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藥學碩士學位論文

Enantioselective Sulfa-Michael additions to α,β-unsaturated ketones via *Cinchona*-derived Organocatalysts.

Cinchona 유래 유기촉매를 활용한 α,β-unsaturated ketones의 입체 선택적인 Sulfa-Michael additions

2021年 **2**月

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약학과 약품제조화학 전공

김 혜 란

Enantioselective Sulfa-Michael additions to α,β-unsaturated ketones via Cinchona-derived Organocatalysts.

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2021年 1月

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국문 초록

Cinchona 알카로이드를 이용한 비대칭 유기촉매 (Asymmetric Organocatalyst)는 값이 싸고, 완만한 반응조건, 그리고 재사용할 수 있다는 장점을 가지고 있다. 이와 같은 장점으로 인해 입체선택적 dihydroxylation 반응 등 유기촉매에 관한 연구가 활발히 연구되어왔다. 본 연구실에서는 지난 20여년 동안 cinchona organocatalyst에 대한 연구를 수행한 바 있고, 최근 benzimidazole 구조를 부분 구조로 한 cinchona bifunctional organocatalyst의 개발과 응용에 대한 연구를 수행하고 있다. 이러한 연구의 일환으로 본 연구는 다양한 *cinchona* bifunctional organocatalyst를 sulfur compound 합성 방법에 응용하고자 하였다. 구체적으로는 *N*-(6-hydroxycinchonan-9-yl)benzimidazole 촉매 존재 하에 친전자체로 2-cyclohexen-1-one, 친핵체로 thiophenol를 사용하는 입체선택적 Sulfa-Michael additions을 수행하여 최대 99%의 수율과, 87%의 광학 수율로 sulfa-Michael adduct를 얻을 수 있었다. 개발된 본 반응은 향후 다양한 키랄 sulfur 화합물을 합성하는데 응용할 수 있을 것으로 생각된다.

주요어 : *Cinchona* Alkaloid, Asymmetric Organocatalysis, Asymmetric Sulfa-Michael Addition

학　번 : 2019-29687

국문초록.....1

목　　차 3

Figure 목록 5

Scheme 목록 6

Table 목록 7

Ⅰ. 서 론.....8

1. Asymmetric cinchona organocatalyst 8

2. *Cinchona* organocatalyst and sulfur compound 11

3. *Cinchona* organocatalyst and sulfa Michael addition 16

Ⅱ. 본 론.....20

1. 반응 조건의 최적화 과정.....20

1-1. 용매 탐색.....21

1-2. 온도 탐색.....22

1-3. 촉매의 양 탐색.....23

1-4. Molecular sieve 탐색.....24

1-5. Weak acid 의 탐색.....25

1-6. 촉매 유도체들의 탐색.....27

2. Michael acceptor의 선정과 탐색.....30

3. Michael donor의 선정과 탐색.....32

4. 생성물의 절대 배열 및 Plausible mechanism.....36

Ⅲ. 결 론.....37

Ⅳ. 실 험.....38

Ⅴ. 참고문헌.....74

Ⅵ. Abstract.....75

Ⅶ. 부 록.....76

Figure 목록

Figure 1. Examples of Cinchona alkaloid

Figure 2. Functions of cinchona alkaloid structure

Figure 3. Representative Classes of valuable biologically active organosulfur compounds present in nature and organosulfur drugs

Figure 4. General strategies for the catalytic generation of C-S bond

Figure 5. Representative Catalysts of Lewis Base－Brønsted Acid/ Lewis Base

Figure 6. Amino catalyst using iminium activation

Figure 7. 9 Kinds of Michael acceptor

Figure 8. Michael donors

Figure 9. Plausible Transition state

Scheme 목록

Scheme 1. *Cinchona*-Derived Urea Promoted Thiolysis of Azlactones with Benzyl Thiols

Scheme 2. Addition of Thiols to Morita−Baylis−Hillman (MBH) Carbonates

Scheme 3. Enantioselective sulfur Michael addition using Quinine

Scheme 4. Enantioselective Sulfa Michael addition using iminium activation catatlyst

Scheme 5. Enantioselective sulfur Michael addition using *Cinchona* organocatalysts

Scheme 6. Enantioselective sulfur Michael addition using *Cinchona*-benzimidazole organocatalysts

Table 목록

Table 1. Solvent screening

Table 2. Temperature screening

Table 3. Catalyst's scale screening

Table 4. Molecular sieve screening

Table 5. Weak acid screening

Table 6. Catalyst's derivatives screening Ⅰ

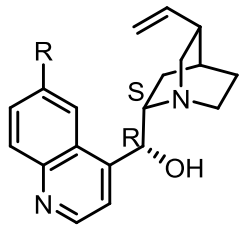
Table 7. Catalyst's derivatives screening Ⅱ

Table 8. Enantioselective SMA of 6 kinds of Michael acceptors

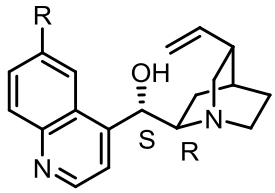
Table 9. Enantioselective SMA of 13 kinds of Michael donors

Ⅰ. 서 론

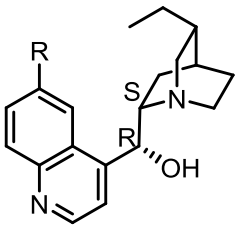
1. Asymmetric cinchona organocatalysts



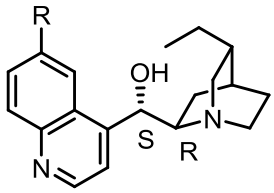
Quinine (Q) (R=OMe)
Cinchonidine (CD) (R=H)



Quindine (QD) (R=OMe)
Cinchonine (CN) (R=H)



Dihydroquinine (DHQ) (R=OMe)
Dihydrocinchonidine (DHCD) (R=H)



Dihyroquindine (DHQD) (R=OMe)
Dihydrocinchonine (DHCN) (R=H)

Figure1. Examples of *Cinchona* alkaloid

Cinchona alkaloids (Figure 1) 는 천연 식물인 *Cinchona*의 껍질에서 추출된 물질로, 그 종류에는 quinine(QN), quinidine (QD), cinchonine (CN), cinchonidine (CD) 등이 있다.[1] 1800년대부터 Cinchona alkaloid는 의약품으로 사용되기 시작하였으며, quinine은 항말라리아제, quinidine은 항부정맥약으로

사용되고 있다. 이에 더하여 Cinchona alkaloid는 여러 개의 stereogenic center를 [C(8), C(9), C(3), C(4), N(1)] 가지고 다양한 치환기를 가지기 때문에 1970년대부터는 asymmetric organocatalyst로 연구되기 시작하였다 (Figure 2).[2][3]

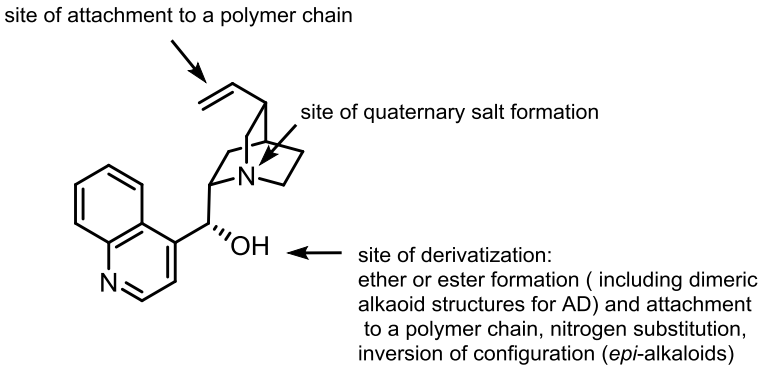


Figure 2. Functions of cinchona alkaloid structure

Asymmetric organocatalysts는 비대칭 유기촉매로서 유기반응의 반응속도를 증가시키며 반응 시간을 단축 시킨다는 특징을 가진다. 또한 입체선택적인 생성물을 얻을 수 있다는 장점이 있다. 이러한 대표적인 비대칭 유기촉매로는 Chiral phosphoric acid catalysts, Maruoka catalysts, Cinchona organocatalysts 등이 있다.

Asymmetric organocatalysts로 사용되는 Cinchona organocatalysts는 Cinchona alkaloid의 C(6′), C(9)부분에 기질과 interaction 할 수 있는 여러 가

지 치환기들을 도입하여 사용하는 것이 보편적이고, N(1)자리에 다양한 치환기를 달아 phase transfer catalyst로 응용하여 사용하기도 한다. 이렇게 구조가 변화된 Cinchona organocatalyst는 2개의 site에서 기질과 상호작용을 한다. 첫 번째로는 C(9)에 있는 치환기와 hydrogen bonding으로 하나의 기질과 상호작용이 있다. 두 번째 상호작용은 quinuclidine의 nitrogen이 있는 부분에서 이루어지며, N(1)이 base로 작용한 후 형성되는 ammonium salt와 다른 기질과의 ion-pair interation이다.

Cinchona organocatalyst는 여러 반응에 적용되고 있다. Aldol reaction, Henry reaction, Morita-Baylis-Hillman reaction, Friedel-Crafts reaction 등의 반응에서 사용되고 있으며, 본 연구에서는 Michael addition을 이용하여 입체 선택적인 sulfur compound 합성에 대해 언급하고자 한다.

2. *Cinchona* organocatalyst and sulfur compound[4]

자연에서 organosulfur compound 는 쉽게 찾을 수 있다. 황 화합물은 다양한 곳에서 중요한 역할을 하는데, 예를 들어 생물학적인 물질로 우리가 필요로 하는 아미노산인 cysteine, 항산화 역할을 하는 glutathione 이 있으며, 의약품으로는 penicillin 계열의 항생제, 항바이러스제, 고지혈증 치료약물인 statin 계열 약물 그리고 진균치료제인 azole 등이 있다.

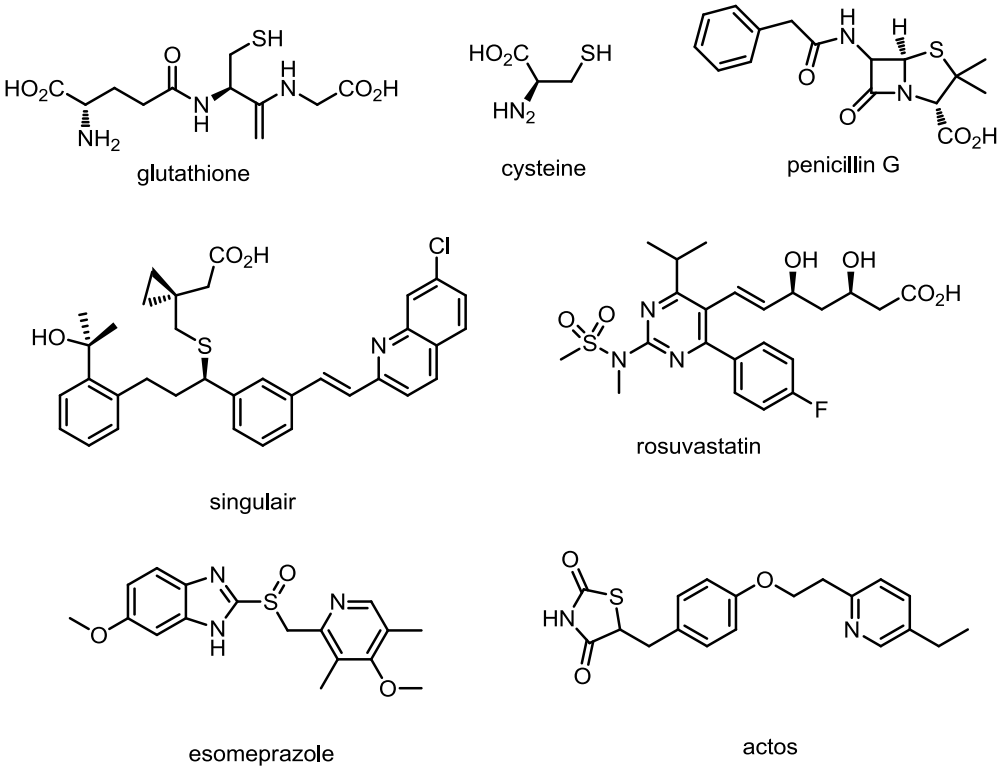


Figure 3. Representative Classes of valuable biologically active organosulfur compounds present in nature and organosulfur drugs

이러한 황 화합물을 얻기 위해 과학자들은 여러 종류의 carbon-sulfur bond formation 에 관한 반응을 연구하였다. Sulfur compound 를 합성하는 방법으로는 상기의 다양한 방법이 있다 (figure 4). Alkene 과 Alkyne 의 1,2-addition 또는 epoxide 나 aziridine 과 같은 heteroatom 원자가 포함된 ring 을 open 하는 thiolysis 가 있다. 이에 더하여 최근에 활발한 연구가 이루어 지고 있는 metal 을 이용한 alkyl 과 sulfur reagent 와의 cross coupling reaction 이 있고, sulfur 가 electrophile 을 직접 공격하는 substitution 등이 있다. 이 중 본

연구에서는 온화한 condition 에서 비교적 쉽게 이루어지는 sulfa - Michael addition 에 대해 설명 하고자 한다. 본론에 들어가기 앞서 *cinchona* organocatalyst 를 이용한 2 가지 반응의 예를 살펴보도록 하겠다.

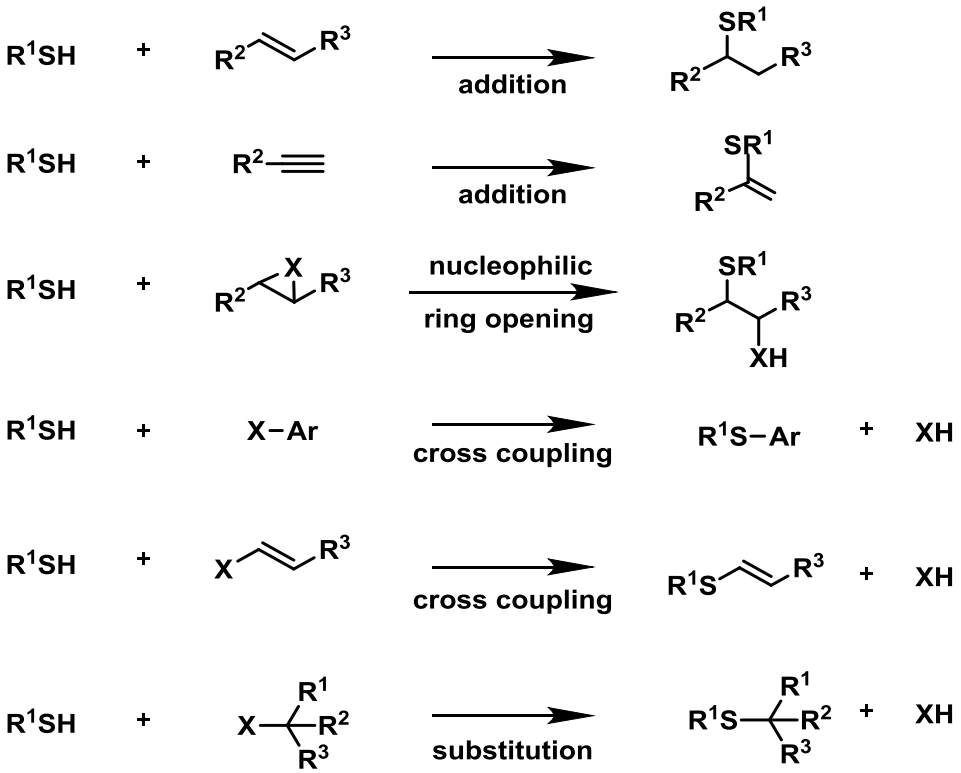
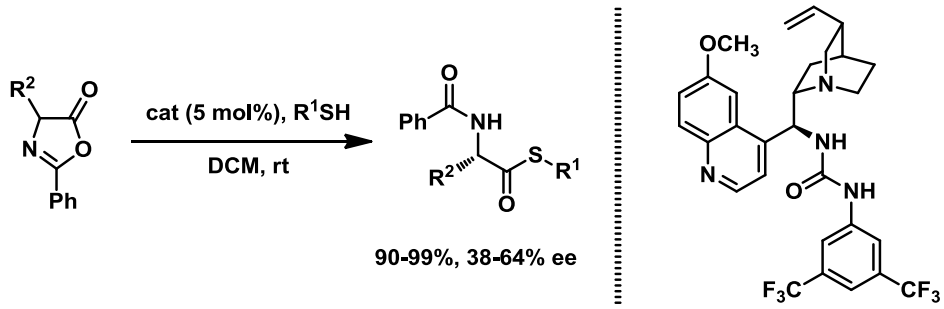


Figure 4. General strategies for the catalytic generation of carbon-sulfur bond[5][6][7]

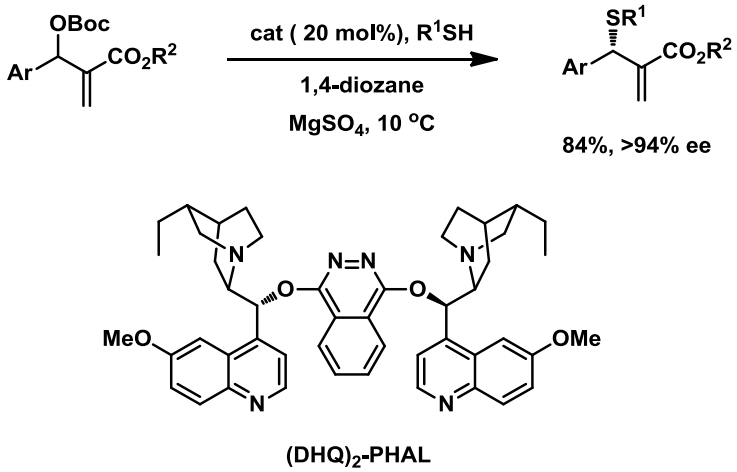


Scheme 1. *Cinchona*-Derived Urea Promoted Thiolysis of Azlactones with Benzyl Thiols

Scheme 1[8]은 azlactone의 구조를 가진 친전자체를 친핵체인 thiol이 공격하여 입체 선택적으로 thiolysis를 하는 반응이다. 이 때 사용하는 촉매는 C(9) 위치에 urea가 치환된 구조이며, 이 catalyst는 thiolysis 외에도 Michael addition, 1,2-addition, 1,4-addition등 많은 반응에서 적용되어진다. 기질과 촉매 간의 상호작용으로는 quinuclidine이 염기로 작용하면서 시작된다. Quinuclidine의 질소가 thiophenol을 deprotonation시키고 난 후 cation을 형성하여, 친핵체와 상호작용을 한다. 또 다른 기질과의 상호작용으로는 urea를 구성하는 질소의 수소와 azlactone의 carbonyl과의 수소결합이 있다. 이러한 입체 배열을 형성함으로 chiral한 생성물을 얻을 수 있게 된다.

다음의 반응은 dimer형태의 cinchona catalyst를 이용한 Morita–Baylis–Hillman (MBH) reaction이다 (Scheme 2).[9] 이 반응은 quinuclidine의 질소가 α, β-unsaturated ketone의 4번 위치 탄소를 공격하고 전자가 이동하면서 Boc group이 deprotection된다. 그 후 친핵체가 입체선택적으로 친전자체를 공격

하며, chiral center를 가지는 생성물을 얻을 수 있다.



Scheme 2. Addition of Thiols to Morita−Baylis−Hillman (MBH) Carbonates

이처럼 다수의 반응에서 *cinchona* organocatalyst는 적용되고 있으며, 높은 화학수율과 광학수율을 보고하고 있다.

3. *Cinchona* organocatalyst and Sulfa Michael addition

Michael addition은 온화한 반응조건에서 C-C bond 나 C-heteroatom bond를 형성할 수 있다. 이러한 특징 때문에 Michael addition에 관한 연구는 많이 보고 되었다. 또한 다른 반응들에 비해 다양한 nucleophile과 electrophile을 적용해 볼 수 있다는 특징을 가지고, 촉매와 같이 사용했을 경

우 product에 chiral center를 부여할 수 있다는 장점을 가진다. 마찬가지로 황을 이용한 sulfa-Michael addition (SMA) 에서도 많은 연구가 이루어지고 있다. 본 연구에 들어가기에 앞서 보고된 다양한 SMA에 대해 살펴보고자 한다.

SMA는 사용된 촉매의 역할에 따라 크게 2가지로 유형으로 나눌 수 있다. 첫 번째는 Lewis Base–Brønsted Acid/ Lewis Base Catalyst에 의한 반응, 두 번째로는 Iminium activation을 이용한 Amino Catalyst를 이용한 반응이다. Lewis Base–Brønsted Acid/ Lewis Base Catalyst에 의한 반응에 해당되는 촉매의 특징으로는 주로 Lewis Base역할을 하는 3차 nitrogen을 가지며, 다른 부분에는 기질과 hydrogen bonding을 하는 Brønsted Acid 성질을 가지는 부분이 있다. 대표적인 예로는 *cinchona* catalyst가 있으며, 이외에도 rigid한 quinine의 골격은 없지만 필요한 작용기만을 가지고 있는 Takemoto 촉매가 있다 (Figure 5). 반응의 예로는 scheme 3가 있다.[10]

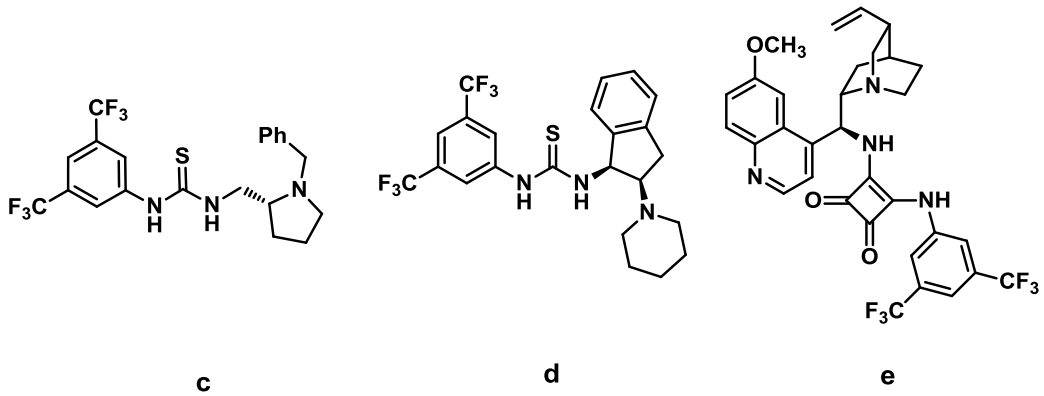
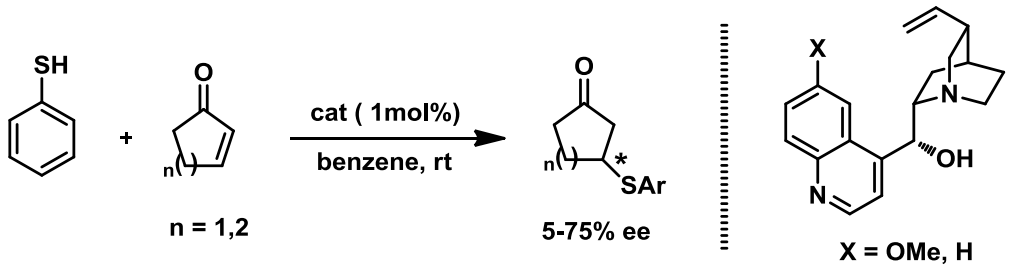


Figure 5. Representative Catalysts of Lewis Base–Brønsted Acid/ Lewis Base



Scheme 3. Enantioselective sulfur Michael addition using Quinine

Iminium activation을 이용한 Amino Catalyst의 경우는 주로 1차, 2차 아민을 포함하는 촉매를 사용하여, 기질의 carbonyl과 iminium을 형성하여 좋은 electrophile를 만든 후 반응이 시작된다 (Figure 6). 그 예를 Scheme 4 에 나타내었다.[11]

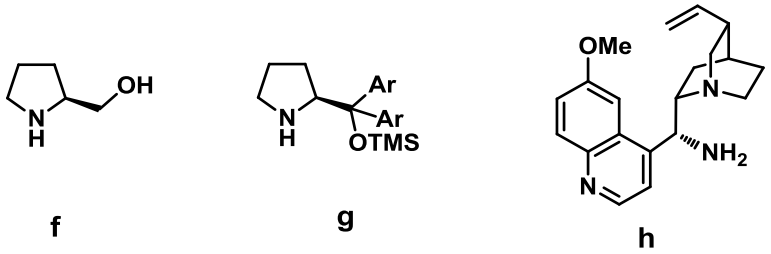
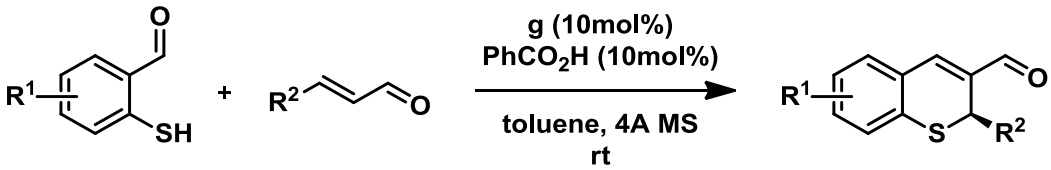
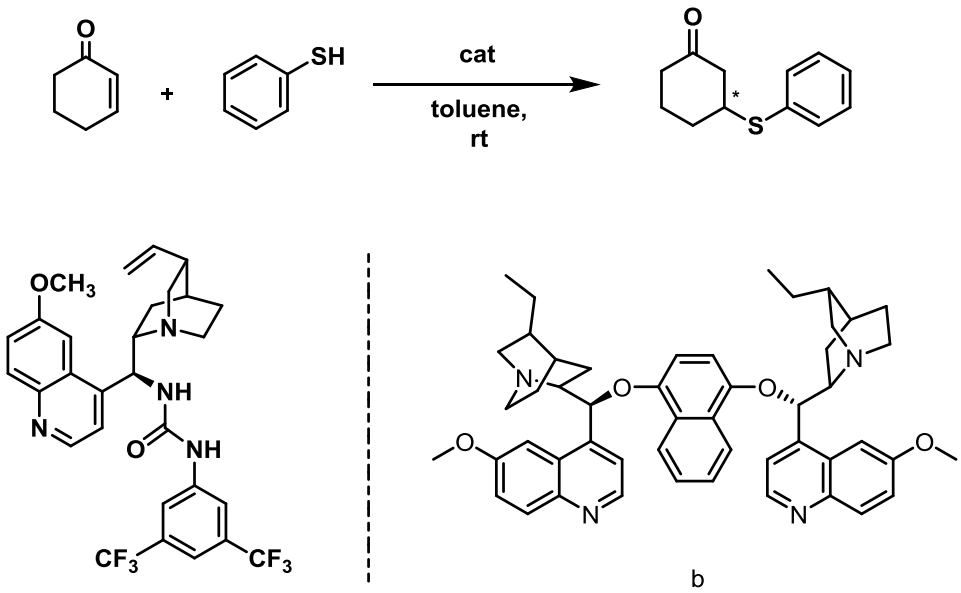


Figure 6. Amino catalyst using iminium activation



Scheme 4. Enantioselective Sulfa Michael addition using iminium activation catatlyst

이 연구는 첫 번째 에 해당되는 유형의 촉매를 사용하였다. Lewis Base–Brønsted Acid/ Lewis Base 역할을 하는 catalyst를 이용하여 친전자체로는 2-cyclohexen-1-one, 친핵체로는 thiophenol을 사용하였다. 지금부터는 본 연구와 연관된 선행연구에 대해 살펴보고자 한다.

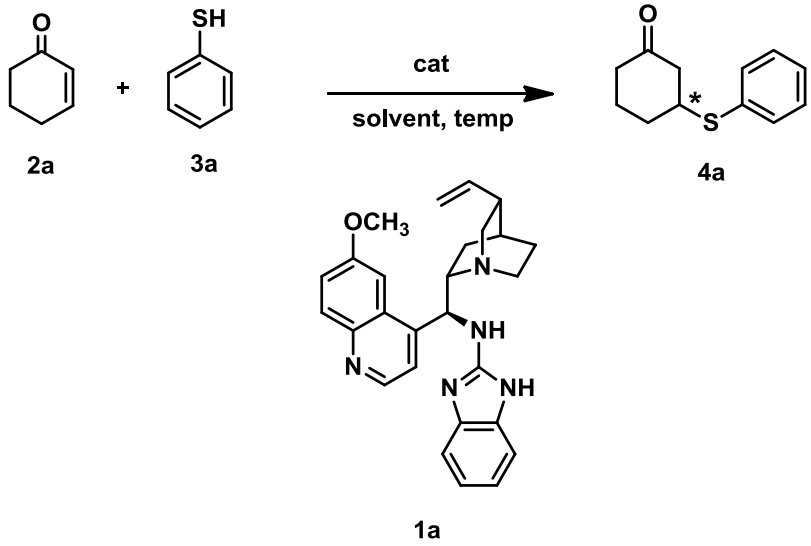


Scheme 5. Enantioselective sulfur Michael addition using Cinchona organocatalysts

친전자체로 2-cyclohexen-1-one, 친핵체로 thiophenol을 사용하며 *cinchona* catalyst를 적용한 연구는 현재까지 3종류가 보고되었다. 1980년대 Wynberg's group에서 quinine을 촉매로 하여 최대 75%의 광학 수율을 최초로 보고한 바 있다. (scheme 3) 하지만 낮은 화학수율과 광학수율을 가진다는 단점이 있었다. 이를 보완한 연구로 2002년 Deng's group에서 dimeric cinchona organocatalyst (b)를 이용한 연구가 보고 되었다. 앞선 논문보다 다양한 친핵체와 친전자체에 적용이 가능하고 전보다 향상된 결과값을 보고하였다. 가장 최근에 보고된 연구로는 Singh's group에서 2010년 *cinchona*-derived urea organocatalyst (a)를 이용하여 보고한 것이 있다. 이 연구의 특징으로는 비교적 적은 촉매의 양 0.1mol%를 반응에 적용하였다는 점이며, 99% yield와 99% ee를 보고하였다.[12] 본 연구는 위의 선행연구들을 참고하여 *cinchona*-derived benzimidazole organocatalyst를 적용한 SMA반응을 진행하였다.

Ⅱ. 본 론

Cinchona organocatalyst 를 이용한 SMA 를 진행하기 위해 우선 적절한 친핵체와 친전자체를 탐색하였다. Michael addition 에서 적합한 친전자체로 α, β–unsaturated ketone 을 사용하고자 하였으며, 그 중에서도 *cinchona* organocatalyst 와 함께 많이 사용된 2-cyclohexen-1-one 을 선정하였다. 친핵체로는 nucleophilicity 가 큰 thiophenol 을 선택하였다. 반응에 사용하는 촉매는 2009 년 본 연구실에서 최초로 합성하여 nitroolefin Michael addition 반응에 성공적으로 응용한 quinine 의 C(9) 부분에 aminobenzimidazole 이 붙은 형태의 촉매를 선택하여 SMA 을 진행하였다.

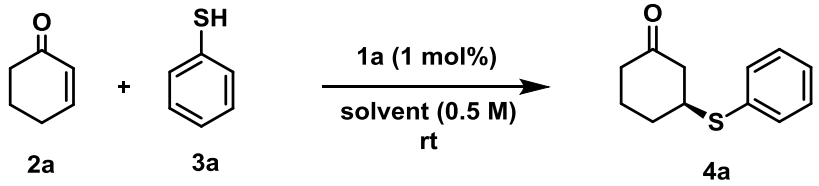


Scheme 6. Enantioselective sulfur Michael addition using *Cinchona*-benzimidazole organocatalysts

1-1. 용매 탐색

C(9) 위치에 benzimidazole 이 붙은 촉매 (**1a**, 1 mol%)를 이용하여 2-cyclohexen-1-one (1 당량)과 thiophenol (1.2 당량), rt 온도 조건에서 용매의 탐색을 진행하였다 (Table 1).

Table 1. Solvent screening



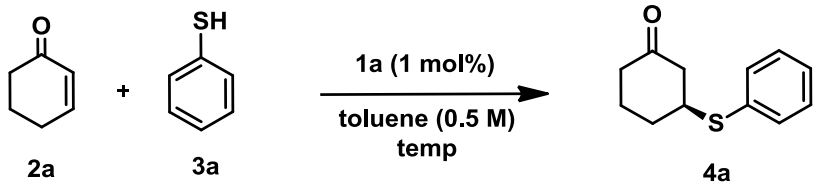
Entry	Solvent	Time (h)	Yield (%)	ee (%)
1	Toluene	2	99	87
2	MeCN	4	99	8
3	DCM	4	97	71
4	1,2-DCE	6	97	75
5	Ether	4	73	61
6	THF	6	94	60
7	Dioxane	6	99	75

다양한 용매를 사용해 본 결과 toluene 에서 가장 높은 화학수율 (99%) 과 광학수율 (87% ee)을 얻을 수 있었다.

1-2. 온도 탐색[13]

앞서 선택한 촉매 (**1a**) 와 2-cyclohexen-1-one (1 당량), thiophenol (1.2 당량), toluene (0.5 M) 용매 조건 하에 반응 온도 조건을 탐색하였다 (Table 2).

Table 2. Temperature screening



Entry	Temperature(˚C)	Time (h)	Yield (%)	ee (%)
1	50	1.5	99	78
2	rt	2	99	87
3	0	3	99	75
4	-40	19	98	66

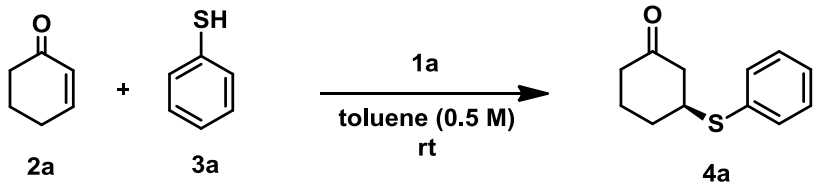
온도를 다양하게 탐색해 보았을 때, 온도에 따른 경향성은 특별히 관찰 할 수 없었다. 일반적으로 온도가 낮아짐에 따라 촉매의 기질에 대한 입체 선택성이 증가하여 광학수율이 증가하는 경향이 있으나, 본 연구에서는

저온에서보다 rt 에서 가장 좋은 화학적 수율 (99%)과 광학 수율 (87%)을 얻을 수 있었다. 이 같은 이유는 저온일수록 반응시간이 길어 짐에 따라 촉매를 경유하지 않는 비촉매 반응이 증가하기 때문인 것으로 예상된다.

1-3. 촉매의 양 탐색

용매는 toluene, 온도는 rt 로 고정하고 촉매 (**1a**)의 양에 따른 SAM 반응의 화학수율과 광학수율을 관찰해 보았다 (Table 3).

Table 3. Catalyst's scale screening



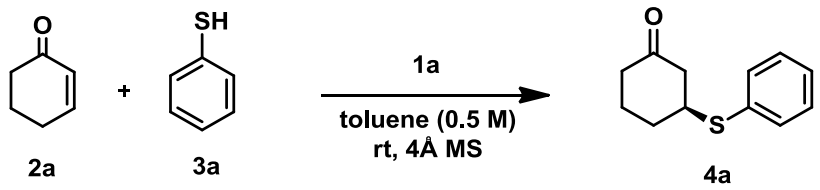
Entry	Cat. Amount (mol%)	Time (h)	Yield (%)	ee (%)
1	10	1	99	70
2	2	1.5	98	84
3	1	2	99	87
4	0.5	4	96	84
5	0.1	4	96	84

그 결과, 비교적 적은 촉매의 양 (1 mol%)에서 가장 좋은 화학수율 (99%) 과 광학 수율(87%)을 관찰할 수 있었다.

1-4. Molecular sieve 의 탐색

앞서 최적화한 반응 조건하에서 무수 정도가 반응 결과에 미치는 영향을 알아보고자 하였다. 일반적으로 무수 조건을 위해 사용하는 molecular sieve 의 양을 달리하여 무수의 정도를 변화시켰다 (Table 4).

Table 4. Molecular sieve screening



Entry	4Å MS (mg)	Time	Yield (%)	ee (%)
1	1.5	2.5h	92	77
2	15	1.5h	94	80
3	75	1h	96	84
4	95	1h	94	83
5	150	1h	94	74
6	300	45min	88	60
7	450	20min	89	30

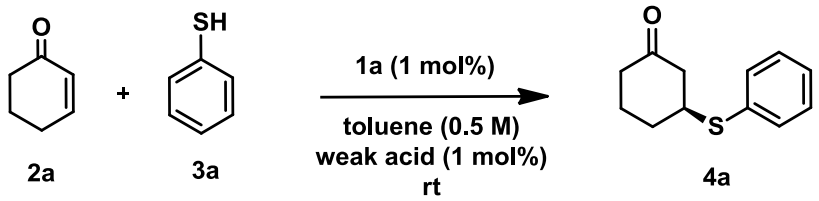
그 결과 molecular sieve 의 양이 증가함에 따라 반응시간은 감소하였고, 화학수율 과 광학수율이 증가하였다. 그러나 일정 이상의 양에서는

광학수율의 감소가 관찰 되었다. 이는 많은 양의 molecular sieve 가 기질과 촉매와의 결합을 방해하기 때문이라고 생각된다.

1-5. Weak acid 의 탐색

본 연구는 **1a** 의 촉매를 선택하여 SMA 를 진행하였다. Benzimidazole 을 포함하는 촉매를 사용하였을 경우, weak acid 를 additive 로 촉매량 만큼 첨가해 주었을 때 광학수율이 증가됨을 보고한 논문들이 다수 있었다. 이를 참고하여 본 연구에서도 weak acid 에 관한 효과를 보고자 하였다 .[14]

Table 5. Weak acid screening

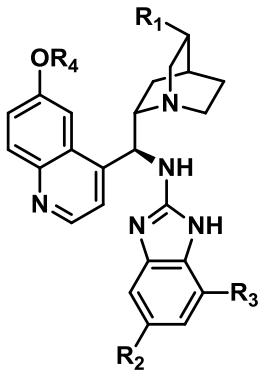


Entry	Weak acid (1mol%)	Time(h)	Yield (%)	ee (%)
1	TFA	4	99	47
2	AcOH	4	98	49
3	BzOH	4	94	31

위의 결과를 보면, 본 연구에서는 촉매량의 weak acid 첨가하였을 경우 향상된 결과값을 얻지 못하였다. 본 연구에서 사용하는 촉매는 benzimidazole

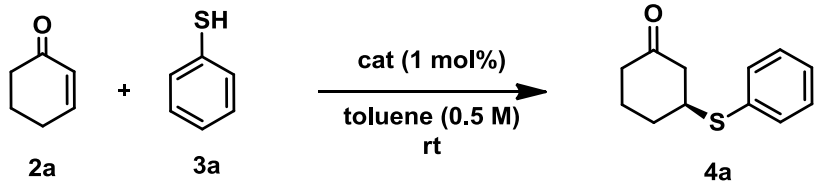
뿐만 아니라 quinuculidine 을 포함 하고 있다. Weak acid 를 첨가할 경우, benzimidazole 의 guanidine 이 아닌 상대적으로 더 강한 염기를 띄는 quinuculidine 에 proton 이 붙게 된다. 이러한 영향으로 촉매와 기질간의 상호작용이 약해져 광학수율이 떨어지는 것으로 생각된다. [15]

1-6. 촉매의 탐색



광학 수율의 향상을 위하여 촉매 **1a** 구조의 여러 부분을 변화시켜 다양한 유도체들을 이용하고자 하였다. 크게 세 부분을 변화시켰는데, 첫 번째 (R_1)로는 quinuclidine 의 vinyl 기를 ethyl 로 환원시킨 형태를 얻었다. 두 번째 (R_2, R_3)로는 benzimidazole 에 EDG 혹은 EWG 를 치환시켜 보았으며, 세 번째 (R_4)로는 C(6)위치에 다양한 alkyl 또는 aryl group 으로 변화시켜 보았다. 먼저, R_1, R_2 , R_3 의 변화에 따른 반응을 관찰하였다 (Table 6).

Table 6. Catalyst screening Ⅰ

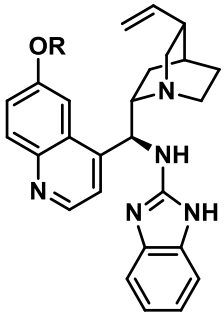


Entry	R_1	R_2	R_3	Cat	Time(h)	Yield (%)	ee (%)
1	$-CH=CH_2$	H	H	**1a**	2	99	87
2	$-CH=CH_2$	CF_3	CF_3	**1b**	2	84	71
3	$-CH=CH_2$	CH_3	H	**1c**	4	84	67
4	$-CH_2-CH_3$	H	H	**1d**	2.5	99	79
5	$-CH_2-CH_3$	CF_3	CF_3	**1e**	2	84	67

R_1 의 경우, ethyl보다 vinyl기를 가졌을 때 더 좋은 화학적 수율(99%)과 광학수율(87%)을 관찰 할 수 있었다. R_2 와 R_3의 경우, EWG가 있을 때보다 EDG가 있을 때 상대적으로 더 좋은 결과를 보였으나, 가장 좋은 결과를 보인 경우는 치환기가 없이 수소가 있을 경우였다 (entry 1, **1a**).

다음으로는 R_4자리를 다양한 alkyl 또는 aryl로 변화시켜 얻은 유도체들의 촉매로 사용하였다 (Table 7).[16]

Table 7. Catalyst screening Ⅱ

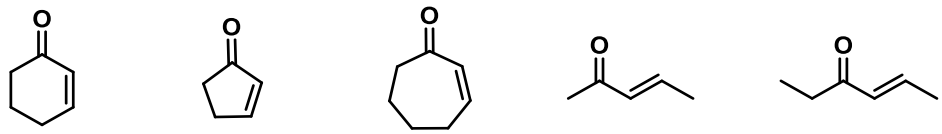


Entry	-OR	Cat.	Time(h)	Yield (%)	ee (%)
1	-OMe	**1a**	2	99	87
2	-OH	**1f**	5	95	58
3	-OEt	**1g**	10	97	64
4	-Opr	**1h**	10	97	60
5	-OCH_2F	**1i**	20	97	63
6	-Oipr	**1j**	21	98	52
7	-Onaphthyl	**1k**	10	98	72
8	-OdiphMe	**1l**	20	97	64
9	-Otrit	**1m**	10	96	62

C(6) 위치에 여러 alkyl 과 aryl 을 도입한 유도체를 얻어 반응에 적용해 본 결과 가장 좋은 반응시간 (2h), 화학적 수율 (99%), 광학 수율 (87% ee)은 C(6) 위치에 methoxy 가 있는 **1a** 임을 관찰 할 수 있었다.

1. Michael acceptor 탐색

지금까지의 최적화된 SMA 반응조건을 이용하여 다양한 Michael acceptor 에 응용하였다. 이를 위하여 다음의 5 가지 α,β-unsaturated ketone 을 선정하였다 (Figure 7).

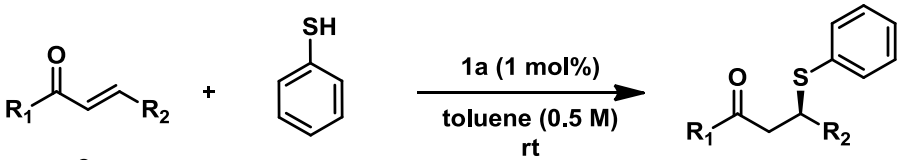


2a 2b 2c 2d 2e

Figure 7. Michael acceptors

선정된 5 가지 Michael acceptor (1 당량)와 thiophenol (1.2 당량), 촉매 **1a** (1 mol%), toluene (0.5 M), rt 조건에서 SMA 를 진행하였다 (Table 8). 그 결과 acylic 한 형태보다는 cyclic 한 형태에서 빠른 반응 시간 내에 높은 광학 수율을 얻을 수 있었으며, cyclic α,β-unsaturated ketone 의 경우 5 환 과 7 환의 경우 6 환의 경우보다 낮은 광학수율을 보였다.

Table 8. Enantioselective SMA of Michael acceptors



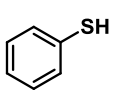
2 3a 4

Entry	Michael acceptor	Product	Time (h)	Yield (%)	ee (%)

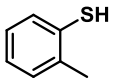
1	**2a**	**4a**	2	99	87
2	**2b**	**4b**	2	97	65
3	**2c**	**4c**	2	95	35
4	**2d**	**4d**	4	99	27
5	**2e**	**4e**	4	99	40

2. Michael donor 탐색

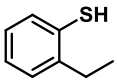
가장 높은 광학활성을 보인 2-cyclohexen-1-one (1 당량)을 Michael acceptor 로 고정하고 촉매 **1a** (1 mol%), toluene (0.5 M), rt 조건 하에서 하기의 다양한 Michael donor (1.2 당량)를 적용하여 SMA 를 진행하였다 (Table 9).



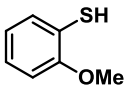
3a



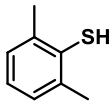
3b



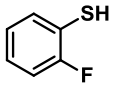
3c



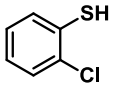
3d



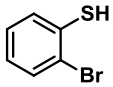
3e



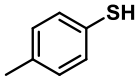
3f



3g



3h



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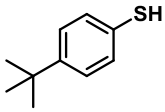

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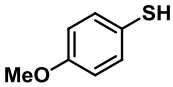

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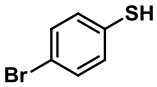

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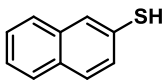
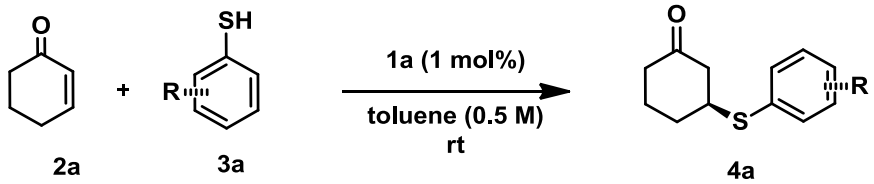


3m

Figure 8. Michael donors

Table 9. Enantioselective SMA of 2-cyclohexen-1-one with Michael donors



Entry	Michael donor	Product	Time (h)	Yield (%)	ee (%)
1	**3a**	**5a**	2	99	87
2	**3b**	**5b**	12	98	81
3	**3c**	**5c**	15	98	80
4	**3d**	**5d**	72	90	84
5	**3e**	**5e**	48	82	57
6	**3f**	**5f**	4	96	28
7	**3g**	**5g**	4	99	43
8	**3h**	**5h**	4	99	55
9	**3i**	**5i**	12	98	67
10	**3j**	**5j**	15	80	64
11	**3k**	**5k**	20	88	80
12	**3l**	**5l**	30	90	11

13	**3m**	**5m**	45	80	11

그 결과 *ortho* 위치보다 *para* 에 치환기가 존재할 경우, 광학 수율이 전반적으로 감소한 것을 관찰할 수 있었다. 이는 촉매와 Michael donor 가 결합 할 때 para 의 치환기들이 촉매의 benzimidazole 의 판상구조와 입체장애를 형성하여 촉매와 기질의 상호작용을 저해하기 때문으로 생각된다. 또한 Michael donor 의 *ortho* 에 치환기가 있을 경우, Electron Withdrawing Group (EWG) 보다 Electron Donating Group (EDG) 이 있을 때 더 높은 광학 수율을 얻을 수 있었으나, 가장 높은 광학 수율은 치환기가 아무것도 존재하기 않은 친핵체 **3a** 에서 관찰할 수 있었다. EWG 가 *ortho* 에 있을 경우 pka 값이 감소하여 낮은 광학 수율을 보였는데, 이는 촉매와 기질이 상호작용을 하기 전에 진행되는 비촉매 반응 때문인 것으로 생각된다. 또 다른 이유로는 *ortho* 에 치환기가 없을 때, 치환기가 있을 때보다 입체장애가 감소하여 촉매를 경유한 반응이 더 잘 일어나기 때문에 더 높은 광학 수율을 보이는 것으로 생각된다.

4. 생성물의 절대 배열 및 Plausible Transition state

앞서 얻은 전반적인 결과를 토대로 기질과 촉매간의 상호작용에 대하여 제안해 보았다. 기질과 촉매 간 크게 2 가지의 상호작용이 있을 것으로 생각된다. 즉, 첫 번째로는 촉매 C(9) 부분의 aminobenzimidazole 과 Michael

acceptor 간의 hydrogen bonding 이고, 두 번째는 quinuclidine 의 질소가 Michael donor 를 deprotonation 시킨 후 cation 을 형성하게 되고, 이 cation 이 anion 을 띄고 있는 Michael donor 와의 ion pairing 을 이룬다. 이러한 2 가지의 상호작용을 통하여 기질과 촉매간의 3 차원적 배향이 유지되어 *Si* face attack 이 일어나고 그 결과 (S)-form 의 생성물을 얻을 수 있다 (Figure 9).

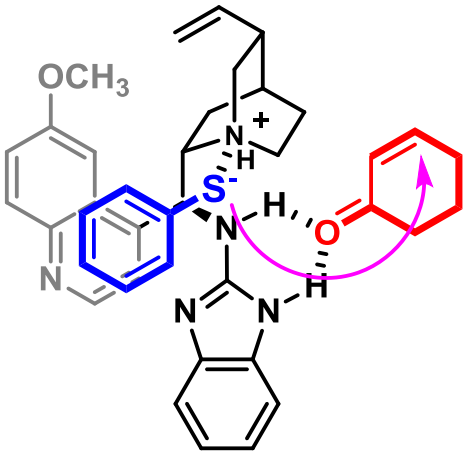
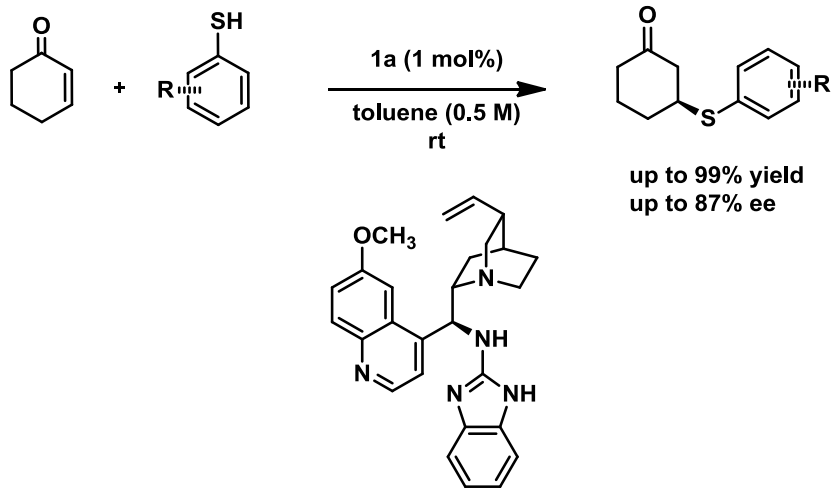


Figure 9. Plausible transition state

Ⅲ. 결 론

본 연구에서는 생물학적으로 또는 의약품적으로도 의미가 있는 황을 포함하는 유기 화합물을 합성하고자 하였다. 이를 위하여 비대칭 *cinchona* 알칼로이드 계열의 촉매 **1a** 를 이용하여 성공적으로 광학활성 sulfur compound 를 얻을 수 있었다. 즉, Michael acceptor 로 2-cyclohexen-1-one, Michael donor 로 thiophenol 유도체들을 사용하였으며 촉매로는 **1a** 를 사용하여 상온에서 높은 화학 수율 (99%)와 광학 수율 (87%)를 얻을 수 있었다. 본 연구를 통하여 개발된 반응을 통하여 향후 생리활성이 있는 천연물 또는 다양한 황 화합물 유도체를 얻을 수 있을 것으로 기대된다.



1a

Ⅳ. 실　험

1. 일반적인 방법

반응에 사용된 초자는 flamed-dried 된 초자를 사용하였으며, 모든 반응은 무수 조건 (Ar 치환)에서 수행되었다. 용매는 무수용매를 사용하였으며, 반응 시약들은 다른 정제과정을 거치지 않은 구입한 것을 사용하였다.

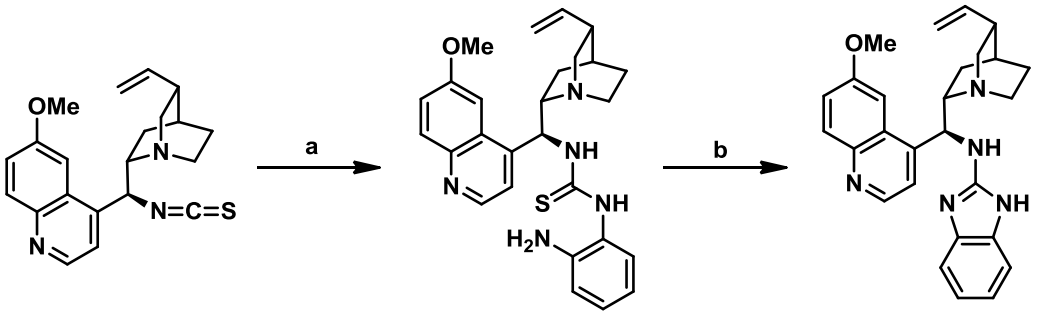
1-1. 크로마토그래피와 HPLC

TLC 는 Merck precoated TLC plate (silica gel 60 GF_{254}, 0.25 mm)를 사용하였다. Flash column chromatography 은 E. Merch Kieselgel 60 (230~400 mesh)를 사용하였으며, HPLC 기계는 Instrument (Hitachi, L-2130) 와 software (Hitachi, Version LaChrom 8908800-07) 를 사용하여 측정하였다. 물질의 거울상이성질체과잉율 (enantiomeric excess, ee)은 4.6 mm x 250 mm Daicel Chiralpak AD-H, Chiralcel AS-H columns 을 사용하여 HPLC 기기로 측정하였다.

1-2. Spectral data

Nuclear magnetic resonance (^{1}H-NMR & ^{13}C-NMR) spectra 는 JEOL JNM-ECZ 400S/L [400 MHz (^{1}H), 100 MHz (^{13}C)] spectrometer 와 5-mm triple resonance inverse cryoprobe 가 있는 Bruker Avance Ⅲ HD [800 MHz (^{1}H),

200 MHz (^{13}C)] spectrometer 를 사용하였다. ^{1}H-NMR & ^{13}C-NMR spectra 는 $CDCl_3$ (δ 7.24)를 내부 기준으로 하여 측정하였으며, chemical shift 는 ppm(parts per million) 단위로, coupling constant (J)는 Hz 로 표기하였다. Infrared (IR) spectra 는 JASCO FT/IR-300E and Perkin-Elmer 1710 FT spectrometer 를 사용하였다. Low-resolution mass spectra (LRMS)와 high-resolution mass spectra (HRMS)는 JEOL JMS 700, JEOL JMS 600-W spectrometer, or Agilent 6530 Q-TOF spectrometer 로 측정하였다. 녹는점은 Büchi B-540 melting point apparaturs 를 사용하였다. Optical rotations 은 a JASCO polarimeter P-2000 series 를 사용하여 측정하였다.



2. Catalyst derivatives

실험방법 (a)

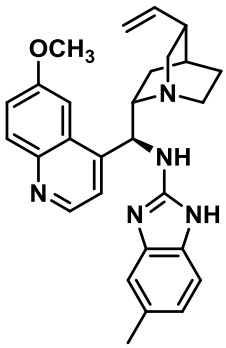
100 mL 둥근플라스크 (rbf)에 4-[(5-vinyl-1-aza-bicyclo[2.2.2]oct-2-yl)-isothiocyanato-methyl]-6-methoxy-quinoline [QN-NCS] (77.6 mg, 0.212 mmol), 3,4-diaminotoluene(42.8 mg, 0.35 mmol), 용매 acetonitrile (7 mL)을 넣은 후 온도는 rt 조건에서 20 시간 교반하였다. TLC 결과를 관찰하여 기질이 사라진

후 반응을 종결시켰다. 반응용매를 감압 evaporation 으로 제거한 후, DCM : MeOH = 10 :1 조성에서 medium pressure liquid chromatography 를 통해 정제하여 생성물을 얻었다 (63% yield, 20h).

실험방법 (b)

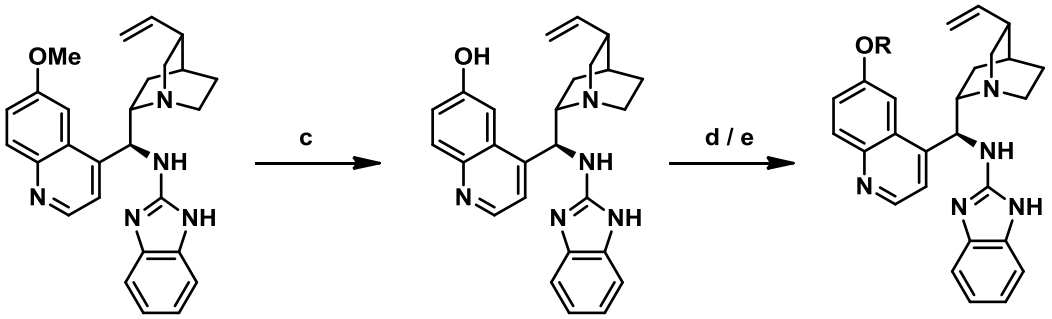
100 mL 2-Neck-rbf 에 1-(2-Amino-4-methyl-phenyl)-3-[(5-ethyl-1-aza bicyclo[2.2.2]oct-2-yl)-(6-methoxy-qunolin-4-yl)-methyl]-thiourea[QN-TU] (65 mg, 0.133 mmol), mercury oxide (57.7 mg, 0.267 mmol), sulfur (0.8 mg, 0.027 mmol)을 넣고, 용매 ethanol (6 mL) 넣은 후 8 시간 동안 reflux 하였다. TLC 로 기질이 사라진 것을 확인 후 반응을 종결시켰다. 반응 혼합물을 celite 로 여과한 후, 얻은 여액을 evaporation 하였다. 얻은 crude 생성물을 DCM : MeOH = 10 :1 조성에서 medium pressure liquid chromatography 를 통해 정제하여 생성물을 얻었다 (73% yield, 8h).

(5-Methyl-1H-benzimidazole-2-yl)-9-epi-quinine amine (1c)



위의 실험방법 (a), (b)를 통하여 white solid 로 물질 **1c** 를 얻었다.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 4.6 Hz, 1H), 7.95 (d, J = 2.8 Hz, 1H), 7.90 (d, J = 9.2 Hz, 1H), 7.64 (d, J = 5.1 Hz, 1H), 7.38 (dd, J = 9.2, 2.8 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 6.94 (s, 1H), 6.73 (dd, J = 7.8, 0.9 Hz, 1H), 5.91-5.82 (m, 1H), 5.65 (d, J = 10.1 Hz, 1H), 5.07-4.98 (m, 2H), 3.91 (s, 3H), 3.60 (s, 1H), 3.45 (dd, J = 17.0, 10.1 Hz, 1H), 2.88-2.78 (m, 2H), 2.40 (s, 1H), 2.29 (s, 3H), 1.89-1.52 (m, 4H), 1.26-1.19 (m, 1H), 1.05 (q, J = 6.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 158.0, 154.4, 147.4, 144.5, 144.2, 140.2, 137.8, 136.0, 131.5, 131.3, 129.9, 128.2, 122.0, 121.4, 115.1, 112.6, 112.2, 102.3, 60.4, 55.8, 55.0, 41.0, 38.7, 29.6, 27.1, 27.0, 25.9, 21.4 ppm; IR (KBr) 2930, 2349, 2320, 1658, 1621, 1571, 1029, 916, 852, 772, 687cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{28}H_{32}N_5O]^+$($[M+H]^+$) 454.2607; found 454.2604. m.p = 160-165 °C, $[\alpha]_D^{20}$ = +4.39 (*c* 1.0, $CHCl_3$).



실험방법 (c)

100 mL 2-neck-rbf 에 **1a**[17] (300 mg, 0.683 mmol)를 넣은 후, anhydrous DCM (6.8 mL) 를 넣고 0 °C 에서 교반하였다. Boron tribromide (683.9 mg, 2.730 mmol) 를 반응 용액에 dropwise 로 넣어주었다. 그 후 온도는 rt 로 유지하였다. TLC 로 기질이 사라진 후 반응을 종결시켰다. 그 후 1N NaOH (3 mL)를 넣어 반응 용액을 중화 시켰다. 그 후 evaporation 하고 얻은 결과물을 medium pressure liquid chromatography 로 정제하여 생성물을 얻었다.

실험방법 (d)[18]

100 mL Rbf 에 anhydrous DMF (0.2 M)를 넣은 후, **1f** (1 당량), cesium carbonate (2 당량)을 넣고 60 °C 에서 교반하면서 alkyl bromide (1.5 당량)을 넣어준다. TLC 로 기질이 사라진 것을 확인한 후 반응을 종결시켰다. 그 후 반응용매를 evaporation 시켜 제거한 후, medium pressure liquid chromatography 를 정제하여 생성물을 얻었다.

실험방법 (d-2)

100 mL Rbf 에 anhydrous DMF (0.2 M)를 넣은 후, **1f** (1 당량), cesium carbonate (2 당량)을 넣고 0 °C 에서 교반하면서 alkyl bromide (1.5 당량)을 넣어준다. TLC 로 기질이 사라진 것을 확인한 후 반응을 종결시켰다. 그 후

반응용매를 evaporation 시켜 제거한 후, medium pressure liquid chromatography 를 정제하여 생성물을 얻었다.

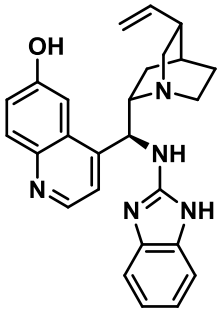
실험방법 (d-3)

100 mL Rbf 에 acetone (0.2 M)를 넣은 후, **1f** (1 당량), cesium carbonate (2 당량)을 넣고 60 °C 에서 교반하면서 alkyl bromide (1.1 당량)을 넣어준다. TLC 로 기질이 사라진 것을 확인한 후 반응을 종결시켰다. 그 후 반응용매를 evaporation 시켜 제거한 후, medium pressure liquid chromatography 를 정제하여 생성물을 얻었다.

실험방법 (e)

100 mL rbf 에 sodium hydroxide (3 당량)과 water (60 μL)를 넣은 후, **1f** (1 당량)와 tetrabutyl ammonium bromide (0.1 당량) 을 넣고 rt 에서 15 분 동안 교반하였다. 그 후, trityl bromide (1.1 당량) 을 dicholoromethane (86 μL)에 녹인 후 반응용액에 dropwise 하였다. TLC 로 기질이 사라진 것을 확인한 후 반응을 종결시켰다. 그 후 반응용매를 evaporation 시켜 제거한 후, medium pressure liquid chromatography 를 정제하여 생성물을 얻었다.

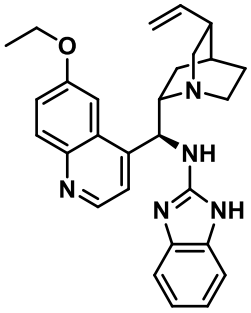
***N*-(6-hydroxycinchonan-9-yl) benzimidazole (1f)**



실험방법 (c)를 이용하여 white solid 형태의 물질 **1f** 를 얻었다 (55% yield, 반응시간 4 시간).

^{1}H-NMR (400 MHz, MeOD) δ 8.57 (d, J = 4.6 Hz, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 2.8 Hz, 1H), 7.64 (d, J = 4.6 Hz, 1H), 7.34-7.31 (m, 1H), 7.13-7.08 (m, 2H), 6.88 (td, J = 6.4, 3.4 Hz, 2H), 5.83-5.74 (m, 1H), 5.48 (d, J = 18.8 Hz, 1H), 5.02-4.92 (m, 2H), 3.37 (s, 1H), 2.83-2.76 (m, 2H), 2.34 (s, 1H), 1.75 (td, J = 9.4, 4.7 Hz, 1H), 1.62 (d, J = 2.3 Hz, 2H), 1.36-1.21 (m, 2H), 1.07 (q, J = 7.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, MeOD) δ 155.8, 147.5, 144.4, 142.0, 131.4, 123.5, 121.5, 115.3, 113.1, 56.3, 42.1, 40.4, 28.7, 27.9, 26.2 ppm; IR (KBr) 2939, 2865, 2843, 1632, 1600, 1574, 1504, 1465, 1410, 1346, 1321, 1269, 1243, 1054, 1032, 1014, 917, 855, 835, 804cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{26}H_{29}N_5O]^+$($[M+H]^+$) 427.2372; found 427.2378. m.p = 235-240 °C, $[\alpha]_D^{20}$ = -15.07 (*c* 1.0, MeOH).

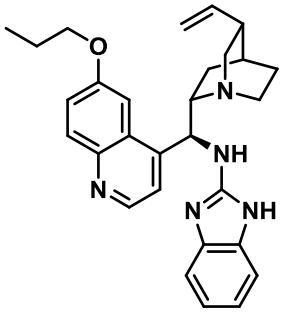
***N*-(6-ethoxycinchonan-9-yl) benzimidazole (1g)**



물질 **1f** 를 출발물질로 하여 실험방법 (d) 를 이용하여 yellow solid 형태의 물질 **1g** 를 얻었다 (46% yield, 반응시간 24h).

^{1}H-NMR (400 MHz, MeOD) δ 8.66 (d, J = 4.6 Hz, 1H), 8.01-7.97 (m, 1H), 7.92 (q, J = 4.7 Hz, 1H), 7.65 (d, J = 5.1 Hz, 1H), 7.39 (dd, J = 9.2, 2.3 Hz, 1H), 7.16-7.10 (m, 2H), 6.93 (td, J = 6.5, 3.5 Hz, 2H), 5.94-5.85 (m, 1H), 5.66 (d, J = 10.6 Hz, 1H), 5.08-4.99 (m, 2H), 4.27-4.20 (m, 1H), 4.12-4.01 (m, 1H), 3.61 (q, J = 6.9 Hz, 1H), 3.44 (dd, J = 17.5, 10.1 Hz, 1H), 2.82-2.74 (m, 2H), 2.39 (d, J = 2.3 Hz, 1H), 1.83-1.51 (m, 4H), 1.38 (t, J = 6.9 Hz, 3H), 1.32-1.24 (m, 1H), 1.05-0.96 (m, 1H), 0.92-0.85 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 154.8, 147.4, 144.7, 140.6, 131.6, 122.4, 120.5, 115.0, 112.6, 102.7, 72.6, 71.3, 70.5, 70.4, 69.8, 66.7, 64.0, 63.6, 61.7, 61.7, 55.3, 40.9, 39.1, 31.6, 29.7, 27.3, 27.3, 25.9, 19.2, 15.0, 14.6, 13.9 ppm; IR (KBr) 2931, 2867, 2349, 2320, 1461, 1396, 1338, 1318, 1267, 1242, 1219, 1113, 1043, 854, 772, 687 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{28}H_{32}N_5O]^+$($[M+H]^+$) 454.2607; found 454.2606. m.p = 110-115 °C, $[\alpha]_D^{20}$ = -38.15 (*c* 1.0, $CHCl_3$).

***N*-(6-propoxycinchonan-9-yl) benzimidazole (1h)**

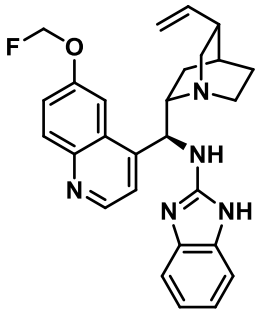


물질 **1f** 를 출발물질로 하여 실험방법 (d) 를 이용하여 yellow solid 형태의 물질 **1g** 를 얻었다 (49% yield, 반응시간 24h).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 4.6 Hz, 1H), 8.05-7.96 (m, 2H), 7.65-7.59 (m, 1H), 7.37 (td, J = 8.6, 2.5 Hz, 1H), 7.28-7.27 (m, 1H), 7.02-6.94 (m, 3H), 6.62 (s, 1H), 5.76-5.62 (m, 2H), 5.04-4.95 (m, 2H), 4.14 (t, J = 6.4 Hz, 2H), 4.03-3.83 (m, 2H), 3.34 (dd, J = 13.6, 10.3 Hz, 2H), 2.88-2.70 (m, 2H), 2.39 (d, J = 6.9 Hz, 1H), 1.11 (t, J = 7.6 Hz, 3H), 0.89 (q, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 154.7, 147.3, 144.6, 139.8, 137.7, 131.4, 128.2, 122.5, 120.4, 120.2, 115.4, 112.4, 102.7, 69.9, 60.4, 54.9, 41.0, 38.5, 29.6, 27.1, 26.7, 25.7, 23.9, 22.4, 21.0, 14.1, 10.6 ppm; IR (KBr) 3065.3, 2930.31, 2349.84, 2320.91 1619.91, 1596.77, 1563.99, 1549.52,1132.01, 1011.48, 984.482, 914.093, 853.347, 772.351 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{26}H_{29}N_5O]^+$($[M+H]^+$) 206.0765; found 206.0766. m.p = 180-185 °C, $[\alpha]_D^{20}$ = -

74.79 (*c* 1.0, $CHCl_3$).

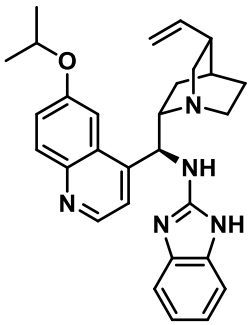
***N*-(6-fluoromethoxycinchonan-9-yl) benzimidazole (1i)**



물질 **1f** 를 출발물질로 하여 실험방법 (d-2) 를 이용하여 white solid 형태의 물질 **1i** 를 얻었다 (16% yield, 반응시간 24h).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.83 (d, J = 4.3 Hz, 1H), 8.14 (t, J = 9.2 Hz, 2H), 7.62-7.50 (m, 2H), 7.17 (q, J = 2.9 Hz, 2H), 6.98 (q, J = 3.1 Hz, 2H), 5.96-5.92 (m, 1H), 5.82-5.78 (m, 1H), 5.75-5.66 (m, 1H), 5.20 (d, J = 4.3 Hz, 1H), 5.02-4.96 (m, 2H), 3.38-3.25 (m, 3H), 2.88-2.78 (m, 2H), 1.72-1.63 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 154.6, 149.0, 145.8, 140.8, 132.3, 127.6, 121.7, 120.6, 114.9, 112.7, 107.3, 101.6, 99.4, 72.5, 70.5, 69.8, 66.7, 63.6, 61.7, 55.4, 40.8, 39.2, 30.9, 27.4, 27.3, 25.7, 15.0 ppm; IR (KBr) 2931, 2349, 2320, 1921, 1867, 1509, 1488, 1461, 1417, 1338, 1269, 1219, 1093, 855, 772, 687 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{27}H_{29}N_5OF]^+$($[M+H]^+$) 458.2356; found 458.2349. m.p = 140-145 °C, $[[\alpha]_D^{20}$ = -21.64 (*c* 1.0, $CHCl_3$).

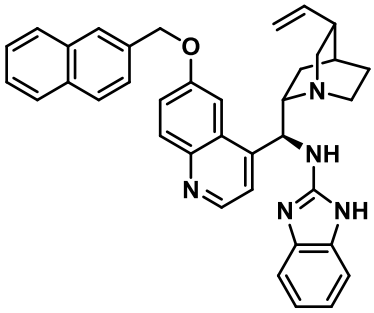
***N*-(6-isopropxycinchonan-9-yl) benzimidazole (1j)**



물질 **1f**를 출발물질로 하여 실험방법 (d) 를 이용하여 yellow solid 형태의 물질 **1j**를 얻었다 (25% yield, 반응시간 24h).

^{1}H-NMR (400 MHz, MeOD) δ 8.65 (d, J = 4.6 Hz, 1H), 8.00-7.90 (m, 2H), 7.64 (d, J = 4.6 Hz, 1H), 7.36 (dd, J = 9.2, 2.8 Hz, 1H), 7.15 (q, J = 3.1 Hz, 2H), 6.92 (dt, J = 9.5, 3.6 Hz, 2H), 5.93-5.84 (m, 1H), 5.65-5.57 (m, 1H), 5.07-4.99 (m, 2H), 3.68-3.56 (m, 1H), 3.43 (dd, J = 17.7, 9.9 Hz, 1H), 2.85-2.73 (m, 2H), 2.38 (s, 1H), 1.78-1.52 (m, 4H), 1.37 (d, J = 6.0 Hz, 3H), 1.28-1.20 (m, 1H), 1.16-1.11 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 154.9, 147.3, 144.5, 141.1, 131.5, 128.0, 123.1, 120.4, 114.7, 112.6, 104.2, 72.5, 70.4, 70.1, 69.8, 66.6, 61.5, 55.6, 40.7, 39.3, 27.6, 27.3, 26.0, 21.8, 21.6, 21.0, 15.0ppm; IR (KBr) 3066, 2975, 2933, 2865, 2349, 2320, 1658, 1619, 1567, 1508, 1461, 1338, 1267, 1241, 1219, 1112, 772, cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{29}H_{34}N_5O]^+$($[M+H]^+$) 468.2763; found 468.2765. m.p = 130-135 °C, $[\alpha]_D^{20}$ = -38.15 (*c* 1.0, $CHCl_3$).

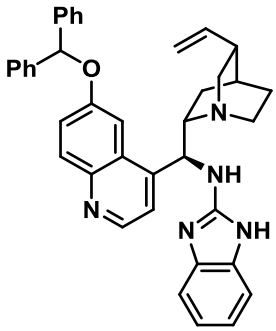
***N*-[6-(2-naphthyl)methoxycinchonan-9-yl) benzimidazole (1k)**



물질 **1f** 를 출발물질로 하여 실험방법 (d-3) 를 이용하여 yellow solid 형태의 물질 **1k** 를 얻었다. (18% yield, 반응시간 24h)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 4.6 Hz, 1H), 8.05 (d, J = 9.2 Hz, 1H), 7.93 (s, 1H), 7.88-7.79 (m, 4H), 7.59 (dd, J = 8.3, 1.4 Hz, 1H), 7.53-7.47 (m, 4H), 7.14 (d, J = 28.5 Hz, 2H), 6.96 (dt, J = 9.3, 3.7 Hz, 2H), 6.12 (s, 1H), 5.65-5.56 (m, 1H), 5.41 (dd, J = 20.0, 12.6 Hz, 2H), 5.06-4.80 (m, 3H), 3.19 (dd, J = 13.8, 10.1 Hz, 2H), 3.02 (s, 1H), 2.70-2.62 (m, 2H), 2.23 (s, 1H), 2.02 (t, J = 8.3 Hz, 1H), 1.60-1.29 (m, 4H), 0.88-0.71 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 154.9, 147.3, 144.5, 141.1, 131.5, 128.0, 123.1, 120.4, 114.7, 112.6, 104.2, 72.5, 70.4, 70.1, 69.8, 66.6, 61.5, 55.6, 40.7, 39.3, 27.6, 27.3, 26.0, 21.8, 21.6, 21.0, 15.0 ppm; IR (KBr) 2349, 2320, 1867, 1509, 1488, 1460, 1396, 1338, 1268, 1219, 1122, 818, 772, 687, 673 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{37}H_{36}N_5O]^+$($[M+H]^+$) 566.2920; found 566.2923. m.p = 150-155 °C; $[\alpha]_D^{20}$ = -36.33 (*c* 1.0, $CHCl_3$).

***N*-(6-diphenylmethoxycinchonan-9-yl) benzimidazole (1l)**

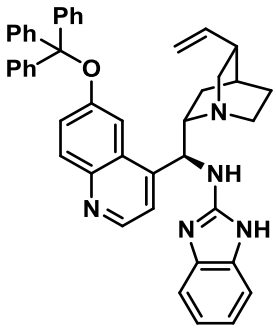


물질 **1f**를 출발물질로 하여 실험방법 (d) 를 이용하여 yellow solid 형태의 물질 **1l**를 얻었다 (52% yield, 반응시간 24h).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.62 (t, J = 4.4 Hz, 1H), 8.08 (d, J = 2.8 Hz, 1H), 7.97-7.91 (m, 1H), 7.63 (t, J = 4.8 Hz, 1H), 7.60-7.56 (m, 3H), 7.44 (d, J = 7.4 Hz, 2H), 7.31 (dd, J = 8.0, 7.1 Hz, 4H), 7.27-7.15 (m, 4H), 6.91 (q, J = 3.2 Hz, 2H), 6.83 (s, 1H), 5.78-5.70 (m, 1H), 5.48-5.45 (m, 1H), 5.00-4.92 (m, 2H), 3.24-3.12 (m, 2H), 2.75-2.69 (m, 2H), 2.29 (s, 1H), 1.46 (d, J = 17.0 Hz, 3H), 1.27-1.20 (m, 1H), 0.64 (d, J = 4.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 154.7, 147.5, 144.7, 141.1, 140.7, 131.5, 128.7, 128.5, 128.0, 127.8, 127.6, 126.9, 126.8, 123.2, 120.5, 114.7, 105.1, 82.1, 72.5, 70.4, 69.8, 66.7, 61.6, 55.4, 40.6, 39.4, 27.5, 27.3, 25.8, 15.0 ppm; IR (KBr) 2866, 2371, 2320, 1867, 1658, 1620, 1597, 1568,1509, 1461, 1267, 1240, 1219, 1132, 1082, 1010, 914, 852, 772, 742, 700, 671 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{39}H_{38}N_5O]^+$($[M+H]^+$)

592.3076; found 592.3080. m.p = 160-165 °C; $[\alpha]_D^{20}$ = -47.84 (*c* 1.0, $CHCl_3$).

***N*-(6-triphenylmethoxycinchonan-9-yl) benzimidazole (1m)**

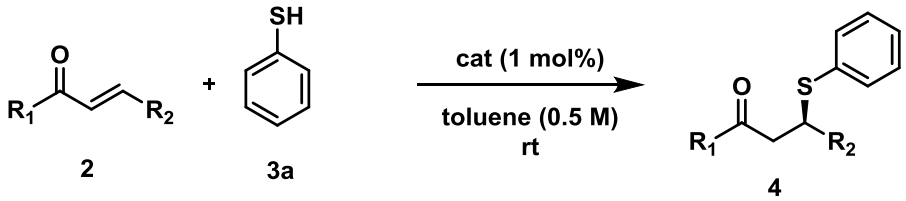


물질 **1f** 를 출발물질로 하여 실험방법 (e) 를 이용하여 white solid 형태의 물질 **1m** 를 얻었다 (26% yield, 반응시간 24h).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 4.1 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.65-7.46 (m, 8H), 7.21-6.97 (m, 13H), 6.60 (d, J = 28.8 Hz, 1H), 5.68-5.60 (m, 1H), 4.97-4.91 (m, 2H), 4.27 (d, J = 6.4 Hz, 1H), 3.17 (dd, J = 13.7, 10.1 Hz, 1H), 2.96-2.63 (m, 4H), 2.20 (s, 1H), 2.01 (t, J = 9.4 Hz, 1H)ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 154.5, 148.1, 143.2, 141.2, 130.9, 128.9, 128.6, 127.9, 127.6, 126.7, 120.5, 114.6, 113.0, 90.5, 72.5, 71.2, 70.6, 70.5, 70.3, 70.1, 70.0, 69.9, 66.7, 63.7, 61.8, 61.8, 61.7, 55.5, 40.5, 39.5, 31.6, 30.9, 29.7, 27.3, 27.1, 19.2, 15.1 ppm; IR (KBr) 2931, 2867, 2349, 2320, 1689, 1679, 1620, 1564, 1551, 1507, 1489, 1459, 1219, 1187, 1130, 772, 703, 672 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{45}H_{42}N_5O]^+$($[M+H]^+$) 668.3389; found 668.3381. m.p = 160-165 °C; $[\alpha]_D^{20}$ = -

76.13 (c 1.0, $CHCl_3$).

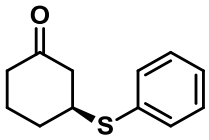
2- Michael acceptor



실험방법

Sealed tube 에 Ar 치환을 한 후, 촉매 stock solution 에서 1 mol% 를 주시기를 통해 넣고 교반하였다. 그 후, Michael acceptor (1 당량, 0.499mmol)을 넣고 충분히 교반하면서, thiophenol (1.2 당량, 0.599mmol)을 넣었다. TLC 상에서 기질이 모두 사라진 후 반응을 종결시켰다. 반응 용매를 evaporation 시킨 후, medium pressure liquid chromatography 로 정제하여 생성물을 얻었다.

(*S*)-3-(phenylthio)cyclohexan-1-one (4a)

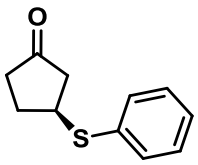


물질 **2a**를 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **4a**를 얻었다 (99% yield, 101.3mg). 절대배열은 참고문헌의 기지의 물질

의 선광도 및 chiral HPLC data 를 비교하여 S form 임을 확인하였다.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43-7.39 (m, 2H), 7.33-7.27 (m, 3H), 3.45-3.38 (m, 1H), 2.70-2.65 (m, 1H), 2.40-2.25 (m, 3H), 2.19-2.09 (m, 2H), 1.78-1.64 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 133.3, 133.0, 132.9, 132.9, 132.7, 129.1, 128.9, 128.7, 128.6, 127.8, 127.6, 47.7, 47.6, 45.9, 40.7, 31.2, 31.0, 30.9, 24.0, 23.9, 23.7 ppm; IR (KBr) 3735, 3056, 2943, 2867, 2348, 2309, 1713, 1583, 1508, 1479, 1438, 1419, 1341, 1314, 1281, 1221, 1175, 1090 1067, 1024, 970, 908, 880, 742, 692 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{12}H_{14}OS]^+$($[M+H]^+$) 206.0765; found 206.0766. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 13.12min, major isomer 10.65 min, 87% ee, $[\alpha]_D^{20}$ = -74.79 (*c* 1.0, $CHCl_3$).

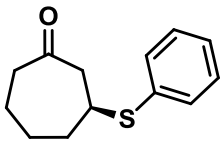
(*S*)-3-(phenylthio)cyclopentan-1-one (4b)



물질 **2b** 를 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **4b** 를 얻었다 (97% yield, 93.15mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41-7.37 (m, 2H), 7.33-7.24 (m, 3H), 3.92-3.86 (m, 1H), 2.60 (dd, J = 18.7, 7.1 Hz, 1H), 2.52-2.41 (m, 1H), 2.38-2.16 (m, 3H), 2.06-1.98 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.1, 134.0, 131.7, 128.9, 127.2, 45.0, 43.1, 42.9, 36.5, 29.1 ppm; IR (KBr) 3901, 3841, 3756, 3734, 3646, 3565, 3056, 2964, 2349, 2310, 1744, 1704, 1680, 1646, 1583, 1541, 1508, 1480, 1456, 1438, 1402, 1275, 1248, 1220, 1157, 1091, 1024, , 772., 743cm^{-1}; HRMS (FAB) m/z: [M+H]+ Calcd for [$C_{11}H_{12}OS$]+([M+H]+) 192.0609; found 192.0602. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AD-H, hexane : ethanol = 90 : 10, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 24.42min, major isomer 29.65min, 65% ee, $[\alpha]_D^{20}$ = 0.53 (c 1.0, $CHCl_3$)

(*S*)-3-(phenylthio)cycloheptan-1-one (4c)

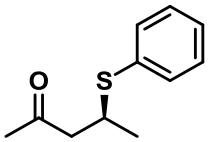


물질 **2c** 를 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **4c** 를 얻었다 (95% yield, 104mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41-7.38 (m, 2H), 7.33-7.23 (m, 5H), 3.40 (tt, J = 9.8, 3.1 Hz, 1H), 2.81-2.68 (m, 2H), 2.60-2.44 (m, 2H), 2.17-2.12 (m, 1H), 2.01-1.94 (m, 1H), 1.89-1.80 (m, 1H), 1.77-1.65 (m, 2H), 1.53-1.49 (m, 1H) ppm; ^{13}C

NMR (100 MHz, $CDCl_3$) δ 211.2, 133.9, 132.2, 128.9, 127.2, 49.3, 43.9, 43.8, 43.7, 36.6, 36.5, 27.9, 23.7 ppm; IR (KBr) 3901, 3756, 3646, 3565, 3056, 2930, 2857, 2349, 2320, 1800, 1699, 1647, 1583, 1508, 1480, 1438, 1405, 1344, 1286, 1249, 1191 1158, 1091, 1067, 1024, 999, 934, 889, 857, 741, 692 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{13}H_{16}OS]^+$($[M+H]^+$) 220.0922; found 220.0924. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AS-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 20.03 min, major isomer 24.83 min, 35% ee, $[\alpha]_D^{20}$ = -1.61 (c 1.0, $CHCl_3$)

(*S*)-4-(phenylthio)pentan-2-one (4d)

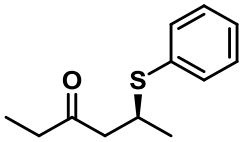


물질 **2d** 를 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **4d** 를 얻었다 (99% yield, 95.9mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44-7.38 (m, 2H), 7.33-7.22 (m, 3H), 3.73-3.64 (m, 1H), 2.74 (dd, J = 17.2, 5.5 Hz, 1H), 2.59-2.50 (m, 1H), 2.12 (s, 3H), 1.28 (d, J = 6.7 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 206.3, 137.5, 134.0, 132.1, 128.8, 127.1, 50.1, 38.0, 37.8, 30.4, 20.8 ppm; IR (KBr) 3565, 3057, 2965, 2926, 2348, 2320, 1867, 1800, 1714, 1646, 1582, 1542, 1508, 1474, 1438,1360, 1304,

1241, 1219, 1158, 1090, 1067, 1024, 966, 772, 692 , 671, 645, 617cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{11}H_{14}OS]^+$($[M+H]^+$) 194.0765; found 194.0769. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AD-H, hexane : ethanol = 90 : 10, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 6.4min, major isomer 8.5min, 27% ee, $[\alpha]_D^{20}$ = +0.51 (*c* 1.0, $CHCl_3$).

(*S*)-5-(phenylthio)hexan-3-one (4e)

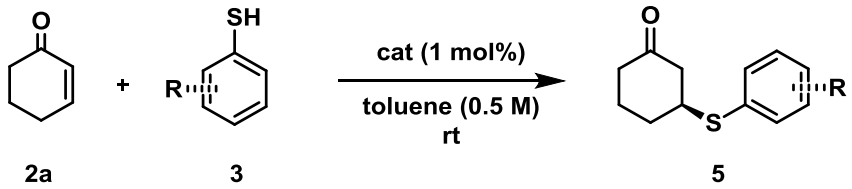


물질 **2e** 를 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **4e** 를 얻었다 (99% yield, 102.69mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 (dt, J = 8.4, 1.8 Hz, 2H), 7.31-7.21 (m, 4H), 3.76-3.67 (m, 1H), 2.72 (dd, J = 16.9, 5.2 Hz, 1H), 2.57-2.50 (m, 1H), 2.42-2.36 (m, 2H), 1.26 (q, J = 7.4 Hz, 3H), 1.02 (t, J = 7.4 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.3, 134.3, 132.2, 128.9, 127.2, 49.1, 38.3, 36.7, 21.0, 7.6 ppm; IR (KBr) 3901, 3840, 3756, 3734, 3647, 3565., 3057, 2975, 2937., 2348, 2320, 1867, 1713, 1646, 1583, 1543, 1508, 1474, 1456, 1438, 1410, 1361, 1302, 1219, 1119, 1024, 986, 772, 691, 671cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{12}H_{16}OS]^+$($[M+H]^+$) 208.0922; found 208.0932. The enantioselectivity was

determined by chiral HPLC analysis (DIACEL Chiralcel AD-H, hexane : ethanol = 90 : 10, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 6.22min, major isomer 7.59min, 40% ee, $[\alpha]_D^{20}$ = +2.35 (c 1.0, $CHCl_3$).

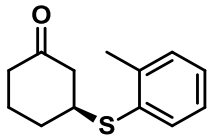
3- Michael donor



실험방법

Sealed tube 에 Ar 치환을 한 후, 촉매의 stock solution 에서 촉매 1 mol%를 주사기로 넣은 후 교반하였다. 그 후, 2-cyclohexen-1-one (1 당량, 0.499mmol)을 넣고 충분히 교반시키며 Michael donor (1.2 당량, 0.599mmol)을 넣었다. TLC 로 기질이 모두 사라진 후 반응을 종결시켰다. 반응 용매를 evaporation 시킨 후, medium pressure liquid chromatography 로 정제하여 생성물을 얻었다.

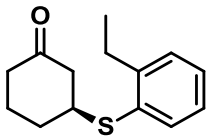
(S)-3-(o-tolylthio)cyclohexan-1-one (5b)



물질 **3b** 를 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **5b** 를 얻었다 (98% yield, 107.73mg).

^{1}H-NMR (400 MHz, CDC_{l3}) δ 7.38 (d, J = 6.7 Hz, 1H), 7.22-7.12 (m, 3H), 3.40 (td, J = 9.4, 4.9 Hz, 1H), 2.67 (dd, J = 14.1, 4.3 Hz, 1H), 2.41-2.29 (m, 6H), 2.14 (td, J = 9.4, 3.7 Hz, 2H), 1.81-1.65 (m, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 208.5, 140.3, 133.0, 132.4, 130.4, 127.5, 126.3, 47.5, 45.4, 40.8, 31.1, 23.9, 20.7 ppm; IR (KBr) 3848, 3565, 3057, 2943, 2321, 1799, 1713, 1589, 1469, 1455, 1423, 1379, 1341, 1314, 1280, 1220, 1175, 1096, 1063, 1047, 1033, 970, 908, 879, 770, 753,. 713, 678. cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{13}H_{16}OS]^+$($[M+H]^+$) 220.0922; found 220.0926, The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AS-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: major isomer 10.22 min, minor isomer 14.09. min, 81% ee, $[\alpha]_D^{20}$ = -42.26 (c 1.0, $CHCl_3$).

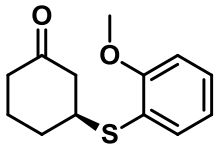
(S)-3-((2-ethylphenyl)thio)cyclohexan-1-one (5c)



물질 **3c** 를 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **5c** 를 얻었다 (98% yield, 114mg).

^{1}H-NMR (100 MHz, $CDCl_3$) δ 7.51-7.40 (m, 1H), 7.29-7.16 (m, 3H), 3.49-3.42 (m, 1H), 2.94-2.79 (m, 2H), 2.74-2.67 (m, 1H), 2.46-2.26 (m, 3H), 2.19-2.12 (m, 2H), 1.91-1.67 (m, 2H), 1.33-1.16 (m, 3H) ppm; ^{13}C-NMR (400 MHz, $CDCl_3$) δ 208.6, 146.3, 133.2, 131.9, 128.8, 127.8, 126.3, 47.6, 46.0, 40.8, 31.2, 27.1, 24.0, 15.2 ppm; IR (KBr) 2963, 2869, 2349, 2320, 1713, 1468, 1339, 1314, 1281, 1220, 1175, 1061, 1028, 970, 879, 772, 675 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{14}H_{18}OS]^+$($[M+H]^+$) 234.1078; found 234.1081. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AD-H, hexane : ethanol= 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 7.768 min, major isomer 13.375 min, 80% ee, $[\alpha]_D^{20}$ = -56.45 (c 1.0, $CHCl_3$).

(S)-3-((2-methoxyphenyl)thio)cyclohexan-1-one (5d)

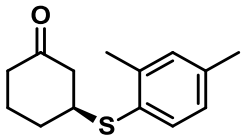


물질 **3d** 를 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **5d** 를 얻었다 (90% yield, 106.38mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, J = 7.6, 1.5 Hz, 1H), 7.28 (td, J = 7.9, 1.6 Hz, 1H), 6.92-6.87 (m, 2H), 3.87 (s, 3H), 3.57-3.51 (m, 1H), 2.64 (dd, J = 14.4, 4.6 Hz, 1H), 2.39-2.26 (m, 3H), 2.16-2.08 (m, 2H), 1.77-1.64 (m, 2H) ppm; ^{13}C-

NMR (100 MHz, $CDCl_3$) δ 208.9, 158.9, 134.4, 129.3, 120.8, 120.6, 110.8, 55.6, 47.6, 43.7, 40.8, 30.9, 23.9 ppm; IR (KBr) 3061, 3003, 2940, 2867, 2836, 2348, 1712, 1581, 1476, 1448, 1432, 1342, 1313, 1273, 1244, 1221, 1179, 1161, 1131, 1096, 1070, 1042, 1024., 796, 753, 684 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{13}H_{16}O2S]^+$($[M+H]^+$) 236.0871; found 236.08. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 13.578 min, major isomer 20.855 min, 84% ee, $[\alpha]_D^{20}$ = -57.80 (c 1.0, $CHCl_3$).

(S)-3-((2,4-dimethylphenyl)thio)cyclohexan-1-one (5e)

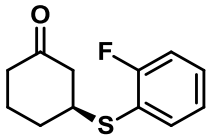


물질 **3e** 를 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **5e** 를 얻었다 (82% yield, 95.67mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.15-7.09 (m, 3H), 3.18 (tt, J = 10.4, 4.0 Hz, 1H), 2.61-2.56 (m, 1H), 2.52 (s, 6H), 2.42-2.28 (m, 3H), 2.16-2.04 (m, 2H), 1.83-1.74 (m, 1H), 1.70-1.62 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 208.9, 143.3, 131.5, 128.5, 128.2, 47.9, 46.2, 40.9, 31.7, 24.3, 22.2 ppm; IR (KBr) 3054, 2944, 2869, 2320, 1705, 1570, 1460, 1424, 1376, 1340, 1316, 1285, 1243, 1220, 1170,

1055, 971, 879, 774 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{14}H_{19}OS]^+$($[M+H]^+$) 235.1157; found 235.1150. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AD-H, hexane : ethanol = 90 : 10, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 5.221 min, major isomer 5.900 min, 57% ee, m.p = 80-85 °C, $[\alpha]_D^{20}$ = -50.36 (c 1.0, $CHCl_3$).

(S)-3-((2-fluorophenyl)thio)cyclohexan-1-one (5f)

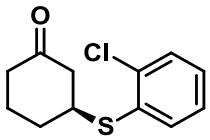


물질 **3f** 를 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **5f** 를 얻었다 (96% yield, 107.26 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.51-7.41 (m, 1H), 7.33-7.27 (m, 1H), 7.15-7.04 (m, 2H), 3.52-3.45 (m, 1H), 2.67-2.62 (m, 1H), 2.44-2.25 (m, 3H), 2.20-2.08 (m, 2H), 1.77-1.63 (m, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 208.3 (excess peaks due to C-F coupling), 163.7, 161.3 (d, *J* = 244.4 Hz), 135.9, 130.3 (d, *J* = 8.6 Hz), 124.4 (d, *J* = 3.8 Hz), 119.5 (d, *J* = 18.2 Hz), 116.0 (d, *J* = 22.9 Hz), 115.8, 47.6, 45.1, 40.6, 31.0, 23.7 ppm; IR (KBr) 2945, 2348, 2320, 1713, 1472, 1446, 1283, 1259, 1220, 879, 823, 772, 676 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{12}H_{13}OSF]^+$($[M+H]^+$) 224.0671; found 224.0675. The enantioselectivity was

determined by chiral HPLC analysis (DIACEL Chiralcel AS-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 23.778 min, major isomer 14.966 min, 28% ee, $[\alpha]_D^{20}$ = -21.64 (c 1.0, $CHCl_3$).

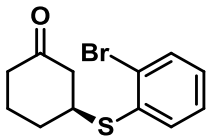
(S)-3-((2-chlorophenyl)thio)cyclohexan-1-one (5g)



물질 **3g** 를 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **5g** 를 얻었다 (99% yield, 118.22mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44-7.40 (m, 2H), 7.22-7.19 (m, 1H), 3.60-3.54 (m, 1H), 2.69 (dd, J = 14.4, 4.6 Hz, 1H), 2.45-2.30 (m, 3H), 2.19-2.14 (m, 2H), 1.83-1.71 (m, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 208.2, 136.6, 133.4, 132.3, 130.0, 128.5, 127.1, 47.3, 44.6, 40.7, 30.8, 23.9 ppm; IR (KBr) 2944, 2349, 2320, 1801, 1712, 1450, 1430, 1339, 1314, 1219, 1176, 1115, 1034, 970, 879, 772, 688 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{12}H_{13}OSCl]^+$($[M+H]^+$) 240.0376; found 240.0380. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AS-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 35.668 min, major isomer 26.776 min, 43% ee, $[\alpha]_D^{20}$ = -2.74 (c 1.0, $CHCl_3$).

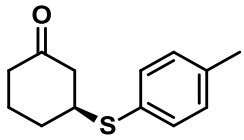
(S)-3-((2-bromophenyl)thio)cyclohexan-1-one (5h)



물질 **3h** 를 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **5h** 를 얻었다 (99% yield, 140mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, J = 8.0, 1.2 Hz, 1H), 7.43 (dd, J = 8.0, 1.8 Hz, 1H), 7.27 (td, J = 7.4, 1.6 Hz, 3H), 7.12 (td, J = 7.7, 1.4 Hz, 1H), 3.59 (tt, J = 10.0, 4.0 Hz, 1H), 2.72 (dd, J = 14.4, 4.6 Hz, 1H), 2.48-2.31 (m, 3H), 2.22-2.13 (m, 2H), 1.86-1.69 (m, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 208.3, 134.6, 133.4, 133.0, 128.6, 127.8, 127.2, 47.3, 45.0, 40.8, 30.8, 24.0 ppm; IR (KBr) 2942, 2349, 2320, 1711, 1447, 1426, 1219, 1175, 1020, 970, 772 cm-1; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{12}H_{13}OSBr]^+$($[M+H]^+$) 286.9928; found 283.9863. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AD-H, hexane : 2-propanol = 99 : 1, flow rate = 0.5 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 39.333 min, major isomer 44.740 min, 55% ee, $[\alpha]_D^{20}$ = -36.43 (c 1.0, $CHCl_3$).

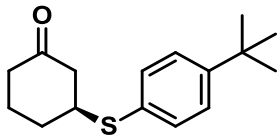
(S)-3-(p-tolylthio)cyclohexan-1-one (5i)



물질 **3i** 를 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **5i** 를 얻었다 (98% yield, 107.6mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39-7.19 (m, 2H), 7.15-7.05 (m, 2H), 3.39-3.26 (m, 1H), 2.68-2.57 (m, 1H), 2.37-2.16 (m, 6H), 2.11-1.98 (m, 2H), 1.72-1.53 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 137.8, 133.6, 129.6, 128.9, 47.5, 46.1, 40.6, 30.9, 23.7, 20.9 ppm; IR (KBr) 2942, 2348, 2320, 1712, 1646, 1491, 1447, 1219, 1177, 1094, 1018, 970, 878, 810, 772 cm-1; HRMS (FAB) m/z: [M+H]+ Calcd for $[C_{13}H_{16}OS]^{+}$([M+H]$^{+}$) 220.0922; found 220.0925. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AD-H, hexane : ethanol = 90 : 10, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 19.207 min, major isomer 12.679 min, 67% ee, $[\alpha]_D^{20}$ = -46.51 (c 1.0, $CHCl_3$).

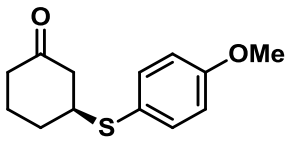
(S)-3-{[4-(tert-butyl)phenyl]thio]cyclohexan-1-one (5j)



물질 **3j** 를 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **5j** 를 얻었다 (80% yield, 105.1mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44-7.31 (m, 4H), 3.40-3.33 (m, 1H), 2.66 (dd, J = 14.2, 4.6 Hz, 1H), 2.45-2.24 (m, 3H), 2.16-2.05 (m, 2H), 1.86-1.63 (m, 2H), 1.34-1.23 (m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 151.1, 133.4, 129.2, 126.0, 47.8, 46.2, 40.8, 34.5, 31.3, 31.1, 24.0 ppm; IR (KBr) 3077, 2961, 2904, 2867, 2349, 2320, 1800, 1748, 1714, 1488, 1457, 1418, 1396, 1362, 1339, 1314, 1268, 1219, 1175, 1120, 1095.37, 1013, 970, 879, 829, 772 cm-1; HRMS (FAB) m/z: [M+H]+ Calcd for $[C_{16}H_{22}OS]^{+}$($[M+H]^{+}$) 262.1391; found 262.1389. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AD-H, hexane : ethanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 17.369 min, major isomer 10.745 min, 64% ee, $[\alpha]_D^{20}$ = -40.31 (c 1.0, $CHCl_3$).

(S)-3-((4-methoxyphenyl)thio)cyclohexan-1-one (5k)

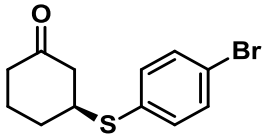


물질 **3k** 를 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **5k** 를 얻었다 (88% yield, 103.67mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40-7.37 (m, 2H), 6.86-6.83 (m, 2H), 3.80 (s, 3H),

3.24-3.19 (m, 1H), 2.62 (dd, J = 14.4, 4.6 Hz, 1H), 2.38-2.22 (m, 3H), 2.16-2.02 (m, 2H), 1.73-1.64 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.0, 159.8, 136.7, 136.4, 136.1, 122.7, 114.7, 114.4, 55.2, 47.6, 46.9, 40.7, 31.1, 30.8, 23.9 ppm; IR (KBr) 2941, 2836, 2349, 2320, 1711, , 1591, 1569, 1493, 1460, 1444, 1418, 1340, 1313, 1285, 1245, 1220, 1173, 1103, 1029, 970, 878, 830, 799, 772 cm-1; HRMS (FAB) m/z: [M+H]+ Calcd for $[C_{13}H_{16}OS]^+$($[M+H]^+$) 236.0871; found 236.0875. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 35.968 min, major isomer 23.539 min, 80% ee, $[\alpha]_D^{20}$ = -49.15 (c 1.0, $CHCl_3$).

(S)-3-((4-bromophenyl)thio)cyclohexan-1-one (5l)

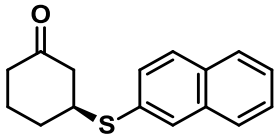


물질 **3l** 을 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **5l** 를 얻었다 (90% yield, 128.45mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45-7.39 (m, 2H), 7.33-7.25 (m, 3H), 3.43-3.36 (m, 1H), 2.68-2.63 (m, 1H), 2.39-2.26 (m, 3H), 2.17-2.08 (m, 2H), 1.78-1.64 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 134.7, 132.2, 122.1, 47.6, 46.2, 40.8,

31.1, 24.0 ppm; IR (KBr) 2942, 2348, 2320, 1800, 1712, 1473, 1446, 1418, 1219, 1175, 1092, 1068, 1008, 970, 816, 772 cm-1; HRMS (FAB) m/z: [M+H]+ Calcd for $[C_{12}H_{13}OSBr]^+$($[M+H]^+$) 285.9850; found 285.9865. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AD-H, hexane : 2-propanol = 99 : 1, flow rate = 0.5 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 18.889 min, major isomer 20.806 min, 87% ee, m.p = 70-75 °C, $[\alpha]_D^{20}$ = +16.43 (c 1.0, $CHCl_3$).

(S)-3-(naphthalen-2-ylthio)cyclohexan-1-one (5m)



물질 **3m** 을 출발물질로 하여 상기의 실험방법을 통하여 pale caramel 형태의 물질 **5m** 를 얻었다 (80% yield, 102.24mg).

1H-NMR (401 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.83-7.78 (m, 3H), 7.52-7.48 (m, 3H), 3.58-3.51 (m, 1H), 2.73 (dt, J = 14.3, 2.3 Hz, 1H), 2.46-2.27 (m, 3H), 2.22-2.10 (m, 2H), 1.83-1.67 (m, 2H) ppm; 13C-NMR (101 MHz, CHLOROFORM-D) δ 208.6, 133.5, 132.4, 132.0, 130.3, 130.1, 128.5, 127.6, 127.4, 126.5, 126.3, 47.6, 45.9, 40.8, 31.1, 23.9 ppm; IR (KBr) 3052, 2941, 2348, 2320, 1801, 1710, 1282, 1219, 1175, 1132, 1097, 1066, 852, 815, 772cm-1; HRMS (FAB) m/z: [M+H]+ Calcd for $[C_{16}H_{16}OS]^+$($[M+H]^+$) 256.0922; found 256.0926. The

enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AD-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 18.519 min, major isomer 15.126 min, 11% ee, $[\alpha]_D^{20}$ = -9.12 (c 1.0, $CHCl_3$).

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VⅡ. Abstract

Asymmetric Oraganocatalysis has convenient functions and advantages in the organic reactions. It is inexpensive, reusable and relatively safe. For such reasons, there has been extensive research in the asymmetric organocatalysis. Among the various catalysts, *Cinchona*-derived organocatalyst is one of our major interest.

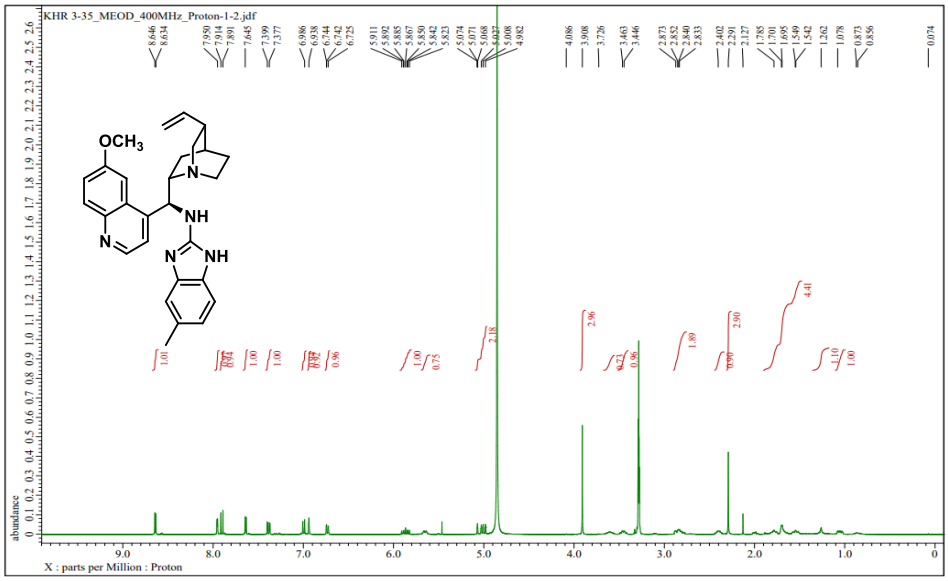
In this report, we have developed the synthesis of organosulfur compound through asymmetric *sulfa*-Michael addtion with organocatalyst. We initially selected 2-cyclohexen-1-one as the electrophile and thiophenol as the nucleophile. Reaction conditions such as catalyst amount, solvent, and temperature were screened. Also, various Michael acceptors and Michael donors were applied. As a result, we optimized the reaction condition, and came up with up to 99% chemical yield and up to 87% ee. We expect the method we have developed to be utilized in synthesis of various sulfur compounds.

Key Words: Cinchona Alkaloid, Asymmetric Organocatalysis, Asymmetric Sulfa-Michael Addition

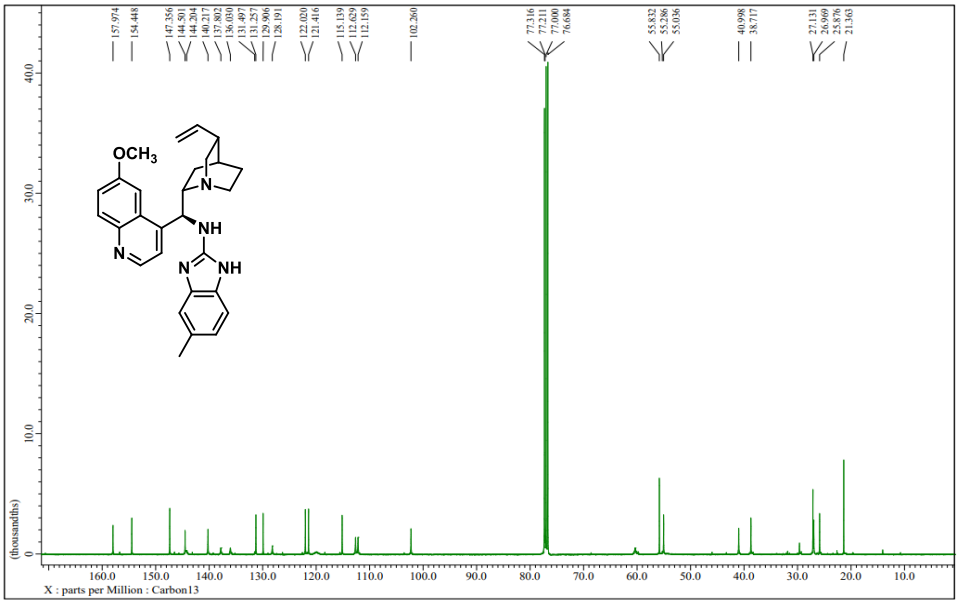
Student ID : 2019-29687

Ⅶ. 부 록

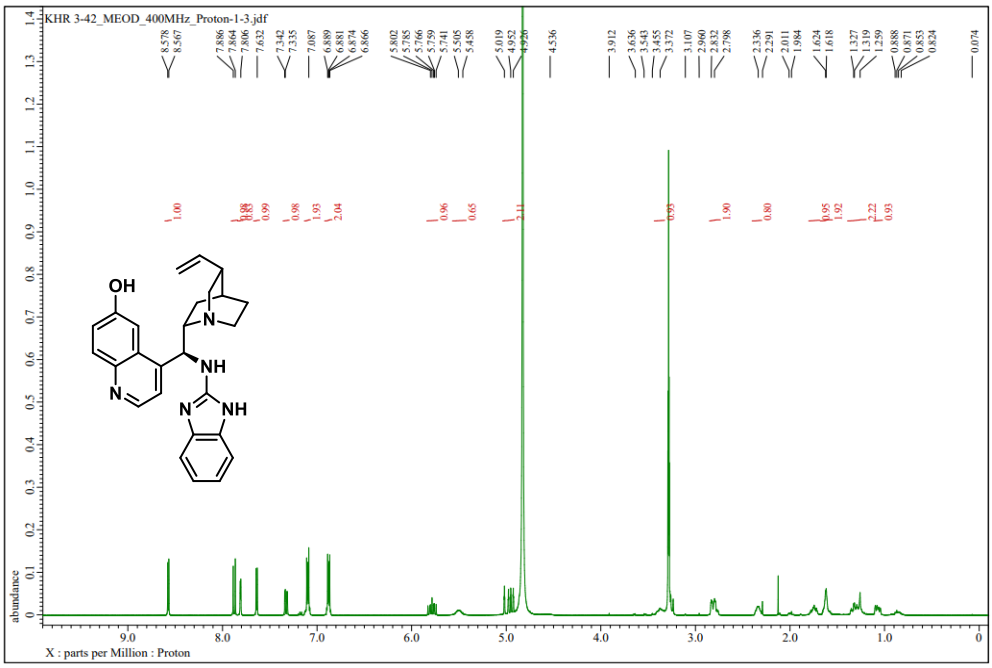
^{1}H-NMR of compound **1C** (400 MHz, $CDCl_3$)



^{13}C-NMR of compound **1C** (100 MHz, $CDCl_3$)



^{1}H-NMR of compound **1f** (400 MHz, MeOD)



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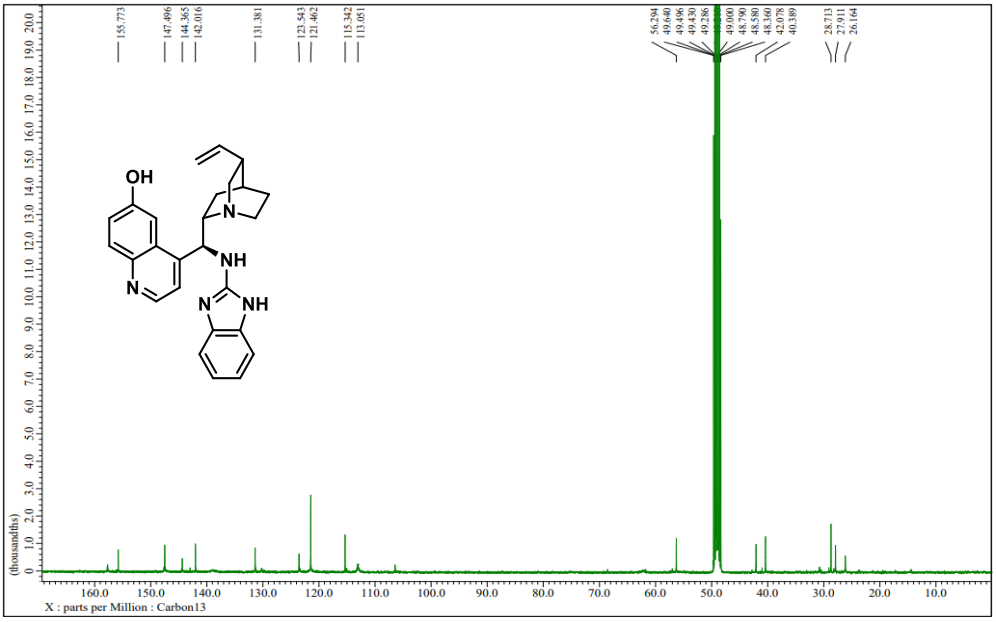
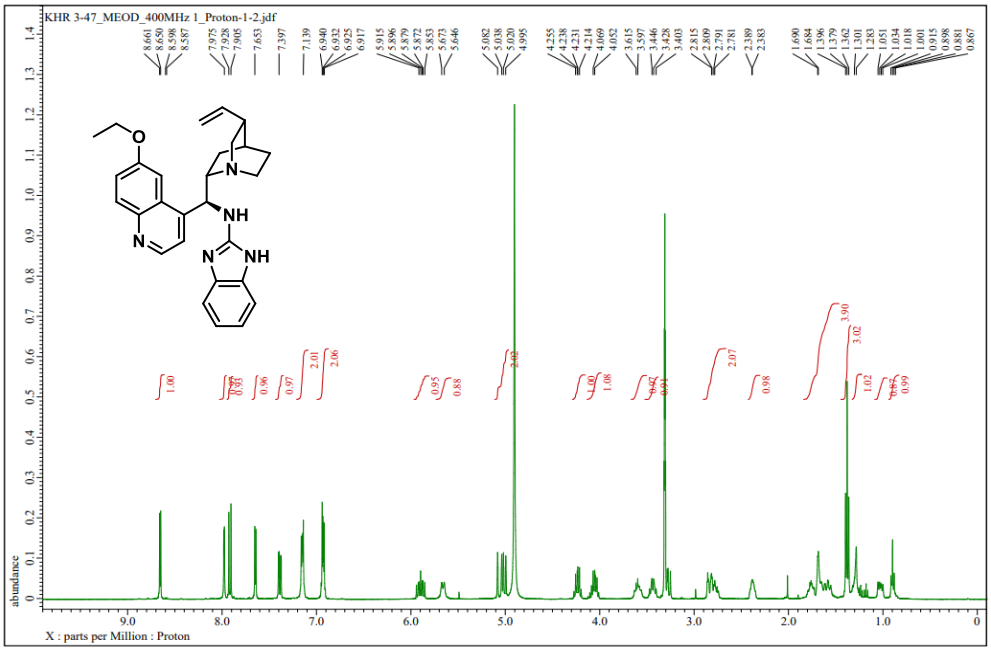


^{1}H-NMR of compound **1g** (400 MHz, MeOD)



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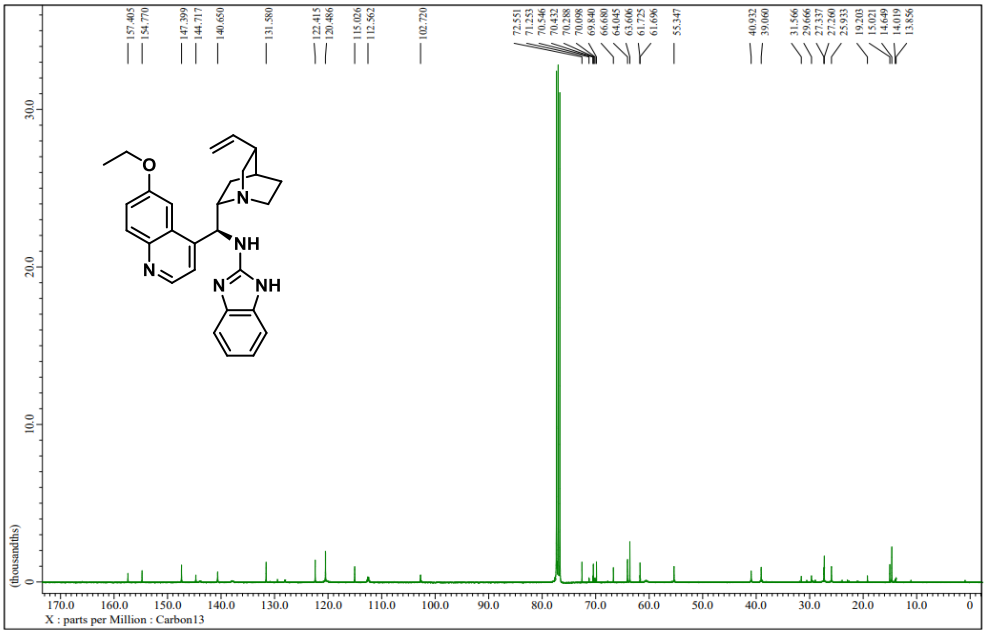

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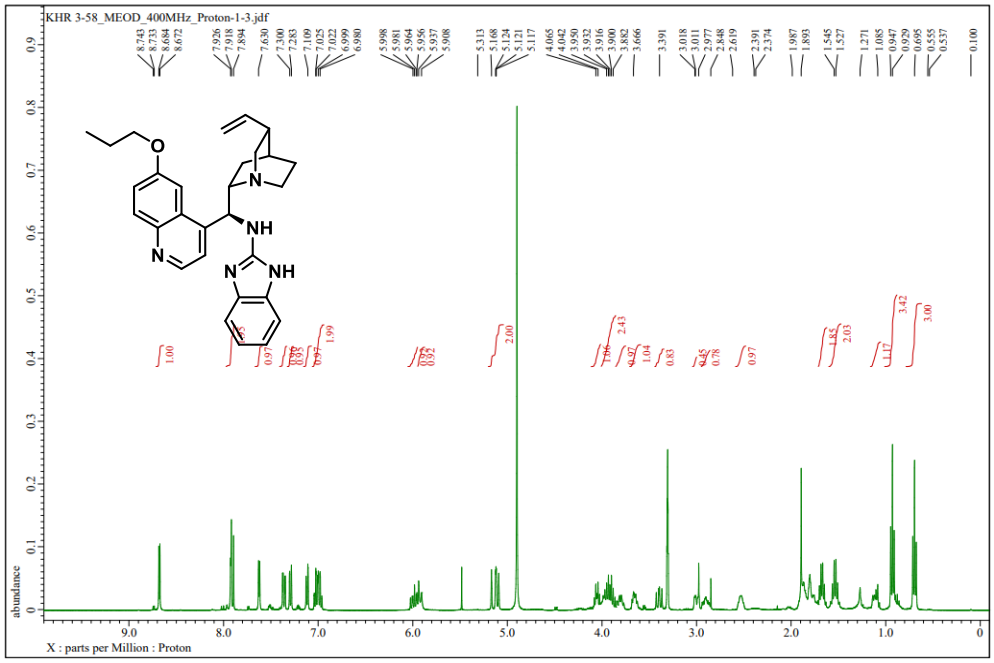
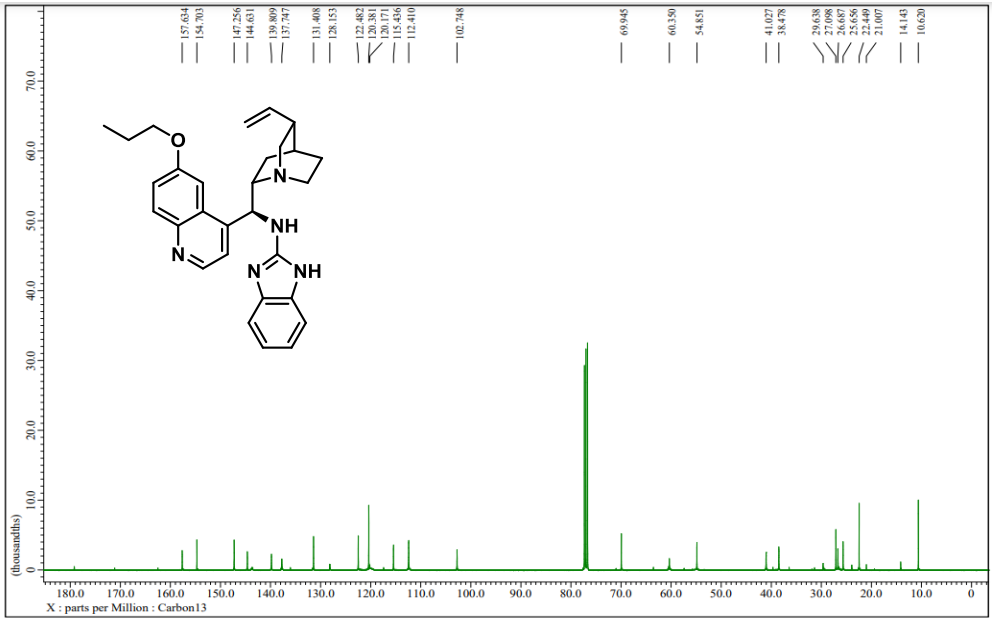


^{13}C-NMR of compound **1h** (100 MHz, $CDCl_3$)



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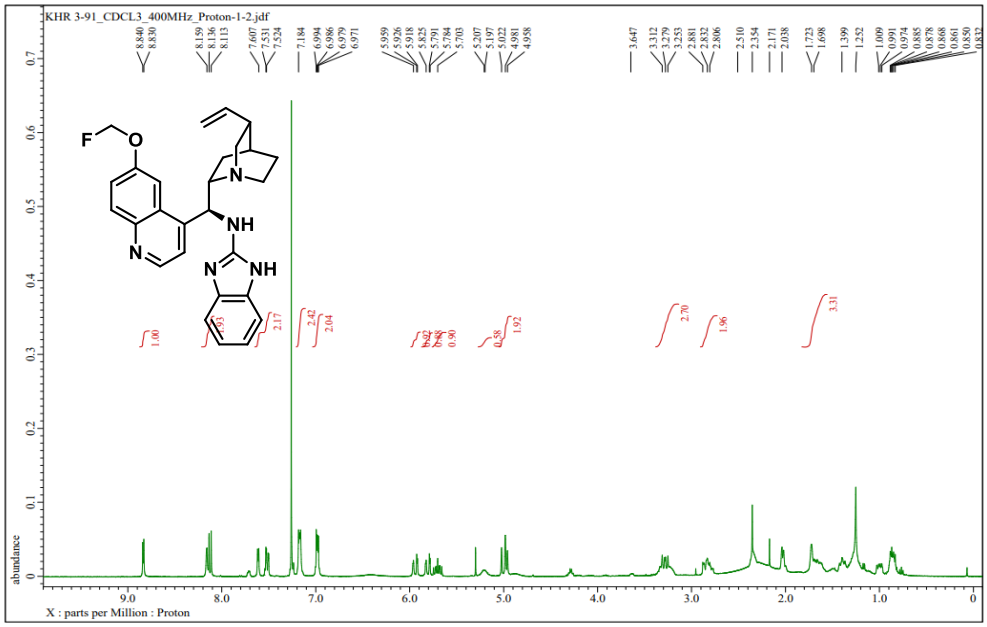
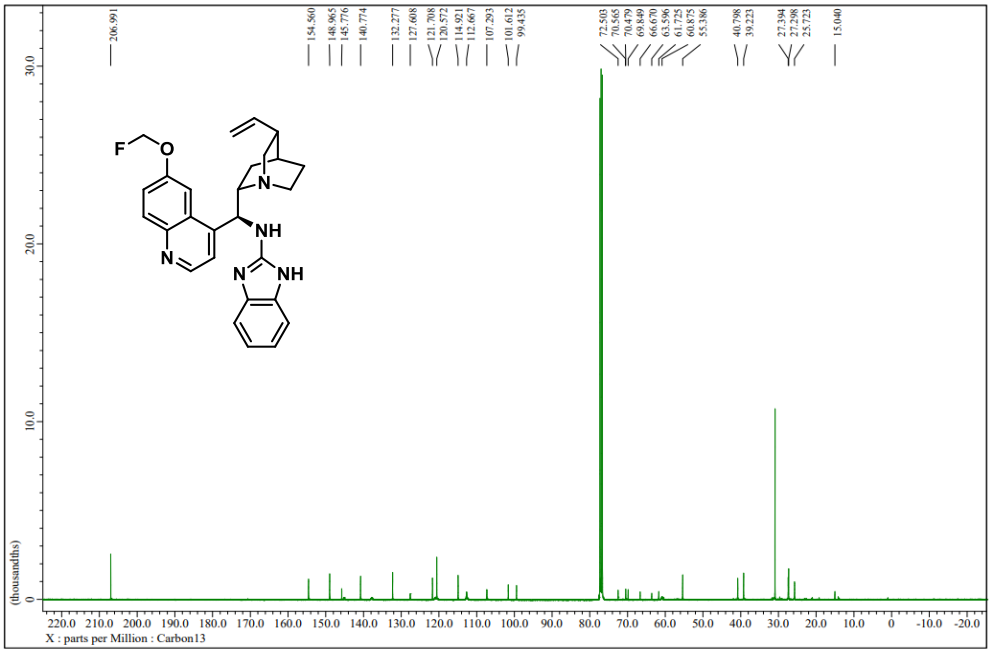
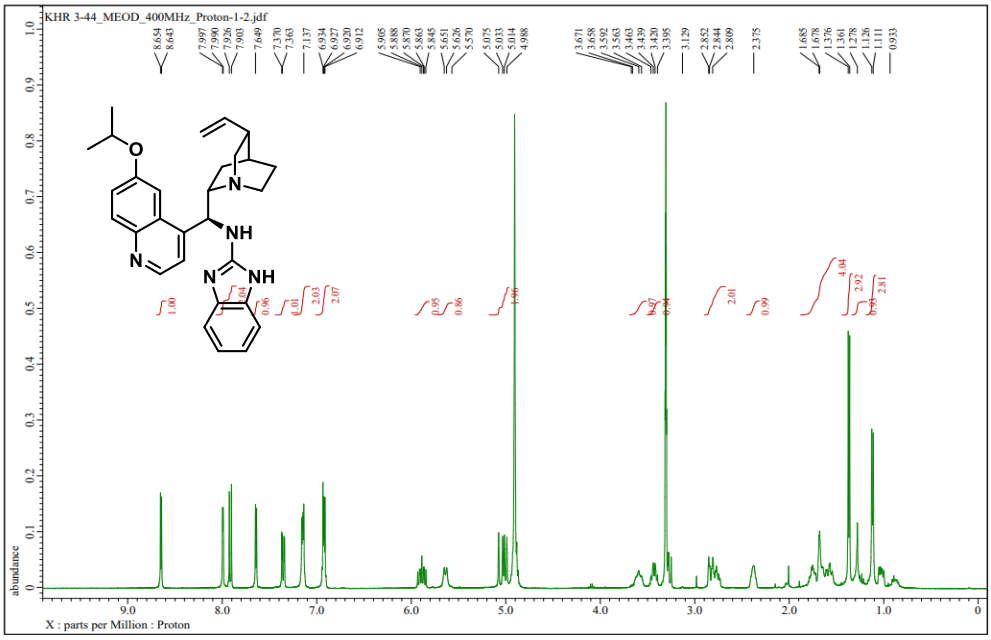


^{13}C-NMR of compound **1i** (100 MHz, $CDCl_3$)



^{1}H-NMR of compound **1j** (400 MHz, MeOD)



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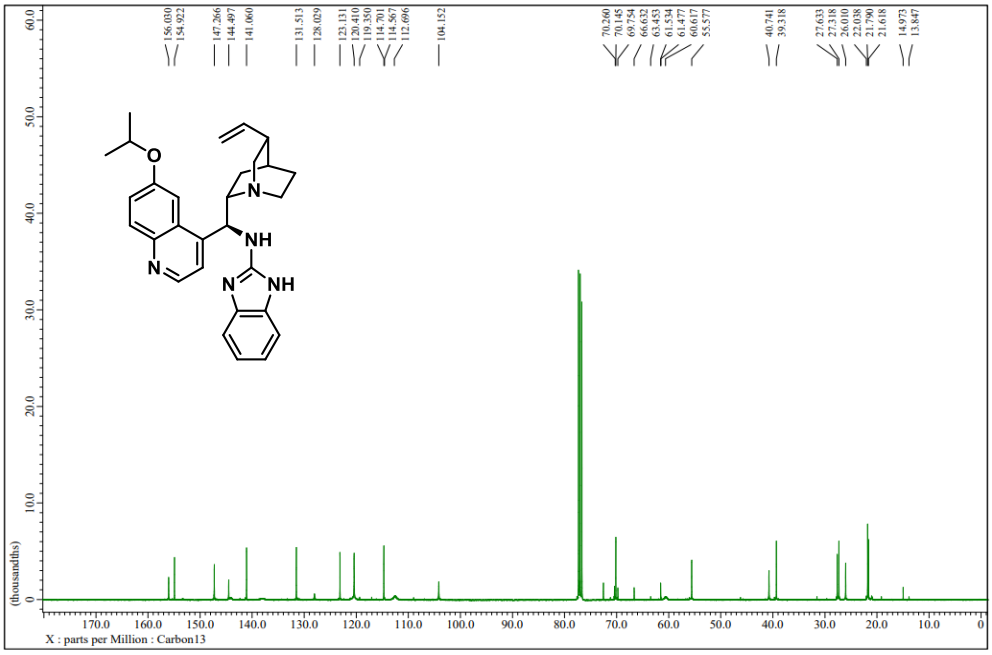

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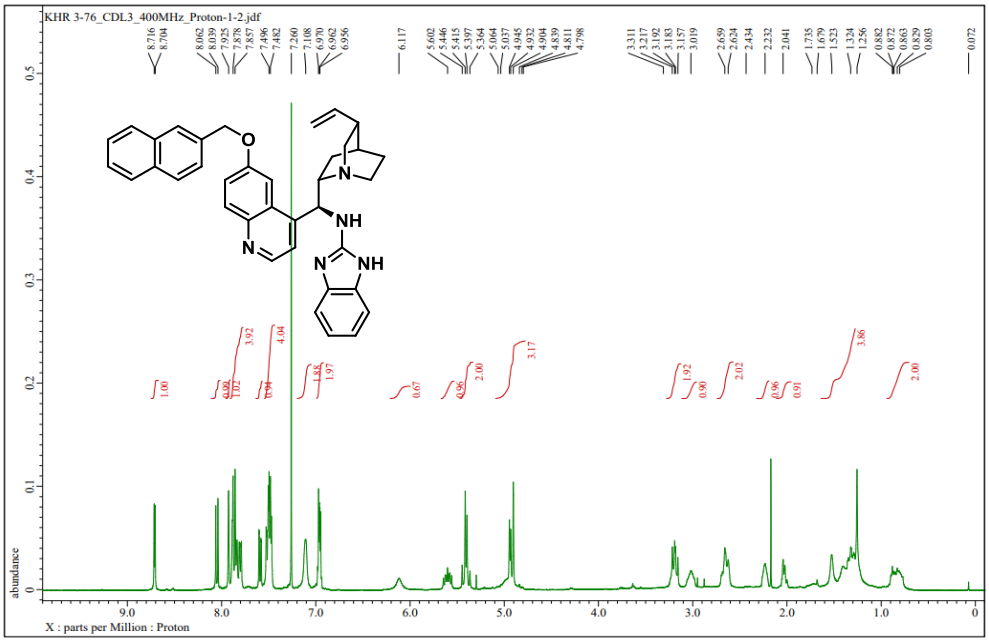

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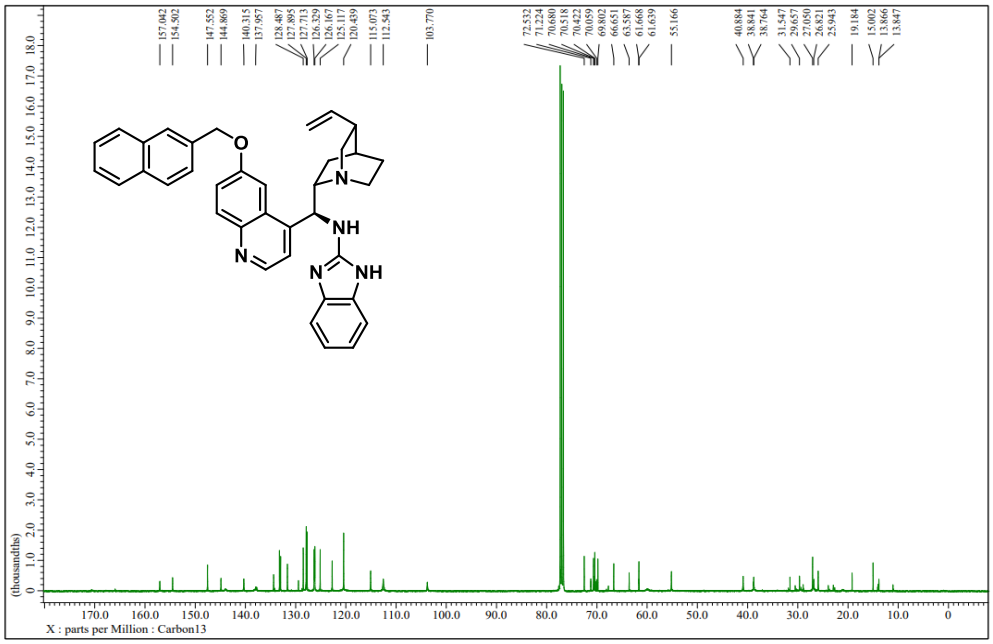

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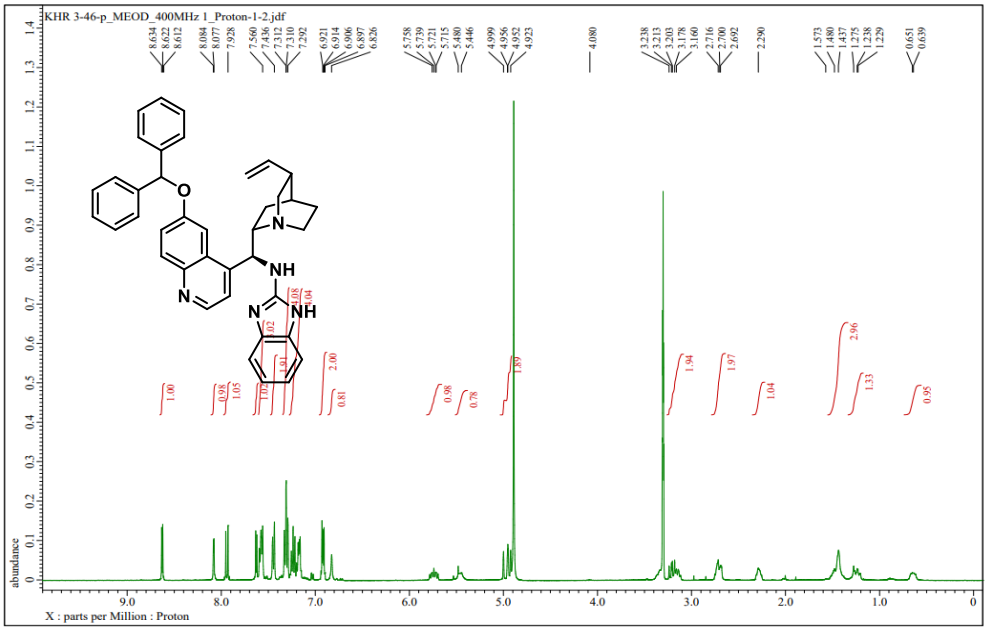
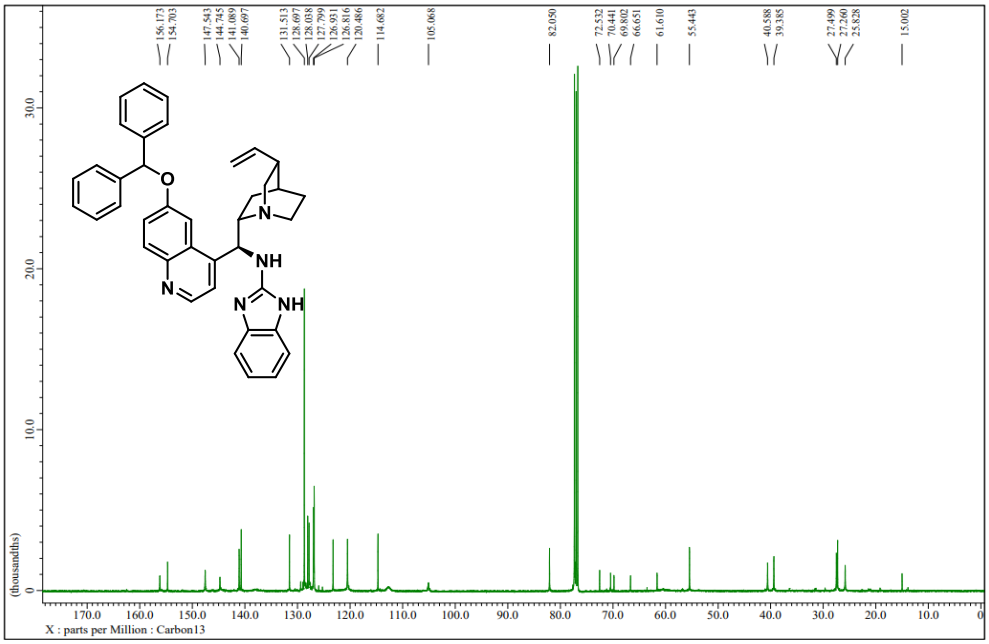


^{13}C-NMR of compound **1l** (100 MHz, $CDCl_3$)



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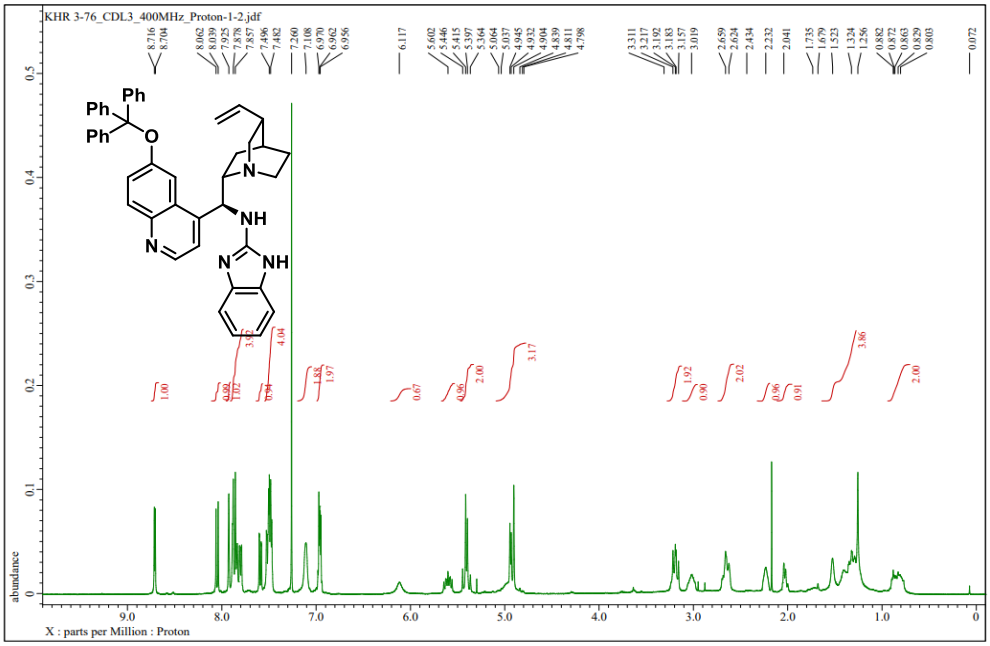

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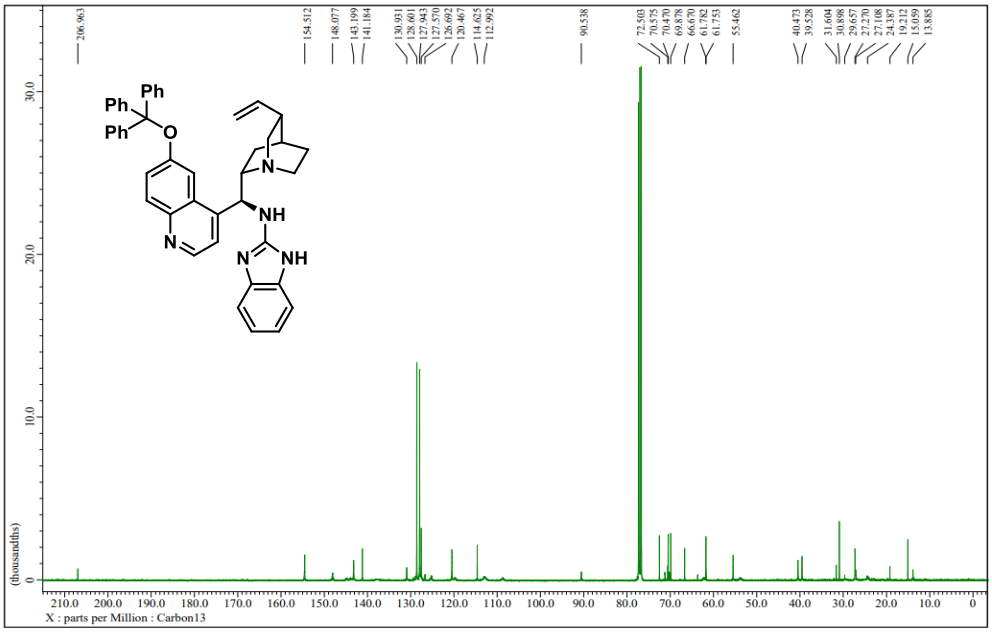
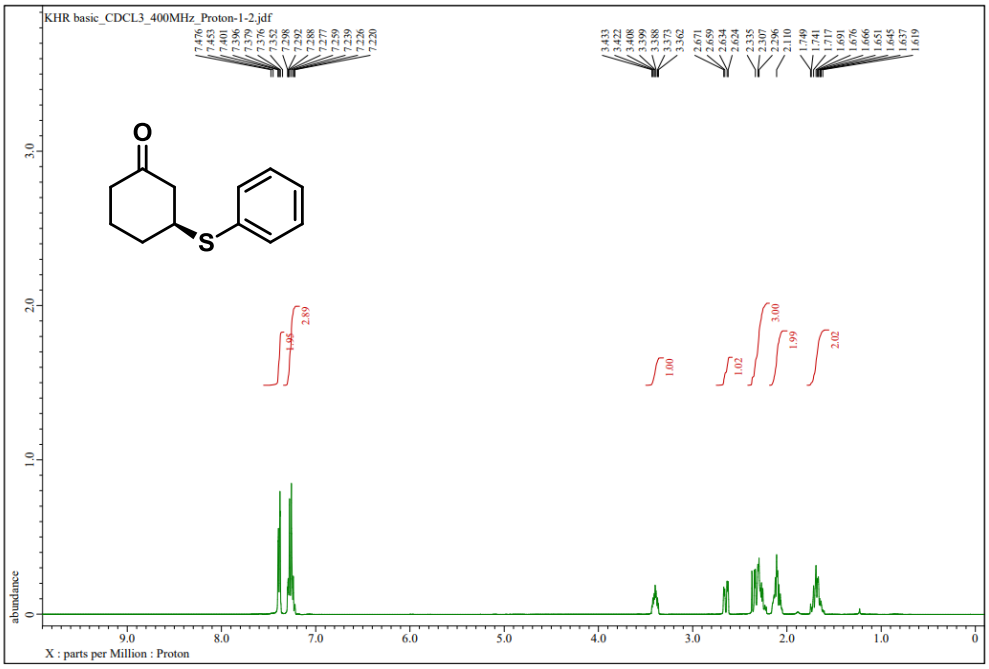
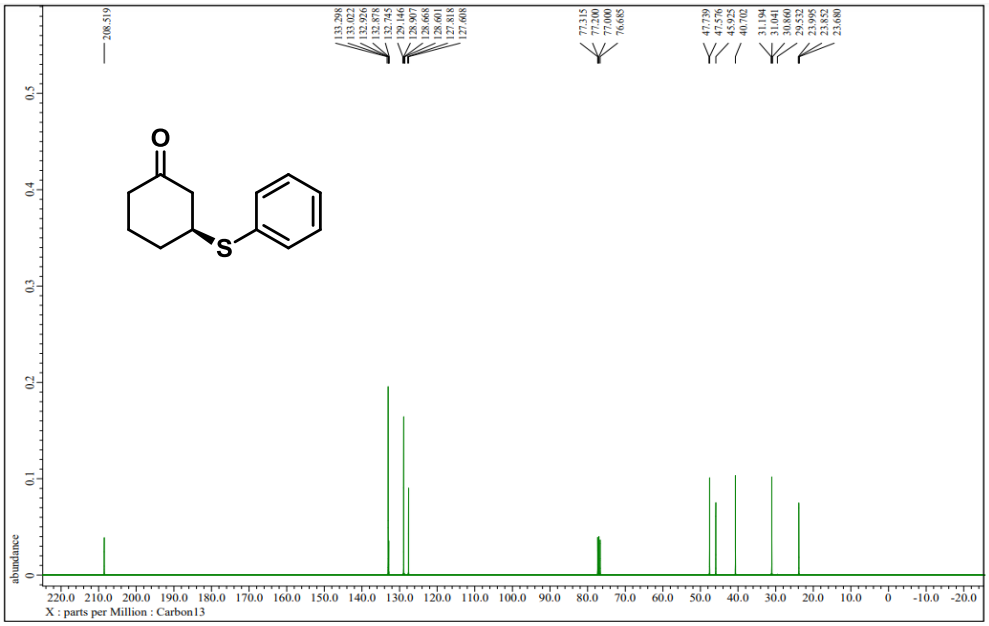


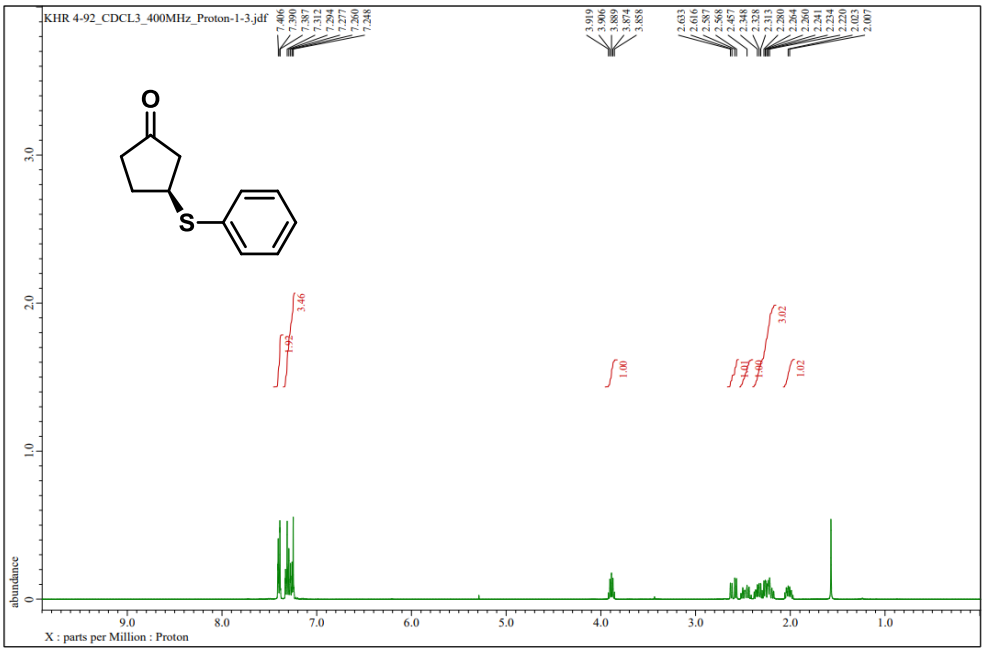
^{1}H-NMR of compound **4a** (400 MHz, $CDCl_3$)



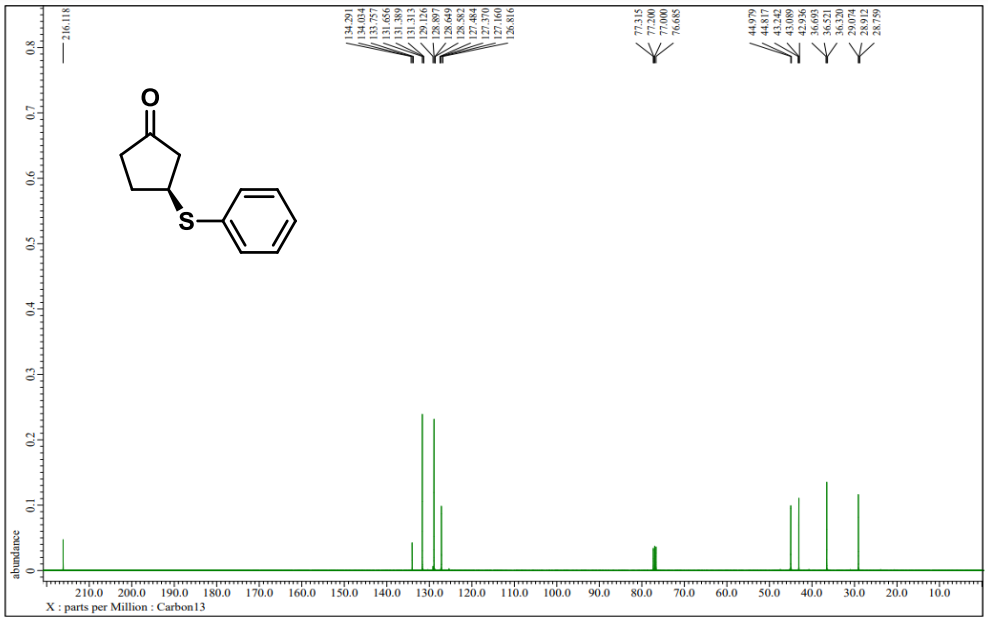
^{13}C-NMR of compound **4a** (100 MHz, $CDCl_3$)



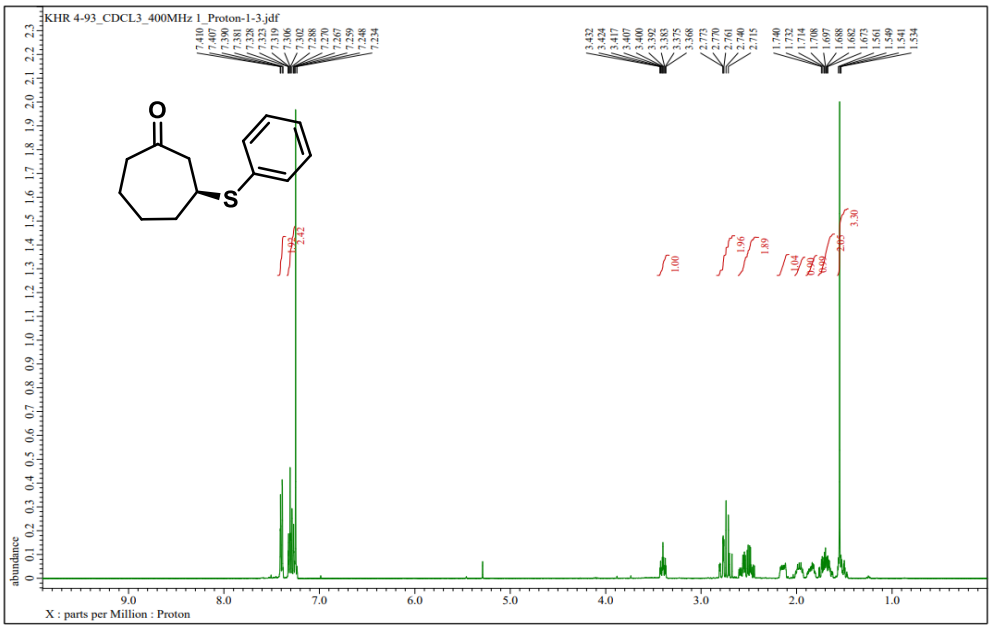
^{1}H-NMR of compound **4b** (400 MHz, $CDCl_3$)



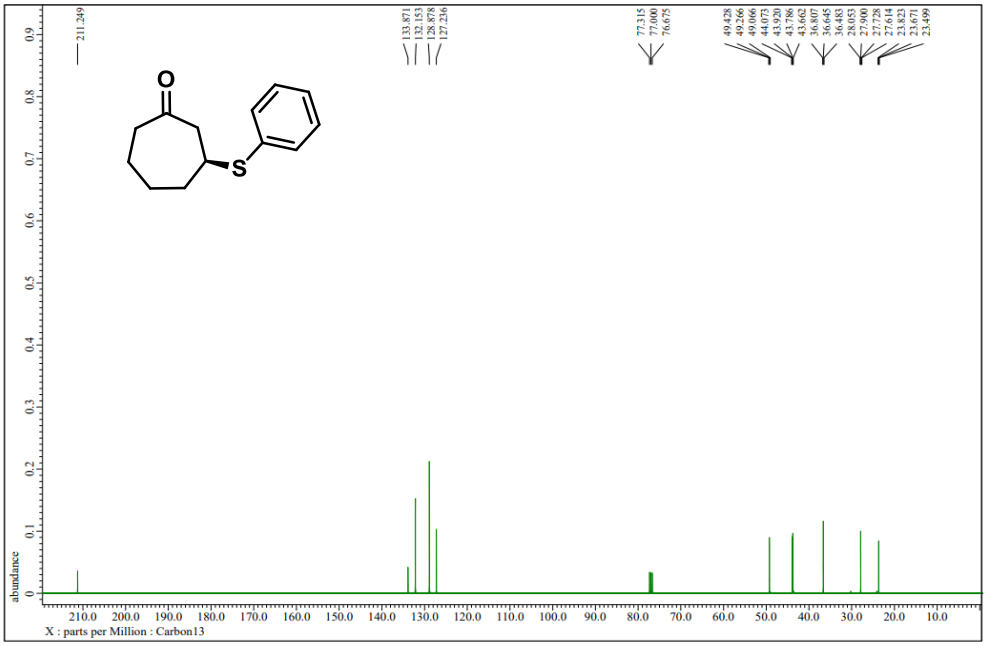
^{13}C-NMR of compound **4b** (100 MHz, $CDCl_3$)



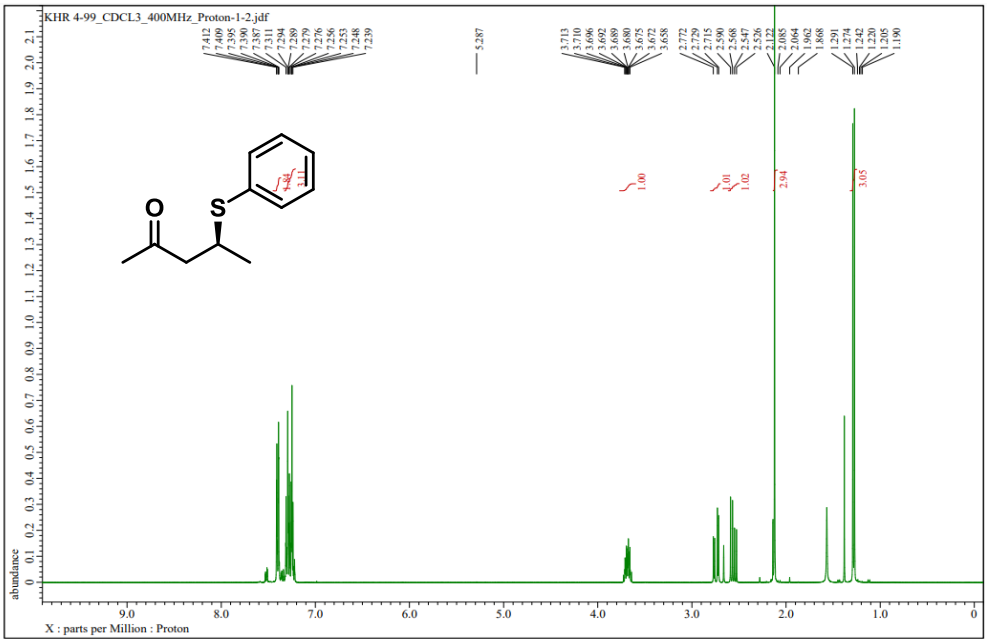
^{1}H-NMR of compound **4c** (400 MHz, $CDCl_3$)



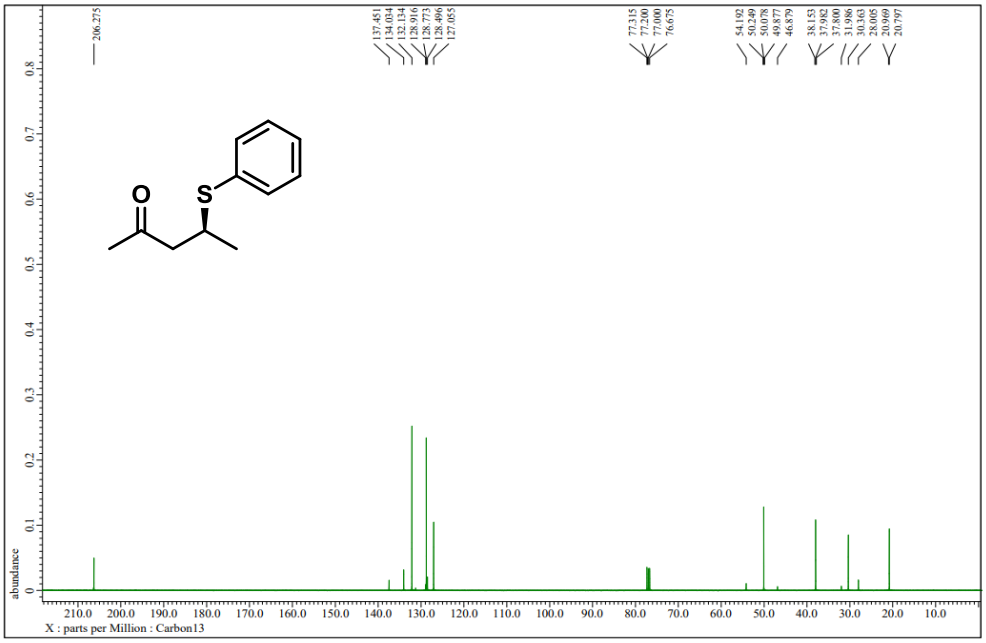
^{13}C-NMR of compound **4c** (100 MHz, $CDCl_3$)



^{1}H-NMR of compound **4d** (400 MHz, $CDCl_3$)



^{13}C-NMR of compound **4d** (100 MHz, $CDCl_3$)



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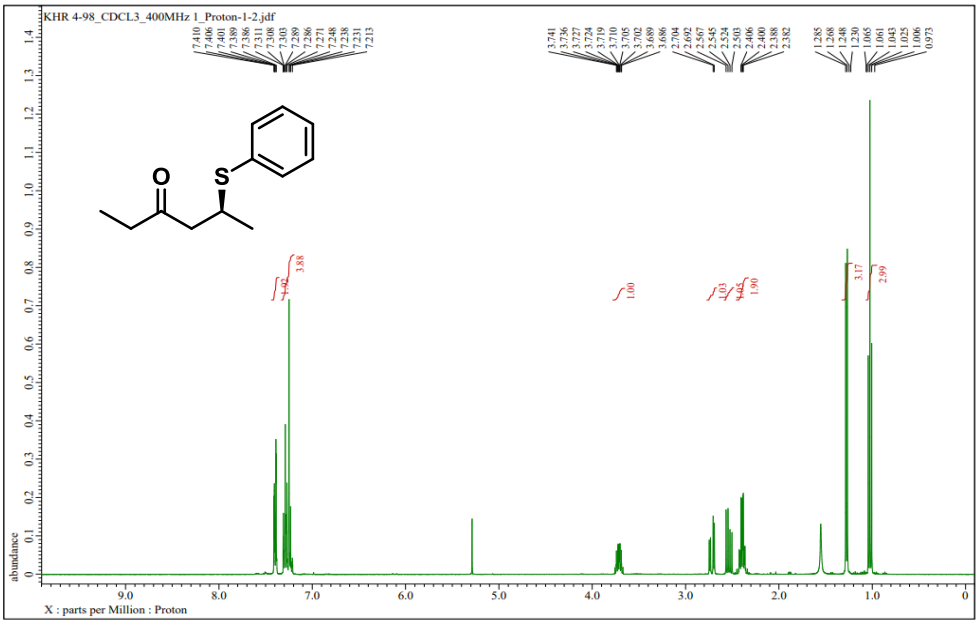
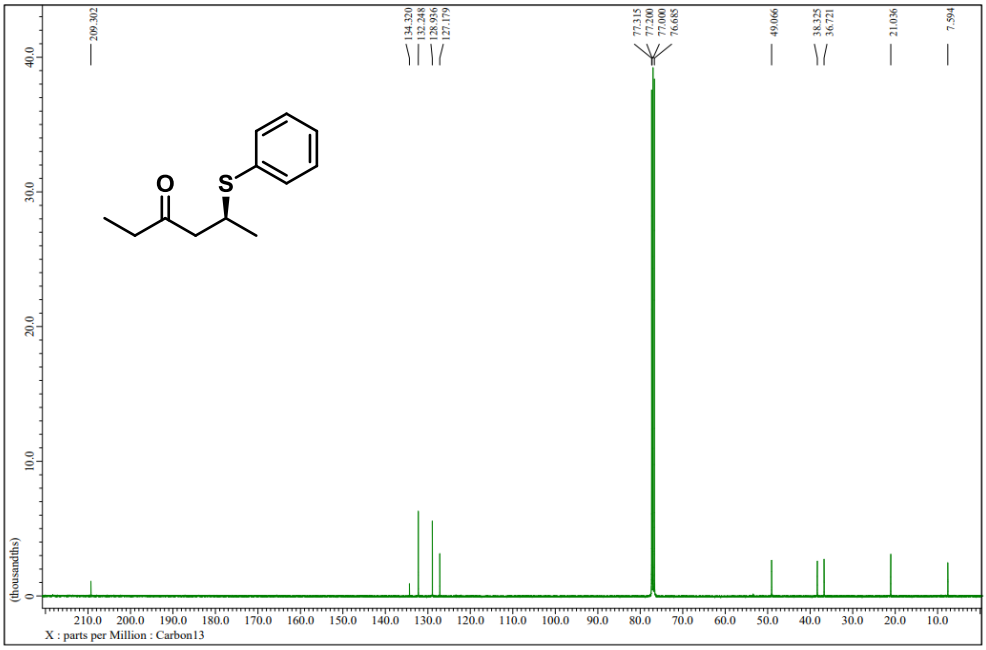
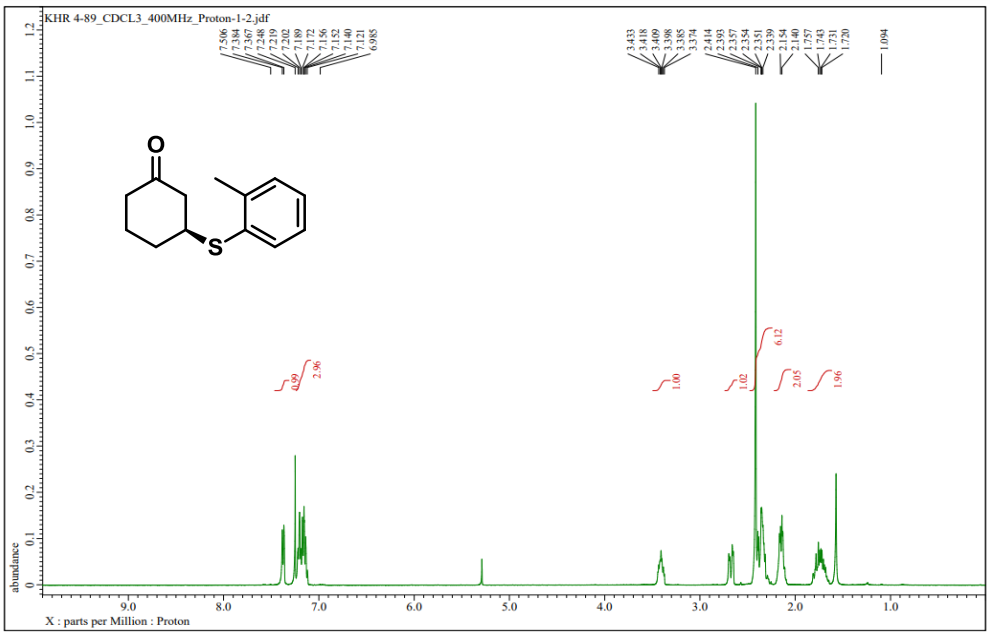


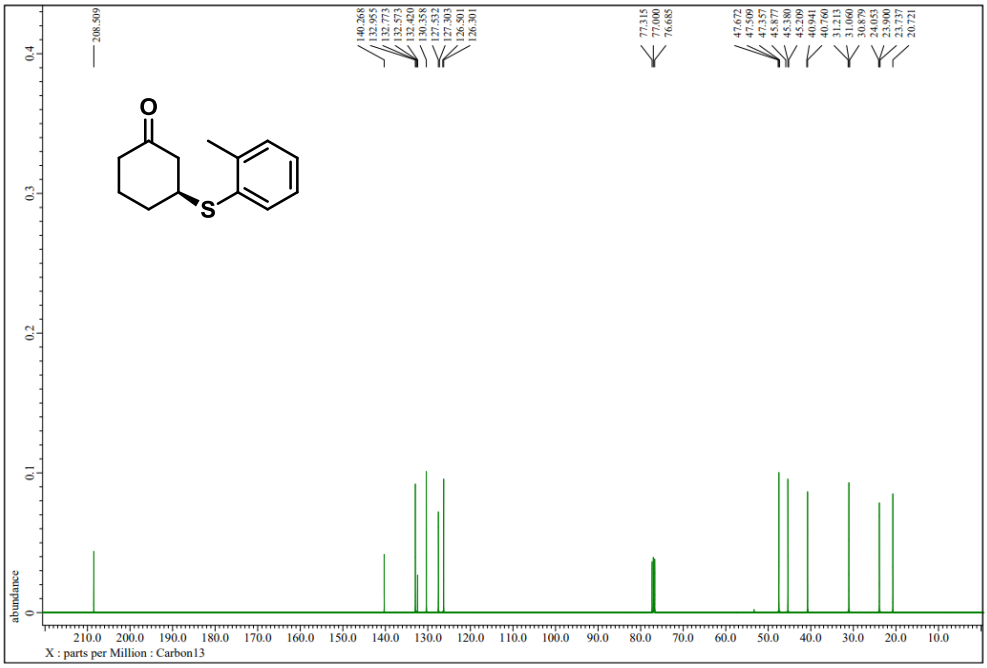
^{13}C-NMR of compound **4e** (100 MHz, $CDCl_3$)



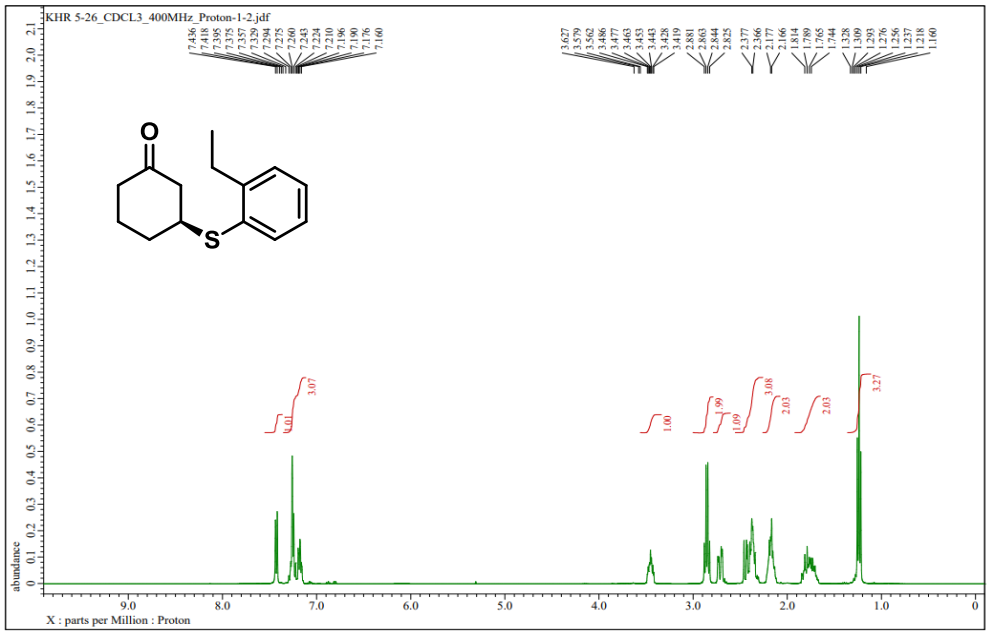
^{1}H-NMR of compound **5b** (400 MHz, $CDCl_3$)



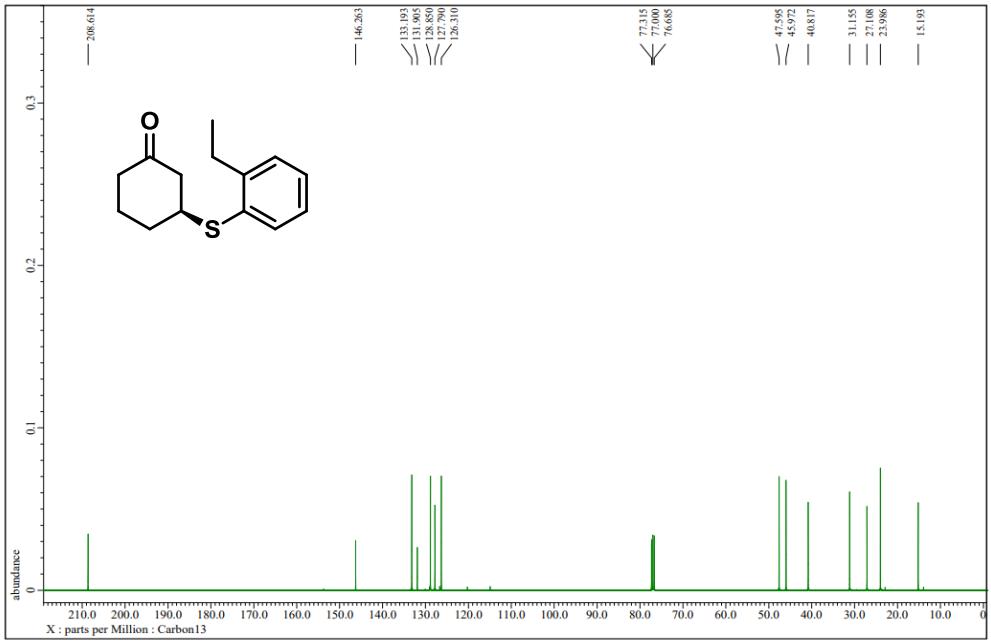
^{13}C-NMR of compound **5b** (100 MHz, $CDCl_3$)



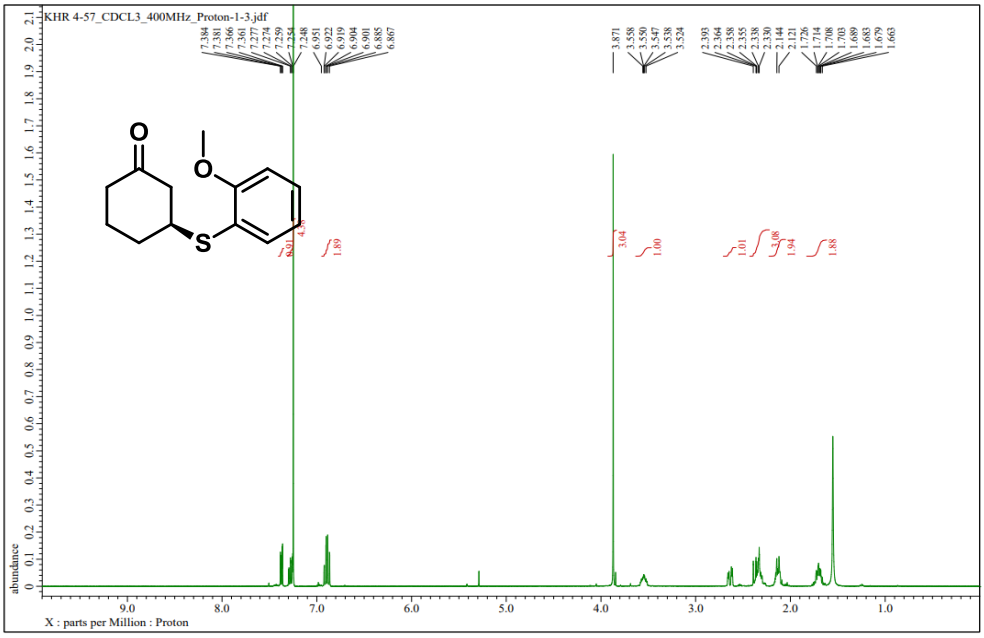
^{1}H-NMR of compound **5c** (400 MHz, $CDCl_3$)



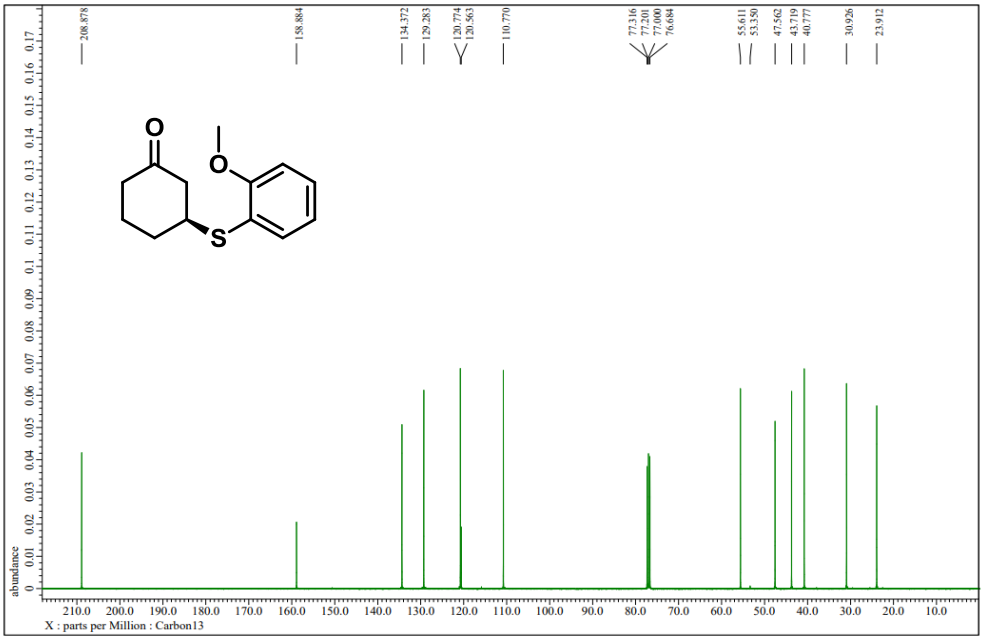
^{13}C-NMR of compound **5c** (100 MHz, $CDCl_3$)



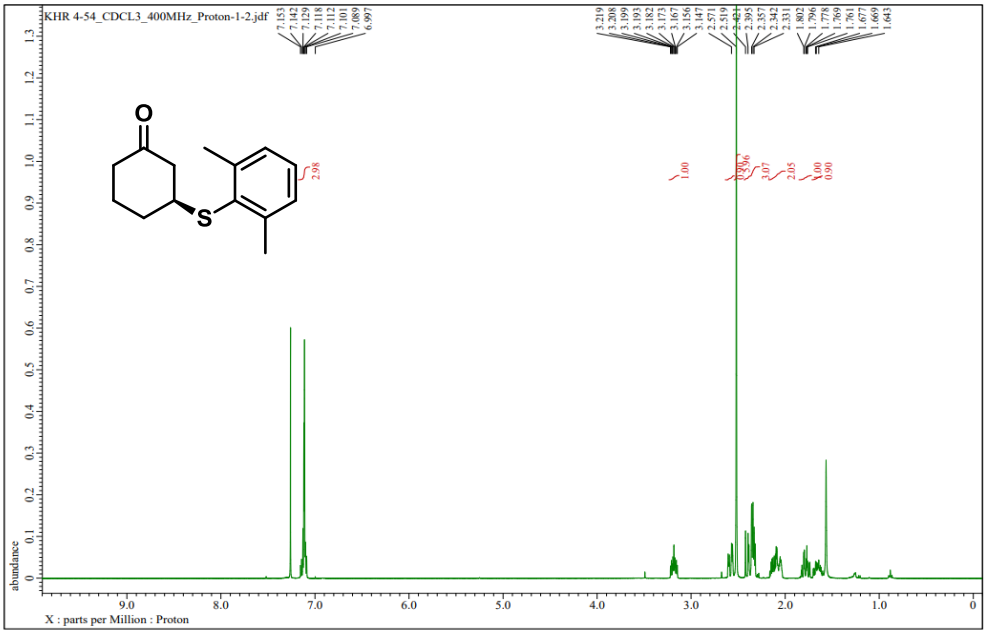
^{1}H-NMR of compound **5d** (400 MHz, $CDCl_3$)



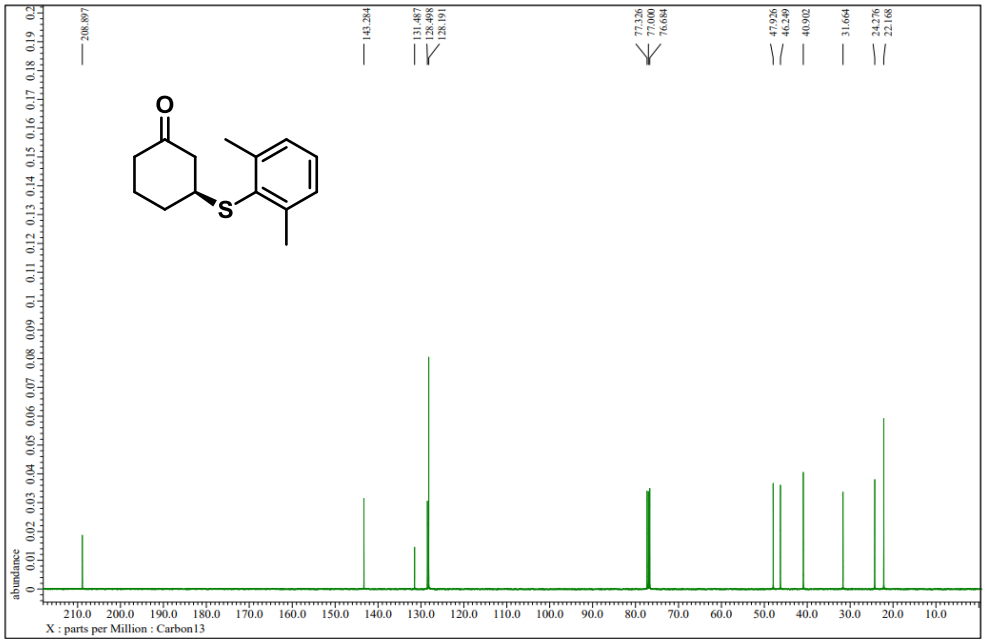
^{13}C-NMR of compound **5d** (100 MHz, $CDCl_3$)



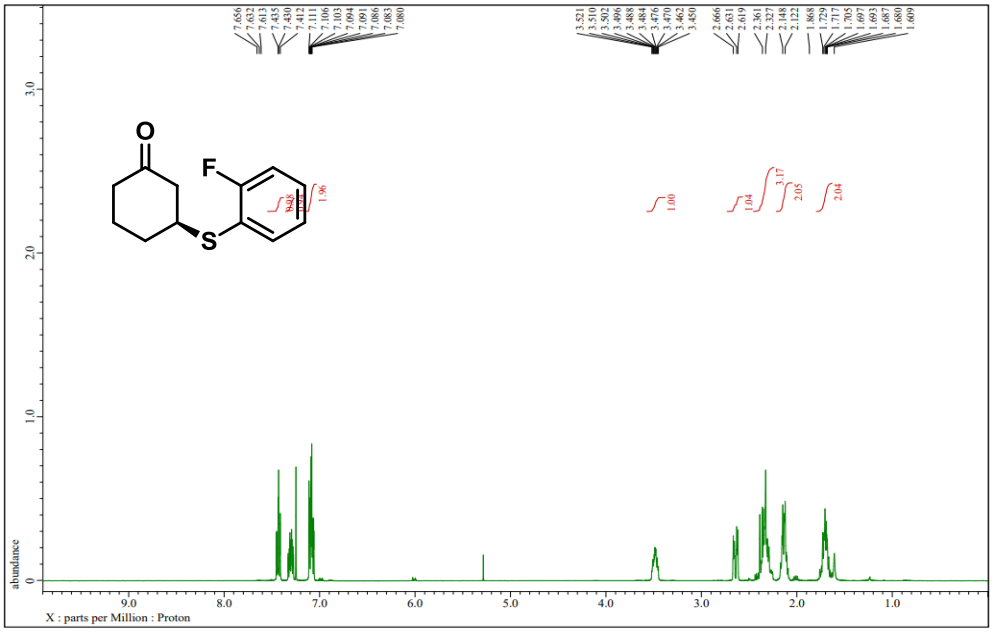
^{1}H-NMR of compound **5e** (400 MHz, $CDCl_3$)



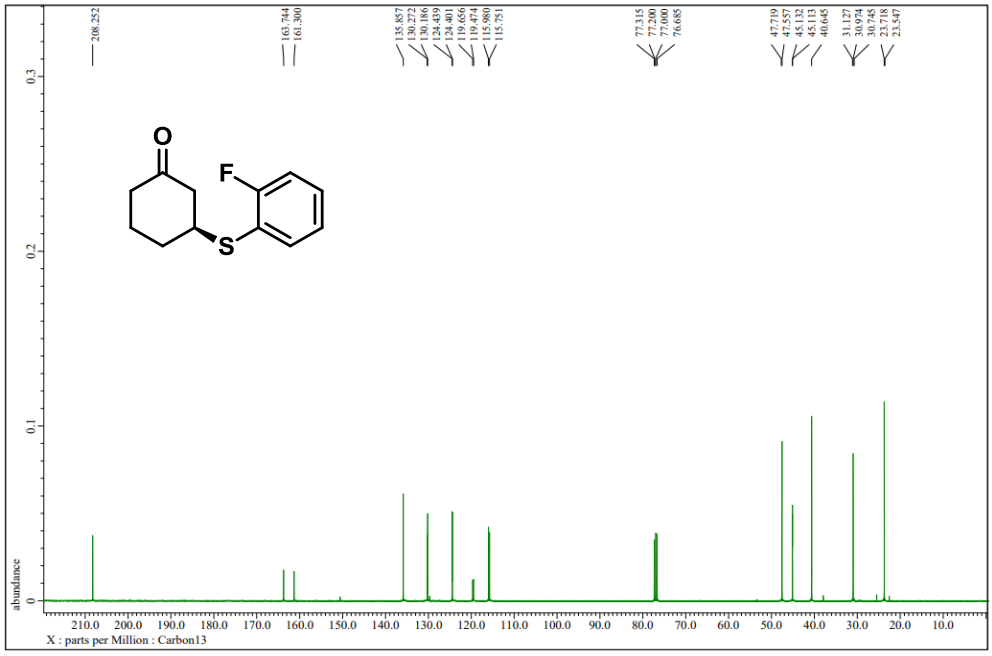
^{13}C-NMR of compound **5e** (100 MHz, $CDCl_3$)



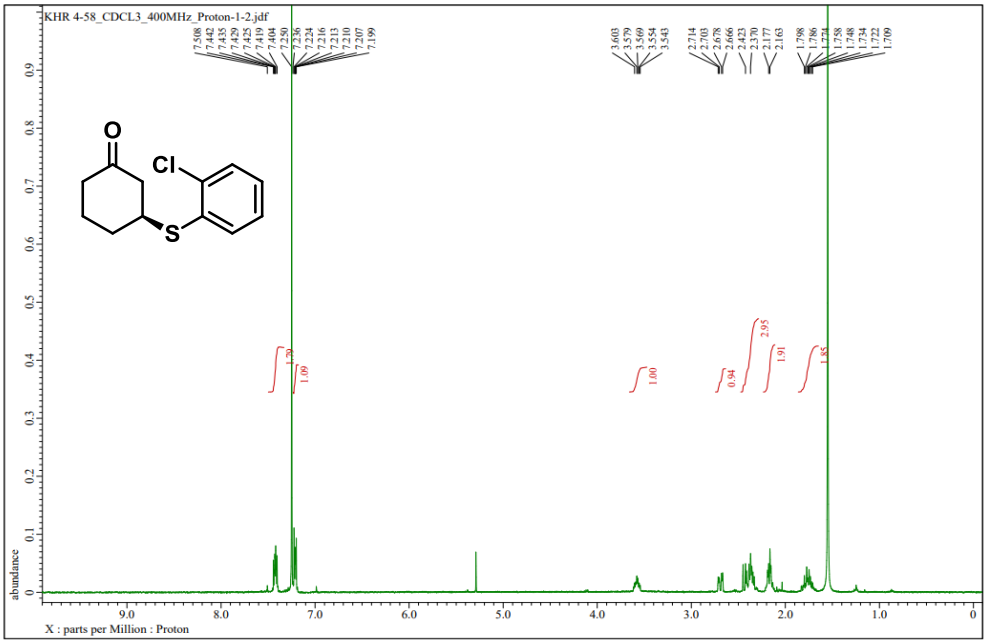
^{1}H-NMR of compound **5f** (400 MHz, $CDCl_3$)



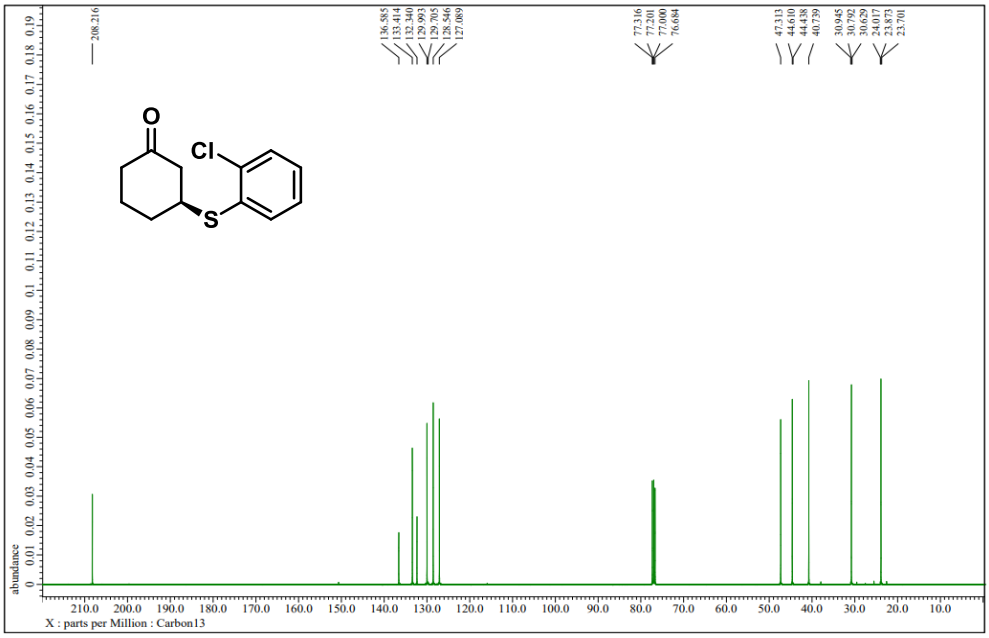
^{13}C-NMR of compound **5e** (100 MHz, $CDCl_3$)



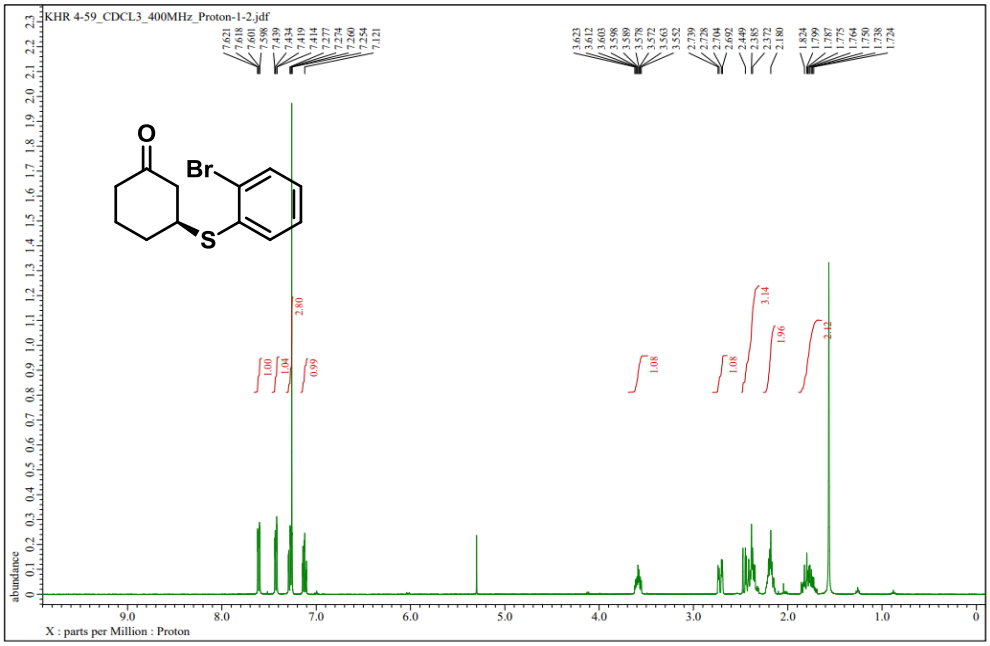
^{1}H-NMR of compound **5g** (400 MHz, $CDCl_3$)



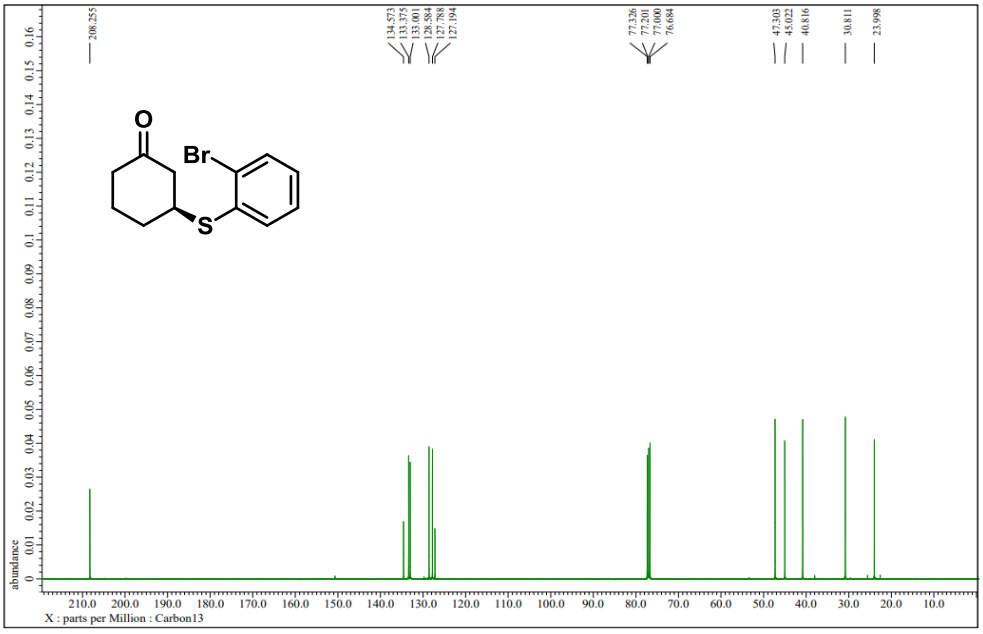
^{13}C-NMR of compound **5g** (100 MHz, $CDCl_3$)



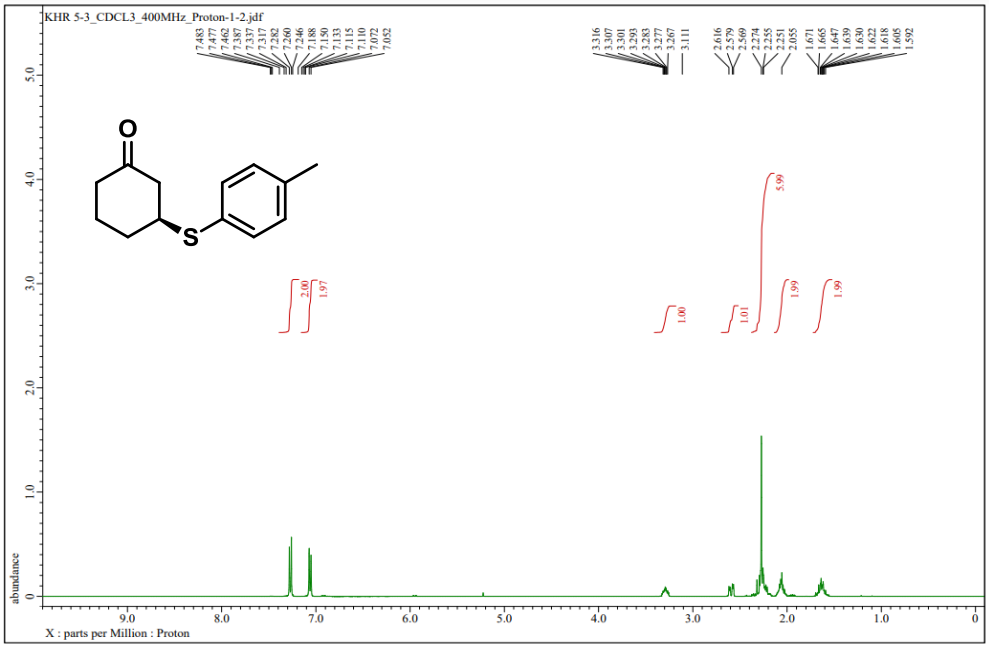
^{1}H-NMR of compound **5h** (400 MHz, $CDCl_3$)



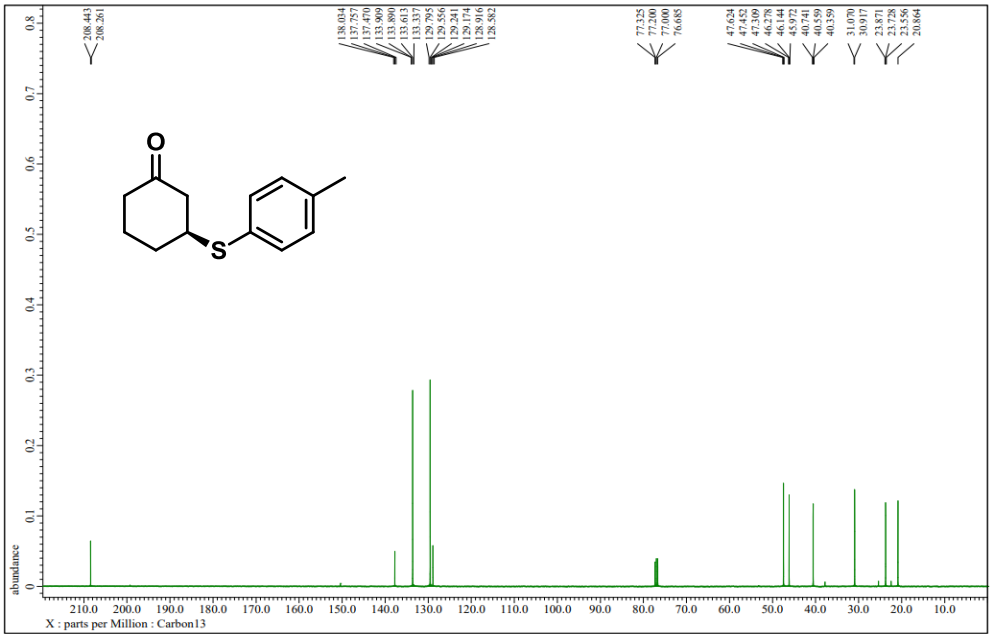
^{13}C-NMR of compound **5h** (100 MHz, $CDCl_3$)



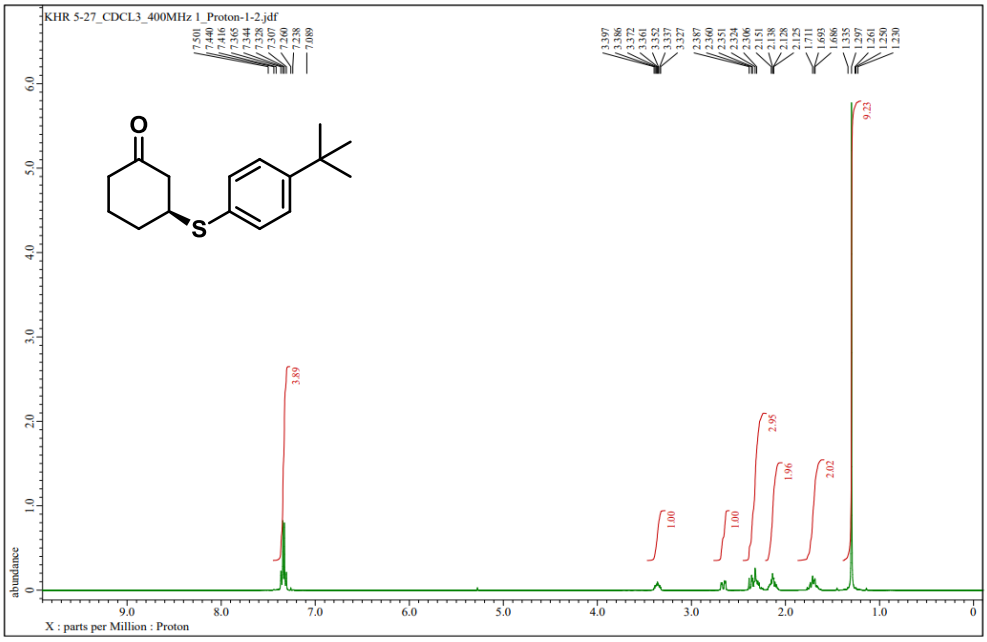
^{1}H-NMR of compound **5i** (400 MHz, $CDCl_3$)



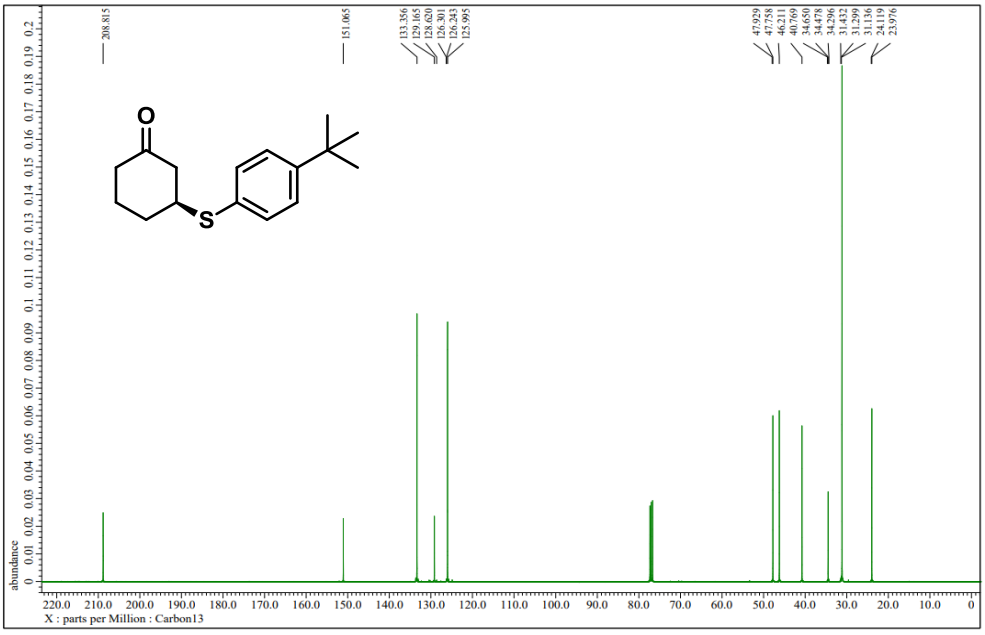
^{13}C-NMR of compound **5i** (100 MHz, $CDCl_3$)



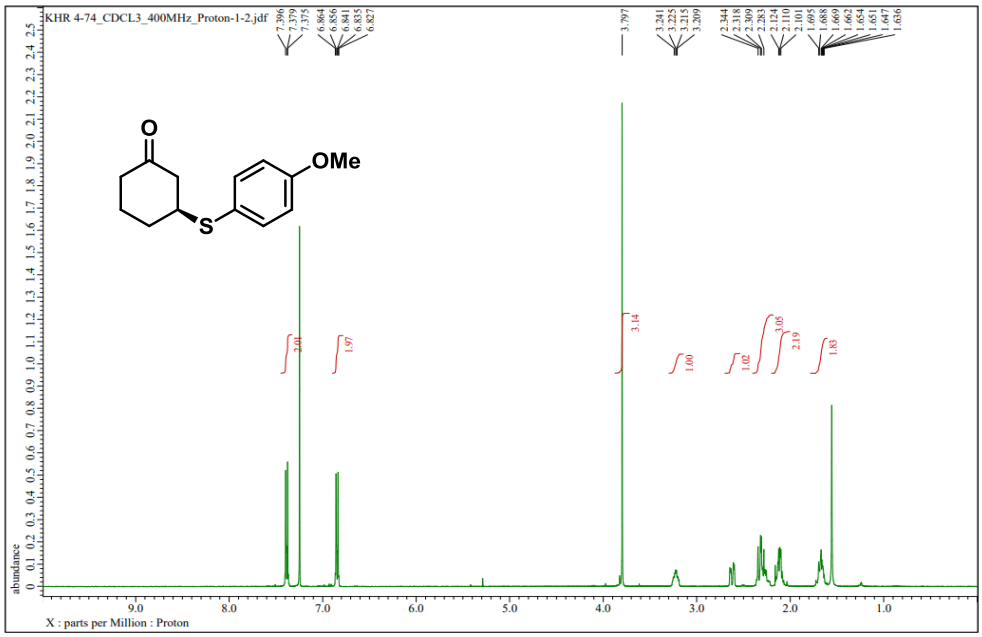
^{1}H-NMR of compound **5j** (400 MHz, $CDCl_3$)



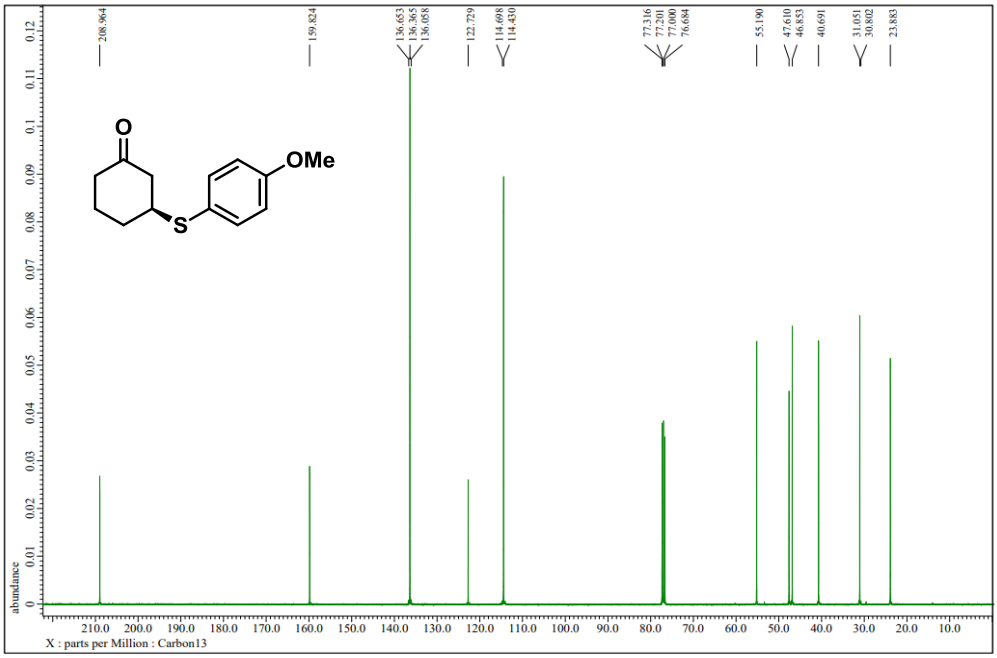
^{13}C-NMR of compound **5j** (100 MHz, $CDCl_3$)



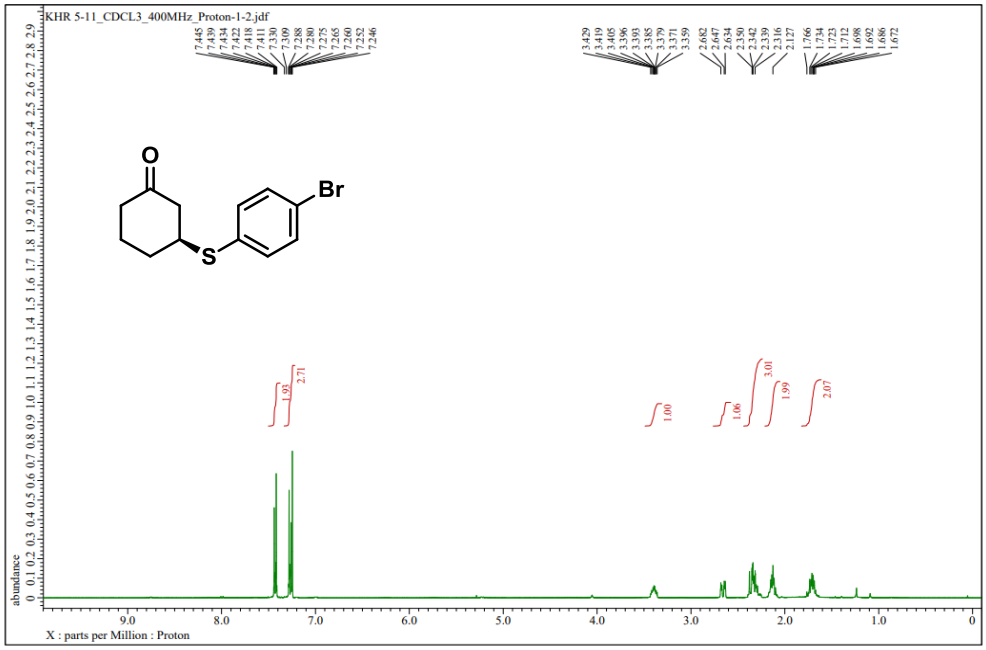
^{1}H-NMR of compound **5k** (400 MHz, $CDCl_3$)



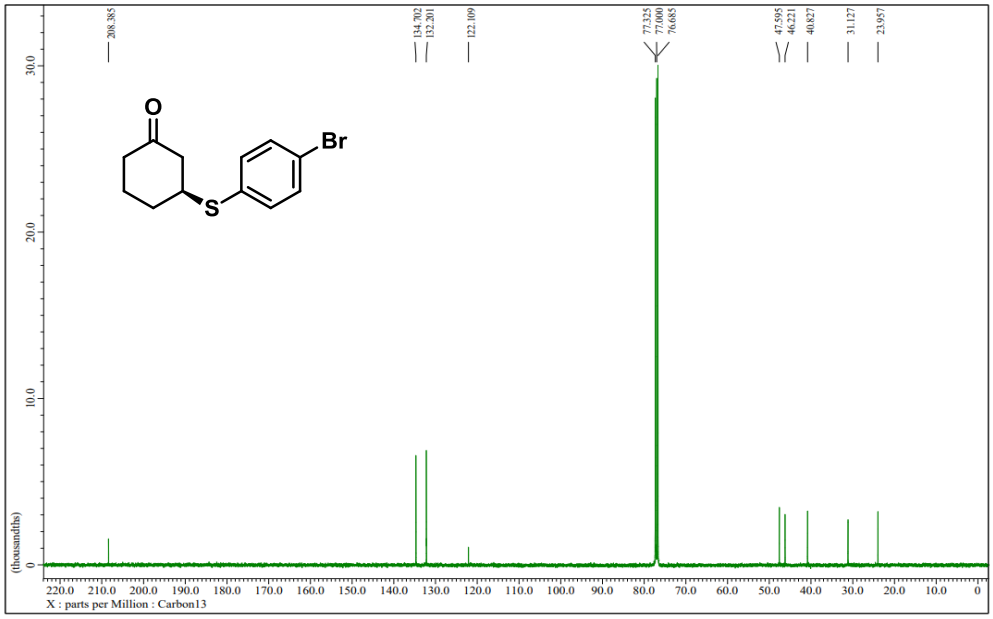
^{13}C-NMR of compound **5k** (100 MHz, $CDCl_3$)



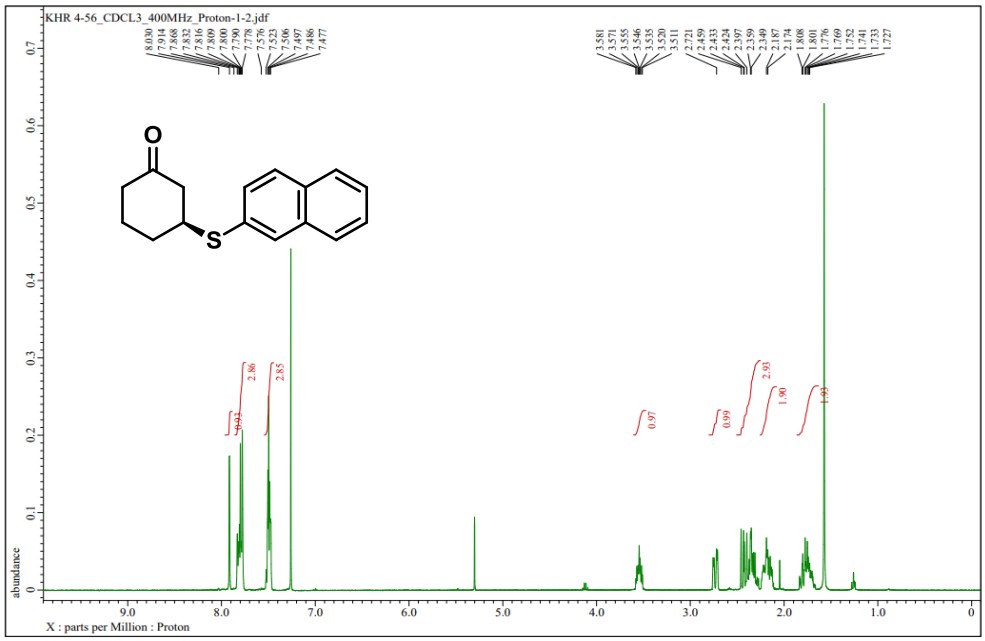
^{1}H-NMR of compound **5l** (400 MHz, $CDCl_3$)



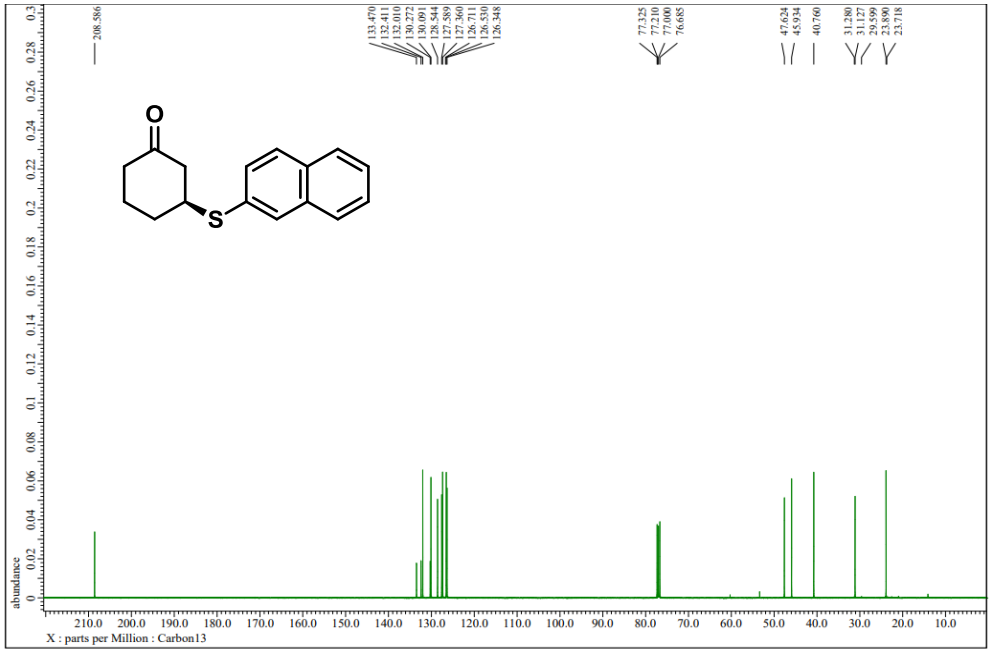
^{13}C-NMR of compound **5l** (100 MHz, $CDCl_3$)



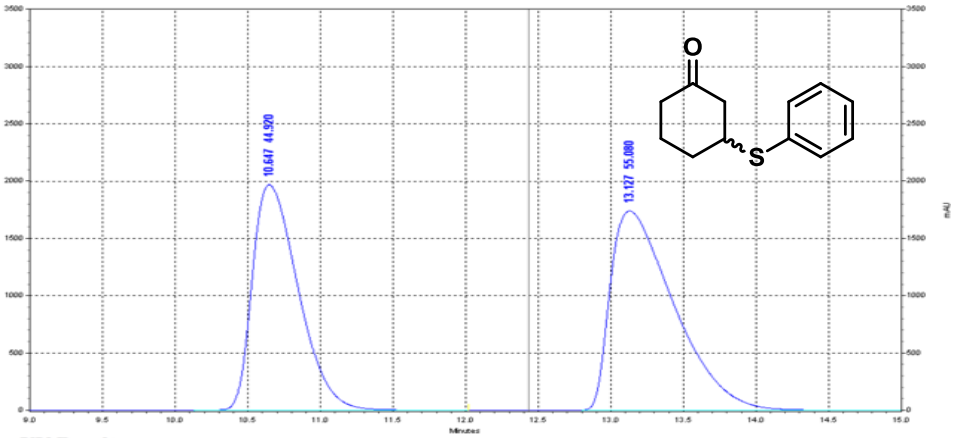
^{1}H-NMR of compound **5m** (400 MHz, $CDCl_3$)



^{13}C-NMR of compound **5m** (100 MHz, $CDCl_3$)



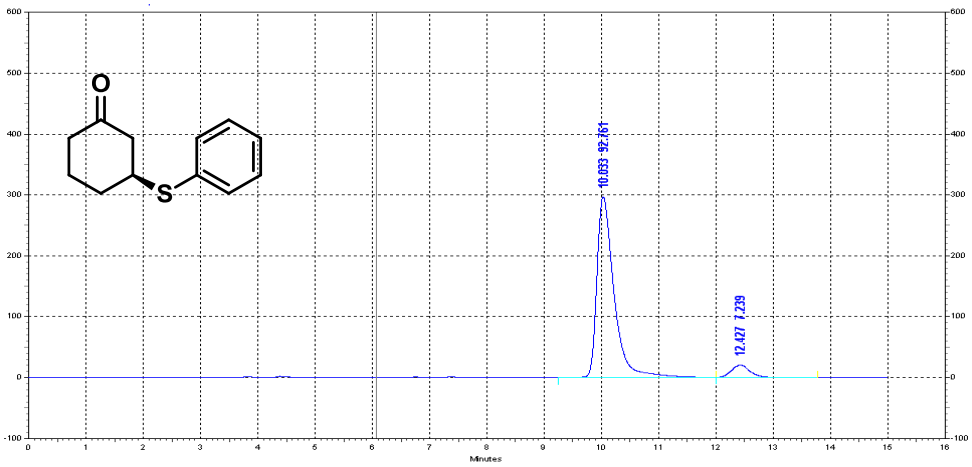
HPLC Graph of ***rac*-4a**



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	10.647	172550025	44.920	II
	13.127	211575223	55.080	IE
Totals		384125248	100.000	

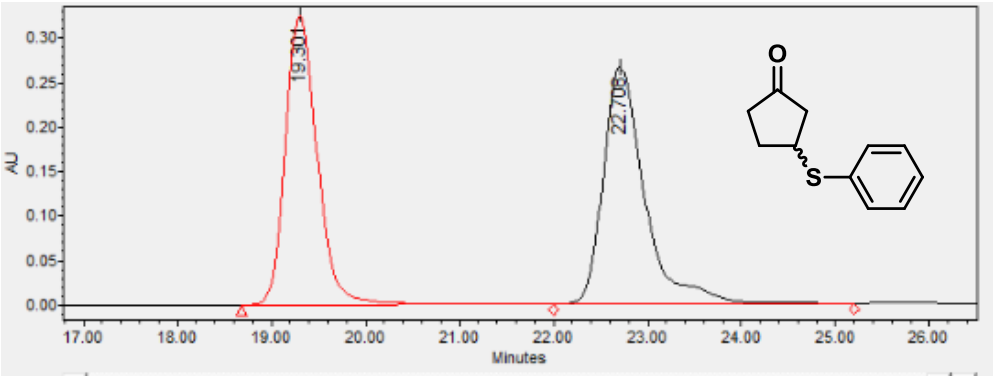
HPLC Graph of ***chiral*-4a**



UV Results

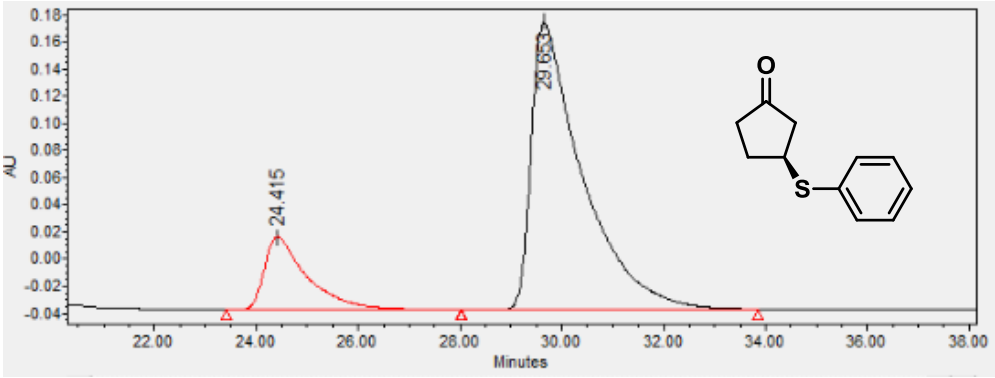
Name	Retention Time	Area	Area Percent	Integration Codes
	10.033	24873300	92.761	Mx
	12.427	1941153	7.239	xM
Totals		26814453	100.000	

HPLC Graph of ***rac*-4b**



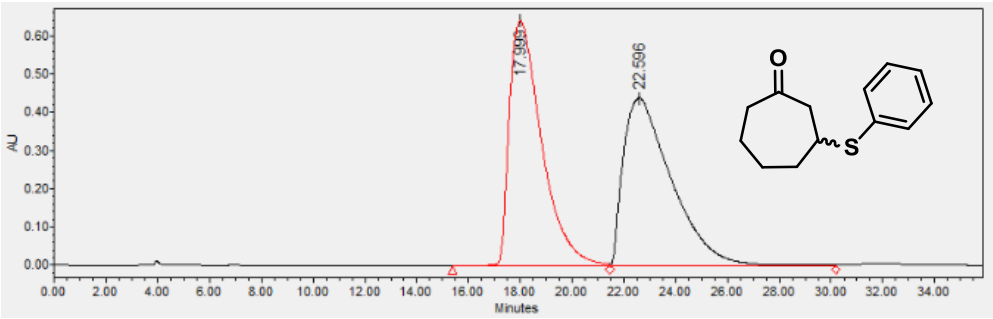
	RT	Area	% Area	Height
1	19.301	7726691	48.44	325605
2	22.708	8224817	51.56	266853

HPLC Graph of ***chiral*-4b**



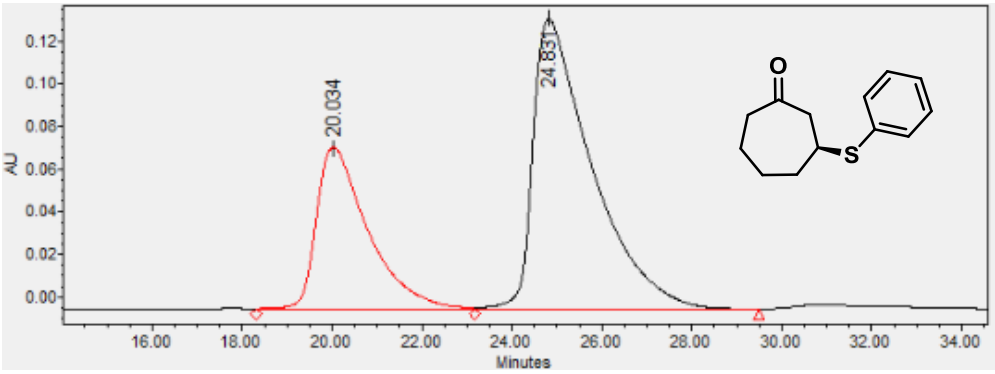
	RT	Area	% Area	Height
1	24.415	3096776	17.36	53615
2	29.653	14738973	82.64	211785

HPLC Graph of ***rac*-4c**



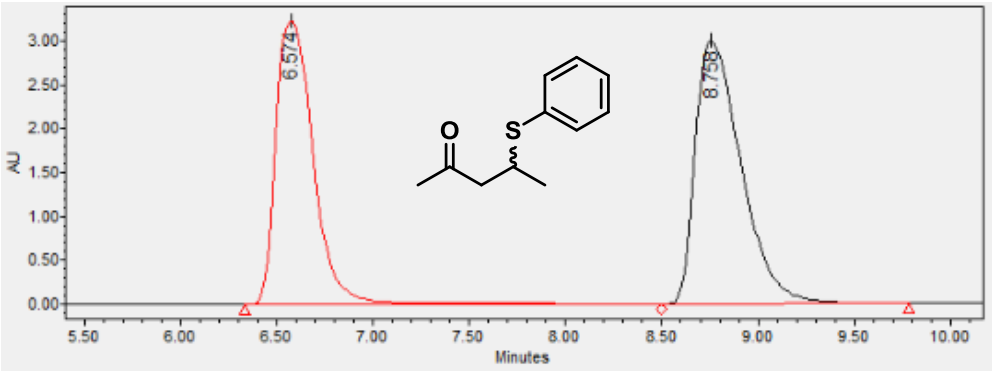
	RT	Area	% Area	Height
1	17.999	55211145	49.58	638803
2	22.596	56137435	50.42	438066

HPLC Graph of ***chiral*-4c**



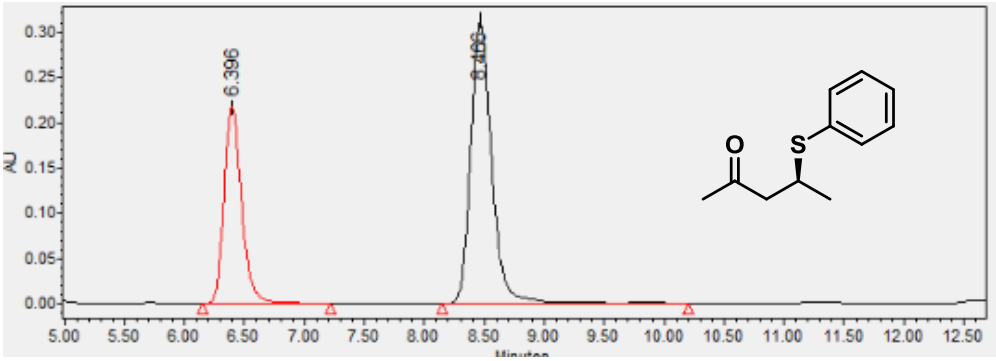
	RT	Area	% Area	Height
1	20.034	6016883	32.76	75765
2	24.831	12349858	67.24	135964

HPLC Graph of ***rac*-4d**



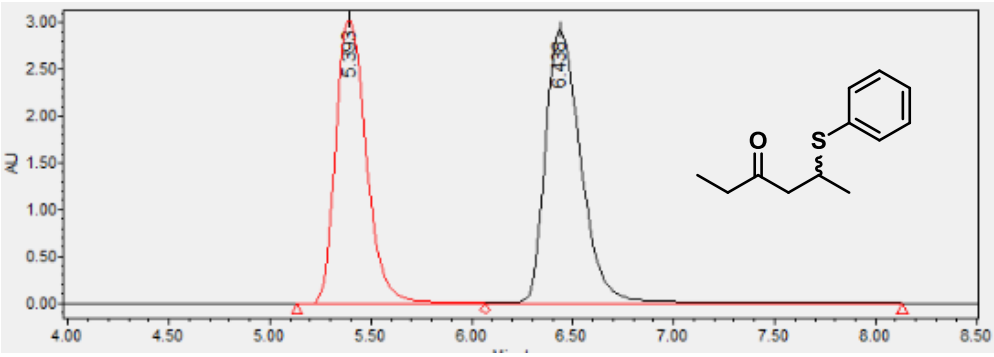
	RT	Area	% Area	Height
1	6.574	43971337	47.08	3233051
2	8.758	49417750	52.92	2999931

HPLC Graph of ***chiral*-4d**



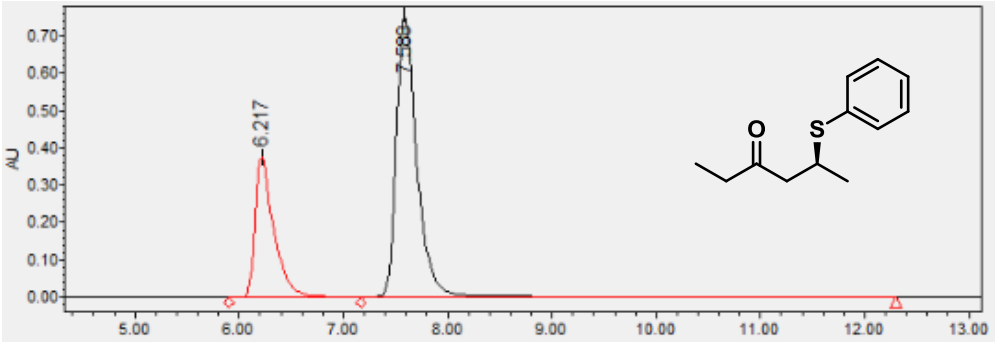
	RT	Area	% Area	Height
1	6.396	2225842	36.75	217852
2	8.466	3831178	63.25	311096

HPLC Graph of ***rac*-4e**



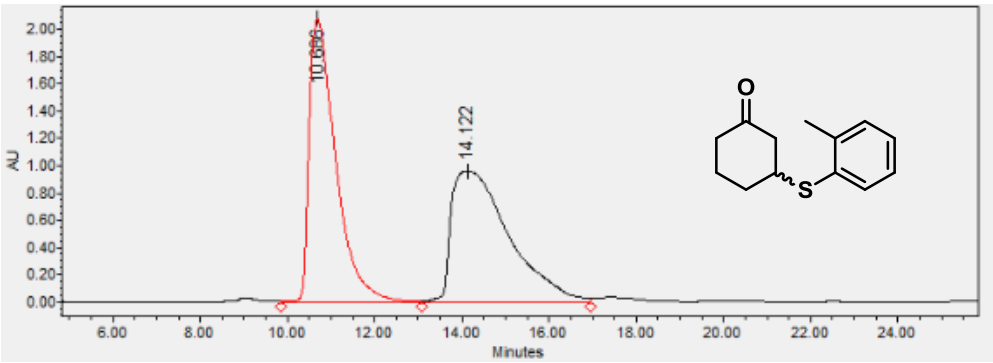
	RT	Area	% Area	Height
1	5.393	32451765	47.14	3051081
2	6.438	36382758	52.86	2936124

HPLC Graph of ***chiral*-4e**



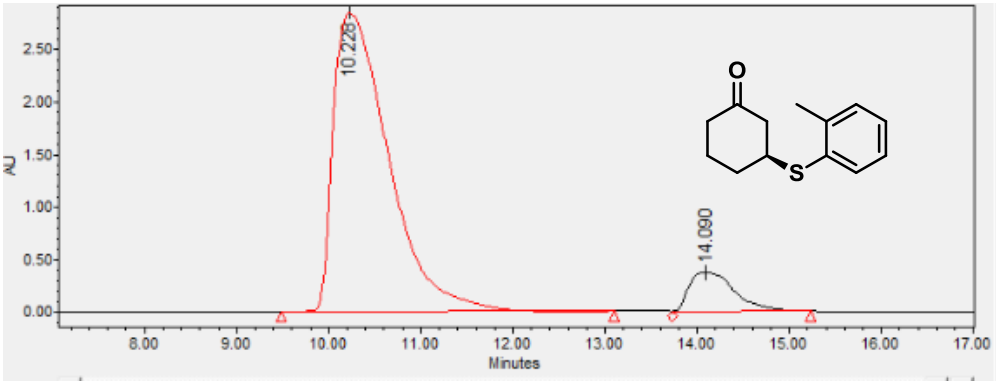
	RT	Area	% Area	Height
1	6.217	4758339	30.81	377405
2	7.588	10684717	69.19	759974

HPLC Graph of ***rac*-5b**



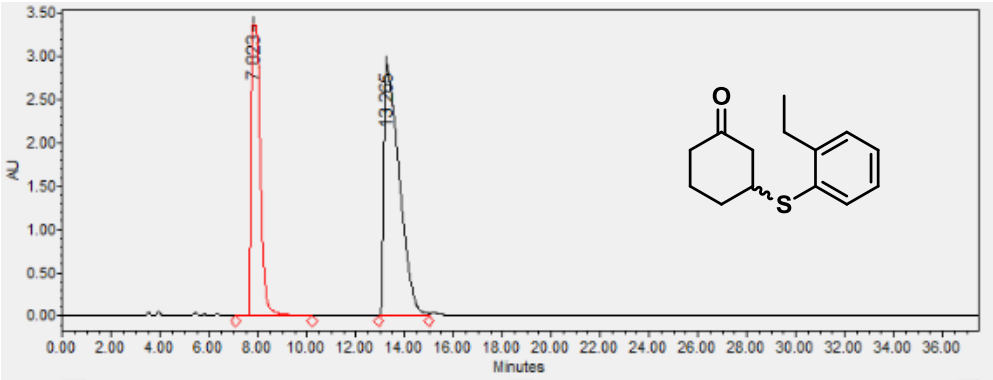
	RT	Area	% Area	Height
1	10.686	87750610	49.82	2079663
2	14.122	88378509	50.18	964651

HPLC Graph of ***chiral*-5b**



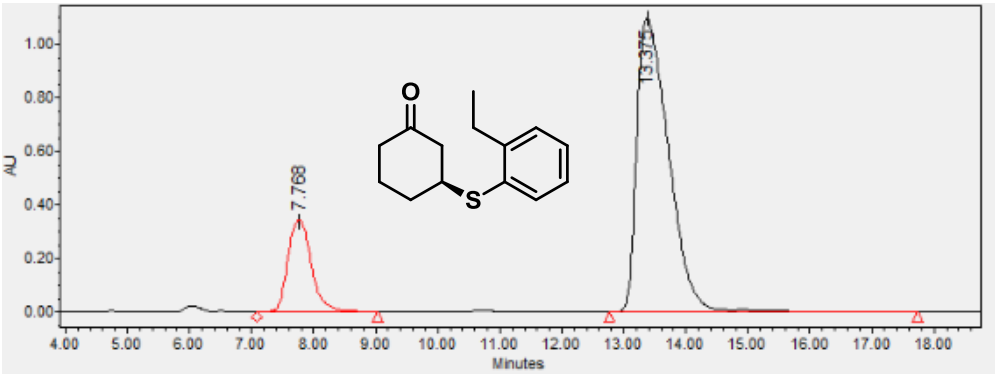
	RT	Area	% Area	Height
1	10.228	118560742	90.34	2845140
2	14.090	12672121	9.66	371043

HPLC Graph of ***rac*-5c**



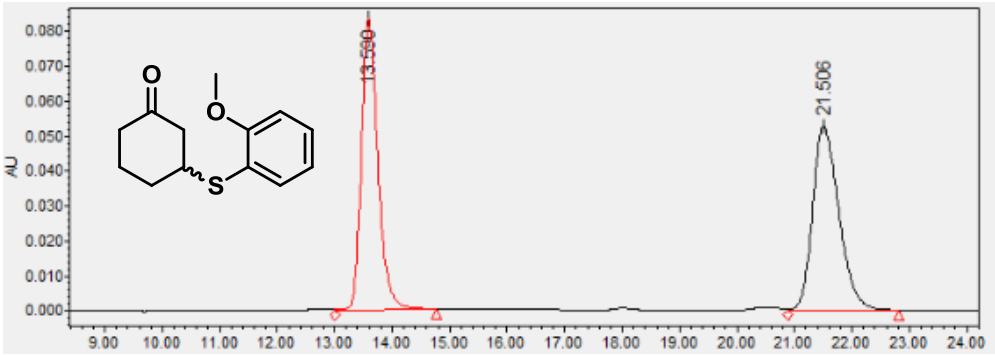
	RT	Area	% Area	Height
1	7.823	89213354	41.16	3365558
2	13.265	127532680	58.84	2919481

HPLC Graph of ***chiral*-5c**



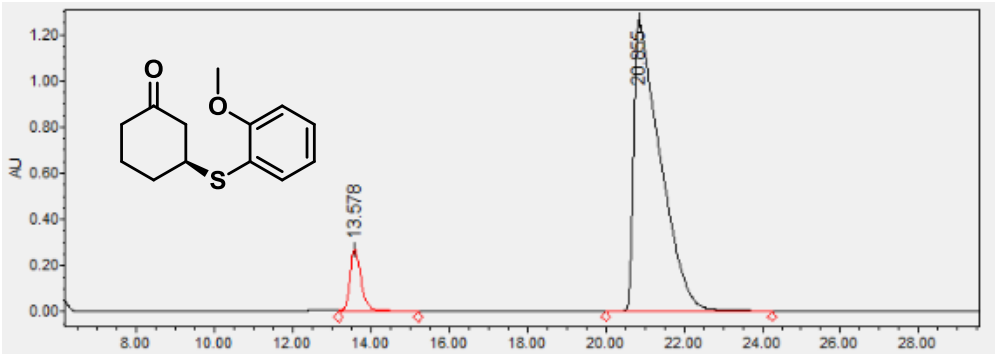
	RT	Area	% Area	Height
1	7.768	9026511	18.67	340896
2	13.375	39311343	81.33	1093843

HPLC Graph of ***rac*-5d**



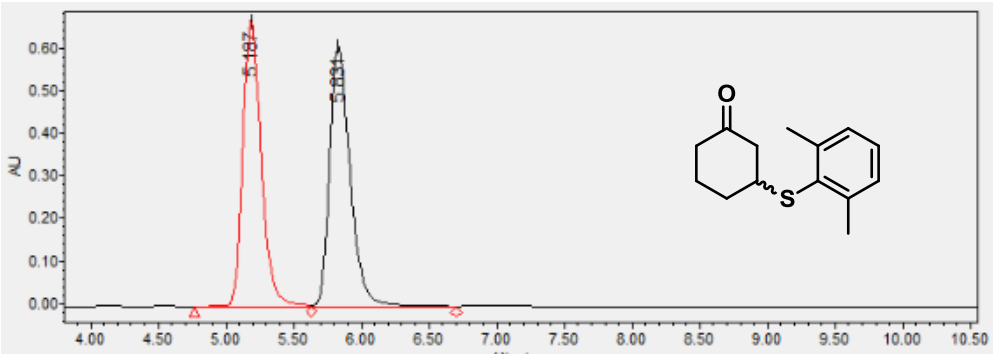
	RT	Area	% Area	Height
1	13.590	1668669	49.92	83465
2	21.506	1674017	50.08	52941

HPLC Graph of ***chiral*-5d**



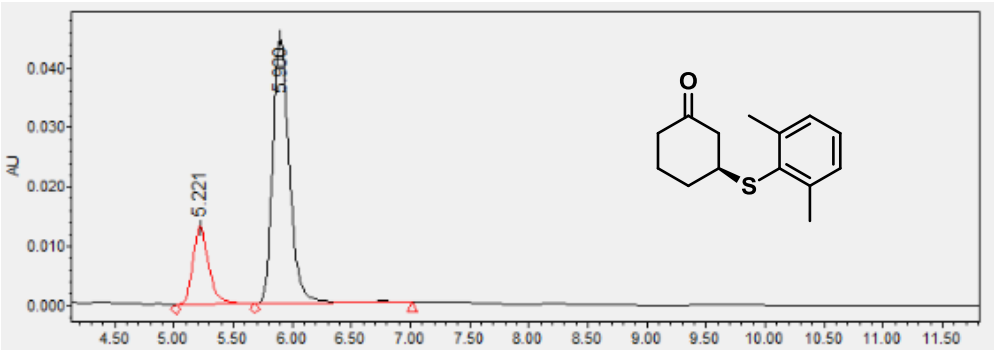
	RT	Area	% Area	Height
1	13.578	5741979	8.75	270364
2	20.855	59868072	91.25	1261210

HPLC Graph of ***rac*-5e**



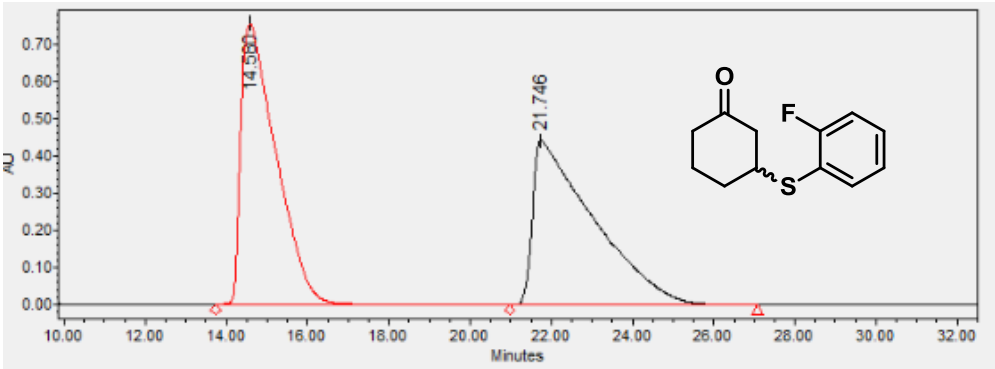
	RT	Area	% Area	Height
1	5.187	6384327	49.63	671258
2	5.831	6479042	50.37	609796

HPLC Graph of ***chiral*-5e**



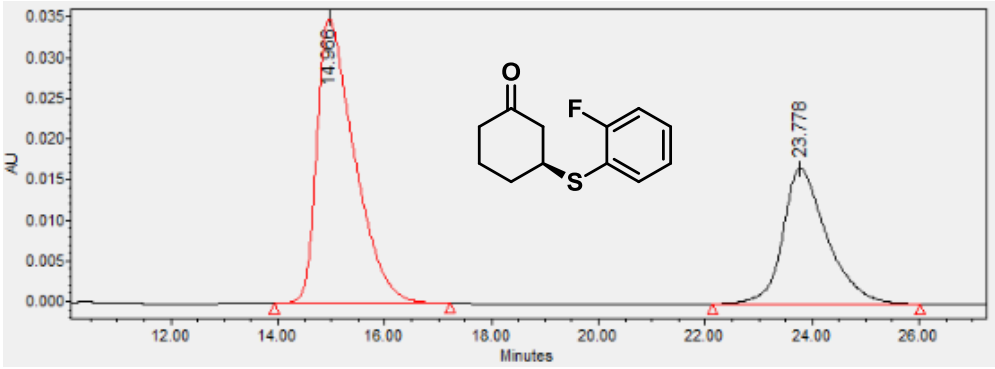
	RT	Area	% Area	Height
1	5.221	138220	23.11	13443
2	5.900	459921	76.89	45288

HPLC Graph of ***rac*-5f**



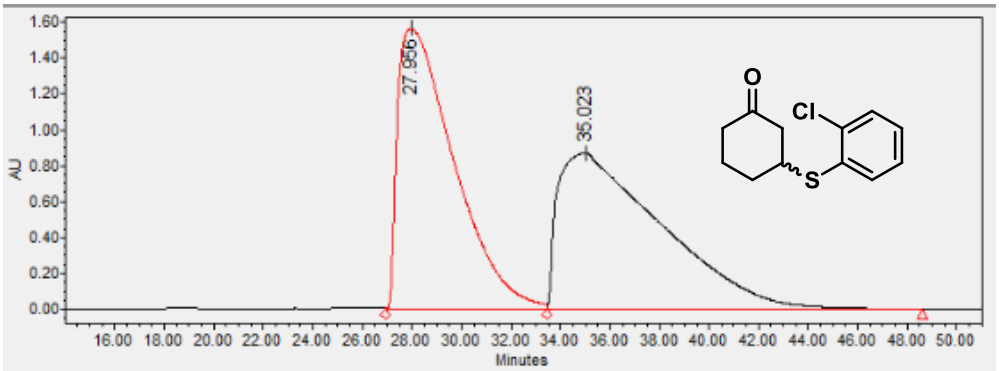
	RT	Area	% Area	Height
1	14.580	45609486	49.92	753422
2	21.746	45761897	50.08	442001

HPLC Graph of ***chiral*-5f**



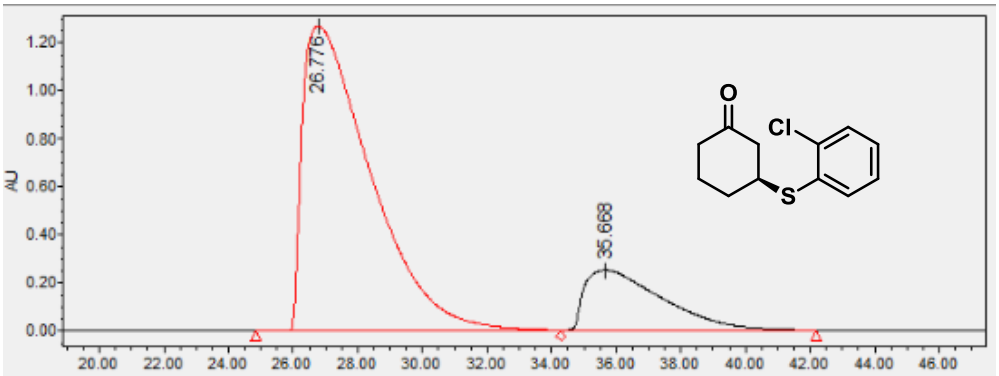
	RT	Area	% Area	Height
1	14.966	1712874	64.08	34977
2	23.778	960039	35.92	16680

HPLC Graph of ***rac*-5g**



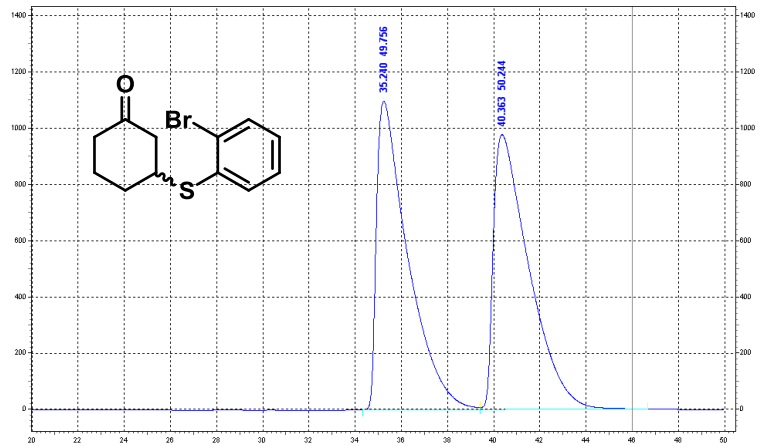
	RT	Area	% Area	Height
1	27.956	247272768	49.55	1563118
2	35.023	251723302	50.45	872086

HPLC Graph of ***chiral*-5g**



	RT	Area	% Area	Height
1	26.776	185784705	81.51	1266831
2	35.668	42145800	18.49	251930

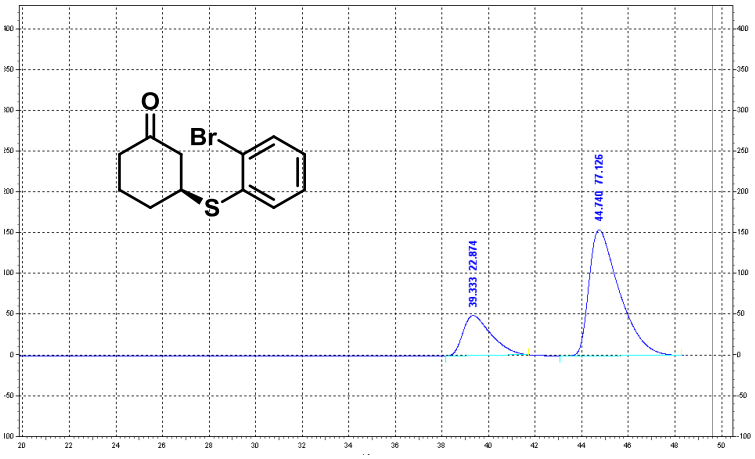
HPLC Graph of ***rac*-5h**



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	35.240	413657075	49.756	BV
	40.363	417712626	50.244	VI
Totals		831369701	100.000	

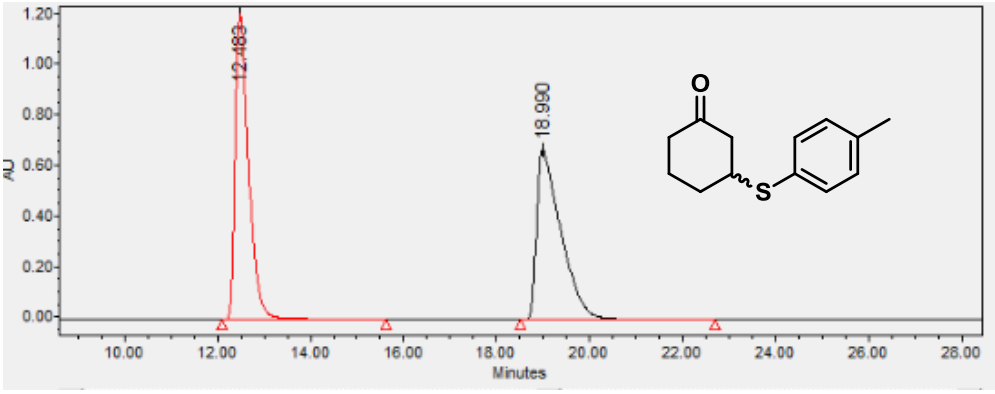
HPLC Graph of ***chiral*-5h**



UV Results

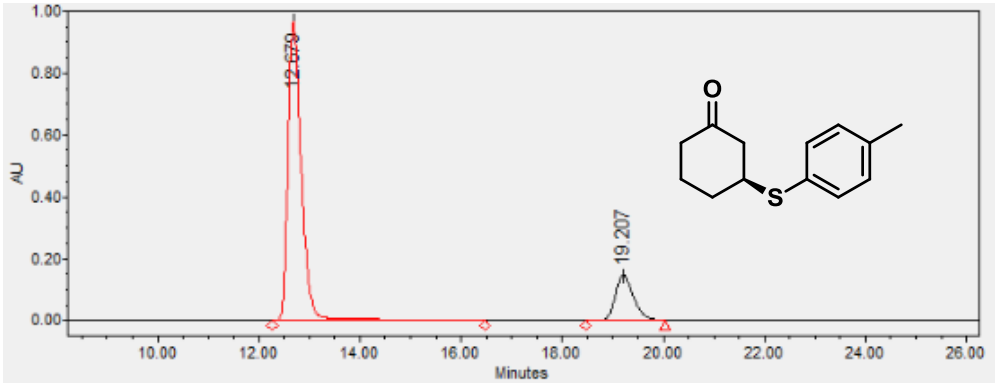
Name	Retention Time	Area	Area Percent	Integration Codes
	39.333	16545067	22.874	MM
	44.740	55785211	77.126	MM
Totals		72330278	100.000	

HPLC Graph of ***rac*-5i**



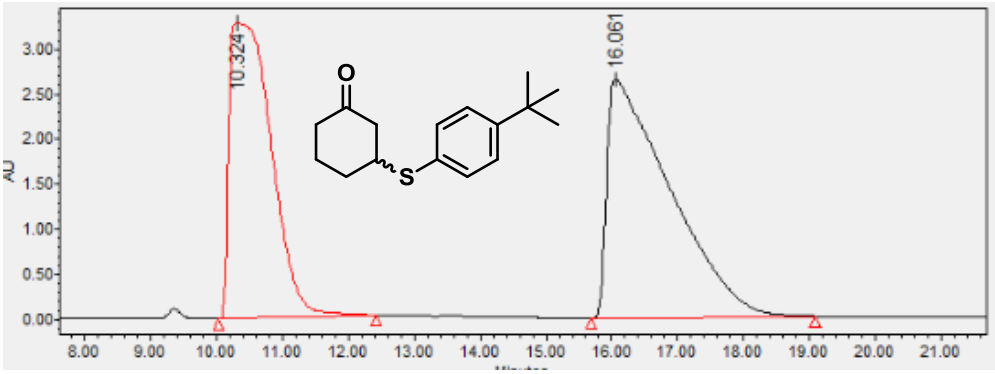
	RT	Area	% Area	Height
1	12.483	24212667	49.86	1206597
2	18.990	24345827	50.14	674439

HPLC Graph of ***chiral*-5i**



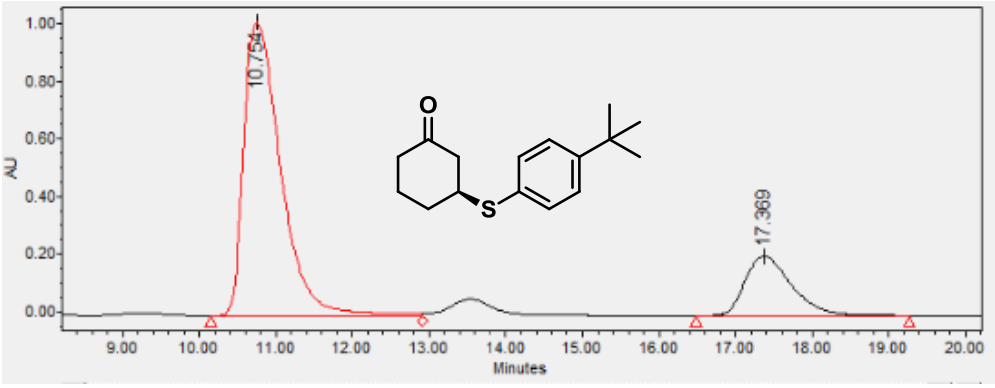
	RT	Area	% Area	Height
1	12.679	17718851	83.23	965332
2	19.207	3571030	16.77	144969

HPLC Graph of ***rac*-5j**



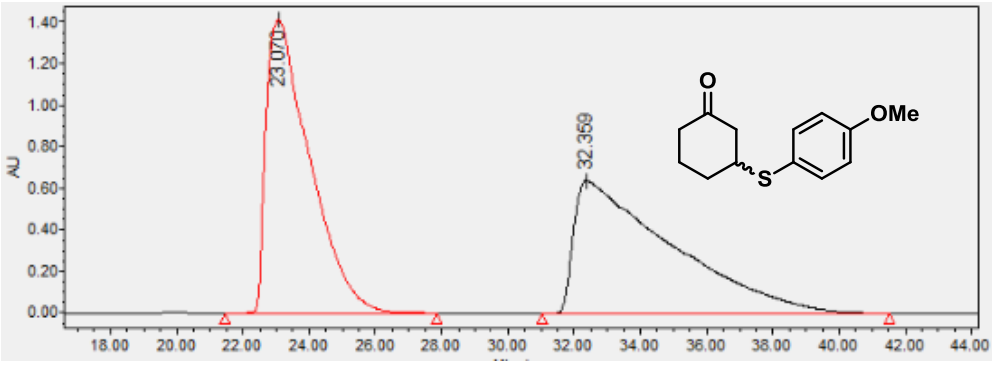
	RT	Area	% Area	Height
1	10.324	145189634	45.10	3275387
2	16.061	176761926	54.90	2659587

HPLC Graph of ***chiral*-5j**



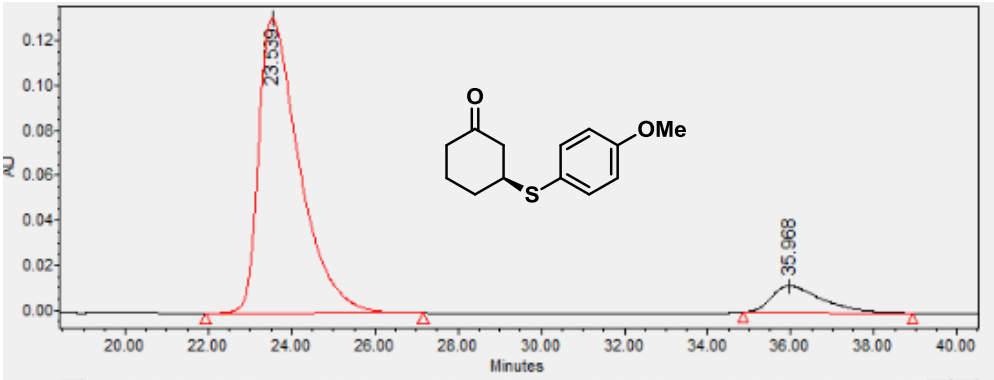
	RT	Area	% Area	Height
1	10.754	34338624	79.71	1021164
2	17.369	8738903	20.29	206992

HPLC Graph of ***rac*-5k**



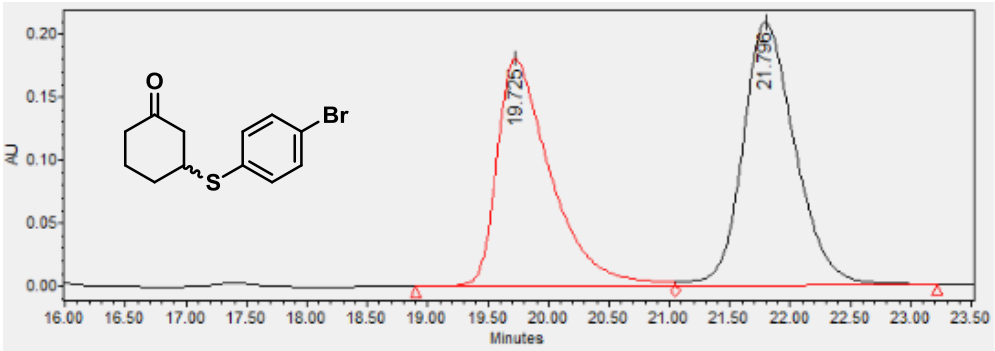
	RT	Area	% Area	Height
1	23.070	129357904	49.80	1411272
2	32.359	130409256	50.20	638759

HPLC Graph of ***chiral*-5k**



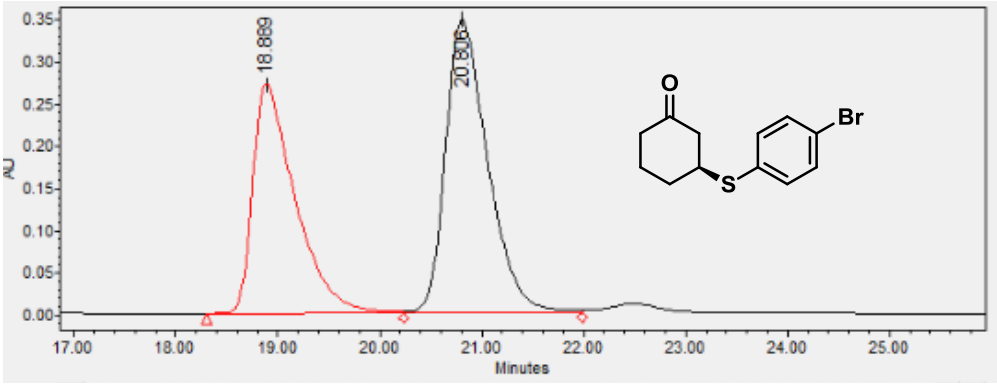
	RT	Area	% Area	Height
1	23.539	8905124	89.92	131145
2	35.968	998178	10.08	11861

HPLC Graph of ***rac*-5l**



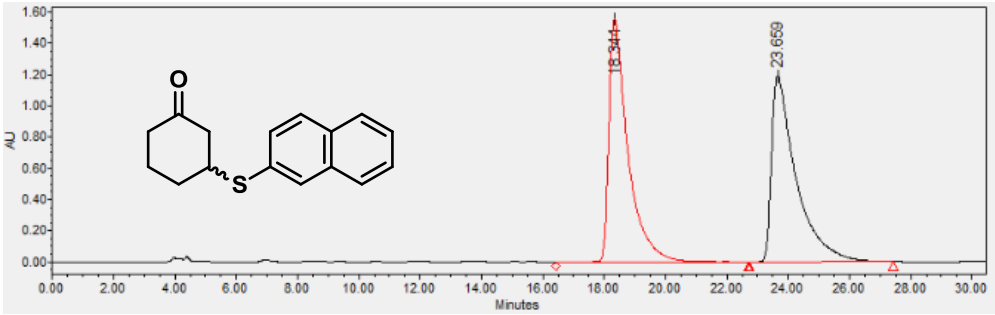
	RT	Area	% Area	Height
1	18.889	7857116	44.02	271710
2	20.806	9991360	55.98	347714

HPLC Graph of ***chiral*-5l**



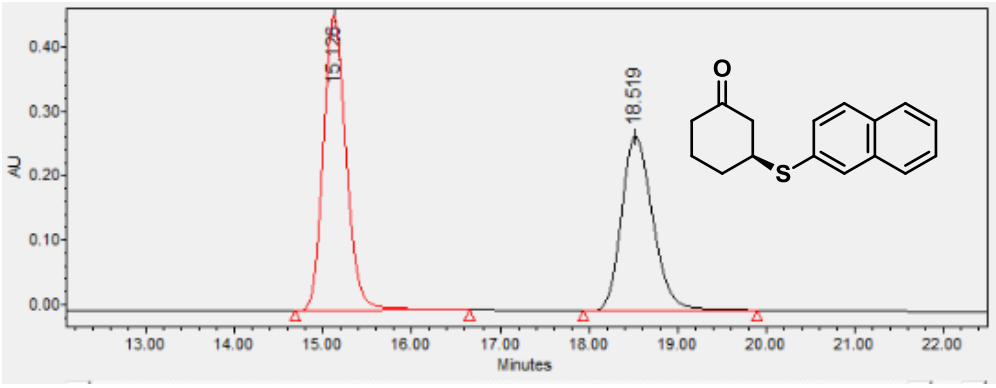
	RT	Area	% Area	Height
1	18.889	7857116	44.02	271710
2	20.806	9991360	55.98	347714

HPLC Graph of ***rac*-5m**



	RT	Area	% Area	Height
1	18.344	66577536	50.12	1553685
2	23.659	66257509	49.88	1192850

HPLC Graph of ***chiral*-5m**



	RT	Area	% Area	Height
1	15.126	8283739	55.45	457991
2	18.519	6655835	44.55	270772