Catalysis *via* Induced Intramolecularity:

Carbonyl-catalyzed Hydration of α-Amino Nitriles

by

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Abstract

In the last decade, there has been a surge of interest from the chemistry community in developing synthetic catalysts that emulate the remarkable rate accelerations observed for enzymatic reactions. One approach utilized by enzymes involves preorganization of substrate(s) using a favourable binding event to orient the substrate(s) in a reactive arrangement. Although the "induced intramolecularity" is entropically unfavourable, it is facilitated by the enzymes and utilized to accelerate the subsequent chemical transformation. Chemists have often used a conceptually related *stepwise* approach in which temporary tethers are assembled to induce a temporary intramolecularity. This preorganization often enables difficult intermolecular reactions, and typically leads to increased regio-, chemo-, and stereoselectivity in chemical reactions. Seeking to develop a catalytic approach, we focused our efforts in developing a mild, carbonyl-catalyzed hydration protocol for α- and β-amino nitriles to give the corresponding α- and β-amino amide and acid. This work highlights the value of employing induced intramolecularity in accessing structurally important chemical motifs that otherwise require harsh reaction conditions. Additionally, this thesis presents the background material, design process, optimization and scope of this reactivity.

Acknowledgements

It has been an exciting and life-changing experience as a graduate student at the University of Ottawa. Not only did I have the opportunity to learn a great deal about chemistry, but I had the pleasure to engage with extremely intelligent and highly motivated students, lab mates, and members of the faculty and administration. First and foremost, I would like to extend my gratitude to Professor Andre Beauchemin who accepted me as a graduate student. Undoubtedly, Andre is one of the most brilliant chemists that I know of, whose sincere passion and enthusiasm for chemistry inspired me every day to work hard and pursue my best. Even in times of difficulty, Andre was always positive and supportive, making my stay even more enjoyable. Of course the graduate experience would not be the same without the support of my lab mates. It was a pleasure to have a work desk next to Amanda, who always had a positive attitude and a work ethic I looked up to. It was always fun to have chats with Colin, whether it was about chemistry or just random topics. Nick was my mentor when I first started – a brilliant chemist whom I hope to cross paths with again in the future. J.F.'s intensity in both chemistry and squash matches will be missed – although I will still be in Ottawa so we can have a rematch! I've also really enjoyed the chats with Chris about chemistry and life after graduate school. A special thanks goes out to Kashif and Sampada, whom I've worked closely with on my thesis project. Both are extremely hard working and clever chemists and I wish them the best in their future endeavors. I'd also like to thank my remaining lab mates who have been very supportive: Nic, Pouyan, Melissa, Keira, Lyanne, Charlotte, Kaitlyn, and Brittany. Additionally, the enjoyable times with my next-door lab mates Aboud and Meshal will also be missed.

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List of Abbreviations

Ac	acetyl
acac	acetylacetonyl
anti	against, opposite
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
Bu	butyl
°C	degree Celsius
cat.	catalytic
CDG	catalytic directing group
cis	on the same side
COD	1,5-cyclooctadiene
conc.	concentrated
Cy	cyclohexyl
δ	chemical shift in parts per million
d	deuterium (in NMR solvents)
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	*N,*N-diisopropylethylamine

D_2O	deuterium oxide
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
E	*Ger*., entgegen
ee	enantiomeric excess
EI	electron impact
equiv	equivalent
Et	ethyl
FT	Fourier transform
g	gram
h	hour
*h*ν	light; electromagnetic radiation
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HRMS	high-resolution mass spectrometry
Hz	Hertz
i	iso
IAD	intramolecular aglycon delivery
IR	infrared
J	coupling constant
L	litre; ligand
µL	microlitre
m	meta

M	molar; metal
Me	methyl
mg	milligram
min	minute
mL	millilitre
mmol	millimole
MS	molecular sieves
n	normal
Nu	nucleophile
NMO	*N*-methylmorpholine-N-oxide
NMR	nuclear magnetic resonance
p	para
PMB	2-*O*-*para*-methoxybenzyl
PMP	pentalmethylpiperidine
Ph	phenyl
ppm	parts per million
Pr	propyl
py	pyridine
PPY	4-pyrrolidinopyridine
R	carbon-based substituent
rt	room temperature
s	secondary

s	second
sat.	saturated
syn	together, same side
t	tertiary
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxy
TBAF	tetra-n-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilane
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranone
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tosyl	*p*-toluenesulfonyl
TPS	*tert*-butyldiphenylsilyl
UV	ultra-violet
Z	*Ger*., zusammen

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Chapter 1. **Introduction and Tethering Strategies in Synthesis**

1.1 Introduction

Enzymes are biological molecules that enable a variety of biochemical reactions at rates necessary to sustain life. Their fundamental role is to function as selective catalysts that accelerate the rate of reactions taking place within the cell. Additionally, in comparison to man-made catalysts, enzymes generate enhanced reaction activity and specificity at moderate temperatures and pressures and possess the capacity for regulation.[1] These remarkable properties have inspired chemists for decades in the pursuit of developing synthetic catalysts that mimic enzyme reactivity and serve useful functions.

In an enzymatic reaction, the molecules at the beginning of the process, called substrates, are converted into different molecules, called products. This transformation is characterized by Michaelis-Menten kinetics, where the substrate **S** reversibly and non-covalently binds to an enzyme **E** (Scheme 1.1). Subsequently, this enzyme-substrate **(E•S)** intermediate undergoes reversible or irreversible chemical transformations generating the enzyme-product **(E•P)** adduct either directly or indirectly through bound intermediates **(E•I)**. The product **P** is released in the final step allowing for the regeneration of the enzyme. With rate accelerations ranging from 10^6 to 10^{17}, considerable interest from the synthetic community has been focused on a fundamental question: How do Nature's catalysts accelerate reactions?[2]

[1] Voet, D.; Voet, J. G. *Biochemistry*, 3rd ed., Wiley, New York, **2004**.
[2] Radzicka, A.; Wolfenden, R. *Science* **1995**, *267*, 90.

Scheme 1.1: Enzymatic Catalysis; E: Enzyme; S: Substrate; I: Chemical intermediate; P: Product

One significant contribution arises from an enzyme's ability to stabilize the transition state or destabilize the ground state.[3] Enzyme efficiency also arises from their ability to perform substrate activation while favouring substrate preassociation and preorganization to enable challenging intermolecular reactions. In the context of organic chemistry, substrate activation is achieved through a variety of ways including: Lewis acid or base activation, hydrogen bond activation, enamine formation, iminium formation and metal complexation, among others.[4] Preassociation of substrates is a technique utilized by enzymes to overcome the inherent energetic barrier associated with intermolecular reactions. These enzyme-substrate interactions align and orient functional groups in close proximity, thereby inducing intramolecular character to the reaction. Conceptually, the enzymes help minimize the entropic penalty associated with the intermolecular reaction. Thus, this down payment in entropy can be utilized to accelerate the subsequent chemical transformation, allowing the intermolecular process to proceed in an intramolecular fashion. Additionally, the preorganization that results from "induced intramolecularity" usually leads to increased regio-, chemo-, and stereoselectivity in chemical reactions.

[3] Richard, J. P. *Biochemistry* **2013**, *52*, 2009.
[4] (a) Walsh, P/ J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis*; University Science Books: Sausalito, 2009. (b) Yamamoto, H.; Kazuaki, I.., Eds.; *Acid Catalysis in Modern Organic Synthesis*, Wiley-VCH: Weinheim, 2008. (c) Denmark, S. E.; Beutner, G. L. *Angew Chem., Int. Ed.* **2008**, *47*, 1560.

Efforts towards emulating this enzymatic process have resulted in a variety of strategies devised by research groups. One approach involves the use of disposable tethers that enable the "temporary" union of two reacting centres.[5] Once the desired reaction takes place, the tether can be selectively removed, but may also be transformed into other functionalities, displaying the synthetic versatility of this approach. Despite the tremendous success of this tethering methodology in a wide variety of chemical transformations, there remain significant drawbacks. For example, the poor atom and step economy associated with installation and cleavage of tethers generally involving two or three additional steps. As a consequence, there has been a recent surge of interest from research groups in developing catalytic variants that benefit from this induced intramolecular reactivity. In this regard, the simultaneous use of metal and organic catalysts to promote organic transformations (termed metal organic cooperative catalysis) has enjoyed great success and applicability.[6] In this type of catalysis, a ligand forms a reversible covalent bond to the substrate, inducing a fast intramolecular reaction. However, the inherent high cost and toxicity associated with rare earth metals limits the long term applicability. As a result, non-metal catalysts – particularly organocatalysts – have been explored as viable alternatives.6[a,7] Through reversible covalent bonds, a binding step will bring the catalyst and substrates in close proximity to initiate a subsequent intramolecular reaction. Despite the feasibility of this approach, only a limited number of transformations have been reported in the literature, most of which have been applied to hydrolysis reactions. This

[5] For reviews, see: (a) Diederich, F. S.; Stang, P. J. *Templated Organic Synthesis*; Wiley-VCH: Chichester, 2000. (b) Gauthier, Jr., D. R.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289. (c) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813. (d) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253.
[6] For reviews, see: (a) Tan, K.L. *ACS Catalysis* **2011**, *1*, 877. (b) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450.
[7] For a review, see: Pascal, R. *Eur. J. Org. Chem*. **2003**, 1813.

first chapter will survey transformations made possible predominantly through induced intramolecularity through the following strategies: 1) Tethering, 2) Metal Catalysis, 3) Organocatalysis.

1.2 Tethering Approach

The use of temporary tethers that anchor reactants is a valuable approach in synthetic organic chemistry. By tethering reactants and promoting a temporary intramolecular reaction, it is possible to obtain significant rate enhancements and high regio-, chemo-, and stereoselectivity compared to the corresponding intermolecular reaction. Once the desired transformation is complete, the tether can be selectively removed (Figure 1.1).

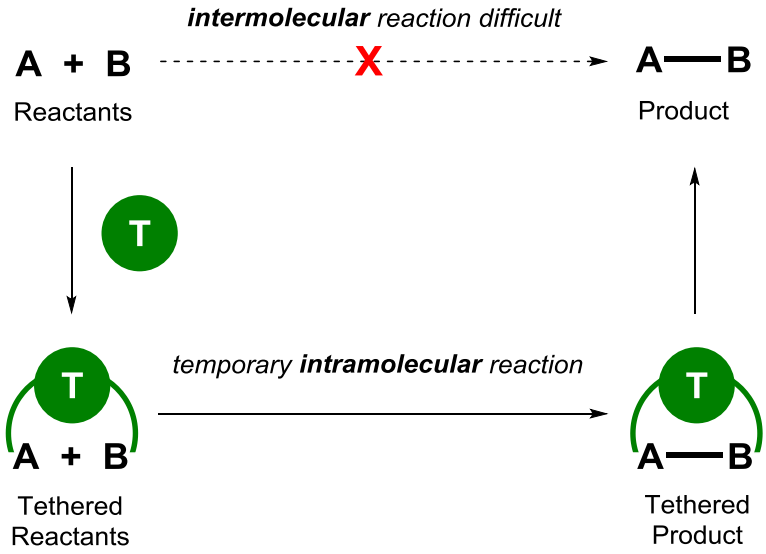
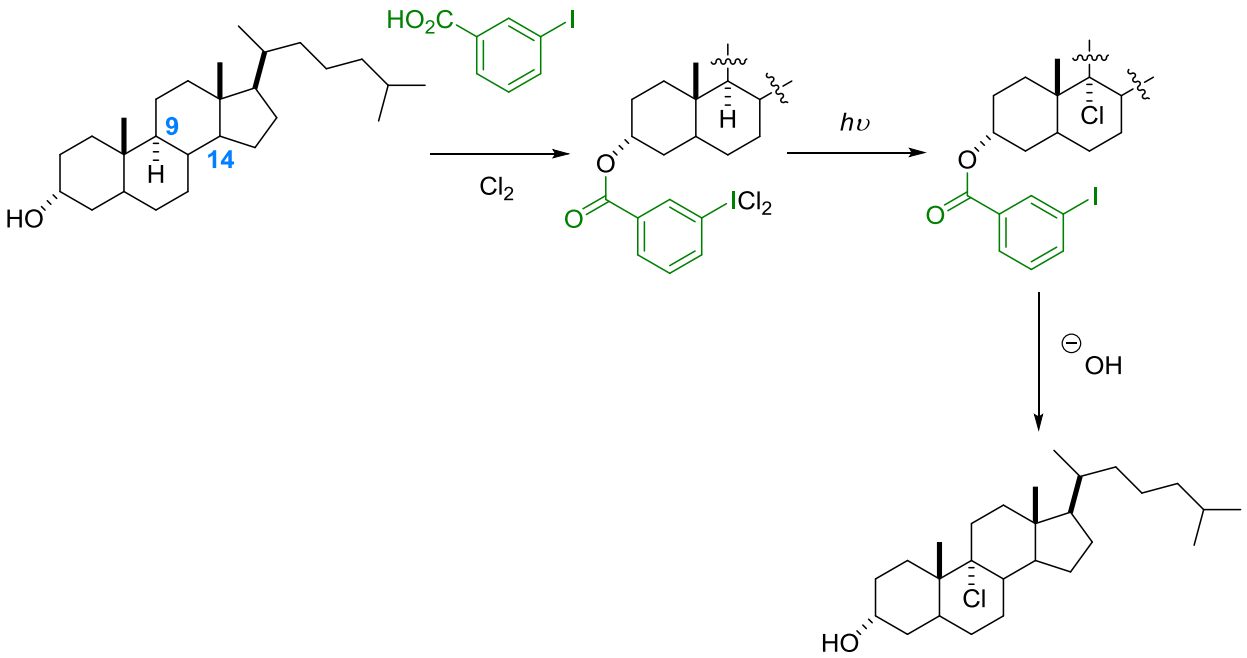


Figure 1.1: General Tethering Strategy

In 1974, Breslow reported one of the first tethering examples (Scheme 1.2).[8] By installing a phenyliodine dichloride ester tether on the steroid substrate, it was possible to initiate an intramolecular free-radical chlorination selectively at C-9. Subsequent hydrolysis of the ester afforded the desired steroid product in excellent yield. It was proposed that chemical selectivity was geometrically controlled. Indeed, extending the length of the iodoaryl tether resulted in a selective attack on C-14 (further from the attachment point). This proof of concept set the stage for the next few decades as numerous new chemical transformations based on this methodology emerged.



Scheme 1.2: Breslow Selective Free-radical Chlorination

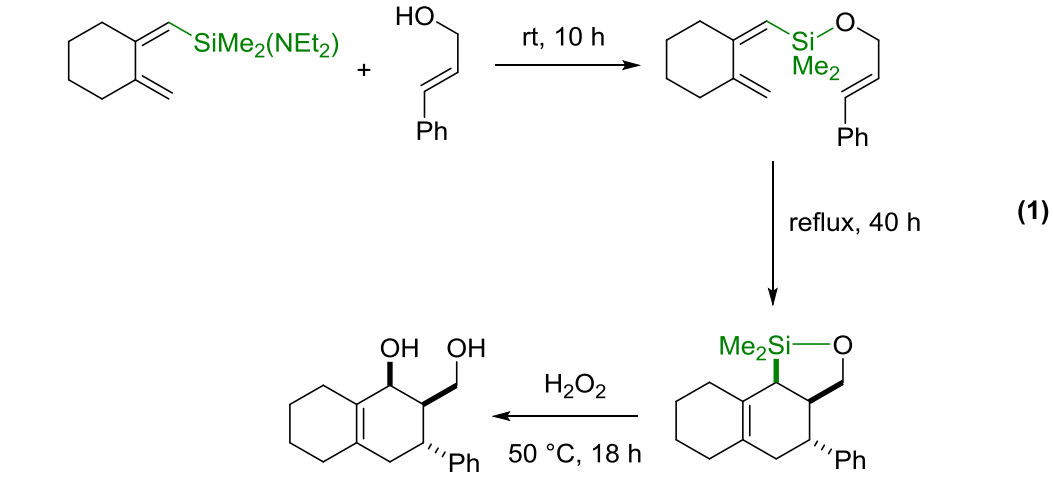
[8] (a) Breslow, R.; Corcoran, R.; Dale, J. A.; Liu, S.; Kalicky, P. *J. Am. Chem. Soc.* **1974**, *99*, 905. (b) Breslow, R.; Corcoran, R. J.; Snider, B. B.; Doll, R. J.; Khanna, P. L.; Kaleya, R. *J. Am. Chem. Soc.* **1977**, *99*, 905.

1.2.1 ***Diels-Alder reaction***

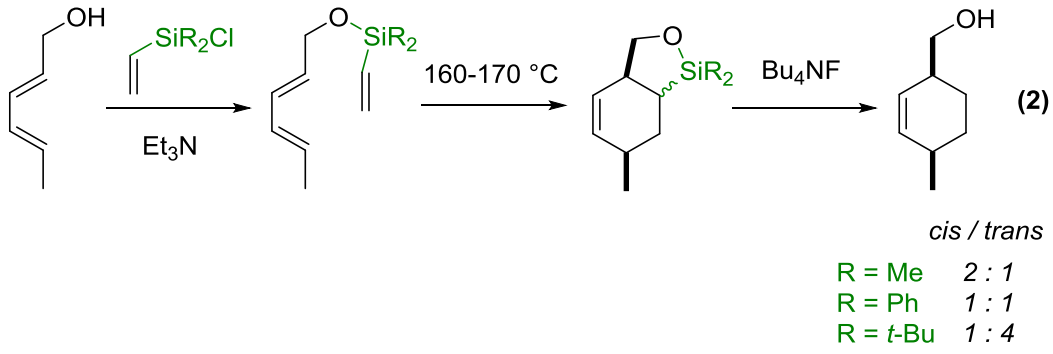
The intermolecular Diels-Alder reaction is a powerful transformation widely used in synthetic organic chemistry for the synthesis of substituted cyclohexene systems. The use of temporary tethers has been shown to enhance the regio- and stereoselectivity in this transformation. The first reported example by Tamao in 1989 involved an alkylsilane tether that anchored a dienol to generate a highly regio- and stereoselective intramolecular Diels-alder reaction (Scheme 1.3, Eqn 1).[9] Oxidative conditions cleaved the alkylsilane tether to afford the diol as a single isomer. Shortly after, Sieburth investigated 3-atom silicon tethers, primarily dealing with vinylsilanes as dienophiles (Scheme 1.3, Eqn 2).[10] Sieburth demonstrated that the bulkier silyl groups generated preference for the 1,2-*trans* product formed by exo-cyclization. This was justified by the unfavourable steric interactions between the silicon alkyl groups and the diene in the *endo*-transition state. Similarly, Stork studied a variety of substituted dieneophiles and applied the methodology to intramolecular hetero-Diels-Alder reactions.[11]

[9] Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6478.
[10] Sieburth, S. M.; Fensterbank, L. *J. Org. Chem.* **1992**, *57*, 5279.
[11] Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578.

Tamao 1989



Sieburth 1992

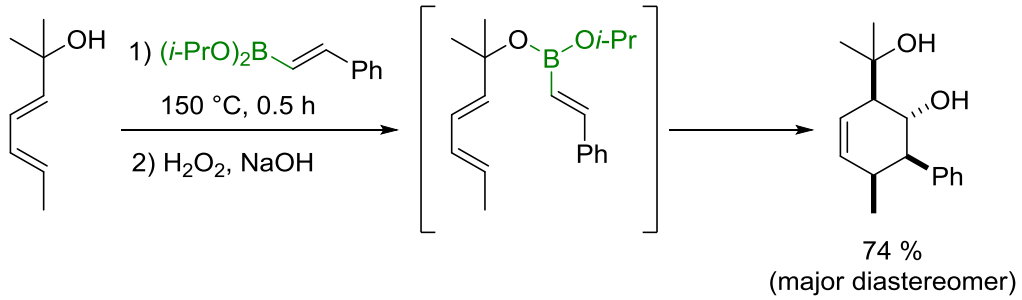


Scheme 1.3: Diels-Alder Tethering Using Alkyl Silanes

Batey established the first boron-tethered Diels-Alder reaction using readily available alkenyl boronic esters as dienophilic components (Scheme 1.4).[12] Similar to what Sieburth observed, adding sterically hindered groups on the tether enhanced selectivity and allowed

[12] Batey, R. A.; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450.

significant Thorpe-Ingold rate acceleration. Examples of this approach using C–Mg–O and C–Al–O Lewis acid templates have also been reported.[13]



Scheme 1.4: Batey's Boron-tethered Diels-Alder Reaction

1.2.2 ***Olefin Metathesis***

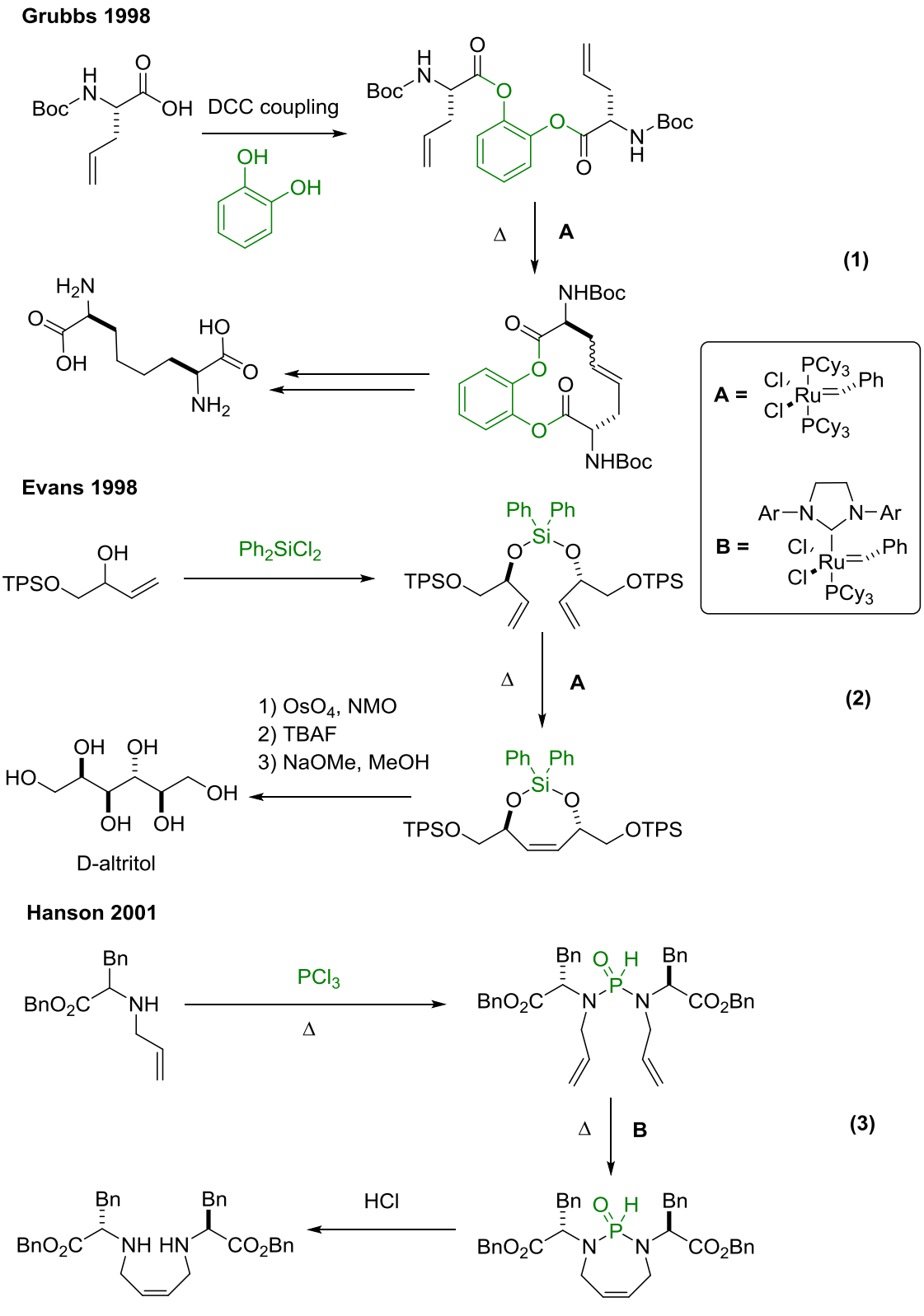
Olefin metathesis has become an important tool for synthetic organic and polymer chemists, especially since catalyst improvements have led to new applications in ring closing metathesis (RCM), cross metathesis and materials synthesis. Although Ruthenium-promoted intermolecular metathesis has been reported in systems with diverse functionality, Grubbs demonstrated the reaction was unsuitable for Boc-protected allylglycine methyl ester (Scheme 1.5, Eqn 1).[14] However, by anchoring catechol to the ester substrate, the intramolecular RCM variant proceeded cleanly in good yields. Subsequent functional group interconversions afforded the bis-amino acid.

[13] (a) Stork, G.; Chan, T. Y. *J. Am. Chem. Soc.* **1995**, *117*, 6595. (b) Abaee, M. S.; Ward, D. E. *Org. Lett.* **2000**, *2*, 3937.
[14] O'Leary, D. J.; Miller, S. J.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 1689.

Drawing inspiration from this approach, several research groups expanded this methodology to various substrates. In 1998, Evans used optically enriched allylic alcohols to develop a temporary silicon-tethered RCM protocol for the enantioselective synthesis of protected C_2-symmetrical *cis*-1,4-diols (Scheme 1.5, Eqn 2).[15] Dihydroxylation of the cyclic alkene followed by treatment with tetra-N-butylammonium fluoride allowed for the potentially powerful application of this methodology for the preparation of the reduced carbohydrate D-altritol. Evans later demonstrated it was possible to control the stereoselectivity of the dihydroxylation through long-range asymmetric induction.[16] While alkenyl alcohols generated *cis*-1,4 diols, homologated alkenyl alcohols displayed a reversal in diastereoselectivity favouring the more thermodynamically stable *trans* isomer.

Additionally, Hanson developed an efficient method to synthesize C_2-symmetric and unsymmetric 1,4 diamines containing the *(Z)*-1,4diaminobut-2-ene subunit via a phosphorus-tethered RCM/hydrolysis sequence (Scheme 1.5, Eqn 3).[17]

[15] Murthy, V. S.; Evans, P. A. *J. Org. Chem.* **1998**, *63*, 6768.
[16] Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem. Int. Ed.* **2003**, *42*, 1734.
[17] Sprott, K. T.; McReynolds, M. D.; Hanson, P. R. *Org. Lett.* **2001**, *3*, 3939.



Scheme 1.5: Tethered RCM Approaches

1.2.3 ***Glycosylations***

Carbohydrates are the most abundant class of biomolecules and play a key role in all biological systems; therefore, their chemistry and synthesis are of considerable interest. The assembly of carbohydrates to oligosaccharides occurs through a glycosylation reaction. One of the most challenging transformations is the formation of 1,2-*cis* glycosidic bonds with absolute control of anomeric stereochemistry. A common approach to overcome this challenge is the use of a two-step tethering-glycosylation process called intramolecular aglycon delivery (IAD).[18] In the first step, the aglycon is tethered to the 2-position of the glycosyl donor by a temporary tether. A subsequent intramolecular glycosylation step occurs to form the 1,2-*cis* product. Cleavage of the tether gives the glycoside with 2-OH free. A plethora of IAD methodologies have been reported including acid-catalyzed acetal tethering,[19] silicon[20] and iodonium[21] tethering, and the use of 2-*O*-*para*-methoxybenzyl (PMB) protected glycosyl donors developed by Ogawa.[22] The development of PMB protected glycosyl donors has been the most successful approach for the synthesis of complex targets, such as the core *N*-glycan pentasaccharide. The first paper describes the use of mannosyl fluorides as donors (Scheme 1.6, Eqn 1).[22f] Oxidation of a tethered PMB group generates an oxocarbenium ion that can form a mixed acetal on addition of an alcohol. If the alcohol is an appropriate aglycon, the resulting mixed acetals can undergo an intramolecular glycosylation reaction to give the 1,2-*cis* glycoside product.

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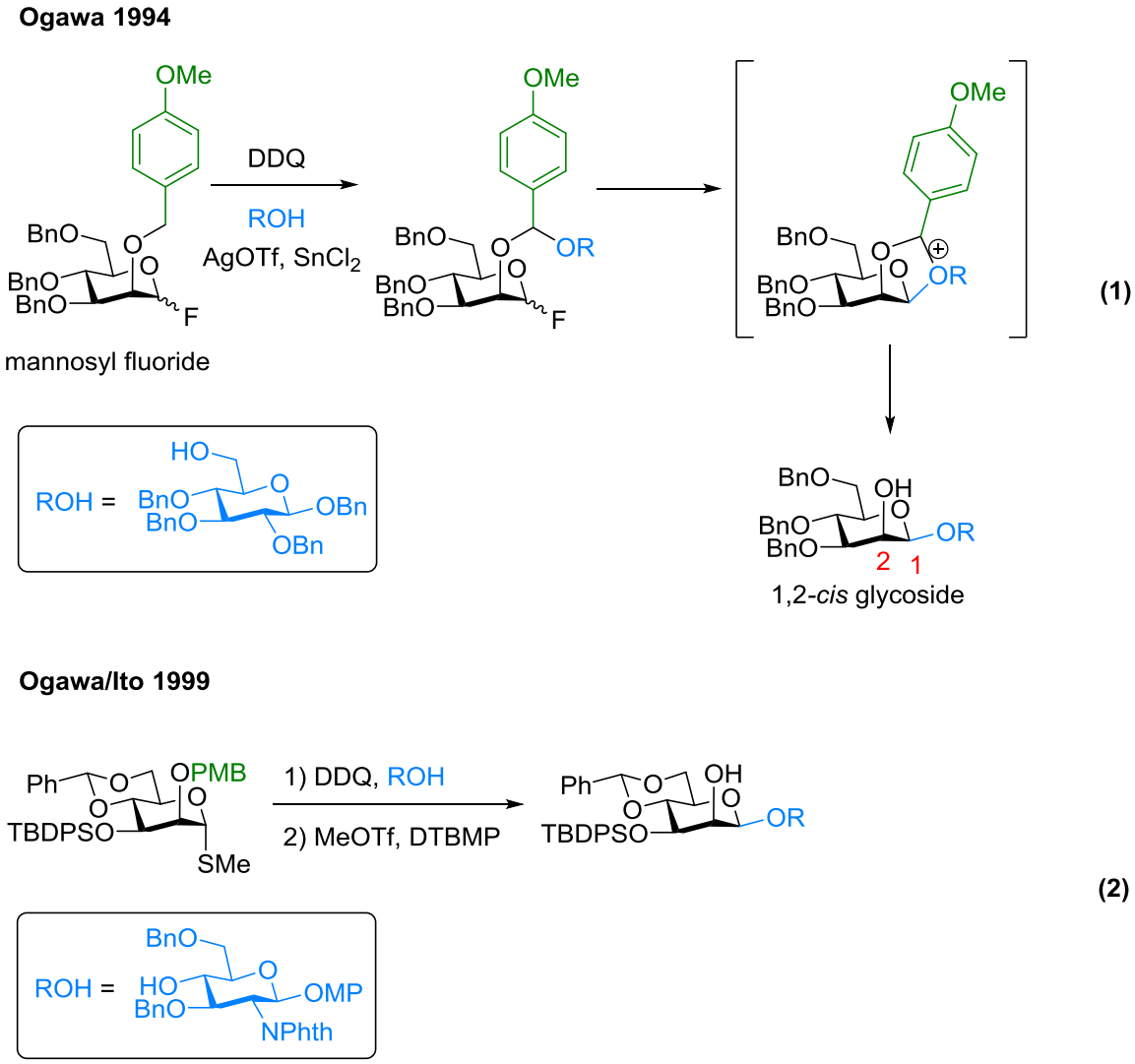
[18] Cumpstey, I. *Carbohydrate Research* **2008**, 1553.
[19] Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9376.
[20] Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087.
[21] Fairbanks, A. J. *Synlett* **2003**, 1945.
[22] (a) Lergenmuller, M.; Nkada, T.; Kuramochi, K.; Dan, A.; Ogawa, T.; Ito, Y. *Eur. J. Org. Chem.* **1999**, 1367; (b) Dan, A.; Lergenmuller, M.; Amano, M.; Nakahara, Y.; Ogawa, T.; Ito, Y. *Chem. Eur. J.* **1998**, *4*, 2182; (c) Ito, Y.; Ohnishi, Y.; Ogawa, T.; Nakahara, Y. *Synlett* **1998**, 1102; (d) Dan, A.; Ito, Y.; Ogawa, T. *J. Org. Chem.* **1995**, *60*, 4680; (e) Dan, A.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1995**, *36*, 7487; (f) Ito, Y.; Ogawa, T. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1765.

Subsequent papers by the Ogawa/Ito group explored methyl thioglycosides as glycosyl donors to efficiently synthesize *N*-glycan oligosaccharades (Scheme 1.6, Eqn 2).[22a-c]



Scheme 1.6: Intramolecular Aglycon Delivery (IAD)

1.2.4 ***Conclusion***

The strategy of employing temporary tethers and inducing intramolecularity that minimizes the entropic penalty associated with intermolecular reactions is a valuable tool in a chemist's synthetic toolbox. It has been applied to a wide variety of transformations and has the added benefit of enhancing regio-, chemo-, and stereoselectivity. In addition to the examples presented, tethering groups have been employed in cycloadditions such as [2+2] photocycloadditions[23], [5+2] cycloadditions[24], [3+2] dipolar additions[25], and *meta* photocycloadditions[26]. Furthermore, alkene-alkyne metatheses[27], radical cyclizations[28], and total syntheses of complex molecules such as taxol[29], (+)-aloperine[30], and (−)-mucocin[31] benefited from the installment of disposable tethers. Although this tethering strategy has demonstrated broad applicability, the synthetic burden of installing and cleaving the tethering atoms limits the efficiency of this approach.

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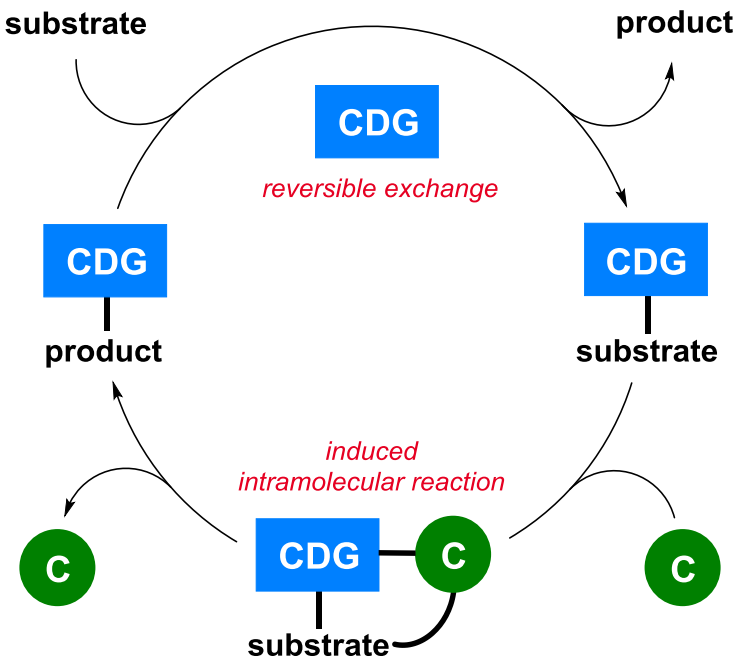
[23] (a) Crimmins, M. T.; Guise, L. E. *Tetrahedron Lett.* **1994**, *35*, 1657. (b) Fleming, S. A.; Ward, S. C. *Tetrahedron Lett.* **1992**, *33*, 1013. (c) Ward, S. C.; Fleming, S. A. *J. Org. Chem.* **1994**, *59*, 6476.
[24] Gülten, S.; Sharpe, A.; Baker, J. R.; Booker-Milburn, K. I. *Tetrahedron* **2007**, *63*, 3659.
[25] (a) Garner, P. P.; Cox, P. B.; Klippenstein, S. J.; Youngs, W. J.; McConville, D. B. *J. Org. Chem.* **1994**, *59*, 6510. (b) Righi, P.; Marotta, E.; Landuzzi, A.; Rosini, G. *J. Am. Chem. Soc.* **1996**, *118*, 9446. (c) Denmark, S. E.; Hurd, A. R.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668.
[26] (a) Penkett, C. S.; Byrne, P. W.; Teobald, B. J.; Rola, B.; Ozanne, A.; Hitchcock, P. B. *Tetrahedron* **2004**, *60*, 2771. (b) Sugimura, T.; Yamasaki, A.; Okuyama, T. *Tetrahedron: Asymmetry* **2005**, *16*, 675.
[27] (a) Yao, Q. *Org. Lett.* **2001**, *3*, 2069. (b) Grimm, J. B.; Otte, R. D.; Lee, D. *J. Organomet. Chem.* **2005**, *690*, 5508.
[28] (a) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298. (b) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. (c) Kurek-Tyrlik, A.; Wicha, J.; Snatzke, G. *Tetrahedron Lett.* **1988**, *29*, 4001. (d) Kurek-Tyrlik, A.; Wicha, J.; Zarecki, A.; Snatzke, G. *J. Org. Chem.* **1990**, *31*, 4445. (e) Batey, R. A.; Smil, D. V. *Angew. Chem. Int. Ed.* **1999**, *38*, 1798.
[29] Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634.
[30] Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700.
[31] Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702.

1.3 Metal Catalysis Approach

The requirement of stoichiometric and stepwise installation of tethers has been a major drawback to tethering reactions. As a result, metal catalysis using reversible covalent bonding has recently proven to be an effective alternative to the stepwise tethered approach. In this methodology, a catalyst-directing group (CDG) reversibly binds to the substrate and increases its affinity for the metal catalyst (Scheme 1.7). This increased affinity raises the concentration of substrate-bound catalyst – through induced intramolecularity – and often accounts for large reaction rate accelerations.

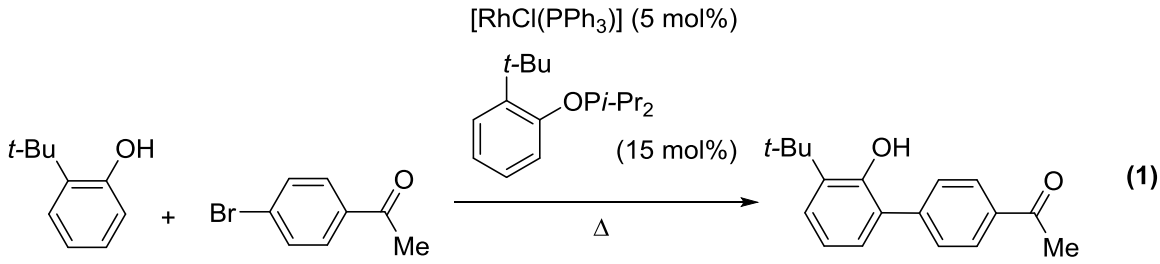


Scheme 1.7: Metal Catalyst-Directing Group (CDG) Approach; C: Catalyst

1.3.1 *Rhodium-Catalyzed Intermolecular ortho-Arylation of Phenols*

Catalytic C-H activation and functionalization is a tremendously important area in organic chemistry. A general strategy to selectively functionalize a relatively inert C-H bond in the presence of many others remains as a synthetic challenge to chemists. In 2003, Bedford applied the CDG methodology to catalyze the intermolecular *ortho*-selective arylation of phenols by direct C-H activation (Scheme 1.8, Eqn 1).[32] Using the Wilkinson catalyst and a phosphinite co-catalyst directing group, the transformation relies on two key stages: 1) coordination of the aryl phosphinite to the Rhodium (III) center allowing for a directed *ortho*-metalation, and 2) reductive elimination followed by transesterification with the phenolic substrate to regenerate the aryl phosphinite (Scheme 1.8, Eqn 2). Although this reaction worked well on various substituted phenols, the main limitation was the need to prepare the phosphinite co-catalyst from the corresponding phenolic substrate. To circumvent this limitation, Bedford demonstrated the *in situ* generation of the phosphinite using commercially available chlorophosphine.[33] Recently, this methodology has been applied towards the synthesis of tyrosine analogues.[34]

[32] (a) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem. Int. Ed.* **2003**, *42*, 112; (b) Bedford, R. B.; Limmert, M. E.; *J. Org. Chem.* **2003**, *68*, 8669.
[33] Bedford, R. B.; Betham, M.; Caffyn, A. J. M.; Charmant, J. P. H.; Lewis-Alleyne, L. C.; Long, P. D.; Polo-Ceron, D.; Prashar, S. *Chem. Commun*. **2008**, 990.
[34] Bedford, R. B.; Haddow, M. F.; Webster, C. J.; Mitchell, C. J. *Org. Biomol. Chem.* **2009**, *7*, 3119.



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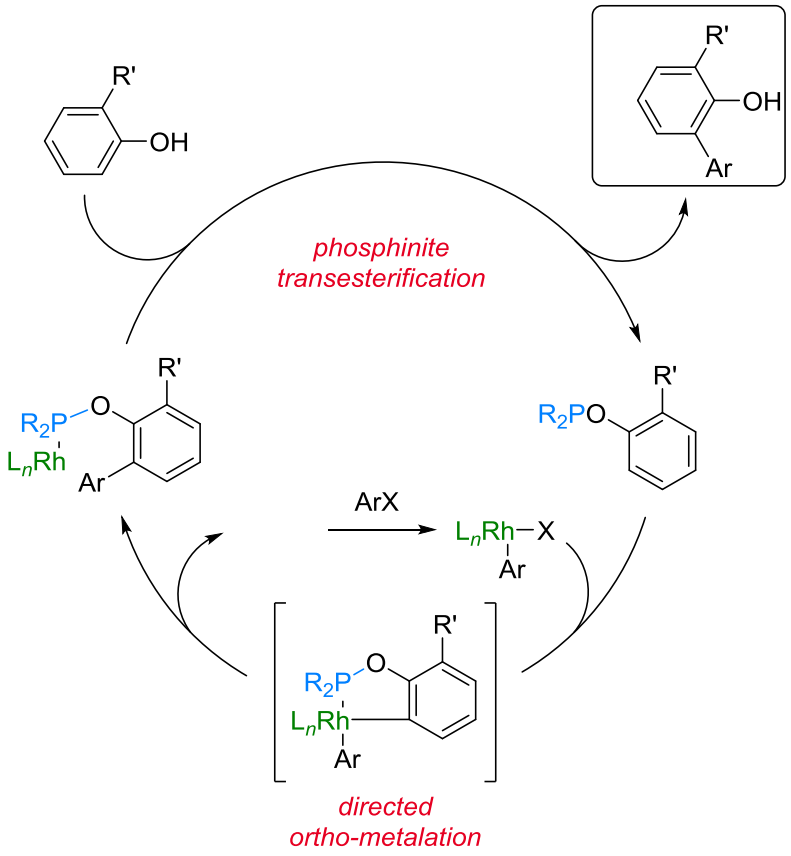


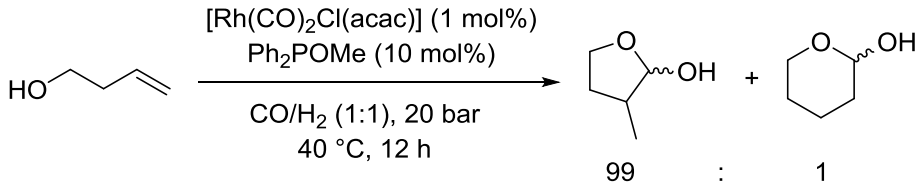
(2)

Scheme 1.8: Rhodium-Catalyzed *ortho*-Arylation of Phenols

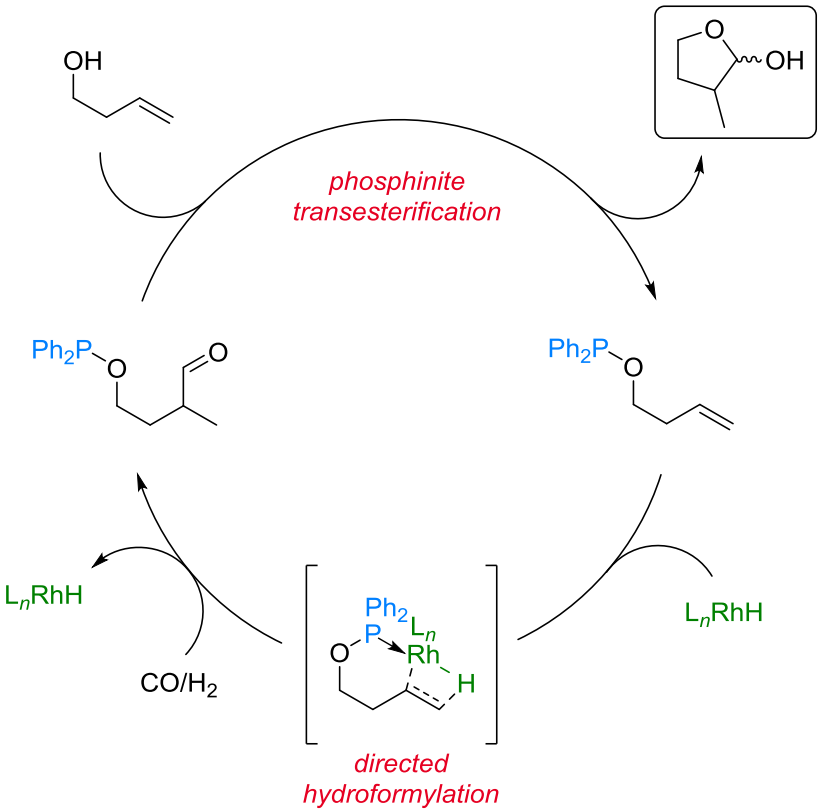
1.3.2 *Rhodium-Catalyzed Branched-Selective Hydroformylation*

Hydroformylation is an important industrial process for the production of aldehydes from alkenes.[35] Although many catalysts exist for the formation of linear aldehydes, only a few catalysts have been developed for the selective hydroformylation of alkenes to form branched aldehydes. Recently, Breit reported the use of phosphinites as reversibly bound CDGs for the branched-selective hydroformylation of homoallylic alcohols (Scheme 1.9, Eqn 1).[36] The proposed catalytic cycle involves formation of the phosphinite by transesterification of the homoallylic alcohol, followed by regioselective hydroformylation to give the phosphinite-containing product (Scheme 1.9, Eqn 2). An additional transesterification releases the desired product, which readily cyclizes to form the corresponding γ-lactol, along with regeneration of the phosphinite. The stereoselectivity of the transformation was probed by subjecting bis-homoallylic alcohols with a stereogenic centre in the 3-position to similar reaction conditions. Interestingly, good levels of acyclic stereocontrol were achieved favouring the *trans* product which was rationalized by minimization of the $A^{1,3}$ strain in the transition state (Figure 1.2).

[35] Ojima, I.; Tsai, C.Y.; Tzamarioudaki, M.; Bonafoux, D. *Org. React.* **2000**, *56*, 1.
[36] Grunanger, C. U.; Breit, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 7346.

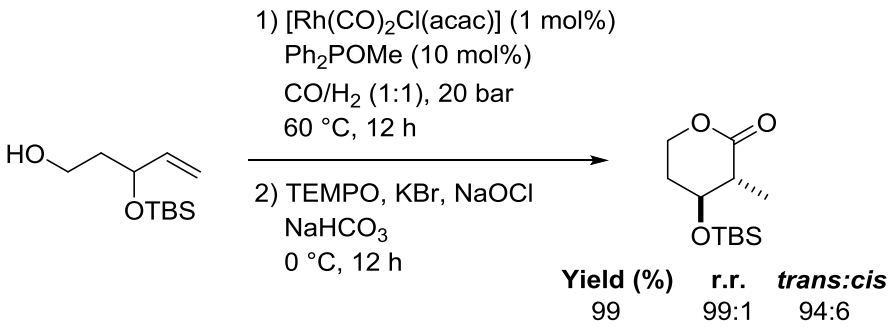


(1)



(2)

Scheme 1.9: Regioselective Hydroformylation of Homoallylic Alkenes



Scheme 1.10: Regio- and Stereoselective Hydroformylation of Bis-homoallylic Alcohols

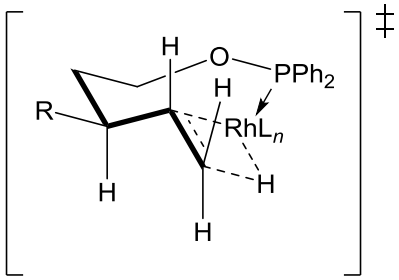


Figure 1.2: Origin of Stereoselectivity in Hydroforymlation Transition State

In 2008, Tan reported a phosphane-functionalized CDG which promoted branched-selective hydroformylation of homoallylic alcohols.[37] More recently, Tan's phosphane-functionalized CDG has been applied towards regioselective hydroformylation of allylic sulfonamides to generate corresponding β-amino aldehydes.[38] The same catalyst system has been extended to synthesize quaternary carbon centres from 1,1-disubstituted olefins.[39] By installing chiral centers on the phosphane-functionalized CGD, Tan also expanded this methodology to achieve regioselective and enantioselective hydroformylations of allylic alcohols[40], *N*-protected amines[41] and aniline derivatives[42].

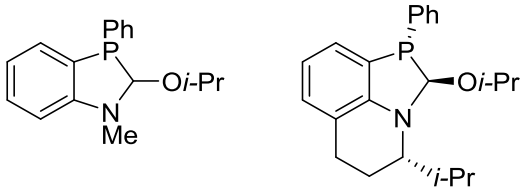


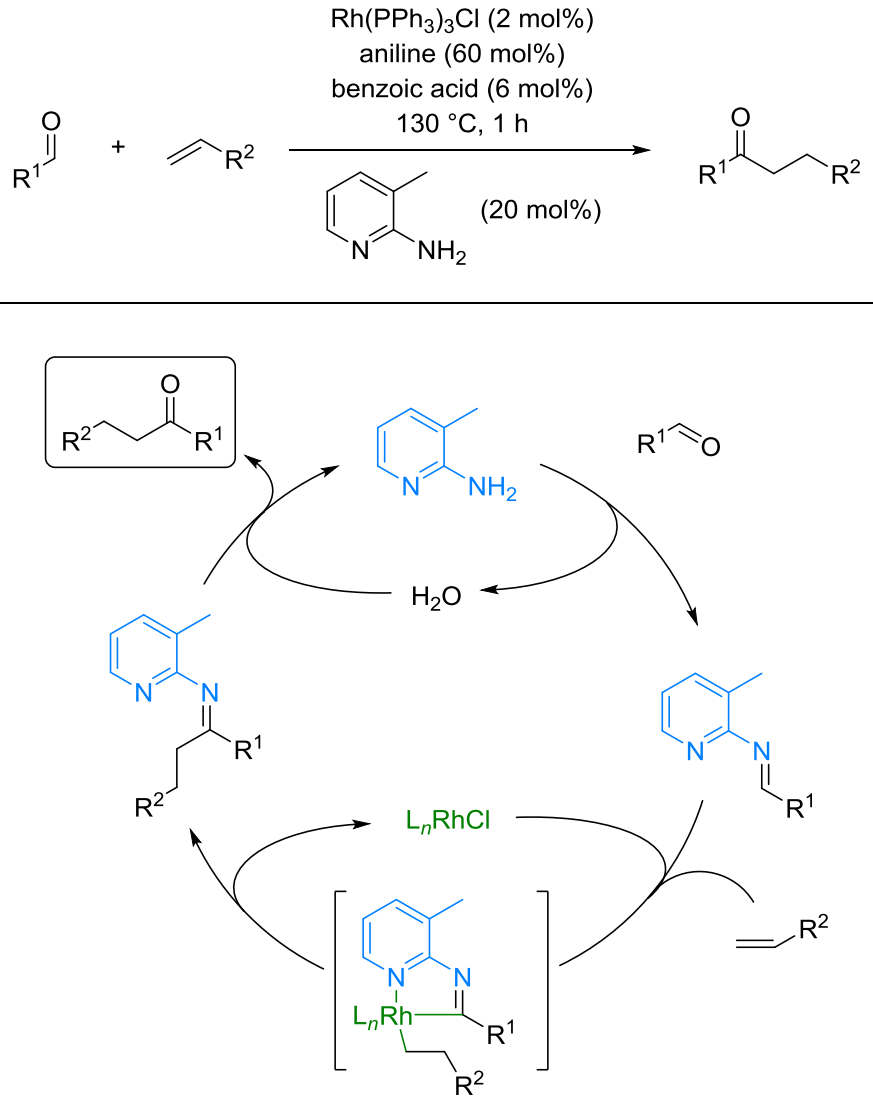
Figure 1.3: Tan's Phosphane-functionalized CDGs

[37] Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130*, 9210.
[38] Worthy, A. D.; Gagnon, M. M.; Dombrowski, M. T.; Tan, K. L. *Org. Lett.* **2009**, *11*, 2764.
[39] Sun, X.; Frimsong, K.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 11841.
[40] Lightburn, T. E.; De Paolis, O. A.; Cheng, K. A.; Tan, K. L. *Org. Lett.* **2011**, *13*, 2686.
[41] Worthy, A.D.; Joe, C.L.; Lightburn, T.E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 14757.
[42] Joe, C. L.; Tan, K. L. *J. Org. Chem.* **2011**, *76*, 7590.

1.3.3 *Rhodium-catalyzed Intermolecular Hydroacylation*

Hydroacylation is a synthetically valuable method for preparing ketones from aldehydes and olefins through C-H bond activation by transition metal complexes. Although intramolecular hydroacylations have been reported in the literature, examples of intermolecular variants remain rare. An additional challenge in this area has been the suppression of decarbonylation, which deactivates the catalyst. In 1997, Jun developed a general intermolecular hydroacylation of alkenes by using a Rhodium (I) complex and 2-aminopicoline as a CDG (Scheme 1.11).[43] Improved efficiencies were observed upon addition of catalytic amounts of benzoic acid and aniline.

[43] Jun, C. H.; Lee, H.; Hong, J. *J. Org. Chem.* **1997**, *62*, 1200.



Scheme 1.11: Rhodium-catalyzed Intermolecular Hydroacylation of Alkenes

The proposed catalytic cycle begins with condensation of 2-aminopicoline onto the aldehyde substrate to generate the aldimine. Through ligand-assisted C-H activation followed by alkene hydrometalation, the resulting Rhodium (III) complex can undergo reductive elimination to produce the masked imine product. Subsequent hydrolysis furnishes the desired ketone product and regenerates 2-aminopicoline. The catalytic amounts of benzoic acid and

aniline are proposed to function as a buffered proton source to help facilitate the transimination step.

Expanding on this ligand-assisted hydroacylation approach, Jun applied the same catalyst system towards alkynes (Scheme 1.12, Eqn 1).[44] Gratifyingly, the transformation was regioselective in giving the branched enone product. When *tert*-butyl alkynes were subjected to the same reaction conditions, the linear enone product was formed exclusively. This was rationalized by the minimization of steric repulsion in the transition state. Internal alkenes were also tolerated well in the substrate scope to give the corresponding ketone (Scheme 1.12, Eqn 2).[45] However, the additive cyclohexylamine was required for efficient reactivity, and the regioselectivity of unsymmetrical alkynes was largely dependent on the steric bulk of the alkyne substituents.

The success of ligand-assisted hydroacylation has been applied to the activation of C-C bonds (Scheme 1.12, Eqn 3).[46] By introducing an exogenous olefin to the Rhodium (III) intermediate, a new ketone product is formed. The reaction is driven to completion by the generation of a conjugated olefin which tends to polymerize under the reaction conditions.

More recently, Dong demonstrated the preparation of β-hydroxy ketones by regioselective hydroacylation.[47] This was accomplished by coupling salicylaldehyde with allylic alcohols in hydroacylation conditions, which promoted the phosphinite directed branched-selective ketone product (Scheme 1.12, Eqn 4).

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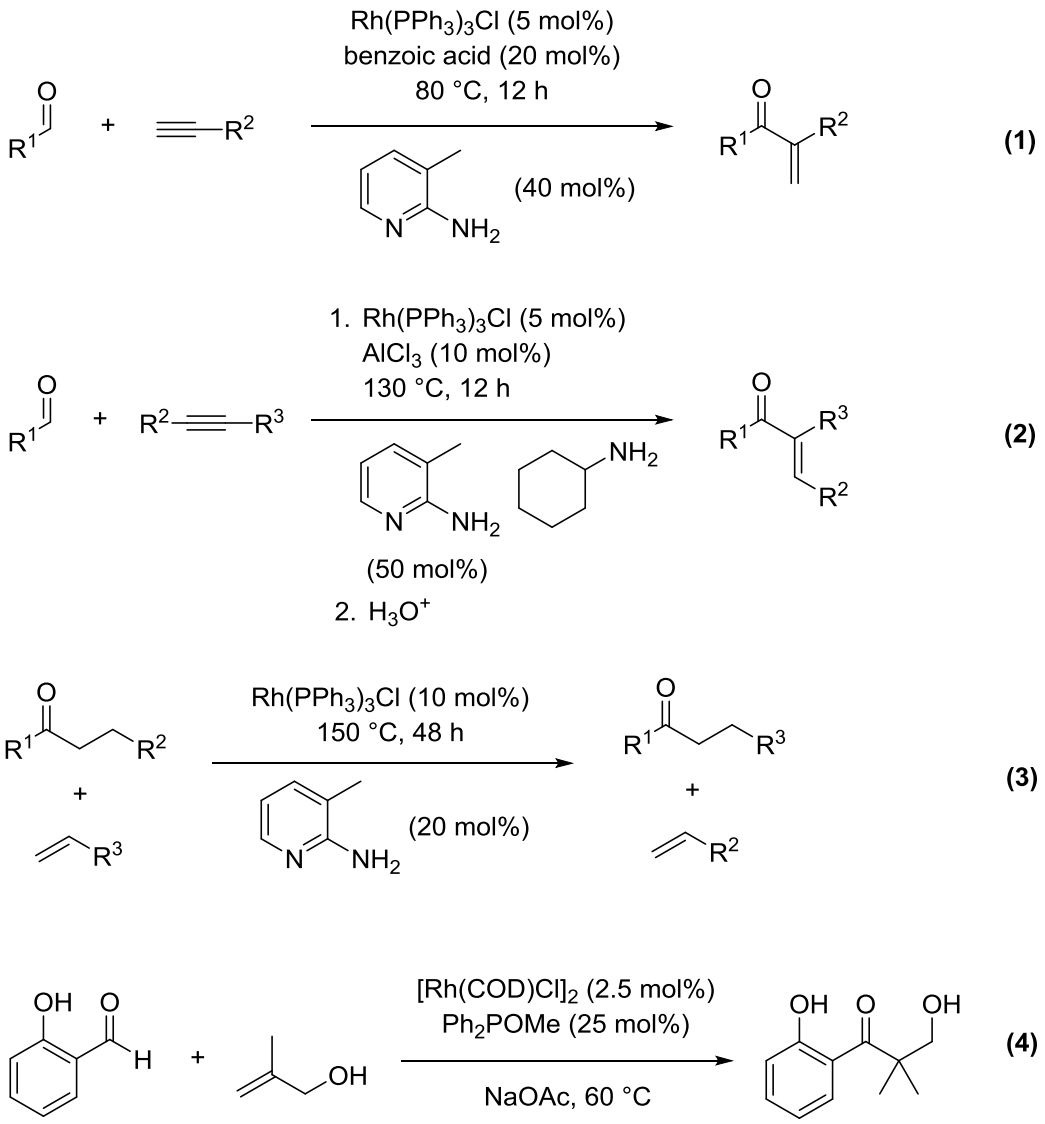
[44] Jun, C. H.; Lee, H.; Hong, J.; Kwon, B. *Angew. Chem.* **2002**, *114*, 2250; *Angew. Chem. Int. Ed.* **2002**, *41*, 2146.
[45] Lee, Y.; Hong, B.; Cho, E.; Lee, H.; Jun, C. H. *J. Am. Chem. Soc.* **2003**, *125*, 6372.
[46] Jun, C. H.; Lee, H. *J. Am. Chem. Soc.* **1999**, *121*, 880.
[47] Murphy, S. K.; Coulter, M.; Dong, V. M. *Chem. Sci.* **2012**, *3*, 355.



Scheme 1.12: Various Applications of Rhodium-catalyzed Intermolecular Hydroacylations

1.3.4 *Conclusion*

Catalyst-directing groups have been employed in a variety of reactions as anchors that form a reversible covalent bond with a substrate, inducing an intramolecular reaction. Although this approach has demonstrated reaction rate accelerations, high stereoselectivity, and

suppression of undesired reactions, common to all the examples presented is the use of rhodium, one of the rarest elements in the Earth's crust.[48] Consequently, the high cost and complex industrial extraction of rhodium has fuelled interest among chemists to find a more cost-effective and sustainable alternative.

1.4 Organocatalysis Approach

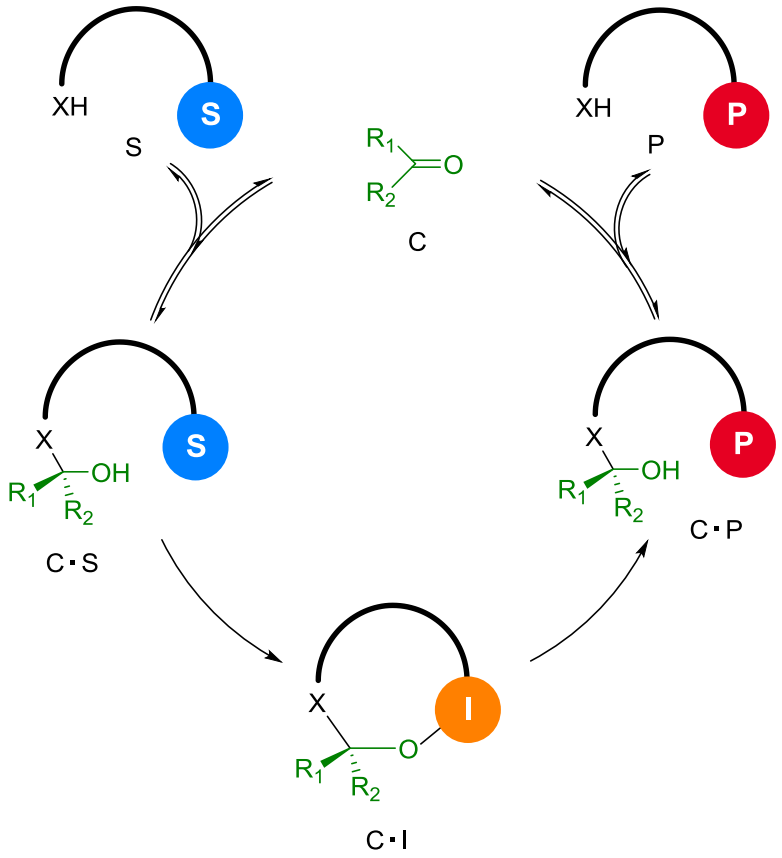
Organocatalysis, or the use of small organic molecules to accelerate chemical reactions, has generated considerable interest from the chemical synthesis community. Since 1998, at least 2,000 manuscripts have been published on this topic so far and more than 130 discrete reaction types were described in these publications.[49] These are remarkable numbers given that organocatalysts have only been documented intermittently over the past century; between 1960 and 1998, there were no review articles about the use of organocatalysts. The advent of organic catalysts brought about numerous advantages over the complementary approach of using metal catalysts including their insensitivity to moisture and oxygen, ready availability, low cost, and low toxicity. However, the utilization of organic molecules for chemical transformations *via* induced intramolecularity remains limited to simple hydrolysis reactions. Rarely have complex examples been reported in the literature that benefit from this mode of catalysis.[50]

[48] Krebs, R. E. *The History and Use of Our Earth's Chemical Elements*; Greenwood Press: USA, 2006.
[49] MacMillan, D. W. C.; *Nature* **2008**, *455*, 304.
[50] *Hydroaminations are the most complex examples. See references and examples below.*

1.4.1 *Carbonyl-catalyzed systems*

Several efficient catalyst systems utilizing aldehydes and ketones in hydrolytic or solvolytic reactions have been reported. Common to all these systems is organic carbonyl-containing molecules which can be viewed as very simple enzyme mimics. As illustrated below (Scheme 1.13), the adduct **C•S** is reversibly formed by the nucleophilic addition of the substrate **S** to the catalyst **C**. The newly-formed hydroxyl group is temporarily positioned to undergo an intramolecular addition to generate a transient cyclic intermediate **I**, that subsequently collapses and generates the desired product **P**. Due to the equilibrium giving adducts **C•S** and **C•P**, the **X** component of the substrate is often an amine, thiol, or alcohol which enables the reversible formation of the corresponding hemiaminal, hemithioacetal, and hemiacetal, respectively. Nitrogen and sulfur nucleophiles are most common in the literature because they have a tendency to react with the carbonyl group by several orders of magnitude higher than oxygen nucleophiles.[51]

[51] (a) Jencks, W. P. *Prog. Phys. Org. Chem.* **1964**, *2*, 63. (b) Le Henaff, P. *C. R. Seances Acad. Sci. C.* **1966**, *262*, 1667.



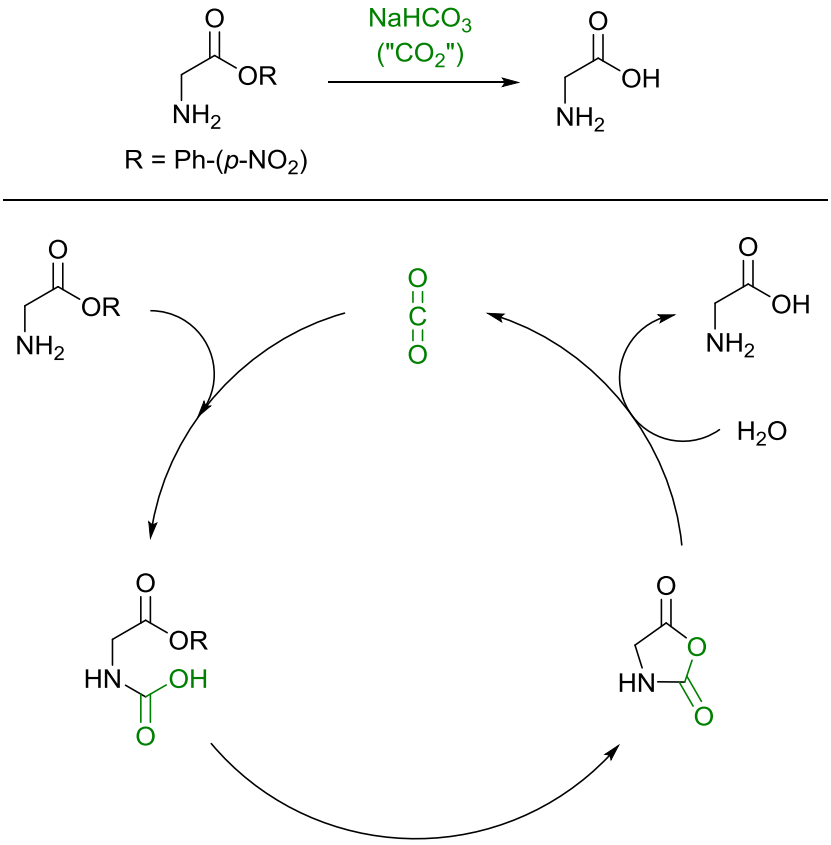
Scheme 1.13: Intramolecular Reactions by Carbonyl-Containing Catalysts; X = N, O, S

1.4.2 *Hydrolysis of Esters*

In 1956, Wieland reported one of the first reactions to involve induced intramolecularity through carbonyl compound adducts.[52] Bicarbonate was used as a catalyst for the hydrolysis of a glycine ester. The postulated mechanism involves formation of a carbamic acid from the free amine and carbon dioxide (Scheme 1.14). The carboxyl group then undergoes an intramolecular cyclization onto the ester moiety to generate a *N*-carboxy

[52] Wieland, T.; Lambert, R.; Lang, H. U.; Schramm, G. *Justus Liebigs Ann. Chem.* **1955**, *597*, 181. (b) Wieland, T.; Jaenicke, F. *Justus Liebigs Ann. Chem.* **1956**, *599*, 125.

anhydride intermediate. Subsequent hydrolysis of this intermediate regenerates carbon dioxide and yields the carboxylic acid product. However, oligopeptides are also produced as side products because *N*-carboxy anhydrides are highly susceptible to polymerization. Discussions on the implications of bicarbonate-catalyzed polypeptides in the primitive earth have been reported elsewhere.[53]

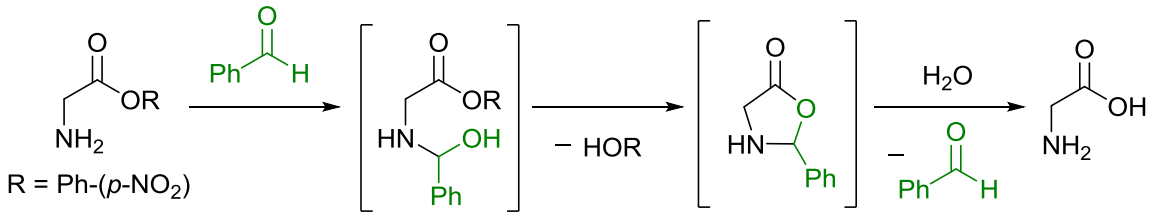


Scheme 1.14: CO_2-Catalyzed Ester Hydrolysis

Such intramolecular activation was extended to aromatic aldehydes, which increased the rate of hydrolysis of glycine, phenylalanine, and leucine *p*-nitrophenyl esters (Scheme

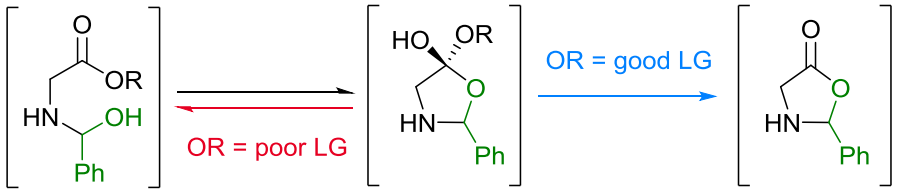
[53] (a) Brack, A. *Biosystems* **1982**, *15*, 201. (b) Brack, A. *Origins Life* **1987**, *17*, 367.

1.15).[54] The proposed catalytic pathway is similar to the bicarbonate catalyzed reaction: 1) addition of the amine to the aldehyde to generate a hemiaminal, 2) intramolecular addition of the hemiaminal to the ester moiety to form an oxazolidinone intermediate, 3) hydrolysis to form the acid product and regeneration of the aldehyde catalyst.



Scheme 1.15: Aldehyde-Catalyzed Ester Hydrolysis

Although the first examples of induced intramolecularity demonstrate the viability of this approach, the catalysis was only observed in activated *p*-nitrophenyl esters. The proposed mechanism involves formation of a tetrahedral intermediate that breaks down into the 5-membered cyclic intermediate (Scheme 1.16). The ease of expulsion of the leaving group is strongly influenced by the R group of the ester. Good leaving groups such as *p*-nitrophenoxide are more easily expelled compared to poor leaving groups such as methoxide, which revert to the reactants.

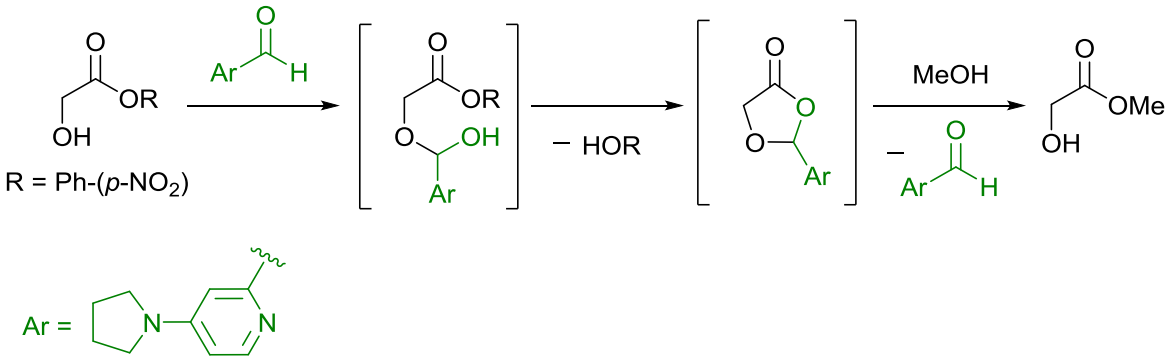


[54] (a) Capon, B.; Capon, R. *J. Chem. Soc., Chem. Commun.* **1965**, *20*, 502. (b) Hay, R. W.; Main, L. *Aust. J. Chem.* **1968**, *21*, 155.

Scheme 1.16: Proposed Influence of Leaving Group (LG) in Catalytic Pathway

1.4.3 *Alcoholysis of Esters*

With the success in aldehyde-catalyzed hydrolysis of esters, Sammakia extended this methodology to the methanolysis of α-hydroxy esters (Scheme 1.17).[55] Using aldehyde and ketone derivatives of 4-pyrrolidinopyridine (PPY) as catalysts, rate enhancements of up to 1700 times were observed. Similar to previous aldehyde-promoted reactions, the catalytic pathway is proposed to proceed through a transient hemiacetal that undergoes an intramolecular addition to form a dioxolanone. Methanolysis releases the desired product and catalyst that can re-enter the catalytic cycle. Mechanistic studies have shown that the dioxolanone intermediate is the resting state of the catalyst and its reaction with methanol is the rate-limiting step of the overall process. The addition of electron withdrawing groups to the pyridine moiety of the catalyst was found to increase the rate of catalysis.



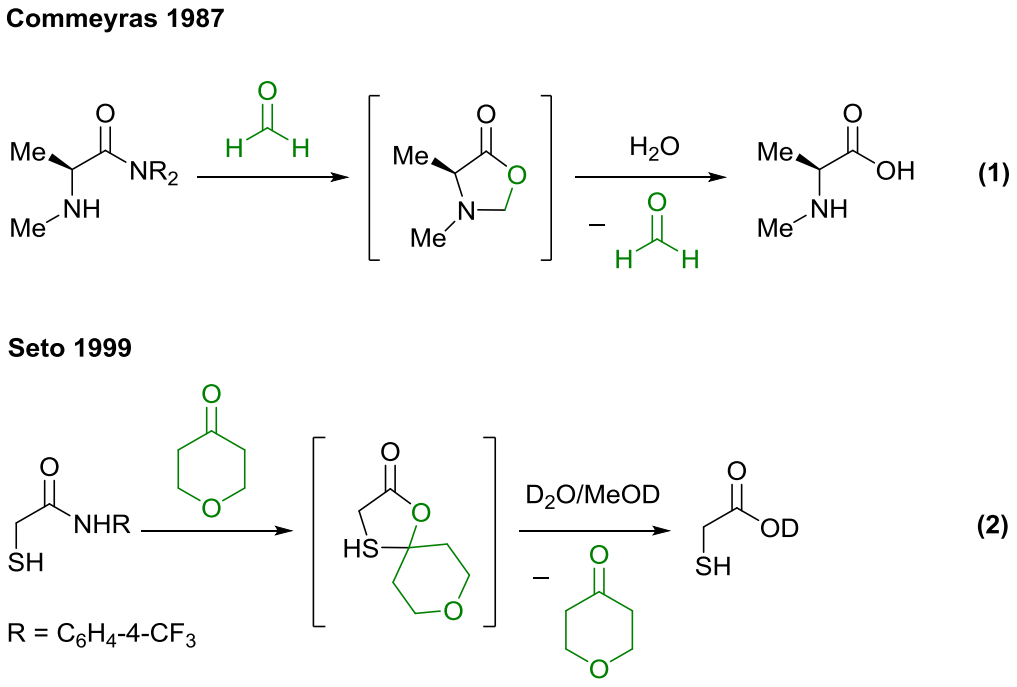
Scheme 1.17: Methanolysis of α-Hydroxy Esters

[55] (a) Sammakia, T.; Hurley, T. B. *J. Am. Chem. Soc.* **1996**, *118*, 8967. (b) Sammakia, T.; Hurley, T. B. *J. Org. Chem.* **1999**, *64*, 4652. (c) Sammakia, T.; Hurley, T. B. *J. Org. Chem.* **2000**, *65*, 974.

1.4.4 *Hydrolysis of Amides*

A desirable reaction in organic chemistry is the hydrolysis of amide bonds catalytically and under mild conditions. Nature has developed proteases that are capable of sequence-specific hydrolysis of peptides with remarkable rate accelerations. Consequently, organic chemists strive to emulate the activity and specificity of protein-based catalysts by designing artificial catalysts in the laboratory. In 1987, Commeyras discovered that formaldehyde efficiently catalyzed the hydrolysis of α-amino amides through a similar proposed mechanism to the aldehyde-catalyzed hydrolysis of esters presented above (Scheme 1.18, Eqn 1).[56] Described as a serine protease mimic, this system involves the α-amino amide reversibly linking with formaldehyde to form an oxazolidinone intermediate, which is subsequently hydrolyzed to form the amino acid product. About a decade later, Seto extended this methodology to α-mercaptoamides by using cyclic ketones as catalysts (Scheme 1.18, Eqn 2).[57] Hydrolysis rate accelerations of up to ~1500 times compared to no ketone present were reported.

[56] Pascal, R.; Lasperas, M.; Taillades, J.; Commeyras, A. *New J. Chem.* **1987**, *11*, 235.
[57] Ghosh, M.; Conroy, J. L.; Seto, C. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 514.



Scheme 1.18: Carbonyl-Catalyzed Amide Hydrolysis

1.4.5 *Hydroaminations*

Hydroamination, the addition of an N-H bond of an amine across an unsaturated carbon-carbon bond, represents one of the simplest and most desirable synthetic transformations for which no general solution exists. The challenges faced by this reaction include the high activation barrier associated with the electron-rich substrate and the amine nucleophile as well as the unfavourable entropy accompanied with intermolecular variants. Although progress has been accomplished using transition-metal catalysis, there remains

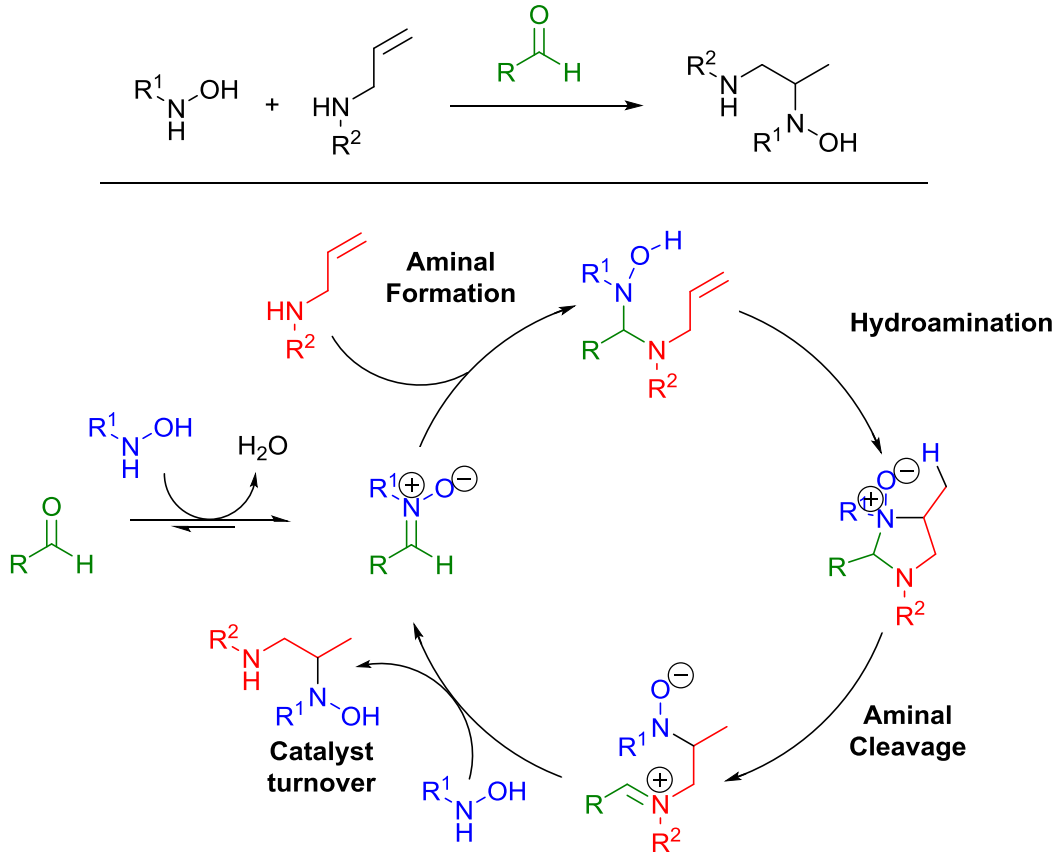
significant challenges including selectivity and functional group tolerance, which are often associated with the use of reactive catalysts and high temperature reaction conditions.[58]

Recognizing the opportunity in developing mild hydroamination alternatives, Beauchemin developed aldehyde-based organocatalysts that form a temporary tether between hydroxylamines and allylic amines *in situ*, thus enabling room-temperature directed intermolecular metal-free hydroaminations (Scheme 1.19: Aldehyde-Catalyzed Hydroamination).[59] The proposed mechanism involves condensation of the hydroxylamine onto an aldehyde to form a nitrone. Next, the allyl amine adds to the nitrone forming an aminal intermediate that is positioned to undergo a facile intramolecular Cope-type hydroamination. Subsequent aminal cleavage and condensation of a second molecule of hydroxylamine completes the catalytic cycle and releases the hydroamination product. Using only 5 mol% of formaldehyde as a tethering catalyst produced hydroamination products in near quantitative yields.[60] This methodology was expanded to include the synthesis of enantiopure 1,2-diamine motifs using chiral α-oxygenated aldehydes (Figure 1.4). The importance of this work was the demonstration that simple α-oxygenated chiral aldehydes can function as effective catalysts capable of efficiently inducing asymmetry through temporary intramolecularity.

[58] For selected reviews on hydroamination see: (a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev*. **2008**, *108*, 3795. (b) Aillaud, I.; Collin, J.; Hannedouche, J.; Schulz, E. *Dalton Trans.* **2007**, 5105. (c) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (d) Nobis, M.; Drieβen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983. (e) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

[59] (a) MacDonald, M. J.; Hesp, C. R.; Schipper, D. J.; Pesant, M.; Beauchemin, A. M. *Chem. Eur. J.* **2013**, *19*, 2597. (b) Guimond, N.; MacDonald, M. J.; Lemieux, V.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16571. (c) MacDonald, M. J.; Schipper, D. J.; Ng, P. J.; Moran, J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 20100.

[60] MacDonald and Hesp unpublished results.



Scheme 1.19: Aldehyde-Catalyzed Hydroamination

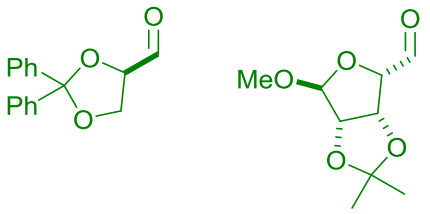


Figure 1.4: Selected Examples of Efficient Chiral Aldehydes

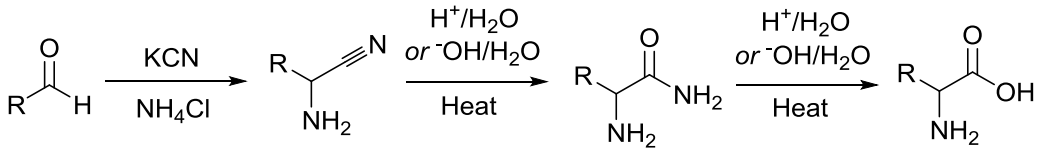
1.4.6 ***Hydration of Nitriles***

The hydration of nitriles is the most atom-economical reaction and sustainable method for the preparation of primary amides. Classically this transformation is carried out under highly acidic or basic conditions at elevated temperatures, often causing overhydrolysis of the amides to the corresponding carboxylic acids and the formation of polymeric side products.[61] Additionally, from an industrial perspective, the final neutralization step produces copious salt formation with inconvenient product contamination. To address these limitations, enzymatic catalysis protocols have been developed for nitrile hydrations permitting cleaner, safer and more selective alternatives.[62] However, the high isolation costs and narrow substrate specificity of the currently available enzymes limits the applicability on the commercial level. Moreover, heterogeneous and homogeneous transition-metal catalysis have received considerable attention in the last two decades owing to the greater substrate scope they offer. However, these transformations often require high pressures and temperatures or long reaction times.[63]

The hydration of α-amino nitriles is also an important route towards accessing amino amide and acid derivatives, which are privileged structural motifs found ubiquitously in natural or synthetic molecules of biological and commercial interest. The synthesis of α-amino nitriles was first devised by Strecker and involves condensation of an aldehyde with an amine in the presence of a cyanide source (Scheme 1.20).[64] The resulting α-amino nitrile is subjected to

[61] Moorthy, J. N.; Singhal, N. *J. Org. Chem.* **2005**, *70*, 1926.
[62] Kobayashi, M.; Shimizu, S. *Curr. Opin. Chem. Biol.* **2000**, *4*, 95.
[63] Ahmed, T. J.; Knapp, S. M. M.; Tyler, D. R. *Coord. Chem. Rev.* **2011**, *255*, 949.
[64] Strecker, A.; Strecker H. *Liebigs Ann.* **1850**, *75*, 27.

harsh acidic or basic conditions at high temperatures to yield the corresponding α-amino amide and acid.[65] The harsh reaction conditions, wasteful by-products, and poor functional group tolerance of this approach has garnered interest from the synthetic community in developing milder alternatives, including the use of asymmetric auxiliaries[66] or asymmetric catalysts[67] to obtain enantiopure amino nitriles, which lead to amino amides and acids upon hydrolysis.

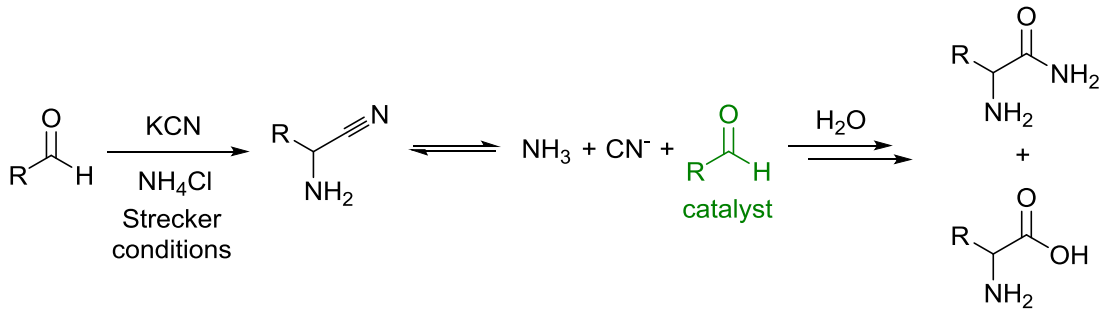


Scheme 1.20: Strecker Amino Acid Synthesis

In the 1970's, Commeyras fortuitously discovered an alternative approach to synthesizing amino amides and acids. Observing that α-amino nitriles react at a significantly faster rate towards hydration compared to other nitriles, Commeyras proposed that the rate acceleration was a consequence of the α-amino nitriles decomposing into the parent aldehydes and ketones, which serve as catalysts for the reaction (Scheme 1.21).[68] To validate this autocatalytic pathway hypothesis, a simple ketone such as acetone was added to the reaction, which resulted in significant improvements in yield and reactions times. Similar to the aldehyde-catalyzed ester hydrolysis, the proposed catalytic cycle begins with the transient

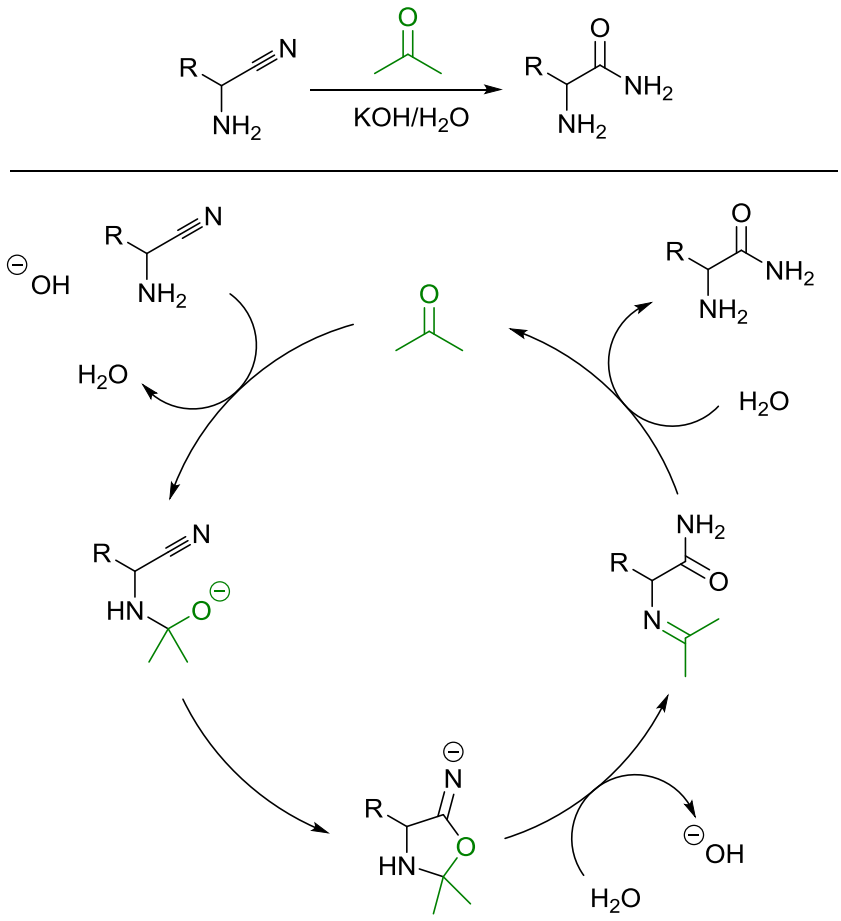
[65] Zuend, S.; Coughlin, M.; Lalonde, M.; Jacobsen, E. *Nature* **2009**, *461*, 968.
[66] Davis, F. A. *Tetrahedron Lett.* **1994**, *35*, 9351.
[67] Huang, J.; Corey, E. J. *Org. Lett.* **2004**, *6*, 5027.
[68] (a) Pascal, R.; Taillades, J.; Commeyras, A. *Bull. Soc. Chim. Fr. II* **1978**, *177*, 184. (b) Pascal, R.; Taillades, J.; Commeyras, A. *Tetrahedron* **1978**, *34*, 2275. (c) Pascal, R.; Taillades, J.; Commeyras, A. *Tetrahedron* **1980**, *36*, 2999. (d) Sola, R.; Taillades, J.; Brugidou, J.; Commeyras, A. *New J. Chem.* **1989**, *13*, 881.

formation of a hemiaminal comprising of an alcoholate portion optimally positioned to undergo an intramolecular addition onto the nitrile moiety (Scheme 1.22). Subsequent opening of the resulting intermediate followed by hydrolysis forms the amide and regenerates the acetone catalyst. Remarkably, this proposed mechanism bears several similarities to the action of nitrile hydratase, an enzyme that catalyzes the hydration of nitriles to their corresponding amides in living systems.[69] Noteworthy is the enzyme's ability to pre-organize the nitrile substrate through non-covalent interactions and generate a cyclic intermediate similar to the one proposed by Commeyras.



Scheme 1.21: Autocatalytic Pathway for Hydration of α-Amino Nitriles

[69] Yu, H.; Liu, J.; Shen, Z. *J. Mol. Graphics Modell.* **2008**, *27*, 522.

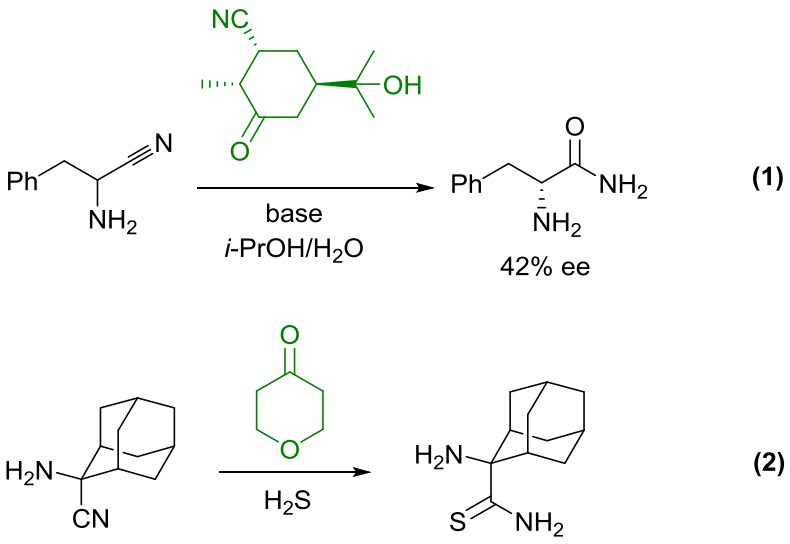


Scheme 1.22: Proposed Catalytic Pathway of Acetone-Catalyzed α-Amino Nitrile Hydration

This mode of catalysis was extended to chiral ketone catalysts where kinetic resolution was employed to achieve enantiomeric excess of up to 42% (Scheme 1.23, Eqn 1).[70] While this value is modest, it demonstrates the important concept that chiral tethering catalysts are capable of inducing enantioselectivity by favouring reactivity of a specific enantiomer. Using a similar approach, Edward demonstrated bubbling H_2S in a reaction vessel containing an α-

[70] Tadros, Z.; Lagriffoul, P. H.; Mion, L.; Taillades, J.; Commeyras, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1373.

amino nitrile and ketone produced the corresponding α-amino thioamide (Scheme 1.23, Eqn 2).[71]



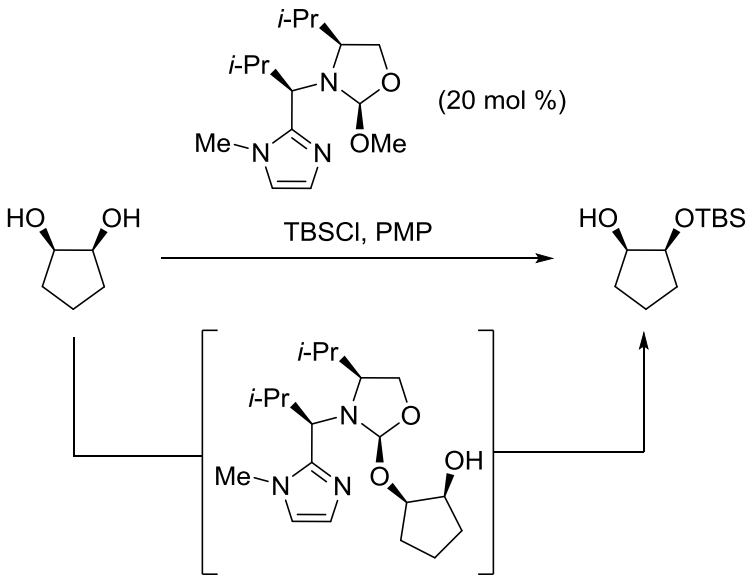
Scheme 1.23: Ketone-Catalyzed α-Amino Nitrile Hydration

1.4.7 *Desymmetrization and Site-Selective Catalysis*

In 2011, Tan reported a highly enantioselective, catalytic desymmetrization of meso diols at room temperature in which the catalyst utilizes reversible covalent bonding to the substrate to achieve high selectivity and rate acceleration (Scheme 1.24).[72] The proposed mechanism involves reversibly binding the diol, then, through an intramolecular transfer or deprotonation, functionalization of the free alcohol. Since the binding of the catalyst to the substrate is entropically neutral, the subsequent functionalization step (silylation) is

[71] (a) Paventi, M.; Chubb, F. L.; Edward, J. T. *Can. J. Chem.* **1987**, *65*, 2114. (b) Paventi, M.; Edward, J. T. *Can. J. Chem.* **1987**, *65*, 282.
[72] Sun, X.; Worthy, A. D.; Tan, K. L. *Angew. Chem. Int. Ed*. **2011**, *50*, 8167.

intramolecular; consequently, the enantioselectivity could be the result of the binding step, functionalization step, or a combination of the two.

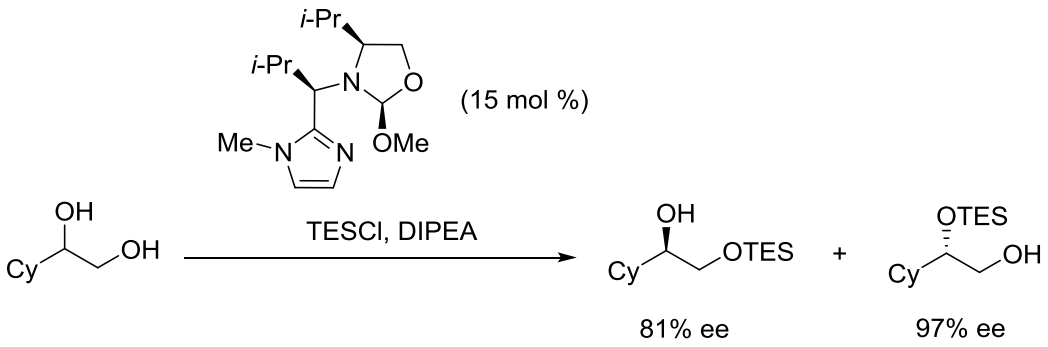


Scheme 1.24: Tan's Desymmetrization of Meso Diols

Using the same catalyst, Tan was also able to selectively functionalize a secondary hydroxyl in preference to the primary hydroxyl of a 1,2-diol.[73] The site selectivity was made possible by implementing a catalyst that was highly stereoselective and had a preference for binding less hindered hydroxyls covalently. This approach was applied to a divergent kinetic resolution on a racemic mixture making it possible to access highly enantioenriched secondary-protected 1,2-diols in a single step (Scheme 1.25). Additionally, this methodology of site-

[73] Worthy, A. D.; Sun, X.; Tan, K. L. *J. Am. Chem. Soc.* **2012**, *134*, 7321.

selective functionalization has been applied to complex molecules such as monosaccharides and natural products.[74]



Scheme 1.25: Divergent Kinetic Resolution of a Racemic Mixture

1.4.8 ***Conclusion***

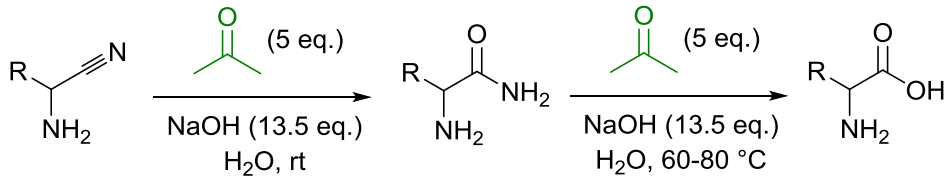
Besides the numerous advantages of using organocatalysts including their insensitivity to moisture and oxygen, low cost and toxicity, their unique ability to form reversible covalent bonds allow for significant acceleration of reaction rates through intramolecular activation. Furthermore, the conformational restrictions imposed by covalent bonds has been exploited for the purpose of inducing asymmetry in molecules in a highly selective manner.

[74] Sun, X.; Lee, H.; Lee, S.; Tan, K. L. *Nat. Chem.* **2013**, *5*, 790.

Chapter 2. **Re-investigation of the Commeyras Carbonyl-catalyzed Hydration of α-Amino Nitriles**

2.1 Results and Discussion

While the seminal work of Commeyras demonstrated that aldehydes can function as effective catalysts in accelerating the rate of hydration of α-amino nitriles, this approach utilized stoichiometric quantities of catalyst (Scheme 2.1). Consequently, the catalytic efficiency of this reactivity has not been addressed. Additionally, the reaction conditions required a harsh, alkaline medium that was extremely dilute, making this approach impractical on larger scales. Furthermore, the reaction scope only included a limited number of examples and the enantioselective variant produced a modest 42% ee.



Scheme 2.1: Commeyras Reaction Conditions for α-Amino Nitrile and Amide Hydrolysis

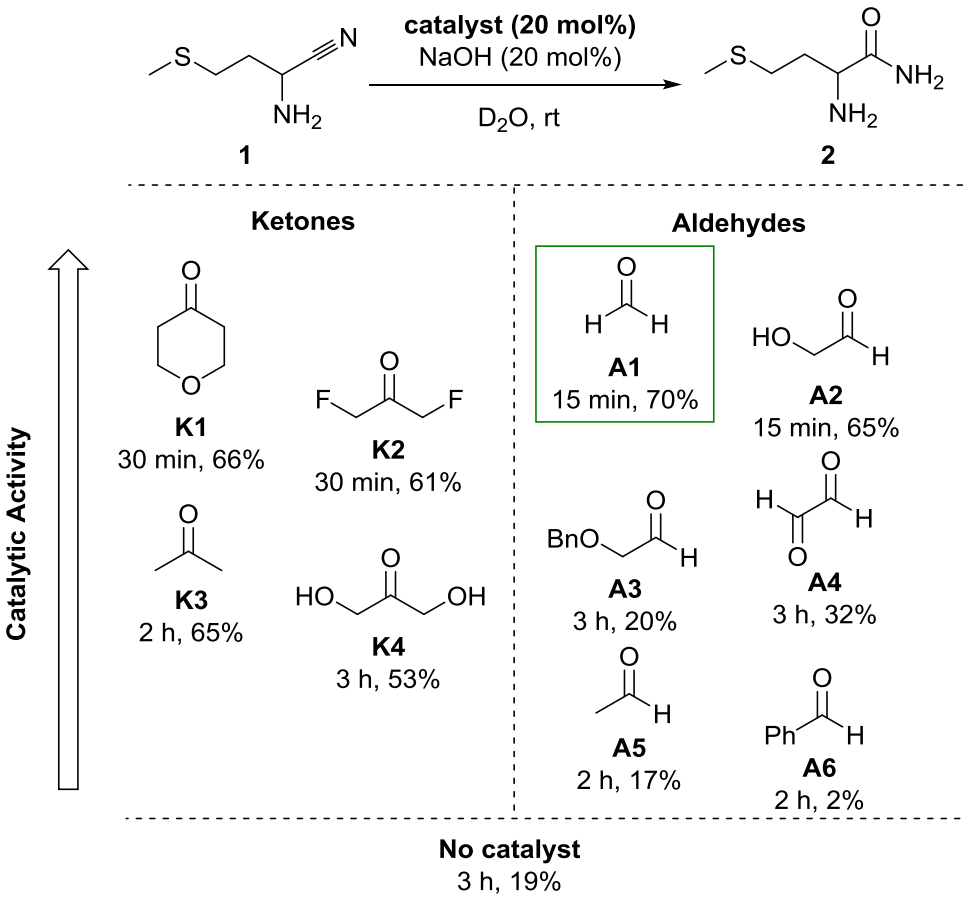
Inspired by the remarkable seminal discoveries by Commeyras that seem to have been overlooked in the literature, a central goal of our project was to determine if the systems were truly catalytic by introducing sub-stoichiometric quantities of catalyst and to probe the catalytic efficiencies of various catalysts. Our secondary goal included investigating milder conditions for this reactivity allowing for broader applicability in terms of functional group tolerance. Additionally, diversifying the substrate scope and identifying catalysts capable of improving enantioselectivity was important for demonstrating the power of induced

intramolecularity. In this section, a complete picture of the incremental steps taken to achieve these goals will be presented along with insight into potential future directions for this project.

2.1.1 *Carbonyl Catalyst Scan*

A search was required to identify carbonyl-based catalysts capable of performing the α-amino nitrile hydration in sub-stoichiometric quantities under milder reaction conditions. First, synthesis of an appropriate α-amino nitrile was needed to perform the catalyst screening. α-Amino nitriles are conveniently obtained by the Strecker reaction, although yields are notoriously low and the products often decompose on standing.[75] Thus, 2-amino-4-methylthiobutyronitrile **1** was synthesized and subjected to our milder conditions: an alkaline D_2O solution (20 mol % of NaOH (5M)) and a catalytic amount (20 mol %) of various ketones (entries **K1-K4**) and aldehydes (entries **A1-A4**) (Figure 2.1) to give the corresponding amide **2**.

[75] Garst, M. E.; Dolby, L. J.; Esfandiari, S.; Avey, J.; Arthur, A. Method of making imidazole-2-thiones. U.S. Patent 7,115,748, Oct 3, 2006.



Conditions: α-Amino nitrile (1 eq., 1.0 M) in D_2O, NMR yield (%) given; determined using 1,3,5-trimethoxybenzene as an internal standard.

Figure 2.1: Screening of Ketone and Aldehyde Catalysts

Gratifyingly, high catalytic activity was observed for both cyclic and acyclic ketones and aldehydes in sub-stoichiometric amounts of both catalyst and base. Noteworthy is the high catalytic activity exhibited by tetrahydropyranone (THP) **K1** which has also been used by Seto as an effective catalyst in the hydrolysis of α-amino thioamides.[57] Seto suggests that the oxygen atom in the γ-position of the cyclohexanone ring system promotes electrostatic interactions that should alter the pK_a of the intermediate hemiaminal hydroxyl group which is involved in

catalysis. However, the oxygen atom is effectively three carbons away in this intermediate; a distance that is too far to have more than a very minor influence. Alternatively, the γ-position oxygen is likely to be involved in making the preassociation step more favorable. However, the differences in reactivity between the ketone catalysts are not significant suggesting that the structure of the carbonyl catalyst may not be critical in the association preequilibrium for primary α-amino nitriles. Consistent with this observation is the kinetic experiments on the hydrolysis of α-amino nitriles by Commeyras, who suggests the rate-determining step in the catalytic pathway is the cyclization of the hemiaminal anion intermediate.[76] This infers that the preassociation step of the substrate binding to the catalyst reaches equilibrium faster than nitrile hydrolysis.

With respect to the aldehyde catalysts, formaldehyde **A1** displayed the highest catalytic activity. This was not surprising as formaldehyde has previously been reported to be an effective tethering catalyst in hydroaminations[59b] and amide hydrolyses.[56] Glycoaldehyde **A2** also demonstrated promising reactivity, although the subsequent entries (**A3-A6**) were not as effective, even though destabilized aldehydes such as 2-(benzyloxy)acetaldehyde **A3** have been successfully utilized in tethered hydroaminations.[59c] Noteworthy, the basic reaction conditions performed in the absence of catalyst gave product in 19% yield after 3 hours; within the first hour only traces of product were observed (which is consistent with the autocatalytic behavior reported by Commeyras).

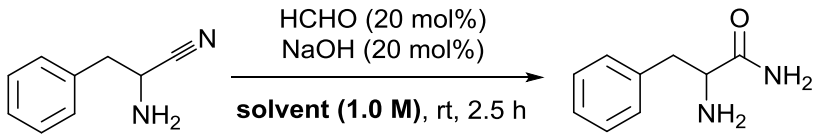
[76] Pascal, R.; Taillades, J.; Commeyras, A. *Tetrahedron* **1980**, 36, 2999.

Overall, these results showed some catalyst structure-activity relationship. Stable, carbonyl-containing catalysts such as benzaldehyde were inefficient; however, introducing electron-withdrawing groups to both acetaldehyde and acetone resulted in enhanced catalytic activity, most likely due to favouring of the preassociation step.

2.1.2 *Optimization: Solvent Scan and Catalyst Loading*

Following these exciting results, optimization of the reaction conditions was performed, beginning with a solvent scan. The solvent scan served the function of determining if the same reactivity could be achieved using organic solvents which would be preferable in terms of achieving a homogeneous reaction mixture. This would avoid the emulsions formed in the current aqueous reactions conditions, allowing for more accurate reaction monitoring as well as simpler product isolation. Due to the readily accessible 2-amino-3-phenylpropionitrile **3**, a solvent scan was performed on this substrate, giving the hydrated amide product **4** (Table 2.1). The best reactivity was again achieved using D_2O (entry 1) while various organic solvents (entries 2-5) showed little to no reactivity. Although a homogeneous mixture of D_2O:dioxane (entry 6) also showed excellent reactivity, the isolation of the amide product proved to be difficult. The other D_2O-miscible solvent mixtures generated only moderate reactivity. These results indicated that water is a critical component to ensure a high catalytic efficiency. Indeed upon closer examination of the catalytic cycle, the actual catalyst responsible for turnover is a molecule of water. An alternative explanation could also be the increased stabilization of anionic intermediates that is possible in water.

Table 2.1: Investigation of Organic and Water-Miscible Solvents



3 **4**

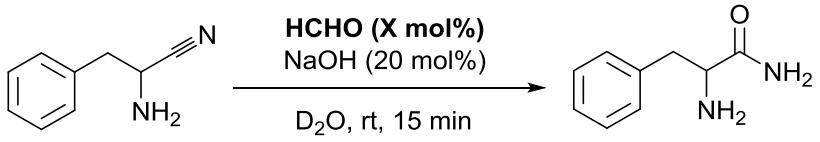
Entry	Solvent	Conversion (%)[a]
1	D_2O	99 (63)
2	Isopropanol	0
3	Acetonitrile	10
4	DMSO-d_6	0
5	EtOH	0
6	D_2O:dioxane (1:1)	99 (25)
7	D_2O:THF (1:1)	58
8	D_2O:isopropanol (1:1)	47
9	D_2O:acetonitrile (1:1)	22
10	D_2O:DMSO-d_6 (1:1)	35

[a] Estimated based on relative integration of remaining α-amino nitriles to product. Isolated yield in parenthesis.

Reactions were further probed with varying D_2O concentrations ranging from 0.07 M to 1M; the reaction efficiencies remained similar regardless of the concentration. Additionally, reactivity was evaluated using a catalyst loading as low as 10 mol% (Table 2.2). The reaction proved just as efficient as with 20 mol% catalyst loading; however, the low molecular weight of formaldehyde required additions of as low as 8 µL of the formalin solution (37% formaldehyde in H_2O), making reaction reproducibility cumbersome. Consequently, 20 mol% was selected as the optimal catalyst loading. Given the high efficiency of the reaction, varying the quantity of

base was not evaluated further; although this investigation may prove to be worthwhile in future work.

Table 2.2: Investigation of Catalyst Loading



3 **4**

Entry	Catalyst Loading (mol%)	Conversion (%)[a]
1	50	98
2	20	99
3	10	99

[a] Estimated based on relative integration of remaining α-amino nitrile to product.

2.1.3 *Influence of N-substitution*

After identifying the optimal solvent and reaction conditions, efforts carried out by Dr. Sampada Chitale were directed towards exploring the effects of nitrogen substitution of the α-amino nitrile on hydration reactivity. It was reasoned that preassociation could be less kinetically and thermodynamically favorable with hindered secondary α-amino nitriles. In addition to providing a more complete picture of the catalytic efficiency profile of this reaction, *N*-substituted α-amino nitriles would be simpler to isolate due to their lower polarity. Indeed, isolation of these derivatives using flash column chromatography was significantly easier compared to the corresponding unsubstituted α-amino nitriles. 2-(Allylamino)-3-

phenylpropanenitrile **5** was selected as the *N*-substituted α-amino nitrile for the catalyst scan and was subjected to the optimized reactions conditions (Figure 2.2) to give the amide **6**.

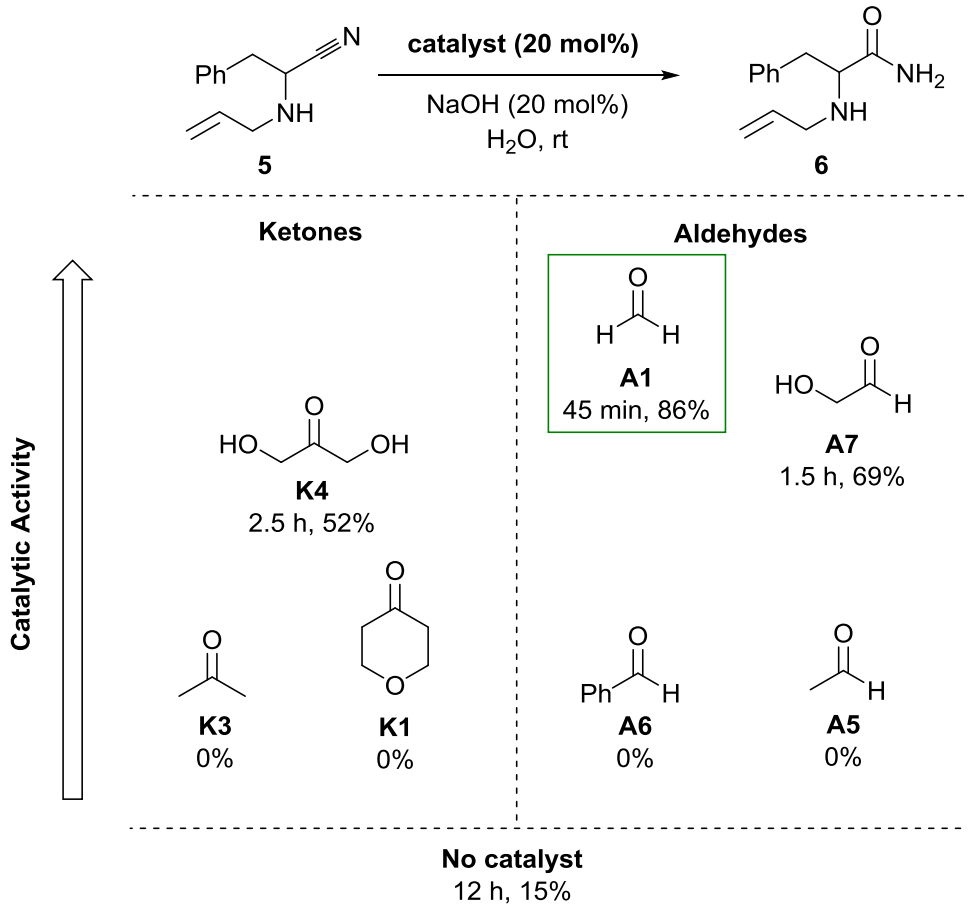
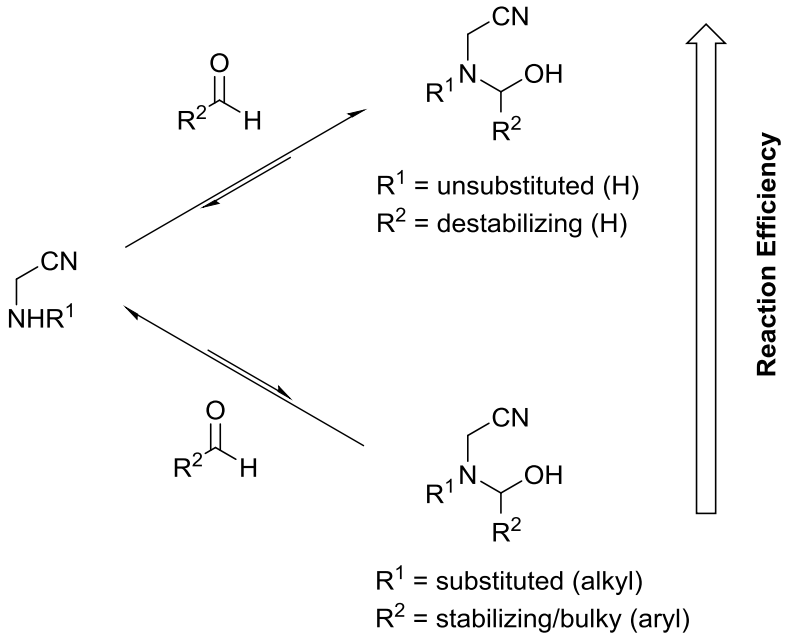


Figure 2.2: Screening for Aldehyde Catalysts Using a *N*-substituted α-Amino Nitrile

Similar to Figure 2.1, the inductively destabilized carbonyl catalysts (entries **K4** and **A7**) showed promising reactivity, with formaldehyde **A1** again demonstrating the highest catalytic activity. However, the remaining catalysts showed no activity, including THP and acetone which previously demonstrated excellent reactivity with the hydration of **1**. These findings support the

importance of the pre-association step that requires formation of the hemiaminal – an intermediate necessary for catalysts operating via temporary intramolecularity. The inductively destabilized aldehydes likely favour thermodynamically the formation of hemiaminals. Additionally, the use of substrates with sterically hindered *N*-substituents, of more stable/hindered carbonyl catalysts (e.g. ketones or conjugated aldehydes) will also disfavour this preassociation equilibrium in favour of the starting materials (Scheme 2.2). This working hypothesis is consistent with the catalyst reactivity trends observed in aldehyde-catalyzed hydroaminations.[59b]

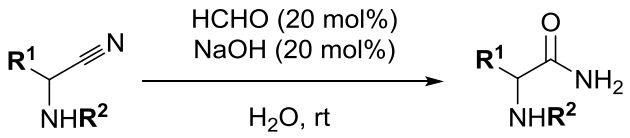


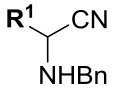
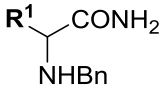
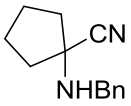
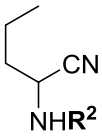
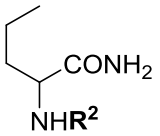
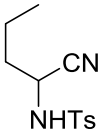
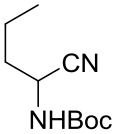
Scheme 2.2: General Structure-Activity Trends

To further probe the effect of *N*-substitution, various electron withdrawing and donating *N*-substituted α-amino nitriles were subjected to the optimized reaction conditions (Table 2.3). Gratifyingly, the *N*-benzyl protected α-amino nitrile **7a** was hydrated quantitatively

within 5 minutes. This exciting result warranted further investigation of *N*-benzyl derivatives. Unfortunately, several C2-substituted variants including **7b**, **7c**, and **7d** gave no amide product – only decomposition and a complex mixture was observed by NMR. Introducing organic solvents such as acetonitrile and dioxane to improve solubility of the heterogeneous mixture proved to not be fruitful. The fast decomposition of **7d** is consistent with results reported by Commeyras, who demonstrated that under basic conditions, α-amino nitriles that are doubly-substituted at the C2 position favour the decomposition pathway over the hydration pathway.[68b] *N*-Alkyl substituted derivatives such as *N*-propyl **7g**, *N*-allyl **7h**, and *N*-cyclopropyl **7i** gave the hydrated product in moderate to excellent yields, although the *N*-methyl substrate **7f** produced mostly decomposition products. The electron-withdrawing *N*-tosyl **7j** and *N*-Boc **7k** substrates performed poorly under the reaction conditions, presumably due to deactivation of the amine.

Table 2.3: Investigation of *N*-substituted α-Amino Nitriles



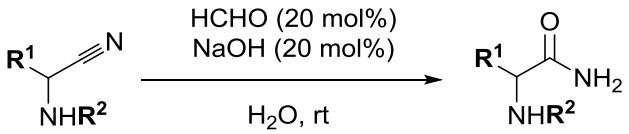
Entry	Substrate		Product	Time	Yield (%)[a]
					
1	R^1 = H	**7a**	**8a**	5 min	99
2	R^1 = isopropyl	**7b**	No product[b]	18 h	-
3	R^1 = Bn	**7c**	No product[b]	18 h	-
4		**7d**	No product[b]	18 h	-
					
5	R^2 = Bn	**7e**	No product[b]	16 h	-
6	R^2 = Me	**7f**	No product[b]	16 h	-
7	R^2 = propyl	**7g**	**8b**	30 min	55
8	R^2 = allyl	**7h**	**8c**	30 min	64
9	R^2 = cyclopropyl	**7i**	**8d**	1 h	85
10		**7j**	No product[b]	12 h	-
11		**7k**	No product[b]	12 h	-

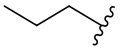
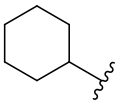
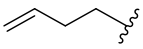
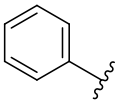
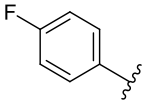
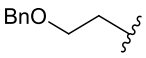
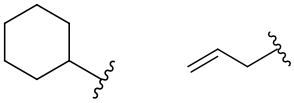
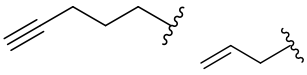
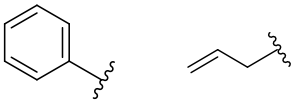
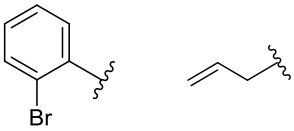
[a] Conditions: α-Amino nitrile (1 eq., 1.0 M) in H_2O. [b] Degregation of starting material after 8 h.

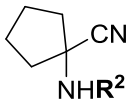
2.1.4 *Full substrate Scope*

The studies investigating the effects of nitrogen substitution of the α-amino nitrile revealed that the readily accessible *N*-allyl substituted α-amino nitriles were hydrated the most efficiently, giving the corresponding α-amino amide in short reaction times and high yields. Consequently, a more comprehensive substrate scope was compiled using both *N*-H and *N*-allyl substituted α-amino nitriles subjected to the optimized reaction conditions of 20 mol% of formaldehyde and NaOH in water at room temperature (Table 2.4). Gratifyingly, a diverse substrate scope was established beginning with Cα position substitution with alkyl substituents (entries 1-3). Longer reaction times were observed for more sterically encumbered substrates. Terminal alkenes were also well tolerated (entry 4), although subsequent isolation *via* column chromatography lead to decomposition, giving a low isolated yield. The hydration reaction also tolerated mono and di-substituted aryl groups (entries 5-6) and ethers (entry 7). The reaction scope was further probed with *N*-allyl protected α-amino nitriles by varying the Cα position substituent. The reaction also proved to be robust for alkyl substituents (entries 8-9), terminal alkynes (entry 10), and mono and di-substituted aryl groups (entries 11-12). The challenging reaction of the quaternary α-amino nitrile 1-(*N*-allylamino)cyclopentanecarboxamide proved to be successful, although higher catalyst loading was required to offset the degradation of the substrate. Overall, the *N*-allyl protected α-amino nitriles gave the corresponding amide product in higher yields, presumably due to low degradation of substrates under the reaction conditions and the simpler isolation procedure involved in these less polar substrates. Mechanistic studies are currently underway to validate this hypothesis.

Table 2.4: Complete Substrate Scope



Entry	R^1	R^2	Substrate	Product	Time	Yield (%)
1		H	**9a**	**10a**	10 min	64
2		H	**9b**	**10b**	1.5 h	74
3		H	**9c**	**10c**	4 h	68
4		H	**9d**	**10d**	5 min	23
5		H	**9e**	**10e**	2 h	62
6		H	**9f**	**10f**	20 min	78
7		H	**9g**	**10g**	15 min	61
8			**9h**	**10h**	30 min	80
9			**9i**	**10i**	15 min	80
10			**9j**	**10j**	30 min	79
11			**9k**	**10k**	15 min	81
12			**9l**	**10l**	2 h	78

13		**9m**	**10m**	15 min	77

2.1.5 *Additional Carbonyl Catalyst Scans – Implications in the Emergence of Life*

The remarkable efficiency with which formaldehyde catalyzes the hydration of α-amino nitriles through induced intramolecularity triggered our interest in exploring the role aldehydes may have played in the emergence of life. Indeed, the process of understanding the origins of the chemistry of life begins with consideration of the molecules that might have existed on prebiotic earth and the mechanism for assembly of these molecules into complex informational polymers capable of self-replication and transmittance of genetic information. Rudimentary molecules such as water, methane, ammonia, hydrogen, carbon dioxide and aldehydes (formaldehyde, glycoaldehyde, glyceraldehyde and other simple carbohydrates) were probably present on the primitive earth.7 The first indication of the involvement of some of these molecules in the processes resulting in the emergence of life was demonstrated in Miller's experiments, where amino acids were formed under prebiotic conditions.[77] A proposed pathway for the formation of these amino acids was through the hydration of α-amino nitriles through aldehyde catalysis.[78] Since sugars are believed to have been formed from formaldehyde on prebiotic earth in a process called the formose reaction,[79] we became interested in surveying carbohydrates and carbohydrate precursors as carbonyl catalysts under

[77] Miller, S.L. *J. Am. Chem. Soc.* **1955**, *77*, 2351.
[78] (a) Pascal, R.; Taillades, J.; Commeyras, A. *Tetrahedron* **1980**, *36*, 2999. (b) Taillades, J.; Beuzelin, I.; Garrel, L.; Tabacik, V.; Bied, C.; Commeyras, A. *Origins Life Evol. Biosphere* **1998**, *28*, 61.
[79] Boutlerow, A. *Annalen der Chemie*, **1861**, *120*, 295.

our optimized reaction conditions (Figure 2.3). Additionally, establishing that enantiopure carbohydrates could operate as asymmetric catalysts became a natural extension of this work.

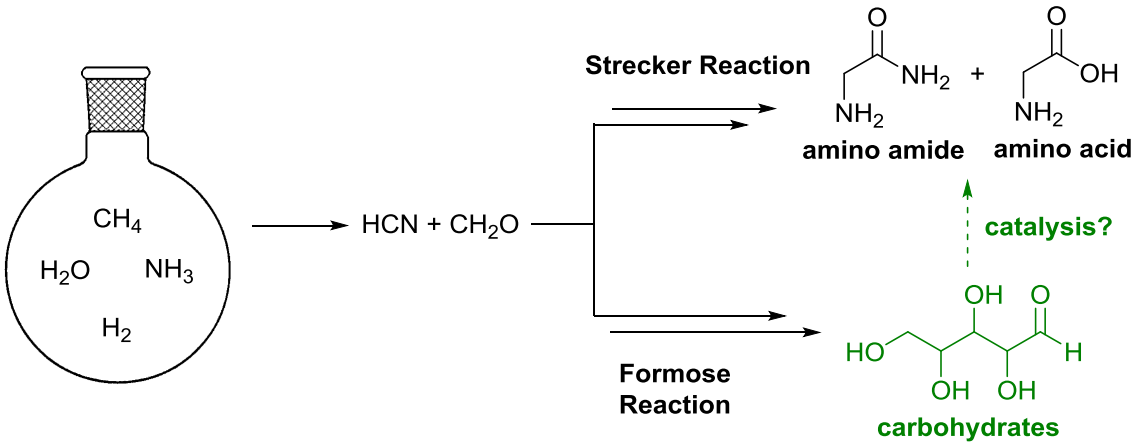


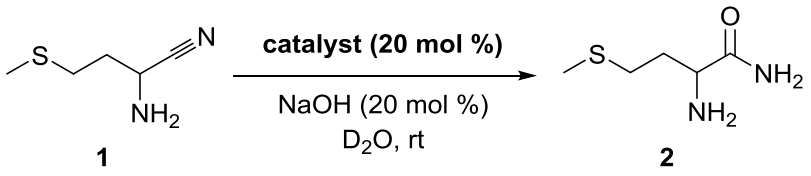
Figure 2.3: Proposed Carbohydrate-catalyzed Hydration of α-Amino Nitriles

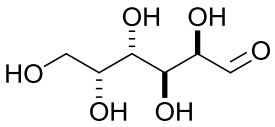
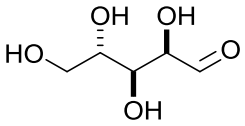
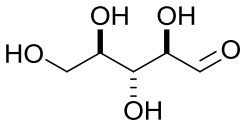
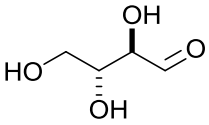
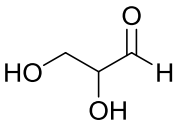
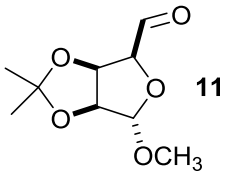
Several commercially available carbohydrate derivatives were surveyed for catalyst activity by subjecting **1** to the hydration conditions involving 20 mol% of NaOH (Table 2.1). Unfortunately, the hexose and pentose sugars (entries 1-2) produced no reactivity, although their presence inhibited the background conversion to amide product. Since the reactivity depends largely on the content of free aldehyde, it was proposed that D-(-)-ribose (entry 3) would generate some reactivity, as it contains a higher level of free aldehyde compared to other sugars.[80] Gratifyingly, very modest reactivity was observed. Several smaller sugars were explored including D-(-)-erythrose (entry 4) and DL-glyceraldehyde (entry 5), which showed the highest catalytic activity, comparable to formaldehyde. Drawing inspiration from the

[80] Dworkin, J. P.; Miller, S. L. *Carbohydrate Res.* **2000**,*329*, 359.

Beauchemin aldehyde-catalyzed hydroaminations,[81] the bicyclic aldehyde (entry 6) also showed impressive reactivity. Although ee was not measured, these results support the hypothesis that carbohydrates may have played a role in the emergence of amino amides and acids in primordial earth.

Table 2.5: Carbohydrate Scan for Hydration of α-Amino Nitriles



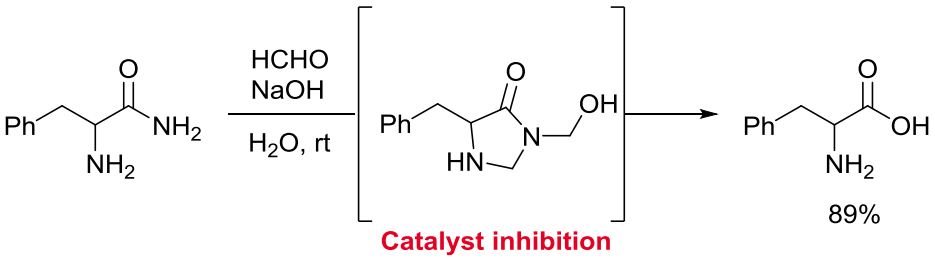
Entry	Catalyst	Time	NMR Yield (%)
1		3 h	0
2		3 h	0
3		3 h	29
4		30 min	70[a]
5		2 h	65
6	 **11**	1 h	99[b]

[a] 1 equiv. of catalyst used. [b] Calculated as percentage conversion of substrate.

[81] Beauchemin, A. M. *Org. Biomol. Chem.* **2013**,

2.1.6 *Towards Accessing α-Amino Acids and β-Amino Amides and Acids*

Efforts towards extending this approach to accessing α-amino acids were undertaken by Dr. Chitale and the preliminary results have been promising. By subjecting α-amino amides to the optimized reaction conditions for nitrile hydration, the corresponding α-amino acid was obtained in good yields and short reaction times (Scheme 2.3). Improved yields were observed when higher catalyst loading and excess base were introduced, presumably due to competing formation of an imidazolidinone intermediate acting as a source of catalyst inhibition at lower loadings.[82]

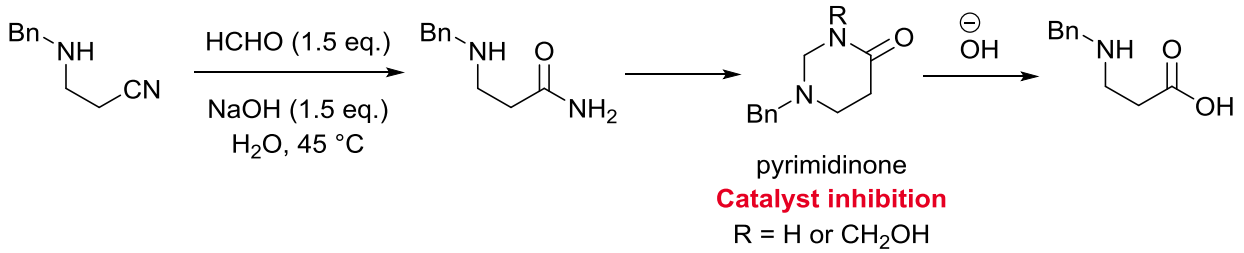


Scheme 2.3: Towards Accessing α-Amino Acids

Furthermore, our approach has been extended towards accessing β-amino amides and acids, important structural motifs in medicinal chemistry.[83] Lead by Kashif Tanveer, the carbonyl-catalyzed hydration procedure was applied to β-amino nitriles to give the corresponding β-amino amide and acid (Scheme 2.4). Similiar to the catalyst inhibition observed in amide hydration, a pyrimidinone intermediate was identified as an off-cycle pathway leading to unproductive by-products. By introducing larger catalyst loading and base,

[82] Pascal, R.; Lasperas, M.; Taillades, J.; Perez-Rubalcaba, A.; Commeyras, A. *Bull. Soc. Chim. Fr.* **1984**, 329.
[83] Grayson, J. I.; Roos, J.; Osswald, S. *Org. Process Res. Dev.* **2011**, *15*, 1201.

as well as heat to the reaction mixture, the acid product was formed faster with significantly improved yields.



Scheme 2.4: Towards Accessing β-Amino Amides and Acids

2.2 Conclusion and Outlook

In summary, an organocatalytic tethering strategy has been developed and applied to the hydration of α-amino nitriles to their corresponding α-amino amide under mild conditions. By exploiting the reversible covalent bond formation of amines with aldehydes, significant accelerations of reaction rates were achieved through temporary intramolecularity. Using sub-stoichiometric amounts of base and a carbonyl catalyst at room temperature, this transformation proved to be particularly robust with destabilized aldehydes such as formaldehyde. A wide substrate scope was established, including excellent reactivity with unsubstituted α-aminonitriles and more challenging *N*-substituted α-aminonitriles. This approach has been extended towards accessing α-amino acids, β-amino amides and acids, with encouraging preliminary results. The highlight of this work includes the discovery of a mild and efficient alternative route to accessing structurally important chemical motifs that otherwise require harsh reaction conditions. The next steps in this work involve establishing a broader

substrate scope, improving catalytic reactivity, and exploring stereoselective variants of this reaction that may be possible with chiral aldehydes.

Chapter 3. **Supporting Information**

3.1 General Methods

^{1}H and ^{13}C spectra were recorded in $CDCl_3$, D_2O or DMSO-d_6 solutions on a Bruker AVANCE 300 MHz or a Bruker AVANCE 400 MHz. The chemical shifts are reported in parts per million (ppm) relative to the corresponding protio-solvent signal. High resolution mass spectra were obtained by EI on a Kratos Concept IIH. Infrared analysis was performed on an ABB Bomem Arid-Zone and the spectra were obtained as neat films on a sodium chloride window. Column chromatography was performed using silica gel, 40 microns flash silica. Thin layer chromatography was performed on silica gel (Silica Gel 60 F254) glass plates/aluminium back plates and the compounds were visualized by UV, 0.5% $KMnO_4$ in 0.1 M aqueous NaOH solution and/or 5% ninhydrin in EtOH. Unless otherwise noted, all reagents were used as is from commercial sources and all other compounds have been reported in the literature or are commercially available.

Full experimental procedures and characterization data of compounds **7b, 7c, 7d, 7e, 7f, 7g, 7h, 7i, 7j, 7k, 8b, 8c,** and **8d** are available.[84] Catalyst **11** was prepared according to the procedure of Beauchemin.[59a]

3.2 Carbonyl Catalyst Screening

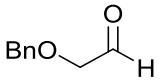
General procedure for catalyst screening with unprotected α-aminonitriles:

2-Amino-4-methylthiobutyronitrile (0.500 mmol, 65.1 mg) was taken up in D_2O and NaOH (5 M in H_2O, 20.0 µL) was added followed by the catalyst. The mixture was allowed to stir for desired time at room temperature. The reaction mixture was then quenched with a 1:1 D_2O:DMSO mixture and 1,3,5-trimethoxybenzene (0.167 mmol, 28.0 mg) was added. ^{1}H NMR was taken and the yield was calculated using the 1,3,5-trimethoxybenzene as an internal standard.

General procedure for catalyst screening with N-allyl-α-aminonitriles:

2-(Allylamino)-3-phenylpropanenitrile (0.390 mmol, 54.0 mg) was taken up in H_2O and NaOH (5 M in H_2O, 16 µL) was added followed by the catalyst. The mixture was allowed to stir for desired time at room temperature under argon. The reaction mixture was then diluted with EtOAc (5 mL) and H_2O (1 mL). Aqueous and organic layers were separated. Aqueous layer was extracted with EtOAc (4 X 5 mL). Combined organic layer was dried and concentrated. The crude was weighed and 1,3,5-trimethoxybenzene (0.100 mmol, 17.0 mg) was added. The resulting mixture was then dissolved in $CDCl_3$. ^{1}H NMR was taken and the yield was calculated using the 1,3,5-trimethoxybenzene as an internal standard.

[84] Chitale and Beauchemin unpublished results.



2-(Benzyloxy)acetaldehyde (6). Prepared from 1,4-bis(benzyloxy)but-2-ene[85] according to a modified procedure of Hiersemann.[86] Through a solution of alkene (15.0 mmol, 4.02 g) in CH_2Cl_2 (50 mL) at -78 °C was bubbled a stream of ozone until the colourless solution became blue. Nitrogen was bubbled to remove excess ozone, and then triphenyl phosphine (18.0 mmol, 4.72 g) was added at -78 °C. The reaction was allowed to warm to room temperature and stirred for 2 h. The solution was concentrated under reduced pressure to remove volatiles and then distilled under reduced pressure to afford the product as a colourless liquid (3.35 g, 93%). Spectral data was consistent with literature.

3.3 Synthesis of α-aminonitriles

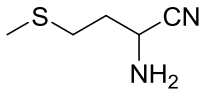
General procedure for the synthesis of α-aminonitriles (A):

α-Aminonitriles were synthesized by subjecting the corresponding aldehyde or ketone to Strecker conditions according to the procedure by Garst.[87]

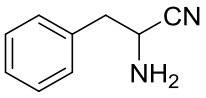
General procedure for the synthesis of α-aminonitriles (B):

α-Aminonitriles were also synthesized by subjecting the corresponding aldehyde or ketone to Strecker conditions according to a modified procedure by Xenon Pharmaceuticals Incorporated.[88] To a stirred solution of NaCN (1 eq.) in water (5.0 M) was added NH_4Cl (1.1 eq.). When all NH_4Cl was dissolved, a solution of aldehyde (1 eq.) in MeOH (5.0 M) was added. The resulting reaction mixture was stirred for 3 h and then quenched with water. The aqueous phase was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated to give the crude product. The crude residue was purified by flash column chromatography on silica gel if necessary (see below for specific eluent composition) to afford the α-aminonitrile.

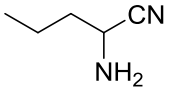
[85] Dunn, T. B. PhD. Thesis, Harvard University, June 2005.
[86] Pollex, A.; Millet, A.; Müller, J.; Hiersemann, M.; Abraham, L. *J. Org. Chem.* **2005**, *70*, 5579.
[87] Garst, M. E.; Dolby, L. J.; Esfandiari, S.; Avey, J.; Arthur, A. Method of making imidazole-2-thiones. U.S. Patent 7,115,748, Oct 3, 2006.
[88] Kamboj, R.; Zhang, Z.; Fu, J.; Kodumuru, V.; Sviridov, S.; Sadalapure, K.; Liu, S.; Sun, S.; Hou, D. Heterocyclic Derivatives and Their Use as Therapeutic Agents. U.S. Patent WO 2006/034440 A2, Mar 3, 2006.



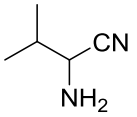
2-amino-4-methylthiobutyronitrile (1). The reaction was carried out following general procedure A using 85.0 mmol (1 eq.) of the aldehyde, 93.5 mmol (1.1 eq.) of KCN, and 102 mmol (1.2 eq.) of NH_4Cl to afford 4.00 g (36 %) of the desired compound. Spectral data was consistent with literature.**Error! Bookmark not defined.**
^{1}H NMR (400 MHz, D_2O) δ 3.99 (t, *J*=7.2 Hz, 1 H) 2.74-2.59 (m, 2 H) 2.10 (s, 3 H) 2.08-1.98 (m, 2 H)



2-amino-3-phenylpropionitrile (3). The reaction was carried out following general procedure A using 85.0 mmol (1 eq.) of the aldehyde, 93.5 mmol (1.1 eq.) of KCN, and 102 mmol (1.2 eq.) of NH_4Cl to afford 4.54 g (37 %) of the desired compound. Spectral data was consistent with literature.[87]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5 H) 3.92 (t, *J*=6.5 Hz, 1 H) 3.01 (dd, *J*=6.5, 1.6 Hz, 2 H) 1.63 (br. s., 2 H)



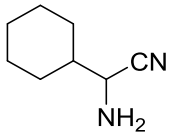
2-amino-2-pentanenitrile (9a). The reaction was carried out following general procedure B using butyraldehyde (56.0 mmol, 4.00 g). The residue was purified by column chromatography using (1% NH_4OH/50% petroleum ether/EtOAc) to afford an orange oil (2.10 g, 38 %). Spectral data was consistent with literature.[88]
^{1}H NMR (300 MHz, D_2O) δ 3.86 (t, *J*=7.1 Hz, 1 H) 1.77-1.69 (m, 2 H) 1.52-1.43 (m, 2 H) 1.13 (br m., 2 H) 0.95 (t, *J*=7.3 Hz, 3 H)



2-amino-3-methyl-butyronitrile (9b). The reaction was carried out following general procedure A using 85.0 mmol (1 eq.) of the aldehyde, 93.5 mmol (1.1 eq.) of KCN, and 102 mmol (1.2 eq.) of NH_4Cl to afford 4.01 g (48 %) of the desired compound. Spectral data was consistent with literature.[89]

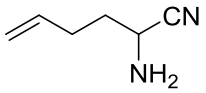
[89] Mclaughlin, M.; Mohareb, R.M.; Rapoport, H. *J. Org. Chem*. **2003**, *61*, 50.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.50 (d, *J*=5.6 Hz, 1 H) 1.98-1.82 (m, 1 H) 1.05 (d, *J*=2.5 Hz, 3 H) 1.03 (d, *J*=2.5 Hz, 3 H)



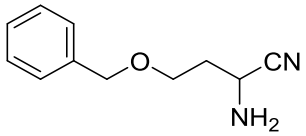
2-amino-2-cyclohexylacetonitrile (9c). The reaction was carried out following general procedure A using 25.0 mmol (1 eq.) of the aldehyde, 27.5 mmol (1.1 eq.) of KCN, and 30.0 mmol (1.2 eq.) of NH_4Cl to afford 0.420 g (12 %) of the desired compound. Spectral data was consistent with literature.[90]

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.53 (d, *J*=5.9 Hz, 1 H) 1.96-1.78 (m, 6 H) 1.71 (s, 1 H) 1.67-1.54 (m, 1 H) 1.36-1.07 (m, 5 H)



2-aminohex-5-enenitrile (9d). The reaction was carried out following general procedure B using 4-penten-1-al (11.9 mmol, 1.00 g). The residue was purified by column chromatography using 50% EtOAc/petroleum ether to afford a clear oil (726 mg, 55 %). Spectral data was consistent with literature.[91]

^{1}H NMR (300 MHz, D_2O) δ 5.87 (ddt, *J*=17.1, 10.4, 6.7, 6.7 Hz, 1 H) 5.18-5.03 (m, 2 H) 3.85 (t, *J*=7.2 Hz, 1 H) 2.34-2.12 (m, 2 H) 1.92-1.78 (m, 2 H)



2-amino-4-(benzyloxy)butanenitrile (9g). To a 50 mL round bottom flask containing 5.5 mL of NH_4OH was added NaCN (13.6 mmol, 0.667 g) and NH_4Cl (16.3 mmol, 0.874 g). The resulting solution was stirred until the contents had completely dissolved. Next, 3-benzyloxypropanal was added drop-wise to the reaction mixture over 30 minutes. The mixture was stirred for 16 hours and then washed with CH_2Cl_2 (20 mL x 3). The combined organic fractions were then washed with saturated NaCl, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide 1.86 g (90 %) of the product as a clear yellow oil.

TLC R_f 0.57 (1% NH_4OH/5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.28 (m, 5 H) 4.54 (s, 2 H) 3.97 (t, *J*=6.9 Hz, 1 H) 3.79-3.71 (m, 1 H) 3.71-3.63 (m, 1 H) 2.04 (m, 2 H) 1.75 (br. s., 1 H)

---

[90] Schafer, I.; Opatz, T. *Synthesis*. **2011**, 1691.

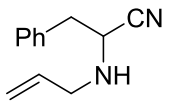
[91] Roscini, C.; Cubbage, K. L.; Orr-Ewing, A. J.; Booker-Milburn, K. I.; Berry, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8716.

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 128.3, 127.6, 127.5, 121.8, 73.0, 65.8, 40.9, 34.9
IR (film): 3393, 3321, 3097, 3063, 3023, 2960, 2937, 2869, 2801, 2226.6, 1603, 1497, 1451, 1360 cm^{-1}
HRMS (ESI): Exact mass calcd for $C_{11}H_{14}N_2O$ $[M-H]^+$: 189.1028. Found: 188.9653.

3.4 Synthesis of N-allyl-α-aminonitriles

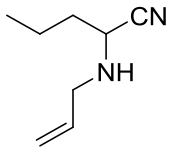
General procedure for the synthesis of N-allyl-α-aminonitriles (C):

N-allyl-α-aminonitriles were synthesized by subjecting the corresponding aldehyde or ketone to Strecker conditions according to a modified procedure by Giacomini.[92] Aldehyde (1.00 mmol) and amine (1.00 mmol) was taken up in H_2O (5.0 mL). This was stirred vigorously for 10 min at rt. After 10 min, additional H_2O (4.0 mL) was added followed by acetonecyanohydrin (1.00 mmol). The reaction mixture was stirred at rt for 8-10 h. After completion, as indicated by TLC (85% petroleum ether/EtOAc), the reaction mixture was diluted with EtOAc (10 mL). The aqueous and organic layers were separated and the aqueous layer was extracted with EtOAc (15 mL x 4). The combined organic layer was dried and concentrated. The crude was purified using flash column chromatography (petroleum ether/EtOAc).



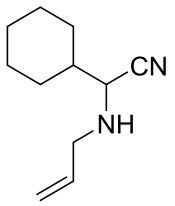
2-(Allylamino)-3-phenylpropanenitrile (5). Synthesized according to the procedure of Sajitz.[93] NaCN was dissolved in H_2O (26 mL). Allylamine (3.00 g, 52.5 mmol) was then added and the reaction mixture was stirred for 5-10 min at rt. Phenylacetaldehyde (6.30 g, 52.5 mmol) dissolved in MeOH (26 mL) was then added drop-wise to the reaction mixture. The resulting mixture was stirred at rt for 12 h. After completion of the reaction, as indicated by TLC (85% petroleum ether/EtOAc), the reaction mixture was diluted with EtOAc (30 mL) and H_2O (10 mL). The aqueous and organic layers were separated. The aqueous layer was extracted with EtOAc (25 mL X 4). The combined organic layer was dried and concentrated to give an orange-red oil as a crude. Purification by column chromatography on silica gel (85% petroleum ether/EtOAc to 80% petroleum ether/EtOAc) afforded the desired product as a pale orange oil (3.98 g, 40%). Spectral data was consistent with literature.93
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.27 (m, 5 H) 5.83 (dddd, *J*=17.0, 10.2, 6.6, 5.5 Hz, 1 H) 5.25 (dddd, *J*=17.2, 1.6, 1.6, 1.6 Hz, 1 H) 5.16 (dddd, *J*=10.2, 1.4, 1.4, 1.4 Hz, 1 H) 3.79 (dd, *J*=7.3, 5.6 Hz, 1 H) 3.53 (ddd, *J*=5.5, 1.5, 1.5 Hz, 1 H) 3.28 (ddd, *J*=6.6, 1.3, 1.3 Hz, 1 H) 3.13-2.98 (m, 2 H) 1.38 (br. s., 1H)

[92] Galletti, P.; Pori, M.; Giacomini, D. *Eur. J. Org. Chem.* **2011**, *2011*, 3896.
[93] Schafer, L.; Lee, A.; Sajitz, M. *Synthesis* **2008**, *2009*, 97.



2-(Allylamino)pentanenitrile (9h). The reaction was carried out following general procedure C. Purification by column chromatography on silica gel (85% petroleum ether/EtOAc to 80% petroleum ether/EtOAc) afforded the desired product as a clear oil (60%). Spectral data was consistent with literature.[94]

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (m, 1 H) 5.25 (m, 1 H) 5.15 (m, 1 H) 3.55-3.47 (m, 2 H) 3.27 (m, 1 H) 1.77-1.69 (m, 2 H) 1.61-1.43 (m, 2 H) 1.39 (br s, 1 H) 0.95 (t, *J*=7.3 Hz, 3 H)



2-(Allylamino)-2-cyclohexylacetonitrile (9i). The reaction was carried out following general procedure C. Purification by column chromatography on silica gel (85% petroleum ether/EtOAc to 80% petroleum ether/EtOAc) afforded the desired product as a colourless oil (60%).

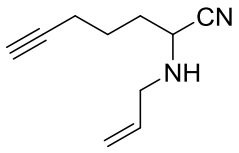
TLC R_f 0.25 (85% petroleum ether/EtOAc)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (m, 1 H) 5.25 (dddd, *J*=17.2, 1.5, 1.5, 1.5 Hz, 1 H) 5.14 (dddd, *J*=10.2, 1.2, 1.2, 1.2 Hz, 1 H) 3.50 (dddd, *J*=13.7, 2.7, 1.4, 1.4 Hz, 1 H) 3.33 (d, *J*=6.1 Hz, 1 H) 3.25 (dddd, *J*=13.7, 2.2, 1.1, 1.1 Hz, 1 H) 1.85-1.75 (m, 3 H + NH) 1.69-1.60 (m, 2 H) 1.32-1.06 (m, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 135.0, 119.5, 117.4, 55.5, 50.4, 40.7, 29.7, 28.7, 26.0, 25.7, 25.6

IR (film): 2930, 2854, 2224, 1451, 1097 cm^{-1}

HRMS (EI): Exact mass calcd for $C_{11}H_{18}N_2$ $[M]^+$: 178.1470. Found: 178.1376.



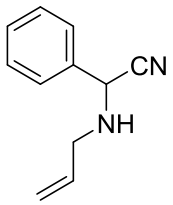
2-(Allylamino)hept-6-ylonitrile (9j). The reaction was carried out following general procedure C. Purification by column chromatography on silica gel (85% petroleum ether/EtOAc to 80% petroleum ether/EtOAc) afforded the desired product as a colorless oil (42%).

TLC R_f 0.25 (85% petroleum ether/EtOAc)

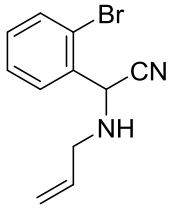
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (m, 1 H) 5.26 (dddd, *J*=17.1, 1.6, 1.6, 1.6 Hz, 1H) 5.15 (dddd, *J*=10.2, 1.3, 1.3, 1.3 Hz, 1 H) 3.56 (t, *J*=7.0 Hz, 1 H) 3.51 (dddd, *J*=13.7, 3.0, 1.5, 1.5 Hz, 1 H) 3.28

[94] Galletti, P.; Pori, M.; Giacomini, D. *Eur. J. Org. Chem.* **2011**, *2011*, 3896.

(dddd, *J*=13.7, 2.6, 1.3, 1.3 Hz, 1 H) 2.28-2.22 (m, 2 H) 1.97 (t, *J*=2.6 Hz, 1 H) 1.93-1.85 (m, 2 H) 1.77-1.67 (m, 2 H) 1.31 (br. s., 1 H)
^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 119.9, 117.6, 83.0, 69.3, 50.1, 49.2, 32.3, 24.3, 17.8
IR (film): 3081, 2936, 2871, 2228, 1110 cm^{-1}
HRMS (ESI): Exact mass calcd for $C_{10}H_{13}N_2$ $[M-H]^+$: 161.1079. Found: 161.1102.

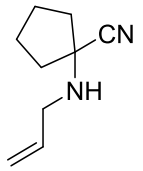


2-(Allylamino)-2-phenylacetonitrile (9k). The reaction was carried out following general procedure C. Purification by column chromatography on silica gel (85% petroleum ether/EtOAc to 80% petroleum ether/EtOAc) afforded the desired product as a pale yellow oil (1.21 g, 75%). Spectral data was consistent with literature.[95]
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.52 (m, 2 H) 7.45-7.37 (m, 3 H) 5.90 (dddd, *J*=17.0, 10.2, 6.5, 5.6 Hz, 1 H) 5.32 (dddd, *J*=17.2, 1.6, 1.6, 1.6 Hz, 1 H) 5.21 (dddd, *J*=10.2, 1.3, 1.3, 1.3 Hz, 1 H) 4.80 (s, 1 H) 3.56-3.38 (m, 2 H) 1.64 (br. s., 1H)



2-(Allylamino)-2-(2'-bromophenyl)acetonitrile (9l). The reaction was carried out following general procedure C. Purification by column chromatography on silica gel (85% petroleum ether/EtOAc to 80% petroleum ether/EtOAc) afforded the desired product as a pale yellow oil (2.35 g, 63%).
TLC R_f 0.25 (85% petroleum ether/EtOAc)
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (td, *J*=7.8, 7.8, 1.3 Hz, 2 H) 7.39 (ddd, *J*=7.6, 1.3, 1.3 Hz, 1 H) 7.26 (ddd, *J*=7.6, 1.7, 1.7 Hz, 1 H) 5.91 (dddd, *J*=17.0, 10.2, 6.7, 5.6 Hz, 1 H) 5.33 (dddd, *J*=17.1, 1.5, 1.5, 1.5 Hz, 1 H) 5.21 (dddd, *J*=10.2, 1.2, 1.2, 1.2 Hz, 1 H) 5.08 (s, 1 H) 3.54 (m, 1 H) 3.43 (m, 1 H) 1.79 (br. s., 1 H)
^{13}C NMR (75 MHz, $CDCl_3$) δ 134.4, 134.1, 133.4, 130.6, 129.0, 128.0, 123.2, 118.2, 118.1, 53.0, 50.1
IR (film): 3326, 3074, 2839, 2228, 1194 cm^{-1}
HRMS (EI): Exact mass calcd for $C_{11}H_{10}N_2Br$ $[M-H]^+$: 250.1145. Found: 250.0090.

[95] Blacker, J.; Clutterbuck, L. A.; Crampton, M. R.; Grosjean, C.; North, M. *Tetrahedron: Asymmetry* **2006**, *17*, 1449.

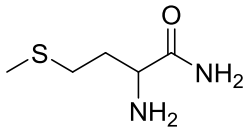


1-(Allylamino)-1-cyclopentanecarbonitrile (9m). The reaction was carried out following general procedure C. Purification by column chromatography on silica gel (85% petroleum ether/EtOAc to 80% petroleum ether/EtOAc) afforded the desired product as a colorless oil (48%).
TLC R_f 0.25 (85% petroleum ether/EtOAc)
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (m, 1 H) 5.15 (dddd, *J*=17.1, 1.5, 1.5, 1.5 Hz, 1 H) 5.02 (dddd, *J*=10.2, 1.4, 1.4, 1.4 Hz, 1 H) 3.26-3.24 (m, 2 H) 2.06-1.96 (m, 2 H) 1.76-1.68 (m, 6 H) 1.42 (br. s., 1H)
^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 122.7, 116.3, 60.9, 48.3, 38.8, 23.4
IR (film): 3321, 2971, 2221, 1206 cm^{-1}
HRMS (ESI): Exact mass calcd for $C_9H_{13}N_2$ $[M-H]^+$: 149.1079. Found: 149.1072.

3.5 Synthesis of α-aminoamides via formaldehyde-catalyzed hydration of α-aminonitriles

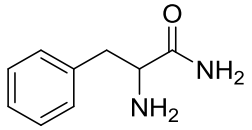
General procedure for formaldehyde catalyzed hydration of α-aminonitriles (D):

To a solution of α-aminonitrile (1 eq.) in H_2O (1.0 M) at rt was added NaOH (5 M, 0.2 eq.) and formalin (37% in H_2O, 0.2 eq.). The reaction was allowed to stir until completion (5 min – 4 h). The reaction was diluted with EtOAc and brine and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were dried, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel if necessary (see below for specific eluent composition) to afford the α-aminoamide.

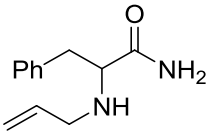


Methionine amide (2). The reaction was carried out following general procedure D using 2-amino-4-methylthiobutyronitrile (1.00 mmol, 130 mg). After the reaction was complete, the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography (dry pack) using 1% NH_4OH/10% MeOH/CH_2Cl_2 to afford an off-white solid (82.4 mg, 70%).
TLC R_f 0.19 (1% NH_4OH/10% MeOH/CH_2Cl_2)
^{1}H NMR (400 MHz, D_2O) δ 3.50 (dd, *J*=7.3, 6.0 Hz, 1 H) 2.56 (t, *J*=7.5 Hz, 2 H) 2.09 (s, 2 H) 1.96-1.88 (m, 1 H) 1.86-1.81 (m, 1 H)

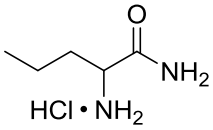
^{13}C NMR (100 MHz, D_2O) δ 180.0, 53.3, 33.4, 29.2, 14.0
IR (film): 3325, 3160, 1650, 1438 cm^{-1}
HRMS (ESI): Exact mass calcd for $C_5H_{12}N_2OS$ $[M+H]^+$: 149.0749. Found: 149.0800.
Melting Point: Consistent with literature.[96]



Phenylalanine amide (4). The reaction was carried out following general procedure D using 2-amino-3-phenylpropionitrile (1.00 mmol, 146 mg). The residue was purified by column chromatography using 1% NH_4OH/10% MeOH/CH_2Cl_2 to afford a white solid (95.0 mg, 65%). Spectral data was consistent with literature.[97]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.19 (m, 5 H) 3.63 (dd, *J*=9.5, 4.0 Hz, 1 H) 3.28 (dd, *J*=13.6, 4.0 Hz, 1 H) 2.73 (dd, *J*=13.7, 9.4 Hz, 1 H)



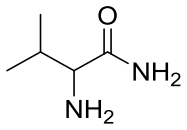
***N*-Allyl-phenylalanine amide (6).** The reaction was carried out following general procedure D using 2-(Allylamino)-3-phenylpropanenitrile (1.00 mmol, 186 mg). The residue was purified by column chromatography using 95% EtOAc/MeOH to afford a white solid (175 mg, 86%).
TLC R_f 0.25 (95% EtOAc/MeOH)
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.19 (m, 5H) 7.07 (br s, 1H) 5.91 (br s, 1H) 5.65 (m, 1H) 5.02 (dddd, *J*=7.6, 3.1, 1.5, 1.5 Hz, 1H) 4.98 (m, 1H) 3.34 (dd, *J*=9.5, 4.3 Hz, 1H) 3.22-3.13 (m, 2H) 3.01 (m, 1H) 2.74 (dd, *J*=13.8, 9.5 Hz, 1H) 1.64 (br s, 1H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 137.7, 136.0, 129.5, 129.2, 127.3, 116.7, 63.4, 51.2, 39.6
IR (film): 3322, 3074, 2858, 1651, 1093 cm^{-1}
HRMS (EI): Exact mass calcd for $C_{10}H_{16}N_2O$ $[M]^+$: 204.1257. Found: 204.1249.
Melting Point: 76-78 ^oC



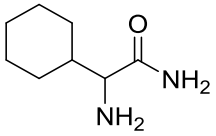
2-aminopentanamide hydrochloride salt (10a). The reaction was carried out following general procedure D using 2-amino-2-pentanenitrile (1.00 mmol, 98.1 mg). The reaction mixture was acidified with 1N HCl until pH = 1 was achieved. The aqueous layer was then washed with

[96] Jones, R.G. *J. Am. Chem. Soc.* **1949**, *71*, 78.
[97] Taillades, J.; Boussac, P.; Collet, H.; Brugidou, J.; Commeyras, A. *Bull Soc Chim Fr*. **1991**, *3*, 423.

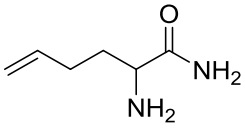
EtOAc (3 X 10 mL). The aqueous layer was then filtered through DOWEX-50 WX8 and concentrated to give a pale yellow solid (64%). Spectral data was consistent with literature.[98]
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (t, *J*=6.4 Hz, 1H) 1.90-1.82 (m, 2H) 1.48-1.35 (m, 2H) 0.95 (t, *J* = 7.2 Hz, 3H)



Valine amide (10b). The reaction was carried out following general procedure D using 2-amino-3-methyl-butyronitrile (1.00 mmol, 98.1 mg). The product obtained was a clear oil (86.2 mg, 74%).
TLC R_f 0.24 (1% NH_4OH/10% MeOH/CH_2Cl_2)
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (br. s., 1 H) 5.85 (br. s., 1 H) 3.24 (br. s., 1 H) 2.26 (td, *J*=6.9, 3.5 Hz, 1 H) 1.71 (br. s., 2 H) 1.00 (d, *J*=7.0 Hz, 3 H) 0.87 (d, *J* = 6.9 Hz, 3 H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 60.2, 30.8, 19.6, 16.1
IR (film): 3344, 3188, 2963, 2933, 2876, 1671, 1466, 1386 cm^{-1}
HRMS (ESI): Exact mass calcd for $C_5H_{12}N_2O$ $[M-H]^+$: 115.0871. Found: 115.0900.



Cyclohexylglycine amide (10c). The reaction was carried out following general procedure D using 2-amino-2-cyclohexylacetonitrile (0.520 mmol, 71.8 mg). The product obtained was a clear oil (38.2 mg, 47%).
TLC R_f 0.23 (1% NH_4OH/5% MeOH/CH_2Cl_2)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (br. s., 1 H) 6.01 (br. s., 1 H) 3.22 (d, *J*=4.1 Hz, 1 H) 1.88-1.71 (m, 3 H) 1.70-1.53 (m, 5 H) 1.33-1.19 (m, 2 H) 1.18-1.02 (m, 3 H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 60.1, 41.1, 30.2, 26.7, 26.3, 26.2, 26.1
IR (film): 3321, 3156, 2923, 2850, 1699, 1667, 1582 cm^{-1}
HRMS (ESI): Exact mass calcd for $C_8H_{16}N_2O$ $[M-H]^+$: 155.1184. Found: 155.0737.

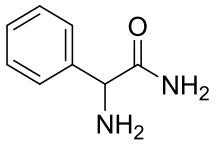


2-Amino-5-hexenoic acid amide (10d). The reaction was carried out following general procedure D using 2-aminohex-5-enenitrile (1.00 mmol, 110 mg). The residue was purified by

[98] Lee, Y. B.; Goo, Y. M.; Lee, Y. Y.; Lee, J. K. *Tetrahedron Lett.* **1989**, *30*, 7439.

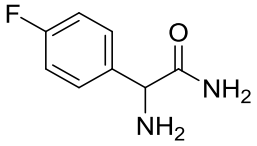
column chromatography using 10% MeOH/CH_2Cl_2 to afford a clear oil (30.1 mg, 23%). Spectral data was consistent with literature.[99]

^{1}H NMR (300 MHz, D_2O) δ 5.87 (ddt, *J*=17.1, 10.3, 6.6, 6.6 Hz, 1 H) 5.13-5.00 (m, 2 H) 3.41 (t, *J*=6.7 Hz, 1 H) 2.19-2.06 (m, 2 H) 1.83-1.58 (m, 2 H)



Phenylglycine amide (10e). The reaction was carried out following general procedure D using commercially available 2-amino-2-phenylacetonitrile hydrochloride (1.00 mmol, 169 mg) and an additional equivalent of NaOH (5M, 1.20 mmol, 0.240 mL) to neutralize the hydrochloride salt *in situ*. The residue was purified by column chromatography using 1% NH_4OH/10% MeOH/CH_2Cl_2 to afford a clear oil (93.2 mg, 62%). Spectral data was consistent with literature.[100]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.50-7.27 (m, 5 H) 4.54 (s, 1 H)



Fluoro-phenylglycine amide (10f). The reaction was carried out following general procedure D using 2-amino-2-(4-fluorophenyl)-acetonitrile (1.00 mmol, 150 mg). The residue was purified by column chromatography using 1% NH_4OH/10% MeOH/CH_2Cl_2 to afford a white solid (118 mg, 70%).

TLC R_f 0.18 (1% NH_4OH/10% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, D_2O) δ 7.42-7.35 (m, 2 H) 7.16-7.09 (m, 2 H) 4.55 (s, 1 H)

^{13}C NMR (100 MHz, D_2O) δ 178.5, 162.3 (d, *J*=244.6 Hz), 135.8, 128.7 (d, *J*=8.8 Hz), 115.7 (d, *J*=22.1 Hz), 57.7

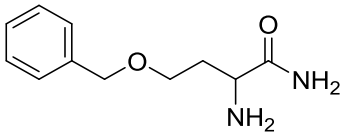
IR (film): 3300, 3179, 1684, 1670, 1602, 1501, 1404, 1217, 1156, 1092, 829, 560 cm^{-1}

HRMS (ESI): Exact mass calcd for $C_8H_{10}FN_2O$ $[M+H]^+$: 169.0777. Found: 169.0900.

Melting Point: 120-121 °C

[99] Blaauw, R.; Kingma, I. E.; Laan, J. H.; van der Baan, J. L.; Balt, S.; de Bolster, M. W. G.; Klumpp, G. W.; Smeets, W. J. J.; Spek, A. L. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1199.

[100] Lin, J.; Dasgupta, D.; Debarshi, C.; Seda, S.; Albertus, P. H. J. *Beilstein J. Org. Chem*. **2010**, *6*, 960.



2-amino-4-(benzyloxy)butanamide (10g). The reaction was carried out following general procedure D using 2-amino-4-(benzyloxy)butanenitrile (1.50 mmol, 285 mg). The residue was purified by column chromatography using 5% NH_4OH/10% MeOH/CH_2Cl_2 to afford a yellow oil (190 mg, 61%).

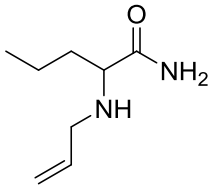
TLC R_f 0.25 (1% NH_4OH/5% MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5 H) 7.16 (br. s., 1 H) 5.49 (br. s., 1 H) 4.52 (s, 2 H) 3.74-3.62 (m, 2 H) 3.55 (dd, *J*=8.3, 4.2 Hz, 1 H) 2.15 (ddt, *J*=14.6, 7.0, 4.3 Hz, 1 H) 1.91-1.81 (m, 1 H) 1.79 (br. s., 2 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 138.0, 128.3 (2C), 127.6, 127.5 (2C), 72.9, 68.0, 53.7, 34.5

IR (film): 3374, 3199, 3093, 3062, 3032, 2922, 2868, 2796, 1667, 1626, 1496, 1451, 1367 cm^{-1}

HRMS (ESI): Exact mass calcd for $C_{11}H_{16}N_2O_2$ $[M+H]^+$: 209.1290. Found: 209.1800.



2-(Allylamino)pentanamide (10h). The reaction was carried out following general procedure D using 2-(Propylamino)pentanenitrile (1.00 mmol, 138 mg). The residue was purified by column chromatography using 100% EtOAc to 95% EtOAc/MeOH to afford a white solid (106 mg, 68%).

TLC R_f 0.25 (95% EtOAc/MeOH)

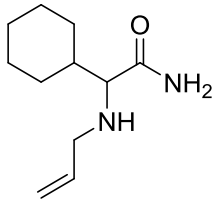
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (br s., 1H) 5.85 (dddd, *J*=17.1, 10.2, 6.4, 5.4 Hz, 1H) 5.79 (br s., 1H) 5.19 (dddd, *J*=17.1, 1.6, 1.6, 1.6 Hz, 1H) 5.11 (dddd, *J*=10.2, 1.3, 1.3, 1.3 Hz, 1H) 3.21 (m, 2H) 3.11 (dd, *J*=7.5, 5.2 Hz, 1H) 1.97 (br s., 1H) 1.69 (m, 1H) 1.52 (m, 1H) 1.44-1.33 (m, 2H) 0.93 (t, *J*=7.2 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 135.8, 116.6, 62.0, 51.1, 35.6, 19.2, 13.9

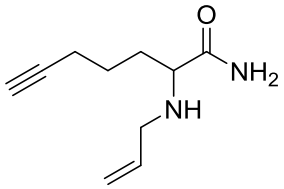
IR (film): 3080, 2961, 2875, 1663, 1402 cm^{-1}

HRMS (ESI): Exact mass calcd for $C_8H_{16}N_2O$ $[M - H^+]$: 155.1184. Found: 155.0714.

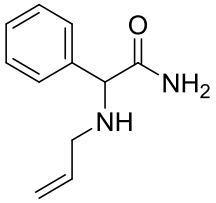
Melting Point: 49-50 ^oC



2-(Allylamino)-2-cyclohexyl amide (10i). 2-(Allylamino)-2-cyclohexylacetonitrile (1.00 mmol, 178 mg) was taken up in H_2O (0.5 mL) and CH_3CN (0.5 mL). NaOH (5 M, 0.200 mmol, 40.0 µL) was added followed by formaldehyde (37% in H_2O, 0.200 mmol, 14.9 µL). The reaction mixture was stirred at rt. The progress of the reaction was monitored by TLC. After completion of the reaction, it was diluted with H_2O (2 mL) and EtOAc (10 mL). The aqueous and organic layers were separated and the aqueous layer was extracted with EtOAc (10 mL X 4). The combined organic layers were dried and concentrated. Purification by column chromatography using 100% EtOAc to 95% EtOAc/MeOH afforded a white solid (157 mg, 80%).
TLC R_f 0.25 (95% EtOAc/MeOH)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (br s., 1H) 5.85 (dddd, *J*=17.0, 10.2, 6.6, 5.4 Hz, 1H) 5.62 (br s., 1H) 5.19 (dddd, *J*=17.1, 1.6, 1.6, 1.6 Hz, 1H) 5.12 (dddd, *J*=10.2, 1.2, 1.2, 1.2 Hz, 1H) 3.26 (ddt, *J*=14.3, 5.4, 1.6 Hz, 1H) 3.15 (ddt, *J*=14.2, 6.6, 1.2 Hz, 1H) 2.96 (d, *J*=4.4 Hz, 1H) 1.79-1.64 (m, 6H) 1.33-1.03 (m, 5H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 136.3, 116.6, 67.7, 52.0, 41.5, 30.4, 28.6, 26.5, 26.5, 26.4
IR (film): 3381, 2925, 2825, 1655, 1406, 1119 cm^{-1}
HRMS (ESI): Exact mass calcd for $C_{11}H_{21}N_2O$ [M+H$^+$]: 197.1654. Found: 197.1748.
Melting Point: 81-83 ^oC



2-(Allylamino)hept-6-ylocarboxamide (10j). The reaction was carried out following general procedure D using 2-(Allylamino)hept-6-ylonitrile (1.00 mmol, 162 mg). The residue was purified by column chromatography using 100% EtOAc to 95% EtOAc/MeOH to afford a white solid (142 mg, 79%).
TLC R_f 0.25 (95% EtOAc/MeOH)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (br s., 1H) 5.96 (br s., 1H) 5.87 (dddd, *J*=16.9, 10.2, 6.4, 5.6 Hz, 1H) 5.22 (dddd, *J*=17.1, 1.5, 1.5, 1.5 Hz, 1H) 5.08 (dddd, *J*=10.2, 1.5, 1.5, 1.5 Hz, 1H) 3.68 (br s., 1H) 3.32-3.18 (m, 3H) 2.23 (m, 2H) 1.96 (t, *J*=2.6 Hz, 1H) 1.81-1.75 (m, 2H) 1.91-1.72 (m, 2H) 1.67-1.60 (m, 2H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 135.8, 116.5, 83.8, 69.0, 61.4, 50.8, 32.5, 24.7, 18.2
IR (film): 3186, 2954, 2856, 1677, 1458, 1149 cm^{-1}
HRMS (ESI): Exact mass calcd for $C_{10}H_{16}N_2O$ [M–H$^+$]: 179.1184. Found: 179.0459.
Melting Point: 88-91 ^oC



***N*-Allyl-phenylglycine amide (10k).** The reaction was carried out following general procedure D using 2-(Allylamino)-2-phenylacetonitrile (1.00 mmol, 172 mg). The residue was purified by column chromatography using 100% EtOAc to 95% EtOAc/MeOH to afford a white solid (154 mg, 81%).

TLC R_f 0.25 (95% EtOAc/MeOH)

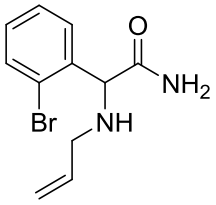
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H) 7.00 (br s., 1H) 6.39 (br s., 1H) 5.86 (dddd, *J*=17.1, 10.2, 6.0, 6.0 Hz, 1H) 5.18 (dddd, *J*=17.1, 1.6, 1.6, 1.6 Hz, 1H) 5.12 (dddd, *J*=10.2, 1.3, 1.3, 1.3 Hz, 1H) 4.19 (s, 1H) 3.29-3.20 (m, 2H) 1.98 (br s., 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 139.0, 135.6, 128.8, 128.2, 127.3, 116.6, 66.5, 50.7

IR (film): 3322, 3074, 2858, 1651, 1093 cm^{-1}

HRMS (ESI): Exact mass calcd for $C_{11}H_{15}N_2O$ $[M+H^+]$: 191.1184. Found: 191.1217.

Melting Point: 75-76 ^oC



2-(Allylamino)-2-(2'-bromophenyl)carboxamide (10l). The reaction was carried out following general procedure D using 2-(Allylamino)-2-(2'-bromophenyl)acetonitrile (1.00 mmol, 251 mg). The residue was purified by column chromatography using 100% EtOAc to 95% EtOAc/MeOH to afford a pale yellow oil (210 mg, 78%).

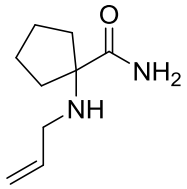
TLC R_f 0.25 (95% EtOAc/MeOH)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J*=8.0, 1.2 Hz, 1H) 7.40 (dd, *J*=7.7, 1.8 Hz, 1H) 7.32 (m, 1H) 7.17 (m, 1H) 6.97 (br s, 1H) 5.88 (dddd, *J*=17.1, 10.2, 6.0, 6.0 Hz, 1H) 5.81 (br s, 1H) 5.20 (dddd, *J*=17.1, 3.2, 1.6, 1.6 Hz, 1H) 5.13 (dddd, *J*=10.2, 2.8, 1.3, 1.3 Hz, 1H) 4.68 (s, 1H), 3.34-3.19 (m, 2H) 2.10 (br s, 1H)

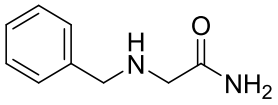
^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 138.4, 135.8, 133.5, 129.9, 129.8, 128.2, 124.5, 117.2, 65.2, 51.0

IR (film): 3312, 3074, 2842, 1682, 1471, 1020 cm^{-1}

HRMS (ESI): Exact mass calcd for $C_{10}H_{11}BrN$ $[M-CONH_2]^+$: 224.0075. Found: 224.0059.



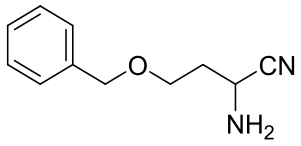
1-(*N*-allylamino)cyclopentanecarboxamide (10m). The reaction was carried out following general procedure D using 1-(Allylamino)-1-cyclopentanecarbonitrile (1.00 mmol, 150 mg) and formaldehyde (0.400 mmol, 29.8 µL,). The residue was purified by column chromatography using 100% EtOAc to 95% EtOAc/MeOH to afford a white solid (130 mg, 77%).
TLC R_f 0.25 (95% EtOAc/MeOH)
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (br s., 1H) 5.85 (dddd, *J*=17.1, 10.3, 5.6, 5.6 Hz, 1H) 5.48 (br s., 1H) 5.22 (dddd, *J*=17.1, 1.7, 1.7, 1.7 Hz, 1H) 5.08 (dddd, *J*=10.3, 1.5, 1.5, 1.5 Hz, 1H) 3.11 (m, 1H) 3.09 (m, 1H) 2.17-2.07 (m, 2H) 1.81-1.75 (m, 2H) 1.73-1.63 (m, 4H) 1.49 (br s., 1H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 179.7, 136.7, 115.6, 70.1, 47.0, 36.0, 24.5
IR (film): 3080, 2871, 1646, 1451, 1090 cm^{-1}
HRMS (ESI): Exact mass calcd for $C_9H_{16}N_2O$ [M–H$^+$]: 167.1184. Found: 167.0638.
Melting Point: 53-54 ^oC



Benzylglycine amide (8a). The reaction was carried out following general procedure D using commercially available 2-(benzylamino)acetonitrile hydrochloride (1.00 mmol, 183 mg) and an additional equivalent of NaOH (5M, 1.2 mmol, 0.24 mL) to neutralize the hydrochloride salt *in situ*. The residue was purified by column chromatography using 1% NH_4OH/5% MeOH/CH_2Cl_2 to afford a white solid (164 mg, 99%). Spectral data was consistent with literature.[101]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5 H) 3.80 (s, 2 H) 3.32 (s, 2 H)

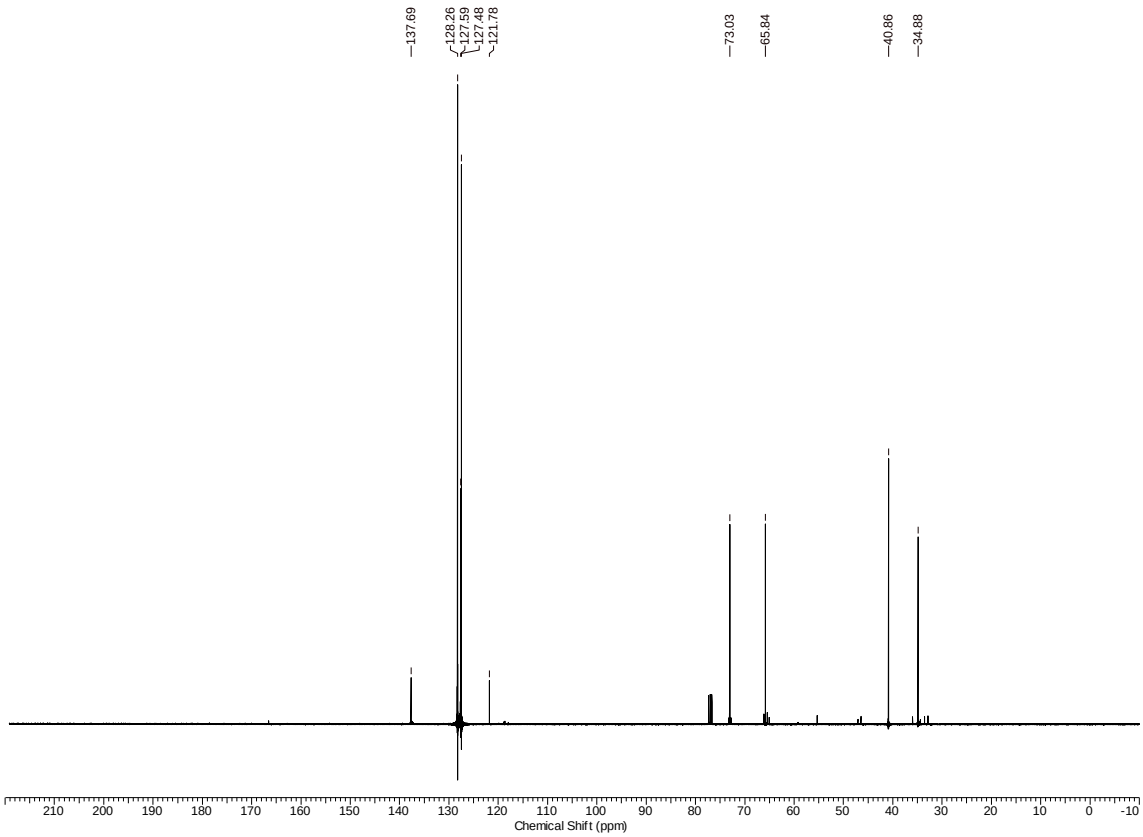
[101] Salauen, A.; Favre, a.; Grel, B. L.; Potel, M.; Le, P. *J. Org. Chem*. **2006**, *71*, 150.

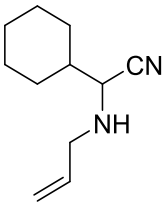
Appendix I. Proton and Carbon NMR Spectra



9g

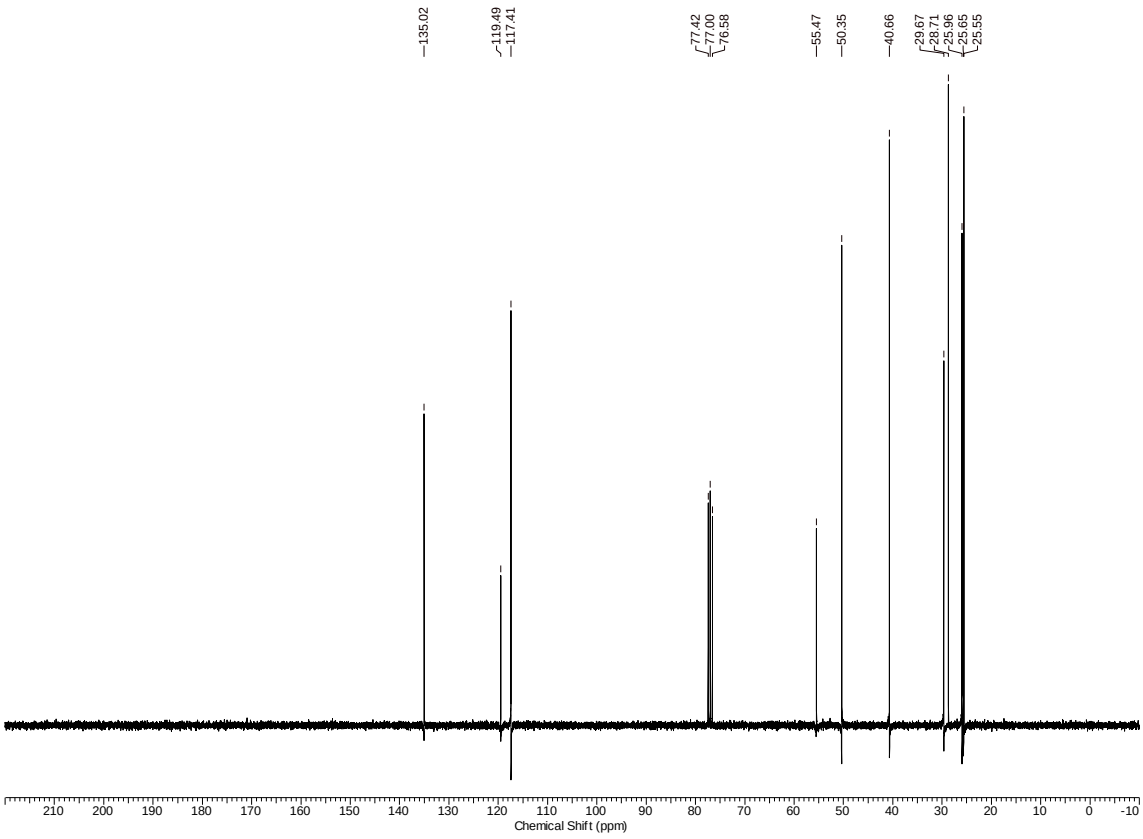
Table 2.4, entry 7

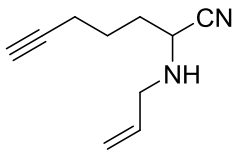




9i

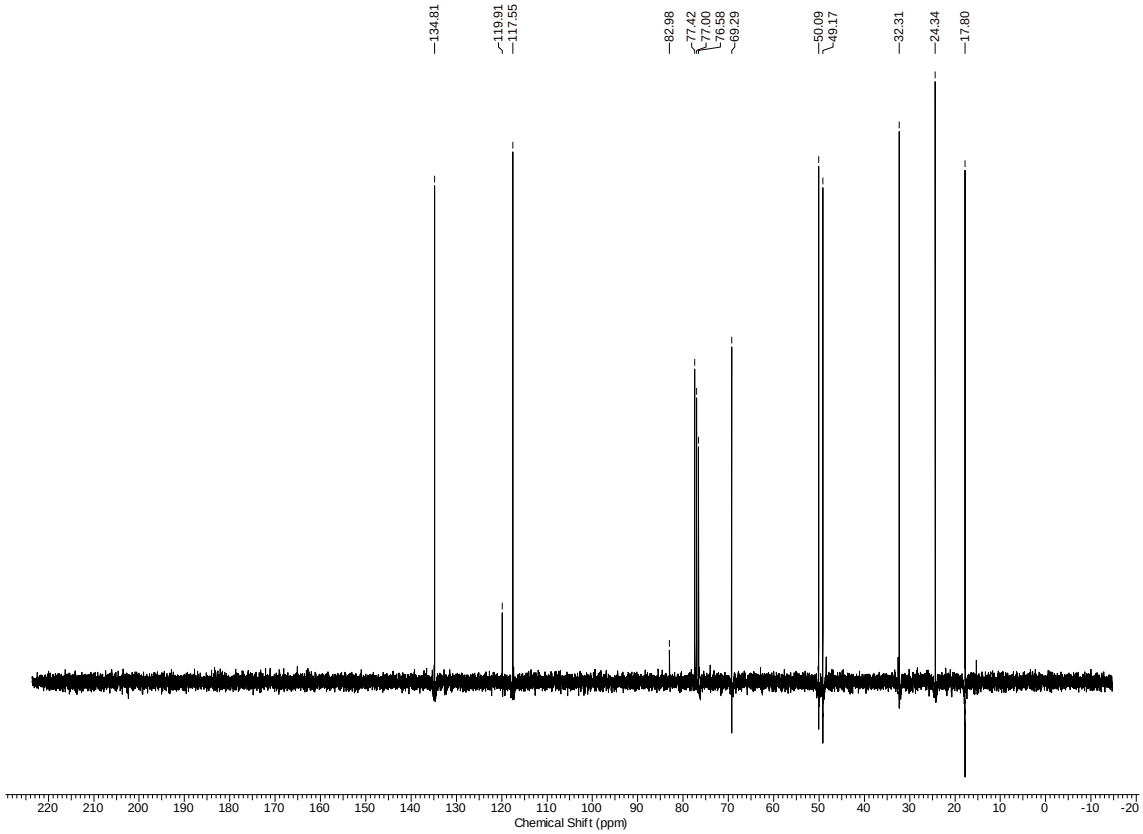
Table 2.4, entry 9

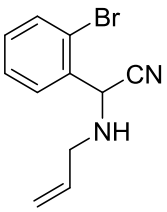




9j

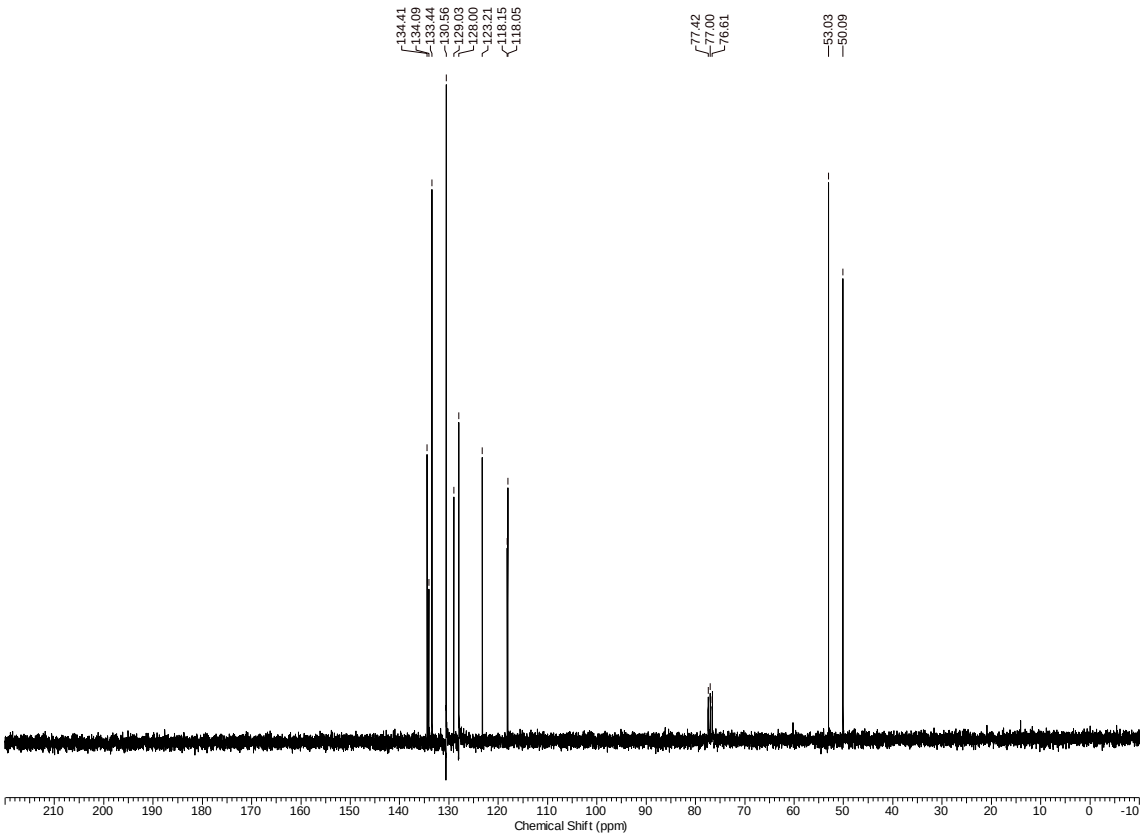
Table 2.4, entry 10

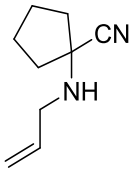




9l

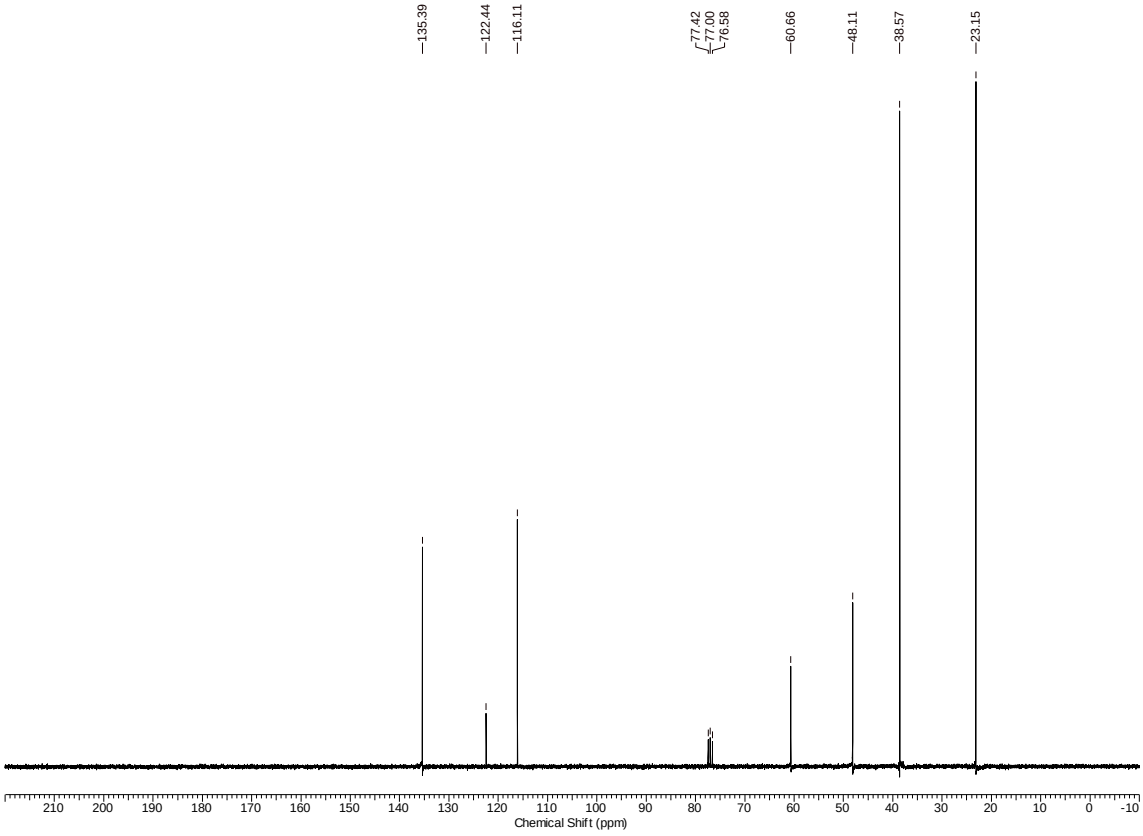
Table 2.4, entry 12

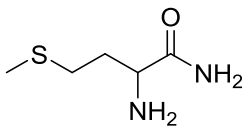




9m

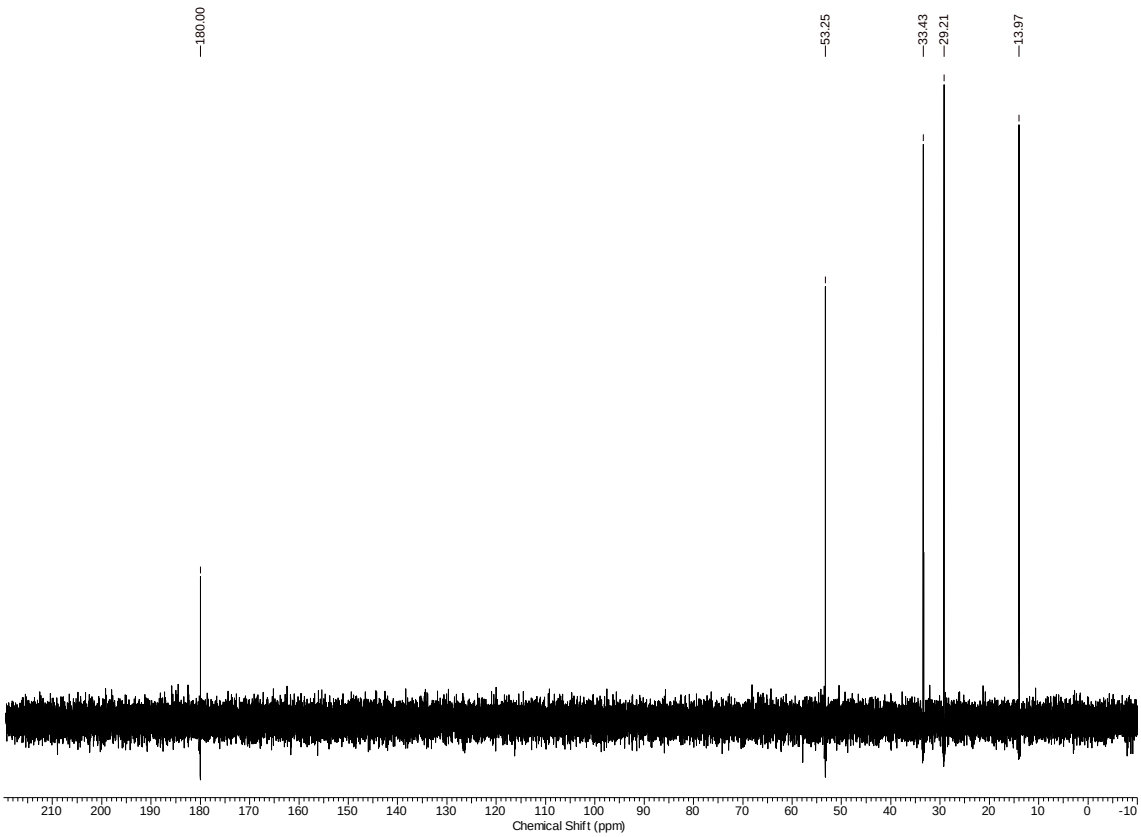
Table 2.4, entry 13

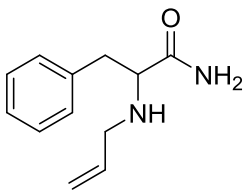



O
S
NH2
NH2

2

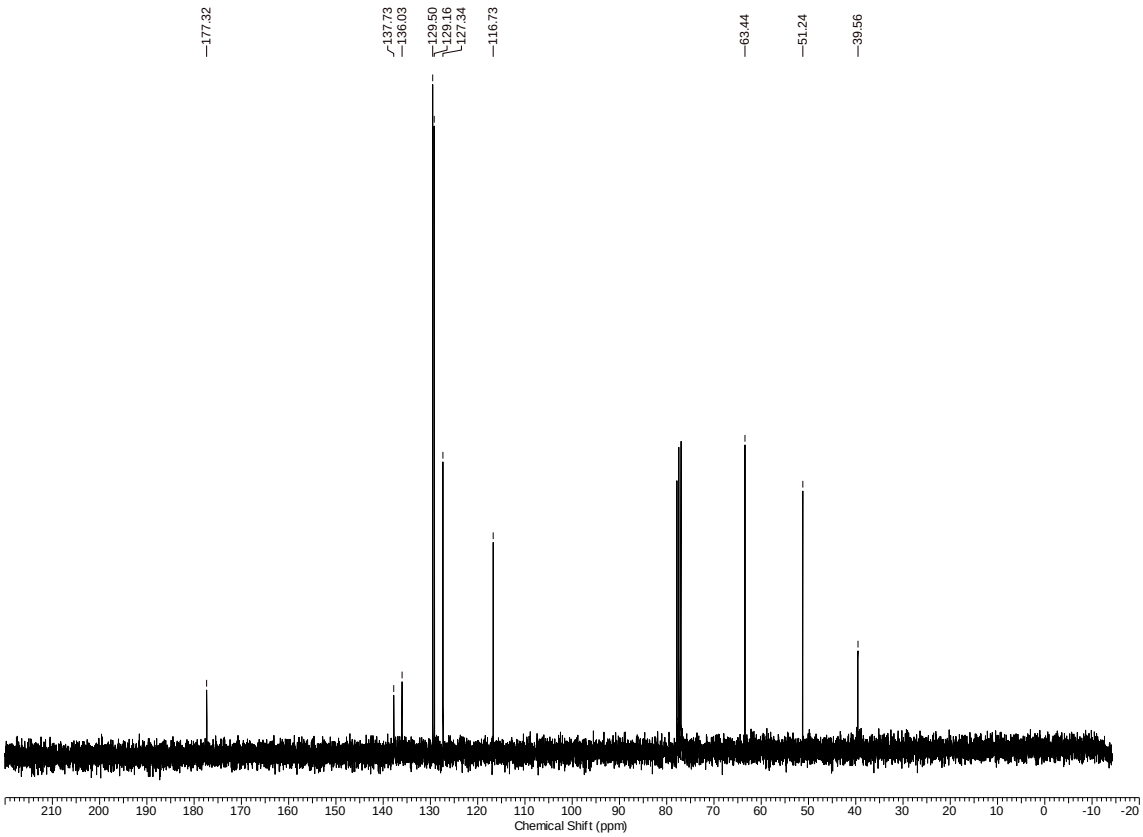
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

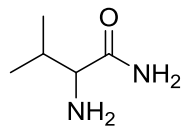

180.00
53.25
33.43
29.21
13.97
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


O
NH2
NH

6

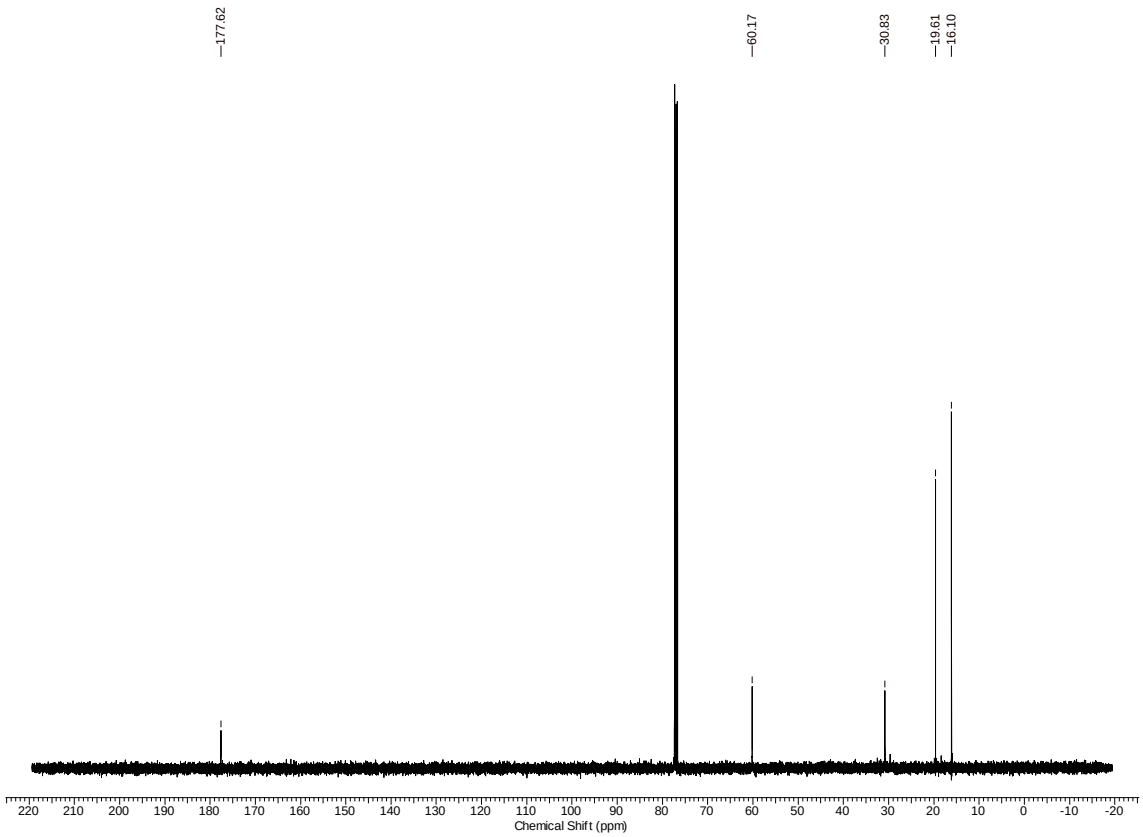
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

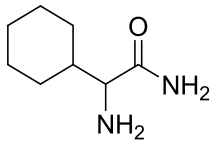

177.32
137.73
136.03
129.50
129.16
127.34
116.73
63.44
51.24
39.56
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
Chemical Shift (ppm)



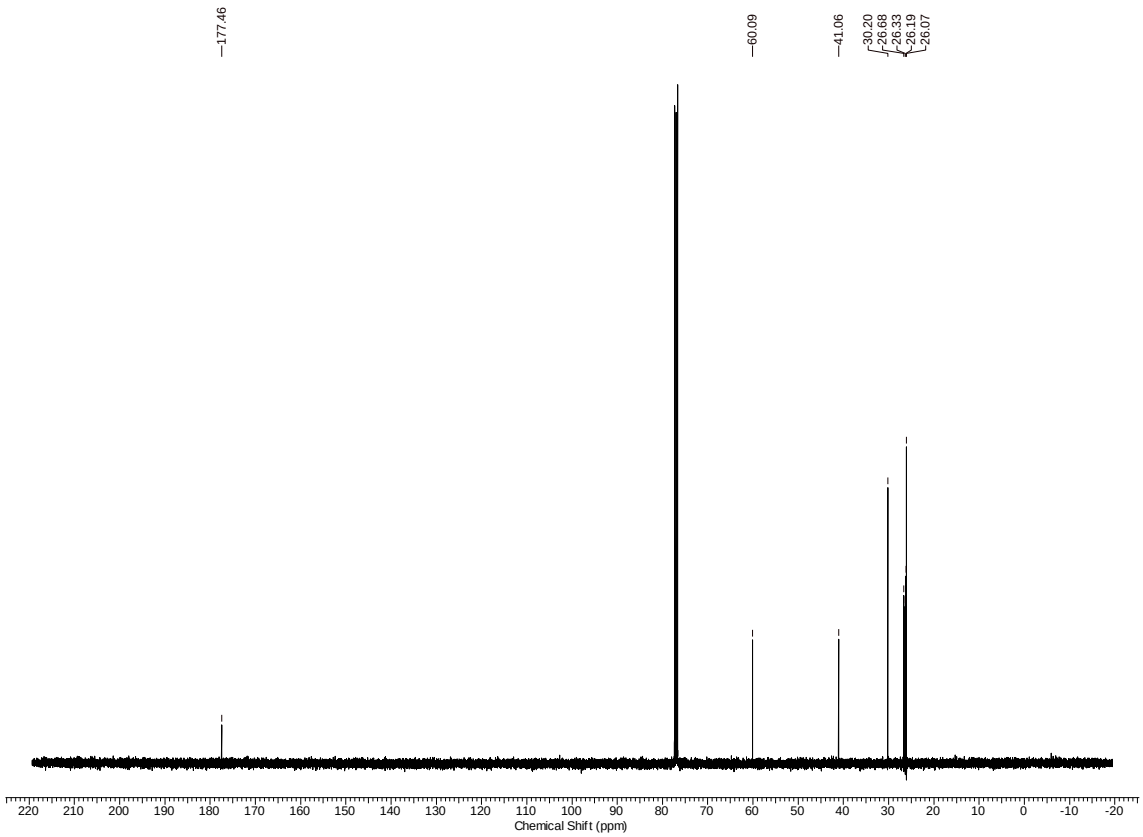
10b

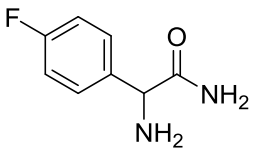
Table 2.4, entry 2





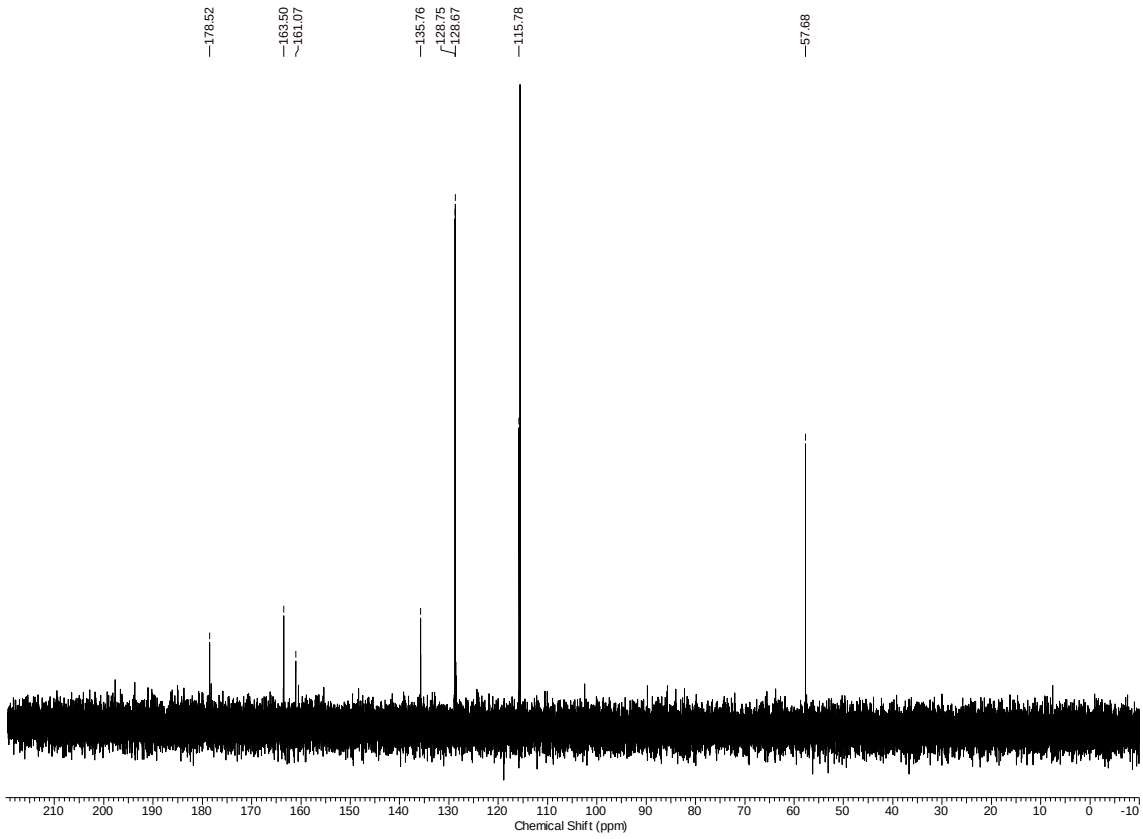
10c
Table 2.4, entry 3

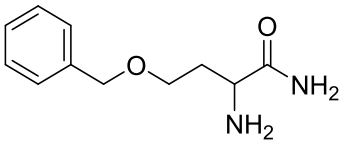




10f

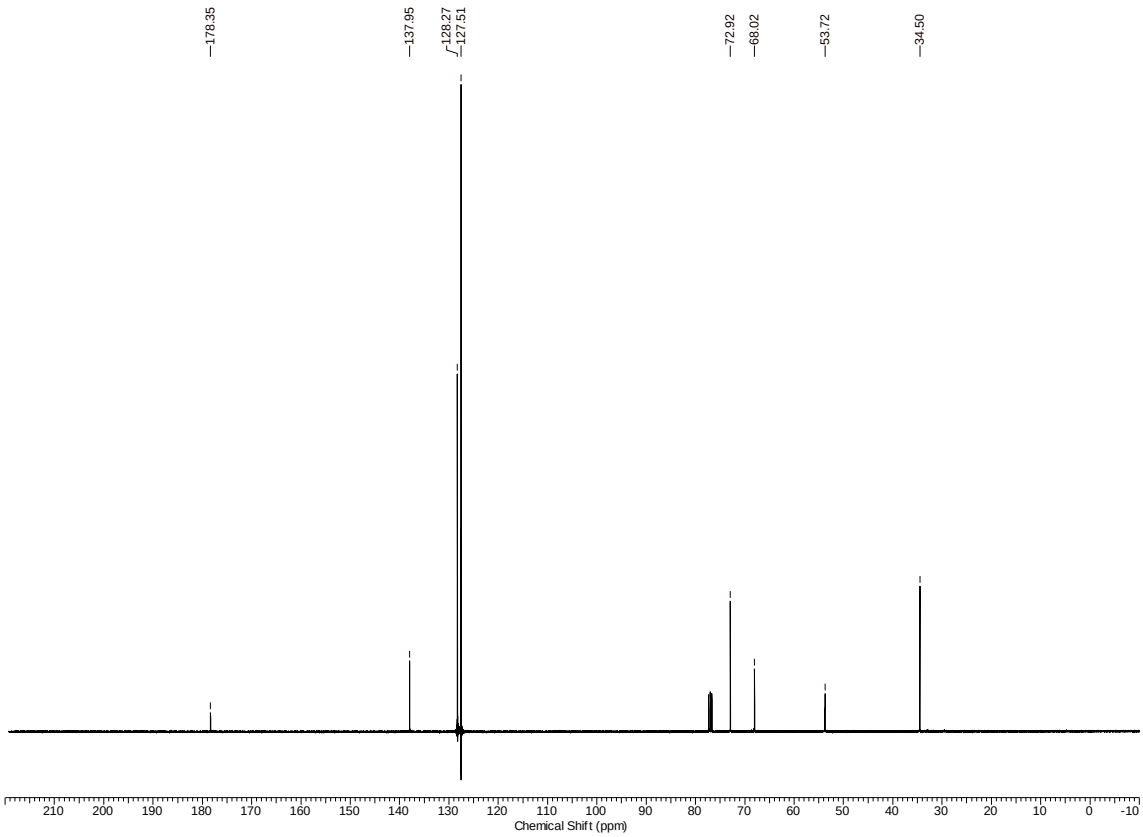
Table 2.4, entry 6

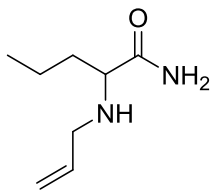




10g

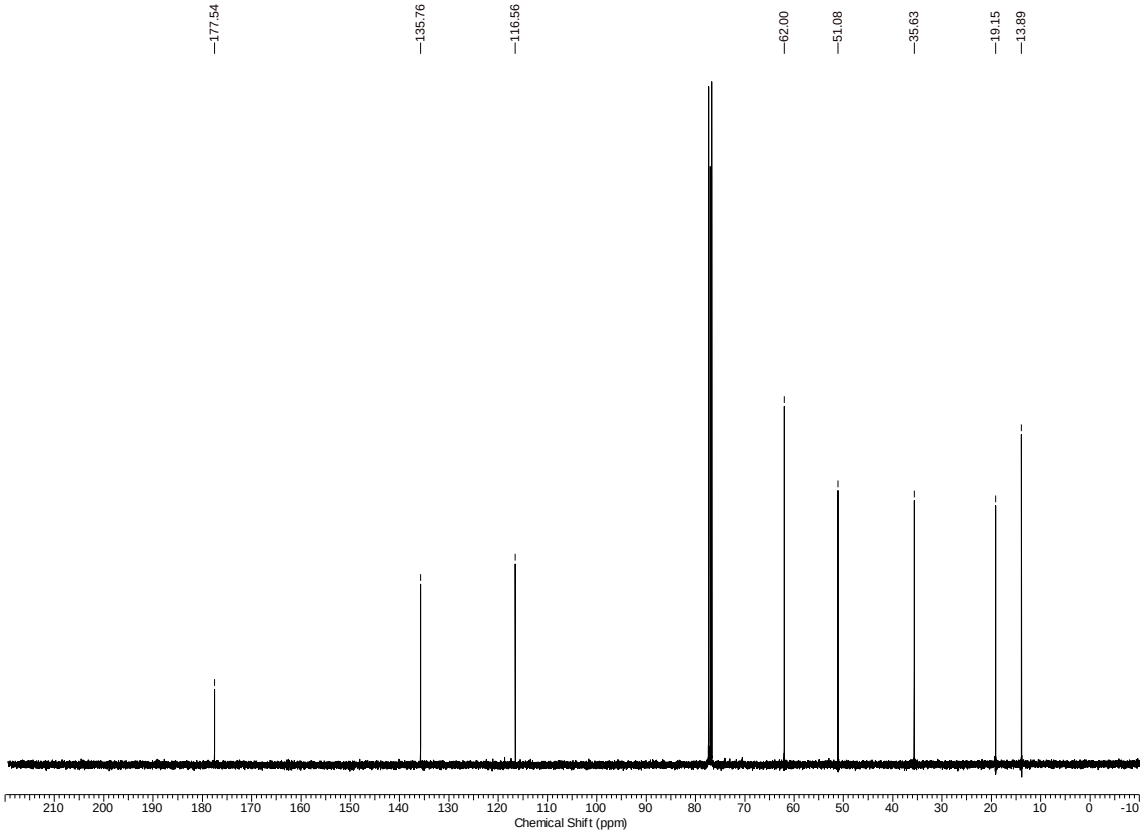
Table 2.4, entry 7

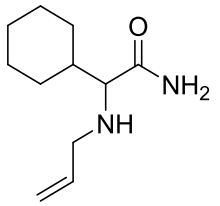




10h

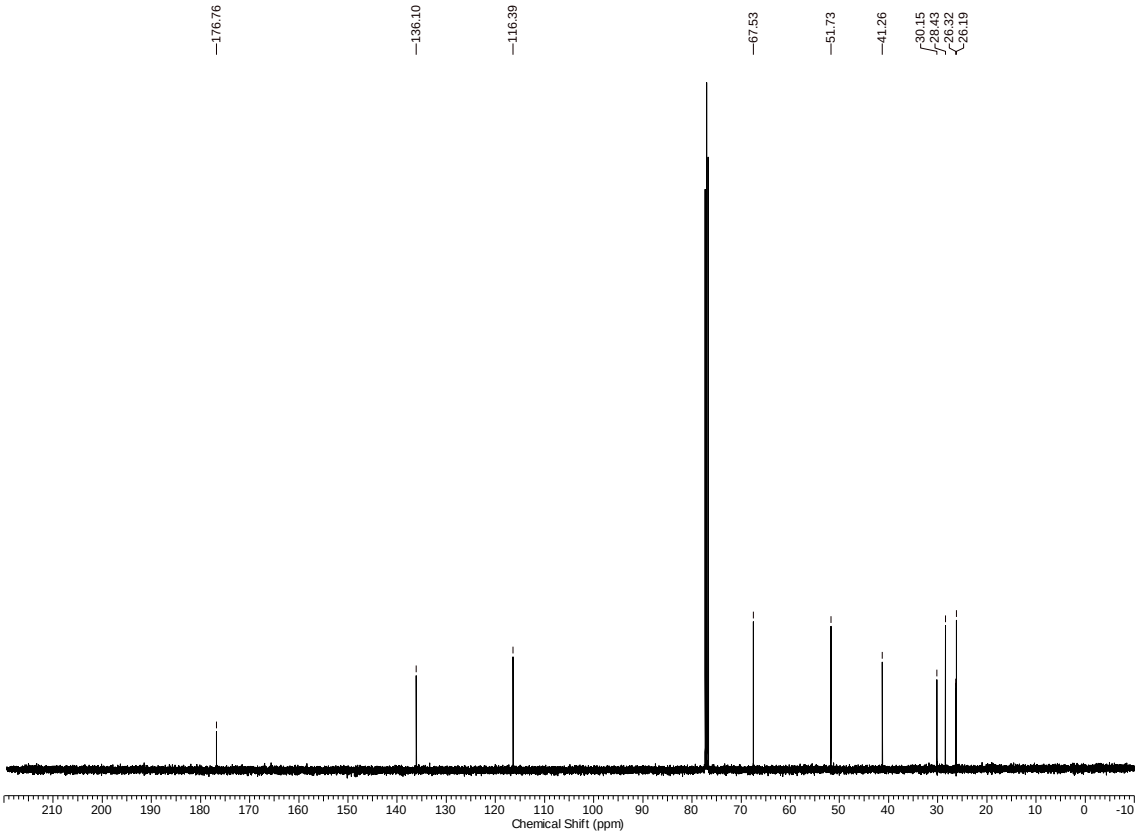
Table 2.4, entry 8

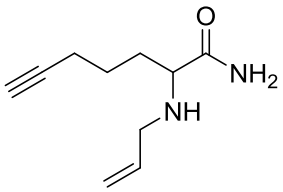




10i

Table 2.4, entry 9





10j
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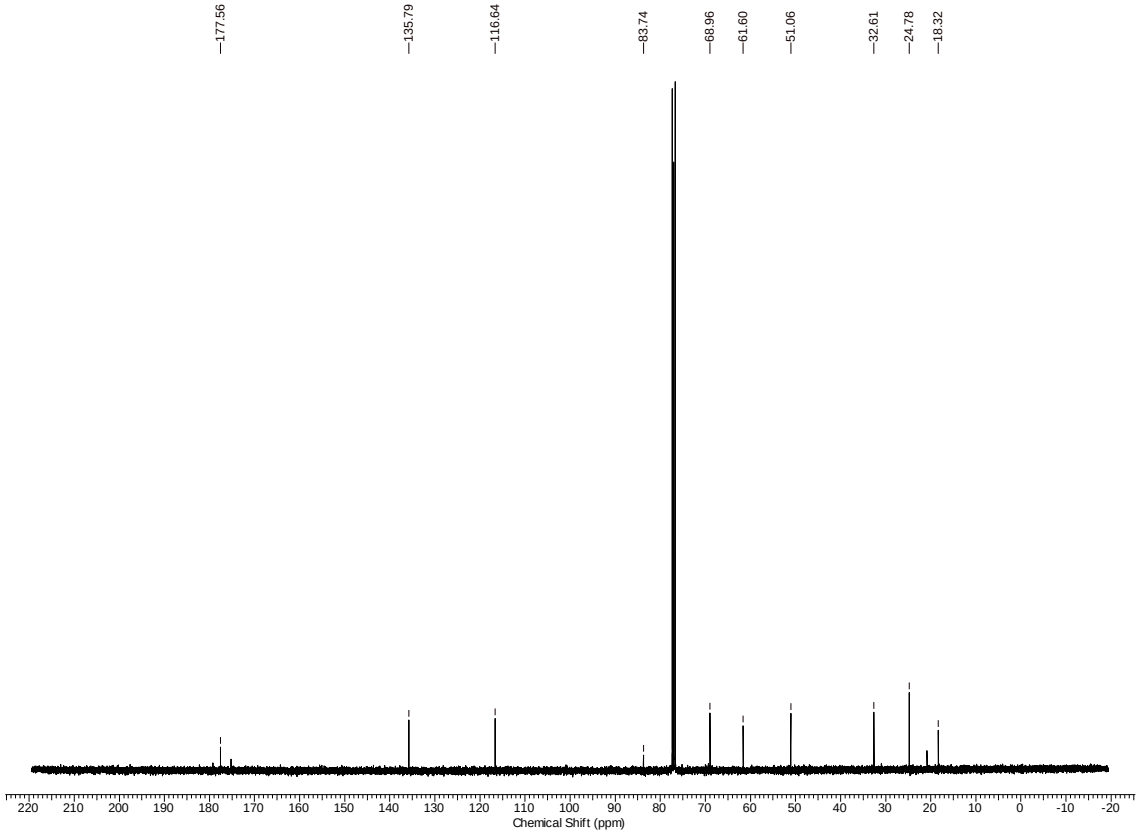
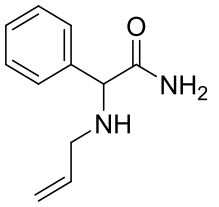
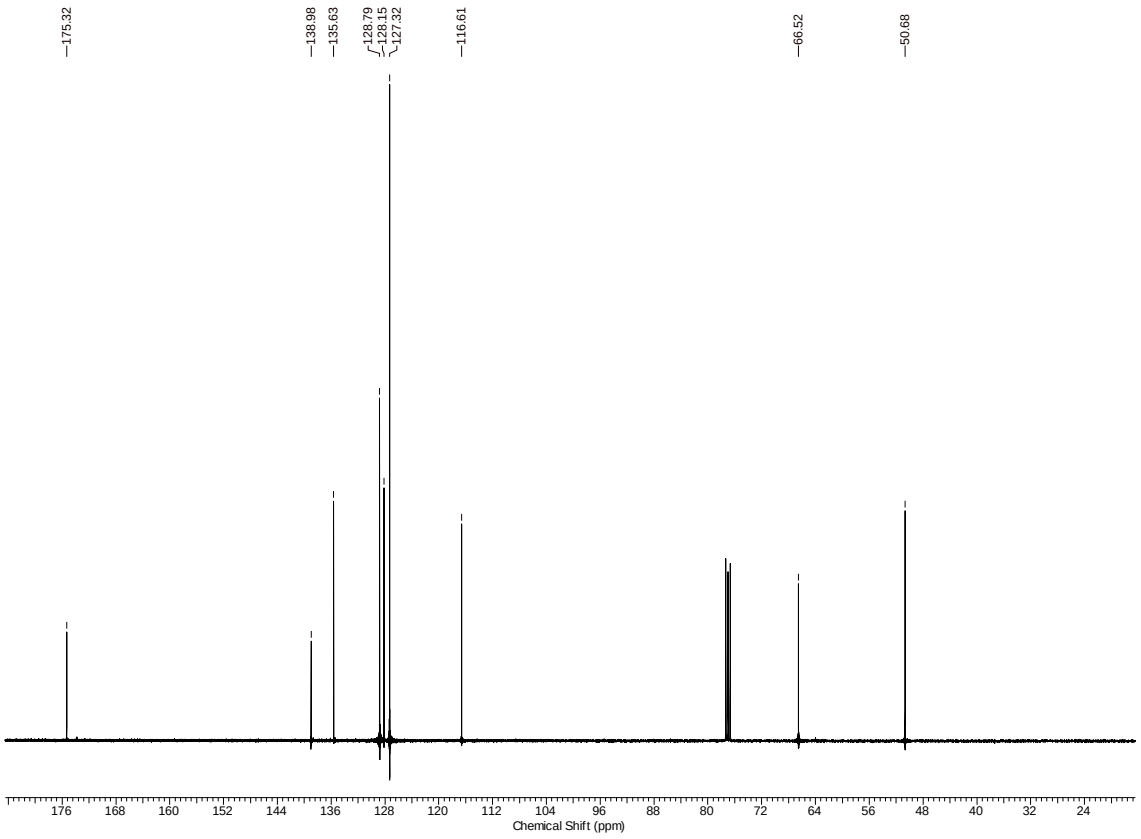
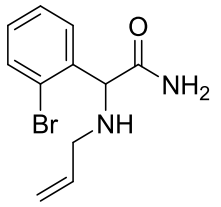




10k

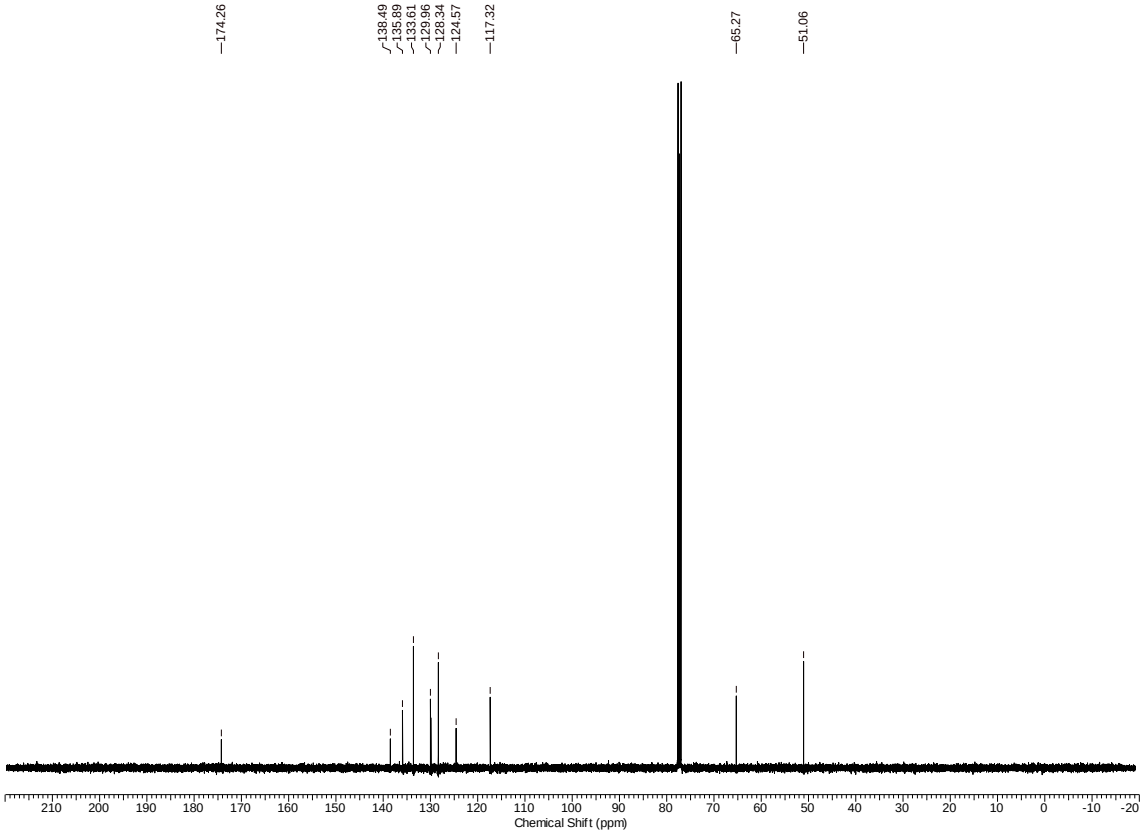
Table 2.4, entry 11

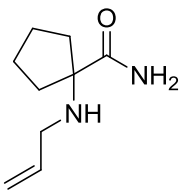




10l

Table 2.4, entry 12





10m

Table 2.4, entry 13