# ORGANOCATALYZED CONJUGATE ADDITION FOR THE TOTAL SYNTHESIS OF NATURAL PRODUCTS AND DEVELOPMENT OF RELAY CATALYTIC METHODOLOGY

by
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A dissertation submitted to the Department of Chemistry,
University of Houston
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

in Chemistry

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*For all the members of my family:*
*the ones who were there from the beginning,*
*and the ones who joined along the way.*

# ACKNOWLEDGMENTS

Thank you very much first and foremost, to my advisor, Professor Jeremy May. Through his support and guidance, I've grown as a researcher, writer, scientist, teacher, and leader. I've learned an incredible amount during my graduate studies, and I owe it all to Professor May's belief in my abilities, his willingness to let me pursue avenues I found exciting, his advice, and his encouragement. He's taught me so much about chemistry, but also generally about doing good work and being good to others, and I'll always be immensely grateful to him for taking me on as a graduate student.

Thank you also to a mentor from long ago – Mr. Tom Kelly, who taught AP chemistry at Stevenson High School. Besides my parents, he was the first person to spot and encourage my interest in chemistry and taught me the fundamentals I needed to get where I am today.

Thank you to all of the wonderful people I've had the opportunity to work alongside while I've been in graduate school. I'm so grateful for the mentorship of Dr. Krit Setthakarn, who taught me everything I needed to know when I joined the lab and was always ready to help and answer any (and all) questions I had. Dr. Scott Smith has taught me so much about NMR spectroscopy and has helped me figure out some truly baffling spectra. I'm also very thankful for the help of Dr. Ettore Rastelli, who's been an amazing friend and guide through the process of graduate school, publications, dissertation writing, and beyond. Dr. Andrew Bollinger has been a steadying force in the storm that is graduate school, and I'm so grateful for his friendship and help during this time.

Thank you to all the May group members that have been amazing friends and colleagues. Specifically, Qinxuan Wang and Jirong Luo, thanks for being there to talk chemistry and assorted miscellaneous topics, and for your support in the lab. Amy Boylan has been the most supportive group member and friend I could have asked for, and I'm so grateful for having her in the lab and in my life for the last five years.

Thank you also to those graduate students I wasn't lucky enough to have as group members – Sabrina Aderibigbe, Corie McHale, Lisa Yawn and Srujana Lam. I have treasured Sabrina's friendship and help from the moment we started struggling through Synthesis together. Corie has been an amazing

colleague and friend and through these five years. I wouldn't have made it through the summer between my first and second year without Lisa's kindness and support. Suji's friendship and openness and has meant the world to me.

Thank you so much to Agne Janusauskaite, who's been there for me through all my academic (and personal) ups and downs since the first day of undergrad. She's always ready to answer all my biology questions. Florida is much further than the other bunk bed, but she's been such a huge support, nonetheless. It is my sincere hope that she will continue to not get eaten by alligators.

I feel that I have to acknowledge all the members of the MCS who we left back in Chicago, but who've been willing to have us crash on their couches and have come to crash on ours. Their friendship has been what kept me sane the past several years. So, thank you so very much to Ashley Mason, Ashwin Raman, Ellis Lee, Harpreet Singh, Kwang-Moo Lee, Michael Smith, and Sam Swaminathan. I wouldn't be here if it wasn't for their love and support.

The biggest thank you of all to my fiancé, Mike Greiner. This one I really can't express in words, but he has my eternal gratitude for putting me first and going on this crazy journey with me. Also, I'll always be thankful for him sitting through all my practice talks, always listening to my chemistry complaints and giving good advice. I'm grateful for his overwhelming positivity, patience, and kindness. I am so glad to be together with him on this journey through life, and he has been the best partner and the best friend it's possible to have, while in graduate school and beyond.

I am incredibly, overwhelmingly, grateful to my family: Tatiana, Sergey, and Alice Oleynichenko. I am so thankful for their encouragement and support, their advice, and their patience. I am so appreciative of the sacrifices they made to give me access to the opportunities I needed to succeed. My parents have always encouraged me to choose a path and work hard to be successful. I have kept our 'family motto' close to my heart these last five years, and I will always live my life by these words – "to fight, to seek, to find, and not to yield".

# LIST OF ABBREVIATIONS

| | |
|---|---|
| 9-BBN | 9-benzobycyclononane |
| Ac | acetyl |
| acac | acetylacetone |
| AChE | acetylcholinesterase |
| aq | aqueous |
| Ar | aryl |
| binap | 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl |
| BINOL | 1,1'-bi-2-naphthol |
| Bn | benzyl |
| Boc | tert-butoxycarbonyl |
| BOP | (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate |
| Bpin | pinacolborane |
| bpy | bipyridine |
| Bs | benzylsulfonyl |
| Bu | butyl |
| cat | catalyst |
| Cbz | carboxybenzyl |
| COD | cyclooctadiene |
| COD | 1,5-cyclooctadiene |
| CSA | camphorsulfonic acid |
| DCA | dichloroacetic acid |
| DCE | dichloroethane |

| | |
|---|---|
| DCM | dichloromethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DFT | density functional theory |
| DMA | dimethylacetamide |
| DMAP | dimethylaminopyridine |
| DMAP | 4-dimethylaminopyridine |
| DMF | dimethylformamide |
| DMSO | dimethylsulfoxide |
| dppb | 1,4-bis(diphenylphosphino)butane |
| dppf | 1,1'-bis(diphenylphosphino)ferrocene |
| EDC | 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| EDG | electron donating group |
| ee | enantiomeric excess |
| Et | ethyl |
| EWG | electron withdrawing group |
| GC | gas chromatography |
| h | hour |
| Het | heteroaryl |
| HOBt | hydroxybenzotriazole |
| HPLC | high-performance liquid chromatography |
| HRMS | high resolution mass spectrometry |
| Int | intermediate |
| iPr | isopropyl |

| | |
|---|---|
| LDA | lithium diisopropyl amine |
| Me | methyl |
| MeSer | methylserine |
| MOM | methoxymethyl |
| MS | mass spectrometry |
| MS | mass spectrometry |
| MVK | methyl vinyl ketone |
| NBS | n-bromosuccinimide |
| n-Bu | n-butyl |
| nESI | negative electrospray ionization |
| NIS | n-iodosuccinimide |
| NMM | n-methylmaleimide |
| NMR | nuclear magnetic resonance |
| Nu | nucleophile |
| PCC | pyridinium chlorochromate |
| Ph | phenyl |
| Ph | phenyl |
| PhMe | toluene |
| Phth | phthalimide |
| pyr | pyridine |
| RT | room temperature |
| SEM | 2-(trimethylsilyl)ethoxymethyl |
| SES | 2-(trimethylsilyl)ethanesulfonyl |

| | |
|---|---|
| SM | starting material |
| TADDOL | α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol |
| TBAF | tetrabutylammonium fluoride |
| TBAI | tetrabutylammonium iodide |
| TBS | tert-butyldimethylsilyl |
| Tf | triflate |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMEDA | tetramethylethylenediamine |
| TMEDA | tetramethylethylenediamine |
| TMP | 2,2,6,6-tetramethylpiperidine |
| TMS | trimethylsilyl |
| Ts | tosyl |

# ABSTRACT

This dissertation covers two projects utilizing organodiol catalyzed conjugate addition. The first project uses BINOL-derived organocatalysts to synthesize indolyl-propylene glycol natural products. The second project covers reactivity of organodiol catalyzed conjugate addition with vinylogous ester and amide electrophiles alongside the development of relay catalysis.

Organocatalyzed conjugate addition has been used in the pursuit of the synthesis of natural products, primarily mucronatins A and B. These natural products are challenging to synthesize due to the need for stereoselective synthesis in the presence of sensitive diindole cores. Previously developed methods allow for the conjugate addition of heteroaryl trifluoroborate salt nucleophiles to electron-rich electrophiles containing indoles. Mucronatins A and B are only two examples of these types of structures, and similar structures have also been targeted.

The reactivity of the diol catalysts previously utilized by our group and intriguing results from mechanistic studies led us to consider using very electron-rich electrophiles as conjugate addition partners. Vinylogous esters and amides were tested as electrophiles and were found to undergo conjugate addition, followed by elimination of the β-leaving group. This reactivity was optimized for the synthesis of polyunsaturated ketones and ene/ynones with a simplified organodiol catalyst.

This reactivity was further explored to synthesize the dienones from the alkyne precursors of vinylogous esters and amides directly. Using catalytic amounts of methyl aniline, the reaction could be performed in one step without the need to isolate vinylogous esters and amides. This relay catalytic process was optimized for a faster reaction rate and superior yields when compared to the sequence of two individual steps.

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*The numbering of compounds restarts in each chapter.*

# CHAPTER 1: CONJUGATE ADDITION REACTIONS

## 1.1 Origins of Conjugate Addition

Carbon–carbon bond forming reactions have been highly sought after in synthetic organic chemistry since the inception of the field. The formation of such bonds allows for the combination of molecular building blocks and increase of structural complexity. Many researchers focus extensively on developing novel ways to form carbon–carbon bonds, including using transition metal catalysis,[1–3] photochemistry,[4–6] and organocatalysis.[7–10] Particularly desirable are those variants of such reactions which allow for enantioselective synthesis, as many natural products are a single enantiomer, and drug molecules can have vastly different modes of activity based on their absolute stereochemistry.

Conjugate addition reactions have been known since the 1880s when these reactions were first studied in detail by Arthur Michael (Figure 1.1). [11] Michael reactions are 1,4-conjugate additions which form a bond at an electron deficient carbon β to a carbonyl. In the most common form of this reaction, an enolate acts as the nucleophile to attack the electron deficient β-position of an α,β-unsaturated carbonyl compound, forming a new carbon–carbon bond. This reactivity is incorporated into the Robinson annulation, where it's combined with another name reaction, the Aldol condensation, to create novel cyclic structures.

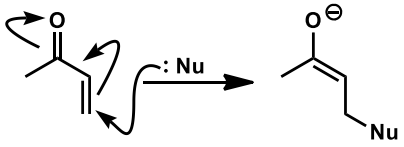



**Figure 1.1**. Conjugate additions - Michael reaction

While enolates generated *in situ* were the original nucleophile in the Michael addition, many other nucleophiles have been employed to enact 1,4-conjugate addition. Organometallic reagents

such as Grignard reagents are a popular choice of nucleophile in conjugate addition.[12] These nucleophiles have been extensively studied and are commercially available or readily synthesized from common building blocks.

The main drawback of organometallic reagents and enolate nucleophiles, while they are highly reactive and effective in conjugate additions, is their incompatibility with certain labile functional groups such as amines and hydroxyls. Another drawback is the competition with 1,2-addition for regioselectivity of addition, as these reactions can be difficult to control.

## 1.2 Development of Non-Transition Metal Catalyzed Conjugate Additions with Boron Nucleophiles

### 1.2.1 Organoboronate Nucleophiles

In the pursuit of highly tolerant and versatile conjugate addition nucleophiles, Herbert Brown developed a protocol for the syntheses of γ,δ–unsaturated ketones using 9-BBN derived organoboronate nucleophiles **2** to enact conjugate addition (Figure 1.2).[13] The organoboronates could be generated by reaction of acetylenes **1** with 9-BBN, followed by conjugate addition, mainly to methyl vinyl ketone (MVK, **3**). Hydrolysis of the resulting structures provided the unsaturated ketones **4** in yields up to 93%. This work, preformed in 1976, was the first report of conjugate additions using organoboronate nucleophiles.

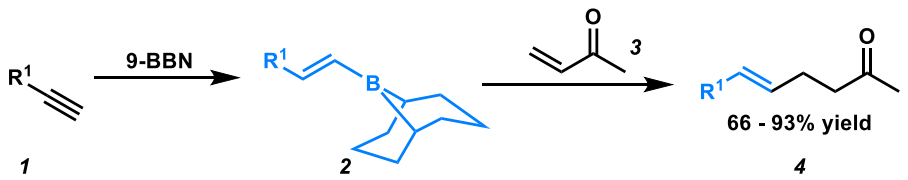



**Figure 1.2.** First report of organoboronate conjugate addition

Following Brown's work, Akira Suzuki further used organoboronates to enact Michael-type reactions.[14,15] It was found that when using a halogenated variant of 9-BBN (**6**) the halogen

and borane added to alkynes in a trans-fashion (Figure 1.3). After this, conjugate addition of the resulting species **7** to methyl vinyl ketone (**3)** gives the resulting halo-alkene (**8)**. This reaction allowed for a simple route to linear chain natural products, as well as more complicated syntheses,[16] and set further precedent for the application of organoboronates in conjugate additions.

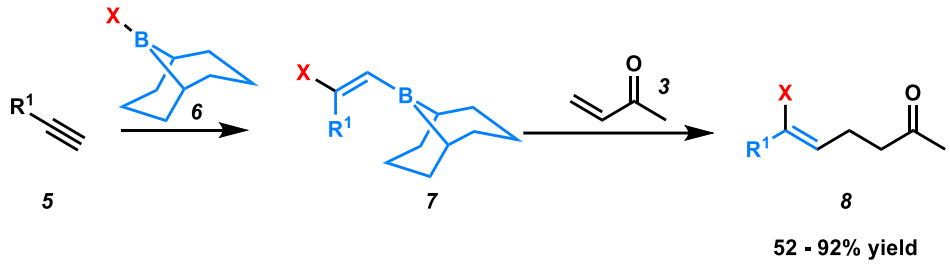



**Figure 1.3.** First use of organoboronates by Suzuki

Suzuki continued to explore the reactivity of organoboronate compounds (Figure 1.4), expanding the nucleophile scope to boronic esters (and one example of a boronic acid).[17] The nucleophiles derived from 9-BBN were occasionally difficult to synthesize and not as stable as boronic esters. The discovery of conditions for the use of triisopropyl borates and boronic acids in 1990 allowed for an expansion of nucleophiles while maintaining high yields and regioselectivity. The inherent lower reactivity was mediated by using Lewis acid catalysis. Otherwise, the overall reactivity remained the same, with an organoboronate nucleophile **10** adding regioselectively to an unsaturated carbonyl in **9**.

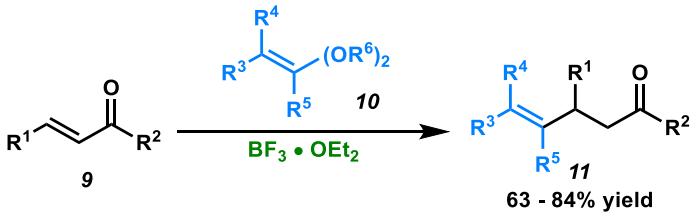



**Figure 1.4.** Organoboronate expansion by Suzuki

## 1.3 Transition Metal Catalyzed Enantioselective Conjugate Additions

Michael additions often form stereocenters. Classically, stereocontrol could be achieved only by the stereochemical preference of the starting materials due to existing stereochemistry. One such approach is to enact conjugate additions on chiral substrates and then removing the chiral directing group, resulting in a selective C–C bond formation.[18] However, other methods to allow for enantioselective reactions have been developed, including a great amount of work into catalytic methods. Both transition metal and organocatalysis have been employed in pursuit of this goal.

### 1.3.1 Copper-Catalyzed Enantioselective Conjugate Additions

A variety of chiral ligands have been utilized in copper catalysis to enact enantioselective conjugate additions. These ligands include oxazoline ligands as well as TADDOL and BINOL derived species as notable examples.[12] These ligands tend to be rather large, allowing for enantioinduction in the C–C bond forming step, and the reaction conditions rely on nucleophiles which are unreactive except in the presence of a copper catalyst, such as organozinc compounds. A key example is the use of chiral phosphorous amidite **13** by Feringa in 1996 (Figure 1.5).[14]

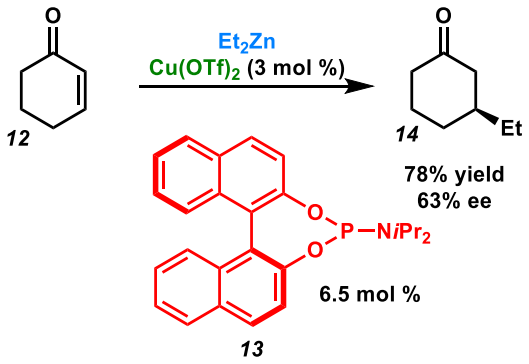



**Figure 1.5**. Copper catalysis for enantioselective conjugate addition.

There are some interesting exceptions to the BINOL/TADDOL derivatives, especially with oxazoline ligands. As an example, the stereoselective reaction developed by Sammakia in 1997 features chiral ferrocene ligand **15** as well as Grignard nucleophiles (Figure 1.6).[19]

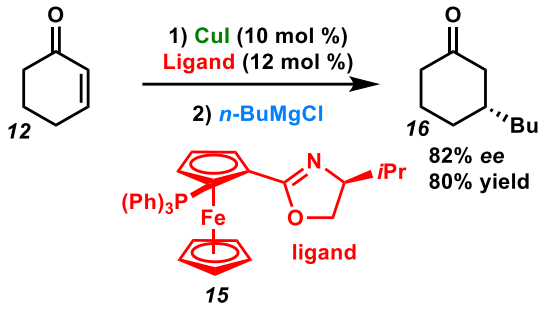



**Figure 1.6.** Sammakia's work with chiral ferrocene ligands.

Generally, copper catalyzed reactions have been well-developed and explored, both in terms of ligands and nucleophiles. These methods often rely on organometallic nucleophiles, which suffer from lack of stability as well as high reactivity, leading to the inability to use such methods to synthesize compounds containing labile functional groups.

### 1.2.1 Other Transition Metal Catalyzed Enantioselective Conjugate Additions

Other metals used in enantioselective conjugate additions include cobalt and nickel.[20] These metals are less common for these transformations, likely due to the lack of stereoselectivity reported with these catalysts. These catalysts also tend to be limited with electrophile and nucleophile scopes, making them less appealing than copper or rhodium in the realm of transition metal catalysis. This chemistry also typically relies on the use of organozinc nucleophiles.

### 1.2.2 Rhodium-Catalyzed Enantioselective Conjugate Additions

Rhodium has been a popular metal in conjugate addition reactions.[21] Rhodium catalysis with organoboronate nucleophiles was used to enact conjugate additions by Miyaura in 1997 (Figure 1.7).[22] While this reaction excelled with unsubstituted ketones, such as methyl vinyl ketone **3**, β-substitution led to decreased yields. This led to further work with rhodium catalyzed methods and exploration into the use of organoboronates for such additions with transition metal catalysts.[21]

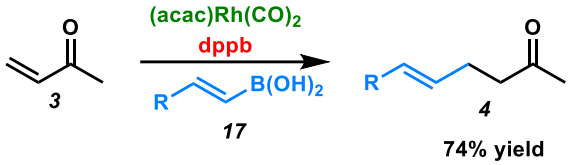



**Figure 1.7.** Original rhodium catalyzed conjugate addition with organoboronates

Rhodium catalysis was first used to catalyze enantioselective conjugate additions in 1998.[23] Chiral biphosphine (binap) ligands, when used with rhodium (I) catalysts, allowed for the synthesis of highly enantiopure conjugate addition adducts (**18**, Figure 1.8).

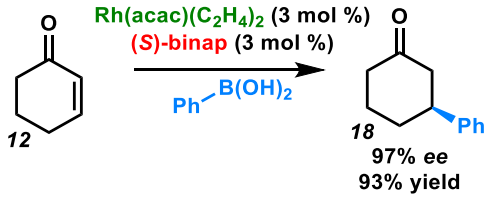



**Figure 1.8.** Asymmetric conjugate addition with rhodium catalysts

Following this work, other ligands were explored, with many successful variants developed in subsequent years. Organoboronates are popular nucleophiles in these reactions, with boronic acids, esters, and pinacolboranes represented. Trifluoroborate salt nucleophiles were also shown to be effective in such reactions, providing high yields and high enantioselectivities.[24,25]

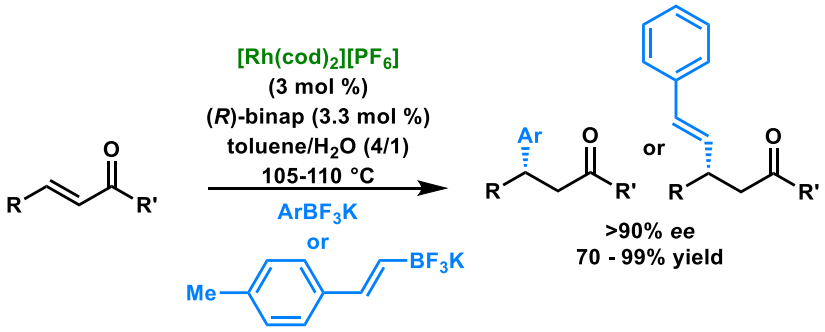



**Figure 1.9.** Enantioselective rhodium catalysis with trifluoroborate salt nucleophiles

Rhodium-catalyzed conjugate addition of organoboronates is proposed to proceed through transmetalation of the organoboronate, and then coordination to the double bond of the α,β-unsaturated compound. The enantioselectivity in this case is imparted by the location of the open coordination site which the α,β-unsaturated ketone enters. An example is the original Miyaura work with boronic acids (Figure 1.9).[23]

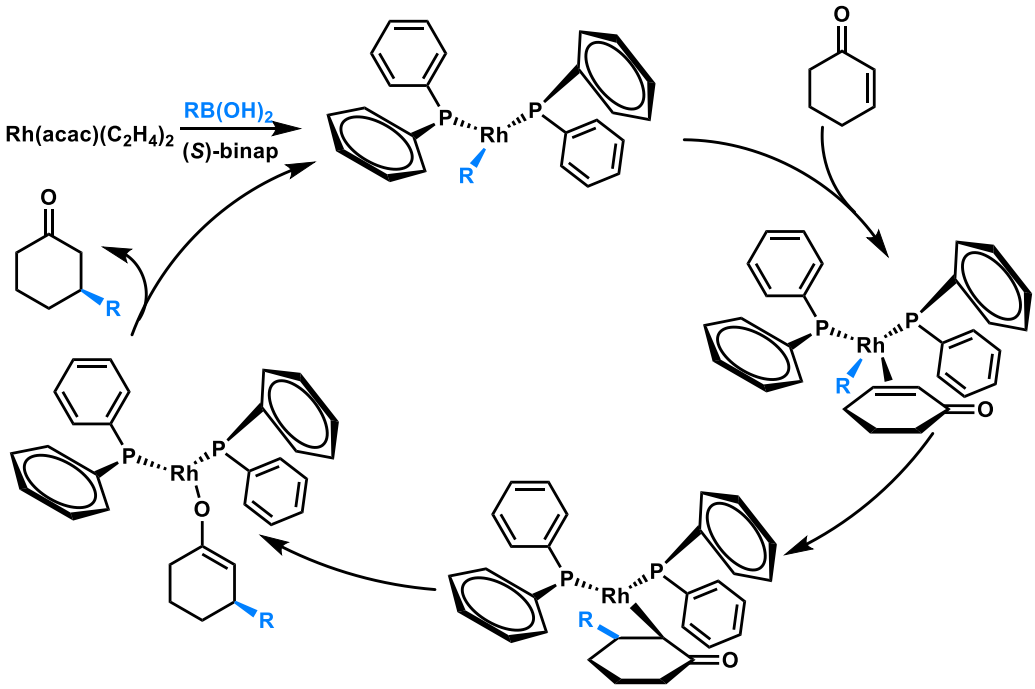



**Figure 1.10.** Stereoselective rhodium conjugate addition catalytic cycle

### 1.2.3 Lewis Acid Catalysis

Following Suzuki's work with organoboronates, J. Michael Chong recognized the potential for developing an enantioselective transformation without the use of transition metals.[26] He recognized that an alternate way to activate the organoboronate is potentially through the esterification of the organoboronate with an organodiol.

Using a large BINOL-derived stoichiometric ligand (**19**), the Chong group was able to enact conjugate additions of alkynyl boronates enantioselectively using Lewis acid catalysis

(Figure 1.11). The initial step of the reaction relied on a different method of boron nucleophile activation than that featured in transition metal catalysis. In the initial step, the trialkoxy ate complex undergoes transesterification with the BINOL-derived ligand. The resulting nucleophile was able to perform conjugate additions enantioselectively at the β-position of an α,β-unsaturated ketone with *ee* exceeding 80%.

Both enantioselectivity and yields of this reaction were high, but the necessity of a large enantiopure ligand in stoichiometric quantities was a considerable drawback.

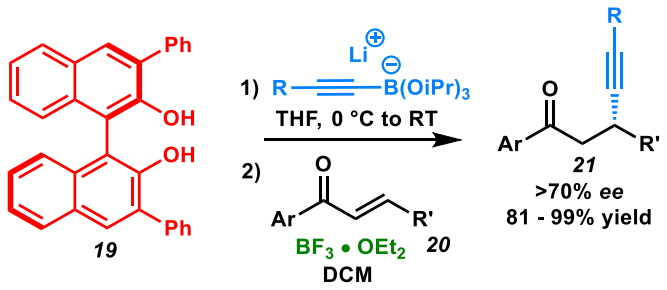



**Figure 1.11.** Enantioselective Lewis-acid catalyzed conjugate addition

## 1.3 Organocatalyzed Enantioselective Conjugate Additions with Organoboronates

### 1.3.1 First Report – J. Michael Chong

Building on their Lewis acid catalyzed approach, the Chong group presented a methodology that relied on the same method of activation of organoboronate nucleophiles in 2007.[27] They were able to use BINOL-derived organodiols as catalysts, with the carbon–carbon bond formation proceeding enantioselectively in a similar manner to that achieved in the Lewis acid catalyzed work.

Their proposed catalytic cycle was initiated by transesterification as in the Lewis acid catalyzed approach (Figure 1.12). Following activation of the boronic ester **23** by the organodiol **22** to complex **I,** conjugate addition would allow the formation of a carbon-carbon bond enantioselectively at the β-position (**II**). The BINOL complex could potentially be transesterified

with another equivalent of the boronic ester (**III**), and then hydrolyzed to the final conjugate addition product, and re-entered into the cycle.

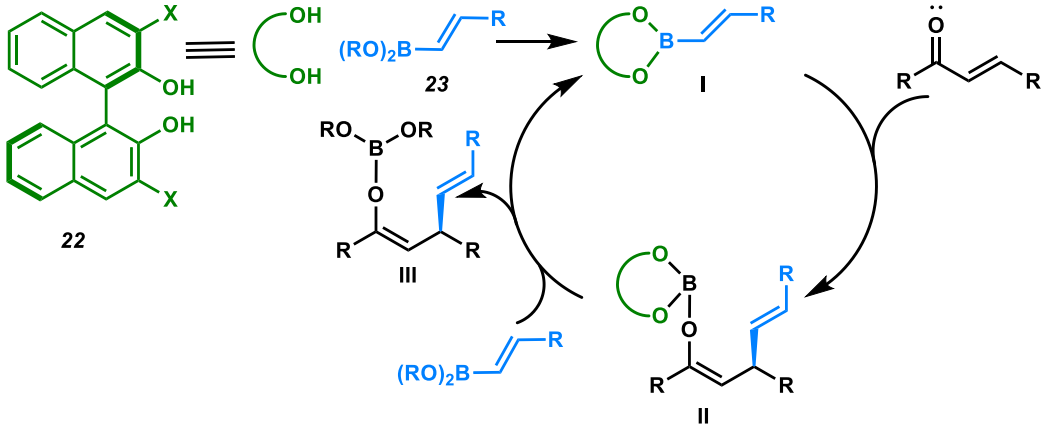



**Figure 1.12.** Catalytic pathway with organodiols and organoboronate nucleophiles proposed by Chong

The Chong group found that BINOL and BINOL-derived compounds featuring electron withdrawing groups, such as halogens, at the 3 and 3' positions specifically (such as **25**), were effective at enacting this esterification and facilitating the conjugate addition as predicted (Figure 1.13). The electron withdrawing groups likely make the formation of complex **I** more favorable by providing a stronger binding in the ate complex. Furthermore, Chong found these BINOL derived reagents could turn over catalytically, and therefore be used in catalytic amounts. In this chemistry, methyl boronate esters were most commonly used as nucleophiles. A few examples of boronic acids and triisopropyl boronate esters were also effective. This was the first report of enantioselective conjugate addition not requiring a transition metal or Lewis acid.

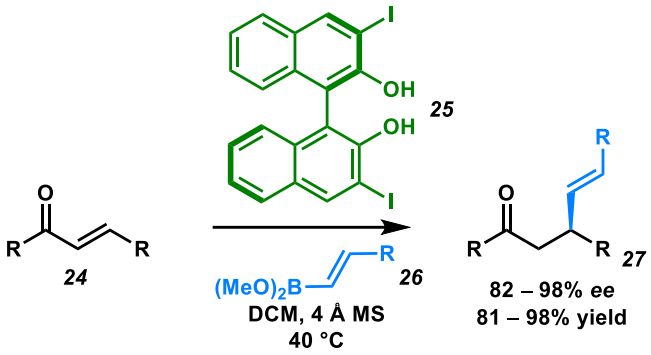



**Figure 1.13.** First report of enantioselective organocatalyzed conjugate addition.

There were some drawbacks to Chong's work. The nucleophile scope was limited to alkenylboronates, with no examples of aryl or heteroaryl organoboronates. The reactions were slow, with some nucleophiles requiring up to 96 hours for reaction completion. However, this methodology was highly promising, tolerated a wide range of nucleophile modifications, and featured very mild conditions. The nucleophiles, similar to the organozinc compounds used in some transition metal catalysis, were not reactive without catalyst, which is desirable in reactions useful to the building of complex structures such as drugs and natural products that contain many labile functional groups. Such reactions tend to be considerably more regioselective and chemoselective in complex molecule synthesis.

### 1.3.2 Further Developments – David MacMillan

In 2007, MacMillan reported the use of trifluoroborate salt nucleophiles in conjugate additions with imidazolidinone catalysts (Figure 1.14).[28] Trifluoroborates **29** had been demonstrated to be viable nucleophiles in transition metal catalysis, but not as partners in organocatalyzed reactions. This methodology allowed for the use of aldehyde **28** as an electrophile with good yields and enantioselectivities.

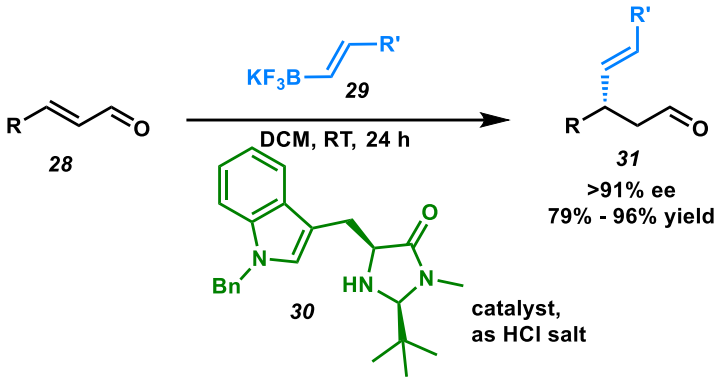



**Figure 1.14.** MacMillan's iminium catalyzed conjugate addition with trifluoroborate salts

The MacMillan group screened two iminium catalysts, but the one shown (**30**, Figure 1.**13**) provided higher conversions and enantioselectivities. They were also able to show reactivity with nucleophiles beyond the vinyl boronates shown by Chong. Furan and indole trifluoroborates were reactive under the iminium catalyzed conditions. Also, boronic acid nucleophiles were effective (see **32h-j**), but with limited electrophile scope and lower enantioselectivity.

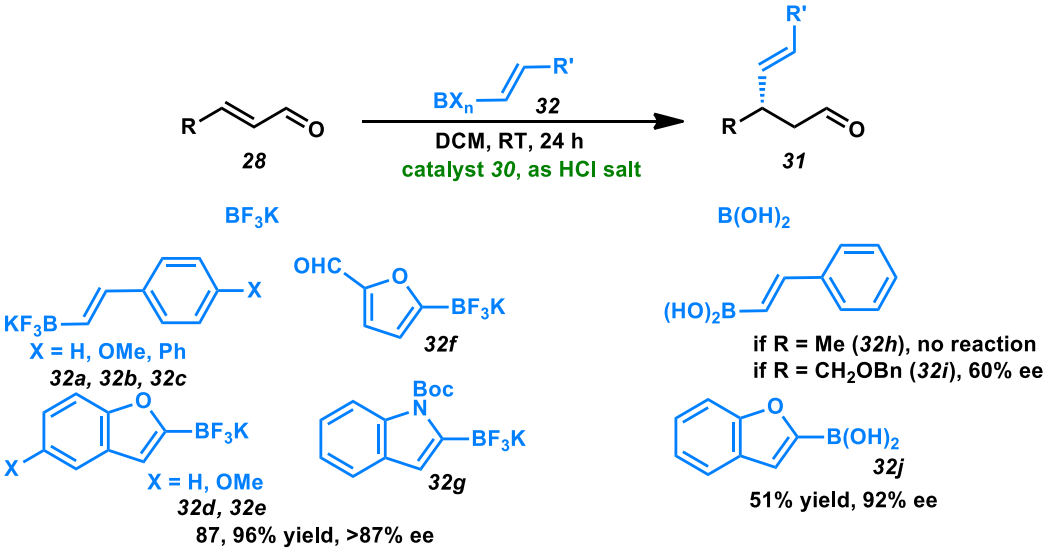



**Figure 1.15.** Nucleophile scope for Macmillan imminum catalysis

The mode of activation in this methodology is different than either Chong's work or transition metal catalysis. It involved activation of the electrophile rather than of the boronate complex as in Chong's work and rather than the transmetallation required with transition metal catalysis. This allows for catalyst control by blocking one face of the π-system of the formed iminium intermediate with the large substitutents of the catalyst, leading to *Re*-face attack (Figure 1.16).

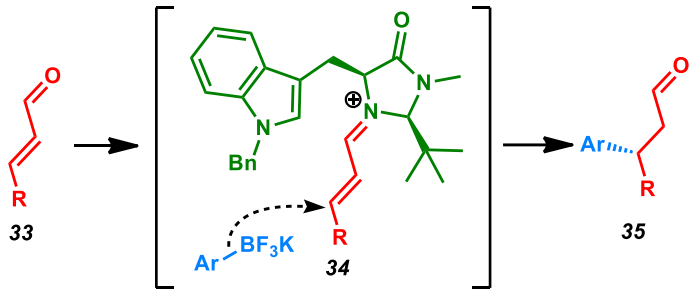



**Figure 1.16.** Organocatalytic activation with iminium catalysts

The MacMillan group utilized this methodology in a total synthesis of (+)-frondosin B after deriving a method to allow for the use of aryl trifluoroborate nucleophiles (i.e., **37**) more effectively (Figure 1.17).[29] They were able to add an acid co-catalyst (dichloroacetic acid, DCA) and change the solvents to allow for increased reactivity. From those results, they found they could use the commercially available boronic acid **37** and transform it to a reactive species *in situ* by using HF as an acid additive. This allowed for the synthesis of the natural product (**41**) in 3 steps.

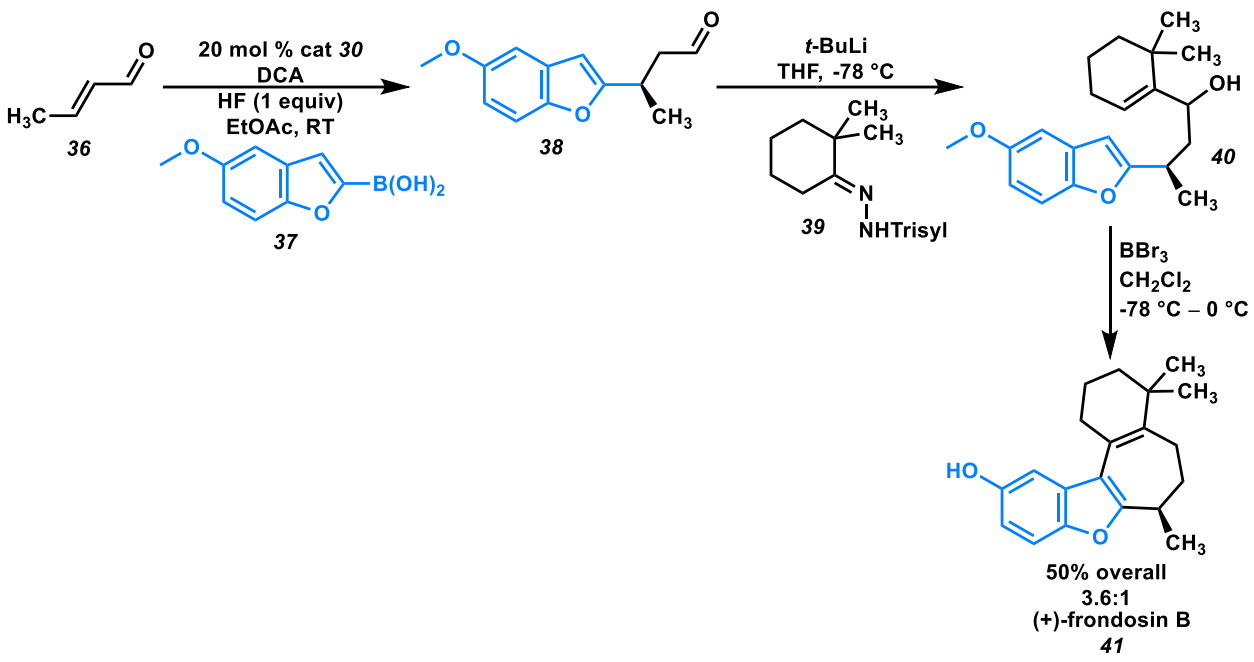



**Figure 1.17.** Total synthesis of (+)-frondosin B by the MacMillan group

### 1.3.3 Thiourea Organocatalysts – Yoshiji Takemoto

The thiourea catalyzed reactions developed by Takemoto use boronic acids as nucleophiles (Figure 1.18).[30] This methodology featured the use of unprotected hydroxyls in the electrophiles (**42)** as a necessary tether for the catalyst (**44**) to promote reactivity. Without the presence of the hydroxyl, the catalysts were not reactive, limiting the electrophile scope considerably.

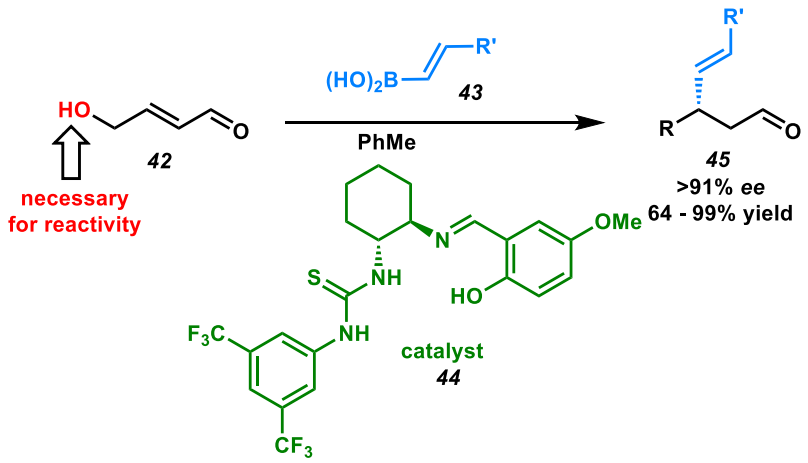



**Figure 1.18**. Takemoto's conjugate addition with thiourea catalysts

### 1.3.4 Tartrate Catalysts – Masharu Sugiura, Kazuaki Kudo

In a mechanism of action similar to that of BINOL-derived organocatalysts, tartaric acids were able to catalyze conjugate additions of boronic acids to variously substituted α,β-unsaturated ketones (**46**, Figure 1.19).[31] A tert-butyl substituted benzoate ester of the tartrate provided the highest enantioselectivity (**47**), which tended to be lower than reactions with organodiol catalysts. Effective nucleophiles included furan and benzofuran boronic acids.

The Sugiura group was also able to expand this methodology to the synthesis of cyclopentenones containing a stereocenter (**50**) in an unconventional manner (Figure 1.19).[32] Starting from dienones, they were able to follow conjugate addition with cyclization, preserving the stereochemistry as set by the tartrate catalyst.

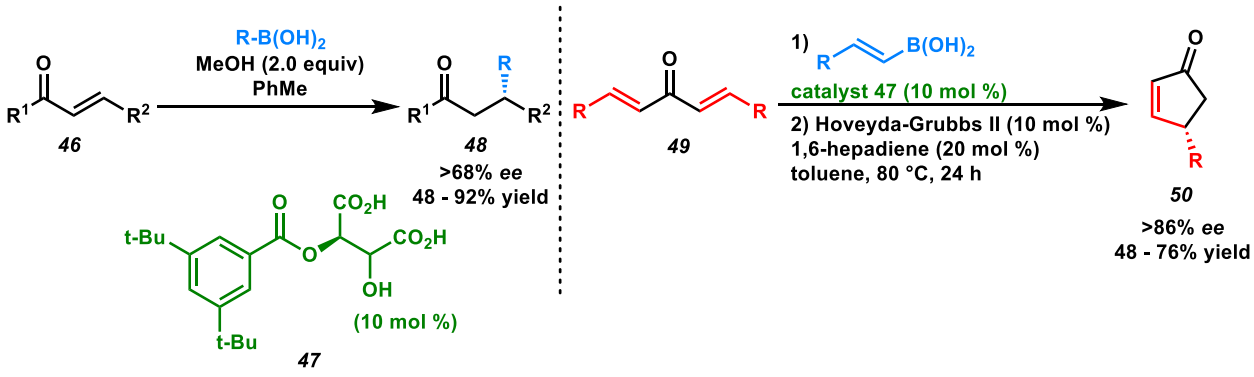



**Figure 1.19.** Sugiura group chemistry with tartaric acid catalysts

The Sugiura group followed their work in tartaric acid catalysis with a mechanistic study in partnership with Silvina Pellegrinet.[33] Using DFT calculations, they were able to propose a mechanism that explained the selectivity and necessity of the free hydroxyl in the catalyst. In their proposed mechanism, the free hydroxyl and the hydroxyl of the carboxylic acid adjacent to it coordinate to the boron (**I**, Figure 1.20), while the other hydroxyl of the other carboxylic acid is able to form a hydrogen bond. It was also proposed, based on DFT calculations, that there is

hydrogen bonding interaction between the two hydrogens shown in **II** to the benzoate carbonyl (Figure 1.20). In general, the mechanism of activation is quite similar to BINOL catalysis.

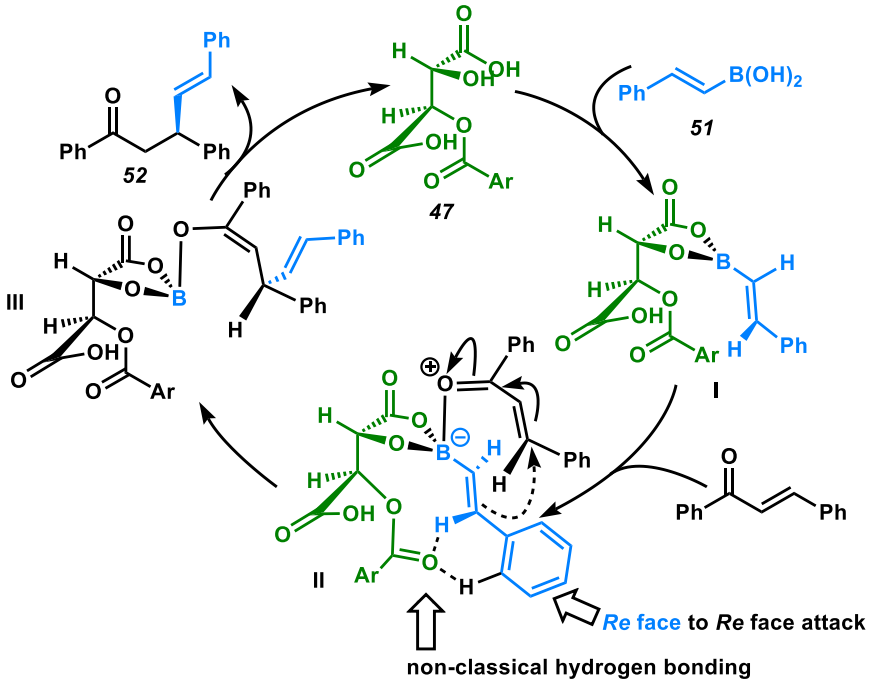



**Figure 1.20.** Pellegrinet and Sugiura mechanism study.

Kudo and coworkers were able to utilize tartrate catalysts similar to Takemoto's (Figure 1.21).[34] The presence of the γ-free hydroxyl in the electrophile was necessary for reactivity, but the method excelled in the ability to use unsaturated aldehydes **53** as electrophiles. The products resulting from conjugate addition could easily be further modified into synthetically useful structures (**54**). Most nucleophiles were familiar alkenyl compounds (**55**), with a few examples of heteroaryls that disappointingly gave decreased yields and selectivities (**56**, **57**).

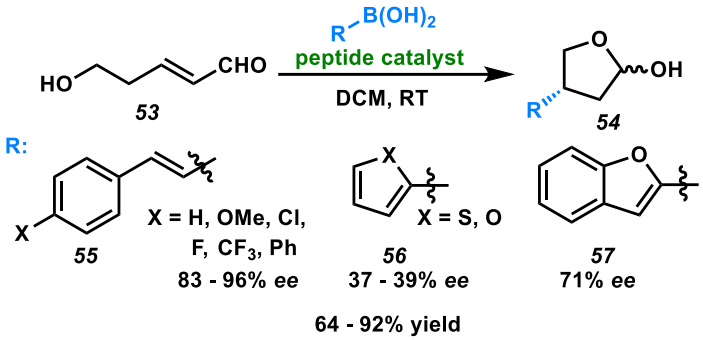



**Figure 1.21.** Peptide catalyzed conjugate addition/cyclization

## 1.4 Organocatalyzed Enantioselective Conjugate Additions in the May Laboratory

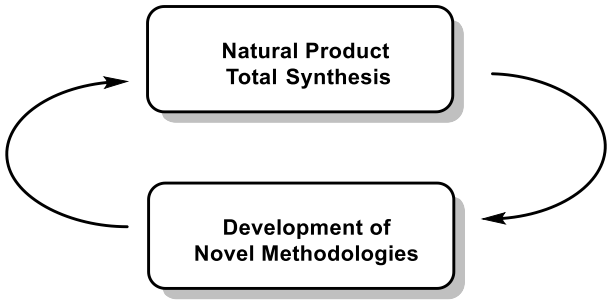



**Figure 1.22.** "Catalytic cycle"

Commonly, methodological development inspires synthesis, and challenges in complex molecule synthesis inspire the development of novel methodologies (Figure 1.22).[35] Some of the May laboratory's first work revolved around using existing methods in total synthesis. Organocatalytic methods subsequently developed in the lab were also utilized in synthesis of complex natural products, completing the cycle.

### 1.4.1 Synthesis of Flinderole-Class Compounds

The structures of the flinderoles (**61, 62, 64**, Figure 1.23) include a stereogenic center next to an indole ring. The biomimetic synthesis of these compounds was originally reported from borrerine **58**.[36] This synthesis was not enantioselective, affording a mixture of diasteromers.

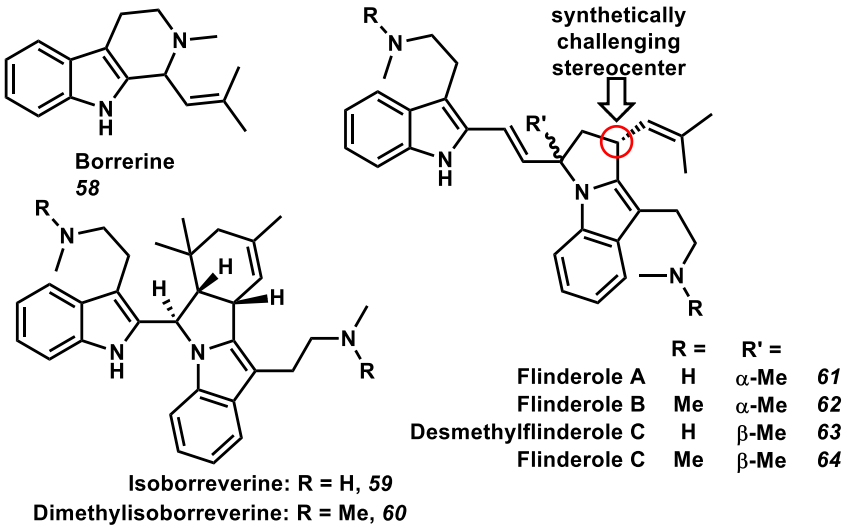



**Figure 1.23.** The flinderole family of compounds

While the flinderoles could be synthesized biomimetically from borrerine upon addition of TFA, the stereocenter indicated in Figure 1.23 presented a synthetically interesting challenge. Based on reported enantioselective conjugate additions, it was hypothesized that it would be possible to form the key stereocenter via enantioselective conjugate addition.

### 1.4.2 Development of Conjugate Addition Methodology Compatible with Indoles

The key synthetic challenge to be addressed was the conjugate addition to electrophiles with a β indole ring. Indole rings are quite electron-rich heterocycles, causing the β position to be weakly electrophilic for conjugate addition. Organocatalysis by BINOL derived catalysts provided a promising precedent to the development of novel methodology.

Chong and others showed that there was a strong correlation between electron withdrawing groups at the 3 and 3' positions of BINOL-derived organocatalysts and their reactivity.[27,37] Therefore, 3,3'-diiodo-BINOL and 3,3'-bispentafluorophenyl-BINOL (**67**) were selected for screening.

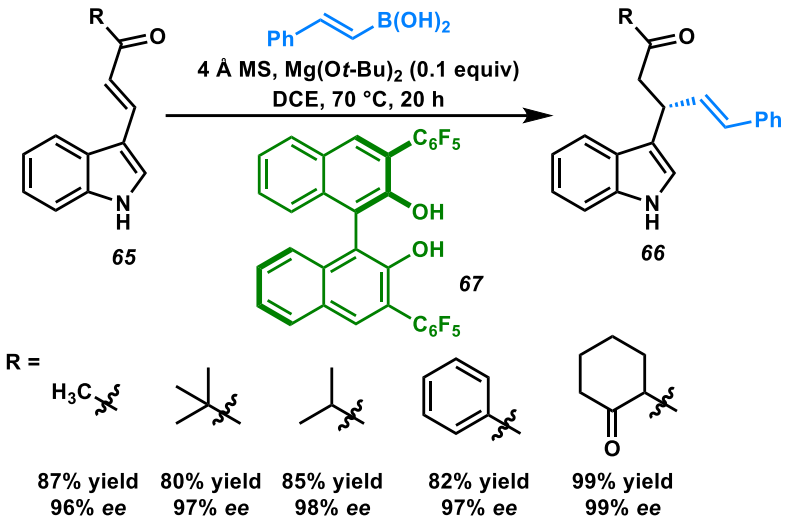



**Figure 1.24.** Conjugate addition to electron rich heterocycles

Satisfyingly, this mode of catalysis gave high yields and enantioselectivities (Figure 1.24). It also allowed for the use of unprotected indole electrophiles (**65**), setting it apart from other methods of conjugate addition, especially those utilizing organometallic reagents. The reaction was quite tolerant of different ketone substitution (see R group variation, Figure 1.24).

Boronic acid nucleophiles were used, and alkenyl and alkynyl nucleophiles proved to be effective. Aryl and heteroaryl boronic acids were not stable in the reaction conditions (Figure 1.25). One example of a boronic ester (**73**) was also shown. In the case of alkenyl boronic acids, both α- and β-substitution was well tolerated, providing somewhat less enantiopure products.

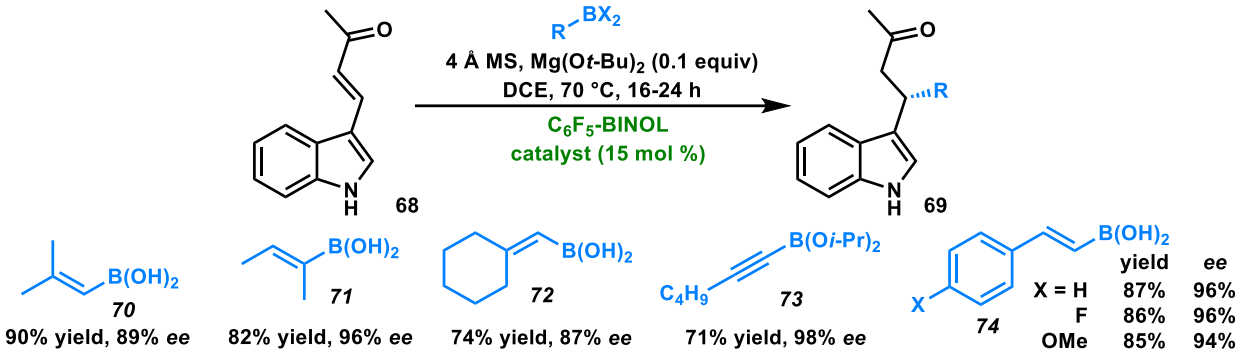



**Figure 1.25.** Conjugate addition to indole electrophiles

### 1.4.3 General Method Development

The general challenge of utilizing heterocycle-appended enones was addressed by our group in 2012.[38] By expanding on the methodology developed for indole-appended enones, the reaction was made more general.

The modifications were made to the BINOL-derived organocatalyst. Chong's reports used electron withdrawing halogens or trifluoromethyl groups, and previous efforts by our group used pentafluorophenyl groups at the 3 and 3' positions. Changing the pentafluorophenyl (**67**) groups for those derived from perfluorotoluene (**76**) allowed for an increase in reactivity as well as maintaining the high *ee*'s, likely due to the increased electron withdrawing nature compared to the pentafluorophenyl substituents.

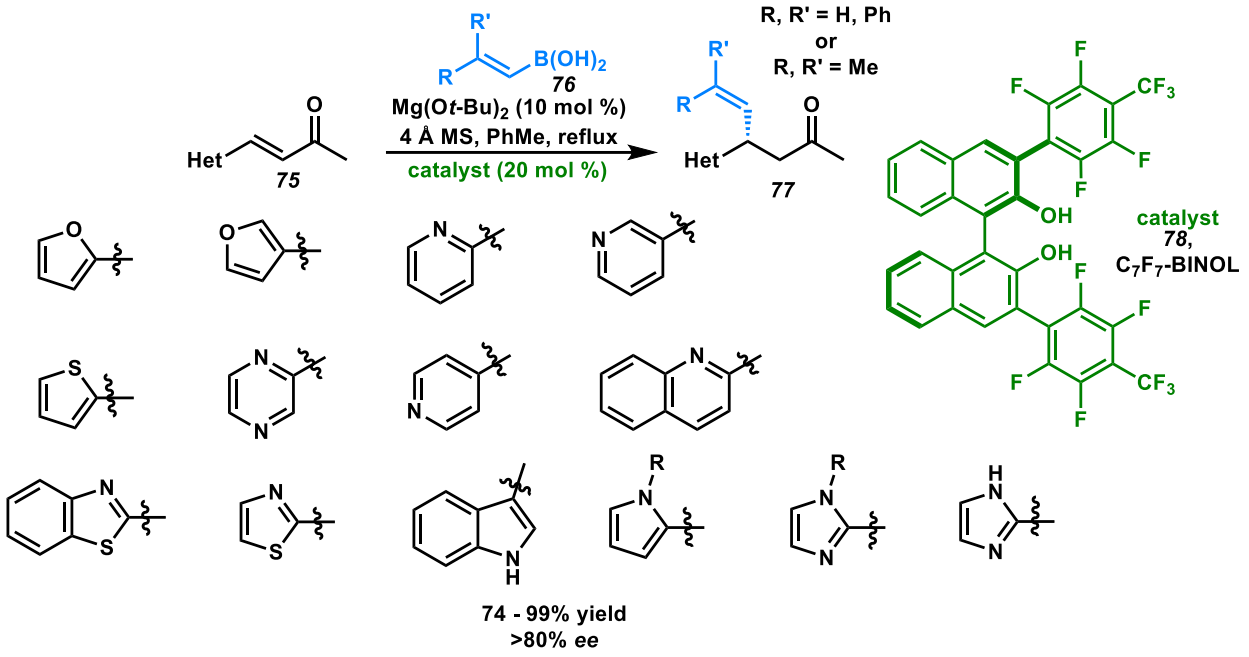



**Figure 1.26.** Expanded methodology

A variety of furan, thiophene, pyridine, quinoline and pyrazine electrophiles were shown to be effective in the transformation with high yields and high *ee*'s (Figure 1.26). Magnesium tert-butoxide was hypothesized to be effective due to its ability to facilitate proton transfer between the intermediates. While the nucleophile scope was still limited to alkenyl and alkynyl nucleophiles, reactivity and selectivity were increased.

### 1.4.4 Mechanistic Study

Following the development of this chemistry, a study was performed to determine reactivity trends and elucidate the mechanism.[39] Mechanisms proposed by Suzuki and Chong for the conjugate addition of organoboronates, as well as Pellegrinet and Goodman's work with DFT calculations, formed the basis for the mechanistic study[26,27,33,37,40–42]

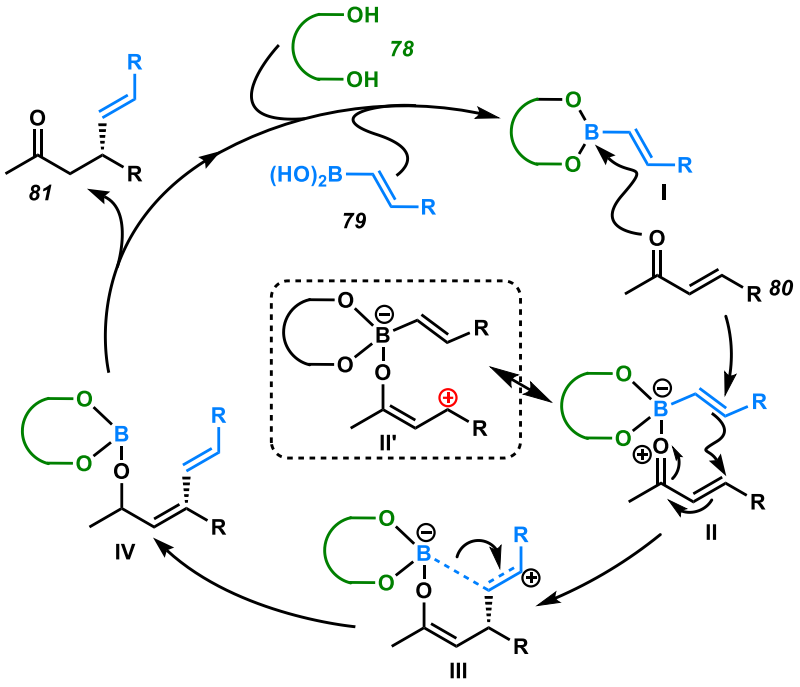



**Figure 1.27.** Proposed catalytic cycle

The proposed mechanism involved the formation of complex **I** between the BINOL derived catalyst **78** and the boronic acid nucleophile **79** (Figure 1.27), explaining the increase in reactivity of electron-deficient BINOL complexes, as the more electron-deficient catalytic complexes can bind more tightly to the carbonyl. The rate-determining step was proposed to be either complexation of the boron with the carbonyl oxygen, forming **II** or carbon-carbon bond formation (**III**). If the rate determining step was formation of the zwitterionic complex **II**, stabilization of the positive charge by electron donating groups would increase stability, and therefore reaction rate, and electron withdrawing groups would decrease reaction rate.

Hammett plot analysis was used to confirm this hypothesis. By using a variety of β-substituents of the unsaturated carbonyl and tracking the relative rates of product formation, it was found that stronger electron-withdrawing substituents para to the β-position accelerated the

reaction rate. It was concluded that stabilization of cationic charge at the β position increased the reaction rate.

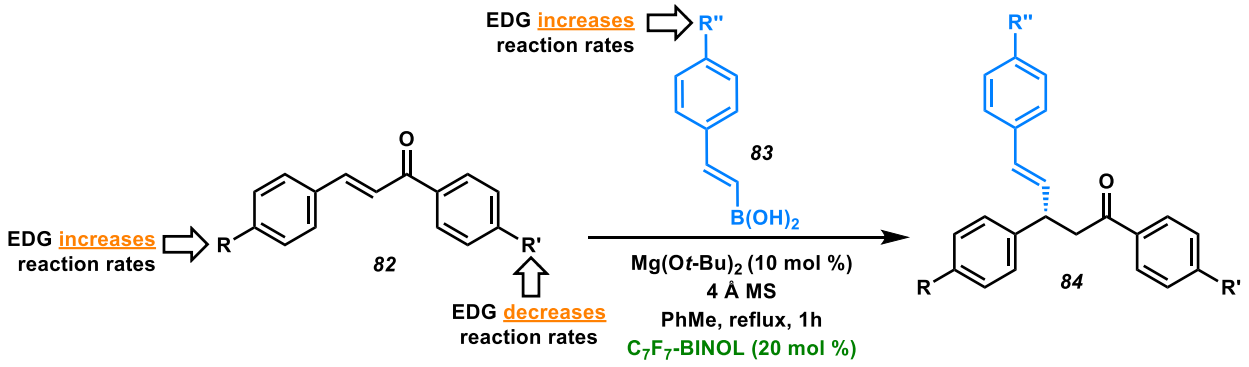



**Figure 1.28**. Trends in reactivity

The carbonyl-adjacent group was also varied. It was found that more electron-donating groups in the para position decreased the reaction rate (Figure 1.28). This implies that stabilization of the charge at the oxygen-bearing carbon decreases reaction rate, meaning the formation of the boron-oxygen bond is likely not involved in the rate determining step.

Nucleophile trends were also tested. It was found that more electron-rich nucleophiles increased reaction rates. This unusual trend: electron-rich electrophiles increase reaction rates, while electron-rich nucleophiles are also more reactive, was attributed to the zwitterionic ate complex formed in the reaction mechanism.

### 1.4.5. Expansion to Aromatic Nucleophiles

As mentioned previously, aromatic nucleophiles were not effective in the organocatalyzed transformations described. In 2015, our group was able to overcome this drawback by making several key modifications to the methodology as described.[43]

First, as introduced in the discussion of organometallic approaches, trifluoroborate salts (**86**) are often desirable nucleophiles due to their stability. In fact, in some previous efforts, major setbacks were due to the instability of the boronic acid nucleophiles. It was hypothesized that

trifluoroborate salts should also be effective nucleophiles, as the reactive species is a catalyst-combined ate complex that could form from the trifluoroborate salt as well. It was found that with the inclusion of molecular sieves as a fluoride scavenger, the more stable and crystalline trifluoroborate salts could be used.

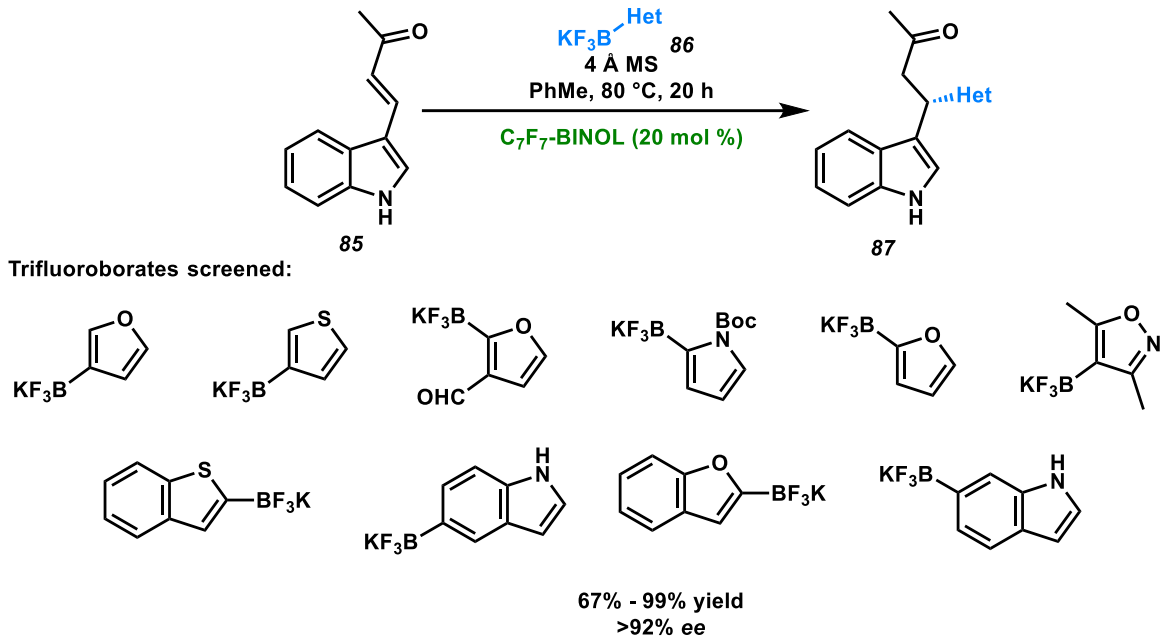



**Figure 1.29.** Aromatic nucleophile expansion

With confirmation of the effectiveness of trifluoroborate nucleophiles, nucleophile expansion studies were performed (see scope, Figure 1.29). Generally, the reaction was highly tolerant of a variety of heteroaryl nucleophiles, with exceptional enantioselectivity in most cases. In the case of aromatic nucleophiles, LiBr (and in some cases, LiCl or LiI) was necessary as an additive. Generally, this methodology overcame the largest challenge found previously – the inability to use aryl and heteroaryl nucleophiles.

### 1.4.6 Application to the Total Synthesis of Discoipyrrole D

With this development, the indole-containing natural product Discoipyrrole D was targeted for total synthesis.[43] The indole-bearing stereocenter in the natural product provided a perfect opportunity to show the utility of the developed conjugate addition chemistry.

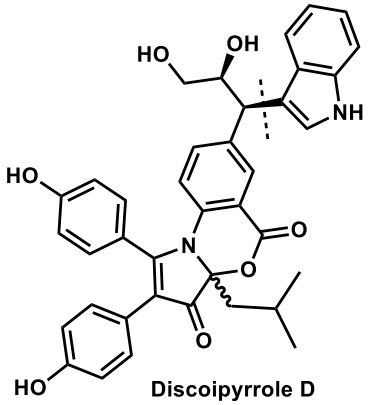



**Figure 1.30.** Structure of natural product, discoipyrrole D

The synthesis began with a three-component coupling between **88, 89,** and **90**, which was followed by a Heck reaction to add the unsaturated aldehyde (Figure 1.31). A commercially available indole 3-boronic acid (**93**) was successfully incorporated using the developed conditions in high yield with outstanding enantioselectivity (**94**). Following this, a proline-controlled hydroxylation allowed for the diastereoselective addition of the hydroxyl. Reduction gave the protected product **95** in fair yield.

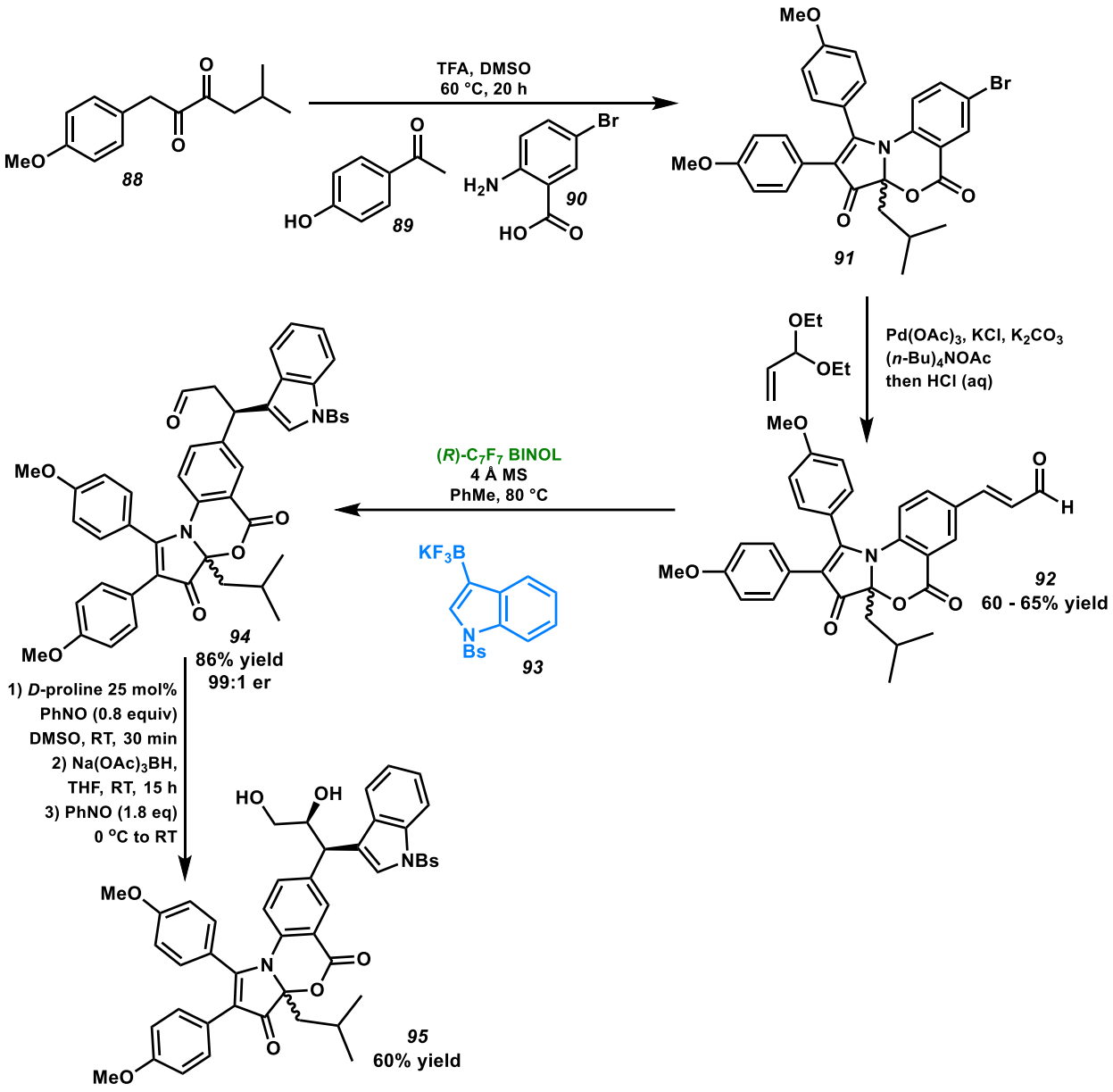



**Figure 1.31.** Synthetic approach to discoipyrrole D.

There were key issues with completion of the synthesis. The hydroxyls were protected as methoxy groups, but all attempts at demethylation fragmented the fragile core. The indole boronic acid precursor to **93** was commercially available only with a benzenesulfonyl group, which also could not be removed.

### 1.4.7 Banwell Approach to Discoipyrrole D

While the May group did not complete the synthesis of discoipyrrole D in the initial report, the total synthesis of the molecule has since been completed by the Banwell group (Figure 1.32).[44] While relying on a different, molybdenum catalyzed approach to synthesize the core of the structure, they nonetheless utilized May group chemistry to complete the synthesis. There were two key differences in their approach which allowed for the successful synthesis of the natural product. First, while considerably longer in step count, their synthesis of the core of discoipyrrole allowed for the use of TMS protecting groups for the hydroxyls. Second, they used Boc-indole trifluoroborate for the conjugate addition, which was easier to de-protect than the benzenesulfonyl used in our approach. Their synthesis provided the natural product in 2.3% yield over 13 steps.

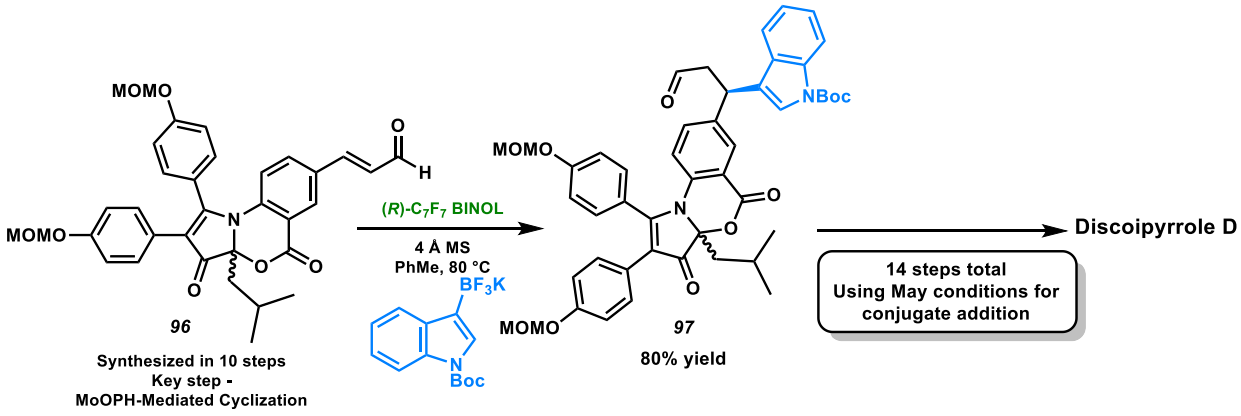



**Figure 1.32**. Banwell synthesis of discoipyrrole D

### 1.4.8. Current Studies

The work presented henceforth revolves around conjugate addition reactions from two perspectives. The first is expanding previous work by the May group in the use of organocatalyzed conjugate addition to compounds structurally similar to discoipyrrole D. The second is using the knowledge gained from the mechanistic study to explore new reactivity with different

nucleophiles. These projects rely on the extensive studies presented by our group and others that have provided a wealth of knowledge applicable to future projects.

Work on conjugate addition in the May lab is constantly ongoing, with efforts focused on novel applications of the methodologies, creative substrate design, and natural product total synthesis. Each project inspires other branches of the chemistry, and the methodology/total synthesis cycle continues.

# CHAPTER 2: ORGANOCATALYZED CONJUGATE ADDITION FOR THE SYNTHESIS OF MUCRONATINS A AND B

## 2.1 Background

### 2.1.1 Mucronatin A and B Isolation and Biological Activity

Natural products isolated from psychotropic plants are quite often able to cross the blood brain barrier, making them intriguing targets for isolation and study.[45,46] Mucronatins A and B were isolated as secondary metabolites from the bark of *Tetrapterys mucronata*, a plant found in Brazil that is used recreationally as part of a cocktail of psychotropic plants called "Ayahuasca".[47] A hypothesis was proposed that acetylcholinesterase (AChE) inhibitors may be found in this variety of plants, and indeed the mucronatins showed such biological activity.

The structures of mucronatin A and B differ only by the substitution of the free amine (Figure 2.1). While the connectivity of the molecules was successfully determined, the relative stereochemistry is unknown, although the absolute stereochemistry of a single sterocenter was proposed. There are two chiral centers in the molecule, meaning there are 4 diastereomers possible that could be the naturally occurring variant.

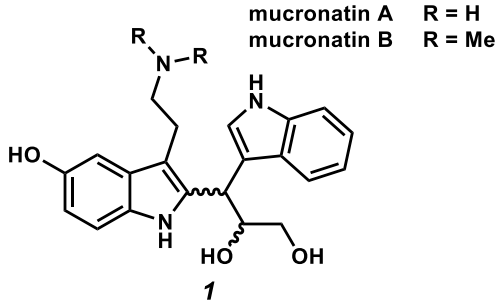



**Figure 2.1**. Mucronatin A and B

As mentioned, these compounds were hypothesized to have AChE inhibitory properties, and when tested, they showed successful in inhibition with $IC_{50}$ values of 11.7 μM (mucronatin A) and 12.7 μM (mucronatin B). Acetylcholinesterase is a target for the treatment of Alzheimer's

and Parkinson's diseases. As these diseases suffer from a lack of treatment options, novel natural product-derived sources for potential treatment are very desirable.

These natural compounds have also never been synthesized previously, which along with their potential utility makes them attractive targets for synthesis.

### 2.1.2 Retrosynthetic Analysis

We envisioned two possible disconnections of the mucronatins. In both cases, the key step would be accomplished by the organocatalyzed conjugate addition developed by our group. As this chemistry was effective at using heterocyclic trifluoroborate nucleophiles, we were confident this would be an effective approach to synthesize the challenging bis-indole core (Figure 2.2).

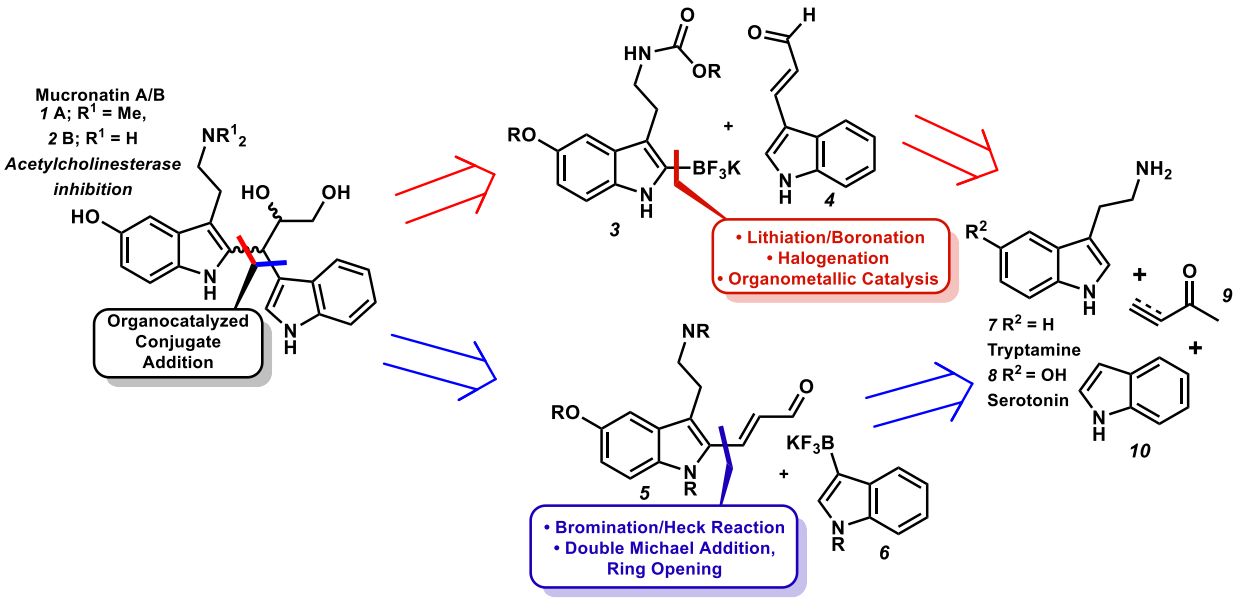



**Figure 2.2.** Retrosynthetic analysis of the mucronatins

In the first approach, we hypothesized that it may be possible to use a tryptamine-derived nucleophile with the trifluoroborate salt at the 2-position of the indole **3**. The corresponding electrophile (**4**) is a known compound that was used as part of an alternate synthetic route to discoipyrrole D.[43] Borylations are known at the indole 2-position by lithiation/borylation, but not

with tryptamine or serotonin derived substrates, which were necessary in this case. Nonetheless, we hypothesized lithiation/borylation as a potential route to the requisite nucleophiles.

In case lithiation/boronation were unsuccessful, we considered the possibility of halogenation followed by Miyaura borylation to form the carbon-boron bond at the 2-position. The difficulty with this approach would be finding a reagent that would accomplish selective halogenation in high yields. The last approach would be to use transition metal catalysis, such as Hartwig's well developed iridium chemistry.

On the other hand, in the May group's approach to discoipyrrole D, commercially available protected 3-$BF_3K$ indole **6** was used. The Banwell group also used the same structure type, but with a different protecting group in their synthesis.[44] The proposed synthesis of the electrophile **5** in this disconnection was originally halogenation (as in the previous disconnection), with a subsequent Heck reaction. Precedent from the synthesis of the flinderoles[36] also led us to consider the possibility of using a propargyl aldehyde in a double Michael addition, followed by ring-opening to give the unsaturated aldehyde necessary for the conjugate addition.

Both routes would start with commercially available starting materials (tryptamine, serotonin, indole) and would be completed with reactions already developed in our synthetic effort to synthesize discoipyrrole D. For example, proline-controlled hydroxylation followed by reduction set the alcohol stereocenter, allowing for the synthesis of a single diastereomer, and the same approach could be used in the synthesis of the mucronatins in the conversion of the aldehyde **11** to diol **12** (Figure 2.3).

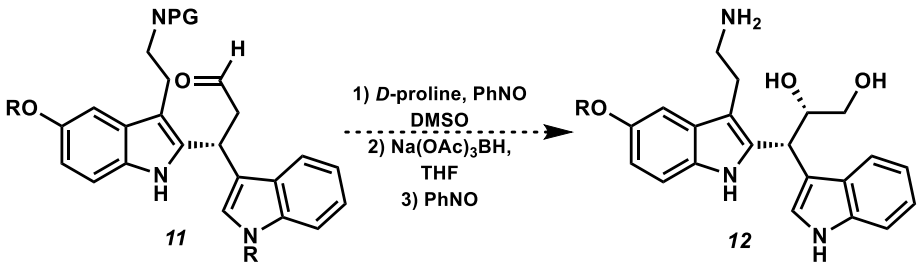



**Figure 2.3.** Proline controlled oxidation and subsequent reduction

In both synthetic routes, the stereochemistry is fully controlled by the catalysts used. In the conjugate addition, the selection of (*R*)- or (*S*)-$C_7F_7$ BINOL sets the benzylic stereocenter in generally high *ee*'s. The second stereocenter is controlled by the proline catalyst (*D*- or *L*-proline) again with usually quite high selectivity. Ideally, the protecting groups chosen could be removed in this step as well. These disconnections would allow for the synthesis of any of the four possible diastereomers of the natural product and allow for the determination of the configuration of the naturally occurring molecule. Furthermore, this will allow for greater breadth of biological testing, as it is possible a non-natural diastereomer will have even tighter binding to AChE, giving higher biological activities.

## 2.2 Disconnection A: Tryptamine/Serotonin-Derived Nucleophile

### 2.2.1 Synthesis of the Zincke Aldehyde Electrophile

During development of the synthetic route for discoipyrrole D, our group found a well-precedented strategy to synthesize the aldehyde at the indole 3-position (**17**).[48] While cyanogen bromide is not an ideal reagent due to safety concerns, this synthesis is robust and scaleable (Figure 2.4). It begins with the synthesis of the boroxine **14**, followed by a Suzuki coupling to give **16**. The ring opening of the pyridine with cyanogen bromide gave the Zincke aldehyde **17** in high yield. Having synthesized the electrophile, we turned our attention to developing a synthetic route to the corresponding tryptamine/serotonin derived nucleophile.

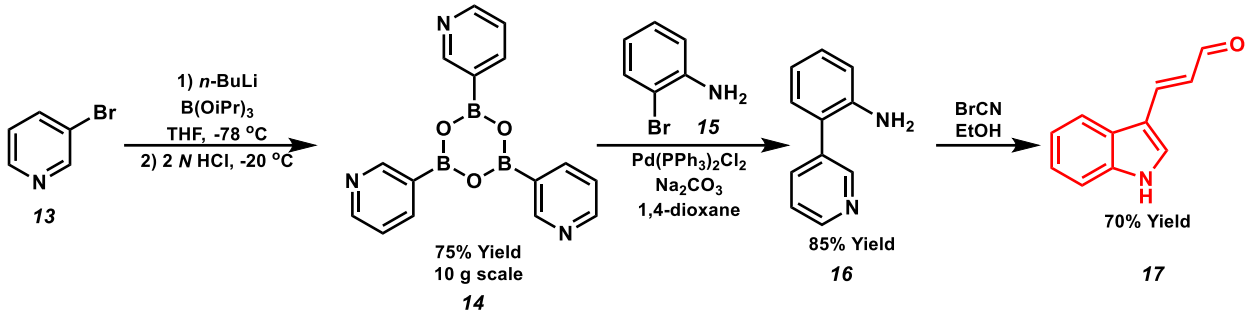



**Figure 2.4**. Synthesis of Zincke aldehyde electrophile

### 2.2.2 Lithiation/Borylation

To confirm the viability of the proposed approach, several lithiation/borylation reactions were tested with conditions reported in literature (Figure 5).[49,50] Skatole (**18**) could be smoothly converted to the corresponding boronic acid (**20**) by lithiation/borylation with *n*-butyllithium as base and triisopropyl borate as the boron source.

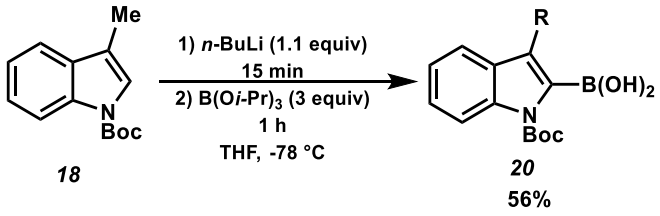



**Figure 2.5.** Known lithiation/borylation of indole compounds

Tryptamine (**7**) was chosen as a model system for the synthesis of the mucronatins, as tryptamine is considerably more cost-effective as a starting material for reaction development. Serotonin is commercially available as the HCl salt; however, its relative rarity increases its price. Protection of both tryptamine and serotonin with a variety of protecting groups is well documented in literature.[51–54] For lithiation, both the free amine and indole nitrogen were protected with Cbz and Boc groups, respectively (Figure 2.6).

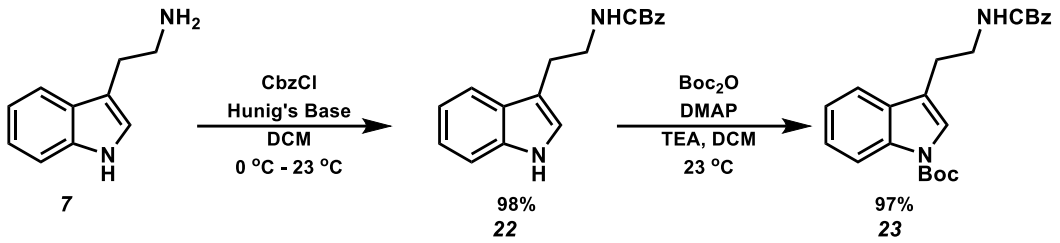



**Figure 2.6**. Protection of tryptamine

When the same lithiation/borylation conditions in Figure 2.5 were applied to protected tryptamine compounds, no lithiation-borylation was observed (Figure 2.7). We considered several possible reasons why no lithiation/borylation occurred. First, it's possible the protecting groups chosen were incompatible with this method. We switched to several different protecting groups for both the indole nitrogen and the free amine. Among those tested were Boc, Cbz, and MOM groups. In the interest of atom economy and decreased steric bulk, we also attempted the lithiation chemistry with smaller ether protecting groups, such as the methyl ether. Regardless of the choice of protecting group, lithiation/borylation was ineffective. Furthermore, the initial choice of Cbz as the preferred protecting group was very intentional, as this would allow for facile deprotection in the final steps of the proposed synthesis.

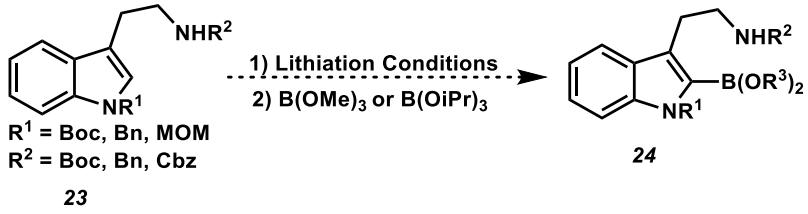



**Figure 2.7**. Lithiation of tryptamine derived compounds

Second, we attempted to use a variety of lithium sources for this reaction, and we changed the equivalents thereof to provide a higher effective concentration of butyllithium to facilitate the lithiation step (Figure 2.8). Neither proved effective, even with quite strong bases such as *sec*-

butyllithium. In fact, stronger bases contributed to the decomposition of the indole core of compound **24**.

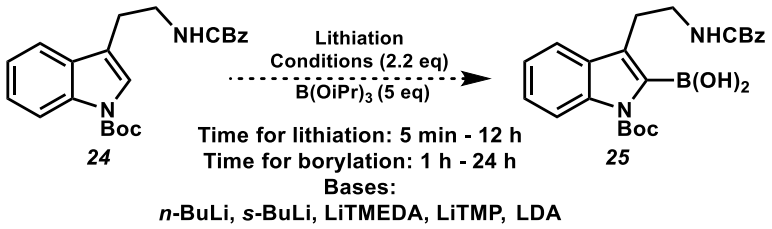


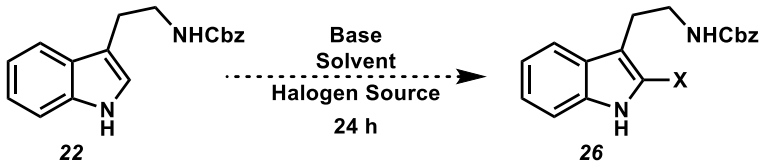

**Figure 2.8.** Lithiation screening

Third, reaction time was investigated. Generally, lithiation/borylation reactions can be quite fast, with a shorter time necessary for the carbon-lithium bond formation and a longer time for the borylation to complete.[55] Increasing the time for both lithiation or borylation did not provide the boronated compound **25**, leading to decomposition or recovery of starting material **24**.

### 2.2.3 Miyaura Borylation

We moved on from these experiments to attempt to halogenate the indole at the 2-position, envisioning the use of Miyaura borylation to form the carbon-boron bond following the halogen integration. A variety of bases were screened with oxidant and tryptamine-derived compound **22**, which was left unprotected at the indole nitrogen (Table 1). Regardless of the choice of base, solvent, or halogen source, halogenation was not observed in these conditions. Some halogenating reagents caused decomposition of the indole core. Initially, the indole nitrogen was left unprotected, but we also attempted strongly basic conditions with protected indoles, though with no observed product formation. In similar conditions, the methyl ester **19** gave iodination selectively at the 2-position in fair yields as reported in literature.[56]

**Table 1.** Halogenation of tryptamine-derived compounds




| Entry | Base | Halogen Source | Solvent | Result |
|---|---|---|---|---|
| *a* | $K_2CO_3$ (aq) | $I_2$ (in THF) | acetone | deprotection |
| *b* | $Na_2CO_3$ (aq) | $I_2$ (in THF) | acetone | deprotection |
| *c* | $K_2CO_3$ (s) | $I_2$ (in THF) | acetone | no reaction |
| *d* | $Na_2CO_3$ (s) | $I_2$ (in THF) | acetone | no reaction |
| *e* | $K_2CO_3$ (s) | ICl | acetone | decomposition |
| *f* | $K_2CO_3$ (s) | NIS (in THF) | acetone | deprotection |
| *g* | $K_2CO_3$ (s) | NBS (in THF) | acetone | decomposition |
| *h* | *n*-BuLi | NBS | THF | decomposition |

Previous work showed that using phthalimide-protected tryptamine with pyridinium tribromide as the halogenation reagent gave selective bromination (Figure 2.9).[57] These conditions provided high yields of the brominated indole **30**. However, the product of the Miyaura borylation (**31**) could not be purified. The crude compound was used in salt formation conditions with methanol and aqueous potassium hydrogen bifluoride in an attempt to synthesize the trifluoroborate salt **32**, which could then be purified by recrystallization. However, the salt could also not be purified, and only protodeboronation of the pinacolborane was observed.

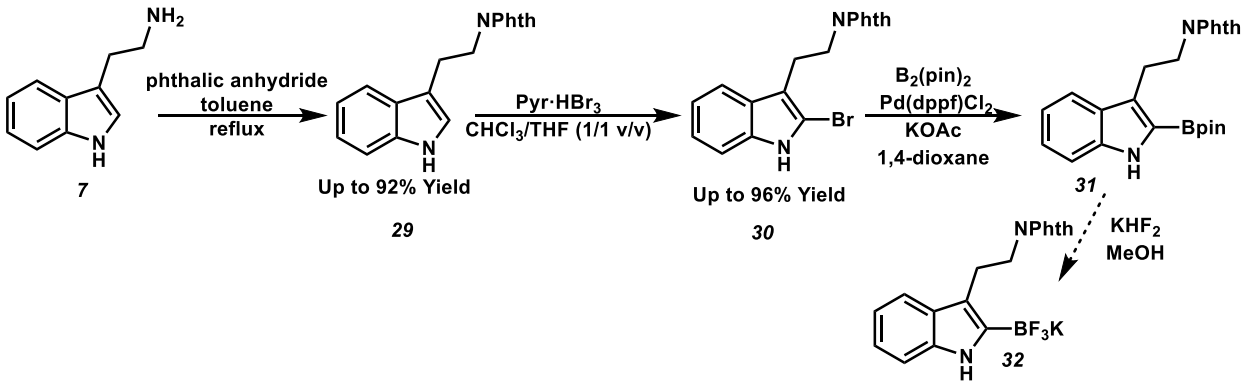



**Figure 2.9**. Halogenation of phthalimide-protected tryptamine and subsequent synthetic path

We considered that the phthalimide protecting group used may be causing the issue in the Miyaura borylation. The bromination with pyridinium tribromide was attempted with Cbz-

protected tryptamine **22**, but the reaction provided considerably lower yields when compared to the phthalimide-protected **36** (Figure 2.10). The product of the Miyaura borylation (**36**) could be purified in decent yields, however. Boc-protected tryptamine **33** did not provide the brominated compound.

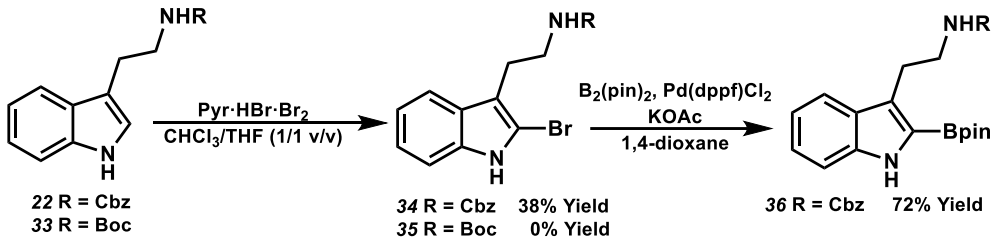



**Figure 2.10**. Bromination of Cbz-protected indole

Therefore, with the brominated phthalimide-protected tryptamine **30** in hand, hydrazine was used to remove the phthalimide group (**37**, Figure 2.11). The compound was re-protected with Cbz (**38**), and the Miyaura borylation was performed. The Miyaura borylation was effective on small scale, giving **39** selectively, but attempting to increase the scale to synthetically useful amounts of compound reduced the yield considerably. Again, the trifluoroborate salt formation was not successful, this time because of protodeboronation. There were other drawbacks with this approach, even if the conversion to the salt were successful. The protecting group switch necessary for effective reactivity in the Miyaura borylation was not ideal, as it added two steps to make the nucleophile. Pinacolboranes can also be difficult to convert to trifluoroborate salts, giving byproducts that are difficult to remove from the desired borate salts.

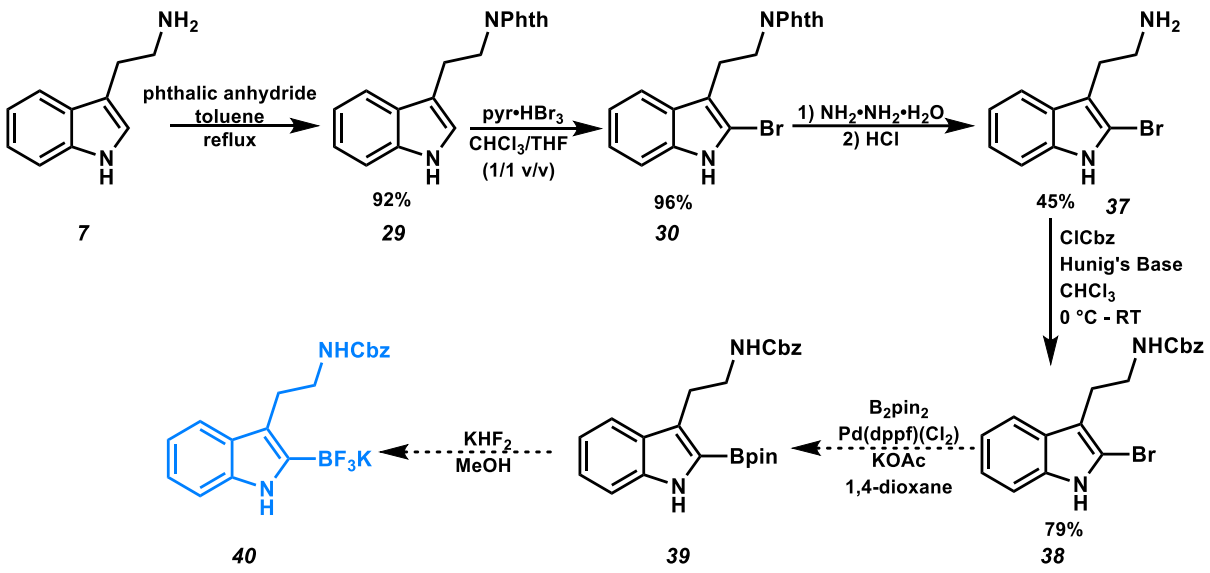



**Figure 2.11.** Synthesis of trifluoroborate salt from phthalimide-protected tryptamine

### 2.2.3 Hartwig Iridium-Catalyzed Borylation

The synthesis was re-evaluated. Hartwig iridium chemistry is known to be a highly regioselective method to borylate indoles.[58–63] Conditions were reported for selectively borylating indoles and other heterocycles at various positions, but those useful in this synthesis would selectively borylate the 2-position of substituted indoles (Figure 2.12).

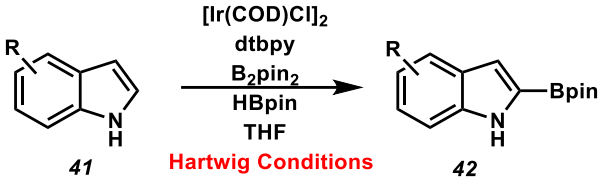
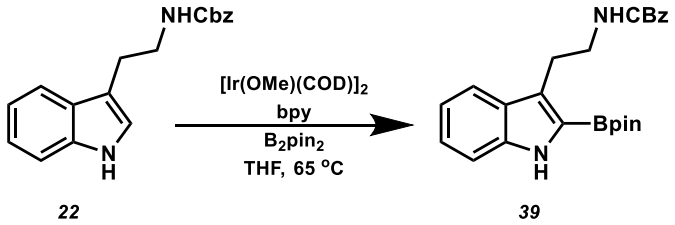



**Figure 2.12**. Hartwig iridium catalyzed borylation of indoles

Using [Ir(OMe)(COD)]$_2$ with a simple bipyridyl ligand as the catalyst, the first attempt at borylation allowed for the addition of boron to the 2-position of Cbz-protected tryptamine (entry a, Table 2). The resulting compound could be purified by column chromatography. After optimization of

the reaction conditions via solvent variation (entries a-c) and concentration/time screening (entries d-f), the catalysis was able to provide the borylated compound in nearly quantitative yields (entry f).

**Table 2.** Iridium-catalyzed borylation of protected tryptamine




| Entry | Time | Concentration | Solvent | Yield |
|---|---|---|---|---|
| *a* | 24 h | 0.2 M | DCE | No reaction |
| *b* | 24 h | 0.2 M | DCM | No reaction |
| *c* | 3 h | 0.2 M | THF | 81% |
| *d* | 3 h (scale up) | 0.2 M | THF | 76% |
| *e* | 3.5 h | 0.2 M | THF | 93% |
| ***f*** | **3.5 h** | **0.1 M** | **THF** | **99%** |

This route was a considerable improvement on the 6-step synthesis necessary to form the same indole using halogenation/Miyaura borylation (Figure 2.13). The resulting pinacolborane could be converted to the trifluoroborate salt on small scale, with 68% overall yield (Figure 2.14). Disappointingly, attempts to increase the scale of the conversion of the pinacolborane to the trifluoroborate salt were unsuccessful, with a large percentage of the compound protodeboronating during recrystallization. Attempts to use the crude trifluoroborate salt in the conjugate addition conditions with the aldehyde were unsuccessful.

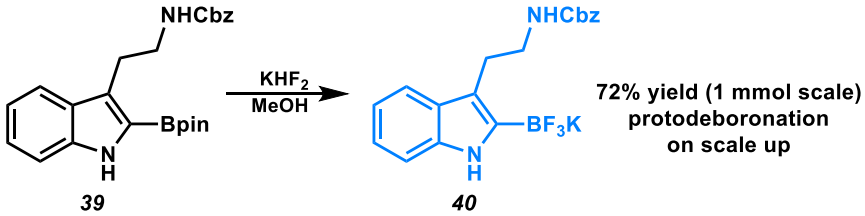



**Figure 2.13**. Conversion of pinacolborane to trifluoroborate salt.

We considered the possibility that the serotonin-derived trifluoroborate salt **43** may be less prone to protodeboronation due to the increased electron density of the indole ring. Indeed, the same synthetic pathway provided the trifluoroborate salt **43** when applied to serotonin (Figure 2.14). While it could not be recrystallized due to its solubility in most typical crystallization solvents it was possible to obtain indole **43** as a relatively pure solid.

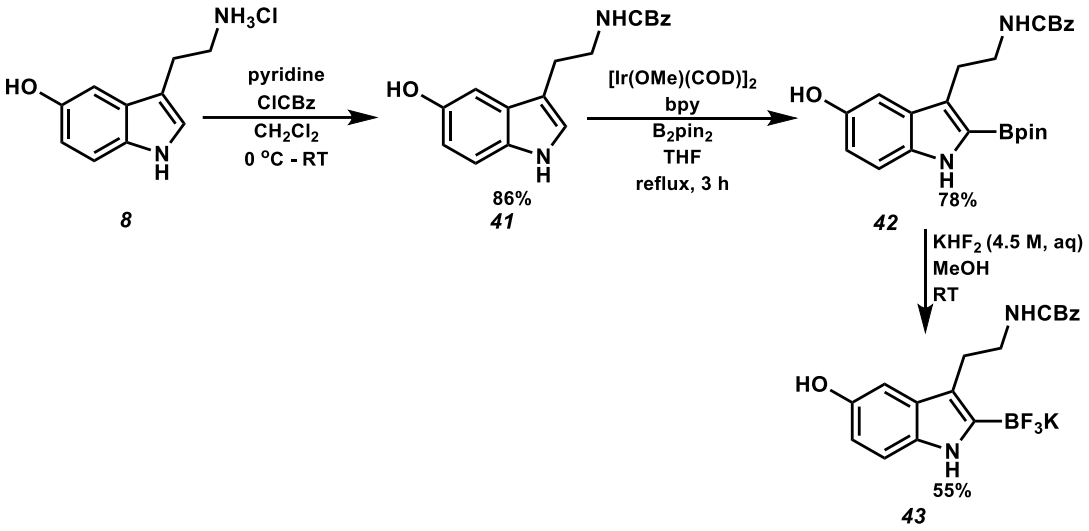
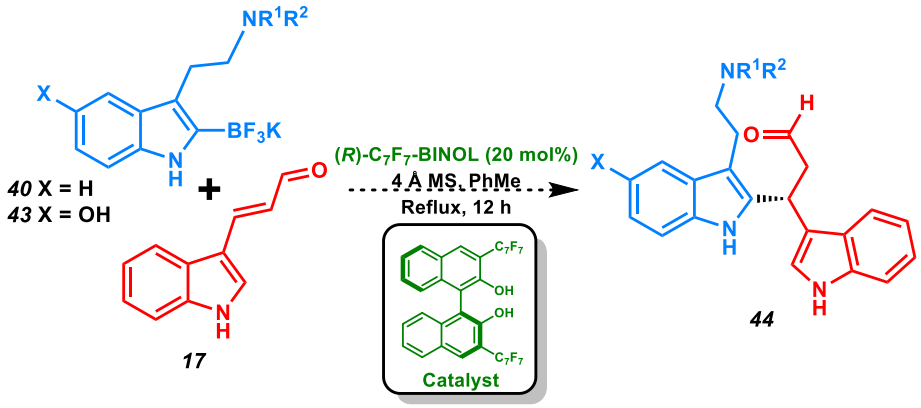



**Figure 2.14**. Serotonin-derived nucleophile synthesis

### 2.2.4 Attempts at the Conjugate Addition Step

Disappointingly, when compound **43** is used in conjugate addition conditions, protodeboronation was observed even with the serotonin derived trifluoroborate (Table 3). While the reaction conditions for conjugate addition are very mild, they do nonetheless involve heating the reaction in toluene. For heterocyclic nucleophiles, this reaction can take a considerable amount of time. Following the reaction, all compounds observed by TLC were characterized, and it was found that the aldehyde and protodeboronated serotonin nucleophile had a nearly identical $R_f$. No conjugate addition product **44** was observed by NMR in the crude reaction mixture.

**Table 3**. Conjugate addition attempts, disconnection A




| Entry | $R^1$ | $R^2$ | X | Result |
|---|---|---|---|---|
| a | H | Cbz | H | Decomposition both SM |
| b | H | Cbz | OH | Protodeboronation |
| c | Phth | | OH | Decomposition of nucleophile |

Therefore, even if the trifluoroborate salt could be synthesized, conjugate addition conditions were found to cause protodeboronation or decomposition. Phthalimide-protected nucleophiles were not compatible with conjugate addition. Serotonin and tryptamine derived nucleophiles with other protecting groups were found to be unstable to conjugate addition conditions or recrystallization. This synthetic route was found to be an ineffective way to approach the synthesis of the mucronatins.

### 2.3 Disconnection B: Tryptamine/Serotonin Derived Electrophile

The major problem with the previous synthetic route is likely due to the choice of position of the carbon-boron bond. The 2-position of indole compounds is particularly susceptible to protodeboronation (Figure 2.15).

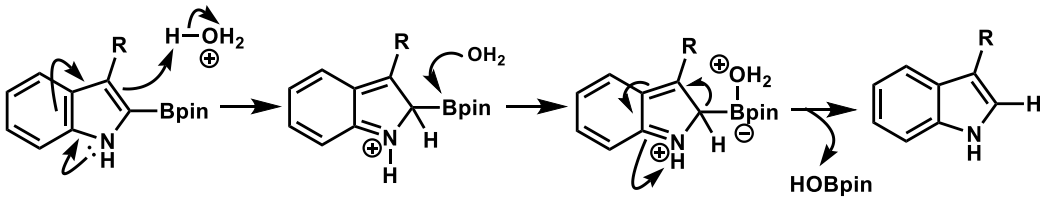



**Figure 2.15.** Protodeboronation of indoles

### 2.3.1 Synthesis of the Nucleophile

In the second disconnection proposed for the synthesis of the mucronatins (Figure 2.16), the trifluoroborate salt would instead be at the 3-position of a protected indole. These compounds are not only known, the boronic acids of some variants are commercially available.

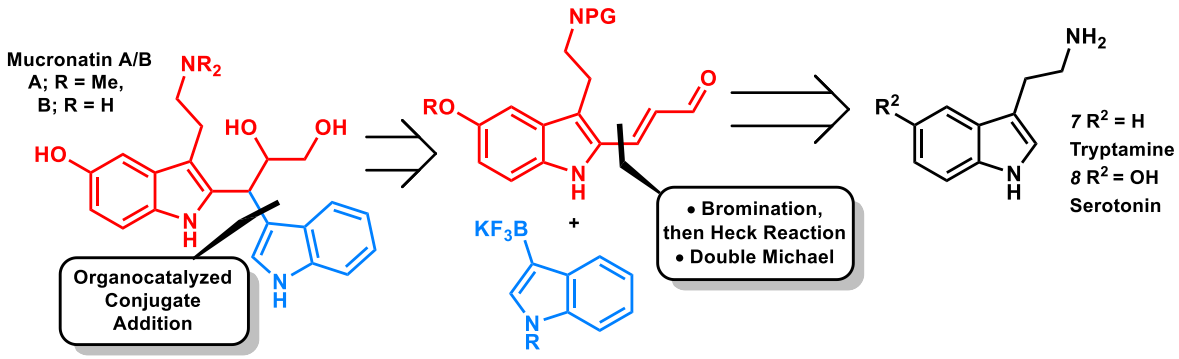



**Figure 2.16.** Disconnection B for the synthesis of mucronatins A and B

The 3-position trifluoroborate salts **48** and **51** (Figure 2.17) could also be very easily accessed from Boc-protected indole **46** in good yields, even with a difficult purification of the resulting salt **48**. When Cbz was used as a protecting group for the indole nitrogen (**49**), the synthetic route gave slightly higher yields, even on a larger scale.

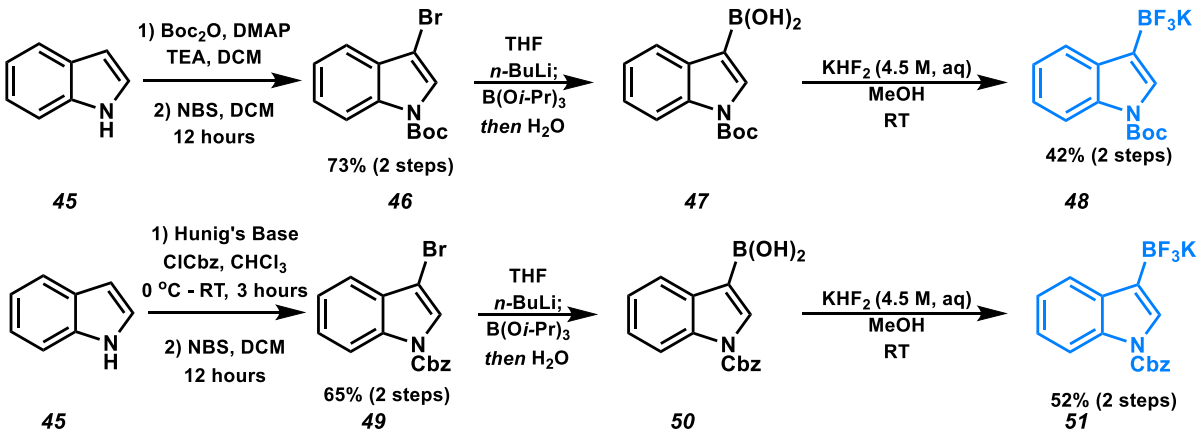



**Figure 2.17**. Synthesis of 3-$BF_3K$ nucleophiles

### 2.3.2 Synthesis of Electrophile: Halogenation/Heck Reaction

The synthetic challenge then becomes the formation of the 2-position unsaturated aldehyde tryptamine/serotonin derived electrophile. Recalling our work on the previous disconnection, we considered the possibility of synthesizing this compound from the brominated compound **30** via a Heck reaction (Figure 2.18). Phthalimide protection of tryptamine as before proceeding in high yield (**7** to **29**). Pyridinium tribromide was again used as the brominating reagent, and a subsequent Boc-protection gave the heck precursor **52** in 73% over three steps, with no purification until the last step. A Heck reaction, utilizing the same conditions developed for the synthesis of discoipyrrole D, gave the resulting unsaturated aldehyde **53** in 60% yield without optimization.

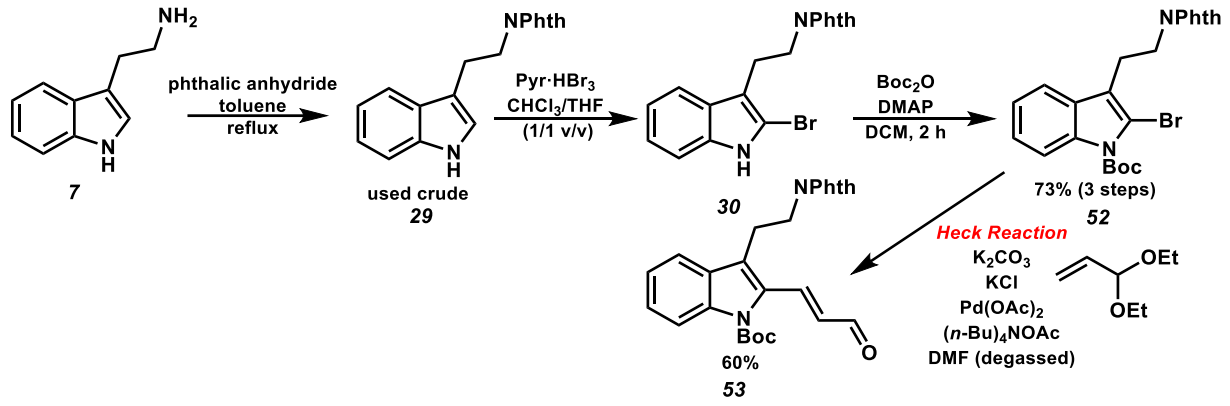



**Figure 2.18.** Halogenation/Heck reaction approach

Utilizing this compound in conjugate addition conditions proved difficult, however. Attempting the conjugate addition with Boc-protected indole salt **48** afforded no product. Instead, considerable degradation of the electrophile was observed by NMR. This confirmed that phthalimides are generally unstable to conjugate addition conditions. As previously noted, bromination with the preferred protecting group, Cbz, did not afford sufficient product. This led us to consider other approaches, even though it is possible to halogenate tryptamines with other protecting groups at the free amine.[64]

### 2.3.3 Synthesis of Electrophile: Double Michael Addition/Ring Opening

We were inspired by a highly convergent synthesis of an unsaturated indoloketone first published in 1984[65] and used in the synthetic studies of the flinderoles[36,66] and May lab conjugate addition chemistry (Figure 2.19).[38] This synthesis relied on a double-Michael addition in which the first step was addition of 3-butyn-2-one to the amine of tryptamine (**7**), and the second was a ring-closing promoted by TFA. The resulting structure **55** could be protected with Cbz (**56**), and base could be used to open the ring, providing the desired 4-carbon unsaturated ketone at the 2-position (**57**).

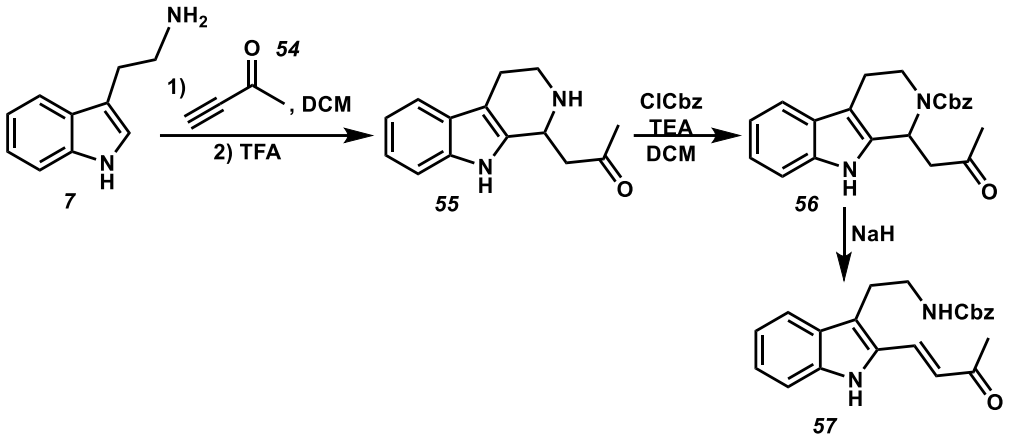



**Figure 2.19**. Double-Michael addition to form unsaturated ketone

In the synthesis of the mucronatins, instead of a ketone, an aldehyde would be required. We assumed a similar approach would be successful with propargyl aldehyde **60** (Figure 2.20).

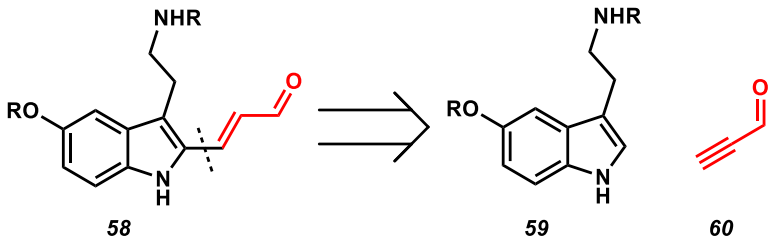
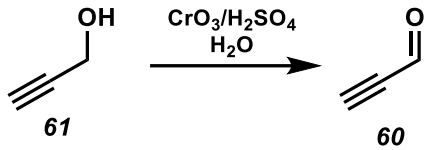



**Figure 2.20**. Disconnection for the mucronatins.

This proposal would create an intriguing practical challenge, as even though the synthesis of propargyl aldehyde can easily be accomplished by the oxidation of commercially available propargyl alcohol **61**, the aldehyde is highly volatile with a boiling point of 54-57 °C. Purification of this volatile, highly reactive compound can be very difficult (Table 4).

**Table 4.** Synthesis of propargyl aldehyde




*61* *60*

| Entry | Conditions | Result |
|---|---|---|
| *a* | 2 M Jones reagent (Sigma-Aldrich)<br>acetone | Product formed, used crude |
| *b* | $CrO_3$ in 2:3 $H_2SO_4/H_2O$<br>2-propanol | Distilled from crude, 0.5 M with SM |
| *c* | $CrO_3$ in 2:3 $H_2SO_4/H_2O$<br>DCM | Crude 0.02 M solution in DCM |
| *d* | $CrO_3$ in 2:3 $H_2SO_4/H_2O$<br>DCM | Distillation afforded no product |
| *e* | $CrO_3$ in $H_2SO_4/H_2O$<br>$H_2SO_4/H_2O$<br>*Reduced pressure oxidation* | 47% yield (pure)<br>400 mmol scale |

Several attempts were made with traditional oxidations, using Jones reagent to oxidize propargyl alcohol and using distillation to purify the resulting aldehyde (Table 4, entries a-d). However, upon application of heat the aldehyde decomposed quickly due to its reactive nature. Also, there was a paradox – a solvent that was effective for the oxidation could not be effectively purified from the resulting aldehyde. Consequently, a classical synthesis and purification of the aldehyde published in 1964 was utilized with some modification.[67]

A solution of chromium trioxide in water and sulfuric acid was added to a flask containing propargyl aldehyde connected to two traps in sequence. The oxidizing solution was added dropwise, under reduced pressure. The two traps, both at -78 °C, effectively condensed the propargyl aldehyde as it formed and was immediately volatilized by the vacuum applied to the

system. Propargyl aldehyde, as it formed, was immediately volatilized by the vacuum applied to the system and was effectively condensed by the two cold traps, both at -78 °C. This resulted in high purity propargyl aldehyde at a very large scale, without further need for distillation (entry e, Table 4).

Aldehyde **60** was used in the proposed double Michael reaction (Figure 2.21). The second Michael reaction gave inconsistent results, and optimation of this synthetic route is still ongoing. However, we were able to observe the formation of the cyclized structure **62** by NMR. Due to the likely instability of this compound, it was immediately Boc-protected. In contrast to ketone **57**, protection resulted in the formation of the unsaturated aldehyde directly without the need for additional base. Unfortunately, low overall yields of **63** were observed for the two steps.

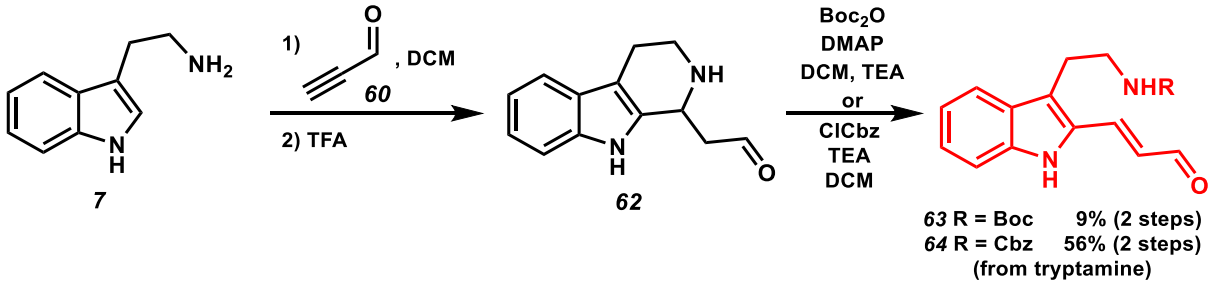



**Figure 2.21.** Double Michael Addition with propargyl aldehyde

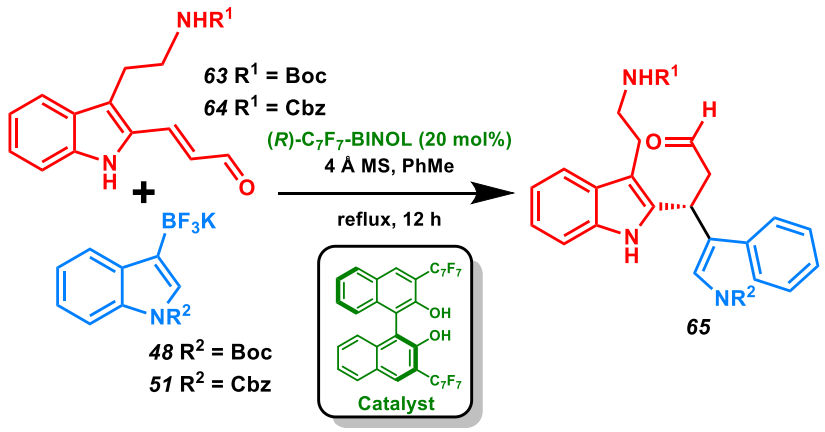
This was not the case when Cbz was used as the protecting group, as a 56% yield from tryptamine (**64**) was obtained while maintaining the reactivity and undergoing ring-opening without the use of sodium hydride. This synthetic route was highly preferable to the bromination/Heck coupling described previously, as it required only two steps to synthesize the electrophilic enal, which reduced the overall synthesis by 3 steps. Furthermore, both transformations had short reaction times, with neither exceeding 4 hours. There was also no need

for transition metal catalysts. The preferred Cbz protecting group could also be used more effectively.

### 2.3.4 Conjugate Addition, Route B

A variety of protected nucleophiles and electrophiles were tested under conjugate addition reaction conditions (Table 5). While no reaction was observed with Boc protection at either position, the conjugate addition afforded 20% yield in 12 hours when both the indole nucleophile and the electrophile were Cbz-protected (entry c). This highly promising result is being investigated further – conjugate additions with aromatic nucleophiles can be quite slow, as shown in our previous work.[43] In order to utilize this reaction on a larger scale, conditions to form the trifluoroborate salt formation needed to be perfected and a method of purification needed to be determined. The boronic acid was somewhat stable to silica, so current work focuses on purifying after carbon-boron bond formation, followed by transformation to the trifluoroborate salt.

**Table 5**. Conjugate addition reactions with varied nucleophiles and electrophiles




| Entry | $R^1$ | $R^2$ | Result |
|---|---|---|---|
| *a* | Boc | Boc | 0% (and protodeboronation) |
| *b* | Cbz | Boc | 0% (and protodeboronation) |
| *c* | Cbz | Cbz | ~20% (not to completion) |

The double-Michael reaction needs to be made consistent. Our hypothesis is that the purity of the propargyl aldehyde greatly affects its reactivity. While working on this interesting synthetic

challenge, we are continuing to explore the possibility of synthesizing a similar structure with an alternate protecting group by Heck reaction (Figure 2.23). It seems that the identity of the protecting group has a great impact on reactivity in the conjugate addition, so it may be possible that an alternate route would provide a more reactive compound, such as the tosyl-protected enal **68** (Figure 2.22).

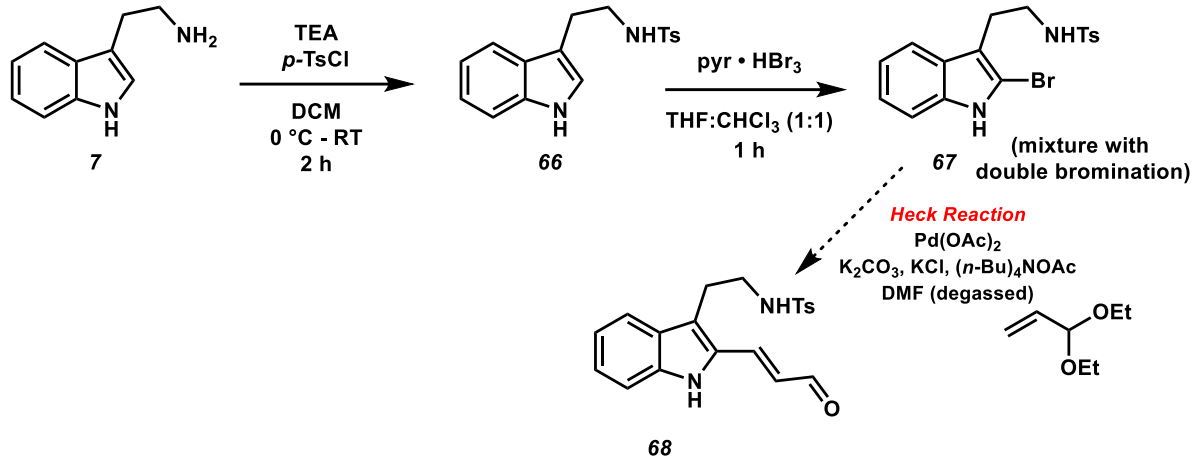



**Figure 2.22.** Alternate synthesis of electrophile

The conditions developed need to be applied to serotonin as well as tryptamine. In our experience, the double Michael/protection sequence works on serotonin similarly to tryptamine but provides a greater challenge for purification due to the increased polarity of the compound (Figure 2.23).

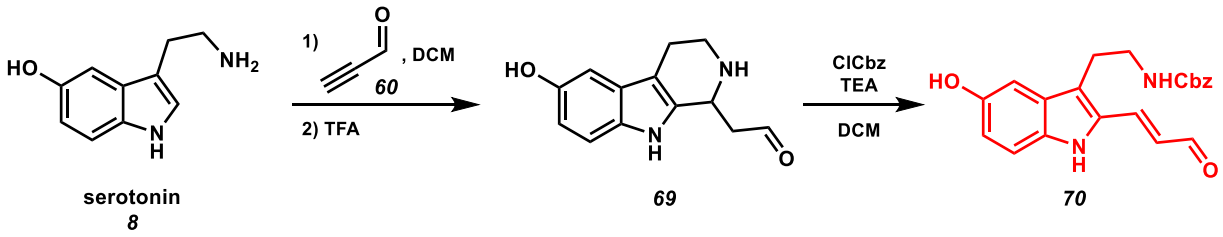



**Figure 2.23.** Serotonin-derived electrophile synthesis

Unprotected hydroxyls have been accommodated in conjugate addition conditions before, so the presence of serotonin's hydroxyl is not likely to interfere with the key step.

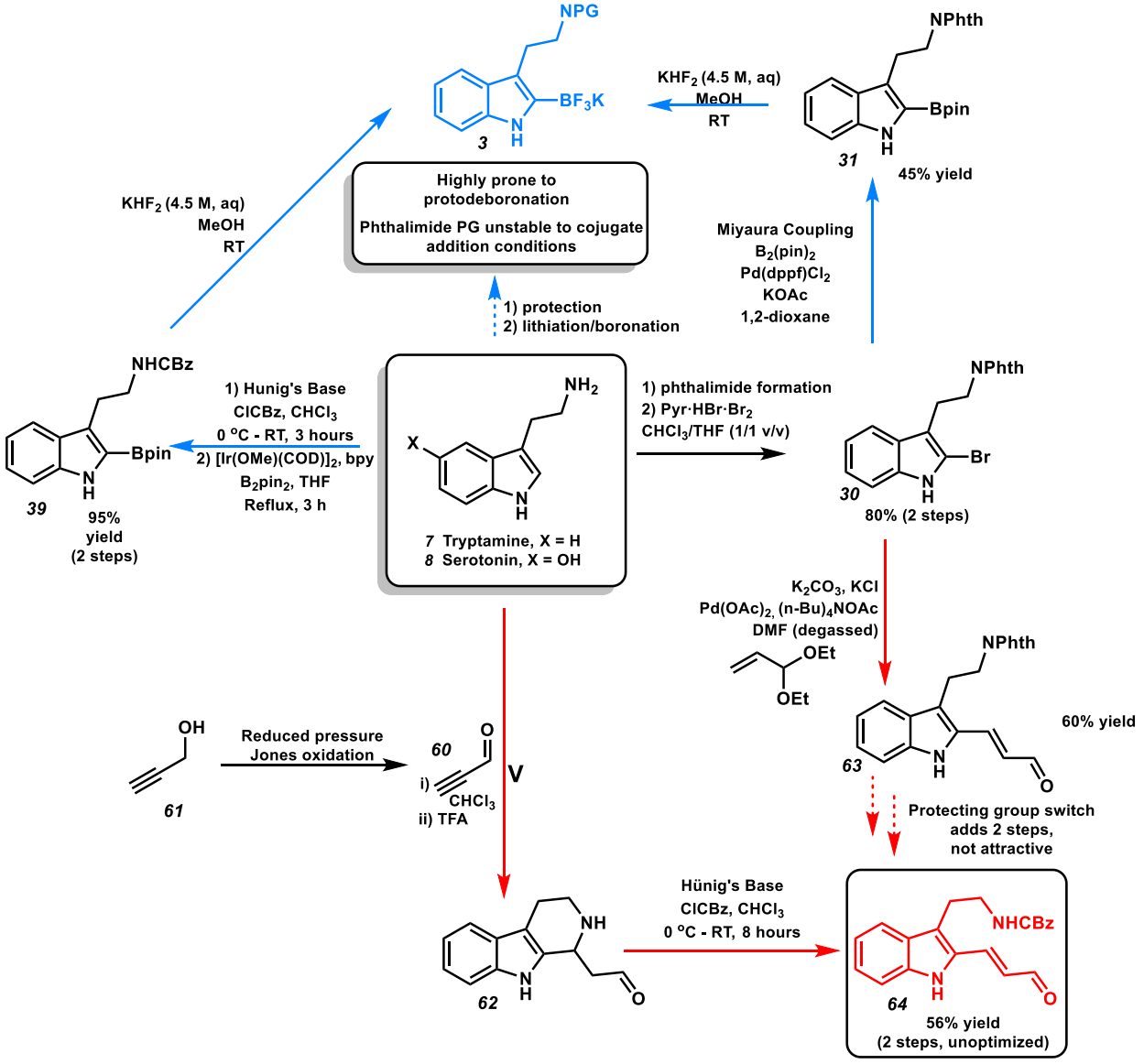



**Figure 2.24**. Summary of electrophiles and nucleophiles derived from tryptamine and serotonin

## 2.4 Future Work

The completion of the synthesis will rely on well-developed chemistry as reported previously for similar structures for the synthesis of discoipyrrole D. A *D*-proline controlled oxidation will give the alcohol enantioselectively followed by reduction of the carbonyl to an

alcohol (**71**, Figure 2.25). The Cbz groups will be deprotected by Pd/C reduction with hydrogen gas, giving mucronatin A. The dimethylation of mucronatin B with formaldehyde and sodium cyanoborohydride will provide mucronatin A.

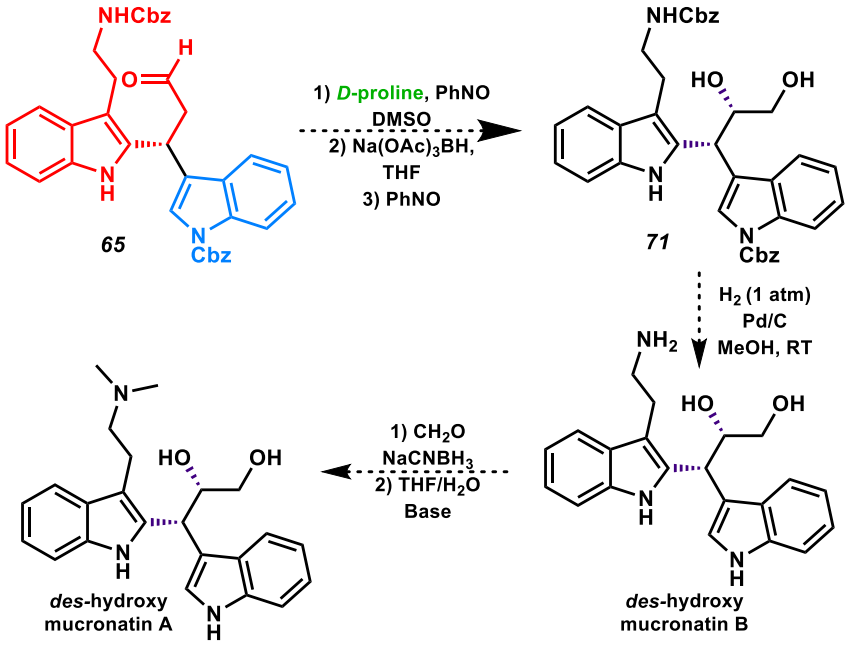



**Figure 2.25**. Completion of synthesis

In summary, we've shown the effectiveness of conjugate addition as a key step in the synthesis of diindole natural products, mucronatins A and B. The completion of the total syntheses of both molecules soon is anticipated. The knowledge gained from this synthetic effort is applicable to other molecules, including syntheses of disoipyrrole D and cytoblastin.

## 2.5 Experimental

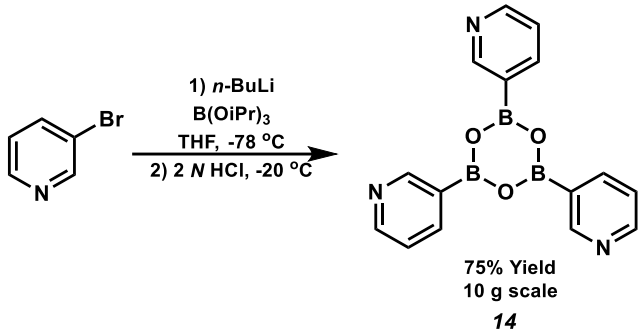
### 2.5.1 General Considerations

All reactions were carried out in flame-dried glassware under an argon atmosphere. THF, $Et_2O$, toluene, and $CH_2Cl_2$ were purged with argon and dried over activated alumina columns. Flash chromatography was performed on 60 Å silica gel (EMD Chemicals Inc.). Analytical thin layer chromatography was performed on EMD silica gel/TLC plates and imaged by fluorescence

at 254 nm, *p*-anisaldehyde or potassium permanganate stain. The $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectra were recorded on a JEOL ECA-600, 500, ECZ-400 or ECX-400P spectrometer using the residual solvent peak as an internal standard ($CDCl_3$: 7.26 ppm for $^{1}H$ NMR and 77.2 ppm for $^{13}C$ NMR). NMR yields were determined by the addition of 1.0 equivalent of methyl 4-nitrobenzoate as an internal standard to the crude reaction mixture and comparing the integration of the standard's peaks to those of the starting material and product (16 scans, 30 second relaxation delay). IR spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. HRMS analyses were performed under contract by University of Houston's mass spectrometric facility via an nESI method and a Thermo Exactive + Advion Nanomate instrument. Analysis by HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Chiralpak or Chiralcel (250 mm x 4.6 mm) column (column details provided for specific compounds). Commercially available compounds were purchased from Aldrich, Acros, Ark Pharm, Alfa Aesar, Beantown Chemical, TCI, and Combi-Blocks and were used without further purification. IUPAC chemical names were generated using Cambridgesoft ChemBioDraw Ultra 12.0.

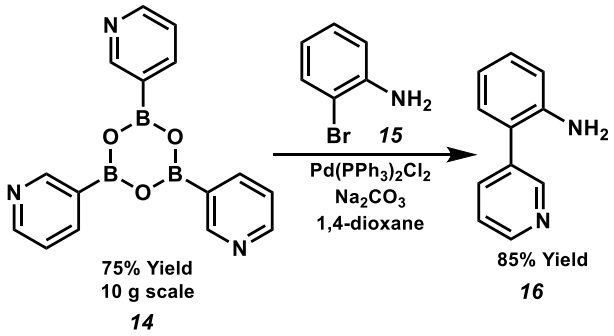
### 2.5.2 Synthesis of Aldehyde 17

**2,4,6-tri(pyridin-3-yl)-1,3,5,2,4,6-trioxatriborinane (14)**



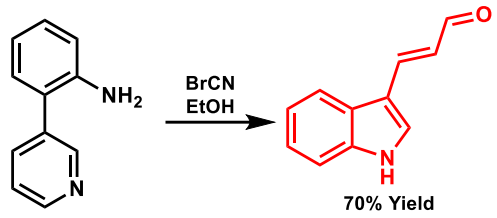

Compound 14 was prepared following a procedure described in literature.[68] The title compound was obtained in 75% yield (7.9765 g). All spectral data were identical to those reported in literature.

**2-(pyridin-3-yl)aniline (16)**




Compound 16 was synthesized following a procedure described in literature.[68] Compound **15** was purchased from Sigma Aldrich and used in the reaction without further purification. The product was obtained in 85% yield (1.1437 g). All spectral data were identical to those reported in literature.

**(*E*)-3-(1H-indol-3-yl)acrylaldehyde (17)**




*16* *17*

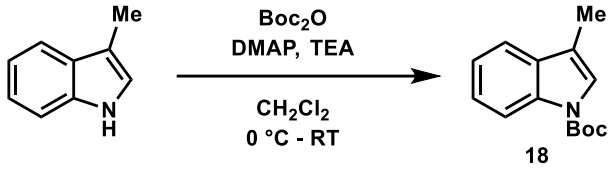
Compound **17** was synthesized following a procedure described in literature.[48] The product was obtained in 70% yield (0.5286 g). All spectral data were identical to those reported in literature.

### 2.5.3 Lithiation Control Experiments

**General Procedure for Boc Protection**

The starting material was added to a flame-dried round bottom flask equipped with stir bar under argon atmosphere. To this flask, anhydrous dichloromethane (0.2 M) was added, and the solution was stirred until the starting material was fully dissolved. The solution was cooled to 0 $^{o}$C and TEA (1.2 equiv) was added, slowly, as one portion. The solution was allowed to stir for 5 minutes, after which, DMAP (0.2 equiv) was added, followed by addition of $Boc_2O$ (3 equiv) as one portion. The reaction was stirred at room temperature for 3 hours, or until to be complete by TLC. The reaction was quenched by water, extracted thrice with $CH_2Cl_2$, and washed with brine. The combined organic layers were dried over $MgSO_4$ and the solvent removed by rotary evaporation. The resulting product was purified by column chromatography.

***tert*-butyl 3-methyl-1*H*-indole-1-carboxylate (18)**



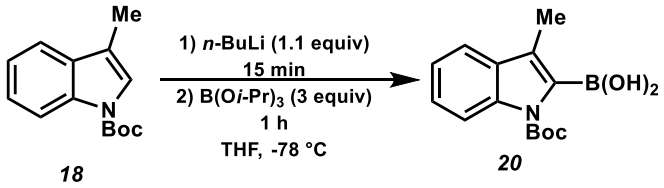
18

The title compound was synthesized following the general procedure for Boc protection. The title compound was purified by silica gel chromatography using 10% ethyl acetate/hexanes as eluent and obtained in 99% yield (1.0124 g). All spectral data were identical to those reported in literature.[69]

**General Procedure for Lithiation**

The starting material was added to a flame dried round-bottom flask equipped with stir bar, under Ar (g). The flask was evacuated and backfilled with argon three times. THF (0.2 M) was added to the flask, and while stirring, the resulting solution was cooled to -78 $^{o}$C in a dry ice/acetone bath. The lithiation reagent (2.2 equiv) was added dropwise to the reaction mixture. The resulting solution was stirred for the indicated time, after which, triisopropyl borate (1.2 equiv) was added as one portion. The solution was stirred for the indicated time. The solution was warmed to room temperature, then quenched with water, and allowed to stir for 5 minutes. The reaction was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were removed by rotary evaporation, and the product was purified by silica gel chromatography.

**(1-(*tert*-butoxycarbonyl)-3-methyl-1*H*-indol-2-yl)boronic acid (20)**

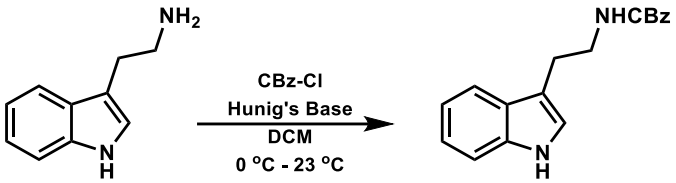



*18* *20*

The title compound was prepared following the general procedure for lithiation. The title compound was purified by silica gel chromatography using 10-50% ethyl acetate/hexanes and obtained in 56% yield (143.5 mg). All spectral data were identical to those reported in literature.[70]

### 2.5.4 Protection of Tryptamine for Lithiation

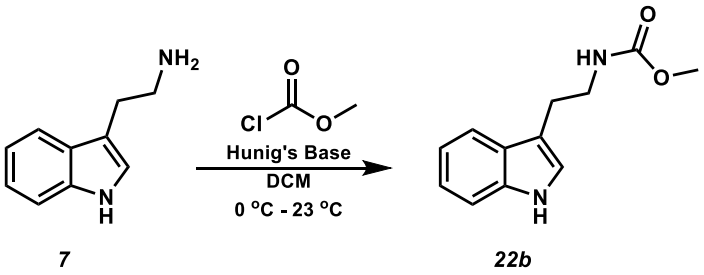
**(2-indol-3-yl-ethyl)-carbamic acid benzyl ester (22a)**




*7* *22a*

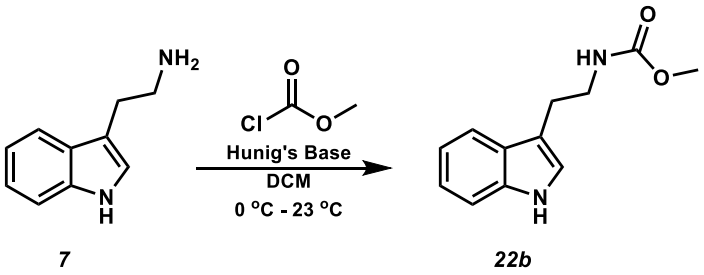
The title compound was prepared following a procedure reported in literature.[71] The compound was purified by silica gel chromatography using 10-50% ethyl acetate/hexanes as eluent. The product was obtained in 98% yield (1.8001 g, 6.12 mmol). All spectral data match those reported in literature.[71]

**(2-indol-3-yl-ethyl)-carbamic acid methyl ester (22b)**



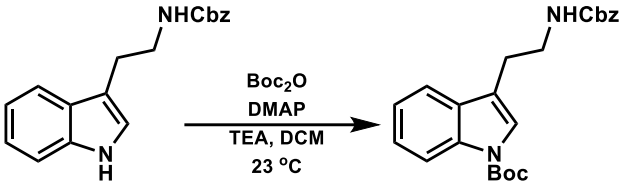

The title compound was prepared following a procedure reported in literature. The compound was purified by silica gel chromatography using 50% ethyl acetate/hexanes as eluent. The product was obtained as a pale-yellow oil in 97% yield (0.3390 g). All spectral data were identical to those reported in literature.[72]

**(2-indol-3-yl-ethyl)-carbamic acid ethyl ester (22b)**




The title compound was prepared following a procedure reported in literature. The compound was purified by silica gel chromatography using 50% ethyl acetate/hexanes as eluent. The product was obtained as a pale-yellow oil in 81% yield (0.3012 g). All spectral data were identical to those reported in literature.[73]

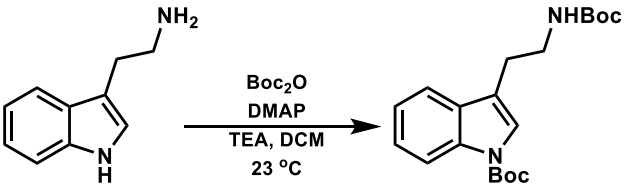
**tert-butyl 3-(2-(((benzyloxy)carbonyl)amino)ethyl)-1H-indole-1-carboxylate (23a)**




*22* *23a*

The title compound was prepared following a procedure reported in literature. The compound was purified by silica gel chromatography using 5-20% ethyl acetate/hexanes as eluent. The product was obtained in 81% yield (0.3012 g). All spectral data were identical to those reported in literature.[74]

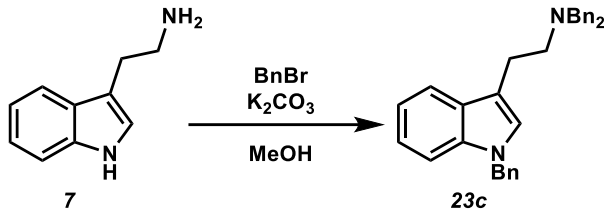
**3-(2-tert-butoxycarbonylamino-ethyl)-indole-1-carboxylic acid tert-butyl ester (23b)**




*22* *23b*

The title compound was synthesized following a procedure reported in literature.[75] The compound was purified by silica gel chromatography using 5-30% ethyl acetate/hexanes as eluent. The product was obtained in 26% yield (0.6221 g). All spectral data were identical to those reported in literature.

***N*-benzyl-2-(1-benzyl-1*H*-indol-3-yl)ethanamine (23c)**




*7* *23c*

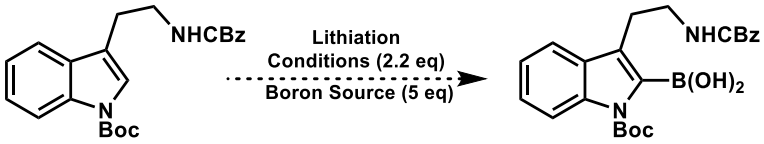
In a round-bottom flask, starting material (300 mg, 1.9 mmol) was dissolved in THF. NaH (374 mg, 9.4 mmol, 60% in mineral oil, 5 equiv) was added as two portions to the reaction mixture. The reaction was stirred at room temperature for 10 minutes, after which, BnBr was added, dropwise (0.90 mL, 7.6 mmol, 4 equiv). The reaction was stirred overnight at room temperature, after which, it was quenched with water and extracted with ethyl acetate three times. The combined organic layers were dried over $MgSO_4$ and the solvents removed by rotary evaporation. The compound was purified by silica gel flash column chromatography using 1% ethyl acetate/hexanes as eluent. The product was obtained as a yellow oil in 38% yield (310.5 mg, 0.72 mmol).

**$^1$H-NMR** (400 MHz, chloroform-D) δ 7.45 (t, J = 7.1 Hz, 5H), 7.36-7.25 (m, 12H), 7.21-7.09 (m, 4H), 6.89 (s, 1H), 5.26 (s, 2H), 3.75 (s, 4H), 3.05 (t, J = 7.6 Hz, 2H), 2.88 (t, J = 7.8 Hz, 2H) **$^{13}$C-NMR** (101 MHz, chloroform-D) δ 138.4, 136.4, 135.1, 129.0, 127.3, 127.2, 127.0, 126.9, 126.7, 126.5, 126.0, 125.6, 125.3, 125.3, 124.3, 120.1, 117.6, 117.3, 112.2, 108.1, 56.9, 52.5, 48.3, 21.6 **IR** 3059, 3026, 2924, 2794, 2360, 1739, 1603, 1481, 1466, 1356, 1330, 1129 **HRMS-ESI m/z** Calculated for $C_{31}H_{31}N_2$ $[M + H]^+$ 431.2487, found 431.2466

### 2.5.5 Lithiation Experiments

The starting material was added to a flame dried round-bottom flask equipped with stir bar, under Ar (g). The flask was evacuated and backfilled with argon three times. THF (0.2 M) was added to the flask, and while stirring, the resulting solution was cooled to -78 $^o$C in a dry ice/acetone bath.

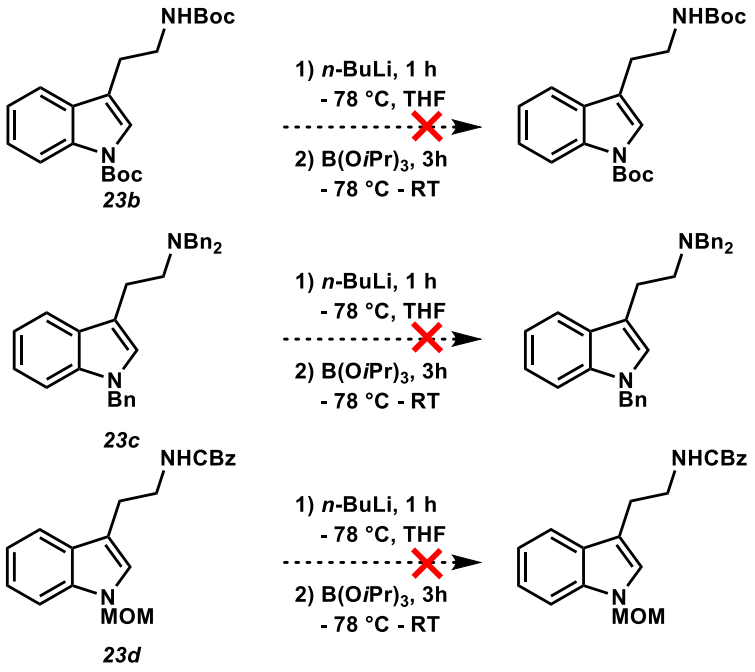
The resulting solution was stirred for the indicated time, after which, the boron source was added as one portion. The solution was stirred for the indicated time. The solution was warmed to room temperature, then quenched with water, and allowed to stir for 5 minutes. The reaction was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were removed by rotary evaporation, and the crude reaction mixture was analyzed by $^{1}H$ and $^{11}B$ NMR.




| Lithium Source | Lithium Time | Boron Source | Boron Time | Result |
|---|---|---|---|---|
| *n*-BuLi | 15 min | B(O*i*Pr)$_3$ | 3 h | recovery SM |
| *n*-BuLi | 1 h | B(O*i*Pr)$_3$ | 3 h | recovery SM |
| *n*-BuLi | 3 h | B(O*i*Pr)$_3$ | 3 h | decomposition SM |
| *n*-BuLi | 1 h | B(O*i*Pr)$_3$ | 3 h | recovery SM |
| *n*-BuLi | 12 h | B(O*i*Pr)$_3$ | 12 h | decomposition SM |
| *n*-BuLi | 2 h allowed to warm to RT | B(O*i*Pr)$_3$ | 3 h | recovery SM |
| *n*-BuLi | 1 h | B(O*i*Pr)$_3$ | 12 h | recovery SM |
| *n*-BuLi | 1 h | B(O*i*Pr)$_3$ | 24 h | recovery SM |
| LiTMP | 1 h | B(O*i*Pr)$_3$ | 12 h | recovery SM |
| LiTMEDA | 1 h | B(O*i*Pr)$_3$ | 12 h | recovery SM |
| *s*-BuLi | 1 h | B(O*i*Pr)$_3$ | 12 h | decomposition SM |
| *n*-BuLi | 1 h | B(OMe)$_3$ | 12 h | recovery SM |
| *n*-BuLi | 15 min | B(OMe)$_3$ | 3 h | recovery SM |

General procedure for lithiation as above was followed. No formation of carbon-boron bond was observed by $^{11}B$ NMR. Decomposition of starting material refers to the inability to recover starting material from crude reaction mixture. Starting material is an oil, and was weighed directly into tared vials, and extensively dried under vacuum (at least 2 hours). Alternately, azeotropically dried starting material was dissolved in toluene and used as a solution (0.5 M).

All protected versions of tryptamine tested failed to provide the boronated products.

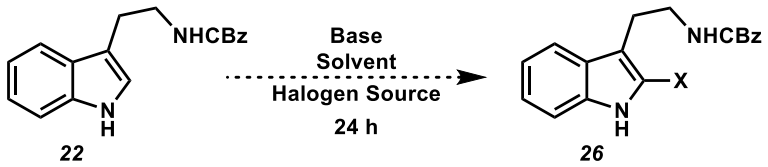



### 2.5.6 Halogenation Experiments

**General Procedure for Halogenation**

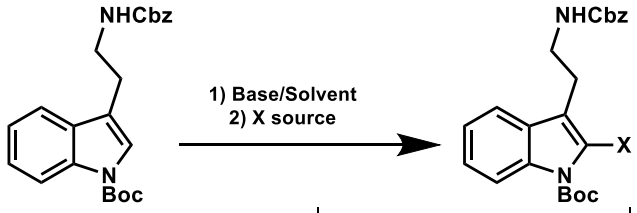
In a flame dried 4-dram vial equipped with stir bar, starting material was dissolved in the solvent (0.2 M). The base (5 equiv) was added to the reaction mixture and allowed to stir for 10 minutes. The halogen source (2 equiv) was then added in the manner indicated in the table. The resulting solution was allowed to stir for the indicated time. The solution was quenched with water and extracted with ethyl acetate 3 times. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were removed by rotary evaporation. The crude reaction mixture was analyzed by $^1H$ NMR. In some cases, purification was attempted, but no halogenated product was observed.

*Note*: if aqueous base or water as a solvent were used, the reaction vessel was not flame dried.



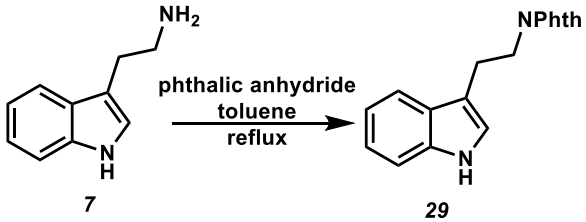

*22* *26*

| **Base/Solvent** | **Halogenation Conditions** | **Time** | **Result** |
|---|---|---|---|
| Acetone/$K_2CO_3$ (aq) 3/1 v/v | $I_2$ in THF | 6 h | No reaction |
| Acetone/$K_2CO_3$ (aq) 3/1 v/v | $I_2$ in THF | 4 h | No reaction |
| Acetone/$K_2CO_3$ (aq) 3/1 v/v | $I_2$ in THF (slow addition, 1 h) | 12 h | No reaction |
| Acetone/$K_2CO_3$ (aq) 3/1 v/ | $I_2$ in THF (100 mg/1 mL) added dropwise until color persisted | 12 h | No reaction |
| Acetone/$K_2CO_3$ (aq) 3/1 v/v | $I_2$ in THF | No stirring, 12 h | No reaction |
| Acetone/$K_2CO_3$ (aq) 3/1 v/v | $I_2$ in THF | No stirring, not protected from light, 12 h | Decomposed |
| Acetone/$Na_2CO_3$ (aq) 3/1 v/v | $I_2$ in THF | 10 min | Decomposed |
| Acetone/$K_2CO_3$ (aq) 3/1 v/v | $I_2$ in THF | 45 min | No SM, no desired product |
| Acetone/$Na_2CO_3$ (aq) 3/1 v/v | $I_2$ in THF | 45 min | No SM, no desired product |
| Acetone/$K_2CO_3$ (aq) 3/1 v/v | $I_2$ in THF | 24 h | Deprotection to tryptamine |
| Acetone/$K_2CO_3$ (s) | $I_2$ in THF | 24 h | No reaction |
| Acetone/$K_2CO_3$ (s) | $I_2$ in acetone | 24 h | No reaction |
| Acetone/$K_2CO_3$ (s) | ICl in acetone | 24 h | Deprotection to tryptamine |
| n-BuLi/THF | $I_2$ in THF | -78 $^oC$ – 23$^oC$, 12 h | Deprotected |
| n-BuLi/THF | $I_2$ in THF | -78 $^oC$ – 23$^oC$, 12 h | Decomposed |
| Acetone/$K_2CO_3$ (s) | $I_2$ as a solid | 2 hr | No reaction |




| **Base/Solvent** | **X Source** | **Conditions** | **Result** |
|---|---|---|---|
| Acetone/$K_2CO_3$ (s) | NIS (in 1 mL acetone) | 30 min with $K_2CO_3$<br>12 h with NIS | Boc deprotection |
| Acetone/$K_2CO_3$ (s) | NBS (in 1 mL acetone) | 30 min with $K_2CO_3$<br>12 h with NBS | No product |
| Acetone/$K_2CO_3$ (s) | ICl (in 1 mL acetone) | 30 min with $K_2CO_3$<br>12 h with ICl | No product |
| Acetone/$K_2CO_3$ (s) | $I_2$ (in 1 mL acetone) | 30 min with $K_2CO_3$<br>12 h with $I_2$ | No product |
| THF/$K_2CO_3$ (s) | NIS | 30 min with $K_2CO_3$<br>24 h with NIS | No product |
| THF/$K_2CO_3$ (s) | NBS | 30 min with $K_2CO_3$<br>24 h with NBS | Decomposed |
| THF/$K_2CO_3$ (s) | ICl | 30 min with $K_2CO_3$<br>24 h with Icl | No reaction |
| Acetone/$K_2CO_3$ (s) | NBS | 30 min with $K_2CO_3$<br>Added 2 mL acetone after 2 h reaction, 12 h | Decomposed |
| THF/n-BuLi | NIS (neat) | 30 min *n*-BuLi<br>12 h NIS | No reaction |
| THF/n-BuLi | NBS (neat) | 30 min *n*-BuLi<br>12 h NBS | No reaction |
| THF/n-BuLi | ICl (in 1 mL THF) | 30 min *n*-BuLi<br>12 h ICl | No reaction |
| THF/n-BuLi | $I_2$ (in 1 mL THF) | 30 min *n*-BuLi<br>12 h $I_2$ | No reaction |
| THF/LDA | $I_2$ (in 1 mL THF) | 30 min *n*-BuLi<br>12 h $I_2$ | No reaction |
| THF/LiTMP | $I_2$ (in 1 mL THF) | 30 min *n*-BuLi<br>24 h $I_2$ | No reaction |

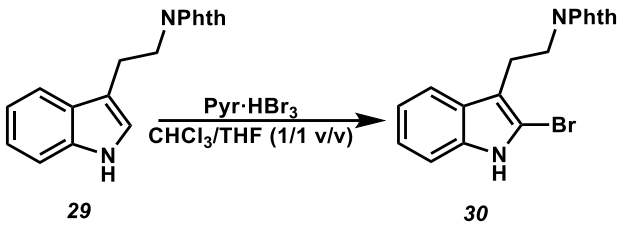
**2-(2-(1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (29)**




*7* *29*

The title compound was synthesized following a procedure reported in literature. The compound was purified by washing with toluene and obtained as an off-white solid in 86% yield (4.6597 g) All spectral data were identical to those reported in literature.[75]

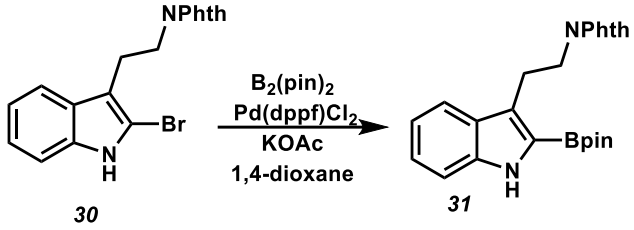
**2-(2-(2-bromo-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (30)**




*29* *30*

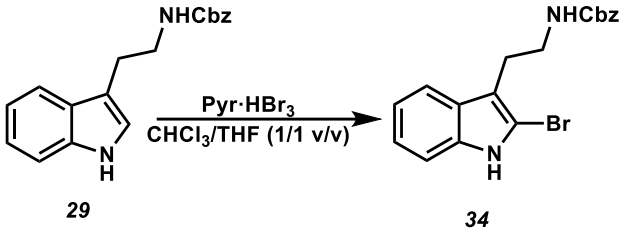
The title compound was synthesized following a procedure reported in literature. The title compound was purified by silica gel column chromatography using 1-10% MeOH/DCM and obtained as a pale yellow solid in 95% yield (119.2 mg). All spectral data were identical to those reported in literature.[75]

**2-(2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (31)**




Procedure was modified from literature reports.[76] To a vial containing starting material (100.0 mg, 0.27 mmol), added $B_2pin_2$ (82.5 mg, 0.33 mmol, 1.2 equiv), $Pd(dppf)Cl_2$ (10.0 mg, 0.014 mmol, 5 mol %) and KOAc (79.8 mg, 0.81 mmol, 3 equiv). The vial was evacuated and backfilled with argon three times. To the vial, added 1,4-dioxane (1.5 mL, 0.2 M). The resulting mixture was degassed for 30 minutes with $N_2$ gas. The vial was sealed and heated to 80 $^oC$. The solution was stirred for 24 hours. After the reaction was complete, the mixture was diluted with dichloromethane and washed with saturated $Na_2CO_3$. The aqueous layer was extracted with DCM. The combined organics were dried over $MgSO_4$, and the solvents were removed by rotary evaporation. The product was purified by column chromatography, using 5-30% ethyl acetate/hexanes as an eluent. The product was obtained as a pale yellow oil in 82% yield (92.4 mg). All spectral data matched those reported in literature.[77]

**benzyl (2-(2-bromo-1H-indol-3-yl)ethyl)carbamate (34)**



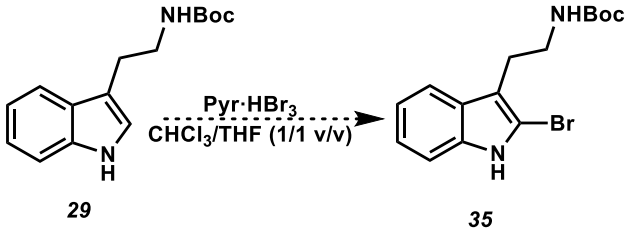

*29* *34*

The product was prepared following the procedure described in literature for compound **30**. The starting material was added to a flame dried 4-dram vial equipped with stir bar. The solvent mixture was added (3.4 mL, 0.1 M), and the resulting mixture was cooled to 0 $^{o}$C, after which pyridinium tribromide (141.4 mg, 0.44 mmol, 1.3 equiv) was added. The reaction was allowed to warm to room temperature and stirred for 14 hours. The reaction was quenched with $Na_2S_2O_3$ (5 mL) and extracted 3 times with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvents were removed by rotary evaporation. The title compound was purified by silica gel column chromatography using 50% ethyl acetate/hexanes as eluent. The product was obtained as a brown oil in 39% yield (49.5 mg).

Note: On scale up, the reaction failed to provide the brominated compound in greater than 8% yield.

**$^{1}$H-NMR** (600 MHz, chloroform-D) δ 8.17 (s, 1H), 7.59 (d, J = 8.2 Hz, 1H), 7.31 (d, J = 43.3 Hz, 8H), 7.19 (t, J = 7.2 Hz, 1H), 7.11 (t, J = 7.2 Hz, 1H), 6.98 (s, 1H), 5.11 (d, J = 21.3 Hz, 2H), 3.53 (q, J = 6.2 Hz, 2H), 2.97 (t, J = 6.2 Hz, 2H) **$^{13}$C-NMR** (151 MHz, chloroform-D) δ 156.5, 136.7, 136.5, 128.6, 128.2, 127.4, 122.2, 119.5, 118.8, 112.8, 111.4, 77.4, 77.2, 77.0, 66.7, 41.4, 25.8 **IR** 3325, 2927, 1696, 1519, 1456, 1356, 1226, 1134, 1082, 1044 cm$^{-1}$

***tert*-butyl (2-(2-bromo-1*H*-indol-3-yl)ethyl)carbamate (34)**

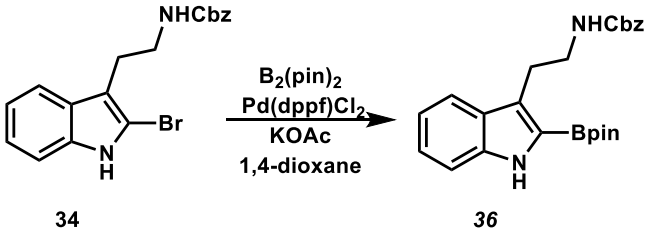



*29* *35*

The product synthesis was attempted following the procedure described for **34** above. However, no brominated product was observed in the crude reaction mixture.

### 2.5.7 Miyaura Borylation

**benzyl (2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)ethyl)carbamate (36)**

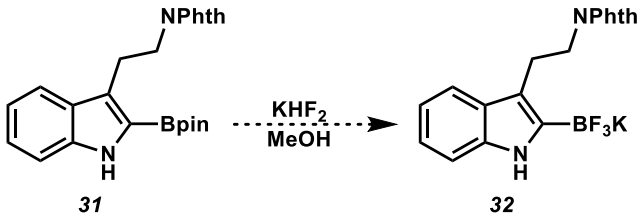



*34* *36*

Procedure was modified from literature reports.[76] To a vial containing starting material (50.0 mg, 0.13 mmol), added $B_2pin_2$ (40.8 mg, 0.16 mmol, 1.2 equiv), $Pd(dppf)Cl_2$ (4.9 mg, 0.007 mmol, 5 mol %) and KOAc (39.5 mg, 0.40 mmol, 3 equiv). The vial was evacuated and backfilled with argon three times. To the vial, added 1,4-dioxane (1.5 mL, 0.1 M). The resulting mixture was degassed for 30 minutes with $N_2$ gas. The vial was sealed and heated to 80 $^oC$. The solution was stirred for 24 hours. After the reaction was complete, the mixture was diluted with dichloromethane and washed with saturated $Na_2CO_3$. The aqueous layer was extracted with DCM. The combined organics were dried over $MgSO_4$, and the solvents were removed by rotary evaporation. The product was purified by column chromatography, using 5-30% ethyl

acetate/hexanes as an eluent. The product was obtained as a pale-yellow oil in 72% yield (40.56 mg). Spectral data matched those obtained by Hartwig iridium borylation, see below.

**(3-(2-(((benzyloxy)carbonyl)amino)ethyl)-1H-indol-2-yl)potassium trifluoroborate salt (32)**

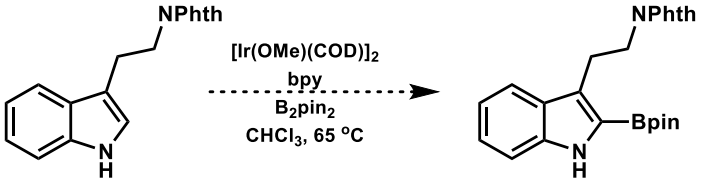



*31* *32*

Despite repeated attempts to synthesize and purify compound **32** following established procedures, the only observed outcome was protodeboronation.[43]

### 2.5.8 Hartwig Iridium-Catalyzed Borylation

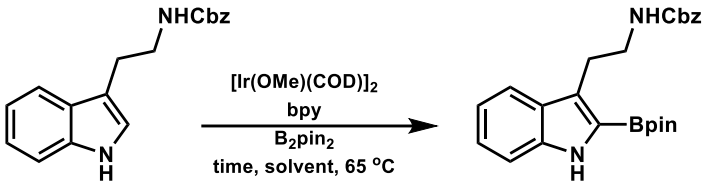
**2-(2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (SUPPLEMENTARY-1)**




Procedure was modified from literature reports.[60,78] Chloroform was dried over activated 4 Å MS overnight prior to use. Added starting material (100 mg, 0.35 mmol), iridium catalyst (3.4 mg, 0.05 mmol, 1.5 mol %), bpy (27.9 mg, 0.18 mmol, 0.5 equiv), and $B_2pin_2$ (177 mg, 0.69 mmol, 2 equiv) to a flame dried vial equipped with stir bar. The vial was evacuated and backfilled with argon, three times. Chloroform was added to the vial (2.2 mL, 0.15 M), which was then well sealed and heated to 65 °C. The crude reaction mixture was rotovaped and analyzed by $^{1}H$ and $^{11}B$ NMR. The product was not obtained, and carbon-boron bond formation was not observed in crude $^{11}B$

NMR. The reaction was also attempted using THF and dichloromethane as a solvent, giving no result.

**benzyl (2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)ethyl)carbamate (39)**




Procedure was modified from literature reports.[60,78] Added starting material (200 mg, 0.70 mmol), iridium catalyst (13.3 mg, 0.03 mmol, 1.5 mol %), bpy (54.7 mg, 0.35 mmol, 0.5 equiv), and $B_2pin_2$ (356 mg, 1.4 mmol, 2 equiv) to a flame dried vial equipped with stir bar. The vial was evacuated and backfilled with argon, three times. Solvent was added to the vial (1.4 mL, 0.5 M), which was then well sealed and heated to 65 °C. The solvents from the crude reaction mixture were removed by rotary evaporation and the crude mixture was analyzed by $^1H$ and $^{11}B$ NMR.

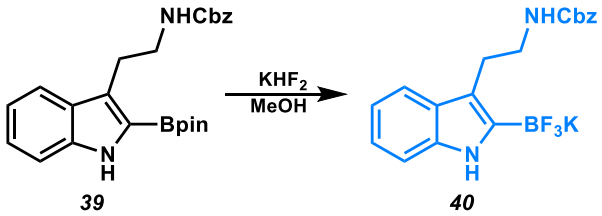
| Solvent | Time | Result |
|---|---|---|
| $CHCl_3$ | 24 h | recovery SM (twice) |
| DCE | 24 h | no C-B bond formation |
| DCM | 24 h | no C-B bond formation |
| THF | 3 h | 81% yield (0.7 mmol scale) |
| DCM | 3 h | no C-B bond formation |
| THF | 3 h | 76% yield (trial 1)<br>67% yield (trial 2) |
| THF | 3.5 h, reflux | 93% yield (3.5 mmol scale) |
| THF | 3.5 h, reflux | 99% yield (7 mmol scale) |

The title compound was purified by silica gel column chromatography using 20% ethyl acetate/hexanes as eluent. The product was obtained as a clear, colorless oil (2.7493 g, last entry in table above).

**$^{1}$H-NMR** (500 MHz, acetone-D6) δ 9.90-10.29 (1H), 7.66 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.32-7.27 (m, 3H), 7.15 (t, J = 7.2 Hz, 1H), 7.00 (d, J = 6.9 Hz, 1H), 6.11-6.35 (1H), 5.01 (d, J = 2.3 Hz, 2H), 3.40 (q, J = 6.5 Hz, 2H), 3.22-3.19 (m, 2H), 1.33 (d, J = 13.2 Hz, 12H) **$^{13}$C-NMR** (126 MHz, acetone-D6) δ 156.2, 139.0, 137.7, 128.3, 127.8, 127.8, 127.7, 125.3, 123.3, 123.2, 119.4, 118.8, 111.9, 84.0, 83.9, 83.8, 65.5, 42.6, 24.3, 20.0 **$^{11}$B-NMR** (160 MHz, methanol-D4) δ 28.3 **IR** 3452, 2978, 1708, 1546, 1454, 1372, 1324, 1263, 1137 **HRMS-ESI m/z** Calculated for $[M + H]^+$ 412.2299, found 421.2313

### 2.5.9 Trifluoroborate Salt Formation

**(3-(2-(((benzyloxy)carbonyl)amino)ethyl)-1H-indol-2-yl)potassium trifluoroborate salt (40)**




*39* *40*

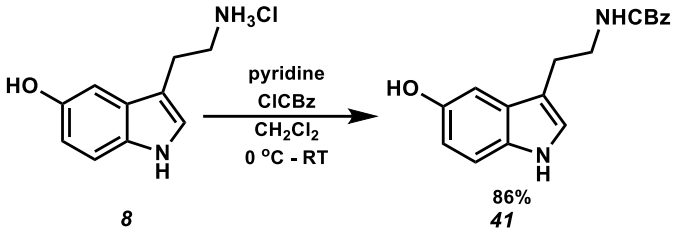
The procedure was modified from literature reports. The starting material was added to a vial, equipped with stir bar, and dissolved in MeOH. The solution was stirred until the starting material fully dissolved. After this, $KHF_2$ (aqueous, 4.5 M, 2.8 equiv) was added to the reaction mixture dropwise, causing the solution to become cloudy. The resulting mixture was allowed to stir at room temperature for 1 hour. After the reaction was complete, the solvents were fully removed by rotary evaporation, after which, the residual solids were dried under high vacuum for an hour. The solids were re-dissolved in acetone, and the solution was filtered to remove excess inorganic salt. The solvents were evaporated by rotary evaporation. The residual solids were re-dissolved in methanol and the solvent removed by rotary evaporation twice more. The resulting solid was dried under

high vacuum overnight and stored at 0 °C under argon. The title compound was obtained as an off-white solid in 62% yield (224.3 mg).

**$^1$H-NMR** (600 MHz, DMSO-D6) δ 10.77 (s, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.43-7.27 (m, 6H), 7.10 (s, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 5.00 (t, J = 8.6 Hz, 2H), 3.23 (q, J = 6.9 Hz, 2H), 2.78 (t, J = 7.6 Hz, 2H) **$^{11}$B-NMR** (193 MHz, acetone-D6) δ -0.6 **IR** 3418, 2970, 2363, 1700, 1528, 1455, 1365, 1239, 1217, 1140 $cm^{-1}$

### 2.5.10 Serotonin Derived Nucleophile

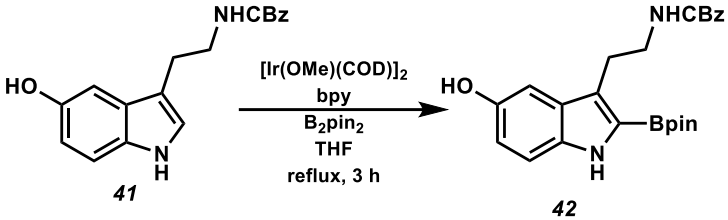
**benzyl (2-(5-hydroxy-1H-indol-3-yl)ethyl)carbamate (41)**




*8* *41*

The title compound was prepared following procedures described in literature. All spectral data were identical to those found in literature.[77]

**benzyl (2-(5-hydroxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)ethyl)carbamate (42)**



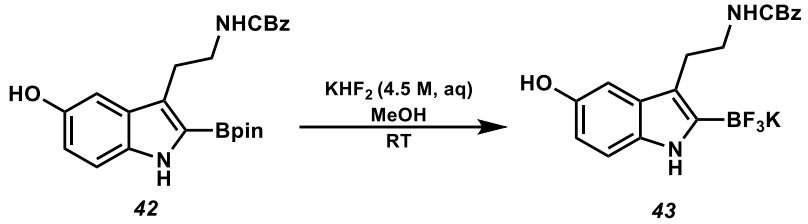

*41* *42*

Procedure was modified from literature reports.[60,78] Added starting material (0.650 g, 2.1 mmol), iridium catalyst (20.8 mg, 0.03 mmol, 1.5 mol %), bpy (0.160 g, 1.1 mmol, 0.5 equiv), and $B_2pin_2$

(1.070 g, 1.4 mmol, 2 equiv) to a flame dried round bottom flask equipped with stir bar. The flask was evacuated and backfilled with argon, three times. Solvent was added to the round bottom flask (21 mL, 0.1 M), which was then well sealed and heated to 65 °C. The title compound was purified by silica gel column chromatography using 40% ethyl acetate/hexanes as eluent. The product was obtained as a mixture with starting material and used as this mixture in the transformation to the trifluoroborate salt.

**$^{1}$H-NMR** (500 MHz, chloroform-D) δ 7.98-8.16 (1H), 7.27-7.52 (5H), 7.06-7.20 (1H), 6.93-7.06 (1H), 6.82-6.93 (1H), 6.67-6.82 (1H), 5.22-5.36 (1H), 5.02-5.16 (2H), 3.38-3.50 (2H), 2.70-2.93 (2H), 1.20-1.27 (12H) **$^{13}$C-NMR** (126 MHz, chloroform-D) δ 149.9, 131.6, 128.6, 128.3, 123.3, 112.2, 112.0, 103.3, 83.2, 77.4, 77.2, 76.9, 75.4, 66.8, 60.6, 53.6, 41.3, 25.9, 24.9, 24.6, 21.2, 14.3, 1.11 **$^{11}$B-NMR** (160 MHz, chloroform-D) δ 21.5

**(3-(2-(((benzyloxy)carbonyl)amino)ethyl)-5-hydroxy-1H-indol-2-yl)potassium trifluoroborate salt (43)**



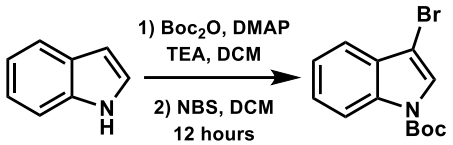

*42* *43*

The procedure was modified from literature reports. The starting material was added to a vial, equipped with stir bar, and dissolved in MeOH. The solution was stirred until the starting material fully dissolved. After this, $KHF_2$ (aqueous, 4.5 M) was added to the reaction mixture dropwise, causing the solution to become cloudy. The resulting mixture was allowed to stir at room temperature for 1 hour. After the reaction was complete, the solvents were fully removed by rotary evaporation, after which, the residual solids were dried under high vacuum for an hour. The solids were re-dissolved in acetone, and the solution was filtered to remove excess inorganic salt. The

solvents were evaporated by rotary evaporation. The residual solids were re-dissolved in methanol and the solvent removed by rotary evaporation twice more. The resulting solid was dried under high vacuum overnight and stored at 0 °C under argon. The product was obtained as a yellow solid in 55% yield and used without further purification.

### 2.5.11 Synthesis of 3-$BF_3K$ Indole Nucleophiles

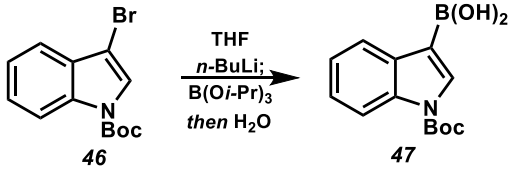
**tert-butyl 3-bromo-1*H*-indole-1-carboxylate (46)**




*45* *46*

The title compound was synthesized following a procedure reported in literature. The title compound was purified by silica gel column chromatography using 1-5% ethyl acetate/hexanes as eluent and obtained in 62% yield (7.6342 g). All spectral data were identical to those reported in literature.[79]

**(1-(tert-butoxycarbonyl)-1*H*-indol-3-yl)boronic acid (47)**

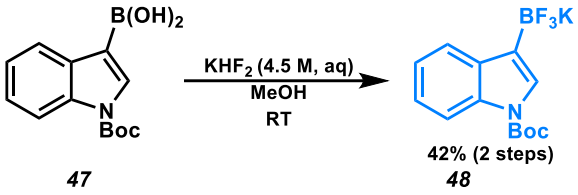



*46* *47*

A round bottom flask, equipped with stir bar, was flame dried and placed under an argon atmosphere. The starting material was added and dissolved in THF. The resulting solution was cooled to -78 °C and *n*-BuLi was added with a syringe pump over 1 hour. The resulting solution was stirred at -78 °C for an hour more, after which, triisopropyl borate was added as one portion. The reaction was allowed to warm to room temperature and allowed to stir for 2 hours. After this,

$H_2O$ was added to the reaction mixture. The solution was allowed to stir for 20 minutes, after which it was extracted three times with ethyl acetate. The combined organic portions were washed with $NH_4Cl$, then with brine. The organic layers were dried over $MgSO_4$ and the solvents removed by rotary evaporation. The title compound was purified by silica gel chromatography, using 20% ethyl acetate/hexanes as eluent and obtained in 14% yield (1.3427 g). The spectra matched those of a pure sample of the title compound purchased from Sigma Aldrich.

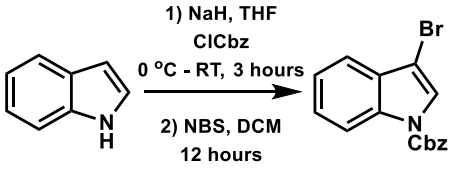
**(1-(tert-butoxycarbonyl)-1*H*-indol-3-yl)potassium trifluoroborate salt (47)**




*47* *48*

The procedure was modified from literature reports. All spectral data were identical to those reported in literature.[44]

**benzyl 3-bromo-1H-indole-1-carboxylate (49)**



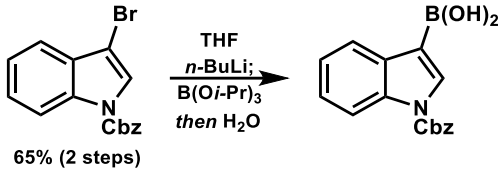

*45* *49*

To a flame dried flask, equipped with stir bar, added starting material. The starting material was dissolved in THF and cooled to 0 °C in an ice bath. While stirring, NaH was added to the reaction, which was allowed to stir for 30 minutes. After the 30 minute stir, ClCbz was slowly added to the reaction mixture. The mixture was allowed to warm to room temperature and stirred for 3 hours, after which time it was quenched with water and diluted with ethyl acetate. The organic layer was

washed thrice with water, after which the organics were dried over $Na_2SO_4$. The solvents were removed by rotary evaporation.

The resulting crude was re-dissolved in DCM in the same round bottom flask. To the solution, NBS was added as one portion. The solution was stirred for 12 hours at room temperature, then quenched with water and extracted three times with DCM. The combined organic phases were dried over $MgSO_4$ and the solvents were removed by rotary evaporation. The compound was purified by silica gel chromatography using 1-40% ethyl acetate/hexanes as eluent. The title compound was obtained as an orange oil in 46% yield (13.0213 g).

**(1-((benzyloxy)carbonyl)-1H-indol-3-yl)boronic acid (50)**

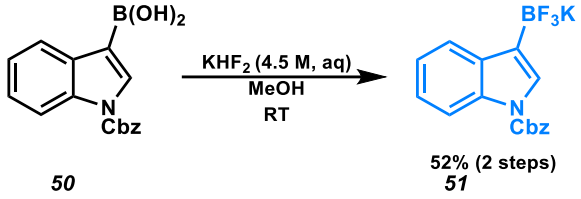



65% (2 steps)

*49* *50*

A round bottom flask, equipped with stir bar, was flame dried and placed under an argon atmosphere. The starting material was added and dissolved in THF. The resulting solution was cooled to -78 $^oC$ and *n*-BuLi was added with a syringe pump over 1 hour. The resulting solution was stirred at -78 $^oC$ for an hour more, after which, triisopropyl borate was added as one portion. The reaction was allowed to warm to room temperature and allowed to stir for 2 hours. After this, $H_2O$ was added to the reaction mixture. The solution was allowed to stir for 20 minutes, after which it was extracted three times with ethyl acetate. The combined organic portions were washed with $NH_4Cl$, then with brine. The organic layers were dried over $MgSO_4$ and the solvents removed by rotary evaporation. **IR** 3034, 1717, 1484, 1453, 1396, 1343, 1327, 1240, 1211, 1119, 1080, 1027 $cm^{-1}$ **HRMS-ESI m/z** Calculated for $C_{16}H_{13}BrNO_2$ $[M + H]^+$ 330.0130, found 330.0967.

**(1-((benzyloxy)carbonyl)-1H-indol-3-yl)potassium trifluoroborate salt (51)**

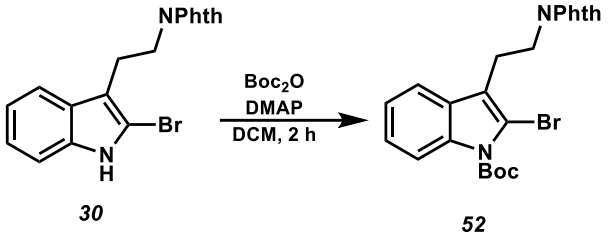



*50* *51*

The procedure was modified from literature reports. The starting material was added to a vial, equipped with stir bar, and dissolved in MeOH. The solution was stirred until the starting material fully dissolved. After this, $KHF_2$ (aqueous, 4.5 M) was added to the reaction mixture dropwise, causing the solution to become cloudy. The resulting mixture was allowed to stir at room temperature for 1 hour. After the reaction was complete, the solvents were fully removed by rotary evaporation, after which, the residual solids were dried under high vacuum for an hour. The solids were re-dissolved in acetone, and the solution was filtered to remove excess inorganic salt. The solvents were evaporated by rotary evaporation. The residual solids were re-dissolved in methanol and the solvent removed by rotary evaporation twice more. The resulting solid was dried under high vacuum overnight and stored at 0 $^{o}$C under argon. The product was obtained as an off white solid in 55% yield and used without further purification.

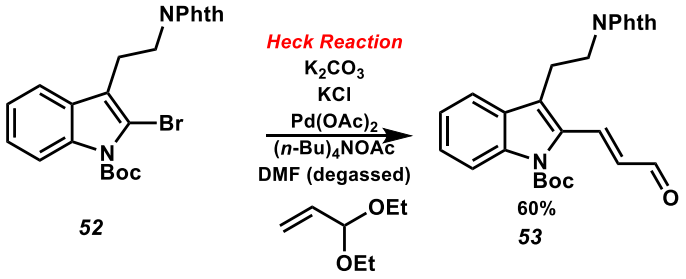
### 2.5.12 Heck Reaction

**tert-butyl 2-bromo-3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1H-indole-1-carboxylate (52)**




The title compound was prepared following a procedure reported in literature. The title compound was purified by silica gel column chromatography using 5-15% ethyl acetate/hexanes as eluent and obtained in 25% yield (over 2 steps, 239.6 mg). All spectral data were identical to those reported in literature.[73]

**(E)-tert-butyl 3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-(3-oxoprop-1-en-1-yl)-1H-indole-1-carboxylatecarboxylate (53)**

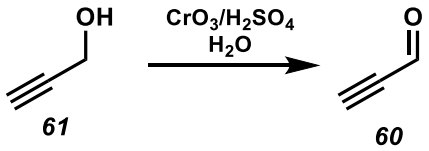



The title compound was prepared following a modification of a procedure described in literature.[43] To a flame dried round bottom flask equipped with stir bar, added starting material (1 equiv), $K_2CO_3$, KCl, $Pd(OAc)_2$ and ($n$-Bu)$_4$NOAc. The flask was evacuated and backfilled with argon three times. Degassed DMF (xx mL) was added to the flask, followed by acrolein diethyl acetal. The reaction flask was sealed and heated to 80 $^oC$ for 16 hours. After 16 hours, the flask was cooled and 3 M HCl was added to the reaction mixture. The reaction was allowed to stir for 30 minutes,

after which it was extracted with ethyl acetate. The organic phase was washed with brine, then dried over $MgSO_4$. The solvents were removed by rotary evaporation, after which the reaction mixture was purified by silica gel column chromatography using 10-30% ethyl acetate/hexanes as the eluent. The title compound was obtained as an orange oil in 60% yield (0.5321 g). **$^1$H-NMR** (600 MHz, chloroform-D) δ 9.72 (d, J = 7.2 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 15.8 Hz, 1H), 7.84 (q, J = 2.7 Hz, 3H), 7.80 (d, J = 5.5 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.71 (q, J = 2.7 Hz, 3H), 7.37 (t, J = 7.9 Hz, 1H), 7.28 (t, J = 7.4 Hz, 1H), 6.68 (q, J = 8.0 Hz, 1H), 3.93 (t, J = 7.9 Hz, 2H), 3.19 (t, J = 7.9 Hz, 2H), 1.67 (d, J = 8.2 Hz, 9H) **$^{13}$C-NMR** (151 MHz, chloroform-D) δ 193.7, 168.2, 150.3, 143.0, 136.9, 134.2, 132.1, 130.4, 129.5, 126.8, 123.6, 123.5, 123.4, 121.8, 119.7, 115.9, 85.2, 77.3, 77.1, 76.9, 37.4, 28.3, 24.4 **IR** 2979, 1711, 1684, 1455, 1396, 1362, 1327, 1253, 1148, 1107 **HRMS-ESI m/z** Calculated for $C_{18}H_{21}NO_3$ $[M + H]^+$ 445.1763, found 445.1751.

### 2.5.13 Synthesis of Propargyl Aldehyde

**propiolaldehyde (61)**




| Conditions | Result |
|---|---|
| 2 M Jones reagent (Sigma-Aldrich), acetone | Product formed, used crude |
| $CrO_3$ in 2:3 $H_2SO_4/H_2O$, 2-propanol | Distilled from crude, 0.5 M with SM |
| $CrO_3$ in 2:3 $H_2SO_4/H_2O$, DCM | Crude 0.02 M solution in DCM |
| $CrO_3$ in 2:3 $H_2SO_4/H_2O$, DCM | Distillation afforded no product |
| $CrO_3$ in $H_2SO_4/H_2O$<br>$H_2SO_4/H_2O$<br>*Reduced pressure oxidation* | 47% yield (pure)<br>400 mmol scale |

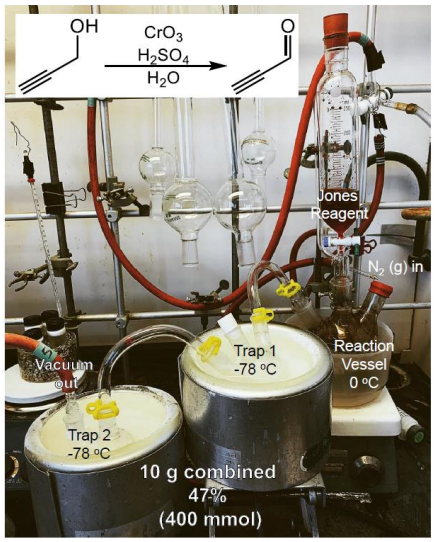
***Conditions for oxidation/distillation***

In a flame dried flask, added propargyl alcohol and reaction solvent (**61**). A two-neck flask was equipped with an addition funnel and cooled to -20 $^{o}$C in a salt water bath. Jones reagent was added to the funnel and added dropwise at a rate that ensured the internal temperature of the reaction mixture did not rise above -20 $^{o}$C. After addition of all the Jones reagent, the product was either distilled from the crude reaction mixture or extracted with DCM (when DCM was used as the reaction solvent) and then distilled from the solvent mixture. Product formation was observed by NMR, but pure product could not be obtained, as heating the solution led to polymerization of the product.

***Conditions for reduced pressure oxidation***

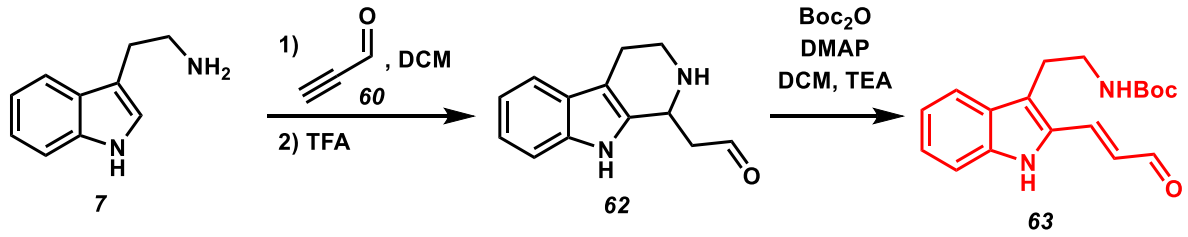
The title compound was prepared following a modification of literature procedures.[67] To a three-necked round bottom flask, added propargyl alcohol, sulfuric acid, and water. The center neck of the flask was equipped with an addition funnel and filled with a pre-mixed solution of chromium trioxide in water/sulfuric acid. A septum was placed into one of the other two necks, with a line connected to a low pressure of $N_2$ gas through the septum, with a sufficiently long needle that the nitrogen would bubble through the reaction solution. To the other neck of the round bottom flask, added a U-shaped glass tube with ground glass joints on either side. The other end of the tube was connected to a 3 neck round bottom flask (trap 1), with the middle neck sealed, and the other side connected to a second U-shaped tube. The other end was connected to a two-neck round bottom flask (trap 2). The unoccupied neck was connected to a variable pressure vacuum pump. The reaction vessel was cooled to -20 $^{o}$C in an ice/salt mixture. The two traps were then cooled to -78 $^{o}$C in dry ice/acetone baths. The pressure in the system was reduced to 40-60 mm Hg, and the oxidizing solution in the addition funnel was added dropwise to the reaction vessel, while stirring,

over the course of about 3 hours. The pressure was then reduced to 14-20 mm Hg, and the reaction mixture was allowed to warm to room temperature stirred for an additional 20 minutes. The traps were disconnected, sealed, and allowed to warm to room temperature. The combined contents of the traps were analyzed and found to be analytically nearly pure propargyl aldehyde. The aldehyde was used without further purification.




### 2.5.14 Double Michael Addition for Electrophile Synthesis

**(E)-tert-butyl (2-(2-(3-oxoprop-1-en-1-yl)-1H-indol-3-yl)ethyl)carbamate (63)**




To a flame dried vial, equipped with stir bar, added starting material and dichloromethane. The resulting slurry was cooled to 0 °C in an ice bath, and propargyl aldehyde was added, dropwise. The reaction was stirred for 5 minutes, after which TFA was added, slowly. The reaction was removed from the cooling bath and allowed to stir for 15 minutes. The reaction mixture was

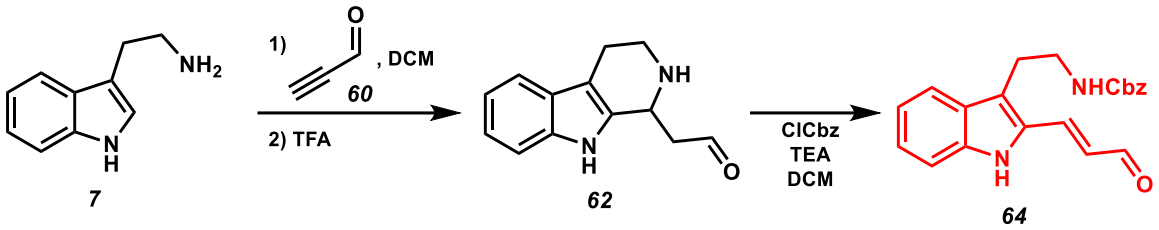
quenched with $H_2O$, then washed with $Na_2CO_3$ and brine, extracting with DCM each time. The combined organics were dried over $MgSO_4$, and the solvent removed by rotary evaporation.

The crude was immediately used in the next reaction without further purification.

The crude residue was dried under high vacuum for at least 1 hour, after which, a stir bar was added to the roundbottom flask. Dichloromethane was added to the flask, and the solution was stirred until the starting material fully dissolved. The reaction vessel was cooled to 0 $^oC$, and TEA was added as one portion, followed by $Boc_2O$, then DMAP. The solution changed color after addition of DMAP. The reaction was allowed to warm to room temperature and stirred for 4 hours. The reaction was quenched with $NH_4Cl$, and washed with water, then brine. The combined organic extracts were dried over $MgSO_4$, then the solvents were removed by rotary evaporation. The title compound was purified by column chromatography using 40-70% ethyl acetate/hexanes as eluent and obtained in 9% yield (2 steps, 173.2 mg).

**$^1$H-NMR** (600 MHz, chloroform-D) δ 9.20 (d, J = 7.6 Hz, 1H), 8.20 (s, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.26 (t, J = 7.9 Hz, 2H), 7.16 (d, J = 8.2 Hz, 1H), 5.81 (s, 1H), 5.45 (dd, J = 12.7, 7.9 Hz, 1H), 3.72 (s, 2H), 2.97-2.82 (m, 2H), 2.42 (s, 1H), 1.72 (s, 9H) **$^{13}$C-NMR** (151 MHz, chloroform-D) δ 190.3, 149.5, 136.3, 128.0, 125.4, 123.2, 118.5, 115.9, 115.3, 85.3, 77.6, 77.3, 77.1, 76.9, 45.0, 43.6, 28.2 **IR** 3368, 2970, 2360, 1734, 1706, 1606, 1454, 1419, 1365, 1220, 1141, 1115, 1045 $cm^{-1}$

**(E)-benzyl (2-(2-(3-oxoprop-1-en-1-yl)-1H-indol-3-yl)ethyl)carbamate (64)**




To a flame dried vial, equipped with stir bar, added starting material and dichloromethane. The resulting slurry was cooled to 0 °C in an ice bath, and propargyl aldehyde was added, dropwise. The reaction was stirred for 5 minutes, after which TFA was added, slowly. The reaction was removed from the cooling bath and allowed to stir for 15 minutes. The reaction mixture was quenched with $H_2O$, then washed with $Na_2CO_3$ and brine, extracting with DCM each time. The combined organics were dried over $MgSO_4$, and the solvent removed by rotary evaporation.

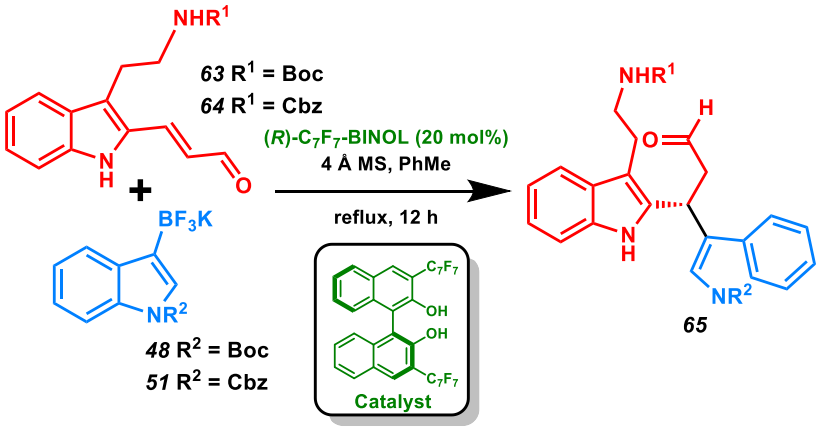
The crude was immediately used in the next reaction without further purification.

The crude residue was dried under high vacuum for at least 1 hour, after which, a stir bar was added to the roundbottom flask. Dichloromethane was added to the flask, and the solution was stirred until the starting material fully dissolved. The reaction vessel was cooled to 0 °C, and TEA was added as one portion, followed by dropwise addition of ClCbz. The reaction was allowed to warm to room temperature and stirred for 5 hours. The reaction was quenched with $NH_4Cl$, and washed with water, then brine. The combined organic extracts were dried over $MgSO_4$, then the solvents were removed by rotary evaporation. The title compound was purified by column chromatography using 40-70% ethyl acetate/hexanes as eluent and obtained as an orange solid in 58% yield (2 steps, 124.8 mg).

**$^1$H-NMR** (500 MHz, chloroform-D) δ 9.42 (d, J = 7.4 Hz, 1H), 8.16-8.03 (m, 2H), 7.43 (d, J = 28.1 Hz, 4H), 7.35 (d, J = 8.0 Hz, 3H), 7.19 (t, J = 7.4 Hz, 1H), 7.06 (s, 1H), 6.97 (s, 1H), 5.72 (q, J = 7.3 Hz, 1H), 5.19 (s, 2H), 3.88 (t, J = 7.7 Hz, 2H), 3.02 (t, J = 7.7 Hz, 2H) **$^{13}$C-NMR** (126

MHz, chloroform-D) δ 192.1, 150.4, 136.3, 134.8, 129.0, 128.9, 128.8, 128.6, 127.2, 122.3, 119.8, 118.6, 111.7, 111.4, 111.2, 77.4, 77.2, 76.9, 69.6, 46.1, 36.7, 29.8, 24.8, 23.0, 14.3 **IR** 3390, 2959, 1704, 1619, 1456, 1414, 1358, 1221, 1185, 1143, 1092 $cm^{-1}$ **HRMS-ESI m/z** Calculated for $C_{21}H_{21}N_2O_3$ $[M + H]^+$ 349.1552, found 349.1539.

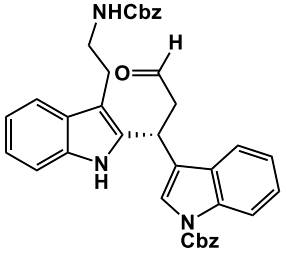
### 2.5.15 Conjugate Addition




| Entry | $R^1$ | $R^2$ | Result |
|---|---|---|---|
| *a* | Boc | Boc | 0% (and protodeboronation) |
| *b* | Cbz | Boc | 0% (and protodeboronation) |
| *c* | Cbz | Cbz | ~20% (not to completion) |

To a 4-dram vial equipped with a stir bar, added 4 Å MS (250 mg/0.2 mmol). The vial was flame dried under high vacuum. The vial was cooled to room temperature and placed under an argon atmosphere. The starting material, indole trifluoroborate salt, and catalyst were added to the vial. Toluene was added to the vial, which was then well sealed and heated to 80 °C for the indicated time. Following reaction completion, the reaction mixture was filtered through celite, washing well with ethyl acetate. The solvents were removed by rotary evaporation.

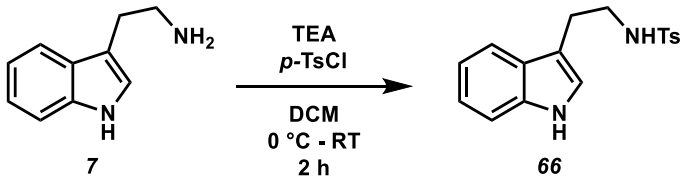
**(R)-benzyl 3-(1-(3-(2-(((benzyloxy)carbonyl)amino)ethyl)-1H-indol-2-yl)-3-oxopropyl)-1H-indole-1-carboxylate (65)**




The product was purified by silica gel column chromatography, using 1-10% ethyl acetate/hexanes as eluent. The title compound was obtained as a colorless oil in 17% yield (6.8 mg). **$^1$H-NMR** (500 MHz, chloroform-D) δ 9.20-9.33 (0H), 7.30-7.71 (10H), 6.89-7.22 (6H), 6.56-6.80 (1H), 5.15-5.32 (2H), 3.87-3.97 (1H), 3.31-3.59 (1H), 3.11-3.31 (1H), 2.89-3.05 (1H), 1.10-1.32 (3H), *preliminary result*

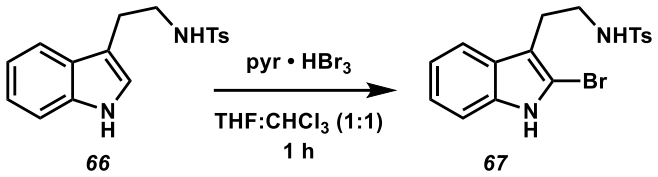
### 2.5.16 Alternate Electrophile

**N-(2-(1H-indol-3-yl)ethyl)-4-methylbenzenesulfonamide (66)**




The title compound was prepared following a procedure reported in literature. Spectral data were identical to those reported in literature.[64]

**N-(2-(2-bromo-1H-indol-3-yl)ethyl)-4-methylbenzenesulfonamide (66)**



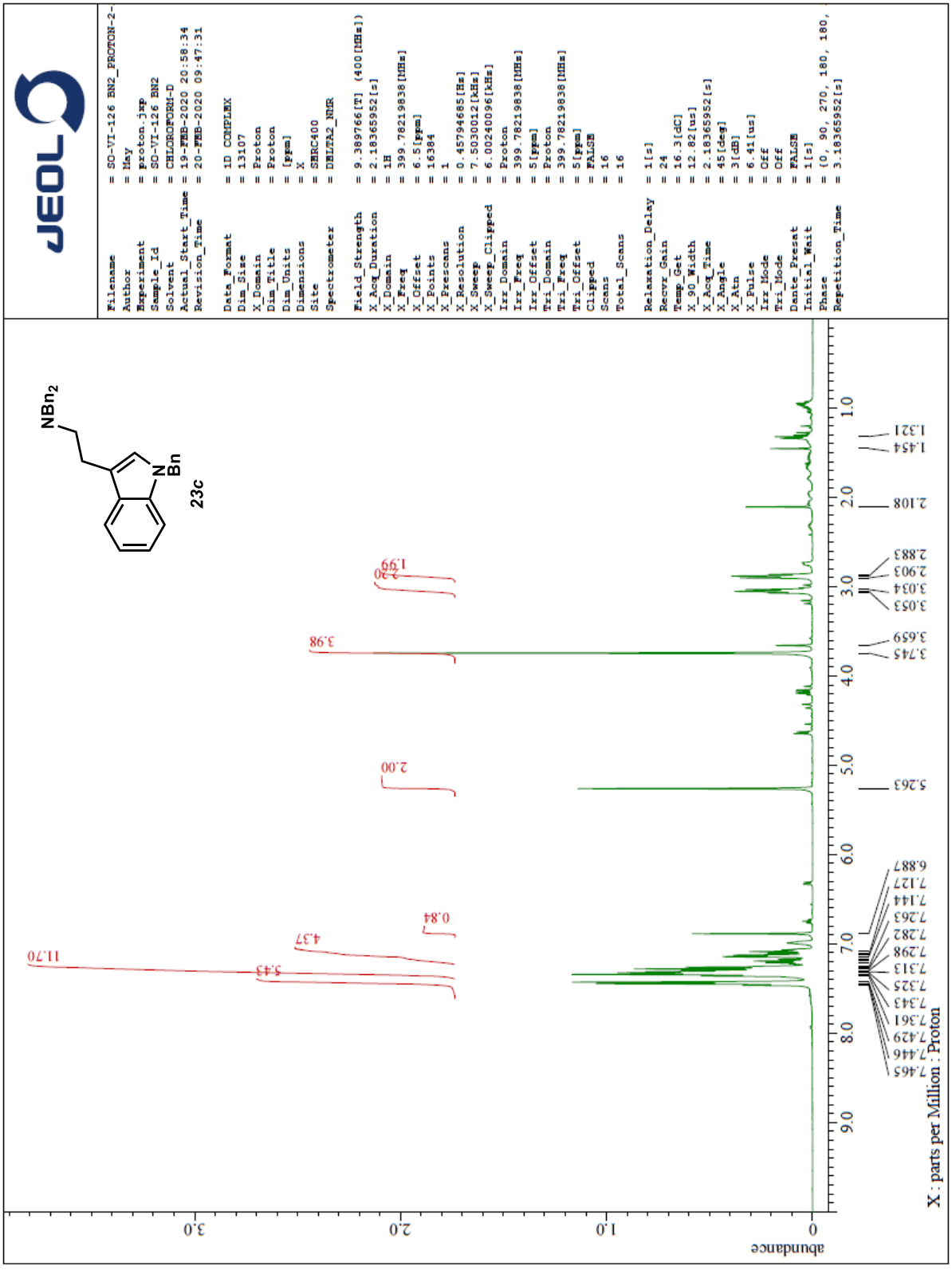

*66* *67*

The title compound was prepared following a procedure reported in literature. Spectral data were identical to those reported in literature.[64]

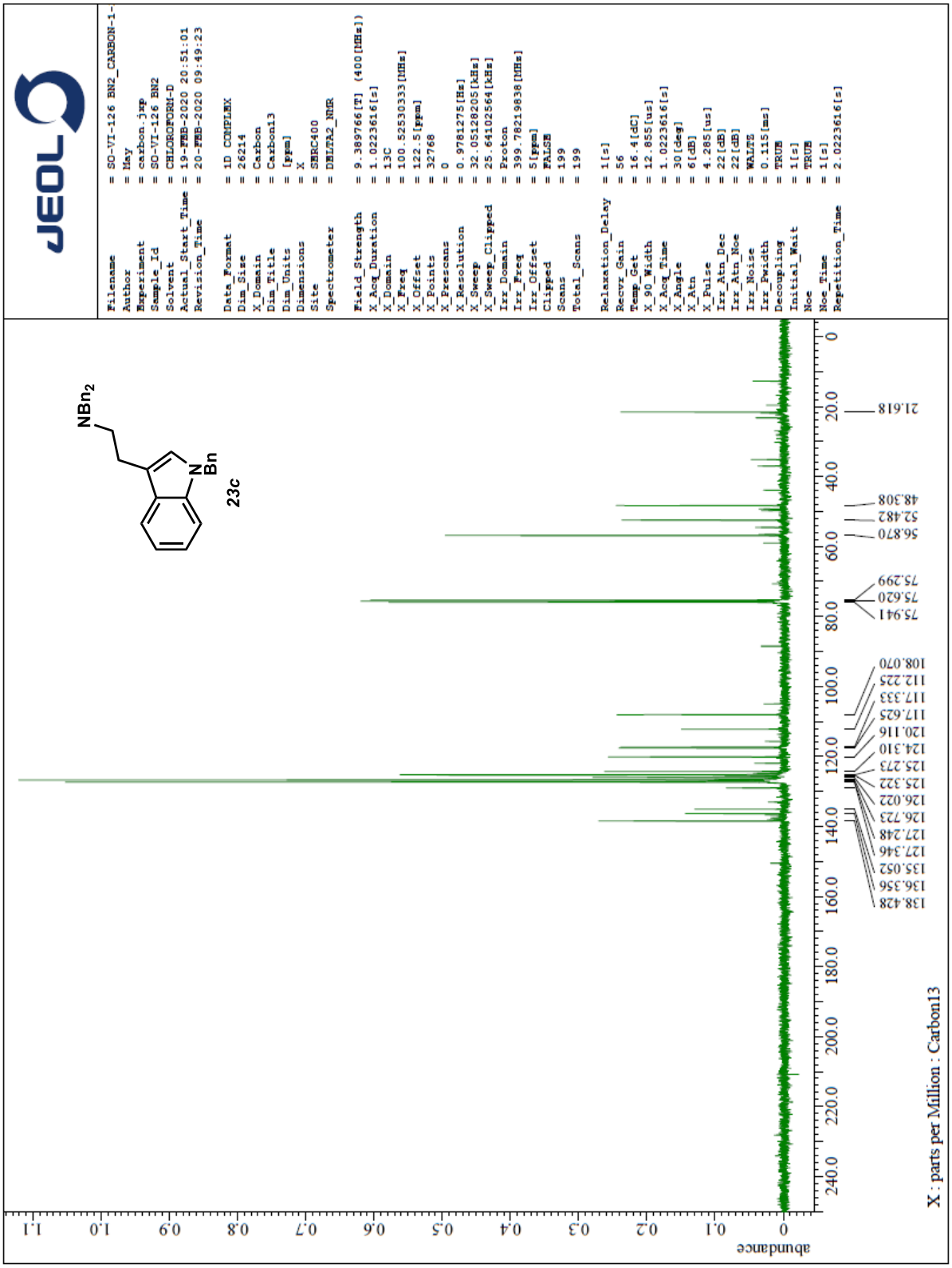
**APPENDIX – CHAPTER TWO**

Spectra Relevant to Chapter Two

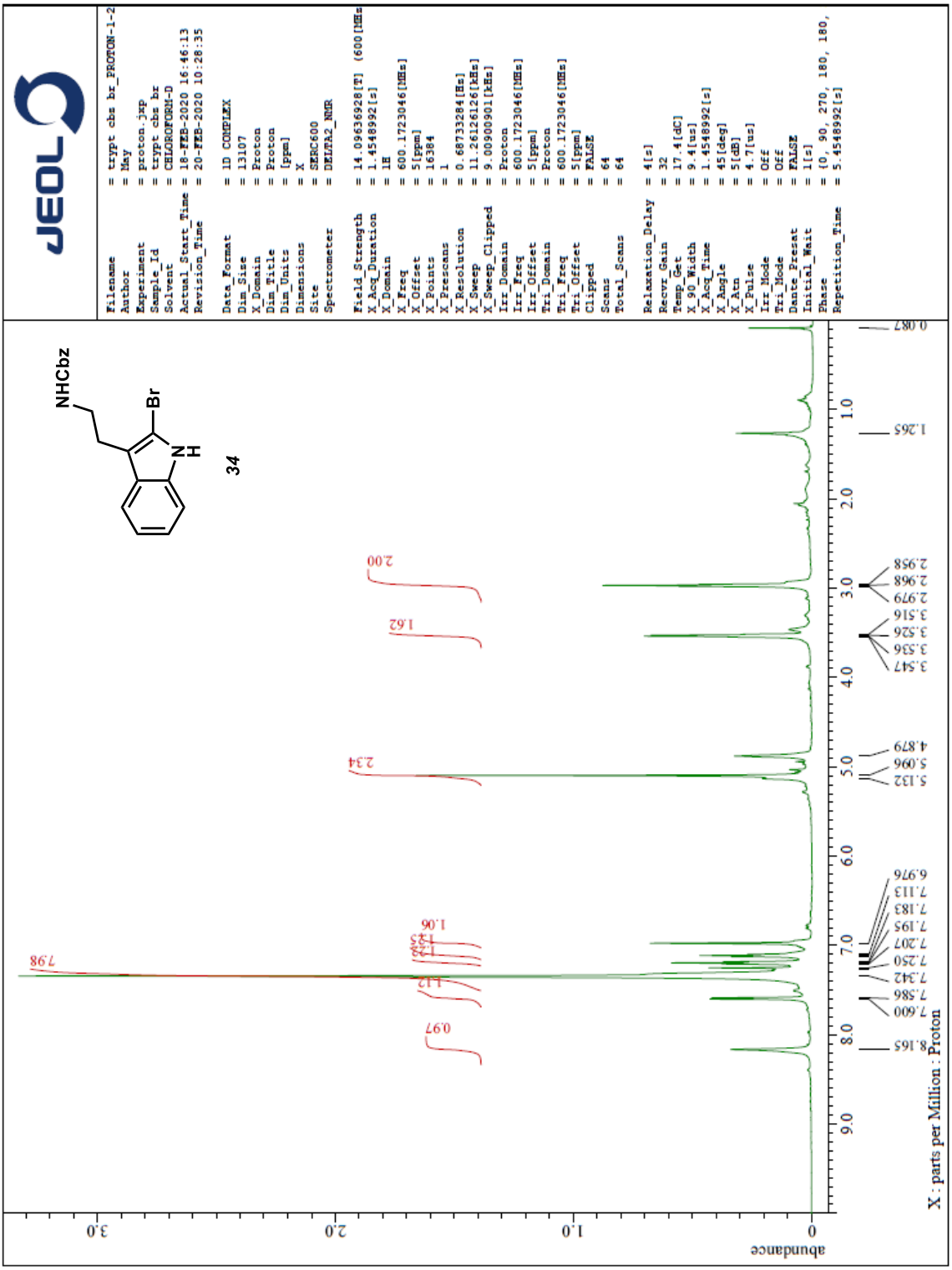
# Organocatalyzed Conjugate Addition for the Synthesis of Mucronatins A and B



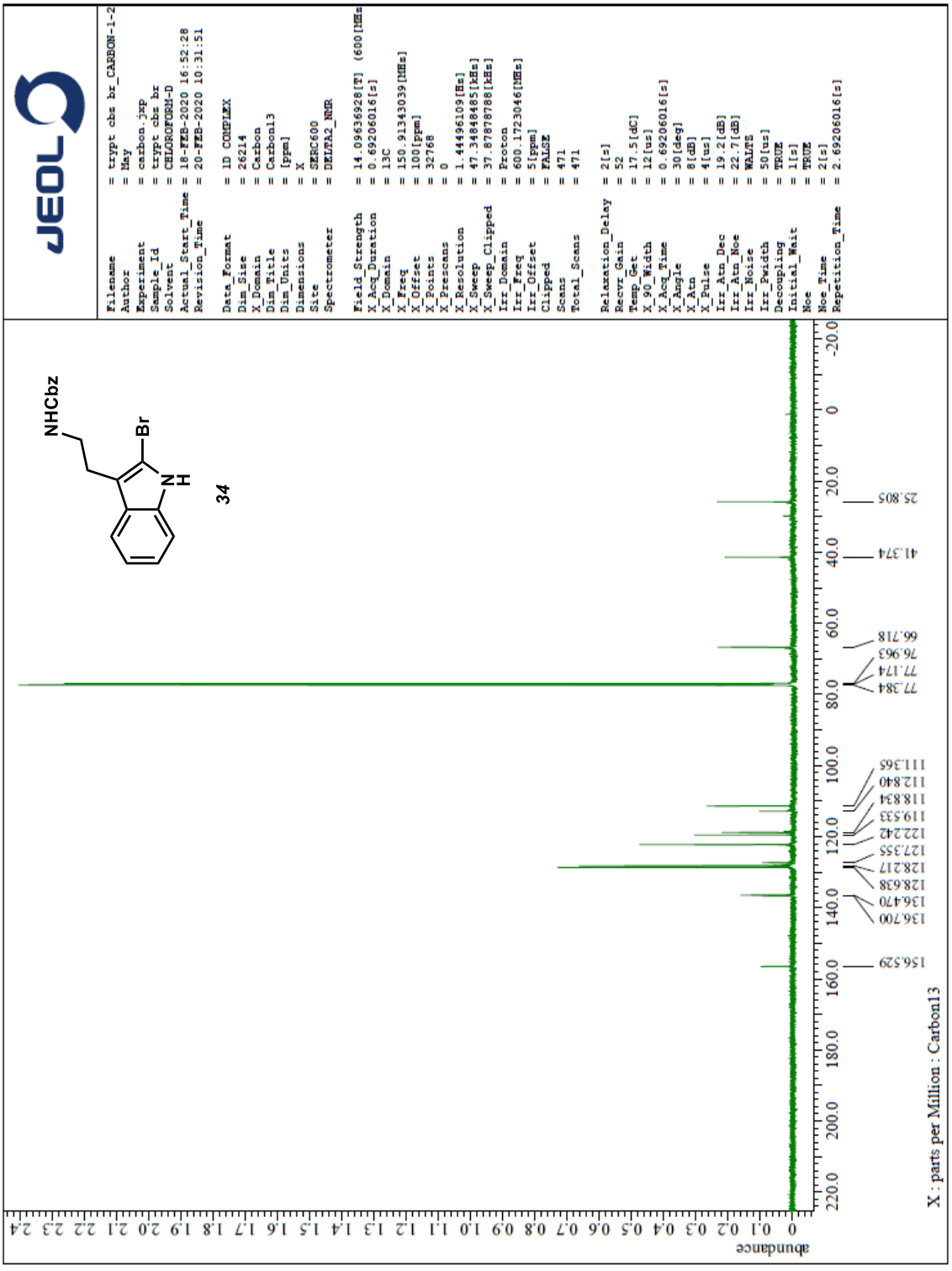

**$^{1}$H NMR of *N*-benzyl-2-(1-benzyl-1*H*-indol-3-yl)ethanamine (23c)**



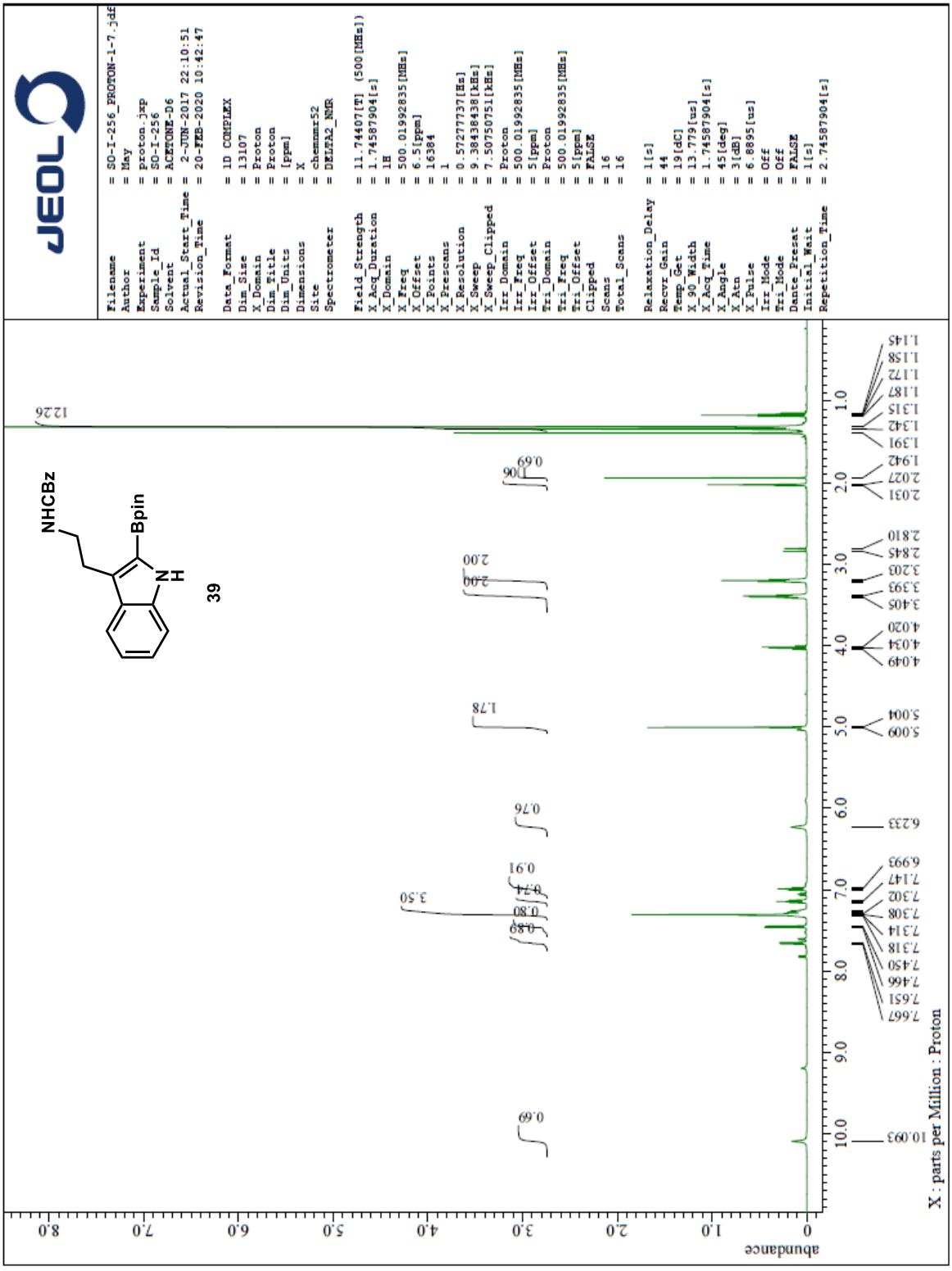

**$^{13}$C NMR of N-benzyl-2-(1-benzyl-1H-indol-3-yl)ethanamine (23c)**



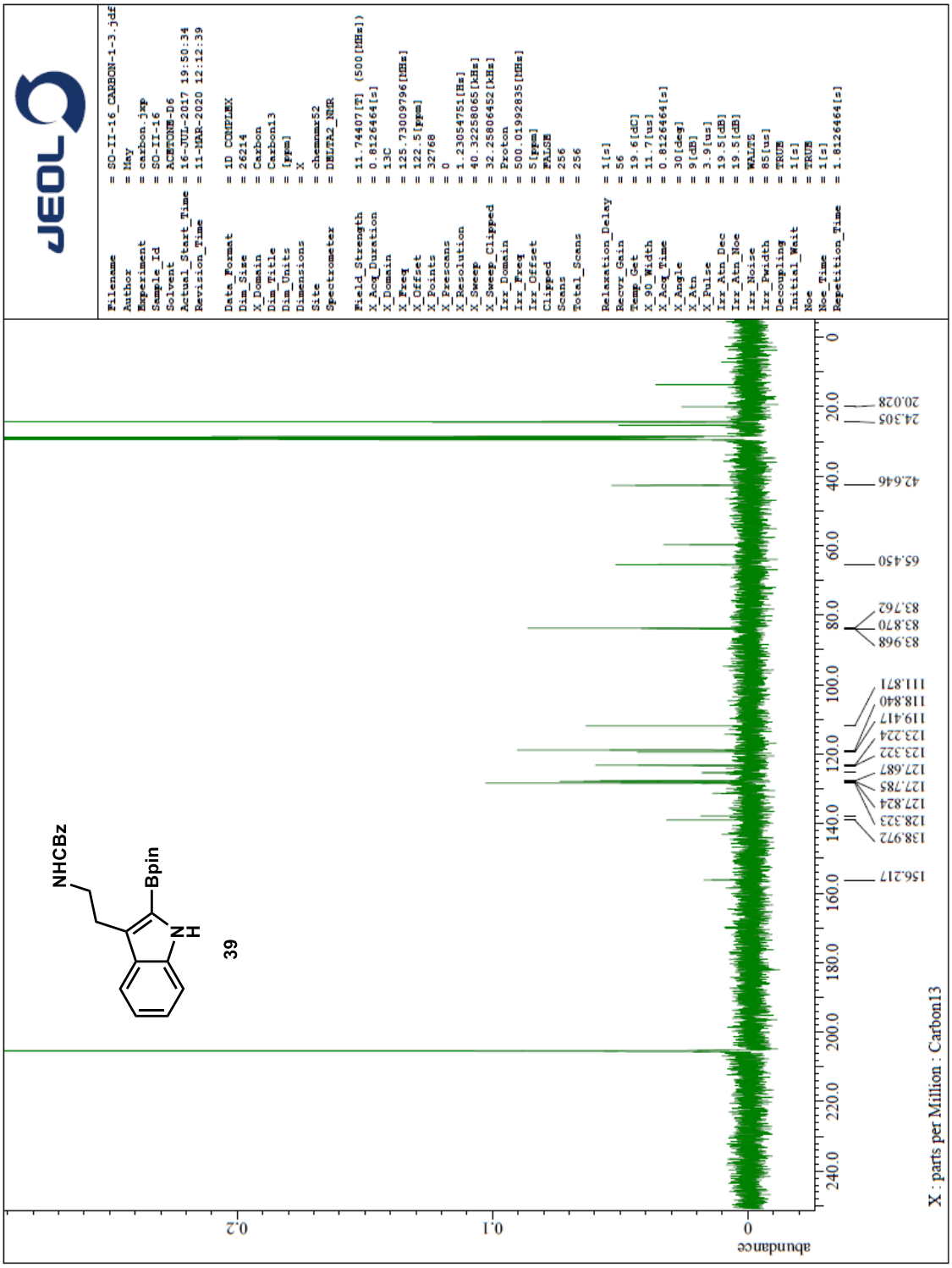

**$^{1}$H NMR of benzyl (2-(2-bromo-1H-indol-3-yl)ethyl)carbamate (34)**



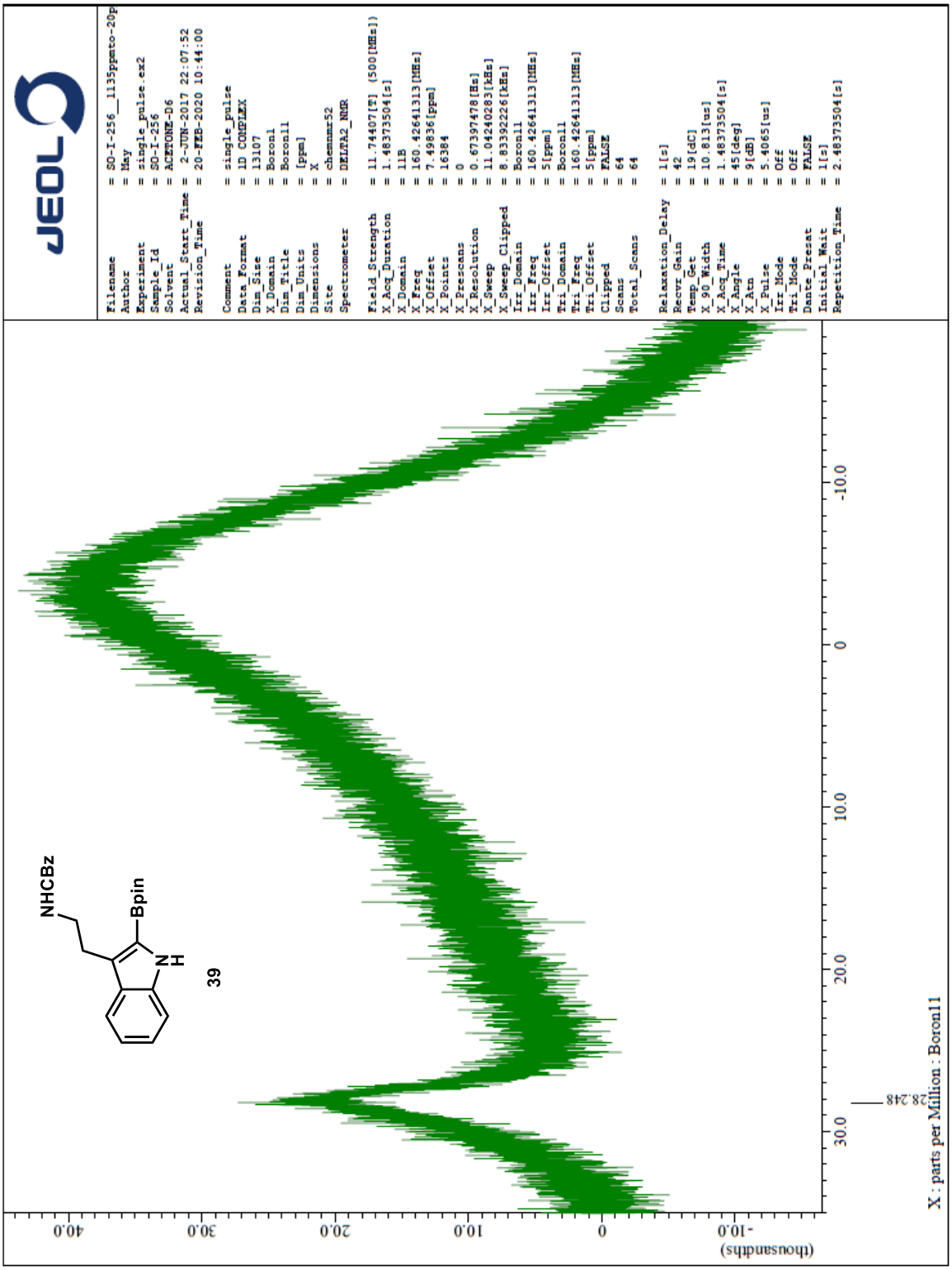

**$^{13}$C NMR of benzyl (2-(2-bromo-1H-indol-3-yl)ethyl)carbamate (34)**



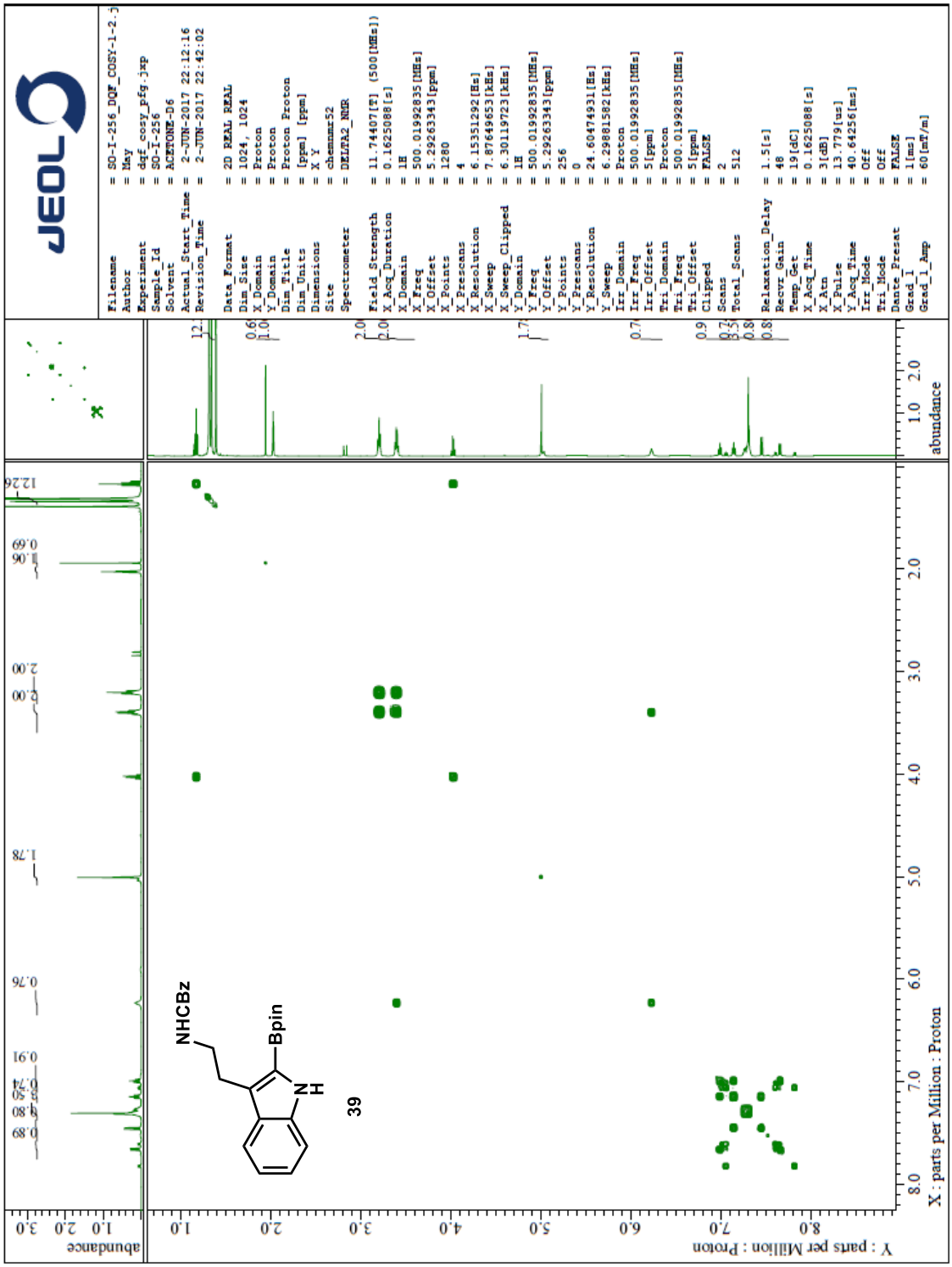

**$^{1}$H NMR of benzyl (2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)ethyl)carbamate (39)**



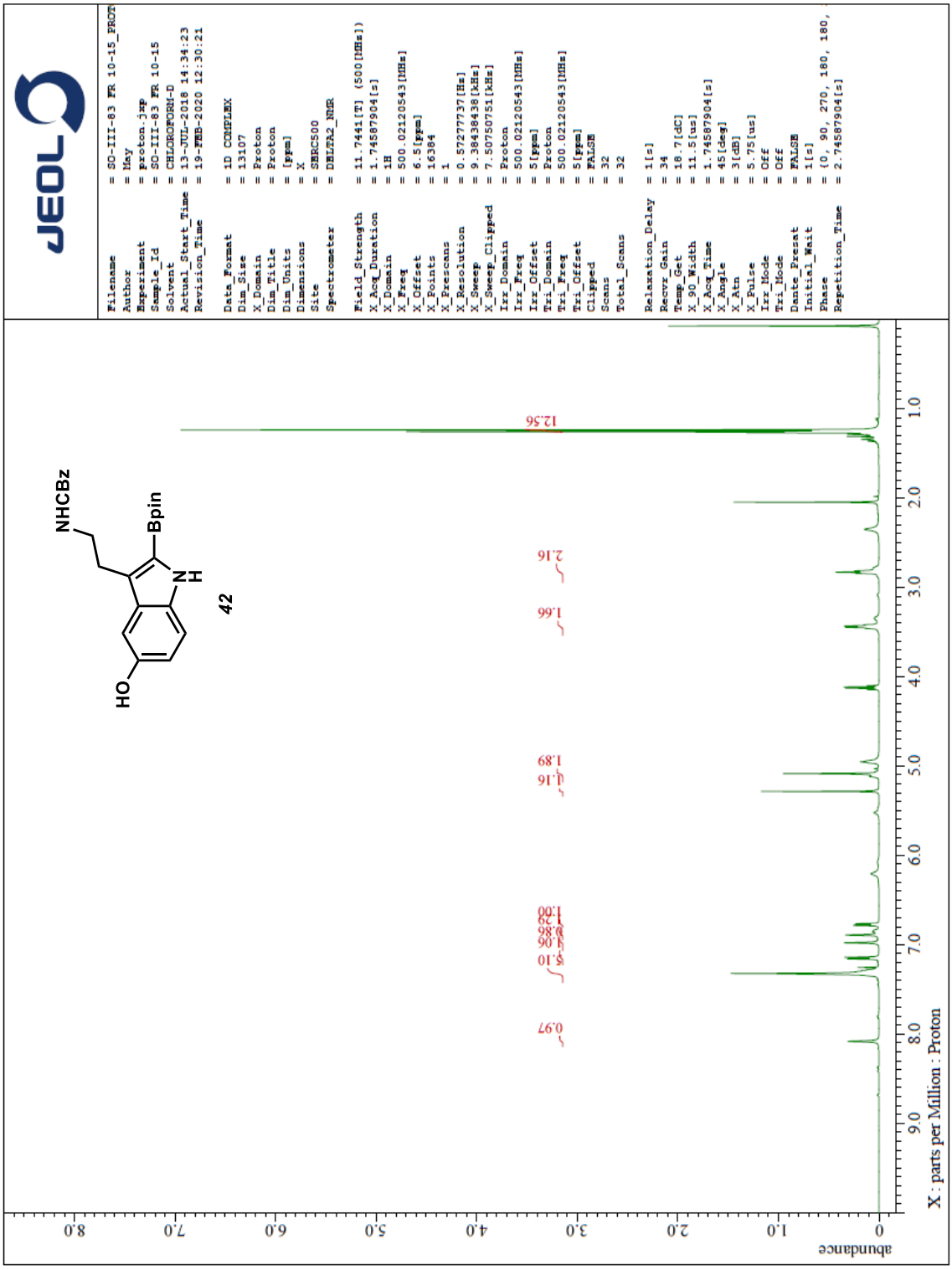

**$^{13}$C NMR of benzyl (2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)ethyl)carbamate (39)**



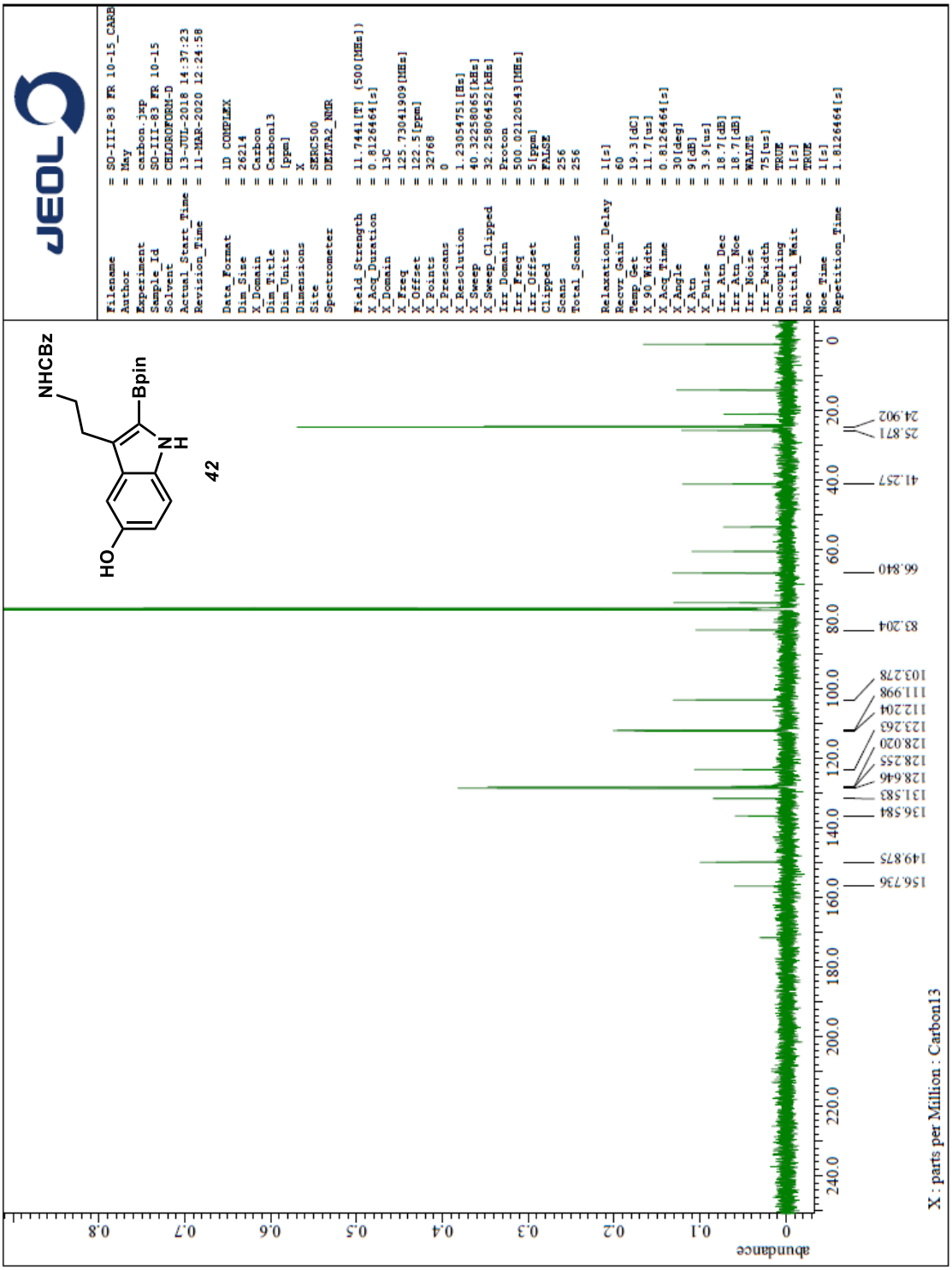

**$^{11}$B NMR Spectrum of benzyl (2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)ethyl)carbamate (39)**



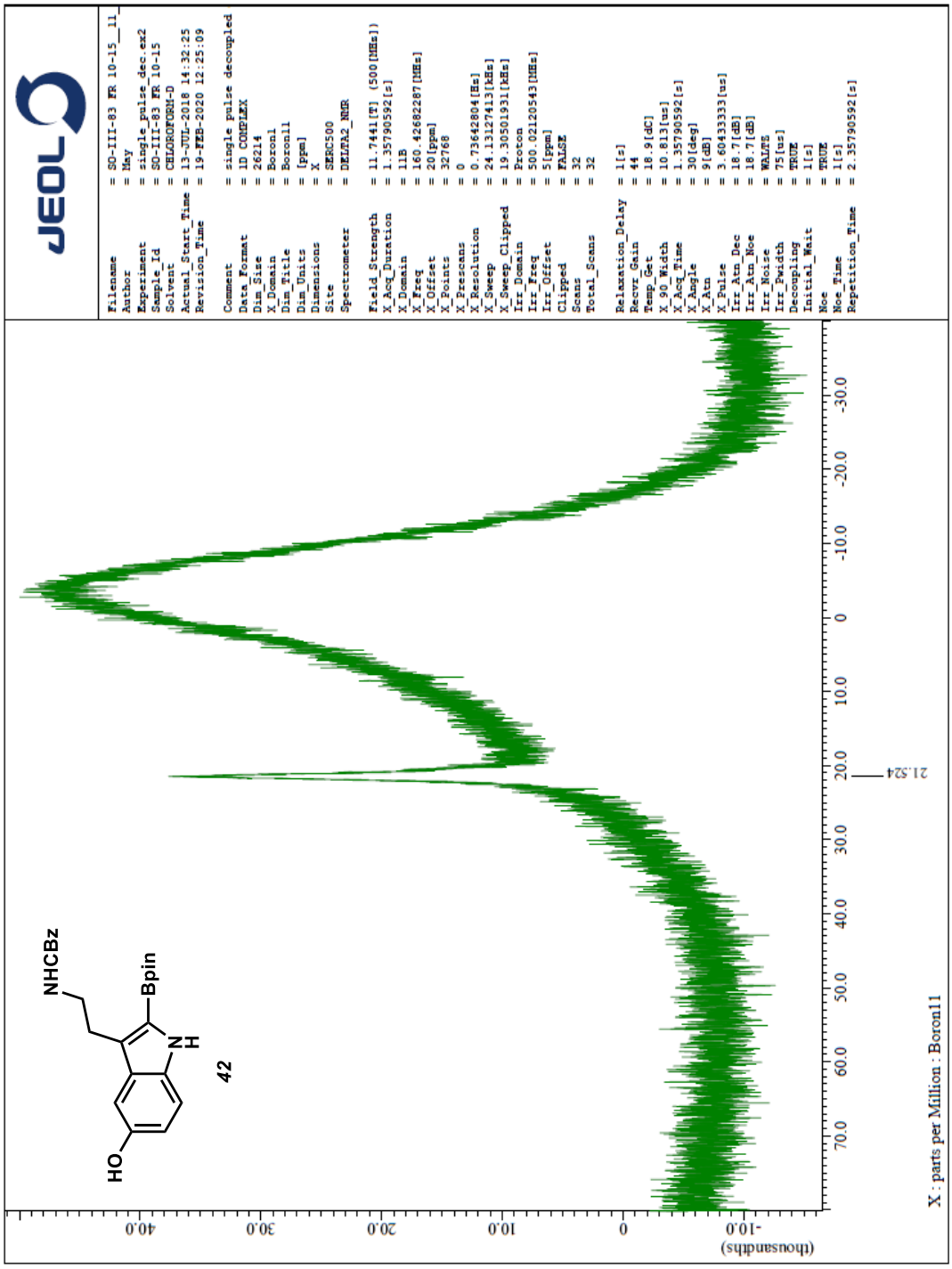

**$^{1}$H-$^{1}$H COSY NMR Spectrum of benzyl (2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)ethyl)carbamate (39)**



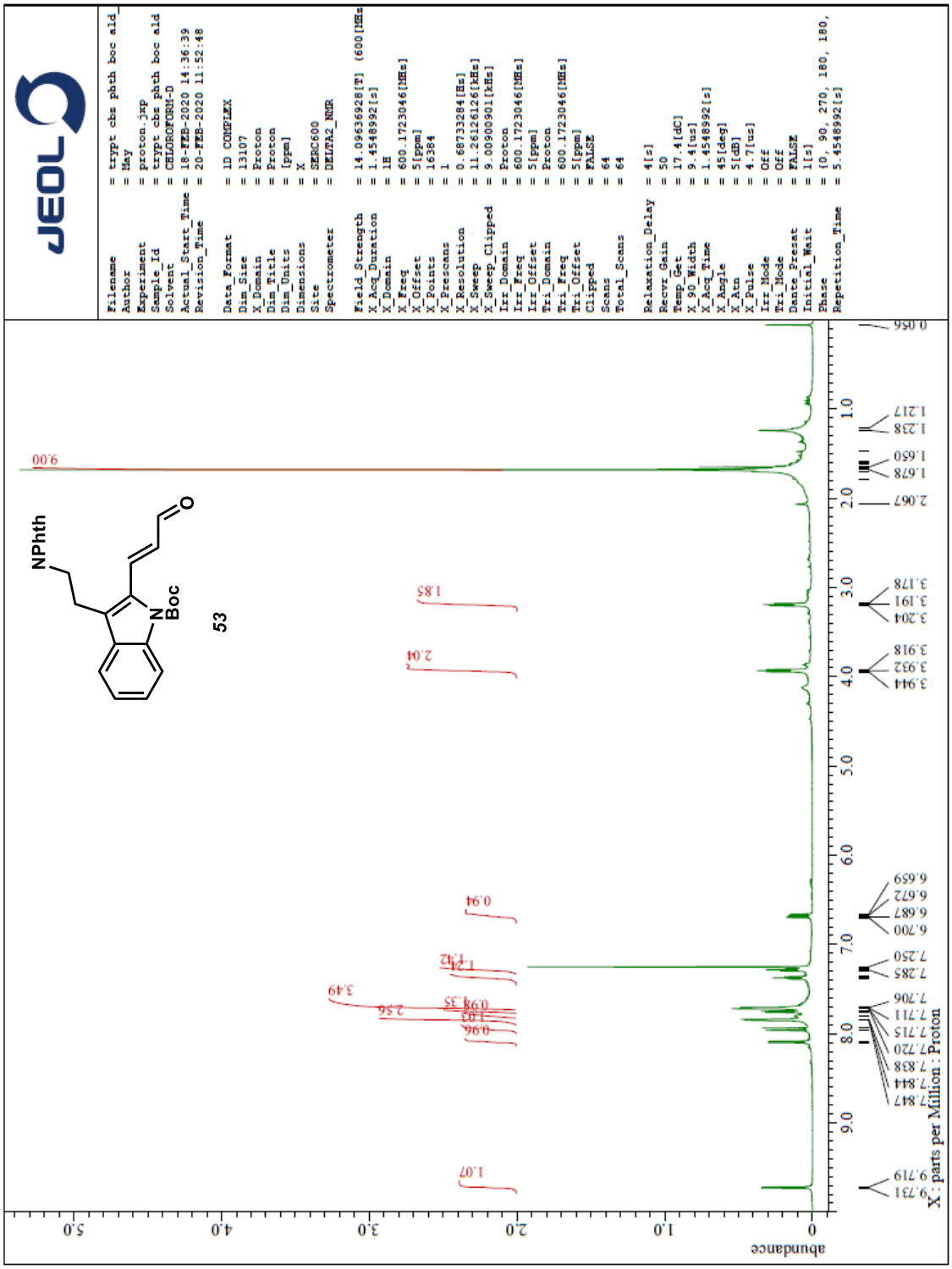

**$^{1}$H NMR of benzyl (2-(5-hydroxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)ethyl)carbamate (42)**



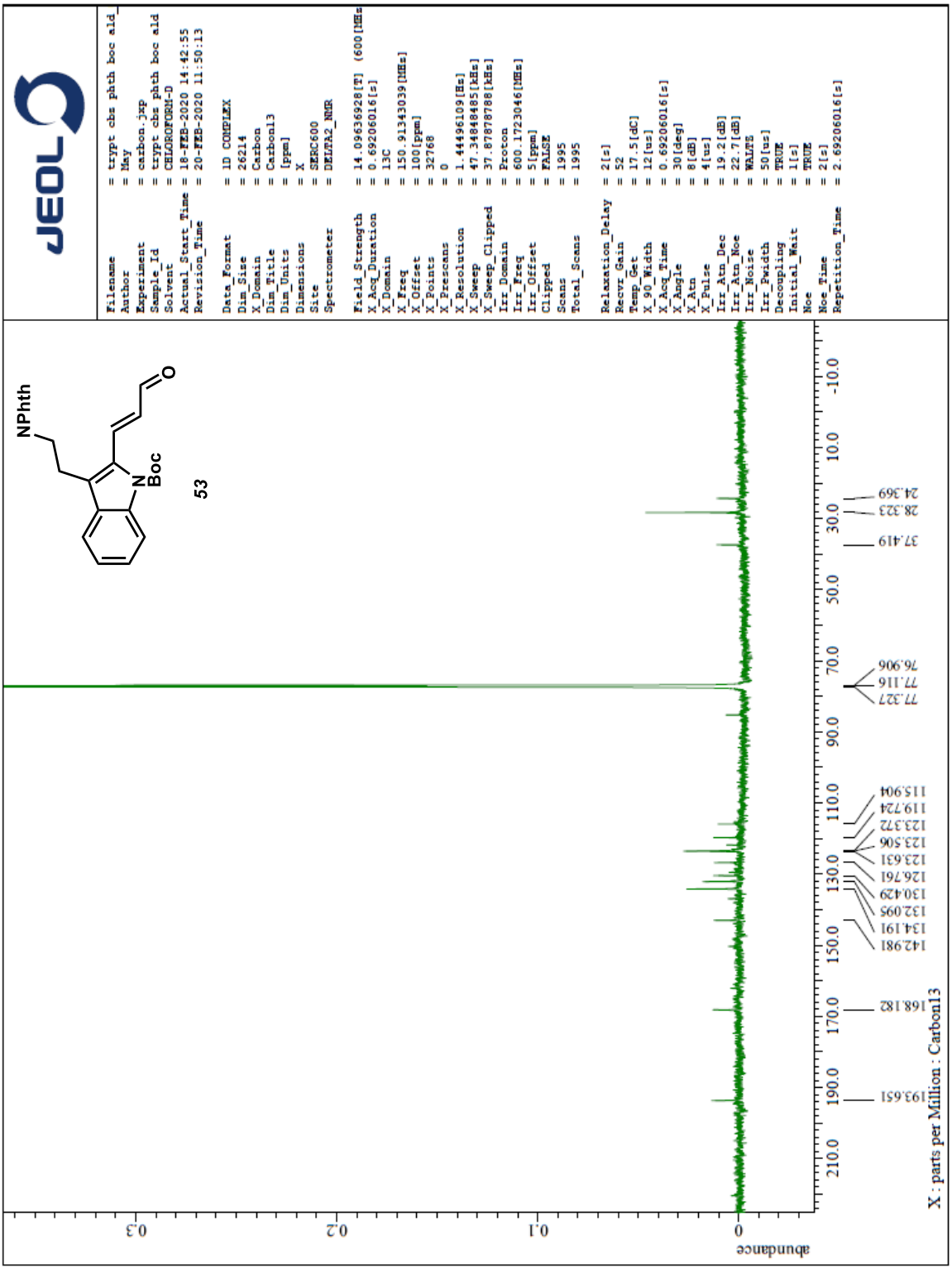

**$^{13}$C NMR of benzyl (2-(5-hydroxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)ethyl)carbamate (42)**



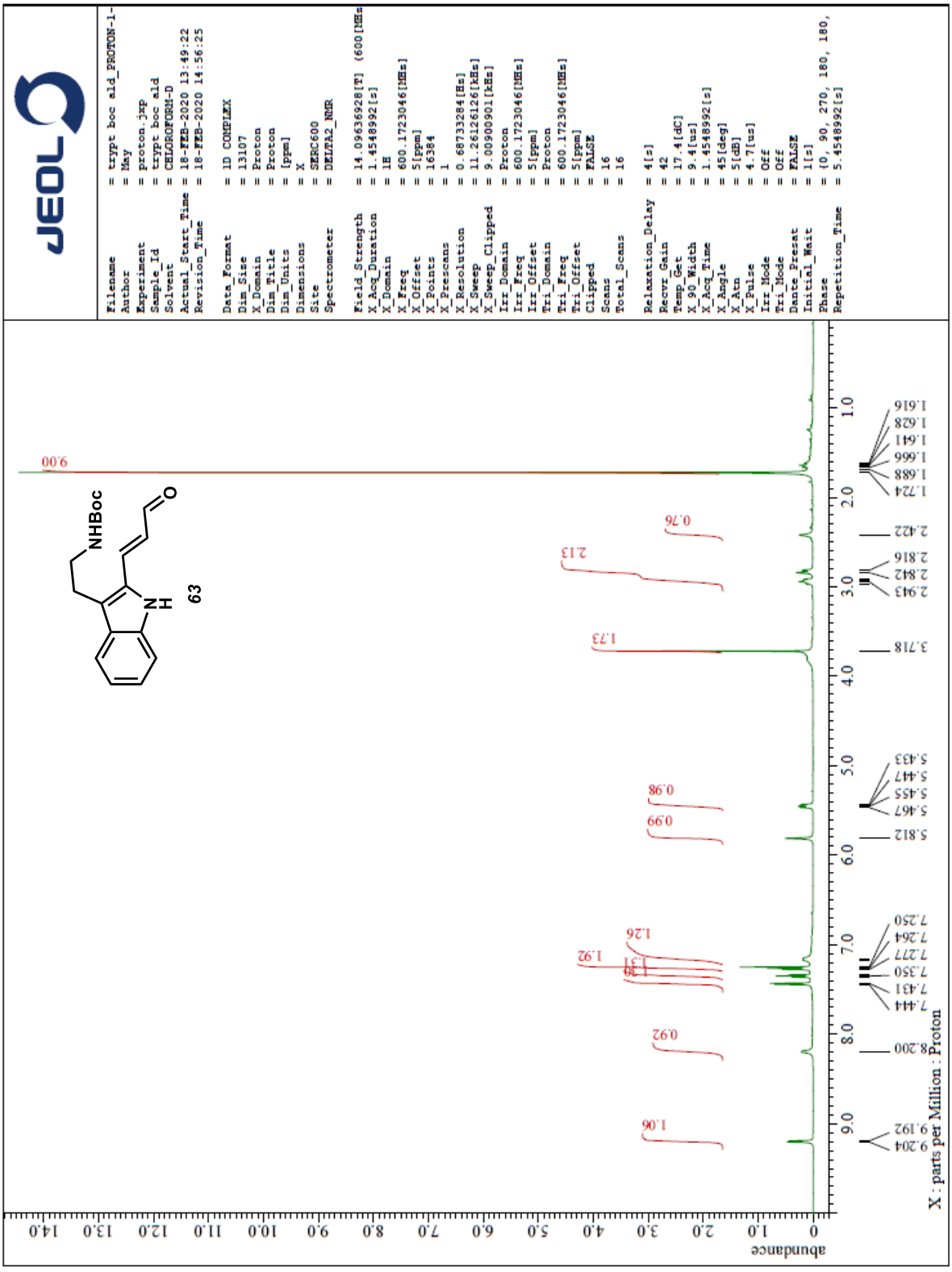

**$^{11}$B NMR Spectrum of benzyl (2-(5-hydroxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)ethyl)carbamate (42)**



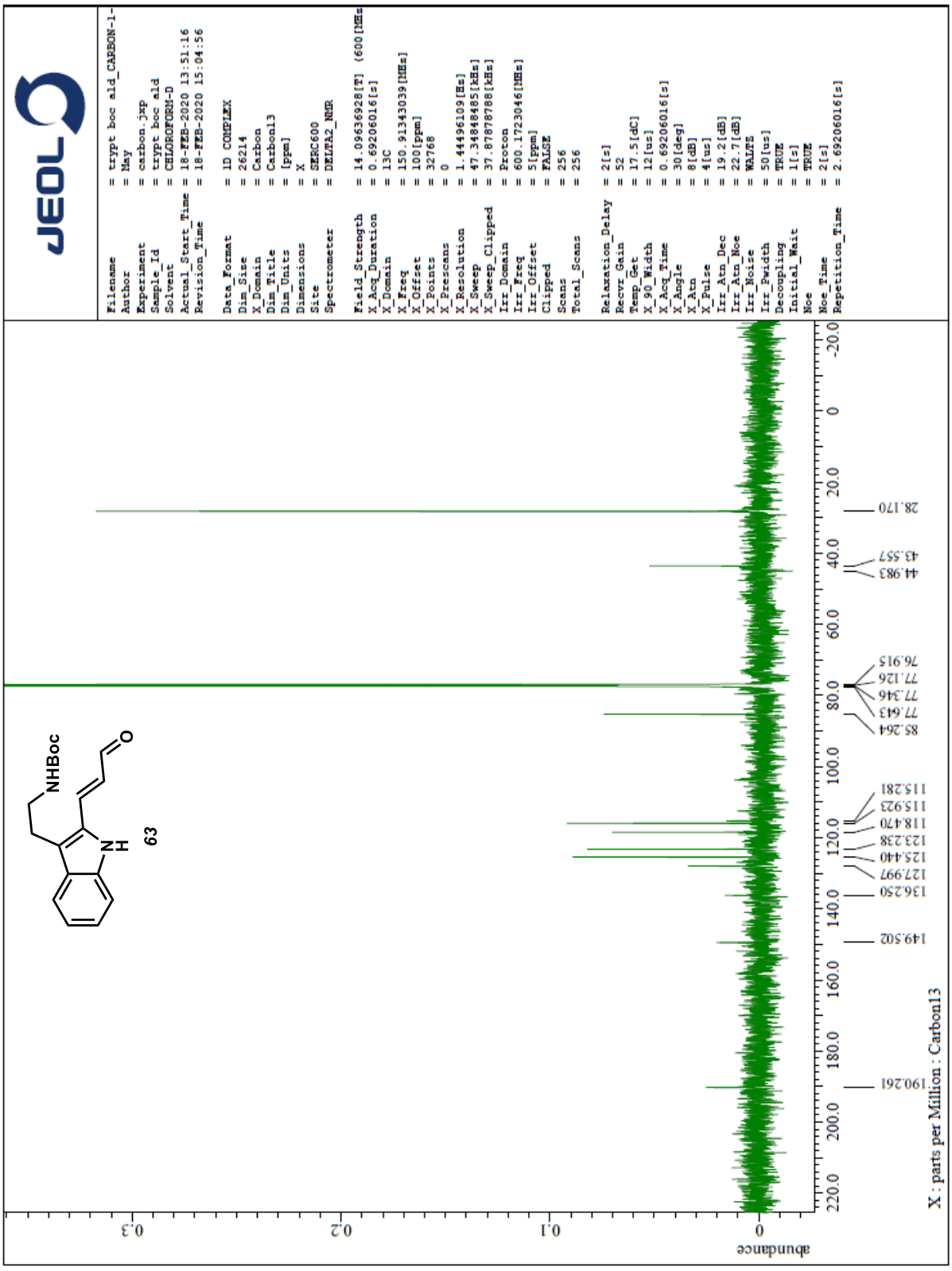

**$^{1}$H NMR of (E)-tert-butyl 3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-(3-oxoprop-1-en-1-yl)-1H-indole-1-carboxylatecarboxylate (53)**



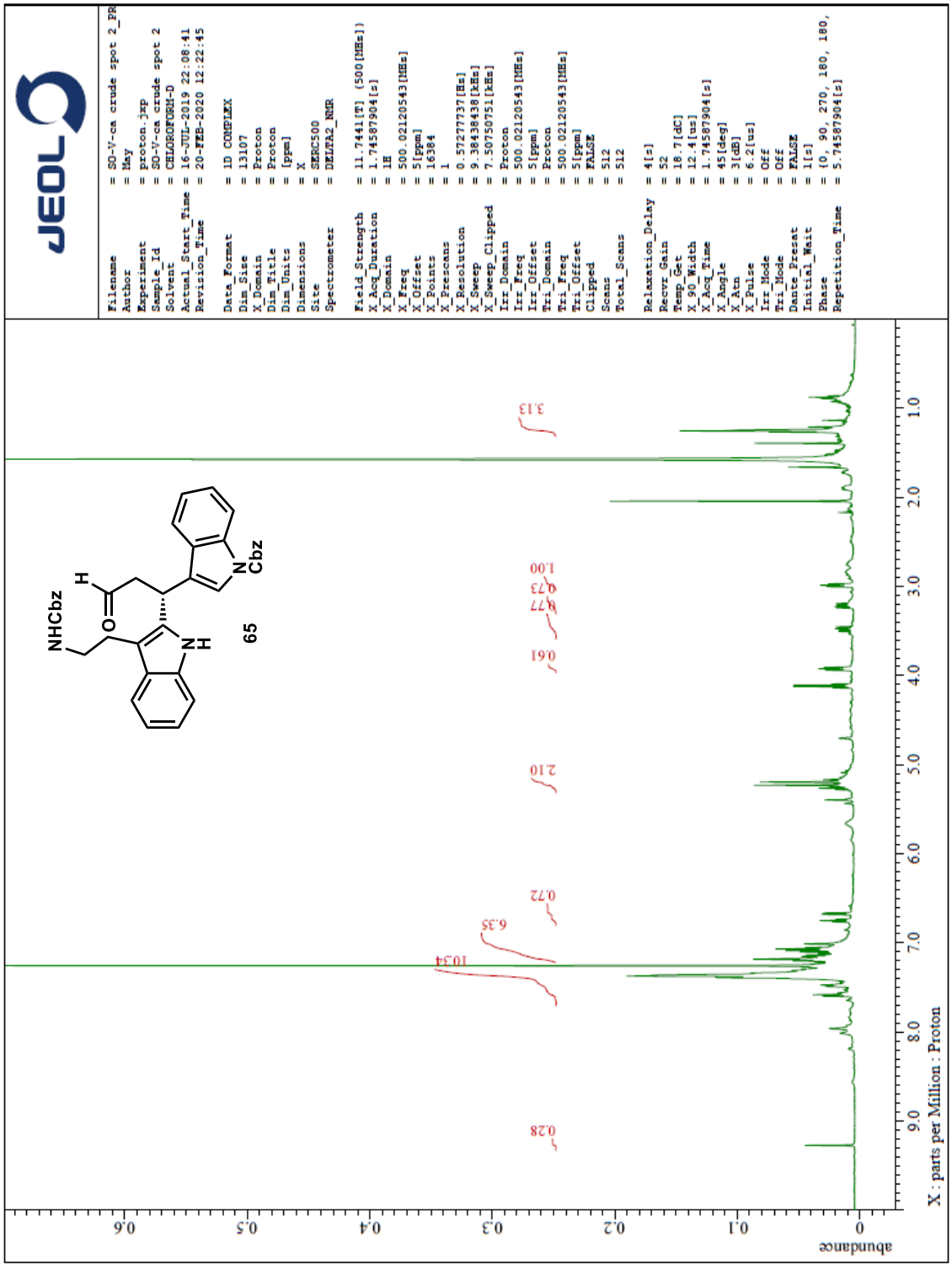

**$^{13}$C NMR of (E)-tert-butyl 3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-(3-oxoprop-1-en-1-yl)-1H-indole-1-carboxylatecarboxylate (53)**



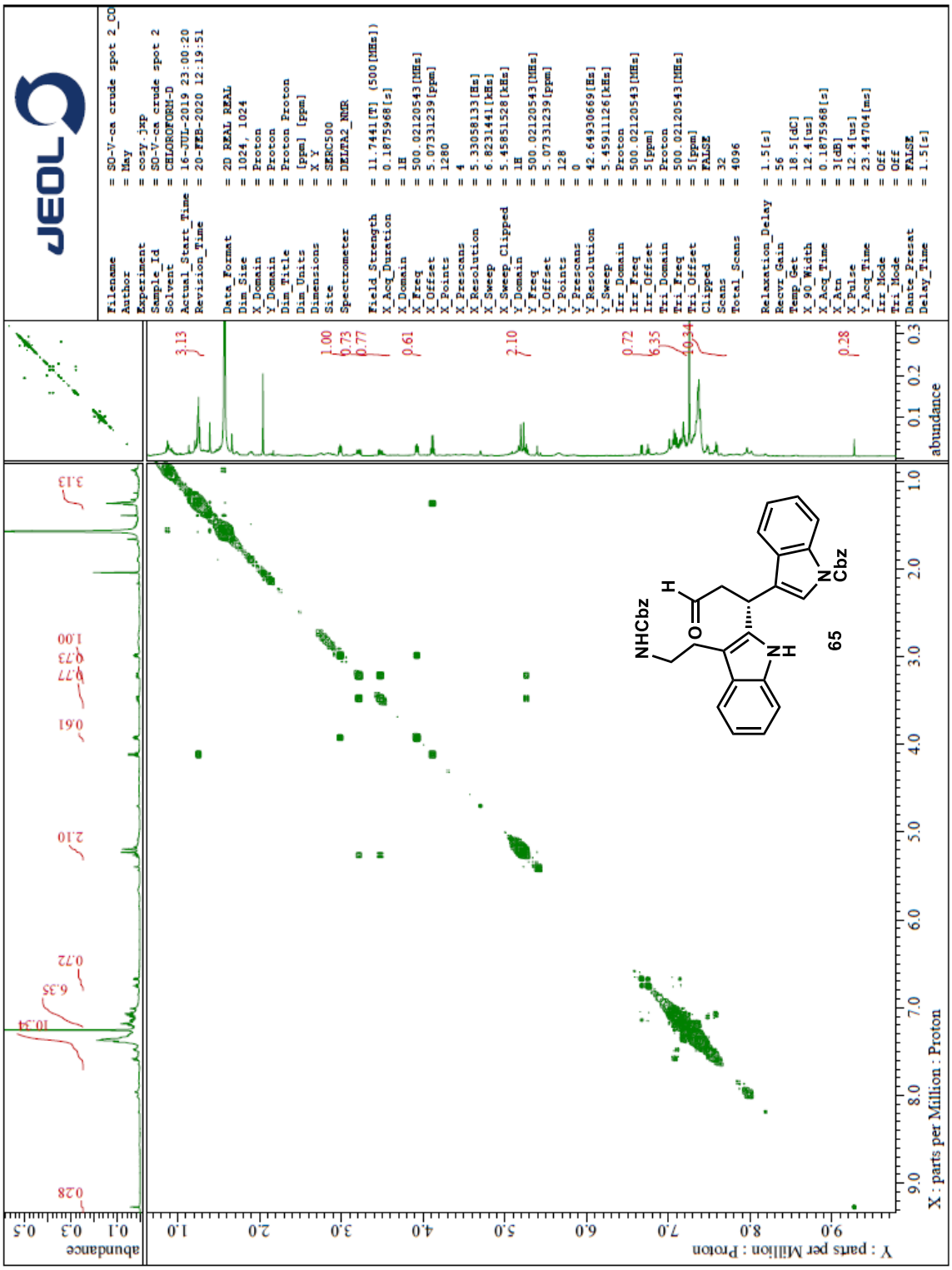

**$^{1}$H NMR of (E)-tert-butyl (2-(2-(3-oxoprop-1-en-1-yl)-1H-indol-3-yl)ethyl)carbamate (63)**




**$^{13}$C NMR of (E)-tert-butyl (2-(2-(3-oxoprop-1-en-1-yl)-1H-indol-3-yl)ethyl)carbamate (63)**




**$^{1}$H NMR of (R)-benzyl 3-(1-(3-(2-(((benzyloxy)carbonyl)amino)ethyl)-1H-indol-2-yl)-3-oxopropyl)-1H-indole-1-carboxylate (65)**




**$^{1}$H-$^{1}$H COSY NMR Spectrum of (*R*)-benzyl 3-(1-(3-(2-(((benzyloxy)carbonyl)amino)ethyl)-1*H*-indol-2-yl)-3-oxopropyl)-1*H*-indole-1-carboxylate (65)**

## CHAPTER 3: OTHER INDOLYL-PROPYLENE GLYCOL NATURAL PRODUCTS

In addition to the total syntheses of mucronatin A and B, we are working on completing the total synthesis of discoipyrrole D by modifying the approach proposed originally[43] but relying on different protecting groups (Figure 3.1). A third target, cytoblastin[1], has been synthesized (and the natural diastereomer identified) by the Kishi group,[80] but with a high step count and low overall yields. We anticipate that our key conjugate addition step will allow for the synthesis of both discoipyrrole D and cytoblastin in high yields, with high selectivity, and a lower step count.

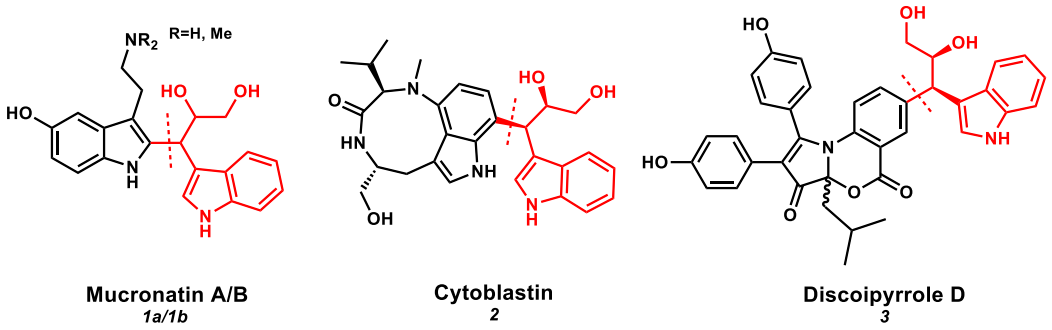



**Figure 3.1.** Indolyl-propylene glycol natural products.

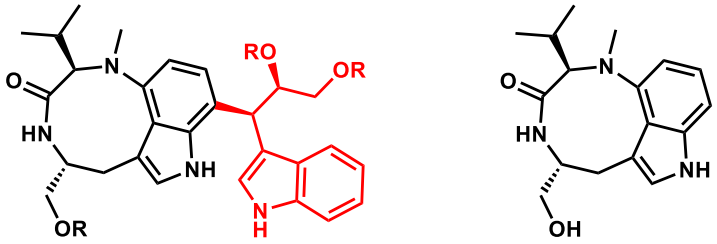
### 3.1. Cytoblastin

#### 3.1.1. Isolation and Activity

Cytoblastin was isolated from bacterial cultures of *Streptoveticillium eurocidicum* in 1991 and was found to be a promising biologically active compound.[81] The compound was isolated along with two corresponding structures, triacetylcytoblastin (**4**), a structural analogue, and indolactam V (**5**),[82] presumably a precursor. Extensive NMR studies were performed to determine the connectivity of the discovered compound. Structural similarities were drawn to indolactam V and the teleocidin class of compounds,[83,84] both of which are known tumor-promoters and

[1] Cytoblastin shares a name with a commercial drug used in the treatment of cancer, in which the active ingredient is vinblastine. The structures both contain diindole cores, but vinblastine is related to vincristine, not cytoblastin or indolactam V.

inflammatory agents. However, cytoblastin did not exhibit either of these properties, but did increase proliferation of T cells. These promising results led to synthetic interest in the molecule.



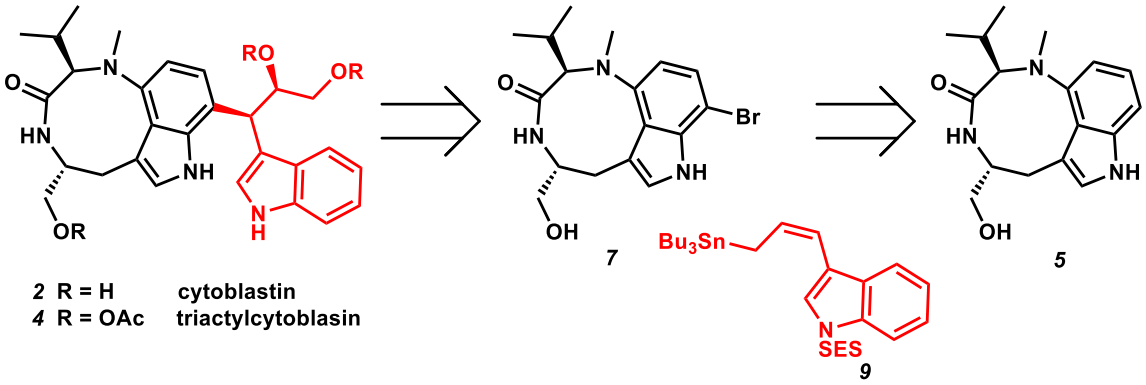

*3* R = H cytoblastin
*4* R = OAc triactylcytoblasin

indolactam v
*5*

**Figure 3.2.** Cytoblastin and associated isolated compounds

### 3.1.2 Kishi's Synthesis and Stereochemical Determination

Due to similarities in structure to indolactam V (**5**), the Kishi group proposed that the corresponding portion of cytoblastin (**2**) should have the same stereochemistry (Figure 3.3).[80,85]




*2* R = H cytoblastin
*4* R = OAc triactylcytoblasin

**Figure 3.3.** Retrosynthetic analysis of cytoblastin by the Kishi group

Based on a comparison of NMR spectra from indolactam V and cytoblastin, the relative stereochemistry was determined to be the same, leading to the choice to begin the synthesis of cytoblastin from indolactam V. Indolactam V was synthesized following a published procedure that required 10 steps with a 17% overall yield (Figure 3.4, 10 steps reported by authors, 11 step longest linear sequence).[82]

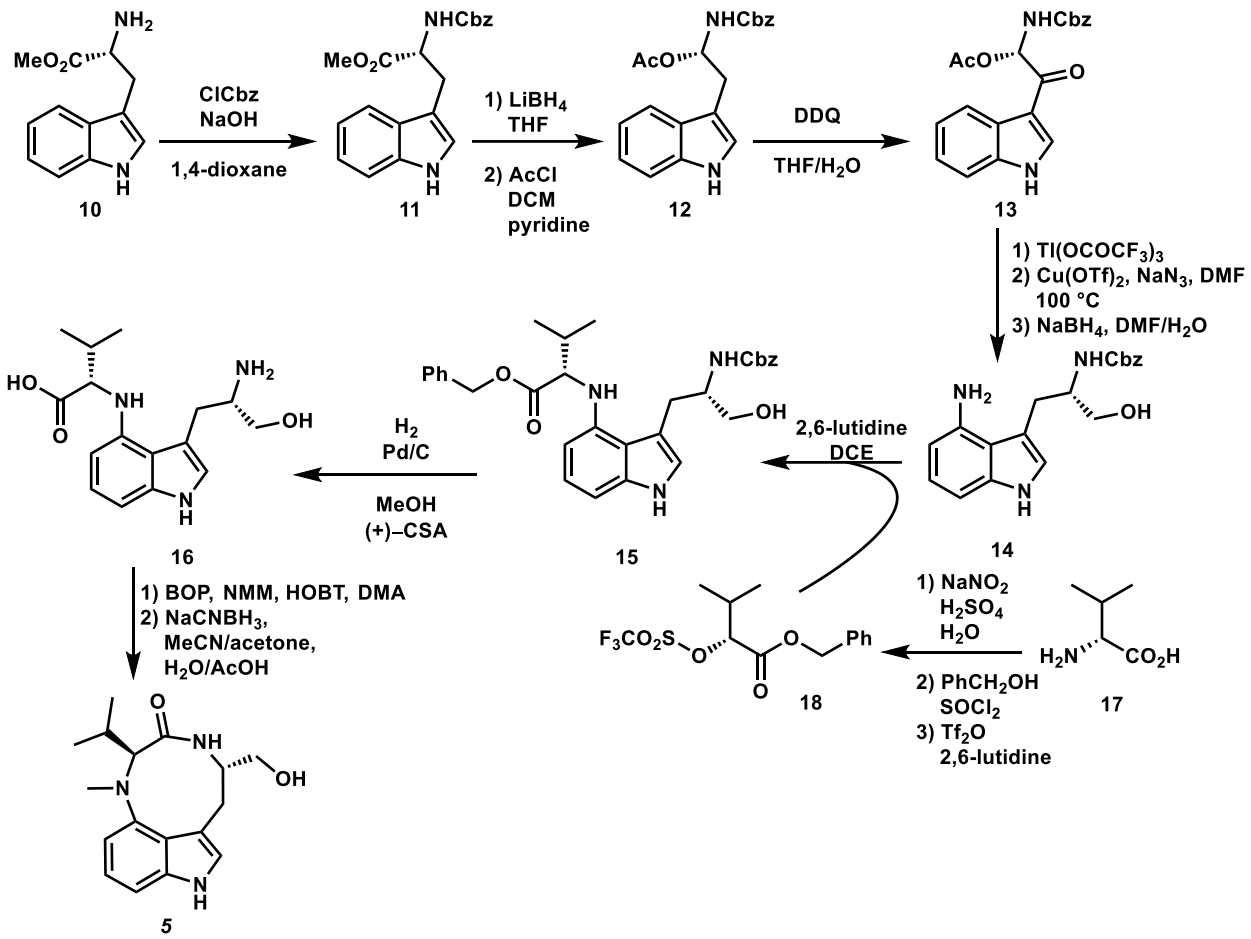



**Figure 3.4.** The Kagan group's synthetic route to (-)-indolactam V

The bromination of indolactam V by Kishi required a four-step sequence (Figure 3.5). The hydroxyl was protected first, followed by protection of the indole nitrogen. The bromination at the indole 4-position was accomplished by the use of NBS. The hydroxyl was then deprotected using TBAF, giving brominated and protected product **19**. While no intermediate purifications were necessary, this was nonetheless a 4-step sequence not reported in the main text of the article.

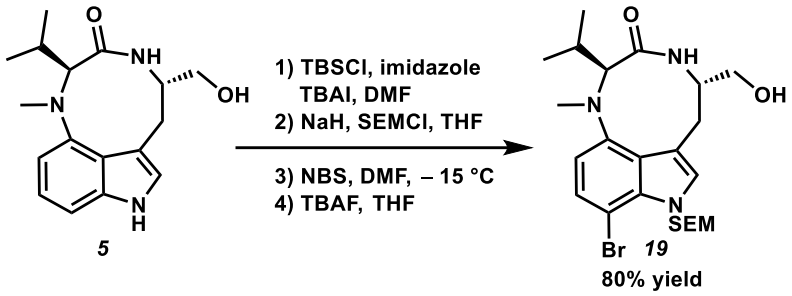



**Figure 3.5.** Bromination of indolactam V

The tributyltin reagent for the Heck reaction also needed to be synthesized, with protection of **20** with SES followed by the in-situ synthesis of the two-carbon tetrabutyltin Wittig reagent and then addition to the aldehyde. This allowed access to structure **9** in 50-60% yield over two steps.

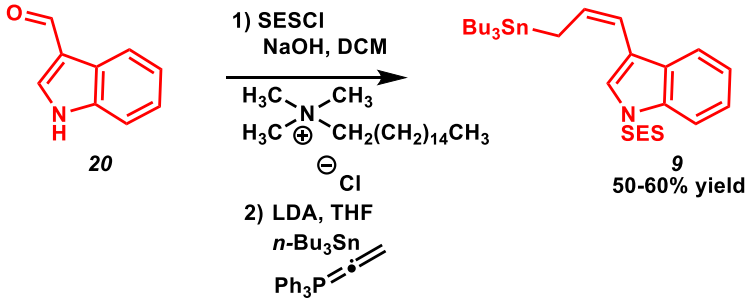



**Figure 3.6.** Synthesis of tributyltin reagent necessary for Kishi synthesis.

Addition of **9** to the brominated indolactam V **19** via Heck reaction was performed under catalysis by palladium to provide **21** in 80% yield of mainly one diastereomer (Figure 3.7). Oxidation of the resulting structure gave **22**. The subsequent removal of the protecting groups under increased pressure provided cytoblastin in 90% yield, as the only diastereomer. While overall a nice synthetic effort, it is quite involved as it required a 10-step synthesis of indolactam, a 4-step bromination, and a 3-step conversion to the natural product requiring a synthesized nucleophile. Overall, from indolactam, the synthesis is 7 steps with a 40% overall yield. If the

synthetic pathway needed to synthesize indolactam is included, the synthesis is 17 steps, with a 7% yield if the optimal yield reported by the Kagan group is achieved.

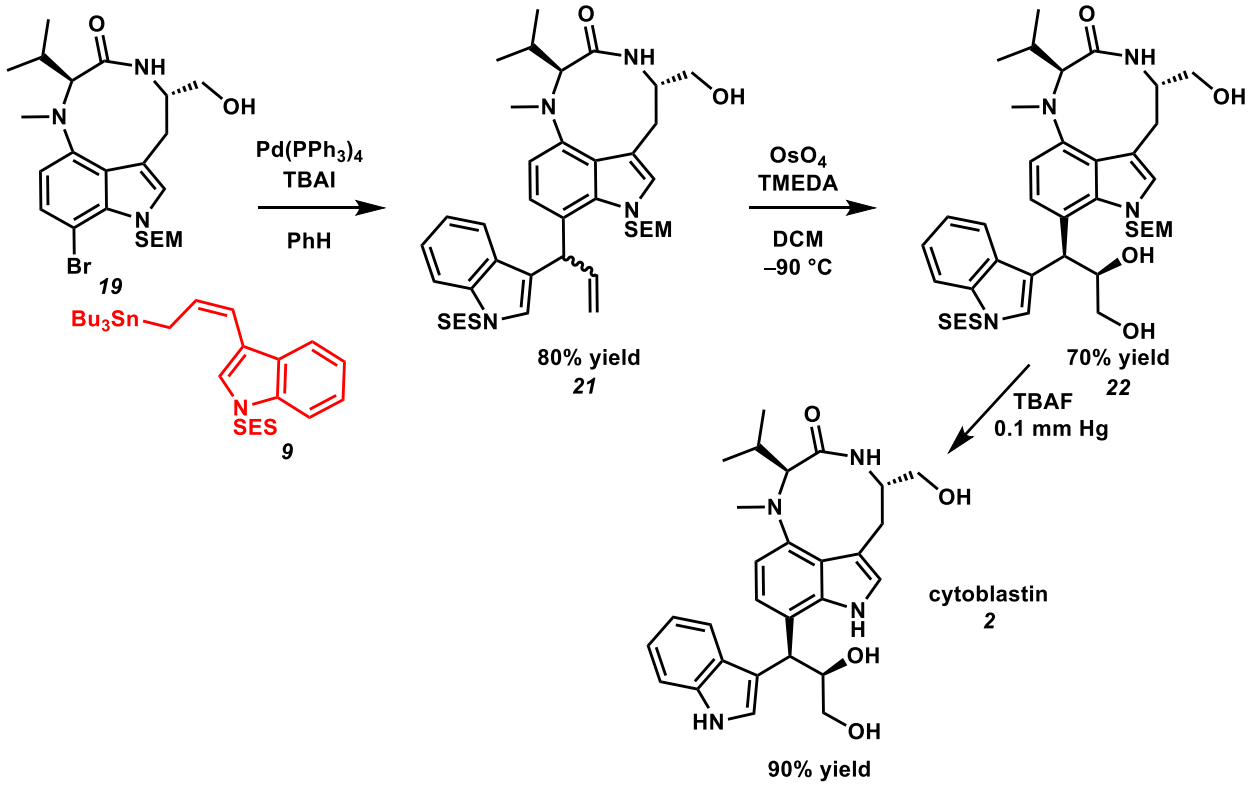



**Figure 3.7.** Synthesis of cytoblastin

### 3.1.3 Improvement of the Synthetic Route to Indolactam V

Since Kishi's publication of the synthesis of cytoblastin, several groups have synthesized indolactam V in pathways preferable to the Kagan approach, due to simplicity, reagent appeal, step count, and yields. While multiple syntheses have been shown to be effective,[86–90] the Billingsley group's synthesis is highly effective, approachable, and high yielding.[91] This approach is the one we chose to adapt for the scale-up of the synthesis of cytoblastin.

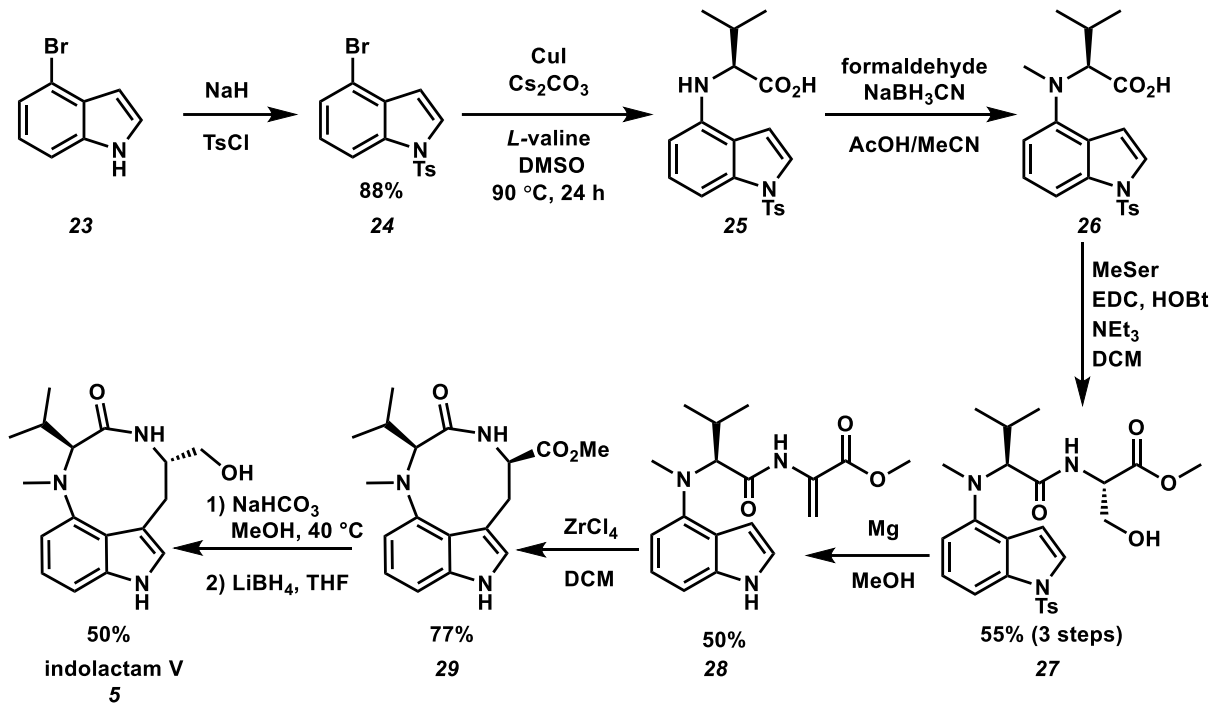



**Figure 3.8.** Billingsley synthesis of indolactam V

The reported synthesis begins with tosylation commercially available 5-bromoindole **23**. The resulting brominated compound undergoes C–N bond formation with *L*-valine (**25**), is methylated (**26**), and coupled with serine methyl ester to give structure **27** without purification until the last step, with a 55% yield over three steps. The reduction with magnesium was reported to be quite sensitive, but when optimized, provides the double bond necessary for the coupling in structure **28**. Previously, Neil Garg reported the cyclization of **28** to **29** with the use of $ZrCl_4$ and the same conditions were used here. The conversion of the methyl ester gave 50% yield of indolactam V.

The overall synthesis is 8-steps and requires only easily accessible, commercially available starting materials. While the overall yield is 9% (compared to 17% over 10 steps reported by the Kagan group) the shorter synthesis and accessibility of the coupling partners led us to choose this method for synthesis and scale-up.

### 3.1.4 Work to Scale Up Billingsley Synthesis

As our intention is to use indolactam V as a starting material for a synthetic effort towards cytoblastin, there is a need to increase the scale of the synthesis of the natural product compared to the small scale of the Billingsley group reports. We've made some efforts in this in the beginning stage of the synthesis of cytoblastin (Figure 3.9).

The protection of the indole was performed in aqueous conditions with a phase transfer catalyst to avoid large-scale column chromatography, as the resulting product is quite pure after an aqueous wash. The subsequent three-step sequence, carried out without purification as reported, is considerably less robust on scale. Furthermore, the conversion of **27** to **28** was reported as being very sensitive to variation in conditions, especially to the equivalents of magnesium employed. In our efforts, we suspect the amount of magnesium oxide on the surface of the magnesium changes the reactivity considerably, especially on large scale. We have achieved the synthesis of **28** as an inseparable mixture with side products.

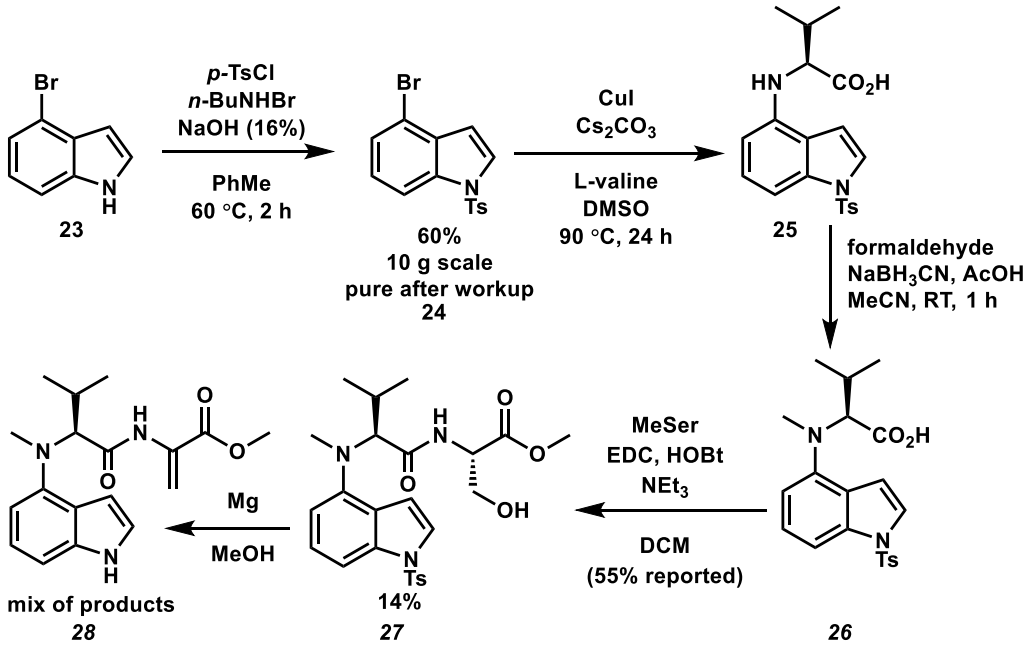



**Figure 3.9.** Efforts towards scale up of Billingsley synthesis

Work continues on the scale up of this synthesis, with screening of conditions for the dehydration (conversion of **27** to **28**) as well as determination of the low yielding step of the three-step sequence. It is also possible to use a different synthetic route, for example the Garg approach[86] or the Kagan approach used by Kishi, though the latter is longer and involves more expensive and dangerous reagents (such as thalium (III) trifluoroacetate).

### 3.2 Proposed Synthetic Route to Cytoblastin

After a scaleable route to indolactam is found, the total synthesis of cytoblastin should be quite accessible by the use of our conjugate addition methodology as developed for the mucronatins and as in our original approach to discoipyrrole D (Figure 3.10). There are two possible disconnections, as in the mucronatins.

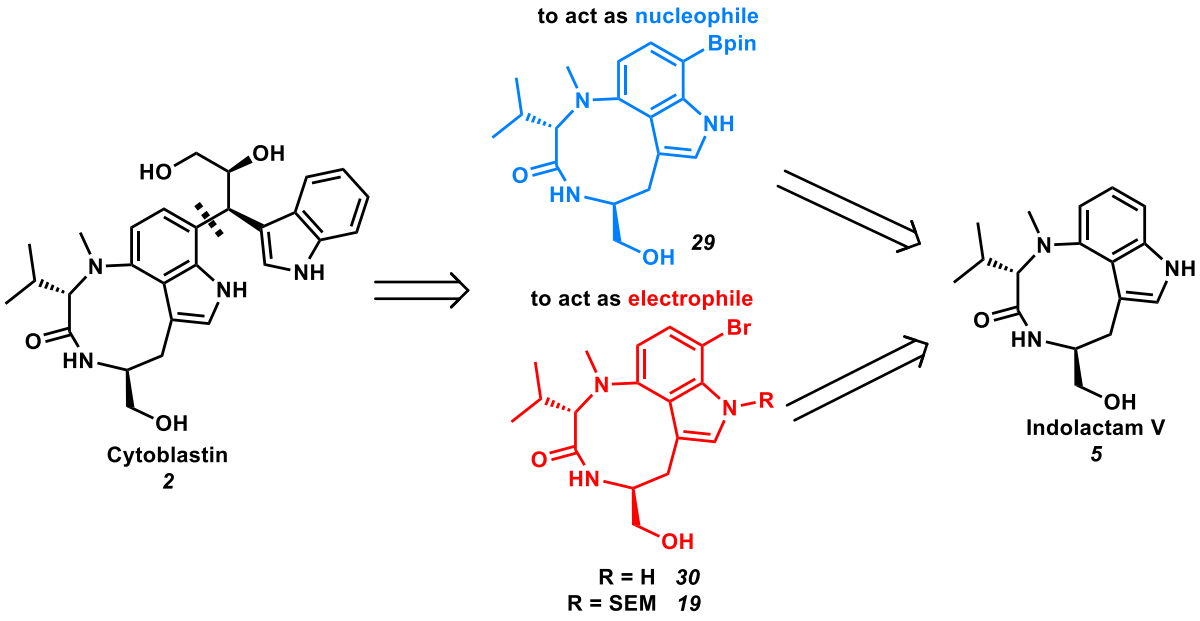



**Figure 3.10.** Two routes to cytoblastin.

Hartwig iridium chemistry has been used to borylate the 7-position of the indole.[60,61,92,93] Conditions have been reported for selective 7-borylation with a variety of substituted indoles with high functional group tolerance and selectivity, making it possible to synthesize compound **29**

from indolactam V without protection of the indole nitrogen. On the other hand, it was possible to brominate at the 7-position, as in the Kishi synthesis of cytoblastin (compound **19**). As this would require a four-step sequence, we are considering other possibilities for halogenation. For example, the Garg synthesis accomplishes the bromination of TBS protected cytoblastin in one step with NBS.[86]

From **19** or **30**, a Heck reaction could provide the three-carbon aldehyde needed for conjugate addition with a 3-$BF_3K$ indole, as in mucronatins and discoipyrrole. We are quite interested in using the indole as an electrophile, and it is our hypothesis that the 7-position C–B bond will be considerably more resistant to protodeboronation than a 2- or 3- position C–B bond.

### 3.3 Completion of the Synthesis of Discoipyrrole D

The completion of the synthesis of discoipyrrole D is the final target in the indolyl-propylene glycol class. In the May group's original study, the molecule could not be successfully deprotected (Figure 3.11).

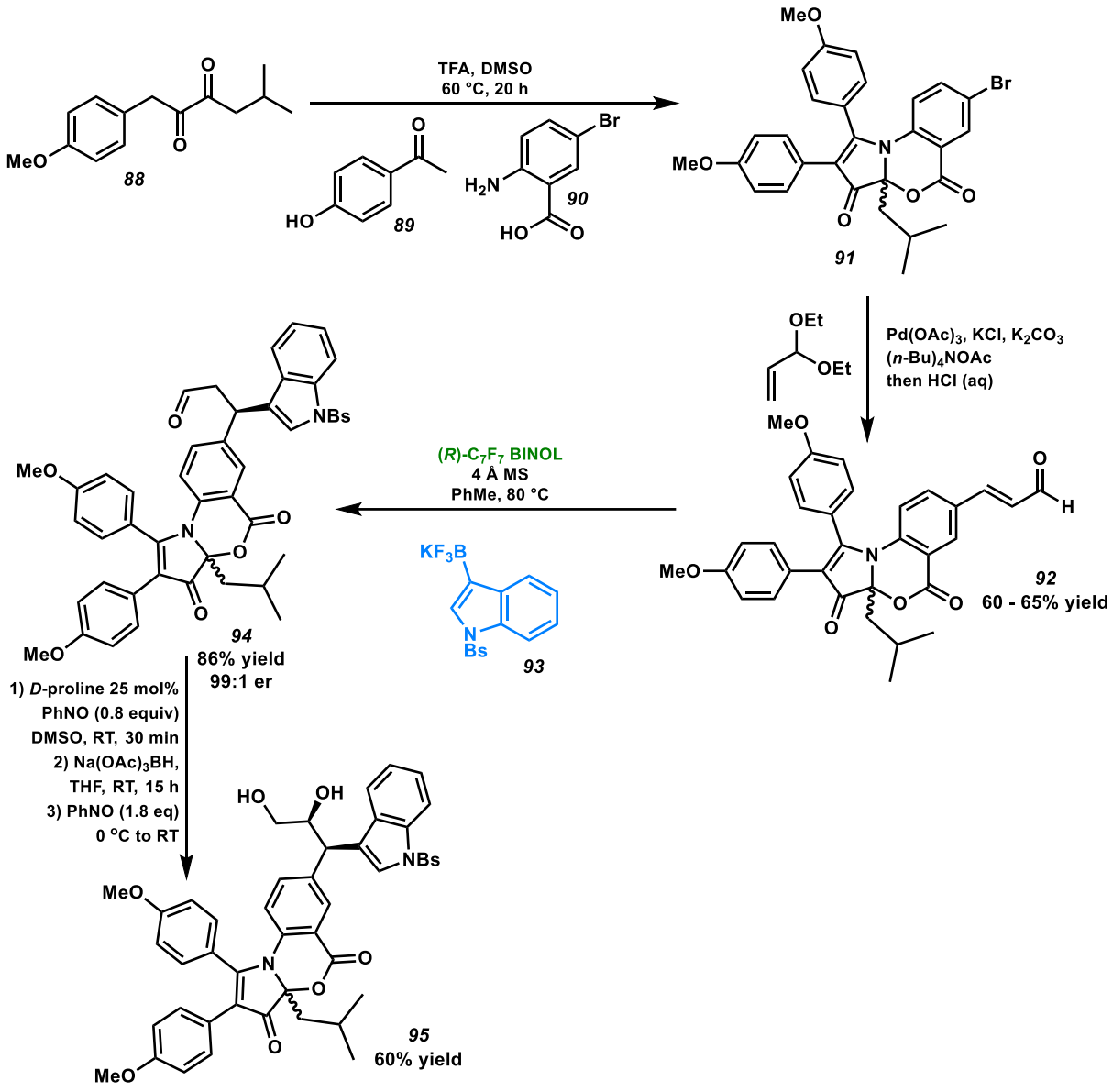



**Figure 3.11**. Original route to protected discoipyrrole D.

Two potential revisions to the initial approach[43] are reversal of the synthetic steps and modification of the protecting groups in the three-component coupling (Figure 3.12). John MacMillan, who first reported the structure of discoipyrrole D showed that it is possible to perform the three-component coupling with free hydroxyls (**40** and **41**) instead of the methoxy groups present in **31** and **32**. Furthermore, adding DMAP to the reaction conditions has been shown by

the MacMillan group to improve coupling yields.[94] It should also be possible to perform the Heck reaction prior to the three-component coupling, using **33** to synthesize unsaturated aldehyde **39**, which could then be used in the coupling to synthesize **42**, with free hydroxyls.

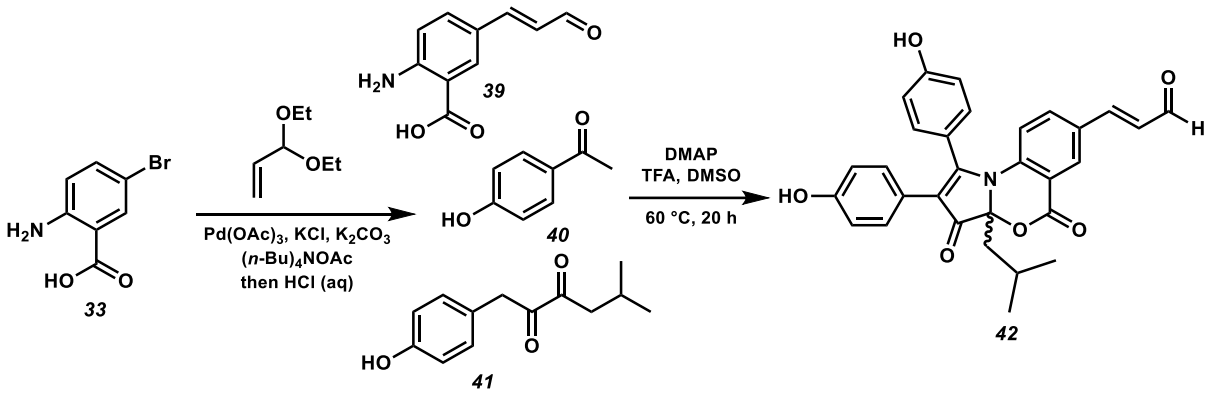



**Figure 3.12.** Step reversal approach

The other revision simply relies on utilizing a protecting group other than methyl to ensure discoipyrrole D can be deprotected late in the synthesis, avoiding the problem in the original approach. One possibility with some precedent, including by Kishi in the studies of cytoblastin[85] is using long-chain tethered protecting groups (Figure 3.13). It is possible this would increase the yield of the three-component coupling, as it would render part of the synthesis intramolecular. Furthermore, the resulting compounds would be easier to purify, allowing for ease of synthesis.

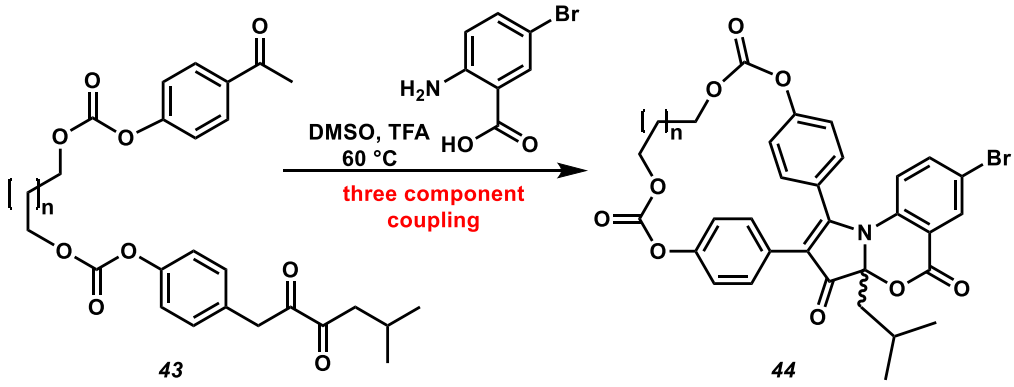



**Figure 3.13.** Alternate long-chain protecting group

### 3.4 Conclusion

All three natural products discussed in this chapter have intriguing biological activities, making them synthetically interesting. Furthermore, they not only come from different biological sources, but they have differing biological activities. We hope to complete all three syntheses shortly. Our methodology allows for a modular synthesis, with the capability of modification of electrophiles and nucleophiles. Also, our conjugate addition methods are quite tolerant of many functional groups. This method could be used to synthesize not only these natural products, but their analogues, allowing for structure-activity relationship and medicinal chemistry studies of the structures.

# CHAPTER 4: CONJUGATE ADDITION FOR VINYLOGOUS SUBSTITUTION WITH ORGANOBORATES[2]

## 4.1 Mechanistic Studies of Organocatalyzed Conjugate Addition

Our group, among others, has studied the mechanism of conjugate addition with BINOL-derived organocatalysts.[39] Among those who have studied the mechanism of conjugate addition, Goodman and Pellegrinet presented several computation-backed studies of such conjugate additions.[95–97] The Schaus group has also proposed mechanisms for similar allylboration of ketones.[98,99] In the conjugate addition of organoboronates with modified BINOL catalysts, Chong has proposed a possible mechanism.[27] Our group has recently collaborated with Steven Wheeler's computational group to evaluate the reaction and develop more effective catalysts.[100]

### 4.1.2 Chong's Suggested Mechanistic Pathway

Upon publication of conditions for the conjugate addition of organoboronate esters, the Chong group proposed a possible mechanistic pathway for this reaction.[26,27,37,101] As described in Chapter 1, they hypothesized that the catalyst would facilitate trans-esterification of the boron, giving **I**, which could then react with **3** in a conjugate addition reaction. The enantioselectivity of the reaction was proposed to be determined by the identity of the BINOL derivative. In the original proposal, Chong suggested that the selectivity may be due to the reaction proceeding through a chair-like transition state. If this was the case, one of the transition states where the attack would be pseudo-equatorial is destabilized by a steric interaction with the catalyst (see Figure 3.2).

In the Chong group's initial screen, BINOL was found to catalyze the reaction when it was unfunctionalized, leading to high enantioselectivities in product formation, but in low yields. Therefore, the catalyst was modified with electron-withdrawing groups at the 3,3'-positions. The

[2] The research described in this chapter has been published in part in Organic Letters (*Org. Lett.* 2020, 22, 4, 1355-1359).

Chong group hypothesized that this was due to the increased Lewis acidity of the trans-esterified complex **1** which made the complex more reactive (Figure 4.1).

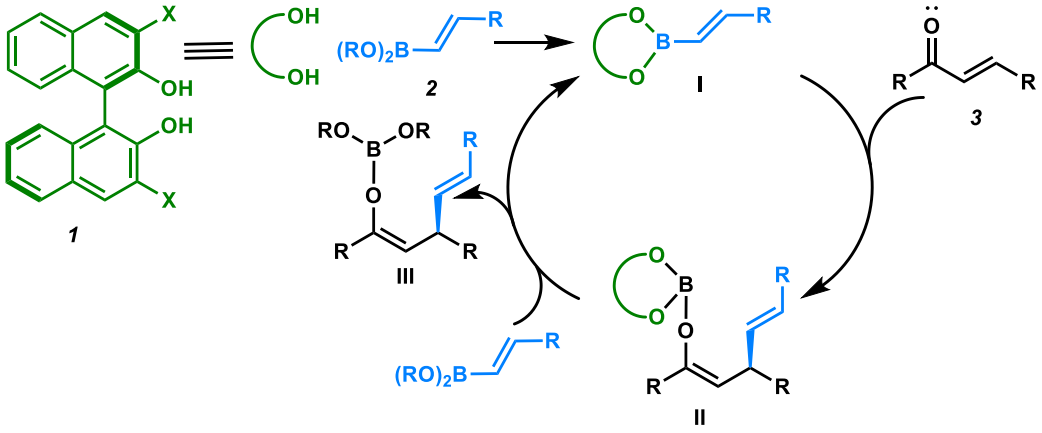



**Figure 4.1.** Chong's mechanistic proposal

### 4.1.3 Pellegrinet and Goodman's Mechanistic Studies

Pellegrinet and Goodman were able to computationally elucidate the mechanism as proposed by Chong.[41] The group chose the iodo-BINOL **1** (X = I) for computational analysis. They analyzed the reactivity with alkynyl boronate esters rather than the vinyl nucleophiles (**2**).

They were able to show computationally that Chong's proposed mechanistic pathway was likely, with confirmation that **2** is unlikely to react with **3** without catalyst involvement. They also showed that the complex **I** is indeed a viable intermediate.

In a later paper, Pellegrinet and Goodman showed that the proposed chair-like transition state was unlikely (**5a** and **5b**, Figure 4.2), with the molecules adopting a sofa-like conformation in the transition states (**6**). They were able to confirm that the BINOL-derived catalyst and boronate ester complex is highly Lewis acidic. The conjugate addition was found to be irreversible. This

computational analysis confirmed many of the proposals from Chong et. al. and led to greater understanding of the reaction pathways.

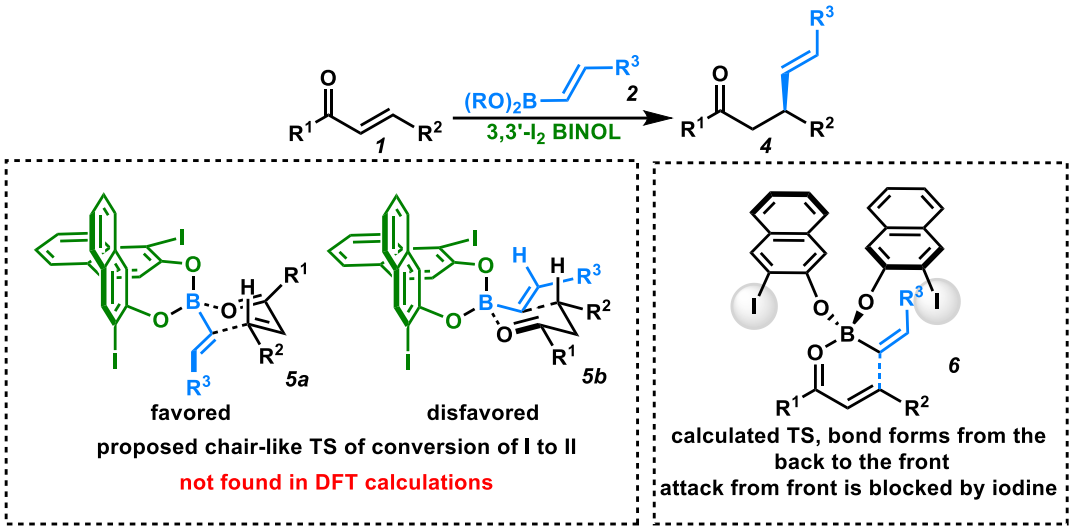



**Figure 4.2.** Pellegrinet and Goodman analysis of transition states and rationale for enantioselectivity

### 4.1.4 May Group Mechanistic Study

The May group performed Hammett plot analysis of the conjugate addition reaction for conditions developed by our group (Figure 4.3). Rather than querying the reasons behind the stereochemical outcome, our group focused on the electronics of the reaction by varying the substitution of the α,β-unsaturated ketone ($R^1$ and $R^2$ in **7**) and the organoboronate nucleophile ($R^3$ in **8**).

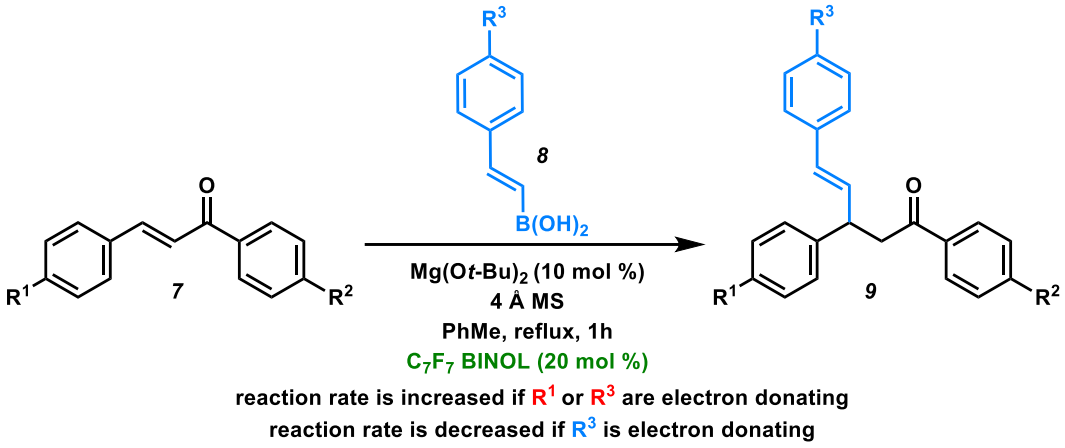



**Figure 4.3**. May group conjugate addition study

Contrary to expectation, it was found that if $R^1$ was electron donating, the reaction rate was increased. The increased rate is likely due to stabilization of the forming partial cationic charge in **II** as seen in **II**' (Figure 4.4). It's likely that electron donating groups can stabilize this charge by resonance (Figure 4.5) and induction.

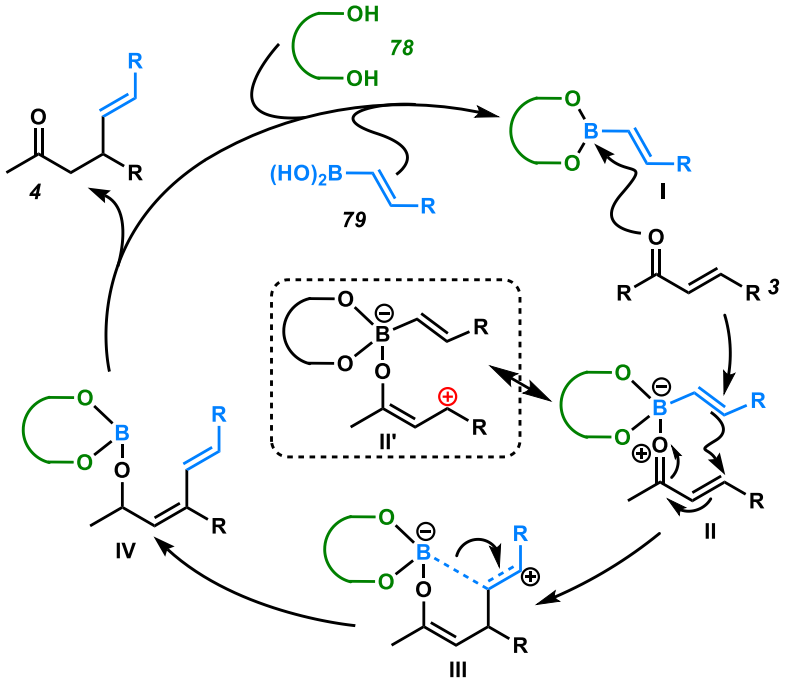



**Figure 4.4.** Catalytic cycle

For example, para-methoxy electrophile **10** can be shown as the resonance structure **10'**. This increases stability of **II**, ensuring the reaction can proceed to the carbon-carbon bond formation necessary to form **III**.

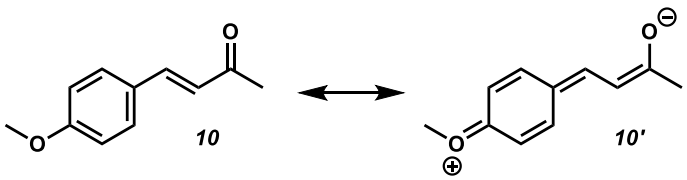



**Figure 4.5**. Resonance stabilization of the electrophiles for conjugate addition

This ability to use electron-rich electrophiles inspired the use of heterocycle-appended enones, which was covered in chapters 2 and 3. Related work was proposed after the results of the mechanistic study were obtained that would utilize stronger β-donating groups.

### 4.2 Vinylogous Esters and Amides

In light of rate acceleration by electron rich β-substituents, we proposed the possibility of using a rarely used class of electrophiles – vinylogous esters and amides. These are not viable electrophiles for traditional conjugate additions due to being overly electron rich. However, in the case of the organocatalyzed conjugate addition of organoboronate nucleophiles, the stabilization of positive charge developing in the transition state would increase reaction rate. This led us to believe the conjugate additions may be quite robust with these electrophiles due to their ability to directly contribute to resonance stabilization (**11** and **11'**, Figure 4.6).

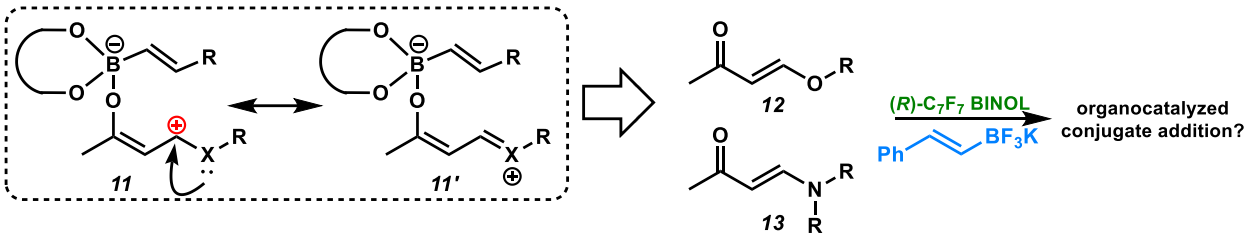



**Figure 4.6.** Proposal for organocatalyzed conjugate addition with vinylogous esters and amides

### 4.2.1 Palladium Catalyzed Conjugate Additions to Vinylogous Amides

There have been two examples of conjugate addition to vinylogous esters and amides, reported by the Wan[102] and Wu[103] groups. These examples both rely on palladium catalysis.

#### *4.2.1.1 Wan Group*

In the case of the Wan group,[102] the use of palladium was necessary for the synthesis of the products (Figure 4.7). When using dimethyl vinylogous amide **14** they observed conjugate addition followed by the elimination of the dimethyl amine anion. However, with palladium catalysis the structure resulting from single addition is more reactive to conjugate addition than the initial vinylogous amide; therefore, only double addition products were isolated from the reactions.

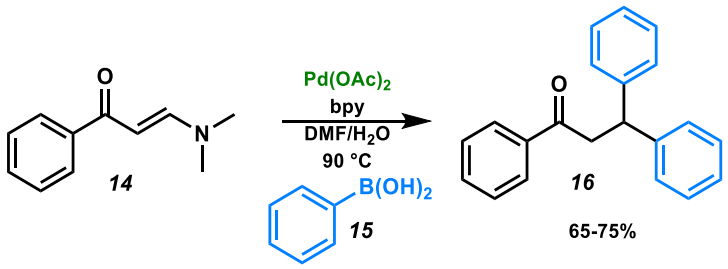



**Figure 4.7**. Conjugate addition of organoboronates to vinylogous amides by the Wan group

Furthermore, this reaction was very limited in nucleophile scope, thus offering limited utility. The palladium catalysis was also not ideal, as it utilized a toxic transition metal and a costly ligand.

#### *4.2.1.2 Wu Group*

The Wu group was able to catalyze conjugate additions without elimination using palladium (Figure 4.8).[103] They observed elimination (**17**) and double addition (**16**) products as

impurities. They were able to optimize conditions and solvents to synthesize structures **18** enantioselectively, with aims to use the oxazolidinones as directing groups.

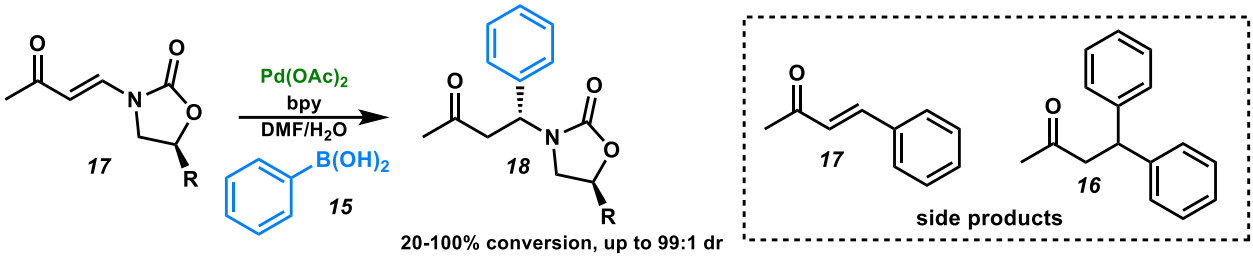



**Figure 4.8.** Conjugate addition of organoboronates by the Wu group

### 4.3 Organocatalyzed Conjugate Addition to Vinylogous Esters and Amides

In 2015, we began studies of conjugate additions with vinylogous amide and ester electrophiles. We were able to show that conjugate addition was possible with several examples of these. The addition was followed by elimination of the β-amine or alkoxy anion (**19**), resulting in formation of polyene **20** (Figure 4.9). When using a BINOL-derived catalyst, the reaction worked best with the vinylogous phenyl ester **18b**. The use of trifluoroborate salt nucleophiles and catalyst **24** was based on previous work with electron-rich heterocycle appended enones and was predicted to give the best reactivity.

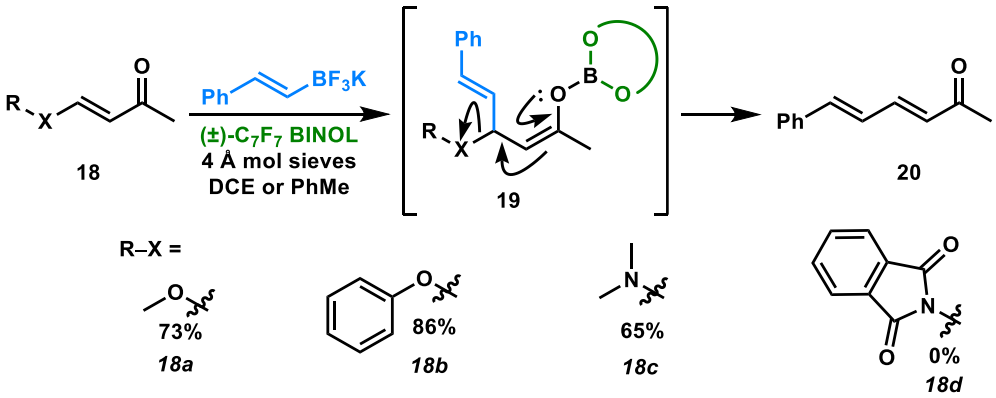



**Figure 4.9**. Organodiol catalyzed conjugate addition to vinylogous esters and amides, preliminary results

### 4.3.1 Catalyst Evaluation and Screening

However, as the products thus formed are not chiral, a chiral catalyst is unnecessary. While our synthesis of the catalyst is well developed and requires only one purification in the final step, it is nonetheless a three-step synthesis requiring a large excess of perfluorotoluene in the conversion of **23** to **24** and the somewhat costly BINOL as a starting material (Figure 4.10). The $C_7F_7$ groups are exceptionally effective at increasing catalyst activity due to their electron withdrawing nature, and the BINOL-derived diol is able to effectively control stereochemistry of the forming bond, resulting in high enantioselectivities.

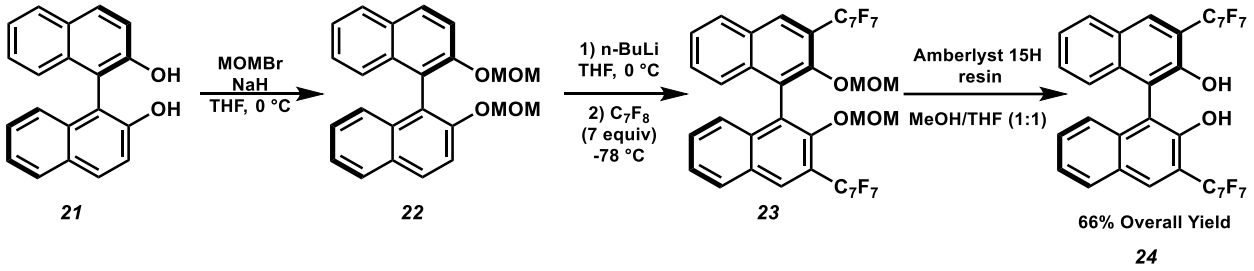
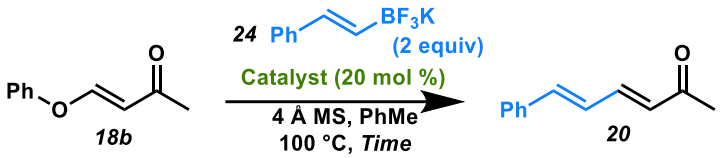


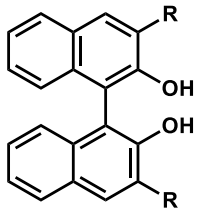

**Figure 4.**10. $C_7F_7$-BINOL catalyst synthesis

We hypothesized that it was possible to simplify the catalyst for the reaction (Table 1). We screened a variety of organodiols, finding that unfunctionalized BINOL and biphenol were able to catalyze the reaction (entry 3 and entry 4, respectively), but with decreased yields when compared to bis-$C_7F_7$-BINOL (entry 1). In particular, 2,2'-biphenol, which is attractive due to cost and small size, had comparable conversion, but required a longer reaction time than bis-$C_7F_7$-BINOL (entry 4).

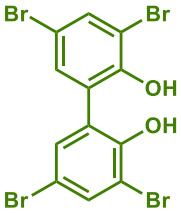
**Table 1.** Catalyst screen.



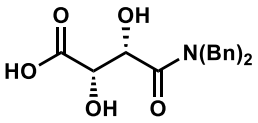

| entry | catalyst | time | yield |
|---|---|---|---|
| 1 | (±)-$C_7F_7$-BINOL | 24 hours | 86[b] |
| 2 | (±)-IODO-BINOL | 24 hours | 85[a] |
| 3 | (±)-BINOL | 24 hours | 81[b] |
| 4 | 2,2´-biphenol | 48 hours | 82[b] |
| **5** | **TBBol** | **18 hours** | **82[b]** |
| 6 | (L)-tartaric acid | 72 hours | 77[a] |
| 7 | (L)-tartramide | 48 hours | 6[a] |
| 8 | 1,4-butanediol | 48 hours | 42[a] |
| 9 | none | 48 hours | 61[a] |




R = I; IODO BINOL (*25*)
R = $C_7F_7$; $C_7F_7$ BINOL (*24*)



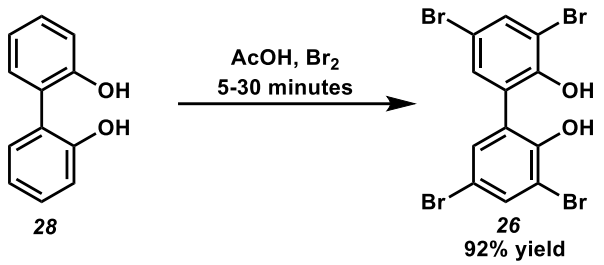

TBBol (TetraBromoBiphenol)
26




(*L*)-tartramide
27

[a]NMR yield. [b]Isolated yield, average of 3 trials.

**T**etra**B**romo**Bi**phen**ol** (TBBol), synthesized in one step from biphenol (Figure 4.11), was able to perform the reaction in a comparable time to $C_7F_7$-BINOL with similar yields. A tartramide catalyst as used by the Schaus group[104] for organodiol catalyzed Petasis reactions decreased yield considerably (entry 7), as did unmodified tartaric acid itself (entry 6). The reaction does show a considerable reactivity even when uncatalyzed (entry 9); however, organodiol catalysts considerably increased the rate of reaction.




*28* *26*
92% yield

**Figure 4.11**. Synthesis of TBBol

### 4.3.3. Leaving Group Effects

In the interest of assessing the effect of the leaving group on the reactivity of vinylogous esters and amides, a variety of leaving groups was screened (Figure 4.12). Vinylogous esters and amides were synthesized by reaction of the alcohol or amine with 3-butyn-2-one (**27**), which occasionally required DABCO catalysis for high yields. A commercially available β-chloroenone (**18p**) was also tested. It was determined that vinylogous esters were quite effective in the reaction, with 4-phenoxy-but-3-en-one (**18b**), providing the polyene in the greatest yield (82%). Disubstituted vinylogous amides were even more reactive, with the best-case amide, **18j**, providing the polyene product in 92% yield. Most vinylogous esters and amides provided the polyene product in high yields, except for phthalimide leaving group (**18p**) that provided no polyene. It instead showed a great deal of decomposition in the NMR spectrum. Primary amines (i.e. **18i, 18l**) gave decreased yields of the polyene structures, possibly due to the high reactivity of the leaving group. In all cases, no addition without elimination was observed, even for less stable leaving groups.

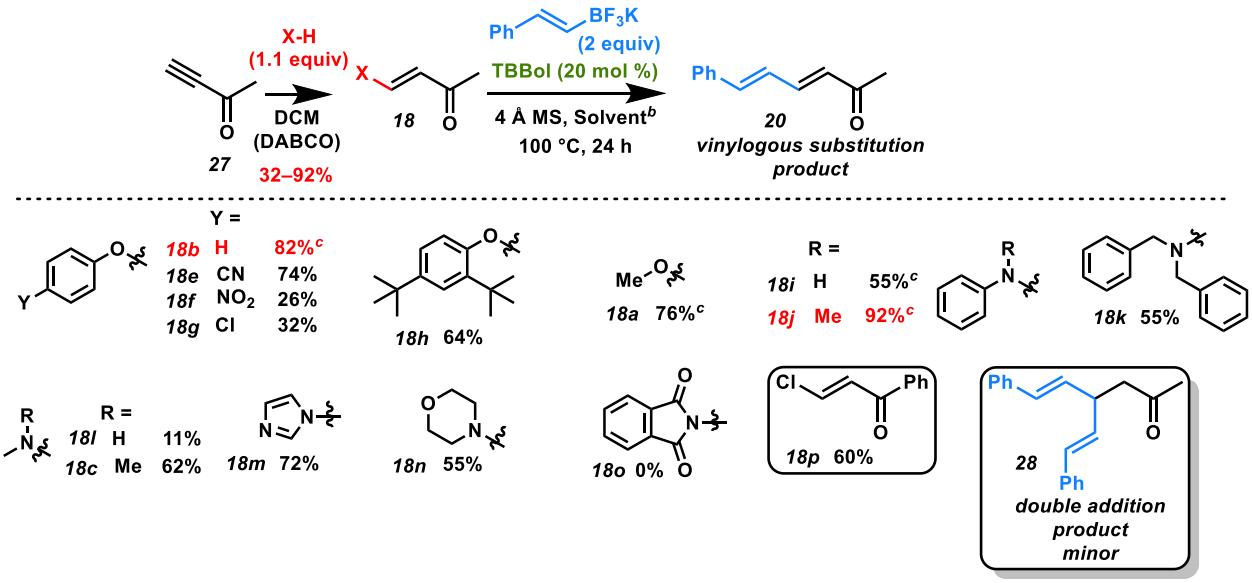



**Figure 4.12.** Conjugate addition to various vinylogous esters and amides

### 4.3.4. Additive Effects

A variety of additives were screened with the goal of increasing reaction rate and/or preventing elimination of the leaving group. Regardless of additive, no conjugate addition without elimination was observed. In most cases, reactivity was not increased. A side product observed in these reactions was the symmetrical disubstituted product **28**, the result of a second conjugate addition. This second conjugate addition is considerably slower, reversing the reactivity for palladium catalyzed reactions. It is possible to increase the rate of formation and synthesize the double addition product by using ammonium carbonate as an additive and $C_7F_7$-BINOL as the (Figure 4.13). To confirm the generality of this effect, the additive was tested in a known reaction with β-indole unsaturated ketone **29** and was found to increase reaction rate, allowing for conversion to product in half the time required without the additive.

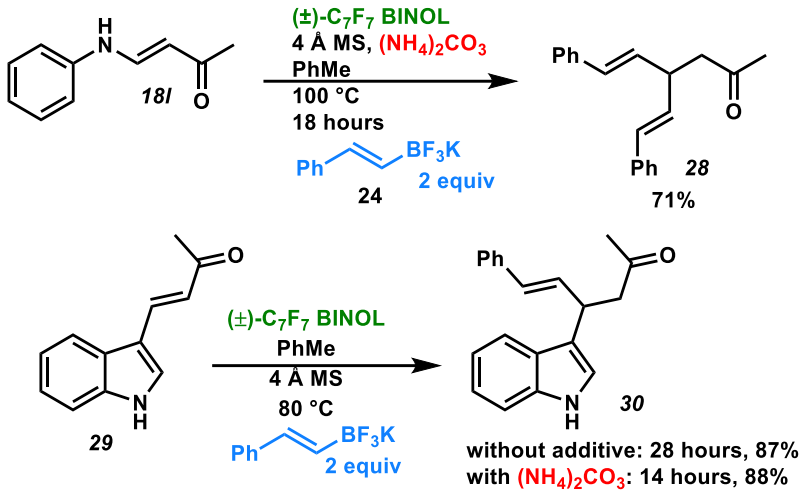



**Figure 4.13**. Effects of ammonium carbonate on reaction rates

### 4.3.5 Nucleophile Evaluation

A variety of organoboronates were tested in vinylogous substitution using the β-methyl aniline electrophile due to its high reactivity. Boronic acids were not as effective as trifluoroborate salts, but a variety of nucleophiles were reactive in the conditions. Aromatic nucleophiles gave decreased yields, likely due to the need for dearomatization during carbon-carbon bond formation in the reaction mechanism. Increasing reaction times for less reactive nucleophiles allowed for higher conversions. Generally, diene and ene/yne structures could be synthesized effectively by this methodology.

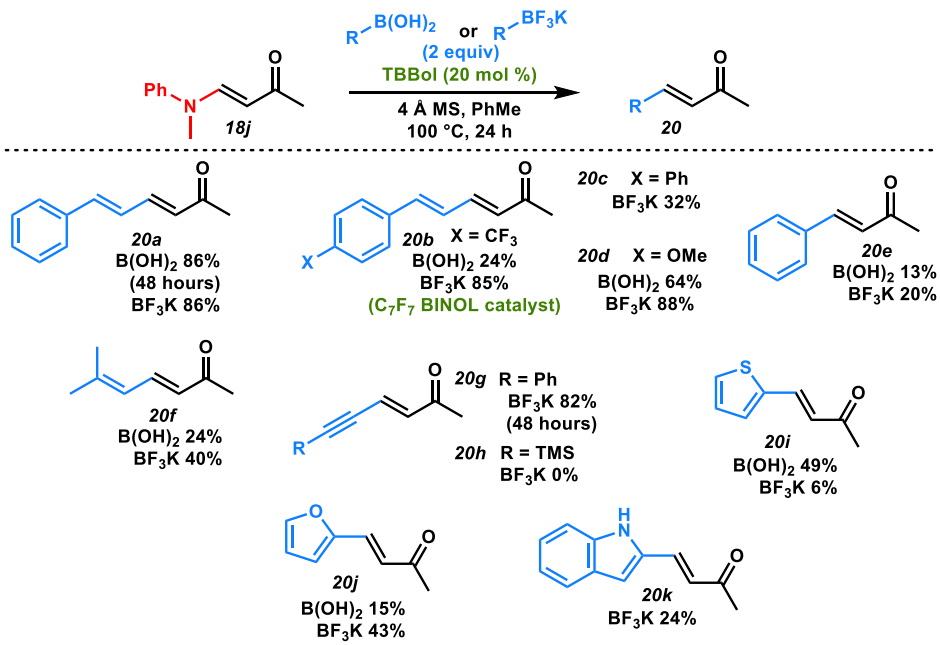



**Figure 4.14.** Nucleophile screen

### 4.3.6 Electrophile Expansion

Expanding the scope and utility of this reaction required the synthesis of differently substituted esters and amides. While the methyl ketone vinylogous esters and amides were readily synthesized from the corresponding alkyne, differently substituted carbonyl derivatives were difficult to synthesize and purify, giving low yields (Figure 4.15). These esters and amides were reactive to conjugate addition; however, the low yields to form starting materials were prohibitive to a wide-ranging application of this methodology.

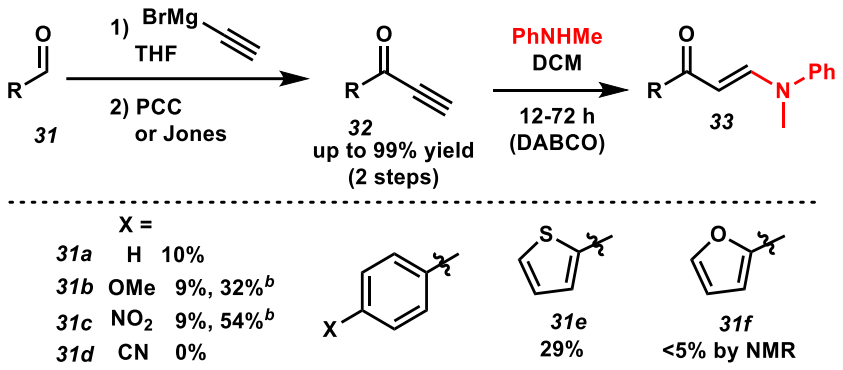



**Figure 4.15**. Varied vinylogous esters and amides

### 4.3.7 Other Substrates

We considered the possibility of using other vinylogous esters and amides, with particular effort made to synthesize tetrasubstituted carbon centers. We hypothesized using cyclic vinylogous esters and amides to synthesize such structures. Several examples were synthesized and examined in this methodology (Figure 4.16).

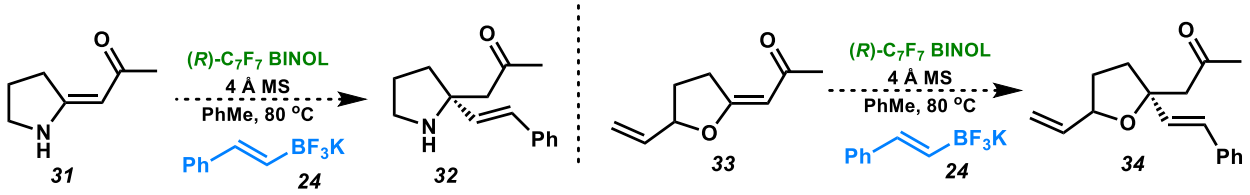



**Figure 4.16**. Attempts to form tetrasubstituted carbon centers

The cyclic vinylogous amide **31** and the cyclic ester **33** were used as electrophiles in test reactions. We were hopeful these substrates would be reactive to conjugate addition and form tetrasubstituted centers β-to the carbonyl. Unfortunately, no conjugate addition was observed in either case, regardless of additives or reaction conditions.

Another test substrate was the cyclic vinylogous ester **35** (Figure 4.17). In this case, conjugate addition was observed, but the diastereoselectivity could not be determined. When vinylogous ester **37** was used, elimination of the hydroxyl led to the formation of compound **38**.

This reaction was not enantioselective, even with a chiral catalyst. This has led us to consider future work with substrates bearing sacrificial leaving groups. Careful substrate design could potentially allow for the synthesis of difficult to access products.

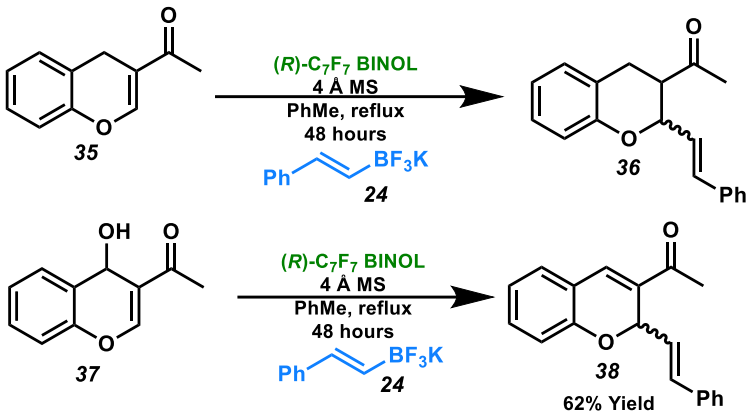



**Figure 4.17**. Cyclic vinylogous esters

### 4.4 Conclusion

Conjugate additions with organodiol catalysts were shown for the first time to be effective with vinylogous ester and amide nucleophiles. The nucleophile scope made this an intriguing method of synthesizing polyenes and ene/ynes. However, the synthesis of certain esters and amides was prohibitive, making the methodology less general and applicable. It would be difficult to compete with existing synthesis methodologies with these limitations. After consideration, we were able to reformulate the methodology to enact the same transformation in a relay catalytic approach.

## 4.5 Experimental

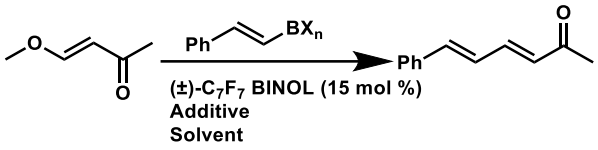
General considerations

All reactions were carried out in flame-dried glassware under an argon atmosphere. THF, $Et_2O$, toluene, and $CH_2Cl_2$ were purged with argon and dried over activated alumina columns. Flash chromatography was performed on 60 Å silica gel (EMD Chemicals Inc.). Analytical thin layer chromatography was performed on EMD silica gel/TLC plates and imaged by fluorescence at 254 nm or *p*-anisaldehyde stain. The $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectra were recorded on a JEOL ECA-600, 500, ECZ-400 or ECX-400P spectrometer using the residual solvent peak as an internal standard ($CDCl_3$: 7.26 ppm for $^{1}H$ NMR and 77.2 ppm for $^{13}C$ NMR). NMR yields were determined by the addition of 1.0 equivalent of methyl 4-nitrobenzoate as an internal standard to the crude reaction mixture and comparing the integration of the standard's peaks to those of the starting material and product (16 scans, 30 second relaxation delay). IR spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. HRMS analyses were performed under contract by University of Houston's mass spectrometric facility via an nESI method and a Thermo Exactive + Advion Nanomate instrument. Analysis by HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Chiralpak or Chiralcel (250 mm x 4.6 mm) column (column details provided for specific compounds). Commercially available compounds were purchased from Aldrich, Acros, Ark Pharm, Alfa Aesar, Beantown Chemical, TCI, and Combi-Blocks and were used without further purification. IUPAC chemical names were generated using Cambridgesoft ChemBioDraw Ultra 12.0.

### 4.5.2 Vinylogous Substitution Optimization

*Procedures in section 4.5.6.*

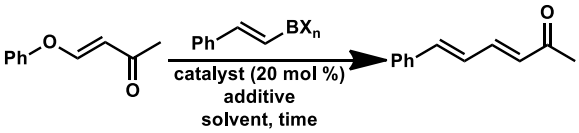
**Initial Studies**



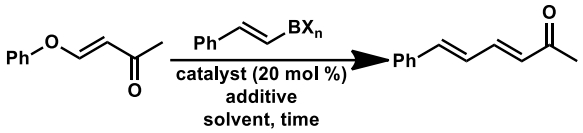

| entry | $BX_n$ | equiv | temp (°C) | time (h) | solvent | additives | yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | $B(OH)_2$ | 1.2 | 70 | 24 | DCE | $SiO_2$ | Decomposition |
| 2 | $BF_3K$ | 1.2 | 70 | 24 | DCE | 4 Å MS | 73 |
| 3 | $BF_3K$ | 1.2 | 70 | 24 | DCE | LiBr | 71 |
| 4 | $BF_3K$ | 1/2 | 110 | 24 | PhMe | 4 Å MS | 69 |

Starting material was purchased from Sigma Aldrich.

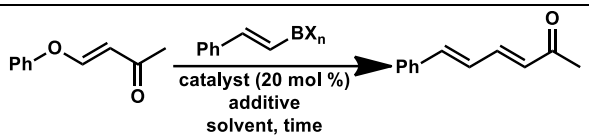
**Phenoxide Leaving Group; Optimization Studies**



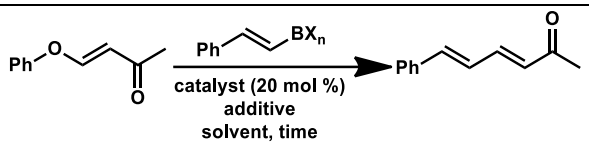

| entry | catalyst | $BX_n$ | equiv | temp (°C) | time (h) | solvent | additives | yield (%) |
|---|---|---|---|---|---|---|---|---|
| Catalyst and Salt Loading: Initial Screen | | | | | | | | |
| 1 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 1.2 | 70 | 18 | DCE | 4 Å MS | 81 (average of 7) |
| 2 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS | 83, 75 |
| 3 | (±)-$C_7F_7$ BINOL (10 mol %) | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS | 67 |
| 4 | (±)-$I_2$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS | 70 (average of 3) |
| Additive Screening | | | | | | | | |
| 5 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS *t*-BuOH (1 equiv) | 57 (average of 3) |
| 6 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS TEA (0.1 equiv) | 32 |
| 7 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS TEA (0.5 equiv) | Decomp |




| entry | catalyst | $BX_n$ | equiv | temp (°C) | time (h) | solvent | additives | yield (%) |
|---|---|---|---|---|---|---|---|---|
| Additive Screening | | | | | | | | |
| 8 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS TFA (0.1 equiv) | 53.7 |
| 9 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS TFA (0.5 equiv) | Decomp |
| 10 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS $BCl_3$ (1 equiv) | 0 |
| 11 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS $BH_3$*THF (1 equiv) | 0 |
| 12 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS $BF_3$*OEt (1 equiv) | 53 |
| 13 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS $AlCl_3$ (1 equiv) | 40 |
| 14 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS $BBr_3$ (1 equiv) | 0 |
| 15 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS $Br_2$ (1 equiv) | Decomposition |
| 16 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS $AlMe_3$ (1 equiv) | 0 |
| 17 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS $TiCl_4$ (1 equiv) | Decomposition |
| 18 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | None | 0 (70 % SM recovered) |
| 19 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | LiBr (3 equiv) | 47 |
| Expanded Organodiol Catalyst Screen | | | | | | | | |
| 20 | (±)-BINOL | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS | 69 (average of 3) |
| 21 | 2,2'-Biphenol | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS | 75 |
| 22 | 1,4-Butanediol | $BF_3K$ | 2 | 70 | 48 | DCE | 4 Å MS | 49 |
| 23 | 2,2'-Biphenol | $BF_3K$ | 2 | 70 | 12 | DCE | 4 Å MS | 19 |
| 24 | 2,2'-Biphenol | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS | 80 |
| 25 | 2,2'-Biphenol | $B(OH)_2$ | 2 | 70 | 24 | DCE | 4 Å MS | 76 |

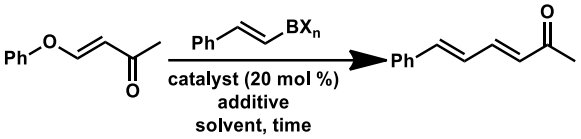



| entry | catalyst | $BX_n$ | equiv | temp (°C) | time (h) | solvent | additives | yield (%) |
|---|---|---|---|---|---|---|---|---|
| Expanded Organodiol Catalyst Screen | | | | | | | | |
| 26 | 2,2'-Biphenol | $BF_3K$ | 2 | 70 | 48 | DCE | 4 Å MS | 61 |
| 27 | None | $BF_3K$ | 2 | 70 | 24 | DCE | Phenol (2 equiv) | 18 |
| 28 | None | $BF_3K$ | 2 | 70 | 24 | DCE | Phenol (0.2 equiv) | 34 |
| 29 | None | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS | 38 |
| 30 | 2,2'-Biphenol | $BF_3K$ | 2 | 80 | 48 | DCE | 4 Å MS | 82 |
| 31 | TBBol | $BF_3K$ | 2 | 80 | 24 | DCE | 4 Å MS | 79 |
| 32 | Schaus tartramide | $BF_3K$ | 2 | 100 | 24 | 1,4-Dioxane | 4 Å MS | 8 |
| 33 | L-tartaric acid | $BF_3K$ | 2 | 75 | 14 | 1,4-Dioxane | 4 Å MS | 0, 54% SM recovered |
| 34 | *L*-tartaric acid | $BF_3K$ | 2 | 100 | 24 | 1,4-Dioxane | 4 Å MS | 77 |
| TBBol Catalyst Solvent Screen | | | | | | | | |
| 35 | TBBol | $BF_3K$ | 2 | 80 | 28 | DCE | 4 Å MS | 68 |
| 36 | TBBol | $BF_3K$ | 2 | 75 | 14 | 1,4-Dioxane | 4 Å MS | 96 |
| 37 | TBBol | $BF_3K$ | 2 | 75 | 14 | DCE | 4 Å MS | 80 |
| 38 | TBBol | $BF_3K$ | 2 | 75 | 14 | DCM | 4 Å MS | 89 |
| 39 | TBBol | $BF_3K$ | 2 | 75 | 14 | THF | 4 Å MS | 64 |
| 40 | TBBol | $BF_3K$ | 2 | 75 | 14 | PhMe | 4 Å MS | 82 |
| 41 | TBBol | $BF_3K$ | 2 | 75 | 14 | MeCN | 4 Å MS | 43 |
| 42 | TBBol | $BF_3K$ | 2 | 75 | 14 | $Et_2O$ | 4 Å MS | 95 |
| 43 | TBBol | $BF_3K$ | 2 | 75 | 14 | Benzene | 4 Å MS | 0 |
| 44 | TBBol | $BF_3K$ | 2 | 75 | 14 | Acetone | 4 Å MS | 43 |




| entry | catalyst | $BX_n$ | equiv | temp (°C) | time (h) | solvent | additives | yield (%) |
|---|---|---|---|---|---|---|---|---|
| TBBol Catalyst Solvent Screen | | | | | | | | |
| 46 | TBBol | $BF_3K$ | 2 | 75 | 14 | DMA | 4 Å MS | 0 |
| 47 | TBBol | $BF_3K$ | 2 | 75 | 14 | TBME | 4 Å MS | 88 |
| 48 | TBBol | $BF_3K$ | 2 | 75 | 14 | $CHCl_3$ | 4 Å MS | 87 |
| 49 | TBBol | $BF_3K$ | 2 | 75 | 14 | 1,4-Dioxane | 4 Å MS | 78 (ISOLATED) |
| 50 | TBBol | $BF_3K$ | 2 | 75 | 4 | $CHCl_3$ | 4 Å MS $(NH_4)_2CO_3$ | Full conversion by GC |
| TBBol Catalyst Temperature Screen | | | | | | | | |
| 51 | TBBol | $BF_3K$ | 2 | reflux | 18 | 1,4-Dioxane | 4 Å MS | 92 |
| 52 | TBBol | $BF_3K$ | 2 | 80 | 18 | 1,4-Dioxane | 4 Å MS | 33 |
| 53 | TBBol | $BF_3K$ | 2 | 70 | 18 | 1,4-Dioxane | 4 Å MS | 30 |
| 54 | TBBol | $BF_3K$ | 2 | 60 | 18 | 1,4-Dioxane | 4 Å MS | 37 |
| 55 | TBBol | $BF_3K$ | 2 | 50 | 18 | 1,4-Dioxane | 4 Å MS | 43 |
| 56 | TBBol | $BF_3K$ | 2 | 40 | 18 | 1,4-Dioxane | 4 Å MS | 34 |
| 57 | TBBol | $BF_3K$ | 2 | RT | 18 | 1,4-Dioxane | 4 Å MS | 5 |
| Avoiding Double Addition Side Product | | | | | | | | |
| 58 | TBBol | $BF_3K$ | 2 | 100 | 24 | 1,4-Dioxane | 4 Å MS | 71 (average of 3 Trials, isolated) |
| 59 | TBBol | $BF_3K$ | 2 | 100 | 24 | 1,4-Dioxane | 4 Å MS | 69 (30% double addition)<br>71 (27 double addition) |
| 60 | TBBol | $BF_3K$ | 1 | 100 | 24 | 1,4-Dioxane | 4 Å MS | 14 |
| 61 | TBBol | $BF_3K$ | 1.2 | 100 | 24 | 1,4-Dioxane | 4 Å MS | 68 |

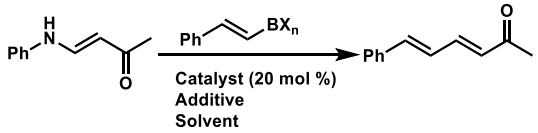
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 62 | TBBol | $BF_3K$ | 2 | 100 | 14 | 1,4-Dioxane | 4 Å MS | 50 |
| 63 | TBBol | $BF_3K$ | 2 | 100 | 15 | 1,4-Dioxane | 4 Å MS | 63 |
| 64 | TBBol | $BF_3K$ | 2 | 100 | 16 | 1,4-Dioxane | 4 Å MS | 67 |




Avoiding Double Addition Side Product

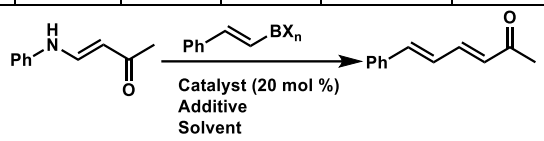
| entry | catalyst | $BX_n$ | equiv | temp (°C) | time (h) | solvent | additives | yield (%) |
|---|---|---|---|---|---|---|---|---|
| 65 | TBBol | $BF_3K$ | 2 | 100 | 18 | 1,4-Dioxane | 4 Å MS | 77 SM consumed, no double addition |
| Water Sensitivity | | | | | | | | |
| 66 | 2,2'-Biphenol | $BF_3K$ | 2 | 70 | 24 | DCE | 4 Å MS Water (1 equiv) | 78 |
| 67 | 2,2'-Biphenol | $BF_3K$ | 2 | 70 | 48 | DCE | 4 Å MS Water (10 equiv) | 0 |

**Phenylamine Leaving Group**




| entry | catalyst | $BX_n$ | equiv | temp (°C) | time (h) | solvent | additives | yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | TBBol | $BF_3K$ | 2 | 80 | 24 | DCE | 4 Å MS | 42 |
| 2 | TBBol | $BF_3K$ | 2 | 80 | 24 | PhMe | 4 Å MS | 50 |
| 3 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 80 | 24 | PhMe | 4 Å MS | 55 |
| 4 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 80 | 16 | PhMe | 4 Å MS | 28 |
| 5 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 80 | 16 | MeCN | 4 Å MS | 5 |
| Additive Screen | | | | | | | | |
| 6 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 80 | 16 | PhMe | 4 Å MS LiBr | 31 |
| 7 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 80 | 16 | PhMe | LiBr (3 equiv) | 55 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 8 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 80 | 16 | PhMe | 4 Å MS NaOtBu | 24 |
| 9 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 80 | 16 | PhMe | 4 Å MS KOtBu | 76 |
| 10 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 80 | 16 | PhMe | 4 Å MS NaHMDS | decomposition |
| 11 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 80 | 16 | PhMe | 4 Å MS KHMDS | decomposition |

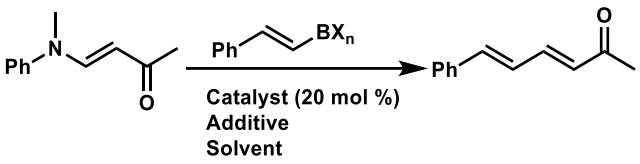



Additive Screen

| entry | catalyst | $BX_n$ | equiv | temp (°C) | time (h) | solvent | additives | yield (%) |
|---|---|---|---|---|---|---|---|---|
| 12 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 80 | 16 | PhMe | LiBr (1 equiv) | 0 |
| 13 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 110 | 16 | PhMe | 4 Å MS $LiClO_4$ | 16 |
| 14 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 110 | 16 | PhMe | 4 Å MS LiOtBu | 44 |
| 15 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 110 | 16 | PhMe | 4 Å MS $(NH_4)_2CO_3$ | 71 double addition product |
| 16 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 110 | 16 | PhMe | 4 Å MS $NH_4HCO_3$ | 28 |
| 17 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 110 | 16 | PhMe | 4 Å MS KHMDS (0.2 equiv) | 30 |
| 18 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 110 | 16 | PhMe | 4 Å MS KHMDS (0.5 equiv) | 7 |
| 19 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 110 | 16 | PhMe | 4 Å MS KHMDS (1 equiv) | 0 |
| 20 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 110 | 16 | PhMe | 4 Å MS n-BuLi (1 equiv) | 25 |
| 21 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 110 | 16 | PhMe | 4 Å MS NaH (0.2 equiv) | 42 |
| 22 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 110 | 16 | PhMe | 4 Å MS NaH (0.5 equiv) | 39 |
| 23 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 110 | 16 | PhMe | 4 Å MS NaH (1 equiv) | 55 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Catalyst Evaluation | | | | | | | | |
| 24 | (±)-BINOL | $BF_3K$ | 2 | 100 | 24 | PhMe | 4 Å MS | 14 |
| 25 | Schaus tartramide | $B(OH)_2$ | 2 | 100 | 16 | EtOAc | $Yt(OTf)_3$ | 0 |
| 26 | TBBol | $BF_3K$ | 1.1 | 110 | 4 | PhMe | 4 Å MS $(NH_4)_2CO3$ | 21 |
| 27 | TBBol (10 mol%) | $BF_3K$ | 2 | 110 | 4 | PhMe | 4 Å MS $(NH_4)_2CO3$ | 17 |
| 28 | TBBol (5 mol%) | $BF_3K$ | 2 | 110 | 4 | PhMe | 4 Å MS $(NH_4)_2CO3$ | 12 |

**Methyl Phenyl Amine Leaving Group**

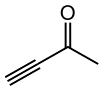



| entry | catalyst | $BX_n$ | equiv | temp (°C) | time (h) | solvent | additives | yield (%)[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | TBBol | $BF_3K$ | 2 | 80 | 24 | DCE | 4 Å MS | 71 (average of 2) |
| 3 | (±)-$C_7F_7$ BINOL | $BF_3K$ | 2 | 80 | 24 | PhMe | 4 Å MS | 55 |
| Solvent Screen | | | | | | | | |
| 5 | TBBol | $BF_3K$ | 2 | 75 | 14 | DCE | 4 Å MS | 52 |
| 6 | TBBol | $BF_3K$ | 2 | 75 | 14 | 1,4-Dioxane | 4 Å MS | 79 |
| 7 | TBBol | $BF_3K$ | 2 | 75 | 14 | DCE | 4 Å MS | 46 |
| 8 | TBBol | $BF_3K$ | 2 | 75 | 14 | DCM | 4 Å MS | 63 |
| 9 | TBBol | $BF_3K$ | 2 | 75 | 14 | THF | 4 Å MS | 32 |
| | TBBol | $BF_3K$ | 2 | 75 | 14 | PhMe | 4 Å MS | 32 |
| | TBBol | $BF_3K$ | 2 | 75 | 14 | MeCN | 4 Å MS | 68 |
| | TBBol | $BF_3K$ | 2 | 75 | 14 | $Et_2O$ | 4 Å MS | 16 |
| | TBBol | $BF_3K$ | 2 | 75 | 14 | Benzene | 4 Å MS | 52 |
| Avoiding Double Addition | | | | | | | | |
| | TBBol | $BF_3K$ | 2 | 100 | 18 | PhMe | 4 Å MS | 37 (31% Double Addition) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | TBBol | $BF_3K$ | 2 | 100 | 24 | Benzene | 4 Å MS | 93 (Average of 3 Trials) |
| | TBBol | $BF_3K$ | 2 | 100 | 18 | PhMe | 4 Å MS | 89 |
| | None | $BF_3K$ | 2 | 100 | 48 | PhMe | 4 Å MS | 29 |
| | TBBol | $BF_3K$ | 2 | 100 | 48 | PhMe | 4 Å MS | 70 (Average of 3 Trials) |
| | L-Tartaric acid | $BF_3K$ | 2 | 75 | 18 | PhMe | 4 Å MS | 0 (60% SM recovered) |
| | L-Tartaric acid | $BF_3K$ | 2 | 75 | 18 | PhMe | 4 Å MS $Yt(OTf)_3$ | 29 |

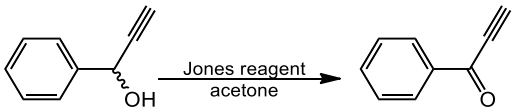
### 4.5.3 Synthesis of Alkynes

**but-3-yn-2-one (27)**



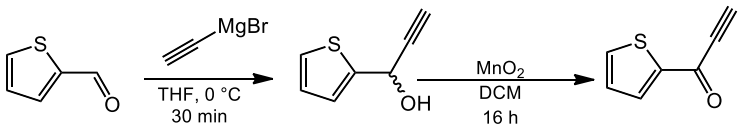
The title compound was purchased from Matrix Scientific and used without further purification. Stored at -20 °C.

**1-phenylprop-2-yn-1-one (SUPPLEMENTARY-1)**



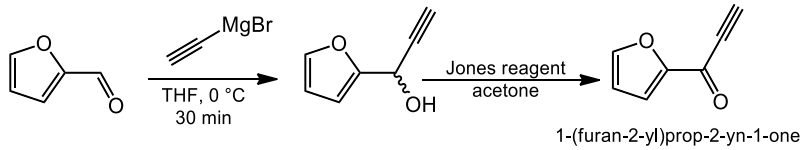

Prepared following literature procedures.[105] Spectral data were identical to those found in literature.[106]

**1-(thiophen-2-yl)prop-2-yn-1-one (SUPPLEMENTARY-2)**



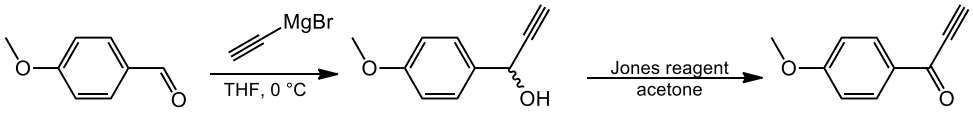

Prepared following literature procedures,[107] all spectral data match literature reports.[108]

**1-(furan-2-yl)prop-2-yn-1-one (SUPPLEMENTARY-3)**



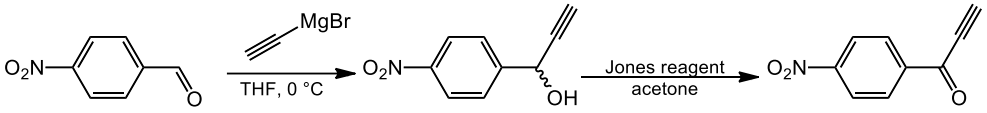

Prepared following literature procedures, all spectral data match literature reports.[109]

**1-(4-methoxyphenyl)prop-2-yn-1-one (SUPPLEMENTARY-4)**



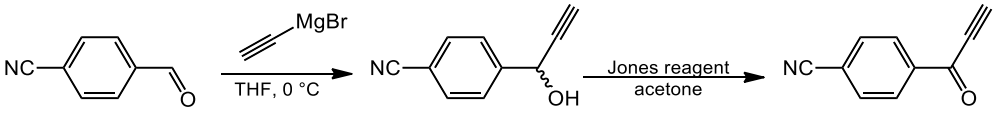

Prepared following literature procedures,[110] all spectral data match literature reports.[105]

**1-(4-nitrophenyl)prop-2-yn-1-one (SUPPLEMENTARY-5)**




Prepared following literature procedures, [105] all spectral data match literature reports.[111]

**4-propioloylbenzonitrile (SUPPLEMENTARY-6)**




Prepared following literature procedures,[112] all spectral data match literature reports.[113]

### 4.5.4 Synthesis of Vinylogous Esters and Amides

General Procedure for the Addition of Alcohols/Amines to Alkynes:

**Procedure A**

The procedure was modified from literature reports.[114] In a round bottom flask or vial equipped with stir bar, under atmospheric conditions, the alcohol or amine starting material was dissolved in 95% ethanol (0.5 M). While stirring, the alkyne (1.1 equiv) was added dropwise to the reaction mixture. Following this addition, DABCO (0.5 equiv) was slowly added to the reaction mixture while stirring, usually eliciting a considerable color change of the reaction mixture (pale yellow or colorless reaction mixtures changed to a darker yellow or brown). The reaction was allowed to stir at room temperature until the alcohol or amine starting material was shown to be consumed by TLC chromatography (p-anisaldehyde stain was used to visualize the plates). The solvent was removed by rotary evaporation. The products were purified by silica gel flash chromatography using a gradient of ethyl acetate/hexanes as the eluent.

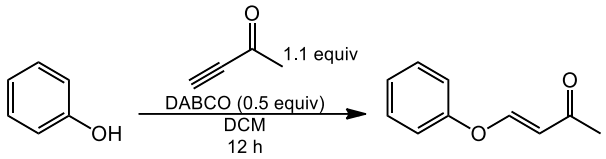
**Procedure B**

The procedure was modified from literature reports.[115] In a flame dried round bottom flask or vial equipped with stir bar, under Ar(g), the alcohol or amine starting material was dissolved in anhydrous DCM (0.5 M). While stirring, the alkyne (1.1 equiv) was added dropwise to the reaction mixture. Following this addition, DABCO (0.5 equiv) was slowly added to the reaction mixture, usually eliciting a considerable color change of the reaction mixture (pale yellow or colorless reaction mixtures changed to a darker yellow or brown). The reaction was allowed to stir at room temperature until complete by TLC (p-anisaldehyde stain was used to visualize plates). Following

completion, the solvent was removed by rotary evaporation. The products were purified by silica gel flash chromatography using a gradient of ethyl acetate/hexanes as eluent. $CDCl_3$

**Note**: Products were isolated as a thermodynamic E/Z mixture of stereoisomers and used without further purification.

**(*E*)-4-phenoxybut-3-en-2-one (18b)**

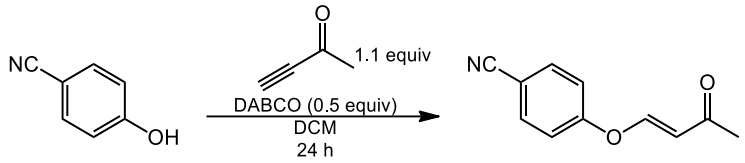



Prepared following Procedure B. Product was purified by silica gel flash column chromatography, using 1-20% ethyl acetate/hexanes as eluent to yield the title compound in quantitative yield as a nearly colorless oil (0.819 g, 5.05 mmol).

*Note*: Atmospheric conditions with ethanol for 48 hours were not as effective, providing the product in only 53% yield (2.731 g, 16.85 mmol).

**$^{1}$H-NMR** (400 MHz, chloroform-D) δ 7.72 (d, J = 12.0 Hz, 1H), 7.37 (t, J = 7.7 Hz, 2H), 7.19 (t, J = 7.4 Hz, 1H), 7.05 (d, J = 8.6 Hz, 2H), 5.89 (d, J = 12.6 Hz, 1H), 2.21 (s, 3H) **$^{13}$C-NMR** (101 MHz, chloroform-D) δ 197.5, 159.2, 155.9, 130.1, 125.3, 118.3, 111.8, 28.5, **IR** (neat) 3016, 2969, 1737, 1605, 1365, 1217, 756, 693, 587 $cm^{-1}$ **HRMS-ESI m/z** Calculated for $C_{10}H_{10}O_2$ $[M + H]^+$ 163.0759, found 163.0756

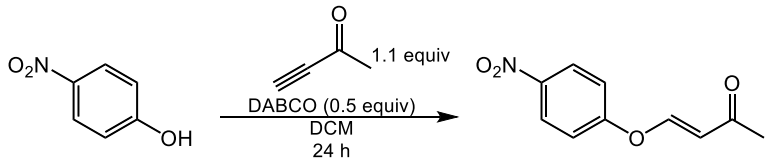
**(*E*)-4-((3-oxobut-1-en-1-yl)oxy)benzonitrile (18e)**




Prepared following Procedure B. The product was purified by silica gel flash column chromatography, using 1-20% ethyl acetate/hexanes as eluent to yield the title compound in 88% yield as a light brown solid (average of 2 trials, trial 1: 330 mg, 1.76 mmol, 84% yield; trial 2: 357 mg, 1.91 mmol, 91% yield).

**$^{1}$H-NMR** (600 MHz, chloroform-D) δ 7.67-7.70 (m, 3H), 7.15-7.17 (m, 2H), 6.04 (d, J = 12.4 Hz, 1H), 2.24 (s, 3H) **$^{13}$C-NMR** (151 MHz, chloroform-D) δ 197.2, 158.6, 158.5, 158. 4, 158.4, 156.4, 154.3, 140.4, 130.6, 130.1, 119.6, 112.1, 112.0, 111.7, 111.7, 81.9, 81.9, 77.4, 77.2, 76.9, 28.7, 28.7, 28.6 **IR** (neat) 3016, 2970, 1738, 1486, 1365, 1227, 1217 cm$^{-1}$ **HRMS-ESI m/z** Calculated for $C_{11}H_9NO_2$ $[M + H]^+$ 188.0712, found 188.0708

**(*E*)-3-(methyl(phenyl)amino)-1-(4-nitrophenyl)prop-2-en-1-one (18f)**

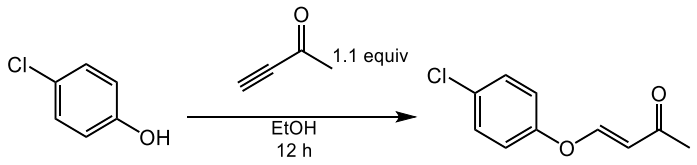



Prepared following Procedure B. The product was purified by silica gel flash column chromatography, using 1-20% ethyl acetate/hexanes as eluent to yield the title compound in 72% yield as a pale brown solid (267 mg, 1.29 mmol).

**$^{1}$H-NMR** (600 MHz, chloroform-D) δ 8.23 (dd, J = 8.8, 2.2 Hz, 2H), 7.69 (q, J = 6.0 Hz, 1H), 7.15 (td, J = 5.8, 2.5 Hz, 2H), 6.04 (dd, J = 12.0, 1.7 Hz, 1H), 2.22 (d, J = 2.7 Hz, 3H) **$^{13}$C-NMR** (151

MHz, chloroform-D) δ 197.0, 160.2, 155.7, 155.5, 144.5, 126.3, 126.2, 126.0, 117.9, 113.8, 77.3, 77.1, 76.9, 29.1 **IR** 3068, 2998, 1653, 1565, 1490, 1343, 1214, 1132, 1114, 947, 851, 750, 495 $cm^{-1}$ **HRMS-ESI m/z** Calculated for $C_{10}H_9NO_4$ $[M+H]^+$ 208.0610, found 208.0607

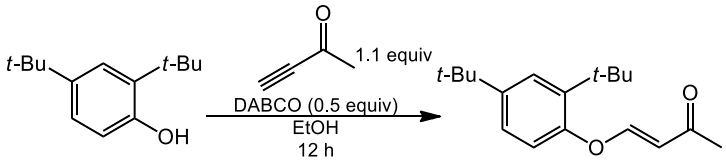
**(*E*)-4-(4-chlorophenoxy)but-3-en-2-one (18g)**




Prepared following Procedure A. Product was purified by silica gel flash column chromatography, using 1-20% ethyl acetate/hexanes as eluent to yield the title compound in 32% yield as a colorless oil (321 mg, 1.63 mmol).

**$^1$H-NMR** (600 MHz, chloroform-D) δ 7.65 (d, J = 12.4 Hz, 1H), 7.32 (d, J = 8.9 Hz, 2H), 6.99 (d, J = 8.9 Hz, 2H), 5.88 (d, J = 11.7 Hz, 1H), 2.20 (d, J = 5.5 Hz, 3H) **$^{13}$C-NMR** (151 MHz, chloroform-D) δ 197.2, 158.6, 158.5, 158.4, 158.4, 156.5, 154.3, 140.4, 130.6, 130.1, 119.6, 112.1, 112.0, 111.7, 111.7, 81.9, 81.9, 28.7, 28.7, 28.6 **IR** 3072, 2990, 2228, 1740, 1688, 1593, 1503, 1362, 1229, 962, 720, 553, 545 $cm^{-1}$ **HRMS-ESI m/z** Calculated for $C_{10}H_{10}ClO_2$ $[M + H]^+$ 197.0369, found 197.0368

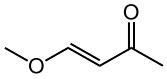
**(*E*)-4-(2,4-di-tert-butylphenoxy)but-3-en-2-one (18h)**




Prepared following procedure A. Product was purified by silica flash column chromatography, using 10-20% ethyl acetate/hexanes as eluent to yield the title compound in 92% yield as a pale yellow gelatinous solid (606 mg, 2.21 mmol).

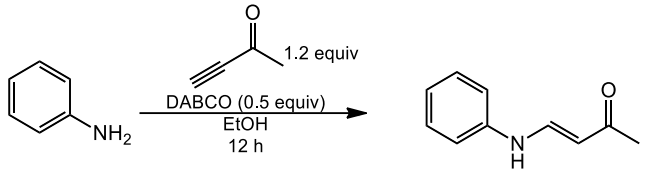
**$^{1}$H-NMR** (600 MHz, chloroform-D) δ 7.71-7.56 (1H), 7.40-7.29 (1H), 7.20-7.14 (1H), 6.89-6.80 (1H), 5.99-5.85 (1H), 2.25-2.16 (3H), 1.33-1.29 (9H), 1.29-1.26 (9H) **$^{13}$C-NMR** (151 MHz, chloroform-D) δ 197.5, 160.3, 153.0, 147.9, 139.5, 124.4, 124.3, 118.8, 111.8, 35.0, 34.7, 31.5, 30.3, 28.2 **IR** 2956, 2868, 1738, 1636, 1391, 1362, 1216, 1120, 954, 819 cm$^{-1}$ **HRMS-ESI m/z** Calculated for $C_{18}H_{26}O_2$ $[M + H]^+$ 275.2011, found 275.2006

**(*E*)-4-methoxybut-3-en-2-one (18a)**



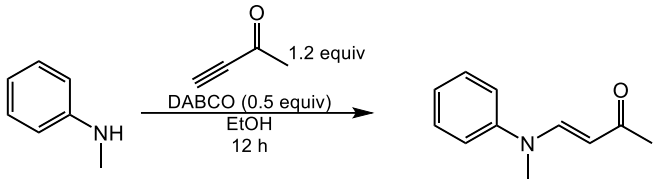

The title compound was purchased from Sigma Aldrich and used without further purification.

**(*E*)-4-(phenylamino)but-3-en-2-one (18i)**



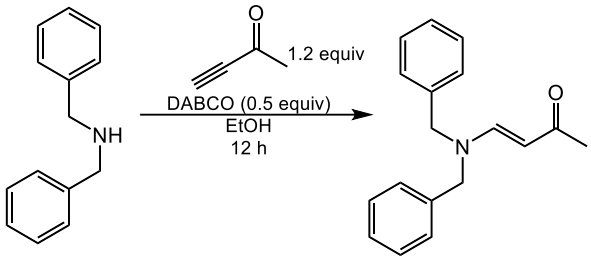

Prepared following Procedure A. The product was purified by silica gel flash column chromatography, using 10-30% ethyl acetate/hexanes as eluent, and the title compound was obtained in 89% yield (3.147 g, 19.52 mmol). Spectral data were identical to those reported in literature.[116]

**(*E*)-4-(methyl(phenyl)amino)but-3-en-2-one (18j)**



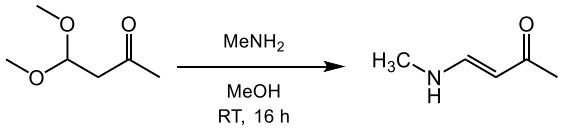

Prepared following Procedure A. The product was purified by silica gel flash column chromatography, using 5-10% ethyl acetate/hexanes as eluent, and the title compound was obtained in 84% yield (2.685 g, 15.32 mmol). Spectral data were identical to those reported in literature.[117]

**(*E*)-4-(dibenzylamino)but-3-en-2-one (18k)**



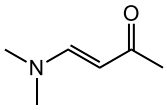

Prepared following Procedure A. The product was purified by silica gel flash column chromatography, using 1-5% ethyl acetate in hexanes as eluent, and the title compound was obtained in 76% yield (2.097 g, 7.90 mmol). Spectral data were identical to those reported in literature.[118]

**(*E*)-4-(methyl(phenyl)amino)but-3-en-2-one (18l)**



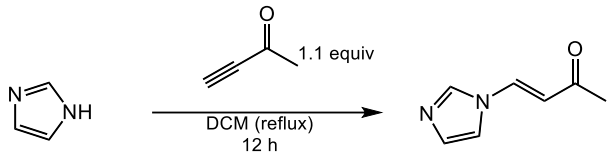

Prepared following procedure modified from literature. [117] To a vial containing a stir bar, added the starting material. The starting material was dissolved in methanol. Methylamine was added as one portion, and the reaction was stirred at room temperature for 16 hours, after which the stir bar was removed, and the solvent removed by rotary evaporation. The product was purified by silica gel flash column chromatography, using 30-100% ethyl acetate in hexanes, and the title compound was obtained in 70% yield (263 mg, 2.65 mmol). Spectral data were identical to those reported in literature.[117]

**(*E*)-4-(dimethylamino)but-3-en-2-one (18c)**



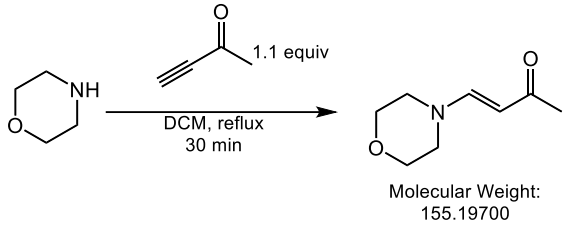
The title compound was purchased from Sigma Aldrich and used without further purification.

**(*E*)-4-(1H-imidazol-1-yl)but-3-en-2-one (18m)**



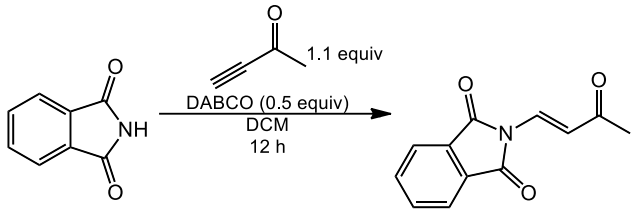

Prepared following Procedure B, without inclusion of DABCO and at reflux in DCM. The product was purified by silica gel flash column chromatography, using 5-30% ethyl acetate/hexanes, and the title compound was obtained in 84% yield (688 mg, 5.06 mmol). Spectral data were identical to those reported in literature.[118]

**(*E*)-4-morpholinobut-3-en-2-one (18n)**




Prepared following Procedure B, without inclusion of DABCO and at reflux in DCM. The product was purified by silica gel flash column chromatography, using 5-30% ethyl acetate in hexanes, and the title compound was obtained in 78% yield (1.210 g, 7.80 mmol). Spectral data were identical to those reported in literature.[118]

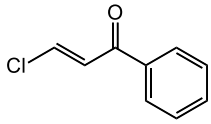
**(*E*)-2-(3-oxobut-1-en-1-yl)isoindoline-1,3-dione (18o)**




Prepared following Procedure B. Purified by silica gel flash chromatography using 20% ethyl acetate/hexanes as eluent. The title compound was obtained in 72% yield as an orange powder (773 mg, 3.59 mmol).

**$^{1}$H-NMR** (500 MHz, chloroform-D) δ 7.94 (q, J = 2.9 Hz, 1H), 7.80-7.83 (m, 2H), 7.28 (d, J = 14.9 Hz, 1H), 2.34 (s, 2H) **$^{13}$C-NMR** (151 MHz, chloroform-D) δ 198.2, 168.0, 165.7, 135.5, 135.3, 134.6, 134.3, 132.7, 131.5, 130.3, 130.0, 124.6, 124.5, 124.3, 123.8, 123.6, 116.7, 28.7 **IR** 3026, 1772, 1723, 1613, 1465, 1307, 1244, 1176, 168, 669, 582, 520, 451 $cm^{-1}$ **HRMS-ESI m/z** Calculated for $C_{12}H_9NO_3$ $[M + H]^+$ 216.0661, found 216.0657.

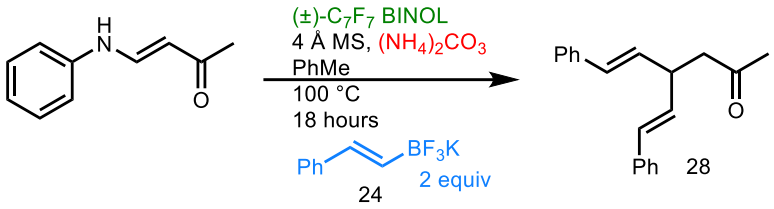
**(*E*)-3-chloro-1-phenylprop-2-en-1-one (18p)**




The title compound was purchased from Sigma Aldrich and used without further purification.

### 4.5.6 Optimized Double Addition and Utility of Additive

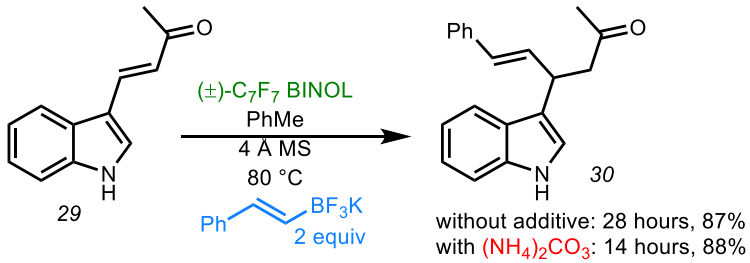
**(*E*)-6-phenyl-4-((*E*)-styryl)hex-5-en-2-one (28)**



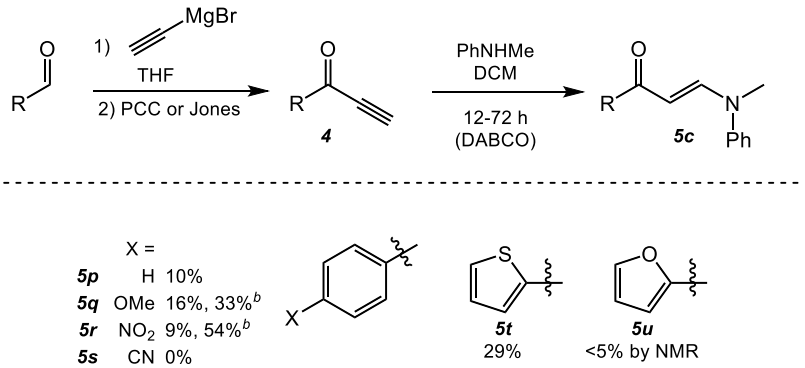

A vial was equipped with 4 Å MS (25 mg) and a stir bar and flame dried. The starting material (16.12 mg, 0.1 mmol) was added, under argon, followed by PhMe (1 mL). To the reaction mixture, added catalyst (14.4 mg, 0.02 mmol, 0.2 equiv), $(NH_4)_2CO_3$ (9.6 mg, 0.1 mmol, 1 equiv), and trifluoroborate salt **24** (42 mg, 0.2 mmol, 2 equiv). The vial was well sealed with Teflon tape and heated to reflux. After 18 hours, the reaction was diluted with ethyl acetate and filtered through a celite plug, washing with ethyl acetate. The solvents were removed by rotary evaporation. The title compound was purified by silica gel column chromatography using 1% EtOAc/Hexanes in 71% yield (19.6 mg). White solid.

**$^{1}$H-NMR** (500 MHz, chloroform-D) δ 7.22-7.30 (m, 8H), 7.15 (t, J = 7.2 Hz, 2H), 6.39 (d, J = 16.0 Hz, 2H), 6.14 (q, J = 7.6 Hz, 2H), 3.56-3.62 (m, 1H), 2.68 (d, J = 6.9 Hz, 2H), 2.11 (s, 3H) **$^{13}$C-NMR** (151 MHz, chloroform-D) δ 207.1, 137.2, 131.1, 130.8, 130.6, 128.6, 127.5, 126.3, 123.7, 48.7, 41.5, 36.7, 30.9 **IR** 2924, 2854, 2360, 1718, 1494, 1482, 1450, 1340, 1149, 990, 967, 748, 720, 694 **HRMS-ESI m/z** Calculated for $C_{20}H_{20}O$ $[M + Na]^+$ 299.1412, found 299.1409

**(E)-4-(1H-indol-3-yl)-6-phenylhex-5-en-2-one (30)**

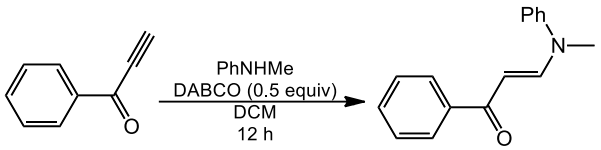



A vial was equipped with 4 Å MS (25 mg) and a stir bar and flame dried. The starting material (50.0 mg, 0.3 mmol) was added, under argon, followed by PhMe (3 mL). To the reaction mixture, added catalyst (43 mg, 0.06 mmol, 0.2 equiv), (if added) $(NH_4)_2CO_3$ (29 mg, 0.3 mmol, 1 equiv), and trifluoroborate salt **24** (42 mg, 0.6 mmol, 2 equiv). The vial was well sealed with Teflon tape and heated to reflux, and monitored by TLC. After 18 hours, the reaction containing additive was found to be complete by TLC (starting material was fully consumed), and the quantitative NMR yield was found to be 88%. Without additive, starting material was not consumed until 28 hours, after which time quantitative NMR yield was found to be 87% yield. All spectral data matched those reported in literature.[66]



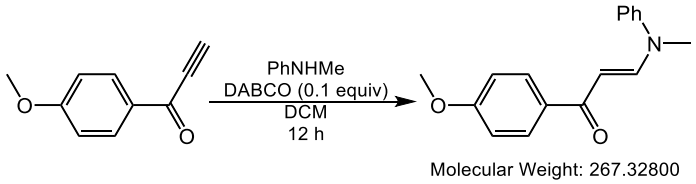

Summary of synthesis of vinylogous esters and amides.

**(*E*)-3-(methyl(phenyl)amino)-1-phenylprop-2-en-1-one (31a)**



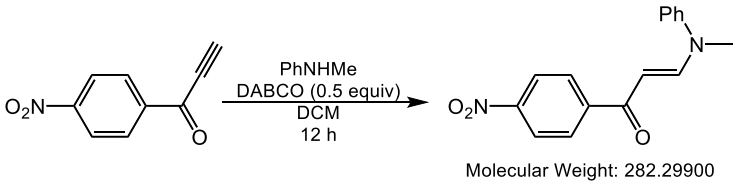

Prepared following Procedure B. The product was purified by silica gel flash column chromatography, using 5-15% ethyl acetate/hexanes as eluent and the title compound was obtained in 10% yield (101 mg, 0.42 mmol). Spectral data were identical to those found in literature.[119]

**(*E*)-1-(4-methoxyphenyl)-3-(methyl(phenyl)amino)prop-2-en-1-one (31b)**




Prepared following Procedure B. The product was purified by silica gel flash column chromatography, using 5-20% ethyl acetate/hexanes as eluent. The product was obtained in 16% yield (without DABCO, 27 mg, 0.10 mmol) and 33% yield (with 0.1 equivalents of DABCO, 23 mg, 0.09 mmol). Spectral data were identical to those found in literature.**Error! Bookmark not defined.**

**(*E*)-3-(methyl(phenyl)amino)-1-(4-nitrophenyl)prop-2-en-1-one (31c)**

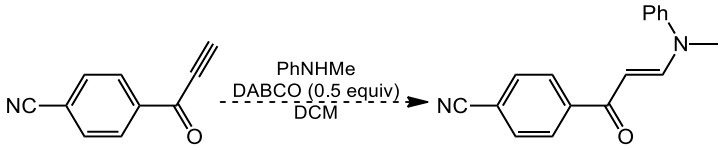



Prepared following Procedure B. The product was purified by silica gel flash chromatography with 1-15% ethyl acetate/hexanes as eluent. The product was obtained in 9% yield (15 mg, 0.05 mmol,

without DABCO) and 54% yield (206 mg, 0.73 mmol, with 0.5 equivalents of DABCO) as an orange solid.

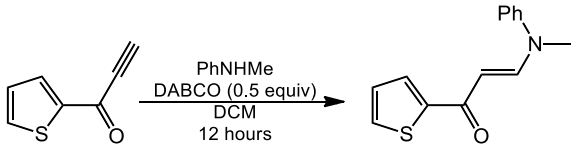
**$^{1}$H-NMR** (600 MHz, chloroform-D) δ 8.26 (d, J = 8.2 Hz, 3H), 8.04 (d, J = 7.6 Hz, 2H), 7.40 (t, J = 7.9 Hz, 2H), 7.21 (d, J = 8.2 Hz, 3H), 6.16-5.93 (1H), 3.43 (s, 3H) **$^{13}$C-NMR** (126 MHz, chloroform-D) δ 187.1, 151.4, 149.4, 145.5, 129.8, 128.6, 125.8, 123.7, 120.8, 96.4, 37.4 **IR** 3050, 1641, 1610, 1589, 1514, 1490, 1343, 1172, 1114, 1006, 856, 659, 572 cm$^{-1}$ **HRMS-ESI m/z** Calculated for $C_{16}H_{15}N_2O_3$ $[M + H]^+$ 283.1083, found 283.1079

**(*E*)-4-(3-(methyl(phenyl)amino)acryloyl)benzonitrile (31d)**




Attempted with both anhydrous and atmospheric reaction conditions, only starting materials were recovered from the reaction mixture, even after 48 hours.

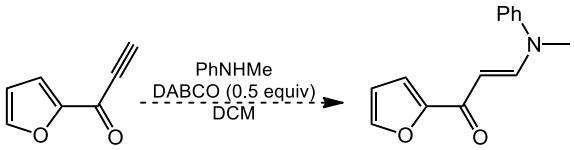
**(*E*)-3-(methyl(phenyl)amino)-1-(thiophen-2-yl)prop-2-en-1-one (31e)**




Prepared following Procedure B. Purified using silica gel flash chromatography with 20% ethyl acetate/hexanes as eluent. The product was obtained in 29% yield as a yellow-brown solid (52 mg, 0.21 mmol).

**$^{1}$H-NMR** (600 MHz, chloroform-D) δ 8.12 (d, J = 13.1 Hz, 1H), 7.60 (s, 1H), 7.43 (d, J = 4.8 Hz, 1H), 7.29 (t, J = 7.6 Hz, 2H), 7.07-7.12 (m, 3H), 7.02 (t, J = 4.1 Hz, 1H), 5.91 (d, J = 12.4 Hz, 1H), 3.30 (s, 3H) **$^{13}$C-NMR** (151 MHz, chloroform-D) δ 181.6, 149.4, 147.1, 146.4, 135.6, 131.2, 129.6, 129.3, 127.9, 125.1, 120.5, 112.5, 96.6, 77.4, 77.2, 77.0, 37.5, 30.9 **IR** 2970, 1739, 1628, 1531, 1490, 1217, 1120, 1080, 1063, 803, 757, 567, 528 cm$^{-1}$ **HRMS-ESI m/z** Calculated for $C_{14}H_{13}NOS$ $[M + H]^+$ 244.0796, found 244.0791

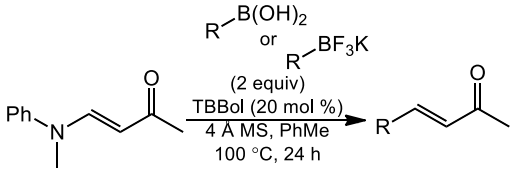
**(*E*)-1-(furan-2-yl)-3-(methyl(phenyl)amino)prop-2-en-1-one (31f)**




Attempted with both anhydrous and atmospheric reaction conditions, only starting materials were recovered from the reaction mixture, even after 48 hours.

### 4.5.7 Unsaturated Products of Vinylogous Substitution/Relay Catalysis

**General Procedures for Vinylogous Substitution**




**For Solid Starting Materials**

A 2 or 4 dram vial was equipped with 4 Å MS (250 mg/mmol) and a stir bar, then flame dried, activating the mol sieves.[3] Under argon, the trifluoroborate salt (or acid) (2 equiv), organodiol catalyst (20 mol %), and starting material were added to the vial. The solvent (0.2 M) was then

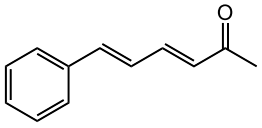
[3] Pre-activating molecular sieves and using oven-dried glassware reduces the yield.

added. If additional additives were included, they were added to the reaction mixture after the solvent. The vial was sealed well with Teflon tape and heated to reaction temperature in an aluminum bead bath, oil bath, or aluminum block. After the reaction was complete, the reaction mixture was diluted with ethyl acetate and filtered through celite. The celite pad was washed with ethyl acetate. The combined solvents were removed by rotary evaporation. Products were purified by silica gel flash chromatography using ethyl acetate/hexanes as the eluent.

**For Oil or Liquid Starting Materials**

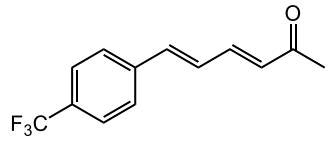
A 100 mg/mL stock solution of starting material was prepared with corresponding solvent in a flame dried vial. The stock solution was added after the solvent in the same procedure as above.

**(3*E*,5*E*)-6-phenylhexa-3,5-dien-2-one (20a)**



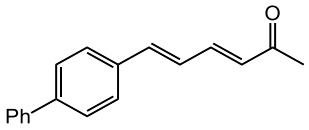
The title compound was synthesized from (*E*)-styrylboronic acid in 86% yield after 48 hours (74.0 mg, 0.43 mmol). It was also synthesized from the (*E*)-styryltrifluoroborate salt in 88% yield after 24 hours (76 mg, 0.44 mmol). The product was purified by silica gel flash column chromatography, using 1% ethyl acetate/hexanes as eluent. Spectral data were identical to those reported in literature.[120]

**(3*E*,5*E*)-6-(4-(trifluoromethyl)phenyl)hexa-3,5-dien-2-one (20b)**




The title compound was synthesized from (*E*)-(4-(trifluoromethyl)styryl)boronic acid in 24% yield (12 mg, 0.05 mmol) and from the (*E*)-(4-(trifluoromethyl)styryl)trifluoroborate salt in 85% yield (102 mg, 0.43 mmol). For the trifluoroborate salt reaction, $C_7F_7$-BINOL catalyst was used. The product was purified by silica gel flash column chromatography, using 1% ethyl acetate/hexanes as eluent. Spectral data were identical to those reported in literature.[121]

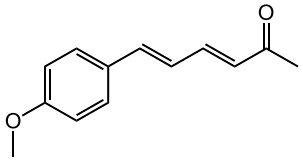
**(3*E*,5*E*)-6-([1,1'-biphenyl]-4-yl)hexa-3,5-dien-2-one (20c)**




The title compound was synthesized from (E)-(2-([1,1'-biphenyl]-4-yl)vinyl)trifluoroborate salt in 32% yield and purified by silica flash chromatography using 1% ethyl acetate/hexanes as eluent (40 mg, 0.16 mmol). White solid.

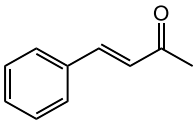
**$^1$H-NMR** (500 MHz, chloroform-D) δ 7.59 (d, J = 7.4 Hz, 4H), 7.54 (d, J = 8.0 Hz, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.33-7.36 (m, 1H), 7.29 (d, J = 13.2 Hz, 1H), 6.89-6.99 (m, 2H), 6.26 (d, J = 15.5 Hz, 1H), 2.31 (s, 3H) **$^{13}$C-NMR** (126 MHz, chloroform-D) δ 198.6, 143.6, 142.1, 140.9, 140.4, 135.0, 130.5, 129.0, 127.8, 127.8, 127.6, 127.1, 126.7, 27.5 **IR** 2922, 2852, 1653, 1616, 1488, 1184, 1150, 997, 844, 721, 692, 562 $cm^{-1}$ **HRMS-ESI m/z** Calculated for $C_{18}H_{16}O$ $[M + H]^+$ calculated 249.1279, found 249.1277

**(3*E*,5*E*)-6-(4-methoxyphenyl)hexa-3,5-dien-2-one (20d)**



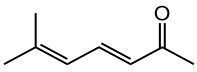
The title compound was synthesized from (*E*)-(4-methoxystyryl)boronic acid in 64% yield (26 mg, 0.13 mmol) and from (*E*)-(4-methoxystyryl)trifluoroborate salt in 88% yield (89 mg, 0.44 mmol). The product was purified by silica gel flash column chromatography, using 1-5% ethyl acetate/hexanes as eluent. Spectral data were identical to those reported in literature.[Error! Bookmark not defined.]

**(*E*)-4-phenylbut-3-en-2-one (20e)**



The title compound was synthesized from phenyl boronic acid in 13% yield (11 mg, 0.07 mmol) and from phenyl trifluoroborate salt in 20% yield (17 mg, 0.11 mmol). The product was purified by silica gel flash column chromatography, using 1-10% ethyl acetate/hexanes as eluent. Spectral data were identical to those reported in literature.[43]

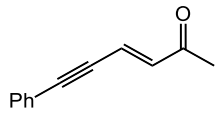
**(*E*)-6-methylhepta-3,5-dien-2-one (20f)**



The title compound was synthesized from (*E*)-(4-methylpenta-1,3-dien-1-yl)boronic acid in 24% yield (17 mg, 0.14 mmol) and from (*E*)-(4-methylpenta-1,3-dien-1-yl)trifluoroborate salt in 40%

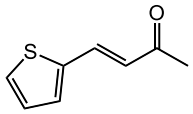
yield (28 mg, 0.23 mmol). The product was purified by silica gel flash column chromatography, using 1-5% ethyl acetate/hexanes as eluent. Spectral data were identical to those reported in literature.[122]

**(*E*)-6-phenylhex-3-en-5-yn-2-one (20g)**



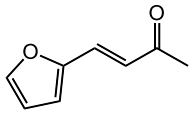

The title compound was synthesized from (phenylethynyl)trifluoroborate salt in 82% yield after 48 hours (56.0 mg, 0.33 mmol). The product was purified by silica gel flash column chromatography, using 1-15% ethyl acetate/hexanes as eluent. Spectral data were identical to those reported in literature.**Error! Bookmark not defined.**

**(*E*)-4-(thiophen-2-yl)but-3-en-2-one (20i)**



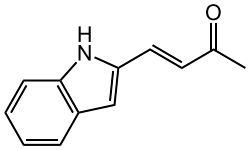

The title compound was synthesized from thiophen-2-ylboronic acid in 49% yield (14.9 mg, 0.10 mmol) and from thiophen-2-yltrifluoroborate salt in 6% yield (1.7 mg, 0.01 mmol). The product was purified by silica gel flash column chromatography, using 5-20% ethyl acetate/hexanes as eluent. Spectral data were identical to those reported in literature.[43]

**(*E*)-4-(furan-2-yl)but-3-en-2-one (20j)**



The title compound was synthesized from thiophen-2-ylboronic acid in 15% yield (4.1 mg, 0.03 mmol) and from thiophen-2-yltrifluoroborate salt in 43% yield (11.8 mg, 0.09 mmol). The product was purified by silica gel flash column chromatography, using 5-15% ethyl acetate/hexanes as eluent. Spectral data were identical to those reported in literature.[123]

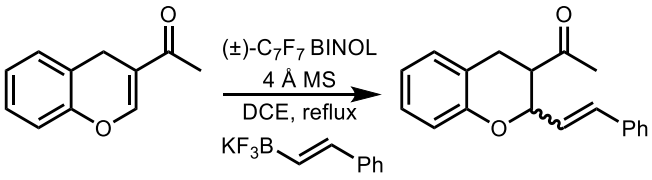
**(*E*)-4-(1H-indol-2-yl)but-3-en-2-one (20k)**



The title compound was synthesized from (1-(tert-butoxycarbonyl)-1H-indol-2-yl)trifluoroborate salt in 24% yield (11.0 mg, 0.06 mmol). The Boc-group protecting the indole nitrogen was found to have been removed in the product. The product was purified by silica gel flash column chromatography, using 1-20% ethyl acetate/hexanes as eluent. Spectral data were consistent with those found in literature.[124]

### 4.5.8 Other Electrophiles

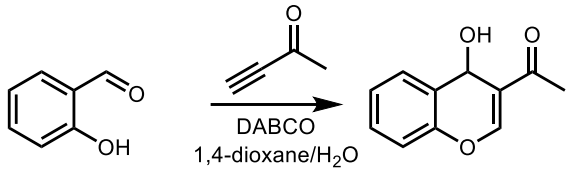
**1-(2-styrylchroman-3-yl)ethanone (36)**




A 4-dram vial was equipped with 4 Å MS (250 mg/mmol) and a stir bar, then flame dried, activating the mol sieves. Under argon, the trifluoroborate salt (143 mg, 0.68 mmol, 2 equiv),

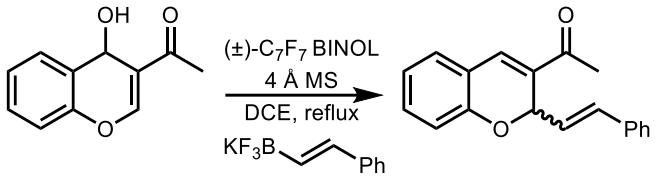
organodiol catalyst (79 mg, 0.11 mmol, 20 mol %), and starting material[125] (100 mg, 0.57 mmol) were added to the vial. DCE (6 mL, 0.1 M) was then added. The vial was sealed well with Teflon tape and heated to reflux in an aluminum block. After the reaction was complete, the reaction mixture was diluted with ethyl acetate and filtered through celite. The celite pad was washed with ethyl acetate. The combined solvents were removed by rotary evaporation. Products were purified by silica gel flash chromatography using 25 – 40% ethyl acetate/hexanes as the eluent.

**1-(4-hydroxy-4H-chromen-3-yl)ethanone (37)**



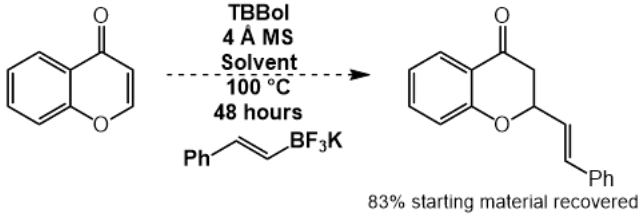

Added 1,4-dioxane/$H_2O$ to a 50 mL round bottom flask (20 mL each, 1:1 v/v). While stirring, added starting material (3.2 mL, 30 mmol, 3 equiv) and 3-butyn-2-one (0.8 mL, 10 mmol, 1 equiv). Added DABCO (0.224 g, 2 mmol, 0.2 equiv) to the reaction mixture and allowed to stir for 12 hours. After the reaction time was complete, added 40 mL saturated $NaHCO_3$ and allowed to stir for 10 minutes. Neutralized with 1 M HCl (to pH of 7) and extracted with DCM. Washed with water, then with brine. The organic phase was dried over $MgSO_4$ and the solvents removed by rotary evaporation. The title compound was purified by silica gel column chromatography using 5-40% ethyl acetate/hexanes as eluent. The title compound was obtained as a yellow solid in 40.3% yield (767 mg). All spectral data matched those reported in literature.[126]

**1-(2-styryl-2H-chromen-3-yl)ethanone (38)**

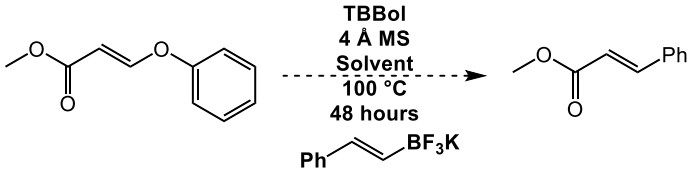



A 4-dram vial was equipped with 4 Å MS (250 mg/mmol) and a stir bar, then flame dried, activating the mol sieves. Under argon, the trifluoroborate salt (143 mg, 0.68 mmol, 2 equiv), organodiol catalyst (79 mg, 0.11 mmol, 20 mol %), and starting material (100 mg, 0.57 mmol) were added to the vial. DCE (6 mL, 0.1 M) was then added. The vial was sealed well with Teflon tape and heated to reflux in an aluminum block. After the reaction was complete, the reaction mixture was diluted with ethyl acetate and filtered through celite. The celite pad was washed with ethyl acetate. The combined solvents were removed by rotary evaporation. Products were purified by silica gel flash chromatography using 25 – 40% ethyl acetate/hexanes as the eluent. **$^{1}$H-NMR** (600 MHz, chloroform-D) δ 7.39 (s, 1H), 7.31-7.28 (m, 3H), 7.25-7.19 (m, 4H), 6.95 (t, J = 6.9 Hz, 2H), 6.63 (d, J = 15.8 Hz, 1H), 6.21 (dd, J = 15.6, 6.4 Hz, 1H), 6.00 (d, J = 6.2 Hz, 1H), 2.44 (s, 3H) **$^{13}$C-NMR** (151 MHz, chloroform-D) δ 195.9, 154.2, 136.3, 133.6, 133.6, 133.0, 132.2, 132.1, 129.5, 129.4, 128.6, 128.1, 126.8, 125.4, 121.8, 120.4, 117.1, 73.4, 73.3, 25.4 **HRMS-ESI m/z** Calculated for $C_{19}H_{17}O_2$ [M+H] 277.1229, found 277.1217

### 4.5.9 Additional Control Experiments




Even after a considerable reaction time, no product was observed, and starting material was recovered. In this case, likely the *s-trans*-conformation does not allow for reactivity.




Even after a considerable reaction time, no product was observed, and starting material was recovered. Esters are likely not reactive in vinylogous substitution reactions.

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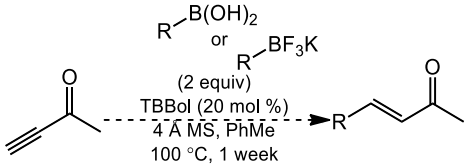
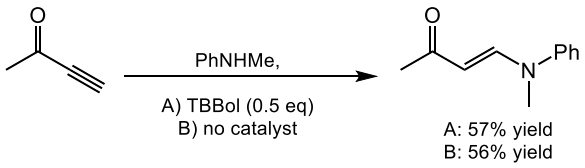
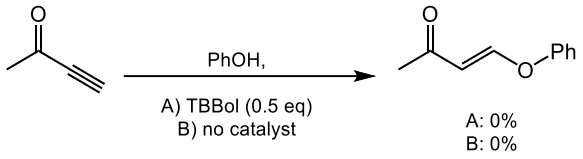



Even after extended reaction time, the alkyne is not reactive without the presence of methyl aniline to initiate relay catalysis.




In the case of methyl aniline, the presence of TBBol did not increase the yield of vinylogous amide when compared to the uncatalyzed reaction.




In the case of phenol, the presence of TBBol did not allow for formation of the vinylogous ester, which is consistent with the uncatalyzed reaction.

### 4.5.10 Catalyst Synthesis

2,2'-biphenol, *L*-tartaric acid, 1,4-butanediol and (±)-BINOL were purchased from Sigma Aldrich and used without further purification as catalysts.

**$C_7F_7$-BINOL, IODO-BINOL**

**(3r)-3,3'-bis(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-[1,1'-binaphthalene]-2,2'-diol, 3,3'-diiodo-[1,1'-binaphthalene]-2,2'-diol**

Prepared as previously reported.[43]

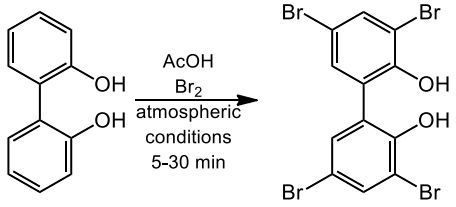
**(*L*)-tartramide**

(2*R*,3*R*)-4-(dibenzylamino)-2,3-dihydroxy-4-oxobutanoic acid

Prepared following literature procedures.[127]

**TBBol**

3,3',5,5'-tetrabromo-[1,1'-biphenyl]-2,2'-diol



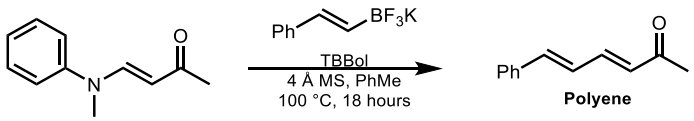

The procedure was modified from literature reports.[128] In a round bottom flask equipped with a large stir bar, under atmospheric conditions, 2,2'-biphenol (2.0 g, 12.4 mmol) was added. Acetic acid was slowly added (25 mL, 0.2 M). The reaction mixture was stirred until the starting material was fully dissolved, approximately 1 minute. Bromine (3.1 mL, 62 mmol, 5 equiv) was slowly added to the reaction mixture. The reaction mixture was stirred vigorously until a yellow solid precipitated out of solution (5-30 min, depending on the scale). The reaction was quenched with excess $Na_2S_2O_3$, then extracted with DCM (3 times). The combined organic layers were washed with water and extracted with 50 mL of DCM (3 times), then again washed with brine, extracting with 50 mL of DCM (3 times). The combined DCM portions were dried over $Na_2SO_4$. The solvent was removed by rotary evaporation. The solid obtained was usually >96% pure (by NMR), but it could be crystallized from ethanol if required (if color considerably deviates from pale orange to white).

The spectral data were identical to those reported in literature.[129]

**$^1$H-NMR** (600 MHz, chloroform-D) δ 7.66 (d, J = 2.1 Hz, 2H), 7.33 (d, J = 2.7 Hz, 2H), 5.85 (s, 2H) **$^{13}$C-NMR** (151 MHz, chloroform-D) δ 148.90, 134.64, 134.59, 133.55, 125.83, 112.97, 112.05

### 4.5.11 Functional Group Screen

Functional group screens were adapted from protocols developed by the Glorius group.[130–132] Quantitative NMR was used to analyze yields. Reactions were set up in tandem with the same batch of starting materials and catalyst(s). All reaction vials were equipped with stir bars and mol sieves, then flame dried. The trifluoroborate salt was added as a solid, as it is not soluble in the reaction mixture. The remaining components, including standards, were pre-mixed as a stock solution and added to the vials containing mol sieves and trifluoroborate salt. After the reaction time, the reaction mixtures were filtered through celite plugs (in pipettes) and solvent was removed by rotary evaporation. NMR yields were determined by the addition of 1.0 equivalent of methyl 4-nitrobenzoate as an internal standard to the crude reaction mixture and comparing the integration of the standard's peaks to those of the starting material, additive, and product (16 scans, 30 second relaxation delay, JEOL ECZ-400 spectrometer, by autosampler).

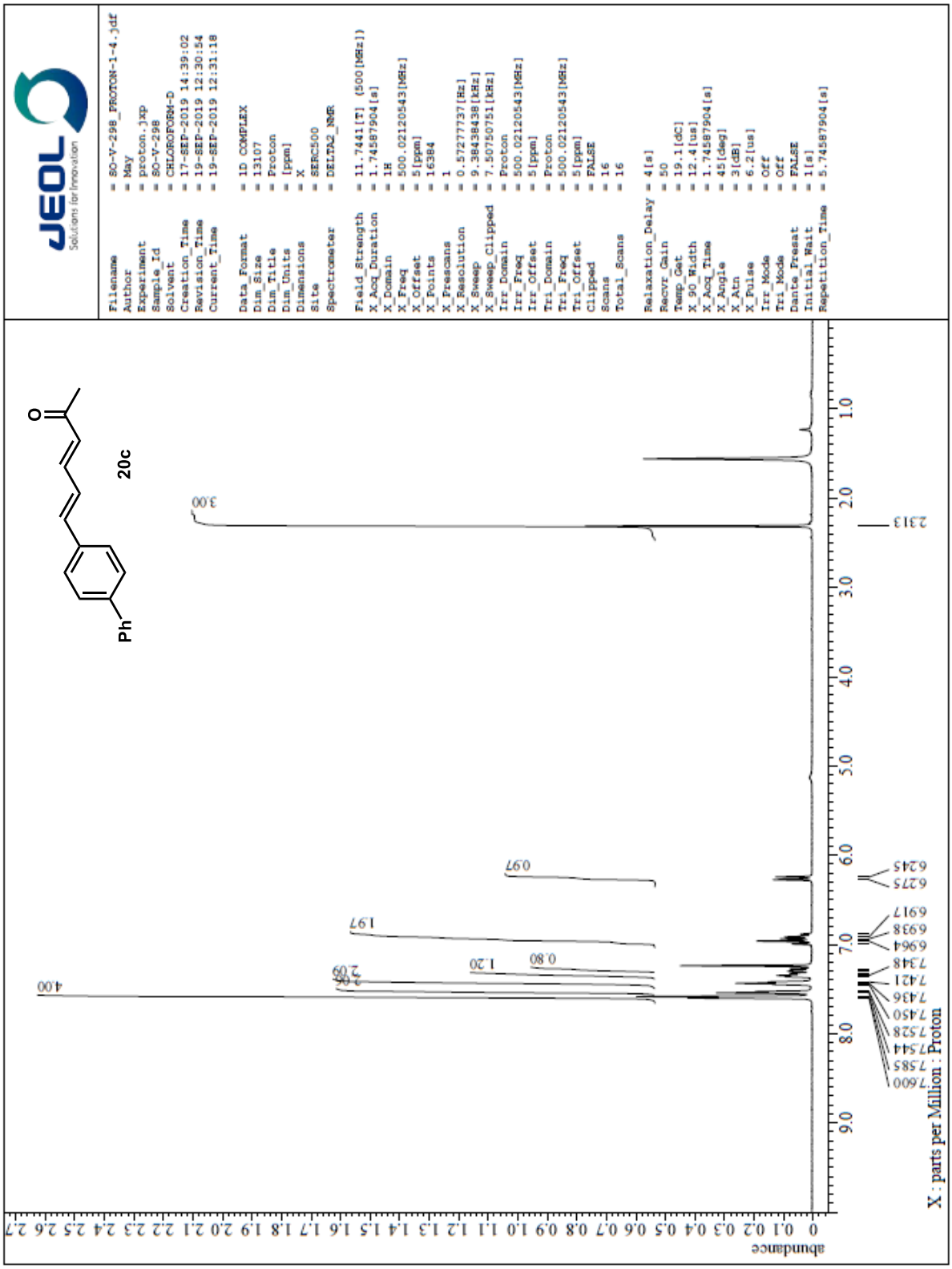



| Entry | Additive | % Yield | % Recovery Additive | % Recovery Starting Material |
|---|---|---|---|---|
| 1 | **None - Control** | **77** | **control** | 1 |
| 2 | 1-undecene | **74** | **12** | 22 |
| 3 | 1-octyne | **73** | **0** | 22 |
| 4 | tridecanenitrile | **82** | **92** | 1 |
| 5 | chloroheptane | **72** | **1** | 11 |
| 6 | decylamine | **11** | **99** | 48 |
| 7 | 6-undecanone | **71** | **91** | 26 |
| 8 | nonanol | **70** | **76** | 30 |
| 9 | acetanilide | **74** | **88** | 18 |
| 10 | methyl benzoate | **78** | **100** | 17 |
| 11 | 2-vinynaphthalene | **72** | **100** | 23 |
| 12 | 4-octyne | **76** | **0** | 18 |
| 13 | benzonitrile | **55** | **35** | 42 |
| 14 | benzylamine | **0** | **0** | 0 |
| 15 | benzaldehyde | **49** | **70** | 29 |
| 16 | phenol | **42** | **100** | 44 |
| 17 | 1-benzylpyrrole | **77** | **93** | 0 |
| 18 | 1-methylimidazole | **12** | **87** | 62 |
| 19 | 2-n-butylfuran | **76** | **0** | 0 |
| 20 | 2-chloroquinoline | **74** | **100** | 0 |
| 21 | benzoxazole | **76** | **75** | 0 |
| 22 | chromone | **42** | **77** | 0 |
| 23 | 3,5-lutidine | **62** | **31** | 0 |
| 24 | 4-methylthiazole | **74** | **0** | 0 |
| 25 | 2-n-butylthiophene | **73** | **8** | 0 |
| 26 | 2,3-benzofuran | **68** | **77** | 0 |
| 27 | n-methylacetanilide | **69** | **100** | 1 |
| 28 | 2-chloropyridine | **81** | **100** | 0 |
| 29 | benzothiazole | **65** | **100** | 0 |
| 30 | 2-picoline-*N*-oxide | **44** | **53** | 24 |

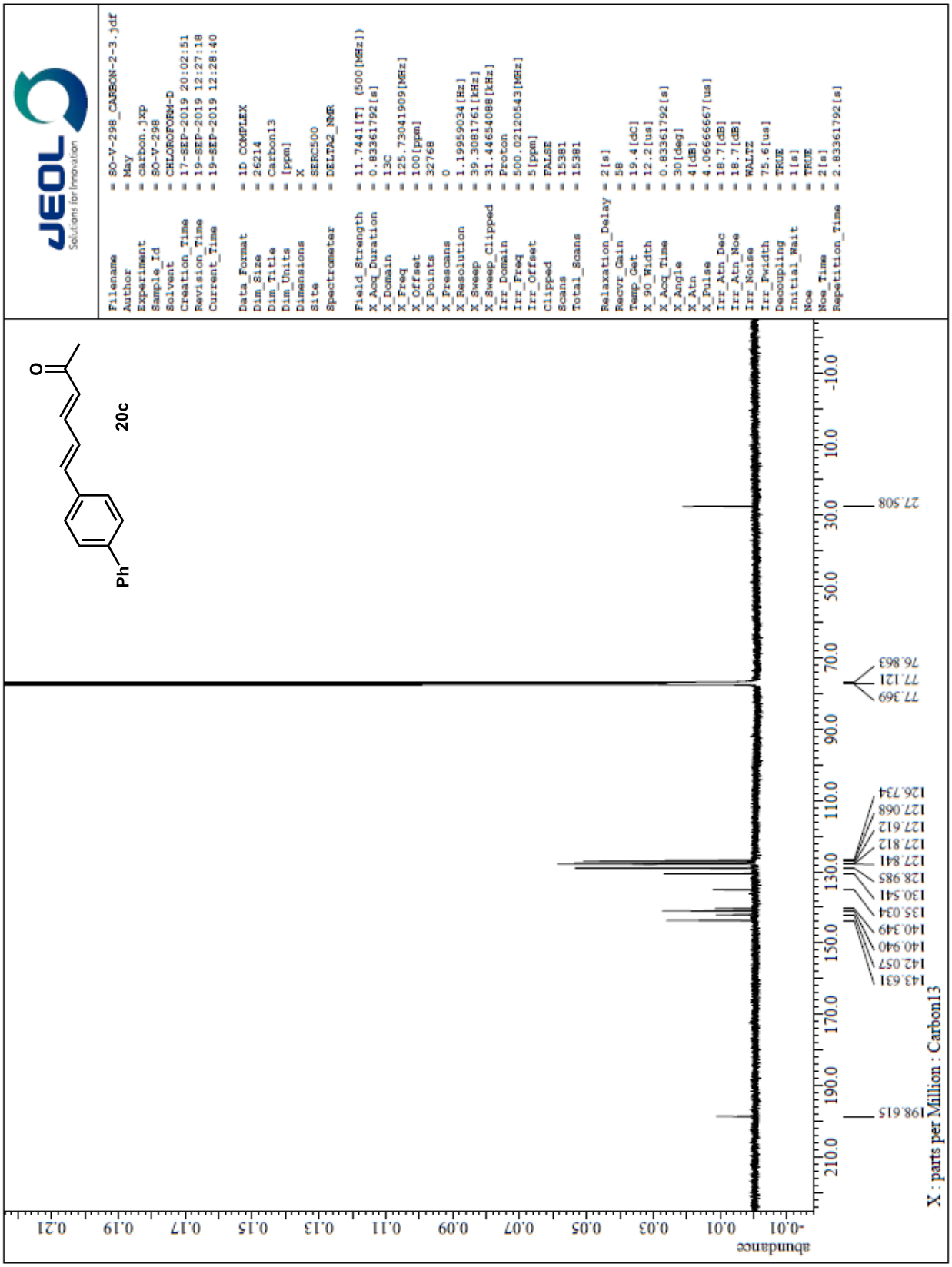
**APPENDIX – CHAPTER FOUR**

Spectra Relevant to Chapter Four

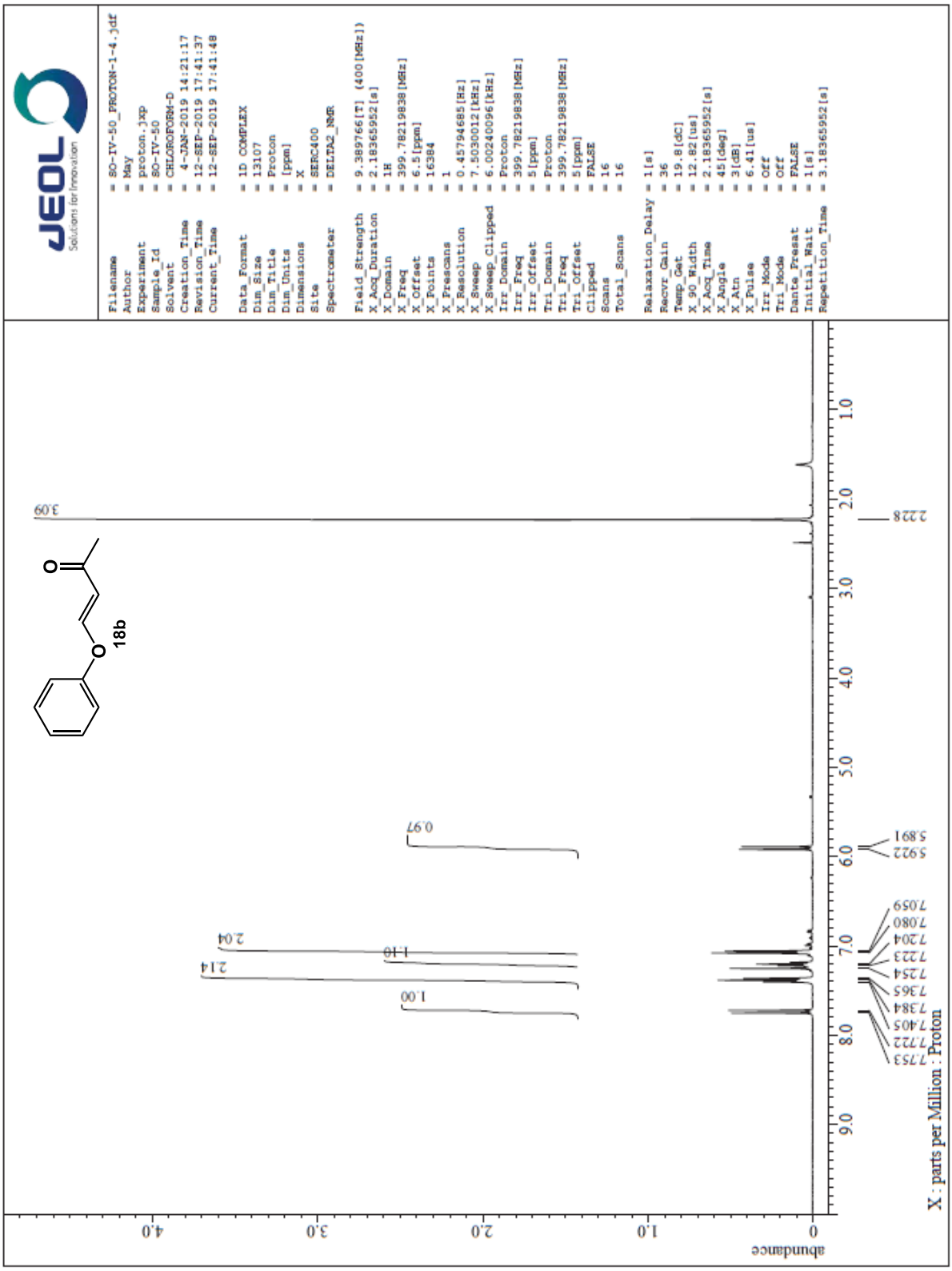
# Conjugate Addition for Vinylogous Substitution with Organoborates



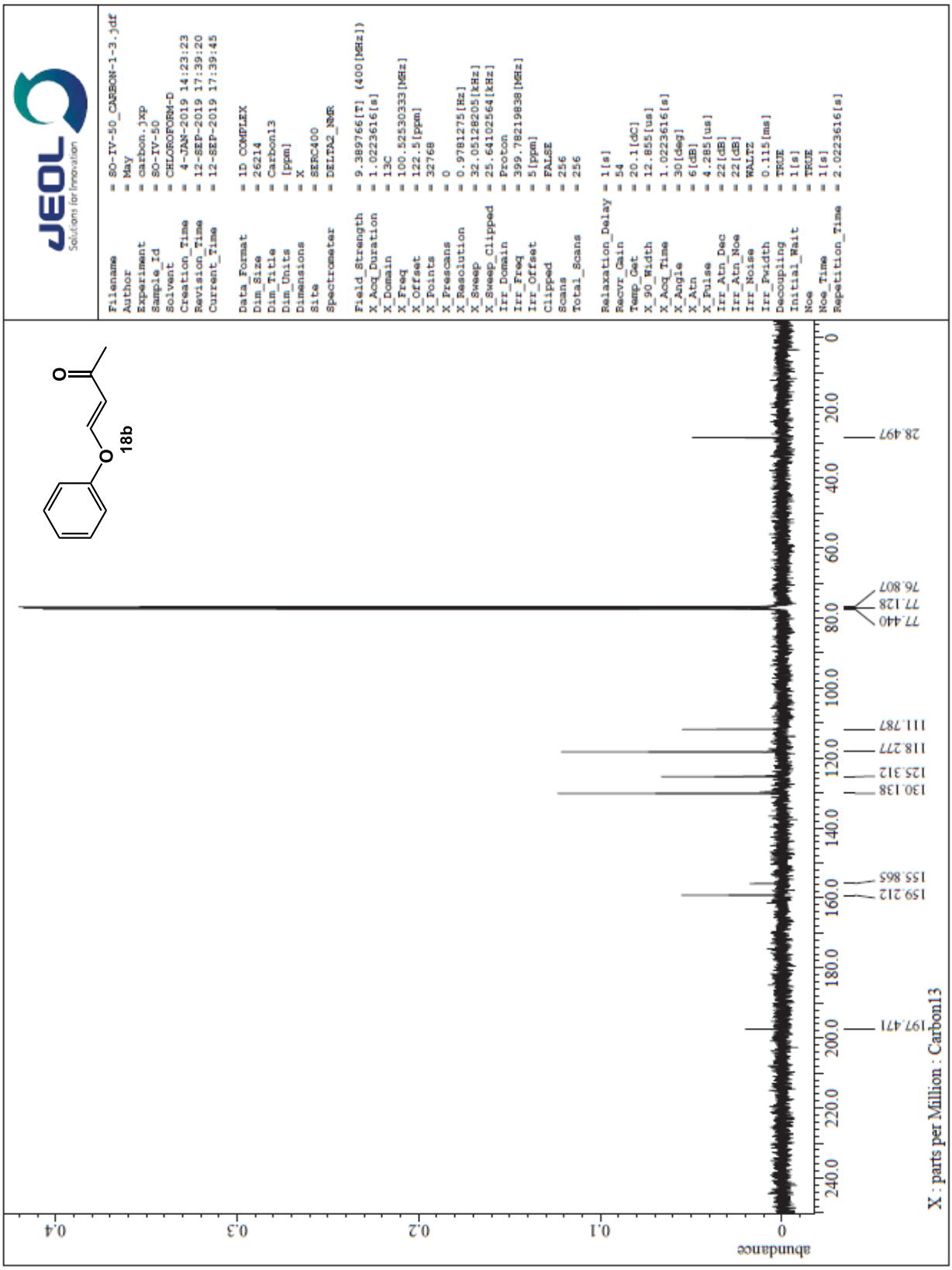

**$^{1}$H NMR Spectrum of (3E,5E)-6-([1,1'-biphenyl]-4-yl)hexa-3,5-dien-2-one (20c)**



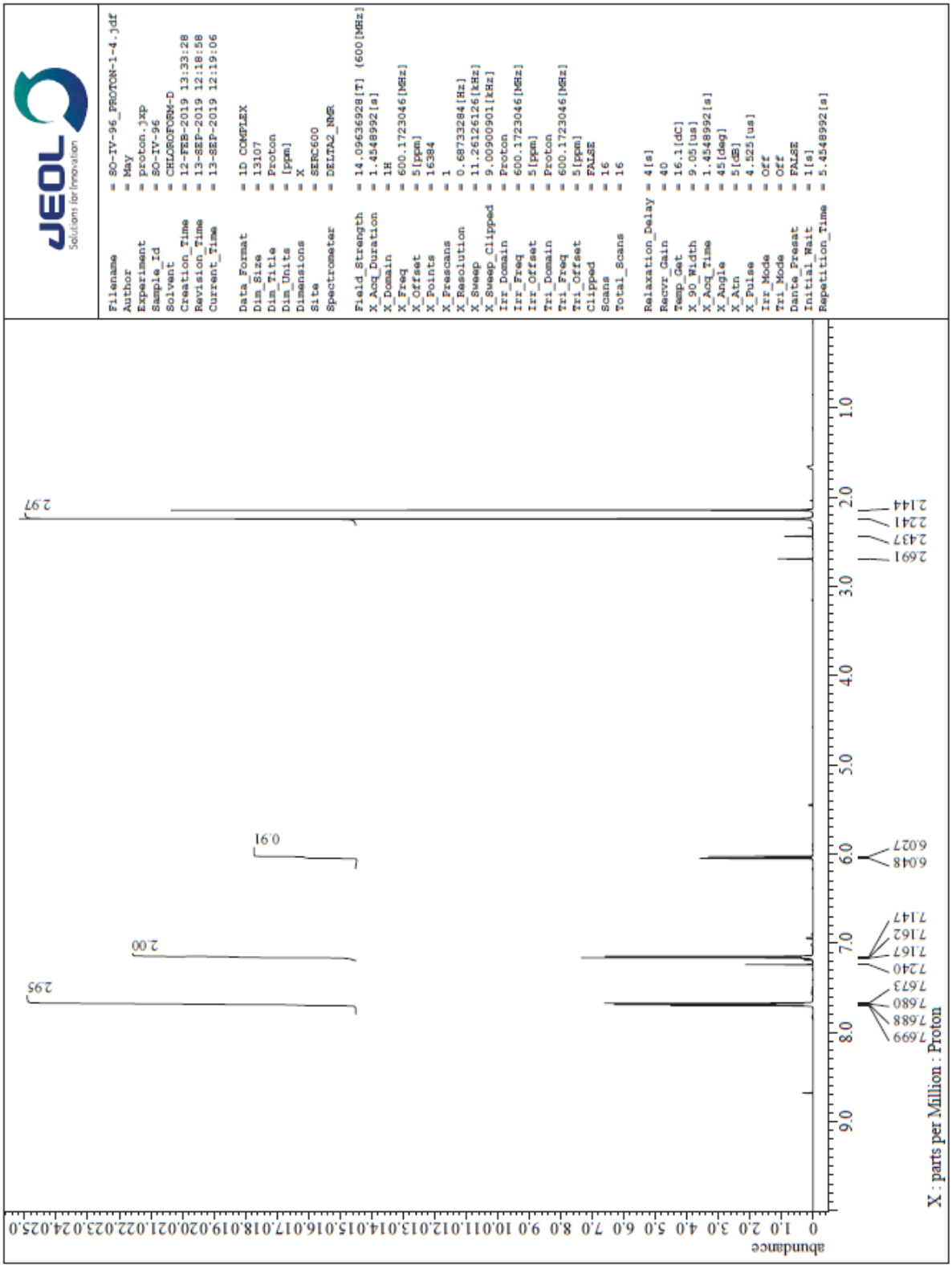

**$^{13}$C NMR Spectrum of (3E,5E)-6-([1,1'-biphenyl]-4-yl)hexa-3,5-dien-2-one (20c)**



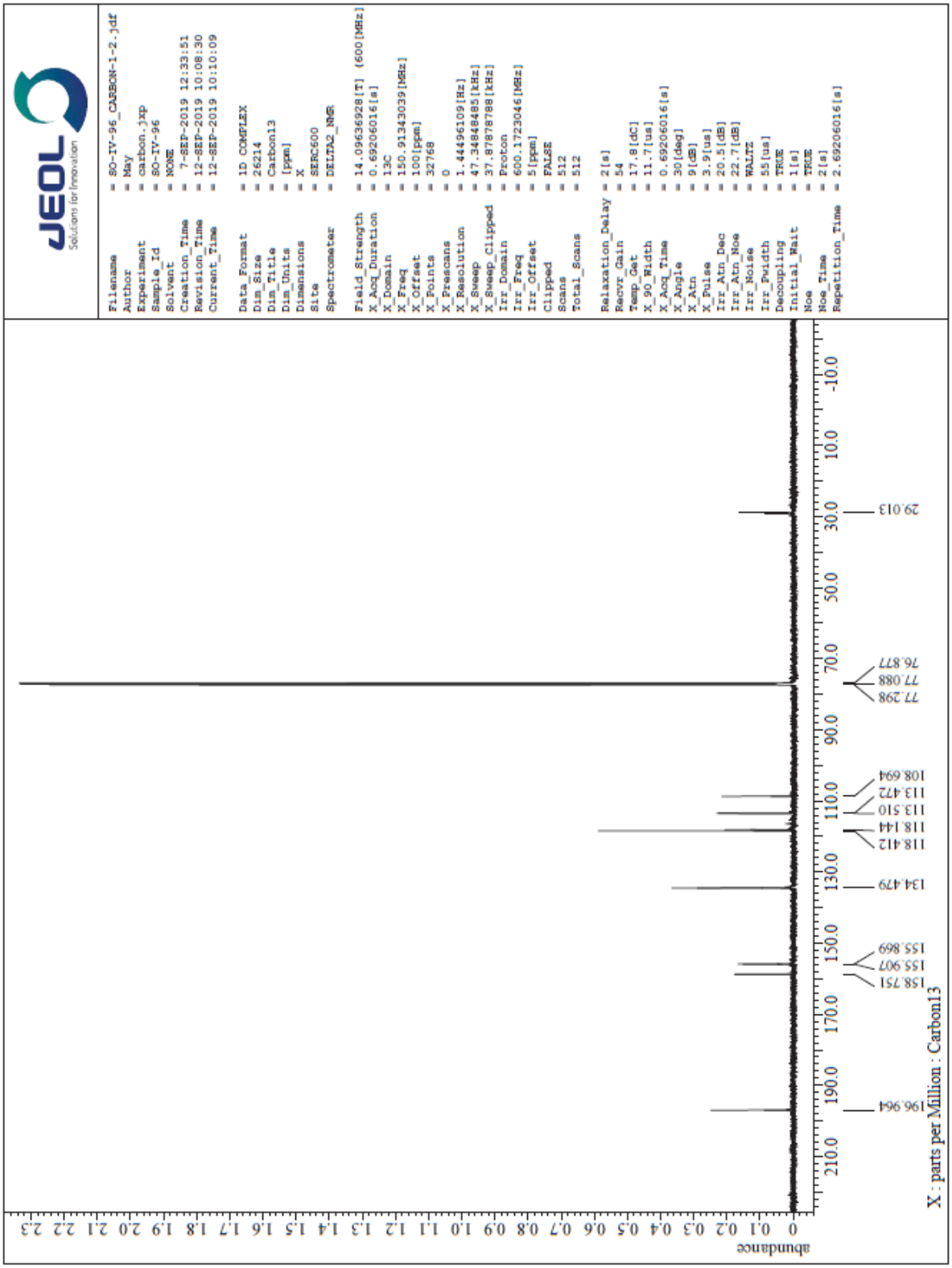

**$^{1}$H NMR spectrum of (*E*)-4-phenoxybut-3-en-2-one (18b)**



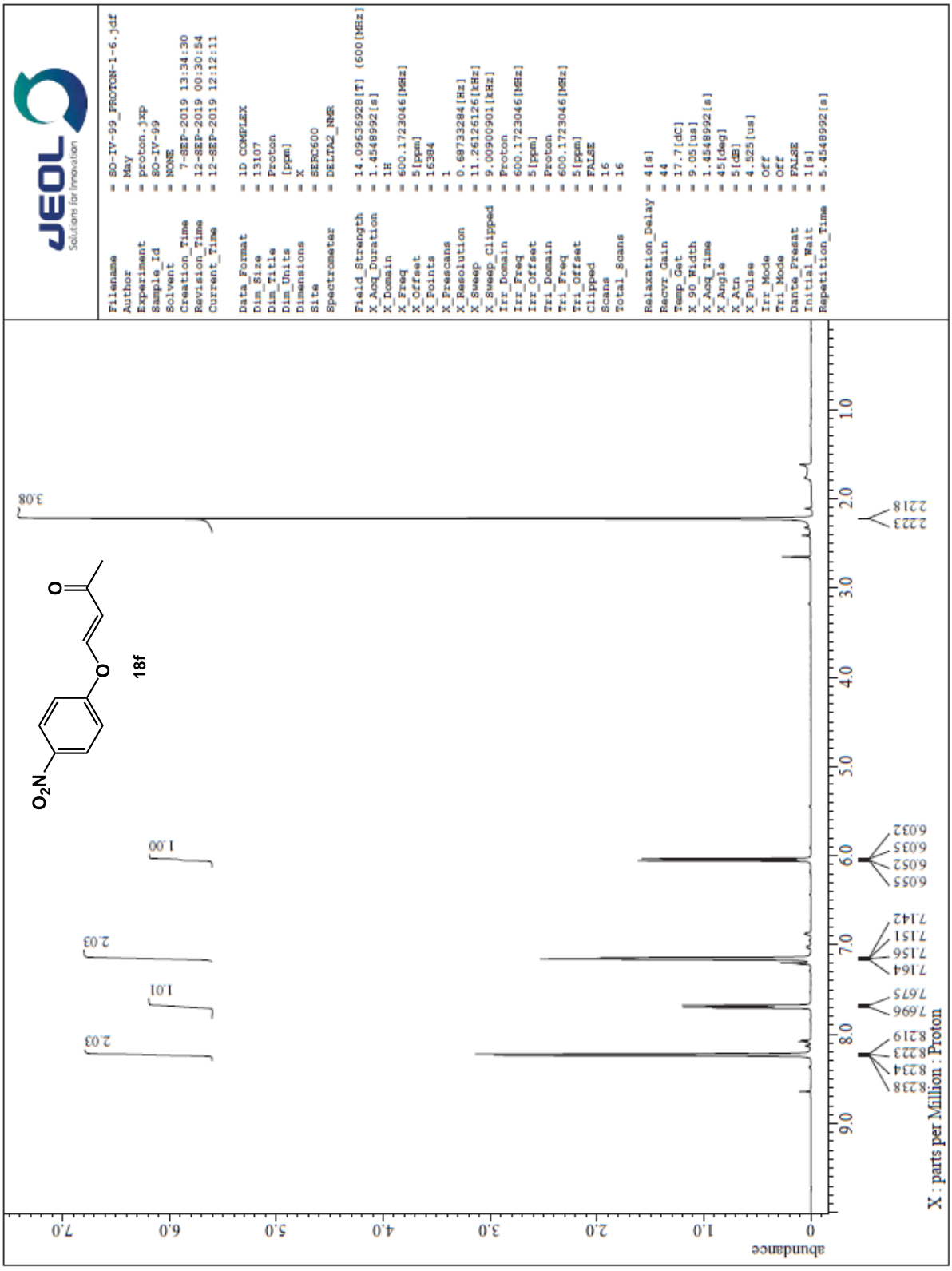

**$^{13}$C NMR spectrum of (*E*)-4-phenoxybut-3-en-2-one (18b)**



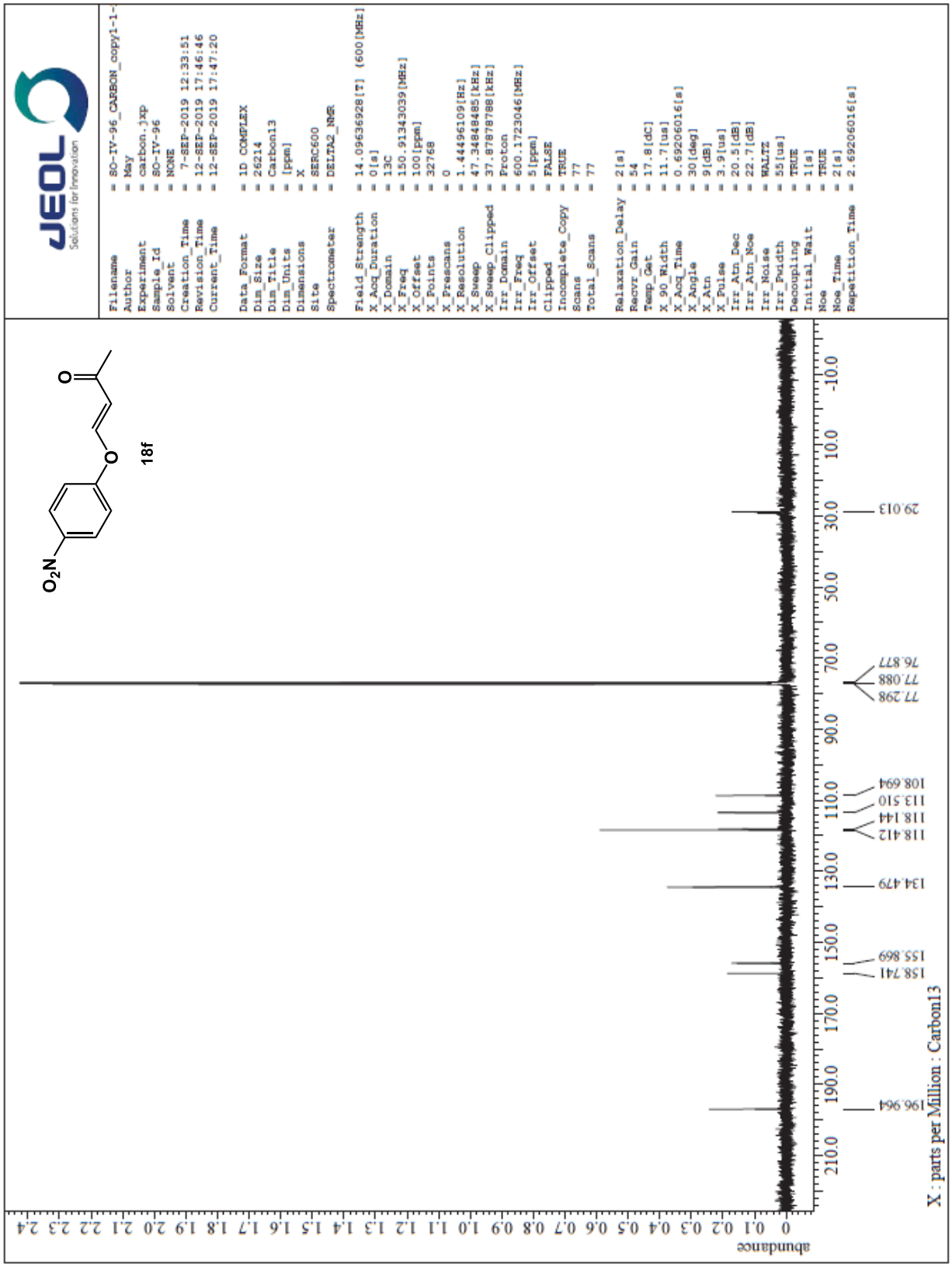

**$^{1}$H NMR spectrum of (*E*)-4-((3-oxobut-1-en-1-yl)oxy)benzonitrile (18e)**



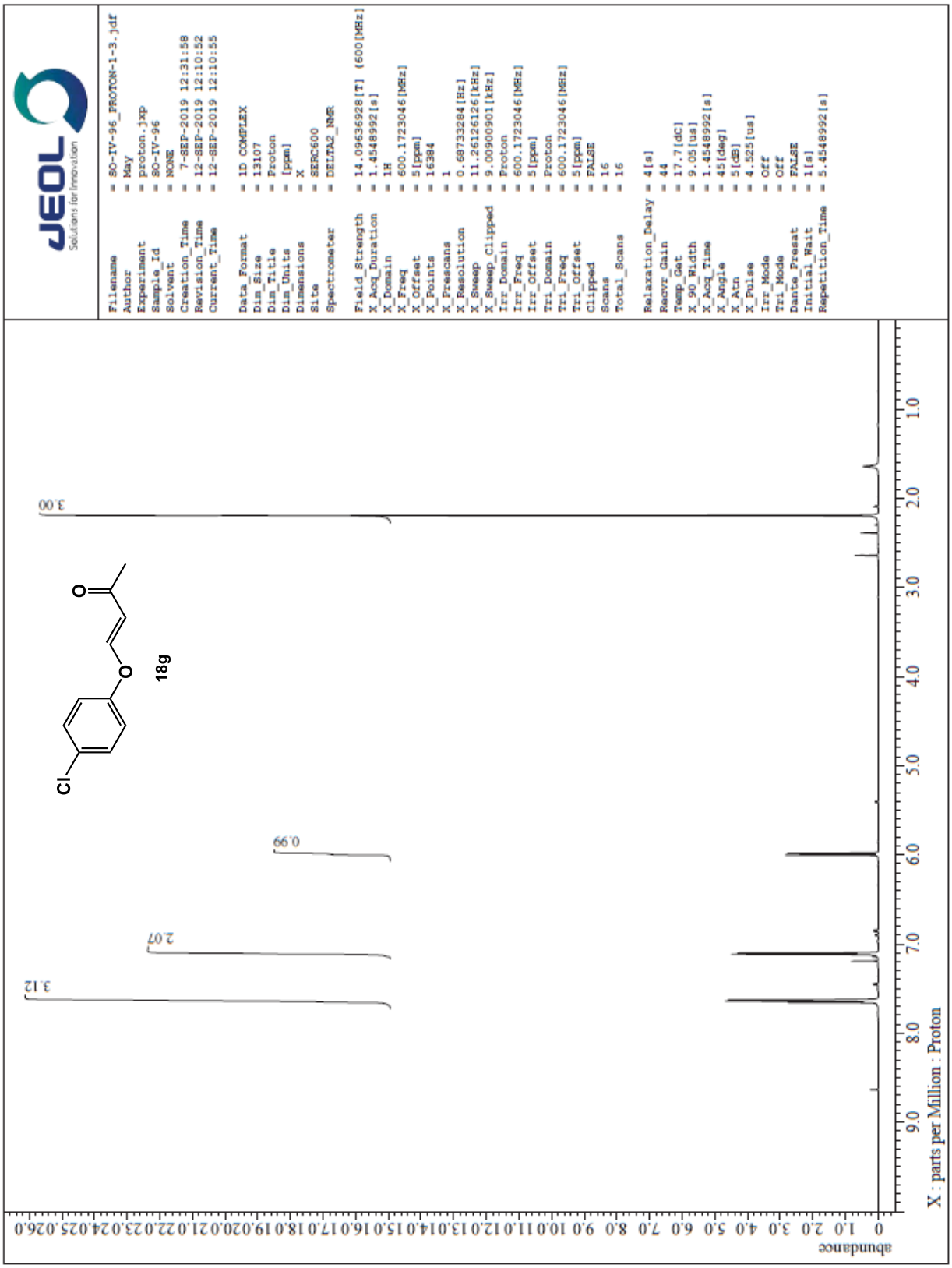

**$^{13}$C NMR spectrum of (*E*)-4-((3-oxobut-1-en-1-yl)oxy)benzonitrile (18e)**



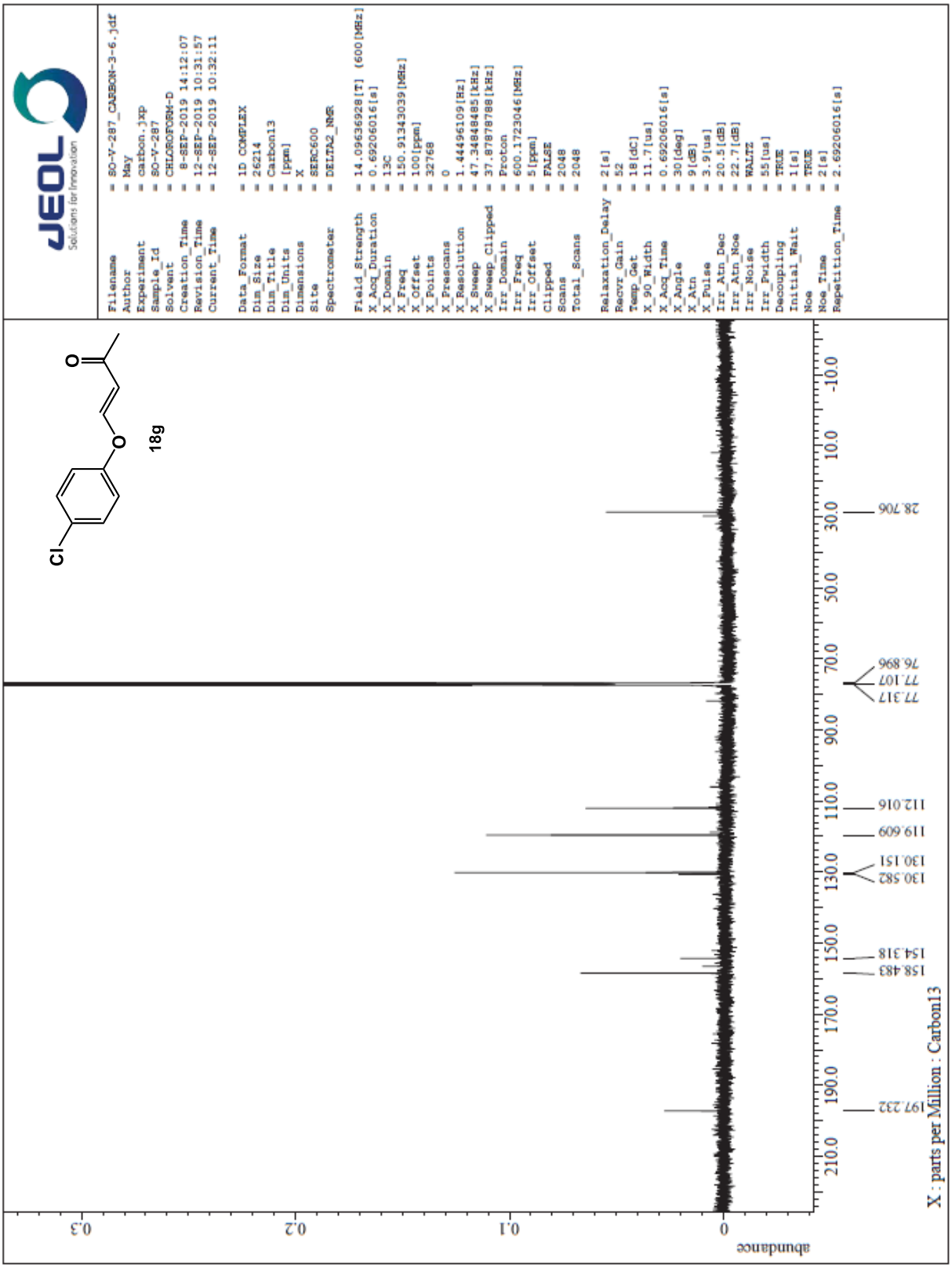

**$^{1}$H NMR spectrum of (*E*)-3-(methyl(phenyl)amino)-1-(4-nitrophenyl)prop-2-en-1-one (18f)**



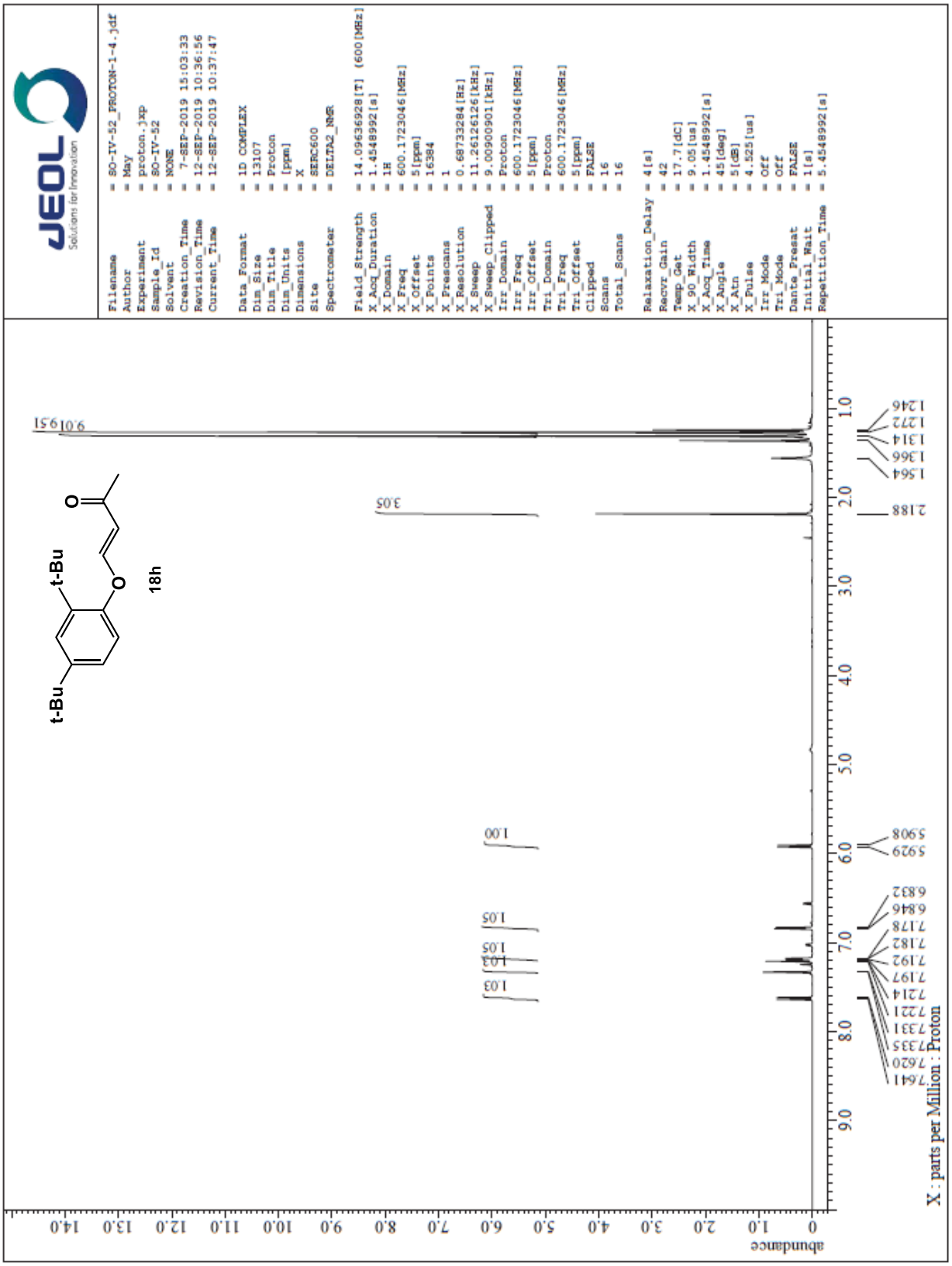

**$^{13}$C NMR spectrum of (*E*)-3-(methyl(phenyl)amino)-1-(4-nitrophenyl)prop-2-en-1-one (18f)**



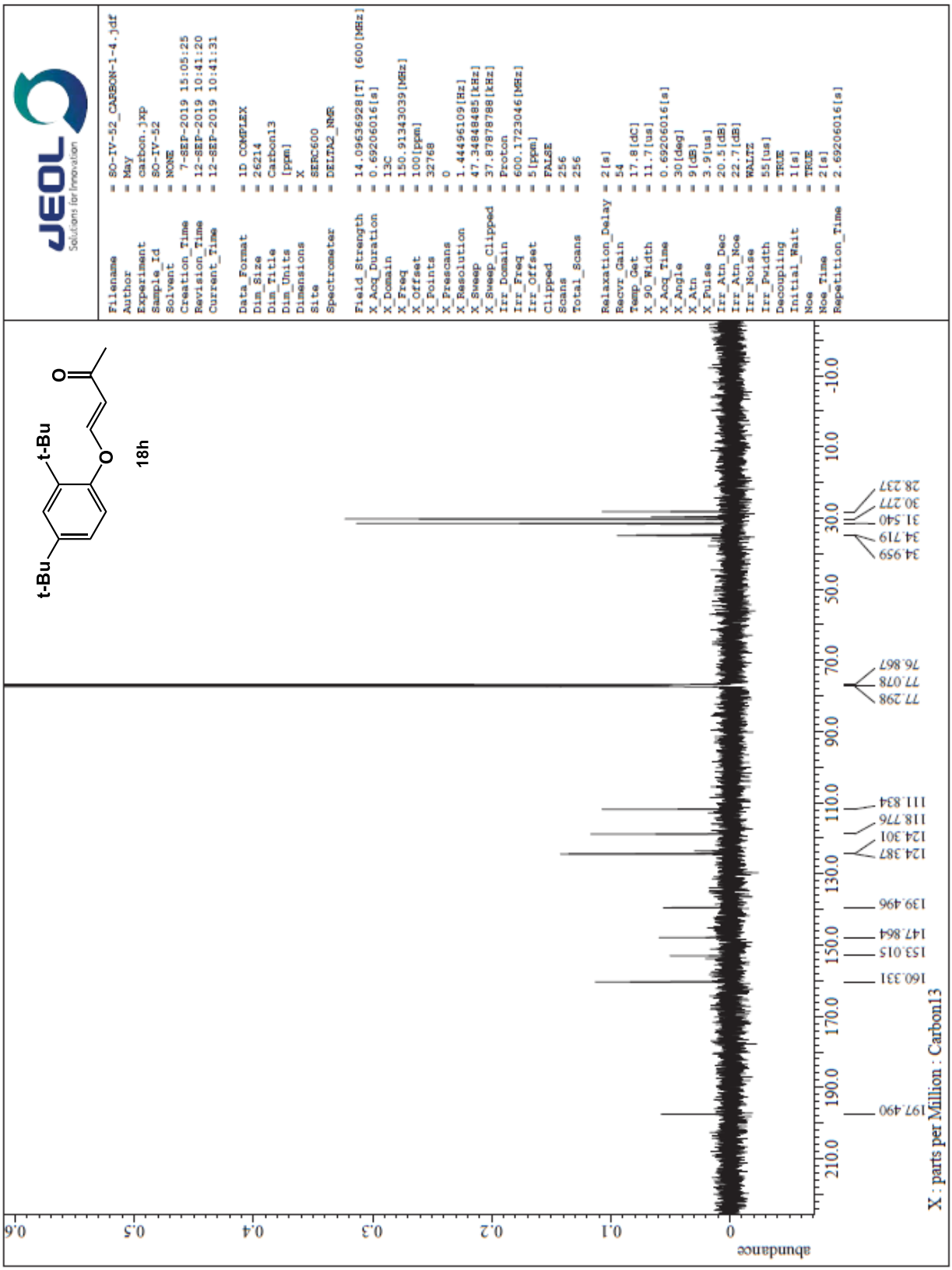

**$^{1}$H NMR spectrum of compound (*E*)-4-(4-chlorophenoxy)but-3-en-2-one (18g)**



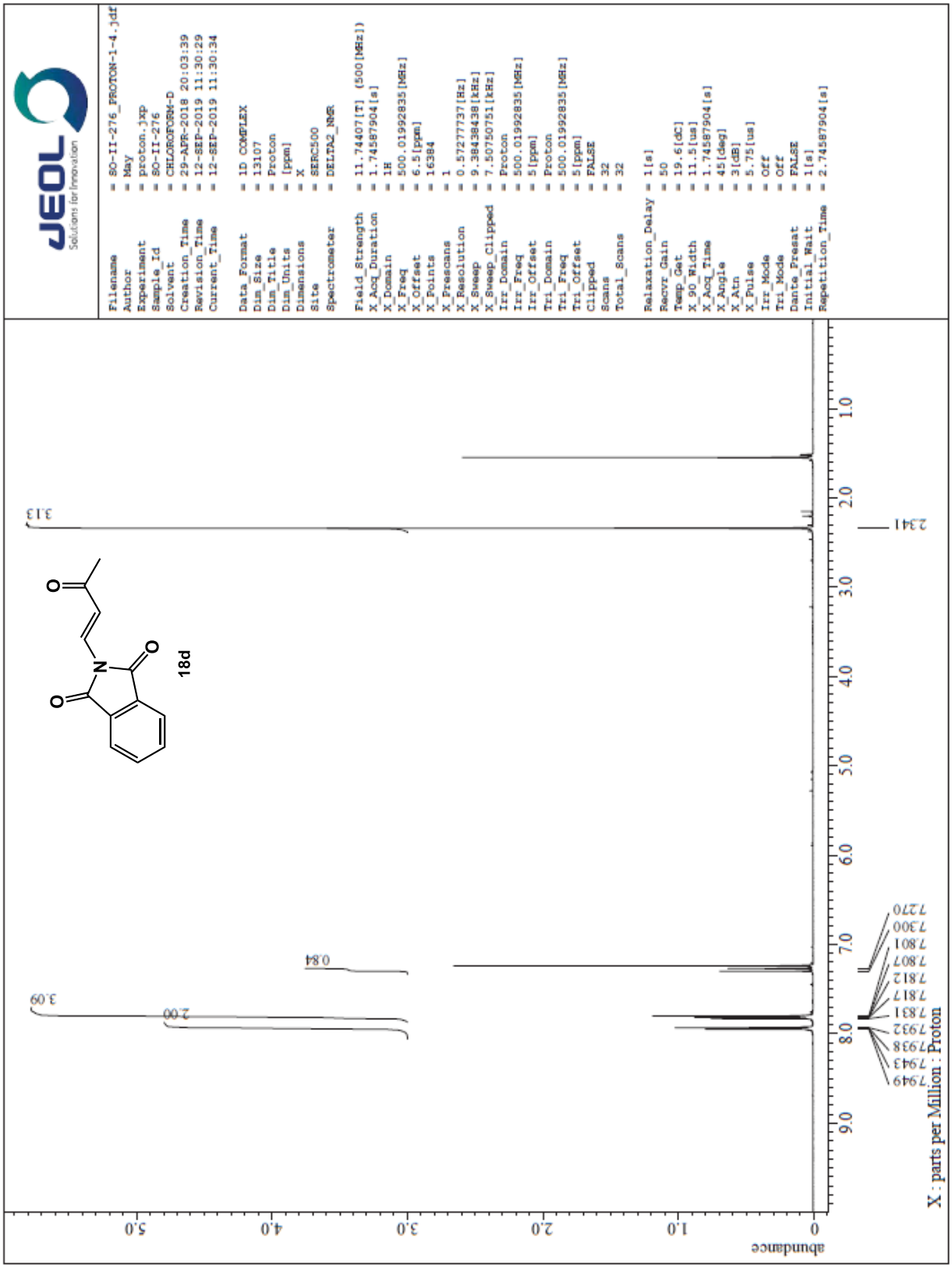

**$^{13}$C NMR spectrum of compound (*E*)-4-(4-chlorophenoxy)but-3-en-2-one (18g)**



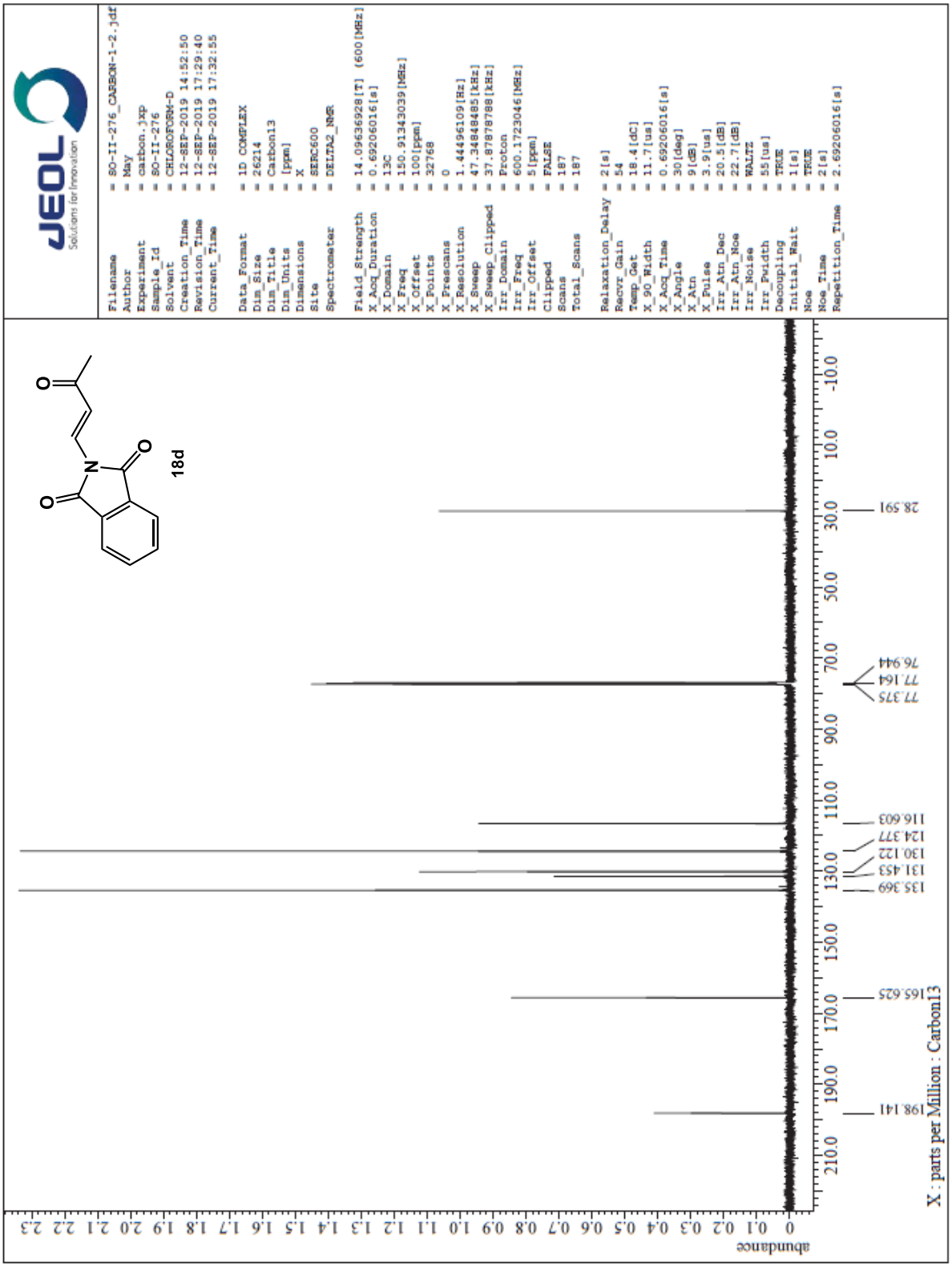

**$^{1}$H NMR spectrum of (*E*)-4-(2,4-di-tert-butylphenoxy)but-3-en-2-one (18h)**



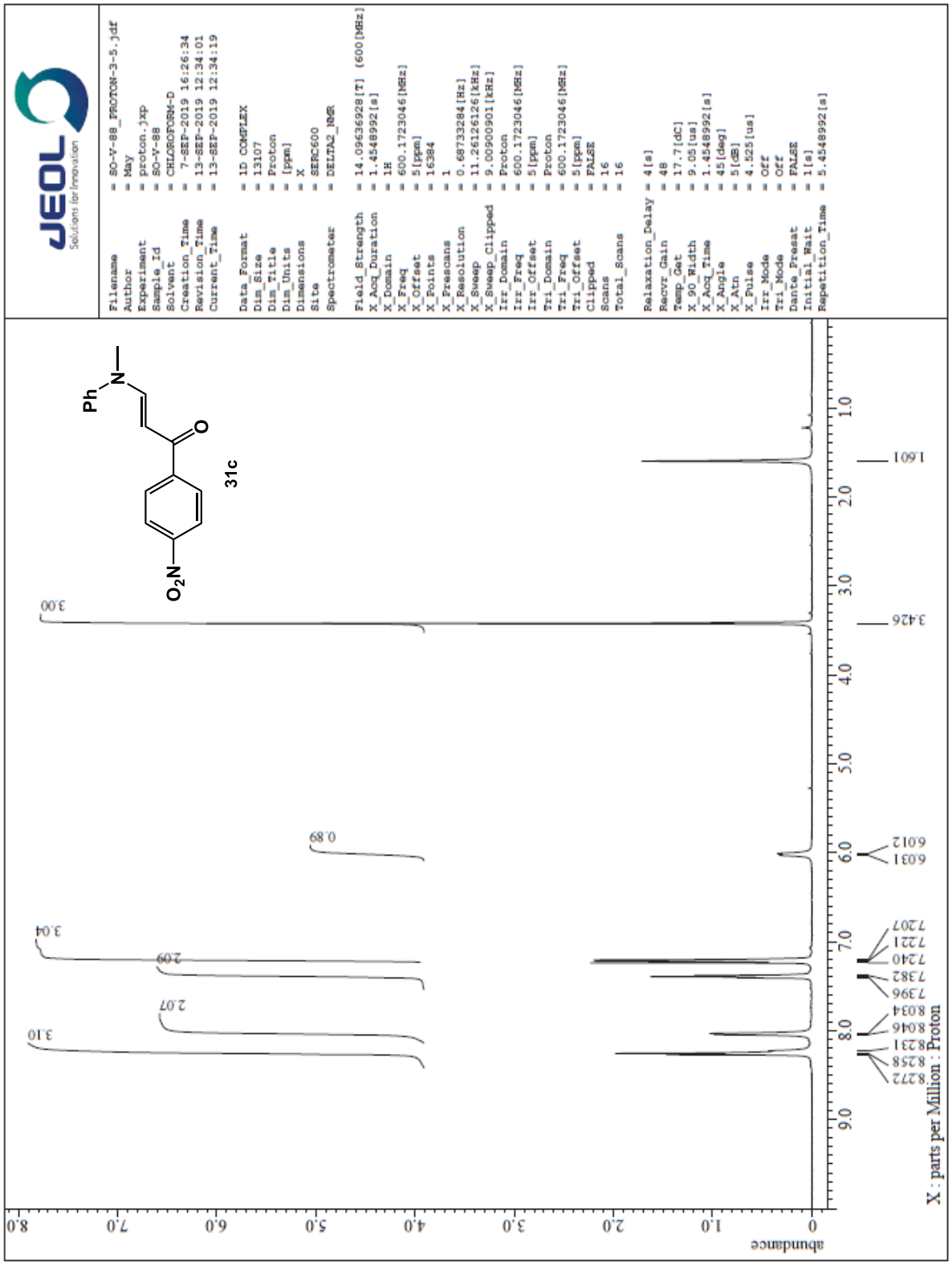

**$^{13}$C NMR spectrum of (*E*)-4-(2,4-di-tert-butylphenoxy)but-3-en-2-one (18h)**



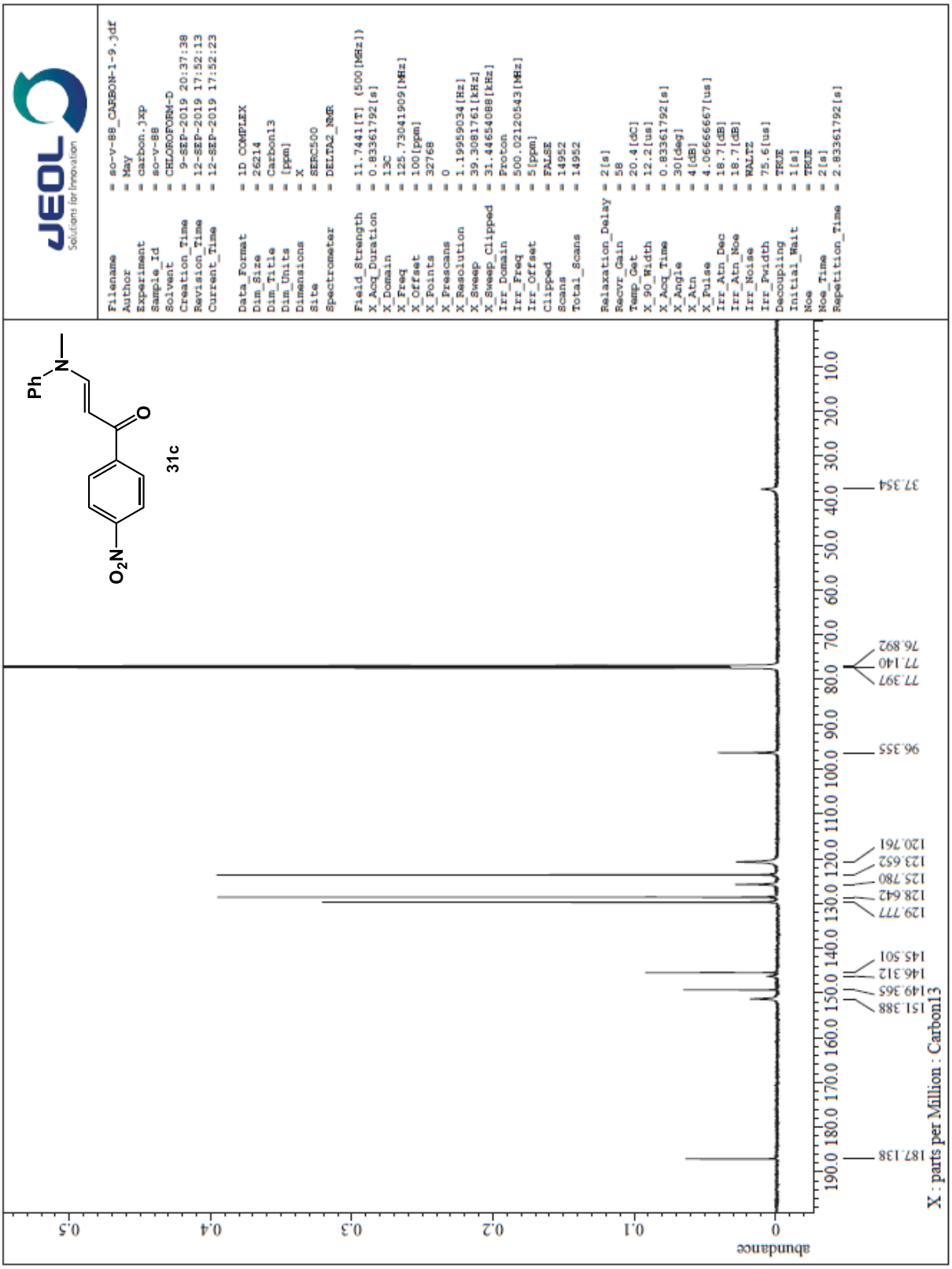

**$^{1}$H NMR spectrum of (*E*)-2-(3-oxobut-1-en-1-yl)isoindoline-1,3-dione (18d)**



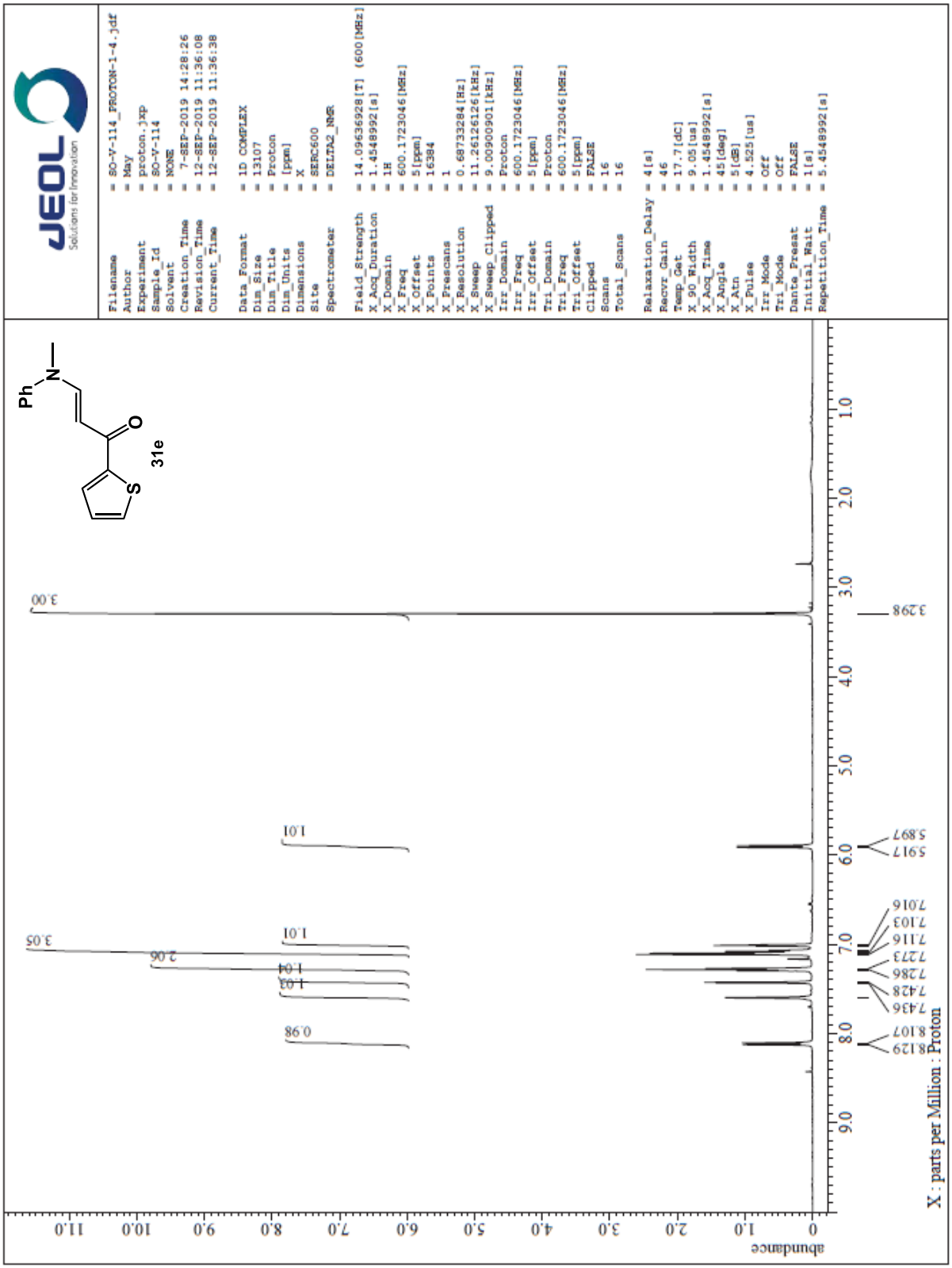

**$^{13}$C NMR spectrum of (*E*)-2-(3-oxobut-1-en-1-yl)isoindoline-1,3-dione (18d)**



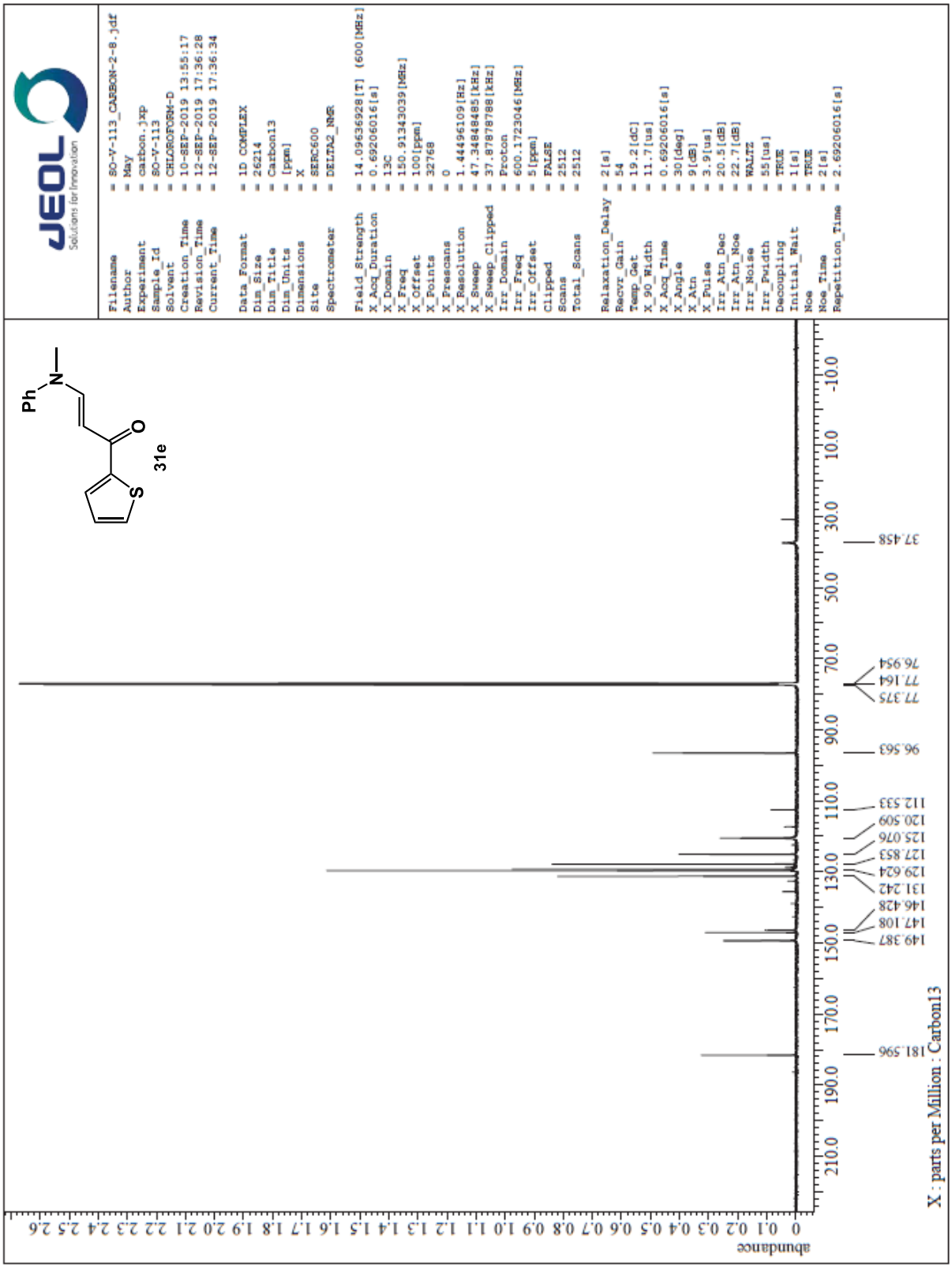

**$^{1}$H NMR spectrum of (*E*)-3-(methyl(phenyl)amino)-1-(4-nitrophenyl)prop-2-en-1-one (31c)**



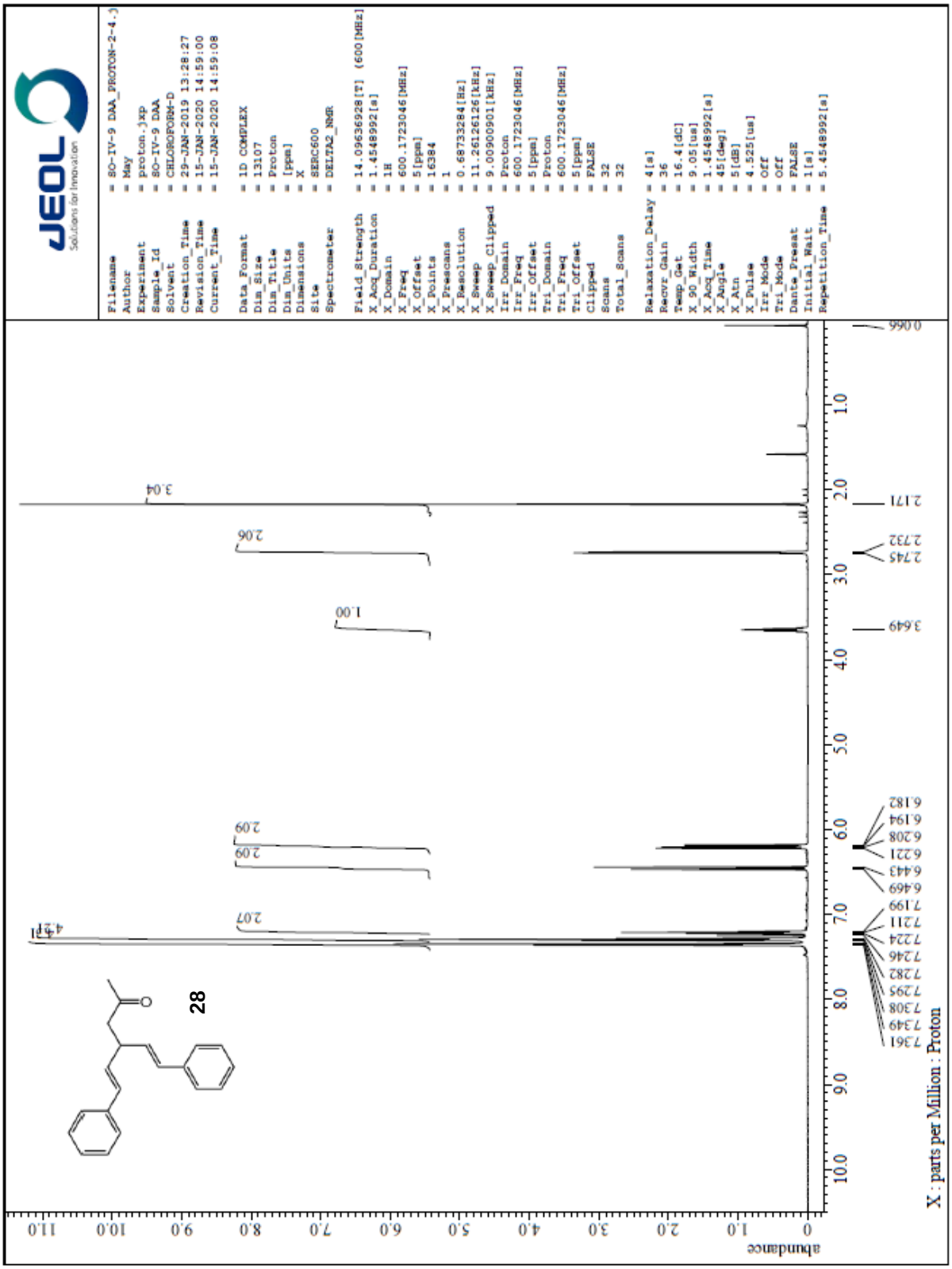

**$^{13}$C NMR spectrum of (*E*)-3-(methyl(phenyl)amino)-1-(4-nitrophenyl)prop-2-en-1-one (31c)**



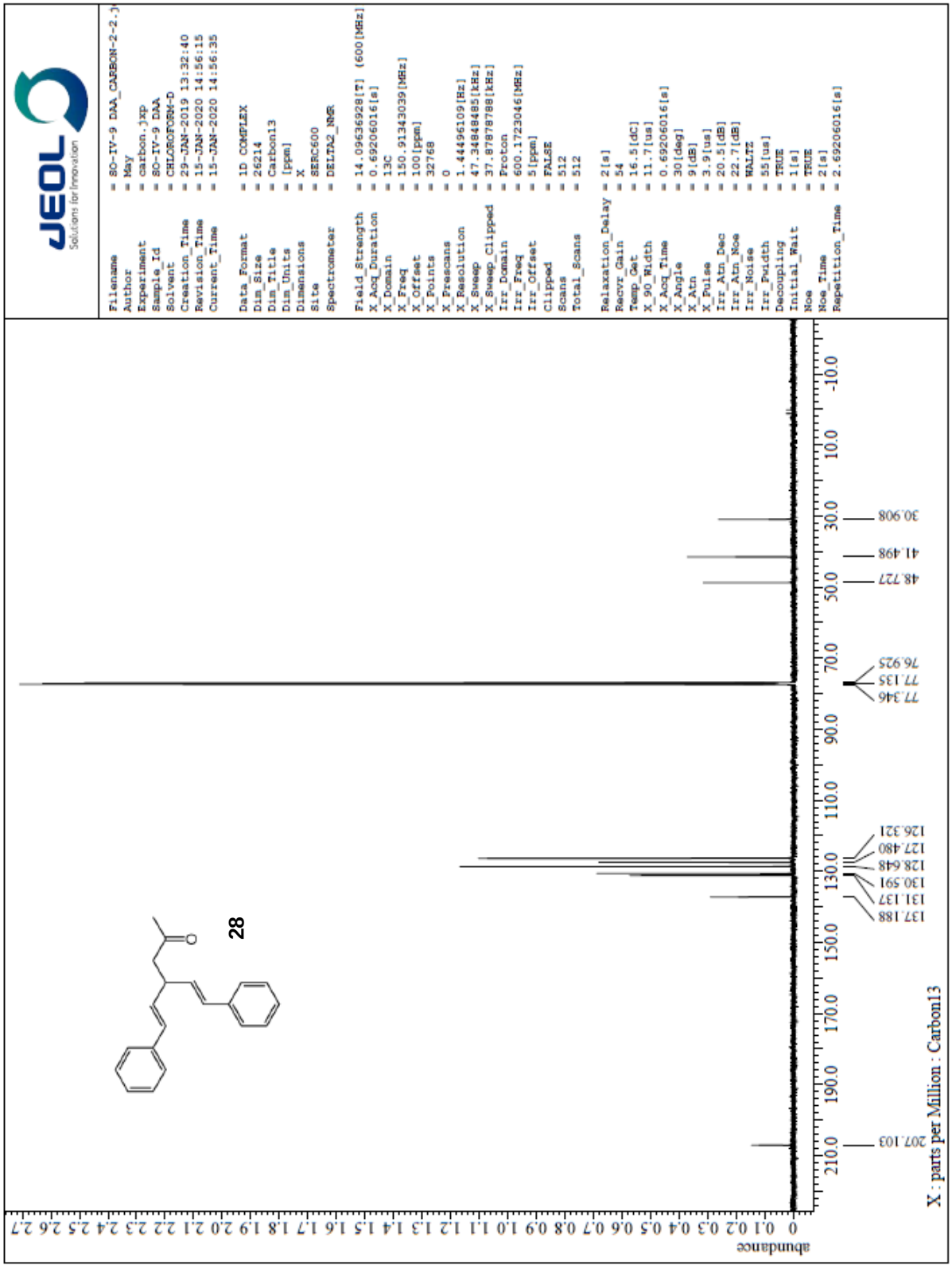

**$^{1}$H NMR spectrum of (*E*)-3-(methyl(phenyl)amino)-1-(thiophen-2-yl)prop-2-en-1-one (31e)**




**$^{13}$C NMR spectrum of (*E*)-3-(methyl(phenyl)amino)-1-(thiophen-2-yl)prop-2-en-1-one (31e)**




**$^{1}$H NMR spectrum of (*E*)-6-phenyl-4-((*E*)-styryl)hex-5-en-2-one (28)**




**$^{13}$C NMR spectrum of (*E*)-6-phenyl-4-((*E*)-styryl)hex-5-en-2-one (28)**

# CHAPTER 5: ORGANOCATALYZED VINYLOGOUS SUBSTITUTION FOR RELAY CATALYSIS[4]

## 5.1 Synthesis of Polyenes and Ene/Yne Structures

Polyenes have been synthesized by a variety of synthetic strategies, including various transition metal cross-couplings (Stille,[133] Sonogashira,[134] Suzuki,[135,136] and Negishi[137,138] couplings) and Wittig[139,140] olefination, as well as the Horner-Wadsworth-Emmons[141,142] reaction (Figure 5.1).[143] These strategies are very effective for the synthesis of such structures, but nonetheless, some drawbacks exist.

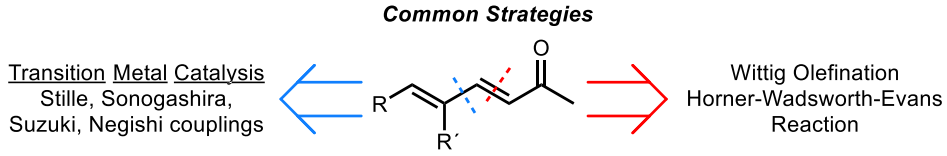



**Figure 5.1**. Strategies for the synthesis of polyene structures

Transition metal cross-couplings have limitations in functional group tolerance and often require harsh conditions in order to provide high yields. Such catalysts are often difficult to recover, expensive, and toxic. There are also considerable environmental concerns when transition metal catalysts are used on large scale in industrial settings.[144]

Both Wittig and Horner-Wadsworth-Evans reactions require specialty reagents which are not always commercially available, especially for more complex synthetic targets. The synthesis of such reagents can be time consuming and increases material cost.

The synthetic strategy described in Chapter 4 has certain advantages over these synthetic approaches – the strategy utilizes quite mild conditions, the catalyst is very facile to synthesize and recover, and the reaction is not sensitive to various functional groups. The difficulty of

[4] The research described in this chapter has been published in part in Organic Letters (*Org. Lett.* 2020, 22, 4, 1355-1359).

synthesizing and corresponding vinylogous esters and amides with varied ketone substituents, however, makes substitution of vinylogous esters and amides a poor competitor to these robust and well-established approaches. This led us to consider possible modifications and expansions of the methodology.

### 5.2 Relay Catalysis

Relay catalysis, while a relatively new term, has been used by many groups. The concept relies on using two catalysts in a combined catalytic cycle to perform one overall transformation (Figure 5.2). Most examples of relay catalysis utilize two metal catalysts to enact the chemical change.[145–149] An example of the utility of such transformations is the use of one metal for generation of radicals *in situ* and subsequent reaction of the reactive radical by means of a second metal.[148,145]

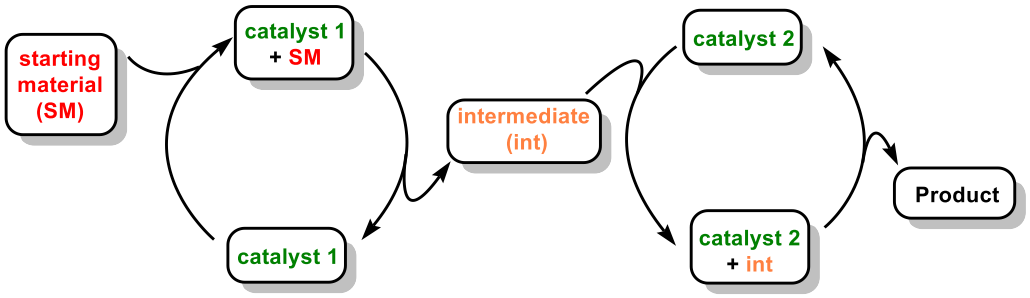



**Figure 5.2.** General diagram of relay catalysis

Beyond the use of two metals in relay catalysis, organocatalysis and metal catalysis have been combined in the development of robust reactions.[150–155] A variety of reactions have exploited transition metal activation of starting materials, followed by the use of organocatalysis to intercept the transient structures in a second catalytic step. Chiral transformations have been enacted by using chiral organocatalysts with achiral metals and chiral organometallic complexes with achiral organocatalysts, allowing for a great breadth of possible reactivity.[153]

## 5.2 Doubly Organocatalytic Relay Catalysis for Synthesis of Polyenes and Ene/Ynes

### 5.2.1 Original Concept

When evaluating the possible applications of the vinylogous substitution of vinylogous esters and amides, we considered the flaws in the vinylogous substitution methodology. The difficulty in synthesis of the problematic vinylogous esters and amides, shown in Figure 5.3, was particularly discouraging. Like Morita-Baylis-Hilman reactions, these syntheses can be catalyzed by DABCO or triphenylphosphine. Nevertheless, the synthesis of most vinylogous esters and amides does not require base catalysis, as the alcohols and amines can spontaneously add to the alkynes. These reactions take longer and provide lower yields than when they are base catalyzed, but spontaneous addition is observed in most cases.

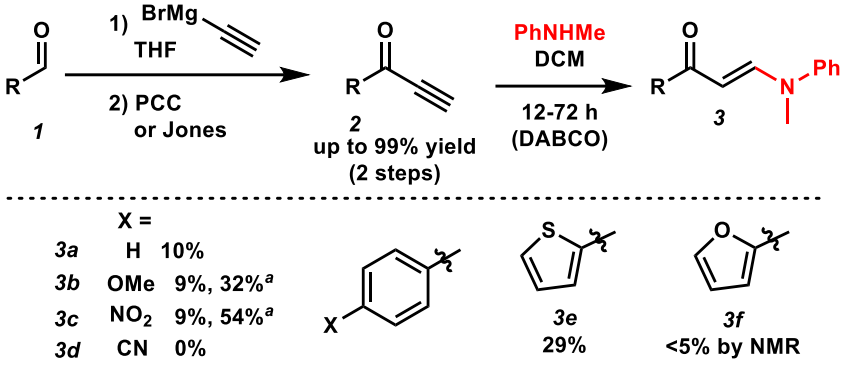



**Figure 5.3.** Vinylogous esters and amides which are difficult to synthesize. [a] With DABCO catalysis, 24 hour reaction time

### 5.2.2 Preliminary Results

We attempted conjugate additions directly to alkynes **2**, but they did not react as electrophiles in conjugate addition, likely due to the geometry of the π-system being too distal for attack (Figure 5.4).

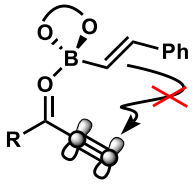



**Figure 5.4**. Geometry of alkyne electrophile

This, combined with the reactivity of these species in conjugate addition conditions, inspired us to consider relay catalysis for the synthesis of polyene structures differing in ketone substitution. This would not only allow access to these polyenes, but it would also expand the applicability of our developed methodology. Our proposed synthesis would allow for the use of substoichiometric quantities of an amine or alcohol (e.g., methylaniline), which could then spontaneously add to the desired alkyne **2** to form the vinylogous amide or ester **3** needed for conjugate addition (Figure 5.5). Unlike the alkynes, this amide or ester would be able to undergo conjugate addition, as shown in **II**, followed by possible Lewis acid complexation as in **IV** and elimination to provide the desired polyene structures **4**. The Lewis acid complex could then re-enter the catalytic cycle, with the organocatalyst activating another equivalent of trifluoroborate salt, **5**, and the methylaniline forming another equivalent of the vinylogous amide **3**.

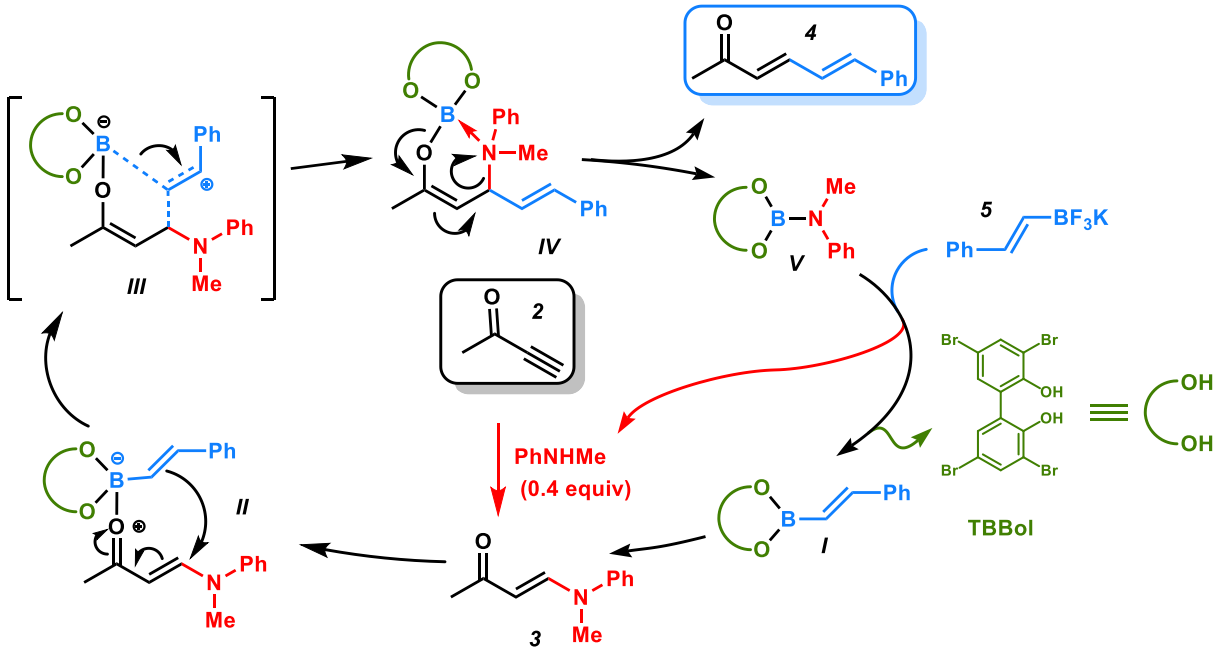



**Figure 5.5**. Proposed catalytic cycle for organocatalyzed relay catalysis

We tested phenol and methylamine, the two most effective leaving groups we found in studies of vinylogous substitution. No formation of the polyene was observed when phenol was used; however, with a stoichiometric quantity of methylaniline, the polyene **4** was formed in 27% yield (Figure 5.6).

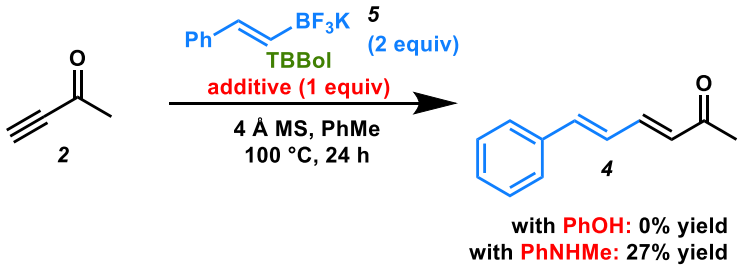


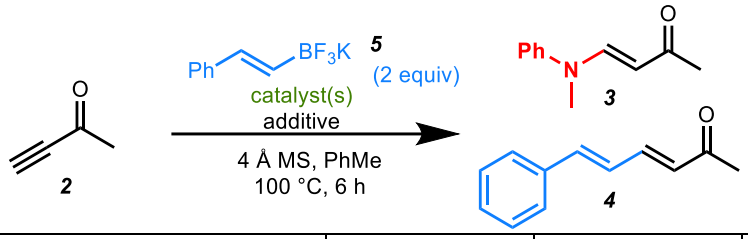

**Figure 5.6.** Relay catalysis – initial results

### 5.3.3 Control Experiments and Optimization

Optimization of reaction conditions allowed an improved yield of 96% with substoichiometric methylaniline (40 mol %, entry 1, Table 1) in only 6 hours rather than the 24 needed for

vinylogous substitution. With only TBBol, no vinylogous amide **3** or polyene **4** was observed (entry 2). With methylaniline only, the product ratios were consistent with the previously observed rates of background reaction (entry 3). With DABCO, neither product was observed, and phosphine was also not an effective catalyst (entries 4-6 and 7-9, respectively). Combined, these results support the relay catalytic cycle as proposed and exclude the possibility of C-C bond formation by a Morita-Baylis-Hilman reaction.

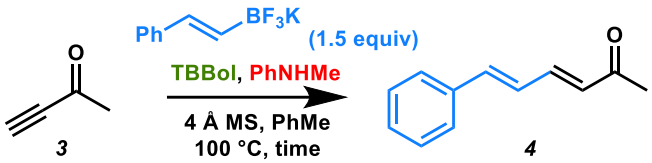
**Table 1.** Control experiments of relay catalysis




| entry | catalysts | | additive (40 mol %) | yield of 4 (%) | Yield of 3 (%) |
|---|---|---|---|---|---|
| | TBBol | PhNHMe | | | |
| *1* | 20 mol % | 40 mol % | none | **96** | 0 |
| *2* | 20 mol % | none | none | 0 | 0 |
| *3* | none | 40 mol % | none | 31 | 30 |
| *4* | 20 mol % | none | DABCO | 0 | 0 |
| *5* | none | 40 mol % | DABCO | 0 | 31 |
| *6* | none | none | DABCO | 0 | 0 |
| *7* | 20 mol % | none | $PBu_3$ | 0 | 0 |
| *8* | none | 40 mol % | $PBu_3$ | 19 | 13 |
| *9* | none | none | $PBu_3$ | 0 | 0 |

In the case of a specific reaction, the yields and catalyst loadings could be optimized. For example, in the case of the methyl alkynyl ketone **3**, loadings were decreased to as low as 10% TBBol/20% methyl aniline (Table 3). The trifluoroborate salt could also be used in a lower excess, with only 1.5 equivalents necessary. These reactions excelled on scale up. Both TBBol and methyl aniline could be recovered from the reactions, allowing them to be recycled.

**Table 2.** Optimization and scale up of conjugate addition relay catalysis reaction




| entry | scale | TBBol loading | PhNHMe loading | concentration | time | yield |
|---|---|---|---|---|---|---|
| 1 | 2 mmol | 20 mol % | 40 mol % | 0.1 M | 6 h | 95% |
| 2 | 2 mmol | 10 mol % | 10 mol % | 0.5 M | 14 h | 60% |
| 3 | 2 mmol | 5 mol % | 5 mol % | 0.5 M | 14 h | 49% |
| 4 | 5 mmol | 10 mol % | 20 mol % | 0.5 M | 6 h | 55% |
| 5 | 5 mmol | 10 mol % | 20 mol % | 0.5 M | 42 h | 88% |

### 5.3.4 Nucleophile and Electrophile Variation

The alkynyl ketone variations that were difficult substrates to synthesize were effective in the relay catalytic system (Figure 5.7). These substrates allowed for the formation of the corresponding polyenes in high yields with electron-rich heterocycles (**4c**, **4d**), with lower yields in the case of substituted phenyl rings (**4e**, **4f**). If the reaction time were increased, the corresponding polyenes could be synthesized in higher yields (**4b**).

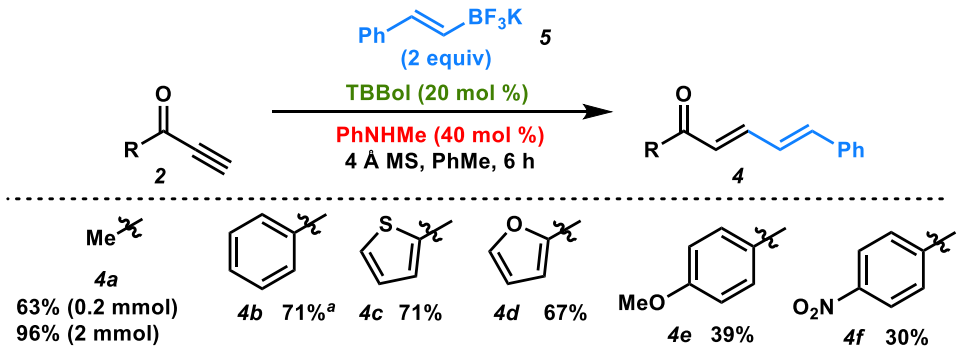



**Figure 5.7**. Varied ketone substitution in relay catalysis. [a]24 hours.

A variety of boronic acid and trifluoroborate nucleophiles were screened and compared to the results from vinylogous substitution (Figure 5.8). Similar trends were observed. Again, aryl trifluoroborates did not provide high yields, likely due to the need for dearomatization during C–

C bond formation. Most vinyl (**4a, 4g-i**) and some alkynyl trifluoroborates (**4m**) provided fair yields of polyenes and ene/ynes. The use of naphthalene-derived trifluoroborate salts in the reaction, with **4o** and **4p** giving higher yields than phenyl trifluoroborate **4j**, supports the idea that dearomatization is the barrier to high yields as aromaticity in naphthalene is weaker. Boronic acids generally gave decreased yields when compared to the more stable trifluoroborate salts.[43]

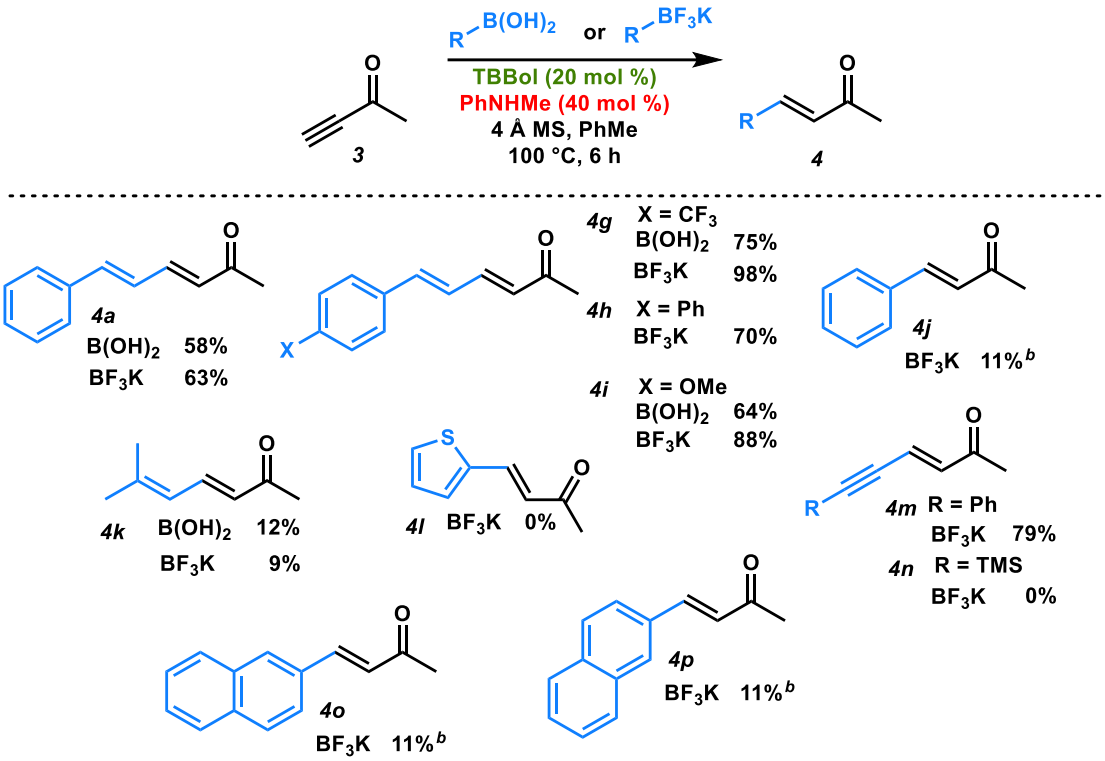



**Figure 5.8.** Nucleophile screen. [b]24 hours.

Functional group compatibility was assessed in a screen as developed by the Glorius group.[130,132,156] The reaction was found to be highly compatible with most functional groups. Yields were moderately decreased in the catalytic vinylogous substitution reaction when amides or alcohols were added, which was consistent with previous experiments where adding excess of the corresponding leaving group slowed the reaction. However, in the doubly catalytic reaction lower yields were not observed, likely due to the substoichiometric loading of methyl aniline in

the reaction. The observed decomposition of some additives was hypothesized to be thermally driven due to elevated reaction temperatures. This reaction experiences only minor reductions in yield when the temperature is decreased to as low as 50 °C, and any thermally sensitive groups could be preserved with an increase in reaction time at the lower temperature.

### 5.3.4 Applications

This method of synthesizing of ene/yne structures such as **4m** was intriguing, as these substrates can be difficult to synthesize and tend to be quite reactive. We considered the fact that the polyene structures formed by this methodology are still able to be modified by further conjugate addition reactions. Few examples exist of stereoselective modifications of such compounds.[157–159]

We were able to enact a second conjugate addition with ene/yne **4m**, providing the β-branched ketone **5** in high yield with high enantioselectivity when a chiral diol was used (Figure 5.9). The reaction was comparatively slow, requiring 72 hours for full conversion. It was also possible to use the thiophene trifluoroborate nucleophile, even though lower yields were observed (**6**). We are unaware of any other reports of enantioselective formation of β-alkynyl/β-alkenyl ketones. These structures are highly intriguing for further modification and use in synthesis.

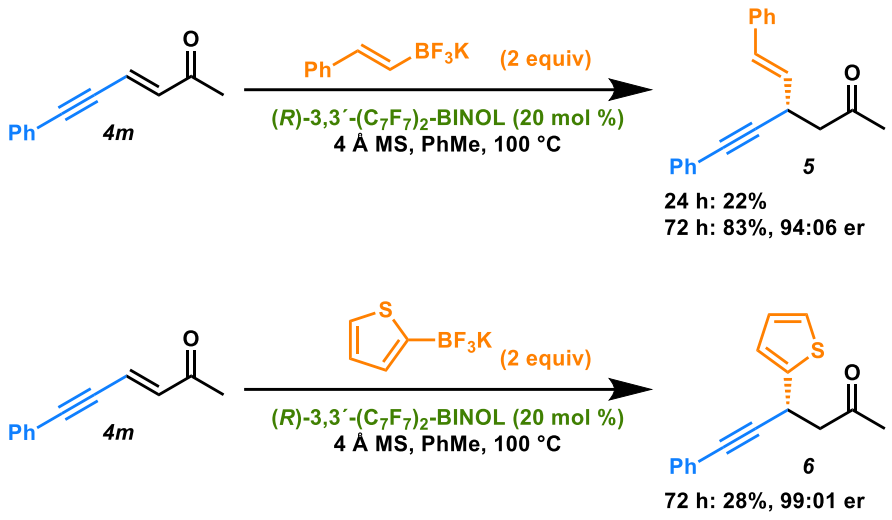



**Figure 5.9**. Applications of ene/yne structures synthesized by relay catalysis

## 5.5 Future Work

We are interested in pursuing competition experiments as depicted in Figure 5.10. It is likely that both conjugate addition, giving **8**, and relay catalysis, giving **9**, will proceed under the reaction conditions, but the ratios and reaction rate will provide valuable information about the nature of the mechanism.

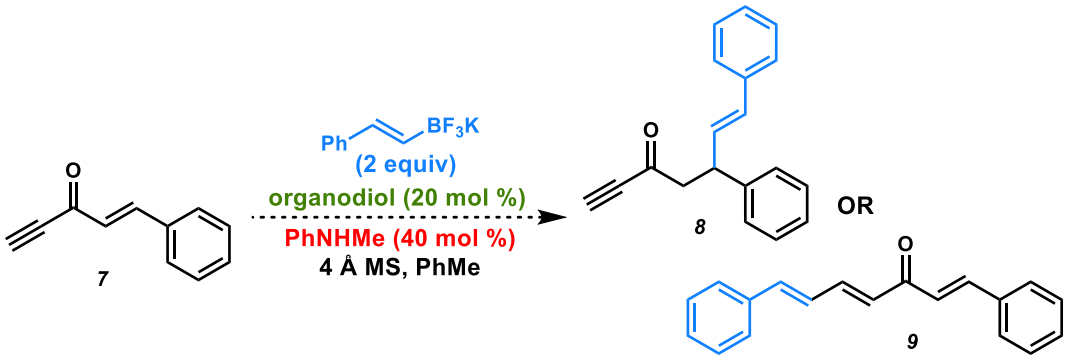



**Figure 5.10.** Conjugate addition versus relay catalysis control experiments

We have considered the possible application of this methodology to the synthesis of polymers, as well as the synthesis of polyene-containing natural products. Further work is ongoing.

## 5.6 Conclusion

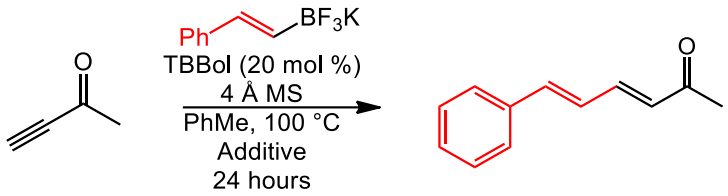
Conjugate addition reactions as developed in the May lab were applied in a rationally designed proposal to a new class of electrophiles, vinylogous esters and amides. These electrophiles were able to react in conjugate additions with the alcohol or amine acting as a leaving group, forming the unsaturated ketones. This reactivity was then exploited to develop a relay catalytic pathway for the synthesis of the same structures, allowing for conversion of alkynes directly to the polyenes and ene/ynes. This method of synthesizing these structures is mild and highly functional group tolerant. The resulting structures were also used as starting materials in a uniquely enantioselective conjugate addition, providing β-alkynyl/β-alkenyl products in high yields with high enantioselectivities.

## 5.8 Experimental

### 5.8.1 General considerations

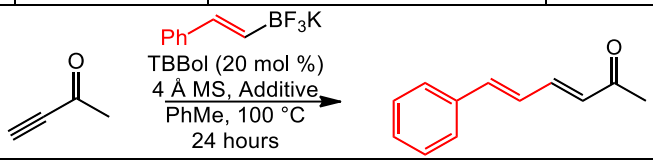
All reactions were carried out in flame-dried glassware under an argon atmosphere. THF, $Et_2O$, toluene, and $CH_2Cl_2$ were purged with argon and dried over activated alumina columns. Flash chromatography was performed on 60 Å silica gel (EMD Chemicals Inc.). Analytical thin layer chromatography was performed on EMD silica gel/TLC plates and imaged by fluorescence at 254 nm or *p*-anisaldehyde stain. The $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectra were recorded on a JEOL ECA-600, 500, ECZ-400 or ECX-400P spectrometer using the residual solvent peak as an internal standard ($CDCl_3$: 7.26 ppm for $^{1}H$ NMR and 77.2 ppm for $^{13}C$ NMR). NMR yields were determined by the addition of 1.0 equivalent of methyl 4-nitrobenzoate as an internal standard to the crude reaction mixture and comparing the integration of the standard's peaks to those of the starting material and product (16 scans, 30 second relaxation delay). IR spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. HRMS analyses were performed under contract by University of Houston's mass spectrometric facility via an nESI method and a Thermo Exactive + Advion Nanomate instrument. Analysis by HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Chiralpak or Chiralcel (250 mm x 4.6 mm) column (column details provided for specific compounds). Commercially available compounds were purchased from Aldrich, Acros, Ark Pharm, Alfa Aesar, Beantown Chemical, TCI, and Combi-Blocks and were used without further purification. IUPAC chemical names were generated using Cambridgesoft ChemBioDraw Ultra 12.0.

### 5.8.2 Relay Catalysis Optimization




| Additive | Equivalents | Salt Equivalents | Time | Yield |
|---|---|---|---|---|
| Initial Screen | | | | |
| PhOH | 1 | 2 | 24 | 0 |
| PhNHMe | 3 | 2 | 24 | 0 |
| PhNHMe | 1 | 2 | 24 | 27 |
| PhNHMe Equivalent Screen | | | | |
| PhNHMe | 0.5 | 2 | 24 | 45 |
| PhNHMe | 0.2 | 2 | 24 | 26 |
| PhNHMe | 0.9 | 2 | 24 | 34 |
| PhNHMe | 0.6 | 2 | 24 | 40 |
| PhNHMe | 0.4 | 2 | 24 | 50 |
| PhNHMe | 0.5 | 2 | 24 | 46 |
| PhNHMe Pre-activated MS | 0.1 | 2 | 8 | 30 |
| PhNHMe Pre-activated MS | 0.2 | 2 | 8 | 46 |
| PhNHMe Pre-activated MS | 0.3 | 2 | 8 | 45 |
| PhNHMe Pre-activated MS | 0.4 | 2 | 8 | 52 |
| PhNHMe Pre-activated MS | 0.5 | 2 | 8 | 43 |
| PhNHMe Pre-activated MS | 0.6 | 2 | 8 | 39 |
| PhNHMe Pre-activated MS | 0.7 | 2 | 8 | 39 |
| PhNHMe Pre-activated MS | 0.8 | 2 | 8 | 43 |
| PhNHMe Pre-activated MS | 0.9 | 2 | 8 | 43 |
| PhNHMe Pre-activated MS | 1.0 | 2 | 8 | 48 |
| PhNHMe Pre-activated MS | 2.0 | 2 | 8 | 31 |
| PhNHMe Pre-activated MS | 3.0 | 2 | 8 | 31 |

| | | | | |
|---|---|---|---|---|
| PhNHMe<br>Pre-activated MS | 4.0 | 2 | 8 | 34 |
| PhNHMe<br>Pre-activated MS | 5.0 | 2 | 8 | 21 |
| PhNHMe<br>Pre-activated MS | 1 | 2 | 1 | 18 |

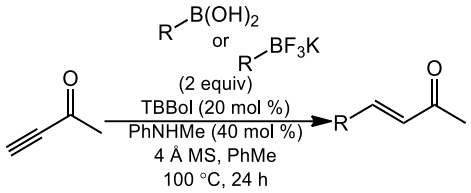



| Additive | Equivalents | Salt Equivalents | Time | Yield |
|---|---|---|---|---|
| Time Screen | | | | |
| PhNHMe<br>Pre-activated MS | 1 | 2 | 2 | 15 |
| PhNHMe<br>Pre-activated MS | 1 | 2 | 3 | 17 |
| PhNHMe<br>Pre-activated MS | 1 | 2 | 4 | 20 |
| PhNHMe<br>Pre-activated MS | 1 | 2 | 5 | 24 |
| PhNHMe<br>Pre-activated MS | 1 | 2 | 6 | 25 |
| PhNHMe<br>Pre-activated MS | 1 | 2 | 24 | 42 |
| PhNHMe<br>Pre-activated MS | 1 | 2 | 28 | 38 |
| Order of Addition Screen | | | | |
| PhNHMe (added with SM) | 1 | 2 | 6 | 54 |
| PhNHMe (added with SM) | 1 | 2 | 24 | 55 |
| PhNHMe<br>(added last) | 1 | 2 | 6 | 44 |
| PhNHMe<br>(added last) | 1 | 2 | 24 | 45 |
| PhNHMe | 1 | 2 | 8 | 60 |
| Salt Equivalents Screen | | | | |
| PhNHMe | 1 | 2 | 8 | 51 |
| PhNHMe | 1 | 1.2 | 8 | 60 |
| PhNHMe | 1 | 3 | 8 | 53 |
| PhNHMe | 1 | 4 | 8 | 55 |
| PhNHMe | 1 | 0.9 | 6<br>24 | 45<br>46 |

| | | | | |
|---|---|---|---|---|
| PhNHMe | 1 | 1 | 6 | 60 |
| | | | 24 | 65 |
| PhNHMe | 1 | 1.2 | 6 | 45 |
| | | | 24 | 69 |
| PhNHMe | 1 | 1.4 | 6 | 58 |
| | | | 24 | 78 |
| PhNHMe | 1 | 1.6 | 6 | 77 |
| | | | 24 | 80 |
| PhNHMe | 1 | 1.8 | 6 | 71 |
| | | | 24 | 73 |
| PhNHMe | 1 | 2.0 | 6 | 95 |
| | | | 24 | 99 |

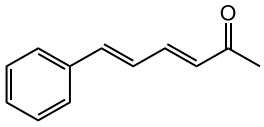
### 5.8.3 Unsaturated Products of Vinylogous Substitution/Relay Catalysis

**General Procedures for Relay Catalysis**



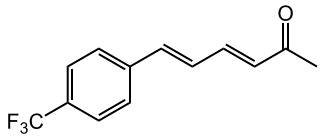

A 2- or 4-dram vial was equipped with 4 Å MS (250 mg/mmol) and a stir bar, then flame dried, activating the mol sieves. Under argon, the trifluoroborate salt (or acid) (2 equiv) and TBBol catalyst (20 mol %) were added to the vial. The solvent (0.2 M) was then added. To the reaction mixture, methyl aniline and the alkyne starting material were added as one portion. If additional additives were included, they were added to the reaction mixture after this step. The vial was sealed well with Teflon tape and heated to reaction temperature in an aluminum bead bath, oil bath, or aluminum block. After the reaction was complete, the reaction mixture was diluted with ethyl acetate and filtered through celite. The celite pad was washed with ethyl acetate. The combined solvents were removed by rotary evaporation. Products were purified by silica gel flash chromatography using ethyl acetate/hexanes as the eluent.

**(3*E*,5*E*)-6-phenylhexa-3,5-dien-2-one (3a)**



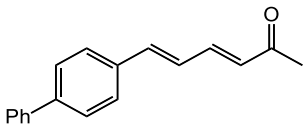
The title compound was synthesized from (*E*)-styrylboronic acid in 59% yield after 6 hours (40.5 mg, 0.24 mmol). It was also synthesized on 0.4 mmol scale from the (*E*)-styryltrifluoroborate salt in 63% yield after 6 hours (43.7 mg, 0.28 mmol). Upon scale up to 5 mmol, the same conditions provided the title compound in 88% yield (759.5 mg, 4.42 mmol). The product was purified by silica gel flash column chromatography, using 1% ethyl acetate/hexanes as eluent. Spectral data were identical to those reported in literature.[120]

**(3*E*,5*E*)-6-(4-(trifluoromethyl)phenyl)hexa-3,5-dien-2-one (3b)**



The title compound was synthesized from (*E*)-(4-(trifluoromethyl)styryl)boronic acid in 75% yield (72 mg, 0.30 mmol) and from the (*E*)-(4-(trifluoromethyl)styryl)trifluoroborate salt in 98% yield (94 mg, 0.39 mmol). The product was purified by silica gel flash column chromatography, using 1% ethyl acetate/hexanes as eluent. Spectral data were identical to those reported in literature.[121]

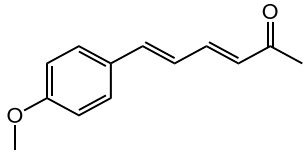
**(3*E*,5*E*)-6-([1,1'-biphenyl]-4-yl)hexa-3,5-dien-2-one (3c)**




The title compound was synthesized from (*E*)-(2-([1,1'-biphenyl]-4-yl)vinyl)trifluoroborate salt in 70% yield and purified by silica flash chromatography 1% ethyl acetate/hexanes as eluent (35 mg, 0.14 mmol). White solid.

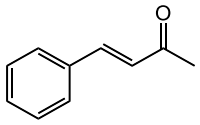
**$^{1}$H-NMR** (500 MHz, chloroform-D) δ 7.59 (d, J = 7.4 Hz, 4H), 7.54 (d, J = 8.0 Hz, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.33-7.36 (m, 1H), 7.29 (d, J = 13.2 Hz, 1H), 6.89-6.99 (m, 2H), 6.26 (d, J = 15.5 Hz, 1H), 2.31 (s, 3H) **$^{13}$C-NMR** (126 MHz, chloroform-D) δ 198.6, 143.6, 142.1, 140.9, 140.4, 135.0, 130.5, 129.0, 127.8, 127.8, 127.6, 127.1, 126.7, 27.5 **IR** 2922, 2852, 1653, 1616, 1488, 1184, 1150, 997, 844, 721, 692, 562 $cm^{-1}$ **HRMS-ESI m/z** Calculated for $C_{18}H_{16}O$ $[M + H]^+$ calculated 249.1279, found 249.1277

**(3*E*,5*E*)-6-(4-methoxyphenyl)hexa-3,5-dien-2-one (3d)**



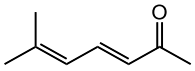

The title compound was synthesized from (*E*)-(4-methoxystyryl)boronic acid in 76% yield and from (*E*)-(4-methoxystyryl)trifluoroborate salt in 65% yield (23 mg, 0.11 mmol). The product was purified by silica gel flash column chromatography, using 1-5% ethyl acetate/hexanes as eluent. Spectral data were identical to those reported in literature.[Error! Bookmark not defined.]

**(*E*)-4-phenylbut-3-en-2-one (3e)**



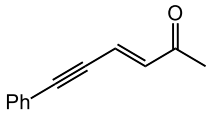
The title compound was synthesized from phenyl trifluoroborate salt in 11% yield (3 mg, 0.02 mmol), with 1 equivalent of LiBr added to the reaction mixture, and the reaction was allowed to proceed for 48 hours. The product was purified by silica gel flash column chromatography, using 1-10% ethyl acetate/hexanes as eluent. Spectral data were identical to those reported in literature.[160]

**(*E*)-6-methylhepta-3,5-dien-2-one (3f)**



The title compound was synthesized from (*E*)-(4-methylpenta-1,3-dien-1-yl)boronic acid in 9% yield (4.5 mg, 0.04 mmol) and from (*E*)-(4-methylpenta-1,3-dien-1-yl)trifluoroborate salt in 12% yield (6.0 mg, 0.05 mmol). The product was purified by silica gel flash column chromatography, using 1-5% ethyl acetate/hexanes as eluent. Spectral data were identical to those reported in literature.[161]

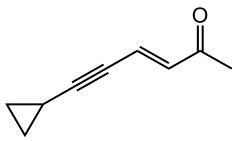
***(E*)-6-phenylhex-3-en-5-yn-2-one (3g)**




The title compound was synthesized from (phenylethynyl)trifluoroborate salt in 79% yield after 48 hours (55.3 mg, 0.32 mmol). The product was purified by silica gel flash column

chromatography, using 1-15% ethyl acetate/hexanes as eluent. Spectral data were identical to those reported in literature.[Error! Bookmark not defined.]

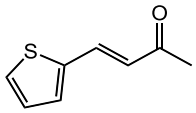
**(*E*)-6-cyclopropylhex-3-en-5-yn-2-one (Supplementary-1)**



Prepared from (cyclopropylethynyl)trifluoroborate salt in 12% yield (6.5 mg, 0.05 mmol). The product was purified by silica gel flash column chromatography, using 1-10% ethyl acetate/hexanes as eluent. Off-white solid. Title compound could not be fully isolated and could only be obtained with some impurities (catalyst/methyl aniline).

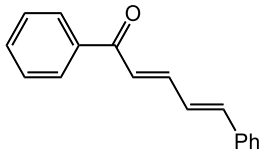
**$^{1}$H-NMR** (600 MHz, chloroform-D) δ 6.56 (dd, J = 15.8, 2.1 Hz, 1H), 6.35 (d, J = 16.5 Hz, 1H), 2.22 (s, 3H), 1.61 (s, 1H), 1.41 (td, J = 5.3, 2.3 Hz, 1H), 0.90 (td, J = 7.6, 4.6 Hz, 2H), 0.80 (td, J = 5.8, 3.4 Hz, 2H) **$^{13}$C-NMR** (151 MHz, chloroform-D) δ 197.5, 137.1, 135.8, 125.1, 106.2, 73.9, 27.5, 9.4, 0.8 **IR** 3455, 3016, 2970, 1738, 1454, 1435, 1365, 1229, 1217, 1092, 895, 539, 528 cm$^{-1}$ **HRMS-ESI m/z** Calculated for $C_9H_{10}O$ $[M + Na]^+$ 157.0629, found 157.0627

**(*E*)-4-(thiophen-2-yl)but-3-en-2-one (3i)**



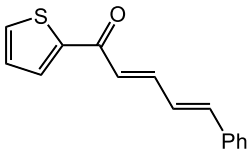
The title compound could not be isolated from the reaction mixture, and only starting materials and the vinylogous amide catalytic precursor could be recovered.

**(2E,4E)-1,5-diphenylpenta-2,4-dien-1-one (3l)**



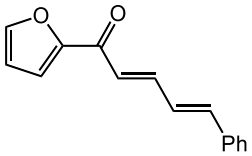

Prepared and isolated from the corresponding alkyne and (E)-styryltrifluoroborate salt in 71% yield (66.5 mg, 0.28 mmol). Spectral data were consistent with those found in literature.[162]

**(2E,4E)-5-phenyl-1-(thiophen-2-yl)penta-2,4-dien-1-one (3m)**



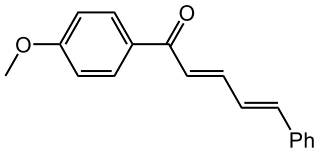

Prepared and isolated from the corresponding alkyne and (*E*)-styryltrifluoroborate salt in 71% yield (68.5 mg, 0.29 mmol). Spectral data were consistent with those found in literature.[163]

**(2E,4E)-1-(furan-2-yl)-5-phenylpenta-2,4-dien-1-one (3n)**



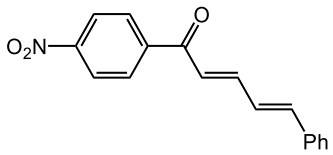

Prepared and isolated from the corresponding alkyne and (E)-styryltrifluoroborate salt in 67% yield (60.4 mg, 0.27 mmol). Spectral data were consistent with those found in literature.[164]

**(2E,4E)-1-(4-methoxyphenyl)-5-phenylpenta-2,4-dien-1-one (3o)**



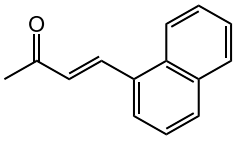

Prepared and isolated from the corresponding alkyne and (E)-styryltrifluoroborate salt in 39% yield (40.8 mg, 0.15 mmol). Spectral data were consistent with those found in literature.[165]

**(2E,4E)-1-(4-nitrophenyl)-5-phenylpenta-2,4-dien-1-one (3p)**



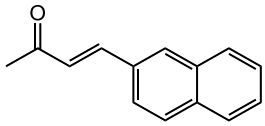

Prepared and isolated from the corresponding alkyne and (E)-styryltrifluoroborate salt in 30% yield (33.2 mg, 11.9 mmol). Spectral data were consistent with those found in literature.[166]

**(*E*)-4-(naphthalen-1-yl)but-3-en-2-one (3q)**



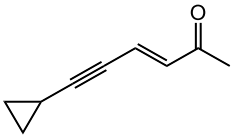

Prepared and isolated from (naphthalen-1-yl)trifluoroborate salt in 78% yield (153.3 mg, 0.78 mmol) after a 48 hour reaction time. (Note: after 6 hours, only a small amount of product was observed by NMR). The product was purified by silica gel flash column chromatography, using 5% ethyl acetate/hexanes as eluent. Spectral data were consistent with those found in literature.[167]

**(*E*)-4-(naphthalen-1-yl)but-3-en-2-one (3r)**



Prepared from (naphthalen-2-yl)trifluoroborate salt in 92% yield after a 48 hour reaction time (180.4 mg, 0.92 mmol). (Note: after 6 hours, only a small amount of product was observed by NMR). The product was purified by silica gel flash column chromatography, using 5-10% ethyl acetate/hexanes as eluent. Spectral data were consistent with those found in literature.[25]

**(*E*)-6-cyclopropylhex-3-en-5-yn-2-one (SUPPLEMENTARY-8)**

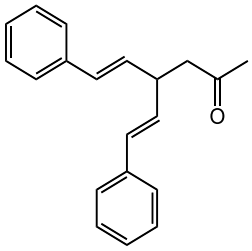


*Relay Catalysis*

Prepared from (cyclopropylethynyl)trifluoroborate salt in 12% yield (6.5 mg, 0.05 mmol). The product was purified by silica gel flash column chromatography, using 1-10% ethyl acetate/hexanes as eluent. Off-white solid. Title compound could not be fully isolated and could only be obtained with some impurities (catalyst/methyl aniline).

**$^{1}$H-NMR** (600 MHz, chloroform-D) δ 6.56 (dd, J = 15.8, 2.1 Hz, 1H), 6.35 (d, J = 16.5 Hz, 1H), 2.22 (s, 3H), 1.61 (s, 1H), 1.41 (td, J = 5.3, 2.3 Hz, 1H), 0.90 (td, J = 7.6, 4.6 Hz, 2H), 0.80 (td, J = 5.8, 3.4 Hz, 2H) **$^{13}$C-NMR** (151 MHz, chloroform-D) δ 197.5, 137.1, 135.8, 125.1, 106.2, 73.9, 27.5, 9.4, 0.8 **IR** 3455, 3016, 2970, 1738, 1454, 1435, 1365, 1229, 1217, 1092, 895, 539, 528 cm$^{-1}$ **HRMS-ESI m/z** Calculated for $C_9H_{10}O$ $[M + Na]^+$ 157.0629, found 157.0627

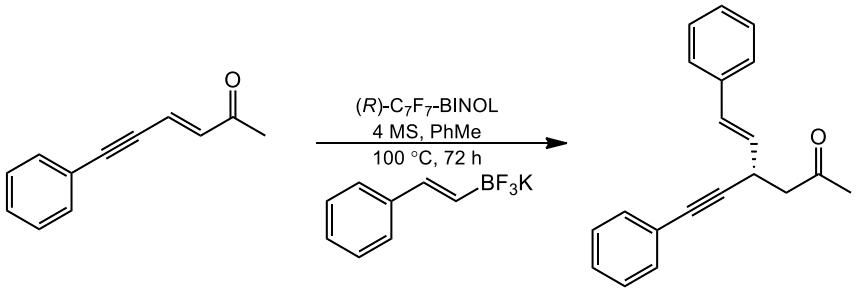
**(*E*)-6-phenyl-4-((*E*)-styryl)hex-5-en-2-one (6)**



Minor product observed in reactions with phenyl vinyl trifluoroborate salt. Isolated from reaction mixture using 1% EtOAc/Hexanes (8.9 mg). White solid.

**$^{1}$H-NMR** (500 MHz, chloroform-D) δ 7.22-7.30 (m, 8H), 7.15 (t, J = 7.2 Hz, 2H), 6.39 (d, J = 16.0 Hz, 2H), 6.14 (q, J = 7.6 Hz, 2H), 3.56-3.62 (m, 1H), 2.68 (d, J = 6.9 Hz, 2H), 2.11 (s, 3H) **$^{13}$C-NMR** (151 MHz, chloroform-D) δ 207.1, 137.2, 131.1, 130.8, 130.6, 128.6, 127.5, 126.3, 123.7, 48.7, 41.5, 36.7, 30.9 **IR** 2924, 2854, 2360, 1718, 1494, 1482, 1450, 1340, 1149, 990, 967, 748, 720, 694 **HRMS-ESI m/z** Calculated for $C_{20}H_{20}O$ $[M + Na]^+$ 299.1412, found 299.1409

**(*S*,*E*)-6-phenyl-4-(phenylethynyl)hex-5-en-2-one (8)**




A 4 dram vial was equipped with 4 Å MS (250 mg/mmol) and a stir bar, then flame dried, activating the mol sieves.[5] Under argon, the trifluoroborate salt (2 equiv), chiral diol catalyst (20 mol %), and starting material were added to the vial. Toluene (0.2 M) was added. The vial was sealed well with

[5] Pre-activating molecular sieves and using oven-dried glassware reduces the yield.

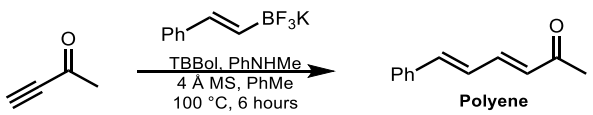
Teflon tape and heated to reaction temperature in an aluminum bead bath. After the reaction was complete, the reaction mixture was diluted with ethyl acetate and filtered through celite. The celite pad was washed with ethyl acetate. The combined solvents were removed by rotary evaporation. The title compound was isolated in 83% yield (33.4 mg, 0.12 mmol) by silica gel flash chromatography using 1-5% ethyl acetate/hexanes as the eluent. The enantiomeric ratio was calculated as 94:06, with the major enantiomer determined by analogy to previous work. Yellow oil. The chiral HPLC column used for the separation of enantiomers was Chiralcel OD-H: Cellulose tris-(3,5-dimethylphenylcarbamate) coated on 5 μm silica gel.

**$^{1}$H-NMR** (600 MHz, chloroform-D) δ 7.37 (s, 2H), 7.31 (s, 2H), 7.24 (s, 5H), 7.18 (d, J = 8.9 Hz, 1H), 6.70 (d, J = 15.8 Hz, 1H), 6.15 (dd, J = 15.8, 2.7 Hz, 1H), 3.94 (s, 1H), 2.85-2.88 (m, 1H), 2.72-2.75 (m, 1H), 2.17 (s, 3H) **$^{13}$C-NMR** (151 MHz, chloroform-D) δ 205.6, 136.5, 131.4, 130.9, 128.3, 128.0, 127.8, 127.3, 126.2, 123.0, 88.9, 83.7, 77.0, 76.8, 76.6, 49.1, 30.4, 30.3 **IR** 3058, 3029, 2923, 2203, 1711, 1490, 1447, 1357, 1158, 966, 752, 691 cm$^{-1}$ **HRMS-ESI m/z** Calculated for $C_{20}H_{18}O$ $[M+H]^+$ 275.1436, found 275.1434.

### 5.8.4 Functional Group Screen

Functional group screens were adapted from protocols developed by the Glorius group.[130–132] GCMS was used to analyze yields. Reactions were set up in tandem with the same batch of starting materials and catalyst(s). All reaction vials were equipped with stir bars and mol sieves, then flame dried. The trifluoroborate salt was added as a solid, as it is not soluble in the reaction mixture. The remaining components, including standards, were pre-mixed as a stock solution and added to the vials containing mol sieves and trifluoroborate salt. After the reaction time, the reaction mixtures were filtered through celite plugs (in pipettes) and solvent was removed by rotary evaporation.

Relay catalysis was evaluated by GC. Calibration curves were generated for product and all additives. Calibration standards were prepared containing no more than 8 additives. From these standards, 5 dilute samples were prepared, with mesitylene added to represent concentrations of additives equivalent to 100%, 80%, 60%, 40%, and 20% compared to standard (i.e., 0.1 mmol of standard/0.08 mmol additives representing 80% recovery). Curves were generated for the concentration/GC response for each additive. The best fit line equation of each was used to calculate recovery of additives in the reaction mixture.

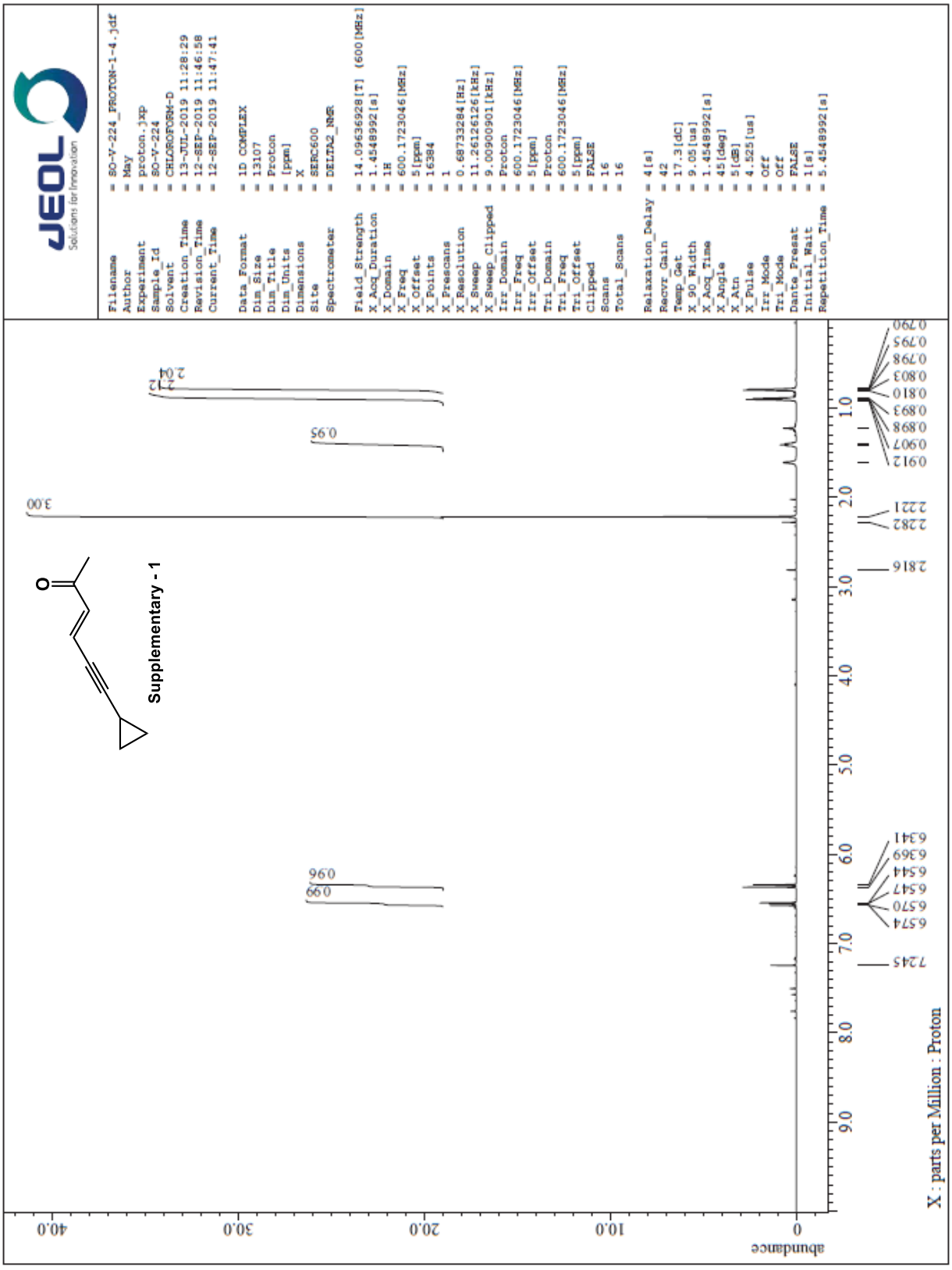



| Entry | Additive | % Yield | Recovery Additive |
|---|---|---|---|
| 1 | **None - Control** | **73 (average of 3)** | **--** |
| 2 | 1-undecene | **80** | **46** |
| 3 | 1-octyne | **72** | **70** |
| 4 | tridecanenitrile | **71** | **59** |
| 5 | chloroheptane | **30** | **42** |
| 6 | decylamine | **73** | **0** |
| 7 | 6-undecanone | **73** | **71** |
| 8 | nonanol | **73** | **56** |
| 9 | acetanilide | **77** | **60** |
| 10 | methyl benzoate | **75** | **80** |
| 11 | 2-vinynaphthalene | **80** | **96** |
| 12 | 4-octyne | **93** | **64** |
| 13 | benzonitrile | **81** | **81** |
| 14 | chlorobenzene | **65** | **33** |
| 15 | benzylamine | **74** | **59** |
| 16 | benzaldehyde | **66** | **30** |
| 17 | phenol | **95** | **48** |
| 18 | 1-benzylpyrrole | **63** | **30** |
| 19 | 1-methylimidazole | **74** | **77** |
| 20 | 2-n-butylfuran | **74** | **11** |
| 21 | indole | **72** | **65** |
| 22 | 2-chloroquinoline | **68** | **42** |
| 23 | benzoxazole | **81** | **100** |
| 24 | chromone | **85** | **96** |
| 25 | 3,5-lutidine | **75** | **34** |
| 26 | 4-methylthiazole | **63** | **30** |
| 27 | 2-n-butylthiophene | **71** | **63** |
| 28 | 2,3-benzofuran | **93** | **65** |
| 29 | n-methylacetanilide | **87** | **81** |
| 30 | 2-chloropyridine | **98** | **42** |
| 31 | benzothiazole | **71** | **73** |
| 32 | 2-picoline-N-oxide | **80** | **0** |

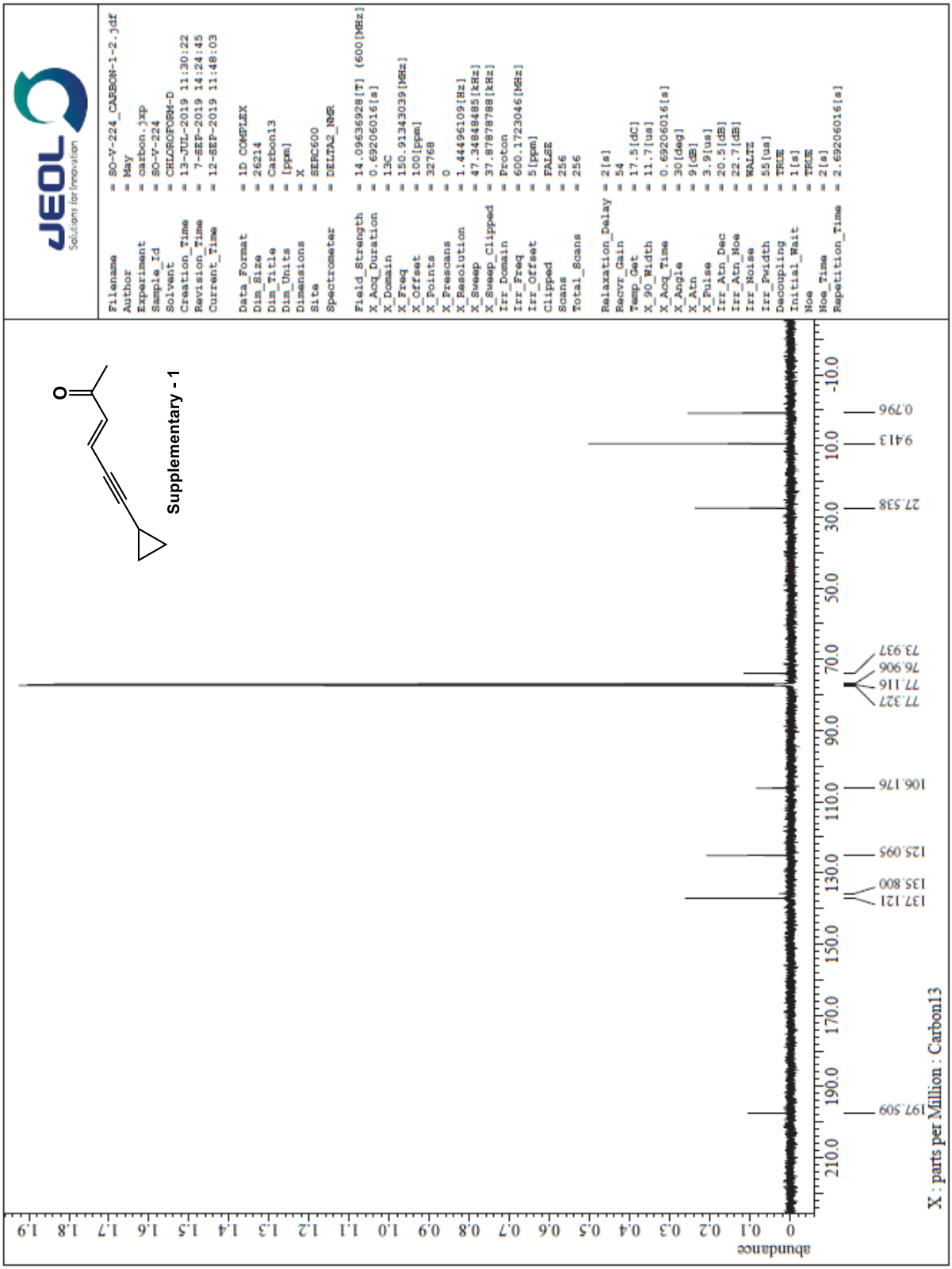
**APPENDIX – CHAPTER FIVE**

Spectra Relevant to Chapter Four

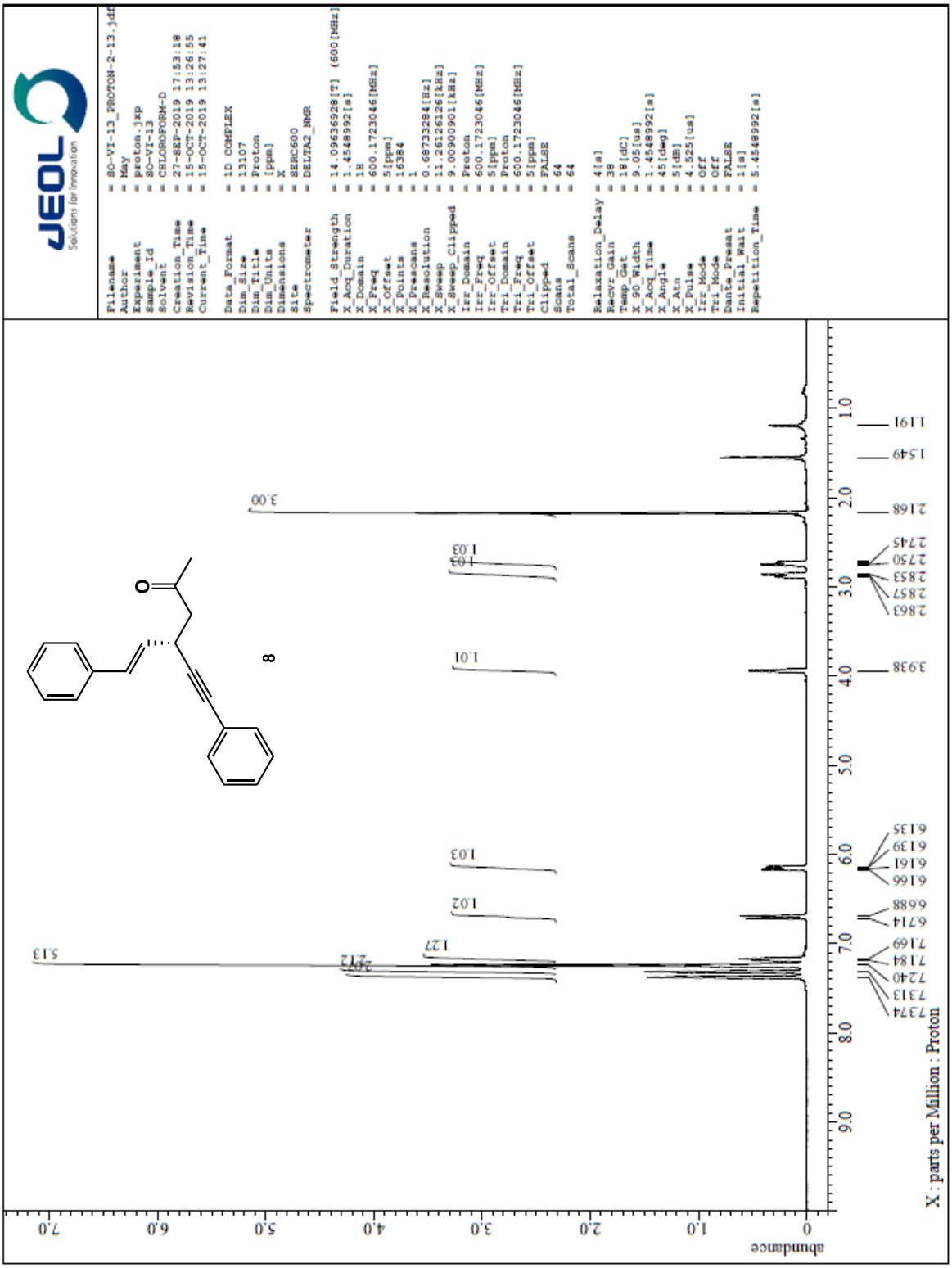
# Organocatalyzed Vinylogous Substitution for Relay Catalysis



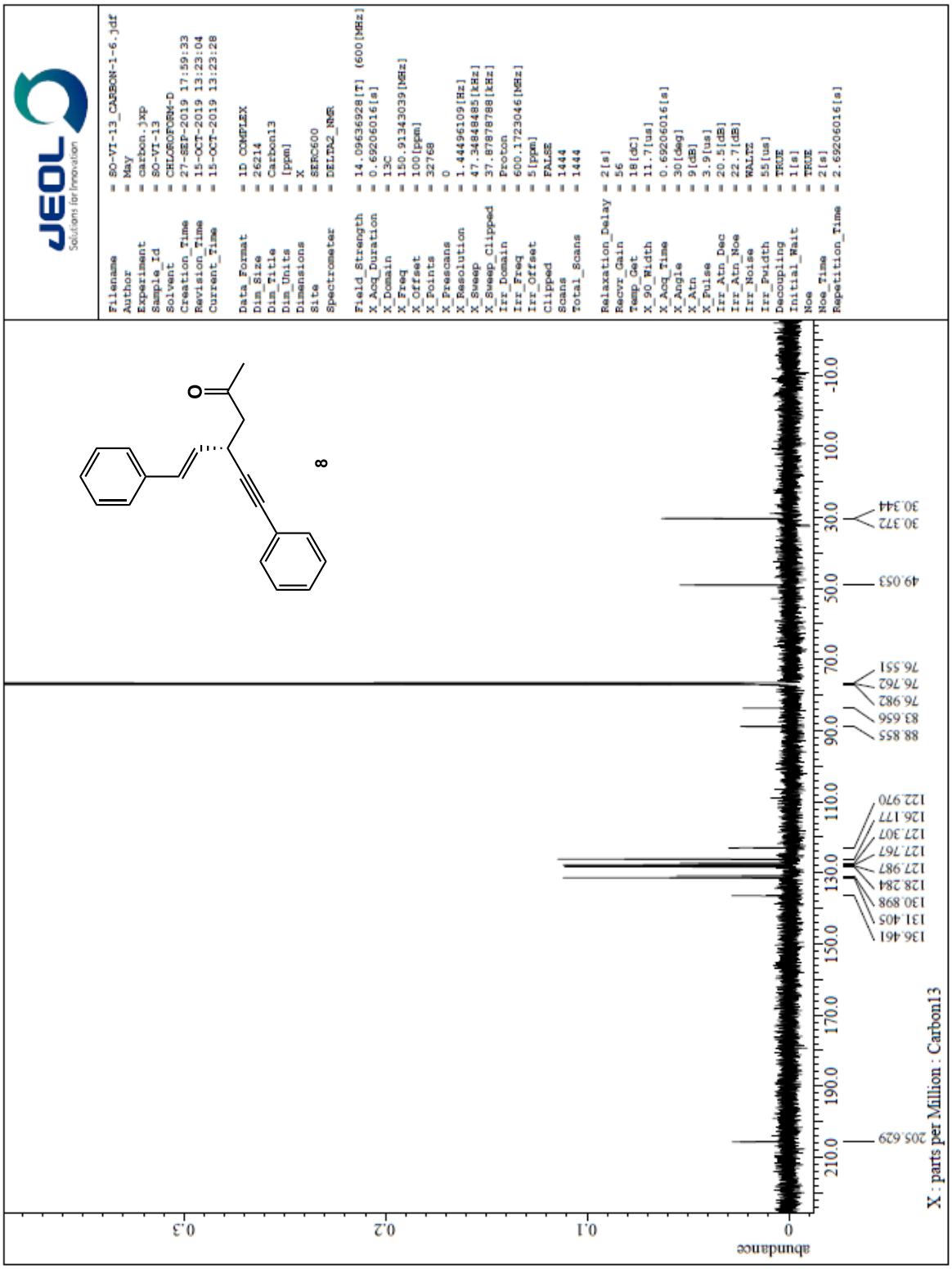

**$^{1}$H NMR spectrum of (*E*)-6-cyclopropylhex-3-en-5-yn-2-one (SUPPLEMENTARY-1)**




**$^{13}$C NMR spectrum of (*E*)-6-cyclopropylhex-3-en-5-yn-2-one (SUPPLEMENTARY-1)**




**$^{1}$H NMR of (*S*,*E*)-6-phenyl-4-(phenylethynyl)hex-5-en-2-one (8)**




**$^{13}$C NMR of (*S*,*E*)-6-phenyl-4-(phenylethynyl)hex-5-en-2-one (8)**

# ==== Shimadzu LCsolution Analysis Report ====

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| | |
|---|---|
| Acquired by | : Admin |
| Sample Name | : SO-VI-8A |
| Sample ID | : SO-VI-8A |
| Tray# | : 1 |
| Vail # | : 1 |
| Injection Volume | : 5 uL |
| Data File Name | : SO-VI-8A 20 min slow 4.lcd |
| Method File Name | : pos5_90%_20min.lcm |
| Batch File Name | : Batch_table_5-90%_20min_C6F5_cat_BINOL.lcb |
| Report File Name | : Default.lcr |
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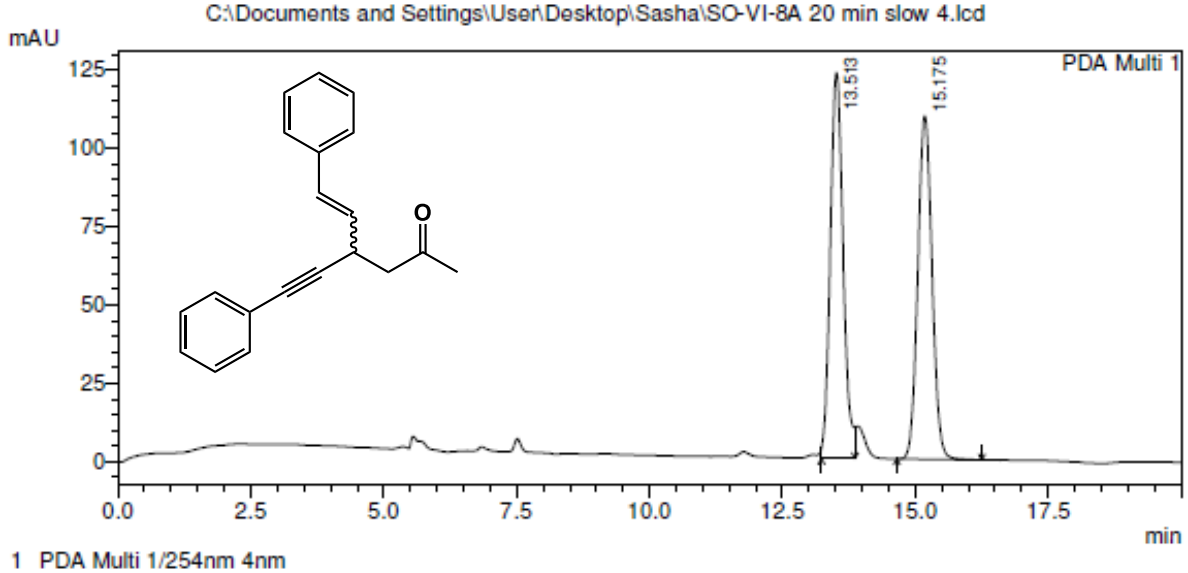


1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|---|---|---|---|---|---|
| 1 | 13.513 | 2067334 | 123047 | 50.236 | 52.911 |
| 2 | 15.175 | 2047912 | 109507 | 49.764 | 47.089 |
| Total | | 4115245 | 232554 | 100.000 | 100.000 |

**HPLC of (*rac)*-6-phenyl-4-(phenylethynyl)hex-5-en-2-one (8)**

# ==== Shimadzu LCsolution Analysis Report ====

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| | |
|---|---|
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| Sample ID | : SO-VI-8B |
| Tray# | : 1 |
| Vail # | : 2 |
| Injection Volume | : 5 uL |
| Data File Name | : SO-VI-8B 20 min slow 2.lcd |
| Method File Name | : pos5_90%_20min.lcm |
| Batch File Name | : Batch_table_5-90%_20min_C6F5_cat_BINOL.lcb |
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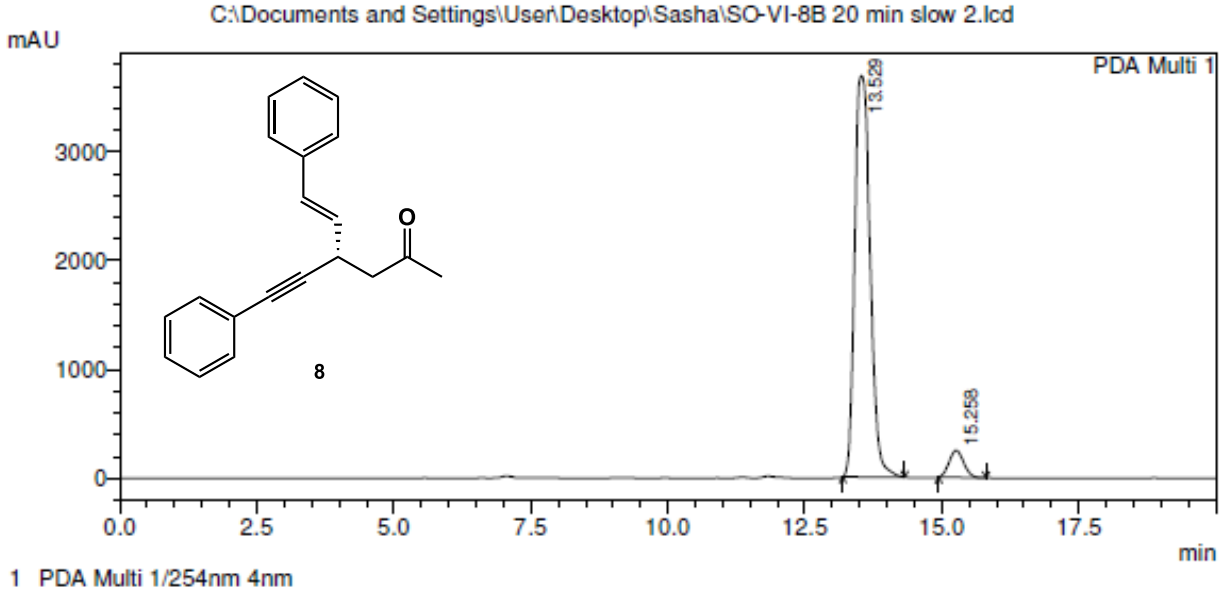
**<Chromatogram>**




1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|---|---|---|---|---|---|
| 1 | 13.529 | 72313571 | 3690060 | 94.032 | 93.697 |
| 2 | 15.258 | 4589303 | 248241 | 5.968 | 6.303 |
| Total | | 76902873 | 3938301 | 100.000 | 100.000 |

**HPLC of (*S*,*E*)-6-phenyl-4-(phenylethynyl)hex-5-en-2-one (8)**

# CHAPTER 6: CONCLUSIONS – ORGANODIOL CATALYZED CONJUGATE ADDITIONS FOR TOTAL SYNTHESIS AND METHODOLOGICAL DEVELOPMENT

## 6.1 Total Synthesis

Conjugate additions developed in the May lab excel at utilizing electron-rich heterocycle-appended electrophiles.[168] This reactivity was key in the development of a synthetic route to the mucronatins,[47] as well as the planned syntheses of cytoblastin[81] and completion of discoipyrrole D[43,169] (Figure 6.1).

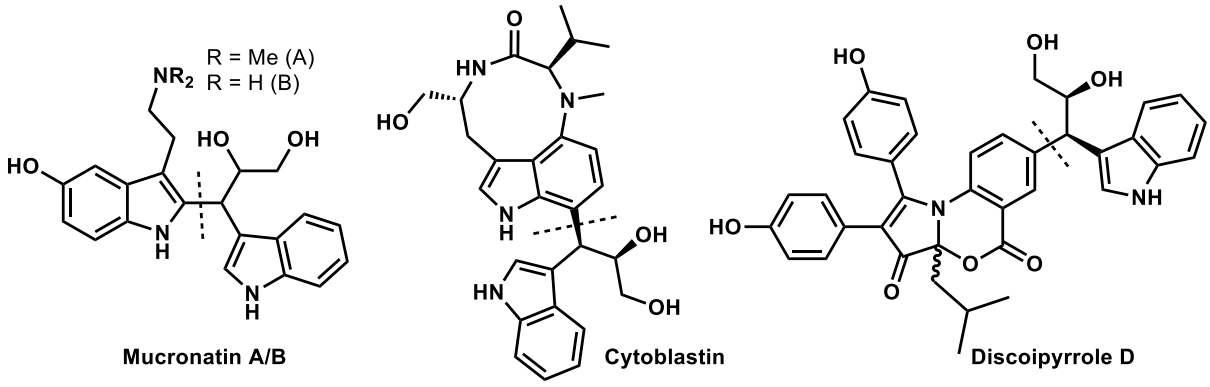



**Figure 6.1.** Indolyl propylene glycol natural products

Two disconnections were proposed and attempted, both with electron-rich heterocycle appended enones (Figure 6.2). The first approach using tryptamine or serotonin derived nucleophile **3** required formation of the carbon-boron bond at the 2-position of a tryptamine (**7**) or serotonin (**8**) derived nucleophile, while the electrophile was a known unsaturated aldehyde **4** synthesized by a Zincke aldehyde strategy.[48] The synthesis and use of indole boronate **3** in the conjugate addition proved to be prohibitively challenging.

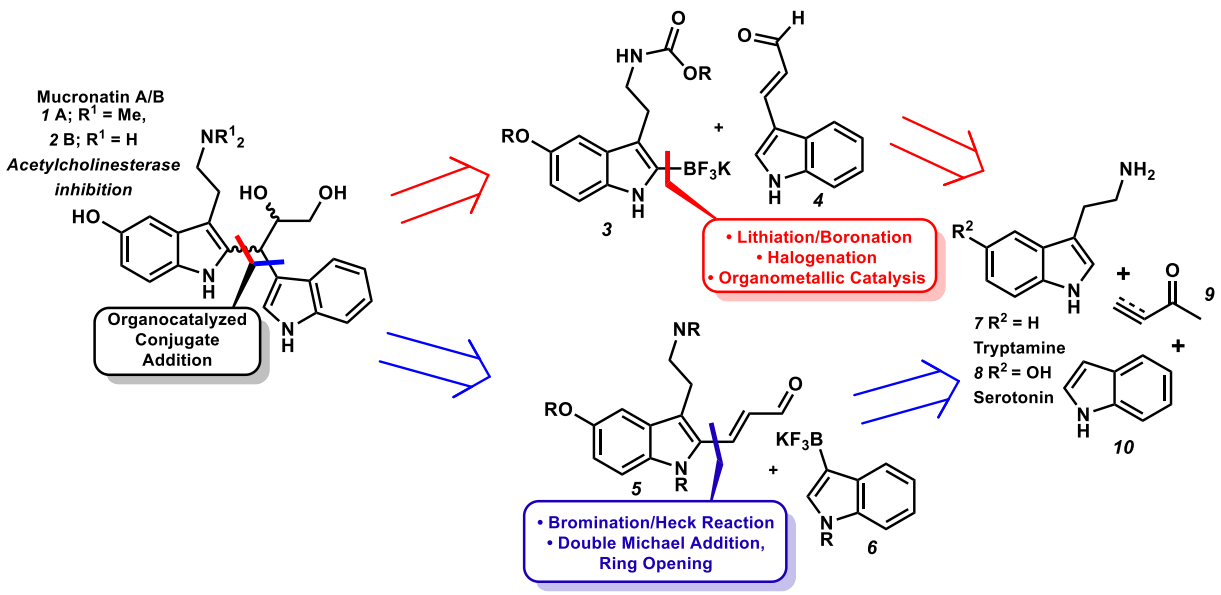



**Figure 6.2.** Disconnections in the synthesis of the mucronatins

In the second approach, tryptamine or serotonin derived electrophiles **5** and the 3-position indolyl trifluoroborate salt (**6**) were used. The salt, **6** could be easily synthesized, and some variants are even commercially available. The synthesis of the electrophile **5** can be accomplished by a double Michael addition without the use of transition metal catalysis, resulting in promising reactivity that is being optimized currently as it suffers from some inconsistency. The option of returning to the use of a Heck reaction to synthesize this electrophile remains available should this route prove difficult to optimize.

Nonetheless, the key conjugate reaction step of the synthesis has been shown to be effective, and the synthesis is nearly complete (Figure 6.3). The final steps have been well developed in the synthetic approach to discoipyrrole D.[43] We anticipate completion of this synthesis, as well as those of cytoblastin and discoipyrrole D, shortly.

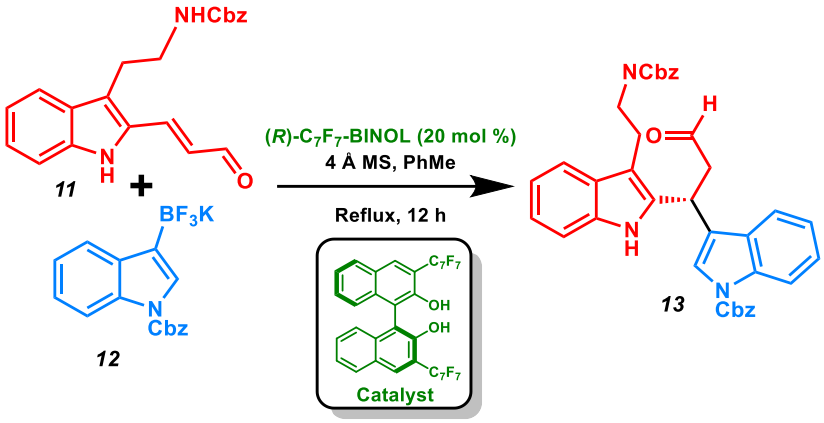



**Figure 6.3.** Key conjugate addition of mucronatin A/B total synthesis

## 6.2 Vinylogous Substitution and Relay Catalysis

As electron-rich electrophiles are effective in conjugate additions developed by our group,[39] the use of vinylogous esters and amides as electrophiles in such reactions was attempted. This resulted in nearly unprecedented reactivity, effectively providing conjugate addition with subsequent elimination of the alcohol or amine leaving group (Figure 6.4). The resulting polyene structures were synthesized in good yields.

This methodology was then applied an effective synthesis of polyene structures. Relay catalysis allowed for the use of substoichiometric quantities of methylaniline to be used to form the vinylogous amides *in situ*, and the resulting structures could participate in conjugate addition reactions with an organodiol catalyst to provide the polyenes in high yields with shorter reaction times.

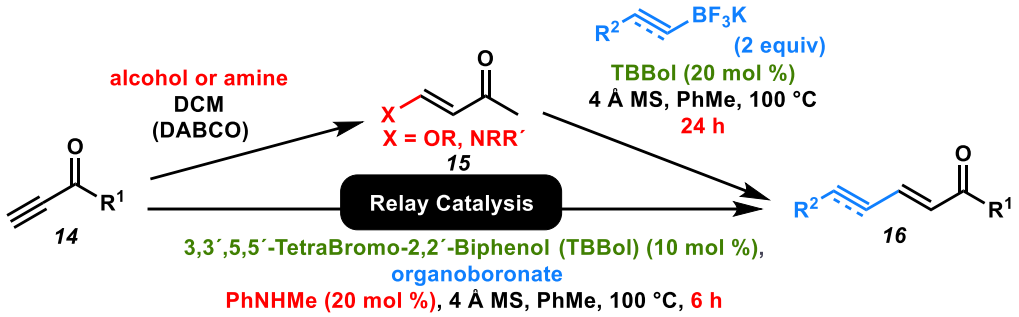



**Figure 6.4.** Vinylogous substitution and relay catalysis

One of the products of the relay catalytic reaction, the ene/yne ketone **17**, was used in a second conjugate addition to give the β-alkynyl/β-alkenyl **18** in high yields with high enantioselectivity. Work continues for the enantioselective conjugate addition to occur in the same flask as the relay catalysis/vinylogous substitution by relying on the reactivity of the nucleophiles to provide control in the reaction pathway. Applications of this methodology are anticipated to provide novel reactivity pathways in future work in methodological development and synthesis.

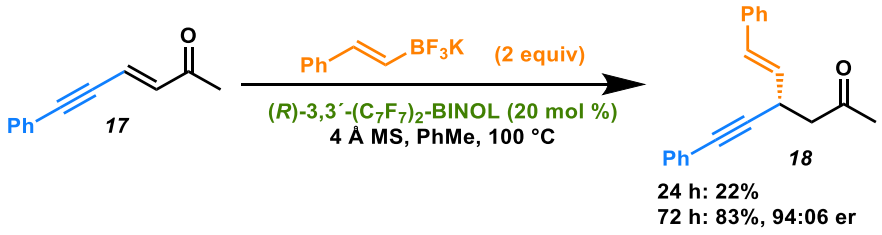



**Figure 6.5.** Utility of the products of relay catalysis

## 6.3 Concluding Remarks

Both projects explored in this dissertation were based on organocatalyzed conjugate addition reactions developed in the May lab. Both have provided valuable information in the development of synthetic pathways and methods. The developed synthetic routes excel at setting stereocenters in an enantioselective fashion, allowing for the synthesis of a variety of product diastereomers that could be used in SAR and biological activity studies. The methodology

developed used unusual electrophiles and provided access to promising structures that can be used for natural product synthesis or new reactions. Synthesis and methodology have been considerably intertwined, where advances in one contributed to the other, and that is expected to continue in future work. Both projects have represented a considerable advancement in the methods and syntheses of our group and generated promising ideas.

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