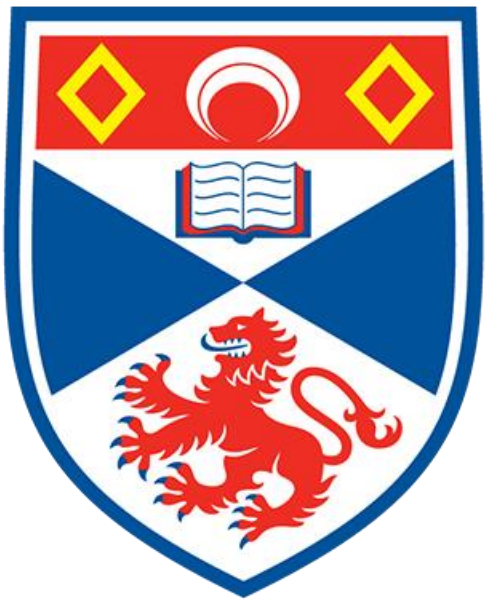
Development of Coupling Strategies for Peri-Substitution in Main Group Systems



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1. INTRODUCTION

Synthesis is one of the fundamental disciplines within chemistry, where routes to form specific molecules are determined. This field is particularly important for practical applications of chemistry, from pharmaceuticals to large scale industrial processes. These processes require a high level of efficiency to make them feasible on large scales and currently many of reactions require rare-earth elements as catalysts in order to improve efficiency, which are expensive but also often toxic. The Kilian research group focuses on the synthesis of strained molecular systems; specifically, *peri*-substituted ring systems, which ultimately may be used as catalysts in large scale reactions. *Peri*-substitution is substitution that occurs at positions 5 and 6 of acenaphthene or positions 1 and 8 of naphthalene, as shown in Figure 1.

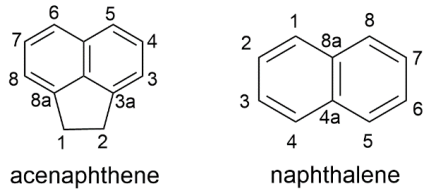


Figure 1 – Numbering of bond positions in acenaphthene and naphthalene

Substitution at these positions can be used to lock atoms into specific geometries. The atoms attached at the *peri*-positions sit closer to each other than expected, in sub Van-der-Waals distances. This results in orbital overlap between the atoms, which cannot be avoided due to the 'locking' nature of the aromatic ring. As such, new and unexpected bonds can therefore form between the two atoms at the *peri*-positions, known as a coupling reaction. Coupling reactions allow for previously unstable compounds to be synthesised and stored which opens up a whole host of opportunities for potential applications. Examples of the coupling reaction are shown below[1].

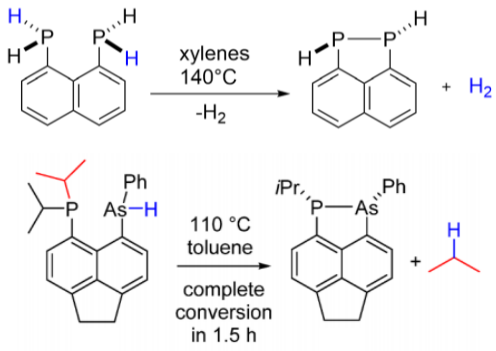


Figure 2 – Example of group 15 coupling reaction from the Kilian Research Group, taken from JACS, 2017.

The coupling reaction is of particular interest mainly due to the by-products of the reaction, which can be altered depending on the functional groups that are attached at the *peri*-positions. The mechanism that the reaction proceds by shows that a variety of bond forming reactions may occur, some of which when formed in other ways require hevy-metal and toxic catalysts.

Since the discovery of peri-bonding in naphthalene and acenaphthene a variety of *peri*-bonded combinations have been established and synthesised. The Kilian research group has focused on *peri*-bonding combinations within group 15, with positive results. As such, one area of particular interest is the *peri*-bonding between groups 14 and 15, particularly carbon and phosphorus. The use of group 14 and 15 atoms at the peri-positions would result in C-C bond formation as a side product of the coupling reaction, which is of great interest in synthetic chemistry. As such, a synthetic route to form the precursor for this coupling reaction is required but has yet to be determined. The formation of a synthetic route for the precursors is therefore the area of research focused on in this report.

2. Synthetic Routes

The focus of the research was to place a carbon atom at one of the two *peri*-positions in acenaphthene, at either position 5 or 6. There seemed to be two possible methods in which to achieve this; either adding a large carbon group directly onto position 5 in one step, or to add a single carbon at position 5, then use further reactions to increase the length of the carbon chain attached to the carbon at position 5. Initially, both ideas were researched.

For all synthetic routes, the starting materials for synthesis was acenaphthene, which was converted to 5,6-dibromoacenaphthene through a well-established reaction using N-bromosuccinimide (NBS) and dimethylformamide (DMF) at 0 ˚C[2]. As such, for the synthetic route concepts, the starting compound was the dibrominated form.

2.1 Direct Alkylation

Furthering on from the work of J. Shapland (MSci Student 2019/20), the first route developed was looking into the addition of a carbon chain directly to the peri-position, known as direct alkylation. There were two options to achieve this; either using a Grignard's Reagent, or through the formation of organolithium compounds. The use of a Grignard's Reagent was previously worked on and did not allow for any direct alkylation at position 5. As a result, the alternative route using organolithium was researched.

Use of Benzyne Intermediate

The first idea for direct alkylation at position 5 was using a benzyne intermediate in an elimination-addition reaction. In the presence of a strong Brönsted Base, often referred to as a superbase, elimination of a hydrogen at the position adjacent to a substituent can be removed, forming a triple bond in an aromatic ring called benzyne. Another molecule of superbase can then add, breaking the triple bond. Protonation occurs and the target molecule has been synthesised. The proposed mechanism is shown below in Figure 3.

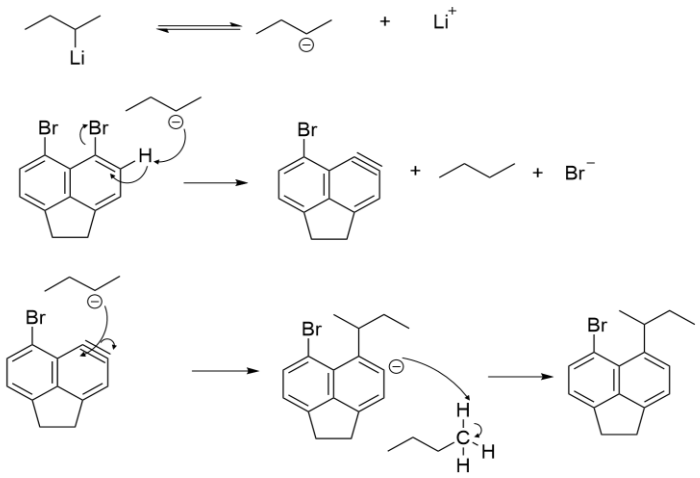


Figure 3 - Elimination-Addition Mechanism using a benzyne intermediate

This proposed mechanism has several flaws. Firstly, due to the formation of a benzyne intermediate, addition of the superbase in the second step of the reaction could occur at either side of the triple bond. This would result in a maximum efficiency of the reaction to be 50%. Secondly, the use of *n*-BuLi as the superbase was not possible. Due to metal-halogen exchange, the lithium cation reacts with one bromine on 5,6-dibromo-1,2-dihydroacenaphthene preferentially to the butyl anion. A way to combat this was to introduce a second reaction that removed Li^+ ions from the reaction, allowing $C_4H_9^-$ to react as required. However, despite *n*-BuLi being referred to as a single molecule, it is a cluster of molecules and as such the lithium ions cannot be removed from the reaction. This synthetic route was therefore established as impossible.

Direct Lithiation

A second idea was an alteration to a route established by J. Shapland. This idea looked into using *n*-BuLi followed by a haloalkane for substitution in the required location. In the first step of the reaction, lithium is substituted for bromine on the acenaphthene ring. In the second step, the lithium reacts with the halogen in the haloalkane, and the carbon chain is added onto acenaphthene at the correct position. From experimental results obtained by Shapland, it was shown that using a bromoalkane did not produce the required target. This reaction was altered to use a chloroalkane to see if this route produced the required molecule. This reaction relies on the difference in electronegativity in the C-Li and C-X (X= Cl, Br, I) bonds respectively. This produces partial charges at different points within the molecules allowing them to react. By changing the halogen used from bromine to chlorine, the greater difference in electronegativity could result in the reaction following the proposed route, producing the target molecule. This mechanism is shown in Figure 4.

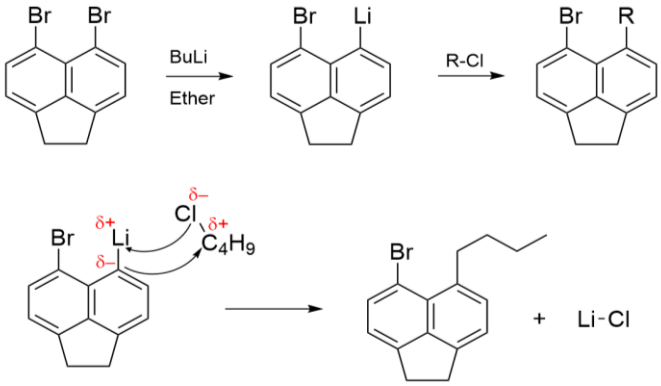


Figure 4 - Direct lithiation synthetic route using n-BuLi and Bu-Cl

However, this route is unlikely to produce the required molecule because the difference in electronegativity may not be enough to result in a meaningful change to the reaction mechanism. Despite this, this synthetic route will be tested experimentally.

2.2 Addition of Single Carbon Group Then Further Reactions

The second method investigated was the addition of one carbon group, then reacting the molecule produced further in order to add a larger group onto the carbon at position 5.

Nucleophilic Aromatic Substitution Using Cyanide Ions

The first idea for addition of a single carbon atom onto position 5 of acenaphthene was through nucleophilic aromatic substitution using a nitrile group. After the substitution of the nitrile group, further reactions were conducted to reduce the nitrile group to an aldehyde, then a further reduction from the aldehyde to a primary alcohol, removing the nitrogen atom entirely. This mechanism is seen in Figure 5.

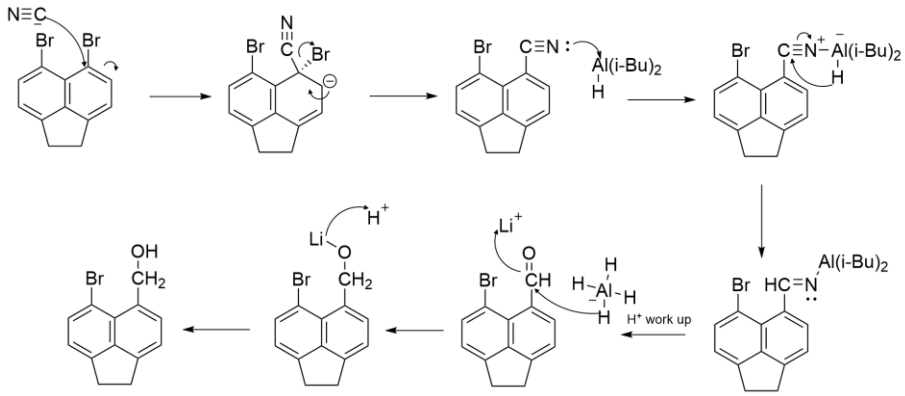


Figure 5 - Nucleophilic Aromatic Substitution using a nitrile group in order to substitute a carbon atom to position 5.

This method was different to ones previously pursued and showed some promise, however, had some drawbacks, specifically the use of a nitrile group. In order to introduce this into the reaction, the use of potassium cyanide and hydrogen cyanide would be required. These compounds are too toxic for use, so this specific route was deemed too dangerous and was not pursued.

Other forms of Nucleophilic Aromatic Substitution

The mechanism of nucleophilic aromatic substitution did lead to other possible routes. Work from the Congrave Group at the University of Cambridge[3] established a single step reaction from 5,6-dibromo-1,2-dihydroacenaphthene **(2)** to 5-bromo-6-acenaphthaldehyde (**3**) without the use of *n*-BuLi. From this step, two possible reaction routes were developed. The first involved conversion of the aldehyde group to the corresponding alkene **(4)**, using the Wittig reaction. The alkene formed could then be hydrogenated to form the corresponding alkane **(5)**.

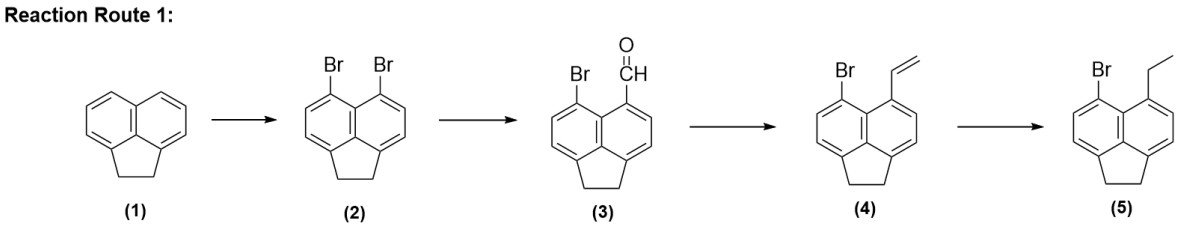


Figure 6 - Proposed reaction route proceeding via the Wittig Reaction

The second route established was using the aldol condensation with acetophenone to form another C-C bond, in the form **(6)**. This would then undergo reduction and hydrogenation to remove oxygen and the C=C double bond, resulting in the final compound **(8)**.

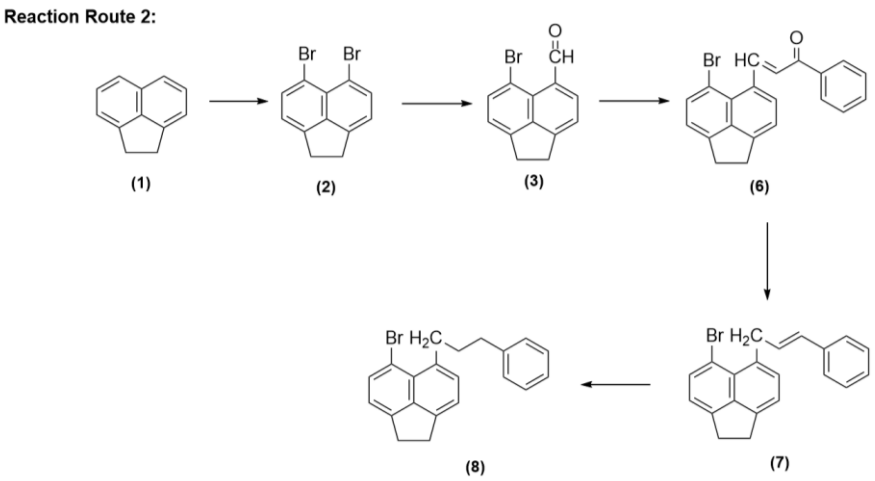


Figure 7 - Proposed reaction route proceeding via the Aldol Condensation

A major advantage to both of these reaction routes is the ability to change which reagents are used, so different final compounds can form. One of the biggest challenges faced with coupling reactions was determining which compounds would lead to successful coupling reactions. Calculations can be run to give an indication of the likelihood of successful coupling, but synthetic routes like these allow or alterations to the final product with relative ease. As a result, both methods were developed further.

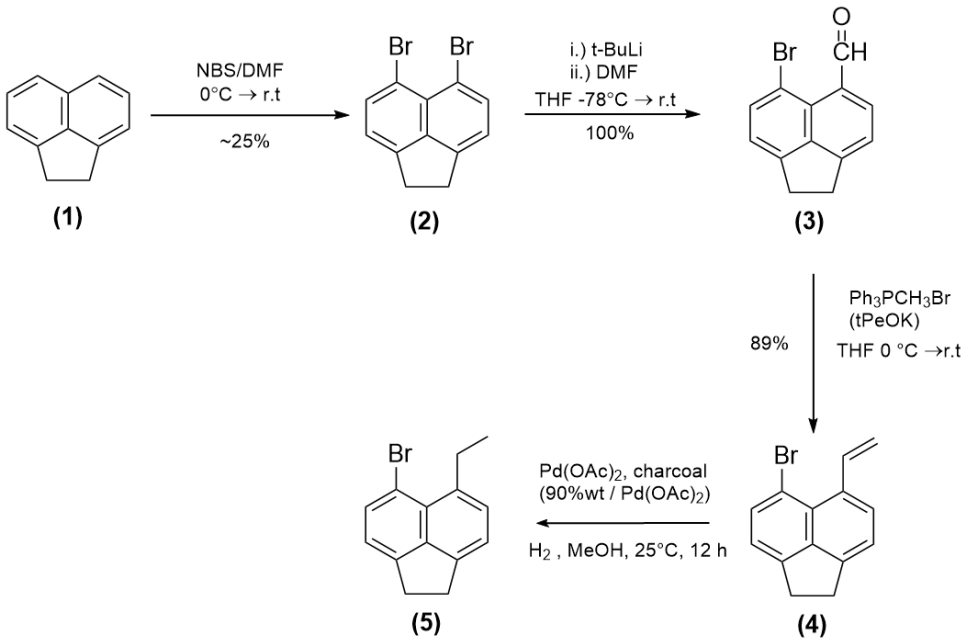
Further Development

The Wittig Reaction, shown in reaction route 1 of Figure 6 is one method of carbon-carbon bond formation, proceeding via a phosphorus ylid intermediate[4]. For this reaction to occur, a triphenylphosphine reagent is required. Depending on the reagent used, the alkene formed differs. A follow-on step from this can be used to convert the alkene to the corresponding alkane, which is of interest in this study.

Another route for carbon-carbon bond formation is the Aldol condensation. This synthetic route requires the use of an aldehyde and ketone which combine to form a new carbon-carbon bond in the mechanism determined by Perrin and Chang at the University of California at San Diego in 2016[5]. The mechanism shows the conversion of the ketone into the corresponding enol. Depending on the aldehyde and ketone used, several side reactions can occur, most notably self-condensation reactions. In order to stop this, one of the reagents needs to be un-enolisable. In the mechanism for the Aldol reaction, the reaction proceeds by forming an enol, where electron density from the double bond of the carbonyl group moves to form a C=C double bond leaving a negative charge on the oxygen.[5] In the proposed reaction route, 5-bromo-6-acenaphthaldehyde **(3)** is un-enolisable due to a lack of hydrogens sitting at the α position. As a result, only the ketone reagent used can form the enol. By using a ketone such as acetophenone, which is less electrophilic than **(3)**, the reaction is forced to produce only the required product **(6)**. In the following steps, **(6)** can be reduced to form the alkane equivalent. This route showed promised, and so a more precise stepwise synthetic route was determined.

3. METHODOLOGY

3.1 ROUTE 1: SYNTHESIS OF COMPOUND 5



Scheme 1 - Synthetic Route for the preparation of 5-bromo-6-ethyl-acenaphthene

*Preparation of 5,6-dibromoacenaphthene **(2)***

Acenaphthene **(1)** is converted to **(2)** following literature proceedure[2]; N-bromosuccinimide (NBS) (2.2 eq.) in DMF was added in portions to an ice-cooled suspension of acenaphthene (1 eq.) in DMF over a period of 5 h. The temperature of mixture was not allowed exceed 0˚C. The mixture was stirred for a further 12 h and then allowed to warm to room temperature. The precipitate was filtered with suction, washed with ethanol, and purified by stirring overnight in refluxing ethanol. The solution was cooled to room temperature, filtered, washed with ethanol, and dried in vacuo.

*Preparation of 5-bromo-6-acenaphthaldehyde **(3)***

Based off literature procedure[3] with an adaptation to use *n*-BuLi rather than *t*-BuLi. This alteration increases the reflux time by an extra 2 hours but use of *n*-BuLi is preferred due to its lower toxicity. *n*-BuLi (2.20 eq.) was added dropwise to a suspension of **(2)** (1.00 eq.) in dry THF over ca. 10 min, which was cooled to –78 °C under argon in a dry ice bath. The mixture was stirred at – 78 °C for 2 hours 30 min, treated with DMF (4 mL) dropwise over ca. 5

min and stirred at –78 °C for a further 20 min. The reaction mixture was then warmed to room temperature and stirred for 20 min, and finally quenched with water (50 mL). The mixture was concentrated under reduced pressure to remove THF and diluted with further water (200 mL). The formed precipitate was then isolated by filtration and washed with water (3 × 50 mL) to afford 5-bromo-6-acenaphthaldehyde **(3)**.

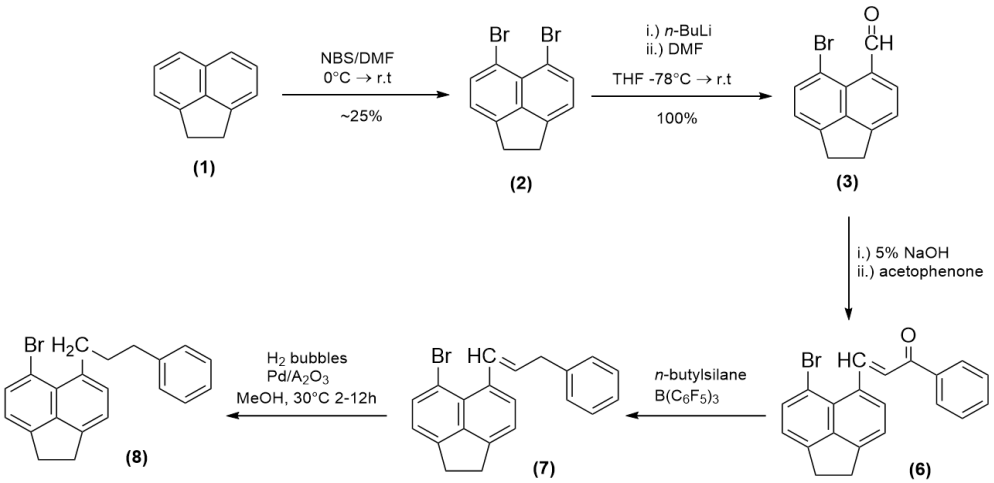
*Preparation of 5-bromo-6-vinyl-acenaphthene **(4)***

Following literature procedure[6]; Ph_3PCH_3Br was added in portions to **(3)** cooled in an ice-bath. The reaction flask is then combined with potassium tert-pentoxide (tPeOK) in THF and stirred from 0 °C to room temperature. The solvent was then removed by rotary in vacuo. 40:60 petroleum ether was added to the flask and stirred the resulting suspension with a glass rod to precipitate as triphenylphosphine oxide, then filtered under vacuum. Rinse out the flask and wash the solid with 40-60 petrol (20 cm^3) and concentrate the filtrate under reduced pressure to afford crude product. Purify the crude product by flash chromatography on silica, eluting with 40:60 petroleum ether and ethyl acetate (9:1). Be careful to take fractions of a suitable size.

*Preparation of 5-bromo-6-ethyl-acenaphthene **(5)***

The final compound, **(8)** was prepared using literature procedure[7]. Charcoal (90 wt%/Pd) and $Pd(OAc)_2$ (THF solution, 0.05 mol%) were added to a stirred solution of **(7)** (5 mmol) in MeOH at 25˚C. The resulting mixture was stirred for 12 h under H_2 atmosphere (1 atm, balloon), filtered and concentrated under reduced pressure. The crude was usually isolated with analytical purity.

3.2 ROUTE 2: SYNTHESIS OF COMPOUND 8



Scheme 2 - Synthetic route for the preparation of 5-Bromo-6-(3-Phenylpropyl)-1,2-dihydroacenapthene

*Preparation of 5,6-dibromoacenaphthene **(2)***

Refer to synthetic route of 5,6-dibromoacenaphtene developed in section 3.1.

*Preparation of 5-bromo-6-acenaphthaldehyde **(3)***

Based off literature procedure[3] with an adaptation to use *n*-BuLi rather than *t*-BuLi. This alteration increases the reflux time by an extra 2 hours but use of *n*-BuLi is preferred due to its lower toxicity. *n*-BuLi (2.20 eq.) was added dropwise to a suspension of **(2)** (1.00 eq.) in dry THF over ca. 10 min, which was cooled to –78 °C under argon in a dry ice bath. The mixture was stirred at – 78 °C for 2 hours 30 min, treated with DMF (4 mL) dropwise over ca. 5 min and stirred at –78 °C for a further 20 min. The reaction mixture was then warmed to room temperature and stirred for 20 min, and finally quenched with water (50 mL). The mixture was concentrated under reduced pressure to remove THF and diluted with further water (200 mL). The formed precipitate was then isolated by filtration and washed with water (3 × 50 mL) to afford 5-bromo-6-acenaphthaldehyde **(3)**.

*Preparation of 5-bromo-6-(1-phenylprop-2-en-1-one) **(6)***

Conversion to **(6)** proceeds via an Aldol Condensation Reaction using acetophenone. Added in the following order, aldehyde (**3)** and acetophenone in a 1:1 ratio, followed by of ethanol. The reaction flask contents were

stirred and then 5% NaOH solution was added. Crystals were deposited as the reaction proceeds, with continued stirring for 25 minutes. The reaction flask was cooled in an ice bath for 10 minutes the crystals were filtered off under reduced pressure. Ice-cold ethanol was added to reaction flask and used to wash the filter cake. The filter cake was washed again with water and allowed to dry.

Preparation of 5-bromo-6-(3-phenylprop1-en-1-yl) ***(7)***

(7) was prepared from a modified literature procedure[8] for an analogue. Under a nitrogen environment, **(6)** (1 eq.) was added then the flask was purged with argon. Catalyst ($B(C_6F_5)_3$, 5–10 mol %) was introduced via syringe as a freshly prepared solution in anhydrous dichloromethane. Stirring was continued for 10 min and then 2 equiv. of *n*-butylsilane (99% pure) was added for each carbonyl group present in the substrate. A static atmosphere of argon was established using an argon balloon. The reaction was stirred for about 0.5–10 h depending upon the number of carbonyls present. After complete conversion of the starting material, the reaction mixture was quenched with triethylamine. The crude mixture was purified by silica gel flash column chromatography with hexane as eluent or hexane–ethyl acetate (50:1) to elute silyl ethers.

Preparation of 5-bromo-6-(phenylpropyl)acenaphthene ***(8)***

The final compound, **(8)** was prepared using literature procedure[7]. Charcoal (90 wt%/Pd) and $Pd(OAc)_2$ (THF solution, 0.05 mol%) were added to a stirred solution of **(7)** (5 mmol) in MeOH at 25˚C. The resulting mixture was stirred for 12 h under H_2 atmosphere (1 atm, balloon), filtered and concentrated under reduced pressure. The crude was usually isolated with analytical purity.

4. DFT CALCULATIONS

Computational modelling of the coupling reaction was conducted for a series of different molecules with carbon sitting at position 5 of acenaphthene. These calculations were determined from the predicted mechanism of the coupling reaction. For each step of the mechanism, energies; both enthalpy and Gibbs energies were calculated, as seen below in Figure 8.

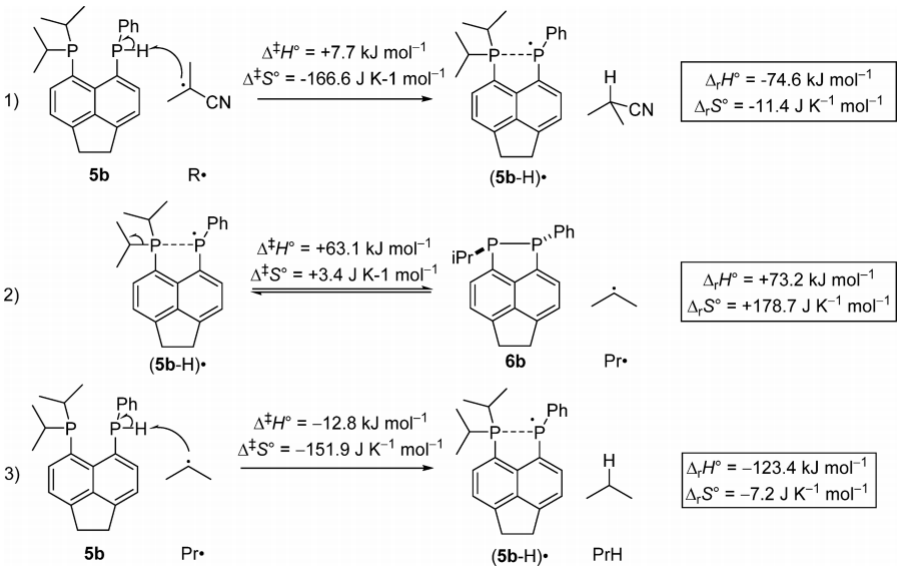


Figure 8 – Predicted mechanism for the formation of the peri-bond in main group ring systems

In the reaction mechanism above, developed by Taylor *et. al*[1], the first step showed homolytic fission reaction with a isobutyronitrile radical to form a phosphorus radical, referred to as the abstraction step. This radical went on to react with the second phosphorus atom in the coupling step of the reaction. The formation of the P-P *peri*-bond resulted in the removal of an isopropyl radical, which then was involved in the final step of the reaction. The final step of the mechanism showed the removal of hydrogen bonded to a phosphorus, forming propane, and another phosphorus based aromatic ring system radical. This radical goes on to react further until equilibrium forms, producing the *peri*-bonded ring system and propane.

This mechanistic route was the basis of the calculations run, but at one of the *peri*-positions a carbon-based group replaced one of the phosphorus groups. Attached to this carbon were a series of different functional groups, ranging from simple like a methyl group, to far more complicated, for example Me_2EtOH. For each substituent combination, the enthalpy ($\Delta H^{\ddagger}$) and Gibbs energy ($\Delta G^{\ddagger}$) for each transition state were calculated.

The results of the calculations showed that generally the coupling reactions were unfeasible. From experimental studies, the limit of feasibility was determined to sit at around 120 $kJmol^{-1}$. The calculations showed that for the 1st transition state; the abstraction step which has been determined rate determining, $\Delta G^{\ddagger}$ was far too high. This data was significantly different from calculations run previously on other main group systems. By placing a carbon at one of the *peri*-positions, the acenaphthene ring provided added stability to the *peri*-position carbon. The stability come from overlap of the delocalised orbitals in the acenaphthene ring system and the 2p orbital of the *peri*-position carbon. Therefore, in the second step of the reaction where the *peri*-bond is formed between carbon and phosphorus, the hydrogen bonded to the carbon will be removed preferentially than any further carbon group. The longer the carbon chain attached at the carbon *peri*-atom, the greater the stability, further adding to the preference of the carbon-hydrogen bond to break.

5. Conclusion

A series of synthetic routes were developed to produce molecules with a carbon-based functional group at one *peri*-position. Calculations were also run to establish whether the coupling mechanism was feasible with the molecules developed. The calculations suggested that the mechanism is not energetically feasible if a hydrogen atom is attached to the carbon at the *peri*-position. However, these results suggest further research into forming a carbon-based functional group with no hydrogen bonded on the *peri*-position, or species containing weaker C-X bonds such as C-S, or C-Se should be undertaken as this may lead to successful coupling.

6. Acknowledgements

Many thanks must go to Dr. Kilian and the Kilian research group within the University of St Andrews School of Chemistry for such interesting work, and especially for Dr. Kilian and his never-ending patience at the changes in this project due to the pandemic. Thanks as well to Ali Goodfellow for running computational calculations on many molecules to allow for some developments in synthetic methodology whilst labs were shut. Finally, and by no means least, thanks must go to Lord Laidlaw of Rothiemay for the funding enabling me to do this research. His generosity to the scholarship is hugely appreciated.

7. References

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