Diisopinocampheylborane Trifluoromethanesulfonate-Mediated Aldol Reactions Using an Aldehyde and an Amide

By

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Abstract

PARKER, CAMILLE; Diisopinocampheylborane Trifluoromethanesulfonate-Mediated Aldol Reactions Using an Aldehyde and an Amide

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Aldol reactions are one of the most powerful reactions in organic chemistry because of the formation of new carbon-carbon bonds. A downside of aldol reactions is that they generate a mix of stereoisomers, therefore a lot of work has gone into developing methods that selectively favor a certain stereoisomer. We report an enatio and diastereoselective diisopinocampheylborane trifluoromethanesulfonate ($(Ipc)_2BOTf$) mediated aldol reaction with an amide and an aldehyde. Traditionally, $(Ipc)_2BOTf$-mediated reactions were not applied to amides, except with the use of strong bases. Here we developed a $(Ipc)_2BOTf$ aldol reaction of amides using mild bases ($i Pr_2NEt$). Our lab was able to achieve an enantioselective and diastereoselective reaction, with an enantiomeric excess (ee) and diastereomeric ratio (d.r.) of up to >95% and >19:1, respectively for aliphatic aldehydes. We also expanded the scope of this reaction to include aromatic aldehydes and protected alcohol aldehydes.

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Table of Contents

Acronyms

1) Benzyloxymethyl Chloride- BOM-Cl
2) Chloroform-D- $CDCl_3$
3) Chromium (III) tris(dipivaloylmethane)- $Cr(dpm)_3$
4) Dichloromethane- DCM
5) DHP- Dihydropyran
6) $(Ipc)_2BH$- (Diisopinocampheyl)borane
7) $(Ipc)_2BOTf$- Diisopinocampheylborane Trifluoromethanesulfonate
8) Diisopropyl Ethylamine- $i Pr_2NEt$
9) N,N-Dimethyl Formamide- DMF
10) Di-tert-butyl Dicarbonate- Boc_2O
11) Ethyl Acetate- EtOAc
12) Hexanes- H
13) Hydrochloric Acid- HCl
14) Lithium Aluminum Hydride- $LiAlH_4$
15) Magnesium Sulfate- $MgSO_4$
16) Methanol- MeOH
17) Methanesulfonyl Chloride- MsCl
18) Nitrogen- N_2
19) Sodium Dichromate- $Na_2Cr_2O_7$
20) Sodium Sulfate- Na_2SO_4
21) Tert-butyldimethylsilyl Chloride- TBDMS-Cl
22) Tert-Butyldimethylsilyl Trifluoromethanesulfonate- TBS-OTf

23) Tetrahydrofuran- THF

24) Tetra-n-butylammonium Fluoride- TBAF

25) Triisopropylsilyl chloride- TIPS-Cl

26) Thionyl Chloride- $SOCl_2$

27) Triethylamine- Et_3N

28) Triphenylphosphine- PPh_3

1.Introduction

The formation of carbon-carbon bonds provides the framework for many organic compounds such as pharmaceuticals, dyes, and cosmetics. Aldol reactions are commonly used in the formation of new carbon-carbon bonds and were first described in 1848 by Kane.[1] In an aldol reaction a ketone or aldehyde reacts with an enolizable carbonyl compound forming a new carbon-carbon bond. The enolizable carbonyl acts as a nucleophile by having at least one acidic proton in the α-position.[1] The reactions result in the formation of a β-hydroxycarbonyl compound.[2] Traditionally, reactions were carried out using catalytic amounts of acidic or basic species.[2] Over the years a lot of research has been done to expand on the aldol reaction and improve it. Some of these developments include enolization strategies to form (E) and (Z) enolates, Lewis acid catalyzed additions, chiral enolates with good pi-face selectivity and using metal architectures for kinetic diastereoselective aldol additions.[1]

1.1- Traditional Aldol Reaction

The traditional aldol reaction is mediated by an acid or base and is run in a protic solvent, Figure 1.[1]

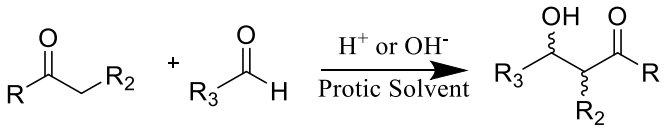


Figure 1. Traditional aldol reaction.

This reaction is reversible especially under these reaction conditions. The enol or enolate that is generated acts as a nucleophile and is generated in the presence of the ketone or aldehyde which acts as an electrophile.[1] The traditional aldol reaction was considered state

of the art until the early 1970s, however, the reversibility of the reaction caused substantial problems.[1] Another problem that occurs is a mixture of products when performing a mixed aldol reaction.[1] These problems led to the development of new synthetic methods of aldol reactions.

1.2- Asymmetric Aldol: Evans Reaction

There are a few different methods that are used when performing enantioselective aldol reactions of chiral and achiral enolates with achiral aldehydes.[3] Enantioselectivity is a method that favors a certain enantiomer over the other. Stereoselective synthesis controls the stereochemistry of the chiral centers of molecules. This is especially important for pharmaceuticals since different biological activity can be observed between enantiomers of chiral compounds.[2] In stereoselective aldol reactions the relative conformation of the aldol adduct is known and in enantioselective reactions the absolute configuration can be determined.[4]

The Z-enolate leads to the preferential formation of the 1,2-*syn* product and the E-enolate leads to the formation of the 1,2-*anti* product when the reaction proceeds via a closed transition state.[4] The *syn* product has the substituents on the same side while the *anti*-product has the substituents on opposite sides of the molecule, shown in Figure 2.

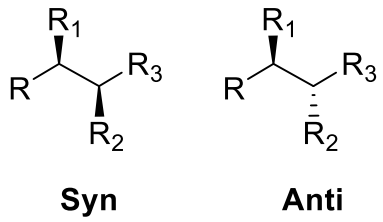


Figure 2. Scheme showing the *syn* and *anti*-versions of a molecule.

Enantioselective aldol methods can be split into three groups. The first is the use of carbonyl compounds with chiral auxiliaries that can be removed from the final product easily. Second, using metal enolates (titanium, tin or lithium) or metalloid enolates with chiral ligands typically boron. The third is by running the reaction in the presence of a chiral catalyst.

The traditional approach to asymmetric aldol reactions is the Evans reaction. The Evans aldol reaction is able to achieve two goals, high enantioselectivity and high diastereoselectivity.[5] Diastereoselectivity is the formation of one diastereomer over the other, either *syn* or *anti*, or E/Z. This reaction involves an aldehyde and Evans chiral auxiliary. The chiral auxiliary forms an enolate which acts as a nucleophile and reacts with an electrophile, which proceeds through a six-membered transition state, shown in Figure 3. The chiral auxiliary is then removed from the desired product.[7]

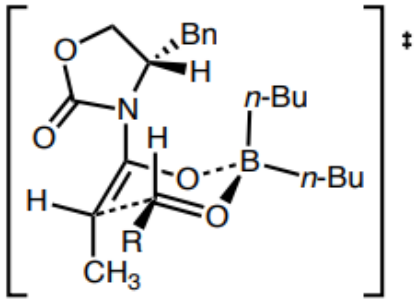


Figure 3. 6-membered transition state that determines the stereochemistry of the product for the Evans aldol reaction.

The benzyl group of the auxiliary blocks one face of the enolate, thereby increasing facial selectivity. The highly ordered closed transition state with the Z-(O)-enolate increases diastereoselectivity.

The use of asymmetric enolates or nucleophiles is more general and gives high stereoselectivity because of the highly ordered nature of the transition state, which proceeds through a closed transition model, Figure 3.[8] A downside of this type of reaction is that the chiral auxiliary must be removed from the final product adding an additional step.[8] Another disadvantage is that it can require the installation of the auxiliaries if the starting material is not commercially available. A new method was employed to avoid the additional step of removing the chiral auxiliary from the final aldol product. This new method reacted achiral carbonyl compounds with achiral enolates in the presence of additional chiral auxiliaries. However, it requires stoichiometric amounts of the chiral information.[8] The problems encountered while performing asymmetric aldol reactions with chiral electrophiles or enolates led to the development of new methods in the synthesis of enantioselective aldol reactions.

1.3- Asymmetric Aldol: Metal Complex Catalysis

Since the 1980s the use of metal complex catalysts to mediate enantioselective aldol reactions has been studied extensively.[2] Early research focused on Lewis acidic complexes, which were designed to activate the aldehyde or facilitate enolate formation from an aldol donor. The chiral environment, created by the ligands, around the metal controls the enantioselectivity of the aldol reaction.[2] One method of this type of aldol reaction is using rare earth metal (RE) triflates ($RE(OTf)_3$) as catalysts.[4] These catalysts are water tolerant Lewis acids and can also be easily recovered. The catalyst involves chiral crown ether

ligands and large, rare-earth metals such as lanthanum, cerium, praseodymium, and neodymium, Figure 4 is an example of this reaction .[4]

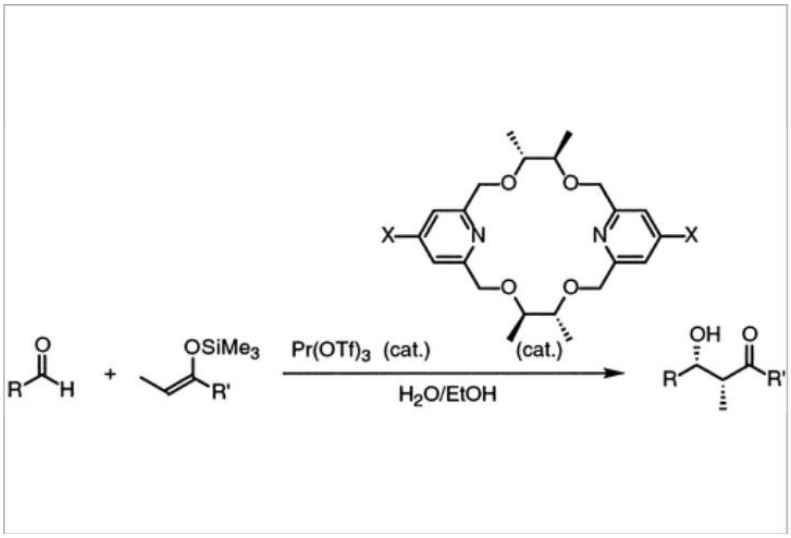


Figure 4. Aldol reaction catalyzed by a metal complex and a crown ligand.[9]

1.4 -Asymmetric Aldol: Lewis Acid Catalyzed

Lewis acid catalyzed aldol reactions are also used when performing enantioselective synthesis.[10] In 1973 a new aldol reaction was reported by Mukaiyama *et al*. during which Lewis acids activate either an aldehyde or ketone in the presence of a carbon nucleophile. Lewis acids have an empty orbital that is capable of accepting an electron pair from a Lewis base. The activation allows for the nucleophile to attack which forms the new carbon-carbon bond. This reaction was first reported using silyl enol ethers (SEE) reacting with aldehydes in the presence of titanium tetrachloride, a Lewis acid. The Mukaiyama aldol reaction led to the development of a number of carbon-carbon bond forming reactions utilizing this type of chemistry. A general scheme for Lewis acid catalyzed aldol reactions is shown below in Figure 5.[10]

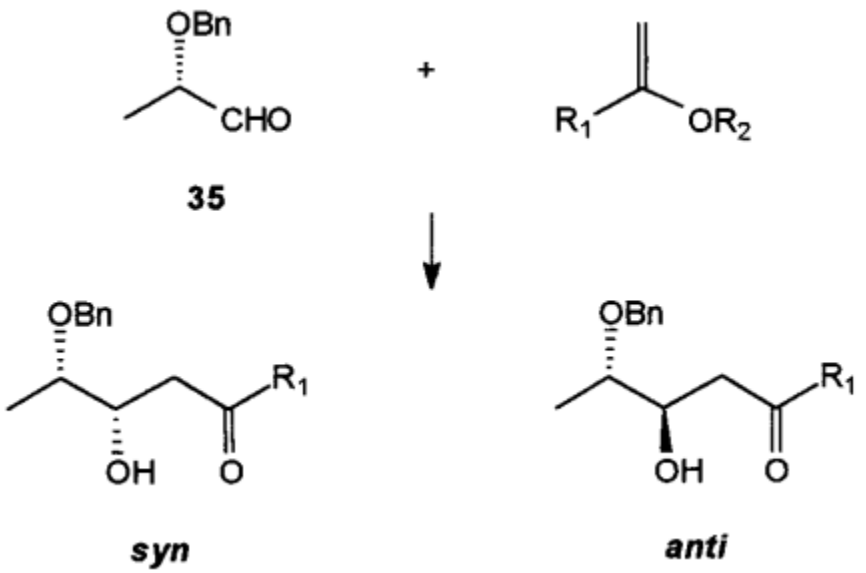


Figure 5. Scheme showing Lewis acid catalyzed aldol reactions.[8]

Multiple different Lewis acids were used including $SnCl_4$, $TiCl_4$ and BF_3 and the authors reported the ratio of *syn* and *anti*-products.[8]

1.5- Asymmetric Aldol: Chiral Lewis Base Catalyzed

Chiral Lewis bases have also been used as catalysts in enantioselective aldol reactions this method was first reported in 1996.[4] In these reactions the electron pair of the Lewis base interacts with an acceptor atom on the enolate making it more reactive.[4] An example of this reaction uses a weak achiral Lewis acid, $SiCl_4$, with a chiral Lewis base catalyst, phosphoramide, generating a strong activated chiral Lewis acid. An example of this is shown in Figure 6, below.

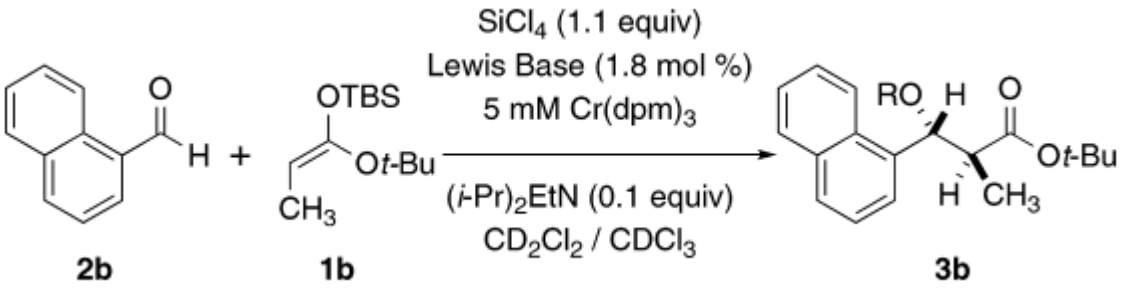


Figure 6. Scheme showing a Lewis base catalyzed asymmetric aldol reaction.[11]

Typically, aldol reactions were limited to ketones, esters or aldehydes as the donor substrates because of their relatively low pK_a values ranging from 19-20 which limits the scope of aldol reactions.[12] Catalytic aldol reactions between amides and aldehydes have been reported using metal alkoxides and strong bases.[12] These reactions, published in 2006, were the first to yield highly *anti*-selective direct-type catalytic aldol reactions between aldehydes and amides.[12] Since this publication more research has been done on developing methods for aldol reactions involving amides and aldehydes as well as obtaining the *anti*-product. Strong bases such as LDA have been used in aldol reactions involving amides, however, this can cause the reaction to suffer from strongly basic reaction conditions. Strong bases are incompatible with many functional groups, which limits the scope of many reactions.[10]

1.6- Boron-Mediated Aldol Reaction for Small Molecule Synthesis

Our research focuses on using chiral Lewis acids to introduce chirality, specifically the use of diisopinocampheylboron trifluoromethanesulfonate ($(Ipc)_2BOTf$). The use of $(Ipc)_2BOTf$ has shown success with ketones or imides because of their relatively low pK_a values.[3] This project has three main goals: $(Ipc)_2BOTf$-mediated enantio and

diastereoselective aldol reactions using an aldehyde and an amide for small molecule synthesis, testing the compatibility of the reaction with different alcohol protecting groups, and testing different Lewis acids to obtain the *anti*-product in reductive aldol reactions.

(Diisopinocampheyl)borane ($(Ipc)_2BH$) is a chiral organoborane that can be used in asymmetric synthesis.[13] $(Ipc)_2BH$ is obtained through a relatively easy one-step synthesis using (α)-pinene, which is readily available and cheap. $(Ipc)_2BH$ serves as a precursor for a wide range of reagents including $(Ipc)_2BOMe$, $(Ipc)_2BCl$, and our focus $(Ipc)_2BOTf$.[13] Reductive aldol reactions with high enantioselectivity have been successfully carried out using $(Ipc)_2BH$ in previous studies.[13] These include reactions between 4-acryloylmorpholine and chiral and achiral aldehydes to produce *syn*-products as well as the synthesis of *anti*-α-methyl-β-hydroxy propionate esters using the hydroboration of *tert*-butyl acrylate and chiral and achiral aldehydes.[14, 17] Enolborinate intermediates are exceptionally useful for asymmetric aldol reactions because of their tight, closed, structurally well-defined transition state.[14] The reactions we are studying are all mediated by a variation $(Ipc)_2BH$, $(Ipc)_2BOTf$, to obtain the desired product.

We plan to develop boron-mediated aldol reactions between an aldehyde and an amide that are enantio and diastereoselective. As stated previously, aldol reactions are successful with ketones, aldehydes, and esters because of their relatively low pKa. Amides have a higher pKa value making them harder to deprotonate so strong bases are often used.

Our synthesis uses $(Ipc)_2BOTf$ as a Lewis acid, diisopropylethylamine a mild base, phenyl acetyl morpholine, and an aldehyde (Figure 7).

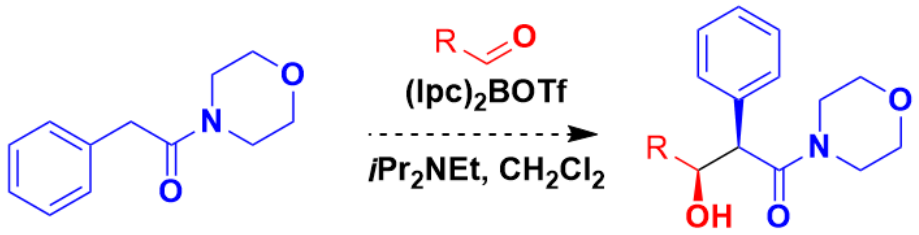


Figure 7. $(Ipc)_2BOTf$-mediated aldol reaction[6]

Methylphenidate, commonly known as Ritalin, will be used in order to demonstrate the utility of this methodology. Ritalin is a well-known pharmaceutical used to manage neurodevelopmental disorders such as ADD and ADHD.[15] Due to the two stereocenters Ritalin has four possible isomers (2R, 2'R), (2S, 2'S), (2R, 2'S), and (2S, 2'R), shown in Figure 8.

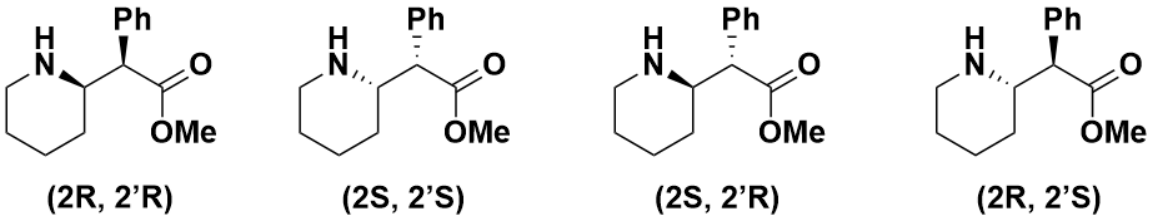


Figure 8. Four isomers of methylphenidate.[6]

Typically, methylphenidate is administered as a mixture of (2R, 2'R) and (2S, 2'S) however (2R, 2'R) is the more active isomer. There are minimal therapeutic effects exhibited by the (2S, 2'R) and the (2R, 2'S) isomers and they often cause some unwanted

toxicities.[15] The synthesis of enantiomerically pure (2R, 2'R) methylphenidate is highly sought after; we will apply our $(Ipc)_2BOTf$-mediated amide aldol reaction to synthesize (2R, 2'R) methylphenidate.

1.7- Boron-Mediated Aldol Using Protected Alcohols

Often during synthesis of complex molecules side reactions from secondary functional groups will occur.[16] A lot of research has gone into solutions to this problem, one such solution is adding a protecting group to the secondary functional group. The protecting group is added, the desired synthesis is performed, and the protecting group is then removed from the desired product. Deprotection is typically performed by using an aqueous acid or base. Our lab will perform the $(Ipc)_2BOTf$-mediated aldol reaction with different protecting groups on the aldehyde. To do this a protecting group will be added to one of the hydroxyl groups on propanediol and the other hydroxyl group will be oxidized to an aldehyde. The protected aldehyde will then be used in our $(Ipc)_2BOTf$-mediated reaction. The protecting groups we plan to investigate include various silyl ethers and chloroalkyl ethers. Figure 9, below, shows the reaction scheme for the protected $(Ipc)_2BOTf$-mediated aldol reaction.

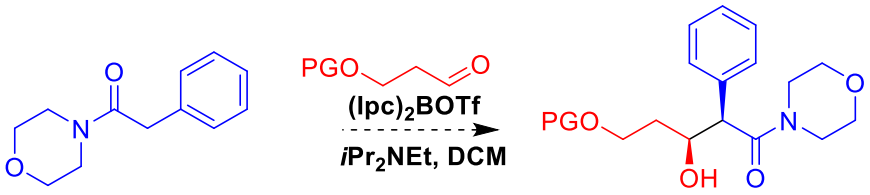


Figure 9. Protected $(Ipc)_2BOTf$-mediated aldol reaction scheme where PG is protecting group[6]

1.8- Lewis Acid Catalyzed Anti-Selective Aldol Reactions

The formation of *syn*-aldols with good stereoselectivity is well established using many different methods. However, the formation of *anti*-aldols with useful diastereo and enantioselectivity is still a work in progress.[17] Some notable contributions to enantioselective *anti*-aldol reactions include a Rh-catalyzed reductive aldol reactions of acrylates and aromatic aldehydes reported by Nishiyama in 2005. A boron mediated *anti*-selective aldol reaction was reported by Roush *et al.* in 2013 using $(Ipc)_2BH$ as a reducing agent.[17] Our lab plans to research Lewis acid catalyzed reductive aldol reactions to obtain *anti* products. The *anti*-product is obtained because the reaction goes through an open transition state rather than a closed one. The proposed reaction uses 4-acryloylmorpholine and different Lewis acids such as titanium tetrachloride to obtain the *anti*-aldol product. A planed reaction scheme of this reaction is shown in Figure 10.

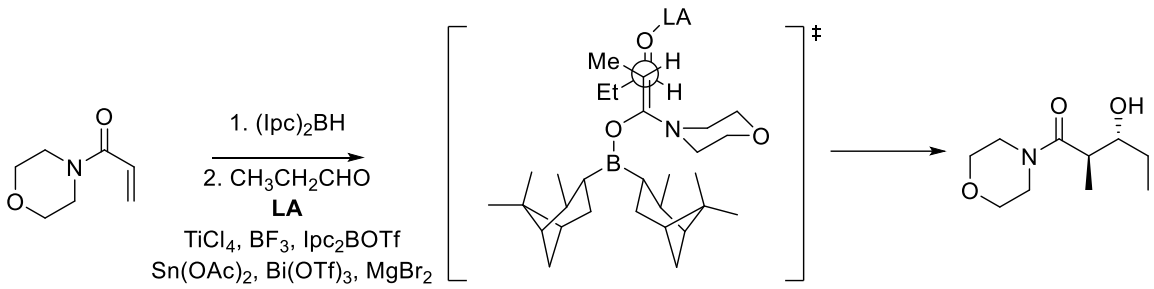


Figure 10. Scheme showing the general reaction to obtain the *anti*-product using Lewis acids.

In summary, our lab is interested in researching three things: 1. Expanded the scope of the $(Ipc)_2BH$ mediated aldol reaction, 2. Apply this method to the synthesis of methylphenidate, 3. Explore further stereoselective reactions, including *anti*-selective aldol reactions.

2. Results and Discussion

Our lab had 3 main goals for $(Ipc)_2BOTf$ mediated aldol reactions. These included expanding the scope of the reaction by using a variety of different aliphatic and aromatic aldehydes, applying this method to the stereo and enantioselective synthesis of a pharmaceutical target and applying this method to a variety of different protected alcohols. All of the results we obtained are outlined in sections 2.1-2.5 below.

2.1- $(Ipc)_2BH$ Results

$(Ipc)_2BH$ needs to be synthesized for this reaction as it is not commercially available. It is synthesized from relatively cheap and abundant starting materials making it a good candidate for stereo and enantioselective aldol reactions. We were able to synthesize **1** from borane-dimethylsufide and (-)-(α)-pinene with yields ranging from 40-70%. The reaction proceeds via a hydroboration reaction and the two faces of the alkene have different sterics making it possible to obtain **1** in high enantiomeric excess.

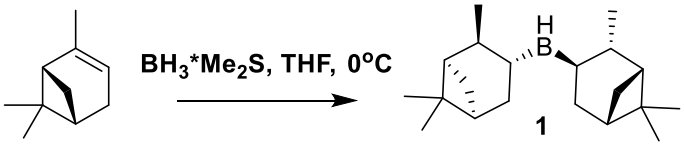
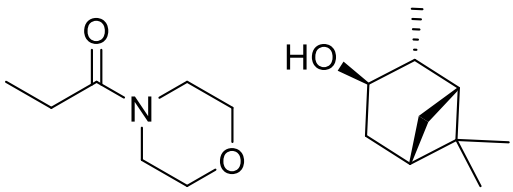


Figure 11. Synthesis of $(Ipc)_2BH$ (**1**).

The $(Ipc)_2BH$ is stored in the freezer in a glovebox because when in the presence of moisture, it decomposes to $(Ipc)_2OH$ and is unusable for our reaction. The $(Ipc)_2BH$ lasted about 5 months when kept in the freezer in the glove box. Our lab also performed other reactions to test the viability of the $(Ipc)_2BH$ including a reduction of 4-acryloylmorpholine to form **2** and the oxidation of $(Ipc)_2BH$ to form **3**.



2 **3**

Figure 12. Products **2** and **3** which were synthesized to test the quality of the $(Ipc)_2BH$.

These reactions helped us to determine the efficacy of the $(Ipc)_2BH$ and to see if any had decomposed. We tested the viability because the first aldol reaction we tried with the $(Ipc)_2BH$, an aldol reaction with propionaldehyde, failed. The first thing we did was take a proton NMR of the $(Ipc)_2BH$ to make sure it had not been oxidized to $(Ipc)_2BOH$. The NMR spectrum validated that the product was not $(Ipc)_2BOH$. We then moved on to the synthesis of **2** and **3** to ensure that the $(Ipc)_2BH$ was viable and had not decomposed. After determining that the $(Ipc)_2BH$ was not the reason the reaction failed we assessed other conditions including the iPr$_2$NEt and the propionaldehyde. We took a proton NMR of the base, which had been distilled before the reaction, the spectrum showed that the base was not the problem. From here we decided to distill the propionaldehyde to eliminate water from the reaction completely.

2.2- Scope of Reaction

We wanted to explore the scope of the reaction by applying it to aliphatic and aromatic aldehydes. We also used this method to perform reductive aldol reactions with 4-acryloylmorpholine to produce the *syn*-product. The first aldehyde we tried was propionaldehyde, an aliphatic aldehyde, which is commercially available and shelf stable. We distilled the aldehyde before use to ensure it was anhydrous and pure. Figure 13 shows

the synthesis of the $(Ipc)_2BOTf$ aldol reaction using propionaldehyde which produced product **4**.

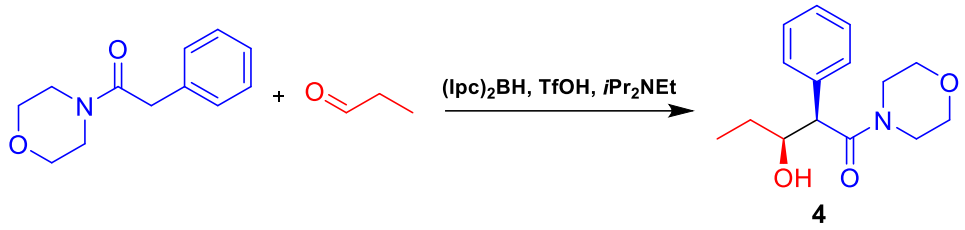


Figure 13. Synthesis of **4**, $(Ipc)_2BOTf$ mediated aldol reaction using propionaldehyde.

The reaction produced aldol product **4** with a high yield indicating that the reaction should work for aliphatic aldehydes. The crude NMR spectrum was used to determine the diastereomeric ratio (d.r.) of **4** to be >19:1.

Mosher esters were then used to determine the enantiomeric excess (ee) of **4**. The NMR spectrum of the Mosher esters, showed that the ee was >95%. The ee and d.r. values for product **4** lead us to conclude that using $(Ipc)_2BH$ to mediate aldol reaction gives both enantio and diastereoselective products with an aliphatic aldehyde.

The aromatic aldehyde used to explore this reaction was 4-nitrobenzaldehyde. This aldehyde was selected because it is a shelf stable solid so we didn't have to distill it before use. Figure 10, below, shows the scheme for this reaction yielding 30% of compound **5**.

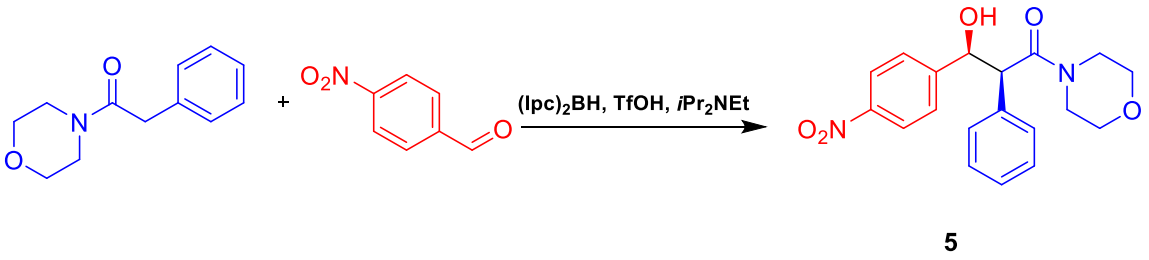


Figure 14. $(Ipc)_2BOTf$ mediated aldol reaction using 4-nitrobenzaldehyde to produce **5**.

The reaction produced compound **5** with a low yield, 30%, a reason for this might be that the $(Ipc)_2BH$ used was a few months old making it less effective in the synthesis. We were also unable to cool the reaction to -78°C when adding the aldehyde which would affect the stereochemistry of the reaction. The ee of **5** was not determined since the yield was so low and we were unable to cool the reaction.

2.3- Results for the Synthesis of Methylphenidate

Our lab proposed a synthesis of (2R, 2'R) methylphenidate using the $(Ipc)_2BOTf$ mediated aldol reaction shown in Figure 15.

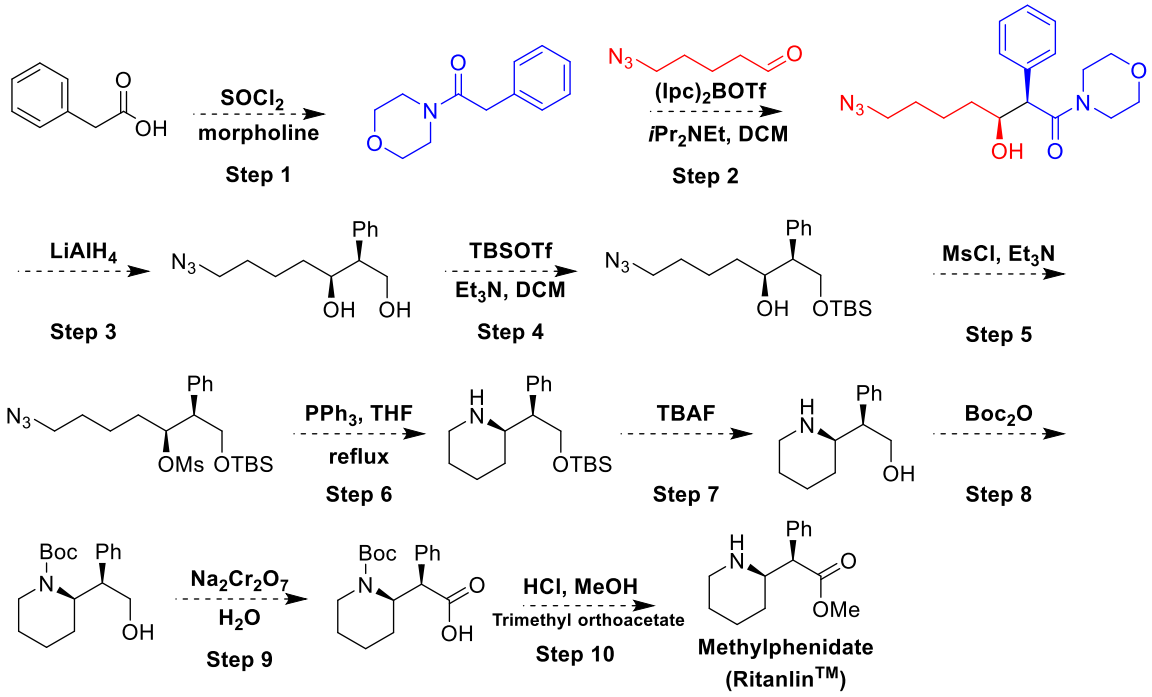


Figure 15. Proposed synthesis of (2R, 2'R) methylphenidate using an $(Ipc)_2BOTf$ mediated aldol reaction.

Step 2 of the reaction scheme is the new method our lab is exploring. Starting with phenylacetic acid we were able to synthesize **6** through the addition of thionyl chloride followed by morpholine. Aldehyde **8** was synthesized from 5-chloropentan-1-ol by the

addition of sodium azide in an S_N2 reaction followed by oxidation of the alcohol using pyridinium chlorochromate. Figure 16, below, shows the synthesis of the starting materials.

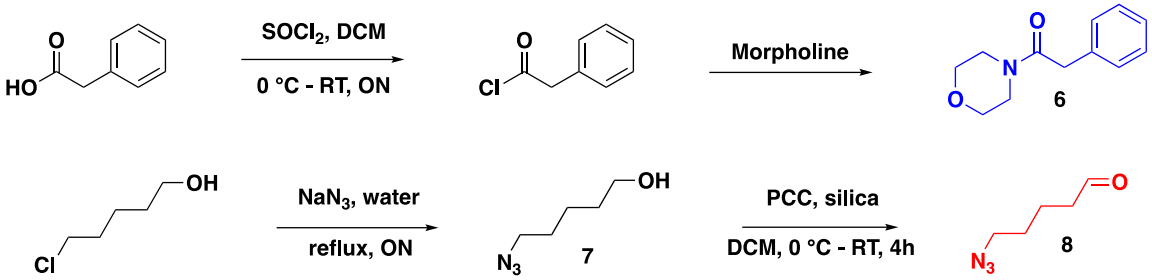


Figure 16. Scheme showing the synthesis of **6** (top), **7** and **8** (bottom).

The alcohol was oxidized to an aldehyde right before use because the stability of **8** is unknown. The aldehyde was synthesized the day before the reaction then kept in solution in the freezer overnight. A short column was used to purify the aldehyde right before use. All the necessary starting materials were obtained with good purity and relatively high yields.

After the synthesis of the starting materials, we were able to attempt our crucial amide aldol reaction with an azide-containing aliphatic aldehyde. Product **9** (Figure 15 above) was then synthesized yielding the desired aldol product by combining $(Ipc)_2BH$, triflic acid, $i Pr_2NEt$, amide **6** and aldehyde **8**. The d.r. was >19:1, determined using the crude NMR spectrum, shown in Figure 17. The ee of **9** was not determined.

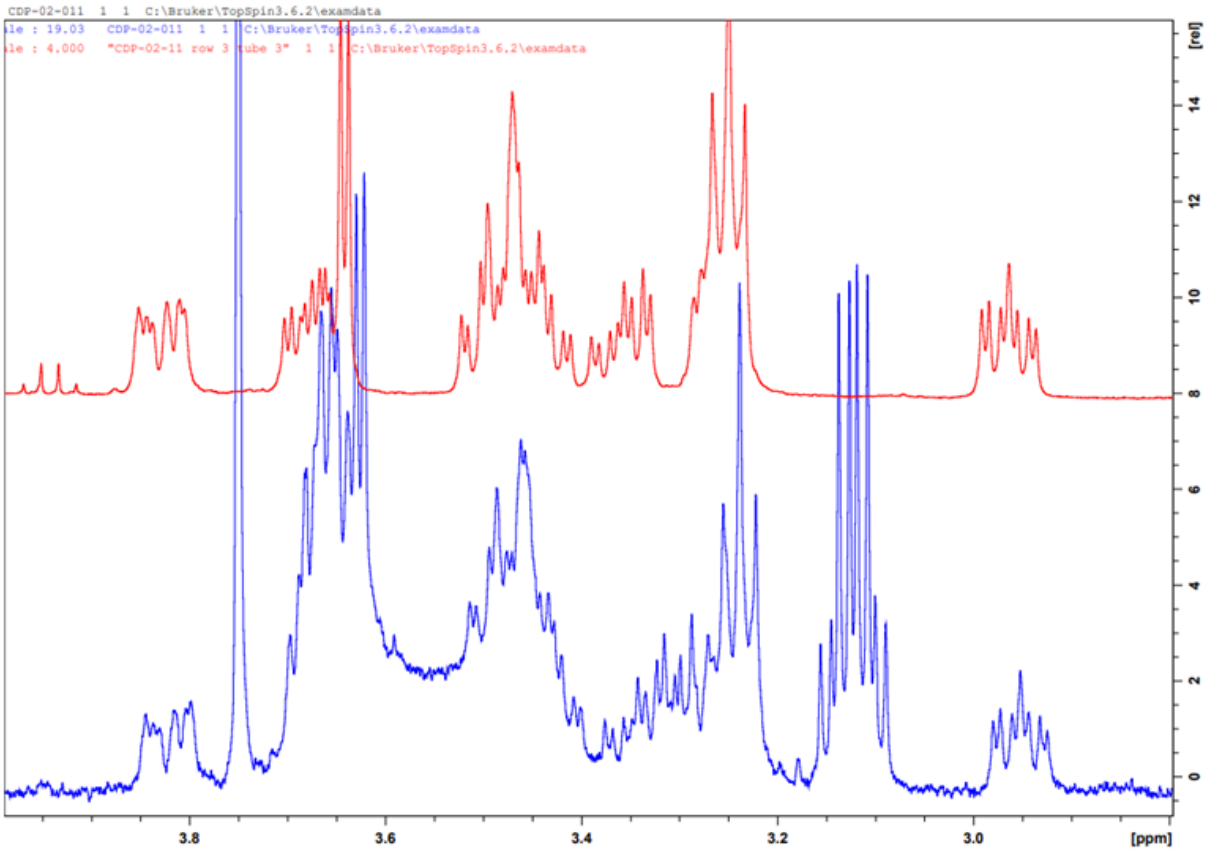


Figure 17. NMR spectrum of **9**, the crude product is shown in blue and purified product is shown in red. The crude NMR spectrum was used to determine the d.r..

The next steps of the reaction, 3 and 4, involve reducing the amide to an alcohol by using lithium aluminum hydride then protecting that alcohol with TBS-OTf. Step 5 involves activation of the secondary alcohol as a mesylate before attempting the second key step of the synthesis, step 6. This involves a tandem Staudinger reduction followed by an intermolecular S_N2 reaction to form the piperidine ring. This is a risky reaction that faces potential elimination of the mesylate group resulting in a conjugated alkene. We hope the neutral conditions of the Staudinger reduction will minimize this unwanted side reaction. Step 7 then removes the TBS-protecting group from the alcohol using TBAF. This ends

the formal synthesis of (2R, 2'R) methylphenidate as the remaining three steps have been performed by the Novartis group. The next step, 8, adds a Boc-protecting group to the amine to protect it from the oxidation performed in step 9. The alcohol is then oxidized using sodium dichromate ($Na_2Cr_2O_7$) to a carboxylic acid. The final step, 10, removes the protecting group from the amine using HCl while transforming the carboxylic acid to an ester yielding the final product, (2R, 2'R) methylphenidate.

2.4- Protected Alcohols

Our lab wanted to expand the scope of this reaction to protected alcohols as well. We added four different protecting groups including TIPS, TBDMS, DHP, and BOM to propanediol. The products from these reactions are shown in Figure 18.

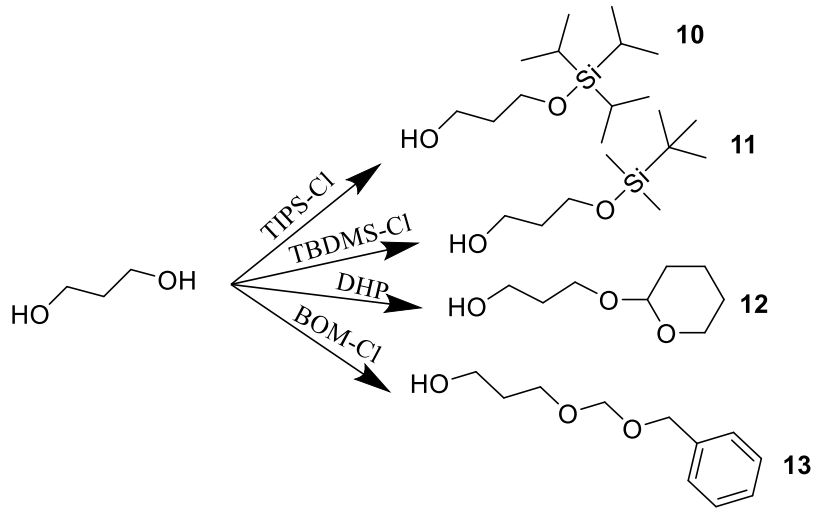
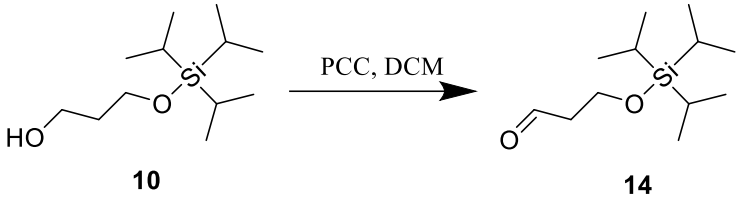


Figure 18. Scheme showing the 4 different protected alcohols synthesized for the $(Ipc)_2BOTf$ mediated aldol reactions.

The syntheses of the protected alcohols were simple one step reactions performed at room temperature and all products were purified using flash chromatography. One of the main

problems encountered with this reaction was getting the dimer rather than the monomer. We did not encounter this problem with product **11** and obtained a relatively high yield, 74%. However, the reaction involving TIPS-Cl yielded both the monomer and the dimer. We were able to separate them using flash chromatography; however, we only got a 10% yield of **10**. The DHP and BOM protected alcohols both gave the monomer and the dimer as well. However, we were unable to separate them using flash chromatography.

The first $(Ipc)_2BOTf$ mediated aldol reaction we tried was with the TIPS protected alcohol. We oxidized the alcohol to an aldehyde a day before the aldol reaction and purified it the day of the reaction using a short plug of silica. Figure 19 shows the oxidation of alcohol **10** to an aldehyde to form **14**.



10 **14**

Figure 19. Scheme for the oxidation of alcohol **10** to aldehyde **14**.

This oxidation produced a pure aldehyde with a high yield, 95%. We then followed the same aldol procedure that we used to get products **4** and **9** making sure to cool the reaction to -78^{o}C when the aldehyde was added and keeping the reaction at -20^{o}C overnight. The scheme showing the synthesis of **15** is shown below in Figure 20.

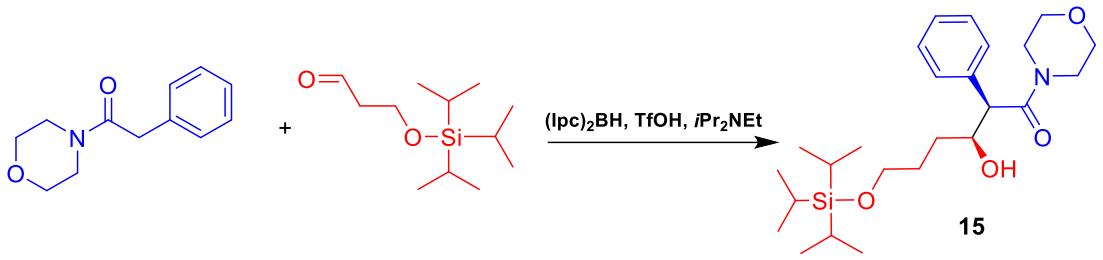


Figure 20. $(Ipc)_2BOTf$ mediated aldol reaction using a TIPS protected alcohol to form aldol product **15**.

We believe that the correct product was synthesized based on the crude NMR. After doing flash chromatography we took another NMR revealing that the product was collected however it was not totally pure. A second column was run but only 16 mg (11%) of product was collected from the second column and it still wasn't totally pure. This led us to believe that the diastereomer could have been present in the final product and that it was collected from the column instead of the desired product. Although we were able to get the reaction to proceed with the protected alcohol, we were not able to determine the stereochemistry of the product since we did not obtain enough to do Mosher esters and the product was also not totally pure.

The next protected alcohol we tried was **11**. The first time we attempted to oxidize **11** we used silica in solution with the PCC and DCM, which had previously worked when synthesizing **8**. However, we were not successful in oxidizing **11** when we used this method, so we excluded the silica and just used PCC in DCM as shown in Figure 21, below.

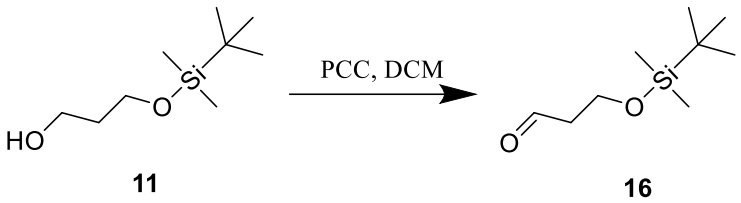


Figure 21. Oxidation of **11** to form aldehyde **16** used in $(Ipc)_2BOTf$ mediated reactions.

The second oxidation of **11** to form aldehyde **16** was successful and produced **16** with good purity in high yield, 96%.

We then proceeded with the $(Ipc)_2BOTf$ mediated aldol reactions following all of the same conditions used to synthesize **4**, **9** and **15**. The synthesis of aldol product **17** is shown in Figure 22, below.

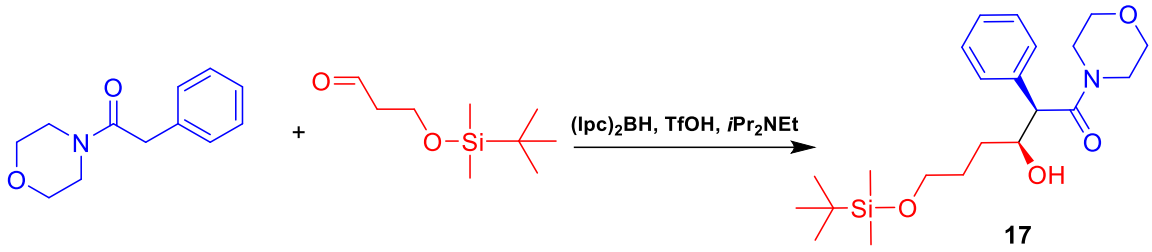


Figure 22. $(Ipc)_2BOTf$ mediated aldol reaction with TBDMS protected alcohol to form aldol product **17**.

A crude NMR was taken of **17** leading us to believe that the reaction was successful, so the crude product was purified using flash chromatography. After the column the reaction yielded 124 mg of product (90%) which was the highest yield we obtained from any of the aldol reactions. This could be because of the $(Ipc)_2BH$ used since it had been synthesized

very close to the date of the aldol reaction. We were unable to explore the stereochemistry of **17** however due to time restraints.

Alcohols **12** and **13** were made and purified however they have not yet been used in the $(Ipc)_2BOTf$ mediated aldol reactions. From the two reactions performed with protected alcohols we determined that the reaction can proceed with silyl protected alcohols. However, we were not able to examine the stereochemistry of the products because of the challenges previously stated.

2.5 Reductive Aldol for the syn-Product

As previously stated, $(Ipc)_2BH$ can be used to perform reductive aldol reactions yielding the *syn*-product. We used 4-acryloylmorpholine as a starting material for this as it is readily available and quite inexpensive. Figure 23, below, shows the reductive aldol reaction yielding product **18**.

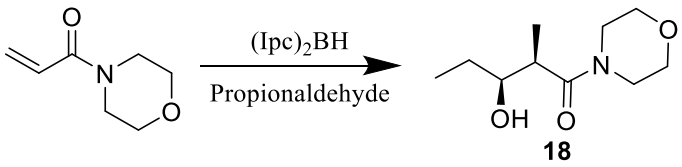


Figure 23. Reductive aldol reaction using $(Ipc)_2BH$ to produce the *syn*-product.

The reaction was successful and after purification we obtained an 89% yield of product **18**. These reactions go through a 6-membered closed transition state which gives the final product a *syn* conformation.

3. Conclusion

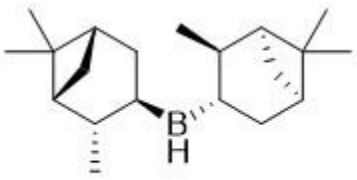
The use of $(Ipc)_2BOTf$ mediated aldol reactions between amides and aliphatic aldehydes offers high enantio and stereoselectivity in the product. The d.r. and ee for the aldol reaction using propionaldehyde were >19:1 and >95%, respectively. Steps 1 and 2 of

the proposed synthesis for methylphenidate have been completed successfully. This method can be used with aromatic aldehydes; however, the stereochemistry is still being explored. We were also successful in completing these $(Icp)_2BOTf$ mediated aldol reactions with silyl protected alcohols. The stereochemistry of the protected aldol products is still being explored. Reductive aldol reactions using $(Ipc)_2BH$ to obtain a *syn*-product were also conducted successfully.

4. Experimental

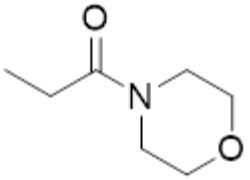
All reactions were performed under N_2, using dry solvents and in flame-dried glassware. All ^1H NMR spectra were taken using a 400 MHz Bruker NMR.

4.1) (Diisopinocampheyl)borane (1). THF (21 mL) was combined with borane dimethyl sulfide (2 mL, 22 mmol) in a three neck round bottom flask equipped with a thermometer, under a N_2 atmosphere. The solution was cooled to 0^oC and (-)-(α)-pinene (5 mL, 42 mmol) was added dropwise over 30 minutes. The thermometer was removed, all septa wrapped with parafilm and the reaction was placed in a 0^oC fridge for 46 hours. After 46 hours the reaction was brought back to room temperature and the supernatant was removed via cannula. The reaction was washed 3X using 10 mL of diethyl ether then dried under vacuum overnight (16 h). The white solid was moved to the glove box still under N_2, crushed and weighed yielding 2.17 g (71%) of a white powder. ^1H NMR (400 MHz, d^8-THF) δ: 0.85, 0.87, 0.89, 0.91, 0.92, 0.93, 0.94, 0.96, 0.97, 0.99, 1.00, 1.02, 1.04, 1.05, 1.06, 1.07, 1.09, 1.12, 1.13, 1.14, 1.15, 1.17 (2), 1.19, 1.21, 1.23, 1.24, 1.27, 1.64 (m), 1.65-2.45 (m), 5.18 (m).



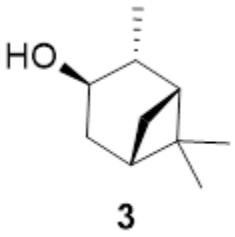
1

4.2) 1-Morpholinopropan-1-one (2). $(Ipc)_2BH$ (**1**) (72 mg, 0.25 mmol) was combined with 1 mL of diethyl ether. The suspension was cooled to 0°C and 4-acryloylmorpholine (40 µL, 0.275 mmol) was added. After 2 hours of stirring 0.5 mL of pH 7 phosphate buffer, 0.5 mL MeOH and 0.5 mL of THF were added. The reaction was brought back to room temperature and stirring continued for 20 hours. After stirring the reaction was partitioned between water and 30 mL of DCM and the aqueous phase was extracted 2X with 10 mL of DCM. The organics were combined, washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure.



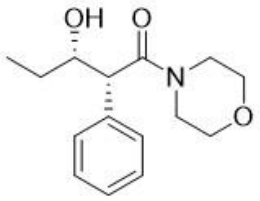
2

4.3) (2R,3R)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-ol (3). $(Ipc)_2BH$ (**1**) (100 mg, 0.35 mmol) was combined with 1.2 mL of THF. To the solution, 10 µL of water was added slowly under N_2 then 70 mg of $NaBO_3$ was added making sure the reaction did not exceed 35°C. The reaction was stirred overnight (16 h). After stirring the reaction was partitioned between ice cold water and diethyl ether, the aqueous layer was extracted 2X with 10 mL of diethyl ether. The organics were combined, washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.08-4.04 (m, 1H), 1.93 (m, 2H), 1.80 (m, 1H), 1.22 (s, 3H), 1.13 (d, 3H, J= 8), 0.92 (s, 3H).



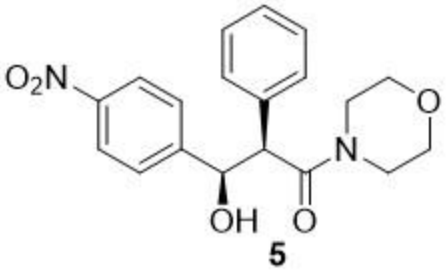
3

4.4) (2R,3S)-3-Hydroxy-1-morpholino-2-phenylpentan-1-one (4). $(Ipc)_2BH$ (**1**) (210 mg, 0.349 mmol) was combined with 2.7 mL of DCM under N_2 forming a white suspension. The reaction was cooled in an ice bath and triflic acid (70 μL, 0.726 mmol) was added dropwise and the reaction stirred at room temperature for 1 hour. After an hour the solution was cooled in an ice bath and diisopropylethylamine (0.4 mL, 1.432 mmol) was added followed by phenyl acetyl morpholine (**6**) (71.7 mg, 0.349 mmol) in 0.8 mL of DCM and the solution was stirred in for 3 hours in an ice bath. The reaction was cooled to -78°C and propionaldehyde (38 μL, 0.524 mmol) in 0.8 mL of DCM was added dropwise, the solution continued stirring at -78°C for 1 hour. After an hour the reaction was warmed to -20°C and continued stirring overnight. The reaction was brought back to room temperature and quenched using 1.5 mL pH 7 phosphate buffer, 1.5 mL MeOH and 1.5 mL H_2O_2 and stirred for 6 hours. The reaction was concentrated under reduced pressure then partitioned between 30 mL of DCM and 30 mL of water. The aqueous layer was extracted 3X with 20 mL of DCM, washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified using flash chromatography (1:2 H:EtOAc to 100% EtOAc) yielding 76.0 mg (84%) of a yellow oil. R_f= 0.64 (1:2 H:EtOAc), ee >95%, d.r. >19:1. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.29 (m, 3H), 7.26-7.23 (m, 2H), 4.38 (s, 1H), 4.15-4.11 (m, 1H), 3.85-3.80 (m, 1H), 3.66-3.50 (m, 2H), 3.52-3.42 (m, 3H), 3.37-3.32 (m, 2H), 2.99-2.93 (m, 1H), 0.98 (t, 3H, J= 15.2).



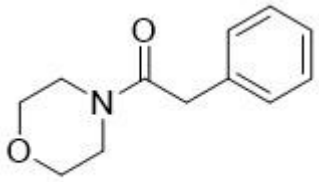
4

4.5) (2S,3S)-3-Hydroxy-3-(4-nitrophenyl)-2-phenyl-1-(piperidin-1-yl)propan-1-one (5). $(Ipc)_2BH$ (**1**) (209 mg, 0.349 mmol) was combined with 2.7 mL of DCM under N_2 forming a white suspension. The reaction was cooled in an ice bath and triflic acid (70 μL, 0.726 mmol) was added dropwise, the reaction stirred at room temperature for 1 hour. After an hour the solution was cooled in an ice bath and diisopropylethylamine (0.4 mL, 1.432 mmol) was added followed by phenyl acetyl morpholine (**6**) (75.6 mg, 0.349 mmol) in 0.6 mL of DCM and the solution was stirred in for 3 hours in an ice bath. The reaction was cooled to 0°C and 4-nitrobenzaldehyde (80 mg, 0.524 mmol) in 0.8 mL of DCM was added dropwise, the solution continued stirring at 0°C for 1 hour. After an hour the reaction was warmed to room temperature and continued stirring overnight. The reaction was quenched using 1.5 mL pH 7 phosphate buffer, 1.5 mL methanol and 1.5 mL H_2O_2 and stirred for 6 hours. The reaction was concentrated under reduced pressure then partitioned between 30 mL of DCM and 30 mL of water. The aqueous layer was extracted 2X with 20 mL of DCM, washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified using flash chromatography (1:2 H:EtOAc to 100% EtOAc) yielding 37.5 mg (30%) of a yellow solid. R_f= 0.66 (9:1 CH_2Cl_2:MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.08 (s, 1H), 8.06 (s, 1H), 7.25-7.18 (m, 5H), 6.81 (s, 2H, J= 8), 5.54 (d, 1H, J=8), 3.91-3.87 (m, 1H), 3.81 (d, 1H, J=8), 3.72-3.68 (m, 2H), 3.54-3.59 (m, 2H), 2.95-2.90 (m, 1H).



5

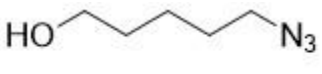
4.6) 1-Morpholino-2-phenylethan-1-one (6).



6

Phenylacetic acid (502.5 mg, 3.7 mmol) was combined with 9 mL of dry DCM under a N_2 atmosphere. The solution was cooled in an ice bath and thionyl chloride (2.2 mL, 11 mmol) was added dropwise. The reaction was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and DCM was added to make a 1M solution (3.7 mL). The reaction mixture was cooled in an ice bath and morpholine (0.97 mL, 11 mmol) was added. The reaction was brought back to room temperature and stirred for 30 minutes. The reaction was diluted with ethyl acetate and the organic layer was separated. The organic layer was washed with 1M HCl, washed with saturated sodium bicarbonate, washed with brine, dried with Na_2SO_4, and concentrated *in-vacuo*. The crude product was purified using flash chromatography (9:1 DCM:MeOH) affording 646.5 mg (86%) of **1** as a white solid. R_f=0.60 (9:1 DCM:MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.31 (t, 2H), 7.25 (t, 4H), 3.74 (s, 2H), 3.65 (s, 4H), 3.46 (t, 2H), 3.43 (t, 2H).

4.7) 5-Azidopentan-1-ol (7). Sodium azide (1.12 g, 17.3 mmol) and 5-chloropentan-1-ol (1 mL, 8.65 mmol) were combined with 9.4 mL of water, the solution was refluxed overnight (12 h). The reaction was extracted with diethyl ether 5x and the organic layers were combined, washed with brine, dried with $MgSO_4$, and concentrated *in-vacuo* yielding 838.2 mg (75%) of **2** as a colorless oil. R_f=0.68 (100% EtAOc). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.67 (t, 2H, J= 12), 3.29 (t, 2H, J= 14), 1.62 (m, 4H), 1.48 (m, 2H).

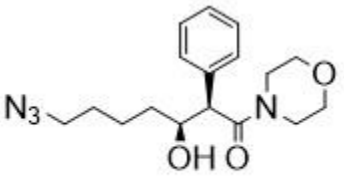


7

4.8) 5-Azidopentanal (8). Pyridinium chlorochromate (401 mg, 1.9 mmol) and 100 mg of silica were added to 3 mL of DCM. The reaction mixture was cooled to 0°C and 5-chloropentan-1-ol (**7**) (200 mg, 1.5 mmol) in 0.3 mL of DCM was added. The reaction mixture was brought back to room temperature and stirred for 6 hours. The reaction was concentrated *in-vacuo* and purified using flash chromatography (2:1 H:EtOAc) yielding 170 mg (88%) of a clear oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.32 (s, 1H), 3.67 (t, 2H, J= 12), 3.29 (t, 2H, J= 14), 1.62 (m, 4H), 1.48 (m, 2H).

8

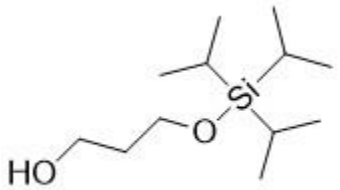
4.9) (2S,3R)-7-Azido-3-hydroxy-1-morpholino-2-phenylheptan-1-one (9). $(Ipc)_2BH$ (**1**) (202 mg, 0.349 mmol) was combined with 2.7 mL of DCM under N_2 forming a white suspension. The reaction was cooled in an ice bath and triflic acid (65 μL, 0.726 mmol) was added dropwise, the reaction stirred at room temperature for 1 hour. After an hour the solution was cooled in an ice bath and diisopropylethylamine (0.35 mL, 1.432 mmol) was added followed by phenyl acetyl morpholine (**6**) (74 mg, 0.349 mmol) in 0.8 mL of DCM and the solution was stirred in for 3 hours in an ice bath. The reaction was cooled to -78°C using dry ice and acetone and 5-azidopentanal (**8**) (64 mg, 0.524 mmol) in 0.8 mL of DCM was added dropwise, the solution continued stirring at -78°C for 1 hour. After an hour the reaction was warmed to -20°C by placing it in an isopropyl alcohol bath cooled with a cryocool and continued stirring overnight. The reaction was brought back to room temperature and quenched using



9

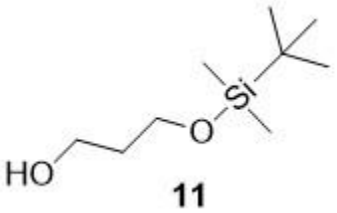
1.5 mL pH 7 phosphate buffer, 1.5 mL MeOH and 1.5 mL H_2O_2 and stirred for 6 hours. The reaction was concentrated under reduced pressure then partitioned between 30 mL of DCM and 30 mL of water. The aqueous layer was extracted 3X with 20 mL of DCM, washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified using flash chromatography (1:2 H:EtOAc to 100% EtOAc) yielding 61 mg (53%) of a clear oil. R_f= 0.16 (7:3 H:EtOAc), d.r. >19:1. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.29 (m, 3H), 7.26-7.24 (m, 2H), 4.24-4.20 (m, 1H), 3.85-3.80 (m, 1H), 3.70-3.67 (m, 1H), 3.65 (d, 1H, J= 4), 3.50-3.41 (m, 3H), 3.40-3.34 (m, 1H), 3.25 (t, 3H, J= 8).

4.10) 3-((Triisopropylsilyl)oxy)propan-1-ol (10). To a solution of 10 mL DMF and propanediol (1 mL, 10 mmol) imidazole (686 mg, 10 mmol), 4-*N*,*N*-dimethylaminopyridine (19 mg, 1 mmol) and triisopropylsilyl chloride (2 mL, 9.3 mmol) was added at 0°C and stirred for 1 hour. After stirring for an hour, the reaction was warmed to room temperature and stirring continued overnight. The reaction was partitioned between water and diethyl ether and the aqueous phase was extracted 2X with diethyl ether. The organics were combined, dried using Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified using flash chromatography 10% EtOAc in hexanes yielding 217 mg of the monomer (10%) as a clear oil. R_f= 0.55 (2:1 H:EtOAc). (400 MHz, $CDCl_3$) δ 3.60-3.55 (m, 2H), 3.51-3.46 (m, 2H), 2.91-2.84 (m, 1H), 1.10-1.04 (m, 21H).



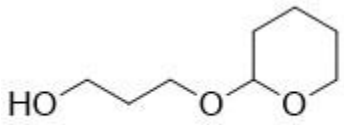
10

4.11) 3-((Tert-butyldimethylsilyl)oxy)propan-1-ol (11). Propanediol (2 mL, 17.8 mmol) was added to 30 mL of DCM. To the solution imidazole (360 mg, 5.2 mmol) and *tert*-butyldimethylsilyl chloride (794 mg, 5.24 mmol) were added and the reaction was stirred for 20 hours at room temperature. The reaction was washed with water twice, the organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified using flash chromatography 1:1 EtOAc:H yielding 742 mg (74.3%) of a clear oil. R_f= 0.53 (2:1 H:EtOAc). ^{1}HNMR (400 MHz, $CDCl_3$) δ 3.84-3.3.79 (m, 2H), 1.81-1.75 (m, 1H), 1.26 (t, 2H, J= 8), 0.90 (s, 6H), 0.078 (s, 3H).



11

4.12) 3-((Tetrahydro-2H-pyran-2-yl)oxy)propan-1-ol (12). Propanediol (4.5 mL, 60 mmol), dihydropyran (1.4 mL, 12 mmol), and p-toluenesulfonic acid (206 mg, 75 mmol) were combined and stirred at room temperature for 4 hours. The reaction was partitioned between CH_2Cl_2 and water and the aqueous phase was extracted 3x with CH_2Cl_2. The organics were combined, washed with brine, dried with $MgSO_4$, filtered and concentrated. The crude product was purified using flash chromatography (1:1 H:EtOAc) yielding 729 mg (38%) of a clear oil.



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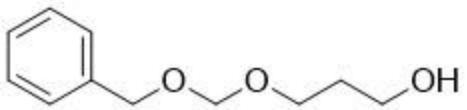
4.13) 3-((Benzyloxy)methoxy)propan-1-ol (13). Diisopropylethyl amine (2 mL, 11 mmol), propanediol (1 mL, 14 mmol) and chloromethyl benzyl ether (1 mL, 7 mmol) were



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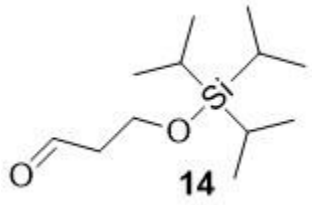
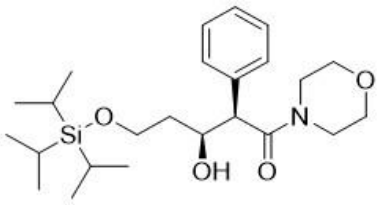
added to 15 mL of DCM and stirred at room temperature for 18 h. After stirring 30 mL of water was added and the aqueous phase was extracted 3X with DCM. The organics were combined, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified using flash chromatography (3:1 H:EtOAc) yielding (18%) of a clear oil.

4.14) 3-((Triisopropylsilyl)oxy)propanal (14). Pyridinium chlorochromate (243 mg, 1.1 mmol) was added to 1.5 mL of DCM. 3-((triisopropylsilyl)oxy)propan-1-ol (**10**) (117 mg, 0.9 mmol) in 0.5 mL of DCM was added at room temperature. The reaction mixture was stirred for 6 hours. The solution was filtered from the black insoluble solid and the solid was extracted 3x using 10 mL of diethyl ether. The organics were combined and filtered through a short plug of silica. The reaction was concentrated *in-vacuo* yielding 197.5 mg (95%) of an orange oil. (400 MHz, $CDCl_3$) δ 9.71 (t, 1H), 3.60-3.55 (m, 2H), 3.51-3.46 (m, 2H), 2.91-2.84 (m, 1H), 1.10-1.04 (m, 21H).



14

4.15) (2R,3S)-3-Hydroxy-1-morpholino-2-phenyl-5-((triisopropylsilyl)oxy)pentan-1-one (15). $(Ipc)_2BH$ (**1**) (211 mg, 0.349 mmol) was combined with 2.7 mL of DCM under N_2 forming a white suspension. The reaction was cooled in an ice bath and triflic acid (64.27 μL, 0.726 mmol) was added dropwise, the reaction stirred at room temperature for 1 hour. After an hour the solution was cooled in an ice bath and diisopropylethylamine (0.36 mL, 1.432 mmol) was added followed by phenyl



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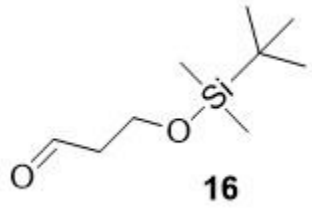
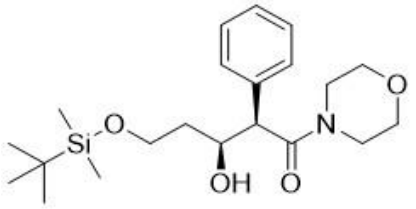
acetyl morpholine (**6**) (72.1 mg, 0.349 mmol) in 0.7 mL of DCM and the solution was stirred in for 3 hours in an ice bath. The reaction was cooled to -78^{o}C and 3-((triisopropylsilyl)oxy)propanal (**14**) (198 mg, 0.454 mmol) in 0.8 mL of DCM was added dropwise, the solution continued stirring at -78^{o}C for 1 hour. After an hour the reaction was warmed to -20^{o}C and continued stirring overnight. The reaction was brought back to room temperature and quenched using 1.5 mL pH 7 phosphate buffer, 1.5 mL methanol and 1.5 mL H_2O_2 and stirred for 6 hours. The reaction was concentrated under reduced pressure then partitioned between 30 mL of DCM and 30 mL of water. The aqueous layer was extracted 3X with 20 mL of DCM, washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified using flash chromatography (1:2 H:EtOAc to 100% EtOAc) yielding 16 mg (11%) of a clear oil. R_f= 0.13 (2:1 H:EtOAc).

4.16) 3-((Tert-butyldimethylsilyl)oxy)propanal (16). Pyridinium chlorochromate (272 mg, 1.5 mmol) was added to 1.5 mL of DCM. 3-((tert-butyldimethylsilyl)oxy)propan-1-ol (**11**) (114 mg, 0.60 mmol) in 0.5 mL of DCM was added at room temperature. The reaction mixture was stirred for 3 hours. The solution was filtered from the black insoluble solid and the solid was extracted 3x using 7 mL of diethyl ether. The organics were combined and filtered through a short plug of silica. The reaction was concentrated *in-vacuo* yielding 109 mg (96%) of an orange oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 9.83 (t, 1H), 3.84-3.3.79 (m, 2H), 1.81-1.75 (m, 1H), 1.26 (t, 2H, J= 8), 0.90 (s, 6H), 0.078 (s, 3H).



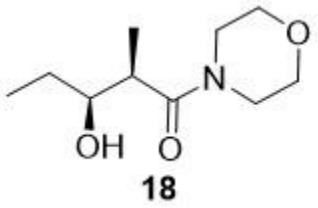
16

4.17) (2R,3S)-5-((Tert-butyldimethylsilyl)oxy)-3-hydroxy-1-morpholino-2-phenylpentan-1-one (17). $(Ipc)_2BH$ (**1**) (214 mg, 0.349 mmol) was combined with 2.8 mL of DCM under N_2 forming a white suspension. The reaction was cooled in an ice bath and triflic acid (80 μL, 0.726 mmol) was added dropwise, the reaction stirred at room temperature for 1 hour. After an hour the solution was cooled in an ice bath and diisopropylethylamine (0.41 mL, 1.432 mmol) was added followed by phenyl acetyl morpholine (**6**) (72.1 mg, 0.349 mmol) in 0.8 mL of DCM and the solution was stirred in for 3 hours in an ice bath. The reaction was cooled to -78°C and 3-((tert-butyldimethylsilyl)oxy)propanal (**16**) (109 mg, 0.531 mmol) in 0.8 mL of DCM was added dropwise, the solution continued stirring at -78°C for 1 hour. After an hour the reaction was warmed to -20°C and continued stirring overnight. The reaction was brought back to room temperature and quenched using 1.5 mL pH 7 phosphate buffer, 1.5 mL methanol and 1.5 mL H_2O_2 and stirred for 6 hours. The reaction was concentrated under reduced pressure then partitioned between 30 mL of DCM and 30 mL of water. The aqueous layer was extracted 3X with 20 mL of DCM, washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified using flash chromatography (1:2 H:EtOAc to 100% EtOAc) yielding 124 mg (91%) of an orange oil. R_f= 0.31 (1:1 H:EtOAc).



17

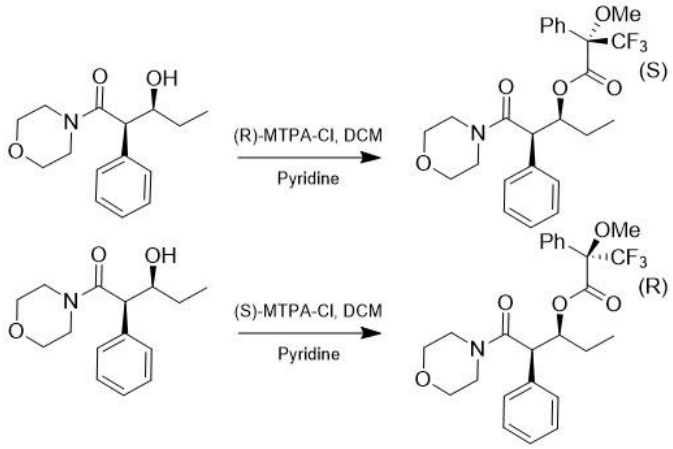
4.18) (2S,3R)-3-Hydroxy-2-methyl-1-morpholinopentan-1-one (18). $(Ipc)_2BH$ (**4**) (72 mg, 0.25 mmol) was combined with 1 mL of diethyl ether. The suspension was cooled to 0°C and 4-acryloylmorpholine (35 µL, 0.275 mmol) was added, stirring continued for 2 hours. After 2 hours the reaction was cooled to -75°C using a cryocool and propionaldehyde (15 µL, 0.213 mmol) was added. The reaction was stirred overnight (17 h) at -75°C using a cryocool then brought to room temperature and quenched with 0.5 mL of pH 7 buffer, 0.5 mL of MeOH and 0.5 mL of THF, stirring continues for 6 hours at room temperature. After stirring the aqueous layer was extracted 3x with 10 mL DCM. The organics were combined, washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified using flash chromatography starting with 1:1 DCM:EtOAc increasing to 1:3 DCM:EtOAc yielding 49.3 mg (89.2%) of a clear oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.28 (s, 1H), 3.82 (m, 1H), 3.68 (m, 6H), 3.50 (t, 2H, J= 8), 2.65-2.59 (m, 1H), 1.14 (d, 3H, J=8), 0.97 (t, 3H, J= 8), 3.85-3.80 (m, 1H), 3.66-3.50 (m, 2H), 3.52-3.42 (m, 3H), 3.37-3.32 (m, 2H), 2.99-2.93 (m, 1H), 0.98 (t, 3H, J= 15.2).



18

4.19) Mosher esters for 5 (19). (R)-Mosher chloride (1.7 µL, 0.009 mmol) was added to a small vial and (S)-Mosher chloride was added to another vial (1.7 µL, 0.009 mmol). Distilled pyridine (1.23 µL, 0.015 mmol) was added to each vial along with 1.3 mg **5**

dissolved in 0.08 mL of DCM. The vials were capped and left to stir overnight (16 h). After stirring the reactions were concentrated under reduced pressure and analyzed by ^{1}H NMR.



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