NEW STRATEGIES FOR THE P*ERI* LITHIATION OF NAPHTHALAMIDES

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ABSTRACT

NEW STRATEGIES FOR THE PERI LITHIATION

OF NAPHTHALAMIDES

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Directed metalation reactions are an interesting area of synthetic chemistry. They provide a powerful regiospecific method for functionalizing complex aromatic rings. Presently, directed *ortho* metalations are well understood. However, there has been very little progress in the remote metalation of naphthalene derivatives.

Presently the *peri* lithiation of naphthalamides is a reaction that has not been solved to a level that allows for it to be deployed in a vast number of synthetic schemes. The processes by which *peri* functionalized naphthalamides are present obtained required several steps and give poor yields. Previously attempts directed toward the *peri* lithiation in the Schwan lab have met with little success.

Herein experiments were preformed to understand why the pervious attempts failed and other experiments were performed in an effort to acheive the *peri* lithiation of a specific naphthalamide. The mechanism of previous chemical observations was understood by trapping experiments and clearly demonstrated how problematic acidic sites can interfere with intended directed metalation. The acidic site was sterically hindered by employing strategic protecting groups. However, the steric demand of the

protecting groups considered was not sufficient to eliminate the problematic acidic site. This led to the consideration of an alternative strategy for the *peri* lithiation by removing the acidic center of the specific substrate. This however, resulted in remote addition of lithiating reagents to the naphthalamide and clearly showed that several naphthalamides are not a suitable directed metalation group for the *peri* lithiation.

Acknowledgements

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List of Abbreviations

ADP	adenosine diphosphate
AIDS	acquired immune deficiency syndrome
Bn	benzyl
De	diastereomeric excess
DMAP	dimethylaminopyridine
DMC	Directed Metalation Chemistry
DMG	Directed Metalation Group
DNA	deoxyribonucleic acid
E^+	electrophile
eEF-2	endogenous Elongation factor 2
Et	ethyl
EWG	electron withdrawing group
Gly	glycine
HMPA	hexamethylphosphoramide
Hz	Hertz
IC_{50}	inhibitor concentration at 50%
*i*Pr	*iso*propyl
IR	Infrared
LDA	lithium diisopropylamide
LTMP	2,2,6,6-tetramethyl piperidide
Me	methyl
MS	mass spectrometry

NAD^+	nicotinamide adenine dinucleotide
*n*BuLi	*normal* butyllithium
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PARP	poly-ADP ribose olymerase enzymes
Ph	phenyl
PG	protecting group
ppm	part per million
PTSA	paratoluenesulfonic aicd
*sec*BuLi	secondary butyllithium
*tert*Bu	tertiary butyl
*tert*BuLi	tertiary butyllithium
*tert*BuOH	tertiary butanol
TMEDA	tetramethylene ethylene diamine
TBDPS	*tert*-butyldimethyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
THF	tetrahydrofuran
UV	ultraviolet

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1. Introduction and Overview

Billions of dollars are spent annually by universities and pharmaceutical companies worldwide, researching new organic compounds with medicinal applications.[1] Cystic fibrosis, for instance, has long been a focal point of drug development. One in 2500 children is born with this disease; of these sixty percent will die of untreatable secondary infections due to their weakened immune system.[2]

A new class of naphthalene derivatives has recently shown promise in the treatment of these secondary infections.[3] *Peri* functionalized naphthalenes, in particular, have been effective in experimental studies as an antibacterial agent. This new area of research has the potential to save or extend the lives of millions of children around the world.

To date, efforts in the Schwan group to efficiently synthesize these new compounds have been largely unsuccessful. Yields in the last step of the synthesis do not exceed 27% due to deleterious reactions forming unwanted compounds.[4] Therefore, strategies to counteract these side reactions are required to carry forward this research. Furthermore, to become a commercially viable pharmaceutical product, yields of 90% or higher will be necessary to justify *in vitro* trials.

Accordingly, the primary goal of this research project is to develop effective strategies to counter these undesired reactions, resulting in higher yields of *peri* functionalized naphthalene compounds for the potential treatment of cystic fibrosis. Trapping experiments will give insight into the identity of intermediates in the synthetic chemistry, both desired and undesired. Our protection strategies aim to block the site on the naphthalene derivative where the undesired reaction occurs.

However, before the research is discussed, a detailed review of background work in this and related areas is presented to introduce the reader to the background, justify the investigation and identify potential avenues of productive experimentation. Simpler protection approaches have been successful in other areas and may provide direction for this particular application. Trapping and protecting group experiments will be carried out to assess the yields. Finally, as a secondary objective, the overall chemistry of the naphthalene derivatives will be explored to gain insight which may be useful in expanding the known chemistry and possibly optimizing the medicinal efficacy of the compounds.

2. Background Discussion

2.01 Cystic Fibrosis

Cystic fibrosis is one of the most common genetic disorders affecting the Caucasian population.[2] One child in 2500 is born with it; although, of every 250 people, one will carry the lethal disorder in their genes. The disease manifests itself with thick mucus production in the lungs and deficiencies of certain pancreatic enzymes. This results in a weakened immune system response and frequent infection of the lungs.[5] In fact, the majority of people living with cystic fibrosis do not die as a direct result of the disease but die because of a secondary infections. Those patients rarely live past twenty years of age.

Over the past 20 years, great progress has been made in the treatment of these infections; however, *Pseudomonas aeruginosa*, which accounts for 60% percent of all

secondary infections, is presently untreatable. *P. aeruginosa* becomes lethal after 10 to 20 years because of the tissue damage it causes in the lungs.

This common bacteria is typically found in ground water and soil samples.[6] In addition to affecting those with cystic fibrosis, it is the third most common cause of blood-borne infections.[7] Those with suppressed immune systems, such as burn victims and people suffering with acquired immune deficiency syndrome (AIDS) or undergoing cancer treatment, are especially at risk.

P. aeruginosa produces several toxic factors, of which the most potent is exotoxin A.[8] This 66 kg/mol protein has a 50% lethal dosage (LD_{50}) of only 0.2 μg/animal.[9] The lethality of exotoxin A comes from its ability to inhibit protein synthesis, leading to cell death.[10] It does so by permitting transfer of the ADP-ribosyl moiety NAD^+, shown in black, onto the diphthamide residue, shown in blue (Figure 1), of endogenous elongation factor 2 (eEF-2), an essential catalytic protein highly conserved in the ribosome. The catalytic ribosomal transferase activity is facilitated by the C-terminal one third domain of the toxin P24, shown in red.[3] This process prevents eEF-2 from operating properly, as illustrated below (Figure 1).

Although the damaged gene associated with cystic fibrosis has been completely characterized, the development of a gene based therapy is unlikely in the near future.[11,12] The retro viruses required to insert the undamaged gene into a patient's damaged DNA have not yet been asertained.[13]

Instead, current treatments focus on alleviating the symptoms and routing the secondary infections associated with the disease. As *Pseudomonas aeruginosa* is so

prevalent in people with cystic fibrosis, an antibiotic treatment targeting these bacteria will significantly extend and improve the quality of patients' lives.

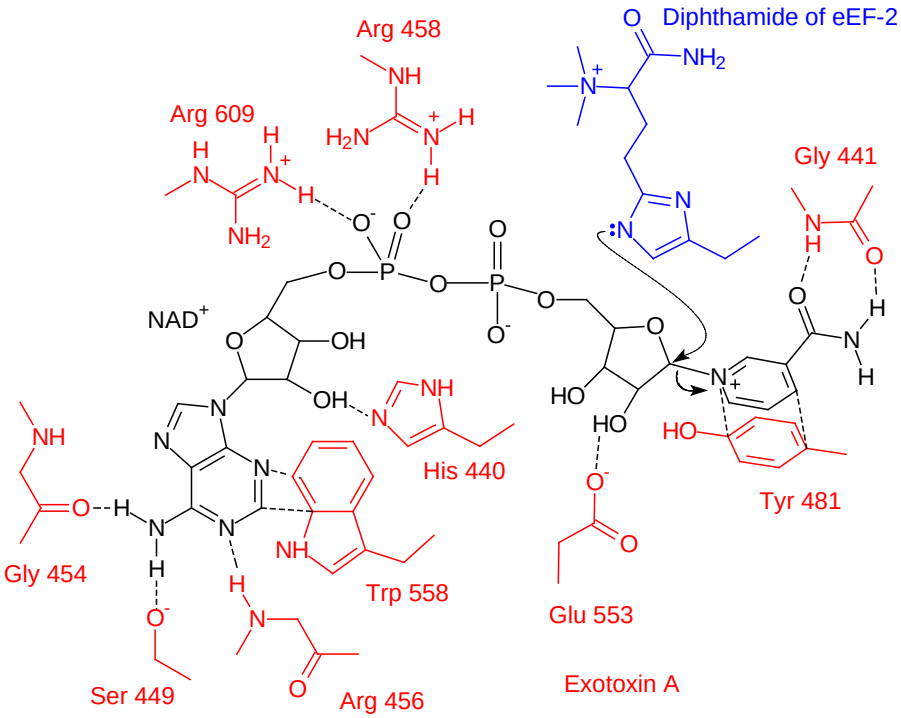


Figure 1: *The ADP-ribosyltransferase mechanism of Exotoxin A.*

2.02 PARP Inhibitors

The catalytic PE24 domain of exotoxin A is structurally similar to the catalytic domain of several poly-ADP ribose polymerase enzymes (PARPs).[14] PARPs become active when DNA is damaged or being replicated and during cellular transformation and differntiation.[15] PARP inhibitors are normally structural mimics of nicotinamide (**1**). These inhibitors occupy the binding site of NAD^+, assisted by hydrogen bonding through amide and lactam functional groups. The inhibitor bonds to the Gly^{863} residue of PARP,

much like the nicotinamide functionality of NAD^+ and also the Gly^{441} residue of exotoxin A (Figure 1).

Early on, it was shown that nicotinamide, a byproduct of the polymerase reaction, was a weak feed-back PARP inhibitor. The inhibitor concentration at 50% (IC_{50}) was measured to be approximately 100 μM. Despite the high IC_{50}, the analogous 3-aminobenzamide (**2**) was much more potent, with an IC_{50} of 20 μM. Furthermore, it was deduced that benzamide functionality in its *s*-trans conformation provided optimal binding.[16,17] Bicyclic (**3**), tricyclic (**4**), and tetracyclic (**5**) analogues were also synthesized for evaluation. Bicyclic benzamides (**6**) were also sought because they are locked in the *s*-trans confirmation by intramolecular hydrogen bonding.[18] The Merrill group has used these compounds (Figure 2) to scout lactams suitable for treating *P. aeruginosa* infection. Known PARP inhibitors show an IC_{50} in the μM range; likewise, 1,8-naphthalimide (**7**) was determined to be a competitive inhibitor with an IC_{50} of 87 nM.[14]

Though these results are encouraging, the search for a treatment of *P. aeruginosa* still faces many challenges. Notably, compounds like **7** have limited solubility in aqueous solutions; thus, the IC_{50} has proven difficult to elucidate. Although no efficient methods exist in literature for synthesizing analogues of **7,** directed metalation chemistry may provide a solution to the challenges.

2.03 Directed Metalations

Directed metalation was discovered 65 years ago by Gilman & Bebb[19] and by Wittig & Fuhrman.[20] Ever since, it has been a powerful tool in the regiospecific

synthesis of substituted aromatic compounds. Although there are alternatives, such as the classical electrophilic aromatic substitution, yields often vary depending on ring functionalization. Furthermore, these substitution reactions often require harsh conditions, which can lead to isomerization. Directed metalation chemistry is very specific and is performed under milder conditions. As more compounds with complex polysubstituted aromatic ring systems are found to have pharmaceutical value, directed metalation reactions will increase in significance. Thus, addressing the issues that arise in directed metalation chemistry is becoming increasingly pertinent.

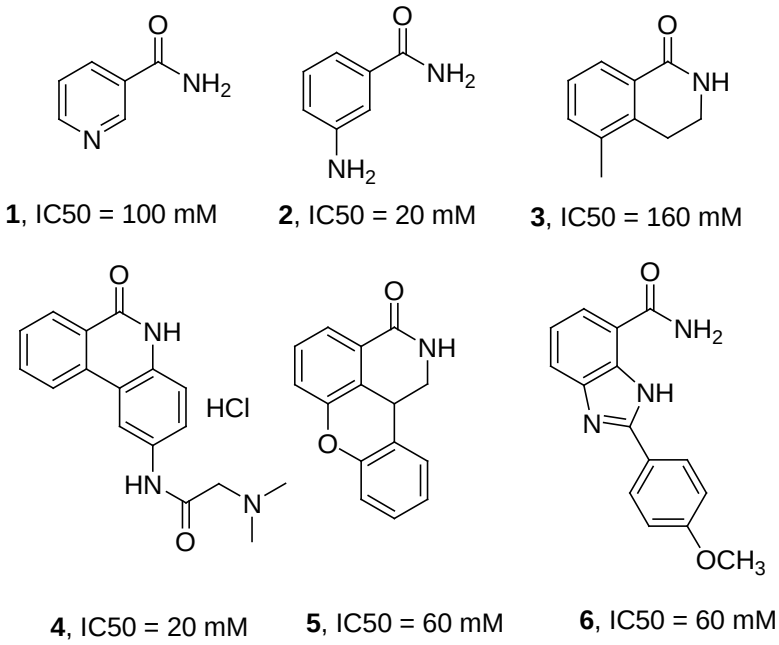
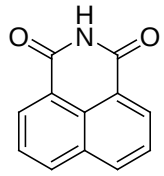


Figure 2: *PARP structures and associated IC_{50} values*



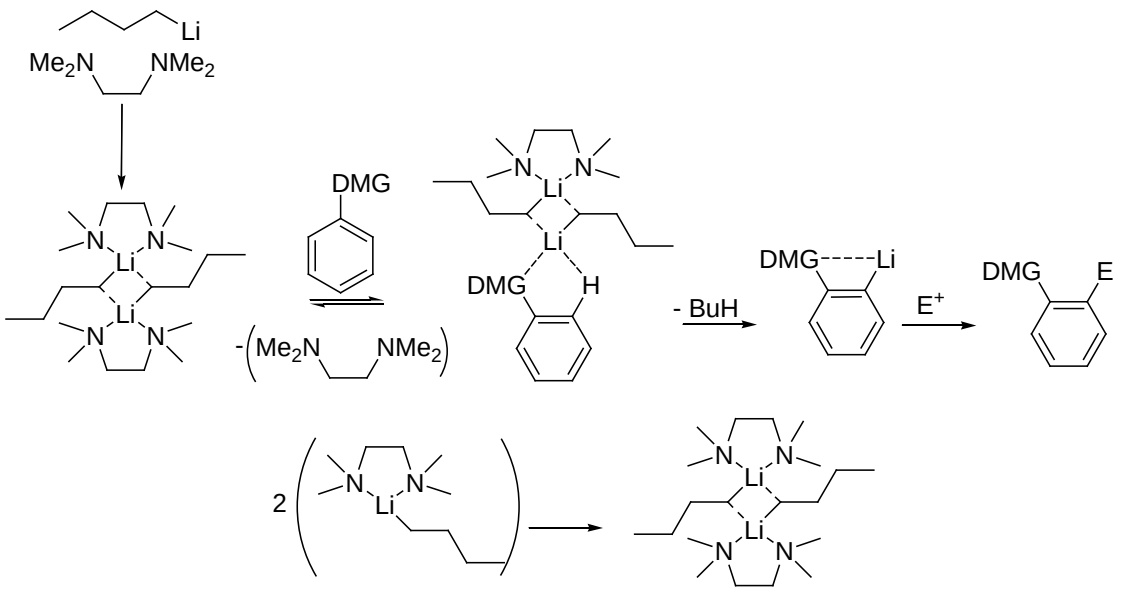
7, IC_{50} = 87 μM

Figure 3: *1,8-Naphthalimide, a competitive inhibitor for exotoxin A*

2.04 Directed *Ortho* Metalation

Directed ortho metalation is a reliable technique for making polyfunctionalized aromatic compounds. Historically, the mechanism is believed to initiate with the coordination between an alkyllithium base and an added bidentate ligand, such as tetramethylethylenediamine (TMEDA). This coordination increases the basicity of the lithiated alkane, which, in turn, complexes with the directing metalation group (DMG) on an aromatic ring (Scheme 1).[21] This allows the base to extract a hydrogen atom from the *ortho* carbon, replacing it with lithium. An electrophile subsequently replaces the lithium metal.[21] It should be noted that directed *ortho* lithations have been achieved without a bidentate ligand, thus casting some doubt on the generality of the proposed mechanism.[22]

Despite questions pertaining to the necessity of TMEDA, the reaction can be repeated, giving tri-substituted aromatics. Furthermore, after both *ortho* positions have been functionalized, the *meta* positions can be functionalized if the electrophile that was used for the quench is a DMG itself.[21,23] Thus, the method can reliably produce polysubstituted aromatics in high yield.



Scheme 1: *The first proposed mechanism for direct ortho metalation*

Contradictory evidence has fueled the debate concerning the role of the bidentate ligand. While coordination has been observed between lithium and the ligand, MP2 calculations performed by the Schleyer group on phenol and fluorobenzene using lithium hydride as a base suggest that the electronegative DMG induces a favourable charge arrangement, stabilizing the intermediate.[24] This work has given rise to the "kinetically enhanced metalation" model, which states that no intermediate exists with a finite lifetime in the reaction pathway.

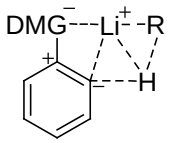


Figure 4: *Charge distribution in the directed metalation transition state.*[24]

Beak and coworkers undertook the task of resolving the controversy.[25] Using the kinetic isotope effect, Beak had hoped to show a difference in the reaction rates between *ortho* hydrogen and *ortho* deuterium. A primary kinetic isotope effect would suggest a one step mechanism and a secondary kinetic isotope effect would support a two step mechanism. Beak showed that the complexation of the alkyllithium base with the DMG was very quick. However, his data could not definitively rule either mechanism. He surmised that the reaction proceeds both by complexation with a bidenate ligand and by immediate complexation with the DMG; competing reactions, both producing the same product.[25]

Whether the reaction proceeds by a two-step or one-step mechanism is not exactly a pragmatic concern; although, with respect to practical application, the reaction has proven quite useful due to the wide variety of amenable DMG groups. In 1946, Roberts studied various DMGs and formulated the first set of general rules describing their influence.[23] Generally, directing-power follows the trend: F > Cl, F > O-CH_3 > CF_3 > H & O > S > N. Since Roberts' study, much more work has been done. For instance, amines,[26] amides,[25] sulfonamides,[27] alcohols,[25] alkoxides,[27] carbmates[21] and ethers[28] are all very good DMG's and have found widespread use. Other groups are also being investigated or have found limited use. Amides are of particular interest because of their occurrence in many pharmaceuticals.[29] Furthermore, they have been studied in great detail by Snieckus and have proved to be among most powerful directed metalation groups.[21]

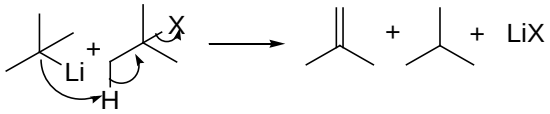
The amide's ability to direct metalation onto the *ortho* position is partially the result of its electronegativity. The amide group draws electron density out of the

aromatic ring system, causing the *ortho* hydrogen atoms to become more acidic. Also, the carbonyl of the amide complexes with the lithium, the alkyllithium base close in proximity to the acidic hydrogen. Thus, directed *ortho* metalation provides a reliable method for functionalizing compounds indentified as potentially suitable in treating *P. aeruginosa* infection.

2.05 Amide Bases and Halogen Exchange

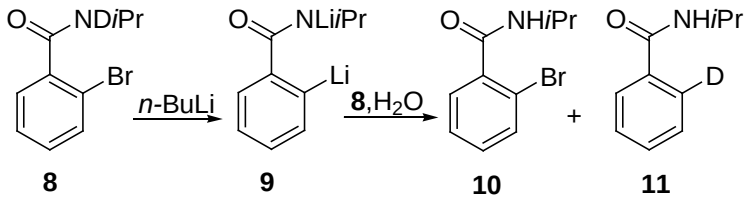
Another method of generating lithiated aromatics, similar to DMC products, is a lithium halogen exchange reaction. This method can give products that are not accessible through DMG reactions.[30] This process was discovered by Wittig[31] in 1938 and then synthetically employed the following year by Gilman.[32] The reaction employs a strong alkyllithium base and a halogenated aryl starting material. The lithium and halide exchange to give a more stable set of products; in the case of an aryl halide the lithium aryl compound is more stable and thus lithiated.[33] Subsequently, the lithiated aryl compound can be quenched with an electrophile to give a similar type product as DMC.

As with some equilibrium processes, treating with an excess amount of reagent is required to push the reaction to completion. However, in the case of the lithium halogen exchange there is the risk that the base will attack the newly formed alkyl halide byproduct and will lead to a lower yield. This is mitigated by employing two equivalents of *tert*butyllithium[34] as it reacts faster with the alkyl halide than the halide does with the desired product (Scheme 2).[30] This permits a very high yielding reaction.



Scheme: *Tertbutyllithium reacting with the alkyl halide*

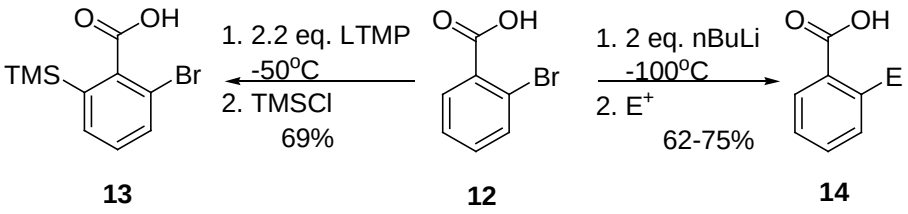
Problems can arise when doing a lithium halogen exchange in the presence of an acidic site in the molecule. This has been shown by Beak who used *N*-deuterio-*N*-isopropyl-o-bromobenzamide to study this problem. In his studies he found that there was partial incorporation of the deuterium to the *ortho* position upon regeneration of starting material. In short, he surmised that lithium halogen exchange is quick but deprotonation of the amide is quicker resulting in the formation a dilithiated species faster than stirring. This created regional areas of dilithiated **9** a species which underwent an intramolecular exchange with an unlithiated **8** molecule to install the deuterium at the *ortho* position.[35] As such, this type of reactivity with an acidic center can reduce the yield of the overall reaction. However, this problem can be solved by simply first deprotonating the acidic hydrogen with a weaker base.



Scheme: *Deuterium scattering in a lithium halogen exchange reaction*

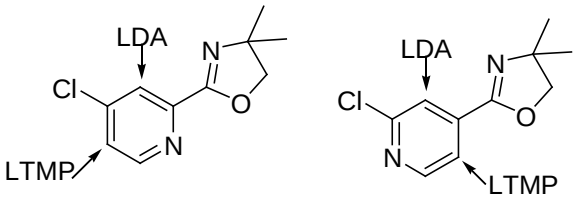
In more complex cases, one where halides and DMGs are present, the choice of base becomes very important. Selecting the appropriate base will control whether or not the lithium halogen exchange or DMC reaction is favoured. One specific example of this

is 2-bromobenzoic acid, **12** (Scheme 4), where two different bases gave different results. It was shown that the amide base lithium 2,2,6,6-tetramethylpiperidide (LTMP) gave the DMC product, **13** where as *n*BuLi gave the exchange product **14**. The isolation of 7% benzoic acid from the LTMP chemistry indicated that some lithium halogen exchange was occurring.



Scheme 4: *Selective DMC and lithium halogen exchange reaction*

In addition to limiting lithium halogen exchange, amide bases have also been employed in directed metalation for their added steric factors. It has been shown that using LTMP favours lithiation at a less hindered site on an aromatic ring compared to lithium diisopropylamide (LDA). Hence, the Hoarau group has been able to selectively lithiate different positions on an aromatic ring system.[36] In order to take advantage of this, the more sterically hindered site on the aromatic ring must also be the more favoured position to do the desired chemistry.



Scheme 5: *Regioselective directed metalation*

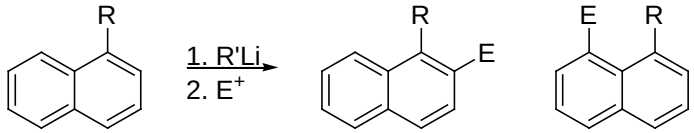
One subtlety of this chemistry is temperature dependence. The above studies were carried out at temperatures ranging from -30°C to -50°C. This detail can be easily neglected as most directed metalation reactions are carried out at -78°C. As such, a false conclusion that LDA on LTMP do not lithiate aromatic rings could be reached if this detail is overlooked.

2.06 Directed *Peri* Metalation

Synthesizing some of the analogues to test as inhibitors in the synthesis of exotoxin A will require going beyond the well understood directed *ortho* lithiation chemistry and lithium halogen exchange reaction. Using 1,8-naphthalimide as a starting point, directed metalation may give analogues of 1,8-naphthalimide. However, directed metalation chemistry has not been thoroughly studied with naphthalene derivatives.[37] Although DMGs have been shown to direct metals to the *ortho* site, the *peri* position of the naphthalene ring will need to be functionalized in order to make analogues of the lead compound under study here.

Presently the highest yielding route to 1,8 functionalized naphthalene derivatives takes several steps.[37] The process finishes with a lithium halogen exchange reaction to install a lithium *peri* to the other functional group. As previously discussed, there are also challenges associated with lithium halogen exchange reactions. Further, there are limited 1,8-naphthalene derivatives available from commercial sources. Combined together, it has led to the belief that, if realized, the *peri* lithiation would be a simpler and more efficient route to 1,8-functionalized naphthalenes.[37]

The *peri* lithiation, in which the DMG directs deprotonation to the C-8 position of the naphthalene derivative, is far less prevalent in the literature. Clayden has been at the forefront, developing this lithiation chemistry.[37] In most of the cases he has documented, lithiation occurs at the *ortho* position (Table 1). He surmised that the best DMGs for the *peri* metalation were functional groups that did not acidify and hence activate the *ortho* position.

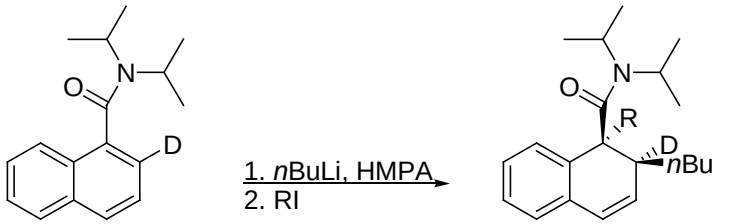


15 **16** **17**

Table 1: *Results of peri lithiation reaction with various substituents*

			Yield (%)		
R	Conditions	E^+	**16**	**17**	Reference
OH	*n*-BuLi, THP, 50°C, 4 h	Me_2S_2	19	50	[38]
OMe	*t*-BuLi, cyclohexane, 20°C, 26 h	CO_2	0	35	[27]
OMe	*t*-BuLi, TMEDA, 20°C	CO_2	59	0	[27]
SO_2NHt-Bu	*n*-BuLi x 3	CO_2	0	14	[39]
$OCONR_2$	*s*-BuLi, TMEDA, THF, -78°C	MeI	90	0	[21]
NMe_2	*n*-BuLi, Et_2O, 20°C, 48 h	DMF	0	76	[26]
CH_2NMe_2	*n*-BuLi, Et_2O, hexane, 20°C, 24 h	$PhCO_2H$	0	58	[40]
$CH(OMe)_2$	*t*-BuLi, Et_2O, 0°C	MeI	13	27	[41]
$CONEt_2$	*s*-BuLi, TMEDA, THF, -78°C	TMSCl	80	0	[21]
$CONi$-Pr_2	*s*-BuLi, THF, -78°C	TMSCl	76	0	[42]

Clayden also documented that amides are also susceptible to nucleophilic attack by alkyllithium bases. This was discovered when he substituted the *ortho* hydrogen with deuterium to take advantage of a kinetic isotope effect. Clayden hoped to slow down the directed *ortho* metalation reaction enough to provide enough time for the *peri* lithiation reaction to occur. Clayden treated **18** with *n*BuLi at -78°C and did not get a reaction. Warming the reaction to -40°C and adding HMPA allowed for chemistry to occur on **18**. However, instead of extracting a hydrogen *peri* the alkyllithium base performed a nucleophilic attack *ortho* to the amide and dearomatized the ring. Quenching this reaction with methyl iodide or *n*propyl iodide gave **19a** and **19b** as a single diastereomers from the addition reaction.



18

19a, R = Me, 61%
19b, R = *n*Pr, 52%

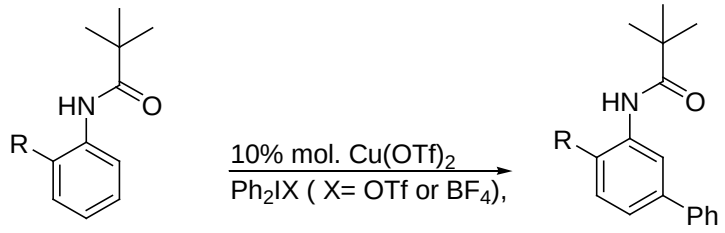
Scheme 6: *Ortho addition of nBuLi to an amide with attempting to direct peri*

From this it can be concluded that the kinetic isotope effect did hinder directed *ortho* lithiation. However, since the *ortho* site was still activated by the electron withdrawing nature of the amide the *peri* lithiation did not occur. This further supports Clayden's conclusions that in order to lithiate *peri* the directed metalation group can not be electron withdrawing as it will activate the *ortho* position in one manner or another.

2.07 Directed *Meta* Metalation

Directed metalation chemistry is a very active area of research. As such, new DMC strategies are being explored.[21] Traditionally DMC is done with an alkyllithium base such as *sec*BuLi**,** *n*BuLi or *tert*BuLi but this does not always have to be the case. Metalation has been achieved with magnesium,[43] zinc,[44,45] aluminum,[46,47] and manganese(II).[48] The basis of this research is that the less polar metal can be coordinated to more elaborate organic components to induce different regioselective and regiospecific reactions. Although, the mechanisms by which these reactions proceed do not fit the classical criteria for being classified as directed metalation reactions they do involve the replacement of aryl hydrogen with a metal. Palladium and copper catalyzed CH activation reactions in certain circumstances can be viewed as directed metalation reactions.

In one specific study directed metalation was achieved specifically for a *meta* isomer with a copper catalysis.[49] Gaunt and Phipps treated several N-phenylpivalamide derivatives, **20a-f**, with copper (II) triflate and diphenyl iodode triflate to exclusively install the phenyl group *meta* to the pivalamide, **21a-f**, via an electrophilic metalation. This result complements the well understood[21] directed ortho metalation reaction very well. Previously, in order to direct *meta* one would have to functionalize *ortho* with a stronger DMG than the original DMG and then do another directed *ortho* metalation resulting in a trifunctionalized aromatic. This new method provides a direct route to the *meta* functionalized compound. The results, Table 2, clearly show that electron withdrawing groups give lower yields, which is indicative of an electrophilic aromatic substitution.



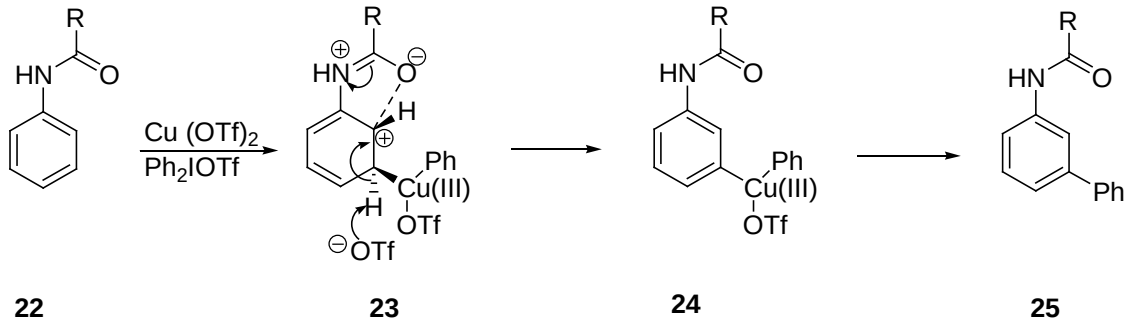
20a-f **21a-f**

Table 2: *Selected results of directed meta metalation*

Compound	R	Yield (%)
21a	Me	79
21b	*i*Pr	86
21c	MeO	93
21d	Ph	84
21e	F	55
21f	$MeSO_2$	11

Previously, Gaunt and Phipps showed that copper can be used for electrophilic aromatic metalation and propose a mechanism based on this.[50] They suggest the formation of an electrophilic copper (III) species, which is attacked selectively *meta*. They hypothesize that the attack is specific for the *meta* site is due to a stabilized cation at the *ortho* position facilitated by the amide. Although they do not have any mechanistic information to support this, the reaction does not work without the amide present and conclude it must participate in some manner. The non-trivial zwitterionic structure **23**, in which there is a negative charge on the oxygen, could interact with the *ortho* carbocation stabilizing it allowing for preferential *meta* attack. This is followed by a rearomatization

reaction to give **24** and a subsequent reductive elimination to regenerate copper (II) triflate and install the phenyl group metal yielding the product **25**.



Scheme 7: *Proposed mechanism for meta electrophilic metalation*

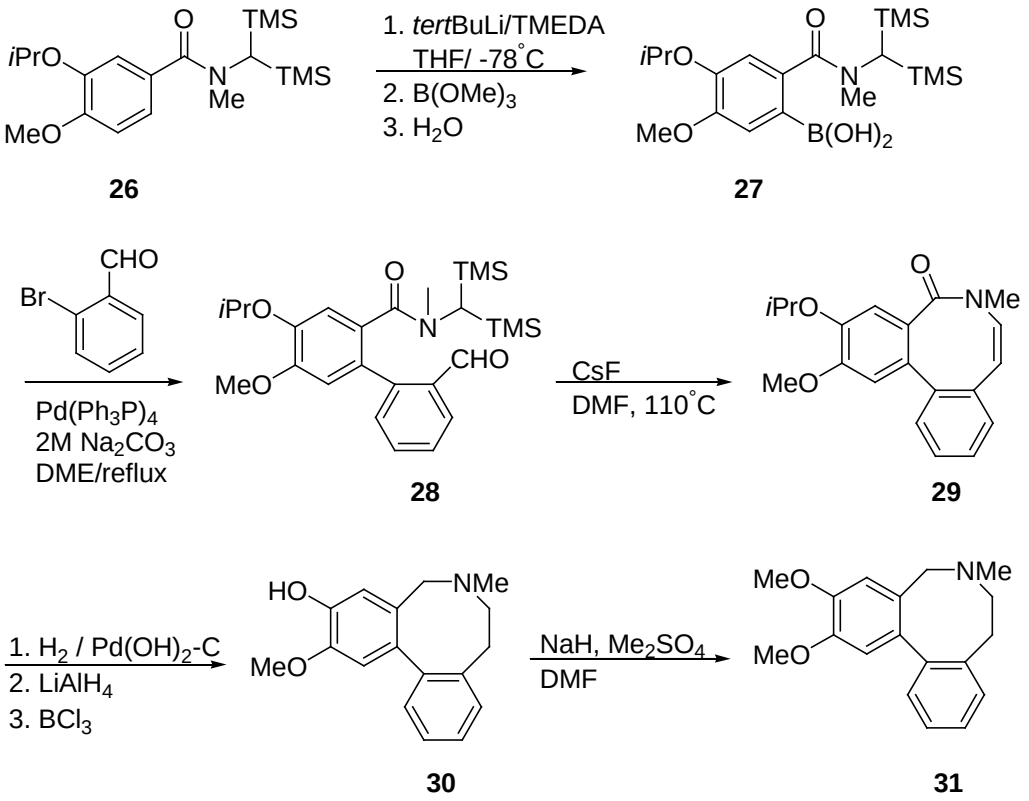
Although this result does not have any immediate consequences to solving the *peri* lithiation, it suggests a strategy that could be used in tandem with more tradition DMC methods to obtain complex polyfunctional benzenes and naphthalenes. Furthermore, if the *peri* lithiation was solved with an amide one could then expand the methodology to naphthyl pivalamides and then obtain 1,3,8-functionalized naphthalenes.

2.08 Synthetic Utility of Directed Metalations

There is a vast library of directed metalation reactions which provide a set of powerful tools for synthetic chemistry. Understanding and exploiting subtleties in DMC can allow for accessing polyfunctional aromatics that would be difficult to achieve with electrophilic aromatic substitution reactions. One such case was the total synthesis of 8-*O*-demethylbuflavine.[51] Although the synthesis was already known, directed *ortho* metalation provided a more direct route because a trisubstituted aromatic could be used as a starting material.

Beginning with the synthetically accessible disilylated amide **26**, Snieckus deployed a regioselective directed ortho metalation reaction which was quenched with

$B(OMe)_3$ then treated with water to give the aryl boronic acid **27**. The regioselectivity of this reaction is a consequence of employing *tert*BuLi as a lithiating reagent with the isopropyl group. Directed metalation reactions can be influenced by steric effects.[36] As such, lithiating selectively on the *ortho* side of the amide without the sterically demanding isopropyl group *meta* is the preferred side for lithiation to occur on.



Scheme 8: *Total synthesis of 8-O-demethylbuflavine*

A subsequent Suzuki coupling reaction with the aryl boronic acid **27** with *ortho* bromobenzaldehyde furnished the uncyclized product **28.** Sneickus then treated **28** with cesium fluoride at high temperature to deprotect the amide and allow for a condensation reaction between the amide and the aldehyde. At this point **29** contained the major ring system of buflavine, all that remained was to adjust several functional groups. This was accomplished by hydrogenating the double bond of **29** then reducing the amide to an

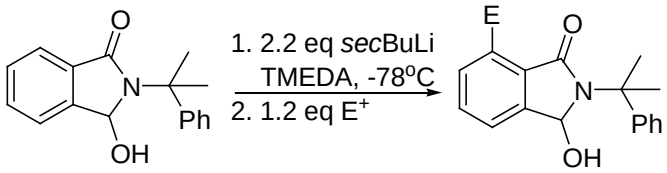
amine using lithium aluminum hydride. Subsequent removal of the isopropyl group using a Lewis acid gave **30** which was O-methylated to give the target product 8-*O*-demethylbuflavine, **31,** in 17% yield overall.

The total synthesis of 8-*O*-dimethylbuflavine speaks to the synthetic applicability of directed metalation reactions. Snieckus's key directed metalation step exploited the subtleties of steric hindrance to selectively produce a key intermediate which could not easily be accessed through electrophilic aromatic substitution. Directed metalation reactions are not just an exercise in methodology but can furnish difficult natural products or as in the above case provide more direct routes.

2.09 Relevant Background Work

Despite the few known examples of the *peri* lithiation reaction, some methodological work has been done by the Snieckus group on related compounds, such as phthalimidine.[52] Snieckus has shown that, when a lithiation can occur either *ortho* to an amide or an aminol, the amide is the more influential DMG (Scheme 9). These compounds, if easily adapted to naphthalene derivatives, may be *peri* directing while blocking the *ortho* position from directed *ortho* lithiation chemistry as well as addition chemistry.

What is more encouraging about this specific example is that it contains the benzamide functionality, a key feature of PARP inhibitors. If similar naphthalene versions can be made, they would be ideal candidates to test for activity against exotoxin A.



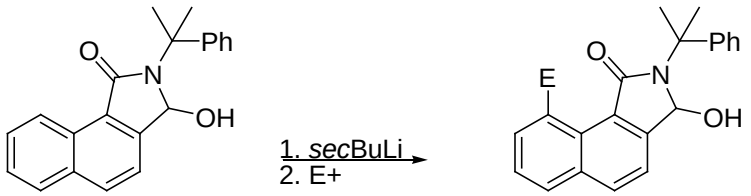
Scheme 9: *Preferential ortho lithiation*

2.10 Previous Efforts

Several years ago Petar Duspara, a former Schwan group member, undertook the challenge of synthesizing a PARP inhibitor intended for the treatment of *P. aeruginosa.* He used the phthalimidine structure as a means of blocking the ortho position of a similar naphthalene derivative (Scheme 10). He proposed that **32** could undergo a *peri* lithiation reaction, providing a class of analogues (**33**) suitable for evaluation in treating *P. aeruginosa* infection.

Duspara devised an efficient synthesis of **32** but encountered difficulties characteristic of the naphthalene derivatives.[4] For instance, the compounds showed minimal solubility in diethyl ether, ethyl acetate, hexanes, and other organic solvents. Consequently, purification by column chromatography proved difficult. Fortunately, his naphthalene derivatives were soluble in toluene and recrystallizable, thereby solving the problem of purification.

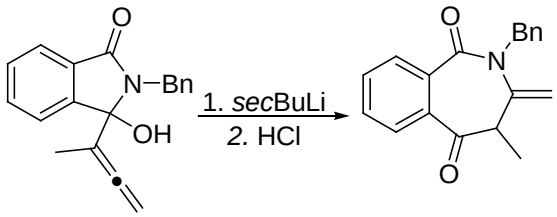
However, Duspara's attempts at the *peri* lithiation reaction were low yielding, rarely exceeding 20% for the above reaction. The success of the reaction was assessed by quenching with deuteriomethanol and measuring the percent deuteration at the *peri* position by NMR. The reaction conditions and reagents were varied with minimal success. Even after optimization, Duspara could not achieve greater than 27% deuteration *peri*.[4]



32 **33**

Scheme 10: *A potential solution for the peri lithiation reaction*

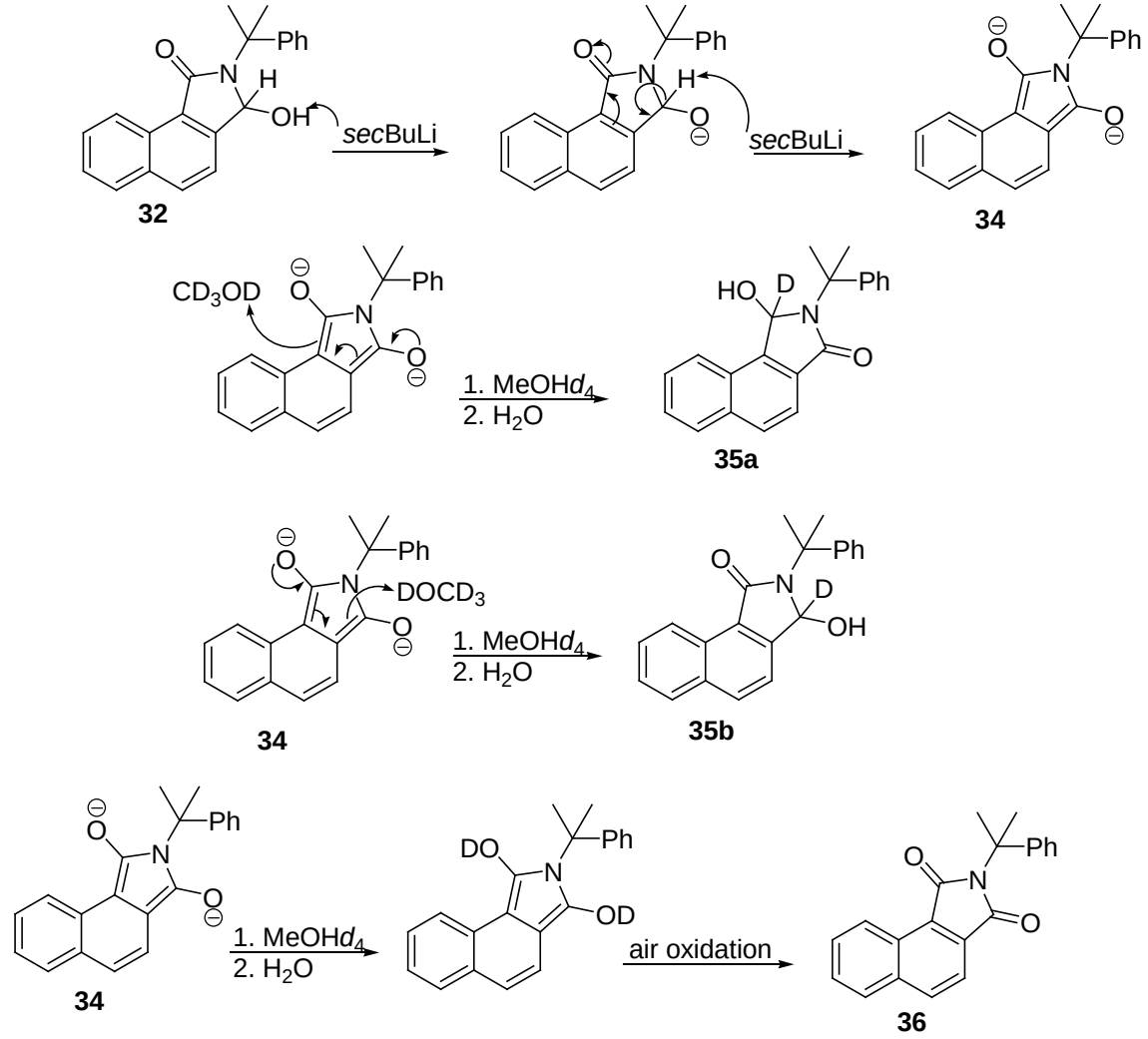
To rationalize his low yields and account for other observed products, Duspara proposed that the lactam ring was opening. Arguing on the basis of pKa, he felt that the alkyllithium would preferentially attack the acidic hydrogen of the alcohol rather than coordinate with the amide group. Opening a lactam ring is known to occur at room temperature[53] but must be observed using a ring expansion reaction, Scheme 11, as they often recyclize quickly. This seemed like a logical explanation. However, NMR analysis of the reaction side products did not support the ring opening hypothesis. Furthermore, Snieckus did not report a ring opening reaction during his studies of phthalimidine.[54]



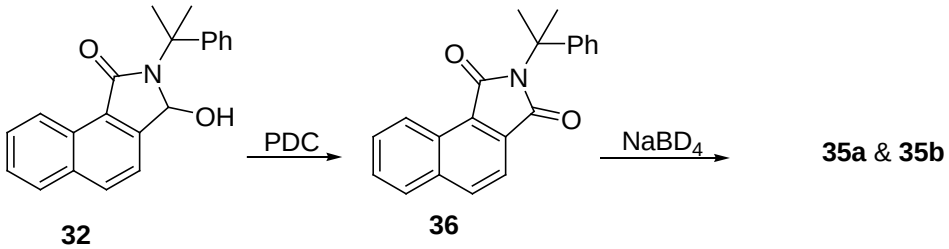
Scheme 11: *Ring opening of an allenyl aminol*

Alternatively, deprotonation of the alcohol might be followed by the removal of the carbinolic hydrogen. This would result in two potential products with deuteration occurring on the lactam ring (Scheme 12). After isolating the side products and comparing their NMR spectra with the proposed compounds prepared from an oxidation and deuterium enriched reduction (Scheme 13), identities of **35a**, **35b** and **36** were confirmed. After several attempts to solve this rearrangement issue, Duspara took his

work in another direction, leaving this and all subsequent questions pertaining to **32** unaddressed.[22]



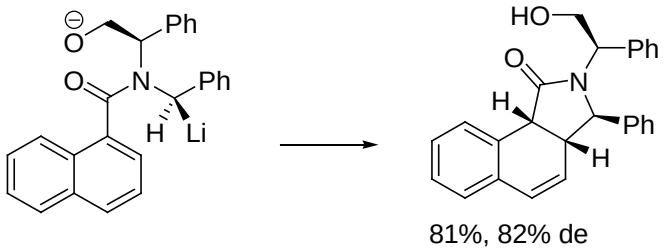
Scheme 12: *The proposed mechanism of the rearrangement*



Scheme 13: *Preparation of suspected side product*

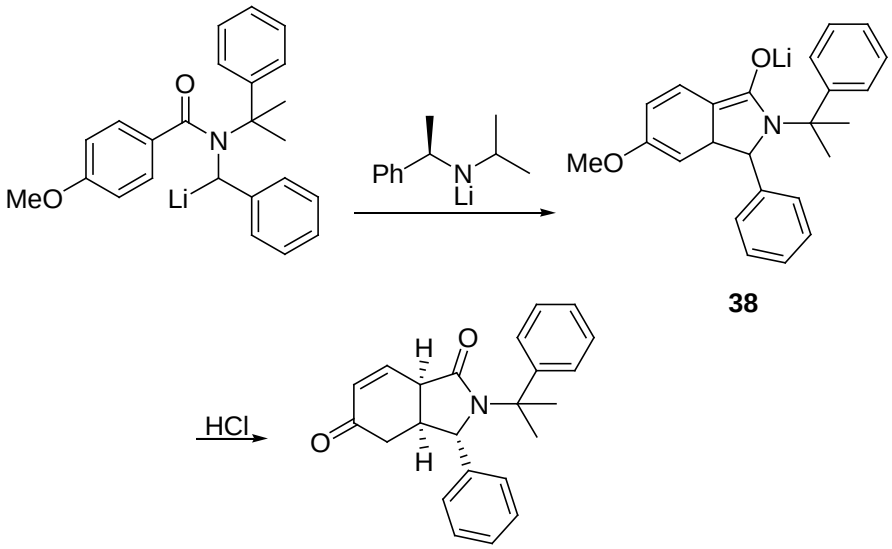
2.11 Aromatic dearomatization

Clayden's work on dearomatizing aromatic rings provides several insights into the different modes of reactivity of benzene versus naphthalene aromatic ring systems. Clayden has shown that naphthalene derivatives can be easily dearomatized with alkyllithium bases in one ring to give a stable product[55] (Scheme 14). However, he notes, that doing similar dearomatization reactions on benzene systems are considerably more difficult.



Scheme 14*: A dearomatization reaction of a naphthalene derivative*

Clayden was able to destroy the aromaticity in a benzene system (Scheme 15), however, he had to employ a trapping strategy in order to isolate a stable compound.[56] Installing the 4-methoxy group before hand was required in order to isolate compound **37**. Quenching the reaction with strong acid allowed for **38** to tautomerize into a ketone. Otherwise without the 4-methoxy the ring system would rearomatize back to starting material upon work up.



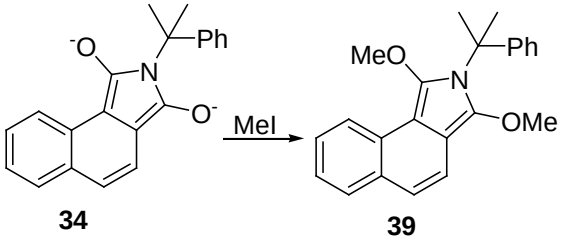
Scheme 15: *Dearomatizing a benzene system*

Thus, from Clayden's work an argument can be put forward that the aryl ring of **32** is more reactive than Snieckus' corresponding benzene system. This makes the unexpected side reaction much easier in the naphthalene system allowing it to proceed. Where as in the benzene system the process is less favoured and hence, is not observed.

2.12 Trapping

Although the mechanism proposed by Duspara fits the results, a more in-depth investigation is required to validate it. In addition, proper mass spectrometric analysis to confirm the products, trapping experiments may provide the required evidence and other valuable insights. These experiments involve intercepting the reaction at suspected intermediate stage where **34** is present and forcing it along another path in an irreversible direction.[57] A simple S_N2 reaction (Scheme 16) may be the best method to access a trapped intermediate such as **39**. More complex reagents may do undesired chemistry resulting in purification difficulties or a failed reaction. As such, treating the

intermediate with methyl iodide will likely be the best possible method to access the intermediate.



34 **39**

Scheme 16: *Proposed trapping experiment*

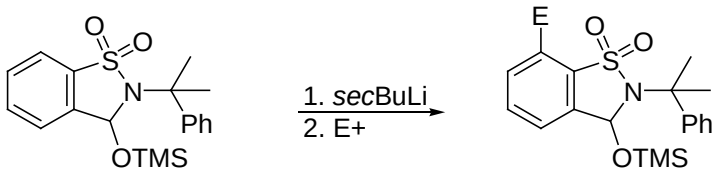
2.13 Phthalimidine Chemistry

A potential solution to the rearrangement is to block the reactive center with a common protecting group. Silyl protection strategies encompass an array of reagents that range from small groups, such as trimethylsilyl (TMS), to very bulky groups, like *tert*-butyldiphenylsilyl (TBDPS).[58] Thus, reactivity and selectivity can be tuned by selecting from many suitable protecting groups.

One particularly interesting silyl protecting group is TMS. Despite its reputation for being labile, the Snieckus group demonstrated that it remains intact and permits reasonable yields when a variety of lithiation conditions were preformed on sulfonamide **40** (Table 2).[52,59] Adapting this procedure to naphthalene derivatives may adequately deactivate their carbinolic centers, thereby directing a *peri* lithation. Also, a procedure for silylating **32** with TMS could likely be adapted for larger more robust protecting groups.

Snieckus also reports that the reaction is successful without TMS protection on the alcohol.[52] Regardless, this provides a good starting point for the protection of the lactam ring alcohol. If the TMS proves insufficient to protect the compound during the

novel *peri* lithiation reaction, then more robust groups can be employed; *tert*-butyldimethylsilyl (TBS), for instance, which is 10^4 times less susceptible than TMS to hydrolysis.[58] TBS is a reliable protecting group and has added steric bulk which may prove beneficial. If necessary, TBDPS may be employed; it is roughly 100 times more resistant to hydrolysis than TBS.[60] Should TBDPS prove inadequate protection, then this would provide negative evidence against the proposed mechanism.



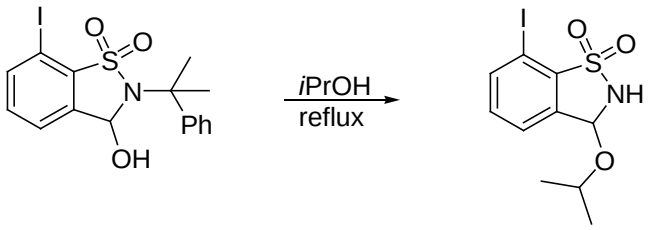
40 **41a-c**

Table 3: *Selected lithiation reaction results*

Product	E^+	E	yield
41a	TMSCl	TMS	65%
41b	MeSSMe	Me	57%
41c	I_2	I	69%

The isopropyl ether group is another avenue of oxygen protection used by Snieckus, though not completely explored.[52] Snieckus successfully affixed the isopropyl (*i*Pr) group on the alcohol of his sulfonamide analogue by heating it with an excess of *i*PrOH; (Scheme 17) however, he did not test its reactivity in a lithiation reaction. This specific reaction is particularly interesting because the isopropyl group, on the other hand, is removed by refluxing under acidic conditions; thus, eliminating the possibility of

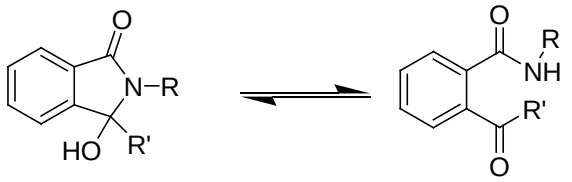
premature deprotection during lithiation.[61] Thus, *i*Pr is also a promising avenue of protection of **32.**



Scheme 17: *Creation of an isopropyl ether*

Protection of the alcohol of **32** will also prevent the possibility of the lactam ring opening. It is believed that the ring opening equilibrium lies so far to the closed form that it can be considered an irreversible reaction. This assumption is based upon previous NMR and preparative studies which suggest the aminol prefers the ring closed form even once deprotonated.

Flitsch performed an NMR study of a variety of analogous compounds, table 4.[62] He examined the exchangeable hydrogen as well as the R' group using ^{1}H NMR spectroscopy and could use these signals to determine whether the ring of **42a-d** was opened or closed. An open ring would result in **43a-d**, where the R' group would show up between 2.1 and 3.6 ppm if a ketone were formed, where as the aldehyde would present a proton signal at 10 ppm. The closed ring system would have either a carbinolic hydrogen, visible around 6.6 ppm[52] or a CH_3 which presents itself around 1.8 ppm.[63] Flitsch's observations all supported the ring closed form, **42a-d**.



42a-d **43a-d**

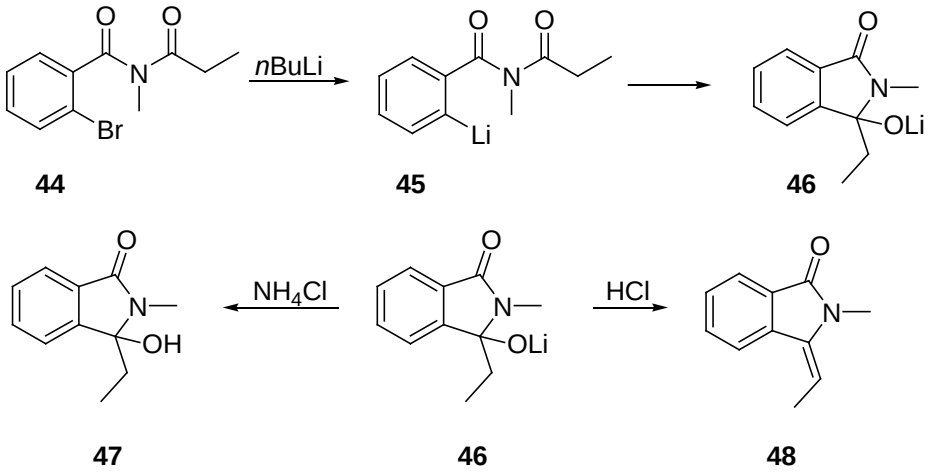
Table 4: *Selected results from Flitsch's study*

Compound	R	R'	Cyclic/open
42a	H	H	Cyclic
42b	CH_3	H	Cyclic
42c	H	CH_3	Cyclic
42d	CH_3	CH_3	Cyclic

Deprotenating the alcohol of the lactam ring is of greater concern as the alkoxide is more prone to undergo a retro aldol. Wolfe did lithiation chemistry on a similar system and contended that the ring remained closed.[64] He used lithium halide exchange chemistry to access cyclic ring systems starting with benzamides, Scheme 18. He obtained his desired product **49**, by treating **44** with *n*BuLi at -78°C. He then quenched the intermediate product **46** with HCl to get an elimination reaction to occur giving **48**. However, to determine whether or not **46** was cyclic or not the reaction was quenched with ammonium chloride to give **47**. From this he concluded that the intermediate, **46**, must be cyclic.

The ring open chemistry of an allenyl aminol, Scheme 11, was done at room temperature where as the chemistry done by Wolfe was at -78°C. It stands to reason that the large variation in temperature may account for this change in chemistry. Heating

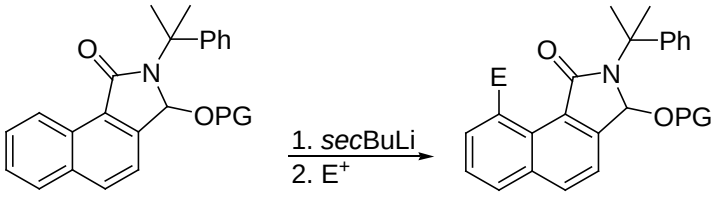
these deprotonated alcohols could supply enough energy for the equilibrium to become more prevalent.



Scheme 18: *Synthetic route executed by Wolfe*

3.0 Proposal for Research

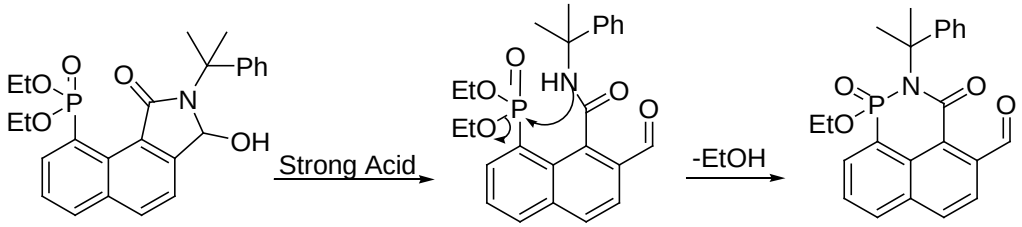
Pseudomonas aeruginosa infection is a serious threat for people with cystic fibrosis.[2] Thus, the ultimate goal of this research is to improve and extend these lives by developing novel molecules, active against the bacteria. It is expected that these novel molecules, based upon the structure of 1,8-naphthalimide, will possess high medicinal efficacy and improved water solubility (Table 5). The synthesis will feature the *peri* lithiation of **32**, facilitated by judiciously chosen protecting groups. A trapping mechanism should provide an understanding of the undesired side reactions. Beyond this, it should be possible to open the lactam ring, forming 1,8-naphthyl lactam (Scheme 19) and providing another set of compounds for the Merrill group at the University of Guelph to evaluate.



49 **50a-d**

Table 5: *Possible electrophiles for quenching the lithiation reaction*

Product	E^+	E
50a	$ClCO_2Et$	CO_2Et
50b	Cl_2SO_2	$ClSO_2$
50c	$ClPO(OEt)_2$	$PO(OEt)_2$
50d	CH_3CHNCH_3	$CH_3CHNHCH_3$



50c **51**

Scheme 19: *Opening of the lactam ring*

Merrill has suggested that planar geometry of **7** is important in the competitive inhibition of *P. aeruginosa*. As such **51** (Scheme 19) would be an excellent analogue of **7**.[14] The aldehyde is another center from which other functional groups can easily be obtained; thus, expanding the number of compounds accessible after quenching the lithiation reaction with an electrophile. Furthermore, the phosphonate will greatly increase water solubility, particularly if hydrolyzed, addressing another challenge facing the optimization of 1,8-naphthalimide.

However, before the compounds can be tested, the cumyl group (Figure 5) must be cleaved. This transformation will bring about increased solubility in organic solvents and decrease it in aqueous solvents. Fortunately, Snieckus has shown the cumyl group can be cleaved with trifluoroacetic acid (TFA) and BF_3 Et_2O.[52] In fact, it may be possible to open the lactam ring and cleave the cumyl group in one step.

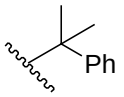


Figure 5: *The cumyl group*

The first leg of the project will focus on the trapping reactions and on evaluating protecting groups. A variety of protecting group experiments will be conducted to determine their viability and stability during lithiation chemistry. Some protecting groups, promising because of their robustness and size, include TMS, TIPS, TBS and TBDPS.

Of these, TMS is the least resilient and is easily removed by hydrolysis under mildly acidic conditions. However, Snieckus has shown that TMS will not be removed during *ortho* lithiations; thus, TMS may adequately protect the center. Even if TMS is removed during the *peri* lithiation chemistry, the procedure for placing it on **32** will be instructive as to whether more robust groups such as TBS or TIPS need to be installed;. These larger groups normally have to be removed using fluoride under aprotic conditions. As such, the chances of success may be greater with TBS than TIPS.

Should these protecting groups fail, TBDPS will be used to protect **32**. TBDPS is a very large protecting group with two phenyl rings and a *tert*-butyl group. It is removed with exposure to a fluoride source for 1 to 5 hrs, or with a strong aqueous base.[65] Also, it may be difficult to install the protecting groups, as both it and **32** are very large

molecules. The silyl chloride may be sterically impeded from coming close enough to the alcohol for a reaction to occur.

Trapping will be done in tandem with the protecting group experiments, as both should provide insight into the mechanism of the rearrangement. Trapping may reveal some kinetics, that is how quickly the intermediate is formed and its persistence. However, the trapping experiments present their own challenges.

Trapping provides a reactive intermediate with an alternate lower energy pathway, leading to a distinct product. However, it is anticipated that this will be difficult to observe while the reaction is proceeding. Traditional organic reactions are monitored by thin layer chromatography (TLC), where the reaction mixture is spotted against the starting material. When starting material is no longer observed, the reaction is quenched to the products. However, with **32,** the lithiation may proceed to **34** which will hydrolyze to either **35a** or **35b** as silica gel is inherently acidic. Molecules **36** have a different retention factor (R_f) than **32**; thus, no information is gained about the intermediate.

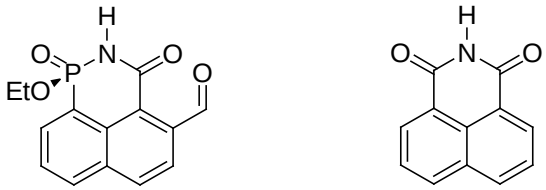
Observing the chemistry using of **32** with a React-IR™ instrument may provide insights in to how the chemistry proceeds. The MT React-IR™ is an infrared (IR) spectrometer that continually monitors a reaction, providing a real-time picture of its progress.[66] It can be applied to observe the trapping of **32** with an electrophile in a simple alkylation reaction.

Enolates have distinct diagnostic bands, between 1670-1600 cm^{-1},[67] which can be used for assistance with the trapping experiments. The disappearance the amide carbonyl band[4] at 1700 cm^{-1} and the appearance of a band between 1670-1600 cm^{-1} would suggest the formation of **34.** Further, the disappearance of these bands subsequently would be in

agreement with **34** having been reacted to another product. Thus the MT React-IR™ can be used to assist in the trapping experiments.

Once the *peri* lithiation is understood, the second leg of the project will be performed. Experiments using various electrophiles will be conducted. Possible electrophiles have been highlighted (Table 5), although many others can be employed should they suit some of Merrill's criteria such as higher water solubility than 1,8-naphthalimide.

Also, the electrophiles will also be evaluated on the basis of stability to strong acid. Strong acid will be used to open the lactam ring and cleave the cumyl group to compounds of the form **51** which bears structural similarities to **7** (Figure 6)**.** This will be the ultimate end game of the project with regards the chemistry.



51 **7**

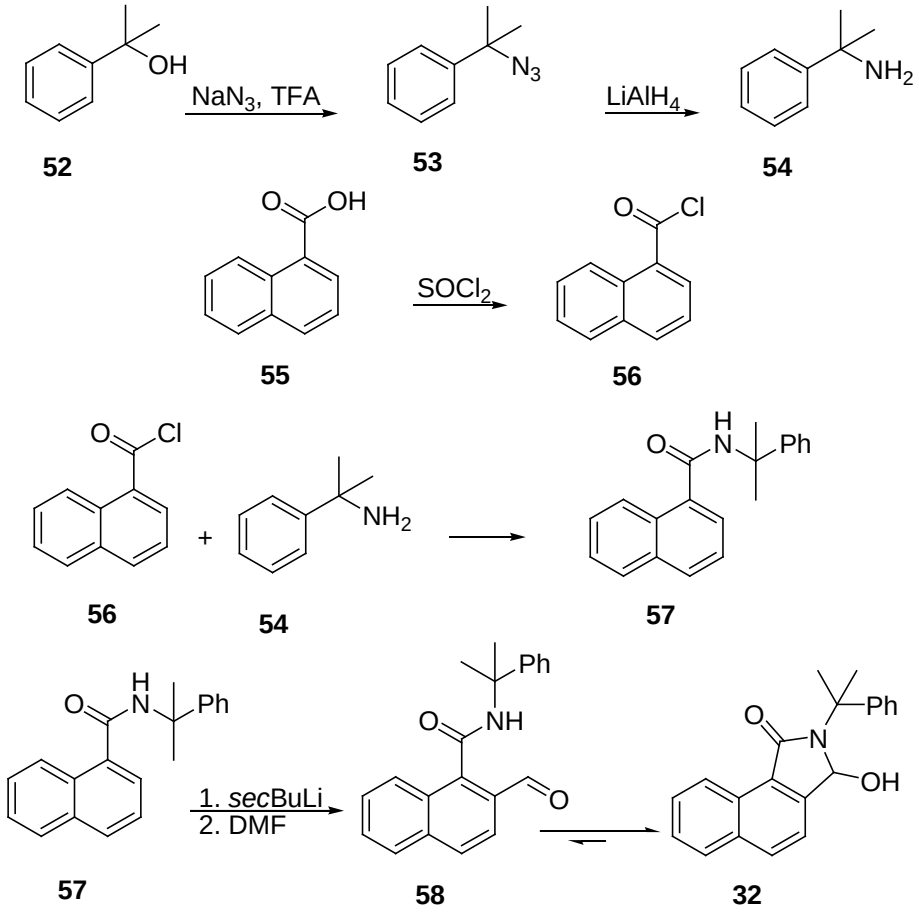
Figure 6: *A target molecule versus the original lead*

4.0 Results and Discussion

4.01 Starting Materials

The substrate, **32**, employed for the development *peri* lithiation reaction is not commercially available and had to be synthesized. However, Duspara developed a quick and efficient synthesis of **32**.[4,22] The synthesis began with cumyl alcohol (**52**), which when treated with strong acid and NaN_3 produced the benzylic cation which is attacked

by the azide ion, producing the cumyl azide, **53** (Scheme 18). The cumyl azide was reduced to the cumyl amine (**54**) using two equivalents of lithium aluminum hydride. Duspara prepared the requisite amide from naphthoic acid (**55**), treating it with thionyl chloride to produce the acid chloride **56**. To this chloride, amine **54** was added, yielding the amide **57**, a compound suitable for a directed *ortho* lithiation reaction to form lactam **32**.



Scheme 20: *Established Synthesis of **32***

Although the synthesis of **32** is already established,[22] modifications of Duspara's original synthesis were performed due to limited commercial availability of certain reagents. Thionyl chloride was not employed in the synthesis as it cannot be imported in

to Canada. Oxalyl chloride was employed as a cost effective substitute. Furthermore, oxalyl chloride is a much milder and user friendly reagent.

4.02 Mechanistic Investigation

The investigation of the suspected dearomatization chemistry of **32** was performed using the React-IR™, proper mass spectrometric analysis and trapping experiments. The starting point of this investigation was the attempted optimization of *peri* lithiation of **32** and proper mass spectrometry of selected. This was achieved by repeating the previously reported literature reaction: treating **32** with methyllithium at -78°C, charging with TMEDA, adding *sec*BuLi and finally quenching with deuteriomethanol to ascertain the extent of lithiation. The equivalents of *sec*BuLi were varied to assess the optimal conditions for the targeted lithiation. The equivalents of methyllithium were not varied in the optimization as its role is to the acidic hydrogen from the hydroxyl group.

The results of these experiments (Table 6) show that increasing the equivalents of *sec*BuLi increases the formation of **36** and **35a** which are believed to be accessed though carbinolic deprotonation of **32**. Furthermore, increasing the amount of *sec*BuLi promotes an overall decrease in total reaction yield of the three products.

These results are consistent with a mechanism proposed by Duspara: the carbinolic center is the preferred center of attack. It can be surmised from this that adding more *sec*BuLi pushed the reaction, Scheme 20, more to completion, formation of intermediate **34**. At this point, **34** can attack from either side of the ring, scheme **20**. Isolating relatively similar amounts of **35a** and **35b** when more *sec*BuLi is used would

suggest the there is no preference between which side of the 5 member ring performs the conjugate enol attack and extracts a deuterium from deuteriomethanol.

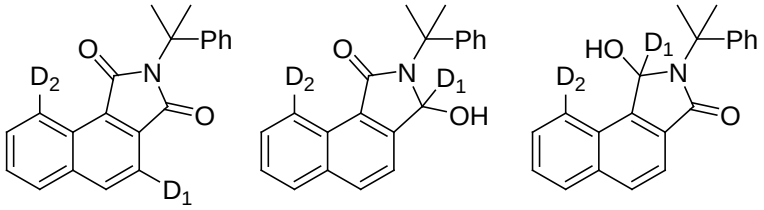
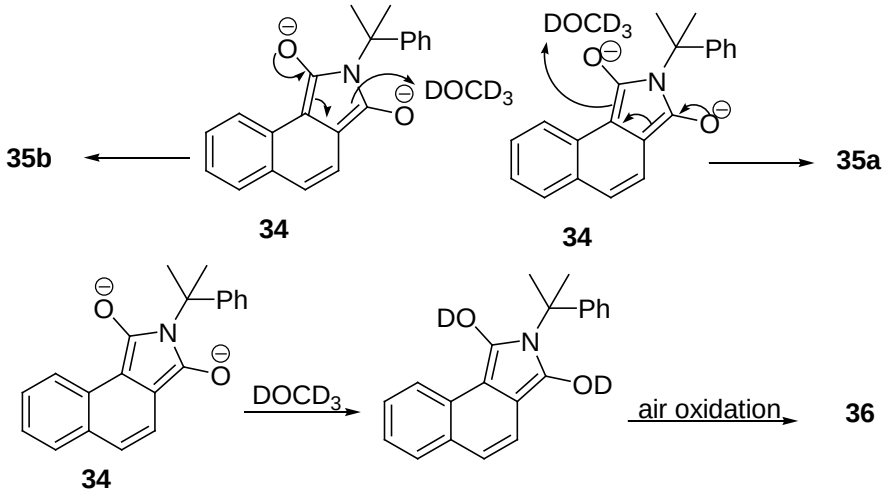


Table 6: *Optimization of the peri lithiation*

	36	**35b**	**35a**
Eq. *sec*BuLi	Yield %(%D_1, %D_2)	Yield %(%D_1, %D_2)	Yield %(%D_1, %D_2)
1.2	1.0 (0, 0)	78 (28, 68)	1 (100, 90)
1.8	18 (0, 12)	27 (8, 73)	20 (100, 78)
2.3	10 (10, 25)	15 (20, 75)	14 (100, 86)
2.8	22 (0, 0)	16 (10, 80)	21 (88, 40)
3.3	19 (14, 12)	9 (11, 82)	15 (100, 74)

% deuterium incorporation is +/- 11%



Scheme 20: *Formation of **35a & b** and **36** from **34***

Proper mass spectrometry was performed on **35b**, specifically with 3.3 equivalents of *sec*BuLi trial. This was done to validate and possibly better understand the % deuterium incorporation. Electron impact ionization was used to obtain M^+ ions for **35b** and **32.** Compound **32** was used to obtain a fragmentation pattern baseline for comparison with against **35b**, Table 7**.** The 317.2 g/mol ion corresponds to the exact mass of **32** and compound **35b** shows no 317.2 g/mol ion. As such it can be concluded that every molecule of **35b** bears at least one deuterium with in the molecule, although the exact site cannot be specifically ascertained.

Table 7: *Ions of interest found in the mass spectrum of **32** and **35b***

32		**35b**	
Ion M^+, g/mol	Normalized intensity	Ion M^+, g/mol	Normalized intensity
317.2	100	318.2	100
318.2	23.74	319.2	49.24
319.2	3.21	320.2	9.70
		321.1	1.25

Since the specific entry under consideration has 82% deuterium incorporation at the *peri* site and 11% deuterium incorporation at the carbinolic site it stands to reason that there is more deuterium incorporation within molecule **35b** than measures by NMR**.** This presumably arises from measuring errors associated with the NMR method or minor deuterium incorporation at other sites within the molecule which cannot be seen in the proton NMR.

Examining the other ions associated with **35b** and **32** lends weight to the NMR analysis having the lack of sensitivity to measure the deuterium incorporation accurately. This can be logically deduced by looking at the two other ions of **32,** 318.2 and 319.2 g/mol. If a sample containing 100% deuteration at the *peri* and carbinolic position was analyzed using mass spectrometry one would expect the ion fragmentation pattern to shift by two mass units. The last major ion one would expect to observe would be 321.2 g/mol. However, if there was deuterium at a third site within the molecule, not detected by ^{1}H NMR, one would expect another ion weighing 322.2 g/mol to be observed in the low resolution mass spectrum. The absence of this specific ion, 322.2 g/mol, implies that there is no third site of deuteration within molecule **35b** and that all the deuteration within **35b** is at its carbinolic and *peri* positions.

Theoretical calculations using WSEARCH32[68] mass spectrum software were performed in an effort to better interpret the data. The program was employed to first obtain the ions associated with **32** bearing one deuterium and two deuterium atoms within the molecule (Table 8) in low resolution electron impact mass spectrometry. The ions of the parent compound, **32,** were not taken into account. The ions obtained with **35b** did not have an observed ion corresponding to 317.2 g/mol. This ion corresponded to the major ion of the starting material **32** with no deuterium incorporation. The absence of a 317.2 g/mol ion in the mass spectrum of **35b** implied that every molecule of **35b** had at least one deuterium residing within every molecule of the sample.

Then using Microsoft Excel, computer iterations were done to obtain an approximate ratio of single and doubly deuterated **32** that would be required to observe

the four ions and at their specific normalized intensities. The calculations showed that 80% of **35b** had one deuterium and 20% of it had a second deuterium.

Table 8: *Predicted ions associated with the mono and doubly deuterated **32***

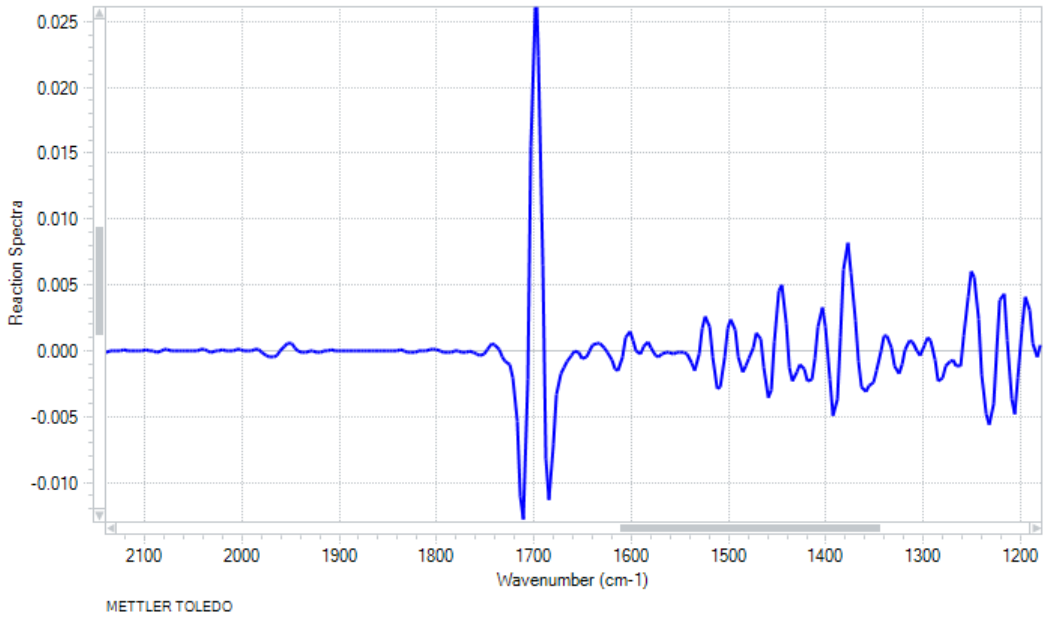
32, 100% mono deuterated		**32**, 100% doubly deuterated		Theoretical	Observed
Ion, M^+ g/mol	Normalized intensity	Ion, M^+ g/mol	Normalized intensity	80% Mono 20% Doubly	
318.1	100			100	100
319.1	24.26	319.1	100	49.26	49.24
320.1	3.22	320.1	24.28	9.29	9.70
321.1	0.3	321.1	3.2	1.1	1.2

After these calculations were completed it was decided that the results shown in Table 6 of the percent deuteration measured by ^{1}H NMR's should bear an error of 11%. Further study of the chemistry of **32** was done using the React-IR™. The React-IR™ was used to help establish the suspected intermediate **34**. The reaction was done exactly as Duspara had reported but with a 10 fold increase in concentration to increase the signal-to noise ratio of the analysis, helping in the collection of quality spectra. Representative spectra of key points of the experiment are shown below.

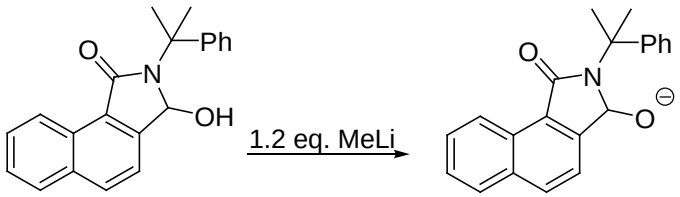
The experiment began with collection of a reference spectrum (Spectrum 1) of **32** dissolved in THF at -78^{o}C. This was followed by treatment of the reaction solution with 1.2 equivalents of methyllithium. At this point (Spectrum 2, Scheme 22), a slight shift in the carbonyl stretching frequency from 1699 to 1679 cm^{-1} was observed. This change of frequency is consistent with a reduction in double bond character of the carbonyl, a

situation that may arise when electron donating groups can donate electron density. For deprotonated **32**, it is possible that some elongation of the amide nitrogen to carbinol carbon bond occurs which gives the nitrogen more electron density to share with the carbonyl and reduces its bond order.

No new carbonyl bands were observed, if the lactam ring of **58** were to open once the alcohol was deprotonated one would expect to observe a second carbonyl band around 1706 cm^{-1} brought about from the newly formed aldehyde. Further more, there would be bands appearing around 2850 and 2750 cm^{-1} corresponding to the C-H stretch of an aldehyde. Spectrum 2 implies the lactam ring of **58** is closed at the particular stage of the reaction.

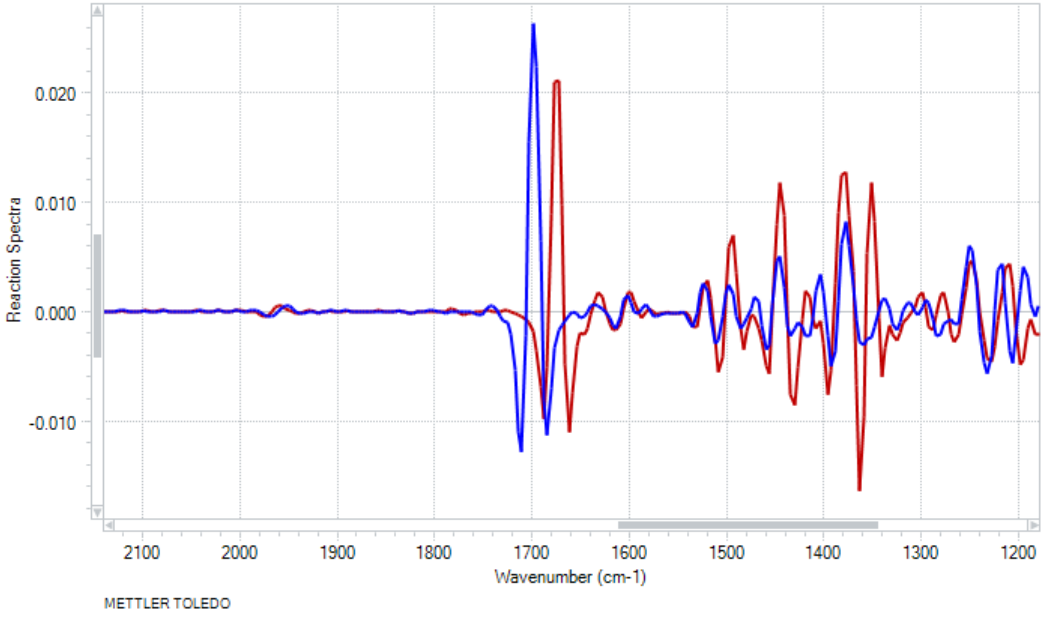


Spectrum 1: ***32*** *Dissolved in THFat -78°C*



32 **58**

Scheme 22: *Treatment of **32** with methyllithium*

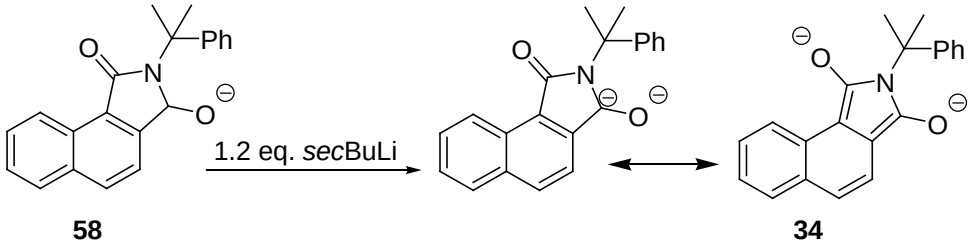


Spectrum 2: *Compound 32 shown in blue treated with methyllithium shown in red*

After one hour of stirring at -78°C, the solution was then charged with TMEDA and then treated with *sec*BuLi (Spectrum 3, Scheme 23). The carbonyl peak of the amide began to reduce in intensity and eventually disappear. No other carbonyl bands were observed at this stage of the reaction. This suggested that the lactam ring was still closed. The loss of the amide band coupled with no new carbonyl bands in Spectrum 3 supports the proposed dearomatization reaction as per Scheme 12.

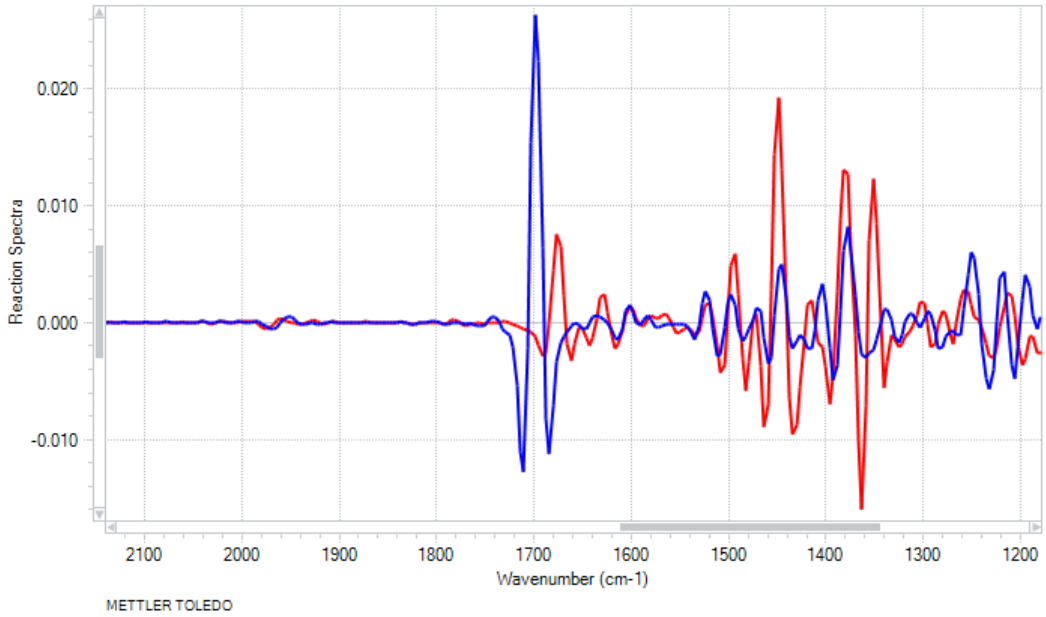
After stirring for 1 more hour at -78 ^{o}C the reaction was then quenched with deuteromethanol. The reaction was stirred at -78 ^{o}C for one half hour then warmed to

room temperature. The incorporation of deuterium in Spectrum 4 is shown by the carbon-deuterium alkyl stretching at 2028 and 2158 cm^{-1}.[69]



58 **34**

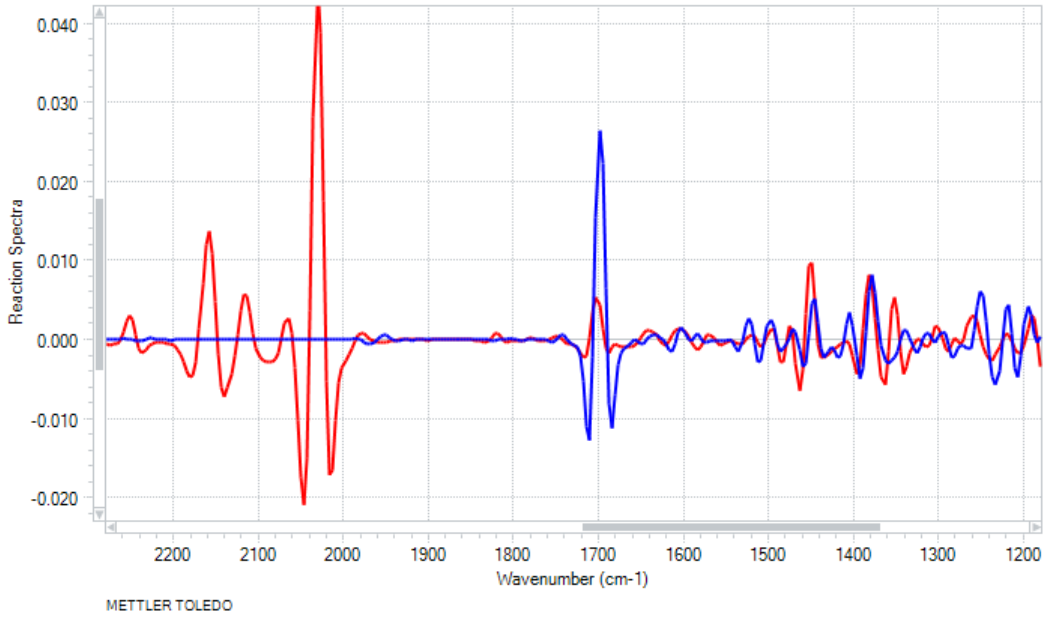
Scheme 23: *Treatment of **32** with 1.2 equivalences of secBuLi*



Spectrum 3: *Compound **32** shown in blue treated with methyllithium and secBuLi shown in red*

The information acquired with the React-IR™ lends weight to the previously proposed mechanism. As diagnostic bands for this proposed mechanism were observed and bands anticipated for the ring opening were not. At this point, it was a reasonable assumption that the originally proposed mechanism was in fact the prominent side reaction in the proposed *peri* lithiation of **32**. With a good understanding of how **32**

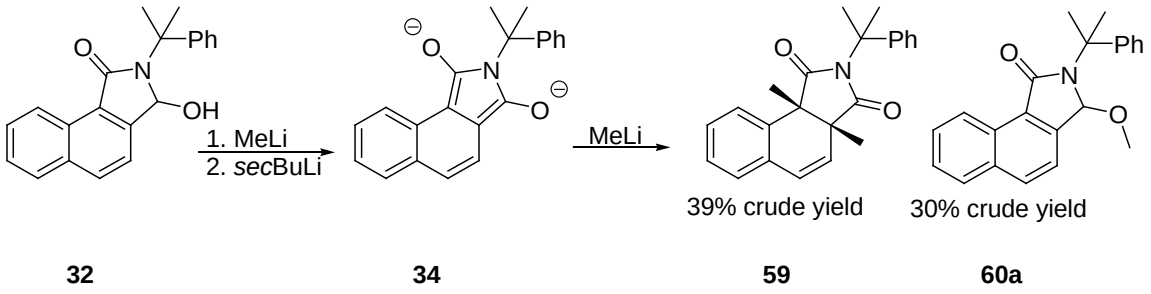
reacted with alkyllithium bases in hand, trapping of **34** to better support the mechanism was undertaken.



Spectrum 4: *Copound **32** shown in blue after quench with deutromethanol shown in red*

Trapping proved to be a very difficult aspect of the mechanistic study of **32**. Several different reactions were occurring at the same time yielding several products. When **32** was quenched with one of the simplest electrophile, deuteriomethanol, **35a** & **b** and **36** were isolated as a complex mixture of partially deuteriated samples. As such when methyl iodode was used as a quenching agent six different products were observed in the ^{1}H NMR spectrum of the crude reaction mixture which made purification very difficult. However, the reaction was substantially improved when the quenching agent, methyl iodode, was added to the lithiated mixture at -78°C in an identical amount of volume of THF as the reaction mixture. Furthermore, holding the reaction at -78°C for one hour after addition of methyl iodide greatly improved the separability of the components of crude reaction mixture.

Originally, the expectation was O-methylation of **34**, however, the ^{1}H NMR spectrum of the crude reaction mixture suggested otherwise. The two principal products observed, scheme 24, were **59** and **60a**. Their crude yields were measured using an internal standard. A known amount of 1,4-dimethoxybenzene was the added to the sample before acquiring a ^{1}H NMR spectrum. Compound **59** is the product of bridgehead alkylation of **34** and **60a** is due to simple O-methylation of **32**, presumably resulting from no reaction of **58** with *sec*BuLi.

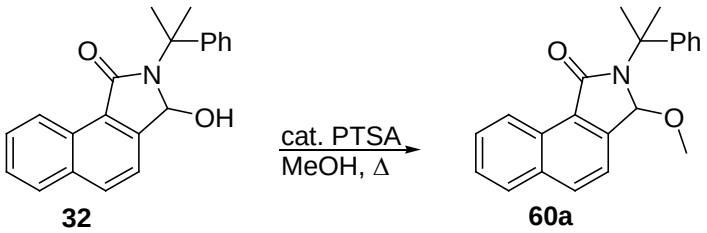


Scheme 24: *Major products of trapping **34** with MeI.*

Purification of the two major products also proved to be a challenging task. The two products had very similar polarity and had to be separated through centrifugal chromatographic using 35% dichloromethane in pentane as eluent. After three hours several pure fractions for **59** were obtained in an over 14% yield. The stereochemistry of compound **59** was assigned using a Nuclear Overhauser Experiment (NOE). The results showed an interaction between the two bridgehead methyl groups. This suggested the two bridgehead methyl's of **59** reside on the same face of the molecule as the mixture of enantiomers.

However, the majority of the products were still coming off the plate as mixture. Compound **60a** was prepared from **32** by refluxing in methanol with a catalytic amount

of PTSA to obtain a pure sample for comparison (scheme 25).[52] This necessitated the internal standard for the NMR spectrum of the crude reaction for reporting the yields of both products.



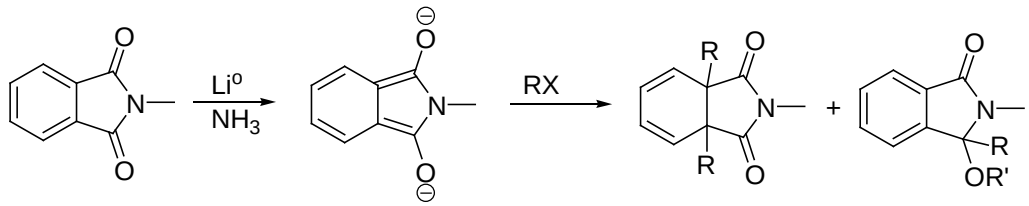
32 **60a**

Scheme 25: *Preparation of **60** from simpler chemistry*

This isolation of the bridgehead alkylation product **59** has been reported before. A study performed by Flynn on N-methylphthalimide, **61**, showed the chemistry observed with **34**.[70] Flynn performed a dissolving metal reduction on **61** to get compound **62** which he then quenched with a variety of electrophiles, Table 9, to get two different types of products; bridgehead alkylation, **63,** and benzylic alkylation, **64.** Methyl iodide gave a mixture of the two products, as did ethyl iodide. However, there was a much larger preference in the ethyl iodide quench for benzylic alkylation than when **62** was treated with methyl iodide. Expanding this chemistry to larger electrophiles such as benzyl bromide and TMSCl gave only benzylic functionalized products. He surmised after using various electrophiles that smaller electrophiles favour the bridgehead alkylation on the basis of sterics.

It is however, interesting that no naphthylic alkylation products were observed when **34** was quenched with methyl iodide. This may come about from differences in the reactivity of **34** versus **62.** Alternatively, **59** could be the kinetic product of the reaction of **34** with methyl iodide. The reaction was held at -78°C for one hour after quenching with methyl iodide. Holding a reaction at cold temperature allows for the kinetics of a

given reactions to dictate which product is formed. Whereas allowing a reaction to warm may allows for the thermodynamics to control which product is formed.

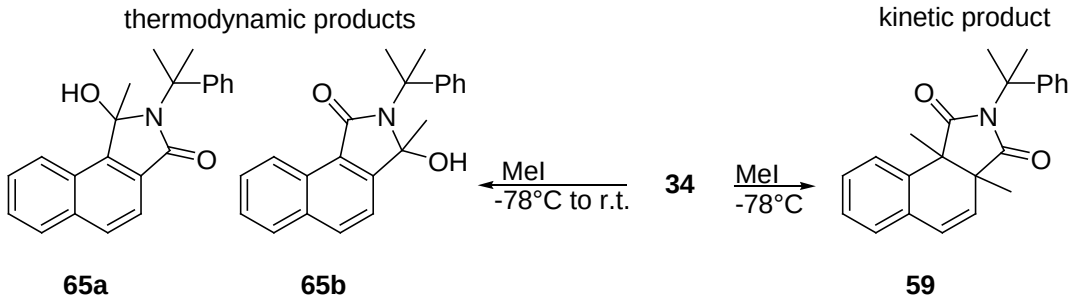


61 **62** **63a-d** **64a-d**

Table 9: *Electrophiles used to quench the dianion of N-methylphthalimide*

Entry	Electrophile	**63**	**64**
a	MeI	36 %	37 % R = Me, R' = H
b	EtI	Trace	85 % R = Et, R' = H
c	BnBr	Trace	96 % R = Bn, R' = H
d	TMSCl	None	85 % R = H, R' = TMS

Flynn allowed his reaction to warm to room temperature slowly immediately after quenching. This may allow the thermodynamic more stable product **64** to from resulting in a mixture of products. If the reaction of **34** with methyl iodide was allowed to warm up to room temperature immediately after the addition one would expect to observe the formation **65a** and **65b**, Scheme 26. This may have been the case in other earlier experiments designed to trap **34** as there were several products produced. However, the resulting mixture of products could never be successfully purified. As such, there is no basis to rule out or confirm the presences of them.



Scheme 26: *Three different products possible from quenching **34** with methyl iodide*

This leads to a level of ambiguity with regards to the difference in reactivity between **34** and **62**. It may come about from keeping **34** under kinetic control after quenching with methyl iodide or be attributed to differences in the chemistry. Regardless, the reasons for only observing bridgehead alkylation with **34** to obtain **59** are a secondary concern.

The most important aspect of obtaining compound **59** from the treatment of **32** with methyl lithium and *sec*BuLi and subsequently quenching with methyl iodide is that it supports the intermediacy of **34**. The only reasonable mechanism for observing bridgehead alkylation is the generation of **34** which then performs a simple enol addition to capture the electrophile and install a methyl group α to the carbonyl.

The attempted optimization of the *peri* lithiation and proper mass spectrometry of **35b** showed that the formation of the three products **35a** and **35b** and **36** was the favoured process when treating **32** with alkyllithium reagents. The React-IR™ experiment demonstrated that the lactam ring of **32** did not open once treated with strong base at cold temperature and isolating **59** from a methyl iodide quench proved the existence of **34**. All the evidence provides support for the mechanism proposed by Duspara.

4.03 Protecting Groups for the Hydroxyl Group

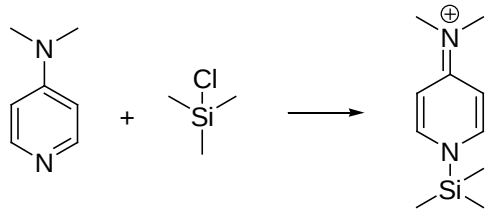
Having achieved an improved understanding of the deprotonation chemistry of **32**, efforts were focused on functionalization and hence protection of the hydroxyl group. Initially, TMS was considered for the protection of **32** as there is already literature precedent of its use in directed metalation chemistry by Snieckus.[52] However, the realization of a TMS protected form of **32** proved quite difficult. Only after many failed attempts with varying conditions was this product isolated in an acceptable yield. The installation of TMS on the alcohol center of **32** began with the classic Corey conditions,[71] wherein TMSCl, triethylamine and the compound of interest are dissolved in dichloromethane. However, this procedure did not work, even after varying the temperature and equivalents of reagents extensively.

The next procedure attempted was that reported by Snieckus for the protection of his sulfonamide analogue **40**. This protocol involved treating the starting material with lithium diisopropylamide, LDA, at 0 °C in dichloromethane along with TMSCl and warming the reaction mixture overnight while stirring. Again, none of the desired product was formed. As such, commercially available LDA was replaced with freshly prepared LDA to eliminate the concern that the LDA had decomposed since the time of purchase or was of generally poor quality. Unfortunately, the fresh LDA did not furnish the protected alcohol.

In a final effort to install TMS on the hydroxy group of **32**, the substrate was treated with methyl lithium at -78^{o}C in THF and allowed to stir for two hours at -78°C. After which, the reaction was quenched with TMSCl then warmed to room temperature

overnight. These reaction conditions did not yield silyation in good yield and any positive results were not reproducible.

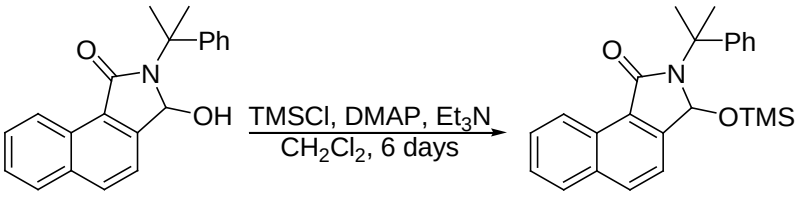
Eventually, it was decided to use a more activated form of trimethylsilylating agent. Employing a 10% molar equivalent of dimethylaminopyridine, **65,** (DMAP) is one additive that has been used before on similar substrates with success.[72] This modification operates by the heteroaromatic nitrogen of DMAP attacking the TMSCl, **66**, to create a more activated TMS compound **67**.[72] The DMAP is a better leaving group than chloride and turns the TMS into a stronger electrophile allowing for attack by weaker nucleophiles.



65 **66** **67**

Scheme 27: *Activation of TMSCl with DMAP*

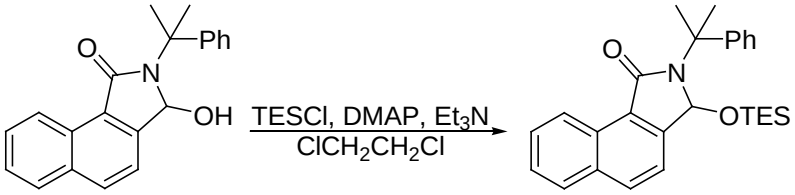
The installation of TMS on **32** was finally accomplished using the DMAP activation technique.[72] The reaction proved quite simple in practice, producing **68** in a satisfactory yield of 73%. However, the reaction did take several days to complete. This is likely reflection of the poor nucleophile generated when **32** is treated with base.



32 **68**

Scheme 28: *Protection* of ***32*** *with TMS*

With the successful installation of the TMS protecting group the same procedure was employed to install larger protecting groups on the alcohol and give a more complete library of compounds for evaluation. The next protecting group for evaluation was triethylsilyl (TES). Using very similar conditions to the TMS procedure, TES was installed to give **69** in a comparable yield of 69%, Scheme 29. One improvement that was discovered involved changing the solvent from dichloromethane to dichloroethane and refluxing the reaction overnight to dramatically reduce the time of the reaction from several days to overnight.

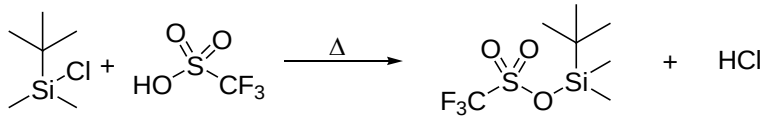


32 **69**

Scheme 29: *Installation of TES on **32***

With this positive result, the next protecting groups pursued for the installation of steric bulk α to the carbinolic proton of **32** were TBS and TIPS. Using the identical conditions for TES a successful reaction was not observed. This suggested that more powerful methods of installing larger protecting groups would be required. After evaluation of numerous unsuccessful methods for the installation of TBS and TIPS, it was decided to attempt silyation with a triflate leaving group. A silyl triflate is regarded as one of the most powerful methods to place silyl protecting groups at hindered sites.[65] As such, TBS triflate and TIPS triflate were prepared according to a previously established procedure.[65] Specifically, the triflates were obtained by heating molar

equivalents of the silyl chloride with triflate acid overnight, Scheme 30, and purifying by distillation under reduced pressure.

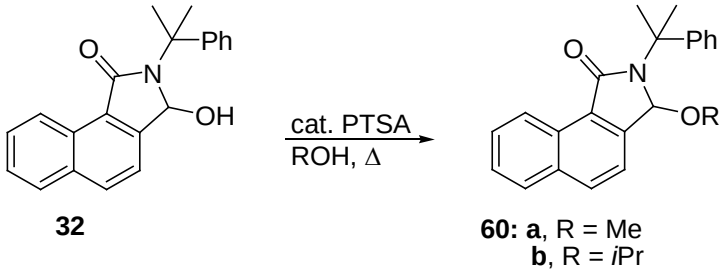


Scheme 30: *Preparation of a silyltriflate*

Several attempts to silylate **32** were performed with the TBS and TIPS triflate derivatives but this avenue of protection was abandoned as it proved to be fruitless under some conditions and difficult in others. In one case, triisopropylsilylation appeared to proceed, but the compound always appeared to possess too many isopropyl peaks in the ^{1}H NMR spectrum. Further purification attempts did not improve the samples.

In addition to considering silyl protecting groups, ethers were also being studied at the same time. Although Snieckus did not evaluate these types of compounds in his studies, they do constitute a viable method for the protection of **32.** Considering them in addition to silyl protecting groups expands the avenues of exploration for the *peri* lithiation of **32**. The most appealing aspect of using ethers is their stability to hydrolysis.

The specific ethers that were considered for the protecting of **32** were isopropyl and methyl. Simply repeating the Snieckus procedure which was applied to a sulfonamide was sufficient to install an isopropyl group on the alcoholic oxygen of **36**. There was one subtle difference between the two reactions. The sulfonamide lost its cumyl group during the reaction, but conditions were found to maintain corresponding group on **32** hence forming **60 a** & **b**.



32

60: a, R = Me
b, R = *i*Pr

Scheme 31: *Preperation of the ethers **60a** & **b** from alchohol **32***

This specific result was encouraging as the amide portion of substrate **32** was not altered during the protection step. Loss of the cumyl group would have introduced a labile hydrogen at the amide which would add an extra layer of complexity to the protecting group chemistry.

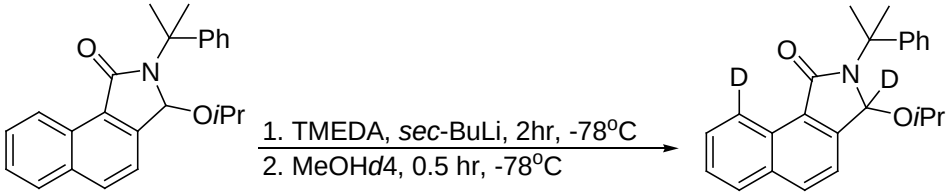
Other ethers were also considered in addition to the isopropyl and methyl systems. One reagent that was of particular interest was using tertiary butanol (*tert*BuOH) as the *tert*butyl group would introduce increased steric bulk versus the isopropyl group. Given how facile other ethers could be installed the incorporation of a *tert*butyl group seemed trivial. However, the reaction yielded no products. The specific reasons for the reaction failure were not investigated for several reasons. *Tert*butyl ethers have been documented to undergo elimination reactions to give the corresponding alcohol and 1,1-dimethylethene.[73] As such, a similar type of reaction could occur resulting in a perceived failed reaction. Furthermore, a suitable library of protecting groups had already been accumulated further investigation would be an unproductive use of laboratory resources

4.04 Evaluation of Oxygen Protecting Groups

With a reasonable library of protected alcohols in hand, evaluation of the protecting group for the *peri* lithiation of protected derivatives of **32** began. The starting

point of this part of the project began with **60b**, as this system showed the most promise of furnishing a lithiation reaction *peri* to the amide.

Initially, compound **60b** was treated with various amounts of *sec*BuLi to effect *peri* lithiation. However, upon quenching with deuteriomethanol most of the deuterium incorporation was at the carbinolic center as assessed by the attenuation of the intensity of the carbinolic proton in the ^{1}H NMR spectrum of **70** (Table 10). As such, the modification of **32** to **60b** did not deactivate the system enough to prevent carbinolic deprotonation. The lithiation did render a single product which was a welcome contrast to the chemistry Duspara observed.



60b **70**

Table 10: *Optimization of* ***70*** *lithiation chemistry*

Eq. *sec*BuLi	% yield	% deuteration carbinolic	% deuteration *peri*
1.2	81.0	84.0	15.0
1.5	100.0	89.0	12.0
1.8	35.2	83.0	46.0

% deuteration ± 11%

Low resolution mass spectrometry was performed on **70** in the 1.5 equivalents of *sec*BuLi trial. The low resolution mass spectrum (Table 11) showed that almost every molecule of **70** contained a single deuterium with slight impurity of the staring material,

60b. This was assessed by comparing the ions observed to those predicted by the WSEARCH32[65] program. The theoretical calculation for the given ion intensity was found to be very similar that of the observed intensity. However, the an ion which corresponded to the molecular weight 359.3 g/mol with a normalized intensity of 1.52. The theoretical calculations did not support this in the singly deuterated fragmentation pattern of **70**. However it was supported by the low resolution mass spectrum of **60b**. This implied the trace amount of **60b** being present in the sample.

The absence of a 363.3 g/mol ion suggested that no molecule of **70** had a second deuterium within it. The M+2 ion is the last major ion associated with the fragmentation pattern calculated for **70** and observed with **60b**. The absence of the 363.3 g/mol ions implies that no material with two deuteriums is present in the sample. The theoretical fragmentation pattern of **70** when it bares one deuterium agrees reasonably well with the observed pattern. From this it was concluded that almost every molecule of **70** contains one deuterium atom and the sample has a trace amount of **60b**.

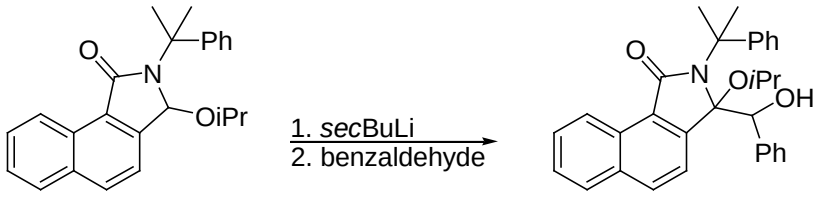
Table 11: *Mass spectrum ions associated with **70***

Ion (g/mol)	Theoretical intensity (normalized)	Observed intensity (normalized)
359.3		1.52
360.3	100	100
361.3	27.7	28.1
362.3	4.1	4.4

With a good understanding of where lithiation occurred in **60b** attained efforts where now focused on the mechanism by which this chemistry was occurring. Compound

60b was studied in detail with the React-IR™ and different quenching electrophiles to confirm the mechanism by which the deuterium incorporated at the carbinolic site of **70** and where specifically the nucleophilic tendencies of the anion existed

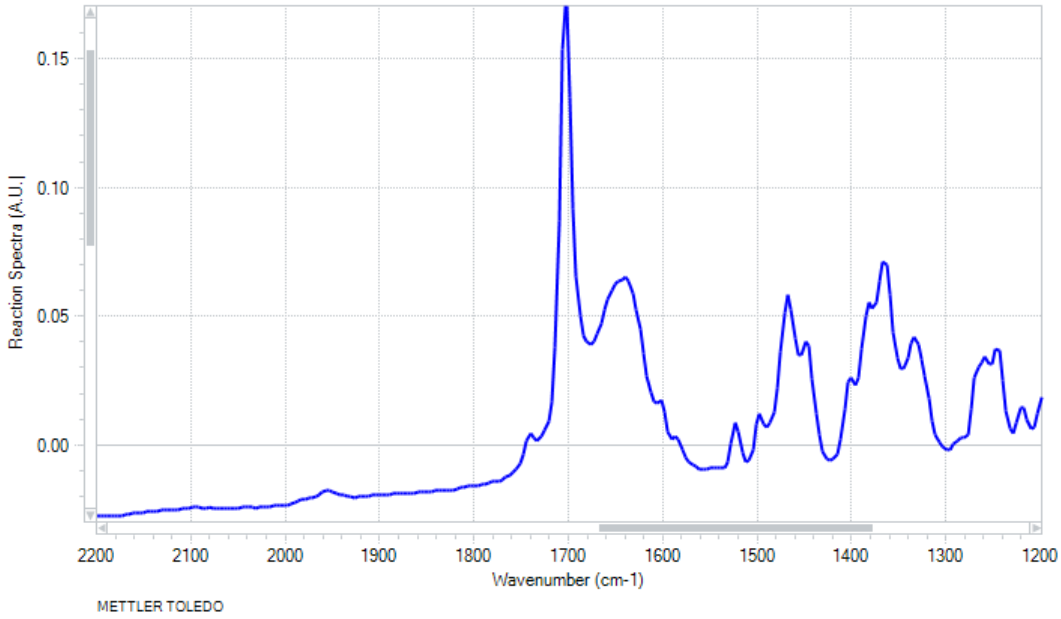
The React-IR™ experiment was the first step in this study as the instrument had proven very useful in the detailed mechanistic study of **32**. Compound **60b** was to be lithiated with *sec*BuLi and subsequently quenched with benzaldehyde, Scheme 32. Benzaldehyde was selected as the electrophile to quench with as it is not susceptible to irreversible attack by the enolate. Thus, the expectation was only a single product would be generated from the chemistry and render purification and interpretation simpler.



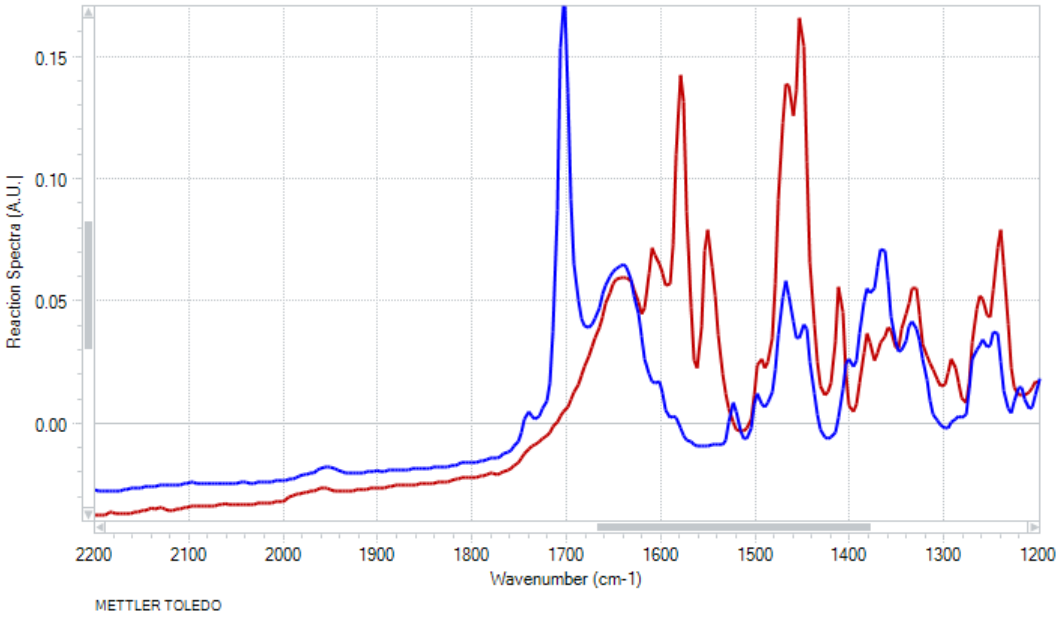
60b

Scheme 32: *Proposed React-IR™ experiment to trap the anion of* ***60b***

The experiment began by collecting a reference spectrum of **60b** dissolved in THF at -78°C with a ten fold increase in the concentration of that reported in the experimental, Spectrum 5. Then the solution was then treated with 1.5 equivalents of TMEDA and 1.5 equivalents of *sec*BuLi and allowed to stir for one hour, Spectrum 6. The carbonyl band of **60b** lithiated with *sec*BuLi shown in red had completely disappeared when compared to unlithiated starting material shown in blue.

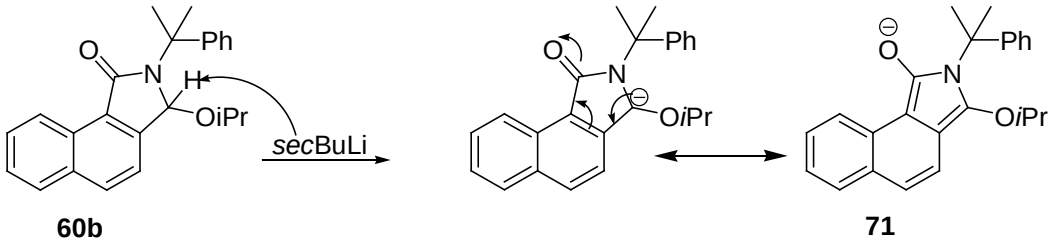


Spectrum 5: *Compound **60b** dissolved in THF at -78°C*



Spectrum 6: *Compound **60b** lithiated -78°C*

This observation is consistent with the React-IR™ experiment with **32.** When **34** was formed, the carbonyl band of **32** was lost through resonance to make a conjugated enolate, Scheme 23. Similarly, the lost of intensity of the carbonyl of **60b** once lithiated would suggest an analogous reaction is occurring, Scheme 33.



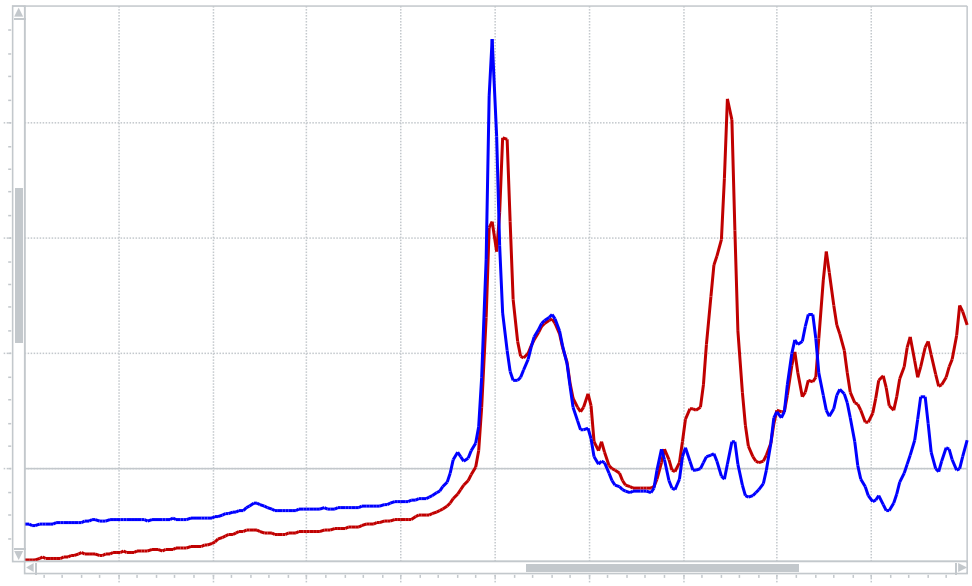
60b **71**

Scheme 33: ***60b*** *dearomitized by resonance to give the anion* ***71***

Furthermore, after inspecting the annotations and IR spectra after the addition of the alkyllithium base, it was apparent that reaction had gone to completion within five minutes of treating **60b** with *sec*BuLi. This meant the reaction time could be lowered from 2 hours to 10 minutes at -78°C before adding the quenching electrophile.

Following the one hour of stirring at -78°C the reaction was quenched with freshly purchased benzaldehyde in THF at -78°C. The IR spectrum, Spectrum 7, shows the reformation of a carbonyl with a slight shift. This suggests two alternatives, the first was the original carbonyl band at 1700cm^{-1} was slightly shifted due to the incorporation of benzaldehyde at the cabinolic site of **60b**, or alternatively the anion was not quenched and the aldehyde of benzaldehyde was causing the appearance of the slightly different carbonyl band.

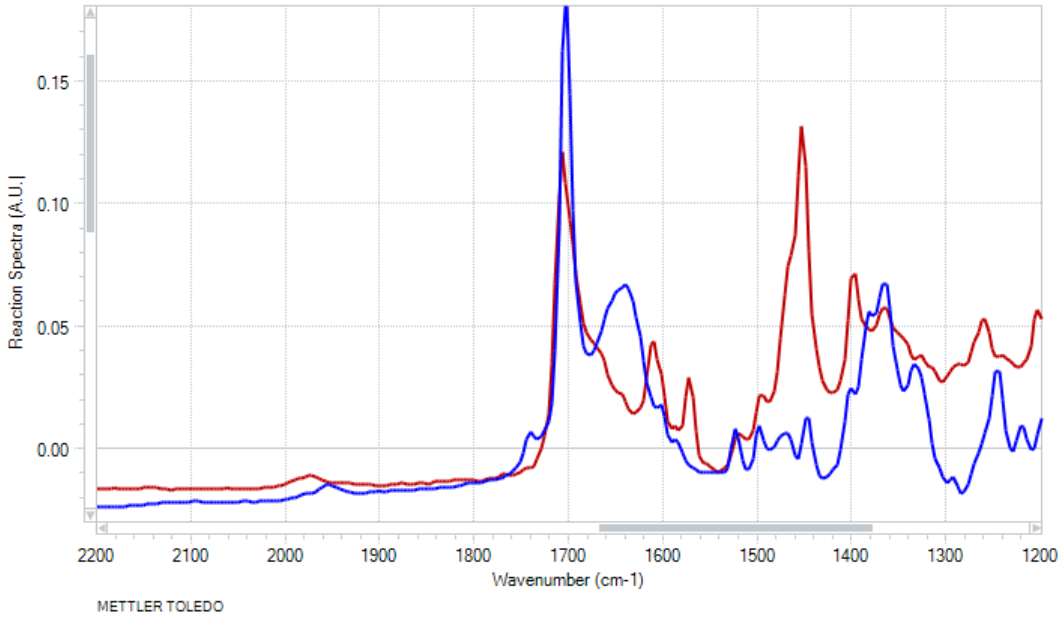
It was decided to allow the reaction to warm up to room temperature overnight with stirring and to continue to collect spectra. Spectrum 8 was taken several hours after the reaction had been quenched and the reaction mixture was now at room temperature. The carbonyl band had changed again, reverting to its original position, suggesting the starting material had reformed.



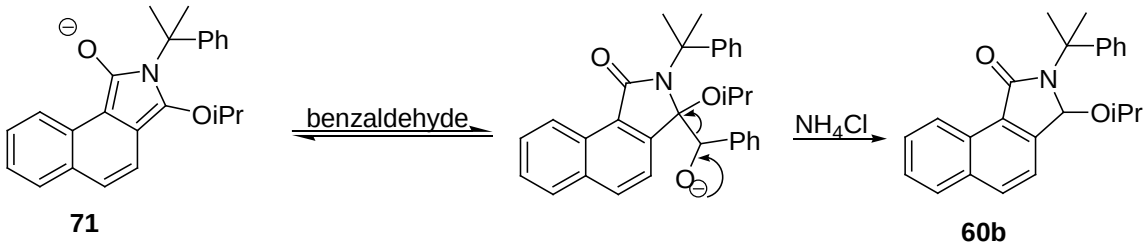
Spectrum 7: ***60b*** *lithated and then quenched with benzaldehyde*

The reaction was quenched with ammonium chloride to either confirm or rebute the regeneration of starting matterial. Upon proper work up the ^{1}H NMR of the crude reaction mixture showed only starting matterial **60b** to be the product of the reaction

The logical explanation for the reversion to starting material upon warming to room temperature is a reverse aldol reaction is occuring with benzaldehyde, Scheme 34. Modifications to the benzadlehyde quench were attempted to elucidate the expected product from the reaction. Quenching with methanol was done at -78°C after the addition of benzaldehyde to eliminate the possibility of the retro aldol occuring at warmed termperature. This modification proved to be unsucessful



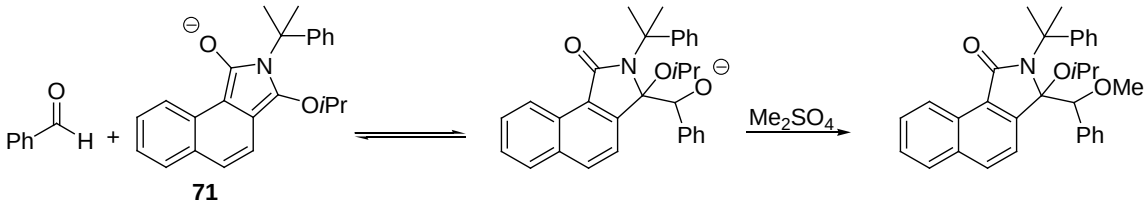
Spectrum 8: ***60b*** *several hours after quenching with benzaldehyde*.



71 **60b**

Scheme 34: *Proposed mechanism for the isolation of* ***60b*** *after quenching with benzaldehyde*

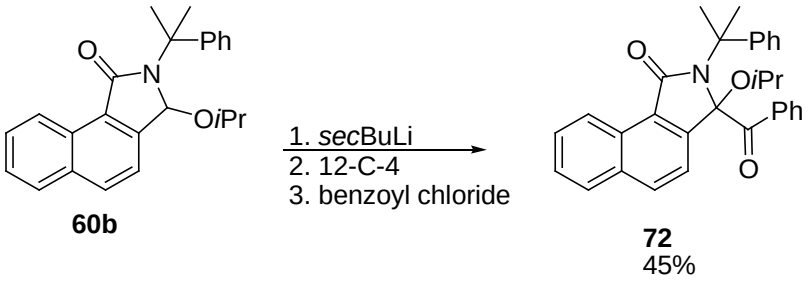
Another modification to the reaction conditions was to quench the reaction with benzaldehyde at -78°C and immediately afterwards quench with dimethyl sulfate. Methylating the alkoxide generated from the attack of benzaldehyde with the anion of **60b** would capture the adduct, preventing reversion to starting material, Scheme 35. This experiment, however, furnished a difficult mixture of products which could not be separated. As such alternative electrophiles were considered as a substitute for benzaldehyde.



Scheme 35: *Proposed solution to the reversibility of benzaldehyde*

Benzoyl chloride was used as a substitute for benzaldehyde to eliminate the possibility of a retro-aldol occurring. The reaction conditions were analogous to those for the chemistry attempted with benzaldehyde except with a shortened time between lithiation and quenching as the React-IR™ had shown unexpected reaction proceeded significantly faster than originally intended.

Initially, the expectation was that benzoyl chloride would favour attack by the alkoxide which the React-IR™ suggested was being formed. However, when the reaction, Scheme 36, was quenched with benzoyl chloride and purified by chromatography the benzoyl chloride was incorporated exclusively at the carbinolic center to give **72**. Adding 1.5 equivalents of 12-crown-4 ether improved the yield to 45%.



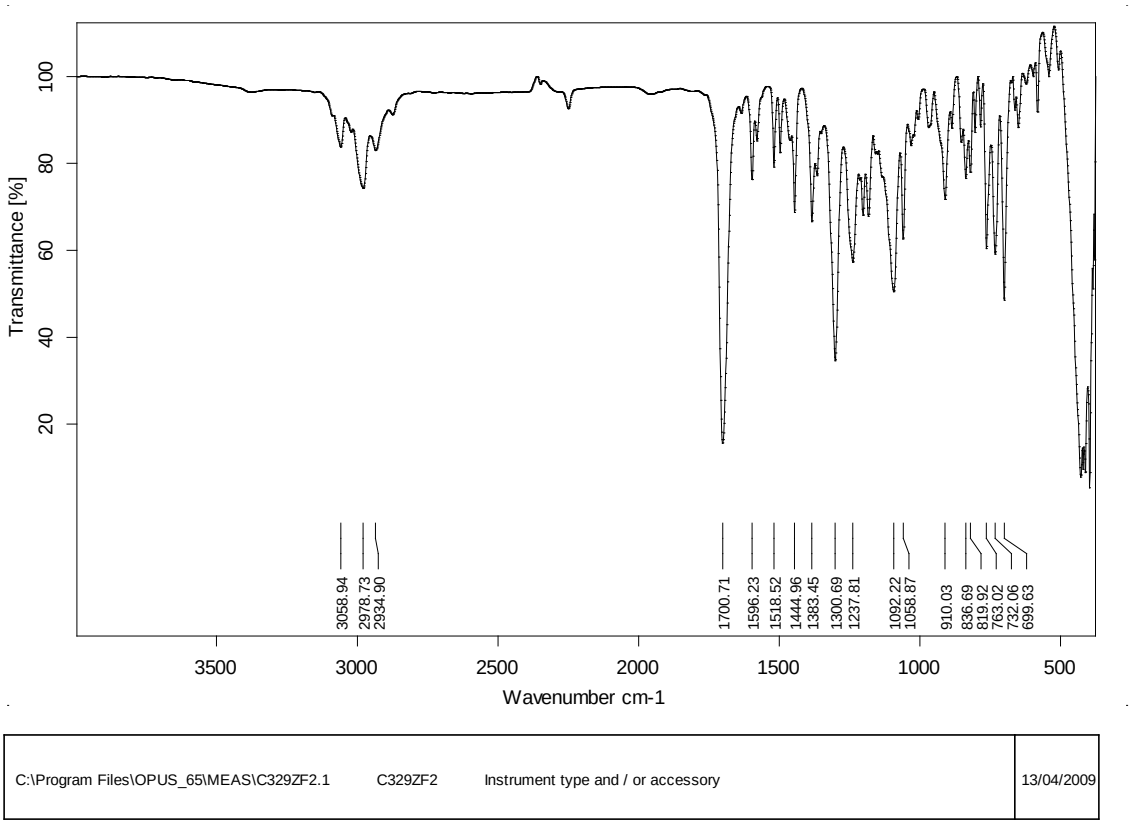
Scheme 36: *Unexpected major product lithiation chemistry with **60b***

Full characterization of the purified compound using ^{1}H and ^{13}C NMR analysis confirmed the isolated product was not dearomatized. The ^{13}C NMR spectrum shows two distinct signals at 197.7 ppm and another at 169.8 ppm which are indicative of a

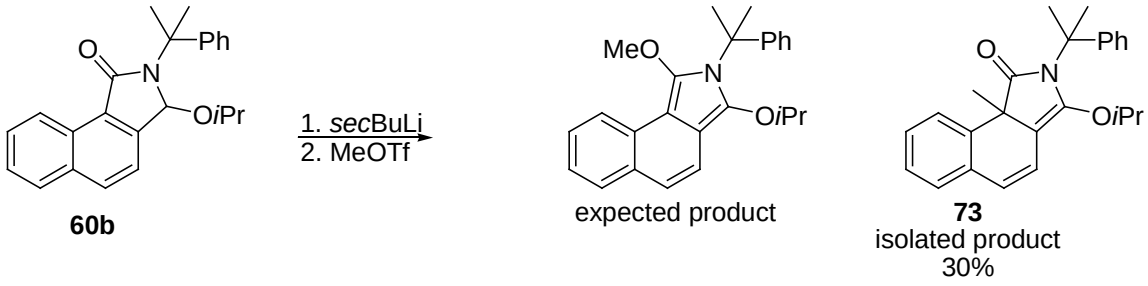
ketone and amide functional groups, respectively. The signal at 197.7 ppm was diagnostic in confirming the benzoyl carbonyl group had been attacked by the carbinolic center. If the benzoyl group had been attacked by the enolate oxygen the chemical shift of this carbonyl carbon be at higher field, indicative of an ester.

An interesting phenomenon was observed while characterizing **72**. The IR spectrum of **72**, Spectrum 9, show only one carbonyl band at 1701 cm^{-1}. The ^{13}C NMR of **72** showed two different carbonyl signals. This came about from the amide and ketone having almost identical C-O stretches that the bands merged and became one larger band Although **72** proved the deprotentation of the carbinolic center of **60b** it did not demonstrate the dearomatization chemistry suggested by the React-IR™. Previously, methyl iodide been used to validate the dearomatized intermediated **34** by a bridge head alkylation reaction to give **59.** This was considered as a good starting point for trapping the intermediate. However, it was decided to employ methyl triflate as a substitute for methyl iodide as it would favour attack by the alkoxide provide evidence for **71**.

Treating **60b** with *sec*BuLi at -78°C and quenching with methyl triflate in THF at -78°C, Scheme 37, yielded **73** the bridgehead alkylation in 30% yield, analogous to the isolation of **59**. Initially the expectation was O-methylation; however, **73,** although unexpected, did support the dearomatization chemistry proposed in Scheme 33.



Spectrum 9: *IR spectrum of **72***



Scheme 37: *Unexpected product formation while trying to access **71***

The chemistry observed with **60b** was analogous to the chemistry of **36** when treated with methyl iodide and it further agrees with Flynn's study on N-methylphthalimide. Flynn surmised that smaller electrophiles favoured bridgehead alkylation, α to the carbonyl, whereas larger electrophiles favour conjugate enol addition products. The isolation of compound **73,** the bridgehead alkylation product**,** coupled with

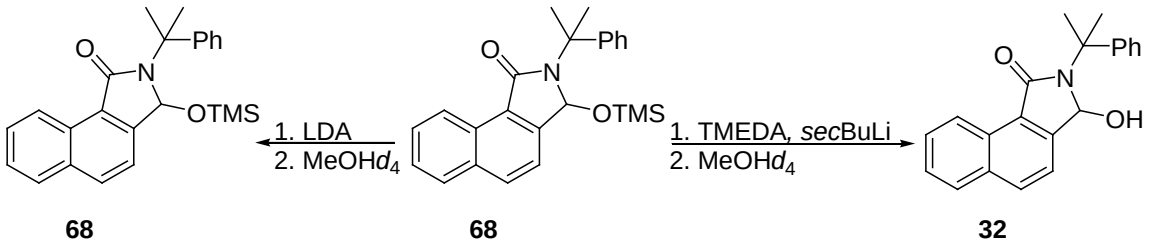
the React-IR™ experiment support the formation of the dearomatized enolate species **71.** Product **72** is expected based on Flynn's conclusions as benzoyl chloride is a larger electrophile and was attacked by the carbinolic site of **71**. The different modes of reactivity observed with **60b** with alkyllithium reagents, conjugate enol addition to give remote substitution or the enol addition to give substitution α to the carbonyl, is a consequence of the electrophile employed during the reaction.

Although the chemistry observed with **60b** was interesting it did not provide any new directions for lithiation *peri* to the amide. Other experiments were conducted with bulkier lithiating agents in order to render the problematic carbinolic hydrogen inaccessible to the lithiating agent during the reaction. Lithiation was attempted with the more sterically demanding LDA. There is precedent for LDA being used during directed *ortho* metalation; as such employing it in the hopes of directing *peri* was determined to be an experiment of interest.

Lithium diisopropylamide did not attack carbinolic hydrogen of **60b**; however, LDA did not do any chemistry at the *peri* site either. This could be a consequence of the *peri* site residing too far from the directed metalation chemistry and not possessing the enhanced acidity associated with directed *ortho* metalation. Adding 0.5 molar equivalents of lithium chloride had been recently shown to speed up the rate of directed metalation chemistry by a considerable amount, with rate accelerations ranging up to 7000 times faster.[74] Hence, the reaction was reattempted with lithium chloride to accelerate any directed metalation chemistry which might be occurring too slowly to be observed. Unfortunately, lithium chloride addition did not demonstrate any improvements in the lithiation chemistry with LDA.

Despite the mechanistic information obtained for the lithiation chemistry of **60b** nothing was gained pertaining to the lithiation *peri* to the amide. Although this left **60a** uninvestigated, it was reasonable to assume that the chemistry observed with **60a** would be observed. Efforts were now focused on evaluating the two remaining silyl protecting groups.

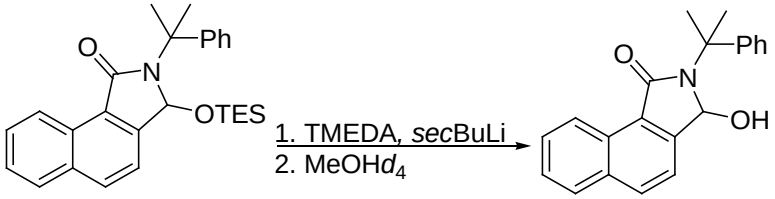
The evaluation of silyl protecting groups began with the evaluation of **68**. Most procedures for directed *ortho* metalation require 2.2 equivalents of *sec*BuLi along with TMEDA to achieve an optimal result. This was the basis on which directed *peri* metalation was attempted with **68** but the reaction conditions did not lend themselves to *peri* lithiation. The reaction of **68** with *sec*BuLi only furnished the deprotection product **32**. Logically, the amounts of *sec*BuLi and TMEDA were varied in an attempt to elucidate the desired chemistry. One noteworthy experiment was to reduce the amount of alkyllithium reagent in hopes of introducing a competitive choice between desilylation and directed metalation chemistry. However, the only product obtained from these experiments was the deprotected substrate **32**. The next experiment attempted was to use LDA as a lithating reagent in place of *sec*BuLi. Although no useful chemistry had been observed with compound **60b**, the experiment was done for completeness. Using LDA in an attempt to lithiate **68** resulted in no reaction, Scheme 38. Clearly, LDA is not reactive enough to lithiate *peri* but is mild enough not to desilylate **68.**



68 **68** **32**

Scheme 38: *Attempted lithiation chemistry with compound **68**.*

The next step in the study was to employ a more robust protecting group for use with alkyllithium reagents. Hence, compound **69** was evaluated for the *peri* lithiation. Originally it was believed that the TES protecting would be a more suitable protecting group as it is less reactive than a TMS group. When compared to TMS, TES has been show to be 10 to 100 times more stable to hydrolysis.[75] Compound **69** was evaluated with *sec*BuLi for *peri* lithiation using analogous conditions to that of compound **68**, Scheme 39. Molecule **69** underwent the same chemistry as **68** with *sec*BuLi and TMEDA, desilylation to give **32**. As such it was determined that the two silyl groups protecting groups were not robust enough to survive the specific lithiation chemistry being attempted.



69 **32**

Scheme 39: *Evaluation of molecule **69** for the peri lithiation*

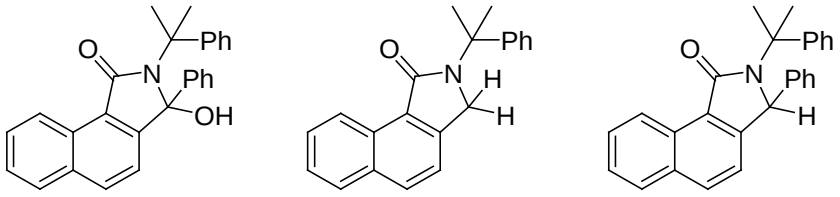
Despite the mechanistic information obtained from the **60b**, the rest of the protection group chemistry demonstrated that introducing steric bulk in proximity to the carbinolic hydrogen of **32** would not mitigate the deprotonation chemistry. Substantial changes would be required to **32** in order to achieve a directed *peri* metalation.

4.05 Alternative Protecting Strategies

Substituting the problematic carbinolic hydrogen was considered. Removal of that hydrogen was achieved by changing the quenching electrophile of the original *ortho* metalation reaction of **59**. Originally DMF was used because there are no acidic hydrogens α to the carbonyl group and the amide was a good leaving group in the

specific reaction conditions. To achieve the goal outlined above, several suitable substitutes for DMF were considered.

Benzaldehyde, formaldehyde and methyl benozoate were all considered, Figure 7. However, it was eventually decided that methyl benzoate would be used. Quenching the reaction with methyl benzoate would yield an intermediate ketone which, followed by ring closing would give the alcohol and a phenyl group in place of the carbinolic hydrogen. Quenching with the two aldehydes considered would produce an alcohol group which would render the subsequent ring closing step non trivial. An extra step would likely be required; heating with PTSA might be need to activate the alcohol enough for an attack to occur by the amide.



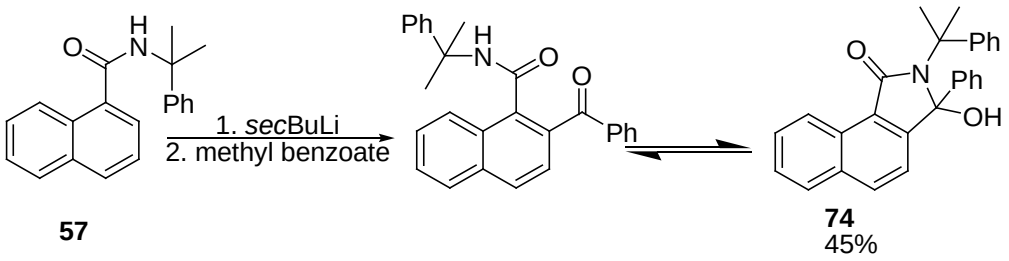
74 **75** **76**

Figure 7: *Anticipated products using new electrophiles in place of DMF*

A formaldehyde quench would yield **75** with an extra hydrogen in place of the alcohol and would likely exacerbate the deprotonation problem at the carbinolic site. Benzaldehyde would give **76** with a bulky phenyl group in place of the alcohol. However, the problematic carbinolic hydrogen would still persist. The methyl benzoate incorporated substrate **74** eliminated the carbinolic hydrogen from the system.

Compound **74** was accessed synthetically using the same procedure that was used for the original starting material except instead of lithiating **57** and quenching with DMF in THF at -78^{o}C, methyl benzoate was used. Purification was also slightly different as

well. The excess methyl benzoate was difficult to remove from the crude product as methyl benzoate had a similar polarity to the desired product and is not very volatile.



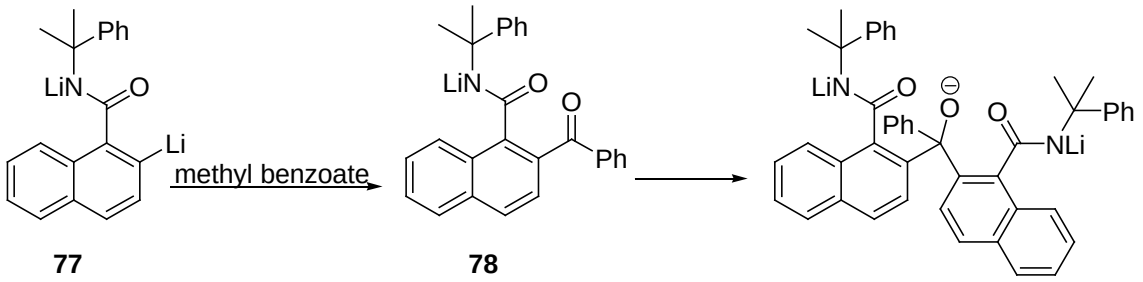
57 **74** 45%

Scheme 40: *Formation of molecule **74***

The excess methyl benzoate and other byproducts were removed by flash chromatography to give compound **74** with a 45% yield. The separation proved to be rather challenging often resulting in impurities and starting material **57** being isolated along side **74**. As such, attempts were made to improve the yield of the reaction by simplifying the purification. The first changes to the reaction conditions were to decrease the equivalents of methyl benzoate used and to redistill it before use. This was done to eliminate any traces of water that could be remaining in the methyl benzoate and quenching **57** once *ortho* lithiated. Furthermore, decreasing the equivalents of methyl benzoate from three to 1.2 equivalents would simplify the subsequent purification by flash chromatography as there would be considerably less methyl benzoate left after the reaction was finished. Despite these subtle changes in the reaction conditions, the reaction still yielded an oil which was difficult and to purify with no measurable improvement in the reaction yield.

The next set of conditions attempted for the optimization of **74** was to change the addition sequence at the quenching stage of the reaction. Normally, quenching a directed

metalation reaction involves the addition of the electrophile to the lithiated compound in solvent at -78°C. However, in this specific case uncyclized intermediate product **78** is a ketone which is more electrophilic than the methyl benzoate. The ketone **78** could be attacked by a second molecule of **77** causing a dimerization reaction to occur discouraging the formation of **73**.

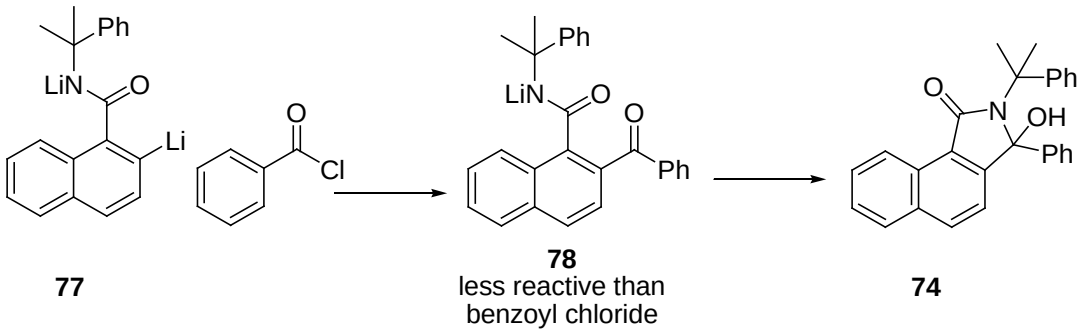


77 **78**

Scheme 41: *Problematic chemistry associated with the use of methyl benzoate*

Hence, adding the lithiated compound **77** to the three equivalents of methyl benzoate would mitigate the dimerization reaction as there would always be an excess of electrophile in the reaction when compared to the intermediate ketone **78**. This modification of the reaction conditions still resulted in the same difficult separation and low yield. At this point it was decided to change the electrophile to improve the yield or eliminate the difficult chromatography.

The next electrophile considered for the synthesis of **74** was benzoyl chloride. This electrophile would result in the same intermediate ketone **78** being formed before the cyclization to the lactam **74.** The improvement in using benzoyl chloride is that the acid chloride remains more reactive electrophile than the intermediate ketone **78**, reducing the risk of a double attack occurring.



77 **78** less reactive than benzoyl chloride **74**

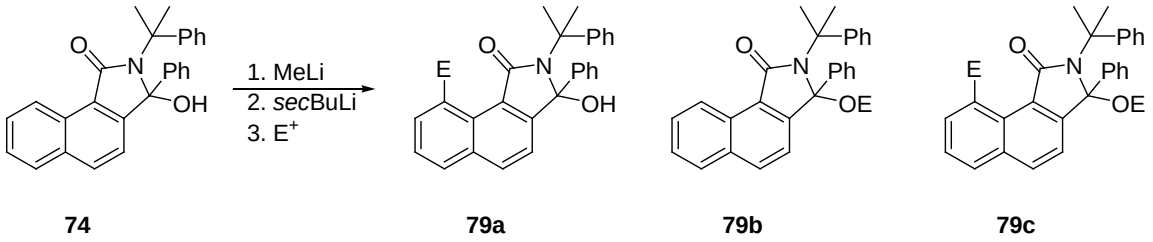
Scheme 42: *Alternative synthetic route to **74.***

The quenching of **77** after three hours of stirring at -78°C was done by adding 1.5 equivalents of benzoyl chloride in solvent at -78°C. The reaction was held at -78°C for an hour after the quench then allowed to warm up to room temperature overnight. Applying a standard work up conditions gave **74** as an impure white solid; this was a welcome contrast to the yellow oils obtained previously.

After careful consideration it was decided that it would be best to alkylate the hydroxyl oxygen of **74** to a methyl ether. This was done to simplify the subsequent chemistry. Having an acidic hydrogen in a molecule while attempting directed metalation requires that one pretreat the molecule with a weaker base to react with the acidic proton. Furthermore, quenching with many electrophiles would result in several products. Dimethylsulfate and TMSCl illustrate this, as they have been used previously to study directed *ortho* metalation[52] and both are susceptible to attack by a carbanion and an alkoxide. This would give a mixture of products which may be difficult to purify and inevitably lower the yield of the reaction of interest.

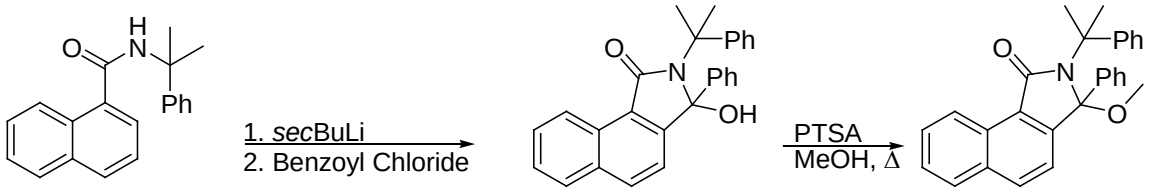
As such, the crude product of the benzoyl quench, Scheme 44, were dissolved in methanol along with a catalytic amount, 0.1 molar equivalents, of PTSA. This solution was refluxed over night to give a complete reaction as judged by TLC. Methanol was

removed from the solution by rotary evaporation to give a brown solid. This solid was recrystallized in a minimum amount of methanol to give **80** as a white crystalline material in 53% over the two steps from amide **58**, Scheme 44**.**



74 **79a** **79b** **79c**

Scheme 43: *Three possible products of DMC with **74***

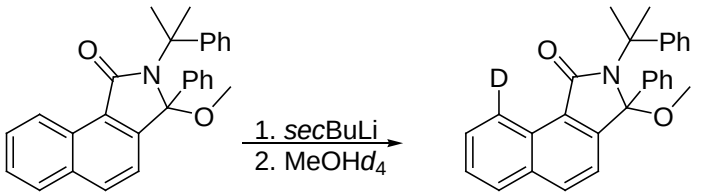


58 **74** **80**
53%

Scheme 44: *Optimized route for compound **80***

4.06 Evaluation of Carbon Based Protecting Group

With a reliable and high yielding route to **80** in hand efforts were now focused on evaluating **80** for directed *peri* lithiation. Initially, **80** was treated with 2.0 equivalents of *sec*BuLi and TMEDA in THF at -78°C then stirred for two hours at -78°C. The reaction was then quenched with deuteriomethanol in THF at -78°C, Scheme 45. This would likely result in a single product establishing where on **80** directed metalation had occurred and to what extent. When this reaction was performed the ^{1}H NMR spectrum of the crude reaction mixture, showed two very similar products. Preliminary analysis of the 9 ppm region of the spectrum suggested that **80** underwent exclusively directed *peri* metalation to give **81**.



80 **81**

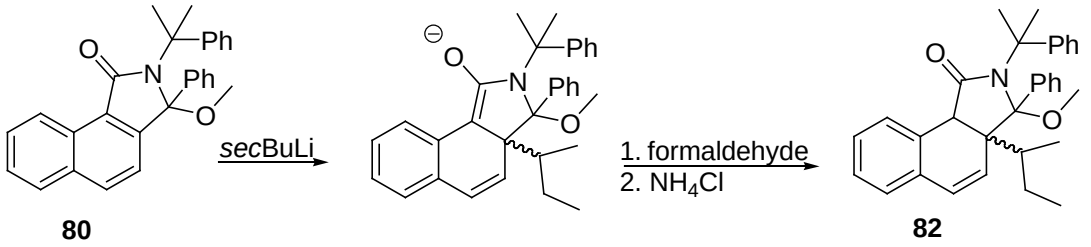
Scheme 45: *Initial conditions for evaluating **80** for the peri lithiation*

The *peri* hydrogen of **80** comes at such high field in ^{1}H NMR because it resides the field of magnetic anisotropy of the carbonyl. This deshields the hydrogen and moves the doublet further downfield than the rest of the aromatic protons making it easy to identify. Replacing this diagnostic proton with a deuterium would result in the loss of this doublet as deuterium is not ^{1}H NMR active. Thus observing a considerably less intense doublet for the *peri* hydrogen of **80** ledto the conclusion that deuterium had been installed in its place giving **81**. As such, efforts were focused on expanding the chemistry to more elaborate electrophiles than deuteriomethanol.

Repeating the reaction, Scheme 46, with formaldehyde as an electrophile gave complex mixtures of products that were difficult to analyze and purify. After a considerable investment of effort and time it was postulated that addition chemistry may be occurring instead of directed *peri* metalation. The crude ^{1}H NMR spectrum of the reaction showed no signals which corresponded to the installation of a primary alcohol. The IR spectrum of the crude reaction mixture also supported this. Employing flash column chromatography gave two similar compounds which had several signals in the ^{1}H NMR which were between 1.2 and 0.8 ppm which correspond to branched alkanes. These signals were originally believed to be an impurity in the ^{1}H NMR spectrum

brought about from a contaminated reagent bottle. However, it was now clear that they were part of the principle product of the reaction.

After careful study of IR and ^{13}C NMR spectrum of the reaction product mixture it was postulated that the *sec*BuLi may be adding to **80**. This was difficult to arrive at as there is a steric barrier at the *ortho* site of **80**. Previously, it was believed that blocking the site *ortho* to the amide would discourage the addition enough to allow directed metalation to occur.



80 **82**

Scheme 46: *Suspected chemistry of **80** with secBuLi*

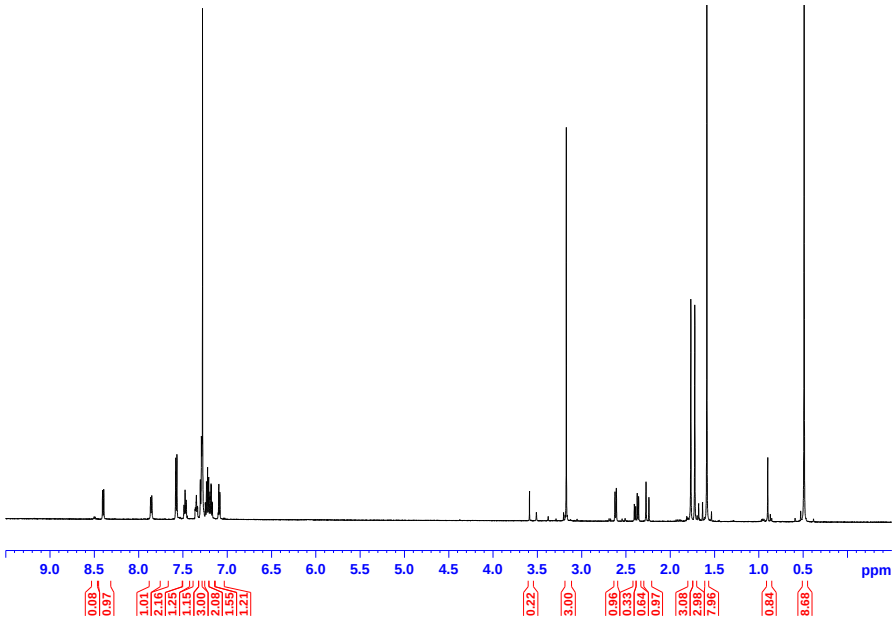
The compound(s) arising from *sec*BuLi addition to **80** were difficult to completely characterize and understand. The resulting products of the reaction, suggested to be **82**, were a complex mixture of diastereomers. As such, in order to complete understand the chemistry *tert*BuLi was used as a substitute for *sec*BuLi as it may simplify the mixture by reducing the number of chiral centres in the molecule. In addition, employing *tert*BuLi was done to simplify the ^{1}H NMR spectrum of the product. The nine hydrogens of the tertiary butyl group are magnetically equivalent and present themselves as a sharp singlet in the ^{1}H NMR spectrum. The secondary butyl group has no such magnetic equivalence and all four carbons are in different magnetic environments along with their associated hydrogens resulting in four different coupled

signals in the ^{1}H NMR spectrum of **82.** Furthermore, the addition chemistry creates diastereomers which presented two very similar molecules rendering complete structural assignment impossible. It was hoped that employing *tert*BuLi would resolve these issues.

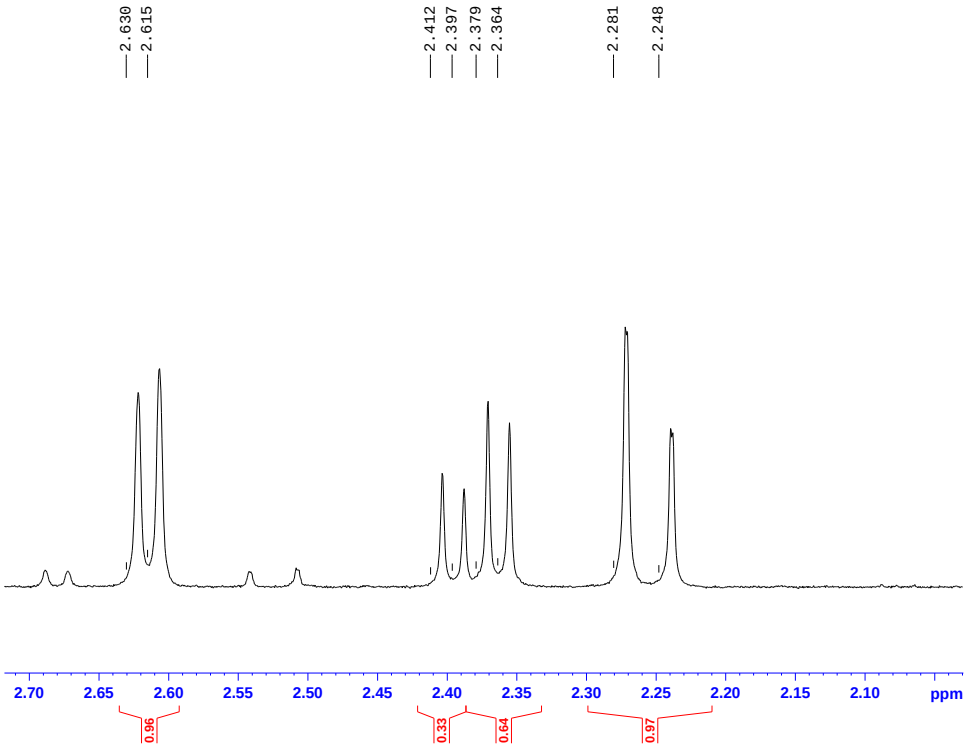
Thus, **80** was treated 1.5 equivalents of *tert*BuLi in THF at -78°C; after one hour of stirring at -78°C the reaction, the mixture was quenched with 2-propanol in THF at -78°C, Scheme 47. After purification by recrystallization from methanol, an opportunity for interpretation of the addition chemistry occurring with **80** was afforded.

The ^{1}H NMR spectrum of the major diastereomer, Spectrum 9 and Spectrum 10, showed an unexpected subtlety to the addition chemistry with **80** that could not be clearly observed with the *sec*BuLi reaction. There were three new signals between of interest between 2.70-2.00 ppm which integrated for three hydrogens. The first signal was a doublet at 2.62 ppm with a coupling constant of 9.1 Hz. The second hydrogen was a doublet of doublets at 2.38 ppm with coupling constants of 19.6 and 9.3 Hz. The final hydrogen was a doublet with a coupling constant of 19.5 Hz at 2.26 ppm. The coupling pattern and constants observed were indicative of an ABM pattern, possibly in a 6-membered ring.

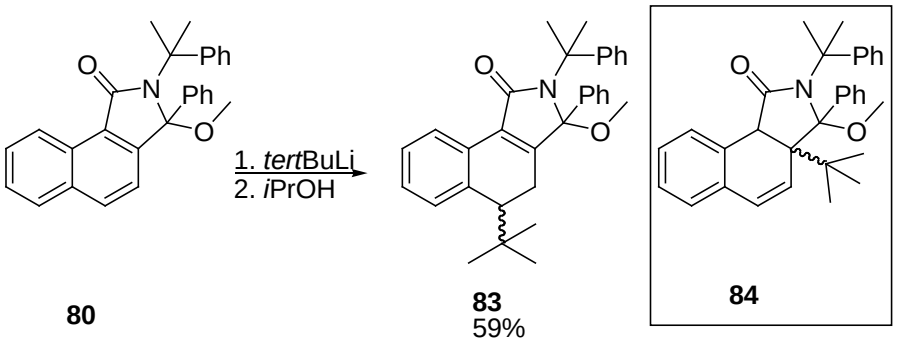
The larger 19.6 Hz coupling is slightly larger than one would expect for a typical geminal coupling. However, the 9.1 Hz coupling constant observed is within the normal range for two axial cyclohexyl protons coupling to each other. This suggested the reaction product was not an analog of **82**, rather addition product **83** was suggested as being formed in the reaction of *tert*BuLi with **80**, Scheme 47.



Spectrum 9: *MR of the tertBuLi addition upon **80***



Spectrum 9: *Enlargment of 2.00 – 2.70 ppm of spectrum 8*



80 **83** 59% **84**

Scheme 47: *Para addition of tertBuLi to **80***

Originally, the expectation was that **84** would be formed as *ortho* addition beside amides has been previously reported.[37] However, the specific examples that are known in literature, Scheme 6, bear no functional groups *ortho* to the amide. It stands to reason that the encumbrances of the Ph and OMe groups of the lactam position of **80** discourage attack conjugate to the carbonyl. An alternative, the site doubly conjugated to the carbonyl succumbs to nucleophilic attack.

When an electron withdrawing group (EWG) is installed on a benzene ring, Figure 8, the electron withdrawing group may have the capacity to induce the *ortho* and *para* site of the benzene ring due to conjugative influences. This can be seen by viewing the associated resonance structures of the system, Scheme 48. Thus, if a strong enough nucleophile, such as a carbanion, is supplied to the aromatic an attack can occur. Applying these principles to **80** accounts for the attack by *tert*BuLi *para* to the amide; it is the most nucleophilic and accessible site of the molecule for *tert*BuLi.

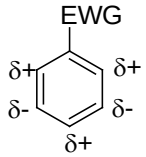
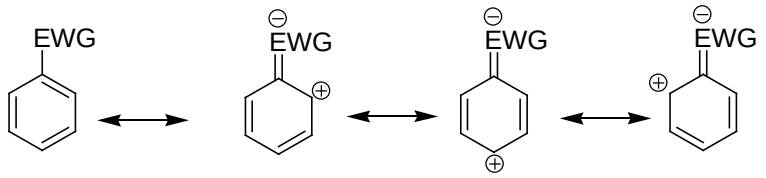


Figure 8: *Charge distribution on an electron withdrawing benzene ring*



Scheme 48: *Resonance structures associated with an electron withdrawing benzene ring*

The crystals of **83** were taken to the 600MHz NMR where proton and carbon spectra were obtained. Following this, a NOE experiment was performed on the compound. Selectively irradiating the hydrogens of the *tert*butyl group would give a through space interaction with all other hydrogens it was in close proximity to. The NOE experiment showed that the *tert*butyl group in the major diastereomer was in close proximity to the phenyl group α to the nitrogen of the amide. Thus it was concluded that the *tert*butyl group attacked *syn* to the phenyl group in the major diastereomer and anti in the minor, Figure 9.

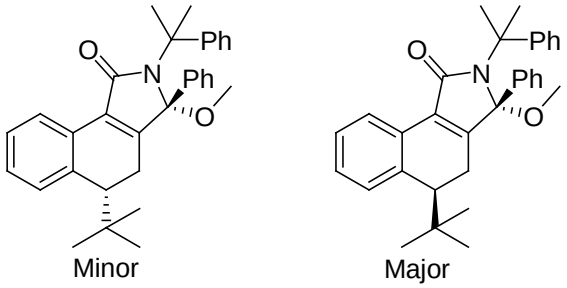


Figure 9: *The major and minor diastereomer of **83** ratio 3:2*

With a good understanding of the addition chemistry that occurs when **80** is treated with an alkyllithium base it was now apparent that molecule **80** was unsuitable for the *peri* lithiation. Although other routes still exist for solving the *peri* lithiation, employing a system analogous to **32** or **80** would be a poor choice as the amide functionality causes too many problems, is not adequately activating.

5.0 Conclusions

It has been clearly shown that amides within a five membered ring are not suitable for synthetically useful *peri* lithiation. Their electron withdrawing nature activates the sites conjugated to the carbonyl for addition chemistry or deprotentation chemistry with an alkyllithium base.[37] Furthermore, protecting the position *ortho* to the amide carbonyl group presents more challenges as this often results in difficult and complex chemistry. In such the instant where the *ortho* site and protecting group have been completely protected from the alkyllithium base, a new mode of addition, *para* addition.

The studies performed on **32** proved that the carbinolic hydrogen was too acidic and became the preferred site of attack for the alkyllithium base. Proving the mechanism proposed by Duspara in Scheme 8 by optimization, proper mass spectrometry and trapping experiments clearly showed this. Further, it helped in constructing the lactam **80** which could not succumb to carbinolic deprotonation. However, **80** was also not suitable for the *peri* lithiation as it underwent *para* addition with alkyllithium bases. As such, one must consider alternate directed metalation groups for the *peri* lithiation, such as, amines and ethers, Figure 9, as they will not activate the *ortho* position or acidify adjacent protons.

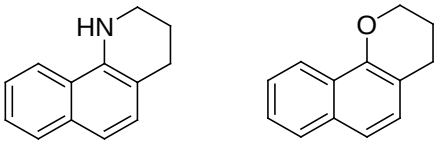
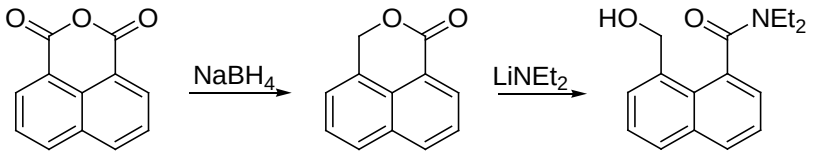


Figure 9: *Two possible molecules for the peri lithation*

In order to synthesize more water soluble analogs of 1,8-naphthalimide, one must rely on already known chemistry for accessing functionalized *peri* naphthalamides. Presently the highest yielding, Scheme 49, process involves the reduction of

1,8-naphthoic anhydride, **85**, with sodium borohydride to the corresponding ester, **86**. The ester, **86**, is subsequently treated with a strong amide base, lithium diethylamide, to give the free alcohol *peri* to the amide, **87**. This process has an overall yield of 20%.[37]



85 **86** **87**

Scheme 49: *Highest yielding route to peri functionalized naphthalamides*

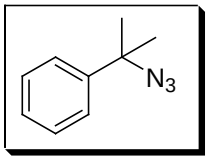
As pharmaceuticals and other target compounds of interest are becoming more complex, having avenues of accessing complex aromatics will become increasingly important. Expanding DMC to functionalize at the *peri* position of a naphthalene derivative will certainly aid in the synthesis of much more complex molecules. In addition new applications of naphthalene compounds are being discovered. Compounds based on 1,8-naphthamides are currently being explored as DNA targeted intercalating agents, useful in the treatment of cancer.[76] Finally, naphthalimides and naphthamide are being explored for use in surgical adhesives,[77] phosphorescent light emitting diodes,[78] and analgesics.[79] The *peri* lithiation reaction will be an indispensable tool for the development of these new technologies. Solving the *peri* lithiation will also open the doors to many new compounds.

6.0 Experimental

6.1 General Experimental

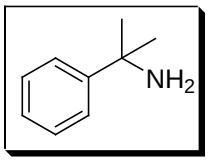
All reactions were carried out in flamed dried round bottom flask under nitrogen; certain reactions were carried out with argon as a substituted and indicated when so done. THF and diethyl ether were freshly distilled from sodium/benzophenone and DMF was distilled from P_2O_5. Ethyl acetate and hexanes were distilled before use in column chromatography. All reagents were transferred using oven dried syringes and needles. All alkyllithium bases were purchased from Aldrich and titrated with N-benzyl benzamide.[80] Flash chromatography was done on either 200-425 mesh Type 60 Å silica gel. All IR spectra were acquired on a Burker Alpha IR machine. NMR spectra were acquired on either the Bruker Avance 300, 400 or 600 MHz machine. All spectra were calibrated to $CDCl_3$, 7.26 ppm for ^1H NMR and 77.0 ppm ^{13}C NMR. Elemental analysis was performed by M.H.W. Laboratories of Phoenix, Arizona. Mass spectrometry was performed by Dr. Richard Smith at the University of Waterloo.

6.2 Synthetic Procedures

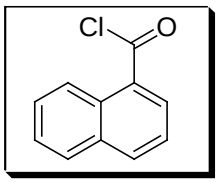


Cumyl azide (**53**):[81] Cumyl Alcohol (6.00 g, 44.1 mmol, 1.0 eq) and sodium azide (5.72g, 88.2 mmol, 2.0 eq) were combine in 200 mL of chloroform to form a slurry. TFA (15.3 mL, 132.3 mmol, 3.0 eq) was diluted in 50 mL of chloroform. The slurry was cooled to -15°C so that the TFA/chloroform solution could be added dropwise using a pressure equalized dropping funnel as to not let the reaction warm above -10°C. After the addition, the reaction was allowed to warm to room temperature overnight with stirring. The reaction was

quenched the next day with NH_4OH, washed with water (3 × 300 mL), then brine (3 × 300 mL) and dried with $MgSO_4$. Removal of the solvent *in vacuo* yielded 6.31 g (89%) of the product as a slightly yellow oil. All the spectroscopic information was in agreement with literature.[81]

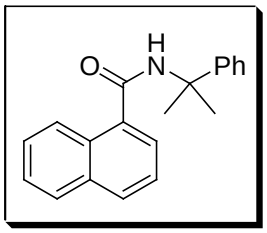


Cumyl amine (**54**):[81] Lithium aluminum hydride (2.97, 78.4 mmol, 2.0 eq) was dissolved in 250 mL of dry diethyl ether at 0°C. Cumyl azide, **53** (6.31 g, 39.2 mmol, 1.0 eq) was then added dropwise via syringe. The resulting mixture was allowed to warm up to room temperature overnight with stirring. The next day the reaction was refluxed for 3 hours. Then the reaction was cooled to 0°C and quenched with 10% aq. KOH (25 mL), then H_2O (50 mL). The aluminum salts were removed by filtration. The layers were separated and the organic layer was extracted with 0.5 M HCl (3 × 70 mL). The aqueous layer was neutralized to pH 11 with 10% aq. KOH and then extracted with ether (3 × 65 mL) and dried with $MgSO_4$. After filtration, the ether was removed under reduced pressure to give 4.68 g (88%) of **54** as an oil. All the spectroscopic data was in agreement with already established literature values.[81]

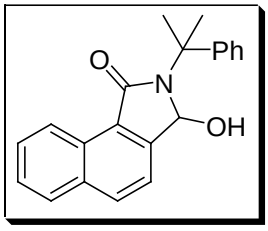


1-Naphthoyl Chloride (**56**): 1-Naphthoic acid (5.50 g, 31.8 mmol, 1.0 eq) was dissolved in 250 mL of dry CH_2Cl_2 to give an opaque gray solution. Oxalyl chloride (4.20 mL, 47.8 mmol, 1.5 eq) was added to the solution dropwise using a syringe. The solution was allowed to stir at room temperature overnight. The next morning the solution had turned translucent yellow colour. The CH_2Cl_2 was removed using reduced pressure to give, 5.80 g (96%) of **56** as a slightly impure yellow oil. Compound **56** was subsequently used without further

purification. All the spectroscopic data was in agreement with spectra provided from Aldrich.[82]



N-Cumyl-1-naphthamide (**57**):[81] Acid chloride **56**, was freshly prepared (4.79 g, 25.1 mmol, 1.0 eq) was dissolved in 250 mL of dry ether at 0°C under argon. Cumyl amine, **54**, (4.00 g, 30.1 mmol, 1.2 eq) was combine with triethylamine (12.6 ml, 90.3 mmol, 3.0 eq). The resulting amine mixture was added to the acid chloride, **56**, dropwise using a syringe. The solution slowly turned from light yellow to opaque white as the reaction was allowed to warm to room temperature overnight while stirring. The resulting white slurry was dissolved in ethyl acetate and washed with water (3 × 200 mL), dried with brine (3 × 200mL) and $MgSO_4$. After filtration, removal of the ethyl acetate *in vacuo* gave 6.82 g (92%) **57**, as white powder. A subsequent recrystallization from toluene gave 6.21 g (86%) of **57** as white crystals. All spectra were in agreement with those previously published in literature.[22]



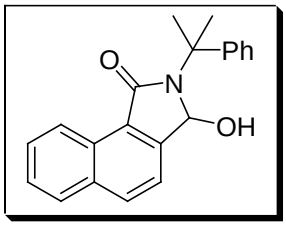
3-Hydroxy-2-(2-phenylpropan-2-yl)-2,3dihydrobenzo[e]isoindol -1-one (32):[22] N-Cumyl-1-naphthamide, **57**, (1.65 g, 5.69 mmol, 1.0 eq) was dissolved in dry THF (75 mL) under argon. The clear colourless solution was cooled to -78^{o}C. The solution was treated with *sec*-butyllithium (12.2 mL, 1.4 M, 17.1 mmol, 3.0 eq) and stirred at -78°C. The solution turned deep red after the addition. DMF (0.95 mL, 17.1 mmol, 3.0 eq) was dissolved in 50 mL of dry THF at -78°C. The DMF/THF solution was added to the lithiated species dropwise and the resulting solution was held at 0°C overnight while

stirring. The pale yellow reaction was quenched with saturated NH_4Cl. The producted was then extracted with ethyl acetate, washed with H_2O (3 × 80 mL) and dried with brine (3 × 80 mL) then $MgSO_4$. The ethyl acetated was removed under reduced pressure to give, 1.62 g (89.7 %) of **32**, as white powder. Recrystallization from toluene gave pure white crystals, 1.50 g (83 %) of **32**. All spectra were in agreement with those previously published in literature.[22]

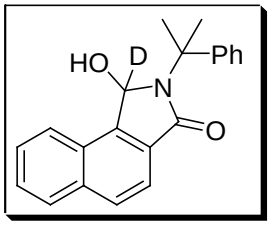
General procedure for deuteration study of 32. 32 (0.300g, 0.945 mmol, 1.0 eq) was dissolved in THF (10mL) then cooled to -78°C. The solution was treated with methyl lithium (0.71 mL, 1.6 M, 1.18 mmol, 1.2 eq.) then allowed to stir for one hour at -78°C. The solution was charged with TMEDA (1.2 eq – 3.3 eq.) then treat with *sec*BuLi (1.2 eq. - 3.3 eq.). The solution was allowed to stir for one hour at -78°C then was quenched with 0.7 mL of methanold_4. The resulting solution was held at -78°C for half and hour then allowed to warm up to room temperature over night while stirring. The reaction was quenched the next morning with saturated ammonium chloride (10mL) and extracted with ethyl acetate (20mL). The extracts were washed with water (3 × 25mL), dried with brine (3 × 25mL) and over anhydrous $MgSO_4$. The ethyl acetate was removed under reduced pressure to give a mixture of **35a**, **35b** and **36** which were separated by flash chromatography (15% ethyl acetate in hexane).

General procedure for React-IR™ study of 32. 32 (0.568g, 1.79 mmol, 1.0 eq) was dissolved in THF (10mL) then cooled to -78°C. The solution was treated with methyl lithium (1.53 mL, 1.6 M, 2.15 mmol, 1.2 eq.) then allowed to stir for one hour at -78°C. The solution was charged with TMEDA (0.336 mL, 2.24 mmol, 1.3 eq.) then treat with *sec*BuLi (1.53mL, 2.15mmol, 1.2 eq.). The solution was allowed to stir for one hour at

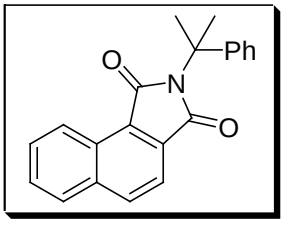
-78°C then was quenched with 0.7 mL of methanold_4. The resulting solution was held at -78°C for half and hour then allowed to warm up to room temperature over night while stirring. The reaction was quenched the next morning with saturated ammonium chloride (10mL) and extracted with ethyl acetate (20mL). The extracts were washed with water (3 × 25mL), dried with brine (3 × 25mL) and over anhydrous $MgSO_4$. The ethyl acetate was removed under reduced pressure to give a mixture of **35a**, **35b** and **36** which were separated by flash chromatography (15% ethyl acetate in hexane).



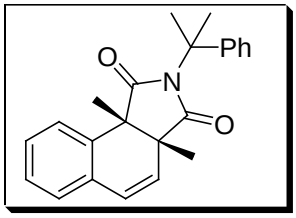
9,3-Dideutero-3-hydroxy-2-cumyl-2,3-dihydrobenzo[*e*]Isoindol-1-one (35b):[22] **32** (0.350 g, 0.11 mmol, 1.0 eq) was dissolved in 11 mL of dry THF under argon. The clear colourless solution was cooled to -78^{o}C then treated with methyllithium (0.94 mL, 1.4 M, 1.31 mmol, 1.2 eq). The resulting solution was then stirred for 1 hour at -78^{o}C, during which time the solution turned dark red. The solution was then charged with TMEDA (0.21 mL, 1.38 mmol, 1.25 eq) and subsequently treated with *sec*-butyllithium (0.94 mL, 1.4 M, 1.31 mmol, 1.2 eq). The solution was then stirred for 1 hour at -78^{o}C then quenched with MeOH-d_4. The solution was then stirred for one half of an hour at -78^{o}C then let to warm up overnight while stirring to room temperature. The reaction was treated with NH_4Cl and extracted with ethyl acetate (30 mL). The organic layer was washed with H_2O (3 X 33 mL) then dried with brine (3 X 30 mL) and $MgSO_4$. Flash chromatography with 15% ethyl acetate and hexanes yielded 0.213 g (78%) of **35b**. All spectra were in agreement with those previously published in literature.[22]



1-Deutero-1-hydroxy-2-(2-phenylpropan-2-yl)-2,3dihydro benzo[e]isoindol-3-one (35a):[22] Isolated in the synthesis of **35b** in 1.4% yield. All spectra were in agreement with those previously published in literature.[22]



2-(2-Phenylpropan-2-yl)-2H-benzo[e]isoindole-1,3-dione (36):[22] Isolated in the synthesis of **35b** in 0.8% yield. All spectra were in agreement with those previously published in literature.[22]



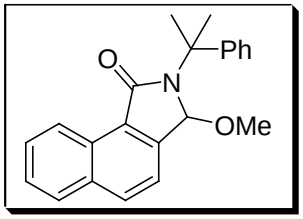
(±)(3aR,9bS)-3a,9b-Dimethyl-2-(2-phenylpropan-2-yl)-2Hcyclopenta[a]naphthalene-1,3(3aH,9bH)-dione (59): Compound **32** (0.300 g, 0.945 mmol, 1.0 eq) was dissolved in 10 mL of THF. The resulting solution was cooled to -78 °C then treated with 1.6 M methyl lithium (0.71 mL, 1.13 mmol, 1.2 eq). The lithiated solution was then allowed to stir at -78 °C for 1 hr after which 1.4 M *sec*BuLi (0.81 mL, 1.13 mmol, 1.2 eq.) was added to the solution. Methyl iodide (0.14 mL, 2.26 mmol, 2.4 eq.) was dissolved in 10 mL of THF and cooled to -78 °C. The lithiated solution was then quenched with the methyl iodide solution at -78 °C. The resulting solution was held at -78 °C for 1 hr. and was allowed to warm up to room temperature overnight with stirring. The following day the reaction was treated with a sat'd aq. solution of NH_4Cl (20 mL) and extracted with ethyl acetate (3 ×30 mL). The extracts were washed with water (3 × 50 mL) and brine (3 × 50 mL) and dried over anhydrous Na_2SO_4. The ethyl acetate was removed under reduced pressure. Separation by chromatography (35% dichloromethane in pentane) yielded 0.048 g (15%) of **59** as a clear colourless oil.

Data for **59**: ^{1}H NMR (600MHz, $CDCl_3$): 7.35 (m, 1 H, Ar H), 7.19 (m, 1 H, Ar H), 7.18 (d, J = 9.1 Hz, 1 H, Ar H), 7.16 (m, 1 H, Ar H), 7.14 (m, 1 H, Ar H), 7.11 (m, 1 H, Ar H), 7.05 (m, 3 H, Ar H), 6.47 (d, J = 9.5 Hz, 1 H , CH), 5.62 (d, J = 9.5 Hz, 1 H, CH), 1.77 (s, 3 H, CH_3), 1.76 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3)

^{13}C NMR (150 MHz, $CDCl_3$): 181.2, 180.7, 146.2, 133.3, 130.7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.5, 127.2, 126.7, 124.2, 62.1, 50.7, 50.2, 28.4, 28.2, 20.5, 19.2.

IR (cm^{-1}): 3061, 3028, 2981, 2935, 2871, 1775, 1710, 1602, 1495, 1448, 1329.

MS (EI), m/z (%): 119 (77), 156 (31), 226 (23), 345 (M+, 30), 347 (2); HRMS, Calc'd for C_{24} $H_{24}NO_2$: 345.1729; Found: 345.1733.



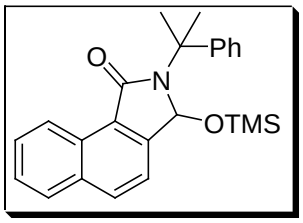
3-Methoxy-2-(2-phenylpropan-2-yl)-2,3-dihydrobenzo[e] isoindol-1-one (60a): Compound **32** (0.820 g, 2.59 mmol, 1.0 eq) was dissolved in methanol (25 mL). PTSA (0.049 g, 0.0359 mmol, 0.1 eq) was added to the solution. The resulting mixture was refluxed overnight while stirring. The reaction was worked up the next day by extracting with ethyl acetate (3 × 30 mL) , washed with water (3 × 30 mL), dried with brine (3 × 30 mL) then $MgSO_4$. Removal of solvent under reduced pressure yielded 0.651 g (76 %) of **60a** as a yellow solid. Recrystallization from toluene gave 0.477 g (51 %) of **60a** as yellow crystals. Mp: 96-98 ^{o}C.

Data for **60^{a}**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.11 (d, J = 7.8 Hz, 1H, Ar H), 8.07 (d, J = 8.4 Hz, 1 H, Ar H), 7.93 (d, J = 7.2 Hz, 1 H, Ar H), 7.60 (m, 3 H, Ar H) 7.45 (d, J = 7.3 Hz, 2 H, Ar H), 7.35 (t, J = 7.8 Hz, 2 H, Ar H) 7.24 (t, J = 7.2 Hz, 1 H, Ar H), 6.34 (s, 1 H, CH), 3.01 (s, 1 H, CH), 2.08 (s, 3 H, CH_3), 1.93 (s, 3 H, CH_3).

^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 147.5, 140.8, 134.2, 133.0, 128.9, 128.3 (two peaks overlapping), 128.1, 127.6, 127.1, 126.5, 124.9, 124.5, 119.8, 86.7, 59.2, 49.3, 28.9, 28.0.

IR (cm^{-1}): 3056, 2979, 2827, 1694, 1597, 1355, 1245, 1187, 1058

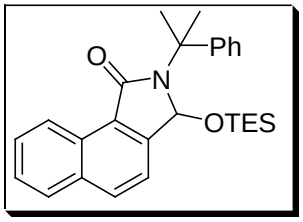
Elemental analysis, calculated for: C 79.73%, H 6.39 %, found: 80.00%, 6.85%



2-(2-Phenylpropan-2-yl)-3-(trimethylsilyloxy)-2,3-dihydro benzo[e]isoindol-1-one (**68**): Compound **32** (1.20 g, 3.78 mmol, 1.0 eq.) and DMAP (0.115 g, 0.945 mmol, 0.25 eq.) were dissolved in CH_2Cl_2 (40 mL) at room temperature. The solution was immediately treated with triethylamine (0.738 mL, 5.29 mmol, 1.4 eq.) and trimethylsilyl chloride (0.526 mL, 4.16 mmol, 1.1 eq.) The resulting solution was stirred for 6 days at room temperature. The reaction was quenched and washed with water (3 × 40 mL), extracted with ethyl acetate (40 mL), dried with brine (3 × 45mL) and $MgSO_4$. After filtration, the ethyl acetate was removed under reduced pressure to furnish **68** as a white impure solid. **68** was recrystallized from toluene to yield 1.06 g (72%) as white solid. Mp: 141- 144 °C. Data for **68**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, J = 7.6 Hz, 1 H, Ar H), 8.04 (d, J = 8.0 Hz, 1 H, Ar H), 8.91 (d, J = 7.2 Hz, 1 H, Ar H), 7.56 (m, 3H, Ar H), 7.44 (d, J = 8.0 Hz, 2 H, Ar H), 7.33 (t, J = 8.0 Hz, 2 H, Ar H), 7.23 (t, J = 7.2 Hz, 1 H, Ar H), 6.40 (s, 1 H, CH), 2.04 (s, 3 H, CH_3), 1.93 (s, 3 H, CH_3), 0.11 (s, 9 H, $Si(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 147.7, 143.7, 134.0, 132.6, 129.0, 128.3 (two peaks overlapping), 128.1, 127.0, 126.7, 126.5, 125.1, 124.6, 119.9, 82.7, 59.2, 29.0, 28.5, 1.4.

IR (cm^{-1}): 2956, 2929, 1690, 1594, 1354, 1090.

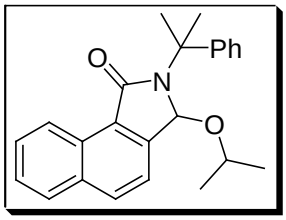


2-(2-Phenylpropan-2-yl)-3-(triethylsilyloxy)-2,3-dihydro benzo[e]isoindol-1-one (**69**): Compound **32** (0.300 g, 0.945 mmol, 1.0 eq.) was dissolved with DMAP (0.012 g, 0.095 mmol, 0.1 eq.) in 1,2-dichloroethane (11 mL). The resulting solution was treated with triethylamine (0.189 mL, 1.32 mmol, 1.4 eq.) and chlorotriethylsilane (0.174mL, 1.04 mmol, 1.1 eq). The reaction mixture was stirred for 48 hours then quenched with sat'd aq NH_4Cl and extracted with ethyl acetate. The resulting organic was washed with water (3 × 20 mL), washed with brine (3 × 20 mL) and dried over $MgSO_4$. The ethyl acetate was removed under reduced pressure to give 0.284 g (66 %) as slightly impure brown solid.

Data for **69**: ^{1}H NMR (400MHz, $CDCl_3$): 9.01 (d, J = 7.2 Hz, 1 H, Ar H), 7.94 (d, J = 8.4 Hz, 1 H, Ar H), 7.81 (d, J = 7.6 Hz, 1 H, Ar H) 7.47 (m, 3 H, Ar H) 7.35 (d, J = 7.6 Hz, 2 H, Ar H), 7.24 (t, J = 7.2 Hz, 2 H, Ar H), 7.15 (t, J = 7.2, 1 H, Ar H), 6.37 (s, 1 H, CH), 1.95 (s, 3 H, CH_3), 1.85 (s, 3H, CH_3), 0.84 (t, J = 7.6 Hz, 9 H, CH_3), 0.53 (q, J = 7.9 Hz, 6 H, CH_2)

^{13}C NMR (100 MHz, $CDCl_3$): 168.8, 147.9, 143.7, 133.9, 132.4, 129.0, 128.2, 128.0, 126.9, 126.6, 126.5, 126.3, 124.9 (two peaks overlapping), 124.6, 119.8, 59.2, 28.8, 28.7, 6.9, 6.4.

IR (cm^{-1}): 2955, 2877, 1700, 1372, 1187, 1087.



3-Isopropoxy-2-(2-phenylpropan-2-yl)-2,3-dihydrobenzo[e] isoindol-1-one (**60b**):[52] Compound **32** (2.00 g, 6.30 mmol, 1.0 eq) was dissolved in isopropyl alcohol (100 mL). PTSA (0.12 g, 0.63 mmol, 0.1 eq) was added to the solution. The resulting mixture was refluxed

overnight while stirring. The reaction was extracted with ethyl acetate (3 × 100 mL), washed with water (3 × 110 mL) and brine (3 × 100 mL) and dried over $MgSO_4$. Removal of solvent under reduced pressure yielded 1.72 g (81.0 %) of **60b** as a white solid. Recrystallization from toluene gave 1.44 g (60.5 %) of **60b** as white crystals. Mp: 130-133 ^{o}C.

Data for **60b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, J = 7.4 Hz, 1H, Ar H), 8.05 (d, J = 8.3 Hz, 1H, Ar H), 7.93 (d, J = 6.9 Hz, 1H, Ar H), 7.67 (d, J = 8.3 Hz, 1 H, Ar H) 7.59 (m, 2 H, Ar H), 7.40 (d, J = 7.3 Hz, 1 H, Ar H), 7.32 (m, 2 H, Ar H), 7.23 (d, J = 6.1 Hz, 2 H, Ar H) 6.35 (s, 1 H, CH), 3.83 (sept, J = 6.1, 1 H, CH), 2.12 (s, 3 H, CH_3), 1.93 (s, 3 H, CH_3), 1.26 (d, J = 6.2 Hz, 3 H, CH_3), 0.97 (d, J = 6.1 Hz, 3 H, CH_3)

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 147.5, 142.0, 133.7, 132.2, 128.5, 128.0, 127.7, 126.8, 126.7, 126.0, 124.4, 124.2, 120.3, 85.5, 66.0, 59.20, 28.7, 28.1, 24.0, 23.3.

IR (cm^{-1}): 2976, 1695, 1521, 1185, 1081

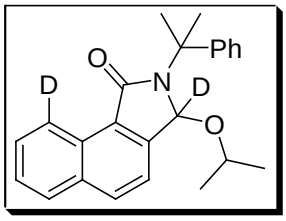
Elemental analysis, calculated for give formula: C 80.19%, H 7.01%, found: C 80.40%, 7.25 %

MS (EI), m/z (%): 182.1 (49), 183.1 (23), 301.2(10), 359.3 (M+, 14), 360.3 (4)

General experimental for lithiation chemistry of 60b. Compound **60b** (0.100 g, 0.270 mmol, 1.0 eq) was dissolved in dry THF (5 mL) under argon. The solution was cool to -78°C and subsequently charged with TMEDA (0.05 mL, 0.33 mmol, 1.25 eq). The solution was then treated with a 1.4 M *sec*-BuLi (1.20 – 1.80 eq) solution in cyclohexane and stirred for 2 hr at -78°C during which time the clear, colourless solution turned a deep dark red colour. The solution was quenched with MeOH-d_4, stirred for another 0.5 hr at -78°C and was allowed to warm up to room temperature overnight with stirring.

The reaction was extracted with ethyl acetate (3 × 20 mL), washed with water (3 × 25 mL) and dried with brine (3 × 25 mL) and $MgSO_4$. Removal of solvent *in vacuo* yielded **70** as a white solid.

General experimental for React-IR™ chemistry of 60b. Compound **60b** (0.715 g, 1.99 mmol, 1.0 eq) was dissolved in dry THF (10 mL) under argon. The solution was cooled to -78^{o}C and subsequently charged with TMEDA (0.462 mL, 0.308 mmol, 1.6 eq). The solution was then treated with a 1.4 M *sec*-BuLi (2.13 mL, 2.90 mmol, 1.5 eq.) solution in cyclohexane and stirred for 5 minutes at -78^{o}C during which time the clear, colourless solution turned a deep dark red colour. The solution was quenched with benzaldehyde (0.402 mL, 3.98 mmol, 2.0 eq), stirred for another 0.5 hr at -78^{o}C and was allowed to warm up to room temperature overnight with stirring. The reaction was extracted with ethyl acetate (3 × 20 mL), washed with water (3 × 25 mL) and dried with brine (3 × 25 mL) and $MgSO_4$. Removal of solvent *in vacuo* yielded **60b** as a white solid.



9,3-Dideutero-3-isopropoxy-2-(2-phenylpropan-2-yl)-2,3-dihyd robenzo[e]isoindol-1-one (70):[22] Compound **60b** (0.100 g, 0.270 mmol, 1.0 eq) was dissolved in dry THF (5 mL) under argon. The solution was cool to -78^{o}C and subsequently charged with TMEDA (0.05 mL, 0.33 mmol, 1.25 eq). The solution was then treated with a 1.4 M *sec*-BuLi (0.24 mL, 0.33 mmol, 1.20 eq) solution in cyclohexane and stirred for 2 hr at -78 ^{o}C during which time the clear, colourless solution turned a deep dark red colour. The solution was quenched with MeOH-d_4, stirred for another 0.5 hr at -78^{o}C and was allowed to warm up to room temperature overnight with stirring. The reaction was extracted with ethyl

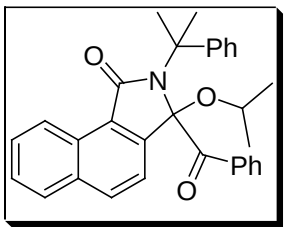
acetate (3 × 20 mL), washed with water (3 × 25 mL) and dried with brine (3 × 25 mL) and $MgSO_4$. Removal of solvent *in vacuo* yielded 0.081 g (81 %) of **70** as a white solid.

Data for **70:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (m, 1 H, Ar H), 8.05 (d, J = 84 Hz, 1 H, Ar H), 7.92 (m, 1 H, Ar H), 7.67 (d, J = 8.3 Hz, 1 H, Ar H), 7.59 (m, 2 H, Ar H), 7.39 (m, 2 H, Ar H), 7.32 (d, J = 8.1 Hz, 2 H, Ar H), 7.23 (d, J = 7.1 Hz, 1 H, Ar H), 6.35 (s, 1 H, CH), 3.82 (sept, J = 6.0 Hz, 1 H, CH), 2.11 (s, 3H, CH_3), 1.92 (s, 3H, CH_3), 1.25 (d, J = 6.3 Hz, 3H, CH_3), 0.96 (d, J = 6.0 Hz, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 147.9, 142.4, 142.3, 134.1, 132.6, 128.9, 128.4, 128.1 (two peaks overlapping), 127.2, 127.1, 127.0, 126.6, 126.4, 125.1, 124.8, 124.6, 120.7,120.5, 98.8, 85.9, 85.8, 85.6, 85.4, 66.3, 66.2, 59.6, 29.7, 29.1, 28.5, 28.3, 24.4, 23.7, 23.5 (certain peaks are overlapping).

IR (cm^{-1}): 3025, 2356, 2341, 1669.

MS (EI), m/z (%): 182 (49), 183 (23), 184 (3), 345 (8), 359 (14), 360 (M +, 4), 361 (1)



3-Benzoyl-3-isopropoxy-2-(2-phenylpropan-2-yl)-2,3dihydro benzo[e]isoindol-1-one (72): Compound **60b** (0.250 g, 0.696 mmol, 1.00 eq.) was dissolved in THF (10 mL) and the solution was cooled to -78^{o}C. The solution was charged with TMEDA (0.16 mL, 1.08 mmol, 1.55 eq.) and with 1.4 M *sec*BuLi (0.76 mL, 1.04 mmol, 1.5 eq.). The lithiated mixture was allowed to stir for 5 minutes at -78^{o}C and treated with 12-crown-4 (0.180 mL, 1.11 mmol, 1.6 eq.). After stirring for 1 hr. , the mixture was quenched with benzoyl chloride (0.103 mL, 0.890 mmol, 1.6 eq.). The reaction was allowed to warm up to room temperature overnight with stirring. The reaction was

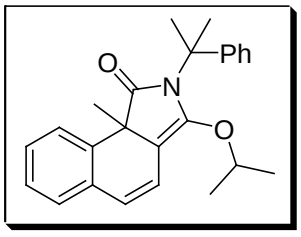
treated with saturated NH_4Cl (15 mL), extracted with ethyl actetate (25 mL), washed with water (3 × 20 mL) washed with brine (3 × 30 mL) and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The product was isolated and purified using flash chromatography (5% ethyl acetate in hexanes) to give 0.134 g, (0.310 mmol, 45%) of **72** as a white solid. Mp: 147 – 150 °C.

Data for **72**: ^{1}H NMR (600MHz, $CDCl_3$): 9.13 (d, J = 8.4 Hz, 1 H, Ar H), 7.92 (broad s 2 H, Ar H), 7.85 (d, J = 9.2 Hz, 1 H, Ar H), 7.80 (d, J = 7.8 Hz, 1 H, Ar H), 7.55 (t, J = 7.8 Hz, 1 H, Ar H), 7.50 (m, 4 H, Ar H), 7.33 (apparent d, J = 8.4 Hz, 3 H, Ar H), 7.18 (m, 4 H, Ar H) 7.10 (t, J = 7.2 Hz, 1 H, Ar H), 4.13 (sept, J = 6.0 Hz, 1 H, CH), 1.88 (s, 3 H, CH_3), 1.72 (s, 3 H, CH_3), 1.02 (d, J = 6.0 Hz, 6 H, CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): 197.7, 169.8, 147.3, 142.6, 136.6, 134.3, 132.9, 132.6, 130.6, 129.1, 128.5, 128.3, 128.2, 127.9,127.5, 126.8, 126.2, 125.6, 124.8, 120.0, 68.7, 61.3, 28.9, 28.0, 24.4, 24.2.

IR (cm^{-1}): 3059, 2979, 2935, 1701, 1596, 1519, 1445, 1383, 1301, 1238, 1092.

MS (ESI): HRMS, Calc'd for $C_{31}H_{29}NO_3$: 463.2137; Found: 464.2226 (M+H).



3-Isopropoxy-9b-methyl-2-(2-phenylpropan-2-yl)-2H-benzo [e]isoindol-1(9bH)-one (**73**). Compound **60b** (0.300 g, 0.840 mmol, 1 eq.) was dissolved in dry THF (8 mL) and cooled to -78°C. The solution was charged with TMEDA (0.20 mL, 1.34 mmol, 1.6 eq.) and then treated with 1.4M *sec*BuLi (0.893 mL, 1.25 mmol, 1.5eq). The resulting solution was stirred for 10 minutes at -78°C, quenched with methyl triflate

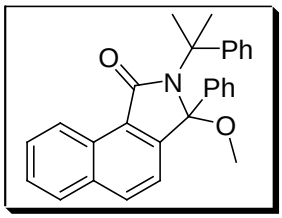
(0.11 mL, 0.93 mmol, 1.1 eq.) and allowed to slowly warm up to room temperature overnight with stirring. The reaction was quenched with ammonium chloride (10mL), extracted with ethyl acetate (20 mL), washed with water (3 × 20 mL), washed with brine (3 × 20 mL) and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. Centrifugal chromatography on a 2 mm plate, eluting with 5% ethyl acetate in hexanes yielded 0.090 g of **74** in 30 % yield as a clear oil.

Data for **74**: ^{1}H NMR (400 MHz, $CDCl_3$): 8.34 (d, J = 7.4 Hz, 1 H, Ar H), 7.35 (m, 4 H, Ar H), 7.29 (m, 3 H, Ar H), 7.18 (m, 1 H, Ar H), 6.44 (d, J = 9.5 Hz, 1 H, CH), 6.28 (d, J = 9.5 Hz, 1 H, CH), 4.62 (sept, J = 6.0 Hz, 1 H, OCH), 2.08 (s, 3 H, CH_3), 2.01 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 0.99 (d, J = 6.1, 3 H, CH_3), 0.92 (d, J = 6.1 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): 178.7, 149.0, 144.8, 136.5, 133.4, 128.1, 126.6, 126.0, 124.6, 124.2, 122.5, 119.4, 91.6, 72.8, 62.0, 49.4, 30.8, 30.3, 29.0, 21.8, 20.7.

IR (cm^{-1}): 3058, 2979, 2933, 2876, 1713, 1644, 1588, 1478, 1448, 1377, 1263, 1313, 1264, 1189, 1107, 1060.

MS (EI), m/z (%):: 119 (11), 198 (34), 255 (18); HRMS, Calc'd for $C_{25}H_{27}NO_2$: 373.2042; Found: 373.2035.



3-Methoxy-3-phenyl-2-(2-phenylpropan-2-yl)-2,3-dihydro benzo[e]isoindol-1-one (**80**). Compound **57** (3.15, 10.9 mmol, 1.0 eq.) was dissolved in dry THF (80 mL) cooled to -78 ^{o}C. The reaction mixture was treated with 1.4 M *sec*BuLi (23.4 mL, 32.7 mmol, 3.0 eq.) and allowed to stir for 3 hours at -78°C. Benzoyl chloride (1.52 mL, 13.1 mmol, 1.2 eq) was dissolved in dry THF (80 mL) and cooled to -78°C. The benzoyl

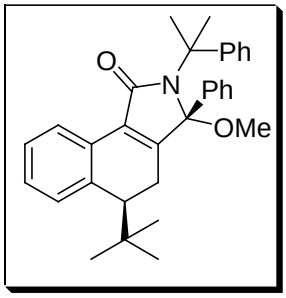
chloride solution was added to the lithiated amide using a syringe. The resulting mixture was held at -78°C for 1 hour and was allowed to warm up overnight to room temperature. The reaction was quenched with ammonium chloride (100 mL), extracted with ethyl acetate (100 mL), washed with saturated sodium bicarbonate (100 mL) then water (3 × 100 mL) and brine (3 × 100 mL) and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The yellow oil was dissolved in methanol (100 mL) along with *p*-toluenesulfonic acid (0.20 g, 1.16 mmol, 0.1 eq.) then refluxed over night. The methanol was removed under *vacuo* and the crude brown solid was recrystallized from methanol to give **80** in 53% (2.51 g, 6.16 mmol). Mp: 172 – 173 °C.

Data for **80**: ^{1}H NMR (600 MHz, $CDCl_3$): 9.17 (d, J = 8.4 Hz, 1 H, Ar H), 7.87 (d, J = 8.5 Hz, 1 H, Ar H), 7.82 (d, J = 8.0 Hz, 1 H, Ar H) 7.60 (t, J = 7.0 Hz, 1 H, Ar H), 7.53 (m, 3 H Ar H) 7.28 (m, 4 H, Ar H), 7.25 (m, 1 H, Ar H), 7.01 (d, J = 8.3 Hz, 1 H, Ar H), 3.18 (s, 3 H, OCH_3), 1.79 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): 169.8, 147.5, 146.4, 140.7, 133.8, 133.2, 128.7, 128.2, 127.9, 127.7, 127.0, 126.2, 125.8, 125.8, 125.3, 124.7, 119.4, 102.5, 96.8, 60.7, 52.1, 27.9, 27.7.

IR (cm^{-1}): 3058, 2987, 2935, 2852, 2832, 1695, 1600, 1582, 1383, 1305, 1242, 1190.

MS (EI), m/z (%):258 (87), 259 (34), 289 (22), 392 (100), 393 (30), 407 (M+, 82), 408 (26); HRMS, Calc'd for $C_{28}H_{25}NO_2$: 407.1885; Found: 407.1882.



(±)(3R,5S)-5-tert-Butyl-3-methoxy-3-phenyl-2-(2-phenyl propan-2-yl)-2,3,4,5-tetrahydrobenzo[e]isoindol-1-one (84): Compound **80** (0.300 g, 0.736 mmol, 1.0 eq.) was dissolved in 7

mL of THF and then cooled to -78°C. The solution was treated with 1.7 M *t*BuLi (0.65 mL, 1.10 mmol, 1.5 eq.) and allowed to stir for 1 hr. at -78°C. 2-Propanol (1 mL) was dissolved in a separate round bottom flask with 7 mL THF and cooled to -78°C. The lithiated solution was quenched with the 2-propanol solution in THF. The solution was allowed to warm up to room temperature overnight with stirring. The reaction mixture was dissolved in ethyl acetate (20 mL), washed with water (3 × 20 mL) and brine (3 × 20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. Separation by centrifugal chromatography (1% iPrOH in hexanes) gave 0.204 g (59%) of **84** as a mixture of two diastereomers in a ratio of 3:2 measured by ^{1}H NMR. Recrystallization with methanol elucidated the major diastereomer for which all spectral data is reported. Mp. 164-167 °C. Data for **84**: ^{1}H NMR (600 MHz, $CDCl_3$): 8.04 (d, J = 7.6 Hz, 1 H, Ar H), 7.86 (d, J = 7.8 Hz, 1 H, Ar H), 7.57 (d, J = 7.7 Hz, 2 H, Ar H), 7.47 (t, J = 7.5 Hz, 1 H, Ar H), 7.35 (t, J = 6.7 Hz, 1 H, Ar H), 7.25 (m, J = 7.2 Hz, 4 H, Ar H), 7.21 (m, 2 H, Ar H), 7.17 (m, 1 H, Ar H) 7.09 (d, J = 7.4 Hz, 1 H, Ar H), 3.17 (s, CH_3, OCH_3), 2.61 (d, J = 9.1 Hz, 1 H, CH), 2.38 (dd, J = 9.3 & 19.6 Hz, 1 H CH), 2.26 (d, J = 19.5 Hz, 1 H, CH), 1.77 (s, 3 H, CH_3), 1.72 (s, 3 H, CH_3), 0.49 (s, 9 H, $C(CH)_3$)

^{13}C NMR (150 MHz, $CDCl_3$): 170.2, 152.9, 146.6, 138.8, 135.2, 130.8, 129.1, 128.8, 128.5, 128.2, 127.7, 127.6, 127.4, 127.0, 126.8, 126.4, 126.3, 125.9, 124.6, 97.5, 60.1, 51.3, 46.8, 34.9, 28.2, 28.0, 22.0.

IR (cm^{-1}): 3059, 2959, 2869, 2832, 1696, 1489, 1388, 1339, 1285, 1244, 1087, 910.

MS (EI), m/z (%): 407 (3), 408 (3), 465 (M+, 12), 466 (4), HRMS, Calc'd for $C_{32}H_{35}NO_2$: 465.2668; Found: 465.2671.

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