STUDIES ON ORGANOCATALYTIC KETONE/NITROALKENE MICHAEL ADDITION REACTIONS

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Studies on Organocatalytic Ketone/Nitroalkene Michael Addition Reactions

By

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Abstract

The organocatalytic Michael addition of aldehydes to ketones is of continuing interest in development of organocatylsts for asymmetric synthesis. The Pansare laboratory has focused on research surrounding organocatalysts developed to aid in fundamental carbon-carbon bond forming reactions including the Michael addition reaction.

Due to the ability to generate up to three stereocenters and products that are useful synthetic intermediates, the organocatalytic Michael addition reaction continues to be of special interest. The work described in this thesis focuses on activation of the nucleophile (Michael donor) through enamine formation with a chiral amine. Simple pyrrolidine-based diamine catalysts showed moderate to high enantioselectivities (up to 92% ee) for conjugate Michael addition reactions of cyclic ketones to nitroalkenes without acid additive. Details regarding the effect of catalyst side chain pK_a on the stereoselectivity as well as the importance of secondary-secondary diamine motif and H-bond donor functionality in the organocatalyst for Michael addition reactions of cyclic ketones to nitroalkenes are discussed.

Acknowledgements

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Chapter 1

Entantioselective Organocatalysis

Chapter 2

Enantioselective Organocatalytic Michael Additions of Ketones to Nitroalkenes

List of Abbreviations

Ac:	acetyl
Ar:	aryl
Bp:	boiling point
Boc:	*t*-butyloxycarbonyl
Cbz:	benzyloxycarbonyl
C-C:	carbon-carbon
DCC:	*N,N*-dicyclohexylcarbondiimide
DCM:	dichloromethane
DMF:	*N,N*-dimethylformamide
dr:	diastereomeric ratio
ee:	enantiomeric excess
Et:	ethyl
EWG:	electron withdrawing group
h:	hour(s)
HPLC:	high performance liquid chromatography
HRMS:	high resolution mass spectrometry
Hz:	Hertz
LAH:	lithium aluminum hydride
IR:	infrared spectroscopy
M:	molar concentration (mol L^{-1})
m:	*meta*
Me:	methyl

mg:	milligram(s)
mL:	milliliter(s)
mmol:	millimole(s)
NMR:	nuclear magnetic resonance spectroscopy
Nu:	nucleophile
o:	*ortho*
p:	*para*
ppm:	parts per million
*i*Pr:	isopropyl
*p*TsOH:	*para*-toluene sulfonic acid
rt:	room temperature
TFA:	trifluroroacetic acid
THF:	tetrahydrofuran
TLC:	thin layer chromatography
TMS:	trimethylsilyl

Chapter 1

Enantioselective Organocatalysis

I. Introduction

Organocatalysis, though a relatively new term, has a fairly old story. The first example of asymmetric catalysis using an organic molecule was by Wiechert *et al.* in the 1970s. Wiechert's use of L-proline for the intermolecular aldol reaction was later exploited and made popular by List and Barbas *et al.* in 2000.[1] Since the turn of the century asymmetric organocatalysis has become one of the most active fields of research in organic chemistry.[2] Organocatalysis provides a mild, practical, and generally simple method of making enantiomerically-enriched products that have great potential in organic chemistry.[3]

I.A Asymmetric catalysis

The efficiency and scope of asymmetric organocatalysts have made them popular alternatives to enzyme and transition metal catalysts.[1] Metal-mediated enantioselective catalysis has played a significant role in asymmetric synthesis as shown by the Nobel Prize winning work of chemists such as Sharpless,[4] Noyori,[5] and Knowles.[6] Its advantages are due to the properties of the metal, including its ability to act as a Lewis acid or a Lewis base, the reactivity of which can be controlled through the ligands surrounding the metal atom. Conventional metal catalysis does have its disadvantages. In a society focused heavily on environmental awareness, the toxicity associated with transition metal catalysis makes organocatalysis a 'green' alternative.[2] Sensitivity to atmospheric oxygen and water [3] as well as high prices[2] makes alternative catalytic processes more favorable. One of those alternative processes includes biocatalysis. Biocatalysis uses enzymes to perform chemical transformations on organic molecules in a catalytic fashion.

Industrial production has benefited greatly from the emergence of biocatalysis. Unfortunately, there are some disadvantages associated with the processes. Enzymatic catalysts are often quite complex in structure and difficult to stabilize and handle.[7]

Organocatalysis for use in asymmetric synthesis has proved advantageous due to its operational simplicity. Organocatalysts are very often more robust, more economical and easier to handle compared to metal-mediated or biocatalytic processes.[2] Organocatalysts are stable, metal-free organic molecules derived from natural chiral-pool sources such as amino acids, nucleic acids and carbohydrates. Mechanistically, organocatalyzed reactions resemble enzyme-catalyzed reactions through formation of reversible complexes with substrates. They also have the ability to mimic Lewis acidity or Lewis basicity through the presence of heteroatoms (mainly N, O, P, and S) in the organocatalysts.[8] Although impressive advances have been made in the field of organocatalysis, many transformations still remain elusive. Therefore asymmetric organocatalysis often complements rather than competes with metal-based or enzyme-based catalysis.[2]

I.B. Organocatalytic conjugate additions

Asymmetric conjugate additions represent one of the most important carbon-carbon and carbon-heteroatom bond forming reactions in organic chemistry. These reactions also account for an exciting and rapidly growing field of organocatalysis.[9a,b] Mechanistically, interactions between the catalyst and the substrates in an asymmetric conjugate addition are different for organocatalysis compared to metal-catalyzed processes. Organocatalysts activate the nucleophile, the electrophile or both reagents by providing a chiral environment in which weak or strong interactions play a role. Weak interactions include hydrogen bonding (Figure 1, **A**) or ion pairing (Figure 1, **B**) and strong interactions include covalent bonding. Covalent bonding

can be further broken into two categories for amine organocatalysts; these are activation of the nucleophile through enamine formation (Figure 1, **C**) and activation of the acceptor through iminium ion formation (Figure 1, **D**).[9]

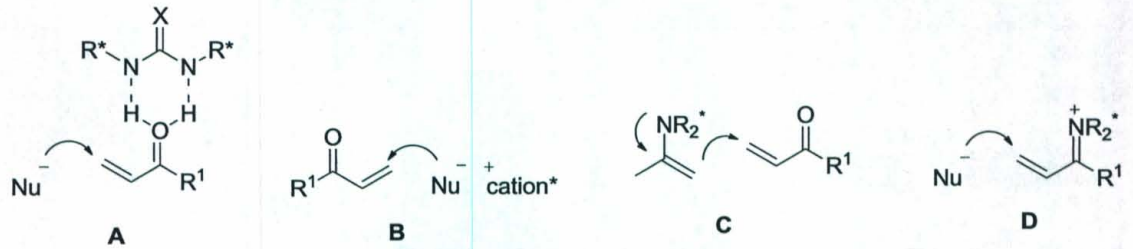
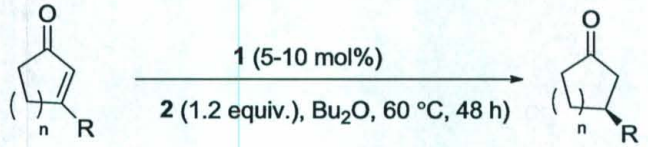
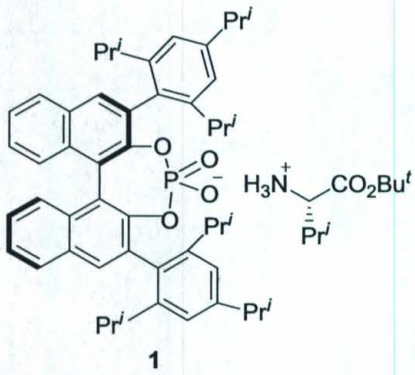


Figure 1: Organocatalytic activations in conjugate addition reactions.[9b]

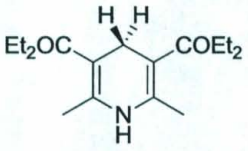
High enantioselection has been discovered for recent organocatalysts used for the conjugate additions of hydride, as well as carbon and hetero-atom nucleophiles to a wide variety of Michael acceptors such as α,β-unsaturated carbonyl compounds, nitroolefins, vinylic sulfones, and acrylonitrones.[9b] The newly formed chiral Michael adducts can be transformed into useful synthetic building blocks in the total synthesis of a variety natural products.[1]

In 2006, List employed an enantioselective transfer hydrogenation of cyclic enones using counterion directed organocatalysis.[10] The use of a chiral cation such as a valine ester phosphate salt and a chiral binaphthol derived phosphate **1** in the presence of Hantzsch ester **2** gave excellent stereoselectivity for the transfer hydrogenation of a variety of cyclic α,β-unsaturated enones (Scheme 1).[10] This new catalyst system widened the substrate scope of the reaction by allowing the reduction of simple aliphatic substrates, such as citral, with high enantioselectivity.[10]





1

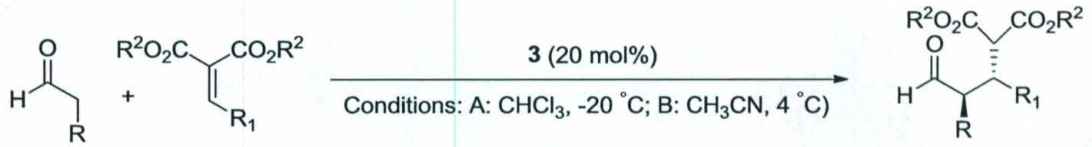


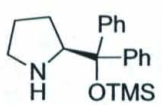
2

n	R	Yield(%)	ee(%)
1	Me	78	98
1	Et	71	96
2	Me	99	94
2	Et	98	96
2	Pr^i	94	98
2	Ph	99	86
3	Me	>99	96

Scheme 1: Enantioselective transfer hydrogenation of cyclic enones catalyzed by 1.[10]

Another recent example of the use of organocatalysis for asymmetric conjugate additions was published in 2008 by Córdova, who presented the first highly enantioselective chiral amine-catalyzed conjugate addition of unmodified aldehydes to alkylidine malonates (Scheme 2).[11] Previously, most of these catalytic asymmetric processes employed organometallic complexes as the catalysts; instead this strategy uses the ability of pyrrolidine-based catalysts to form a strong covalently bonded enamine transition state.



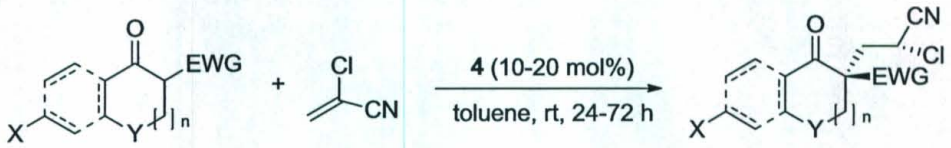


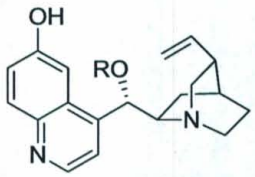
3

R	R^1	R^2	Cond.	Time(h)	Yield(%)	dr	ee(%)
Me	Ph	Me	B	72	96	7:1	>99
Et	4-$O_2NC_6H_4$	Me	A	16	77	14:1	99
Bn	4-$O_2NC_6H_4$	Me	B	48	73	8:1	98

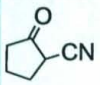
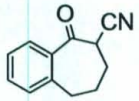
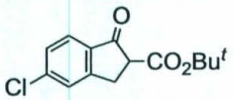
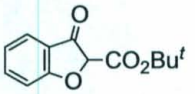
Scheme 2: Organocatalytic conjugate addition of aldehydes to alkylidinemalonates catalyzed by 3.[11]

Deng *et al.* have recently studied a dual-function cinchona alkaloid organocatalyst (**4** and **5**, Scheme 3 and Scheme 4) for use in an asymmetric tandem, one-step conjugate addition-protonation reaction of activated methylenes to β-ketonitriles or β-ketoesters.[12]



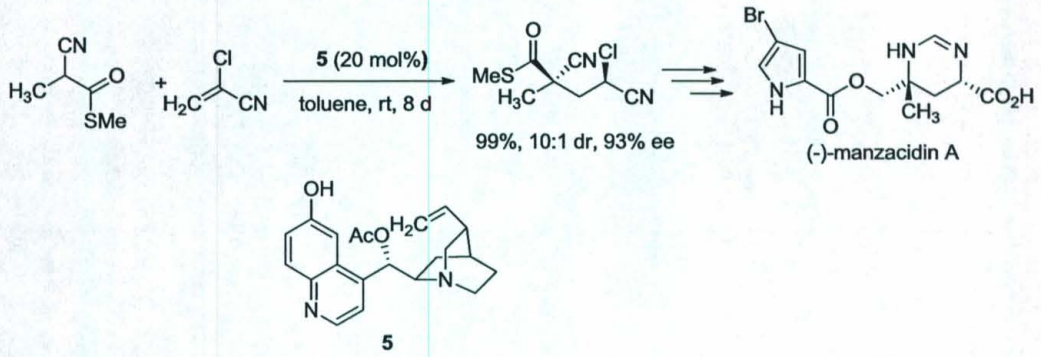


4 (R = phenanthrenyl)

Michael Donor	Yield (%)	Time (h)	dr	ee (%)
	93	60	7:1	91
	88	72	25:1	95
	81	24	20:1	99
	75	48	20:1	98

Scheme 3: Organocatalytic asymmetric tandem conjugate addition-protonation reaction catalyzed by 4.[12]

This type of new and versatile organocatalytic approach for the one-step formation of 1,3-tertiary-quarternary stereocenters has been utilized in the total synthesis of natural product (-)-manzacidin A (Scheme 4).[9] Mechanistic studies have suggested that hydrogen bonding between the reacting substrates and the organocatalyst (**4** or **5**, Scheme 3 and Scheme 4) are important for selectivity.[12]



Scheme 4: Asymmetric formal synthesis of (-)-manzacidin A.[9]

Considerable progress has been made in the area of organocatalytic asymmetric conjugate addition reactions.[9] These reactions represent a synthetic alternative to procedures that were traditionally carried out using metal-mediated catalysis or biosynthesis.[2] Despite the progress that has been made to date, there is still room for improvement regarding the elucidation of transition states and new organocatalytic transformations,[9] as well as reduction of the typically required high organocatalyst loading (5-20 mol%). Application of the Michael adducts in the total synthesis of natural products is also less explored.[2] With these advantages in hand, and in response to the improvements needed in organocatalysis, it seems rational to assume that in the following years, intensive research in this field will lead to new and impressive progress.[2]

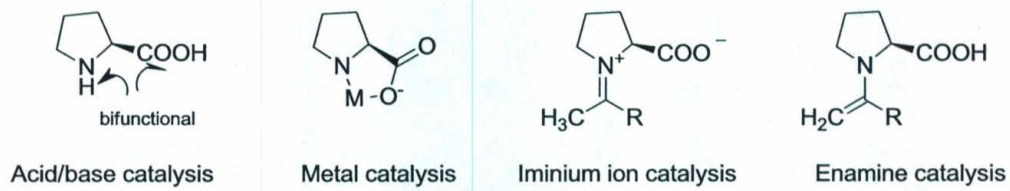
I.C. Classification of organocatalysts

For the purpose of giving organocatalysis a logical structure, broad classifications have been given, namely: Lewis acids, Lewis bases, Brønsted acids and Brønsted bases.[13] Bifunctional catalysts have also been a new addition to the field of organocatalysis, where the catalysts have two distinct functionalities (e.g. a Lewis base and a Brønsted acid) within the same molecule.[14] Another very prominent class of organocatalysts are amine-based catalysts such as amino acids, peptides, alkaloids and synthetic nitrogen-containing molecules.[1]

I.D. Proline – an effective enantioselective organocatalyst

Proline has been one of the most widely studied and modified systems used for organocatalysis. It has been responsible for the vast majority of amine-based catalysts under investigation today.[15]

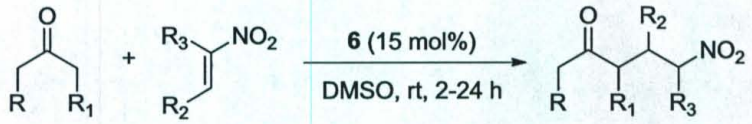
Proline is the only natural amino acid with a secondary amine functionality. This secondary amine allows proline to covalently bond to its substrates forming either an iminium ion or enamine. The bifunctional nature of proline can be attributed to the presence of secondary amine and the carboxylic acid. Proline also has the ability to participate in extensive hydrogen bonding networks.[14]

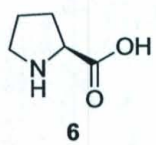


Acid/base catalysis Metal catalysis Iminium ion catalysis Enamine catalysis

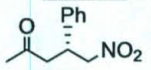
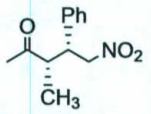
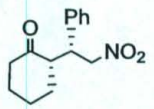
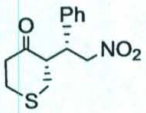
Figure 2: Modes of action in proline-catalysis.[16]

Proline catalysis has been used in a large variety of reactions including asymmetric versions of the aldol, Mannich, and Michael reactions (Scheme 5).[16,17] Despite its utility to provide moderate selectivity in several organic reactions, proline does have its disadvantages, including limited solubility in organic solvents and the need for relatively high catalyst loading.[15]



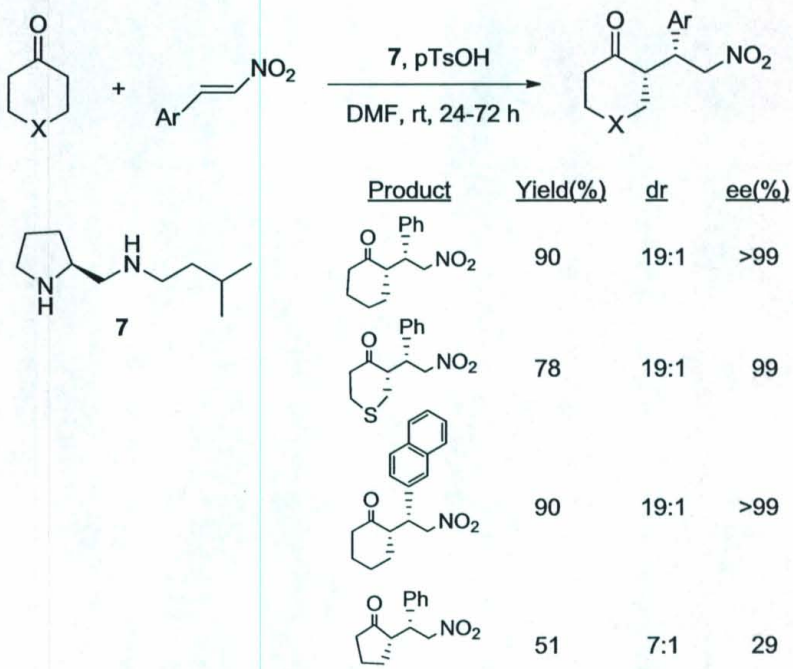


6

Product	Yield(%)	dr	ee(%)
	97		7
	85	3:1	10
	94	>20:1	23
	92	>20:1	10

Scheme 5: Proline (6) catalyzed Michael addition of unmodified ketones to nitroolefins.[16,17]

The ability to modify and optimize novel proline-based catalysts for use in asymmetric conjugate additions has attracted us[18] (along with many other researchers[19]) into the interesting field of organocatalytic Michael addition reactions of cyclic ketones to nitroalkenes.



Scheme 6: Enantioselective conjugate addition of cyclic ketones to nitroalkenes catalyzed by 7.[18]

II. Outline of research described in the thesis

Investigations into the utility of proline-derived secondary-secondary diamines as organocatalysts for the asymmetric Michael addition are discussed in the following chapter. The effects of changes to the *N*-substituent in the catalyst side chain and of the acidity of the pendant secondary amine on the stereoselectivity of the Michael addition are presented in Chapter 2.

References

1 Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123.

2 Vicario, J. L.; Badia, D.; Carrillo, L. *Synthesis* **2007**, 2065.

3 Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Ngoc, T. V. *Drug Discovery Today,* **2007**, 8.

4 Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

5 (a) Miyashita, A; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, 102, 7932. (b) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008.

6 (a) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106. (b) Knowles, W. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1999.

7 Koeller, K. M.; Wong, C. H. *Nature* **2001**, *409*, 232.

8 Gröger, H.; Wilken, J. *Angwe. Chem. Int. Ed.* **2001**, *40*, 529.

9 (a) Anwar, S.; Lee, P.-H.; Chou, T,-Y.; Chang, C.; Chen, K. Tetrahedron. **2011**, *67*, 1171. (b) Almaşi, D.; Alonso, D.A.; Nájera, C. *Tetrahedron: Asymmetry.* **2007**, *18*, 299.

10 Martin, N .J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368.

11 Zhao, G. L.; Vesely, J.; Sun, J.; Christensen, K. E.; Bonneau, C.; Córdova, A. *Adv. Synth. Catal.* **2008**, *350*, 657.

12 Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928.

13 Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3,* 719.

14 Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.

15 Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84.

16 List, B. *Synlett* **2001**, 1675.

17 List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.

18 Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624.

19 Mukherjee, S.; Yang, J. W.; Hoffman, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

Chapter 2

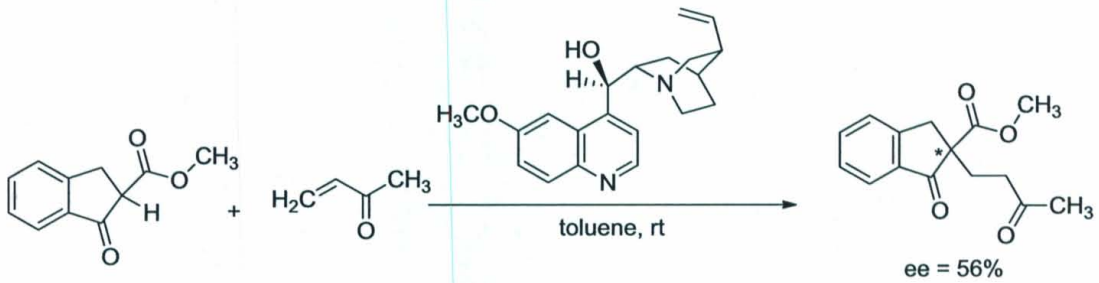
Enantioselective Organocatalytic Michael Additions of Ketones to Nitroalkenes

Part of this work has been published in:

Pansare, S. V.; Heath, R. L. *Tetrahedron* **2009**, *65*, 4557.

I. Introduction

Within the realm of conjugate additions, the Michael addition reaction represents one of the most important carbon-carbon bond forming techniques in organic chemistry[1] since its discovery in the 1880s.[2] Catalytic enantioselective versions of the Michael addition reaction have been of considerable interest to organic chemists starting with Wynberg's use of quinine, a cinchona alkaloid, as a catalyst back in 1975 (Scheme 1).[3]



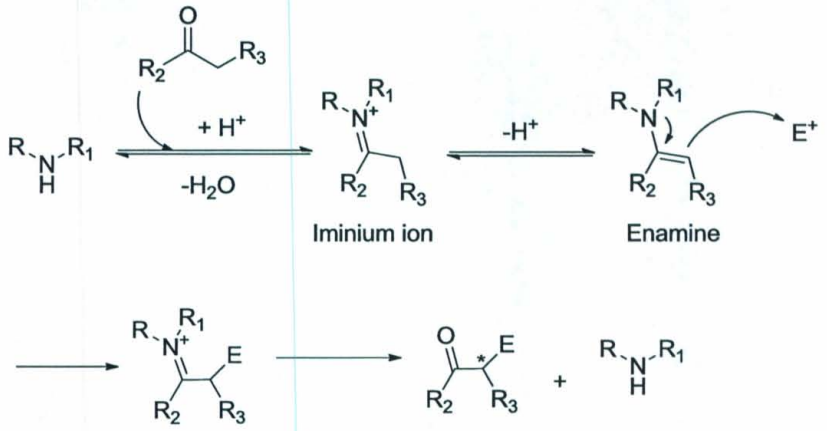
Scheme 1: The early use of quinine as an organocatalyst.[3]

Its atom economy, wide substrate scope, and easily accessible starting materials, along with the ability to generate as many as three stereocenters in a single step contributes to the advantages of the Michael addition reaction for carbon-carbon bond formations.[4]

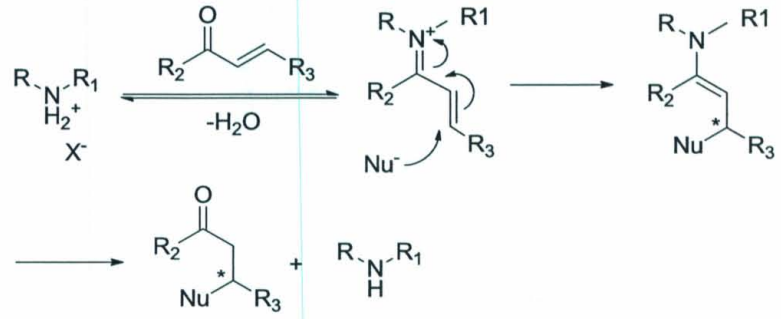
Scheme 2: Generation of contiguous stereocenters in the ketone-nitroalkene Michael addition reaction.

The majority of organicatalyzed Michael addition reactions studied today are amine-based, or aminocatalysed, reactions. Aminocatalysis can be broadly classified as 'covalent' and 'non-covalent' amine catalysts on the basis of the reaction mechanism.[4] The covalently bonded aminocatalysis route operates through two possible pathways: iminium ion catalysis and enamine catalysis.[5]

Enamine Catalysis:



Iminium Ion Catalysis:



Scheme 3: Enamine and iminium ion catalysis of aminocatalysts[5]

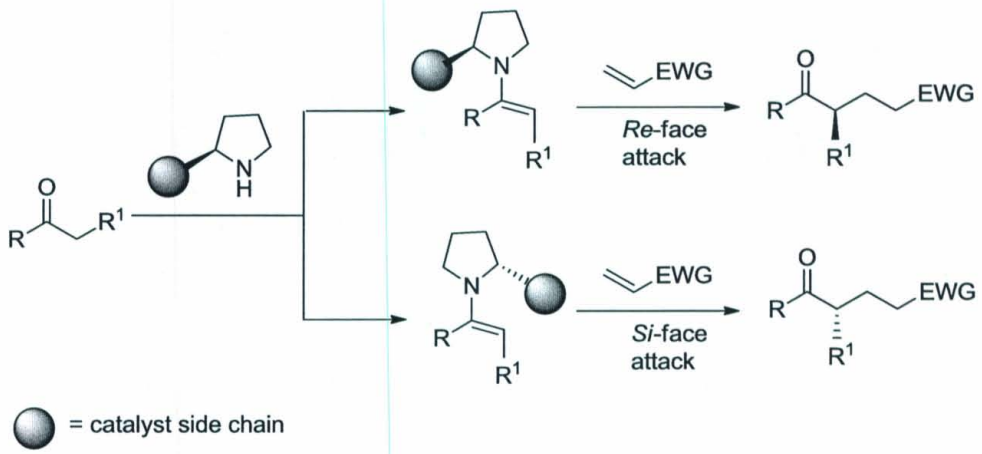
The work described in this thesis focuses on activation of the nucleophile (Michael donor) through enamine formation with a chiral amine.

II. Background

II.A Enamine Catalysis

Since the first example of proline-mediated asymmetric enamine catalysis published by Hajos and Parrish, and Eder, Sauer and Wiechert in the 1970s,[6] a vast amount of research has been done in this area.[7]

One vital consideration for the enamine aminocatalytic reaction is the ability of the catalyst to control the facial selectivity of the intermediate enamine nucleophile as seen in Scheme 4. Rotational isomers of the enamine intermediate would eventually lead to different shielding of the two faces of the enamine, and thus result in a mixture of stereoisomeric products.[1]



Scheme 4: Enamine facial selectivity in asymmetric aminocatalysis.[1]

Another potential limitation of enamine catalysis would be the deactivation of the nucleophilic aminocatalyst by the electrophile. If the electrophile is an alkyl halide then this deactivation is often irreversible. Some electrophiles, such as nitroalkenes, may react only with the enamine and not with the amine catalyst while other electrophiles such as aldehydes, enones and imines can react reversibly with the amine. These side reactions may best be described as *parasitic equilibria* since they can limit reaction rates but still allow the formation of the desired product.[7]

II.B Design of chiral organocatalysts for Michael addition reactions

Organocatalytic Michael addition reactions account for one of the most exciting and rapidly growing fields in organocatalysis.[8] The first aminocatalysed asymmetric Michael

additions of carbonyl compounds to nitroalkenes using proline as the catalyst offered only modest enantioselectivity.[7] These reactions seemingly accelerated the search for more efficient chiral catalysts, a significant amount of which has been devoted to the development of proline-based chiral diamine derivatives.[9] Investigations have been carried out on chiral pyrrolidines containing a tertiary aminomethyl,[10] 2-morpholinomethyl,[11] tetrazole,[12] tetrazolylmethyl,[13] pyrrolidinyl,[14] trifluoromethylsulfonamido,[15] methylpyridyl,[16] and 1((pyrrolidine-2-yl)methyl)pyrrolidine,[17] (fluorous)diphenyl-methanol silyl-ether,[18] carboxymethyl,[19] 2-((imidazolylthio)methyl)[20] functionalities in place of the carboxyl function of proline. Recently, solid-supported proline and proline-derivatives have been studied as recyclable organocatalysts.[21] A few examples of proline-based catalysts used for the asymmetric conjugate addition of aldehydes and ketones to nitroalkenes are shown in Figure 1.

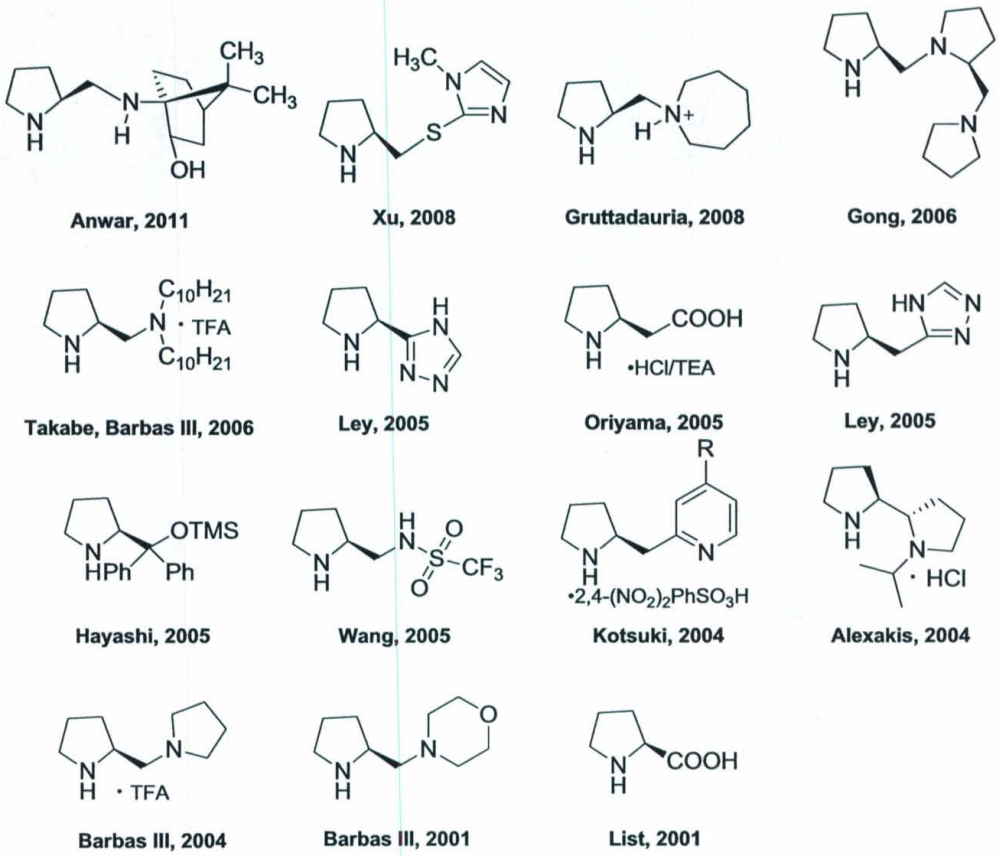


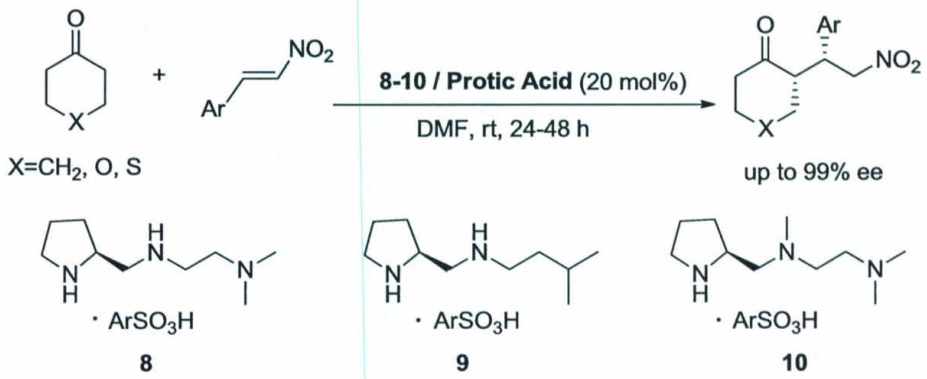
Figure 1: Selected proline-based organocatalysts

Despite the ability of these proline-derived aminocatalysts to successfully catalyze the Michael addition reactions, some limitations still exist. Many of these pyrrolidine catalysts require long reaction times, low temperature and a large excess of ketone as well as relatively high catalyst loading.[22] The development of new, structurally simple aminocatalysts to overcome these limitations would be an asset.

III. Objectives

Several simple protonated triamine and diamine proline-based catalysts have been synthesized and studied previously by the Pansare group (Scheme 5).[23] In the presence of a protic acid, these catalysts showed excellent yields and stereoselectivity for Michael addition

reactions of various cyclic ketones to a number of nitrostyrenes. The results also show the importance of a secondary-secondary diamine motif for the stereoselection of the reactions, with catalyst **8** and **9** showing the highest enantio- and diastereoselectivity. The proposed explanation of these results involves hydrogen bonding of the protonated catalyst side chain with the Michael acceptor (nitroalkenes) as shown in Figure 2, intermediate **A**.[23]



Scheme 5: Proline-based catalysts studied previously by the Pansare Group [23]

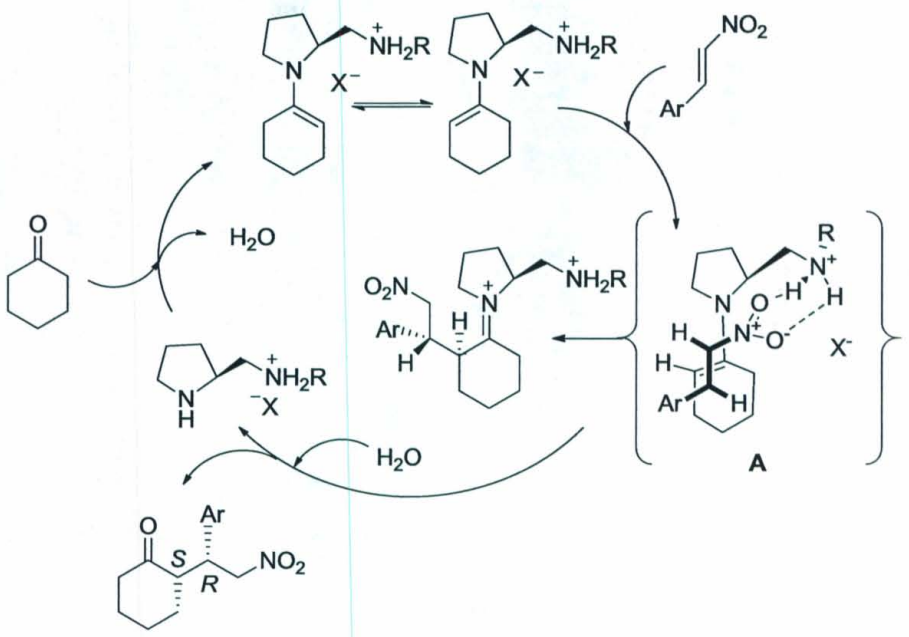
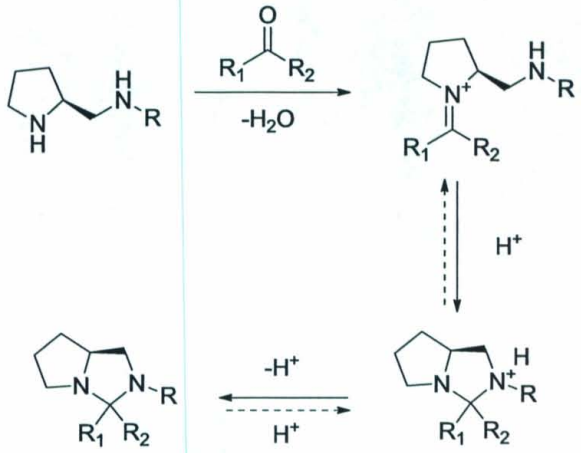


Figure 2: Proposed catalytic cycle for previous work by the Pansare group .[23]

One objective of the present study was to determine the viability of the secondary-secondary proline derived diamine motif for catalysis of Michael addition reactions *without the addition of a protic acid*. We anticipated that aminal formation with secondary-secondary diamines should be reversible as shown in Scheme 6. The water generated *in situ* during aminal formation is available for the reverse reaction to liberate the catalyst and carbonyl compound.[24]



Scheme 6: Aminal generation and reversibility.

The second objective of this study was to modulate the *N*-substituent in the side chain of the proline-based catalysts for optimal selectivity (Figure 3). Modulation of the side chain included studying the effects of having an aliphatic *N*-substituent, as in catalyst **11,** compared to a series of aromatic side chains, as in catalysts **12-14**. The importance of a secondary-secondary diamine motif was also examined through direct comparison of catalyst **14** to the secondary-tertiary diamine catalyst **15**.

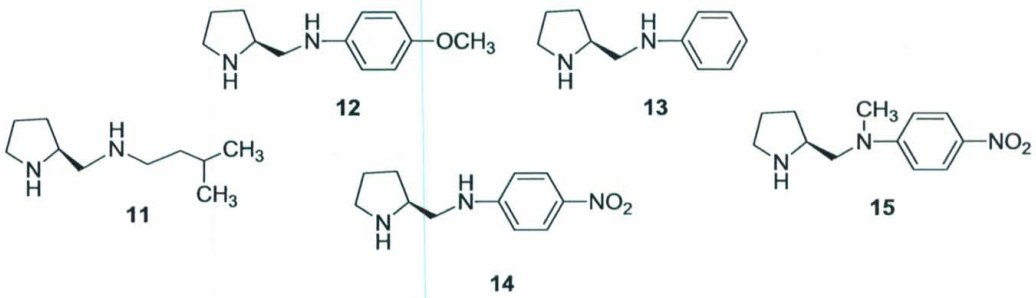


Figure 3: Proposed catalysts.

It was proposed to examine the effect of the catalyst side chain pK_a values[24] on the stereoselectivity for the Michael addition reaction of cyclic ketones to nitrostyrenes (Figure 4).

From the values calculated by using an online pK_a calculator,[24] one would predict catalyst **14**, with the lowest pK_a of 21, to be the superior H-bonding donor and thereby provide the highest stereoselection (assuming a catalytic cycle similar to that seen in Figure 2). For the aromatic series of catalysts it was anticipated the stereoselection would decrease with increasing pK_a values from catalyst **14** to **13** to **12** respectively. It was questioned whether the aliphatic catalyst **11** would be less efficient than the aromatic series (catalysts **12-14**) since its calculated pK_a is much higher at approximately 34 pK_a units.

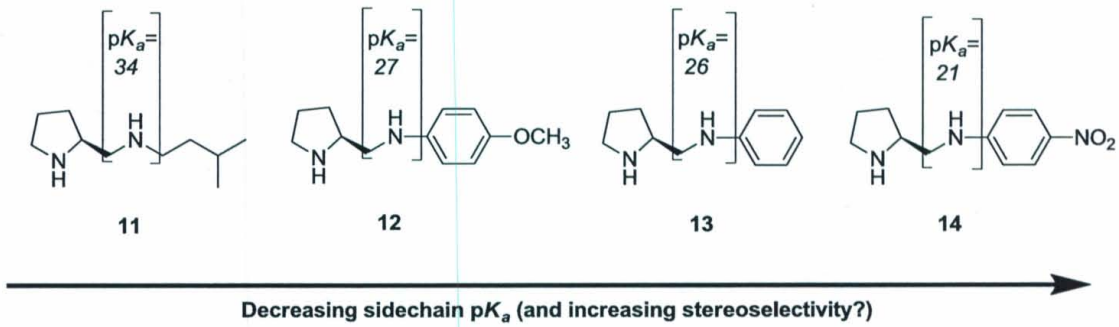
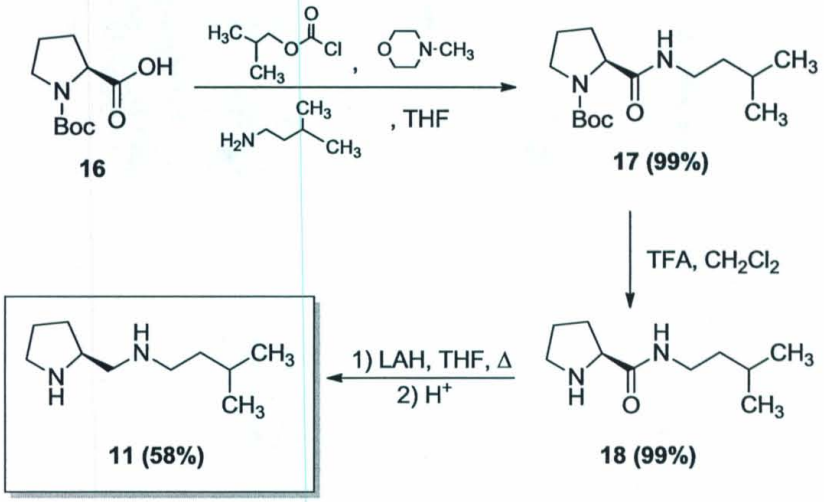


Figure 4: Side chain pK_a.[24]

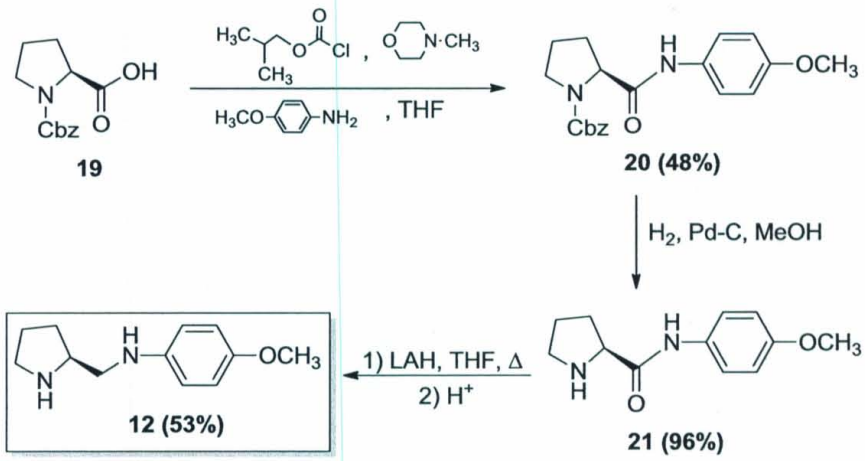
IV. Synthesis of organocatalysts

The proline-derived aliphatic diamine **11** was readily prepared by adaptation of a literature procedure[23] as shown in Scheme 7. This convenient synthesis begins with the condensation of *N*-Boc-proline **16** with isoamyl amine employing the mixed anhydride method to produce amide **17** in excellent yield. Removal of the Boc protecting group by TFA in dichloromethane affords the corresponding amide **18,** which was reduced with LAH to give the desired diamine **11** in moderate yield.



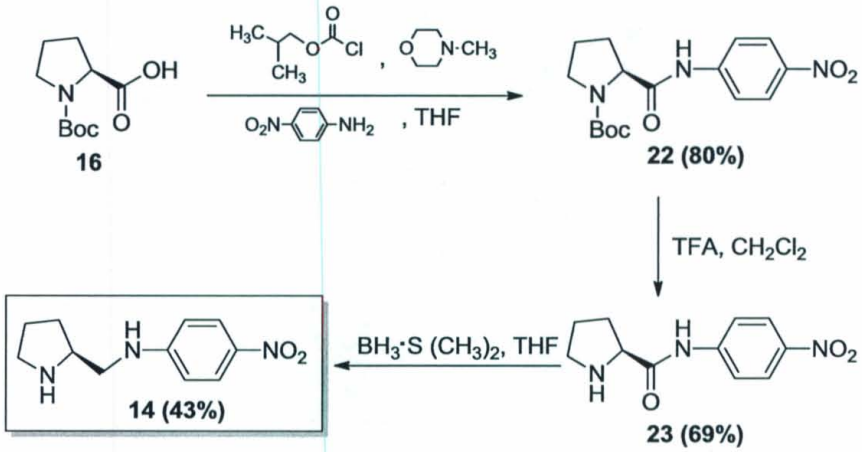
Scheme 7: Synthesis of diamine 11.

Amine **12** was prepared in a similar manner with the exception of starting with Cbz-protected proline **19** as shown in Scheme 8. A mixed-anhydride mediated coupling of **19** with *p*-anisidine provided amide **20,** which was converted to the amino amide **21** by removal of the Cbz group using palladium-catalyzed hydrogenolysis. Reduction of **21** with LAH provided diamine **12** in moderate yield (Scheme 8).



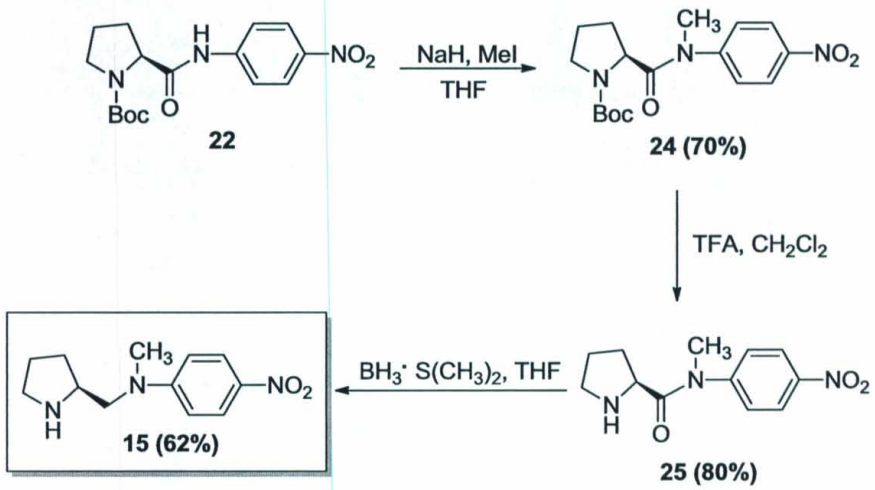
Scheme 8: Synthesis of diamine 12.

Diamine **14** was synthesized in much the same manner as diamine **11** except for the reduction of amide **23** which was achieved using borane/dimethyl sulfide adduct in THF so as to avoid reduction of the nitro group (Scheme 9).



Scheme 9: Synthesis of diamine 14.

The secondary-tertiary diamine **15** was synthesized from *N*-Boc amide **22** by methylation of the amide nitrogen (NaH/MeI) to produce compound **24** in good yield. Removal of the Boc group using TFA followed by reduction of the amide with borane/dimethyl sulfide complex provided desired product **15** in moderate yield (Scheme 10).



Scheme 10: Synthesis of diamine 15.

The diamine **13** is commercially available and was used in this study without further purification. With the *N*-aliphatic secondary-secondary diamine **11**, *N*-aromatic secondary-secondary diamines **12-14**, and *N*-aromatic secondary-tertiary diamine **15** in hand an examination of their efficacy in asymmetric Michael addition reactions of cyclic ketones to nitroalkenes was conducted. The results of these studies are presented below.

V. Asymmetric organocatalytic Michael addition of cyclic ketones to nitroalkenes

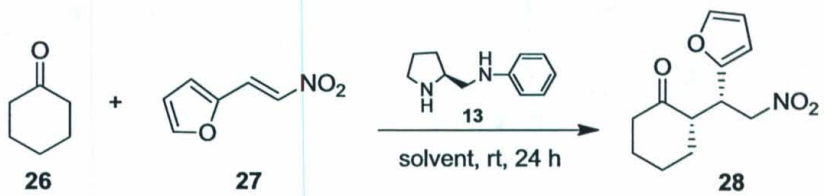
Enantioselective conjugate additions of unmodified carbonyl compounds to a few Michael acceptors have been extensively investigated in recent years.[1,4,5] This study is mostly confined to the use of moderately-sized symmetrical aliphatic cyclic ketones as Michael donors and nitroalkenes as Michael acceptors. Nitroalkenes have remained of special interest as excellent Michael acceptors due to the strong electron-withdrawing effect of the nitro group as well as its ability to engage in hydrogen-bonding interactions.[5] In addition, the products of these reactions may become useful synthetic intermediates for the synthesis of various natural products.

Preliminary results on the enantioselective (up to 92% ee) and diasteroselective (up to 25/1) conjugate addition of cyclic ketones to nitroalkenes catalyzed at ambient temperature by the diamines **11-15** in the *absence of protic acid* are described below.

V.A Results and Discussion

The Michael addition reaction of cyclohexanone to (*E*)-2-(2-nitrovinyl)furan to provide the γ-nitroketone **28** was selected for solvent screening using pyrrolidine-based diamine **13** (Table 1). This reaction had shown moderately good enantioselectivity in previous studies in the Pansare group using amine/protic acid catalyst systems (up to 88% ee and 15/1 dr),[23] and clearly, there is room for optimization of this reaction. Four solvents were examined and toluene emerged as the solvent of choice in terms of product yield and reaction stereoselectivity. Gratifyingly, the secondary-secondary diamine **13** did catalyze the conjugate addition reaction. This observation indicates that aminal formation is not a serious issue with diamine **13**. Presumably, any aminal that is formed reverts back to the iminium ion *in situ.* Somewhat surprisingly, practically no product (<1% yield) was obtained in ethanol. Based on the solvent screening study, it was decided to examine catalysts **11-15** in ketone/nitroalkenes conjugate addition reactions using toluene as the solvent. All reactions were conducted at ambient temperature with 20 mol% catalyst and 2.5 equivalents of the ketone.

Table 1: Solvent screening for asymmetric Michael addition reaction catalyzed by diamine 13.



26 27 28

Entry	Solvent	Yield (%)	dr[b] *(syn/anti)*	ee[c] (%)*(syn)*
1	DMF	53	5/1	68
2	**Toluene**	**89**	**10/1**	**89**
3	DCM	61	6/1	48
4	EtOH	<1	n/a	n/a

[a]Isolated yields. [b]Determined by ^{1}H NMR anaylsis of the crude product. [c]Chiral HPLC analysis.

Table 2 shows some results for the Michael addition reaction of various cyclohexanones with a variety of nitrostyrenes. Increased stereoselectivity for the Michael reactions catalyzed by the aromatic series **(12-14)** of proline-based catalysts was expected over the aliphatic catalyst **11**. It was also proposed that the aromatic series of catalysts would show increasing stereocontrol with a decrease in the pK_a value of the side chain nitrogen (Figure 4). According to the results shown in Table 2, it is evident that the results of the Michael addition reactions were variable with regards to trends. For Michael adducts **29-31**, catalyst **13** showed the highest enantioselectivity, good diastereoselectivity and high yields, whereas the other catalysts did not show any general trend. Catalyst **11** (*N*-isoamyl) showed the highest stereocontrol for Michael adduct **32** but no general trend in side chain pK_a versus stereoselectivity was observed for the other catalysts. Michael addition reactions were also carried out using a secondary-tertiary catalyst **15** as a comparison to the corresponding secondary-secondary catalyst **14** in order to

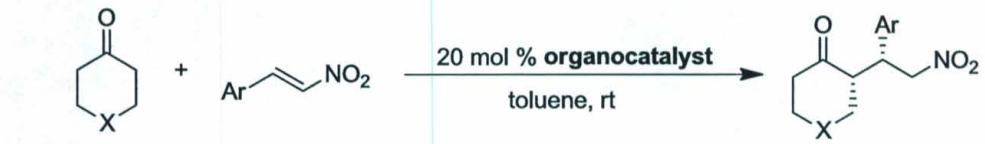
examine the importance of the secondary-secondary diamine motif for stereoselectivity. It is noteworthy that the secondary-tertiary diamine **15** showed very low enantioselectivity for all Michael adducts (Table 2, entries 5, 10, 15, 21, 26).

The stereoselectivity for Michael adducts **33** and **34** did show the anticipated trend within the *N*-aryl catalysts series. Thus, catalyst **14**, the catalyst with the lowest pK_a value, provided the highest enantiomeric excess in the series, whereas catalyst **12**, with the highest pK_a value of the series provided the lowest stereoselectivity. Despite these seemingly logical results, catalyst **11** (*N*-isoamyl catalyst) which has a calculated side-chain pK_a that is significantly higher than catalyst **12**, **13**, or **14** provided the highest stereoselectivity for adducts **33** and **34**. These results are summarized in Table 2. Perhaps even more puzzling is the completely opposite trend seen for product **36** (Table 2). For this case, an increase in stereoselection was seen in going from catalyst **14** to catalyst **12**, and catalyst **11** provided the lowest stereoselectivity. In all three reactions, the secondary-tertiary catalyst **15** provided very low enantioselectivity.

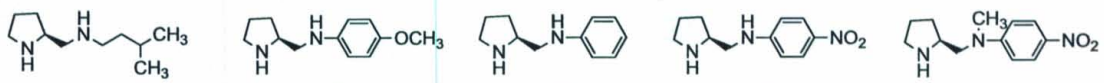
Michael adduct **35** does show some trend within the aromatic series, but the results are opposite to those expected where catalyst **12**, with the higher pK_a value, has the best enantioselectivity of the series. The aliphatic catalyst **11** shows the highest enantiomeric excess for the reaction and catalyst **12** yielded less then 5% of the desired adduct (enantio- and diasterioselectivity was not determined).

Results for Michael adduct **37** shows no general trend for the secondary-secondary diamine catalysts and catalyst **13** seemed to have a significantly lower enantiomeric excess than previously seen. Secondary-tertiary catalyst **15** continued to give near racemic products.

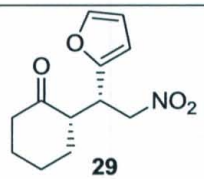
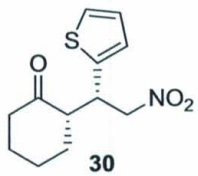
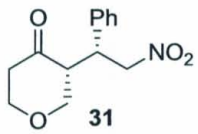
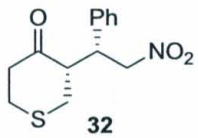
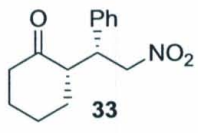
Table 2: Results from enantioselective organocatalytic Michael additions of ketones to nitroalkenes.



Organocatalysts:

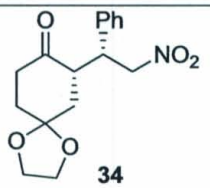
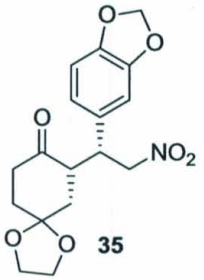
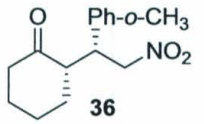
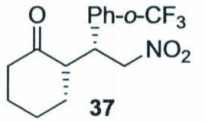
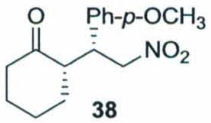
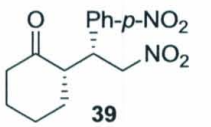


11 **12** **13** **14** **15**

Entry	Product	Catalyst	Yield[a] (%)	dr[b] (*syn/anti*)	ee[c] (%) (*syn*)
1		11	80	11/1	84
2		12	93	11/1	83
3		**13**	**89**	**10/1**	**89**
4		14	81	3/1	82
5	**29**	15	64	3/1	1
6		11	97	6/1	71
7		12	20	16/1	79
8		**13**	**77**	**12/1**	**82**
9		14	89	9/1	77
10	**30**	15	80	7/1	9
11		11	72	10/1	25
12		12	74	15/1	80
13		**13**	**96**	**11/1**	**89**
14	**31**	14	81	>15/1	64
15		15	80	>15/1	9
17		**11**	**71**	**9/1**	**73**
18		12	90	9/1	71
19		13	86	10/1	59
20	**32**	14	74	8/1	72
21		15	98	n/a	16
22		**11**	**69**	**15/1**	**86**
23		12	99	15/1	65
24		13	80	17/1	77
25	**33**	14	67	10/1	86
26		15	77	15/1	3

[a]Isolated yields. [b]Determined by ^{1}H NMR analysis of the crude product. [c]Chiral HPLC analysis.

Table 2 (*continued*): Results from enantioselective organocatalytic Michael additions of ketones to nitroalkenes.

Entry	Product	Catalyst	Yield[a] (%)	dr[b] (*syn/anti*)	ee[c] (%) (*syn*)
27	 **34**	**11**	**79**	**20/1**	**92**
28		12	97	3/1	76
29		13	77	3/1	79
30		14	73	5/1	88
31		15	71	3/1	n/a
32	 **35**	**11**	**48**	**5/1**	**80**
33		12	54	10/1	73
34		13	49	7/1	71
35		14	80	8/1	66
36		15	<5	n/a	n/a
37	 **36**	11	97	15/1	80
38		**12**	**74**	**>20/1**	**90**
39		13	99	15/1	86
40		14	91	18/1	82
41		15	75	20/1	14
42	 **37**	11	72	8/1	65
43		12	74	19/1	64
44		13	80	11/1	40
45		**14**	**82**	**20/1**	**72**
46		15	78	10/1	3
47	 **38**	11	97	25/1	50
48		12	78	12/1	55
49		13	99	20/1	68
50		**14**	**87**	**25/1**	73
51		15	80	20/1	3
52	 **39**	11	73	7/1	74
53		**12**	**76**	**20/1**	**89**
54		13	88	9/1	86
55		14	53	16/1	87
56		15	30	14/1	2

[a]Isolated yields. [b]Determined by ^{1}H NMR analysis of the crude product. [c]Chiral HPLC analysis.

It may be noted that the nitroalkene substrate that provides adduct **36** has an '*ortho*' substituent (OCH_3) in the aromatic ring. Previous studies in the Pansare group[23] had indicated that stereoselectivities with such nitroalkenes were lower than the sterically less crowded *para* isomers. Hence, in order to minimize steric contributions from the substrate, we investigated the 4-OCH_3 nitroalkene isomer as a substrate. At the same time, it was wondered if a direct catalyst-substrate interaction could be better established by changing the electronic properties of the nitroalkene as well. Consequently, the 4-NO_2 nitroalkene substrate was examined as a direct comparison with the 4-OCH_3 substrate. If catalyst side chain pK_a is the dominating factor for reactions of these two substrates, then in addition to a logical trend in pK_a versus stereoselectivity, one should see lower overall stereoselectivity for the 4-NO_2 isomer which would be a weaker H-bond acceptor than the 4-OCH_3 analog. The results of these studies are summarized in Table 2. Again, these results are difficult to rationalize on the basis of a single, predominant effect.

One of the main objectives of the described research was to determine the viability of secondary-secondary proline-based diamine catalysts for the Michael addition reactions of cyclic ketones to nitroalkenes without the use of protic acid additives. Our results indeed show that secondary-secondary diamines are effective at catalyzing the Michael addition reaction for a variety of cyclic ketone and nitrostyrene substrates as shown in Tables 1-2. Moderate to good enantiomeric and diastereomeric excesses (up to 92% ee and 25/1 dr) and yields were achieved with moderate catalyst loading (20 mol%) and cyclic ketone excesses (2.5 eq.) under room temperature conditions. Although the stereoselectivities are not as high as those previously studied by the Pansare group, they do allow for simplicity in the reaction conditions.

Another objective of the detailed project was to establish the importance of a secondary-secondary diamine motif for stereocontrol of the desired Michael reactions. Figure 5 shows a simple graphical interpretation of a portion of the reactions. The drastic difference in enantioselectivity for the reactions can be seen in this presentation where secondary-secondary diamine catalysts **11-14** provide enantiomeric excesses of 40-92% whereas the secondary-tertiary diamine catalyst **15** is far less efficient (1-14% ee).

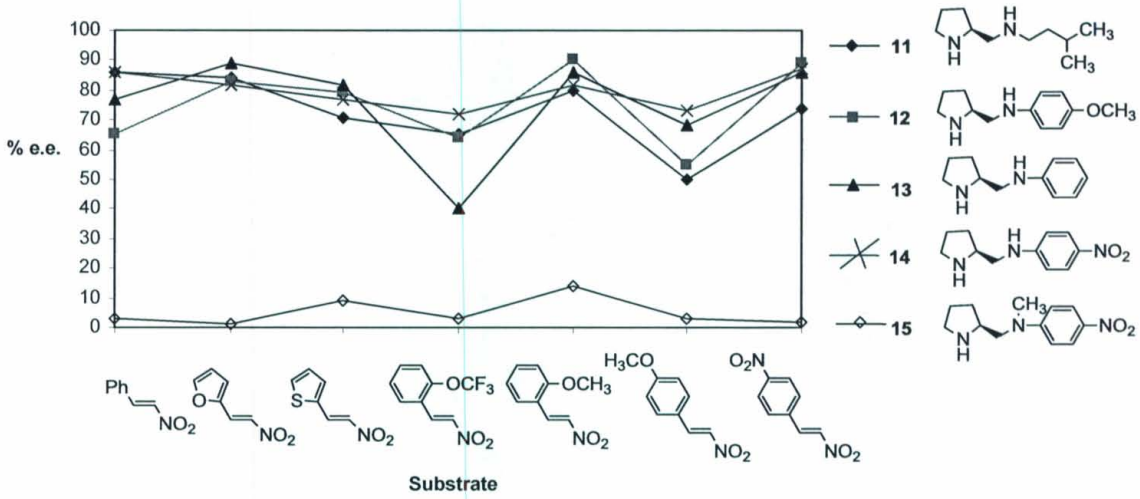


Figure 5: Organocatalytic Michael addition of substrate with cyclohexanone

These findings seem to support the proposed ability of a secondary-secondary diamine catalyst to form a H-bond with nitroalkenes where as the secondary-tertiary diamine catalyst **15** lacks the H-bonding ability (Figure 6). However, it is possible that other factors such as aggregation and substrate-catalyst side chain interactions may also play an important role in deciding reaction stereoselectivity.

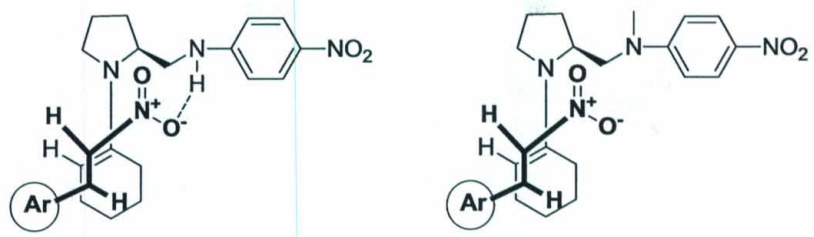


Figure 6: H-bonding of nitroalkene with catalyst 14 and not with catalyst 15.

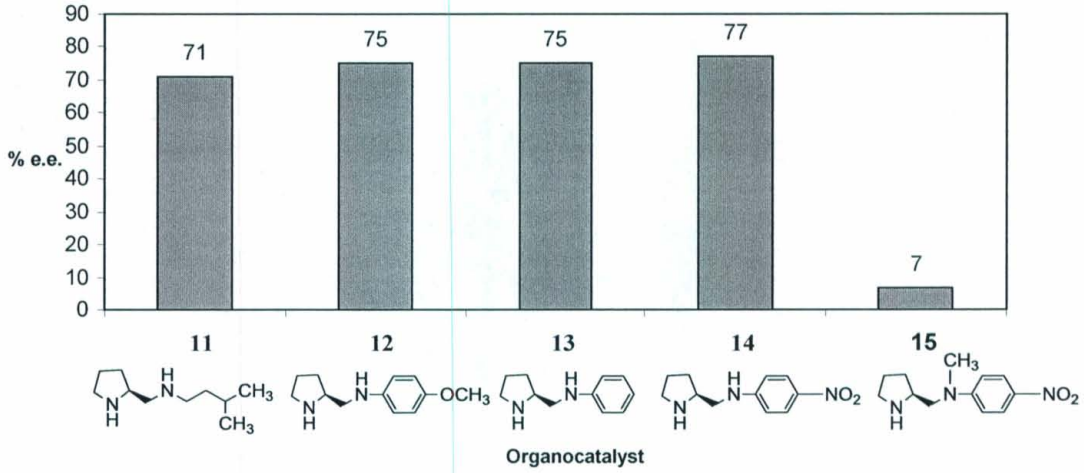


Figure 7: Average Enantioselection for each organocatalyst.

The other objective of this research was to study the effect of changing the pK_a values for the *N*-substituent. This was investigated through testing an aliphatic side chain catalyst to a series of aromatic side chain catalysts where the calculated catalyst side chain pK_a values range from 21 to 34 pK_a units. A general trend of decreased enantioselection of the catalyst with higher pK_a values was anticipated. Figure 7 shows a graphical representation of the average enantiomeric excess for each organocatalyst. According to these results, the *N*-aryl organocatalyts (**12-14**)

occasionally observed a predictable trend side-chain pK_a versus stereoselection. Figure 7 illustrates a distinct trend in side-chain pK_a versus average stereoselection indicating the importance of H-bond donor functionality in the catalyst.

VI. Alternative Michael acceptor

It was also of interest to briefly test the ability of these proline-based diamine catalysts for use in asymmetric conjugate Michael additions with an alternative Michael acceptor. The reaction attempted was that of cyclohexanones and phenyl vinyl sulfone in the presence of organocatalyst **11**. The solvent of choice was DMF on account of limited solubility of the reagents in toluene.

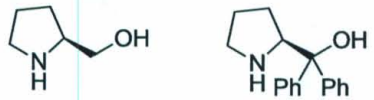
40 **41** **42** (19% yield)

Scheme 11: Michael addition of cyclohexanone to phenyl vinyl sulfone.

As seen in Scheme 11, the reaction did provide the expected Michael adduct **42**, but in low yield (19%). Further investigation into the efficiency and stereoselectivity of this reaction is needed.

VII. Studies with prolinol catalysts

During the course of these studies with diamines, it was noticed that aminoalcohols have not been examined as organocatalysts for conjugate addition reactions. It seemed plausible that amino alcohols should behave like the secondary-secondary diamine catalysts and prolinol (**43**) and diphenyl prolinol (**44**) were examined as alternative organocatalysts for the ketone-nitroalkene Michael addition reaction.

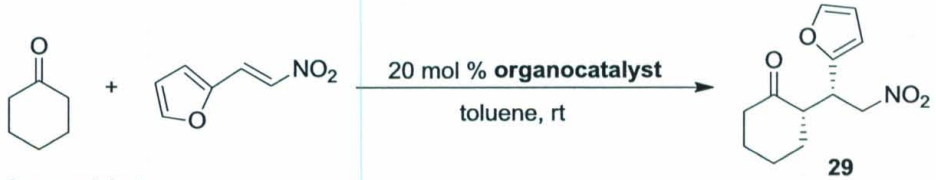


43 **44**

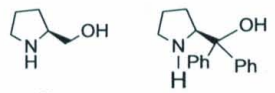
Figure 8: Prolinol organocatalysts examined in this study.

The Michael addition reaction of cyclohexanone and (*E*)-2-(2-nitrovinyl)furan to provide the nitroketone **29** was selected for catalyst testing (Table 3). This reaction had shown moderately good enantioselectivity in previous studies in using secondary-secondary diamine catalysts (up to 89% ee and 10/1 dr, Table 2), and clearly, there is room for optimization of this reaction. The results for this reaction are shown in Table 3 below. The use of prolinol catalyst **43** provided the expected product **29** in low yield (34%) with a diastereomeric ratio of 6/1 and moderate enantioselectivity of 64%. Conversely, diphenylprolinol catalyst **44** yielded no product. It is important to note that these reactions were allowed to proceed for a week as compared to the diamine catalyzed reactions previously discussed which were complete within 24-48 hours.

Table 3: Results from prolinol organocatalytic Michael additions of ketones to nitroalkenes.



Organocatalyst:

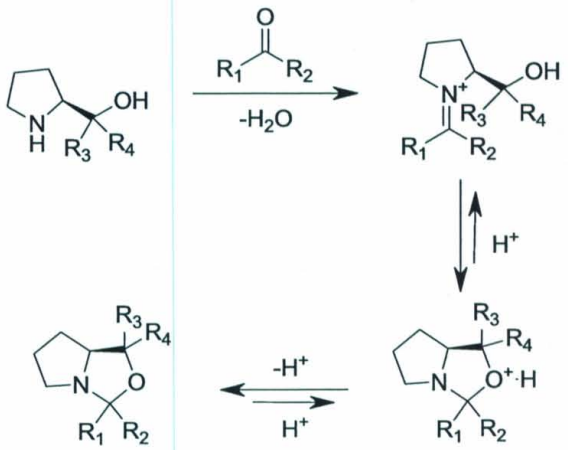


43 **44**

Entry	Catalyst	Yield (%)	dr[b] *(syn/anti)*	ee[c] (%)*(syn)*
1	**43**	34	6/1	64
2	**44**	0	n/a	n/a

[a]Isolated yields. [b]Determined by ^{1}H NMR analysis of the crude product. [c]Chiral HPLC analysis.

It was previously mentioned that secondary-secondary aminocatalysts have the potential to form aminals with carbonyl substrates as shown in Scheme 6. The prolinol catalysts also have the ability to form cyclic intermediates (oxazolidines) as shown in Scheme 12. From the results seen in Table 3, it is likely that the reversibility of any potential oxazolidine intermediates is much less for catalyst **44** than for catalyst **43**, presumably due to the Thorpe-Ingold effect[27] that favours oxazolidine formation from the iminium ion.



Scheme 12: Oxazolidine generation and reversibility.

VIII. Conclusion

In summary, simple pyrrolidine-based diamine catalysts were developed for the moderate to highly enantioselective conjugate Michael addition of cyclic ketones to nitroalkenes without an acid additive. The results support the importance of a secondary-secondary diamine motif for good stereocontrol of the Michael reactions. A predictable trend in side-chain pK_a versus stereoselection for a series of *N*-aryl organocatalysts (**12-14**) was observed in a few cases. More importantly, a distinct trend in side-chain pK_a versus average stereoselection is identified (Figure 7). This observation, combined with the low selectivity of the secondary-tertiary catalyst **15**

emphasizes the importance of a H-bond donor functionality in the catalyst. Further optimization of the pyrrolidine side chains is needed to improve the enantioselectivity of the reaction in the absence of a protic acid.

IX. Experimental Section

Reactions requiring anhydrous conditions were performed under a positive pressure of nitrogen using oven-dried glassware (100 °C). All organic layers obtained from extractions were dried over anhydrous sodium sulfate. THF was distilled from sodium benzophenone ketyl, and dichloromethane was distilled from calcium hydride prior to use. Reactions were monitored by TLC on commercial precoated silica (Merck 60F-254) by staining with iodine. Chromatographic purification of products was done using flash column chromatography on Merck 60F 230-400 mesh silica gel according to the standard procedure. All melting points are uncorrected.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker AVANCE 500 instrument operating at 500 MHz and 125.8 MHz, respectively at room temperature. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.23$) for ^{13}C NMR. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Brucker TENSOR 27 spectrometer and are reported in wavenumbers (cm^{-1}). Mass spectra (APCI or ESI) were obtained on an Atmospheric Pressure Ionization-Mass Spectrometer (API-MS, Agilent 1100 series LC/MSD chromatographic system) at an ionization potential of 70 eV. High-resolution mass spectra (HRMS) were obtained on a Waters/Micromass GCT Time of Flight Mass Spectrometer, (CI gas ammonia). Optical rotations were measured at the sodium D line on a JASCO DIP-370 polarimeter at ambient temperature. Enantiomeric excess (ee) was determined by high performance liquid chromatography (HPLC) on a Waters instrument equipped with a 1525 Binary HPLC pump using either a Chiralpak AD-H column (1.6 x 25 cm) or Chiralpak AS-H

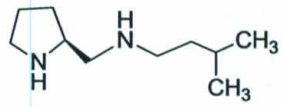
(1.6 x 25 cm) column. All Michael addition reactions were carried out in closed vials without the exclusion of air or moisture.

Materials

All solvents and commercially available chemicals were used as received. Organic substrates cyclohexanone, cyclopentanone, tetrahydrothiophran-4-one, tetrahydropyran-4-one, 4-(1,3-dioxolane)-cyclohexanone, acetone, L-proline, 1-nitro-4-((*E*)-2-nitrovinyl)benzene, 1-methoxy-2-((*E*)-2-nitrovinyl)benzene, 3-methoxy-2-((*E*)-2-nitrovinyl)benzene, 1-(trifluoromethyl)-2-((*E*)-2-nitrovinyl)benzene, 2-((*E*)-2-nitrovinyl)furan, and 2-((*E*)-2-nitrovinyl)thiophene were obtained from commercial sources and were used without any purification. Michael acceptor 1-((*E*)-2-nitrovinyl)benzene was prepared according to the literature procedure.[23]

Procedures

(*S*)-3-Methyl-*N*-(pyrrolidin-2-ylmethyl)butan-1-amine(11):[23]



To a solution of Boc-L-proline **16** (2.15 g, 10.0 mmol) in 10.0 mL dry CH_2Cl_2 at -10 °C under N_2 was added *N*-methylmorpholine (1.10 mL, 10.0 mmol). The resulting mixture was stirred for 15 minutes, treated with isobutylchloroformate (1.30 mL, 10.0 mmol) and stirred an additional 15 minutes. Isoamylamine (1.19 mL, 10.2 mmol) was added and the reaction mixture stirred at room temperature for 48 h. The mixture was diluted with EtOAc (120 mL) and the solution washed with H_2O (1 x 20 mL), saturated aqueous $NaHCO_3$ (1 x 20 mL), 0.500 N HCl (2 x 15 mL), and brine (1 x 5 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to provide 2.95 g (99%) of the *N*-Boc amide **17** as a clear, pale yellow oil that was pure by ^1H NMR and was used further without purification.

To a cold (<5 °C) solution of the crude *N*-Boc-amide **17** (2.95 g, 10.4 mmol) in dry CH_2Cl_2 (10.0 mL) was added TFA (5.50 mL, 104 mmol). The solution was stirred at room temperature for 3 h and then concentrated under reduced pressure to remove excess TFA. The residue was dissolved in CH_2Cl_2 (50.0 mL) and the solution was extracted with water (3 x 15 mL). The aqueous phase was cooled (5 °C), basified with NaOH pellets and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide 1.90 g (99%) of the amino amide **18** as a clear, yellow oil that was pure by ^1H NMR and was used further without purification.

To a solution of the above amino amide (1.90 g, 10.5 mmol) in dry THF (35.0 mL) at 0°C under N_2 was added LAH (1.70 g, 45.0 mmol). The mixture was brought to room temperature,

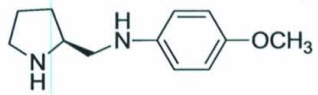
heated to reflux for 24 h and then cooled to 0 °C. Solid $Na_2SO_4 \cdot 10H_2O$ (6.00 g) was added over 1.5 h and the resulting suspension was filtered through Celite® twice. The residue was washed with THF and the combined filtrate was dried (Na_2SO_4) and concentrated under reduced pressure to a give pale yellow liquid. Purification of the crude product by Kugelrohr distillation under reduced pressure gave 1.02 g (58%) of **11**. [23]

Bp: 115°C (air bath)/0.500 torr.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 3.19-3.16 (m, 1H, NC*H*), 2.91-2.88 (m, 2H, NCH_2 (ring)), 2.61-2.57 (m, 4H, CHCH_2NH, NHCH_2, NHCH_2, N*H*), 2.46 (dd, 1H, J = 10.0, 7.0, CHCH_2NH), 1.89-1.85 (m, 1H, CH_2CH$_2$), 1.75-1.73 (m, 1H, CH_2CH$_2$), 1.73-1.68 (m, 1H, CH$_2$CH_2), 1.68-1.60 (m, 1H, CH$_2$CH_2), 1.34-1.26 (m, 3H, CH_2C*H*), 0.90 (d, 6H, J = 7.3, CH(CH_3)$_2$).

(*S*)-4-Methoxy-N-(pyrrolidine-2-ylmethyl)benzenamine (12):[26]



Prepared by adaptation of literature procedure.[26] A solution of Cbz-L-proline **19** (0.750 g, 3.00 mmol) in 40 mL dry THF under N_2 was cooled to -15 °C and stirred for 15 minutes. *N*-methylmorpholine (0.330 mL, 3.00 mmol) was added and the mixture was stirred an additional 15 minutes after which isobutylchloroformate (0.290 mL, 3.00 mmol) was added followed by stirring for 15 minutes. 4-Methoxyaniline (0.380 g, 3.03 mmol) was added and the mixture was stirred at room temperature for 24 h. EtOAc (150 mL) was added, and the solution was washed with H_2O (1 x 50 mL), saturated $NaHCO_3$ (1 x 20 mL), 0.500 N HCl (1 x 20 mL), and brine (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure.

The resulting solid was triturated with hexanes and then recrystallized (EtOAc/hexanes) to provide 0.510 g (48%) of the *N*-Cbz amide **20** as a white solid.

To a solution of *N*-Cbz amide **20** (500 mg, 1.40 mmol) in 10.0 mL methanol under N_2 was added Pd-C (10%) (12.0 mg). The system was flushed with H_2 and stirred at room temperature under H_2. After 3 h, the reaction mixture was filtered through Celite® and washed with methanol. The resulting filtrate was concentrated under reduced pressure to provide 279 mg (96%) of amide **21** as a clear, colourless oil.

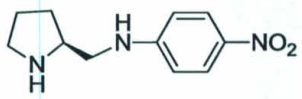
A solution of amide **21** (850 mg, 4.08 mmol) in 20.0 mL of dry THF and cooled on ice. LAH (387 mg, 10.2 mmol) was added carefully to the solution and refluxed under N_2 for 3 h. Sodium sulfate decahydrate (2.00 g) was added and stirred for 1.50 h. The mixture was filtered through Celite® and washed with ethyl ether (2 x 10 mL). The ether layer was concentrated under pressure. Purification of the crude brown oil by Kugelrohr distillation under reduced pressure gave 465 mg (53%) of clear oil **12**.[26]

Bp: 175 °C (air bath)/0.500 torr.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 6.78-6.76 (d, 2H, J = 10.0, Ar*H*, *meta* to OCH_3), 6.62-6.60 (d, 2H, J = 10.0, Ar*H*, *ortho* to OCH_3), 3.75 (s, 3H, OCH_3), 3.39-3.34 (m, 1H, $CHCH_2NH$), 3.13-3.10 (m, 1H, CH_2NH), 2.94-2.88 (m, 4H, CH_2NH, CH_2NH), 1.95-1.87 (m, 1H, CH_2CH_2), 1.83-1.77 (m, 1H, CH_2CH_2) 1.77-1.70 (m, 1H, CH_2CH_2), 1.48-1.45 (m, 1H, CH_2CH_2).

4-Nitro-*N*-(((*S*)-pyrrolidin-2-yl)methyl)benzenamine (14):



Amide **23** (1.900 g, 8.050 mmol) was dissolved in borane-methyl sulfide adduct (2.000 M in THF, 16.00 mL, 32.00 mmol) and the solution was stirred at room temperature under N_2 for 48 h. The reaction mixture was cooled to 0 °C, 6.00 N HCl (30.0 mL) was added followed by stirring for 3 h. The resulting mixture was then concentrated under reduced pressure. The residue was dissolved in H_2O (20.00 mL) and the solution was washed with EtOAc (2 x 10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude product was purified using flash chromatography on silica gel (15:85 – 70:30 EtOAc/hexanes) to provide 644.0 mg (36%) of diamine **14** as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 8.07 (d, 2H, J = 10.0, Ar*H*, *ortho* to NO_2), 6.53 (d, 2H, J = 10.0, Ar*H*, *meta* to NO_2), 5.18 (br, 1H, N*H*Ar), 3.44 (m, 1H, C*H*CH_2NH), 3.24 (m, 1H, CH_2NH), 2.97 (m, 3H, CH_2NH, CH_2NH(ring)), 2.00-1.90 (m, 2H, N*H*, CH_2CH_2NH), 1.89-1.79 (m, 1H, CH_2CH_2), 1.79-1.70 (m, 1H, CH_2CH_2), 1.53-1.43 (m, 1H, CH_2CH_2).

^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 153.8 (*C*NO_2 (*ipso*)), 137.8 (*C*NH (*ipso*)), 126.5 (Ar*C* (*ortho* to NO_2), 111.3 (Ar*C*), 57.2 (*C*HNH(ring)), 47.4 (*C*H_2NH), 46.6 (*C*H_2NH), 29.6 (*C*H_2CH), 25.9 (*C*H_2CH_2).

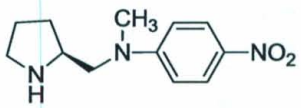
IR (neat):

1600, 1474, 1304, 1111, 827 cm^{-1}

HRMS (EI):

m/z 221.1163 (221.1164 calc. for $C_{11}H_{15}N_3O_2$ (M^+)).

(*S*)-*N*-Methyl-4-nitro-*N*-(pyrrolidin-2-ylmethyl)benzenamine (15):



Amide **25** (0.160 g, 0.100 mmol) was dissolved in borane-methyl sulfide adduct (2.00 M in THF, 1.9 mL, 3.84 mmol) and the solution was stirred at room temperature under N_2 for 48 h. The reaction mixture was cooled to 0 °C, treated with 6.00 N HCl (2 mL) and stirred for 3 h after which time the resulting mixture was concentrated under reduced pressure. The residue obtained was dissolved in H_2O (5 mL) and the solution was washed with EtOAc (2 x 5 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude product was purified using flash chromatography on silica gel (5% CH_3OH/CH_2Cl_2 – 10% CH_3OH/CH_2Cl_2) to provide 94.70 mg (63%) of diamine **15** as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 8.11 (d, 2H, J = 10.0, ArH, *ortho* to NO_2), 6.57 (d, 2H, J = 10.0, ArH, *meta* to NO_2), 3.96 (m, 1H, C*H*CH_2), 3.47 (m, 1H, CH_2N), 3.27 (m, 1H, CH_2N), 2.75 (m, 1H, CH_2NCH_3), 2.60 (m, 1H, CH_2NCH_3), 2.48 (m, 3H, NCH_3), 2.12-2.01 (m, 5H, CH_2CH_2, N*H*)..

^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 152.0 (Ar*C*NO_2), 137.4 (Ar*C*N), 126.7 (Ar*C*, *ortho* to NO_2), 111.3 (Ar*C*), 59.1 (*C*HN), 53.5 (*C*H_2N), 49.0 (*C*H_2N), 37.1 (N*C*H_3), 29.8 (*C*H_2), 23.5 (*C*H_2).

IR (neat):

1594, 1478, 1288, 1195, 1108, 822 cm^{-1}

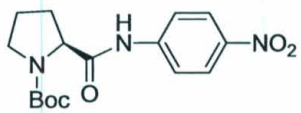
MS (APCI, positive):

m/z 236.1 ($[M+1]^+$, 100)

HRMS:

m/z 235.1324 (235.1321 calc. for $C_{12}H_{17}N_3O_2$ (M^+)).

(*S*)-*tert*-Butyl 2-(4-nitrophenylcarbamoyl)pyrrolidine-1-carboxylate (22):



A solution of Boc-L-proline **16** (3.225 g, 15.00 mmol) in 40.00 mL dry THF under N_2 was cooled to -15 °C and stirred for 15 minutes. *N*-methylmorpholine (1.650 mL, 15.00 mmol) was added and the mixture was stirred an additional 15 minutes after which isobutylchloroformate (1.960 mL, 15.00 mmol) was added followed by stirring for 15 minutes. 4-Nitroaniline (2.130 g, 15.45 mmol) was added and the mixture was stirred at room temperature for 24 h. EtOAc (15 mL) was added, and the solution was washed with H_2O (1 x 50 mL), saturated $NaHCO_3$ (1 x 20 mL), 0.5000 N HCl (1 x 20 mL), and brine (1 x 10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting solid was triturated with hexanes and then recrystallized (EtOAc/hexanes) to provide 4.000 g (80%) of the *N*-Boc amide **22** as a pale yellow solid.

^{1}H NMR (500.0 MHz, $CDCl_3$):

δ 10.24 (brs, 1H, N*H*), 8.19 (d, 2H, J = 10.0, Ar*H*, *ortho* to NO_2), 7.67 (d, 2H, J = 10.0, *ArH*, *meta* to NO_2), 4.50 (br m, 1H, C*H*CO), 3.43-3.36 (br m, 2H, CH_2N), 2.59 (br m, 1H, CH_2CH), 1.95 (br m, 3H, CH_2CH, CH_2CH_2N), 1.52 (br s, 9H, C(CH_3)$_3$).

^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 170.7 (*C*O), 156.5 (N*C*=OO), 144.2 (*C*NHCO (*ipso*)), 143.2 (*C*NO_2 (*ipso*)), 125.9 (Ar*C*

(*ortho* to NO_2)), 118.9 (Ar*C*), 81.32 (*C*$(CH_3)_3$), 59.9 (*C*HCO), 47.3 (*C*H_2NH), 28.1 (C(*C*$H_3)_3$), 27.4 (*C*H_2CH), 24.5 (*C*H_2CH_2N).

IR (neat):

3273, 1703, 1663, 1407, 1111, 986, 926 cm^{-1}

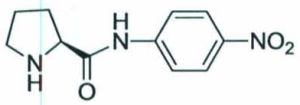
MS (APCI, positive):

m/z 236.1 (100, M-(*t*Boc))

HRMS (EI):

m/z 335.1477 (335.1481 calc. for $C_{16}H_{21}N_3O_5$ (M^+)).

(*S*)-*N*-(4-nitrophenyl)pyrrolidine-2-carboxamide (23):



To a solution of *N*-Boc amide **22** (3.620 g, 10.70 mmol) in dry CH_2Cl_2 (15.00 mL) at 0 °C under N_2 was added TFA (13.30 mL, 161.9 mmol). The reaction mixture was stirred at room temperature for 20 h and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL) and the solution was extracted with H_2O (2 x 15 mL). The aqueous layer was cooled (<5 °C), basified to pH 12 with NaOH pellets and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The resulting solid was recrystallized (EtOAc/hexanes) to provide 1.780 g (69%) of the amide **23** as a yellow solid.

^{1}H NMR (500.0 MHz, $CDCl_3$):

δ 10.18 (s, 1H, N*H*CO), 8.21 (d, 2H, *J* = 10.0, Ar*H*, *ortho* to NO_2), 7.78 (d, 2H, *J* = 10.0, Ar*H meta* to NO_2), 3.90 (m, 1H, C*H*CO), 3.11 (m, 1H, CH_2N), 3.00 (m, 1H, CH_2N), 2.25 (m, 2H, NH, CH_2CH), 2.25 (m, 1H, CH_2CH), 1.79 (m, 2H, CH_2CH_2NH).

^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 174.3 (*C*O), 143.7 (*C*NO_2 (*ipso*)), 143.4 (*C*NHCO (*ipso*)), 125.2 (Ar*C*(*ortho* to NO_2)), 118.8 (Ar*C*), 61.2 (*C*HCO), 47.5 (CH_2NH), 30.8 (CH_2CH), 26.5 (CH_2CH_2NH).

IR (neat):

3203, 1687, 1599, 1403, 1100 cm^{-1}.

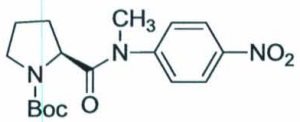
MS (APCI, positive):

m/z 236.1 ($[M+1]^+$, 100.00)

HRMS (EI):

m/z 235.0958 (235.0957 calc. for $C_{11}H_{13}N_3O_3$ (M)).

(*S*)-*tert*-Butyl 2-(methyl(4-nitrophenyl)carbamoyl)pyrrolidine-1-carboxylate (24):



A solution of *N*-Boc-amine **22** (1.440 g, 4.270 mmol) in THF (15.00 mL) was cooled for 10 min (5 °C) under N_2. NaH (170.3 mg, 1.470 mmol) was added cautiously. After 10 minutes CH_3I (2.020 mL, 32.45 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. The mixture was concentrated and then diluted with EtOAc (40 mL). The resulting solution was washed with H_2O (1 x 10 mL) and brine (1 x 10 mL). The organic layer was then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue obtained was purified using flash chromatography on silica gel (50/50 EtOAc/hexanes) to provide 1.040 g (70%) of the amide **24** as a pale yellow gum.

^{1}H NMR (500.0 MHz, $CDCl_3$):

Major rotamer: δ 8.28 (d, 2H, J = 10.0, Ar*H*, *ortho* to NO_2), 7.58 (d, 2H, J = 10.0, Ar*H*, *meta* to NO_2), 4.32 (br, 1H, C*H*CO), 3.56-3.51 (br m, 2H, CH_2N-Boc)), 3.45-3.32 (br s, 3H, NCH_3), 2.04-1.74 (m, 4H, CH_2CH_2), 1.45 (br s , 9H, C(CH_3)$_3$).

Visible signals for the minor rotamer: δ 8.28 (d, 2H, J = 10.0, Ar*H*, *ortho* to NO_2), 7.41 (d, 1H, J = 10.0, ArH), 4.24 (br, 1H, C*H*CO).

^{13}C NMR (125.8 MHz, $CDCl_3$):

Major rotamer: δ 172.6 (*C*O), 154.4 (N*C*=OO), 149.6 (*C*NHCO (*ipso*)), 146.9 (*C*NO_2 (*ipso*)), 128.4 (Ar*C* (*ortho* to NO_2)), 125.1 (Ar*C*), 79.6 (*C*(CH_3)$_3$), 47.0 (*C*HCO), 37.7 (*C*H_2NH), 28.6 (NCH_3), 28.5 (C(*C*H_3)$_3$), 24.3 (*C*H_2CH), 23.5 (*C*H_2CH_2N).

Visible signals for the minor rotamer: δ 172.3 (*C*O), 153.5 (N*C*=OO), 179.2 (*C*NHCO (*ipso*)), 80.0 (*C*(CH_3)$_3$), 57.2 (*C*HCO), 56.9 (*C*H_2NH), 30.2 (NCH_3), 14.2 (*C*H_2CH_2N).

IR (neat):

3279, 1703, 1509, 1407, 1338, 1159, 1111, 853 cm^{-1}

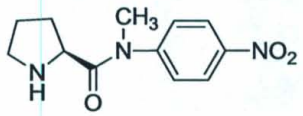
MS (APEI, positive):

m/z 349.2 (([M+1]$^+$, 100.00))

HRMS (EI):

m/z 350.1723 (350.1716 calc. for $C_{17}H_{24}N_3O_5$ (M^+)).

(*S*)-*N*-Methyl-*N*-(4-nitrophenyl)pyrrolidine-2-carboxamide (25):



To a solution of *N*-Boc amide **24** (1.00 g, 2.86 mmol) in dry CH_2Cl_2 (5.00 mL) at 0 °C under N_2 was added TFA (2.35 mL, 28.6 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated under reduced pressure to remove CH_2Cl_2 and TFA. The resulting residue was dissolved in EtOAc (30.0 mL) and the solution was extracted with H_2O (2 x 15.0 mL). The aqueous layer was cooled (<5 °C), basified to pH 12 with NaOH pellets and extracted with CH_2Cl_2 (2 x 15.0 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to provide 571 mg (80%) of the amide **25** as a yellow solid.

^{1}H NMR (500.0 MHz, $CDCl_3$):

δ 8.14 (d, 2H, J = 10.0, Ar*H*, *ortho* to NO_2), 6.56 (d, 2H, J = 10.0, ArH), 4.19-4.17 (m, 1H, C*H*CO), 3.69 (m, 1H, CH_2NH), 3.40-3.35 (m, 2H, CH_2NH, CH_2NH), 2.80 (br s, 3H, NCH_3), 2.31 (m, 2H, CH_2CH_2), 2.12 (m, 1H, CH_2CH_2), 2.02 (m, 1H, CH_2CH_2).

MS (APCI, positive):

m/z 250.1 ($[M+1]^+$, 100.00)

HRMS (EI):

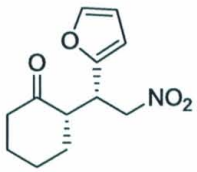
m/z 249.1120 (249.1113 calc. for $C_{12}H_{15}N_3O_3$ (M^+)).

General experimental procedure for the Michael addition of ketones to nitroalkenes:

To a solution of the amine catalyst (0.10 mmol) and the nitroalkene (0.50 mmol) in toluene (1.0 mL) was added the ketone or aldehyde (2.5 mmol), and the solution was stirred at ambient temperature for 24 h except when noted otherwise. Ethyl acetate (10 mL) was added and the solution was washed with water, aqueous 0.50 N HCl, dried (Na_2SO_4), filtered and concentrated to give the crude product, which was purified by flash chromatography on silica gel.

The relative configurations of the products (*syn* or *anti*) were determined by comparison of ^1H NMR spectral data with those reported in the literature. The absolute configurations of each product were determined either by comparison of optical rotation values with those reported in the literature or by comparison of HPLC retention times. All the compounds reported here and in Tables 1-4 have previously been reported in the literature. [23, 15c]

(*S*)-2-((*S*)-1-(Furan-2-yl)-2-nitroethyl)cyclohexanone (28):[23]



Reaction of cyclohexanone (0.260 mL, 2.50 mmol) and 2-((*E*)-2-nitrovinyl)furan (70.0 mg, 0.500 mmol) in the presence of catalyst **13** (17.0 mg, 0.100 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane: 20/80), 210 mg (89%) of **28** as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.57 (br s, 1H, Ar*H*), 6.29 (dd, 1H, J = 3.0, 2.0, Ar*H*), 6.18 (d, 1H, J = 2.0, Ar*H*), 4.80 (dd, 1H, J = 9.0, 6.0, CH_2NO$_2$), 4.68 (dd, 1H, J = 12.0, 9.0, CH_2NO$_2$), 4.00 (dt, 1H, J = 9.0, 4.5 C*H*CH$_2$NO$_2$), 2.78-2.73 (m, 1H, C*H*C(O)), 2.48-2.50 (m, 1H, CH_2C(O)), 2.40-2.33 (m, 1H, CH_2C(O)), 2.18-2.09 (m, 1H, CH_2), 1.92-1.82 (m, 1H, CH_2), 1.82-1.75 (m, 1H, CH_2), 1.71-1.60 (m, 2H, CH_2), 1.35-1.26 (m, 1H, CH_2).

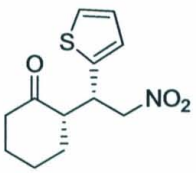
HPLC (Chiralpak AD-H):

(hexane/*i*-PrOH, 95/5, flow rate 1.00 mL/min, conc. 1.00 mL/min., λ = 254 nm):

t_{major} = 13.8 min; t_{minor} = 16.4 min.

ee: 89%

(*S*)-2-((*S*)-2-Nitro-1-(thiophen-2-yl)ethyl)cyclohexanone (30):[23]



Reaction of cyclohexanone (0.260 mL, 2.500 mmol) and 2-((*E*)-2-nitrovinyl)thiophene (77.6 mg, 0.500 mmol) in the presence of catalyst **13** (17 .0 mg, 0.100 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane: 20/80), 97.5 mg (77%) of **30** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ 7.23 (d, 1H, J = 5.0, Ar*H*), 6.94 (dd, 1H, J = 5.0, 3.0, Ar*H*), 6.88 (d, 1H, J = 3.0, 3.0, Ar*H*), 4.90 (dd, 1H, J = 13.0, 4.0, CH_2NO_2), 4.67 (dd, 1H, J = 13.0, 9.0, CH_2NO_2), 4.14 (dt, 1H, J = 9.0, 4.0, $CHCH_2NO_2$), 2.72-2.67 (m, 1H, C*H*C(O)), 2.50-2.46 (m, 1H, CH_2C(O)), 2.42-2.36 (m, 1H, CH_2C(O)), 2.13-2.10 (m, 1H, CH_2), 1.96-1.90 (m, 1H, CH_2), 1.88-1.85 (m, 1H, CH_2), 1.73-1.56 (m, 2H, CH_2), 1.38-1.24 (m, 1H, CH_2).

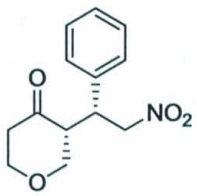
HPLC (Chiralpak AD-H):

(hexane/*i*-PrOH, 95/5, flow rate 1.00 mL/min, conc. 1.00 mL/min., λ = 254 nm):

t_{major} = 15.3 min; t_{minor} = 17.6 min.

ee: 82%

(*S*)-Tetrahydro-3-((*R*)-2-nitro-1-phenylethyl)pyran-4-one (31):[23]



Reaction of tetrahydropyran-4-one (0.230 mL, 2.50 mmol) and 1-((*E*)-2-nitrovinyl)benzene (74.5 mg, 0.500 mmol) in the presence of catalyst **13** (17.6 mg, 0.100 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane: 40/60), 239 mg (96%) of **31** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ: 7.39-7.31 (m, 3H, Ar*H*), 7.21 (d, 2H, *J* = 7.0, *ortho* Ar*H*), 4.96 (dd, 1H, J = 12.5, 4.7, CH_2NO$_2$), 4.68 (dd, 1H, *J* = 12.5, 10.0, CH_2NO$_2$), 4.20-4.15 (m, 1H, C*H*CH$_2$NO$_2$), 3.89-3.79 (m, 2H, OCH_2), 3.73 (dd, 1H, *J* = 12.0, 5.3, OCH_2CH), 3.31 (dd, 1H, *J* = 12.0, 8.8, OCH_2CH), 2.94-2.89 (m, 1H, C*H*C(O)), 2.72-2.67 (m, 1H, CH_2C(O)), 2.62-2.58 (m, 1H, CH_2C(O)).

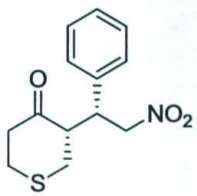
HPLC (Chiralpak AS-H):

(hexane/*i*-PrOH, 50/50, flow rate 0.500 mL/min, conc. 1.00 mg/mL, λ = 247 nm):

t_{major} = 21.3 min, t_{minor} = 17.8 min

ee: 89%

(*S*)-Tetrahydro-3-((*R*)-2-nitro-1-phenylethyl)thiopyran-4-one (32):[23]



Reaction of tetrahydrothiopyran-4-one (290 mg, 2.50 mmol) and 1-((*E*)-2-nitrovinyl)benzene (74.5 mg, 0.500 mmol) in the presence of catalyst **11** (16.7 mg, 0.100 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane: 20/80), 188 mg (71%) of **32** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ: 7.36-7.33 (m, 2H, Ar*H*), 7.33-7.29 (m, 1H, Ar*H*), 7.19 (m, 2H, Ar*H*), 4.73 (dd, 1H, J = 12.7, 4.5, CH_2NO$_2$), 4.63 (dd, 1H, J = 12.7, 10.0, CH_2NO$_2$), 3.98 (dt, 1H, J = 10.0, 4.5, PhC*H*), 3.07-3.00 (m, 1H, C*H*C(O)), 3.00-2.94 (m, 2H, CH_2C(O)), 2.88-2.84 (m, 2H, SCH_2), 2.84-2.77 (m, 1H, SCH_2), 2.64-2.60 (m, 1H, SCH_2CH)), 2.45 (dd, 1H, J = 13.8, 9.7, SCH_2CH).

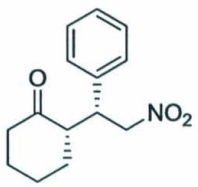
HPLC (Chiralpak AS-H):

(hexane/*i*-PrOH, 50/50, flow rate 0.500 mL min^{-1}, conc. 1.00 mg/mL, λ= 247 nm):

t_{major} = 19.2 min., t_{minor} = 15.9 min.

ee: 73%

(*S*)-2-((R)-2-Nitro-1-phenylethyl)cyclohexanone (33):[23]



Reaction of cyclohexanone (0.260 mL, 2.50 mmol) and 1-((*E*)-2-nitrovinyl)benzene (74.5 mg, 0.50 mmol) in the presence of catalyst **12** (16.7 mg, 0.100 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane: 20/80), 85.0 mg (69%) of **33** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ: 7.37-7.39 (m, 3H, Ar*H*), 7.19 (d, 2H, J = 7.7, *ortho* Ar*H*), 4.96 (dd, 1H, J = 12.4, 4.5, CH_2NO_2), 4.67 (dd, 1H, J = 12.4, 9.5, CH_2NO_2), 3.79 (dt, 1H, J = 10.0, 4.5, $CHCH_2NO_2$), 2.75-2.69 (m, 1H, $CHC(O)$), 2.53-2.50 (m, 1H, $CH_2C(O)$), 2.50-2.39 (m, 1H, $CH_2(O)$), 2.13-2.08 (m, 1H, CH_2), 1.84-1.57 (m, 4H, CH_2), 1.31-1.23 (m, 1H, CH_2).

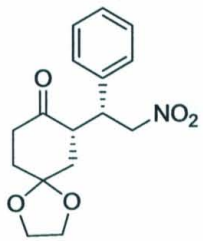
HPLC (Chiralpak AD-H):

(hexane/*i*-PrOH, 90/10, flow rate 1.00 mL min^{-1}, conc. 1.00 mg/mL, λ = 247 nm):

t_{major} = 10.6 min., t_{minor} = 8.84 min.

ee: 86%

(*S*)-2-[(*R*)-2-Nitro-1-phenylethyl]-4-[1,3-dioxolane]cyclohexanone (34):[23]



Reaction of 4-(1,3-dioxolanyl)-cyclohexanone (395 mg, 2.50 mmol) and 1-((*E*)-2-nitrovinyl)benzene (74.5 mg, 0.500 mmol) in the presence of catalyst **12** (16.7 mg, 0.100 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane: 40/60), 241 mg (79%) of **34** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ: 7.35-7.28 (m, 3H, Ar*H*), 7.21 (d, 2H, J = 7.2, *ortho* Ar*H*), 4.95 (dd, 1H, J = 12.5, 4.7, CH_2NO_2), 4.63 (dd, 1H, J = 12.5, 9.8, CH_2NO_2), 4.04-3.81 (m, 5H, PhC*H*, OCH_2CH_2O), 3.10-3.05 (m, 1H, C*H*C(O)), 2.71 (m, 1H, CH_2CH_2), 2.52 (m, 1H, CH_2CH_2), 2.04-2.01 (m, 1H, CH_2CH_2), 2.00-1.91 (m, 1H, CH_2CH_2), 1.72-1.66 (m, 1H, CH_2CH), 1.60-1.52 (m, 1H, CH_2CH).

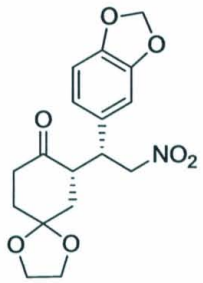
HPLC (Chiralpak AS-H):

(hexane/*i*-PrOH, 90/10, flow rate 0.500 mL min^{-1}, conc. 1.00 mg/mL, λ = 254 nm):

t_{major} = 59.6 min., t_{minor} = 47.5 min.

ee: 92%

(*S*)-2-((*R*)-1-(Benzo(*d*)(1,3)dioxyol-6-yl)-2-nitroethyl)-4-(1,3-dioxolane)-cyclohexanone (35):[15c]



Reaction of 4-(1,3-dioxolanyl)-cyclohexanone (395 mg, 2.50 mmol) and (*E*)-5-(2-nitrovinyl)benzo[1,3]dioxole (96.6 mg, 0.500 mmol) in the presence of catalyst **12** (16.7 mg, 0.100 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane: 30/70), 83.8 mg (48%) of **35** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ:6.72-6.70 (d, 1H, J = 7.9, *ortho* Ar*H*), 6.62-6.58 (m, 2H, Ar*H*), 5.93-5.94 (d, 2H, J = 3.5, OCH_2O), 4.87-4.85 (dd, 1H, J = 12.0, 4.7, CH_2NO$_2$), 4.51-4.48 (dd, 1H, J = 12.0, 10.0, CH_2NO$_2$), 3.97-3.80 (m, 4H, OCH_2CH_2O), 3.77-3.70 (m, 1H, C*H*CH$_2$), 2.97-2.92 (m, 1H, C*H*C(O)), 2.70-2.67 (m, 1H, CH_2CH$_2$), 2.43-2.37 (m, 1H, CH_2CH$_2$), 2.02-1.96 (m, 1H, CH_2CH$_2$), 1.82-1.79 (m, 1H, CH_2CH$_2$), 1.71-1.69 (m, 1H, CH_2CH$_2$), 1.53-1.50 (m, 1H, CH_2CH$_2$).

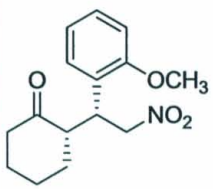
HPLC (Chiralpak AS-H):

(hexane/*i*-PrOH, 60/40, flow rate 1.00 mL/min, conc. 1.00 mg/mL, λ =2 54 nm);

t_{major} = 20.44 min., t_{minor} = 15.8 min.

ee: 80%

(*S*)-2-((*R*)-1-(2-Methoxyphenyl)-2-nitroethyl)cyclohexanones(36):[23]



Reaction of cyclohexanones (0.260 mL, 2.50 mmol) and 1-methoxy-2-((*E*)-2-nitrovinyl)benzene (90.0 mg, 0.500 mmol) in the presence of catalyst **12** (20.6 mg, 0.100 mmol) at room temperature for 24 h gave, 143 mg (74%) of **36** as a clear colorless oil that was pure by ^{1}H NMR.

^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.26 (m, 1H, Ar*H*), 7.10 (dd, 1H, *J* = 7.6, 1.0, Ar*H*), 6.92-6.88 (m, 2H, Ar*H*), 4.88-4.80 (m, 2H, CH_2NO_2), 3.98 (dt, 1H, *J* = 10.0, 5.0, $CHCH_2NO_2$), 3.85 (s, 3H, OCH_3), 3.02-2.96 (m, 1H, CHC(O)), 2.52-2.47 (m, 1H, CH_2C(O)), 2.43-2.36 (m, 1H, CH_2C(O)), 2.10-2.06 (m, 1H, CH_2), 1.81-1.77 (m, 1H, CH_2), 1.71-1.66 (m, 2H, CH_2), 1.66-1.55 (m, 1H, CH_2), 1.27-1.21 (m, 1H, CH_2).

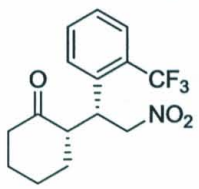
HPLC (Chiralpak AS-H):

(hexane/*i*-PrOH, 90/10, flow rate 0.500 mL/min, conc. 1.00 mg/mL, λ = 254 nm);

t_{major} = 28.8 min., t_{minor} = 24.5 min.

ee: 90%

(*S*)-2-((*R*)-2-nitro-1-(2-(trifluoromethyl)phenyl)ethyl)cyclohexanones (37):[23]



Reaction of cyclohexanones (0.260 mL, 2.50 mmol) and 1-(trifluoromethyl)-2-((*E*)-2-nitrovinyl) benzene (109 mg, 0.500 mmol) in the presence of catalyst **14** (22.2 mg, 0.100 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane; 20/80), 129 mg (82%) of **37** as yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$):

δ = 7.71 (d, 1H, J = 7.5, Ar*H*), 7.57 (t, 1H, J = 7.5, Ar*H*), 7.41 (t, 1H, J = 7.5, Ar*H*), 7.39 (d, 1H, J = 7.5, Ar*H*), 5.05 (dd, 1H, J = 12.0, 7.0, C*H*$_2$NO$_2$), 4.77 (dd, 1H, J = 12.0, 3.7, C*H*$_2$NO$_2$), 4.12-4.07 (m, 1H, C*H*CH$_2$NO$_2$), 3.05-3.0 (m, 1H, C*H*C(O)), 2.53-2.41 (m, 2H, C*H*$_2$C(O)), 2.17-2.11 (m, 1H, C*H*$_2$), 1.83-1.78 (m, 1H, C*H*$_2$), 1.76-1.64 (m, 2H, C*H*$_2$), 1.64-1.55 (m, 1H, C*H*$_2$), 1.38-1.28 (m, 1H, C*H*$_2$).

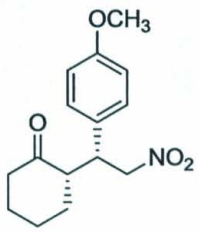
HPLC (Chiralpak AS-H):

(hexane/*i*-PrOH, 90/10, flow rate 1.00 mL/min, conc. 1.00 mg/mL, λ = 254 nm):

t_{major} = 10.4 min., t_{minor} = 8.70 min.

ee: 76%

(*S*)-2-[(*R*)-1-(4-methoxyphenyl)-2-nitroethyl]cyclohexanone (38):[23]



Reaction of cyclohexanone (0.260 mL, 2.50 mmol) and 1-methoxy-4-((*E*)-2-nitrovinyl)benzene (90.0 mg, 0.500 mmol) in the presence of catalyst **12** (22.2 mg, 0.100 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane: 20/80), 241 mg (87%) of **38** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ: 7.09 (d, 2H, J = 8.0, Ar*H*), 6.86 (d, 2H, J = 8.0, Ar*H*), 4.91 (dd, 1H, J = 12.0, 4.5, CH_2NO_2), 4.60 (dd, 1H, J = 12.0, 10.0, CH_2NO_2), 3.80 (s, 3H, OCH_3) 3.72, (dt, 1H, J = 10.5, 5.0, ArC*H*), 2.69-2.63 (m, 1H, C*H*C(O)), 2.50 – 2.46 (m, 1H, CH_2C(O)), 2.42-2.36 (m, 1H, CH_2), 2.10-2.06 (m, 1H, CH_2), 1.82-1.55 (m, 4H, CH_2), 1.28-1.21 (m, 1H, CH_2).

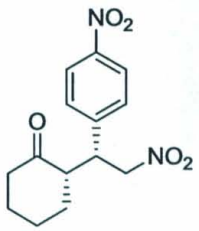
HPLC (Chiralpak AD-H):

(hexane/*i*-PrOH, 90/10, flow rate 0.500 mL min^{-1}, conc. 1.00 mg/mL, λ = 254 nm):

t_{major} = 29.7 min., t_{minor} = 23.7 min.

ee: 73%

(*S*)-2-[(*R*)-2-Nitro-1-(4-nitrophenyl)ethyl]cyclohexanone (39):[23]



Reaction of cyclohexanone (0.260 mL, 2.50 mmol) and 1-nitro-4-((*E*)-2-nitrovinyl)benzene (97.6 mg, 0.500 mmol) in the presence of catalyst **12** (20.6 mg, 0.100 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane: 30/70), 111 mg (76%) of **39** as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$):

δ: 8.19 (d, 2H, J = 9.0, Ar*H*), 7.39 (d, 2H, J = 9.0, Ar*H*), 4.98 (dd, 1H, J = 13.1, 4.5, CH_2NO$_2$), 4.71 (dd, 1H, J = 13.1, 4.4, CH_2NO$_2$), 3.92 (dt, 1H, J = 12.0, 4.5, ArC*H*), 2.74-2.69 (m, 1H, C*H*C(O)), 2.52-2.47 (m. 1H, CH_2C(O)), 2.45-2.34 (m. 1H, CH_2C(O)), 2.14-2.06 (m, 1H, CH_2), 1.85-1.82 (m, 1H, CH_2), 1.73-1.56 (m, 3H, CH_2), 1.33-1.20 (m, 1H, CH_2)

HPLC (Chiralpak AS-H):

(hexane/*i*-PrOH, 90/10, flow rate 1.0 0mL min^{-1}, conc. 1.00 mg/mL, λ = 254 nm):

t_{major} = 26.1 min., t_{minor} = 12.5 min.

ee: 89%

References

1 Vicario, J. L; Badia, D.; Carrillo, L. *Synthesis* **2007**, 2065.

2 (a) Komnenos, T. *Ann. Chem.* **1883**, *218*, 145. (b) Michael, A. *J. Prakt. Chem. (Leipzig)* **1887**, *35*, 349.

3 Wynberg, H.; Helder, R. *Tet. Lett.* **1975,** *16*, 4057.

4 Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007** *18*, 299.

5 Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123.

6 (a) Hajos, Z. G; Parrish, D.R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496. (c) Agami, C.; Platzer, N.; Sevestre, H. *Bull. Soc. Chim. Fr.* **1987**, *2*, 358.

7 List, B. *Synlett* **2001**, *11*, 1675.

8 (a) Koeller, K. M.; Wong, C. H. *Nature* **2001**, 409, 232. (b) Anwar, S.; Lee, P.-H.; Chou, T.-Y.; Chang, C.; Chen, K. *Tetrahedron* **2011,** *67*, 1171. (c) Tan, B.; Shi, Z.; Chua, P. S.; Zhong, G. *Org. Lett.* **2008**, *10*, 3425. (d) Wang, J.; Ma, A.; Ma, D. *Org. Lett.* **2008**, *10,* 5425. (e) Wen, L.; Shen, Q.; Lu, L. *Org. Lett.* **2010**, *12*, 4655.

9 Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Ngoc, T. V. *Drug Discov. Today* **2007**, 8.

10 Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F. *Synthesis* **2004**, 1509.

11 Betancort, J. M; Barbas III, C. F. *Org. Lett.* **2001**, *3*, 3737.

12 Cobb, A. J.; Longbottom, D. A.; Shaw, D. M.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84 .

13 Mitchell, C. E. T.; Cobb, A. J. A.; Ley. S. V. *Synlett* **2005**, 611.

14 Audrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Syn. Catal.* **2004**, *346*, 1147.

15 (a) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369. (b) Wang, W.; Wang, J.; Li, H. WO2006007586. (c) Wang, J.; Li, H., Lou, B.; Zu, L.; Guo, H.; Wang, W. *Chem. Eur. J.* **2006**, *12*, 4321. (d) Zu, L.; Want, J.; Wnag, W. *Org. Lett.* **2006**, *8*, 3077.

16 (a) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558. (b) Otsuki, H. JP2004300134. (c) Otsuki, H. JP2006028105.

17 Zhu, M. K.; Cun, L. F.; Mi, A. Q; Jiang, Y. Z.; Gong, L. Z. *Tetrahedron: Asymmetry* **2006**, *17*, 491.

18 (a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (b) Zu, L.; Li, H.; Wang, J.; Yu, X.; Wang, W. *Tetrahedron Lett.* **2006**, 47, 5131.

19 Terakado, D.; Takano, M.; Oriyama, T. *Chem. Lett.* **2005,** *34*, 962.

20 Xu, D. Q.; Wang, L. P.; Luo, S. P.; Wang, Y. F.; Zhang, S.; Xu, Z. Y. *Eur. J. Org. Chem.* **2008**, 1049.

21 Gruttadauria, M.; Giacalone, F.; Noto, R. *Chem. Soc. Rev.* **2008**, *37*, 1666.

22 Cobb, A .J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84.

23 Pansare, S. V.; Pandya, K., *J. Am. Chem. Soc.* **2006**, *128*, 9624.

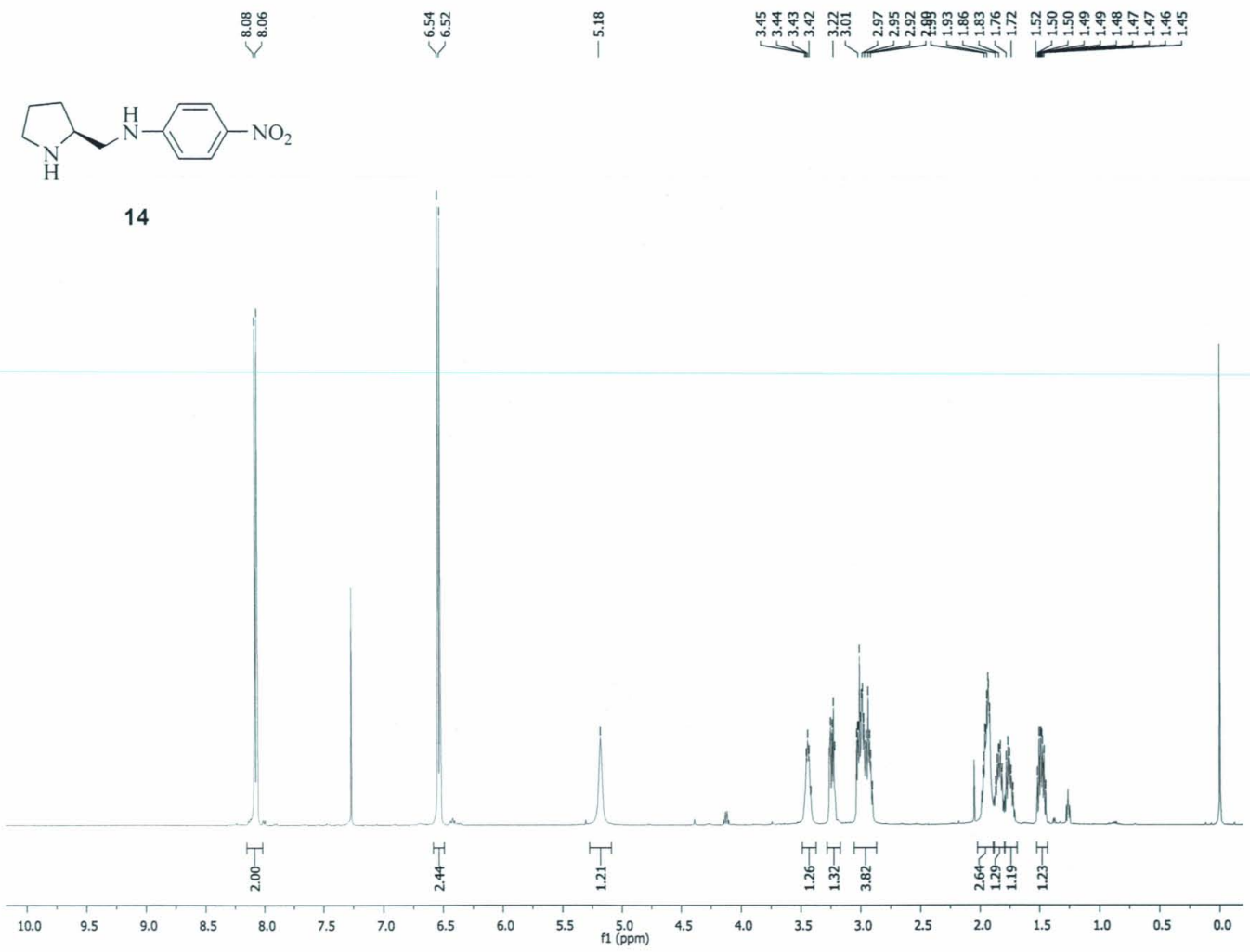
24 Calculated using the online pK_a calculator: *http://ibm1c2.chem.uga.edu/sparc*.

25 Asami, M., Ohno, H., Kobayashi, S., Mukaiyama, T. *Bull. of the Chem. Soc. Jpn.* **1978**, *51*, 1869.

26 (a) Beesley, R.M.; Ingold, C.K.; Thorpe, J.K. *J. Chem. Soc. Trans.* **1915**, *107*, 1080. (b) Kaneti, J.; Kirby, A.J.; Koedjikor, A.H.; Pojarlieff, I.G. *Org. Biomol. Chem.* **2004**, *2*, 1098.

Appendix

Spectra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1.86
1.83
1.76
1.72
1.52
1.50
1.50
1.49
1.49
1.48
1.47
1.47
1.46
1.45
NO2
14
2.00
2.44
1.21
1.26
1.32
3.82
2.64
1.29
1.19
1.23
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.0
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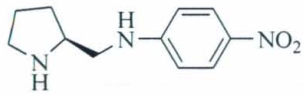
f1 (ppm)



14

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126.40
111.11
57.00
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180
170
160
150
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50
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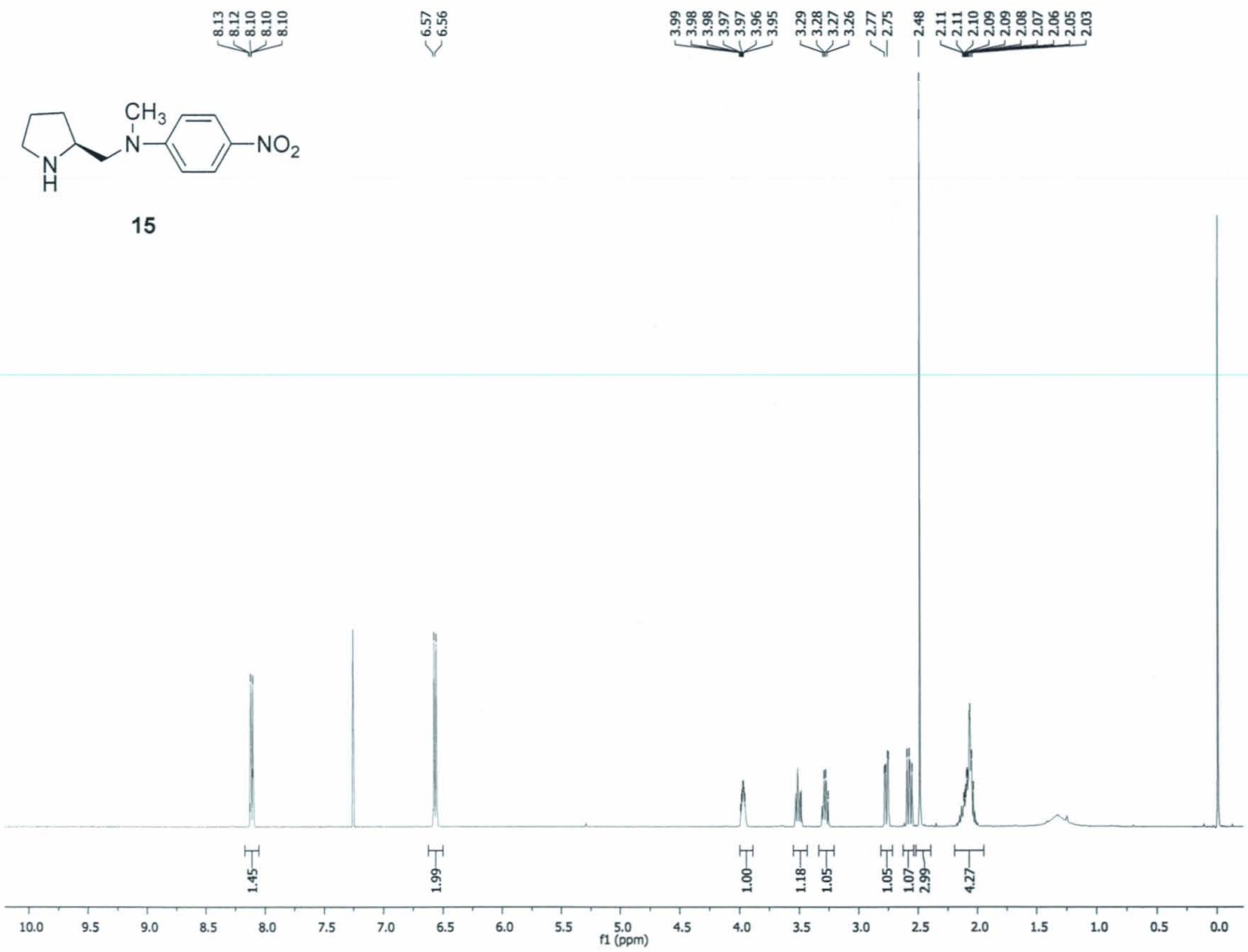
f1 (ppm)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2.10
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2.08
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2.06
2.05
2.03
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15
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1.00
1.18
1.05
1.05
1.07
2.99
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8.0
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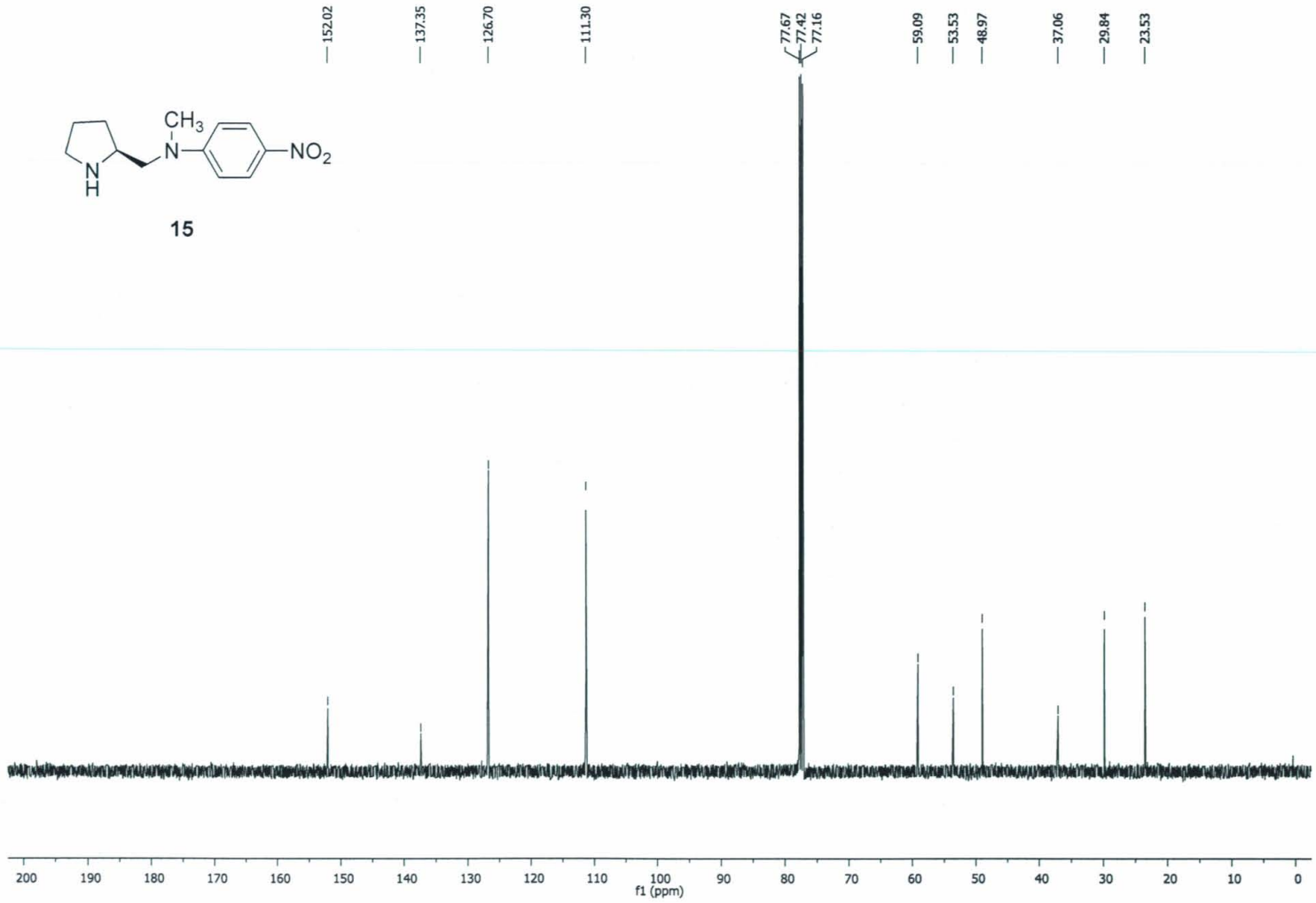
f1 (ppm)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CH3
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H
15
200
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10
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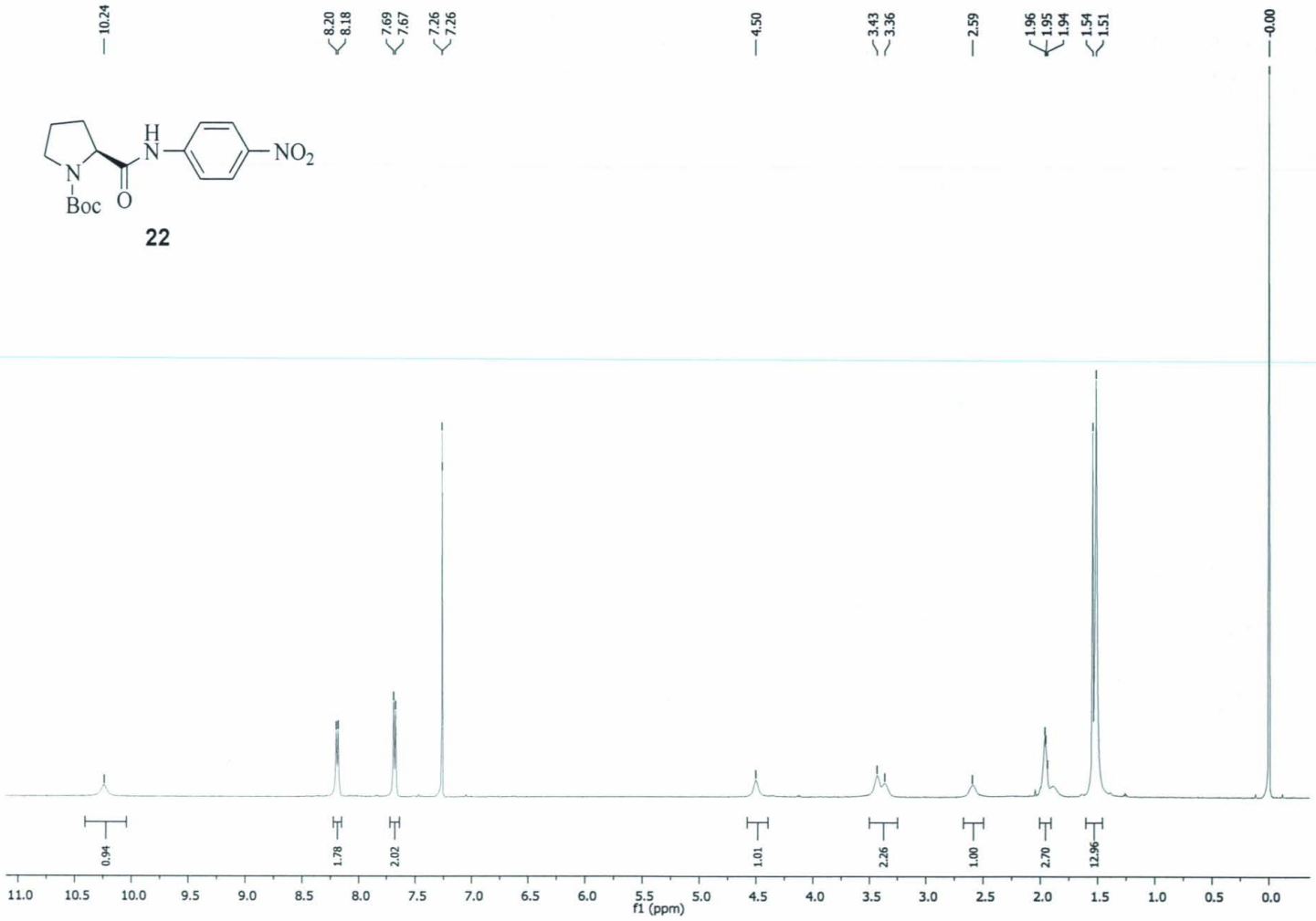
f1 (ppm)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9.5
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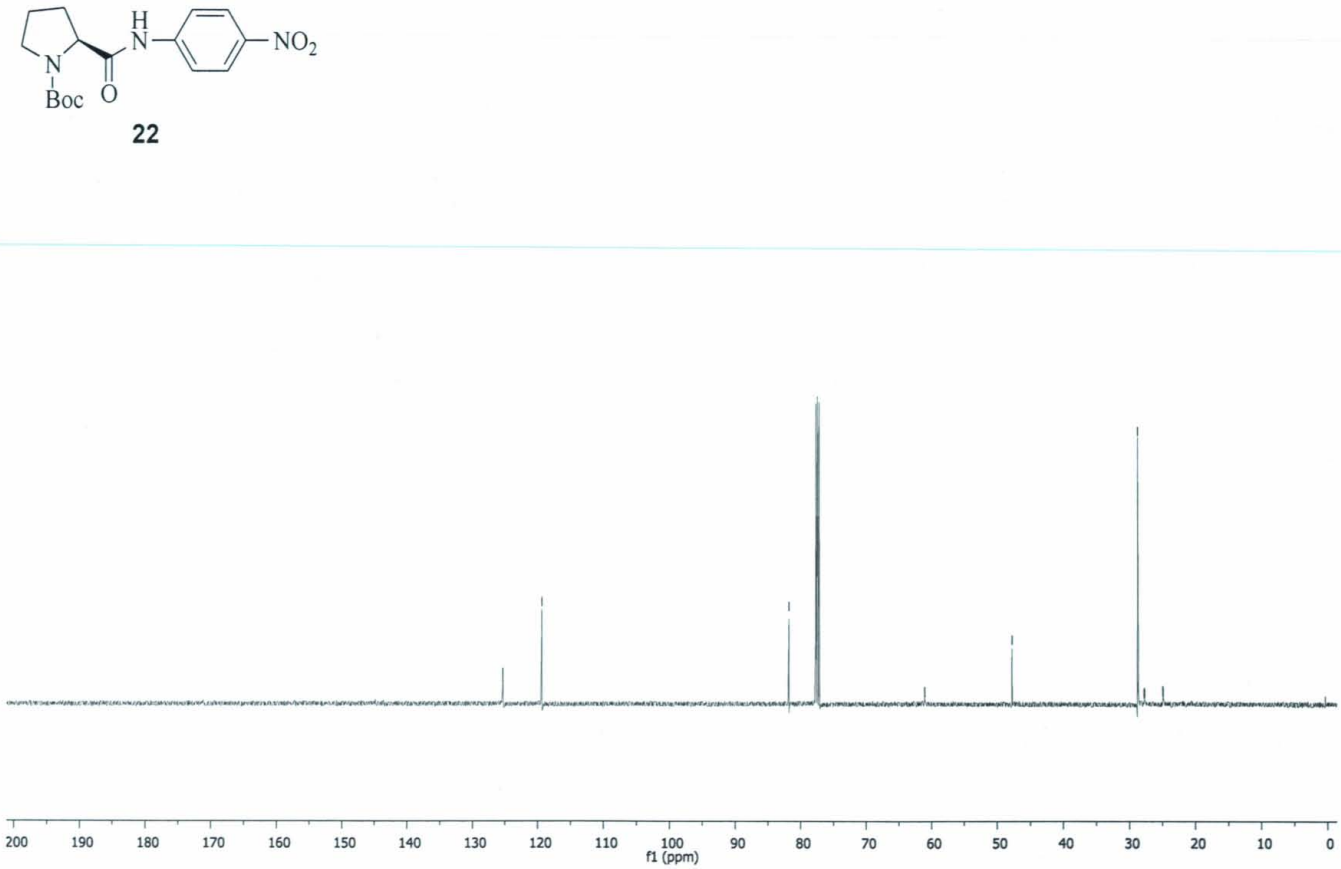
22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180
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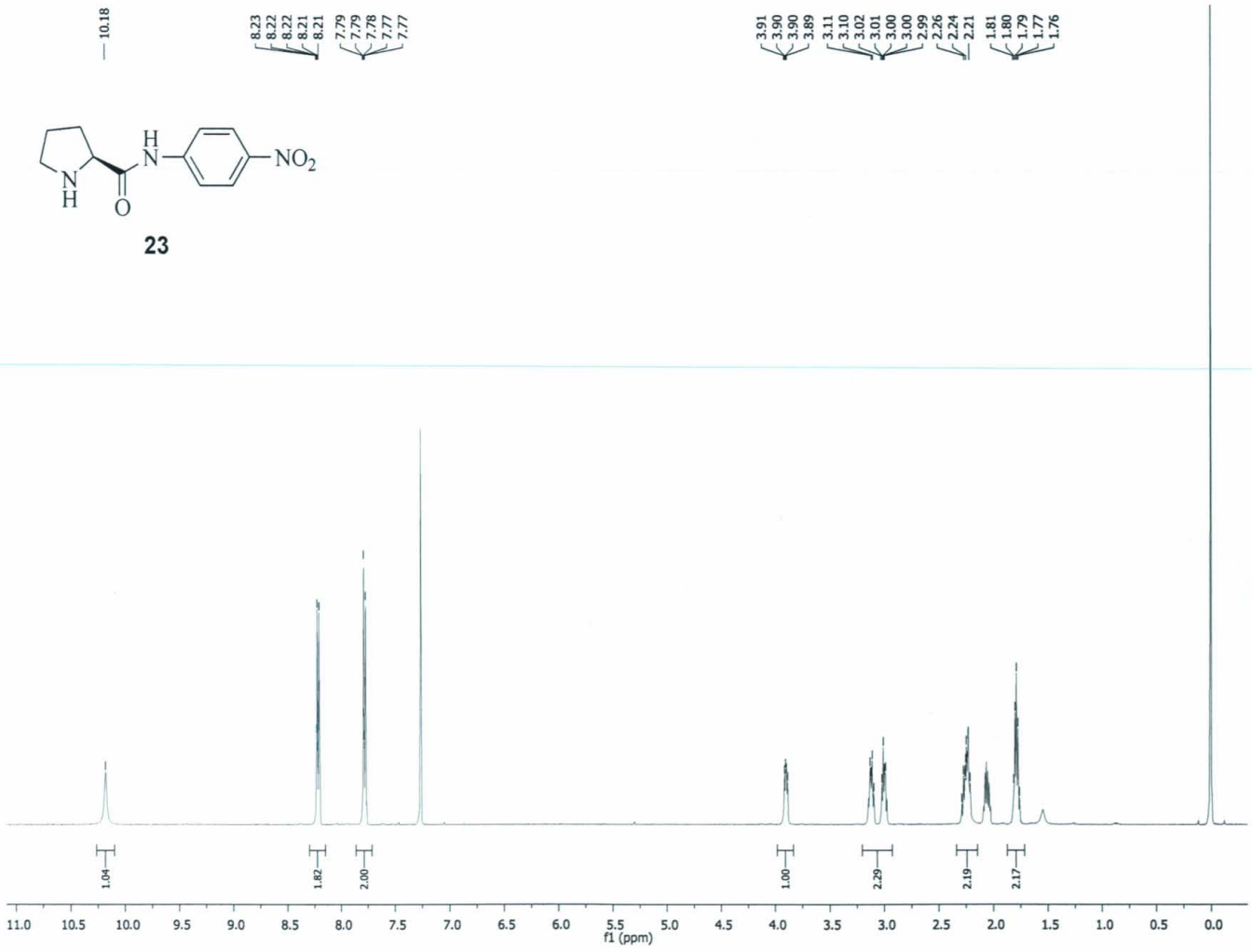
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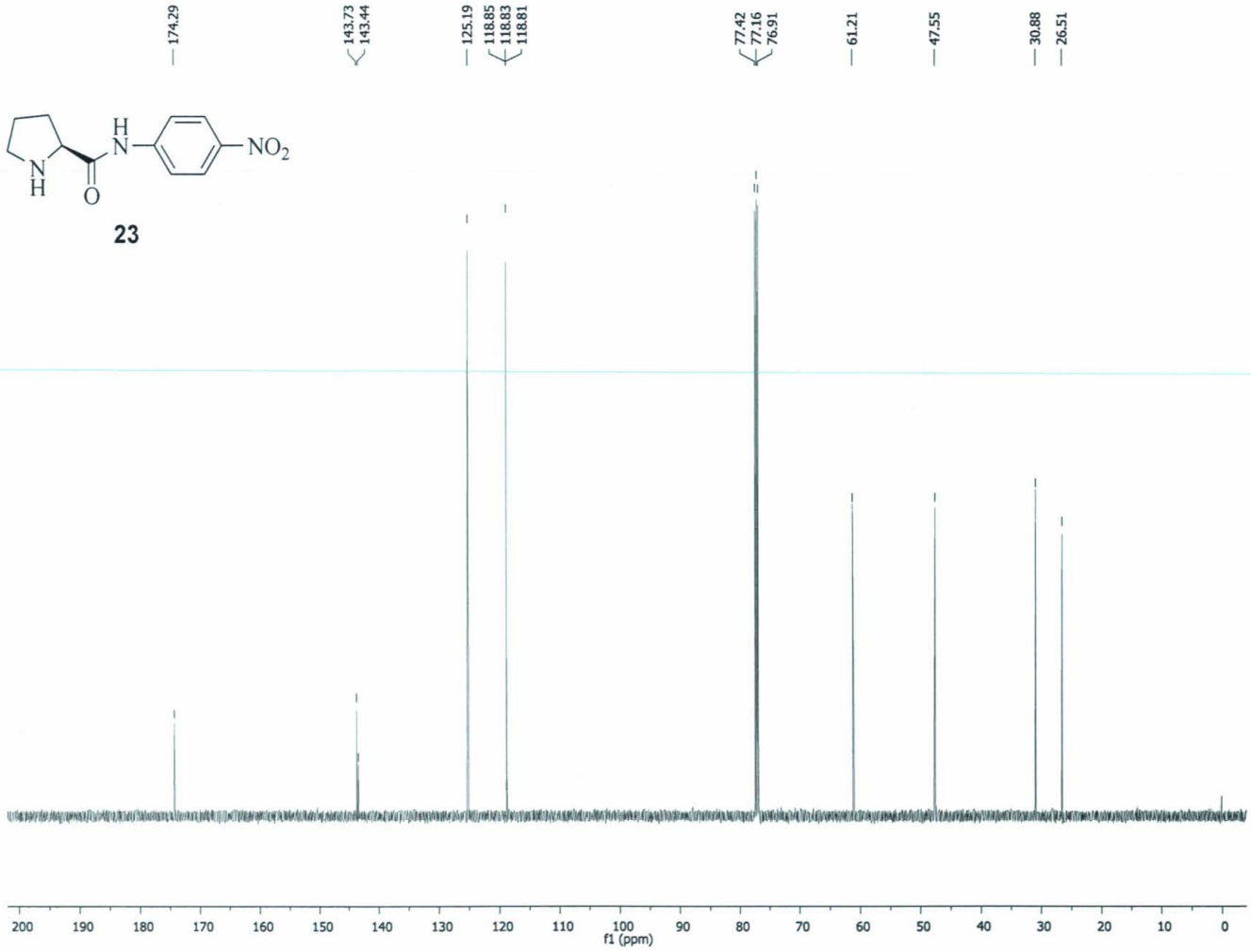
23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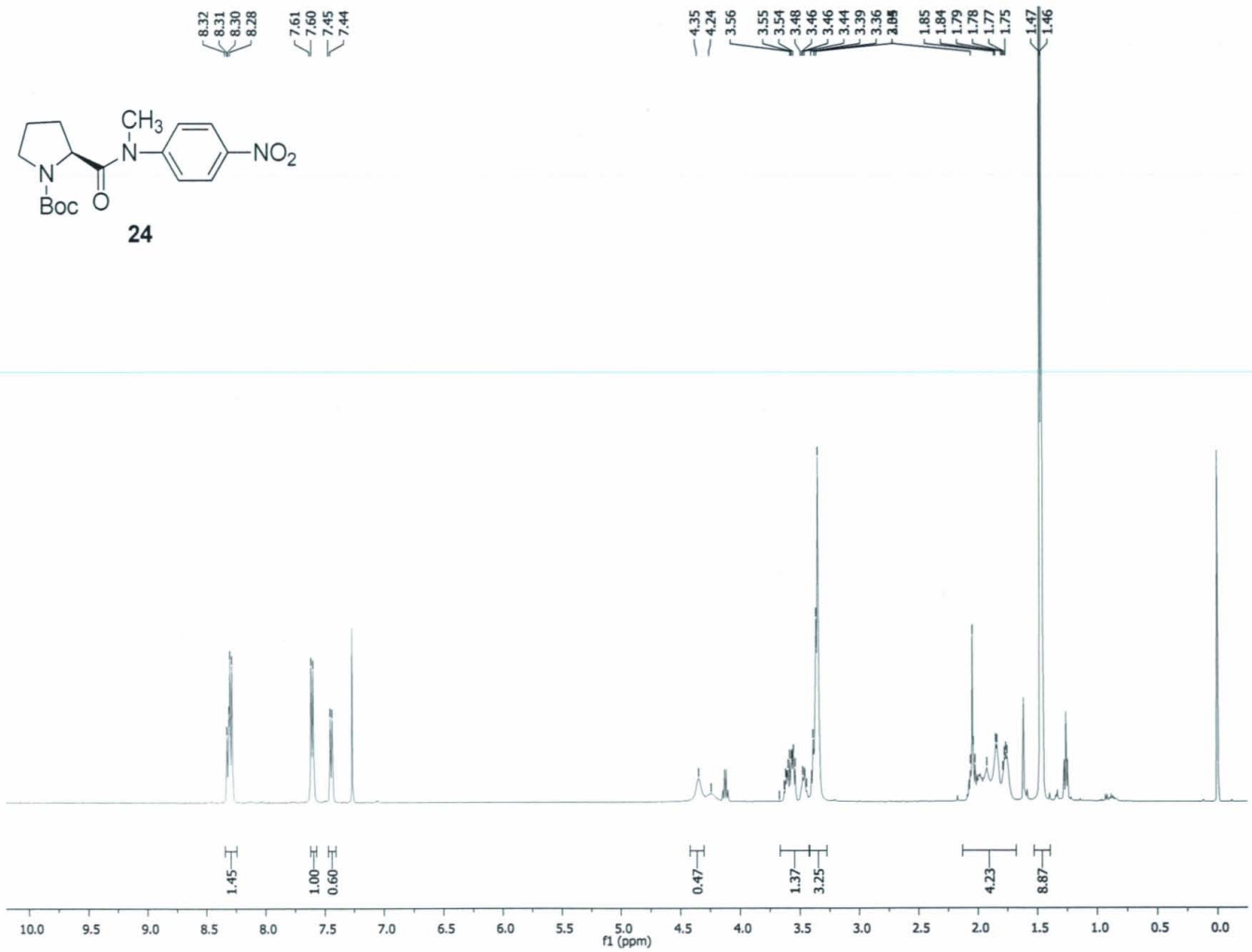
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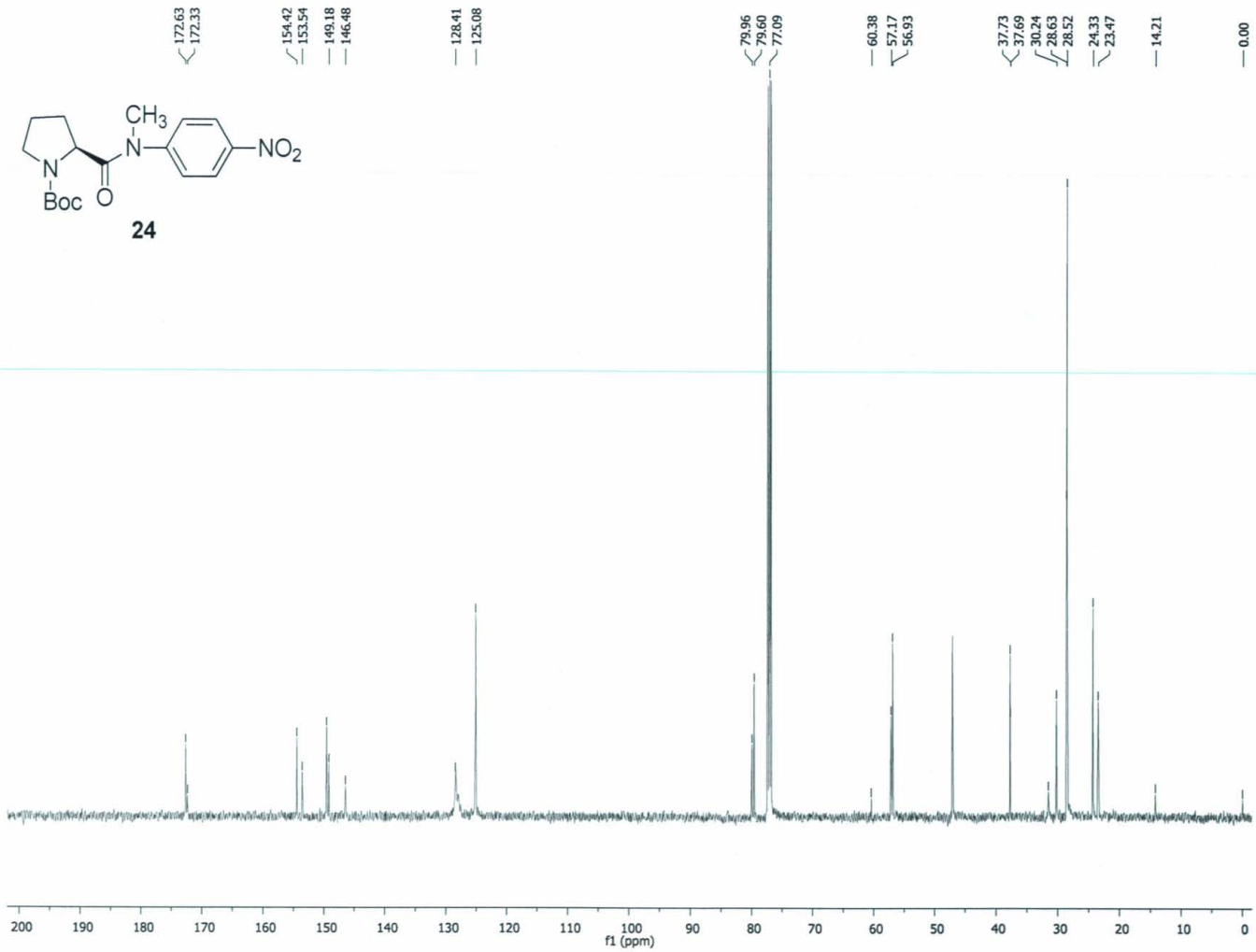
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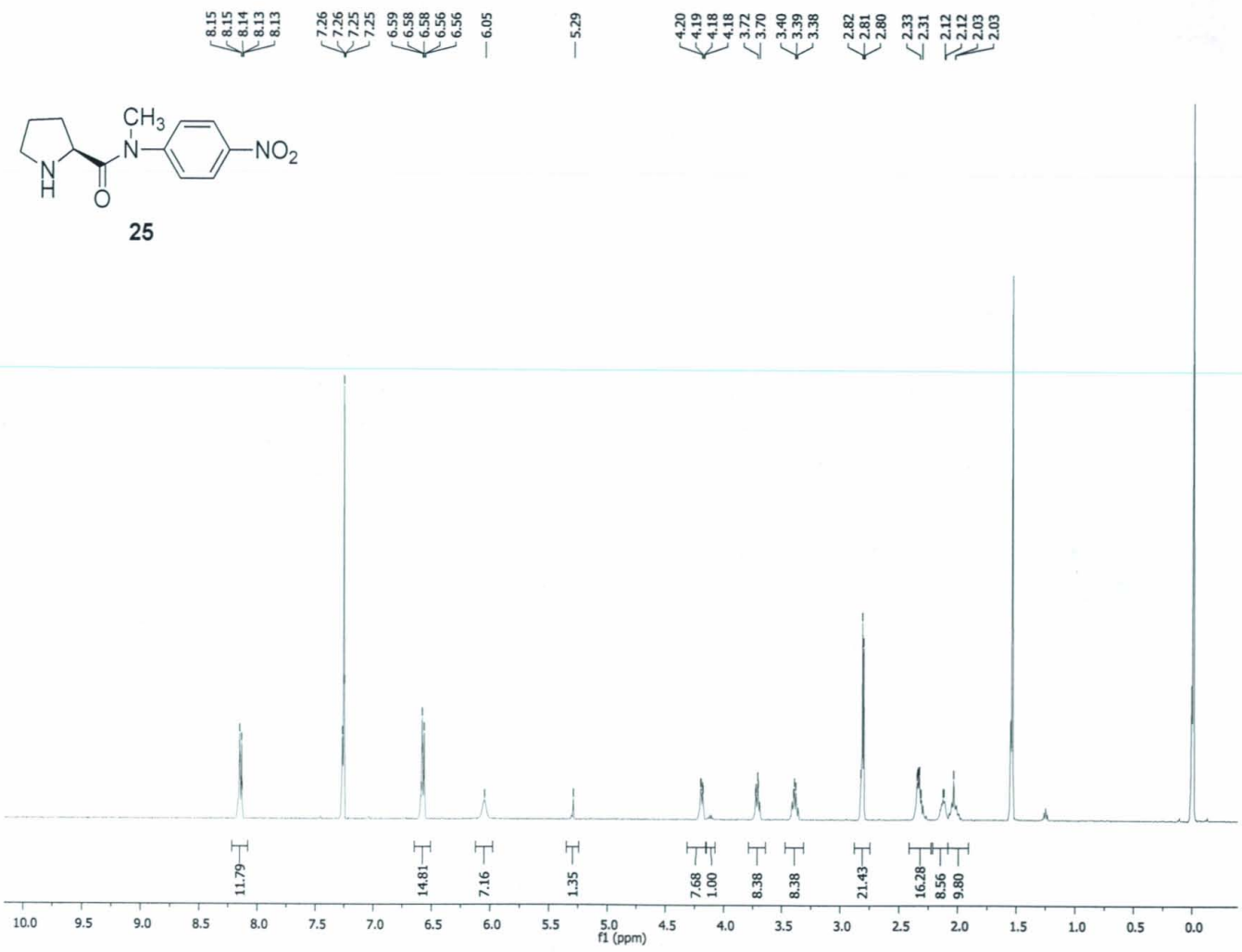
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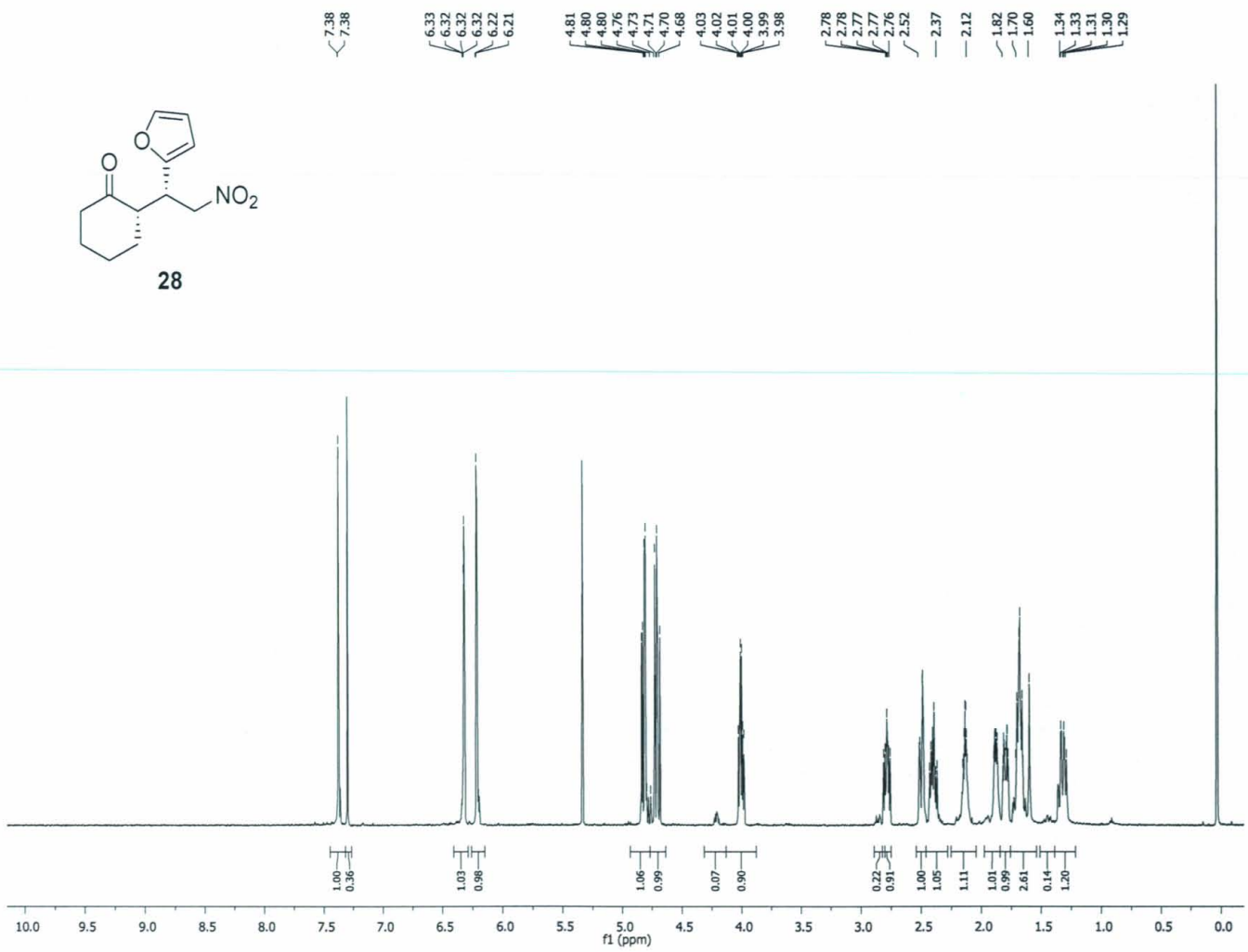
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0.07
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1.11
1.01
0.99
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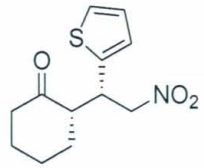
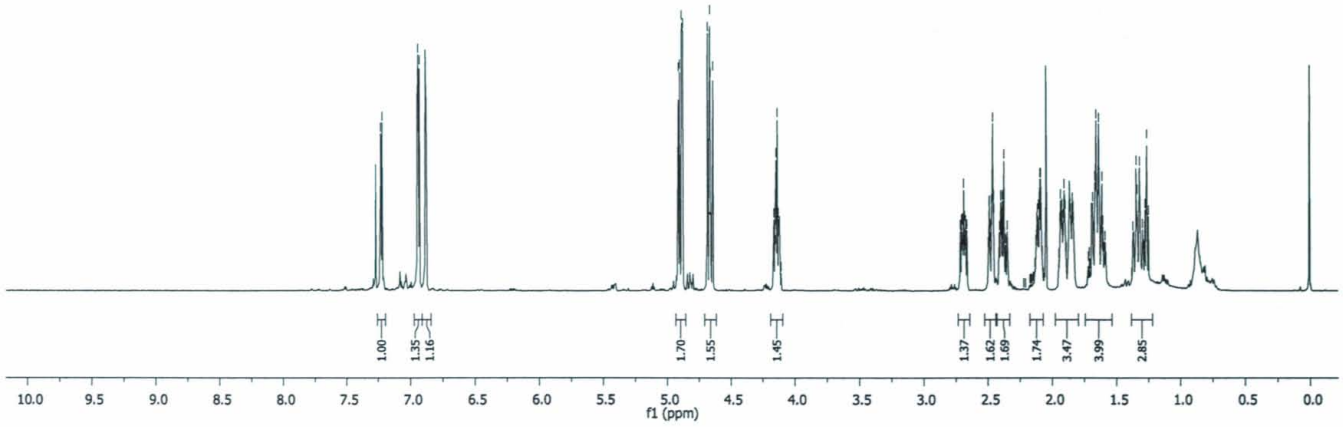

S
O
NO2

30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9.0
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8.0
7.5
7.0
6.5
6.0
5.5
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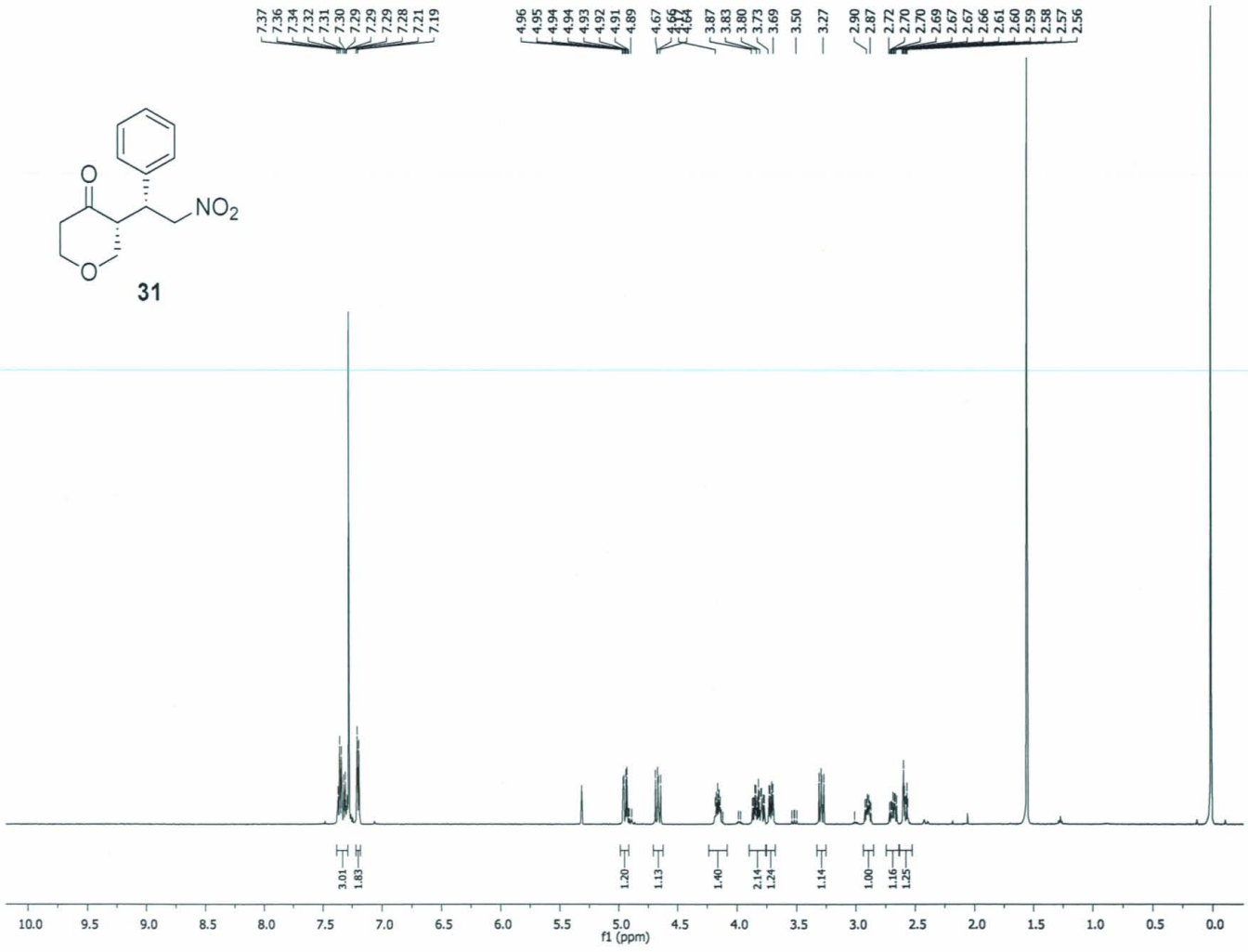
f1 (ppm)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4.95
4.94
4.94
4.93
4.92
4.91
4.89
4.67
4.64
3.87
3.83
3.80
3.73
3.69
3.50
3.27
2.90
2.87
2.72
2.70
2.70
2.69
2.67
2.67
2.66
2.61
2.60
2.59
2.58
2.57
2.56
O
NO2
O
31
3.01
1.83
1.20
1.13
1.40
2.14
1.24
1.14
1.00
1.16
1.25
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9.5
9.0
8.5
8.0
7.5
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6.5
6.0
5.5
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3.0
2.5
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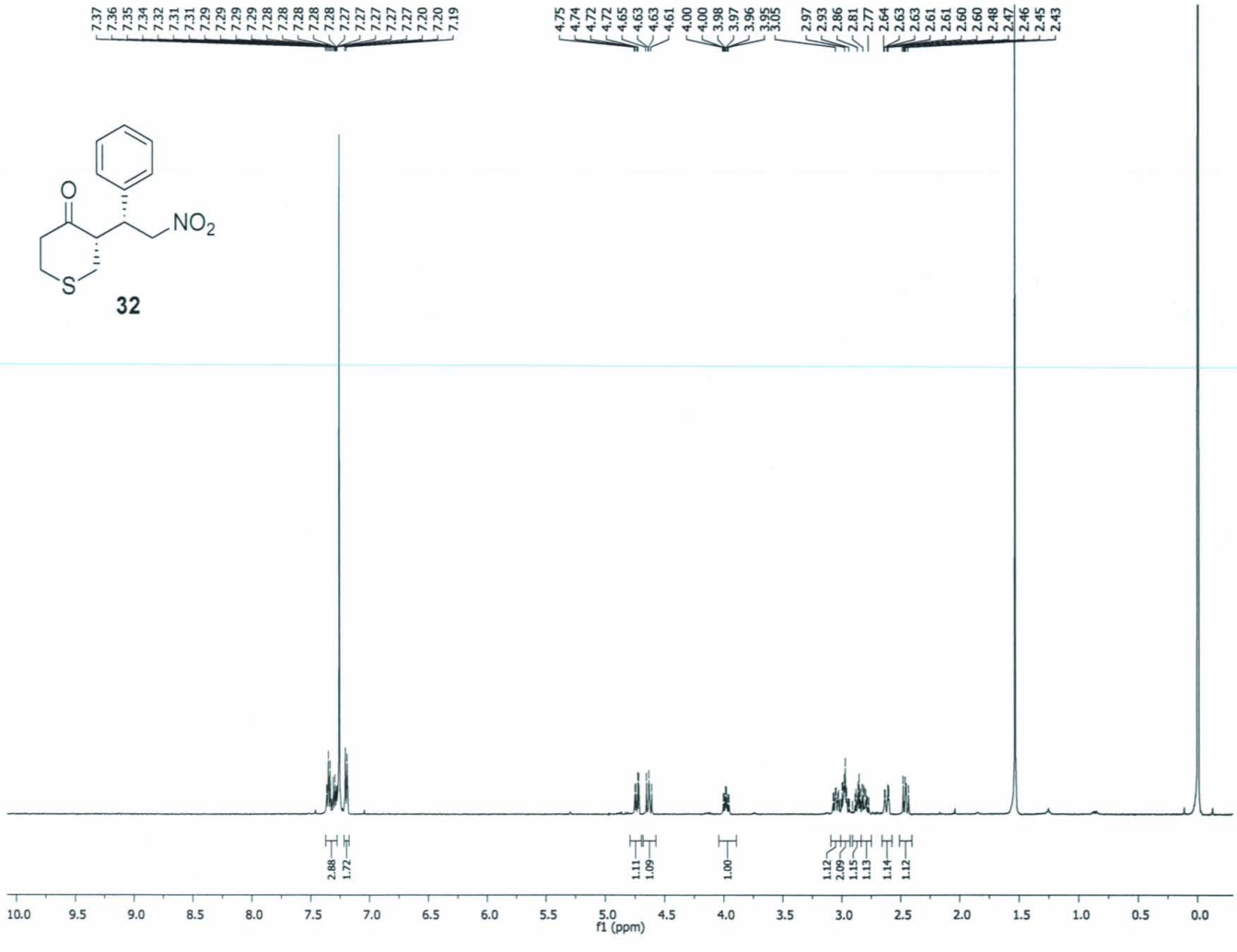
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7.28
7.28
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7.27
7.27
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7.20
7.19
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4.74
4.72
4.72
4.65
4.63
4.63
4.61
4.00
4.00
3.98
3.97
3.96
3.95
3.05
2.97
2.93
2.86
2.81
2.77
2.64
2.63
2.63
2.61
2.61
2.60
2.60
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2.47
2.46
2.45
2.43
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S
32
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1.09
1.00
1.12
2.09
1.15
1.13
1.14
1.12
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8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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1.0
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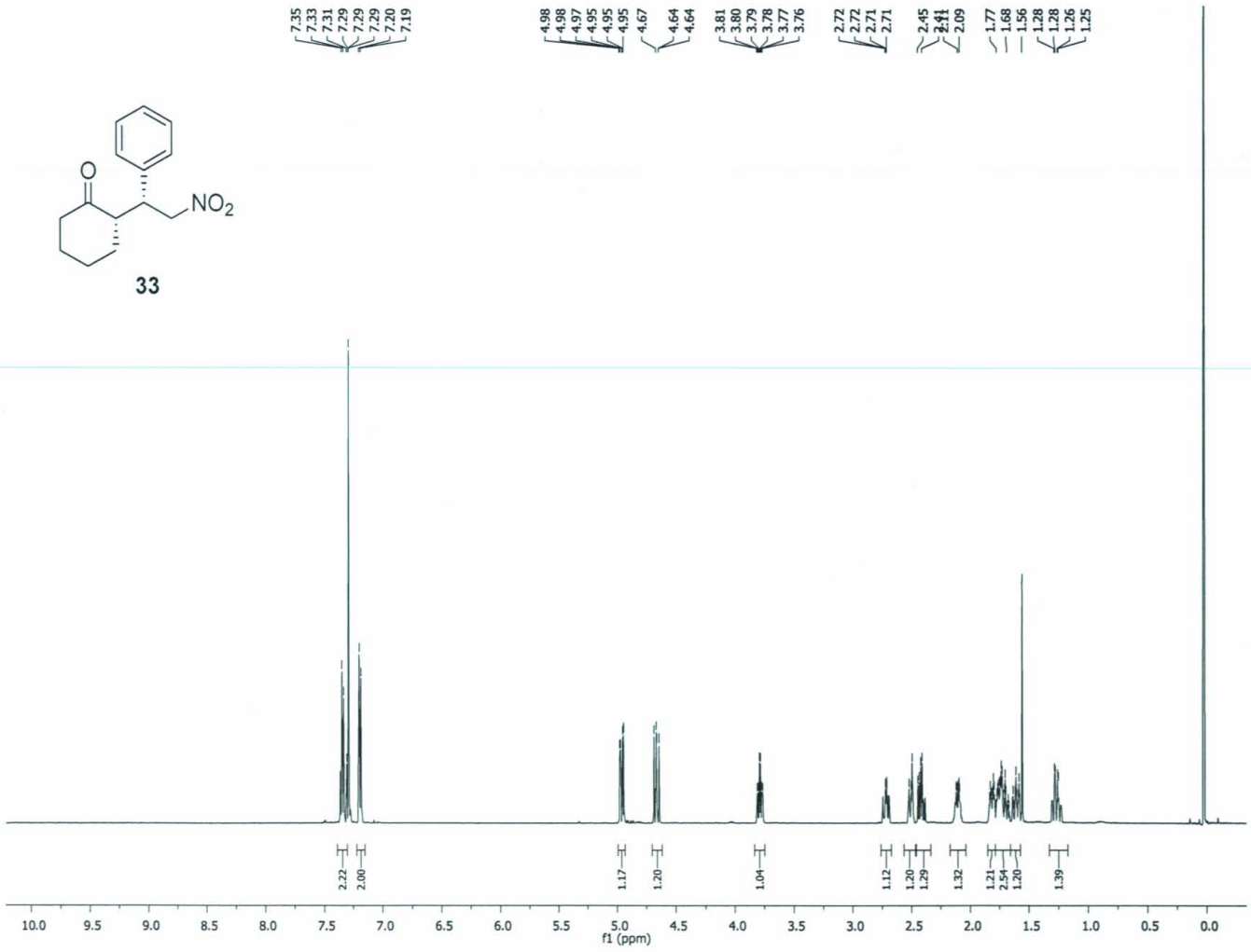
0.0
f1 (ppm)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7.19
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4.98
4.97
4.95
4.95
4.95
4.67
4.64
4.64
3.81
3.80
3.79
3.78
3.77
3.76
2.72
2.72
2.71
2.71
2.45
2.41
2.09
1.77
1.68
1.56
1.28
1.28
1.26
1.25
O
NO2
33
2.22
2.00
1.17
1.20
1.04
1.12
1.20
1.29
1.32
1.21
2.54
1.20
1.39
10.0
9.5
9.0
8.5
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6.5
6.0
5.5
5.0
4.5
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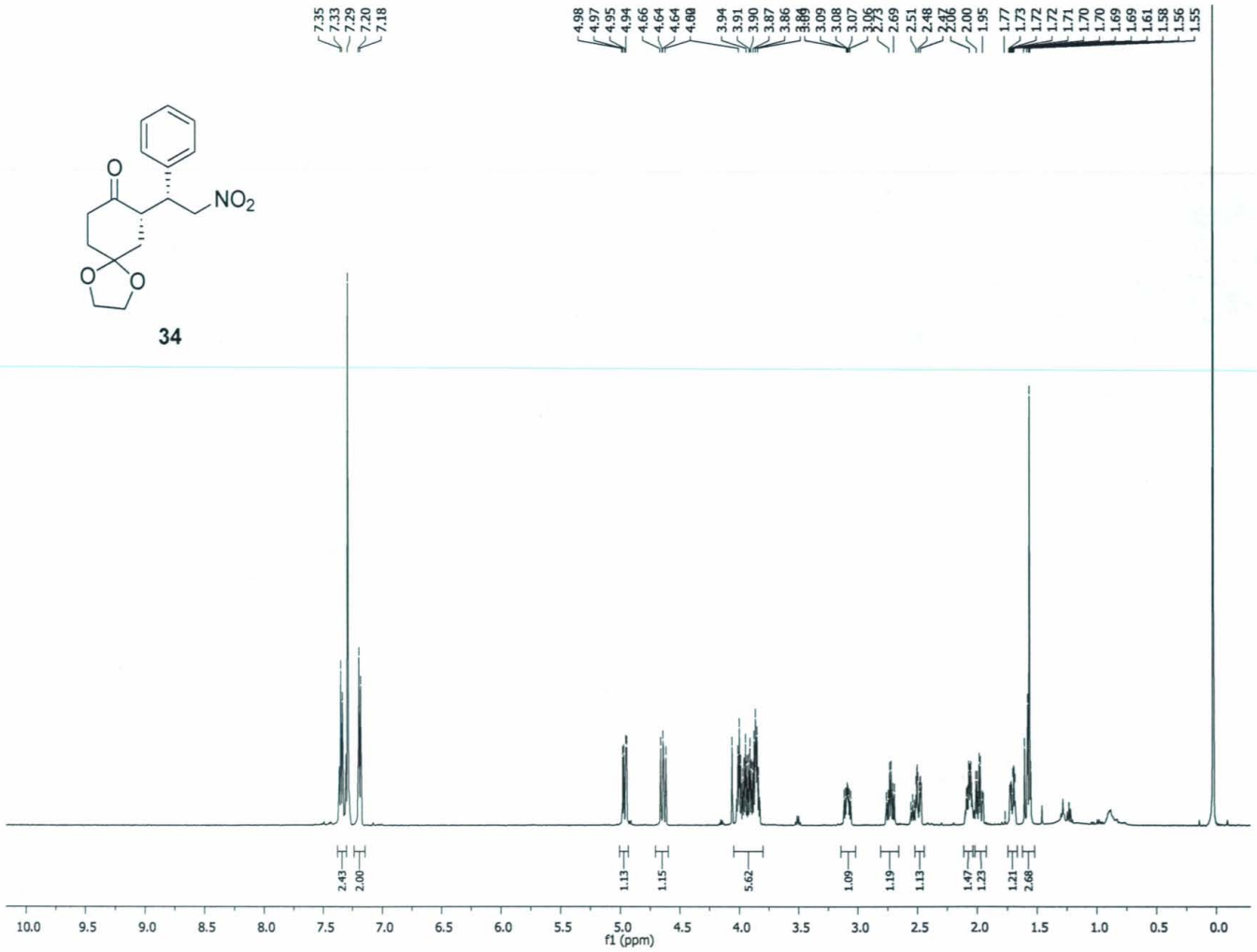
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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O
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7.18
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4.97
4.95
4.94
4.66
4.64
4.64
4.60
3.94
3.91
3.90
3.87
3.86
3.09
3.08
3.07
2.69
2.51
2.48
2.00
1.95
1.77
1.73
1.72
1.72
1.71
1.70
1.70
1.69
1.69
1.61
1.58
1.56
1.55
2.43
2.00
1.13
1.15
5.62
1.09
1.19
1.13
1.47
1.23
1.21
2.68
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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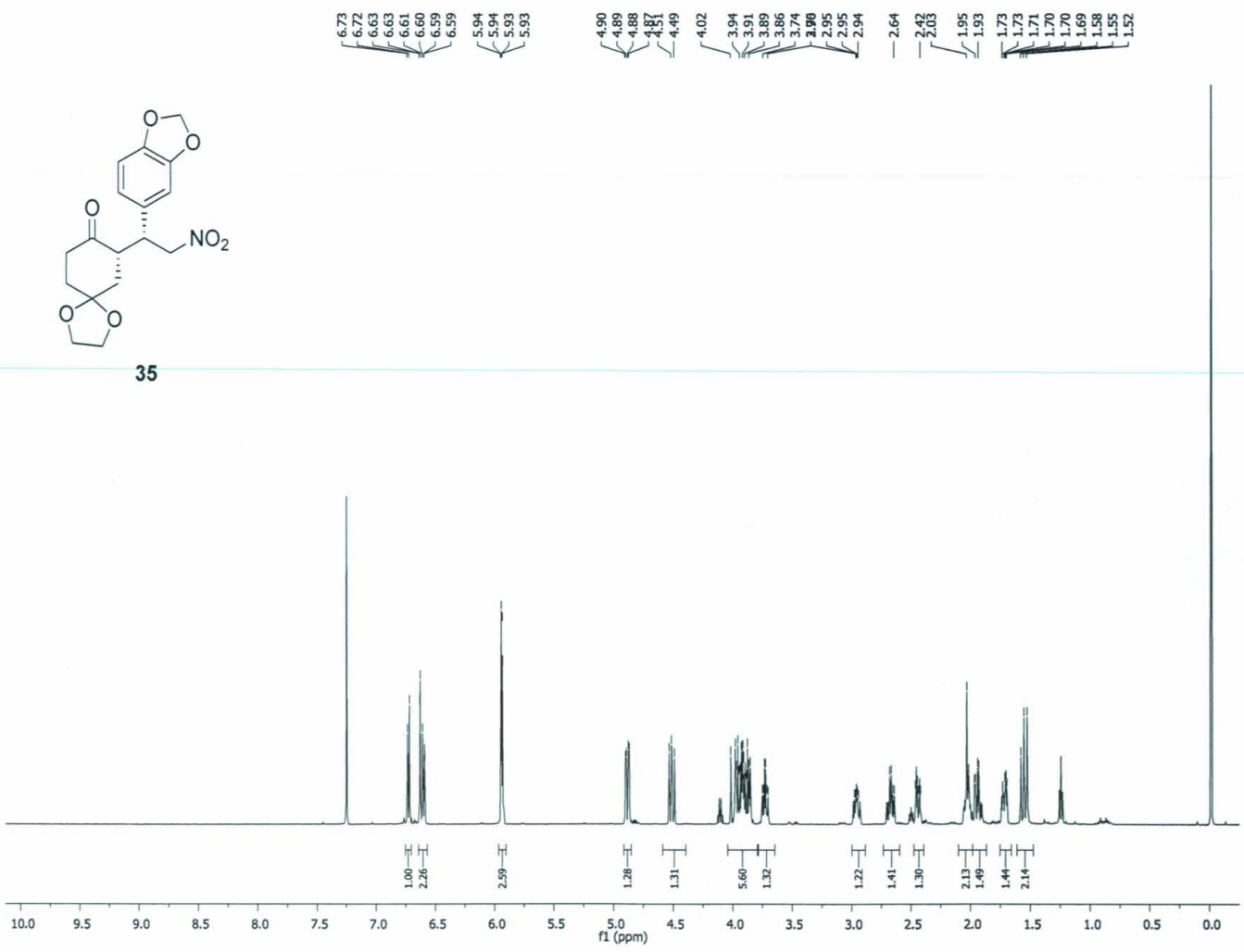
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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6.60
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6.59
5.94
5.94
5.93
5.93
4.90
4.89
4.88
4.87
4.51
4.49
4.02
3.94
3.91
3.89
3.86
3.74
2.95
2.95
2.94
2.64
2.42
2.03
1.95
1.93
1.73
1.73
1.71
1.70
1.70
1.69
1.58
1.55
1.52
O
O
O
O
O
NO2
35
1.00
2.26
2.59
1.28
1.31
5.60
1.32
1.22
1.41
1.30
2.13
1.49
1.44
2.14
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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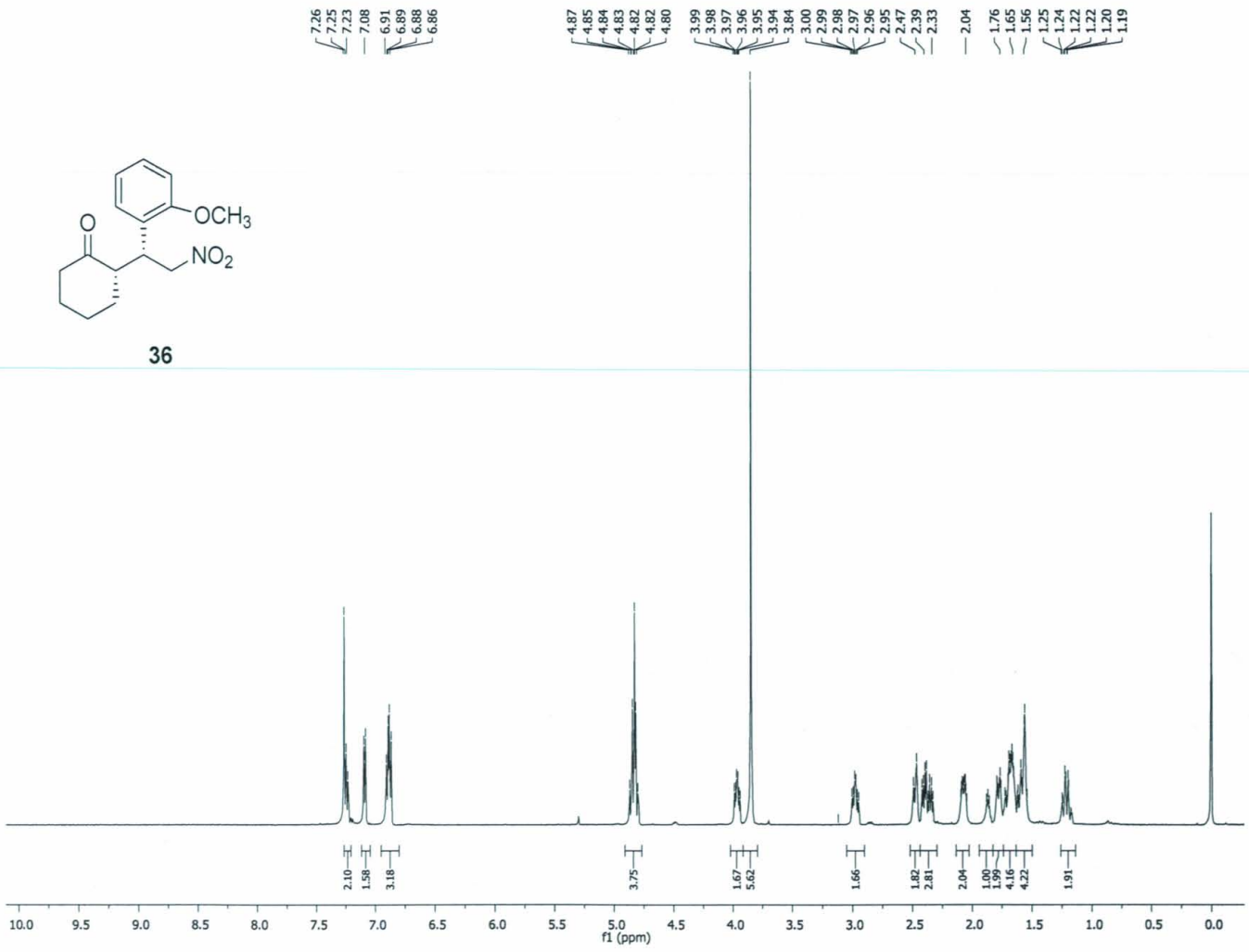
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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4.85
4.84
4.83
4.82
4.82
4.80
3.99
3.98
3.97
3.96
3.95
3.94
3.84
3.00
2.99
2.98
2.97
2.96
2.95
2.47
2.39
2.33
2.04
1.76
1.65
1.56
1.25
1.24
1.22
1.22
1.20
1.19
O
OCH3
NO2
36
2.10
1.58
3.18
3.75
1.67
5.62
1.66
1.82
2.81
2.04
1.00
1.99
4.16
4.22
1.91
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.5
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3.5
3.0
2.5
2.0
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1.0
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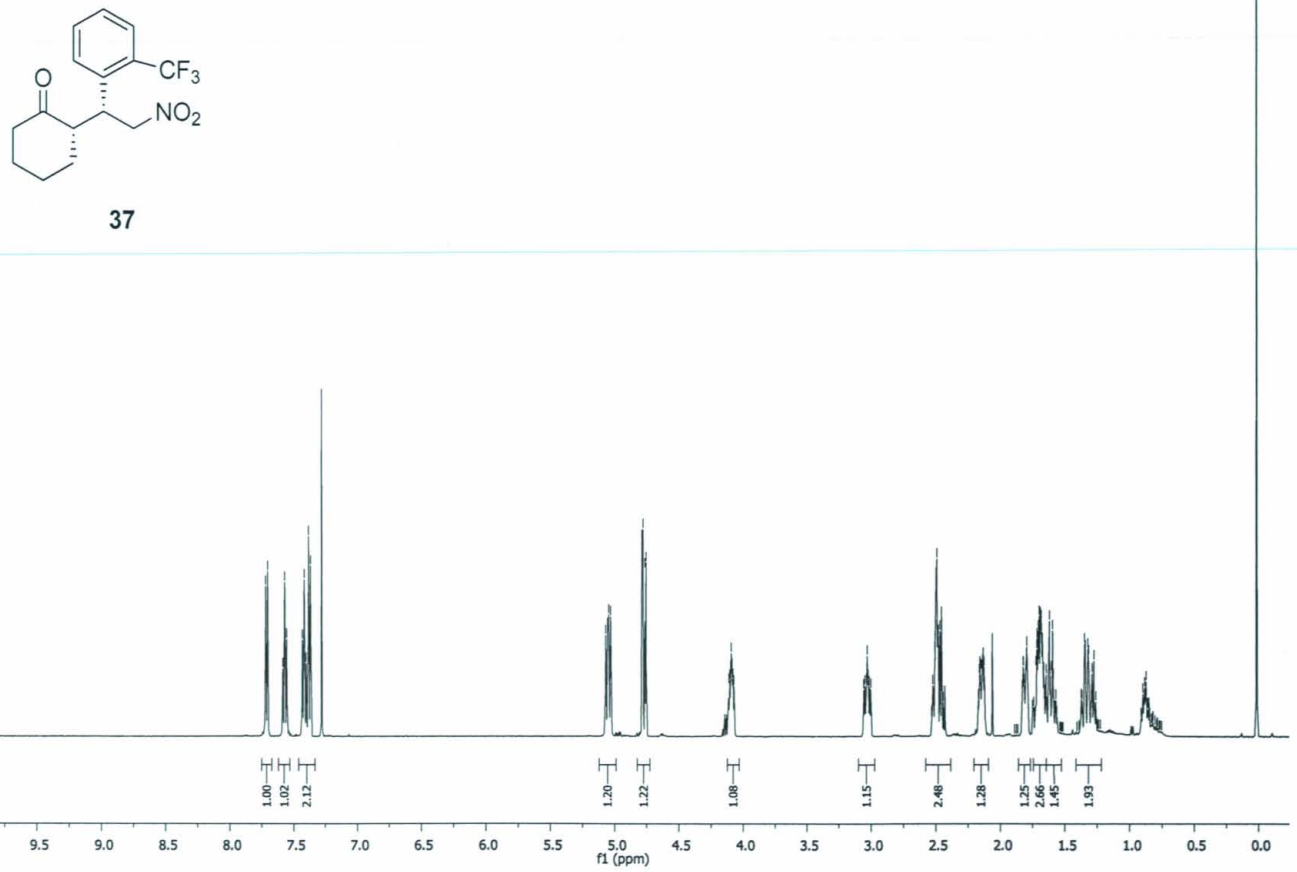
0.0
f1 (ppm)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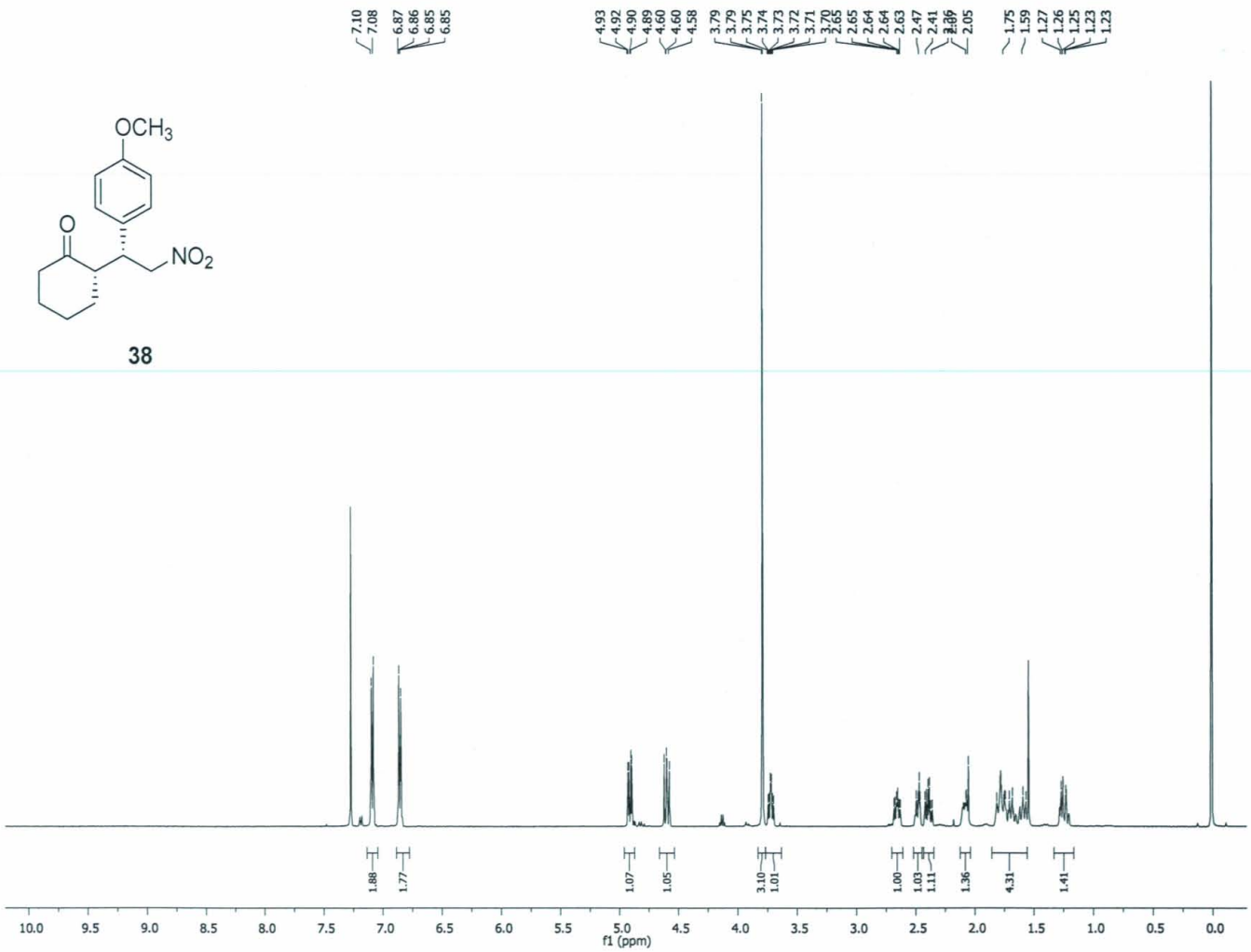
7.40
7.38
7.37
5.07
5.05
5.04
5.03
4.78
4.76
4.75
4.10
4.09
4.09
4.08
4.07
3.06
3.05
3.04
3.03
3.02
3.01
2.47
2.43
2.12
1.80
1.71
1.66
1.60
1.52
1.32
0.87
0.86
0.85
0.83
0.82
0.80
0.79
0.77
0.76
O
CF3
NO2
37
1.00
1.02
2.12
1.20
1.22
1.08
1.15
2.48
1.28
1.25
2.66
1.45
1.93
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OCH3
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38
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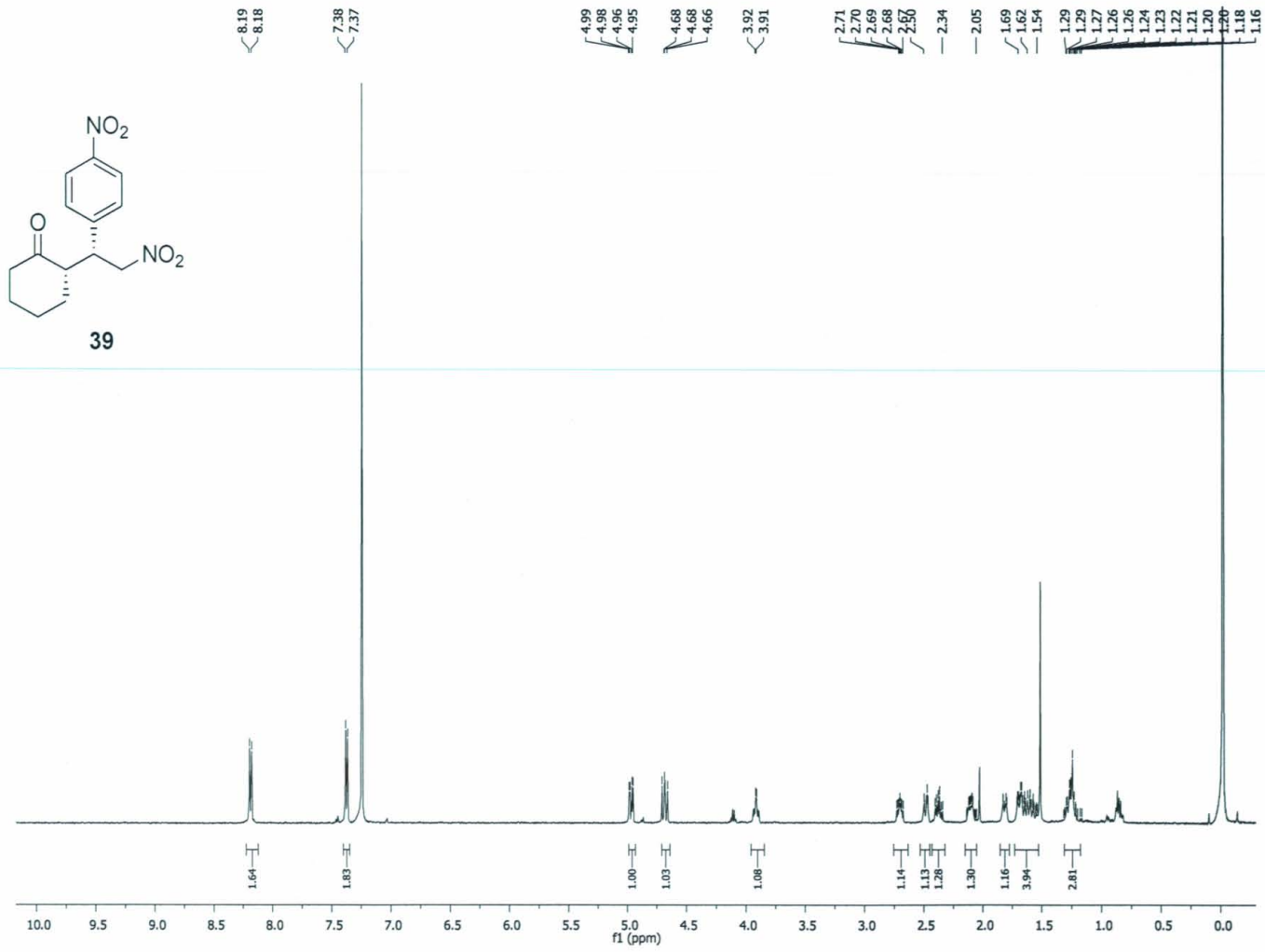
6.87
6.86
6.85
6.85
4.93
4.92
4.90
4.89
4.60
4.60
4.58
3.79
3.79
3.75
3.74
3.73
3.72
3.71
3.70
2.65
2.65
2.64
2.64
2.63
2.47
2.41
2.05
1.75
1.59
1.27
1.26
1.25
1.23
1.23
1.88
1.77
1.07
1.05
3.10
1.01
1.00
1.03
1.11
1.36
4.31
1.41
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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NO2
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4.99
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4.96
4.95
4.68
4.68
4.66
3.92
3.91
2.71
2.70
2.69
2.68
2.34
2.05
1.69
1.62
1.54
1.29
1.29
1.27
1.26
1.26
1.24
1.23
1.22
1.21
1.20
1.18
1.16
1.64
1.83
1.00
1.03
1.08
1.14
1.13
1.28
1.30
1.16
3.94
2.81
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9.0
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8.0
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7.0
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6.0
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5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)