Synthesis of Highly Functionalized Tetrahydroisoquinolines by a Palladium-Catalyzed Domino *ortho*-Alkylation/Heck Reaction Sequence and Diastereoselective Aryne Diels-Alder Reactions

by

Marc-Olivier Turcotte-Savard

A thesis submitted in conformity with the requirements for the degree of Degree Master of Science

Graduate Department of Chemistry
University of Toronto

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Abstract

We report a palladium-catalyzed, norbornene mediated synthesis of tetrahydroisoquinolines via a domino ortho-alkylation/Heck reaction sequence. The desired products are obtained in moderate to excellent yields starting from readily available aryl iodides. The reaction conditions can be extended to the formation of tetrahydroisoquinolinones and tetrahydrobenzo[c]azepines. The reaction allows for sequential intermolecular and intramolecular ortho-alkylations. However, the product yields are higher with ortho-blocked aryl iodides, which simplify the domino process to one intramolecular ortho-alkylation and a Heck reaction.

The Lautens group has previously reported diastereoselective aryne Diels-Alder reactions of benzyne with dienes supporting a chiral auxiliary at its terminal carbon. In an effort to extend this work and allow access to a wider variety of 1,4-dihydronaphthalenes, we attempted the synthesis of dienes supporting a chiral auxiliary at a central carbon. Chiral pyridyne precursors were also synthesized, in an attempt to vary the source of chirality in diastereoselective cycloadditions.

Acknowledgements

Firstly, I would like to acknowledge my supervisor, Mark Lautens, for allowing me to evolve in his talented and successful research group. His enthusiasm towards the discovery of useful methodologies was clearly contagious.

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I also want to thank my family for their constant support. My grandmothers Hélène B. Turcotte and Hélène Boulet, for being good examples of cultivated citizens, and for their love of travelling around the world that inspired me in the last few years. My grandfather, Jean-Yves Savard, for encouraging me to follow his path to graduate studies. My aunts and uncles, Edith Turcotte, Yann Dupréelle, Nathalie Turcotte, Éric Malenfant, for their constant advice and support.

My acknowledgements would be incomplete without mentioning the financial support from the University of Toronto, and from the Natural Sciences and Engineering Research Council of

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Thanks to my friend Bruno Trottier-Pérusse and my suitemate Max Dionisio. Our friendships made my stay in Ontario more enjoyable.

Dedication

This work is dedicated to my parents, François Savard and Josée Turcotte, and to my sister Audrée-Eve Turcotte-Savard for their outstanding love and support.

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List of Abbreviations

(m)	Medium
(s)	Strong
(w)	Weak
[M]	Metal
°C	Degrees Celsius
µL	Microliters
Ac	Acetyl
Ar	Aryl
atm	Atmosphere
B	Base
BDC	Benzenediazonium-2-carboxylate
Bn	Benzyl
cal	Calories
Cp	Cyclopentadienyl
D.e.	Diastereomeric excess
DCC	Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DCU	Dicyclohexylurea
DMA	N,N-dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	N,N-Dimethylformamide
dr	Diastereomeric ratio
EI	Electron ionisation
eq.	Equivalent
ESI	Electro-spray ionisation
Et	Ethyl
EWG	Electron withdrawing group
g	Grams
GC-MS	Gas chromatography coupled to mass spectrometry
HRMS	High resolution mass spectrometry
i-Pr	iso-propyl
IR	Infra red
KHMDS	Potassium hexamethyldisilazane

L	Ligand
L	Liters
LDA	Lithium diisopropylamine
LG	Leaving group
LTMP	Lithium-2,2,6,6-tetramethylpiperidine
M	Molar
m-	*meta*
m/z	Mass/charge ratio
Me	Methyl
MeCN	Acetonitrile
mg	Milligrams
MHz	Mega hertz
min.	Minutes
mL	Milliliters
mp	Melting point
Ms	Mesyl
MW	Micro-wave irradiation
n-Bu	normal-butyl
NMR	Nuclear magnetic resonance
n-Oct	normal-octyl
Nu	Nucleophile
o-	*ortho*
o.n.	Overnight
p-	*para*
Pd	Palladium
PMP	*para*-methoxyphenyl
PNP	Phenylnorbornylpalladium chloride dimer
Pt	Platinum
r.t.	Room temperature
s	Seconds
TBAT	Tetrabutylammonium-triphenyldifluorosilicate
TBS	Tert-butylsilyl
t-bu	Tert-butyl
TCNE	Tetracyanoethylene
Tf	Triflate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMP	2,2,6,6-Tetramethylpiperidine
Ts	Tosyl
v/v	Volume per volume

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List of Schemes

Preface

Chapter 1 presents a novel synthetic method allowing for the selective formation of highly functionalized tetrahydroisoquinolines, tetrahydroisoquinolinones, and tetrahydrobenzo[c]azepines using a palladium-catalyzed, norbornene mediated, domino *ortho* C-H alkylation/Heck reaction sequence.

Chapter 2 presents and discusses our attempts to develop diastereoselective aryne Diels-Alder reactions. Two main methods were explored: the use of a chiral auxiliary supporting diene to trap benzyne in a diastereoselective fashion, and the reaction of chiral pyridyne precursors with asymmetrical dienes.

Compounds within this thesis are numbered according to their chapter and sub-chapter numbers. Hence, **1.1.3** is the third molecule of section **1.1**. Compound **1.1.3c** is an analogue of compound **1.1.3** or **1.1.3a** and **1.1.3b**. It could also refer to an intermediate represented in a scheme with multiple similar intermediates.

There are two different experimental sections, each at the end of a chapter. Their purpose is to describe the synthesis of compounds presented in the current chapter. NMR spectra are presented at the end of the experimental section. J coupling values are expressed in Hertz (Hz). Spectral data was processed with Mest-Re-C software.

“It is not what the man of science believes that distinguishes him, but how and why he believes it.”

Bertrand Russell

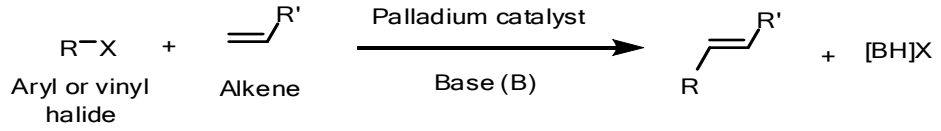
Chapter 1

1 Synthesis of Highly Functionalized Tetrahydroisoquinolines by a Palladium-Catalyzed Domino *ortho*-Alkylation/Heck Reaction Sequence

1.1 Introduction

1.1.1 The Mizoroki-Heck Reaction

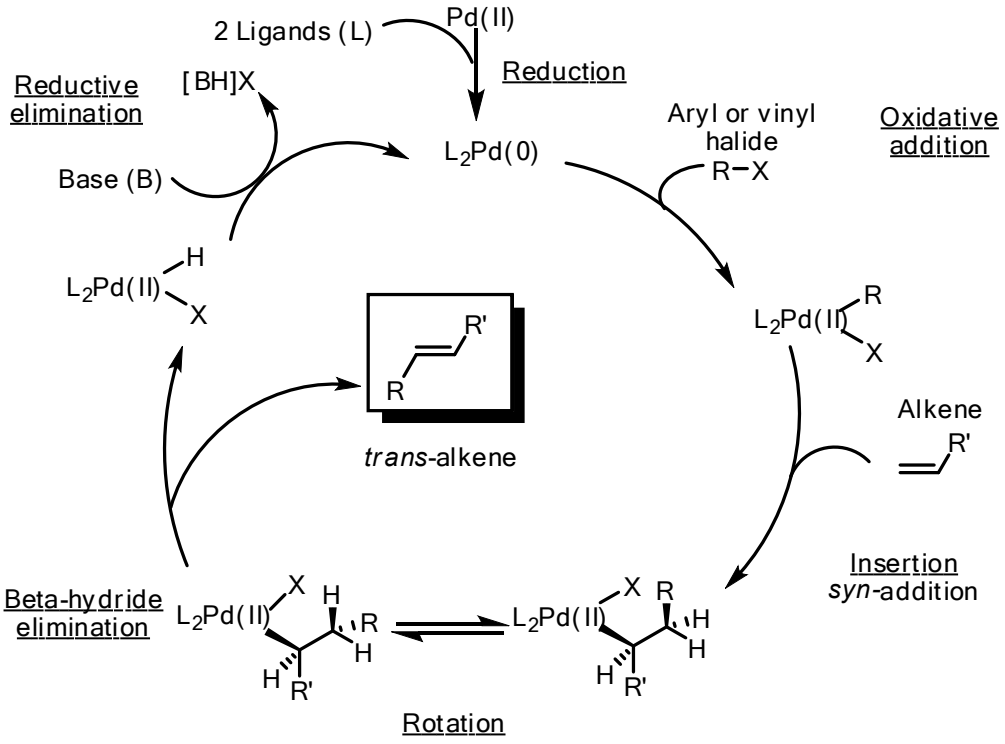
The Mizoroki-Heck reaction[1] has been given much attention in the past few decades as transition-metal catalyzed carbon-carbon bond formation gained in popularity. This palladium-catalyzed coupling reaction allows for the formation of alkenes starting from a less-substituted alkene and an aryl or vinyl halide, as shown in Scheme 1.



Scheme 1. The Mizoroki-Heck reaction

(1) The Mizoroki-Heck reaction will be further referred to as the Heck reaction. a) R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5518. b) Y. Fujiwara, I. Moritani, S. Danno, R. Asans and S. Teranishi, *J. Am. Chem. Soc.* **1969**, *91*, 5518. c) M. Nakayama and T. Mizoroki, *Bull. Chem. Soc. Jpn.* **1969**, *42*, 1124. d) T. Mizoroki, K. Mori and A. Ozaki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

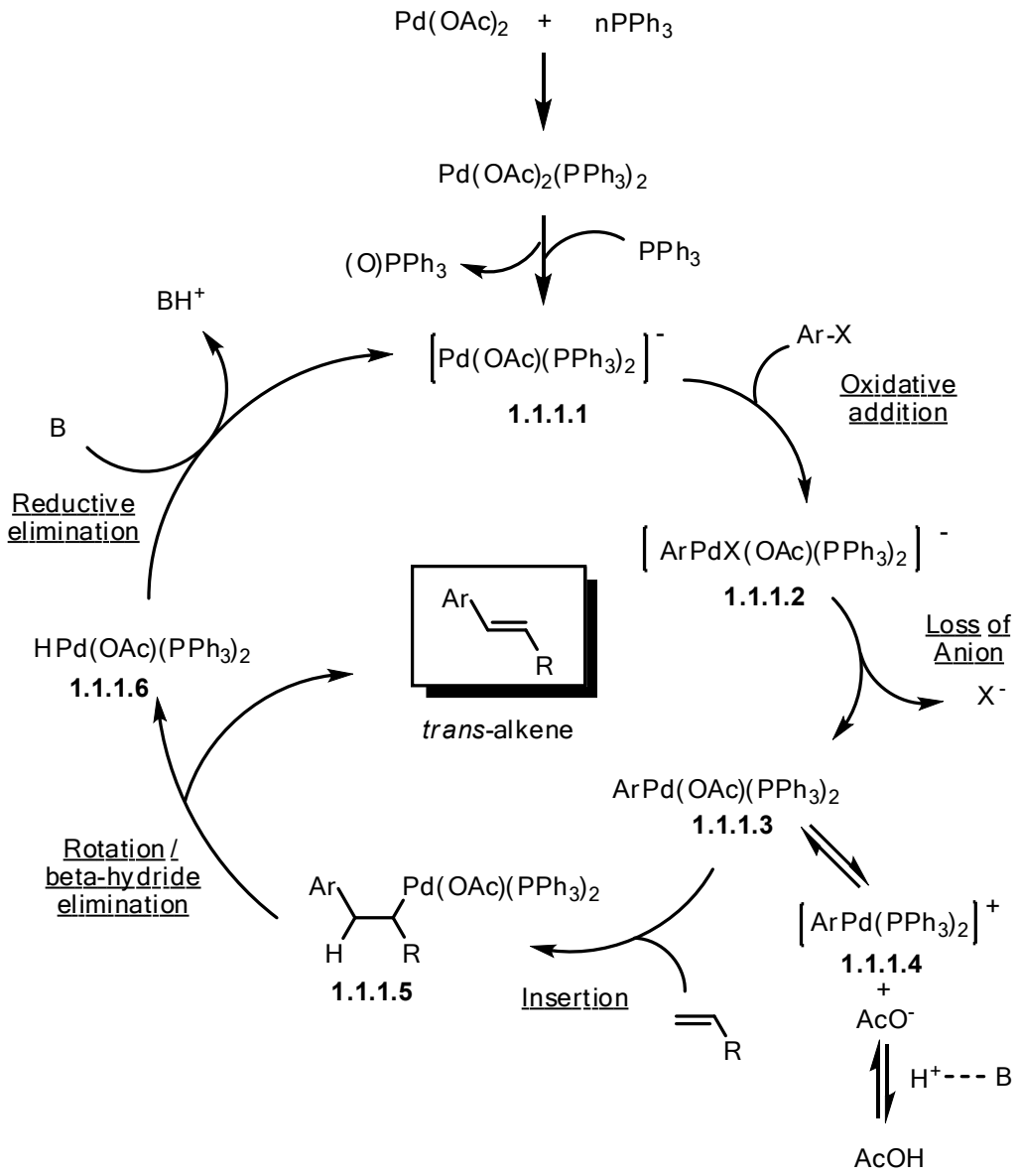
A general mechanism[2] is represented in Scheme 2. The reaction starts with a palladium(0) complex, which undergoes oxidative addition into the carbon-halogen bond of an aryl or vinyl halide to form a palladium(II) complex. *Syn*-1,2-carbopalladation onto the alkene can then occur to give the corresponding palladium(II) complex. The former sp^2 - sp^2 bond, being now a sp^3 - sp^3 bond, can rotate. If the palladium complex is allowed to reach a position where a hydrogen atom is *syn* to a β-hydrogen atom, β-hydride elimination can occur to form the desired alkene along with a palladium(II) hydride. In the presence of a base (B), reductive elimination of HX from the palladium(II) hydride will occur, forming [BH]X and regenerating palladium(0), which can continue to participate in the catalytic cycle. *Trans*-alkenes are preferred, but in the case of more highly substituted alkenes, mixtures of products are possible.



Scheme 2. General mechanism for the Heck Reaction

(2) R. H. Crabtree, *The Organometallic Chemistry of Transition Metals*, Fourth Edition, Wiley-Interscience: Hoboken, New Jersey, **2005**; 265.

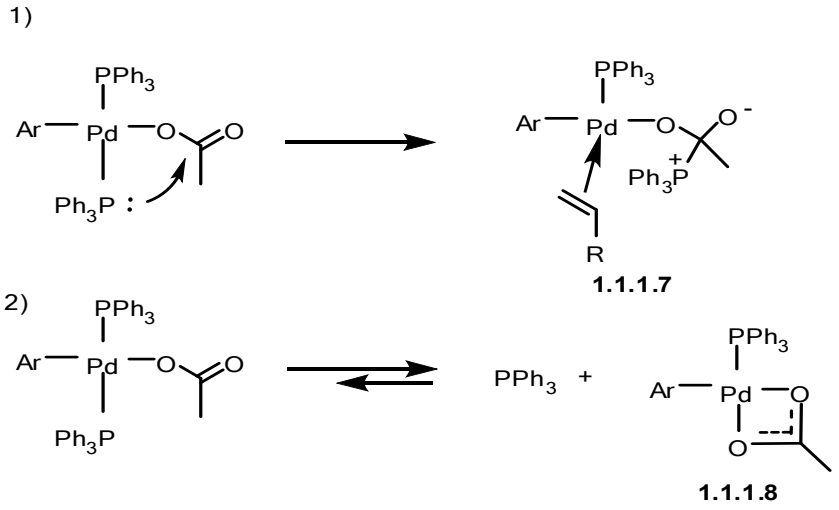
Although different palladium sources and conditions can be used for the Heck reaction, palladium(II) acetate and triphenylphosphine are among the most common catalyst and ligand combinations. Mechanistic studies[3] have shown that Heck reactions under these conditions are more complex than the general mechanism and these additional details are shown in Scheme 3.



Scheme 3. Proposed mechanism for the Heck reaction using palladium acetate and triphenylphosphine

(3) C. Amatore and A. Jutand, *J. Organomet. Chem.* **1999**, *576*, 254.

Palladium acetate is reduced to palladium(0) in the presence of triphenylphosphine to give the anionic complex **1.1.1.1**. Oxidative addition of an aryl halide to complex **1.1.1.1** forms the anionic complex **1.1.1.2**. Note that complex **1.1.1.2** is an 18 electron pentacoordinated palladium(II) complex. After the loss of a halide anion, neutral palladium(II) complex **1.1.1.3** is formed. An equilibrium between complex **1.1.1.3** and its cationic complex **1.1.1.4** plus a dissociated acetate ion could exist. However, the most reactive species is complex **1.1.1.3**.[3] The presence of excess triphenylphosphine inhibits the reaction, suggesting that a free coordination site is necessary to accommodate an incoming alkene. The presence of acetate anions (even in the absence of base) helps to favor better reaction rates. Two possibilities[3] can explain the transformation occurring between complex **1.1.1.3** and complex **1.1.1.5**.



Scheme 4. Possible explanations[3] for the reactivity of $ArPd(OAc)(PPh_3)_2$ in the Heck reaction

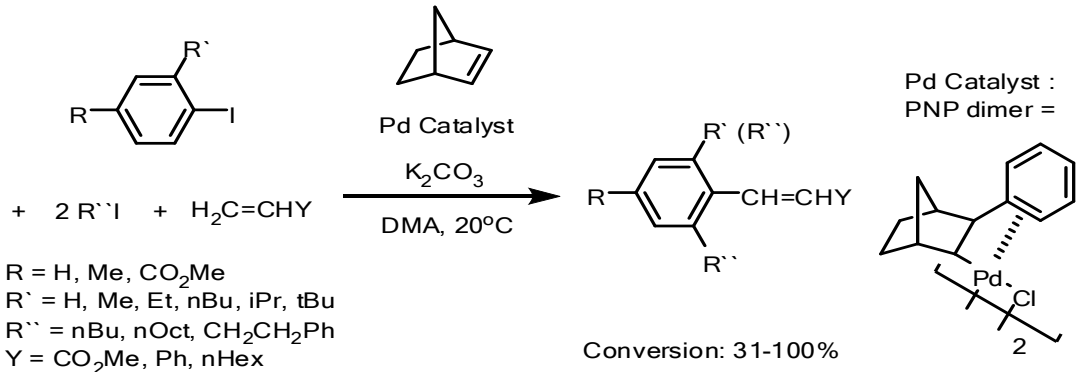
The first possibility is that triphenylphosphine can add to the acetate anion, thus freeing a coordination site on the palladium complex for the alkene as shown by complex **1.1.1.7**. The second possibility is related to the acetate anion's bidentate ability. The acetate could switch from monodentate to bidentate bonding and fill in the unoccupied coordination site following the departure of triphenylphosphine. The alkene could then occupy a coordination site as the acetate

switches again from the bidentate to the monodentate mode of bonding, thus allowing the rest of the catalytic cycle to take place.

After the insertion of the alkene, rotation and β-hydride elimination occurs to form both the desired *trans*-alkene product and the palladium(II) hydride complex **1.1.1.6**. Reductive elimination of the hydride, in the presence of a base, regenerates the palladium(0) anionic complex **1.1.1.1**.

1.1.2 The Catellani Reaction

During the 1990's, Marta Catellani discovered an interesting domino process allowing C-H functionalization of the *ortho* and *ortho'* positions of an aryl halide followed by a Heck reaction.[4,5] The sequence requires the presence of an aryl halide (usually iodide), an alkyl halide, an alkene (Heck acceptor), a palladium catalyst, a ligand, norbornene, and a base. The transformation is shown in Scheme 5.

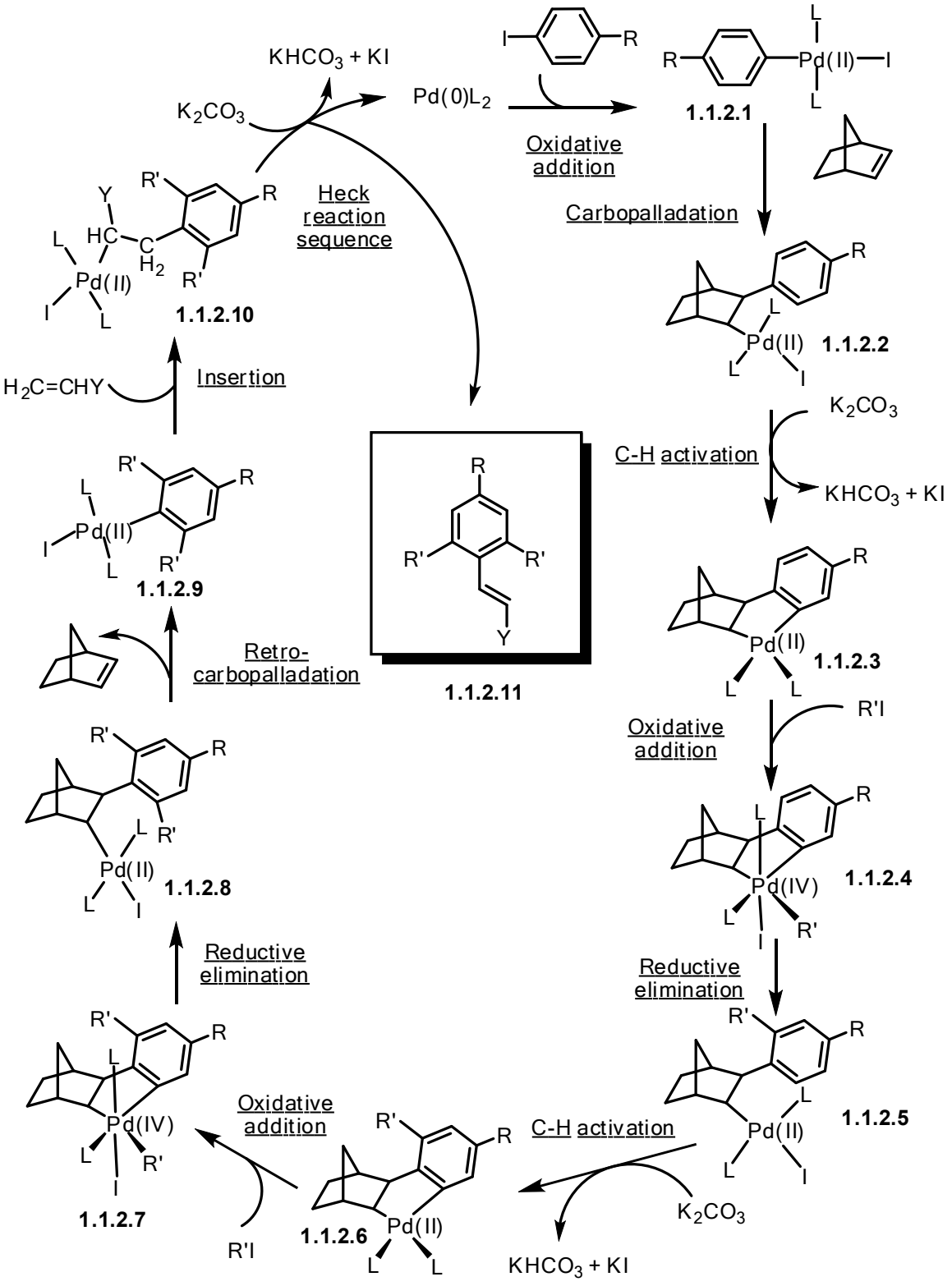


Scheme 5. The Catellani reaction[4,5]

(4) See M. Catellani, *Synlett*, **2003**, *3*, 298. and references therein.

Since this initial publication, modifications to the reaction conditions have been reported. The catalyst can be changed to palladium(II) acetate, which is reduced under the reaction conditions to the reactive palladium(0) complex. Potassium carbonate can be replaced by cesium carbonate, the latter being better for its higher solubility in the organic solvents used for this reaction. Solvents can also be varied[5a] from DMA, to DMF, to acetonitrile.[6] The alkene, or Heck acceptor, can be varied as well, with electron-withdrawing substituents giving the highest yields.[5] Although the original conditions were ligandless, ligands such as triphenylphosphine, can be used under the reaction conditions. Alkyl halides with a variety of functional groups are also well-tolerated.

(5) a) M. Catellani, F. Frignani and A. Rangoni, *Angew. Chem. Int. Ed.* **1997**, *36*, 119. b) M. Catellani and F. Cugini, *Tetrahedron* **1999**, *55*, 6595.
(6) M. Ferraccioli, D. Carenzi, O. Rombola and M. Catellani, *Org. Lett.* **2004**, *6*, 4759.



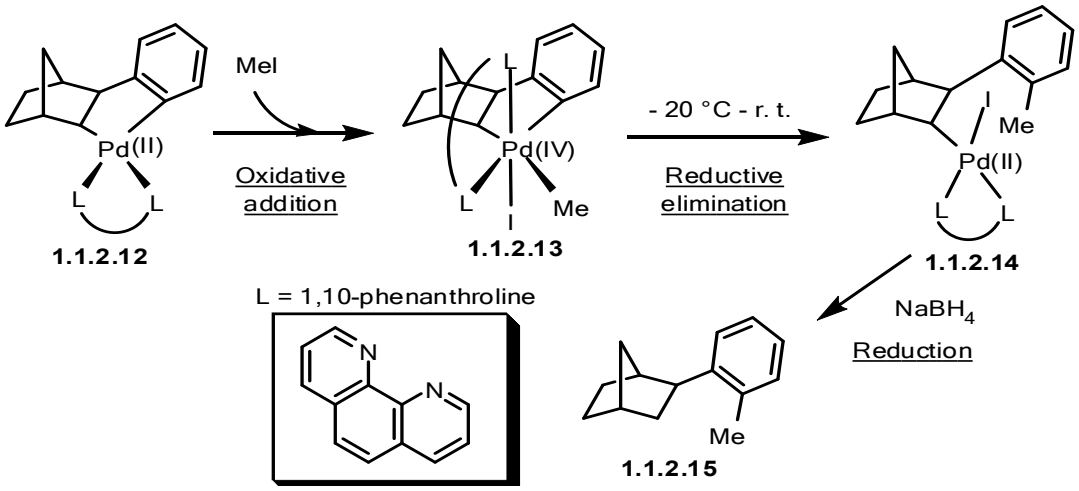
Scheme 6. Proposed mechanism for the Catellani reaction

The mechanism for the Catellani reaction starts with palladium(0) oxidatively adding to the carbon-halogen bond of the aryl iodide to give the palladium(II) complex **1.1.2.1**. This complex undergoes *cis*-*exo*-carbopalladation with norbornene to give **1.1.2.2**.[7a] As there are no *syn* β-hydrogens to the palladium in complex **1.1.2.2**, β-hydride elimination would be rather difficult. Instead, *ortho* C-H bond activation occurs on the aryl moiety, forming the five-membered palladacycle **1.1.2.3**. Rather than undergoing reductive elimination at this stage to give a highly strained four-membered ring,[7b] an excess of alkyl halide drives the oxidative addition of this alkyl halide onto **1.1.2.3** to form **1.1.2.4**, an octahedral palladium(IV) complex. Due to its high oxidation state and increasing steric hindrance, **1.1.2.4** can undergo reductive elimination to irreversibly form the first new carbon-carbon bond of the sequence, thus generating the palladium(II) complex **1.1.2.5**. This process is then repeated for the other *ortho* C-H bond to give *ortho*, *ortho'* substituted palladium(II) complex **1.1.2.8**. Increasing steric hindrance due to these two new *ortho* substituents is believed to cause retro-carbopalladation[7], or extrusion of norbornene, to form palladium(II) complex **1.1.2.9**. This complex **1.1.2.9** is set up to undergo different cross-coupling reactions[2]. Here, in the presence of an alkene and base, a Heck reaction is possible. Formation of the last permanent carbon-carbon bond of the sequence occurs by insertion of the alkene, to give **1.1.2.10**. Rotation and β-hydride elimination forms both the desired *trans*-alkene product **1.1.2.11** and regenerates palladium(0).

Catellani and Chiusoli performed several mechanistic studies to isolate and characterize[8] key intermediates of the reaction sequence as shown in Scheme 7.

(7) a) M. Catellani and M. C. Fagnola, *Angew. Chem. Int. Ed.* **1994**, *33*, 2241. b) M. Catellani, *Synlett*, **2003**, *3*, 298.

(8) M. Catellani and G. P. Chiusoli, *J. Organomet. Chem*. **1988**, *346*, C27.



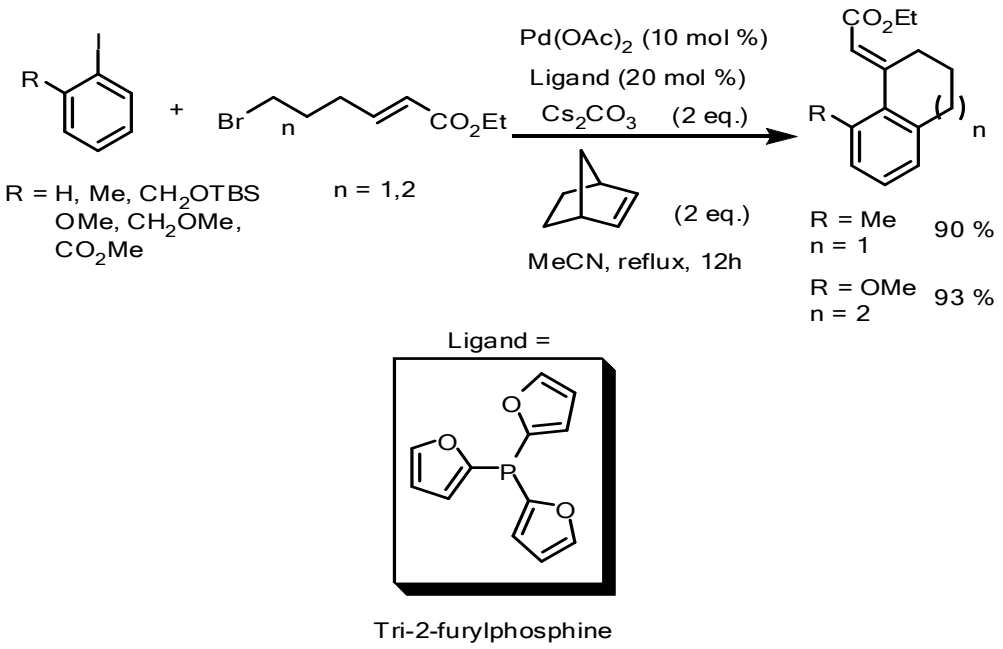
Scheme 7. Isolated intermediates of the Catellani reaction sequence[8]

Using 1,10-phenanthroline as a bidentate ligand, palladacycle **1.1.2.12** could be isolated. Complex **1.1.2.12** is similar to complex **1.1.2.3** as seen in Scheme 6 (where R = H). Complex **1.1.2.12** undergoes oxidative addition with iodomethane to give the palladium(IV) complex **1.1.2.13**. A ^{1}H NMR spectrum of **1.1.2.13** was obtained at -20 °C. When the cold solution of **1.1.2.13** was allowed to reach room temperature, reductive elimination to palladium(II) complex **1.1.2.14** was observed. Compound **1.1.2.15** was recovered when sodium borohydride was added. These observed intermediates suggest that both palladium(II) and palladium(IV) complexes are indeed involved in the reaction sequence presented in Scheme 6. It also shows the stepwise nature of the sequence since each intermediate could be obtained and then sequentially changed to the next intermediate by the addition of a reagent or a change in the reaction conditions.

1.1.3 The Lautens strategies

The Lautens group became interested in exploring the potential of the Catellani reaction, applying this methodology to selective formations of synthetic carbon-carbon bonds in organic synthesis. In particular, Lautens and coworkers were interested in exploring the formation of complex carbocyclic and heterocyclic scaffolds using this approach.

Initial studies by Lautens and Piguel[9] proved the possibility of using a bifunctional alkyl halide combining both the alkyl bromide and the Heck acceptor in one substrate. In this manner, a new ring containing two new carbon-carbon bonds can be formed.



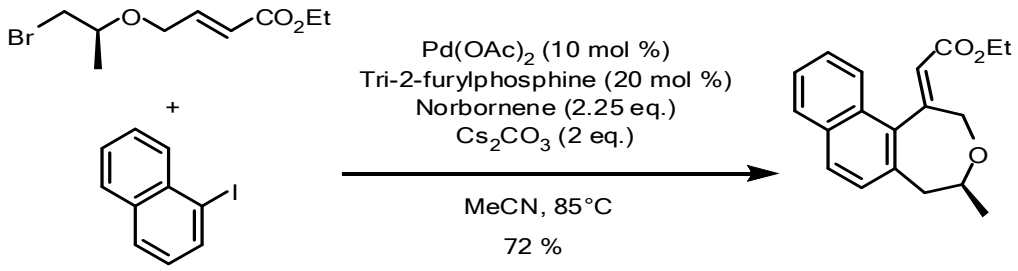
Scheme 8. The first modifications to the Catellani conditions by the Lautens group

Compared to the studies of Catellani and coworkers, several modifications to the reaction conditions were made due to irreproducible results obtained under the first generation conditions. After testing a variety of palladium catalyst and ligand combinations, palladium acetate with tri-2-furylphosphine turned out to be the most high-yielding combination. A variety of solvents were also tried, with acetonitrile being the optimal solvent. Reactions using potassium carbonate and cesium carbonate were also compared. Cesium carbonate usually increased the yield of the expected product. This result was proposed to be due to higher solubility of cesium carbonate compared to potassium carbonate under the reaction conditions. The temperature was also

(9) M. Lautens and S. Piguel, *Angew. Chem. Int. Ed*. **2000**, *39*, 1045.

increased from room temperature to reflux. Since the absence of *ortho* substituents led to complex mixtures, the scope of the reaction was performed with iodoarenes containing one *ortho*-substituent.[10] Alkyl *ortho*-groups gave the best yields, while the electron-withdrawing methyl ester failed to give the desired product under the optimized conditions. Other *ortho*-groups gave moderate to low yields. Yields were usually lower when seven-membered rings were formed compared to six-membered ones. The best yields reported were between 90 and 93%.

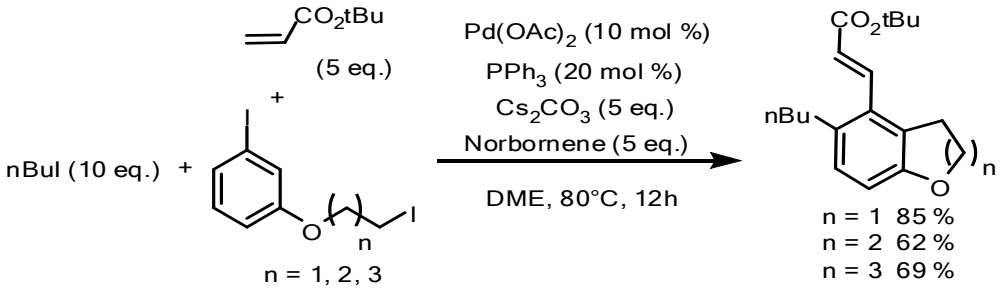
The methodology could also be used with substrates containing a heteroatom as part of the bisacceptor, thus forming 2,5-substituted-4-benzoxepines.[11]



Scheme 9. Formation of a 2,5-substituted-4-benzoxepine

Later, Lautens and Pache reported an extension of this methodology to include intramolecular *ortho*-alkylations with heteroatom tethers on the iodoarene.[12]

(10) These *ortho*-substituted iodoarenes are referred to as *ortho*-blocked.
(11) M. Lautens, J.-F. Paquin, S. Piguel, *J. Org. Chem.* **2002,** *67,* 3972.
(12) S. Pache, M. Lautens, *Org. Lett*. **2003**, *5*, 4827.



Scheme 10. A three component reaction leading to oxacycles[12]

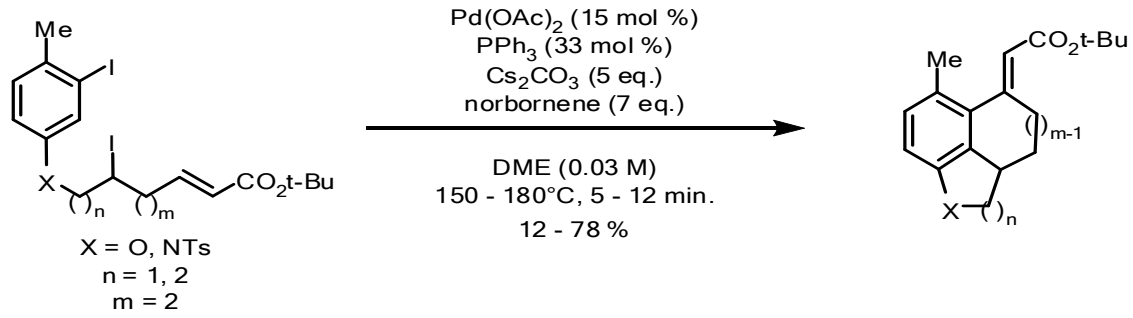
Since both intermolecular and intramolecular *ortho*-alkylations occur, the order of events for this reaction sequence could be intermolecular *ortho*-alkylation followed by intramolecular *ortho*-alkylation, or vice versa. However, at this time it is not known which *ortho*-alkylation occurs first. Both sequences could also be happening simultaneously giving rise to the same product. The optimized conditions differ from the ones previously reported by the Lautens group, namely a change in ligand, solvent, and equivalents of reagents. This methodology allows for the formation of five, six, and seven-membered oxacycles in respectively 85, 62, and 69% yield. Iodobenzyl alcohols could also be used instead of iodophenols, giving good yields of the corresponding oxacyclic products.

Several key aspects of this palladium-catalyzed domino process were learned through the aforementioned reactions. Intra- and intermolecular *ortho*-alkylations and termination reactions can occur. Both the alkyl iodide and the Heck acceptor can be varied, allowing a wide variety of oxacycles to be formed. Heteroatoms are tolerated as a part of the side-chain. Most importantly, complex products can be obtained from commercially available reagents and readily available starting materials.

The palladium-catalyzed synthesis of fused aromatic tricyclic ring systems[13] was also recently demonstrated by the Lautens group (Scheme 11). An intramolecular *ortho*-alkylation with a secondary alkyl iodide, followed by an intramolecular Heck reaction furnishes tricyclic products

(13) A. Rudolph, N. Rackelmann, M. Lautens, *Angew. Chem. Int. Ed*. **2007**, *46,* 1485.

in 12-78% yields. Heteroatoms (oxygen or tosyl protected amine) can be used as part of the linker between the arene and the Heck acceptor.

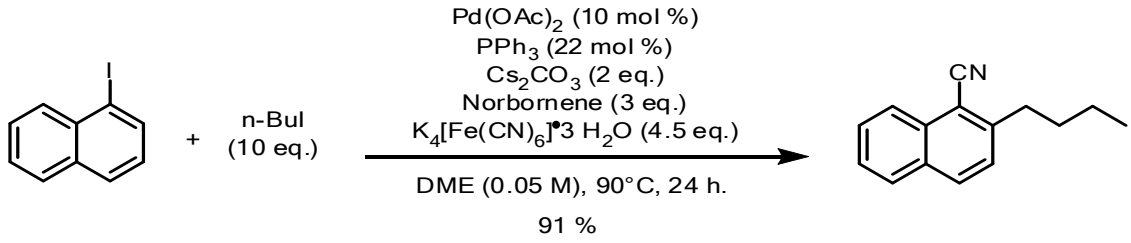


Scheme 11. Palladium-catalyzed synthesis of fused aromatic tricyclic ring systems[13]

Tosylated anilines proved to be successful substrates for this transformation, demonstrating that a nitrogen containing precursors can also be used under these reaction conditions.

Variations of the termination step of the palladium-catalyzed norbornene mediated domino sequence were investigated to broaden the possibilities offered by this method. Cyanation[14] was found to be a viable alternative to the Heck reaction as an inorganic source of cyanide can be used in place of a Heck acceptor. Zinc cyanide and potassium ferrocyanide are adequate cyanide sources for these reactions.

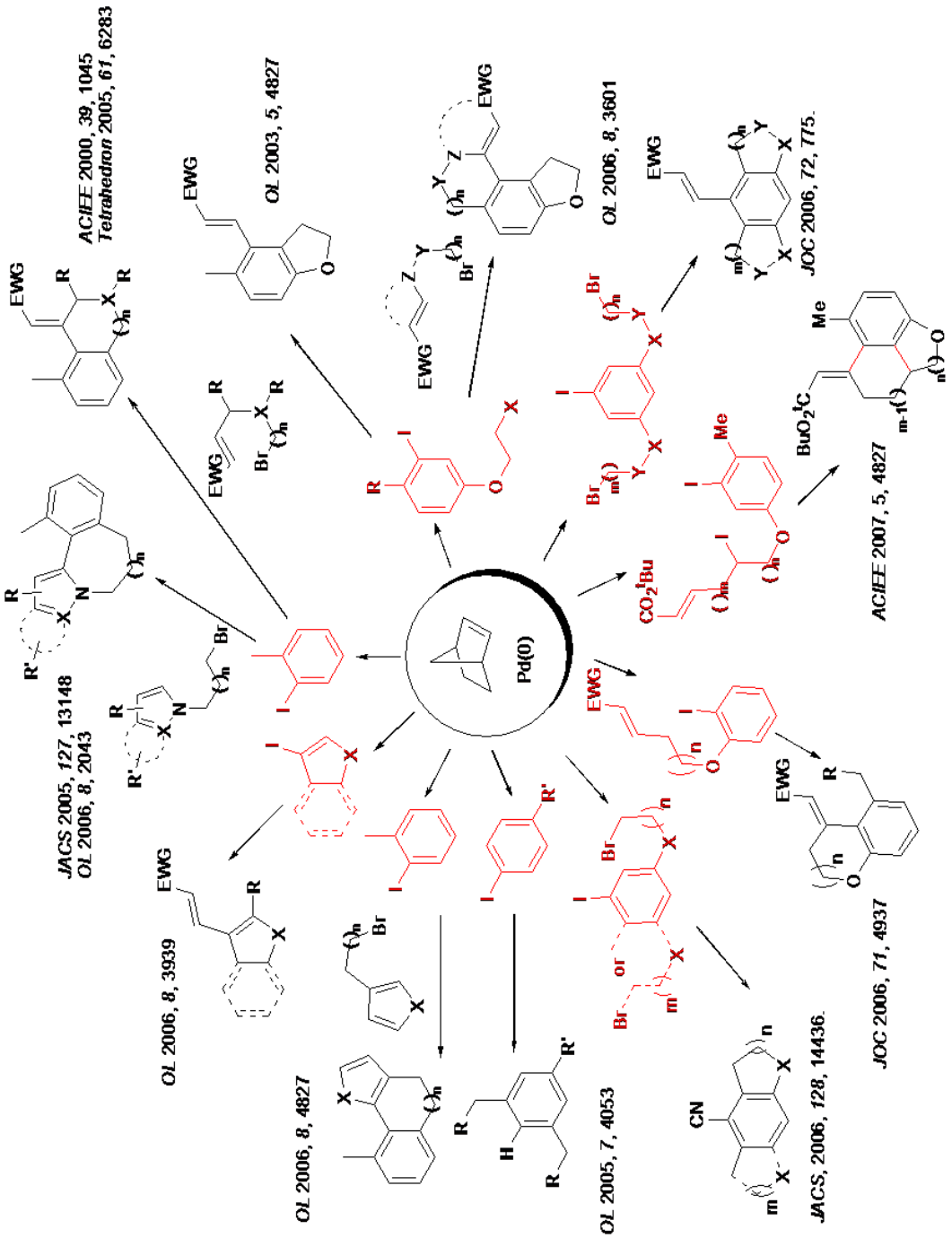
(14) a) B. Mariampillai, D. Alberico, V. Bidau and M. Lautens, *J. Am. Chem. Soc.* **2006**, *128*, 14436. b) B. Mariampillai, J. Alliot, M. Li and M. Lautens, *J. Am. Chem. Soc.* **2007**, *129*, 15372.



Scheme 12. Cyanation as a termination step in the palladium-catalyzed norbornene mediated domino *ortho* C-H alkylation

Other variations of these domino reactions have also been explored. Besides cyanation, other viable termination steps include a reduction[15], direct arylation[16], and amination[17]. A summary of these strategies is shown in Scheme 13.

(15) a) T. Willhelm and M. Lautens, *Org. Lett.* **2005**, *7*, 4053. b) K. Mitsudo, P. Thansandote, T. Willhelm, B. Mariampillai and M. Lautens, *Org. Lett.* **2006**, *8*, 3939.
(16) a) C. Blaszykowsky, E. Aktoudianakis, C. Bressy, D. Alberico and M. Lautens, *Org. Lett.* **2006**, *8*, 2043. b) A. Martins, D. Alberico and M. Lautens, *Org. Lett.* **2006**, *8*, 4827.
(17) P. Thansandote, M. Raemy, A. Rudolph and M. Lautens, *Org. Lett.* **2007**, *9*, 5255.

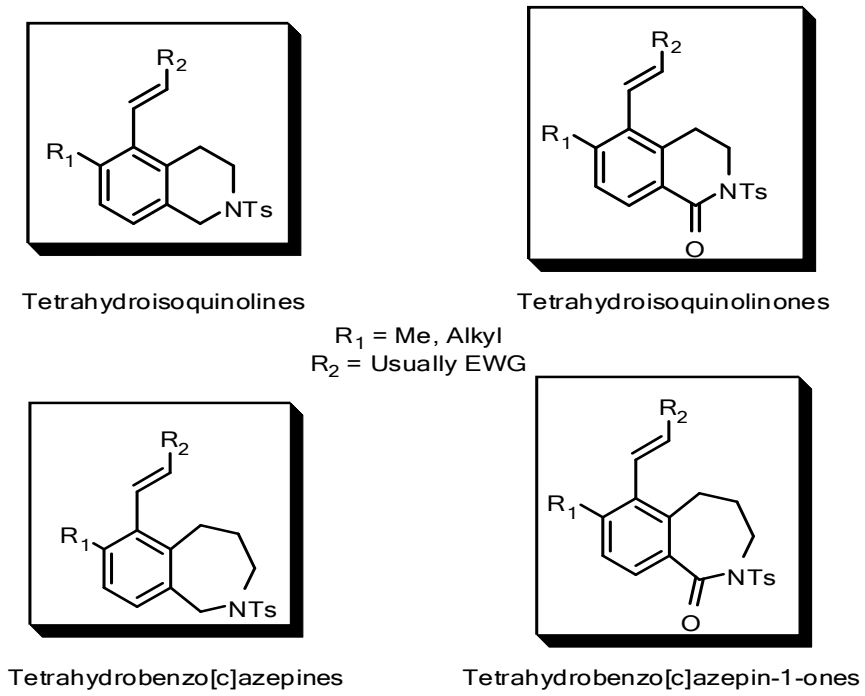


Scheme 13. A summary of the palladium-catalyzed norbornene mediated domino reactions developed by the Lautens group

1.2 Objectives

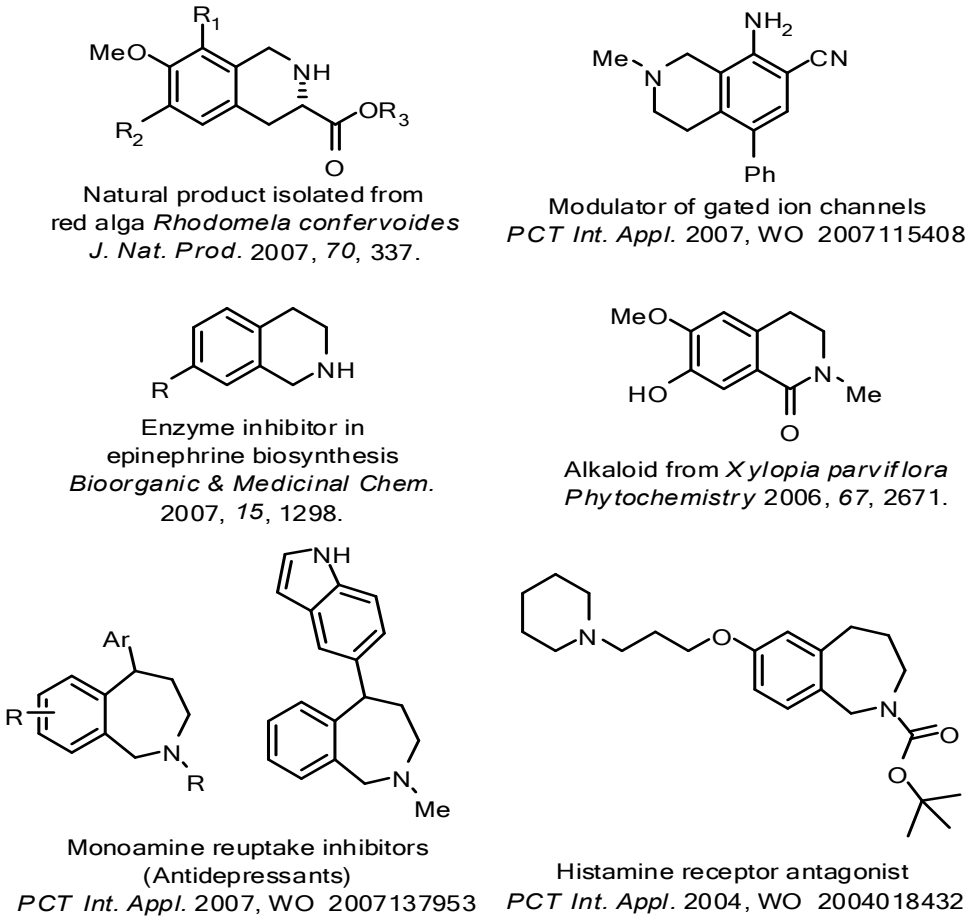
1.2.1 Structures of Interest

New products that could be synthesized via a modified version of aforementioned methods are the desirable tetrahydroisoquinolines and tetrahydroisoquinolinones represented in Scheme 14.



Scheme 14. Four possible products of our proposed reaction sequence

These structures are popular motifs in natural products or biologically active compounds, as illustrated in Scheme 15.

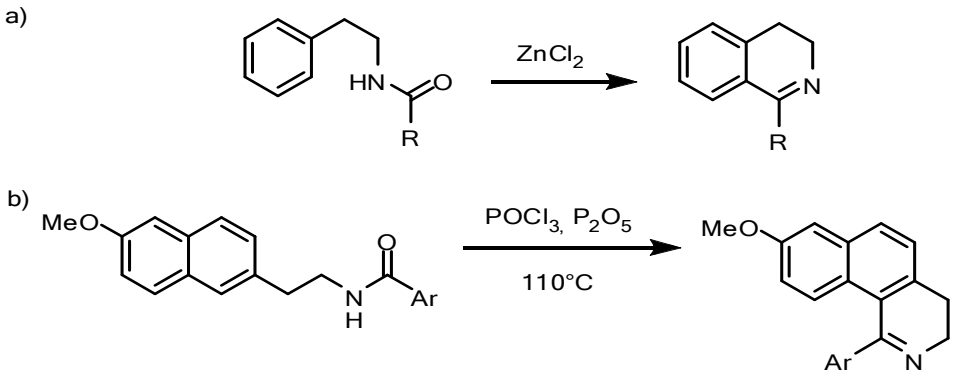


Scheme 15. Biologically active compounds and natural products containing the tetrahydroisoquinoline motif or its homologues

1.2.2 Known Syntheses of Tetrahydroisoquinolines Derivatives

The Bischler-Napieralski reaction[18] is the cyclodehydration of ß-phenethylamides to 3,4-dihydroisoquinoline derivatives. The original reaction is shown in Scheme 16a, and a more recent example is shown in Scheme 16b.[19]

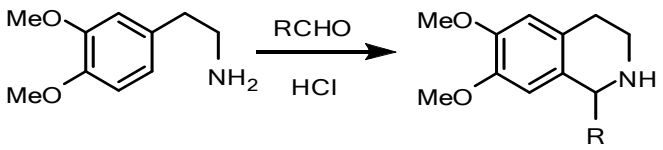
(18) a) A. Bischler and B. Napieralski, *Ber.* **1893**, *26*, 1903. b) W. M. Whaley and T. R. Govindachari, *Org. React.* **1951**, *6*, 74.



Scheme 16. The Bischler-Napieralski reaction[18,19]

The reaction forms one carbon-carbon bond through a ring closure. The resulting imine is usually reduced using sodium borohydride to obtain the tetrahydroisoquinoline product.[19b] Since the reaction requires desired functional groups to be installed either prior to the cyclization, or after it, protecting group chemistry may be necessary. Obtaining substituted tetrahydroisoquinolines by this protocol may thus require multiple steps.

A similar method, the Pictet-Spengler reaction[20], allows the formation of tetrahydroisoquinolines starting from a ß-arylethylamine and an aldehyde in the presence of a strong acid.



Scheme 17. The Pictet-Spengler tetraisoquinoline synthesis[20]

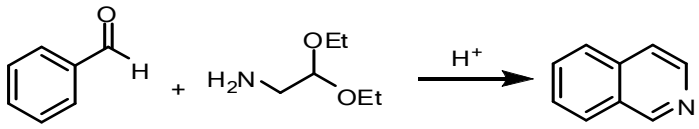
---

(19) a) S. Doi, N. Shirai, and Y. Sato, *J. Chem. Soc., Perkin Trans. 1*, **1997**, 2217. b) M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev*. **2004**, *104*, 3341.

(20) A. Pictet and T. Spengler, *Ber.* **1911**, *44*, 2030. b) W. M. Whaley and T. R. Govindachari, *Org. React.* **1951**, *6*, 74. c) E. D. Cox, J. M. Cook, *Chem. Rev*. **1995**, *95*, 1797. d) M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev*. **2004**, *104*, 3341.

The reaction is similar to the previously mentioned Bischler-Napieralski reaction, the only difference being the imine formed *in situ*. The reaction forms one carbon-carbon bond in the cyclization process, along with a chiral center if the aldehyde is different from formaldehyde.[19c,d]

Another classical method, the Pomeranz-Fritsch reaction[21], is used to synthesize fully aromatic isoquinolines.

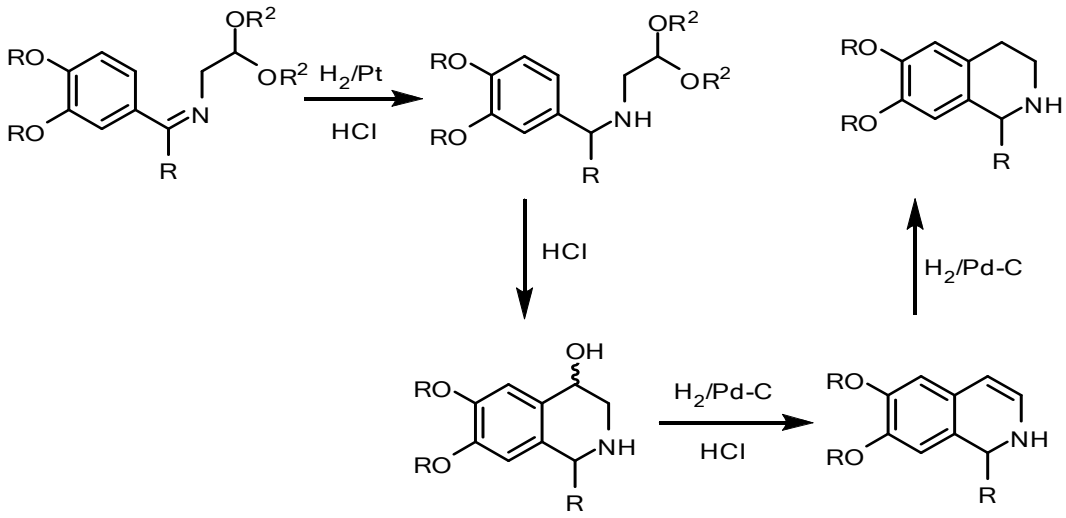


Scheme 18. The Pomeranz-Fritsch reaction[21]

A modification to this reaction known as the Pomeranz-Fritsch-Bobbitt reaction[22], allows the synthesis of tetrahydroisoquinolines in a two step sequence.

(21) a) C. Pomeranz, *Monatsch.* **1893**, *14*, 116. b) P. Fritsch, *Ber.* **1893**, *26*, 419. c) D. L. Boger, C. E. Brotherton and M. D. Kelley, *Tetrahedron* **1981**, *37*, 3977. d) E. L. Larghi and T. S. Kaufman, *Tetrahedron Lett.* **1997**, *38*, 3159.

(22) M. Bobbitt, J. M. Kiely, K. L. Khanna and R. J. Eberman, *J. Org. Chem.* **1965**, *30*, 2247.

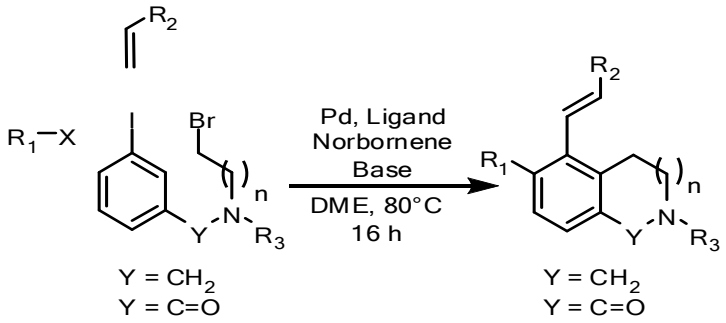


Scheme 19. The Pomeranz-Fritsch-Bobbitt reaction[22]

A variety of other methods also exist, using several classical organic reactions to form various tetrahydroisoquinolines.[20d]

1.2.3 Objective

Using the previously mentioned palladium-catalyzed norbornene-mediated domino strategy, we aimed to find a novel route to tetrahydroisoquinolines. The formation of these structures, along with the closely related tetrahydroisoquinolinones, could be possible according to the equation shown in Scheme 10 under standard reaction conditions.[12] The corresponding seven-membered ring analogues, tetrahydrobenzo[c]azepines and tetrahydrobenzo[c]azepin-1-ones, could also be envisaged using similar conditions. The main challenge is the use of a benzylic amine or amide as a precursor to the desired products as our group and Catellani have not used this type of tether for *ortho*-alkylations.



Scheme 20. Current objective for the synthesis of tetrahydroisoquinolines, tetrahydroisquinolones and their homologues

The formation of up to three new carbon-carbon bonds selectively in a single reaction, two of which are formed by C-H functionalization, is a significant feature of this methodology. Our reaction sequence allows for a rapid increase in molecular complexity, as the products are closely related to biologically active motifs and naturally occurring structures. This is advantageous compared to the aforementioned classical methods, where only one carbon-carbon bond was formed from a cyclization using harsh conditions.

1.2.4 Proposed Mechanism

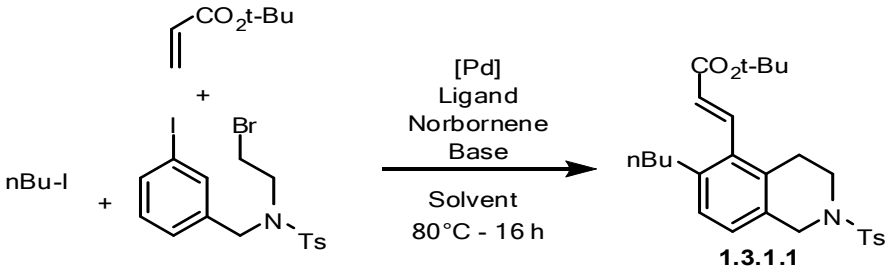
The proposed mechanism is analogous to the mechanism described previously in Scheme 6, using VI, VII, X or XII as the aryl iodide. Currently, we do not know if the intramolecular or intermolecular *ortho* C-H functionalization occurs first for non-*ortho* blocked substrates. Both pathways could also occur competitively. Nonetheless, the same product is obtained at the end of the catalytic cycle.

1.3 Prior Work on the Synthesis of Tetrahydroisoquinolines and Tetrahydroisoquinolinones

1.3.1 Optimization

Initial experiments aimed to investigate the formation of highly substituted tetrahydroisoquinolines. Optimization[23] of the reaction conditions lead to the formation of product **1.3.1.1** in 46 % yield.

Table 1. Optimization[a] for tetrahydroisoquinoline product **1.3.1.1**



1.3.1.1

Entry	Cs_2CO_3 (eq.)	DME (M)	*n*-BuI (eq.)	*t*-butyl acrylate (eq.)	Norbornene (eq.)	Yield (%)[b]
1	5	0.1	10	5	5	11
2	3	0.1	10	5	5	10
3	5	0.1	10	2	5	17
4	5	0.2	10	5	5	19
5	5	0.1	10	5	6	37
6	5	0.1	2	5	5	44
7	3	0.2	2	2	6	46[c]

[a] All reactions conducted with $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3, *n*-BuI, *t*-butyl acrylate and norbornene in DME (amounts indicated) at 80 °C for 16 hours. [b] Yields were determined by ^1H NMR using mesitylene as an internal standard. [c] Isolated yield.

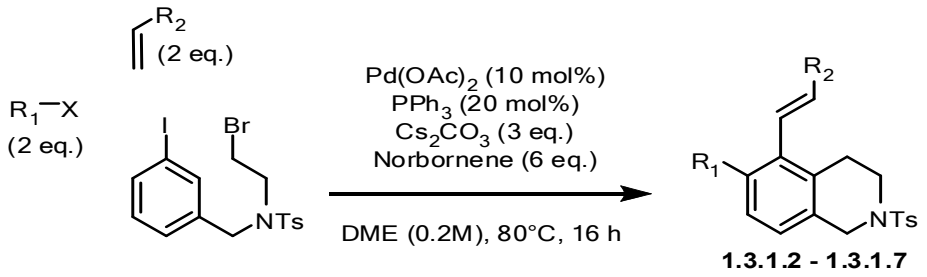
(23) C. Gouliaras, *CHM499 Thesis*, **2008**, pp. 11.

No significant difference was noticed when the amount of cesium carbonate was decreased from five to three equivalents (Entry 1 vs. Entry 2) However, reducing the amount of *tert*-butyl acrylate from five to two equivalents not only reduced the amount of waste but also increased the yield of the reaction. A higher concentration (0.2M from 0.1M) increased the product yield. Increasing the equivalents of norbornene from five to six drastically increased the yield from 11% to 37% (Entry 1 vs. Entry 5). Reducing the amount of alkyl iodide from ten to two equivalents was advantageous and also increased the yield slightly. Combining all of the changes that had a positive influence on the yield gave the optimized isolated yield of 46%.[23]

The effect of varying the protecting group on the benzylic amine was also tested (R_3 in Scheme 20). Among those tested (benzyl, *para*-methoxy benzyl, carboxybenzyl, tosyl and CO_2Et), only the tosylated amine survived the reaction conditions to give the desired tetrahydroisoquinoline. Unprotected amine failed to give the desired product and decomposed under the reaction conditions.

Variation of the Heck acceptor or the alkyl halide under the optimal reaction conditions lead to the formation of a variety of substituted tetrahydroisoquinolines, as shown in Table 2. Overall, the yields of these compounds were poor to moderate. Thus, we proposed that using *ortho*-blocked substrates would simplify the reaction sequence by removing one *ortho*-alkylation from the domino process leading to potentially higher yields. Preliminary results from this strategy are shown in Table 3.

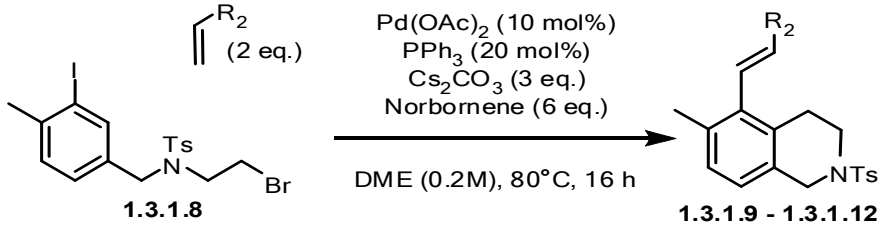
Table 2. Scope for tetrahydroisoquinolines[b]



Entry	R_1X	R_2	Product	Yield (%)[a]
1	*n*-BuI	CO_2t-Bu	**1.3.1.2**	46
2	*n*-BuI	C(O)NH*t*-Bu	**1.3.1.3**	28
3	*n*-BuI	CN	**1.3.1.4**	15
4	methyl 4-bromobutyrate	CO_2t-Bu	**1.3.1.5**	31
5	1-chloro-3-iodopropane	CO_2t-Bu	**1.3.1.6**	38
6	2-methyl-1-iodopropane	CO_2t-Bu	**1.3.1.7**	34

[a] Isolated yields. [b] See reference 23.

Table 3. Scope for *ortho*-blocked tetrahydroisoquinolines

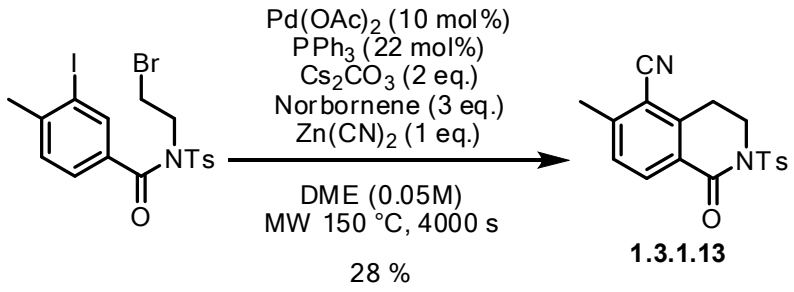


Entry	R^2	Product[b]	Yield (%)[a]
1	CO_2t-Bu	**1.3.1.9**	70
2	CO_2Et	**1.3.1.10**	73
3	CO_2Me	**1.3.1.11**	74
4	CN	**1.3.1.12**	30

[a] Isolated yields. [b] C. Gouliaras and P. Thansandote, See reference 23.

The scope of different Heck acceptors in the reaction of **1.3.1.8** under the conditions described in Table 3 has been studied. *Tert*-butyl, ethyl and methyl acrylate gave respectively 70%, 73% and 74% yields of the expected product. Acrylonitrile gave only 30% of **1.3.1.12.**

An attempt at varying the termination step of the sequence from a Heck reaction to a cyanation[24] was also successful, although with modest yield under the unoptimized conditions for this substrate. The same transformation was attempted for the tetrahydroisoquinoline precursor but none of the desired product has been observed thus far.



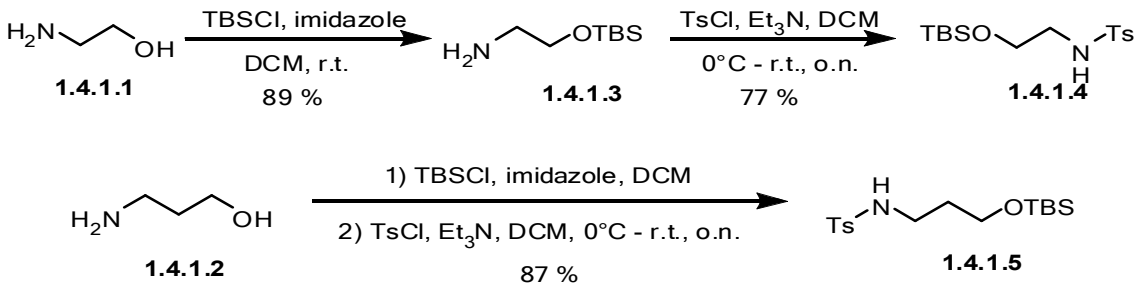
Scheme 21. Reaction sequence with cyanation as the termination step

1.4 Contribution to the Synthesis of Tetrahydroisoquinolines, Tetrahydroisoquinolinones and Tetrahydrobenzo[c]azepines

1.4.1 Starting Material Synthesis

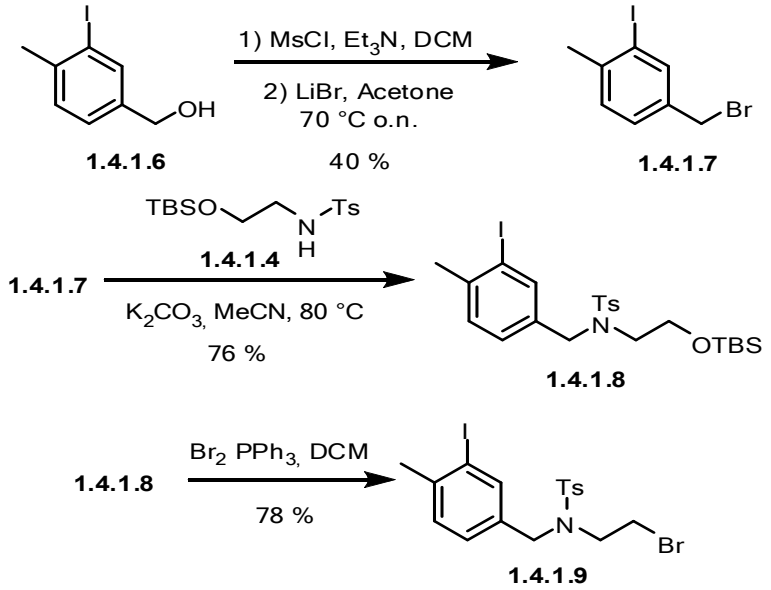
Starting from commercially available 2-amino-1-ethanol **1.4.1.1** or 3-amino-1-propanol **1.4.1.2**, protection of the alcohol using a *tert*-butyl dimethylsilyl group, followed by protection of the amine with a tosyl group generates the protected amino-alcohols **1.4.1.4** and **1.4.1.5**. Flash chromatography is only necessary after both protecting groups are in place.

(24) a) C. Gouliaras and P. Thansandote, *unpublished results*. b) Reaction conditions from: B. Mariampillai, D. Alberico, V. Bidau and M. Lautens, *J. Am. Chem. Soc.* **2006**, *128*, 14436.



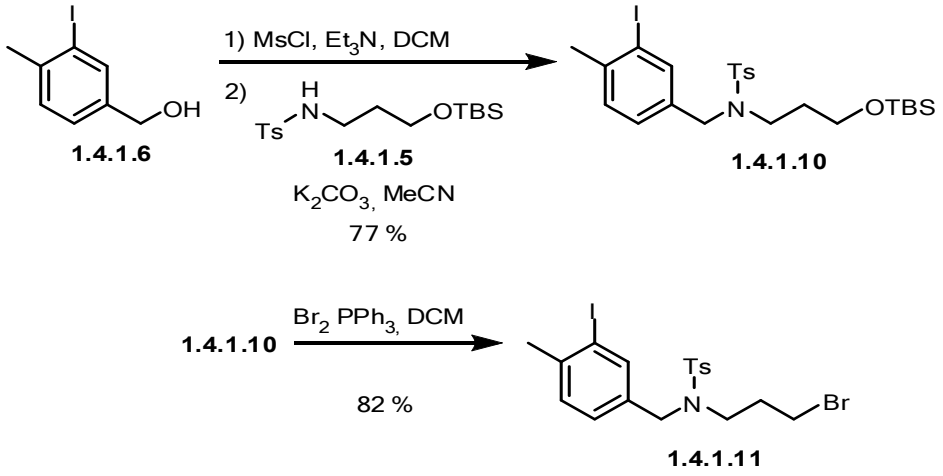
Scheme 22. TBS and tosyl protection of amino-alcohols

Tetrahydroisoquinoline precursor **1.4.1.9** can be made according to the sequence shown in Scheme 23. Although the S_N2 displacement from **1.4.1.7** to **1.4.1.8** is achieved in 76 % yield, a shorter reaction pathway to **1.4.1.8** is possible by omitting the bromination step and performing the S_N2 reaction directly from the mesylate. This sequence was used to form product **1.4.1.10** (Scheme 24).



Scheme 23. Synthesis of the *ortho*-blocked tetrahydroisoquinoline precursor **1.4.1.9**

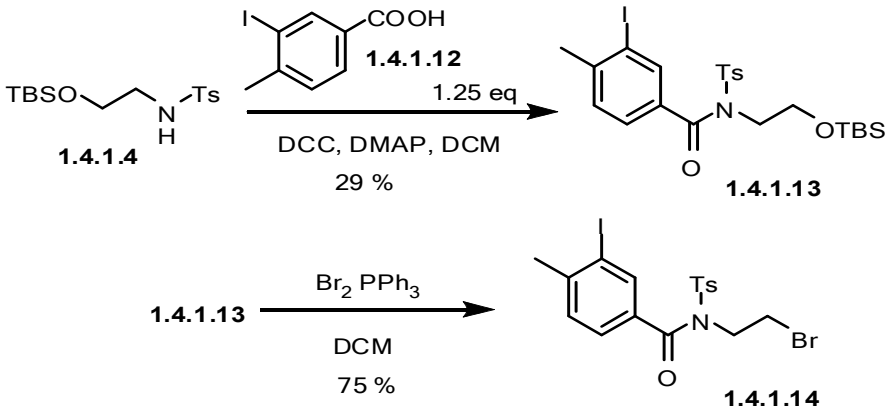
The precursor to *ortho*-blocked tetrahydrobenzo[c]azepine **1.4.1.11** can be obtained by the reaction pathway described in Scheme 24.



Scheme 24. Synthesis of the *ortho*-blocked benzo[c]azepine precursor **1.4.1.11**

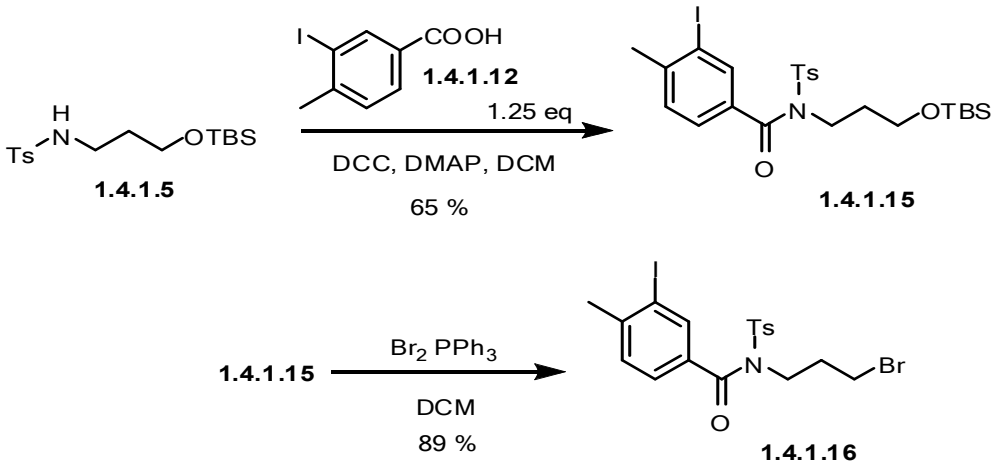
The synthesis of the *ortho*-blocked tetrahydroisoquinolinone precursor **1.4.1.14** is achieved by a DCC coupling[25] of 3-iodo-4-methylbenzoic acid **1.4.1.12** with **1.4.1.4** to obtain **1.4.1.13**, followed by a bromination using triphenylphosphine dibromide. The DCC coupling generates a large amount of DCU, which precipitates as a white solid. Unfortunately, filtration is not sufficient to separate all the DCU from the rest of the reaction mixture. Trituration of the reaction crude with mixtures of pentane and ethyl acetate prior to loading on the column is necessary and, therefore, good yields of **1.4.1.13** were difficult to obtain.

(25) D. Tanner and P. Somfai, *Tetrahedron* **1988**, *44*, 613.



Scheme 25. Synthesis of the *ortho*-blocked tetrahydroisoquinolinone precursor **1.4.1.14**

The *ortho*-blocked benzo[c]azepin-1-one precursor **1.4.1.16** is obtained by using a reaction pathway similar to the one described in Scheme 25. This time, the DCC coupling[25] affords **1.4.1.15** in 65 % yield, much higher than for product **1.4.1.13** under similar conditions.

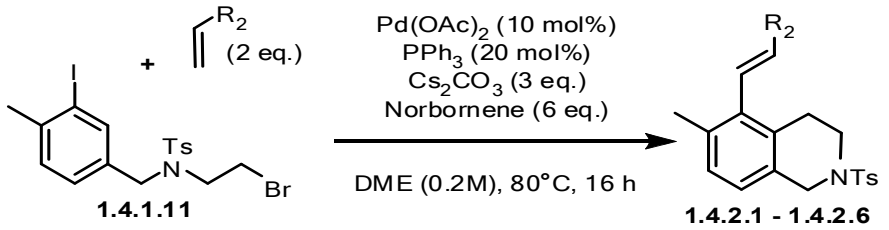


Scheme 26. Synthesis of the *ortho*-blocked benzo[c]azepin-1-one precursor **1.4.1.16**

1.4.2 Results and Discussion

The scope of different Heck acceptors in the reaction of **1.4.1.11** under the conditions described in Table 4 has been studied. *tert*-Butyl acrylamide gave the best yield with 87% of **1.4.2.1** isolated. Phenyl vinyl sulfone failed to give the expected product **1.4.2.6**. This Heck acceptor was also a poor substrate in past investigations with this type of methodology.[12] Styrene and *para*-methoxystyrene both failed to generate the expected products, possibly because they are electron-rich alkenes that will not readily participate as Heck acceptors under the reaction conditions. However, 2-vinylpyridine and methyl vinyl ketone were successful substrates, generating respectively 45 % and 63 % of **1.4.2.2** and **1.4.2.3**. The Heck acceptors that successfully generated the corresponding substituted tetrahydroisoquinolines all contained an electron-withdrawing group.

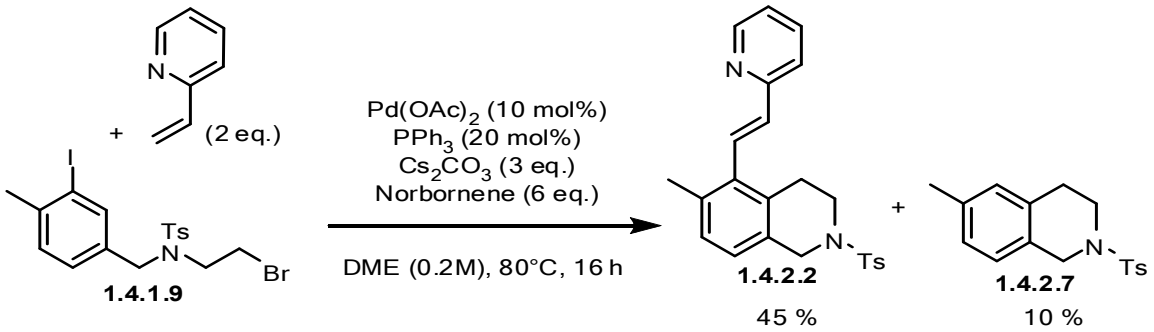
Table 4. Additional scope for *ortho*-blocked tetrahydroisoquinolines



Entry	R^2	Product	Yield (%)[a]
1	C(O)NH*t*-Bu	**1.4.2.1**	87
2	2-pyridine	**1.4.2.2**	45
3	C(O)Me	**1.4.2.3**	63
4	phenyl	**1.4.2.4**	-
5	p-MeO-phenyl	**1.4.2.5**	-
6	$S(O_2)$-phenyl	**1.4.2.6**	-

[a] Isolated yields.

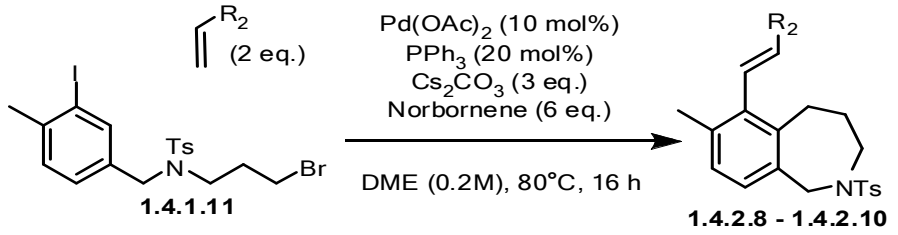
For Entry 2, 45% of the desired product **1.4.2.2** was observed along with 10% of the ring closure/reduction product **1.4.2.7** (Scheme 27). The formation of this by-product was also observed in other cases, namely entries 4 and 5. We do not know what causes the dehalogenation in the absence of a reducing agent. This is an area on-going investigation in our group.



Scheme 27. Products observed during the formation of tetrahydroisoquinoline **1.4.2.2**

The methodology was also extended to the formation of larger ring sizes. The scope for the *ortho*-blocked tetrahydrobenzo[c]azepines shows that, although the seven-membered ring products are formed under the reaction conditions, the yields obtained for products **1.4.2.8**, **1.4.2.9** and **1.4.2.10** are all lower than the yields obtained for their six-membered ring counterparts **1.3.1.9**, **1.4.2.1** and **1.4.2.3** using the same Heck acceptors. For the seven-membered rings, methyl vinyl ketone gave the highest yield with 59% of **1.4.2.10**, whereas *tert*-butylacrylamide gave **1.4.2.9** in 38% yield. Purification of these products can be difficult, often requiring pre-treatment with silica gel prior to two successive flash chromatography isolations.

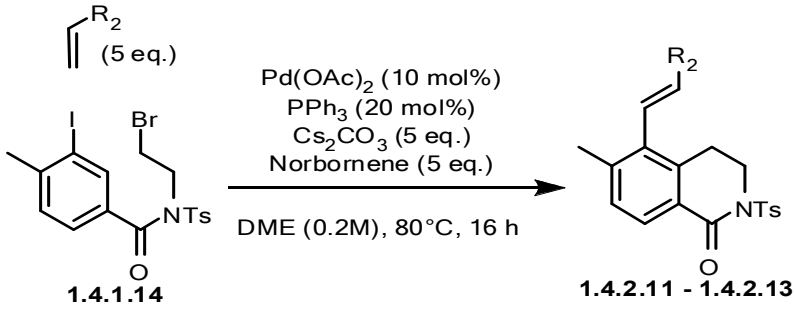
Table 5. Scope for ortho-blocked tetrahydrobenzo[c]azepines



Entry	R2	Product	Yield (%)a
1	CO2t-Bu	**1.4.2.8**	47
2	C(O)NHt-Bu	**1.4.2.9**	38
3	C(O)Me	**1.4.2.10**	59

[a] Isolated yields.

Table 6. Scope for ortho-blocked tetrahydroisoquinolinones

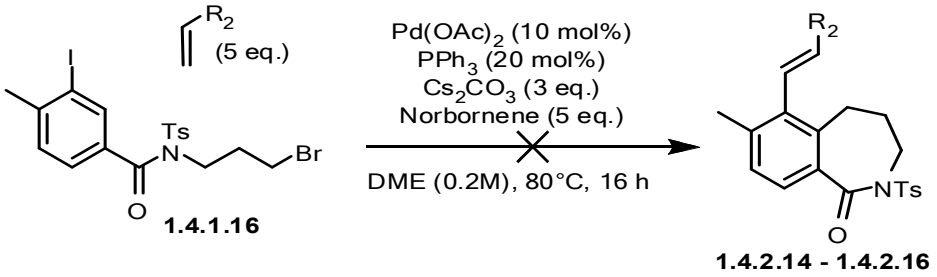


Entry	R^2	Product	Yield (%)[a]
1	CO_2*t*-Bu	**1.4.2.11**	64[b]
2	C(O)NH*t*-Bu	**1.4.2.12**	<15[c]
3	C(O)Me	**1.4.2.13**	-

[a] Isolated yields. [b] C. Gouliaras, see reference 23. [c] Impure.

While we achieved the synthesis of **1.4.2.11** in 64% yield, other *ortho*-blocked substrates failed to give the corresponding tetrahydroisoquinolinones. Although **1.4.2.12** was identified based on ^{1}H NMR, pure compound could not be obtained and thus an accurate yield cannot be reported. None of the expected product was isolated with methyl vinyl ketone as the Heck acceptor (Entry 3). Perhaps separate optimization of these substrates is necessary to obtain the desired products in synthetically useful yields.

Table 7. Scope for *ortho*-blocked tetrahydrobenzo[c]azepin-1-one



Entry	R^2	Product	Yield (%)
1	CO_2t-Bu	**1.4.2.14**	-
2	C(O)NH*t*-Bu	**1.4.2.15**	-
3	C(O)Me	**1.4.2.16**	-

Similar to the tetrahydroisoquinolinones, the formation of *ortho*-blocked tetrahydrobenzo[c]azepin-1-ones was also problematic. Optimization studies may be necessary for these substrates as well if we are to achieve synthetically useful yields.

1.4.3 Conclusions and Future Work

We have successfully extended the use of palladium-catalyzed norbornene mediated domino reactions to the formation of highly substituted tetrahydroisoquinolines and their homologues. Low to moderate yields were obtained when the reaction sequence included two *ortho* C-H functionalizations with a Heck reaction as the termination step. However, the highly selective formation of 3 new carbon-carbon bonds to achieve the formation of popular heterocyclic scaffolds is not readily achieved in one pot by other known methods. Reducing the sequence to include one *ortho* C-H functionalization by using *ortho*-blocked substrates allowed the formation of multi-substituted tetrahydroisoquinolines in moderate to high yields, rendering the transformation synthetically useful. Tetrahydroisoquinolinones and tetrahydrobenzo[c]azepines can also be synthesized under similar conditions. Tetrahydrobenzo[c]azepin-1-ones and

tetrahydroisoquinolinones may require further optimisation of the reaction conditions to achieve satisfactory yields.

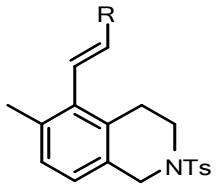
Most of the reagents used are commercially available, and require no further purification prior to their use. Starting materials are efficiently made using well known reactions in very few steps from the commercially available aryl iodides. Various functional groups are tolerated on the substrates, on the alkyl halides and on the Heck acceptor.

The use *ortho*-blocking groups other than a methyl group is currently under investigation in our laboratory. In addition, previously viable termination steps for palladium-catalyzed norbornene mediated domino reactions could possibly be adapted to our method, thus allowing a broader range of products to be accessible. Total synthesis of biologically active compounds could also be envisaged using our methodology.

1.5 Experimental

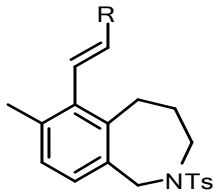
1.5.1 General Procedures

1.5.1.1 General Procedure (GP1) for the Formation of ortho-Blocked Tetrahydroisoquinolines



To an oven-dried 5 ml microwave vessel charged with a dry magnetic stir bar was added **1.4.1.9** (102 mg, 0.2 mmol, 1 eq.), Cs_2CO_3 (195.5 mg, 0.6 mmol, 3 eq.), PPh_3 (10.5 mg, 0.04 mmol, 0.2 eq.), norbornene (113 mg, 1.2 mmol, 6 eq.), $Pd(OAc)_2$ (4.50 mg, 0.02 mmol, 0.1 eq.), and the heck acceptor (0.4 mmol, 2 eq.). The tube was sealed and flushed with argon and dry, degassed DME (1 ml) was added. The reaction was stirred at 80^o C for 16 hours and then cooled to room temperature, diluted with ether (1 ml), quenched with water (1 ml) and extracted with ether (3 times) and water. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure.

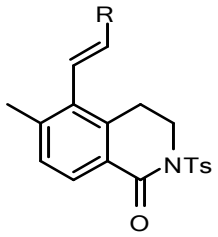
1.5.1.2 General Procedure (GP2) for the Formation of ortho-Blocked Tetrahydrobenzo[c]azepin



To an oven-dried 5 ml microwave vessel charged with a dry magnetic stir bar was added **1.4.1.11** (104.4 mg, 0.2 mmol, 1 eq.), Cs_2CO_3 (195.5 mg, 0.6 mmol, 3 eq.), PPh_3 (10.5 mg, 0.04 mmol, 0.2 eq.), norbornene (113 mg, 1.2 mmol, 6 eq.), $Pd(OAc)_2$ (4.50 mg, 0.02 mmol, 0.1 eq.), and the

heck acceptor (0.4 mmol, 2 eq.). The tube was sealed and flushed with argon and dry, degassed DME (1 ml) was added. The reaction was stirred at 80° C for 16 hours and then cooled to room temperature, diluted with ether (1 ml), quenched with water (1 ml) and extracted with ether (3 times) and water. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure.

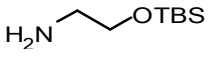
1.5.1.3 General Procedure (GP3) for the Formation of ortho-Blocked Tetrahydroisoquinolinones



To an oven-dried 5 ml microwave vessel with a dry magnetic stir bar was added **1.4.1.14** (99 mg, 0.19 mmol, 1 eq.), cesium carbonate (309 mg, 0.95 mmol, 5 eq.), triphenylphosphine (9.94 mg, 0.038 mmol, 0.2 eq.), norbornene (89.2 mg, 0.95 mmol, 5 eq.), $Pd(OAc)_2$ (4.26 mg, 0.019 mmol, 0.1 eq.), and a Heck acceptor (0.95mmol, 5 eq.). The tube was sealed and flushed with argon and dry, degassed DME (1.9 ml) was added. The reaction was stirred at 80° C for 16 hours and then cooled to room temperature, diluted with ether (1.9 ml), quenched with water (1.9 ml) and extracted with ether (3 times) and water. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure.

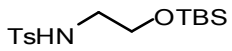
1.5.2 Compounds

1.5.2.1 2-(tert-Butyl-dimethyl-silanyloxy)-ethylamine (1.4.1.3)



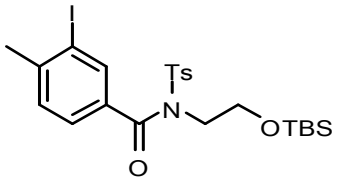
To a magnetically-stirred solution of 2-aminoethanol **1.4.1.1** (19.76ml, 327 mmol) and imidazole (44.58g, 655 mmol) in DCM (328ml), under argon was added TBSCl (51.82g, 344 mmol). The reaction was stirred at room temperature for 2 hours, quenched with water and extracted with DCM. The combined organic phases were dried over $MgSO_4$, filtered and then concentrated under reduced pressure to yield **1.4.1.3** (51.21g, 89% crude) as a transparent, yellow oil. Used without further purification.

1.5.2.2 *N*-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-4-methyl-benzenesulfonamide (1.4.1.4)



To a magnetically-stirred solution of **1.4.1.3** (4.0g, 22.8 mmol) in DCM (11.6 ml) under argon, was added toluenesulfonyl chloride (4.78 g, 25 mmol). Once dissolved, the solution was cooled to 0^oC and Et_3N (3.5 ml, 25 mmol) added. The reaction was stirred at room temperature for one hour, or until TLC indicated completion, and then washed with DCM and water. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification proceeded by flash chromatography on silica gel (ethyl acetate/hexanes, 1:9 v/v) to afford **1.4.1.4** (5.76 g, 77 %) as a transparent, off-white oil.

1.5.2.3 *N*-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-*N*-(3-iodo-4-methyl-benzoyl)-4-methyl-benzenesulfonamide (1.4.1.13)

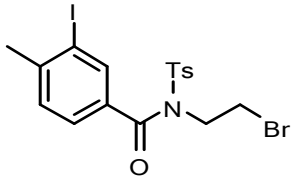


To a magnetically-stirred solution of **1.4.1.4** (2.09 g, 6.34 mmol), DCC (1.51 g, 7.33 mmol) and DMAP (81 mg, 0.67 mmol) in DCM (111 ml) under argon, was added 3-iodo-4-methylbenzoic acid **1.4.1.12** (2.10 g, 8.00 mmol). The reaction was stirred for 2 hours at room temperature. The precipitated DCU was filtered off and the solution washed with dilute $NaHCO_3$ and DCM. The

combined organic extracts were concentrated and the product triturated from ethyl acetate/hexanes (1:9, v/v) to remove remaining DCU. Purification proceeded by flash chromatography on silica gel (ethyl acetate/hexanes, 1:9 v/v) to afford **1.4.1.13** (1.58 g, 43%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.84 (s, 1H), 7.81 (d, 2H, J = 8), 7.48 (d, 1H, J = 8), 7.33 (d, 2H, J = 8), 7.27 (d, 1H, J = 7.6), 4.00 (t, 2H, J = 5.6), 3.80 (t, 2H, J = 5.6), 2.48 (s, 3H), 2.47 (s, 3H), 0.84 (s, 9H), 0.002 (s, 6H)**;** ^{13}C NMR (100MHz, $CDCl_3$) δ = 175.4, 150.8, 150.3, 144.1, 141.8, 139.8, 135.1, 134.7, 133.9, 133.8, 105.7, 66.8. 55.2, 33.8, 31.3, 27.2, 23.8, -0.001; HRMS (ESI) for $C_{23}H_{32}INO_4SSi$ m/z calculated 573.08660, found 574.0938 $[M+H]^+$; IR (neat) υ (cm^{-1}) 2949 (w), 2922 (w), 2853 (w), 1680 (m), 1596 (w), 1470 (w), 1358 (m), 1256 (m), 1167 (m), 1100 (m); mp = 68-70^{o}C.

1.5.2.4 *N*-(2-Bromo-ethyl)-*N*-(3-iodo-4-methyl-benzoyl)-4-methyl-benzenesulfonamide (1.4.1.14)

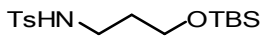


To a magnetically-stirred solution of **1.4.1.13** (1.45 g, 2.52 mmol) in DCM (77 ml) under argon, was added $Br_2 \bullet PPh_3$ (1.17 g, 2.78 mmol). The reaction was stirred for one hour at room temperature, and then concentrated and washed with DCM and water. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification proceeded by flash chromatography on silica gel (ethyl acetate/hexanes, 1:4 v/v) to afford **1.4.1.14** (565 mg, 76%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.75 (d, 1H, J = 2), 7.62 (d, 2H, J = 8.4), 7.46 (dd, 1H, J = 7.6, 2), 7.31 (d, 2H, J = 8.4), 7.28 (d, 1H), 4.16 (t, 2H, J = 6.8), 3.61 (t, 2H, J = 6.8), 2.47 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 169.6, 145.8, 145.4, 138.4, 135.4, 133.9, 129.9, 129.2, 128.5, 128.2, 100.2, 48.2, 29.2, 28.3, 21.8; HRMS (ESI) for $C_{17}H_{17}BrINO_3S$ m/z

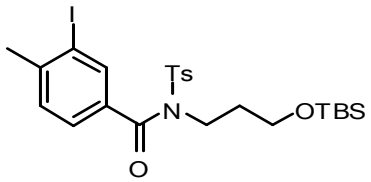
calculated 520.91572, found 521.9230 $[M+H]^+$; IR (neat) υ (cm^{-1}) 2983 (w), 2915 (w), 1680 (m), 1596 (w), 1555 (w), 1361 (m), 1283 (w), 1252 (m), 1164 (m); mp = 80-81^oC.

1.5.2.5 N-(3-(tert-butyldimethylsilyloxy)propyl)-4-methylbenzenesulfonamide (1.4.1.5)



To a magnetically-stirred solution of 3-amino-1-propanol **1.4.1.2** (5.1ml, 66.5 mmol) and imidazole (9.0642g, 133 mmol) in DCM (60ml), under nitrogen was added TBSCl (10.5353g, 69.9 mmol). The reaction was stirred at room temperature overnight, quenched with water and extracted with DCM. The combined organic phases were dried over Na_2SO_4, filtered and then concentrated under reduced pressure. To a magnetically-stirred solution of that crude retaken in DCM (34ml) under nitrogen, was added toluenesulfonyl chloride (13.9613g, 73.2 mmol). Once dissolved, the solution was cooled to 0^oC and Et_3N (10.2 ml, 73.2 mmol) added. The reaction was stirred at room temperature overnight, or until TLC indicated completion, and then washed with DCM and water. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification proceeded by flash chromatography on silica gel (DCM or pentane/ethyl acetate 4:1) to afford **1.4.1.5** (18.9888 g, 83 %) as a transparent, light yellow oil.

1.5.2.6 N-(3-(tert-butyldimethylsilyloxy)propyl)-3-iodo-4-methyl-N-tosylbenzamide (1.4.1.15)

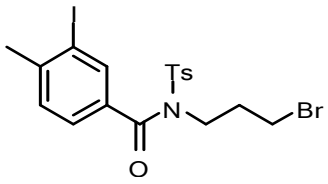


To a magnetically-stirred solution of **1.4.1.5** (2.20 g, 6.4 mmol), DCC (1.5856 g, 7.69 mmol) and DMAP (81 mg, 0.64 mmol) in DCM (100 ml) under nitrogen, was added 3-iodo-4-methylbenzoic acid **1.4.1.12** (2.10 g, 8.00 mmol). The reaction was stirred for 2 hours at room temperature. The precipitated DCU was filtered off and the solution washed with dilute $NaHCO_3$

and DCM. The combined organic extracts were concentrated and the product triturated from ethyl acetate/pentanes (1:4, v/v) to remove remaining DCU. Purification proceeded by flash chromatography on silica gel (ethyl acetate/pentanes, 1:10 v/v) to afford **1.4.1.15** (2.43 g, 65%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.81 (d, 1H, J = 2), 7.74 (d, 2H, J = 8), 7.43 (dd, 1H, J_1 = 7.8, J_2 = 1.8), 7.30 (d, 2H, J = 8), 7.25 (d, 1H, J = 8), 3.87 (t, 2H, J = 7.5), 3.59 (t, 2H, J = 6), 2.45 (s, 3H), 2.44 (s, 3H), 1.86 (m, 2H), 0.82 (s, 9H) -0.02 (s, 6H) **;** ^{13}C NMR (100MHz, $CDCl_3$) δ = 169.8, 145.4, 144.8, 138.2, 136.0, 134.3, 129.6, 129.2, 128.3, 128.0, 100.3,60.1, 45.6, 32.6, 28.2, 25.8, 21.7, 18.1, -5.5 **;** HRMS (ESI) for $C_{24}H_{34}INO_4SSi$ m/z calculated 587.10, found 588.1095 $[M+H]^+$; IR (neat) υ (cm^{-1}) 2936 (w), 2853 (w), 1669 (m), 1597 (w), 1341 (m), 1322 (m), 1293 (m), 1246 (m), 1173 (s), 1103 (m), 1089 (s), 1055 (m), 963 (m), 857 (m), 837 (m), 808 (m), 772 (m), 758 (m), 749 (m), 723 (m), 679 (s) **;** mp = 67- 68 ^{o}C.

1.5.2.7 N-(3-bromopropyl)-3-iodo-4-methyl-N-tosylbenzamide (1.4.1.16)

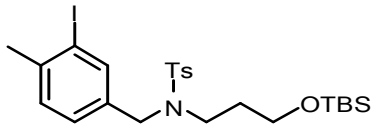


To a magnetically-stirred solution of **1.4.1.15** (2 g, 3.4 mmol) in DCM (102 ml) under nitrogen, was added Br_2 • PPh_3 (1.724 g, 4.08 mmol). The reaction was stirred over night at room temperature, and then concentrated and washed with DCM and water. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification proceeded by flash chromatography on silica gel (ethyl acetate/hexanes, 1:9 v/v) to afford **1.4.1.16** (1.6233 g, 89%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.76 (d, 1H, J = 2), 7.66 (d, 2H, J = 8), 7.43 (dd, 1H, J_1 = 9.6, J_2 = 1.8), 7.30 (d, 2H, J = 8), 7.26 (d, 1H, J = 8), 3.92 (t, 2H, J = 7), 3.39 (t, 2H, J = 6), 2.46 (s, 3H), 2.45 (s, 3H), 2.27 (m, 2H) **;** ^{13}C NMR (100MHz, $CDCl_3$) δ = 169.9, 145.8, 145.4, 138.4, 135.8, 134.4, 130.0, 129.4, 128.4, 128.37, 100.4, 46.6, 32.4, 30.0, 28.5, 21.9**;** HRMS (ESI) for $C_{18}H_{19}BrINO_3S$ m/z calculated 534.93, found 535.9386 $[M+H]^+$; IR (neat) υ (cm^{-1}) 2956 (w),

1675 (s), 1596 (w), 1450 (m), 1353 (s), 1336 (s), 1291 (m), 1258 (m), 1161 (s), 1147 (m), 1087 (m), 1078 (m), 1055 (m), 1030 (m), 886 (w), 837 (w), 816 (m), 748 (m), 718 (s), 694 (s), 663 (s)**;** mp = 65-66 ^{o}C.

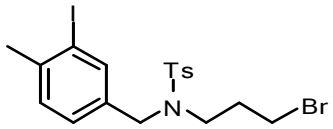
1.5.2.8 N-(3-(tert-butyldimethylsilyloxy)propyl)-N-(3-iodo-4-methylbenzyl)-4-methylbenzenesulfonamide (1.4.1.10)



A magnetically-stirred solution of 3-iodo-4-methylbenzyl alcohol **1.4.1.6** (1.8617 g, 7.96 mmol) in DCM (80 ml), under nitrogen was cooled to 0^{o} C. To the cooled mixture was added first Et_3N (1.22 ml, 8.75 mmol) and then methanesulfonyl chloride (0.68 ml, 8.75 mmol). The solution was stirred for one hour, concentrated and washed with DCM and water. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to yield a transparent, colourless oil, which was used immediately. To this oil was added **1.4.1.5** (2.4845 g, 7.23 mmol) in CH_3CN (110 ml) under nitrogen, along with K_2CO_3 (2.9986 g, 21.7 mmol). The solution was stirred at reflux (75-80^{o} C) overnight, and then washed with DCM and water. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification proceeded by flash chromatography on silica gel (ethyl acetate/pentanes, 1:20 v/v) to afford **1.4.1.10** (2.9075 g, 77%) as a brown oil.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.71 (d, 2H, J = 8), 7.58 (d, 1H, J = 1.4), 7.30 (d, 2H, J = 8), 7.18 (dd, 1H, J_1 = 7.8, J_2 = 1.7), 7.15 (d, 1H, J = 8), 4.25 (s, 2H), 3.45 (t, 2H, J = 6), 3.18 (t, 2H, J = 6.6), 2.44 (s, 3H), 2.39 (s, 3H), 1.57 (m, 2H), 0.82 (s, 9H), -0.04 (s, 6H)**;** ^{13}C NMR (100MHz, $CDCl_3$) δ = 143.3, 140.8, 138.4, 137.0, 135.9, 129.7, 129.68, 128.2, 127.1, 101.1, 60.3, 50.8, 45.3, 31.3, 27.7, 25.8, 21.5, 18.2, -5.4; HRMS (EI) for $C_{24}H_{36}INO_3SSi$ m/z calculated 573.12, found 574.1302 $[M+H]^{+}$**;** IR (neat) υ (cm^{-1}) 2953 (w), 2929 (w), 2857 (w), 1461 (w), 1334 (m), 1250 (m), 1159 (s), 1104 (s), 1090 (s), 1030 (m), 963 (m), 933 (m), 834 (s), 812 (m), 774 (m), 751 (s), 654 (s).

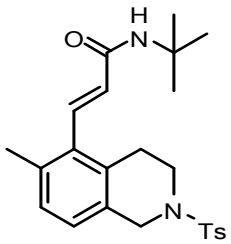
1.5.2.9 N-(3-bromopropyl)-N-(3-iodo-4-methylbenzyl)-4-methylbenzenesulfonamide (1.4.1.11)



To a magnetically-stirred solution of **1.4.1.10** (2 g, 3.49 mmol) in DCM (105 ml) under nitrogen, was added $Br_2 \bullet PPh_3$ (1.766 g, 4.18 mmol). The reaction was stirred overnight at room temperature, and then concentrated and washed with DCM and water. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification proceeded by flash chromatography on silica gel (ethyl acetate/pentanes, 1:10 v/v) to afford **1.4.1.11** (1.4849 g, 82%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.71 (d, 2H, J = 8), 7.57 (s, 1H), 7.33 (d, 2H, J = 8), 7.17 (s, 2H), 4.23 (s, 2H), 3.25 (t, 2H, J = 6.3), 3.21 (t, 2H, J = 7.3), 2.45 (s, 3H), 2.40 (s, 3H), 1.92 (m, 2H)**;** ^{13}C NMR (100MHz, $CDCl_3$) δ = 143.6, 141.2, 138.6, 136.4, 135.4, 129.9, 129.8, 128.3, 127.2, 101.2, 51.6, 47.0, 31.6, 30.3, 27.7, 21.6**;** HRMS (ESI) for $C_{17}H_{19}BrINO_2S$ m/z calculated 520.95, found 521.9593 $[M+H]^+$; IR (neat) υ (cm^{-1}) 2914 (w), 2851 (w), 1599 (w), 1561 (w), 1488 (w), 1436 (m), 1334 (s), 1304 (m), 1222 (m), 1158 (s), 1093 (m), 1035 (m), 923 (m), 817 (m), 768 (s), 665 (m), 656 (s)**;** mp = 101-103 ^oC.

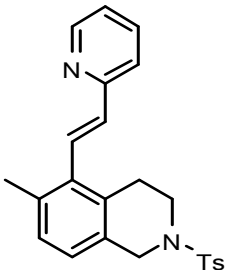
1.5.2.10 (*E*)-N-tert-butyl-3-(6-methyl-2-tosyl-1,2,3,4-tetrahydroisoquinolin-5-yl)acrylamide (1.4.2.1)



Synthesized according to the general procedure using **1.4.1.9** (102 mg, 0.2 mmol) and tert-butyl acrylamide (50.9 mg, 0.4 mmol). Purified by flash chromatography on silica gel (ethyl acetate/pentanes, 1:4 v/v) to afford **1.4.2.1** (76 mg, 87%) as a pale yellow foam.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.69 (d, 2H, J = 8), 7.54 (d, 1H, J = 16), 7.31 (d, 2H, J = 8), 6.98 (d, 1H, J = 8), 6.84, (d, 1H, J = 8), 5.95 (d, 1H, J = 8), 5.88 (s, 1H), 4.17 (s, 2H), 3.23 (t, 2H, J = 6), 2.85 (t, 2H, J = 6), 2.41 (s, 3H), 2.24 (s, 3H), 1.43 (s,9H)**;** ^{13}C NMR (100MHz, $CDCl_3$) δ = 164.9, 144.0, 137.5, 135.3, 135.0, 133.1, 131.7, 130.0, 130.7, 128.7, 128.6, 128.0, 126.1, 51.8, 47.9, 44.1, 29.1, 28.4, 21.7, 20.9**;** HRMS (EI) for $C_{24}H_{30}N_2O_3S$ m/z calculated 426.20, found 425.1899 **;** IR (neat) υ (cm^{-1}) 3296 (w), 2972 (w), 1661 (m), 1625 (m), 1539 (m), 1455 (m), 1335 (m), 1224 (m), 1160 (s), 1098 (m), 959 (m), 813 (m), 750 (m), 656 (s).

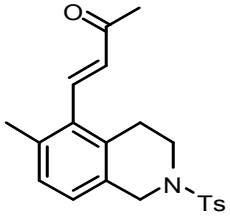
1.5.2.11 (*E*)-6-methyl-5-(2-(pyridin-2-yl)vinyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline (1.4.2.2)



Synthesized according to the general procedure using **1.4.1.9** (102 mg, 0.2 mmol) and 2-vinylpyridine (36μL, 0.4mmol). Purified by flash chromatography on silica gel (ethyl acetate/pentanes, 1:4 v/v) to afford **1.4.2.2** (40,3 mg, 45%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ = 8.61 (d, 1H, J = 4), 7.72 (d, 2H, J = 8), 7.66 (dt, 1H, J_1 = 8.5, J_2 = 1.8), 7.57 (d, 1H, J = 16), 7.31 (d, 3H, J = 8), 7.17 (dd, 1H, J_1 = 7.2, J_2 = 5), 7.05 (d, 1H, J = 8), 6.89 (d, 1H, J = 8), 6.61 (d, 1H, J = 16), 4.24 (s, 2H), 3.29 (t, 2H, J = 6), 2.96 (t, 2H, J = 6), 2.42 (s, 3H), 2.34 (s,3H)**;** ^{13}C NMR (100MHz, $CDCl_3$) δ = 155.4, 149.9, 143.9, 136.9, 136.5, 135.1, 134.3, 133.5, 131.8, 130.2, 129.9, 129.7, 128.5, 128.0, 125.6, 122.6, 122.3, 47.9, 44.1, 28.3, 21.7, 21.0**;** HRMS (EI) for $C_{24}H_{24}N_2O_2S$ m/z calculated 404.16, found 404.1559 **;** IR (neat) υ (cm^{-1}) 2916 (w), 2849 (w), 1597 (w), 1506 (w), 1459 (w), 1346 (m), 1334 (m), 1308 (m), 1163 (s), 1092 (m), 1030 (m), 946 (m) 902 (w), 816 (s), 748 (s), 659 (s) **;** mp = 164-165.5 ^{o}C.

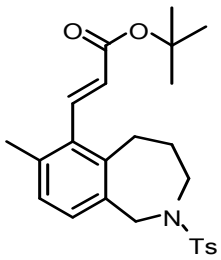
1.5.2.12 (*E*)-4-(6-methyl-2-tosyl-1,2,3,4-tetrahydroisoquinolin-5-yl)but-3-en-2-one (1.4.2.3)



Synthesized according to the general procedure using **1.4.1.9** (102 mg, 0.2 mmol) and methyl vinyl ketone (32.4µL, 0.4mmol). Purified by flash chromatography on silica gel (ethyl acetate/pentanes, 1:4 v/v) to afford **1.4.2.3** (46,9 mg, 63%) as a brown foam.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.71 (d, 2H, J = 8), 7.54 (d, 1H, J = 17), 7.32 (d, 2H, J = 8), 7.05 (d, 1H, J = 8), 6.93 (d, 1H, J = 8), 6.26 (d, 1H, J = 16), 4.22 (s, 2H), 3.32 (t, 2H, J = 6), 2.86 (t, 2H, J = 6), 2.42 (s, 3H), 2.38 (s, 3H), 2.28 (s, 3H)**;** ^{13}C NMR (100MHz, $CDCl_3$) δ = 198.1, 144.0, 140.9, 135.2, 134.2, 133.8, 133.3, 131.8, 130.1, 129.9, 128.9, 128.0, 126.9, 47.9, 43.9, 28.1, 28.0, 21.7, 20.9**;** HRMS (EI) for $C_{21}H_{23}NO_3S$ m/z calculated 369.14, found 369.1399**;** IR (neat) υ (cm^{-1}) 2926 (w), 1668 (m), 1614 (m) 1598 (m), 1461 (m), 1345 (m), 1332 (m), 1254 (m), 1160 (s), 1098 (m), 959 (m), 814 (m), 755 (m), 658 (s).

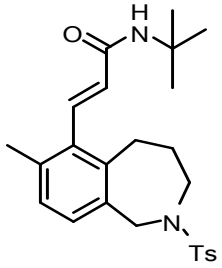
1.5.2.13 (*E*)-tert-butyl-3-(7-methyl-2-tosyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-6-yl)acrylate (1.4.2.8)



Synthesized according to the general procedure (GP2) using **1.4.2.11** (104.4 mg, 0.2 mmol) and tert-butyl acrylate (58 µl, 0.4mmol). Purified by flash chromatography on silica gel (ethyl acetate/pentanes, 1:12 v/v) to afford **1.4.2.8** (46,9 mg, 47%) as a light yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.63 (d, 1H, J = 16), 7.48 (d, 2H, J = 8), 7.17 (dd, 2H, J_1 = 9, J_2 = 0.6), 7.16 (d, 1H, J =7.5), 7.02 (d, 1H, J = 8), 5.64 (d, 1H, J = 16), 4.42 (s, 2H), 3.52 (t, 2H, J = 5.4), 2.83 (t,2H, J = 5.6) 2.38 (s, 3H), 2.26 (s, 3H), 1.59 (m, 2H), 1.53 (s, 9H) **;** ^{13}C NMR (100MHz, $CDCl_3$) δ = 165.8, 143.2, 143.0, 139.4, 137.0, 136.3, 135.6, 135.0, 129.6, 129.3, 128.1, 127.4, 126.9, 81.0, 53.3, 51.4, 30.0, 28.4, 27.0, 21.6, 21.2**;** HRMS (ESI) for $C_{21}H_{23}NO_3S$ m/z calculated 441.20, found, 442.2046 $[M+H]^+$**;** IR (neat) υ (cm^{-1}) 2974 (w), 1707 (m), 1640 (w), 1457 (w), 1334 (m), 1313 (m), 1287 (m), 1149 (s), 1092 (m), 730 (m), 656 (m).

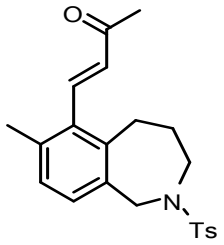
1.5.2.14 (*E*)-N-tert-butyl-3-(7-methyl-2-tosyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-6-yl)acrylamide (1.4.2.9)



Synthesized according to the general procedure (GP2) using **1.4.2.11** (104.4 mg, 0.2 mmol) and tert-butyl acrylamide (50.9 mg, 0.4 mmol). Purified by flash chromatography on silica gel (ethyl acetate/pentanes, 1:1 v/v) to afford **1.4.2.9** (33.6 mg, 38%) as a pale beige foam.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.60 (d, 1H, J = 16), 7.53 (d, 2H, J = 8), 7.19 (d, 2H, J = 8), 7.13 (d, 1H, J = 8), 7.01 (d, 1H, J = 8), 5.67 (d, 1H, J =16), 5.43 (s, 1H), 4.37 (s, 2H), 3.48 (t, 2H, J = 5.2), 2.84 (t, 2H, J = 5.4), 2.39 (s, 3H), 2.25 (s, 3H), 1.61 (m, 2H), 1.43 (s, 9H)**;** ^{13}C NMR (100MHz, $CDCl_3$) δ = 165.8, 143.2, 143.0, 142.96, 139.4, 137.0, 136.3, 135.6, 135.0, 129.6, 129.3, 128.1, 127.4, 126.92, 126.91, 81.0, 53.3, 51.4, 30.0, 28.4, 27.0, 21.6, 21.2**;** HRMS (ESI) for $C_{25}H_{32}N_2O_3S$ m/z calculated 440.21, found, 441.2206 $[M+H]^+$**;** IR (neat) υ (cm^{-1}) 3288 (w), 2923 (w), 1662 (m), 1626 (m), 1539 (m), 1455 (m), 1329 (m), 1154 (s), 1093 (m), 918 (m), 814 (m), 728 (s), 656 (s).

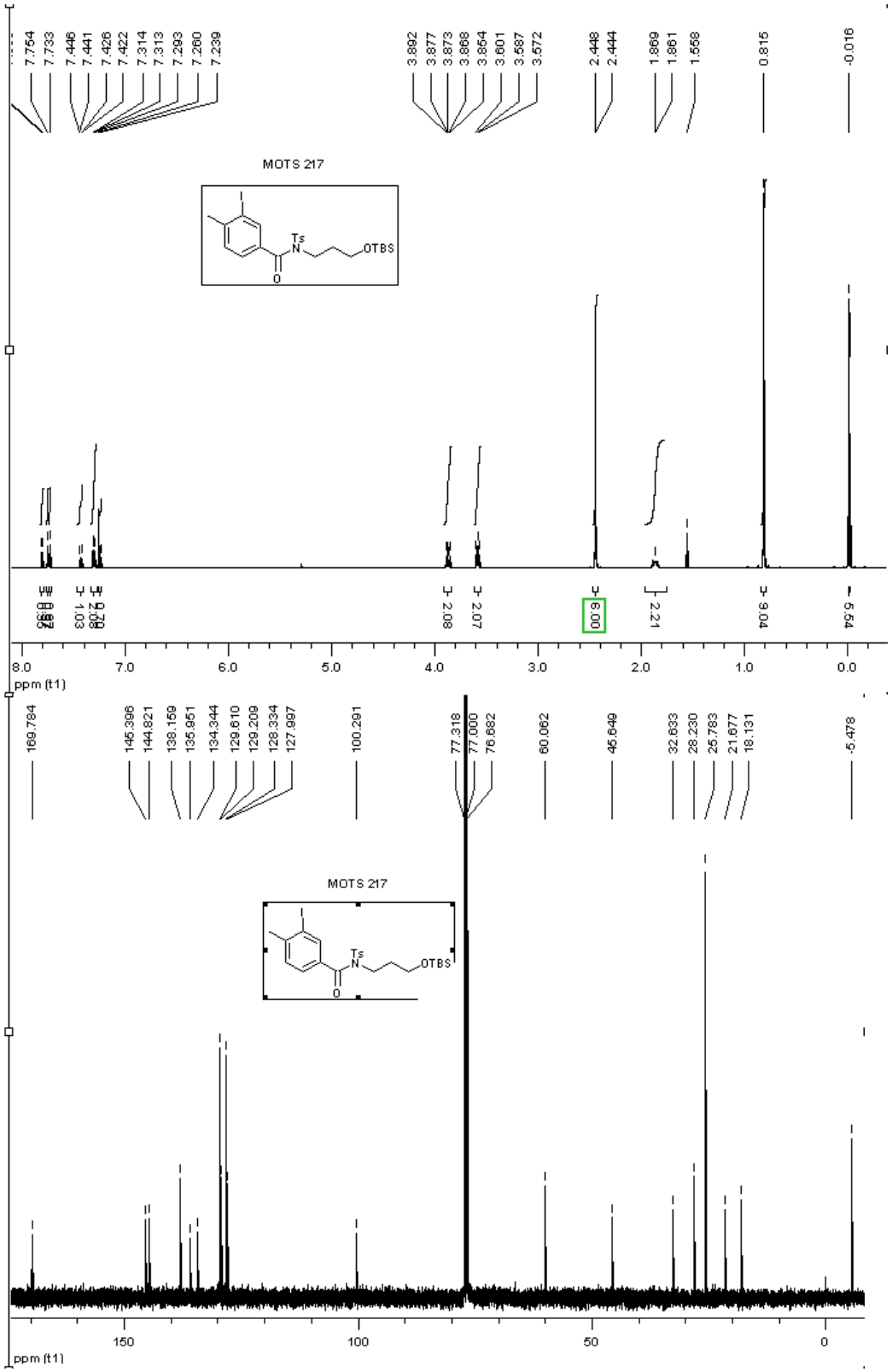
1.5.2.15 (*E*)-4-(7-methyl-2-tosyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-6-yl)but-3-en-2-one (1.4.2.10)

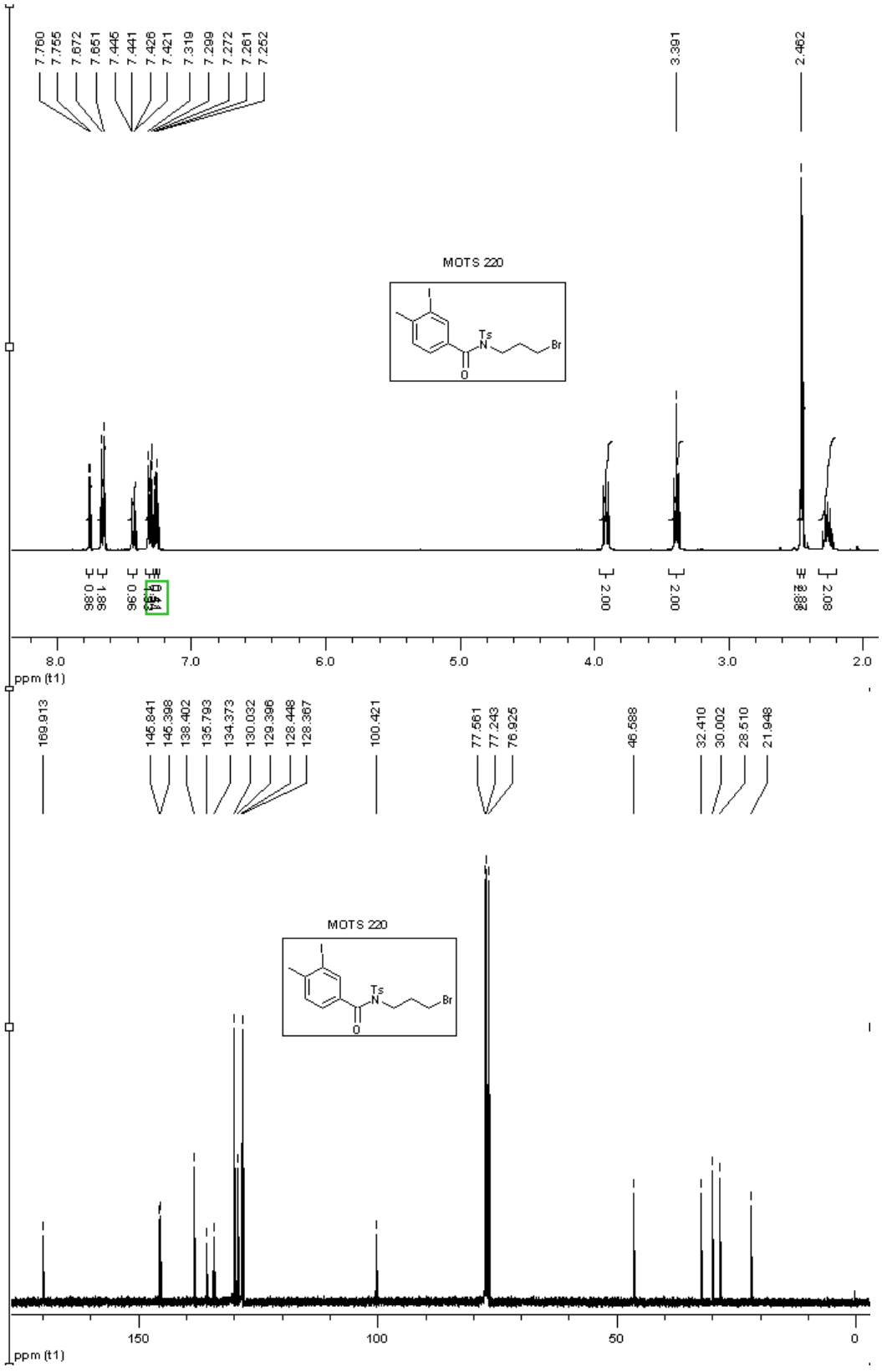


Synthesized according to the general procedure (GP2) using **1.4.2.11** (104.4 mg, 0.2 mmol) and methyl vinyl ketone (32.4 µl, 0.4 mmol). Purified by flash chromatography on silica gel (ethyl acetate/pentanes, 1:6 v/v) to afford **1.4.2.10** (45.3 mg, 59%) as a light brown oil.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.58 (d, 1H, J = 16), 7.51 (d, 2H, J = 8), 7.18 (d, 3H, J = 8), 7.04 (d, 1H, J = 8), 6.00 (d, 1H, J = 16), 4.41 (s, 2H), 3.52 (t, 2H, J = 5.3), 2.83 (t, 2H, J = 5.6), 2.39 (s, 3H), 2.37 (s, 3H), 2.26 (s, 3H), 1.61 (m, 2H)**;** ^{13}C NMR (100MHz, $CDCl_3$) δ = 198.0, 143.3, 142.7, 139.4, 136.9, 136.2, 135.9, 134.8, 134.2, 129.7, 129.6, 128.2, 127.4, 53.3, 51.5, 30.0, 27.8, 27.2, 21.7, 21.2**;** HRMS (ESI) for $C_{22}H_{25}NO_3S$ m/z calculated 383.16, found, 384.1627 $[M+H]^+$**;** IR (neat) υ (cm^{-1}) 2923 (w), 1670 (m), 1615 (m), 1457 (m), 1330 (m), 1253 (m), 1153 (s), 1092 (m), 984 (m), 936 (m), 814 (m), 723 (s), 655 (s).

1.5.3 ^{1}H NMR and ^{13}C NMR Spectra

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7.446
7.441
7.426
7.421
7.319
7.299
7.272
7.261
7.252
3.391
2.462
MOTS 220
I
Ts
N
Br
O
1.86
0.96
2.00
2.00
2.88
2.08
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t1)
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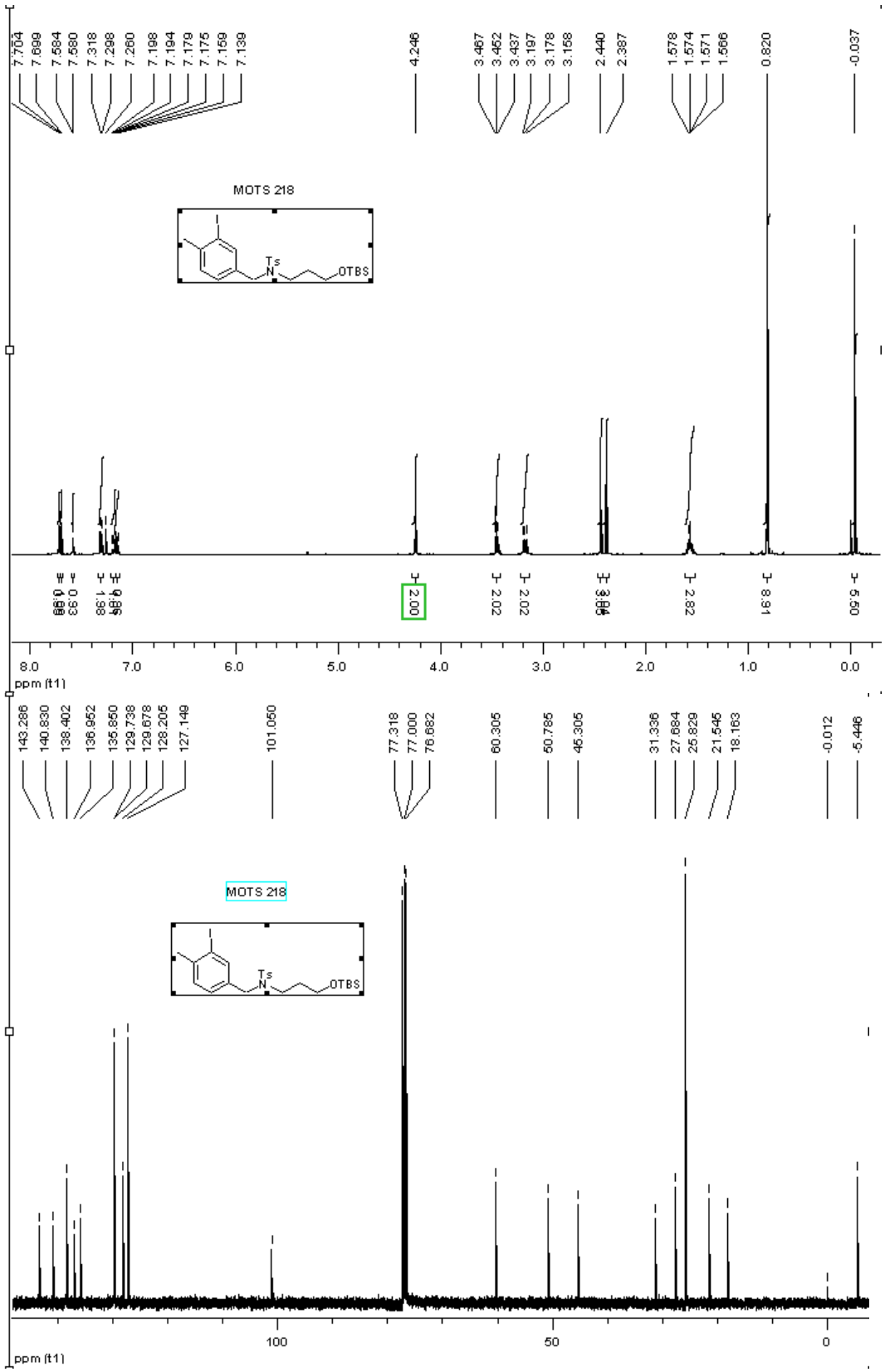
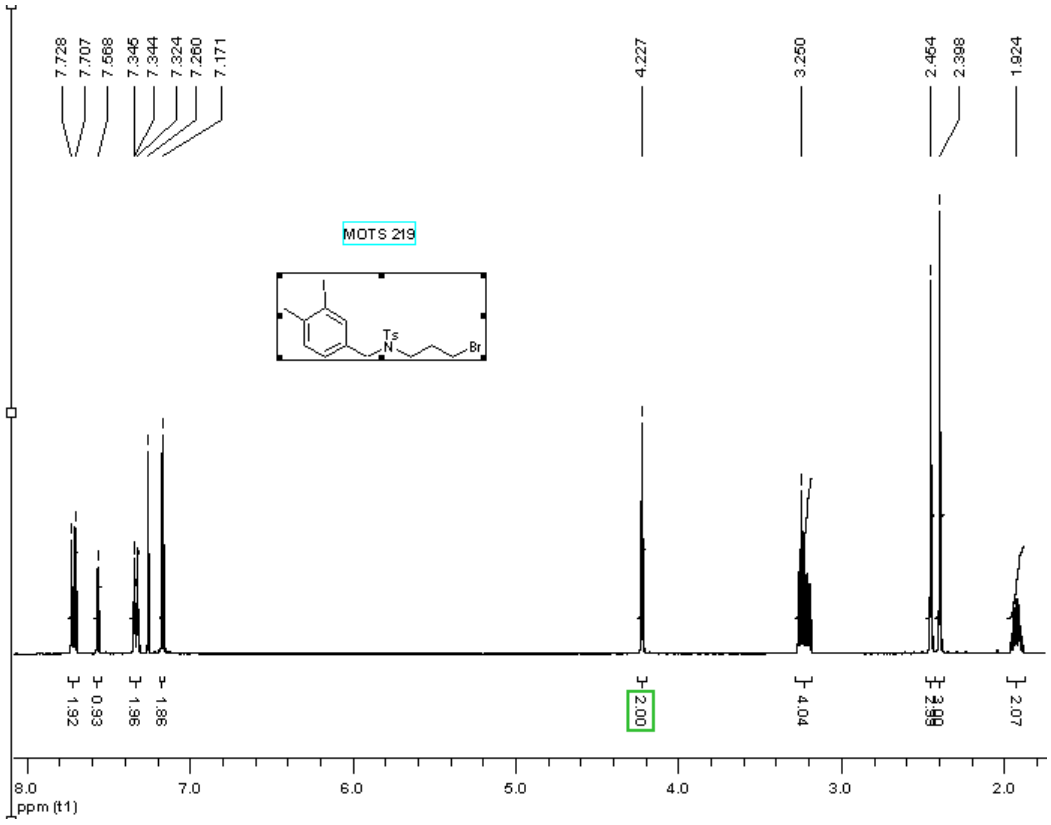
145.841
145.398
138.402
135.793
134.373
130.032
129.396
128.448
128.367
100.421
77.561
77.243
76.925
46.588
32.410
30.002
28.510
21.948
MOTS 220
150
100
50
0
ppm (t1)


MOTS 218
Ts
N
OTBS
ppm (t1)
MOTS 218
Ts
N
OTBS
ppm (t1)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7.568
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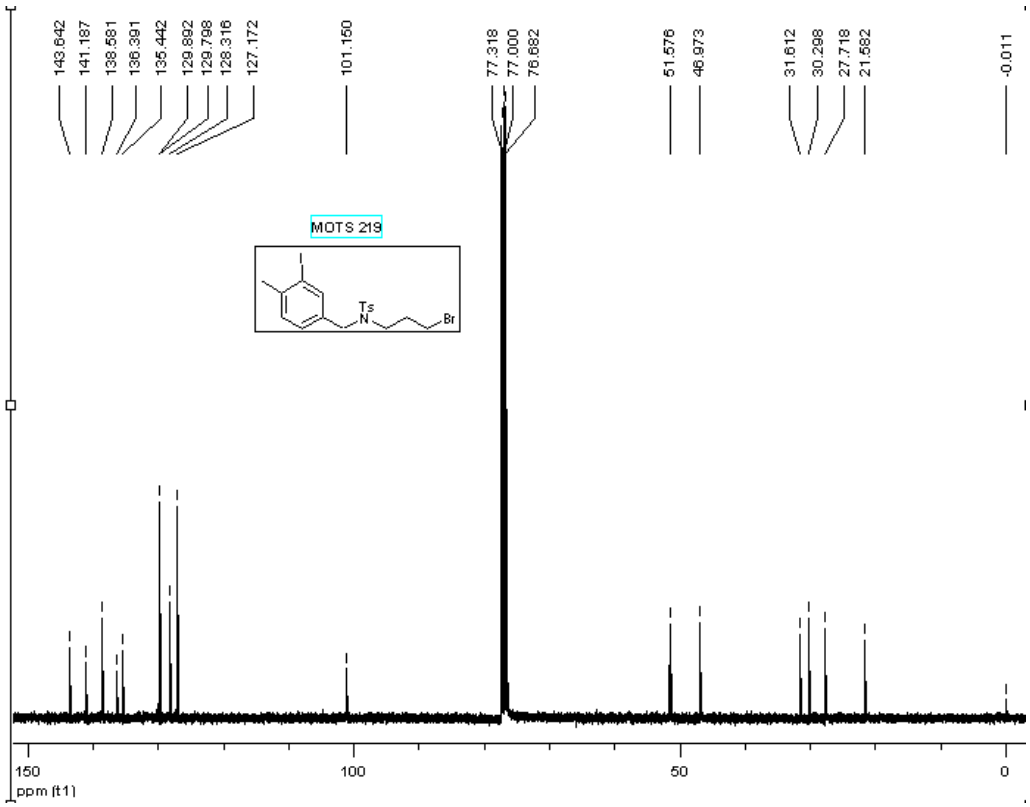
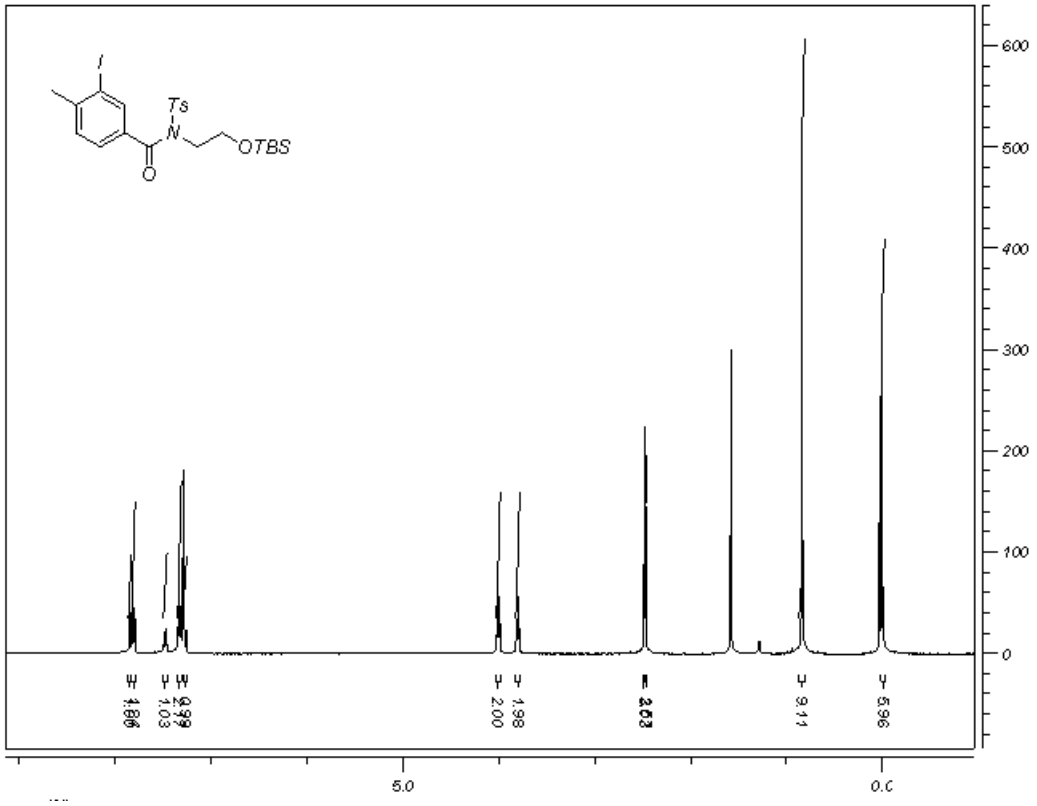
7.344
7.324
7.260
7.171
4.227
3.250
2.454
2.398
1.924
MOTS 219
Ts
N
Br
1.92
0.93
1.36
1.86
2.00
4.04
2.07
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t1)


143.642
141.187
138.581
136.391
135.442
129.892
129.798
128.316
127.172
101.150
77.318
77.000
76.682
51.576
46.973
31.612
30.298
27.718
21.582
-0.011
MOTS 219
Ts
N
Br
150
100
50
0
ppm (t1)


I
Ts
N
OTBS
O
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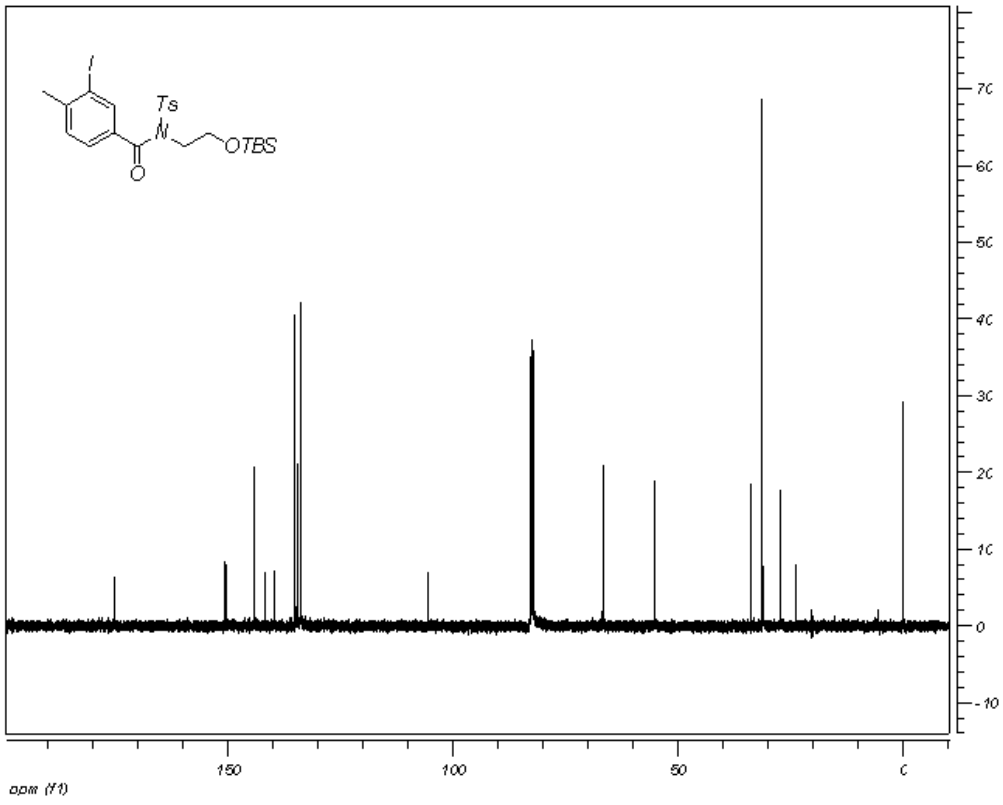
500
400
300
200
100
0
1.00
1.03
2.00
1.98
9.11
5.96
5.0
0.0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Ts
N
OTBS
O
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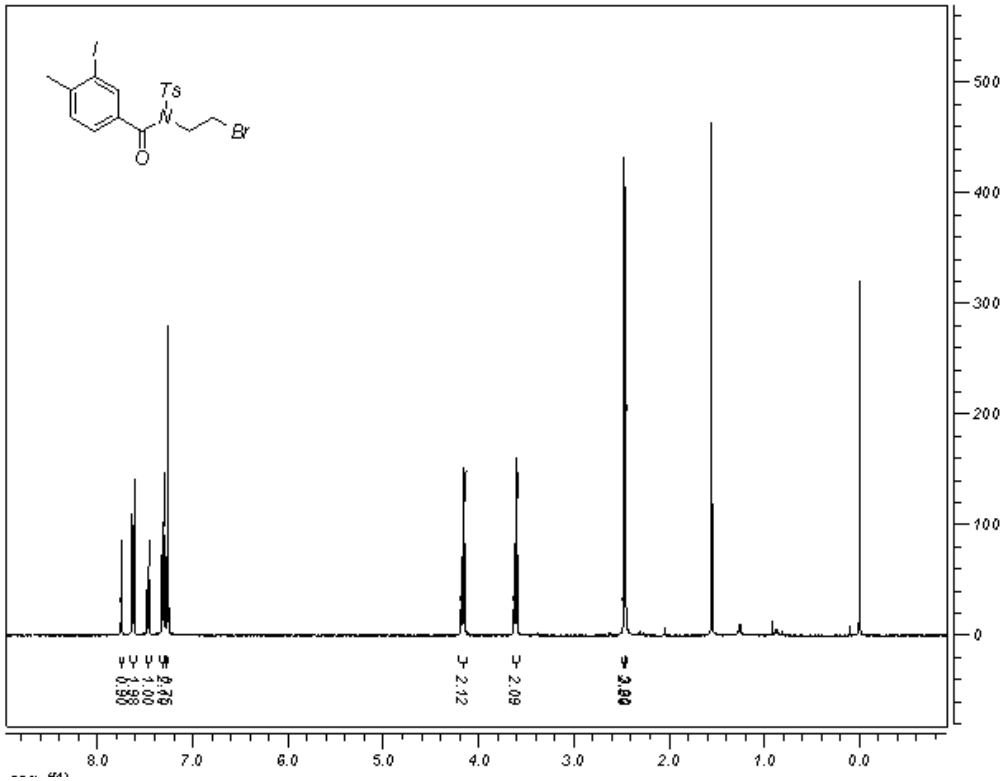
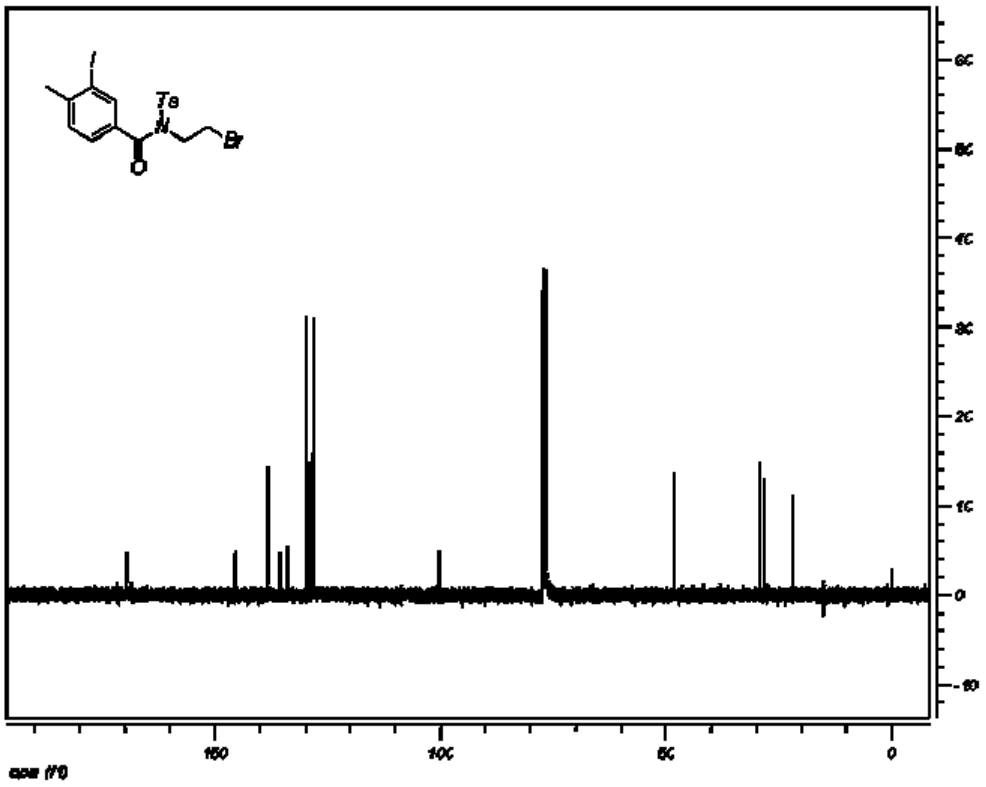
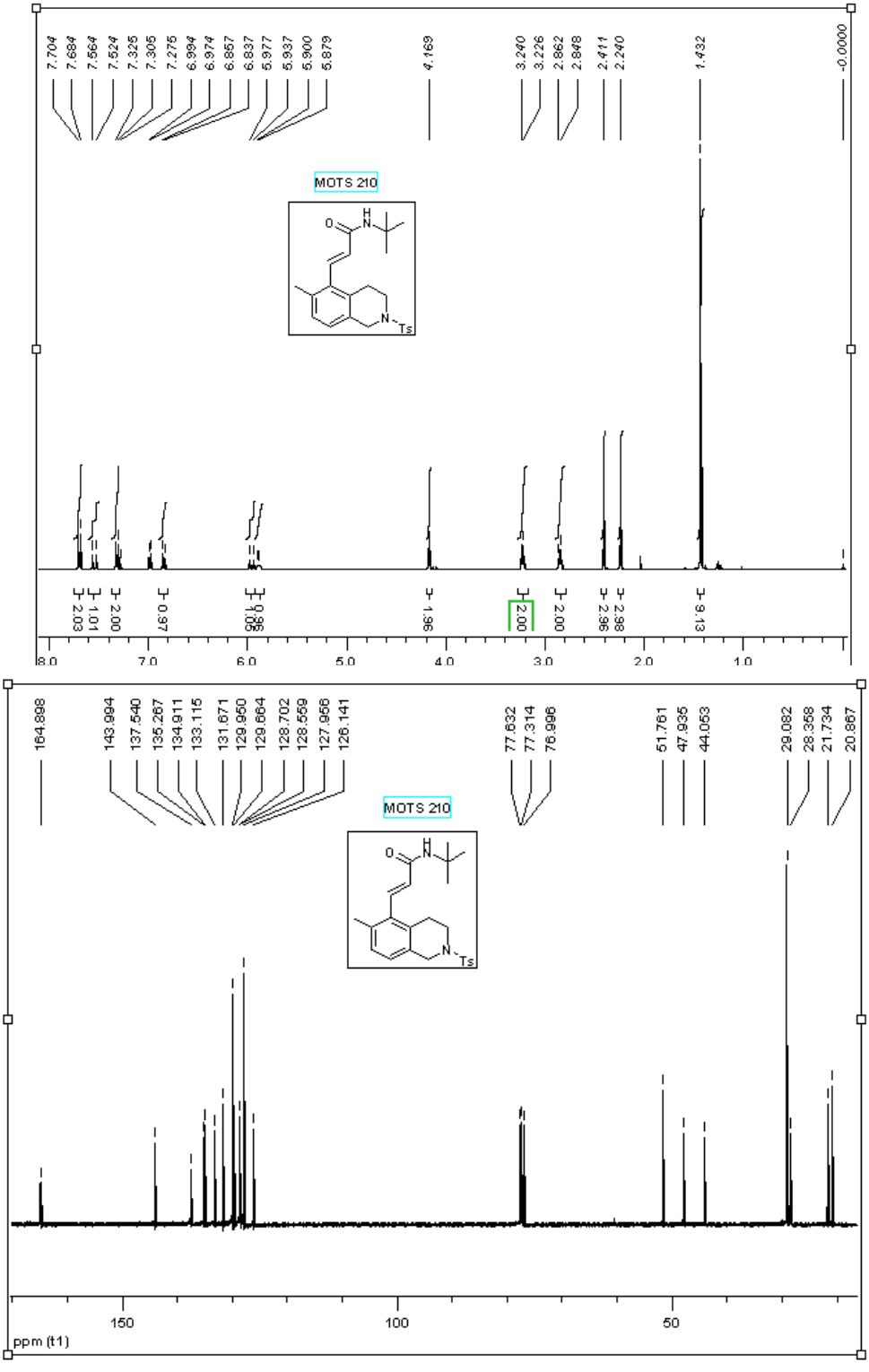
60
50
40
30
20
10
0
-10
150
100
50
0
ppm (f1)


I
Ts
N
Br
O
500
400
300
200
100
0
0.90
1.00
0.79
2.12
2.09
3.80
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


I
Ts
N
Br
O
150
100
50
0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7.305
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6.994
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6.857
6.837
5.977
5.937
5.900
5.879
4.169
3.240
3.226
2.862
2.848
2.411
2.240
1.432
-0.0000
MOTS 210
O
H
N
N
Ts
2.03
1.01
2.00
0.87
0.98
1.96
2.00
2.00
2.96
2.88
9.13
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
164.898
143.994
137.540
135.267
134.911
133.115
131.671
129.950
129.664
128.702
128.559
127.956
126.141
77.632
77.314
76.996
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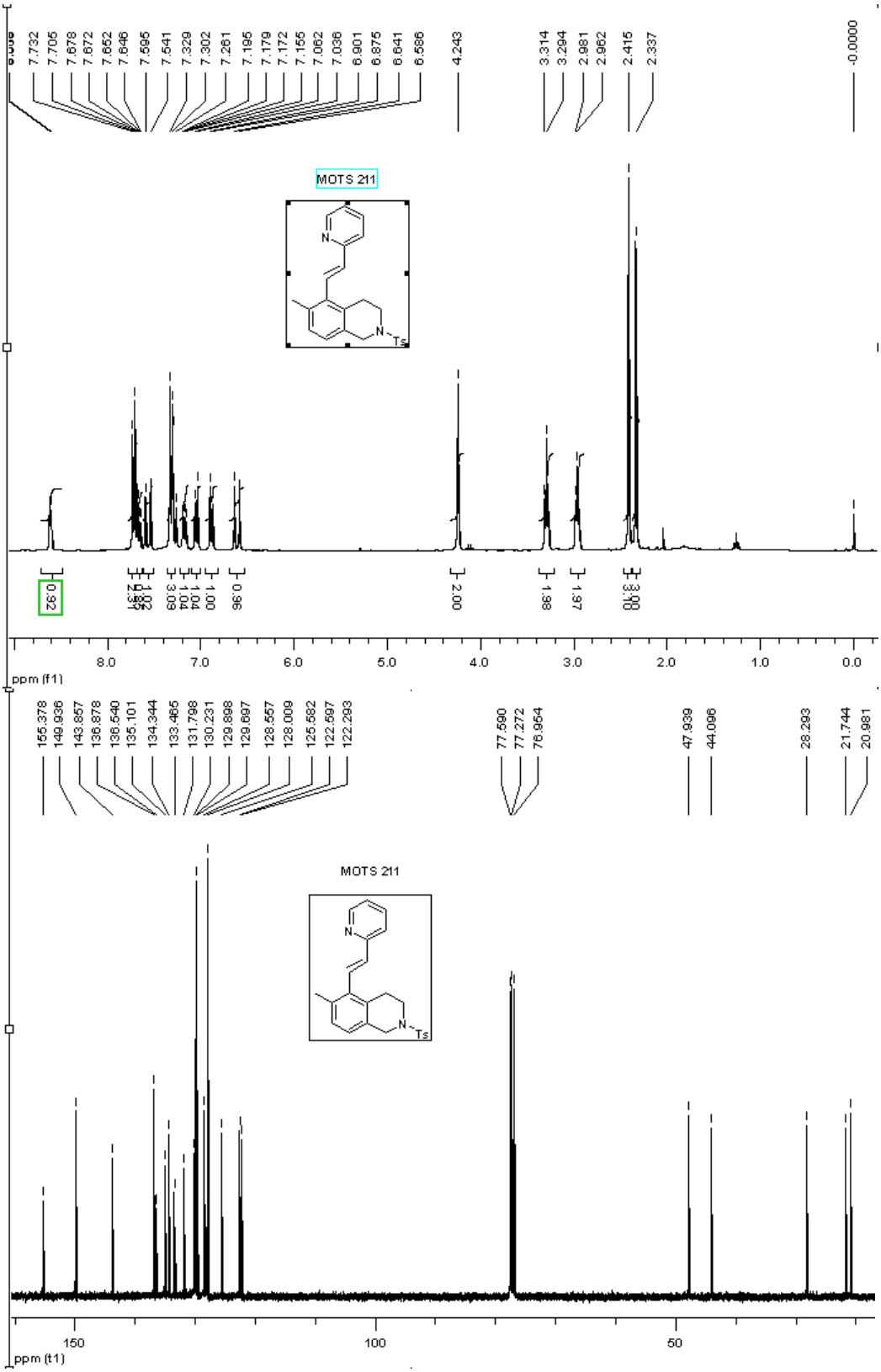
150
100
50
ppm (t1)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7.646
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7.541
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7.261
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7.179
7.172
7.155
7.062
7.036
6.901
6.875
6.641
6.586
4.243
3.314
3.294
2.981
2.962
2.415
2.337
-0.0000
MOTS 211
N
N
Ts
0.92
3.09
1.04
1.04
1.00
0.96
2.00
1.38
1.87
3.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)
155.378
149.936
143.857
136.878
136.540
135.101
134.344
133.465
131.798
130.231
129.898
129.697
128.557
128.009
125.582
122.597
122.293
77.590
77.272
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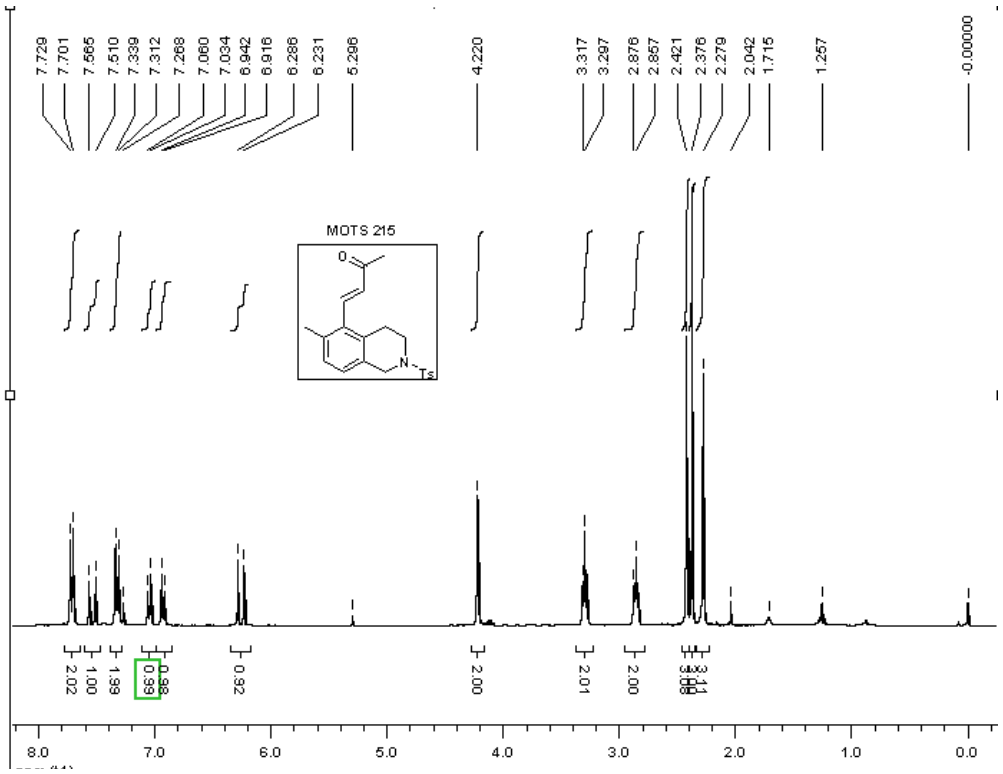
N
N
Ts
150
100
50
ppm (t1)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7.060
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6.916
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6.231
5.296
4.220
3.317
3.297
2.876
2.857
2.421
2.376
2.279
2.042
1.715
1.257
-0.00000
MOTS 215
O
N
Ts
2.02
1.00
1.89
0.89
0.98
0.92
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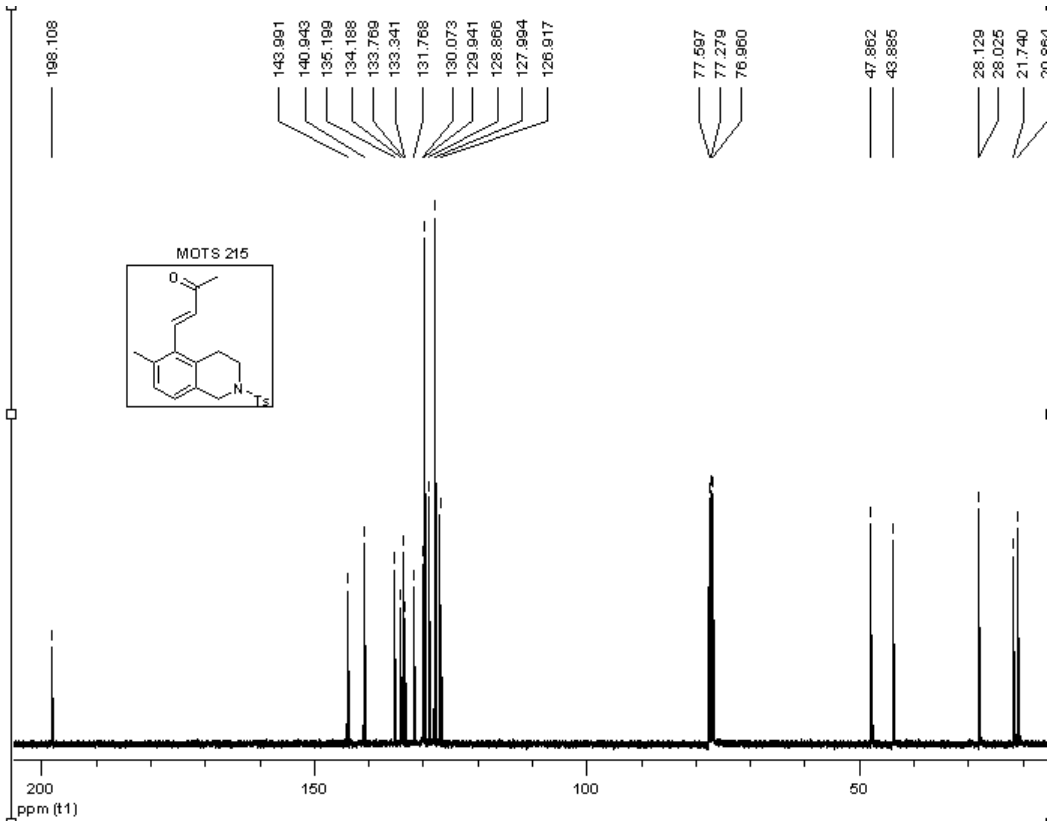
2.01
2.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0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135.199
134.188
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133.341
131.768
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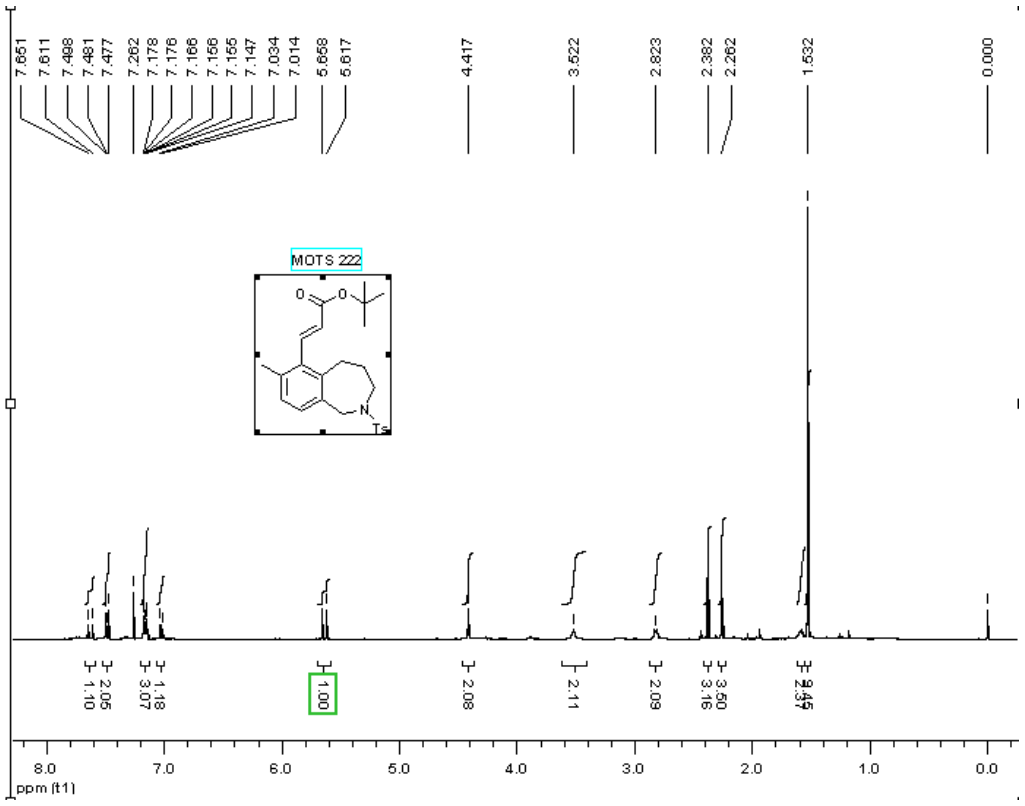
129.941
128.866
127.994
126.917
77.597
77.279
76.960
47.862
43.885
28.129
28.025
21.740
MOTS 215
O
N
Ts
200
150
100
50
ppm (t1)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7.034
7.014
5.658
5.617
4.417
3.522
2.823
2.382
2.262
1.532
0.000
MOTS 222
O
O
N
Ts
1.10
2.06
3.07
1.18
1.00
2.08
2.11
2.09
3.16
3.09
9.45
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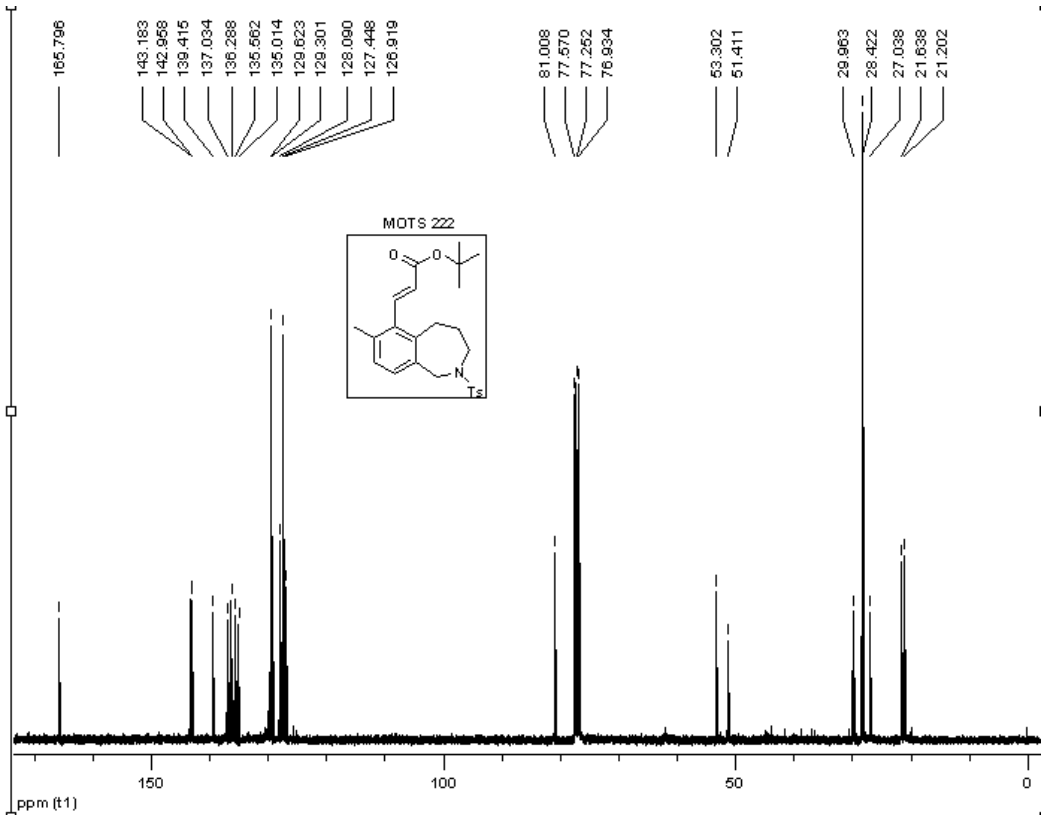
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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135.014
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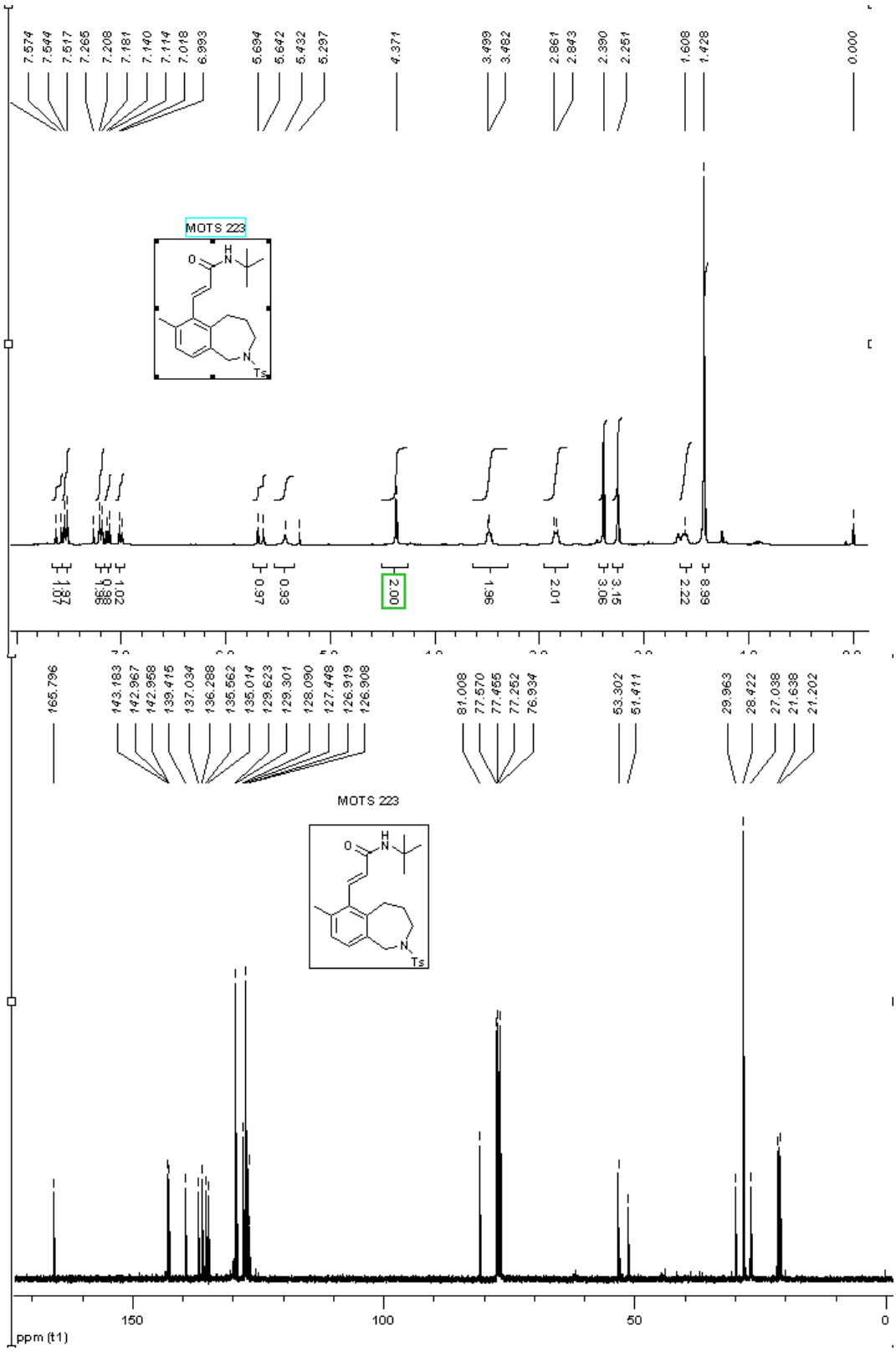
129.301
128.090
127.448
126.919
81.008
77.570
77.252
76.934
53.302
51.411
29.963
28.422
27.038
21.638
21.202
MOTS 222
O
O
N
Ts
150
100
50
0
ppm (t1)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7.114
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6.993
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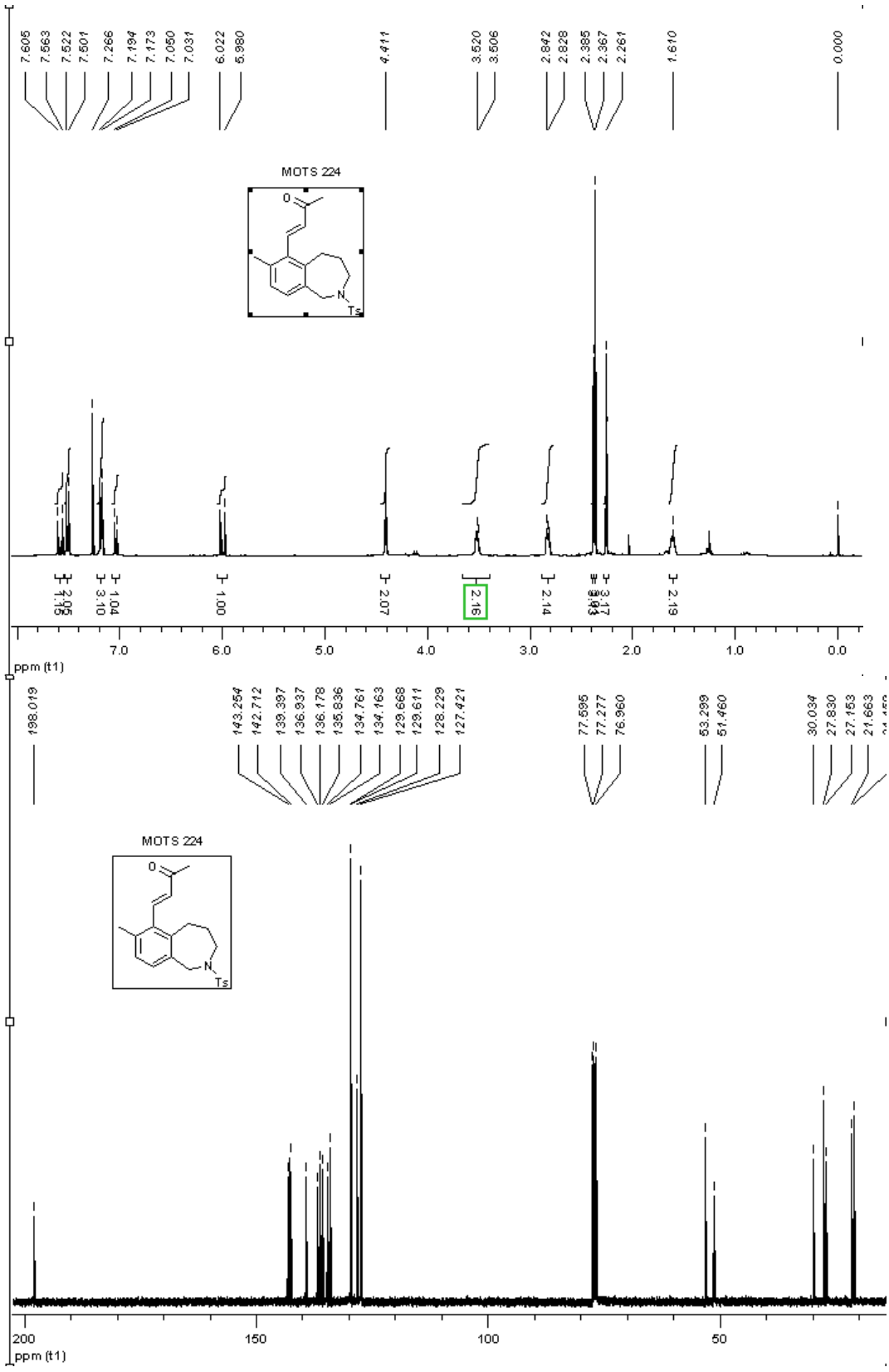
5.297
4.371
3.499
3.482
2.861
2.843
2.390
2.251
1.608
1.428
0.000
MOTS 223
Ts
1.87
0.98
1.02
0.97
0.93
2.00
1.96
2.01
3.06
3.15
2.22
8.89
165.796
143.183
142.967
142.958
139.415
137.034
136.288
135.562
135.014
129.623
129.301
128.090
127.448
126.919
126.908
81.008
77.570
77.455
77.252
76.934
53.302
51.411
29.963
28.422
27.038
21.638
21.202
MOTS 223
Ts
150
100
50
0
ppm (t1)


7.605
7.563
7.522
7.501
7.266
7.194
7.173
7.050
7.031
6.022
5.980
4.411
3.520
3.506
2.842
2.828
2.385
2.367
2.261
1.610
0.000
MOTS 224
O
N
Ts
2.05
1.15
3.10
1.04
1.00
2.07
2.16
2.14
3.17
2.19
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)
198.019
143.254
142.712
139.397
136.937
136.178
135.836
134.761
134.163
129.668
129.611
128.229
127.421
77.595
77.277
76.960
53.299
51.460
30.034
27.830
27.153
21.663
MOTS 224
O
N
Ts
200
150
100
50
ppm (t1)

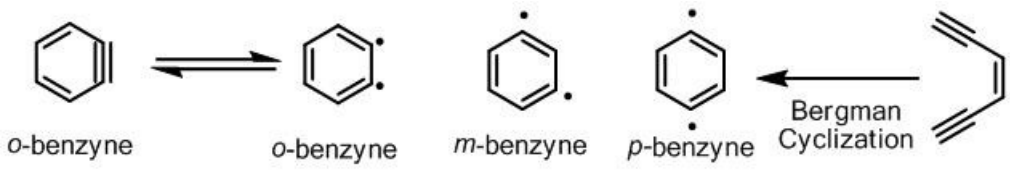
Chapter 2

2 Diastereoselective Aryne Diels-Alder Reactions

2.1 Introduction

2.1.1 Arynes

Ortho-Benzyne was first reported by Roberts[26] in 1953. Benzyne can exist under three different forms, depending on its method of preparation: *para*-benzyne, *meta*-benzyne and *ortho*-benzyne. In this thesis, benzyne will refer to *ortho*-benzyne, since it is the species showing both diradical and fully valent character along with the special reactivity described thereafter. *Para*-benzyne, a product of the Bergman cyclization,[27] and *meta*-benzyne are diradicalar species.



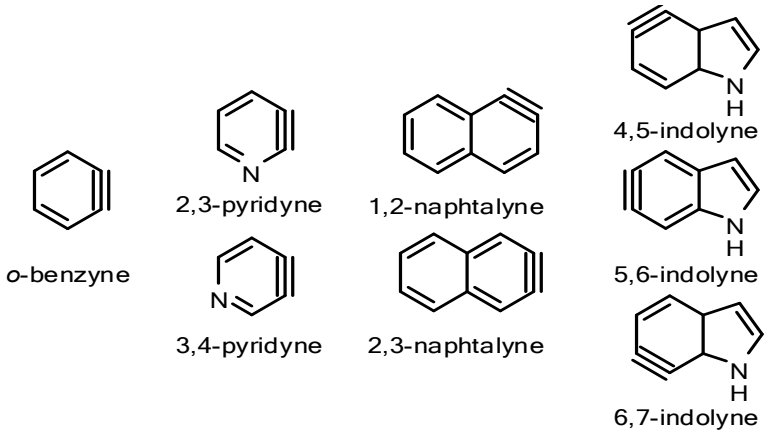
Scheme 28. Three forms of benzyne: *ortho, meta* and *para*-benzyne

(26) J. D. Roberts, H. E. Simmons, L. A. Carlsmith and C. W. Vaughan, *J. Am. Chem. Soc.* **1953**, *75*, 3290.
(27) a) R. R. Jones and R. G. Bergman, *J. Am. Chem. Soc.* **1972**, *94*, 660. R. G. Bergman, *Acc. Chem. Res.* **1973**, *6*, 25.

The enthalpy of formation of benzene is 20 kcal/mol and the enthalpy of formation of benzyne was experimentally evaluated to be 100 kcal/mol.[28] The difference of enthalpy of formation between an alkyne and an alkene is usually ~37 kcal/mol, so benzyne can be viewed as having ~43 kcal/mol of strain energy. This large strain energy can be relieved by reacting benzyne with various partners.

2.1.2 Heteroarynes

Pyridynes,[29] and naphtalynes[30] were observed later as well. More recently, different indolynes were reported.[31] These structures are referred to as arynes, or heteroarynes.[32]

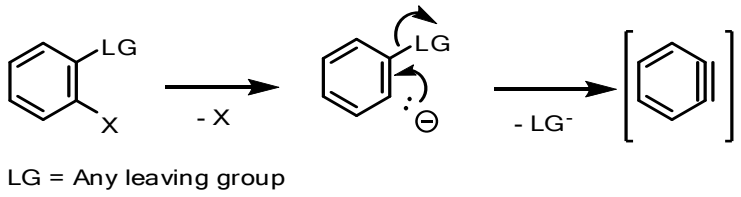


Scheme 29. A sample of arynes and heteroarynes

(28) M. Moini and G. E. Leroi, *J. Phys. Chem.* **1986**, *90*, 4002.
(29) a) T. Kauffmann and F. P. Boettcher, *Angew. Chem.* **1961**, *73*, 65. b) R. J. Martens and H. J. den Hertog, *Tetrahedron Lett.* **1962**, 643.
(30) a) J. F. Bunnett and T. K. Brotherton, *J. Org. Chem.* **1958**, *23*, 904. b) R. Huisgen and L. Zirngibl, *Ber.* **1958**, *91*, 1438.
(31) K. R. Buszek, D. Luo, M. Kondrashov, N. Brown and D. VanderVelde, *Org. Lett.* **2007**, *9*, 4135.
(32) For a review on arynes, see: H. Pellissier and M. Santelli, *Tetrahedron* **2003** *59*, 701.

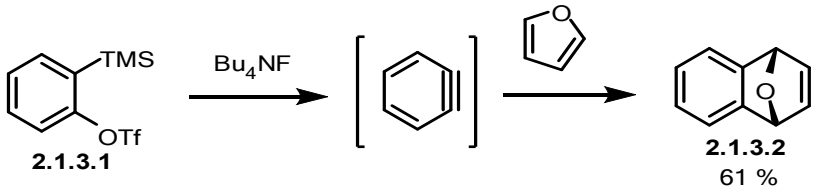
2.1.3 Preparation of Arynes

A variety of different precursors and condition sets can be employed to generate arynes[33], each different method having its own advantages and disadvantages. The following methods were used, or are related to our work described within this document.



Scheme 30. Aryne generation: leaving group ejected by adjacent lone pair

A widely used and mild method of aryne formation uses 2-(trimethylsilyl)phenyl triflate **2.1.3.1** and a fluoride source to generate benzyne via a fluoride anion displacement of the trimethylsilyl group.

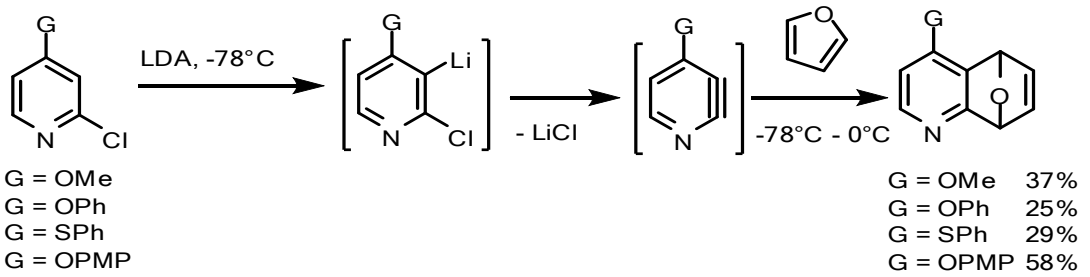


Scheme 31. Kobayashi's generation of benzyne from 2-(trimethylsilyl)phenyl triflate **2.1.3.1** and TBAF[34]

(33) For a review of methods of aryne generation, see: A. M. Dyke, A. J. Hester and G. C. Lloyd-Jones, *Synthesis* **2006**, 4093.
(34) H. Kobayashi, Y. Himeshima, and T. Sonoda, *Chem. Lett.* **1983**, 1211.

This type of method was first reported by Kobayashi,[34] and has seen a variety of uses and modifications as a mild, safe and convenient way to generate benzyne for various purposes.[35]

Another more classical and common aryne generation method involves the removal of a relatively acidic *ortho*-aromatic proton with a strong base, and the elimination of the adjacent leaving group (i.e. a halide). In the following example, 2,3-pyridynes are formed from various 2-chloropyridines reacted with LDA at low temperature. Warming the reaction mixture in presence of furan gave the corresponding 5,8-dihydro-5,8-epoxyquinolines in low to moderate yield.[36]



Scheme 32. Formation of 2,3-pyridynes by *ortho*-aromatic deprotonation/elimination and subsequent [4+2] cycloaddition with furan

Of course, many other ways exist to generate arynes: thermal and photolytic decompositions, numerous metal-halogen exchange/elimination sequences, oxidative decomposition of 1-aminobenzotriazole by lead acetate[37], and various other examples of the aforementioned removal of trimethylsilyl groups/elimination or other *ortho*-aromatic deprotonation/elimination sequences are presented within Dr. Dockendorff's thesis.[38] Most of these methods were not envisaged here for safety or simplicity reasons.

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(35) For examples, see: a) T. Kitamura, M. Yamane, K. Inoue, M. Todaka, N. Fukatsu, Z. Meng, and Y. Fujiwara, *J. Am. Chem. Soc.* **1999**, *121*, 11674. b) T. Kitamura, M. Todaka, and Y. Fujiwara, *Org. Synth.* **2000**, *78*, 104. c) C. D. Gilmore, K. M. Allan, and B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, *130,* 1558.

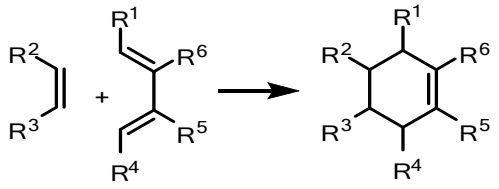
(36) S. J. Connon and A. F. Hegarthy, *Eur. J. Org. Chem.* **2004**, 3477.

(37) C. D. Campbell and C. W. Rees, *J. Chem Soc. (C)* **1969**, 742.

(38) C. J. Dockendorff, *PhD Thesis*, **2006**, University of Toronto, pp. 191-204. See also: H. Pellissier and M. Santelli, *Tetrahedron* **2003** *59*, 701.

2.1.4 The Diels-Alder Reaction

The Diels-Alder reaction[39] allows the formation of a cyclohexenes, starting from a conjugated diene and a dienophile (usually an alkene or an alkyne). This [4+2] cycloaddition reaction is an important transformation in organic chemistry since it allows the formation of 2 new carbon-carbon bonds while forming a six-membered carbocycle.



Scheme 33. The Diels-Alder reaction

Since its discovery in 1928, the Diels-Alder reaction saw much development. Asymmetric versions of the reaction are highly desirable, as they can selectively form up to four stereocenters a single step. Stereocontrol requires a source of chirality to be present in the reaction, and three different approaches can be taken to introduce asymmetry during a Diels-Alder reaction: (I) the use of a chiral catalyst, (II) the use of a chiral dienophile or (III) the use of a chiral diene. Achiral dienes or dienophiles can be made chiral by adding a chiral auxiliary.[40]

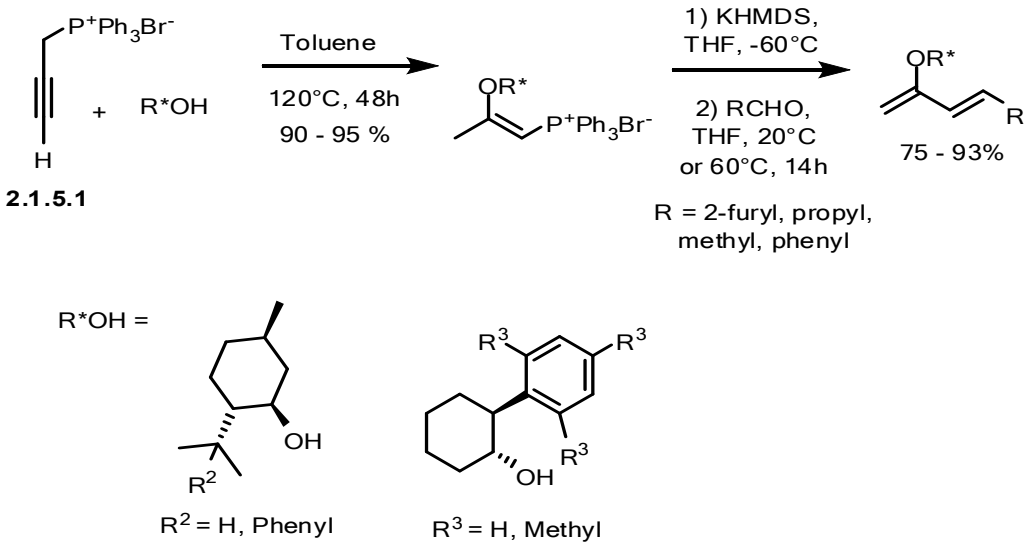
2.1.5 Chiral Heterosubstituted 1,3-Butadienes

(39) a) O. Diels and K. Alder, *Ann.* **1928**, *460,* 98. b) O. Diels and K. Alder, *Ann.* **1929**, *470,* 62. c) O. Diels and K. Alder, *Ber*. **1929**, *62*, 2081 & 2087.

(40) J. Barluenga, A. Surez-Sobrino and L. A. Lopez, *Aldrichimica Acta* **1999**, *32*, 4.

Barluenga and coworkers published a thorough review on the synthesis and cycloaddition reactions of chiral heterosubstituted 1,3-butadienes.[40] The first part of the review presents the synthesis of various 1-heterosubstituted-1,3-butadienes. Although a variety of chiral 1-heterosubstituted-1,3-butadienes are reported along with several [4+2] cycloaddition reactions carried out with common dienophiles, we were more interested by the second part of the review, involving chiral 2-heterosubstituted 1,3-butadienes.

The earliest report of chiral 2-heterosubstituted 1,3-butadienes dates back to the early 1990's. Barluenga proposed the synthesis of chiral 2-heterosubstituted 1,3-butadienes by condensation of a chiral alcohol on prop-2-ynyltriphenylphosphonium bromide **2.1.5.1** followed by Wittig olefination of an aldehyde.[41] The corresponding dienes were formed in good to excellent yields.

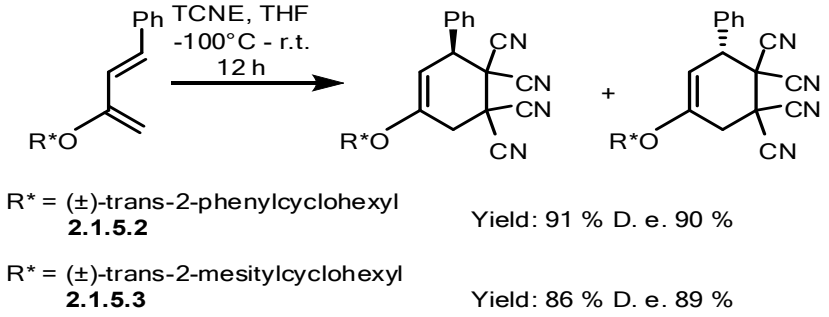


Scheme 34. Barluenga's synthesis of chiral 2-heterosubstituted 1,3-butadienes using a Wittig olefination[41]

Some of these dienes were used in [4+2] cycloaddition reactions with different dienophiles. Good results regarding the formation of the corresponding cycloadducts were observed from

(41) J. Barluenga, M. Tomàs, L. A. Lopez and A. Surez-Sobrino, *Synthesis* **1997**, 967.

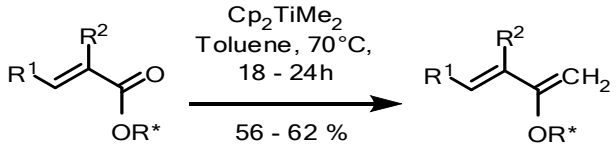
2.1.5.2 and **2.1.5.3**. When they are reacted with TCNE, they provide the products in high yield and high diastereomeric excess.[42]



Scheme 35. [4+2] cycloaddition reactions of 2-alkoxy-1,3-butadienes **2.1.5.2** and **2.1.5.3** with TCNE

Poor diastereomeric excess (< 43 %) were achieved when using dienes derived from menthol, or 8-phenylmenthol.

A second approach to chiral heterosubstituted 1,3-butadienes is the methylenation of the carbonyl group of an α,β-unsaturated ester using titanium based methylenation reagents.[43]



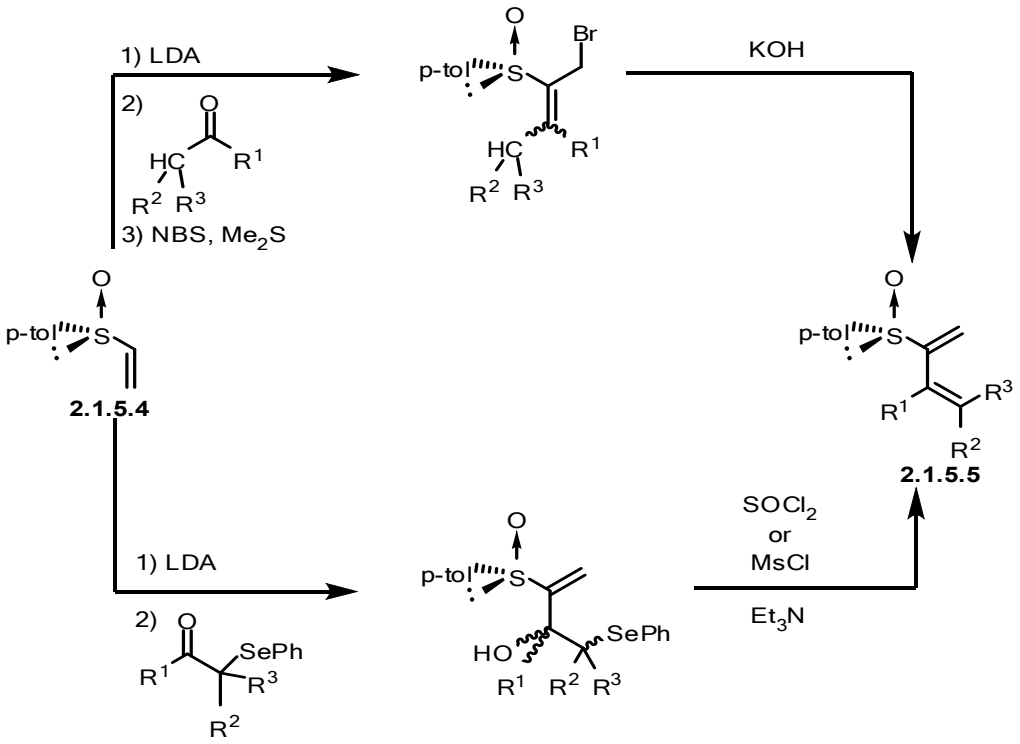
R^1 = H, Ph
R^2 = H, Me
R* = (±)-, (+)-, (-)-,trans-phenylcyclohexyl, (-)-menthyl

Scheme 36. Methylenation of α,β-unsaturated esters using dimethyltitanocene[43]

(42) J. Barluenga, M. Tomas, A. Surez-Sobrino and L. A. Lopez, *J. Chem. Soc., Chem. Commun.,* **1995**, 1785.
(43) a) J. Barluenga, M. Tomàs, L. A. Lopez and A. Surez-Sobrino, *Synthesis* **1997**, 967. b) J. Barluenga, A. Surez-Sobrino and L. A. Lopez, *Aldrichimica Acta* **1999**, *32*, 4.

This method allowed the formation of the corresponding dienes in moderate yields. Unfortunately, when R^2 is an alkoxy group, or an amine, it was reported that intractable mixtures were obtained, limiting the substrates to R^2 = H, alkyl.

Chiral 2-sulfinyl-1,3-butadienes were also previously synthesized by several different methods. The most attractive method noted uses two possible synthetic pathways to dienes **2.1.5.5** starting from both enantiomers of *para*-tolyl vinyl sulfoxide **2.1.5.4**.[44]

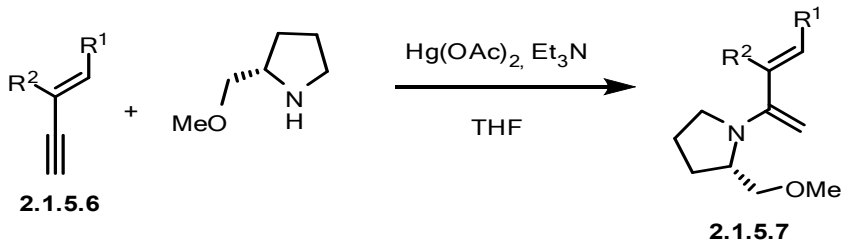


Scheme 37. Synthesis of chiral 2-sulfinyl-1,3-butadienes **2.1.5.5** starting from chiral *para*-tolyl vinyl sulfoxide **2.1.5.4**

Unfortunately, the scope of products **2.1.5.5** is limited, and does not incorporate examples of dienes with R^2 = Aryl.

(44) a) E. Bonfand, P. Gosselin and C. Maignan, *Tetrahedron: Asymmetry* **1993**, *4*, 1667. b) E. Bonfand, P. Gosselin and C. Maignan, *Tetrahedron Lett*. **1992**, *33*, 2347. c) P. Gosselin, E. Bonfand and C. Maignan, *Synthesis* **1996**, 1079.

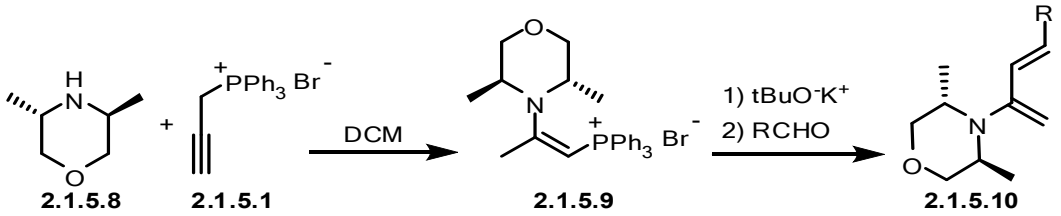
Chiral 2-amino-1,3-butadienes **2.1.5.7** can be obtained by the catalytic aminomercuration of 3-alken-1-yne **2.1.5.6** in moderate yield.[45] Variation of the chiral auxiliary might be possible, thus using other secondary amines derived from proline as the chiral auxiliary.



2.1.5.6 **2.1.5.7**

Scheme 38. Synthesis of chiral 2-amino-1,3-butadienes **2.1.5.7** by a catalytic aminomercuration of SMP on 3-alken-1-yne **2.1.5.6**[45]

The Enders group formed chiral 2-amino-1,3-butadienes **2.1.5.10** by adding the C_2-symmetrical (*S,S*)-3,5-dimethylmorpholine **2.1.5.8** to propargyltriphenylphosphonium bromide **2.1.5.1**, and reacting the obtained phosphonium salt **2.1.5.9** with an aldehyde.[46]



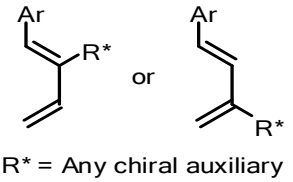
2.1.5.8 **2.1.5.1** **2.1.5.9** **2.1.5.10**

Scheme 39. Formation of 2-amino-1,3-butadienes **2.1.5.10** by addition of (*S,S*)-3,5-dimethylmorpholine **2.1.5.8** on propargyltriphenylphosphonium bromide **2.1.5.1** and subsequent Wittig olefination of an aldehyde

Other methods for the formation of chiral 2-heterosubstituted-1,3-butadienes exist and are mentioned within Barluenga's review[40], but they are not included here because they were not

(45) J. Barluenga, F. Aznar, C. Valdés and M.-P. Cabal, *J. Org. Chem.* **1991**, *56*, 6166.
(46) D. Enders, O. Meyer, G. Raabe, J. Runsink, *Synthesis* **1994**, 66.

considered as a reasonable way to obtain the dienes needed for our studies, or because they do not provide products with the desired substitution pattern or functional groups.

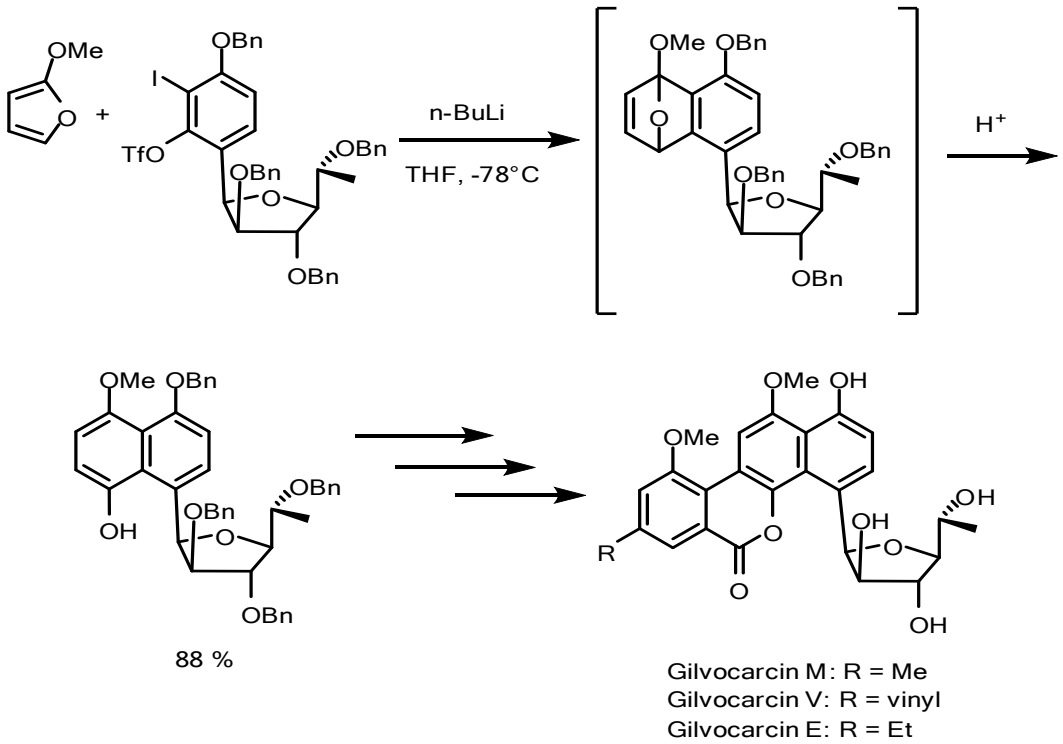


Scheme 40. Dienes required for our studies possess an aryl group on one of the diene's terminal carbon

Also, many of the dienes mentioned above were not, to our knowledge, used for [4+2] cycloaddition reactions with carbon dienophiles. However, encouraging results regarding diastereoselectivity were observed in several cases, leading us to believe that it could be possible to influence the facial selectivity of the reaction during [4+2] cycloaddition reactions of similar dienes with aryne partners.

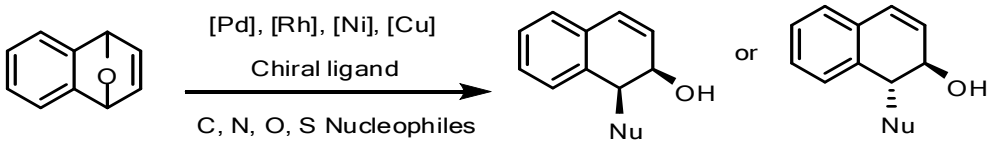
2.1.6 Known [4+2] Cycloadditions of Arynes

Since benzyne is such a highly reactive species, it undergoes a wide variety of reactions. Among these useful and less useful reactions, cycloaddition reactions are important transformations that may prove to be synthetically practical for applications to the total synthesis of molecules of interest. For example, Suzuki reported a synthesis of the gilvocarcins utilizing an aryne Diels-Alder reaction of a substituted benzyne precursor with 2-methoxyfuran as one of the key steps.



Scheme 41. Suzuki's total synthesis of gilvocarcins utilizing an intermolecular benzyne Diels-Alder reaction as one of the key steps

It was found that benzyne is an excellent reaction partner for Diels-Alder reactions with furans. The oxabicyclic alkene adduct generated can be ring-opened under different conditions to afford the corresponding 1,2-dihydronaphthalenes.[47]

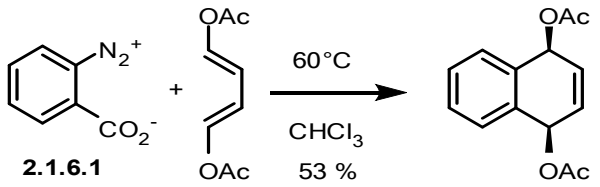


Scheme 42. Ring-opening reactions of oxabicyclic alkenes to generate substituted 1,2-dihydronaphthalenes

(47) For early reviews, see: a) M. Lautens, *Synlett* **1993**, 177. b) S. Woo, and B. A. Keay, *Synthesis* **1996**, 669. c) P. Chiu and M. Lautens, *Top. Curr. Chem.***1997**, *190*, 1. For a review of metal-catalyzed enantioselective ring-openings of oxabicyclic alkenes, see: M. Lautens, K. Fagnou and S. Hiebert, *Acc. Chem. Res.* **2003,** *36***,** 48. and references therein.

Protected azabicycles can also be generated by the Diels-Alder reaction of benzyne with protected pyrroles.

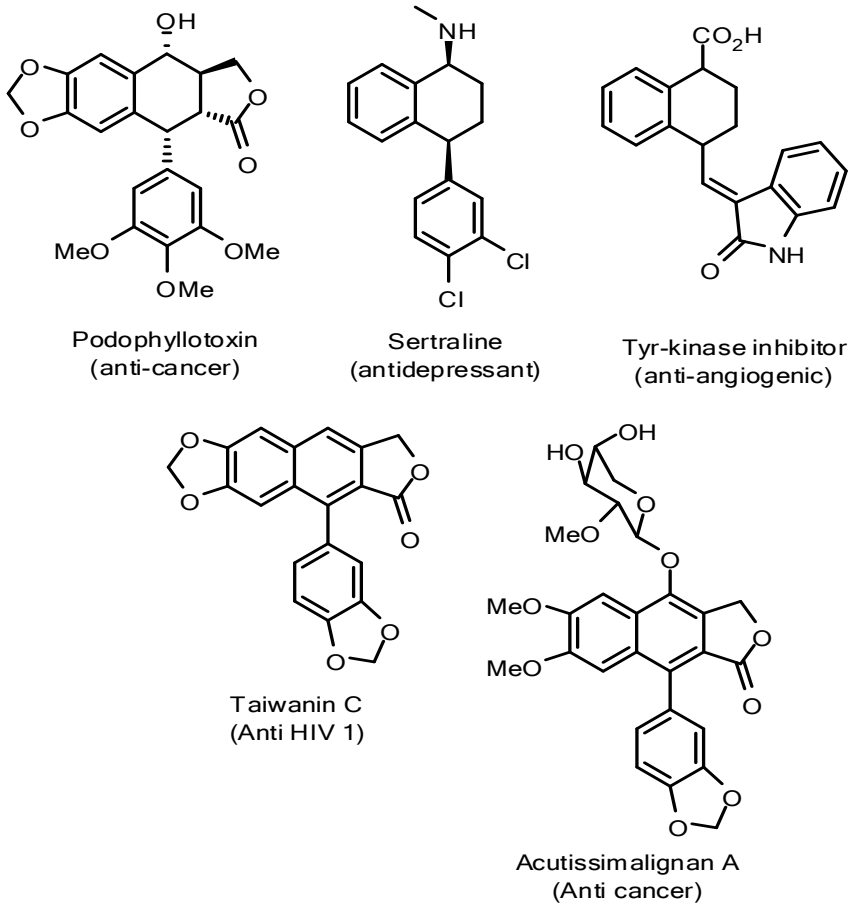
Interestingly, acyclic dienes have not often been used in aryne Diels-Alder reactions in the past. Schmidt reported one of the few synthetically useful intermolecular aryne Diels-Alder reactions of benzyne with an acyclic diene.[48]



Scheme 43. Benzyne Diels-Alder reaction with 1,4-diacetoxy-butadiene[48]

Our group is interested by several targets, mainly naphthalene or polyhydronaphthalene derivatives, for which an intermolecular benzyne Diels-Alder could be a key step during their synthesis. These targets exhibit interesting biological properties, as depicted by Scheme 44.

(48) R. Angerbauer, and R. Schmidt, *Angew. Chem. Int. Ed.* **1979**, *18*, 304.



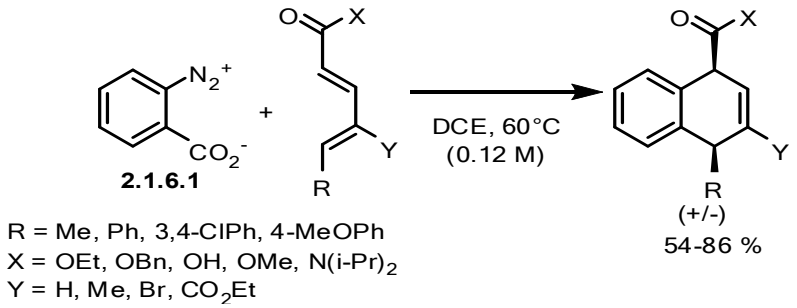
Scheme 44. Various naphthalene or polyhydronaphthalene derivatives exhibiting valuable biological activity

Since our previous efforts to convert 1,2-dihydronaphthalenes to the corresponding 1,4-dihydronaphthalenes were unsuccessful, aryne Diels-Alder reactions seemed to offer a convenient alternative to access these structures.

Our past investigation[49] of intermolecular cycloadditions of acyclic dienes substituted with a carbonyl at the terminal carbon gave the corresponding 1,4-dihydronaphthalenes in moderate to high yields. This is encouraging since cycloadditions with cyclic dienes under similar conditions

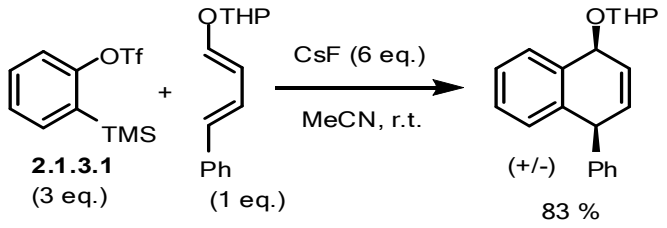
(49) C. Dockendorff, S. Sahli, M. Olsen, L. Milhau, M. Lautens, *J. Am. Chem. Soc.* **2005**, *127*, 15028.

give yields inferior to 70%. In this case, benzyne was generated using benzenediazonium-2-carboxylate **2.1.6.1**.[50]



Scheme 45. Benzyne Diels-Alder reaction with carbonyl substituted dienes[49]

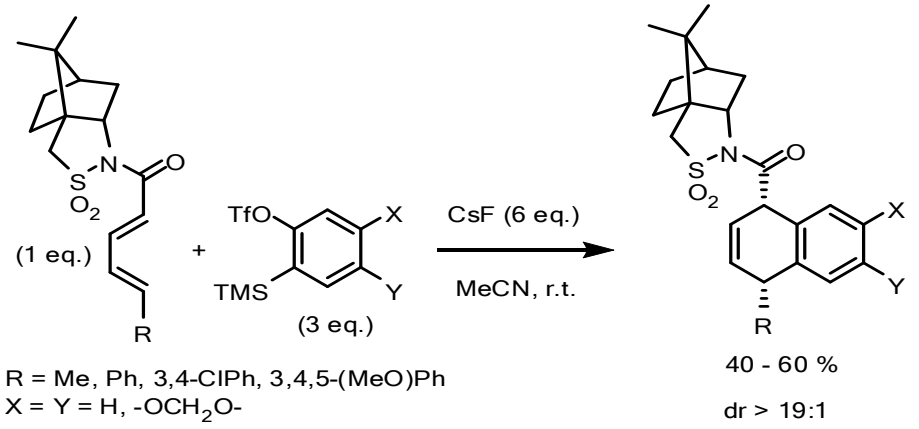
Protected hetero-substituted dienes can be used in the benzyne Diels-Alder reaction as well. This time, benzyne was generated under mild conditions using 2-(trimethylsilyl)phenyl triflate **2.1.3.1** with cesium fluoride in acetonitrile at room temperature.[51] This method is milder than other methods using deprotonation with strong bases, heat, or UV light, but cannot be used with substrates sensitive to fluoride.



Scheme 46. Benzyne Diels-Alder reaction of a hetero-substituted diene[49]

(50) BDC is explosive when dry, it must be carefully handled as a slurry.
(51) Y. Sato, T. Tamura and M. Mori, *Angew. Chem., Int. Ed.* **2004**, *43*, 2436.

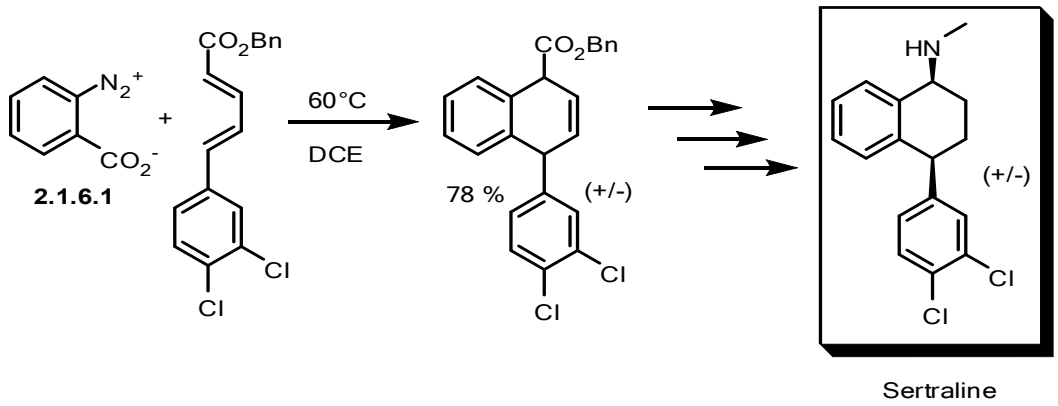
A stereoselective version of the reaction was developped by attaching a chiral auxiliary to the carbonyl group located at the terminal carbon of the diene. Although yields of substituted dihydronaphthalenes are moderate, the diastereomeric ratio is high when using (-)-(2,10)-camphorsultam as a chiral auxiliary.



Scheme 47. Synthesis of enantiomerically enriched 1,4-dihydronaphthalenes using an aryne Diels-Alder reaction[49]

The use of other well known chiral auxiliaries gave diastereomeric ratios that were only poor (1:1) to moderate (3.5:1), making Oppolzer's sultam the best chiral auxiliary for high diastereoselectivity.

A synthesis of racemic sertraline was achieved by our group utilizing an intermolecular benzyne Diels-Alder reaction with an acyclic diene as one of the early steps of the synthesis. A Curtius rearrangement was one of the key steps of the synthesis, proving that the transformation allows easy access to amino-naphthalenes starting from the corresponding esters.



Scheme 48. Synthesis of racemic Sertraline as achieved by the Lautens group[49]

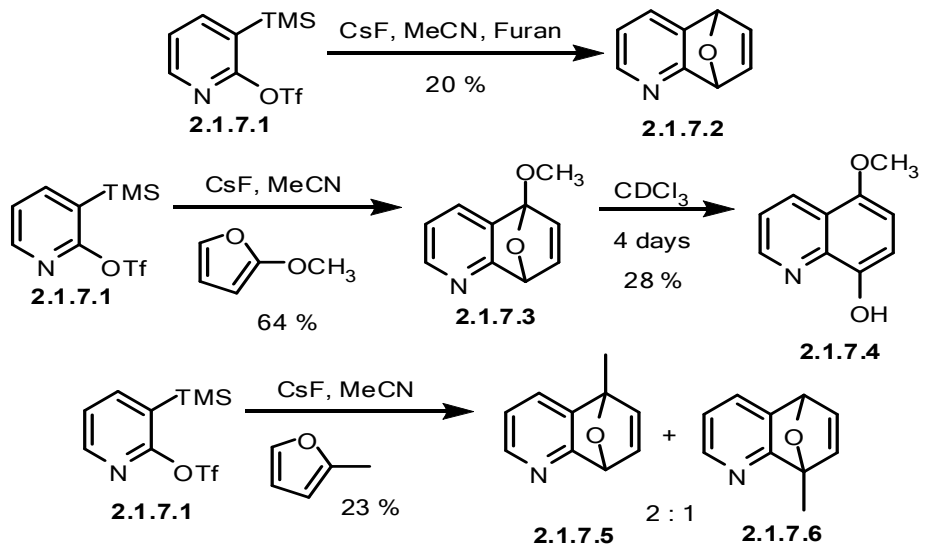
2.1.7 Cycloadditions of 2,3-Pyridynes

Various methods exist to generate 2,3-pyridynes and 3,4-pyridynes[52]. However, we focused on the formation of 2,3-pyridynes.

2,3-Pyridine can be generated by fluoride induced desilylation-elimination of **2.1.7.1**.[53] Upon generation, 2,3-pyridine can react with furan and its substituted homologues to generate the corresponding oxabicyclic alkenes, as shown on Scheme 49.

(52) For a recent generation methods for 3,4-pyridynes, see : W. Lin, L. Chen and P. Knochel, *Tetrahedron* **2007**, *63*, 2787.

(53) M. A. Walters and J. J. Shay, *Synth. Commun.* **1997**, *27*, 3573. The synthesis of **2.1.7.1** is described therein.



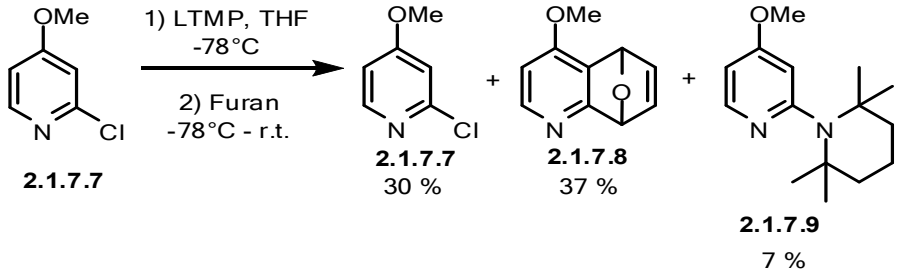
Scheme 49. 2,3-Pyridines generated from **2.1.7.1** and its cycloaddition products with furans

Unfortunately, yields of cycloaddition adducts **2.1.7.2**, **2.1.7.5** and **2.1.7.6** are low. Regioselectivity is observed when 2,3-pyridine undergoes cycloaddition with 2-methylfuran, as **2.1.7.5** is formed preferably over **2.1.7.6** (2:1).[54] After dihydroepoxyquinoline **2.1.7.2** was obtained, it presumably underwent acid-catalyzed ring-opening/rearrangement to give hydroxyquinoline **2.1.7.3**.

The same authors reported the synthesis of **2.1.7.8**, generating this time a 2,3-pyridyne by deprotonation-elimination on precursor **2.1.7.7**.[55]

(54) This was in accord with past observations : M. Mallet, G. Queguiner and P. Pastour, *Comp. Rend.* **1972**, *274*. 719.

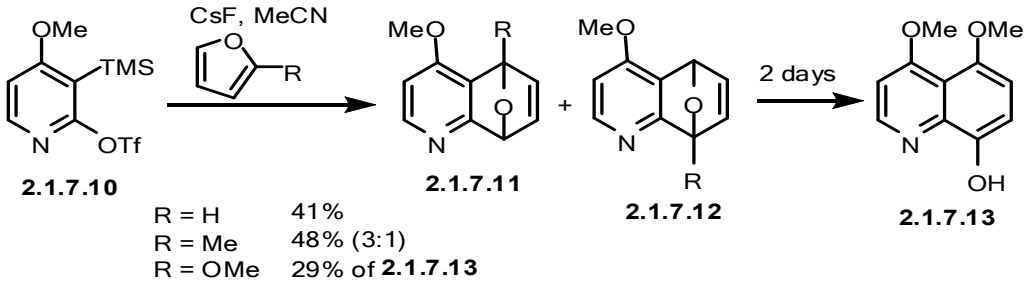
(55) M. A. Walters and J. J. Shay, *Tetrahedron Lett.* **1995**, *36*, 7575.



Scheme 50. Generation of 2,3-pyridyne with precursor **2.1.7.7**, and cycloaddition with furan

Although the expected dihydroepoxyquinoline **2.1.7.8** is formed in 37% yield, 30% of starting material **2.1.7.7** is recovered and 7% of **2.1.7.9** was formed by nucleophilic addition to the pyridyne intermediate.

Another desilylation-elimination sequence is reported. It generates a 2,3-pyridyne starting from precursor **2.1.7.10**.[56]



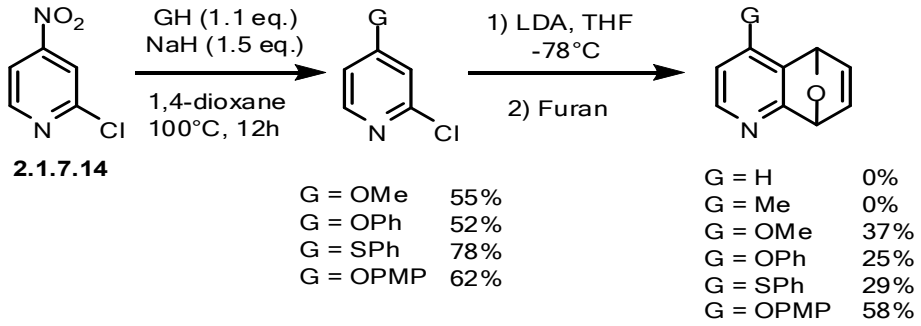
Scheme 51. Cycloaddition of a 4-methoxysubstituted pyridyne with differently substituted furans

Again, the cycloaddition with 2-methylfuran gives regioselectively **2.1.7.11** over **2.1.7.12** (3:1), as observed with **2.1.7.1**. 2-methoxyfuran gave product **2.1.7.13**, which is suggested to be the product of an acid catalyzed ring-opening reaction.

---

(56) For the synthesis of substituted 2,3-pyridyne precursor **2.1.7.10** starting from 4-nitropyridine-N-oxide, see : M. A. Walters and J. J. Shay, *Tetrahedron Lett.* **1995**, *36*, 7575.

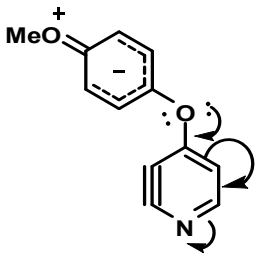
A deprotonation-elimination sequence used on pyridyne precursors, followed by cycloaddition of the resulting 2,3-pyridyne with furan was also reported by Hegarthy.[36] Starting from 4-nitro-2-chloropyridine **2.1.7.14**, various groups can be installed by displacement of the nitro group with sodium alkoxides.[57] Deprotonation at low temperature, then warming the reaction mixture in the presence of furan generates the pyridyne and provokes cycloaddition to give the corresponding dihydroepoxyquinolines.



Scheme 52. Synthesis of various 2,3-pyridyne precursors from 4-nitro-2-chloropyridine **2.1.7.14** and their reactivity with furan under pyridyne Diels-Alder conditions[36]

The larger success of the pyridyne Diels-Alder reaction with G = OPMP is suggested to be a consequence of a more electron-donating group increasing the dienophilicity of the pyridyne intermediate.[36]

(57) G. Finger and L. Starr, *J. Am. Chem. Soc.* **1959**, *81*, 2674.

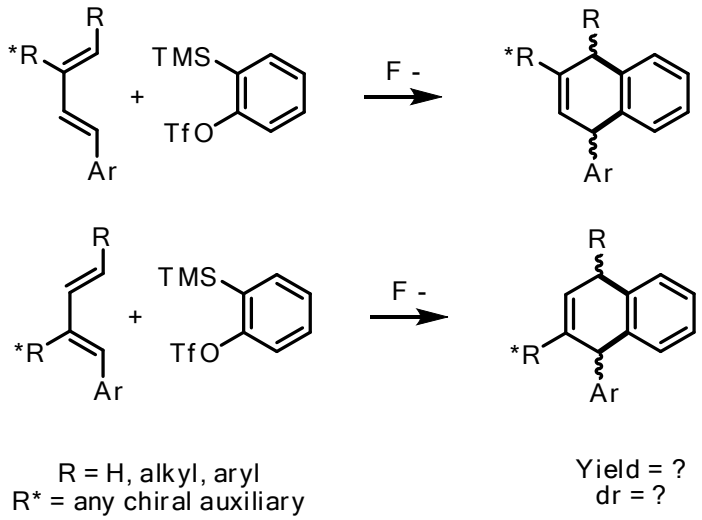


Scheme 53. Rationale for the increased dienophilicity when G = OPMP

Although different sources reported the synthesis of various dihydroepoxyquinolines, nothing was, to our knowledge, reported on potentially useful ring-opening reactions of these structures.

2.2 Objectives

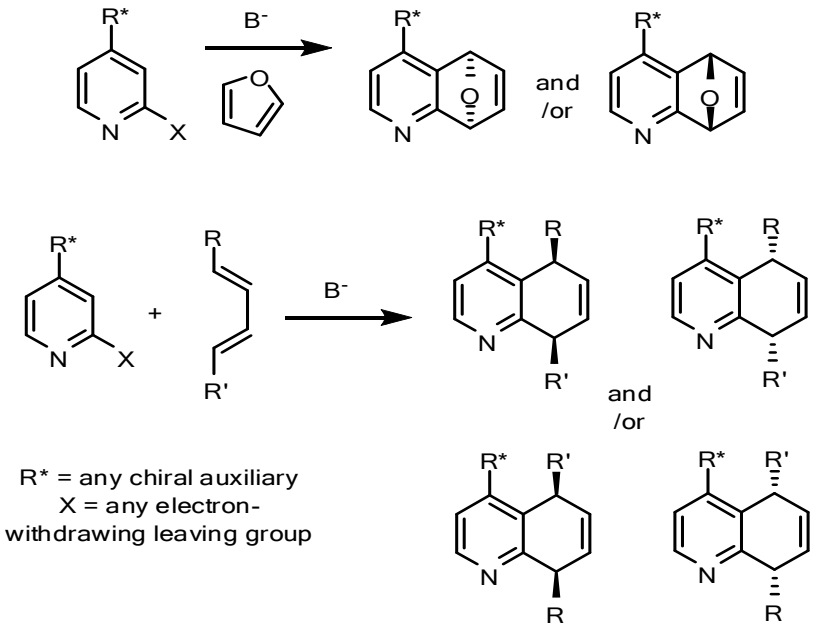
Dienes supporting a chiral auxiliary at a terminal position are already known to give rise to the expected tetralin cores in moderate yields with excellent diastereoselectivity. Testing the reactivity of dienes supporting a chiral auxiliary at a 2 or 3 position is the objective of our investigation, because it would allow access to substituted 1,4-dihydronaphthalene products, with synthetically useful substitution patterns.



Scheme 54. Chiral aryne Diels-Alder reaction of acyclic dienes supporting a chiral auxiliary at the central carbon

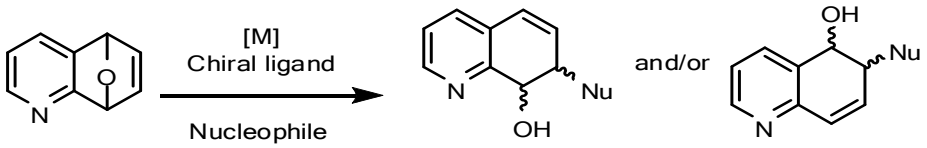
A chiral auxiliary at central carbons on a diene could influence yields and diastereomeric ratios of the 1,4-dihydronaphthalene products.

The synthesis of pyridyne precursors supporting a chiral auxiliary was, to our knowledge, never achieved. These precursors could show regioselectivity in aryne Diels-Alder reactions with unsymmetrical dienes.



Scheme 55. Diastereoselective pyridyne Diels-Alder reaction using a chiral pyridyne precursor

The reactivity of dihydroepoxyquinoline, obtained by the Diels-Alder reaction of pyridyne with furan, has, to our knowledge, not been investigated as an electrophile in asymmetric metal-catalyzed ring opening reactions. These conditions could give rise to chiral and functionalized dihydroquinolines.

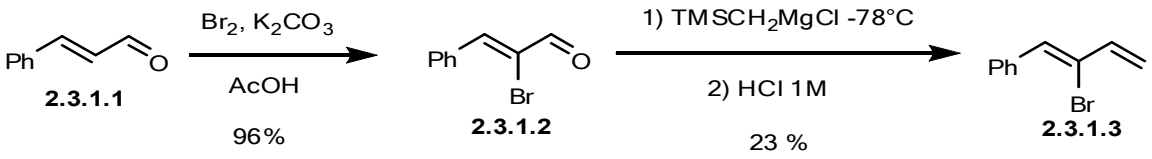


Scheme 56. Functionalization of dihydroquinolines via oxabicyclic ring opening reactions of dihydroepoxyquinolines

2.3 Results and Discussion

2.3.1 Starting Material Synthesis

Synthesis of bromide **2.3.1.3** is achieved in two steps starting from trans-cinnamaldehyde **2.3.1.1**. First, bromination/elimination gives the α-bromocinnamaldehyde **2.3.1.2**, which can undergo a Peterson olefination to give **2.3.1.3**.[58]

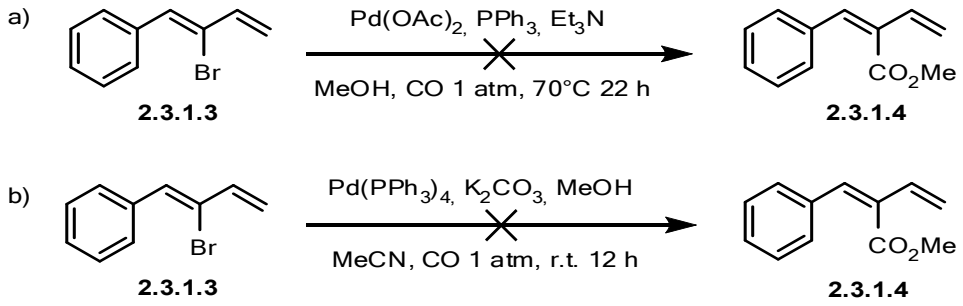


Scheme 57. Synthesis of bromide **2.3.1.3** starting from cinnamaldehyde **2.3.1.1**

Palladium-catalyzed carbonylation reactions were suggested as a way to transform bromide **2.3.1.3** to the corresponding ester. However, two different sets of conditions[59] were tested without success, as shown in scheme 58.

(58) Conditions from Matthew Flemming, unpublished result. The yield previously reported for the Peterson olefination (84 %) could never be reproduced under the same conditions. The Peterson olefination reagent was titrated to confirm its concentration before use.

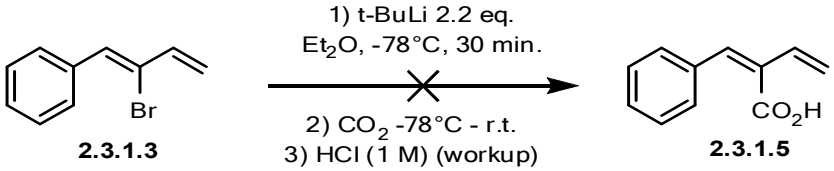
(59) a) C. Ayats, P. Camps, M. D. Duque, M. Font-Bardia, M. R. Munoz, X. Solans and S. Vazquez, *J. Org. Chem.* **2003**, *68*, 8715. b) R. Anacardio, A. Arcadi, G. D'Anniballe and F.Marinelli, *Synthesis*, **1995**, 831.



Scheme 58. Attempted Pd-catalyzed carbonylation reactions

In each case, the reaction was incomplete after running it for an extended length of time, and an unidentified major undesired product was seen on TLC. None of the desired product could be isolated. Published work suggest that bromide **2.3.1.3** could form a pi-allyl complex with palladium(0) and eventually generate an allene.[60] Palladium-catalyzed carbonylation might hence not be a reasonable way to obtain ester **2.3.1.4** starting from bromide **2.3.1.3**.

Lithium halogen exchange on bromide **2.3.1.3** followed by an electrophilic quenching could generate the corresponding acid.

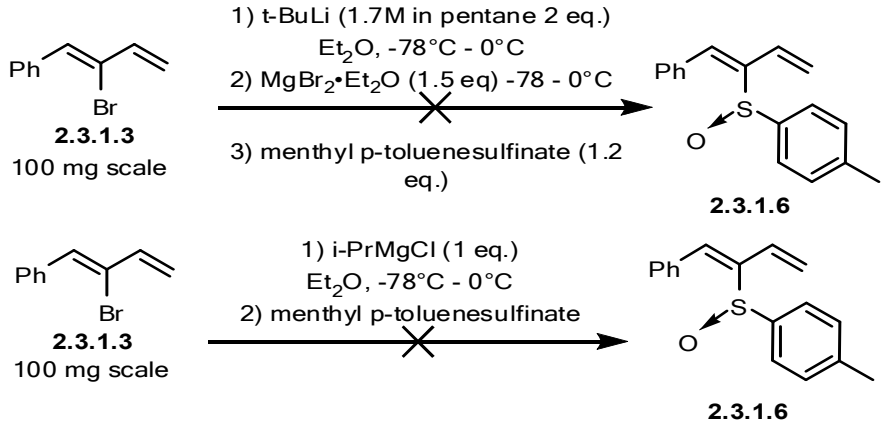


Scheme 59. Unsuccessful lithium-halogen exchange followed by electrophilic quenching to generate **2.3.1.5**

(60) a) M. Ogasawara, H. Ikeda, T. Nagano and T. Hayashi, *J. Am. Chem. Soc.* **2001,** *123,* 2089. b) M. Ogasawara, A. Okada, S. Watanabe, L. Fan, K. Uetake, K. Nakajima and T. Takahashi, *Organometallics* **2007,** *26,* 5025.

However, no trace of the expected carboxylic acid **2.3.1.5** was found. Mass spectrometry of the major product indicated a signal for a mass suggesting that dimerization of **2.3.1.5** possibly occurred, but this was not confirmed by ^{1}H NMR.

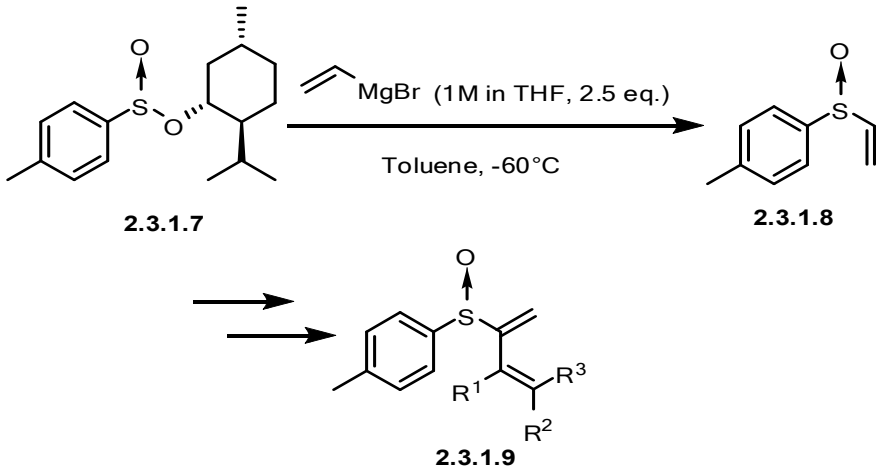
Preparation of sulfinyldiene **2.3.1.6** was attempted starting from bromide **2.3.1.3** using a metal-halogen exchange strategy. However, no product was isolated, and the synthesis of **2.3.1.6** was quickly abandoned after finding that a similar substrate failed to react in an aryne Diels-Alder reaction, as previously reported by a past member of our group.[61]



Scheme 60. Attempted synthesis of sulfinyldiene **2.3.1.6**

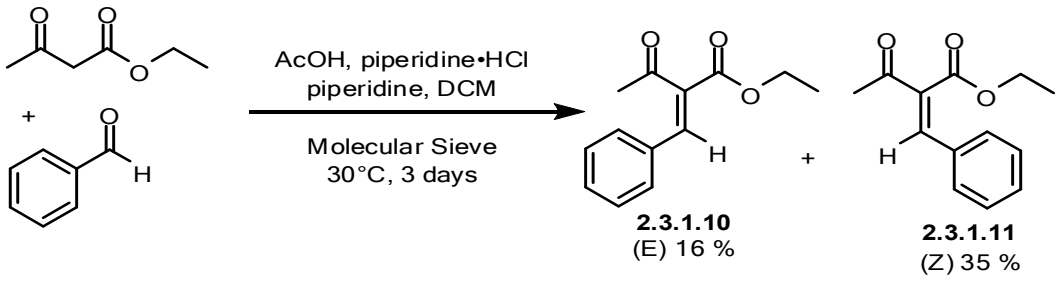
Sulfinyldienes[62] of type **2.3.1.9** were not, to our knowledge, used under aryne Diels-Alder reaction conditions. The synthesis of *para*-tolyl vinyl sulfoxide[63] **2.3.1.8** was thus attempted. Unfortunately, only traces of **2.3.1.8** were observed after three attempted reactions. Since the scope for **2.3.1.9** was limited, and no dienes having R^2 = aryl were known, we decided to reorient our efforts toward other methods.

(61) S. Sahli, *Postdoctoral Research Report,* University of Toronto, **2006**, p.21.
(62) E. Bonfand, P. Gosselin and Christian Magnan, *Tetrahedron :Asymmetry* **1993**, *4*, 1667.
(63) H. Kosugi, M. Kitaoka, K. Tagami, A. Takahashi and H. Uda, *J. Org. Chem.* **1987**, *52*, 1078.



Scheme 61. Preparation of *para*-tolyl vinyl sulfoxide **2.3.1.8**

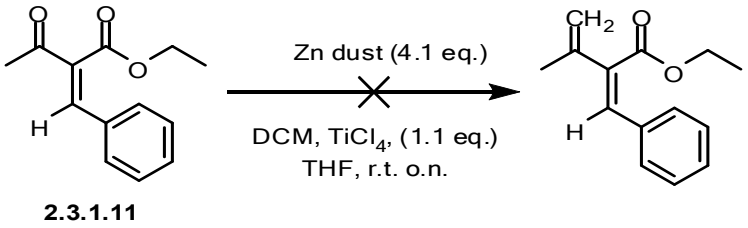
The synthesis of Knoevenagel adduct **2.3.1.11** was achieved.[64] The desired (Z) diastereomer **2.3.1.11** was obtained in 35 % yield, and was easily separated from the (E) diastereomer **2.3.1.10** (16 % yield) by flash chromatography.



Scheme 62. Formation of **2.3.1.11** by a classical Knoevenagel condensation

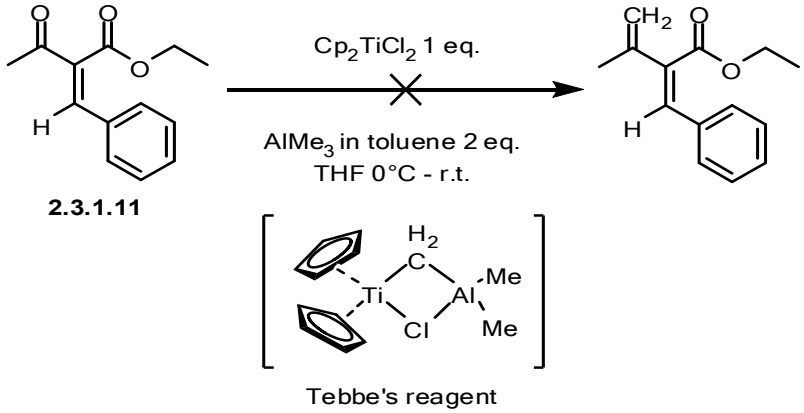
(64) a) T. Inokuchi and H. Kawafuchi, *J. Org, Chem.* **2006**, *71*, 947. b) For Knoevenagel reactions in ionic liquids, see: B. C. Ranu and R. Jana, *Eur. J. Org. Chem.* **2006**, 3767.

It was thought that the ketone on **2.3.1.11** could be selectively olefinated using Lombardo's olefination.[65] However, the reaction failed to give the desired product.



Scheme 63. Attempted Lombardo olefination of **2.3.1.11**[65]

Tebbe's olefination[66] was attempted as well, without success.



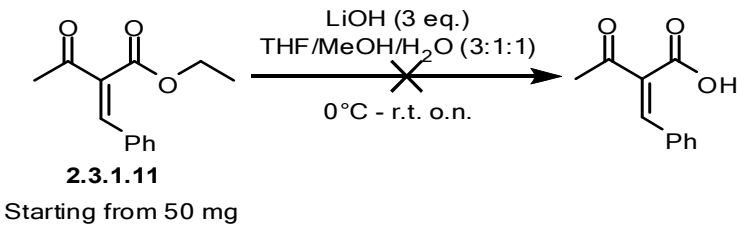
Scheme 64. Attempted Tebbe's olefination on the knoevenagel adduct **2.3.1.11**

Hydrolysis of Knoevenagel adduct **2.3.1.11** with lithium hydroxide gave a complex mixture of unexpected products.

---

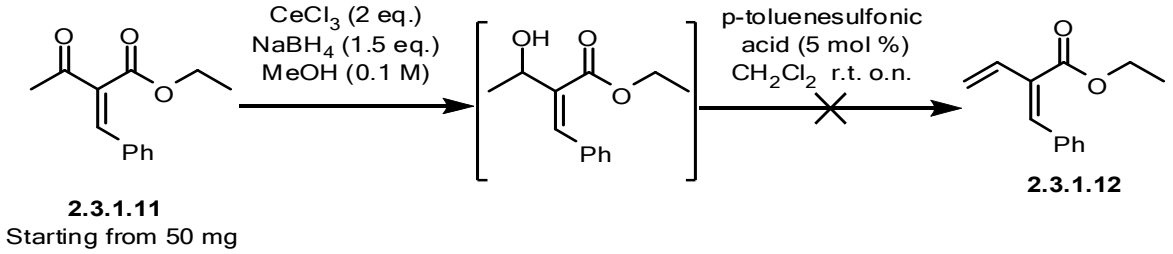
(65) K. Takai, Y. Hotta, K. Oshima and H. Nozaki, *Tetrahedron letters*, **1978**, *27*, 2417.

(66) a) L. F. Cannizzo and R. H. Grubbs, *J. Org. Chem.,* **1985**, *50*, 2386. b) S. H. Pine, G. Kim and V. Lee, *Org. Syn., Coll. Vol. 8,* **1993**, 512.



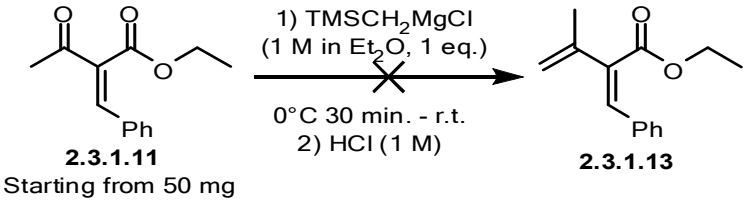
Scheme 65. Attempted hydrolysis of Knoevenagel adduct **2.3.1.11**

Selective reduction of the ketone using sodium borohydride and cerium(III) chloride, followed by elimination of the alcohol using *para*-toluenesulfonic acid failed to generate the desired ester **2.3.1.12**.



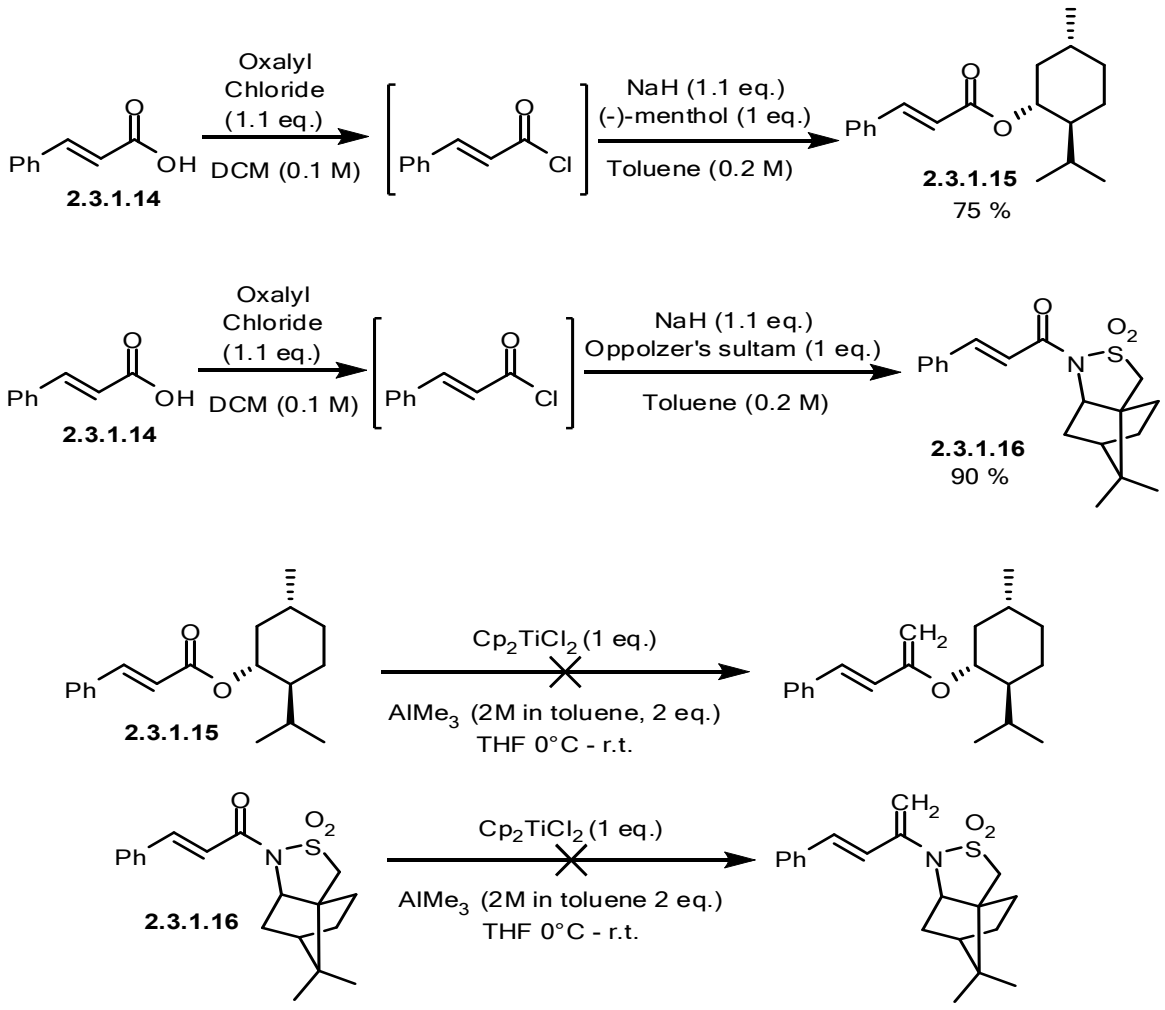
Scheme 66. Attempted reduction-elimination sequence on Knoevenagel adduct **2.3.1.11**

A Peterson olefination was used to convert Knoevenagel adduct **2.3.1.11** to the corresponding diene **2.3.1.13**. None of the expected product was obtained.



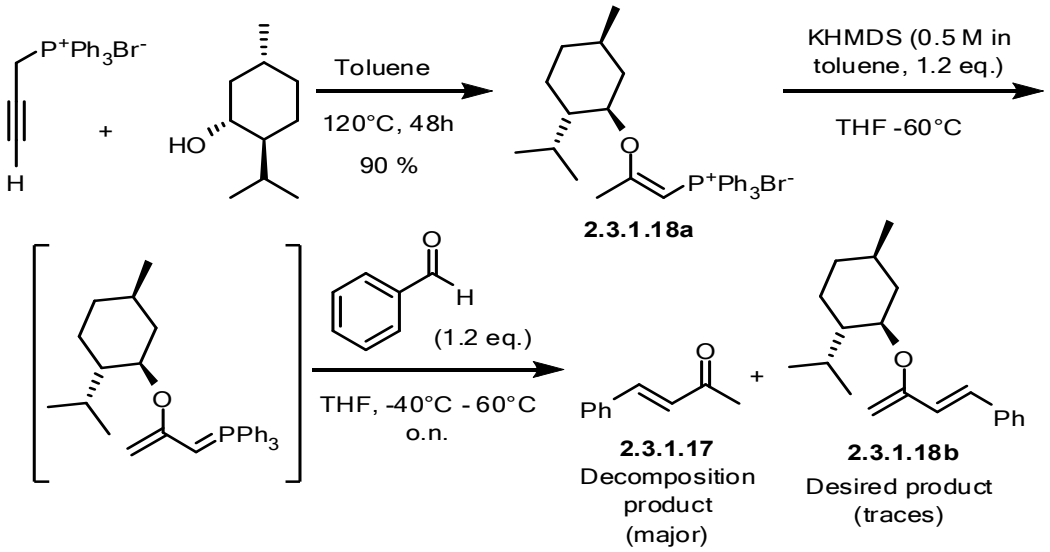
Scheme 67. Attempted Peterson olefination of Knoevenagel adduct **2.3.1.11**

Starting from cinnamic acid **2.3.1.14**, the corresponding (-)-menthyl ester **2.3.1.15** and (-)-(2,10)-camphorsultam amide **2.3.1.16** were formed. Attempted Tebbe's olefination of these two compounds failed to give the desired dienes.



Scheme 68. Attempted synthesis of chiral dienes starting from cinnamic acid **2.3.1.14**

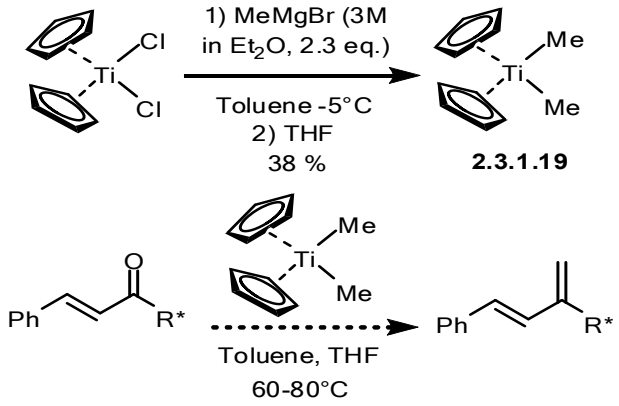
A Wittig olefination strategy giving diene **2.3.1.18b** was reported by Barluenga.[43] This synthesis was attempted, but the product **2.3.1.18b** was always hydrolyzed during the purification process to yield 4-phenyl-3-butene-2-one **2.3.1.17**.



Scheme 69. Synthesis of diene **2.3.1.18b** by a Wittig olefination

Methods using dimethyltitanocene[67] **2.3.1.19** as an olefination reagent were also previously reported by Barluenga.[43] Although we successfully made a solution of dimethyltitanocene, it was not used in olefination reactions due to time constraints. Moreover, this method, yielding sensitive products similar to the ones obtained with previous methods, faces the same purification problems and may not form a stable diene.

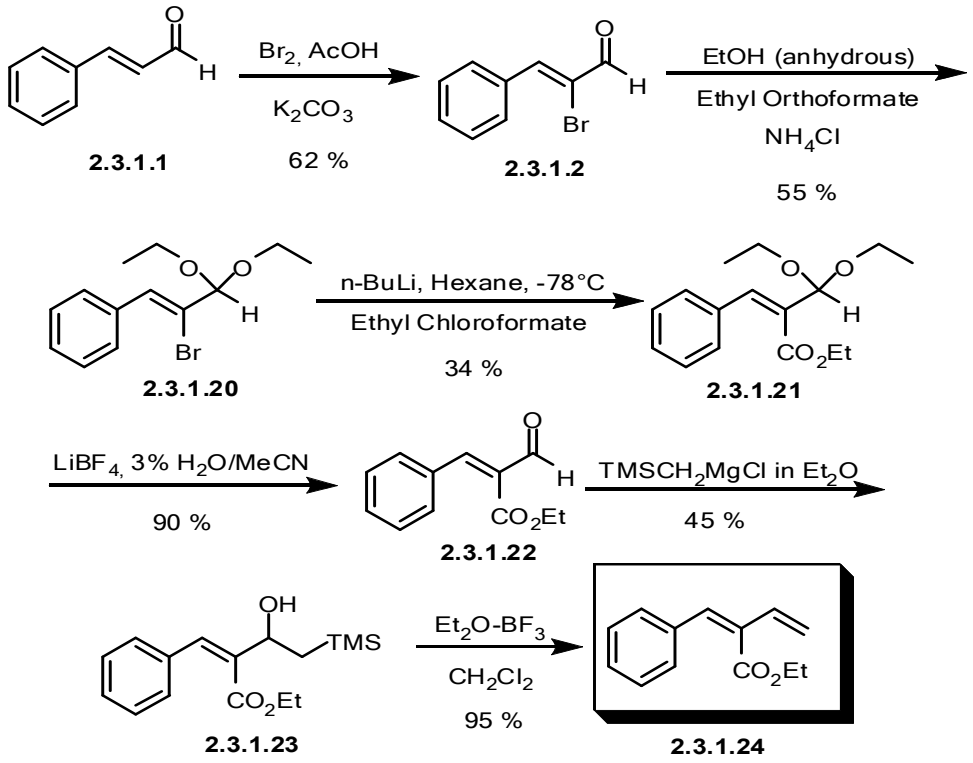
(67) a) J. F. Payack, D. L. Hughes, D. Cai, I. F. Cottrell and T. R. Verhoeven, *Org. Syn., Coll. Vol. 10*, **2004**, 355. b) For a mechanistic study on the olefination of esters using dimethyltitanocene, see: D. L. Hugues, J. F. Payack, D. Cai, T. R. Verhoeven and P. J. Reider, *Organometallics* **1996,** *15,* 663. c) T. Takeda and A. Tsubouchi, *Modern Carbonyl Olefination*, **2004**, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, p. 166.



Scheme 70. Olefination using dimethyltitanocene[67] **2.3.1.19**

The synthesis of the ester **2.3.1.24** was completed following a literature procedure.[68] The yields obtained were lower than the previously reported one, and the overall yield of the sequence, starting from 2.11g of α-bromocinnamaldehyde **2.3.1.2** was a disappointing 5 %. This synthetic pathway proved to be time consuming, and low yielding.

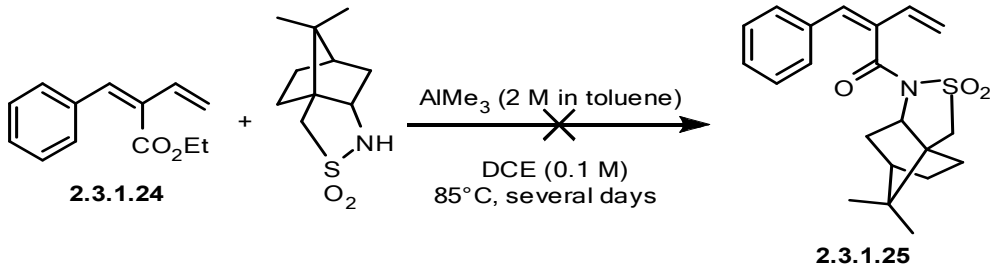
(68) a) See reference 49. b) See reference 61.



Scheme 71. Synthesis of (Z)-ethyl-2-benzylidenebut-3-enoate **2.3.1.24**

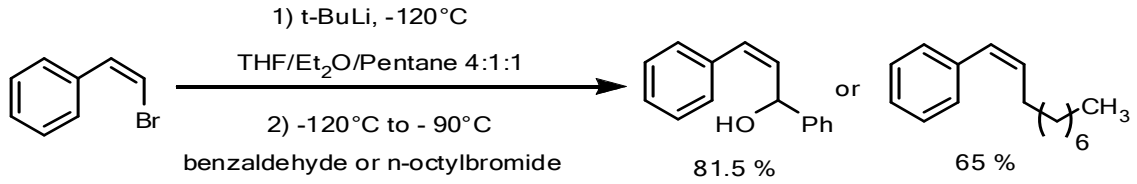
Once diene **2.3.1.24** was obtained, an attempt to form diene **2.3.1.25** supporting (-)-2,10-camphorsultam as a chiral auxiliary was carried out. Heating the ester for several days at 85°C along with (-)-(2,10)-camphorsultam in DCE, in the presence of trimethylaluminium as a lewis acid failed to give the desired product.[69] Addition of excess trimethylaluminium, and heating at 85°C for several extra days failed to convert **2.3.1.24** to the desired product.

(69) The same methodology was applied to other ethyl esters with success, see: a) reference 49. b) H. Miyabe, K. Fujii and T. Naito, *Org. Biomol. Chem.* **2003**, *1*, 381.



Scheme 72. Attempt to form diene **2.3.1.25** supporting camphorsultam using diene **2.3.1.24**

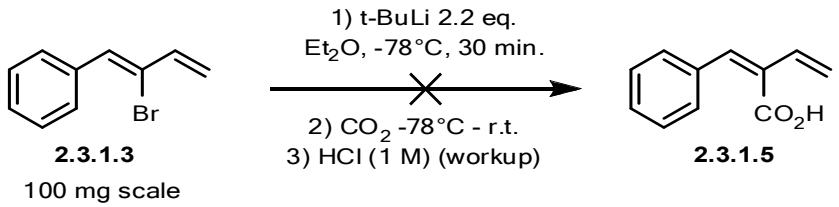
Since the supplies of diene **2.3.1.24** were low, it was necessary to find a way to produce more of it using a shorter and more reliable synthesis than the one presented in Scheme 71. A lithium halogen exchange on diene **2.3.1.3**, followed by an electrophilic quenching could potentially afford the corresponding acid, or ester. An interesting method for the stereospecific formation of vinyllithium derivatives was the closest example found to the desired reaction.[70]



Scheme 73. Lithium halogen exchange conditions to prepare terminal vinyllithium species[70]

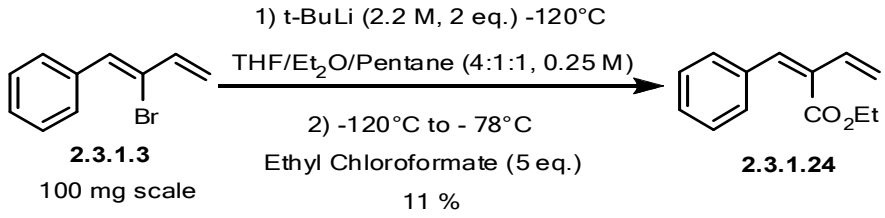
Using diene **2.3.1.3** as the halide source for the lithium-halogen exchange, and using CO_2 as an electrophile, the formation of acid **2.3.1.5** was attempted.

(70) H. Neumann and D. Seebach, *Tetrahedron Letters,* **1976**, *52*, 4839.



Scheme 74. Attempted formation of acid **2.3.1.5** by lithium-halogen exchange-electrophilic quenching sequence

While warming the reaction vessel from -120°C to -78°C, a color change of the mixture from a pale transparent color to a dark green solution occurred. One major product was formed during the reaction, but ^{1}H NMR of the crude was not corresponding to the expected product **2.3.1.5**, as previously reported in the literature.[71] Since previous lithium-halogen exchanges failed when using CO_2 as the electrophile, the same reaction conditions were used changing the electrophile for ethylchloroformate.



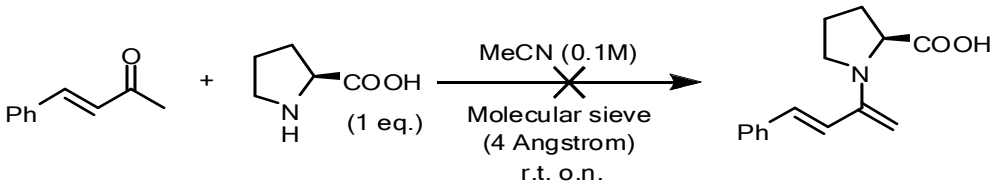
Scheme 75. Formation of ester **2.3.1.24** by lithium-halogen exchange/electrophilic quenching sequence

This time, the expected product **2.3.1.24** was formed in 11 % yield. The product is confirmed by ^{1}H NMR when comparing the obtained spectra (Scheme 71 and 75) to the one previously reported in the literature.[72] The color change at approximately -78°C was observed again, but the reaction was not repeated due to time constraints. An increase in yield might be possible by

(71) H. Alper and G. Vasapollo, *Tetrahedron Letters,* **1989**, *30*, 2617.
(72) See reference 68. The spectrum also matched the one of product **2.3.1.24** obtained previously, as shown on scheme 71.

optimization of the current conditions, allowing this synthetic pathway to become more convenient than the one shown previously in scheme 71.

Generation of a chiral enamine as the diene partner was also envisaged, although the conditions used here were not successful. It was suggested that a reaction under similar conditions refluxing in a Dean-Stark apparatus could potentially generate the desired enamine.

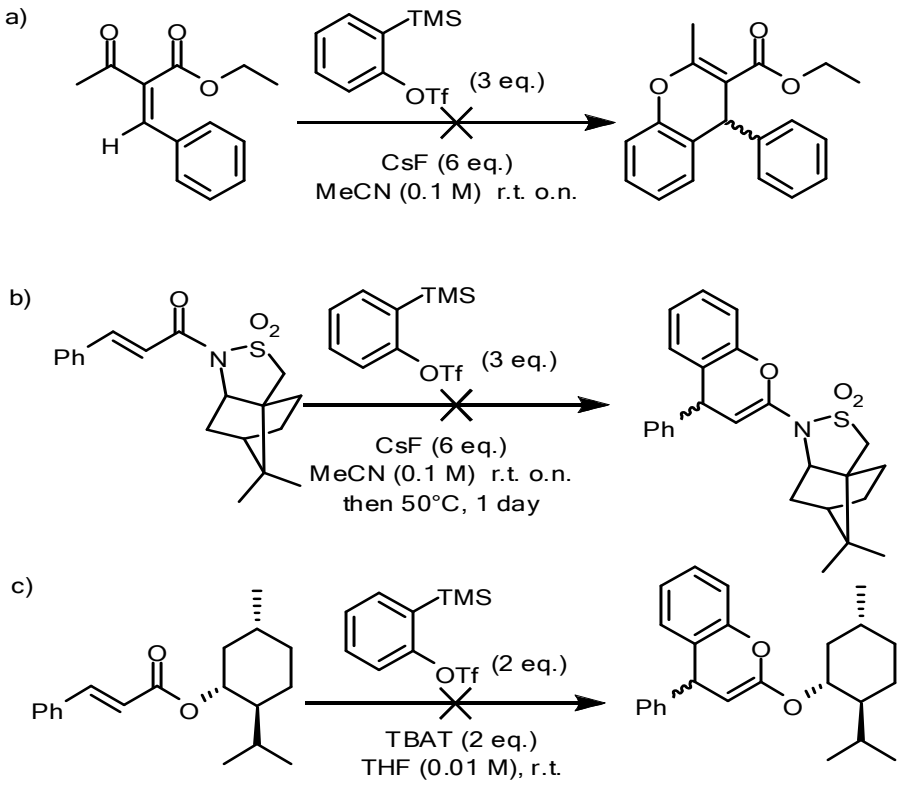


Scheme 76. Failed *in-situ* generation of a chiral auxiliary supporting diene by chiral enamine formation

2.3.2 Attempted Aryne Diels-Alder Reactions

Despite no desired chiral auxiliary supporting dienes could be obtained, several aryne Diels-Alder reactions[73] were attempted on hetero-dienes, as shown in scheme 77. Unfortunately, these reactions were all extremely messy, showing dozens of different byproducts on TLC. No major product of interest could be isolated.

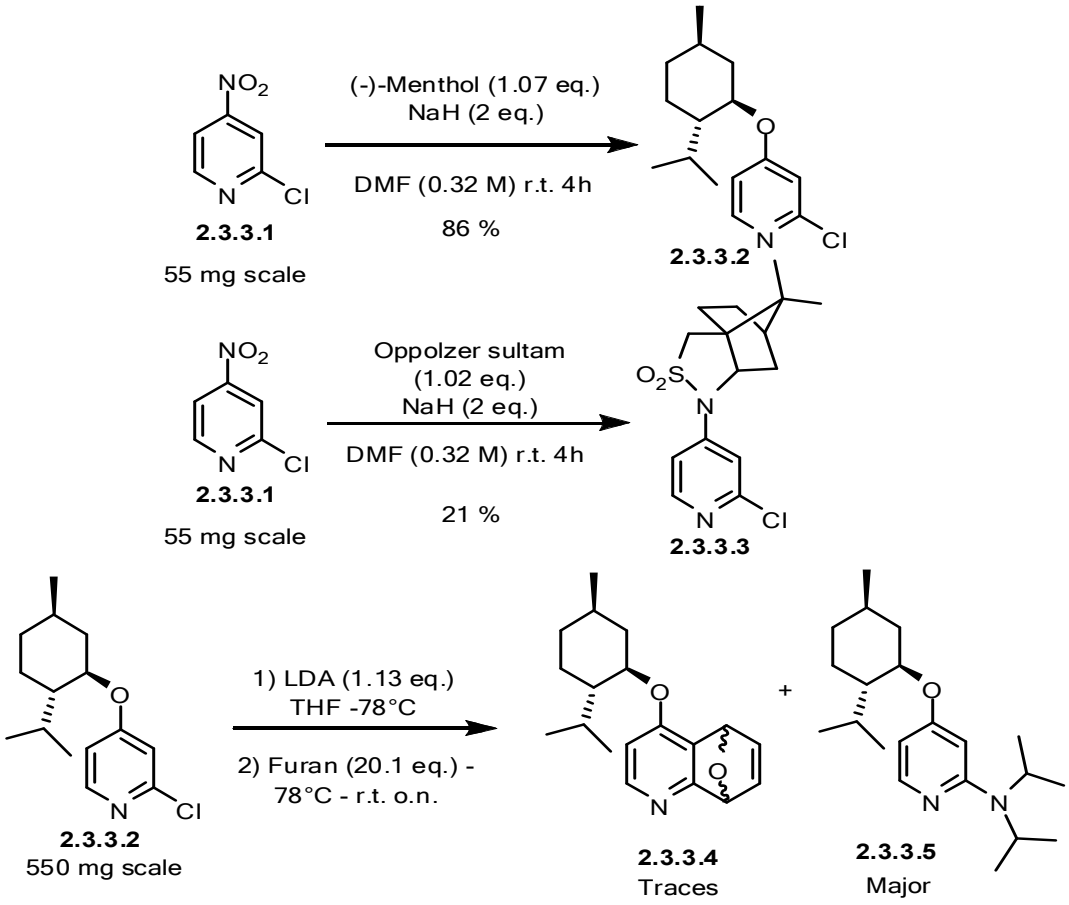
(73) For conditions, see, for entry a) and b) : reference 49. For entry c) : C. D. Gilmore, K. M. Allan, and B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, *130*, 1558.



Scheme 77. Attempted aryne Diels-Alder reactions on various heterodienes

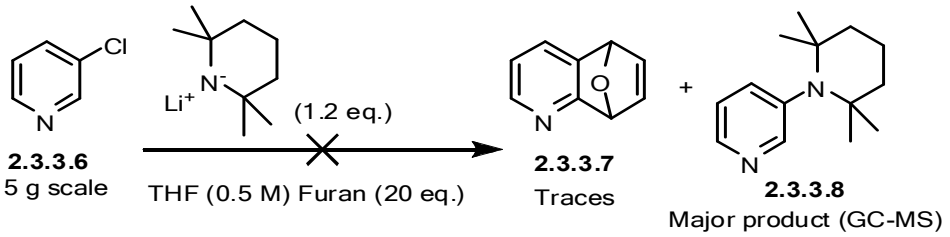
2.3.3 Formation of Chiral 2,3-Pyridyne Precursors

The formation of chiral pyridyne precursors was, to our knowledge, never attempted. The idea to use a chiral dienophile for the Diels-Alder reaction was suggested as it might give rise to a regioselective and diastereoselective transformation. Although chiral pyridyne precursors **2.3.3.2** and **2.3.3.3** were successfully synthesized, the use of **2.3.3.2** in the pyridyne Diels-Alder reaction with furan gave only traces of product **2.3.3.4**.



Scheme 78. Synthesis of chiral pyridyne precursors and attempted pyridyne Diels-Alder reaction

Synthesis of a simple dihydroepoxyquinoline **2.3.3.7** was also attempted starting from 3-chloropyridine **2.3.3.6**, but only traces of product could be observed by GC-MS. No ring-opening reaction could be attempted for a larger amount of **2.3.3.7** would have been required. These methods of generating pyridynes from a precursor with a leaving group and a strong base seemed to always give a large amount of substitution product, similar to **2.3.3.8**, no matter how hindered the base is. The actual Diels-Alder product **2.3.3.7** was only observed in traces by GC-MS and on ^{1}H NMR. Optimization of the reaction conditions or replacement of the pyridyne generation method may be required to achieve synthetically useful yields.



Scheme 79. Attempted synthesis of dihydroepoxyquinoline **2.3.3.7** by a pyridyne Diels-Alder reaction

The synthesis of dihydroepoxyquinoline by different methods and the investigation of typical asymmetric ring opening conditions on this substrate are currently carried out by our group.

2.4 Conclusion and Future Work

Despite our unfruitful attempts at synthesizing chiral acyclic dienes for the diastereoselective aryne Diels-Alder reaction, some progress was made in the right direction. Some methodologies were judged unsatisfactory for the synthesis of precursors to chiral auxiliary supporting dienes. For example, unstable dienes such as enol-ethers and enamines seem to be inconvenient if they cannot be used *in situ* for the following aryne Diels-Alder reaction. Also, the synthesis of dienes by olefination of a corresponding carbonyl containing substrate proved to be generally unsuccessful. Lithium-halogen exchange strategies, although low yielding so far, have shown some success in giving the corresponding esters. Future efforts should be concentrated toward the synthesis of relatively stable chiral dienes, which can be manipulated or preserved over a certain period of time without decomposition occurring. Such dienes will be preferred by anyone willing to use our methodology in the future.

A variety of ester hydrolysis methods should be tested on **2.3.1.24**, hopefully forming the corresponding acid. This acid, in the presence of a chiral auxiliary and submitted to well-known coupling conditions (i.e. DCC coupling) should result in the corresponding chiral auxiliary supporting diene that will be tested under aryne Diels-Alder conditions.

Other generation methods for chiral auxiliary supporting diene could be considered. Formation of a chiral enamine in a Dean-Stark apparatus, or organocatalytic formation of a chiral enamine and its *in situ* reaction with an aryne are to be considered.

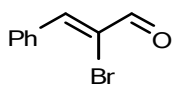
Our successful synthesis of chiral pyridyne precursors has to be further investigated. These precursors have to be tested for yields and selectivity in their pyridyne Diels-Alder reaction with a variety of dienes. If interesting products can be formed in synthetically useful yields and diastereomeric ratios, the methodology might be extended to the formation of other useful chiral auxiliary supporting arynes and heteroarynes.

Finally, dihydroepoxyquinoline should be subjected to various known ring-opening conditions usually in use for oxabicyclic alkenes. If these conditions are successful in ring-opening dihydroepoxyquinolines, chiral substituted dihydroquinolines could be formed rather easily, furnishing new building blocks for synthetic chemists. This methodology could then be extended to a variety of other aryne and heteroaryne adducts, forming a wide variety of chiral building blocks.

2.5 Experimental

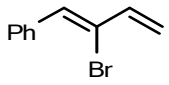
2.5.1 Compounds

2.5.1.1 (*Z*)-2-bromo-3-phenylacrylaldehyde (2.3.1.2)



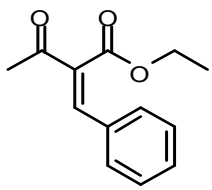
2.3.1.2 was obtained by literature procedure[74] starting from 50 g of *trans*-cinnamaldehyde **2.3.1.1**. Two successive recrystallizations in EtOH/H_2O 4:1 afforded **2.3.1.2** (49.25 g, 62 %) as light beige crystals. ^{1}H NMR was consistent with previously reported spectral data.[74]

2.5.1.2 (*Z*)-(2-bromobuta-1,3-dienyl)benzene (2.3.1.3)



2.3.1.2 (2 g, 9.476 mmol) was weighed in a flame-dried round-bottom flask equipped with a magnetic stir-bar. The flask was purged with dry nitrogen, and Et_2O (20 mL) was added via syringe. The mixture is cooled to -78°C and $TMSCH_2MgCl$ (1 M in Et_2O, 40 mL) was added dropwise. The mixture is then stirred for 30 minute, and warmed to 0°C. The mixture is quenched with water, and extracted with Et_2O. The solvent is evaporated, and the residue is recovered in Et_2O/HCl 1M (1:1, 20 mL: 20 mL) and stirred vigourously at room temperature for an hour. Layers are then separated, and **2.3.1.3** is extracted from the aqueous layer using portions of Et_2O. The combined organic phases are dried on anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford **2.3.1.3** (0.4468 g, 23%) as a clear yellow oil. ^{1}H NMR was consistent with previously reported spectral data.[75]

2.5.1.3 (*Z*)-ethyl 2-benzylidene-3-oxobutanoate (2.3.1.11)

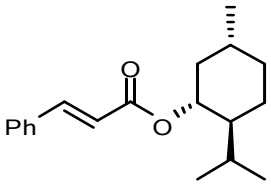


2.3.1.11 was obtained by literature procedure[64] replacing pyridine by piperidine. (Z)- **2.3.1.11** (5.7243 g, 35%) was easily separated from (E)- **2.3.1.10** (2.6407 g, 16 %) by flash

(74) C. F. H. Allen, C. O. Edens, *Org. Synth., Coll. Vol. III* **1955**, 731.
(75) See supporting information, structure **49**, of: N. Chinkov, S. Majumdar and Ilan Marek, *J. Am. Chem. Soc.* **2003**, *125*, 13258.

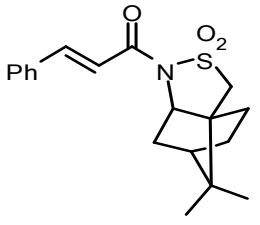
chromatography (hexanes/ethyl acetate 10:1). (Z)- **2.3.1.11** stains red-orange when revealed on TLC in *para*-anisaldehyde while (E)- **2.3.1.10** stains bright orange under the same conditions.

2.5.1.4 (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl cinnamate (2.3.1.15)



To a flame-dried round bottom flask charged with a magnetic stir-bar was added cinnamic acid **2.3.1.14** (0.1482 g, 1 mmol) and DCM (10 mL). The mixture was stirred at room temperature while oxalyl chloride (88 μL, 1 mmol) was added dropwise. The solution was stirred 15 minutes at room temperature, and the solvent was removed under reduced pressure to give the corresponding crude acyl chloride, stored aside under nitrogen. In a separate flame-dried flask was added (-)-menthol (0.1563 g, 1 mmol), Et_3N (0.35 mL, 2.5 mmol) and toluene (10 mL). The mixture was stirred at room temperature until all solids are dissolved, and transferred to the flask containing the acid chloride via cannula. The final mixture is stirred for 30 minutes at room temperature. The solution is washed with a saturated NH_4Cl solution, and extracted with DCM. The combined organic phases are dried on anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford **2.3.1.15** (0.2148 g, 75%). ^1H NMR was consistent with previously reported spectral data.[76]

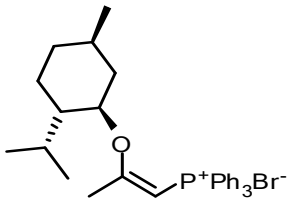
2.5.1.5 (2,10)-(-)-Camphorsultamyl cinnamate (2.3.1.16)



(76) J. H. P. Hutley, M. Güllü and Majid Motevalli, *J. Chem. Soc. Perkin Trans. 1,* **1995**, 1961.

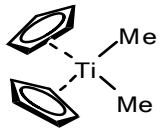
To a flame-dried round bottom flask charged with a magnetic stir-bar was added cinnamic acid **2.3.1.14** (0.1630 g, 1.1 mmol) and DCM (11 mL). The mixture was stirred at room temperature while oxalyl chloride (96 μL, 1.1 mmol) was added dropwise. The solution was stirred 15 minutes at room temperature, and the solvent was removed under reduced pressure to give the corresponding crude acyl chloride, stored aside under nitrogen. In a separate flame-dried flask was added (-)-(2,10)-camphorsultam (0.2153 g, 1 mmol), NaH (0.0438 g, 1.1 mmol) and toluene (5 mL). The mixture was stirred under nitrogen at room temperature until the evolution of hydrogen stopped, and the acyl chloride was transferred to the flask containing the deprotonated sultam via cannula. The final mixture is stirred overnight at room temperature, before being washed with a saturated NH_4Cl solution, and extracted with DCM. The combined organic phases are dried on anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford Y (0.3109 g, 90%). ^{1}H NMR was consistent with previously reported spectral data.[77]

2.5.1.6 ((*Z*)-2-((1R,2R,5R)-2-isopropyl-5-methylcyclohexyloxy)prop-1-enyl)triphenylphosphonium bromide (2.3.1.18a)



Synthesized according to literature procedure[43a] starting from (3.1454g, 8.25 mmol) of commercial prop-2-ynyl-triphenylphosphonium bromide. The reaction afforded **2.3.1.18a** (3.9910 g, 90%) with ^{1}H NMR consistent with previously reported spectral data. [43a]

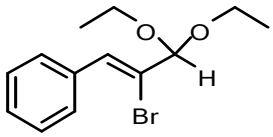
2.5.1.7 Dimethyltitanocene (2.3.1.19)



(77) See supporting info, compound 23 in: N. M. Neisius and B. Plietker, *J. Am. Chem. Soc.* **2008**, *73*, 3218.

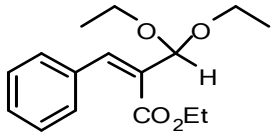
Synthesized following the literature procedure starting from commercially available titanocene dichloride (8.3 g, 33.3 mmol). The reaction afforded **2.3.1.19** (2.6 g, 37%, as a 26 g solution in toluene/THF) with ^{1}H NMR consistent with previously reported spectral data.[67a]

2.5.1.8 (*Z*)-(2-bromo-3,3-diethoxyprop-1-enyl)benzene (2.3.1.20)



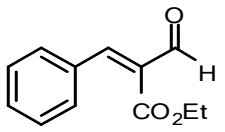
Synthesized following literature procedure[74] starting from **2.3.1.2** (2.1106 g, 10 mmol). The reaction afforded **2.3.1.20** (1.5710 g, 55%) with ^{1}H NMR consistent with previously reported spectral data.[74]

2.5.1.9 (*Z*)-ethyl 2-(diethoxymethyl)-3-phenylacrylate (2.3.1.21)



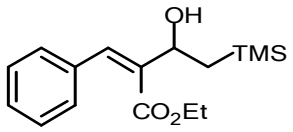
Synthesized following literature procedure[68a] starting from **2.3.1.20** (1.5710 g, 5.509 mmol). The reaction afforded **2.3.1.21** (0.5161 g, 34%) with ^{1}H NMR consistent with previously reported spectral data.[68a]

2.5.1.10 (*Z*)-ethyl 2-formyl-3-phenylacrylate (2.3.1.22)



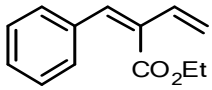
Synthesized following literature procedure[68a] starting from **2.3.1.21** (0.5161 g, 1.854 mmol). The reaction afforded **2.3.1.22** (0.3424 g, 90%) with ^{1}H NMR consistent with previously reported spectral data.[68a]

2.5.1.11 (*Z*)-ethyl 2-benzylidene-3-hydroxy-4-(trimethylsilyl)butanoate (2.3.1.23)



Synthesized following a known procedure[78] starting from **2.3.1.22** (0.2425 g, 1.187 mmol). The reaction afforded **2.3.1.23** (0.1418 g, 41%) with ^{1}H NMR consistent with previously reported spectral data.[78]

2.5.1.12 (*Z*)-ethyl 2-benzylidenebut-3-enoate (2.3.1.24)



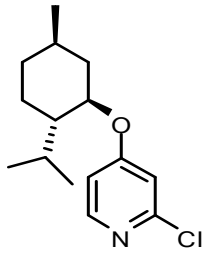
Synthesized following a known procedure[78] starting from **2.3.1.23** (0.2065 g, 0.706 mmol). The reaction afforded **2.3.1.24** (0.1349 g, 95%) with ^{1}H NMR consistent with previously reported spectral data.[79]

Bromide **2.3.1.3** (0.1 g, 0.478 mmol) was weighed in a carefully flame-dried round-bottom flask equipped with a magnetic stir-bar. The flask was quickly covered and its content was flushed with nitrogen. 2 mL of a solvent mixture (THF/Et_2O/pentane 4:1:1) were added via syringe. Solvents used in the mixture need to be completely dry and degassed with nitrogen before use. The mixture is homogenized by stirring at room temperature. Vigorous stirring is continued while the mixture is cooled in a ~ -120°C bath (Et_2O/pentane 2:1 with liquid nitrogen). The temperature of the bath is monitored with a thermocouple so that it stays between -125°C and -

(78) S. Sahli, *Postdoctoral Research report,* University of Toronto, **2006**, p. 44.
(79) See reference 69 and : F. Bellina, A. Carpida, M. De Santis, R. Rossi, *Tetrahedron* **1994**, *50*, 12029.

115°C. Liquid nitrogen and solvent is added when needed to keep the bath at the desired temperature. Tert-butyllithium (2.2 M in pentane, 0.435 mL, 0.957 mmol) is added dropwise via syringe within 10 minutes. The temperature is kept below -112°C for 40 minutes. The reaction is then allowed to warm back to -78°C. At this point, freshly distilled ethyl chloroformate (0.23 mL, 2.4 mmol) is added dropwise at -78°C and the reaction is stirred for 15 minutes at -78°C, before being allowed to return to room temperature while stirring overnight. The mixture is then washed with a saturated solution of ammonium chloride, and extracted with DCM. The combined organic phase is dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Flash chromatography (pentane/Et_2O 25:1) afforded **2.3.1.24** (0.0104 g, 11%) as confirmed by ^1H NMR.[79]

2.5.1.13 2-chloro-4-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)pyridine (2.3.3.2)

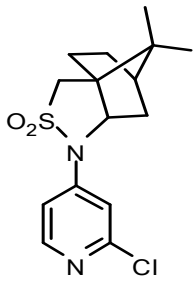


In a flame-dried round-bottom flask equipped with a magnetic stir-bar were quickly added 4-nitro-2-chloropyridine **2.3.3.1** (0.0550 g, 0.347 mmol), NaH (60% in mineral oil, 0.0278 g, 0.694 mmol) and (-)-menthol (0.0580 g, 0.371 mmol). The flask was stoppered with a septum, purged with dry nitrogen and DMF (1.1 mL) was added. The mixture was stirred at room-temperature overnight. 5 mL ethyl acetate/water (1:1) were added at 0°C, the organic layer was separated, and successively washed with water, and brine. The organic phase is then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (pentane/ethyl acetate 14:1) afforded **2.3.3.2** (0.0798 g, 86%) as a white solid.

^1H NMR (300 MHz, $CDCl_3$) δ = 8.12 (d, 1H, J = 5.9), 6.78 (d, 1H, J = 2.2), 6.69 (dd, 1H, J_1 = 2.2, J_2 = 5.8), 4.08 (td, 1H, J_1 = 4.2, J_2 = 5.8), 2.15-1.93 (m, 2H), 1.79-1.65 (m, 2H), 1.58-1.38 (m, 2H), 1.19-0.80 (m, 9H), 0.71 (d, 3H, J = 7)**;** ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.4, 152.8,

150.5, 110.7, 110.5, 78.3, 47.8, 39.8, 34.4, 31.5, 26.4, 23.9, 22.2, 20.8, 16.8; HRMS (EI) for $C_{15}H_{22}ClNO$ m/z calculated 267.14, found, 267.1390.

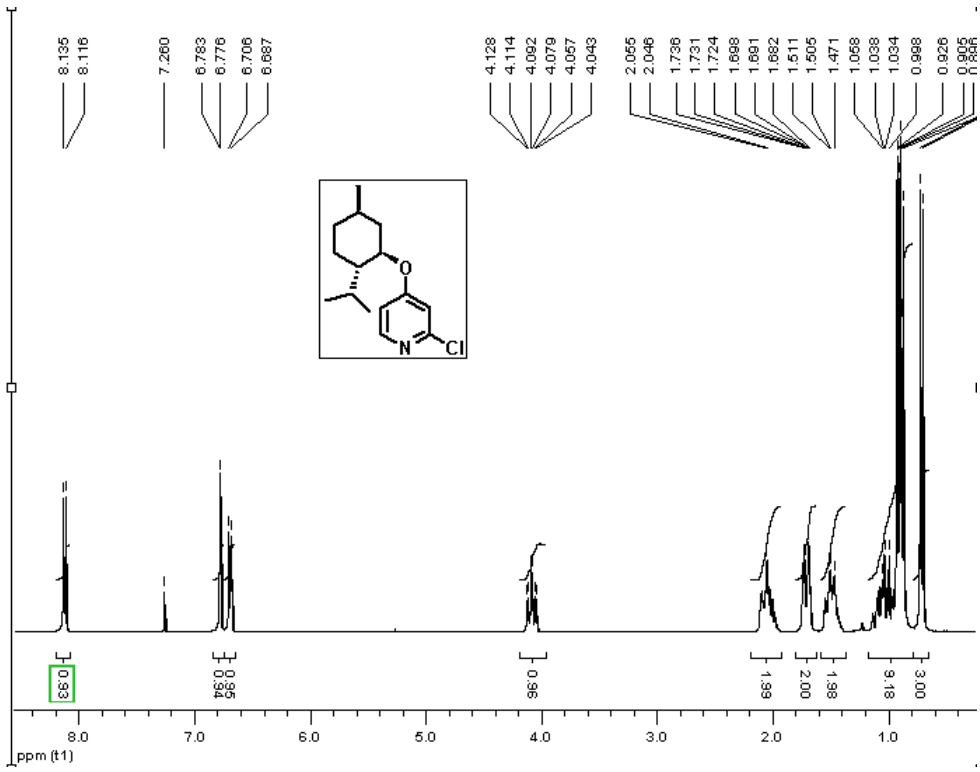
2.5.1.14 2-chloro-4-(camphorsultamyl)pyridine (2.3.3.3)

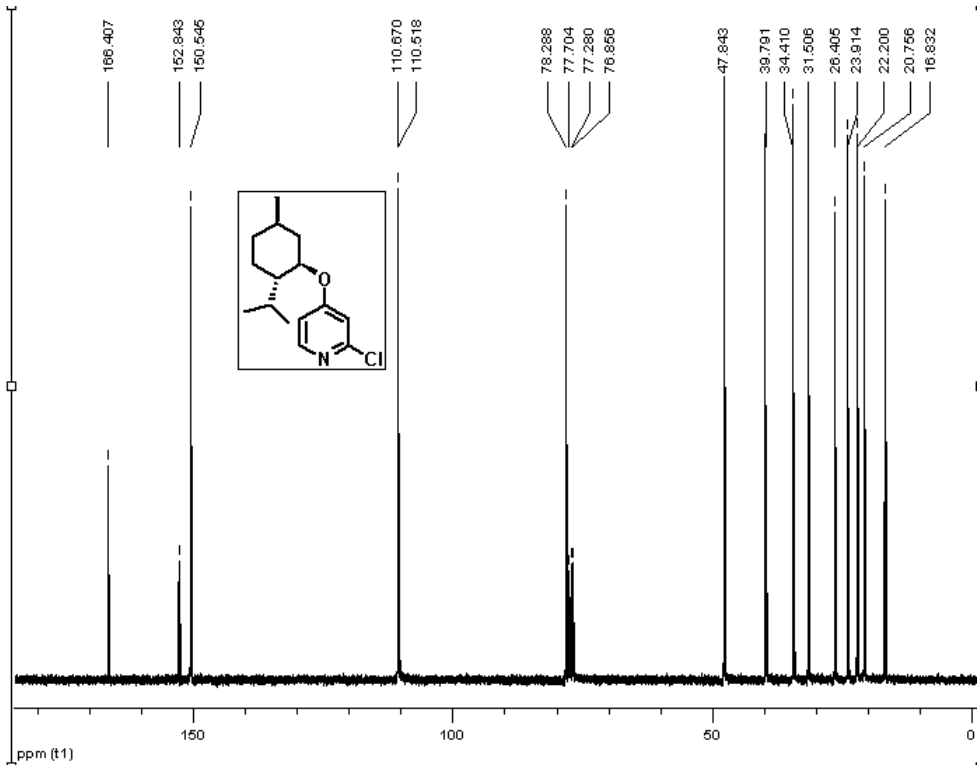


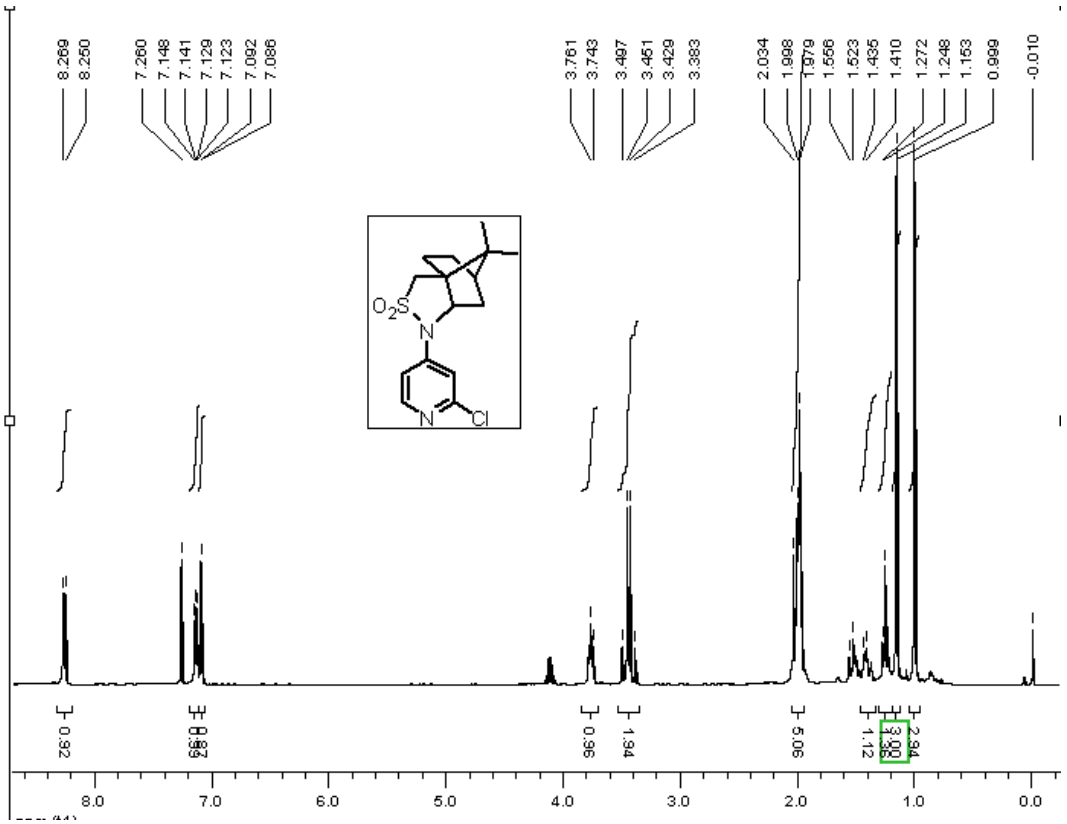
In a flame-dried round-bottom flask equipped with a magnetic stir-bar were quickly added 4-nitro-2-chloropyridine **2.3.3.1** (0.0550 g, 0.347 mmol), NaH (60% in mineral oil, 0.0278 g, 0.694 mmol) and (-)-(2,10)-camphorsultam (0.0762 g, 0.354 mmol). The flask was stoppered with a septum, purged with dry nitrogen and DMF (1.6 mL) was added. The mixture was stirred at room-temperature overnight. 5 mL ethyl acetate/water (1:1) were added at 0°C, the organic layer was separated, and successively washed with water, and brine. The organic phase is then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (pentane/ethyl acetate 2.5:1) afforded **2.3.3.3** (0.0236 g, 21%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.26 (d, 1H, J = 5.6), 7.13 (dd, 1H, J_1 = 2, J_2 = 5.7), 7.09 (d, 1H, J = 1.8), 3.76 (t, 1H, J = 5.3), 3.47 (d, 1H, J = 14), 3.40 (d, 1H, J = 14), 2.05-1.94 (m, 5H), 1.46-1.33 (m, 1H), 1.25 (t, 1H, J = 7.2), 1.15 (s, 3H), 1.00 (s, 3H)**;** ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.7, 150.4, 146.1, 113.8, 113.0, 64.7, 51.7, 50.0, 48.2, 44.9, 37.4, 32.7, 27.1, 20.8, 20.1**;** HRMS (EI) for $C_{15}H_{19}ClN_2O_2S$ m/z calculated 326.09, found, 326.0856.

2.5.2 ^{1}H NMR and ^{13}C NMR Spectra



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1.556
1.523
1.435
1.410
1.272
1.248
1.153
0.999
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0.96
1.94
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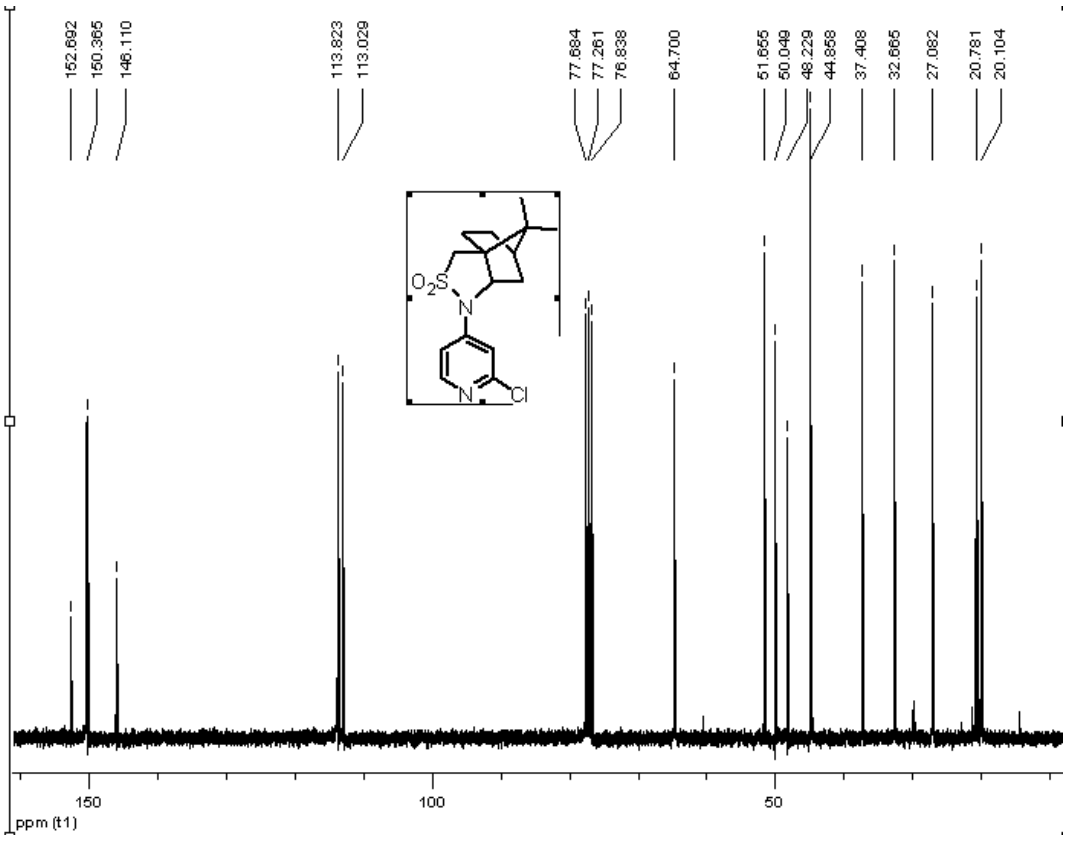
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ppm (t1)