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Site-Selective and Enantioselective C-H Functionalization of Unactivated C–H Bonds in the Presence of Nitrogen Functionality

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An abstract of

a thesis submitted to the Faculty of Emory College of Arts and Sciences

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Abstract

Site-Selective and Enantioselective C-H Functionalization of Unactivated C–H Bonds in the Presence of Nitrogen Functionality

By Qinyan Cai

The rhodium-catalyzed C-H functionalization of unactivated C-H bonds by means of donor/acceptor carbene-induced C-H functionalization was extended to substrates containing nitrogen functionality. The optimum nitrogen protecting group was the phthalimido group and aryldiazoacetates were used as the precursors to the donor/acceptor carbenes. By using Rh_2(S-2-Cl-5-BrTPCP)$_4$ as catalyst, selective C-H functionalization occurred at the most sterically accessible methylene site, whereas the desymmetrization of cyclopentylamine and cyclohexylamine derivatives was possible when $Rh_{2(}$S-TPPTTL)$_4$ was used as catalyst.

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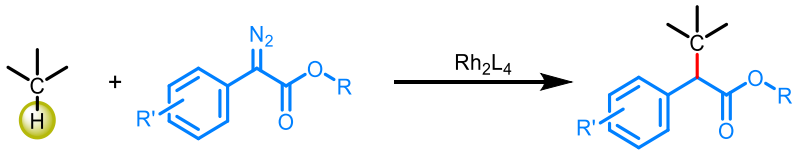
Introduction

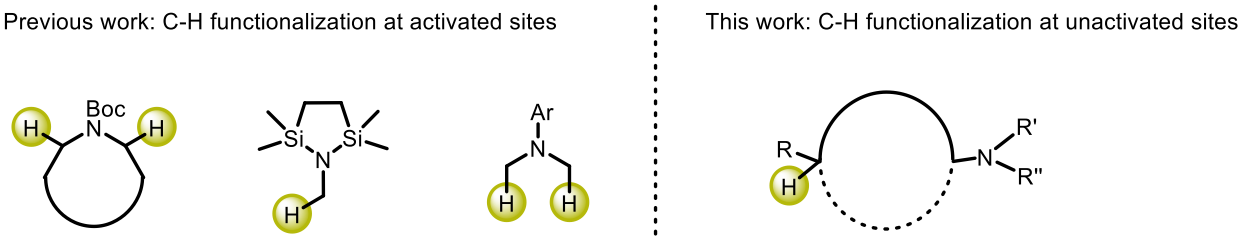
The design of new approaches for catalyst-controlled C-H functionalization is a research area of intense current interest. Various functionalization including C-H oxidation, C-H amination, radical reaction, and carbene-induced C-H alkylation has been explored and developed. The Davies group has been examining the rhodium-catalyzed C-H alkylation chemistry of donor/acceptor carbenes. Donor/acceptor carbenes are privileged in their stability and reactivity, where the acceptor group makes carbene electrophilic enough to functionalize the C-H bond while the donor group stabilizes the carbene and modulates the reactivity to be susceptible to catalyst control. Dirhodium tetracarboxylates, coordinating with donor/acceptor carbenes, are the exceptional catalyst to functionalize C-H bonds (Scheme 1.1). Based on this basic form, dirhodium catalysts with installed chiral ligands can self-assemble to high symmetry structures (D_2, C_4, and C_2), which enable the high levels of asymmetric induction in the carbene reactions [1]. At the current stage, we have prepared a wide variety of structurally well-defined dirhodium catalysts that can dictate which C-H bond in a substrate will be functionalized. The previous studies focused on activated C-H bonds in allylic or benzylic sites, or sites adjacent to oxygen and nitrogen [1]. To broaden the applications of this chemistry, our most recent work has focused on reactions at unactivated C-H bonds, and catalysts have been designed for the functionalization of the most accessible secondary or tertiary bonds.

Scheme 1.1 Carbene-induced C-H functionalization



One of the distinctive advantages of the carbene-induced C-H functionalization with donor/acceptor carbenes is the tolerance for a variety of functional groups in the process of reaction. The compatibility of this chemistry with various functional groups is well demonstrated when the functionalization is at C-H bonds near the functional groups and are activated by those electron-rich functionalities rather than functional groups themselves. However, even when the reaction occurs at the unactivated C-H bonds, the tolerance is preserved that the C-H bonds near the functional groups and the functionalities themselves, including esters, siloxy, halide, *p*-substituted aryl remain intact after the reactions [1]. To greatly increase the versatility of the chemistry, we seek the demonstration of this preference for unactivated C-H bonds in the presence of nitrogen functionalities (Scheme 1.2). However, amine functionality would offer a number of competing reaction pathways such as ylide formation, insertion into N-H bonds, or into the activated C-H bonds adjacent to nitrogen. Furthermore, the amine could poison the catalyst through competitive coordination to the axial sites on the dirhodium. Previously, we have demonstrated that C-H functionalization at activated sites can be conducted in the presence of amino functionality suitably protected as the carbamate, bis-silazide, and N,N-dimethylaniline [2]. In this project, we describe a successful strategy for the C-H functionalization of unactivated sites in substrates with a suitably protected primary amine. The study was conducted with two of the most established chiral catalysts, Rh_2(*S*-2-Cl-5-BrTPCP)$_4$ and Rh_2(*S*-TPPTTL)$_4$ (Figure 1.1).

Scheme 1.2 C-H functionalization in the presence of amino functionality



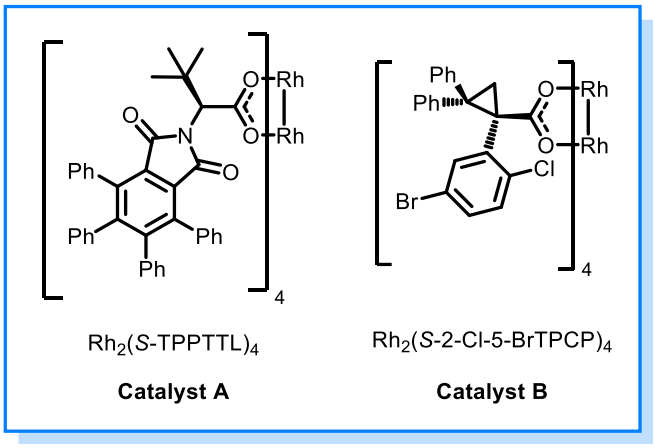
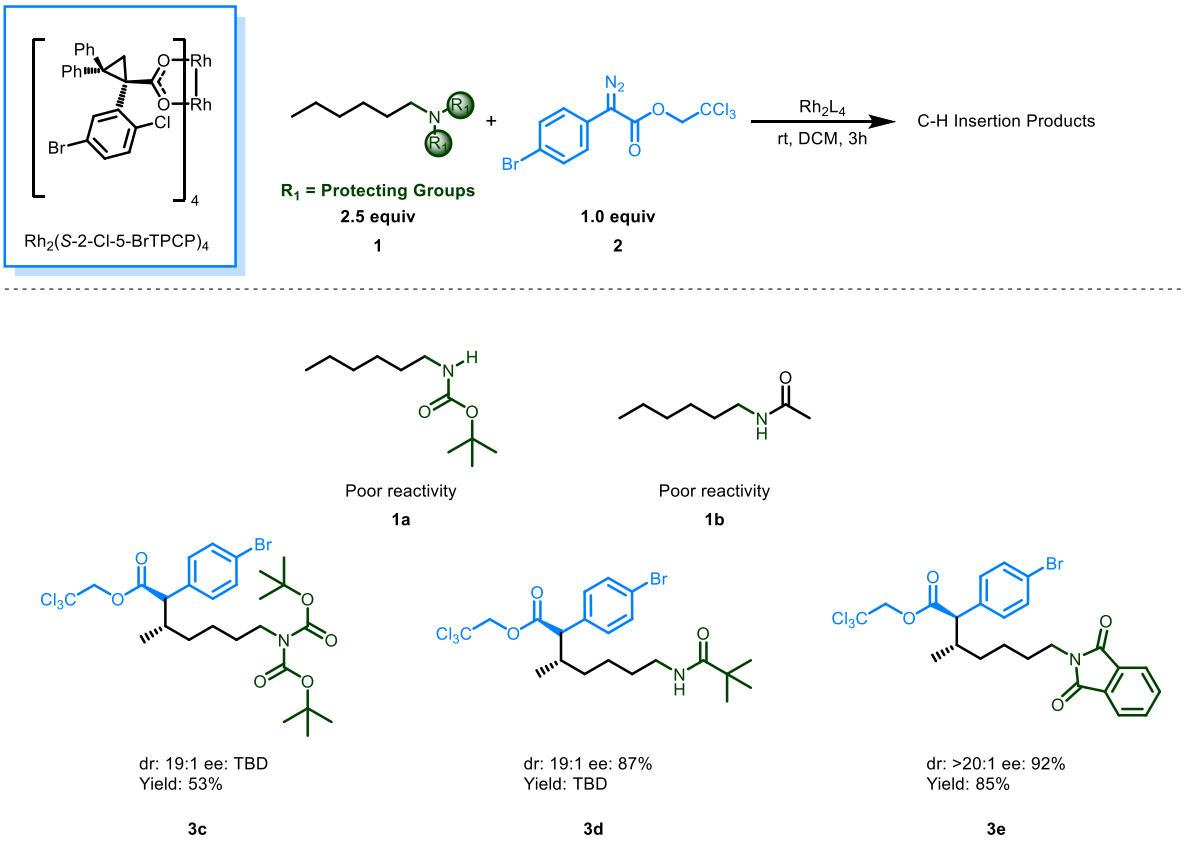


Figure 1.1 Chiral dirhodium catalysts used in this study

Results and Discussion

2.1 Discovery of Protecting Groups for Primary Amines

Scheme 2.1 Protecting Groups Screening



The study began by determining which nitrogen protecting groups would be compatible with carbene-induced C-H functionalization using N-protected 1-hexylamine **1** as test substrates. Based on the conditions of the first discovery of this unusual reversal of reactivity, the study was conducted using Rh_2(*S*-2-Cl-5-BrTPCP)$_4$, a bowl-shaped chiral catalyst, and *p*-bromophenyldiazoacetate, which are known to cause selective C-H functionalization of *n*-alkanes at the C2 position [3].

In the first stage, a typical protecting group, tert-butyloxycarbonyl group was installed to the hexylamine. The one-Boc protected amine **1a** (AC-1-108) failed to fully protect the amine functionality and the insertion to the desired C2 position was not observed. As shown in Figure 2.1, the peak at $\delta = 3.09\ ppm$ indicates the presence of the substrate because this signal belongs to the two protons on the carbon alpha to the nitrogen of the substrate. These two protons are highlighted in blue in the ChemDraw structure of the substrate. While the peak expected as doublet between $\delta = 2.5 - 3.0\ ppm$ indicating the benzylic proton of the desired C-H insertion product was absent. This proton of the desired product is highlighted in blue in the ChemDraw structure. The formed byproducts require further purification and isolation in order to be fully analyzed.

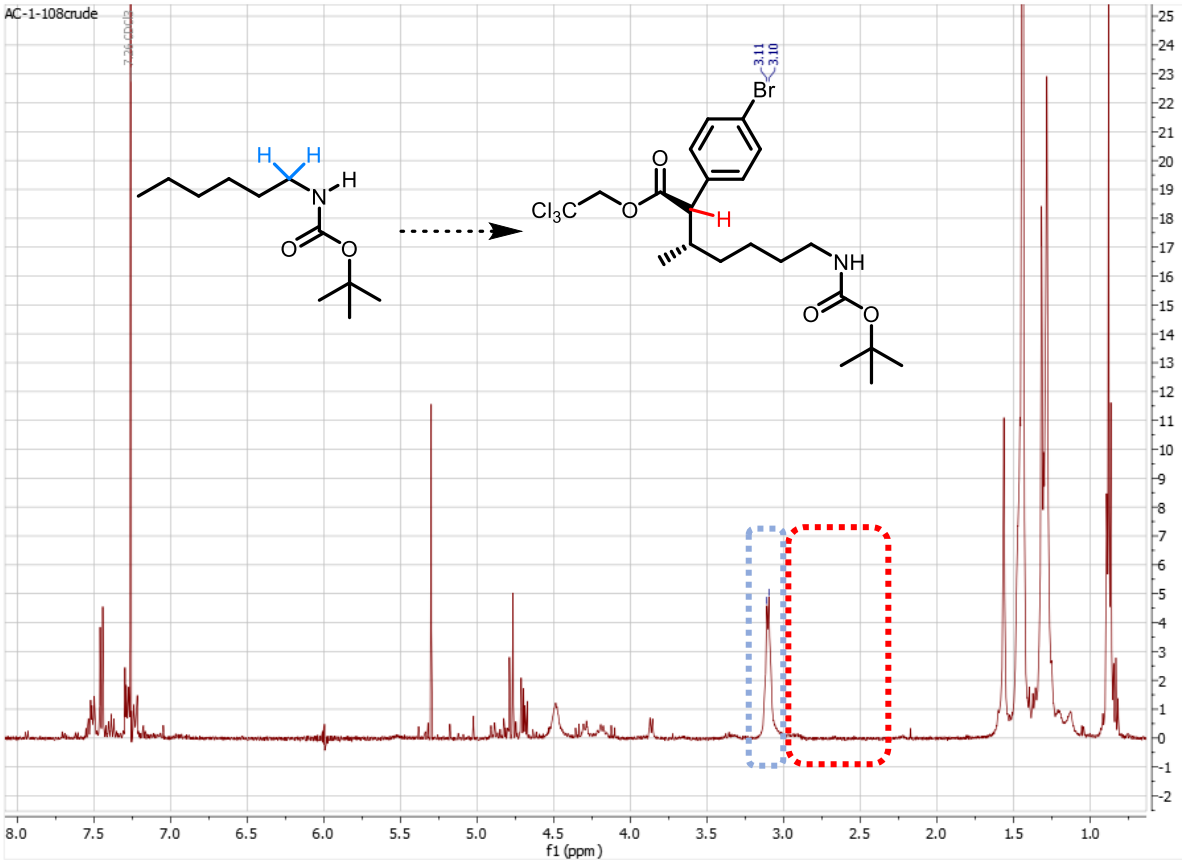


Figure 2.1 Crude NMR for the Reaction with One-Boc Protected Substrate

According to Figure 2.2, a similar result was also obtained when the primary amine was protected by an acetamide **1b** (AC-1-82). The peak for the substrate as well as the unobserved peak for the benzylic proton from the desired product are highlighted in the same fashion.

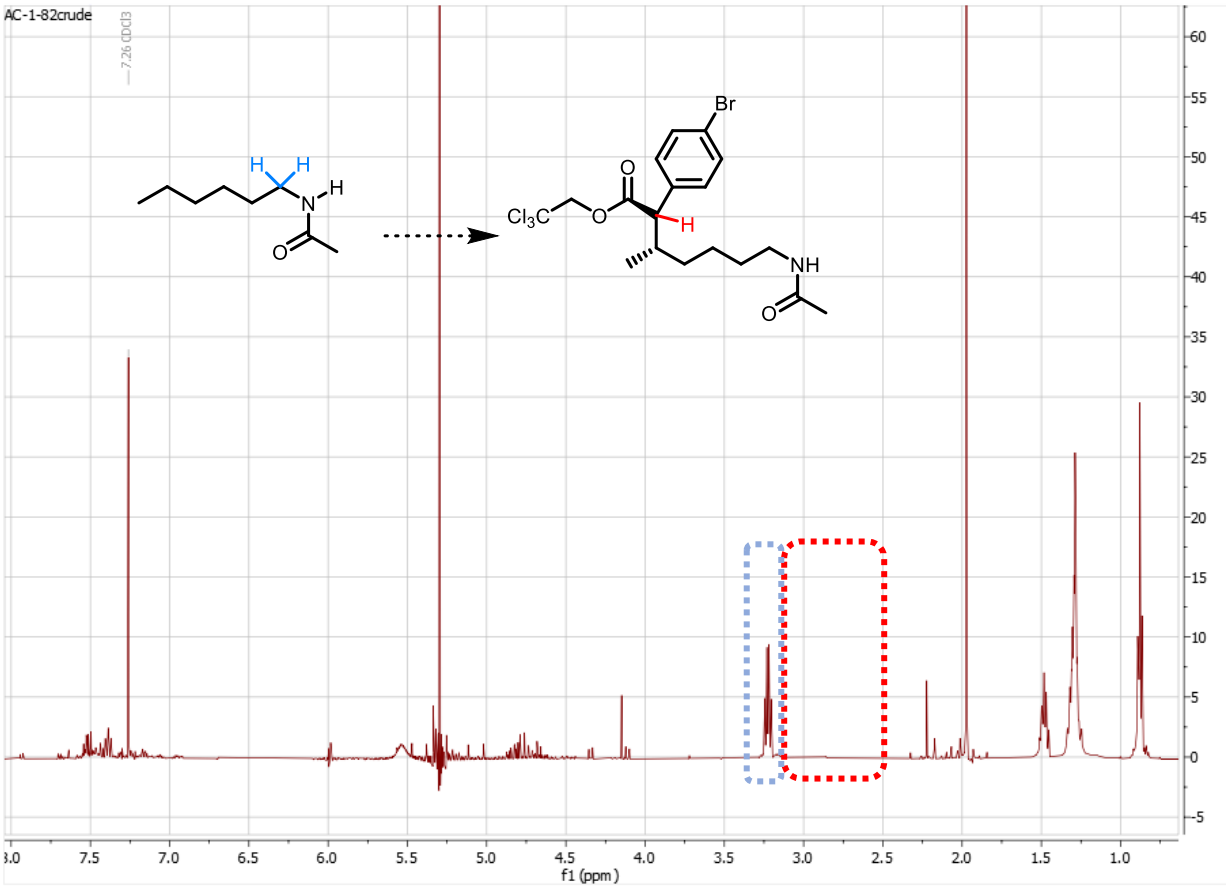


Figure 2.2 Crude NMR for the Reaction with Acetamide Protected Substrate

Based on the previous results, on the expectation that more sterically crowded amine would be more potent to suppress the reaction near nitrogen functionality and direct the reactions towards the most accessible methylene sites, trimethylacetamide-protected hexylamine (AC-1-93) **1d** was then screened as a possible protecting group. To avoid the enrichment of the diastereoselectivity (dr) after purification, dr is obtained based on the crude NMR. Based on Figure 2.3, the product of **3d** is formed with 19:1 dr. The number is obtained by comparing the integration between the peak

at $\delta = 1.04\ ppm$ and the peak at $\delta = 0.69\ ppm$. These two doublets belong to the protons of the terminal methyl from the two diastereomers. These three protons are highlighted in red in the ChemDraw structure of the desired products.

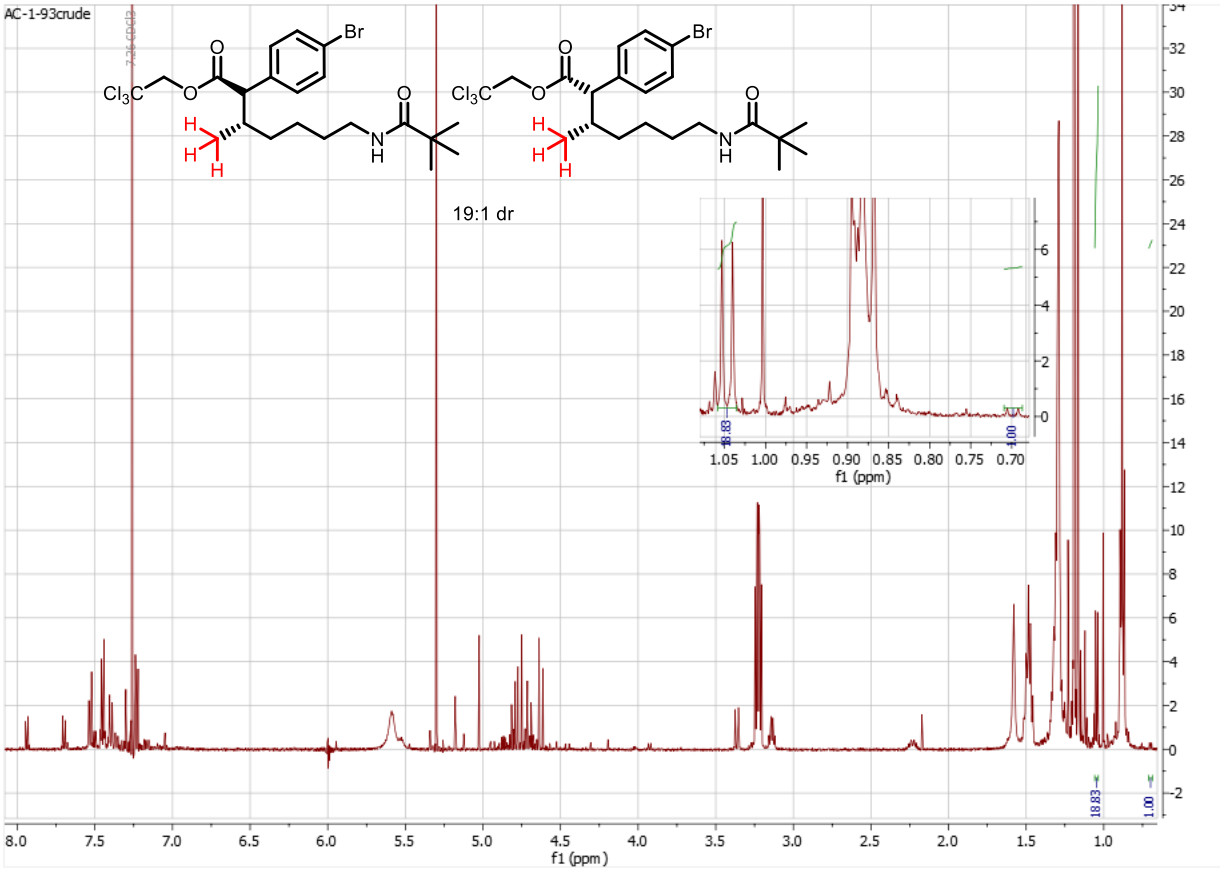


Figure 2.3 Crude NMR for the Reaction with Trimethylacetamide-Protected Substrate

After obtaining the diastereoselectivity, the product was purified by column chromatography and the yield was calculated as 53%. Then, the clean NMR was obtained to make further analysis (Figure 2.4), which is also an example of the NMR for successful insertion to the C2 position of the substrate. First of all, the doublet at $\delta = 3.36\ ppm$ indicates the benzylic proton coupled with one proton at the C2 position of the hexylamine. Meanwhile, the quartet at $\delta = 3.14\ ppm$ indicats the two protons at the carbon alpha to the nitrogen. After the insertion, a stereogenic center is formed at the benzylic position, causing the two protons of the trichloroethyl

to be diastereotopic of each other, appearing as two doublets at $\delta = 4.63\ ppm$ and $\delta = 4.76\ ppm$. Additionally, the broad singlet at $\delta = 5.53\ ppm$ represents the proton on the nitrogen, which is downfield due to the electron withdrawing nature of the nitrogen. Moreover, based on the structure of the desired product, there are 4 protons attached to the aromatic phenyl ring, which matched well with the two doublets in the region for the aromatic protons between $\delta = 7.00\ ppm$ and $\delta = 7.50\ ppm$. Apart from those, the peaks in the upfield region also match with the protons along the carbon chains and the protons from the tert-butyl group.

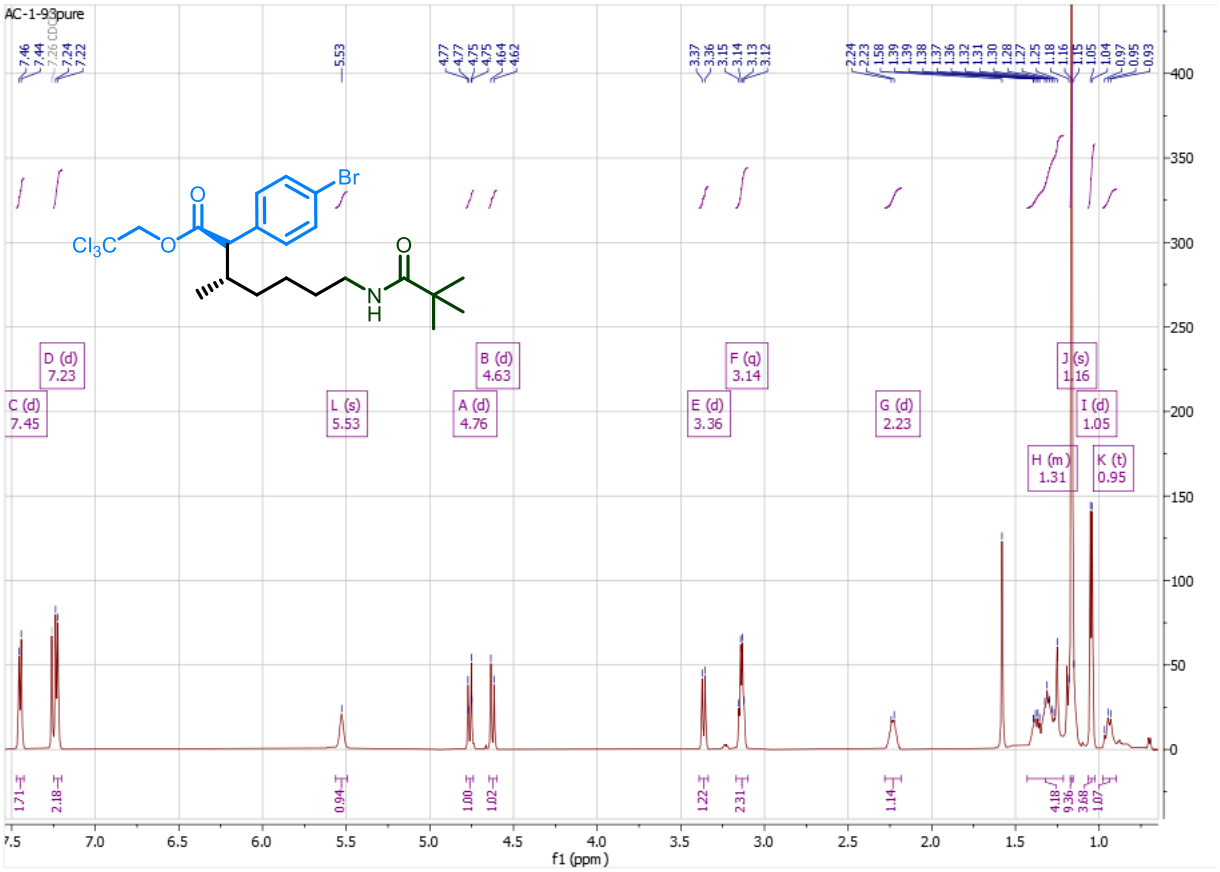


Figure 2.4 Purified NMR for the Reaction with Trimethylacetamide-Protected Substrate

A similar successful insertion was also observed when the substrate was protected by two Boc groups **1c** (AC-1-113) rather than one Boc group with 19:1 dr based on Figure 2.5. The yield needed to be further determined.

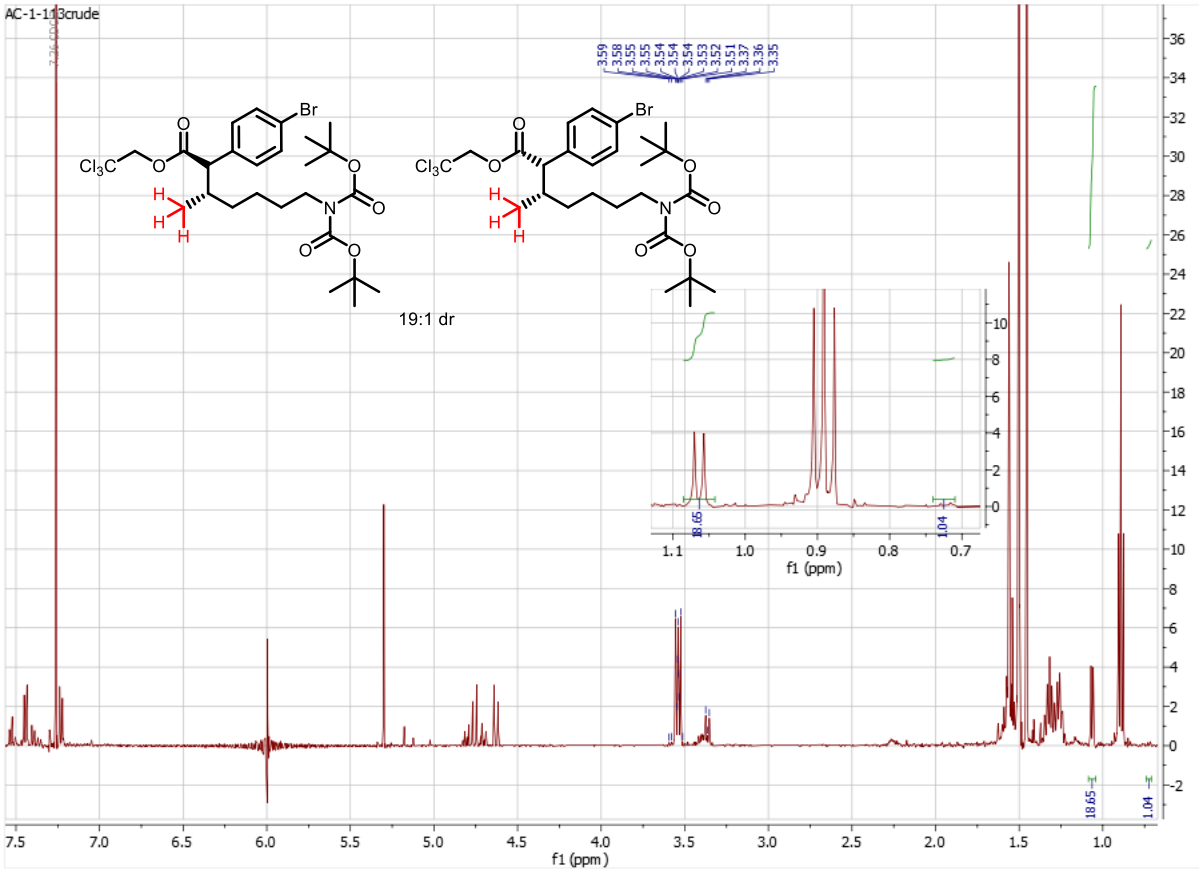


Figure 2.5 Crude NMR for the Reaction with bis N-Boc Protected Substrate

According to Figure 2.6, though the signal for the benzylic proton and the signal for the two protons on the carbon alpha to the nitrogen merged together, a similar pattern was observed in the purified NMR, demonstrating the successful insertion to the desired C2 position. Moreover, the proton counts also matched with the desired product though the shimming of the NMR resulted in relatively less accurate identifications of the spin-spin splits.

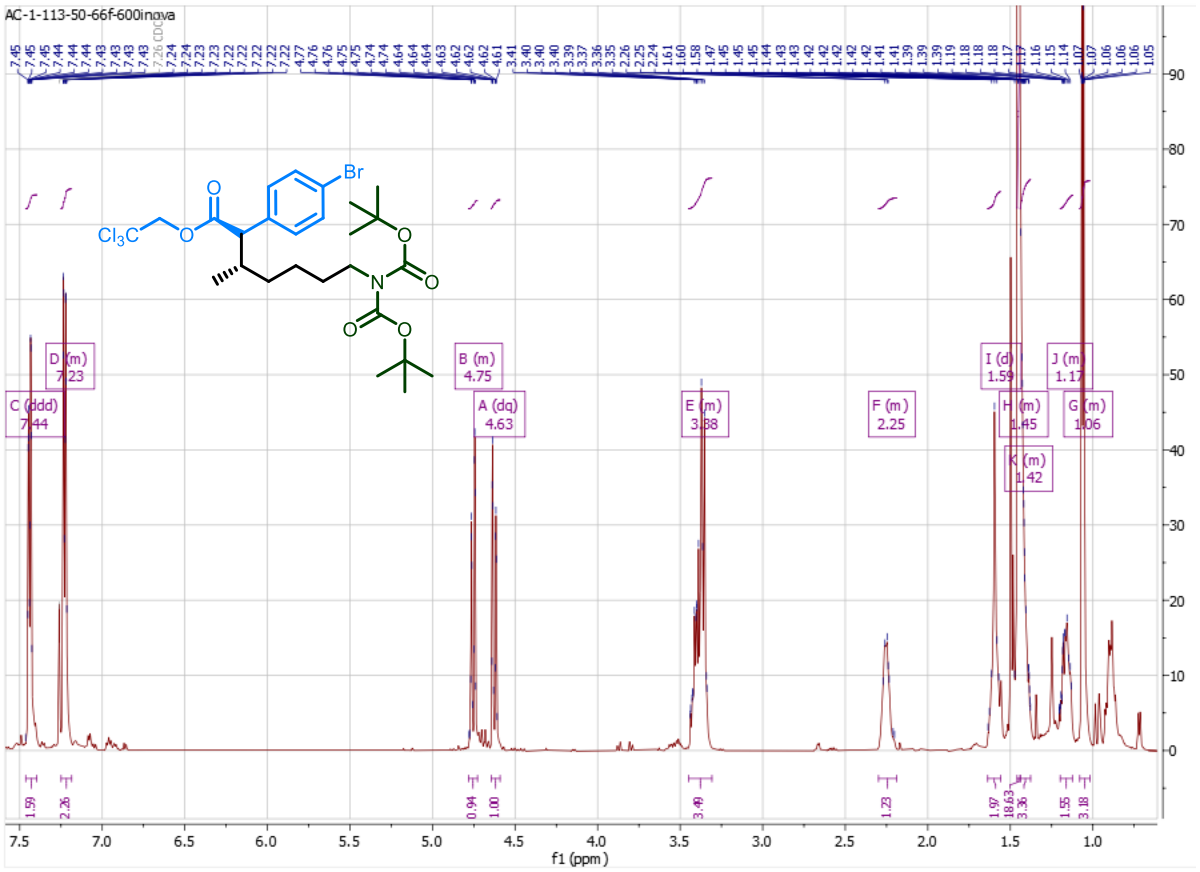


Figure 2.6 Purified NMR for the Reaction with bis N-Boc Protected Substrate

Though the previous two protecting groups successfully suppressed the reactions near or at the amine functionalities, an additional functional group, phthalimido, was also tested in the screening. It turned out that the most effective system was protected by the phthalimido group, **1e** (AC-1-222). The reaction of **1e** generated the desired product **3e** in 85% yield and >20:1 dr based on Figure 2.7. As shown by this figure, most of the limiting reagent, *p*-bromophenyldiazoacetate, was reacted. Moreover, the cleanness of this crude NMR also indicates that the formation of the byproducts was almost not observable, implying a high efficiency of the reaction.

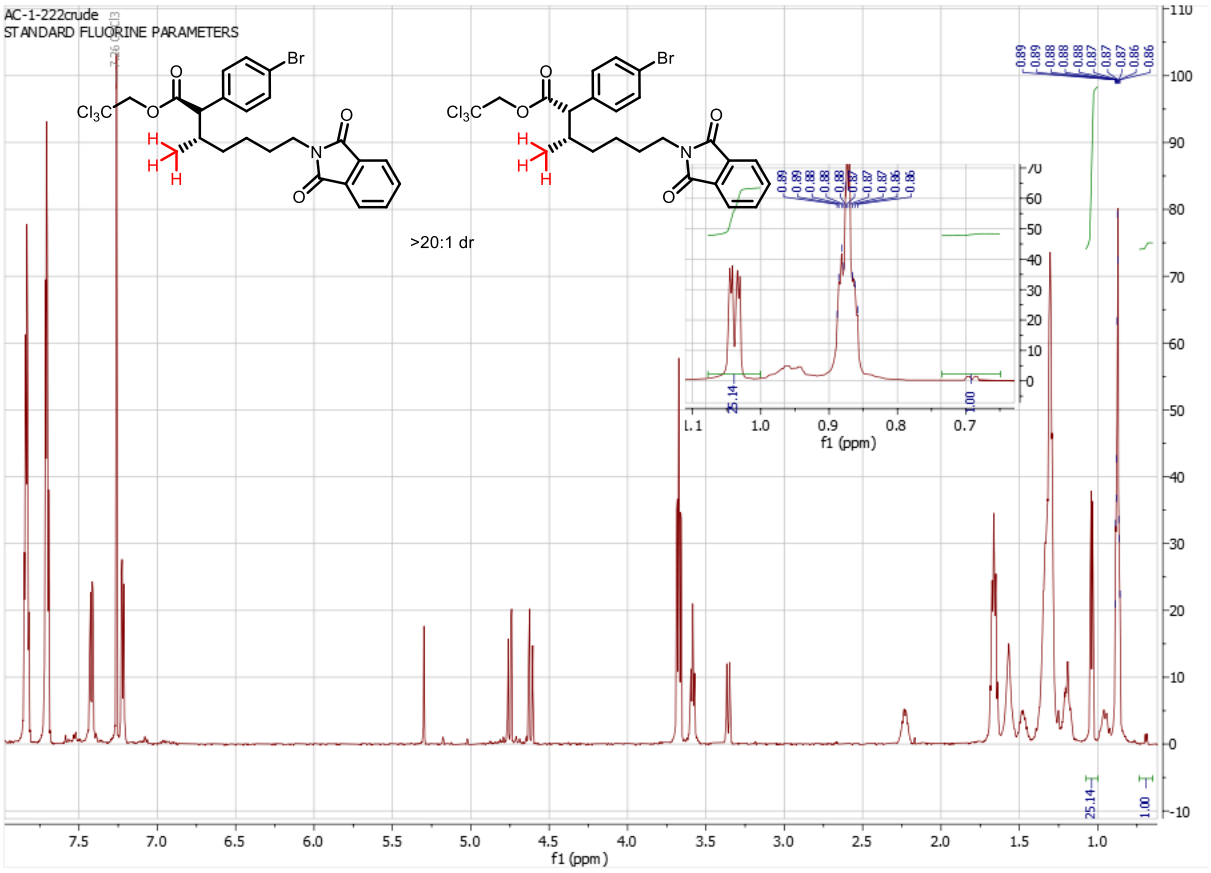


Figure 2.7 Crude NMR for the Reaction with Phthalimido Protected Substrate

According to Figure 2.8 shown below, the purified NMR of the product from phthalimido-protected hexylamine has a similar pattern as shown in Figure 2.6 and Figure 2.4, such as the doublet at $\delta = 3.35$ ppm for the benzylic proton, demonstrating the successful insertion to the desired C2 position. Additionally, the six protons along the carbon chains also matched in the signals as well as the integrations in the region from $\delta = 0.5$ ppm to $\delta = 1.75$ ppm. Moreover, the proton counts also matched with the desired product though the shimming of the NMR resulted in relatively less accurate identifications of the spin-spin splits for some peaks.

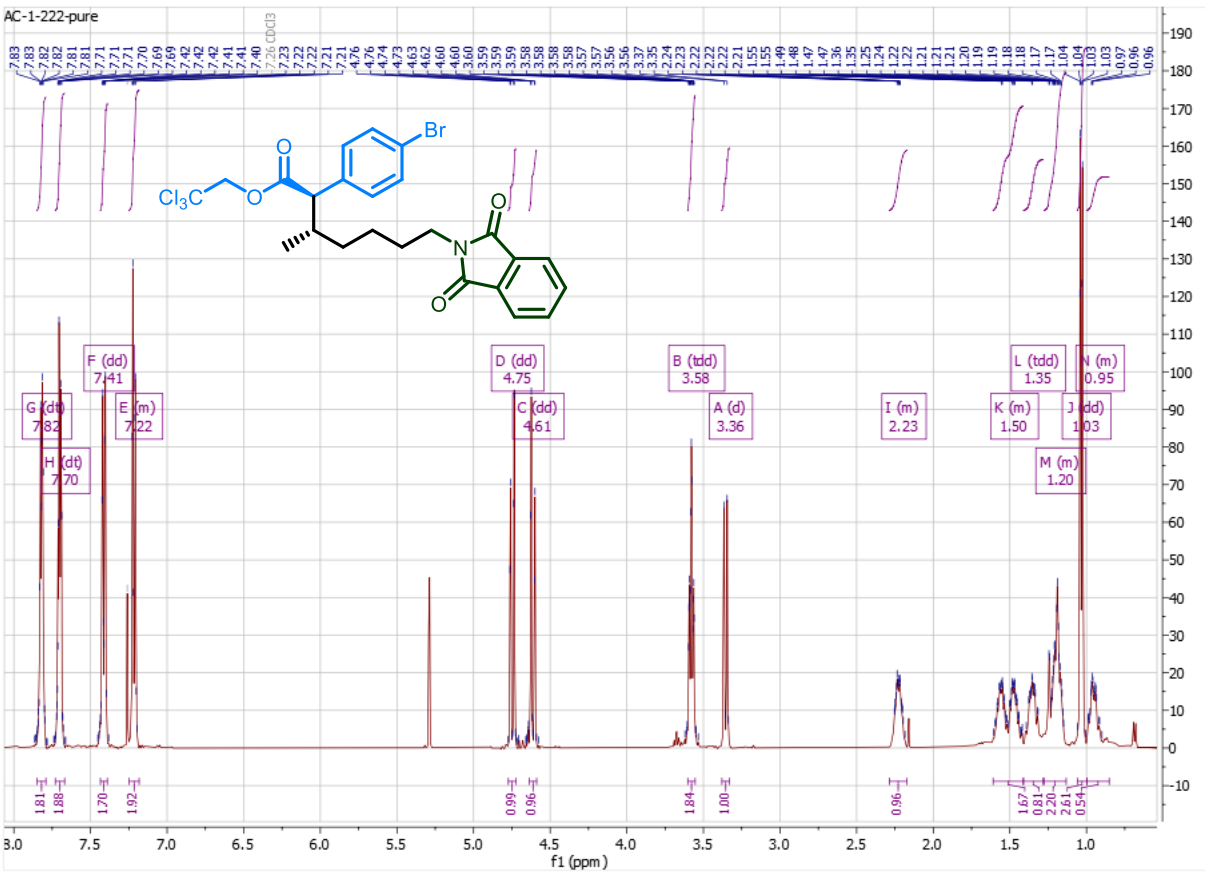
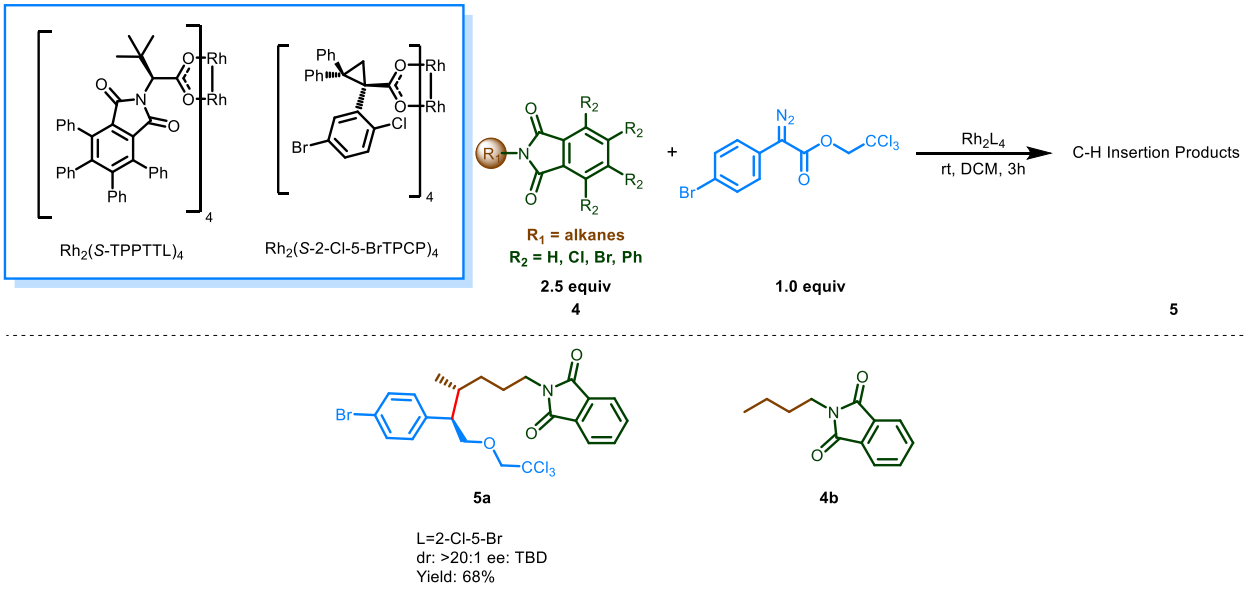


Figure 2.8 Purified NMR for the Reaction with Phthalimido Protected Substrate

Based on the results of **3c** to **3e**, the N-phthalimido group was selected as the protecting group for the rest of the study because it performed very well in the C-H functionalization reactions with high diastereoselectivity, enantioselectivity, and yield and is readily introduced and removed by hydrazine.

2.2 The Study about the Distance from the Primary Amines

Scheme 2.2 Inductive Effects of Phthalimido Group



As illustrated in the screening of the protecting groups, phthalimido group gave the best results among other functionalities with the highest dr, ee, and yield. One reasoning behind these good results is that the selected phthalimido group would be expected to be inductively electron-withdrawing and this inductive effect should protect C-H bonds relatively near to the phthalimido group. To evaluate the inductive effect, shorter alkylamine derivatives were examined. The reaction with pentylamine derivative **4a** (AC-1-198) was still effective, successfully functionalizing the C2 position and resulting in the formation of **5a** in 68% yield (AC-1-200). Surprisingly, the site selectivity was still highly preserved for the C2 position. As shown in Figure 2.9, insertions to C-H bonds other than C2 position are not observable. Therefore, the regioselectivity ratio between C2 insertion and other positions along the carbon chain of the pentylamine derivative is >20:1. Based on this crude NMR in Figure 2.9, the diastereoselectivity is also obtained as >20:1.

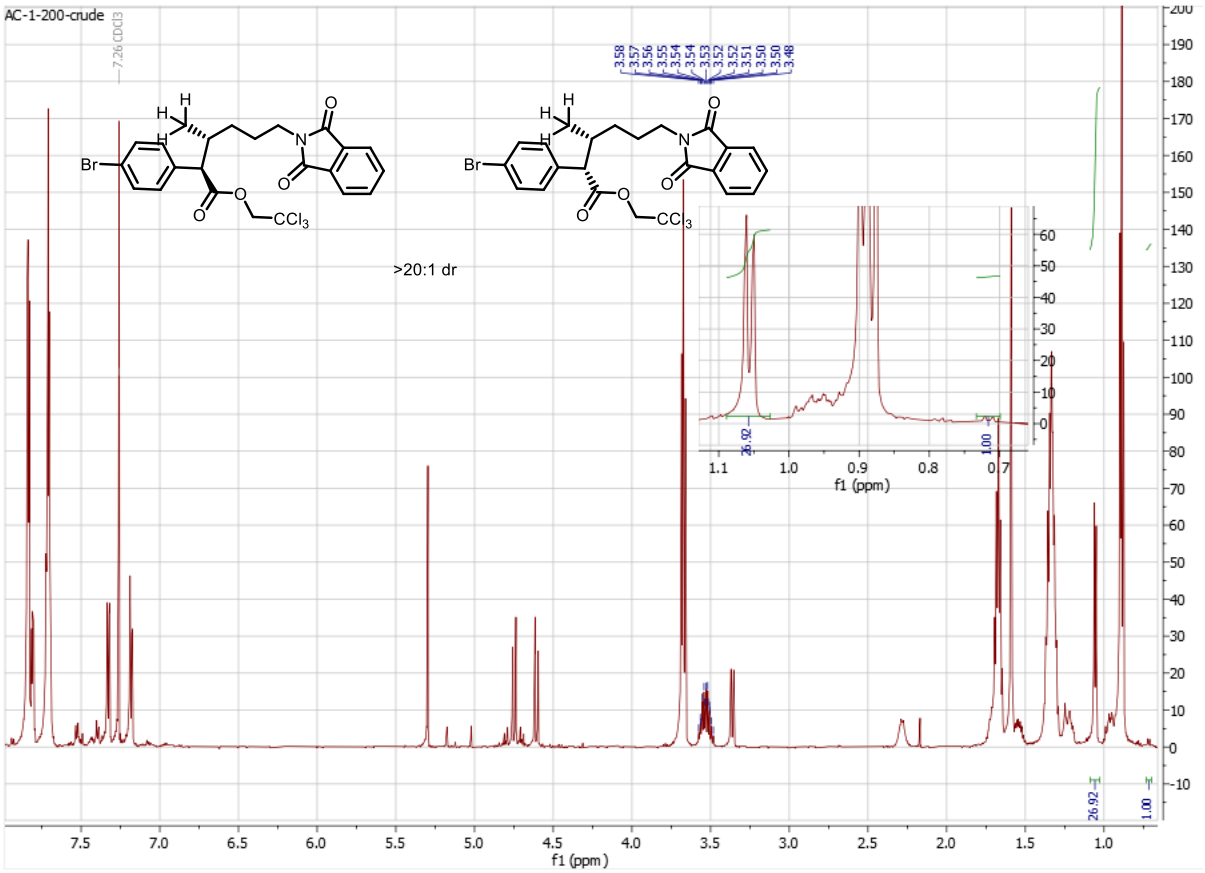


Figure 2.9 Crude NMR for the Reaction with Pentylamine Derivative

After purification, according to Figure 2.10, the signals are matched well with the desired product. This purified NMR is similar to Figure 2.8 due to the similar substrates.

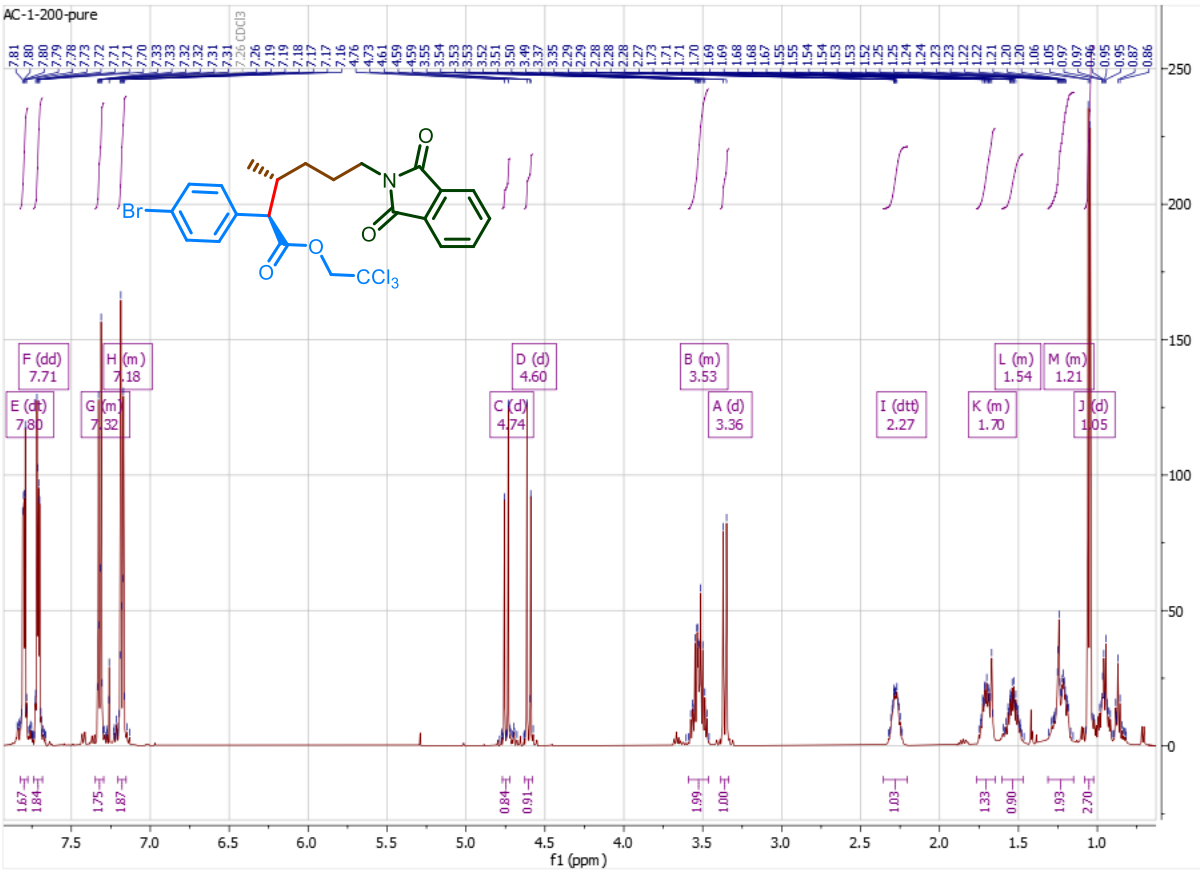


Figure 2.10 Purified NMR for the Reaction with Pentylamine Derivative

In contrast, as shown in Figure 2.11, the reaction with butylamine derivative **4b** failed to have the insertion to the most accessible methylene site as the major reaction though **5b** was still formed at a small number. These results indicate that the inductive effect of the phthalimido group influences the C-H functionalization at sites three carbons away from the amine. Additionally, it is harder for the chiral catalyst to differentiate between the most accessible methylene site and the C-H bond alpha to the nitrogen when the carbon chain becomes shorter. This discovery could be useful for further C-H functionalization studies because the phathlimido group could protect many relatively close C-H bonds from being prone to C-H functionalization.

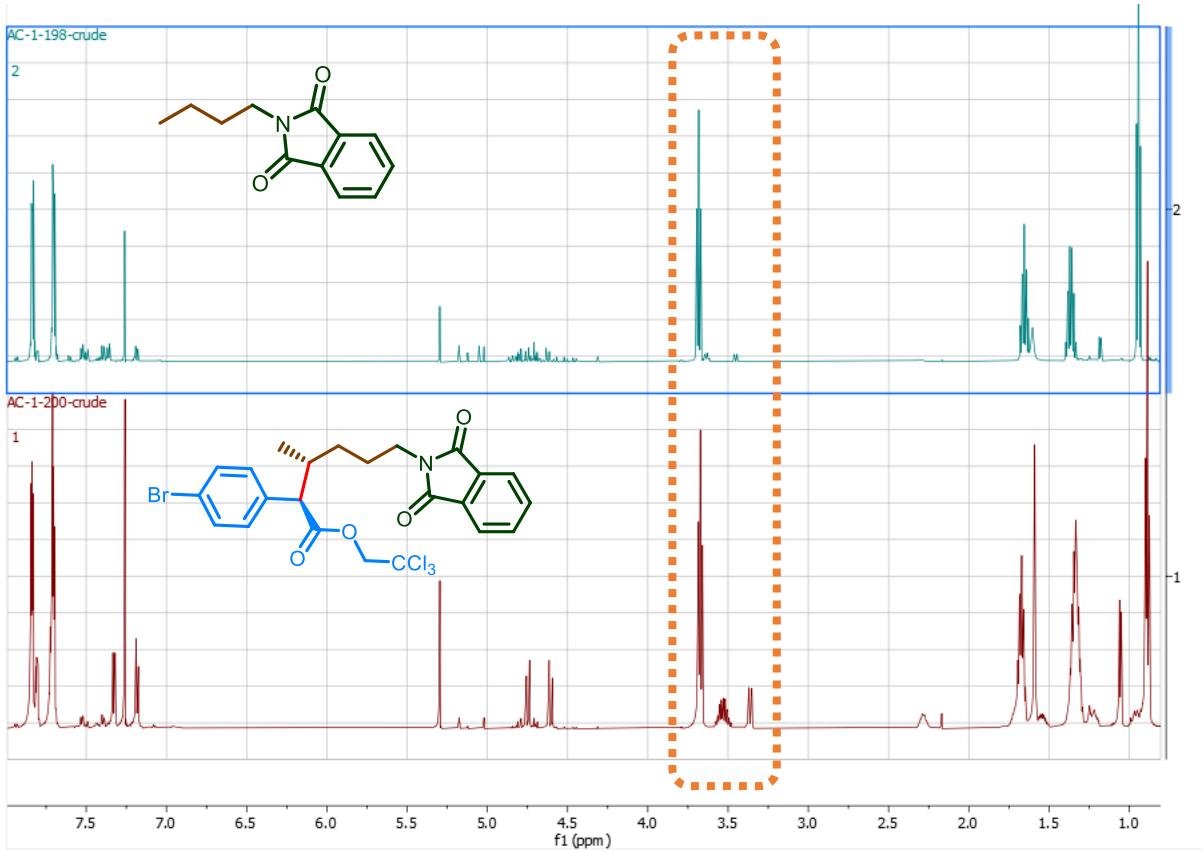
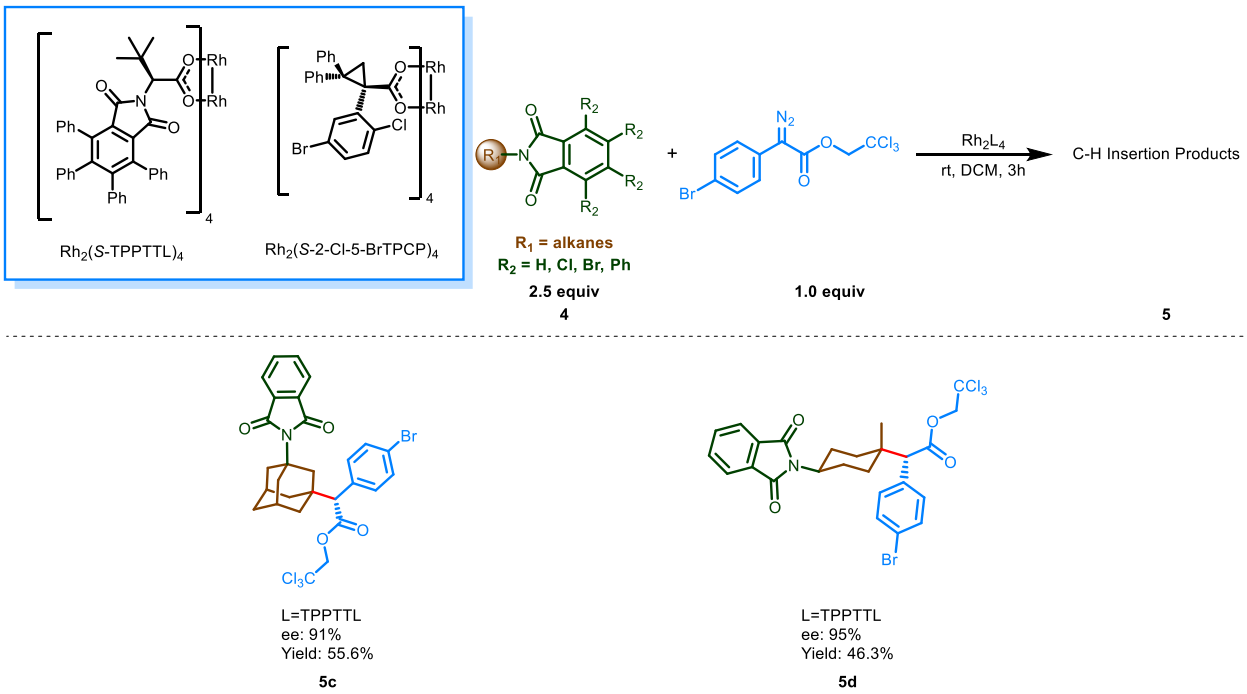


Figure 2.11 Comparison between Crude NMRs for the Reaction with Pentylamine and Butylamine Derivative

2.3 Expansion of the Scope to Tertiary Sites

Scheme 2.3 Reactions with Tertiary Sites



To explore the potential scope of this reaction type, insertions to the 3° C-H bonds are performed. For tertiary C-H functionalization, Rh_2(*S*-2-Cl-5-BrTPCP)$_4$ (Figure 1.1 **B**) is too sterically demanding. Therefore, a less crowded catalyst, Rh_2(*S*-TPPTTL)$_4$ (Figure 1.1 **A**) was used. The reaction with phthalimodo adamantylamine **4c** went smoothly (AC-1-160), generating the tertiary C-H functionalization product **5c** in 56% yield and 91% ee (Scheme 2.3). Different from previous insertions to the secondary C-H bonds, the diastereoselectivity is not an issue for the insertion to the C3 position. Meanwhile, due to insertion to the C3 position, the signal for the benzylic proton will not couple with the other adjacent protons, appearing as a singlet at $\delta = 3.51\ ppm$. However, what remains unchanged is that a stereogenic center is still formed at the benzylic carbon after the insertion, forming two enantiomers. Since dr is not needed, a purified NMR is directly shown in Figure 2.12-a rather than a crude NMR. As illustrated in Figure 2.12-a, the proton counts matched well with the desired product. The formation of **5c** is quite exciting due

to the similarity between its structure and a widely used drug, memantine, to treat moderate to severe Alzheimer's disease shown in Figure 2.12-b.

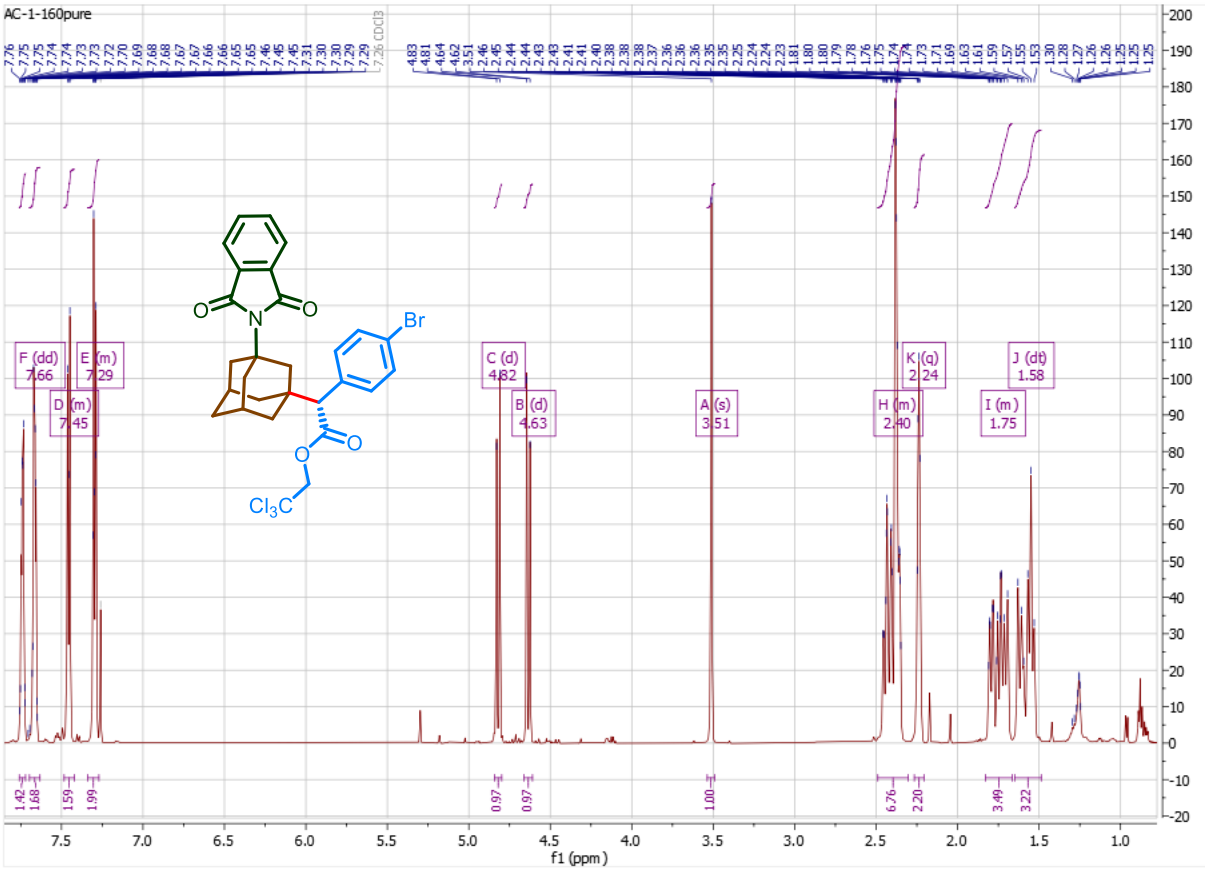
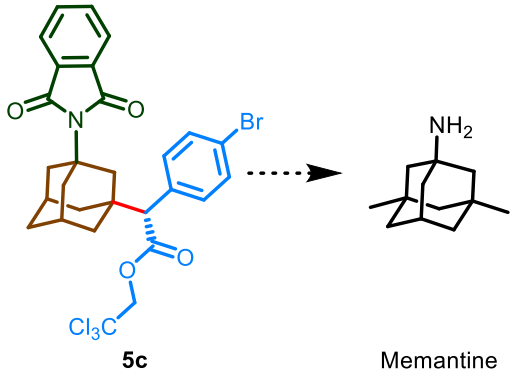


Figure 2.12-a Purified NMR for the Reaction with Adamantly Amine Derivative



5c Memantine

Figure 2.12-b Insertion Product vs. Memantine

Apart from the reaction with adamantylamine derivative, the reaction with the 4-methylcyclohexylamine derivative **4d** illustrates the subtle control that can be exhibited in this C-H functionalization chemistry. The discovery of this special selectivity started with the reaction using diastereomericly pure *trans* isomer of 4-methylcyclohexylamine as starting material (AC-1-171). After taking the crude NMR shown in the top part of Figure 2.14, there was no singlet observed between $\delta = 3.00\,ppm$ to $\delta = 4.00\,ppm$ for the benzylic proton like Figure 2.11, implying that the reaction was not successful. As seeking the explanation for this observation, I recalled one literature published by previous group members (Figure 2.13) about the desymmetrization of the cyclohexane using Rh_2(*S*-TPPTTL)$_4$ as the chiral catalyst [4].

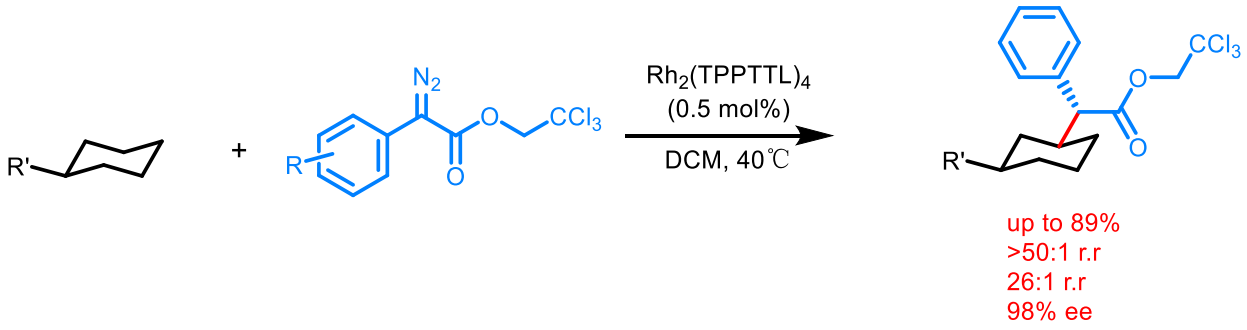


Figure 2.13 Published Work on Desymmetrization of Cyclohexane

In this literature, one crucial observation was that donor/acceptor carbenes have a strong preference for reaction at equatorial hydrogens in cyclohexanes (estimated as about 140:1 in favor of equatorial versus axial) [4]. Recalling the *trans* isomer of 4-methylcyclohexylamine used in the reaction, after equilibration, both protected amine functionality and the methyl group will prefer the equatorial position, blocking the insertion to the equatorial C-H bond at the C4 position. To further validate this hypothesis, the commercially available substrate consists of a mixture of *cis* and *trans* isomers (50:50) of **4d** was then used as the substrate. As expected, the reaction resulted in the formation of **5d** as a single diastereomer, in which only the cis isomer of **4d** has reacted

(AC-1-183). As illustrated in Figure 2.14, the benzylic proton at $\delta = 3.56\, ppm$ indicating successful insertion to the tertiary position appears only when the substrate consists of both *cis* and *trans* isomers (50:50) of **4d**.

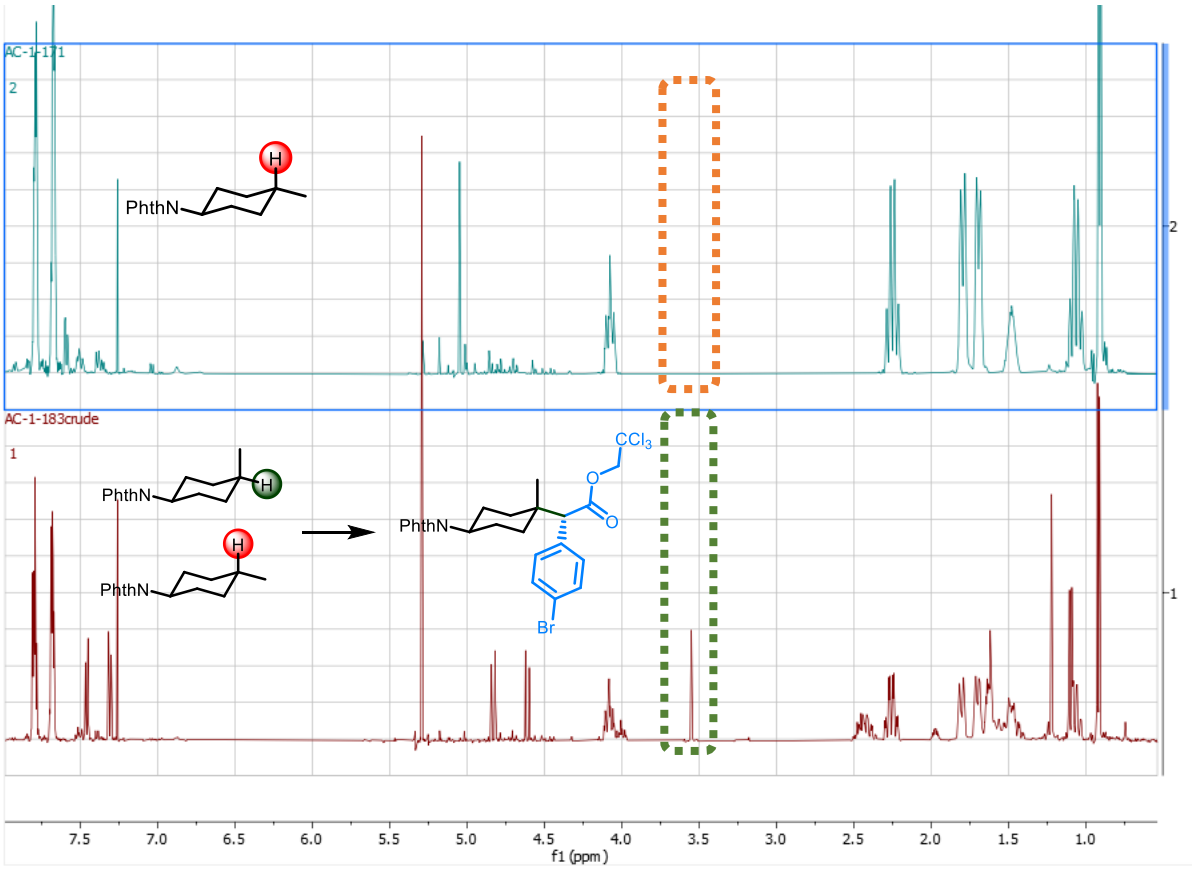


Figure 2.14 Comparison between Crude NMRs for the Reaction with *trans* isomer of 4-methylcyclohexylamine and mixture of diastereomers of 4-methylcyclohexylamine Derivative

To further illustrate the structure of the product from the reaction with *cis* and *trans* isomers (50:50) of **4d**, a purified NMR is presented in Figure 2.15, in which all the protons are matched well with the protons of the desired product though the shimming of the NMR resulted in relatively less accurate identifications of the spin-spin splits. For instance, it is obvious that from Figure 2.15, the benzylic proton at $\delta = 3.56\, ppm$ is expected to be a singlet but was identified as a doublet.

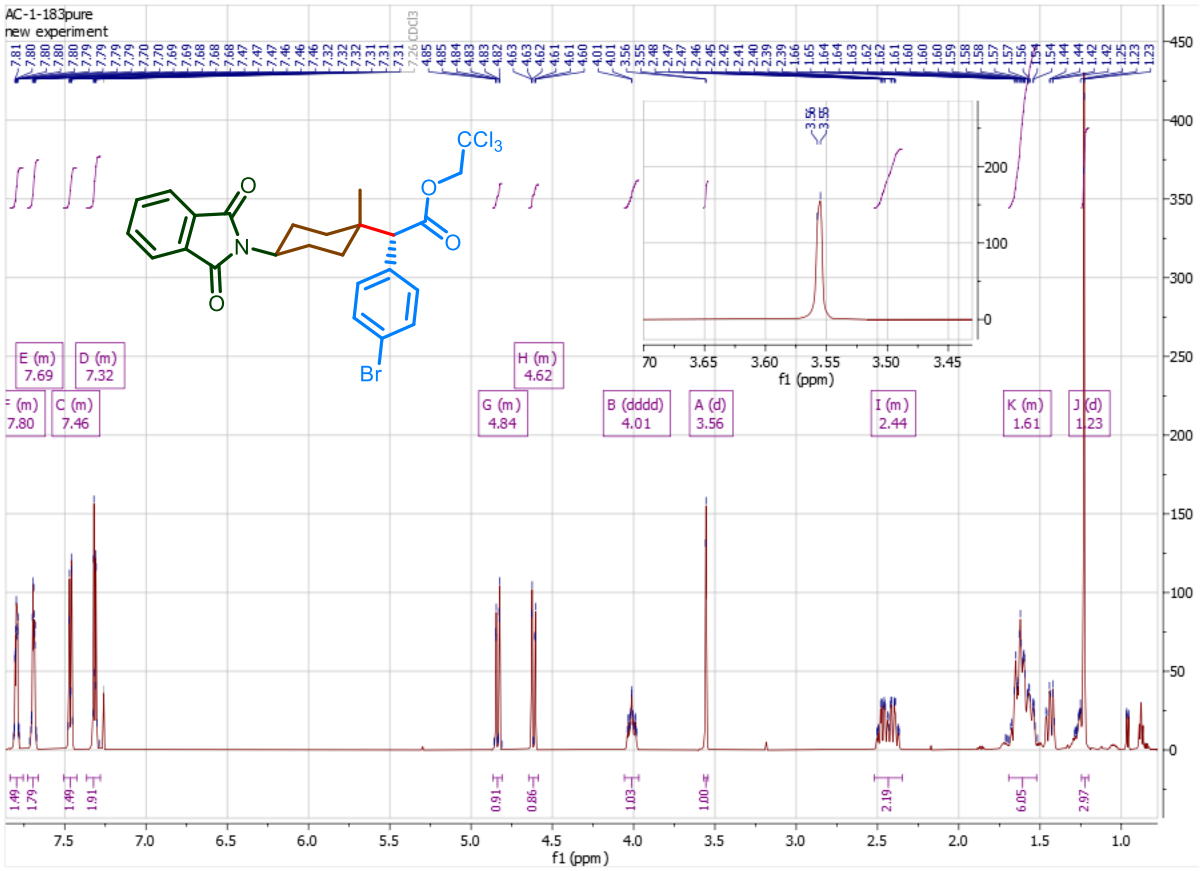
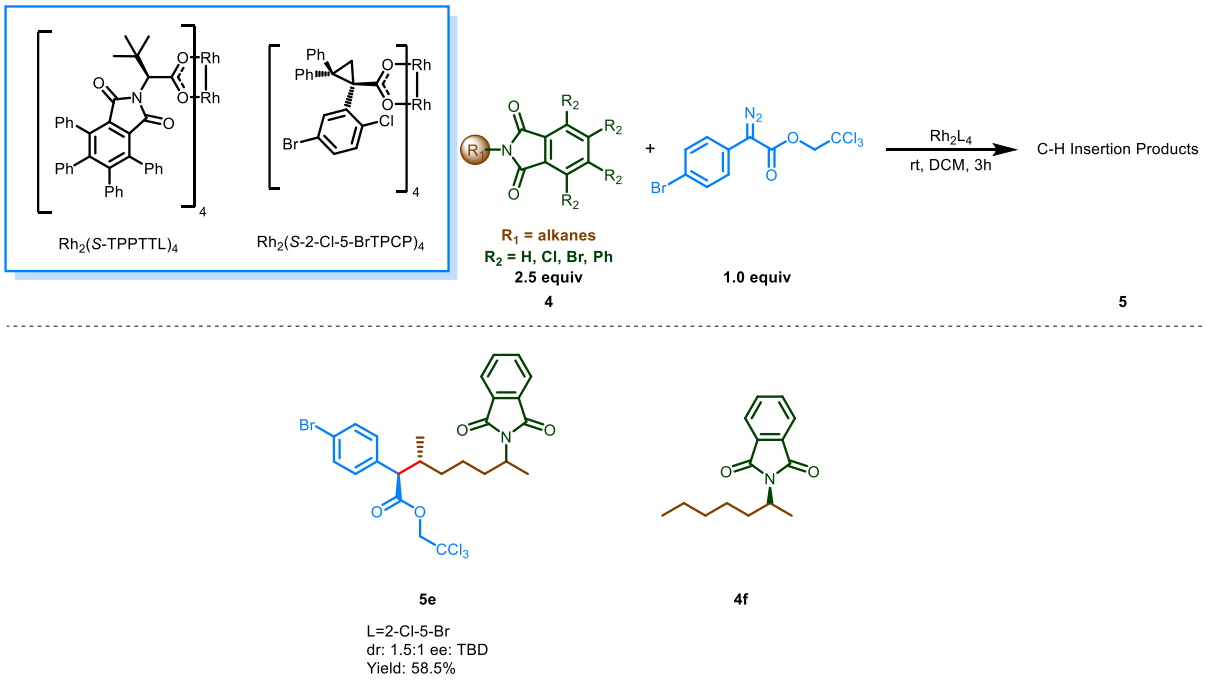


Figure 2.15 Purified NMR for the Reaction with a mixture of *cis* and *trans* isomers (50:50) of 4-methylcyclohexylamine Derivative

2.4 Further Support of Asymmetric Induction

Scheme 2.4 Further Support of Asymmetric Induction



Based on the previous results, this type of reaction is highly enantioselective. Moreover, according to the multiple crude NMRs, these reactions reported to date also have been highly diastereoselective. This catalyst-controlled asymmetric induction was especially interesting when the reactions with the racemic 2-aminoheptane (*R/S* 50:50) derivative were carried out (AC-1-161). Based on Figure 2.16, there are two diastereomers of **5e** formed with the ratio of 1:1.6/1:1.5, but based on the previous insertions, we proposed that those two diastereomers correspond to the racemic substrates, (*R/S)*-2-aminoheptane derivatives. Meanwhile, based on Figure 2.16, the minor diastereomers corresponding to (*R*)-2-aminoheptane derivative and (*S*)-2-aminoheptane derivative respectively can be observed and still remain as the minor products (>20:1 dr). The two major products and two minor products are shown in Figure 2.17. This hypothesis will be further tested by using enantiopure (*S*)-2-amino hexane derivative **4f** to examine the results.

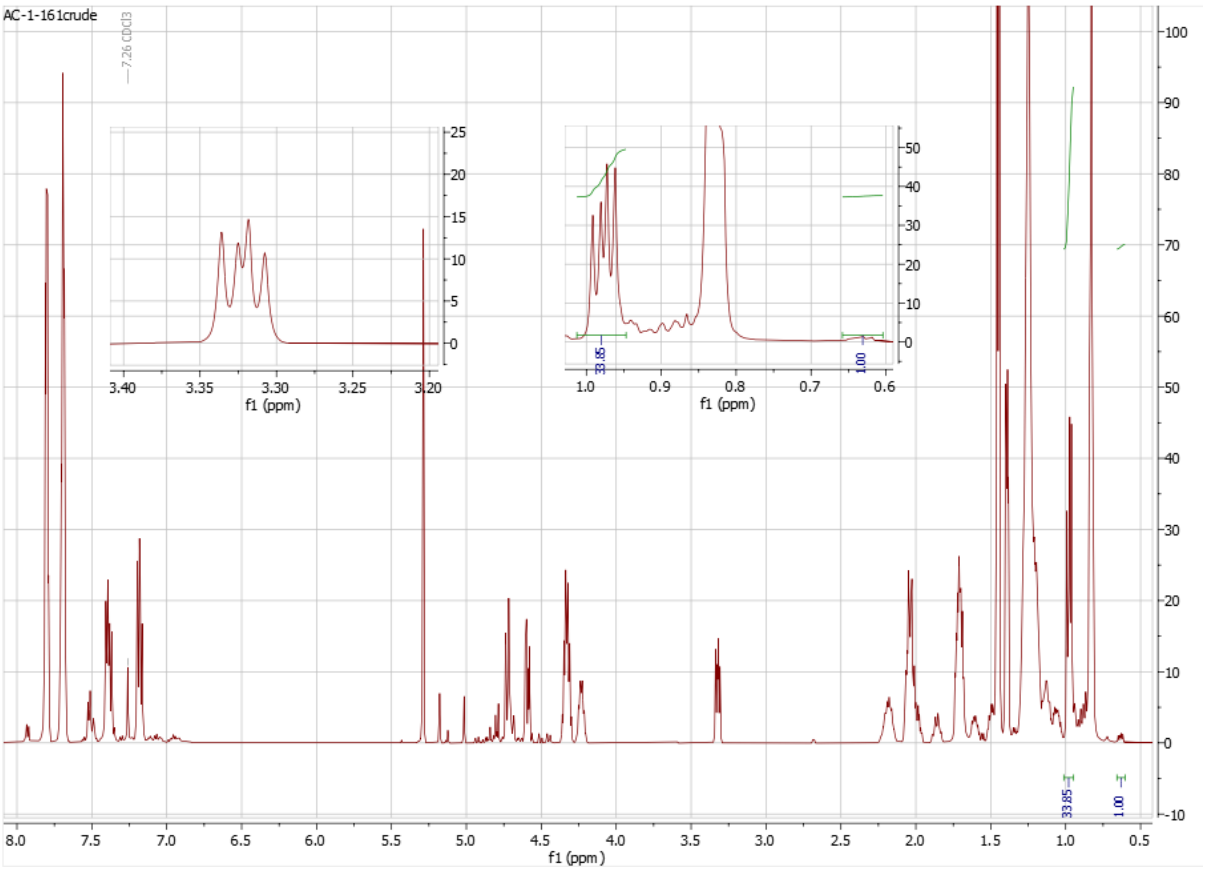
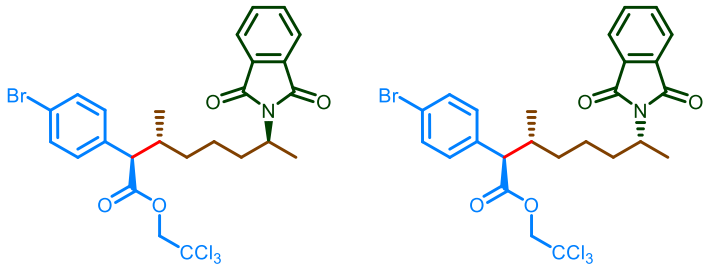
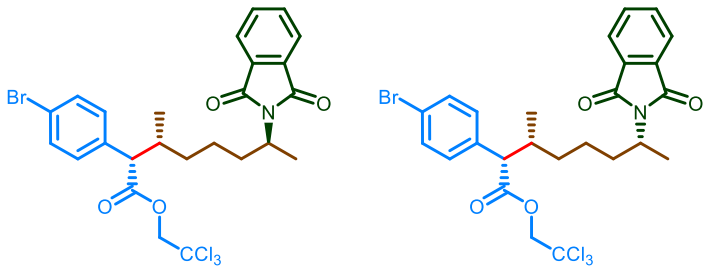


Figure 2.16 Crude NMR for the Reaction with Racemic 2-aminoheptane Derivative



Major products correspond to *R/S* SM



Minor products correspond to *R/S* SM

Figure 2.17 Products from the Reaction with Racemic 2-aminoheptane Derivative

Before presenting the purified NMR for the products, a discussion about how the ratio between the two major products is needed. Since the crucial doublets in the crude NMR are all merged together rather than be separated well down to the baseline for the two major products, the first method used is to obtain this ratio is by integrating half of the doublet for each major product, giving a ratio of 1:1.6 (Figure 2.18). The second method used is to carefully cut in the middle of the two merged doublets, giving a ratio of 1.5 (Figure 2.19).

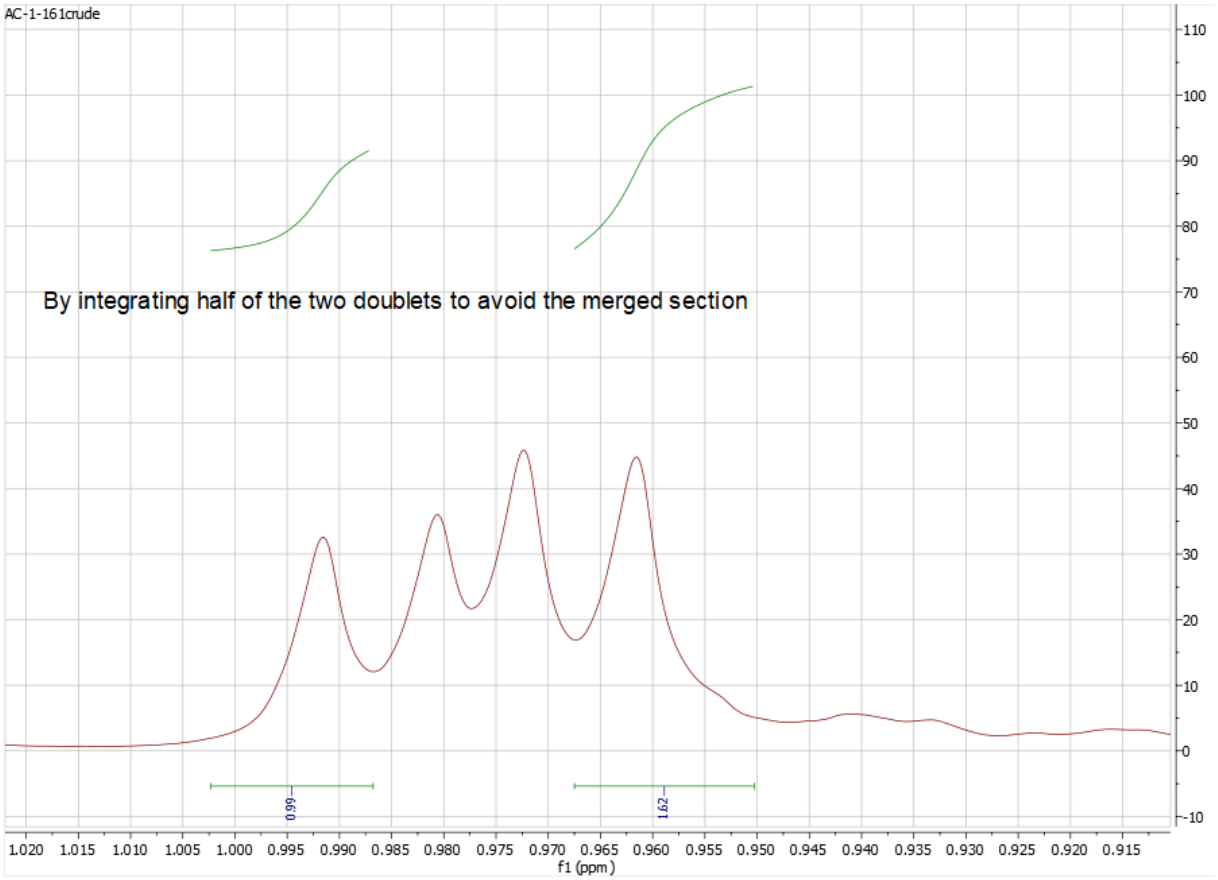


Figure 2.18 Integrating Half of the Two Doublets

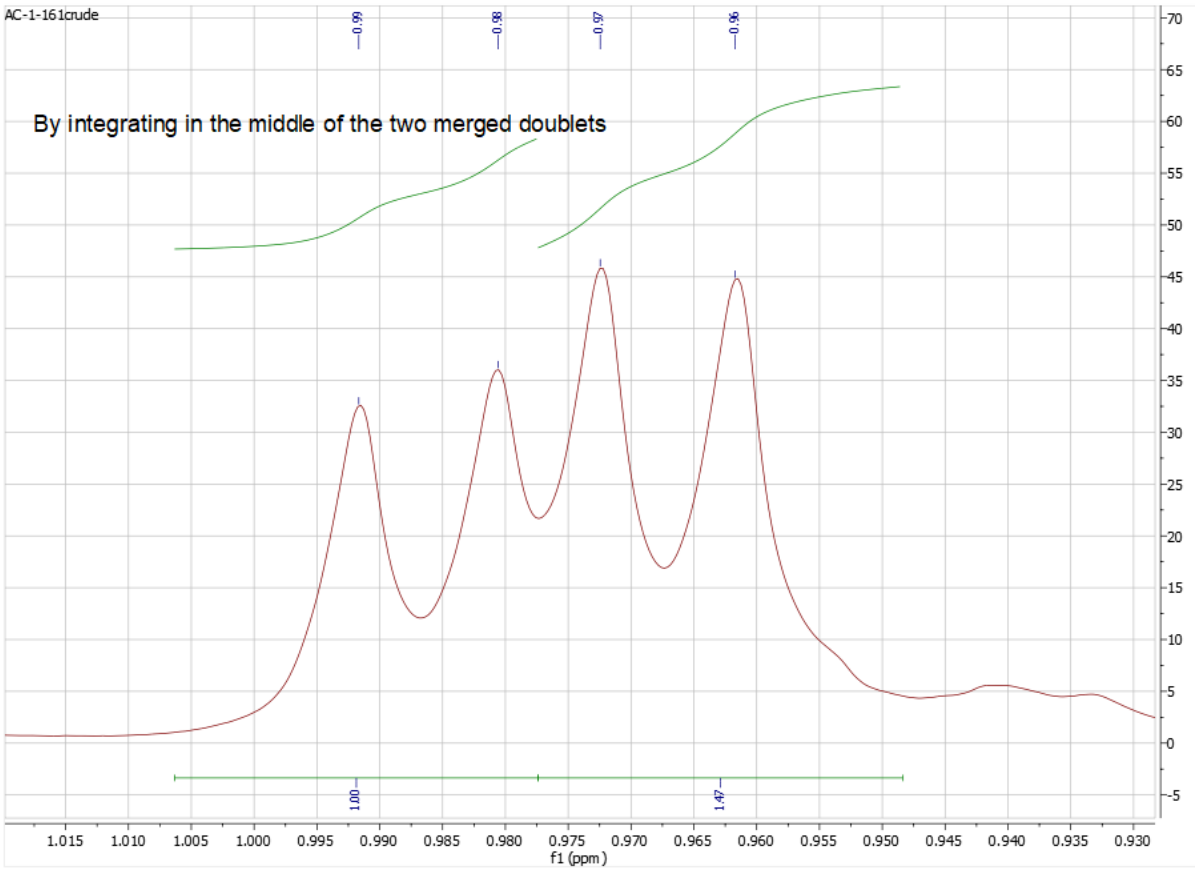


Figure 2.19 Integrating by Cutting in the Middle of the Merged Doublets

With the discussion based on the crude NMR, a purified NMR is then shown in Figure 2.20 which includes both major diastereomers. Similar to all the successful C-H insertion products, the signals in Figure 2.20 follow a similar pattern. However, due to the presence of the two diastereomers in the purified sample and the 1:1.6/1:1.5 ratio between the two major products, the integration cannot fully match with the proton counts for the desired products. Therefore, the identification of the desired product is based on the chemical shifts of the signals as well as the spin-spin split pattern of the peaks.

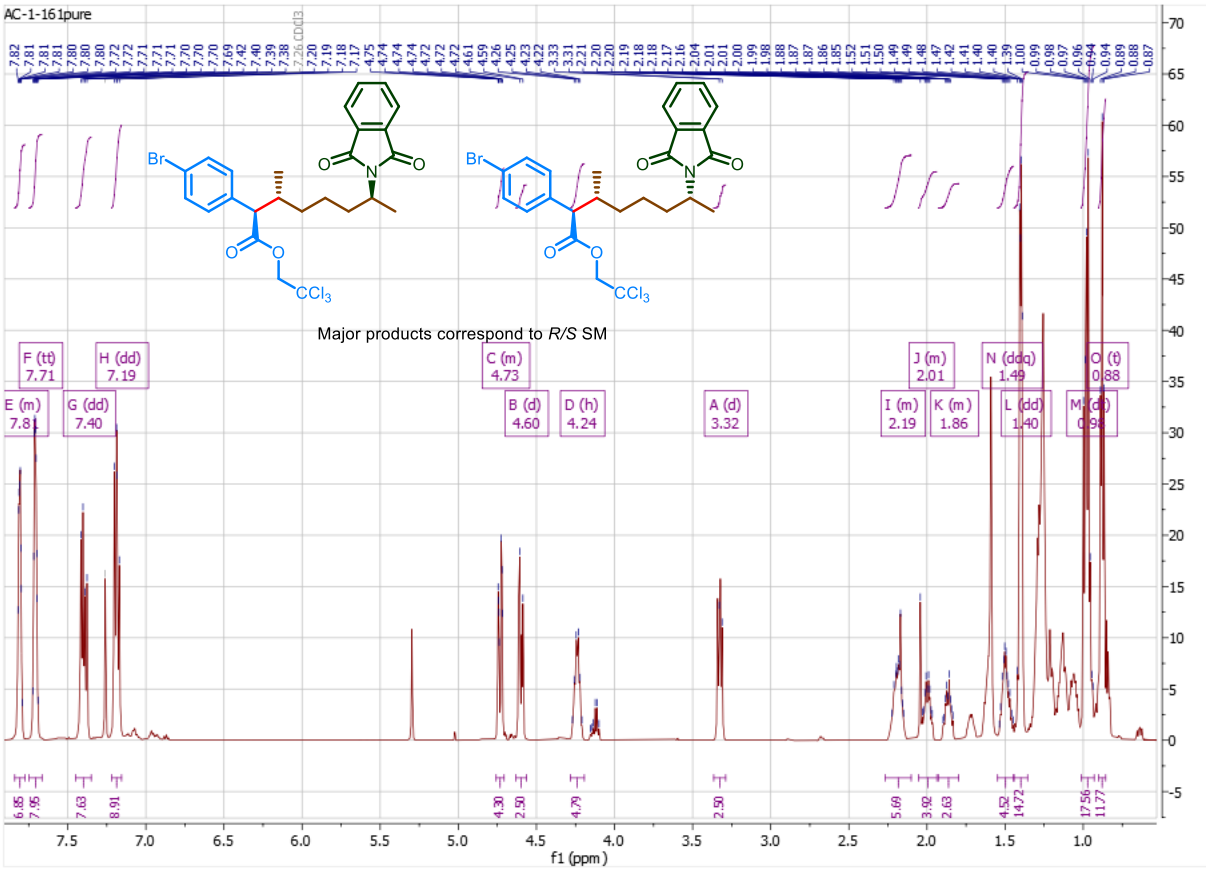
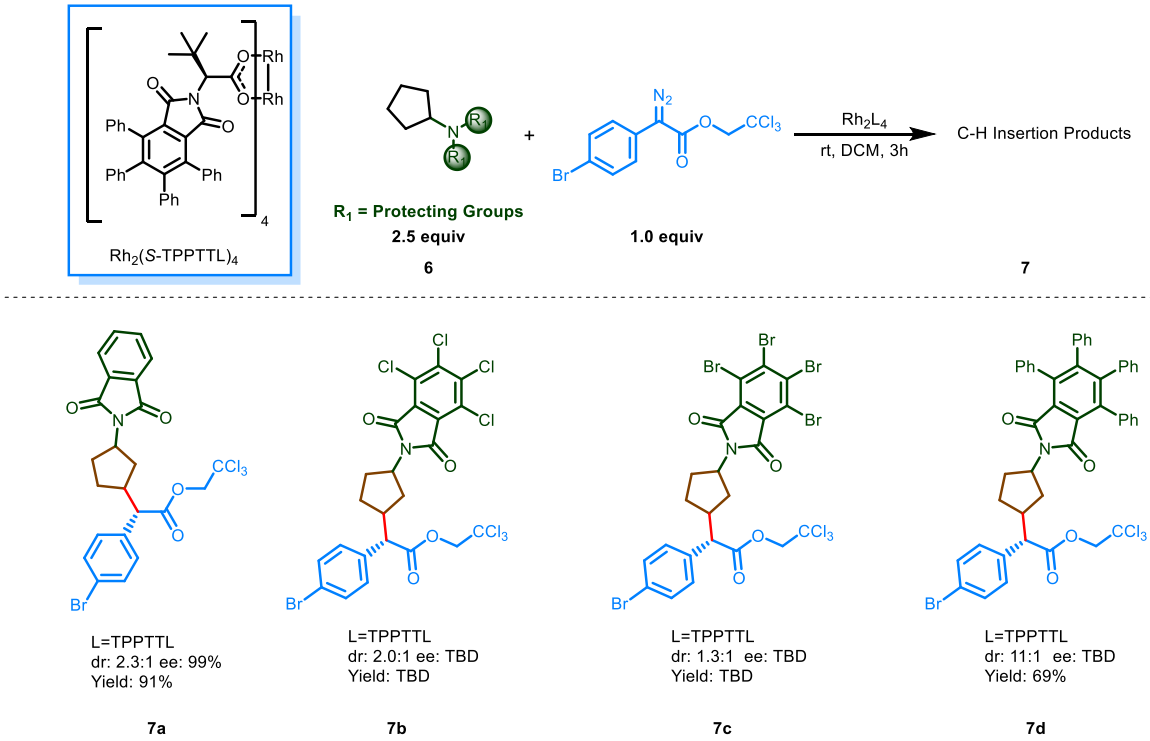


Figure 2.20 Purified NMR for the Reaction with Racemic 2-Aminoheptane Derivatives

2.5 Desymmetrization of Cyclic Systems

Beyond the selectivity observed in the asymmetric structures, one of the most impressive examples of site-selective C-H functionalization with donor/acceptor carbenes is the functionalization of alkylcyclohexanes at C3 under Rh_2(*S*-TPPTTL)$_4$ catalysis (Figure 2.13) [4]. This transformation desymmetrizes the symmetric alkylcyclohexanes by creating three stereogenic centers via C-H insertion. With the high selectivity observed in alkylcyclohexanes, the reaction with cyclopentylamine derivatives **6** was examined [4]. As expected, the reaction was highly enantioselective (99% ee) with good yields, but the diastereoselectivity was not as good as the asymmetric structures (2.3:1 dr) [4]. To improve the diastereoselectivity, changing the steric bulkiness of the protecting groups was tested as a possible method since bulkier groups enable the substrates to be locked in the bowl-shaped catalyst at the early stage of the reaction. As shown in Scheme 2.5, after screening tetrachloro-, **6b** tetrabromo-, **6c,** and tetraphenylphthalimido **6d** groups, tetraphenelyphthalimido-protected substrate gave the best diastereoselectivity with 69% yield and 11:1 dr (AC-1-167, AC-1-236), which is also illustrated by Figure 2.21.

Scheme 2.5 Modification of Phthalimido Group for Desymmetrization of Cyclic Systems



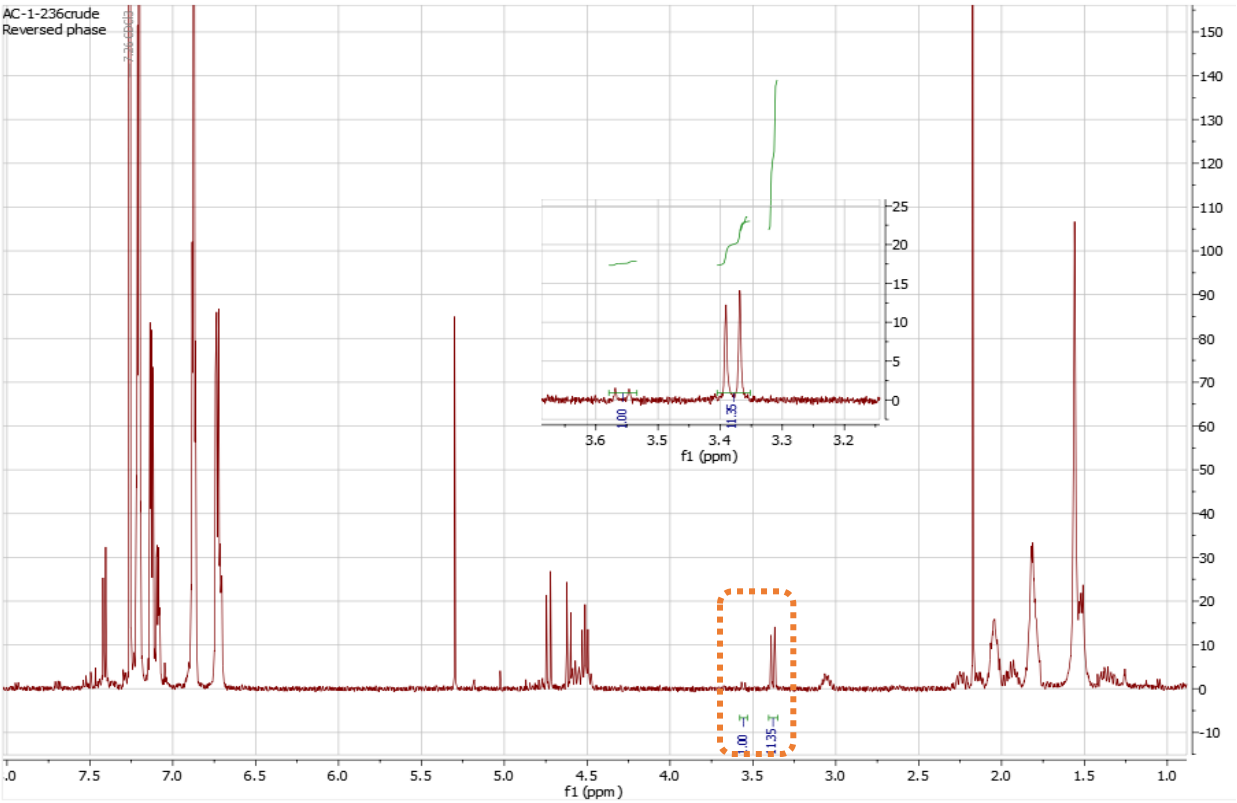


Figure 2.21 Crude NMR for the Reaction with Tetraphenylphthalimido-Protected Cyclopentylamine

To further demonstrate the structure of the obtained product, the purified NMR is attached below (Figure 2.22) with expected split patterns as well as chemical shifts for the peaks. The integration in the aromatic regions is not fully accurate due to the shimming as well as the presence of the minor diastereomer.

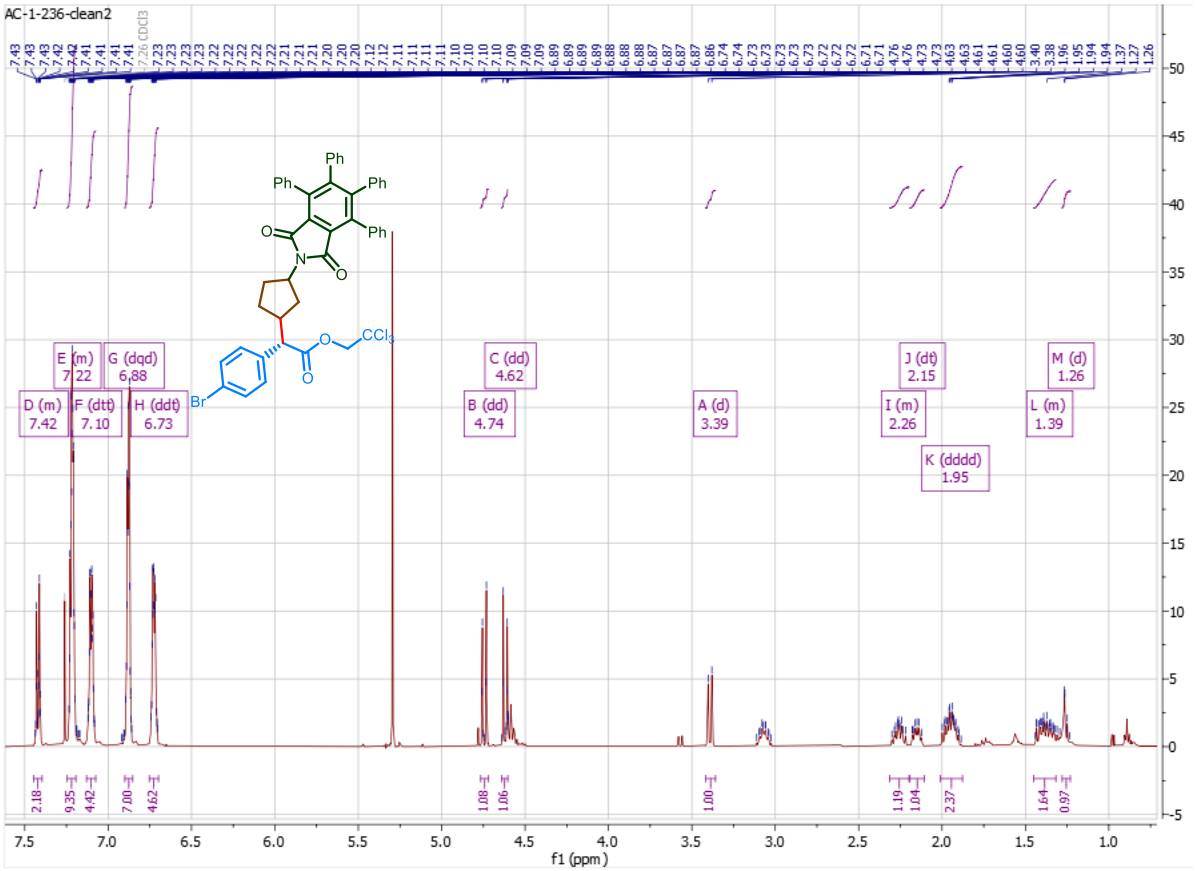
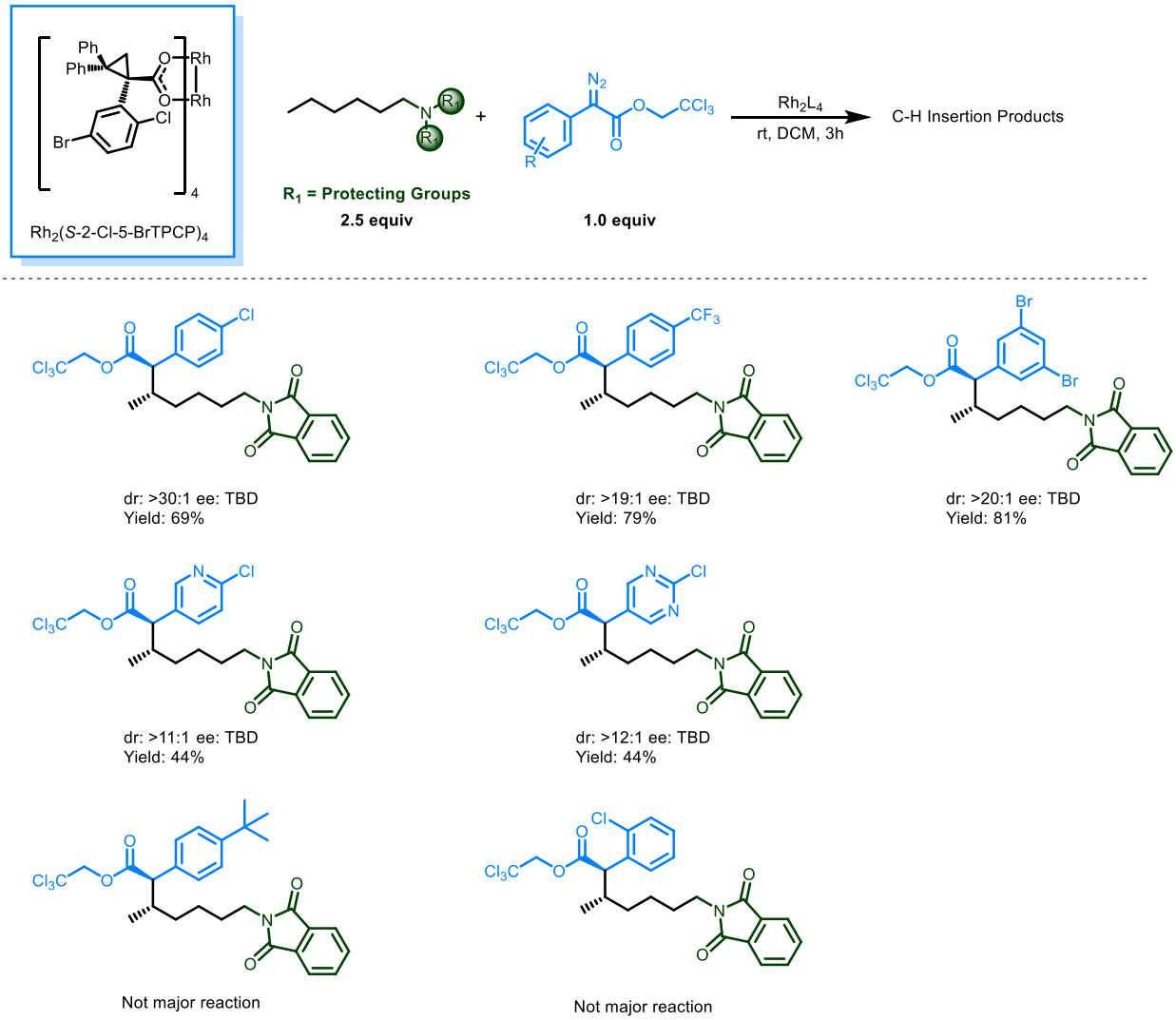


Figure 2.22 Purified NMR for the Reaction with Tetraphenylphthalimido-Protected Cyclopentylamine

2.6 Reaction Scope with Aryldiazoacetates

Up to this point, all the studies have been carried out with *p*-bromophenyldiazoacetate as the donor/acceptor carbene precursor. However, the chemistry is applicable to a range of aryl and heteroaryldizoacetate derivatives with a reaction of hexylamine derivative catalyzed by Rh_2(*S*-2-Cl-5-BrTPCP)$_4$. For all different diazoacetate derivatives, the high diastereoselectivity and high yields are preserved for the halogens and electron-withdrawing functionalities attached to the phenyl (Scheme 2.6).

Scheme 2.6 Reaction Scope of Diazoacetates



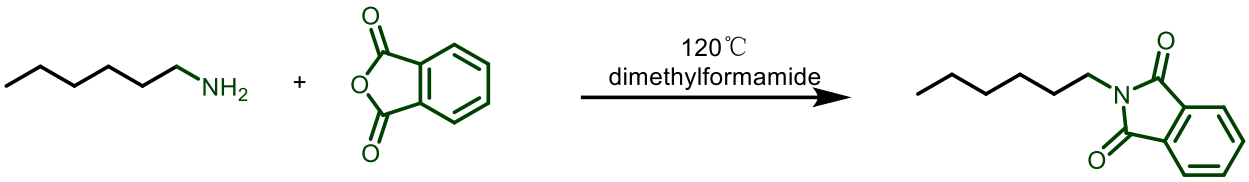
3 Conclusions and Future Directions

In conclusion, the N-phthalimido group was found to be very effective for protecting primary amines, when conducting rhodium-catalyzed functionalization of unactivated C-H bonds with donor/acceptor carbenes. Based on the inductive effects as well as the bulkiness of the phthalimido group, it well protects the C-H bonds near and suppresses reactions at the adjacent C-H bonds. Moreover, this type of method is applicable for both second and tertiary insertions. For both, it remains with high catalyst-controlled asymmetric induction to give high diastereoselectivity and enantioselectivity. Additionally, the relatively large nature of the phthalimido group can also protect sites from C-H functionalization and lead to an enhanced level of stereoselectivity of the symmetric systems. Apart from the tolerance to the hydrocarbon substrates, these studies further underscore the functional group compatibility of donor/acceptor carbenes even though they are capable of reacting with unactivated C-H bonds.

The studies above also indicate supplemental reactions needed to support the high asymmetric induction due to the catalyst. Moreover, there also additional ee for the scope of diazo scope needs to be decided.

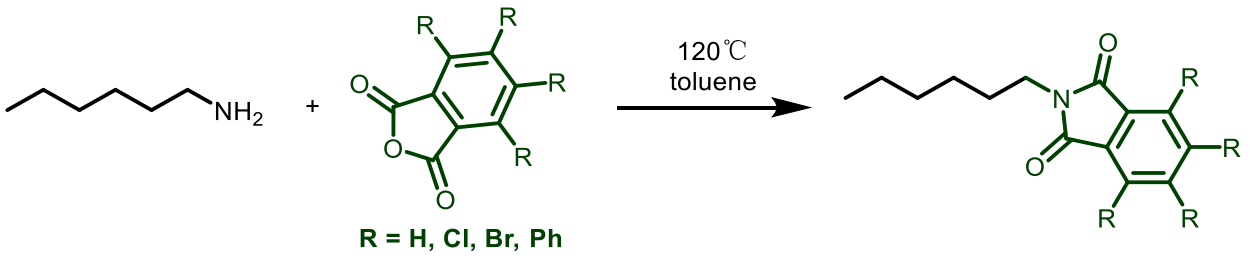
Supplemental Information

General Procedure (1)



To a 50 ml of clean round-bottom flask equipped with a large egg-shaped magnetic stir-bar, phthalic anhydride/its derivatives (0.01 mol, 1.0 equiv.) and hexylamine/hydrocarbons with primary amine (0.01 mol, 1.0 equiv.) were added. Then, to the RBF with two substrates, dimethylformamide (20 ml) is added. The contents are stirred and heated to 120℃ under a condenser for overnight refluxing. The next day, the hot reaction mixture is poured onto crushed ice prepared in a beaker (150 ml) to obtain precipitates. By vacuum filtration, the white precipitates are rinsed with DI water 3 times and then collected to a 20 ml vial to dry under reduced pressure. The obtained product is further purified by silica gel chromatography.

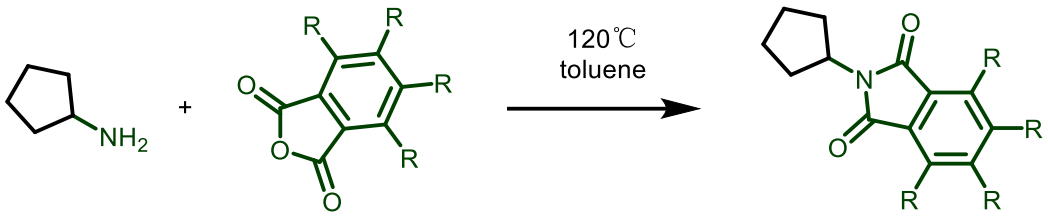
General Procedure (2)



To a 50 ml of clean round-bottom flask equipped with a large egg-shaped magnetic stir-bar, phthalic anhydride/its derivatives (0.01 mol, 1.0 equiv.) and hexylamine/hydrocarbons with primary amine (0.01 mol, 1.0 equiv.) were added. Then, to the RBF with two substrates, dimethylformamide (20 ml) is added. The contents are stirred and heated to 120℃ under a

condenser for overnight refluxing. The next day, the hot reaction mixture was poured onto crushed ice prepared in a beaker (150 ml) to obtain precipitates. If no precipitates crush out, DCM is then added to the mixture to extract the product. After extraction with DCM three times, the organic layer is washed by water and then the brine (for each three to five times). Then the washed product is dried under magnesium sulfate. Lastly, the mixture is concentrated and further purified by silica gel chromatography.

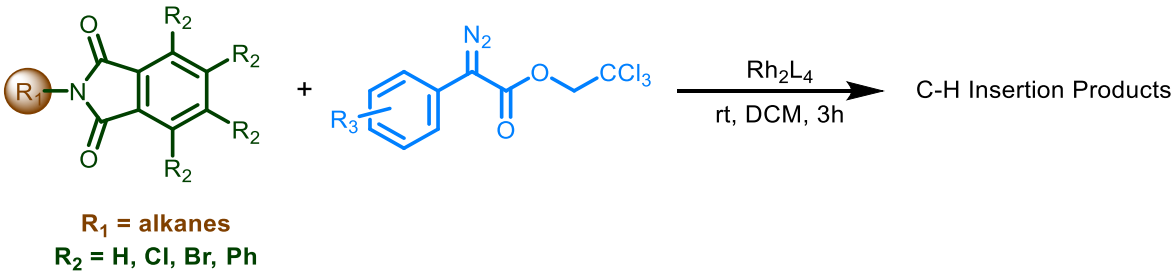
General Procedure (3)



R = H, Cl, Br, Ph

To a 100 ml of clean round-bottom flask equipped with a large egg-shaped magnetic stir-bar, phthalic anhydride/its derivatives (0.01 mol, 1.0 equiv.) and hexylamine/hydrocarbons with primary amine (0.01 mol, 1.0 equiv.) were added. Then, to the RBF with two substrates, toluene (40 ml) is added. The contents are stirred and heated to 120℃ under a condenser with a balloon for overnight refluxing. The next day, the mixture is diluted with ethyl acetate and poured into a separate funnel. This mixture is washed with 0.5M HCl, successively with water and brine. Then, it is dried over magnesium sulfate and concentrated to give solids. The mixture was concentrated and further purified by silica gel chromatography.

General Procedure (4)

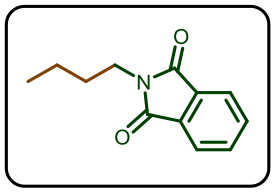


R_1 = alkanes
R_2 = H, Cl, Br, Ph

Taken from the oven, a clean 8.0 ml scintillation vial (vial-A) equipped with a small egg-shaped magnetic stir-bar was evacuated and purged with argon/nitrogen (2-3 times). After cooling down to room temperature, the corresponding dirhodium catalyst (1 mol%) followed by substrate (0.500 mmol, 2.5 equiv.) were then added. The vial was once again evacuated and purged with argon (3-5 times) and 2 ml of dry dichloromethane was added. The vial and its content were then set to sir at room temperature under an argon or nitrogen atmosphere. To a second vial (vial-B) taken from the oven, which is evacuated and purged with argon/nitrogen was added the donor/acceptor diazo compound (0.200 mmol, 1 equiv.). Vial-B and its content were evacuated and purged with argon (2-3 times) and 2.0 ml of dry dichloromethane was then added to obtain a 0.1 M solution of the diazo compound. The 0.1 M solution was transferred into a 5.0 ml plastic syringe (12.46 mm diameter). Using a well-calibrated syringe pump, slow addition (0.667 ml/h) of the diazo solution into the stirring solution of vial-A under an inert atmosphere was initialed. After complete addition (3 hours later), the residual diazo compound in the 5.0 ml plastic syringe was rinsed with 0.5 ml dry dichloromethane and transferred dropwise into the stirring reaction mixture of vial-A. An additional 15 minutes was allowed before concentrating the solution under reduced pressure. The crude product was then purified by silica gel chromatography to obtain the purified C-H functionalization product.

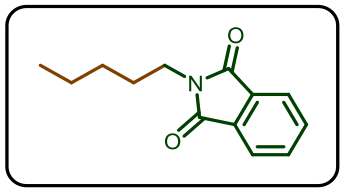
Substrates

AC-1-188 4b



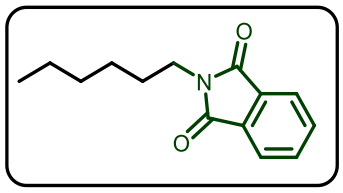
The product was obtained by general procedure (1). The silica gel chromatography was run by Biotage with 20% EtOAc/Hexane. ^{1}H NMR (600 MHz, cdcl3) δ 7.87 – 7.78 (m, 2H), 7.73 – 7.67 (m, 2H), 3.68 (t, J = 7.4 Hz, 2H), 1.69 – 1.60 (m, 2H), 1.41 – 1.31 (m, 2H), 0.94 (t, J = 7.4, Hz, 3H).

AC-1-187 4a



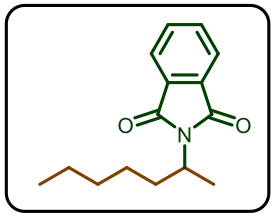
The product was obtained by general procedure (2). The silica gel chromatography was run by Biotage with 10%-15% Et_2O/Hexane. ^{1}H NMR (500 MHz, cdcl3) δ 7.89 – 7.80 (m, 2H), 7.74 – 7.66 (m, 2H), 3.72 – 3.62 (t, 2H), 1.74 – 1.55 (m, 2H), 1.41 – 1.21 (m, 4H), 0.95 – 0.83 (t, 3H).

AC-1-68 1e



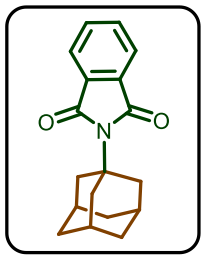
The product was obtained by general procedure (1). No silica gel chromatography was needed. ^{1}H NMR (500 MHz, cdcl3) δ 7.91 – 7.79 (m, 2H), 7.76 – 7.64 (m, 2H), 3.75 – 3.61 (t, 2H), 1.74 – 1.58 (m, 2H), 1.36 – 1.15 (m, 6H), 0.93 – 0.67 (t, 3H).

AC-1-151 4e



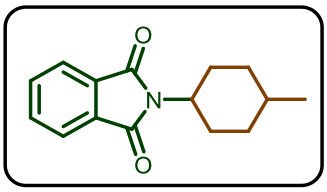
The product was obtained by general procedure (2). The silica gel chromatography was run by Biotage with 10% EtOAc/Hexane. ^{1}H NMR (500 MHz, cdcl3) δ 7.82 – 7.73 (m, 2H), 7.71 – 7.62 (m, 2H), 4.37 – 4.26 (m, 1H), 2.12 – 1.94 (m, 1H), 1.69 (ddtd, J = 13.3, 11.4, 5.7, 1.9 Hz, 1H), 1.50 – 1.36 (m, 3H), 1.32 – 1.12 (m, 5H), 0.81 (tdd, J = 7.3, 4.8, 2.6 Hz, 3H).

AC-1-149 4c



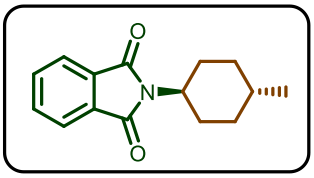
The product was obtained by general procedure (1). The silica gel chromatography was run by Biotage with 10% EtOAc/Hexane. ^{1}H NMR (600 MHz, cdcl3) δ 7.73 (dt, J = 7.3, 3.7 Hz, 2H), 7.65 (dd, J = 5.5, 3.0 Hz, 2H), 2.50 (d, J = 3.1 Hz, 6H), 2.15 (d, J = 7.8 Hz, 3H), 1.81 – 1.60 (m, 7H).

AC-1-181 4d



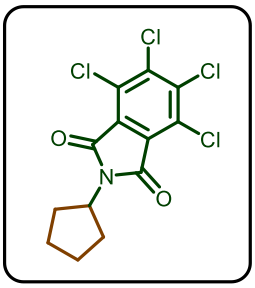
The product was obtained by general procedure (1). The silica gel chromatography was run by Biotage with 8%-10% EtOAc/Hexane. ^{1}H NMR (500 MHz, cdcl3) δ 7.81 (ddd, J = 5.5, 3.1, 1.1 Hz, 2H), 7.69 (ddd, J = 5.3, 3.0, 2.0 Hz, 2H), 4.13 – 4.05 (m, 1H), 2.48 – 2.38 (m, 1H), 2.32 – 2.21 (m, 1H), 1.98 (s, 1H), 1.81 (d, J = 13.4 Hz, 1H), 1.71 (d, J = 12.5 Hz, 1H), 1.63 (dd, J = 8.7, 4.6 Hz, 2H), 1.49 (d, J = 13.2 Hz, 1H), 1.11 (d, J = 7.2 Hz, 3H), 0.93 (d, J = 6.6 Hz, 1H).

AC-1-168 *trans* isomer of 4d



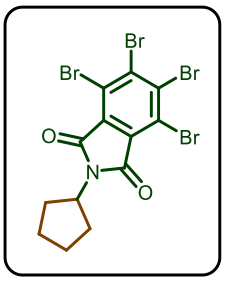
The product was obtained by general procedure (2). The silica gel chromatography was not needed. The product was put under low pressure to evaporate the water. ^{1}H NMR (500 MHz, cdcl3) δ 7.86 – 7.76 (m, 2H), 7.74 – 7.64 (m, 2H), 4.09 (tt, J = 12.4, 4.0 Hz, 1H), 2.27 (qd, J = 12.8, 3.6 Hz, 2H), 1.86 – 1.78 (m, 2H), 1.76 – 1.68 (m, 2H), 1.53 (ddd, J = 8.7, 5.9, 3.3 Hz, 1H), 1.14 – 1.02 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H).

AC-1-155 6b



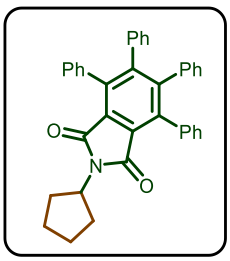
The product was obtained by general procedure (2). The silica gel chromatography was run by Biotage with 3%-5% EtOAc/Hexane. ^{1}H NMR (600 MHz, cdcl3) δ 4.62 (p, J = 8.4 Hz, 1H), 2.09 – 1.99 (m, 2H), 1.99 – 1.87 (m, 4H), 1.69 – 1.59 (m, 2H).

AC-1-174 6c



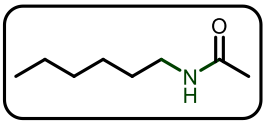
The product was obtained by general procedure (3). The silica gel chromatography was run by Biotage with 3%-5% EtOAc/Hexane. ^{1}H NMR (500 MHz, cdcl3) δ 4.66 (p, J = 8.4 Hz, 1H), 2.11 – 2.00 (m, 2H), 2.01 – 1.88 (m, 4H), 1.70 – 1.60 (m, 2H).

AC-1-229 6d



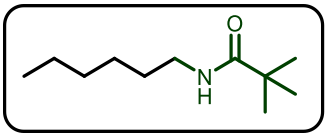
The product was obtained by general procedure (3). The silica gel chromatography was run by Biotage with 6%-8% EtOAc/Hexane. ^{1}H NMR (500 MHz, cdcl3) δ 7.23 – 7.19 (m, 5H), 7.13 (ddt, J = 6.3, 2.2, 1.3 Hz, 5H), 6.90 – 6.82 (m, 5H), 6.76 – 6.70 (m, 5H), 4.51 (t, J = 8.7 Hz, 1H), 2.04 (m, 2H), 1.81 (m, 3H), 1.51 (m, 3H).

AC-1-69 1b



Dissolve 10mmol (1.0 equiv) of hexylamine in acetonitrile and cool the mixture to 0℃ in an ice water bath. Add triethyl amine (20mmol, 2.0 equiv) and acetic anhydride (40mmol, 4.0 equiv) into the cold mixture and stir overnight. The next day, the mixture is concentrated first and added water and stir for another 15 min. Then, the mixture is removed from the ice water bath and diluted with 10 mL of water. Then the product is extracted with DCM (1×15mL) and washed with sulfuric acid (2×15mL), saturated solution sodium bicarbonate (1×15mL), and water (1×15mL). Then, the mixture is dried over magnesium sulfate. The silica gel chromatography was not needed. ^{1}H NMR (500 MHz, cdcl3) δ 5.56 (s, 1H), 3.27 – 3.13 (m, 2H), 1.98 (d, J = 1.4 Hz, 3H), 1.52 – 1.43 (m, 2H), 1.29 (qt, J = 7.7, 2.8 Hz, 6H), 0.94 – 0.84 (m, 3H).

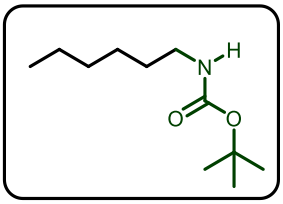
AC-1-81 1d



Dissolve 10mmol (1.0 equiv) of hexylamine in acetonitrile and cool the mixture to 0℃ in an ice water bath. Add triethyl amine (20mmol, 2.0 equiv) and pivalic anhydride (40mmol, 4.0 equiv)

into the cold mixture and stir overnight. The next day, the mixture is concentrated first and added water and stir for another 15 min. Then, the mixture is removed from the ice water bath and diluted with 10 mL of water. Then the product is extracted with DCM (1×15mL) and washed with sulfuric acid (2×15mL), saturated solution sodium bicarbonate (1×15mL), and water (1×15mL). Then, the mixture is dried over magnesium sulfate. The silica gel chromatography is run at 6% EtOAc/Hexane. ^{1}H NMR (500 MHz, cdcl3) δ 5.61 (s, 1H), 3.26 – 3.18 (m, 2H), 1.52 – 1.44 (m, 2H), 1.33 – 1.28 (m, 6H), 1.19 (s, J = 0.9 Hz, 9H), 0.91 – 0.84 (t, 3H).

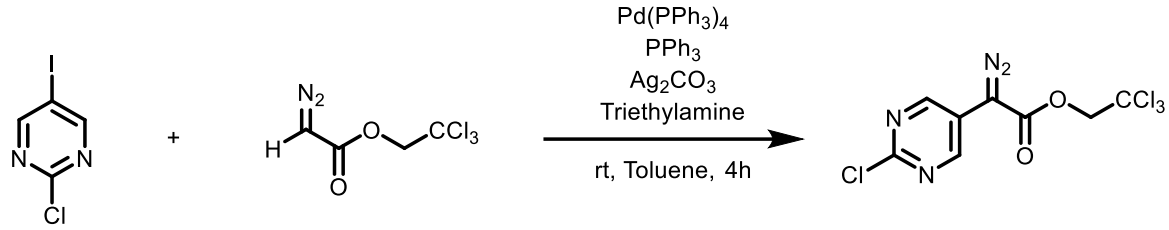
AC-1-102 1a



Dissolve 10mmol (1.0 equiv) of hexylamine and 15mmol (1.5 equiv) of ditertbutyl decarbonate in 150 mL water in a 500 mL round bottom flask for 12 hours at room temperature. The next day, dissolve the reaction mixture into 200 mL $CDCl_3$. The mixture is then transferred to a separate funnel to be washed with water (3×200mL). The organic layer is then dried over sodium sulfate. After the concentration, no further purification is needed. ^{1}H NMR (500 MHz, cdcl3) δ 4.49 (s, 1H), 3.10 (t, J = 6.7 Hz, 3H), 1.44 (m, 7H), 1.35 – 1.20 (s, 9H), 0.93 – 0.84 (t, 3H).

Aryldiazoacetate Derivatives

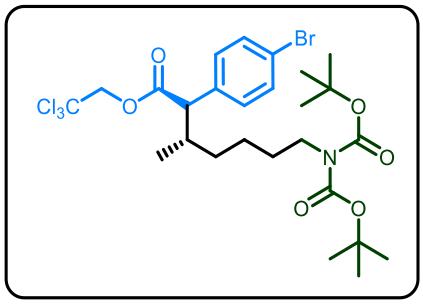
AC-1-232



To a 250 mL of RBF equipped with a magnetic stir-bar and evacuated and purged with nitrogen is added Tetrkis (tri phenyl phosphine) palladium, triphenylphosphine, 2-chloro-5-iodopyridine and silver carbonate are suspended in toluene (30mL) under nitrogen. Then, followed by addition of triethylamine and 2,2,2-trichloroethyl 2-diazoacetate, the resulting solution is stirred at room temperature for 4h and checked by TLC for completion. After the reaction is done, then a plug is run with 15% Et_2O/Hexane to separate and collect the yellow band. The silica gel chromatography was run by Biotage with 10%-15%-20% Et_2O/Hexane.^{1}H NMR ($CDCl_3$): ^{1}H NMR (500 MHz, cdcl3) δ 8.79 (d, J = 0.7 Hz, 2H), 4.94 (s, 2H).

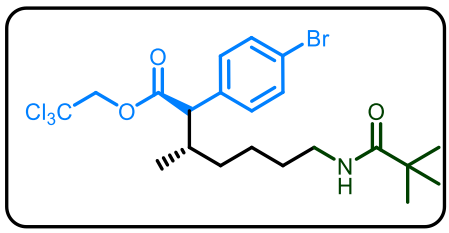
C-H Insertion Products

AC-1-113 3c



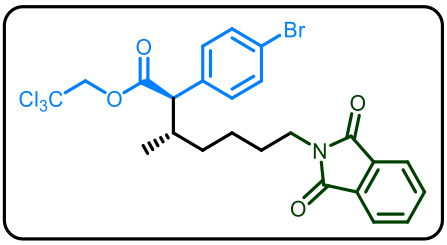
The product was obtained by general procedure (4). The silica gel chromatography was run by Biotage with 5-10% Et_2O/Hexane. ^1H NMR (600 MHz, $cdcl_3$) δ 7.44 (ddd, *J* = 8.4, 2.4, 1.3 Hz, 2H), 7.25 – 7.19 (m, 2H), 4.78 – 4.73 (m, 1H), 4.63 (dq, *J* = 12.0, 1.3 Hz, 1H), 3.45 – 3.31 (m, 3H), 2.30 – 2.19 (m, 1H), 1.59 (d, *J* = 9.0 Hz, 2H), 1.46 – 1.44 (m, 19H), 1.44 – 1.38 (m, 3H), 1.20 – 1.12 (m, 2H), 1.08 – 1.02 (m, 3H).

AC-1-93 3d



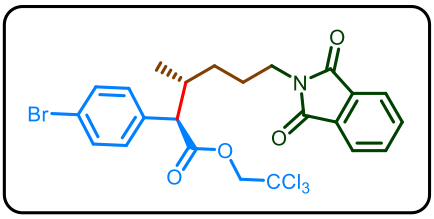
The product was obtained by general procedure (4). The silica gel chromatography was run by Biotage with 8% EtOAc/Hexane. ^1H NMR (600 MHz, $cdcl_3$) δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 5.53 (s, 1H), 4.76 (d, *J* = 12.1 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 3.36 (d, *J* = 10.7 Hz, 1H), 3.14 (q, *J* = 6.5 Hz, 2H), 2.23 (d, *J* = 10.8 Hz, 1H), 1.43 – 1.21 (m, 4H), 1.16 (s, 9H), 1.05 (d, *J* = 6.5 Hz, 4H), 0.95 (t, *J* = 11.3 Hz, 1H).

AC-1-222 3e



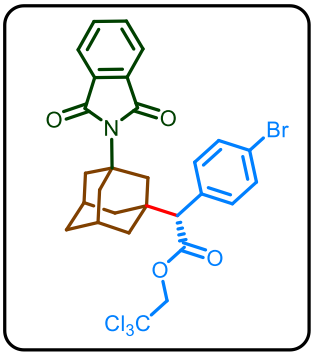
The product was obtained by general procedure (4). The silica gel chromatography was run by Biotage with 10%-15% Et_2O/Hexane. ^1H NMR (500 MHz, cdcl$_3$) δ 7.82 (dt, *J* = 5.4, 3.1 Hz, 2H), 7.70 (dt, *J* = 5.7, 3.0 Hz, 2H), 7.41 (dd, *J* = 8.5, 2.4 Hz, 2H), 7.25 – 7.18 (m, 2H), 4.75 (dd, *J* = 11.9, 1.7 Hz, 1H), 4.61 (dd, *J* = 11.9, 1.9 Hz, 1H), 3.58 (tdd, *J* = 7.4, 2.4, 1.1 Hz, 2H), 3.36 (d, *J* = 10.6 Hz, 1H), 2.29 – 2.17 (m, 1H), 1.61 – 1.41 (m, 2H), 1.35 (tdd, *J* = 13.4, 7.3, 2.0 Hz, 1H), 1.28 – 1.13 (m, 2H), 1.03 (dd, *J* = 6.6, 1.8 Hz, 3H), 1.00 – 0.85 (m, 1H).

AC-1-200 5a



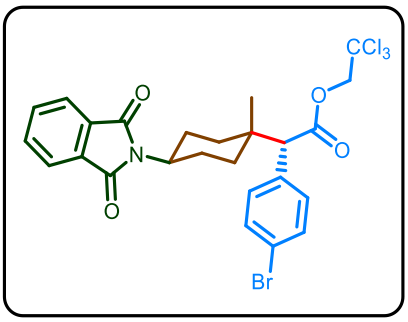
The product was obtained by general procedure (4). The silica gel chromatography was run by Biotage with 6%-12% Et_2O/Hexane. ^1H NMR (500 MHz, cdcl$_3$) δ 7.80 (dt, *J* = 7.1, 3.6 Hz, 2H), 7.71 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.35 – 7.30 (m, 2H), 7.20 – 7.15 (m, 2H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 3.59 – 3.46 (m, 2H), 3.36 (d, *J* = 10.7 Hz, 1H), 2.27 (dtt, *J* = 16.7, 9.8, 3.7 Hz, 1H), 1.76 – 1.65 (m, 1H), 1.60 – 1.47 (m, 1H), 1.31 – 1.15 (m, 2H), 1.05 (d, *J* = 6.5 Hz, 3H).

AC-1-160 5c



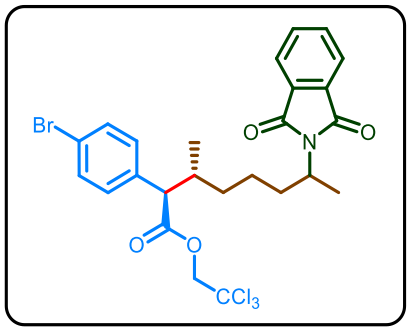
The product was obtained by general procedure (4). The silica gel chromatography was run by Biotage with 10% EtOAc/Hexane. ^{1}H NMR (600 MHz, cdcl$_3$) δ 7.74 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.66 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.48 – 7.42 (m, 2H), 7.34 – 7.27 (m, 2H), 4.82 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 3.51 (s, 1H), 2.49 – 2.30 (m, 7H), 2.24 (q, *J* = 3.2 Hz, 2H), 1.83 – 1.66 (m, 3H), 1.58 (dt, *J* = 38.9, 12.3 Hz, 3H).

AC-1-183 5d



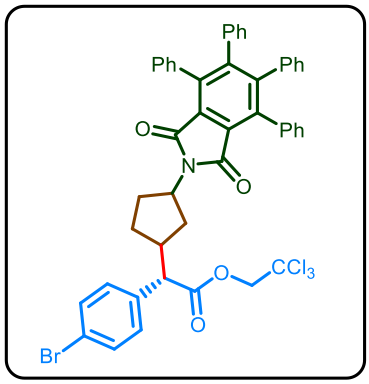
The product was obtained by general procedure (4). The silica gel chromatography was run by Biotage with 8%-10%-15% Et$_2$O/Hexane. ^{1}H NMR (600 MHz, cdcl$_3$) δ 7.84 – 7.76 (m, 2H), 7.73 – 7.66 (m, 2H), 7.51 – 7.43 (m, 2H), 7.36 – 7.28 (m, 2H), 4.86 – 4.81 (m, 1H), 4.65 – 4.59 (m, 1H), 4.01 (dddd, *J* = 12.5, 9.5, 4.6, 2.5 Hz, 1H), 3.56 (d, *J* = 1.5 Hz, 1H), 2.52 – 2.35 (m, 2H), 1.69 – 1.52 (m, 6H), 1.23 (d, *J* = 1.5 Hz, 3H).

AC-1-161 5d



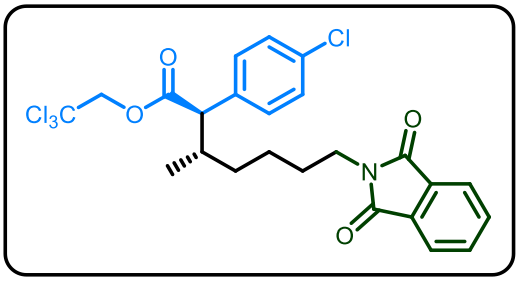
The product was obtained by general procedure (4). The silica gel chromatography was run by Biotage with 8%-10% EtOAc/Hexane. ^{1}H NMR (600 MHz, cdcl$_3$) δ 7.84 – 7.77 (m, 7H), 7.71 (tt, *J* = 3.8, 2.0 Hz, 8H), 7.40 (dd, *J* = 15.4, 8.0 Hz, 8H), 7.19 (dd, *J* = 10.7, 8.0 Hz, 9H), 4.76 – 4.71 (m, 4H), 4.60 (d, *J* = 12.0 Hz, 2H), 4.24 (h, *J* = 6.7 Hz, 5H), 3.32 (d, *J* = 10.7 Hz, 3H), 2.27 – 2.10 (m, 6H), 2.05 – 1.94 (m, 4H), 1.93 – 1.80 (m, 3H), 1.49 (ddq, *J* = 23.6, 13.2, 6.3 Hz, 5H), 1.40 (dd, *J* = 7.1, 3.3 Hz, 15H), 0.98 (dt, *J* = 13.9, 6.8 Hz, 18H), 0.88 (t, *J* = 6.9 Hz, 12H). Due to the presence of the two diastereomers in the purified sample and the 1:1.6/1:1.5 ratio between the two major products, the integration cannot fully match with the proton counts for the desired products. Therefore, the identification of the desired product is based on the chemical shifts of the signals as well as the spin-spin split pattern of the peaks.

AC-1-236 7d



The product was obtained by general procedure (4). The silica gel chromatography was run by Biotage with 8%-10% Et_2O/Hexane. ^1H NMR (500 MHz, cdcl$_3$) δ 7.45 – 7.40 (m, 2H), 7.25 – 7.19 (m, 8H), 7.10 (dtt, *J* = 6.3, 3.6, 1.4 Hz, 4H), 6.88 (dqd, *J* = 3.9, 2.7, 1.6 Hz, 6H), 6.73 (ddt, *J* = 6.3, 2.7, 1.4 Hz, 4H), 4.74 (dd, *J* = 12.0, 1.1 Hz, 1H), 4.62 (dd, *J* = 11.9, 1.2 Hz, 1H), 3.39 (d, *J* = 11.2 Hz, 1H), 2.31 – 2.20 (m, 1H), 2.15 (dt, *J* = 13.3, 7.6 Hz, 1H), 1.95 (dddd, *J* = 17.7, 14.8, 10.9, 7.3 Hz, 2H), 1.45 – 1.32 (m, 2H), 1.26 (d, *J* = 8.6 Hz, 1H).

AC-1-207



The product was obtained by general procedure (4). The silica gel chromatography was run by Biotage with 8%-10% EtOAc/Hexane. ^1H NMR (600 MHz, cdcl$_3$) δ 7.90 – 7.81 (m, 2H), 7.78 – 7.69 (m, 2H), 7.30 (ddq, *J* = 6.1, 4.2, 2.1 Hz, 4H), 4.78 (dd, *J* = 11.8, 1.5 Hz, 1H), 4.64 (dd, *J* = 12.0, 1.5 Hz, 1H), 3.61 (dtd, *J* = 8.4, 6.9, 5.3 Hz, 2H), 3.40 (dd, *J* = 10.7, 1.4 Hz, 1H), 2.31 – 2.22 (m, 1H), 1.64 – 1.45 (m, 2H), 1.39 (qdd, *J* = 13.3, 7.7, 2.3 Hz, 1H), 1.25 – 1.17 (m, 2H), 1.06 (dd, *J* = 6.6, 1.3 Hz, 3H), 1.02 – 0.93 (m, 1H).

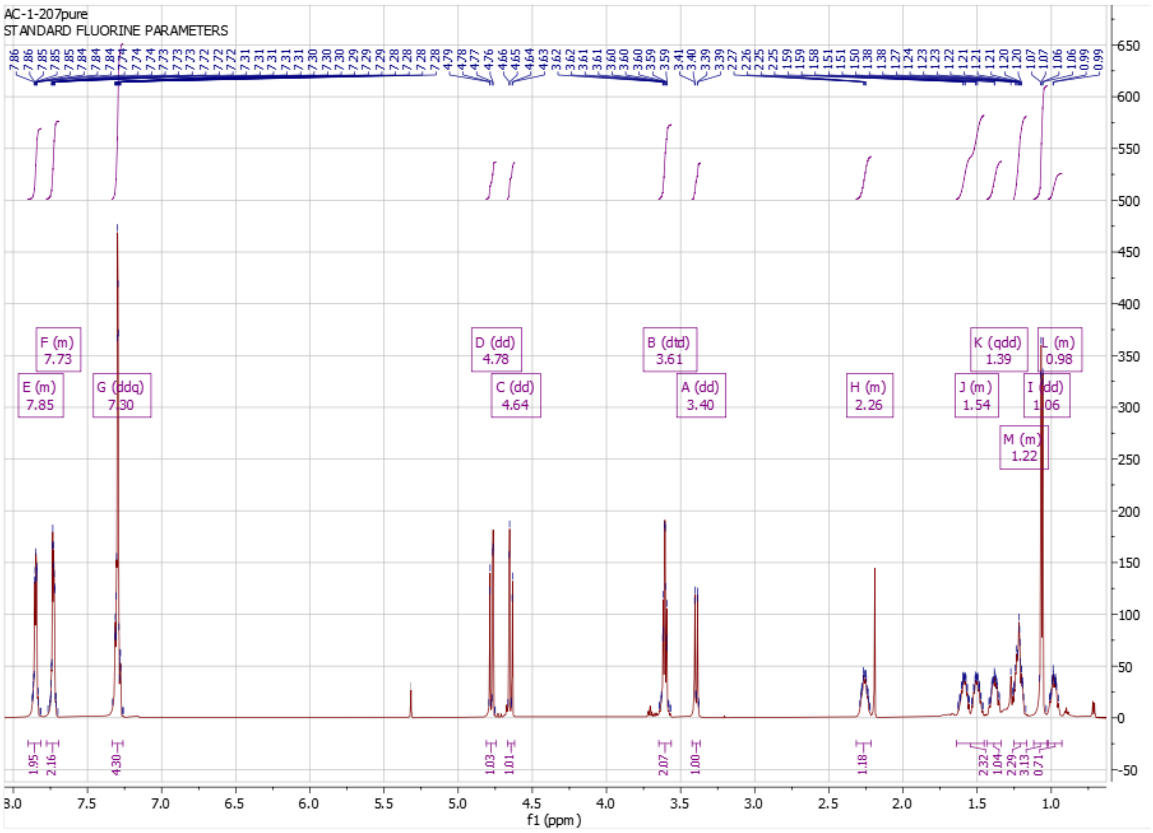
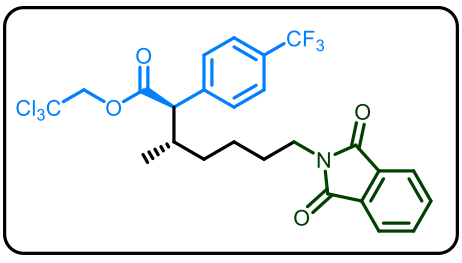


Figure 2.23 Purified NMR for *p*-Cl phenyldiazoacetate

AC-1-208



The product was obtained by general procedure (4). The silica gel chromatography was run by Biotage with 8%-10% EtOAc/Hexane. ^{1}H NMR (600 MHz, cdcl$_3$) δ 7.82 (tp, *J* = 5.5, 2.9 Hz, 2H), 7.77 – 7.65 (m, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 4.76 (dd, *J* = 11.9, 1.4 Hz, 1H), 4.62 (dd, *J* = 12.0, 1.4 Hz, 1H), 3.63 – 3.53 (m, 2H), 3.48 (d, *J* = 10.6 Hz, 1H), 2.29

(tqd, *J* = 9.3, 5.5, 2.0 Hz, 1H), 1.61 – 1.43 (m, 2H), 1.43 – 1.31 (m, 1H), 1.30 – 1.12 (m, 2H), 1.06 (dd, *J* =6.5, 1.2 Hz, 3H), 1.03 – 0.91 (m, 1H).

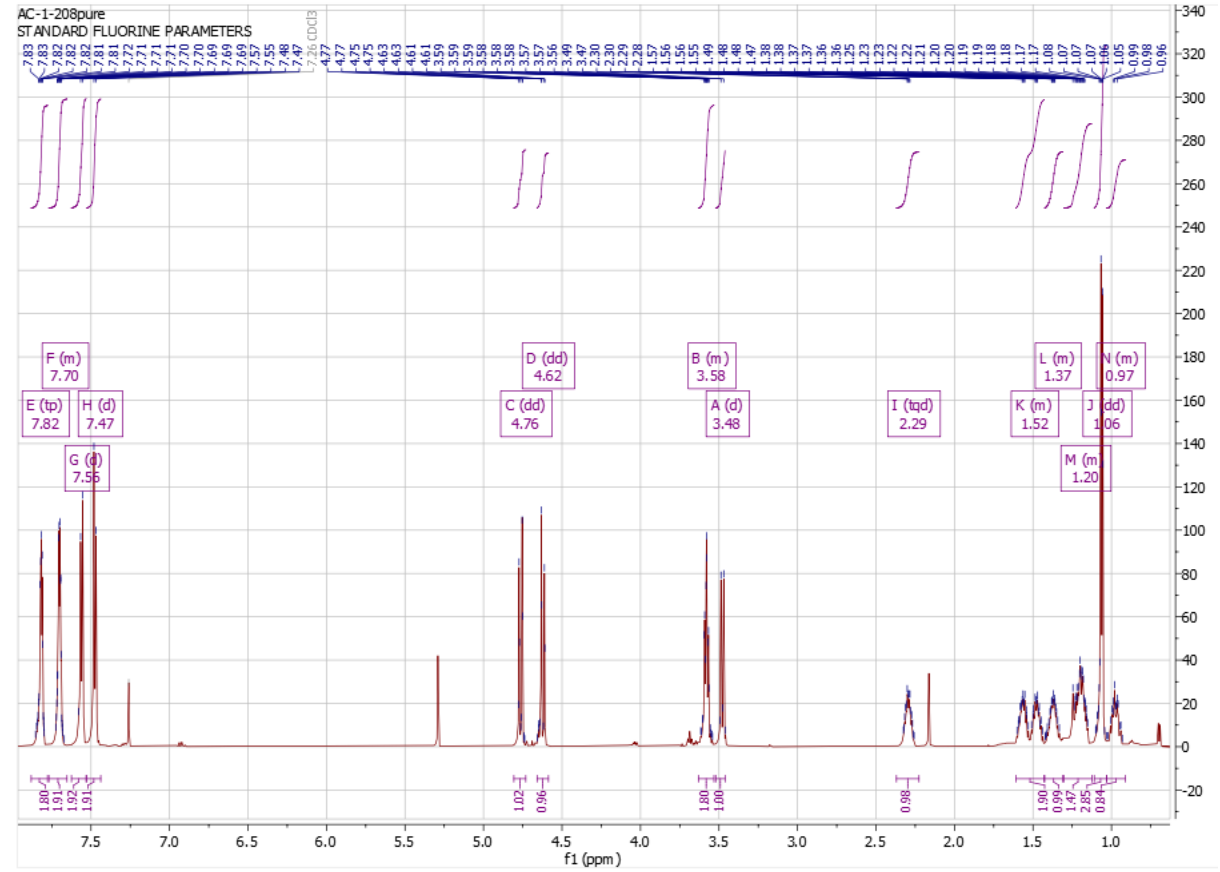
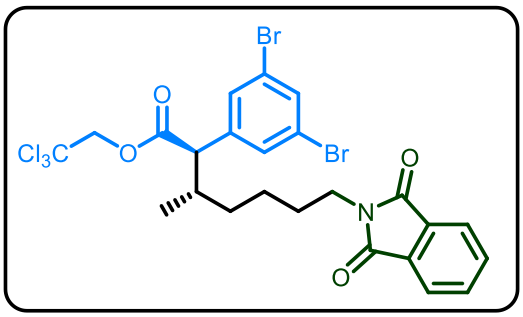


Figure 2.24 Purified NMR for *p*-CF_3 phenyldiazoacetate

AC-1-209



The product was obtained by general procedure (4). The silica gel chromatography was run by Biotage with 8%-10% EtOAc/Hexane. ^{1}H NMR (600 MHz, cdcl$_3$) δ 7.87 – 7.78 (m, 2H), 7.75 – 7.67 (m, 2H), 7.63 (p, *J* = 1.9 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.15 (dq, *J* = 8.2, 1.6 Hz, 1H), 4.77 (dt, *J* = 12.0, 1.6 Hz, 1H), 4.61 (dt, *J* = 12.0, 1.5 Hz, 1H), 3.59 (td, *J* = 7.3, 2.6 Hz, 2H), 3.33 (dd, *J* = 10.5, 1.3 Hz, 1H), 2.27 – 2.17 (m, 1H), 1.63 – 1.54 (m, 1H), 1.49 (ddq, *J* = 13.2, 10.5, 6.9 Hz, 1H), 1.42 – 1.32 (m, 1H), 1.26 – 1.15 (m, 3H), 1.03 (dt, *J* = 6.6, 1.6 Hz, 3H).

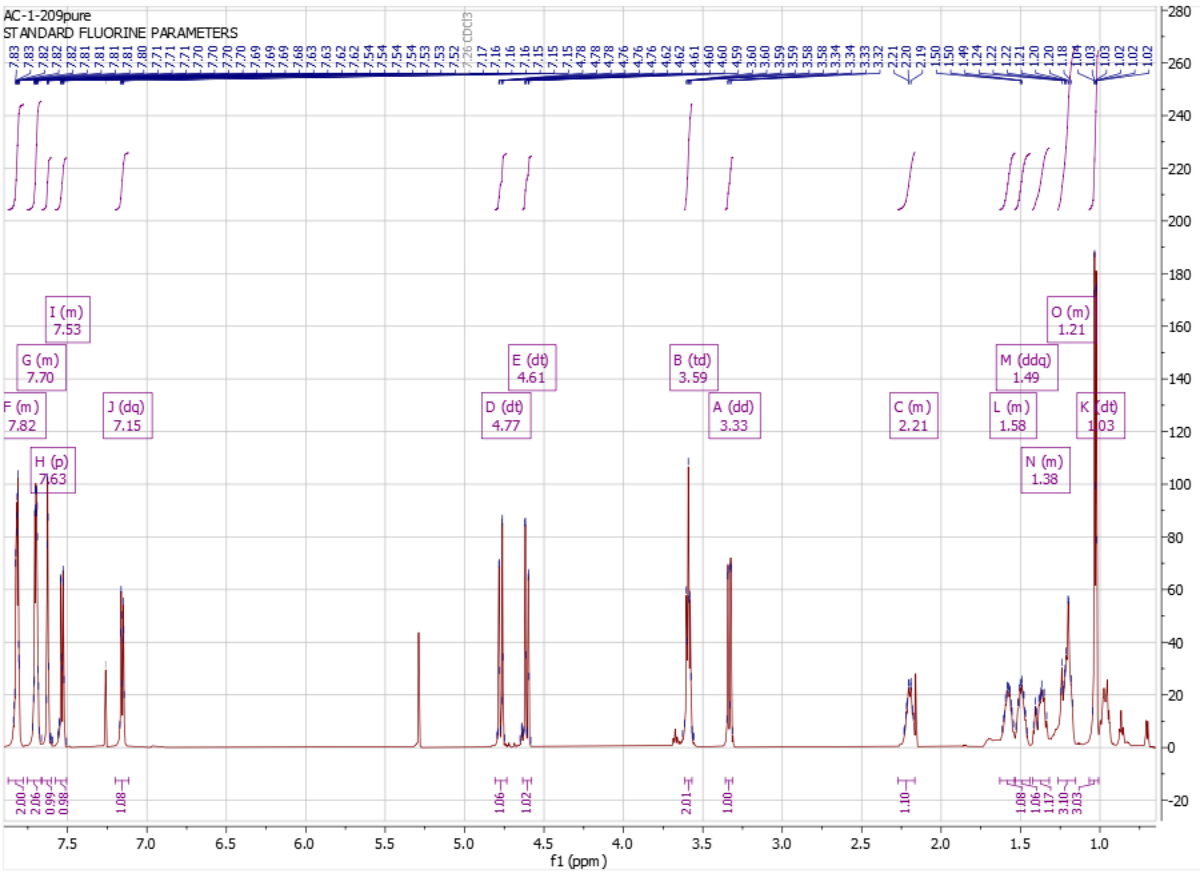
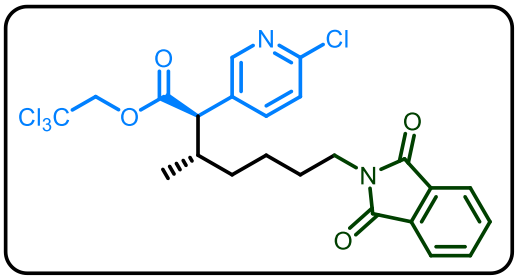


Figure 2.25 Purified NMR for 3,5-Br phenyldiazoacetate

AC-1-215



The product was obtained by general procedure (4). The silica gel chromatography was run by Biotage with 8%-10% EtOAc/Hexane ^{1}H NMR (600 MHz, cdcl$_3$) δ 8.32 (d, *J* = 2.5 Hz, 1H), 7.86 – 7.79 (m, 2H), 7.77 – 7.67 (m, 3H), 7.31 (dd, *J* = 8.3, 1.4 Hz, 1H), 4.76 (dd, *J* = 12.0, 1.4 Hz, 1H), 4.65 (dd, *J* = 12.0, 1.3 Hz, 1H), 3.59 (td, *J* = 7.1, 1.3 Hz, 2H), 3.44 (d, *J* = 10.2 Hz, 1H), 2.23 (qt, *J* = 7.6, 5.1 Hz, 1H), 1.62 – 1.45 (m, 2H), 1.41 – 1.33 (m, 1H), 1.30 – 1.15 (m, 2H), 1.05 (d, *J* = 6.3 Hz, 3H), 1.02 – 0.94 (m, 1H).

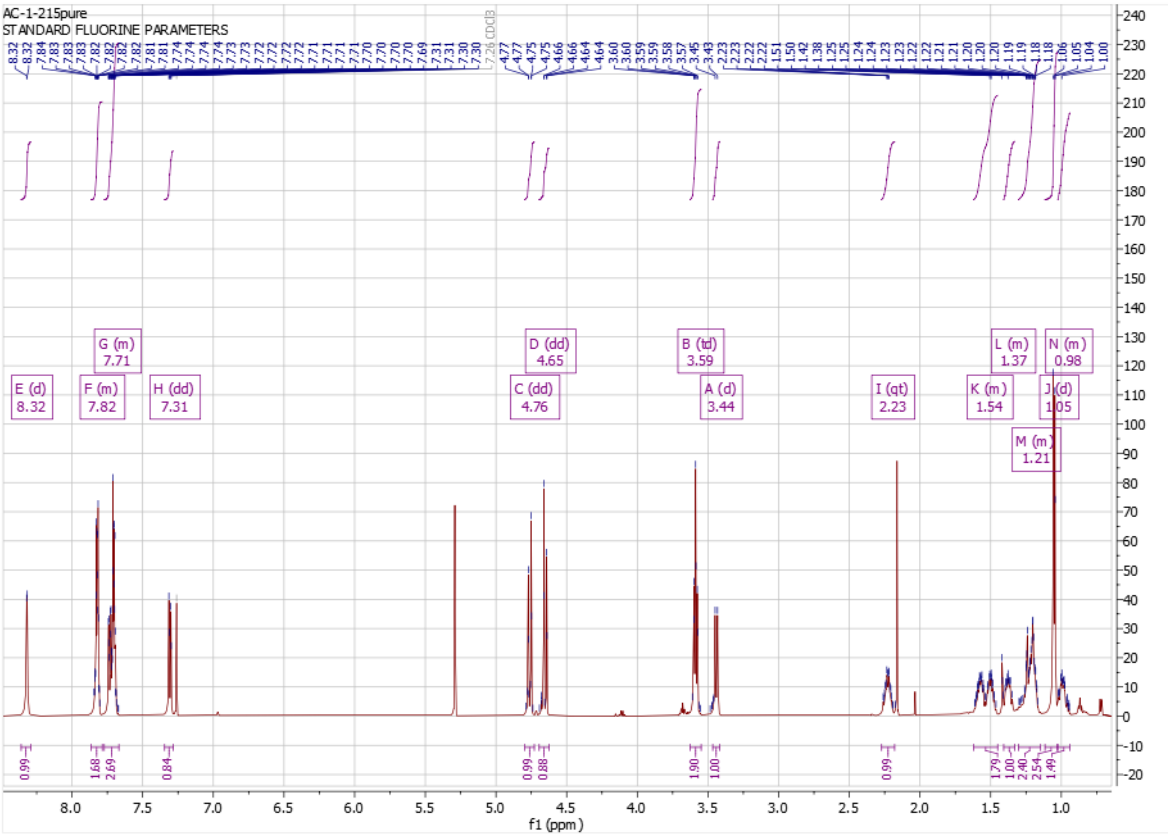
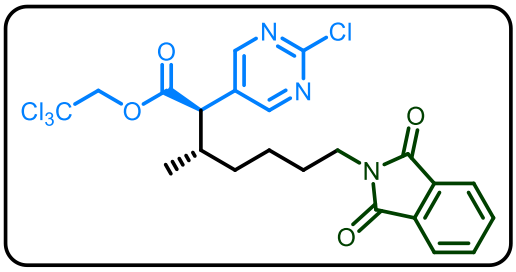


Figure 2.26 Purified NMR for *p*-Cl-pyridyldiazoacetate

AC-1-221



The product was obtained by general procedure (4). The silica gel chromatography was run by Biotage with 8%-10% EtOAc/Hexane. ^{1}H NMR (500 MHz, cdcl$_3$) δ 8.65 (d, *J* = 2.2 Hz, 2H), 7.89 – 7.77 (m, 2H), 7.76 – 7.65 (m, 2H), 4.81 – 4.76 (m, 1H), 4.72 – 4.67 (m, 1H), 3.61 (td, *J* = 7.1,

2.5 Hz, 2H), 3.48 (dd, *J* = 9.6, 1.5 Hz, 1H), 2.25 (dtt, *J* = 9.7, 6.2, 2.9 Hz, 1H), 1.67 – 1.48 (m, 1H), 1.45 – 1.34 (m, 1H), 1.33 – 1.17 (m, 3H), 1.07 (dd, *J* = 6.7, 2.2 Hz, 3H), 1.05 – 0.99 (m, 1H).

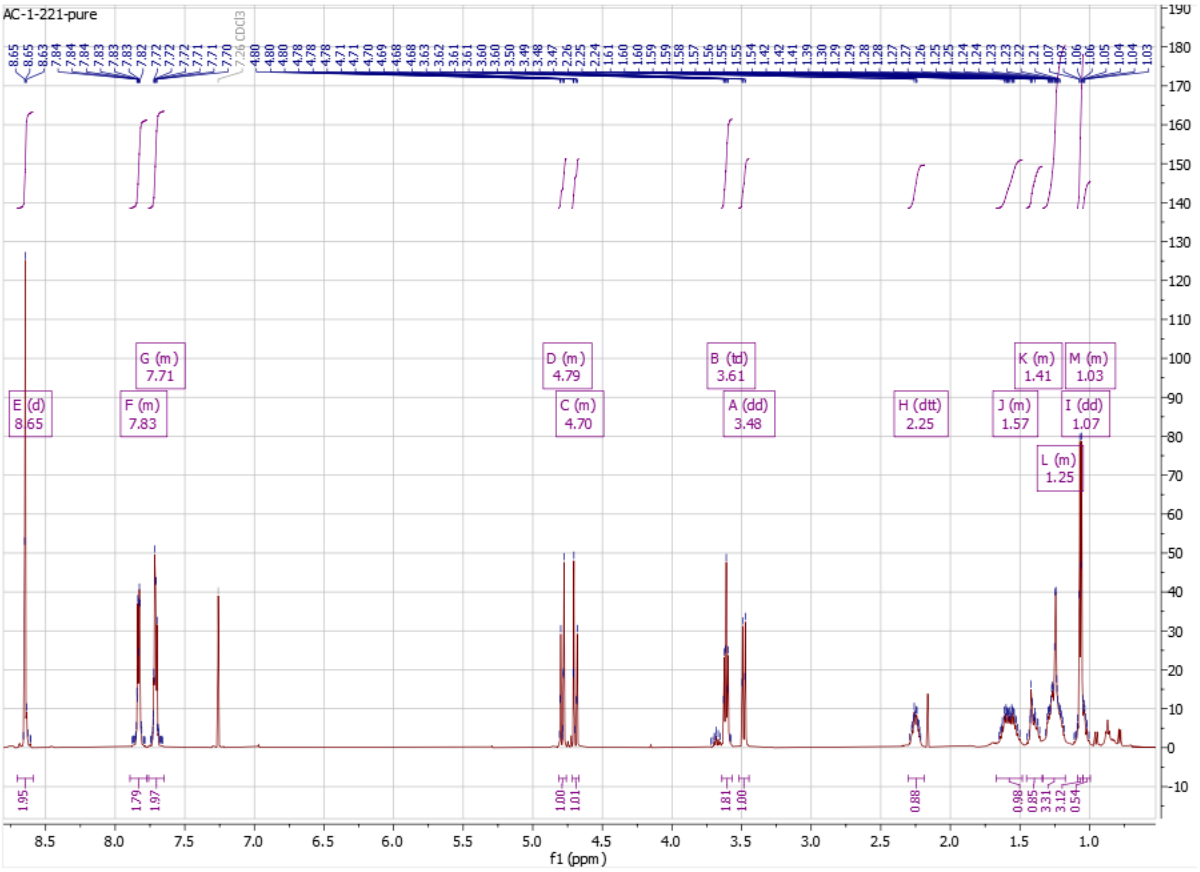


Figure 2.27 Purified NMR for *p*-Cl- pyrimidyldiazoacetate

Reference

[1] Davies, H. M.; Liao, K. Dirhodium tetracarboxylates as catalysts for selective intermolecular C–H functionalization. *Nature Rev. Chem.* **2019,** *3*(6), 347-360.

[2] Davies, H. M.; Ni, A. Enantioselective synthesis of β-amino esters and its application to the synthesis of the enantiomers of the antidepressant Venlafaxine. *Chem. Commun.* **2006**, (29), 3110-3112.

[3] Liu, W.; Ren, Z., Bosse, A. T.; Liao, K.; Goldstein, E. L.; Bacsa, J.; ... Davies, H. M. Catalyst-controlled selective functionalization of unactivated C–H bonds in the presence of electronically activated C–H bonds. *J. Am. Chem. Soc.* **2018**, *140*(38), 12247-12255.

[4] Fu, J.; Ren, Z.; Bacsa, J.; Musaev, D. G.; Davies, H. M. Desymmetrization of cyclohexanes by site-and stereoselective C–H functionalization. *Nature* **2018**, *564*(7736), 395-399.