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Progress towards an Aza-Michael Addition to Ketones

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ABSTRACT

POTTER, BOWMAN Progress towards an Aza-Michael Addition to Ketones.
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The aza-Michael addition to unsaturated ketones under neutral to mildly basic condition is a difficult transformation due to the inherent unreactivity of ketones toward the addition of weak nucleophiles. This thesis reports on efforts to develop an environmentally friendly, stereoselective and low-cost organo-catalyzed aza-Michael reaction between unsaturated ketones and nitrogen nucleophiles, such as phthalimide, under neutral to mildly basic conditions using the most inexpensive chiral secondary amine catalyst, proline.[1]

Both proline and the organic base triethylamine were found to be catalytic in the testing platform of cyclohexen-2-one and phthalimide, and another testing platform of 4-hexen-3-one and phthalimide. Likewise, when screened against proline derivatives and imidazolines (all secondary amines), proline demonstrated the highest yield and enantioselectivity for aza-Michael Addition reactions to ketones. Triethylamine was also determined to be the optimal organic base co-catalyst, in terms of enantioselectivity. The yield and enantioselectivity both heavily depend upon the organic solvent used; indeed, the organic solvent acetonitrile was ideal for yield of the reactions, though with a low enantioselectivity; however, ethyl acetate demonstrated the highest enantioselectivity, but with a lower yield. The highest enantioselectivity observed was 80% ee.

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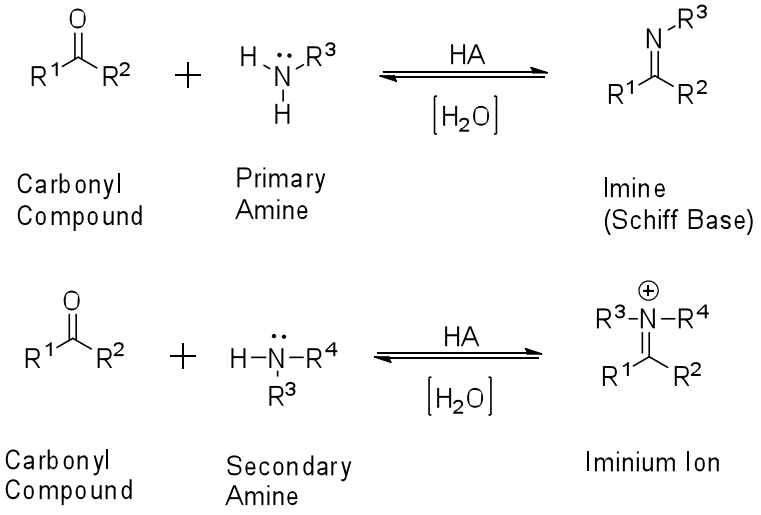
CHAPTER 1

Introduction

The formation of an imine requires two components: an aldehyde or ketone and a primary amine. As demonstrated by Layer[2] this equilibrium affords a reasonable amount of imine, otherwise known as a Schiff base[3], and in an acidic environment an iminium ion is present. Likewise, secondary amines can be condensed with aldehydes and ketones to form iminium ions, without the formation of imines (Scheme 1).

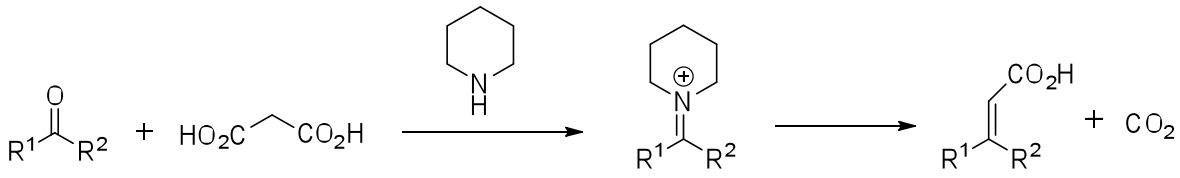
Scheme 1. Formation of Imines and Iminium Ions



Similar to the protonation of a carbonyl group with Brønsted or Lewis acid, the imine/iminium ion is activated towards nucleophilic attack. As Pihko and co-workers acknowledged in their review of iminium cataylsis, the interactions between the electrophilic imine/iminium ion and a nucleophile can be very diverse to include cycloadditions, nucleophilic additions, formation of enamines, and others.[4] In order for these reactions to be catalytic, the amine must be hydrolyzed in the final step of the reaction.

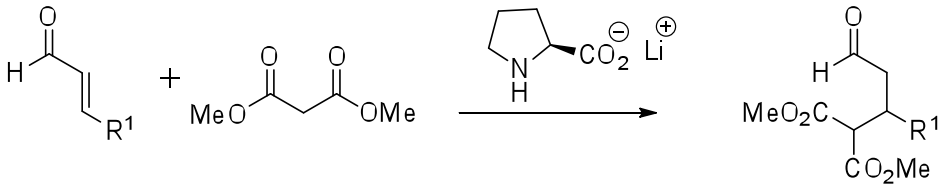
In the late 1890s Knoevenagel discovered the first iminium-catalyzed reaction, a condensation reaction of a carbonyl using a primary or secondary amine catalyst, which was subsequently named after him (Scheme 2).[5,6] While at the time the exact mechanism was unknown, in the subsequent decades the iminium ion pathway was officially studied and recognized.[7]

Scheme 2. Knoevenagel Reaction



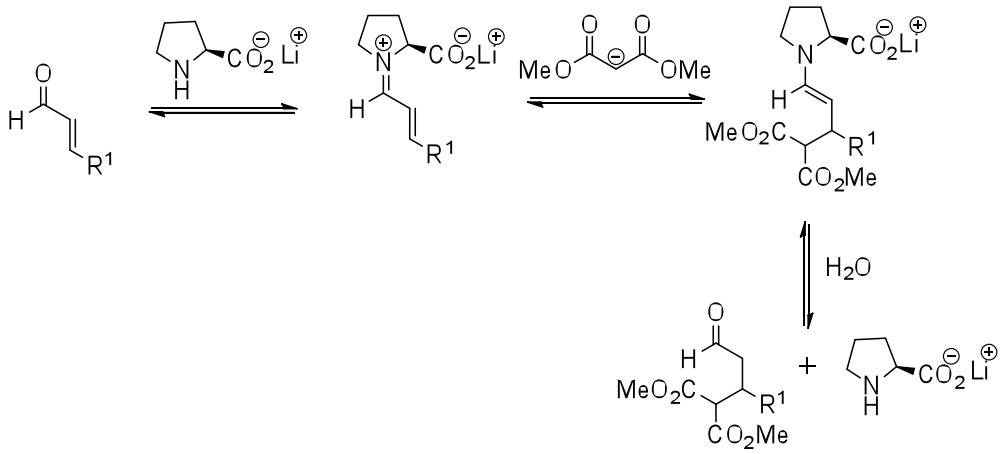
A century later, Yamaguchi reported the first catalytic asymmetric iminium-catalyzed conjugate addition reaction; in other words, a Michael Addition catalyzed by a secondary amine (Scheme 3).[8] This reaction uses an α,β unsaturated carbonyl compound, either an aldehyde or ketone, with a deprotonated form of proline as the secondary amine catalyst; since proline is an amino acid, some have called it the simplest enzyme.[9]

Scheme 3. Yamaguchi Iminium Catalyzed Michael Addition



Scheme 4 depicts an in-depth diagram for the Yamaguchi iminium catalyzed Michael Addition. The deprotonated from of proline forms an iminium ion with the α,β-unsaturated aldehyde. The nucleophilic dimethyl malonate then approaches in the 1,4-conjugate addition pathway allowing for proline to form an enamine; finally, water removes proline through hydrolysis to form the product. It is important to note that proline is regenerated during the reaction and is thus catalytic.

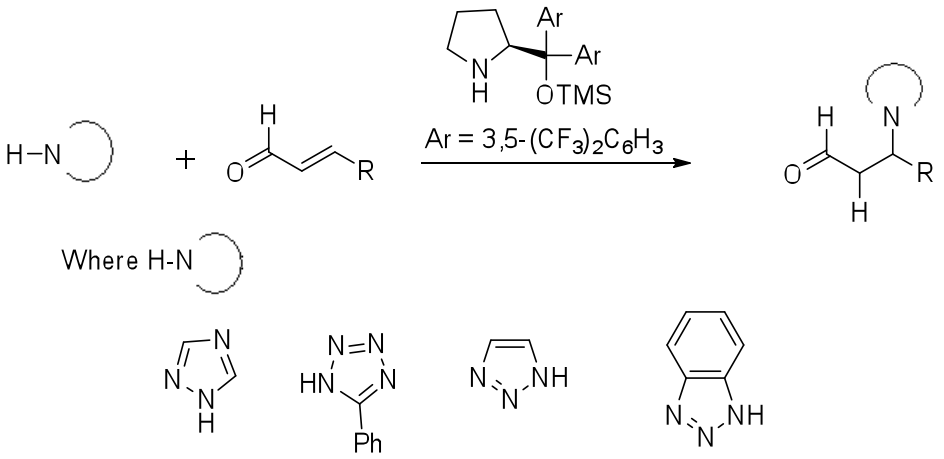
Scheme 4. Mechanistic View of Yamaguchi Iminium Catalyzed Michael Addition



Proline and its derivatives have expanded the nucleophiles for Michael Addition using iminium catalysis to include C-nucleophiles, H-nucleophiles, S-nucleophiles, N-nucleophiles, and O-nucleophiles.[3] Among these, all nucleophiles are able to add to aldehydes and ketones with a secondary amine catalyst; the exception being N-nucleophiles, which using secondary amine catalysis, only adds to aldehydes. Some examples of include research conducted by the MacMillan group which uses silyl amides as the N-nucleophiles to aldehydes with an imidazolidinone catalyst.[10] Córdova and co-workers describe a reaction of hydroxyl amine with aldehydes using a proline derivative as a catalyst.[11,12] The Jørgensen groups published work on a proline derivative catalyzed reaction of N-heterocycles with aldehydes (Scheme 5).[13] The N-nucleophiles include 1,2,4-triazole, tetrazoles, benzotriazole, and 1,2,3-triazole. Another research group conducted a similar reaction with aldehydes and tetrazoles, benzotriazole, or imidizoles but with a chiral imidazolidinone catalyst.[14] Lin and co-workers were able to use pyrazoles as the N-nucleophile with aldehydes and a proline derivative catalyst.[15]

Protected amines have also been shown to be nucleophilic with aldehydes and proline derivative catalyzed.[16] It is important to note the entirety of the reactions use a secondary amine catalyst to perform an Aza-Michael Addition to aldehydes.

Scheme 5. N-Heterocycles used as Nucleophiles by Jórgensen and co-workers



Currently, there are no published results using secondary amine catalysis for ketones and N-nucleophiles in an Aza-Michael mechanism. However, there are examples of Aza-Michael Addition reactions to ketones. While most use metals as catalysts[17], Kim and co-workers used the organic base DBU to promote an Aza-Michael Addition reaction of secondary amines to 3-buten-2-one with good yield.[18] However, there is no mention of iminium catalysis or of enantioselectivity results in this work. Another reaction, developed by Zhao and co-workers, uses a primary amine catalyst to perform an Aza-Michael addition to ketones using 2-pyrazolin-5-ones as nucleophiles.[19] These reactions proceed with excellent yield and ee with methyl, ethyl, and n-Pr ketones. This is the only literature reference that demonstrates an Aza-Michael addition to ketones using iminium

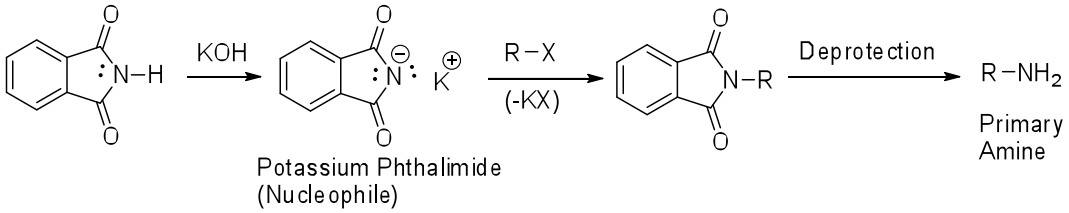
catalysis, albeit with a primary amine catalyst. Clearly, increased research should be performed to examine secondary iminium catalysis of an Aza-Michael addition.

CHAPTER 2

Results and Discussion

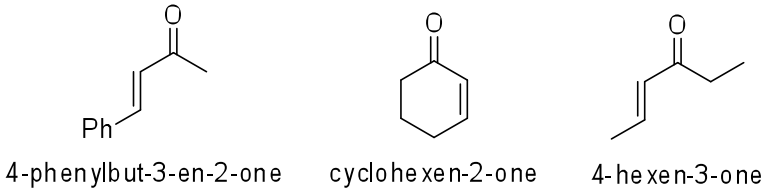
There are two essential components to an Aza-Michael Addition reaction, the α,β-unsaturated carbonyl and N-nucleophile. The N-nucleophile initially investigated was phthalimide. Phthalimide was chosen as it has been shown to be nucleophilic in the Gabriel Primary Amine Synthesis (Scheme 6).[20] This is due to the relative acidic nature of phthalimide (pka 8.3), as the deprotonated form of phthalimide has a high electron density around the nitrogen, which can then undergo a substitution reaction to form a nitrogen-carbon bond. Furthermore, phthalimide has been shown to undergo deprotection reactions to afford a primary amine.[21] Kim and co-workers also demonstrated that phthalimide will add to an α,β-unsaturated ester in a conjugate pathway in the presence of an organic base.[18] This thesis research decided to use phthalimide as the initial nucleophile in the presence of an organic base.

Scheme 6. The Gabriel Amine Synthesis



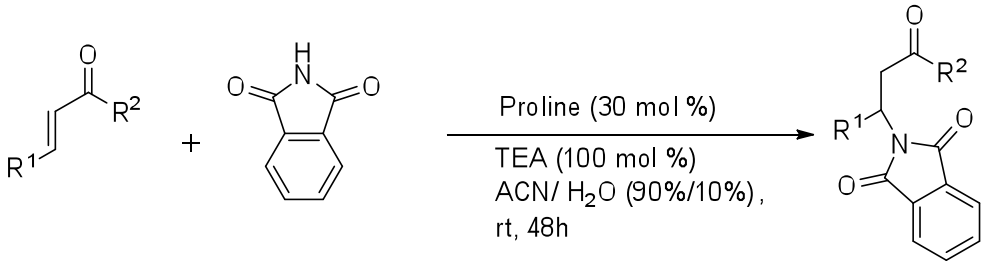
The other essential component of an Aza-Michael Addition, the α,β-unsaturated carbonyl, was also examined. As α,β-unsaturated ketones are the objective of this study, three were selected: an non-cyclic aromatic ketone, a cyclic ketone, and a non-cyclic, non-aromatic ketone (Scheme 7). Upon screening these ketones with phthalimide, organic base, and proline (Scheme 8), it was determined that phthalimide added readily to cyclohexen-2-one and 4-hexen-3-one. However, there was no reaction with 4-phenylbut-3-en-2-one. This could be due to a possible "polystyrene effect" in which the molecule is so highly conjugated that proline cannot form an iminium ion with the ketone, thus not activating the ketone to nucleophilic addition.

Figure 1. Preliminary Ketones



It is important to note that for both cyclohexen-2-one and 4-hexen-3-one the exclusion of the organic base triethylamine (TEA) did not allow for the reaction to proceed. Upon the removal of proline, some background reaction did occur, and the abstraction of both proline and TEA resulted in no reaction occurring. Water was also determined to enhance the reaction as its removal resulted in a decrease in yield.

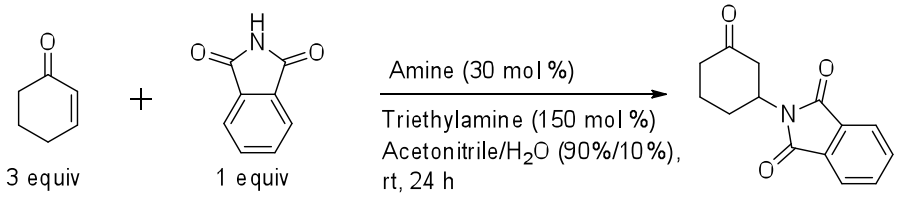
Scheme 7. Initial Ketone Screening Reaction

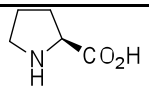
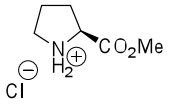
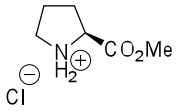
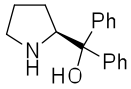
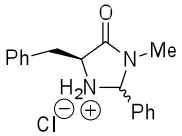
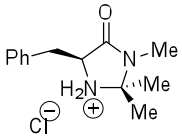


The addition of phthalimide to cyclohexen-2-one (69% isolated yield) was more robust than with 4-hexen-3-one (16% isolated yield). From this, cyclohexen-2-one was chosen as the testing α,β-unsaturated ketone for this Aza-Michael Addition.

As secondary amine catalyst proline was used in the initial test reactions, the question arose as to whether it was the optimal catalyst. Thus, several of its derivatives were investigated as well as some MacMillan catalysts, imidazolines, as displayed in Table 1. Tetradecane was used as an internal standard as it would not interfere with the reaction, and can be easily detected by GC-MS.

Table 1. Results of screening of various amine catalysts in the Aza-Michael Addition of cyclohexen-2-one and phthalimide



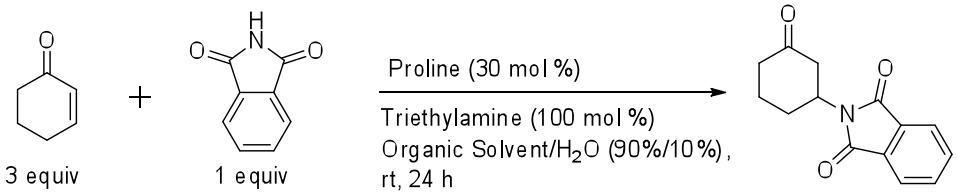
Entry	Amine	Conversion[a] (%)
1		100
2	 (In-House Prepared)	100
3	 (Commercially Available)	83
4		28
5		28
6		29

[a]Yield determined by Internal Standards using GC-MS

Proline and methyl ester proline each had excellent yields by internal standards (Table 1, entries 1-3). Thus, it would appear that the carboxylic acid moiety is not essential for the reaction. However, the more hindered diphenyl-2-pyrrolidinemethanol had a much lower rate of conversion (Table 1, entry 4). This could be due to the substitution of sterically hindered groups for the carboxylic acid group of proline, not allowing for the formation of iminium ions. Also, the imidazoline catalysts had a lower rate of conversion (Table 1, entries 5-6). The isolated yield of the methyl proline catalyzed reaction was only 30% when compared to the isolated yield of proline (69%). Thus, proline was chosen as the testing platform catalyst.

The environment of the reaction was also investigated with common organic solvents (Table 2). Acetonitrile (Table 2, entry 7) yielded the highest conversion percent. It was surprising that the conversion percent for the solvent acetone was as high as 77% as proline can form iminium ions with acetone (Table 2, entry 2). This could indicate a preference of proline to form iminium ions with α,β-unsaturated ketones as opposed to acetone.

Table 2. Results of various solvents in the Aza-Michael Addition of cyclohexen-2-one and phthalimide

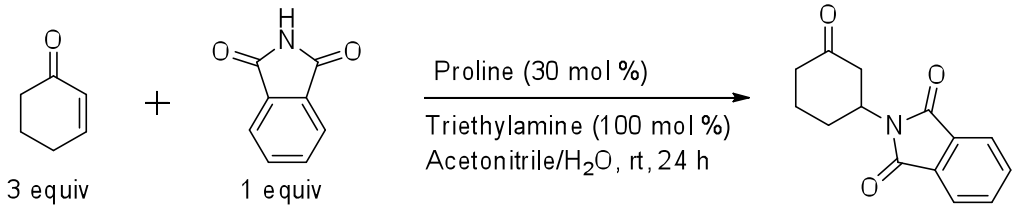


Entry	Organic Solvent	Conversion[a] (%)
1	CH_2Cl_2	18
2	Acetone	77
3	EtOAc	24
4	Ethanol (95 %)	75
5	DMSO	38
6	THF	39
7	ACN	100
8	Toluene	49

[a]Yield determined by Internal Standards using GC-MS

As water had been shown to be correlated to yield in the screening reactions, more investigation was needed to determine the optimal amount of water needed for the reaction. We believed that water was an essential component to the reaction as it is needed to hydrolyze proline from the iminium ion/enamine after phthalimide had been added. Having water readily available would thus be important to the turnover rate of proline.

Table 3. Results of various acetonitrile/H_2O ratios in the Aza-Michael Addition of cyclohexen-2-one and phthalimide



Entry	Acetonirtile/H_2O (%)	Conversion[a] (%)
1	100/0	52
2	90/10	98
3	80/20	100
4	70/30	100
5	60/40	100
6	50/50	100
7	40/60	100
8	30/70	100
9	20/80	99
10	10/90	93

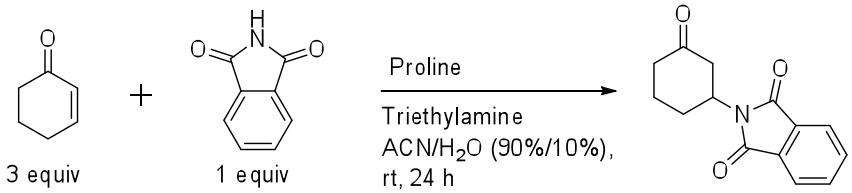
[a]Yield determined by Internal Standards using GC-MS

As displayed in Table 3, upon increasing the ratio of water in the reaction, the conversion increases or stays relatively constant. Without water, the conversion is almost halved (Table 3, entry 1), which supports the earlier stipulation that water is necessary for the reaction. It was surprising that even in highly aqueous environments, the reaction proceeds readily (Table 3, entries 7-10). However, the internal standard tetradecane is not soluble in water, and thus may have concentrated in the organic layer. When the sample was analyzed, the concentration of the internal standard tetradecane could have

been artificially inflated, reflecting a higher yield for the more aqueous entries in Table 3. Though, the Aza-Michael Addition adduct was present in the indicating that the reaction did proceed.

During this time, proline was assumed to be a catalyst for this reaction, while the direct role of TEA was unknown. TEA was needed for the reaction to occur, but on what scale? Various mol percents of each were tested in Table 4.

Table 4. Results of various mol percents of catalyst in the Aza-Michael Addition of cyclohexen-2-one and phthalimide

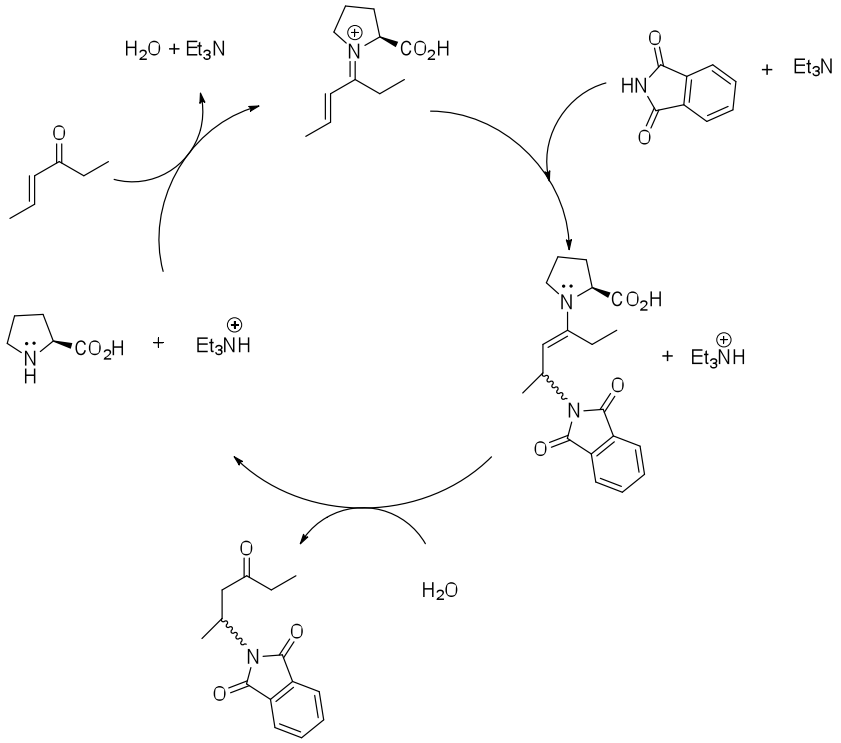


Entry	Proline mol percent	TEA mol percent	Conversion[a] (%)
1	50	100	100
2	30	100	100
3	20	100	49
4	10	100	47
5	5	100	15
7	30	350	12
8	30	100	93
9	30	75	100
10	30	50	100
11	30	25	100

[a]Yield determined by Internal Standards using GC-MS

As displayed in Table 4, proline and TEA were shown to be catalysts for this reaction. Using 30 mol percent of proline demonstrated full conversion (Table 4, entry 2), however a further decrease of proline significantly impacted conversion (Table 4, entries 3-4). A decrease in the mol percent of TEA actually increases the conversion of the reaction (Table 4, entries 7-11). This would contradict conventional thinking, as the more TEA in the reaction would increase the amount of deprotonated phthalimide, thus allowing for more addition. In conclusion, both proline and TEA demonstrated catalytic activity which can be described by the following proposed catalytic cycle (Scheme 8). This cycle closely follows one proposed by Jørgensen and co-workers, save that they did not identify a catalytic base[13].

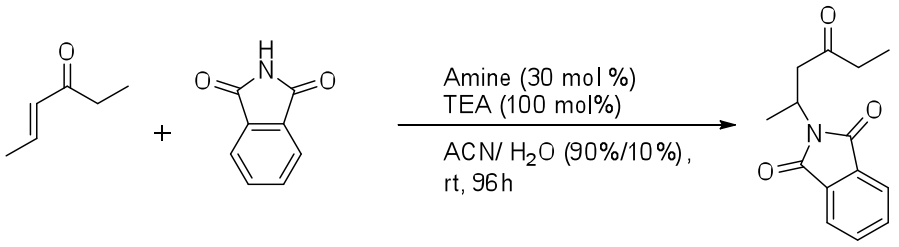
Scheme 8. Proposed Catalytic Cycle

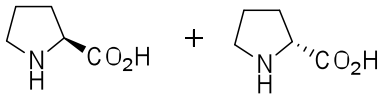
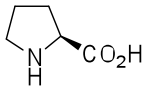
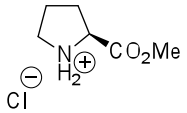
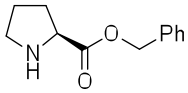
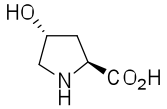


While cyclohexen-2-one appeared to be an optimal testing platform for a secondary amine catalyzed Aza-Michael Addition to ketones, the adduct of the reaction with phthalimide could not be analyzed by chiral NP HPLC or chiral GC-MS. In both instances, the adduct presented itself as a single, inseparable peak. Using extensive temperature ramping programs with the GC-MS, or even a three solvent system with NP HPLC not were able to resolve the adduct peak. Thus, 4-hexen-3-one became the testing platform as its adduct with phthalimide was able to be separated using chiral NP HPLC.

Many of the same reaction parameters were re-tested with the 4-hexen-3-one, phthalimide adduct with the intention of maximization of enantioselectivity. As the conversions by diphenyl-pyrrolidinemethanol and the imidazolidines were low for cyclohexen-2-one, they were not included (Table 1, entries 4-6). Benzyl ester proline[22] and 4-hydroxyproline were supplemented for them (Table 5). Benzyl ester proline was used methyl ester proline had excellent conversion; with the concept being that by making the carboxylic acid moiety more sterically hindered, one face of the iminium ion would be blocked allowing for an enantioselective addition of phthalimide. 4-Hydroxyproline was attempted as the carboxylic acid moiety remained intact but the iminium ion would have different sterics than with proline.

Table 5. Results of screening various amines in the Aza-Michael Addition of 4-hexen-3-one with phthalimide



Entry	Amine	ee[a] (%)
1[b]		0
2[c]		1
3[d]		19
4	 (In-House Prepared)	12
5		11
6		13

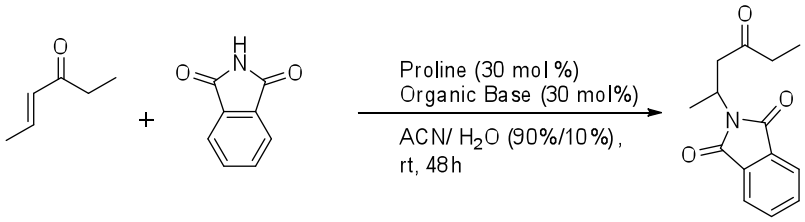
[a]Determined by chiral NP HPLC
[b]In 21days
[c]In 7days
[d]In 48h

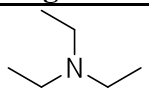
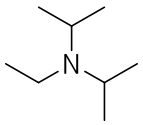
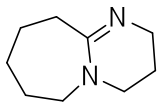
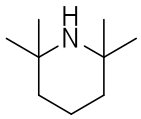
Using GC-MS to monitor the progress of the reactions, all reactions took longer than 24 h. The racemic catalysts pyrrolidine and D/L-proline took a very long time to display a high degree of conversion. Proline took the least amount of time, 48 hours. This

complicates the data as some background reaction does occur, which is racemic by nature (this was displayed in the preliminary screening). While a shorter reaction time could explain why proline has the highest enantioselectivity, the other explanation would be that proline is the optimal, stereoselective catalyst for the reaction. Also, the carboxylic acid moiety appears to be important for conversion and enantioselectivity as the ester proline derivatives have a lower ee.

As TEA was shown to be catalytic in Table 4, other organic bases were tested including Hünig's base, DBU, and 2,2,6,6-tetramethylpiperidine to determine how the sterics of the organic base would influence the reaction (Table 6).

Table 6. Results of screening various organic bases in the Aza-Michael Addition of 4-hexen-3-one with phthalimide



Entry	Organic Base	ee[a] (%)
1		19
2		18
3		0
4		18

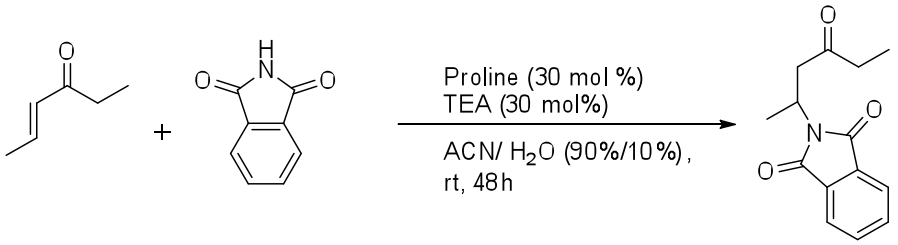
[a]Determined by chiral NP HPLC

TEA had the highest enantioselectivity of 19% and is the least sterically hindered tertiary amine (Table 6, entry 1). By making the base slightly more hindered, with iso-propyl groups instead of ethyl groups for two substituents, Hünig's base had a lower ee (Table 6, entry 2). DBU actually racemized the reaction; as it is the strongest base listed, it may be strong enough to make phthalimide so nucleophilic that it will add without the need for the iminium ion (Table 6, entry 3). With phthalimide reacting so indiscriminately, the reaction would be racemic. 2,2,6,6-tetramethylpiperidine was chosen to examine if a secondary amine base would increase enantioselectivity; the ee

did decrease slightly (Table 6, entry 4). Furthermore, 2,2,6,6-tetramethylpiperidine did not add in an iminium ion pathway as the amine is very sterically hindered by the four methyl groups. Thus, the least sterically hindered, organic base TEA was determined to be the best stereoselective base.

The concentration of the reaction relative to enantioselectivity was also investigated. Based on the literature, most research groups use 1.0 M concentrations10. I wanted to examine if this was based on enantioselectivity changes of the reactions (Table 7). Accordingly, concentrations below 1.0 M, had a lower enantioselectivity (17%) than 1.0 M (19%) for this Aza-Michael Addition (Table 7). Thus all reactions were subsequently conducted at 1.0 M, with respect to the nucleophile.

Table 7. Results of various solvent ratios in the Aza-Michael Addition of 4-hexen-3-one with phthalimide

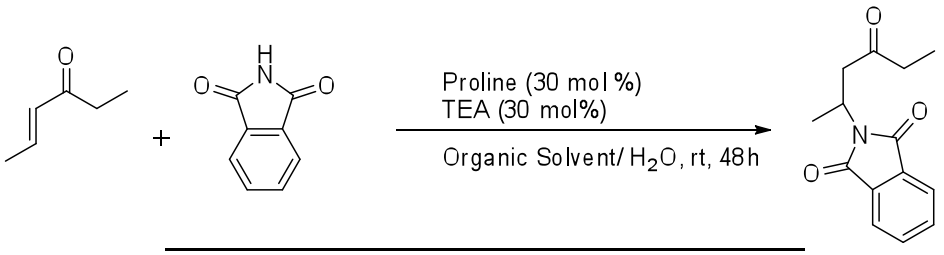


Entry	Concentration	ee[a] (%)
1	0.25	17
2	0.50	17
3	0.75	17
4	1.0	19

[a]Determined by chiral NP HPLC

The reaction environment was again investigated, except this time with 4-hexen-3-one and for enantioselectivity. Many of the same solvents were used.

Table 8. Results of screening various organic solvents in the Aza-Michael Addition of 4-hexen-3-one with phthalimide



Entry	Solvent	Solvent/H_2O (%)	ee[a] (%)
1	CH_2Cl_2	90/10	18
2	Acetone	90/10	9
3	EtOAc	100/0	12
4	EtOAc	90/10	35
5	EtOAc	75/25	12
6	Ethanol	90/10	9
7	DMSO	90/10	5
8	THF	90/10	ND
9	ACN	90/10	19

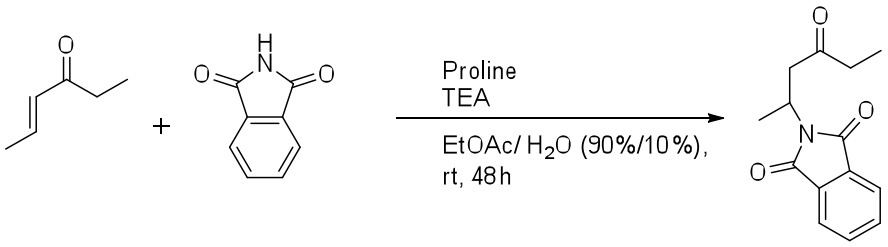
[a]Determined by chiral NP HPLC

As for conversion based on environment, the enantioselectivity results were equally as varied. While the solvent to this point had been acetonitrile, the enantioselectivity when using ethyl acetate was 35% with 90% ethyl acetate to 10% water (Table 8, entry 4). There is not a clear explanation for this development; although a possible reason could be in the dielectric constants. For ethyl acetate (with dielectic constant of 6.02) is much lower than that for acetonitrile (37.5)[23]. Indeed, ethyl acetate has the lowest dielectric constant among all other solvents tested. Unfortunately, the conversion of the reaction in THF was too low and two separate peaks were not seen.

Dichloromethane has a similar dielectric constant (9.1) to ethyl acetate which could aid in understanding why the aza-Michael Addition adduct had relatively high enantioselectivity in that particular solvent.

As catalyst loading is essential to many organic reactions, the mol percents of proline and TEA were varied in Table 9. While keeping the mol percent of TEA constant, the mol percent of proline was lowered (Table 9, entries 1-4), and likewise for TEA (Table 9, entries 5-8). In both cases, the enantioselectivity increased as the catalyst loading decreased. Indeed, the highest ee reported in this study was obtained with 10 mol percent proline and 30 mol percent TEA of 80% (Table 9, entry 4). Unfortunately, as reported in Table 4, conversion decreases with a lower catalyst loading for proline. Thus, as these reactions were performed on a 0.2 mmol scale, analysis became difficult when 10 mol percent proline and 15 mol percent TEA were used as catalyst as so little product was formed. However, scaling the reaction dramatically decreases enantioselectivity; the enantioselectivity of the reaction catalyzed by 10 mol percent proline and 15 mol percent TEA, changes from 80% to 14% upon increase to a 1.0 mmol scale compared to 0.2 mmol.

Table 9. Results of various mol percents of catalyst in the Aza-Michael Addition of 4-hexen-3-one with phthalimide



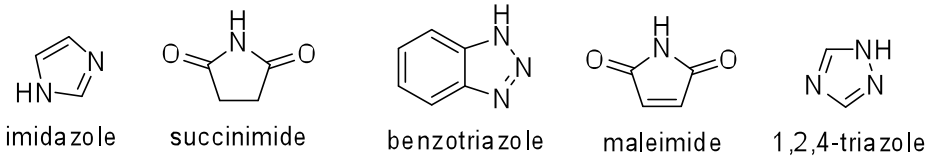
Entry	Proline mol percent	TEA mol percent	ee[a] (%)
1	100	30	19
2	30	30	35
3	20	30	54
4	10	30	80
5	30	100	9
6	30	50	11
7	30	30	35
8	30	15	50

[a]Determined by chiral NP HPLC

The scope of the reaction was also briefly examined concerning ketones and nucleophiles. Regarding nucleophiles, many were too nucleophilic for the reaction. The N-heterocycle imidazole added without the catalysts: without proline, without TEA, and without proline and TEA (Scheme 9). Thus it cannot be enantioselective as it will add indiscriminately. Succinimide was similar to imidazole as it would add without proline, and without both proline and TEA. Though, succinimide would add with solely TEA. Benzotriazole was similar to imidazole as it would attack 4-hexen-3-one without proline. Again, it would not be an appropriate nucleophile as it will add without the need for the iminium ion. Maleimide was not nucleophilic enough to add to the ketone even in the

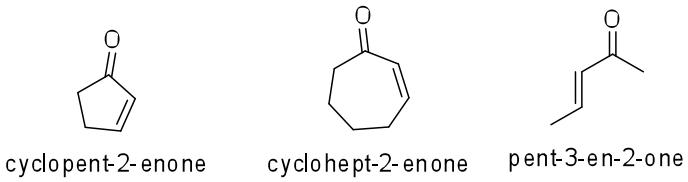
presence of both catalysts. For 1,2,4-triazole, some Aza-Michael Addition adduct was observed without the presence of proline or TEA, but without both proline and TEA there was an increase in product. Interestingly, with both proline and TEA there was no reaction. Thus, proline and TEA acted as inhibitors for this reaction.

Figure 2. N-nucleophiles tested



As previously mentioned, 4-phenylbut-3-en-2-one did not follow the aza-Michael Addition pathway with phthalimide (Scheme 10). Other ketones were able to be the substrate for the reaction including cyclohepten-2-one, cyclopenten-2-one, and penten-2-one with the presence of both proline and TEA. They were however not able to be analyzed for enantioselectivity as multiple unknown peaks persisted.

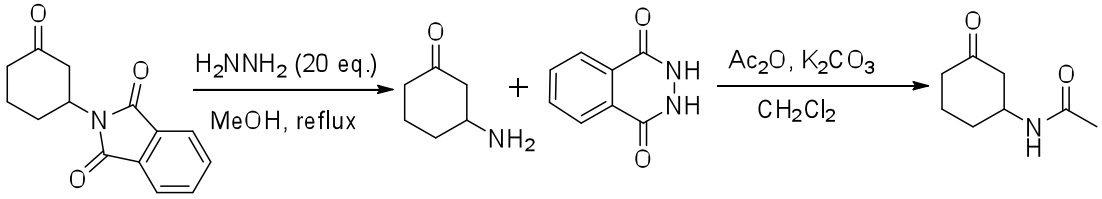
Figure 3. α,β-Unsaturated ketones tested



Various methods of deprotecting the phthalimide group to the free amine after addition by the Aza-Michael pathway were also investigated. In all cases there was a

subsequent reprotection of the free amine with an acetate group to an amide, as the free amine rapidly degrades in the presence of air. The most successful method of deprotection (Scheme 10) was a 90 minute reflux of 50% hydrazine/ 50% water in methanol[24]; followed by a reprotection using acetic anhydride, potassium carbonate, and dichloromethane with a final isolated yield of 31%.[24]

Scheme 9. Deprotection-Reprotection Reaction



Other deprotection attempts were made, while the same reprotection strategy was employed. These included a strong acid deprotection which was unsuccessful as a retro-aza-Michael addition occurred, as demonstrated by the ^{1}H-NMR of the final product.[25]

CHAPTER 3

Conclusion and Future Work

This paper demonstrates that the aza-Michael Addition to ketones using secondary amine catalysis is a viable reaction. Using cyclohexen-2-one and phthalimide, it was established that proline was the ideal secondary amine catalyst when compared to proline derivatives and imidazolines. The organic base triethylamine was also essential for the reaction, and demonstrated that it is catalytic in addition to proline. The highest conversions for this reaction occurred using acetonitrile with a varying amounts of water. However, the product of this reaction could not be separated using chiral NP HPLC or chiral GC-MS.

In the reaction of 4-hexen-3-one and phthalimide, enantioselectivity was studied extensively as the adduct enantiomers could be separated using chiral NP HPLC. Again, proline was the optimal secondary amine catalyst; triethylamine was shown to be the optimal organic base co-catalyst. The highest enantioselectivities observed in this study occurred when the catalysts were loaded in low amounts; however, the reaction occurs with an extremely low yield (<6%). The scale of the reaction was also relatively small (0.2 mmol of limiting reagent), and upon increasing the scale, enantioselectivity dramatically dropped. Also, the organic solvent ethyl acetate dramatically increased the enantioselectivity of the reaction.

More extensive study of this reaction is needed in the future especially with the organic solvent with regards to yield and enantioselectivity. The low yield observed is probably associated with the low solubility of phthalimide in ethyl acetate. Increased effort could also be spent varying the temperature. In preliminary tests at $0^{o}C$, the enantioselectivity did increase when compared to the reaction at room temperature, though with probable detriment to the yield; with an already low yield, this would present even lower yield. Also, the reaction has a lower enantioselectivity at larger scales (1.0 mmol of limiting reagent) when compared to a smaller scale (0.2 mmol); thus, in the future all reactions should be run on a larger scale.

CHAPTER 4

Experimental

2-(4-oxohexan-2-yl)isoindoline-1,3-dione. To a solution of acetonitrile (18 mL) and water (2 mL), was added 4-hexen-3-one (345 μL), triethylamine (140 μL), phthalimide (145 mg), and proline (35 mg). The solution was stirred at room temperature for 24 hours. To quench the reaction, HCl (5 mL, 1.0 M) and CH_2Cl_2 (25 mL) were added, stirred, and separated. The organic phase of the separation was basified using two washes of NaOH (10 mL, 1.0 M). There was a washing of brine (15 mL), and the organic phase was dried over magnesium sulfate, and concentrated *in vacuo* to afford 40 mg (16%) of a yellow oil: IR ($CHCl_3$) 3005, 1712, 1372 cm^{-1}; 200 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.81 (m, 2H), 7.68 (m, 2H), 4.84 (m, 1H), 3.29 (dd, 1H, J=8 Hz, J= 17Hz), 2.97 (dd, 1H, J=8 Hz, J= 17Hz), 2.49 (m, 2H), 1.44 (d, 3H, J=7 Hz). HPLC (Chiralpak AD-H column, hexane/2-propanol = 98:2, 1.0 mL/min; 254 nm, 25^{o}C, t_1 = 9.87 min, t_2 = 11.02 min).

2-(3-oxocyclohexyl)isoindoline-1,3-dione. To a solution of acetonitrile (18 mL) and water (2 mL), was added cyclohexen-2-one (290 μL), triethylamine (140 μL), phthalimide (145 mg), and proline (35 mg). The solution was stirred at room temperature for 24 hours. To quench the reaction, HCl (5 mL, 1.0 M) and CH_2Cl_2 (25 mL) were added, stirred, and separated. The organic phase of the separation was basified using two washes of NaOH (10 mL, 1.0 M). There was a washing of brine (15 mL), and the organic phase was dried over magnesium sulfate, and concentrated *in vacuo* to afford 168 mg

(69%) of a purple solid: mp 146.2-147.0^{o}C; IR ($CHCl_3$) 2972, 1709, 1377 cm^{-1}; 200 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.81 (m, 2H), 7.74 (m, 2H), 4.51 (m, 1H), 2.58 (m, 1H), 2.45 (m, 3H), 2.18 (m, 1H), 1.95 (d, 1H, J=25 Hz), 1.67 (m, 1H); Anal. calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.13; H, 5.47; N, 5.77.

Benzyl Ester Proline. To a stirred heterogeneous mixture of proline (2.303 g) and benzyl alcohol (35 mL) at 0^{o}C was added cold (0^{o}C) $SOCl_2$ (1.7 mL) drop wise. After all of the $SOCl_2$ was added, the ice bath was removed and the stirring continued for 48 h. To the reaction was added diethyl ether (100 mL), and placed in a cold (0^{o}C) refrigerator overnight. White crystals precipitated. Recrystalization with hot ethanol afforded 3.49 g (72%) of white solid crystals: mp 146.0-147.0 ^{o}C; IR ($CHCl_3$) 3455, 1726 cm^{-1}; 200 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.36 (s, 5H), 5.22 (q, 2H, J=6 Hz, J=12 Hz), 4.50 (m, 1H), 3.51 (m, 2H), 2.41 (m, 1H), 2.10 (m, 3H).

N-(3-oxocyclohexyl)acetamide. A stirred solution of 3-phthalimide-cyclohexanone (100 mg), methanol (15 mL), and 50% hydrazine in water (620 mL) was refluxed for 90 minutes. To quench, the solution was concentrated *in vacuo* using a Rotovap to afford white crystals. The crystals were dissolved in HCl (10 mL, 1.0 M) and vacuum filtered using dilute HCl (10 mL, 0.1 M). The filtered aqueous solution was washed with CH_2Cl_2 (2 x 10 mL). To the aqueous solution was added CH_2Cl_2 (10 mL) and acetic anhydride (153 μL) followed portionwise K_2CO_3 to afford a pH~10-11, while stirring at room temperature. The biphasic mixture was stirred for 90 minutes with occasional addition of K_2CO_3 to maintain pH. To quench, the mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). All organics were combined

and dried with magnesium sulfate, filtered, and concentrated *in vacuo* to afford 16 mg (25%) of a brown oil: 200 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm) 5.537 (s, 1H), 4.27 (m, 1H, J=4 Hz), 2.70 (dd, 2H, J=2 Hz, J=5 Hz, J=14 Hz), 2.31 (m, 4H), 2.07 (m, 2H), 1.98 (s, 3H).

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Appendix

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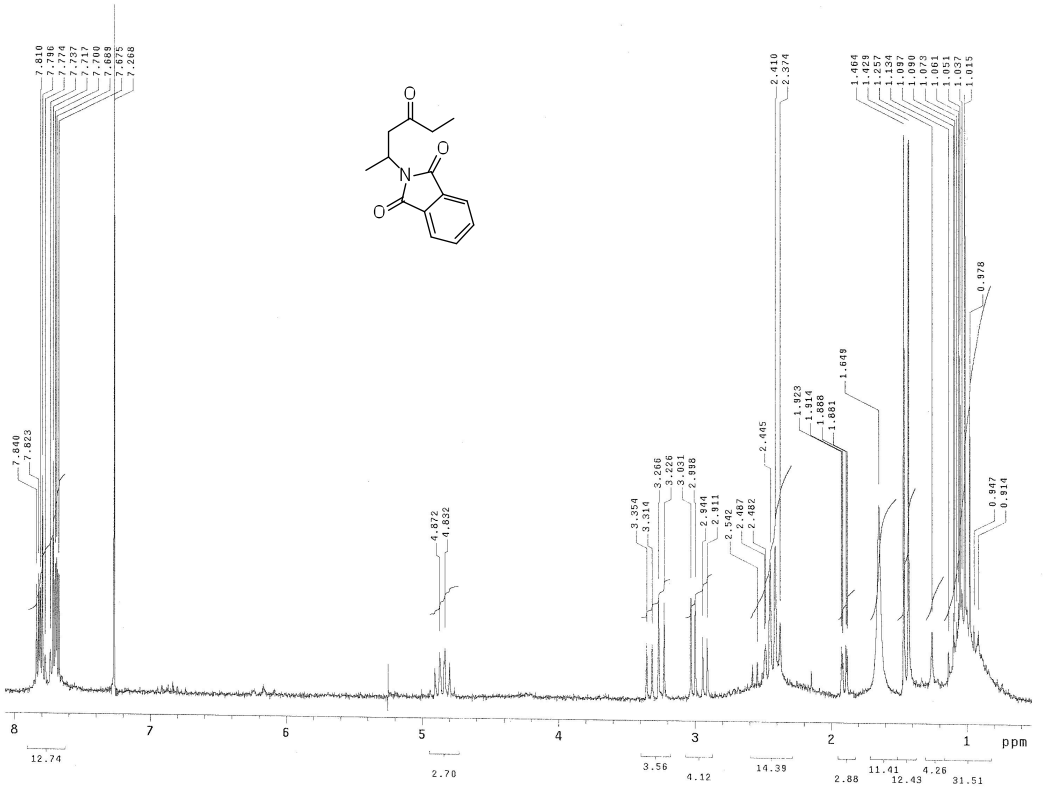
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3.354
3.314
3.266
3.226
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2.542
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2.445
2.410
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1.914
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1.464
1.429
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1.248
1.197
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1.051
1.032
1.015
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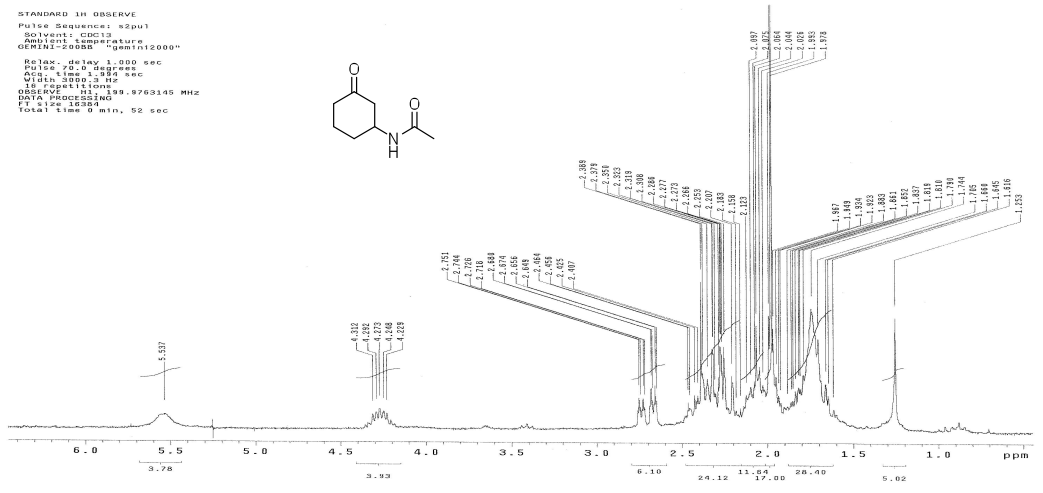
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Width 3000.3 Hz
8 repetitions
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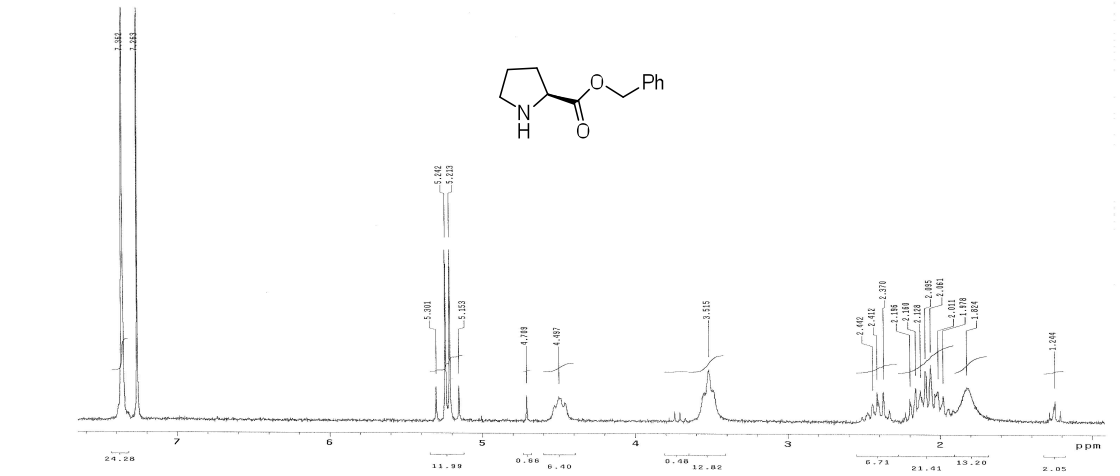
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13.20
2.05

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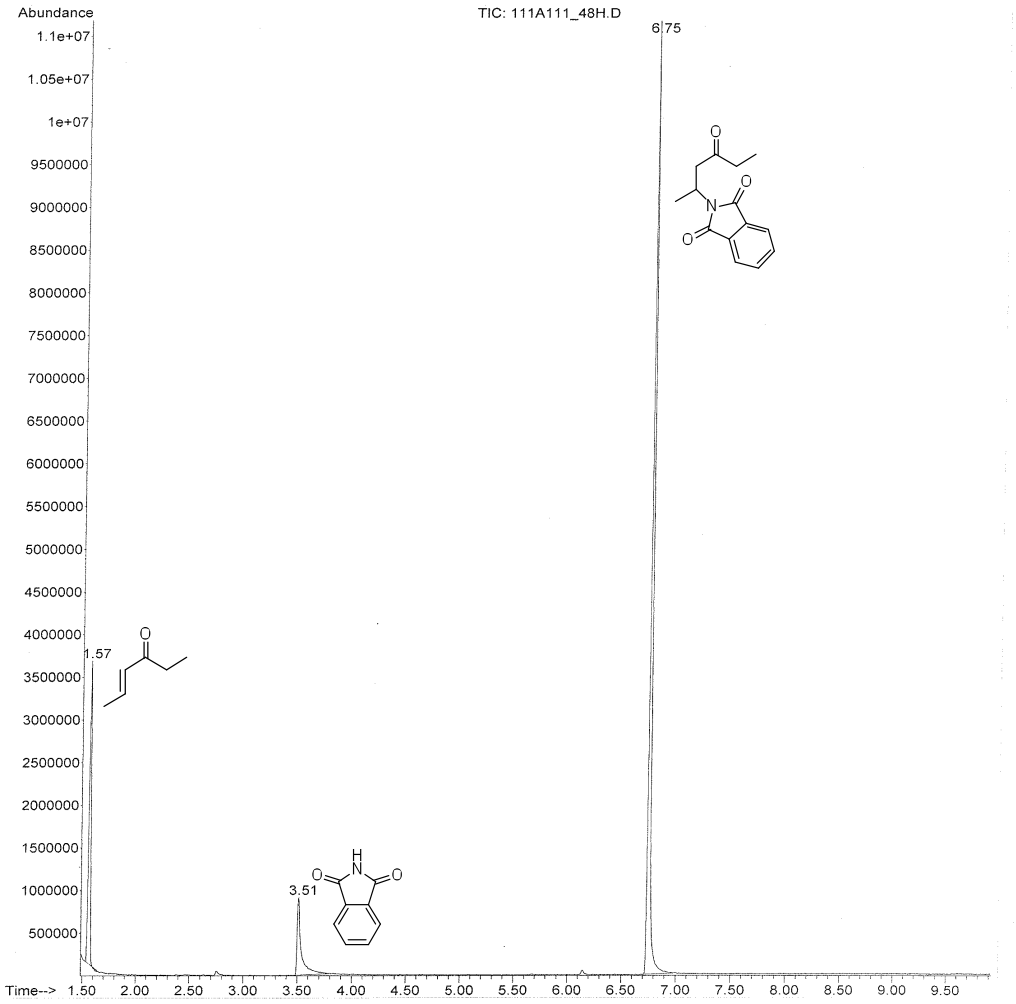

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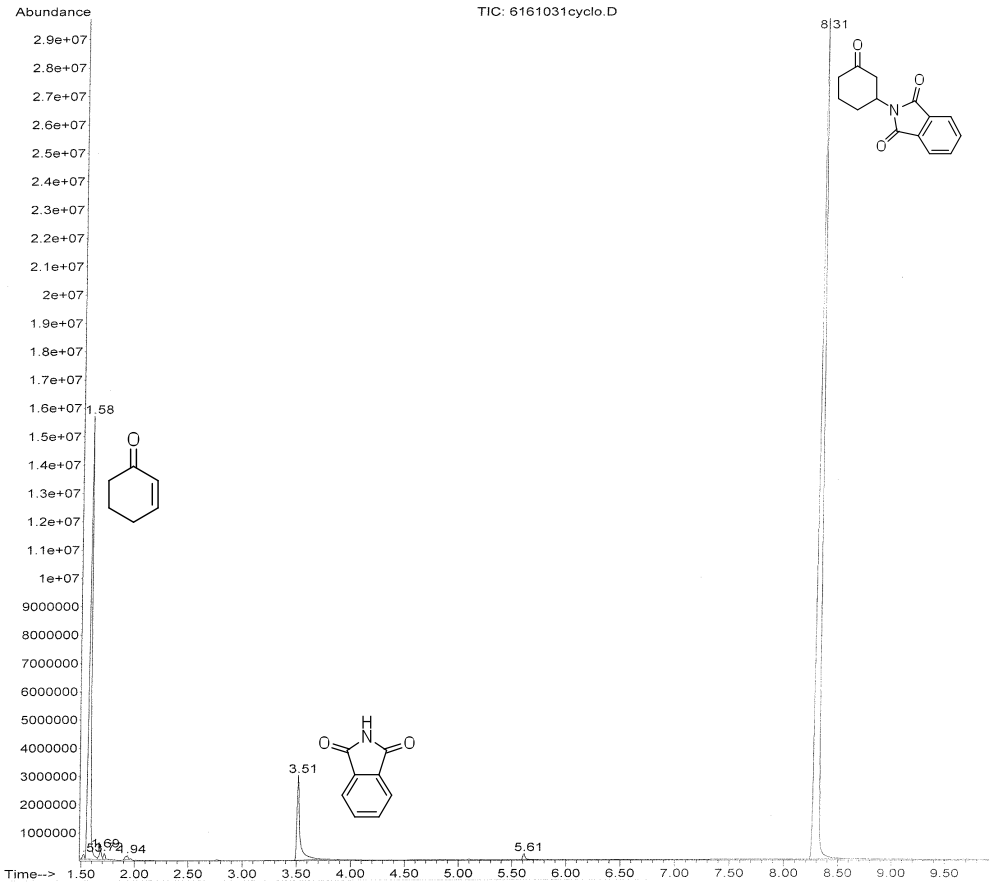

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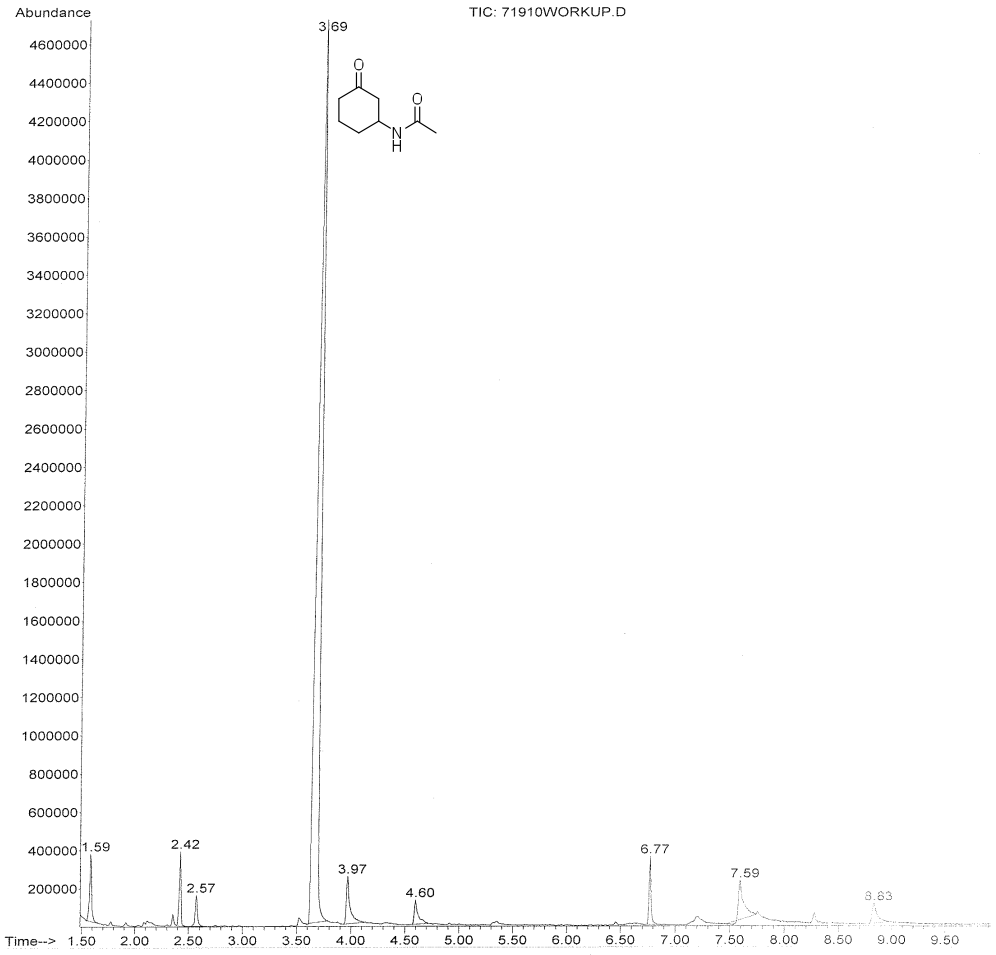

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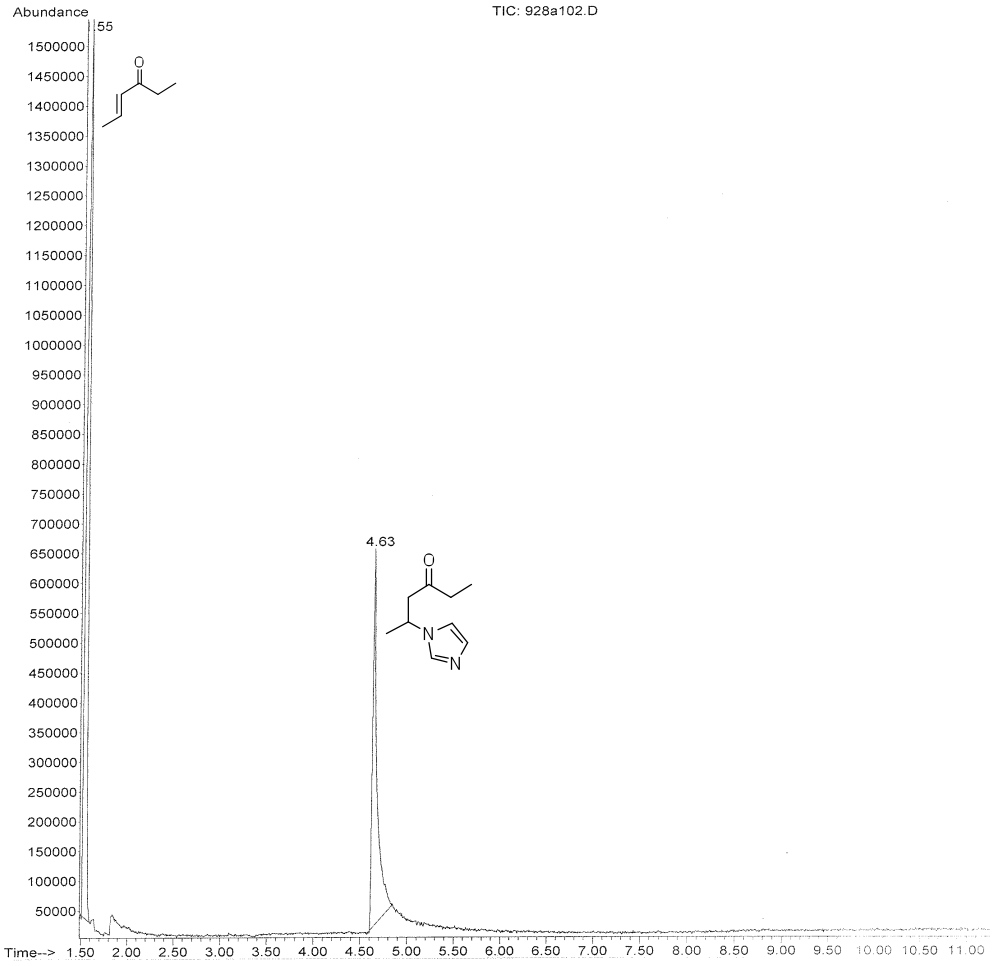

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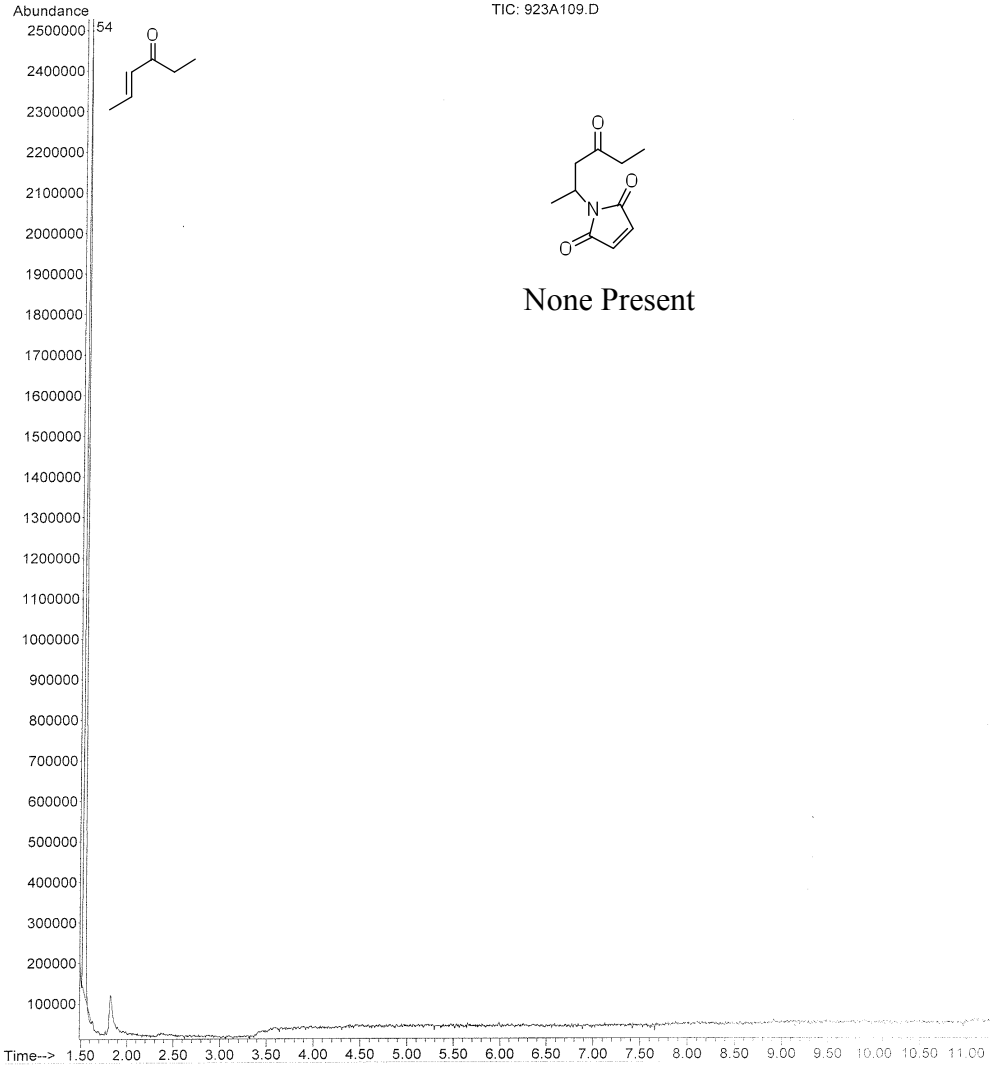
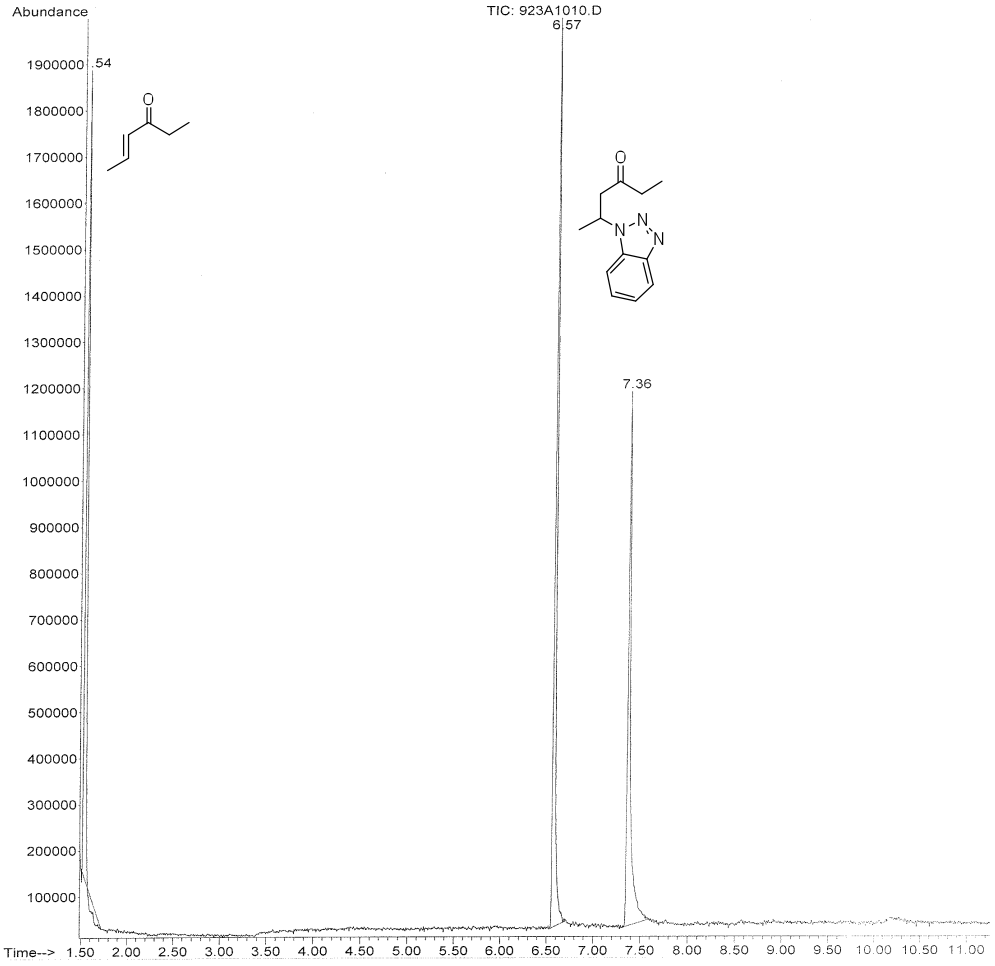
File        :C:\MSDChem\1\DATA\Adrian\BP\9_23a_10\923A109.D
Operator    : BP
Acquired    : 28 Sep 2010    9:46      using AcqMethod BP03
Instrument :    Instrumen
Sample Name: maleimide 90/10 ACN/H2O
Misc Info   :
Vial Number: 28
```

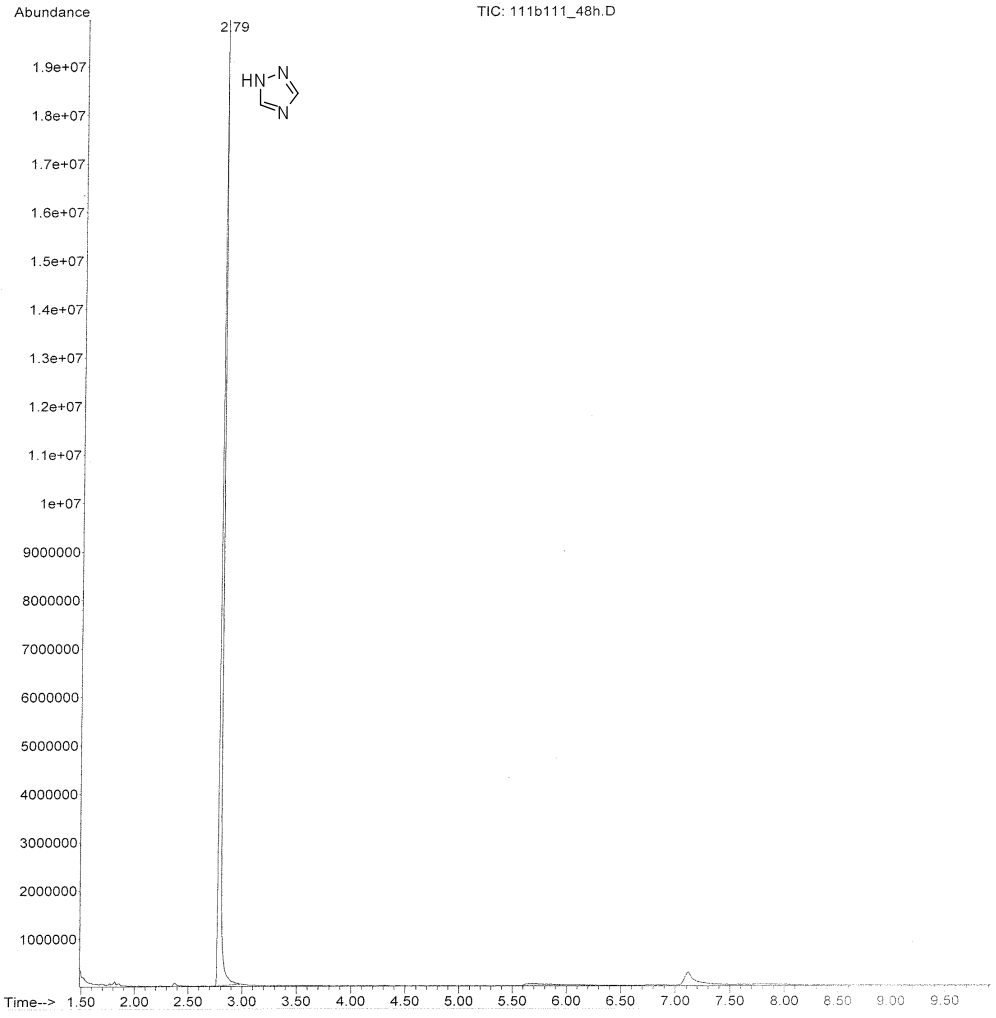


None Present

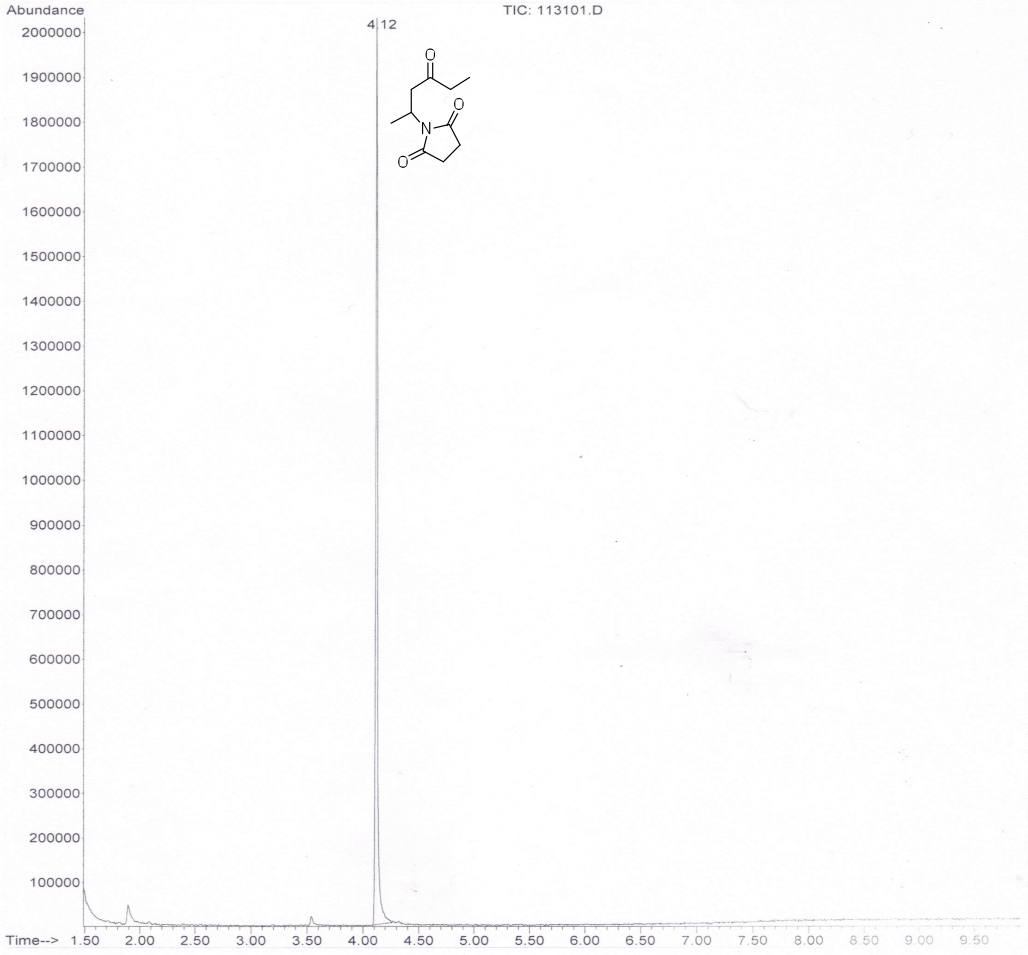
```
File         :C:\MSDChem\1\DATA\Adrian\BP\9_23a_10\923A1010.D
Operator     : BP
Acquired     : 28 Sep 2010   10:01      using AcqMethod BP03
Instrument   :    Instrumen
Sample Name: benzotriazole 90/10 ACN/H2O
Misc Info    :
Vial Number: 29
```



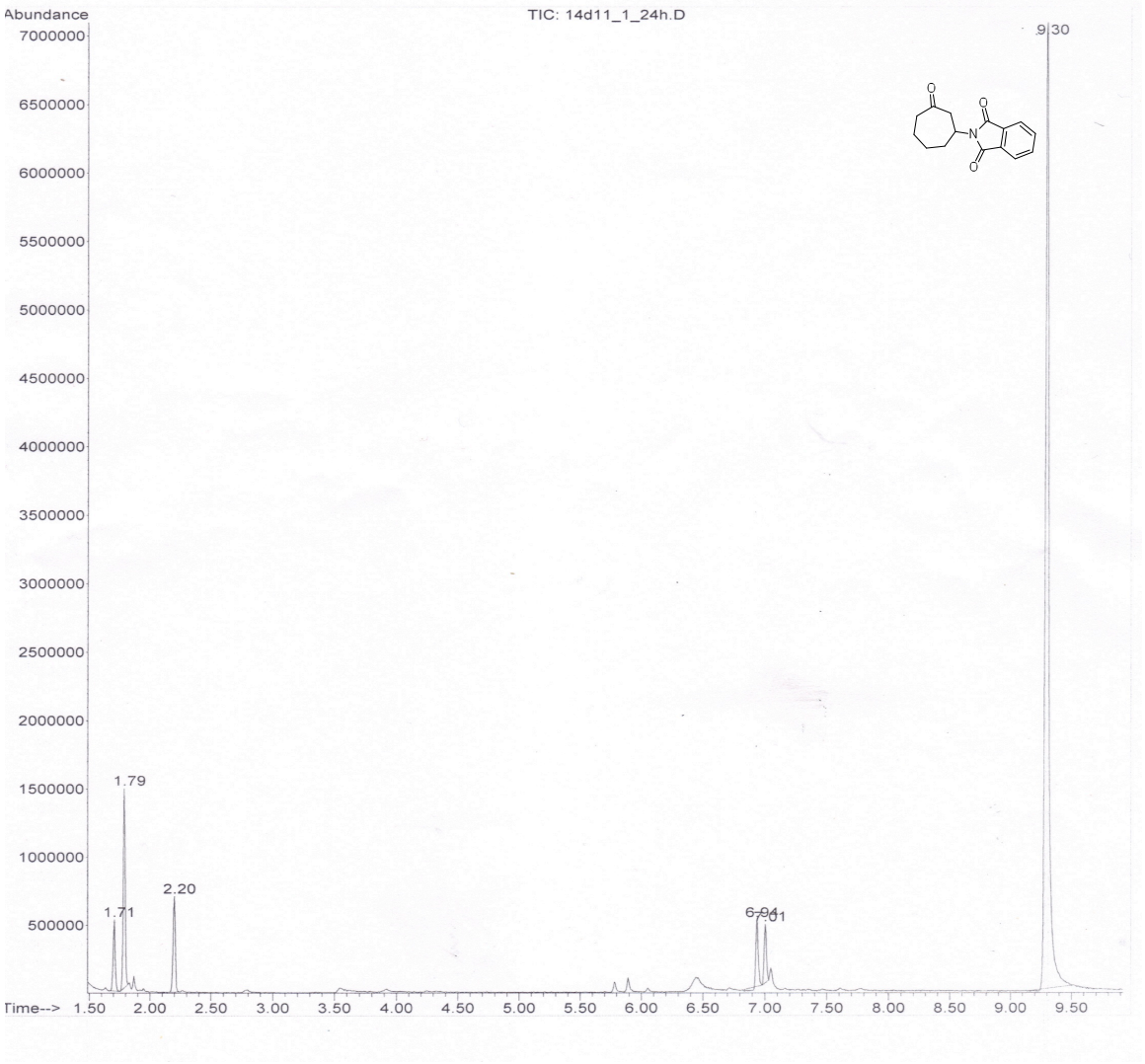
```
File        :C:\MSDChem\1\DATA\Adrian\BP\1_11b_11\111b111_48h.D
Operator    : BP
Acquired    : 13 Jan 2011   15:19      using AcqMethod RP02
Instrument :    Instrumen
Sample Name: all
Misc Info   :
Vial Number: 11
```



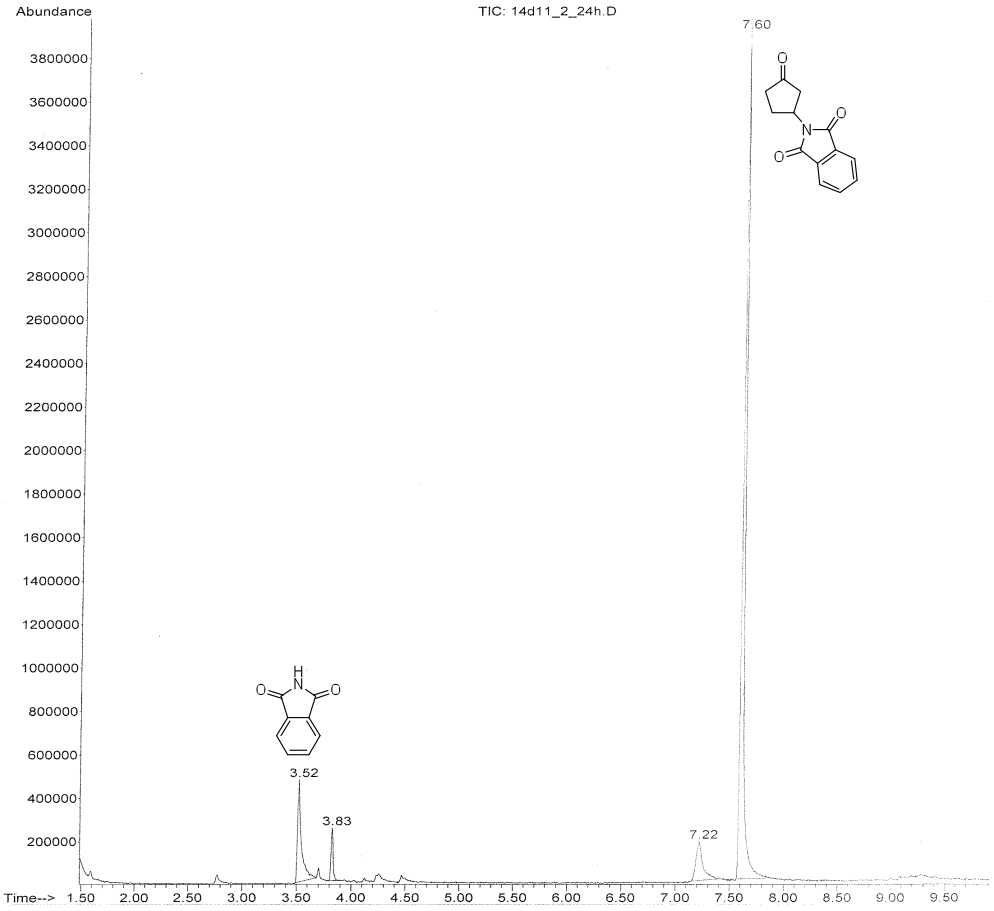
```
File        :C:\MSDChem\1\DATA\Adrian\BP\11_3_10\113101.D
Operator    : BP
Acquired    :  4 Nov 2010  12:15      using AcqMethod RP02
Instrument  :   Instrumen
Sample Name: 4-hex-en and suc
Misc Info   :
Vial Number: 16
```



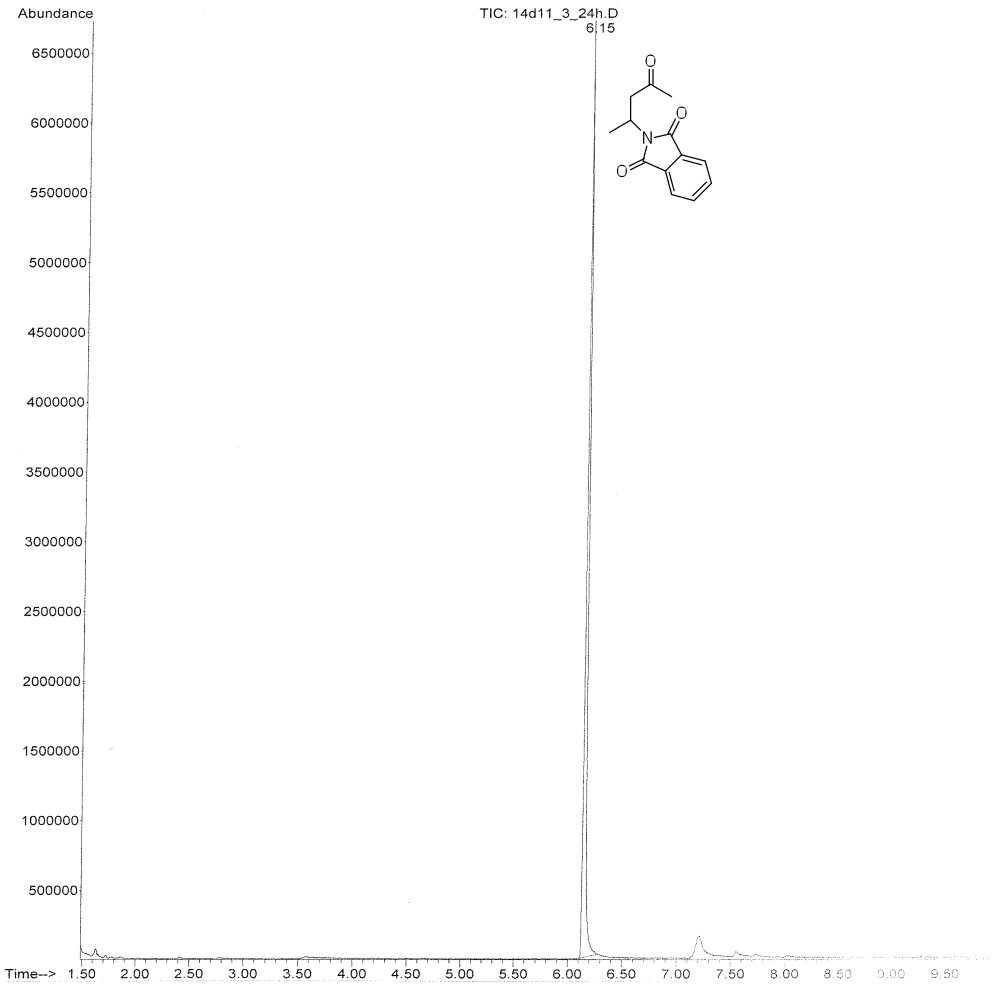
```
File        :C:\MSDChem\1\DATA\Adrian\BP\1_4d_11\14d11_1_24h.D
Operator    : BP
Acquired    :  5 Jan 2011   11:36      using AcqMethod RP02
Instrument  :    Instrumen
Sample Name: 24h
Misc Info   :
Vial Number: 11
```



```
File          :C:\MSDChem\1\DATA\Adrian\BP\1_4d_11\14d11_2_24h.D
Operator      : BP
Acquired      :  5 Jan 2011   11:48      using AcqMethod RP02
Instrument    :   Instrumen
Sample Name:  24h
Misc Info     :
Vial Number:  12
```



```
File        :C:\MSDChem\1\DATA\Adrian\BP\1_4d_11\14d11_3_24h.D
Operator    : BP
Acquired    :  5 Jan 2011   12:01      using AcqMethod RP02
Instrument  :   Instrumen
Sample Name: 24h
Misc Info   :
Vial Number: 13
```

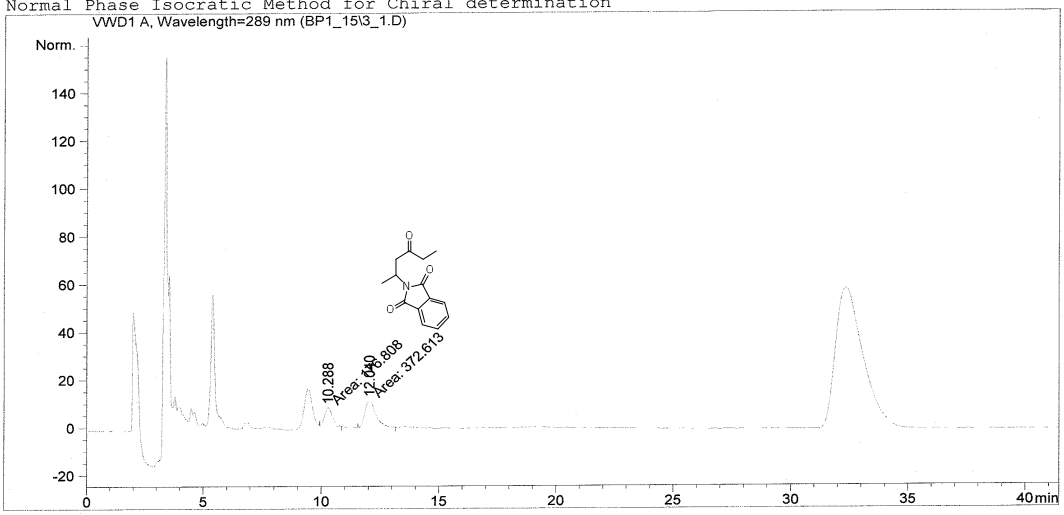


3. Copies of chiral NP HPLC Spectra

Data File C:\HPCHEM\1\DATA\BP1_15\3_1.D Sample Name: ethyl acetate

pro tea cata hexenone phth in ethyl acetate adduct with
1.000 ml/min 98/2% hexanes/IPA

```
==========================================================================
Injection Date  : 1/18/2011 12:27:51 PM
Sample Name     : ethyl acetate                    Location :   -
Acq. Operator   : BP
Acq. Instrument : Instrument 1
Acq. Method     : C:\HPCHEM\1\METHODS\BP01.M
Last changed    : 1/18/2011 11:05:12 AM by BP
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\BP01.M
Last changed    : 7/16/2010 3:17:34 PM by BP
Normal Phase Isocratic Method for Chiral determination
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=289 nm

Peak RetTime Sig Type     Area       Height      Area
  #   [min]            mAU   *s    [mAU   ]       %
----|-------|---|----|----------|----------|--------|
   1  10.288  1  MM    176.80789    7.66775  32.1808
   2  12.040  1  MM    372.61264   11.47368  67.8192

Totals :               549.42053   19.14144

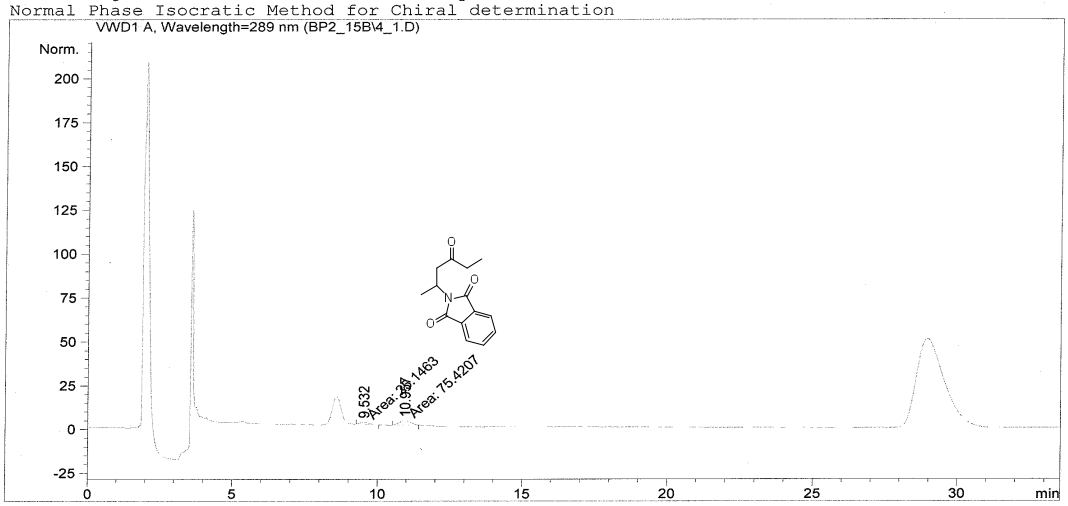
 Results obtained with enhanced integrator!
==========================================================================
                          *** End of Report ***
```

Instrument 1 6/3/2011 11:51:38 AM BP Page 1 of 1

Data File C:\HPCHEM\1\DATA\BP2_15B\4_1.D Sample Name: EtOAc

30 mol%pro 15 mol %tea cata hexenone phth in 90/10 EtOA
c/H2O RT adduct with 1.000 ml/min 98/2% hexanes/IPA

```
==========================================================================
Injection Date  : 3/8/2011 3:21:30 PM
Sample Name     : EtOAc                              Location :   -
Acq. Operator   : BP
Acq. Instrument : Instrument 1
Acq. Method     : C:\HPCHEM\1\METHODS\BP01.M
Last changed    : 2/15/2011 5:30:27 PM by BP
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\BP01.M
Last changed    : 7/16/2010 3:17:34 PM by BP
Normal Phase Isocratic Method for Chiral determination
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=289 nm

Peak RetTime Sig Type    Area      Height     Area
  #   [min]          mAU   *s   [mAU   ]      %
----|-------|---|----|----------|----------|--------|
   1   9.532  1  MM     25.14628    1.23459  25.0045
   2  10.957  1  MM     75.42070    2.58166  74.9955

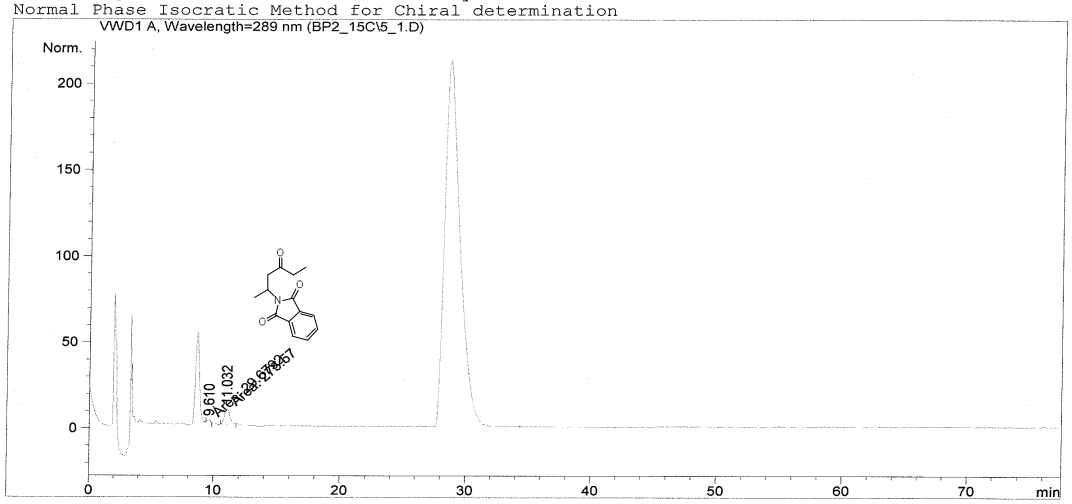
Totals :               100.56698    3.81625

 Results obtained with enhanced integrator!
==========================================================================
                          *** End of Report ***
```

Data File C:\HPCHEM\1\DATA\BP2_15C\5_1.D Sample Name: EtOAc

10 mol%pro 30 mol %tea cata hexenone phth in 90/10 EtOA
c/H2O RT adduct with 1.000 ml/min 98/2% hexanes/IPA

```
==========================================================================
Injection Date  : 3/8/2011 5:40:07 PM
Sample Name     : EtOAc                          Location :   -
Acq. Operator   : BP
Acq. Instrument : Instrument 1
Acq. Method     : C:\HPCHEM\1\METHODS\BP01.M
Last changed    : 2/15/2011 5:30:27 PM by BP
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\BP01.M
Last changed    : 7/16/2010 3:17:34 PM by BP
Normal Phase Isocratic Method for Chiral determination
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=289 nm

Peak RetTime Sig Type    Area      Height     Area
  #   [min]          mAU   *s   [mAU   ]      %
----|-------|---|----|----------|----------|--------|
   1   9.610  1  MM     29.67921    1.73367   9.7229
   2  11.032  1  MM    275.56995    9.16463  90.2771

Totals :               305.24915   10.89831

 Results obtained with enhanced integrator!
==========================================================================
                          *** End of Report ***
```

Instrument 1 6/3/2011 11:53:42 AM BP Page 1 of 1