THE DEVOLOPMENT AND USE OF CHIRAL 4-DIMETHYLAMINOPYRIDINE-N-OXIDE AS AN ORGANOCATALYST

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Title

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

MASTER OF SCIENCE

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ABSTRACT

Organocatalysis is a field that has bloomed over the last decades. With the field's promise of being able to mimic nature and afford products in a synergistic manner to traditional Lewis acid catalysis, several interesting discoveries have been made. Owing to the vastness of the field as it exists today, this document will focus on two main aspects; cinchona alkaloid (and derivatives) as used in common carbon-carbon bond forming reactions and kinetic resolution via 4-dimethyl aminopyridine-N-oxide derivative driven acylation.

Kinetic resolution via organocatalysis has the potential to react one enantiomer of a racemic mixture without affecting the other. The highlight of this screening was an s factor of 9 which was produced using optimized conditions using a catalyst designated DMAPO-IV. There remains much to do in improving the system and elucidating the scope of this catalytic system this report details the efforts made thus far.

ACKNOWLEDGMENTS

I, Jesse J. Joyce, would like to thank all of the people who facilitated this body of work and who pushed me to become a better version of myself. To the support staff of the chemistry department, thank you so much for helping me make sure that my paperwork was in order and facilitating my efforts to prepare for each semester. To my classroom instructors, I would like to say that I appreciate the time and effort invested in detailing ideas I had not previously come across and explaining them. To my former students, thank you for pushing me to find different ways of relating to the class material so that I could explain it more fully. To my lab mates, thank you for challenging me to understand more. To my committee, thank you for your guidance and support. Finally, to Professor Sibi, thank you very much for your time, patience, guidance, support and facilitating my further education.

DEDICATION

Without the care, love and support of my friends and family I would never have been able to write this document.

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LIST OF ABBREVIATIONS

Ph .....Phenyl

Bn .....Benzyl

Bz.....Benzoyl

DMF .....Dimethylformamide

THF .....Tetrahydrofuran

Boc .....tert-Butyloxycarbonyl

EtOH.....Ethanol

MeOH.....Methanol

iPrOH 2-Propanol

TEA .....Triethyl amine

DMAP .....Dimethylaminopyridine

Me.....Methyl

EtOAc .....Ethyl acetate

t-Bu.....*tert*-butyl

HPNP .....2-hydroxypropyl-*p*-nitrophenyl phosphate

Et.....Ethyl

Me.....Methyl

%ee.....Percent enantiomeric excess

c .....Conversion quotient

s factor.....Selectivity factor

SM .....Starting material

P.....Product

dr .....diastereomeric ratio

Ms.....Methanesulfonyl

RNA.....Ribonucleic acid

UV.....Ultra-violet

Vis .....Visible light

k_{obs} .....Observed reaction rate

k_{bg}.....Background reaction rate

KR.....Kinetic resolution

CHAPTER 1: USE OF NUCLEOPHILIC ORGANOCATALYSTS

There is a long and storied tradition of using nucleophilic catalysts in synthetic chemistry.[1-3] The key step of activating a substrate in solution via nucleophilic addition renders an even more reactive intermediate that can then be exploited to form the desired bond. This is a vast topic covering many aspects of chemistry; organic and inorganic synthesis, computational studies, industrial applications and many more besides. In this forward the emphasis will be primarily upon organic molecules that are put to the use as nucleophilic catalysts.

To begin this discussion a review of the use of 4-dimethylaminopyridine would be especially helpful, owing to being a clear representation of this methodology as well as having a direct relation to work that will be described in further pages. Steglich et al.[4] deduced that compared to the parent compound pyridine, the addition of a dimethylamine substituent to the 4 position could dramatically increase the efficacy of pyridine as a nucleophilic catalyst. The same research group[5] would then go on to apply this knowledge to the end of facilitating esterification of carboxylic acids.

From the studies above, several concepts become clear about this process in general. The first concept that is elucidated is that the degree of nucleophilicity, as can be predicted by the availability and ease of donating electrons from the catalyst to other molecules, is of high importance. The previous concept then makes sense in that it is exactly the degree of nucleophilicity that determines how easily the catalyst can activate the intermediate agent. Once the intermediate agent has been activated by the addition of the nucleophilic catalyst, it must also be that the catalyst is stable enough to act as a leaving group as well. This duel nature then outlines the needs that are required to be met to produce a meaningful catalytic system. Finally, as with all catalysts, having a system that is stable to the conditions it is being exposed to is a highly desirable trait as it vastly

increases the number of catalytic turnovers possible in the system. After the necessary components outlined previously the nucleophilic catalytic systems then follow the general needs for any given catalytic system; low cost of catalyst production, less hazardous conditions, ease of isolating catalysts from reaction conditions (where catalyst recovery is possible and economically viable) and low catalyst loading.

Where organic and organometallic catalysts typically shine bright is their use in affording better stereochemical control of the products produced.[6-9] There are many means of achieving this control; asymmetric synthesis, kinetic resolution, dynamic kinetic resolution and chiral resolution to name a few. The addition of organic molecules to otherwise metallic-centered catalytic systems gives rise to the ability to create new stereoselective reactions. A prime example of this idea can be found in the seminal work performed by the Noyori group[10] that led to innovation with regards to stereoselective hydrogenation. The reason that organic molecules are added is owing to the fact that stereochemistry is vastly more likely to be present in organic systems than in inorganic.

From this brief introduction of the theory of nucleophilic organocatalysis will be presented further. Initially a summary of cinchona alkaloids as used in various organic chemical processes will be examined. Following the summary of available knowledge on those aspects of cinchona alkaloids the original research undertaken will then be presented in utilizing 4-dimethylaminopyridine-N-oxide as part of a template-mediated organic catalyst.

CHAPTER 2: CINCHONA ALKALOIDS AS USED IN SMALL MOLECULE CATALYSIS

2.1. Introduction:

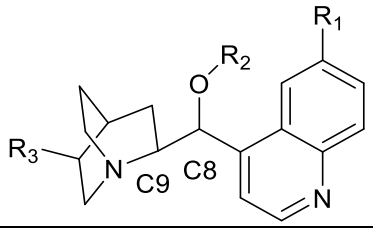
Cinchona alkaloids have been studied and used for centuries.[11] Their impact on medicine has been of interest since before their isolation in the early 1800's[12] and they continue to play an important role as part of the medical community's battle against malaria.[13, 14] As important as they have been in medicine it is their use in organic chemistry, especially in the role of organic catalysis, that will be investigated in this review.

Organocatalysis has emerged as a powerful tool in organic chemistry.[15] Organocatalysts can catalyze reactions through the introduction of sub-stoichiometric amounts of an organic additive. Of interest is the production of enantio-enriched products using chiral organocatalysts. Typically, this is achieved by incorporating natural chiral building blocks, like amino acids, but not exclusively. Other natural products such as sugars, proteins, and metabolites have also seen utility as precursors for organocatalysts.

There are many features that make cinchona alkaloids perhaps uniquely useful in the realm of small molecule catalysis. The naturally occurring and readily available cinchona alkaloids provide access to a variety of catalysts, the principle four of this class are defined in Table 1. One of the most powerful consequences of this variation is the pseudoenantiomeric relationship of the alkaloids where the stereochemistry of the secondary alcohol is inverted, holding all other atomic configurations identical. The benefit of the pseudoenantiomer pairings is the ability to select for the desired stereochemical product by simply switching to the other alkaloid in the pairing. This can be observed in many cases, but perhaps most concretely in the Sharpless diol formation reaction. The

key reagent leading to different stereochemical outcomes in this reaction is the cinchona alkaloid derivative used in the AD-mix.[8]

Table 1. Definition of abbreviations used



Entry	Name	Abbreviation	C8	C9	R^1	R^2	R^3
1	Cinchonidine	CD	S	R	H	H	C_2H_3
2	Cinchonine	CN	R	S	H	H	C_2H_3
3	Quinine	QN	S	R	OCH_3	H	C_2H_3
4	Quinidine	QD	R	S	OCH_3	H	C_2H_3

Cinchona alkaloids, and chiral bases like them, are useful owing to the highly directional effect of the fixed tertiary nitrogen atom (the quinuclidine nitrogen). A tertiary amine, especially one locked in a tricyclic structure, is forced to expose its lone pair of electrons in a fixed area of space. This locking of electron density then leads to the ease with which it can be donated to another species. This causes the nitrogen-containing nucleophilic catalyst to become a more focused nucleophile while ensuring that the elimination of catalyst is also still possible.

There are a variety of ways that cinchona alkaloids have been modified to enhance and/or change their reactivities. By adding an additional alkyl substituent to the tertiary amine it is possible to create a quaternary amine that can act as a phase-transfer catalyst[16] or otherwise better dissolve in polar solvent. Alkylation of the secondary alcohol center can lead to a more tightly ordered catalytic pocket around the tertiary amine.[17]

Though cinchona alkaloids have a long history of use,[18] it has expanded considerably since the pioneering work of Wynberg[19] in the mid-1970's. There are numerous examples of chiral base catalysts so what is particularly interesting is the degree to which the cinchona alkaloid can be

utilized in various ways.[20] Of particular interest to this review will be the use of cinchona alkaloids in Michael reactions,[21] Henry reactions,[22] Mannich reactions[23] and kinetic resolutions.[24]

The Michael reaction remains as one of the most used reactions[25] and a plethora of asymmetric variants of this reaction have been reported in the literature. A systematic diagram of the Michael reaction can be seen in Figure 1. Michael reactions require a soft nucleophile and this type of donor is generally obtained by deprotonation of a relatively acidic proton activated by one or more electron-withdrawing groups. Classically the electron-withdrawing groups would be two carbonyls.[26] Following deprotonation of the Michael donor, the stabilized lone pair from that species will then attack the Michael acceptor (Scheme 1). The Michael acceptor is usually an alkene that is in conjugation with an electron-withdrawing group. Once the carbon-carbon bond has been formed between the Michael donor and an acceptor, the catalytic base can then be reactivated by removal of the extraneous proton. Control in the asymmetric version of this reaction is established by a chiral base which controls the face selectivity of addition.

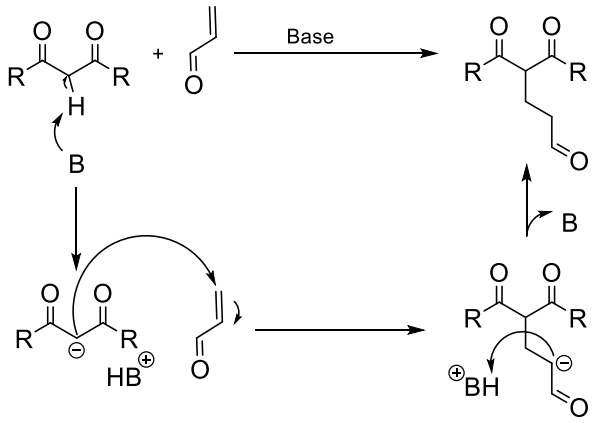


Figure 1. Representation of Michael reaction

The Henry reaction (also known as the nitroaldol) is an important carbon-carbon bond forming reaction.[27] A graphical representation of the mechanism of the Henry reaction can be found

in Figure 2. In this reaction the carbon α to the nitro group must be deprotonated creating a stabilized carbanion. This carbanion will then attack an electrophilic center forming a carbon-carbon bond, from this point there are a variety of conditions that could give rise to several different outcomes. From oxidation to dehydration there are many ways to work up the products of Henry reactions yielding a utility that is the true highlight of this method.

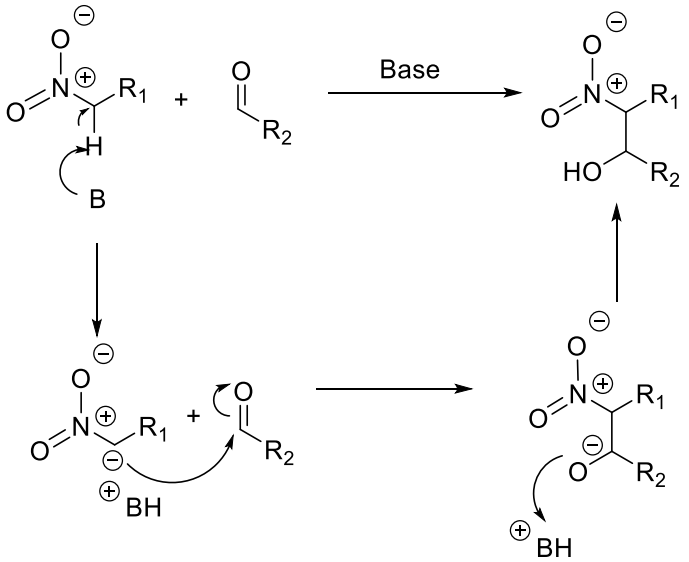


Figure 2. Representation of Henry reaction

The Mannich reaction is a useful three component reaction that brings together and forms a highly functionalized product.[28] The graphical mechanism can be found in Figure 3. Beginning with a nucleophilic attack by a primary or secondary amine on an aldehyde, the reaction proceeds through an iminium intermediate. This iminium intermediate is then attacked by a deprotonated β-ketone, forming a carbon-carbon bond and yielding the product. The initial attack on the aldehyde is crucial, as it leads to a more reactive Schiff base.

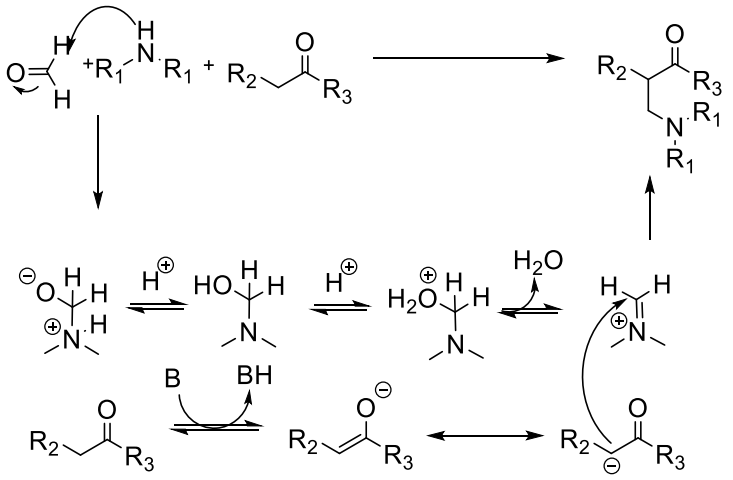


Figure 3. Representation of Mannich reaction

Kinetic resolution is a means by which enantiomers may be separated from one another. This is owing to the fact that enantiomers, while they possess identical physical characteristics, will react with the chiral reagents present in the reaction to afford a product that can be separated from the remaining starting material. In an ideal kinetic resolution the product will be predominantly one enantiomer while the left over starting material will be predominantly the other.

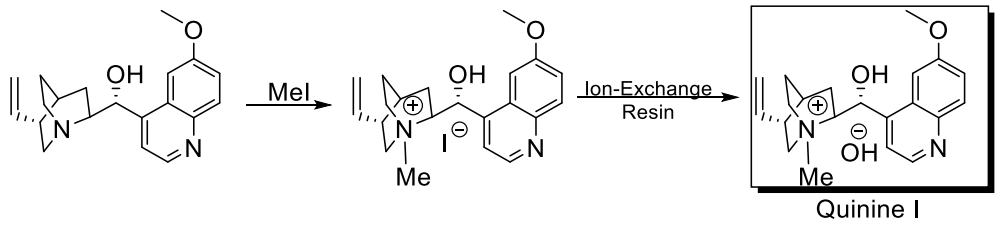
2.2. Michael Reactions:

The Michael reaction is one of the most highly used reactions in organic chemistry.[29-32] The use of an asymmetric base allows access to enantioenriched products. The Michael reaction has been, since its inception, a highly useful and therefore widely used reaction in organic chemistry.[33-36] Naturally the desire to produce enantioenriched Michael products led to the use of cinchona alkaloids.

In 1979 Hermann and Wynberg published a report in which the investigators examined the use of Cinchona alkaloids in Michael reactions.[21] Further research that proposed the production of optically active products being realized from Michael reactions the researchers sought to expand this field of study. They first communicated their attempts of using cinchona alkaloids as catalysts in

Michael reactions[19] and their less than successful attempts at using polymer-supported chiral bases in the same vein.[37] In this full report, the investigators show that the use of seven different catalysts could affect the products formed.

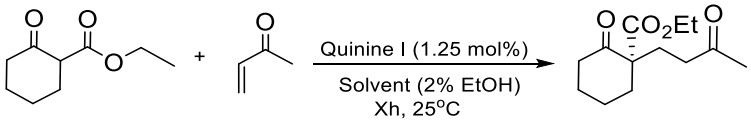
Using commercially available cinchona alkaloids (in the case of quinine, quinidine and eucupine), were crafted according to literature precedent[38, 39] (in the case of *O*-acylquinine and quinine methiodide), or crafted in-house (quinine methohydroxide and quinidine methohydroxide). Where the materials were produced de novo the researchers applied methods from Finklestein et al[38] to the corresponding iodide to produce the catalysts that they would then use via ion-exchange resin. This methodology is detailed in Scheme 1.



Scheme 1. Production of Quinine I

Beginning with a simple cyclohexanone derivative (2-carbethoxycyclohexanone) and a simple enone (3-butene-2-one) the researchers began their investigation. Results with commercially available catalysts were unimpressive but serve to provide inspiration for future work. Initially investigators began with a solvent screen to probe the effects on the products produced. In the end, the solvent screen showed that carbon tetrachloride provided both the highest reaction rate as well as the highest enantioenrichment. The results of this study are summarized in Table 2.

Table 2. Solvent optimization study results



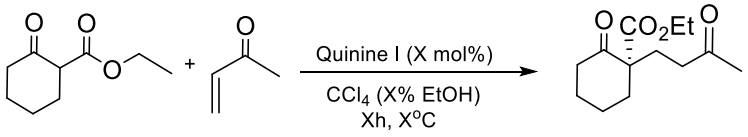
Entry	Solvent	Time (h)	Yield (%)	$[\alpha]^{RT}_{578}$	(%ee)
1	CH_3CN	118	NA	0	0
2	Dioxane	67	99	+4.2	5
3	CH_2Cl_2	43	89	+6.2	8
4	Benzene	74	99	+8.2	10
5	Toluene	18	90	+8.5	10
6	CCl_4	1	98	+13.7	17
7	CCl_4	19	100	+13.7	17

Varying the amount of catalyst and co-solvent (ethanol) had no major effect on the results of the reaction. Decreasing the temperature at which the reactions occurred did raise the enantioselectivity of the reaction slightly. Scaling the reaction up by 10-fold did not lead to a loss of enantioselectivity. The results of this study are summarized in Table 3.

Results using cyclopentanone derivatives showed a propensity for a higher enantioenrichment in the final products isolated. Taking their cue from the ideal conditions shown in the cyclohexanone body of work researchers started their investigation on an indanone derivative. The summary of this study is located in Table 4.

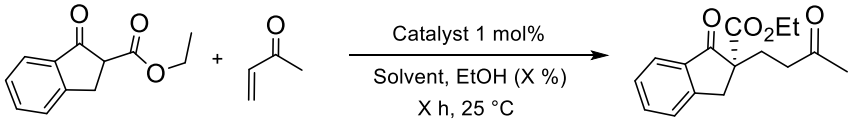
While this paper provided an interesting study, and the results showed promise the overall utility of this body of work turned out to be somewhat low. As shown in the cyclohexanone to the indanone comparison, this catalyst system is highly sensitive to substrate, thus limiting its use in general. In addition, most of the best results required long reaction times. This paper was cited sporadically over the next few decades.

Table 3. Comparative catalyst and co-solvent loading



Entry	Catalyst (X mol%)	EtOH (%)	Temp (°C)	Time (h)	Scale (mmol)	Yield (%)	$[\alpha]^{RT}_{578}$	(%ee)
1	1.25	2	25	19	2.0	100	+13.7	17
2	2.0	2	25	17	2.0	97	+14.6	18
3	1.25	5	25	0.8	2.0	NA	+12	15
4	1.25	2	0	69	2.0	88	+17	21
5	1.25	2	-16	40	20	99	+17.3	21
6	1.25	2	-20	72	2.0	96	+17.8	22

Table 4. Comparative catalyst/solvent/co-solvent on indanone derivative



Entry	Catalyst	Solvent	EtOH (%)	Time (h)	Yield (%)	$[\alpha]^{RT}_{578}$	(%ee)
1	Quinine I	CCl_4	0	18.5	98	-46.3	60
2	Quinine I	Toluene	0	48	98	-40.7	53
3	Quinine I	CCl_4	2	68.5	97	-25.4	33
4	Quinine	Toluene	1	0.4	100	-11.7	15

In 1986 Tatsuya et al[40] sought a means to affect an asymmetric Michael reaction with the end goal of producing an insect sex pheromone derivative. Tatsuya et al referenced but did not use the 1979 Wynberg et al work. Similarly Martin et al.[41] in 1986, Dolling et al.[42] in 1987 and Zhang et al.[43] in 1988 all mention the research from Wynberg et al.[21] without using it directly. The Wynberg et al. work was also included in reviews published by Fuji[44] in 1993 and Benetti et al.[45] in 1995.

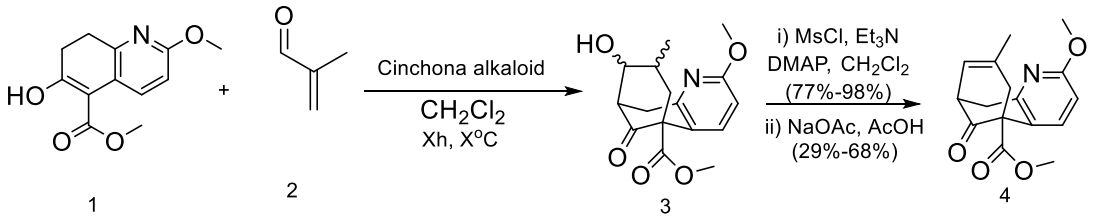
In 1997 Kaneko et al.[46] actually did make use of cinchona alkaloids in a key step towards the production of (-)-huperzine. (-)-Huperzine showed significant activity in the reversible inhibition of acetylcholinesterase[47], and as such it was thought that this compound might hold potential in its use

in treating Alzheimer's disease.[48] Following the formation of compound **4** detailed in Table 5, a further five reactions were required to produce (-)-huperzine.

Overall this paper is interesting, but it does not meet the goals set out in the introduction. The final products are enantioenriched but are not suiTable to use as is, at least for pharmaceutical purposes. As the authors were attempting a total synthesis the substrate scope for this main reaction was not explored. One useful note to make in this critique is that the use of different cinchona alkaloids allows a great deal of control of the final stereochemistry present in the product.

The next major article on the use of cinchona alkaloids in the Michael reaction comes from a 2001 report written by Szollosi and Bartok.[49] This is a focused study using only three β-ketoesters, and eight catalyst systems. The researchers began this investigation owing to the lack of research on this topic since Wynberg et al.[21] Szollosi and Bartok obtained cinchonidine, cinchonine and quinine from commercial sources. They prepared in accordance with literature procedures

Table 5. Comercial cinchona alkaloid catalyst as applied to reaction

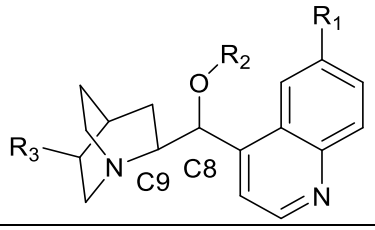


1 2 3 4

Entry	Cinchona alkaloid	Temp (°C)	Time (h)	Yield (%)	Enantiomer 4 (+ or -)	ee (%)
1	quinidine	20	43	100	-	31
2	quinine	20	36	98	+	37
3	dihydrocinchonine	20	88	62	-	55
4	cinchonine	20	115	89	-	55
5	cinchonine	-16	384	45	-	61
6	cinchonidine	20	86	76	+	59
7	cinchonidine	-10	253	43	+	64

dihydrocinchonidine[50], O-acetylcinchonidine[51] and O-methyldihydro-cinchonidine[52] and were given epiquinidine from a generous source. A summary of the additional cinchona alkaloid derivatives used is defined in Table 6.

Table 6. Definition of abbreviations used



Entry	Name	Abbreviation	C8	C9	R^1	R^2	R^3
1	Dihydrocinchonidine	HCD	S	R	H	H	C_2H_5
2	O-Acetylcinchondine	AcOCD	S	R	H	$OCCH_3$	C_2H_3
3	O-Methyldihydrocinconidine	MeOHCD	S	R	H	CH_3	C_2H_5
4	Epiquinindine	EQD	R	R	OCH_3	H	C_2H_3

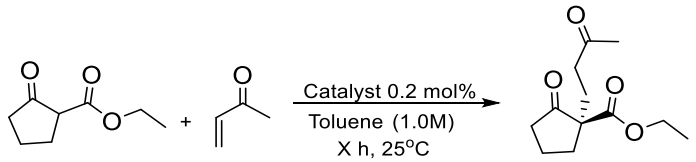
Examination of the different catalysts on a model system of ethyl 2-oxocyclopentanecarboxylate and methyl vinyl ketone were then undertaken by the researchers. These results show that the native cinchona alkaloids can achieve a higher degree of enantioenrichment of the product when compared to the tetraalkyl amine version investigated previously. The summary of results for this study can be found in Table 7.

Szollosi et al made many improvements on the work performed by Wynberg et al. By expanding the catalysts used they were able to show how pseudoenantiomers were able to select for the desired chirality in the product (a result we will see examples of in much of this collection). In addition to detailing a larger body of catalysts, the authors were also able to show how a smaller catalyst loading could be used with no sacrifice in efficacy.

In 2008 Furukawa et al.[17] detailed a synthetic route which would make available fluorinated end products from Michael reactions using quaternary amines derived from cinchona alkaloids.

Owing to the demand for fluorinated compounds this rather timely article managed to explore an underutilized route to these end products.

Table 7. Commercial vs manufactured cinchona alkaloid catalysts

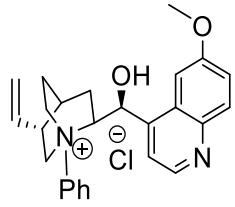


Entry	Catalyst	Time (h)	Yield (%)	$[\alpha]_D^{25c}$	ee (%)
1	CD	8	90	-10.9	56
2	CN	8	85	+7.8	40
3	QN	24	51	-13.5	70
4	QD	8	75	+12.1	63
5	HCD	24	88	-12.0	62
6	AcOCD	24	14	-10.7	54
7	MeOHCD	24	40	+0.9	5
8	EQD	24	4	+1.1	6

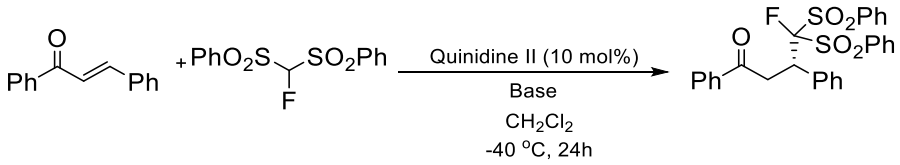
An investigation into the role of the auxiliary base was undertaken and showed the optimal base for this reaction is cesium carbonate. In this screening the researchers showed that increasing the amount of base used from 1 to 10 equivalents did nothing to improve neither yield nor enantioselectivity. Table 8 contains selected results from this study.

A solvent screening showed that the investigators' initial choice of solvent was the optimal one. The overall decrease in both yield and enantioselectivity is due to the degree to which each solvent is able to solubilize some portion of the reaction (often it is the transition state of the reaction). Toluene and tetrahydrofuran must therefore fail to support to solubilize some component of the reaction. In the case of toluene, it is possible that the selected base is unable to dissolve in a meaningful way and thus cannot participate in the reaction. Table 9 details the results from this study.

Table 8. Effect of base on *Quinidine II* Michael reaction



Quinidine II



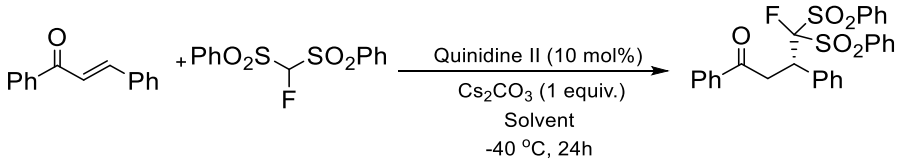
Entry	Base	Equiv. Base	Yield (%)	ee (%)
1	$CsOH * H_2O$	1	62	8
2	K_2CO_3	1	81	44
3	K_2CO_3	10	81	44
4	Cs_2CO_3	1	82	72

Alternative aromatic substituents were also incorporated into the catalyst. The most efficient substituent was both bulky and electron-withdrawing. This was not a smooth trend as can be demonstrated by looking at other substituents. From the unsubstituted phenyl ring to 4-trifluoromethylphenyl substituent a decrease in both yield and enantioselectivity was observed. Switching to a more electron-donating 3,5-dimethoxyphenyl substituent caused further degradation in enantioselectivity but a slight increase in yield. 9-Anthracene as a substituent led to the lowest observed yield and enantioselectivity in the series. Based on the preceding data the investigators were unlikely to expect that the largest substituent would provide the highest yield and greatest enantioselectivity. With no control reactions it is impossible to pick out the effect, if any, of the counter ion in the catalytic complex. Table 10 contains the highlights of the results of this study.

The final piece of relevant information to come from this report was the substrate scope for the reaction. Overall this catalytic system showed excellent substrate scope. There are several interesting results that come out of this body of work, namely the switching of the stereochemistry

of the products produced simply by altering the substituents of the starting material. The summary of the results of this study may be found in Table 11.

Table 9. Solvent effects on *Quinidine II* Michael reactions



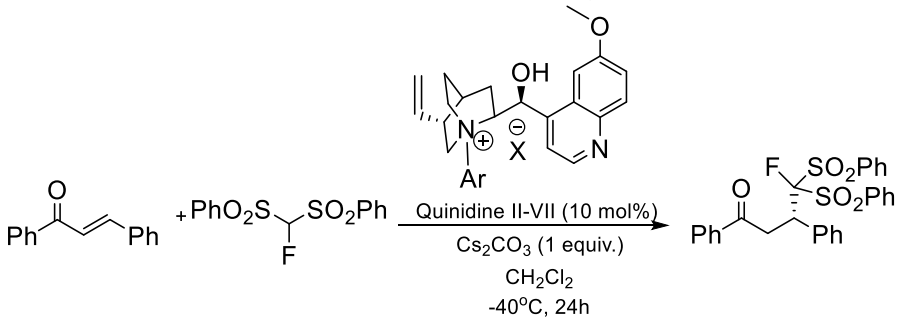
Entry	Solvent	Yield (%)	ee (%)
1	CH_2Cl_2	82	72
2	Toluene	53	41
3	CH_2Cl_2/Toluene	58	55
4	THF	52	36
5	t-BuOMe	2	28

As a continuing demonstration of the versatility of cinchona alkaloids, researchers in this paper show how using the pseudoenantiomer of the catalyst one can access the opposite enantiomeric product. The results of this study can be found in Table 12.

In a 2015 report,[53] researchers sought a way to perform a tandem Michael reaction and oxidation towards the production of pyrazolones. The researchers cite the myriad studies in which the core of a therapeutic compound is a pyrazolone. The core of their investigation was the incorporation of *p*-benzoquinone as the electrophile for the Michael reaction.

From the following table we can draw few conclusions and no real pattern seems to emerge as a result. The catalyst choice seems erratic, especially once the investigators choose to proceed using the parent quinidine as the catalyst going forward. If the investigators merely had these catalysts at hand at the beginning of the investigation however this could be easily said in the report. The use of starting materials occurs in a ratio that doubles the amount of *p*-benzoquinone compared to the pyrazolone used in the same reaction. It is this excess of oxidant that leads to the tandem

Table 10. Effects of aryl substituents on quinidine derivative



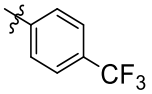
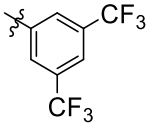
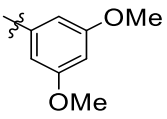
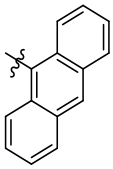
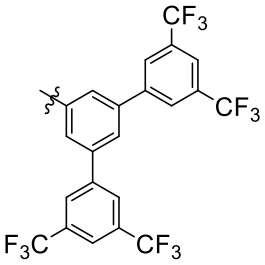
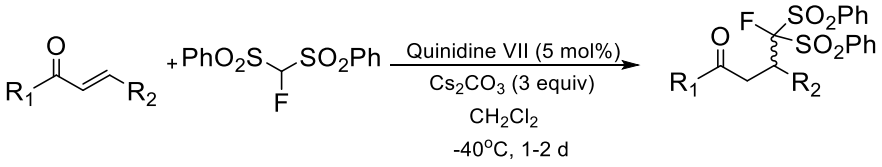
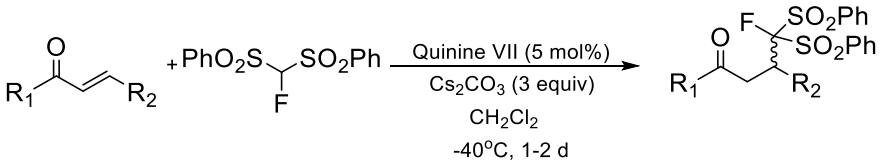
Entry	Quinidine X	Ar	X	Yield (%)	ee (%)
1	Quinidine II		Cl	82	72
2	Quinidine III		Br	60	60
3	Quinidine IV		Br	59	67
4	Quinidine V		Br	67	34
5	Quinidine VI		Br	50	21
6	Quinidine VII		Br	78	97

Table 11. Scope of reagents in *Quinidine VII* Michael Reaction



Entry	R_1	R_2	Stereo center	Yield (%)	ee (%)
1	Ph	Ph	S	80	97
2	Ph	4-ClC_6H_4	S	76	97
3	Ph	3-ClC_6H_4	S	85	98
4	Ph	4-BrC_6H_4	S	86	97
5	Ph	4-MeC_6H_4	S	77	94
6	4-ClC_6H_4	Ph	S	52	91
7	4-BrC_6H_4	Ph	S	82	95
8	4-$BocC_6H_4$	4-BrC_6H_4	S	32	95
9	Ph	Me	R	91	85
10	Ph	Et	R	69	90

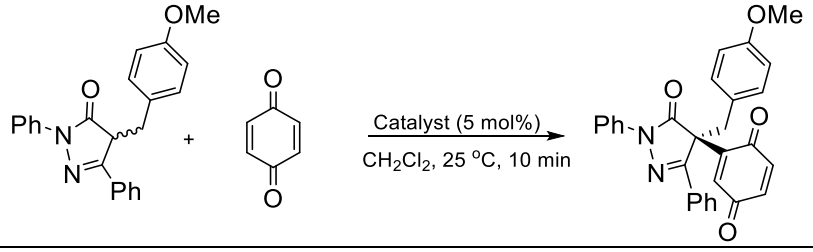
Table 12. Pseudoenantiomer study for *Quinidine VII*

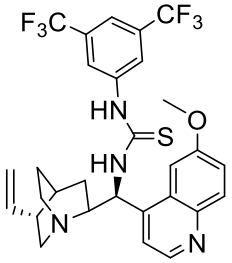
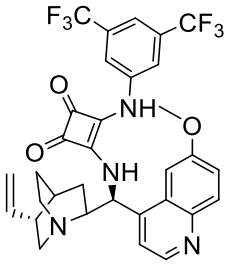
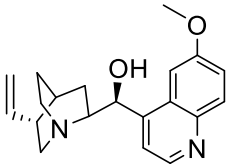
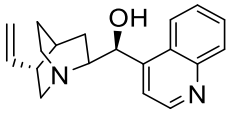
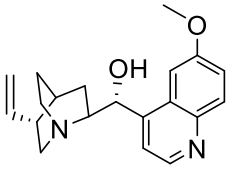


Entry	R_1	R_2	Stereo center	Yield (%)	ee (%)
1	Ph	Ph	R	64	96
2	Ph	4-ClC_6H_4	R	64	96
3	Ph	3-ClC_6H_4	R	77	82
4	Ph	4-BrC_6H_4	R	90	94
5	4-ClC_6H_4	Ph	R	90	89
6	4-BrC_6H_4	Ph	R	68	93
7	Ph	Et	S	56	84

oxidation key to this report. Another troublesome issue was that the stereochemistry of the product is never assigned or otherwise indicated. Finally, there was no indication that the pseudoenantiomer effect occurring in this screening, which is unusual as the products were not even enantiomers. The summary of these efforts can be found in Table 13.

Table 13. Effects of commercial and synthesized cinchona alkaloid catalysts



Entry	Catalyst Label	Catalyst	Yield (%)	ee (%)
1	Quinidine VIII		59	24
2	Quinidine IX		66	23
3	Quinidine		68	30
4	Cinchonidine		69	-11
5	Quinine		71	24

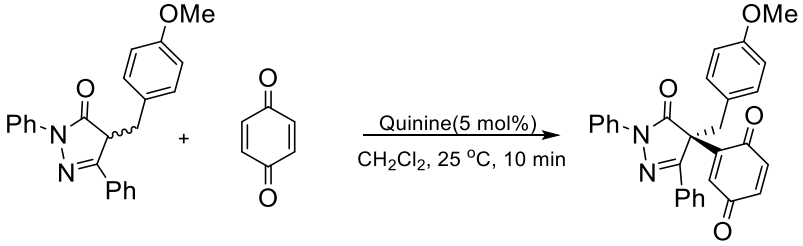
This report continues to examine solvent and some temperature screenings. The final solvent of choice was dichloroethane. Where this report again departs from expected results however is that in allowing the reaction to proceed for a longer period in the same conditions the

yield decreased while the enantioselectivity increased dramatically. There was no rational provide for these interesting results. Table 14 contains the details of the solvent screen discussed above.

This report overall begs as many questions as it works to answer. The discrepancy regarding the amount of time allotted increasing, while the overall yield decreased and the enantiomeric excess improved, is something that the researchers should have addressed in their report. Aside from the open question left to the reader this report does not fully explore the pseudoenantiomer effect observed widely in much of the rest of the literature.

The Michael reaction remains a strong contender for the most useful chemical transformations available. The addition of cinchona alkaloids, where effective, then grants a facile means of influencing a Michael reaction to afford a stereoselective product. As an added incentive it also enables researchers to exploit the pseudoenantiomer effect present in this family of catalysts.

Table 14. Solvent and temperature effects on quinine catalyzed Michael reactions



Entry	Solvent	T (°C)	Time (h)	Yield (%)	ee (%)
1	CH_2Cl_2	25	0.17	68	30
2	$(CH_2Cl)_2$	25	0.17	70	44
3	$CHCl_3$	25	0.17	68	26
4	EtOAc	25	0.17	77	4
5	$(CH_2Cl)_2$	0	0.17	68	19
6	$(CH_2Cl)_2$	40	0.17	70	0
7	$(CH_2Cl)_2$	25	24	62	69
8	$(CH_2Cl)_2$	25	36	62	69

2.3. Henry Reaction:

First reported in 1895[27] the Henry reaction (otherwise known as the nitro-aldol reaction) has been a useful tool for organic synthesis ever since. Specific to this review are the intersections of cinchona alkaloids and the Henry reaction. While typical Henry conditions rely on an achiral base, the use of cinchona alkaloid-derived bases allows for chiral control to be established and maintained throughout the reaction. Since Henry's discovery this reaction has received much attention.[54-57]

A pair of reports in 2006[22, 58] detail different means of using cinchona alkaloids in the framework of the Henry reaction and each has its own merits and detractions. That these two reports came out so close together and examine such a similar phenomenon shows how serendipity in science can lead to researchers passing as proverbial ships in the night.

Beginning with the report by Li et al.[22] it can be seen that this communication means to make use of activated ketones as opposed to aldehydes (a more classic Henry electrophile). By using an activated ketone the authors hope to be able to use the remaining ester in further reactions, thereby increasing the utility of this methodology. While this paper has some interesting information and provides some fascinating insight into the use of cinchona alkaloids it does suffer from a few shortfalls. The most obvious error in judgment encountered in the first page is the lack of clarification in their abbreviations used.

In a set of base screening reactions, the authors make use of the standard triethylamine and various cinchona alkaloid derivatives. A side product that can arise out of the initial reaction conditions is the β-addition (or the addition of the deprotonated nucleophile to the alkene β to the ketone). The rate of β-addition is an issue that must be overcome to provide a useable work-product. Fortunately, the creation of β-addition products can be mostly side-stepped by not using triethylamine. The use of quinidine, β-isocupreidine and various modifications of quinidine and quinine were examined and reported in Table 15.

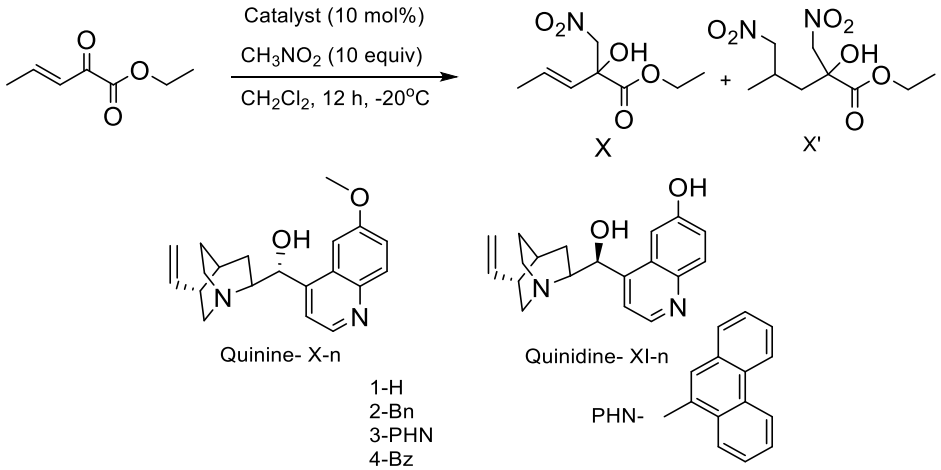
The above information easily leads to a few conclusions. The first conclusion that can be drawn is the crucial role the 6' alcohol plays in the mechanism. Looking from the standard quinidine catalyst to the modified quinidine catalyst the only noTable change in the catalyst structure is the loss of the methyl group from the 6' oxygen. Further modifications led to even more potent catalysts culminating in the quinidine-**1d** catalyst which is able to provide the product with 97% ee. Gratifyingly the pseudoenantiomer of the chosen quinidine catalyst (quinine-**1d**) showed exactly the expected behavior and afforded the same ee but as the opposite enantiomer.

Further experiments showed the substrate-scope of this catalyst and display how further modifications could be accomplished leading to new pathways to products that could mimic amino acids (Table 16). Other pathways could be used to create different molecules in the β-lactam family.

The below data shows that while this method is generalizable to many different substrates (provided they have the required β-ester ketone motif) though it is worth noting that more electron-rich substrates will take longer to react. In addition, it appears larger substituents also require more time to react under these conditions. Interestingly, the authors were also able to demonstrate a reduced need for catalyst in this second screen. When the authors ran these screening reactions again using the quinine-1d catalyst the results were as expected (same yield and enantiomeric excess but opposite chirality found).

While this was a short communication it still managed to demonstrate a very useful methodology. While the authors did not publish a full paper on this same reaction the research group responsible did go on to report work utilizing cinchona alkaloids in various other reactions including: the Mannich reaction,[59] Friedel-Crafts reaction,[60] and Diels-Alder reaction.[61] Again, the utility and versatility of the cinchona alkaloids can be seen in the work reported by a single research group.

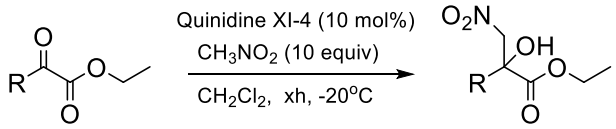
Table 15. Commercial and synthesized catalysts in Henry reaction

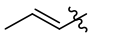
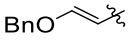
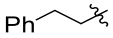
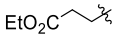


Entry	Catalyst	Conversion (%)	X/X'	ee (%)
1	Triethylamine	>95	80/20	-
2	Quinidine	91	>95/5	.17
3	β-isocupreidine	>95	>95/5	61
4	Quinidine XI-1	>95	>95/5	86
5	Quinidine XI-2	>95	>95/5	70
6	Quinidine XI-3	>95	>95/5	93
7	Quinidine XI-4	>95	>95/5	97
8	Quinine X-4	>95	>95/5	-97

The other 2006[58] report of catalysts for the Henry reaction focuses on the use of cinchona alkaloid-derived thioureas. Thioureas are a class of compounds that show a wide variety of use in various applications, which is a review in and of itself.[62] Through this catalyst Scheme the authors were able to achieve a methodology that adds another available route to worthwhile chemicals. Taking their lead from previous researchers[63] in the field, especially those who focus on thiourea catalysis[64], the authors hypothesized that connecting a thiourea moiety through the 6' position instead of the 9 position of the cinchona alkaloid they would be able to achieve higher enantioselectivities.

Table 16. Substrate scope for *Quinidine XI-4* Henry reaction



Entry	R	Time (h)	Yield (%)	ee (%)
1		14	92	96
2		24	98	94
3	Ph-	35	96	95
4	4-MeS-Ph-	72	86	96
5	4-Cl-Ph-	12	98	97
6	4-CN-Ph-	9	96	94
7	3-Cl-Ph-	11	91	95
8	2-Naphthyl-	60	96	94
9	*n*-Pr-	17	90	93
10		14	88	95
11		15	87	94

The authors had conducted previous research in the use of cinchona alkaloids as catalysts for the Henry reaction,[65] and taking their lead from this body of work they pressed on by modifying the 6' functional group from an alcohol into an amine and used this as a handle to create the desired thiourea. Initially the group investigated the Henry reaction utilizing benzaldehyde and nitromethane. While these conditions are somewhat simplistic they still make an excellent standard against which to gauge future efforts, as well as being very economical for a first step.

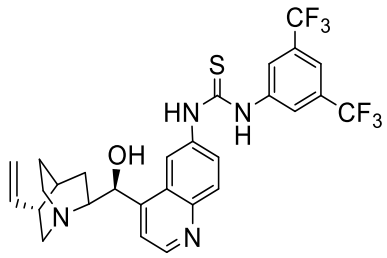
From the initial screening, optimal conditions are deduced and used in future reactions. As can be deduced from Table 17, solvent effects play a significant role in this reaction. The polarity difference between tetrahydrofuran and dichloromethane seemingly shuts down much of the enantioselectivity of the reaction. This suggests that the relevant transition state that determines the enantioselectivity of this reaction is rather polar as well. Indeed, this observation makes a certain amount of sense owing to the mechanism of the Henry reaction. More surprising is that

dichloromethane allows the reaction to proceed so well at all, given how it seems to be unsupportive to the key transition state in the reaction. Running the reaction neat (in nitromethane) seems to be sub-optimal as well. This reaction seems to tolerate polar protic solvents (see methanol) but does not perform especially well in these types of solvents. such.

With a synthetically useful set of conditions at hand, the investigators then set out to show the scope and range of their new catalyst. As can be seen once again in this work, electron-rich substrates performed better in contrast to electron-deficient substrates (at least in terms of reaction times). Overall, the aryl substituents seem to only influence how long the reaction requires to proceed to completion as all of the products isolated were in the same degree of enantioselectivity. Results illustrating the above points may be found in Table 18.

Gratifyingly, the researchers did take the time to examine the effects of using the psuedoenantiomer-derived catalyst. They found that the expected results did indeed come to be by finding the opposite enantiomer of the product. The results of this study may are summarized in Table 19.

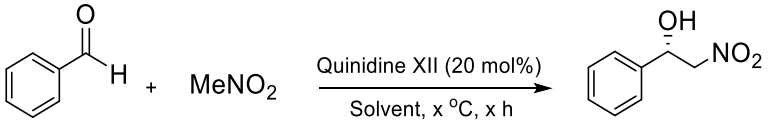
This paper does make some interesting advances in the arena of organocatalysis as applied to the Henry reaction but does not show a great degree of substrate scope. The confirmation of the effects of the pseudoenantiomers was shown as was the high degree of selectivity overall. Near the end of the disclosure of this work is a proposed transition state that predicts how enantioselectivity is achieved in this reaction. Figure 5 is a reproduction of the proposed transition state that the authors hypothesize.



Quinidine XII

Figure 4. *Quinidine XII*

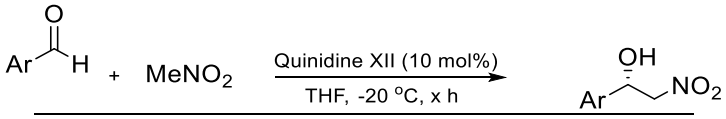
Table 17. Solvent effects of *Quinidine XII* catalyzed Henry reaction



Entry	Solvent	Temp (°C)	t (h)	Conversion (%)	ee (%)
1	Tetrahydrofuran	25	6	90	62
2	CH_2Cl_2	25	6	97	6
3	DMF	25	6	96	67
4	Nitromethane	25	6	92	7
5	Methanol	25	6	91	49
6	Diethyl ether	25	6	99	30
7	Toluene	25	6	83	5
8	DMF	-20	48	90	82
9	Tetrahydrofuran	-20	48	99	89

As can be seen from Figure 5 below, the authors predict that the enantioselectivity is controlled by double-hydrogen bonding to the aldehyde which would orient the electrophile in such a way as to disallow addition of the nucleophile from the more hindered side. When the orientation of the electrophile is coupled with the regional-constraints of the nucleophile the stereochemical outcomes are easy to see. The authors were unable to provide concrete evidence of their proposed transition state and were further unable to elucidate the solvent effects observed in this paper.

Table 18. Substrate scope of *Quinidine XII* Henry reaction



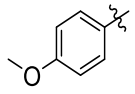
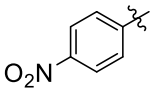
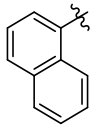
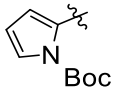
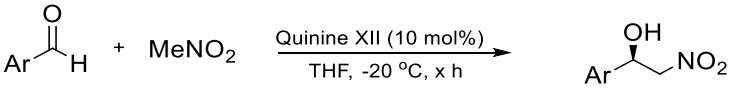
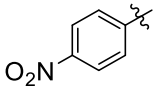
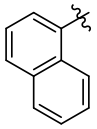
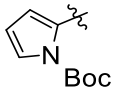
Entry	Ar	t (h)	Yield (%)	ee (%)
1		168	94	89
2		4	91	86
3		48	99	92
4		24	91	86
5		24	95	91

Table 19. Pseudo enantiomer study of *Quinidine XII*



Entry	Ar	t (h)	Yield (%)	ee (%)
1		4	87	93
2		48	97	92
3		24	95	87

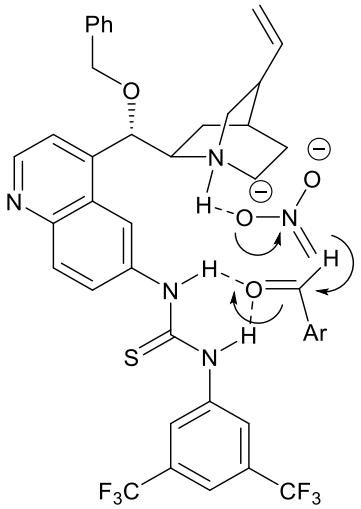
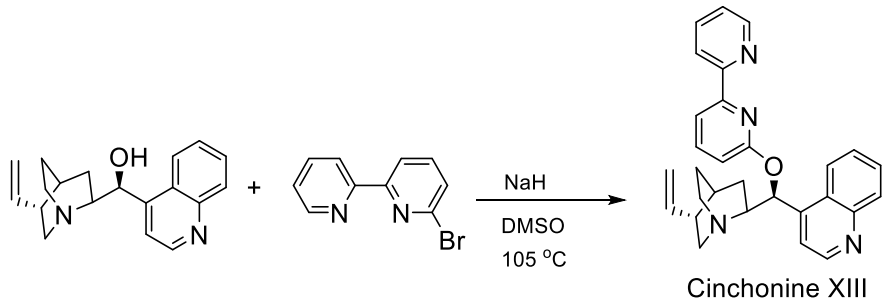


Figure 5. Proposed transition state

A 2013[66] report detailed an investigation in which the investigators showed how relatively simple cinchona alkaloid catalysts could be prepared and used as a co-catalyst with a copper salt in order to afford an asymmetric Henry reaction. The investigators undertook this study in an effort to produce a greater array of β-nitro-alkanols, which the authors cite as being important as building blocks in many natural product syntheses. Taking their lead from research which showed that the donor ligands have a large role to play in catalysis owning to their ability to associate with various metal centers.[67-69] At the onset this investigation sets itself apart from those that came before owing to its use of cinchona alkaloids, which as has been covered before in this review is a readily available chiral source that is also highly diverse.

The means that the investigators used to produce their experimental cinchona alkaloids left open the possibility of scrambling the stereocenter inherent to the natural cinchona alkaloid. Using a simple Williamson ether synthesis, the authors were able to afford a sample of the catalyst (though typically in low yield 30-56 %). The advantage of this synthesis is that it is relatively simple and makes use of relatively low-cost materials. The obvious disadvantage to this method is its low yield and scrambling of the stereocenter. This synthesis is summarized in Scheme 2.



Scheme 2. Simplified synthesis of *Cinchonine XIII*

In the interest of utilizing the variability apparent in cinchona alkaloids the researchers developed a catalyst based upon both quinine and quinidine. It should be noted that early in the investigation the authors determined that the catalysts composed of mixed stereocenters were unable to affect the transformation effectively.

With the catalyst they wished to investigate at hand, the investigators then set about examining a model reaction. Again, the use of benzaldehyde and nitromethane can be observed, though it is worth noting the difference between this trial and others. This model reaction makes use of a polar, protic solvent which is a departure from previous works in which this solvent system was sub-optimal. Both pseudoenantiomers achieved roughly the same results, within 4 % on both yield and enantiomeric excess. This is likely within experimental error, unless a very high number of repetitions were used.

Following the initial testing a more through solvent screening was then used to determine the optimal copper source for this reaction. The copper screen was then followed by a solvent screen, and lastly a substrate scope screening was investigated. Summary of this study may be found in Table 20.

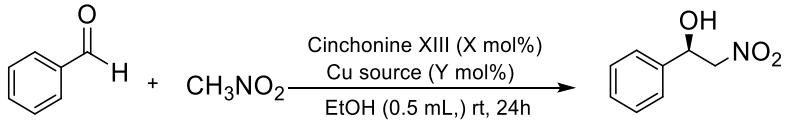
The results from the screening of copper source show that the source of copper matters quite a bit. Having an anhydrous copper source gave different results when different anions were in solution. The overall trend indicates that having less electron-rich copper sources is deleterious to

producing the desired products, to a point at the very least. It would have been instructive if the authors had used copper sources such as copper methoxide or copper hydroxide to see if more electron-rich copper sources would enhance this reaction. Given that in order for this catalytic system to yield an enantioenriched product the ligands native to the copper source must be displaced by the bipyridine moiety on the cinchona alkaloid derivative it would seem logical to conclude that any ligand easily displaced from the copper source would be ideal for facilitating this reaction.

A solvent screening was the next order of business for the authors and once the optimal solvent was found a further step in which additional bases were added was also attempted. The results of these investigations may be found in Table 21.

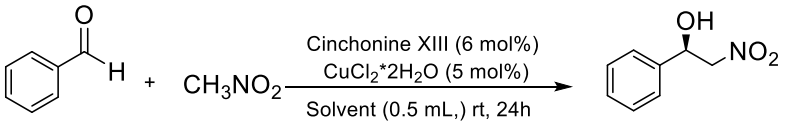
Overall it seems that the first choice for solubilizing this reaction is the one that the investigators used in the first place. Using a polar, protic solvent always gave a higher yield when compared to both polar and nonpolar, aprotic solvents. The overall enantiomeric excess did not vary much throughout the solvent screen.

Table 20. Copper source and ratio study for *Cinchonine XIII* Henry reaction



Entry	Cu source	Ratio (Ligand/Cu) [mol %]	Yield (%)	ee (%)
1	$Cu(OAc)_2*H_2O$	12/10	42	56
2	$Cu(OAc)_2$	12/10	79	49
3	$CuCl_2*2H_2O$	12/10	82	83
4	$CuBr_2$	12/10	60	76
5	$Cu(OTf)_2$	12/10	43	52
6	$CuCl_2*2H_2O$	15/10	61	82
7	$CuCl_2*2H_2O$	6/5	81	83
8	$CuCl_2*2H_2O$	3/2.5	66	70

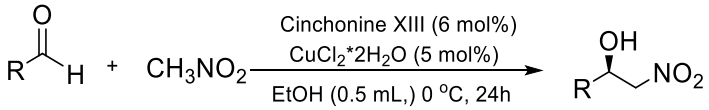
Table 21. Solvent and base study of *Cinchonine XIII* Henry reaction



Entry	Solvent	Base (2 mol%)	Yield (%)	ee (%)
1	EtOH	-	81	83
2	MeOH	-	73	79
3	iPrOH	-	66	81
4	EtOH	TEA	87	66
5	EtOH	DMAP	86	72
6	EtOH	K_2CO_3	88	32
7	EtOH (0 °C)	-	80	92

This suggests that it is a matter of rate of reaction rather than solubilizing the reagents. The addition of an outside base did not aid in formation of product. The decrease in ambient temperature did allow for an increase in enantiomeric excess. Table 22 contains a summary of the data generated from these studies.

Table 22. Substrate scope *Cinchonine XIII* Henry reaction



Entry	R	Yield (%)	ee (%)
1	Ph-	80	92
2	4-F-C_6H_4-	84	81
3	4-Me-C_6H_4-	68	90
4	4-OH-C_6H_4-	71	83
5	2-Thiophenyl-	84	92
6	2-Furyl-	62	81
7	3-Furyl-	76	88
8	$CH_3(CH_2)_2$-	80	82
9	Cyclohexyl-	89	85

The substrate screen gives a lot of insight into the utility of this reaction. Given that it operates in a roughly analogous manner without regard to a large variety of differences in the

substituents. Granted this screening does not display how well this technique would respond to bulky substituents (like adamantyl) or with other functional group tolerance (like ketones).

Overall, this report manages to demonstrate a highly useful technique to catalyze the Henry reaction using a cheap catalyst. There are some parts that could be expanded upon, but these are not glaring in their absence.

2.4. Mannich Reaction:

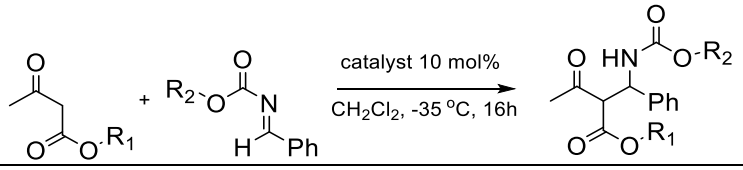
The Mannich reaction, first discovered in 1912 by Carl Mannich[28] and his co-workers, is a particularly interesting reaction as it allows the chemist using this method to bring together three components into one product. This thumbing of the nose towards entropy does require a set of specific functional groups to be present, and as such is less used than more generalized reactions.[70-72] Unfortunately, research on this methodology typically centers on the use of β-ketone esters (sometimes other β-carbonyls) and individually formed imines. While it is certainly easier to control these conditions, researchers miss the opportunity to fully utilize the scope of the Mannich reaction. The most common goal of research in this area is the production of β-amino acids. While rare in nature β-amino acids exhibit some interesting pharmacological properties.[73] It is these self-same properties that stoke intrigue that in turn provides for investigation.

A 2005 communication[52] disclose the use of various cinchona alkaloids in a Mannich-type reaction. While this short communication is somewhat lacking in assignments of stereochemistry, it becomes a useful introduction into a study of this subset of cinchona alkaloid use.

The researchers in this report initiated their investigation by using vinyl acetoacetate and tert-butyl benzylidene carbamate. Later reactions would switch to using methyl acetoacetate, which seems to be more sensible as an initial choice. Lamentably, the researchers do not assign either the diastereomer typically obtained, though it is worth noting that they do so in exactly one case. In the instance where the researchers used methyl acetoacetate, methyl benzylidene carbamate (i.e. R1= Me

and R2= Me) and cinchonine as the catalyst the researchers were able to assign the major diastereomer to be 1R,2S. Table 23 contains a summary of the data generated from the reactions described below.

Table 23. Substrate scope commercial cinchona alkaloid Henry reaction



Entry	R_1	R_2	Catalyst	Yield (%)	dr	ee (%)
1	$-C_2H_3$	-*t*-Bu	Cinchonine	85	3:1	80
2	-Me	-Me	Cinchonine	99	20:1	94
3	-Me	-Me	Cinchonidine	95	20:1	90
4	-Me	-Me	Quinine	97	4:1	60
5	-Me	-Me	Quinidine	98	5:1	65
6	-Me	$-C_2H_3$	Cinchonine	91	2:1	90

From the initial screening the investigators then turned their attention to an easier product to work with. Owing to the diastereomeric possibilities of the first screen the authors chose to investigate a possible route through the decarboxylation of the intermediate product to achieve a more expedient final product. This final product was then assigned stereochemistry and examined in depth. Using a catalytic amount of palladium and methyl acetoacetate the researchers were able to affect a decarboxylation. In Table 24 the results of these studies can be found.

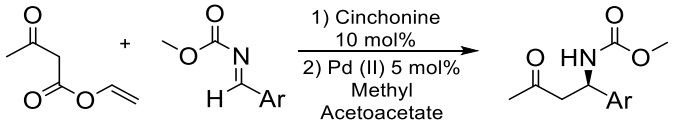
This work is fairly limited in terms of overall utility, but it does open a recent area of study in the vein of Mannich-type reactions via cinchona alkaloid catalysis. The limited substrate scope, lack of utilization of the full power of the Mannich reaction (which unfortunately continues through these collected papers) and the fact that the diastereomers originally created weren't put to better use are all factors that are somewhat disappointing in this original report.

A significant step forward was reported in a 2006 article.[74] In this report the investigators lean into the ability to generate diastereomers to create quaternary centers by utilizing α-substituted β-diketones containing a cyclic moiety and α-substituted β-keto esters with the same type of cyclic moiety.

The researchers set their first goal as testing the compliment of catalysts available at hand, focusing on unaltered, commercially available cinchona alkaloids. In this screening we see the pseudoenantiomer effect come into play and see that each cinchona alkaloid is highly effective in both yield and diastereoselectivity. A summary of the results discussed above can be found in Table 25.

From the initial screening to find optimal catalytic system the investigators then turned to substrate scope investigations. While this investigation didn't vary the substrates in a substantial way it did show that in most of investigated reactions showed the same outcomes. The exception to the general trend is the lactone result in the following data. The data discussed above may be found, in a summarized form in Table 26.

Table 24. Substrate scope cinchonine Henry reaction/ decarboxylation

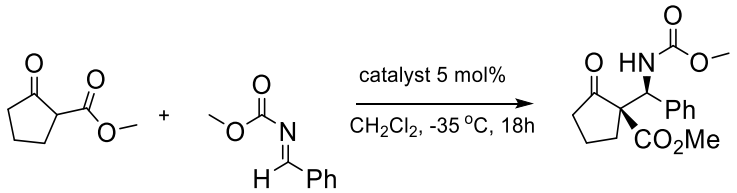


Entry	Ar	Yield (%) [Over 2 Steps]	ee (%)
1	Ph-	80	92
2	4-Cl-Ph-	80	83
3	4-F-Ph-	97	93
4	3-CH_3-Ph-	81	96
5	3-CF_3-Ph-	83	90
6	2-Naphthyl-	83	95

This report then explores the use of acyclic nucleophiles and extended pi systems on the electrophile. The results of the acyclic series were the general destruction of the diastereomeric-selectivity, with one exception that achieved good diastereomeric-selectivity. In the case of the cyclic-containing nucleophile with the extended pi-system containing electrophile the results were generally in line with the previous screening. Tables 27 and 28 disclose the summary of results from the studies mentioned previously.

While this paper does make sizable strides in the utility of cinchona alkaloids in the realm of Mannich-type reactions, it does lack sufficient substrate scope to be a truly generalizable procedure. Further elucidation of the effects of electron-withdrawing substituents on the aromatic system involved in the reaction as well as studies on different carbocycles and heterocycles would create a greater impact overall.

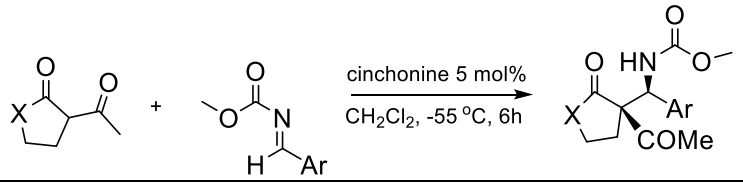
Table 25. Commerical cinchona alkaloid study Henry reaction



Entry	Catalyst	Yield (%)	de (%)	ee (%)
1	Cinchonine	96	93	90
2	Cinchonidine	96	94	-88
3	Quinidine	96	95	18
4	Dihydroquinidine	94	94	88
5	Quinine	95	94	-10

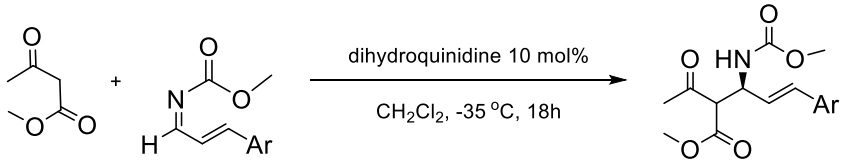
In a 2017[75] report researchers explored the use of synthetic cinchona alkaloids they prepared in lab. The synthetic system under investigation is a thioamide-substituted cinchona alkaloid derivative. Overall this work is rather limited but shows significant foresight in the ability to modify and show use of the modified catalysts.

Table 26. Substrate scope cinchoinine Henry Reaction



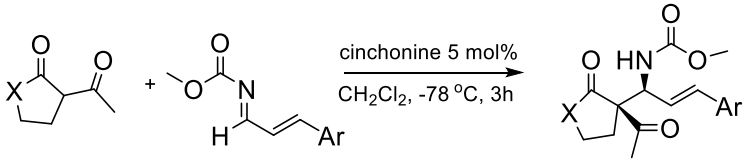
Entry	X	Ar	Yield (%)	de (%)	ee (%)
1	CH_2	Ph	98	98	93
2	CH_2	3-CH_3-C_6H_4-	98	94	94
3	O	3-CH_3-C_6H_4-	88	38	91
4	CH_2	2-C_4H_3O	98	99	99
5	CH_2	3-F-C_6H_4-	98	99	93

Table 27. Substrate scope dihydroquinidine Henry reaction



Entry	Ar	Yield (%)	de (%)	ee (%)
1	Ph	97	67	92
2	2-C_4H_3O	98	0	90

Table 28. Substrate scope cinchonine Henry reaction



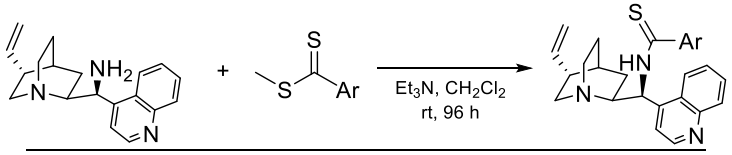
Entry	X	Ar	Yield (%)	de (%)	ee (%)
1	CH_2	Ph	98	95	99
2	O	Ph	88	38	98
3	CH_2	2-C_4H_3O	98	94	98

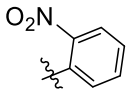
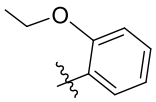
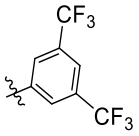
The initial synthesis of the compounds under investigation were a compilation of established protocols[76] to the effect of producing the corresponding amine (though of the opposite enantiomer compared to the starting material). The corresponding amine was then thioacylated to produce the final product to be examined. The products of this synthesis can be found summarized in Table 29.

The starting cinchona alkaloid (cinchonidine) was subject to a modified Mitsunobu-type reaction which produces the inverted C9 azide-cinchona-alkaloid derivative. The azide product was

then subjected to a Staudinger reduction to produce the amine that will be thioacylated. The thioacylation reagent was prepared in a separate sequence. Following their successful synthesis, the investigators then used their cinchona alkaloid derivatives to probe a Mannich-type reaction. In the reaction the investigators probed they used α-amino-malonic acid mono ethyl ester and *N*-tosyl phenylimine in addition to the catalyst they chose to use. Table 30 contains the data from these studies.

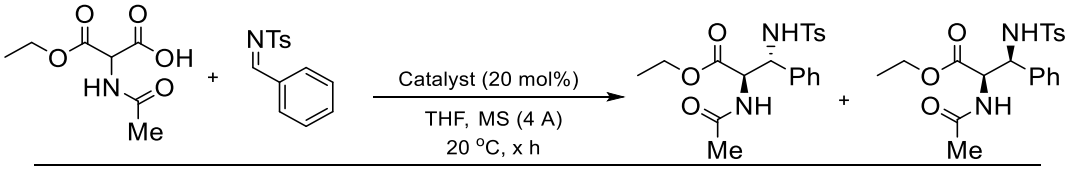
Table 29. Synthesis of cinchonine derivatives



Entry	Catalyst Label	Ar	Yield (%)
1	Cinchonidine XIV		71
2	Cinchonidine XV		71
3	Cinchonidine XVI		54
4	Cinchonidine XVII		51
5	Cinchonidine XVIII		36

Overall this paper makes some significant advances in that it allows for the use of achiral substrates in a decarboxylative Mannich-type reaction. The host of catalysts prepared are readily made from commercial reagents forming an unexplored catalytic platform for future investigations. A larger substrate scope would have helped really increase the apparent utility of this catalytic system. Overall this paper sets up the field to grow by leaps and bounds going forward.

Table 30. Catalyst screening



Entry	Catalyst	t (h)	Yield (%)	dr (anti: syn)	er (anti)	er (syn)
1	Cinchonidine XIV	48	78	66: 34	68: 32	88: 12
2	Cinchonidine XV	48	70	66: 34	58: 42	78: 22
3	Cinchonidine XVI	72	29	67: 33	56: 44	54: 46
4	Cinchonidine XVII	48	76	67: 33	78: 22	87: 13

2.5. Kinetic Resolutions:

The use of cinchona alkaloids in kinetic resolution is a matter of particular interest to our group as kinetic resolution via other means remains a focus of this group's research. The pseudo-enantiomer effect observed earlier hold a large degree of promise if it can be successfully employed in the arena of kinetic resolution, as it would allow the operator control over which enantiomer was left as starting material and which would be transformed into products.

In general, kinetic resolution can be thought of as a means of catalyzing one enantiomer's transformation more than the other enantiomer. The activation energy of the process, after considering the effects on same from the catalyst, is inversely proportional to the rate of reaction (higher activation energy = lower rate of reaction). The differential between the energy of activation for each of the different enantiomer is known as the $\Delta\Delta G^{\ddagger}$. The degree of differential catalyzation is then considered the selectivity of the catalyst. Another important feature in a kinetic resolution is that whatever the rate of racemization between the two enantiomers it must be prohibitive in comparison to the rate of the preferred enantiomer's transformation. In many cases the rate of racemization will also be less than the rate of transformation of the enantiomer not selected by the catalyst. In instances in which the rate of racemization is higher than the rate of transformation of

the enantiomer not selected by the catalyst or is higher than the rate of transformation of either enantiomer, the reaction is then known as a dynamic kinetic resolution.

The history of kinetic resolution is long and storied. Lewis Pasteur documented an account in which a racemic mixture of tartaric acid was given as feed to a colony of Penicillium glaucum.[77] When Pasteur re-isolated the organic feed stock from the reaction he discovered that the remaining tartaric acid was optically active. In this experiment the enzymes of the mold colony provided the chiral environment needed to differentiate the enantiomeric mixture of the tartaric acid, and as such only one enantiomer was metabolized by the mold colony. From this account many more researchers would have access to an enhanced chiral pool. After accounts from Pasteur various others would seek to apply this technique to other systems.[78-84]

A key concept underpinning kinetic resolution is that of reporting the s factor of a particular reaction. The s factor is determined by the relation of the rate constants of transformation for each of the enantiomers in the racemic mixture. The s factor can be thought of as the quotient of the transformation of one enantiomer divided by the rate of the same transformation of the other enantiomer. When the two rates are equal the s factor is then 1, and as the rate of the less likely transformation decreases the s factor quotient increases.

As rates of reaction are difficult to measure it is typically easier to evaluate the enantiomeric excess of both the recovered starting material and the isolated product. Turning the enantiomeric excess into a useful data point to establish s factor requires the use of an additional conversion factor (c) which is merely a means of denoting the fraction of the enantioenriched starting material as a proportion of the sum of the enantioenriched isolated compounds. This value then can be seen as a stand in for the portion of the converted product that can be seen as a direct result of the catalyst and not simply by random chance. The formula then will have the form (equation 1):

$$c = \frac{ee(SM)}{(ee(SM) + ee(P))} \quad \text{(Equation 1)}$$

With the conversion quotient c in hand calculating the s factor becomes significantly easier. Since c is a unit less factor that is directly related to the ratio of products produced it can serve as a useful means of quantifying reaction rate. After adjusting the quotient-driven s factor formula to instead make use of c as the mark of reaction rate measurement the final equation is more complex but the variables required to use the formula are significantly easier to input. The final equation has a form of (equation 2):

$$s\ factor = \frac{\log(1 - c(1 + ee(P)))}{\log(1 - c(1 - ee(P)))} \quad \text{(Equation 2)}$$

A 2012 report[85] describes how investigators explored the use of cinchona alkaloid derivatives in the kinetic resolution of α-bromophenylacetamides using benzenethiolate. The expressed intent for this body of work was the elucidation of further asymmetric routes that could be found with this method. The investigators decided to focus on the use of quinine and its derivatives for the purposes of this report.

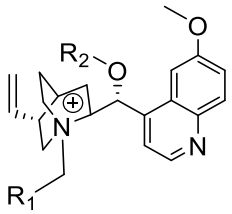
Quinine XVIII-XX were obtained, according to the researchers, for which they claim well documented performance. Details as to how they obtained these catalysts and what performance they were citing is not available in the report given. After detailing some initial experiments the researchers then go on to describe their kinetic resolution experiments. The description of the kinetic resolutions the researchers performed described the yield of the recovered product (with an allowance for a base maximum yield of 50 %), the %ee of the product with experimental details disclosed and the s factor they determined for each reaction. Without the %ee of the recovered starting material being disclosed readers can not independently confirm the s factor determined by the researchers. Table 31 contains a definition of cinchona alkaloid derivatives not disclosed prior.

From the results detailed below, in Table 32, this method of kinetic resolution seems to be lacking. Though the researchers did not impart the %ee of the recovered alcohol and thus did not

calculate the s factor associated with the reactions it is highly unlikely that the s factor would have been high enough to make a mark.

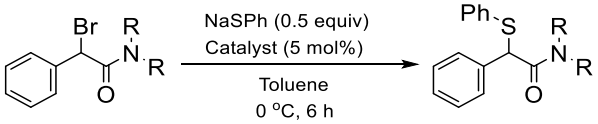
The enantiomeric excess in the product is certainly increased quite a bit in comparison to the previous work shown in this report. Though not disclosed in this report if the s factor derived from these reactions is accurate then the enantiomeric excess in the recovered starting material would only be between 20-29 %ee. This deduction makes sense when combined with the yield reported as is(the researchers are accounting for 28 % of the overall mass balance at best). Further experiments in this paper then seek to examine the physical characteristics of the compounds developed. This data is disclosed in Table 33 found below.

Table 31. Catalyst definitions



Entry	R_1	R_2	Catalyst Name
1	Ph	H	Quinine XIX
2	Et	H	Quinine XX
3	Ph	Bn	Quinine XXI

Table 32. Catalyst screening enantiomeric displacement

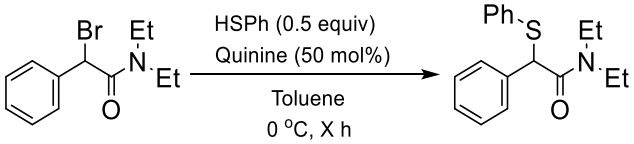


Entry	Catalyst	R	Yield (%)*	%ee (P)
1	Quinine XIX	Et	51	23
2	Quinine XIX	Ph	51	35
3	Quinine XX	Et	54	2
4	Quinine XX	Ph	56	5
5	Quinine XXI	Ph	42	1

*- Based on max 50% yield

Overall this report offers several interesting insights into kinetic resolution via cinchona alkaloid catalysis but does not succeed in adding a great deal of information to the field. Ways in which this report could be improved include; stating the %ee of recovered starting materials, check for the pseudo-enantiomer effect with the best-established conditions and probing further steric effects by using different starting materials with the same motif.

Table 33. *Quinine* for kinetic resolution



Entry	Time (h)	Yield (%)*	%ee (P)	s Factor
1	35	57	65	6
2	98	45	78	10
3	121	46	78	10

*- Based on max 50% yield

A 2014 report[86] details an interesting and surprising set of experiments germane to this area of study. Researchers in this report show how using a prochiral acylating agent in conjunction with a cinchona alkaloid derivative as a catalyst can result in a very effective kinetic resolution. The introduction of the prochiral acylating agent does introduce an extra complication to the

experimental Scheme as it opens the door to diastereomeric mixtures of products, but the results obtained from this innovation speak for themselves. Since the products produced can result in a diastereomeric mixture the enantiomeric enrichment reported for the product isolated is generally the enantiomeric enrichment of the major diastereomer.

Initially the researchers made use of cinchonine and then the free-amine analogue of cinchonine and quinidine before investigating cinchonidine derivatives (cinchonidine XIV and cinchonidine XVII).

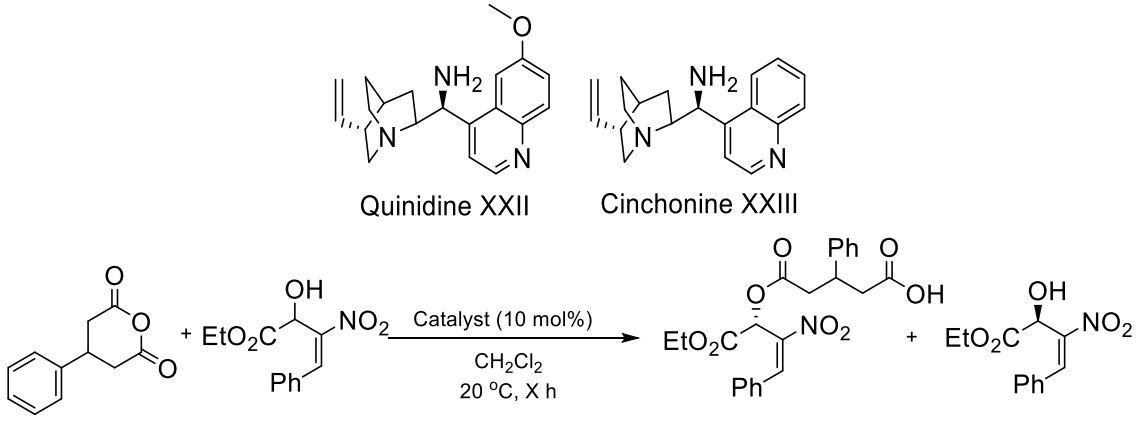
From the table below, Table 34, it can be seen that the researchers were able to establish very useful conditions in short order. Starting from a catalyst that did little to control the stereochemistry of the acylation the researchers were able to find a set of conditions that delivered excellent dr and %ee in the product produced as well as a high %ee in the recovered starting material. While the calculated s factors in this Table do not reflect the portion of the product in the minor diastereomer it is still impressive in its own way.

Further experiments altered the aryl substituent on the starting material and examined further substituents of the acylating agent. The investigators decided to use cinchonidine XIV as it provided the best dr of the catalysts tested up to that point. The investigators also decided to lower the reaction temperature as lower temperatures typically allow for greater discrimination in enantio-selective reactions. Lowering temperatures increases the amount of time a reaction must proceed before completion could be achieved as there is less thermal energy available to the system which limits the rate at which the activation energy of a system can be achieved.

Listed below, in Table 35, are the instances in which the dr of the products produced was at its maximum observed value. The interesting measure that should be highlighted is the increase in %ee by simply increasing reaction time between entries 1 and 2. This might imply that the ester

produced is active as an acylating agent, as the increase in %ee of the product would require a decrease in the amount of the less preferred enantiomer over a long time.

Table 34. Catalyst screening in a kinetic resolution



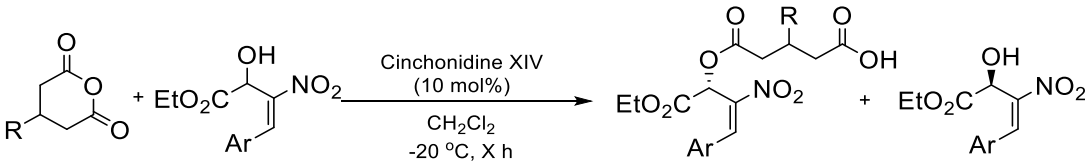
Entry	Catalyst	Time (h)	%ee (SM)	Yield (%)	dr	%ee (P)	s factor*
1	Cinchonine	20	9	45	3:1	9	1
2	Quinidine XXII	48	20	15	15:1	32	2
3	Cinchonine XXIII	48	24	14	13:1	28	2
4	Cinchonidine XIV	4	93	44	14:1	88	53
5	Cinchonidine XVII	4	92	42	10:1	90	62

*-calculated by Equation II, based on major diastereomer only

This report included a number of interesting results and set up the field for even more investigations further on. While the initial starting material is no doubt highly specialized, and thus not immediately generalizable, the results described in this report speak for themselves. It would have been a stronger proof of concept if the authors had shown how this system could be applied to more common-coin secondary alcohols.

A 2016 report[87] examines the rate of reaction directly in the reaction of a phosphoric diester using a cinchona alkaloid derivative functionalized with a guanidinium unit. This catalyst was proposed to aid the transformation by virtue of being bifunctional.

Table 35. Substrate scope Cinchonidine XIV kinetic resolution



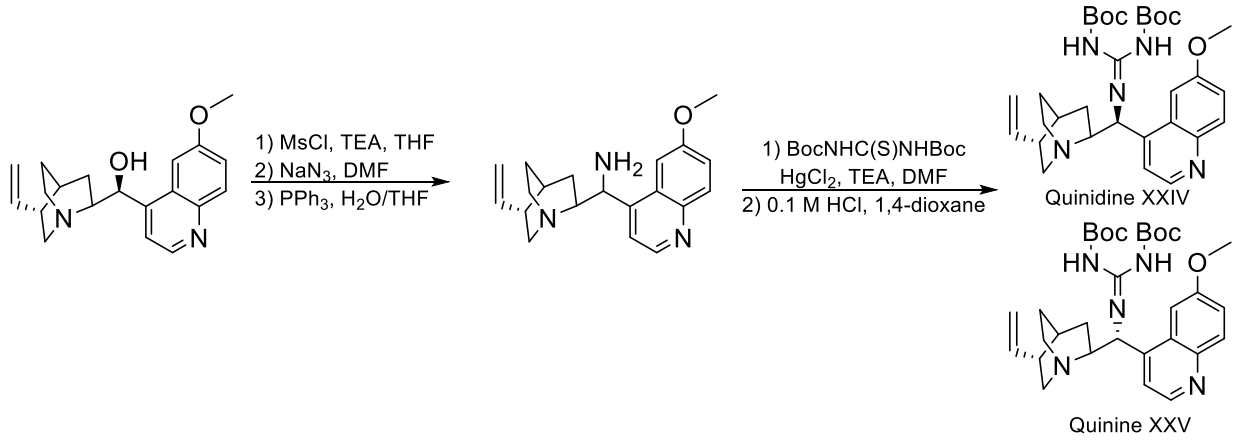
Entry	R	Ar	Time (h)	%ee (SM)	Yield (%)	dr	%ee (P)	s factor*
1	Ph	4-MeC_6H_4	4	86	37	>20:1	83	30
2	Ph	4-MeC_6H_4	120	86	42	>20:1	99	556
3	4-$OMeC_6H_4$	4-MeC_6H_4	120	82	40	>20:1	96	125
4	Me	2-thienyl	72	83	36	>20:1	82	26

*-calculated by Equation II, based on major diastereomer only

The investigation began with the synthesis of the compounds to be used. Production of the quinidine derivative was accomplished by beginning with 9-amino-(9-deoxy)-epi quinine and reacting this with *N,N'*-di-BOC-thiourea in dimethylformamide (DMF) with mercury (II) chloride and triethyl amine. The resulting product was then exposed to hydrochloric acid in 1,4-dioxane to yield the tri-salt of the corresponding catalyst. The quinine derivative was produced with somewhat more effort. Starting with epiquinine (quinidine) the researchers transformed the secondary alcohol into a mesylate leaving group, which was then displaced with sodium azide. The azide substitution inverts the stereochemistry of the secondary functional group, this group was then reduced using triphenyl phosphine. The final catalyst was then produced using the same series of reactions as the quinidine derivative. Scheme 3 contains the synthetic equations for the production of the materials mentioned above.

With the catalysts in hand, and after establishing the pH profile of the catalysts separate from the reaction to be studied, the investigators turned towards studying the reaction they set out to examine. The cleavage of 2-hydroxypropyl-*p*-nitrophenyl phosphate (HPNP), chosen for its resemblance to an RNA linkage, can be monitored by UV-Vis spectroscopy. Determination of the

differential rate of reactivity was completed post-reaction via chiral HPLC analysis of the recovered starting material. Though the use of the cinchona alkaloid derivatives is used in excess defining it as catalytic is still appropriate in that it lowers the energy barrier to reaction and is not consumed in the reaction. It is also an instructive use in kinetic resolution in that the racemic mixture of enantiomers is enantioenriched by the end of the reaction. The results can be found in Table 36.

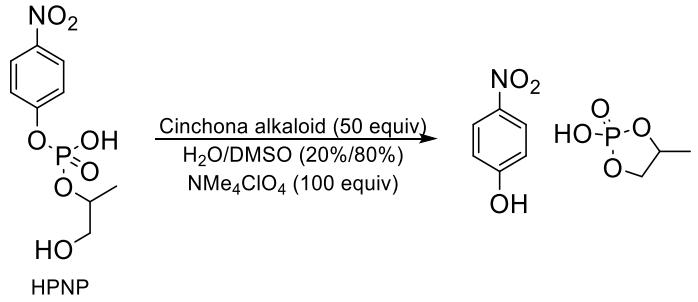


Scheme 3. Synthesis of *Quinidine XXIV* and *Quinine XXV*

The rest of the report investigates various computational methods to elucidate the specifics of the catalytic binding that facilitates the reaction. From these calculations it was concluded that the guanidinium moiety of the catalyst would coordinate to the phosphate moiety in the starting material while the bridgehead nitrogen of the catalyst would coordinate to the free alcohol of the starting material and thus would push it towards the phosphate moiety, driving the reaction forward.

While this report shows a very limited system analysis it is an interesting report in its way. The complete lack of the pseudo-enantiomer effect is highly intriguing and raises questions as to why this should be. It is also an interesting report in that determination of the s factor of the reactions was done with relative rates of reactivity instead of after the fact analysis.

Table 36. Catalyst study kinetic resolution with pH measurements



Entry	Cinchona Alkaloid	pH	k_{obs}/k_{bg}	s factor*
1	Quinidine XXIV	8.7	10600	5.2
2	Quinine XXV	8.9	2400	3.0

2.6. Conclusions:

Through the course of this review numerous examples have been brought to exemplify the scope and ability inherent with the use and investigation of cinchona alkaloids. Through the different areas investigated be it Michael, Henry or Mannich type reactions the utility of cinchona alkaloids can be seen in a large body of work. Among the most useful traits of this catalytic platform is the pseudoenantiomer relationships that exist between sets of cinchona alkaloids, as this relationship typically allows for complimentary products to be produced by using a different cinchona alkaloid. This exciting field of study has already born a dearth of fruitful reactions and methods of production and is posed to give even more going forward.

CHAPTER 3: KINETIC RESOLUTION OF SECONDARY ALCOHOLS USING CHIRAL DMAPO CATALYSTS

3.1. Introduction:

Every organism of which we are aware is composed of chiral building blocks. This simple statement is as obvious as it is mundane, however it has innumerous consequences one of which being that systems built upon these building blocks will respond differently to two different molecules when the sole difference between them is the stereochemistry associated with each. Construction from chiral building blocks, such as amino acids and saccharides, the only outcomes possible are chiral systems and indeed biologic systems are inherently chiral.

This is the underlying reason that two enantiomers, which respond identically to achiral stimuli, will elicit different responses in a biological system. To whit; the smell associated with 2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one (carvone) has been found to differ based upon the enantiomer being studied.[88] This inherent difference in reaction is not always as benign or readily observed as a different smell between two enantiomers. From this then it quickly becomes apparent that when a compound is to be produced for consumption it must be the desired enantiomer that produced and finally ingested.

There are a few processes by which it is possible to separate an enantiomeric pair. As enantiomers have identical physical properties and react identically to achiral compounds any separation method would require a built-in chiral discrimination capability.

To this end it is an established practice to use chiral chromatography as a means of separating enantiomers.[89] Chiral chromatography requires that a set of enantiomers will interact with the set chirality of the solid phase of the chromatographic system. Assuming the preceding to be true the outcome of such an experiment is that one enantiomer will be retained longer than the

other and this will allow the separation of the enantiomeric pair. While this method is highly useful and indeed invaluable in terms of analysis the fact remains that increasing the scale of such a separation increases the cost of the same very quickly.

Another valid method of solving the issue of enantiomer separation is to produce as little of one enantiomer as possible using asymmetric synthetic strategies. Typically, these strategies require the use of chiral reagents or chiral catalysts to influence a transition state of the reaction in order to create an insurmounTable energy barrier for one enantiomer in preference for the other. This method has many applications and offers potentially the best return on investment. However, as with all things, this strategy has several downsides. Many asymmetric synthetic plans require specific functionalities and can be fickle when used in new conditions outside of the original scope of its reported use.

Chiral resolution is a method of incorporating a compound with preexisting stereocenter (such as a modified amino acid) on to a functional group of a enantiomeric pair. The addition of a new stereocenter would normally create two sets of diastereomers and two sets of enantiomers, thereby worsening the issue at hand. However, in the case of chiral resolution as stated before, the added chiral center is fixed and is thus a known quantity. As a direct result of the previous line of reasoning instead of creating a pair of diastereomers and a pair of enantiomers only the pair of diastereomers is created. As diastereomers respond differently to achiral stimuli they have different melting and boiling points and can have different retention times on a set of chromatographic conditions. Following the separation of diastereomers ideally the set stereocenter can then be removed and the rest of the molecule would be otherwise unaffected.

Knowing that enantiomers react differently in chiral conditions opens the option of subjecting an enantiomer pair to a set of conditions that will react one enantiomer preferentially in the presence of the other. This is the fundamental key to understanding kinetic resolution. For the

kinetic resolution to be useful it has to create a set of conditions in which one enantiomer reacts much more quickly than the other, creates a product that is easily separated from the starting material and use cost effective methods to achieve separation of enantiomers. A closely related field of study is dynamic kinetic resolution, differentiated by the inclusion of a racemization procedure to invert the stereocenter or stereocenters that differentiates the set of enantiomers.

Another key to this body of work is a working knowledge of organocatalysis. Catalysts in general are compounds that facilitate reactions by lowering the activation energy of an intermediate step in the reaction pathway and is not consumed in the reaction that it facilitates. The use of catalysts is widespread and has helped to shape entire industries. Organocatalysis then is the application of organic species as a catalyst. Further advantages of organocatalysis include a complimentary set of reactions that can be formed when compared to traditional metal-based catalytic systems.[90-92]

Particularly related to the body of work described herein is the development of the Steglich esterification.[5] In this seminal report Neises and Steglich report the development of a method to form esters from carboxylic acids at ambient conditions. While the use of dicyclohexylcarbodiimide (DCC) in the service of producing esters was known beforehand[93] it was inefficient and produced variable results in many investigations.[94] The relatively simple addition of 4-dimethylaminopyridine (DMAP) in catalytic amounts facilitated a much wider range of ester formations than had previously been reported. The key idea behind this body of work was that the effect of creating a small amount of a more activated intermediate through, in this case, nucleophilic catalysis could result in a much greater amount of product formation.

3.2. Background:

Previous research in our group had demonstrated the utility of DMAP-template mediated catalysts could be applied to the field of kinetic resolution.[95] From this body of work it was

established that from a small amount of fluxionally chiral catalyst, an effective means of separating two enantiomers could be afforded. In addition to this body of work, our group was inspired by a number of reports on the increasing interest in the use of dimethylaminopyridine-N-oxide (DMAPO) as an organocatalyst.[96-100] To this end it was decided that an investigation should be undertaken to evaluate the efficacy of using our established template in conjunction with a DMAPO moiety and these promising avenues of reacting secondary alcohols in such a way as to effect a kinetic resolution.

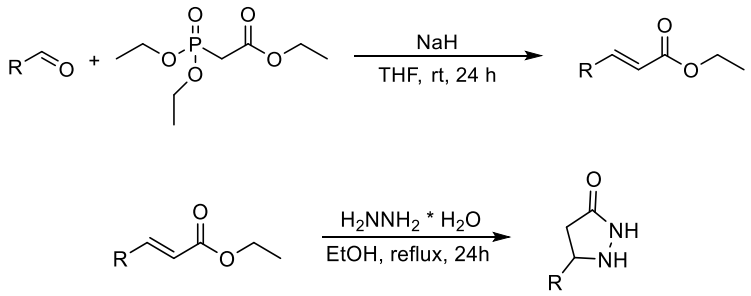
As the bulk of this research was to be conducted using DMAPO derivatives, the obvious issue to address first was to evaluate how DMAPO as the sole catalyst would behave in general. To this end initial screenings were focused upon establishing conditions to allow for reliable repetition across future screening reactions. Initially, benzoic anhydride was selected as the acylating agent as it was easier to monitor the consumption of the anhydride. This choice also facilitated monitoring the removal of the byproducts and leftover anhydride.

3.3. Synthesis:

The synthesis of the catalysts used was in line with previously established methodologies for the 3-template substituted DMAPO catalysts.[95] To that end the initial template was synthesized using a Horner-Wadsworth-Emmon's reaction to form a β-unsaturated ester which when reacted at elevated temperatures with aqueous hydrazine formed the substituted pyrazolidinone. In both past and present research it was demonstrated that more sterically hindering alkyl substituents on the 5 position of the pyrazolidinone ring was preferable in as so far as it tended to lead to a higher s factor.

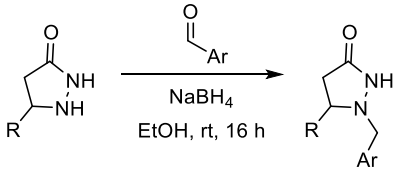
Having synthesized the parent pyrazolidinone, a reductive amination was then used to add a fluxional sterically-hindering element to the template. The regiochemistry of this addition was controlled by the fact that the pyrazolidinone ring has two very different nitrogen atoms in its ring

structure. The nitrogen at the 1 position reacts much more like a typical amine nucleophile while the nitrogen at the 2 position reacts much more like an amide nitrogen and as such is much less nucleophilic. As the fluxional group provides steric hindrance and therefore controls the overall chiral pocket of the catalyst, a large degree of sensitivity is associated with this group. Schemes 4 and 5 contains the synthesis details of the reactions discussed above.



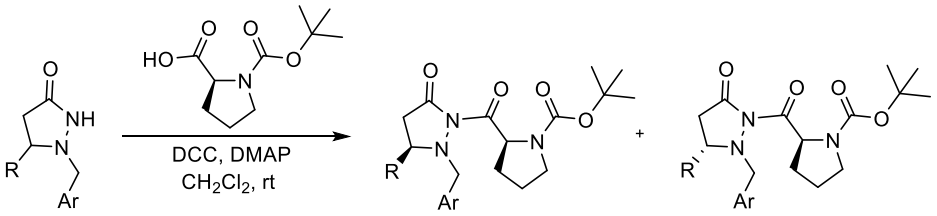
Scheme 4. Preparation of 5-substituted pyrazolidinone template

Following the full assembly of the template there was a racemic mixture of the template at hand. A chiral resolution technology was used to convert the racemic template into a diastereomeric mixture of amide products. The enantiopure material used in this coupling reaction was a protected version of proline, which as an amino acid is fairly economical for this purpose. The resulting amide was a mixture of diastereomers as opposed to enantiomers and as such was able to be separated via traditional column chromatography. Identity was established via chiral HPLC analysis by comparing to previously established reports. The synthesis is disclosed in Scheme 6.

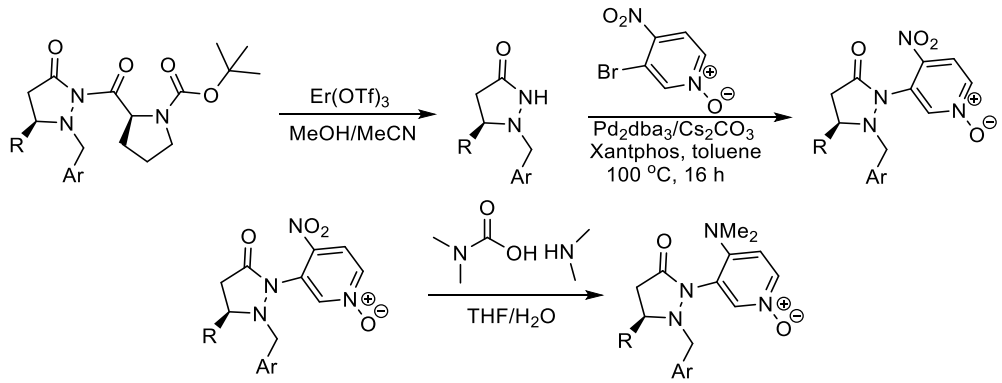


Scheme 5. Arylation of pyrazolidinone template

With a single enantiomer of the template at hand, the coupling to the modified pyridine was then put into place. The modified pyridine was generated by oxidizing 3-bromopyridine with hydrogen peroxide in acetic acid and then subjecting the resulting compound to electrophilic aromatic nitration. The palladium-catalyzed coupling reaction then was used in order to secure the template to the pre-catalytic center. The final catalyst was then produced by allowing the pre-catalyst to react with aqueous dimethylamine dimethylcarbamate mixture. Details of these reactions are disclosed in Scheme 7.



Scheme 6. Chiral resolution of 3,4-substituted pyrazolidinone template



Scheme 7. Synthesis of DMAPO catalysts

While DMAPO II-IV were synthesized with little unexpected challenge, our attention was turned to producing catalysts substituted at the 2-position of the DMAPO moiety and those efforts were met with a much greater deal of frustration and disappointment. The initial efforts to produce these catalysts focused on the similarity of the compounds chemical identity and it was wrongly

assumed, in hindsight, that the chemical reactivity would be the same or nearly so. The coupling reaction alone never afforded more than 15% yield of the desired 4-nitro product. Even with that low yield was the least of the issues encountered however. Figure 6 contains the definitions of the catalyst short hand.

Attempts to displace the nitro group of the pre-catalyst failed to achieve consumption of the starting material using the previously established conditions. Further reactions were undertaken to examine the logical progression of higher temperatures, greater concentrations of the dimethylamine substrate, the source of the dimethylamine substrate and the time the reaction was allowed to run. In the end it was determined that the catalyst was inert to most of these conditions and when it was not it was the degradation products that were isolated. Schemes 8 and 9 details the reactions used to attempt to realize this new class of catalyst.

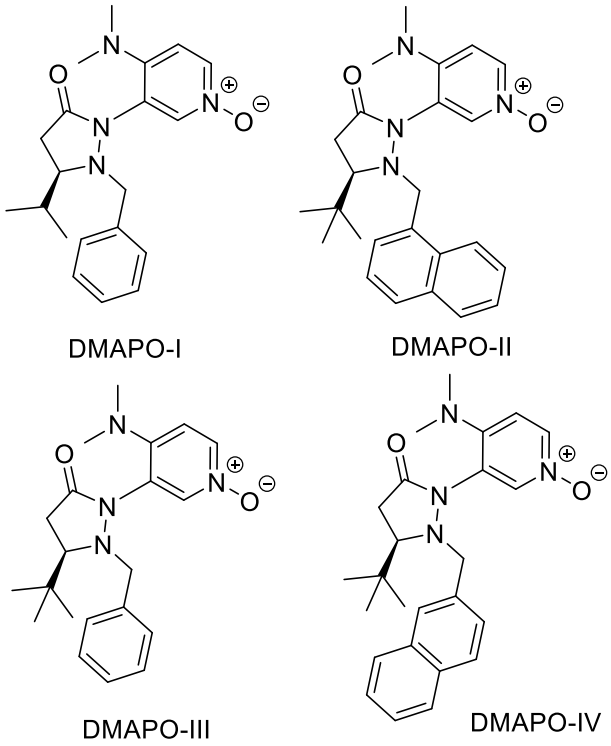
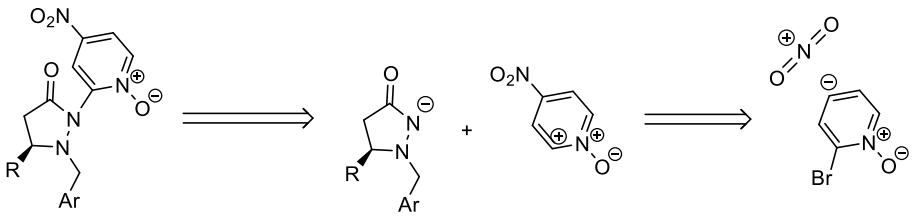
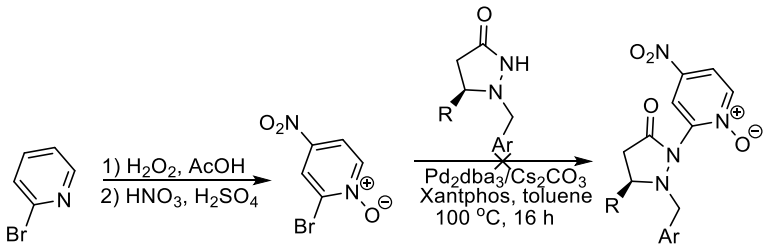


Figure 6. Definition of DMAPO- catalysts

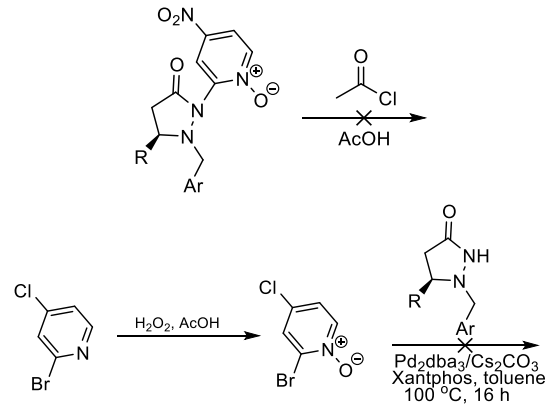


Scheme 8. Retrosynthetic analysis of new class of catalysts



Scheme 9. Attempt to create a new class of catalysts

Knowing that the 4-chloro pre-catalyst was more reactive, owing to work done previously, it was decided that it would be desirous to produce the 4-chloro pre-catalyst. These efforts seem not to work as well in the synthesis of 2- substituted template catalyst. Efforts to use acyl chloride in acetic acid to afford the 4-chloro pre-catalyst only led to degradation products. The next step that was decided upon was to use pre-formed 2-bromo-4-chloropyridine, available from commercial sources, oxidize it and couple it to the template. This promising endeavor met with failure as the 2-bromo-4-chloropyridine failed to couple in any measurable quantity. Scheme 10 details these attempts. With these paths to catalyst creation not having panned out, attention was turned instead to other aspects of the kinetic resolution reactions we believed to be under reported.



Scheme 10. Attempt to create a new class of catalysts

3.4. Experimental Design:

Following the first set of reactions being completed, separation of products and of the starting materials was then the primary concern. Fortunately, after a few rounds of trial and error, a reliable means of achieving separation was found. In large bore pipette column, a step gradient mobile phase was employed, starting from 100% hexanes the polarity was increased to elute more polar materials from the column in each step. To avoid issues with retention times across various column constructs a system revolving around column volumes was established. In order to achieve this a second marked large bore pipette was set atop the silica-containing first, both were marked to a standard level which was denoted as a column volume. The second large bore pipet was then filled with the mobile phase up to the appropriate volume and allowed to drip through the silica-loaded pipet. To keep the mobile phase from seeping out through the gaps in between the two glass pipets a small rubber tube was fitted to exclude air flow from the inside of the column to the outside, this was in evidence as the silica-loaded column always had an air gap between the solvent on top of the silica and the top of the large bore pipet. An illustration of this setup can be found in Figure 7.

The mobile phase step gradient was configured in such a way as to elute any mineral oil or other non-polar contaminants in the hexanes step, the ester in the next (10%/90% ethyl

acetate/hexanes), a catch step to allow for either late ester or early alcohol (20%/80% ethyl acetate/hexanes) and finally the alcohol would be eluted (40%/60% ethyl acetate/hexanes). Further polar steps would often elute only the base or carboxylic acids not sequestered during the aqueous workup, and subsequent extractions. Attempts to separate the catalyst from the reaction mixture yielded only catalyst degradations of one type or another.

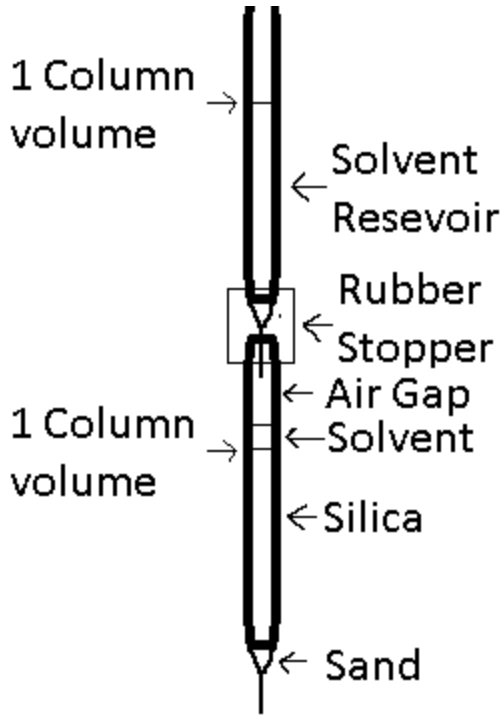


Figure 7. Construction of large bore pipet column

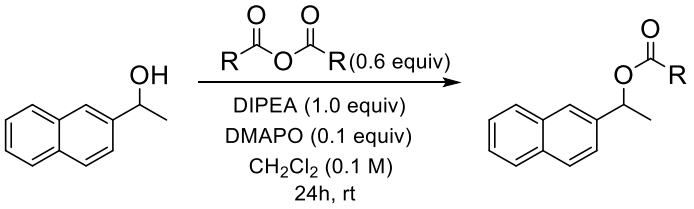
3.5. Results of Kinetic Resolution:

What follows is an annotated reporting of the results achieved by application of the conditions deduced from initial investigations. As mentioned previously, initial investigative reactions focused on the use of the parent catalyst. To that end the most obvious place to start was an investigation into the types of esters would be the most beneficial to create, in terms of ease of

use of the corresponding anhydride, ease of separation of ester from starting alcohol and reactivity in comparison to one another.

An initial foray into this investigation was somewhat ignominious, it became clear that a micro syringe would be needed in order to measure out the needed liquid anhydrides. What is also clearly shown in these results is the lack of robust reliability of the initial experimental sequence and showed how improvements such as additional extractions and more reliable column conditions could be established, and their utility is clearly shown in the work that followed. Benzoic anhydride was decided upon at the time as it is a solid and at the time was easier to measure out and dispense as needed. While not standard procedure, base was added to this set of experiments owing to literature reports of dimethyl aminopyridine-N-oxide as used in phosphorylation reactions in which the base used was crucial to the success of the reaction. It was an intuitive leap to attempt to apply this constraint in these conditions, however, further reactions would show that it was indeed a lucky break. Table 37 details the results of this initial foray.

Table 37. Initial reaction attempt with parent *DMAPO*



Entry	R	Recovered Alcohol* (%)	Ester(%)
1	None	132	0
2	i-Bu	0	67
3	i-Bu	0	87
4	Ph	47	38
5	Ph	18	27

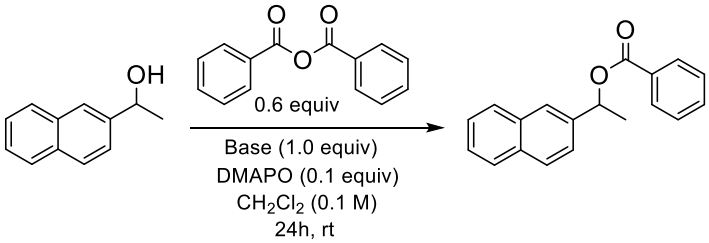
*based on theoretical recovery of 1 equiv.

As stated previously, the addition of base to this reaction was an intuitive leap based upon literature reports on a related, though distinctly different, process. Owing to the recognition of the possible unnecessary complication of additional base it was decided that this facet of the reaction would be elucidated next. From this set of screening reactions, it becomes apparent that greater care was needed in order to establish conditions that would allow all of the alcohol to be isolated. Indeed, that lesson was well taken and after the regretTable loss of alcohol in four of these reactions this issue was addressed and rendered past tense. An additional step of eluting the large bore pipet column with an even more polar mobile phase (50%/50% ethyl acetate/hexanes) was used in all future experiments. A lack of base caused a large drop in the amount of ester produced, and though this was one of the instances in which the amount of alcohol recovered was lower than expected it was apparent from the amount of ester isolated that this was the worst performing condition and was seemingly limited by the amount of catalyst added initially. The use of Proton-Sponge™ caused a complication in that it eluted along with the recovered alcohol in this screening and required an additional column purification. This second column purification was thought to be responsible for the lower than expected recovery of the alcohol in the case of the Proton Sponge™ experiments. It was decided that until the issue with the Proton-Sponge™ was resolved the base used going forward from this screening would be diisopropylethylamine (DIPEA). The results discussed prior may be found in Table 38.

The solvent screening was very useful in that it revealed errors in solvent removal protocol in the product isolation procedure. Additional high vacuum and additional air purges were added to compensate and with these additional steps in place the issue was largely abated. Following the reapplication of these additional techniques to the previous set of screening results the yields came into line with expected values. While toluene did increase the yield of the ester recovered from the reaction it was decided against for future use in these trials owing to the added difficulty in removing

all of the toluene and the more difficult separation of ester and alcohol that came as a result of this. Tetrahydrofuran produced no product in this reaction and so was not used in any experiments that followed. Table 39 contains the details of the reactions mentioned above.

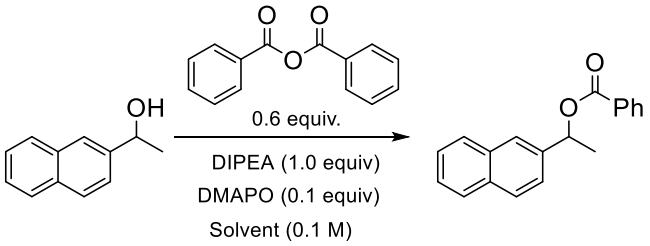
Table 38. Base screening parent *DMAPO* acylation



Entry	Base	Recovered Alcohol* (%)	Ester(%)
1	None	26	10
2	TEA	29	32
3	TEA	50	45
4	DIPEA	21	43
5	DIPEA	53	37
6	PS	29	52
7	PS	48	45

*based on theoretical recovery of 1 equiv.

Table 39. Solvent screen parent *DMAPO* acylation



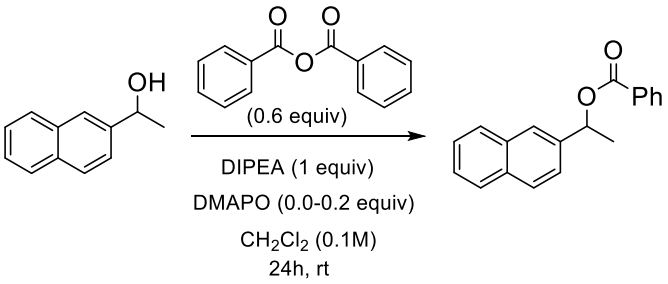
Entry	Solvent	Recovered Alcohol* (%)	Ester(%)
1	CH_2Cl_2	58	38
2	CH_2Cl_2	60	38
3	Toluene	50	48
4	Toluene	52	45
5	THF	90	0
6	THF	85	0

*based on theoretical recovery of 1 equiv.

This set of reactions showed a very interesting result, atypical for many organocatalytic systems the DMAPO acylation could proceed with very little of the catalyst in solution. Indeed, further reactions showed that a catalytic loading of even 1 mol% would be sufficient to catalyze the reaction. This is very encouraging as the chiral-template mediated catalyst under investigation in further reactions, while still fairly easy to synthesize, requires a number of steps to produce and as such using less of the catalyst is highly desirable. As can be seen from Table 40 below the point of diminishing returns is indeed beneath 10 mol% of the dimethyl aminopyridine-N-oxide loading.

Comparisons of the same system between DMAP and DMAPO show very similar conversions. What this meant for the proposed research was a positive indication that the substitution of DMAPO in place of DMAP could make a small enough difference in reactivity that any differences described between the two catalysts would be simply due to the efficacy of the acylation and not merely the rate at which the two catalysts would perform. Overall the trend that can be seen in the following table is the degree of activity of the dimethylaminopyridine-N-oxide.

Table 40. Catalyst loading parent *DMAPO* acylation

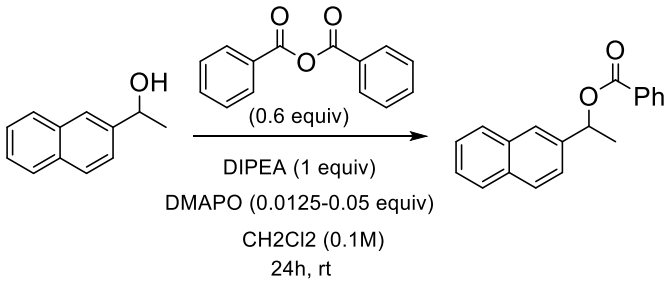


Entry	Equiv DMAPO	Recovered Alcohol* (%)	Ester (%)
1	0.1	47	55
2	0.1	50	61
3	0.2	38	59
4	0.2	47	48
5	0.0	103	0
6	0.0	115	0

*based on theoretical recovery of 1 equiv.

Even at 1 mol% catalyst loading there is little decrease in the efficacy of the catalyst. The same cannot be said for dimethyl aminopyridine which shows a decrease in ester produced as a function of decrease of catalyst loading. This competitive set of reactions added increased interest in the future reactions to be attempted with the produced catalyst later on. Tables 41 and 42 contains the results of these investigations.

Table 41. Catalyst loading using parent *DMAPO* acylation



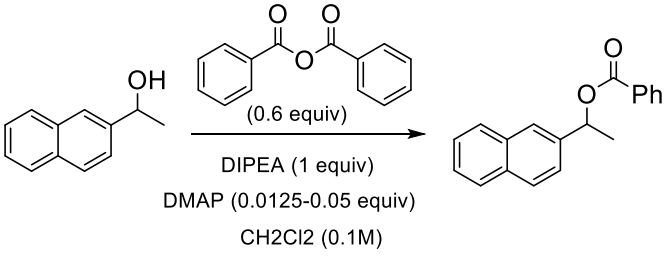
Entry	Equiv DMAPO	Recovered Alcohol* (%)	Ester (%)
1	0.05	35	46
2	0.05	50	46
3	0.025	50	43
4	0.025	47	41
5	0.0125	50	43
6	0.0125	56	43

*based on theoretical recovery of 1 equiv.

All of the enantiomeric excess values were determined by HPLC. Standard conditions for the separation of enantiomers for the esters produced was to employ a Chiral-Pak OD-H column with an isocratic flow of 1%/99% iPrOH/hexanes. Standard conditions for the separation of enantiomers of the alcohols recovered was to employ a Chiral-Pak OD-H column with an isocratic flow of 5%/95% iPrOH/hexanes. The Chiral-Pak columns are a series of columns that contain a media in which there is an inherent chiral bias creating an environment in which different enantiomeric pairs can separate based upon how they interact with the column media. The

chromatogram would then be integrated to account for the total area under the curve present for each of the enantiomers. The reason this works so well is the fact that the enantiomers have identical physical reactions to achiral stimulus, therefore even though they are demonstratively different compounds they will respond the same way to the UV light used to determine the concentration of the compound coming off of the column.

Table 42. Catalyst loading using parent *DMAP* acylation



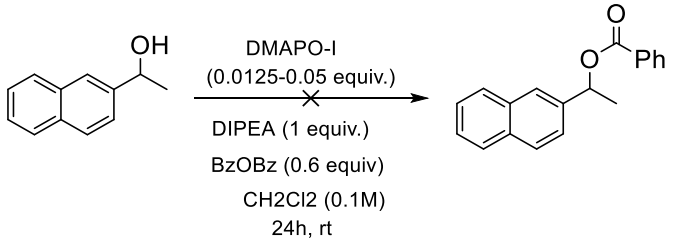
Entry	Equiv DMAP	Recovered Alcohol* (%)	Ester (%)
1	0.0125	68	38
2	0.0125	65	37
3	0.025	59	43
4	0.025	56	43
5	0.05	47	50
6	0.05	47	52

*based on theoretical recovery of 1 equiv.

With the investigation having produced as much information as it could attention was then turned towards investigating the kinetic resolution we originally intended to. It is worth mentioning that an often used measure of utility for reactions such as these are what are termed selectivity factors (s factor from here on). S factors are a means of comparing the enantiomeric excess of the product and the recovered starting material. In this instance that means the enantiomeric excess of the ester produced to the enantiomeric excess of the starting alcohol recovered once the reaction had been completed. To facilitate this a simple excel spreadsheet was generated that would allow for

the input of two pieces of information (%ee of the alcohol and ester respectively) which would then give the conversion of the reaction and then give the s factor as well. For the purposes of this spreadsheet and the calculations it covers %ee is understood as a number from zero to one. To generate the conversion the %ee of the recovered alcohol was divided by the sum of the %ee of the alcohol and the ester (=A2/(A2+B2)). With the conversion on hand the s factor was found by first generating the numerator and divisor of the total s factor separately. Attempts to simplify this into one cell were not successful. The numerator was generated with the function of the natural log of one minus the conversion multiplied by one plus the %ee of the ester (=(LN((1-(C3(1+B2)))))). The divisor was generated with the function of the natural log of one minus the conversion multiplied by one minus the %ee of the ester (=(LN((1-(C3(1-B2)))))). With both of the components of the s factor found the final step was to divide the numerator by the divisor and round to the nearest whole number to avoid reporting fractional s factors (=ROUND(D4/D5,0))).

Attempting to use previously established conditions in conjunction with the initial chiral-template mediated DMAPO resulted in a partial oxidation of the alcohol in addition to forming the desired ester. While it remains to be elucidated exactly how this occurred the existence of the oxidation rendered the need for alternative conditions. To that end further anhydrides were examined in order to establish if this is a general trend or a specific instance. Fortunately, no other anhydride used gave rise to the oxidized product. This attempt is detailed in Scheme 11.



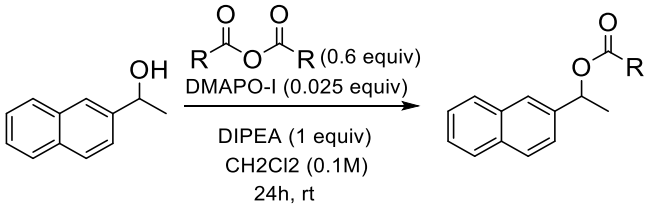
Scheme 11. Attempt at *DMAPO-I* acylation with benzoic anhydride

None of the examined anhydrides resulted in a production of oxidized products. In the realm of the examined anhydrides listed above neither the iso-butyl nor n-butyl anhydride truly stood out above the other, though it is worth noting that the trimethylacetic anhydride did not produce ester. This suggests that there is a requirement of the anhydride to have an angle of approach that facilitates the ester activation. From this set of reactions, it was concluded that more focus would have to be placed on anhydrides that were less sterically hindered than trimethylacetic anhydride. The results of this study are disclosed in Table 43.

This set of reactions led to a very exciting conclusion that compared to the DMAP analogue of this catalytic system, it is 4-fold more active. The modest difference between the lowest catalytic loading and the highest is not enough to warrant the use of the highest catalytic loading going forward. The results show that even at 2.5 mol% catalyst loading the catalyst is able to perform at the same level as the 10 mol% catalyst loading. While the end result of this reaction is not near the s factor realized in previous research[95] it was taken as a challenge to create a more sterically hindered transition state than had been attempted previously. The data generated from these reactions can be found in Table 44.

The next item for consideration was the determination of the optimal catalytic system to afford the kinetic resolution under investigation. Previous research had shown that different fluxional aryl and chiral alkyl substituents on the chiral template connected to the catalytic moiety greatly influences the overall selectivity. To create a closer relation to previous reactions carried out in this body of work so far DMAPO-III was selected, as it only varied in the chiral alkyl substituent, and DMAPO-II, as it varied from DMAPO-III in only the aryl substituent. Though DMAPO-III out performed DMAPO-II, DMAPO-II was selected for further investigations owing to a larger stockpile of the latter. Previous research had indicated that the DMAP analogue of DMAPO-II was

Table 43. Anhydride screening *DMAPO-I* acylation KR

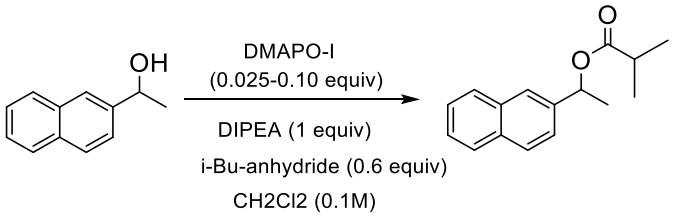


Entry	R	Recovered Alcohol* (%)	Ester (%)	Alcohol (%ee)	Ester (%ee)	s Factor**
1	i-Pr	62	40	20	25	2
2	i-Pr	62	42	20	25	2
3	t-Bu	95	0	0	0	0
4	t-Bu	93	0	0	0	0
5	n-Bu	62	38	20	20	2
6	n-Bu	62	44	20	20	2
7	None	97	0	0	0	

*based on theoretical recovery of 1 equiv.

**s factor=LN((1-(conv.*(1+%ee ester)))/(1-(conv.*(1-%ee ester)))

Table 44. Catalyst loading *DMAPO-I* acylation KR



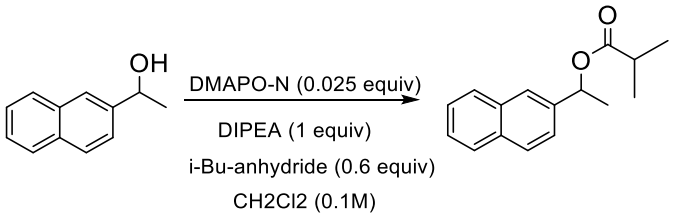
Entry	Cat equiv	Recovered Alcohol* (%)	Ester (%)	Alcohol (%ee)	Ester (%ee)	s Factor**
1	0.025	50	46	25	20	2
2	0.025	50	50	20	20	2
3	0.05	47	-	30	-	
4	0.05	44	54	30	20	2
5	0.1	47	50	30	20	2
6	0.1	50	46	30	20	2
7	None	97	8	0	20	

*based on theoretical recovery of 1 equiv.

**s factor=LN((1-(conv.*(1+%ee ester)))/(1-(conv.*(1-%ee ester)))

superior to other chiral-template mediated nucleophilic catalysts, and thus it was it was synthesized preferentially. The data generated from these investigations can be found in Table 45.

Table 45. Comparative DMAPO-N acylation KR



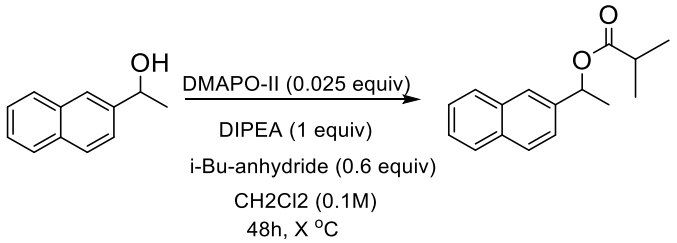
Entry	DMAPO-N	Recovered Alcohol* (%)	Ester (%)	Alcohol (%ee)	Ester (%ee)	s Factor**
1	DMAPO-II	59	35	10	20	2
2	DMAPO-II	56	40	15	20	2
3	DMAPO-II	62	35	10	20	2
4	DMAPO-III	68	33	20	40	3
5	DMAPO-III	62	33	20	40	3
6	DMAPO-III	62	35	20	40	3
7	-	97	-	0	-	

*based on theoretical recovery of 1 equiv.

**s factor=LN((1-(conv.*(1+%ee ester)))/(1-(conv.*(1-%ee ester)))

Knowing that diastereomeric transition states need not be very large to afford a high degree of enantiomeric enrichment lower temperatures were used to control the enantiomeric excess of the products afforded. Knowing that reactions proceed more slowly with lower ambient temperatures additional time was allotted to the reaction. Through each drop of 20 °C there was a reduced yield of ester created observed. However, there was also an increase in the enantiomeric excess of the products produced as well. From this data, listed in Table 46, it was decided that lower temperatures would be employed for the rest of the reactions to be performed.

Table 46. Temperature screening *DMAPO-II* acylation KR



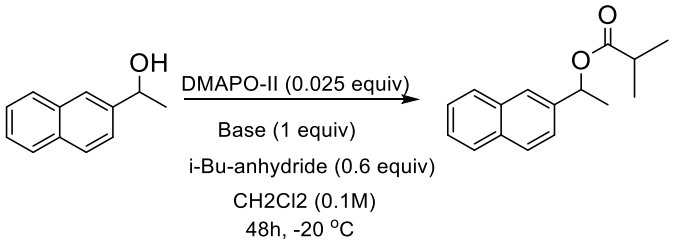
Entry	Temp (°C)	Recovered Alcohol* (%)	Ester (%)	Alcohol (%ee)	Ester (%ee)	s Factor**
1	0	59	40	20	30	3
2	0	59	37	20	30	3
3	-20	65	29	10	40	3
4	-20	65	29	15	40	3
5	20	50	48	20	20	2
6	20	47	46	10	20	2

*based on theoretical recovery of 1 equiv.

**s factor=LN((1-(conv.*(1+%ee ester)))/(1-(conv.*(1-%ee ester)))

In searching for a different base to use in this kinetic resolution it was discovered that Proton Sponge™ might be a useful replacement to the Hünig's base used previously. The previous issue that Proton Sponge™ caused was able to be resolved by allowing extra solvent removal time from the crude mixture. Once again the assumption that base was a useful addition was challenged and once again it was established that base was needed for this reaction. It allowed for a much higher enantiomeric excess to be realized in the recovered starting material. While it is true that the Proton Sponge™ produced a lower enantiomerically enriched ester product it was the first indication that the enantiomeric excess of the alcohol could be influenced as well and as such was taken as the base of choice for the experiments to follow. Table 47 contains the data generated in these investigations.

Table 47. Base screen *DMAPO-II* acylation KR



Entry	Base	Recovered Alcohol* (%)	Ester (%)	Alcohol (%ee)	Ester (%ee)	s Factor**
1	DIPEA	71	21	10	45	3
2	DIPEA	68	21	10	45	3
3	TEA	71	25	10	45	3
4	TEA	76	21	10	45	3
5	PS	-	42	-	40	-
6	PS	65	46	35	35	3
7	None	97	-	0	-	-

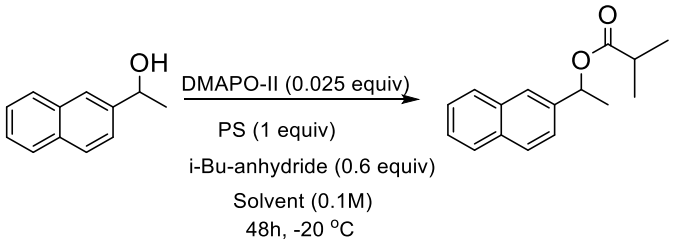
*based on theoretical recovery of 1 equiv.

**s factor=LN((1-(conv.*(1+%ee ester)))/(1-(conv.*(1-%ee ester)))

Seeking to study the effects of more and less polar solvents upon this reaction led to realization of even higher enantiomer excess in both the ester produced and the alcohol recovered. This gratifying result was very welcome as it allowed for improvements in the s factor with a very simple change to the overall reaction conditions. For an unknown reason the experiments performed in toluene did not allow the recovery of the left-over alcohol as all other reactions to this point had. This was a factor in choosing against using toluene in future reactions. Table 48 details the results of these experiments.

To establish that it was not a solely a quality of the DMAPO parent catalyst to act at such low catalyst loading, the catalytic loading of DMAPO-II was investigated as well. This screening confirmed that higher catalyst loading would not improve the overall s factor of the reaction. With this relationship having been confirmed in two separate catalyst systems it was taken as a fact of the matter, rather than an oddity. This set of data may be found in Table 49.

Table 48. Solvent screen *DMAPO-II* acylation KR

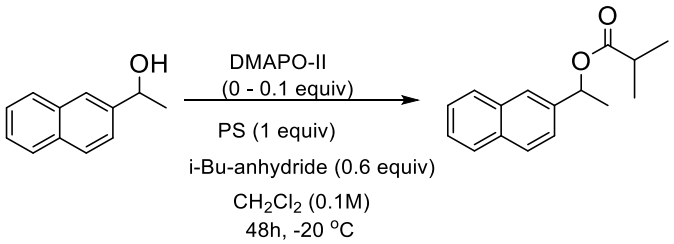


Entry	Solvent	Recovered Alcohol* (%)	Ester (%)	Alcohol (%ee)	Ester (%ee)	s Factor**
1	DCM	47	17	40	40	4
2	DCM	59	37	35	40	4
3	Toluene	29	63		10	
4	Toluene	-	63	-	20	-
5	Ether	47	44	70	50	7
6	Ether	47	44	70	45	6

*based on theoretical recovery of 1 equiv.

**s factor=LN((1-(conv.*(1+%ee ester)))/(1-(conv.*(1-%ee ester)))

Table 49. Catalyst loading *DMAPO-II* acylation KR



Entry	Cat Equiv	Recovered Alcohol* (%)	Ester (%)	Alcohol (%ee)	Ester (%ee)	s Factor**
1	0	91	4	0	0	0
2	0.025	62	31	50	50	5
3	0.025	59	37	50	45	5
4	0.05	53	44	40	40	4
5	0.05	53	35	40	40	4
6	0.1	56	38	40	50	4
7	0.1	56	35	40	40	4

*based on theoretical recovery of 1 equiv.

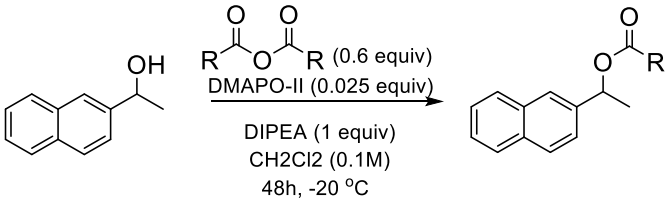
**s factor=LN((1-(conv.*(1+%ee ester)))/(1-(conv.*(1-%ee ester)))

Seeking higher enantioenriched products, alternative anhydrides were investigated. At this lower temperature, the trimethylacetic anhydride failed to acylate the secondary alcohol once again, however the experiment was still a success as it showed the promise of the cyclohexyl anhydride. Indeed the 20 %ee improvement over the previous high-water mark of the iso-butyric anhydride was a significant improvement. Data generated from this set of experiments may be found in Table 50.

Looking towards the sensitivity of the substrate under investigation two additional secondary alcohols were investigated and the results were underwhelming. While neither provided a high s factor it was instructive to note that the structural isomer of the secondary alcohol under investigation to this point provided comparable results. Though it is worth noting that the enantiomeric excess of the ester made is similar the enantiomeric excess of the recovered alcohol was much lower. Future reactions were greatly influenced by this set of reactions as the results indicated a clear improvement from the standard conditions used to this point. Table 51 contains the data generated from these investigations.

A further decrease in reaction temperature was investigated to perhaps increase the s factor realized from this reaction. This increase was found. While the benefits of decreasing temperature should be obvious from this body of work in relation to raising the enantiomeric excess in the isolated compounds, the downside is to increase the cost of putting this technology into practical use. Increasing or decreasing temperature in which a reaction occurs costs additional funds in addition to the material component of putting together the reactants and solvent. As such further decreasing the temperature further might create a greater barrier between the benchtop chemistry shown here and further applications in the future. The details of this study may be found in Table 52.

Table 50. Anhydride screen *DMAPO-II* acylation KR

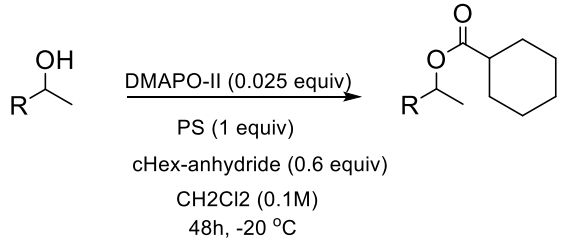


Entry	R-	Recovered Alcohol* (%)	Ester (%)	Alcohol (%ee)	Ester (%ee)	s Factor**
1	i-Pr	-	-	-	-	-
2	i-Pr	65	29	15	40	3
3	t-Bu	82	0	0	0	-
4	t-Bu	82	0	0	0	-
5	cHex	79	19	10	60	5
6	cHex	76	17	10	60	5
7	None	97	-	0	-	

*based on theoretical recovery of 1 equiv.

**s factor=LN((1-(conv.*(1+%ee ester)))/(1-(conv.*(1-%ee ester)))

Table 51. Substrate scope *DMAPO-II* acylation KR

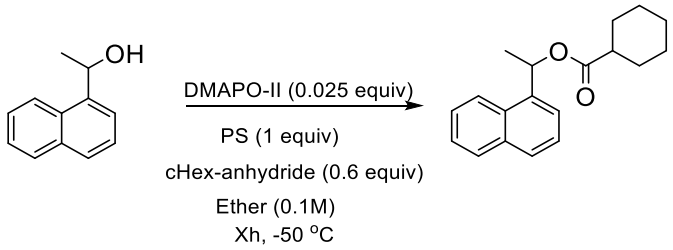


Entry	Substrate (R)	Recovered Alcohol* (%)	Ester (%)	Alcohol (%ee)	Ester (%ee)	s Factor**
1	2-Nap	53	46	60	50	6
2	2-Nap	59	34	60	55	7
3	1-Nap	59	41	40	55	6
4	1-Nap	65	34	40	50	6
5	Ph	46	39	5	10	2
6	Ph	42	43	5	10	2
7	None	0	0	-	-	-

*based on theoretical recovery of 1 equiv.

**s factor=LN((1-(conv.*(1+%ee ester)))/(1-(conv.*(1-%ee ester)))

Table 52. Lower temperature screen *DMAPO-II* acylation KR



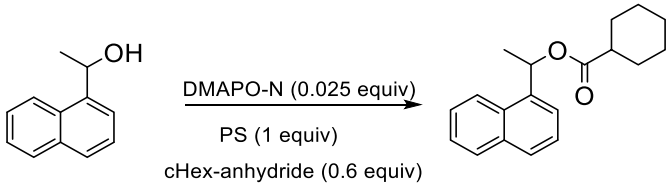
Entry	X (h)	Recovered Alcohol* (%)	Ester (%)	Alcohol (%ee)	Ester (%ee)	s Factor**
1	48	56	33	20	40	3
2	48	59	34	20	40	3
3	48	59	34	20	40	3
4	72	47	52	30	40	4
5	72***	29	27	30	40	4
6	72	44	48	30	40	4

*based on theoretical recovery of 1 equiv.
**s factor=LN((1-(conv.*(1+%ee ester)))/(1-(conv.*(1-%ee ester)))
***-Denotes a spill as the causative agent of low yield

With the best conditions established to date it was decided that it was time to re-examine the catalyst being used. To investigate if the best catalyst for the job was being used, given all of the condition alterations that had been made to this point, a full screening of the catalytic systems to hand was undertaken. Interestingly DMAPO-IV, which had not been previously used, managed to a higher s factor when compared to the others, though it was admittedly a minor improvement. This data is disclosed in Table 53, listed below.

A full series of bases were investigated in order to confirm that the best selection had been made from previous investigations. This turned out to be the case, though it was very interesting to find that cesium carbonate performed so well. It had been added as a foil to ensure that the base to be used required homogenous dispersal but in this instance that was shown not to be the case. The data that this investigation yielded can be found in Table 54.

Table 53. Comparitive catalyst screening DMAPO-N acylation KR



Entry	DMAPO-N	Recovered Alcohol* (%)	Ester (%)	Alcohol (%ee)	Ester (%ee)	s Factor**
1	DMAPO-I	74	25	10	30	3
2	DMAPO-I	71	25	10	40	3
3	DMAPO-II	47	46	50	40	4
4	DMAPO-II	47	52	60	40	5
5	DMAPO-III	68	29	20	40	3
6	DMAPO-III	59	37	20	40	3
7	DMAPO-IV	56	43	65	40	5
8	DMAPO-IV	56	45	55	40	4

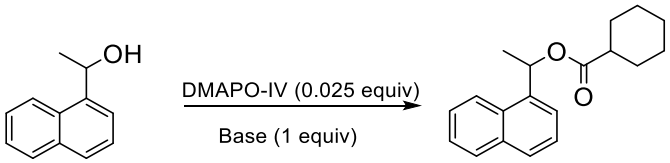
*based on theoretical recovery of 1 equiv.

**s factor=LN((1-(conv.*(1+%ee ester)))/(1-(conv.*(1-%ee ester)))

In order to connect what had been deduced from previous experiments back to the starting point the same base screening as above was investigated using the secondary alcohol used in the beginning. The results of the follow-up screening showed the highest s factor to date with this vein of research, unexpected owing to the fact that this system had already been investigated (though not with the exact conditions used below in Table 55).

In investigating secondary alcohols of a type not investigated previously focused effort was placed on determine how generalizable this method can be, in addition to searching for systems that would yield even higher s factors than had previously observed. In addition to the results disclosed 1,2,3,4-tetrahydro-1-napthanol was also tested, this chemical was not included as it gave rise to more products than simply the starting alcohol and the corresponding ester, including the ketone corresponding to the starting alcohol. The results may be found in Table 56.

Table 54. Base screening *DMAPO-IV* acylation KR

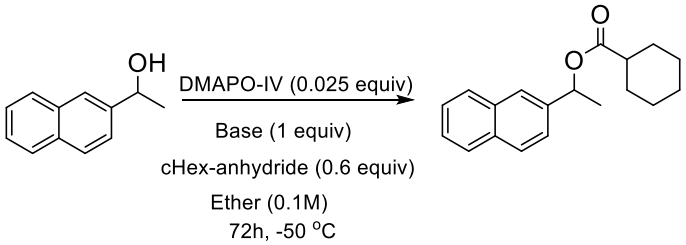


Entry	Base	Recovered Alcohol* (%)	Ester (%)	Alcohol (%ee)	Ester (%ee)	s Factor**
1	PS	56	43	40	40	4
2	PS	50	45	40	40	4
3	TMEDA	56	41	30	50	4
4	TMEDA	53	43	30	50	4
5	DBU	94	4	10	35	3
6	DBU	94	4	10	35	3
7	2,6-tBuP	59	43	50	40	4
8	2,6-tBuP	56	48	55	40	4
9	Cs_2CO_3	62	37	50	40	4
10	Cs_2CO_3	65	32	40	40	4
11	None	91	2	10	50	4

*based on theoretical recovery of 1 equiv.

**s factor=LN((1-(conv.*(1+%ee ester)))/(1-(conv.*(1-%ee ester)))

Table 55. Base screening *DMAPO-IV* acylation KR

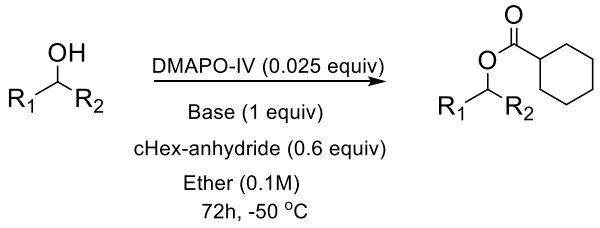


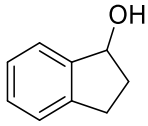
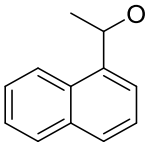
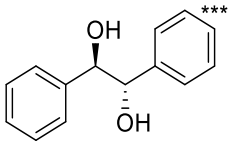
Entry	Base	Recovered Alcohol* (%)	Ester (%)	Alcohol (%ee)	Ester (%ee)	s Factor**
1	PS	47	50	90	50	9
2	PS	47	46	90	40	7
3	TMEDA	41	54	90	30	5
4	TMEDA	41	57	90	30	5
5	2,6-tBuP	79	18	30	50	4
6	2,6-tBuP	76	18	30	60	6
7	DBU	91	4	10	50	4
8	DBU	88	2	15	50	4
9	Cs_2CO_3	47	46	70	50	7
10	Cs_2CO_3	44	50	70	30	4
11	None	91	4	10	50	4

*based on theoretical recovery of 1 equiv.

**s factor=LN((1-(conv.*(1+%ee ester)))/(1-(conv.*(1-%ee ester)))

Table 56. Substrate screening *DMAPO-IV* acylation KR



Entry	Substrate	Recovered Alcohol* (%)	Ester (%)	Alcohol (%ee)	Ester (%ee)	s Factor**
1		50	44	10	80	3
		50	48	10	80	3
2		56	38	40	40	4
		53	37	40	40	4
3		28	15	30	-	-
		23	15	40	-	-

*based on theoretical recovery of 1 equiv.

**s factor=LN((1-(conv.*(1+%ee ester)))/(1-(conv.*(1-%ee ester)))

***-Denotes that alcohol and ester correspond to monoester and diester, respectively.

3.6. Discussion of Results:

Described above are the results from numerous investigations into effecting a kinetic resolution using DMAPO and template-mediated DMAPO catalysts. While this study is a mere starting point in future endeavors to understand how these kinds of systems might find use in facilitating the separation of enantiomers it makes positive strides in that direction.

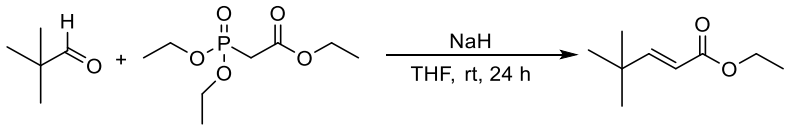
In comparing the results described herein to previous research conducted by our research group,[95] it becomes apparent that this line of catalysts are not as effective as the corresponding DMAP line, though it is worth noting that this line is capable of a four-fold reduction in the amount of catalyst needed to maximize the selectivity factor for the reaction conducted. Other interesting

notes made from this line of inquiry include; the potential for catalytic oxidation with certain systems, the ability to deracemize a meso-compound and the evidence that alternative connectivity to the catalytic center from the chiral-template might well allow for further research into this subclass of nucleophilic catalysts.

3.7. Experimental Details:

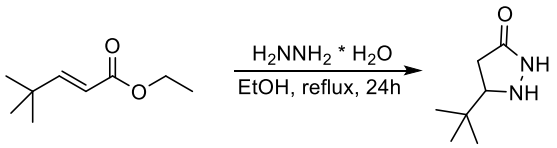
All solvents used in reactions were dried and degassed using a Dry-Solv system and stored under inert atmosphere. All purchased materials were used without further purification. All archived materials used were purified and stored under inert atmosphere before use. Flash chromatography was performed using silica gel 60 (230 X 400 mesh.) Melting points were obtained by use of a Thomas Hoover Uni-Melt Capillary melting point apparatus and are not corrected. ^{1}H NMR spectra were recorded on a Bruker-400 (400MHz) spectrometer. ^{13}C NMR spectra were recorded on a Bruker-400 (100MHz) spectrometer. HPLC analyses were performed with the use of a Waters 515 HPLC pump system coupled to a 2487 dual wavelength absorbance detector which was operated with a workstation PC running Empower workstation program. FT-IR spectra were recorded on Thermo Scientific Smart iTX device operated with a workstation PC running OMNIC software. HRMS were obtained by the use of a Waters T-Wave Ion Mobility device. Reflux condensers were enabled by a 1/250 HP Little Giant fountain pump set into a 1L reservoir of room temperature water filled to ~500mL.The Combi-Flash unit used was a Teledyne Isco model Combi-Flash Rf 200. For temperature-controlled reactions, a Neslab CB 80 Cryo-cool was used with a bath of isopropyl alcohol.

Following published protocols[95] DMAPO III and IV were produced.



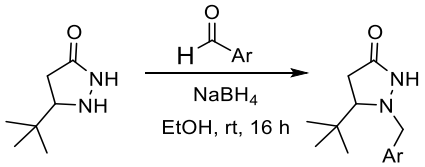
Scheme 12. HWE reaction

In a dried round-bottom flask equipped with a stir bar under an argon atmosphere a mineral oil suspension of sodium hydride (2.200 g, 1.2 equiv) was added. This mineral oil suspension was then stirred in hexanes (20 mL) for 10 minutes. The hexane was then removed, and the process repeated once more. To the washed sodium hydride was added dry tetrahydrofuran (150 mL, 0.3 M), the mixture was watched for gas evolution. If gas evolution was observed then the experiment was restarted. If no gas evolution was observed then triethyl phosphonoacetate (9.8mL, 1.1 equiv) was added via a syringe pump over the course of 30 minutes. Following full addition of the triethyl phosphonoacetate an additional 30 minutes were allowed to enable a high degree of deprotonation. After 30 minutes the pivalaldehyde (4.9 mL, 1 equiv) was set into the syringe pump and added to the mixture over the course of 12 hours. Reaction monitoring via TLC analysis was complicated by a lack of chromophores in either the reagents or products, though use of permanganate staining could show the production of the product. Successful reactions typically had a biphasic mixture, one translucent the other a dark tan. The mixture was then quenched with a saturated aqueous solution of ammonium chloride and then the mixture was then subjected to rotary evaporation. Upon removal of most of the organic solvent a successful reaction typically would develop a biphasic system when 20 mL of water was added. This mixture was then extracted using hexanes (3 X 50 mL) and the organic layer was then concentrated. The material obtained from the extraction and concentration was then used as is.



Scheme 13. 4- Substituted pyrazolidinone template formation

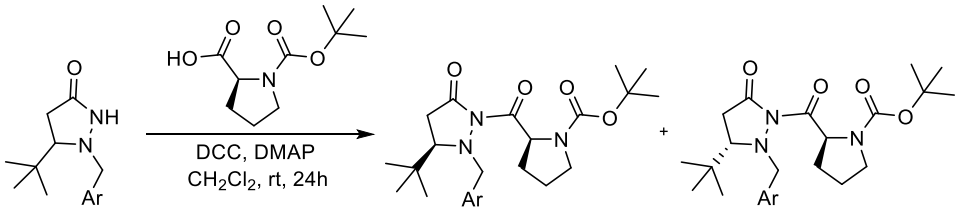
In a round-bottom flask equipped with a stir bar under atmosphere the starting material (3.9 g, 1 equiv) was dissolved in 95% ethanol (50 mL, 0.2 M). A reflux condenser was added to the apparatus and the round-bottom flask was then put into an oil bath and heated to reflux. The reflux condenser was equipped with a recirculating pump. Once the solution was refluxing the hydrazine hydrate was added through the reflux condenser. When all of the hydrazine hydrate was added the reaction was allowed to proceed at reflux until the alkene was no longer detecTable by TLC analysis using permanganate staining. Following the consumption of the starting material the reaction mixture was then concentrated and the crude material was then used in the following reaction.



Scheme 14. Arylation of 4-substituted pyrazolidinone template

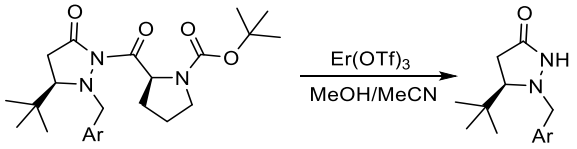
In a round-bottom flask equipped with a stir bar under atmosphere the starting material (1 equiv) was dissolved in 100 % ethanol (0.5 M). Upon full solvation of the starting material the aldehyde (1.1 equiv) was then added. After addition of the aldehyde the solution would typically take on a yellow, opaque color over the course of several hours. The reaction was monitored via TLC (50%/50% ethyl acetate/hexanes) with UV (254 nm) light. After a period of time ranging from 12-16 hours sodium borohydride (1.9 g, 1 equiv) was then added over the course of ~10 minutes to avoid excess gas evolution and frothing. Over the course of another 1 hour the reaction typically consumed the excess sodium borohydride creating a precipitate. After the 1 hour allotted for the

sodium borohydride reduction the reaction was quenched with a saturated aqueous solution of ammonium chloride (5 mL) and then this mixture was allowed to stir for an additional 10 minutes. Distilled water was then added until the reaction mixture became translucent once more. The mixture was then concentrated to remove the ethanol (though removal of some water was ineviTable) and this concentrated mixture was then extracted using ethyl acetate (3 X 50 mL) and the organic layer was then concentrated. The crude mixture was then subjected to column chromatography (20%/80% ethyl acetate/hexanes -> 50%/50% ethyl acetate/hexanes). The final product of these three steps was then isolated.



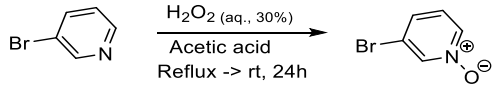
Scheme 15. Chiral resolution of pyrazolidinone template

In a dried round-bottom flask equipped with a stir bar under an argon atmosphere the (tert-butoxycarbonyl)-D-proline (1 equiv), dicyclohexylmethanediimine (1.1 equiv) and 4-dimethylaminepyridine (0.1 equiv) were added. The dry starting materials were subjected to vacuum and the flask was back-filled with argon three times. Following the argon purge dichloromethane (0.4 M) was added and the solid reagents were allowed to dissolve. The template-starting material was pre-dissolved in dichloromethane (5 mL) and added to the reaction. The reaction was typically opaque in the beginning and noticeably more translucent at the end in successful reactions. The reaction was allowed to proceed for 24 hours. After 24 hours the mixture was diluted with dichloromethane (50 mL) and then extracted with distilled water (3 X 50 mL). Upon separation the organic layer was then concentrated and subjected to Combi-Flash chromatography.



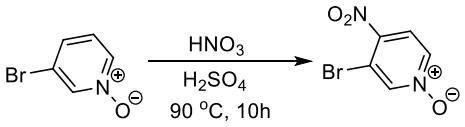
Scheme 16. Cleavage of amino acid

In a vial equipped with a stir bar under an argon atmosphere the protected starting material (1 equiv) was added and then dissolved in 60%/40% methanol /acetonitrile (0.7 M). After the starting material was fully dissolved tris(((trifluoromethyl)sulfonyl)oxy) erbium (III) (0.05 equiv) was added. The reaction was monitored by TLC (50%/50% ethyl acetate/hexanes) and was stopped in 24 hours. The reaction mixture was condensed and the crude product was dissolved in distilled water (2 mL) and extracted with ethyl acetate (3 X 5 mL). The organic layer was concentrated and the crude subjected to column chromatography (20%/80% ethyl acetate/hexanes -> 50%/50% ethyl acetate/hexanes). The product was then isolated.



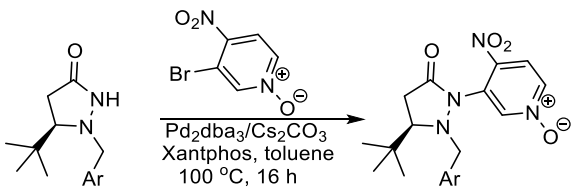
Scheme 17. Oxidation of *3-bromopyridine*

In a round-bottom flask equipped with a stir bar under atmosphere 3-bromopyridine (16.4 mL, 1 equiv) was dissolved in acetic acid (75.0 mL, 1.2 M). After full solvation aqueous hydrogen peroxide (20%, 50mL, 3.4 equiv) was added to the reaction vessel which was then fitted with a reflux condenser. The reaction apparatus was then put into an oil bath and set to reflux for 8 hours. After reflux the reaction was allowed to cool to room temperature and continue reacting for an additional 16 hours. Following reaction completion, as followed by TLC (50%/50% ethyl acetate/hexanes), the reaction was concentrated until the solvent had been removed. The crude was then used without further purification.



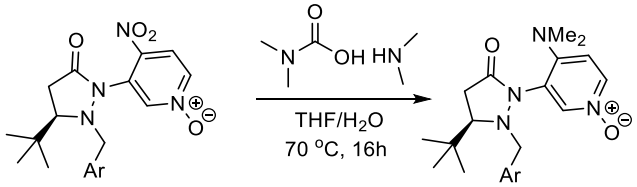
Scheme 18. Nitration of *3-bromopyridine-N-oxide*

In a round-bottom flask equipped with a stir bar under atmosphere on an ice bath 3-bromopyridine-N-oxide (29.6 g, 1 equiv) was dissolved by slowly adding sulfuric acid (35 mL, 1.5 M). Concurrent with solvation a mixture of nitric acid (55mL, 6.5 equiv) and sulfuric acid (35 mL) was prepared by carefully adding the sulfuric acid to the nitric acid which was in an Erlenmeyer flask on an ice bath. Upon full solvation of the 3-bromopyridine-N-oxide in sulfuric acid the acid mixture was added slowly. Rapid heating could lead to issues during this addition and was combated by reducing the addition rate and adding additional ice to the ice bath holding the reaction vessel. The reaction was allowed to stir for 2 hours on an ice bath before being moved to an oil bath which was in turn brought to 90 °C. The reaction was allowed to react at 90 °C for 10 hours and there after was allowed cool to room temperature. The room temperature reaction was then poured over ice in a large beaker and neutralized with sodium hydroxide. The base needed to be added slowly owing to any potential product being just as soluble in basic media as acidic media. When correctly brought to neutral (pH= ~7) precipitate would begin to form and could then be collected with vacuum filtration. The crude product was then recrystallized in a mixture of hexanes and dichloromethane (80%/20% hexanes/dichloromethane).



Scheme 19. Coupling of pyrazolidinone template and pre-catalyst moiety

In a dried round-bottom flask equipped with a stir bar under an argon atmosphere dried toluene (0.5 M) was added and flushed with argon for 10 minutes. After inert gas flushing the chiral starting material (1 equiv), 4-nitro-3-bromopyridine-N-oxide (1.1 equiv), cesium carbonate (1.2 equiv), tris(dibenzylideneacetone)dipalladium (0) (0.05 equiv) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.05 equiv) were added to the reaction vessel. The reaction vessel was then equipped with a reflux condenser and the system flushed with argon for 10 minutes. Following the inert atmosphere flush the apparatus was then put into an oil bath and heated to 100 °C and allowed to react for 12 hours before being allowed to cool to room temperature. The room temperature reaction was then filtered through via vacuum filtration through a bed of celite. The bed of celite was washed with an equal volume of toluene to the reaction mixture to remove as much of the product as possible. The reaction mixture was then concentrated and subjected to column chromatography (10%/90% methanol/dichloromethane). The purified product was then isolated and used further.



Scheme 20. Activation of catalyst moiety

In a vial with a stir bar the starting material (1 equiv) was added and then dissolved in a mixture of tetrahydrofuran and water (70%/30% tetrahydrofuan/water, 0.2 M). Following dissolution dimethylamine dimethylcarbamate (8 equiv) was added. The reaction vial was then sealed and heated in an oil bath to 70 °C. Once heated the reaction was allowed to proceed until TLC (10%/90% methanol/dichloromethane) showed consumption of starting material. Following the completion of the reaction the reaction was allowed to cool to room temperature and was then

concentrated. The crude product was then subjected to column chromatography (10%/90% methanol/dichloromethane). The product was then isolated and used in future reactions.

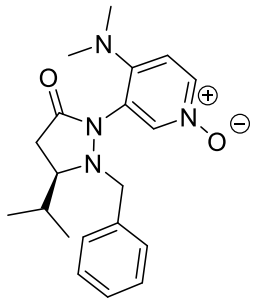


Figure 8. *DMAPO I* Characterization[95]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.72-0.75 (m, 6H), 1.58-1.63 (m, 1H), 2.36 (dd, *J*=16.8, 3.2 Hz, 1 H), 2.88 (s, 6H), 2.94-2.99 (m, 1H), 3.06-3.12 (m, 1H), 3.84 (d, *J*= 12.4 Hz, 1H), 4.1 (d, *J*= 12.4 Hz, 1H), 6.48 (d, *J*= 7.6 Hz, 1H), 7.17-7.23 (m, 5H), 7.80 (dd, *J*= 3.6, 2.0 Hz, 1H), 8.26 (d, *J*= 2.0, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2, 19.4, 31.4, 32.5, 41.5, 61.4, 65.4, 113.1, 123.2, 128.1, 128.5, 129.6, 135.8, 137.9, 138.6, 146.4, 170.6

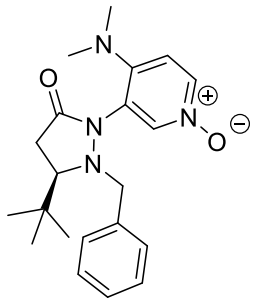


Figure 9. *DMAPO II* Characterization[95]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.66 (s, 9H), 2.45 (dd, *J*= 17.1, 5.6 Hz), 2.93 (s, 6H), 3.01 (dd, *J*=9.8, 1.9 Hz, 1H), 3.24 (dd, *J*=17.1, 9.7 Hz, 1H), 3.86 (d, *J*= 11.7 Hz, 1H), 4.21 (d, *J*= 11.7 Hz, 1H), 6.61 (d, *J*=7.4 Hz, 1H), 7.20-7.33 (m, 5H), 7.90 (dd, *J*= 7.5, 2.3 Hz, 1H), 8.61 (d, *J*=2.2 Hz, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.9, 31.3, 34.7, 41.0, 62.2, 66.8, 113.8, 123.3, 128.5, 128.6, 130.3, 135.4, 136.4, 137.3, 169.1

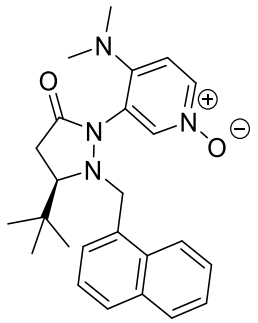


Figure 10 *DMAPO III* Characterization[95]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.50 (s, 9H), 2.46 (m, 1H), 2.69 (s, 6H), 3.13 (dd, *J*= 9.9, 1.5 Hz, 1H), 3.31 (dd, J= 17.2, 10.0 Hz, 1H), 4.2 (d, J= 11.6 Hz, 1H), 4.81 (d, J= 11.6 Hz, 1H), 6.67 (d, J= 7.4, 1H), 7.32-7.52 (m, 3H), 7.63 (ddd, J= 8.4, 6.96, 1.3 Hz, 1H), 7.74-7.85 (m, 2H), 7.88-7.98 (m, 2H), 8.62 (d, J=2.2 Hz, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.7, 31.1, 34.6, 41.3, 59.9, 66.4, 76.9, 77.2, 77.4, 77.5, 113.7, 123.1, 123.7, 124.9, 126.4, 127.4, 128.9, 129.5, 129.7, 131.2, 132.5, 133.8, 137.3, 137.7, 146.0, 169.7

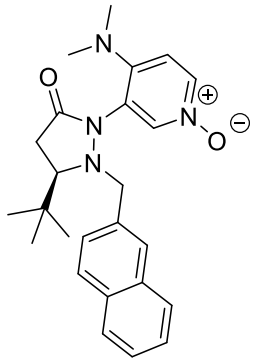


Figure 11. *DMAPO IV* Characterization

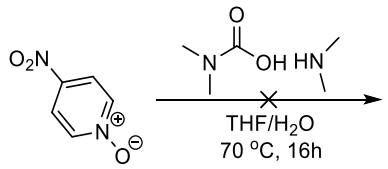
mp. 143-146°

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (s, 9H), 2.51-2.61 (m, 1H), 3.29-3.44 (m, 2H), 4.58 (d, *J*=12.1 Hz, 1H), 4.70 (d, *J*=12.1), 7.22 (dd, *J*= 8.3, 7.0 Hz, 1H), 7.50-7.64 (m, 4H), 7.67-7.76 (m, 2H), 7.86 (d, *J*=19 Hz, 1H), 8.12 (d, *J*=1.9), 8.25 (dq, *J*=8.5, 0.9 Hz, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.9, 34.6, , 41.1, 53.5, 62.8, 67.2, 111.9, 122.0, 126.4, 126.6, 127.6, 127.7, 127.8, 127.9, 128.4, 128.9, 132.6, 132.8, 132.9, 133.0, 136.6, 170

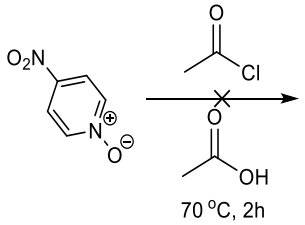
IR 2956, 1693, 1591, 1510, 1475, 1442, 1417, 1363, 1291, 1239, 1195, 1155, 1124, 1067, 963, 910, 860, 797, 729, 641, 598, 507, 480

ESI-HRMS: *m/z* calcd. for $(C_{25}H_{30}N_4O_2Na)^+$ 441.2261; found 441.2249



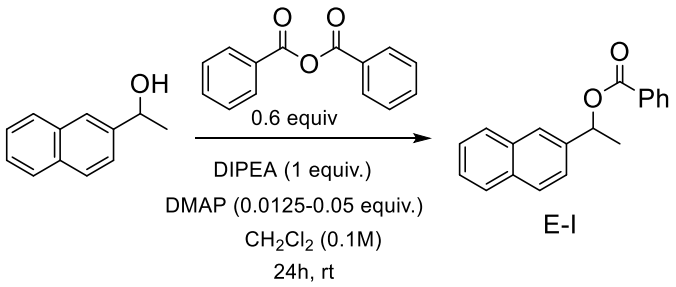
Scheme 21. Attempt to activate *4-nitropyridine-N-oxide*

In a vial with a stir bar 4-nitropyridine-N-oxide (1 equiv) was added and then dissolved in a mixture of tetrahydrofuran and water (70%/30% tetrahydrofuan/water, 0.2 M). Following dissolution dimethylamine dimethylcarbamate (8 equiv) was added. The reaction vial was then sealed and heated in an oil bath to 70 °C. Once heated the reaction was allowed to proceed until TLC (50%/50% ethyl acetate/hexanes) showed consumption of starting material. Across all of the reactions that were attempted in this method none ever consumed the starting material nor did any other products appear on TLC.



Scheme 22. Attempt to activate *4-nitropyridine-N-oxide*

In a vial with a stir bar 4-nitropyridine-N-oxide (1 equiv) was added and then dissolved in acetic acid (0.5 M). After dissolution acetyl chloride (1.5 equiv) was added. The reaction vessel was then heated to 70 °C for two hours. The reaction was quenched by pouring it over crushed ice in a beaker and then neutralized with base (pH=~7). There was no precipitation. Concentrating the aqueous solution gave an off white powder which was then extracted with dichloromethane. The dichloromethane contained no materials that were UV active on TLC (50%/50% ethyl acetate/hexanes).



Scheme 23. Parent *DMAP* acylation

In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), 4-(dimethylamino)pyridine (0.0125 to 0.05 equiv) and benzoic anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry dichloromethane (0.1 M) was added and then di-isopropyl-ethylamine (1.0 equiv) was added. The reaction was allowed to stir for 24 hours undisturbed. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01M). The dilute reaction mixture was then

extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.

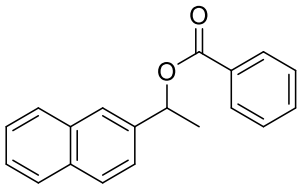
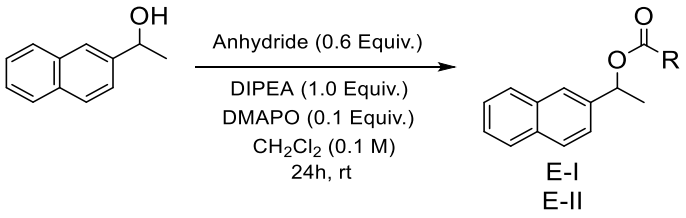


Figure 12. *E-I* Characterization[101]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.79 (d, *J* = 6.6 Hz, 3H), 6.33 (q, *J* = 6.6 Hz, 1H), 7.39 – 7.67 (m, 6H), 7.80 – 7.93 (m, 4H), 8.10 – 8.18 (m, 2H).

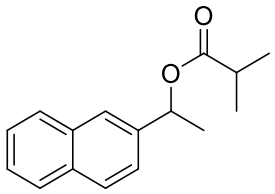
^{13}C NMR (101 MHz, $CDCl_3$) δ 22.4, 73.1, 76.7, 77.0, 77.3, 124.1, 125.0, 126.1, 126.2, 127.7, 128.1, 128.4, 128.4, 129.7, 130.5, 132.9, 133.1, 133.2, 139.1, 165.9.



Scheme 24. Anhdydride Screening parent *DMAPO* acylation

In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), 4-(dimethylamino)pyridine-N-oxide (0.1 equiv) and anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry dichloromethane (0.1M) was added and then di-isopropyl-ethylamine (1.0 equiv) was added. The reaction was allowed to stir for

24 hours undisturbed. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.

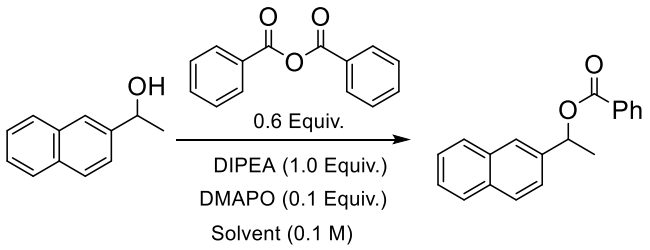


E-II

Figure 13. *E-II* Characterization

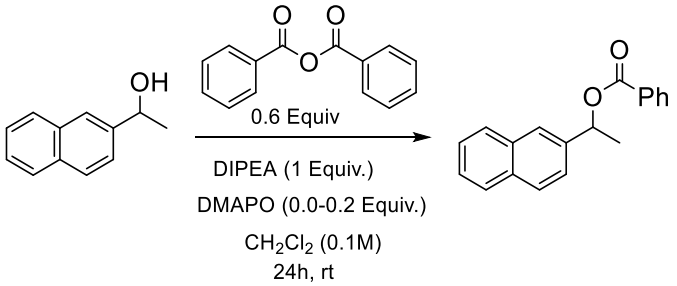
^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.24 (dd, *J* = 14.7, 7.0 Hz, 6H), 1.74 (d, *J* = 6.6 Hz, 3H), 2.67 (hept, *J* = 7.0 Hz, 1H), 6.69 (q, *J* = 6.6 Hz, 1H), 7.48 – 8.17 (m, 7H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 19.0, 19.0, 21.7, 34.3, 69.2, 76.7, 77.1, 77.4, 123.1, 123.3, 125.4, 125.7, 126.2, 128.4, 128.9, 130.3, 133.9, 137.7, 176.4.



Scheme 25. Solvent screening parent *DMAPO* acylation

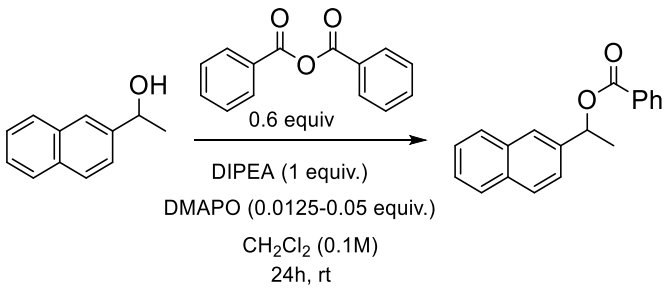
In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), 4-(dimethylamino)pyridine-N-oxide (0.1 equiv) and benzoic anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry solvent was added (0.1 M) and then di-isopropyl-ethylamine (1.0 equiv) was added. The reaction was allowed to stir for 24 hours undisturbed. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.



Scheme 26. Catalyst loading screen parent *DMAPO* acylation

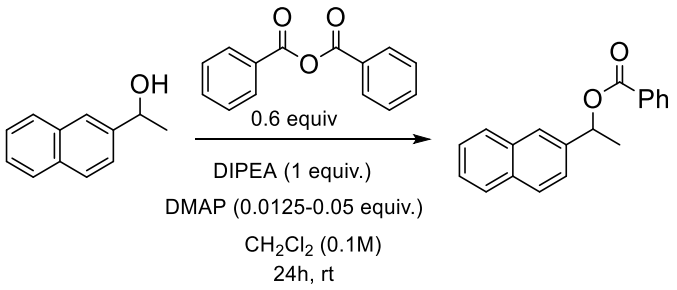
In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), 4-(dimethylamino)pyridine-N-oxide (0.0 to 0.2 equiv) and benzoic anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry solvent was added (0.1M) and then di-isopropyl-ethylamine (1.0 equiv) was added. The reaction was allowed to stir for 24 hours undisturbed. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL).

The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.



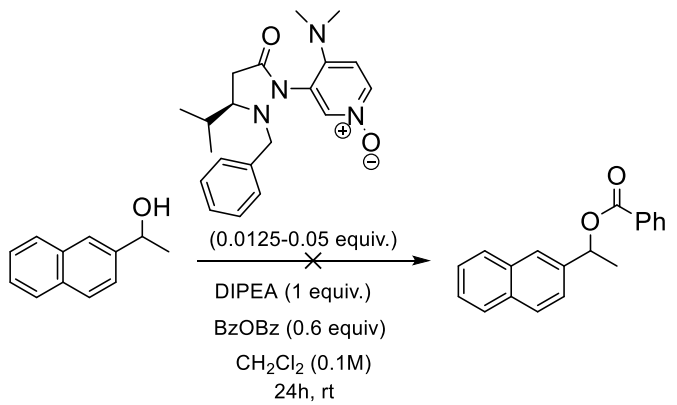
Scheme 27. Catalyst loading screen parent *DMAPO*

In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), 4-(dimethylamino)pyridine-N-oxide (0.0125 to 0.05 equiv) and benzoic anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry solvent was added (0.1 M) and then di-isopropyl-ethylamine (1.0 equiv) was added. The reaction was allowed to stir for 24 hours undisturbed. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.



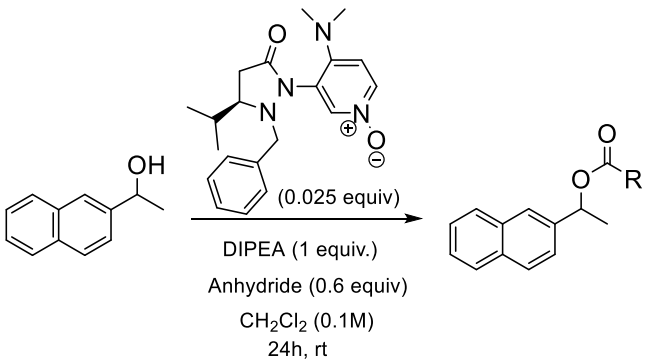
Scheme 28. Catalyst loading screen parent *DMAP* acylation

In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), 4-(dimethylamino)pyridine (0.0125 to 0.05 equiv) and benzoic anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry solvent was added (0.1 M) and then di-isopropyl-ethylamine (1.0 equiv) was added. The reaction was allowed to stir for 24 hours undisturbed. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.



Scheme 29. Attempt at catalyst loading screen *DMAPO-I* acylation KR

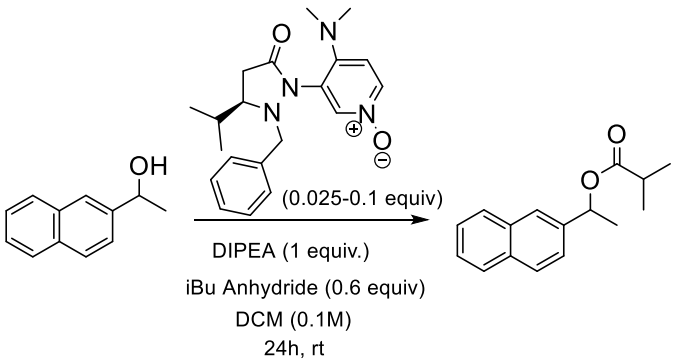
In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), the chiral catalyst (0.0125 to 0.05 equiv) and benzoic anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry dichloromethane (0.1 M) was added and then di-isopropyl-ethylamine (1.0 equiv) was added. The reaction was allowed to stir for 24 hours undisturbed. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). This reaction gave an oxidized product in all instances in which these conditions were used. Owing to this extraneous product the system was re-evaluated.



Scheme 30. Anhydride screen *DMAPO-I* acylation KR

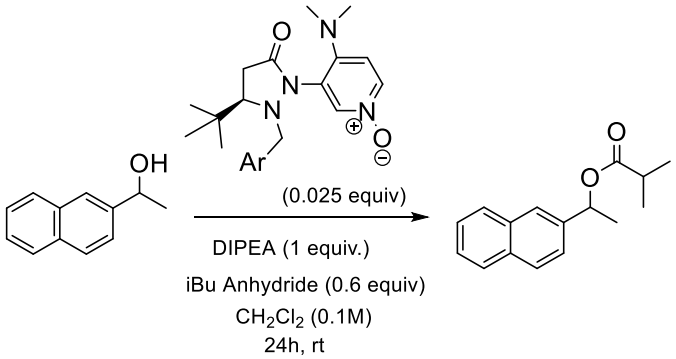
In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), the chiral catalyst (0.025 equiv) and anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry dichloromethane (0.1 M) was added and then di-isopropyl-ethylamine (1.0 equiv) was added. The reaction was allowed to stir for 24 hours undisturbed. Following the completion of the allotted time the reaction was quenched with excess

dichloromethane (~0.01M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.



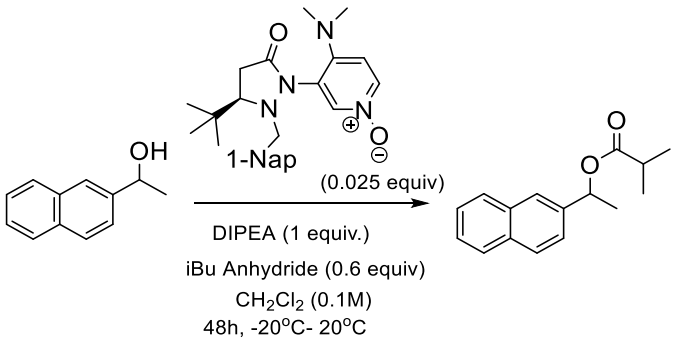
Scheme 31. Catalyst loading screen *DMAPO-I* acylaton KR

In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), the chiral catalyst (0.025 to 0.10 equiv) and isobutyl anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry dichloromethane (0.1 M) was added and then di-isopropyl-ethylamine (1.0 equiv) was added. The reaction was allowed to stir for 24 hours undisturbed. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.



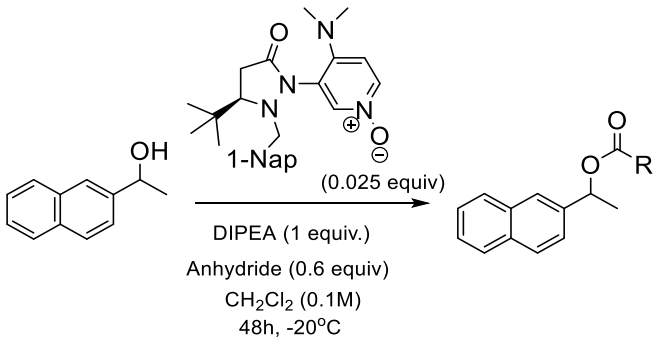
Scheme 32. Comparative DMAPO-N acylation KR

In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), the chiral catalyst (0.025 equiv) and isobutyl anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry dichloromethane (0.1 M) was added and then di-isopropyl-ethylamine (1.0 equiv) was added. The reaction was allowed to stir for 24 hours undisturbed. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.



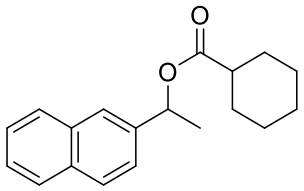
Scheme 33. Temperature screen *DMAPO-II* acylation KR

In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), the chiral catalyst (0.025 equiv) and isobutyl anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry dichloromethane (0.1 M) was added and then di-isopropyl-ethylamine (1.0 equiv) was added. The reaction was allowed to stir for 48 hours undisturbed either in a Cryo-cool device or at ambient tempuratures. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.



Scheme 34. Anhydride screen *DMAPO-II* acylation KR

In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), the chiral catalyst (0.025 equiv) and anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry dichloromethane (0.1 M) was added and then di-isopropyl-ethylamine (1.0 equiv) was added. The reaction was allowed to stir for 48 hours undisturbed in a Cryo-cool device. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.



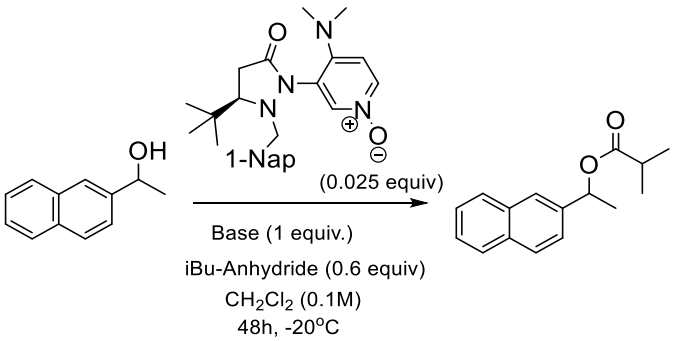
E-III

Figure 14. *E-III* Characterization

^{1}H NMR (400 MHz, Chloroform-d) δ 1.23 – 1.68 (m, 11H), 1.72 – 1.84 (m, 2H), 1.96 (ddqd, J = 14.3, 10.5, 3.5, 1.7 Hz, 2H), 2.38 (tt, J = 11.3, 3.7 Hz, 1H), 6.07 (q, J = 6.6 Hz, 1H), 7.43 – 7.58 (m, 3H), 7.77 – 7.91 (m, 4H).

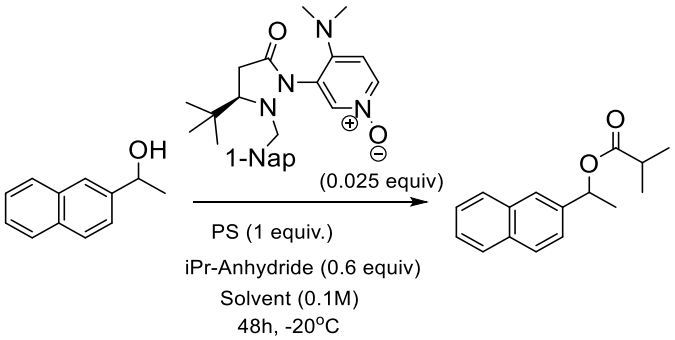
^{13}C NMR (101 MHz, $CDCl_3$) δ 22.3, 25.4, 25.5, 25.8, 29.0, 29.0, 43.4, 71.9, 76.7, 77.0, 77.3, 124.1, 124.9, 126.0, 126.2, 127.7, 128.0, 128.3, 133.0, 133.2, 139.4, 175.3.

IR 2922, 2854, 1808, 1507, 1444, 1372, 1352, 1338, 1306, 1250, 1170, 1126, 1108, 1048, 998, 964, 955, 942, 906, 894, 867, 840, 824, 793, 776, 751, 696, 658, 577, 546, 501, 479, 445, 413



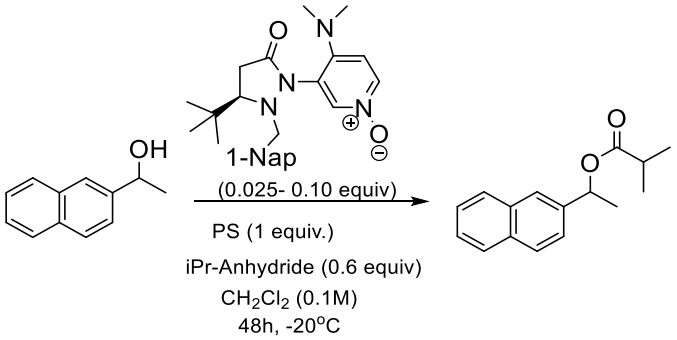
Scheme 35. Base screen *DMAPO-II* acylation KR

In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), the chiral catalyst (0.025 equiv) and isobutyl anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry dichloromethane (0.1 M) was added and the base (1.0 equiv) was added. The reaction was allowed to stir for 48 hours undisturbed in a Cryo-cool device. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.



Scheme 36. Solvent screen *DMAPO-II* acylation KR

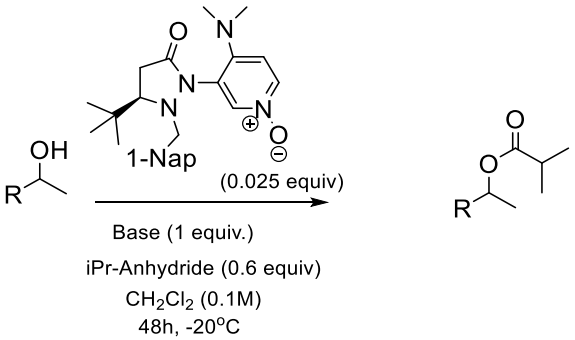
In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), the chiral catalyst (0.025 equiv) and isobutyl anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry solvent (0.1 M) was added and then Proton Sponge™ (1.0 equiv) was added. The reaction was allowed to stir for 48 hours undisturbed in a Cryo-cool device. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.



Scheme 37. Catalyst loading screen *DMAPO-II* acylation KR

In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), the chiral catalyst (0.025 to 0.10 equiv) and isobutyl anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry dichloromethane (0.1 M) was added and then Proton Sponge™ (1.0 equiv) was added. The reaction was allowed to stir for 48 hours undisturbed in a Cryo-cool device. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then

extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.



Scheme 38. Substrate screen *DMAPO-II* acylation KR

In a dried reaction vial equipped with a stir bar under nitrogen was added the secondary alcohol (1 equiv), the chiral catalyst (0.025 equiv) and isobutyl anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry dichloromethane (0.1 M) was added and then the base (1.0 equiv) was added. The reaction was allowed to stir for 48 hours undisturbed in a Cryo-cool device. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.

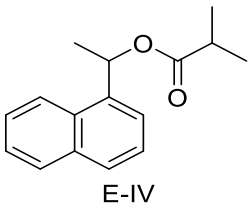
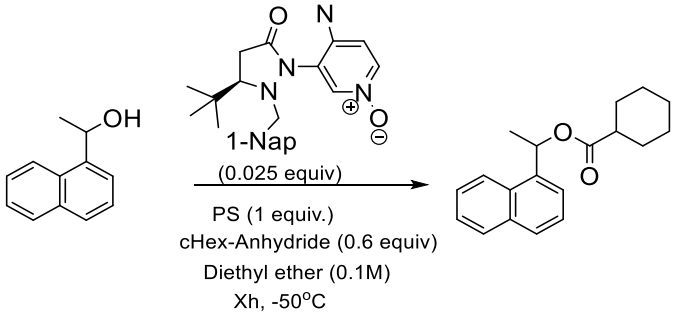


Figure 15. *E-IV* Characterization[95]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.23 (dd, *J* = 14.6, 7.0 Hz, 6H), 1.73 (d, *J* = 6.6 Hz, 3H), 2.66 (hept, *J* = 7.0 Hz, 1H), 6.68 (q, *J* = 6.6 Hz, 1H), 7.46 – 7.67 (m, 4H), 7.79 – 7.94 (m, 2H), 8.12 (dq, *J* = 8.6, 0.9 Hz, 1H).

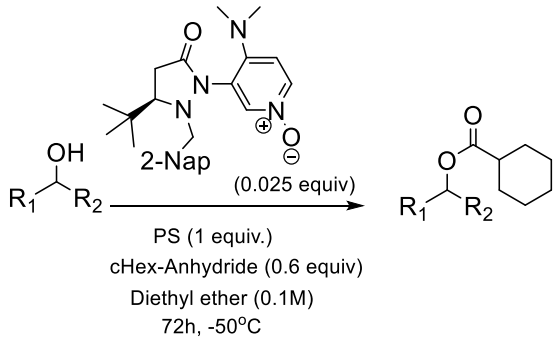
^{13}C NMR (101 MHz, $CDCl_3$) δ 19.0, 19.0, 21.7, 34.3, 69.2, 76.7, 77.0, 77.4, 123.1, 123.3, 125.4, 125.7, 126.2, 128.4, 128.9, 130.3, 133.8, 137.7, 176.4.



Scheme 39. Lower temperature screen *DMAPO-II* acylaton KR

In a dried reaction vial equipped with a stir bar under nitrogen was added 1-(1-naphthyl)ethanol (1 equiv), the chiral catalyst (0.025 equiv) and cyclohexyl anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry diethyl ether (0.1 M) was added and then Proton Sponge™ (1.0 equiv) was added. The reaction was allowed to stir for 48 or 72 hours undisturbed in a Cryo-cool device. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01M). The dilute reaction mixture was then extracted

with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.



Scheme 40. Substrate screen *DMAPO-IV* acylation KR

In a dried reaction vial equipped with a stir bar under nitrogen was added the secondary alcohol (1 equiv), the chiral catalyst (0.025 equiv) and cyclohexyl anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry diethyl ether (0.1 M) was added and then Proton Sponge™ (1.0 equiv) was added. The reaction was allowed to stir for 72 hours undisturbed in a Cryo-cool device. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.

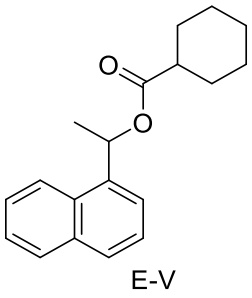


Figure 16. *E-V* Characterization[102]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.17 – 1.40 (m, 4H), 1.41 – 1.57 (m, 2H), 1.58 – 1.85 (m, 7H), 1.97 (ddddd, *J* = 19.0, 12.6, 5.0, 3.4, 1.6 Hz, 2H), 2.40 (tt, *J* = 11.3, 3.6 Hz, 1H), 6.67 (q, *J* = 6.6 Hz, 1H), 7.45 – 7.67 (m, 4H), 7.79 – 7.93 (m, 2H), 8.07 – 8.17 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 21.7, 25.5, 25.5, 25.8, 29.0, 29.0, 43.4, 68.9, 76.7, 77.0, 77.4, 100.0, 123.1, 123.3, 125.4, 125.6, 126.2, 128.3, 128.9, 130.3, 133.8, 137.7, 175.3.

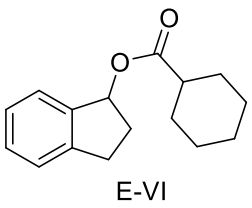
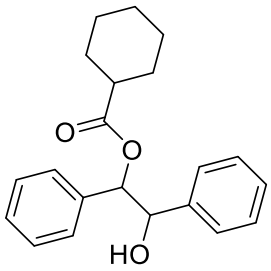


Figure 17. *E-VI* Characterization[103]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.05 – 1.26 (m, 4H), 1.30 – 1.46 (m, 3H), 1.47 – 1.75 (m, 4H), 1.75 – 2.03 (m, 4H), 2.21 (tt, *J* = 11.3, 3.6 Hz, 1H), 2.43 (dddd, *J* = 14.2, 8.5, 7.1, 5.8 Hz, 1H), 2.79 (ddd, *J* = 16.1, 8.6, 5.4 Hz, 1H), 3.01 (ddd, *J* = 16.2, 8.6, 5.8 Hz, 1H), 6.12 (dd, *J* = 7.1, 4.2 Hz, 1H), 7.09 – 7.25 (m, 3H), 7.28 (d, *J* = 7.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 25.4, 25.8, 29.0, 30.2, 32.4, 43.3, 76.7, 77.0, 77.4, 77.8, 124.8, 125.3, 126.7, 128.8, 141.3, 144.2, 176.2.

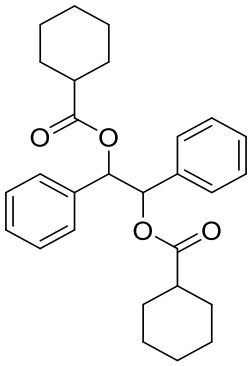


E-VII

Figure 18. *E-VII* Characterization[104]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.09 – 1.42 (m, 6H), 1.53 – 1.90 (m, 7H), 2.26 (tq, *J* = 10.6, 3.4 Hz, 1H), 4.99 (d, *J* = 6.3 Hz, 1H), 5.93 (d, *J* = 6.3 Hz, 1H), 7.17 – 7.44 (m, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 25.3, 25.3, 25.7, 28.8, 43.1, 57.1, 76.6, 76.7, 77.0, 77.2, 77.3, 78.3, 127.1, 127.6, 128.1, 128.1, 128.3, 128.4, 136.9, 139.6, 174.7.



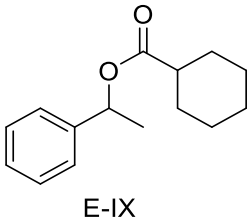
E-VIII

Figure 19. *E-VIII* Characterization

^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.18 – 1.36 (m, 10H), 1.45 – 1.52 (m, 3H), 1.61 – 1.83 (m, 10H), 1.94 – 1.98 (m, 2H), 2.32 (dddd, *J* = 29.4, 14.6, 7.2, 3.6 Hz, 2H), 4.98 (d, *J* = 6.3 Hz, 1H), 5.93 (d, *J* = 6.3 Hz, 1H), 7.31 (dddd, *J* = 15.2, 8.0, 5.5, 2.0 Hz, 10H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 25.3, 25.7, 28.8, 43.1, 76.6, 76.7, 77.0, 77.2, 77.3, 78.3, 127.1, 127.6, 128.1, 128.1, 128.3, 128.3, 136.9, 139.6, 174.7.

IR 3537, 2922, 2853, 1712, 1497, 1449, 1373, 1352, 1320, 1305, 1294, 1198, 1158, 1130, 1079, 1065, 1030, 976, 959, 923, 892, 857, 844, 776, 756, 696, 636, 584, 505, 474

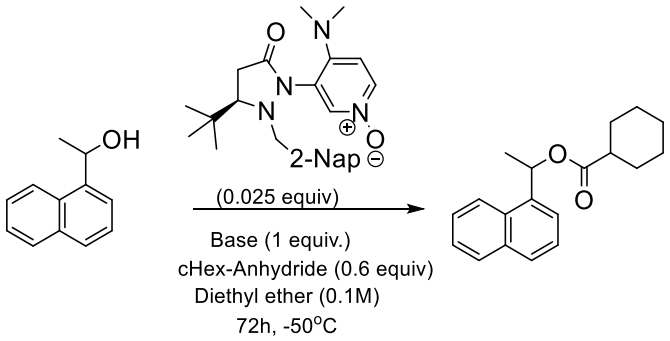


E-IX

Figure 20. *E-IX* Characterization[105]

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 – 1.35 (m, 4H), 1.38 – 1.49 (m, 2H), 1.51 (d, J = 6.6 Hz, 4H), 1.57 – 1.67 (m, 2H), 1.73 (dqd, J = 10.1, 3.4, 1.7 Hz, 3H), 1.90 (dddd, J = 12.7, 7.3, 3.6, 1.7 Hz, 2H), 2.31 (tt, J = 11.3, 3.6 Hz, 1H), 5.87 (q, J = 6.6 Hz, 1H), 7.22 – 7.30 (m, 1H), 7.33 (d, J = 4.4 Hz, 4H)

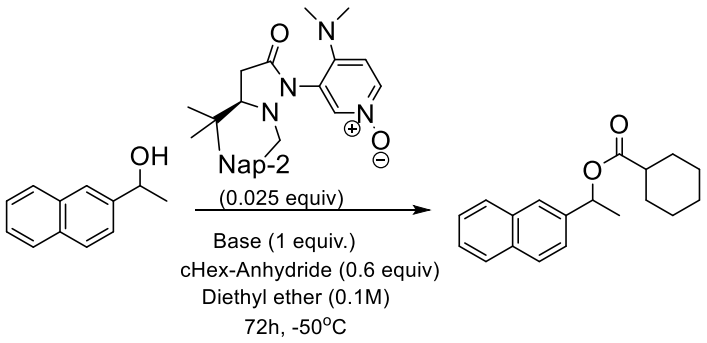
^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.3, 25.4, 25.5, 25.8, 29.0, 29.0, 43.3, 71.7, 76.7, 77.0, 77.4, 125.9, 127.7, 128.5, 142.0, 175.3.



Scheme 41. Base screen *DMAPO-IV* acylation KR

In a dried reaction vial equipped with a stir bar under nitrogen was added 1-(1-naphthyl)ethanol (1 equiv), the chiral catalyst (0.025 equiv) and cyclohexyl anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry diethyl ether (0.1 M) was added and then the

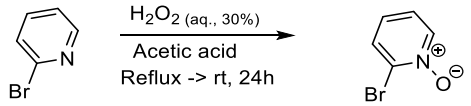
base (1.0 equiv) was added. The reaction was allowed to stir for 72 hours undisturbed in a Cryo-cool device. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.



Scheme 42. Base screen *DMAPO-IV* acylation KR

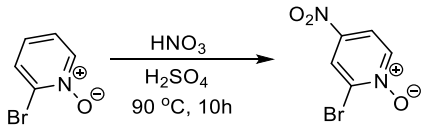
In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), the chiral catalyst (0.025 equiv) and cyclohexyl anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry diethyl ether (0.1 M) was added and then the base (1.0 equiv) was added. The reaction was allowed to stir for 72 hours undisturbed in a Cryo-cool device. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected

to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.



Scheme 43. Oxidation of *2-bromopyridine*

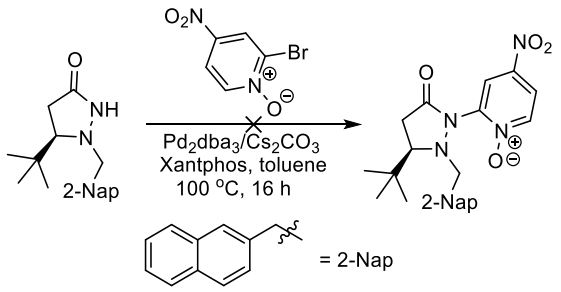
In a round-bottom flask equipped with a stir bar under atmosphere 2-bromopyridine (16.4 mL, 1 equiv) was dissolved in acetic acid (75.0 mL, 1.2 M). After full solvation aqueous hydrogen peroxide (20%, 50 mL, 3.4 equiv) was added to the reaction vessel which was then fitted with a reflux condenser. The reaction apparatus was then put into an oil bath and set to reflux for 8 hours. After reflux the reaction was allowed to cool to room temperature and continue reacting for an additional 16 hours. Following reaction completion, as followed by TLC (50%/50% ethyl acetate/hexanes), the reaction was concentrated until the solvent had been removed. The crude was then used without further purification.



Scheme 44. Nitration of *2-bromopyridine-N-oxide*

In a round-bottom flask equipped with a stir bar under atmosphere on an ice bath 2-bromopyridine-N-oxide (29.6 g, 1 equiv) was dissolved by slowly adding sulfuric acid (35 mL, 1.5 M). Concurrent with solvation a mixture of nitric acid (55 mL, 6.5 equiv) and sulfuric acid (35 mL) was prepared by carefully adding the sulfuric acid to the nitric acid which was in an Erlenmeyer flask on an ice bath. Upon full solvation of the 3-bromopyridine-N-oxide in sulfuric acid the acid mixture was added slowly. Rapid heating could lead to issues during this addition and was combated by

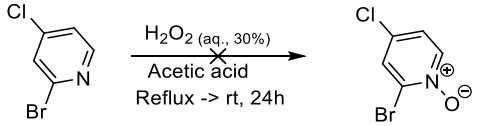
reducing the addition rate and adding additional ice to the ice bath holding the reaction vessel. The reaction was allowed to stir for 2 hours on an ice bath before being moved to an oil bath which was in turn brought to 90 °C. The reaction was allowed to react at 90 °C for 10 hours and there after was allowed cool to room temperature. The room temperature reaction was then poured over ice in a large beaker and neutralized with sodium hydroxide. The base needed to be added slowly owing to any potential product being just as soluble in basic media as acidic media. When correctly brought to neutral (pH= ~7) precipitate would begin to form and could then be collected with vacuum filtration. The crude product was then recrystallized in a mixture of hexanes and dichloromethane (80%/20% hexanes/dichloromethane).



Scheme 45. Attempt to couple pyrazolidinone template with *2-bromo-4-nitropyridine-N-oxide*

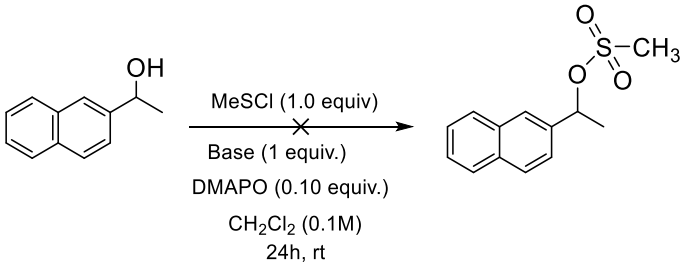
In a dried round-bottom flask equipped with a stir bar under an argon atmosphere dried toluene (0.5 M) was added and flushed with argon for 10 minutes. After inert gas flushing the chiral starting material (1 equiv), 4-nitro-2-bromopyridine-N-oxide (1.1 equiv), cesium carbonate (1.2 equiv), tris(dibenzylideneacetone)dipalladium (0) (0.05 equiv) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.05 equiv) were added to the reaction vessel. The reaction vessel was then equipped with a reflux condenser and the system flushed with argon for 10 minutes. Following the inert atmosphere flush the apparatus was then put into an oil bath and heated to 100 °C and allowed to react for 12 hours before being allowed to cool to room temperature. The room temperature reaction was then filtered through via vacuum filtration through a bed of celite. The bed of celite

was washed with an equal volume of toluene to the reaction mixture to remove as much of the product as possible. This reaction did not yield any usable materials.



Scheme 46. Attempt to oxidize *2-bromo-4-chloropyridine*

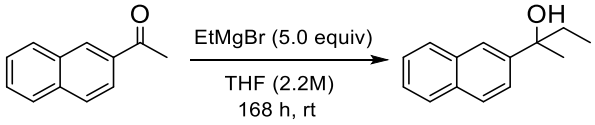
In a round-bottom flask equipped with a stir bar under atmosphere 2-bromo-4-chloropyridine (16.4 mL, 1 equiv) was dissolved in acetic acid (75.0 mL, 1.2 M). After full solvation aqueous hydrogen peroxide (20%, 50 mL, 3.4 equiv) was added to the reaction vessel which was then fitted with a reflux condenser. The reaction apparatus was then put into an oil bath and set to reflux for 8 hours. After reflux the reaction was allowed to cool to room temperature and continue reacting for an additional 16 hours. This reaction failed to yield useful materials.



Scheme 47. Attempt to sulfonylate secondary alcohol

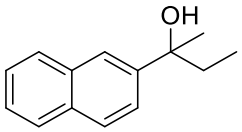
In a dried reaction vial equipped with a stir bar under nitrogen was added α-methyl-2-naphthalenemethanol (1 equiv), 4-(dimethylamino)pyridine-N-oxide (0.10 equiv) and methanesulfonyl chloride (1.0 equiv). Dry dichloromethane (0.1 M) was added and then the base (1.0 equiv) was added. The reaction was allowed to stir for 24 hours undisturbed. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over

sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (10%/90% ethyl acetate/hexanes). This method did not yield useful material.



Scheme 48. Grignard reaction of *2-acetonaphthone* with ethyl magnesium bromide

In a vial equipped with a stir bar 2-aceteonapthanone was dried in an oven for 1 h at 150 °C. This melted starting material was then flushed with nitrogen until solid once more. Ethyl magnesium bromide (2.2 M in tetrahydrofuran, 5.0 equiv) was then added to the reaction vessel. The 2-aceteonapthanone then dissolved into the solution and the reaction was allowed to proceed. TLC analysis was not helpful as both the starting material and the product had the same R_f in all solvent conditions tested. Eventually the most useful solution to this issue was to allow for a long reaction time. After reaction time elapsed the reaction was quenched with saturated ammonium chloride (aqueous, 5 mL). Additional distilled water (10 mL) was added and the reaction was then extracted with dichloromethane (3 X 10 mL). The organic layer was then dried with sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (25%/75% ethyl acetate/hexanes). The product was then isolated and used in further reactions.

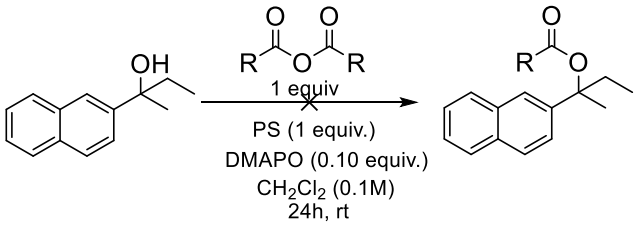


Tertiary Alcohol I

Figure 21. *Tertiary Alcohol I* Characterization[106]

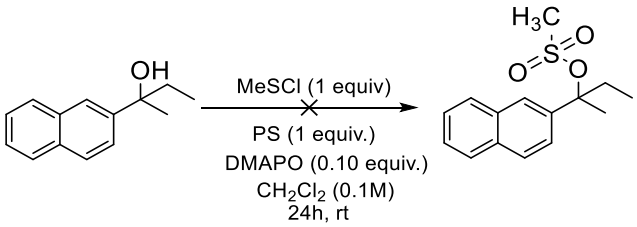
^{1}H NMR (400 MHz, Chloroform-*d*) δ 0.85 (dd, *J* = 7.8, 7.1 Hz, 3H), 1.86 – 2.04 (m, 2H), 7.81 – 7.97 (m, 4H), 1.65 – 1.69 (m, 4H), 1.92 – 2.04 (m, 2H), 1.67 (s, 4H), 1.67 – 1.68 (m, 3H), 7.44 – 7.59 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 8.4, 29.8, 36.5, 75.1, 76.7, 77.0, 77.2, 77.4, 123.3, 123.8, 125.6, 126.0, 127.5, 127.8, 128.1, 132.2, 133.2, 145.1.



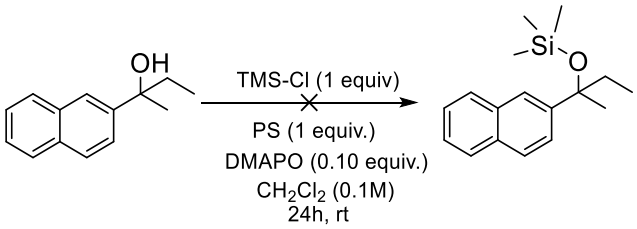
Scheme 49. Attempt to acylate tertiary alcohol

In a dried reaction vial equipped with a stir bar under nitrogen was added the starting tertiary alcohol (1 equiv), 4-(dimethylamino)pyridine-N-oxide (0.1 equiv) and anhydride (0.6 equiv) and the dry reagents were then flushed with nitrogen. Dry dichloromethane (0.1 M) was added and then Proton Sponge™ (1.0 equiv) was added. The reaction was allowed to stir for 24 hours undisturbed. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (5%/95% -> 10%/90% -> 20%/80% -> 50%/50% ethyl acetate/hexanes). The acylated product and the unreacted starting material were able to be isolated independently.



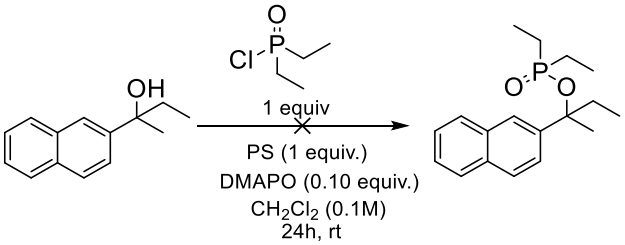
Scheme 50. Attempt to sulfonylate tertiary alcohol

In a dried reaction vial equipped with a stir bar under nitrogen was added the starting material (1 equiv), 4-(dimethylamino)pyridine-N-oxide (0.10 equiv) and methanesulfonyl chloride (1.0 equiv). Dry dichloromethane (0.1 M) was added and then Proton Sponge™ (1.0 equiv) was added. The reaction was allowed to stir for 24 hours undisturbed. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (10%/90% ethyl acetate/hexanes). This method did not yield useful material.



Scheme 51. Attempt to silylate tertiary alcohol

In a dried reaction vial equipped with a stir bar under nitrogen was added the starting material (1 equiv), 4-(dimethylamino)pyridine-N-oxide (0.10 equiv) and trimethylsilyl chloride (1.0 equiv). Dry dichloromethane (0.1 M) was added and then Proton Sponge™ (1.0 equiv) was added. The reaction was allowed to stir for 24 hours undisturbed. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (10%/90% ethyl acetate/hexanes). This method did not yield useful material.



Scheme 52. Attempt to phosphorylate tertiary alcohol

In a dried reaction vial equipped with a stir bar under nitrogen was added the starting material (1 equiv), 4-(dimethylamino)pyridine-N-oxide (0.10 equiv) and diethyl chlorophosphate (1.0 equiv). Dry dichloromethane (0.1 M) was added and then Proton Sponge™ (1.0 equiv) was added. The reaction was allowed to stir for 24 hours undisturbed. Following the completion of the allotted time the reaction was quenched with excess dichloromethane (~0.01 M). The dilute reaction mixture was then extracted with saturated aqueous ammonium chloride (2 X 10 mL) and then extracted again with distilled water (1 X 20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude mixture was then subjected to column chromatography (10%/90% ethyl acetate/hexanes). This method did not yield useful material.

3.8. Spectra:

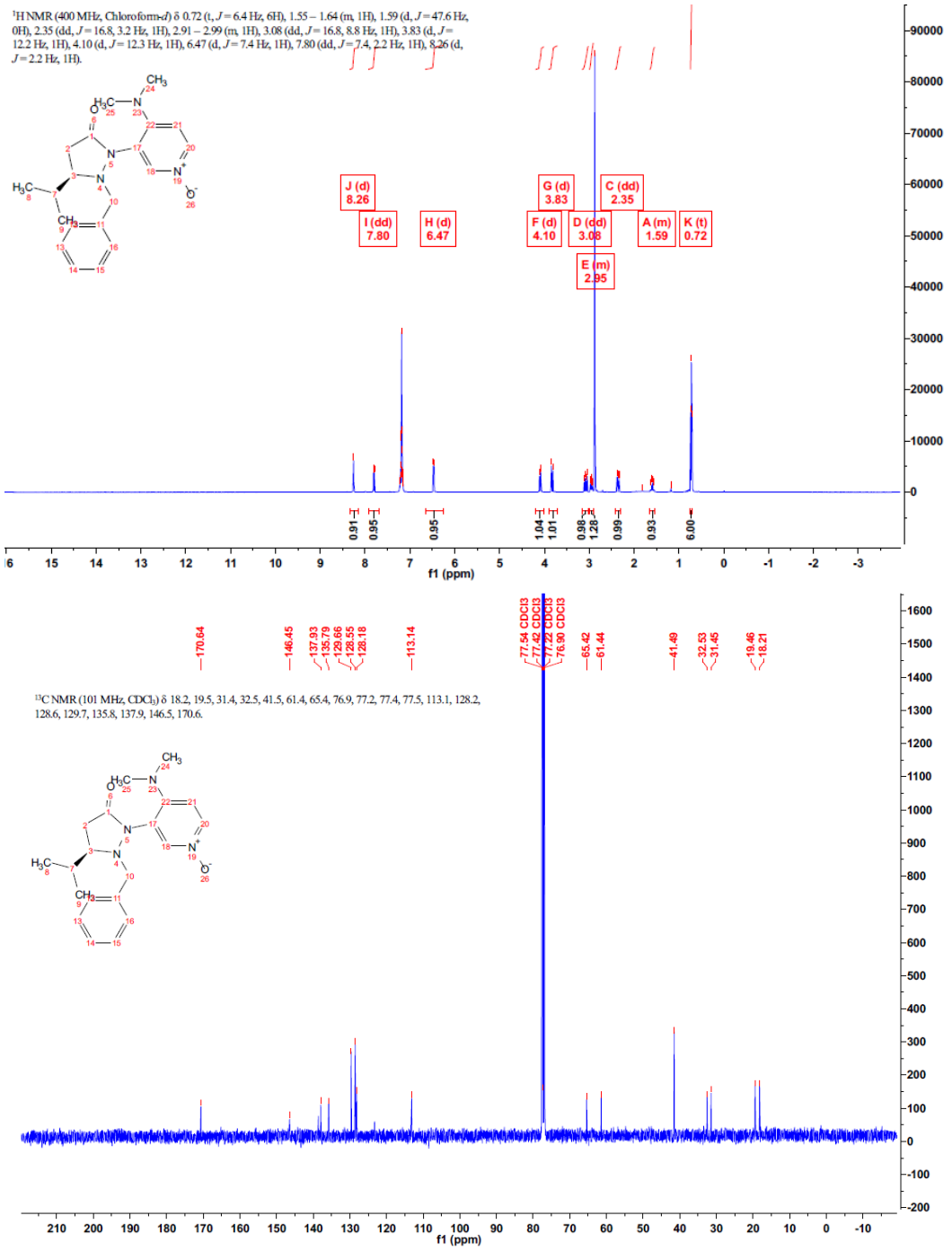


Figure 22. ^{1}H NMR and ^{13}C NMR *DMAPO-I*

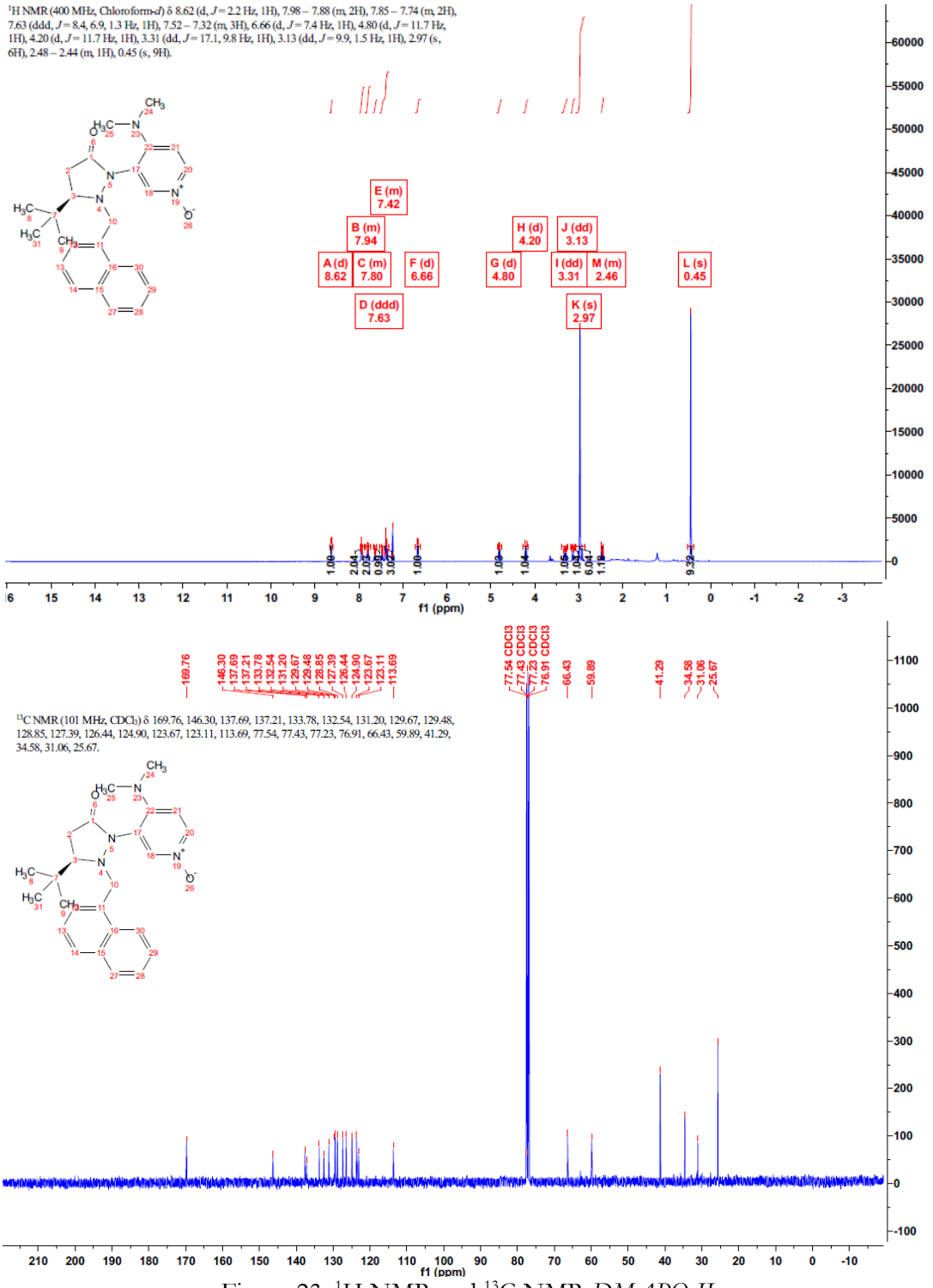


Figure 23. ^{1}H NMR and ^{13}C NMR *DMAPO-II*

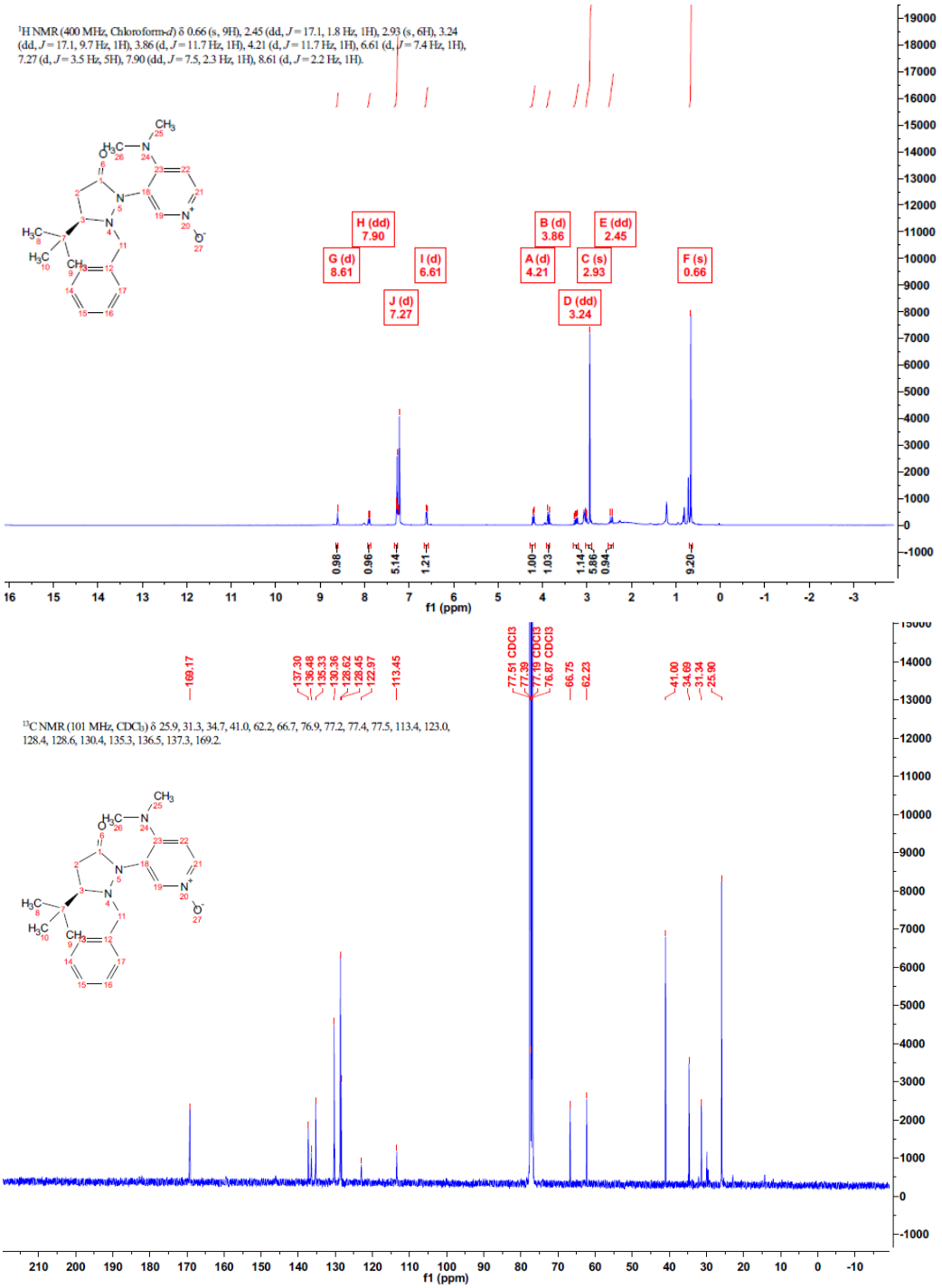


Figure 24. ^{1}H NMR and ^{13}C NMR *DMAPO-III*

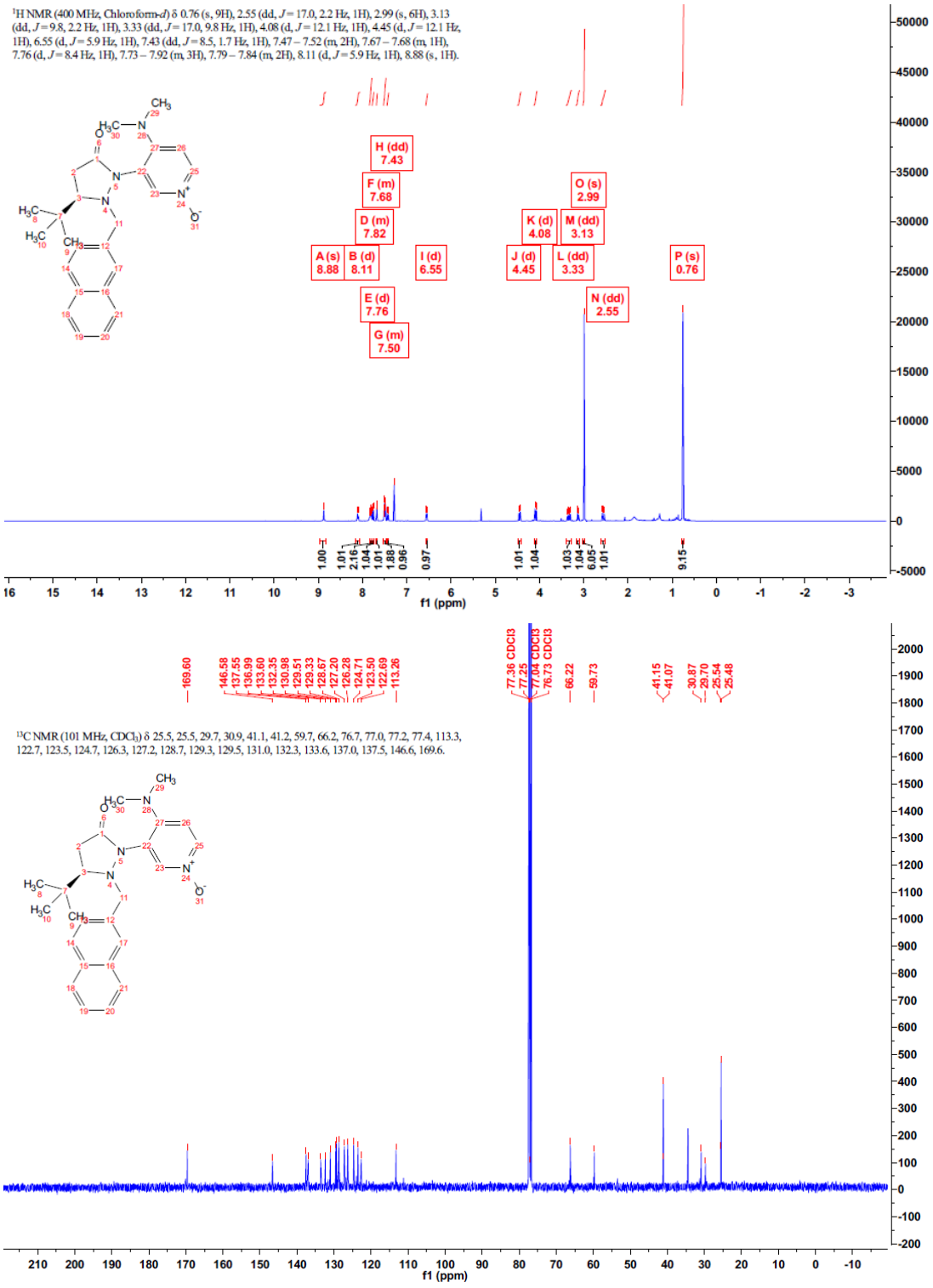


Figure 25. ^{1}H NMR and ^{13}C NMR *DMAPO-IV*

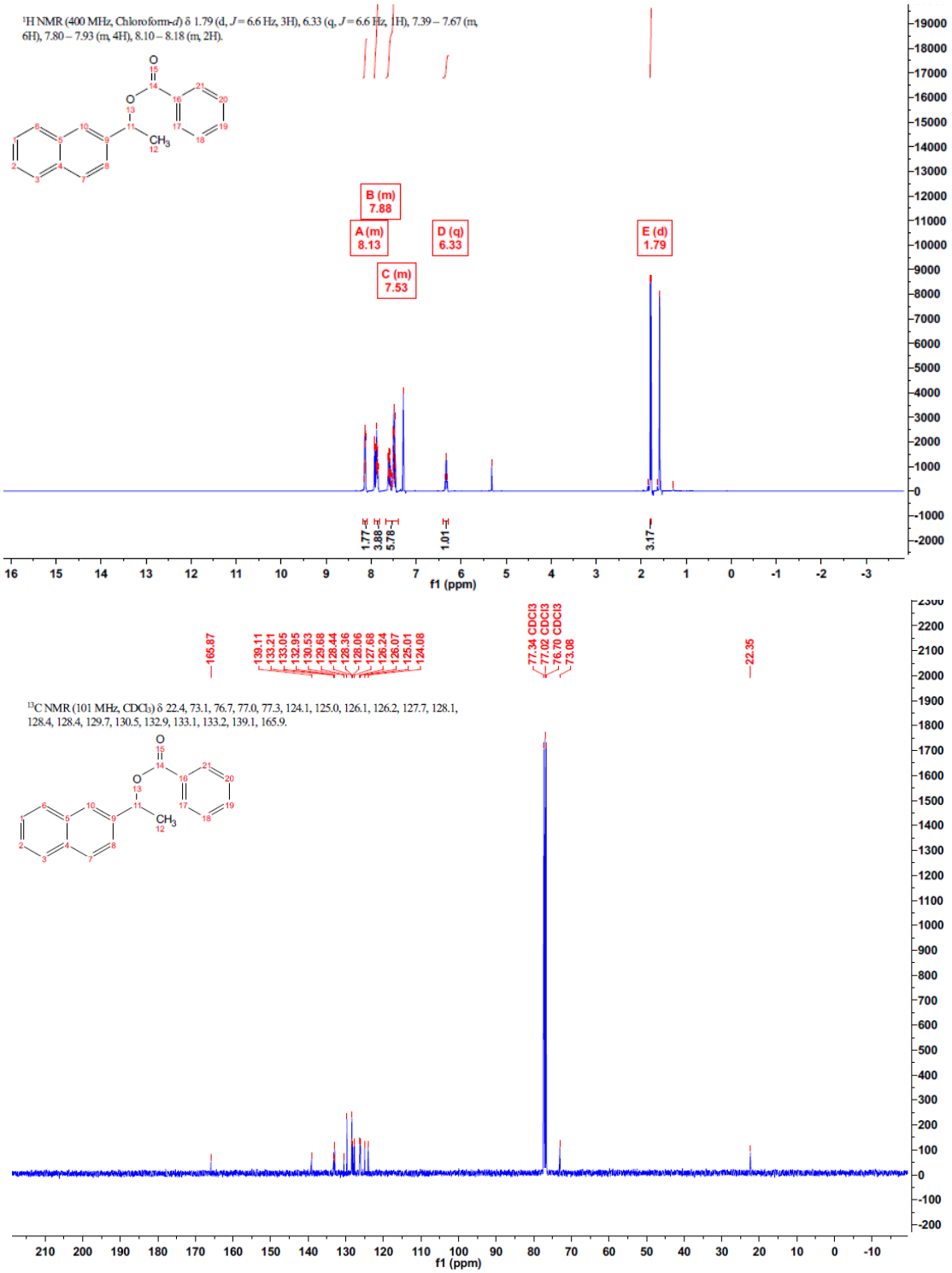


Figure 26. ^{1}H NMR and ^{13}C NMR *E-I*

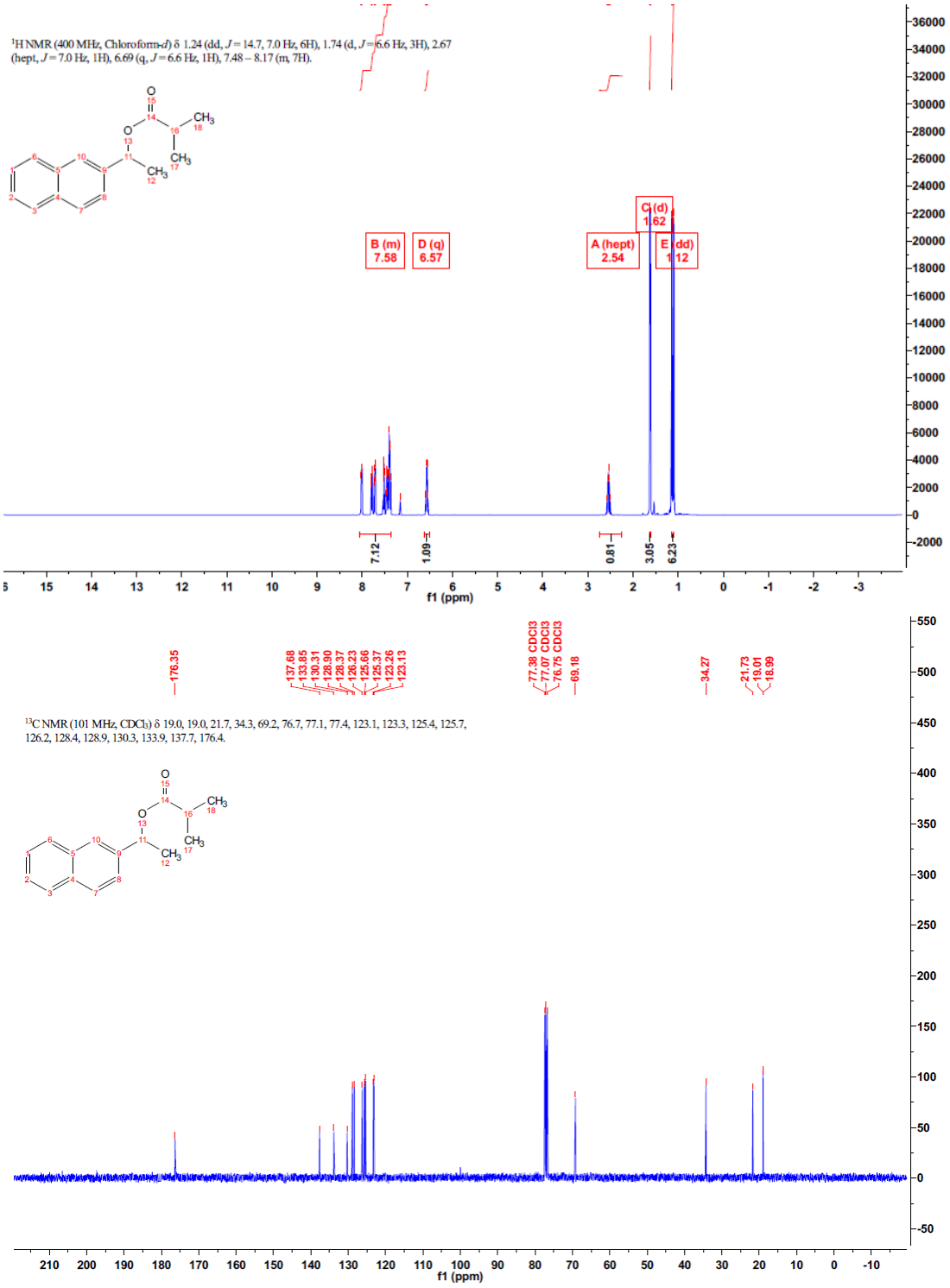


Figure 27. ^{1}H NMR and ^{13}C NMR *E-II*

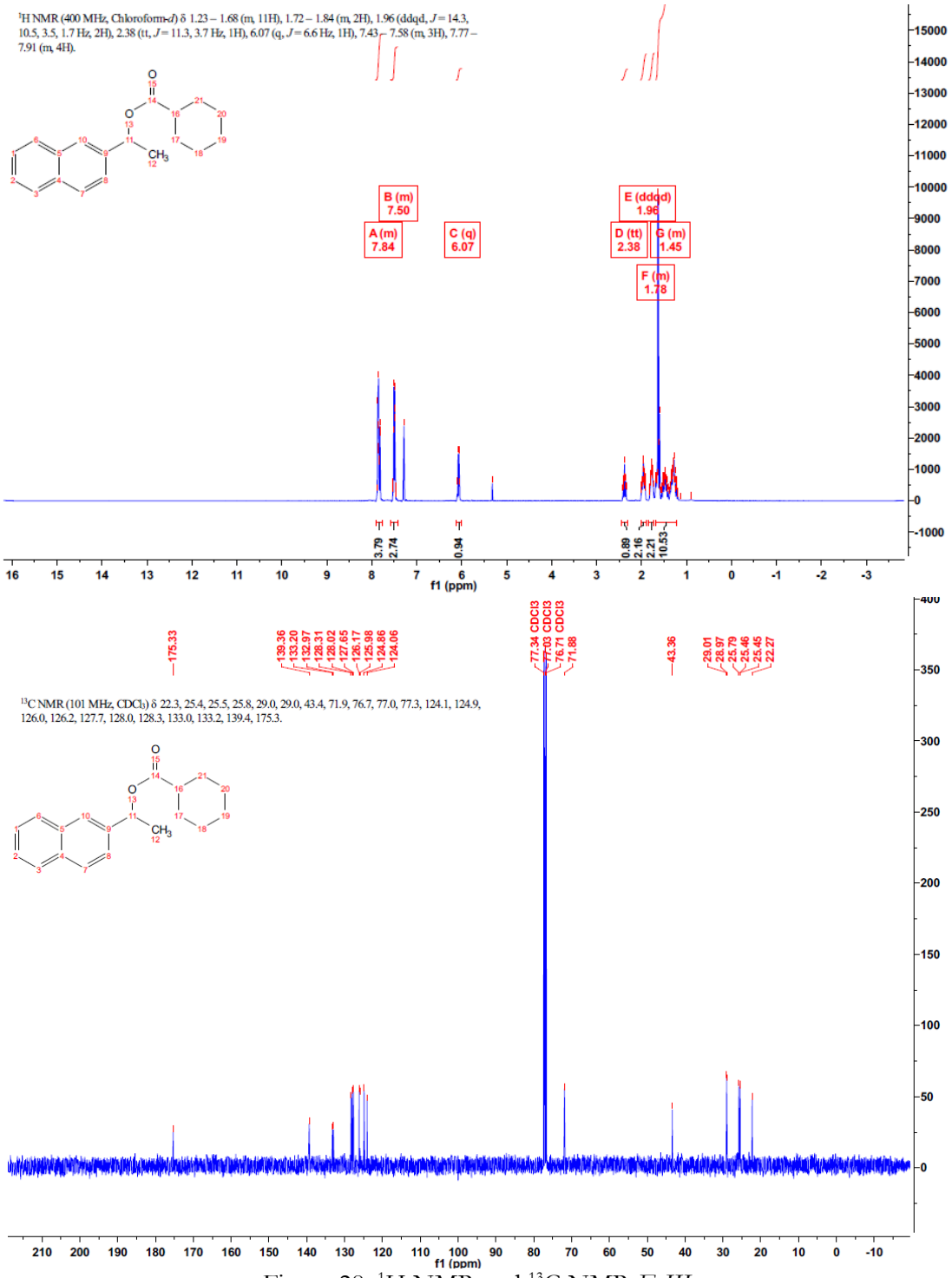


Figure 28. ^{1}H NMR and ^{13}C NMR *E-III*

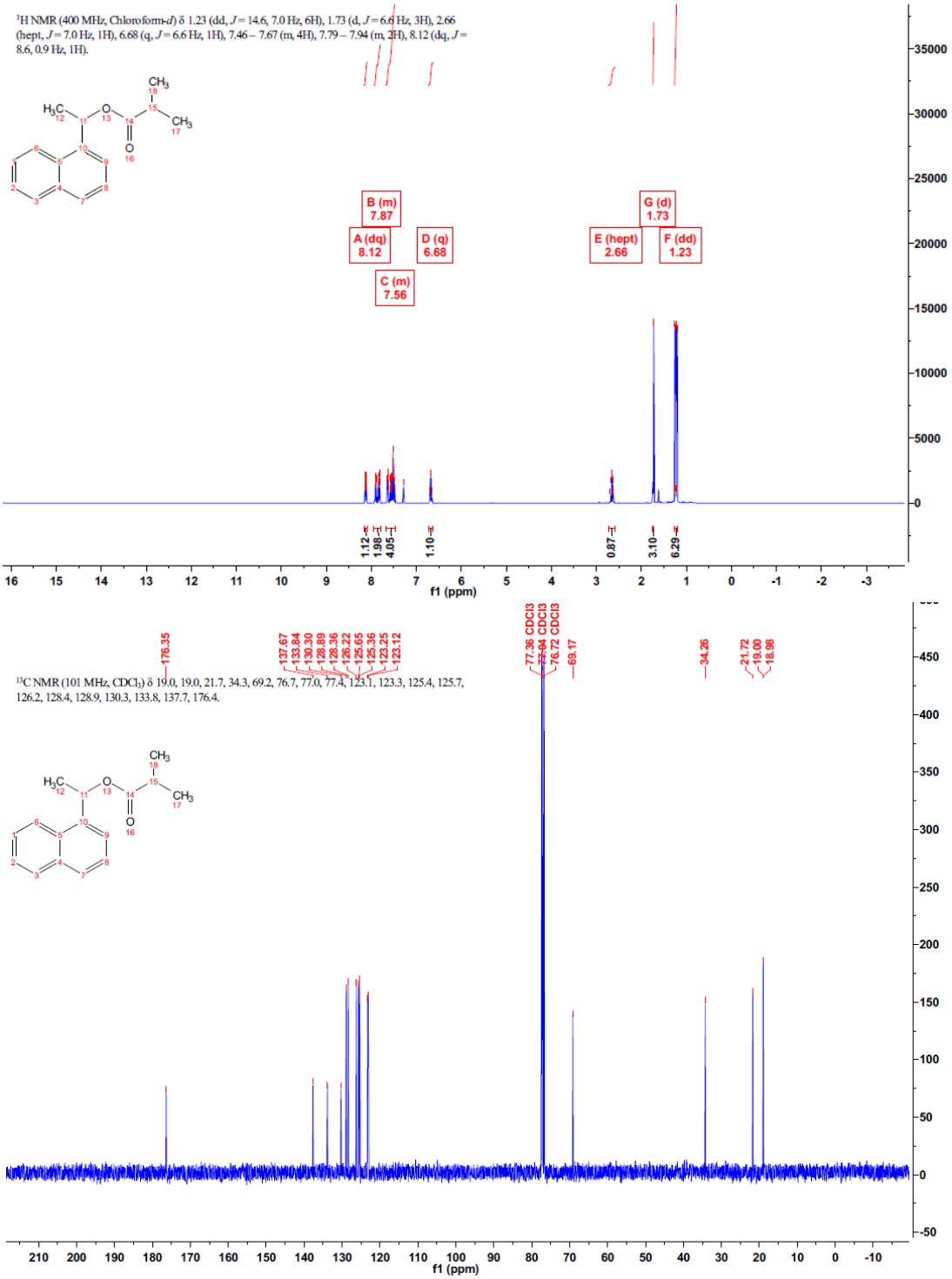


Figure 29. ^{1}H NMR and ^{13}C NMR *E-IV*

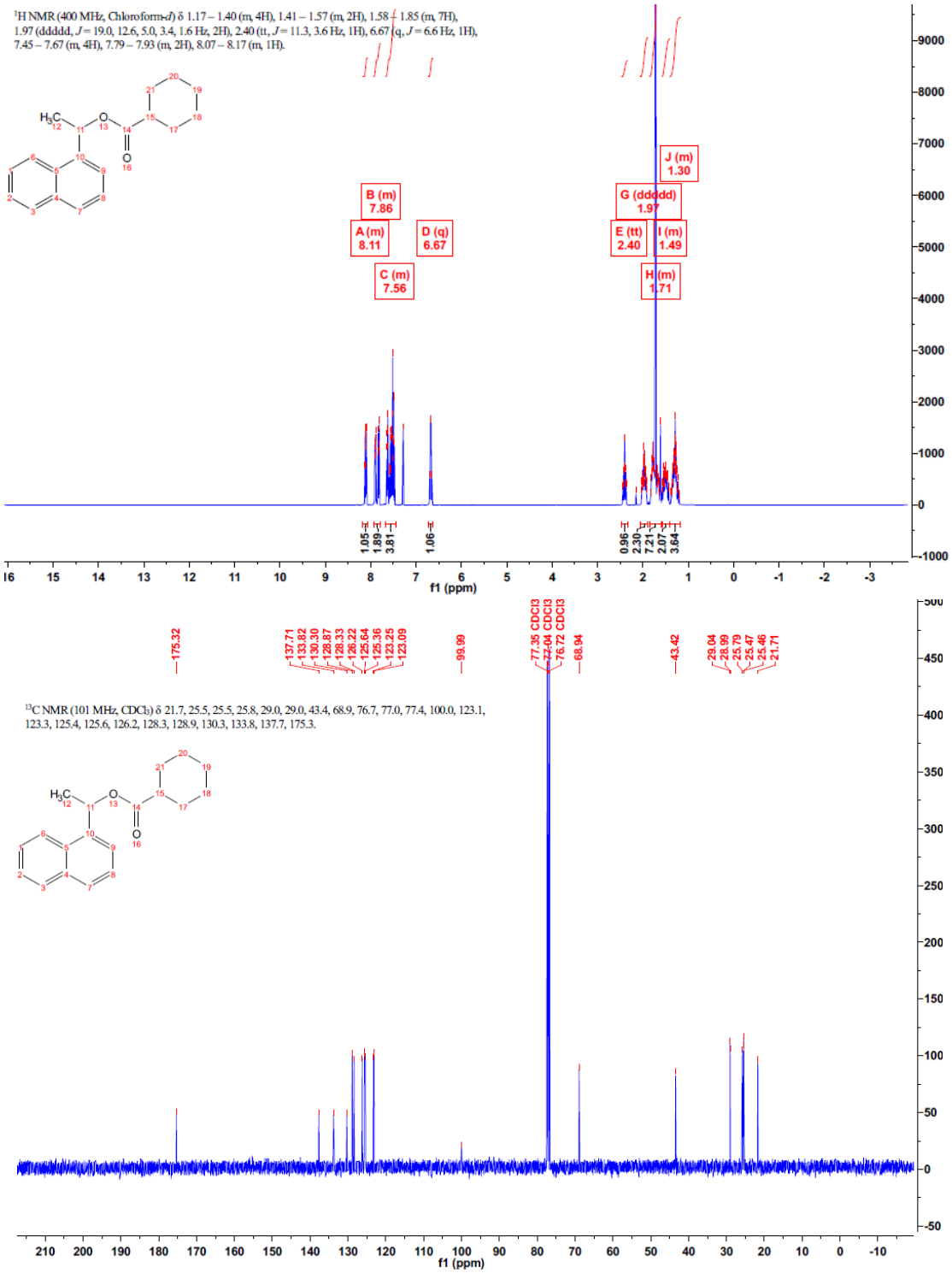


Figure 30. ^{1}H NMR and ^{13}C NMR *E-V*

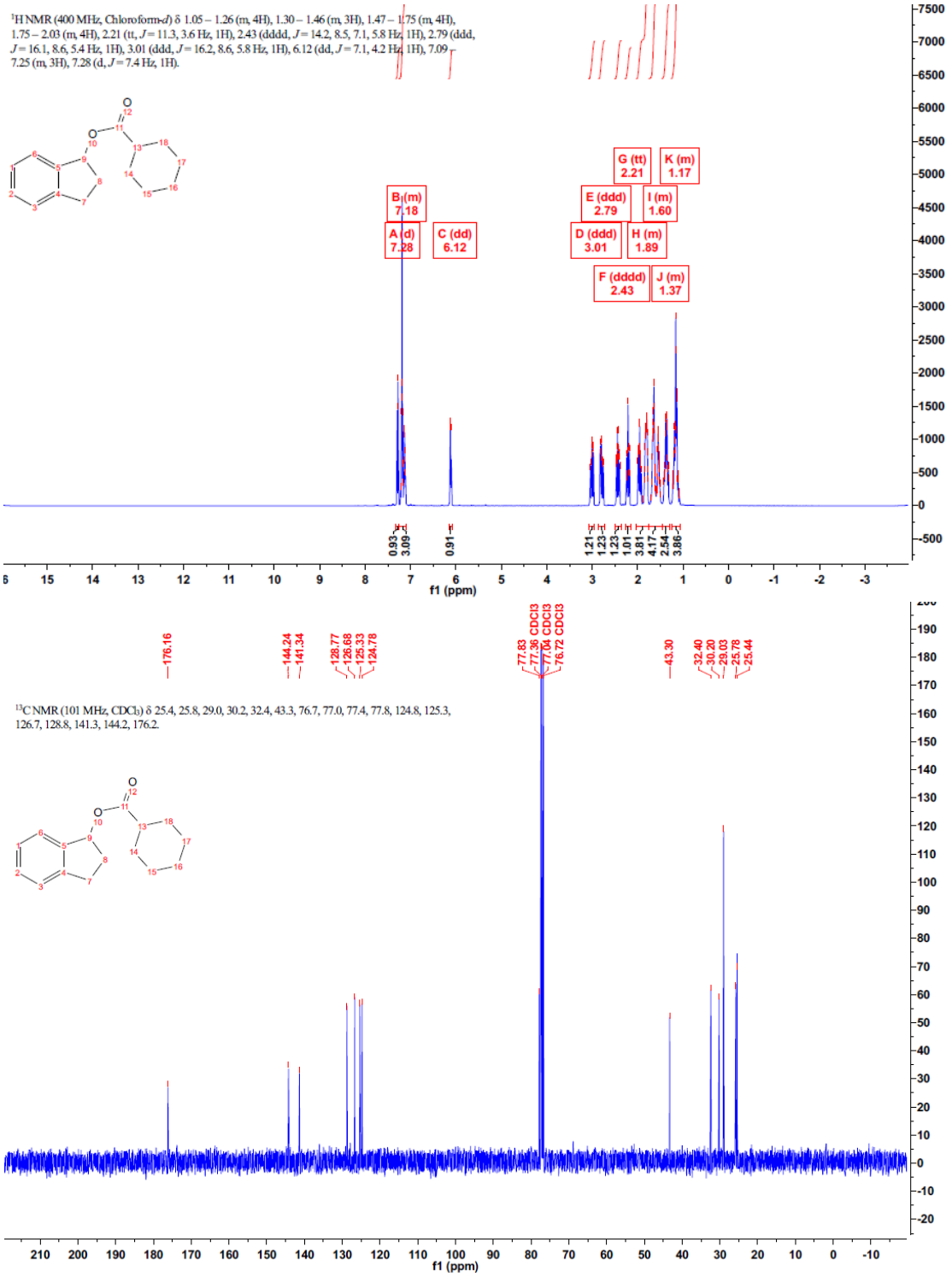


Figure 31. ^{1}H NMR and ^{13}C NMR *E-VI*

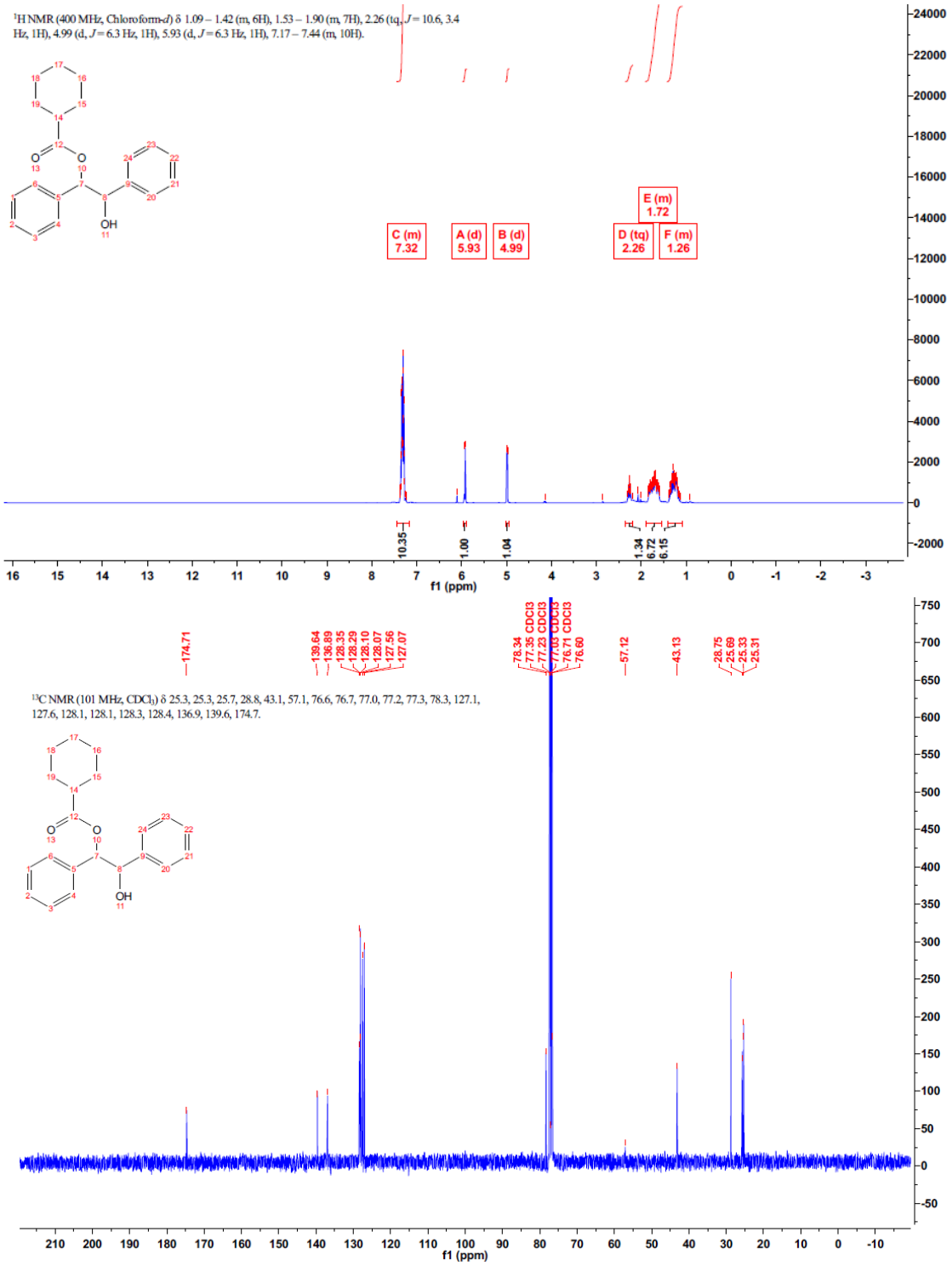


Figure 32. ^{1}H NMR and ^{13}C NMR *E-VII*

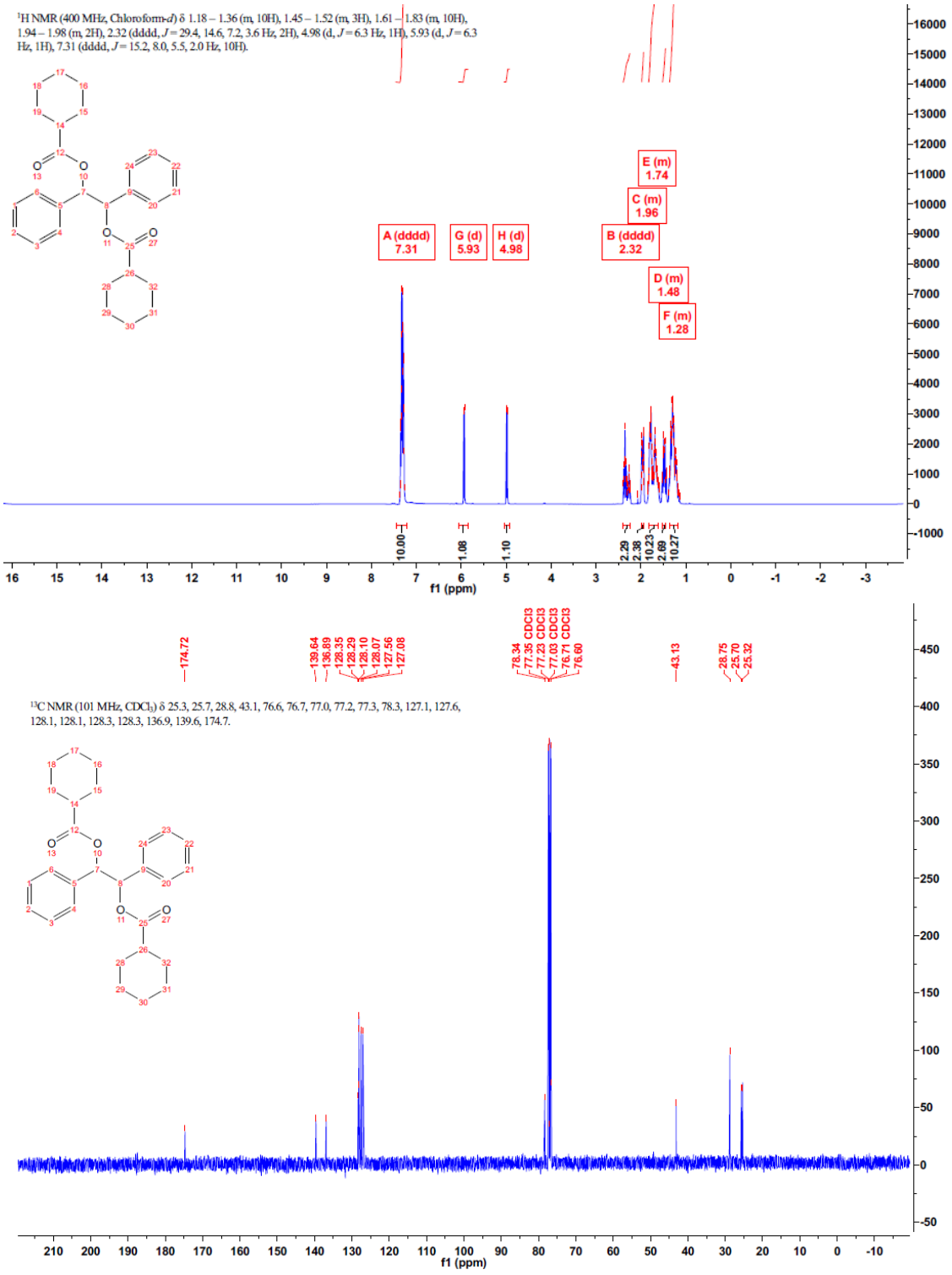
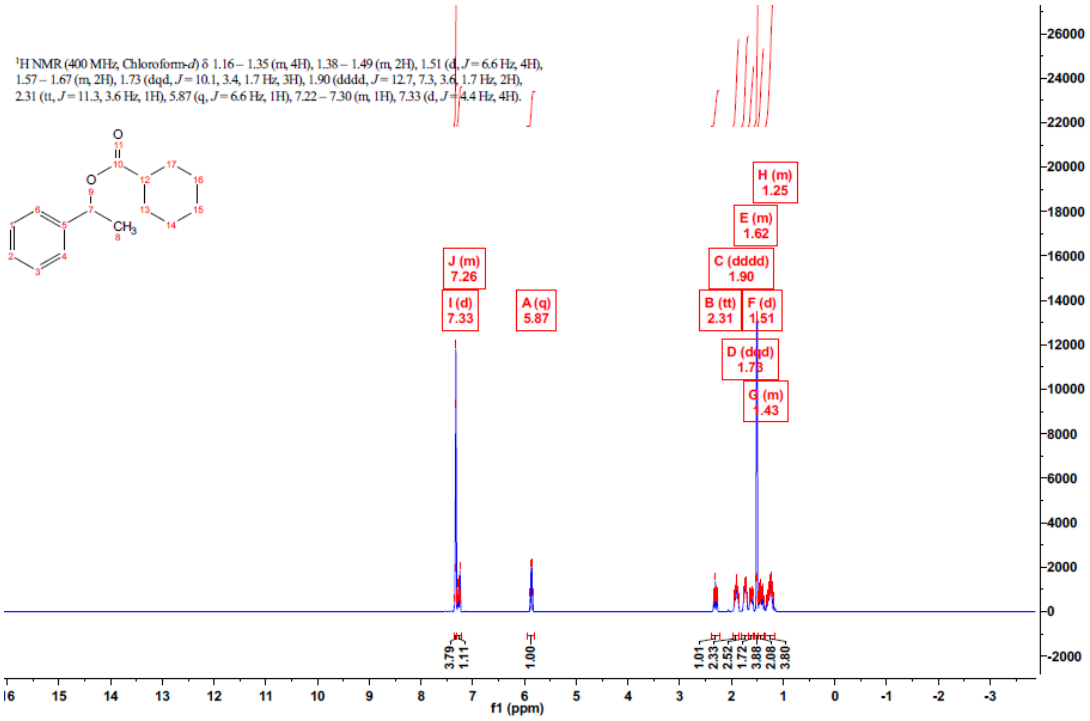


Figure 33. ^{1}H NMR and ^{13}C NMR *E-VIII*



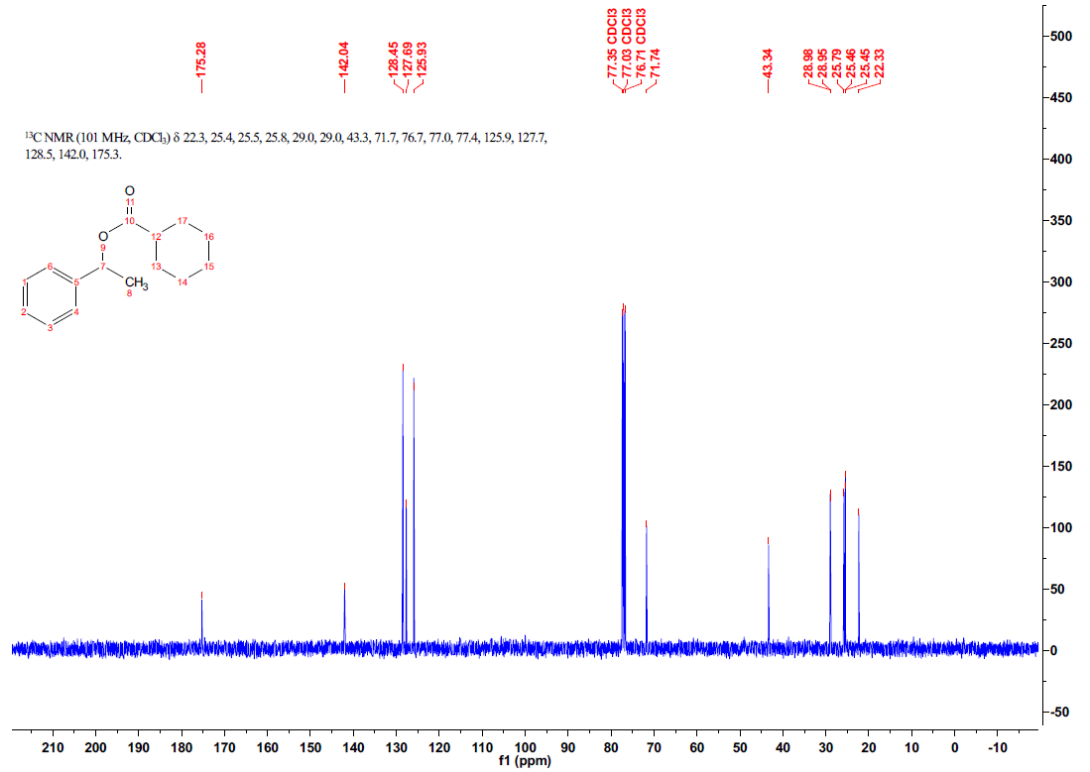


Figure 34. ^{1}H NMR and ^{13}C NMR *E-IX*

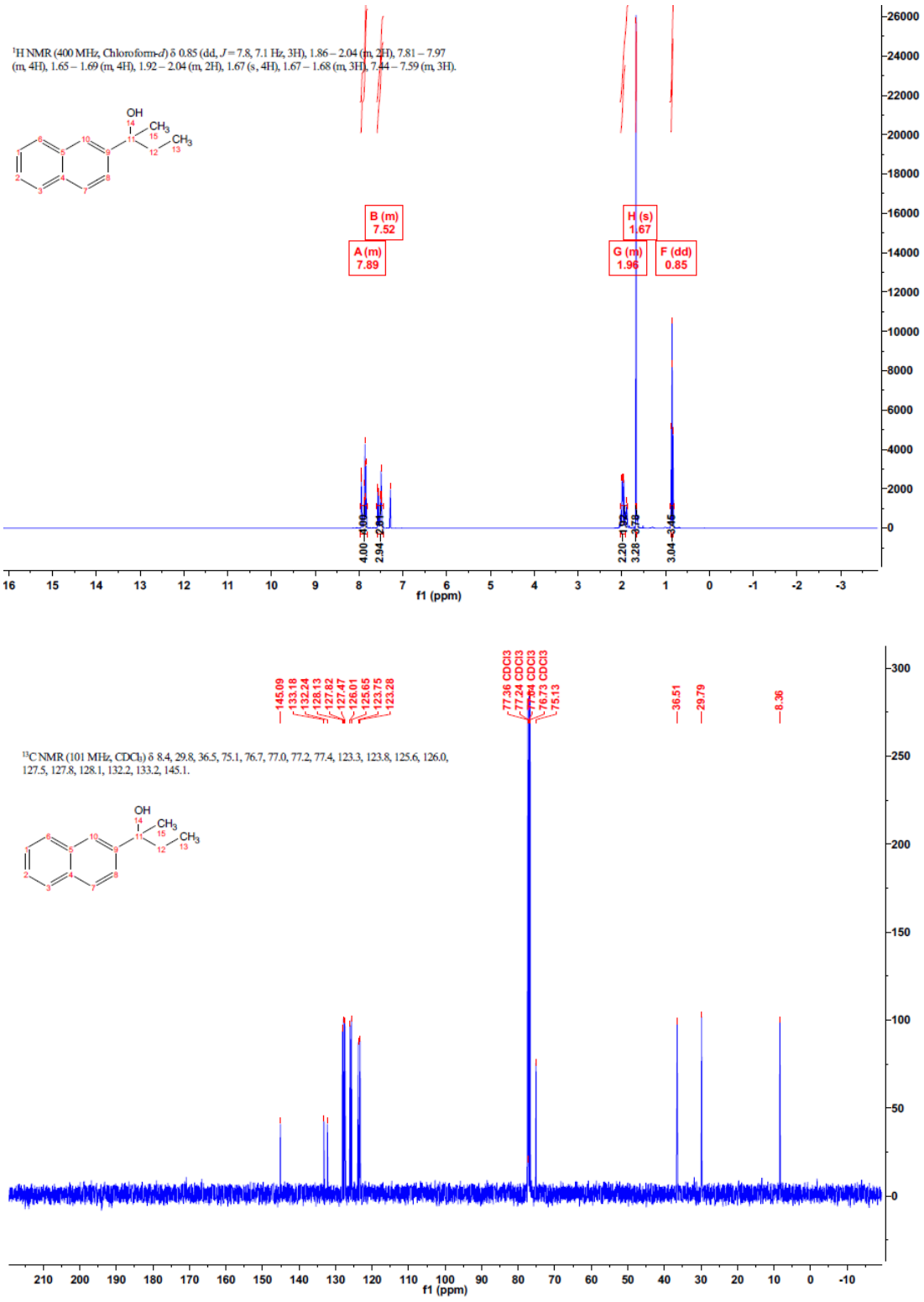


Figure 35. ^{1}H NMR and ^{13}C NMR *Tertiary OH I*

3.9. Conclusions and Future Directions:

From the study conducted the concrete conclusions can be drawn are as follows. Though this DMAPO-N family of catalysts are not as selective as previously established systems they tend to be more generalizable.

There remains a large amount of research and effort needed to advance this study further. Future efforts to produce substituted catalyst might well have to explore a means of producing such a catalyst through de novo synthesis or potentially through hydrogenation of the 4-nitro pre-catalyst with a following di-methylation reaction.

In addition to the production of the 2-template substituted catalysts efforts to examine other means of affecting the kinetic resolution (i.e. via phosphorylation, silylation or other) should be investigated as the products produced could potentially have as much impact as the kinetic resolution itself.

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