise, involving the formation of an intermediate nitronate adduct.





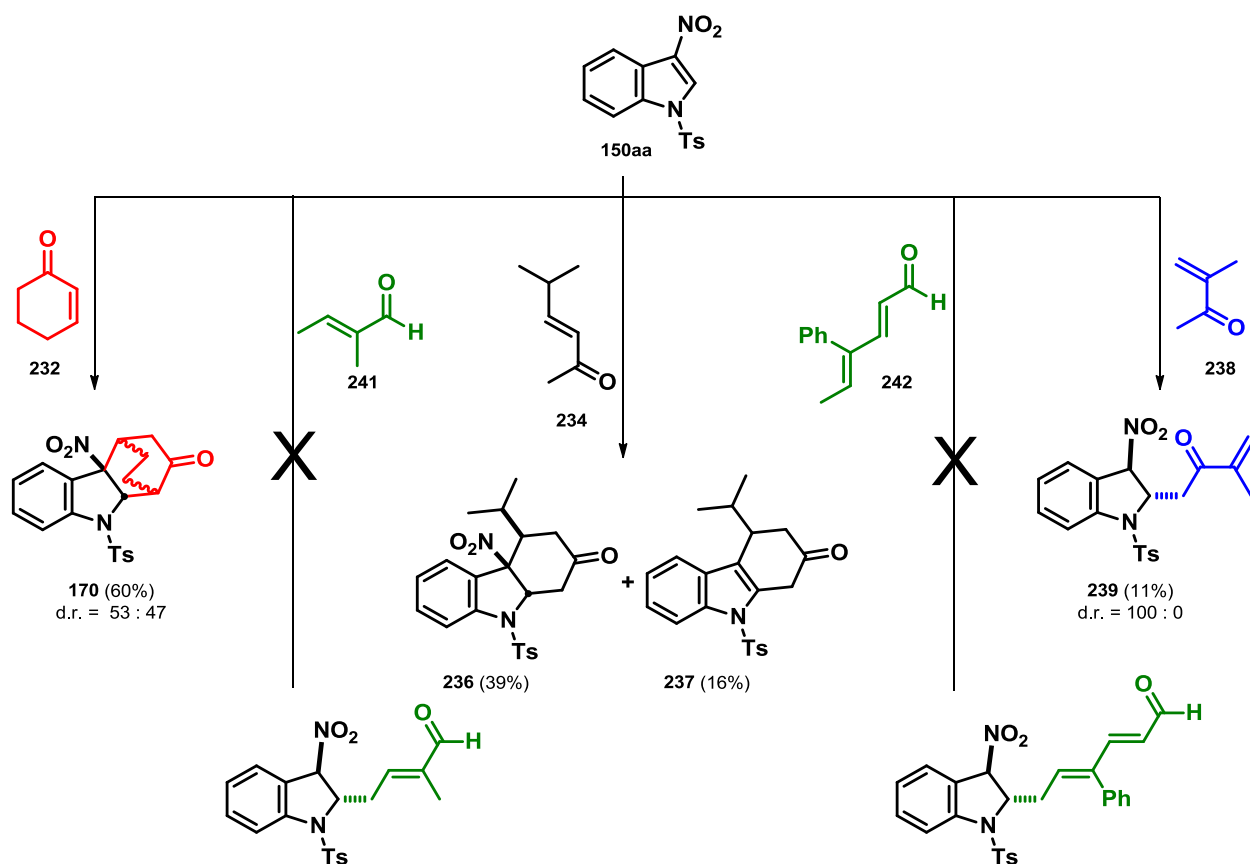
**Scheme 100: Formal (4+2) dearomatizing cycloaddition reactions via lithium enolates.**

Using this methodology, the dearomatization of nitroindole derivatives was achieved to give the corresponding formal cycloadducts or 1,4-Michael adducts, depending on the substrate, in modest diastereoselectivity and satisfactory to excellent yields (Scheme 101).



**Scheme 101: Dearomatization of 3-nitroindole derivatives.**

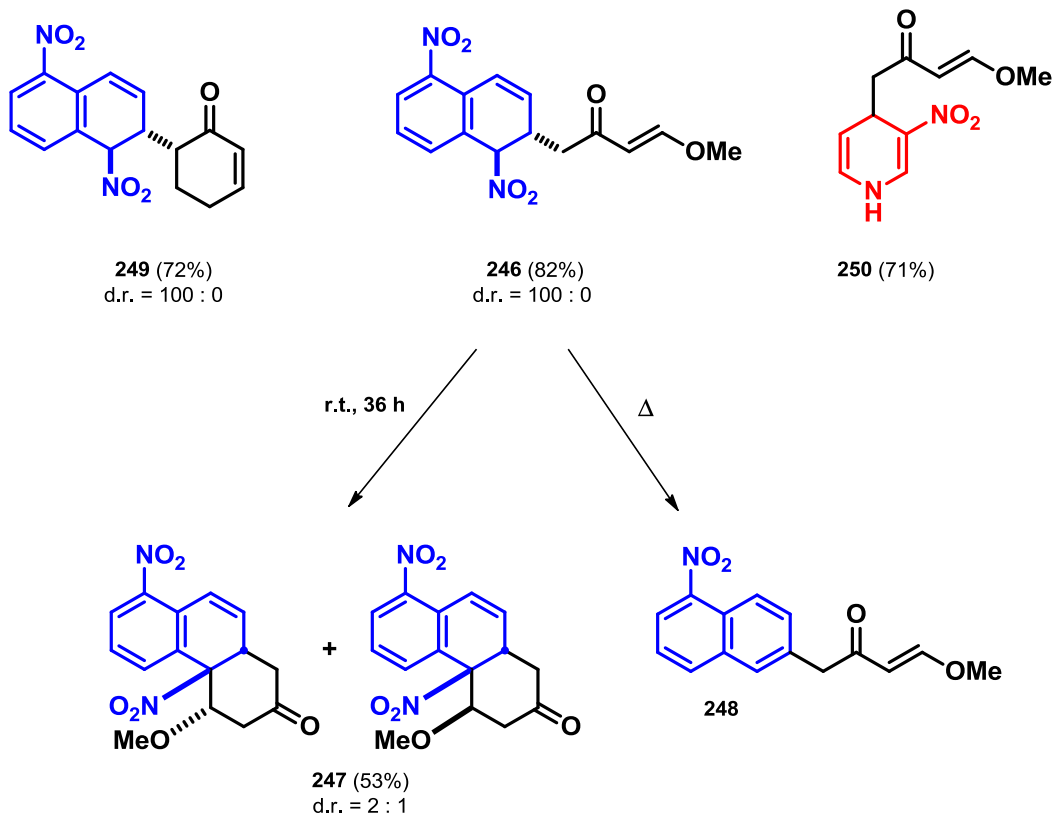
Extending the reaction to other lithium enolates was also carried out giving the corresponding 1,4-Michael adducts, which easily cyclized to the corresponding cycloadducts under weak acidic conditions (Scheme 102).



Scheme 102: Polycyclic indoline structures.

This methodology also made it possible to dearomatize more challenging aromatics in presence of HMPA **245**, a deaggregating agent. This allowed access to dearomatized and functionalized structures derived from 1,5-dinitronaphthalene **116b** and 3-nitropyridine **257** (Scheme 103).

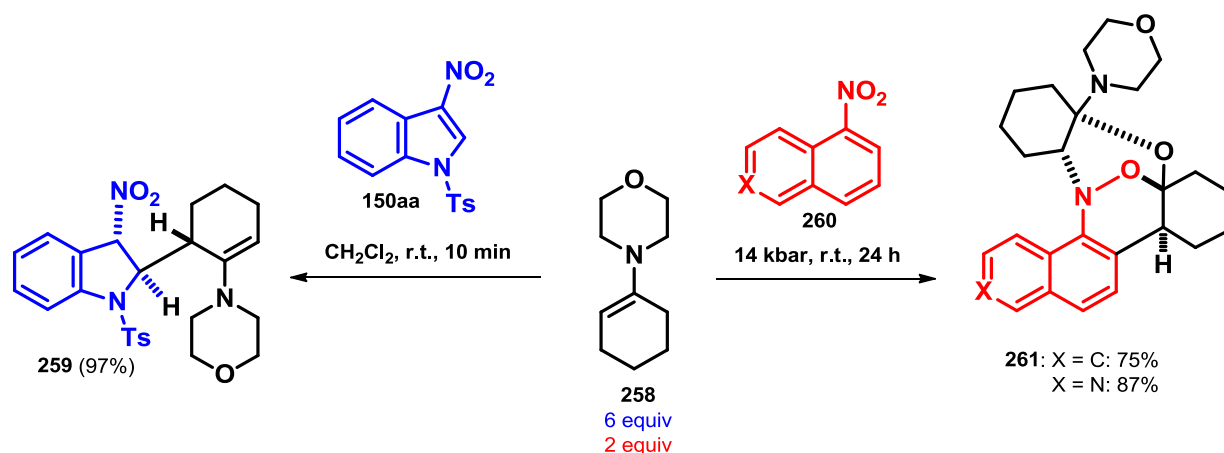
Conclusion & Perspectives



Scheme 103: Dearomatization of 1,5-dinitronaphthalene and 3-nitropyridine.

## 2 Perspectives

In 2016, our group reported the addition of 4-(cyclohex-1-en-1-yl)morpholine **258** on 3-nitroindole **150aa**.<sup>42</sup> This reaction is fast and efficient and requires no activation, neither chemical nor physical. However, this reaction required hyperbaric conditions when going to more challenging nitroarenes **260** and the obtained products were much more complex **261** (Scheme 104).<sup>276</sup>



Scheme 104: Nucleophilic addition of enamine **258** on nitroaromatics.

Noteworthy, when nitroarene and enamine are mixed; a strong coloration of the reaction medium was observed indicating the possible formation of electron donor-acceptor (EDA) complex or charge transfer complex (Figure 39).

<sup>276</sup> Diab, S.; Noël-Duchesneau, L.; Sanselme, M.; Kondo, Y.; De Paolis, M.; Chataigner, I. *Eur. J. Org. Chem.* **2018**, 2048-2052.

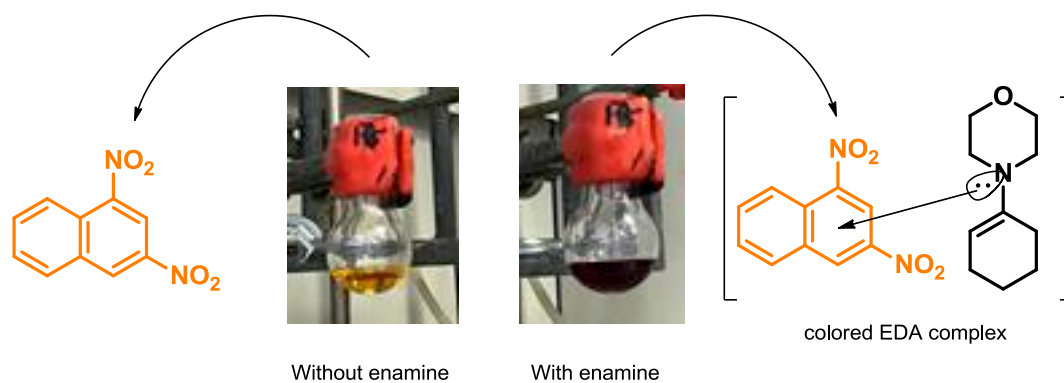
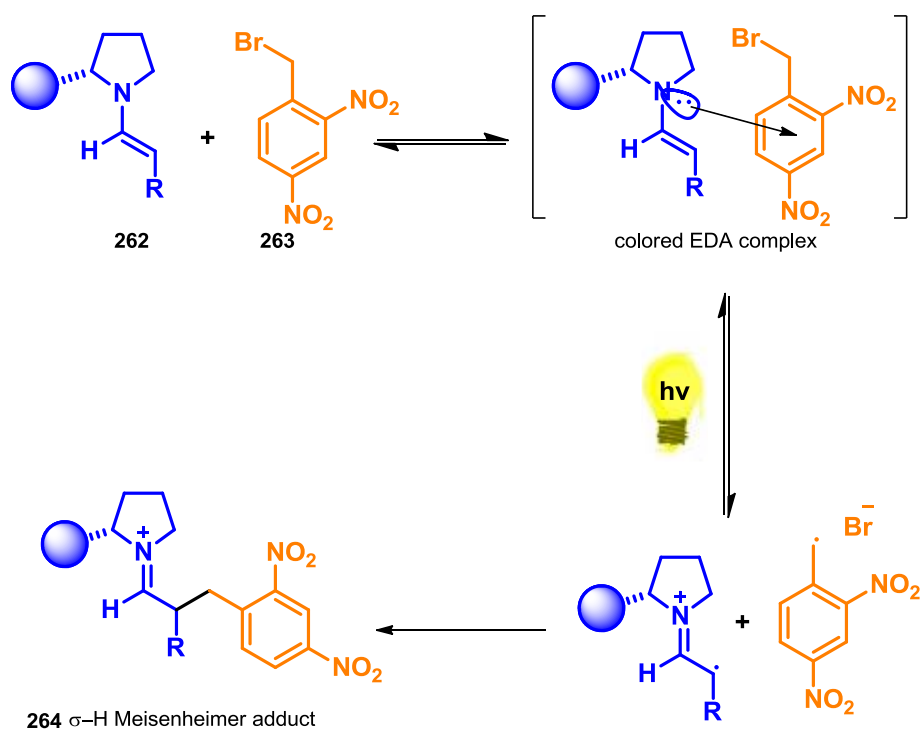


Figure 39: EDA complex between 1,3-dinitronaphthalene and enamine 258.

Such complexes are advantageous because of the possibility to activate them photochemically as reported by Melchiorre et al. (Scheme 105).<sup>277,278,279</sup>



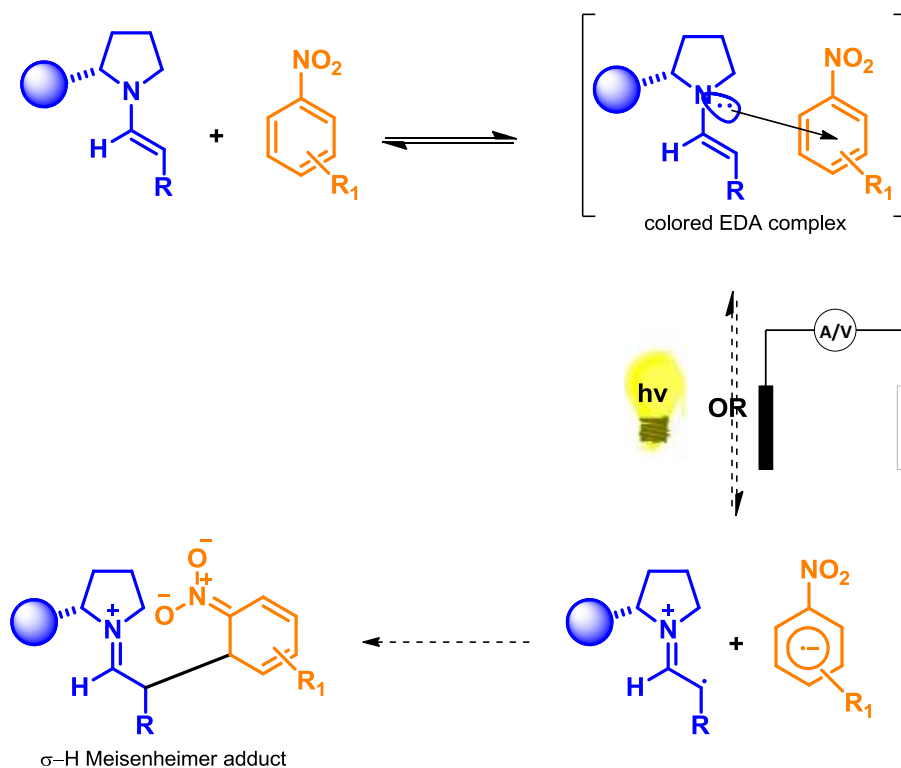
Scheme 105: Light induced  $\alpha$ -alkylation of aldehydes.

<sup>277</sup> Arceo, E.; Jurberg, I. D.; Álvarez-Fernández, A.; Melchiorre, P. *Nat. Chem.* **2013**, *5*, 750-756.

<sup>278</sup> Arceo, E.; Bahamonde, A.; Bergonzini, G.; Melchiorre, P. *Chem. Sci.* **2014**, *5*, 2438-2442.

<sup>279</sup> Kandukuri, S. R.; Bahamonde, A.; Chatterjee, I.; Jurberg, I. D.; Escudero-Adán, E. C.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2015**, *54*, 1485-1489.

We therefore envisaged the activation of the addition of enamines on nitroarenes, photochemically ( $h\nu$ ) or electrochemically.<sup>280,281</sup> In the presence of electron-depleted nitroarenes, this activation would give the radical species (radical anion and radical cation) which could then react to give the dearomatized Meisenheimer complex. This would potentially lead to the formation of a new connection directly on the arene under mild conditions and in the absence of metals (Scheme 106).

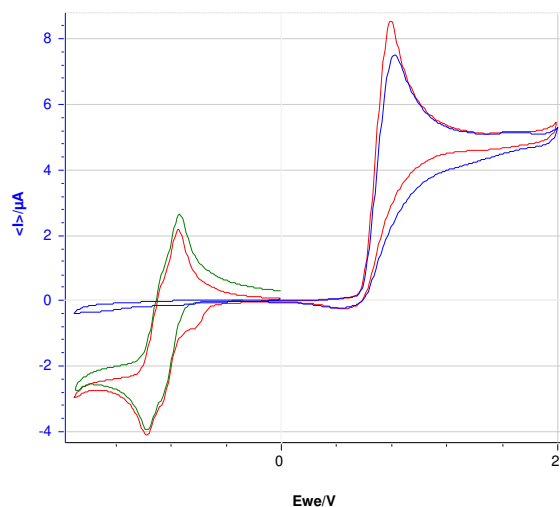


**Scheme 106: New strategy to activate the nucleophilic additions on nitroarenes.**

To confirm this idea, we have first studied the electrochemical behavior of enamine **258**, 1,5-dinitronaphthalene **116b** as well as their mixture (Figure 40). 4-(cyclohex-1-en-1-yl)morpholine **258** is oxidisable at 0.8V/SCE.

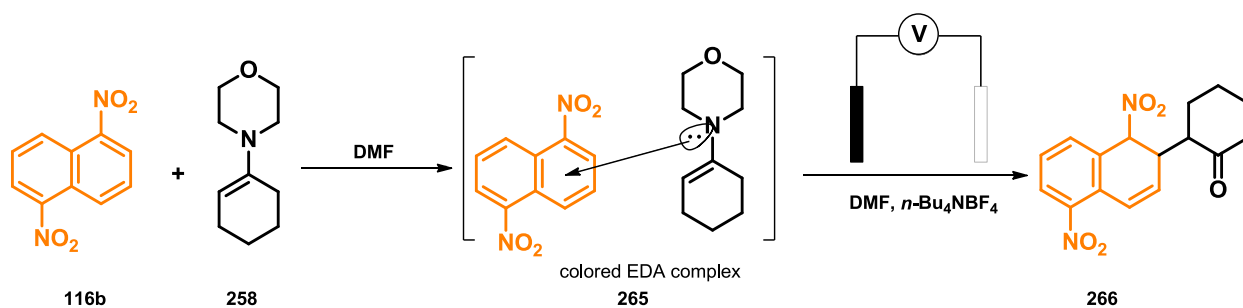
<sup>280</sup> Gallardo, I.; Guirado, G.; Marquet, J. *Chem. Eur. J.* **2001**, *7*, 1759-1765.

<sup>281</sup> Gallardo, I.; Guirado, G.; Marquet, J. *Chem. Commun.* **2002**, 2638-2639.



**Figure 40:** Cyclic voltammograms of enamine **258** (blue), 1,5-DNN **116b** (green) and their mixture (red) in DMF (0.1 M *n*-Bu<sub>4</sub>NBF<sub>4</sub>; scan rate 200 mVs<sup>-1</sup>).

This let us to set up conditions for the electrochemical activation of the enamine. The best results were obtained when performing the electrolysis at a constant voltage of 1 V with graphite cathode and gold anode in DMF in an undivided cell, and *n*-Bu<sub>4</sub>NBF<sub>4</sub> as the electrolyte at room temperature (Scheme 107). Under these conditions, we have isolated a product **266** corresponding to the addition of the enamine **258** to 1,5-dinitronaphthalene **116b**.



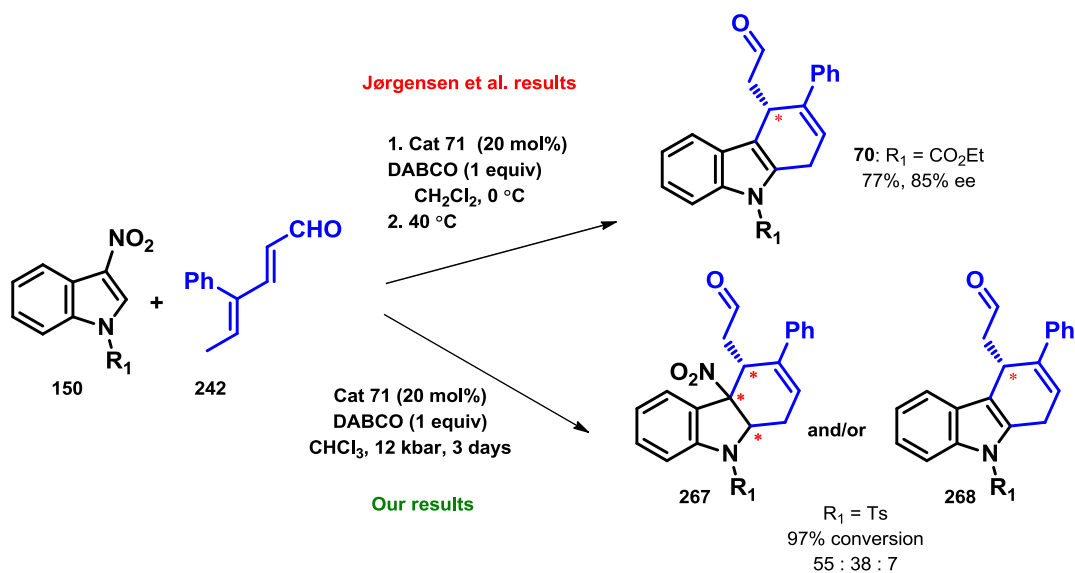
**Scheme 107:** Electrochemical activation of the addition of enamine **258** on 1,5-dinitronaphthalene.

However, this reaction was not reproducible (the starting materials were recovered most of the times), and secondary reactions were taking place (reduction of both the nitro group to NH<sub>2</sub> and the double bond of the enamine). For that, further investigations should be done to confirm the obtained product, to find the best conditions and to enlarge the scope.

On the other hand, we were interested in the addition of trienamines on nitroaromatics. It has been shown by Jørgensen et al. that trienamine (generated *in situ* from dienal and organocatalyst in presence of a base) can react with nitroindole derivatives at 0 °C to give the

corresponding rearomatized cycloadducts after heating in basic conditions at 40 °C.<sup>145</sup> From this result, we wondered if high pressure could activate the trienamine pathway, allowing its reactivity with nitroarenes and thus giving the dearomatized products instead (Scheme 108).

Primary results showed that the reaction could proceed at 12 kbar yielding **267** and/or **268** as 3 products in a 55 : 38 : 7 ratio within 3 days (Scheme 108). We indeed observed the formation of the expected dearomatized cycloadducts **267** (93% of the mixture, 59 : 41 diastereomeric ratio). They were however accompanied by a small amount of the rearomatized compound **268** (7%).



Scheme 108: Our results versus Jørgensen et al. results.

Optimization of the conditions, confirmation of the structures, determination of the stereochemistry of the obtained diastereoisomers and enlarging the scope of this reaction have to be done.





## **Chapter V. Experimental Part**



«If we knew what it was we were doing,  
it would not be called research, would it?»

Albert Einstein



Chromatographic purifications were performed on silica gel (mesh size 60-80  $\mu\text{m}$ ) using the procedure described by Still.<sup>282</sup> Analytical thin layer chromatography was performed on silica gel plates (Merck® TLC Silica gel 60 F254) and the spots were visualized by illumination with a UV lamp ( $\lambda = 254/365 \text{ nm}$ ) and/or staining with  $\text{KMnO}_4$ .

RP-HPLC (Synchronis  $\text{C}_{18}$  column, 3  $\mu\text{m}$ , 100  $\times$  2.1 mm) was performed with  $\text{CH}_3\text{CN}$  and 0.1% trifluoroacetic acid (aq. TFA 0.1%, pH 2.0) as eluents [100% TFA then linear gradient from 0% to 100% of  $\text{CH}_3\text{CN}$ ] at a flow rate of 0.25 mL/min. Detection was achieved in the range of 400-800 nm.

Unless otherwise noted, all chemicals were used as received from commercial sources without further purification. Anhydrous MeOH was purchased from Sigma Aldrich and stored over 4 $\text{\AA}$  molecular sieves. THF was dried on sodium and freshly distilled over Na/benzophenone before use. Dichloromethane and diisopropylamine were dried over calcium hydride. Filtrations were performed on Celite SDS 545 from Acros Organic. HPLC gradient-grade acetonitrile ( $\text{CH}_3\text{CN}$ ) was obtained from VWR. Mobile layers for RP-HPLC were prepared with ultrapure water (18.2 M $\Omega$ .cm) provided by a PURELAB® flex 1 (Elga Veolia).

$^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  NMR spectra were recorded with a Bruker DPX 300 (COBRA, UMR CNRS 6014). Chemical shifts are expressed in parts per million (ppm) using the residual solvent peak for calibration. Coupling constants (J) are expressed in Hz. The following abbreviations were used in the spectral description: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), br (broad signal), m (multiplet).

Infrared spectra (IR) were obtained on Perkin-Elmer spectrum 100 FT-IR. Wavelength ( $\nu$ ) were reported in  $\text{cm}^{-1}$  and only the strongest or structurally most important peaks are listed.

High-resolution mass spectrometry (HRMS) were recorded either on a Thermo LTQ Orbitrap XL apparatus equipped with an ESI source or on a LCT Premier XE bench top orthogonal acceleration time-of-flight (oa-TOF) mass spectrometer (Waters Micromass) equipped with an ESI source.

Melting points (Mp) were measured with a Kofler apparatus from Wagner and Munz.

The hyperbaric reactions were realized with Unipress apparatus for 12 kbar pressure and with Psika Pressure Systems Ltd. apparatus for 16 kbar experiments.

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<sup>282</sup> Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

## 1 Preparation of Starting Materials

### 1.1 Preparation of indole derivatives

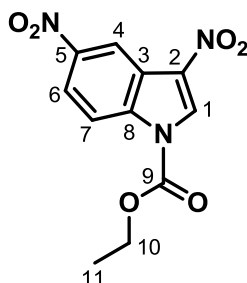
#### Protection:

Protection of indole derivatives was performed as reposted in the literature.<sup>283</sup>

#### Nitration:

Acetyl nitrate was generated by the dropwise addition of acetic anhydride (2 mL) to 100% HNO<sub>3</sub> (10 equiv) at 0 °C and allowed to stand at room temperature for 10 minutes before use. To a stirred solution of the corresponding protected indole (1 equiv) in acetic anhydride (4 mL) at -78 °C was added the acetyl nitrate dropwise. The mixture was stirred for 1 h at -78 °C and 1 h at room temperature before cold ice (25 mL) was added. The aqueous solution was extracted with EtOAc (3\*10 mL), the combined organic layers were dried over MgSO<sub>4</sub>, filtered and the solvents were evaporated under reduced pressure. The crude mixture was purified by recrystallization from hot methanol.

#### Ethyl 3,5-dinitro-1H-indole-1-carboxylate (**150db**)



Following the general procedure, **150db** was obtained as white solid in 50% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.18 (dd, *J* = 2.2, 0.5 Hz, 1H<sup>4</sup>), 8.73 (s, 1H<sup>1</sup>), 8.44 (dd, *J* = 9.3, 0.5 Hz, 1H<sup>7</sup>), 8.37 (dd, *J* = 9.3, 2.2 Hz, 1H<sup>6</sup>), 4.65 (q, *J* = 7.1 Hz, 2H<sup>10</sup>), 1.56 (t, *J* = 7.1 Hz, 3H<sup>11</sup>).

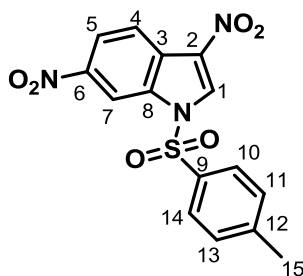
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 149.2 (9), 146.0 (8), 137.1 (5), 133.2 (2), 129.1 (1), 122.1 (6), 121.8 (3), 117.5 (4), 116.5 (7), 66.1 (10), 14.4 (11).

HRMS (ESI<sup>-</sup>) *m/z* Calcd. for C<sub>8</sub>H<sub>4</sub>N<sub>3</sub>O<sub>4</sub> [M-CO<sub>2</sub>Et]<sup>-</sup>: 206.0202; Found: 206.0203.

IR (neat)  $\nu$  cm<sup>-1</sup> = 1755, 1276, 1213, 1101, 745, 423.

Mp = 156.85 °C.

<sup>283</sup> The protection was performed according to reference 197 in the manuscript.

**3,6-dinitro-1-tosyl-1H-indole (150ea)**

Following the general procedure, **150ea** was obtained as a yellow solid in 50% yield.

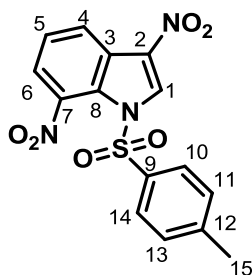
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 8.91 (dd, *J* = 1.9, 0.6 Hz, 1H<sup>7</sup>), 8.77 (s, 1H<sup>1</sup>), 8.40 (dd, *J* = 8.9, 0.6 Hz, 1H<sup>4</sup>), 8.34 (dd, *J* = 8.9, 1.9 Hz, 1H<sup>5</sup>), 7.95 (d, *J* = 8.4 Hz, 2H<sup>10,14</sup>), 7.40 (d, *J* = 8.4 Hz, 2H<sup>11,13</sup>), 2.43 (s, 3H<sup>15</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 147.9 (12), 146.5 (8), 133.2 (9), 132.8 (2), 132.5 (6), 131.8 (1), 131.1 (11,13), 127.8 (10,14), 126.1 (3), 122.1 (4), 120.1 (5), 110.3 (7), 21.1 (15).

**HRMS (ESI<sup>-</sup>)** *m/z* Calcd. for C<sub>15</sub>H<sub>12</sub>N<sub>3</sub>O<sub>7</sub>S [M+OH]<sup>-</sup>: 378.0396; Found: 378.0399.

**IR (neat)**  $\nu$  cm<sup>-1</sup> = 1776, 1580, 1540, 1370, 1343, 1190, 1169, 1019, 671, 581, 542.

**Mp** = 210.8 °C.

**3,7-dinitro-1-tosyl-1H-indole (150fa)**

Following the general procedure, **150fa** was obtained as white solid in 69% yield.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 8.78 (s, 1H<sup>1</sup>), 8.59 (dd, *J* = 8.1, 1.1 Hz, 1H<sup>6</sup>), 7.92 (d, *J* = 8.5 Hz, 2H<sup>10,14</sup>), 7.85 (dd, *J* = 7.9, 1.1 Hz, 1H<sup>4</sup>), 7.58 (dd $\approx$ t, *J* = 8.1, 7.9 Hz, 1H<sup>5</sup>), 7.44 (d, *J* = 8.5 Hz, 2H<sup>11,13</sup>), 2.49 (s, 3H<sup>15</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 147.0 (12), 138.9 (8), 134.3 (9), 133.1 (2), 132.6 (1), 130.3 (11,13), 127.9 (10,14), 126.1 (6), 125.9 (5), 124.9 (3), 124.7 (7), 122.8 (4), 21.1 (15).

**HRMS (ESI<sup>-</sup>)** *m/z* Calcd. for C<sub>15</sub>H<sub>12</sub>N<sub>3</sub>O<sub>7</sub>S [M+OH]<sup>-</sup>: 378.0396; Found: 378.0387.

**IR (neat)**  $\nu$  cm<sup>-1</sup> = 1544, 1390, 1354, 1260, 1175, 975, 899, 660, 565, 529.

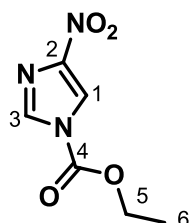
**Mp** = 196.65 °C.



## 1.2 Preparation of imidazole derivatives

To a solution of 4-nitro-4*H*-imidazole (1 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub>, was added DMAP (cat.), iPr<sub>2</sub>EtN (1.5 equiv) and the protecting group (2 equiv). The reaction was stirred overnight at room temperature under argon atmosphere after which water was added. The aqueous solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3\*10 mL), the combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (Cyclohexane/EtOAc: 50/50).

### Ethyl-4-nitro-1*H*-imidazole-1-carboxylate (**181a**)



Prepared following the general procedure. Flash chromatography of the residue (Cyclohexane/EtOAc: 50/50) afforded **181a** (1.2 g, 74%) as a white solid.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.17 (d, *J* = 1.6 Hz, 1H<sup>3</sup>), 8.03 (d, *J* = 1.6 Hz, 1H<sup>1</sup>), 4.52 (q, *J* = 7.1 Hz, 2H<sup>5</sup>), 1.42 (t, *J* = 7.1 Hz, 3H<sup>6</sup>).

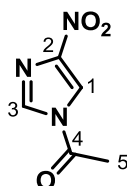
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 148.4 (4), 146.1 (2), 135.5 (1), 116.8 (3), 66.3 (5), 13.9 (6).

MS (Cl, tBuH) *m/z* Calcd. for C<sub>6</sub>H<sub>8</sub>N<sub>3</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 186.0514; Found: 186.0532.

IR (neat) *v* cm<sup>-1</sup> = 1762, 1553, 1491, 1237, 918, 646.

Mp = 62.25 °C.

### 1-(4-nitro-1*H*-imidazol-1-yl)ethanone (**181b**)



Prepared following the general procedure. Flash chromatography of the residue (Cyclohexane/EtOAc: 50/50) afforded **181b** (0.25 g, 37%) as a pale yellow solid.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.23 (d, *J* = 1.7 Hz, 1H<sup>3</sup>), 8.08 (d, *J* = 1.7 Hz, 1H<sup>1</sup>), 2.69 (s, 3H<sup>5</sup>).

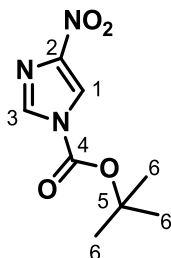
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 165.5 (4), 149.0 (2), 134.9 (1), 115.7 (3), 22.7 (5).

MS (Cl, tBuH) *m/z* Calcd. for C<sub>5</sub>H<sub>6</sub>N<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 156.0409; Found: 156.0419.

IR (neat) *v* cm<sup>-1</sup> = 1757, 1553, 1491, 1236, 857, 647.

**Mp** = 98 °C.

**Tert-butyl-4-nitro-1H-imidazole-1-carboxylate (181c)**



Prepared following the general procedure. The residue was washed with pentane to afford **181c** (1.2 g, 64%) as a white solid.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 8.10 (d, *J* = 1.6 Hz, 1H<sup>3</sup>), 7.96 (d, *J* = 1.6 Hz, 1H<sup>1</sup>), 1.60 (s, 9H<sup>6</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 148.3 (4), 145.3 (2), 135.5 (1), 116.9 (3), 88.8 (5), 27.7 (6).

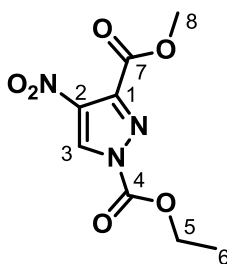
**MS** (CI, tBuH) *m/z* Calcd. for C<sub>3</sub>H<sub>4</sub>N<sub>3</sub>O<sub>2</sub> [M+H-C<sub>5</sub>H<sub>9</sub>O<sub>2</sub>]<sup>+</sup>: 114.0303; Found: 114.0304.

**IR** (neat) *v* cm<sup>-1</sup> = 1760, 1492, 1254, 817, 646.

**Mp** = 90.9 °C.

### 1.3 Preparation of pyrazole derivative

**1-Ethyl-3-methyl-4-nitro-1H-pyrazole-1,3-dicarboxylate (184)**



To a solution of methyl-4-nitro-1H-pyrazole-3-carboxylate (1 equiv)<sup>284</sup> in 15 mL THF at 0 °C, was added NaH (1.2 equiv) and the mixture was stirred at this temperature for 10 minutes under argon. Ethyl chloroformate (1.5 equiv) was then added dropwise and stirring was continued at the same temperature for 30 minutes. After which the reaction was kept to stir at room temperature overnight. The reaction was dissolved in EtOAc/H<sub>2</sub>O (15/15 mL), washed with saturated aqueous NaHCO<sub>3</sub> (20 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and

<sup>284</sup> Methyl-4-nitro-1H-pyrazole-3-carboxylate was prepared according to reference 241 in the manuscript.

concentrated under reduced pressure. The product **184** was obtained as a yellow oil (0.70 g, 99%) without any further purification.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 8.83 (s, 1H<sup>3</sup>), 4.60 (q, *J* = 7.1 Hz, 2H<sup>5</sup>), 3.97 (s, 3H<sup>8</sup>), 1.47 (t, *J* = 7.1 Hz, 3H<sup>6</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 159.6 (7), 147.3 (4), 141.5 (1), 135.6 (2), 131.0 (3), 67.1 (5), 53.6 (8), 14.1 (6).

**HRMS (AP<sup>+</sup>) *m/z* Calcd. for C<sub>8</sub>H<sub>10</sub>N<sub>3</sub>O<sub>6</sub> [M+H]<sup>+</sup>:** 244.0570; Found: 244.0563.

## 2 Experimental Part for Chapter II and Chapter III

### General Procedure 1:

To a stirred solution of the heterocycle (0.2 mmol, 1 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added Danishefsky's diene (0.24 mmol or 0.48 mmol, 1.2 equiv or 2.4 equiv). The solution was stirred under argon atmosphere for the required time at room temperature. The solvent was then evaporated under reduced pressure. The reaction residue was dissolved in 1 mL dry methanol and NH<sub>4</sub>F (1.2 mmol, 6 equiv) was added at -25 °C. The reaction mixture was stirred for 30 min after which methanol was evaporated. The reaction residue was dissolved in EtOAc (5 mL), extracted with saturated aqueous NaHCO<sub>3</sub> solution (3\*2 mL) and brine (2\*2 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (Cyclohexane/Acetone: 80/20).

### General Procedure 2:

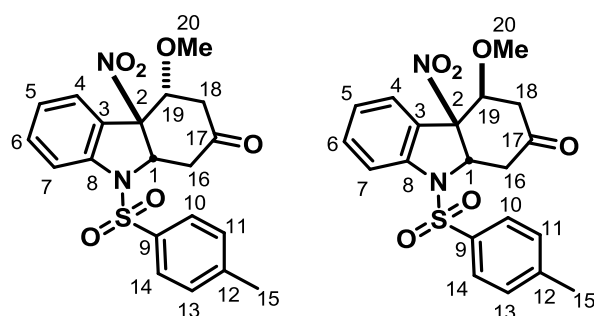
To a stirred solution of the nitroarene (0.1 mmol or 0.2 mmol, 1 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> (0.9 mL) was added the diene (0.4 mmol, 0.6 mmol or 1.2 mmol, 3 equiv, 4 equiv or 6 equiv). The resultant pale orange mixture was transferred into a 0.9 mL Teflon reactor. The reactor was then sealed and allowed to react for the required time at room temperature under 16 kbar pressure. The solvent was then removed under reduced pressure. The reaction residue was dissolved in 2 mL dry methanol and NH<sub>4</sub>F (1.2 mmol, 6 equiv) was added at -25°C. The reaction mixture was stirred for 30 min after which methanol was evaporated. The reaction residue was dissolved in EtOAc (10 mL), extracted with saturated aqueous NaHCO<sub>3</sub> solution (3\*4 mL) and brine (2\*4 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel or reverse phase HPLC (Cyclohexane/EtOAc or water + 0.1% formic acid/ACN).

### General Procedure 3:

A solution of LDA was prepared at -78°C under inert atmosphere: to a solution of diisopropylamine (DiPA) (0.6 or 1.2 mmol, 1.2 or 2.4 equiv) in 1 or 2 mL of dry THF cooled to -

78 °C was added *n*-BuLi (0.6 or 1.2 mmol, 2.5 M in hexane, 1.2 or 2.4 equiv). The enolate precursor (0.6 or 1.2 mmol) was then added slowly. The resultant mixture was stirred at this temperature for 30 min before adding the nitroaromatic compound (0.5 mmol, 1 equiv) dissolved in dry THF. The reaction mixture was then stirred at -78 °C for the required time before being quenched with 10 mL of a saturated aqueous NH<sub>4</sub>Cl solution. The resulting mixture was extracted with EtOAc (3\*10 mL), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. When required, the residue was purified by flash chromatography on silica (Cyclohexane or Petroleum Ether (PE)/EtOAc or Acetone).

**4-Methoxy-4-nitro-9-tosyl-4,4,9,9-tetrahydro-1H-carbazol-2(3H)-one (4S\*,4aR\*,9aS\*) and (4R\*,4aR\*,9aS\*) diastereomers (154aa)**



**154aa** was prepared according to the general procedure 1: 1.2 equiv Danishefsky's diene **79** (46.5  $\mu$ L, 0.24 mmol) was added to a stirred solution of 3-nitro-1-tosyl-1*H*-indole **150aa** (63.26 mg, 0.2 mmol) in 1 mL dry CH<sub>2</sub>Cl<sub>2</sub>. The reaction mixture was stirred at room temperature for 24 h. Flash chromatography of the residue (Cyclohexane/Acetone: 80/20) afforded **154aa** (87.67 mg, 95%) as a brown solid of non-separable diastereomers in a 66 : 34 diastereomeric ratio.

**154aa** was also prepared according to the general procedure 3 using 1.2 equiv LDA and *trans*-4-methoxy-3-buten-2-one **134** (68  $\mu$ L, 0.6 mmol) in 1 mL THF and a solution of 3-nitro-1-tosyl-1*H*-indole **150aa** (158 mg, 0.5 mmol) in 2 mL THF. The reaction mixture was stirred at -78 °C for 4 h. Flash chromatography of the residue (Cyclohexane/EtOAc: 80/20) afforded **154aa** (172 mg, 83%) as a brown solid of non-separable diastereomers in a 85 : 15 diastereomeric ratio.

(4*R*\*, 4*aR*\*,9*aS*\*) major diastereomer:

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  7.75 (d, *J* = 8.2 Hz, 1H<sup>4</sup>), 7.59 (d, *J* = 7.8 Hz, 1H<sup>7</sup>), 7.49 – 7.43 (m, 3H<sup>5,10,14</sup>), 7.20 – 7.13 (m, 3H<sup>6,11,13</sup>), 5.08 (dd $\approx$ t, *J* = 6.2, 4.9 Hz, 1H<sup>1</sup>), 4.67 (dd, *J* = 10.1, 4.5 Hz, 1H<sup>19</sup>), 3.35 (s, 3H<sup>20</sup>), 3.12 (dd, *J* = 16.2, 6.2 Hz, 1H<sup>16</sup>), 3.05 (dd, *J* = 16.2, 4.9 Hz, 1H<sup>16</sup>), 2.71 (dd, *J* = 18.6, 4.5 Hz, 1H<sup>18</sup>), 2.35 (s, 3H<sup>15</sup>), 2.07 (dd, *J* = 18.6, 10.1 Hz, 1H<sup>18</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  202.1 (17), 145.3 (12), 143.2 (8), 132.1 (9), 132.5 (4), 129.1 (11,13), 129.6 (6), 127.2 (10,14), 125.2 (5), 123.6 (3), 116.9 (7), 96.9 (2), 77.1 (19), 63.5 (20), 58.2 (1), 44.6 (16), 40.1 (18), 21.6 (15).

(4*S*\*, 4*aR*\*,9*aS*\*) minor diastereomer:

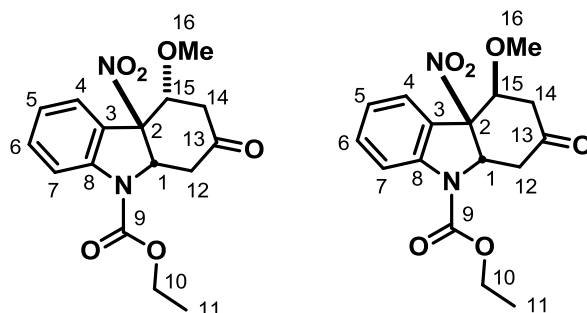
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.73 (d, *J* = 8.2, 1H<sup>4</sup>), 7.65 (d, *J* = 8.4 Hz, 1H<sup>7</sup>), 7.55 (d, *J* = 7.9 Hz, 1H<sup>5</sup>), 7.49 – 7.43 (m, 2H<sup>10,14</sup>), 7.20 – 7.05 (m, 3H<sup>6,11,13</sup>), 5.78 (dd, *J* = 4.9, 3.5 Hz, 1H<sup>1</sup>), 4.65– 4.63 (m, 1H<sup>19</sup>), 3.35 (s, 3H<sup>20</sup>), 3.28– 3.22 (m, 2H<sup>16</sup>), 2.67 – 2.60 (m, 1H<sup>18</sup>), 2.35 (s, 3H<sup>15</sup>), 1.91 (dd, *J* = 18.9, 2.5 Hz, 1H<sup>18</sup>).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 204.2 (17), 145.2 (12), 142.5 (8), 133.1 (9), 132.9 (4), 129.9 (11,13), 129.6 (6), 127.6 (10,14), 125.5 (5), 125.0 (3), 116.6 (7), 95.7 (2), 80.4 (19), 61.6 (20), 44.1 (1), 37.5 (16), 30.9 (18), 26.9 (15).

HRMS (ESI<sup>+</sup>) *m/z* Calcd. for C<sub>20</sub>H<sub>24</sub>N<sub>3</sub>O<sub>6</sub>S [M+NH<sub>4</sub>]<sup>+</sup>: 434.1389; Found: 434.1386.

IR (neat)  $\nu$  cm<sup>-1</sup> = 1726, 1550, 1477, 1357, 1167, 1087, 1014, 659, 571.

**Ethyl-4-methoxy-4-nitro-2-oxo-2,3,4,4-tetrahydro-1*H*-carbazole-9(9*H*)-carboxylate (4*S*\*,4*aR*\*,9*aS*\*) and (4*R*\*,4*aR*\*,9*aS*\*) diastereomers (154ab)**



**154ab** was prepared according to the general procedure 1: 2.4 equiv **79** (93  $\mu$ L, 0.48 mmol) was added to a stirred solution of ethyl-3-nitro-1*H*-indole-1-carboxylate **150ab** (46.84 mg, 0.2 mmol) in 1 mL dry CH<sub>2</sub>Cl<sub>2</sub>. The reaction mixture was stirred at room temperature for 48 h. Flash chromatography of the residue (Cyclohexane/Acetone: 80/20) afforded **154ab** (46mg, 69%) as a yellow oil of non-separable diastereomers in a 64 : 36 diastereomeric ratio.

**154ab** was also prepared according to the general procedure 3 using 1.2 equiv LDA and **134** (68  $\mu$ L, 0.6 mmol) in 1 mL THF and a solution of ethyl-3-nitro-1*H*-indole-1-carboxylate **150ab** (117 mg, 0.5 mmol) in 4 mL THF. The reaction mixture was stirred at -78°C for 5 h. Flash chromatography of the residue on neutralized silica (1% NEt<sub>3</sub>) (Cyclohexane/EtOAc : 60/40) afforded **154ab** (60.4 mg, 37%) as a yellow oil of non-separable diastereomers in a 80 : 20 diastereomeric ratio.

(4*R*\*, 4*aR*\*,9*aS*\*) major diastereomer

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.78 – 7.67 (m, 1H<sup>4</sup>), 7.64 – 7.54 (m, 1H<sup>7</sup>), 7.50 – 7.36 (m, 1H<sup>6</sup>), 7.17 – 7.12 (m, 1H<sup>5</sup>), 5.99 (dd, *J* = 7.0, 2.1 Hz, 1H<sup>1</sup>), 4.88 – 4.77 (m, 1H<sup>15</sup>), 4.41 – 4.20 (m, 2H<sup>10</sup>), 3.43 (s, 3H<sup>16</sup>), 3.05 (dd, *J* = 16.2, 7.0 Hz, 1H<sup>12</sup>), 2.80 (dd, *J* = 18.4, 4.4 Hz, 1H<sup>14</sup>), 2.71 (dd, *J* = 18.4, 3.1 Hz, 1H<sup>14</sup>), 2.13 – 1.99 (m, 1H<sup>12</sup>), 1.42 – 1.32 (m, 3H<sup>11</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 205.1 (13), 152.1 (9), 132.1 (8), 129.3 (5), 124.9 (4), 121.7 (3), 116.4 (6), 115.8 (7), 96.8 (2), 80.0 (15), 61.4 (10), 58.3 (1), 58.2 (16), 42.2 (12), 40.6 (14), 14.9 (11).

(4*S*\*,4*aR*\*,9*aS*\*) minor diastereomer

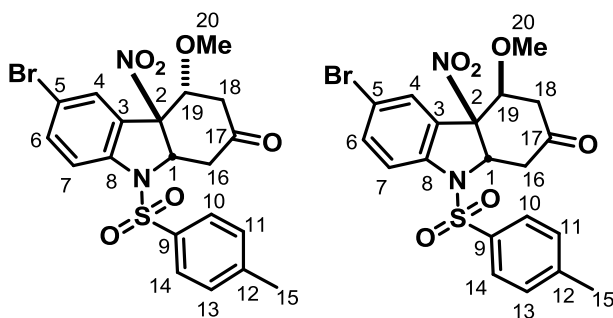
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.78 – 7.67 (m, 1H<sup>4</sup>), 7.64 – 7.54 (m, 1H<sup>7</sup>), 7.50 – 7.36 (m, 1H<sup>6</sup>), 7.17 – 7.12 (m, 1H<sup>5</sup>), 5.37 – 5.25 (m, 1H<sup>1</sup>), 4.92 – 4.80 (m, 1H<sup>15</sup>), 4.41 – 4.20 (m, 2H<sup>10</sup>), 3.43 (s, 3H<sup>16</sup>), 3.24 (dd, *J* = 16.3, 7.0 Hz, 1H<sup>12</sup>), 3.05 (dd, *J* = 16.3, 6.3 Hz, 1H<sup>12</sup>), 2.80 (dd, *J* = 18.4, 4.5 Hz, 1H<sup>14</sup>), 2.71 (dd, *J* = 18.4, 3.1 Hz, 1H<sup>14</sup>), 1.39 (t, *J* = 7.2 Hz, 3H<sup>11</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 203.8 (13), 152.1 (9), 132.4 (8), 129.3 (5), 123.9 (4), 123.5 (3), 116.4 (6), 115.8 (7), 95.5 (2), 78.1 (15), 62.7 (10), 59.8 (1), 58.7 (16), 40.6 (12), 38.1 (14), 14.5 (11).

**HRMS (ESI<sup>-</sup>)** *m/z* Calcd. for C<sub>16</sub>H<sub>17</sub>N<sub>2</sub>O<sub>6</sub> [M-H]<sup>-</sup>: 333.1087; Found: 333.1080.

**IR** (neat) *v* (cm<sup>-1</sup>) = 1709, 1553, 1380, 1257, 1096, 758, 665.

**6-Bromo-4-methoxy-4*a*-nitro-9-tosyl-1,3,4,4*a*,9,9*a*-hexahydro-2*H*-carbazol-2-one (4*S*\*,4*aR*\*,9*aS*\*) and (4*R*\*,4*aR*\*,9*aS*\*) diastereomers (154*ca*)**



**154ca** was prepared according to the general procedure 1: 2.4 equiv **79** (93 μL, 0.48 mmol) was added to a stirred solution of 5-bromo-3-nitro-1-tosyl-1*H*-indole **150ca** (79 mg, 0.2 mmol) in 1 mL dry CH<sub>2</sub>Cl<sub>2</sub>. The reaction was stirred at room temperature for 48 h. Flash chromatography of the residue (Cyclohexane/Acetone: 80/20) afforded **154ca** (89 mg, 90%) as a white solid of separable diastereomers in a 50 : 50 diastereomeric ratio.

**154ca** was also prepared according to the general procedure 3 using 2.4 equiv LDA and **134** (123 μL, 1.2 mmol) in 2 mL THF and a solution of 5-bromo-3-nitro-1-tosyl-1*H*-indole **150ca** (198 mg, 0.5 mmol) in 4 mL THF. The reaction mixture was stirred at -78 °C for 5 h. Flash chromatography

of the residue (Cyclohexane/EtOAc: 95/5) afforded **154ca** (135 mg, 61%) as a white solid of separable diastereomers in a 77 : 23 diastereomeric ratio.

(4*R*<sup>\*</sup>,4*aR*<sup>\*</sup>,9*aS*<sup>\*</sup>) major diastereomer:

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.71 (dd, *J* = 1.9, 0.5 Hz, 1H<sup>6</sup>), 7.65 – 7.58 (m, 2H<sup>4,7</sup>), 7.46 (d, *J* = 8.4 Hz, 2H<sup>10,14</sup>), 7.19 (d, *J* = 8.4 Hz, 2H<sup>11,13</sup>), 5.04 (dd≈t, *J* = 5.3, 5.3 Hz, 1H<sup>1</sup>), 4.64 (dd, *J* = 10.5, 4.6 Hz, 1H<sup>19</sup>), 3.34 (s, 3H<sup>20</sup>), 3.11 – 3.06 (m, 2H<sup>16</sup>), 2.76 (dd, *J* = 18.7, 4.6 Hz, 1H<sup>18</sup>), 2.36 (s, 3H<sup>15</sup>), 2.04 (dd, *J* = 18.7, 10.5 Hz, 1H<sup>18</sup>).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 202.5 (17), 145.7 (12), 142.5 (8), 135.6 (7), 132.7 (9), 132.5 (11,13), 130.2 (6), 127.2 (10,14), 125.4 (3), 118.3 (4), 118.0 (5), 96.3 (2), 77.9 (19), 63.9 (1), 58.3 (20), 44.5 (16), 40.1 (18), 21.7 (15).

(4*S*<sup>\*</sup>,4*aR*<sup>\*</sup>,9*aS*<sup>\*</sup>) minor diastereomer:

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.68 (d, *J* = 2.0 Hz, 1H<sup>6</sup>), 7.63 – 7.59 (m, 3H<sup>4,10,14</sup>), 7.56 (dd, *J* = 8.8, 2.0 Hz, 1H<sup>7</sup>), 7.24 (d, *J* = 8.0 Hz, 2H<sup>11,13</sup>), 5.75 (dd≈t, *J* = 4.3, 4.3 Hz, 1H<sup>1</sup>), 4.59 (dd, *J* = 3.5, 2.5 Hz, 1H<sup>19</sup>), 3.35 (s, 3H<sup>20</sup>), 3.31 – 3.19 (m, 2H<sup>16</sup>), 2.70 (dd, *J* = 18.9, 3.5 Hz, 1H<sup>18</sup>), 2.37 (s, 3H<sup>15</sup>), 1.94 (dd, *J* = 18.9, 2.5 Hz, 1H<sup>18</sup>).

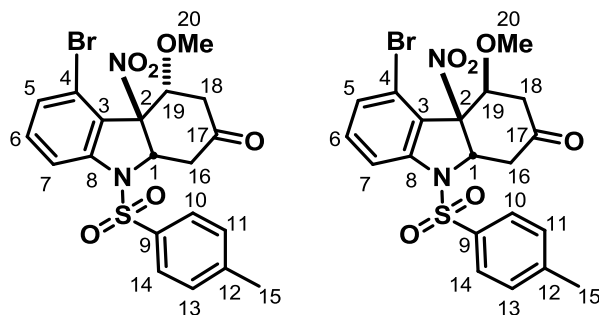
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 203.7 (17), 145.7 (12), 141.9 (8), 136.3 (7), 132.7 (9), 130.2 (11,13), 128.6 (6), 127.8 (10,14), 126.9 (3), 118.2 (4), 117.8 (5), 95.1 (2), 80.5 (19), 61.1 (1), 58.9 (20), 43.9 (16), 37.9 (18), 21.9 (15).

Mp = 154.6 °C.

HRMS (ESI<sup>+</sup>) *m/z* Calcd. for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>SBr [M-H]<sup>+</sup>: 493.0069; Found: 493.0061.

IR (neat) *v* (cm<sup>-1</sup>) = 1733, 1555, 1467, 1362, 1168, 1101, 1086, 666, 576.

**5-bromo-4-methoxy-4-nitro-9-tosyl-4,4a,9,9a-tetrahydro-1*H*-carbazol-2(3*H*)-one**  
(4*S*<sup>\*</sup>,4*aR*<sup>\*</sup>,9*aS*<sup>\*</sup>) and (4*R*<sup>\*</sup>,4*aR*<sup>\*</sup>,9*aS*<sup>\*</sup>) diastereomers (**154ba**)



**154ba** was prepared according to the general procedure 1: 2.4 equiv Danishefsky's diene **79** (93 μL, 0.48 mmol) was added to a stirred solution of 4-bromo-3-nitro-1-tosyl-1*H*-indole **150ba** (79

mg, 0.2 mmol) in 1 mL dry CH<sub>2</sub>Cl<sub>2</sub>. The reaction was stirred at 40 °C for 24 h. Flash chromatography of the residue (Cyclohexane/Acetone: 80/20) afforded **154ba** (66 mg, 67%) as a light yellow solid of non-separable diastereomers in 60 : 40 diastereomeric ratio.

(4*R*<sup>\*</sup>,4*aR*<sup>\*</sup>,9*aS*<sup>\*</sup>) major diastereomer:

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.72 – 7.63 (m, 2H<sup>6,7</sup>), 7.50 (d, *J* = 8.3 Hz, 2H<sup>10,14</sup>), 7.23 – 7.18 (m, 3H<sup>5,11,13</sup>), 5.59 (dd≈t, *J* = 3.4, 2.9 Hz, 1H<sup>1</sup>), 4.86 (dd≈t, *J* = 3.6, 3.6 Hz, 1H<sup>19</sup>), 3.42 (dd, *J* = 16.4, 3.4 Hz, 1H<sup>16</sup>), 3.24 (s, 3H<sup>20</sup>), 3.19 (dd, *J* = 16.4, 2.9 Hz, 1H<sup>16</sup>), 2.84 (dd, *J* = 16.3, 3.6 Hz, 2H<sup>18</sup>), 2.32 (s, 3H<sup>15</sup>).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 203.9 (17), 145.5 (12), 145.1 (8), 134.2 (7), 133.2 (9), 130.1 (11,13), 130.0 (6), 127.3 (10,14), 125.9 (3), 122.1 (5), 115.7 (4), 97.6 (2), 74.1 (19), 64.8 (1), 57.5 (20), 43.8 (16), 39.2 (18), 21.8 (15).

(4*S*<sup>\*</sup>,4*aR*<sup>\*</sup>,9*aS*<sup>\*</sup>) minor diastereomer:

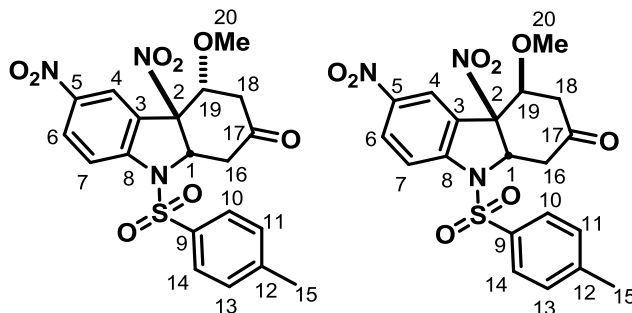
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.76 (dd, *J* = 4.4, 2.5 Hz, 1H<sup>6</sup>), 7.68 (d, *J* = 8.4 Hz, 2H<sup>10,14</sup>), 7.28 (d, *J* = 4.4 Hz, 1H<sup>7</sup>), 7.21 (d, *J* = 2.5 Hz, 1H<sup>5</sup>), 7.15 (d, *J* = 8.4 Hz, 2H<sup>11,13</sup>), 5.59 (dd≈t, *J* = 3.4, 2.9 Hz, 1H<sup>1</sup>), 4.90 (dd≈t, *J* = 3.1, 2.3 Hz, 1H<sup>19</sup>), 3.37 (s, 3H<sup>20</sup>), 3.03 (dd, *J* = 16.8, 3.4 Hz, 1H<sup>16</sup>), 2.92 (d, *J* = 16.8, 2.9 Hz, 1H<sup>16</sup>), 2.71 (dd, *J* = 18.3, 3.1 Hz, 1H<sup>18</sup>), 2.33 (s, 3H<sup>15</sup>), 2.23 (dd, *J* = 18.3, 2.3 Hz, 1H<sup>18</sup>).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 203.8 (17), 145.5 (12), 145.3 (8), 134.4 (7), 133.5 (9), 129.1 (11,13), 129.4 (6), 127.7 (10,14), 122.7 (3), 120.6 (5), 114.9 (4), 97.0 (2), 76.6 (19), 63.5 (1), 58.4 (20), 46.1 (16), 38.1 (18), 21.8 (15).

HRMS (ESI<sup>-</sup>) *m/z* Calcd. for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>SBr [M-H]<sup>-</sup>: 493.0069; Found: 493.0070.

IR (neat) *ν* (cm<sup>-1</sup>) = 1726, 1554, 1360, 1168, 1089, 677, 576.

#### 4-Methoxy-4*a*,6-dinitro-9-tosyl-1,3,4*a*,9,9*a*-hexahydro-2*H*-carbazol-2-one (4*S*<sup>\*</sup>,4*aR*<sup>\*</sup>,9*aS*<sup>\*</sup>) and (4*R*<sup>\*</sup>,4*aR*<sup>\*</sup>,9*aS*<sup>\*</sup>) diastereomers (**154da**)



**154da** was prepared according to the general procedure 1: 1.2 equiv Danishefsky's diene **79** (46.5 μL, 0.24 mmol) was added to a stirred solution of 3,5-dinitro-1-tosyl-1*H*-indole **150da** (72.26 mg,



0.2 mmol) in 1 mL dry CH<sub>2</sub>Cl<sub>2</sub>. The reaction was stirred at room temperature for 48 h. Flash chromatography of the residue (Cyclohexane/Acetone: 80/20) afford **154da** (85.86 mg, 93%) as white solid of separable diastereomers in 50 : 50 diastereomeric ratio.

**154da** was also prepared according to the general procedure 3 with 1.2 equiv LDA and **134** (68 μL, 0.6 mmol) in 1 mL dry THF and a solution of 3,5-dinitro-1-tosyl-1*H*-indole **150da** (181 mg, 0.5 mmol) in 4 mL THF. The reaction mixture was stirred at -78 °C for 6 h. **154da** was obtained without further purification (126 mg, 87%) as an oil of non-separable diastereomers in a 89 : 11 diastereomeric ratio. The attempts to separate them by flash chromatography (Cyclohexane/EtOAc: 70/30) decreased the yield to 54% and afforded **154da** as a white solid of separable diastereomers.

(4*R*<sup>\*</sup>,4*aR*<sup>\*</sup>,9*aS*<sup>\*</sup>) major diastereomer:

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.45 (d, *J* = 2.3 Hz, 1H<sup>4</sup>), 8.36 (dd, *J* = 9.1, 2.3 Hz, 1H<sup>6</sup>), 7.85 (d, *J* = 9.1 Hz, 1H<sup>7</sup>), 7.54 (d, *J* = 8.4 Hz, 2H<sup>10,14</sup>), 7.23 (d, *J* = 8.4 Hz, 2H<sup>11,13</sup>), 5.19 (dd, *J* = 6.1, 5.0 Hz, 1H<sup>1</sup>), 4.72 (dd, *J* = 9.8, 4.4 Hz, 1H<sup>19</sup>), 3.40 (s, 3H<sup>20</sup>), 3.18 (dd, *J* = 15.4, 6.1 Hz, 1H<sup>16</sup>), 3.11 (dd, *J* = 15.4, 5.0 Hz, 1H<sup>16</sup>), 2.80 (dd, *J* = 18.7, 4.4 Hz, 1H<sup>18</sup>), 2.38 (s, 3H<sup>15</sup>), 2.14 (dd, *J* = 18.7, 9.8 Hz, 1H<sup>18</sup>).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 201.9 (17), 148.3 (8), 146.3 (12), 144.9 (5), 132.7 (9), 130.5 (11,13), 128.5 (6), 127.1 (10,14), 126.0 (3), 124.5 (4), 116.2 (7), 95.8 (2), 77.7 (19), 64.6 (1), 58.4 (20), 44.1 (16), 40.1 (19), 21.8 (15).

Mp = 168.2 °C.

(4*S*<sup>\*</sup>,4*aR*<sup>\*</sup>,9*aS*<sup>\*</sup>) minor diastereomer:

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.45 (d, *J* = 2.3 Hz, 1H<sup>4</sup>), 8.35 (dd, *J* = 9.1, 2.3 Hz, 1H<sup>6</sup>), 7.84 (d, *J* = 9.1 Hz, 1H<sup>7</sup>), 7.69 (d, *J* = 8.5 Hz, 2H<sup>10,14</sup>), 7.27 (d, *J* = 8.5 Hz, 2H<sup>11,13</sup>), 5.90 (dd, *J* = 5.4, 3.5 Hz, 1H<sup>1</sup>), 4.73 (dd≈t, *J* = 3.4, 2.6 Hz, 1H<sup>19</sup>), 3.40 (s, 3H<sup>20</sup>), 3.33 – 3.28 (m, 2H<sup>16</sup>), 2.79 (dd, *J* = 19.1, 3.4 Hz, 1H<sup>18</sup>), 2.38 (s, 3H<sup>15</sup>), 1.97 (dd, *J* = 19.1, 2.6 Hz, 1H<sup>18</sup>).

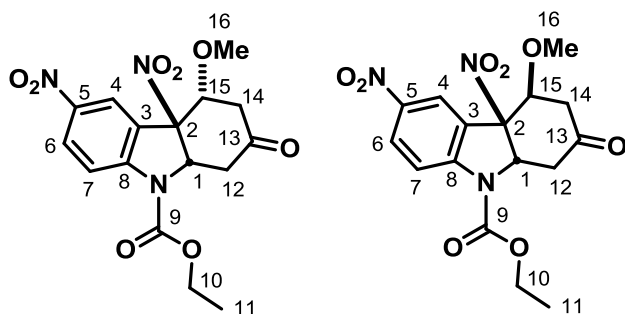
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 203.1 (17), 147.7 (8), 146.3 (12), 144.7 (5), 132.7 (9), 130.4 (11,13), 129.2 (6), 127.6 (10,14), 125.7 (3), 122.1 (4), 116.1 (7), 94.5 (2), 80.2 (19), 62.9 (1), 58.5 (20), 43.7 (16), 37.6 (18), 21.8 (15).

Mp = 199.5 °C

HRMS (ESI<sup>-</sup>) *m/z* Calcd. for C<sub>20</sub>H<sub>18</sub>N<sub>3</sub>O<sub>8</sub>S [M-H]<sup>-</sup>: 460.0815; Found: 460.0818.

IR (neat) ν cm<sup>-1</sup> = 1734, 1557, 1529, 1371, 1345, 1171, 1096, 1087, 725, 665.

**Ethyl-4-methoxy-4*a*,7-dinitro-2-oxo-1,2,3,4,4*a*-9*a*-hexahydro-9*H*-carbazole-9-carboxylate (4*S*<sup>\*</sup>, 4*aR*<sup>\*</sup>, 9*aS*<sup>\*</sup>) and (4*R*<sup>\*</sup>, 4*aR*<sup>\*</sup>, 9*aS*<sup>\*</sup>) diastereomers (154db)**



**154db** was prepared according to the general procedure 1: 1.2 equiv Danishefsky's diene **79** (46.5  $\mu\text{L}$ , 0.24 mmol) was added to a stirred solution of ethyl-3,5-dinitro-1*H*-indole-1-carboxylate **150db** (55.84 mg, 0.2 mmol) in 1 mL dry  $\text{CH}_2\text{Cl}_2$ . The reaction was stirred at room temperature for 48 h. Flash chromatography of the residue (Cyclohexane/Acetone: 80/20) afforded **154db** (71.6 mg, 94%) as brown solid of separable diastereomers in a 64 : 36 diastereomeric ratio.

**154db** was also prepared according to the general procedure 3 using 1.2 equiv LDA and **134** (68  $\mu\text{L}$ , 0.6 mmol) in 1 mL dry THF and a solution of ethyl-3,5-dinitro-1*H*-indole-1-carboxylate **150db** (139.60 mg, 0.5 mmol) in 4 mL THF. The reaction was stirred at  $-78\text{ }^\circ\text{C}$  for 6 h. Flash chromatography of the residue (PE/EtOAc: 60/40) afforded **154db** (178mg, 94%) as a brown solid of separable diastereomers in a 81 : 19 diastereomeric ratio.

(4*R*<sup>\*</sup>, 4*aR*<sup>\*</sup>, 9*aS*<sup>\*</sup>) major diastereomer:

**<sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.59 (d,  $J = 2.4$  Hz,  $1\text{H}^4$ ), 8.35 (dd,  $J = 9.1, 2.4$  Hz,  $1\text{H}^6$ ), 7.95 – 7.93 (m,  $1\text{H}^7$ ), 5.39 (dd,  $J = 6.1, 4.7$  Hz,  $1\text{H}^1$ ), 4.84 (dd,  $J = 10.0, 4.6$  Hz,  $1\text{H}^{15}$ ), 4.36 – 4.32 (m,  $2\text{H}^{10}$ ), 3.47 (s,  $3\text{H}^{16}$ ), 3.09 (dd,  $J = 16.3, 6.1$  Hz,  $1\text{H}^{12}$ ), 2.96 (dd,  $J = 16.3, 4.7$  Hz,  $1\text{H}^{12}$ ), 2.88 (dd,  $J = 18.6, 4.6$  Hz,  $1\text{H}^{14}$ ), 2.20 (dd,  $J = 18.6, 10.0$  Hz,  $1\text{H}^{14}$ ), 1.40 (t,  $J = 7.2$  Hz,  $3\text{H}^{11}$ ).

**<sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  202.7 (13), 151.3 (9), 148.3 (8), 143.7 (5), 128.6 (6), 125.9 (3), 122.8 (4), 115.7 (7), 95.6 (2), 77.1 (15), 63.8 (10), 62.5 (1), 58.5 (16), 41.1 (12), 40.5 (14), 14.5 (11).

**Mp** = 155.2  $^\circ\text{C}$ .

(4*S*<sup>\*</sup>, 4*aR*<sup>\*</sup>, 9*aS*<sup>\*</sup>) minor diastereomer:

**<sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.53 (d,  $J = 2.3$  Hz,  $1\text{H}^4$ ), 8.34 (dd,  $J = 9.1, 2.3$  Hz,  $1\text{H}^6$ ), 7.95 – 7.93 (m,  $1\text{H}^7$ ), 6.08 (dd,  $J = 6.8, 1.8$  Hz,  $1\text{H}^1$ ), 4.88 (dd $\approx$ t,  $J = 2.9, 2.9$  Hz,  $1\text{H}^{15}$ ), 4.39 – 4.35 (m,  $2\text{H}^{10}$ ), 3.46 (s,  $3\text{H}^{16}$ ), 3.29 (dd,  $J = 16.8, 6.8$  Hz,  $1\text{H}^{12}$ ), 2.98 (d,  $J = 16.8, 1.8$  Hz,  $1\text{H}^{12}$ ), 2.78 (dd,  $J = 19.1, 2.9$  Hz,  $1\text{H}^{14}$ ), 2.07 (dd,  $J = 19.1, 2.9$  Hz,  $1\text{H}^{14}$ ), 1.42 (t,  $J = 7.1$  Hz,  $3\text{H}^{11}$ ).

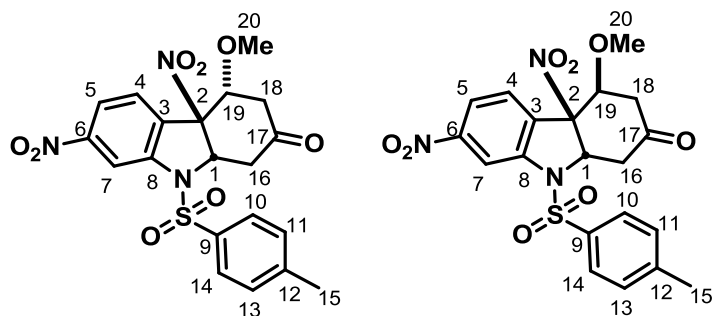
**<sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  203.1 (13), 151.6 (9), 147.9 (8), 143.8 (5), 129.2 (6), 124.6 (3), 121.7 (4), 116.2 (7), 94.3 (2), 80.1 (15), 63.8 (10), 61.0 (1), 58.6 (16), 42.0 (12), 38.1 (14), 14.5 (11).

**Mp** = 135.8  $^\circ\text{C}$ .

HRMS (ESI)  $m/z$  Calcd. for  $C_{16}H_{16}N_3O_8$   $[M-H]^-$ : 378.0937; Found: 378.0931.

IR (neat)  $\nu$   $cm^{-1}$  = 1716, 1600, 1445, 1400, 1248, 1173, 1093, 734.

**4-Methoxy-4a-7-dinitro-9-tosyl-1,3,4,4a,9,9a-hexahydro-2H-carbazol-2-one**  
(**4S<sup>\*</sup>,4aR<sup>\*</sup>,9aS<sup>\*</sup>**) and (**4R<sup>\*</sup>,4aR<sup>\*</sup>,9aS<sup>\*</sup>**) diastereomers (**154ea**)



**154ea** was prepared according to the general procedure 1: 2.4 equiv Danishefsky's diene **79** (93  $\mu$ L, 0.48 mmol) was added to a stirred solution of 3,6-dinitro-1-tosyl-1*H*-indole **150ea** (72.26 mg, 0.2 mmol) in 1 mL dry  $CH_2Cl_2$ . The reaction was stirred at room temperature for 48 h. Flash chromatography of the residue (Cyclohexane/Acetone: 80/20) afforded **154ea** (87.2 mg, 95%) as light yellow solid of separable diastereomers in 52 : 48 diastereomeric ratio.

**154ea** was also prepared according to the general procedure 3 using 1.2 equiv LDA and **134** (68  $\mu$ L, 0.6 mmol) in 1 mL dry THF and a solution of 3,6-dinitro-1-tosyl-1*H*-indole **150ea** (181 mg, 0.5 mmol) in 4 mL THF. The reaction was stirred at  $-78$  °C for 6 h. **154ea** was obtained without further purification (132mg, 86%) as an oil of non-separable diastereomers in a 84 : 16 diastereomeric ratio. The attempts to separate them by flash chromatography (Cyclohexane/EtOAc: 70/30) decreased the yield to 48% and afforded **154ea** as a light yellow solid of separable diastereomers.

(**4R<sup>\*</sup>,4aR<sup>\*</sup>,9aS<sup>\*</sup>**) major diastereomer:

**<sup>1</sup>H NMR (300 MHz,  $CDCl_3$ ):**  $\delta$  8.51 (d,  $J$  = 2.0 Hz, 1H<sup>7</sup>), 8.01 (dd,  $J$  = 8.6, 2.0 Hz, 1H<sup>5</sup>), 7.78 (d,  $J$  = 8.6 Hz, 1H<sup>4</sup>), 7.53 (d,  $J$  = 8.3 Hz, 2H<sup>10,14</sup>), 7.22 (d,  $J$  = 8.3 Hz, 2H<sup>11,13</sup>), 5.18 (dd $\approx$ t,  $J$  = 5.5, 5.5 Hz, 1H<sup>1</sup>), 4.72 (dd,  $J$  = 9.9, 4.4 Hz, 1H<sup>19</sup>), 3.37 (s, 3H<sup>20</sup>), 3.25 – 3.01 (m, 2H<sup>16</sup>), 2.79 (dd,  $J$  = 18.7, 4.4 Hz, 1H<sup>18</sup>), 2.37 (s, 3H<sup>15</sup>), 2.08 (dd,  $J$  = 18.7, 9.9 Hz, 1H<sup>18</sup>).

**<sup>13</sup>C NMR (75 MHz,  $CDCl_3$ ):**  $\delta$  202.0 (17), 151.0 (12), 146.2 (8), 144.3 (9), 132.4 (6), 130.7 (4), 130.4 (11,13), 129.5 (3), 127.2 (10,14), 119.9 (5), 111.6 (7), 95.8 (2), 77.7 (19), 64.3 (1), 58.3 (20), 44.2 (16), 39.1 (18), 21.8 (15).

**Mp** = 173 °C.

(**4S<sup>\*</sup>,4aR<sup>\*</sup>,9aS<sup>\*</sup>**) minor diastereomer:

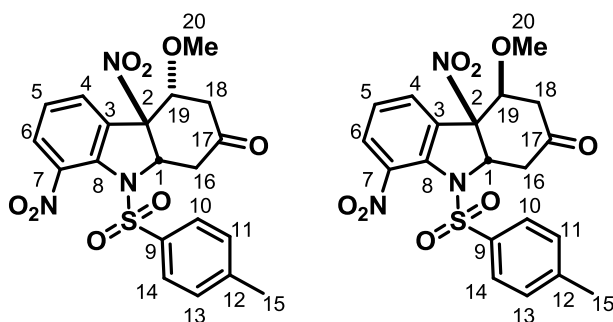
**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.50 (d,  $J = 2.0$  Hz,  $1\text{H}^7$ ), 7.96 (dd,  $J = 8.5, 2.0$  Hz,  $1\text{H}^5$ ), 7.76 (d,  $J = 8.5$  Hz,  $1\text{H}^4$ ), 7.69 (d,  $J = 8.4$  Hz,  $2\text{H}^{10,14}$ ), 7.27 (d,  $J = 8.4$  Hz,  $2\text{H}^{11,13}$ ), 5.87 (dd $\approx$ t,  $J = 4.4, 4.4$  Hz,  $1\text{H}^1$ ), 4.66 (dd,  $J = 3.6, 2.5$  Hz,  $1\text{H}^{19}$ ), 3.39 (s,  $3\text{H}^{20}$ ), 3.17 – 3.00 (m,  $2\text{H}^{16}$ ), 2.74 (dd,  $J = 18.9, 3.6$  Hz,  $1\text{H}^{18}$ ), 2.37 (s,  $3\text{H}^{15}$ ), 1.93 (dd,  $J = 18.9, 2.5$  Hz,  $1\text{H}^{18}$ ).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  203.1 (17), 151.1 (12), 146.2 (8), 144.4 (9), 132.5 (6), 130.7 (4), 130.4 (3), 129.5 (11,13), 127.8 (10,14), 120.0 (5), 111.5 (7), 94.8 (2), 80.3 (19), 62.6 (1), 58.5 (20), 43.8 (16), 37.6 (18), 29.8 (15).

**HRMS (ESI $^-$ )**  $m/z$  Calcd. for  $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_8\text{S}$   $[\text{M}-\text{H}]^-$ : 460.0815; Found: 460.0817.

**IR (neat)**  $\nu$   $\text{cm}^{-1}$  = 1728, 1558, 1530, 1347, 1168, 1088, 664.

**4-Methoxy-4a-8-dinitro-9-tosyl-1,3,4,4a,9,9a-hexahydro-2H-carbazol-2-one (4S\*,4aR\*,9aS\*) and (4R\*,4aR\*,9aS\*) diastereomers (154fa)**



**154fa** was prepared according to the general procedure 1: 1.2 equiv Danishefsky's diene **79** (46.5  $\mu\text{L}$ , 0.24 mmol) was added to a stirred solution of 3,7-dinitro-1-tosyl-1H-indole **150fa** (72.26 mg, 0.2 mmol) in 1 mL dry  $\text{CH}_2\text{Cl}_2$ . The reaction was stirred at room temperature for 24 h. Flash chromatography of the residue (Cyclohexane/Acetone: 80/20) afforded **154fa** (74 mg, 80%) as a light yellow solid of separable diastereomers in a 55 : 45 diastereomeric ratio.

**154fa** was also prepared according to the general procedure 3 with 1.2 equiv LDA and **134** (68  $\mu\text{L}$ , 0.6 mmol) in 1 mL dry THF and a solution of 3,7-dinitro-1-tosyl-1H-indole **150fa** (181 mg, 0.5 mmol) in 4 mL THF. The reaction was stirred at  $-78^\circ\text{C}$  for 6 h. **154fa** was obtained without further purification (106 mg, 89%) as an oil of non-separable diastereomers in a 78 : 22 diastereomeric ratio. The attempts to separate them by flash chromatography (Cyclohexane/EtOAc: 70/30) decreased the yield to 35% and afforded **154fa** as a light yellow solid of separable diastereomers.

*(4R\*,4aR\*,9aS\*) major diastereomer:*

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.01 (dd,  $J = 8.1, 0.9$  Hz,  $1\text{H}^6$ ), 7.94 (dd,  $J = 7.8, 0.9$  Hz,  $1\text{H}^4$ ), 7.52 (d,  $J = 8.3$  Hz,  $2\text{H}^{10,14}$ ), 7.45 (dd $\approx$ t,  $J = 8.1, 7.8$  Hz,  $1\text{H}^5$ ), 7.26 (d,  $J = 8.3$  Hz,  $2\text{H}^{11,13}$ ), 5.27 (dd,  $J = 7.0, 4.6$  Hz,  $1\text{H}^1$ ), 4.61 (dd,  $J = 9.9, 4.7$  Hz,  $1\text{H}^{19}$ ), 3.34 (s,  $3\text{H}^{20}$ ), 2.95 (dd,  $J = 16.1, 7.0$  Hz,  $1\text{H}^{16}$ ), 2.82

(dd,  $J = 18.3, 4.7$  Hz,  $1H^{18}$ ), 2.74 (dd,  $J = 16.1, 4.6$  Hz,  $1H^{16}$ ), 2.43 (s,  $3H^{15}$ ), 2.00 (dd,  $J = 18.3, 9.9$  Hz,  $1H^{18}$ ).

$^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  201.6 (17), 146.4 (12), 142.2 (8), 135.8 (7), 134.5 (4), 132.7 (11,13), 130.4 (9), 129.4 (3), 128.2 (6), 128.1 (10,14), 126.9 (5), 96.5 (2), 78.3 (19), 64.4 (1), 58.4 (20), 43.9 (16), 40.3 (18), 21.9 (15).

Mp = 162.2°C.

(4*S*\*,4*aR*\*,9*aS*\*) minor diastereomer:

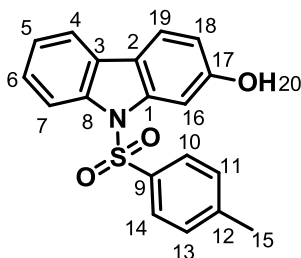
$^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  8.02 (dd,  $J = 8.1, 1.2$  Hz,  $1H^6$ ), 7.94 (dd,  $J = 7.8, 1.2$  Hz,  $1H^4$ ), 7.55 (d,  $J = 8.3$  Hz,  $2H^{10,14}$ ), 7.43 (dd $\approx$ t,  $J = 8.1, 7.8$  Hz,  $1H^5$ ), 7.29 (d,  $J = 8.3$  Hz,  $2H^{11,13}$ ), 5.78 (dd,  $J = 6.8, 3.6$  Hz,  $1H^1$ ), 4.46 (dd,  $J = 4.3, 3.0$  Hz,  $1H^{19}$ ), 3.35 (s,  $3H^{20}$ ), 3.14 (dd,  $J = 16.6, 6.8$  Hz,  $1H^{16}$ ), 2.92 (d,  $J = 18.4, 4.3$  Hz,  $1H^{18}$ ), 2.68 (dd,  $J = 16.6, 3.6$  Hz,  $1H^{16}$ ), 2.43 (s,  $3H^{15}$ ), 1.98 (dd,  $J = 18.4, 3.0$  Hz,  $1H^{18}$ ).

$^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  202.5 (17), 146.2 (12), 145.2 (8), 141.9 (4), 135.0 (7), 132.8 (11,13), 131.1 (9), 130.6 (3), 128.5 (6), 128.1 (10,14), 127.0 (5), 94.7 (2), 80.7 (19), 62.8 (1), 58.4 (20), 43.2 (16), 37.9 (18), 21.8 (15).

HRMS (ESI<sup>+</sup>)  $m/z$  Calcd. for  $C_{20}H_{23}N_4O_8S$  [ $M+NH_4$ ]<sup>+</sup>: 479.1237; Found: 479.1236.

IR (neat)  $\nu$   $cm^{-1}$  = 1728, 1558, 1539, 1356, 1167, 1088, 660.

### 9-tosyl-9H-carbazol-2-ol (**155**)<sup>285</sup>



To a solution of **154aa** (61.7 mg, 0.15 mmol, 1 equiv) in *t*-BuOH (1 mL), was added conc. HCl (75  $\mu$ L, 0.6 mmol, 6 equiv). The reaction was stirred for 4 h at 100 °C, after which it was filtered on celite and washed with EtOAc (3\*10 mL). Flash chromatography of the residue (Cyclohexane/Acetone: 80/20) afforded **155** (30 mg, 60%) as a yellow solid.

$^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  8.25 (dd,  $J = 8.4, 1.2$  Hz,  $1H^4$ ), 7.86 (dd $\approx$ d,  $J = 2.1, 2.1$  Hz,  $1H^{16}$ ), 7.76 (dd,  $J = 7.6, 1.3$  Hz,  $1H^7$ ), 7.71 (ddd $\approx$ d,  $J = 8.4, 8.4, 1.3$  Hz,  $1H^5$ ), 7.67 (d,  $J = 8.4$  Hz,  $2H^{10,14}$ ), 7.39 (ddd,  $J = 8.4, 7.6, 1.2$  Hz,  $1H^6$ ), 7.30 (td,  $J = 8.4, 2.1$  Hz,  $1H^{18}$ ), 7.03 (d,  $J = 8.4$  Hz,  $2H^{11,13}$ ), 6.91 (dd,  $J = 8.4, 2.1$  Hz,  $1H^{19}$ ), 5.29 (bs,  $1H^{20}$ ), 2.20 (s,  $3H^{15}$ ).

<sup>285</sup> See reference 181 in the manuscript.

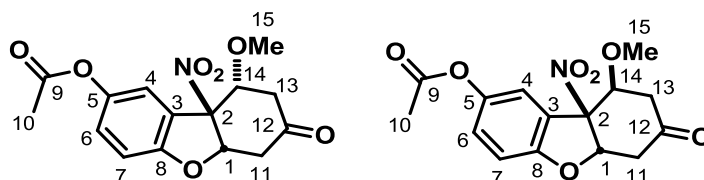
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  156.2 (17), 145.0 (12), 139.7 (9), 138.4 (8), 134.9 (3), 129.8 (11,13), 126.7 (1), 126.6 (10,14), 126.1 (6), 124.1 (18), 120.1 (5), 119.9 (2), 119.2 (7), 115.1 (4), 112.8 (19), 102.1 (16), 21.6 (15).

**HRMS (ESI $^-$ )**  $m/z$  Calcd. for  $\text{C}_{19}\text{H}_{14}\text{NO}_3\text{S}$   $[\text{M}-\text{H}]^-$ : 336.0694; Found: 336.0692.

**IR** (neat)  $\nu$  ( $\text{cm}^{-1}$ ) = 3500-2926 (broad), 1620, 1597, 1458, 1361, 1170, 950, 586.

**Mp** = 41.25 °C.

**9-methoxy-9a-nitro-7-oxo-5a,6,7,8,9,9a-hexahydrodibenzo[*b,d*]furan-2-yl acetate (5a*R* $^*$ , 9*R* $^*$ , 9a*R* $^*$ ) and (5a*R* $^*$ , 9*S* $^*$ , 9a*R* $^*$ ) diastereomers (163)**



**163** was prepared according to the general procedure 1: 1.2 equiv Danishefsky's diene **79** (46.5  $\mu\text{L}$ , 0.24 mmol) was added to a stirred solution of 3-nitrobenzofuran-5-yl acetate **162** (44.23 mg, 0.2 mmol) in 1 mL dry  $\text{CH}_2\text{Cl}_2$ . The reaction was stirred at room temperature for 24 h. Flash chromatography of the residue (Cyclohexane/Acetone: 80/20) afforded **163** (54.8 mg, 85%) as a white solid of separable diastereomers in a 50 : 50 diastereomeric ratio.

**163** was prepared according to the general procedure with 1.2 equiv LDA and **134** (68  $\mu\text{L}$ , 0.6 mmol) in 1 mL dry THF and a solution of 3-nitrobenzofuran-5-yl-acetate **162** (111 mg, 0.5 mmol) in 4 mL THF. The reaction was stirred at -78 °C for 6 h. Flash chromatography of the residue (Cyclohexane/Acetone: 80/20) afforded **163** (127 mg, 79%) as a white solid of separable diastereomers in a 75 : 25 diastereomeric ratio.

(5a*R* $^*$ , 9*S* $^*$ , 9a*R* $^*$ ) major diastereomer:

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.43 (d,  $J$  = 2.6 Hz,  $1\text{H}^4$ ), 7.12 (dd,  $J$  = 8.8, 2.6 Hz,  $1\text{H}^6$ ), 6.83 (d,  $J$  = 8.8 Hz,  $1\text{H}^7$ ), 5.44 – 5.40 (m,  $1\text{H}^1$ ), 4.64 (dd,  $J$  = 12.2, 4.4 Hz,  $1\text{H}^{14}$ ), 3.42 (s,  $3\text{H}^{15}$ ), 3.04 – 2.89 (m,  $2\text{H}^{11}$ ), 2.82 (dd,  $J$  = 18.4, 4.4 Hz,  $1\text{H}^{13}$ ), 2.30 (s,  $3\text{H}^{10}$ ), 1.97 (dd,  $J$  = 18.4, 12.2 Hz,  $1\text{H}^{13}$ ).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  203.0 (12), 169.7 (9), 158.0 (8), 145.0 (5), 126.4 (6), 123.4 (3), 119.2 (4), 110.8 (7), 98.2 (2), 83.1 (1), 78.9 (14), 58.3 (15), 42.6 (11), 40.4 (13), 21.2 (10).

**Mp** = 107.5 °C.

(5a*R* $^*$ , 9*R* $^*$ , 9a*R* $^*$ ) minor diastereomer:

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.44 (d,  $J$  = 2.5 Hz,  $1\text{H}^4$ ), 7.09 (dd,  $J$  = 8.8, 2.5 Hz,  $1\text{H}^6$ ), 6.84 (d,  $J$  = 8.8 Hz,  $1\text{H}^7$ ), 6.16 (dd,  $J$  = 4.5, 2.5 Hz,  $1\text{H}^1$ ), 4.53 (dd,  $J$  = 3.7, 2.0 Hz,  $1\text{H}^{14}$ ), 3.37 (s,  $3\text{H}^{15}$ ), 3.13 (dd,  $J$  =

## Experimental Part

17.5, 4.5 Hz, 1H<sup>11</sup>), 2.95 (dd,  $J = 17.5, 2.5$  Hz, 1H<sup>11</sup>), 2.76 (dd,  $J = 18.4, 3.7$  Hz, 1H<sup>13</sup>), 2.29 (s, 3H<sup>10</sup>), 2.05 (dd,  $J = 18.4, 2.0$  Hz, 1H<sup>13</sup>).

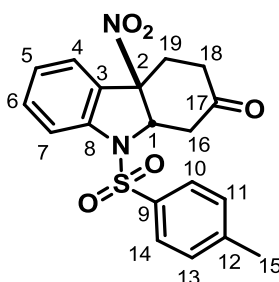
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  203.7 (12), 169.6 (9), 157.1 (8), 145.2 (5), 126.8 (6), 122.3 (3), 118.7 (4), 111.6 (7), 96.1 (2), 81.6 (1), 80.7 (14), 58.4 (15), 41.6 (11), 38.2 (13), 21.1 (10).

Mp = 120.5 °C.

HRMS (ESI<sup>-</sup>)  $m/z$  Calcd. C<sub>13</sub>H<sub>12</sub>NO<sub>6</sub> for [M-C<sub>2</sub>H<sub>3</sub>O]<sup>-</sup>: 278.0665; Found: 278.0667.

IR (neat)  $\nu$  cm<sup>-1</sup> = 1757, 1726, 1618, 1554, 1480, 1178, 499.

### (4aR\*,9aS\*)-4-nitro-9-tosyl-4,4,9,9-tetrahydro-1H-carbazol-2(3H)-one (196):



**196** was prepared according to the general procedure 2: 3 equiv of 2-trimethylsilyloxy-1,3-butadiene **120** (105  $\mu$ L, 0.6 mmol) was added to a stirred solution 3-nitro-1-tosyl-1H-indole **150aa** (63 mg, 0.2 mmol) in 0.9 mL dry CH<sub>2</sub>Cl<sub>2</sub>. The reaction was stirred for 24 h at room temperature under 16 kbar pressure. Flash chromatography of the residue (Cyclohexane/EtOAc: 70/30) afforded **196** (42 mg, 55%) as a yellow solid.

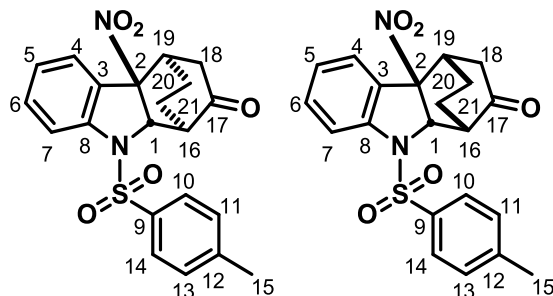
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.76 (d,  $J = 8.2$  Hz, 1H<sup>4</sup>), 7.61 (d,  $J = 8.3$  Hz, 2H<sup>10,14</sup>), 7.51 – 7.38 (m, 2H<sup>5,6</sup>), 7.27 – 7.17 (m, 3H<sup>7,11,13</sup>), 5.42 (dd $\approx$ t,  $J = 6.2, 6.2$  Hz, 1H<sup>1</sup>), 3.17 (dd,  $J = 16.3, 6.2$  Hz, 1H<sup>16</sup>), 3.02 (dd,  $J = 16.3, 6.2$  Hz, 1H<sup>16</sup>), 2.98 – 2.88 (m, 1H<sup>18</sup>), 2.62 (ddd,  $J = 14.6, 7.5, 4.6$  Hz, 1H<sup>18</sup>), 2.46 – 2.28 (m, 4H<sup>15,19</sup>), 2.08 (ddd,  $J = 19.2, 9.4, 4.6$  Hz, 1H<sup>19</sup>).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  205.4 (17), 145.3 (12), 142.5 (8), 133.2 (9), 132.7 (4), 129.1 (11,13), 127.6 (10,14), 127.1 (3), 125.6 (6), 125.5 (7), 116.8 (5), 93.9 (2), 63.5 (1), 44.1 (16), 34.9 (19), 30.6 (18), 21.7 (15).

HRMS (ESI<sup>-</sup>):  $m/z$  Calcd. for C<sub>19</sub>H<sub>17</sub>N<sub>2</sub>O<sub>5</sub>S [M-H]<sup>-</sup>: 385.0858; Found: 385.0853.

IR (neat)  $\nu$  cm<sup>-1</sup> = 1723, 1548, 1358, 1167, 573, 539.

### 4a-Nitro-9-tosyl-4,4a,9,9a-tetrahydro-1H-1,4-ethanocarbazol-2(3H)-one (1S\*,4S\*,4aR\*,9aS\*) and (1R\*,4R\*,4aR\*,9aS\*) diastereomers (170)



**(1R\*,4R\*,4aR\*,9aS\*)-170** was prepared according to the general procedure 2: 4 equiv of 3-trimethylsilyoxy-1,3-cyclohexadiene **168** (75  $\mu$ L, 0.4 mmol) was added to a stirred solution of 3-nitro-1-tosyl-1*H*-indole **150aa** (31.6 mg, 0.1 mmol) in 0.9 mL dry  $\text{CH}_2\text{Cl}_2$ . The reaction was stirred for 24 h at room temperature under 16 kbar pressure. Flash chromatography of the residue (Cyclohexane/EtOAc: 70/30) afforded **(1R\*,4R\*,4aR\*,9aS\*)-170** (25.2 mg, 61%) as a yellow solid as a single diastereoisomer.

**170** was prepared according to the general procedure 3 using 1.2 equiv LDA and cyclohex-2-enone **232** (60  $\mu$ L, 0.6 mmol) in 1 mL dry THF and a solution of **150aa** (158 mg, 0.5 mmol) in 2 mL THF. The reaction mixture was stirred at  $-78^\circ\text{C}$  for 6 h. The crude mixture was dissolved in EtOH (5 mL) and heated at  $40^\circ\text{C}$  with silica gel for 48 hrs. After which it was filtered over celite and purified by flash chromatography on silica (Cyclohexane/EtOAc: 70/30) to afford **170** (124 mg, 60%) as a yellow solid of separable diastereomers in a 53 : 47 diastereomeric ratio.

**(1S\*,4S\*,4aR\*,9aS\*)** major diastereomer:

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.72 – 7.61 (m,  $3\text{H}^{4,10,14}$ ), 7.48 (dd,  $J = 7.7, 0.8$  Hz,  $1\text{H}^5$ ), 7.45 – 7.35 (m,  $1\text{H}^6$ ), 7.21 (d,  $J = 8.1$  Hz,  $2\text{H}^{11,13}$ ), 7.11 (ddd $\approx$ td,  $J = 7.7, 7.7, 0.9$  Hz,  $1\text{H}^7$ ), 5.49 (d,  $J = 3.6$  Hz,  $1\text{H}^1$ ), 3.39 – 3.16 (m,  $2\text{H}^{16,19}$ ), 2.35 (s,  $3\text{H}^{15}$ ), 2.16 (dd,  $J = 19.4, 3.2$  Hz,  $1\text{H}^{18}$ ), 2.09 – 1.65 (m,  $5\text{H}^{18,20,21}$ ).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  208.6 (17), 145.2 (12), 142.6 (8), 133.3 (9), 132.7 (6), 129.1 (11,13), 127.7 (10,14), 126.7 (3), 125.3 (5), 125.3 (7), 116.5 (4), 96.6 (2), 66.4 (1), 48.2 (16), 40.3 (18), 37.4 (19), 21.7 (15), 20.1 (20), 19.3 (21).

**Mp** =  $95.5^\circ\text{C}$ .

**(1R\*,4R\*,4aR\*,9aS\*)** minor diastereomer:

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.83 (d,  $J = 8.6$  Hz,  $1\text{H}^4$ ), 7.67 (d,  $J = 8.1$  Hz,  $2\text{H}^{10,14}$ ), 7.52 – 7.42 (m,  $2\text{H}^{5,6}$ ), 7.21 (d,  $J = 8.1$  Hz,  $2\text{H}^{11,13}$ ), 7.15 (dd,  $J = 7.7, 0.9$  Hz,  $1\text{H}^7$ ), 5.32 (d,  $J = 3.5$  Hz,  $1\text{H}^1$ ), 3.36 – 3.28 (m,  $1\text{H}^{19}$ ), 3.25 – 3.17 (m,  $1\text{H}^{16}$ ), 2.45 – 2.36 (m,  $1\text{H}^{18}$ ), 2.35 (s,  $3\text{H}^{15}$ ), 2.24 (dd $\approx$ t,  $J = 2.7, 2.7$  Hz,  $1\text{H}^{18}$ ), 2.02 – 1.83 (m,  $1\text{H}^{21}$ ), 1.74 – 1.48 (m,  $2\text{H}^{20,21}$ ), 1.44 – 1.23 (m,  $1\text{H}^{20}$ ).



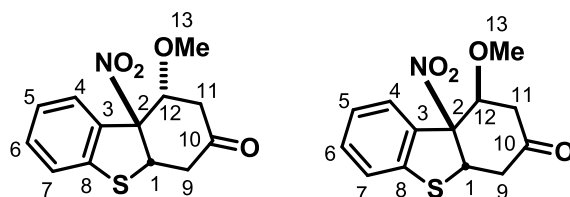
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 209.4 (17), 145.3 (21), 143.3 (8), 133.1 (9), 132.6 (6), 130.0 (11,13), 127.8 (10,14), 127.1 (3), 125.4 (5), 125.1 (7), 116.2 (4), 96.7 (2), 63.5 (1), 48.5 (16), 41.3 (18), 36.7 (19), 21.7 (15), 21.7 (20), 15.3 (21).

**Mp** = 197.6 °C.

**HRMS (ESI<sup>-</sup>)** m/z Calcd. for C<sub>21</sub>H<sub>19</sub>N<sub>2</sub>O<sub>5</sub> [M-H]<sup>-</sup>: 411.1093; Found: 411.1091.

**IR** (neat) ν (cm<sup>-1</sup>) = 1724, 1551, 1168, 1079, 949, 765.

**1-methoxy-9b-nitro-1,4,4a,9b-tetrahydridibenzo[*b,d*]thiophen-3(2*H*)-one (1*S*<sup>\*</sup>, 4*aS*<sup>\*</sup>, 9*bS*<sup>\*</sup>) and (1*R*<sup>\*</sup>, 4*aS*<sup>\*</sup>, 9*bS*<sup>\*</sup>) diastereomers (173)**



**173** was prepared according to the general procedure 2: 6 equiv Danishefsky's diene **79** (232 μL, 1.2 mmol) was added to a stirred solution 3-nitrobenzothiophene **172** (35.8 mg, 0.2 mmol) in 0.9 mL dry CH<sub>2</sub>Cl<sub>2</sub>. The reaction was stirred for 24 h at room temperature under 16 kbar pressure. Flash chromatography of the residue (Cyclohexane/EtOAc: 85/15) afforded **173** (44.6 mg, 80%) as an orange oil of non-separable diastereomers in a 50 : 50 diastereomeric ratio.

(1*R*<sup>\*</sup>, 4*aS*<sup>\*</sup>, 9*bS*<sup>\*</sup>) major *diastereomer*:

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.61 (d, *J* = 7.7 Hz, 1H<sup>7</sup>), 7.42 – 7.05 (m, 3H<sup>4,5,6</sup>), 4.68 (dd, *J* = 4.2, 2.3 Hz, 1H<sup>1</sup>), 4.59 (dd, *J* = 11.1, 4.1 Hz, 1H<sup>12</sup>), 3.35 (s, 3H<sup>13</sup>), 2.81 (ddd, *J* = 15.5, 4.2, 1.3 Hz, 1H<sup>9</sup>), 2.71 (ddd, *J* = 17.1, 4.1, 1.3 Hz, 1H<sup>11</sup>), 2.48 – 2.42 (m, 1H<sup>9</sup>), 2.31 (ddd, *J* = 17.1, 11.1, 0.7 Hz, 1H<sup>11</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 202.9 (10), 142.9 (3), 131.9 (8), 131.0 (4), 127.1 (7), 125.5 (6), 123.3 (5), 102.1 (2), 81.6 (13), 80.4 (12), 58.1 (1), 41.4 (11), 38.5 (9).

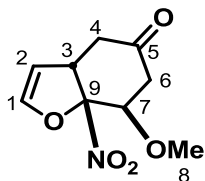
(1*S*<sup>\*</sup>, 4*aS*<sup>\*</sup>, 9*bS*<sup>\*</sup>) minor *diastereomer*:

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.84 (d, *J* = 7.9 Hz, 1H<sup>7</sup>), 7.42 – 7.05 (m, 3H<sup>4,5,6</sup>), 5.31 (dd, *J* = 6.9, 5.6 Hz, 1H<sup>1</sup>), 4.50 (dd, *J* = 10.0, 6.3 Hz, 1H<sup>12</sup>), 3.34 (s, 3H<sup>13</sup>), 3.21 (ddd, *J* = 16.4, 6.9, 1.3 Hz, 1H<sup>9</sup>), 2.95 (ddd, *J* = 15.9, 6.3, 1.3 Hz, 1H<sup>11</sup>), 2.52 – 2.48 (m, 1H<sup>9</sup>), 2.48 – 2.42 (m, 1H<sup>11</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 203.1 (10), 143.1 (3), 132.5 (8), 132.3 (4), 130.5 (7), 125.7 (6), 123.9 (5), 104.6 (2), 58.6 (13), 49.5 (12), 46.4 (1), 46.1 (11), 44.7 (9).

**HRMS (ESI<sup>-</sup>)** m/z Calcd. for C<sub>13</sub>H<sub>12</sub>NO<sub>4</sub>S [M-H]<sup>-</sup>: 278.0487; Found: 278.0495.

**IR** (neat) ν cm<sup>-1</sup> = 1723, 1548, 1090, 755, 735.

**(3a*S*\*, 7*R*\*, 7a*R*\*)-9-methoxy-7a-nitro-3a,4,7,7a-tetrahydrobenzofuran-5(6*H*)-one (177)**

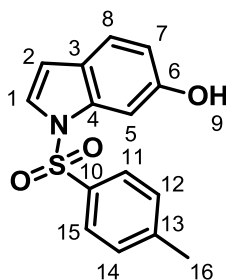
**177** was prepared according to the general procedure 2: 6 equiv Danishefsky's diene **79** (232  $\mu$ L, 1.2 mmol) was added to a stirred solution 2-nitrofuran **174** (22.6 mg, 0.2 mmol) in 0.9 mL dry  $\text{CH}_2\text{Cl}_2$ . The reaction was stirred for 24 h at room temperature under 16 kbar pressure. Flash chromatography of the residue (Cyclohexane/EtOAc: 70/30) afforded **177** (38.3 mg, 90%) as an orange oil in a single diastereomer.

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  6.55 (dd,  $J = 6.3, 1.8$  Hz,  $1\text{H}^1$ ), 6.37 (dd,  $J = 6.3, 1.5$  Hz,  $1\text{H}^2$ ), 5.38 (dddd,  $J = 7.5, 1.5, 0.9, 0.6$  Hz,  $1\text{H}^3$ ), 4.14 (dd,  $J = 8.7, 5.0$  Hz,  $1\text{H}^7$ ), 3.38 (s,  $3\text{H}^8$ ), 3.15 (ddd,  $J = 15.0, 7.5, 0.9$  Hz,  $1\text{H}^4$ ), 2.91 (ddd,  $J = 11.7, 5.0, 0.9$  Hz,  $1\text{H}^6$ ), 2.62 (ddd,  $J = 15.0, 0.6, 0.8$  Hz,  $1\text{H}^4$ ), 2.52 (dd,  $J = 11.7, 8.7$  Hz,  $1\text{H}^6$ ).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  202.4 (5), 136.9 (1), 125.3 (2), 83.1 (3), 78.4 (7), 58.5 (8), 49.7 (6), 44.4 (4).

**HRMS (ESI<sup>+</sup>):**  $m/z$  Calcd. for  $\text{C}_9\text{H}_{12}\text{NO}_5$   $[\text{M}+\text{H}]^+$ : 214.0715; Found: 214.0713.

**IR (neat)**  $\nu$   $\text{cm}^{-1}$  = 1706, 1553, 1371, 1092, 1005, 803.

**1-tosyl-1*H*-indol-6-ol (179)**

**179** was prepared according to the general procedure 2: 6 equiv Danishefsky's diene **79** (232  $\mu$ L, 1.2 mmol) was added to a stirred solution 3-nitropyrrole **176** (22.6 mg, 0.2 mmol) in 0.9 mL dry  $\text{CH}_2\text{Cl}_2$ . The reaction was stirred for 24 h at room temperature under 16 kbar pressure. Flash chromatography of the residue (Cyclohexane/EtOAc: 80/20) afforded **179** (45 mg, 79%) as a white powder.

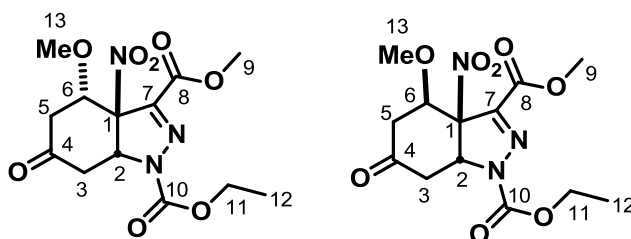
**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.75 – 7.70 (m,  $2\text{H}^{11,15}$ ), 7.51 (ddd,  $J = 2.3, 0.8, 0.5$  Hz,  $1\text{H}^8$ ), 7.43 (d,  $J = 3.7$  Hz,  $1\text{H}^5$ ), 7.35 (dd,  $J = 8.5, 0.5$  Hz,  $1\text{H}^1$ ), 7.20 – 7.15 (m,  $2\text{H}^{12,14}$ ), 6.78 (dd,  $J = 8.5, 2.3$  Hz,  $1\text{H}^2$ ), 6.56 (dd,  $J = 3.7, 0.8$  Hz,  $1\text{H}^7$ ), 5.23 (bs,  $1\text{H}^9$ ), 2.32 (s,  $3\text{H}^{16}$ ).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 153.8 (6), 145.1 (13), 135.9 (4), 135.3 (10), 130.0 (12,14), 126.9 (11,15), 125.3 (8), 124.8 (3), 122.2 (1), 112.9 (2), 109.2 (7), 100.4 (5), 21.7 (16).

**HRMS (ESI<sup>-</sup>):** m/z Calcd. for C<sub>15</sub>H<sub>12</sub>NO<sub>3</sub>S [M-H]<sup>-</sup>: 286.0538; Found: 286.0532.

**1-ethyl-3-methyl-4-methoxy-3a-nitro-6-oxo-3a,4,5,6,7,7a-hexahydro-1H-indazol-1,3-dicarboxylate**

**(3aR<sup>\*</sup>, 4R<sup>\*</sup>, 7aR<sup>\*</sup>) and (3aR<sup>\*</sup>, 4S<sup>\*</sup>, 7aR<sup>\*</sup>) diastereomers (185)**



**185** was prepared according to the general procedure 3: 6 equiv Danishefsky's diene **79** (232 μL, 1.2 mmol) was added to a stirred solution 1-ethyl-3-methyl-4-nitro-1H-pyrazole-1,3-dicarboxylate **184** (48.61 mg, 0.2 mmol) in 0.9 mL dry CH<sub>2</sub>Cl<sub>2</sub>. The reaction was stirred for 24 h at room temperature under 16 kbar pressure. Flash chromatography of the residue (Cyclohexane/EtOAc: 80/20) afforded **185** (57.64 mg, 84%) as an orange oil of non-separable diastereomers in a 66 : 34 diastereomeric ratio.

(3aR<sup>\*</sup>, 4S<sup>\*</sup>, 7aR<sup>\*</sup>) major diastereomer:

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 4.91 (dd, *J* = 11.9, 6.3 Hz, 1H<sup>6</sup>), 4.60 (dd, *J* = 7.2, 2.3 Hz, 1H<sup>2</sup>), 4.19 (q, *J* = 7.1 Hz, 2H<sup>11</sup>), 3.76 (s, 3H<sup>9</sup>), 3.12 (s, 3H<sup>13</sup>), 3.03 (dd, *J* = 17.1, 7.2 Hz, 1H<sup>3</sup>), 2.90 – 2.61 (m, 3H<sup>3,5</sup>), 1.20 (t, *J* = 7.1 Hz, 3H<sup>12</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 202.3 (4), 160.6 (8), 140.4 (10), 130.9 (7), 115.4 (1), 98.8 (6), 64.1 (11), 63.4 (13), 57.7 (9), 53.1 (2), 38.8 (5), 38.8 (3), 14.4 (12).

(3aR<sup>\*</sup>, 4R<sup>\*</sup>, 7aR<sup>\*</sup>) minor diastereomer:

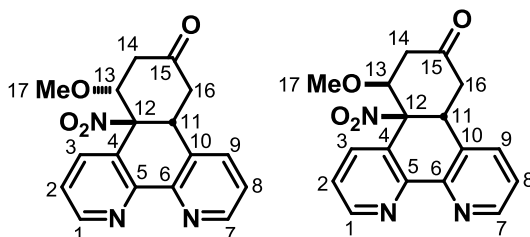
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ = 5.66 (dd, *J* = 7.2, 1.8 Hz, 1H<sup>6</sup>), 5.14 (dd≈t, *J* = 2.9, 2.9 Hz, 1H<sup>2</sup>), 4.20 (q, *J* = 7.1 Hz, 2H<sup>11</sup>), 3.74 (s, 3H<sup>9</sup>), 3.24 (s, 3H<sup>13</sup>), 3.03 (dd, *J* = 17.1, 7.2 Hz, 1H<sup>5</sup>), 2.47 – 2.39 (m, 2H<sup>3,5</sup>), 2.07 (ddd, *J* = 19.3, 2.9, 0.9 Hz, 1H<sup>3</sup>), 1.20 (t, *J* = 7.1 Hz, 3H<sup>12</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 203.3 (4), 160.6 (8), 137.4 (10), 130.0 (7), 96.9 (1), 74.4 (6), 64.3 (11), 61.9 (13), 58.4 (9), 53.4 (2), 40.5 (5), 39.9 (3), 14.4 (12).

**HRMS (ESI<sup>+</sup>):** m/z Calcd. for C<sub>13</sub>H<sub>21</sub>N<sub>4</sub>O<sub>4</sub> [M+NH<sub>4</sub>]<sup>+</sup>: 361.1359; Found: 361.1350.

**IR (neat)** ν cm<sup>-1</sup> = 1714, 1557, 1455, 1417, 1090, 755.

**8-methoxy-8a-nitro-4b,5,8,8a-tetrahydrobenzo[*f*][1.10]phenanthroline-6(7*H*)-one (4*bR*<sup>\*</sup>, 8*S*<sup>\*</sup>, 8*aS*<sup>\*</sup>) and (4*bR*<sup>\*</sup>, 8*R*<sup>\*</sup>, 8*aS*<sup>\*</sup>) diastereomers (187)**



**187** was prepared according to the general procedure 2: 6 equiv Danishefsky's diene **79** (232  $\mu$ L, 1.2 mmol) was added to a stirred solution 5-nitro-1,10-phenanthroline **186** (45.0 mg, 0.2 mmol) in 0.9 mL dry  $\text{CH}_2\text{Cl}_2$ . The reaction was stirred for 24 h at room temperature under 16 kbar pressure. Inverse phase HPLC of the residue (Water+ 0.1% formic acid/ACN: 90/10 to 0/100) afforded **187** (57.3 mg, 88%) as a pink oil of separable diastereomers in a 60 : 40 diastereomeric ratio.

(4*bR*<sup>\*</sup>, 8*R*<sup>\*</sup>, 8*aS*<sup>\*</sup>) major *diastereomer*:

**<sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.98 (dd,  $J = 4.7, 1.5$  Hz, 1H<sup>1</sup>), 8.80 (dd,  $J = 4.7, 1.5$  Hz, 1H<sup>7</sup>), 8.76 (dd,  $J = 8.1, 1.5$  Hz, 1H<sup>3</sup>), 7.55 (dd,  $J = 7.7, 1.5$  Hz, 1H<sup>9</sup>), 7.48 (dd,  $J = 8.1, 4.7$  Hz, 1H<sup>2</sup>), 7.30 (dd,  $J = 7.7, 4.7$  Hz, 1H<sup>8</sup>), 4.65 (dd,  $J = 13.2, 4.7$  Hz, 1H<sup>13</sup>), 3.98 (dd,  $J = 13.7, 5.0$  Hz, 1H<sup>11</sup>), 3.47 (s, 3H<sup>17</sup>), 3.11 (ddd,  $J = 14.7, 4.7, 1.9$  Hz, 1H<sup>14</sup>), 2.81 – 2.67 (m, 1H<sup>14</sup>), 2.61 (ddd,  $J = 15.6, 5.0, 1.9$  Hz, 1H<sup>16</sup>), 2.24 – 2.10 (m, 1H<sup>16</sup>).

**<sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  201.7 (15), 152.4 (1), 152.4 (5), 151.2 (7), 148.1 (6), 139.1 (3), 135.7 (9), 130.2 (4), 124.9 (8), 124.4 (10), 124.4 (2), 93.8 (12), 83.3 (13), 59.2 (17), 45.9 (16), 43.2 (14), 42.7 (11).

(4*bR*<sup>\*</sup>, 8*S*<sup>\*</sup>, 8*aS*<sup>\*</sup>) minor *diastereomer*:

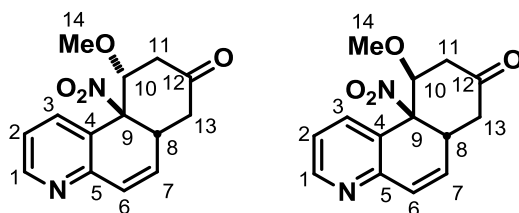
**<sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.96 (dd,  $J = 4.6, 1.2$  Hz, 1H<sup>1</sup>), 8.77 (dd,  $J = 4.7, 1.5$  Hz, 1H<sup>7</sup>), 8.11 (dd,  $J = 8.0, 1.2$  Hz, 1H<sup>3</sup>), 7.69 (dd,  $J = 7.7, 1.5$  Hz, 1H<sup>9</sup>), 7.52 (dd,  $J = 8.0, 4.6$  Hz, 1H<sup>2</sup>), 7.38 (dd,  $J = 7.7, 4.7$  Hz, 1H<sup>8</sup>), 5.10 – 5.01 (m, 1H<sup>13</sup>), 4.61 (dd,  $J = 13.4, 5.4$  Hz, 1H<sup>11</sup>), 3.44 (s, 3H<sup>17</sup>), 3.00 – 2.86 (m, 1H<sup>14</sup>), 2.74 – 2.57 (m, 2H<sup>14,16</sup>), 2.29 – 2.13 (m, 1H<sup>16</sup>).

**<sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  202.6 (15), 152.1 (1), 151.3 (5), 150.4 (7), 147.6 (6), 136.4 (3), 135.7 (9), 134.0 (4), 125.6 (8), 125.0 (10), 124.8 (2), 90.9 (12), 81.2 (13), 58.1 (17), 45.5 (16), 40.04 (14), 38.8 (11).

**HRMS (ESI<sup>+</sup>):**  $m/z$  Calcd. for  $\text{C}_{17}\text{H}_{16}\text{N}_3\text{O}_4$  [M+H]<sup>+</sup>: 326.1141; Found: 326.1132.

**IR (neat)**  $\nu$   $\text{cm}^{-1}$  = 1714, 1547, 1082, 1008, 801, 408.

**10-methoxy-10a-nitro-6a,7,8,9,10,10a-tetrahydrobenzo[*f*]quinolin-8(9*H*)-one (6a*R*<sup>\*</sup>, 10*S*<sup>\*</sup>, 10a*S*<sup>\*</sup>) and (6a*R*<sup>\*</sup>, 10*R*<sup>\*</sup>, 10a*S*<sup>\*</sup>) diastereomers (190a)**



**190a** was prepared according to the general procedure 2: 6 equiv Danishefsky's diene **79** (232  $\mu\text{L}$ , 1.2 mmol) was added to a stirred solution 5-nitroquinoline **188a** (34.8 mg, 0.2 mmol) in 0.9 mL dry  $\text{CH}_2\text{Cl}_2$ . The reaction was stirred for 24 h at room temperature under 16 kbar pressure. Flash chromatography of the residue (Cyclohexane/EtOAc: 20/80) afforded **190a** (49.3 mg, 92%) as a brown oil of separable diastereomers in a 55 : 45 diastereomeric ratio.

(4*R*<sup>\*</sup>,4a*R*<sup>\*</sup>,9a*S*<sup>\*</sup>) major diastereomer:

**<sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.69 (ddd,  $J = 4.9, 1.6, 0.5$  Hz, 1H<sup>1</sup>), 8.58 (ddd,  $J = 8.0, 1.6, 0.6$  Hz, 1H<sup>3</sup>), 7.31 (dd,  $J = 8.0, 4.9$  Hz, 1H<sup>2</sup>), 6.78 (d,  $J = 9.7$  Hz, 1H<sup>6</sup>), 6.29 (dd,  $J = 9.7, 5.8$  Hz, 1H<sup>7</sup>), 4.53 (dd,  $J = 13.4, 4.5$  Hz, 1H<sup>10</sup>), 3.51 (ddd,  $J = 13.6, 5.8, 4.9$  Hz, 1H<sup>8</sup>), 3.43 (s, 3H<sup>14</sup>), 3.04 (ddd,  $J = 14.4, 4.5, 2.0$  Hz, 1H<sup>11</sup>), 2.70 (dd,  $J = 14.4, 13.4$  Hz, 1H<sup>11</sup>), 2.61 (dd,  $J = 15.5, 4.9, 2.0$  Hz, 1H<sup>13</sup>), 1.90 (dd,  $J = 15.5, 13.6$  Hz, 1H<sup>13</sup>).

**<sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  202.5 (12), 153.5 (5), 151.3 (1), 138.6 (3), 131.4 (7), 130.6 (6), 122.8 (2), 122.7 (4), 94.8 (9), 83.2 (10), 59.1 (14), 43.1 (11), 43.1 (13), 38.4 (8).

(4*R*<sup>\*</sup>,4a*S*<sup>\*</sup>,9a*S*<sup>\*</sup>) minor diastereomer:

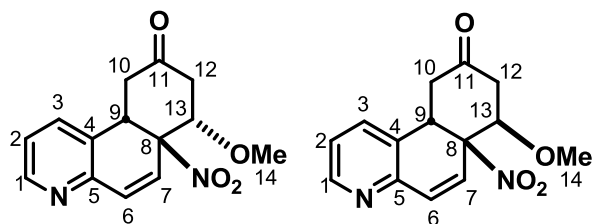
**<sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.63 (dd,  $J = 4.9, 1.5$  Hz, 1H<sup>1</sup>), 7.94 (ddd,  $J = 7.9, 1.5, 0.7$  Hz, 1H<sup>3</sup>), 7.31 (dd,  $J = 7.9, 4.9$  Hz, 1H<sup>2</sup>), 6.65 (dd,  $J = 9.8, 0.7$  Hz, 1H<sup>6</sup>), 6.53 (ddd,  $J = 9.8, 5.6, 0.7$  Hz, 1H<sup>7</sup>), 4.93 (bdd,  $J = 4.1, 2.1$  Hz, 1H<sup>10</sup>), 4.13 (ddd,  $J = 13.2, 5.6, 3.9$  Hz, 1H<sup>8</sup>), 3.39 (s, 3H<sup>14</sup>), 2.89 (ddd,  $J = 15.2, 2.5, 2.1$  Hz, 1H<sup>11</sup>), 2.69 (ddd,  $J = 15.1, 3.9, 2.5$  Hz, 1H<sup>13</sup>), 2.67 (ddd,  $J = 15.2, 4.1, 2.3$  Hz, 1H<sup>11</sup>), 1.98 (ddd,  $J = 15.1, 13.2, 0.7$  Hz, 1H<sup>13</sup>).

**<sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  203.1 (12), 152.5 (5), 151.7 (1), 135.8 (7), 135.7 (3), 127.4 (6), 123.1 (4), 123.1 (2), 92.1 (9), 81.1 (10), 57.9 (14), 42.4 (13), 39.1 (11), 34.6 (8).

**HRMS (ESI<sup>+</sup>):**  $m/z$  Calcd. for  $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_4$   $[\text{M}+\text{H}]^+$ : 275.1032; Found: 275.1024.

**IR (neat)**  $\nu$   $\text{cm}^{-1}$  = 1716, 1551, 1462, 1366, 1231, 1104, 793.

**7-methoxy-6a-nitro-7,8,10,10a-tetrahydrobenzo[*f*]quinolin-9(6a*H*)-one**

**(6aS\*, 7R\*, 10aS\*) and (6aS\*, 10S\*, 10aS\*) diastereomers (190b)**

**190b** was prepared according to the general procedure 2: 6 equiv Danishefsky's diene **79** (232  $\mu\text{L}$ , 1.2 mmol) was added to a stirred solution 6-nitroquinoline **188b** (34.8 mg, 0.2 mmol) in 0.9 mL dry  $\text{CH}_2\text{Cl}_2$ . The reaction was stirred for 72 h at room temperature under 16 kbar pressure. Flash chromatography of the residue (Cyclohexane/Acetone: 85/15) afforded **190b** (40 mg, 73%) as a yellow oil of separable diastereomers in a 50 : 50 diastereomeric ratio.

(6aS\*, 10S\*, 10aS\*) major *diastereomer*:

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.53 (dd,  $J = 4.9, 1.5$  Hz,  $1\text{H}^1$ ), 7.42 (dd,  $J = 7.6, 1.5$  Hz,  $1\text{H}^3$ ), 7.34 (d,  $J = 9.8$  Hz,  $1\text{H}^6$ ), 7.17 (dd,  $J = 7.6, 4.9$  Hz,  $1\text{H}^2$ ), 6.67 (dd,  $J = 9.8, 1.4$  Hz,  $1\text{H}^7$ ), 4.34 (dd,  $J = 12.7, 4.8$  Hz,  $1\text{H}^{13}$ ), 3.89 (ddd,  $J = 13.3, 5.6, 1.4$  Hz,  $1\text{H}^9$ ), 3.39 (s,  $3\text{H}^{14}$ ), 2.96 (ddd,  $J = 13.9, 4.8, 2.1$  Hz,  $1\text{H}^{12}$ ), 2.63 – 2.48 (m,  $2\text{H}^{10,12}$ ), 2.30 (dd,  $J = 14.5, 13.3$  Hz,  $1\text{H}^{10}$ ).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  202.7 (11), 149.9 (5), 149.8 (1), 137.5 (6), 135.0 (3), 129.1 (4), 123.8 (2), 122.1 (7), 91.9 (8) 80.7 (13), 58.2 (14), 46.0 (10), 42.6 (12), 41.5 (9).

(6aS\*, 7R\*, 10aS\*) minor *diastereomer*:

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.49 (dd,  $J = 4.9, 1.5$  Hz,  $1\text{H}^1$ ), 7.54 (dd,  $J = 7.6, 1.5$  Hz,  $1\text{H}^3$ ), 7.22 (dd,  $J = 7.6, 4.9$  Hz,  $1\text{H}^2$ ), 7.10 (d,  $J = 9.5$  Hz,  $1\text{H}^6$ ), 6.30 (dd,  $J = 9.5, 1.4$  Hz,  $1\text{H}^7$ ), 4.52 (dd,  $J = 3.6, 2.5$  Hz,  $1\text{H}^{13}$ ), 4.46 (ddd,  $J = 12.8, 6.1, 1.4$  Hz,  $1\text{H}^9$ ), 3.37 (s,  $3\text{H}^{14}$ ), 2.90 (ddd,  $J = 15.1, 3.6, 2.3$  Hz,  $1\text{H}^{12}$ ), 2.79 (dd,  $J = 15.1, 2.5$  Hz,  $1\text{H}^{12}$ ), 2.61 (ddd,  $J = 15.1, 6.1, 2.3$  Hz,  $1\text{H}^{10}$ ), 2.31 (dd,  $J = 15.1, 12.8$  Hz,  $1\text{H}^{10}$ ).

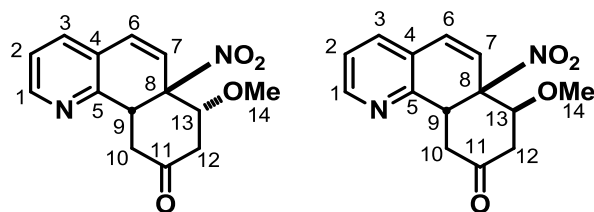
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  203.2 (11), 149.1 (1), 148.5 (5), 136.7 (2), 134.7 (3), 133.1 (4), 125.5 (6), 124.5 (7), 89.2 (8), 83.4 (13), 57.7 (14), 45.1 (10), 39.8 (12), 38.7 (9).

**HRMS (ESI<sup>+</sup>):**  $m/z$  Calcd. for  $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_4$   $[\text{M}+\text{H}]^+$ : 275.1032; Found: 275.1038.

**IR (neat)**  $\nu$   $\text{cm}^{-1}$  = 1723, 1543, 1458, 1377, 1092, 814.

**7-methoxy-6a-nitro-7,8,10,10a-tetrahydrobenzo[*h*]quinolin-9(6a*H*)-one**  
**(6aR\*, 7S\*, 10aS\*) and (6aR\*, 10R\*, 10aS\*) diastereomers (190c)**

## Experimental Part



**190c** was prepared according to the general procedure 2: 6 equiv Danishefsky's diene **79** (232  $\mu\text{L}$ , 1.2 mmol) was added to a stirred solution 7-nitroquinoline **188c** (34.8 mg, 0.2 mmol) in 0.9 mL dry  $\text{CH}_2\text{Cl}_2$ . The reaction was stirred for 24 h at room temperature under 16 kbar pressure. Flash chromatography of the residue (Cyclohexane/Acetone: 50/50) afforded **190c** (40 mg, 89%) as an orange oil of separable diastereomers in a 53 : 47 diastereomeric ratio.

(6aR\*,7R\*,10aS\*) major *diastereomer*:

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.53 (dd,  $J = 4.9, 1.6$  Hz,  $1\text{H}^1$ ), 7.42 (dd,  $J = 7.7, 1.6$  Hz,  $1\text{H}^3$ ), 7.35 (ddd,  $J = 9.8, 0.8, 0.7$  Hz,  $1\text{H}^7$ ), 7.17 (dd,  $J = 7.7, 4.9$  Hz,  $1\text{H}^2$ ), 6.68 (dd,  $J = 9.8, 1.6$  Hz,  $1\text{H}^6$ ), 4.33 (dd,  $J = 12.6, 4.8$  Hz,  $1\text{H}^{13}$ ), 3.89 (ddd,  $J = 13.5, 5.3, 1.6$  Hz,  $1\text{H}^9$ ), 3.39 (s,  $3\text{H}^{14}$ ), 2.96 (ddd,  $J = 13.9, 4.8, 2.1$  Hz,  $1\text{H}^{12}$ ), 2.66 (ddd,  $J = 13.9, 12.6, 0.8$  Hz,  $1\text{H}^{12}$ ), 2.53 (ddd,  $J = 15.1, 5.3, 2.1$  Hz,  $1\text{H}^{10}$ ), 2.30 (ddd,  $J = 15.1, 13.5, 0.8$  Hz,  $1\text{H}^{10}$ ).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  202.6 (11), 149.9 (5), 149.8 (1), 137.5 (7), 135.0 (3), 130.0 (8), 123.7 (2), 123.0 (6), 91.9 (4), 80.7 (13), 58.2 (14), 40.0 (10), 42.6 (12), 41.5 (9).

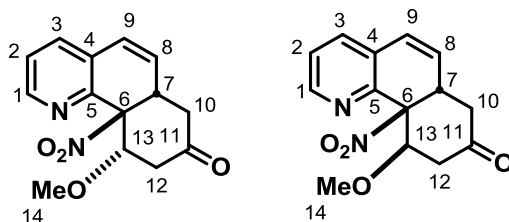
(6aR\*,7S\*,10aS\*) minor *diastereomer*:

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.43 (dd,  $J = 4.9, 1.6$  Hz,  $1\text{H}^1$ ), 7.47 (dd,  $J = 7.7, 1.6$  Hz,  $1\text{H}^3$ ), 7.16 (dd,  $J = 7.7, 4.9$  Hz,  $1\text{H}^2$ ), 7.03 (dd,  $J = 9.5, 0.6$  Hz,  $1\text{H}^7$ ), 6.23 (dd,  $J = 9.5, 1.6$  Hz,  $1\text{H}^6$ ), 4.46 (dd,  $J = 3.7, 2.5$  Hz,  $1\text{H}^{13}$ ), 4.39 (ddd,  $J = 12.7, 6.1, 1.6$  Hz,  $1\text{H}^9$ ), 3.30 (s,  $3\text{H}^{14}$ ), 2.84 (ddd,  $J = 15.1, 3.7, 2.4$  Hz,  $1\text{H}^{12}$ ), 2.74 (ddd,  $J = 15.1, 2.5, 0.6$  Hz,  $1\text{H}^{12}$ ), 2.54 (ddd,  $J = 15.1, 6.1, 2.4$  Hz,  $1\text{H}^{10}$ ), 2.26 (ddd,  $J = 15.1, 12.7, 0.6$  Hz,  $1\text{H}^{10}$ ).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  203.2 (11), 149.1 (1), 148.5 (5), 136.7 (7), 134.7 (3), 133.1 (8), 125.5 (6), 124.5 (2), 89.2 (4), 83.4 (13), 57.7 (14), 45.1 (10), 39.8 (12), 38.7 (9).

**HRMS (ESI<sup>+</sup>):**  $m/z$  Calcd. for  $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_4$   $[\text{M}+\text{H}]^+$ : 275.1032; Found: 275.1044.

**10-methoxy-10a-nitro-6a,7,10,10a-tetrahydrobenzo[*h*]quinolin-8(9H)-one**  
**(6aS\*, 10R\*, 10aR\*) and (6aS\*, 10S\*, 10aR\*) diastereomers (190d)**



**190d** was prepared according to the general procedure 2: 6 equiv Danishefsky's diene **79** (232  $\mu\text{L}$ , 1.2 mmol) was added to a stirred solution 8-nitroquinoline **188d** (34.8 mg, 0.2 mmol) in 0.9 mL dry  $\text{CH}_2\text{Cl}_2$ . The reaction was stirred for 72 h at room temperature under 16 kbar pressure. Flash chromatography of the residue (Cyclohexane/Acetone: 90/10) afforded **190d** (42.8 mg, 78%) as an orange oil of separable diastereomers in a 62 : 38 diastereomeric ratio.

(6a $S^*$ ,10 $S^*$ ,10a $R^*$ ) major *diastereomer*:

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.61 (dd,  $J = 4.8, 1.7$  Hz, 1H $^1$ ), 7.53 (dd,  $J = 7.7, 1.7$  Hz, 1H $^3$ ), 7.35 (dd,  $J = 7.7, 4.8$  Hz, 1H $^2$ ), 6.51 (dd,  $J = 9.6, 1.3$  Hz, 1H $^9$ ), 6.00 (dd,  $J = 9.6, 4.9$  Hz, 1H $^8$ ), 4.66 (dd,  $J = 8.5, 4.1$  Hz, 1H $^{13}$ ), 3.79 (ddd,  $J = 11.2, 5.7, 4.9$  Hz, 1H $^7$ ), 3.28 (s, 3H $^{14}$ ), 3.10 (ddd,  $J = 15.7, 8.5, 0.8$  Hz, 1H $^{12}$ ), 2.99 (ddd,  $J = 15.7, 4.1, 1.3$  Hz, 1H $^{12}$ ), 2.59 (ddd,  $J = 16.2, 5.7, 1.3$  Hz, 1H $^{10}$ ), 2.17 (dd,  $J = 16.2, 11.2$  Hz, 1H $^{10}$ ).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  204.8 (11), 148.5 (1), 148.1 (5), 134.6 (3), 130.2 (4), 128.7 (8), 125.9 (9), 124.9 (2), 93.8 (6), 82.1 (13), 59.4 (14), 42.7 (12), 42.1 (10), 39.8 (7).

(6a $S^*$ ,10 $R^*$ ,10a $R^*$ ) minor *diastereomer*:

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.61 (dd,  $J = 4.8, 1.7$  Hz, 1H $^1$ ), 7.49 (dd,  $J = 7.7, 1.7$  Hz, 1H $^3$ ), 7.37 (dd,  $J = 7.7, 4.8$  Hz, 1H $^2$ ), 6.45 (d,  $J = 9.6$  Hz, 1H $^9$ ), 6.32 (dd,  $J = 9.6, 5.6$  Hz, 1H $^8$ ), 5.37 (dd $\approx$ t,  $J = 3.1, 3.1$  Hz, 1H $^{13}$ ), 4.20 (ddd $\approx$ dt,  $J = 13.4, 5.6, 1.6$  Hz, 1H $^7$ ), 3.39 (s, 3H $^{14}$ ), 2.97 – 2.79 (m, 2H $^{12}$ ), 2.63 (ddd,  $J = 14.9, 5.6, 1.6$  Hz, 1H $^{10}$ ), 1.92 (dd,  $J = 14.9, 13.4$  Hz, 1H $^{10}$ ).

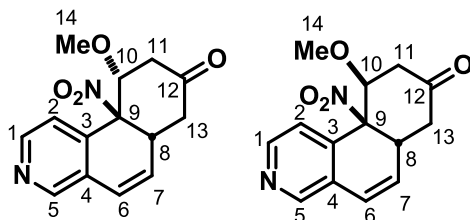
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  204.9 (11), 148.9 (1), 146.1 (5), 134.7 (3), 132.8 (9), 129.4 (4), 125.8 (2), 123.8 (8), 92.1 (6), 81.3 (13), 57.9 (14), 41.7 (10), 40.8 (12), 35.5 (7).

**HRMS (ESI $^+$ ):**  $m/z$  Calcd. for  $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_4$   $[\text{M}+\text{H}]^+$ : 275.1032; Found: 275.1024.

**IR (neat)**  $\nu$   $\text{cm}^{-1}$  = 1718, 1544, 1358, 1099, 1081, 821.

**10-methoxy-10a-nitro-6a,7,10,10a-tetrahydrobenzo[*f*]isoquinolin-8(9H)-one (6a $R^*$ , 10 $S^*$ , 10a $S^*$ ) and (6a $R^*$ , 10 $R^*$ , 10a $S^*$ ) diastereomers (191)**





**191** was prepared according to the general procedure 2: 6 equiv Danishefsky's diene **79** (232  $\mu$ L, 1.2 mmol) was added to a stirred solution 5-nitroisoquinoline **189** (34.8 mg, 0.2 mmol) in 0.9 mL dry  $\text{CH}_2\text{Cl}_2$ . The reaction was stirred for 24 h at room temperature under 16 kbar pressure. Flash chromatography of the residue (Cyclohexane/EtOAc: 30/70) afforded **191** (54.4 mg, 99%) as an orange oil of separable diastereomers in a 53 : 47 diastereomeric ratio.

(6a $R^*$ ,10 $R^*$ ,10a $S^*$ ) major *diastereomer*:

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.65 (d,  $J = 5.2$  Hz, 1H $^1$ ), 8.57 (s, 1H $^5$ ), 8.16 (d,  $J = 5.2$  Hz, 1H $^2$ ), 6.65 (d,  $J = 9.5$  Hz, 1H $^6$ ), 6.12 (dd,  $J = 9.5, 5.9$  Hz, 1H $^7$ ), 4.51 (dd,  $J = 13.0, 4.6$  Hz, 1H $^{10}$ ), 3.50 (ddd,  $J = 13.8, 5.9, 4.6$  Hz, 1H $^8$ ), 3.43 (s, 3H $^{14}$ ), 3.03 (ddd,  $J = 15.5, 4.6, 2.1$  Hz, 1H $^{11}$ ), 2.71 (dd,  $J = 15.5, 4.6$  Hz, 1H $^{13}$ ), 2.57 (ddd,  $J = 15.5, 13.8, 2.1$  Hz, 1H $^{11}$ ), 1.84 (dd,  $J = 15.5, 13.8$  Hz, 1H $^{13}$ ).

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  202.4 (12), 149.1 (1), 148.8 (5), 134.1 (3), 129.6 (4), 128.9 (7), 125.5 (6), 124.9 (2), 93.3 (9), 82.9 (10), 59.0 (14), 43.1 (13), 42.5 (11), 38.3 (8).

(6a $R^*$ ,10 $S^*$ ,10a $S^*$ ) minor *diastereomer*:

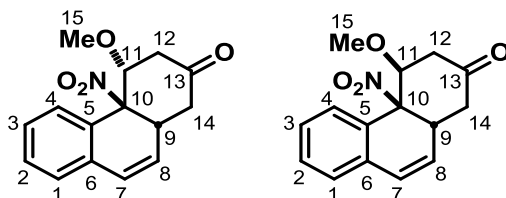
$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.68 (d,  $J = 5.1$  Hz, 1H $^1$ ), 8.50 (s, 1H $^5$ ), 7.54 (d,  $J = 5.1$  Hz, 1H $^2$ ), 6.53 (d,  $J = 9.6$  Hz, 1H $^6$ ), 6.36 (dd,  $J = 9.6, 5.8$  Hz, 1H $^7$ ), 4.95 – 4.92 (m, 1H $^{10}$ ), 4.13 (ddd $\approx$ dt,  $J = 13.1, 5.8$  Hz, 1H $^8$ ), 3.40 (s, 3H $^{14}$ ), 2.96 – 2.80 (m, 1H $^{11}$ ), 2.74 – 2.52 (m, 2H $^{11,13}$ ), 2.02 – 1.80 (m, 1H $^{13}$ ).

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  203.1 (12), 150.2 (1), 148.1 (11), 134.6 (3), 133.0 (7), 128.5 (4), 122.1 (6), 121.1 (2), 90.8 (9), 81.1 (10), 57.1 (14), 41.9 (13), 40.2 (11), 34.5 (8).

HRMS (ESI $^+$ ):  $m/z$  Calcd. for  $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_4$  [M+H] $^+$ : 275.1032; Found: 275.1035.

IR (neat)  $\nu$   $\text{cm}^{-1}$  = 1716, 1193, 1103, 1083, 702, 480.

**4-methoxy-4a-nitro-1,2,4a,10a-tetrahydrophenanthren-2(3H)-one**  
(4 $S^*$ , 4a $S^*$ , 10a $R^*$ ) and (4 $R^*$ , 4a $S^*$ , 10a $R^*$ ) diastereomers (**194**)



**194** was prepared according to the general procedure 2: 6 equiv Danishefsky's diene **79** (232  $\mu\text{L}$ , 1.2 mmol) was added to a stirred solution 1-nitronaphthalene **110** (34.6 mg, 0.2 mmol) in 0.9 mL dry  $\text{CH}_2\text{Cl}_2$ . The reaction was stirred for 72 h at room temperature under 16 kbar pressure. Flash chromatography of the residue (Cyclohexane/EtOAc: 90/10) afforded **194** (52.6 mg, 96%) as yellow oil of separable diastereomers in a 50 : 50 diastereomeric ratio.

(4*R*<sup>\*</sup>,4*aS*<sup>\*</sup>,10*aR*<sup>\*</sup>) major *diastereomer*:

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  8.27 (dd,  $J = 7.8, 0.6$  Hz, 1H<sup>1</sup>), 7.49 (td,  $J = 7.6, 1.4$  Hz, 1H<sup>4</sup>), 7.40 (td,  $J = 7.6, 1.4$  Hz, 1H<sup>3</sup>), 7.29 (dd,  $J = 7.8, 1.4$  Hz, 1H<sup>2</sup>), 6.59 (d,  $J = 9.5$  Hz, 1H<sup>7</sup>), 6.00 (dd,  $J = 9.5, 5.9$  Hz, 1H<sup>8</sup>), 4.51 (dd,  $J = 13.0, 4.7$  Hz, 1H<sup>11</sup>), 3.48 (ddd,  $J = 13.8, 5.9, 4.8$  Hz, 1H<sup>9</sup>), 3.43 (s, 3H<sup>15</sup>), 3.01 (ddd,  $J = 14.4, 4.7, 2.1$  Hz, 1H<sup>12</sup>), 2.83 (dd,  $J = 14.4, 13.0$  Hz, 1H<sup>12</sup>), 2.54 (ddd,  $J = 15.5, 4.8, 2.1$  Hz, 1H<sup>14</sup>), 1.92 (dd,  $J = 15.5, 13.8$  Hz, 1H<sup>14</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  203.7 (13), 134.7 (6), 131.0 (1), 130.8 (4), 129.0 (7), 128.5 (3), 128.2 (2), 126.7 (8), 126.0 (5), 94.1 (10), 83.5 (11), 58.1 (15), 43.3 (12), 42.9 (14), 38.8 (9).

(4*S*<sup>\*</sup>, 4*aS*<sup>\*</sup>,10*aR*<sup>\*</sup>) minor *diastereomer*:

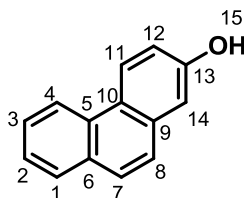
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  7.74 – 7.61 (m, 1H<sup>1</sup>), 7.48 – 7.37 (m, 2H<sup>3,4</sup>), 7.21 – 7.14 (m, 1H<sup>2</sup>), 6.46 (d,  $J = 9.6$  Hz, 1H<sup>7</sup>), 6.24 (dd,  $J = 9.6, 5.9$  Hz, 1H<sup>8</sup>), 5.06 – 4.87 (m, 1H<sup>11</sup>), 4.06 (ddd,  $J = 13.2, 5.9, 5.6$  Hz, 1H<sup>9</sup>), 3.40 (s, 3H<sup>15</sup>), 2.92 – 2.73 (m, 2H<sup>12</sup>), 2.60 (ddd,  $J = 15.0, 5.6, 2.4$  Hz, 1H<sup>14</sup>), 2.00 (dd,  $J = 15.0, 13.2$  Hz, 1H<sup>14</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  204.4 (13), 133.7 (6), 131.1 (4), 130.9 (8), 128.7 (3), 128.2 (2), 127.9 (1), 126.7 (5), 125.4 (7), 92.1 (10), 81.6 (11), 57.9 (15), 42.3 (14), 40.3 (12), 34.7 (9).

**HRMS (AP<sup>-</sup>):**  $m/z$  Calcd. for C<sub>15</sub>H<sub>14</sub>NO<sub>4</sub> [M-H]<sup>-</sup>: 272.0923; Found: 272.0915.

**IR (neat)**  $\nu$  cm<sup>-1</sup> = 1621, 1458, 1263, 1075, 746, 439.

### Phenanthren-2-ol (**112**)



To a solution of the crude **194** (59 mg, 0.12 mmol, 1 equiv) in *t*-BuOH (2 mL), was added concentrated HCl (50  $\mu$ L, 0.6 mmol, 6 equiv). The reaction was stirred for 30 min at 100 °C, after which it was filtered on celite and washed with EtOAc (3\*10 mL). Flash chromatography of the residue (Cyclohexane/EtOAc: 70/30) afforded **112** (20.8 mg, 89%) as a brown solid.

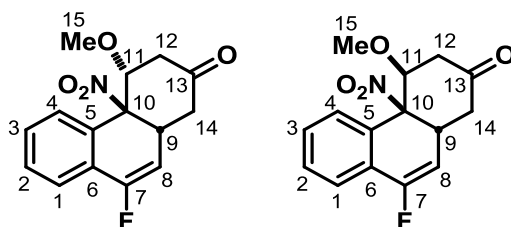
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  8.60 (2d, *J* = 8.9 Hz, 2H<sup>4,11</sup>), 7.88 (dd, *J* = 7.9, 1.5 Hz, 1H<sup>1</sup>), 7.74 (d, *J* = 8.9 Hz, 1H<sup>3</sup>), 7.71 – 7.57 (m, 2H<sup>2,7</sup>), 7.56 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H<sup>8</sup>), 7.29 – 7.21 (m, 2H<sup>12,14</sup>).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  154.3 (13), 133.7 (9), 131.2 (6), 130.6 (5), 128.7 (1), 127.9 (2), 126.9 (3), 126.2 (7), 125.8 (8), 124.9 (10), 124.8 (4), 122.2 (11), 116.8 (14), 111.1 (12).

HRMS (ESI<sup>-</sup>) *m/z* Calcd. for C<sub>14</sub>H<sub>9</sub>O [M-H]<sup>-</sup>: 193.0653; Found: 193.0647.

IR (neat)  $\nu$  (cm<sup>-1</sup>) = 3668-3369 (broad), 1615, 1461, 1227, 1066, 865, 809, 747.

**9-fluoro-4-methoxy-4a-nitro-1,4,4a,10a-tetrahydrophenanthren-2(3H)-one (4S\*, 4aS\*, 10aR\*) and (4R\*, 4aS\*, 10aR\*) diastereomers (196)**



**196** was prepared according to the general procedure 2: 6 equiv Danishefsky's diene **79** (232  $\mu$ L, 1.2 mmol) was added to a stirred solution 1-fluoro-4-nitronaphthalene **195** (38.2 mg, 0.2 mmol) in 0.9 mL dry CH<sub>2</sub>Cl<sub>2</sub>. The reaction was stirred for 72 h at room temperature under 16 kbar pressure. Flash chromatography of the residue (Cyclohexane/EtOAc: 70/30) afforded **196** (56 mg, 96%) as an orange solid of separable diastereomers in a 60 : 40 diastereomeric ratio.

(4R\*,4aS\*,10aR\*) major *diastereomer*:

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  8.33 (dd, *J* = 5.3, 3.8 Hz, 1H<sup>1</sup>), 7.76 – 7.42 (m, 3H<sup>2,3,4</sup>), 5.51 (dd, *J* = 11.2, 6.6 Hz, 1H<sup>8</sup>), 4.51 (dd, *J* = 13.1, 4.6 Hz, 1H<sup>11</sup>), 3.53 (dddd, *J* = 13.4, 6.6, 4.8, 3.5 Hz, 1H<sup>9</sup>), 3.43 (s, 3H<sup>15</sup>), 3.09 – 2.97 (m, 1H<sup>12</sup>), 2.88 – 2.74 (m, 1H<sup>12</sup>), 2.61 (ddd, *J* = 15.5, 4.8, 2.1 Hz, 1H<sup>14</sup>), 1.97 (dd, *J* = 15.5, 13.4 Hz, 1H<sup>14</sup>).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  202.1 (s, 13), 156.7 (d, *J* = 257.8 Hz, 7), 131.2 (d, *J* = 3.6 Hz, 1), 130.9 (s, 2), 129.1 (s, 3), 129.7 (d, *J* = 25.1 Hz, 6), 126.1 (d, *J* = 5.8 Hz, 5), 122.8 (d, *J* = 5.3 Hz, 4), 102.3 (d, *J* = 17.8 Hz, 8), 94.6 (s, 10), 83.3 (s, 11), 59.0 (s, 15), 43.7 (d, *J* = 3.5 Hz, 14), 43.1 (s, 12), 37.8 (d, *J* = 8.2 Hz, 9).

<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):  $\delta$  -123.07.

**Mp** = 132.25 °C.

(4S\*, 4aS\*,10aR\*) minor *diastereomer*:

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.73 – 7.65 (m,  $1\text{H}^1$ ), 7.59 – 7.49 (m,  $3\text{H}^{2,3,4}$ ), 5.75 (dd,  $J = 11.7, 6.6$  Hz,  $1\text{H}^8$ ), 5.01 – 4.91 (m,  $1\text{H}^{11}$ ), 4.24 – 4.03 (m,  $1\text{H}^9$ ), 3.39 (s,  $3\text{H}^{15}$ ), 2.93 – 2.71 (m,  $2\text{H}^{12}$ ), 2.66 (ddd,  $J = 15.1, 5.3, 2.5$  Hz,  $1\text{H}^{14}$ ), 2.04 (dd $\approx$ t,  $J = 15.1, 13.9$  Hz,  $1\text{H}^{14}$ ).

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  203.6 (d,  $J = 1.2$  Hz, 13), 154.6 (d,  $J = 253.6$  Hz, 7), 131.2 (s, 2), 130.1 (s, 3), 128.1 (d,  $J = 26.2$  Hz, 6), 128.3 (d,  $J = 3.8$  Hz, 1), 127.8 (d,  $J = 5.6$  Hz, 5), 122.7 (d,  $J = 5.4$  Hz, 4), 106.3 (d,  $J = 17.0$  Hz, 8), 91.7 (d,  $J = 1.3$  Hz, 10), 81.3 (s, 11), 57.9 (s, 15), 43.1 (d,  $J = 3.6$  Hz, 14), 40.2 (s, 12), 34.0 (d,  $J = 8.3$  Hz, 9).

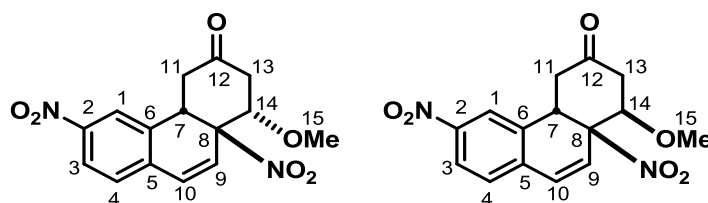
$^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -127.54.

**Mp** = 158.7 °C.

**HRMS** (AP):  $m/z$  Calcd. for  $\text{C}_{15}\text{H}_{13}\text{NO}_4\text{F}$  [M-H] $^-$ : 290.0829; Found: 290.0829.

**IR** (neat)  $\nu$   $\text{cm}^{-1}$  = 1723, 1548, 1113, 772, 427.

**1-methoxy-6,10a-dinitro-1,4,4a,10a-tetrahydrophenanthren-3(2H)-one**  
( $1R^*, 4aS^*, 10aS^*$ ) and ( $1S^*, 4aS^*, 10aS^*$ ) diastereomers (**198**)



**198** was prepared according to the general procedure 2: 6 equiv Danishefsky's diene **79** (232  $\mu\text{L}$ , 1.2 mmol) was added to a stirred solution 2,7-dinitronaphthalene **197** (43.6 mg, 0.2 mmol) in 0.9 mL dry  $\text{CH}_2\text{Cl}_2$ . The reaction was stirred for 24 h at room temperature under 16 kbar pressure. Inverse phase HPLC of the residue (Water+ 0.1% formic acid/ACN: 50/50 to 0/100) afforded **198** (41.1 mg, 65%) as a brown solid of separable diastereomers in a 50 : 50 diastereomeric ratio.

( $1S^*, 4aS^*, 10aS^*$ ) major diastereomer:

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.17 (dd,  $J = 8.3, 2.2$  Hz,  $1\text{H}^3$ ), 8.01 (d,  $J = 2.2$  Hz,  $1\text{H}^1$ ), 7.45 (d,  $J = 8.3$  Hz,  $1\text{H}^4$ ), 7.25 (d,  $J = 9.6$  Hz,  $1\text{H}^{10}$ ), 6.63 (dd,  $J = 9.6, 1.1$  Hz,  $1\text{H}^9$ ), 4.37 (dd,  $J = 12.6, 4.8$  Hz,  $1\text{H}^{14}$ ), 3.98 (dd,  $J = 13.6, 4.9$  Hz,  $1\text{H}^7$ ), 3.40 (s,  $3\text{H}^{15}$ ), 2.99 (ddd,  $J = 14.0, 4.8, 2.0$  Hz,  $1\text{H}^{13}$ ), 2.72 – 2.46 (m,  $2\text{H}^{11,13}$ ), 2.25 (dd,  $J = 14.8, 13.6$  Hz,  $1\text{H}^{11}$ ).

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  202.0 (12), 147.9 (2), 136.1 (5), 135.27 (6), 134.7 (10), 129.2 (4), 124.1 (3), 122.9 (9), 122.8 (1), 91.9 (8), 80.5 (14), 58.2 (15), 45.8 (11), 42.6 (13), 41.6 (7).

Mp = 91.25°C

(1*R*\*,4*aS*\*,10*aS*\*) minor *diastereomer*:

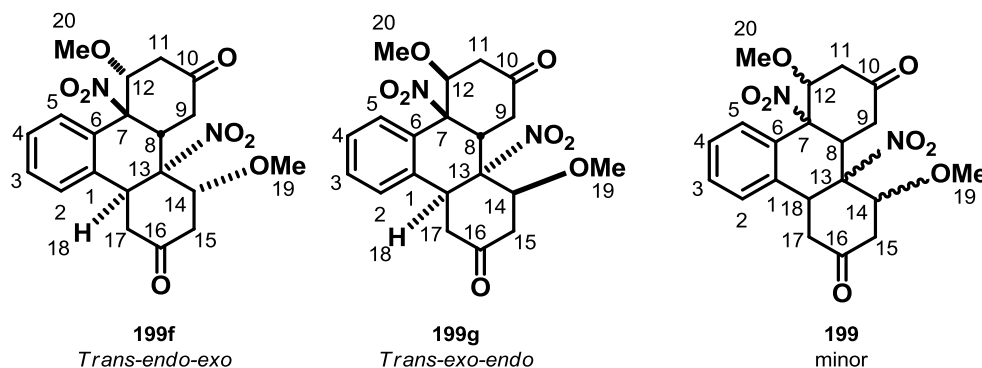
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.22 – 7.85 (m, 2H<sup>2,3</sup>), 7.36 (d, *J* = 9.1 Hz, 1H<sup>4</sup>), 7.00 (d, *J* = 9.4 Hz, 1H<sup>10</sup>), 6.24 (dd, *J* = 9.4, 1.3 Hz, 1H<sup>9</sup>), 4.63 – 4.42 (m, 2H<sup>7,14</sup>), 3.38 (s, 3H<sup>15</sup>), 2.92 (ddd, *J* = 15.1, 3.7, 2.5 Hz, 1H<sup>13</sup>), 2.77 (dd, *J* = 15.1, 2.4 Hz, 1H<sup>13</sup>), 2.66 (ddd, *J* = 15.1, 6.1, 2.4 Hz, 1H<sup>11</sup>), 2.27 (dd, *J* = 15.1, 12.9 Hz, 1H<sup>11</sup>).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 202.6 (12), 148.5 (2), 138.4 (5), 134.4 (6), 133.4 (10), 129.3 (4), 125.1 (3), 123.4 (9), 122.5 (1), 89.2 (8), 83.2 (14), 57.7 (15), 44.8 (11), 39.8 (13), 38.9 (7).

HRMS (ESI): *m/z* Calcd. for C<sub>15</sub>H<sub>13</sub>N<sub>2</sub>O<sub>6</sub> [M-H]<sup>-</sup>: 317.0774; Found: 317.0774.

IR (neat) *v* cm<sup>-1</sup> = 1719, 1518, 1344, 1097, 807, 407.

#### 4,8-dimethoxy-4*a*,8*a*-dinitro-1,4,4*a*,4*b*,5,8,8*a*,12*b*-octahydrotriphenylene-2,6(3*H*,7*H*)-dione diastereomers (**199**)



**199** was prepared according to the general procedure 2: 6 equiv Danishefsky's diene **79** (232 μL, 1.2 mmol) was added to a stirred solution 1,3-dinitronaphthalene **113** (43.6 mg, 0.2 mmol) in 0.9 mL dry CH<sub>2</sub>Cl<sub>2</sub>. The reaction was stirred for 24 h at room temperature under 16 kbar pressure. Inverse phase HPLC of the residue (Water+ 0.1% formic acid/ACN: 90/10 to 0/100) afforded **199** (76.9 mg, 92%) as a yellow solid of separable diastereomers in a 53 : 26 : 21 diastereomeric ratio.

#### *Trans-endo-exo* (**199f**)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.81 (d, *J* = 7.4 Hz, 1H<sup>5</sup>), 7.49 (td, *J* = 7.4, 1.1 Hz, 1H<sup>2</sup>), 7.40 – 7.33 (m, 1H<sup>4</sup>), 7.27 (d, *J* = 7.4 Hz, 1H<sup>3</sup>), 4.54 – 4.51 (m, 1H<sup>8 or 18</sup>), 4.47 (dd, *J* = 8.0, 2.5 Hz, 1H<sup>12 or 14</sup>), 4.37 (dd, *J* = 11.9, 6.0 Hz, 1H<sup>12 or 14</sup>), 3.83 (dd, *J* = 8.5, 4.9 Hz, 1H<sup>8 or 18</sup>), 3.33 (s, 3H<sup>19 or 20</sup>), 3.23 (s, 3H<sup>19 or 20</sup>), 3.11 – 2.55 (m, 8H<sup>9,11,15,17</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 202.6 (10 or 16), 201.6 (10 or 16), 138.0 (1), 131.5 (2), 130.2 (5), 128.6 (3), 127.9 (4), 127.4 (6), 93.3 (7 or 13), 91.8 (7 or 13), 80.8 (8 or 18), 79.8 (8 or 18), 59.2 (19 or 20), 58.0 (19 or 20), 46.4 (9 or 11 or 15 or 17), 41.3 (9 or 11 or 15 or 17), 39.9 (9 or 11 or 15 or 17), 38.9 (12 or 14), 38.4 (12 or 14), 36.2 (9 or 11 or 15 or 17).

**Mp** = 103.75 °C.

#### ***Trans-exo-endo* (199g)**

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.92 – 7.86 (m, 1H<sup>5</sup>), 7.49 – 7.39 (m, 2H<sup>2,4</sup>), 7.24 – 7.14 (m, 1H<sup>3</sup>), 5.07 (dd, *J* = 8.5, 6.4 Hz, 1H<sup>12 or 14</sup>), 4.84 (dd, *J* = 3.9, 2.1 Hz, 1H<sup>8 or 18</sup>), 4.50 (dd, *J* = 6.3, 3.5 Hz, 1H<sup>8 or 18</sup>), 4.06 (dd, *J* = 10.8, 6.3 Hz, 1H<sup>12 or 14</sup>), 3.41 (s, 3H<sup>19 or 29</sup>), 3.08 (s, 3H<sup>19 or 20</sup>), 2.89 – 2.29 (m, 8H<sup>9,11,15,17</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 203.4 (10 or 16), 203.3 (10 or 16), 138.3 (1), 131.2 (2 or 4), 129.9 (5), 128.4 (3), 128.3 (2 or 4), 127.7 (6), 94.2 (7 or 13), 92.8 (7 or 13), 83.2 (8 or 18), 80.7 (8 or 18), 58.3 (19 or 20), 55.8 (19 or 20), 44.6 (2C, 9 or 11 or 15 or 17), 40.2 (9 or 11 or 15 or 17), 39.6 (9 or 11 or 15 or 17), 39.0 (12 or 14), 36.8 (12 or 14).

**Mp** = 82.35 °C.

#### **199 minor diastereoisomer**

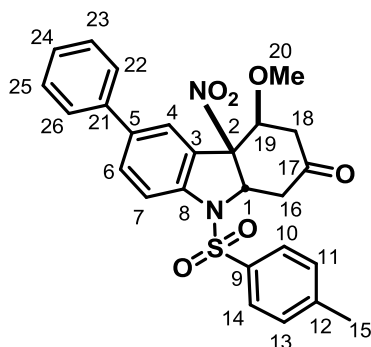
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.76 (d, *J* = 7.6 Hz, 1H<sup>5</sup>), 7.47 (dd, *J* = 7.5, 1.2 Hz, 1H<sup>2</sup>), 7.41 – 7.33 (m, 1H<sup>4</sup>), 7.28 (d, *J* = 7.5 Hz, 1H<sup>3</sup>), 4.96 – 4.90 (m, 1H<sup>8 or 18</sup>), 4.83 (t, *J* = 8.2 Hz, 1H<sup>12 or 14</sup>), 4.55 – 4.48 (m, 1H<sup>8 or 18</sup>), 4.33 (dd, *J* = 12.4, 6.7 Hz, 1H<sup>12 or 14</sup>), 3.57 (dd, *J* = 15.3, 6.8 Hz, 1H<sup>9 or 11 or 15 or 17</sup>), 3.35 (s, 3H<sup>19 or 20</sup>), 2.99 (s, 3H<sup>19 or 20</sup>), 2.83 – 2.59 (m, 7H<sup>9,11,15,17</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 203.1 (10 or 16), 203.1 (10 or 16), 139.8 (1), 131.6 (2), 129.0 (3), 128.0 (4), 127.8 (5), 126.3 (6), 93.1 (7 or 13), 90.8 (7 or 13), 81.8 (8 or 18), 81.2 (8 or 18), 58.7 (19 or 20), 58.1 (19 or 20), 46.8 (9 or 11 or 15 or 17), 41.1 (9 or 11 or 15 or 17), 39.1 (9 or 11 or 15 or 17), 39.5 (12 or 14), 38.2 (12 or 14), 36.0 (9 or 11 or 15 or 17).

**HRMS (ESI<sup>+</sup>):** *m/z* Calcd. for C<sub>20</sub>H<sub>21</sub>N<sub>2</sub>O<sub>8</sub> [M-H]<sup>+</sup>: 417.1298; Found: 417.1304.

**IR** (neat) *v* cm<sup>-1</sup> = 1724, 1546, 1085, 800, 729, 422.

#### **(4S\*,4aR\*,9aS\*)-4-methoxy-4a-nitro-6-phenyl-9-tosyl-4,4a,9,9a-tetrahydro-1H-carbazol-2(3H)-one (226)**



Suzuki coupling was performed as reported in the literature<sup>286</sup>. An oven-dried test tube was charged with **(4S\*,4aR\*,9aS\*)-154ca** (0.14 mmol, 1 equiv), boronic acid (0.28 mmol, 2 equiv), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (2 mol%), and K<sub>3</sub>PO<sub>4</sub> (0.28 mmol, 2 equiv). The reaction vessel was evacuated and backfilled with argon three times. Dioxane (1 mL) and H<sub>2</sub>O (0.2 mL) were then added via syringe, and the test tube placed in a preheated oil bath and stirred at 60 °C overnight. The reaction mixture was then cooled to room temperature and was subsequently filtered through a short plug of celite, the filter cake washed with EtOAc (3\*5 mL), and the solvent removed under vacuum. Flash chromatography of the residue (Cyclohexane/EtOAc: 80/20) afforded **226** (50 mg, 72%) as an orange solid.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.80 (d, *J* = 8.5 Hz, 1H<sup>ar</sup>), 7.75 (d, *J* = 1.6 Hz, 1H<sup>ar</sup>), 7.69 (dd, *J* = 8.5, 1.7 Hz, 2H<sup>ar</sup>), 7.64 (d, *J* = 8.6 Hz, 1H<sup>ar</sup>), 7.55 – 7.35 (m, 5H<sup>ar</sup>), 7.23 (d, *J* = 8.1 Hz, 2H<sup>ar</sup>), 5.82 (dd≈t, *J* = 4.2, 4.2 Hz, 1H<sup>1</sup>), 4.71 (dd≈t, *J* = 2.9, 2.9 Hz, 1H<sup>19</sup>), 3.37 (s, 3H<sup>20</sup>), 3.30 – 3.28 (m, 2H<sup>16</sup>), 2.70 (dd, *J* = 18.9, 2.9 Hz, 1H<sup>18</sup>), 2.36 (s, 3H<sup>15</sup>), 1.99 (dd, *J* = 18.9, 2.9 Hz, 1H<sup>18</sup>).

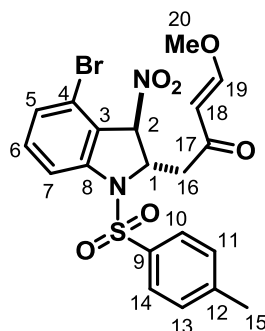
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 204.3 (17), 145.4 (12), 141.9 (8), 139.3 (9), 138.8 (21), 133.0 (5), 132.1 (C<sup>ar</sup>), 130.1 (2C<sup>ar</sup>), 129.2 (2C<sup>ar</sup>), 128.1 (C<sup>ar</sup>), 127.8 (2C<sup>ar</sup>), 126.1 (2C<sup>ar</sup>), 125.8 (3), 123.81 (C<sup>ar</sup>), 117.0 (C<sup>ar</sup>), 95.7 (2), 80.6 (19), 62.1 (1), 58.3 (20), 44.2 (16), 37.8 (18), 21.8 (15).

**HRMS (ESI<sup>+</sup>)** *m/z* Calcd. for C<sub>26</sub>H<sub>28</sub>N<sub>3</sub>O<sub>6</sub>S [M+NH<sub>4</sub>]<sup>+</sup>: 510.1699; Found: 510.1693.

**IR (neat)** *v* (cm<sup>-1</sup>) = 1726, 1548, 1476, 1361, 1158, 1088, 576.

**(E)-1-((2S\*,3R\*)-4-bromo-3-nitro-1-tosylindolin-2-yl)-5-methylhex-3-en-2-one (228ba)**

<sup>286</sup> See reference 261 in the manuscript.



**228ba** was prepared according to the general procedure 3 using 2.4 equiv LDA and **134** (123  $\mu$ L, 1.2 mmol) in 2 mL dry THF and a solution of 4-bromo-3-nitro-1-tosyl-1*H*-indole **150ba** (198 mg, 0.5 mmol) in 4 mL THF. The reaction was stirred at -78 °C for 5 h. Flash chromatography of the residue (Cyclohexane/EtOAc: 95/5) afforded **228ba** (198 mg, 80%) as a white solid as a single diastereomer.

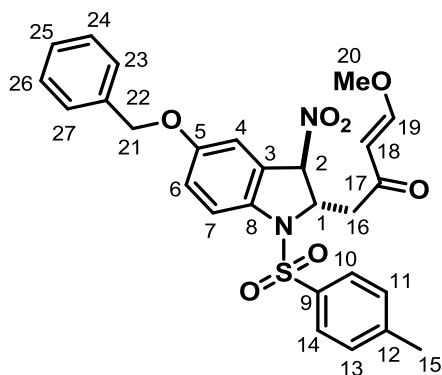
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  7.77 (dd,  $J$  = 8.0, 0.6 Hz, 1H<sup>5</sup>), 7.70 (d,  $J$  = 12.7 Hz, 1H<sup>19</sup>), 7.65 (d,  $J$  = 8.3 Hz, 2H<sup>10,14</sup>), 7.34 (dd $\approx$ t,  $J$  = 8.0, 8.0 Hz, 1H<sup>6</sup>), 7.28 (dd,  $J$  = 8.0, 0.6 Hz, 1H<sup>7</sup>), 7.25 (d,  $J$  = 8.3 Hz, 2H<sup>11,13</sup>), 5.65 (d,  $J$  = 12.7 Hz, 1H<sup>18</sup>), 5.62 (d,  $J$  = 1.8 Hz, 1H<sup>2</sup>), 4.97 (ddd,  $J$  = 10.1, 3.3, 1.8 Hz, 1H<sup>1</sup>), 3.76 (s, 3H<sup>20</sup>), 3.42 (dd,  $J$  = 17.1, 3.3 Hz, 1H<sup>16</sup>), 3.04 (dd,  $J$  = 17.1, 10.1 Hz, 1H<sup>16</sup>), 2.40 (s, 3H<sup>15</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  195.2 (17), 164.3 (12), 145.3 (6), 144.7 (8), 133.6 (9), 133.5 (3), 129.1 (10,14), 128.1 (7), 127.3 (11,13), 124.7 (4), 121.8 (3), 115.1 (19), 105.4 (18), 89.4 (2), 63.8 (1), 57.1 (20), 45.1 (16), 21.6 (15).

**HRMS (ESI<sup>+</sup>)**  $m/z$  Calcd. for C<sub>20</sub>H<sub>20</sub>BrN<sub>2</sub>O<sub>6</sub>S [M+H]<sup>+</sup>: 495.0225; Found: 495.0221.

**IR (neat)**  $\nu$  cm<sup>-1</sup> = 1620, 1594, 1556, 1361, 1165, 577.

**(E)-1-((2*S*\*,3*R*\*)-5-(benzyloxy)-3-nitro-1-tosylindolin-2-yl)-4-methoxybut-3-en-2-one (228ga)**



**228ga** was prepared according to the general procedure with 1.2 equiv LDA and **134** (13  $\mu$ L, 0.12 mmol) in 0.5 mL dry THF and a solution of 5-(benzyloxy)-3-nitro-1-tosyl-1*H*-indole **150ga** (44 mg,



0.1 mmol) in 2 mL THF. The reaction was stirred at -78 °C for 4 h. After washing with pentane, **228ga** was obtained (42 mg, 77%) as a brown oil as a single diastereomer.

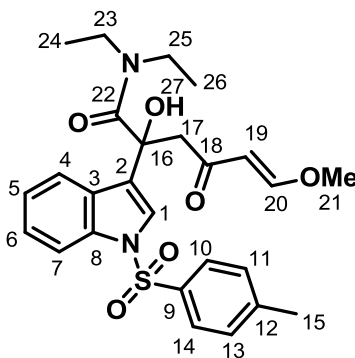
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.91 (d, *J* = 9.1 Hz, 1H<sup>6</sup>), 7.64 (d, *J* = 12.7 Hz, 1H<sup>19</sup>), 7.53 (d, *J* = 8.1 Hz, 2H<sup>10,14</sup>), 7.44 – 7.28 (m, 7H<sup>ar</sup>), 7.21 (d, *J* = 8.1 Hz, 2H<sup>11,13</sup>), 5.91 (d, *J* = 1.5 Hz, 1H<sup>2</sup>), 5.60 (d, *J* = 12.7 Hz, 1H<sup>18</sup>), 5.23 (d, *J* = 11.6 Hz, 1H<sup>21</sup>), 5.17 (d, *J* = 11.6 Hz, 1H<sup>21</sup>), 5.06 (ddd, *J* = 9.1, 2.3, 1.5 Hz, 1H<sup>1</sup>), 3.74 (s, 3H<sup>20</sup>), 3.34 (dd, *J* = 17.0, 2.3 Hz, 1H<sup>16</sup>), 3.11 (dd, *J* = 17.0, 9.1 Hz, 1H<sup>16</sup>), 2.37 (s, 3H<sup>15</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 195.1 (17), 164.5 (19), 149.3 (5), 145.8 (12), 137.8 (22), 137.6 (9), 135.3 (8), 133.0 (3), 130.4 (2C<sup>ar</sup>), 129.0 (2C<sup>ar</sup>), 128.7 (C<sup>ar</sup>), 127.7 (C<sup>ar</sup>), 127.4 (3C<sup>ar</sup>), 121.2 (6), 120.1 (C<sup>ar</sup>), 119.8 (C<sup>ar</sup>), 105.5 (18), 86.9 (2), 72.5 (21), 63.8 (1), 58.2 (20), 44.9 (16), 21.9 (15).

**HRMS (ESI<sup>+</sup>)** *m/z* Calcd. C<sub>27</sub>H<sub>25</sub>N<sub>2</sub>O<sub>7</sub>S for [M-H<sub>2</sub>+H]<sup>+</sup> (oxidized compound): 521.1382; Found: 521.1391.

**IR** (neat) *v* cm<sup>-1</sup> = 1656, 1561, 1534, 1357, 1161, 661, 584, 543.

**(E)-*N,N*-diethyl-2-hydroxy-6-methoxy-4-oxo-2-(1-tosyl-1*H*-indol-3-yl)hex-5-enamide (231)**



**231** was prepared according to the general procedure 3 using 2.4 equiv LDA and **134** (136 μL, 0.8 mmol) in 2 mL dry THF and a solution of *N,N*-diethyl-2-oxo-2-(1-tosyl-1*H*-indole-3-yl) acetamide **78** (199.3 mg, 0.5 mmol) in 4 mL THF. The reaction was stirred at -78 °C for 4 h. Flash chromatography of the residue (Cyclohexane/EtOAc: 95/5) afforded **231** (153 mg, 62%) as brown oil.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 8.03 (d, *J* = 8.3 Hz, 1H<sup>4</sup>), 7.78 (d, *J* = 8.5 Hz, 2H<sup>10,14</sup>), 7.73 (d, *J* = 7.9 Hz, 1H<sup>7</sup>), 7.66 (s, 1H<sup>1</sup>), 7.65 (d, *J* = 12.7 Hz, 1H<sup>20</sup>), 7.37 – 7.30 (m, 2H<sup>5,6</sup>), 7.23 (d, *J* = 8.5 Hz, 2H<sup>11,13</sup>), 6.55 (bs, 1H<sup>27</sup>), 5.64 (d, *J* = 12.7 Hz, 1H<sup>19</sup>), 3.70 (s, 3H<sup>21</sup>), 3.65 (d, *J* = 16.1 Hz, 1H<sup>17</sup>), 3.49 (dt, *J* = 14.0, 7.0 Hz, 2H<sup>23 or 25</sup>), 3.10 (dt, *J* = 14.0, 7.0 Hz, 2H<sup>23 or 25</sup>), 2.54 (d, *J* = 16.1 Hz, 1H<sup>17</sup>), 2.35 (s, 3H<sup>15</sup>), 1.01 (t, *J* = 7.0 Hz, 3H<sup>24 or 26</sup>), 0.71 (t, *J* = 7.0 Hz, 3H<sup>24 or 26</sup>).

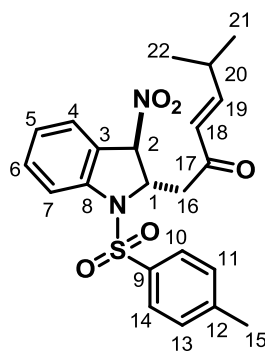
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 202.0 (18), 170.8 (22), 164.2 (2), 145.1 (12), 135.6 (8), 135.3 (9), 129.9 (11,13), 127.5 (1), 126.9 (10,14), 124.9 (5 or 6), 124.7 (3), 123.5 (5 or 6), 122.1 (20), 120.81

(7), 113.8 (4), 105.1 (19), 78.8 (16), 57.7 (21), 49.2 (17), 41.9 (23 or 25), 41.2 (23 or 25), 21.6 (15), 13.5 (24 or 26), 12.5 (24 or 26).

**HRMS** (ESI<sup>+</sup>) *m/z* Calcd. for C<sub>26</sub>H<sub>31</sub>N<sub>2</sub>O<sub>6</sub>S [M+H]<sup>+</sup>: 499.1903; Found: 499.1897.

**IR** (neat)  $\nu$  cm<sup>-1</sup> = 3500-3100 (broad), 1620, 1583, 1369, 1272, 1172, 567.

**((E)-5-methyl-1-((2S\*,3R\*)-3-nitro-1-tosylindolin-2-yl)hex-3-en-2-one (235)**



**235** was prepared according to the general procedure using 1.8 equiv LDA and **234** (47.5  $\mu$ L, 0.36 mmol) in 2 mL dry THF and a solution of **150aa** (63 mg, 0.2 mmol) in 2 mL THF. The reaction was stirred at -78 °C for 24 h. The crude was washed with pentane, the solid was removed and the filtrate was evaporated to afford crude **235**, as an orange oil of 5% of unreacted 3-nitro-1-tosyl-1*H*-indole **150aa** (86 mg, 95% conversion) in a single diastereomer.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  7.84 (dd, *J* = 8.9, 0.9 Hz, 1H<sup>4</sup>), 7.75 (d, *J* = 8.4 Hz, 2H<sup>10,14</sup>), 7.51 – 7.31 (m, 2H<sup>5,6</sup>), 7.29 (d, *J* = 8.4 Hz, 2H<sup>11,13</sup>), 7.17 (ddd $\approx$ td, *J* = 7.6, 7.6, 0.9 Hz, 1H<sup>7</sup>), 6.96 (dd, *J* = 16.1, 6.7 Hz, 1H<sup>19</sup>), 6.12 (dd, *J* = 16.1, 1.3 Hz, 1H<sup>18</sup>), 5.57 (d, *J* = 2.1 Hz, 1H<sup>2</sup>), 5.32 (ddd, *J* = 11.0, 3.5, 2.1 Hz 1H<sup>1</sup>), 3.70 (dd, *J* = 17.9, 3.5 Hz, 1H<sup>16</sup>), 3.13 (dd, *J* = 17.9, 11.0 Hz, 1H<sup>16</sup>), 2.57 – 2.45 (m, 1H<sup>20</sup>), 2.43 (s, 3H<sup>15</sup>), 1.15 (dd, *J* = 6.8, 1.3 Hz, 6H<sup>21,22</sup>).

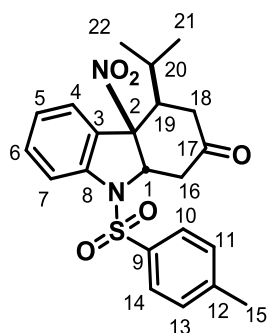
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  197.9 (17), 156.3 (19), 145.1 (12), 142.5 (8), 133.5 (9), 132.4 (5 or 6), 129.9 (11,13), 127.6 (10,14), 127.6 (18), 126.6 (5 or 6), 124.8 (7), 124.6 (3), 116.3 (4), 89.0 (2), 62.1 (1), 44.2 (16), 31.5 (20), 21.8 (22), 21.3 (15), 19.2 (21).

**HRMS** (ESI<sup>+</sup>) *m/z* Calcd. for C<sub>22</sub>H<sub>25</sub>N<sub>2</sub>O<sub>5</sub>S [M+H]<sup>+</sup>: 429.1484; Found: 429.1489.

**IR** (neat)  $\nu$  cm<sup>-1</sup> = 1718, 166.8, 1557, 1464, 1167, 1089, 757, 573.

The crude mixture of **235** (62 mg, theoretically 0.144 mmol) was dissolved in EtOAc and stirred on silica at room temperature for 6 hours. The crude was then purified by chromatography (Cyclohexane/EtOAc: 98/2) to afford **236** and **237** as brown solid (24 mg, and 9 mg, 39% and 16% yield respectively).

**(4*S*\*,4*aR*\*,9*aS*\*)-4-isopropyl-4-nitro-9-tosyl-1,3,4,4*a*,9,9*a*-tetrahydro-1*H*-carbazol-2(3*H*)-one (236)**



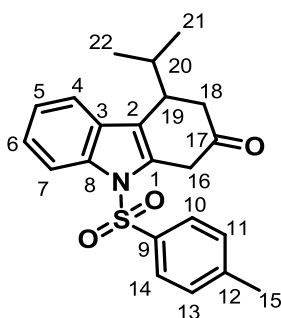
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.78 (d, *J* = 8.2 Hz, 1H<sup>4</sup>), 7.63 (d, *J* = 7.7 Hz, 1H<sup>7</sup>), 7.54 – 7.46 (m, 1H<sup>5</sup>), 7.5 (d, *J* = 8.1 Hz, 2H<sup>10,14</sup>), 7.35 – 7.25 (m, 1H<sup>6</sup>), 7.16 (d, *J* = 8.1 Hz, 2H<sup>11,13</sup>), 5.48 (dd, *J* = 10.7, 6.1 Hz, 1H<sup>1</sup>), 3.19 (dd, *J* = 17.4, 6.1 Hz, 1H<sup>16</sup>), 2.69 – 2.50 (m, 3H<sup>16,18,19</sup>), 2.39 – 2.28 (m, 5H<sup>15,18,20</sup>), 1.02 (d, *J* = 7.0 Hz, 3H<sup>21</sup>), 0.70 (d, *J* = 7.0 Hz, 3H<sup>22</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 205.7 (17), 145.2 (12), 141.2 (8), 134.0 (9), 132.6 (5), 129.1 (11,13), 128.6 (3), 127.2 (7), 127.1 (10,14), 125.7 (6), 117.5 (4), 96.2 (2), 64.4 (1), 45.0 (19), 43.7 (16), 36.6 (18), 27.5 (20), 23.1 (22), 21.8 (15), 16.7 (21).

**HRMS (ESI<sup>-</sup>)** *m/z* Calcd. for C<sub>22</sub>H<sub>23</sub>N<sub>2</sub>O<sub>5</sub>S [M-H]<sup>-</sup>: 427.1328; Found: 427.1332.

**IR (neat)** *v* cm<sup>-1</sup> = 1723, 1601, 1544, 1479, 1360, 1167, 765, 573, 539.

**4-isopropyl-9-tosyl-3,4-dihydro-1*H*-carbazol-2(9*H*)-one (237)**



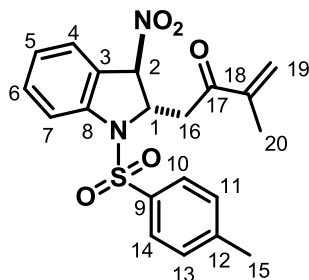
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 8.19 (d, *J* = 7.7 Hz, 1H<sup>4</sup>), 7.63 (d, *J* = 8.4 Hz, 2H<sup>10,14</sup>), 7.43 (d, *J* = 7.5 Hz, 1H<sup>7</sup>), 7.37 – 7.24 (m, 2H<sup>5,6</sup>), 7.19 (d, *J* = 8.4 Hz, 2H<sup>11,13</sup>), 3.88 (d, *J* = 22.7 Hz, 1H<sup>16</sup>), 3.79 (d, *J* = 22.7 Hz, 1H<sup>16</sup>), 3.21 (ddd, *J* = 6.9, 5.2, 1.8 Hz, 1H<sup>19</sup>), 2.78 (dd, *J* = 15.3, 1.8 Hz, 1H<sup>18</sup>), 2.58 (dd, *J* = 15.3, 6.9 Hz, 1H<sup>18</sup>), 2.33 (s, 3H<sup>15</sup>), 2.03 – 1.84 (m, 1H<sup>20</sup>), 0.89 (d, *J* = 6.8 Hz, 3H<sup>21</sup>), 0.71 (d, *J* = 6.8 Hz, 3H<sup>22</sup>).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 208.1 (17), 145.2 (12), 137.1 (8), 135.8 (9), 131.7 (1), 130.1 (11,13), 129.2 (2), 126.4 (10,14), 124.7 (6), 123.7 (5), 121.2 (3), 119.2 (7), 114.9 (4), 41.3 (18), 40.1 (16), 38.0 (19), 33.4 (20), 21.7 (15), 20.7 (21), 18.9 (22).

HRMS (ESI<sup>-</sup>)  $m/z$  Calcd. for C<sub>22</sub>H<sub>22</sub>NO<sub>3</sub>S [M-H]<sup>-</sup>: 380.1320; Found: 380.1327.

IR (neat)  $\nu$  cm<sup>-1</sup> = 3664, 2957, 2923, 1712, 1602, 1367, 1166, 1087, 567, 540.

### 3-methyl-1-((2S\*,3R\*)-3-nitro-1-tosylindolin-2-yl)but-3-en-2-one (239)



**239** was prepared according to the general procedure 3 using 1.2 equiv LDA and 3-methylbut-3-en-2-one **238** (51 mg, 0.6 mmol) in 1 mL dry THF and a solution of **150aa** (158 mg, 0.5 mmol) in 4 mL THF. The reaction was stirred at -78 °C for 21 h. Flash chromatography of the residue (PE/Acetone: 80/20) afforded **239** (21 mg, 11%) as a white solid as a single diastereomer.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.80 – 7.76 (m, 1H<sup>4</sup>), 7.68 (d,  $J$  = 8.4 Hz, 2H<sup>10,14</sup>), 7.49 – 7.39 (m, 2H<sup>5,6</sup>), 7.22 (d,  $J$  = 8.4 Hz, 2H<sup>11,13</sup>), 7.10 (td,  $J$  = 7.6, 0.9 Hz, 1H<sup>7</sup>), 6.07 (d,  $J$  = 1.5 Hz, 1H<sup>19</sup>), 5.91 (d,  $J$  = 1.5 Hz, 1H<sup>19</sup>), 5.47 (d,  $J$  = 2.3 Hz, 1H<sup>2</sup>), 5.26 (ddd,  $J$  = 11.1, 3.5, 2.3 Hz, 1H<sup>1</sup>), 3.78 (dd,  $J$  = 17.9, 3.5 Hz, 1H<sup>16</sup>), 3.16 (dd,  $J$  = 17.9, 11.1 Hz, 1H<sup>16</sup>), 2.36 (s, 3H<sup>15</sup>), 1.87 (s, 3H<sup>20</sup>).

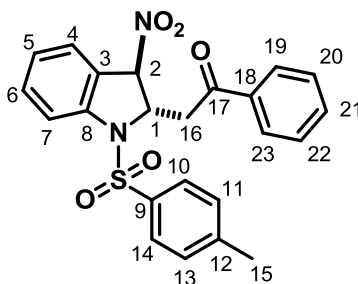
<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  199.2 (17), 145.1 (12), 144.0 (18), 142.6 (8), 133.6 (9), 132.4 (5), 129.1 (10,14), 127.7 (11,13), 126.1 (19), 126.7 (6), 124.8 (7), 124.5 (3), 116.3 (4), 89.1 (2), 62.4 (1), 42.5 (16), 21.8 (15), 17.3 (20).

HRMS (ESI<sup>-</sup>)  $m/z$  Calcd. for C<sub>20</sub>H<sub>19</sub>N<sub>2</sub>O<sub>5</sub>S [M-H]<sup>-</sup>: 399.1011; Found: 399.1011.

IR (neat)  $\nu$  cm<sup>-1</sup> = 1678, 1556, 1351, 1167, 756, 670, 577.

Mp = 139.0 °C.

### 2-((2S\*,3R\*)-3-nitro-1-tosylindolin-2-yl)-1-phenylethanone (255)



**255** was prepared according to the general procedure 3 using 1.2 equiv LDA and acetophenone **254** (70  $\mu$ L, 0.6 mmol) in 1 mL dry THF and a solution of **150aa** (158 mg, 0.5 mmol) in 2 mL THF.

### Experimental Part

The reaction was stirred at  $-78\text{ }^{\circ}\text{C}$  for 4 h. Flash chromatography of the residue (Cyclohexane/EtOAc: 80/20) afforded **255** (196.4 mg, 90%) as a white solid as a single diastereomer.

The chiral versions were performed in the same manner using 1.2 equiv LDA and acetophenone **254** (70  $\mu\text{L}$ , 0.6 mmol) in 1 mL dry THF and chiral amine (0.6 mmol) at  $-78\text{ }^{\circ}\text{C}$ . The reaction was then stirred for 10 min at  $-20\text{ }^{\circ}\text{C}$ . After which a solution of **150aa** (158 mg, 0.5 mmol) in 2 mL THF was added at  $-78\text{ }^{\circ}\text{C}$  and the reaction was stirred at this temperature for 4 h. Flash chromatography of the residue (Cyclohexane/EtOAc: 80/20) afforded **255** (196.4 mg, 90%) as a white solid as a single diastereomer.

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.02 – 7.94 (m,  $2\text{H}^{19,23}$ ), 7.80 (dd,  $J = 8.4, 0.8\text{ Hz}$ ,  $1\text{H}^{21}$ ), 7.71 (d,  $J = 8.4\text{ Hz}$ ,  $2\text{H}^{20,22}$ ), 7.61 (ddd,  $J = 6.7, 3.9, 1.2\text{ Hz}$ ,  $1\text{H}^4$ ), 7.5 (d,  $J = 7.9\text{ Hz}$ ,  $2\text{H}^{7,5}$ ), 7.44 (d,  $J = 8.2\text{ Hz}$ ,  $2\text{H}^{10,14}$ ), 7.23 (d,  $J = 8.2\text{ Hz}$ ,  $2\text{H}^{11,13}$ ), 7.11 (td,  $J = 7.9, 0.8\text{ Hz}$ ,  $1\text{H}^6$ ), 5.58 (d,  $J = 2.4\text{ Hz}$ ,  $1\text{H}^2$ ), 5.41 (ddd,  $J = 11.1, 3.5, 2.4\text{ Hz}$ ,  $1\text{H}^1$ ), 4.09 (dd,  $J = 18.2, 3.5\text{ Hz}$ ,  $1\text{H}^{16}$ ), 3.45 (dd,  $J = 18.2, 11.1\text{ Hz}$ ,  $1\text{H}^{16}$ ), 2.37 (s,  $3\text{H}^{15}$ ).

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  197.5 (17), 145.1 (8), 142.6 (12), 135.9 (18), 134.2 (4), 133.6 (9), 132.5 (7 or 5), 129.1 (13,16), 128.1 (10,14), 128.3 (19,23), 127.7 (20,22), 126.6 (7 or 5), 124.8 (6), 124.6 (3), 116.3 (21), 89.2 (2), 62.3 (1), 43.5 (16), 21.8 (15).

**HRMS (ESI<sup>+</sup>)**  $m/z$  Calcd. for  $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}_5\text{S}$   $[\text{M}+\text{H}]^+$ : 437.1171; Found: 499.1172.

**IR** (neat)  $\nu\text{ cm}^{-1} = 1682, 1556, 1349, 1166, 753, 572$ .

**Mp** =  $181.95\text{ }^{\circ}\text{C}$ .





## Résumé

Les composés aromatiques sont largement accessibles, que ce soit à partir de la pétrochimie, ou de molécules naturelles. Ainsi, des efforts importants ont été faits pour convertir ces molécules simples et facilement disponibles en structures 3D complexes d'intérêts synthétiques tels que des polycycles possédant des centres tétrasubstitués, utiles par exemple dans la synthèse de produits naturels ou pharmaceutiques. Même si plusieurs méthodes efficaces de désaromatisation ont été décrites, le développement de méthodologies complémentaires reste nécessaire.

Dans ce contexte, les cycloadditions (4+2) représentent une approche attrayante pour obtenir des composés polycycliques complexes à partir de substrats aromatiques simples. Au cours de ce travail, nous avons examiné la réactivité de différents composés nitroaromatiques vis-à-vis des silyloxydiènes lors de cycloadditions de Diels-Alder à demande électronique normale. Ces réactions se font sous pression ambiante pour les dérivés du nitroindole ; tandis qu'une pression élevée est nécessaire pour les nitroaromatiques moins réactifs.

Une méthodologie complémentaire basée sur l'activation nucléophile du diène, par la formation de son énolate de lithium, a été développée. La désaromatisation des nitroarènes par des énolates lithiés peut également avoir lieu dans un processus formel de cycloaddition (4+2).

**Mots clés :** Désaromatisation, réactions de cycloaddition (4+2), silyloxydiènes, énolate de lithium.

## Abstract

Aromatic compounds are common substrates, obtained either from the petrochemical industry or from natural products. Thus, important efforts have been made to convert these simple and easily available molecules into complex 3D structures of synthetic interest such as polycycles featuring tetrasubstituted centers, for example, useful in the synthesis of natural or pharmaceutical products. Even if several efficient dearomatizing methods have been reported, the development of complementary methodologies is still needed.

In this context, (4+2) cycloadditions represent an attractive approach to obtain complex polycyclic compounds from simple aromatic substrates. In the course of this work, we have examined the reactivity of different nitroaromatics towards silyloxydienes in Normal Electron Demand Diels-Alder cycloadditions. These reactions showed to proceed under ambient pressure for nitroindole derivatives, while high pressure conditions were needed for more challenging nitroaromatics.

A complementary methodology based on the nucleophilic activation of the diene, through the formation of its lithium enolate has been developed. The dearomatization of nitroarenes by lithiated enolates can also take place following a formal (4+2) cycloaddition process.

**Keywords:** Dearomatization, (4+2) cycloaddition, silyloxydienes, lithium enolate.