ORGANOCATALYTIC VINYLOGOUS REACTIONS: NOVEL DIENAMINE-CATALYZED *GAMMA*-FUNCTIONALIZATIONS OF *ALPHA,BETA*-UNSATURATED ALDEHYDES

By

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ABSTRACT OF THE DISSERTATION

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Dissertation Director:

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While organocatalysis has emerged as a significant component in modern organic synthesis, being recognized as the third pillar of catalysis, alongside biocatalysis and transition metal catalysis, its scope is still relatively limited. This is particularly the case with dienamine catalysis, in which the majority of reactions developed have been Diels-Alder-type cylcoadditions or have been focused on functionalization in the α-position, due to issues with stereoselectivity and regioselectivity in the remote γ-position. As such, the development of linear asymmetric γ-functionalizations and organocascades has great potential to introduce novel complexity to α,β-unsaturated aldehydes and provide precursors to biologically relevant molecules. This dissertation presents a comprehensive review of dienamine catalysis, as well as the development of novel linear organocatalytic vinylogous functionalizations of α,β-unsaturated aldehydes. With the goal of generating diversity through cascades and heteroatomic substrates, the research conducted was focused on four main topics: 1). The synthesis of γ-amino alcohols via a novel

dienamine-iminium cascade involving a γ-amination, followed by transfer hydrogenation. 2). Exploration into the potential of this cascade to provide heteroatomic asymmetric complexity with the introduction of different nucleophiles, and the many difficulties that arise from these reactions. 3). The development of an unprecedented metal-free allylic oxidation, forming various nitrones via a novel dienamine catalyzed redox mechanism, which displayed unique divergent reactivity that could be exploited to obtain varied libraries of heterocyclic compounds. 4). The synthesis of analogues to elucidate the absolute stereochemistry of an organocatalytic vinylogous Michael product. These studies have illustrated the potential, as well as some of the limitations of dienamine catalysis.

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LIST OF SYMBOLS AND ABBREVIATIONS

2º	secondary
2D NMR	two-dimensional nuclear magnetic resonance
Å	angstrom
$[\alpha]_D$	optical rotation
Ac	acetyl
AcO	acetate
AcOH	acetic acid
Ar	aryl
BHT	dibutylhydroxytoluene
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
$BnNH_2$	benzylamine
Boc	*tert*-butoxylcarbonyl
br	broad
Bu	butyl
Bz	benzoyl
BzOH	benzoic acid
c	concentration
°C	degrees Celsius
^{13}C NMR	carbon-13 nuclear magnetic resonance
calc	calculated
calcd	calculated

cat	catalyst
Cbz	carboxylbenzyl
$CDCl_3$	deuterated chloroform
CD_3CN	deuterated acetonitrile
cod	1,5-cyclooctadiene
conc	concentrated
Cy	tricyclohexylphosphine
δ	nuclear magnetic shift
d	doublet
DABCO	1,4-diazabyciclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DFT	density functional theory
DIBAL-H	diisobutylaluminum hydride
DIC	*N,N′*-diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPP	diphenylphosphine

dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
E^+	electrophile
EDG	electron-donating group
ee	enantiomeric excess
enal	α,β-unsaturated aldehyde
epi	epimer
equiv	equivalents
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
Et_2O	diethyl ether
Et_3N	triethylamine
EWG	electron-withdrawing group
FT-IR	Fourier transform infrared spectroscopy
g	gram
h	hour
^{1}H NMR	proton nuclear magnetic resonance
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resonance mass spectrometry

Hz	Hertz
IBX	2-iodoxybenzoic acid
IEDDA	inverse-electron-demand Diels-Alder
inc	incomplete
IPA	*iso*-propyl alcohol
*i*Pr	*iso*-propyl
iPrOH	*iso*-propyl alcohol
IR	infrared
J	coupling constant
LPS	lipopolysaccharide
LUMO	lowest unoccupied molecular orbital
m	multiplet
M	molar
M^+	positively charged mass
M^-	negatively charged mass
μM	micromolar
mM	millimolar
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeO	methoxy
MeOH	methanol
Me_2S	dimethylsulfide

mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
mol	mole
mol%	mole percent
MsCl	methanesulfonyl chloride
MS	molecular-sieves
NaOAc	sodium acetate
Nap	naphthyl
NBS	*N*-bromosuccinimide
nd	not done
*n*BuLi	*n*-butyl lithium
NFSI	N-fluorobenzenesulfonimide
NMO	N-Methylmorpholine-N-oxide
*n*Pr	*n*-propyl
Nu^-	nucleophile
[O]	oxidant
obs	observed
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
pdts	products

Ph	phenyl
pH	potential of hydrogen
$PhCF_3$	trifluorotoluene
$PhCO_2H$	benzoic acid
pK_a	ionization constant
PMP	*para*-methoxyphenyl
psi	pounds per square inch
*p*NBA	*para*-nitrobenzoic acid
p-TsOH	*para*-toluenesulfonic acid
Q-TOF	quadrupole time-of-flight
rac	racemic
rt	room temperature
rxn	reaction
s	singlet
t	triplet
T	temperature
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
*t*Bu	*tert*-butyl
TBME	*tert*-butyl methylether
*t*BuOH	*tert*-butyl alcohol
*t*BuOK	potassium *tert*-butoxide
*t*BuSH	*tert*-butylthiol

TCA	trichloroacetic acid
Temp	temperature
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TES	triethylsilyl
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl
$TsNH_2$	tosylamine
UV	ultraviolet
μL	microliter
wt.% ?	weight percent

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CHAPTER 1

DIENAMINES IN ORGANOCATALYSIS

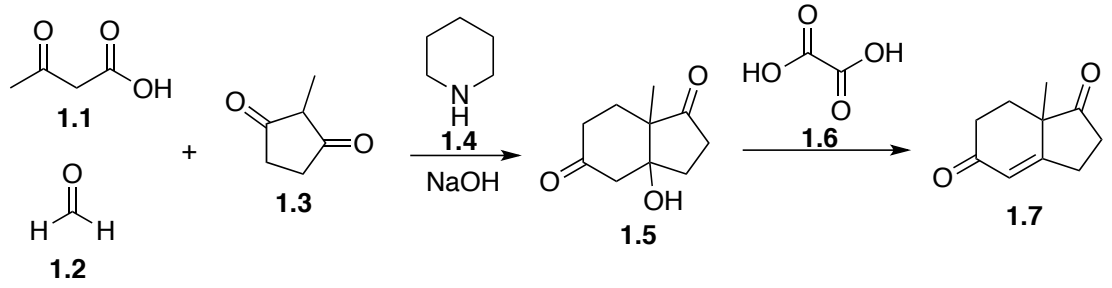
1.1 ORGANOCATALYSIS

Catalysis is an essential part of synthetic chemistry, as well as the life it creates and sustains. Enzymes, proteins, and various other molecules interact in the body enabling countless biological processes. In chemistry, catalysts mimic these biological systems by decreasing the activation energy required for transformations to occur through coordination, hydrogen-bonding, and covalent interactions. For many years, catalysts employed by chemists consisted mainly of transition metals in various oxidation states in the presence of ligands used to add an asymmetric element or to assist in reactivity. The high cost and toxicity that can be inherent to many transition metals, while manageable, led to a desire to find alternative means to accomplish catalyzed reactions.

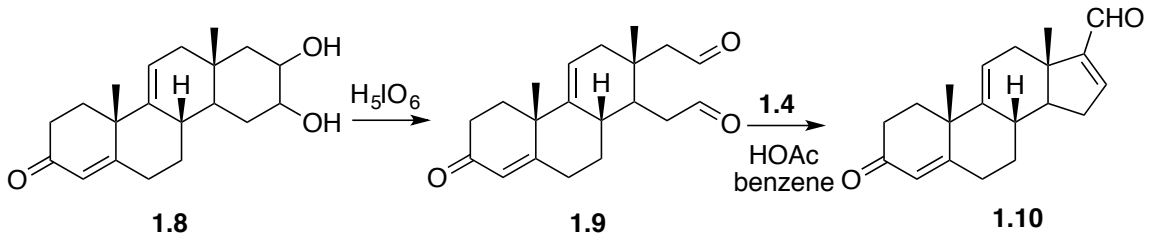
Organocatalysis is defined as catalysis using "small organic molecules where an inorganic element is not part of the active principle."[1] Over the past sixteen years, organocatalysis has emerged as a significant component in modern organic synthesis, being recognized as the third pillar of catalysis, alongside biocatalysis and transition metal catalysis. The scope of organocatalysis has seen immense growth, but is still relatively limited, the reaction rates are frequently slower, and catalyst loadings often need to be higher in comparison to other types of catalysis. On the other hand, some of the advantages over traditional catalysis are lowered costs and reduced toxicity due to the removal of the need for metals, tolerance of a wider variety of reaction conditions, and a complementary set of reactions not usually accessible through other catalytic means.

While the field has grown dramatically since the early 2000's, the first precedent for the use of organic molecules as catalysts appeared in 1954 when Stork used secondary amines to alkylate and acylate ketones.[2] Ten years later, it was proposed that class I aldolases involve enamine intermediates in their catalytic cycle, requiring lysine residues for catalytic activity.[3] This led to the use of secondary amines, such as piperidine (**1.4**), as biomimetic catalysts in the total synthesis of steroids by Woodward, using the formation of the Wieland-Miescher ketone (**1.7**, **Scheme 1.1**) and **1.10** (**Scheme 1.2**).[4,5]

Scheme 1.1 Piperidine assisted formation of the Wieland-Miescher ketone.



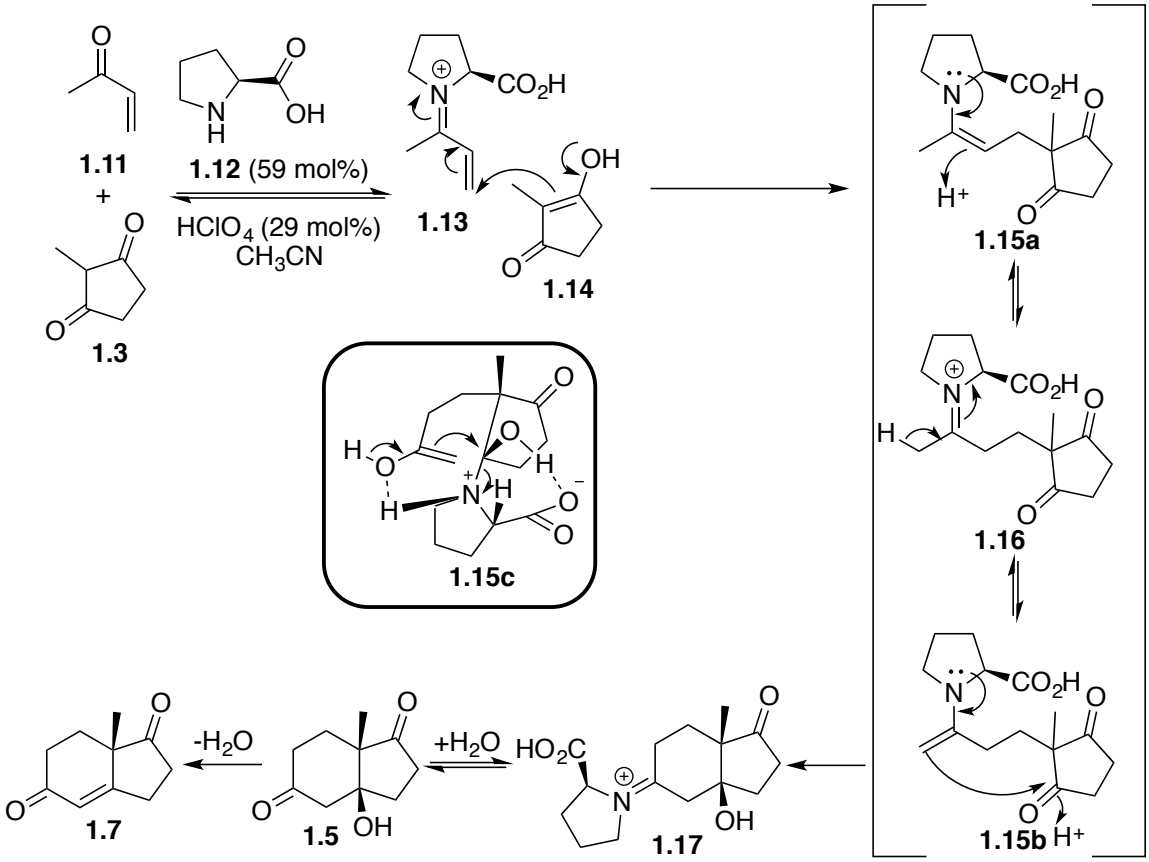
Scheme 1.2 Woodward-Wieland-Miescher enamine cyclization for steroid synthesis.



Then, in the early 1970's Wiechert and coworkers, as well as Hajos and coworkers, developed the first asymmetric catalytic one-pot Michael addition-intramolecular aldol condensation cascade using (*L*)-proline (**1.12**) to asymmetrically form the Wieland-Miescher ketone (**1.7**, **Scheme 1.3**).[6,7] This transformation has since been known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction. While there has been some debate over the

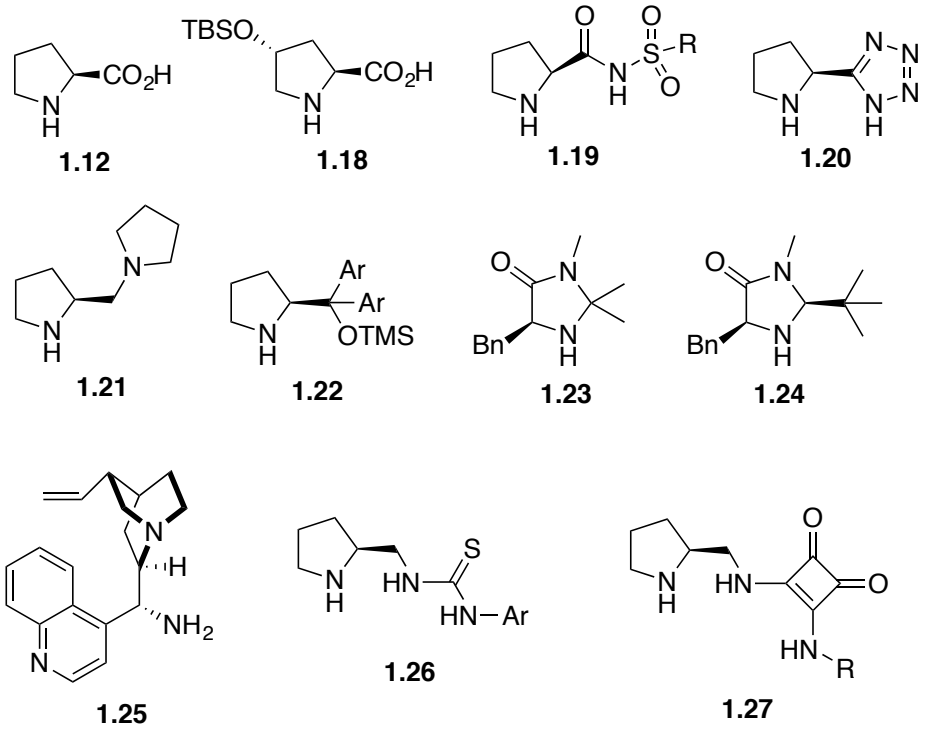
years regarding the mechanism of this transformation, Hajos and Parrish proposed a mechanism that reacted via an enol with a sterically hindered hemiaminal (**1.15c**, **Scheme 1.3**), the widely accepted mechanism is displayed in **Scheme 1.3**.[7–13]

Scheme 1.3 Enamine catalyzed Hajos-Parrish-Eder-Sauer-Wiechert reaction.



It was not until the rediscovery of aminocatalysis independently by Barbas' and MacMillan's research groups in 2000, that organocatalysis commenced its rapid growth.[14,15] **Figure 1.1** displays a number of amine-based organocatalysts that have been developed and have been used over the past sixteen years.[14–24]

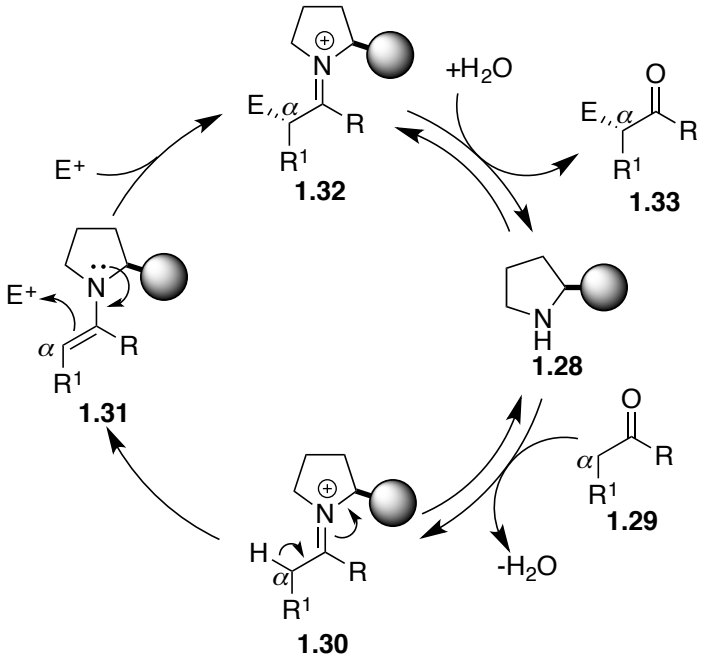
Figure 1.1 Examples of organocatalysts.



Amine catalyzed reactions can proceed through a variety of different reactive intermediates, activating aldehydes or ketones through HOMO-raising or LUMO-lowering intermediates. Following condensation of chiral catalyst (**1.28**, **Scheme 1.4**) onto a carbonyl (**1.29**), iminium ion **1.30** forms, followed by α-deprotonation to form enamine **1.31**. This HOMO-raised α-nucleophile can react with an electrophile in solution, producing α-functionalized iminium ion **1.32**, which will produce α-functionalized carbonyl **1.33** and regenerate catalyst **1.28** following hydrolysis. If catalyst **1.28** contains a chiral auxiliary as seen in **Figure 1.1**, stereoinduction is possible by directing the facial approach through hydrogen-bonding (catalysts **1.12**, **1.18-1.21**, **1.25-1.27**) or through facial blocking (catalysts **1.22-1.24**), the latter being demonstrated in **Scheme 1.4**. This

enamine mechanism is commonly used in aldol condensations, Mannich reactions, Michael reactions, and halogenations.[1]

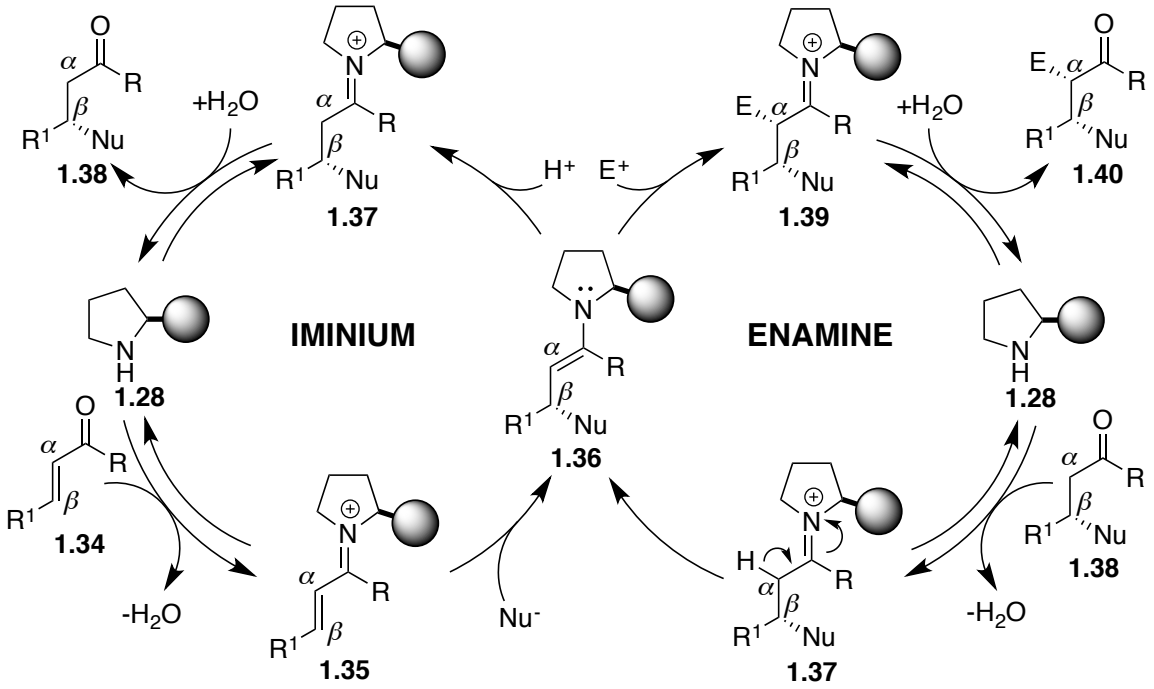
Scheme 1.4 Enamine organocatalytic cycle.



In iminium catalysis, a conjugated iminium ion intermediate (**1.35**, **Scheme 1.5**) is formed, following condensation of catalyst **1.28** onto an α,β-unsaturated aldehyde or ketone (**1.34**). The LUMO-lowered iminium ion intermediates are activated as a Michael acceptor at the β-position. Conjugate addition to the β-position follows the same mode of asymmetric induction, depending on the catalyst, as in enamine catalysis. The enamine (**1.36**) generated by the conjugate addition is again activated as a nucleophile and can produce a monosubstituted carbonyl (**1.38**) by reacting with a proton, followed by hydrolysis, or can produce an α,β-disubstituted carbonyl (**1.40**) by introducing an electrophile to the solution. These latter transformations, known as a organocascades, are powerful tools for condensing multistep syntheses of multifunctional asymmetric products

into single-pot processes, providing economical routes to natural products and other biologically active molecules, or their precursors.[25–28]

Scheme 1.5 Iminium and iminium-enamine cascade catalytic cycles.



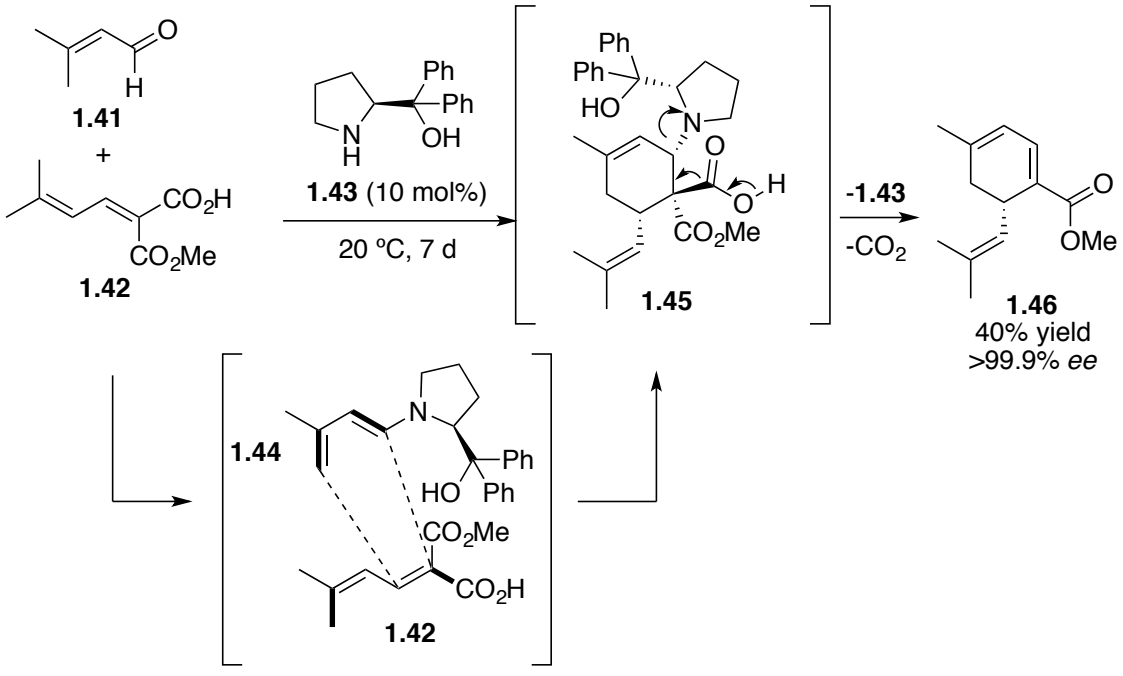
1.2 DIENAME ORGANOCATALYSIS

Dienamines have long been useful reactive species in organic synthesis. They were first synthesized by Mannich in 1936 as an extension of his research into enamines, and were first used by Snyder as a diene for Diels-Alder reactions.[29,30] Dienamines became an excellent tool for the activation and stereocontrol of Diels-Alder and hetero-Diels-Alder reactions, being easy to synthesize and providing easily removable amines in the Diels-Alder products.[31,32] Once the field of organocatalysis began to flourish, it was not long before dienamine catalyzed reactions began to emerge due to their potential for organocatalytically controlled cycloadditions, as well as their potential to participate in organocascade reactions yielding unique multifunctional asymmetric compounds.

1.2.1 Normal-Electron-Demand Diels-Alder-type Cycloadditions

In 1998, prior to what is considered to be the inception of the field of organocatalysis, Serebryakov and coworkers reported the first dienamine catalyzed asymmetric Diels-Alder cycloadditions.[33] They had previously shown that preforming the reactive dienamine was not necessary, and in this research they introduced a catalytic amount of 2º amine catalyst (**1.43**) to α,β-unsaturated aldehyde (**1.41**) while in the presence of dienophile (**1.42**), to provide a diene product (**1.46**) in a single step. This product was obtained in a moderate 40% yield, but high >99.9% *ee* after reacting for 7 days at room temperature (**Scheme 1.6**).[34]

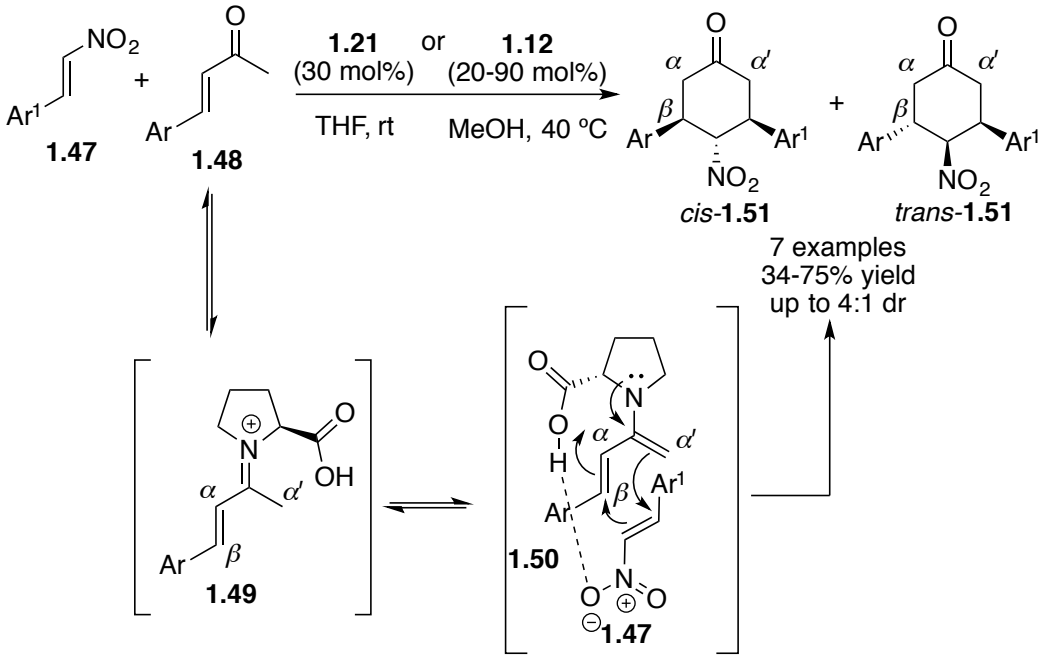
Scheme 1.6 Serebryakov's dienamine catalyzed synthesis of asymmetric cycohexa-1,3-dienes.[33]



In 2002, Barbas and coworkers also expanded their research into the organocatalytic formation of dienamines for Diels-Alder cycloadditions. In their research, they combined non-Michael donating nitro olefins (**1.47**, **Scheme 1.7**) with iminium

activated α,β-unsaturated ketones (**1.49**), which could generate 2-amino-1,3-dienes (**1.50**) through deprotonation at the α'-carbon.[35] This allowed for a cycloaddition to occur, generating cyclohexanones in 35-75% yield and diastereomeric ratio up to 8:1 in favor of diastereomer *cis*-**1.51**. Prior to this work, 2-amino-1,3-dienes were preformed and isolated before use, so this was considered a much more economical route to accomplishing the same Diels-Alder reactions.[31,36–39]

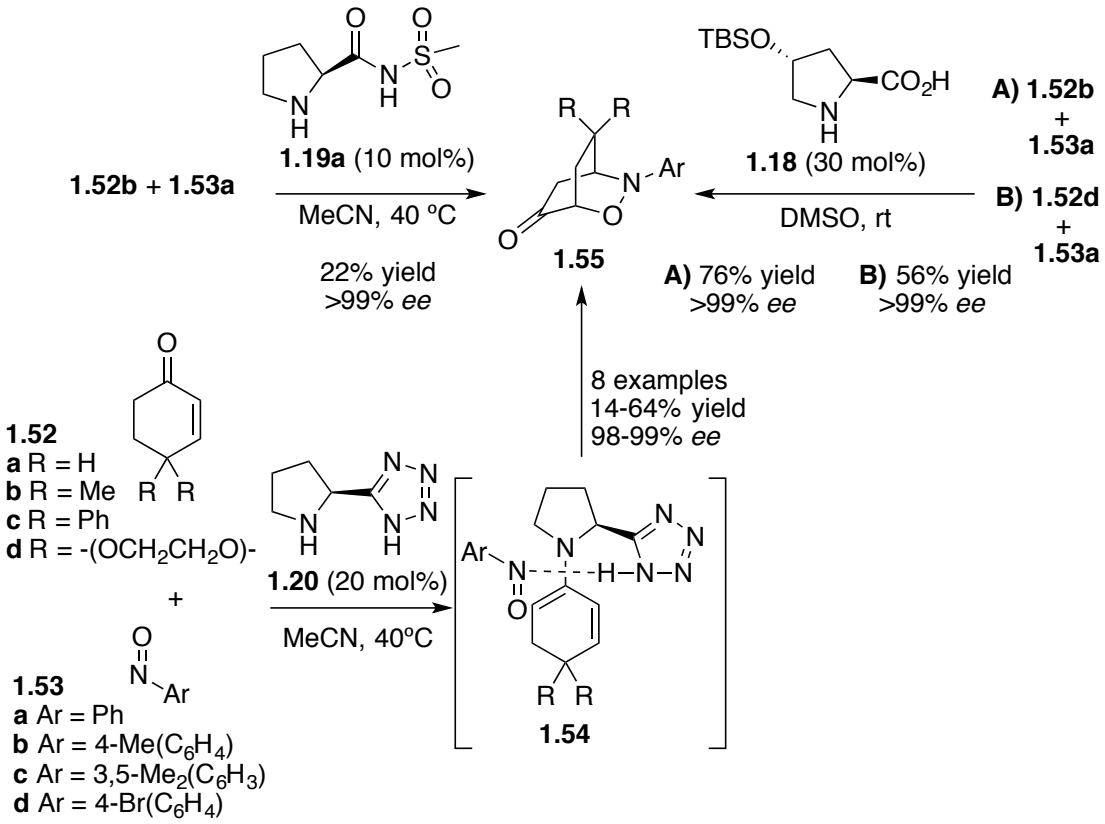
Scheme 1.7 Barbas' cross-dienamine catalyzed asymmetric Diels-Alder cycloadditions.[35]



In 2004, Yamamoto and coworkers and Hayashi and coworkers independently reported a tandem *O*-nitroso aldol/Michael reaction with nitrosobenzene (**1.53a**) and dienamine activated α,β-unsaturated ketones (**1.52**, **Scheme 1.8**).[18,40] Yamamoto's group synthesized nitroso Diels-Alder adducts (**1.55**) in good yields and excellent enantioselectivities using pyrrolidine-based tetrazole catalyst **1.20**, while Hayashi's group used 4-siloxyproline catalyst **1.18** to afford the cycloadduct in higher yield and equally high enantioselectivity. The following year, Córdova and coworkers also reported this

transformation, reporting the same results as Yamamoto while using the tetrazole catalyst **1.20**.[20] Using proline-derived *N*-sulfonylcarboxamide catalyst **1.19a**, however, they were able to improve the enantioselectivity, although dramatically decreasing product yields. Yamamoto and coworkers continued work on the synthesis of nitroso Diels-Alder adducts and in 2007 reported a more complete study of this reaction.[41]

Scheme 1.8 Dienamine mediated tandem *O*-nitroso aldol/Michael reactions.[18,20,40,41]



In 2006, Hong and coworkers reported the first non-heteroatomic, organocatalyzed [3+3] and direct [4+2] cycloadditions using α,β-unsaturated aldehydes.[42] In this research, (*L*)-proline (**1.12**) was reacted with various enals to provide both activated dienamine (**1.59**) and iminium ion (**1.58**) intermediates for cycloadditions that formed **1.64** and **1.68** in moderate to high yields and a range of enantioselectivities (**Scheme 1.9**). In reactions with less steric hindrance at the dienamine β-position, Hong proposed a Morita-Baylis-

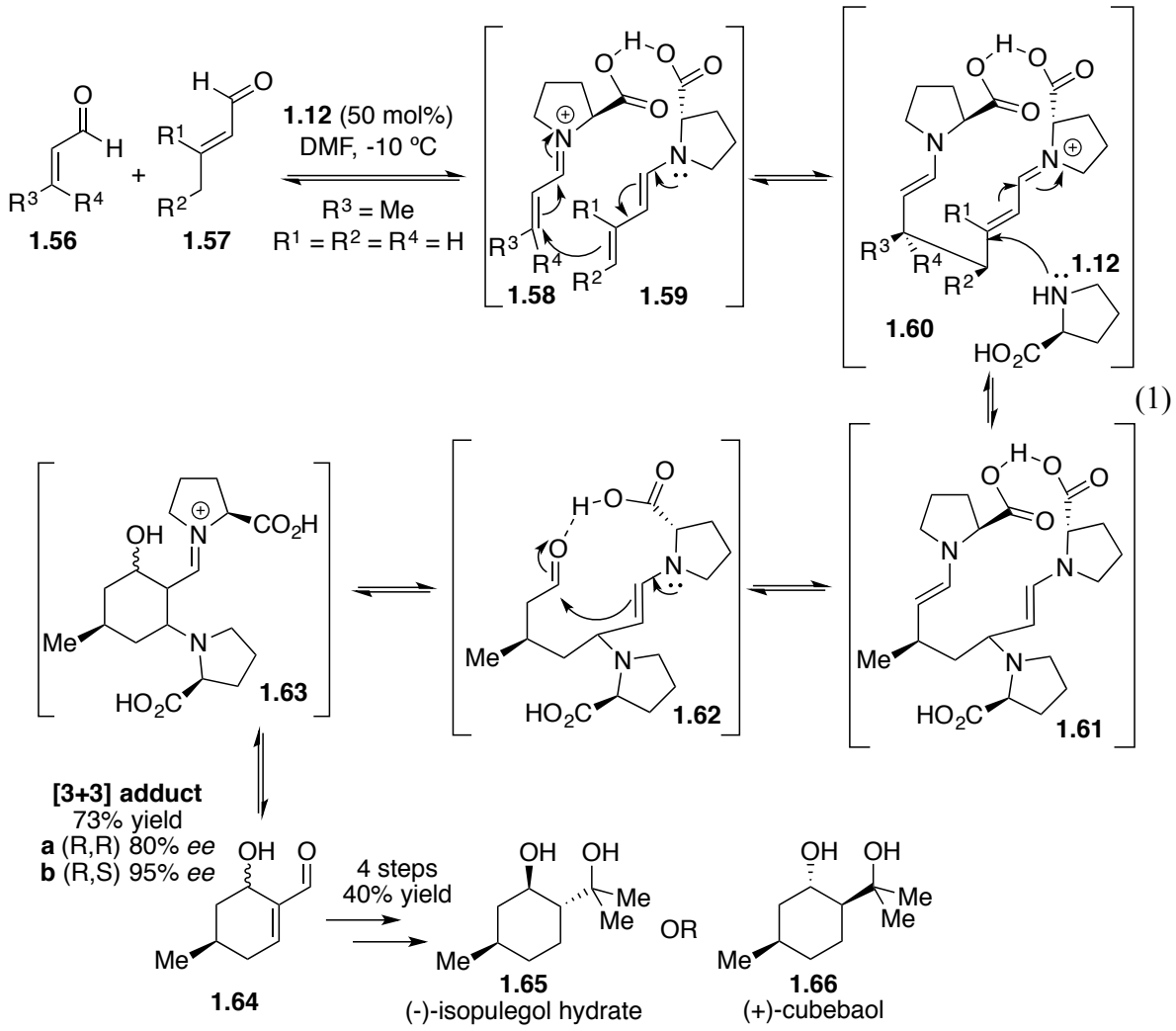
Hillman-like pathway for synthesis of the [3+3] adduct **1.64** (eq 1). These products were then derivatized to synthesize (-)-isopulegol hydrate (**1.65**) or (+)-cubebaol (**1.66**), depending on the *R* or *S* stereochemistry of the alcohol at C7, respectively. More sterically hindered dienamines, however, were proposed to follow a Mannich reaction pathway to afford [4+2] adducts **1.68** (eq 2).

In 2007, Hong and coworkers expanded their methodology for the [3+3] and [4+2] cycloadditions of α,β-unsaturated aldehydes to the synthesis of aromatic aldehydes (**1.72** and **1.73**, eq 1, **Scheme 1.10**).[43] They found that some aromatic products were formed spontaneously following [3+3] or [4+2] cycloaddition, while most were synthesized with the assistance of oxidizers such as MnO_2 or DDQ. They were also able to synthesize both aromatic (**1.76** and **1.78**) and non-aromatic bicyclic aldehydes (**1.75** and **1.77**) through intramolecular cycloadditions in mostly high yields and low to high enantioselectivities where applicable (eq 2, **Scheme 1.10**).

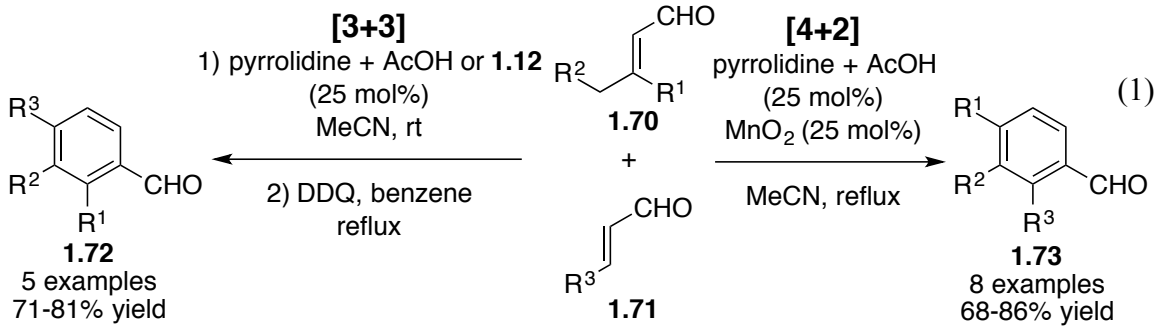
Following these preliminary reports, Hong and coworkers reported a highly enantioselective organocatalytic Diels-Alder reaction of α,β-unsaturated aldehydes (**Scheme 1.11**).[44] Reaction yield and enantioselectivity varied greatly depending on the conditions used for each substrate. Generally, they noted that lowering the reaction temperature increased enantioselectivity, but decreased yield and increased reaction rate. Yield could be increased and reaction rate decreased at low temperature by introducing tertiary amine cocatalysts, such as triethylamine or (-)-sparteine. Optimal yields could be obtained using *L*-proline or diaryl prolinol silyl ethers **1.22a** or **1.81** as catalysts, triethylamine and (-)-sparteine as cocatalysts, and temperatures ranging from -40 ºC to 0 ºC. They then applied this methodology to the total synthesis of (+)-palitantin (**1.82**), which

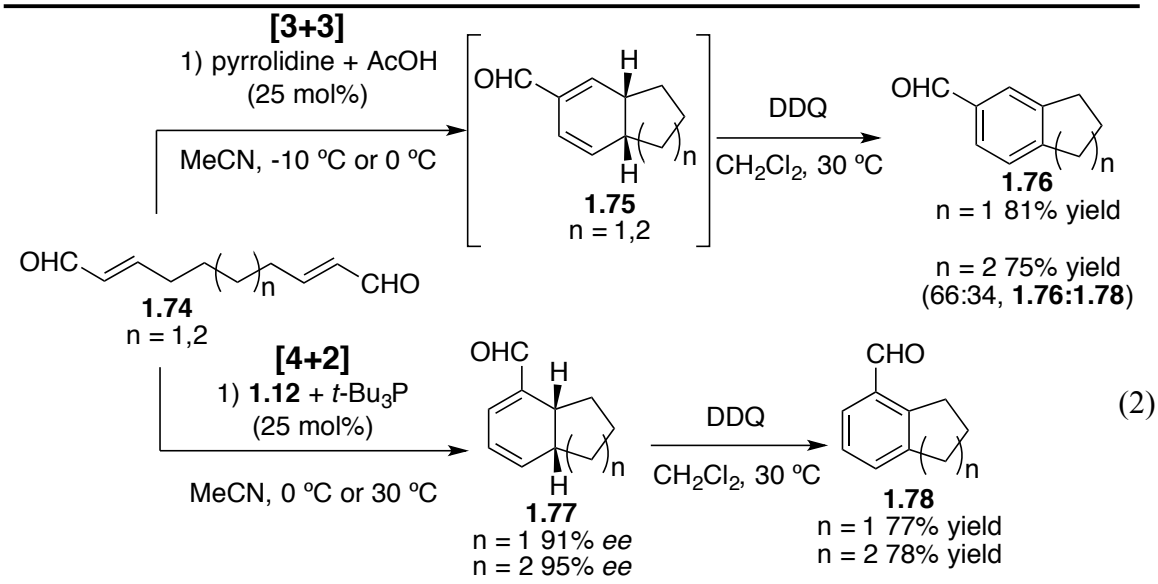
was accomplished in a 10 step yield of 13%.

Scheme 1.9 Hong's proposed mechanisms for selective synthesis of [3+3] or [4+2] adducts.[42]

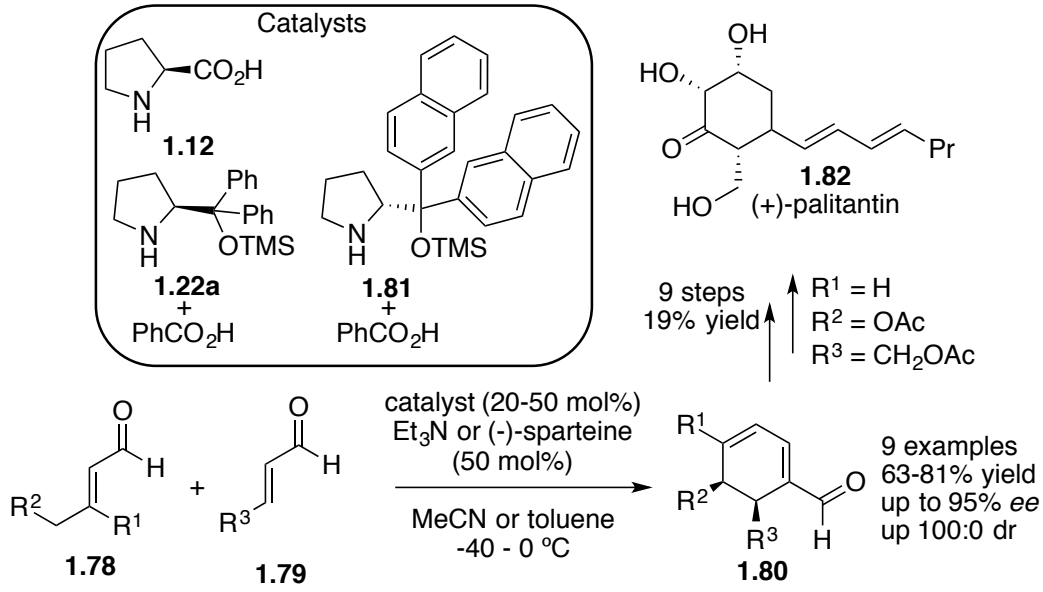


Scheme 1.10 Hong's syntheses of multifunctional aromatic aldehydes and dienes.[43]



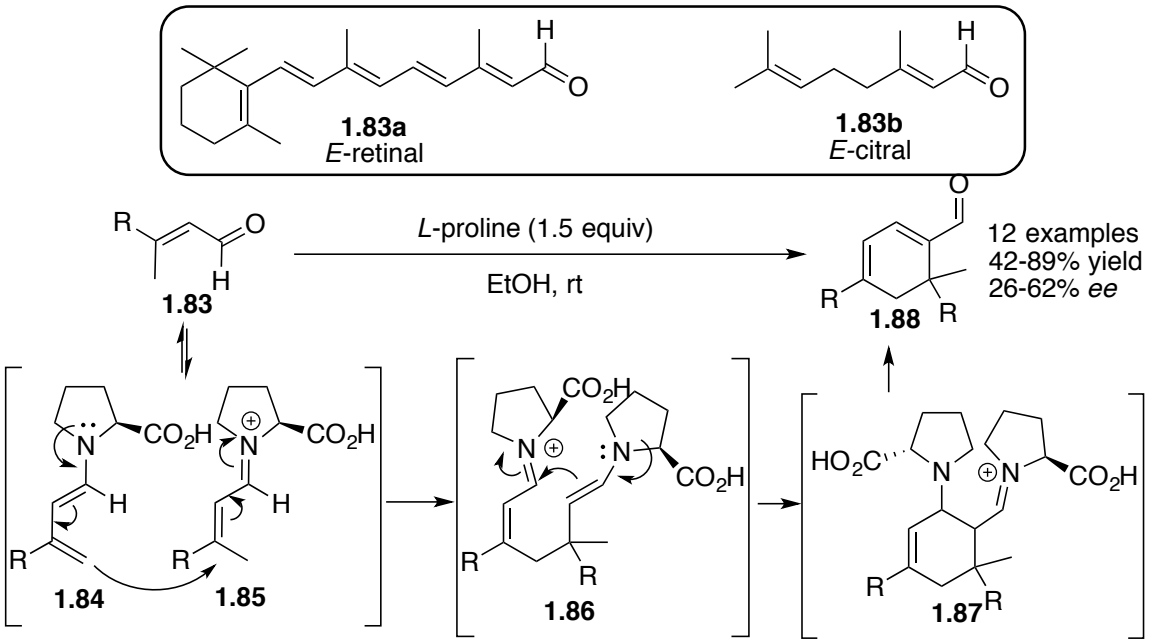


Scheme 1.11 Dienamine mediated synthesis of a precursor to (+)-palitantin (**1.82**).[44]



In 2006, Watanabe and coworkers developed a proline catalyzed homodimerization, which combined dienamine and iminium ion catalysis to form cyclic 1,3-dien-1-als (**1.88**, **Scheme 1.12**).[45] This was employed as a strategy to synthesize the self-condensation products of retinoids, such as retinal (**1.83a**), which have been implicated as a contributor to age-related macular degeneration, and citral (**1.83b**), which is a natural product known to exhibit antibacterial activity.[46–50] The optimized reaction employed excess *L*-proline, rather than a catalytic amount, and while yields were moderate to high, enantioselectivities were only moderate. This was attributed to the remote location of the γ-position in relation to the proline chiral auxiliary. As it was unclear to them whether the reaction was accomplished in a concerted [4+2] Diels-Alder cycloaddition or a conjugate addition followed by a Mannich addition, they reasoned that the limited stereocontrol implicated the latter mechanism, as reactivity at the *ipso*-position in a concerted reaction could afford better stereocontrol than was observed.

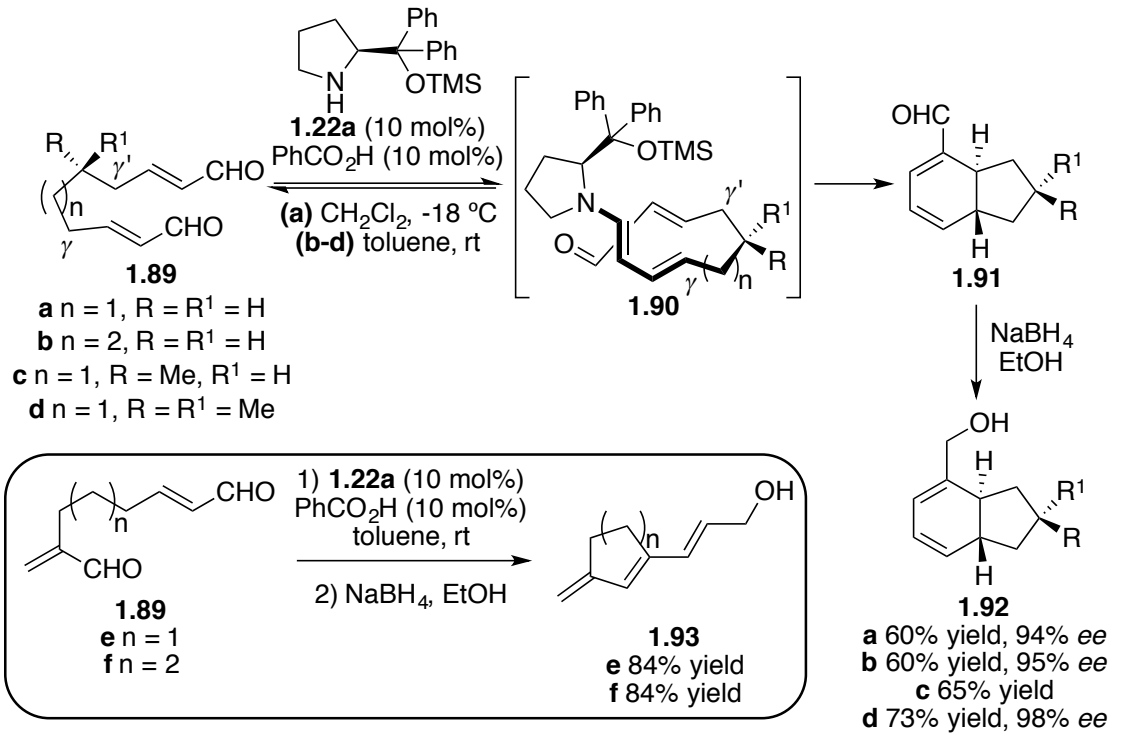
Scheme 1.12 Dienamine catalyzed homodimerization of α,β-unsaturated aldehydes.[45]



In 2008, Christmann and coworkers used the formation of dienamines with amino catalysts to create an electron rich diene for asymmetric intramolecular Diels-Alder cycloaddition (**Scheme 1.13**).[51] In their research, they introduced dialdehydes (**1.89**) of various chain lengths to diphenylprolinol silyl ether catalyst (**1.22a**) to afford bicyclic dienols (**1.92**), following proton elimination of the catalyst and $NaBH_4$ reduction of the aldehyde (**1.91**), in moderate yields and high enantioselectivity. In asymmetric dialdehydes (**1.89c** and **1.89d**), dienamine activation was favored at the less hindered γ-positions, providing regioisomeric products in a 2:1 ratio for **1.92c** and a 4:1 ratio for **1.92d**. Christmann attributed this selectivity to the decreased rate of dienamine formation at the γ'-position with one or two methyl groups in the adjacent δ'-position. They also accomplished dienamine activated vinylogous aldol condensations using this methodology, generating monocyclic structures **1.93** in high yields from dialdehydes **1.89e** and **1.89f**.

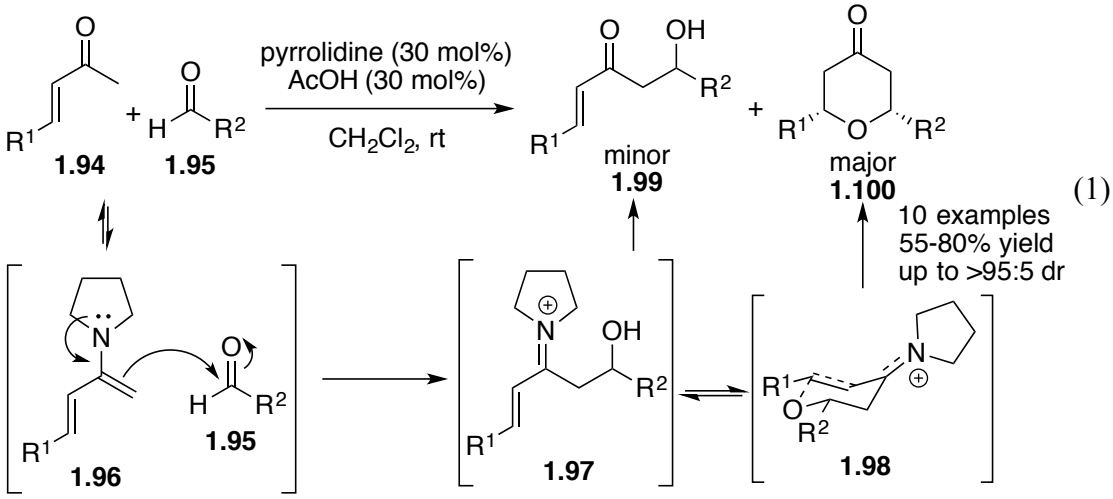
In 2008, Xiao and coworkers reported the first dienamine catalyzed normal-electron-demand oxa-Diels-Alder reactions, synthesizing substituted tetrahydropyran-4-ones (**1.100**) from α,β-unsaturated ketones (**1.94**) and aldehydes (**1.95**).[52] In their seminal work they used pyrrolidine as a secondary amine catalyst for the majority of their substrates, achieving moderate to high yields with excellent *syn/anti* diastereoselectivity, with up to 15% of product being isolated as the aldol adduct (**1.99**). This was an indication that the reaction was following an aldol/oxa-Michael cascade mechanism rather than a concerted [4+2] cycloaddition mechanism. They also tried an asymmetric version of this reaction using **1.101** as a bifunctional organocatalyst to generate **1.100aa'** in 45% yield and 40% *ee*, with a lowered dr of 77:23.

Scheme 1.13 Christmann's dienamine catalyzed intramolecular Diels-Alder and aldol condensations.[51]



In 2009, Melchiorre and coworkers developed a dienamine catalyzed synthesis of spirocyclic oxindoles (**1.107**, **Scheme 1.15**), a moiety found in a number of natural products.[53] In their research, they used cinchona alkaloid derivative **1.104** to generate dienamine **1.105**, upon condensation with ketone **1.103**, at which point, a Michael-Michael cascade could occur with the compound **1.102**. Products were obtained in moderate to high yields, with the exception of reactions using cyclohexenones which afforded the lowest yields of 24% and 28%. Enantioselectivities were high in all examples and diastereoselectivities were good to excellent.

Scheme 1.14 Xiao's report of first dienamine catalyzed normal-electron-demand oxa-Diels-Alder reactions.[52]



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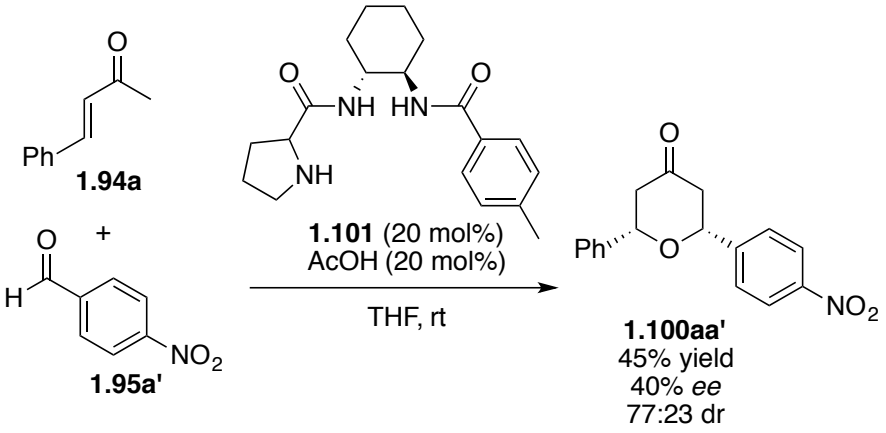
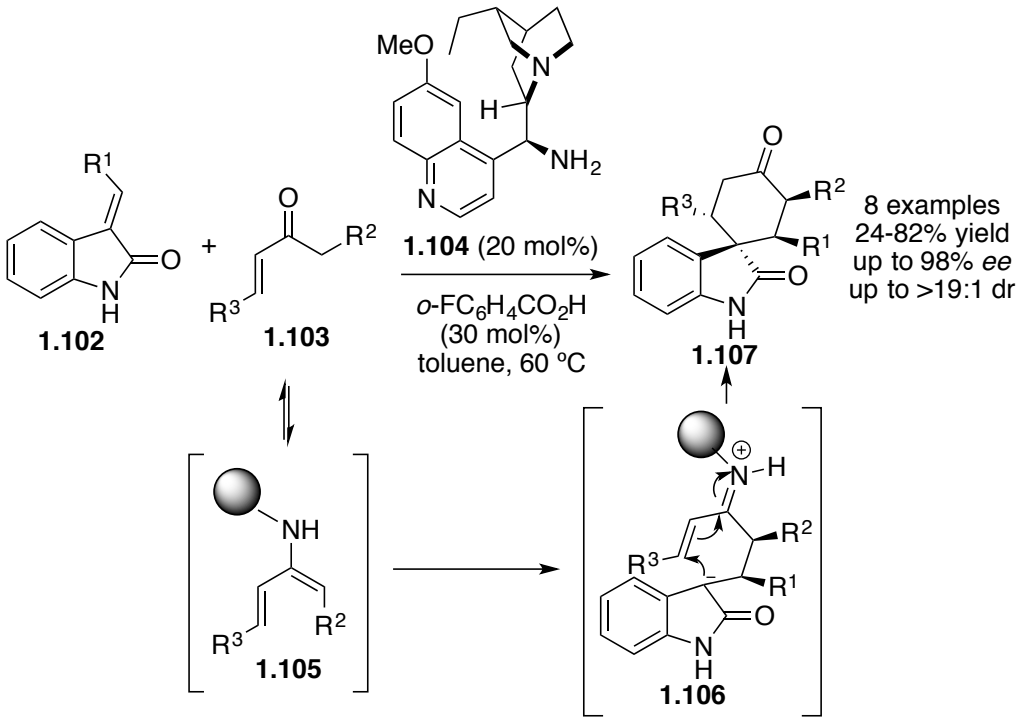


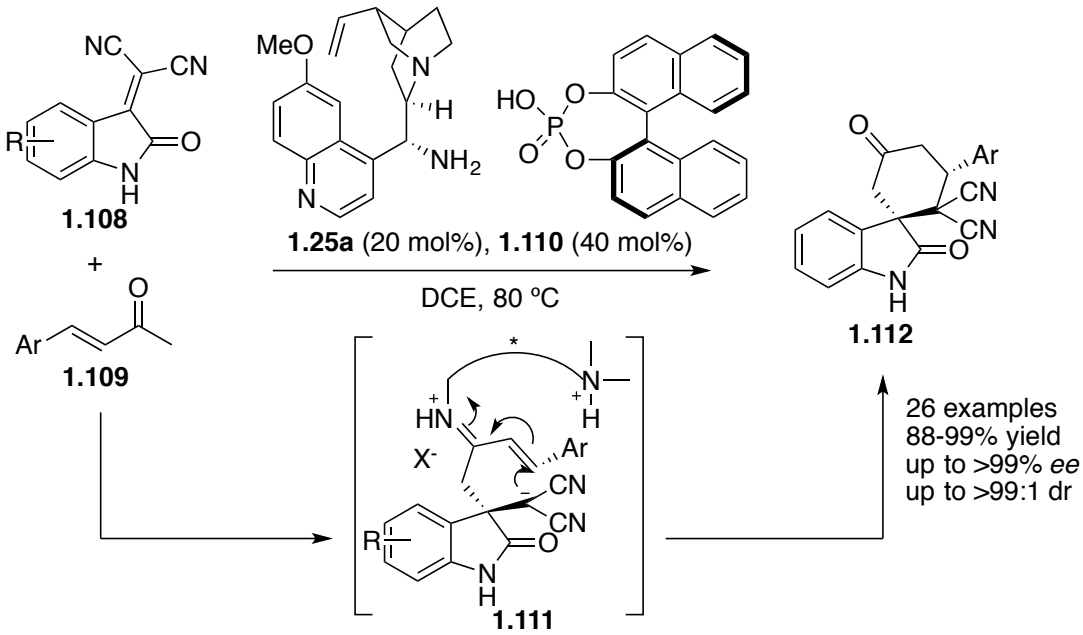
(2)

In 2011, Wang and coworkers developed their own dienamine catalyzed synthesis of optically pure spirocyclic oxindoles (**1.112**, **Scheme 1.16**).[54] While their mechanism similarly followed that of a Michael-Michael cascade, the use of isatylidene malonitriles (**1.108**) caused a reversal in the electronics at the alkene, leading to spiro[cyclohexane-1,3'-indoline]-2',3-diones (**1.112**), rather than the dione (**1.107**) observed in **Scheme 1.15**. Using a combination of cinchona alkaloid catalyst **1.25a** and (*R*)-BINOL-phosphoric acid (**1.110**) cocatalyst, products were obtained in high yields and excellent enantioselectivities and diastereoselectivities.

Scheme 1.15 Melchiorre's Michael-Michael cascade synthesis of spirocyclic oxindoles **1.107**.[53]



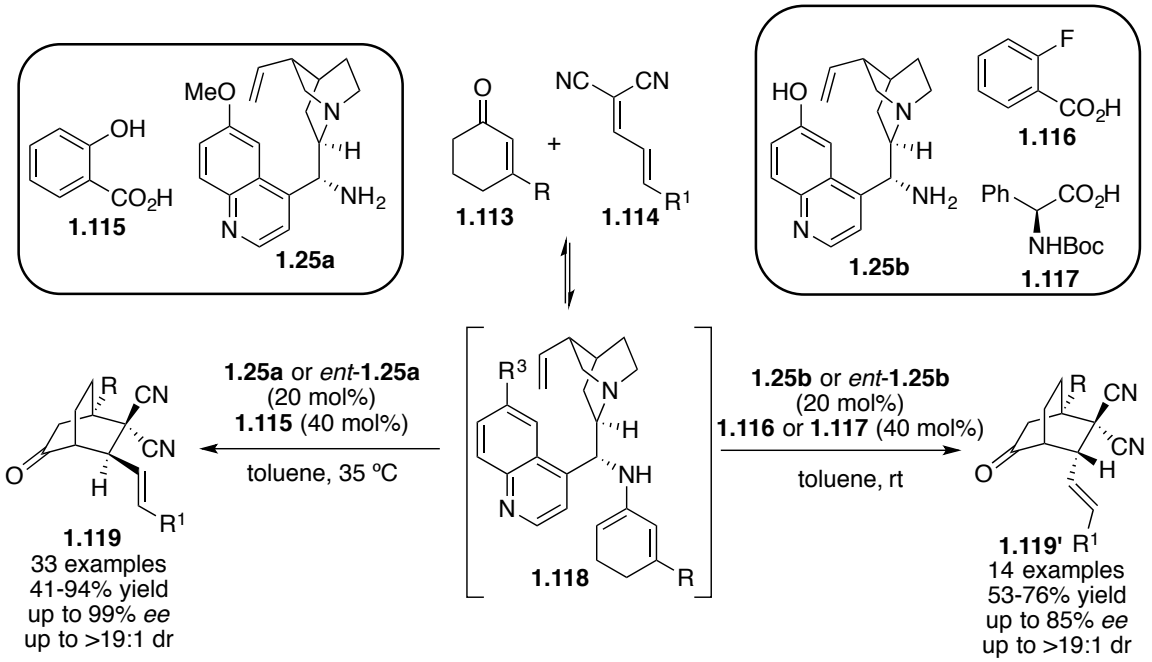
Scheme 1.16 Wang's dienamine catalyzed synthesis of spirocyclic oxindoles **1.112**.[54]



In 2012, Chen and coworkers began studying dienamine catalysis of *β*-

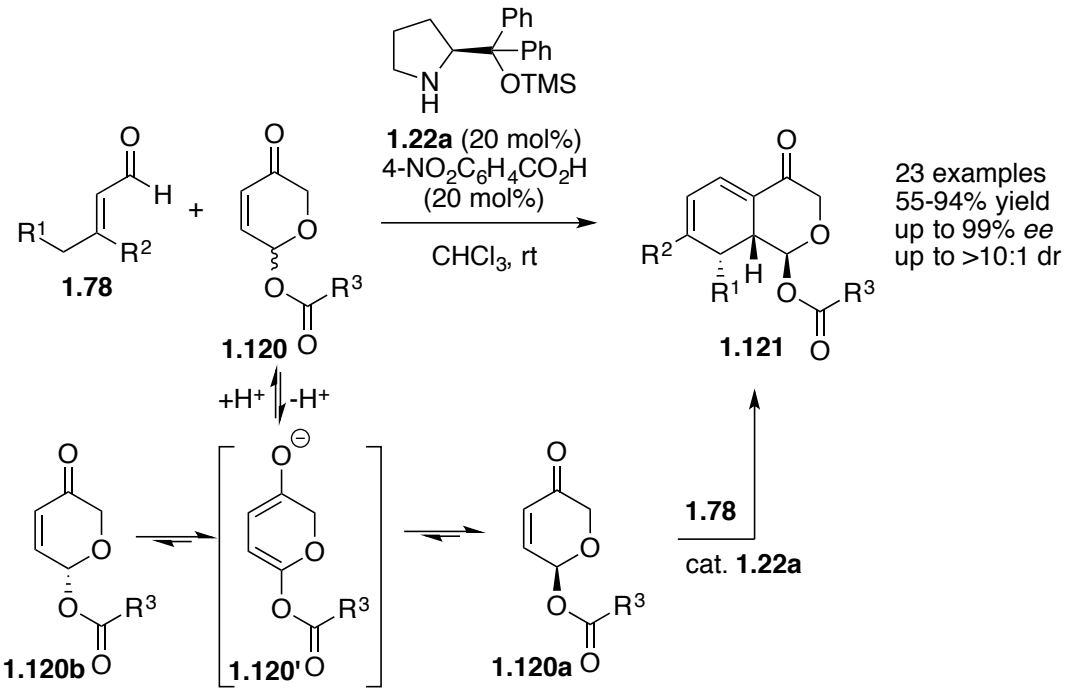
methylcyclohexenones (**1.113**) with allylidenemalononitriles (**1.114**, **Scheme 1.17**).[55] Melchiorre and coworkers, previously described highly γ-regioselective direct vinylogous Michael additions using β-methylcyclohexenone and either nitroalkenes or benzylidenemalonitrile in the presence of cinchona alkaloid-derived catalysts (vide infra).[56] When Chen and coworkers used allylidenemalononitriles, they found that the reaction pathway unexpectedly shifted to a [4+2] cycloaddition through the α'-activated 2-amino-1,3-diene (**1.118**), generating bicyclo[2.2.2]octane derivatives (**1.119**). Depending on the conditions, high yields and enantioselectivities could be achieved favoring the endo cycloadduct (**1.119**) using catalysts **1.25a** or *ent*-**1.25a** in the presence of salicylic acid (**1.115**) additive, or favoring the exo cycloadduct (**1.119'**) using catalyst **1.25b** or *ent*-**1.25b** in the presence of *o*-fluorobenzoic acid (**1.116**) or amino acid **1.117** additives. This stereodivergence was attributed to the different hydrogen bonding capabilities of **1.25a** and **1.25b**.

Scheme 1.17 Chen's endo and exo dienamine-mediated [4+2] cycloadditions.[55]



Having an interest in expanding the scope of non-homodimeric [4+2] cycloadditions of α,β-unsaturated aldehydes (**1.78**), Vicario and coworkers reported the dienamine catalyzed formation of multifunctional heterobicycles (**1.121**, **Scheme 1.18**).[57] They found that they exclusively formed cycloadducts, with no competition from α- or γ-vinylogous additions, and that the mechanism involved a dynamic kinetic resolution that generated a single enantiomer of high enantiopurity from racemic pyranone starting materials (**1.120**). The best yields and stereocontrol were obtained using catalyst **1.22a**, and a substrate scope generated a large library of cycloadducts in moderate to high yield and high enantioselectivities, with unsubstituted aldehydes (R^2 = H) being the exception.

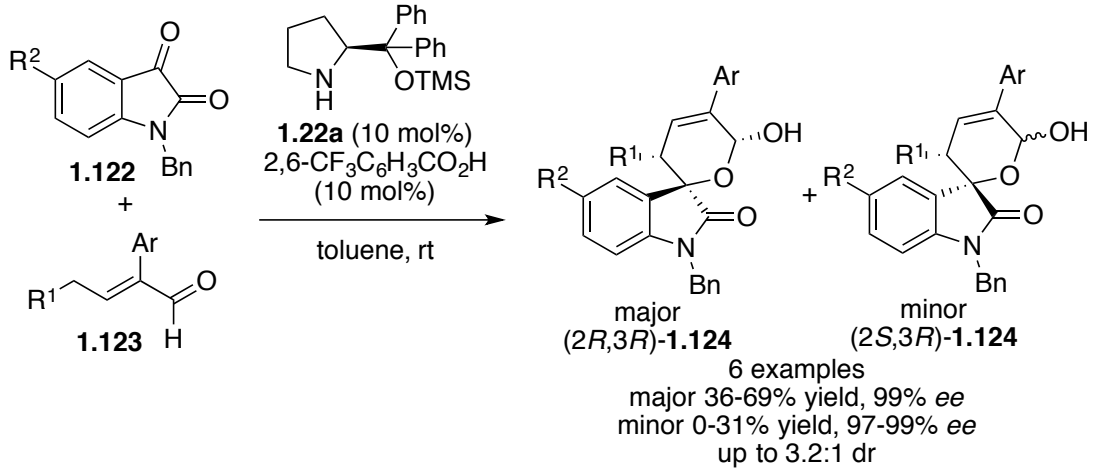
Scheme 1.18 Vicario's synthesis of tetrahydro-1H-isochromanes via a dienamine-mediated dynamic kinetic resolution.[57]



During their investigations into the scope of direct vinylogous aldolizations between α-substituted α,β-unsaturated aldehydes and isatins (vide infra), Melchiorre

discovered that α-aryl α,β-unsaturated aldehydes (**1.123**) would undergo hetero-Diels-Alder reactions with isatins (**1.122**, **Scheme 1.19**).[58] The products generated were spiroxindole lactols (**1.124**), which are useful scaffolds found in a large number of natural and unnatural products.[59] Products were obtained in moderate to good yields and high enantioselectivities in both the major and minor diastereomers.

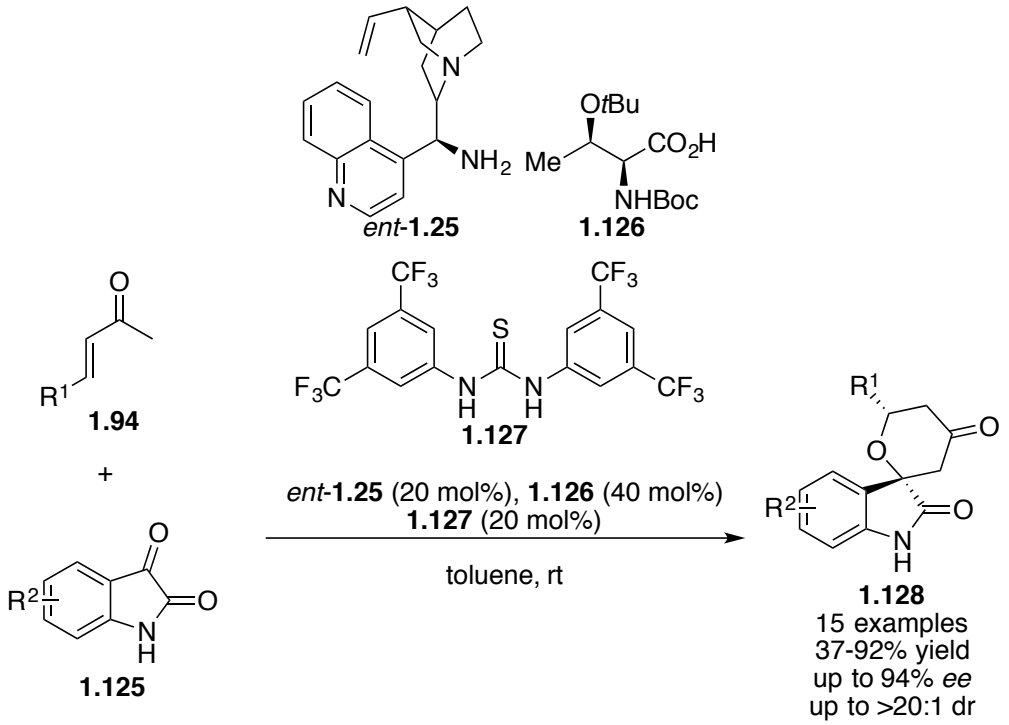
Scheme 1.19 Melchiorre's hetero-Diels-Alder-type reaction to access spiroxindoles.[58]



In 2013, Tanaka and coworkers reported an organocatalytic formal hetero-Diels-Alder reaction between isatins (**1.125**) and linear α,β-unsaturated ketones (**1.94**) to provide spiroxindole tetrahydropyranones (**1.128**, eq 1, **Scheme 1.20**).[60] In developing this difficult reaction, they found that a combination of cinchona alkaloid catalyst *ent*-**1.25** and amino acid cocatalyst **1.126** granted optimal yields and stereoselectivities, while inclusion of thiourea catalyst **1.127** as an additive provided a hydrogen bond donor that could block isatin imine formation with the catalyst, increasing the yield and preventing side reactions. Using a variety of aliphatic substrates, low to high yields were obtained, as were high enantioselectivities and mostly high diastereoselectivities. The group then demonstrated the utility of this reaction by synthesizing derivatives (**1.130**, **1.131**, and **1.132**) of **1.128a**

in good yields, while maintaining enantiopurity (eq 2).

Scheme 1.20 Tanaka's dienamine catalyzed hetero-Diels-Alder synthesis of spiroxindole tetrahydropyranones **1.28**.[60]



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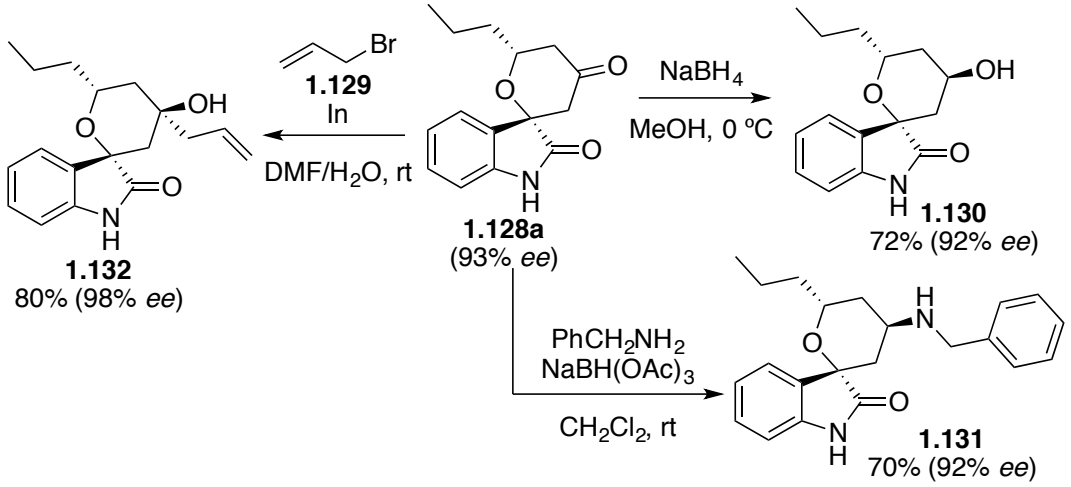
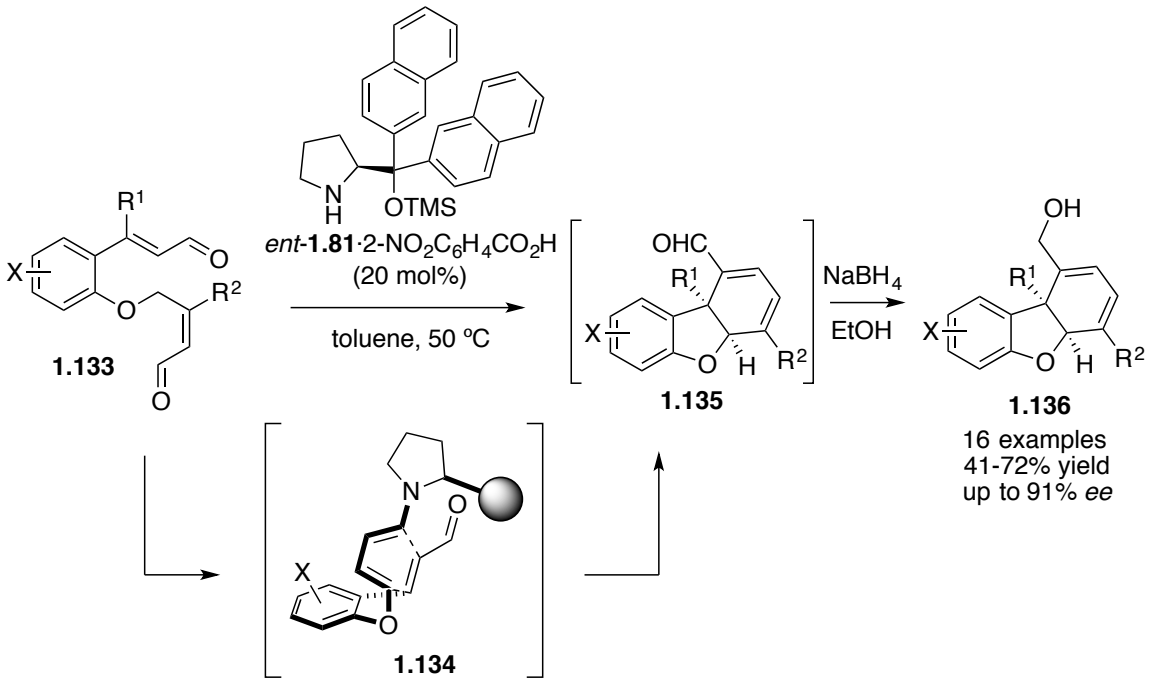


(2)

In 2013, Yang and coworkers reported development of an intramolecular dienamine-mediated synthesis of various dihydrobenzofurans (**1.136**, **Scheme 1.21**), a moiety found in many natural products and biologically important compounds.[61] Due to

the rigid structure of the initial dienal (**1.133**), reactions needed to be run at higher temperatures in order to maximize the yield and needed to use more sterically bulky catalysts to maximize *ee*. They found that by running the reaction at 50 ºC and using bulky diaryl prolinol silyl ether catalyst *ent*-**1.81** and 2-nitrobenzoic acid cocatalyst, they were able to synthesize the tricyclic products in moderate to high yields and good enantioselectivities, via an exo transition state (**1.134**).

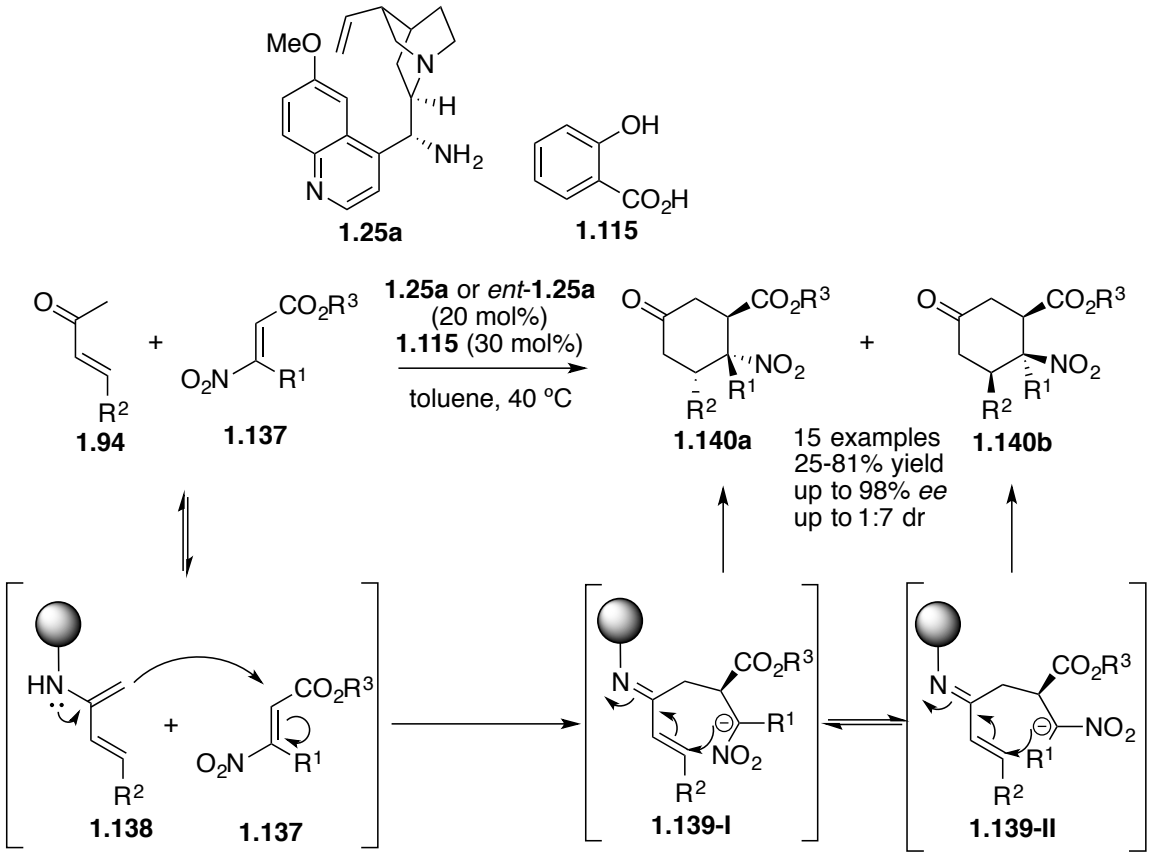
Scheme 1.21 Intramolecular dienamine-mediated synthesis of dihydrobenzofurans **1.136**.[61]



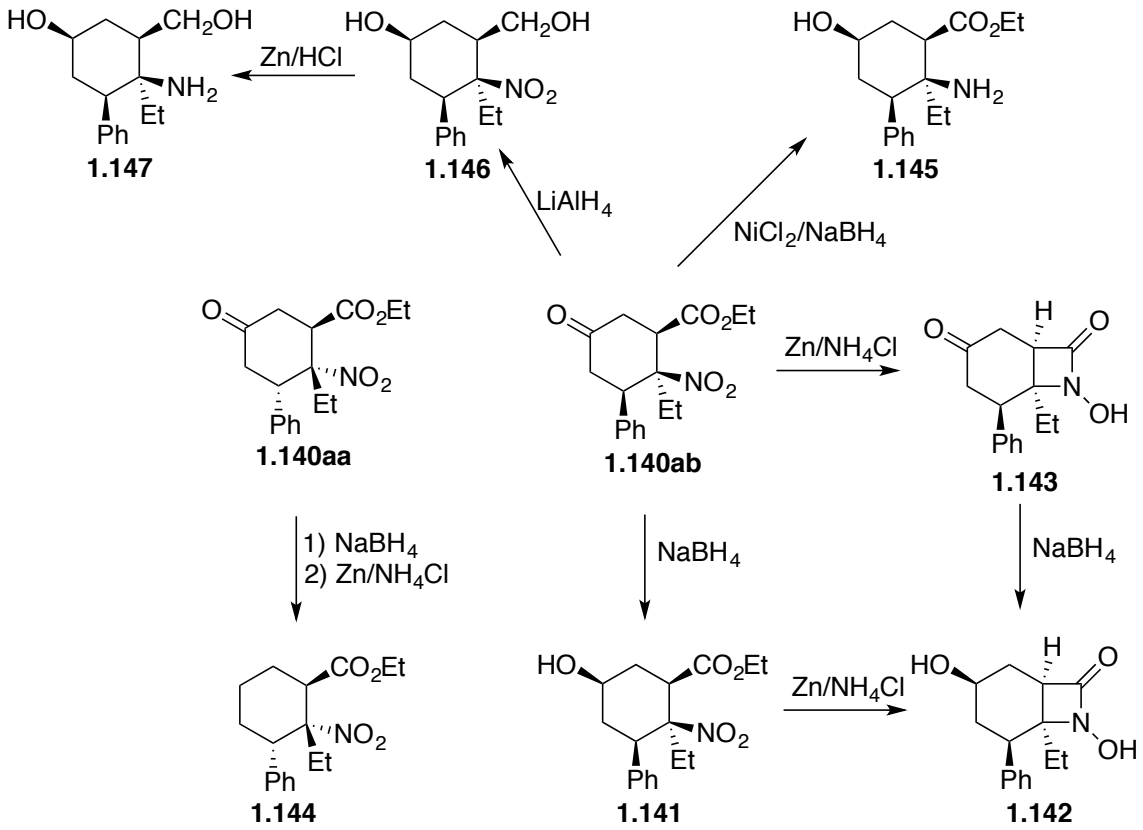
In 2014, Forni and coworkers developed a dienamine catalyzed synthetic route to 2-nitrocyclohexanecarboxylic esters (**1.140**, **Scheme 1.22**), important and flexible precursors to alkaloid derivatives in the lycorine, crinine, and caranine series, as well as difficult to obtain β-amino esters containing a hydroxyl functionality.[62] Using cinchona alkaloid catalyst **1.25a**, α,β-unsaturated ketones were reacted with β-nitroacrylates to afford cyclic diastereomers **1.140a** and **1.140b** in low to high yields and high

enantioselectivities. The methodology favored the synthesis of the unexpected *cis* diastereomer **1.140b**, which was a strong indicator that the mechanism was not that of a concerted [4+2] cycloaddition, but instead a Michael-Michael cascade reaction that allowed for free rotation upon formation of a nitro-stabilized carbanion in **1.139-I** and **1.139-II**. Following these studies, they synthesized derivatives of **1.140aa** and **1.140ab** to demonstrate the synthetic versatility of these products (**Scheme 1.23**).

Scheme 1.22 Dienamine catalyzed synthesis of 2-nitrocyclohexanecarboxylic esters **1.140**.[62]

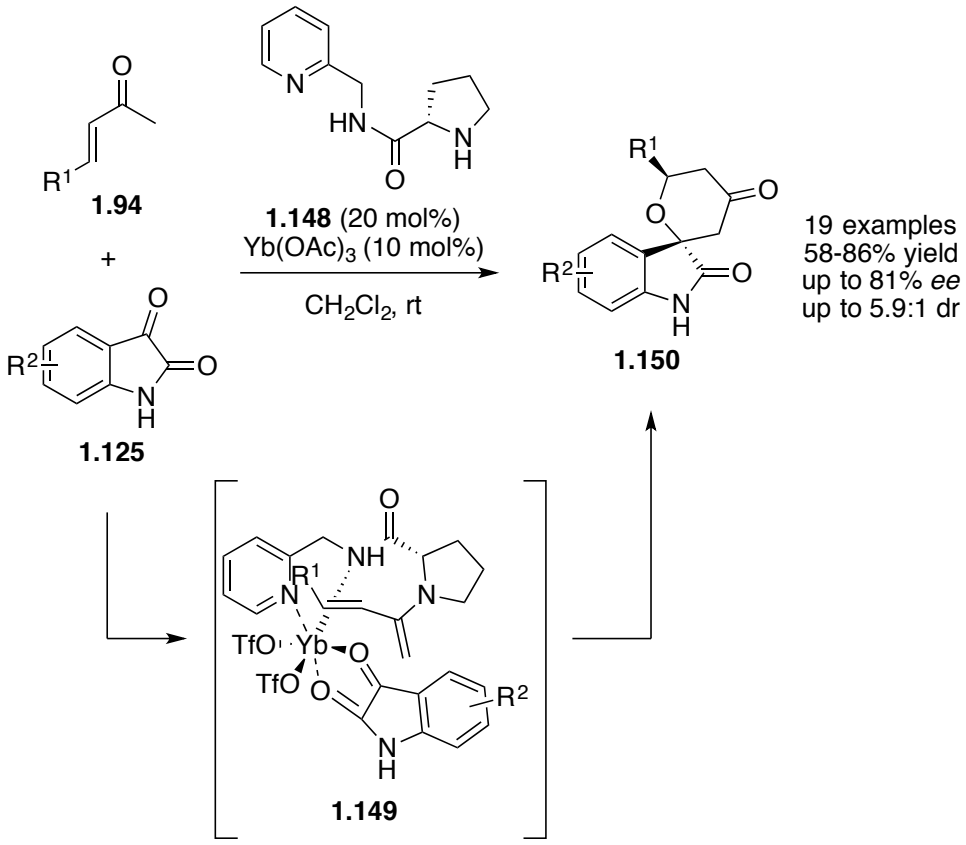


Scheme 1.23 Synthetic versatility of chiral 2-nitro-3-aryl-ketocyclohexanecarboxylic esters.[62]



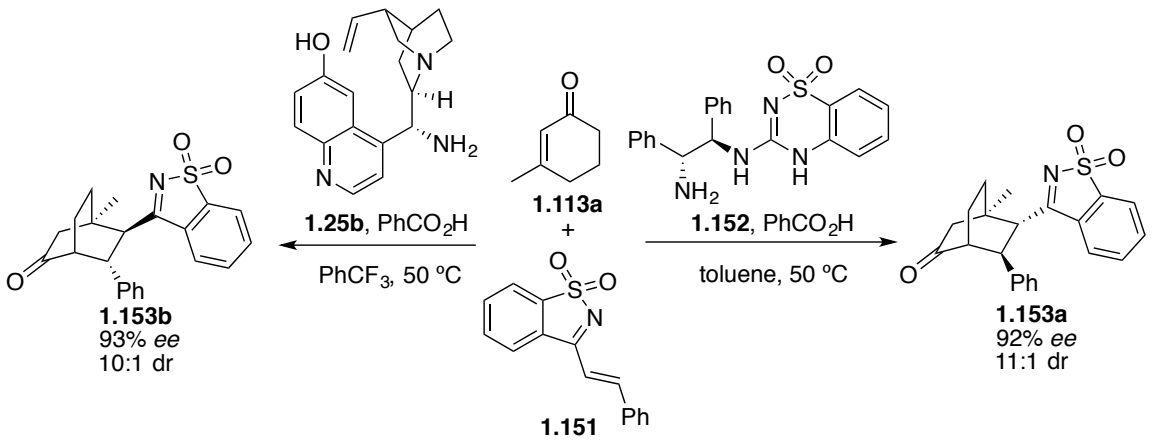
While many organocatalytic reactions avoid metallic components, in 2014 Wang and coworkers combined a dienamine generating secondary amine (**1.148**, **Scheme 1.24**), containing a chiral auxiliary capable of chelating to a metal complex, with $Yb(OAc)_3$ in order to accomplish cooperative dienamine-Lewis acid-catalyzed oxa-Diels-Alder reactions.[63] When these components were combined with α,β-unsaturated ketones (**1.94**) and isatins (**1.125**), they were proposed to form transition state **1.49**, in which the isatin and dienamine coordinate in an ytterbium complex. This brings the two reactive species into closer proximity, enabling this difficult transformation. Moderate to high yields were obtained using a variety of different aromatic ketones, however, only moderate enantioselectivities and diastereoselectivities could be achieved.

Scheme 1.24 Cooperative dienamine-metal Lewis-acid catalyzed synthesis of spiroxindole tetrahydropyranones **1.150**.[63]



In 2014, Chen and coworkers reported [4+2] cycloaddition reactivity between *β*-methylcyclohexenone (**1.113a**) and (*E*)-3-styrylbenzoisothiazole-1,1-dioxide (**1.151**, **Scheme 1.25**).[64] Interestingly, they found that by employing a bifunctional primary amine catalyst (**1.152**) the *endo*-diastereomer (**1.153a**) was favored, exclusively in some examples. However, employing cinchona alkaloid derivative (**1.25b**) as the catalyst afforded the *exo*-diastereomer (**1.153b**) in equally favorable diastereoselectivity. Utilizing this methodology, a number of highly functionalized, bridged [2.2.2] octane and [2.2.1] heptane compounds were synthesized using **1.151**, as well as the analogous 4-styryl-1,2,3-benzoxathiazine-2,2-dioxide, in good yields and diastereoselectivities.

Scheme 1.25 Diastereodivergent cross-conjugated dienamine catalyzed [4+2] cycloadditions.[64]

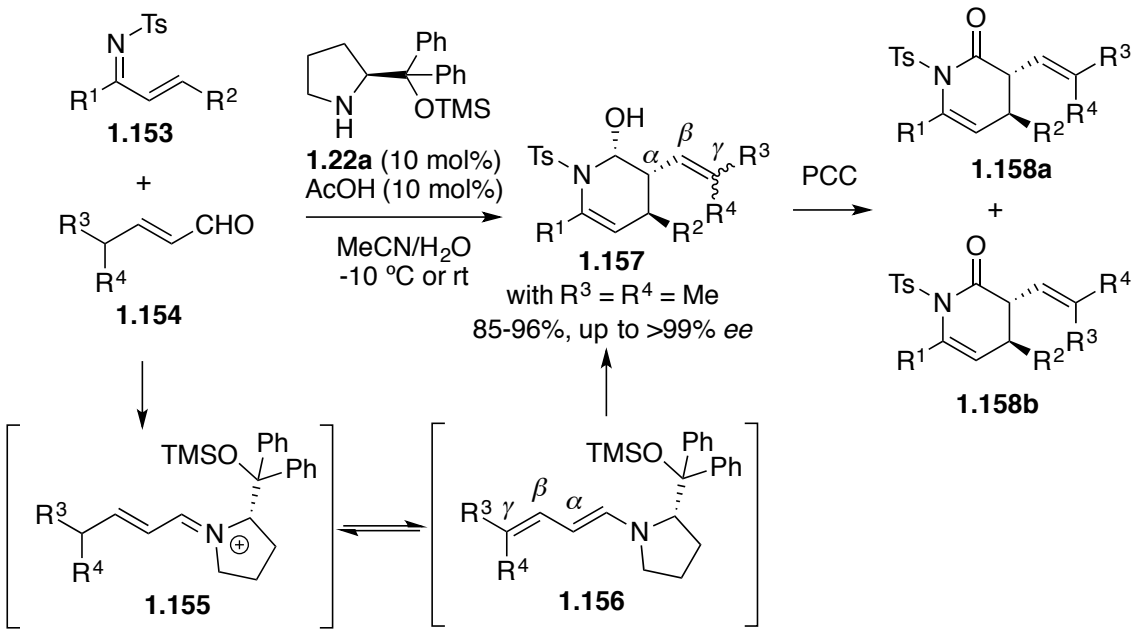


1.2.2 INVERSE-ELECTRON-DEMAND DIELS-ALDER CYCLOADDITIONS

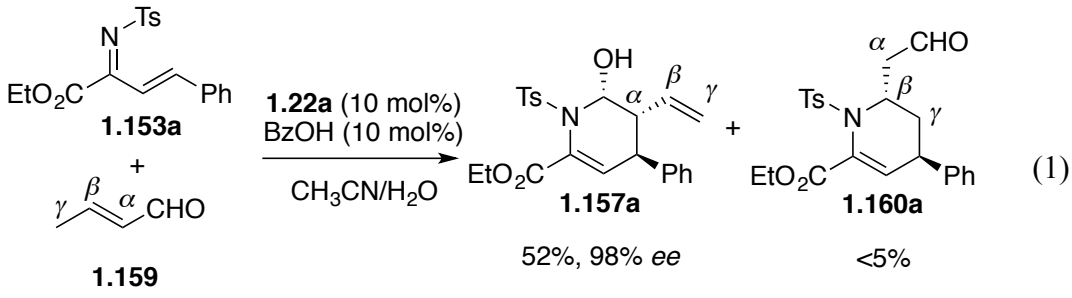
The first dienamine-catalyzed inverse-electron-demand Diels-Alder cycloaddition appeared in 2008 from the Chen group.[65] This work was inspired by Jørgensen's earlier generation of dienamines from iminium activated α,β-unsaturated aldehydes (vide infra), as well as Chen and coworkers' recently developed enamine catalyzed inverse-electron-demand aza-Diels-Alder reactions.[66,67] In their work, condensation of catalyst **1.22a** onto various α,β-unsaturated aldehydes (**1.154**) and subsequent deprotonation at the γ-position generated two HOMO-activated dienophiles that could react with *N*-tosyl-1-aza-1,3-butadienes (**1.153**) to synthesize multifunctional piperidines (**1.157**, **Scheme 1.26**). They found that their initial conditions favored α-selectivity in high yields and *E*/*Z* ratio up to 8.9:1, with excellent enantioselectivity. When the dienamine was generated from crotonaldehyde, however, they found that there was trace formation of the β,γ-adduct, **1.160a**, as well (**Scheme 1.27**, eq 1). Changing the *N*-tosyl-1-aza-1,3-butadiene to **1.153b**

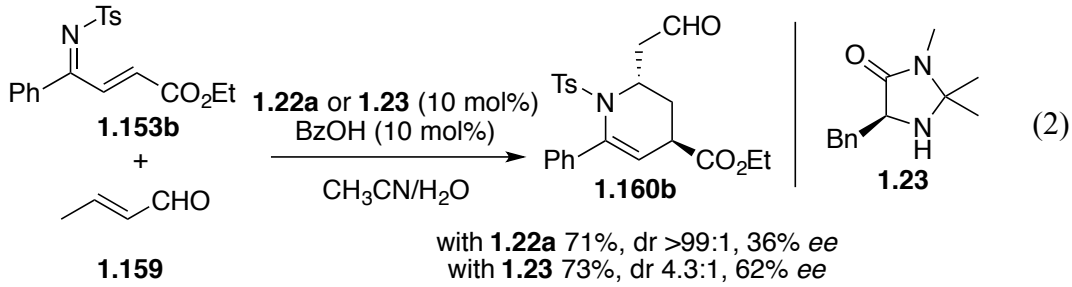
exclusively favored *β,γ*-dienophile reactivity in high yield and >99:1 dr, but low enantioselectivity (**Scheme 1.27**, eq 2). This enantioselectivity was explained to be an effect of the increased distance between the reaction site and the chiral catalyst, and moderate *ee* was obtained by switching to MacMillan catalyst **1.23**. To demonstrate the synthetic versatility of their multifunctional piperidine derivatives, they subjected their products to a number of different organic transformations, showing great scaffold diversification (**Scheme 1.28**). All transformations were achieved in excellent yields and diastereoselectivities.

Scheme 1.26 Chen's asymmetric inverse-electron-demand aza-Diels-Alder synthesis of multifunctional piperidines.

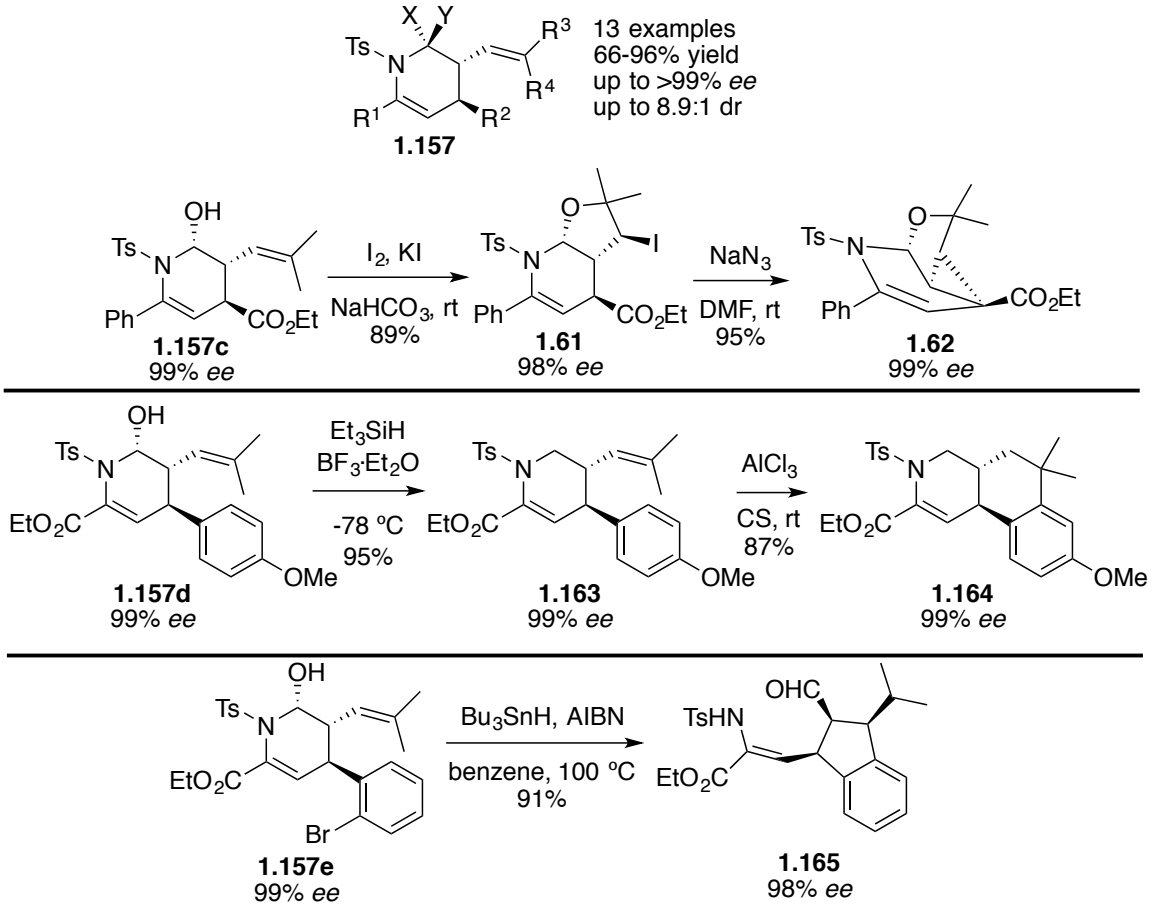


Scheme 1.27 Regioselectivity in the inverse-electron-demand aza-Diels-Alder reaction.



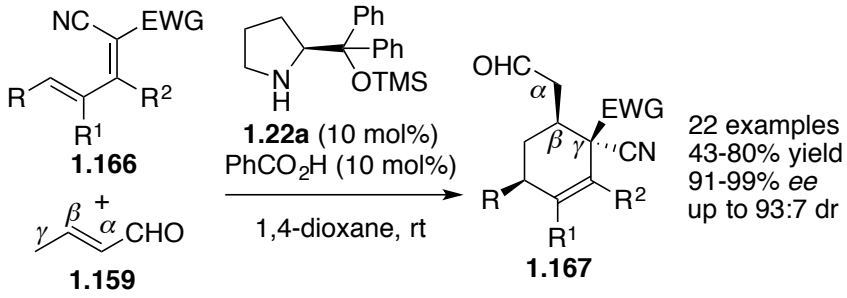


Scheme 1.28 Substrate scope and derivatives of piperidines **1.157**.

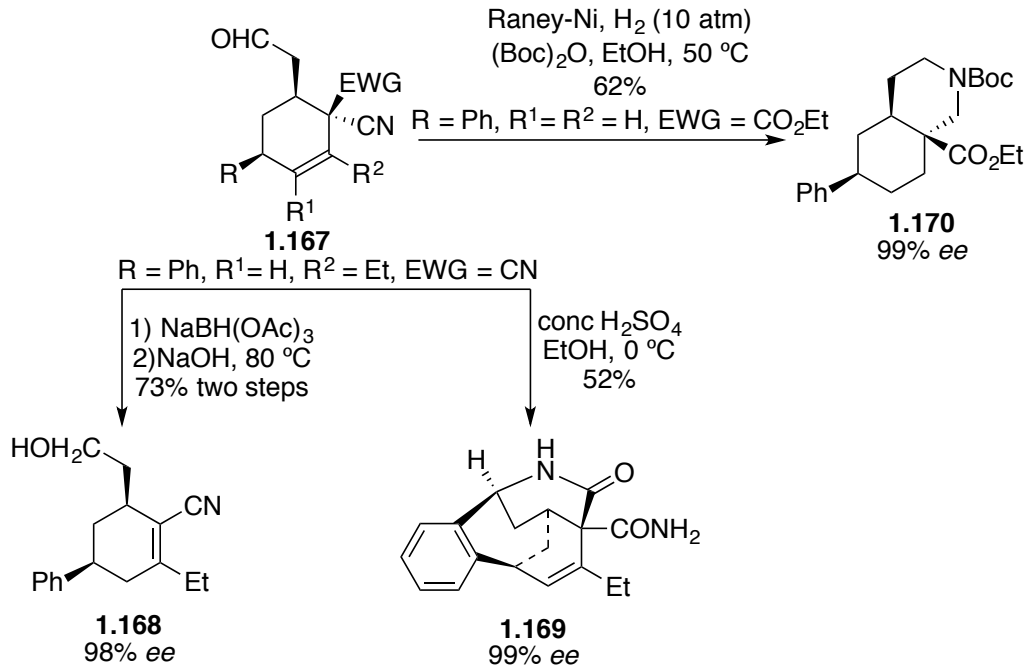


In 2010, Chen and coworkers continued to broaden the scope of all-carbon-based inverse-electron-demand Diels-Alder reactions.[68] They used readily available electron-deficient dienes (**1.166**) with crotonaldehyde (**1.159**), which reacted exclusively as a *β,γ*-dienophile to form multifunctional cycloadducts (**1.167**) in moderate to high yields and excellent enantioselectivities and diastereoselectivities (**Scheme 1.29**). These conditions tolerated various levels of substitution on the diene as well as the presence of both electron-withdrawing and electron-donating aromatic groups. The minor diastereomer was also isolated in good enantioselectivity. Synthetic transformations of the multifunctional products were performed as well in order to obtain interesting and useful derivatives, such as caged polycyclic compound **1.169** and decahydroisoquinoline derivative **1.170**, in moderate to high yields while maintaining enantiopurity (**Scheme 1.30**).

Scheme 1.29 Chen's all-carbon-based inverse-electron-demand Diels-Alder reactions.[68]



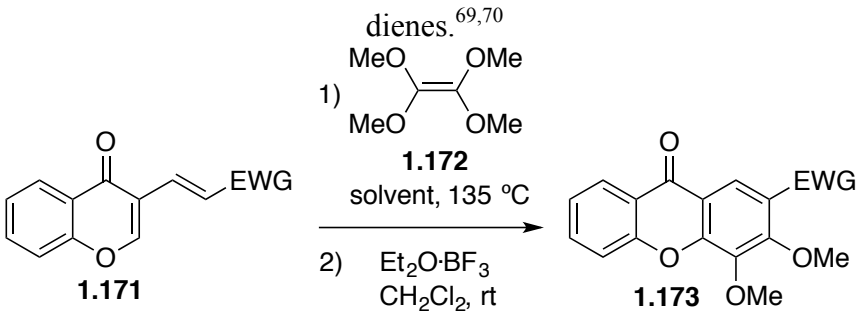
Scheme 1.30 Derivatives of Diels-Alder products.



Chen and coworkers continued to study this all-carbon inverse-electron-demand Diels-Alder reaction.[69] They were interested in expanding their methodology into natural product synthesis, following work done in 2008 by Bodwell and coworkers, in which chromone-fused dienes (**1.171**, eq1, **Scheme 1.31**) were reacted with highly electron-rich ethenes (**1.172**) to synthesize 2-substituted xanthones (**1.173**).[70] This work inspired Chen and coworkers to explore the previously unstudied synthesis of chiral tetrahydroxanthone derivatives (**1.176**, eq 2).[71–76] Despite the lack of *β,γ*-reactivity with any aldehyde other than crotonaldehyde ($R^2 = R^3 = R^4 = H$), Chen and coworkers were encouraged by their recent work with trienamine mediated normal-electron-demand Diels-Alder reactions, in which sterics were used to raise the HOMO of the preferred diene.[77] Thus, use of *β,β*-disubstituted *α,β*-unsaturated aldehydes (**1.175**), with an additional electron-donating group at the *β*-position (i.e., $R^2 = R^3 = H$, $R^4 = Me$), in combination with steric hindrance

at the α-position of a dienamine, raised the HOMO to favor β,γ-reactivity (eq 2, **Scheme 1.31**). This strategy was very effective, however the product being formed in high yields and excellent enantioselectivities and diastereoselectivities was that of an unexpected caged tetrahydroxanthone (**1.178**).

Scheme 1.31 Inverse-electron-demand Diels-Alder reactions of chromone-fused dienes.[69,70]



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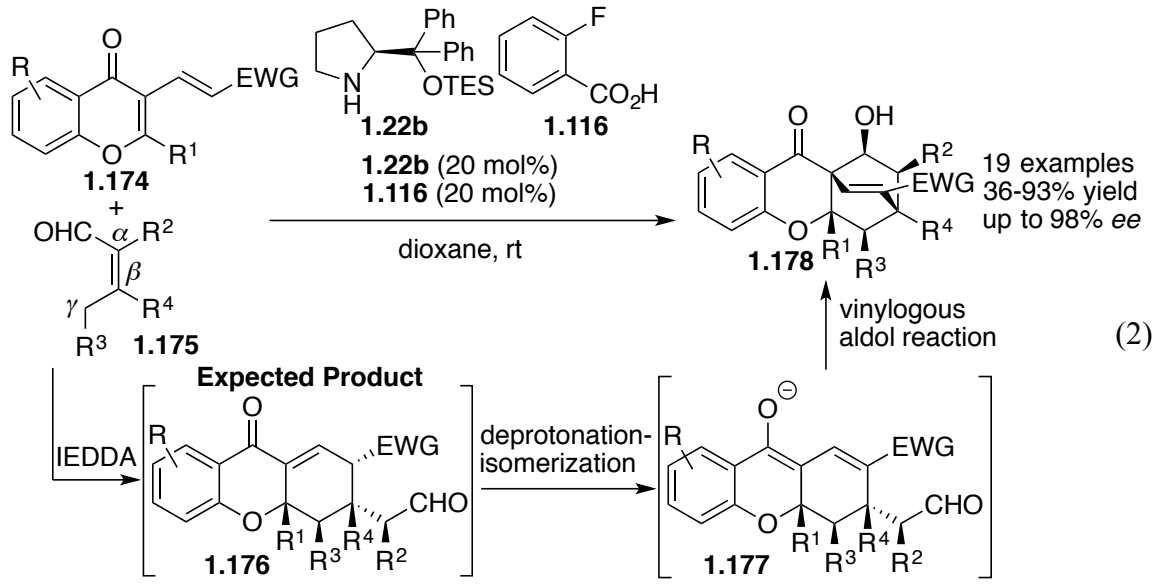


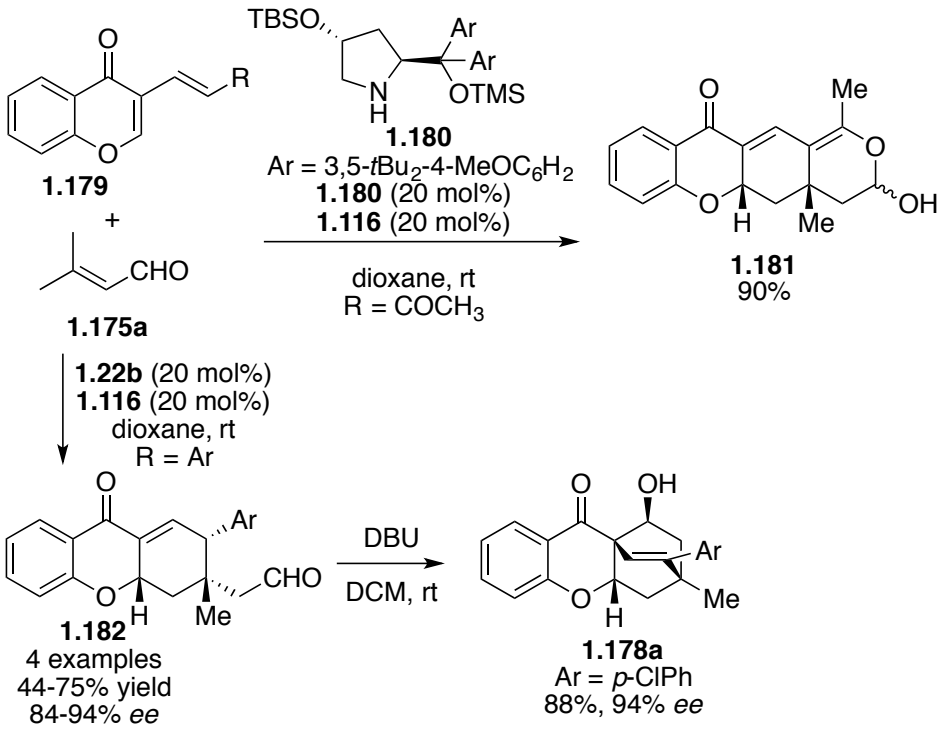
(2)

This product was formed via a cascade reaction, in which the inverse-electron-demand Diels-Alder was followed by deprotonation to form dienolate **1.177**. Then a vinylogous aldol reaction formed the caged tertrahydroxanthone (**1.178**). In the substrate scope, a wide variety of chromone-fused diene derivatives containing both electron-withdrawing and electron-donating R substituents provided the expected products in

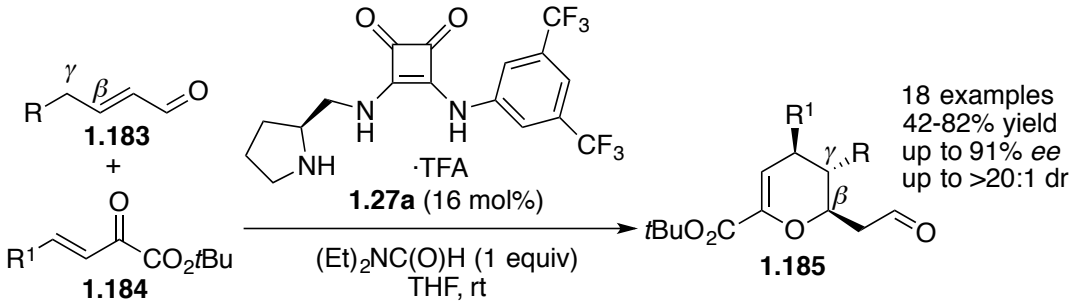
moderate to high yields and high enantioselectivities. In varying the aldehydes, enantioselectivities remained high, while yields ranged broadly depending on the substrate. Replacing the electron-withdrawing group of **1.174** with an acetyl functional group in the chromone structure could create scaffold diversity by changing the nature of the cascade reaction, providing tetracyclic product **1.181** from **1.179** (R = R^1 = H) in high yield (**Scheme 1.32**). More diversity could also be obtained by replacing the electron withdrawing group of **1.174** with aryl groups to prevent the domino cyclization and provide **1.182** in low to high yields.

In 2012, Jørgensen and coworkers developed a dienamine-mediated regioselective inverse-electron-demand oxa-Diels-Alder reaction that utilized a bifunctional proline-derived catalyst (**1.27a**, **Scheme 1.33**).[78] This catalyst contained a squaramide hydrogen-bond-directing moiety that could not only direct the facial-approach of the diene, but also the regioselectivity to favor the distal γ,β-olefin of the dienamine intermediate. They were able to synthesize dihydropyrans (**1.185**) from β,γ-unsaturated α-ketoesters (**1.184**) and α,β-unsaturated aldehydes (**1.183**) in moderate to high yields and good to excellent enantioselectivities.

Scheme 1.32 Chen's variations on inverse-electron-demand Diels-Alder reactions with chromone dienes.[69]



Scheme 1.33 Jørgensen's approach to the synthesis of asymmetric dihydropyrans (**1.185**) using bifunctional organocatalyst **1.27a**.[79]



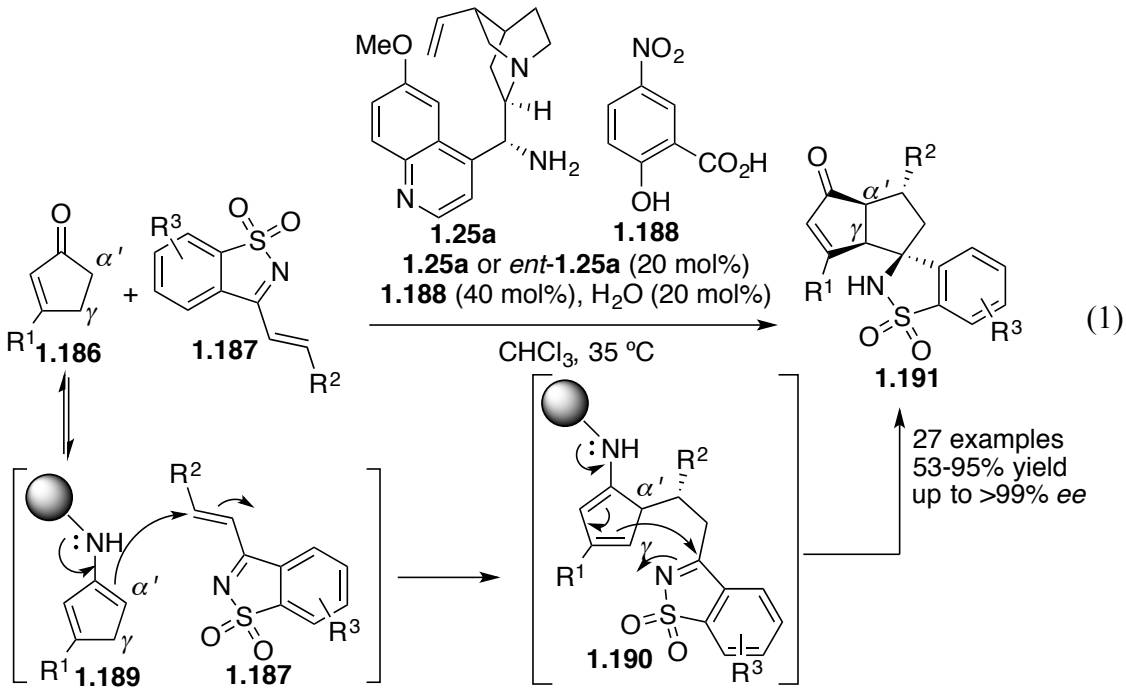
In 2014, Chen and coworkers developed a unique dienamine-dienamine cascade to accomplish a formal [5+3] cycloaddition with cyclic α,β-unsaturated ketones (**1.186**) and electron-poor 1-azadienes (**1.187**) to form products **1.191** (eq 1, **Scheme 1.34**).[80] This

reaction operated as a domino reaction featuring a cross-conjugated dienamine (**1.189**) activated towards α'-regioselective Michael addition, followed by a 1-amino-dienamine (**1.190**) activated towards γ-regioselective intramolecular Mannich reaction. The products were obtained in high yields and excellent enantioselectivities, with most substrates, the exception being simple cyclopentenone. Cyclohexenone (**1.52a**) was able to provide a more challenging bridged cycloadduct (**1.193**) when the conditions were altered slightly (eq 2, **Scheme 1.34**). Due to the highly structural and stereogenic complexity of the products, they explored their potential applications in chemical biology and medicinal chemistry.[81–83] A number of their compounds were evaluated in vitro against lung adenocarcinoma epithelial cell line A549, prostate cancer cell line DU145, esophageal squamous carcinoma cell line Eca109, breast cancer cell line MDA-MB-231, and leukemic monocyte lymphoma cell line U937. Eight of the compounds showed promising results with IC_{50} values ranging from 2.3 μM to >200 μM.

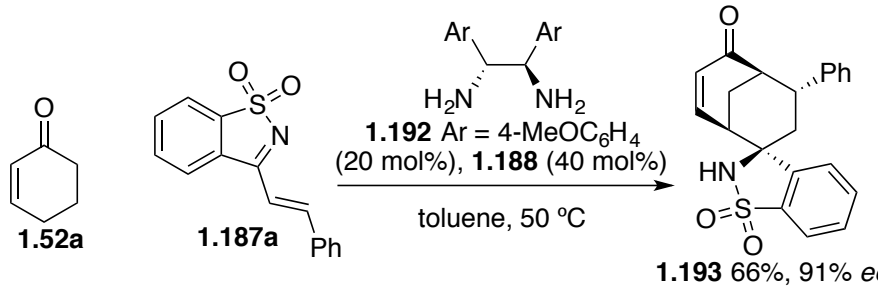
In 2014, Jørgensen and coworkers continued work with bifunctional organocatalysis in the development of new inverse-electron-demand oxa-Diels-Alder reactions.[84] In this new work, they incorporated a phosphonate moiety into the electron-poor diene (**1.194**, **Scheme 1.35**). This acted as a versatile group to assist in stereo- and regiocontrol through LUMO lowering hydrogen-bond activation, and introduced a bioactive component that could remain on or be cleaved off of the final product.[85–90] Products were obtained in moderate to high yields and good enantioselectivities with both electron-withdrawing and electron-donating R^1 groups tolerated on the organophosphonates, as well as dienamines (R). Notably, diarylprolinol silyl ether catalysts (**1.22**, see **Scheme 1.29**) were not effective in accomplishing these reactions,

highlighting the importance of the LUMO lowering effect of the H-bonding component in **1.27a**. The final dihydropyrans (**1.195**) were derivatized to produce more elaborate compounds while maintaining enantiopurity, including tetrahydropyrans containing five contiguous stereogenic centers (**1.196** & **1.198**, **Scheme 1.36**) and lactones (**1.197**), which upon reduction of the latter will provide uncommon sugar components of bacterial lipopolysaccharides (LPS) isolated from various pathogenic microorganisms.[91–93]

Scheme 1.34 Dienamine-dienamine-mediated formal [5+3] cycloadditions.

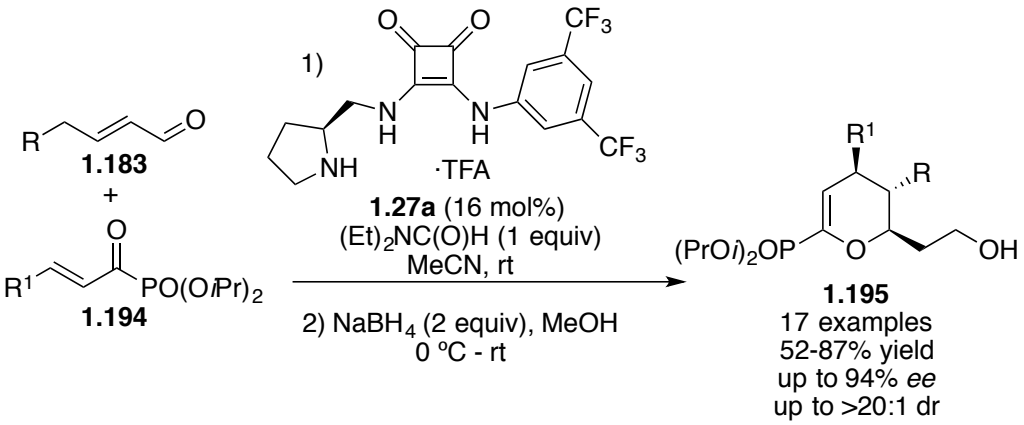


(1)

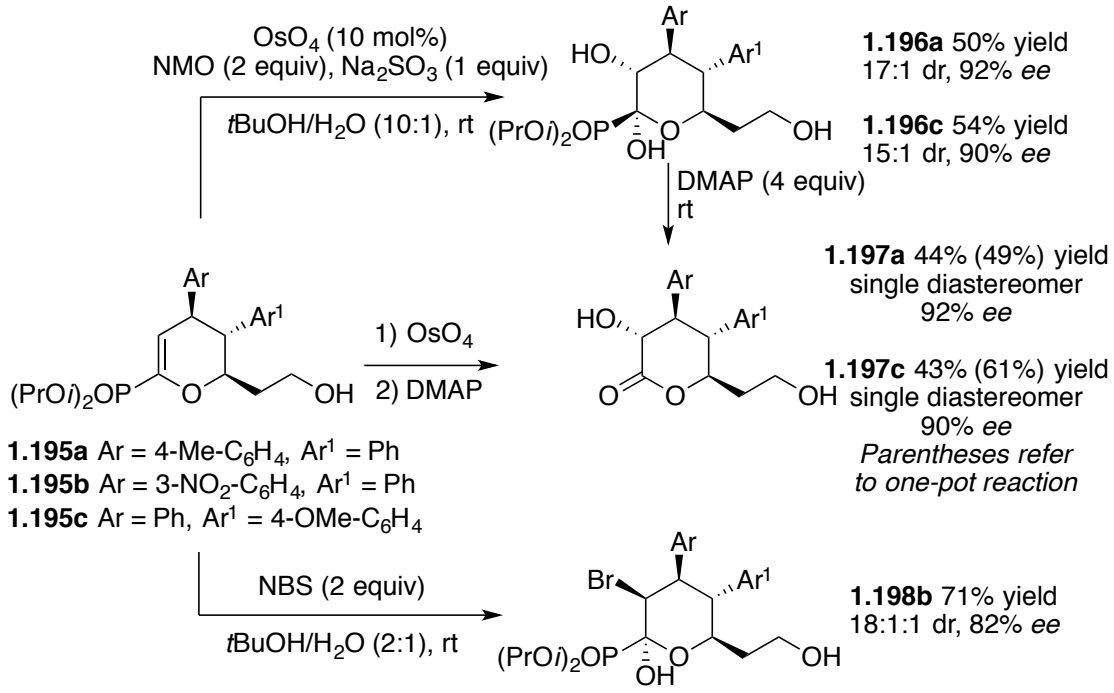


(2)

Scheme 1.35 Jørgensen's inverse-electron-demand oxa-Diels-Alder reactions of organophosphates **1.194**.[84]



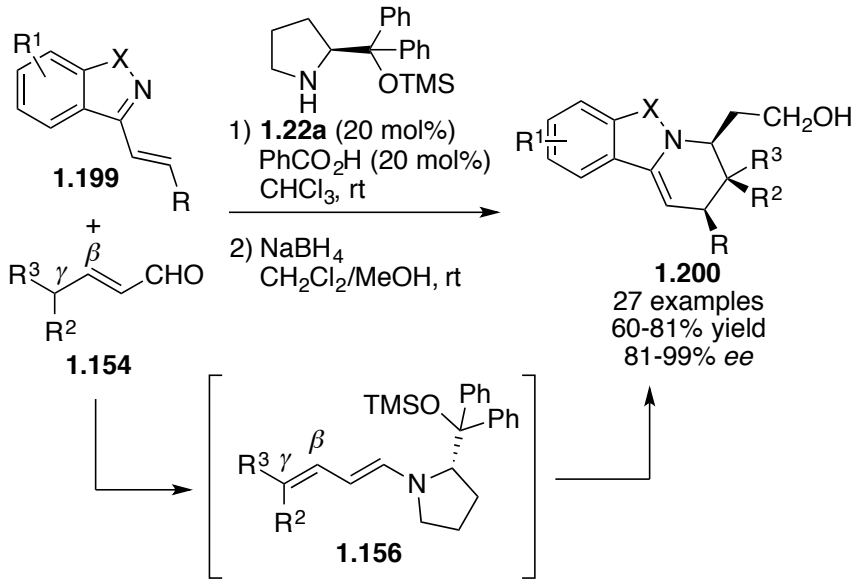
Scheme 1.36 Jørgensen's strategies for increasing stereocomplexity of dihydropyran phosphonates **1.195**.[84]



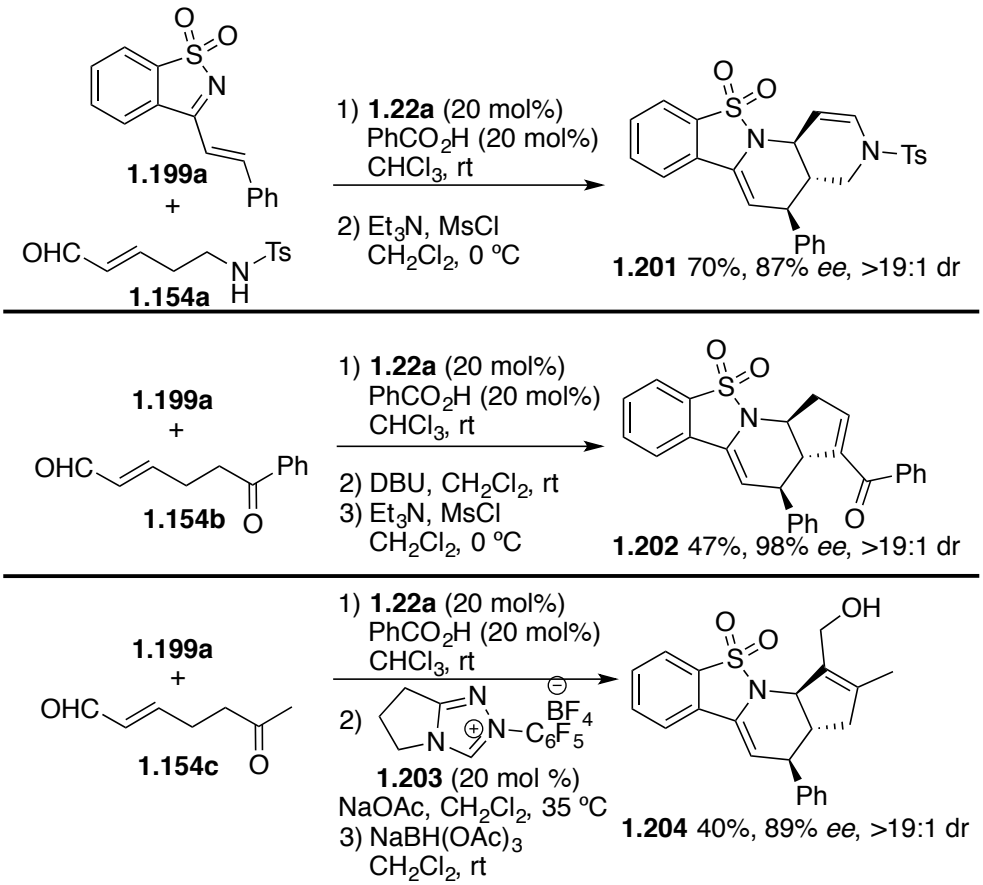
In 2014, Chen and coworkers reported an improvement on their earlier work concerning an inverse-electron-demand aza-Diels-Alder reaction (**Scheme 1.26**).[94] Utilizing a more rigid, cyclic 1-azadiene, 1,2-benzoisothiazole-1,1-dioxides and 1,2,3-

benzoxathiazin-2,2-dioxides (**1.199**), along with steric shielding catalyst **1.22a** and α,β-unsaturated aldehydes (**1.154**), they were able to favor β,γ-regioselectivity of dienamine intermediate **1.156** to produce tricyclic product **1.200** in high yields and excellent enantioselectivities (**Scheme 1.37**). Interestingly, bifunctional catalyst **1.27a**, used in the previous example by Jørgensen to activate electron-poor organophosphonates for inverse-electron-demand oxa-Diels-Alder reactions (**Scheme 1.35**), led to poor reactivity and only fair enantioselectivity for the aza-Diels-Alder reaction. Due to the tolerance of this reaction to diverse functional groups, enals were introduced with reactive functional groups at R^3 (R^2 = H) that could be used for intramolecular reactions to construct heterocycles with higher molecular complexity (**Scheme 1.38**).

Scheme 1.37 Chen's inverse-electron-demand aza-Diels-Alder synthesis of tricyclic heterocycles **1.200**.[94]



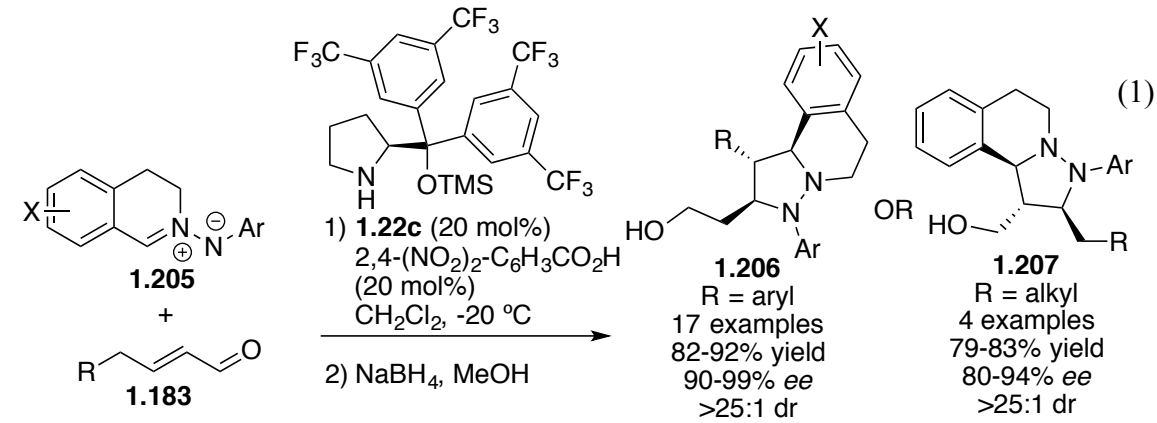
Scheme 1.38 Creating tetracyclic heterocycles from functionalized enals **1.154**.[94]



In 2014, Du, Wang, and coworkers, as well as Alemán, Fraile, and coworkers, independently reported chemoselective control over the dual reactivity of dipoles **1.205**, tuning the conditions to undergo either iminium-activated normal-electron-demand or dienamine-activated inverse-electron-demand 1,3-dipolar cycloadditions (eq 1 & eq 2, **Scheme 1.39**).[95,96] Du, Wang, and coworkers reported that the exclusive reactivity was variable simply by changing the R group on **1.183** from aromatic, which provided the dienamine-mediated products **1.206**, to aliphatic functionalities, which provided the iminium-mediated products **1.207** (eq 1). They speculated that this change in selectivity was due to aliphatic α,β-unsaturated aldehydes favoring the LUMO-lowered iminium-ion intermediate. However, Alemán, Fraile, and coworkers raised issue with these reports, as

their studies showed competing reactivity, where conditions could be adjusted to favor **1.208** versus **1.209**, though never remove the other's presence entirely. As they were preparing their manuscript when Du and Wang's research was published, they were able to test the reported conditions to attempt to reproduce their results. Alemán and Fraile directly contradicted the reports by Du and Wang of exclusive reactivity, reporting a mixture of **1.206** and **1.207** in which they found that the dienamine-mediated product (**1.206**) was never favored. In light of these results, they propose their own solution to providing exclusive dienamine reactivity (eq 2, **Scheme 1.40**).

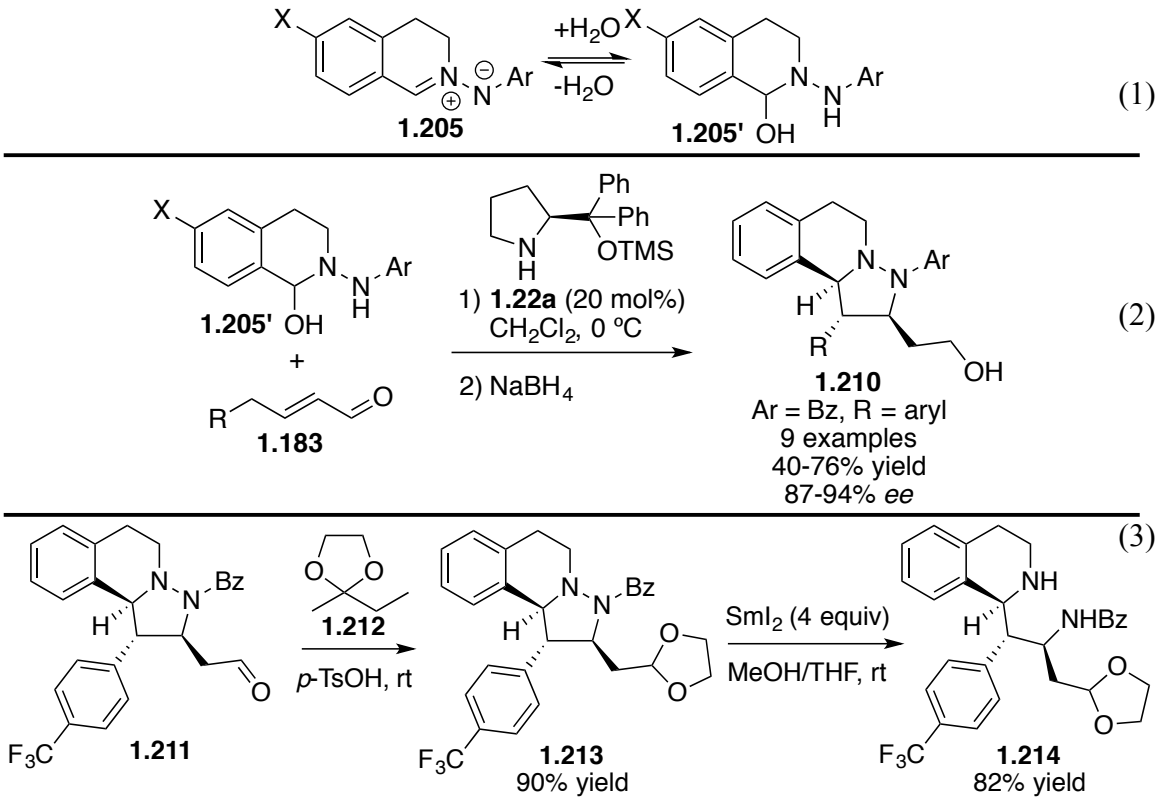
Scheme 1.39 Conflicting research in dienamine-mediated 1,3-dipolar cycloadditions.[95,96]



During their investigations, Alemán, Fraile, and coworkers, found that over time discrepancies developed between the same reactions, in which the dienamine-mediated product **1.208** was favored more than they previously observed.[96] They were able to

attribute this to a gradual increase in water content in dipole **1.205**, which created an equilibrium with **1.205'** in solution (eq 1, **Scheme 1.40**). Due to this discovery, they were able to isolate **1.205'** and use this dipole to almost exclusively (>98:2 in all cases) form dienamine-mediated inverse-electron-demand dipolar cycloaddition products (**1.210**, eq 2, **Scheme 1.40**). These conditions tolerated electron-rich and electron-poor dipoles (**1.205'**) as well as electron-rich and electron-poor aromatic aldehydes (**1.183**). Chemical transformations to modify the cycloadducts proceeded in high yields (eq 3).

Scheme 1.40 Alemán and Fraile's approach to dienamine-catalyzed 1,3-dipolar cycloadditions.[96]

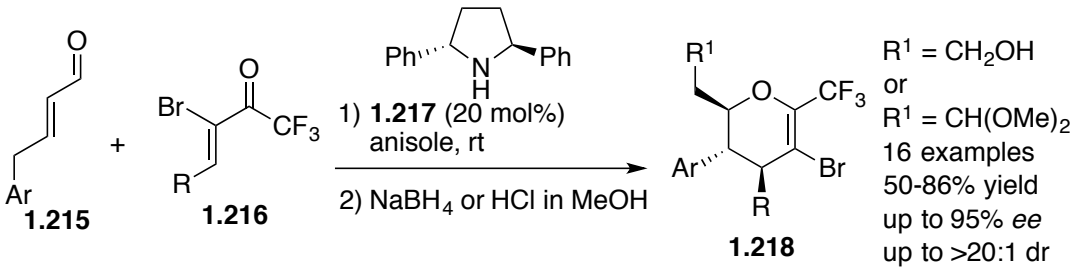


In 2015, Jørgensen and coworkers reported their use of the inverse-electron-demand oxo-Diels-Alder reaction to synthesize trifluoromethyl-containing 3,4-dihydro-2H-pyrans (**1.218**, **Scheme 1.41**).[97] This was a novel concept for combining the

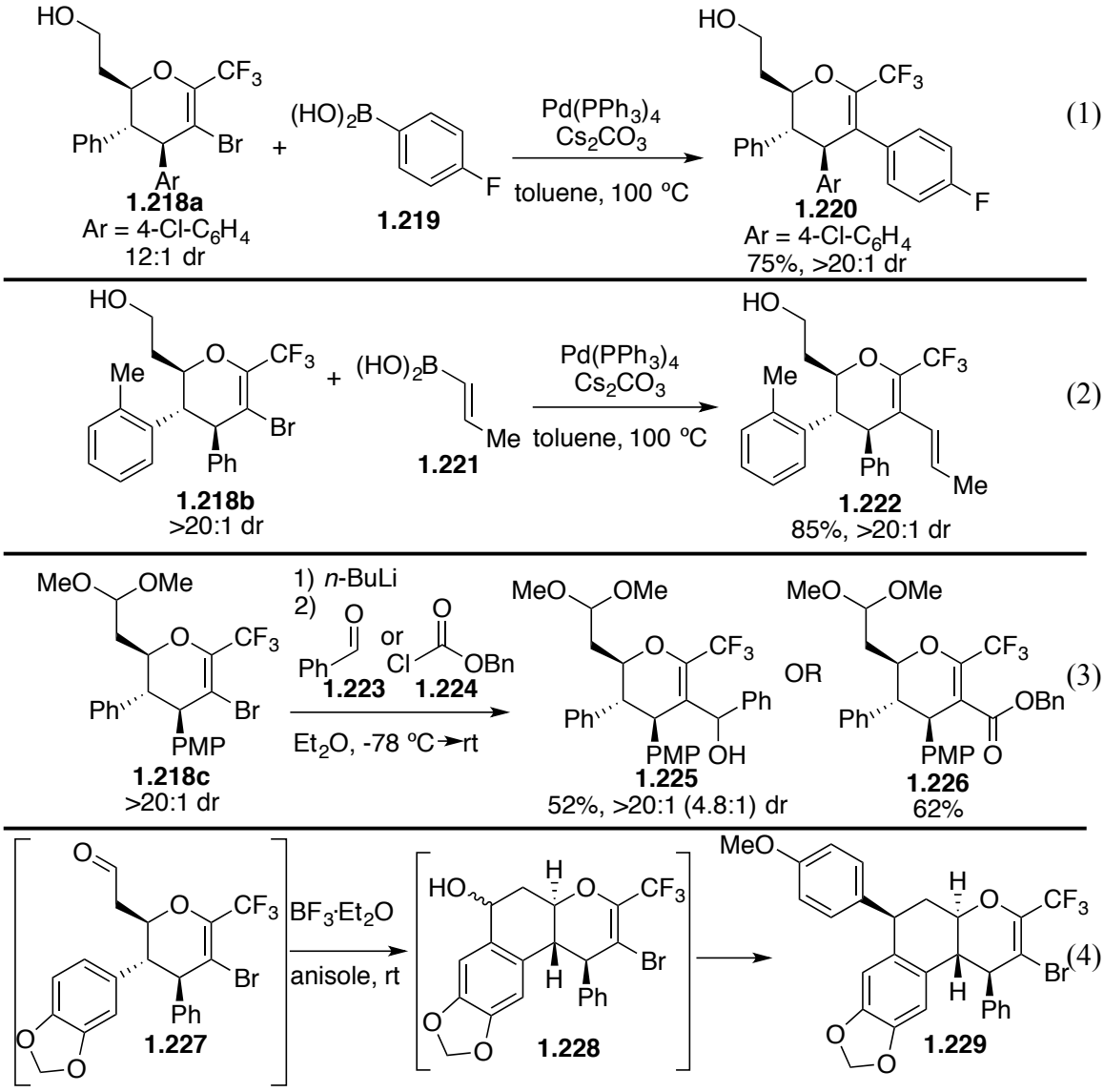
biologically important 3,4-dihydro-2H-pyran motif with fluorine atoms, which often have a useful impact on the activity of medicinal compounds.[98–102] In utilizing α-bromo-CF_3-enones (**1.216**), they also introduced a C(sp^2)–Br functionality that could be readily used in the modification of the products. The products were obtained in moderate to high yields and high enantioselectivities, while tolerating electron-withdrawing and electron-donating R and Ar groups on both the diene and dienophile. Derivatives were synthesized utilizing the bromine through Suzuki coupling reactions, as well as lithiation followed by organolithium reactions (eq 1-3, **Scheme 1.42**). Tetracyclic systems could also be synthesized through a Friedel-Crafts hydroalkylation, which was unexpectedly followed by solvent insertion to produce compound **1.229** (eq 4).

In 2015, Reyes, Vicario, and coworkers reported an enantioselective [5+2] cycloaddition between benzopyranones (**1.230**), which generate oxidopyrylium ylides (**1.231**) from basic deprotonation in situ, and dienamine activated α,β-unsaturated aldehydes (**1.232**) to synthesize an 8-oxabicyclo[3.2.1]octane product (**1.233**, **Scheme 1.43**).[103] These reactions were performed using hydrogen bond-directing pyrrolidine-squaramide bifunctional catalyst **1.27b**, which provided products in good yields in most substrates, with high enantioselectivity and moderate to high diastereoselectivity. They did not report any competition between the γ,β-enamine and the α- or ε,δ-positions of dienamine or trienamine intermediates, although one of the substrates capable of forming a trienamine did provide the lowest yield of 39%. Various aromatic and aliphatic R groups were tolerated in these conditions for both the aldehydes and the benzopyranones.

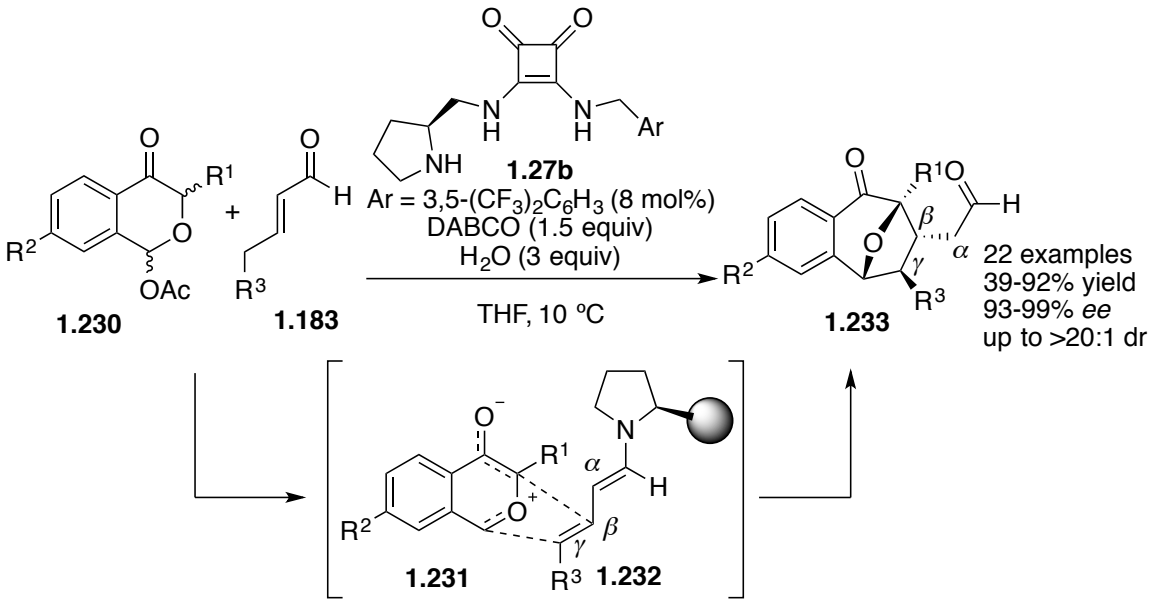
Scheme 1.41 Jørgensen's synthesis of trifluoromethyl-containing 3,4-dihydro-2H-pyrans **1.218**.[97]



Scheme 1.42 Derivatives of 3,4-dihydro-2H-pyrans.[97]

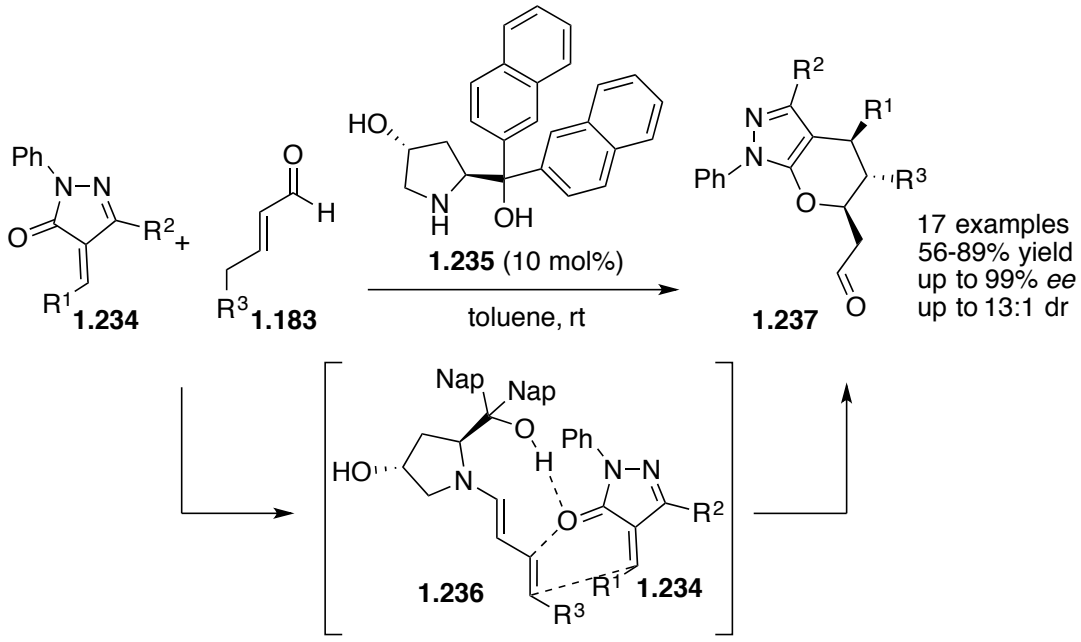


Scheme 1.43 Reyes and Vicario's [5+2] cycloadditions between dienamines and oxidopyrylium ylides (**1.231**).[103]



In 2016, Pericàs and coworkers expanded further on inverse-electron-demand oxa-Diels-Alder reactions by using alkylidene pyrazolones (**1.234**) and α,β-unsaturated aldehydes (**1.183**) in the presence of hydrogen-bond directing catalyst **1.235** to synthesize the medicinally useful tetrahydropyranopyrazoles (**1.237**, **Scheme 1.44**).[104] Products contained three contiguous stereocenters and were synthesized in high yields, enantioselectivities and diastereoselectivities. The method tolerated R^1 and R^3 substrates containing both electron-withdrawing and electron-donating components and they only reported a dramatic drop in stereoselectivity when using crotonaldehyde (R^3 = H). Converting the tetrahydropyranopyrazole products to their N-Ts counterparts enabled unambiguous determination of the absolute configuration by single crystal X-ray analysis.

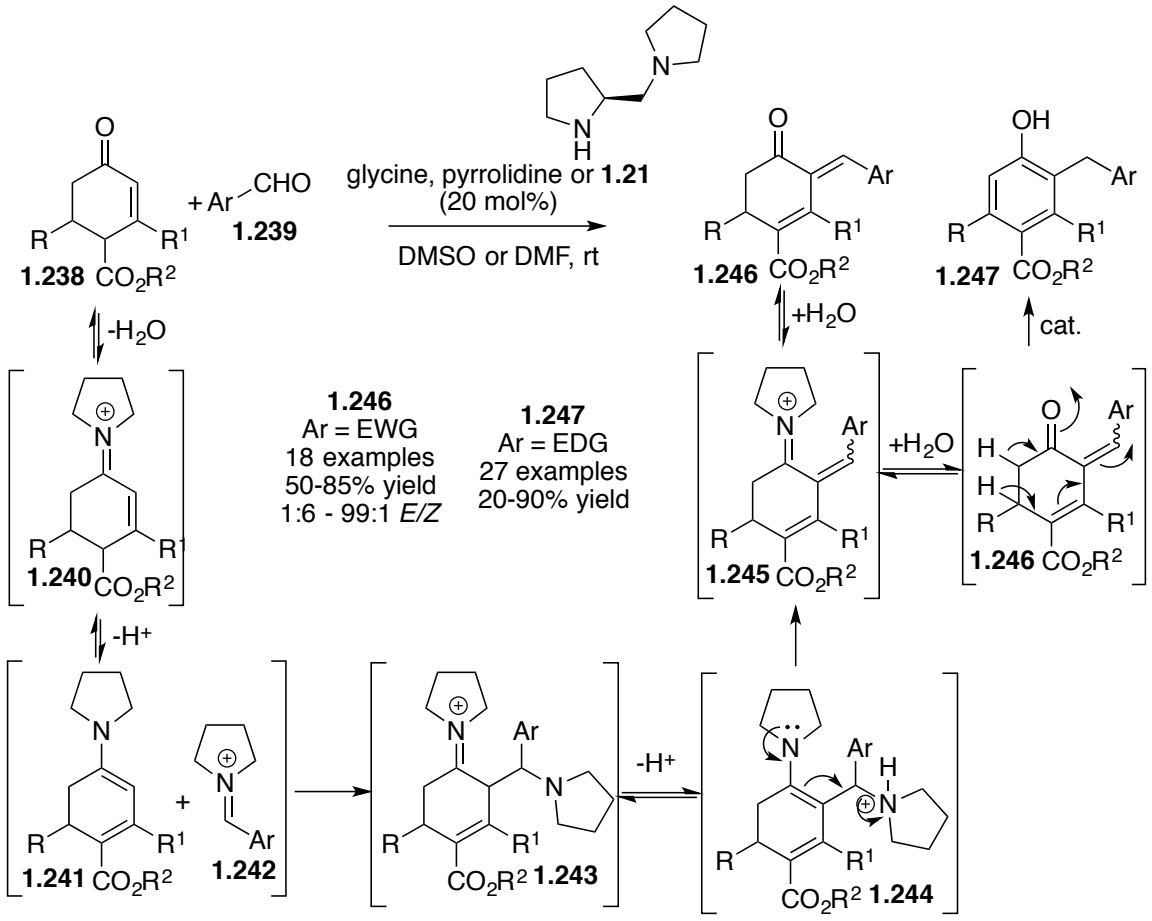
Scheme 1.44 Pericàs' H-bond directed dienamine catalyzed inverse-electron-demand oxa-Diels-Alder reaction.[104]



1.2.3 PUSH-PULL DIENAMINES

In 2005, Ramachary and coworkers developed push-pull dienamines (**1.241**) as organocatalytic intermediates for tandem Claisen-Schmidt/iso-aromatization reactions (**Scheme 1.45**).[105] The authors proposed that using glycine, pyrrolidine, or organocatalyst **1.21**, they converted Hagemann's esters (**1.238**) into dienamines that were activated at the α-position for aldol condensations that generated 2-arylidene cyclohexanones (**1.246**) when in the presence of iminium ion activated aromatic aldehydes (**1.242**).[106,107] If these aldehydes contained an electron-withdrawing Ar group, iso-aromatization would occur, producing substituted phenols (**1.247**) in good yields through their proposed mechanism, shown in **Scheme 1.45**. Ramachary and coworkers continued to expand their library of multifunctional phenols using this methodology, reporting many more examples in 2010.[108]

Scheme 1.45 Ramachary's push-pull dienamine mediated Claisen-Schmidt/iso-aromatization reactions.[105,108]

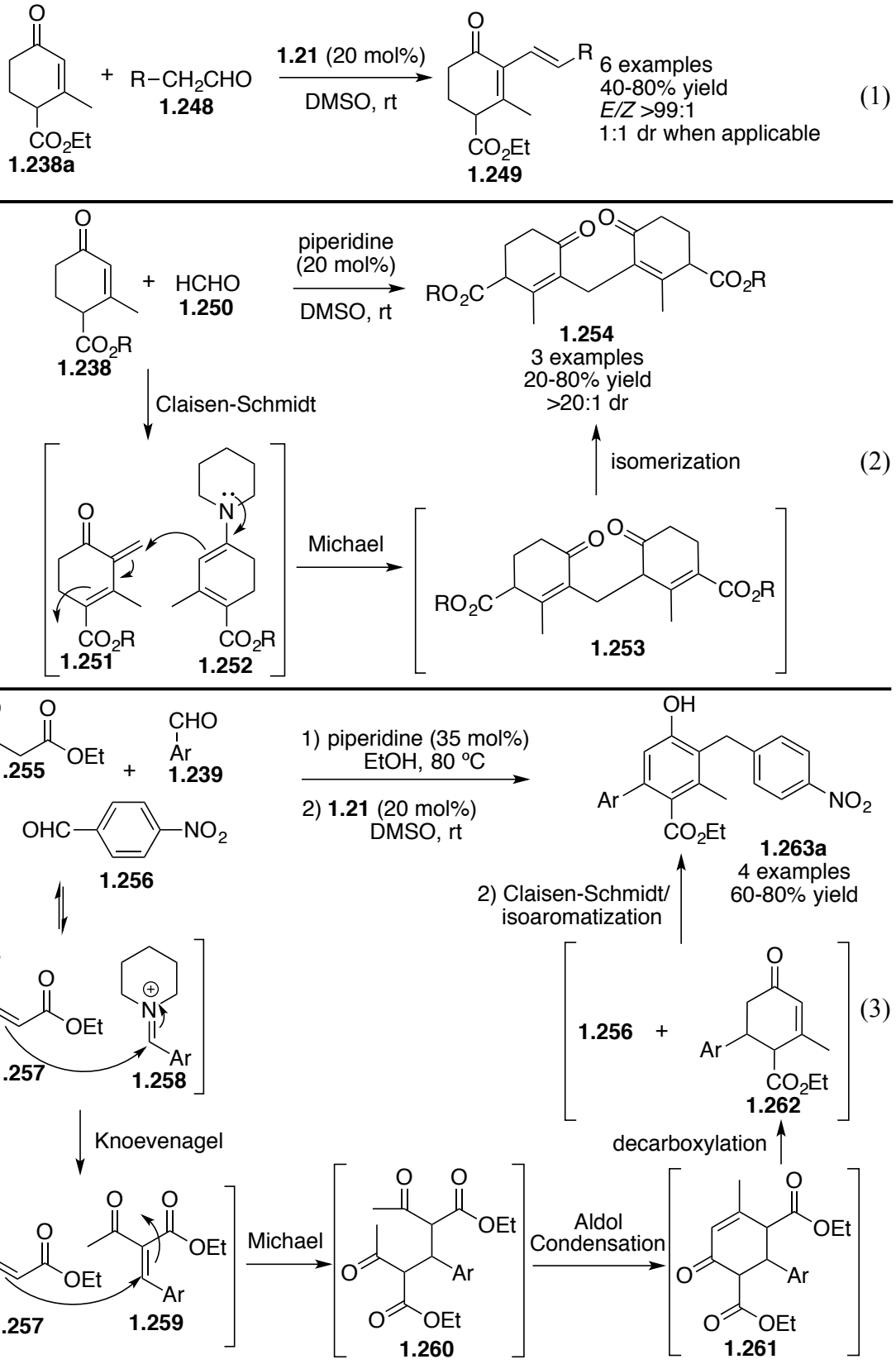


In this 2010 paper, they also introduced these Hagemann ester dienamines to aliphatic aldehydes containing α-hydrogens (**1.248**, eq 1, **Scheme 1.46**).[108] Following the Claisen-Schmidt reaction, these products (**1.246**) would isomerize to form 1,3-dienes (**1.249**) in very good yields and >99:1 *E/Z* selectivity. They also reported the use of formaldehyde (**1.250**) with push-pull dienamines to synthesize functionalized *bis*-enones (**1.254**) via a Claisen-Schmidt/Michael/isomerization cascade reaction (eq 2, **Scheme 1.46**). They proposed that these *bis*-enones could be suitable intermediates for terpenoid natural product synthesis. They also demonstrated a Knoevenagel/Michael/aldol

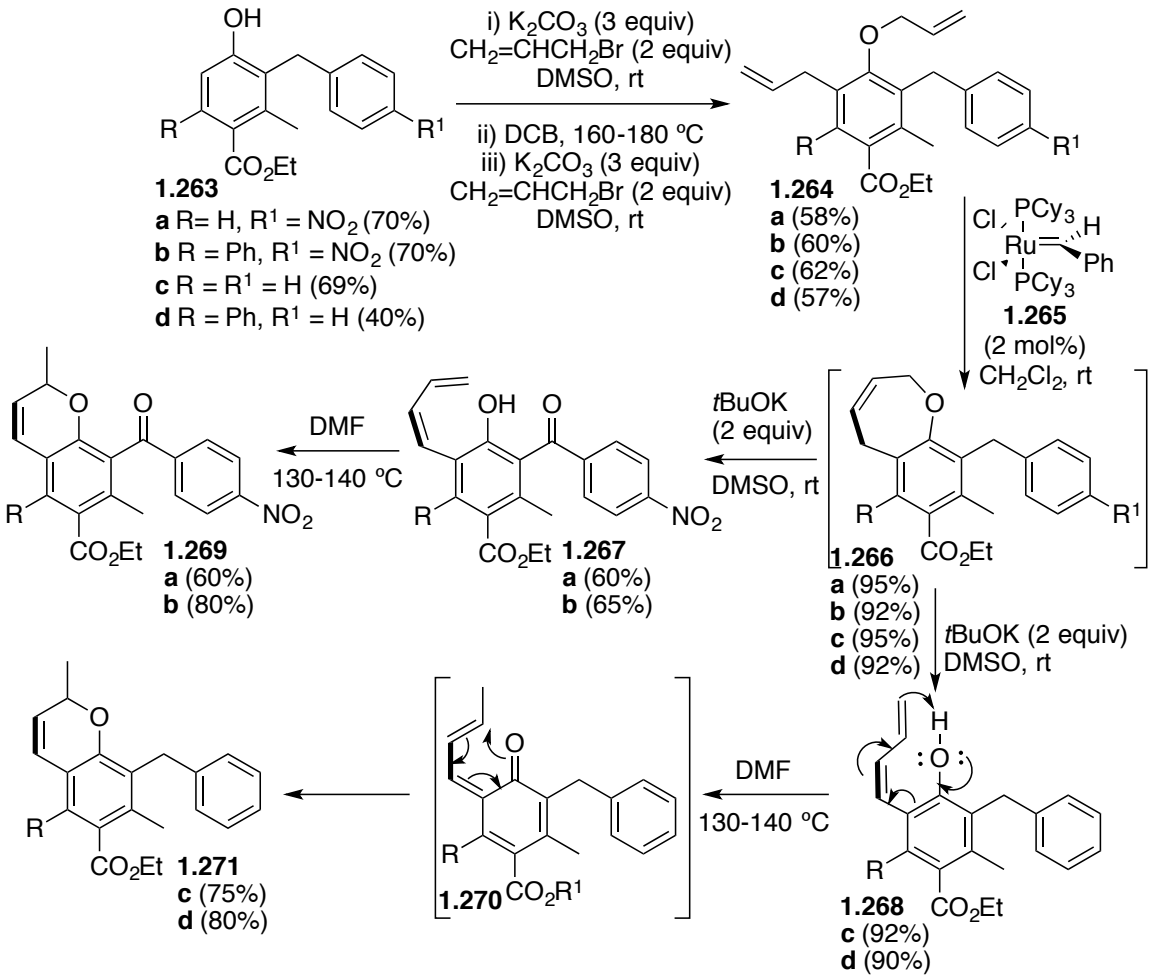
condensation/decarboxylation cascade followed by the Claisen-Schmidt/iso-aromatization cascade to synthesize **1.263a** from three simple components in a one-pot process (eq 3).

Ramachary and coworkers then used this product in the synthesis of highly functionalized 2-methyl-2*H*-chromenes (**1.269** and **1.271**, **Scheme 1.47**), using a procedure they had used previously in 2008 (vide infra).[108,109] They were able to apply the synthesis to a few derivatives and found that the electronics afforded by R^1, affect the outcome of the ring-closing metathesis/base-induced ring-opening cascade from compound **1.264**. When R^1 was an electron withdrawing nitro group (**1.264a** and **1.264b**), base-induced ring-opening was followed by benzylic oxidation to produce **1.267**, while when R^1 was a proton (**1.264c** and **1.264d**), the product was the non-oxidized **1.268**. Heating these compounds provided two distinct chromene products (**1.269** and **1.271**) following a 1,7-sigmatropic hydrogen shift.

Scheme 1.46 Other dienamine-mediated reactions with push-pull dienamines.[108]



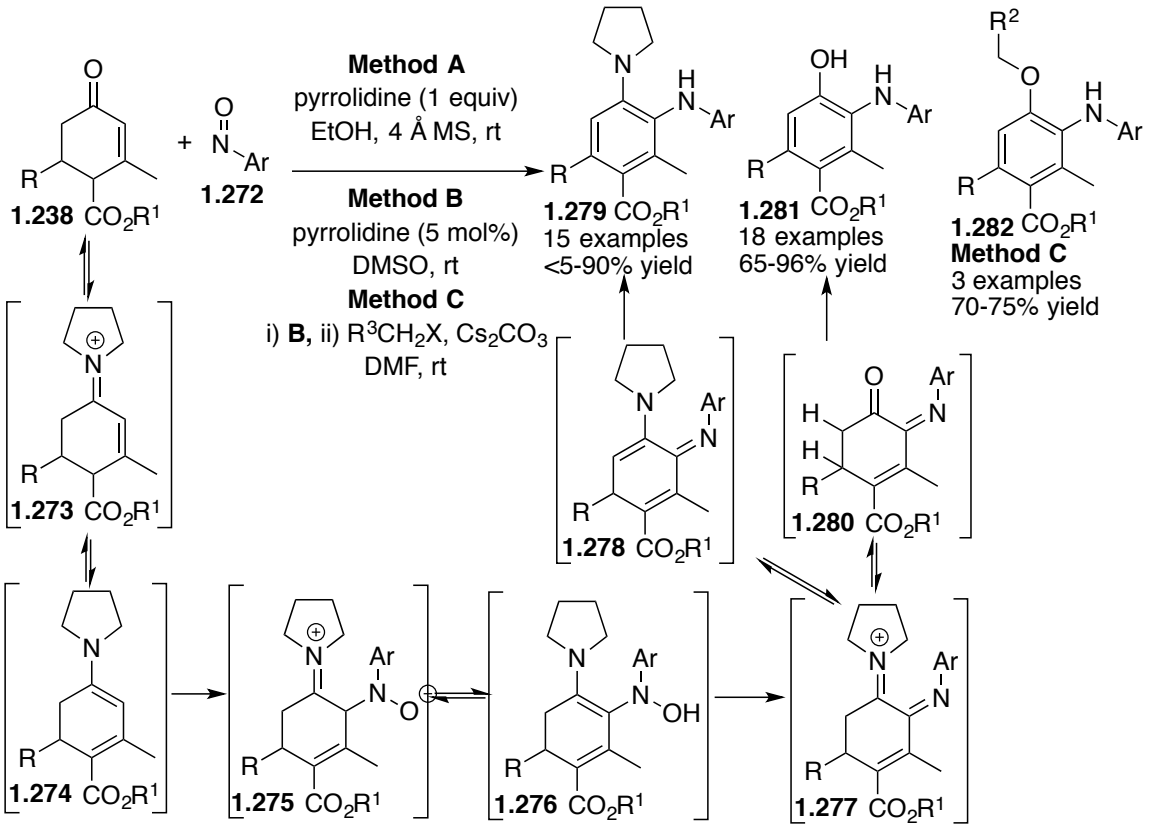
Scheme 1.47 Ramachary's synthesis of highly functionalized 1-methyl-2*H*-chromenes **1.269** and **1.271**.[108]



Ramachary and coworkers used the push-pull dienamine catalysis platform to develop different organocascades as well. In 2007, they reported a novel, metal-free, green technology for the synthesis of highly substituted *o*-pyrrolidin-1-yldiarylamines (**1.279**), *o*-hydroxydiarylamines (**1.281**), and *o*-alkoxydiarylamines (**1.282**, **Scheme 1.48**).[110] The cascade involved an enamine catalyzed amination with nitrosoaryl compounds (**1.272**), followed by iso-aromatization. In the presence of 4Å molecular-sieves (**Method A**), hydrolysis of pyrrolidine catalyst is blocked, providing products **1.279**, while following normal hydrolysis (**Method B**), phenols (**1.281**) are generated. These phenols can be

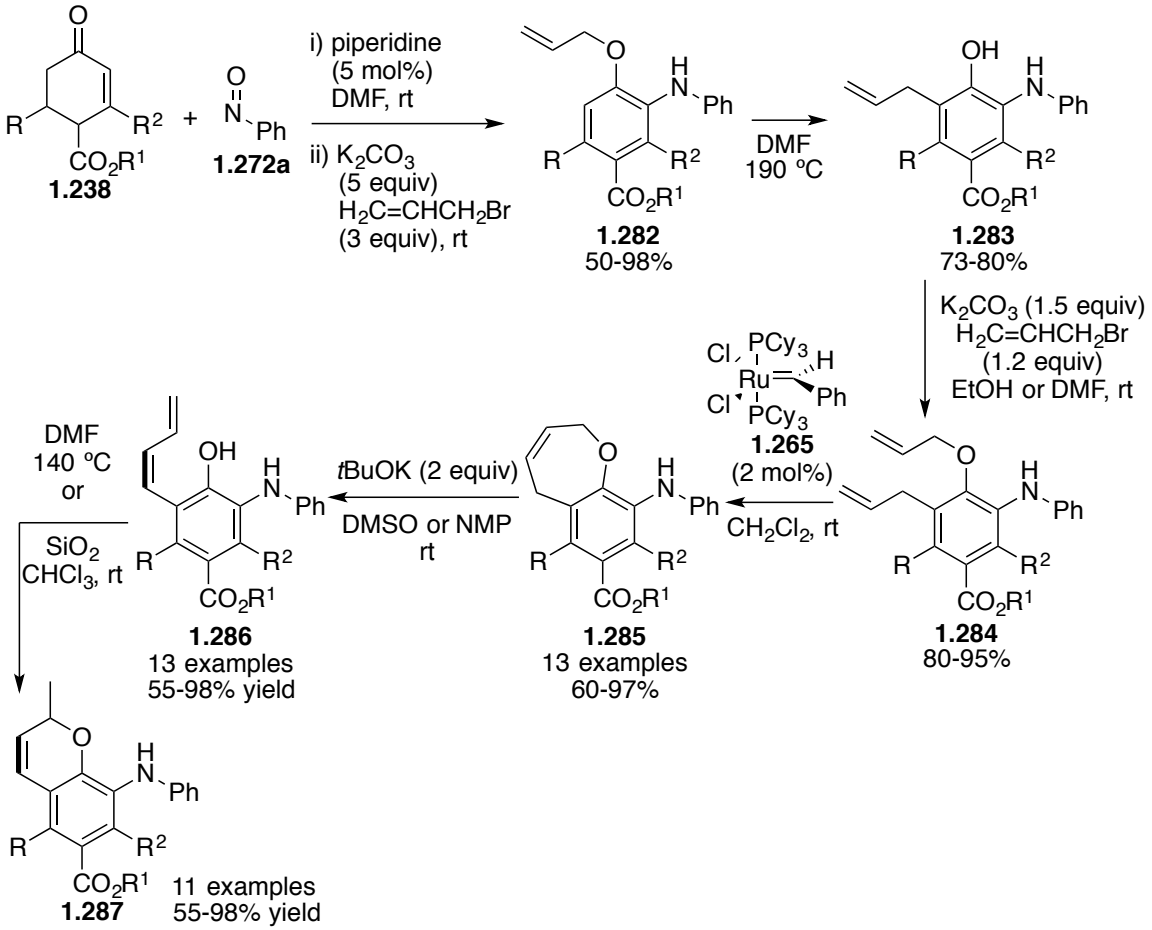
alkylated through the introduction of Cs_2CO_3 and alkyl halides to produce **1.282**.

Scheme 1.48 Push-pull dienamine-mediated diarylamine syntheses.[110]



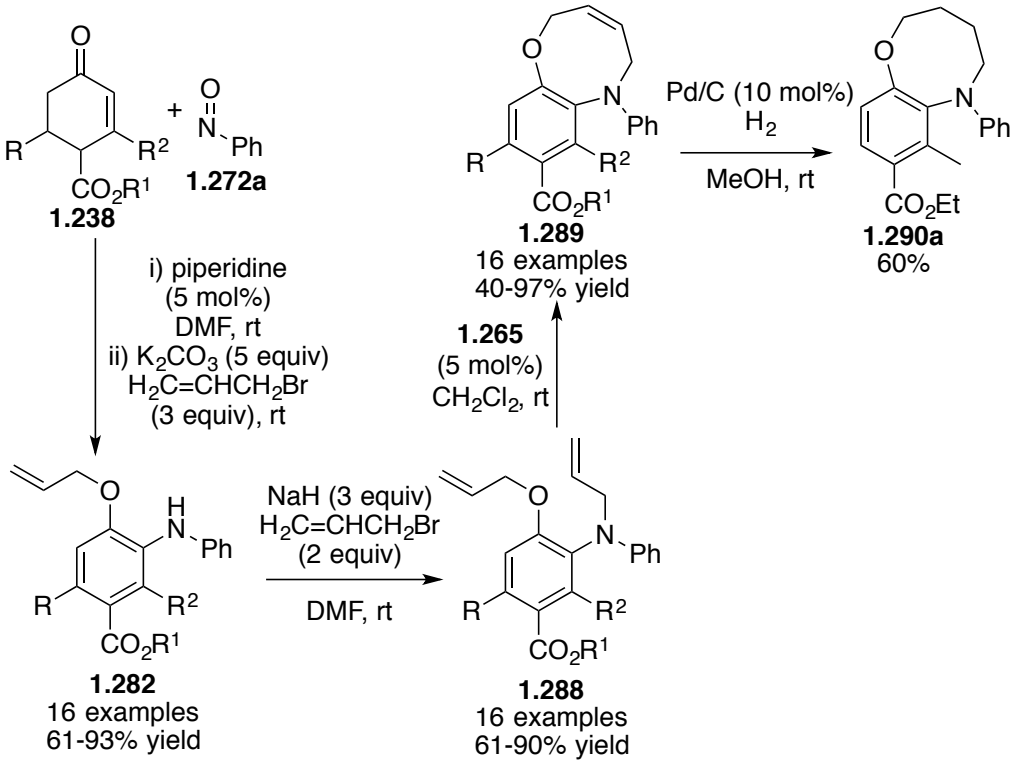
In 2008 and 2009, they used this method for the synthesis of *o*-alkoxydiarylamines (**1.282**) as a precursor to the syntheses of (*Z*)-2-(buta-1,3-dienyl)phenols (**1.286**, **Scheme 1.49**), 2-methyl-2*H*-chromenes (**1.287**, **Scheme 1.49**), and Nefopam analogues (**1.289** and **1.290a**, **Scheme 1.50**).[109,111] Developing their method further, they synthesized a number of different *o*-alkoxydiarylamines (**1.282**, **Scheme 1.49**) in good yields. Claisen rearrangement of **1.282** produced **1.283**, which could then be *O*-alkylated again to produce **1.284** in good yields. First generation Grubbs-catalyst metathesis provided **1.285** in high yields, then base induced ring opening produced (*Z*)-2-(buta-1,3-dienyl)phenols (**1.286**) in moderate to good yields. A 1,7-sigmatropic hydrogen shift converted this to the 2-methyl-2*H*-chromenes (**1.287**) in moderate to high yield.

Scheme 1.49 Push-pull dienamine application to the synthesis of (*Z*)-2-(buta-1,3-dienyl)phenols (**1.286**) and 2-methyl-2*H*-chromenes (**1.287**).[109]



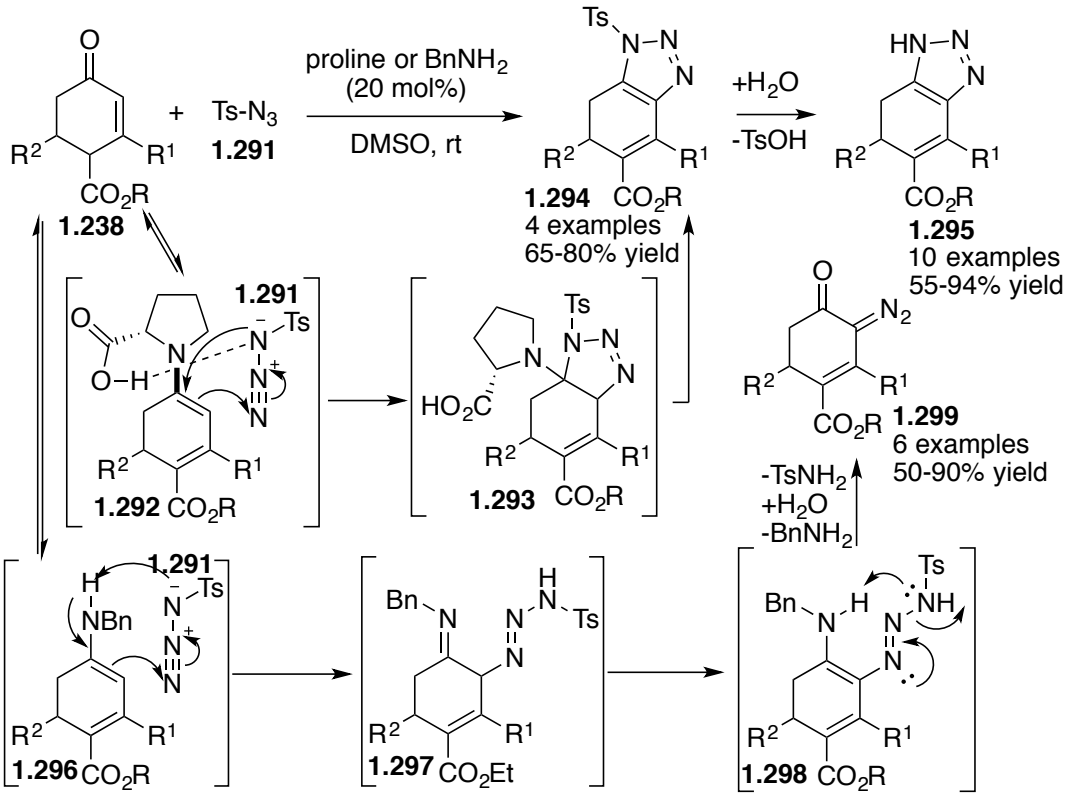
To produce the Nefopam analogues, Ramachary and coworkers alkylated the amine of **1.282** to provide **1.288** in good yields, and subjected the compound to Grubbs-catalyst-mediated ring-closing metathesis, to generate Nefopam analogues (**1.289**, **Scheme 1.50**) in moderate to high yields. Hydrogenation of one of these analogues provided another Nefopam analogue (**1.290a**) in 60% yield.

Scheme 1.50 Ramachary's synthesis of Nefopam analogues **1.284** and **1.285a** using a push-pull dienamine method.[111]



In 2008, the same group reported a [3+2] cycloaddition/hydrolysis cascade that provided 1,2,3-triazole "click chemistry" products (**1.294** and **1.295**), through a copper-free mechanism (**Scheme 1.51**).[112] Using organocatalysts to generate push-pull dienamines (**1.292** and **1.296**) from Hagemann's esters (**1.238**), libraries of diazo-products (**1.299**) with catalytic benzylamine or 1,2,3-triazole products (**1.294**) with proline as a catalyst could be synthesized in moderate to high yields. Prolonging the reaction times and increasing the water content of the solvent led to hydrolyzed 1,2,3-triazole products (**1.295**) being produced in moderate to high yields.

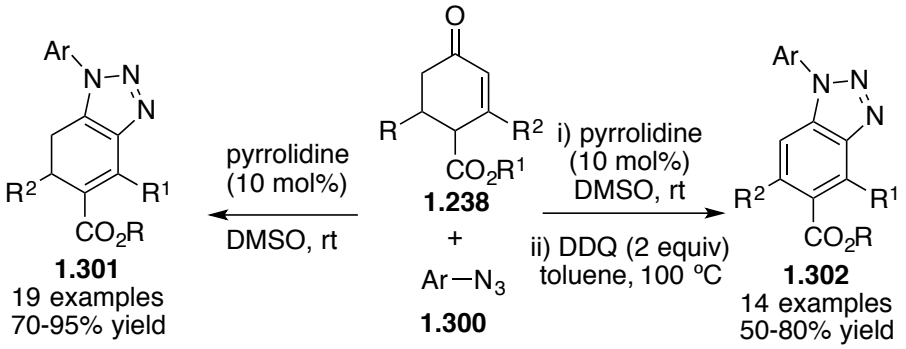
Scheme 1.51 Push-pull dienamine-mediated reactions with *p*-toluenesulfonyl azide (**1.291**).[112]



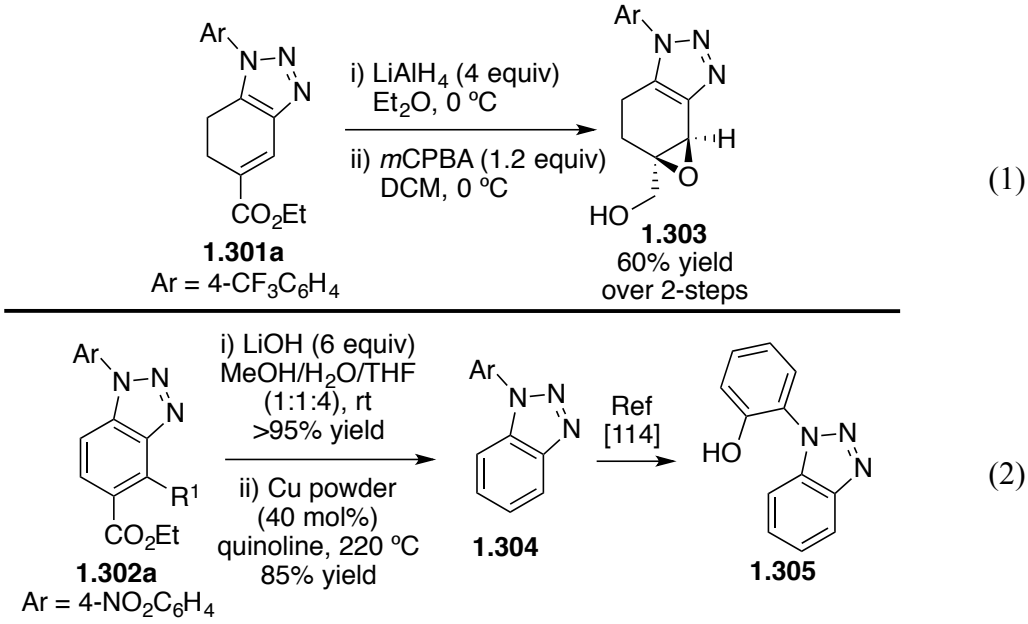
In 2013, Ramachary and coworkers advanced their previously reported syntheses of triazoles using push-pull dienamines to the synthesis of *N*-aryl-1,2,3-triazoles (**1.301**), as well as *N*-arylbenzotriazoles (**1.302**, **Scheme 1.52**).[113] In this research, they used aryl azides (**1.300**) as dipoles for the regioselective [3+2] cycloaddition. They found that their optimized reaction conditions, using pyrrolidine as the catalyst, were effective at synthesizing *N*-aryl-1,2,3-triazoles (**1.301**) using a wide variety of substituted Hagemann's esters (**1.238**) and electron-poor azides in good to excellent yields. Foregoing isolation, adding DDQ sequentially to the reaction following the cycloaddition led to oxidative aromatization, providing an additional library of *N*-arylbenzotriazoles (**1.302**) in good to excellent yields. They were able to diversify these libraries further with the introduction of

different reagents, including synthesizing a precursor (**1.304**) to potassium channel activator **1.305** (eq 2, **Scheme 1.53**).[114]

Scheme 1.52 Push-pull dienamine-mediated synthesis of *N*-aryl-1,2,3-triazoles (**1.301**) and *N*-arylbenzotriazoles (**1.302**).[113]



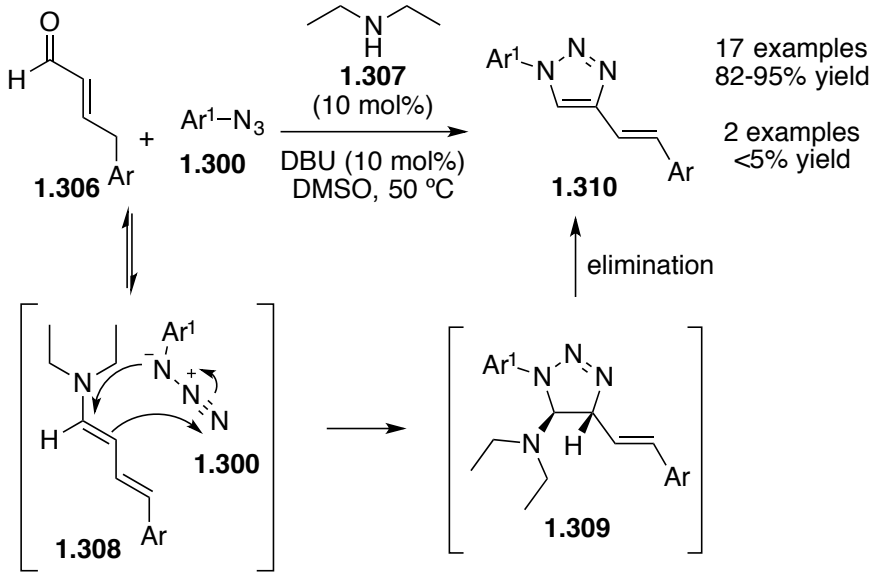
Scheme 1.53 Derivatization of *N*-aryl-1,2,3-triazoles (**1.301**) and *N*-arylbenzotriazoles (**1.302**).[113,114]



That same year, Wang and coworkers developed a dienamine catalyzed α-regioselective 1,3-dipolar cycloaddition of a α,β-unsaturated aldehydes (**1.306**) and aromatic azides (**1.300**) to provide triazole-olefins (**1.310**, **Scheme 1.54**), without the use

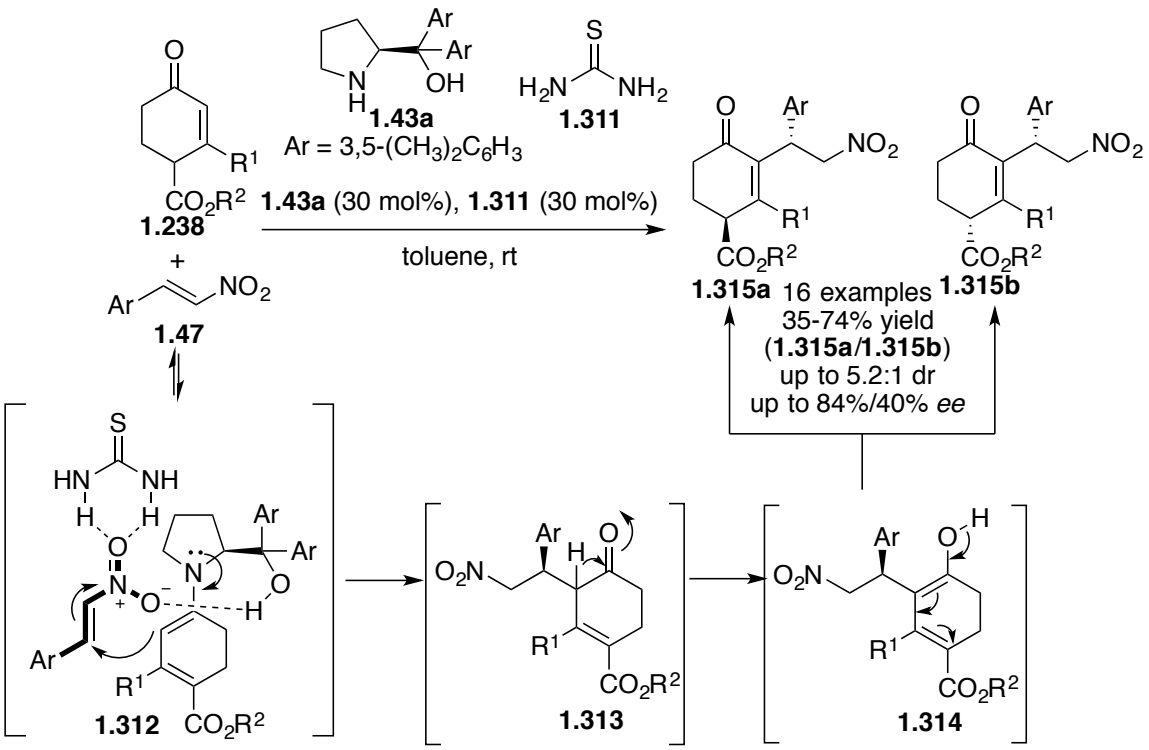
of Ramachary's push-pull dienamine platform.[115] They found that the reaction was exclusively regioselective and tolerated electron-rich and electron poor azides and aldehydes, obtaining high yields with all substrates, excepting with the use of azides with methyl and ethyl linkers that disrupted the conjugated system, which afforded yields <5%.

Scheme 1.54 Wang's non-push-pull dienamine platform synthesis of triazole-olefins (**1.310**).[115]



In 2011, Ramachary and coworkers reported the use of push-pull dienamines (**1.312**) to synthesize Morita-Baylis-Hillman-type products (**1.315**, **Scheme 1.55**).[116] This was the first dienamine catalyzed Michael-addition to β-nitrostyrenes from the α-position of α,β-unsaturated ketones. Following thiourea (**1.311**) cocatalyst aided conjugate addition to **1.47** through proposed transition state **1.312**, and hydrolysis to **1.313**, deprotonation at the α-position generated a push-pull dienol (**1.314**). Finally, protonation at the γ-position provided the α,β-unsaturated ketone product (**1.315**) in low to high yields with high enantioselectivity for the major diatereomer (**1.315a**).

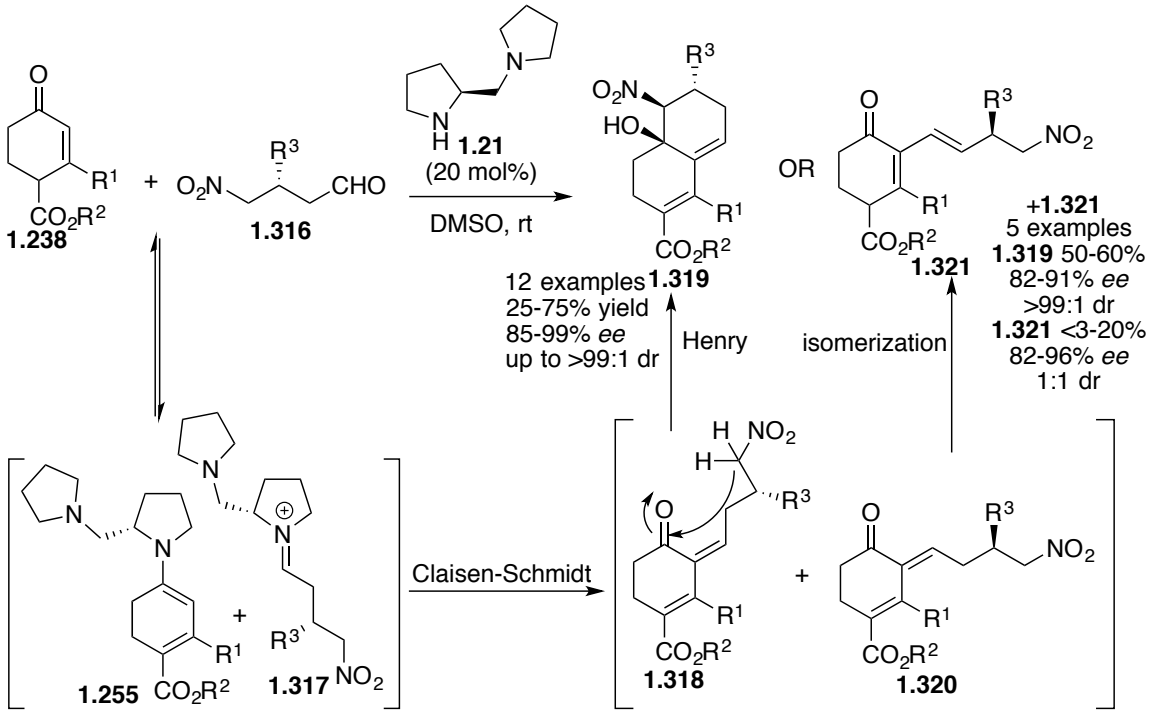
Scheme 1.55 Ramachary's push-pull dienamine-mediated syntheses of Morita-Baylis-Hillman-type products (**1.315**).[116]



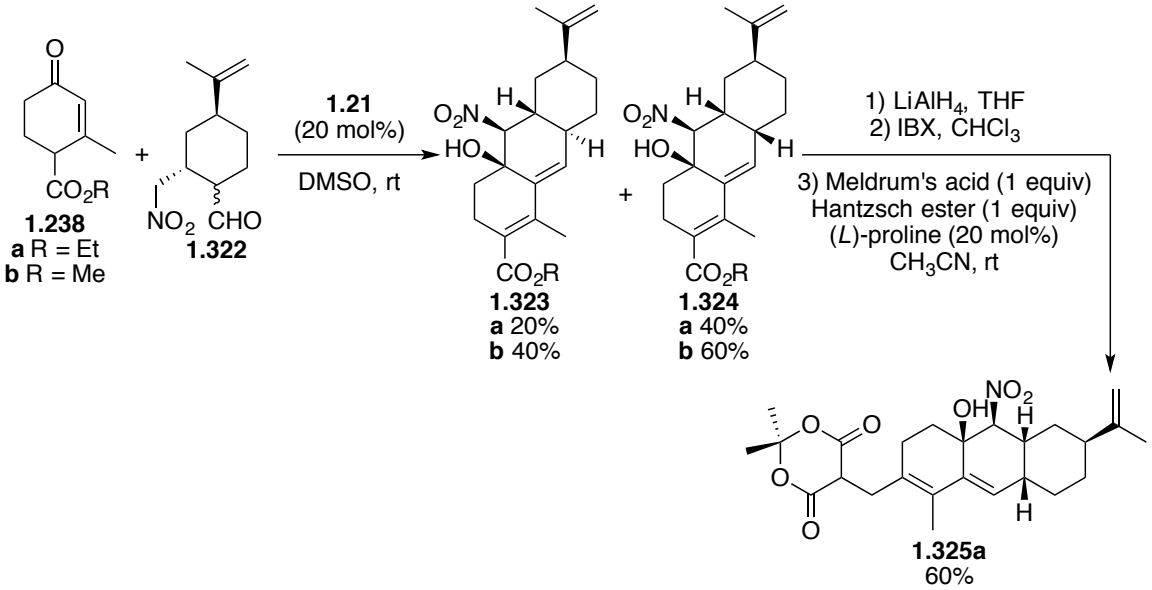
The most recently reported organocascade using the Hagemann's ester derived push-pull dienamine platform was a 2015 paper by Ramachary and coworkers reporting the synthesis of asymmetric decalines (**1.319**) via a domino Claisen-Schmidt/Henry reaction (**Scheme 1.56**).[117] In this work, they combined Hagemann's esters (**1.238**) with asymmetric 3-substituted-4-nitroaldehdyes (**1.316**) and secondary amine catalyst **1.21** to generate Claisen-Schmidt intermediates **1.318** and **1.320**. The *Z*-isomer, **1.318**, could then undergo an intramolecular Henry reaction to provide **1.319** in low to high yields and high enantioselectivity and diastereoselectivity. When the R^3 group was aliphatic, there was a minor Claisen-Schmidt product (**1.321**) that could be generated from *E*-intermediate **1.320** via double bond migration. To demonstrate the utility of this process, Claisen-Schmidt/Henry domino reactions were also performed using a cyclic nitroaldehyde (**1.322**)

to form tricyclic products **1.323** and **1.324** in low to moderate yields (**Scheme 1.57**). These could be converted to a chiral terpenoid-type product (**1.325a**) in 60% yield.

Scheme 1.56 Push-pull dienamine-mediated Claisen-Schmidt/Henry domino reaction.[117]



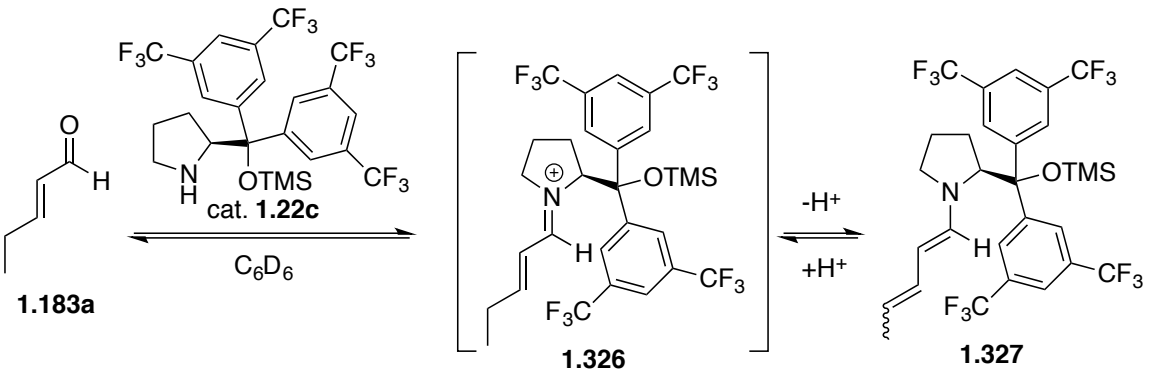
Scheme 1.57 Applications to the Claisen-Schmidt/Henry domino products.[117]



1.2.4 LINEAR DIENAMINE CATALYZED SYSTEMS

While there have been many examples of dienamine-mediated cycloadditions, there are fewer examples of dienamine-catalyzed functionalizations of linear substrates, particularly γ-functionalizations of aldehydes and ketones. In 2006, Jørgensen and coworkers discovered the preferential formation of dienamine intermediates (**1.327**) during ^{1}H NMR studies intended to characterize the iminium ion intermediates (**1.326**) formed from the condensation of catalyst **1.22c** onto **1.183a** (**Scheme 1.58**).[66] This was unexpected, as these components are typically used for activation in organocatalytic conjugate additions and the only example of γ-functionalization via dienamine catalysis prior to 2006 was Serebryakov's seminal [4+2] cycloaddition in 1998.[33]

Scheme 1.58 Jørgensen's discovery of catalytic dienamine formation in α,β-unsaturated aldehydes.[66]



In order to explore the potential of this electron-rich species, diethyl azodicarboxylate (DEAD, **1.328**) was used as an electrophile due to its versatility in organocatalytic α-aminations (**Scheme 1.59**). They discovered that DEAD was not only highly regioselective, exclusively providing the γ-aminated product **1.331**, but highly stereoselective for the *R*-enantiomer. This was the opposite enantiomer than was

anticipated through use of sterically shielding catalyst **1.22c**, however this, as well as the exclusive regioselectivity could be mechanistically explained by reaction via an *s*-cis dienamine (*E*,*s*-cis,*E*)-**1.327** (**Scheme 1.59**). DFT calculations had shown no significant energy difference between the α- and γ-nucleophilic positions to account for the exclusively γ-regioselectivity, but the Diels-Alder cycloaddition reaction mechanism provided an energetically favorable explanation. Following regeneration of the iminium ion **1.330** through C-N bond cleavage, reformation of the *E*-alkene was possible without epimerization of the γ-position, which they propose to occur through reversible addition of a nucleophile, such as water or **1.22c**, to **1.330**. This proposed [4+2] mechanism was further supported by a representative synthesis of **1.332** using *N*-methylmaleimide as a dienophile to trap and isolate the cyclic amine intermediate (**Figure 1.2**). In this research they also provided a substrate scope varying the R group of the enal with moderate yields, but high enantioselectivity.

Scheme 1.59 Jørgensen's regioselective γ-amination through an *s*-cis dienamine.[66]

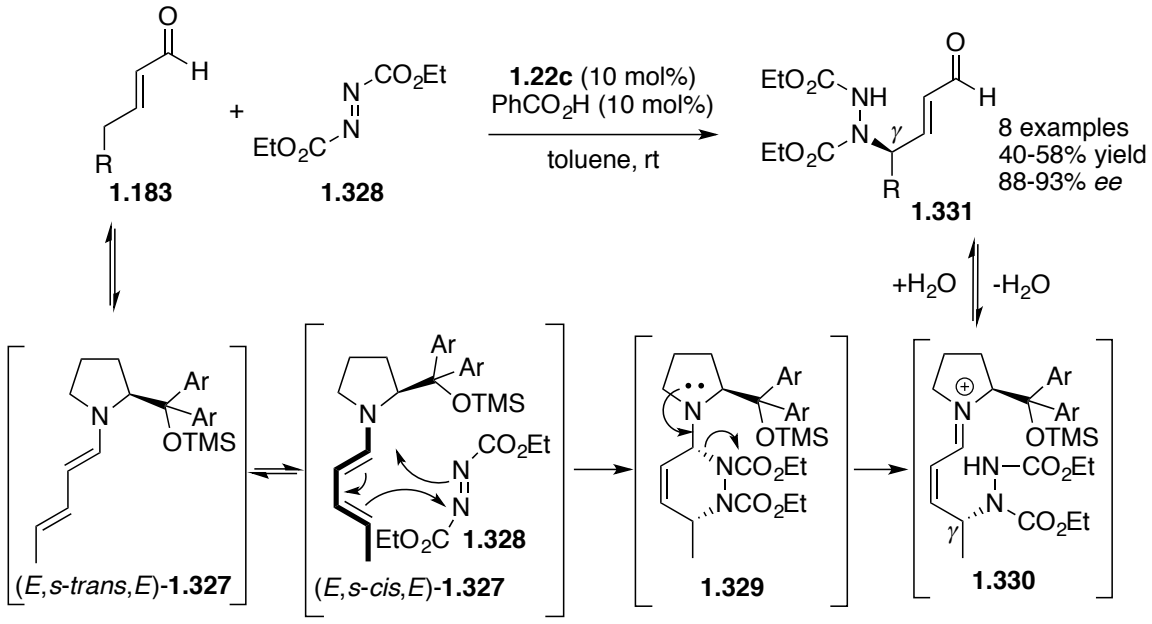
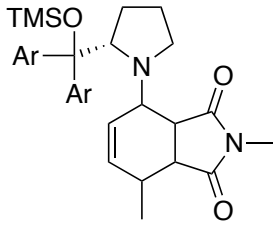


Figure 1.2 Isolable mechanistic evidence of an intermolecular Diels-Alder reaction with a dienamine intermediate.[66]



1.332

Ar = 3,5-$(CF_3)_2C_6H_3$

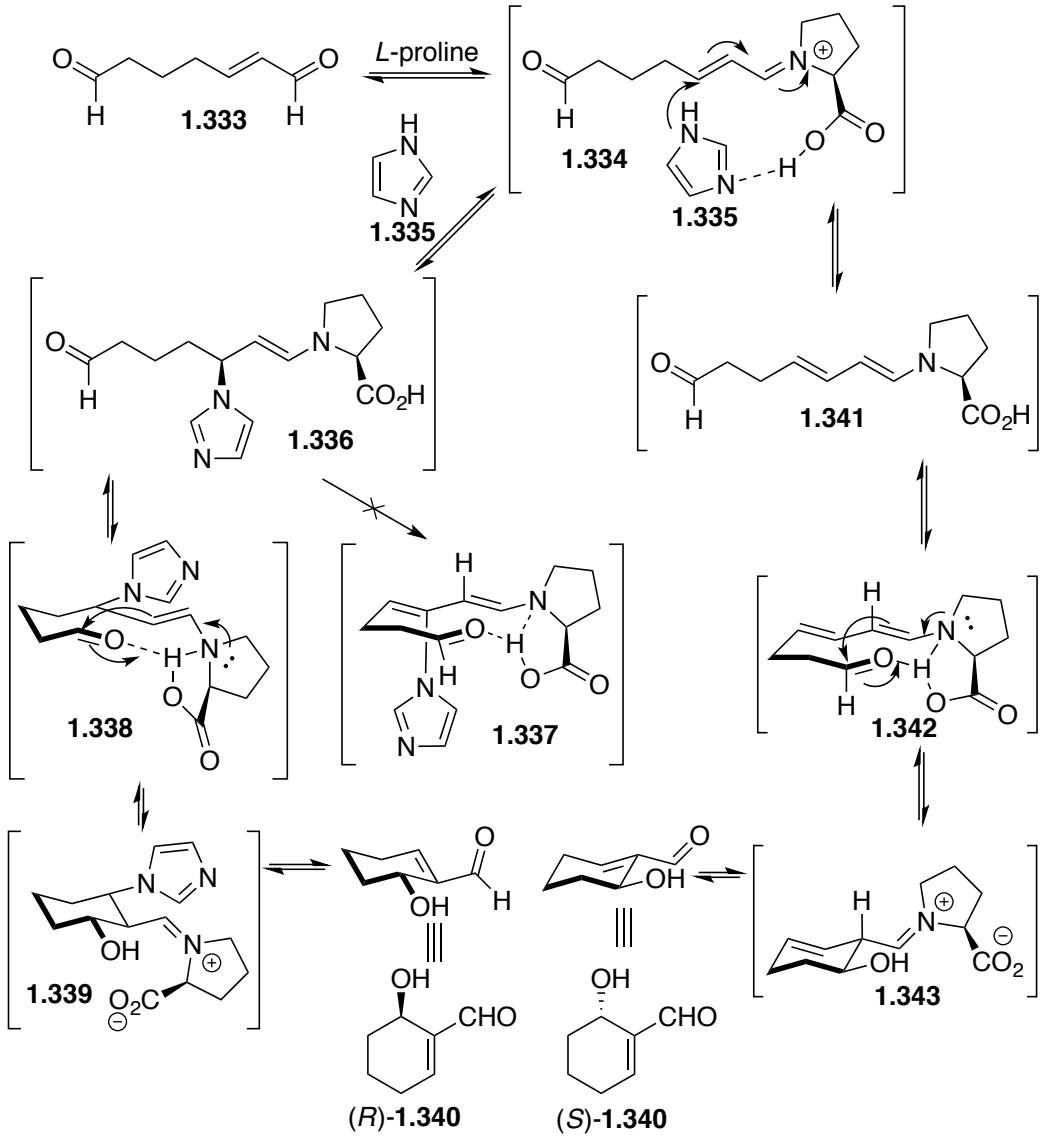
In 2005, Hong and coworkers developed the first intramolecular enantioselective Morita-Baylis-Hillman reaction (**Scheme 1.60**).[118] In the development of their proline-catalyzed reaction, they observed that an inversion in the stereochemistry of the product occurred when they included an imidazole (**1.335**) additive, which they attributed to a change in the mechanism. While imidazole was present, they proposed the normal Morita-Baylis-Hillman mechanism, involving proline-directed conjugate addition of the additive at the β-position of iminium ion **1.334**, to generate the reactive enamine (**1.336**). The presence of the imidazole forces the formation of transition state **1.338**, leading to (*R*)-**1.340**. Without the imidazole present, the dienamine intermediate (**1.341**) forms a different transition state (**1.342**) due to different sterics, leading to formation of (*S*)-**1.340**.

Following this work, Tanaka, Barbas, and coworkers, and Córdova and coworkers independently reported proline-catalyzed aza-Morita-Baylis-Hillman reactions between α,β-unsaturated aldehydes (**1.344**) and protected imines (**1.345** and **1.348**, **Scheme 1.61**).[119,120] Although they used an imidazole additive, Tanaka and Barbas proposed a mechanism involving a dienamine-catalyzed asymmetric Mannich-type reaction, followed by isomerization to the Morita-Baylis-Hillman-type product (**1.346**), due to the isolation

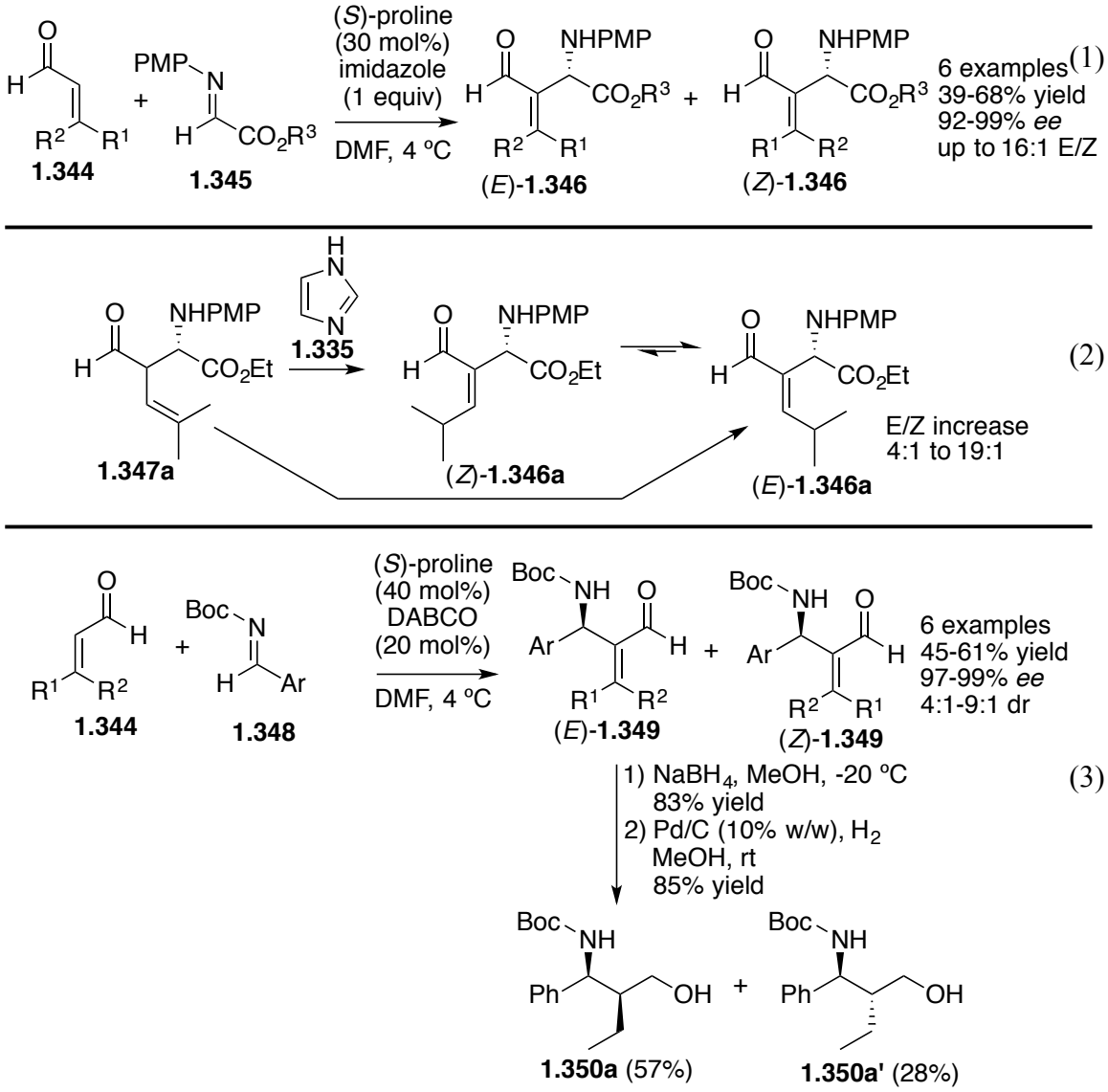
of the unconjugated Mannich product **1.347a** alongside the expected product when using (*E*)-4-methylpent-2-enal. Addition of imidazole (**1.335**) to a mixture of **1.347a** and **1.346a** led to a decrease in **1.347a** and an increase in **1.346a** over time, further supporting their proposed mechanism (eq 2, **Scheme 1.61**). Further evidence for a dienamine mechanism is the lack of any formation of Morita-Baylis-Hillman products with acrolein and cinnamaldehyde, as these aldehydes could undergo a conjugate addition by imidazole, but cannot form a dienamine. In Córdova's work, a similar transformation was developed in which a Boc-protected imine and a catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO) were used, rather than imidazole (eq 3, **Scheme 1.61**). The reaction was reported to proceed in moderate yields and with high enantioselectivities, however, no evidence was presented indicating whether DABCO was acting as a catalytic base or as a nucleophile in the reaction. These products were then converted to γ-amino alcohols (**1.350**).

In 2008, Woggon and coworkers developed a synthesis of α-tocopherol (**1.360**) using a dienamine catalyzed aldol/oxa-Michael domino reaction (**Scheme 1.62**).[121] In this reaction they combined α,β-unsaturated aldehyde phytenal (**1.352**), and organocatalyst **1.22d** to generate dienamine **1.353**, which could react with functionalized salicylaldehyde **1.351** to generate aldol product **1.354**. This iminium ion now possessed an activated β-position for nucleophilic attack by the phenol. Catalyst turnover followed by hemiacetal formation generated lactol **1.355** in 58% yield. This could be oxidized with PCC to the corresponding lactone **1.356** in 90% yield, and the diastereomeric excess was determined to be 97% by chiral-phase HPLC. The following steps were accomplished in good yields and (2*S*, 4'*R*, 8'*R*)-α-tocopherol was obtained in an overall 5-step yield of 32%.

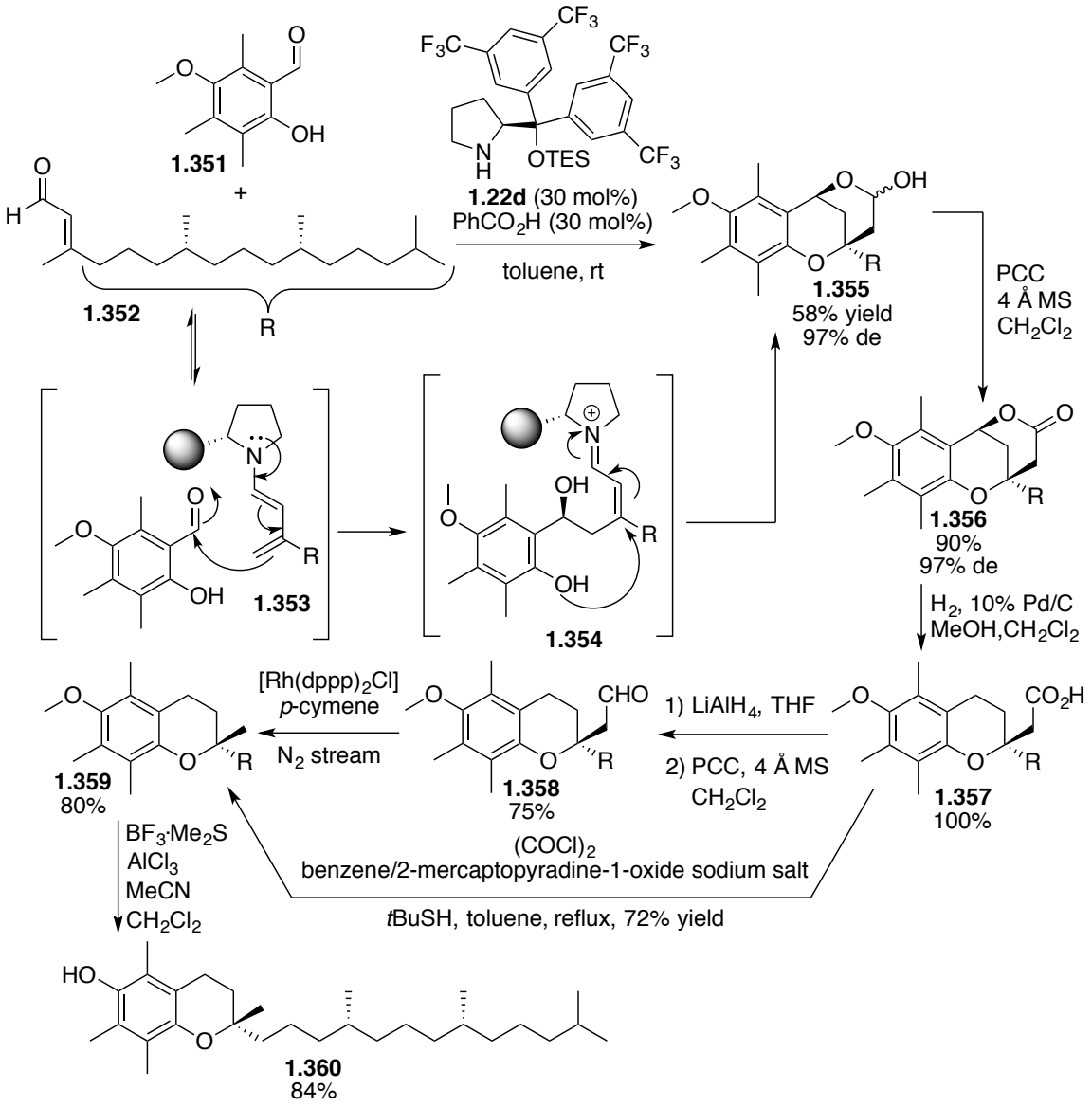
Scheme 1.60 Hong's discovery of a stereodivergent intramolecular Morita-Baylis-Hillman reaction.[118]



Scheme 1.61 Tanaka, Barbas, and Córdova's reports on the synthesis of aza-Morita-Baylis-Hillman-type products through organocatalysis.[119,120]



Scheme 1.62 Woggon's synthesis of α-tocopherol **1.360** via an initial aldol/oxa-Michael domino reaction.[121]



In 2009, Christmann and coworkers reported a dienamine-catalyzed intramolecular Rahut-Currier-type reaction to form asymmetric cyclopentenals (**1.366**, **Scheme 1.63**), which could be considered precursors to iridoid natural products.[122] Combining β,β-disubstituted α,β-unsaturated aldehydes, containing a tethered a Michael acceptor, with catalyst **1.22a**, led to formation of dienamine (**1.363**) via iminium ion (**1.362**). The α-

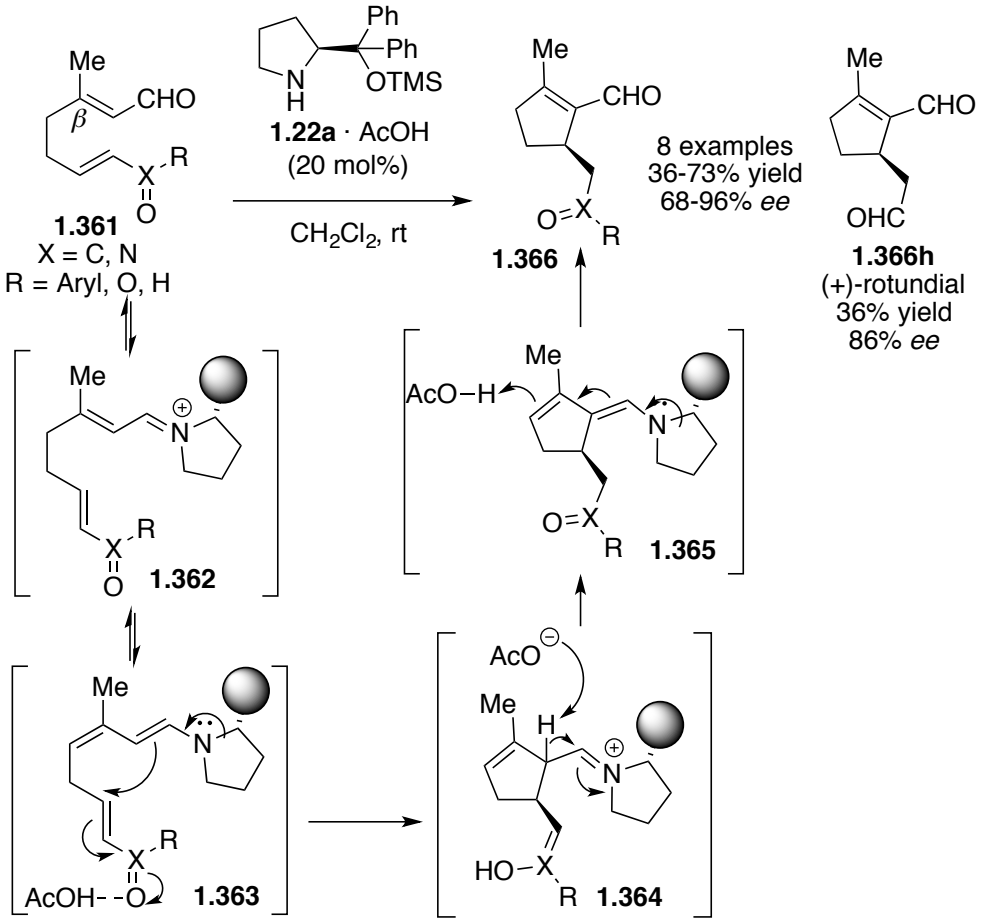
position of this dienamine was activated as a Michael donor to generate cyclopentene **1.364**, which isomerized and underwent hydrolysis to provide **1.366** in moderate to high yields and good enantioselectivities. Substrates that contained electron-rich aromatic R groups had dramatically decreased rates of reaction, while a nitroolefin Michael acceptor exhibited a decrease in enantioselectivity. Using an asymmetric dienal led to the formation of the powerful mosquito repellent, (+)-rotundial (**1.366h**), providing the lowest yield of 36%, but good enantioselectivity of 86%.

In 2009, Chen and coworkers reported their attempts to develop the first direct chemo-, regio-, and stereoselective Michael addition of α,β-unsaturated aldehydes to nitroolefins (**1.367**) via dienamine catalysis (**Scheme 1.64**).[123] In their initial studies they observed self-dimerization of the aldehydes in the presence of secondary amine catalyst (**1.22a**), most likely due to the formation of both the dienamine and iminium ion species. Therefore, they decided to use γ,γ-disubstituted α,β-unsaturated aldehydes (**1.154**) to inhibit this activity. Upon introduction of various nitroolefins (**1.367**), exclusively α-regioselective Michael additions occurred to generate **1.368** in moderate to high yields and excellent diastereoselectivities and enantioselectivities, as determined through isolation of the reduced products, **1.369**.

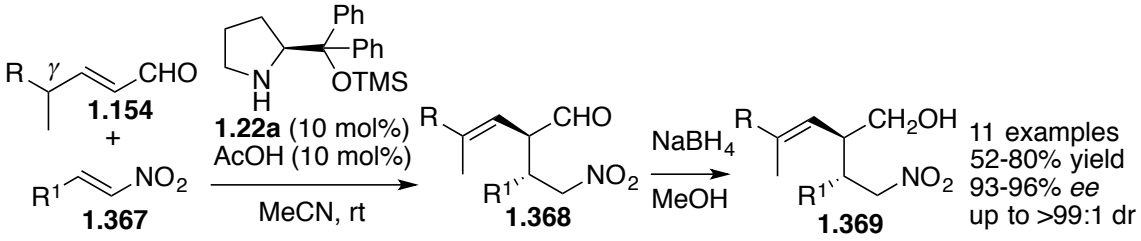
In 2010, Bella and coworkers reported the first dienamine catalyzed vinylogous aldol condensation between an α,β-unsaturated ketone, cyclohexenone (**1.52a**), and aldehydes (**1.248**) using a proline-lithium salt catalyst (**Scheme 1.65**).[124] The aldol condensation product, **1.370**, could only be obtained in low to moderate yields, with self-dimerization product **1.371** forming in low yields as well. This major product was promising, as it is a structural motif that is featured in many natural products and fragrance

compounds. When solvent was changed from toluene to chloroform in the reaction optimization, the reactivity switched to that of a cross-dienamine catalyzed Diels-Alder reaction, generating amino acids (**1.372**) in low to moderate yields and low enantioselectivity.

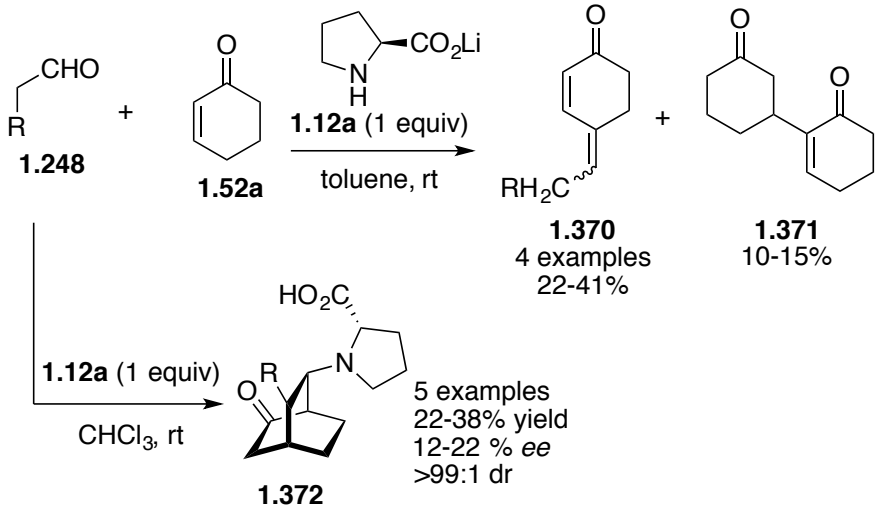
Scheme 1.63 Dienamine catalyzed crossed intramolecular Rahut-Currier-type reactions.[122]



Scheme 1.64 The first stereoselective, α-regioselective, dienamine catalyzed Michael addition of γ,γ-disubstituted α,β-unsaturated aldehydes and nitroolefins.[123]

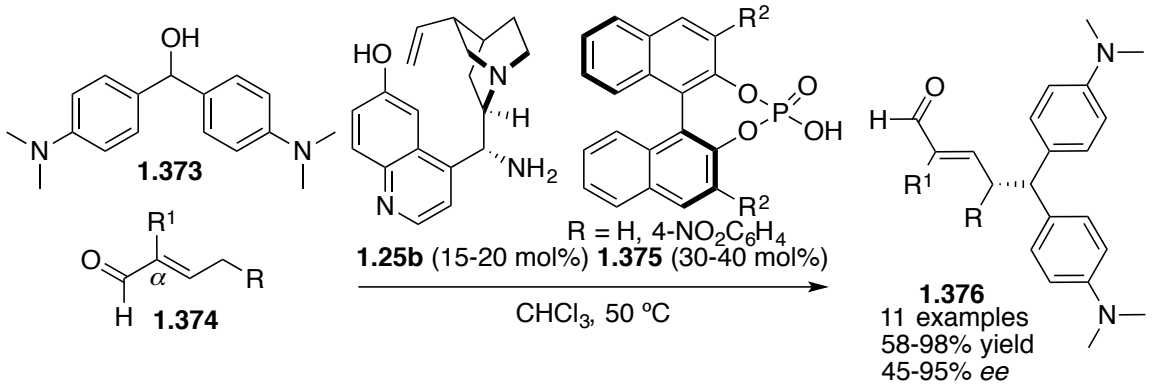


Scheme 1.65 Bella's report of the first direct, dienamine catalyzed aldol condensation.[124]



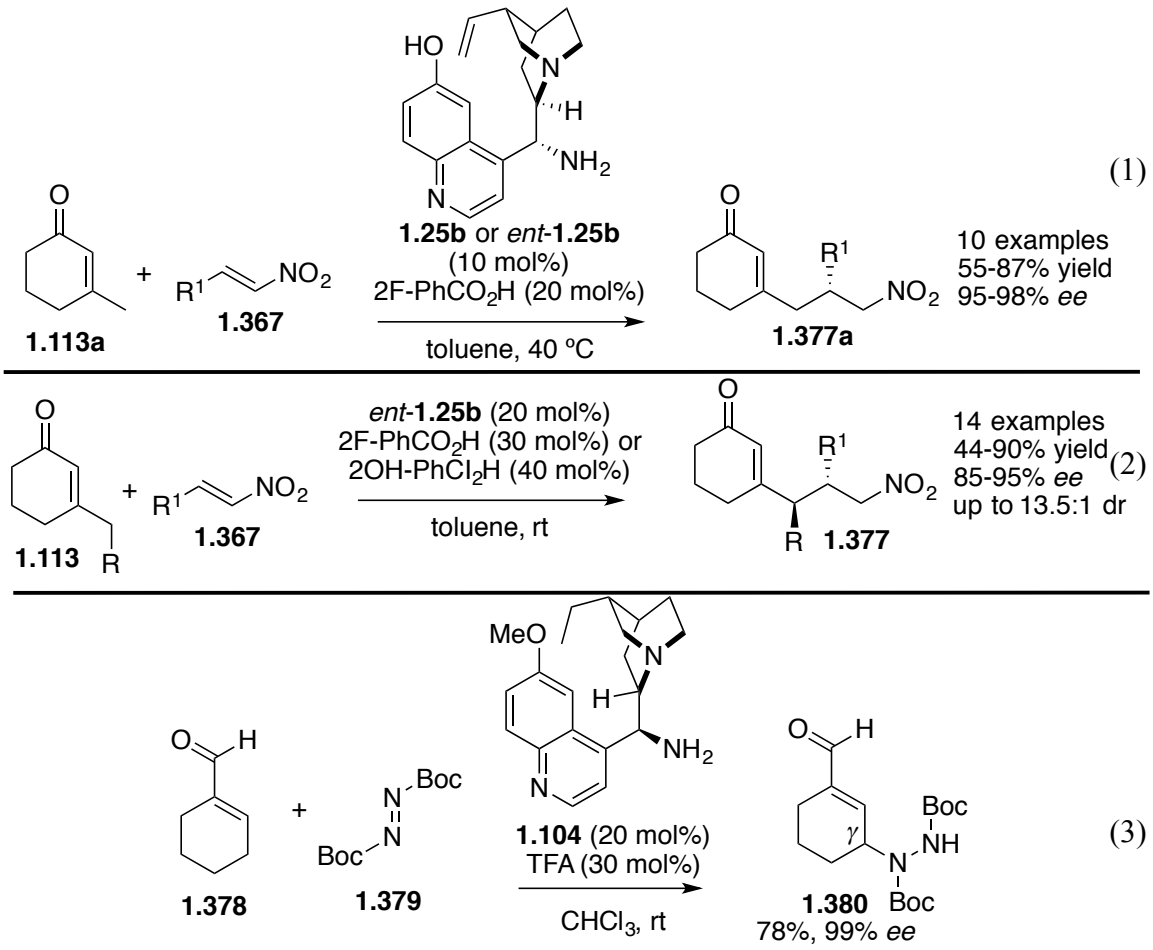
In 2010, Melchiorre and coworkers reported direct S_N1-type asymmetric γ-alkylations of α-substituted α,β-unsaturated aldehydes (**1.374**) using cinchona alkaloid-derived primary amine catalyst **1.25b** in conjunction with chiral phosphoric acid cocatalyst **1.375** (**Scheme 1.66**).[125] In this work, they reported exclusive γ-regioselectivity with various aliphatic and aromatic R groups, synthesizing **1.376** in high yield and enantioselectivity in every instance except with α-phenylpentenal (R^1 = Ph, R = CH_3), which saw a drop in *ee* to 45%.

Scheme 1.66 Melchiorre's report of direct asymmetric γ-alkylations using dienamine catalysis.[125]



In 2010, the same group reported a dienamine catalyzed direct vinylogous Michael addition of cyclic α,β-unsaturated ketones (**1.113**) to nitroolefins (**1.371**), in the presence of cinchona alkaloid derived primary amine catalysts (**1.25b**, **Scheme 1.67**).[56] In this publication they observed moderate to high yields and high enantioselectivities (eq 1), as well as good diastereoselectivity when applicable (eq 2). This exclusively *exo* reactivity was extended to other Michael accepters as well, including a β,β-disubstituted nitrostyrene and *trans*-α-cyanocinnamate to showcase the versatility of the method. γ-Functionalized *endo* products were possible as well, by using α,β-unsaturated aldehyde **1.378** and diazodicarboxylate **1.379**, affording **1.380** in high yield and enantioselectivity (eq 3). This final discovery was later disproven by List and coworkers during their studies in organocatalytic α-benzoyloxylation (vide infra).[126]

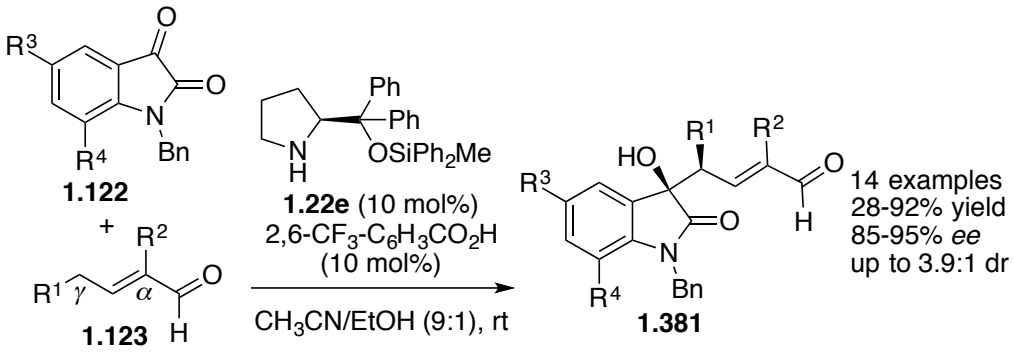
Scheme 1.67 Melchiorre's direct vinylogous Michael additions via dienamine catalysis.[56]



Previously, in section **1.2.1**, Melchiorre and coworkers' oxa-Diels-Alder reaction between α-branched α,β-unsaturated aldehydes (**1.123**) and isatins (**1.122**) was discussed (**Scheme 1.19**).[58] In that same paper, they reported a dienamine catalyzed vinylogous aldol reaction using these same components, forming **1.381** in mostly moderate to high yields and high enantioselectivities (**Scheme 1.68**). The difference in reactivity was seen when the α-substitution on **1.123** was an alkyl group versus an aryl group. In this linear reaction, they found that the procedure tolerated various functionalities at the γ-position of the aldehyde, including those containing heteroatoms, without affecting the regioselectivity,

and site selectivity and enantioselectivity were unaffected by modification of the α-substituent. The reaction also tolerated various electon-rich and electron-poor R^3 and R^4 substituents on the isatin. While diastereoselectivity was not very high, individual diastereomers were easily isolated by column chromatography following $NaBH_4$ reduction of products.

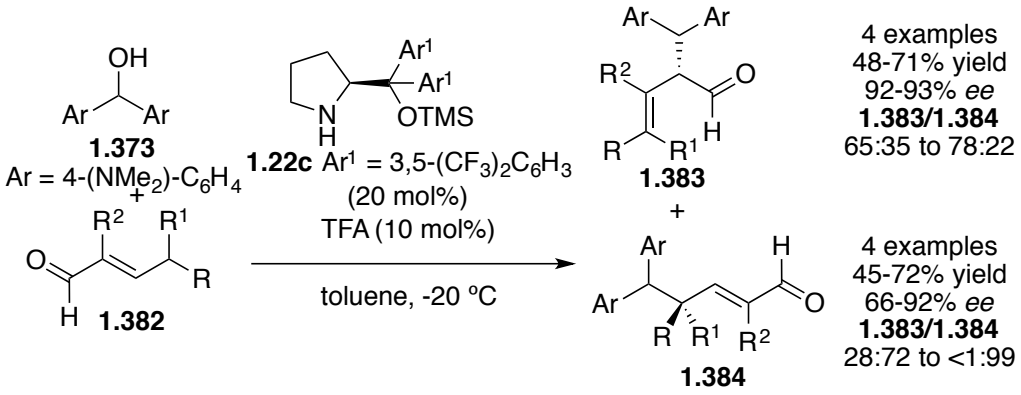
Scheme 1.68 Melchiorre's dienamine catalyzed vinylogous aldol of α-branched α,β-unsaturated aldehydes (**1.123**) with isatins (**1.122**).[58]



In 2011, Christmann and coworkers reported dienamine catalyzed alkylations of α,β-unsaturated aldehydes with **1.373**, in the presence of secondary amine catalyst **1.22c** (**Scheme 1.69**).[127] This differed from Melchiorre's previously reported work (**Scheme 1.66**), as it did not require the use of a primary amine cinchona alkaloid catalyst combined with Brønsted acid catalyst, and it did not exclusively use α-substituted α,β-unsaturated aldehydes.[56] The drawback to Christmann's report was thus competition between the α- and γ-alkylations. They found that using γ,γ-disubstituted aldehydes favored α-alkylations, providing **1.383** in moderate to high yields and high enantioselectivities, but γ-monosubstituted aldehydes favored γ-alkylations, providing **1.384** in moderate to high yields and lower enantioselectivities. The only instance of exclusive formation of **1.384** was in the use of an α-branched aldehyde ($R \neq H$). In this case, the yield was at its highest,

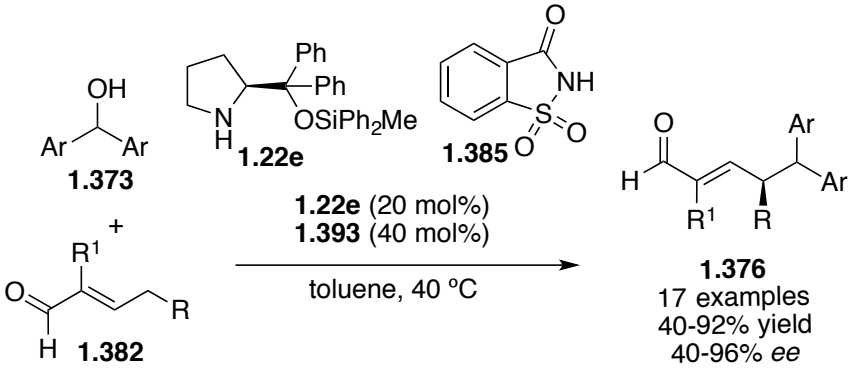
although the enantioselectivity was at its lowest and there was an *E/Z* ratio of 7:1.

Scheme 1.69 Christmann's dienamine catalyzed α- and γ-alkylations of α,β-unsaturated aldehydes.[127]



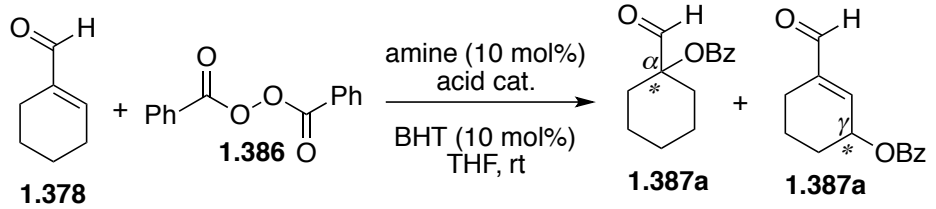
In 2012, Melchiorre continued his exploration of γ-alkylation reactions, having been influenced by Christmann's report to remove the expensive Brønsted acid cocatalyst (**1.375**, **Scheme 1.66**). Instead, a more sterically bulky secondary amine catalyst (**1.22e**) was used to improve enantioselectivity and saccharin (**1.385**) was used as an inexpensive Brønsted acid cocatalyst (**Scheme 1.70**).[128] A variety of functionalities on the aldehyde, as well as different aryl groups on the alcohol provided moderate to high yields of **1.376** in mostly high enantioselectivities.

Scheme 1.70 Melchiorre's secondary amine catalyzed exclusive γ-alkylation of α-branched α,β-unsaturated aldehydes.[128]

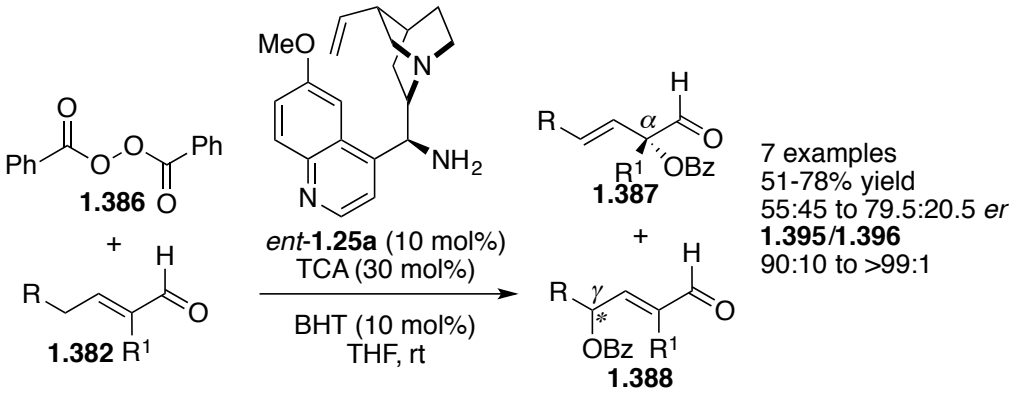


In their research on organocatalytic α-benzoyloxylations of aldehydes, List and coworkers wanted to extend the method they developed to α,β-unsaturated aldehydes in order to study the regioselectivity of dienamine catalyzed reactions.[126] Use of cyclic aldehyde **1.378** in the presence of anhydrous benzoyl peroxide (**1.386**), radical inhibitor BHT, and various amine catalysts and acid additives, afforded both α- and γ-benzoylalkylated products (**1.387a** and **1.388a**, respectively) in moderate to high yields, but strongly favored the α-benzoyloxylated product (eq 1, **Scheme 1.71**). In their substrate scope, α-benzoyloxylated products **1.387** were obtained exclusively using linear α-substituted α,β-unsaturated aldehydes, and in a 9:1 ratio using cyclic aldehydes (eq 2, **Scheme 1.71**). These results contrasted with previous reports that appear to disfavor formation of quaternary centers through dienamine catalysis, thus explaining the less hindered products. These discoveries regarding regioselectivity prompted List and coworkers to test Melchiorre's exclusive γ-selectivity with cyclic aldehydes as described previously (eq 3, **Scheme 1.67**).[56] List and coworkers' findings directly contradicted this report, having isolated the α-aminated product, the structure of which was unambiguously assigned by 2D-NMR spectroscopy and X-ray crystallography (**1.389**, eq 3, **Scheme 1.71**). This indicated that the forces involved in dienamine regioselectivity are not fully understood.

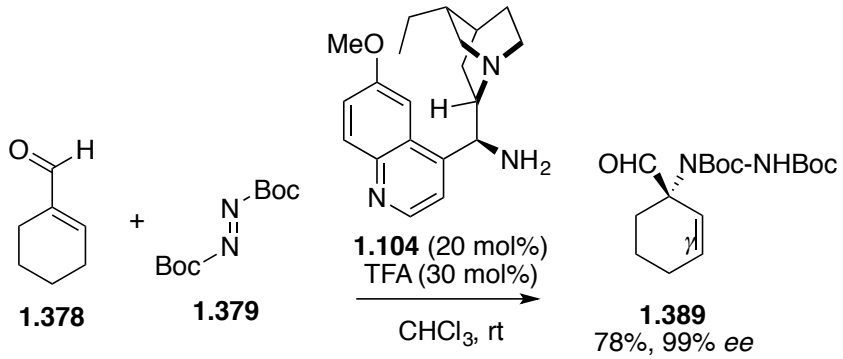
Scheme 1.71 List's dienamine catalyzed α-selective benzoyloxylations of α,β-unsaturated aldehydes and studies on regioselectivity.[126]



(1)



(2)

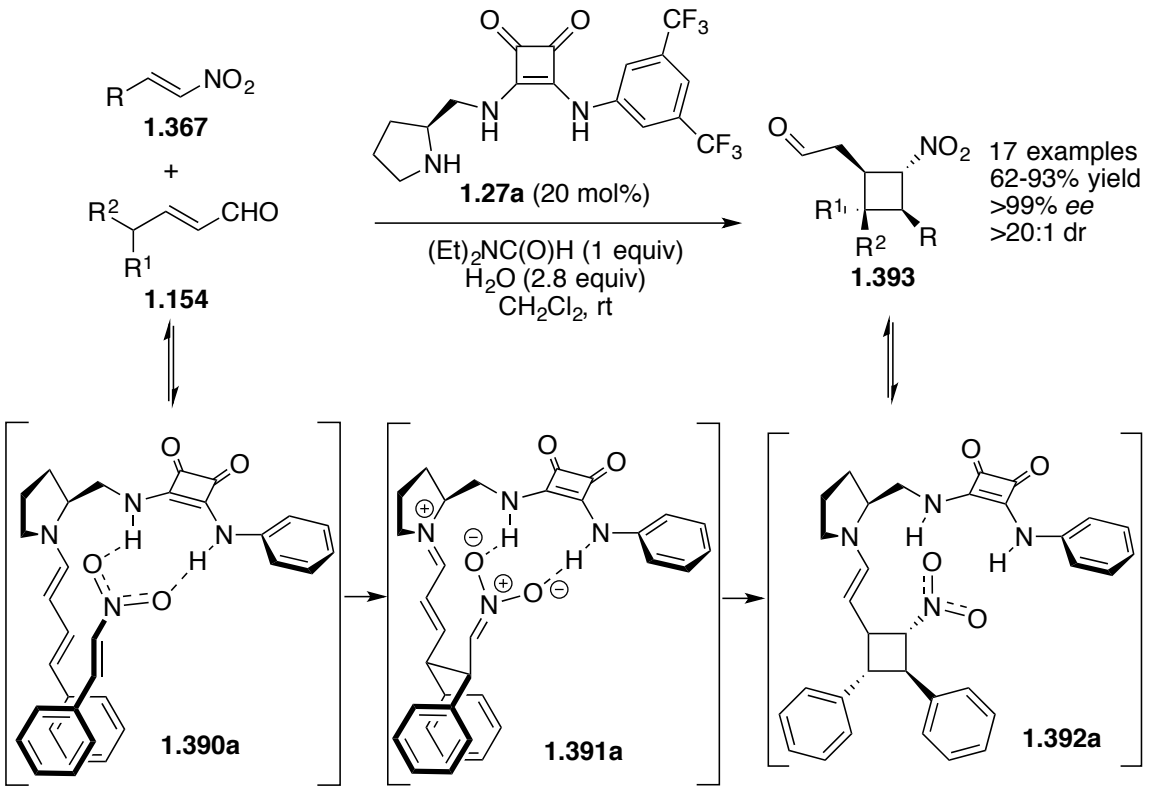


(3)

In 2012, Jørgensen and coworkers and Vicario and coworkers independently reported dienamine-catalyzed formal [2+2] cycloadditions, via a dienamine/iminium ion organocascade of α,β-unsaturated aldehydes (**1.154**) and nitroolefins (**1.367**, **Scheme 1.72** and **1.393**, **Scheme 1.73**).[129,130] Jørgensen's strategy sought to develop a bifunctional pyrrolidine derivative with a hydrogen bonding moiety to assist in activation of the nitroolefin electrophile, stereoinduction, and the regiochemical approach toward γ-functionalization. Following successful reactivity with squaramide catalyst **1.27a**, they

performed computational studies providing insight into the reactivity and the mechanism of this reaction. Their calculations revealed a stepwise mechanism, which involved a conjugate addition from the γ-position of the dienamine (**1.390a**) forming **1.391a**, followed by bond formation between the nitro-enolate and the β-carbon of the iminium ion to form **1.392a**. Catalyst turnover provided the asymmetric cyclobutane aldehydes (**1.393**) in good yields and excellent enantioselectivities and diastereoselectivities.

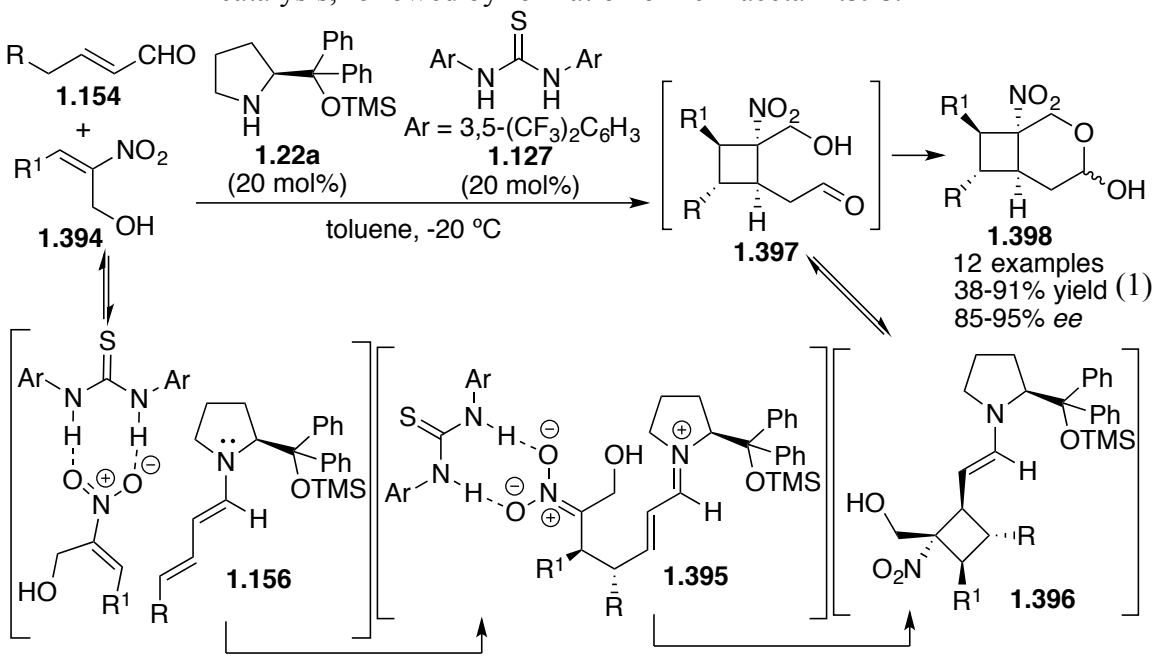
Scheme 1.72 Jørgensen's formal [2+2] cycloadditions via bifunctional dienamine H-bonding catalysis.[129]

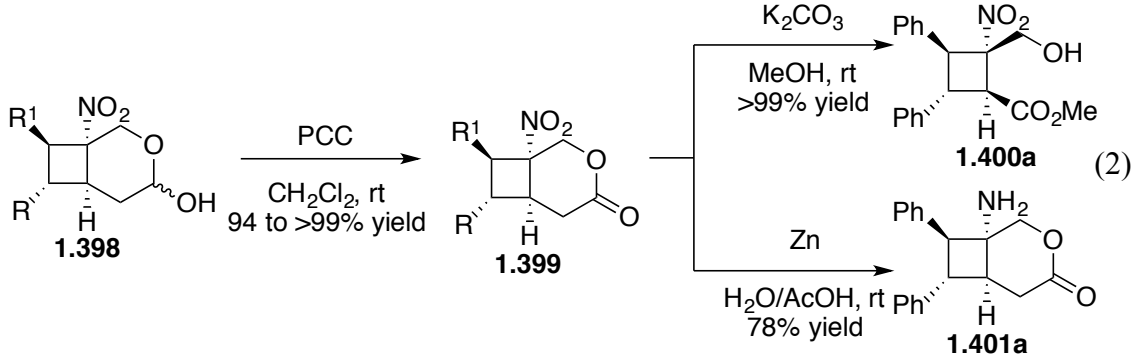


Vicario's strategy instead employed the use of sterically blocking catalyst **1.22a** for dienamine activation, alongside achiral thiourea hydrogen-bonding co-catalyst **1.127** for nitroolefin activation (eq 1, **Scheme 1.73**).[130] In their research, they combined dienamine-activated α,β-unsaturated aldehydes (**1.156**) with α-hydroxymethylnitroolefins (**1.394**), so

that following the Michael-Michael cascade and catalyst turnover, bicyclic hemiacetals (**1.398**) could readily form. These products could also form other bicyclic heterocycles, as well as cyclobutane **1.400a**, through simple synthetic transformations (eq 2).

Scheme 1.73 Vicario's formal [2+2] cycloadditions via dienamine and H-bonding co-catalysis, followed by formation of hemiacetal **1.398**.[130]

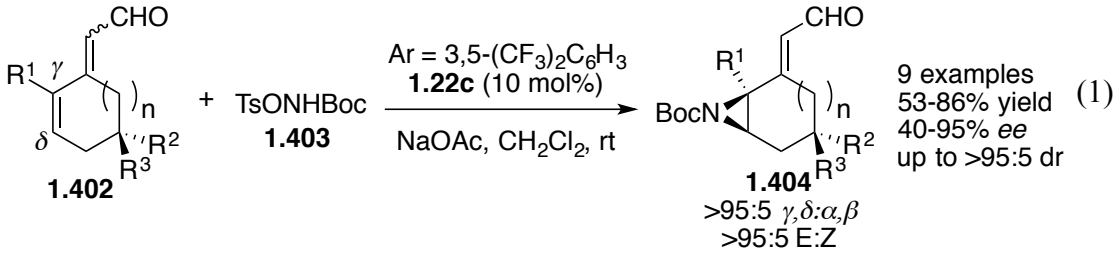


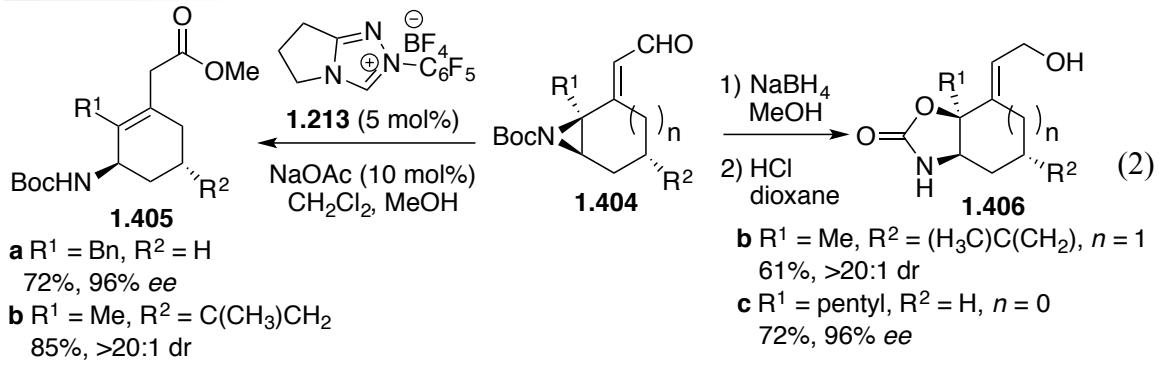


In 2013, Jørgensen and coworkers reported a remote enantioselective aziridination of 2,4-dienals (**1.402**) via a novel tandem vinylogous iminium ion/dienamine cascade reaction (**Scheme 1.74**).[131] In this reaction, TsONHBoc (**1.403**) could act as a nucleophile for conjugate addition to the δ-position of iminium activated 2,4-dienals, followed by

nucleophilic attack by the γ-position of the dienamine, then hydrolysis to form **1.404**. The substrate scope tolerated aliphatic, aromatic, and heteroatomic R^1 substituents, as well as 5- to 7-membered rings. The reactions were also highly regioselective toward γ,δ-aziridination. Finally, these products were readily derivatized to δ-amino esters (**1.405**) and oxazolidinones (**1.406**, eq 2).

Scheme 1.74 Jørgensen's remote aziridination of 2,4-dienals via iminium ion/dienamine cascade reaction.[131]

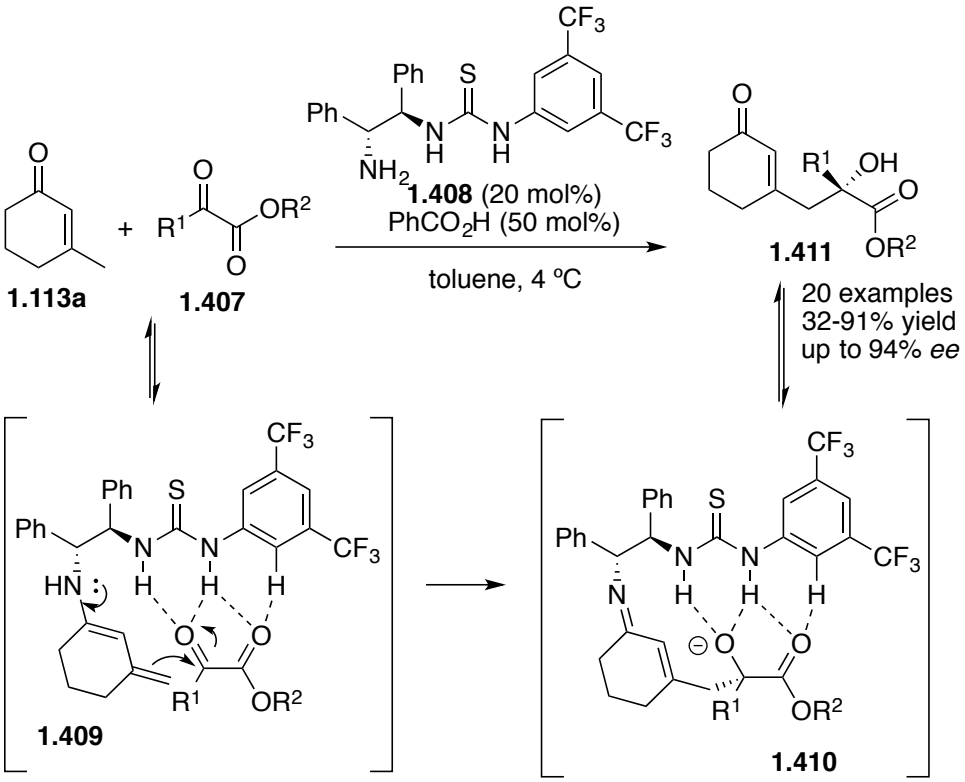




In 2013, Melchiorre and coworkers developed a direct vinyogous aldol reaction, using a primary amine bifunctional thiourea catalyst (**1.408**) to activate the *exo* dienamine of 3-methyl cyclohexanone (**1.113a**) toward nucleophilic attack (**Scheme 1.75**).[132] In their studies they used α-ketoesters (**1.407**) as aldol acceptors in order to more readily hydrogen-bond with the thiourea catalyst for both stereoinduction and regioselection of the γ-position of the dienamine. As a result, they observed high yields and enantioselectivities in all

examples of aliphatic and aromatic α-ketoesters with two exceptions: low yield occurred when R^1=4-methoxyphenyl; and poor enantioselectivity was observed when R^1=2-thiophenyl. Modifications to the scaffold of enone **1.113a** led to a complete loss in reactivity and no other substitution patterns on the ring structure were tested.

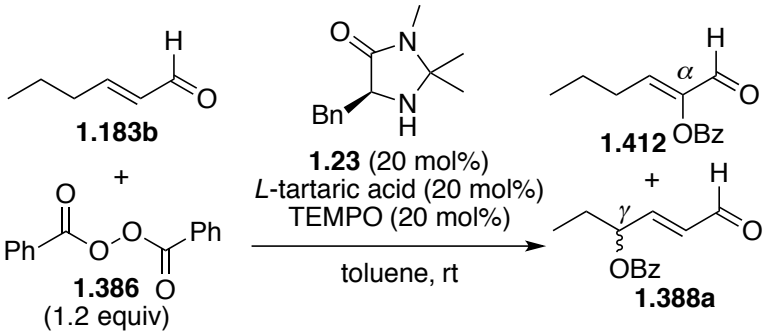
Scheme 1.75 Melchiorre's direct vinylogous aldol of α-ketoesters with dienamine activated α,β-unsaturated ketones via bifunctional organocatalysis.[132]



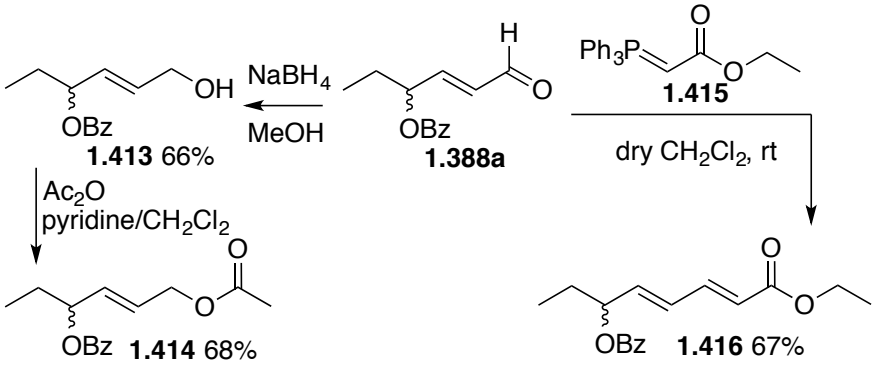
In 2014, Gryko and coworkers reported their attempts at regioselective γ-oxidation using dienamine catalysis.[133] Dienamine catalyzed γ-oxidation of *trans*-2-hexenal (**1.183b**) was tested with a number of primary and secondary amino acids and their derivatives, but ultimately MacMillan imidazolidinone catalyst **1.23** was able to provide the two easily distinguishable products, **1.388a** and **1.412** (eq 1, **Scheme 1.76**). Further optimizations showed that the cleanest reactions were achieved in toluene with radical scavenger,

TEMPO. Product yield increased with increasing p*K*a of the acid additive, and *L*-tartaric acid was able to suppress unwanted side products and the competing α-oxidation. Unfortunately, the highest yield of γ-benzoyloxylation product **1.388a** obtained was 26% and the product was racemic, but the products were readily modifiable (eq 2).

Scheme 1.76 Gryko's attempts at selective γ-oxidation of *trans*-2-hexenal via dienamine catalysis.[133]



(1)

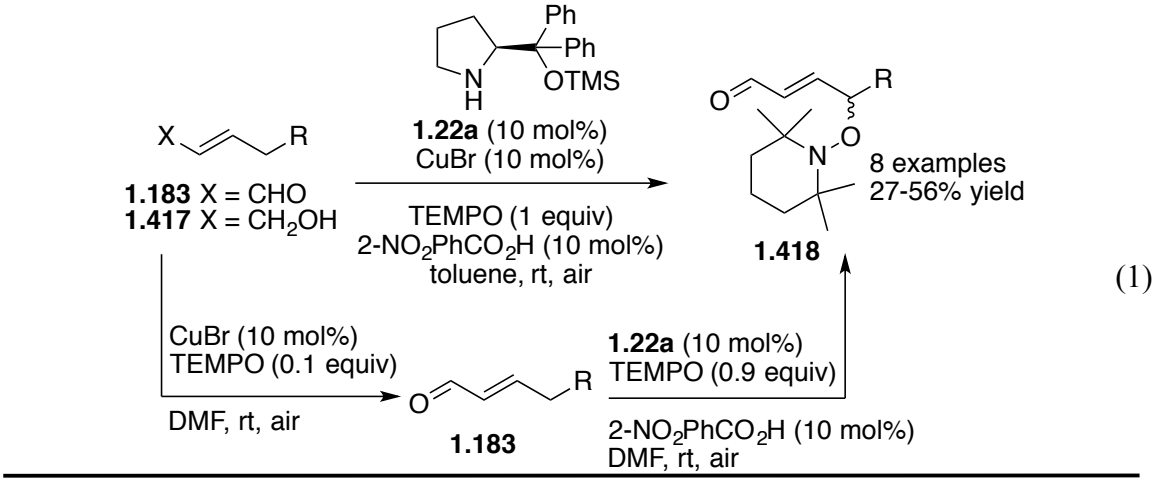


(2)

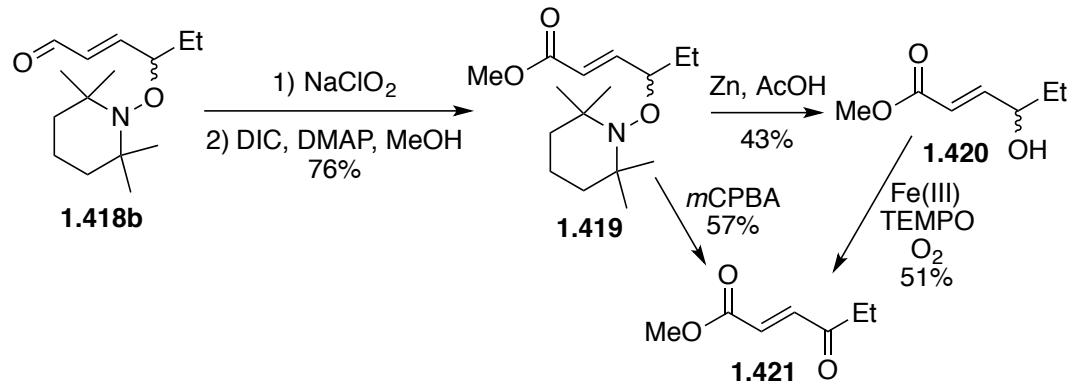
In 2014, Jang and coworkers reported a different strategy for γ-oxidation, a copper-dienamine cocatalyzed reaction.[134] They used TEMPO, activated by catalytic CuBr, as the source for oxygen addition to the corresponding dienamine of α,β-unsaturated aldehydes **1.183** to synthesize γ-aminooxylated products **1.418** (eq 1, **Scheme 1.77**). Noting that CuBr and TEMPO are also reagents for the catalytic oxidation of alcohols, they developed a one-pot synthesis of **1.418** from unsaturated alcohols (**1.417**), through either a single step or sequential addition procedure. Regardless of the route, yields of products **1.418** were low

to moderate at best, as well as racemic. Product utility was demonstrated by oxidation of **1.418b** to the corresponding ester (**1.419**) in good yield, then cleavage of the N-O bond to provide either the alcohol (**1.420**) or ketone products (**1.421**, eq 2, **Scheme 1.77**).

Scheme 1.77 Jang's cooperative copper/dienamine catalyzed γ-oxidations.[134]



(1)

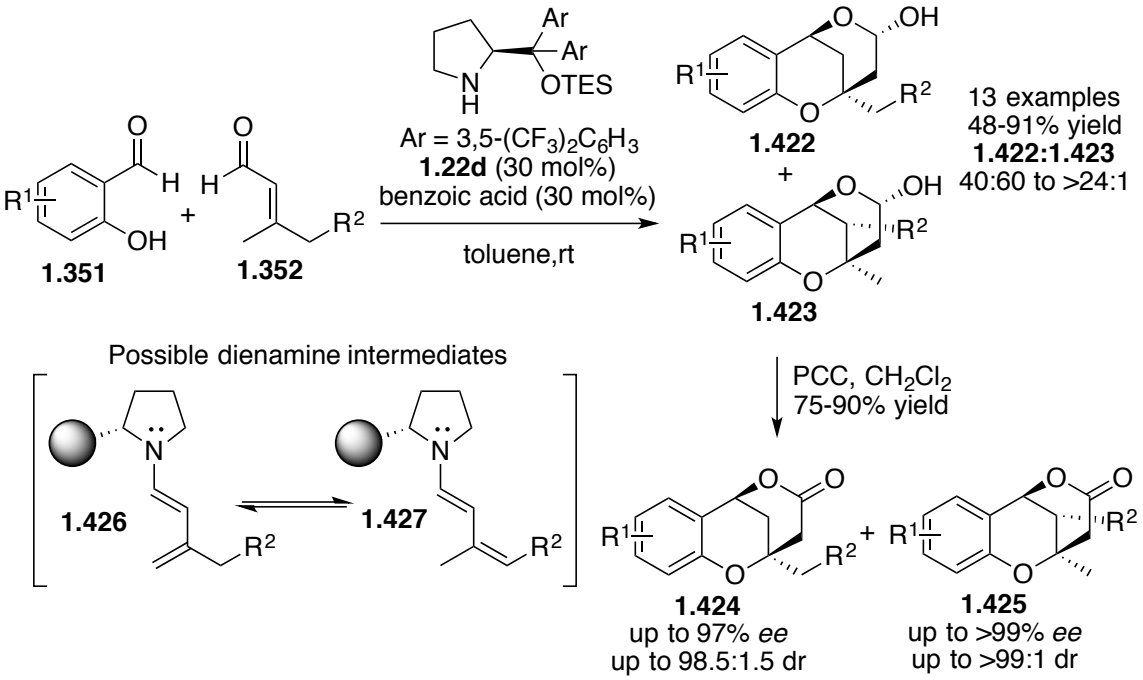


(2)

In 2015, Liu and Jiang reported a domino aldol-oxa-Michael reaction via a dienamine/iminium ion cascade, as a strategy for the synthesis of chroman-based intermediates with a quaternary stereocenter.[135] Previously, Woggon used this synthetic strategy to form α-tocopherol precursor **1.355** (**Scheme 1.62**), and now the group was interested in broadening the scope to more precursors (**1.422** and **1.424**) of the vitamin E family (**Scheme 1.78**).[121] Salicylaldehydes (**1.351**) with various substitution patterns were reacted with different α,β-unsaturated aldehydes (**1.352**). When the salicylaldehydes were

less sterically hindered, an unexpected product (**1.423**), formed via reaction with the non-terminal dienamine (**1.427**), was observed. The formation of this unexpected product was tied heavily to the steric bulk of the R^2 substitutents, being favored with fewer substitutions on the salicylaldehydes and with shorter R^2 groups on the aldehyde. This increased the potential of this method to synthesize precursors to various natural products containing multi-ring heteroatomic systems with quaternary stereocenters.

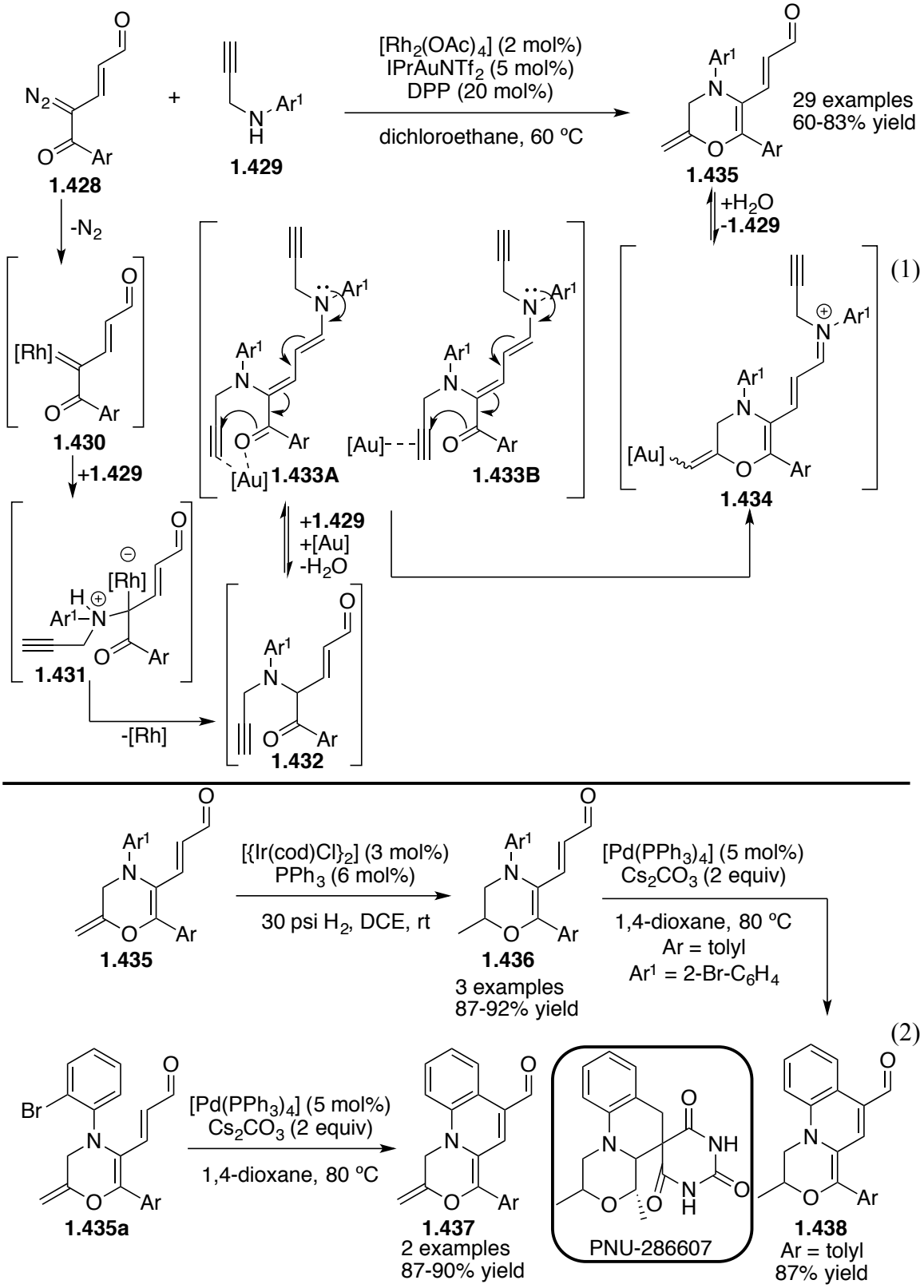
Scheme 1.78 Liu and Jiang's domino aldol-oxa-Michael synthesis of vitamin E precursors **1.422** and **1.424**.[135]



In 2016, Katukojvala and Kalepu reported a cooperative rhodium(II)/dienamine/gold(I)-catalyzed synthesis of 1,4-oxazines (**1.435**) from diazo enals (**1.426**, **Scheme 1.79**).[136] In their reaction, they developed a unique form of dienamine activation and reactivity, illustrated in the proposed mechanism in **Scheme 1.79**. The introduction of the rhodium catalyst to diazo enals (**1.426**) provides a carbenoid (**1.430**) for insertion into the N-H bond of *N*-propargyl anilines **1.428**, leading to *γ*-

aminated α,β-unsaturated aldehyde **1.432**. Additional aniline **1.428** in solution can condense onto the aldehyde and form push-pull dienamine (**1.433**). The gold catalyst then activates the alkyne and likely coordinates with the dienamine-activated δ-carbonyl (**1.433a**). Nucleophilic attack on the alkyne provided conjugated iminium-ion oxazine **1.434**, which hydrolyzes to form product **1.435**. An extensive substrate scope was run using numerous combinations of electron rich and poor aromatic groups on both the amine and the aldehyde, generating oxazine products in good yields. Subsequent transformations were also performed to show versatility, forming selectively reduced products (**1.436**, eq 2) and fused tricyclic systems (**1.437** and **1.438**, eq 2), which contain the [1,4]oxazino[4,3-a]quinolone core present in the antibacterial agent PNU-286607.

Scheme 1.79 Katukojvala and Kalepu's rhodium(II)-dienamine-gold(I) catalyzed synthesis of oxazines (**1.435**).[136]



1.3 CONCLUSIONS

Since the inception of organocatalysis, dienamine activation has provided novel routes for asymmetric modifications to α,β-unsaturated aldehydes and ketones. While normal-electron-demand and inverse-electron-demand [4+2] cycloadditions have been extensively studied for both all-carbon and heteroatomic systems, there are more limited examples of acyclic and cascade reactions. In these reactions, regioselective competition and poor stereochemical induction has led to a dearth of γ-functionalizing reactions, particularly with heteroatomic species. In fact, independent of cycloadditions, γ-aminations and γ-oxidations via organocatalysis are exceedingly rare. However, their potential to provide novel complexity and modifiability to natural product and drug precursors serve as strong motivations to find the conditions that will allow these unique transformations to proceed regioselectively and enantioselectively.

1.4 REFERENCES

(1) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107* (12), 5471–5569.
(2) Stork, G.; Terrell, R.; Szmuszkovicz, J. *J. Am. Chem. Soc.* **1954**, *76*, 2029–2030.
(3) Rutter, W. J. *Fed. Proc. Am. Soc. Exp. Biol.* **1964**, *23*, 1248.
(4) Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215–2228.
(5) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223–4251.
(6) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10* (1958), 496–497.
(7) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39* (12), 1615–1621.
(8) Spencer, T. A.; Neel, H. S.; Flechtner, T. W.; Zayle, R. A. *Tet. Lett.* **1965**, *6* (43), 3889–3897.
(9) Agami, C.; Meynier, F.; Puchot, C.; Guilhem, J.; Pascard, C. *Tetrahedron* **1984**, *40* (6), 1031–1038.
(10) Limbach, M. *Tet. Lett.* **2006**, *47*, 3843–3847.
(11) Seebach, D.; Beck, A. K.; Badine, D. M.; Limbach, M.; Eschenmoser, A.; Treasurywala, A. M.; Hobi, R.; Prikoszovich, W.; Linder, B. *Helv. Chim. Acta* **2007**, *90* (3), 425–471.
(12) List, B. *Angew. Chem. Int. Ed.* **2010**, *49* (10), 1730–1734.
(13) Zhou, P.; Zhang, L.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2012**, *77* (5), 2526–2530.
(14) List, B.; Lerner, R. a; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
(15) Ahrendt, K. A.; Borths, C. J.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.
(16) Bui, T.; Barbas, C. F. *Tet. Lett.* **2000**, *41* (36), 6951–6954.
(17) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124* (24), 6798–6799.
(18) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346* (12), 1435–1439.
(19) Cobb, A. J. a; Shaw, D. M.; Longbottom, D. a; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3* (1), 84–96.
(20) Sundén, H.; Dahlin, N.; Ibrahem, I.; Adolfsson, H.; Córdova, A. *Tet. Lett.* **2005**, *46* (19), 3385–3389.
(21) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44* (27), 4212–4215.
(22) Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127* (19), 6964–6965.
(23) Shen, Z.; Zhang, Y.; Jiao, C.; Li, B.; Ding, J.; Zhang, Y. *Chirality* **2007**, *19* (4), 307–312.
(24) Dong, Z.; Jin, X.; Wang, P.; Min, C.; Zhang, J.; Chen, Z.; Zhou, H. B.; Dong, C. *Arkivoc* **2011**, No. 9, 367–380.
(25) McGarraugh, P. G.; Brenner, S. E. *Org. Lett.* **2009**, *11* (24), 5654–5657.
(26) Appayee, C.; Brenner-Moyer, S. E. *Org. Lett.* **2010**, *12* (15), 3356–3359.
(27) McGarraugh, P. G.; Brenner-Moyer, S. E. *Org. Lett.* **2011**, *13* (24), 6460–6463.
(28) McGarraugh, P. G.; Jones, J. H.; Brenner-Moyer, S. E. *J. Org. Chem.* **2011**, *76*

(15), 6309–6319.
(29) Mannich, C.; Handke, K.; Roth, K. *Eur. J. Inorg. Chem.* **1936**, *69* (9), 2112–2123.
(30) Snyder, H. R.; Hasbrouck, R. B.; Richardson, J. F. *J. Am. Chem. Soc.* **1939**, *61* (4), 3558–3560.
(31) Enders, D.; Meyer, O. *Liebigs Ann.* **1996**, 1023–1035.
(32) Ramachary, D. B.; Reddy, Y. V. *European J. Org. Chem.* **2012**, *2012* (5), 865–887.
(33) Serebryakov, E. P.; Nigmatov, A. G.; Shcherbakov, M. A.; Struchkova, M. I. *Russ. Chem. Bull.* **1998**, *47* (1), 82–90.
(34) Nigmatov, A. G.; Serebryakov, E. P. *Russ. Chem. Bull.* **1993**, *42*, 213.
(35) Thayumanavan, R.; Dhevalapally, B.; Sakthivel, K.; Tanaka, F.; Barbas, C. F. *Tet. Lett.* **2002**, *43* (21), 3817–3820.
(36) Enders, D.; Meyer, O.; Raabe, G. *Synthesis (Stuttg).* **1992**, 1242–1244.
(37) Barluenga, J.; Aznar, F.; Valdés, C.; Martin, A.; García-Granda, S.; Martin, E. *J. Am. Chem. Soc.* **1993**, *115*, 4403–4404.
(38) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1997**, *62*, 6746–6753.
(39) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1998**, *63*, 10052–10056.
(40) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126* (19), 5962–5963.
(41) Momiyama, N.; Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129* (5), 1190–1195.
(42) Hong, B. C.; Wu, M. F.; Tseng, H. C.; Liao, J. H. *Org. Lett.* **2006**, *8* (11), 2217–2220.
(43) Hong, B. C.; Tseng, H. C.; Chen, S. H. *Tetrahedron* **2007**, *63* (13), 2840–2850.
(44) Hong, B. C.; Wu, M. F.; Tseng, H. C.; Huang, G. F.; Su, C. F.; Liao, J. H. *J. Org. Chem.* **2007**, *72*, 8459–8471.
(45) Bench, B. J.; Liu, C.; Evett, C. R.; Watanabe, C. M. H. *J. Org. Chem.* **2006**, *71* (25), 9458–9463.
(46) Fishkin, N. E.; Sparrow, J. R.; Allikmets, R.; Nakanishi, K. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102* (20), 7091–7096.
(47) Fishkin, N. E.; Pescitelli, G.; Itagaki, Y.; Berova, N.; Allikmets, R.; Nakanishi, K.; Sparrow, J. R. *Invest. Ophthalmol. Vis. Sci.* **2004**, *45E-abstra*, 1803.
(48) Holst, P. B.; Anthoni, U.; Christophersen, C.; Nielsen, P. H.; Bock, K. *Acta Chem. Scand.* **1994**, *48*, 765–768.
(49) Peters, L.; Wright, A. D.; Kehraus, S.; Gündisch, D.; Tilotta, M. C.; König, G. M. *Planta Med.* **2004**, *70*, 883–886.
(50) Peters, L.; König, G. M.; Wright, A. D.; Pukall, R.; Stackebrandt, E.; Eberl, L.; Riedel, K. *Appl. Environ. Microbiol.* **2003**, *69*, 3469–3475.
(51) de Figueiredo, R. M.; Fröhlich, R.; Christmann, M. *Angew. Chem. Int. Ed.* **2008**, *47* (8), 1450–1453.
(52) Lu, L. Q.; Xing, X. N.; Wang, X. F.; Ming, Z. H.; Wang, H. M.; Xiao, W. J. *Tet. Lett.* **2008**, *49*, 1631–1635.
(53) Bencivenni, G.; Wu, L. Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M. P.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 7200–7203.

(54) Lan, Y. B.; Zhao, H.; Liu, Z. M.; Liu, G. G.; Tao, J. C.; Wang, X. W. *Org. Lett.* **2011**, *13* (18), 4866–4869.
(55) Feng, X.; Zhou, Z.; Zhou, R.; Zhou, Q.-Q.; Dong, L.; Chen, Y.-C. *J. Am. Chem. Soc.* **2012**, *134* (48), 19942–19947.
(56) Bencivenni, G.; Galzerano, P.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Proc. Natl. Acad. Sci.* **2010**, *107* (48), 20642–20647.
(57) Orue, A.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Org. Lett.* **2012**, *14* (14), 3740–3743.
(58) Cassani, C.; Melchiorre, P. *Org. Lett.* **2012**, *14* (21), 5590–5593.
(59) Trost, B. M.; Brennan, M. K. *Synthesis (Stuttg).* **2009**, 3003.
(60) Cui, H. L.; Tanaka, F. *Chem. - A Eur. J.* **2013**, *19* (20), 6213–6216.
(61) Wang, Z. Y.; Wong, W. T.; Yang, D. *Org. Lett.* **2013**, *15* (19), 4980–4983.
(62) Massolo, E.; Benaglia, M.; Annunziata, R.; Palmieri, A.; Celentano, G.; Forni, A. *Adv. Synth. Catal.* **2014**, *356* (2-3), 493–500.
(63) Liu, L.; Daka, P.; Sarkisian, R.; Deng, Y.; Wheeler, K.; Wang, H. *Synth.* **2014**, *46* (10), 1339–1347.
(64) Zhou, R.; Xiao, W.; Yin, X.; Zhan, G.; Chen, Y.-C. *Acta Chim. Sin.* **2014**, *72* (7), 862–866.
(65) Han, B.; He, Z. Q.; Li, J. L.; Li, R.; Jiang, K.; Liu, T. Y.; Chen, Y. C. *Angew. Chem. Int. Ed.* **2009**, *48* (30), 5474–5477.
(66) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128* (39), 12973–12980.
(67) Han, B.; Li, J. L.; Ma, C.; Zhang, S. J.; Chen, Y. C. *Angew. Chem. Int. Ed.* **2008**, *47* (51), 9971–9974.
(68) Li, J. L.; Kang, T. R.; Zhou, S. L.; Li, R.; Wu, L.; Chen, Y. C. *Angew. Chem. Int. Ed.* **2010**, *49* (36), 6418–6420.
(69) Li, J. L.; Zhou, S. L.; Chen, P. Q.; Dong, L.; Liu, T. Y.; Chen, Y. C. *Chem. Sci.* **2012**, *3* (6), 1879–1882.
(70) Dang, A. T.; Miller, D. O.; Dawe, L. N.; Bodwell, G. J. *Org. Lett.* **2008**, *10* (2), 233–236.
(71) Nohara, A.; Kuriki, H.; Saijo, T.; Ukawa, K.; Murata, T.; Kanno, M.; Sanno, Y. *J. Med. Chem.* **1975**, *18* (1), 34–37.
(72) Kumar, S.; Singh, B. K.; Pandey, A. K.; Kumar, A.; Sharma, S. K.; Raj, H. G.; Prasad, A. K.; Van der Eycken, E.; Parmar, V. S.; Ghosh, B. *Bioorg. Med. Chem.* **2007**, *15* (8), 2952–2962.
(73) Patonay, T.; Kiss-Szikszai, A.; Silva, V. M. L.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; Jeko, J. *Eur. J. Org. Chem.* **2008**, 1937–1946.
(74) Gong, J.; Xie, F.; Chen, H.; Hu, Y. *Org. Lett.* **2010**, *12* (17), 3848–3851.
(75) Chen, H.; Xie, F.; Gong, J.; Hu, Y. *J. Org. Chem.* **2011**, *76* (20), 8495–8500.
(76) Kim, D.; Hong, S. *Org. Lett.* **2011**, *13* (16), 4466–4469.
(77) Jia, Z. J.; Jiang, H.; Li, J. L.; Gschwend, B.; Li, Q. Z.; Yin, X.; Grouleff, J.; Chen, Y. C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133* (13), 5053–5061.
(78) Albrecht, Ł.; Dickmeiss, G.; Weise, C. F.; Rodríguez-Escrich, C.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2012**, *51* (52), 13109–13113.
(79) Albrecht, L.; Dickmeiss, G.; Weise, C. F.; Rodríguez-Escrich, C.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2012**, *51* (52), 13109–13113.

(80) Yin, X.; Zheng, Y.; Feng, X.; Jiang, K.; Wei, X. Z.; Gao, N.; Chen, Y. C. *Angew. Chem. Int. Ed.* **2014**, *53* (24), 6245–6248.
(81) Wetzel, S.; Bon, R. S.; Kumar, K.; Waldmann, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 10800–10826.
(82) Waldmann, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 6284–6285.
(83) Narayan, R.; Potowski, M.; Jia, Z.-J.; Antonchick, A. P.; Waldmann, H. *Acc. Chem. Res.* **2014**, *47* (4), 1296–1310.
(84) Weise, C. F.; Lauridsen, V. H.; Rambo, R. S.; Iversen, E. H.; Olsen, M. L.; Jørgensen, K. A. *J. Org. Chem.* **2014**, *79* (8), 3537–3546.
(85) Albrecht, Ł.; Albrecht, A.; Krawczyk, H.; Jørgensen, K. A. *Chem. Eur. J.* **2010**, *16* (1), 28–48.
(86) Breuer, E. *The Chemistry of Organophosphorus Compounds*, Vol. 4.; Hartly, F. R., Ed.; John Wiley and Sons: New York, 1996.
(87) Grif, K.; Dierich, M. P.; Pfaller, K.; Miglioli, P. A.; Allerberger, F. *J. Antimicrob. Chemother.* **2001**, *48* (0305-7453), 209–217.
(88) Bhatia, M. S.; Jit, P. *Experientia* **1976**, *32* (9), 1111.
(89) Reddy, M. V. N.; Kumar, B. S.; Balakrishna, A.; Reddy, C. S.; Nayak, S. K.; Reddy, C. D. *ARKIVOC* **2007**, *14*, 246–254.
(90) Polozov, A. M.; Cremer, S. E. *J. Organomet. Chem.* **2002**, *646*, 153–160.
(91) Pakulski, Z.; Zarmojski, A. *Pol. J. Chem.* **1995**, *69*, 509.
(92) Aspinall, G. O.; Monteiro, M. A.; Pang, H.; Kurjanczyk, L. A.; Penner, J. L. *Carbohydr. Res.* **1995**, *279*, 227–244.
(93) Aspinall, G. O.; Monteiro, M. A.; Pang, H. *Carbohydr. Res.* **1995**, *279*, 245–264.
(94) Gu, J.; Ma, C.; Li, Q. Z.; Du, W.; Chen, Y. C. *Org. Lett.* **2014**, *16* (15), 3986–3989.
(95) Li, W.; Wei, J.; Jia, Q.; Du, Z.; Zhang, K.; Wang, J. *Chem. Eur. J.* **2014**, *20*, 6592–6596.
(96) Izquierdo, C.; Esteban, F.; Parra, A.; Alfaro, R.; Alemán, J.; Fraile, A.; Ruano, J. L. G. *J. Org. Chem.* **2014**, *79* (21), 10417–10433.
(97) Donslund, B. S.; Monleón, A.; Larsen, J.; Ibsen, L.; Jørgensen, K. A. *Chem. Commun.* **2015**, *51* (71), 13666–13669.
(98) Petrov, V. A. *Fluorinated Heterocyclic Compounds: Synthesis; Chemistry and Application*; Wiley: Hoboken, 2009.
(99) Dua, R.; Shrivastava, S.; Sonwane, S. K.; Srivastava, S. K. *Adv. Biol. Res. (Rennes).* **2011**, *5* (3), 120–144.
(100) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330.
(101) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; Del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114* (4), 2432–2506.
(102) Herman, G. A.; Stevens, C.; Van Dyck, K.; Bergman, A.; Yi, B.; De Smet, M.; Snyder, K.; Hilliard, D.; Tanen, M.; Tanaka, W.; Wang, A. Q.; Zeng, W.; Musson, D.; Winchell, G.; Davies, M. J.; Ramael, S.; Gottesdiener, K. M.; Wagner, J. A. *Clin. Pharmacol. Ther.* **2005**, *78* (6), 675–688.
(103) Orue, A.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2015**, *54* (10), 3043–3046.
(104) Wang, S.; Rodriguez-Escrich, C.; Pericàs, M. A. *Org. Lett.* **2016**, *18* (3), 556–559.

(105) Ramachary, D. B.; Ramakumar, K.; Kishor, M. *Tet. Lett.* **2005**, *46*, 7037–7042.
(106) McAndrew, B. A. *J. Chem. Soc. Perkin Trans. I* **1979**, *7*, 1837–1846.
(107) Begbie, A. L.; Golding, B. T. *J. Chem. Soc. Perkin Trans. I* **1972**, *4*, 602–605.
(108) Ramachary, D. B.; Ramakumar, K.; Bharanishashank, A.; Narayana, V. V. *J. Comb. Chem.* **2010**, *12* (6), 855–876.
(109) Ramachary, D. B.; Narayana, V. V.; Ramakumar, K. *European J. Org. Chem.* **2008**, No. 23, 3907–3911.
(110) Ramachary, D. B.; Ramakumar, K.; Narayana, V. V. *J. Org. Chem.* **2007**, *72* (4), 1458–1463.
(111) Ramachary, D. B.; Narayana, V. V; Prasad, M. S.; Ramakumar, K. *Org. Biomol. Chem.* **2009**, *7*, 3372–3378.
(112) Ramachary, D. B.; Ramakumar, K.; Narayana, V. V. *Chem. Eur. J.* **2008**, *14* (30), 9143–9147.
(113) Ramachary, D. B.; Shashank, A. B. *Chem. Eur. J.* **2013**, *19* (39), 13175–13181.
(114) Biagi, G.; Calderone, V.; Giorgi, I.; Livi, O.; Scartoni, V.; Baragatti, B.; Martinotti, E. *Farm.* **2001**, *56* (11), 841–849.
(115) Li, W.; Jia, Q.; Du, Z.; Wang, J. *Chem. Commun.* **2013**, *49* (86), 10187–10189.
(116) Ramachary, D. B.; Ramakumar, K. *Eur. J. Org. Chem.* **2011**, No. 14, 2599–2605.
(117) Shashank, A. B.; Ramachary, D. B. *Org. Biomol. Chem.* **2015**, *13* (18), 5110–5114.
(118) Chen, S.-H.; Hong, B.-C.; Su, C.-F.; Sarshar, S. *Tet. Lett.* **2005**, *46*, 8899–8903.
(119) Utsumi, N.; Zhang, H.; Tanaka, F.; Barbas, C. F. *Angew. Chem. Int. Ed.* **2007**, *46* (11), 1878–1880.
(120) Vesely, J.; Dziedzic, P.; Córdova, A. *Tet. Lett.* **2007**, *48* (39), 6900–6904.
(121) Liu, K.; Chougnet, A.; Woggon, W. D. *Angew. Chem. Int. Ed.* **2008**, *47* (31), 5827–5829.
(122) Marqués-López, E.; Herrera, R. P.; Marks, T.; Jacobs, W. C.; Könning, D.; De Figueiredo, R. M.; Christmann, M. *Org. Lett.* **2009**, *11* (18), 4116–4119.
(123) Han, B.; Xiao, Y.-C.; He, Z.-Q.; Chen, Y.-C. *Org. Lett.* **2009**, *11* (20), 4660–4663.
(124) Renzi, P.; Overgaard, J.; Bella, M. *Org. Biomol. Chem.* **2010**, *8* (5), 980–983.
(125) Bergonzini, G.; Vera, S.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2010**, *49* (50), 9685–9688.
(126) Demoulin, N.; Lifchits, O.; List, B. *Tetrahedron* **2012**, *68* (37), 7568–7574.
(127) Stiller, J.; Marqués-López, E.; Herrera, R. P.; Fröhlich, R.; Strohmann, C.; Christmann, M. *Org. Lett.* **2011**, *13* (1), 70–73.
(128) Silvi, M.; Cassani, C.; Moran, A.; Melchiorre, P. *Helv. Chim. Acta* **2012**, *95* (10), 1985–2006.
(129) Albrecht, Ł.; Dickmeiss, G.; Cruz Acosta, F.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134* (5), 2543–2546.
(130) Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Angew. Chem. Int. Ed.* **2012**, *51* (17), 4104–4107.
(131) Halskov, K. S.; Naicker, T.; Jensen, M. E.; Jørgensen, K. A. *Chem. Commun.* **2013**, *49* (57), 6382–6384.
(132) Bastida, D.; Liu, Y.; Tian, X.; Escudero-Adán, E.; Melchiorre, P. *Org. Lett.* **2013**, *15* (1), 220–223.
(133) Chrominski, M.; Giedyk, M.; Gryko, D. *ARKIVOC* **2014**, 135–145.

(134) Ho, X.-H.; Jung, W.-J.; Shyam, P. K.; Jang, H.-Y. *Catal. Sci. Technol.* **2014**, *4* (7), 1914.
(135) Liu, K.; Jiang, X. *Eur. J. Org. Chem.* **2015**, 6423–6428.
(136) Kalepu, J.; Katukojvala, S. *Angew. Chem. Int. Ed.* **2016**, 7831–7835.

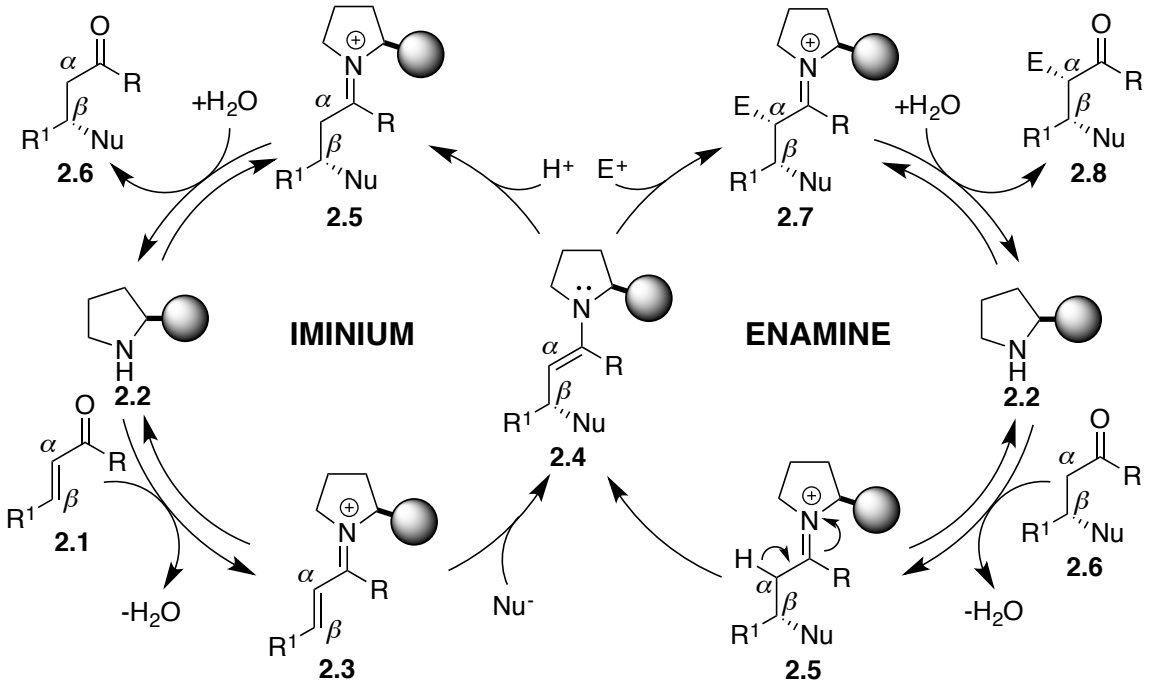
CHAPTER 2

SCOPE OF A DIENAMINE-IMINIUM CASCADE THAT PRODUCES γ-AMINO ALCOHOLS

2.1 Organocatalytic Cascade Reactions

One of the benefits of organocatalysis is the efficient asymmetric synthesis of natural product and drug precursors without the assistance of expensive and potentially toxic metal catalysts. One of the avenues to rapidly developing asymmetric molecular complexity has been cascade reactions, in which nucleophiles and electrophiles are subjected to reactive iminium- (**2.3**) and enamine-intermediates (**2.4**), successively, to form asymmetric α,β-difunctionalized aldehydes (**2.8**) or ketones in a one-pot process (**Scheme 2.1**).

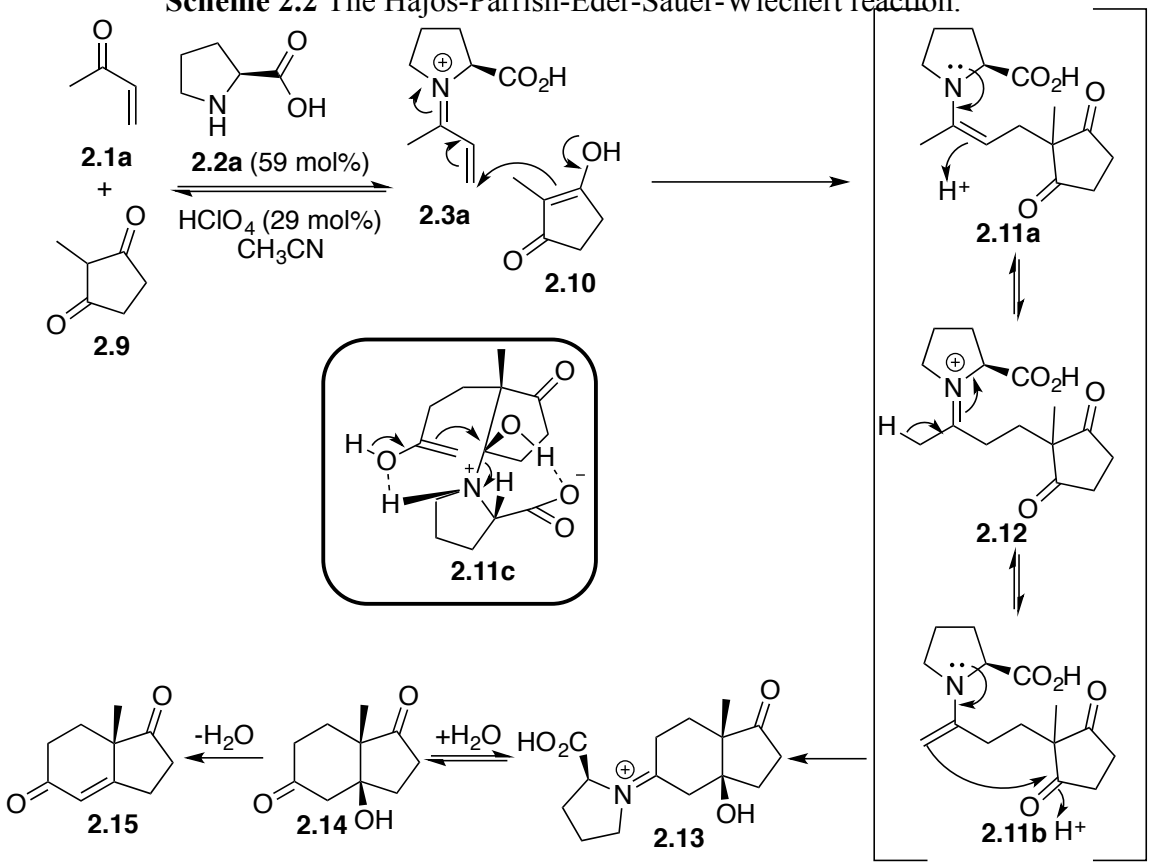
Scheme 2.1 Iminium-enamine cascade mechanism.



This has been accomplished in numerous ways, starting at the advent of

organocatalysis with the Hajos-Parrish-Eder-Sauer-Wiechert reaction (**Scheme 2.2**) to form the Wieland-Miescher ketone (**2.15**).[1,2] The mechanism involves the condensation of a catalytic amount of proline (**2.2a**) onto ketone **2.1a** to create the LUMO-lowered conjugated iminium ion intermediate **2.3a**, which is activated as a Michael acceptor for conjugate addition by nucleophile **2.10**, the tautomer of **2.9**. Intramolecular aldol of the product **2.12**, followed by hydrolysis produces **2.14**, which can be dehydrated to form the Wieland-Miescher ketone (**2.15**).

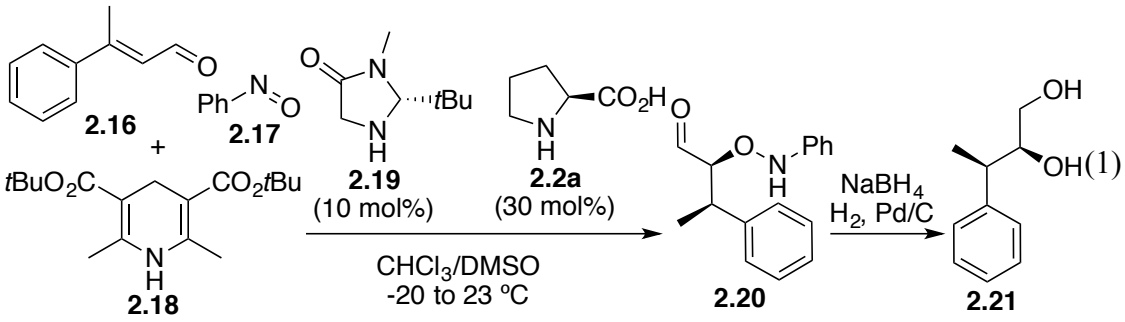
Scheme 2.2 The Hajos-Parrish-Eder-Sauer-Wiechert reaction.[1,2]

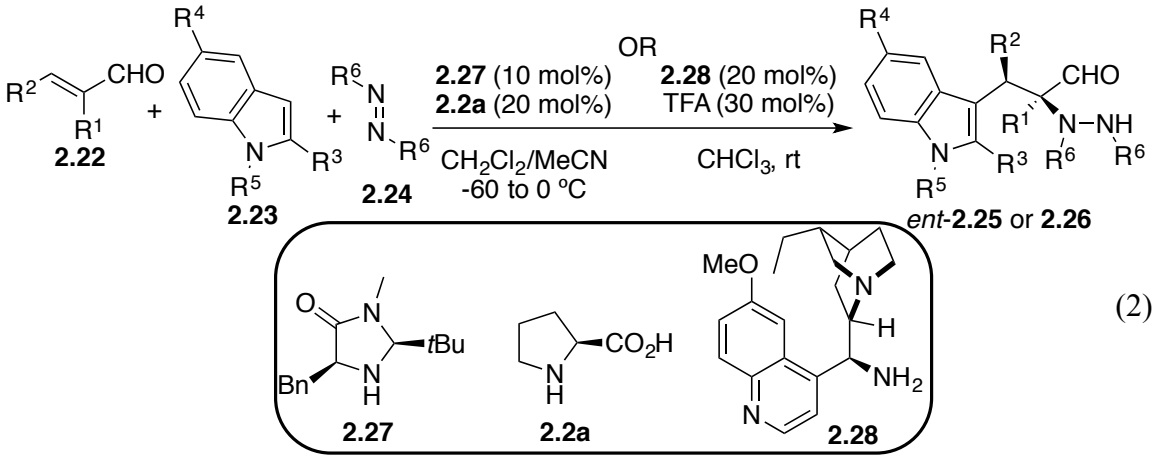


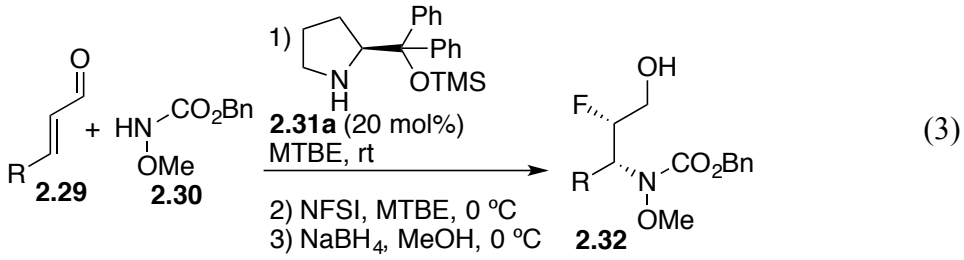
With the increase in organocatalytic research in the 2000's, came an increase in the variety of organocascade reactions. Some examples of iminium-enamine asymmetric cascade reactions are shown in **Scheme 2.3**.[3–6] Introducing heteroatomic cascades in particular has allowed the introduction of more labile bonds to assist in the derivatization

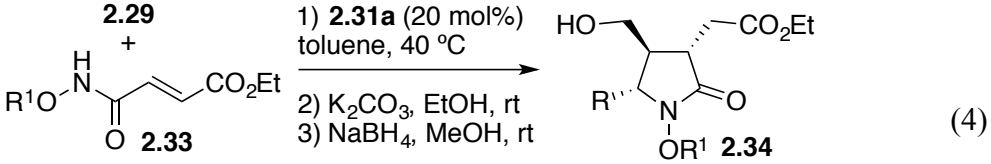
of these intermediates in subsequent steps (eq 1), as well as increased the syntheses of highly desirable medicinal moieties (eq 3) and heterocycles (eq 4). As mentioned in **Chapter 1**, however, organocatalytic cascade reactions originating in the γ-position of α,β-unsaturated aldehydes were virtually nonexistent, except for ring-forming reactions, prior to this research. Thus studies were begun to expand the capabilities of organocatalysis.

Scheme 2.3 Examples of iminium-enamine organocascade reactions.[3–6]





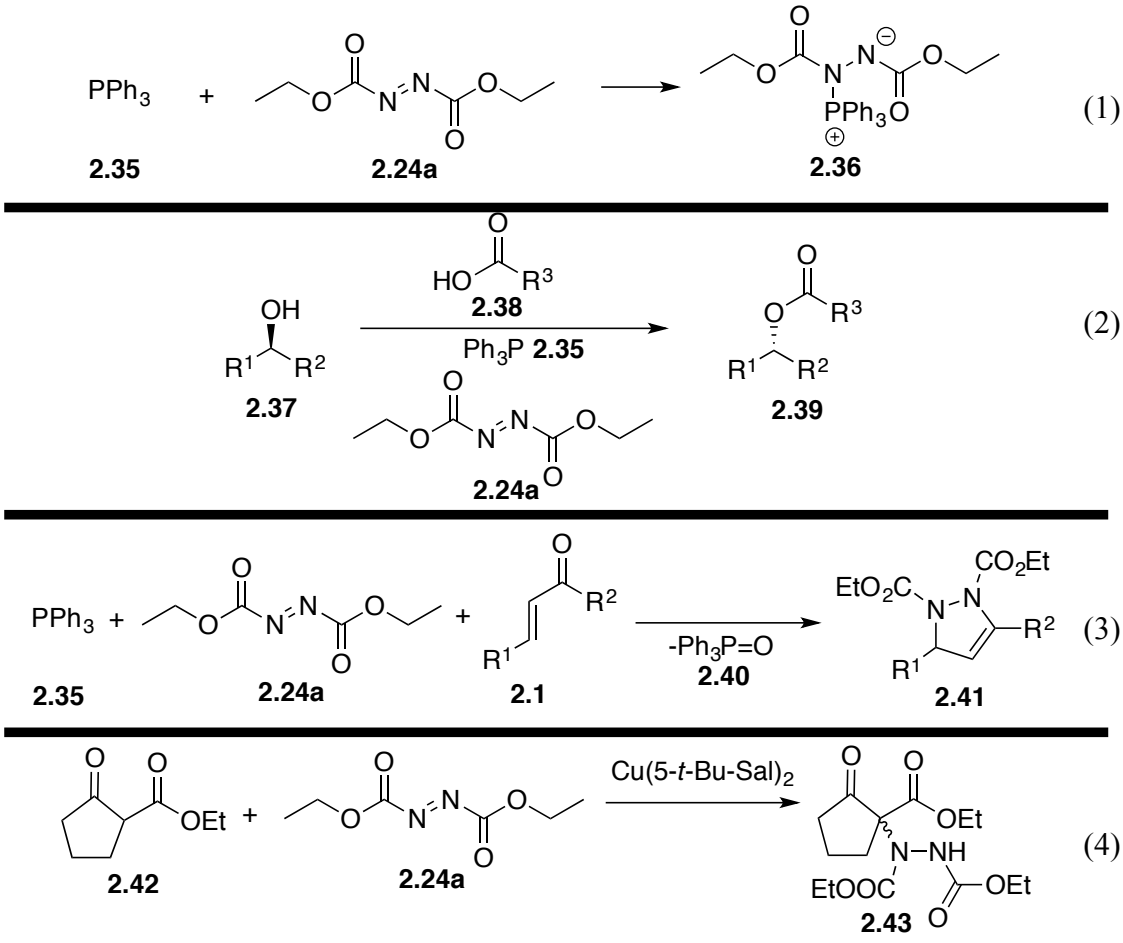




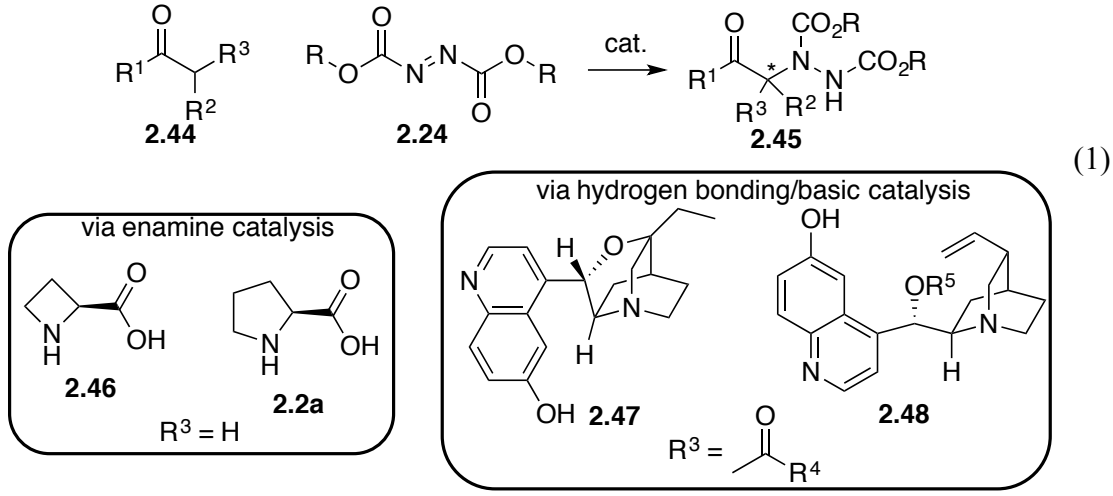
2.1.1 The Electrophile: Diethyl Azodicarboxylate

Diethyl azodicarboxylate (DEAD) **2.24a** is an electrophile that has many uses in organic synthesis (**Scheme 2.4**). As a good Michael acceptor, DEAD can be reacted with triphenylphosphine to form the "Huisgen Zwitterion" **3.18** (eq 1) to participate in the Mitsunobu reaction (eq 2).[7–10] It can also be used to form unique heterocycles (eq 3), as well as be used directly in aminations (eq 4).[11,12] DEAD has proven to be an essential building block in the synthesis of complex organic compounds. It is also tolerant of a variety of organocatalysts and conditions for enamine-catalyzed Michael reactions, in both single component (eq 1, **Scheme 2.5**) and cascade reactions (eq 2).[13–23]

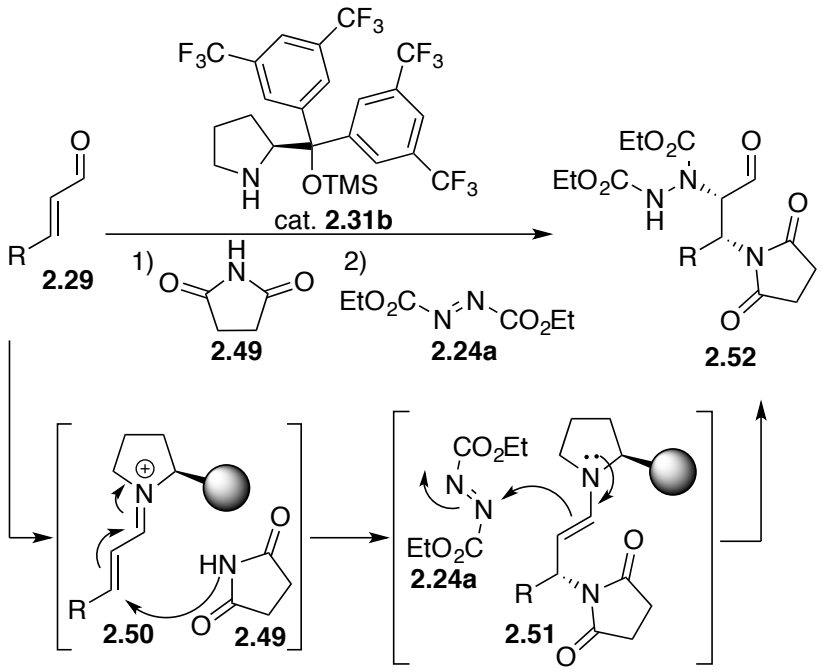
Scheme 2.4 Uses of DEAD in organic synthesis.[7–12]



Scheme 2.5 Uses of DEAD in organocatalysis.[13–23]



(1)



(2)

2.1.2 DEAD in Dienamine Catalysis

As discussed in **Chapter 1**, Jørgensen and coworkers discovered a highly regioselective and stereoselective γ-amination between dienamine activated α,β-unsaturated aldehydes (**2.53**) and DEAD (**2.24a**).[24] Through empirical and computational experimentation, they discovered that this γ-aminated product **2.58**, was stereoselectively and exclusively regioselectively formed in the (*R*)-enantiomer through use of catalyst

2.31b, both of which were explained mechanistically through reacting via an *s*-cis dienamine (**2.55**, **Scheme 2.6**). DFT calculations had shown no significant energy difference between the α- and γ-nucleophilic position to account for the exclusively γ-regioselectivity, but the Diels-Alder reaction mechanism provided an energetically favorable explanation. Following regeneration of the iminium ion **2.57** through C-N bond cleavage, reformation of the *E*-alkene was possible without epimerization of the γ-position. This proposed [4+2] mechanism was further supported by a representative synthesis of **2.59** using *N*-methylmaleimide as a dienophile to trap and isolate the cyclic amine intermediate (**Figure 2.1**). In this research they also provided a substrate scope with moderate yields, but high enantioselectivity.

Scheme 2.6 Jørgensen's reaction and proposed mechanism for regioselective γ-amination through an *s*-cis dienamine.[24]

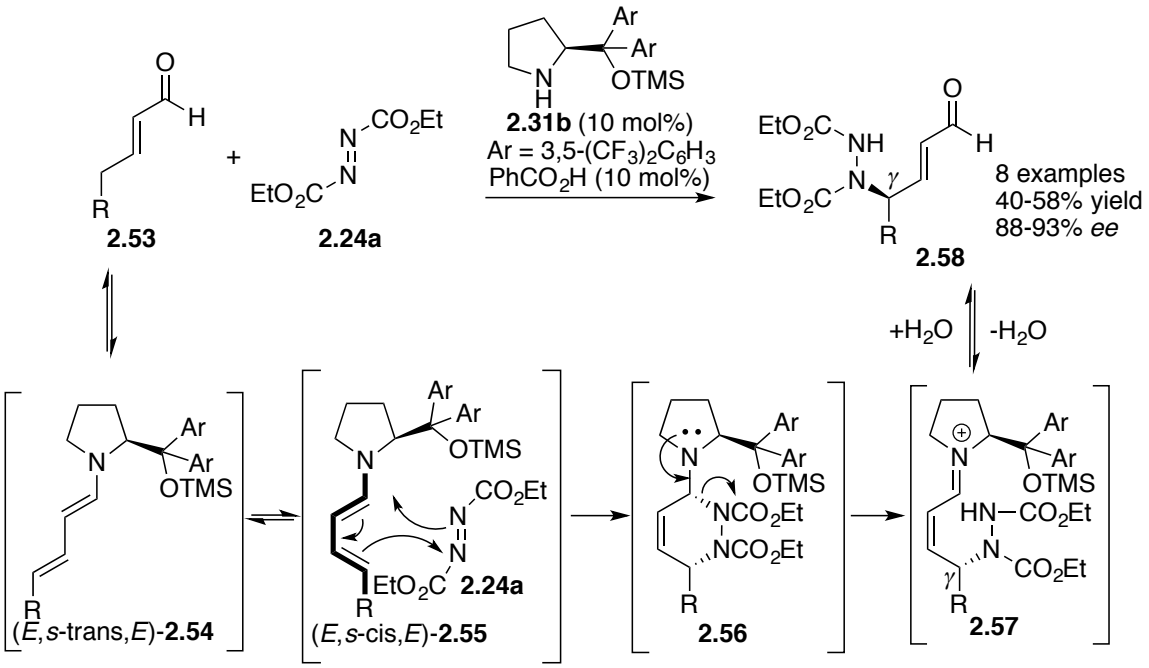
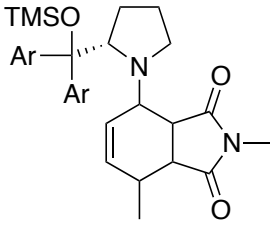


Figure 2.1 Isolable mechanistic evidence of an intermolecular Diels-Alder reaction with a dienamine intermediate



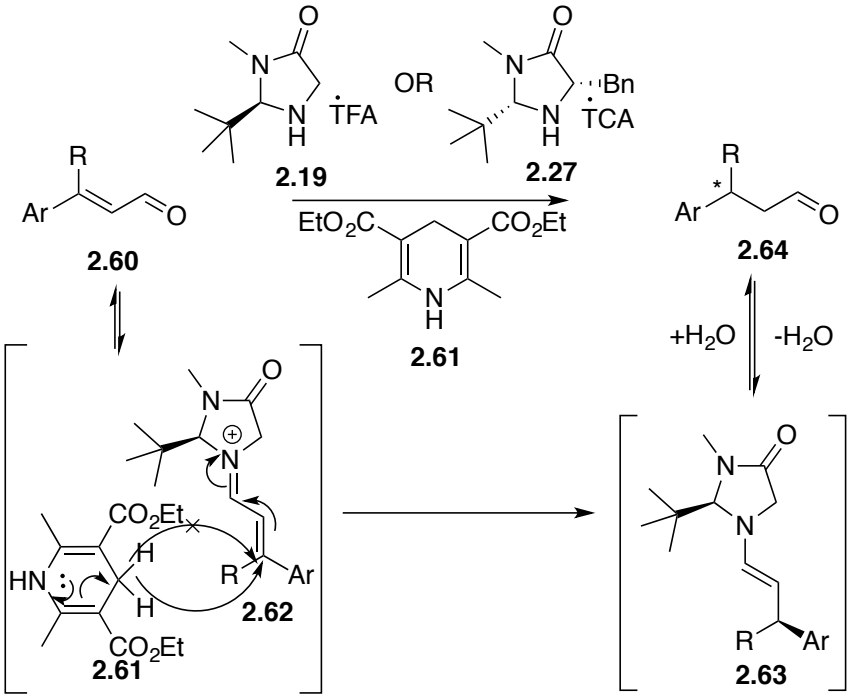
2.59

Ar = 3,5-$(CF_3)_2C_6H_3$

2.1.3 Transfer-Hydrogenation: Hantzsch Ester

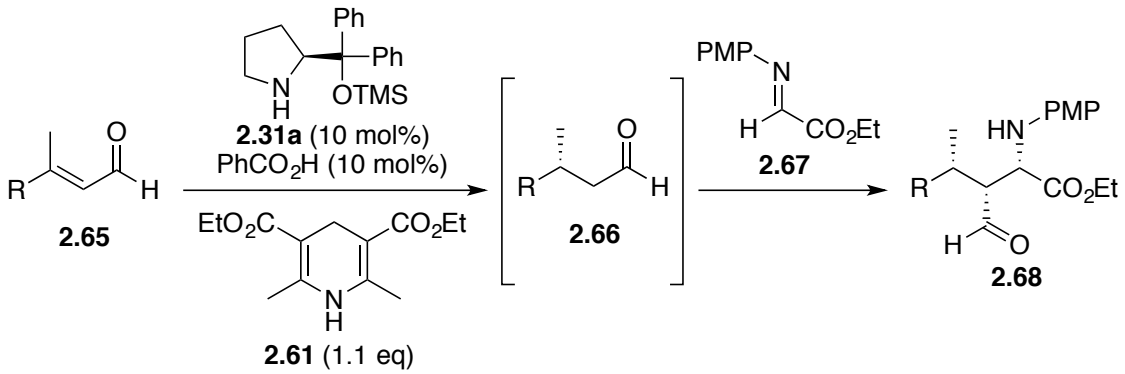
Asymmetric catalytic hydrogenations are useful in large-scale industrial production of pharmaceutical and fine chemicals. Typically, these reactions require metal catalysts or stoichiometric amounts of metal hydrides, however living organisms can accomplish these transformations efficiently with organic cofactors, such as nicotinamide adenine dinucleotide (NADH), in combination with metalloenzymes.[25,26] In 2005, David MacMillan and Benjamin List independently reported the first synthetic metal-free catalytic asymmetric transfer-hydrogenations of α,β-unsaturated aldehydes using diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (Hantzsch ester), **2.61**, in the presence of MacMillan imidazolidinone catalysts **2.19** or **2.27** (**Scheme 2.7**).[27,28]

Scheme 2.7 Organocatalytic transfer-hydrogenation with Hantzsch ester.[27,28]



In 2006, Zhao and Córdova demonstrated an organocascade reaction utilizing Hantzsch ester in the iminium catalyzed step, providing asymmetrically reduced product **2.66**, which was then followed by enamine catalyzed asymmetric Mannich reaction to form **2.68** (**Scheme 2.8**).[29]

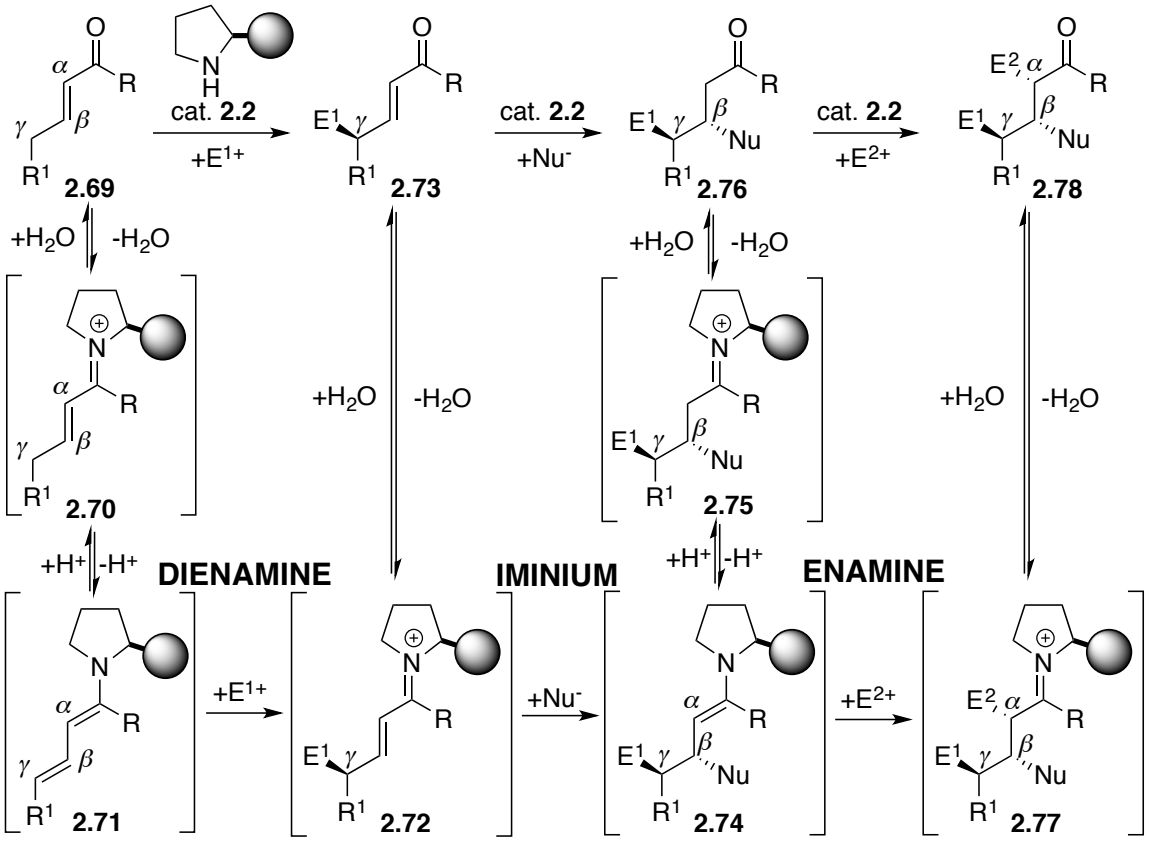
Scheme 2.8 Organocatalytic reductive Mannich reaction.[29]



2.1.4 The planned dienamine/iminium catalyzed organocascade.

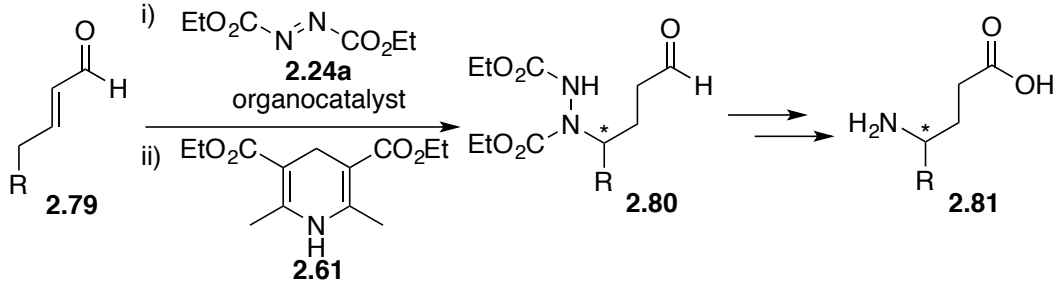
With the introduction of the acyclic, regioselective and stereoselective dienamine catalyzed formation of γ-functionalized products, there was potential for the development of asymmetric dienamine/iminium/enamine catalyzed triple cascades (**Scheme 2.9**). In such a procedure, following dienamine catalyzed formation of **2.72**, a nucleophile could be introduced for conjugate addition, generating the γ,β-difunctionalized enamine (**2.74**). This could then react with a proton or another electrophile in solution and hydrolyze to form either the γ,β-difunctionalized product (**2.76**) or the γ,β,α-trifunctionalized product (**2.78**), respectively.

Scheme 2.9 Proposed dienamine/iminium/enamine cascade mechanism.



In order for this development to occur, the dienamine/iminium catalyzed double cascade would first need to be studied. To accomplish this, DEAD (**2.24a**) would be used for the dienamine step, due to the exclusive regioselectivity and high stereoselectivity. For the iminium step, Hantzsch ester (**2.61**) would be used as a proof of principle. While this hydrogen source would not provide a stereocenter in the *β*-position, it would test the ability of the iminium ion to accept conjugate addition in the presence of the sterically bulky *γ*-hydrazine obtained from the dienamine step. This would provide saturated *γ*-amino aldehydes (**2.80**), which are precursors to useful asymmetric *γ*-amino acids (**2.81**, **Scheme 2.10**).

Scheme 2.10 Proposed dienamine/iminium cascade reaction.

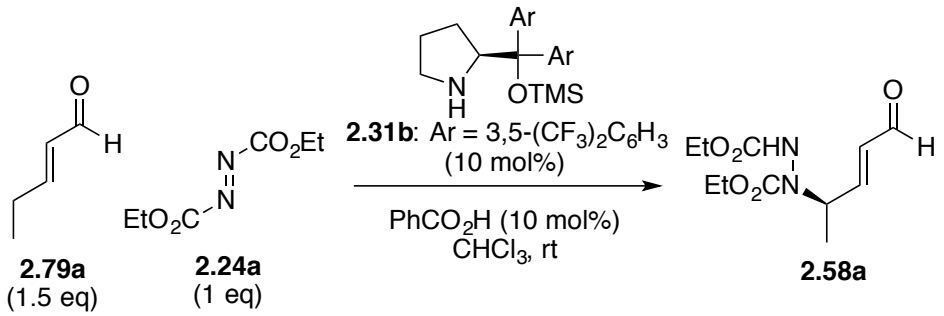


2.2 Results and Discussion

The bulk of the cascade reaction optimization was performed previously.[30] In Jørgensen's research with DEAD, he reported polymeric decomposition of DEAD in the presence of secondary amines.[23] While he was referring to succinimide (**2.49**), in this research, it was noted that this decomposition occurred in the presence of catalyst **2.31a**. This undesired reaction caused the catalyst (**2.31a**) to be fully consumed by the time DEAD was also consumed, requiring loading of an additional 10 mol% of catalyst before the introduction of Hantzsch ester in the second step. Slow addition of DEAD over 1 and 3 hours was

attempted to limit the loss of catalyst in the first step through this side-reaction after some promising data with portionwise addition (**Table 2.1**, entry 1 and entry 2). However, these reactions showed the lowest conversions by ^{1}H NMR analysis of the starting material and product aldehyde peaks, therefore slow addition was not pursued further. The final reaction conditions for the dienamine step are summarized in entry 3 of **Table 2.1**.

Table 2.1 Optimization of dienamine catalyzed step of cascade reaction.



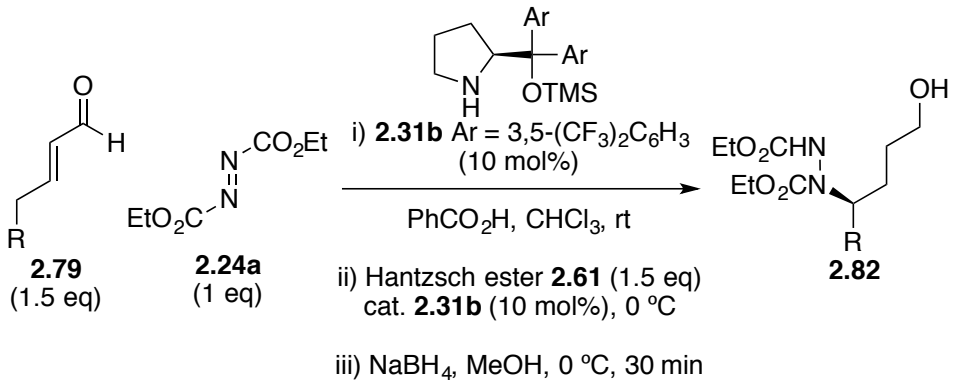
entry	concentration	slow addition	reaction time[a]	yield[b] (%)
1	2 M	3 h	22 h	33
2	2 M	1 h	20 h	35
3[c]	**0.25 M**	**--**	**16 h**	**72**

[a] Monitored by ^{1}H NMR. [b] ^{1}H NMR yield using internal standard. [c] Fully optimized conditions.

The initial optimized reaction conditions determined for the full dienamine/iminium cascade, to be used for the substrate scope, are summarized in **Table 2.2**. The reaction was initially run with 10 mol% benzoic acid as an acid additive (**Table 2.2**, entry 1 and entry 3). After some months, however, the yields began to decrease and reaction times increase. ^{1}H NMR analysis of the enal starting materials revealed the presence of acid impurity **2.83** due to air oxidation (**Scheme 2.11**). In order to rectify this

problem, all enals were freshly distilled before use and stored under argon to avoid oxidation to the acid. This initially decreased yields and increased reaction times as well, but addition of an additional 10 mol% of the benzoic acid co-catalyst during the first step of the cascade reaction improved yields and reaction times (**Table 2.2**, entry 2 and entry 4).

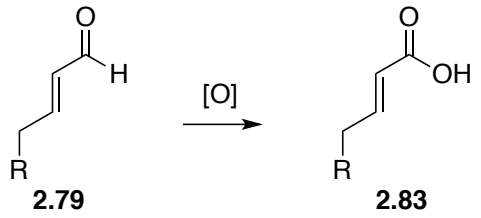
Table 2.2 Reoptimization of additive loading.



entry	R	$PhCO_2H$ (%)	time for step (i)[a]	time for step (ii)[a]	yield[b] (%)	ee[c] (%)
1	**2.79b** – Et	10	19 h	23 h	**2.82b** – 69	--
2	**2.79b** – Et	20	16 h	23 h	**2.82b** – 72	92
3	**2.79c** – *n*Pr	10	40 h	24 h	**2.82c** – 67	--
4	**2.79c** – *n*Pr	20	23 h	20 h	**2.82c** – 70	93

[a] Monitored by ^{1}H NMR. [b] Isolated yield. [c] Determined by chiral phase HPLC of 4-chlorobenzoyl chloride protected derivative.

Scheme 2.11 Air oxidation of enals over time.

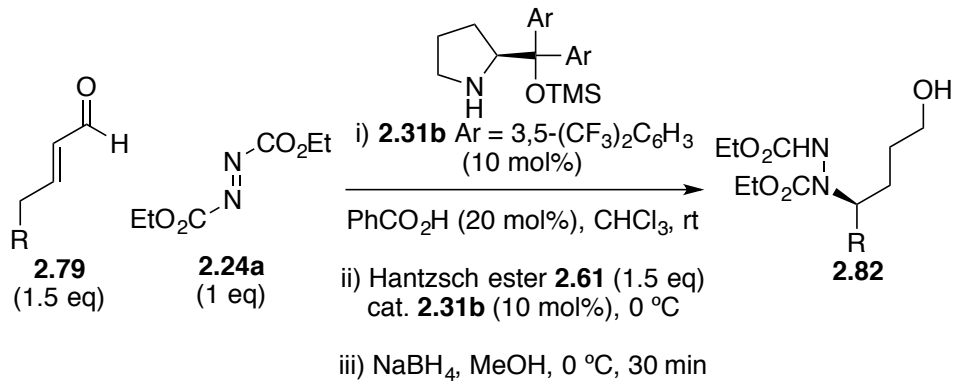


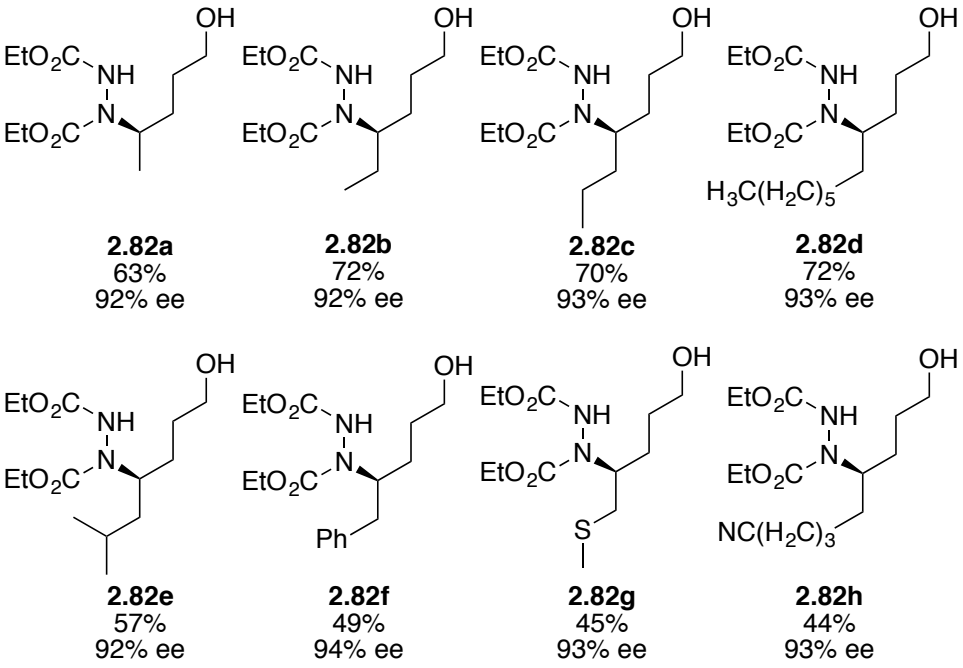
2.79 **2.83**

Using these optimal reaction conditions, the rest of the substrate scope was undertaken using various *α,β*-unsaturated aldehydes as starting materials (**Scheme 2.12**). With the exception of the reaction with trans-2-heptenal **2.79c**, full consumption of DEAD in the first step was always achieved within 16 hours. All of the substrates completed the second step in the cascade between 20 and 24 hours, with the majority taking 23 hours. Allowing the reaction to run longer than it took for complete consumption of materials in each step led to rapid decomposition and lowered yields of desired product, indicating that this method is very time-sensitive. The yields were varied between substrates. The simple, unbranched alkyl chains of the distilled commercially available enals afforded yields of 63% for **2.82a**, 72% for **2.82b**, 70% for **2.82c**, and 72% for **2.82d**, showing that these conditions are tolerant of various chain lengths. This was a significant improvement compared to Jørgensen's original data for just the dienamine catalyzed *γ*-amination with DEAD.[24] Yields with the remaining enals were moderate. The bulkier iso-butyl enal **2.79e**, gave a 57% yield of **2.82e**, and the benzyl enal, **2.79f**, gave a 49% yield of **2.82f**. This showed that this method was tolerant of steric bulk and aromatic systems. Enals **2.79g** and **2.79h** provided yields at 45% for **2.82g**, and 44% for **2.82h**, demonstrating that the methodology tolerates the presence of adjacent heteroatoms and reactive species,

respectively. It should be noted that a yield of 44% corresponds to a yield of 66% for each step.

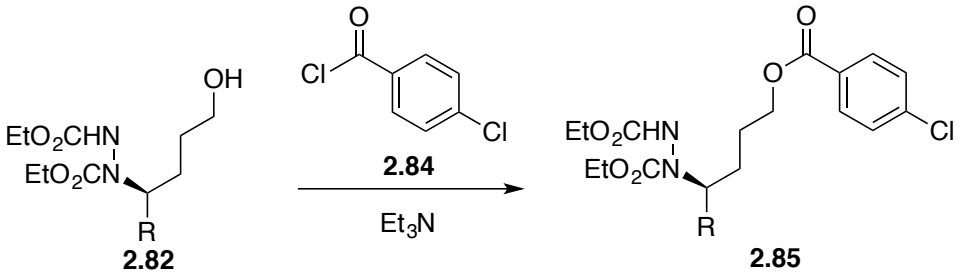
Scheme 2.12 Scope of optimized cascade reaction.





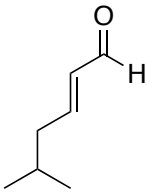
Although there was some variation in yields, enantioselectivity remained high for all substrates. All of the ee data was determined by chiral-phase HPLC of the ester derivatives (**2.85**) of the γ-amino alcohol products (**Scheme 2.13**), with the exception of **2.82f**, which did not need to be modified to enable UV detection.

Scheme 2.13 Derivatization for chiral-phase HPLC analysis.

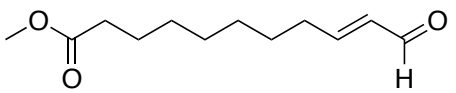


Other non-commercial enals were explored in the substrate scope for this methodology as well (**Figure 2.2**). Iso-propyl enal **2.79i** was not included in the data due to a lack of reactivity in the second step. This is most likely due to the steric bulk of the isopropyl group coupled with the steric bulk of the DEAD, which seems to be blocking the approach of Hantzsch ester to deliver the hydride for transfer-hydrogenation (**Scheme 2.14**). Due to this non-reactivity, the iso-butyl enal, **2.79e**, was used instead without any problems, to afford **2.82e**. Enal **2.79j** also had reactivity problems in the second step, which never saw full consumption of the *α,β*-unsaturated aldehydes by transfer-hydrogenation. This, coupled with a dramatically longer reaction time for the second step and gradual decomposition of aldehyde products led to the abandonment of this *α,β*-unsaturated aldehyde as a substrate.

Figure 2.2 Unsuccessful substrates.

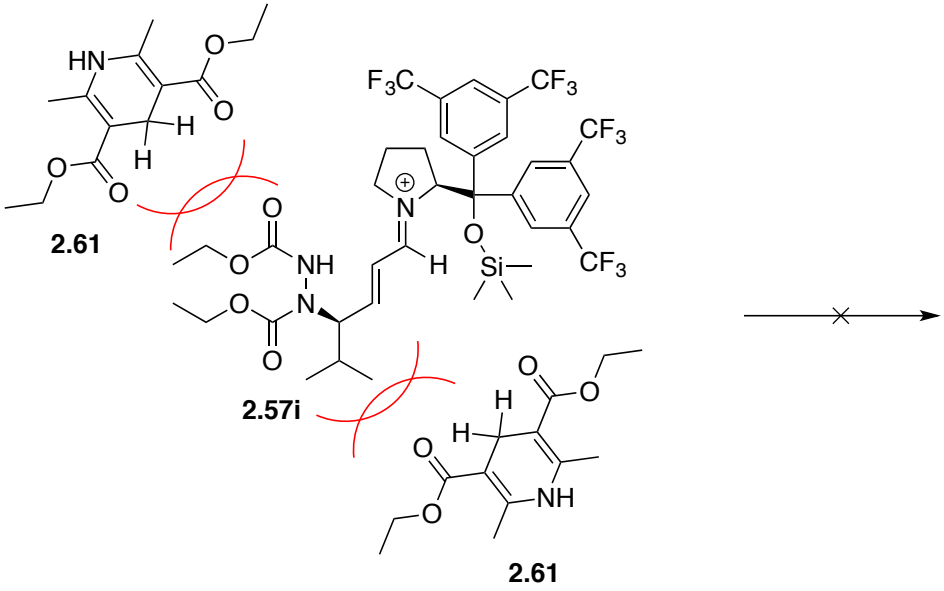


2.79i



2.79j

Scheme 2.14 Possible steric blocking of Hantzsch ester.



2.3 Conclusion

The first organocatalytic intermolecular dienamine-iminium cascade reaction was developed, using simple organic starting materials to make γ-amino alcohols.[31] These alcohols were synthesized in moderate to high yields and in high enantioselectivities, tolerating various chain lengths, some degree of steric bulk, aromaticity, heteroatoms, and reactive functional groups. This shows great potential for future intermolecular cascade reactions, leading to more complex products with two or three contiguous stereogenic centers that could be used in the synthesis of more complex molecules. This method was used in a formal synthesis of (*S*)-vigabatrin, the bioactive enantiomer of the anticonvulsant, Sabril.[31] Additionally, the use of a heteroatomic nucleophile in the second step of the γ,β-cascade provided an enantiopure β-functionalized-γ-amino alcohol, which contained vicinal stereocenters. This would serve as precedent for investigations into the use of other

nucleophiles for iminium catalyzed conjugate additions, following γ-amination in an organocascade reaction.

2.4 References

(1) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10* (1958), 496–497.
(2) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39* (12), 1615–1621.
(3) Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2009**, *48* (24), 4349–4353.
(4) Galzerano, P.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2009**, *48* (42), 7892–7894.
(5) Appayee, C.; Brenner-Moyer, S. E. *Org. Lett.* **2010**, *12* (15), 3356–3359.
(6) Yokosaka, T.; Hamajima, A.; Nemoto, T.; Hamada, Y. *Tet. Lett.* **2012**, *53* (10), 1245–1248.
(7) Cookson, R. C.; Locke, J. M. *J. Chem. Soc.* **1963**, 6062–6064.
(8) Brunn, E.; Huisgen, R. *Angew. Chem. Int. Ed.* **1969**, *8* (7), 513–515.
(9) Huisgen, R. *The Adventure Playground of Mechanisms and Novel Reactions: Profiles, Pathways, and Dreams*; Seeman, J. I., Ed.; American Chemical Society: Washington DC, 1994.
(10) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40* (10), 2380–2382.
(11) Nair, V.; Mathew, S. C.; Biju, A. T.; Suresh, E. *Angew. Chem. Int. Ed.* **2007**, *46* (12), 2070–2073.
(12) Comelles, J.; Moreno-Mañas, M.; Pérez, E.; Roglans, A.; Sebastián, R. M.; Vallribera, A. *J. Org. Chem.* **2004**, *69* (20), 6834–6842.
(13) Janey, J. M. *Angew. Chem. Int. Ed.* **2005**, *44* (28), 4292–4300.
(14) Duthaler, R. O. *Angew. Chem. Int. Ed.* **2003**, *42* (9), 975–978.
(15) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41* (10), 1790–1793.
(16) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124* (22), 6254–6255.
(17) List, B. *J. Am. Chem. Soc.* **2002**, *124* (20), 5656–5657.
(18) Suri, J. T.; Steiner, D. D.; Barbas, C. F. *Org. Lett.* **2005**, *7* (18), 3885–3888.
(19) Chowdari, N. S.; Barbas, C. F. *Org. Lett.* **2005**, *7* (5), 867–870.
(20) Vogt, H.; Vanderheiden, S.; Bräse, S. *Chem. Commun.* **2003**, No. 19, 2448–2449.
(21) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126* (26), 8120–8121.
(22) Liu, X.; Li, H.; Deng, L. *Org. Lett.* **2005**, *7* (2), 167–169.
(23) Jiang, H.; Nielsen, J. B.; Nielsen, M.; Jørgensen, K. A. *Chem. Eur. J.* **2007**, *13*, 9068–9075.
(24) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128* (39), 12973–12980.
(25) Dickinson, F. M.; Dalziel, K. *Nature* **1967**, *214*, 31–33.
(26) Alberts, B.; Bray, D.; Lewis, J.; Raff, M.; Roberts, K.; Watson, J. D. *Molecular Biology of the Cell*, 3rd ed.; Garland: New York & London, 2002.
(27) Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44* (1), 108–110.
(28) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127* (1), 32–33.
(29) Zhao, G.-L.; Córdova, A. *Tet. Lett.* **2006**, *47*, 7417–7421.

(30) Optimization performed by Dr. Chandrakumar Appayee.
(31) Appayee, C.; Fraboni, A. J.; Brenner-Moyer, S. E. *J. Org. Chem.* **2012**, *77* (19), 8828–8834.

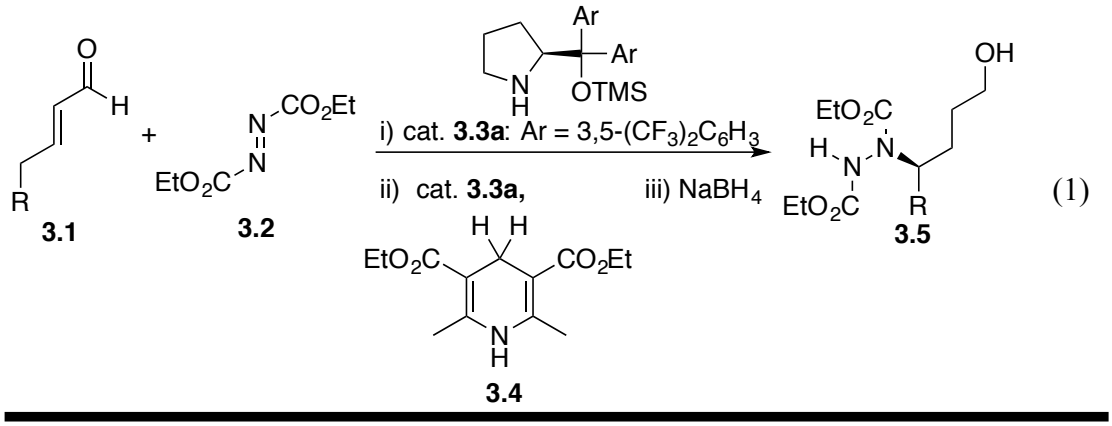
CHAPTER 3

DIENAMINE-IMINIUM CASCADE REACTIONS

3.1 OXIMES

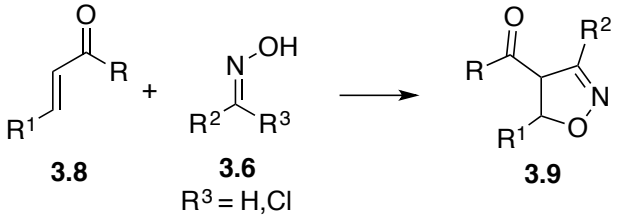
In **Chapter 2** the first cascade reaction entailing intermolecular dienamine and iminium-catalyzed reactions was discussed. This reaction used diethyl azodicarboxylate (DEAD), **3.2**, as an electrophile and Hantzsch ester (**3.4**) as a transfer-hydrogenation reagent (**Scheme 3.1**, eq 1).[1] In the conclusion, it was mentioned that a heteroatomic nucleophile was also introduced using this methodology, providing precedent for nucleophiles other than a hydride, and producing a compound with γ,β-vicinal stereocenters. This involved using benzaldehyde oxime, **3.6a**, as an oxa-Michael donor to replace the Hantzsch ester in the second step, providing **3.7** in a moderate unoptimized yield with high ee and dr (**Scheme 3.1**, eq 2).

Scheme 3.1 Dienamine-iminium cascade reactions.

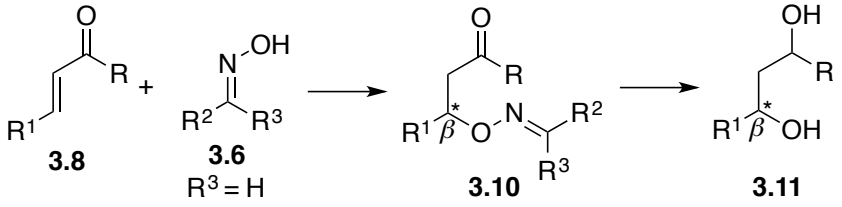


Benzaldehyde oxime was chosen as the nucleophile for a number of reasons. Oximes have long been established as powerful oxygen nucleophiles for [3+2]-dipolar cycloadditions and conjugate additions in organic synthesis.[2–10] They are effective in cycloadditions providing highly desirable isoxazolines (**Scheme 3.2**, eq 1). They have also been used in direct linear syntheses to provide β-alkoxy aldehyde and ketone building blocks that possess labile bonds for the formation of β-hydroxy compounds (**Scheme 3.2**, eq 2).[5,11–22]

Scheme 3.2 Reactions with oximes.



(1)

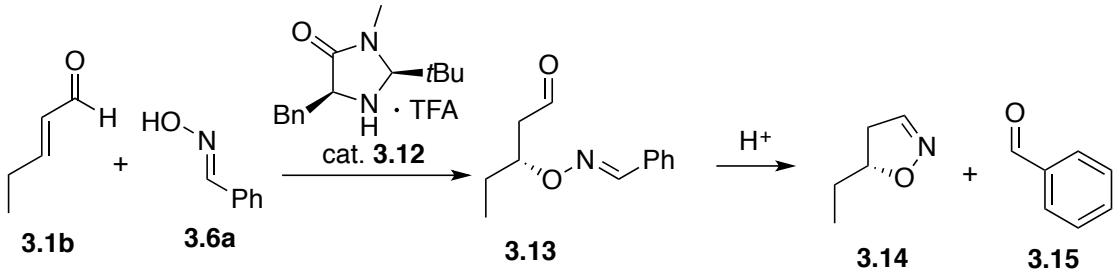


(2)

The favorability of oxime reactivity stems from the presence of an α-nitrogen, creating a softer (HSAB) oxygen nucleophile than that present in alcoholic and phenolic nucleophiles. The benefits of this α-effect include: a diminished reversibility in conjugate additions, allowing for highly asymmetric products; a preference for 1,4- versus 1,2-additions to activated enals, preventing undesired acetal formation; and facile N-O bond cleavage, broadening the scope of this methodology as a precursor to other heteroatomic compounds.[12–14,23] Oximes have also been reported in organocatalytic reactions, including in the asymmetric syntheses of 1,3-diols (**3.11**, **Scheme 3.2**), as well as 2-isoxazolines

(**3.14**, **Scheme 3.3**), via iminium-catalyzed oxa-Michael reactions.[15,16,20,21,24,25]

Scheme 3.3 Organocatalytic synthesis of 2-isoxazolines.

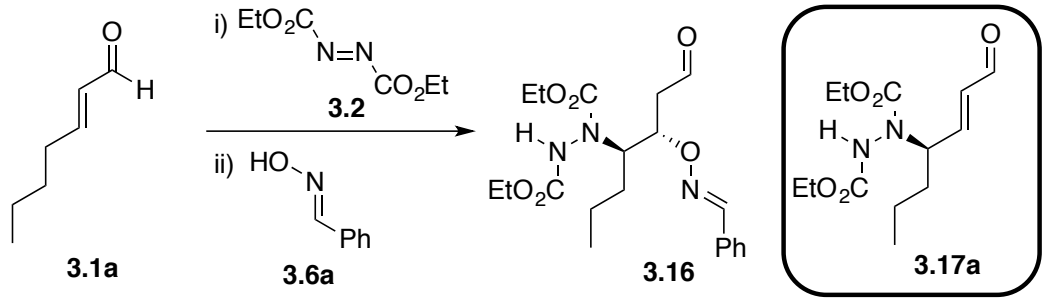


3.1.1 Results and Discussion

The optimization of this cascade was limited by the solvents and concentrations that had already been optimized for the *γ*-amination step of the cascade, therefore toluene (3 M) and chloroform (0.375 M) were tested (**Table 3.1**). The solvent conditions from the previous project (chloroform, 0.375 M) proved too dilute, as incomplete consumption (inc) of both **3.1a** and **3.17a** during the second step of the reaction was observed (entry 1), therefore toluene was used for the rest of the optimization. As with the cascade in **Chapter 2**, due to the polymeric degradation of catalyst **3.3a** in the presence of DEAD in first step of the cascade, additional catalyst needed to be added in the second step of the reaction.[1,26] The first reactions using toluene were run to determine reaction time and work out conditions for isolation (entries 2-3). In these reactions it was determined that additional acid in the second step of the reaction reduced the time to complete consumption of starting aldehydes by about four hours. These reactions also helped determine that both the aldehyde product, **3.16**, and the corresponding alcohol were unstable on silica gel. The amount of decomposition of the alcohol could be limited, but not eliminated entirely, by running column chromatography with a $N_{2(l)}$ cooled mobile-phase. This slowed the

optimization process significantly; therefore, the majority of reaction yields were determined by running crude ^{1}H NMR spectra with a *tert*-butyl methylether (TBME) or cyclohexene internal standard added upon reaction completion. The internal standard peaks observed by ^{1}H NMR were integrated against the product aldehyde protons to obtain the yield. Initially, 2-nitrobenzaldehyde was also tested as a potential internal standard due to the presence of its ^{1}H NMR chemical shifts in an unobstructed region of the spectra for these reactions, however it began reacting with the products upon addition to the reaction mixture (entry 4). It was determined by running parallel reactions that both TBME and cyclohexene were effective internal standards for this transformation (entries 5-6), therefore throughout the rest of the optimization they were used interchangeably depending on availability.

Table 3.1 Optimization of cascade reaction.[a]



entry	cat (step ii) (mol %)	$PhCO_2H$ (step i/ii) (mol %)	time (step i/ii)	yield[b,c]
1[d]	6.7	13.3/0	17 h/5 d	inc
2[e]	6.7	6.7/6.7	19 h/24 h	nd
3[e]	6.7	6.7/0	18 h/28 h	nd
4[e]	6.7	6.7/6.7	21 h/ 24 h	--[f]
5[e]	6.7	6.7/6.7	42 h/24 h	13%[g]
6[e]	6.7	6.7/6.7	42 h/24 h	13%[h]
7	6.7	13.3/0	16 h/21 h	13%
8	10	6.7/3.3	16 h/2 h	inc (29%)
9	10	6.7/3.3	15 h/6 h	inc (15%)
10	10	6.7/3.3	16 h/6 h	24% (26%)
11	10	6.7/3.3	16 h/6 h	18% (15%)
12[e,i]	6.7	6.7/6.7	17.5h/22.5h	28%[j]
13[k]	6.7	6.7/6.7	17.5h/6d	inc
14[l]	6.7	6.7/6.7	18h/22.5h	30%

[a] Reaction conditions: Step i) **3.1a**, **3.2** (neat, 0.67 equiv), cat. **3.3a** (0.067 equiv), $PhCO_2H$, toluene (3 M), rt. Step ii) **3.6a** (3 equiv), cat. **3.3a**, $PhCO_2H$, 0 ºC. [b] Determined by ^1H NMR using TBME or cyclohexene as an internal standard. [c] Number in parentheses = percentage of unreacted **3.1a** and **3.17**. [d] Reaction solvent = $CHCl_3$ (0.375 M). [e] Used **3.2** (40% solution in toluene). [f] Internal standard, 2-nitrobenzaldehyde, reacted with products. [g] TBME internal standard used. [h] Cyclohexene internal standard used. [i] **3.16** reduced to alcohol *in situ*: using $NaBH_4$ (1.5 equiv), MeOH (0.5 M), 30 min. [j] Yield determined by ^1H NMR of isolated alcohol product using TBME as an internal standard. [k] 100 mg 4 Å molecular sieves added to reaction in step ii. [l] 10 mg 4 Å molecular sieves added to reaction in step ii.

In the early cascade reactions using toluene, a 40% solution of DEAD in toluene was used, instead of the neat DEAD used in the previous project and in $CHCl_3$. After a few

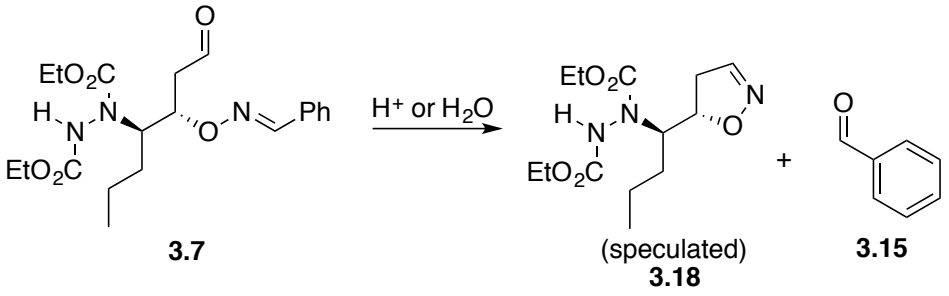
weeks of using this reagent, the reaction time for full consumption of DEAD in the first step dramatically increased due to degradation of DEAD, as determined by TLC and ^{1}H NMR. Therefore, neat DEAD was used alongside the catalyst and acid loadings used in **Chapter 2**, which decreased the reaction time of the first step to 16 hours while maintaining the yields observed in entries 5 and 6 (entry 7). Decreasing the acid additive in the first step of the reaction had no effect on reaction time, but increasing the additional loading of catalyst and benzoic acid in the second step increased the yield and the reaction time (entries 8-11). The reaction was observed to be making significant progress in the second step after only two hours of reactivity, however this reactivity slowed significantly, as the reaction was still incomplete after six hours and appeared to decompose overnight (entries 8-9). Checking the yield at the six-hour time point showed an increased yield, but also a 6 percentage point difference between isolated yields and a large variation in the consumption of starting materials (entries 10-11). This inconsistency led to investigations of the second step of the reaction independent of the cascade (**Table 3.2**).

While the cascade was optimized further, it was determined that decreasing the catalyst loading and increasing acid loading in the second step improved the yield, resulting in an isolated yield of the alcohol of 28% (entry 12, **Table 3.1**). It was also at this point that one of the major side products being formed was identified by ^{1}H NMR as benzaldehyde (**3.15**). This was attributed to the hydrolytic formation of 2-isoxazoline **3.18**, which would typically form under strongly acidic conditions (**Scheme 3.4**).[20] Due to this revelation, and the fact that the products were unstable on silica gel, it was decided that potential sources of hydrolysis, such as acid or water, should be removed from the synthetic process if not necessary for the catalytic cycle. It was thought that the addition

of 4 Å molecular sieves could reduce the amount of hydrolytic cyclization possibly occurring as a side-reaction and increase reaction yield, however this either prevented reactivity altogether or had a minimal effect depending on the amount added, likely due to water's role in the catalytic cycle (entries 13 and 14).

Another potential hydrolytic source was the $CDCl_3$ NMR solvent being used to determine the yield, which can contain water and acid impurities, therefore the NMR spectrum was run in CD_3CN. This increased the yield significantly, even though benzaldehyde was still present as a side product (entry 1, **Table 3.2**). Following this reaction, there was still inconsistency in the reaction times and yields (entries 2-3). Lowering the reaction temperature to -30 ºC to attempt to limit this side reactivity increased the reaction time dramatically and led to an incomplete reaction (entry 4).

Scheme 3.4 Proposed formation of benzaldehyde.

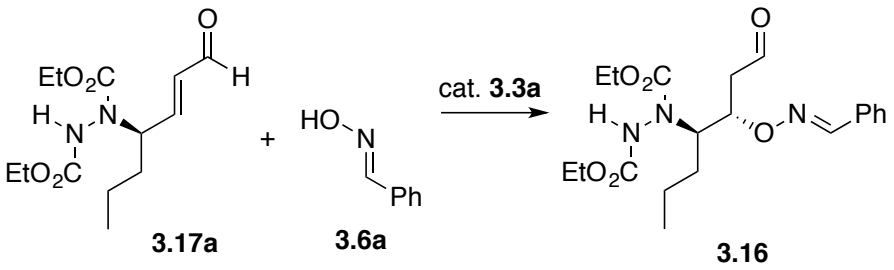


At this point, a new batch of benzaldehyde oxime was synthesized, which formed a low melting yellow solid, rather than the viscous yellow liquid previously synthesized. This, however, was consistent with most literature accounts of the melting point and there was no detectable difference in the TLC or ^1H NMR spectra, so optimization studies were resumed.[27–33] This new batch of oxime resulted in increased reaction times, while still providing inconsistent yields from reaction to reaction, ranging from 35% to 61% at the 24

hour time point (entries 6-8). The 61% yield outlier (entry 7) was likely due to inhomogeneity in the reaction, as a result of stirring being interrupted at some point during the night. Another reaction was also allowed to continue stirring for 5 days following reaction completion, during which time no decomposition was observed by TLC or ^{1}H NMR (entry 5). This is an indication that the time sensitivity observed in the cascade reaction is likely due to the presence of components from the first reaction step.

Dramatically decreasing the concentration to 0.25 M increased the reaction time significantly and led to an incomplete reaction (entry 9), while decreasing the concentration to 1 M improved the yield (entry 10). However, a comparable yield was accomplished when the cold room being used to run 0 ºC reactions for long periods of time unexpectedly warmed to room temperature overnight (entry 11). This led to running the reaction at room temperature in entries 13 and 14, which in a single iminium step achieved the highest yield of 62% (entry 14). This route, however, was not pursued further as this optimization would not improve upon the previously established reaction conditions (eq 2, **Scheme 3.1**), and the presence of the previous step's components in the cascade would likely increase decomposition at room temperature.

Table 3.2 Independent optimization of step ii of cascade reaction.[a]



3.17a **3.6a** **3.16**

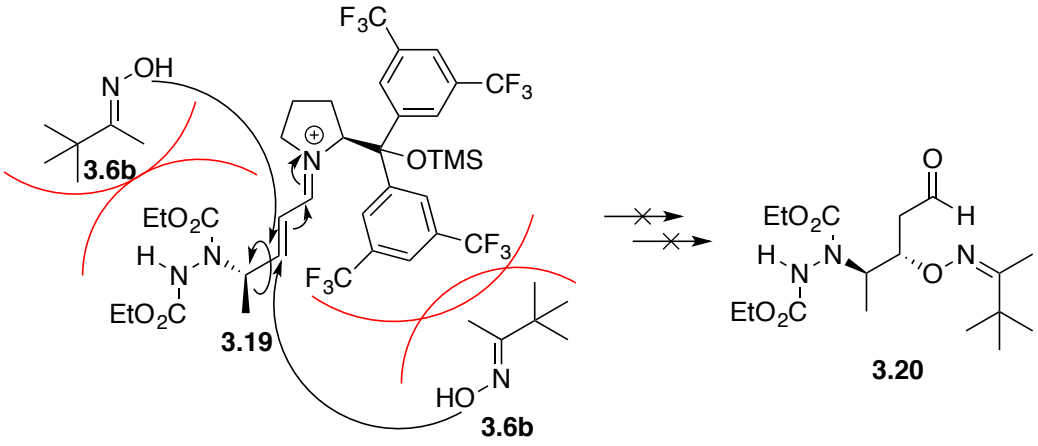
entry	T (ºC)	time	yield[b,c]
1	0	5.5 h/5.7 h	42%[d]/58%[e]
2	0	4 h	47%
3	0	7 h	51%
4	-30	21.5 h	inc (61%)
5	0	20 h - 5 d[f]	nd
6	0	19 h	24% (6%)
7	0	24 h	61% (10%)
8	0	24 h	35% (4%)
9[g]	0	7 d	inc
10[h]	0	24 h	44%
11[i]	0 - rt	16 h	44%
12	0	22 h	40%
13	rt	4 h	47%
14	rt	5 h	62%

[a] Reaction conditions: **3.17a**, **3.6a** (3 equiv), cat. **3.3a** (0.1 equiv), $PhCO_2H$ (0.1 equiv), toluene (3 M). [b] Determined by ^1H NMR using TBME or cyclohexene as an internal standard. [c] Number in parentheses = percentage of unreacted **3.17a**. [d] ^1H NMR run in $CDCl_3$. [e] ^1H NMR run in CD_3CN. [f] No observation of decomposition following reaction completion at 20 h time point. [g] Reaction concentration = 0.25 M. [h] Reaction concentration = 1 M. [i] Cold room used for running long-term reactions at 0 ºC stopped running and raised the temperature overnight.

In a final attempt to remove the possibility of forming the suspected 2-isoxazoline side products and improve the yield, pinacolone oxime (**3.6b**) was explored as an alternative to benzaldehyde oxime, **3.6a** (**Scheme 3.5**). Pinacolone oxime was used based on literature precedent showing that it will not undergo the acid catalyzed formation of 2-

isoxazolines due to its steric bulk.[20] However, most likely due to this molecule's steric bulk, coupled with the steric bulk of iminium ion intermediate **3.19**, the reaction time dramatically increased, reactions never reached completion, and new side-products prevented clean isolation. With the difficulties associated with using these oximes in a dienamine-iminium cascade scenario, other heteroatomic nucleophiles for organocatalytic conjugate addition were investigated.

Scheme 3.5 Pinacolone oxime as a nucleophile for conjugate addition.



3.2 2-NITROSOPHENOLS

One of the difficulties in working with oxygen nucleophiles has been the reversibility inherent in oxa-Michael reactions. While this is a problem that has been alleviated for asymmetric oxidations with oximes, it has proven difficult in the synthesis of other desirable asymmetric ethers. One of the ways this has been overcome has been by attaching electrophilic tethers to the *ortho*-positions of phenols. In previous work this *ortho*-tether has been the carbon of a carbonyl or a *β*-nitroolefin, which, following oxa-Michael addition, could act as an electrophile in an iminium/enamine domino reaction (**Scheme**

3.6).[34–52] In the search for alternate oxygen nucleophiles for the iminium-catalyzed portion of the proposed cascade reaction, 2-nitrosophenol (**3.27a**) and its derivatives were proposed as new oxa-Michael donors/hetero-aldol acceptors (**Figure 3.1**).[53–60] This would also accomplish an asymmetric diheteroatomic iminium-enamine cascade.

Scheme 3.6 *Ortho*-tether strategy for asymmetric organocatalyzed oxa-Michael reactions.[34–52]

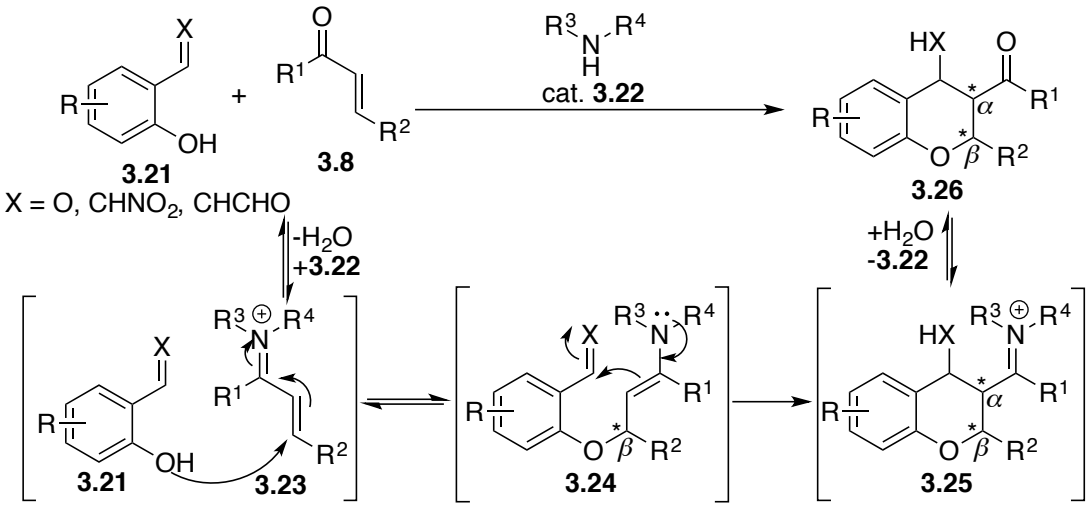
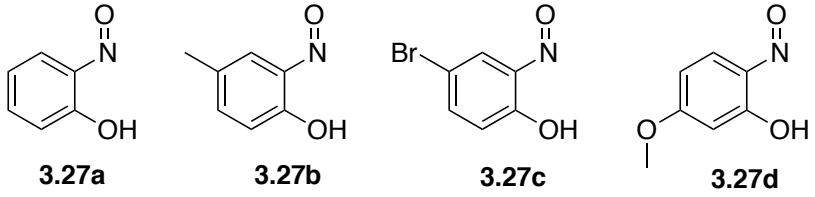


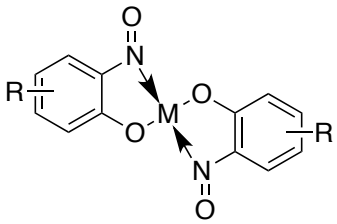
Figure 3.1 2-Nitrosophenols.



There is not much modern literature on free 2-nitrosophenols except in synthesizing dyes such as Nile blue, Nile red, and cyanine, likely due to their instability; many readily oxidize in air and sublime in their uncomplexed forms.[61–64] They can form and be stored as various stable metal complexes (**3.28**, **Figure 3.2**), and freed under acidic conditions,

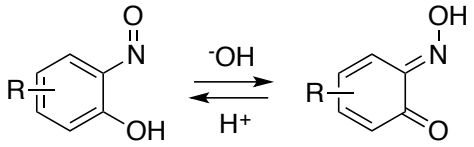
however removal of and handling outside of solvent can be difficult due to their volatility and air sensitivity. Free 2-nitrosophenols (**3.27**) could be converted to their 2-quinone oxime forms (**3.29**), which have different solubility properties, under basic conditions and then re-acidified so that the precipitated solid (**3.27**) could be collected for immediate use in the planned organocascade reactions (**Schemes 3.7** and **3.8**).

Figure 3.2 Metal complexes of 2-nitrosophenols.



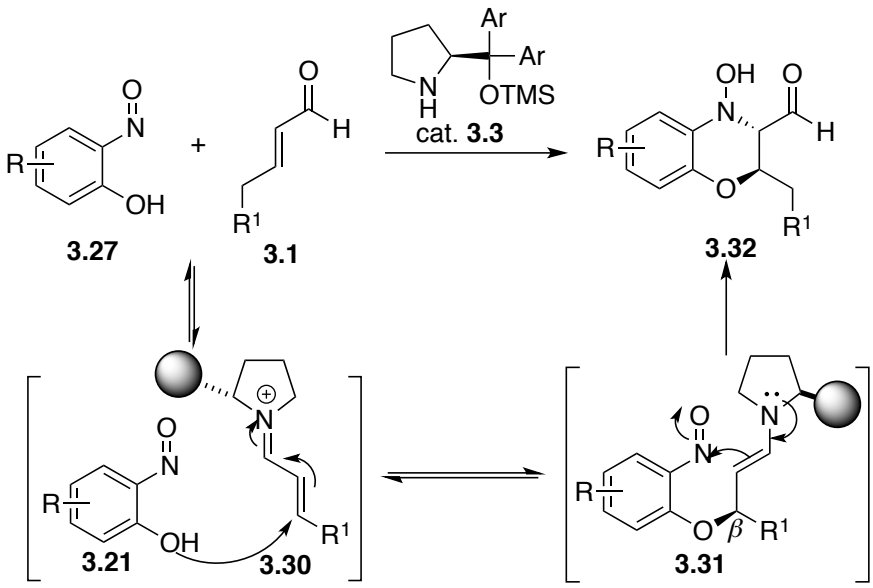
3.28

Scheme 3.7 Acid-base interconversion of 2-nitrosophenol and 2-quinone oxime.



3.27 **3.29**

Scheme 3.8 Planned organocascade with 2-nitrosophenols.

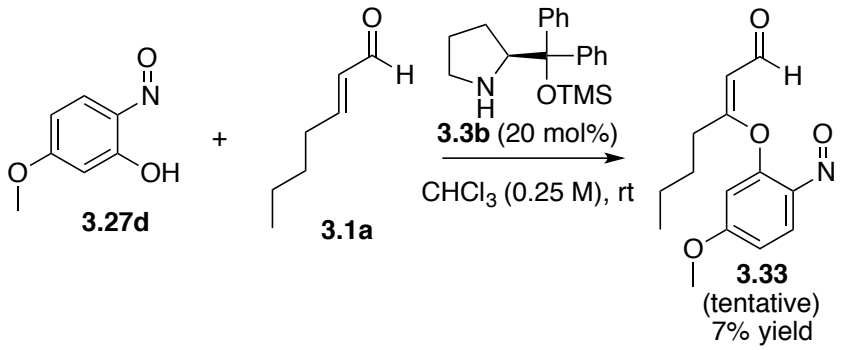


3.2.1 Results and discussion

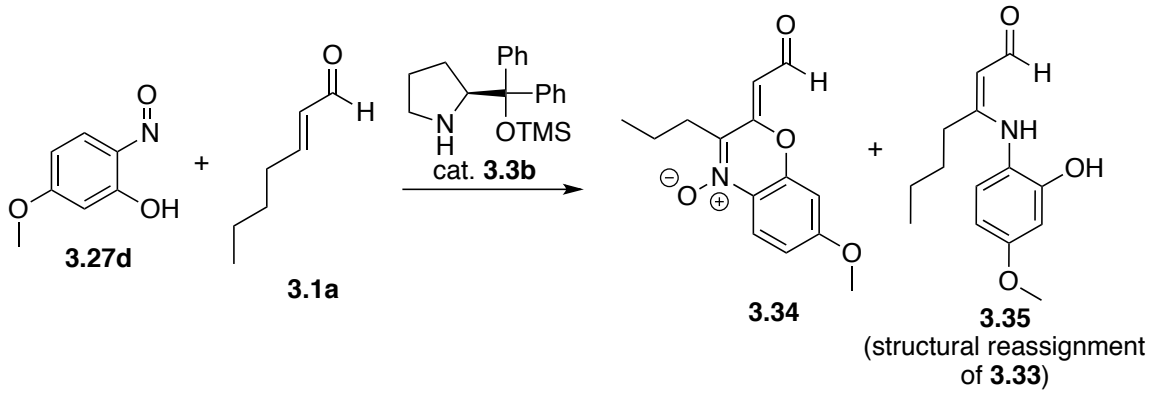
The reactions performed using the 2-nitrosophenols shown in **Figure 3.1** were largely unsuccessful. The only conditions that yielded any major aldehyde products used commercially available 2-nitrosoresorcinol monomethylether (**3.27d**) and diphenyl prolinol silyl ether catalyst (**3.3b**) under neutral conditions in chloroform (**Scheme 3.9**). Only one of the two major products could be identified at the time and it was initially believed to be the unexpected product **3.33** in 7% isolated yield. It was later determined that the two major aldehydes formed were actually nitrone **3.34**, and enamine **3.35**, the formation of which will be discussed in **Chapter 4** (**Scheme 3.10**). Assuming that the compound being formed was **3.33**, addition of other organocatalysts to assist the enamine α-oxyamination to yield **3.32d**, proved to be ineffective. In addition, derivatization of the assumed product through asymmetric transfer-hydrogenation also did not yield an

asymmetric product. It was determined that 2-nitrosophenols were too reactive and too difficult to handle to be used in the proposed cascade reactions.

Scheme 3.9 Reaction of 5-methoxy-2-nitrosophenol with trans-2-heptenal.



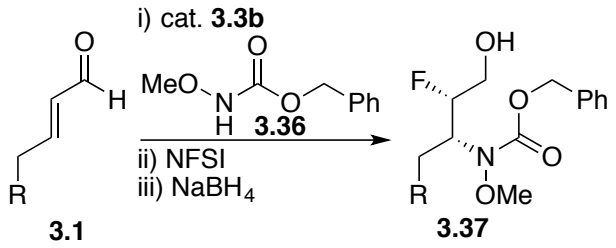
Scheme 3.10 Reaction of 5-methoxy-2-nitrosophenol with trans-2-heptenal.



3.3 *N*-METHOXYBENZYLCARBAMATE

The Brenner research group had previously worked with *N*-methoxybenzylcarbamate (**3.36**) while working on organocatalytic aminofluorinations of α,β-unsaturated aldehydes (**Scheme 3.11**).[65] The nucleophile in the iminium-catalyzed step in this case would be a nitrogen, rather than an oxygen, but the ultimate goal of this research was the addition of heteroatoms in a dienamine-iminium cascade that could be used to further functionalize the enal.

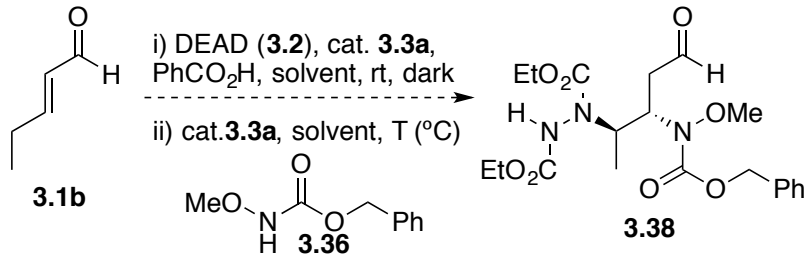
Scheme 3.11 Organocatalytic aminofluorination of α,β-unsaturated aldehydes.[65]



3.3.1 Results and Discussion

While the reaction conditions reported for the Brenner group's aminofluorination called for catalyst **3.3b**, addition of this catalyst during the iminium-catalyzed step in the planned dienamine-iminium cascade, following γ-amination, led to a large number of indistinguishable undesired side reactions, consuming enals **3.1b** and **3.17b** in the process. Even at room temperature this did not occur with catalyst **3.3a**, therefore the cascade was attempted using this catalyst instead (**Table 3.3**). ^{1}H NMR and TLC monitoring indicated that reaction was occurring, however many products were still forming and the intended product, **3.38**, was unable to be identified and isolated under a variety of conditions.

Table 3.3 Dienamine-iminium cascade optimization with *N*-methoxybenzylcarbamate.[a]

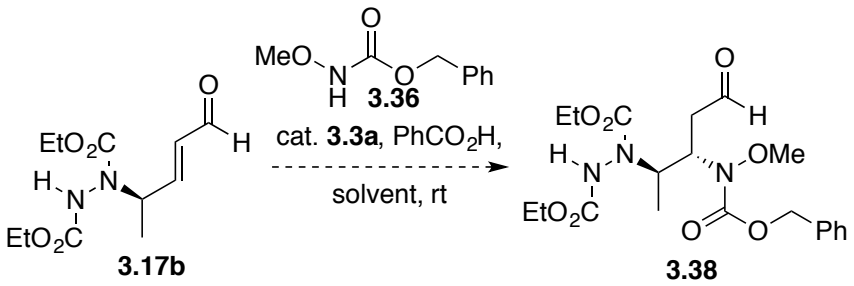


entry	solvent (step i)	solvent (step ii)	T (ºC)	time[b]	yield
1	$CHCl_3$ (0.25 M)	--	-20 - rt	12 d	-- (inseparable pdts)
2	$CHCl_3$ (0.25 M)	--	0	3 d	-- (inseparable pdts)
3	toluene (2 M)	+ toluene (0.4 M)	rt	6 d	-- (**3.1** decomposed)
4	toluene (2 M)	+ toluene (0.4 M)	rt	22 h	-- (**3.1** decomposed)

[a] Reaction conditions: Step i) **3.1b** (1.5 equiv), **3.2** (1 equiv), cat. **3.3a** (0.1 equiv), $PhCO_2H$ (0.2 equiv), solvent, rt, dark. Step ii) cat. **3.3a** (0.2 equiv), **3.36** (3 equiv), solvent. [b] Monitored by TLC and ^1H NMR.

The iminium-catalyzed aza-Michael reaction was then run with isolated **3.17b** in order to determine if the intended reaction was occurring. Three additional reaction conditions reported by the Brenner group for the original aza-Michael reactions were tested, revealing that no aldehyde products were forming and the starting materials were either slowly or rapidly being consumed (**Table 3.4**).

Table 3.4 Iminium catalysis optimization with *N*-methoxybenzylcarbamate.[a]

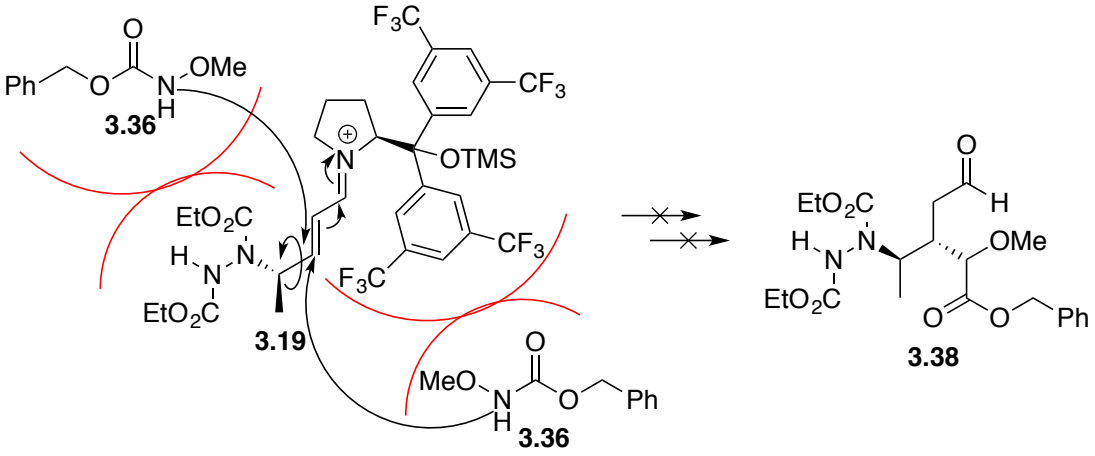


entry	cat (mol %)	solvent(s)	time[b]	yield
1	20	toluene (0.625 M)	22 h	-- (SM decomposed)
2	10	30:70 toluene:TBME (0.625 M)	5 d	-- (No rxn)
3	10	30:70 toluene:$CHCl_3$ (0.625 M)	22 h	-- (SM decomposed)
4	10	10% IPA/$CHCl_3$ (0.3 M)	5 d	-- (No rxn)

[a] Reaction conditions: **3.17b**, **3.36** (2 equiv), cat. **3.3a**, $PhCO_2H$ (0.1 equiv), solvent, rt. [b] Monitored by TLC and ^1H NMR.

The lack of Michael reactivity was once again attributed to the steric bulk of iminium ion **3.19**, which could likely prevent the nucleophilic approach of the bulky secondary amine (**Scheme 3.12**).

Scheme 3.12 Steric hindrance in the catalytic aza-Michael of *N*-methoxybenzylcarbamate.



3.4 *N*-METHYL-*N*-HYDROXY BENZYLCARBAMATE

Although *N*-methoxybenzylcarbamate was unsuccessful as a nucleophile in the dienamine-iminium cascade, the presence of an N-O bond could favor nucleophilicity at the oxygen similar to that of oximes, if unprotected. Such an oxygen nucleophile may also exhibit slightly less steric bulk due to it being a terminal nucleophile. There had been previous work done with benzyl hydroxycarbamate, **3.39**, however this work used an organocatalytic tandem 1,4-addition of the nitrogen, followed by 1,2-addition of the oxygen to form 5-hydroxyisoxazolidines, **3.40** (**Scheme 3.13**).[66] In order to avoid nitrogen reactivity, *N*-methyl-*N*-hydroxy benzylcarbamate, **3.41**, was synthesized and explored as a potential oxa-Michael nucleophile (**Figure 3.3**).[67,68]

Scheme 3.13 Organocatalytic formation of 5-hydroxyazolidines.

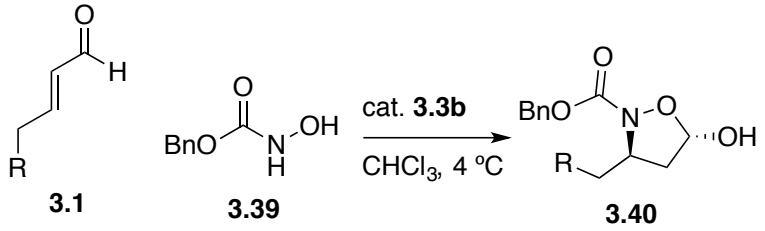
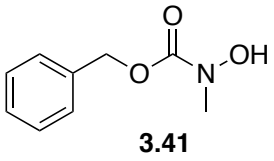


Figure 3.3 *N*-methyl-*N*-hydroxy benzylcarbamate



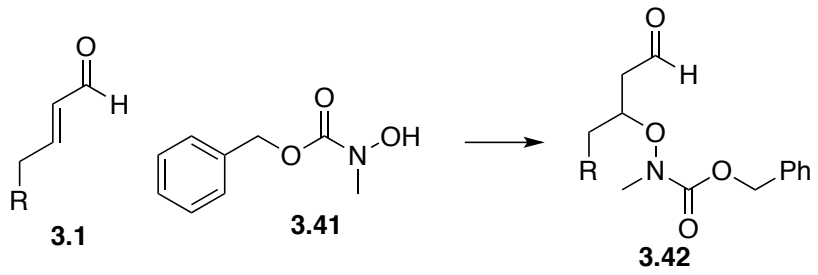
3.4.1 Results and discussion

Since hydroxycarbamate, **3.41**, had never been used in an organocatalytic oxa-Michael reaction, this was explored before attempting a cascade. In reactions with **3.1b** in the presence of catalytic **3.3a**, multiple aldehydes were forming as determined by ^{1}H NMR,

however none formed in significant quantities and were indistinguishable by TLC (entries 1-2, **Table 3.5**). Removal of acid additive in favor of a base additive led to preference for one product that could still not be isolated (entry 3), as did changing solvent from chloroform to toluene (entries 4-5). Removing the acid additive in toluene led to the formation of multiple products in addition to **3.42** (entry 6). While base additive was beneficial to the reaction in chloroform, in toluene a low conversion to **3.42** was observed before additional products began forming (entry 7). Increasing the loading of **3.41** increased conversion to **3.42** (entry 8). As **3.42** formed readily under acidic, neutral, and basic conditions, the catalyst was removed as a control. While reaction time increased, a reaction still occurred favoring much cleaner formation of the major product previously observed, allowing for isolation of **3.42** in 32% yield (entry 9). This demonstrated that the conjugate addition that was occurring was not organocatalytic.

In light of this revelation, the reaction was run without catalyst with no additive, with benzoic acid additive, and with sodium acetate additive to try to find the conditions most likely to suppress this spontaneous reactivity (entries 1-3, **Table 3.6**). The product was found to be very stable under all three of these reaction conditions and the lowest conversion was detected under neutral conditions (entry 1). The reaction temperature was then lowered to 0 ºC and -30 ºC and run under neutral conditions, as well as acidic conditions since the intended dienamine step would be acidic, in an attempt to suppress spontaneous reactivity. This was achieved at -30 ºC (entries 6-7), and reactivity was restored upon addition of catalyst **3.3a** to the flask (entry 7).

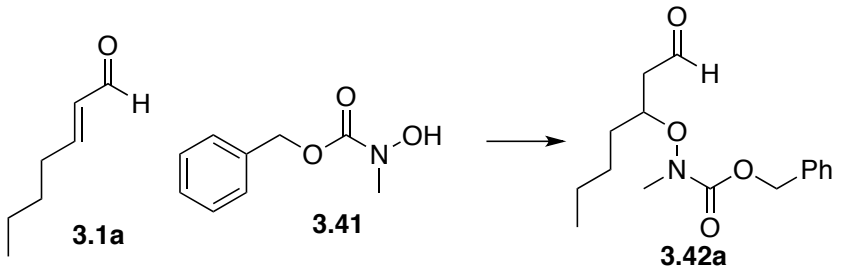
Table 3.5 Optimization of conjugate addition of *N*-methyl-*N*-hydroxy benzylcarbamate.[a]



entry	R	solvent (conc)	**3.3a** (mol %)	additive (mol %)	time	conversion[b]
1	Me	$CHCl_3$ (0.25 M)	20	$PhCO_2H$ (20)	5 d	--
2	Me	$CHCl_3$ (0.25 M)	20	none	26 h	--
3	Me	$CHCl_3$ (0.25 M)	20	NaOAc (20)	26 h	33%
4	Me	toluene (2 M)	10	$PhCO_2H$ (10)	5 h	40%
5[c]	Me	toluene (2 M)	10	$PhCO_2H$ (10)	16 h	50%
6	Pr	toluene (2 M)	10	none	20 h	--
7	Pr	toluene (2 M)	10	NaOAc (10)	20 h	25%
8[d,e]	Pr	toluene (2 M)	10	NaOAc (10)	25 h	61%
9[d]	Pr	toluene (2 M)	0	NaOAc (10)	47 h	59% (32%)[f]

[a] Reaction conditions: **3.1** (1 equiv), **3.41** (1 equiv), cat. **3.3a**, additive, solvent. [b] Calculated using ^{1}H NMR. [c] Reaction temperature = 0 ºC. [d] Used 3 equivalents of **3.41**. [e] Reduced to alcohol form with $NaBH_4$. [f] Isolated yield.

Table 3.6 Non-organocatalytic conjugate addition of *N*-methyl-*N*-hydroxy benzylcarbamate.[a]



3.1a **3.41** **3.42a**

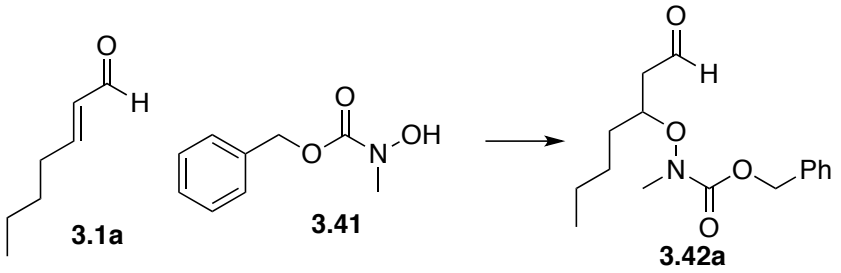
entry	additive (mol %)	T (ºC)	time	conversion[b]
1	none	rt	5 d	27%
2	$PhCO_2H$ (10)	rt	5 d	35%
3	NaOAc (10)	rt	4 d	61%
4	$PhCO_2H$ (10)	0	4 d	11%
5	none	0	4 d	61%
6	none	-30	4 d	6%
7	$PhCO_2H$ (10)	-30	4 d	3% then 77%[c]

[a] Reaction conditions: **3.1a**, **3.41** (3 equiv), additive, toluene (2M). [b] Calculated using ^{1}H NMR. [c] Conversion observed upon addition of cat. **3.3a** and reaction for 20 hours after 4-day time point.

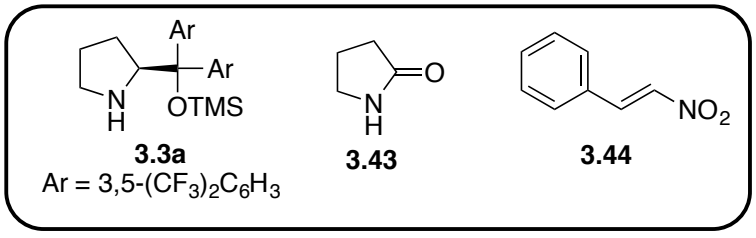
Reintroduction of catalyst under these conditions complicated isolation, so reduction to the alcohol product was required (entries 1-2, **Table 3.7**). Upon isolation and chiral-phase HPLC analysis of the spontaneous product and the catalyzed reaction product it was revealed that both products were racemic, therefore the catalyst was not restoring asymmetric reactivity. To elucidate the likely mechanism of reactivity, 2-pyrrolidinone (**3.43**) and triethylamine (TEA) were used in catalytic amounts in reactions as a replacement for catalyst **3.3a** (entries 3-4). 2-pyrrolidinone is a secondary amine that cannot easily undergo iminium ion formation nor act as a strong base, but it can hydrogen bond. The lack of reactivity using **3.43** indicates that the reaction is not catalyzed through

hydrogen bonding activation (entry 3). Triethylamine also cannot form an iminium ion but is strongly basic, therefore the high conversion observed in entry 4 indicates that catalyst **3.3a** might simply be acting as a base, likely helping to deprotonate **3.41** to increase reactivity, rather than activate through hydrogen bonding or an iminium ion intermediate.

Table 3.7 Organocatalytic conjugate addition of *N*-methyl-*N*-hydroxy benzylcarbamate.[a]



entry	cat. (mol %)	additive (mol %)	time	conversion[b]
1	**3.3a** (10)	$PhCO_2H$ (10)	21 h	--[c]
2	**3.3a** (10)	$PhCO_2H$ (10)	24 h	nd (9%)[d]
3	**3.43** (10)	None	17 h	--
4	**TEA** (10)	None	17 h	74%
5	**3.3a** (10)	$PhCO_2H$ (10) + **3.44** (2 equiv)	3 d	74%



[a] Reaction conditions: **3.1a**, **3.41** (3 equiv), catalyst, additive, toluene (2M), -30 ºC. [b] Calculated using ^{1}H NMR. [c] Unable to isolate aldehyde on column. [d] Isolated yield of $NaBH_4$ reduced **3.42a**.

Due to the spontaneous reactivity of *N*-methyl-*N*-hydroxy benzylcarbamate (**3.41**) iminium catalysis was not an option for producing an optically active oxa-Michael product.

It is possible that future work could utilize the molecule's oxa-Michael reactivity in a kinetic resolution utilizing enamine chemistry to diastereoselectively functionalize the α-carbon.[69,70] A potential kinetic resolution using trans-β-nitrostyrene (**3.44**) was attempted, however, the addition of catalyst led to the sole formation of **3.42a**, with no indication of α-functionalization (entry 5, **Table 3.7**).

3.5 CONCLUSIONS

While organocatalytic conjugate additions and cascades are heavily studied, cascades originating in the γ-position present additional difficulties. The presence of the bulky dicarbamate from DEAD following γ-amination may interfere with normally feasible conjugate additions through steric blocking, enabling undesirable reactivity that can reduce yields, inhibit product formation, or render products non-isolable. Determining new and different compounds to examine proved to be difficult as well, as options were limited to those substrates compatible with reaction conditions that were optimal for γ-amination, and each compound brought unique properties to these reactions.

Oximes provided moderate asymmetric reactivity, but the tendency toward cyclization to 2-isoxazolines was exacerbated in the presence of the γ-aminated enal, reducing the yield of the desired product. Conditions to favor 2-isoxazoline formation could provide unique products, however this would necessarily preclude a one-pot dienamine-iminium-enamine triple-cascade. The use of oximes reported to exhibit no cyclization unfortunately proved too bulky to be reactive following γ-amination. This steric

problem was also observed in reactions with *N*-methoxybenzylcarbamate, in which no viable products were formed in the cascade.

Most 2-nitrosophenols were too reactive to lead to any viable products. The only promising results were observed in reactions with 2-nitrosoresorcinol monomethylether, which led to unexpected products that will be discussed further in **Chapter 5**. Finally, *N*-methyl-*N*-hydroxy benzylcarbamate exhibited promising results with the initial setback of difficult isolation, but it was discovered that this was reaction was uncatalyzed. This reaction could be suppressed by lowering the reaction temperature to -30 ºC, then reactivated by introducing catalyst, however, the products were racemic, suggesting that the catalyst was acting as a base, rather than forming the reactive iminium ion. While γ-amination with DEAD is a good first step for some organocascades, other electrophiles will need to be explored in order to expand the scope of organocatalyzed dienamine-iminium cascade reactions.

3.6 REFERENCES

(1) Appayee, C.; Fraboni, A. J.; Brenner-Moyer, S. E. *J. Org. Chem.* **2012**, *77* (19), 8828–8834.
(2) Fritsch, von W.; Seidl, G.; Ruschig, H. *Justus Liebigs Ann. Chem.* **1964**, *677*, 139–149.
(3) Balaban, A. T. *Tetrahedron* **1968**, *24*, 5059–5065.
(4) Shimizu, T.; Hayashi, Y.; Yamada, K.; Nishio, T.; Teramura, K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 217–222.
(5) Akcamur, Y.; Kollenz, G. *Org. Prep. Proced. Int. New J. Org. Synth.* **1987**, *19* (1), 52–56.
(6) Harris, T. M.; Harris, C. M.; Oster, T. a; Brown, L. E.; Lee, J. Y. *J. Am. Chem. Soc.* **1988**, *110* (18), 6180–6186.
(7) Moriya, O.; Nakamura, H.; Kageyama, T.; Urata, Y. *Tet. Lett.* **1989**, *30* (30), 3987–3990.
(8) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585–4595.
(9) Waldmann, H. *Liebigs Ann. Chem.* **1990**, 1013–1017.
(10) Mancera, M.; Roff, I.; Galbis, J. A. **1995**, *51* (22), 6349–6362.
(11) Galley, G.; Jones, P. G.; Pätzel, M. *Tetrahedron: Asymmetry* **1996**, *7* (7), 2073–2082.
(12) Vanderwal, C. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126* (45), 14724–14725.
(13) Bhuniya, D.; Mohan, S.; Narayanan, S. *Synthesis (Stuttg).* **2003**, *34* (7), 1018–1024.
(14) Bhuniya, D.; Gujjary, S.; Sengupta, S. *Synth. Commun.* **2006**, *36* (2), 151–164.
(15) Bertelsen, S.; Dinér, P.; Johansen, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 1536–1537.
(16) Carlone, A.; Bartoli, G.; Bosco, M.; Pesciaioli, F.; Ricci, P.; Sambri, L.; Melchiorre, P. *Eur. J. Org. Chem.* **2007**, No. 33, 5492–5495.
(17) Tan, B.; Shi, Z.; Chua, P. J.; Li, Y.; Zhong, G. *Angew. Chem. Int. Ed.* **2009**, *48* (4), 758–761.
(18) Pohjakallio, A.; Pihko, P. M. *Chem. Eur. J.* **2009**, *15*, 3960–3964.
(19) Andersen, N. R.; Hansen, S. G.; Bertelsen, S.; Jørgensen, K. A. *Adv. Synth. Catal.* **2009**, *351*, 3193–3198.
(20) Pohjakallio, A.; Pihko, P. M.; Laitinen, U. M. *Chem. Eur. J.* **2010**, *16*, 11325–11339.
(21) Quintard, A.; Alexakis, A. *Chem. Commun. (Camb).* **2011**, *47* (25), 7212–7214.
(22) Shibatomi, K.; Narayama, A.; Abe, Y.; Iwasa, S. *Chem. Commun.* **2012**, *48*, 7380–7382.
(23) Miyabe, H.; Matsumura, A.; Moriyama, K.; Takemoto, Y. *Org. Lett.* **2004**, *6* (24), 4631–4634.
(24) Andersen, N. R.; Hansen, G.; Bertelsen, S.; Jørgensen, K. A. *Adv. Synth. Catal.* **2009**, *351*, 3193–3198.
(25) Dinér, P.; Nielsen, M.; Bertelsen, S.; Niess, B.; Jørgensen, K. A. *Chem. Commun.* **2007**, No. 35, 3646–3648.
(26) Jiang, H.; Nielsen, J. B.; Nielsen, M.; Jørgensen, K. A. *Chem. Eur. J.* **2007**, *13*,

9068–9075.
(27) Forster, M.; Holmes, H. *Proc. Chem. Soc. London* **1908**, *24*, 8.
(28) Forster, M.; Holmes, H. *J. Chem. Soc. Trans.* **1908**, *93*, 242–252.
(29) Gass, L.; Bope, F. W. *J. Am. Pharm. Assoc. Sci. Ed.* **1959**, *48*, 186–189.
(30) Bellasio, E.; Parravicini, F.; La Noce, T.; Testa, E. *Ann. Chim.* **1968**, *58* (4), 407–417.
(31) Haney, W. G.; Brown, R. G.; Isaacson, E. I.; Delgado, J. N. *J. Pharm. Sci.* **1977**, *66* (11), 1602–1606.
(32) Mohamed, M. A. A.; Siedlecka, U.; Suwinski, J. *Pol. J. Chem.* **2003**, *77* (5), 577–590.
(33) Huang, K.; Chen, H.; Lin, G. *J. Chinese Chem. Soc.* **2004**, *51* (3), 619–627.
(34) Govender, T.; Hojabri, L.; Moghaddam, F. M.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2006**, *17* (12), 1763–1767.
(35) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun.* **2007**, No. 5, 507–509.
(36) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem. Eur. J.* **2007**, *13* (2), 574–581.
(37) Volz, N.; Bröhmer, M. C.; Nieger, M.; Bräse, S. *Synlett* **2009**, 550–553.
(38) Kotame, P.; Hong, B.-C.; Liao, J.-H. *Tet. Lett.* **2009**, *50* (6), 704–707.
(39) Luo, S.-P.; Li, Z.-B.; Wang, L.-P.; Guo, Y.; Xia, A.-B.; Xu, D.-Q. *Org. Biomol. Chem.* **2009**, *7* (21), 4539–4546.
(40) Hong, B.-C.; Kotame, P.; Tsai, C.-W.; Liao, J.-H. *Org. Lett.* **2010**, *12* (4), 776–779.
(41) Xia, A. B.; Xu, D. Q.; Luo, S. P.; Jiang, J. R.; Tang, J.; Wang, Y. F.; Xu, Z. Y. *Chem. Eur. J.* **2010**, *16* (3), 801–804.
(42) Alemán, J.; Núñez, A.; Marzo, L.; Marcos, V.; Alvarado, C.; García Ruano, J. L. *Chem. Eur. J.* **2010**, *16* (31), 9453–9456.
(43) Shen, H.; Yang, K. F.; Shi, Z. H.; Jiang, J. X.; Lai, G. Q.; Xu, L. W. *Eur. J. Org. Chem.* **2011**, 5031–5038.
(44) Wang, C.; Yang, X.; Raabe, G.; Enders, D. *Adv. Synth. Catal.* **2012**, *354* (14-15), 2629–2634.
(45) Mao, H. B.; Lin, A. J.; Tang, Y.; Shi, Y.; Hu, H. W.; Cheng, Y. X.; Zhu, C. J. *Org. Lett.* **2013**, *15* (16), 4062–4065.
(46) Zhang, Y.; Tortorella, M. D.; Wang, Y.; Liu, J.; Tu, Z.; Liu, X.; Bai, Y.; Wen, D.; Lu, X.; Lu, Y.; Talley, J. J. *ACS Med. Chem. Lett.* **2014**, *5* (10), 1162–1166.
(47) Xia, A. B.; Wu, C.; Wang, T.; Zhang, Y. P.; Du, X. H.; Zhong, A. G.; Xu, D. Q.; Xu, Z. Y. *Adv. Synth. Catal.* **2014**, *356* (8), 1753–1760.
(48) Liu, L.; Zhu, Y.; Huang, K.; Wang, B.; Chang, W.; Li, J. *Eur. J. Org. Chem.* **2014**, 4342–4350.
(49) Liu, K.; Jiang, X. *Eur. J. Org. Chem.* **2015**, 6423–6428.
(50) Zhang, J.; Ajitha, M. J.; He, L.; Liu, K.; Dai, B.; Huang, K.-W. *Adv. Synth. Catal.* **2015**, *357* (5), 967–973.
(51) Zheng, W.; Zhang, J.; Liu, S.; Yu, C.; Miao, Z. *RSC Adv.* **2015**, *5* (111), 91108–91113.
(52) D'Orazio, G.; Colombo, L.; Salmona, M.; La Ferla, B. *Eur. J. Org. Chem.* **2016**, 1660–1664.

(53) Baudisch, O.; Smith, S. H. *Naturwissenschaften* **1939**, *27*, 769.
(54) Baudisch, O. *Science* **1940**, *92* (2389), 336–337.
(55) Baudisch, O. *J. Am. Chem. Soc.* **1941**, *63*, 622.
(56) Cronheim, G. *J. Org. Chem.* **1947**, *12* (1), 1–6.
(57) Nemodruk, A. A. *Zhurnal Obs. Khimii* **1958**, *28*, 2672–2676.
(58) Maruyama, K.; Tanimoto, I.; Goto, R. *J. Org. Chem.* **1967**, *32* (8), 2516–2520.
(59) Ionov, a. M.; Lyubchenko, S. N.; Kogan, V. a.; Tsivadze, a. Y. *Russ. J. Coord. Chem.* **2011**, *34* (3), 195–197.
(60) Valizadeh, H.; Gholipour, H. *Comptes Rendus Chim.* **2011**, *14* (10), 963–966.
(61) Yao, W.; Huang, D. *Org. Lett.* **2010**, *12* (4), 736–738.
(62) Jose, J.; Burgess, K. *J. Org. Chem.* **2006**, *71* (20), 7835–7839.
(63) Jose, J.; Ueno, Y.; Burgess, K. *Chem. - A Eur. J.* **2009**, *15* (2), 418–423.
(64) Shindy, H. A.; El-Maghraby, M. A.; Eissa, F. M. *Color. Technol.* **2008**, *124* (3), 159–164.
(65) Appayee, C.; Brenner-Moyer, S. E. *Org. Lett.* **2010**, *12* (15), 3356–3359.
(66) Ibrahem, I.; Rios, R.; Vesely, J.; Zhao, G.-L.; Córdova, A. *Synthesis (Stuttg).* **2008**, *2008* (7), 1153–1157.
(67) Defoin, A.; Pires, J.; Streith, J. *Helv. Chim. Acta* **1991**, *74* (8), 1653–1670.
(68) Labeeuw, O.; Phansavath, P.; Genêt, J. P. *Tet. Lett.* **2004**, *45* (38), 7107–7110.
(69) McGarraugh, P. G.; Brenner-Moyer, S. E. *Org. Lett.* **2011**, *13* (24), 6460–6463.
(70) McGarraugh, P. G.; Johnston, R. C.; Martínez-Muñoz, A.; Cheong, P. H.-Y.; Brenner-Moyer, S. E. *Chemistry* **2012**, *18* (34), 10742–10752.

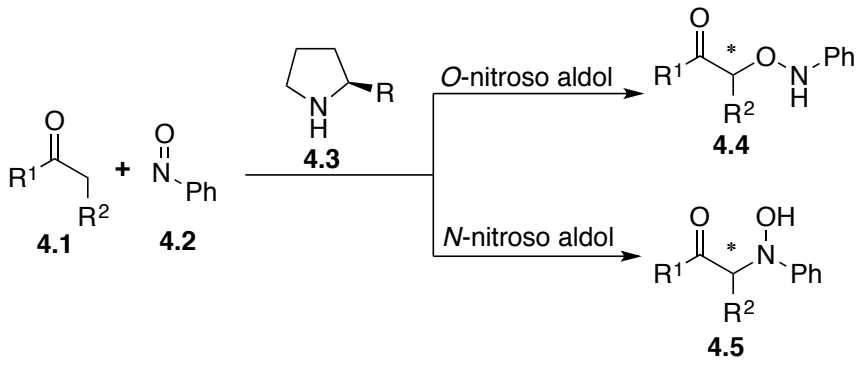
CHAPTER 4

DIENAMINE-CATALYZED REDOX FORMATION OF NITRONES

4.1 Nitrosobenzene

Once it was determined that organocascades using nucleophiles larger than a hydride were problematic in conjugate additions following γ-amination with DEAD, a new heteroatomic electrophile was sought out for the dienamine-catalyzed step. This search very quickly pointed in the direction of nitrosobenzene **4.2** for a number of reasons. Nitrosobenzene, like DEAD, has long been established as an electrophile for enamine catalyzed reactions (**Scheme 4.1**).[1–7]

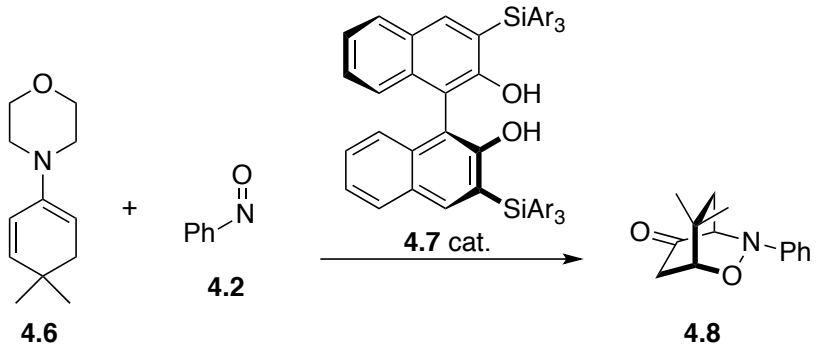
Scheme 4.1 Enamine catalyzed nitroso aldol



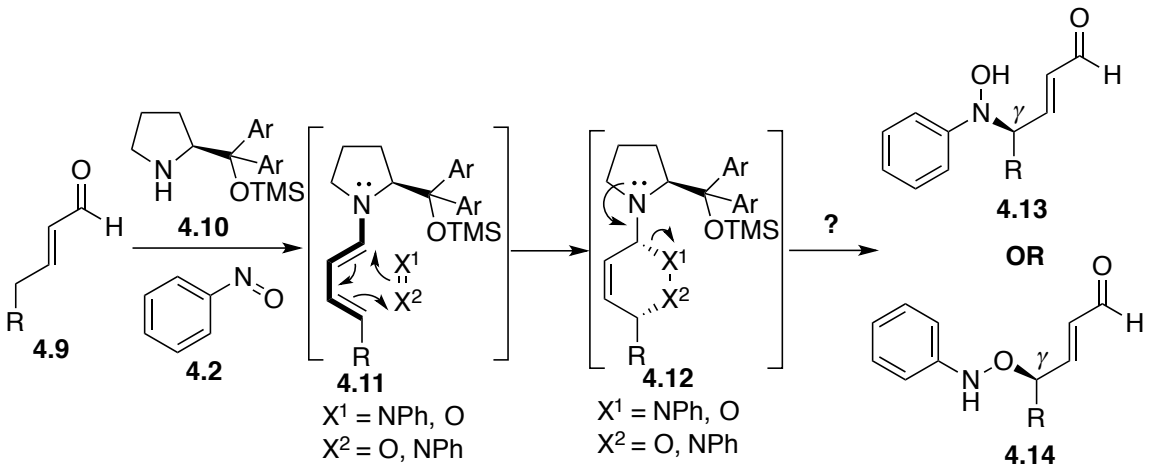
Reactions have been reported to proceed in the presence of various secondary amine catalysts that are commonly used in cascade reactions. Unlike DEAD, nitrosobenzene can act as either a nitrogen electrophile or an oxygen electrophile, depending on the reaction conditions. Typically, under neutral conditions an oxyaminated product, **4.5**, is formed, while acidic conditions yield an aminooxylated product, **4.4**. This indicated the potential

to broaden the scope of dienamine-catalyzed reactions to include another amination as well as an oxylation. Finally, nitrosobenzene's N=O π-system's reported ability to act as a dienophile (**Scheme 4.2**), like DEAD, and provide a labile C-N or C-O bond for ring-opening provided the final impetus for exploration as a regioselective electrophile (**Scheme 4.3**).

Scheme 4.2 Organocatalytic cycloaddition with nitrosobenzene.



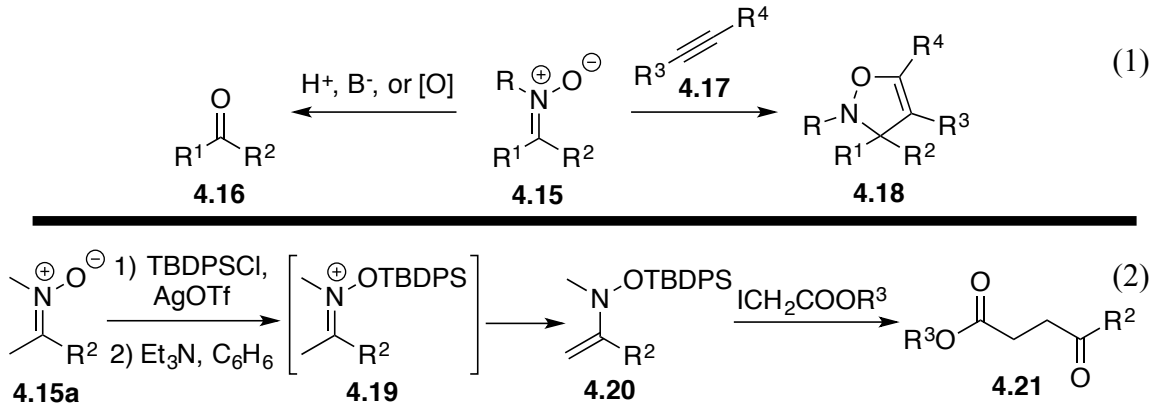
Scheme 4.3 Proposed organocatalytic cycloaddition with nitrosobenzene.



4.2 Nitrones

Nitrones (**4.15**, **Scheme 4.4**) are very useful functional groups in organic synthesis. Nitrones can be hydrolyzed in the presence of acid, base, or oxidant to form aldehydes or ketones (**4.16**, eq 1).[8–22] They can also undergo characteristic [3+2]-dipolar cycloadditions to form useful heterocycles, such as dihydroisoxazoles (**4.18**, eq 1).[23–30] In addition, nitrones can be used for radical alkylation by converting to an *N*-siloxy enamine nucleophile (**4.20**, eq 2).[31]

Scheme 4.4 Reactions of nitrones.



(1)

(2)

Nitrones are typically synthesized through condensation of a hydroxylamine onto an aldehyde or ketone, or by the oxidation of imines.[32–36] These conditions, however, would not retain aldehyde functionality, so most syntheses would require protection and deprotection steps to retain both aldehyde and nitrone functionalities. There are two instances of direct nitrone synthesis in the presence of aldehydes, one isolated example of a carbon-nitrogen ylide reacting with 4-nitrosobenzaldehyde, and a method for *N*-alkylation of aldoximes with enals.[37,38]

4.3 Results and Discussion

4.3.1 Optimization

Instead of providing one of the anticipated products (**4.13** or **4.14**, **Scheme 4.3**), the 1D and 2D ^{1}H NMR spectra of the product showed a lack of γ-protons, which seemingly indicated that the reaction formed a γ-imine enal (**4.25**, **Scheme 4.5**). This was believed to be the result of the condensation mechanism illustrated in **Scheme 4.5**. The structure was called into question once HRMS data indicated the presence of an additional oxygen on the product. While this could have been explained by rapid oxidation to the carboxylic acid before HRMS was run, air oxidation was very slow with this product, so the only other likely explanation was that an oxygen was present on the nitrogen. This was ultimately proven when crystals were grown for X-ray crystallography, revealing the structure definitively as a nitrone as well as the major (*E*,*E*) isomer (**4.26a**, **Figure 4.1**). This was an unprecedented formation of a conjugated γ-nitrone enal (**4.26a**, **Scheme 4.6**).

Scheme 4.5 Initially proposed formation of γ-imines (**4.25**).

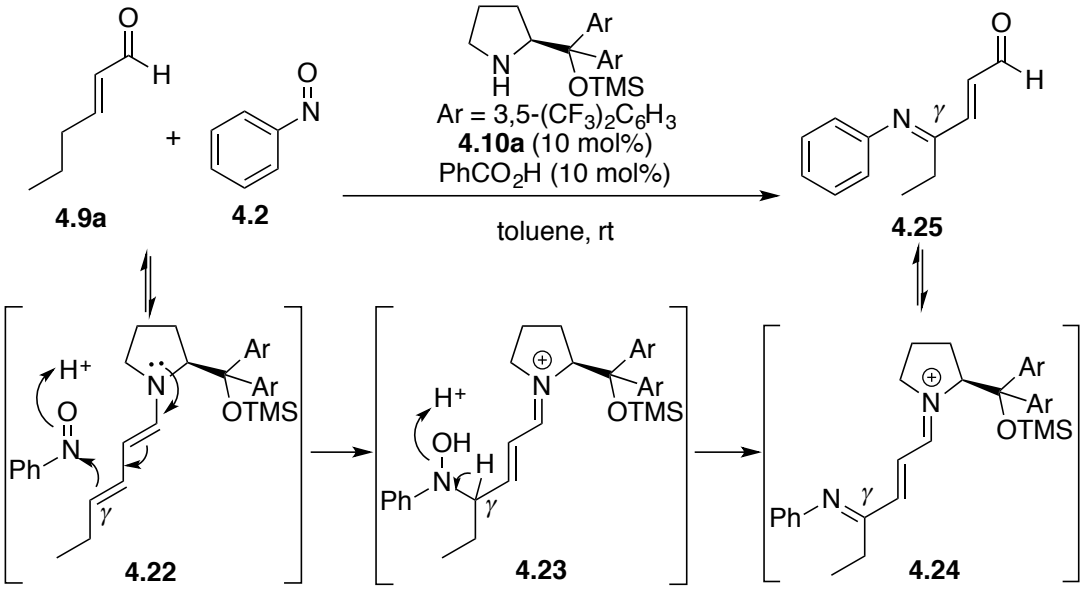
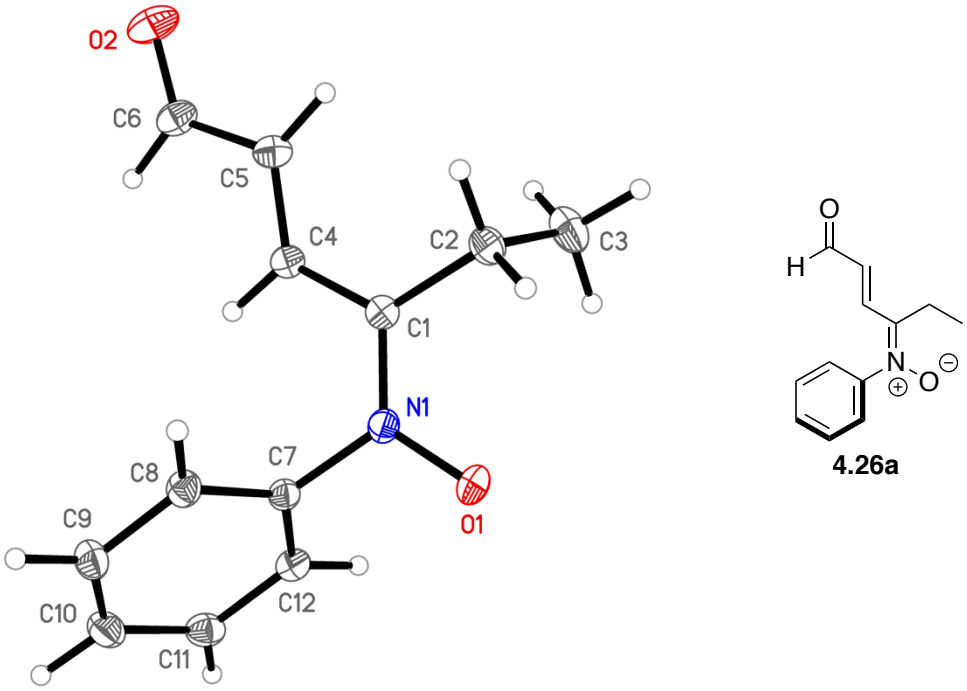
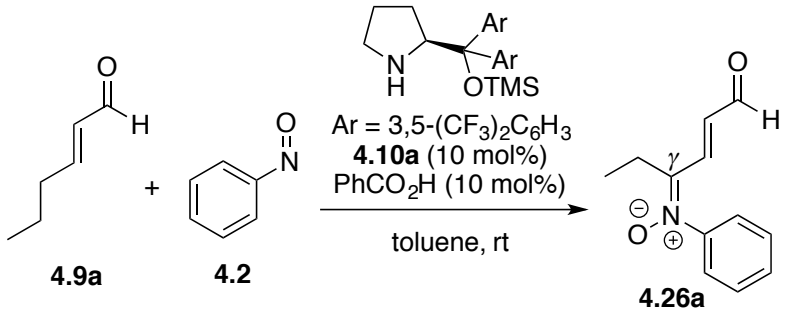


Figure 4.1 X-ray crystal structure of **4.26a**.

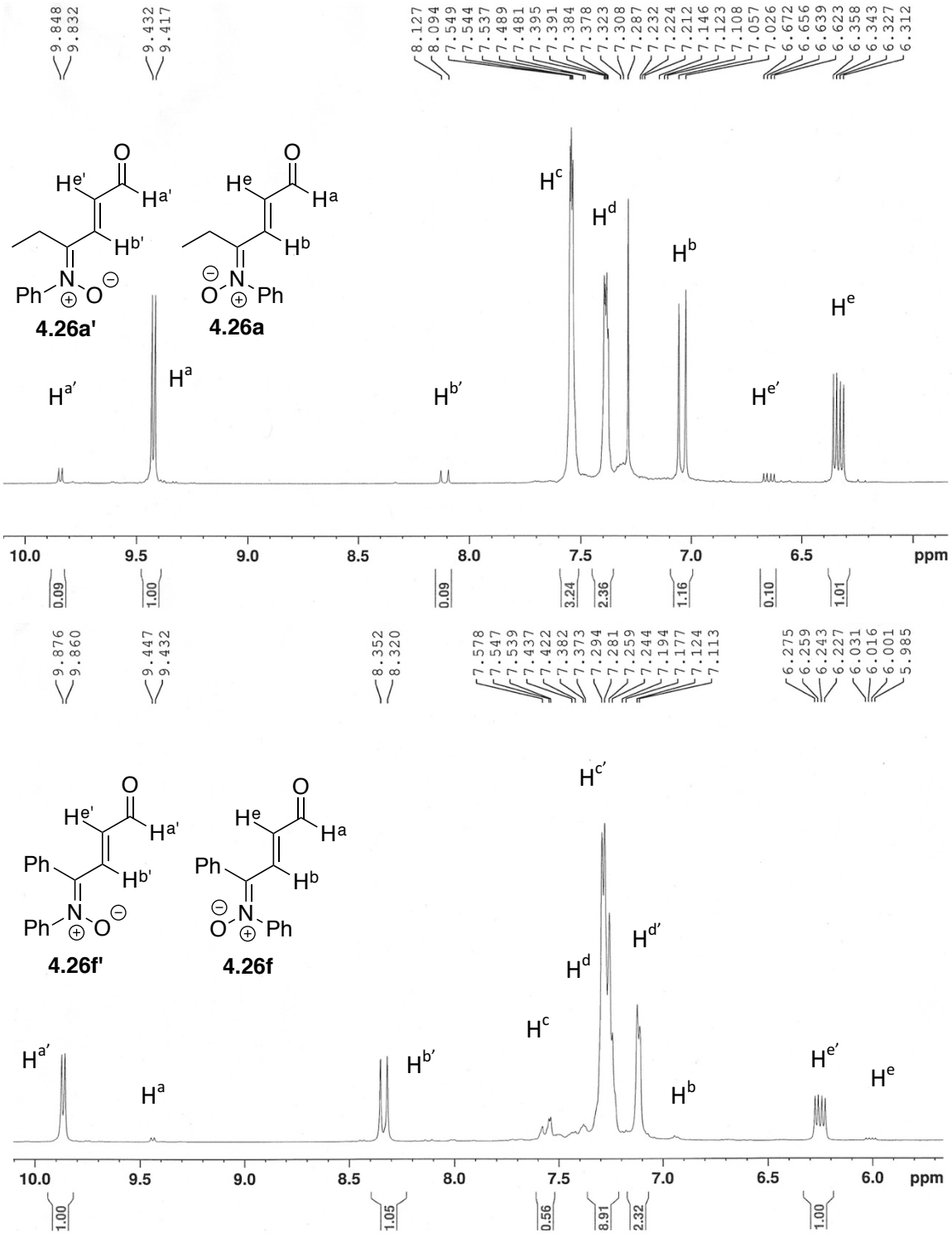


Scheme 4.6 Unprecedented organocatalytic nitrone formation.



The first organocatalytic reactions that took place with nitrosobenzene and an enal gave one major product in low yield. The minor (*E*,*Z*) isomer **4.26a'** was not identified until **4.26f'** was synthesized during the substrate scope studies (**Figure 4.2**). The NMR spectrum of **4.26f'** showed the corresponding aldehyde and alkene peaks shifted downfield from those in **4.26a**, likely due to through-space deshielding from the nitrone oxide. Mass spectrometry of this product confirmed that it was indeed a configurational isomer.

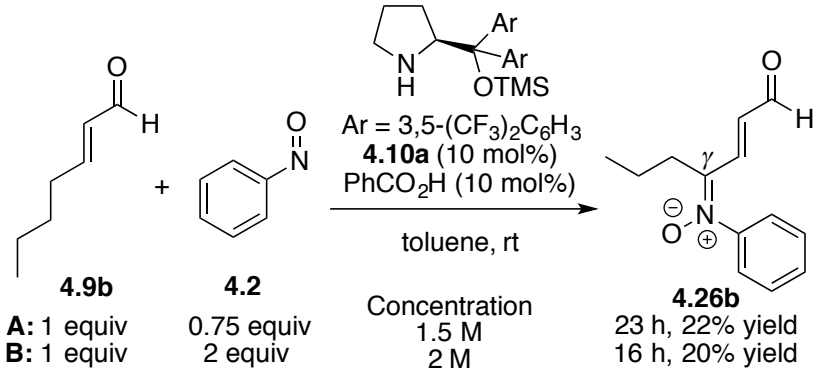
Figure 4.2 Comparison of isomers by ^{1}H-NMR.



Other than the first two reactions, which used trans-2-heptenal, **4.9b**, all of the optimizations were run with trans-2-hexenal **4.9a**. The initial reaction conditions used 0.75

equivalents of nitrosobenzene at a concentration of 1.5 M in toluene, using catalyst **4.10a** and benzoic acid additive at a 10 mol % loading (Conditions **A**, **Scheme 4.7**). The reaction was run at room temperature for 23 hours, the point at which nitrosobenzene was fully consumed as determined by ^{1}H NMR, and the product was isolated by flash chromatography to yield product **4.26b** in 22% yield. A subsequent reaction that increased loading of nitrosobenzene to 2 equivalents and the concentration to 2M, gave a comparable isolated yield of 20% in a decreased reaction time of 16 hours with full consumption of enal as well as nitrosobenzene (Conditions **B**, **Scheme 4.7**). At this point, the enal was switched to trans-2-hexenal due to availability in the lab. This change did not affect the yield or reaction time, so it was used for the rest of the optimization.

Scheme 4.7 Initial studies with trans-2-heptenal (**4.9b**).

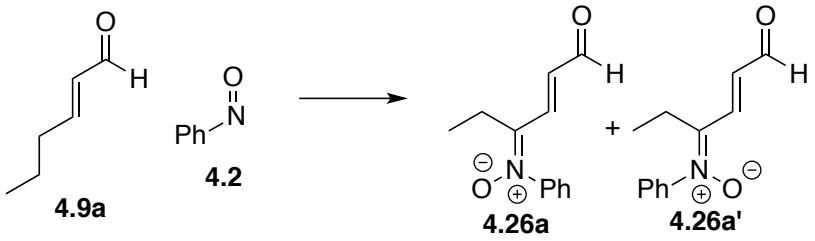


During the subsequent optimization, yield was determined by comparing ^{1}H NMR product peaks to those of an internal standard following full consumption of starting materials, in order to avoid lengthy isolations. Decreasing the concentration to 1 M improved solubility of the excess nitrosobenzene while maintaining a 21% yield and 10:1 dr over 21 hours (entry 1, **Table 4.1**). At this point, a catalyst screen was run incorporating a number of common organocatalysts. The other commonly used Hayashi-Jørgensen

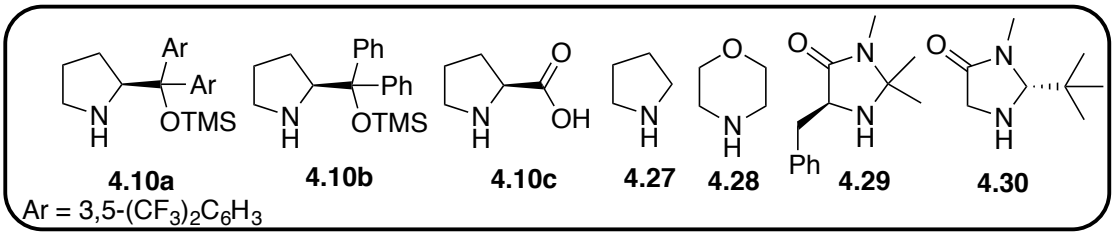
catalyst, diphenyl prolinol silyl ether (**4.10b**), dramatically decreased the reaction time while increasing the yield to 31% (entry 2, **Table 4.1**). Proline (**4.10c**) showed no reactivity after one week (entry 3). Due to the product being non-asymmetric, achiral catalysts pyrrolidine, **4.27**, and morpholine, **4.28**, were used. Pyrrolidine reacted very quickly, however a yield of 21% did not compare favorably to the 31% yield using **4.10b** (entry 4 vs. entry 2). Likewise, morpholine was comparable to **4.10a** in reaction time, but only provided an 11% yield (entry 5 vs. entry 1). MacMillan imidazolidinone **4.29** led to a reaction time and yield comparable to catalyst **4.10a** (entry 6 vs. entry 1). While morpholine and the imidazolidinone did have remaining starting material, any time points after those reported showed no improvement in yields.

The catalyst screen was also run with 1 equivalent of nitrosobenzene (**4.2**), instead of 2 equivalents (entries 7-13). Catalysts **4.10a** and **4.10b** gave results consistent with the data using 2 equivalents of nitrosobenzene (entry 7 vs. entry 1, entry 8 vs. entry 2). Pyrrolidine (**4.27**), however, showed a marked improvement, providing the product in the best yield, at 33% (entry 9). With morpholine (**4.28**) and MacMillan imidazolidinone catalyst **4.29**, product yields were lower than when 2 equivalents of nitrosobenzene were used (entry 10 vs. entry 5, entry 11 vs. entry 6). Finally, MacMillan imidazolidinone catalysts **4.29** and **4.30** in the presence of DCA and TCA instead of benzoic acid, respectively, led to the lowest yields obtained in this screening so far (entries 12 and 13).

Table 4.1 Initial catalyst screen.[a]



entry	cat.	time (h)	yield[b-c] (%)	dr[d] (**4.26a**:**4.26a'**)
1	**4.10a**	21	21 (4)	9:1
2	**4.10b**	1	31 (7)	3:1
3	**4.10c**	168	--	--
4	**4.27**	1	21 (8)	3:1
5	**4.28**	23	11 (40)	100:0
6	**4.29**	20	21 (56)	4:1
7[e]	**4.10a**	22	24 (24)	11:1
8[e]	**4.10b**	4	29 (9)	3:1
9[e]	**4.27**	4	33 (14)	3:1
10[e]	**4.28**	96	6 (36)	100:0
11[e]	**4.29**	96	18 (39)	1:1
12[e]	**4.29** + DCA[f]	2	8 (27)	100:0
13[e]	**4.30** + TFA[f]	2	2 (6)	100:0



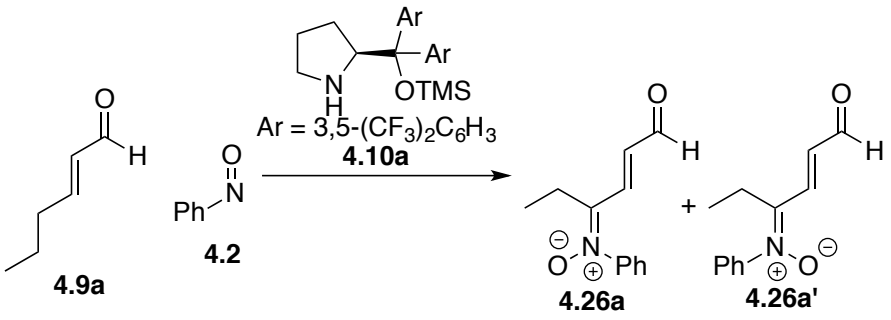
[a] Reaction conditions: **4.9a**, **4.2** (2 equiv), cat. (0.1 equiv), $PhCO_2H$ (0.1 equiv), toluene (1 M), rt. [b] Determined by ^1H NMR using 1,4-dioxane as internal standard. [c] Number in parentheses is percentage of unreacted **4.9a** remaining. [d] Determined by ^1H NMR. [e] 1 equivalent of **4.2** used. [f] Acid additive replaces $PhCO_2H$.

At this point, solvent screens were commenced with **4.10a**, **4.10b**, and pyrrolidine (**4.27**) simultaneously. As both 1 and 2 equivalents of nitrosobenzene (**4.2**) yielded promising results, both conditions were tested during the solvent screening with catalyst **4.10a** (**Table 4.2**). Using 2 equivalents, dichloromethane and acetonitrile improved the yield the most in comparison to toluene (entries 2 and 5 vs. entry 1). THF also showed some improvement in yield, however the reaction rate dropped dramatically (entry 4). Ethanol showed an improvement in the reaction rate, but additional products were detected in the aldehyde region of the ^{1}H NMR spectrum and rapid decomposition occurred at later time points (entry 3). Using 1 equivalent of nitrosobenzene, the yields with toluene and THF remained consistent (entry 6 vs. entry 1, entry 9 vs. entry 4), while dichloromethane and acetonitrile showed significant drops in yield (entry 7 vs. entry 2, entry 10 vs. entry 5). Methanol was used as a replacement for ethanol, but the yield with this solvent was even lower, although the rate of decomposition also decreased (entry 8 vs. entry 3). DMSO was also introduced as a solvent, however the yield was not notably affected and it appeared that the nitrosobenzene (**4.2**) was consumed so quickly, that a significant amount of **4.9a** remained unreacted (entry 11).

Solvent screens using catalysts **4.10b** and **4.27** are summarized in **Table 4.3**. Using **4.10b**, THF was the only solvent to provide an improvement in yield over toluene (using 2 equivalents of nitrosobenzene), but it also decreased the reaction rate (entry 5 vs. entry 1). Methanol and DMSO also decreased the reaction rate, but product yields were lower than both toluene examples (entries 4 and 7 vs. entries 1 and 2). Dichloromethane and acetonitrile both resulted in a significant drop in product yield (entry 3 and entry 6). Pyrrolidine (**4.27**) catalyst showed only a decrease in yield in every solvent except for

toluene (entries 8-13), and even though toluene provided the product in the best yield (entry 9), numerous side products were detected in the aldehyde region.

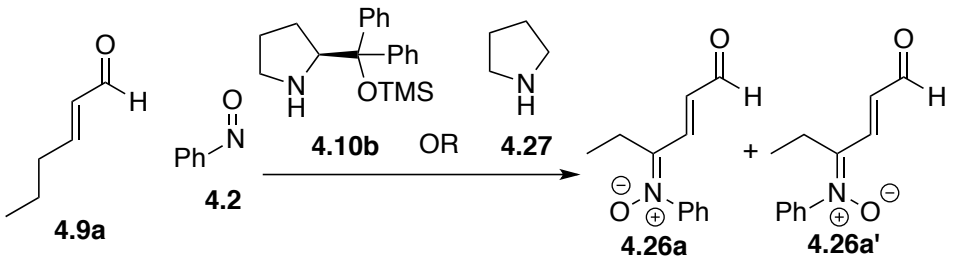
Table 4.2 Solvent screen with catalyst **4.10a**.[a]



entry	solvent	time (h)	yield[b-c] (%)	dr[d] (**4.26a**:**4.26a'**)
1	toluene	21	21 (4)	9:1
2	DCM	21	38 (10)	4:1
3	EtOH	5	23 (47)	nd
4	THF	120	31 (15)	3:1
5	MeCN	22	41 (31)	5:1
6[e]	toluene	22	24 (24)	11:1
7[e]	DCM	19	29 (18)	2:1
8[e]	MeOH	26	8 (15)	nd
9[e]	THF	120	31 (31)	3:1
10[e]	MeCN	26	19 (31)	4:1
11[e]	DMSO	19	27 (57)	2:1

[a] Reaction conditions: **4.9a**, **4.2** (2 equiv), **4.10a** (0.1 equiv), $PhCO_2H$ (0.1 equiv), solvent (1 M), rt. [b] Determined by ^1H NMR using 1,4-dioxane as internal standard. [c] Number in parentheses is percentage of unreacted **4.9a** remaining. [d] Determined by ^1H NMR. [e] 1 equivalent of **4.2** used.

Table 4.3 Solvent screen using catalysts **4.10b** and **4.27**.[a]



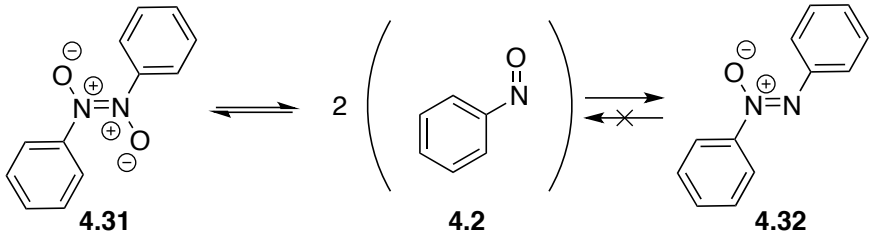
entry	catalyst	solvent	time (h)	yield[b-c] (%)	dr[d] (**4.26a**:**4.26a'**)
1[e]	**4.10b**	toluene	1	31 (7)	3:1
2	**4.10b**	toluene	4	29 (9)	3:1
3	**4.10b**	DCM	1	22 (6)	2:1
4	**4.10b**	MeOH	19	11 (27)	nd
5	**4.10b**	THF	19	35 (21)	2:1
6	**4.10b**	MeCN	3	11 (6)	5:1
7	**4.10b**	DMSO	19	26 (51)	6:1
8[e]	**4.27**	toluene	1	21 (8)	3:1
9	**4.27**	toluene	4	33 (14)	3:1
10	**4.27**	DCM	4	18 (50)	4:1
11	**4.27**	THF	21	18 (67)	100:0
12	**4.27**	MeCN	2	9 (59)	8:1
13	**4.27**	DMSO	1	25 (69)	3:1

[a] Reaction conditions: **4.9a**, **4.2** (1 equiv), cat. (0.1 equiv), $PhCO_2H$ (0.1 equiv), solvent (1 M), rt. [b] Determined by ^1H NMR using 1,4-dioxane as internal standard. [c] Number in parentheses is percentage of unreacted **4.9a** remaining. [d] Determined by ^1H NMR. [e] 2 equivalents of **4.2** used.

The dimerization of nitrosobenzene in solution to **4.31** is well documented and does not affect reactivity,[39–41] however, the rapid consumption of **4.2** was attributed to the irreversible formation of **4.32**, identified by comparison with literature ^1H NMR data (**Scheme 4.8**).[42] While the solvent screens were ongoing, portionwise addition and slow addition of nitrosobenzene (**4.2**) experiments were run to try to limit its decomposition to **4.32** during the reaction (**Table 4.4**). When adding the nitrosobenzene portion-wise (entries

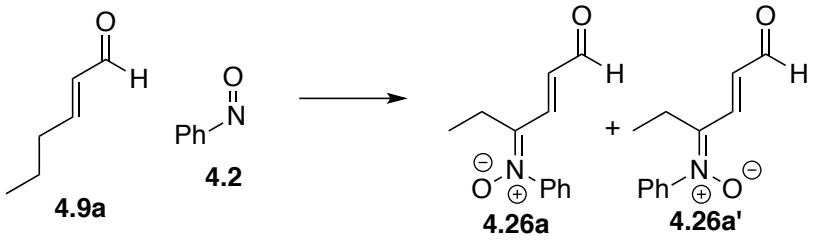
1-4), the best yield was obtained by splitting 1 equivalent into four equal portions, and adding each portion once the previous was fully consumed as determined by ^{1}H NMR (entry 2). This yield and reaction rate, however, did not improve upon existing results, and the amount of **4.32** in the reaction grew steadily with each addition of **4.2**.

Scheme 4.8 Formation of nitrosobenzene dimers.



As for the slow addition reactions, initially catalyst **4.10b** was used since the reaction rate was faster with this catalyst. However, the nitrosobenzene was fully consumed immediately after slow addition was complete, a large amount of **4.32** had formed, and the yield was only 23% (entry 5). Slow addition over two hours using catalyst **4.10a** was not beneficial, as the reaction still required an overnight reaction time in order to reach completion and there was only a moderate improvement in yield over the one-hour slow addition, affording 28% of the product (entry 6 vs. entry 5). Adding the nitrosobenzene over 24 hours did not improve the yield and the nitrosobenzene was fully consumed after only 28 hours, but interestingly the amount of **4.9a** remaining was almost fully accounted for by conversion to the **4.26a** and **4.26a'**, rather than other unknown side products (entry 7).

Table 4.4 Screening of nitrosobenzene addition conditions. [a]



entry	**4.2** (equiv)	portions	addition time (h)	reaction time (h)	yield[b-c] (%)	dr[d] (**4.26a**:**4.26a'**)
1[e]	1.5	2	--	22	14 (20)	7:1
2	1	4	--	21	23 (32)	7:1
3	2	2	--	28	17 (3)	10:1
4	1	2	--	29	20 (13)	8:1
5[f]	1	--	1	1	23 (17)	2:1
6	1	--	2	20	28 (43)	4:1
7	1	--	24	28	23 (74)	2:1

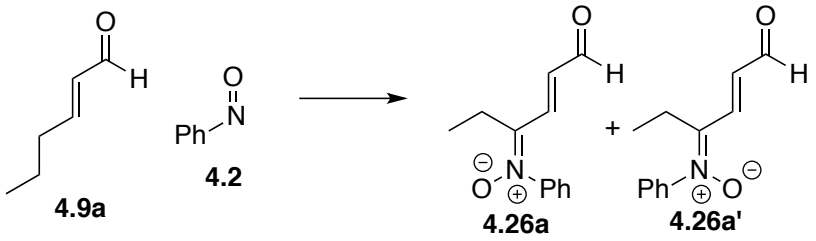
[a] Reaction conditions: **4.9a** (1 equiv), **4.2**, **4.10a** (0.1 equiv), $PhCO_2H$ (0.1 equiv), toluene (1 M), rt. [b] Determined by ^1H NMR using 1,4-dioxane as internal standard. [c] Number in parentheses is percentage of unreacted **4.9a** remaining. [d] Determined by ^1H NMR. [e] Concentration = 1.5 M. [f] Catalyst = **4.10b** (10 mol%).

At this point in the optimization process new chemicals, including new batches of catalyst, were purchased. Upon recommencing the optimization, it was discovered that the reactions were not proceeding as previously observed. The optimal catalyst and solvent conditions had previously been use of **4.10a** in acetonitrile, however, when run with a new batch of catalyst **4.10a**, it was found that the reaction rate rose dramatically, product yield dropped to 13%, and numerous new aldehyde side products were detected, without fully consuming **4.9a** or **4.2** (entry 3 vs. entry 1, **Table 4.5**). The catalyst was found to be impure by TLC and ^1H NMR and another new batch of **4.10a** evaluated. Use of this new batch of **4.10a** increased the product yield to 32%, although this result still did not compare with the previous data (entry 4 vs. entry 1). In addition, the dr also dropped significantly,

nitrosobenzene (**4.2**) had not been fully consumed by the 48 h time point, and multiple new aldehyde side products were forming where previously there were none detected. Switching to toluene, since it was previously the most consistent solvent, there was a slight improvement in yield, but a decrease in dr, and both the aldehyde **4.9a** and nitrosobenzene (**4.2**) had not been fully consumed (entry 4 vs. entry 2). This inconsistency in results with commercial catalysts **4.10a** and **4.10b** was recently documented by Boeckman Jr. and coworkers.[43]

The old and new batches of **4.10b** performed similarly in toluene and acetonitrile, with the new batch generating the product in high dr in toluene (entries 6 and 8, 9 and 10). In order to compensate for the amount of **4.32** formed from **4.2**, the reaction temperature was lowered to -30 ºC (entries 11-14). At -30 ºC, decomposition of nitrosobenzene to **4.32** was greatly limited. Product yield increased using acetonitrile, but the reaction rate decreased (entry 11 vs. 10). Toluene was found to be a superior solvent to THF, affording the highest yield yet, albeit in a longer reaction time (entry 12 vs. entry 13). Upon switching the additive to AcOH, the reaction time decreased to 15 hours while maintaining a 42% yield (entry 14). When 0.5 equivalents nitrosobenzene were used, it was fully consumed, but the combined yield of **4.26a** and **4.26a'** was only 20% (entry 15).

Table 4.5 Optimization with new catalyst batches.[a]



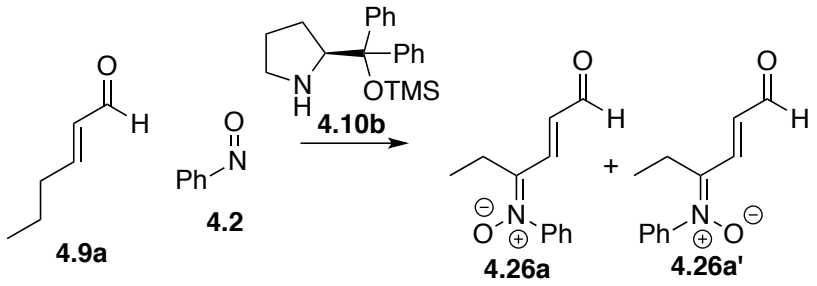
entry	catalyst	solvent	temp (ºC)	time (h)	yield[b-c] (%)	dr[d] (**4.26a**:**4.26a'**)
1	**4.10a**	MeCN	rt	22	41 (31)	5:1
2	**4.10a**	toluene	rt	21	21 (4)	9:1
3	**4.10a**[e]	MeCN	rt	72	13 (7)	nd
4	**4.10a**[f]	MeCN	rt	48	32 (20)	2:1
5	**4.10a**[f]	toluene	rt	22	27 (13)	4:1
6	**4.10b**	toluene	rt	1	31 (7)	3:1
7	**4.10b**	THF	rt	19	35 (21)	2:1
8	**4.10b**	MeCN	rt	3	11 (6)	5:1
9	**4.10b**[g]	toluene	rt	3	27 (7)	6:1
10	**4.10b**[g]	MeCN	rt	3	15 (16)	4:1
11	**4.10b**[g]	MeCN	-30	108	22 (13)	5:1
12	**4.10b**[g]	toluene	-30	66	42	3:1
13[h]	**4.10b**[g]	THF	-30	48	trace	nd
14[h]	**4.10b**[g]	toluene	-30	15	42	4:1
15[i]	**4.10b**[g]	toluene	-30	7	20 (0)	2:1

[a] Reaction conditions: **4.9a**, **4.2** (2 equiv), cat. (0.1 equiv), $PhCO_2H$ (0.1 equiv), solvent (1 M), rt. [b] Determined by ^1H NMR using 1,4-dioxane or cyclohexene as internal standard. [c] Number in parentheses is percentage of unreacted **4.9a** remaining. [d] Determined by ^1H NMR. [e] New batch of **4.10a**. [f] 2nd new batch of **4.10a**. [g] New batch of **4.10b**. [h] AcOH used instead of $PhCO_2H$. [i] 0.5 equiv of **4.2** used.

At this point, a screening of numerous acidic and basic additives was begun (**Table 4.6**). Other than AcOH, the most promising yield was obtained with CF_3CH_2OH, affording a 38% yield in a much longer reaction time (entry 8). Basic additives dramatically increased

the reaction time at -30 ºC (entries 2-4), and at rt were unable to achieve even a matching yield (entries 5-7).

Table 4.6 Additive screen.[a]



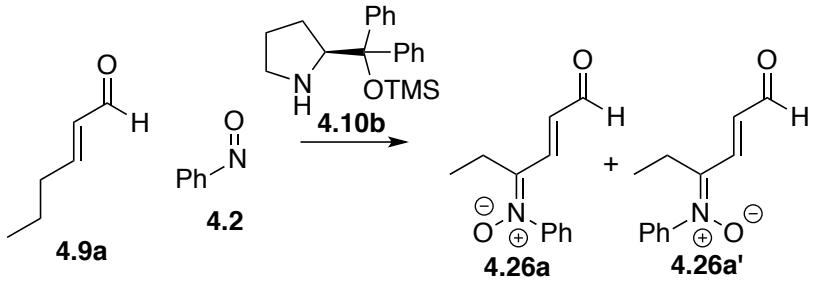
entry	additive	time (h)	yield[b-c] (%)	dr[d] (**4.26a**:**4.26a'**)
1	AcOH	14.5	42	4:1
2	Et_3N	46.25	2 (77)	100:0
3	K_2CO_3	17.25	0.5 (99)	100:0
4	NaOAc	17.25	4 (97)	3:1
5[e]	Et_3N	63	23	10:1
6[e]	K_2CO_3	88	16	7:1
7[e]	NaOAc	38.75	27	8:1
8	CF_3CH_2OH	45.5	38	4:1
9	*p*TsOH	19.5	2	100:1
10	Cl_3CCO_2H	18.5	7	1:1
11	*p*NBA	18.5	28	3:1
12	H_3PO_4	26	17	3:1
13	NH_4Cl	25.75	4	4:1

[a] Reaction conditions: **4.9a**, **4.2** (1 equiv), **4.10b** (0.1 equiv), additive (0.1 equiv), toluene (1 M), -30 ºC. [b] Determined by ^{1}H NMR using cyclohexene as internal standard. [c] Number in parentheses is percentage of unreacted **4.9a** remaining. [d] Determined by ^{1}H NMR. [e] Reaction run at rt.

Additional optimization with catalyst **4.10b** and AcOH was done, varying the loading, temperature, as well as previously unexplored solvents (**Table 4.7**). Lowering the reaction temperature further to -78 ºC suppressed reactivity to the point of inactivity (entry

2), even when the concentration was doubled (entry 3). Running the reaction at -50 ºC, nearly achieved the same yield and dr as at -30 ºC, however reaction time increased significantly (entry 4 vs. entry 1). Lowering the catalyst loading to try to prevent side reaction at -30 ºC also did not increase yield and increased reaction time (entry 5). Decreasing the solvent concentration necessitated a reaction temperature of rt in order for it to proceed, however product yield decreased, although the dr increased significantly (entry 6). Ethanol was revisited as a solvent, and run at a reaction temperature of -30 ºC in order to decrease the previously observed side product formation, however product yield was significantly lowered (entry 7). Trifluoroethanol was also tested as a solvent, due to its previously observed effectiveness as an additive, however it suppressed the reaction entirely (entry 8). Finally, stoichiometric amounts of catalyst **4.10b** and AcOH were used at various low temperatures, but this only afforded lower yields of desired product (entries 9-11). These studies ultimately did not improve the yield or reaction time and showed that the optimal loading was 10 mol% at -30 ºC.

Table 4.7 Optimizations with **4.10b** and AcOH.



entry	equiv **4.10b** and AcOH	solvent	time (h)	temp (ºC)	yield[b] (%)	dr[c] (**4.26a**:**4.26a'**)
1	0.1	toluene	15	-30	42	4:1
2	0.1	toluene	89	-78	3	2:1
3[d]	0.1	toluene	63	-78	3	2:1
4	0.1	toluene	39	-50	40	3:1
5	0.05	toluene	68	-30	38	4:1
6[e]	0.1	toluene	17	rt	34	10:1
7	0.1	EtOH	17	-30	17	7:1
8	0.5	TFE	>96	-30	nr	--
9	1	toluene	1	-30	14	2:1
10	1	toluene	2	-50	15	1:1
11	1	toluene	67	-78	13	100:1

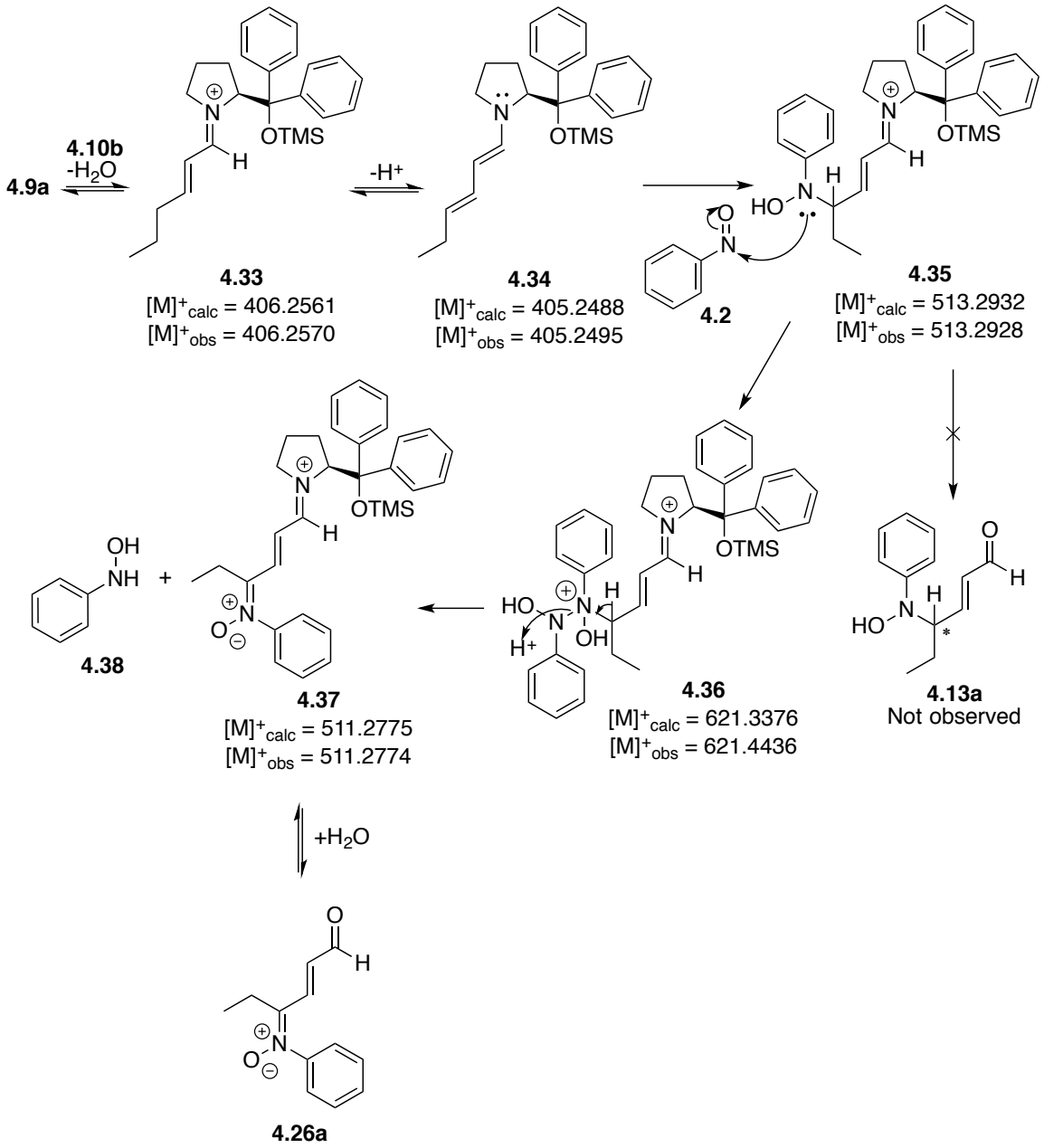
[a] Reaction conditions: **4.9a**, **4.2** (2 equiv), **4.10b**, AcOH, solvent (1 M). [b] Determined by ^{1}H NMR using cyclohexene as internal standard. [c] Determined by ^{1}H NMR. [d] Reaction concentration = 2M. [e] Reaction concentration = 0.25M.

Studies into the mechanism of this transformation were conducted to potentially identify new avenues for optimization. Upon injection of aliquots of the reaction at various time points onto an HRMS by ESI, a number of different intermediates were identified, giving insight into the mechanism (**Scheme 4.9**). Iminium ion intermediates containing both a monomer (**4.35**) and a dimer (**4.36**) of nitrosobenzene in the γ-position were identified, however there was no way to indicate whether or not the dienamine (**4.34**)

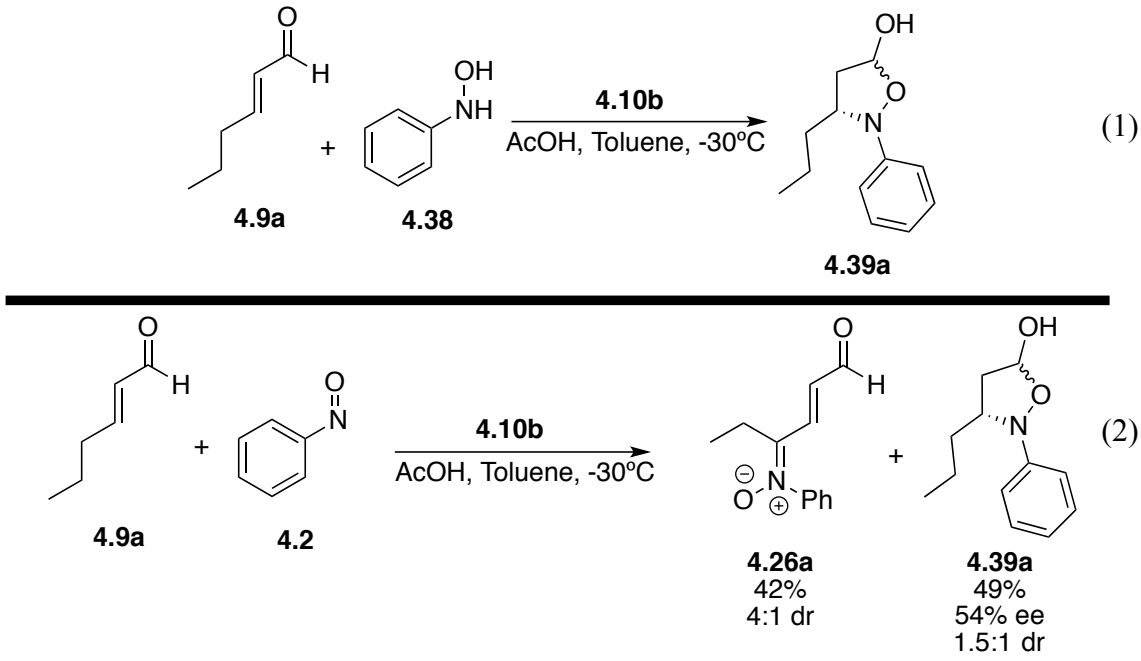
reacted via a [4+2] cycloaddition. The fact that neither HRMS nor ^{1}H NMR detected the oxyaminated aldehyde intermediate (**4.13a**) indicates that the formation of **4.36** is kinetically more favorable than catalyst turnover of **4.35**. This also supports the need for more than one equivalent of nitrosobenzene as it seems the second equivalent is a sacrificial oxidant, acting as a leaving group in the oxidation to the nitrone (**4.37**), generating *N*-phenylhydroxylamine as a byproduct (**4.38**).

As further confirmation of the proposed mechanism, the byproduct (**4.38**) was suspected to act as an aza-Michael donor to form isoxazolidine **4.39a**, consuming the starting enal and limiting the maximum yield of nitrone **4.26a**. Thus *N*-phenylhydroxylamine was examined under the reaction conditions and the product isolated and characterized (**Scheme 4.10**, eq 1). This product was compared with the crude ^{1}H NMR spectrum of the reaction and the isolable side product was identified. Once isolated from the main reaction, its yield was determined to be 49% (eq 2). This meant that the difficulties in improving the yield beyond 42% could be attributed to half of the starting enal being consumed by the **4.38** generated. This is a rare example of divergent reactivity that, with further optimization, could potentially be exploited to rapidly access libraries of desirable heterocycles.

Scheme 4.9 Proposed redox mechanism based on HRMS data.

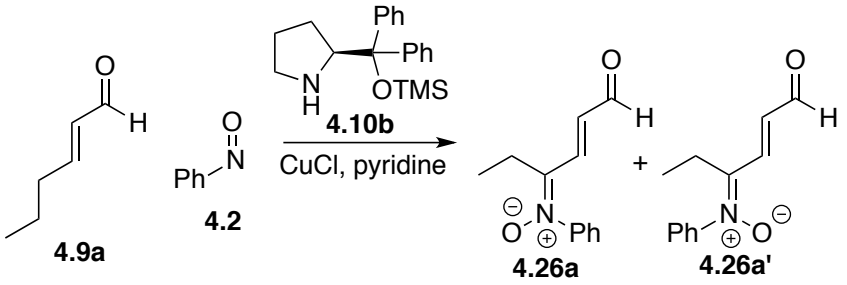


Scheme 4.10 Examination of *N*-phenylhydroxylamine under reaction conditions.



In light of this discovery, efforts were refocused on the optimization of the unprecedented redox formation of nitrones. Now that the culprit in the loss of starting material had been identified, attempts were made to limit this divergent reactivity through reoxidation of **4.38** back to **4.2** in situ. Catalytic CuCl, with pyridine, has been used to oxidize *N*-phenylhydroxylamine to nitrosobenzene in situ and is known to be compatible with organocatalysts, so an optimization with these additives was performed (**Table 4.8**).[44,45] While the presence of CuCl, with and without pyridine, did prevent the formation of isoxazolidine **4.39a**, the yield of the product was dramatically decreased. Due to the added complexity of the reaction conditions, the previous optimization data was reexamined to identify conditions that may have unknowingly suppressed the formation of the side product at the time.

Table 4.8 In situ *N*-phenylhydroxylamine reoxidation.[a]



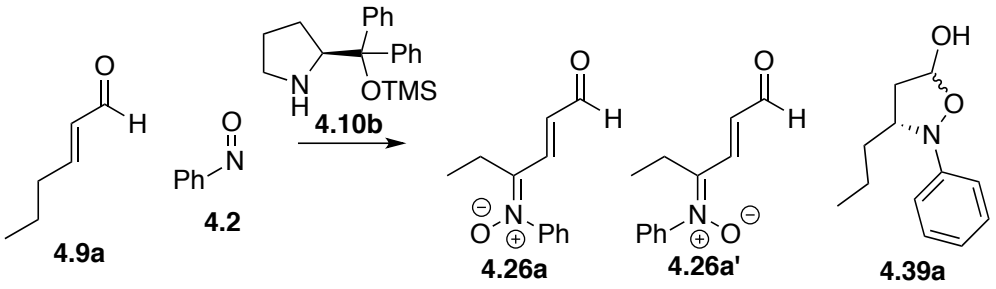
entry	equiv CuCl	equiv pyridine	time (h)	temp (ºC)	yield[b] (%)
1	0.1	0	19	rt	13
2	0.1	0.025	27	rt	19
3	0.1	0	19	0	11
4	0.1	0	25	0	21
5	0.1	0.025	19	0	23
6	0.1	0.025	42	0	34
7[c]	0.1	0.025	120	0	33
8	0.1	0.05	24	0	30
9	0.2	0.05	72	0	33

[a] Reaction conditions: **4.9a**, **4.2** (2 equiv), **4.10b** (0.1 equiv), AcOH (0.1 equiv), CuCl, pyridine, toluene (1 M). Reaction run open to air. [b] Determined by ^{1}H NMR using cyclohexene as internal standard. [c] Reaction run without AcOH.

This identified 1,4-dioxane as a potential solvent. 1,4-dioxane had not been examined in the solvent screening; in early experiments it had been used as an internal standard rather than cyclohexene. In these early experiments, 1,4-dioxane was not added at the point of reaction completion, but was present from the start of the reaction. In these reactions, it was observed that there was a slight decrease in the formation of isoxazolidine side product as compared to reactions not containing this internal standard from the outset. An additional reaction was run using 1,4-dioxane as the solvent at room temperature, as the melting point would not permit temperatures below 12 ºC, which in 27 hours afforded

a comparable yield without full consumption of aldehyde starting material and dramatic reduction of isoxazolidine (entry 2 vs. entry 1, **Table 4.9**).[46] Since nitrosobenzene had been fully consumed, in another experiment 4 eq of nitrosobenzene was added to allow full reaction of enal, a 48% yield was obtained with only 17% yield of isoxazolidine (entry 3). It is worth noting that using 1,4-dioxane as a solvent increased the dr relative to using toluene as solvent. While the dr did not have a bearing on the final yield, a higher favorability toward **4.26a** over **4.26a'** could affect the results of future reactions. Increasing and decreasing the solvent concentration did not dramatically increase or decrease the yield, nor did it affect side product formation or dr (entries 4-5). Finally, doubling the catalyst and acid loading increased the yield to 53%, with only 23% isoxazolidine side product (entry 6). Scaling the reaction by a 10-fold increase maintained the yield and dr (entry 7).

Table 4.9 Optimization with 1,4-dioxane solvent.[a]



entry	**4.2** (equiv)	time (h)	temp (ºC)	yield[b-c] (%)	dr[d] (**4.26a**:**4.26a'**)
1[e]	2	14.5	-30	42 (2, 49)	4:1
2	2	41	rt	40 (21, 23)	9:1
3	4	41	rt	48 (2, 17)	9:1
4[f]	4	39	rt	43	10:1
5[g]	4	144	rt	49	12:1
6[h]	4	15	rt	53	10:1
7[h-i]	4	15.5	rt	54	10:1

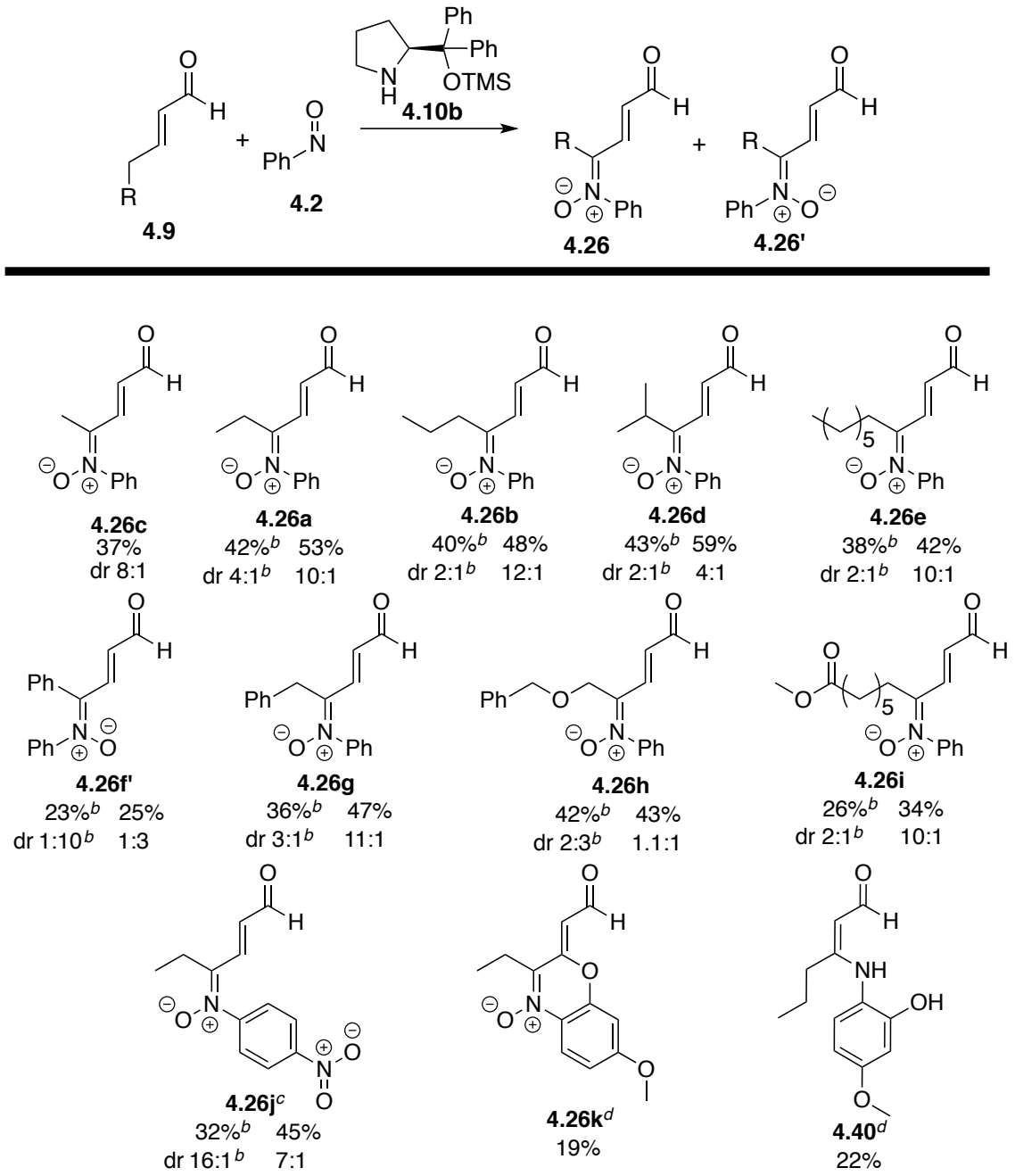
[a] Reaction conditions: **4.9a**, **4.2**, **4.10b** (0.1 equiv), AcOH (0.1 equiv), 1,4-dioxane (1 M). [b] Determined by ^{1}H NMR using cyclohexene as internal standard. [c] Numbers in parentheses are (percentage of unreacted **4.2** remaining, percentage of **4.39a** formed). [d] Determined by ^{1}H NMR. [e] Toluene is reaction solvent. [f] Reaction concentration = 2 M. [g] Reaction concentration = 0.5 M. [h] 0.2 equivalents of **4.10b** and AcOH used. [i] Reaction scaled 10-fold, using **4.9a** (2.5 mmol).

4.3.2 Substrate Scope

A substrate scope was run using these conditions (**Scheme 4.11**). **Scheme 4.11** also displays the data for the substrate scope run prior to the reoptimized 1,4-dioxane conditions, as a comparison. With almost every substrate, yields were moderate with excellent dr. In the case of **4.26f'**, yield was comparably low and, as mentioned previously, the major isomer was opposite what was observed with all other substrates. For this substrate, the best yield was obtained using the previously optimized reaction conditions

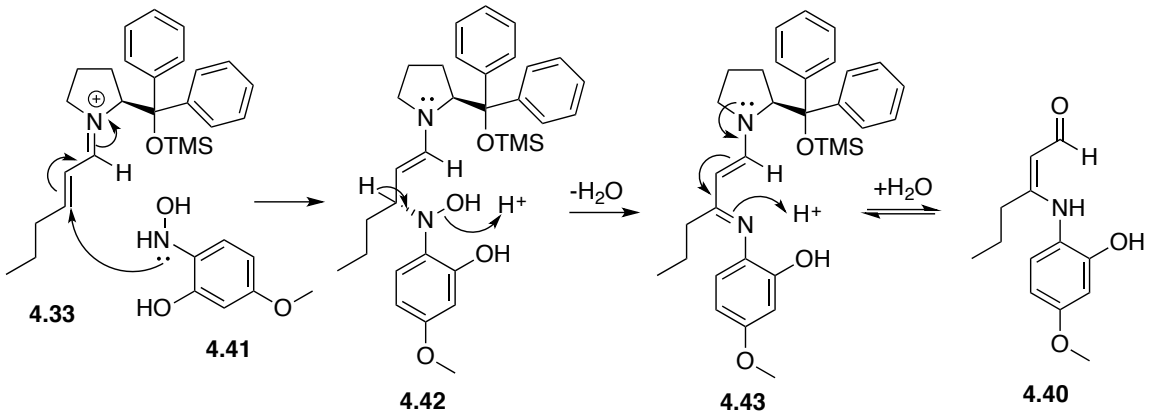
that led to divergent reactivity. The highest yield obtained was 59% (**4.26d**) with enal **4.9d**. 4-nitronitrosobenzene was also used to afford moderate yield and good dr of **4.26j**. The commercially available nitrosophenol used in chapter 4, 2-nitrosoresorcinol monomethylether, yielded two major products in lower yield, oxazine **4.26k** in 19% and enamine **4.40** in 22%. This reaction also required the use of the different reaction conditions, those used in chapter 4, in order to obtain the best yield. A proposed mechanism for the synthesis of **4.40** through an aza-Michael/dehydration reaction with the redox product of 2-nitrosoresorcinol monomethylether (**4.41**) is shown in **Scheme 4.12**. Through this substrate scope, it was shown that these conditions were tolerant of various chain lengths, branching functional groups, and heteroatoms, as well as different variations of nitrosobenzene.

Scheme 4.11 Substrate scope.[a]



[a] Reaction conditions: **4.9**, **4.2** (4 equiv), **4.10b** (0.2 equiv), AcOH (0.2 equiv),1,4-dioxane (1 M), rt, 14−18 h. Yield and dr determined by ^{1}H NMR using cyclohexene as internal standard. [b] Reaction conditions: **4.9**, **4.2** (2 equiv), **4.10b** (0.1 equiv), AcOH (0.1 equiv), toluene (1 M), −30 °C. [c] Used 4-nitronitrosobenzene in place of **4.2**. [d] Reaction conditions: **4.9**, 2-nitrosoresorcinol monomethylether (2 equiv), **4.10b** (0.1 equiv), $CHCl_3$ (0.5 M), rt.

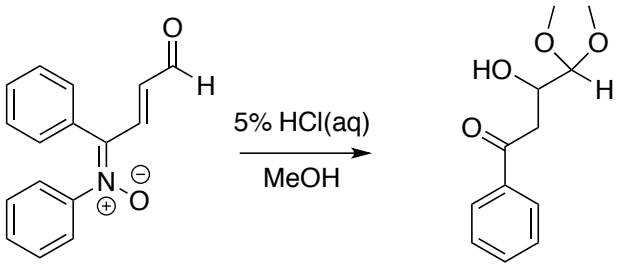
Scheme 4.12 Proposed formation of **4.40**, via hydroxylamine **4.41**.



4.3.3 Derivatives

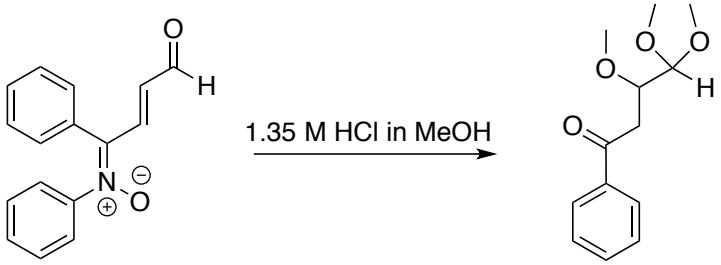
Investigations into the earlier proposed derivatives **4.16** and **4.18** were commenced following the substrate scope. Hydrolysis of the nitrone was explored first because the transformation is heavily reported under various acidic and basic conditions, but these reactions were never performed in the presence of aldehydes.[8–22] From the start, the presence of the aldehyde caused problems. Running the reaction with aqueous hydrochloric acid in methanol afforded many inseparable products (**Scheme 4.13**). The main product identified, indicated that hydrolysis does occur, but with acetal formation from the methanol and conjugate addition from the water at the ketone's β-position to form **4.44** in <5% yield (eq 1). As this conjugate addition was not desired, using anhydrous HCl in methanol was proposed, as the formation of acetals could be reversed. In this case, however methanol replaced the water as the nucleophile for conjugate addition, following hydrolysis and acetal formation, albeit in a 36% yield of **4.45** in a much cleaner reaction (eq 2).

Scheme 4.13 Acid hydrolysis of *γ*-nitrone enal **4.26f'**.



4.26f' **4.44** <5%

(1)



4.26f' **4.45** 36%

(2)

At this point, conditions from a recent paper that reported the hydrolysis of a hydrazine (**4.46**) using Amberlyst-15 and paraformaldehyde were evaluated (**Scheme 4.14**).[47] As these were inexpensive components, it was worth exploring whether these conditions could translate to a nitrone as well. Using the reaction conditions as reported showed some promise, a new aldehyde product was visible by ^{1}H NMR, with very little decomposition apparent, but after four days the reaction did not approach completion. This aldehyde was isolated and confirmed by ^{1}H and ^{13}C NMR, as well as HRMS, to be **4.48** obtained in 18% yield (entry 1, **Table 4.10**). Increasing the reaction temperature to 40 ºC led to complete consumption of nitrone in 2.5 days with a 32% isolated yield (entry 2). At this point, optimizing the loading of paraformaldehyde and Amberlyst-15, as well as the concentration and the reaction temperature improved the reaction yield. Ultimately it was

determined that the best yield of **4.48**, 63% in 21 hours, could be obtained by quadrupling the loading of Amberlyst-15 at 40 ºC (entry 8).

Scheme 4.14 Hydrolysis method using paraformaldehyde and Amberlyst-15.[47]

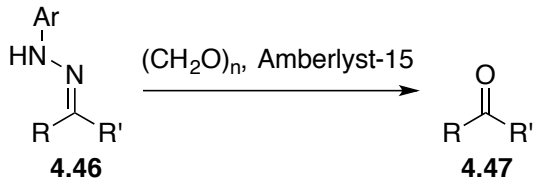
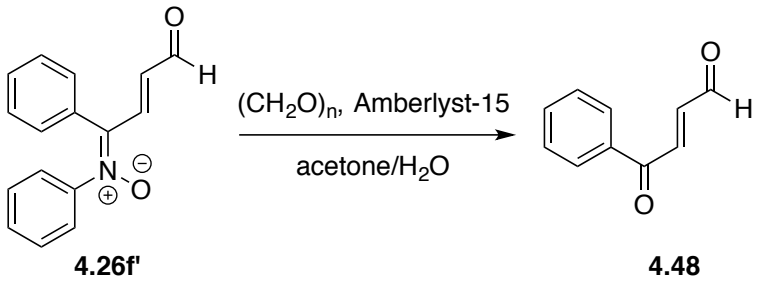


Table 4.10 Optimization of hydrolysis conditions.[a]



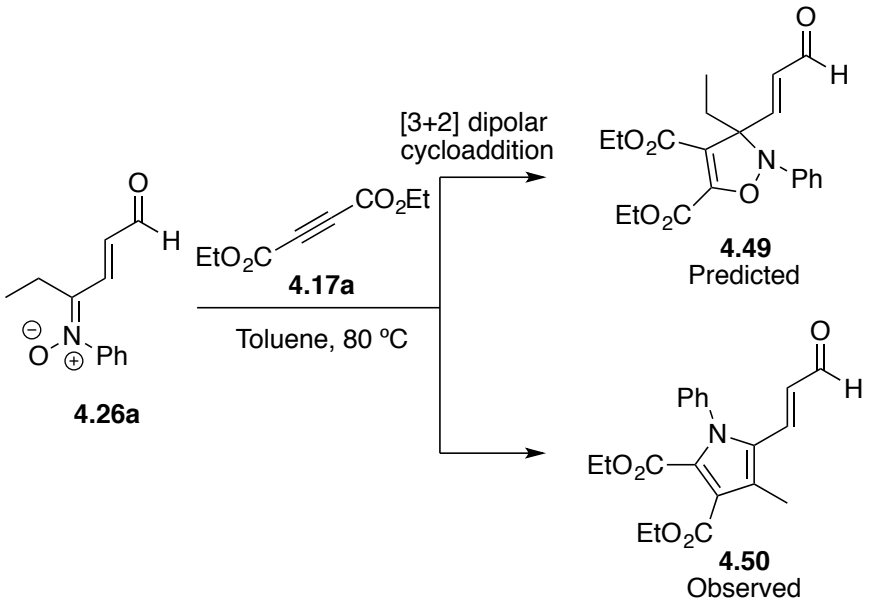
entry	$(CH_2O)_n$ (eq)	Amberlyst-15 (mass $(CH_2O)_n$/1.4)	temp (ºC)	time (h)	yield[b] (%)
1	8.1	x1	rt	96	18[c]
2	8.1	x1	40	60	32[c]
3	8.1	x1	50	60	22
4	16.2	x0.5	40	72	--
5	8.1	x2	40	44	42
6[d]	8.1	x1	40	72	--
7	8.1	x8	40	9	59
8	8.1	x4	40	21	63

[a] Reaction conditions: **4.26f'**, $(CH_2O)_n$, Amberlyst-15 (mass $(CH_2O)_n$/1.4), acetone (0.083 M), water (0.83 M). [b] Determined by ^{1}H NMR using cyclohexene as internal standard. [c] Isolated yield. [d] Concentration acetone = 0.166 M and concentration water = 1.66 M.

A [3+2] dipolar cycloaddition with diethyl acetylene dicarboxylate (**4.17a**) was explored as well. Initial reaction conditions afforded one major product in very low yield.

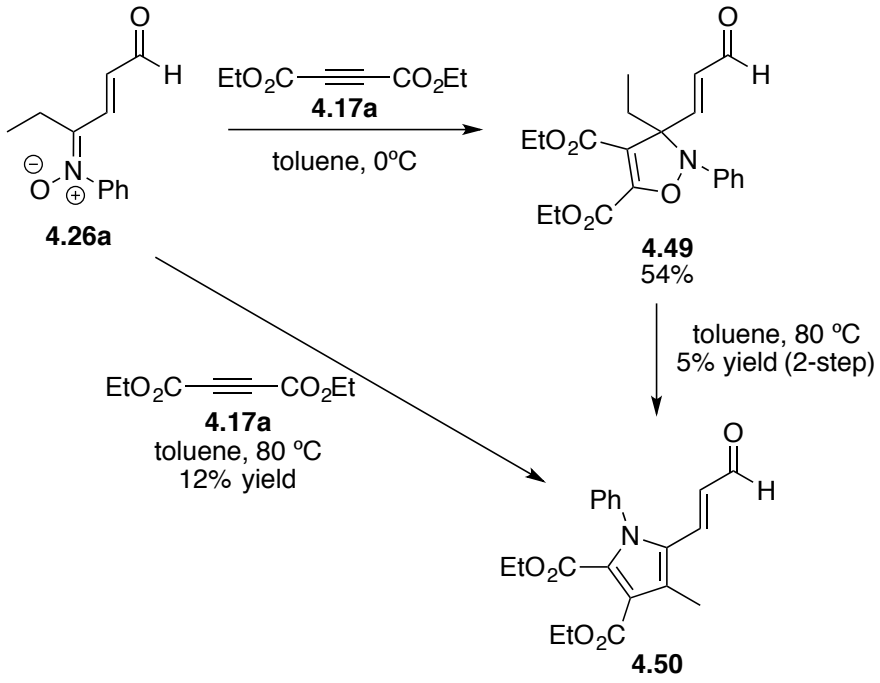
This turned out not to be the expected dihydroisoxazole, **4.49**, but instead a pentasubstituted pyrrole, **4.50** (**Scheme 4.15**).

Scheme 4.15 Cycloaddition with diethyl acetylene dicarboxylate (**4.17a**).

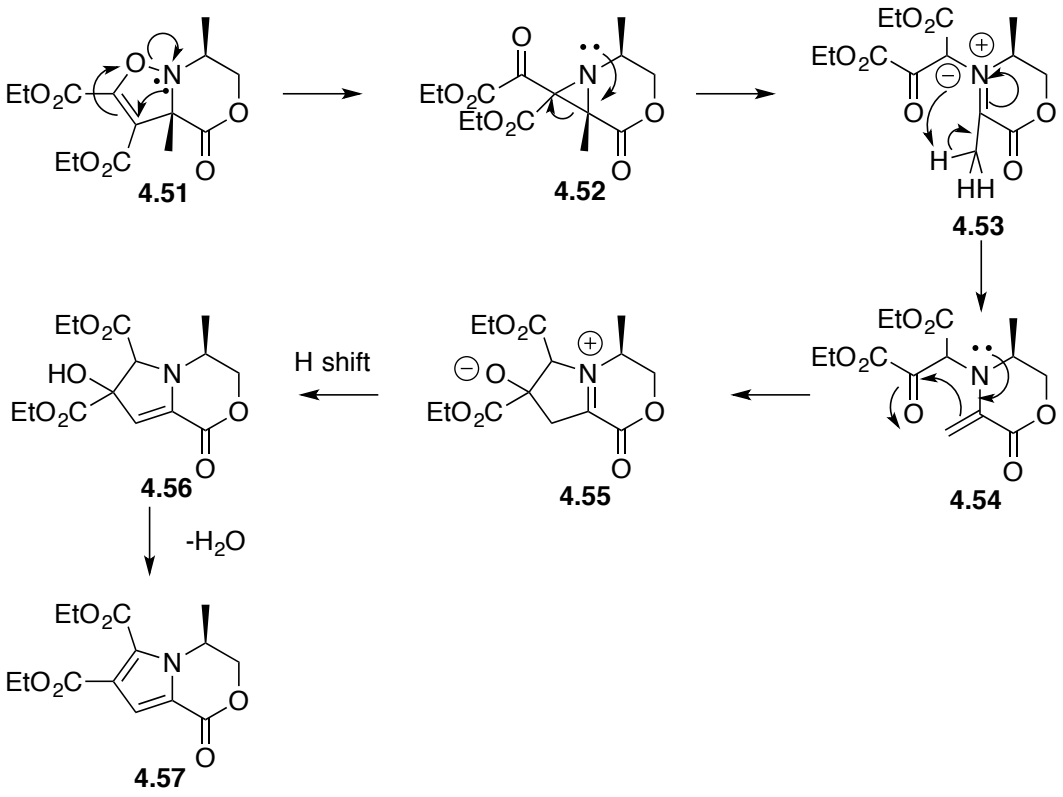


Bringing down the reaction temperature revealed rapid formation of **4.49**, followed by gradual formation of **4.50** as **4.49** is consumed. Once brought to 0 ºC, it was found that the predicted product formed preferentially, with a yield of 54%, while at 80 ºC the pyrrole formed in 12% yield (**Scheme 4.16**). Additionally, heating the isolated dihydroisoxazole (**4.49**) formed the pyrrole in 5% yield, which supported the intermediacy of dihydroisoxazoles (i.e. **4.49**, **4.51**) in the synthesis of pyrroles (i.e. **4.50**, **4.57**) as per literature reports (**Scheme 4.17**).[26]

Scheme 4.16 Synthesis of dihydroisoxazole and pyrrole.



Scheme 4.17 Literature mechanism for pyrrole formation.[26]



4.4 Conclusions

In this project, the first catalytic method to directly introduce nitrone functionality in the presence of an aldehyde was developed. This is an unprecedented organocatalytic redox reaction, in which an enal is oxidized to a conjugated γ-nitrone enal via dienamine catalysis, while an additional equivalent of nitrosobenzene is reduced to *N*-phenylhydroxylamine. In toluene, the presence of the *N*-phenylhydroxylamine leads to the divergent synthesis of both nitrones and isoxazolidines in 91% combined yield. This could potentially be exploited to create three separate libraries of desirable heterocycles (i.e. isoxazolidines, dihydroisoxazoles, and pyrroles) with high conservation of almost all starting materials, the formation of pyrrole **4.42** being the exception. However, running the reaction in 1,4-dioxane suppressed the formation of isoxazolidines and increased the yield of nitrone. The nitrone could be hydrolyzed to obtain γ-keto enals, thereby achieving a synthesis of the latter, which is not typically possible using non-metallic reagents, by taking advantage of this new metal-free allylic oxidation.[48–52] Importantly, the reaction products have two handles for further functionalization, and the nitrone can be manipulated orthogonally to the aldehyde.[53]

4.5 References

(1) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125* (36), 10808–10809.
(2) Zhong, G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4247–4250.
(3) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tet. Lett.* **2003**, *44*, 8293–8296.
(4) Momiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101* (15), 5374–5378.
(5) Kano, T.; Ueda, M.; Takai, J.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6046–6047.
(6) Palomo, C.; Vera, S.; Velilla, I.; Mielgo, A.; Gómez-Bengoa, E. *Angew. Chem. Int. Ed.* **2007**, *46*, 8054–8056.
(7) Mielgo, A.; Velilla, I.; Gómez-Bengoa, E.; Palomo, C. *Chem. Eur. J.* **2010**, *16*, 7496–7502.
(8) Grela, K.; Konopski, L. *Tetrahedron* **2010**, *66*, 3614–3622.
(9) Grela, K.; Konopski, L. *Tetrahedron* **2010**, *66*, 3608–3613.
(10) Freisleben, A.; Schieberle, P.; Rychlik, M. *J. Agric. Food Chem.* **2002**, *50*, 4760–4768.
(11) Krohn, K.; Küpke, J. *J. Prakt. Chem.* **1999**, *341* (5), 509–511.
(12) Kurtzweil, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3426–3434.
(13) Lin, C.-T.; Din, L.-W.; Wang, S.-L. *Heterocycles* **1989**, *29* (2), 263–268.
(14) Arjona, O.; De La Pradilla, R. F.; Perez, R. A.; Plumet, J. *Tetrahedron* **1988**, *44* (23), 7199–7204.
(15) Black, D. S. C.; Strauch, R. J. *Aust. J. Chem* **1988**, *41*, 183–193.
(16) Black, D. S. C.; Strauch, R. J. *Aust. J. Chem* **1988**, *41*, 1613–1619.
(17) Greenfield, S.; Mackenzie, K. *J. Chem. Soc., Perkin Trans. II* **1986**, 1651–1666.
(18) Coates, R. M.; Firsan, S. J. *J. Org. Chem.* **1986**, *51*, 5198–5209.
(19) Matoba, K.; Morita, T.; Yamazaki, T. *Chem. Pharm. Bull.* **1983**, *31* (12), 4368–4375.
(20) Matoba, K.; Morita, T.; Yamazaki, T. *Chem. Pharm. Bull.* **1982**, *30* (10), 3863–3864.
(21) Schenk, C.; De Boer, T. J. *Tetrahedron* **1979**, *35*, 147–153.
(22) Leanza, W. J.; Conbere, J. P.; Rogers, E. F.; Pfister 3rd, K. *J. Am. Soc. Chem.* **1954**, *76*, 1691–1694.
(23) Yu, Y.; Ohno, M.; Eguchi, S. *Tet. Lett.* **1991**, *32* (37), 4965–4968.
(24) Letcher, R. M.; Sin, D. W. M.; Cheung, K.-K. *J. Chem. Soc., Perkin Trans. I* **1993**, 939–944.
(25) Díaz, M.; Guitián, E.; Castedo, L. *Synlett* **2001**, No. 7, 1164–1166.
(26) Heaney, F.; Fenlon, J.; O'Mahony, C.; McArdle, P.; Cunningham, D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3382–3392.
(27) Aly, A. A.; Hopf, H.; Ernst, L.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2006**, 3001–3006.
(28) Murray, W. V; Francois, D.; Maden, A.; Turchi, I. *J. Org. Chem.* **2007**, *72*, 3097–3099.
(29) Lopes, S. M. M.; Nunes, C. M.; Pinho e Melo, T. M. V. D. *Tetrahedron* **2010**, *66*, 6078–6084.

(30) Wu, M.-Y.; He, W.-W.; Liu, X.-Y.; Tan, B. *Angew. Chem. Int. Ed.* **2015**, *54*, 9409–9413.
(31) Song, H.-J.; Lim, C. J.; Lee, S.; Kim, S. *Chem. Commun.* **2006**, 2893–2895.
(32) Grigor'ev, I. A. In *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; Feuer, H., Ed.; John Wiley & Sons: Hoboken, 2008; pp 129–434.
(33) Jeong, J.; Lee, D.; Chang, S. *Chem. Commun.* **2015**, *51*, 7035–7038.
(34) Hwang, H.; Kim, J.; Jeong, J.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136* (30), 10770–10776.
(35) Hutchinson, D. K.; Flentge, C. A.; Donner, P. L.; Wagner, R.; Maring, C. J.; Kati, W. M.; Liu, Y.; Masse, S. V.; Middleton, T.; Mo, H.; Montgomery, D.; Jiang, W. W.; Koev, G.; Beno, D. W. A.; Stewart, K. D.; Stoll, V. S.; Molla, A.; Kempf, D. J. *Bioorganic Med. Chem. Lett.* **2011**, *21*, 1876–1879.
(36) Adam, W.; Zhao, C.-G.; Jakka, K. *Org. React.* **2008**, *69*, 1–364.
(37) Nour, T. A.; Ebaid, W. S. *Chem. Ind.* **1986**, 143.
(38) Nakama, K.; Seki, S.; Kanemasa, S. *Tet. Lett.* **2001**, *42*, 6719–6722.
(39) Chemica, C.; Ccacaa, A.; Knežević, A.; Medančić, T.; Milovac, S.; Biljan, I.; Halasz, I.; Vančik, H. *Croat. Chem. Acta* **2011**, *84* (1), 21–24.
(40) Biljan, I.; Cvjetojevic, G.; Smrecki, V.; Novak, P.; Mali, G.; Plavec, J.; Babic, D.; Mihalic, Z.; Vancik, H. *J. Mol. Struc.* **2010**, *979*, 22–26.
(41) Orrell, K. G.; Sik, V.; Stephenson, D. *Magn. Reson. Chem.* **1987**, *25*, 1007–1011.
(42) Ramachary, D. B.; Barbas, C. F. *Org. Lett.* **2005**, *7*, 1577–1580.
(43) Boeckman, R. K.; Biegasiewicz, K. F.; Tusch, D. J.; Miller, J. R. *J. Org. Chem.* **2015**, *80* (8), 4030–4045.
(44) Frazier, C. P.; Engelking, J. R.; Read De Alaniz, J. *J. Am. Chem. Soc.* **2011**, *133* (27), 10430–10433.
(45) Frazier, C. P.; Bugarin, A.; Engelking, J. R.; Read De Alaniz, J. *Org. Lett.* **2012**, *14* (14), 3620–3623.
(46) Suzuki, T.; Fujisawa, M.; Takagi, S.; Kimura, T. *J. Therm. Anal. Calorim.* **2006**, *85*, 545–550.
(47) Miles, D. H.; Guasch, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137* (24), 7632–7635.
(48) D'Auria, M.; De Mico, A.; D'Onofrio, F.; Scettri, A. *Synthesis (Stuttg).* **1985**, 988–990.
(49) Fernandes, R. A.; Kumar, P. *Tet. Lett.* **2003**, *44*, 1275–1278.
(50) Yu, J. Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125* (11), 3232–3233.
(51) McLaughlin, E. C.; Choi, H.; Wang, K.; Chiou, G.; Doyle, M. P. *J. Org. Chem.* **2009**, *74* (2), 730–738.
(52) Zope, D. D.; Patnekar, S. G.; Kanetkar, V. R. *Indian Perfum.* **2011**, *55*, 27–28.
(53) Fraboni, A. J.; Brenner-Moyer, S. E. *Org. Lett.* **2016**, *18*, 2146–2149.

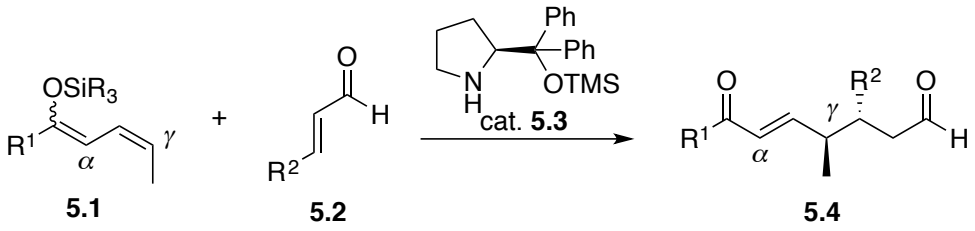
CHAPTER 5

STEREOCHEMISTRY DETERMINATION FOR THE PRODUCTS OF DIRECT VINYLOGOUS MICHAEL ADDITIONS OF LINEAR ENONES

5.1 VINYLOGOUS MICHAEL REACTIONS

As mentioned in **Chapter 1**, vinylogous Michael reactions have been synthetically challenging due to difficulties arising from the competing nucleophilicity of the α- and γ-positions of dienamines and dienolates.[1,2] Most of these reactions have used cyclic vinylogous Michael donors that contain at least one electron-rich endocyclic alkene in combination with steric and/or electronic biases towards γ-substitution.[1–20] More recently, indirect linear vinylogous Mukaiyama-Michael donors (**5.1**) were reported utilizing bulky R^1-groups to block the α-nucleophilic position from reacting, obtaining high stereoselectivity and high yields of **5.4** (**Scheme 5.1**).[21,22]

Scheme 5.1 First indirect vinylogous Michael additions with linear substrates.

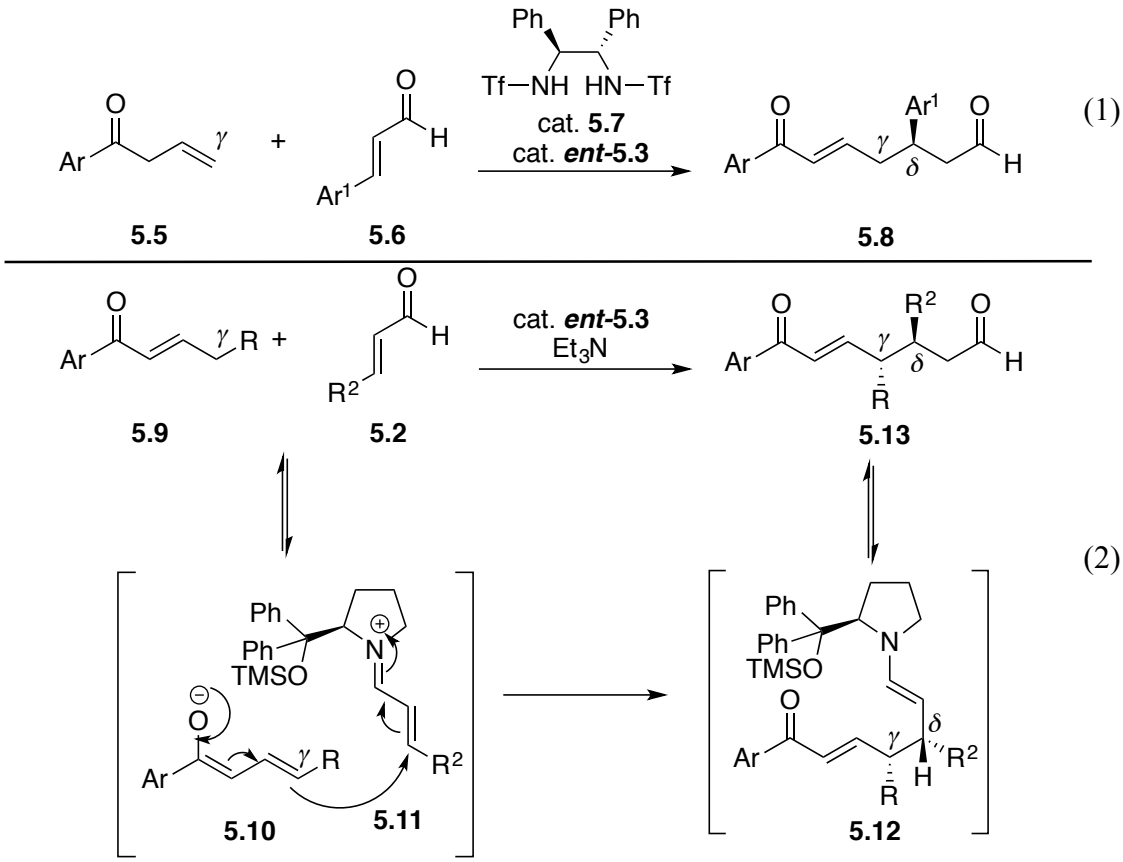


5.1.1 Direct organocatalytic linear vinylogous Michael reactions

The Xu and Brenner-Moyer groups have recently reported the only two direct vinylogous Michael reactions with linear substrates.[23,24] Xu and coworkers used β,γ-unsaturated ketones (**5.5**), which were unhindered by substitution at the γ-position, while

cocatalyst **5.7** was proposed to block reactivity at the α-position through hydrogen bonding with the ketone (**Scheme 5.2**, eq 1). The Brenner-Moyer group introduced a complementary method that utilized conjugated ketones both with and without substitution at the γ-position (**5.9**, **Scheme 5.2**, eq 2). In this work, high regioselectivity for the γ-position was reported as well, however this was attributed to steric effects from the R^2-group on Michael acceptor **5.2**.

Scheme 5.2 First direct vinylogous Michael additions with linear substrates

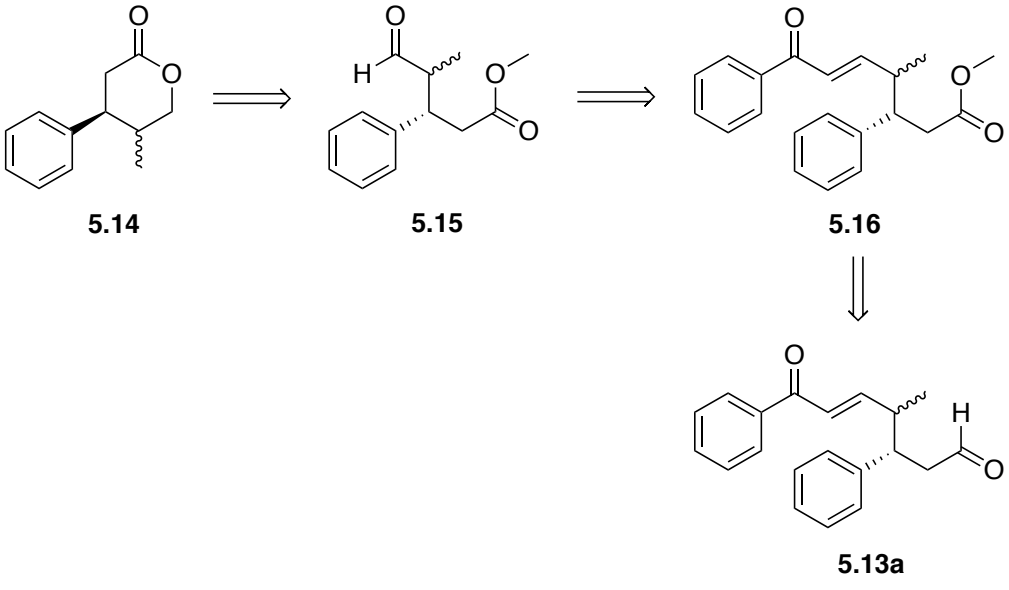


The stereochemistry at the δ-position of products **5.13** could be easily determined through analogy with similar products of conjugate additions using organocatalyst ***ent*-5.3**, such as **5.8** (eq 1). The stereochemistry at the γ-position, however, was difficult to assign

as previous research on the subject either did not have the complexity or were not linear, thus simplifying the determination of the stereostructure.

After several failed attempts at stereochemical determination, it was determined that in order to elucidate the absolute stereochemistry of **5.13a**, a derivative would need to be synthesized that would be easily distinguishable between its stereoisomers. The target chosen was lactone **5.14**, as it is well documented as having distinctive ^{1}H NMR spectra between the *cis*- and *trans*-isomers.[21] Working backwards from this lactone, a procedure to transform **5.15** to **5.15** already existed, so the goal would be to get up to this point from **5.13a** (**Scheme 5.3**). Oxidation of the aldehyde to the ester would be the first step. This would be accomplished with mild reaction conditions, such as Pinnick oxidation followed by an esterification to give **5.16**. Next, OsO_4 followed by $NaIO_4$ could be safely employed to yield **5.15** with, ideally, few side products.

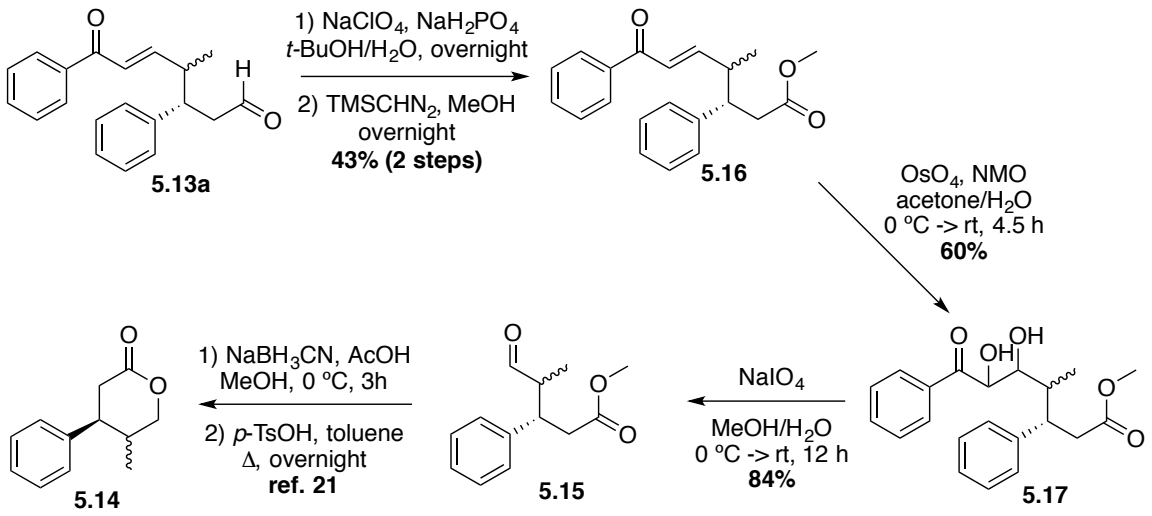
Scheme 5.3 Retrosynthetic plan



5.2 Results and Discussion

The product, **5.13a**, was converted to the carboxylic acid using Pinnick oxidation conditions. Following reaction completion, the crude acid was protected using trimethylsilyldiazomethane to form the methyl ester **5.16**, in a 43% two-step yield. The ester could now be oxidized with OsO_4 to diol, **5.17**, in 60% yield. The diol then underwent oxidative cleavage, using $NaIO_4$ to form aldehyde **5.15** in 84% yield. Finally, using known procedures, this aldehyde was selectively reduced to the alcohol using $NaBH_3CN$, followed by lactonization to form **5.14**.[21]

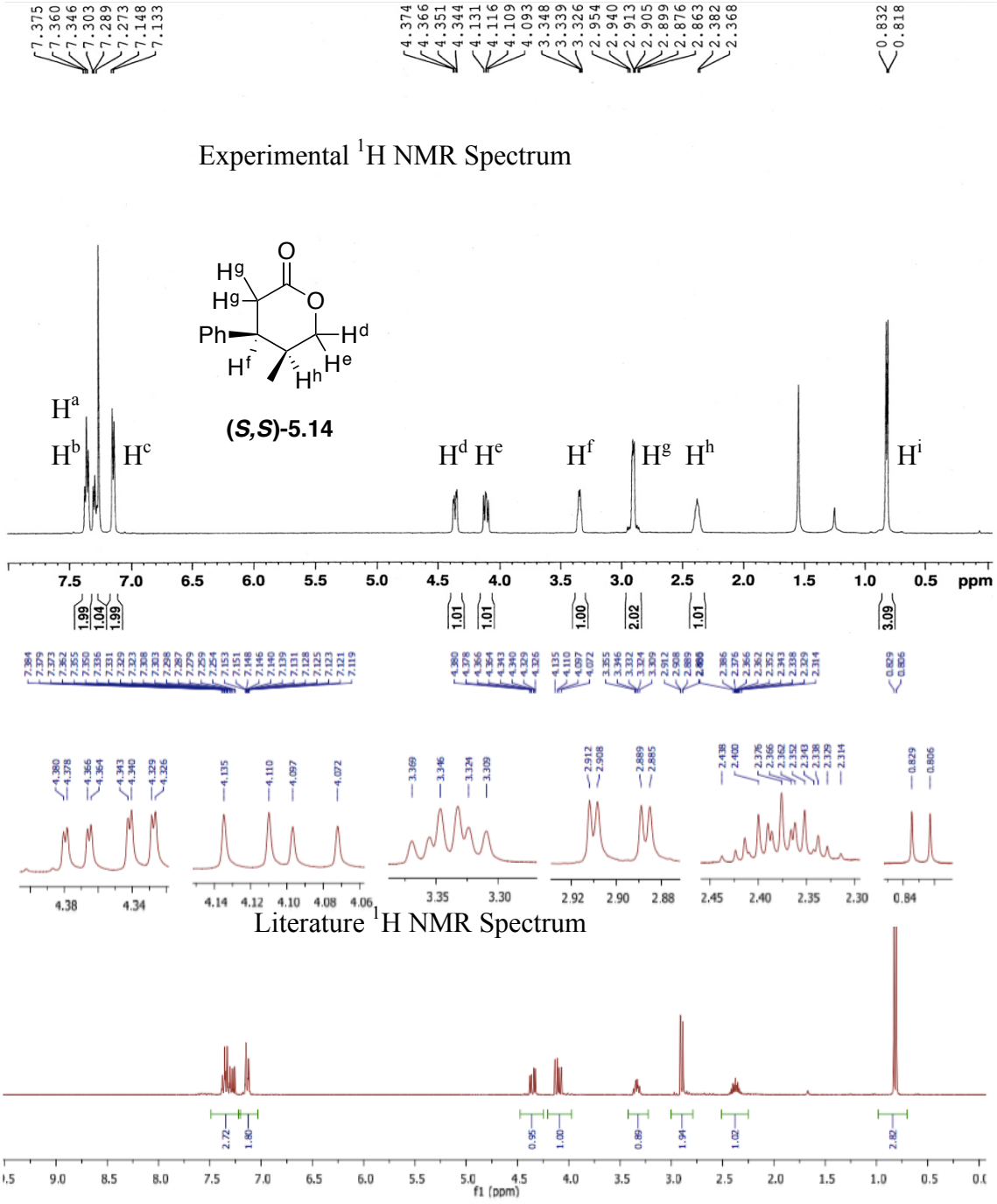
Scheme 5.4 Synthesis of lactone



The relative stereochemistry was determined by examining characteristic peaks in the ^{1}H NMR spectrum as compared to literature data (**Figure 5.1**).[21] The protons appearing as multiplets at 3.35-3.33 ppm (H^f) and 2.38-2.37 ppm (H^h) are shifted downfield from where they would appear in the *trans*-lactone, and they match the corresponding literature data for the *cis*-lactone. The two protons appearing as the 2.95-2.86 ppm multiplet (H^g) match the shift for the corresponding *cis*-lactone as well, while in the *trans*-lactone these

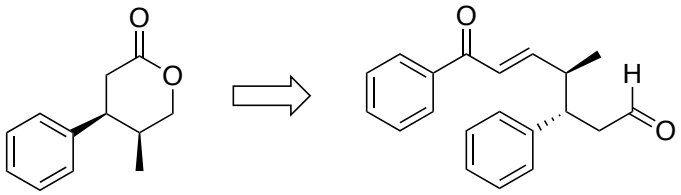
protons would be diastereotopically split, having distinct chemical shifts at 2.76 ppm and 2.66 ppm. Another distinction is the doublet of doublets appearing at 4.11 ppm (H^e), which is shifted slightly downfield from the triplet associated with the same proton in the *trans*-lactone.

Figure 5.1 Comparison between experimental and literature spectra.[21]



This evidence led to the conclusion that lactone **5.14** is in fact in the *cis*-configuration, which could be used to determine that the relative stereochemistry of the product is *trans*-isomer **(*S,S*)-5.13a** (**Scheme 5.5**).

Scheme 5.5 Translating the absolute stereochemistry of **5.21** to **5.10a**



(*S,S*)-5.14 **(*S,S*)-5.13a**

5.3 Conclusion

This research was able to accomplish one of the first direct vinylogous Michael additions with linear substrates. The products were isolated in moderate to high yields, with high regioselectivity for the γ-product and high stereoselectivity. While the stereochemistry at the δ-position could be determined by analogy with similar organocatalytic reactions, the linear nature of the molecule and the lack of crystallinity of the products for X-ray crystallography made determination of the stereochemistry at the γ-position more elusive. Ultimately, the product was derivatized in order to synthesize a product that had notable spectral differences between the two potential diastereomers. This revealed that the structure was that of the (*S,S*)-isomer. This also showed that the product was stable enough to undergo a number of transformations while preserving the stereochemistry, demonstrating the utility of this methodology in organic synthesis.

5.4 References

(1) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111* (5), 3076–3154.
(2) Schneider, C.; Abels, F. *Org. Biomol. Chem.* **2014**, *12* (22), 3531–3543.
(3) Dell'Amico, L.; Rassu, G.; Zambrano, V.; Sartori, A.; Curti, C.; Battistini, L.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *J. Am. Chem. Soc.* **2014**, *136* (31), 11107–11114.
(4) Li, Q.-Z.; Gu, J.; Chen, Y.-C. *RSC Adv.* **2014**, *4* (71), 37522.
(5) Alizadeh, A.; Sedighian, H.; Bayat, F. *Synlett* **2014**, *25* (3), 389–392.
(6) Rout, S.; Ray, S. K.; Unhale, R. A.; Singh, V. K. *Org. Lett.* **2014**, *16* (21), 5568–5571.
(7) Brindani, N.; Rassu, G.; Dell'Amico, L.; Zambrano, V.; Pinna, L.; Curti, C.; Sartori, A.; Battistini, L.; Casiraghi, G.; Pelosi, G.; Greco, D.; Zanardi, F. *Angew. Chem. Int. Ed.* **2015**, 7386–7390.
(8) Joie, C.; Deckers, K.; Raabe, G.; Enders, D. *Synthesis (Stuttg).* **2014**, *46* (11), 1539–1546.
(9) Chen, Y. R.; Das, U.; Liu, M. H.; Lin, W. *J. Org. Chem.* **2015**, *80* (3), 1985–1992.
(10) Gu, X.; Guo, T.; Dai, Y.; Franchino, A.; Fei, J.; Zou, C.; Dixon, D. J.; Ye, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 10249–10253.
(11) Wang, Z.-H.; Wu, Z.-J.; Huang, X.-Q.; Yue, D.-F.; You, Y.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Chem. Commun.* **2015**, *51* (87), 15835–15838.
(12) Sekikawa, T.; Kitaguchi, T.; Kitaura, H.; Minami, T.; Hatanaka, Y. *Org. Lett.* **2015**, *17* (12), 3026–3029.
(13) Chen, Q.; Wang, G.; Jiang, X.; Xu, Z.; Lin, L.; Wang, R. *Org. Lett.* **2014**, *16* (5), 1394–1397.
(14) Xiao, X.; Mei, H.; Chen, Q.; Zhao, X.; Lin, L.; Liu, X.; Feng, X. *Chem. Commun.* **2015**, *51*, 580–583.
(15) Di Iorio, N.; Righi, P.; Ranieri, S.; Mazzanti, A.; Margutta, R. G.; Bencivenni, G. *J. Org. Chem.* **2015**, *80* (14), 7158–7171.
(16) Rassu, G.; Zambrano, V.; Pinna, L.; Curti, C.; Battistini, L.; Sartori, A.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal.* **2014**, *356* (10), 2330–2336.
(17) Zhang, Y.; Wei, B.; Lin, H.; Cui, W.; Zeng, X.; Fan, X. *Adv. Synth. Catal.* **2015**, *357* (6), 1299–1304.
(18) Steinkamp, A.-D.; Frings, M.; Thomé, I.; Schiffers, I.; Bolm, C. *Chem. Eur. J.* **2015**, *21*, 7705–7708.
(19) Li, J.; Huang, R.; Xing, Y.-K.; Qiu, G.; Tao, H.-Y.; Wang, C.-J. *J. Am. Chem. Soc.* **2015**, 150804132353001.
(20) Jadhav, A. P.; Bhaskara Rao, V. U.; Singh, P.; Gonnade, R. G.; Singh, R. P. *Chem. Commun. (Camb).* **2015**, *51* (73), 13941–13944.
(21) Gupta, V.; Sudhir, S. V.; Mandal, T.; Schneider, C. *Angew. Chem. Int. Ed.* **2012**, *51* (50), 12609–12612.
(22) Basu, S.; Gupta, V.; Nickel, J.; Schneider, C. *Org. Lett.* **2014**, *16* (1), 274–277.
(23) Gu, Y.; Wang, Y.; Yu, T. Y.; Liang, Y. M.; Xu, P. F. *Angew. Chem. Int. Ed.* **2014**, *53* (51), 14128–14131.
(24) Guo, Q.; Fraboni, A. J.; Brenner-Moyer, S. E. *Org. Lett.* **2016**, *18*, 2628–2631.

CHAPTER 6
EXPERIMENTAL AND CHARACTERIZATION

6.1 General Information

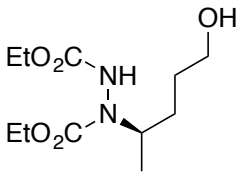
All chemicals and solvents were purchased from Sigma-Aldrich, Fisher Scientific, or TCI America. ^{1}H, ^{13}C, and ^{15}N NMR data were acquired on Bruker 400 MHz and 500 MHz NMR spectrometers and use the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublets of doublets, brm = broad multiplet, brs = broad singlet. HRMS spectra were acquired using an MS spectrometer with Q-TOF mass analyzer. Flash chromatography was carried out with F60, 40−63 mm, 60 Å silica gel and EMD silica 60 F254 glass TLC plates. Solvents were dried and kept air-free in a solvent purification unit, and were evaporated using a standard rotovapor and high vacuum. All reactions were carried out in oven- dried glassware, under an Ar atmosphere. All enals were distilled freshly before use. Reactions were cooled to -30ºC and below using a ThermoFisher Scientific EK90 cryocooler. Crystallographic data obtained by William W. Brennessel of the University of Rochester Department of Chemistry X-ray Crystallographic Facility.

6.2 Experimental and Characterization for Chapter 2

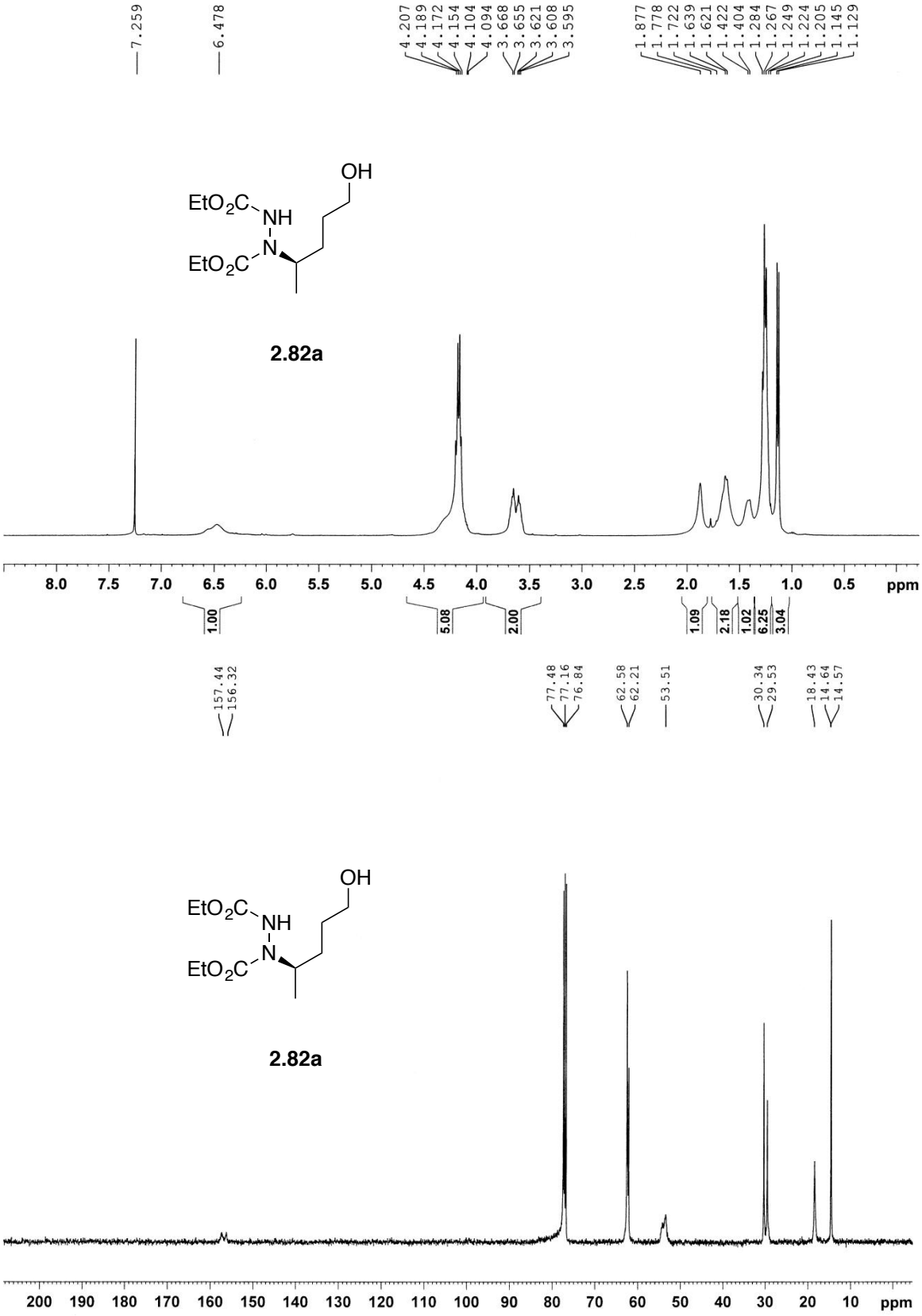
Preparation of Catalyst (2.31b), Enals (2.79e−g,i−j).
Catalyst **2.31b**[1] was prepared from the corresponding diarylprolinol[2] using a known procedure. Enals **2.79e**,[3] **2.79f**,[4] **2.79g**,[4] and **2.79h**,[5] were prepared using known procedures.

General Procedure for the synthesis of γ-amino alcohols 2.82.
To a mixture of catalyst **2.31b** (15 mg, 0.025 mmol) and benzoic acid (6 mg, 0.05 mmol) was added $CHCl_3$ (1 mL), and the mixture was stirred at rt. After 5 min, enal **2.79** (0.375 mmol) was added. After 10 min, **2.24a** (0.25 mmol) was added, and the reaction was stirred in the dark until complete consumption of **2.24a** as observed by ^{1}H NMR. The reaction was cooled to 0 °C, catalyst **2.31b** (15 mg, 0.025 mmol) was added followed by **2.61** (95 mg, 0.375 mmol), and the reaction was stirred at 0 °C until complete consumption of enal as observed by ^{1}H NMR. The reaction was diluted with MeOH (2.5 mL), $NaBH_4$ (57 mg, 1.5 mmol) was added in portions, and the mixture was stirred at 0 °C for 30 min and then quenched with saturated NH_4Cl and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and filtered. After removal of solvent under reduced pressure, the residue was purified by flash chromatography (EtOAc:petroleum ether) to yield γ-amino alcohol **2.82**.

2.82a:



(*R*)-Diethyl 1-(5-hydroxypentan-2-yl)hydrazine-1,2-dicarboxylate.
Colorless oil (41 mg, 63%): $[\alpha]_D^{22}$ = -9.9 (c = 0.55 in $CHCl_3$); IR (thin film, KBr) 3292, 2982, 2936, 1710, 1523, 1418, 1379, 1236, 1058, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.48 (brm, 1H), 4.21-4.09 (m, 5H), 3.67-3.60 (m, 2H), 1.88 (brs, 1H), 1.72-1.62 (m, 2H), 1.42-1.40 (m, 1H), 1.28-1.21 (m, 6H), 1.14 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 156.3, 62.6, 62.6, 62.2, 53.5, 30.3, 29.5, 18.4, 14.6, 14.5 ppm; HRMS (ESI) $[M + H]^+$ calcd. for $[C_{11}H_{23}N_2O_5]$ 263.1607, found 263.1603.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6.478
4.207
4.189
4.172
4.154
4.104
4.094
3.668
3.655
3.621
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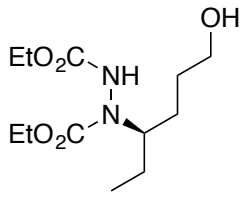
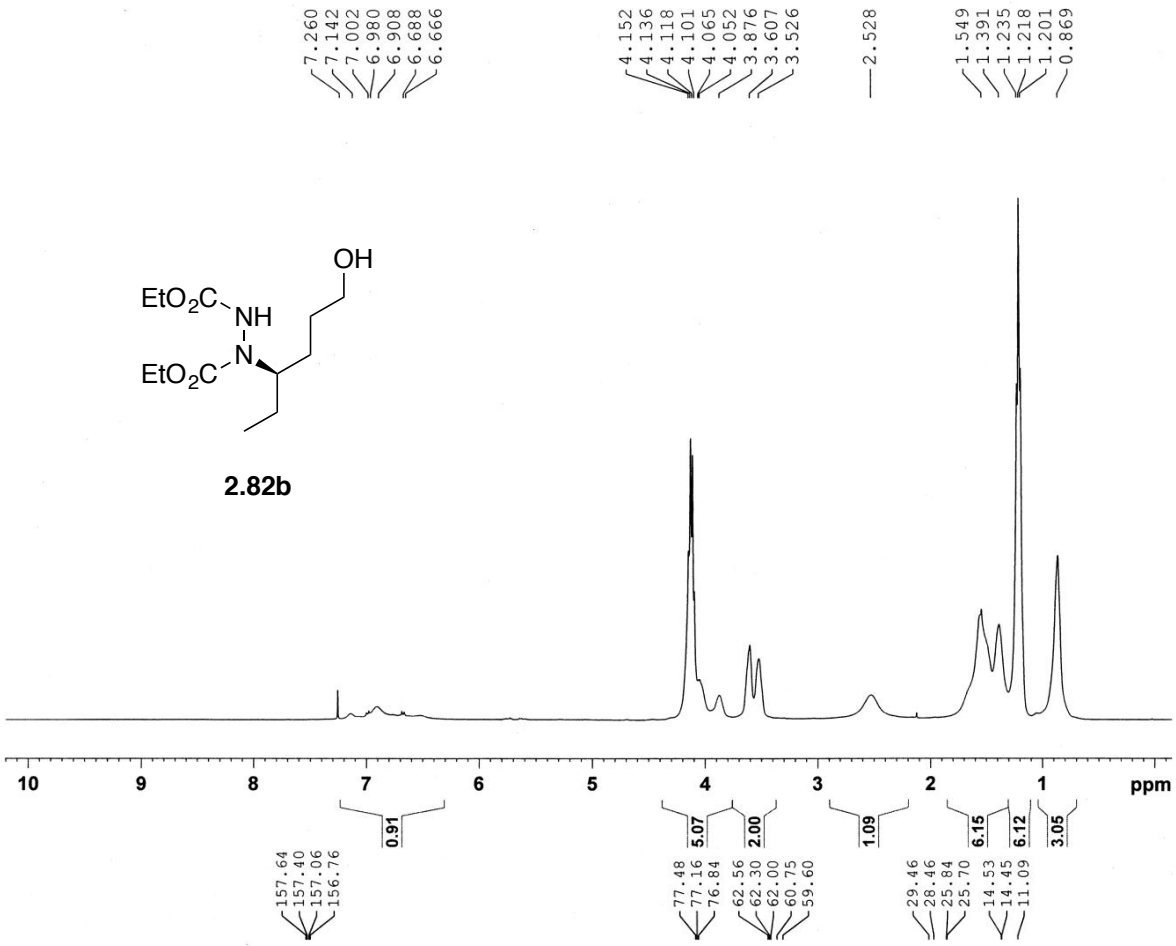
3.595
1.877
1.778
1.722
1.639
1.621
1.422
1.404
1.284
1.267
1.249
1.224
1.205
1.145
1.129
OH
EtO2C
NH
N
EtO2C
2.82a
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
5.08
2.00
1.09
2.18
1.02
6.25
3.04
157.44
156.32
77.48
77.16
76.84
62.58
62.21
53.51
30.34
29.53
18.43
14.64
14.57
OH
EtO2C
NH
N
EtO2C
2.82a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

2.82b:



(*R*)-Diethyl 1-(6-hydroxyhexan-3-yl)hydrazine-1,2-dicarboxylate. Colorless oil (50 mg, 72%): $[\alpha]_D^{23}$ = 4.5 (c = 1.2 in $CHCl_3$); IR (thin film, KBr) 3284, 2979, 2935, 1693, 1525, 1416,1383, 1262, 1058, 937 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14-6.67 (m, 1H), 4.15-3.87 (m, 5H), 3.61-3.53 (m, 2H), 2.53 (brs, 1H), 1.55-1.39 (m, 6H), 1.24-1.20 (m, 6H), 0.87 (brs, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6/157.4, 157.1/156.8, 62.6, 62.3, 62.0, 60.8/59.6, 29.5, 28.5, 25.8/25.7, 14.5, 14.4, 11.1 ppm; HRMS (ESI) $[M + H]^+$ calcd. for $[C_{12}H_{25}N_2O_5]$ 277.1763, found 277.1766.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6.980
6.908
6.688
6.666
4.152
4.136
4.118
4.101
4.065
4.052
3.876
3.607
3.526
2.528
1.549
1.391
1.235
1.218
1.201
0.869
OH
EtO2C
NH
N
EtO2C
2.82b
10
9
8
7
6
5
4
3
2
1
ppm
0.91
5.07
2.00
1.09
6.15
6.12
3.05
157.64
157.40
157.06
156.76
77.48
77.16
76.84
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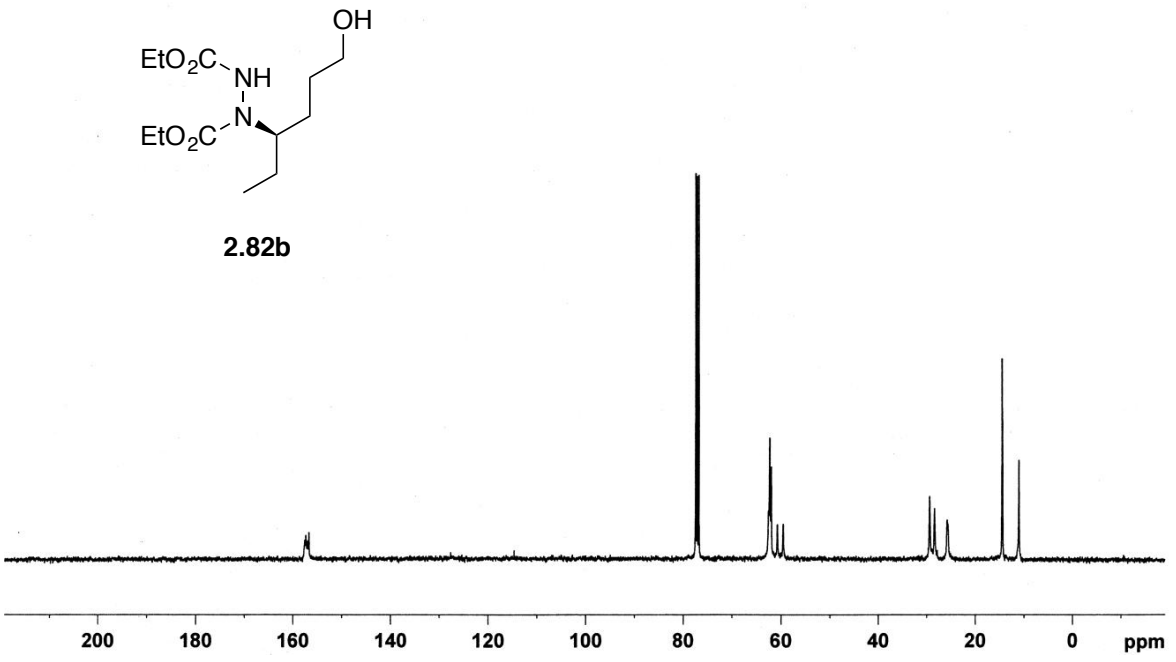
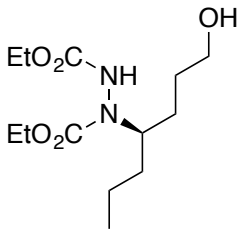
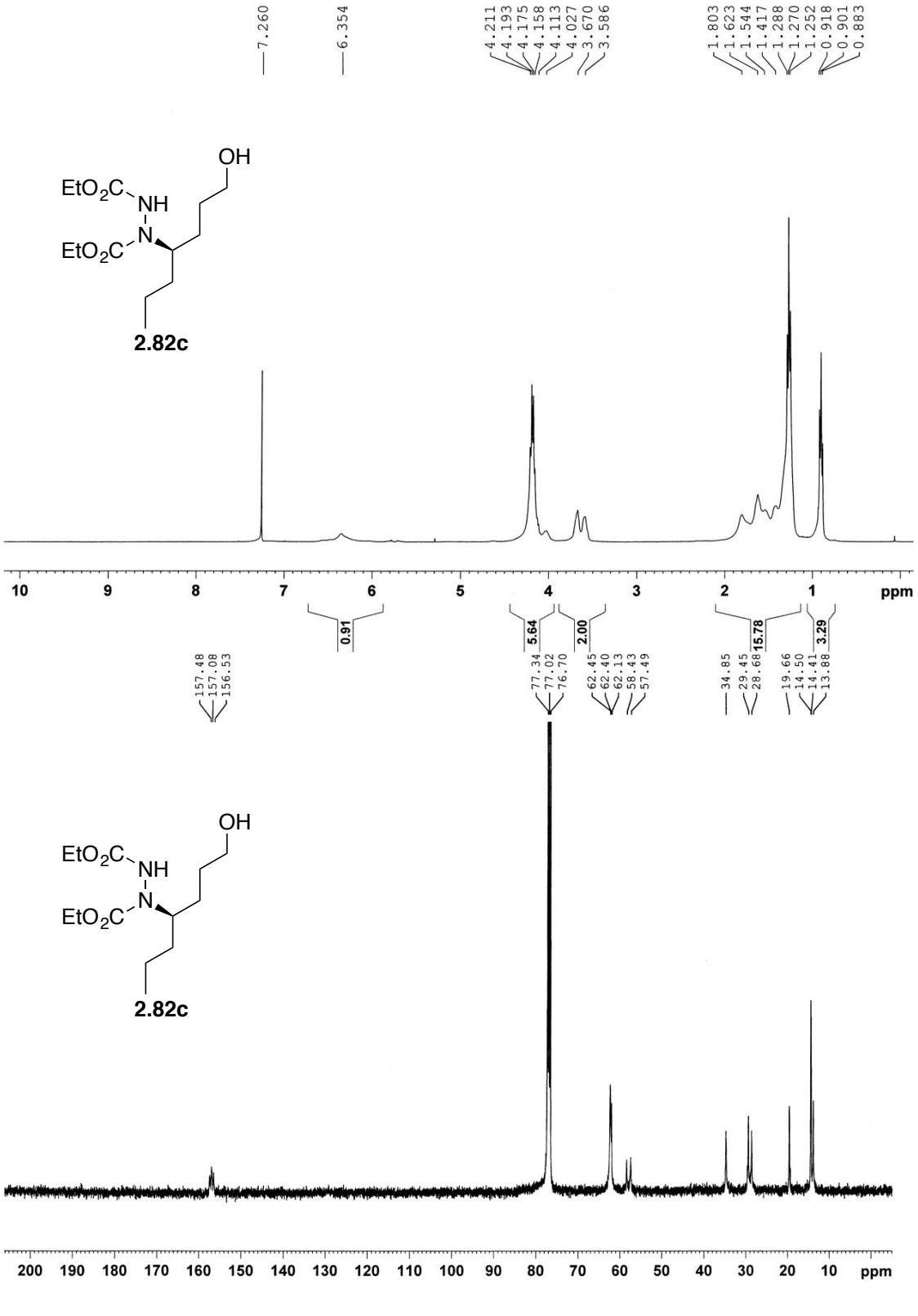
25.84
25.70
14.53
14.45
11.09


OH
EtO2C
NH
N
EtO2C
2.82b
200
180
160
140
120
100
80
60
40
20
0
ppm

2.82c:



(*R*)-Diethyl 1-(1-hydroxyheptan-4-yl)hydrazine-1,2-dicarboxylate.
Colorless oil (51 mg, 70%): $[\alpha]_D^{23} = 3.6$ (c = 1.0 in $CHCl_3$); IR (thin film, KBr) 3466, 3283, 2960, 2933, 1711, 1417, 1257, 1060, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.35 (brm, 1H), 4.21-4.03 (m, 5H), 3.67-3.59 (m, 2H), 1.80-1.42 (m, 8H), 1.29-1.25 (m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5/157.1, 156.5, 62.4, 62.4, 62.1, 58.4/57.5, 34.9, 29.5, 28.7, 19.7, 14.5, 14.4, 13.9 ppm; HRMS (ESI) $[M + H]^+$ calcd. for $[C_{13}H_{27}N_2O_5]$ 291.1920, found 291.1920.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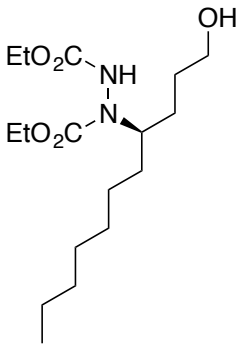
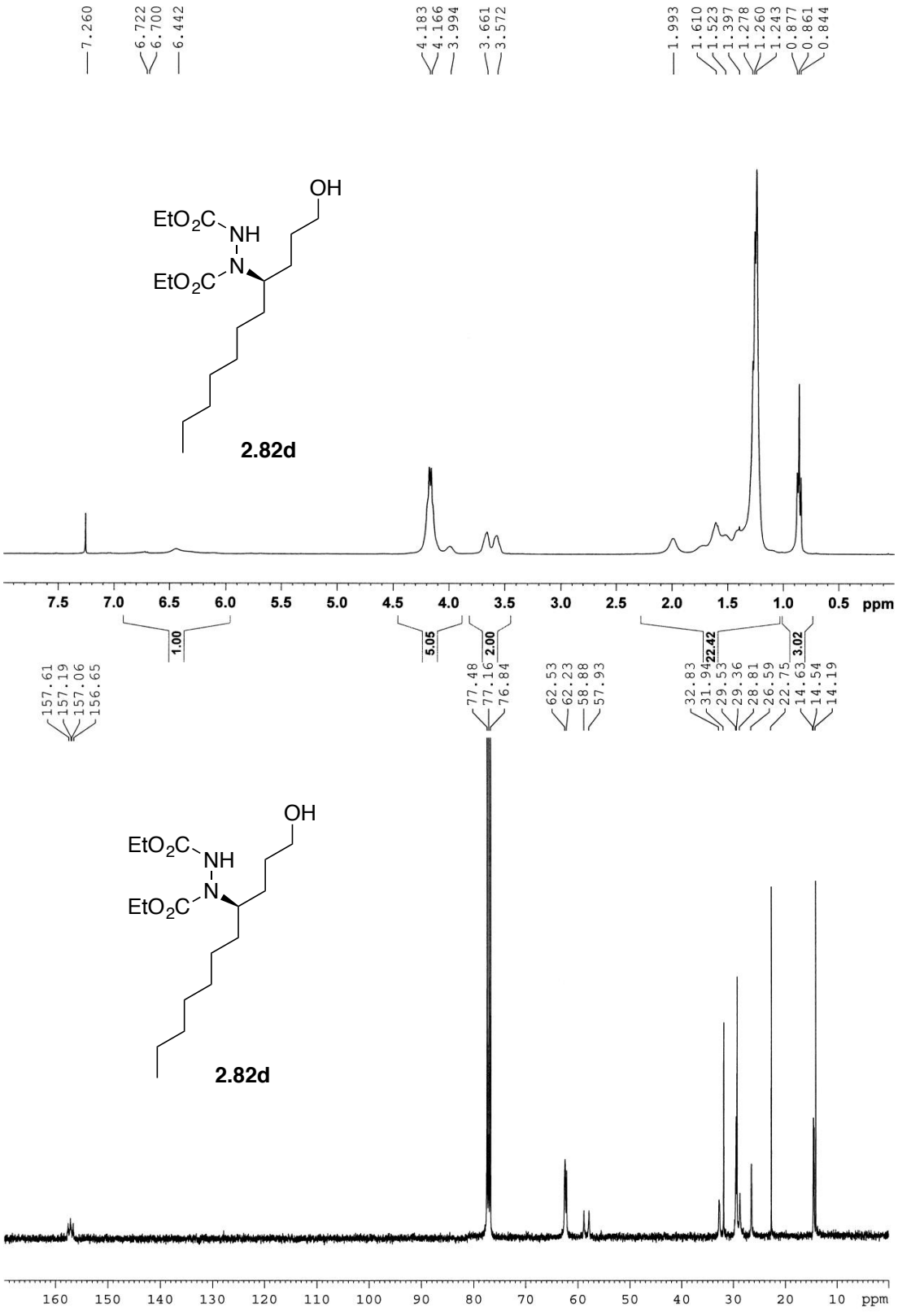
4.211
4.193
4.175
4.158
4.113
4.027
3.670
3.586
1.803
1.623
1.544
1.417
1.288
1.270
1.252
0.918
0.901
0.883
OH
EtO2C
NH
N
EtO2C
2.82c
10 9 8 7 6 5 4 3 2 1 ppm
0.91
5.64
2.00
15.78
3.29
157.48
157.08
156.53
77.34
77.02
76.70
62.45
62.40
62.13
58.43
57.49
34.85
29.45
28.68
19.66
14.50
14.41
13.88
OH
EtO2C
NH
N
EtO2C
2.82c
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

2.82d:



(*R*)-Diethyl 1-(1-hydroxyundecan-4-yl)hydrazine-1,2-dicarboxylate.
Colorless oil (62 mg, 72%): $[\alpha]_D^{23}$ = 3.8 (c = 1.58 in $CHCl_3$); IR (thin film, KBr) 3453, 3277, 2926, 2856, 1757, 1712, 1416, 1260, 1062, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.44 (brm, 1H), 4.18-3.99 (m, 5H), 3.66-3.57 (m, 2H), 1.99-1.24 (m, 16H), 1.28-1.24 (m, 6H), 0.86 (t, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6/157.2, 157.1/156.7, 62.5, 62.2, 62.1, 58.9/57.9, 32.8, 31.9, 29.5, 29.4, 28.8, 26.6, 22.8, 14.6/14.5, 14.2 ppm; HRMS (ESI) $[M + H]^+$ calcd. for $[C_{17}H_{35}N_2O_5]$ 347.2546, found 347.2555.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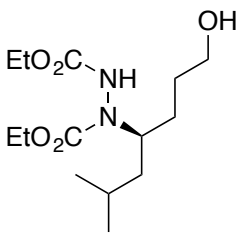
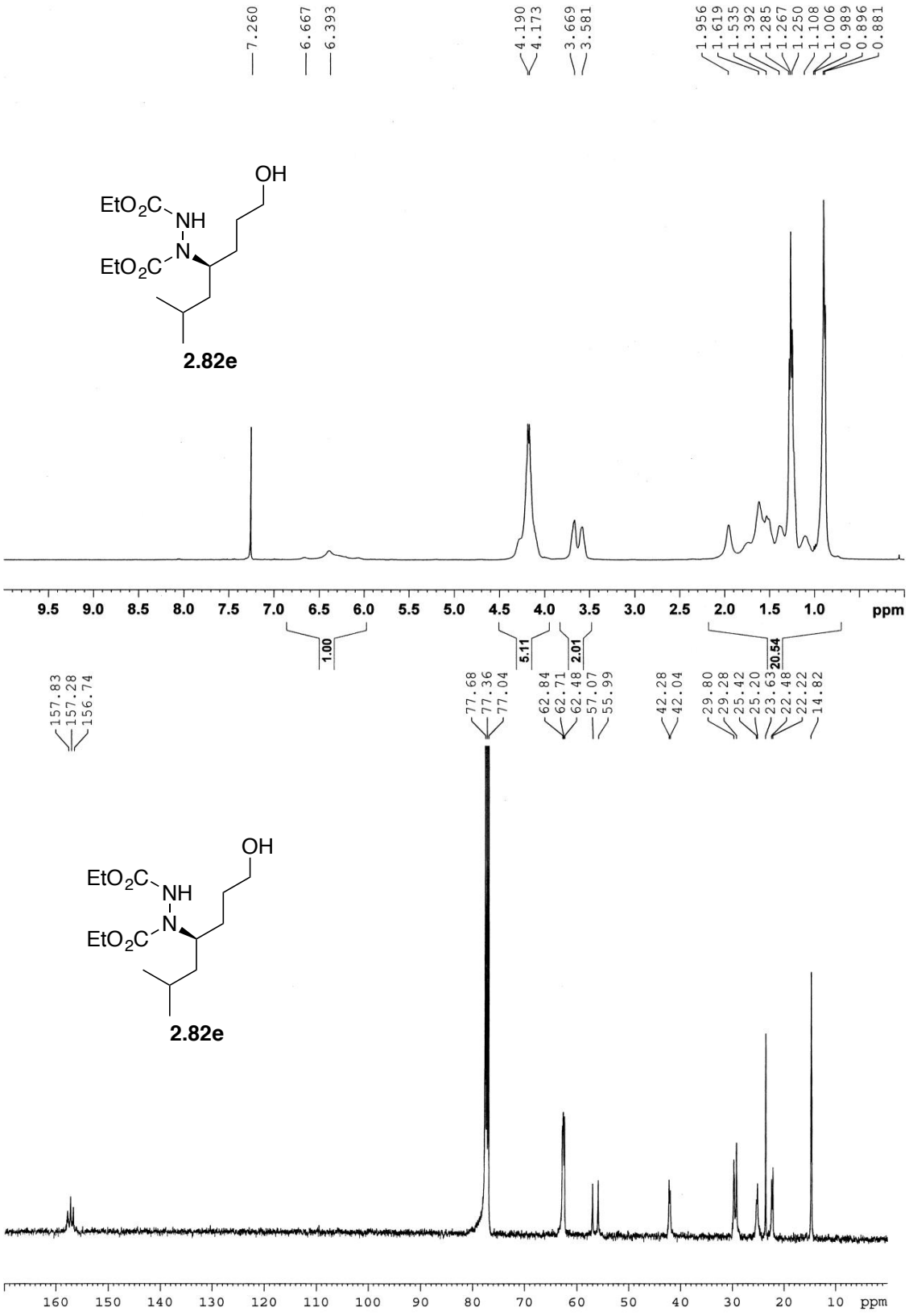
1.993
1.610
1.523
1.397
1.278
1.260
1.243
0.877
0.861
0.844
OH
EtO2C
NH
N
EtO2C
2.82d
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
5.05
2.00
22.42
3.02
157.61
157.19
157.06
156.65
77.48
77.16
76.84
62.53
62.23
58.88
57.93
32.83
31.94
29.53
29.36
28.81
26.59
22.75
14.63
14.54
14.19
OH
EtO2C
NH
N
EtO2C
2.82d
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

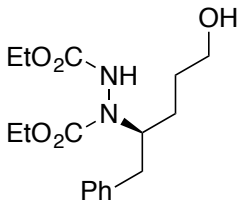
2.82e:



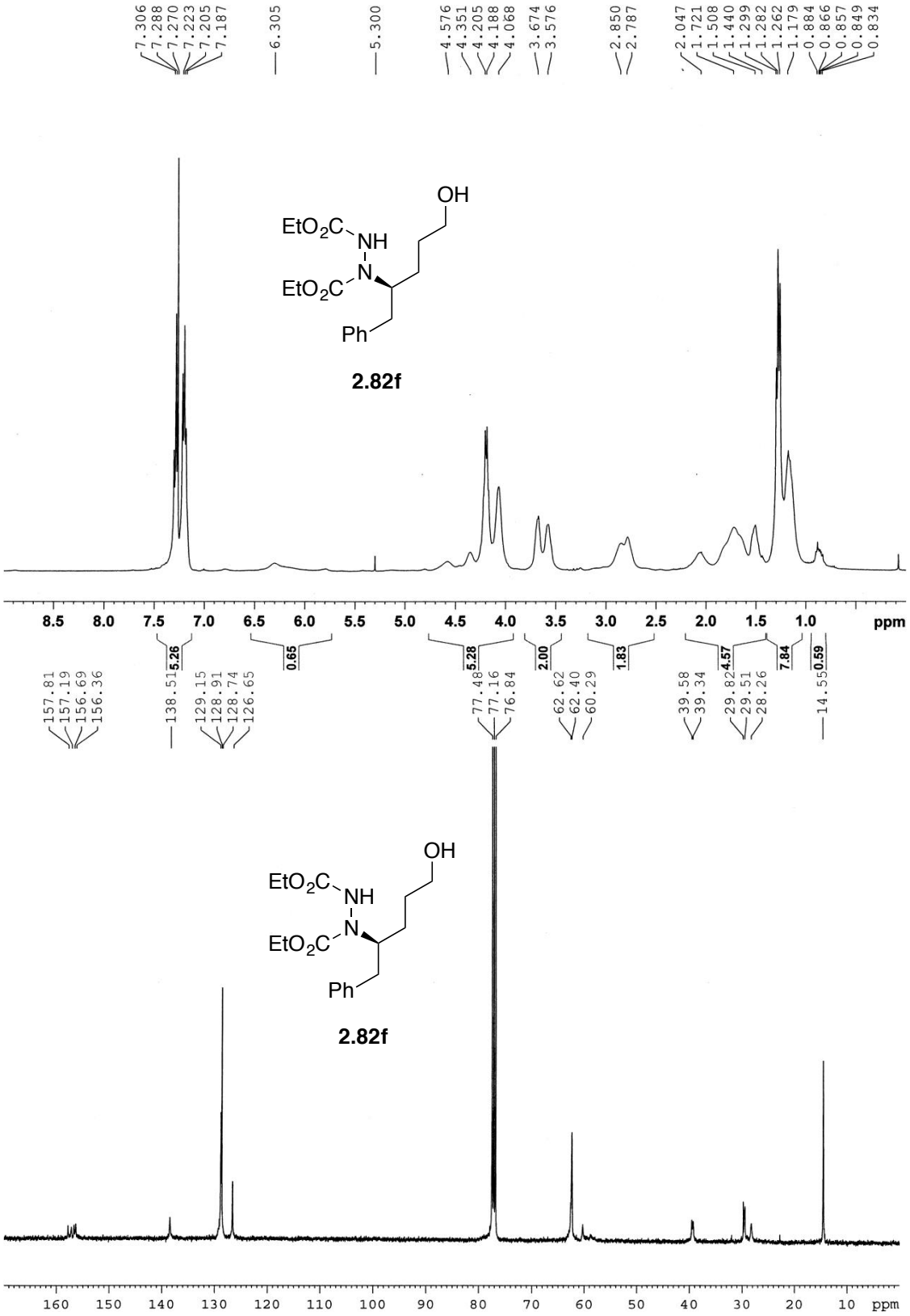
(*S*)-Diethyl 1-(1-hydroxy-6-methylheptan-4-yl)hydrazine-1,2-dicarboxylate.
Colorless oil (43 mg, 57%): $[\alpha]_D^{23}$ = 1.9 (c = 2.12 in $CHCl_3$); IR (thin film, KBr) 3465, 3284, 2957, 2870, 1756, 1711, 1417, 1259, 1062, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.39 (brm, 1H), 4.19-4.17 (m, 5H), 3.67-3.58 (m, 2H), 1.96-1.11 (m, 8H), 1.29-1.25 (m, 6H), 0.90-0.88 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 157.3/156.7, 62.8, 62.7, 62.5, 57.1/56.0, 42.3/42.0, 29.8/29.3, 25.4/25.2, 23.6, 22.5/22.2, 14.8 ppm; HRMS (ESI) $[M + H]^+$ calcd. for $[C_{14}H_{29}N_2O_5]$ 305.2076, found 305.2072.


7.260
6.667
6.393
4.190
4.173
3.669
3.581
1.956
1.619
1.535
1.392
1.285
1.267
1.250
1.108
1.006
0.989
0.896
0.881
OH
EtO2C
NH
N
EtO2C
2.82e
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
5.11
2.01
20.54
157.83
157.28
156.74
77.68
77.36
77.04
62.84
62.71
62.48
57.07
55.99
42.28
42.04
29.80
29.28
25.42
25.20
23.63
22.48
22.22
14.82
OH
EtO2C
NH
N
EtO2C
2.82e
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

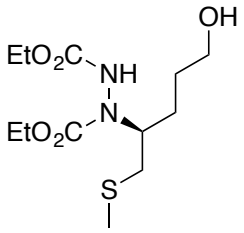
2.82f:



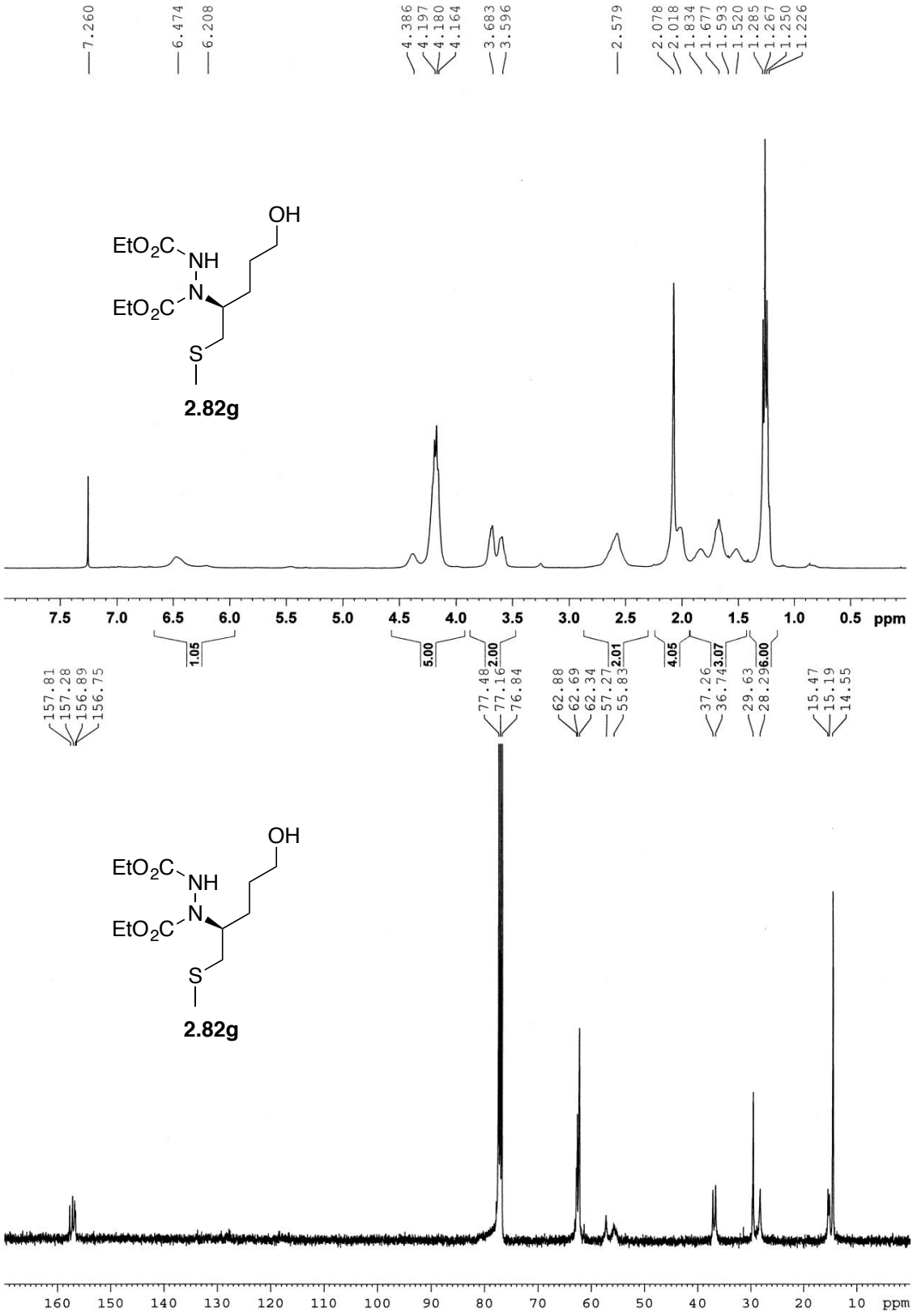
(*S*)-Diethyl 1-(5-hydroxy-1-phenylpentan-2-yl)hydrazine-1,2-dicarboxylate.
Colorless oil (41 mg, 49%): $[\alpha]_D^{23}$ = 14.4 (c = 0.94 in $CHCl_3$); IR (thin film, KBr) 3285, 2981, 2929, 1712, 1414, 1291, 1233, 1063, 758, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.19 (m, 5H), 6.31 (brm, 1H), 4.58-4.07 (m, 5H), 3.67-3.58 (m, 2H), 2.85-2.79 (m, 2H), 2.05-1.51 (m, 4H), 1.30-1.18 (m, 7H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8/157.2, 156.7/156.4, 138.5, 128.9, 128.7, 126.7, 62.6, 62.4, 60.3, 39.6.1/39.3, 29.5, 28.3, 14.6 ppm; HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 39.6 min, minor enantiomer t_R = 33.5 min; HRMS (ESI) $[M + H]^+$ calcd. for $[C_{17}H_{27}N_2O_5]$ 339.1920, found 339.1920.


7.306
7.288
7.270
7.223
7.205
7.187
6.305
5.300
4.576
4.351
4.205
4.188
4.068
3.674
3.576
2.850
2.787
2.047
1.721
1.508
1.440
1.299
1.282
1.262
1.179
0.884
0.866
0.857
0.849
0.834
OH
EtO2C
NH
N
EtO2C
Ph
2.82f
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
5.26
0.65
5.28
2.00
1.83
4.57
7.84
0.59
157.81
157.19
156.69
156.36
138.51
129.15
128.91
128.74
126.65
77.48
77.16
76.84
62.62
62.40
60.29
39.58
39.34
29.82
29.51
28.26
14.55
OH
EtO2C
NH
N
EtO2C
Ph
2.82f
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

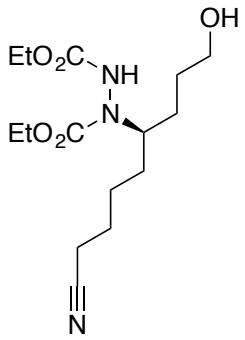
2.82g:



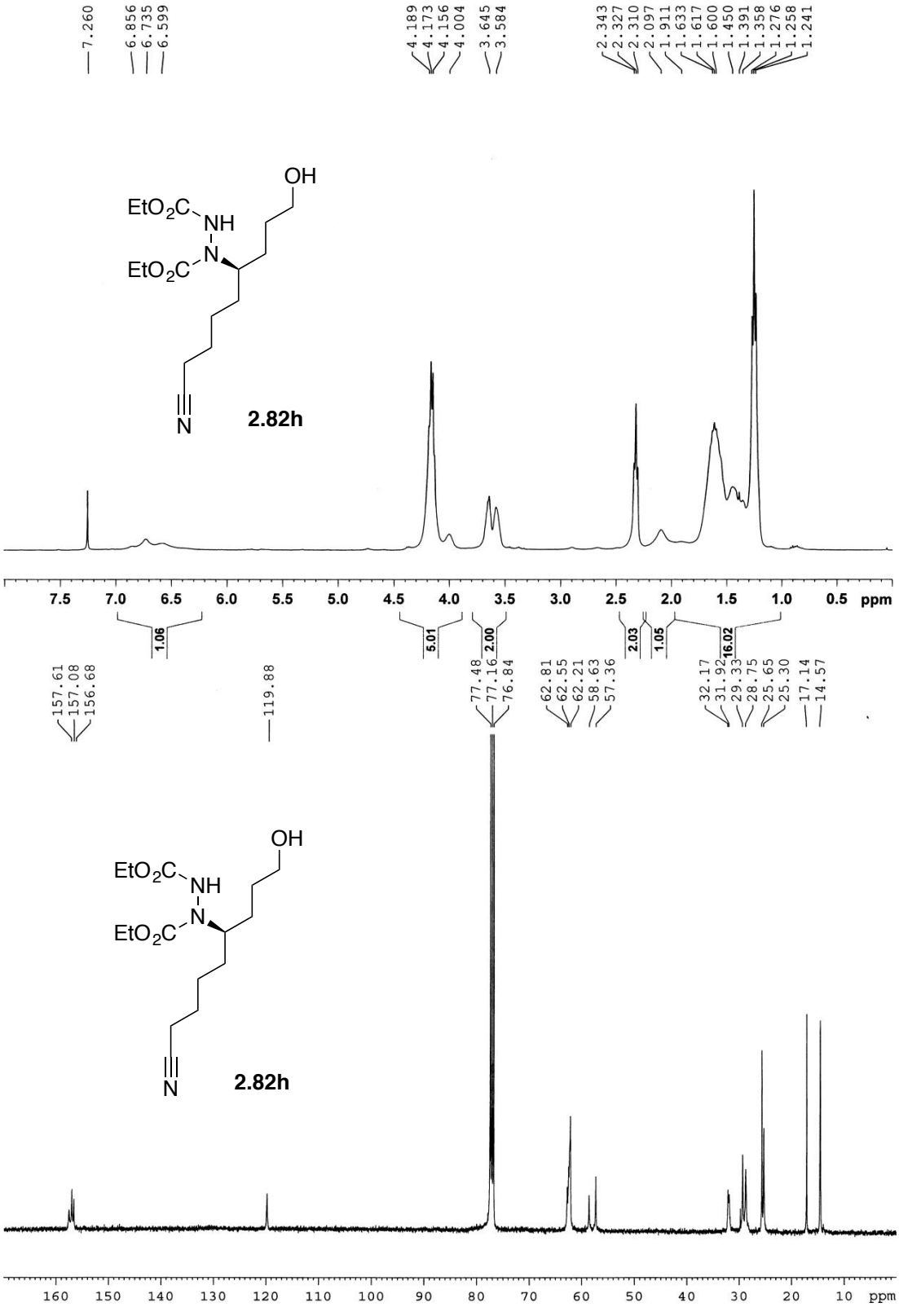
(*S*)-Diethyl 1-(5-hydroxy-1-(methylthio)pentan-2-yl)-hydrazine-1,2-dicarboxylate. Colorless oil (35 mg, 45%): $[\alpha]_D^{23}$ = 31.5 (c = 1.07 in $CHCl_3$); IR (thin film, KBr) 3465, 3284, 2980, 2922, 2871, 1712, 1414, 1331, 1249, 1063, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.47 (brm, 1H), 4.39-4.16 (m, 5H), 3.68-3.60 (m, 2H), 2.58 (brs, 2H), 2.08 (s, 3H), 2.02 (brs, 1H), 1.83-1.52 (m, 3H), 1.27 (t, *J* = 7.0 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8/157.3, 156.9/156.8, 62.9, 62.7, 62.3, 57.3/55.8, 37.3/36.7, 29.6, 28.3, 15.5/15.2, 14.6 ppm; HRMS (ESI) $[M + H]^+$ calcd. For $[C_{12}H_{25}N_2O_5S]$ 309.1484, found 309.1492.


7.260
6.474
6.208
4.386
4.197
4.180
4.164
3.683
3.596
2.579
2.078
2.018
1.834
1.677
1.593
1.520
1.285
1.267
1.250
1.226
OH
EtO2C
NH
N
EtO2C
S
2.82g
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.05
5.00
2.00
2.01
4.05
3.07
6.00
157.81
157.28
156.89
156.75
77.48
77.16
76.84
62.88
62.69
62.34
57.27
55.83
37.26
36.74
29.63
28.29
15.47
15.19
14.55
OH
EtO2C
NH
N
EtO2C
S
2.82g
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

2.82h:

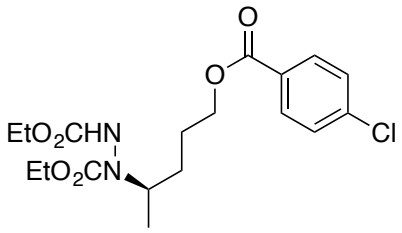


(*R*)-Diethyl 1-(8-cyano-1-hydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate.
Colorless oil (36 mg, 44%): $[\alpha]_D^{23}$ = 8.9 (c = 1.62 in $CHCl_3$); IR (thin film, KBr) 3473, 3285, 2934, 2869, 2246, 1752, 1708, 1417, 1260, 1233, 1058, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (brm, ^1H), 4.19-4.00 (m, 5H), 3.65-3.58 (m, 2H), 2.33 (t, *J* = 6.6 Hz, 2H), 2.10 (brs, 1H), 1.91-1.24 (m, 10H), 1.26 (t, *J* = 7.0 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 157.1/ 156.7, 119.9, 62.8, 62.6, 62.2, 58.6/57.4, 32.2/31.9, 29.3/28.8, 25.7, 25.3, 17.1, 14.6 ppm; HRMS (ESI) $[M + H]^+$ calcd. for $[C_{15}H_{28}N_3O_5]$ 330.2029, found 330.2030.

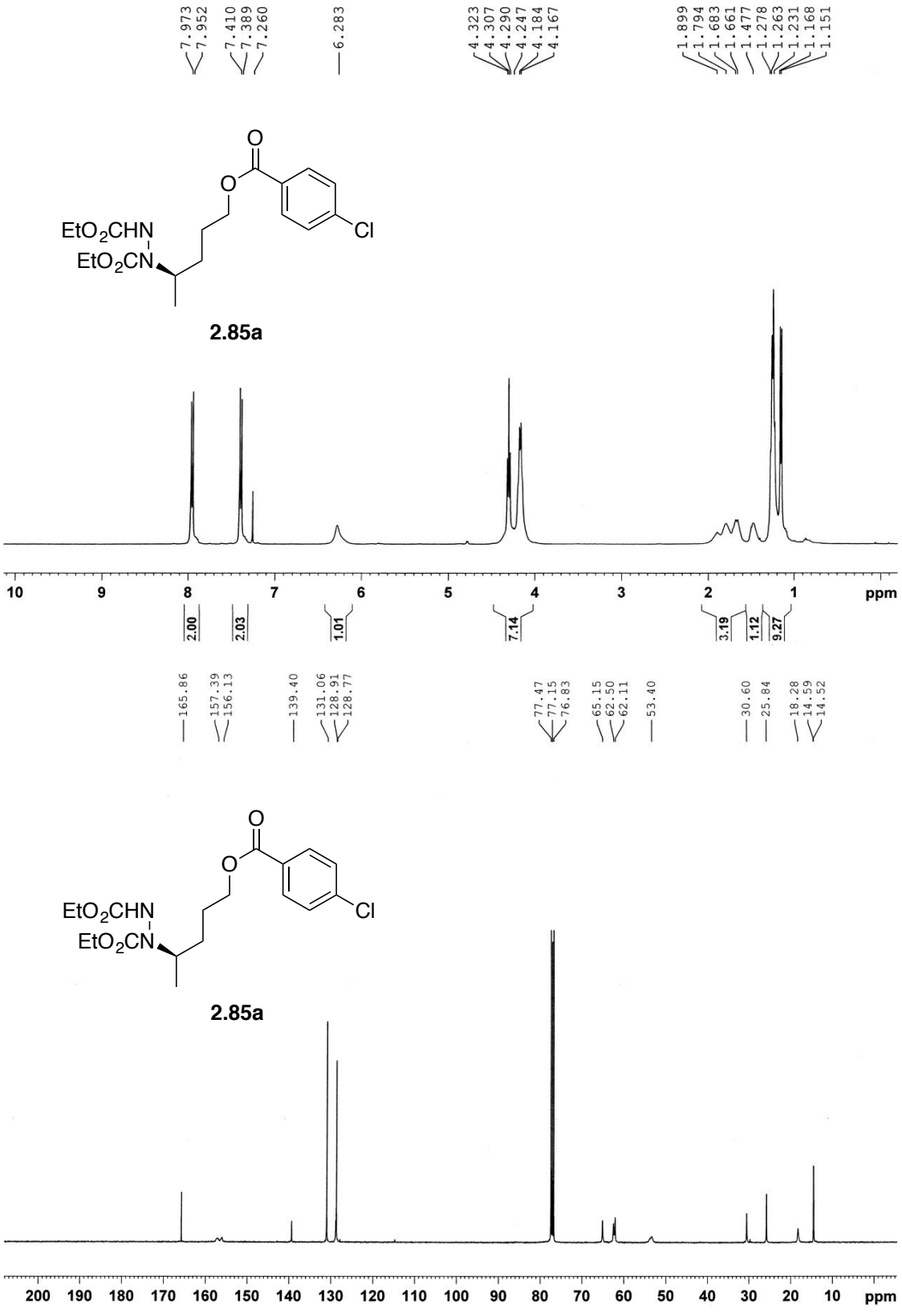

7.260
6.856
6.735
6.599
4.189
4.173
4.156
4.004
3.645
3.584
2.343
2.327
2.310
2.097
1.911
1.633
1.617
1.600
1.450
1.391
1.358
1.276
1.258
1.241
OH
EtO2C
NH
N
EtO2C
N
2.82h
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.06
5.01
2.00
2.03
1.05
16.02
157.61
157.08
156.68
119.88
77.48
77.16
76.84
62.81
62.55
62.21
58.63
57.36
32.17
31.92
29.33
28.75
25.65
25.30
17.14
14.57
OH
EtO2C
NH
N
EtO2C
N
2.82h
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

General Procedure for Preparation of Esters 2.85a−e, 2.85g-h.
To alcohol **2.82** (1 equiv) in CH_2Cl_2 (0.1 M) was added Et_3N (1.3 equiv) and 4-chlorobenzoyl chloride (1.3 equiv). After disappearance of alcohol by TLC, the solvent was removed under reduced pressure, and the product was purified by flash chromatography (EtOAc/ petroleum ether).

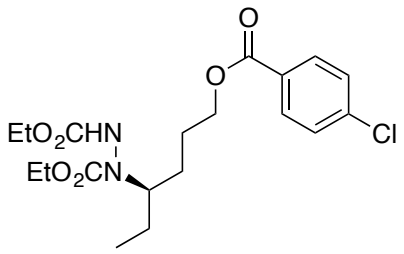
2.85a:



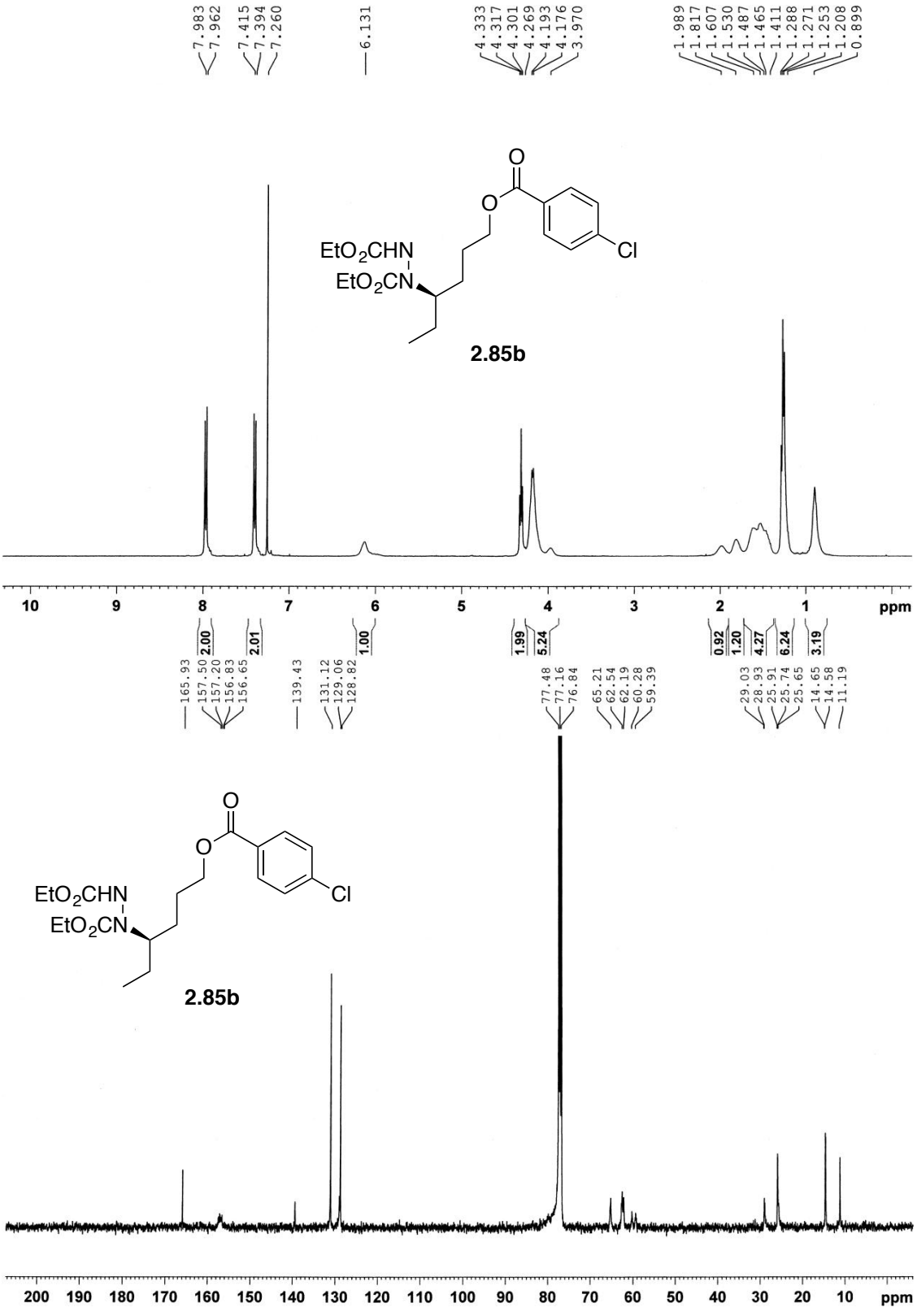
(*R*)-Diethyl 1-(5-((4-chlorobenzoyl)oxy)pentan-2-yl)-hydrazine-1,2-dicarboxylate.
Colorless oil (62 mg, 78%): $[\alpha]_D^{22}$ = -8.8 (c = 1.02 in $CHCl_3$); IR (thin film, KBr) 3300, 2980, 2934, 1756, 1720, 1595, 1405, 1274, 1172, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.28 (brs, 1H), 4.31 (t, *J* = 6.4 Hz, 2H), 4.32-4.17 (m, 5H), 1.90-1.67 (m, 3H), 1.48 (brs, 1H), 1.28-1.23 (m, 6H), 1.60 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 157.4, 156.1, 139.4, 131.1, 128.9, 128.8, 65.2, 62.5, 62.1, 53.4, 30.6, 25.8, 18.3, 14.6, 14.5 ppm; HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 28.7 min, minor enantiomer t_R = 38.9 min; HRMS (ESI) $[M + H]^+$ calcd. for $[C_{18}H_{26}ClN_2O_6]$ 401.1479, found 401.1477.


7.973
7.952
7.410
7.389
7.260
6.283
4.323
4.307
4.290
4.247
4.184
4.167
1.899
1.794
1.683
1.661
1.477
1.278
1.263
1.231
1.168
1.151
O
O
EtO2CHN
EtO2CN
Cl
2.85a
10
9
8
7
6
5
4
3
2
1
ppm
2.00
2.03
1.01
7.14
3.19
1.12
9.27
165.86
157.39
156.13
139.40
131.06
128.91
128.77
77.47
77.15
76.83
65.15
62.50
62.11
53.40
30.60
25.84
18.28
14.59
14.52
O
O
EtO2CHN
EtO2CN
Cl
2.85a
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

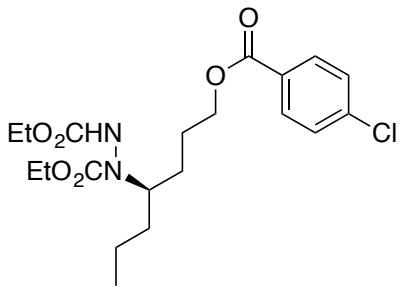
2.85b:



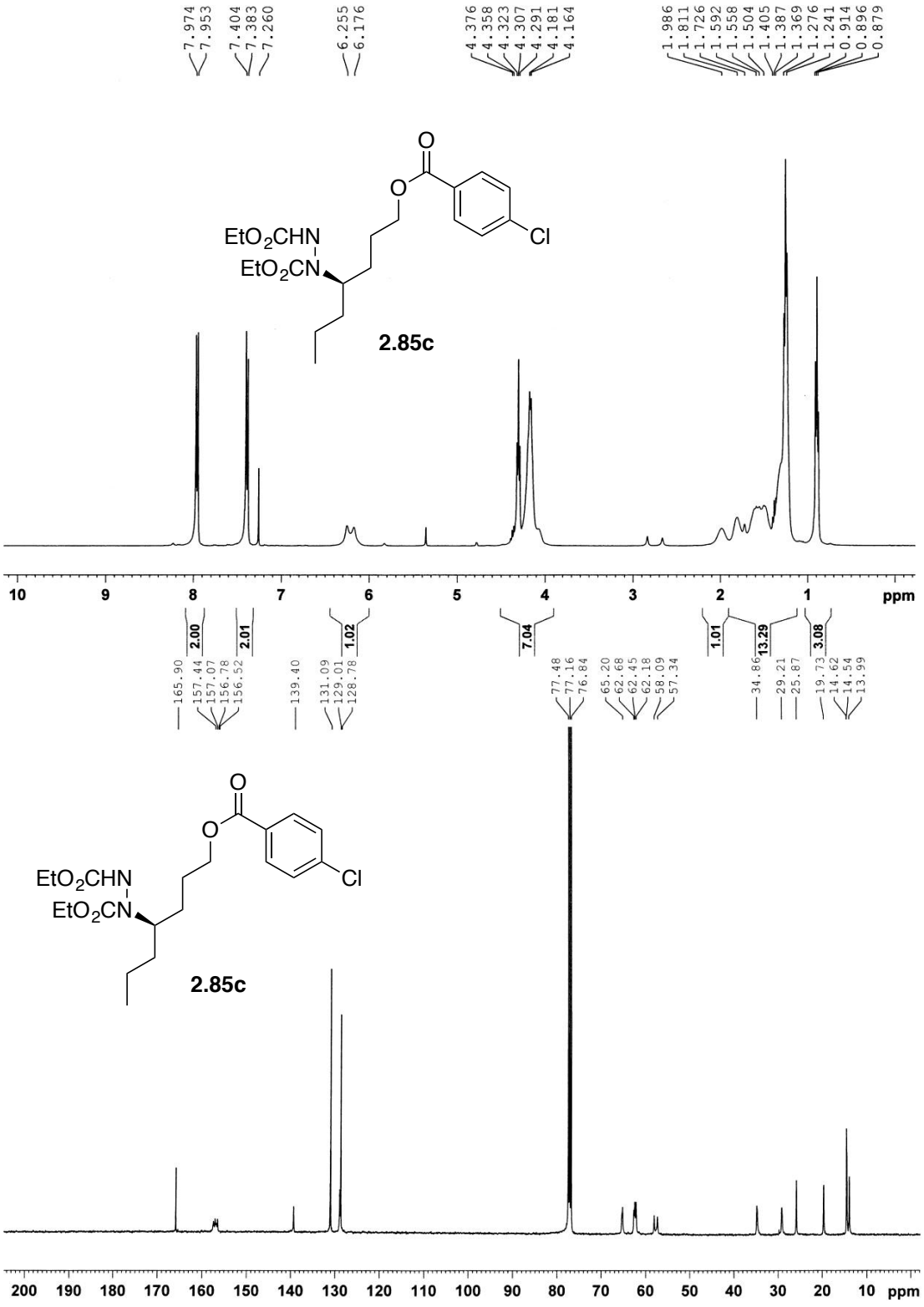
(*R*)-Diethyl 1-(6-((4-chlorobenzoyl)oxy)hexan-3-yl)-hydrazine-1,2-dicarboxylate. Colorless oil (42 mg, 84%): $[\alpha]_D^{23}$ = -9.6 (c = 0.7 in $CHCl_3$); IR (thin film, KBr) 3296, 2978, 2934, 1757, 1718, 1595, 1405, 1274, 1093, 1015, 928 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.13 (brs, 1H), 4.32 (t, *J* = 6.4 Hz, 2H), 4.19-3.97 (m, 5H), 1.99 (brs, 1H), 1.82 (brs, 1H), 1.53-1.41 (m, 4H), 1.29-1.21 (m, 6H), 0.90 (brs, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 157.5/157.2, 156.8/156.7, 139.4, 131.1, 129.1, 128.8, 65.2, 62.5, 62.2, 60.3/59.4, 29.0/28.9, 25.9, 25.7/25.6, 14.7, 14.6, 11.2 ppm; HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 15.9 min, minor enantiomer t_R = 25.2 min; HRMS (ESI) $[M + H]^+$ calcd. for $[C_{19}H_{28}ClN_2O_6]$ 415.1636, found 415.1638.


7.983
7.962
7.415
7.394
7.260
6.131
4.333
4.317
4.301
4.269
4.193
4.176
3.970
1.989
1.817
1.607
1.530
1.487
1.465
1.411
1.288
1.271
1.253
1.208
0.899
EtO2CHN
EtO2CN
Cl
2.85b
10 9 8 7 6 5 4 3 2 1 ppm
2.00 2.01 1.00 1.99 5.24 0.92 1.20 4.27 6.24 3.19
165.93
157.50
157.20
156.83
156.65
139.43
131.12
129.06
128.82
77.48
77.16
76.84
65.21
62.54
62.19
60.28
59.39
29.03
28.93
25.91
25.74
25.65
14.65
14.58
11.19
EtO2CHN
EtO2CN
Cl
2.85b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

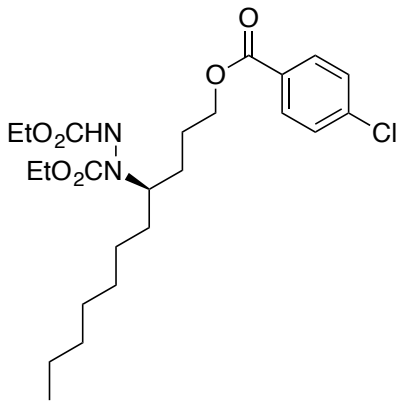
2.85c:



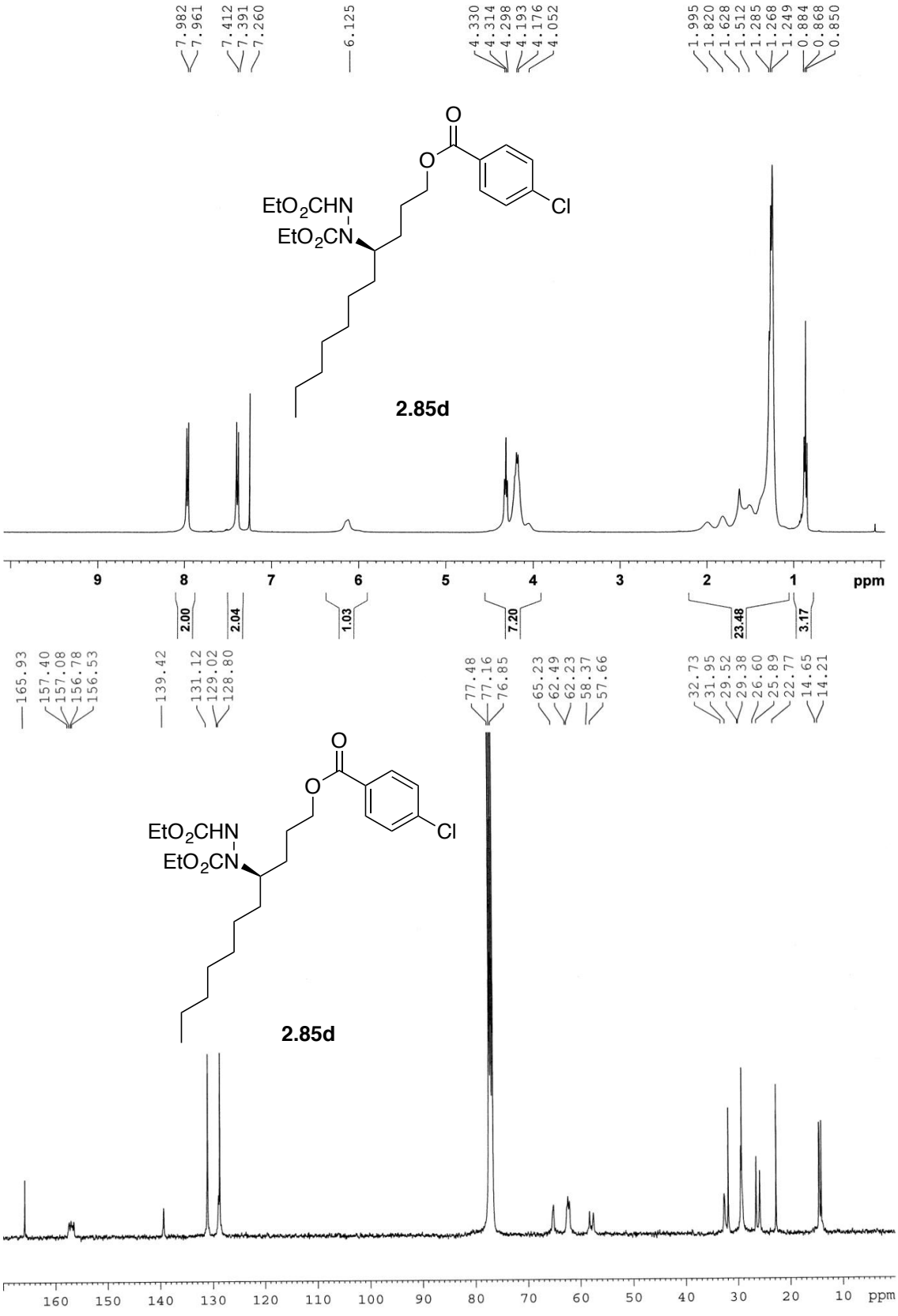
(*R*)-Diethyl 1-(1-((4-chlorobenzoyl)oxy)heptan-4-yl)- hydrazine-1,2-dicarboxylate. Colorless oil (82 mg, 91%): $[\alpha]_D^{24}$ = -10.5 (c = 1.4 in $CHCl_3$); IR (thin film, KBr) 3293, 2961, 2933, 1757, 1717, 1274, 1093, 1015, 851 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 6.25-6.18 (brm, 1H), 4.38-4.16 (m, 5H), 4.31 (t, *J* = 6.4 Hz, 2H), 1.99 (brs, 1H), 1.81-1.50 (m, 7H), 1.41-1.28 (m, 6H), 0.90 (t, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 157.4/157.1, 156.8/156.5, 139.4, 131.1, 129.0, 128.8, 65.2, 62.7/62.5, 62.2, 58.1/57.3, 34.9, 29.2, 25.9, 19.7, 14.6, 14.5, 14.0 ppm; HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 13.2 min, minor enantiomer t_R = 18.9 min; HRMS (ESI) $[M + H]^+$ calcd. For $[C_{20}H_{30}ClN_2O_6]$ 429.1792, found 429.1788.


7.974
7.953
7.404
7.383
7.260
6.255
6.176
4.376
4.358
4.323
4.307
4.291
4.181
4.164
1.986
1.811
1.726
1.592
1.558
1.504
1.405
1.387
1.369
1.276
1.241
0.914
0.896
0.879
O
O
EtO2CHN
EtO2CN
Cl
2.85c
10 9 8 7 6 5 4 3 2 1 ppm
2.00
2.01
1.02
7.04
1.01
13.29
3.08
165.90
157.44
157.07
156.78
156.52
139.40
131.09
129.01
128.78
77.48
77.16
76.84
65.20
62.68
62.45
62.18
58.09
57.34
34.86
29.21
25.87
19.73
14.62
14.54
13.99
O
O
EtO2CHN
EtO2CN
Cl
2.85c
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

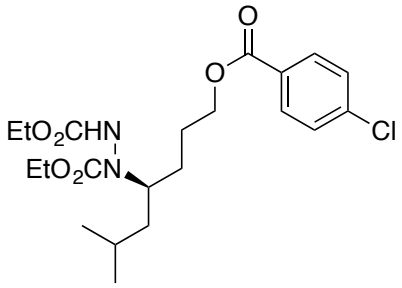
2.85d:



(*R*)-Diethyl 1-(1-((4-chlorobenzoyl)oxy)undecan-4-yl)-hydrazine-1,2-dicarboxylate. Colorless oil (33 mg, 49%): $[\alpha]_D^{23}$ = -8.8 (c = 1.0 in $CHCl_3$); IR (thin film, KBr) 3299, 2957, 2928, 2856, 1759, 1721, 1405, 1274, 1228, 1118, 1104, 1093, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.13 (brm, 1H), 4.33-4.05 (m, 5H), 4.31 (t, *J* = 6.4 Hz, 2H), 2.00-1.25 (m, 16H), 1.29-1.25 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 157.4/157.1, 156.8/156.5, 139.4, 131.1, 129.0, 128.8, 65.2, 62.5, 62.2, 58.4/57.7, 32.7, 32.0, 29.5, 29.4, 26.6/25.9, 22.8, 14.7, 14.2 ppm; HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 8.5 min, minor enantiomer t_R = 11.0 min; HRMS (ESI) $[M + H]^+$ calcd. for $[C_{24}H_{38}ClN_2O_6]$ 485.2418, found 485.2409.

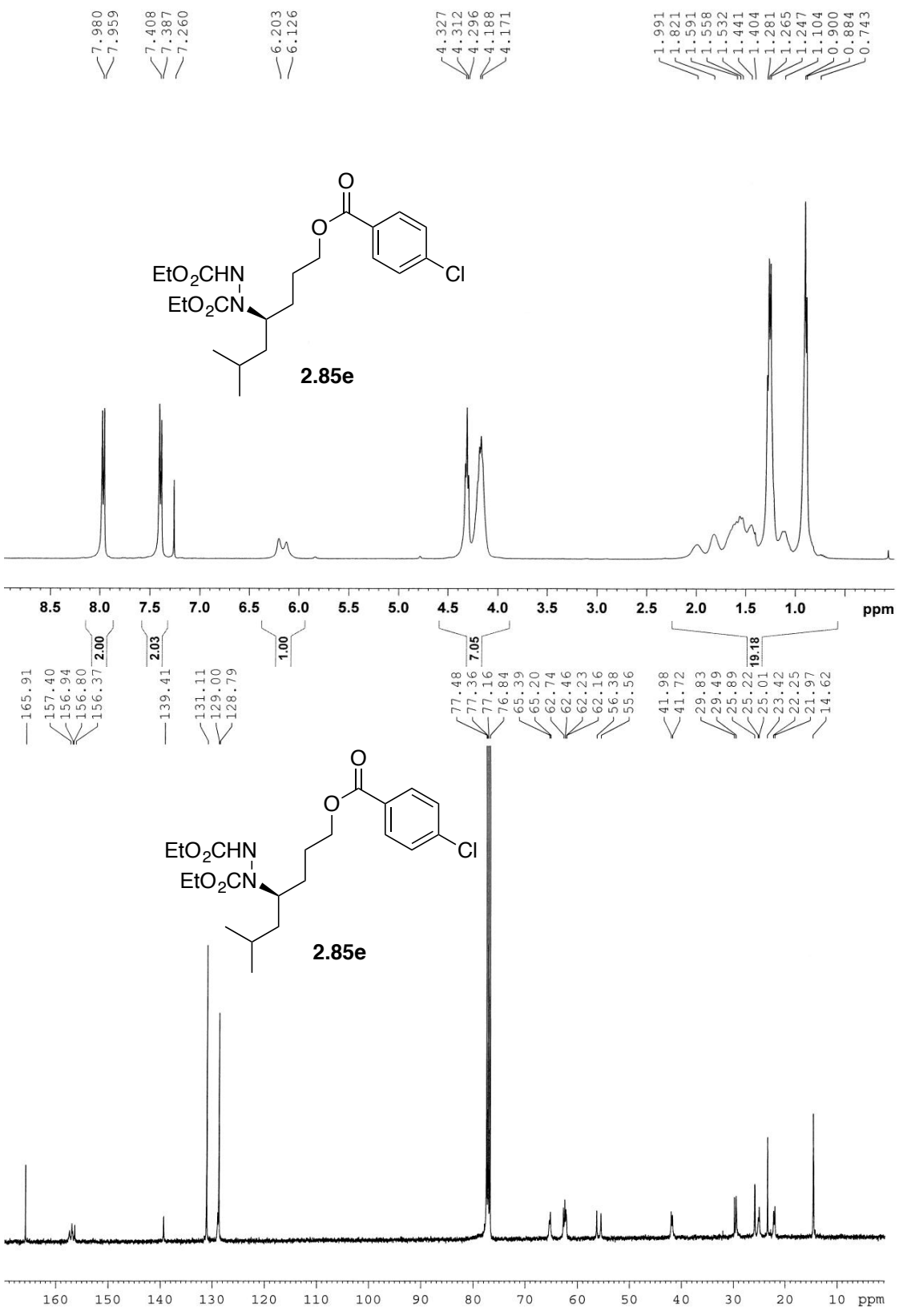

7.982
7.961
7.412
7.391
7.260
6.125
4.330
4.314
4.298
4.193
4.176
4.052
1.995
1.820
1.628
1.512
1.285
1.268
1.249
0.884
0.868
0.850
O
O
EtO2CHN
EtO2CN
Cl
2.85d
9
8
7
6
5
4
3
2
1
ppm
2.00
2.04
1.03
7.20
23.48
3.17
165.93
157.40
157.08
156.78
156.53
139.42
131.12
129.02
128.80
77.48
77.16
76.85
65.23
62.49
62.23
58.37
57.66
32.73
31.95
29.52
29.38
26.60
25.89
22.77
14.65
14.21
O
O
EtO2CHN
EtO2CN
Cl
2.85d
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

2.85e:

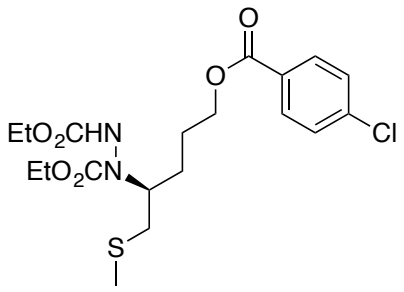


(*S*)-Diethyl 1-(1-((4-chlorobenzoyl)oxy)-6-methylheptan-4-yl)hydrazine-1,2-dicarboxylate.

Colorless oil (38 mg, 77%): $[\alpha]_D^{23}$ = -8.5 (c = 2.06 in $CHCl_3$); IR (thin film, KBr) 3301, 2958, 2869, 1759, 1720, 1405, 1273, 1218, 1105, 1093, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.20-6.13 (brm, 1H), 4.33-4.17 (m, 5H), 4.31 (t, *J* = 6.2 Hz, 2H), 1.99-0.74 (m, 7H), 1.28-1.27 (m, 6H), 0.90-0.88 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 157.4/156.9, 156.8/156.4, 139.4, 131.1, 129.0, 128.8, 65.4/65.2, 62.7/62.5, 62.2/62.2, 56.4/55.6, 42.0/41.7, 29.5, 25.9, 25.2/25.0, 23.4, 22.3/22.0, 14.6 ppm; HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 95:5), 0.5 mL/min; major enantiomer t_R = 24.2 min, minor enantiomer t_R = 30.0 min; HRMS (ESI) $[M + H]^+$ calcd. for $[C_{21}H_{32}ClN_2O_6]$ 443.1949, found 443.1939.

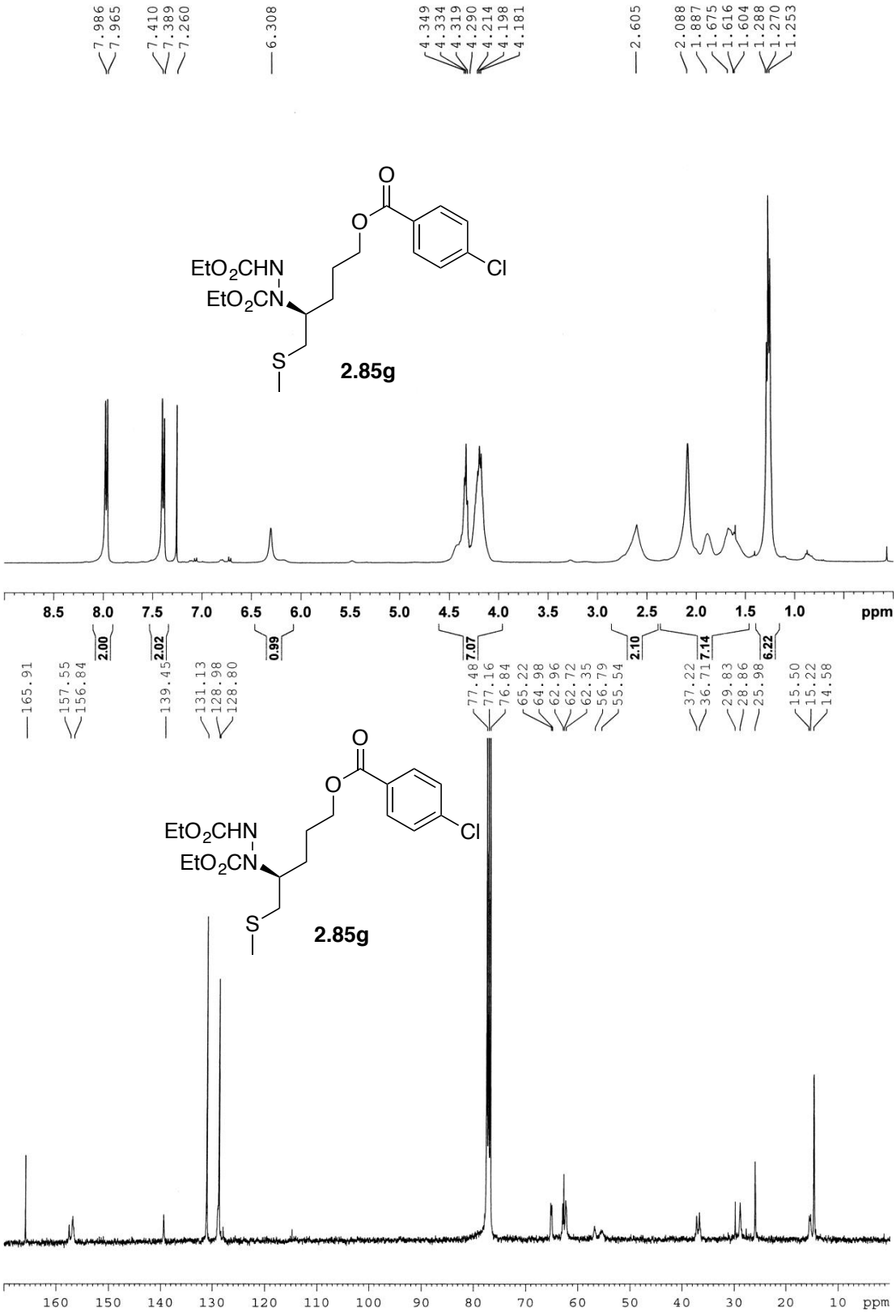

7.980
7.959
7.408
7.387
7.260
6.203
6.126
4.327
4.312
4.296
4.188
4.171
1.991
1.821
1.591
1.558
1.532
1.441
1.404
1.281
1.265
1.247
1.104
0.900
0.884
0.743
EtO2CHN
EtO2CN
Cl
2.85e
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.00
2.03
1.00
7.05
19.18
165.91
157.40
156.94
156.80
156.37
139.41
131.11
129.00
128.79
77.48
77.36
77.16
76.84
65.39
65.20
62.74
62.46
62.23
62.16
56.38
55.56
41.98
41.72
29.83
29.49
25.89
25.22
25.01
23.42
22.25
21.97
14.62
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

2.85g:

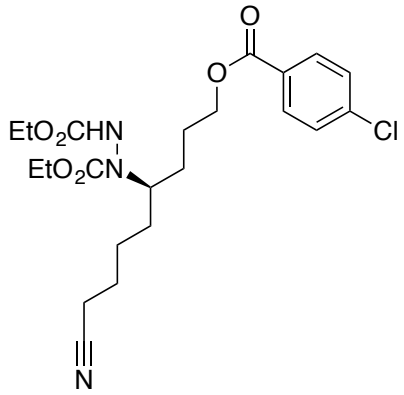


(*S*)-Diethyl 1-(5-((4-chlorobenzoyl)oxy)-1-(methylthio)-pentan-2-yl)hydrazine-1,2-dicarboxylate.

Colorless oil (35 mg, 79%): $[\alpha]_D^{23}$ = 7.9 (c = 0.71 in $CHCl_3$); IR (thin film, KBr) 3299, 2980, 2922, 1755, 1719, 1404, 1275, 1121, 1092, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.31 (brm, 1H), 4.35-4.18 (m, 5H), 4.33 (t, *J* = 6.0 Hz, 2H), 2.61 (brs, 2H), 2.09-1.60 (m, 7H), 1.29-1.25 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 157.6, 156.8, 139.5, 131.1, 129.0, 128.8, 65.2/65.0, 63.0/62.7, 62.4, 56.8/55.5, 37.2/36.7, 28.7, 26.0, 15.5/15.2, 14.6 ppm; HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 26.6 min, minor enantiomer t_R = 41.5 min; HRMS (ESI) $[M + H]^+$ calcd. For $[C_{19}H_{28}ClN_2O_6S]$ 447.1357, found 447.1347.

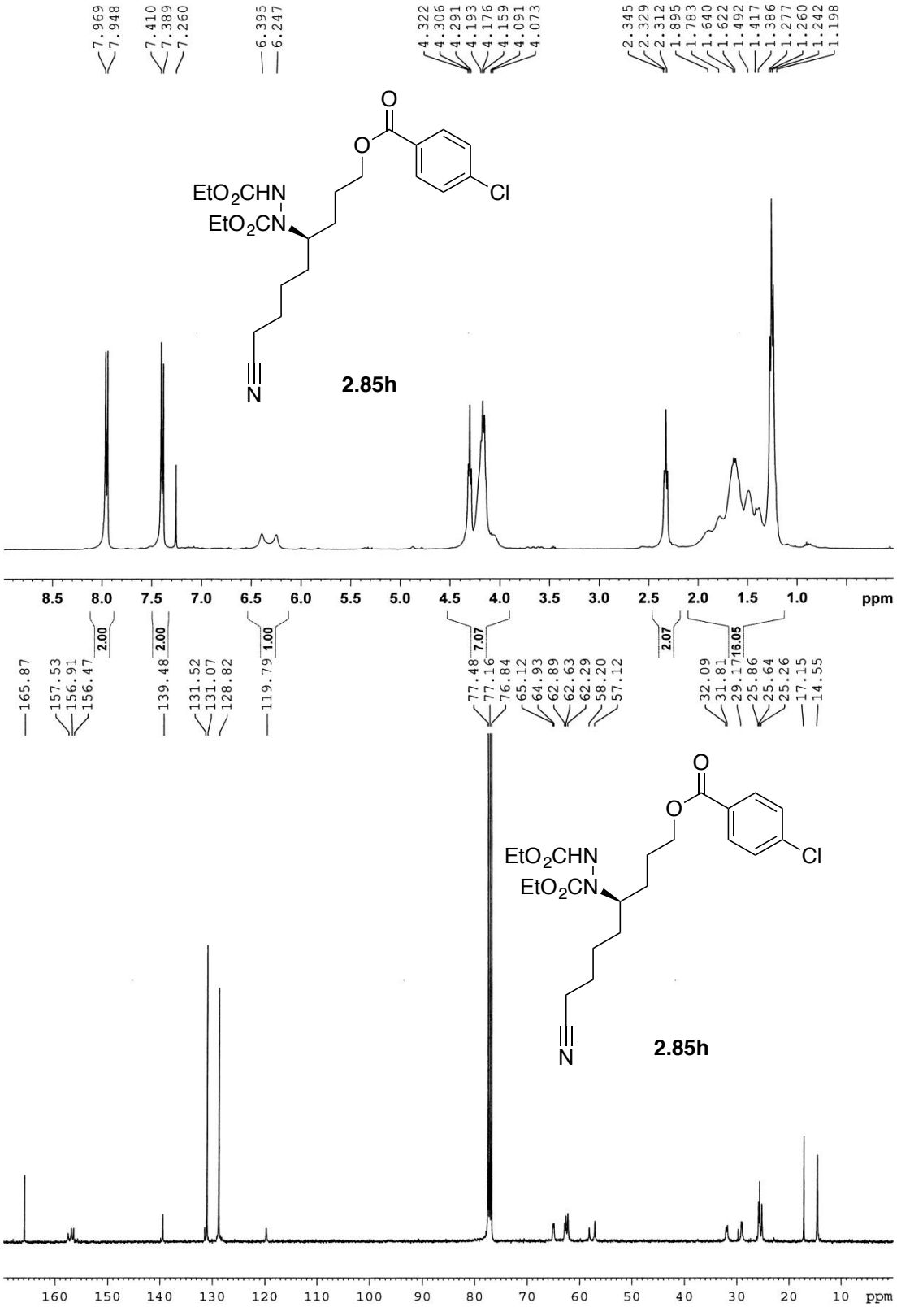

7.986
7.965
7.410
7.389
7.260
6.308
4.349
4.334
4.319
4.290
4.214
4.198
4.181
2.605
2.088
1.887
1.675
1.616
1.604
1.288
1.270
1.253
EtO2CHN
EtO2CN
Cl
S
2.85g
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.00 2.02 0.99 7.07 2.10 7.14 6.22
165.91
157.55
156.84
139.45
131.13
128.98
128.80
77.48
77.16
76.84
65.22
64.98
62.96
62.72
62.35
56.79
55.54
37.22
36.71
29.83
28.86
25.98
15.50
15.22
14.58
EtO2CHN
EtO2CN
Cl
S
2.85g
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

3.25h:



(*R*)-Diethyl 1-(1-((4-chlorobenzoyl)oxy)-8-cyanooctan-4-yl)-hydrazine-1,2-dicarboxylate.

Purified by flash chromatography (5% Et2O/CH2Cl2). Colorless oil (37 mg, 68%): $[\alpha]_D^{23}$ = -1.9 (c = 1.42 in $CHCl_3$); IR (thin film, KBr) 3298, 2934, 2869, 2246, 1755, 1717, 1405, 1274, 1232, 1093, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.40-6.25 (brm, 1H), 4.32-4.07 (m, 5H), 4.31 (t, *J* = 6.2 Hz, 2H), 2.33 (t, *J* = 6.6 Hz, 2H), 1.90-1.20 (m, 10H), 1.28-1.24 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 157.5, 156.9/156.5, 139.5, 131.5, 131.1, 128.8, 119.8, 65.1/64.9, 62.9/62.6, 62.3, 58.2/57.1, 32.1/31.8, 29.2, 25.9, 25.6, 25.3, 17.2, 14.6 ppm; HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 47.6 min, minor enantiomer t_R = 36.2 min; HRMS (ESI) $[M + H]^+$ calcd. for $[C_{22}H_{31}ClN_3O_6]$ 468.1901, found 468.1891.


7.969
7.948
7.410
7.389
7.260
6.395
6.247
4.322
4.306
4.291
4.193
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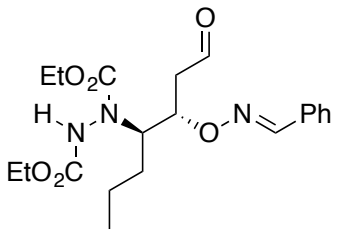
4.159
4.091
4.073
2.345
2.329
2.312
1.895
1.783
1.640
1.622
1.492
1.417
1.386
1.277
1.260
1.242
1.198
EtO2CHN
EtO2CN
Cl
O
O
N
2.85h
ppm
2.00
2.00
1.00
7.07
2.07
16.05
165.87
157.53
156.91
156.47
139.48
131.52
131.07
128.82
119.79
77.48
77.16
76.84
65.12
64.93
62.89
62.63
62.29
58.20
57.12
32.09
31.81
29.17
25.86
25.64
25.26
17.15
14.55
EtO2CHN
EtO2CN
Cl
O
O
N
2.85h
ppm

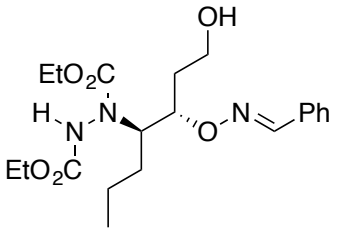
6.3 Experimental and Characterization for Chapter 3

Preparation of Nucleophiles.
Nucleophiles that were not commercially available (oximes **3.6a-b**,[6] 2-nitrosophenols **3.27a-c**,[7–15] methoxybenzylcarbamate **3.36**,[16] *N*-hydroxy-*N*-methylbenzylcarbamate **3.41**[17]) were prepared using known procedures.

3.16:

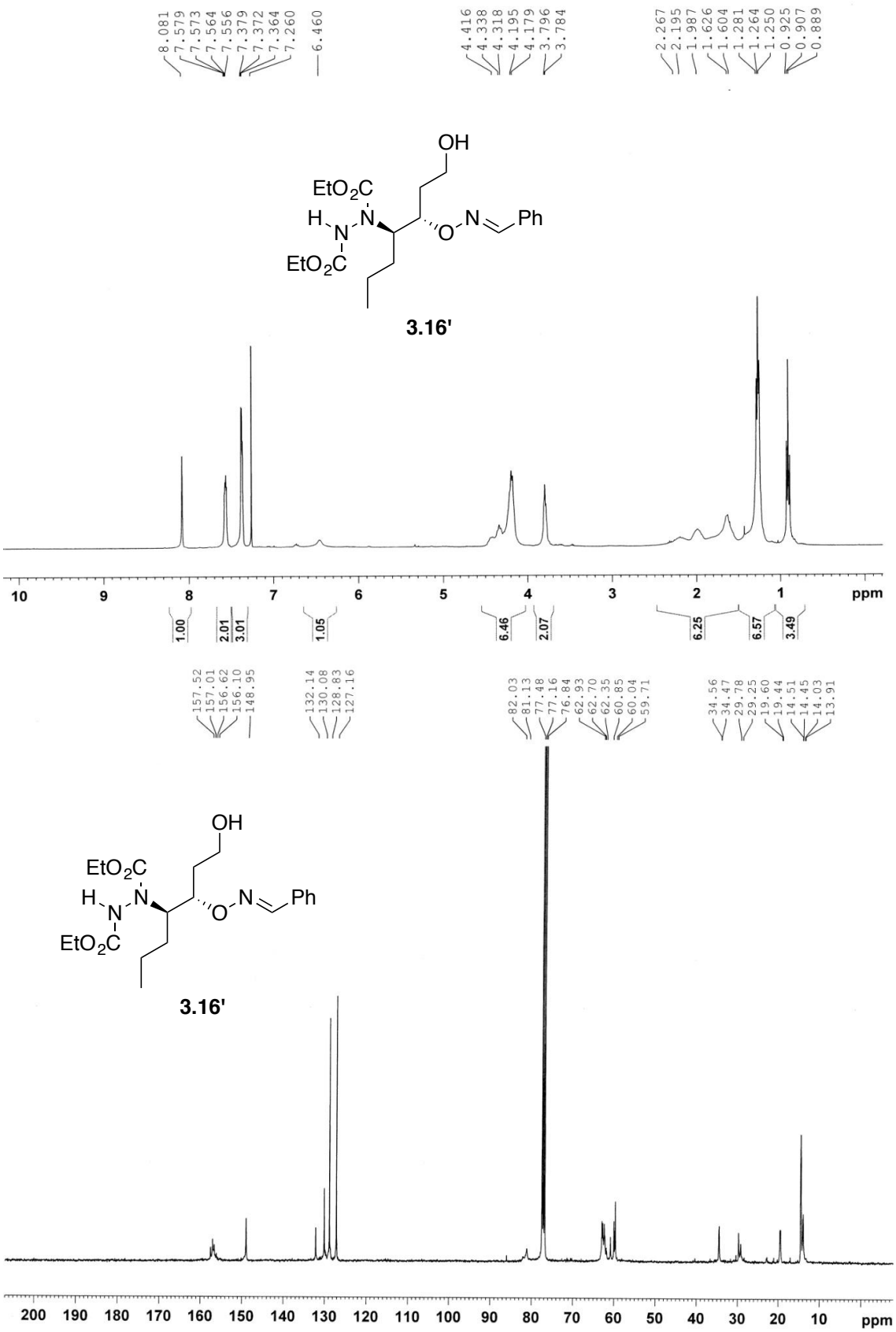


Procedure for the synthesis of Diethyl 1-((3*S*,4*R*)-3-(((*Z*)-benzylideneamino)oxy)-1-hydroxyheptan-4-yl)hydrazine-1,2-dicarboxylate. (3.16).
To a mixture of catalyst **3.3a** (14.9 mg, 0.025 mmol) and benzoic acid (3.1 mg, 0.025 mmol) was added toluene (125 μL), and the mixture was stirred at rt. After 5 min enal **3.1a** (50 μL, 0.375 mmol) was added. After 10 min **3.2** (39 μL, 0.25 mmol) was added, and the reaction was stirred in the dark. After 21 h (complete consumption of **3.2** observed by ^{1}H NMR), the reaction was cooled to 0 °C and catalyst **3.3a** (15 mg, 0.025 mmol) and benzoic acid (3 mg, 0.025 mmol) were added. The reaction was stirred for 5 min, then oxime **3.6a** (136.3 mg, 1.125 mmol) was added, and the reaction was stirred at 0 °C for 21 h (complete disappearance of enal peaks in ^{1}H NMR).



3.16'

To isolate: MeOH (0.75 mL) and $NaBH_4$ (21 mg, 0.565 mmol) were added simultaneously to crude **3.16**, and the reaction was stirred for 15 min. The reaction was then quenched with saturated NH_4Cl and extracted with CH_2Cl_2 (3 ×15 mL). The combined organic layers were dried over $MgSO_4$ and filtered. After removal of solvent under reduced pressure, the residue was purified by flash chromatography (cold column, 20% Et_2O/ CH_2Cl_2) to yield **3.16'** as a colorless oil: IR (thin film, KBr) 3277, 2962, 2873, 1714, 1414, 1253, 1058, 947, 759, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.58-7.56 (m, 2H),7.38-7.36 (m, 3H), 6.46 (brs, 1H), 4.42-4.18 (m, 6H), 3.80-3.78 (m, 2H), 2.27-1.60 (m, 6H), 1.28-1.25 (m, 6H), 0.91 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5/157.0, 156.6/156.1, 149.0, 132.1, 130.1, 128.8, 127.2, 82.0/81.1, 62.9/62.7, 62.4, 60.9/60.0, 59.7, 34.6/34.5, 29.8/29.3, 19.6/ 19.4, 14.5, 14.4, 14.0/13.9 ppm; HRMS (ESI) $[M + H]^+$ calcd. for $[C_{20}H_{32}N_3O_6]$ 410.2291, found 410.2289.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7.573
7.564
7.556
7.379
7.372
7.364
7.260
6.460
4.416
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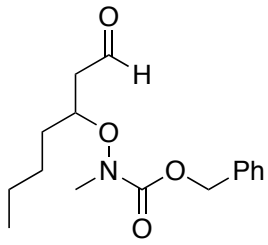
4.318
4.195
4.179
3.796
3.784
2.267
2.195
1.987
1.626
1.604
1.281
1.264
1.250
0.925
0.907
0.889
OH
EtO2C
H
N
N
EtO2C
O
N
Ph
3.16'
10
9
8
7
6
5
4
3
2
1
ppm
1.00
2.01
3.01
1.05
6.46
2.07
6.25
6.57
3.49
157.52
157.01
156.62
156.10
148.95
132.14
130.08
128.83
127.16
82.03
81.13
77.48
77.16
76.84
62.93
62.70
62.35
60.85
60.04
59.71
34.56
34.47
29.78
29.25
19.60
19.44
14.51
14.45
14.03
13.91
OH
EtO2C
H
N
N
EtO2C
O
N
Ph
3.16'
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

3.42a:



Procedure for synthesis of 3.42a

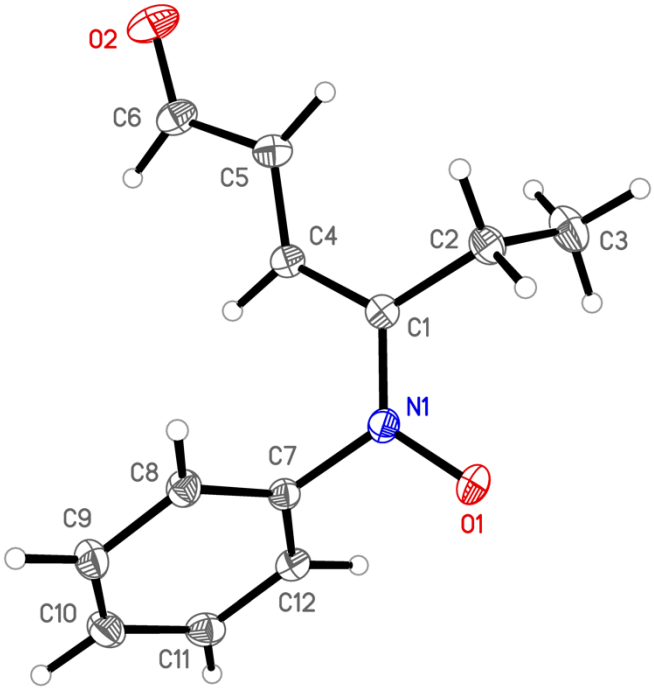
To an oven-dried flask was added NaOAc (2.1mg, 0.025mmol) and anhydrous toluene (125 µL). The solution was stirred 5 minutes at room temperature under argon. Enal **3.1a** (33.0 µL, 0.25 mmol) was added and the solution was stirred an additional 5 minutes. *N*-methyl-*N*-hydroxy benzylcarbamate **3.41** (117µL, 0.75mmol) was added to the solution. The reaction mixture was stirred until complete consumption of **3.1a**, as determined by ^{1}H NMR. Purify via flash chromatography.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (d, J = 2 Hz, 1H), 7.79-7.35 (m, 5H), 5.19 (s, 2H), 4.42 (m, 1H), 3.13 (s, 3H), 2.67 (ddd, J = 16.5, 7.6, 3.0 Hz, 1H), 2.54 (dd, J = 16.2, 4.1 Hz, 1H), 1.76-1.65 (m, 1H), 1.59-1.51 (m, 1H), 1.42-1.28 (m, 4H), 0.90 (t, J = 6.6 Hz, 3H) ppm.

6.4 Experimental and Characterization for Chapter 4

Diastereomeric Ratio Determination The dr was determined by using the ^{1}H NMR integrations of the major and minor aldehyde peaks when NMR yield was obtained.

Crystallography The crystal structure of **4.26a** (CCDC=1451744) was used along with HRMS data to confirm the presence of a nitrone versus an imine, as well as determine the stereochemistry of the major isomer, confirming both the C=C and C=N as *E*. This, along with the previously discussed ^{1}H NMR data, allowed for extrapolation to the stereostructure of the major isomer of **4.26f'**, with the C=C as *E*, and the C=N as *Z*.



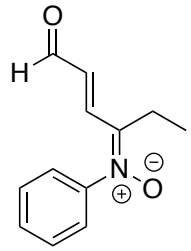
Mechanistic Studies
HRMS evidence to support the proposed mechanism for the formation of nitrone **4.26a**, shown in **Scheme 4.9**, was obtained by dilution of an aliquot of the reaction mixture to 20μM in dichloromethane after two hours of reactivity. This solution was injected onto a Bruker Apex-ultra 70 hybrid FTMS by ESI and the masses for our proposed mechanistic intermediates were compared to the output.

Preparation of enals (4.9d,f-i), and *p*-nitronitrosobenzene.
Enals **4.9d**,[18,19] **4.9f**,[18,19] **4.9g**,[20] and **4.9h**,[21] **4.9i**,[22] and *p*-nitronitrosobenzene[23] were prepared using known procedures.

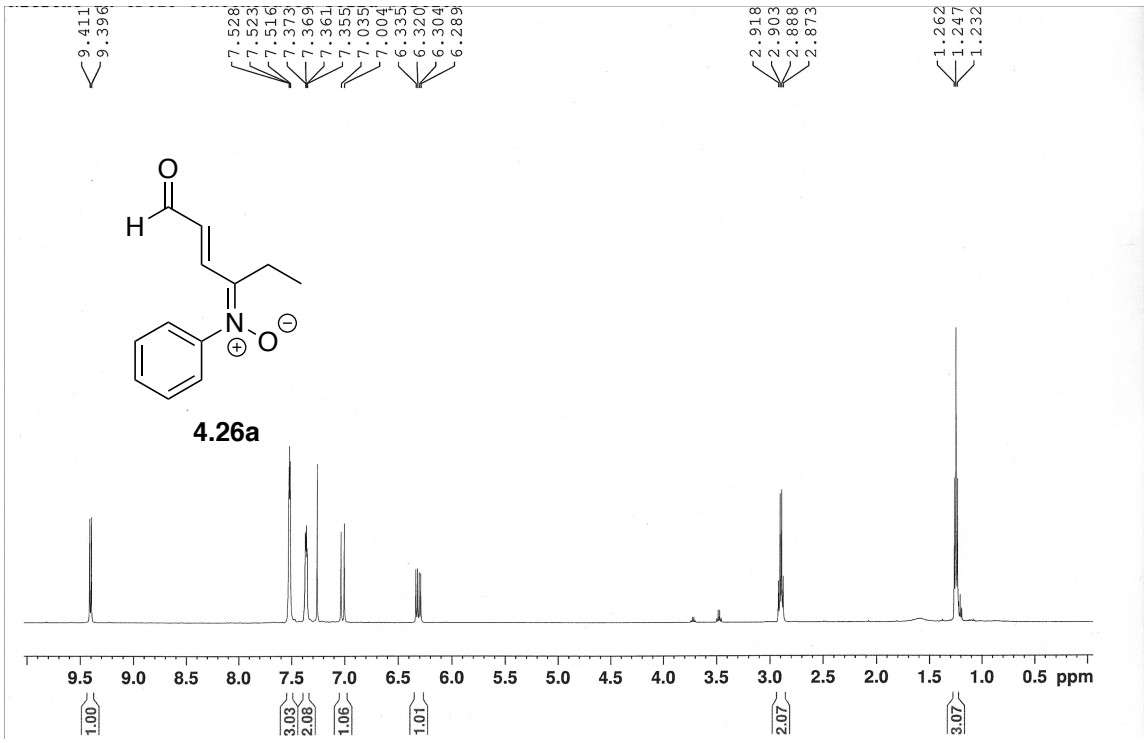
General Procedure for formation of nitrone enals 4.26.
To a solution of catalyst **4.10b** (16.3 mg, 0.05 mmol) in 1,4-dioxane (0.25 mL), was added acetic acid (2.9 μL, 0.05 mmol) and the solution stirred for 5 minutes. Freshly distilled enal

4.9 (0.25 mmol) was added, the reaction stirred for 10 minutes, then nitrosobenzene **4.2** (107.1 mg, 1.0 mmol) was added. The reaction was stirred at rt until complete consumption of enal, as observed by ^{1}H NMR. The crude reaction was immediately loaded onto silica gel and purified by flash chromatography (20% EtOAc:petroleum ether). Solvent was removed under reduced pressure by rotary evaporation at room temperature to yield pure nitrone **4.26**.

4.26a:



(*E*)-*N*-((*E*)-6-oxohex-4-en-3-ylidene)aniline oxide.
Yellow solid (27 mg, 53%): mp 90-92 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (d, J = 7.5 Hz, 1H), 7.53-7.52 (m, 3H), 7.37-7.36 (m, 2H), 7.02 (d, J = 15.5 Hz, 1H), 6.31 (dd, J = 15.5, 7.5 Hz, 1H), 2.90 (q, J = 7.5 Hz, 2H), 1.25 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 151.2, 145.5, 140.6, 130.5, 129.8, 129.0, 124.4, 20.4, 9.7 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{12}H_{14}NO_2]$ 204.1025, found 204.1022.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9.396
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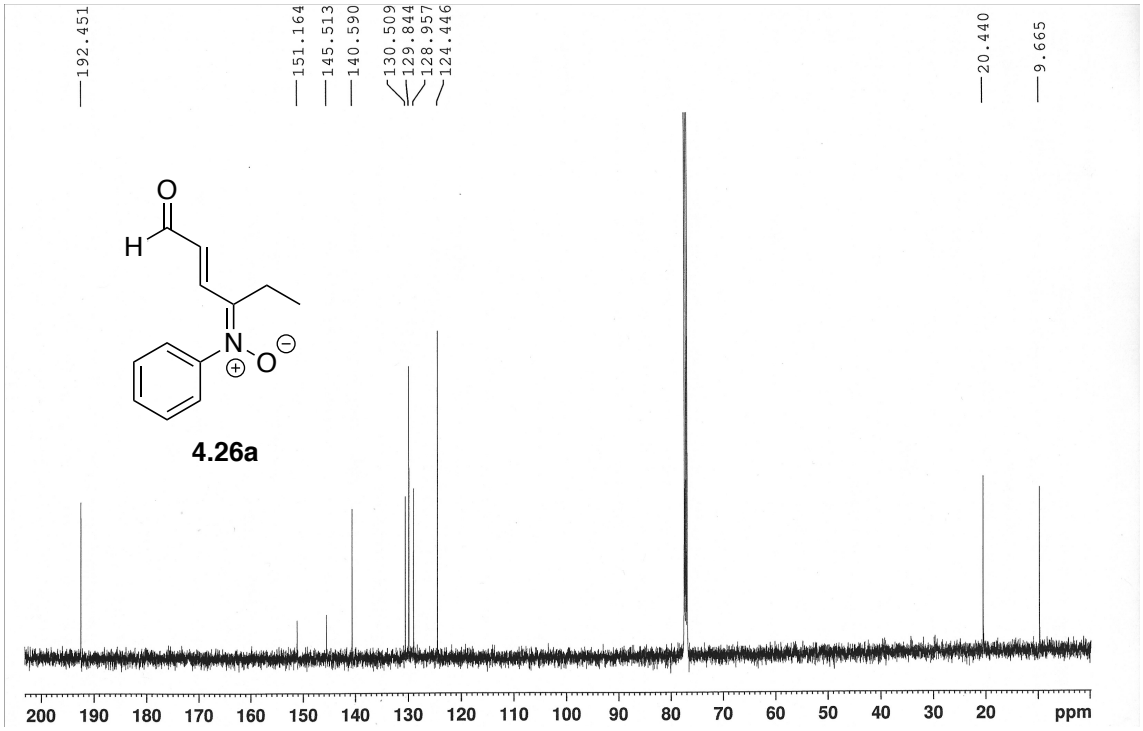
7.523
7.516
7.373
7.369
7.361
7.355
7.035
7.004
6.335
6.320
6.304
6.289
2.918
2.903
2.888
2.873
1.262
1.247
1.232
4.26a
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
3.03
2.08
1.06
1.01
2.07
3.07


192.451
151.164
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140.590
130.509
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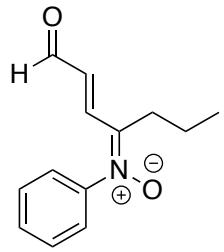
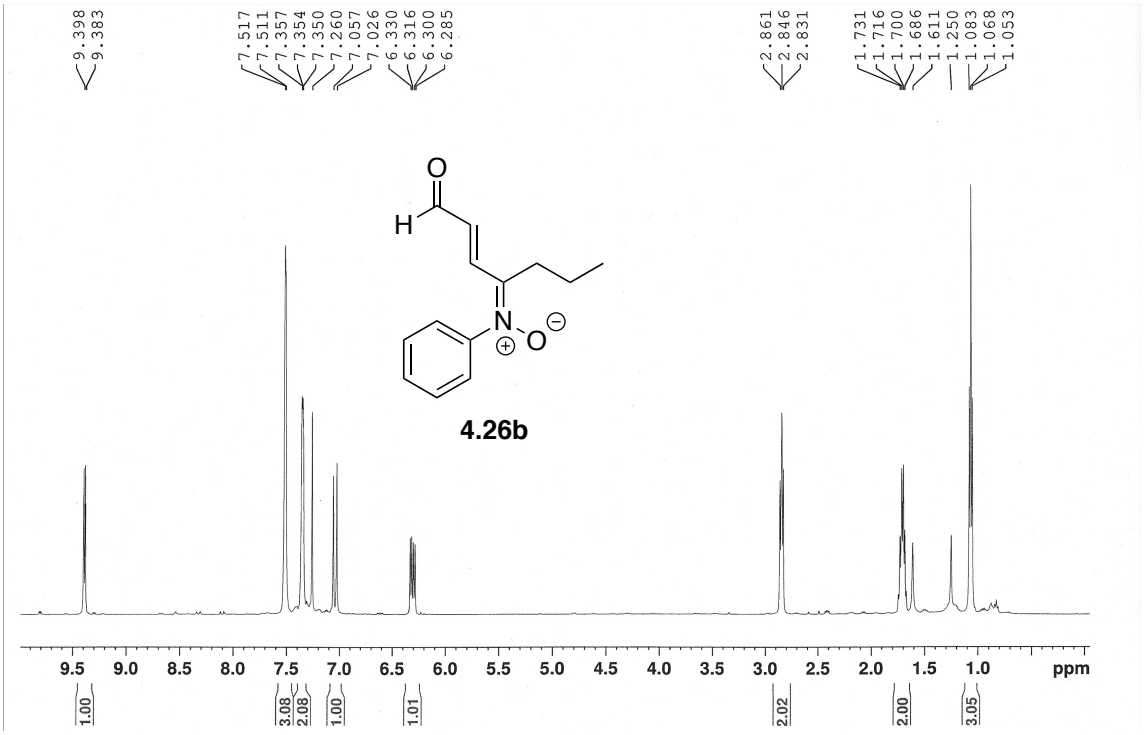
128.957
124.446
20.440
9.665
4.26a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

4.26b:



(*E*)-*N*-((*E*)-1-oxohept-2-en-4-ylidene)aniline oxide.
Yellow oil (26 mg, 48%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (d, J = 7.5 Hz, 1H), 7.52-7.51 (m, 3H), 7.36-7.35 (m, 2H), 7.04 (d, J = 15.5 Hz, 1H), 6.31 (dd, J = 15.5, 7.5 Hz, 1H), 2.85 (t, J = 7.5 Hz, 2H), 1.73-1.69 (m, 2H), 1.07 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 150.2, 145.6, 141.2, 130.5, 129.8, 129.1, 124.4, 28.8, 18.9, 14.3 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{13}H_{16}NO_2]$ 218.1181, found 218.1174.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7.354
7.350
7.260
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7.026
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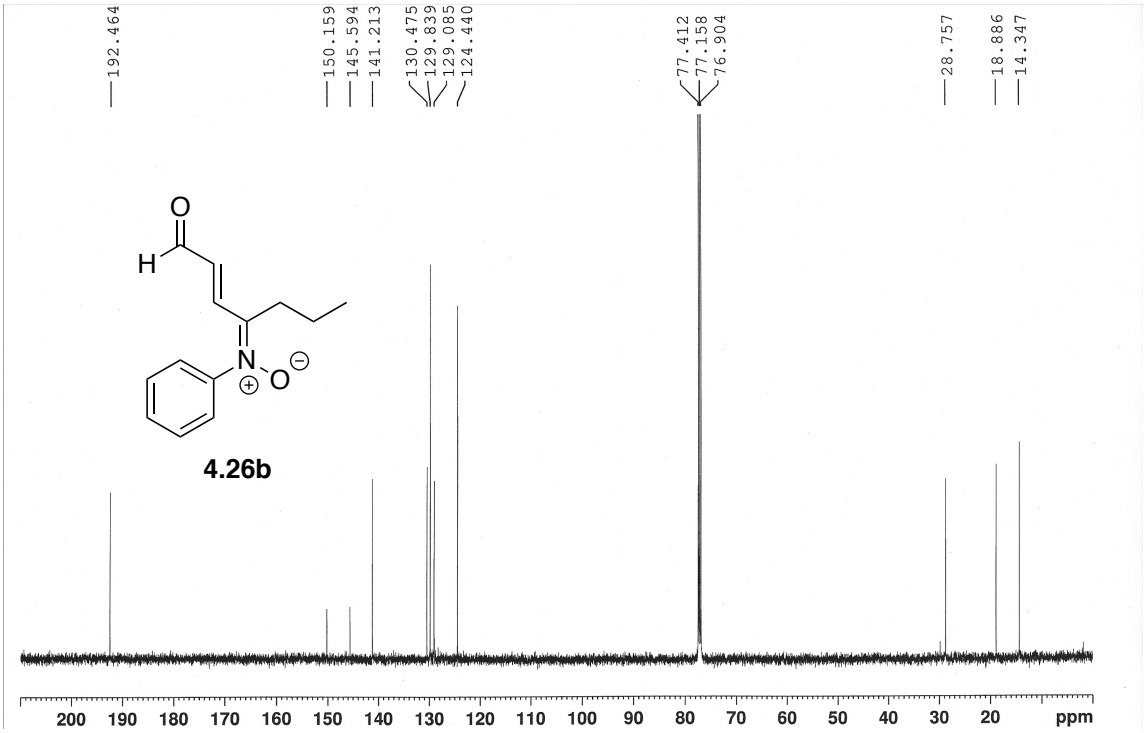
6.316
6.300
6.285
2.861
2.846
2.831
1.731
1.716
1.700
1.686
1.611
1.250
1.083
1.068
1.053
O
H
N
O
4.26b
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
3.08
2.08
1.00
1.01
2.02
2.00
3.05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124.440
77.412
77.158
76.904
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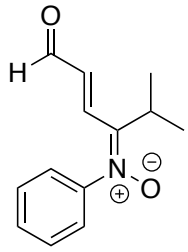
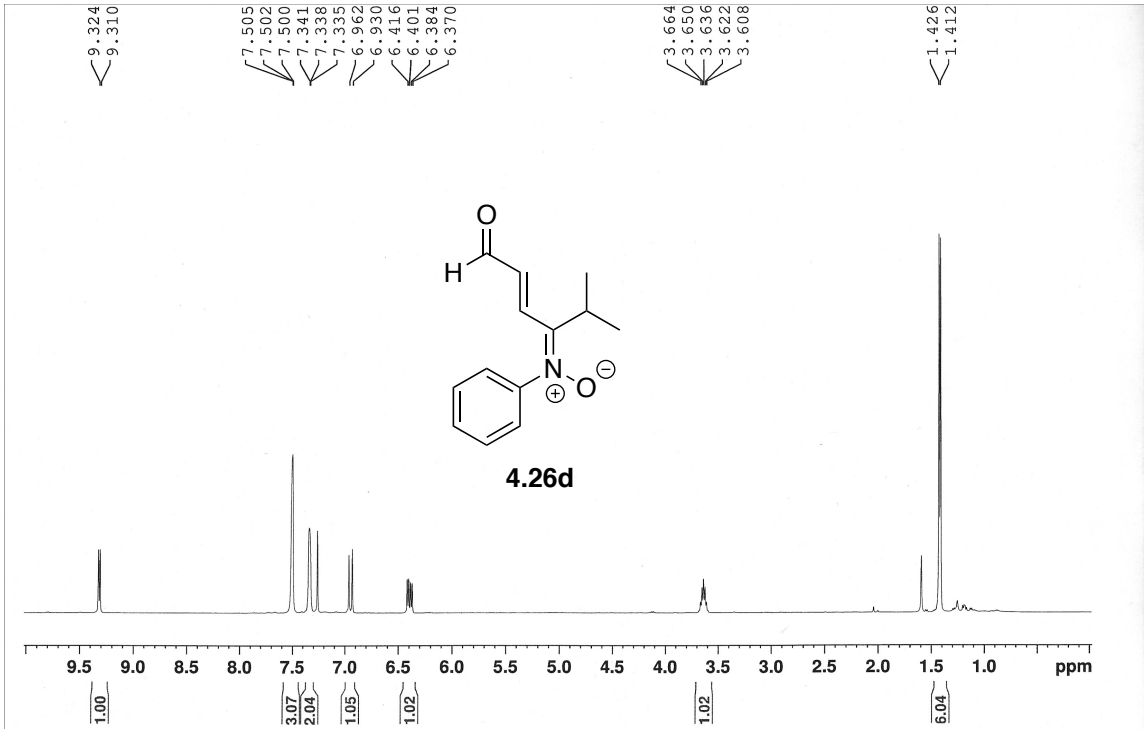
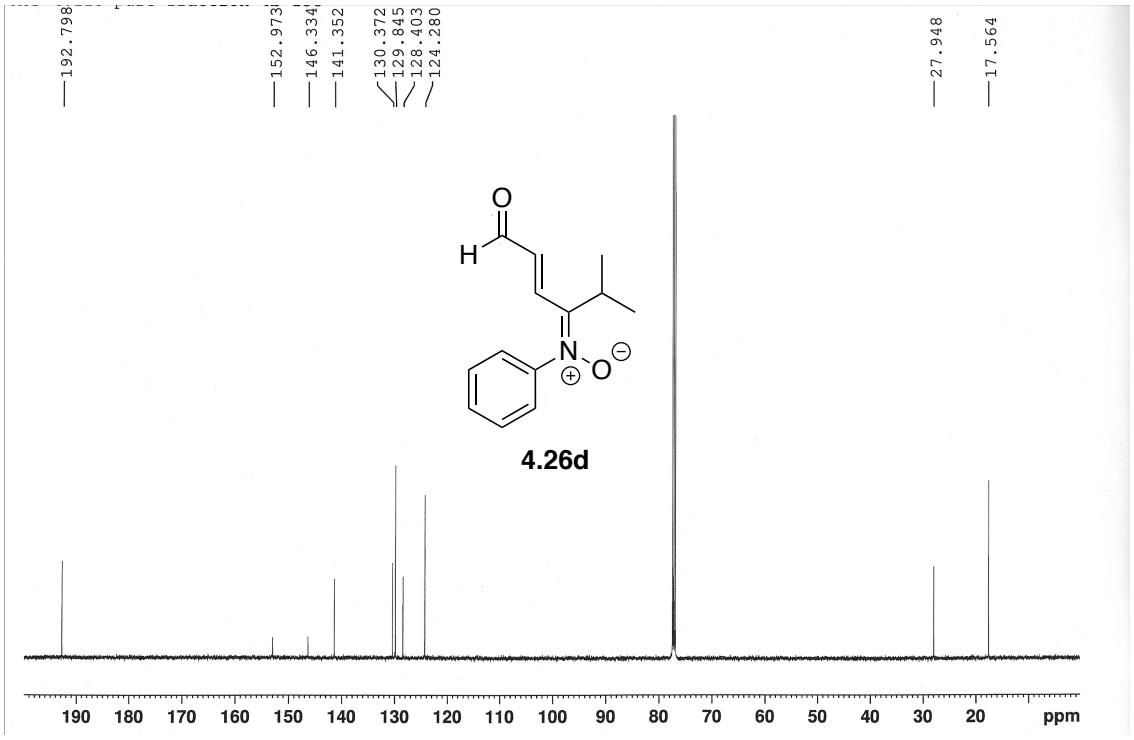
O
H
N
O
4.26b
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

4.26d:

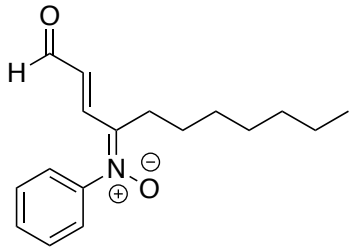


(*E*)-*N*-((*E*)-2-methyl-6-oxohex-4-en-3-ylidene)aniline oxide.
Yellow oil (32 mg, 59%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (d, J = 7.0 Hz, 1H), 7.51-7.50 (m, 3H), 7.34-7.33 (m, 2H), 6.95 (d, J = 16.0 Hz, 1H), 6.39 (dd, J = 16.0, 7.5 Hz, 1H), 3.64 (septet, J = 7.0 Hz, 1H), 1.42 (d, J = 7.0 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 153.0, 146.3, 141.4, 130.4, 129.8, 128.4, 124.3, 27.9, 17.6 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{13}H_{16}NO_2]$ 218.1181, found 218.1181.

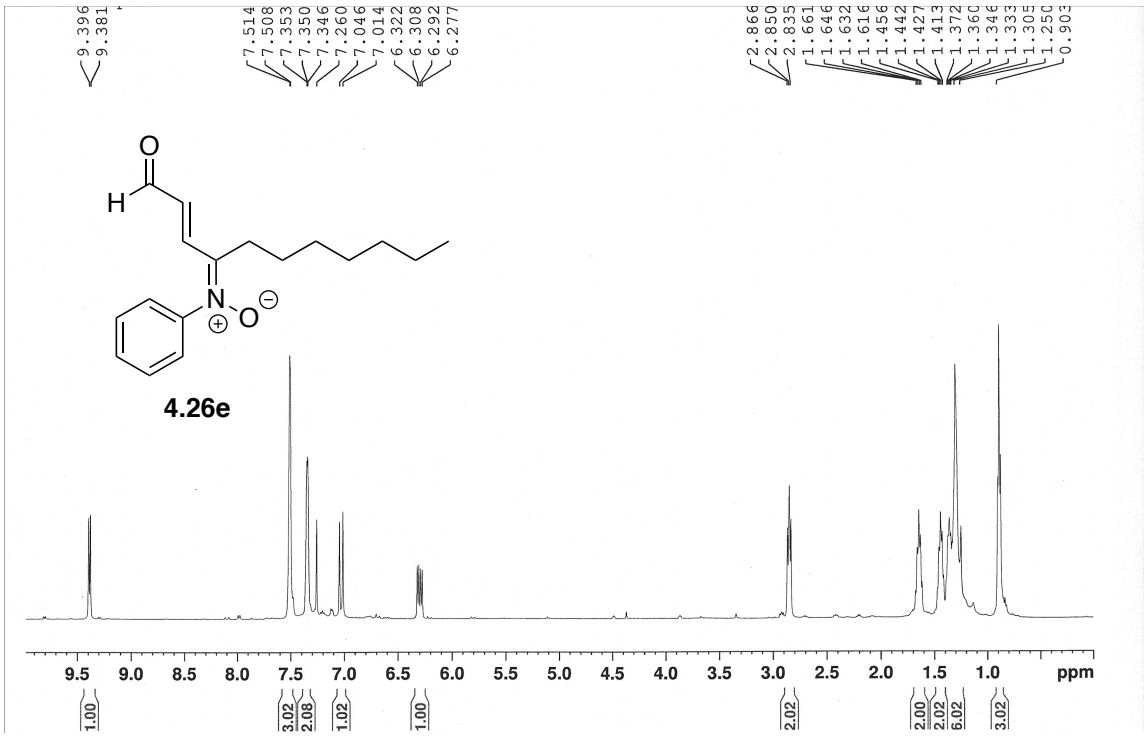

9.324
9.310
7.505
7.502
7.500
7.341
7.338
7.335
6.962
6.930
6.416
6.401
6.384
6.370
3.664
3.650
3.636
3.622
3.608
1.426
1.412
O
H
N
O
4.26d
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
3.07
2.04
1.05
1.02
1.02
6.04

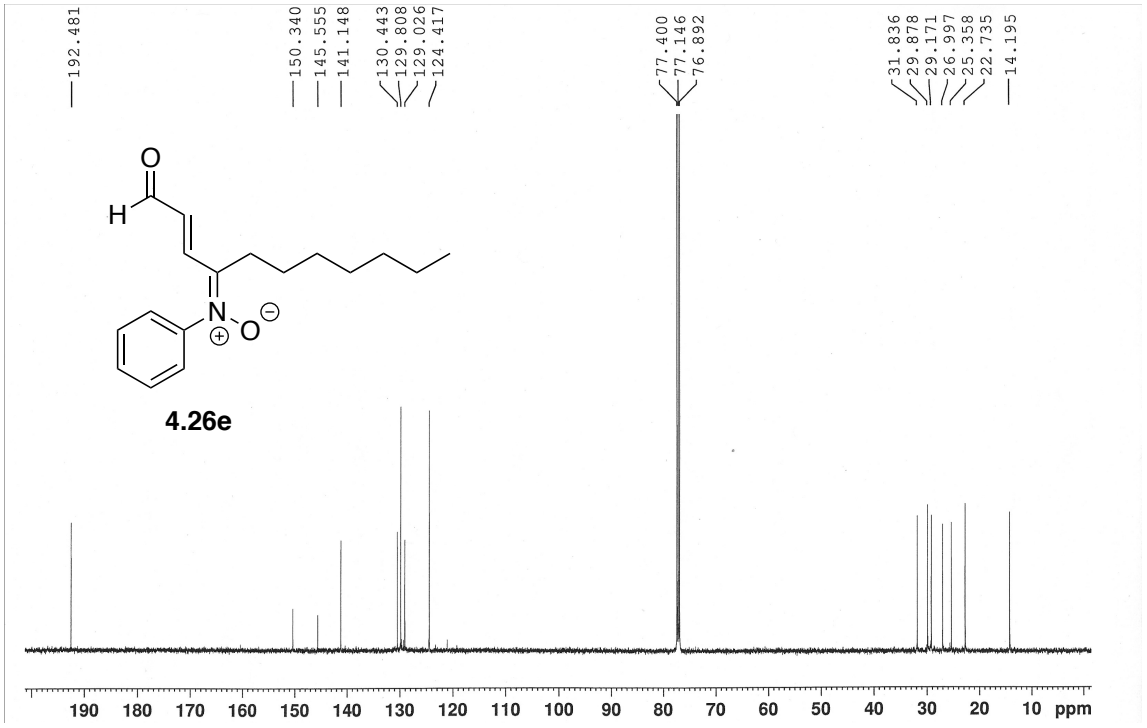

192.798
152.973
146.334
141.352
130.372
129.845
128.403
124.280
27.948
17.564
O
H
N
O
4.26d
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

4.26e:

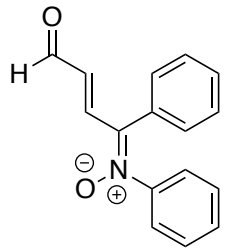


(*E*)-*N*-((*E*)-1-oxoundec-2-en-4-ylidene)aniline oxide.
Yellow oil (29 mg, 42%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (d, J = 7.5 Hz, 1H), 7.51 (m, 3H), 7.35 (m, 2H), 7.03 (d, J = 16.0 Hz, 1H), 6.30 (dd, J = 15.5, 7.5 Hz, 1H), 2.85 (t, J = 8.0 Hz, 2H), 1.66-1.62 (m, 2H), 1.46-1.41 (m, 2H), 1.37-1.25 (m, 6H), 0.89 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 150.3, 145.6, 141.1, 130.4, 129.8, 129.0, 124.4, 31.8, 29.9, 29.2, 27.0, 25.4, 22.7, 14.2 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{17}H_{24}NO_2]$ 274.1807, found 274.1802.

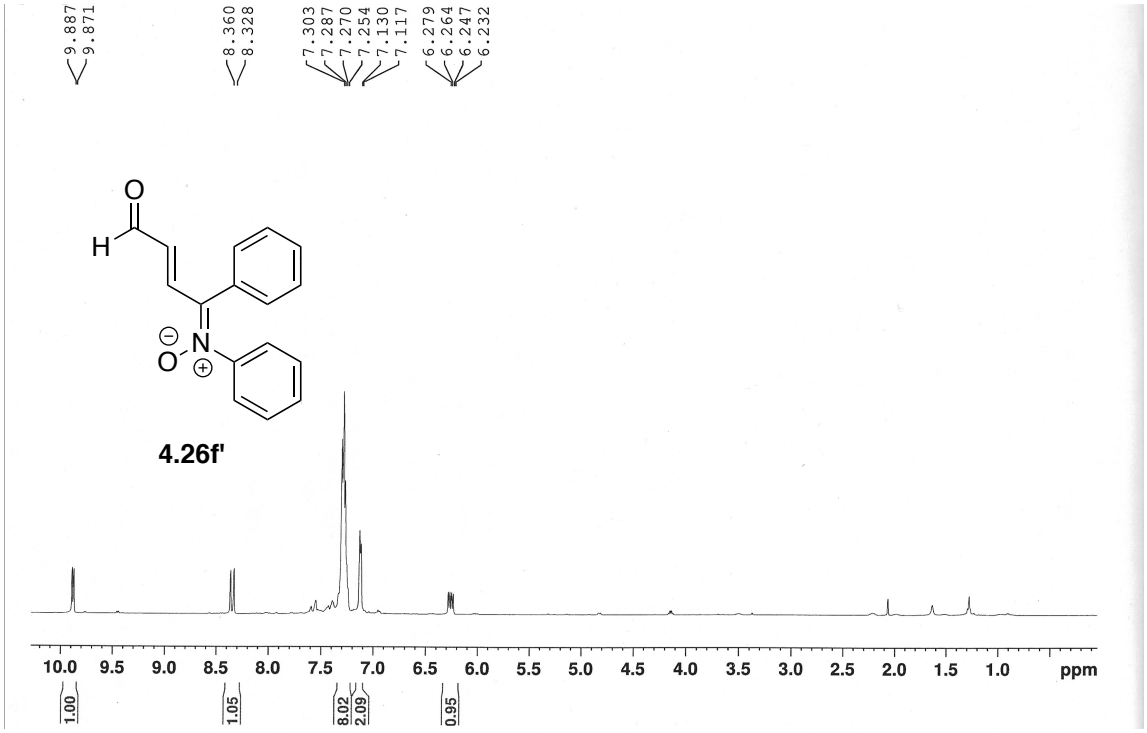

9.396
9.381
7.514
7.508
7.353
7.350
7.346
7.260
7.046
7.014
6.322
6.308
6.292
6.277
2.866
2.850
2.835
1.661
1.646
1.632
1.616
1.456
1.442
1.427
1.413
1.372
1.360
1.346
1.333
1.305
1.250
0.903
O
H
N
O
4.26e
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
3.02
2.08
1.02
1.00
2.02
2.00
2.02
6.02
3.02

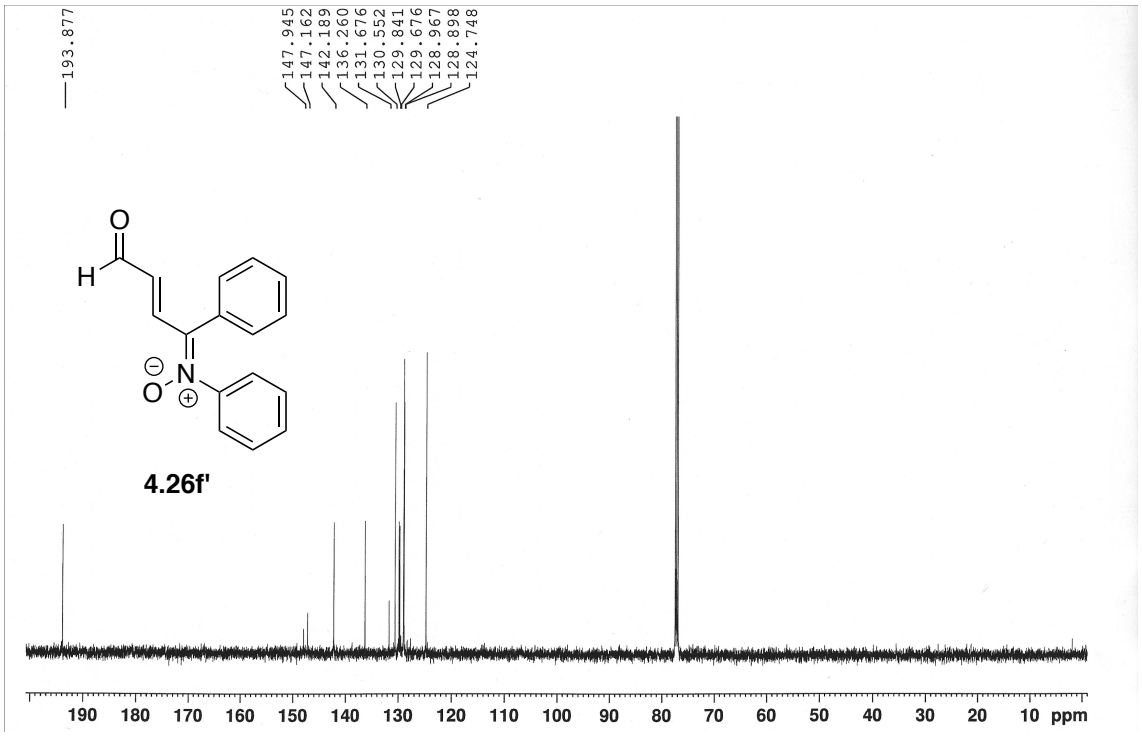

192.481
150.340
145.555
141.148
130.443
129.808
129.026
124.417
77.400
77.146
76.892
31.836
29.878
29.171
26.997
25.358
22.735
14.195
O
H
N
O
4.26e
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

4.26f':

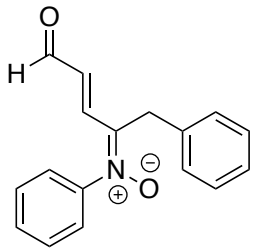


(*E*)-*N*-((*E*)-4-oxo-1-phenylbut-2-en-1-ylidene)aniline oxide.
Dark yellow oil (15 mg, 23%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.88 (d, J = 8.0 Hz, 1H), 8.34 (d, J = 16.0 Hz, 1H), 7.30-7.25 (m, 8H), 7.13-7.12 (m, 2H), 6.26 (dd, J = 16.0, 7.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.9, 147.9, 147.2, 142.2, 136.3, 131.7, 130.6, 129.8, 129.7, 129.0, 128.9, 124.7 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{16}H_{14}NO_2]$ 252.1025, found 252.1023.

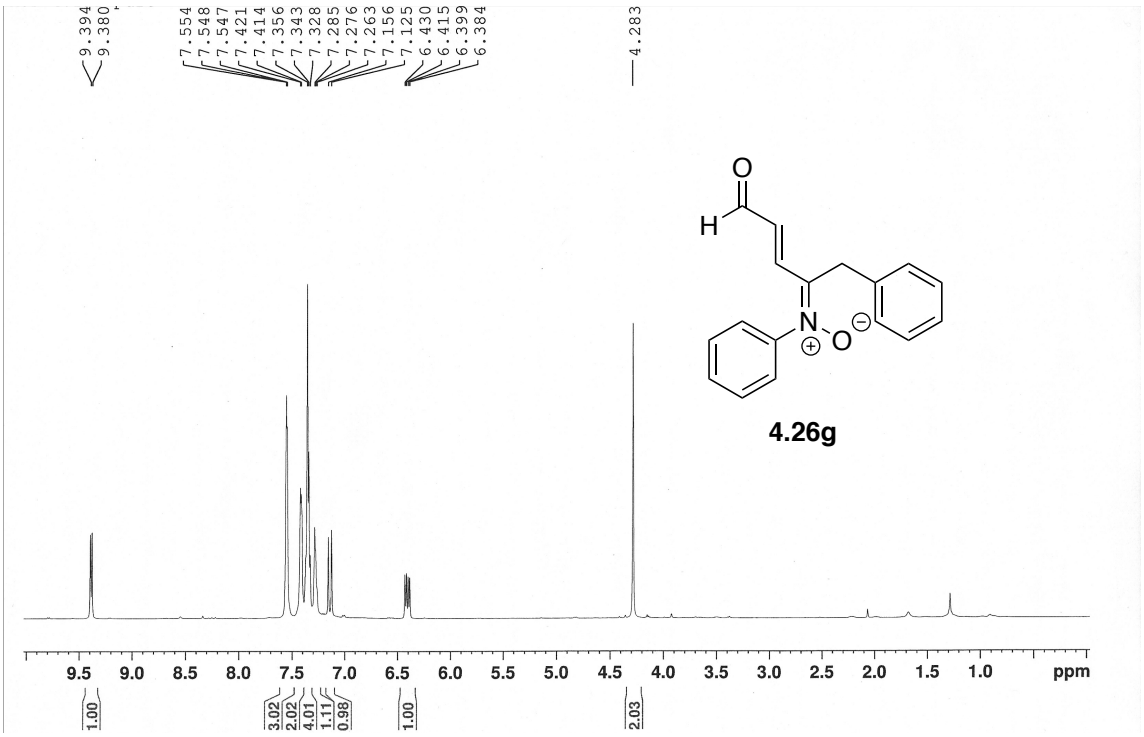

9.887
9.871
8.360
8.328
7.303
7.287
7.270
7.254
7.130
7.117
6.279
6.264
6.247
6.232
O
H
N
O
4.26f'
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.05
8.02
2.09
0.95

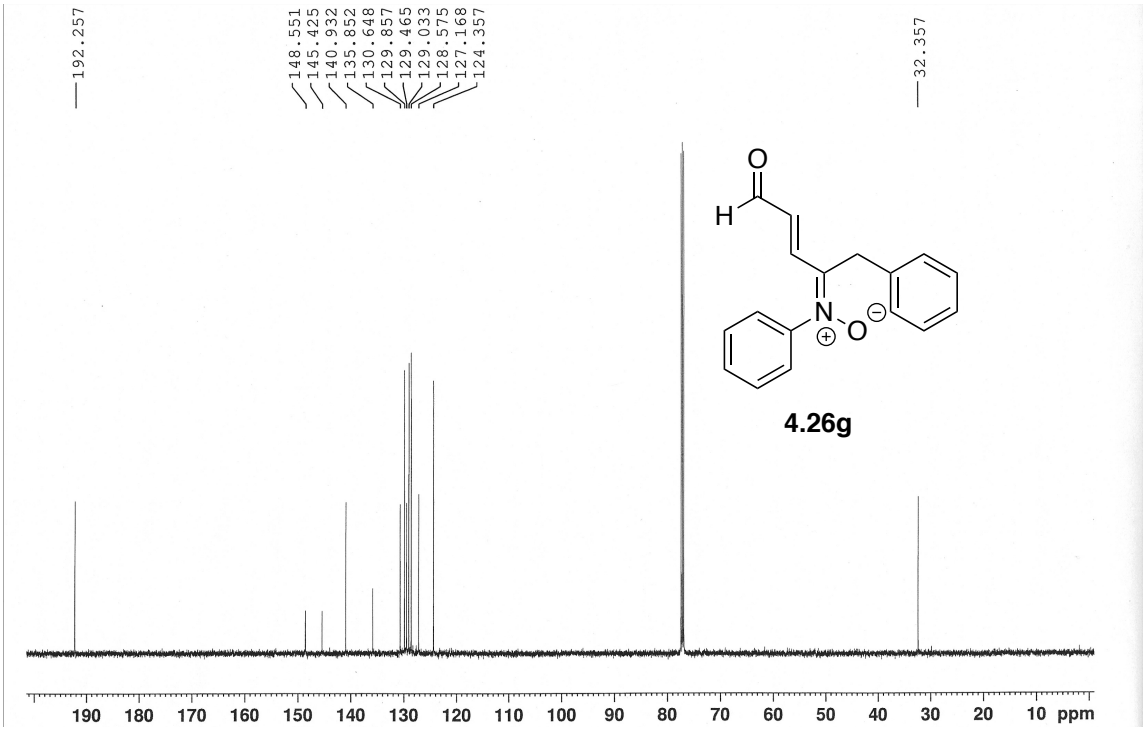

193.877
147.945
147.162
142.189
136.260
131.676
130.552
129.841
129.676
128.967
128.898
124.748
O
H
N
O
4.26f'
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

4.26g:

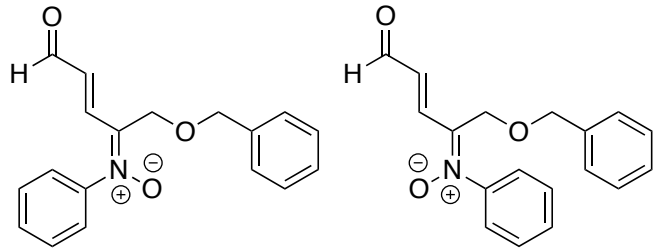


(*E*)-*N*-((*E*)-5-oxo-1-phenylpent-3-en-2-ylidene)aniline oxide.
Yellow oil (31 mg, 47%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (d, J = 7.0 Hz, 1H), 7.55 (m, 3H), 7.42-7.41 (m, 2H), 7.36-7.33 (m, 4H), 7.29-7.26 (m, 1H), 7.14 (d, J = 15.5 Hz, 1H), 6.41 (dd, J = 15.5, 7.5 Hz, 1H), 4.28 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.3, 148.6, 145.4, 140.9, 135.9, 130.6, 129.9, 129.5, 129.0, 128.6, 127.2, 124.4, 32.4 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{17}H_{16}NO_2]$ 266.1181, found 266.1178.

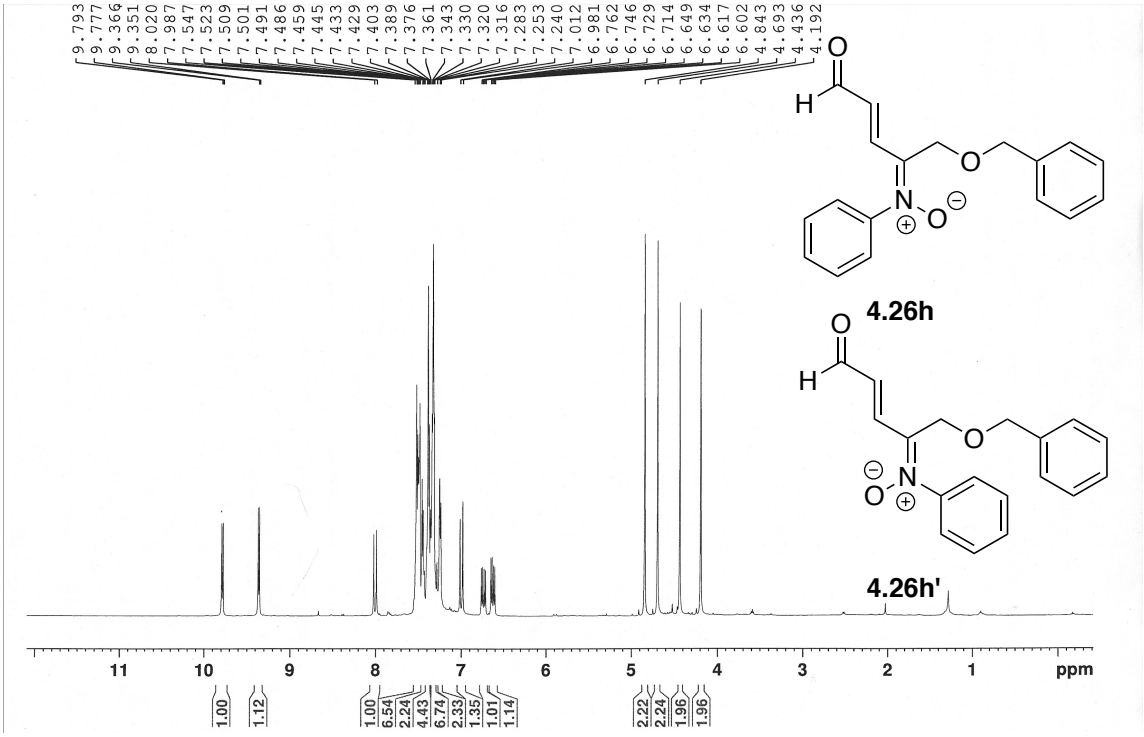

9.394
9.380
7.554
7.548
7.547
7.421
7.414
7.356
7.343
7.328
7.285
7.276
7.263
7.156
7.125
6.430
6.415
6.399
6.384
4.283
O
H
N
O
4.26g
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
3.02
2.02
4.01
1.11
0.98
1.00
2.03

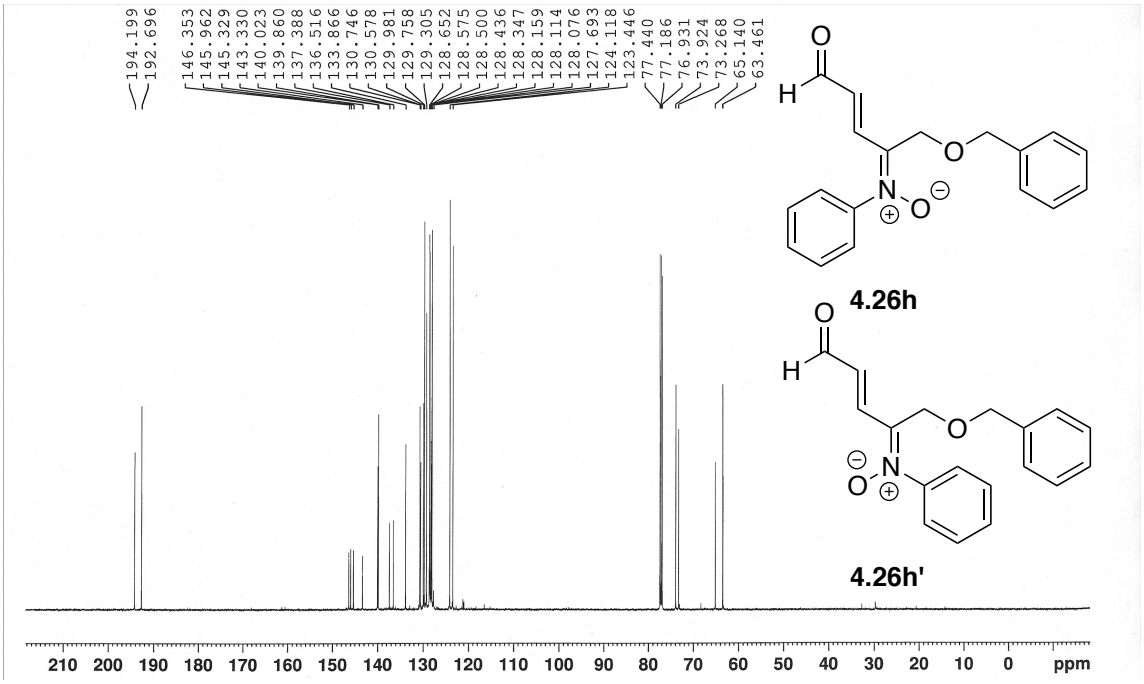

192.257
148.551
145.425
140.932
135.852
130.648
129.857
129.465
129.033
128.575
127.168
124.357
32.357
O
H
N
O
4.26g
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

4.26h/4.26h':

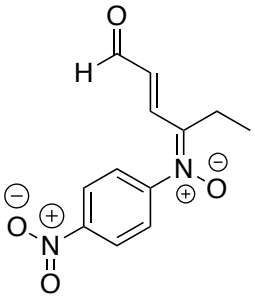


(2*Z*,3*E*)-1-(benzyloxy)-5-oxo-*N*-phenylpent-3-en-2-imine
(2*E*,3*E*)-1-(benzyloxy)-5-oxo-*N*-phenylpent-3-en-2-imine oxide.
Yellow oil (32 mg, 43%): ^{1}H NMR (500 MHz, $CDCl_3$) δ Z-isomer: 9.36 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 15.5 Hz, 1H), 6.63 (dd, J = 16.0, 7.5 Hz, 1H), 4.84 (s, 2H), 4.69 (s, 2H) E-isomer: 9.79 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 16.5 Hz, 1H), 6.74 (dd, J = 16.5, 8.0 Hz, 1H), 4.44 (s, 2H), 4.19 (s, 2H) Both: 7.55-7.49 (m, 6H), 7.45 (d, J = 7.0 Hz, 2H), 7.40-7.37 (m, 4H), 7.34-7.32 (m, 6H), 7.25 (d, J = 6.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.2, 192.7, 146.4, 146.0, 145.3, 143.3, 140.0, 139.9, 137.4, 136.5, 133.9, 130.7, 130.6, 130.0, 129.8, 129.3, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 127.7, 124.1, 123.4, 73.9, 73.3, 65.1, 63.5 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{18}H_{18}NO_3]$ 296.1287, found 296.1280.

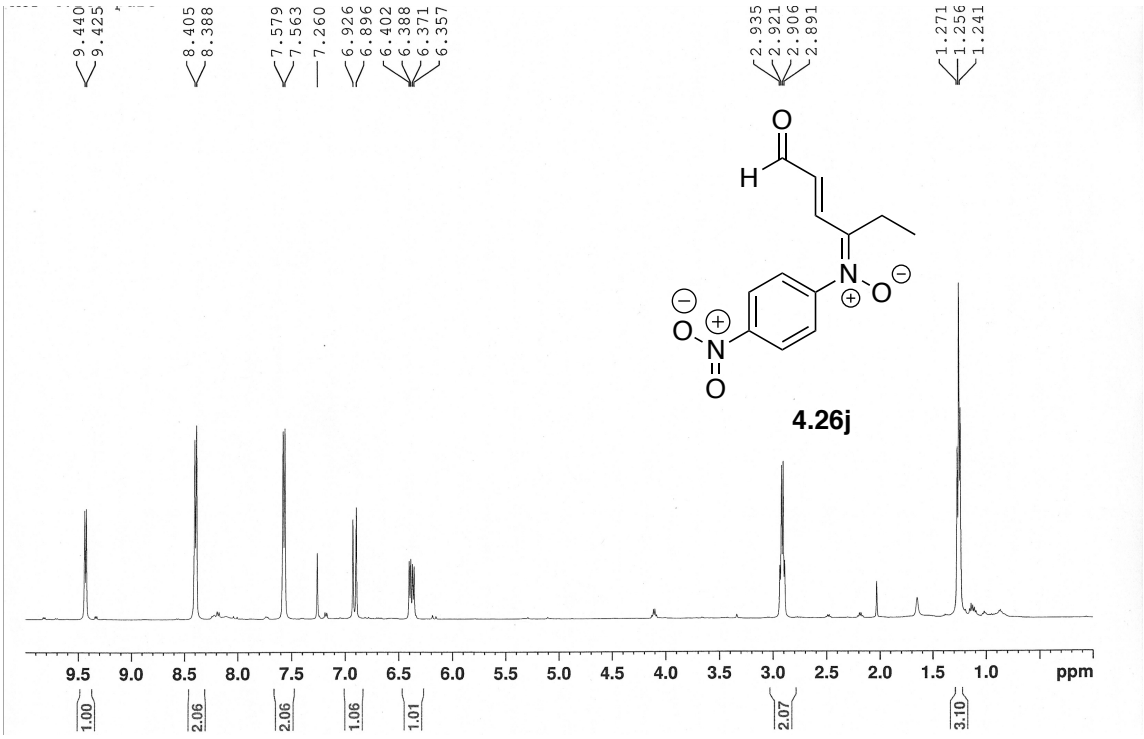

9.793
9.777
9.366
9.351
8.020
7.987
7.547
7.523
7.509
7.501
7.491
7.486
7.459
7.445
7.433
7.429
7.403
7.389
7.376
7.361
7.343
7.330
7.320
7.316
7.283
7.253
7.240
7.012
6.981
6.762
6.746
6.729
6.714
6.649
6.634
6.617
6.602
4.843
4.693
4.436
4.192
4.26h
4.26h'
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.12
1.00
6.54
2.24
4.43
6.74
2.33
1.35
1.01
1.14
2.22
2.24
1.96
1.96

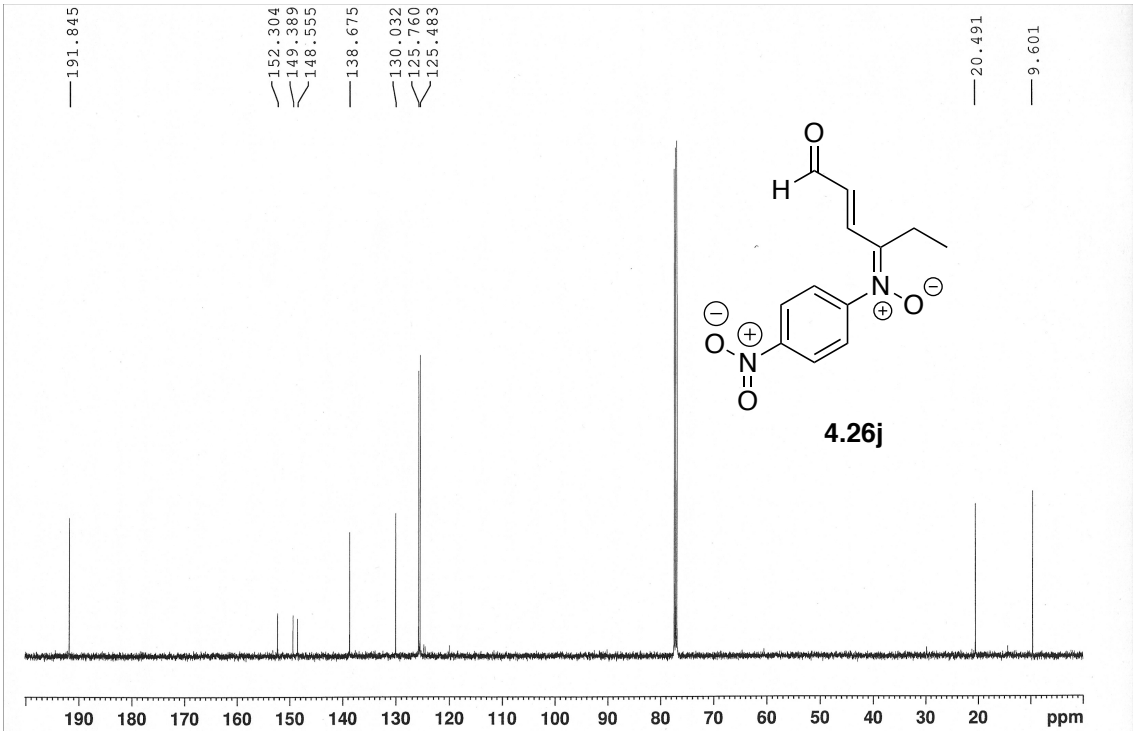

194.199
192.696
146.353
145.962
145.329
143.330
140.023
139.860
137.388
136.516
133.866
130.746
130.578
129.981
129.758
129.305
128.652
128.575
128.500
128.436
128.347
128.159
128.114
128.076
127.693
124.118
123.446
77.440
77.186
76.931
73.924
73.268
65.140
63.461
4.26h
4.26h'
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

4.26j:



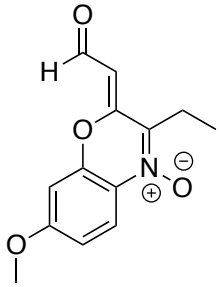
(*E*)-4-nitro-*N*-((*E*)-6-oxohex-4-en-3-ylidene)aniline oxide.
Yellow solid (28 mg, 45%): mp 107-d ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (d, J = 7.5 Hz, 1H), 8.40 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 15.0 Hz, 1H), 4.88 (dd, J = 15.5, 7.0 Hz, 1H), 2.91 (q, J = 7.5 Hz, 2H), 1.26, (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.8, 152.3, 149.4, 148.6, 138.7, 130.0, 125.8, 125.5, 20.5, 9.6 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{12}H_{13}N_2O_4]$ 249.0875, found 249.0867.


9.440
9.425
8.405
8.388
7.579
7.563
7.260
6.926
6.896
6.402
6.388
6.371
6.357
2.935
2.921
2.906
2.891
1.271
1.256
1.241
4.26j
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.06
2.06
1.06
1.01
2.07
3.10

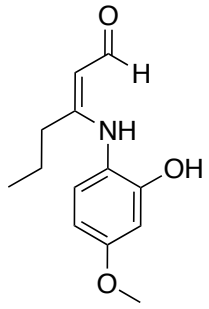

191.845
152.304
149.389
148.555
138.675
130.032
125.760
125.483
20.491
9.601
4.26j
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

Procedure for formation of (*Z*)-3-ethyl-7-methoxy-2-(2-oxoethylidene)-2*H*-benzo[*b*][1,4]oxazine 4-oxide (4.26k) and (*Z*)-3-((2-hydroxy-4-methoxyphenyl)amino)hex-2-enal (4.40).

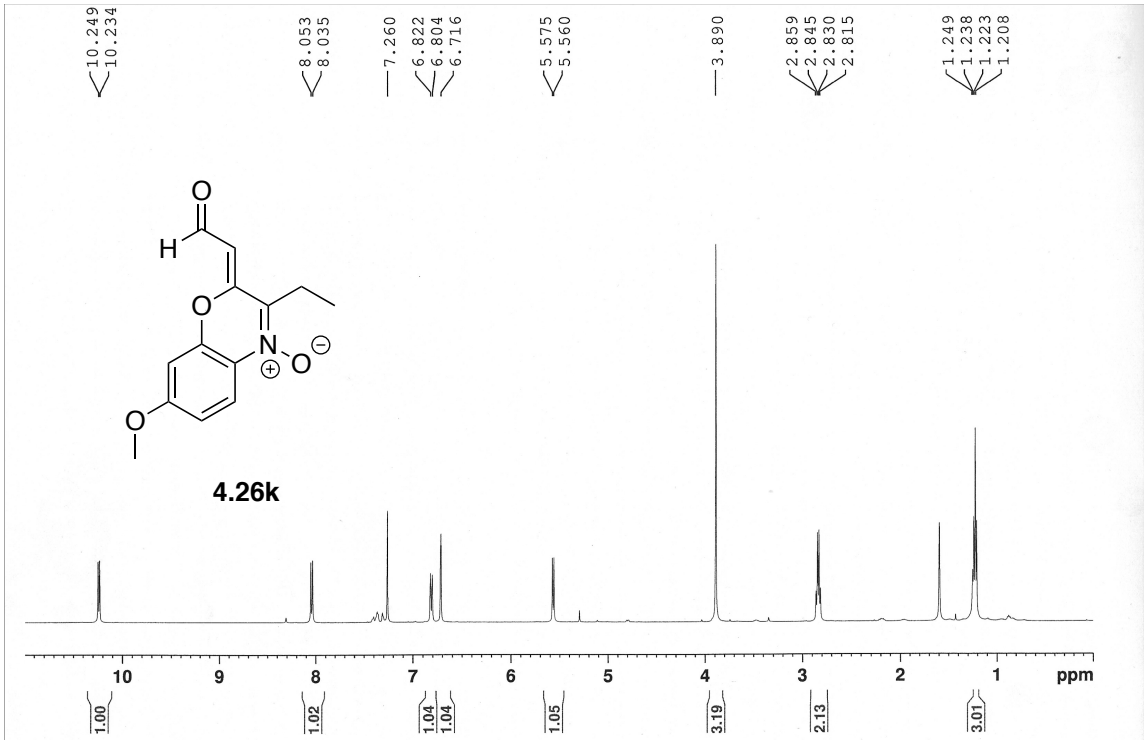
To a solution of catalyst **4.10b** (32.6 mg, 0.1 mmol) in chloroform (2.0 mL), was added freshly distilled enal **4.9a** (58.0 μL, 0.5 mmol). The reaction was stirred for 10 minutes, then 2-nitrosoresorcinol monomethyl ether (153.1 mg, 1.0 mmol) was added. The reaction was stirred at rt until complete consumption of enal, as observed by ^{1}H NMR.



To obtain **4.26k**: The crude reaction was immediately loaded onto silica gel and purified by flash chromatography (5% Et_2O:dichloromethane). Solvent was removed under reduced pressure by rotary evaporation at room temperature to yield pure **4.26k**. Orange solid (24 mg, 19%): mp 174-d ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.24 (d, J = 7.5 Hz, 1H), 8.04 (d, J = 9.0 Hz, 1H), 6.81 (d, J = 9.0 Hz, 1H), 6.72 (s, 1H), 5.57 (d, J = 7.5 Hz, 1H), 3.89 (s, 3H), 2.84 (q, J = 7.5 Hz, 2H), 1.22 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.2, 162.9, 156.8, 147.9, 139.3, 123.7, 121.3, 111.7, 105.5, 100.5, 56.2, 19.5, 9.3 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{13}H_{14}NO_4]$ 248.0923, found 248.0920.



To obtain **4.40**: The crude reaction was immediately loaded onto silica gel and purified by flash chromatography (20% EtOAc:petroleum ether). Solvent was removed under reduced pressure by rotary evaporation at room temperature to yield pure **4.40**. Red oil (26 mg, 22%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.63 (brs, 1H), 8.86 (d, J = 2.0 Hz, 1H), 8.42 (brs, 1H), 6.91 (d, J = 9.0 Hz, 1H), 6.56 (d, J = 2.5 Hz, 1H), 6.43 (dd, J = 8.5, 2.5 Hz, 1H), 5.13 (d, J = 2.5 Hz, 1H), 3.79 (s, 3H), 2.08 (t, J = 7.5 Hz, 2H), 1.45 (q, J = 7.5 Hz, 2H), 0.84 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.2, 170.8, 160.5, 153.8, 129.1, 117.7, 106.5, 102.7, 96.6, 55.6, 33.9, 21.1, 14.0 ppm; ^{15}N (INEPT) NMR (50 MHz, $CDCl_3$) δ 119.15 ppm HRMS (ESI) $[M+H]^+$ calcd. for $[C_{13}H_{17}NO_3]$ 236.1287, found 236.1286.


10.249
10.234
8.053
8.035
7.260
6.822
6.804
6.716
5.575
5.560
3.890
2.859
2.845
2.830
2.815
1.249
1.238
1.223
1.208
4.26k
10
9
8
7
6
5
4
3
2
1
ppm
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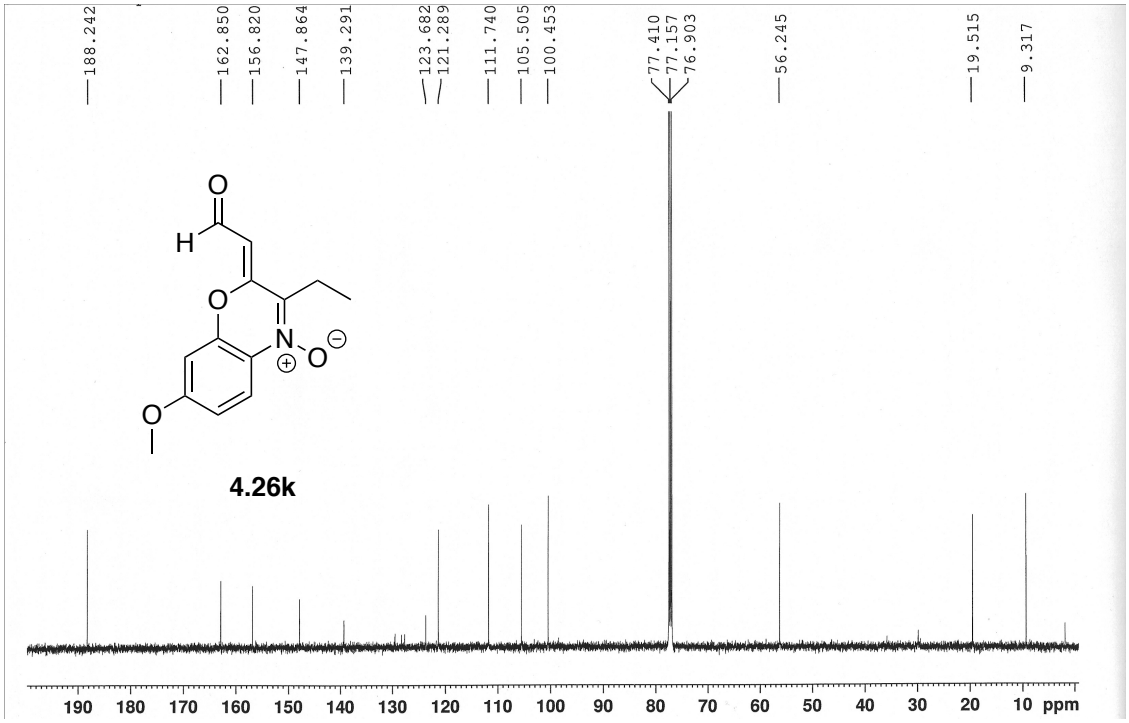
1.02
1.04
1.04
1.05
3.19
2.13
3.01


188.242
162.850
156.820
147.864
139.291
123.682
121.289
111.740
105.505
100.453
77.410
77.157
76.903
56.245
19.515
9.317
4.26k
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150
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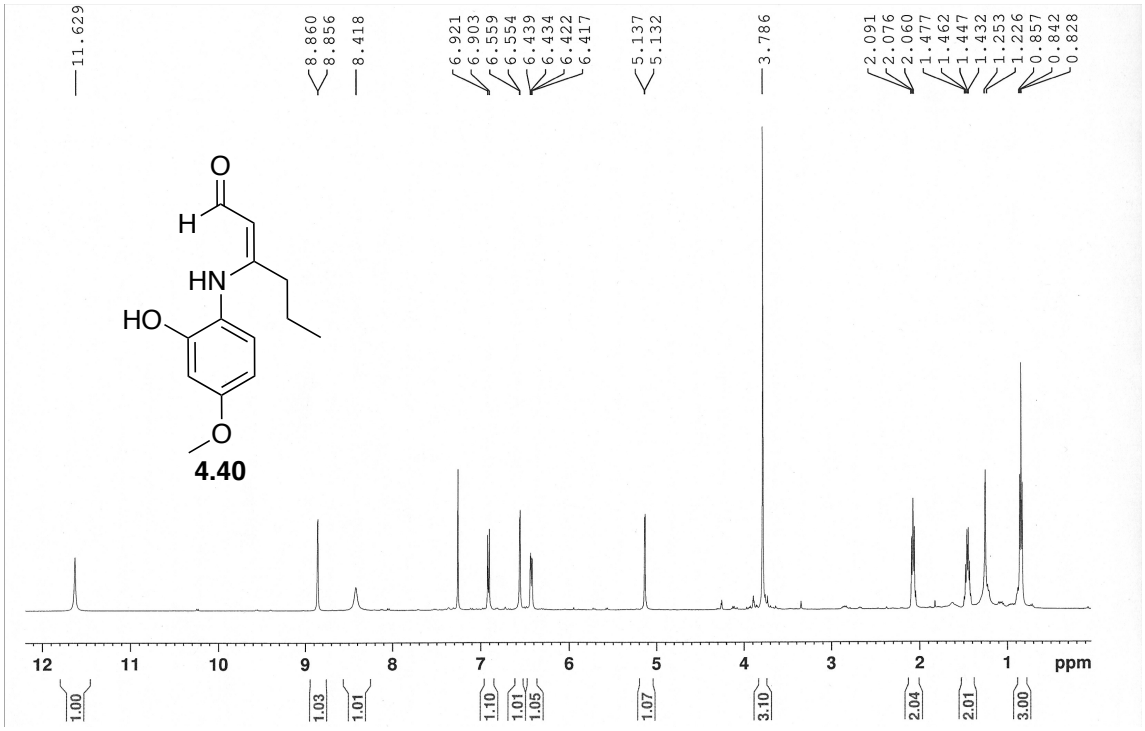
120
110
100
90
80
70
60
50
40
30
20
10
ppm


11.629
8.860
8.856
8.418
6.921
6.903
6.559
6.554
6.439
6.434
6.422
6.417
5.137
5.132
3.786
2.091
2.076
2.060
1.477
1.462
1.447
1.432
1.253
1.226
0.857
0.842
0.828
O
H
HN
HO
O
4.40
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.03
1.01
1.10
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1.07
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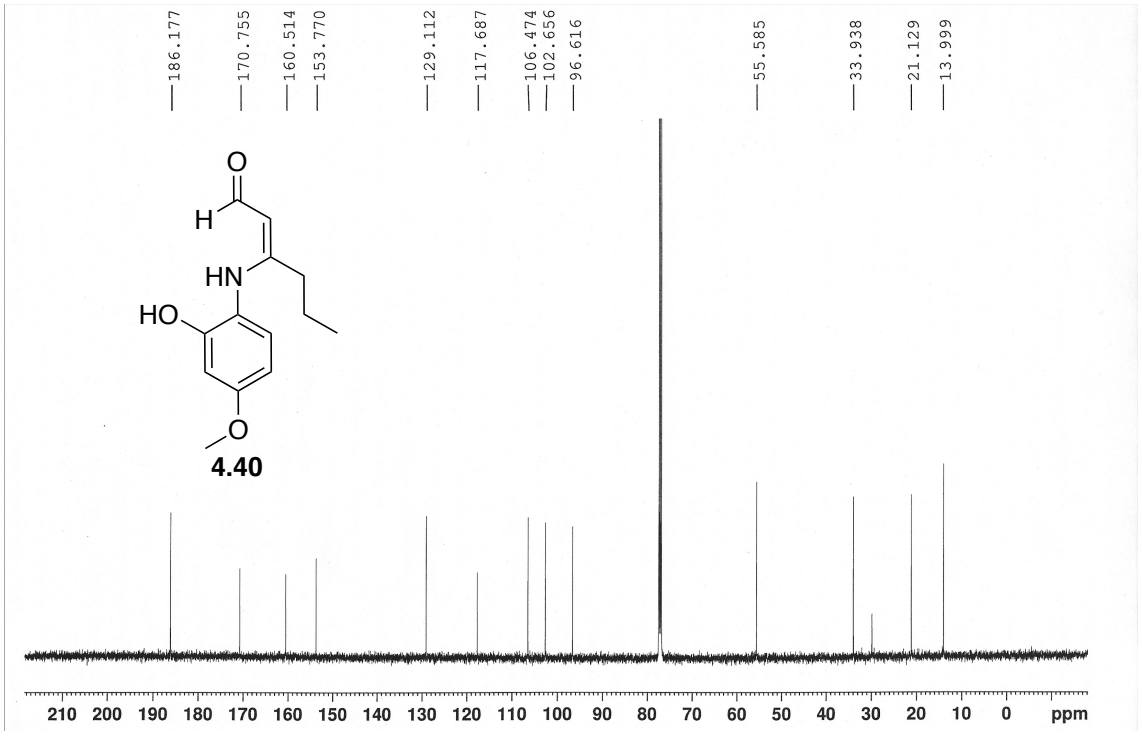
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13.999
O
H
HN
HO
O
4.40
210
200
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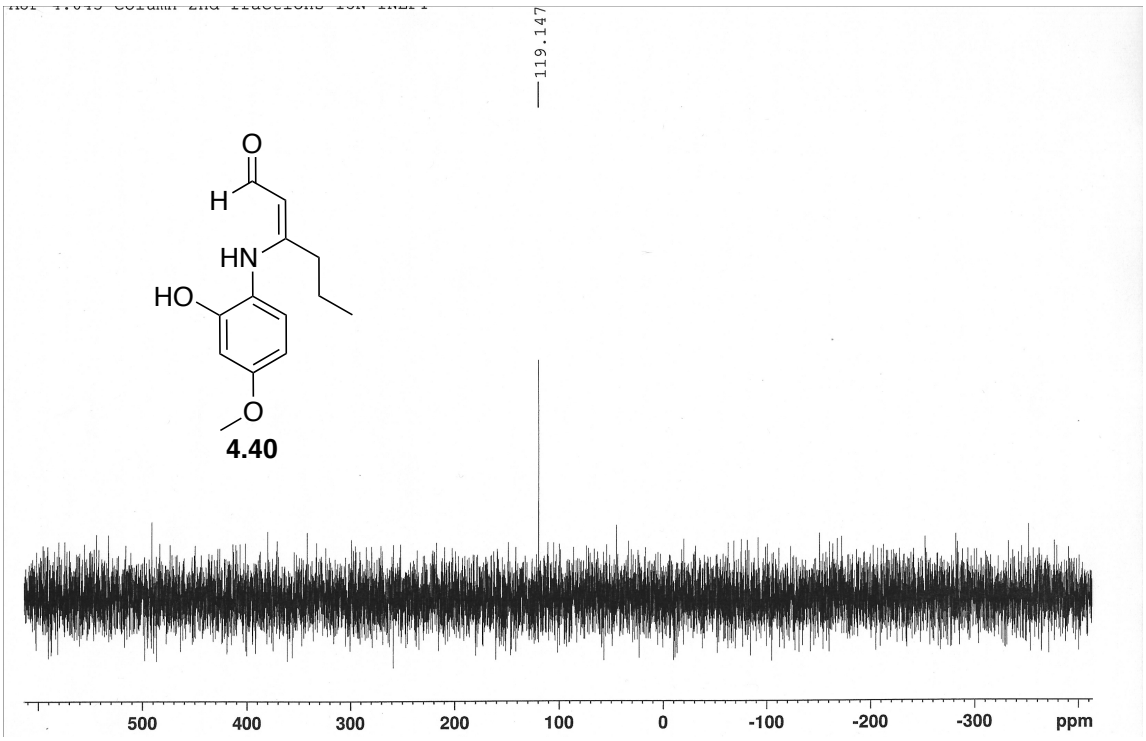

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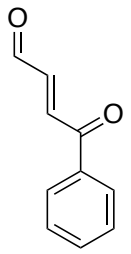
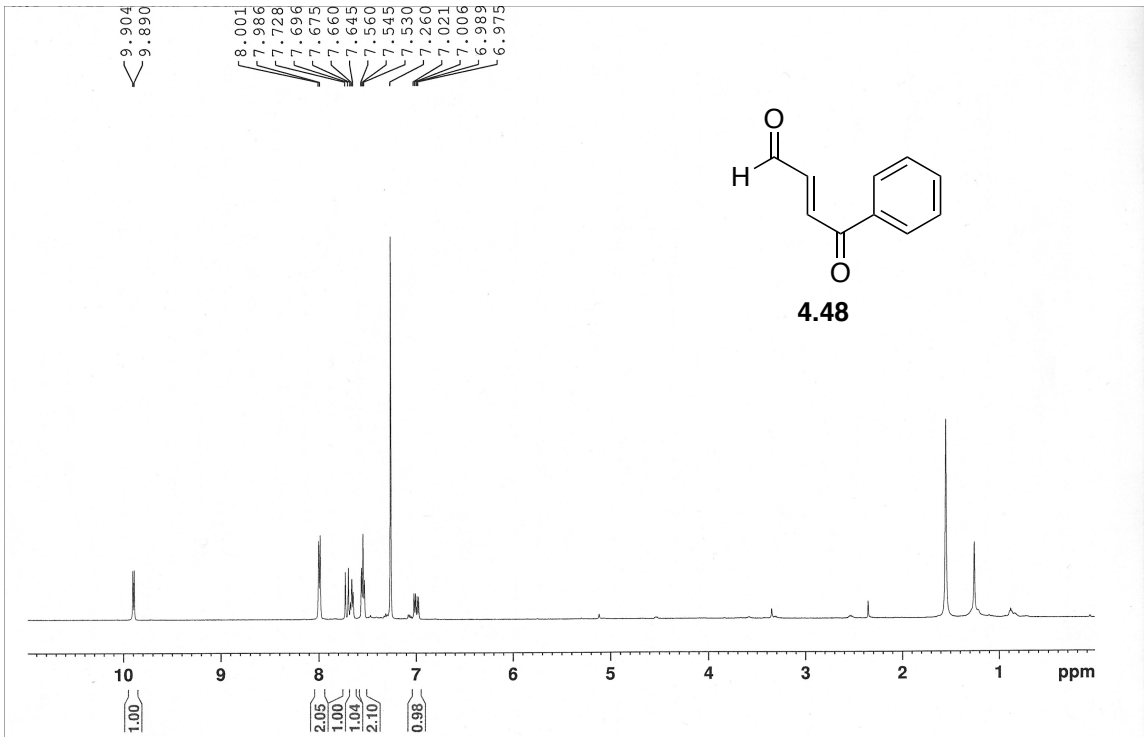


Procedure for synthesis of (*E*)-4-oxo-4-phenylbut-2-enal (4.48).
To a solution of nitrone **4.26f'**(50.0 mg, 0.20 mmol) in acetone/water (2.4 mL/0.24 mL) in a pressure tube, was added paraformaldehyde (48.4 mg, 1.61 mmol) and Amberlyst-15 (138.3 mg). The reaction was heated to 40 ºC and stirred for 21 hours until disappearance of starting material by ^{1}H NMR. Reaction was cooled to rt, loaded directly onto silica gel and purified by flash chromatography (5% EtOAc:petroleum ether). Solvent was removed under reduced pressure by rotary evaporation at room temperature to yield pure compound **4.48**. Yellow oil (20 mg, 63%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (d, J = 7.0 Hz, 1H), 7.99 (d, J = 7.5 Hz, 2H), 7.71 (d, J = 16.0 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 2H), 7.00 (dd, J = 16.0, 7.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 189.9, 142.2, 139.3, 136.4, 134.3, 129.2, 129.0 ppm; HRMS (ESI) $[M]^+$ calcd. for $[C_{10}H_8O_2]$ 160.0524, found 160.0521.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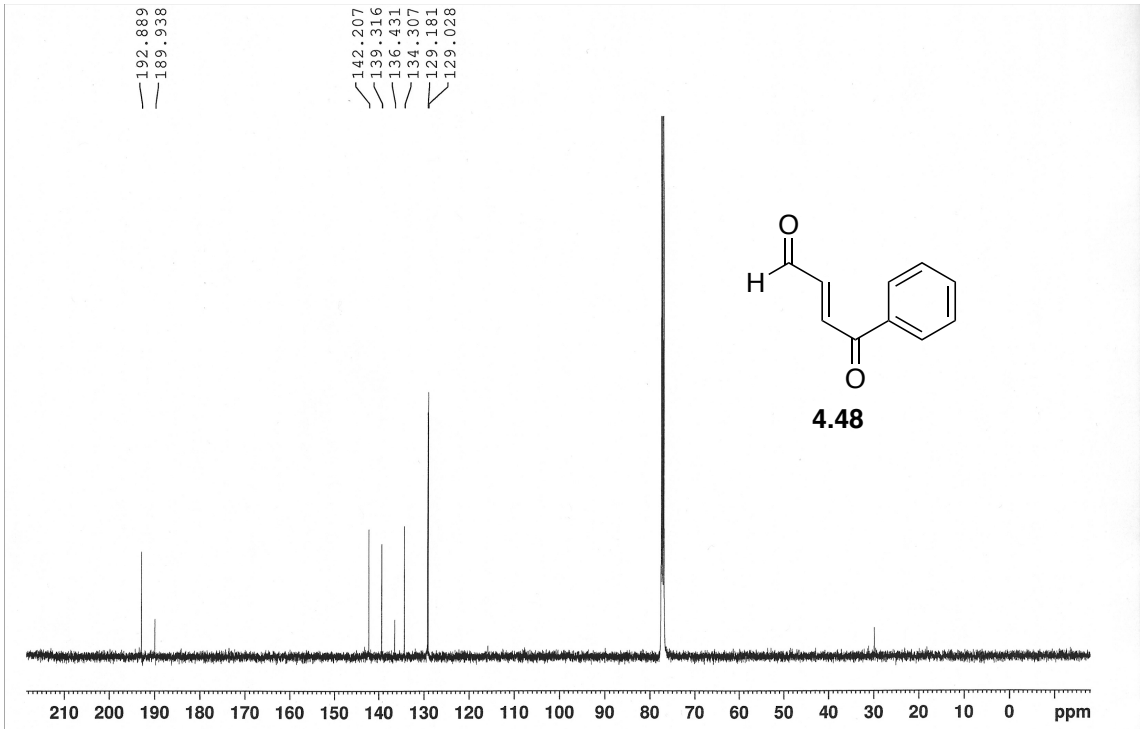
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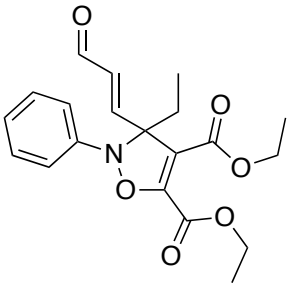
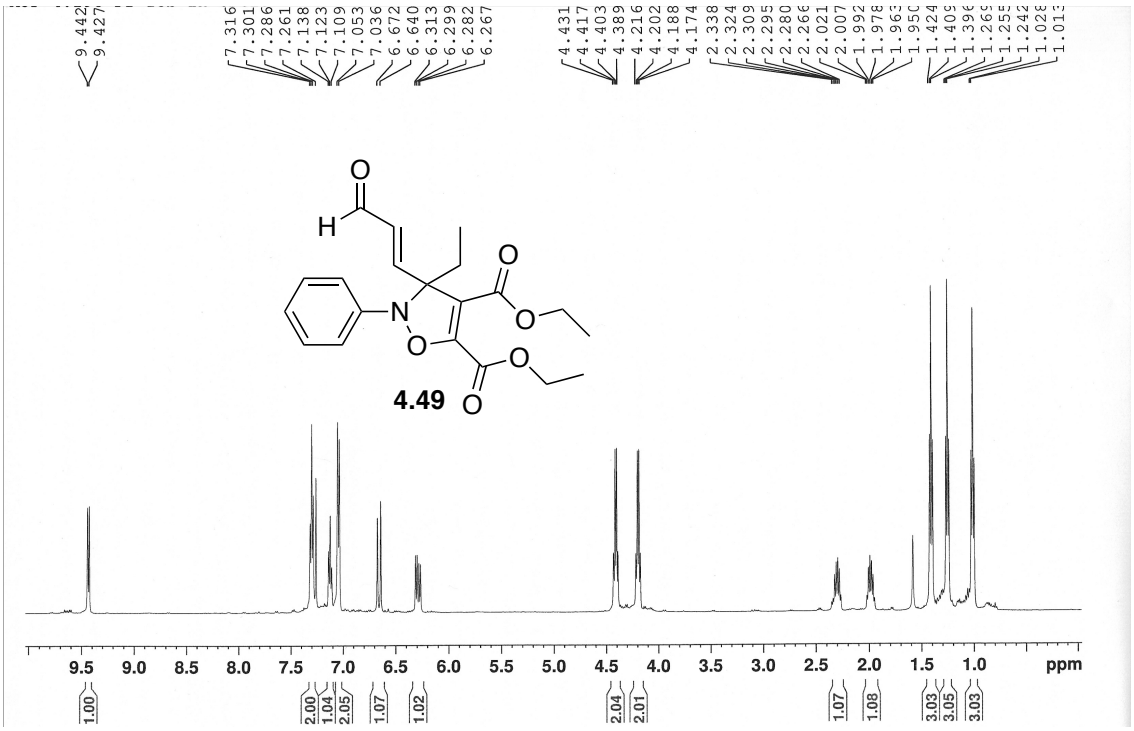
4.49:



Procedure for synthesis of (*E*)-diethyl 3-ethyl-3-(3-oxoprop-1-en-1-yl)-2-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylate (**4.49**).

To a solution of nitrone **4.26a** (100.0 mg, 0.49 mmol) in toluene (2.5 mL) was added diethyl acetylenedicarboxylate (236.3 µL, 1.48 mmol) at 0 ºC. Reaction was stirred at 0 ºC for 37 hours until complete consumption of nitrone, as observed by ^{1}H NMR. The crude reaction was immediately loaded onto silica gel and purified by flash chromatography (15-20% Et_2O:petroleum ether gradient). Solvent was removed under reduced pressure by rotary evaporation at room temperature to yield pure **4.49**. Yellow oil (99 mg, 54%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (d, J = 7.5 Hz, 1H), 7.30 (t, J = 7.5 Hz, 2H), 7.12 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 8.5 Hz, 2H), 6.66 (d, J = 16 Hz, 1H), 6.29 (dd, J = 16, 7.5 Hz, 1H), 4.41 (q, J = 7.0 Hz, 2H), 4.20 (q, J = 7.0 Hz, 2H), 2.30 (sextet, J = 7.0 Hz, 1H), 1.99 (sextet, J = 7.0 Hz, 1H), 1.41 (t, J = 7.5 Hz, 3H), 1.26 (t, J = 7.0 Hz, 3H), 1.01 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.2, 161.6, 158.7, 155.6, 153.0, 145.0, 133.3, 129.0, 125.4, 118.9, 108.2, 77.7, 63.2, 61.1, 27.5, 14.1, 8.3 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{20}H_{24}NO_6]$ 374.1604, found 374.1596.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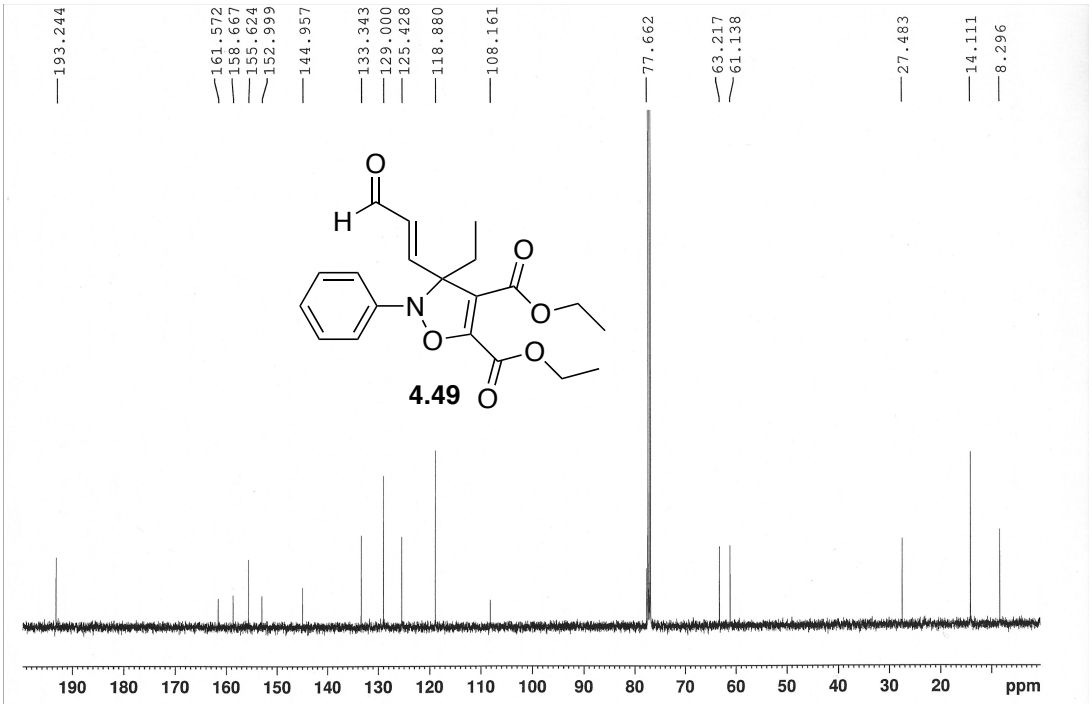
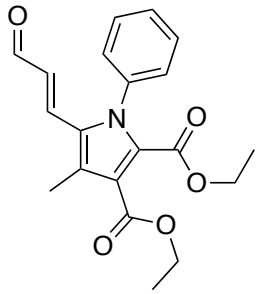

4.49
ppm

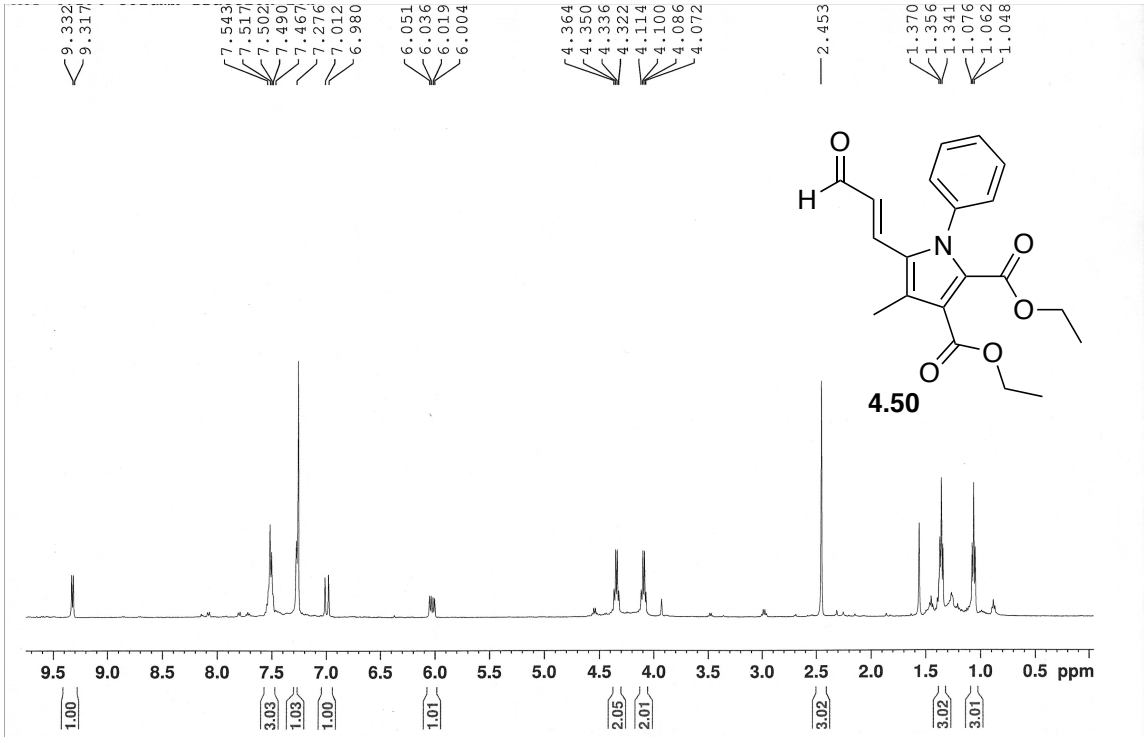
4.50:



Procedure for synthesis of (*E*)-diethyl 4-methyl-5-(3-oxoprop-1-en-1-yl)-1-phenyl-1*H*-pyrrole-2,3-dicarboxylate (4.50).

a) A solution of pure 2,3-dihydroisoxazole **4.49** (28.95 mg, 0.08 mmol) in toluene (390 μL) in a sealed pressure tube was heated to 80 ºC. The reaction was heated for 5 days until complete consumption of 2,3-dihydroisoxazole, as observed by ^{1}H NMR. The crude reaction was immediately loaded onto silica gel and purified by flash chromatography (1% Et_2O:dichloromethane). Solvent was removed under reduced pressure by rotary evaporation at room temperature to yield pure pyrrole **4.50**.

b) To a solution of nitrone **4.26a** (50.0 mg, 0.26 mmol) in toluene (1.2 mL) in a pressure tube, was added diethyl acetylenedicarboxylate (118.1 μL, 0.74 mmol). The reaction was heated to 50 ºC and allowed to stir for two days until complete consumption of nitrone, as observed by ^{1}H NMR. The crude reaction was immediately loaded onto silica gel and purified by flash chromatography (1% Et_2O:dichloromethane). Solvent was removed under reduced pressure by rotary evaporation at room temperature to yield pure **4.50**. Yellow oil (15 mg, 16%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (d, J = 7.5 Hz, 1H), 7.52-7.46 (m, 3H), 7.26 (m, 2H), 7.00 (d, J = 16.5 Hz, 1H), 6.03 (dd, J = 16, 7.5 Hz, 1H), 4.35 (q, J = 7.5 Hz, 2H), 4.10 (q, J = 7.0 Hz, 2H), 2.46 (s, 3H), 1.36 (t, J = 7.0 Hz, 3H), 1.06 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 164.5, 160.7, 139.2, 136.9, 131.1, 129.9, 129.6, 129.3, 128.2, 127.5, 126.4, 120.0, 61.7, 61.0, 14.3, 13.9, 11.9 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{20}H_{22}NO_5]$ 356.1498, found 356.1491.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6.004
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4.336
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4.50
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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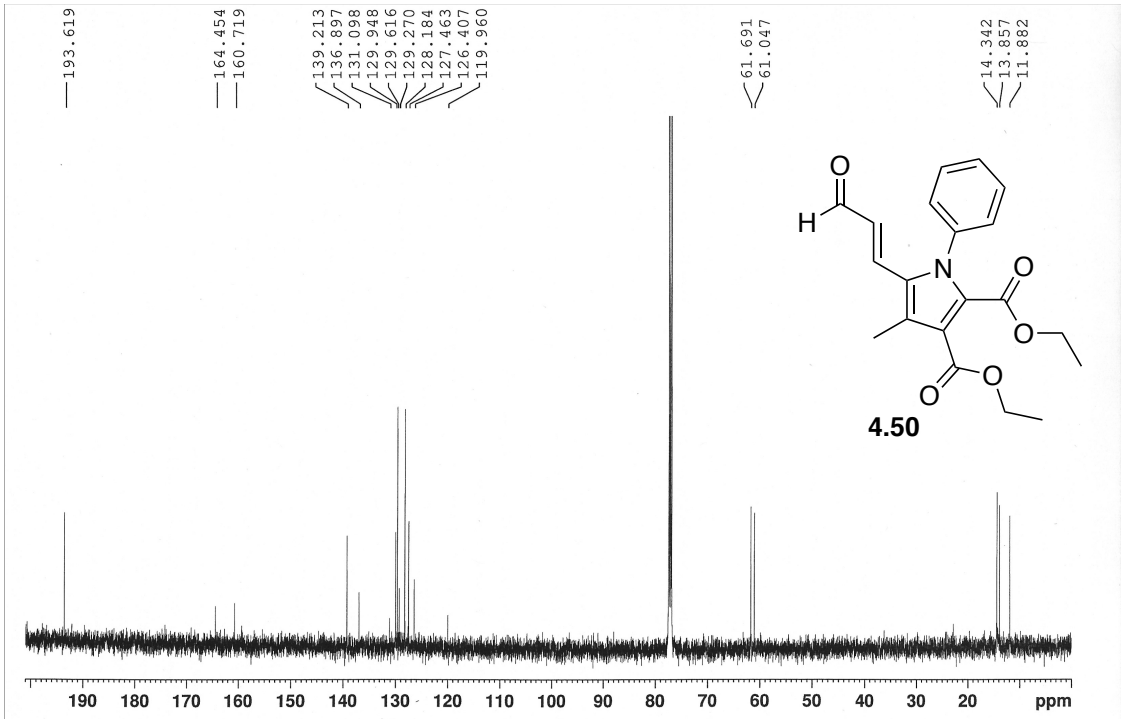
3.01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4.50
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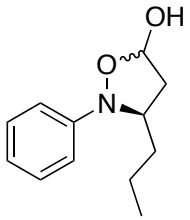
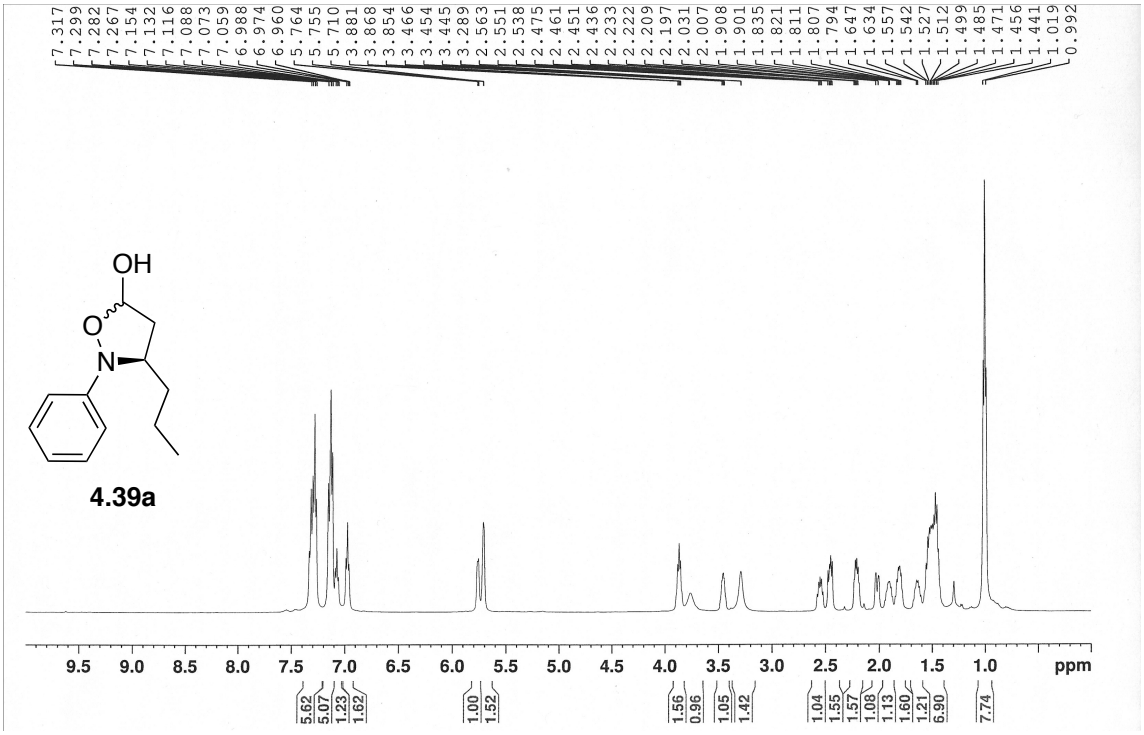
4.39a



2-phenyl-3-propylisoxazolidin-5-ol.
Yellow oil (104 mg, 50%): $[\alpha]_D^{23}$ = -87.07 (*c* = 1.0 in $CHCl_3$ for 54% ee, 1.5:1 dr); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.27 (m, 5H), 7.15-7.12 (m, 5H), 7.07 (t, *J* = 7.0 Hz, 1H), 6.97 (t, *J* = 7.0 Hz, 1H), 5.76 (m, 1H), 5.71 (m, 1H), 3.88-3.85 (m, 1H), 3.72 (brs, 1H), 3.47-3.45 (m, 1H), 3.29 (brs, 1H), 2.56-2.54 (m, 1H), 2.46 (dd, *J* = 12.0, 7.0 Hz, 1H), 2.23-2.20 (m, 1H), 2.02 (d, *J* = 12.0 Hz, 1H), 1.91-1.90 (m, 1H), 1.84-1.79 (m, 1H), 1.65-1.63 (m, 1H), 1.56-1.44 (m, 3H), 0.99 (t, *J* = 13.5 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 151.1, 128.9, 128.7, 123.6, 121.8, 117.5, 115.5, 98.2, 97.0, 67.4, 64.0, 42.0, 41.7, 37.2, 36.2, 20.4, 20.0, 14.2, 14.1 ppm; HPLC with an AD-H column (*n*-hexane/*i*-PrOH = 90:10), 0.5 mL/min; major diastereomer: major enantiomer t_R = 19.4 min, minor enantiomer t_R = 15.2 min; minor diastereomer: major enantiomer t_R = 17.4 min, minor enantiomer t_R = 16.6 min; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{12}H_{18}NO_2]$ 208.1338, found 208.1331.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1.485
1.471
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O
N
4.39a
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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5.07
1.23
1.62
1.00
1.52
1.56
0.96
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1.42
1.04
1.55
1.57
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1.13
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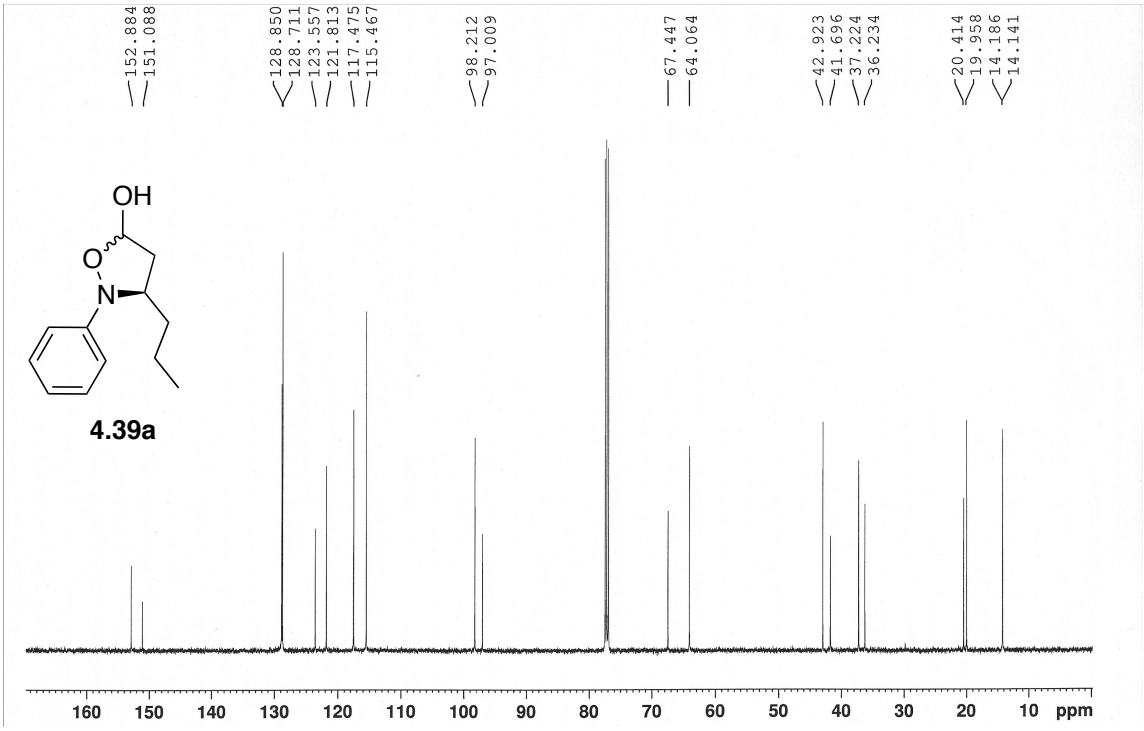
7.74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N
4.39a
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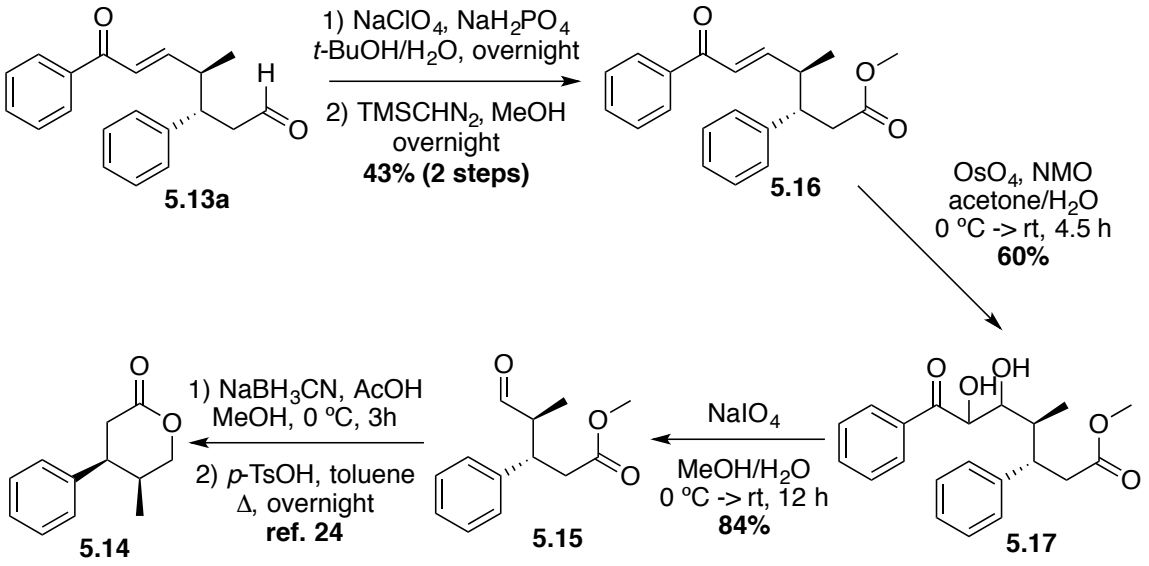
6.5 Experimental and Characterization for Chapter 5

5.14:



Synthesis of (4*S*,5*S*)-5-methyl-4-phenyltetrahydro-2*H*-pyran-2-one (5.14).

To a solution of $NaClO_2$ (167.4 mg, 1.85 mmol) and $NaHPO_4$ (255.4 mg, 1.85 mmol) in H_2O (3.3 mL) was added a solution of **5.13a** (135.3 mg, 0.46 mmol) in *t*-BuOH (6.6 mL). The reaction was stirred at room temperature overnight until complete consumption of **5.13a**, as observed by TLC. The reaction was diluted with brine (5.0 mL) and extracted with EtOAc (3 x 10.0 mL), then dried over Na_2SO_4 and concentrated under reduced pressure to give the crude acid.

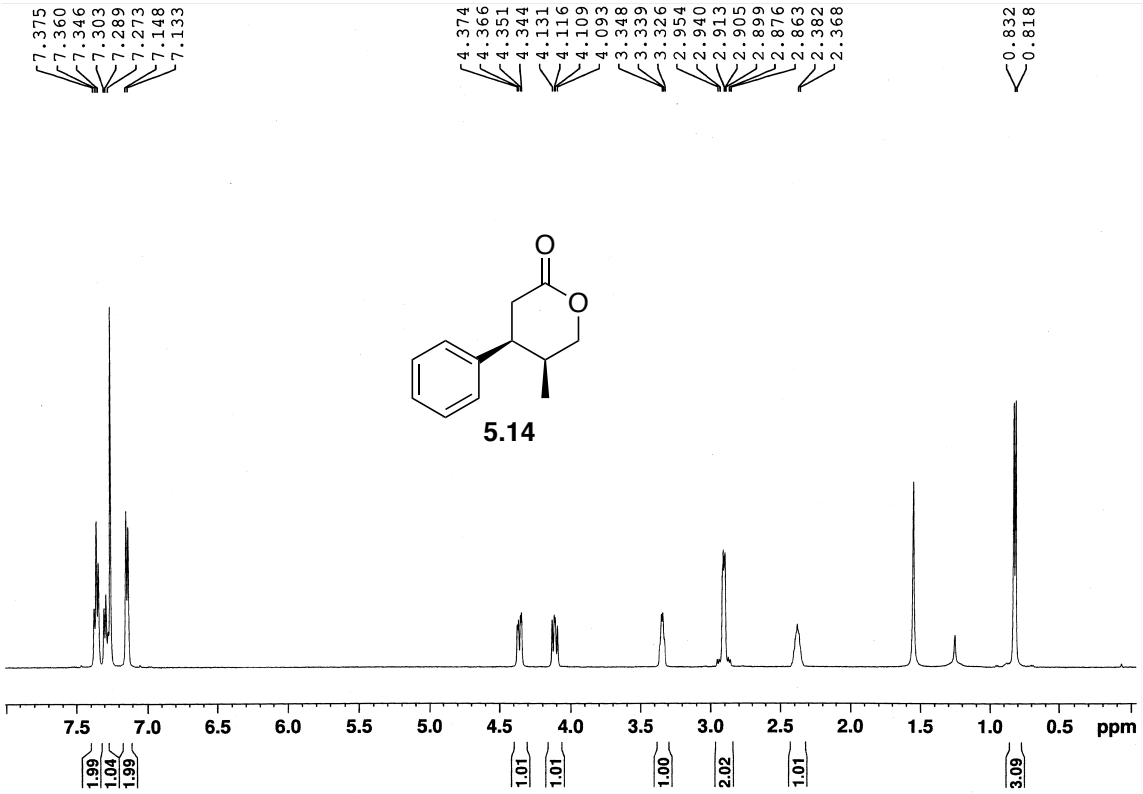
The crude acid was dissolved in anhydrous MeOH (1.84 mL) and cooled to 0 ºC. To the stirred solution was added $TMSCHN_2$ (920 µL, 1.84 mmol) dropwise. The reaction was allowed to slowly warm to room temperature and react overnight. The crude reaction was concentrated by rotary evaporation and purified by flash chromatography (5-7.5% EtOAc:petroleum ether gradient) to obtain ester **5.16** in a two-step yield of 43%.

To a solution of ester **5.16** (33.1 mg, 0.1 mmol) in acetone (710 µL) and H_2O (14 µL), was added NMO (50% in H_2O, 62 µL, 0.18 mmol), followed by *t*-BuOH (76 µL). The solution was cooled to 0 ºC and stirred for 5 minutes. OsO_4 (4% in H_2O, 76 µL, 0.012 mmol) was added dropwise and the reaction stirred at 0 ºC for 15 minutes. The reaction was brought to room temperature and stirred until complete consumption of **5.16**, as observed by TLC. The reaction was quenched with a 10% solution of $Na_2S_2O_3$ (0.8 mL) and extracted with EtOAc (3 x 5.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The crude diol was concentrated under reduced pressure and purified by flash chromatography (20% EtOAc:petroleum ether) to obtain pure diol **5.17** in 60% yield.

Diol **5.17** (21.9 mg, 0.06 mmol) was dissolved in MeOH (12.9 mL) and H_2O (4.3 mL) and cooled to 0 ºC. To this solution was added $NaIO_4$ (161.7 mg, 0.76 mmol) and the reaction was slowly brought to room temperature and stirred until complete consumption of diol, as observed by TLC. The reaction was concentrated under reduced pressure and extracted with diethyl ether (3 x 30.0 mL). The combined organic phases were dried over Na_2SO_4, concentrated, and purified by flash chromatography (12.5% EtOAc:petroleum ether) to obtain pure aldehyde **5.15** in 84% yield.

As per reference,[24] to a solution of aldehyde **5.15** (11.4 mg, 0.05 mmol) in anhydrous methanol (352 µL) and glacial AcOH (118 µL) at 0 ºC, was added $NaBH_3CN$ (6.5 mg, 0.1 mmol). The reaction was stirred at 0 ºC until full consumption of **5.15**, as observed by TLC. The reaction was quenched with saturated $NaHCO_3$ (2.0 mL) and extracted with dichloromethane (3 x 10.0 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude alcohol.

As per reference,[24] the crude alcohol was dissolved in toluene (3.24 mL), followed by addition of *p*-TsOH (1.0 mg, 0.005 mmol). The reaction was heated to 80 ºC and stirred overnight, then cooled to room temperature. To the reaction was added saturated $NaHCO_3$ (10.0 mL) and the aqueous layer was extracted with EtOAc (3 x 10.0 mL). The organic layers were combined and washed with brine (30.0 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (17% EtOAc:petroleum ether) to yield pure lactone **5.14**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 7.0 Hz, 1H), 7.14 (d, J = 7.5 Hz, 2H), 4.36 (dd, J = 11.5, 4.0 Hz, 1H), 4.11 (dd, J = 11.0, 7.5 Hz, 1H), 3.35-3.33 (m, 1H), 2.95-2.86 (m, 2H), 2.38-2.37 (m, 1H), 0.83 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 139.5, 128.7, 128.0, 127.4, 73.0, 41.2, 33.7, 32.2, 12.5 ppm; HRMS (ESI) $[M+H]^+$ calcd. for $[C_{12}H_{15}O_2]$ 191.1072, found 191.1074.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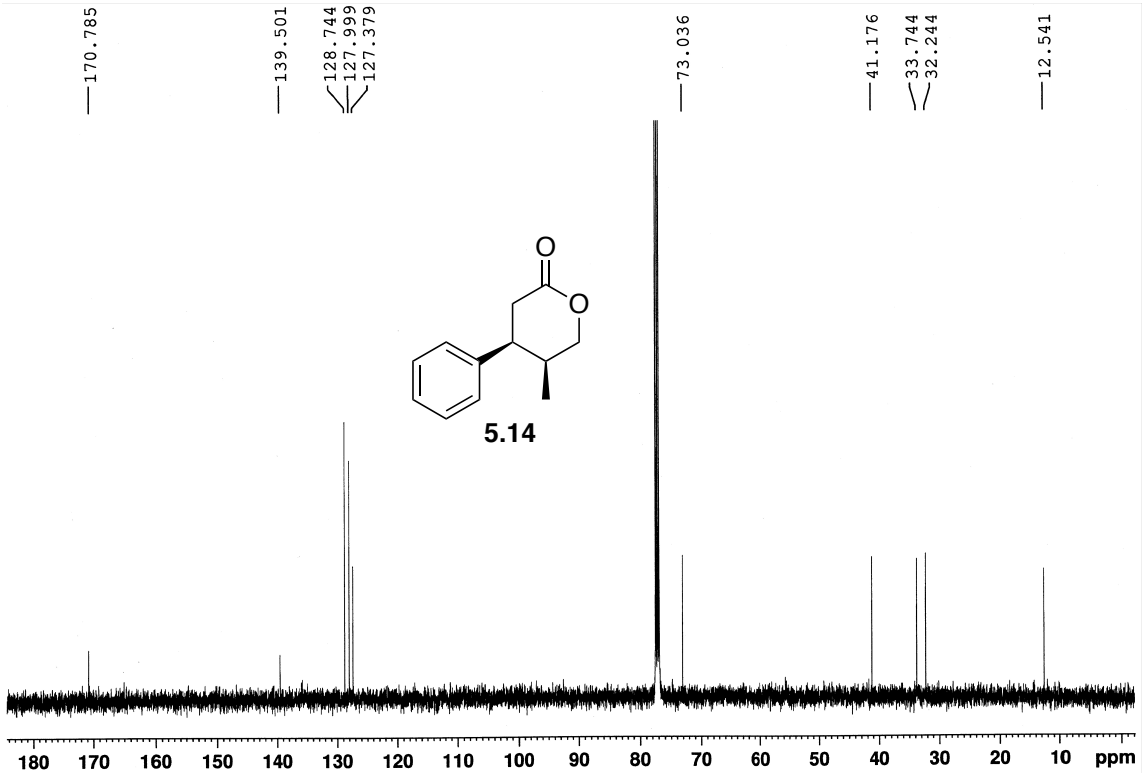
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170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

6.6 References

(1) Lin, Q.; Meloni, D.; Pan, Y.; Xia, M.; Rodgers, J.; Shepard, S.; Li, M.; Galya, L.; Metcalf, B.; Yue, T. N.; Liu, P.; Zhou, J. *Org. Lett.* **2009**, *11* (9), 1999–2002.

(2) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751–762.

(3) Sepe, V.; D'Auria, M. V.; Bifulco, G.; Ummarino, R.; Zampella, A. *Tetrahedron* **2010**, *66* (38), 7520–7526.

(4) Cardani, S.; De Toma, C.; Gennari, C.; Scolastico, C. *Tetrahedron* **1992**, *48* (27), 5557–5564.

(5) Appayee, C.; Brenner-Moyer, S. E. *Org. Lett.* **2010**, *12* (15), 3356–3359.

(6) Ramón, R. S.; Bosson, J.; Díez-González, S.; Marion, N.; Nolan, S. P. *J. Org. Chem.* **2010**, *75* (4), 1197–1202.

(7) Baudisch, O. *Science* **1940**, *92* (2389), 336–337.

(8) Baudisch, O.; Smith, S. H. *Naturwissenschaften* **1939**, *27*, 769.

(9) Baudisch, O. *J. Am. Chem. Soc.* **1941**, *63*, 622.

(10) Cronheim, G. *J. Org. Chem.* **1947**, *12* (1), 1–6.

(11) Nemodruk, A. A. *Zhurnal Obs. Khimii* **1958**, *28*, 2672–2676.

(12) Maruyama, K.; Tanimoto, I.; Goto, R. *J. Org. Chem.* **1967**, *32* (8), 2516–2520.

(13) Lyubchenko, S. N.; Ionov, a. M.; Shcherbakov, I. N.; Aleksandrov, G. G.; Kogan, V. a.; Tsivadze, a. Y. *Russ. J. Coord. Chem.* **2006**, *32* (8), 539–544.

(14) Ionov, a. M.; Lyubchenko, S. N.; Kogan, V. a.; Tsivadze, a. Y. *Russ. J. Coord. Chem.* **2011**, *34* (3), 195–197.

(15) Valizadeh, H.; Gholipour, H. *Comptes Rendus Chim.* **2011**, *14* (10), 963–966.

(16) Quintard, A.; Alexakis, A. *Chem. Commun.* **2011**, *47*, 7212–7214.

(17) Labeeuw, O.; Phansavath, P.; Genêt, J. P. *Tet. Lett.* **2004**, *45* (38), 7107–7110.

(18) List, B.; Doehring, A.; Hechavarria Fonseca, M. T.; Job, A.; Rios Torres, R. *Tetrahedron* **2006**, *62* (2-3), 476–482.

(19) Fernandes, R. a. *Tetrahedron: Asymmetry* **2008**, *19* (1), 15–18.

(20) Barbazanges, M.; Meyer, C.; Cossy, J. *Org. Lett.* **2008**, *10* (20), 4489–4492.

(21) Albrecht, Ł.; Dickmeiss, G.; Cruz Acosta, F.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134* (5), 2543–2546.

(22) Grayshan, R.; Keal, C. A.; Sackville, M. A. *J. Chem. Res. Synopses* **1986**, 282–283.

(23) Zhao, D.; Johansson, M.; Bäckvall, J. E. *European J. Org. Chem.* **2007**, 4431–4436.

(24) Gupta, V.; Sudhir, S. V.; Mandal, T.; Schneider, C. *Angew. Chem. Int. Ed.* **2012**, *51* (50), 12609–12612.