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GRADU AMAIERAKO LANA

Exploring α-branched nitroalkanes as substrates for asymmetric catalysis

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Exploring α-branched nitroalkanes as substrates for asymmetric catalysis

Laburpena

Gradu Amaierako Lan hau Donostiako Kimika Fakultateko Kimika Organikoa I Departamentuan garatu da, Antonia Mielgo Vicente irakaslearen zuzendaritzapean. Proiektu honetan planteatutako ikerketa Kimika Organikoaren arloan kokatzen da, zehatzago, katalisi asimetrikoaren barruan. Lan honetan α-adarkatutako nitroalkanoen erreaktibotasuna aztertu da katalisi duala (Metala + Brønsted Basea, BB) erabiliz Michael adizio erreakzioan, zehatzago, α posizioan talde elektroerakarleak ez dituzten α-nitroalkanoena. Horretarako, bi estrategia ikertu dira; lehenengoan, bi katalizatzaileren prestaketa saiatu da zeintzuk Brønsted Basea eta egitura kelatatzailea molekula berean dauzkaten; bigarren estrategian, Brønsted Basea eta egitura kelatzailea entitate ezberdinetan mantendu dira. Beraz, lehenik katalizatzaileen sintesia gauzatu da deskribatutako metodoen egokitzapenak eginez eta bertan hainbat zailtasun aurkitu dira. Bigarrenik, α-adarkatutako nitroalkanoen sintesia gauzatu da bibliografian deskribatutako metodoak eta egokitzapenak eginez. Hirugarrenik, komertzialak den elektrozale baten sintesia gauzatu da bibliografiako prozedura jarraituz. Azkenik, sistema katalitikoak probatu dira baldintza ezberdinetan sistemen erreaktibotasuna, etekina eta estereokontrola determinatzeko asmoz. Ikusi da entitate berean Brønsted basea eta egitura kelatatzailea erakusten dituztela konposatuek disolbagarritasun arazoak dauzkatela, aldiz, entitate ezberdinetan daukaten sistema katalitikoak erabiliz erreakzioa ematen da nahiz eta optimizazioa gauzatu beharra dagoen oraindik.

Summary

This research project has been developed in the Department of Organic Chemistry I at the Faculty of Chemistry in Donostia, under the guidance of professor Antonia Mielgo Vicente. Research carried out in this project belong to the Organic Chemistry field, more specifically to Asymmetric Catalysis. During this project, the reactivity of α-branched nitroalkanes in Michael addition reactions has been studied making use of dual catalysis (Metal + Brønsted Base, BB); more specifically, α-branched nitroalkanes that do not bear an electron withdrawing group at the α position. Two strategies are designed for that purpose; in the first one, the synthesis of two catalysts which contain the Brønsted Base and the chelating structure in the same molecule has been explored; in the second strategy, the Brønsted Base and the chelating structure are in different entities. So, firstly the synthesis of the catalyst has been performed by adapting described methods and some difficulties have been found in the process. Secondly, the synthesis of α-branched nitroalkanes has been performed following procedures in the literature. Thirdly, preparation of a commercially non available electrophile has been performed. Lastly, the catalytic systems have been tested out in different conditions with the objective to determine the reactivity, reaction yield and stereocontrol. It has been observed that the catalyst containing the Brønsted Base attached to the chelating structure show solubility problems, while systems that have them in separated entities are able to promote the reaction happens even though optimization still hasn't been made.

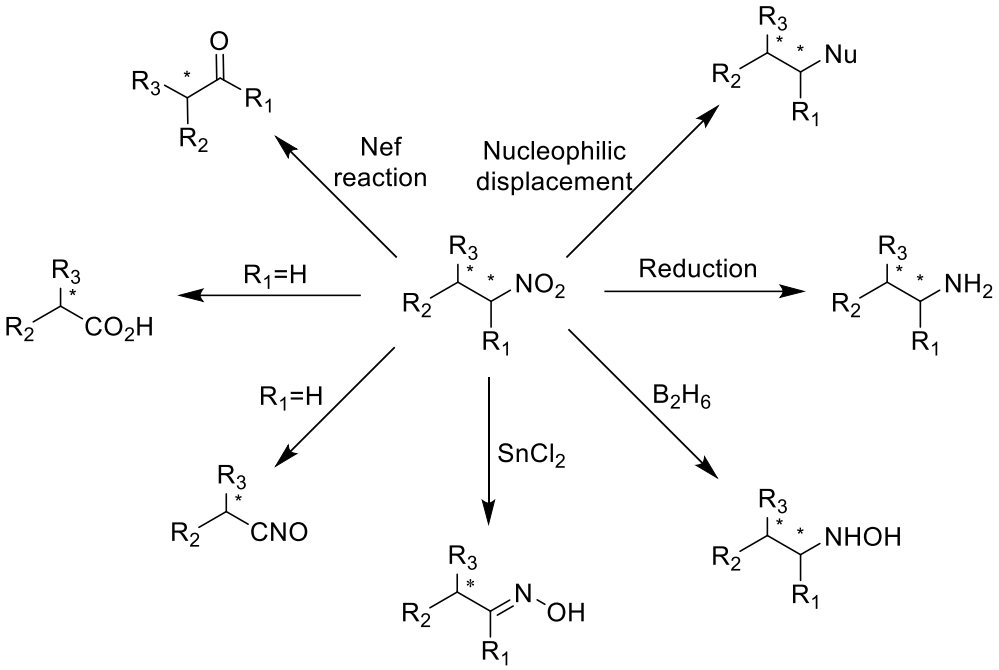
Abbreviations and acronyms

Ac	Acetate
AcOH	Acetic Acid
BB	Brønsted Base
BINAP	2,2'-bis(diphenylphosphaneyl)-1,1'-binaphthalene
Cat.	Catalyst / Catalytic
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIPA	Diisopropylamine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
ee	Enantiomeric excess
eq.	Equivalent
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron-withdrawing group
FGI	Functional Group Interchange
H	Hour
Hex	Hexane
HPLC	High Performance Liquid Chromatography
HRMS	High-Resolution Mass Spectrometry
iPr	Isopropyl
Me	Methyl
MHz	Megahertz
min	Minute
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
on	Overnight
OTf	Triflate
ow	Over weekend
RT	Room Temperature
t	Time
T	Temperature
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahidrofuran
TLC	Thin Layer Chromatography
δ	Chemical Shift
λ	Wavelenght

INDEX

1. Introduction

Nitroalkanes are an important group of compounds in the field of organic chemistry. This relevance relies on the manoeuvrability of the nitro group which can be converted into other functional groups[1] such as nitrile oxides[2], ketones[3], amines[4], hydroxylamines[5], oximes[6] or carboxylic acids. The Nef reaction, nucleophilic displacements[7], reductions to the amino group using metal hydrides, reductions to hydroxylamine using boranes, the oxidation to carboxylic acid via Mioskowski reaction, the reduction to oxime with $SnCl_2$ or the conversion to nitrile oxide are some examples of the possible transformations that enable this group (Scheme 1).



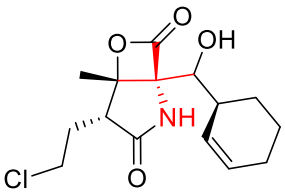
Scheme 1: Examples of the transformations of the nitro compounds.

Additionally, as nitro is a highly electron withdrawing functional group, the reactivity of nitroalkanes is high and they have been successfully employed in reactions involving C-

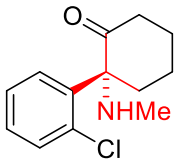
[1] Seebach, D.; Colvin, E.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1-18. b) Ono, N. *The Nitro Group in Organic Synthesis*, Wiley, New York, **2001**. c) Ballini, R.; Palmieri, A. *Nitroalkanes: Synthesis, reactivity and Applications* **2021**, Wiley-VCH.
[2] Mukaiyama, T.; Hoshino, T. J. Am. Chem. Soc. 1960, 82 (20), 5339–5342.
[3] a) Nef, J. U. *Justus Liebigs Ann. Chem.* **1894**, *280* (2–3), 263–291; b) Pinnick, H. W. *The Nef Reaction. In Organic Reactions*; Wiley, 1990; 655–792; c) Ballini, R.; Petrini, M. *Adv. Synth. Catal.* **2015**, *357* (11), 2371–2402.
[4] a) Barrett, A. G. M.; Spilling, C. D. *Tetrahedron lett.* **1998**, *29* (45), 5733-5734; b) Chi, Y.; Gua, L; Kopf, N. A; Gellman, S. H. *J. Am. Chem. Soc.* **2008**, *130* (17), 5608-5609; c) Goksu, H.; Sert, H.; Kilbas, B.; Sen, F. *Curr. Org. Chem.* **2017**, *21* (9), 794-820
[5] Feuer, H.; Bartlett, R. S.; Vincent, B. F.; Anderson, R. S. *J. Org. Chem.* **1965**, *30* (9), 2880–2882.
[6] Shunyou C.; Shaolong Z.; Yaohong Z. *et al. Org. Lett.* **2013**, *15* (11), 2660–2663
[7] Tamura, R.; Kamimura, A.; Ono, *N. Synthesis*, **1991**, *6*, 423–434.

C and C-X bond formation such as Henry, nitro-Michael or nitro-Mannich (also known as aza-Henry).[1b] As a consequence of their convertibility and their reactivity, nitroalkanes are useful intermediates for synthesis of natural products, pharmaceutical materials, drugs and many other fields.[8] There are natural products which contain the nitro group and exhibit diverse biological activities, however the number of nitro compounds in drug discovery is scarce due to the fact that they tend to form radical species with the risk to be toxic or muagenic. Therefore, they are classified as "Structural alerts".[9]

In this context, α-stereogenic nitro compounds are building blocks of high versatility that have attracted great interest. More specifically, upon reduction of the nitro group the corresponding α-stereogenic tertiary amines could be obtained. These are indispensable fragments for the production of natural products and bioactive compounds. In fact, these chiral amine units are present in approximately 20 % of the drugs sold on the market.[10] Some examples of these compounds are salinosporamide A and ketamine, among others (Figure 1).[11]



Salinosporamide A



Ketamine

Figure 1: Examples of drugs containing chiral α-tertiary amines.

The compounds listed above show different biological activities and they are used as drugs. Salinosporamide A is a protease inhibitor showing anticarcinogenic properties, it is being studied for chemotherapy against myeloma[12]. Ketamine is used as an anaesthetic agent and it is also being studied to treat depression[13]. These simple examples underline the significance of α-stereogenic chiral tertiary amines for the production of pharmaceutical products and therefore, efficient methods for their feasible acquisition are indispensable.

[8] Sukhorukov, A. Y.; *Frontiers in Chemistry*, **2020**, *8*, 595246
[9] Walsh, J. S., Miwa, G. T.; *Annu. Rev. Pharmacol. Toxicol.*, **2011**, *51*, 145–167.
[10] Blacker A. J., Stirling M. J., Page, M. I; *Org. Process Res. Dev.*, **2007**, 11 (3), 642–648
[11] Sukach, V.A., Tkachuk, V. M., Gillaizeau, I. *et al.*; *Theor Exp Chem*, **2022**, *57*, 387–420.
[12] Gholami, H., Kulshrestha, A., Favor, O. K., Staples, R. J., Borhan, B.; *Angew. Chem. Int. Ed.*, **2019**, *131* (30), 10216–10219
[13] Pribish, A., Wood, N., Kalava, A.; *Anesthesiol. Res. Pract.*; **2020**, 2020, 5798285

In this context, one of the most direct approach for the obtention of these α-stereogenic chiral tertiary amines is the asymmetric C_α-H functionalization of α-branched nitroalkanes. However, this field progresses slowly, probably due to the difficulties this transformation shows. Whilst the enantioselective C_α-H functionalization of primary nitroalkanes has been achieved and efficient procedures with very good results have been reported[14], in the case of α-branched nitroalkanes, C_α -H functionalization still remains difficult to achieve and the enantioselectivity is in general improvable.[15] This may be attributed to the steric hindrance of R_1 and R_2 groups. This steric constraint causes a diminution in the reactivity as well as an increasing difficulty for the stereocontrol due to the generation of a quaternary centre in the α position.[16] In order to diminish these problems, researchers have used α-branched nitroalkanes containing an EWG at the α-position that, in one hand could increase the reactivity and on the other hand would offer additional coordinating points to the catalyst, an aspect that could help in the reaction stereocontrol.[17]

In this context asymmetric catalysis is probably one of the most attractive tools to investigate the stereoselective C_α-H functionalization of α-branched nitroalkanes. In asymmetric catalysis, the objective is to catalyse the reaction and to obtain the most of an enantiomer than from the other; in other words, the objective is to obtain the closest possible to an enantiopure mixture by using substoichiometric amounts of an appropriate chiral molecule as the catalyst.[18] This property makes asymmetric catalysis a very appealing method for the optimization of reactions. Not only is it appealing from the economical point of view but it is greener too. As the desired enantiomer is favourited, less product is discarded and as a consequence less money is spent and less residues are generated.

[14] a) (conjugate additions) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005,** *105*, 933-971; b) (Henry reaction) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915-945; c) (Nitro-Mannich) Noble, A.; Anderson, J. C. *Chem. Rev.* **2013**, *113*, 2887-2939

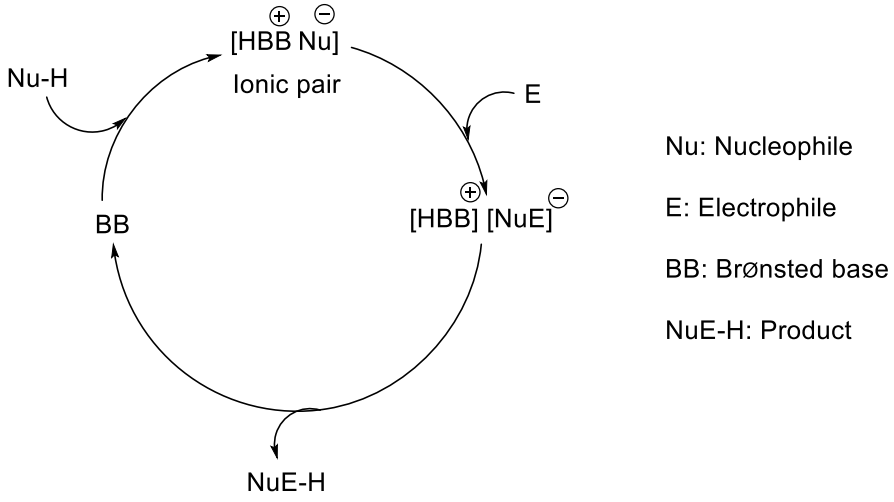
[15] a) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975-2978. b) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331-8338. c) Tsogoeva, S. B.; Hagtap, S. B.; Ardemasova, Z. A.; Kalikhevich, V. N. *Eur. J. Org. Chem.* **2004**, 4014-4019.

[16] For more information about the creation of tetrasubstituted stereocenters: a) Christoffers, J.; Baro, A.; *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Wiley, **2006**; b) Liu, Y.; Han, S. J.; Liu, W. B.; Stoltz, B. M., *Acc. Chem. Res.*; **2015**; *48* (3), 740-751; Bella, M.; Gasperi, T.; *Synthesis*, **2009**, 2009 (10), 1583-1614.

[17] a) Ohmatsu, K.; Ito, M.; Kunieda, T.; Ooi, T. Ion-Paired Chiral Ligands for Asymmetric Palladium Catalysis. *Nat. Chem.* **2012**, *4*, 473–477. b) Trost, B. M.; Schultz, J. E.; Bai, Y.; *Angew. Chem., Int. Ed.* **2019**, *58*, 11820-11825. (c) Davison, R. T.; Parker, P. D.; Hou, X.; Chung, C. P.; Augustine, S. A.; Dong, V. M. Enantioselective Coupling of Nitroesters and Alkynes. *Angew. Chem., Int. Ed.* **2021**, *60*, 4599-4603

[18] Seebach, D.; Hungerbühler, E. *Synthesis of Enantiomerically Pure Compounds (EPC-Synthesis) in Modern Synthetic Methods*, Scheffold, R. 1980, page 94, Salle + Saurerländer, Frankfurt.

Among all the asymmetric catalytic strategies developed to date, the catalysis mediated by Brønsted bases (BB) has experimented a great development.[19] In this case the catalytic cycle begins with the deprotonation of the nucleophile by the BB resulting in an ionic pair [HBB^+Nu^-] (Scheme 2). Afterwards, the nucleophile is capable of attacking the electrophile and that way the intermediate $[HBB]^+[NuE]^-$ is generated. Finally, a proton transfer occurs from the protonated $[HBB]^+$ towards $[NuE]^-$ resulting in the final product NuE-H and the regeneration of the BB catalyst. Moreover, if the catalyst is chiral, it could also control the stereochemistry of the process.



Scheme 2: Catalytic cycle mediated by Brønsted bases.

Among the developed chiral Brønsted base catalytic systems, the most efficient ones consist in bifunctional Brønsted bases (Figure 2).[20] The advantage of these catalysts is that they incorporate H-bond donor groups. When, the BB deprotonates the nucleophile another H-bond donor (BBH^+) is formed. It is via these H-bond donors that both the nucleophile and the electrophile can coordinate with the catalyst and this enables in general increased reactivity and higher stereoselectivity because the nucleophilic attack is more favourited from one of the enantiotopic faces.[20b]

[19] Revisions about reactions catalysed by BrØnsted base catalysts: a) Pellisser, H. *Adv. Synth. Catal*, **2019**, *361*, 1733-1755; b) Palomo C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.*, **2009**, *38*, 632-653, c) Ting, A.; Goss, J. M.; McDougal, N. T.; Schaus, S. E.;*Top. Curr. Chem.*, **2010**, *291*, 145-200.

[20] For some revisions about bifunctional BrØnsted bases: a) Quintavalla, A.; Cerisoli, L.; Montroni E. *Curr. Organocatalysis*, **2014**, *1*, 107-171. b) Nájera, C.; Sansano, J. M.; Gómez-Bengoa, E.; *Pure Appl. Chem.* **2016**, *88*, 561-578. c) Okino, T.; Hoashi, Y.; Takemoto, Y.; *J. Am. Chem. Soc.*; **2003**; *125*; 12672-12673. d) McCooey, S. H.; Connon, S. J.; *Angew. Chem. Int. Ed.*; **2005**; *44*; 6367-6370. e) Malerich, J. P.; Hagihara, K.; Rawal, V. H.; *J. Am. Chem. Soc.*; **2008**; *130*; 14416-14417. f) Diosdado, S.; Etxabe, J.; Landa, A.; Mielgo, A.; Olaizola, I.; Lopez, R.; Palomo, C.; *Angew. Chem. Int. Ed.*; **2013**; *52*; 11846-11851.

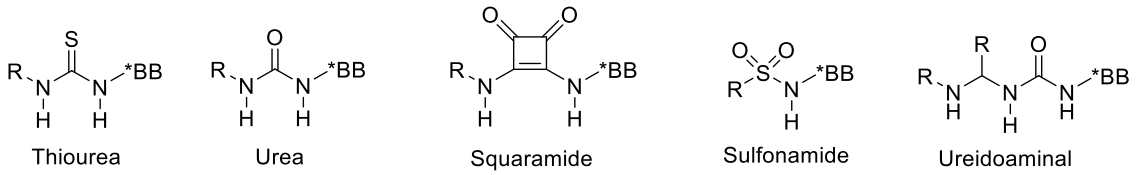
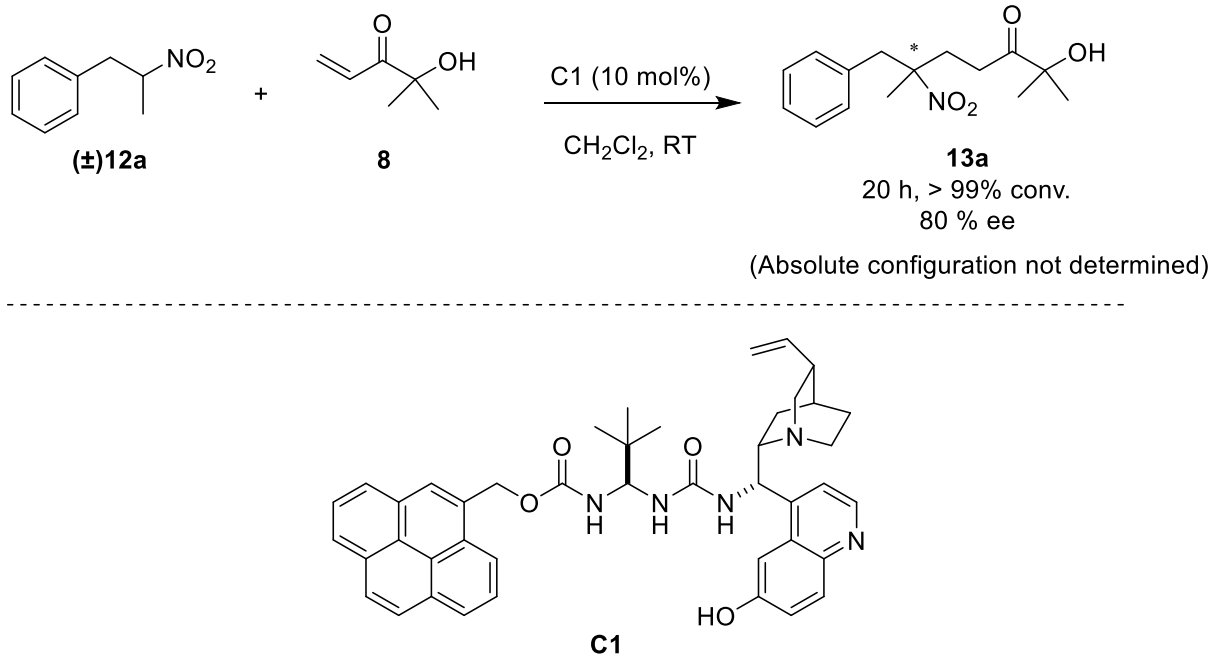


Figure 2: General H-bond donor motifs of bifunctional BB catalysts.

In this context, in our group Dr. Ane García together with Prof. Jesús García from the Navarre Public University (UPNA) started a joint project aiming to investigate the catalytic and asymmetric α-functionalization of secondary nitroalkanes lacking activating groups at the α-position; that is α-alkyl or aryl nitroalkanes. Their results show that the nitroalkane **(±)12a** can be easily activated by bifunctional Brønsted bases to react with the α-hydroxy enone **8** efficiently (Scheme 3). Among all the tested bifunctional Brønsted bases the ureidoaminal, **C1** provided the best results.



Scheme 3: Optimized Michael addition of α-branched nitroalkane **(±)12a** to α-hydroxy enone **8** (Dr. A. García and Prof. J. M. García)

2. Precedents

The success of the above reaction can be attributed to the nature of the catalyst and the electrophile. The catalyst belongs to a new catalyst subfamily[21] developed in the group of Prof. Palomo wherein a chiral tertiary amine is combined with an ureidoaminal fragment as H-bond donor. This H-bond donor unit is particularly interesting as it provides three NH groups for the interaction with the reaction substrates.

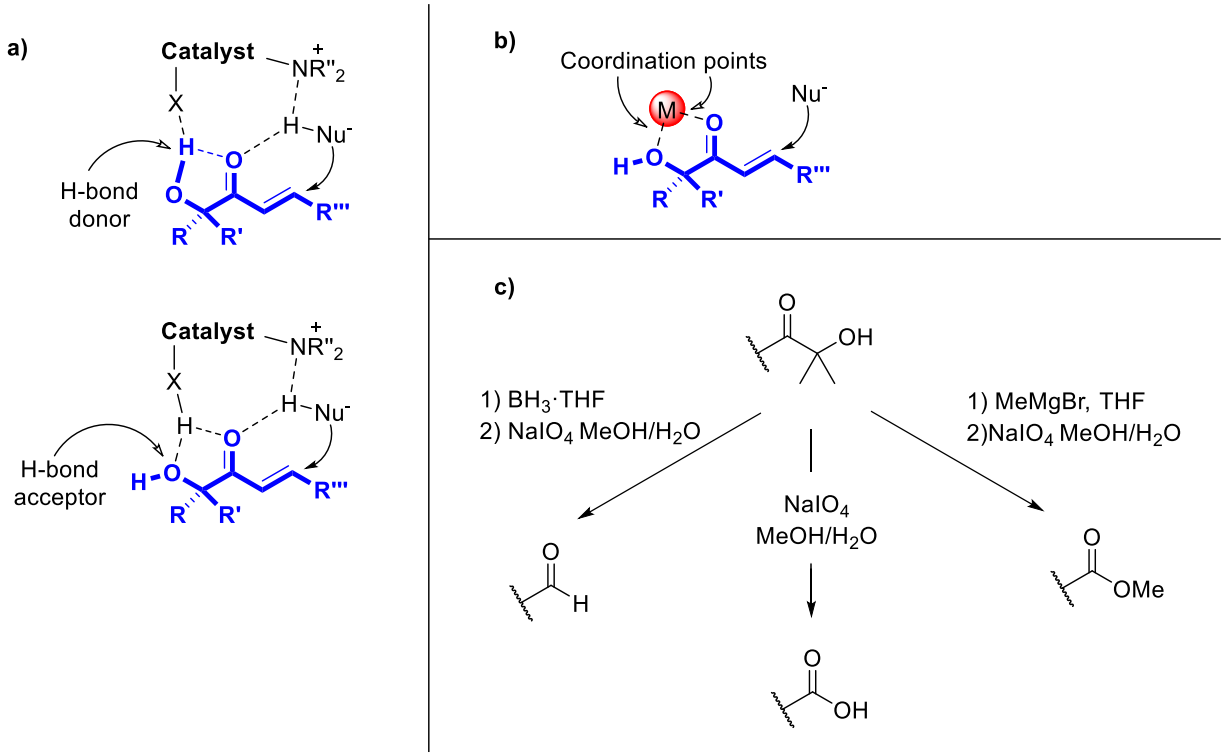
On the other hand, α-hydroxy enone **8** is also a new electrophile developed by the research group which has demonstrated to be an efficient electrophile[22] in various metal catalysed[1a, 23] and organocatalytic asymmetric transformations[24]. This success can be explained by the two coordination points the α-hydroxy enone moiety offers for coordination to the catalyst; the carbonyl group and the hydroxy group (Scheme 4a). Moreover, the α-hydroxy ketone can easily be converted into other functional groups such as ketone, aldehyde or carboxylic acid (Scheme 4b). This makes these α-hydroxy enones synthetic equivalents of enones, enals and α,β-unsaturated esters.

[21] For the first example of this catalyst type, see: a) Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C.; *Augew. Chem. Int. Ed.*; **2013**; *52*; 11846-11851. For a recent review on the subject, see: b) López, R.; Palomo, C.; *Chem. Eur. J.*; **2021**; *27*; 20-29.

[22] For a general review, see: a) Palomo, C.; Oiarbide, M.; García, J. M. *Chem.Soc. Rev.* **2012**, *41*, 4150–4164. For the first use (as chiral auxiliaries), see: b) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 7077–7079. c) Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 557–558.

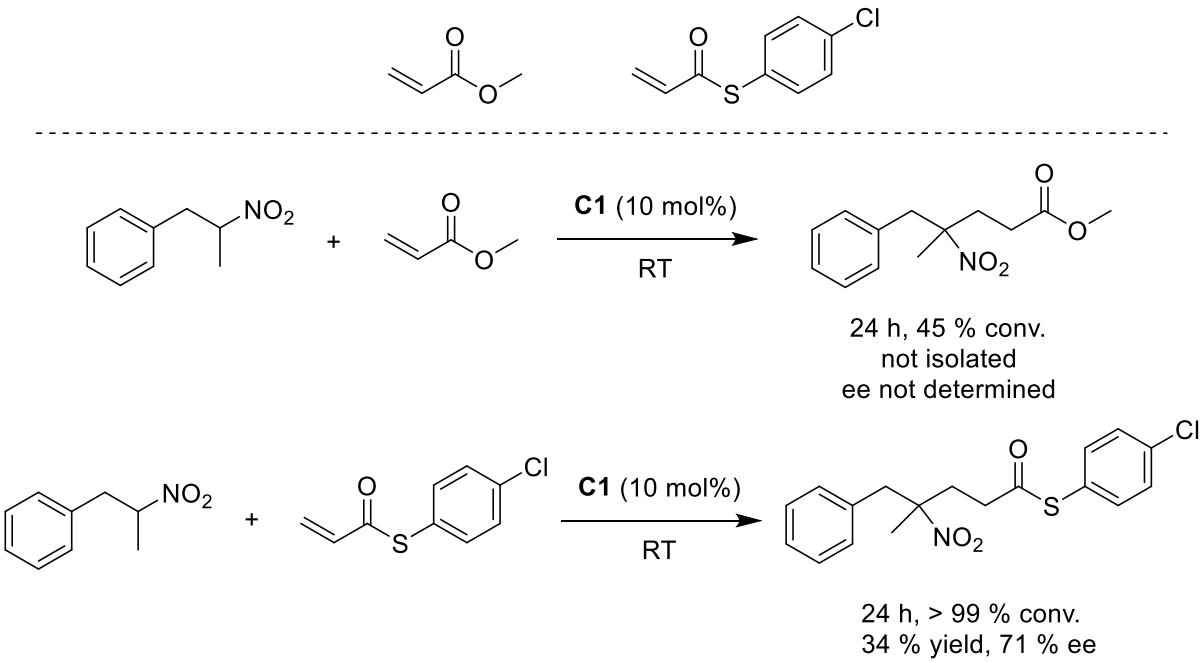
[23] For metal catalyzed Michael additions, see: a) Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.*; **2004**, *126*, 9188–9189. b) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.*; **2005**, *127*, 4154–4155, c) Palomo, C.; Pazos, R.; Oiarbide, M.; García, J. M. *Adv. Synth. Catal.*; **2006**, *348*, 1161–1164. d) Palomo, C.; Oiarbide, M.; García, J. M.; Bañuelos, P.; Odriozola, J. M.; Razkin, J.; Linden, A. *Org. Lett.*; **2008**, *10*, 2637–2640.

[24] For the first report on the use of these substrates in asymmetric organocatalysis involving the creation of tetrasubstituted stereocenters, see: E. Badiola, B. FIsher, E. Gómez-Bengoa, A. Mielgo, I. Olaizola, I. Urruzuno, J. M. García, J. M. Odriozola, J. Razkin, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.*; **2014,** *136*, 17869.17881



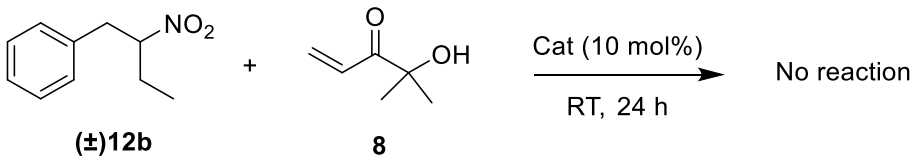
Scheme 4. Characteristics of α-hydroxy enones: a) H-bonding catalysis. b) Metal catalysis. c)Transformations of α-hydroxy enones into aldehydes, ketones or carboxylic acids.

Dr. A. García also tested the reaction of nitroalkane **(±)12a** with electrophiles other than α-hydroxy enones, such as methyl acrylate and thyoacrilate in the presence of catalyst **C1** (Scheme 5). In both cases the final adduct was produced although in the case of methyl acrylate with moderate conversion, and for the thioacrylate in moderate yield but quite good enantioselectivity.



Scheme 5: Other electrophiles tested by Dr. A. García.

Upon this research work, it was noticed that, for other electrophiles the reaction did not happen or if they did, with improvable results. Moreover, if the nucleophile was changed from (2-nitropropyl)benzene to (2-nitrobutyl)benzene), the reaction with α-hydroxy enone **8** did not work (Scheme 6)



Scheme 6: Reaction between (2-nitrobutyl)benzene **(±)12a** and α-hydroxy enone **8** by Dr. A. García

Taking into account the conclusions provided above, the objective of the present project has been to investigate the extension of the reactions of α-branched nitroalkanes lacking EWG at the α-position to other electrophiles and other α-branched nitroalkanes, as well as make an attempt in improving their results. In this context, it was considered that one option to improve the relatively low reactivity and the difficulty in controlling the stereoselectivity in the reaction with these α-branched nitroalkanes as nucleophiles would be dual catalysis; combining Brønsted bases together with metal catalysis[25]. This latter could on the one hand be beneficial to increase the reactivity of

[25] For revisions about this theme: a) Chen, D. F.; Han, Z. Y.; Zhou, X. L.; Gong, L. Z.; *Acc. Chem. Res.*; **2014**; *47*; 2365-2377. b) Stegbauer, L.; Sladojevich, F.; Dixon, D. J.; *Chem. Sci.*; **2012**; *3*; 942-958. c) Yamashita, Y.; Kobayashi, S.; *Chem. Eur. J.*; **2013**; *19*; 9420-9427.

the substrates and on the other hand to provide more anchoring points for the substrates which could also help in controlling the stereoselectivity.

To achieve this goal, two different strategies were considered in a first instance:

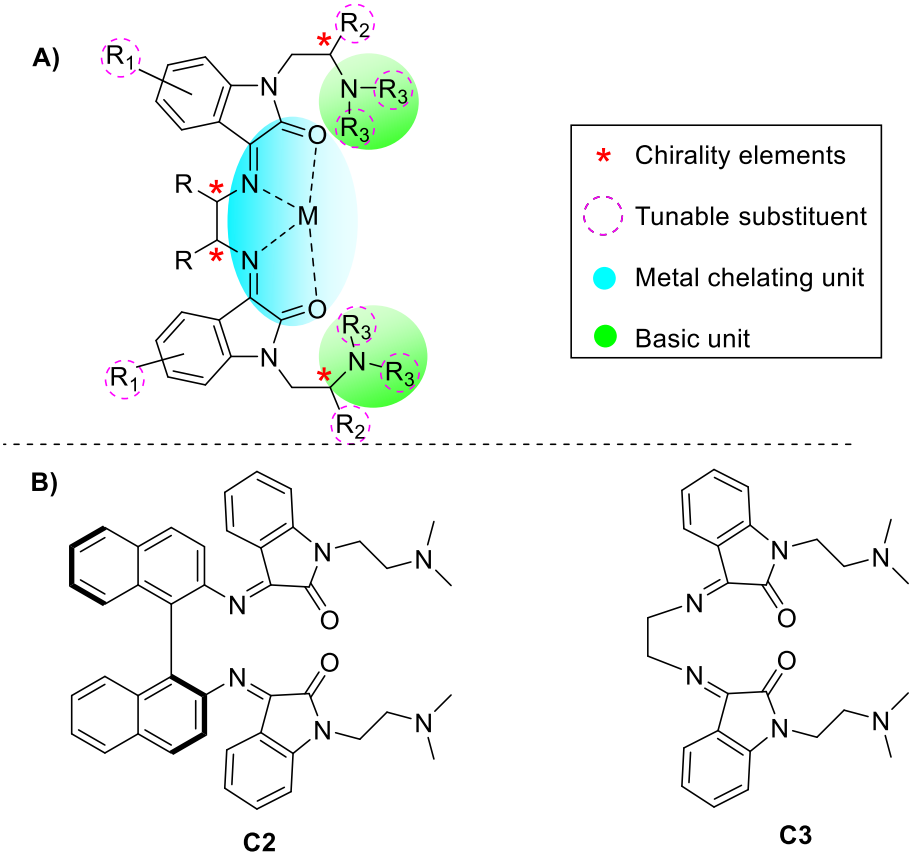
a. The combination of a metal chelating unit and a Brønsted base functionality in the same molecule.
b. The dual catalysis by two different entities: one molecule acting as metal chelating entity and a second one acting as a Brønsted base.

The key point when developing these strategies is the appropriate choice of the metal and the Brønsted base because depending on their nature they could interfere one another.

3. Objectives

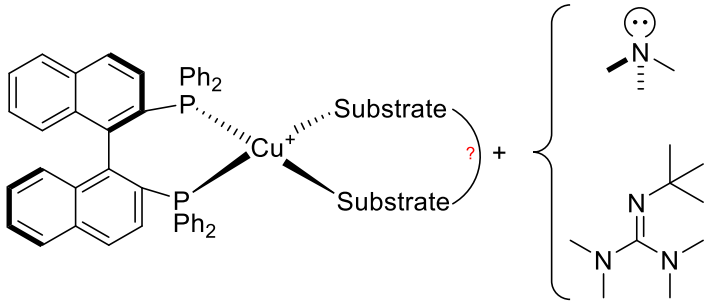
In this context, the main objective of this project has been to explore the catalytic and asymmetric α-functionalization of α-branched nitroalkanes lacking activating groups making use of dual catalysis and to explore the extension of the reactions described by Dr. A. García and Prof. J. M. García's group to other electrophiles and, if possible, improve their results.

For the first strategy, chelating group and BB in the same molecule, the following pattern was designed (Scheme 7a) and the following catalysts **C2** and **C3** were proposed for first investigations. In this case, the BB functionality is located at a specific position wherein the interaction with the metal centre is considered to be not very probable. Divalent metals (Cu(II), Mg, Zn) could form the complex shown below (Scheme 7a) and could be appropriate for the proposed goal.



Scheme 7: a) General structure of the proposed catalysts. b) Specific catalysts considered for first investigations.

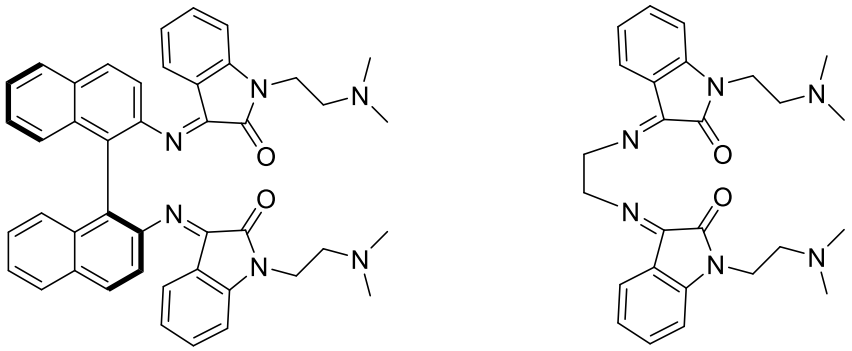
For the second strategy, chelating group and BB in different entities Cu(I) and nitrogenated base functionalities were proposed such as tertiary amines (TEA) and guanidines (Barton's base)[26]. BINAP was considered as the first ligand to explore which could create the following complex with Cu(I) (Scheme 8). The reaction substrates could this way coordinate to the complex which could be beneficial for reactivity and/or stereoselectivity.



Scheme 8: Catalytic system for the second proposal with the chelating structure and the BB in different entities.

Therefore, according to the above proposal the specific objectives were the following ones:

1) Synthesis of the previously mentioned catalysts **C2** and **C3** (Scheme 9).

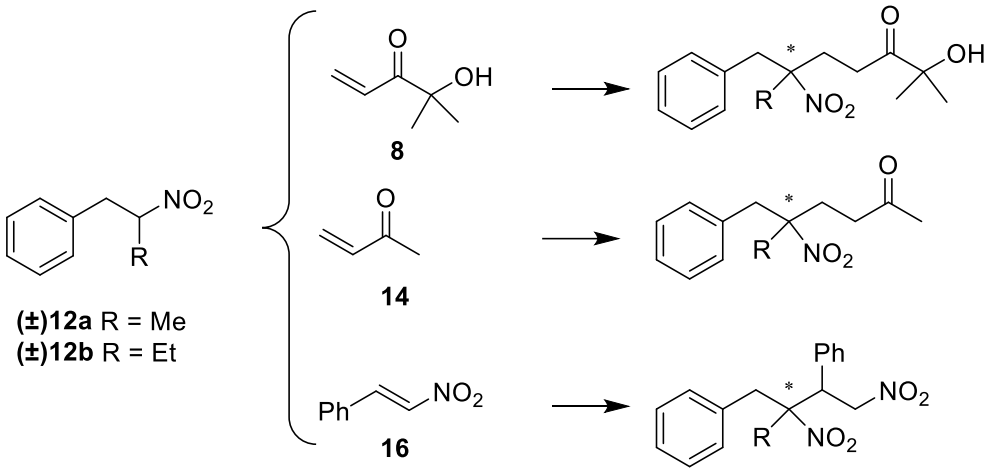


C2 **C3**

Scheme 9: Structures of the proposed catalysts **C2** and **C3**.

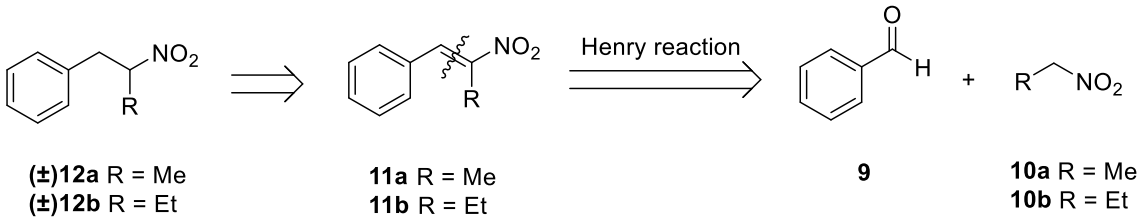
[26] For some examples on the compatibility of Cu(I) and these bases in asymmetric catalysis, see: a) Gröger, H. (2016). *Eur. J. Org. Chem.*, **2016**, *2016*(24), 4116–4123. b) Shibasaki, M., Kanai, M., Matsunaca, S., & Kumagai, N. (2009). Recent progress in asymmetric bifunctional catalysis using multimetallic systems. *Accounts of Chemical Research*, **2009**, *42*(8), 1117–1127.

2) Exploration of the mentioned catalytic systems in the following reactions in order to check the reactivity and/or stereoselectivity when possible (Scheme 10).



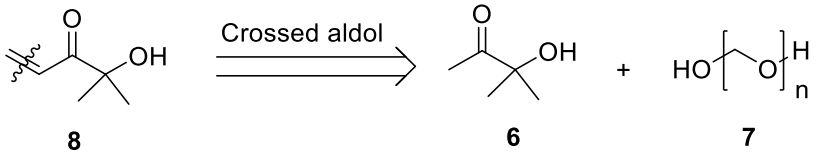
Scheme 10: Reactions to be studied.

3) Synthesis of the nucleophiles. The nucleophiles could be synthetized according to literature protocols via Henry reaction followed by reduction of the resulting nitroalkenes (Scheme 11).



Scheme 11: Retrosynthetic scheme for α-nitroalkanes.

4) Synthesis of the not commercial electrophiles. Of the three proposed electrophiles, the α-hydroxy enone is not commercially available and for its synthesis the aldol reaction previously followed by the research group was considered (Scheme 12).



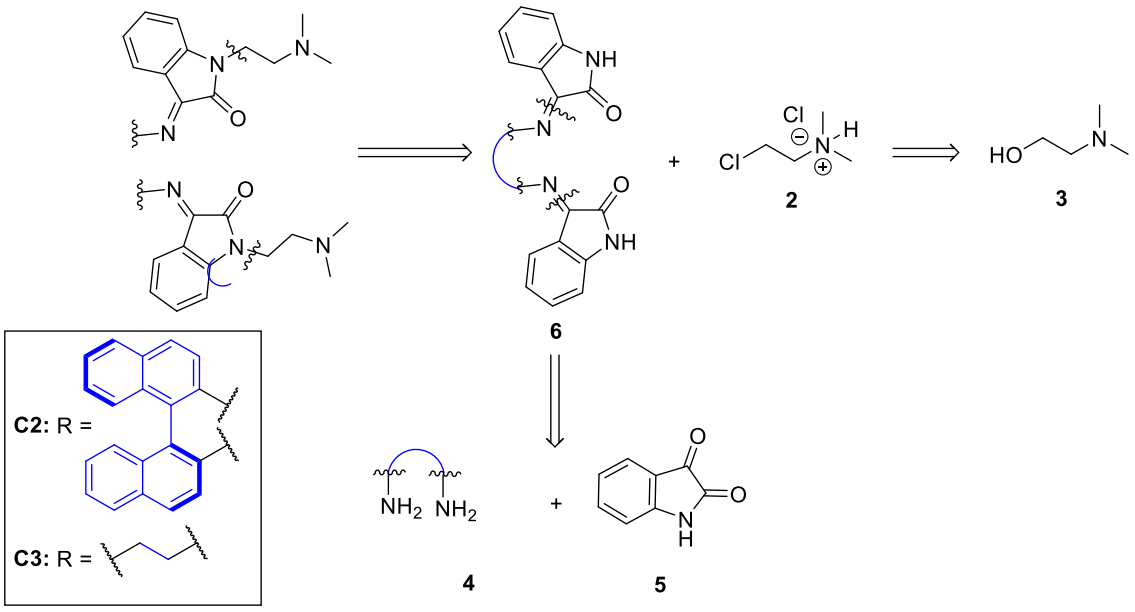
Scheme 12: Retrosynthetic scheme for α-hydroxy enone **8**.

4. Results and discussion

In this chapter, the results of this research are presented. Firstly, the synthesis of the catalysts **C2** and **C3** is described followed by synthesis of the electrophiles and the nucleophiles and finally, the study of the catalytic systems is presented.

4.1 Synthesis of the catalysts

According to the objectives first established, the synthesis of **C2** and **C3** catalysts which will contain both a Bronsted base and a metal chelating structure for the metal in the same molecule was investigated (Scheme 13). The reactions were performed following procedures in the literature and if necessary, adapting them. For the retrosynthesis of both catalysts **C2** and **C3**, reaction of alkyl chloride **2** and imines **6a** or **6b** was considered. Imines **6a** and **6b** could be obtained through the reaction between diamine **4a** or **4b** and isatin **5**. Finally, the alkyl chloride **2** could be synthetised through a functional group interchange (FGI) from commercially available *N,N*-dimethyl ethanolamine **3**.



Scheme 13: General scheme for the retrosynthesis of catalysts **C2** and **C3**.

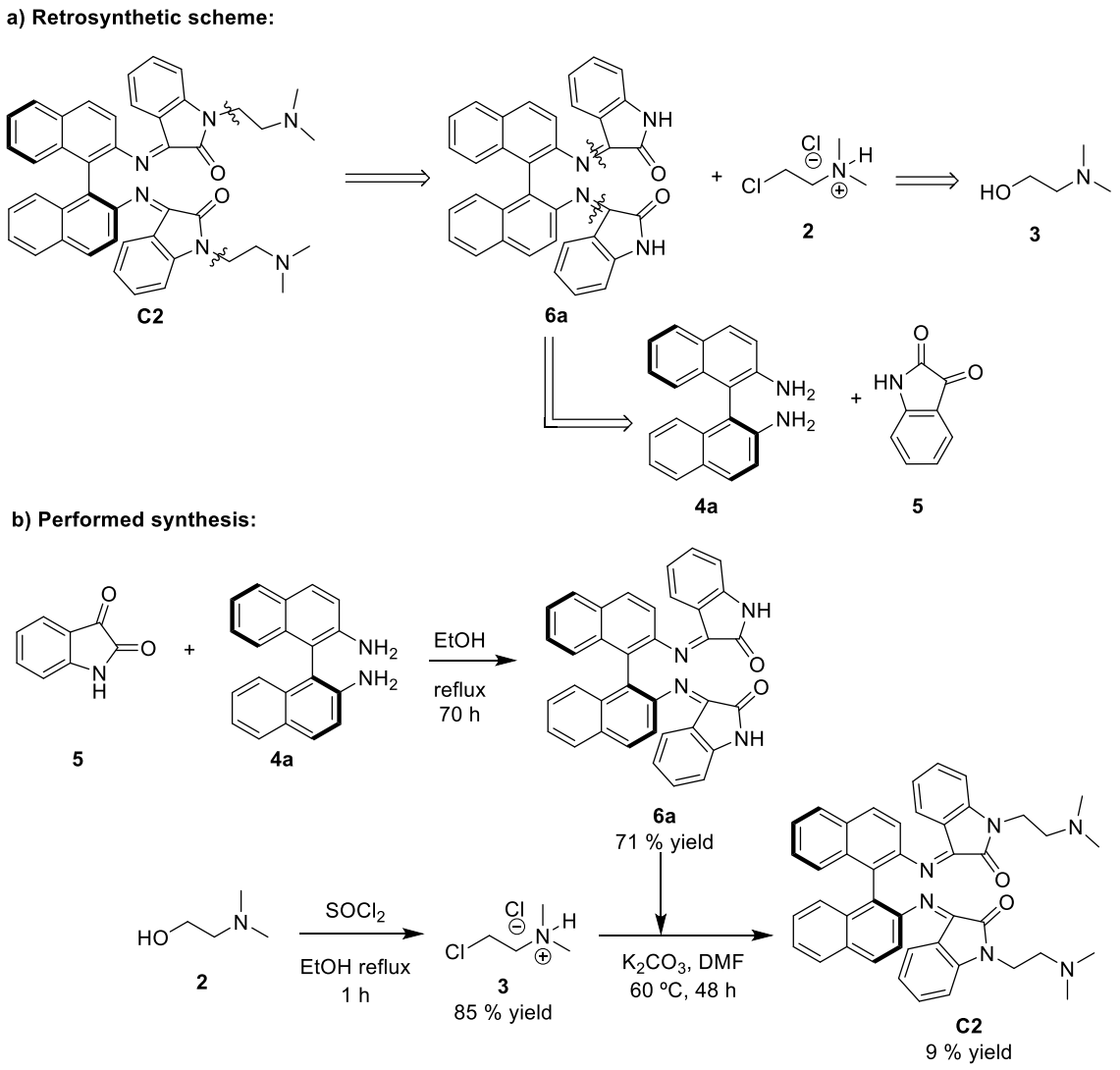
However, there were several inconveniences during the synthesis. First of all, due to the imine groups, which are rather susceptible to react, depending on the conditions of the reaction environment the Schiff bases can be hydrolysed. For example, in the case of pH, in a basic environment the hydrolysis of the imine was observed. Moreover, the alkylation of the imine was difficult to obtain. The monoalkylated product was detected but the dialkylated one was difficult to obtain even though more base and substrate

were added. Additionally, the alkyl chloride used for the alkylation of the imine was unstable and it had a lifespan of approximately 3 days since the synthesis even though it was stored in the fridge.

All these inconveniences during the synthesis resulted in very low yields, especially for the alkylation reactions and thus, the total yield was undesirably low. More precisely, the overall yield was 9 % for **C2** and 2 % for **C3**.

Considering all the problems experienced in the synthetic pathway for **C2** and **C3** and that the reaction yields were also low; in parallel the second strategy was explored. This consisted in having the Bronsted base and the chelating structure in different molecules as it will be explained later.

4.1.1 Synthesis of Catalyst C2



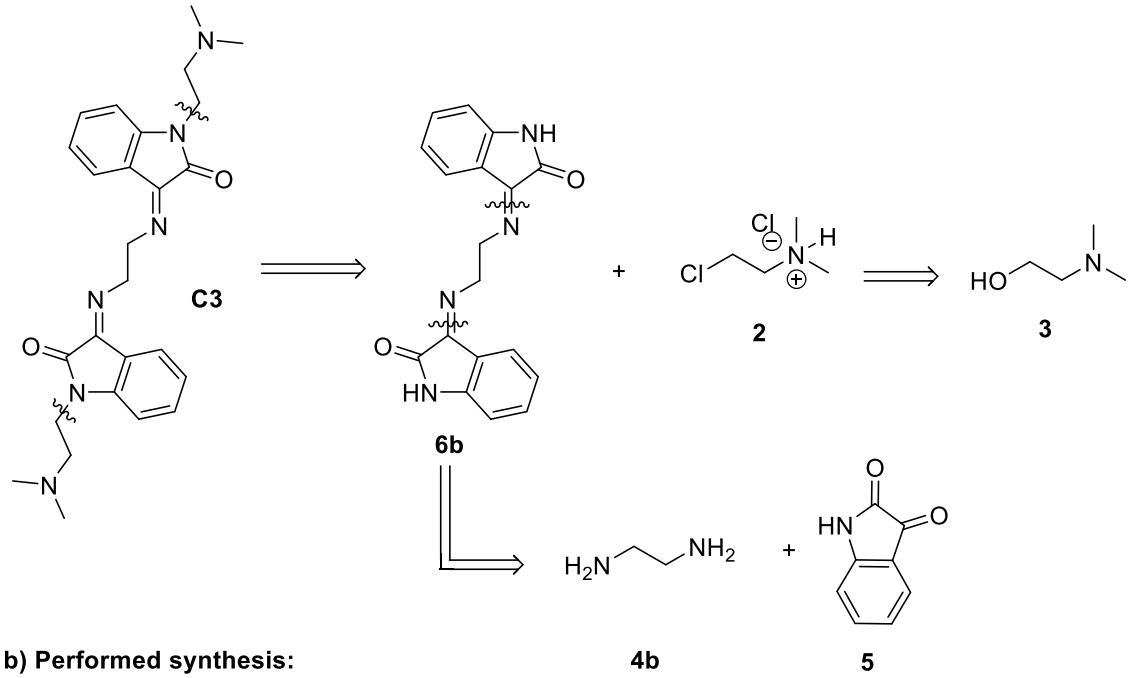
Scheme 14: Scheme for the obtention of **C2**. a) Retrosynthetic scheme. b) Performed synthesis.

This synthesis begun by reacting (S_A)-2,2-diamino-1,1-binaphthyl **4a** and isatin **5** in ethanol, both of them commercial and available in the laboratory; the mixture was stirred at reflux for 70 hours to afford the imine[27] **6a** in 71 % yield. During that process, the reaction was followed by TLC and ^{1}H-NMR analysis. In parallel, *N,N*-dimethyl ethanolamine **3** was reacted with $SOCl_2$ in refluxing ethanol for one hour[28] to obtain *N,N*-dimethyl aminoethyl chloride hydrochloride **2** with 85 % yield. Finally, imine **6a** was dissolved in DMF, K_2CO_3 was added followed by the alkyl chloride **2**[29]. The mixture was stirred at 60 ºC overnight. After this time, as the starting imine was still detected by TLC analysis, 1.5 eq. of alkyl chloride **2** and 3 eq. K_2CO_3 were added in order to boost the formation of the dialkylated product as only the monoalkylated was detected initially. After stirring the mixture for additional 24 h and the usual work-up, the catalyst **C2** was obtained in only 9 % yield.

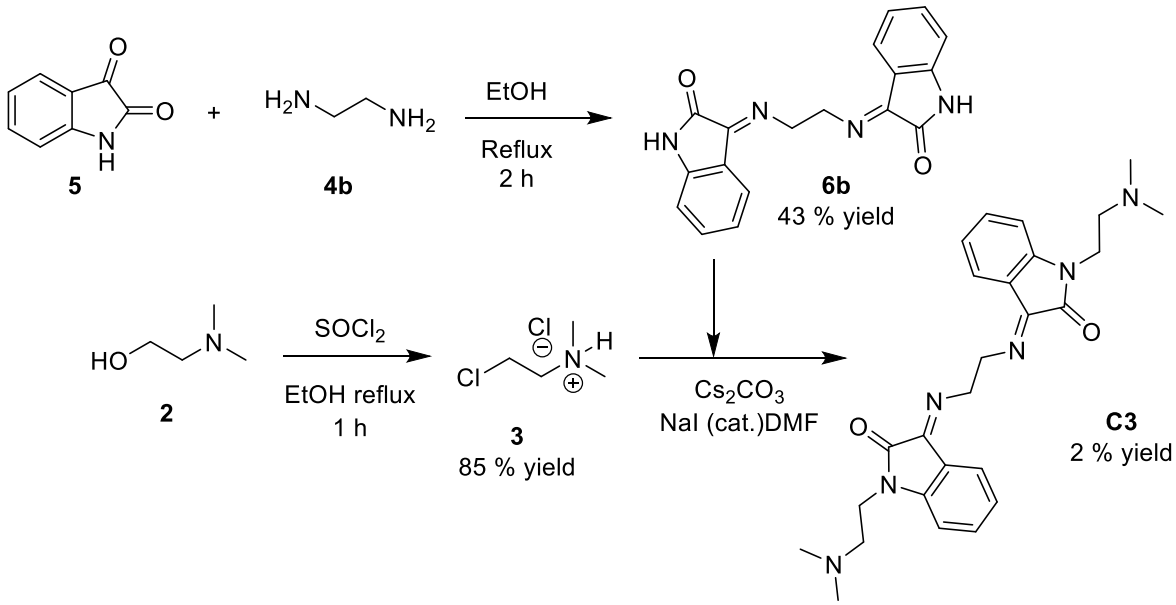
[27] Adapted from: A., Pathak, D. P., Kamboj, P., & Amir, M.; *Int. Res. J. Pharm.*; **2019**,*10*(9), 223–230.
[28] Adapted from: Jie, Z., Zhang, B., Zhao, L., Yan, X., & Liang, J. (2014).. *J. Mater. Sci.*; **2014**; *49*(9), 3391–3399.
[29] Adapted from: Singh, G., Arora, A., Singh, A., Kalra, P., Rani, S., Singh, K., Maurya, I. K., Mandal, R. S.; *ChemistrySelect*, **2018**, *3*(6), 1942–1952.

4.1.2 *Synthesis of Catalyst C3*

a) Retrosynthetic scheme:



b) Performed synthesis:



Scheme 15: Scheme for the obtention of **C3**. a) Retrosynthetic scheme. b) Synthesis performed.

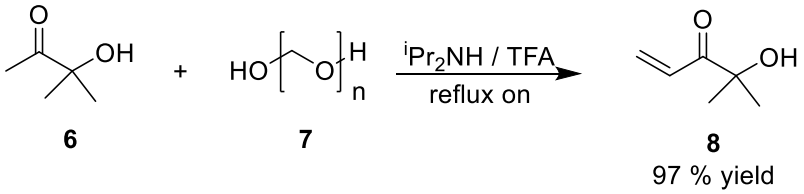
A mixture of Isatin **5** and ethylenediamine **4b** in EtOH was refluxed for 2 hours to obtain imine **6b** in 43 % yield[30]. In parallel, to a solution of *N,N*-dimethyl ethanolamine **2** in ethanol $SOCl_2$ (1.1 eq.) was added and the mixture was heated at for 1h reflux to obtain

[30] Adapted from: Sharma, V. K.; Srivastava, A.; Srivastava, S.; *J. Serb. Chem. Soc.*; **2006**; *71*, 917–928.

N,N-dimethyl aminoethyl hydrochloride[28] **3** in 85 % yield. In the last step, the imine **6b** was dissolved in DMF and Cs_2CO_3, NaI and alkyl chloride **3** were added; the resulting mixture was heated at reflux over weekend[31] to provide catalyst **C3** in 2 % yield. With this small amount only ^{1}H-NMR analysis could be performed.

4.2 Synthesis of the electrophiles

Among the electrophiles initially proposed for this project, all of them are commercially available except of α-hydroxy enone 4-hydroxy-4-methylpent-1-en-3-one **8** which had to be synthetized following the procedure previously used in the research group[32]. This procedure consisted in a cross-aldol reaction between α-hydroxy ketone **6** and paraformaldehyde **7** under the conditions shown in Scheme 16. For the purification, a vacuum distillation was performed which enabled a fast purification of the product as well as a high purity.



6 **7** **8**
97 % yield

Scheme 16: Synthesis of 4-hydroxy-4-methylpent-1-en-3-one **8**.

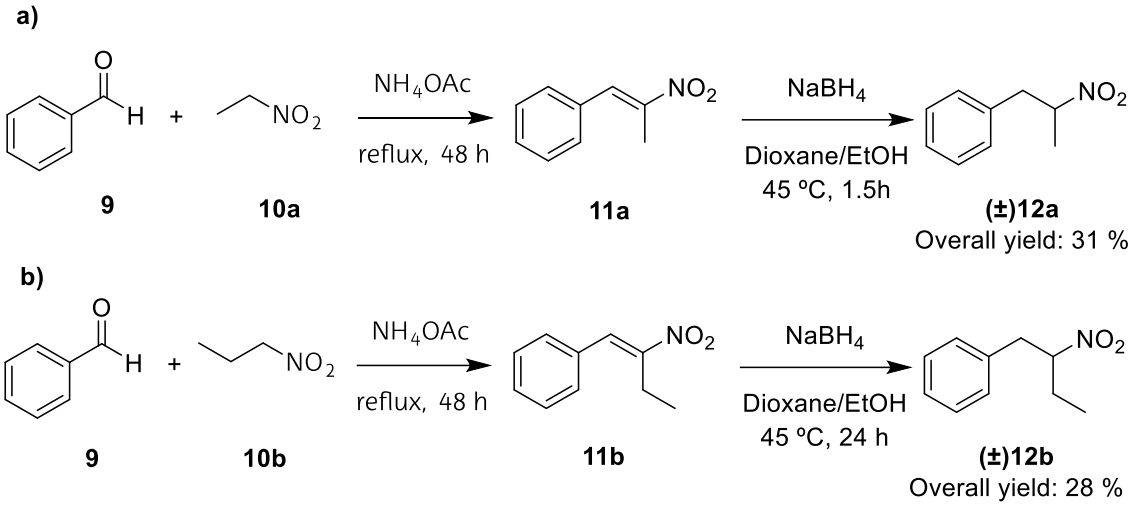
4.3 Synthesis of the nucleophiles

The required nucleophiles for the reactions were synthetized following described protocols in the literature[33] (Scheme 17). The synthesis was carried out in two steps; firstly, a Henry reaction was performed between benzaldehyde **9** and the corresponding nitroalkane **10a or 10b** heating the mixture to reflux to afford the nitroalkene **11a** or **11b**. Later, this nitroalkene, **11a** or **12b**, was selectively reduced with $NaBH_4$ in a mixture of dioxane and ethanol at 45 ºC and that way the corresponding nitroalkane were obtained; **(±)12a** in 31 % yield or **(±)12b** in 28 % yield.

[31] Adapted from: Zanzoul, A.; Chollet, A.; Piedra-Arroni, E.; Stigliani, J. L.; Bernardes-Genisson, V. *et al. Lett. Org. Chem.*; **2015**; *12* (10); 727-733

[32] E. Badiola, B. FIsher, E. Gómez-Bengoa, A. Mielgo, I. Olaizola, I. Urruzuno, J. M. García, J. M. Odriozola, J. Razkin, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.*, **2014,** *136*, 17869-17881

[33] For the synthesis of (2-nitropropyl)benzene**1**, see: Liu, G., Liu, X., Cai, Z., Jiao, G., Xu, G., & Tang, W.; *Angew. Chem. Int. Ed.*, **2013** , *52* (15), 4235–4238. b) For the reduction: Bhattacharjya, A.; Mukhopadhyay, R.; Pakrashi, S. C.; *Synthesis*, **1985**, *9*, 886–887.



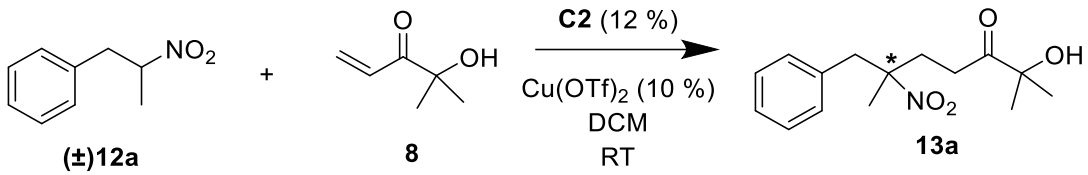
Scheme 17: a) Synthesis of (2-nitropropyl)benzene **(±)12a** b) Synthesis of (2-nitrobutyl)benzene **(±)12b**

4.4 Study of the catalytic systems in the reaction of nitroalkanes

Once the substrates were synthetised, it was the moment for testing the reactions and the conditions for them to happen. To do so, many attempts were performed at different temperature, concentration of catalyst and times. In the following sections the results one by one of the reactions with the different electrophiles are presented.

*4.4.1 Reactions with α-hydroxy enone **8***

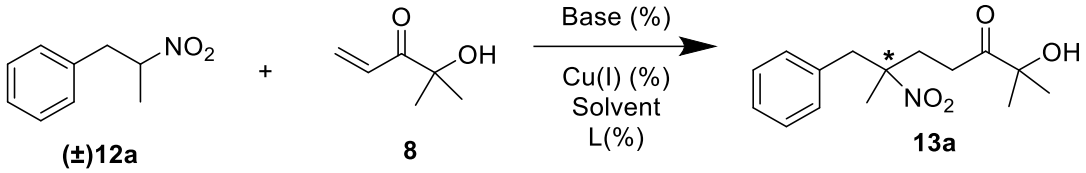
The study began following the research by Dr. Ane García and Prof. J. M. García, so the first electrophile tested was α-hydroxy enone **8**. To begin with, a test with the catalyst **C2** was performed in the reaction between α-nitroalkane **(±)12a** and α-hydroxy enone **8** as shown in scheme 18. To a suspension of $Cu(OTf)_2$ in DCM **C2** was added and the Cu(II) dissolved. However, soon after it had dissolved, a new precipitate appeared which was thought to be the complex between Cu(II) and **C2** (see Scheme 7a). Then, the substrates of the reaction were added. At 26 h reaction time at RT no reaction was observed in ^{1}H-NMR aliquots, so it was deduced that the reaction did not happen due to the precipitation of the catalyst. Some other experiments on the complex formation by mixing whe $Cu(OTf)_2$ and **C2** at RT and in other solvents (THF, and Toluene) revealed the formation of a similar precipitate.



Scheme 18: Michael addition of α-nitroalkane **(±)12a** into α-hydroxy enone **8** catalysed by **C2**/Cu(II).

In parallel, the second strategy, having the chelating structure and the BB in separated entities, was tested. Table 1 reunites the results obtained by the Michael addition of **α**-nitroalkane **(±)12a** into α-hydroxy enone **8**. First the racemic reaction was explored in the presence of 50 % mol TEA, 10 % mol Cu(I) and 10 % mol (±)BINAP (entry 1). Under these conditions no reaction was detected after 54 h. Therefore the same experiment was carried out maintaining the percentage of TEA but increasing the amounts of Cu(I) to 30 % mol and (±)BINAP to 20 % mol (entry 2). In these conditions after 17 h reaction at RT 95 % conversion was measured and after the corresponding purification racemic adduct **13a** was isolated in 64 % yield. In parallel, the exploration of the asymmetric reaction was also carried out (entry 3). By using 20 % mol of TEA and 20 % mol Cu(I) together with 22 % mol of (*S*)-BINAP, adduct **13a** was isolated in 81 % yield after 118h reaction at RT. At this step the enantioselectivity of the reaction was checked by HPLC analysis (see experimental section) and was found to be only 0.2 % (racemic). This could imply that either the catalytic system is not effective in controlling the stereoselectivity and/or the racemic reaction is promoting in parallel. So experiment in entry 4 was considered with the aim to find the temperature at which TEA alone doesn't promote the reaction. After 71h under the conditions shown in entry 1 54 % of conversion was detected. These results indicate that other conditions or ligands should be investigated for the asymmetric reaction.

Table 1: Results obtained for the Michael addition of α-branched nitroalkane **(±)12a** into α-hydroxyenone **8**[a].



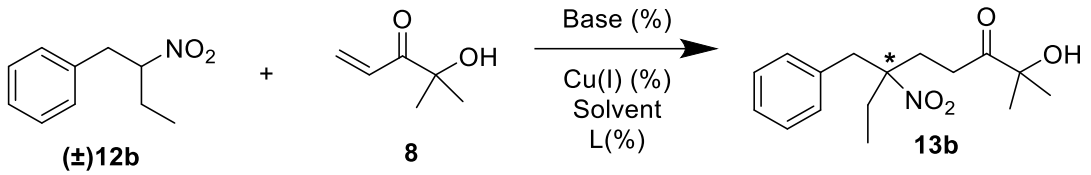
(±)12a **8** **13a**

Entry	Base	Cu(I) L	Solvent	T	T (h)	Conv. (%)[b]	Yield (%)[c]	ee[d]
1	TEA 50 %	$Cu[CH_3CN]_4PF_6$ 10 % (±)-BINAP 10 %	THF 0.6 mL	rt	28 h	0	--	-
					54 h	0	--	-
2	TEA 50 %	$Cu[CH_3CN]_4PF_6$ 30 % (±)-BINAP 20 %	THF 0.6 mL	rt	17 h	95 %	64 %	-
3	TEA 20 %	$Cu[CH_3CN]_4PF_6$ 20 % (S)-BINAP 22 %	THF 0.6 mL	rt	17 h	38 %	-	-
					46 h	81 %	-	-
					118 h	97 %	81 %	1
4	TEA 50 %	--	THF 0.6 mL	-20 ºC	17		-	-
					64		-	-
					71	54 %	nd	-

[a] Reactions carried out at 0.2 mmol scale (with mmol ratio nitroalkane/hydroxyenone 5:1) and with the mmol ratio catalyst shown in the table. [b] Determined by the disappearance of α-hydroxy enone by ^{1}H-NMR analysis of an aliquot. [c] Yield of the isolated product after purification. [d] Determined by chiral HPLC analysis. nd: not determined.

Table 2 reunites the results obtained in the Michael addition of α-nitroalkane **(±)12b** to α-hydroxy enone **8**. We can see that in the presence of TEA(entries 1 and 2)the reaction times are higher than for nitroalkane**(±)12a**. This could be caused by the lower reactivity of the substrate. However, if Barton's base is used, which is a guanidine and thus a more powerful base, the reaction times diminish considerably (entries 4, 5 and 6). Looking at the yields, the values are lower than what we desired but still acceptable. The asymmetric reaction using (*R*)-BINAP (entry 1) shows that the stereocontrol is not good being 26 % the value obtained for ee.

Table 2: Results obtained for Michael addition of α-branched nitroalkane **(±)12b** to α-hydroxy enone **8**[a].



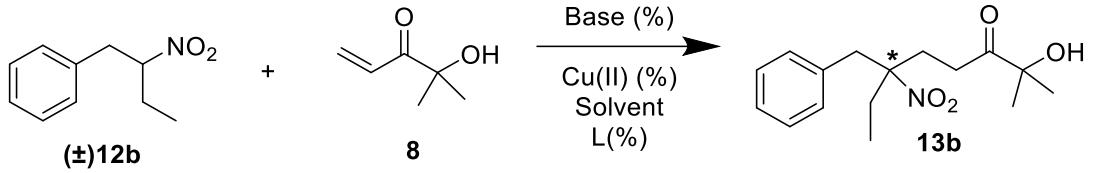
(±)12b **8** **13b**

Entry	Base	Cu(I) L	Solvent	T	t (h)	Conv. (%)[b]	Yield (%)[c]	ee[c]
1	TEA 30 %	$Cu[CH_3CN]_4PF_6$ 35 % (R)-BINAP 30 %	THF 0.6 mL	rt	15 h	0 %	--	--
					47 h	24 %	--	--
					117 h	58 %	--	--
					7 day	86 %	62	26
2	TEA 30 %	--	THF 0.6 mL	rt	15 h	0 %	--	--
					47 h	37 %	--	--
					117 h	62 %	--	--
					7 day	84 %	67	--
3	Barton's 21 %	--	THF 0.6 mL	rt	16 h	> 99 %	--	--
4	Barton's 7 %	--	THF 0.6 mL	- 35 ºC	30 h	> 99 %	--	--
5	Barton's 7 %	--	THF 0.6 mL	-70 ºC	22 h	61 %	--	--
				-50 ºC	25 h	85 %	--	--

[a] Reactions carried out at 0.2 mmol scale (with mmol ratio nitroalkane/hydroxyenone 5:1) and with the mmol ratio catalyst shown in the table. [b] Determined by the disappearance of α-hydroxy enone by ^{1}H-NMR analysis of an aliquot. [c] Yield of the isolated product after purification. [d] Determined by chiral HPLC analysis. nd: Not determined.

As Cu(I) is easily oxidized to Cu(II) under the atmosphere oxygen, a control experiment under the same conditions on entry 1 in Table 2 was performed by using $Cu(OTf)_2$ instead of Cu(I). However, no progression of the reaction was detected, so we can conclude that the results on entry 1 in Table 2 are produced by Cu(I) and not Cu(II), but if Cu(I) is oxidized to Cu(II) the reaction stops.

Table 3: Results obtained for Michael addition of α-branched nitroalkane **(±)12b** to α-hydroxy enone **8** with Cu(II) [a].



(±)12b **8** **13b**

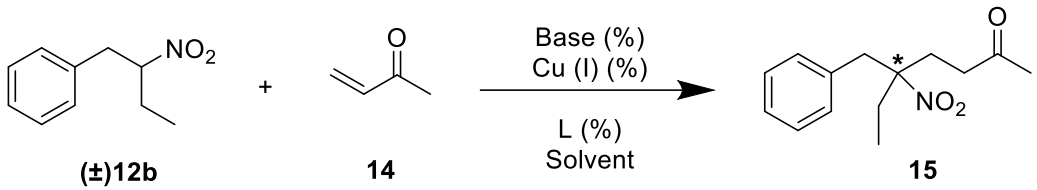
Entry	Base	Cu(II) L	Solvent	T (ºC)	t (h)	Conv (%)[b]	Yield (%)	ee
1	TEA 30 %	$Cu(OTf)_2$ 30 % (S)-BINAP 33 %	THF 0.6 mL	rt	22 h	0	--	--
					94 h	0	--	--

[a] Reactions carried out at 0.2 mmol scale (with mmol ratio nitroalkane/hydroxyenone 5:1) and with the mmol ratio catalyst shown in the table. [b] Determined by the disappearance of α-hydroxy enone by ^{1}H-NMR analysis of an aliquot.

4.4.2 *Reactions with methyl vinyl ketone **14***

As the objective of the project was to extend the reactions described by Dr. Ane García to other electrophiles, methyl vinyl ketone **14** was investigated with that purpose. Moreover, this electrophile could let us see the difference in reaction with α-hydroxy enone because methyl vinyl ketone can only coordinate with the metal from the carbonyl and this could cause a difference (Table 4).

Table 4: Results obtained for the Michael addition of α-branched nitroalkane **(±)12b** into methyl vinyl ketone **14**[a].



(±)12b **14** **15**

Entry	Base	Cu(I) L	Solvent	T (ºC)	t (h)	Conv. (%)[b]	Yield (%)[c]	ee[d]
3	DBU % 30	--	THF 0.6 mL	rt	16 h	> % 99	%72	4
4	Barton's % 20	$Cu[CH_3CN]_4PF_6$ % 20 (R)-BINAP % 22	THF 0.6 mL	rt	2 h	> 99 %	% 67	11
5	Barton's % 20	$Cu[CH_3CN]_4PF_6$ % 20 (S)-BINAP % 22	THF 0.6 mL	-70 ºC	8 h	0	--	--
				-50 ºC	27 h	0	--	--
					99 h	% 96	% 70	1

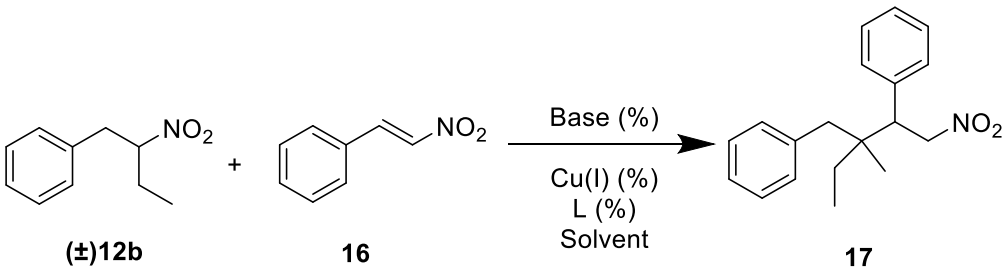
[a] Reactions carried out at 0.2 mmol scale (with mmol ratio nitroalkane/hydroxyenone 5:1) and with the mmol ratio catalyst shown in the table. [b] Determined by the disappearance of α-hydroxy enone by ^{1}H-NMR analysis of an aliquot. [c] Yield of the isolated product after purification. [d] Determined by chiral HPLC analysis. nd: Not determined.

In table 4 it can be seen that the reaction times are significantly lower than those using α-hydroxy enone. This is a surprising phenomenon because the α-hydroxyenone can be considered a better electrophile than methyl vinyl ketone due to its hydroxy group and thus, it should be more reactive and lead to lower reaction times than methyl vinyl ketone. In this case, the reaction yields are similar to the values with α-hydroxy enone obtained in table 2 but reactivity is higher and the stereoselectivity has not been so good as the values for ee are very low being the best value 11 % (Table 4, entry 4).

*4.4.3 Reactions with (2-nitrovinyl)benzene **16***

With the purpose to further extend the reaction to other electrophiles, (2-nitrovinyl)benzene **16** was also chosen. The corresponding results are shown in Table 5. However, the reactions did not take place in the presence of TEA. In order to explain what happened, steric hindrance was the first option evaluated. The nitronate could not attack the nitroalkene due to the phenyl groups in both electrophile and nucleophile which would cause high steric constraint. Other conditions or stronger bases could be considered for further investigations.

Table 5: Results obtained for the Michael addition of α-branched nitroalkane **(±)12b** into (2-nitrovinyl)benzene **16**[a].



Entry	Base	Cu(I) L	Solvent	T (ºC)	t (h)	Conv. (%)[b]	Yield (%)	ee
1	TEA % 20	$Cu[CH_3CN]_4PF_6$ % 20 (R)-BINAP % 20	THF 0.6 mL	rt	16 h	nd	--	--
					48 h	nd	--	--
					5 day	nd	--	--
2	TEA % 20	--	THF 0.6 mL	rt	26 h	nd	--	--
					4 day	nd	--	--

[a] Reactions carried out at 0.2 mmol scale (with mmol ratio nitroalkane/hydroxyenone 5:1) and with the mmol ratio catalyst shown in the table. [b] Determined by the disappearance of α-hydroxy enone by ^{1}H-NMR analysis of an aliquot. nd: Not Determined.

4.5 Optimal conditions for the HPLC

HPLC conditions for ee determination in reactions obtaining **13b** and **15** had to be found. After trying different conditions for the separation of the enantiomers in the HPLC, the following conditions were found.

For the separation of **13b** the best condition was found with an ADH column and at 95/5 Hex/^{i}PrOH and 1.0 mL/min flux (Figure 3).

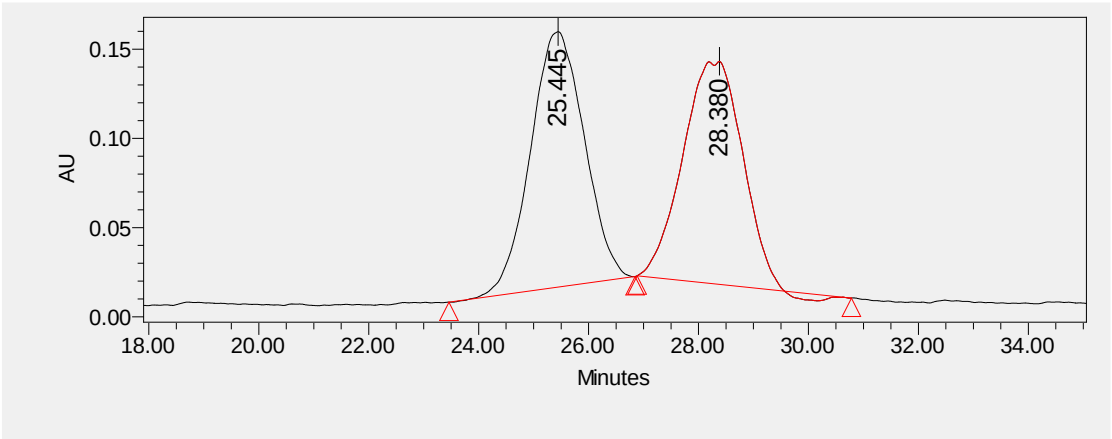


Figure 3: Chromatogram of the separation of **13b** in ADH colum with 95/5 Hex/^{i}PrOH and 1.0 mL/min flux.

For the separation of **15** the best condition was found with an IF column and at 95/5 Hex/^{i}PrOH and 0.5 mL/min flux.

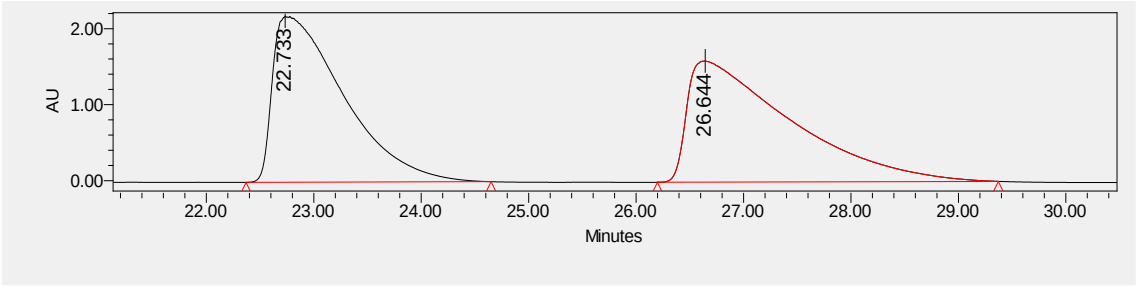


Figure 4: Chromatogram of the separation of **15** in IF colum with 95/5 Hex/^{i}PrOH and 1.0 mL/min flux.

5. Conclusions

These are the conclusions which can be drawn from this research work:

- Synthesis of **C2** has been achieved although the reaction yield is lower than hoped. On the other hand, synthesis of **C3** was obtained in the sufficient amount to perform an ^{1}H-NMR. Moreover, **C3** was not stable even in the fridge and it was degraded. The synthesis of both **C2** and **C3** require further investigation.
- α-Branched nitroalkanes **(±)12a** and **(±)12b** were successfully synthetized.
- α-Hydroxy enone **8** was successfully synthetized.
- The Michael addition of α-branched nitroalkane **(±)12a** and α -hydroxy enone **8** catalysed by **C2** and Cu(II) has not been achieved probably due to solubility problems of the resulting complex between **C2** and Cu(II). More research is required to solve this handicap.
- The Michael addition of α-branched nitroalkanes **(±)12a** and **(±)12b** to different electrophiles **8** and **14** making use of BB and chelating structure in different entities has been achieved and the products have been characterized. However, more research is required in order to improve the stereocontrol and reactivity.
- The Michael addition of α-branched nitroalkanes **(±)12b** to electrophile **16** has not been achieved. Further research will be necessary to accomplish this reaction.
- Conditions for the enantiomers' separation by HPLC of compounds **13b** and **15** have been found.

6. Experimental section

6.1 Techniques and materials

6.1.1 Nuclear Magnetic Resonance (NMR)

NMR spectra were recorded using a Bruker Avance DPX 300 (300 MHz for 1H, 75 MHz for 13C) spectrometer. The solvent used is CDCl3, unless otherwise is specified. Chemical shifts (δ) are quoted in parts per million referenced to the residual CDCl3 peak, ^{1}H (δ = 7.26) and ^{13}C (δ = 77.0), in the cases that DMSO-D_6 was used ^{1}H (δ = 2.50) and ^{13}C (δ = 39.52) and in the cases that Acetone-D_6 was used ^{1}H (δ = 2.05) and ^{13}C (δ = 29.8) . The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd double doublet. Coupling constants (J) are reported in Hertz (Hz).

For the processing and the interpretation of the spectra the software MestReNova 14.2.1-27684 was used.

6.1.2 Chromatography

Reactions and flash chromatographic columns were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light, Fisher Bioblock lamp VL-4LC, λ = 254 and 365 nm. In addition, TLC plates were stained with a dipping solution of potassium permanganate (1 g $KMnO_4$, 100 mL H_2O), followed by heating.

Chromatographic purification was performed on Merck ROCC 60 silica gel 40-63 μm as stationary phase and a suitable mixture of solvents (hexane/ethyl acetate or CH_2Cl_2/CH_3OH) as eluent.

6.1.3 Determination of enantiomeric excess

Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on Waters 600 (equipped with Photodiode Array Detector Waters 2996). The used column and the flow solvent conditions are given for each compound.

6.1.4 Reagents and solvents

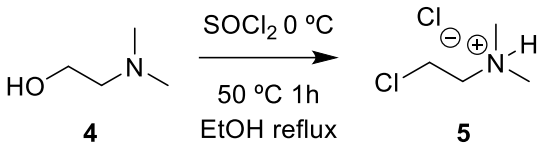
Reagents were purchased from different commercial suppliers (Sigma-Aldrich, Acros Organics, Alfa Aesar, Fluka, TCI, Merck, Fluorochem, etc.) stored as specified by the manufacturer and used without previous purification unless otherwise is stated.

6.1.5 Mass spectrometry

MS spectra were recorded on an ESI-ion trap Mass spectrometer Agilent 1100 series LC/MSD, SL model, on an UPLC-DAD-QTOF, Ultra High-Performance Liquid Chromatography-Mass spectrometer, Waters UPLC ACQUITY, Waters PDA detector, Waters Sunapt G2 or on an Agilent Thermoquest LCT spectrometer. Mass spectrometry analyses were performed in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU).

6.2 Synthesis of Catalysts C2 and C3

6.2.1. *2-Chloro-N,N-dimethylaminoethyl chloride hydrochloride* **5**.[28]

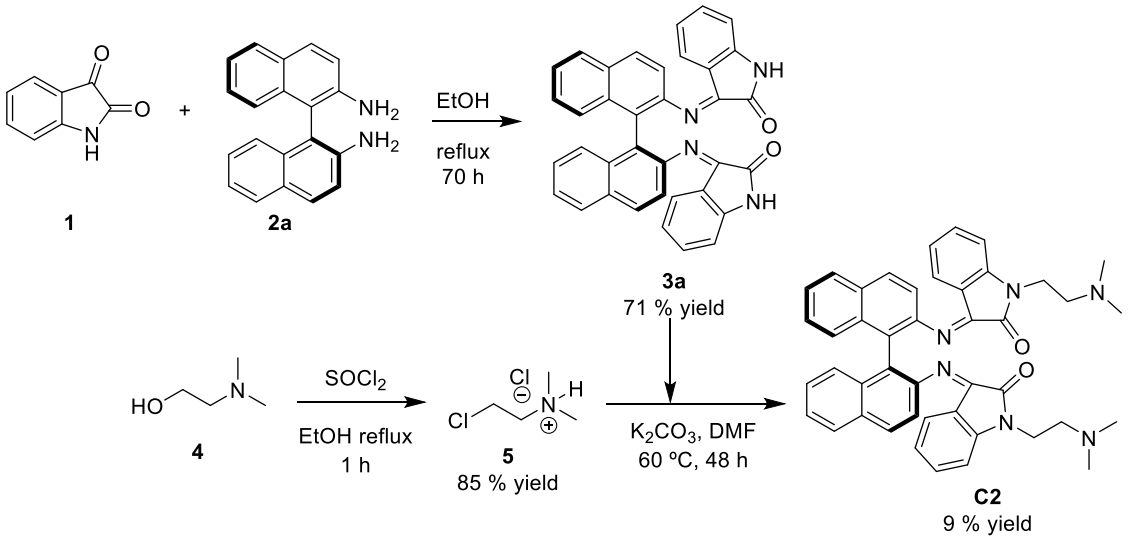


4 **5**

In a three neck round bottomed flask, a thermometer, a condenser and an inert gas balloon were attached. $SOCl_2$ (1.2 mL, 16.5 mmol, 1.1 eq.) was added at 0ºC and afterwards 2-dimethylaminoethanol **4** (1.5 mL, 15 mmol, 1 eq.) was added dropwise at the same temperature. The reaction mixture was then heated between 35 and 50 ºC for 1 hour. After this time, a precipitate appeared. Then, EtOH (22.5mL) was added and the mixture was stirred at reflux for 1 hour and then at is let RT overnight. The solvent was then removed under vacuum to provide 2-chloro-*N,N*-dimethylethanamine hydrochloride **5** (2.008 g, 13.94 mmol, 85 %) as a white solid. All the spectroscopic data were consistent with those previously described[34]. ^{1}H NMR (300 MHz, DMSO) δ 10.87 (s, 1H), 4.01 (t, J = 6.7 Hz, 2H), 3.45 (t, J = 6.7 Hz, 2H), 2.78 (s, 6H).

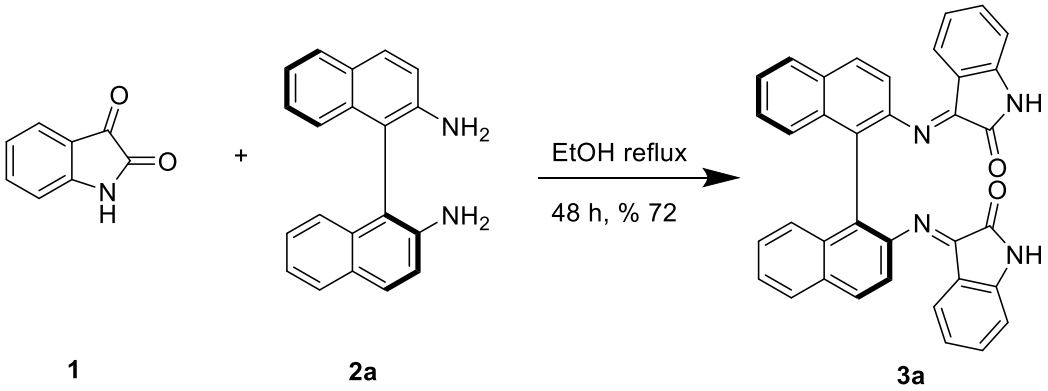
[34] *SpectraBase*. Bio-Rad Laboratories. https://spectrabase.com/spectrum/JkFwqeid2Xm (accessed 2022-06-26).

6.2.1 *Synthesis of catalyst* ***C2***



1st Step: Synthesis of the Imine 3a.[29]

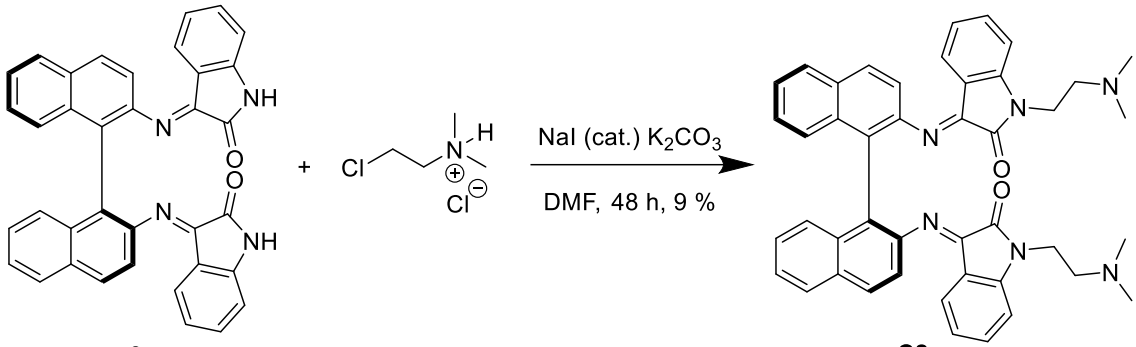
3,3'-(((*S*)-[1,1'-Binaphthalene]-2,2'-diyl)bis(azaneylylidene))bis(indolin-2-one)



A mixture of isatin **1** (1.8 g, 12 mmol, 2 eq.) and S_A-binaphtyldiamine **2a** (853 mg, 3 mmol, 1eq.) in EtOH (75 mL) and AcOH (0.12 mL) was heated at reflux observing since the beginning the formation of a clear red solution. The solution was stirred at the same temperature for 48 h when 85 % conversion was determined. Then the solvent was removed under vacuum to afford an orange solid which was purified by trituration in DCM. This afforded the expected imine **3a** (1.1652 g, 2.15 mmol, 72 %). ^{1}H NMR (300 MHz, Acetone-D_6) δ 9.04 (s, 1H), 8.03 (dd, *J* = 8.3, 4.8 Hz, 7H), 7.62 (td, *J* = 7.7, 1.4 Hz, 2H), 7.57 – 7.52 (m, 2H), 7.48 (ddd, *J* = 8.2, 6.5, 1.7 Hz, 2H), 7.38 – 7.29 (m, 2H), 7.24 – 7.18 (m, 2H), 7.17 – 7.09 (m, 2H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.67 (d, *J* = 6.4 Hz, 2H), 6.62 – 6.51 (m, 2H). ^{13}C NMR (75 MHz, Acetone-D_6) δ 163.6, 156.0, 149.1, 147.7, 139.3, 134.9, 134.0, 132.9, 130.09, 129.2, 127.7, 127.2, 126.9, 126.2, 122.9, 119.6, 117.1, 111.7. $[\alpha]_D^{25}$ = **-0.206** (c=**1.00**, Acetone).

***2nd Step: Alkylation of the amine* 3a.**[29]

3,3'-(((S)-[1,1'-binaphthalene]-2,2'-diyl)bis(azaneylylidene))bis(1-(2-(dimethylamino)ethyl)indolin-2-one)

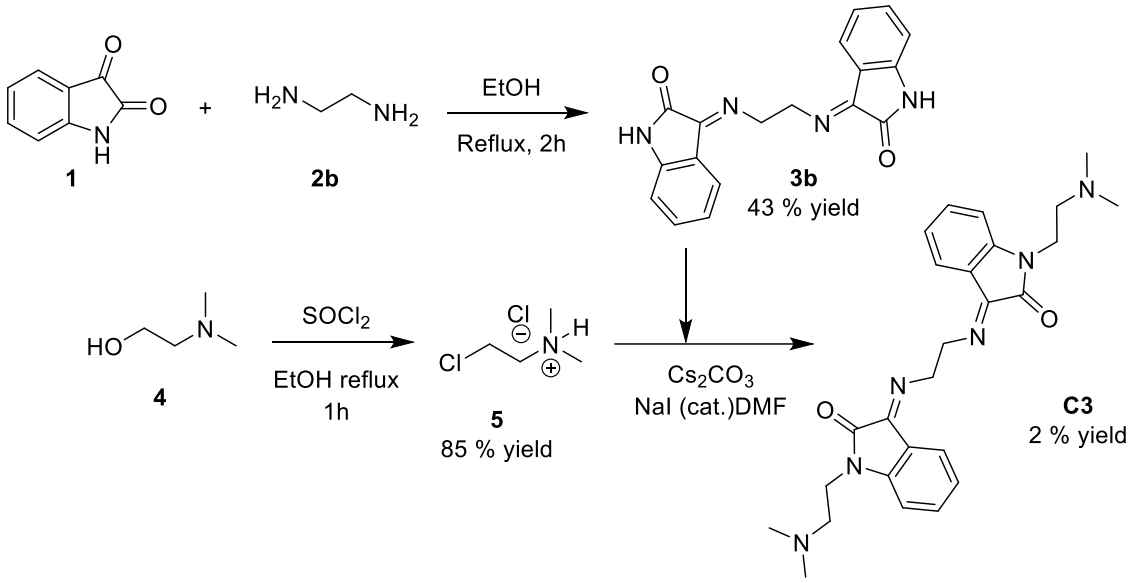


3a **5** **C2**

A mixture of the imine **3a** (550 mg, 1 mmol) and K_2CO_3 (3.56 g, 12 mmol, 6 eq.) in dry DMF (15 mL) under Ar atmosphere was stirred for 30 minutes at room temperature. Next, 2-chloro-*N,N*-dimethyletanamine hydrochloride **5** (869 mg, 6 mmol, 3 eq.) and NaI (45 mg, 30 %) were added at 0 ºC and the resulting mixture was stirred for 10 minutes at the same temperature and then brought to RT to check the pH. If necessary, more eq. of K_2CO_3 were added until the pH was alkaline. Once the mixture was basic, it was stirred at 60 ºC overnight. After this time, the starting imine was still detected by TLC and therefore 1.5 eq. of alkyl chloride **5** and 3 eq. of K_2CO_3 were added and the mixture was stirred at 60 ºC overnight. Then, water was added (10 mL) and the mixture was extracted with EtOAc (7 x 30 mL) and the organic phases were combined and washed with brine (10 x 20 mL). The organic phase was dried over MgSO4 and the solvent was evaporated under vacuum. The crude product was purified by flash column chromatography (85:10:5 DCM/MeOH/TEA)to afford the impure imine which was then triturated in Hex and DCM to provide catalyst **C2** as an orange solid (63.8 mg, 0.09 mmol, 9 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (t, *J* = 9.3 Hz, 2H), 7.45 (t, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.69 (t, *J* = 7.6 Hz, 1H), 6.47 (d, *J* = 7.9 Hz, 1H), 3.72 (d, *J* = 8.2 Hz, 1H), 2.92 (dd, *J* = 8.8, 6.9 Hz, 1H), 2.35 (t, *J* = 7.2 Hz, 2H), 2.24 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 154.1, 147.5, 146.7, 133.4, 133.1, 132.0, 129.3, 128.0, 127.1, 126.9, 126.8, 125.8, 124.8, 122.8, 118.2, 115.4, 108.4,

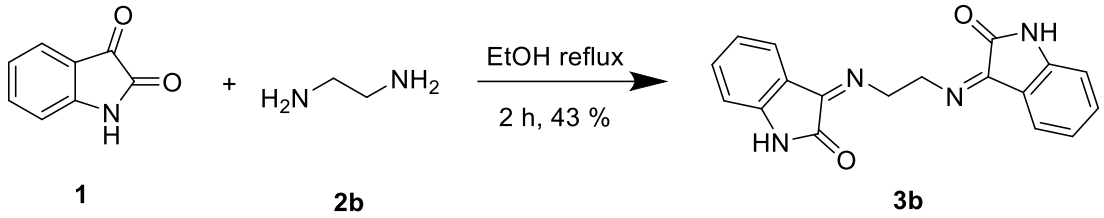
55.8, 53.0, 45.6, 38.2. HRMS calculated for $C_{44}H_{41}N_6O_2$ $[M+H]^+$: 685.3291, found: 685.3306. $[\alpha]_D^{25}$ = -0.075 (c=1.00, CH_2Cl_2).

6.2.2 *Synthesis of catalyst **C3***



1st Step: Synthesis of the Imine 3b.[30]

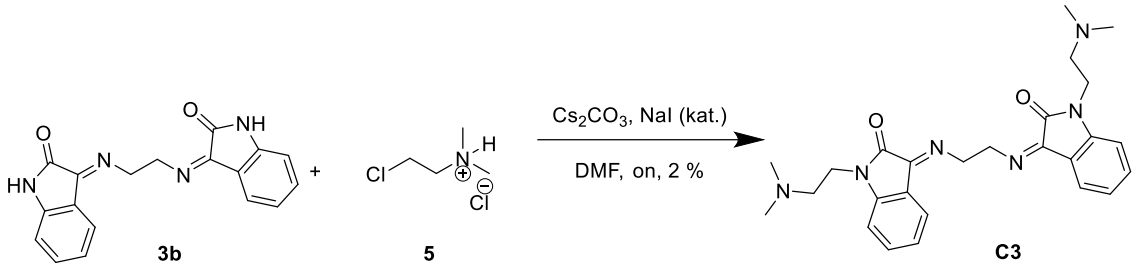
3,3'-(Ethane-1,2-diylbis(azaneylylidene))bis(indolin-2-one) **3b**



To a mixture of isatin **1** (2.94 g, 20 mmol, 2 eq.) in EtOH (250 mL). ethylenediamine **2b** (0.6 mL, 10 mmol, 1 eq.) was added and the resulting solution was stirred at reflux, observing since the beginning the formation of a dark orange solution. After the 2h had passed, the end of the reaction was confirmed by ^{1}H-NMR and TLC. Then the solvent was removed under vacuum to afford and orange solid which was purified by trituration in DCM. This afforded the expected imine **3b** (2.7 g, 8.481 mmol, 43 %). All the spectroscopic data are consisted with those previously described.[30] ^{1}H NMR (300 MHz, DMSO-D_6) δ 10.38 (s, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 6.99 (td, *J* = 7.7, 1.1 Hz, 2H), 6.62 (td, *J* = 7.7, 1.1 Hz, 2H), 6.48 (d, *J* = 7.2 Hz, 2H), 3.99 (s, 4H).

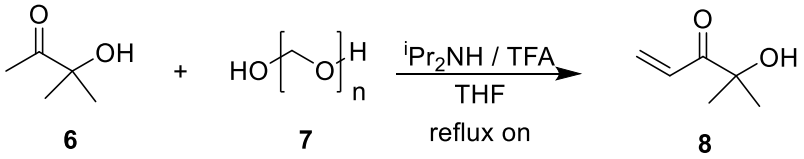
2nd Step: Alkylation of the imine 3b.[31]

1-(2-(Dimethylamino)ethyl)-3-((2-((1-(2-(dimethylamino)ethyl)-2-oxoindolin-3-yl)imino)ethyl)imino)indolin-2-one **C3**



To a mixture of the imine **3b** (159 mg, 0.5 mmol, 1 eq.) and Cs_2CO_3 (1.63 g, 5 mmol, 1.25 eq.) in in DMF (1.5 mL) under Ar atmosphere, alkyl chloride **5** (216 mg, 1.5 mmol, 1.5 eq.) and NaI (15 mg, 0.1 mmol, 20 %) were added at 0 ºC. The temperature was raised to 80 ºC and the reaction mixture was heated at this temperature over weekend and the end of reaction was determined by TLC. Then, water was added (10 mL) and the mixture was extracted with EtOAc (5 x 10 mL) and the organic phases were combined and washed with brine (10 x 20 mL). The organic phase was dried over $MgSO_4$ and the solvent was evaporated under vacuum. The crude product was triturated in hexane and DCM and later the crude product was separated by flash column chromatography (97:3 DCM/MeOH)to provide the catalyst **C2** as an orange solid (5 mg, 0.1 mmol, 2 %) in a very small quantity, only a ^{1}H-NMR analysis could be performed.

6.3 Synthesis of α-Hydroxy enone 8.[24]

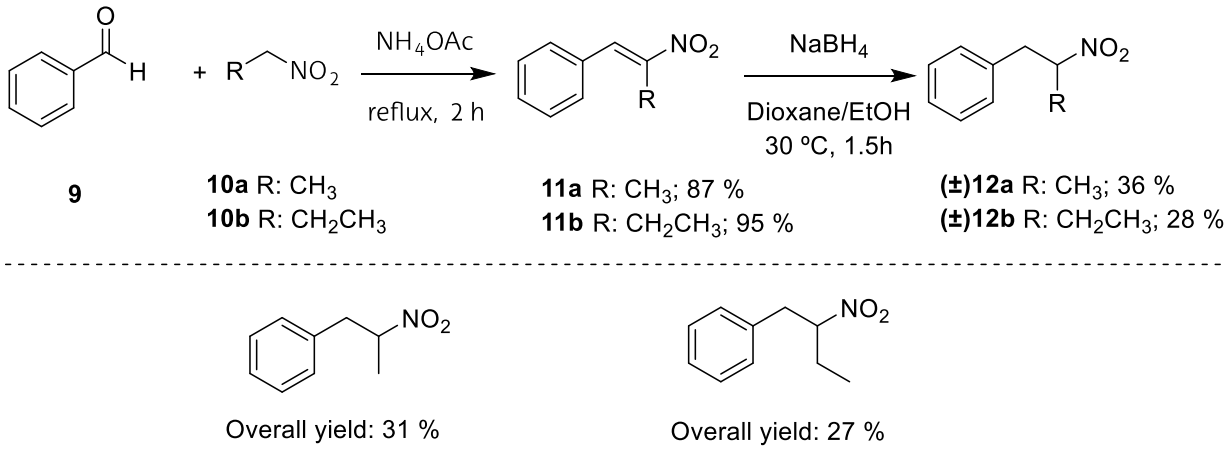


To a mixture of DIPA (7 mL, 50 mmol, 2 eq.) and TFA (4.8 mL, 62.5 mL, 2.5 eq.) in dry THF (125 mL), 3-hydroxy-3-methylbutan-2-one **6** (2.65 mL, 25 mmol, 1 eq.) and paraformaldehyde **7** (1.5 g, 50 mmol, 2 eq.) were added. The mixture was stirred at reflux and every 2 h additional paraformaldehyde (1.5 g, 50 mmol, 2 eq.) for a total of 3 times. The mixture was stirred at reflux overnight and then cooled down to room temperature. The reaction mixture was diluted with DCM (60 mL) and washed with 1M HCl (3 x 15 mL), 1 M NaOH (3 x 15 mL) and brine (3 x 15 mL). The organic phase was collected and dried

over $MgSO_4$ and the solvent was removed under controlled vacuum (430 mbar). For the purification, a vacuum distillation in 2 steps was performed. On the first step, the remaining solvent was distilled using a Vacuubrand 6 pump. On the second step, the expected product was distilled using an Edwards 5 pump providing α-Hydroxy enone: 4-hydroxy-4-methylpent-1-en-3-one **8** as a transparent liquid of high purity (2.766 g, 24.2 mmol, 97 %). All the spectroscopic data were consistent with the previously reported.[24] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (dd, J = 17.0, 10.3 Hz, 1H), 6.53 (dd, J = 17.0, 1.9 Hz, 1H), 5.85 (dd, J = 10.3, 1.9 Hz, 1H), 1.40 (s, 6H).

6.4 Synthesis of the α-Branched nitroalkanes

General procedure:[33]

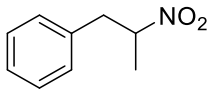


1st Step: Benzaldehyde **9** (1.9 mL, 20 mmol, 1 eq.) and ammonium acetate (2 g, 26 mmol) were dissolved in the corresponding nitroalkane (60 mL). The mixture was stirred at reflux and the reaction was followed by TLC and ^{1}H-NMR. Once the reaction had finished, the solvent was evaporated under vacuum. The resulting residue was dissolved in DCM (50 mL) and the product was washed using brine (5 x 15 mL) and water (5 x 15 mL). The organic phase was dried over $MgSO_4$ and evaporated under vacuum to provide the expected nitroalkene which was used in the next step without further purification.

2nd Step: A stirred mixture of NaBH4 (1.3 g, 34.72 mmol, 2.17 eq.) in EtOH/dioxane (1:3 proportion, 35 mL) was heated to 30 ºC and a previously prepared solution of the corresponding nitroalkene (16 mmol, 1 eq.) in dioxane (26.67mL) was added dropwise over the course of 45 min while observing the creation of H_2 bubbles. The mixture was stirred at 30 ºC and the progression was followed by TLC. The mixture was then quenched using an ice/water mixture (≈ 30 mL) and the excess of metal hydride was destroyed by acetic acid (≈ 8 mL, 50 % in volume). The mixture was concentrated under

vacuum and extracted using DCM (3 x 15 mL). The organic layers were washed with H_2O (3 x 15mL) and brine (3 x 15 mL). The organic phase was dried over $MgSO_4$ and the solvent was evaporated under vacuum. For the purification, a silica gel flash column chromatography was performed (eluent system from 100:1:1 Hex/EtOAc/TFA to 98:2 Hex/EtOAc) providing the expected nitroalkane.

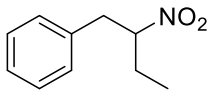
6.4.1 *(2-Nitropropyl)benzene* ***(±)12a***



(±)12a

The general procedure was followed starting from nitroethane **10a**. After work-up the title product was obtained as a yellow solid (943.6 mg, 5.72 mmol, overall yield 31 %). All the spectroscopic data were consistent with the previously reported.[35,33b] Nitroalkene **11a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.46 – 7.42 (m, 8H), 2.46 (d, *J* = 1.1 Hz, 11H). Nitroalkane **(±)12a**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.23 (m, 3H), 7.21 – 7.11 (m, 2H), 4.87 – 4.70 (m, 1H), 3.33 (dd, *J* = 13.9, 7.4 Hz, 1H), 3.01 (dd, *J* = 14.0, 6.8 Hz, 1H), 1.55 (d, *J* = 6.6 Hz, 3H).

6.4.2 *(2-nitrobutyl)benzene* ***(±)12b***



(±)12b

The general procedure was followed starting from nitropropane **10b**. After work-up the title product was obtained as a yellow oil (1.633 g, 9.11 mmol, overall yield 28 %). Nitroalkene **11b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.44 (d, *J* = 3.1 Hz, 5H), 2.14 – 1.96 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H). Nitroalkane **(±)12b**, all the spectroscopic data were consisted with those previously described[36]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 3H), 7.16 (dd, *J* = 8.0, 1.7 Hz, 2H), 4.71 – 4.55 (m, 1H), 3.27 (dd, *J* = 14.1, 8.5 Hz, 1H), 3.03 (dd, *J* = 14.2, 5.9 Hz, 1H), 2.13 – 1.75 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).

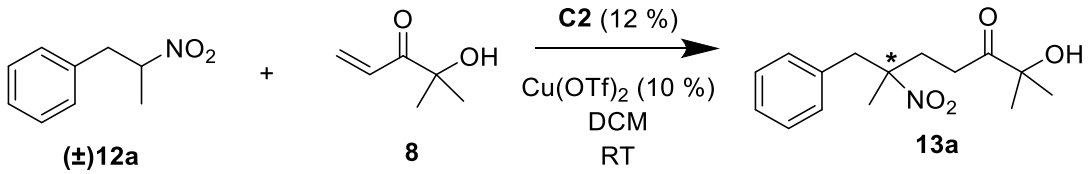
[35] Aalberg, L., Andersson, K., Bertler, C., Borén, H., Cole, M. D., Dahlén, J., Finnon, Y., Huizer, H., Jalava, K., Kaa, E., Lock, E., Lopes, A., Poortman-Van Der Meer, A., & Sippola, E.; *Forensic Sci. Int.*, **2005**;*149* (2–3), 219–229.
[36] Gildner, P. G.; Gietter, A. A. S.; Watson, D. A.; *J. Am. Chem. Soc;* **2012**, *134* (24), 9942-9945

6.5 Michael addition reaction

6.5.1 *Addition to α-hydroxy enone **8**.*

2-Hydroxy-2,6-dimethyl-6-nitro-7-phenylheptan-3-enone

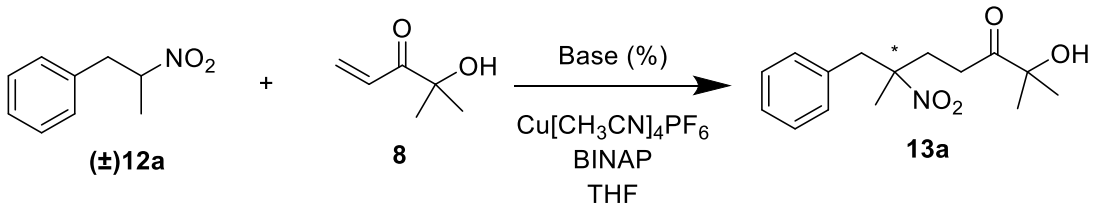
- Catalysed by **C2**/Cu(II)



(±)12a 8 13a

To a suspension of $Cu(OTf)_2$ (7 mg, 0.02 mmol, 10 mol %) in DCM (0.6 mL), **C2** was added (16 mg, 0.024 mmol, 12 mol %). At first the suspension dissolved but shortly after, in approximately 5 mins, a brown oil precipitated. (2-nitropropyl)benzene **(±)12a** (165 mg, 1 mmol, 5 eq.) and α-hydroxy enone **8** (23 mg, 0.2 mmol, 1 eq.) were added and the mixture was let stirring overnight and the conversion followed by ^{1}H-NMR. However, in all conditions studied, no Michael adducts were detected.

- Catalysed by TEA, Cu(I) and BINAP

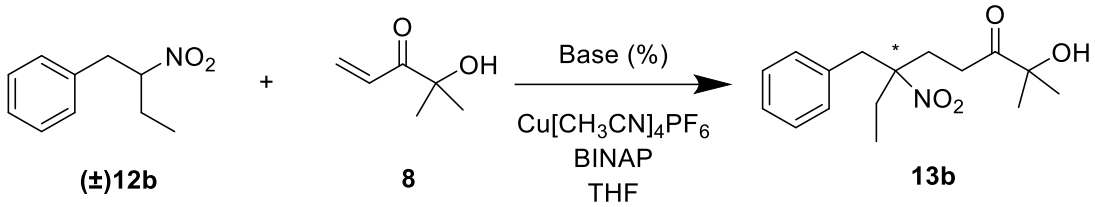


(±)12a 8 13a

To a stirred solution of (2-nitropropyl)benzene **(±)12a** (165 mg, 1 mmol, 5 eq.) in THF (0.6 mL) under Ar atmosphere, α-hydroxy enone **8** (23 mg, 0.2 mmol, 1 eq.), $Cu[CH_3CN]_4PF_6$ and the corresponding ligand were added in the indicated amount followed by the corresponding base. The mixture was stirred for the indicated time and the conversion followed by ^{1}H-NMR. Then the product was purified by flash column chromatography (95:5 Hex/EtOAc). The best result was obtained when using $Cu[CH_3CN]_4PF_6$ (15 mg, 0.04 mmol, 20 mol %) with *S*-BINAP (27 mg, 0.044 mmol, 22 mol %) and TEA (5.8 µL, 0.04 mmol, 20 mol %), Table 1, entry 3. After 118h reaction at RT the crude product is purified by flash column chromatography (eluent: 90/10 Hex/EtOAc), the expected adduct, 2-hydroxy-2,6-dimethyl-6-nitro-7-phenylheptan-3-enone **13a** was obtained as a white solid (45 mg, 0.16 mmol, 81 %). The enantiomeric excess was found to be 0.2 % and was

determined by chiral HPLC analysis (IA column, 95/5 Hex/^{i}PrOH, flow 0.5 mL/min. Retention times: major enantiomer 33.796 min; minor enantiomer 30.909 min). The spectroscopic data were consistent with those previously reported.[37] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 5.0, 2.0 Hz, 3H), 7.12 – 7.05 (m, 2H), 3.37 (d, *J* = 13.8 Hz, 1H), 3.08 (d, *J* = 13.8 Hz, 1H), 2.62 – 2.38 (m, 2H), 2.20 – 2.04 (m, 2H), 1.48 (s, 3H), 1.36 (s, 6H). 13C NMR (75 MHz, CDCl3) δ (ppm) = 213.1, 134.6, 130.5, 129.0, 128.1, 91.5, 46.9, 33.4, 30.7, 27.0, 21.8. UPLC-DAD-QTOF: $C_{15}H_{21}NO_4Na$ [M+Na]+ calculated.: 302.1368, found: 302.1366.

6-Benzyl-2-hydroxy-2-methyl-6-nitrooctan-3-one



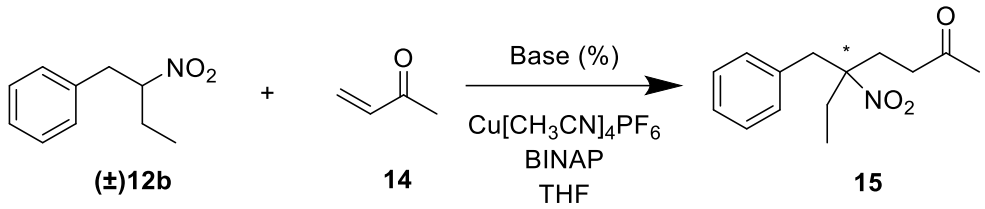
(±)12b **8** **13b**

To a stirred solution of (2-nitrobutyl)benzene **(±)12b** (179 mg, 1 mmol, 5 eq.) in THF (0.6 mL) under Ar atmosphere, α-hydroxy enone **8** (23 mg, 0.2 mmol, 1 eq.), $Cu[CH_3CN]_4PF_6$ and the corresponding ligand were added in the indicated amount followed by the corresponding base. The mixture was stirred for the indicated time and the conversion followed by ^{1}H-NMR. Then the product was purified by flash column chromatography (95:5 Hex/EtOAc). The best result was obtained when using $Cu[CH_3CN]_4PF_6$ (26 mg, 0.07 mmol, 35 mol %) with *R*-BINAP (37 mg, 0.06 mmol, 30 mol %) and TEA (8.7 µL, 0.06 mmol, 30 mol %), Table 2 entry 1. After 7 days reaction at RT purification was performed by flash column chromatography (eluent: 90/10 Hex/EtOAc), the expected adduct, 6-Benzyl-2-hydroxy-2-methyl-6-nitrooctan-3-one **13b,** was obtained as a white solid (37 mg, 0.124 mmol, 62 %). The enantiomeric excess was found to be 26 % and was determined by chiral HPLC analysis (ADH column, 95/5 Hex/^{i}PrOH, 1 mL/min flow. Retention times: major enantiomer 24.948 min; minor enantiomer 28.281 min). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 5.1, 2.0 Hz, 3H), 7.07 (dd, *J* = 7.1, 2.5 Hz, 2H), 3.24 (s, 2H), 2.55 (t, *J* = 8.1 Hz, 2H), 2.35 – 2.09 (m, 2H), 1.95 (q, *J* = 7.5 Hz, 2H), 1.36 (s, 6H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9, 134.5, 129.9, 128.8, 127.7, 94.8, 76.6, 30.2, 28.9, 27.9, 26.7, 8.5.

[37] A. García, Doctoral Thesis UPV/EHU, April 2022, *Short Peptide-Derived Bifunctional BrØnsted Base Catalysts in Asymmetric Michael Reactions.*

6.5.2 *Addition to methyl-vinyl ketone **14**.*

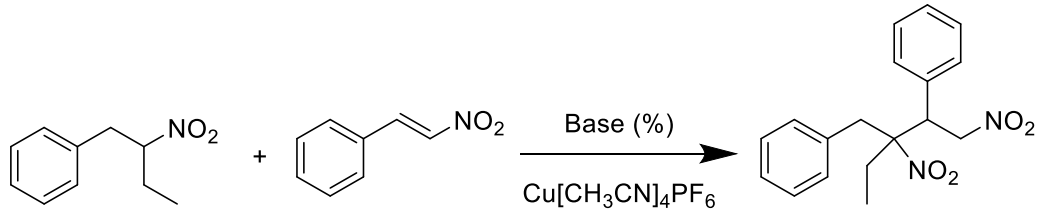
5-Benzyl-5-nitroheptan-2-one



(±)12b **14** **15**

To a stirred solution of (2-nitrobutyl)benzene **(±)12b** (179 mg, 1 mmol, 5 eq.) in THF (0.6 mL) under Ar atmosphere, **methyl vinyl ketone 14** (19 µL, 0.2 mmol, 1 eq.), $Cu[CH_3CN]_4PF_6$ and the corresponding ligand were added in the indicated amount followed by the corresponding base. The mixture was stirred for the indicated time and the conversion followed by ^{1}H-NMR. Then the product was purified by flash column chromatography (90:10 Hex/EtOAc). The best result was obtained when using $Cu[CH_3CN]_4PF_6$ (15 mg, 0.04 mmol, 20 mol %) with R-BINAP (27 mg, 0.044 mmol, 22 mol %) and Barton's Base (8.2 µL, 0.044 mmol, 20 mol %). After 2 h reaction at RT, the crude product was purified by flash column chromatography (eluent: 90/10 Hex/EtOAc), the expected adduct, 5-benzyl-5-nitroheptan-2-one **15**, was obtained as a white solid (33 mg, 0.134 mmol, 67 %). The enantiomeric excess was found to be 10.42 % and was determined by chiral HPLC analysis (IF column, 90/10 Hex/^{i}PrOH 0.5 mL/min flow. Retention times: major enantiomer 26.018 min; minor enantiomer 22.606 min). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 5.5 Hz, 3H), 7.08 – 7.03 (m, 2H), 3.21 (d, J = 5.1 Hz, 2H), 2.52 – 2.35 (m, 2H), 2.30 – 2.06 (m, 2H), 2.14 (s, 3H), 2.01 – 1.82 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.4 134.6, 129.9, 128.8, 127.7, 110.1, 94.8, 41.8, 38.0, 30.2, 28.8, 27.6, 8.6.

6.5.3 *Addition to nitroalkene **16**.*



(±)12b **16** **17**

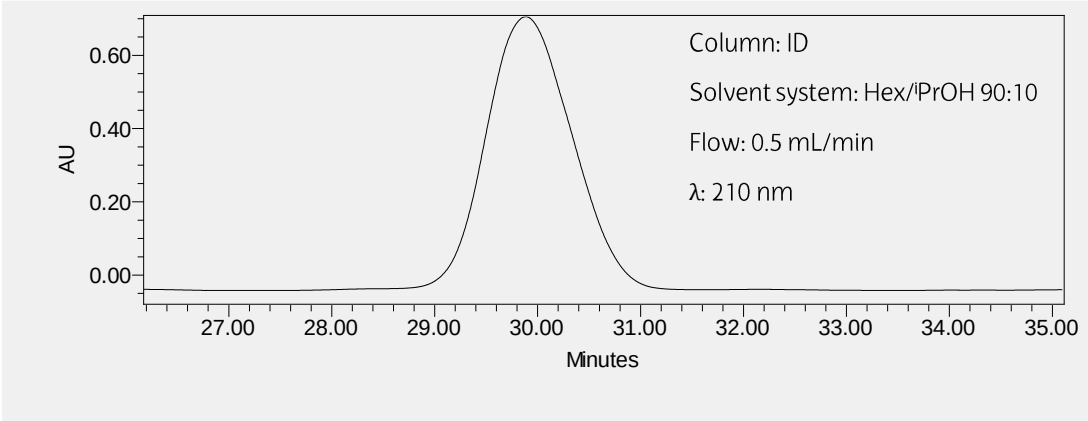
To a stirred solution of (2-nitrobutyl)benzene **(±)12b** (179 mg, 1 mmol, 5 eq.) in THF (0.6 mL) under Ar atmosphere, **(2-nitrovinyl)benzene 16** (30 mg, 0.2 mmol, 1 eq.), $Cu[CH_3CN]_4PF_6$ and the corresponding ligand were added in the indicated amount followed by the corresponding base. The mixture was stirred for the indicated time and

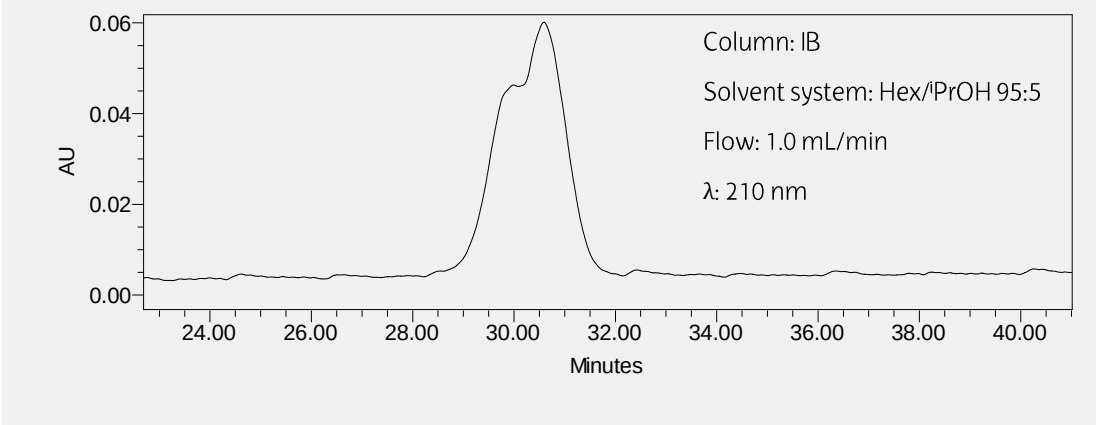
the conversion followed by ^{1}H-NMR. However, in all the studied conditions the Michael adducts were not detected.

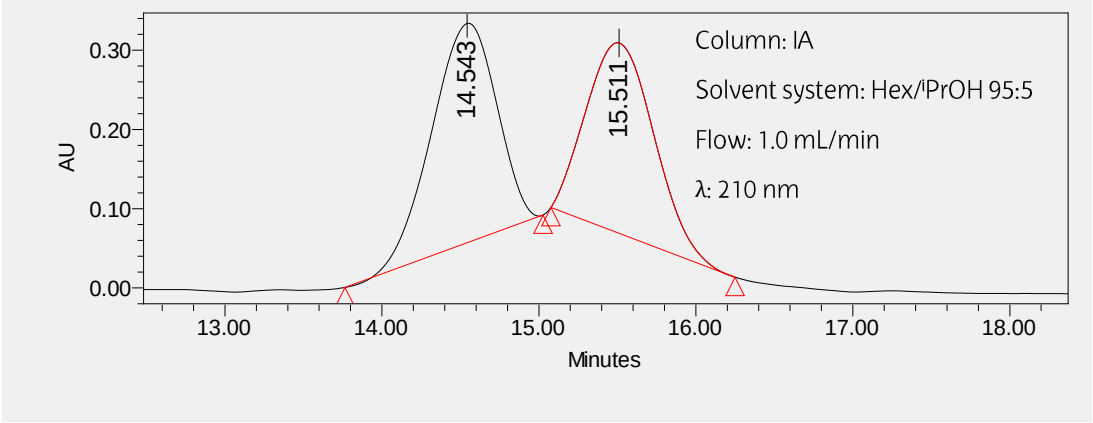
6.6 HPLC chromatograms

*6.6.1 Search of conditions for the separation of **13b***

In order to separate the enantiomers in **13b** several attempts were tried in the HPLC and different conditions were tried until the optimal ones were found.

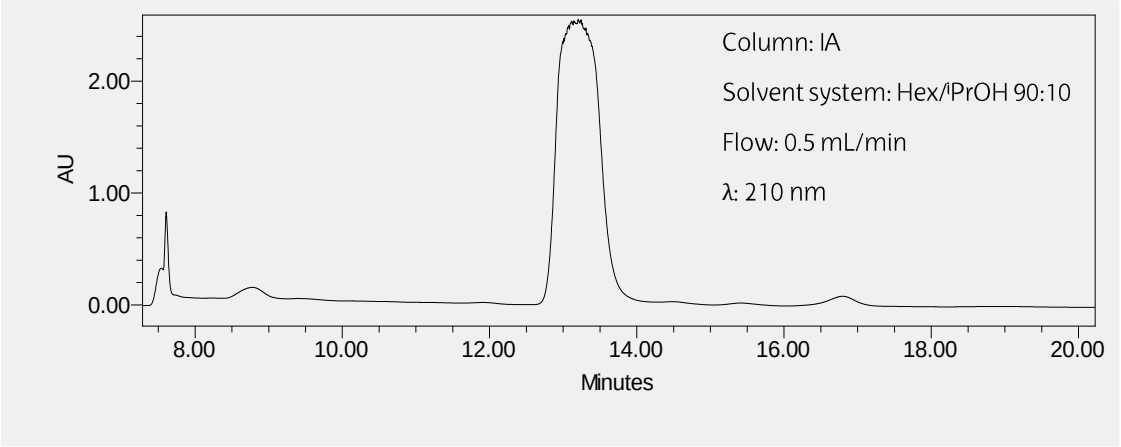




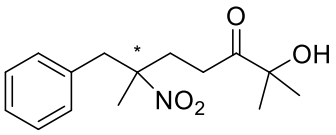


6.6.2 *Search of conditions for the separation of **15***

In order to separate the enantiomers in **15**, one attempt was made in the HPLC before finding the optimal conditions.



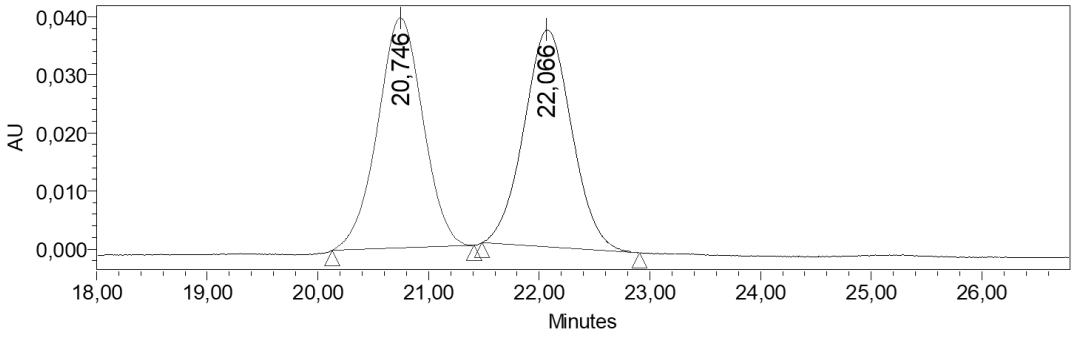
6.6.3 *Optimal conditions for the HPLC*



13a

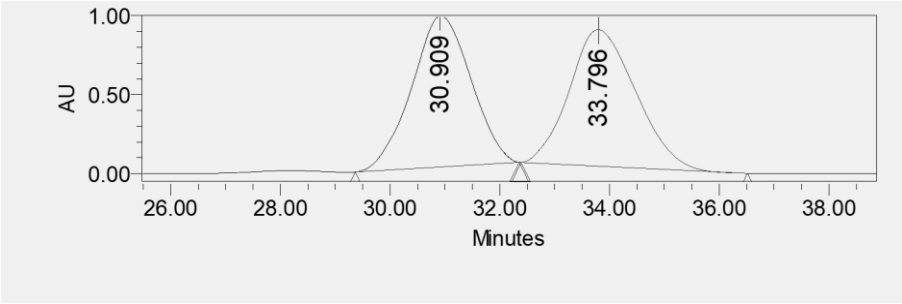
Column: IA
Solvent system: Hex/^{i}PrOH 95:5
Flow: 0.5 mL/min
λ: 210 nm

Racemic sample

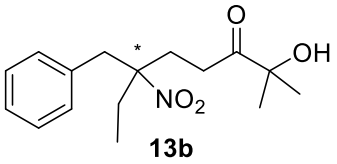


Peak	Retention time	% Area
1	20.746	50.12
2	22.066	49.88

Asymmetric sample:



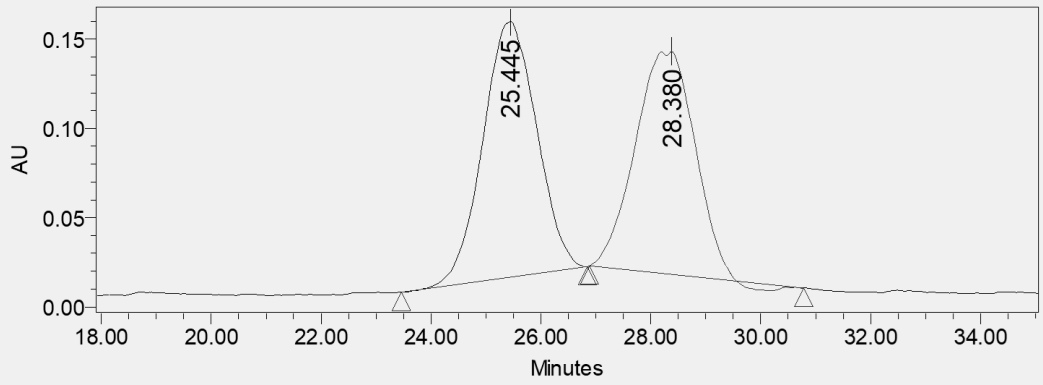
Peak	Retention time	% Area
1	30.909	49.62
2	33.796	50.38



13b

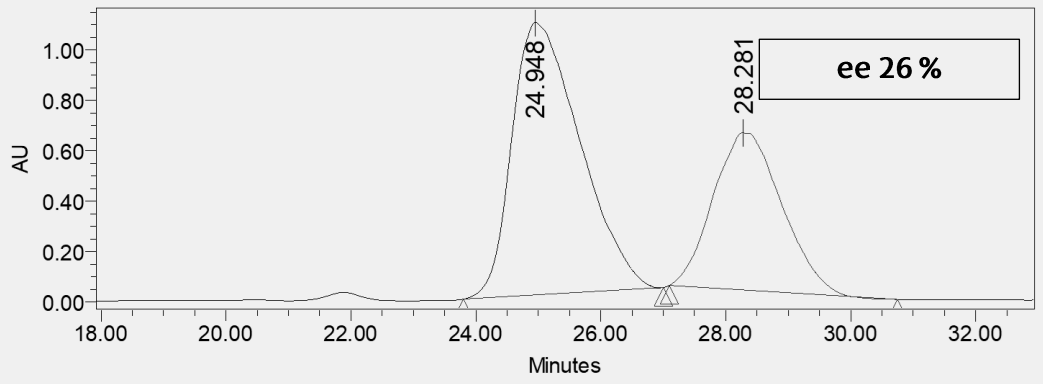
Column: ADH
Solvent system: Hex/^{i}PrOH 95:5
Flow: 1.0 mL/min
λ: 210 nm

Racemic sample:

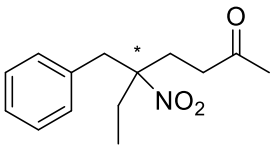


Peak	Retention time	% Area
1	25.445	50.32
2	28.380	49.68

Asymmetric sample:



Peak	Retention time	% Area
1	24.948	63.11
2	28.281	36.89



15

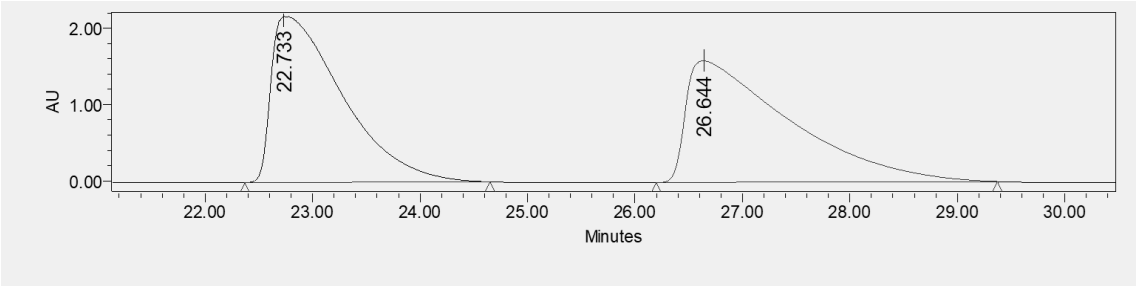
Column: IF

Solvent system: Hex/^{i}PrOH 90:10

Flow: 0.5 mL/min

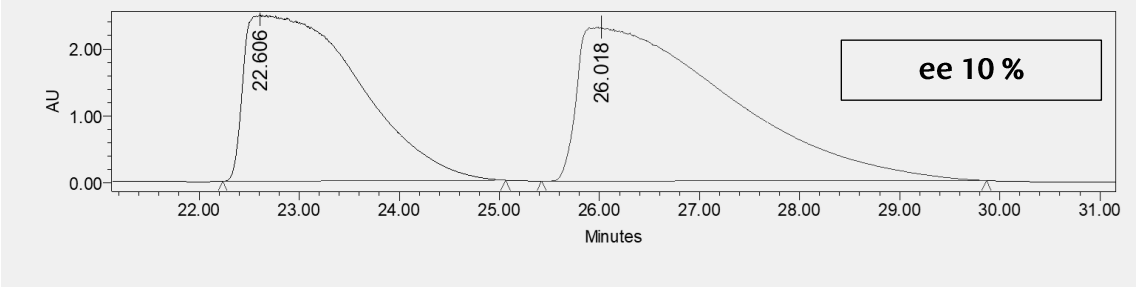
λ: 210 nm

Racemic sample:



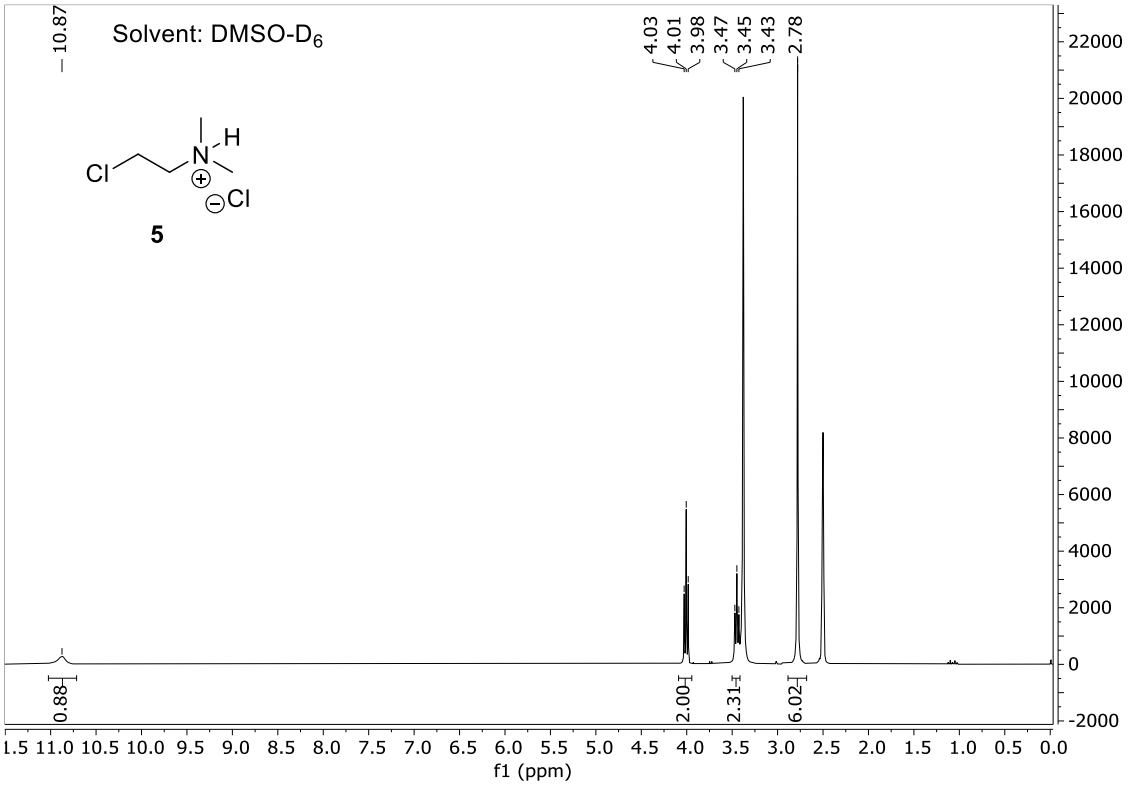
Peak	Retention time	% Area
1	22.733	48.51
2	26.644	51.49

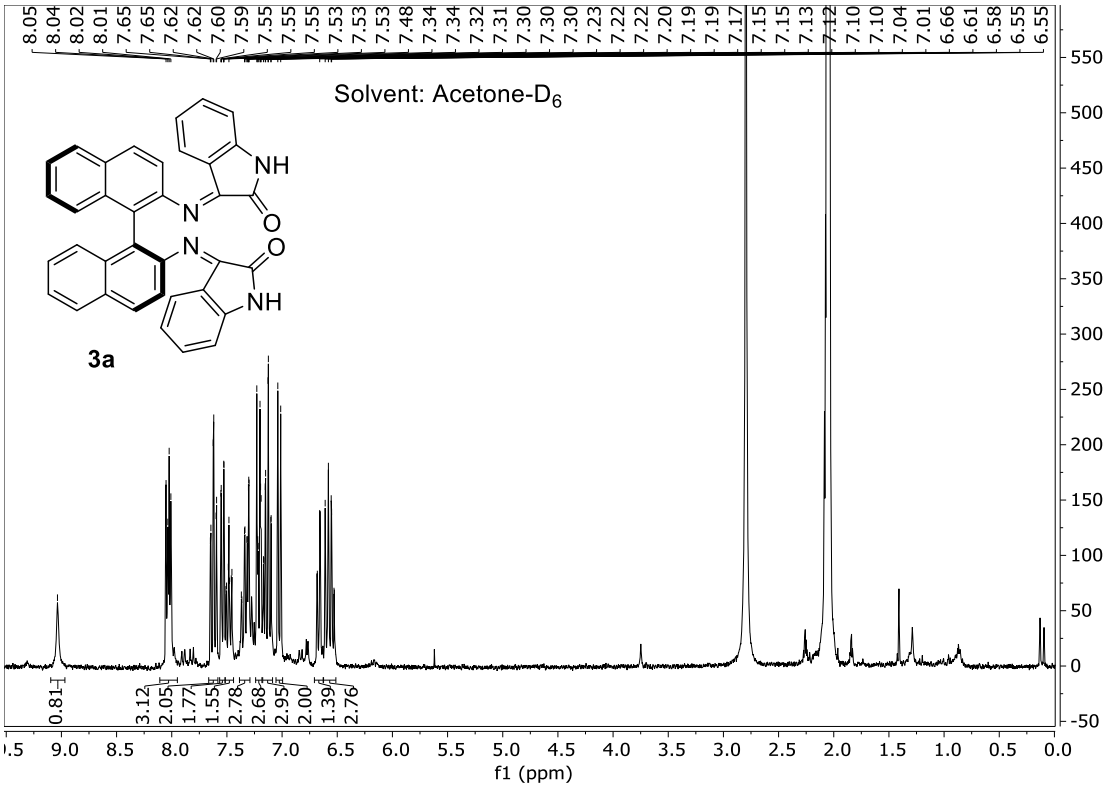
Asymmetric sample:

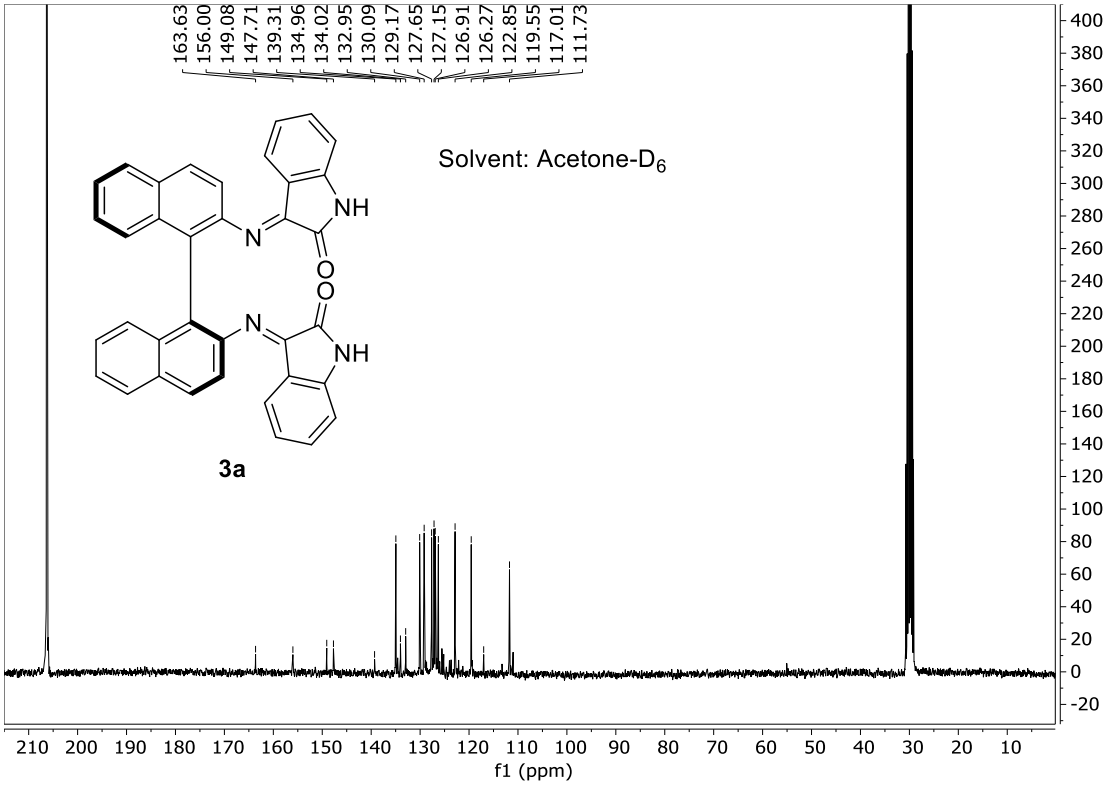


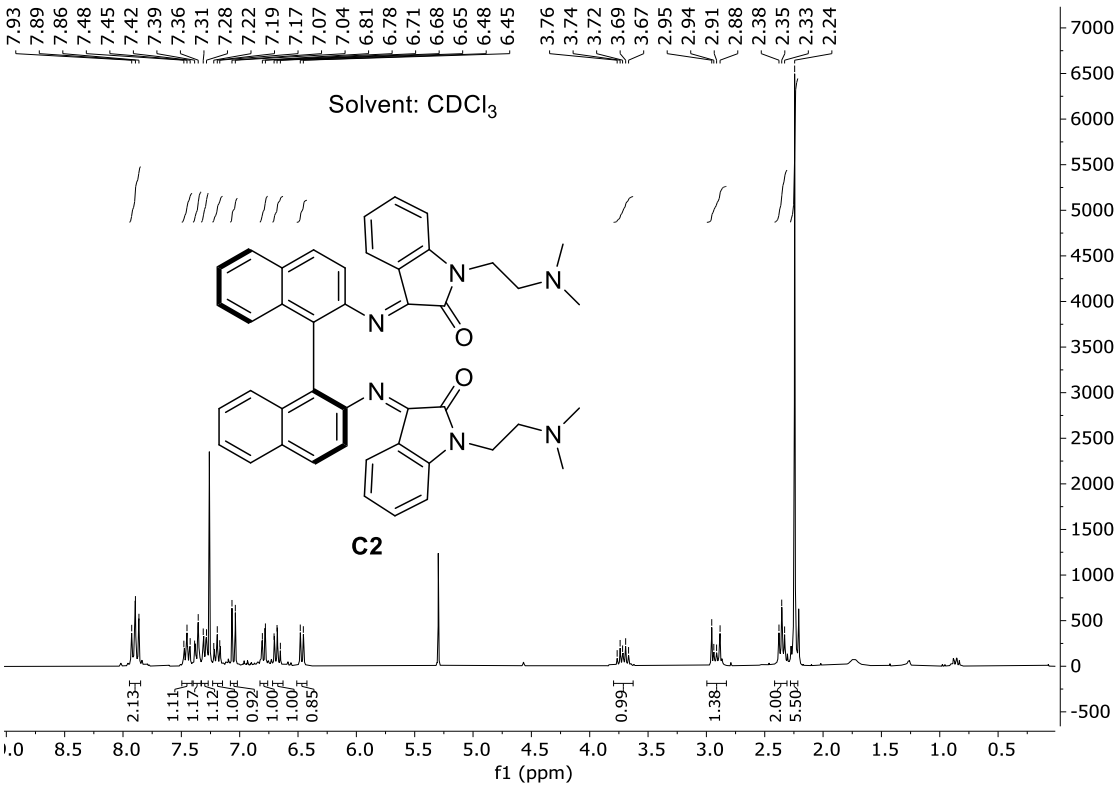
Peak	Retention time	% Area
1	22.608	44.79
2	26.018	55.21

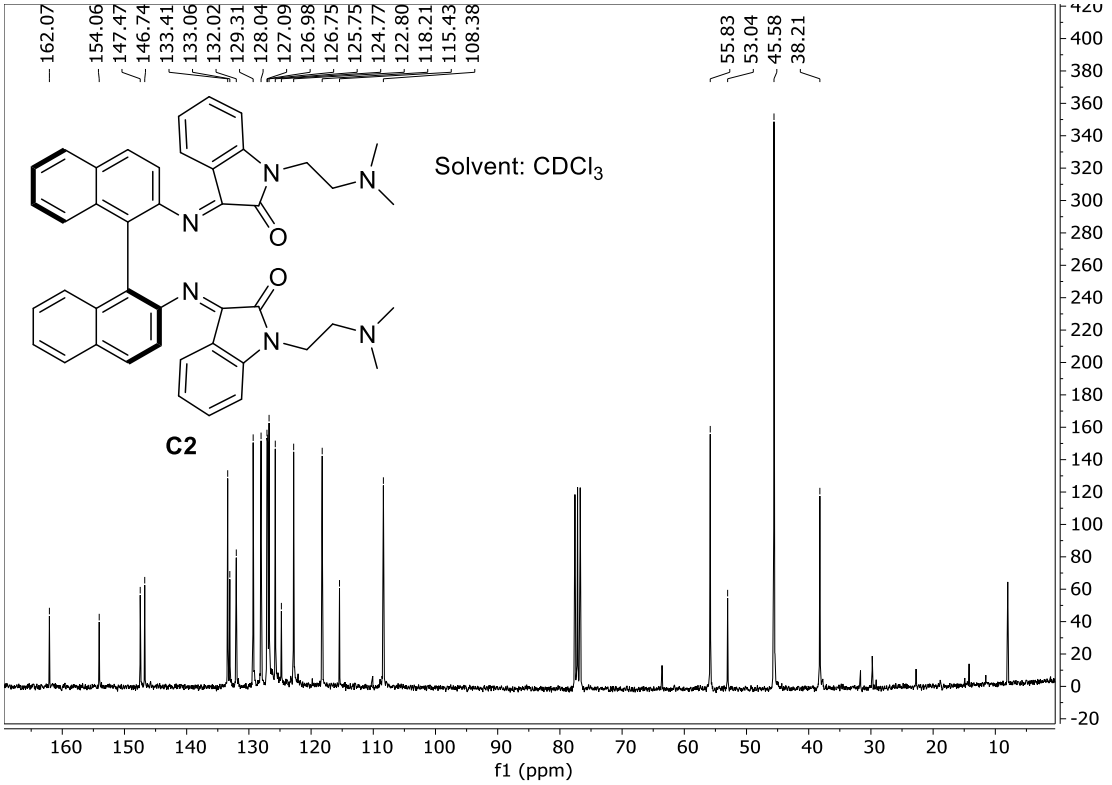
6.7 NMR spectra

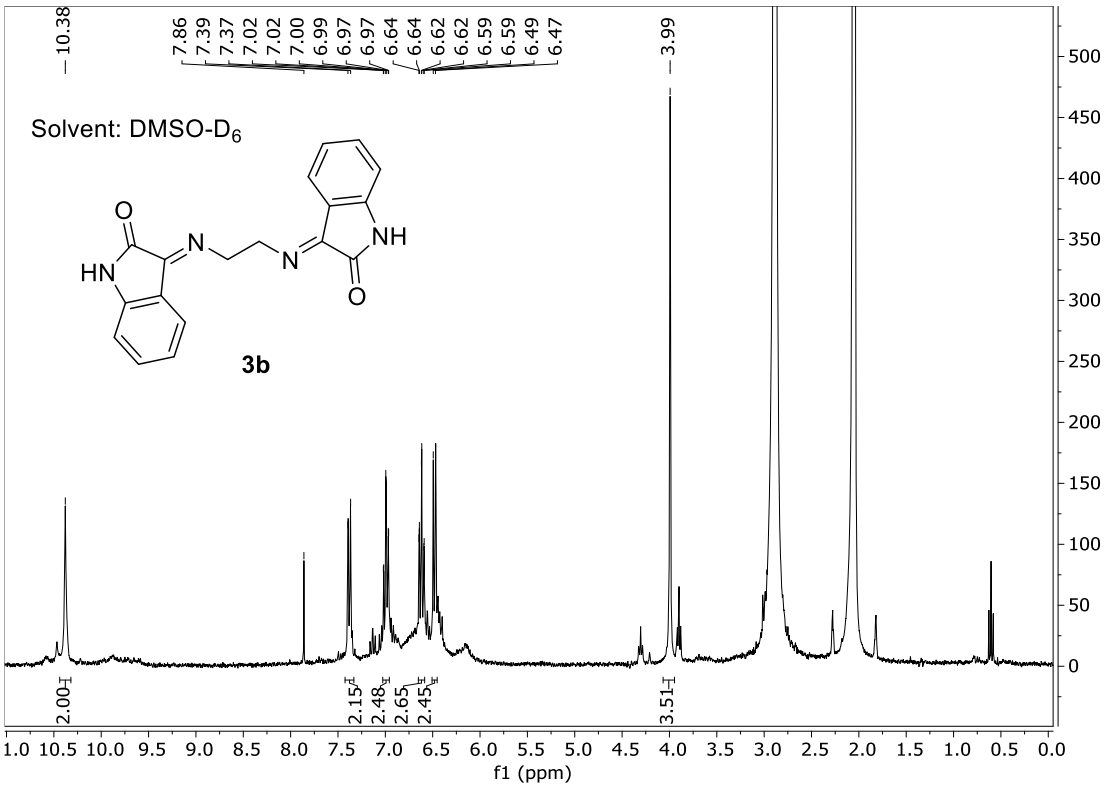


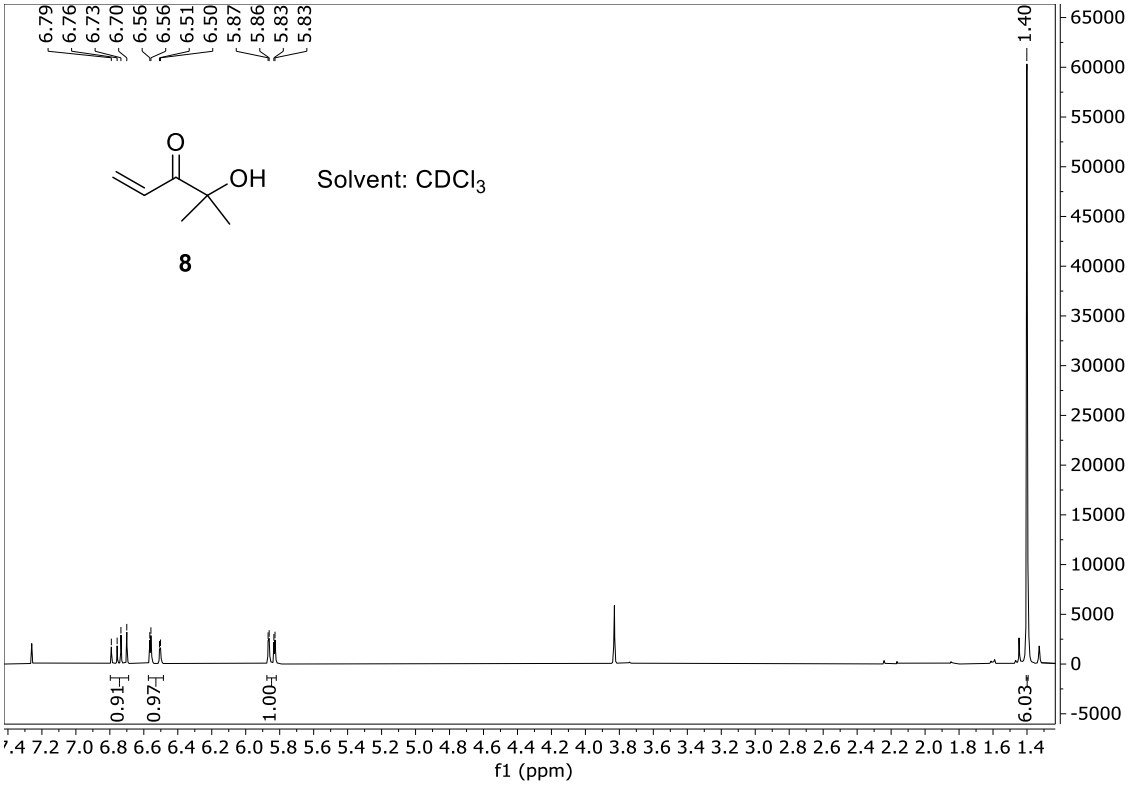


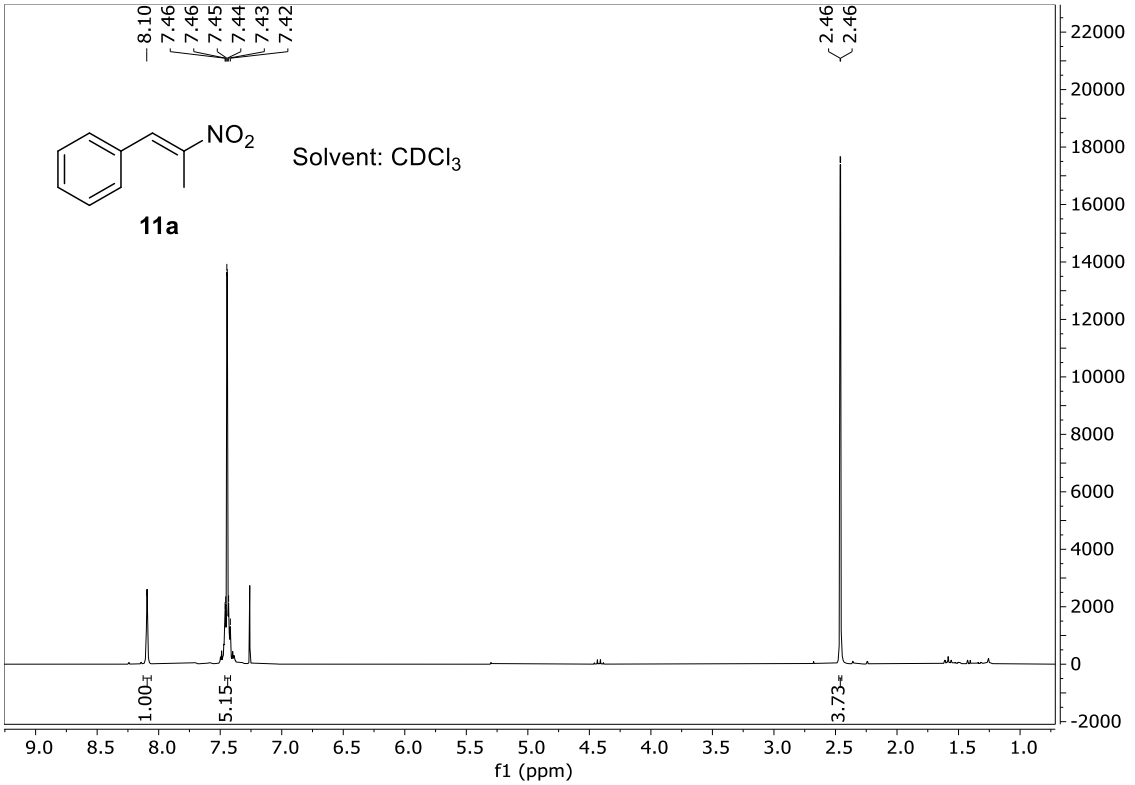

163.63
156.00
149.08
147.71
139.31
134.96
134.02
132.95
130.09
129.17
127.65
127.15
126.91
126.27
122.85
119.55
117.01
111.73
Solvent: Acetone-D6
NH
N
O
O
N
NH
3a
f1 (ppm)

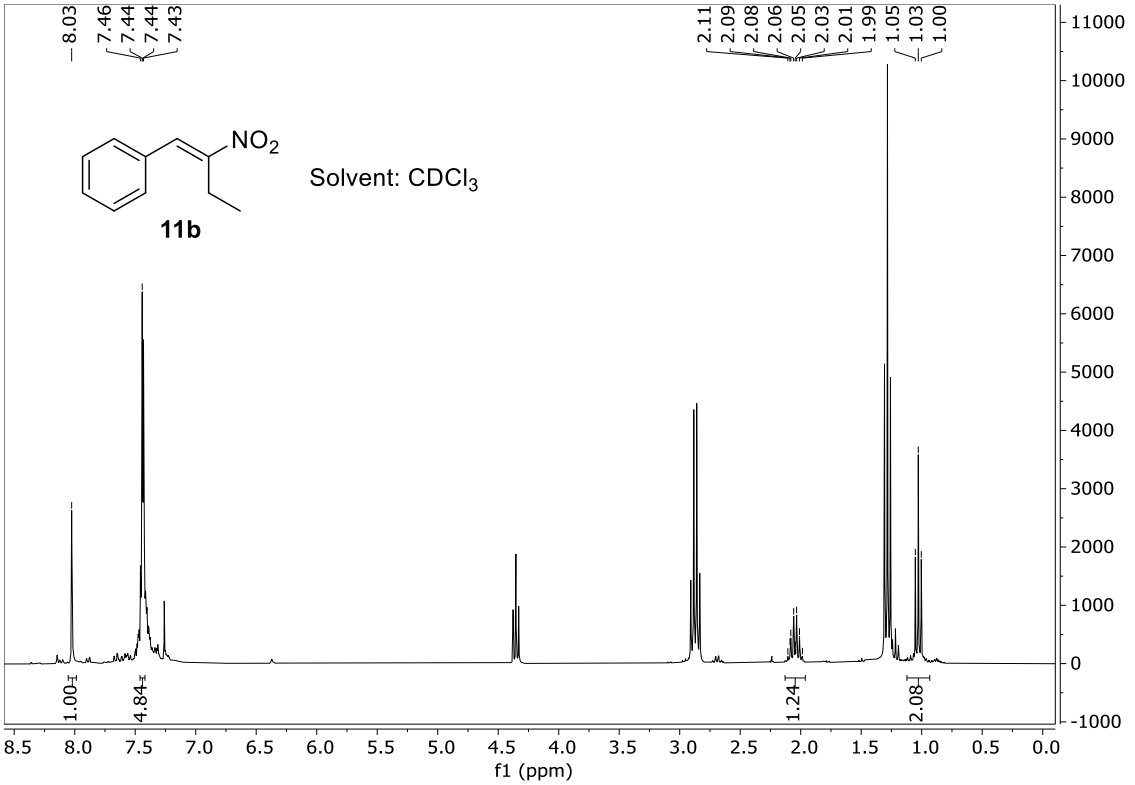

7.93
7.89
7.86
7.48
7.45
7.42
7.39
7.36
7.31
7.28
7.22
7.19
7.17
7.07
7.04
6.81
6.78
6.71
6.68
6.65
6.48
6.45
3.76
3.74
3.72
3.69
3.67
2.95
2.94
2.91
2.88
2.38
2.35
2.33
2.24
Solvent: CDCl3
N
N
O
N
O
N
N
C2
2.13
1.11
1.17
1.12
1.00
0.92
1.00
1.00
0.85
0.99
1.38
2.00
5.50
f1 (ppm)

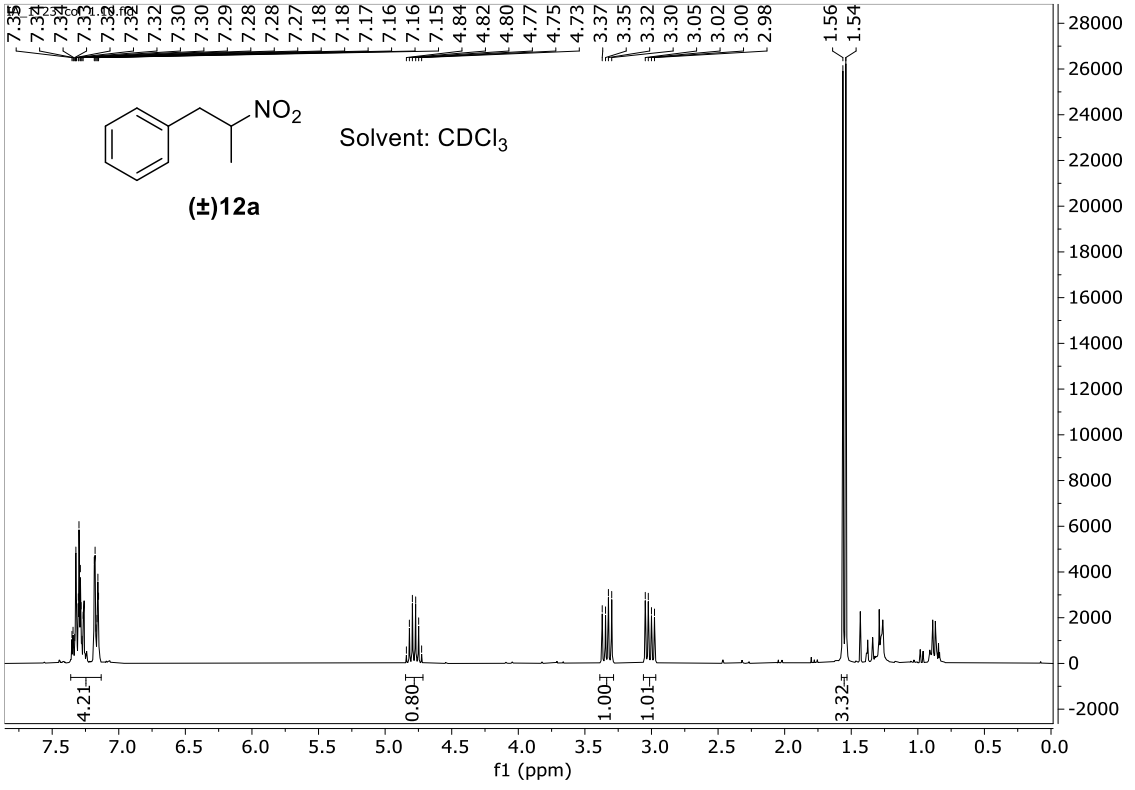

162.07
154.06
147.47
146.74
133.41
133.06
132.02
129.31
128.04
127.09
126.98
126.75
125.75
124.77
122.80
118.21
115.43
108.38
55.83
53.04
45.58
38.21
Solvent: CDCl3
C2
f1 (ppm)

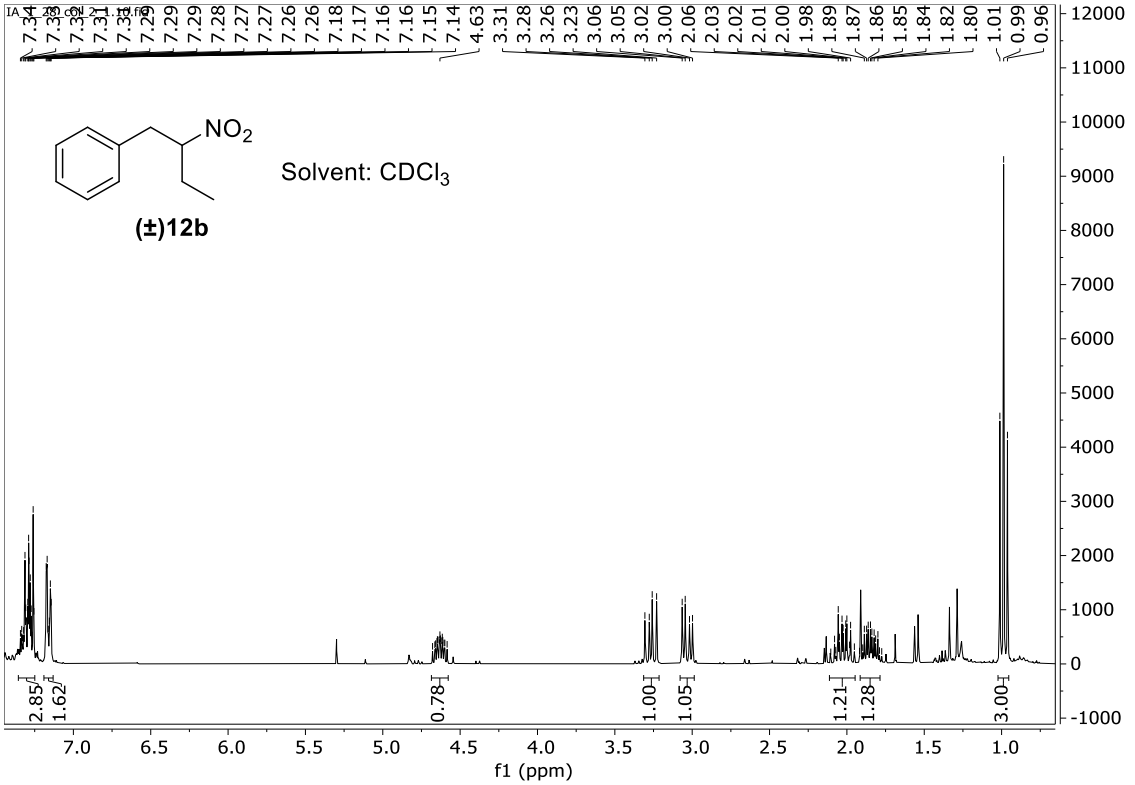

10.38
7.86
7.39
7.37
7.02
7.02
7.00
6.99
6.97
6.97
6.64
6.64
6.62
6.62
6.59
6.59
6.49
6.47
3.99
Solvent: DMSO-D6
3b
2.00
2.15
2.48
2.65
2.45
3.51
f1 (ppm)

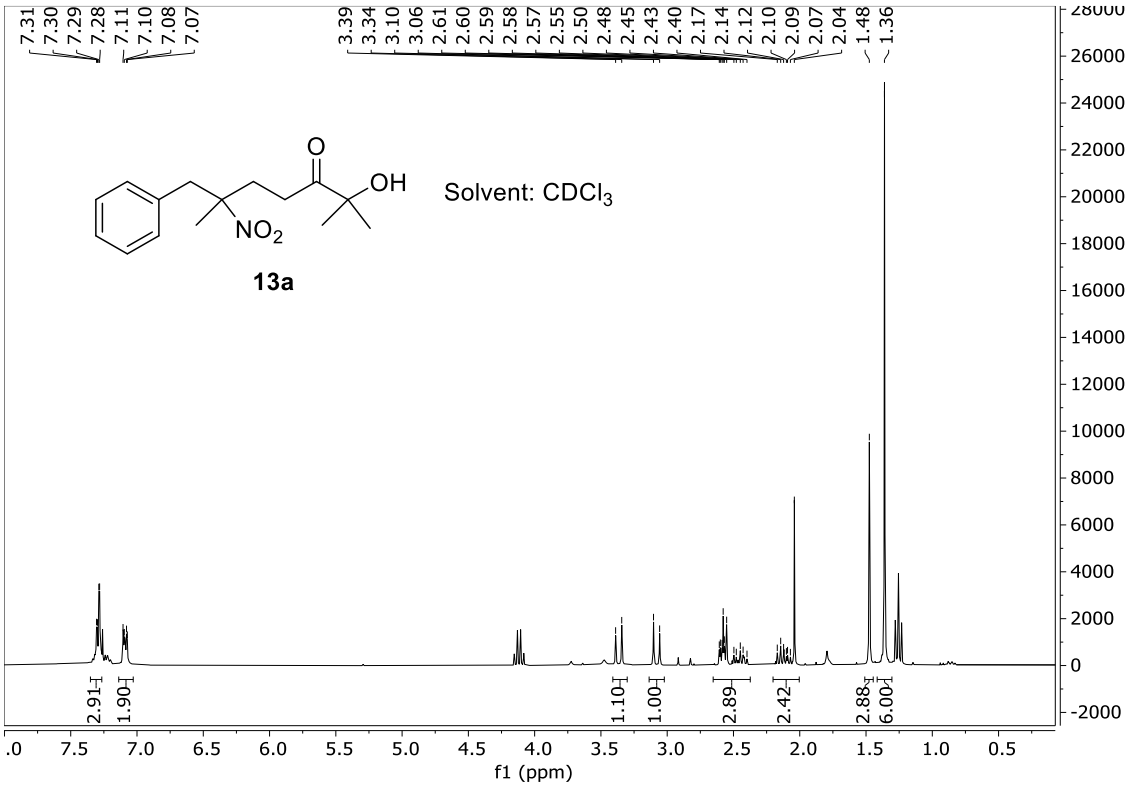

6.79
6.76
6.73
6.70
6.56
6.56
6.51
6.50
5.87
5.86
5.83
5.83
1.40
O
OH
Solvent: CDCl3
8
0.91
0.97
1.00
6.03
f1 (ppm)

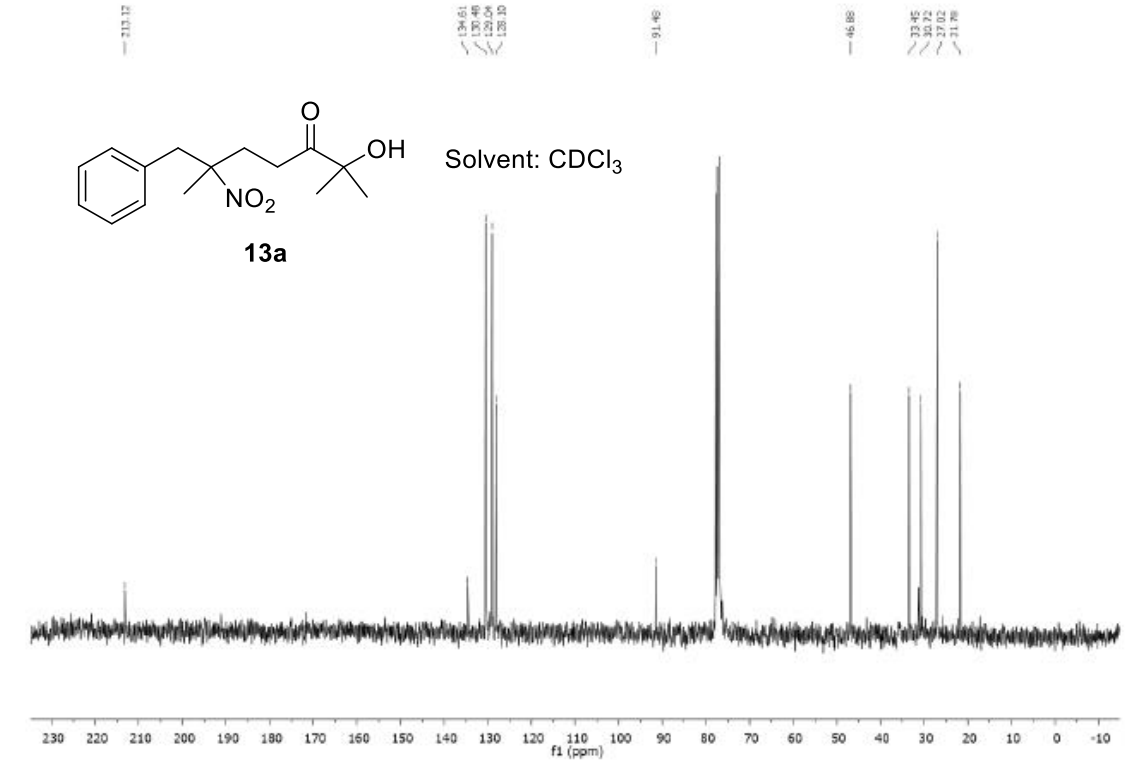

8.10
7.46
7.46
7.45
7.44
7.43
7.42
2.46
2.46
NO2
Solvent: CDCl3
11a
1.00
5.15
3.73
f1 (ppm)

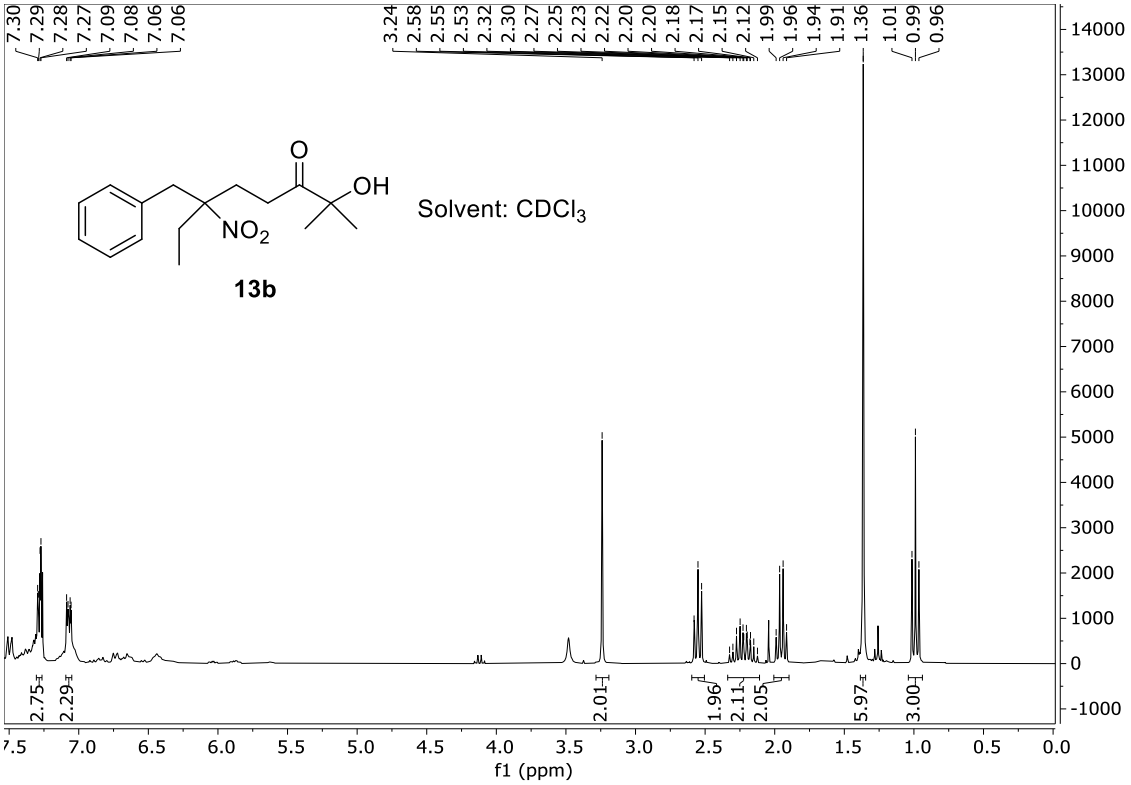

8.03
7.46
7.44
7.44
7.43
2.11
2.09
2.08
2.06
2.05
2.03
2.01
1.99
1.05
1.03
1.00
NO2
Solvent: CDCl3
11b
1.00
4.84
1.24
2.08
f1 (ppm)

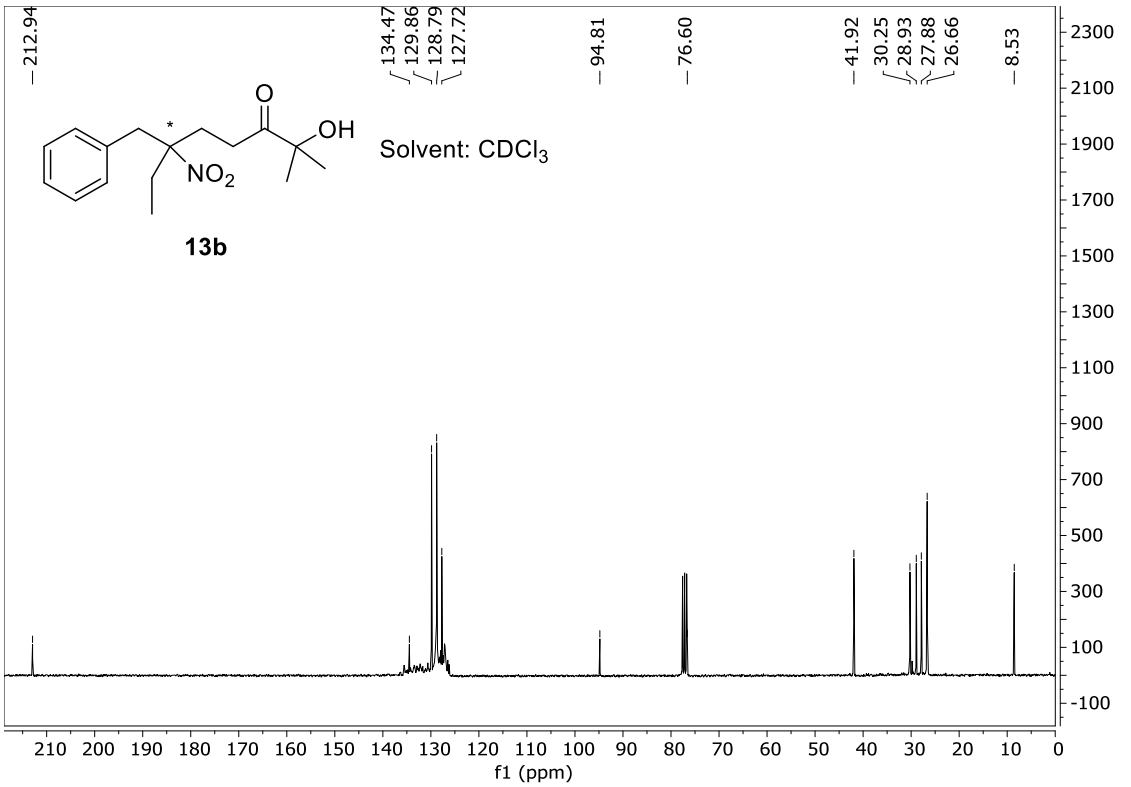

7.35
7.32
7.34
7.33
7.32
7.32
7.30
7.30
7.29
7.28
7.28
7.27
7.18
7.18
7.17
7.16
7.16
7.15
4.84
4.82
4.80
4.77
4.75
4.73
3.37
3.35
3.32
3.30
3.05
3.02
3.00
2.98
1.56
1.54
NO2
Solvent: CDCl3
(±)12a
4.21
0.80
1.00
1.01
3.32
f1 (ppm)

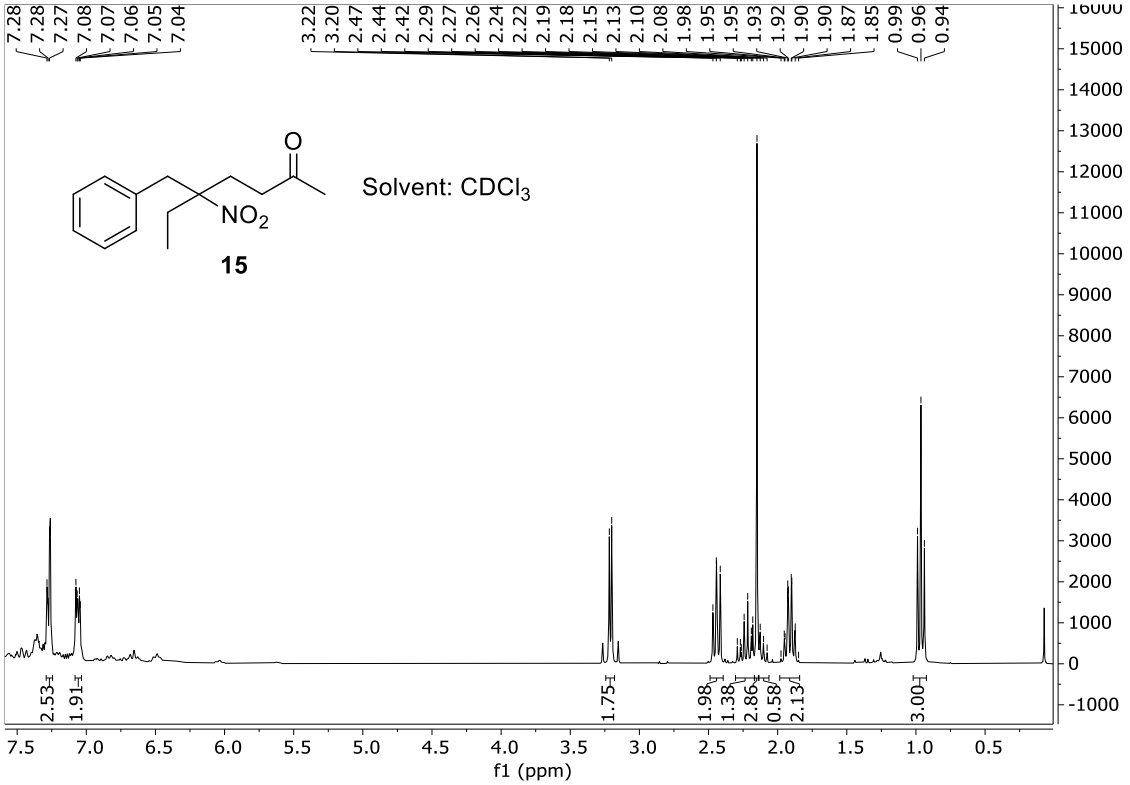

NO2
Solvent: CDCl3
(±)12b
f1 (ppm)

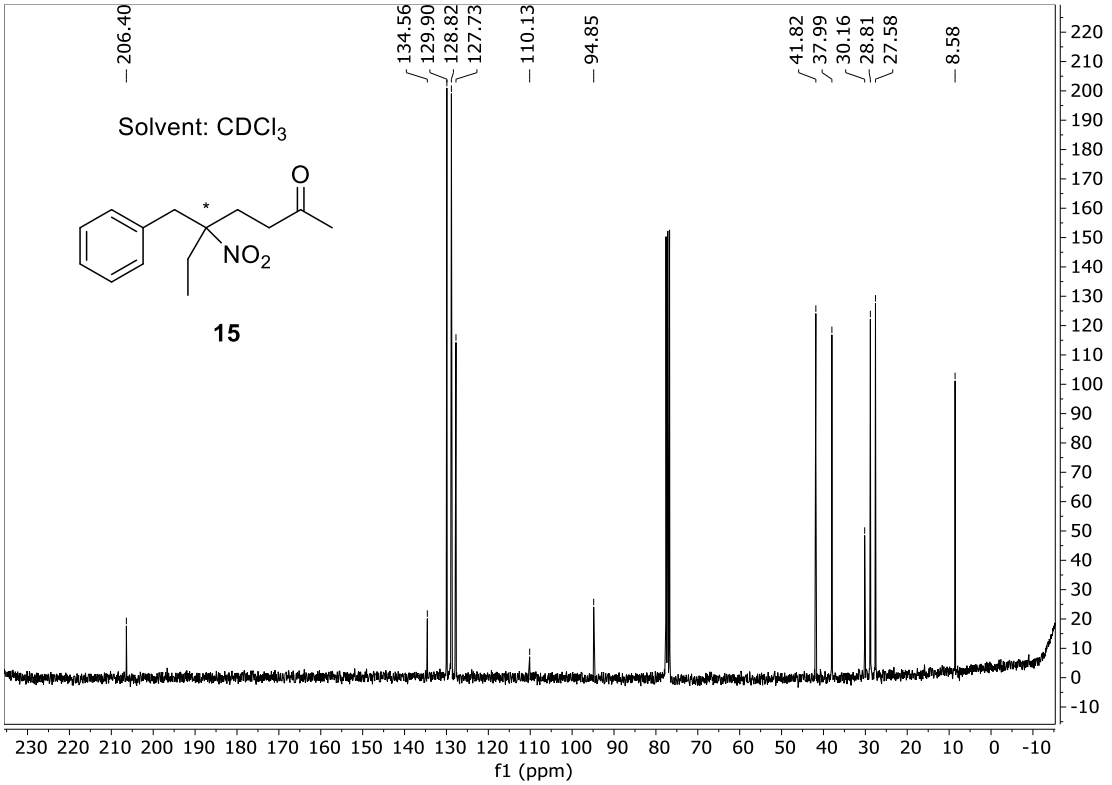

7.31
7.30
7.29
7.28
7.11
7.10
7.08
7.07
3.39
3.34
3.10
3.06
2.61
2.60
2.59
2.58
2.57
2.55
2.50
2.48
2.45
2.43
2.40
2.17
2.14
2.12
2.10
2.09
2.07
2.04
1.48
1.36
O
OH
NO2
13a
Solvent: CDCl3
2.91
1.90
1.10
1.00
2.89
2.42
2.88
6.00
f1 (ppm)


O
OH
NO2
13a
Solvent: CDCl3
f1 (ppm)


7.30
7.29
7.28
7.27
7.09
7.08
7.06
7.06
3.24
2.58
2.55
2.53
2.32
2.30
2.27
2.25
2.23
2.22
2.20
2.20
2.18
2.17
2.15
2.12
1.99
1.96
1.94
1.91
1.36
1.01
0.99
0.96
O
OH
NO2
Solvent: CDCl3
13b
2.75
2.29
2.01
1.96
2.11
2.05
5.97
3.00
f1 (ppm)


212.94
134.47
129.86
128.79
127.72
94.81
76.60
41.92
30.25
28.93
27.88
26.66
8.53
O
OH
NO2
Solvent: CDCl3
13b
f1 (ppm)


Solvent: $CDCl_3$
15
f1 (ppm)


Solvent: $CDCl_3$
15
f1 (ppm)