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藥學碩士學位論文

상전이 촉매 반응을 통한 *tert*-butyl oxycarbamates의 입체 선택적인 aza-Michael Reactions

Enantioselective aza-Michael Reactions of *tert*-butyl oxycarbamates via Phase-Transfer Catalysis

2020年 **2**月

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반 정 우

국문 초록

β-Amino carbonyl 골격은 β-lactams 을 포함하여 amino alcohols, diamines, β-amino acids 등 다양한 질소 함유 중간체에서 중요한 구조를 차지하고 있다. 본 연구실에서는 상전이 촉매 반응(Phase-Transfer Catalysis)을 이용하여 *tert*-butyl benzyloxycarbamate 와 electron-deficient olefins 들을 대상으로 한 aza-Michael addition 을 성공적으로 보고한 바 있다. 50% aqueous potassium hydroxide(KOH) 와 toluene 용매 조건으로 상전이 촉매 반응을 진행하였을 때, 높은 수율(>99%)을 얻었다.

본 연구에서는 cyclic β-Amino carbonyl 골격을 입체 선택적으로 합성하기 위해 *tert*-butyl benzyloxycarbamate 와 2-cyclohexen-1-one 을 기질로 PTC aza-Michael reaction 을 진행하였다. 다양한 상전이 촉매를 사용하여 0°C 에서 높은 광학수율 (87% ee)을 보이는 상전이 촉매를 발견하였다. 이렇게 확립한 상전이 촉매를 사용하여 *tert*-butyl oxycarbamates 14 가지와 cyclic enones 9 가지를 대상으로 phase-transfer catalytic aza-Michael addition 을 진행하였다.

최종적으로 *tert*-butyl (naphthalene-2-ylmethoxy)carbamate 와 2-cyclohexen-1-one 을 기질로 aza-Michael reaction 을 진행하였을 때 높은 수율 (>99%)과 높은 광학수율 (98% ee)을 얻을 수 있었다. 이는 촉매와 기질간의 상호작용에 기인한 것으로 보이며, 다음과 같은 3 가지 상호작용이 관여하고 있음을 제안해보았다. (Ion-pair interaction, π-π interaction, Hydrogen-bonding interaction). 또한, TFA acidic 조건과 Hydrogen & Pd/C 조건하에서 선택적으로 deprotection 을 진행하여, cyclic β-amino carbonyl 골격을 chiral 하게 갖고 있는 천연물을 합성하기 위한 전구 물질로 활용 가능함을 확인하였다.

주요어 : asymmetric aza-Michael reaction, chiral cyclic *β*-amino carbonyl functionality, *tert*-butyl oxycarbamates, Phase-transfer catalysis

학 번 : 2018-26663

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Table 4. 온도 탐색 (Ⅱ)

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Ⅰ. 서 론

1. 비대칭 상전이 촉매 반응 (Phase-Transfer Catalysis)

1-1. 비대칭 상전이 촉매 반응 개요

Phase-transfer catalysis(PTC)는 서로 섞이지 않는 반응상 사이에서 일어 나는 반응으로 분자 또는 이온들의 이동을 매개하는 촉매를 이용하여 반응속도를 증가시킬 수 있는 합성법이다. 일반적으로, 유기용매와 물과의 반응으로 많이 알려져 있으며, 1971년 Starks가 상전이 촉매 반응을 최초로 실험하여 mechanism을 제안하였다. [1]

수층-유기층 시스템에서 촉매량의 quaternary onium salt (Q+X-)와 과량의 metal salt (M+Y-) 존재 하에 촉매가 수층에 있는 음이온인 Y- 를 유기층으로 옮겨 alkyl halide (R-X)의 친핵성 치환반응이 일어난다고 설명하였다 (**Figure 1**).

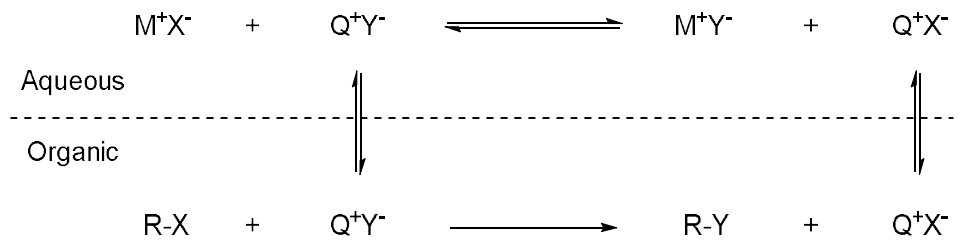


Figure 1. Stark의 extraction mechanism [1]

반면에, 1975년 M. Makosza는 phase boundary라고 불리는 계면 영역(interfacial region)을 이용하여 mechanism을 설명하였다. [2] 계면 영역은 두 개의 서로 섞이지 않는 상의 접촉 영역으로의 분자들의 움직임으로 인해 두 상에 있는 물질들의 농도 기울기가 생긴다. [3] Makosza는 계면 영역에 있는 reacting anion과 quaternary ammonium 사이에 이온쌍을 형성하며 이 반응에 참여하는 염기에 의해 proton의 추출도 일어난다고 제안하였다 (**Figure 2**).

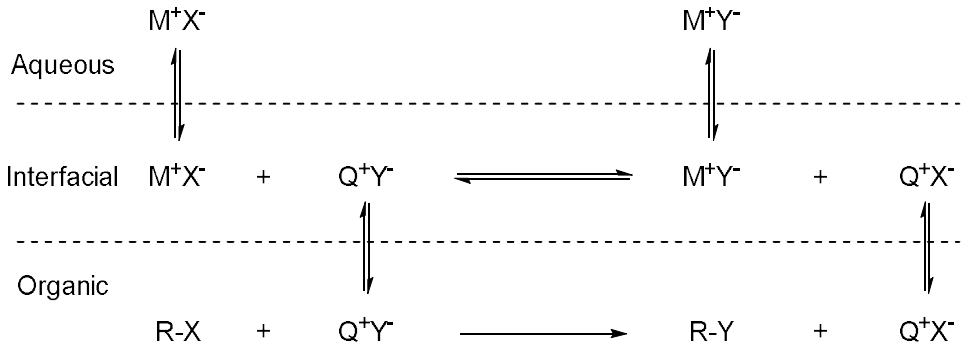
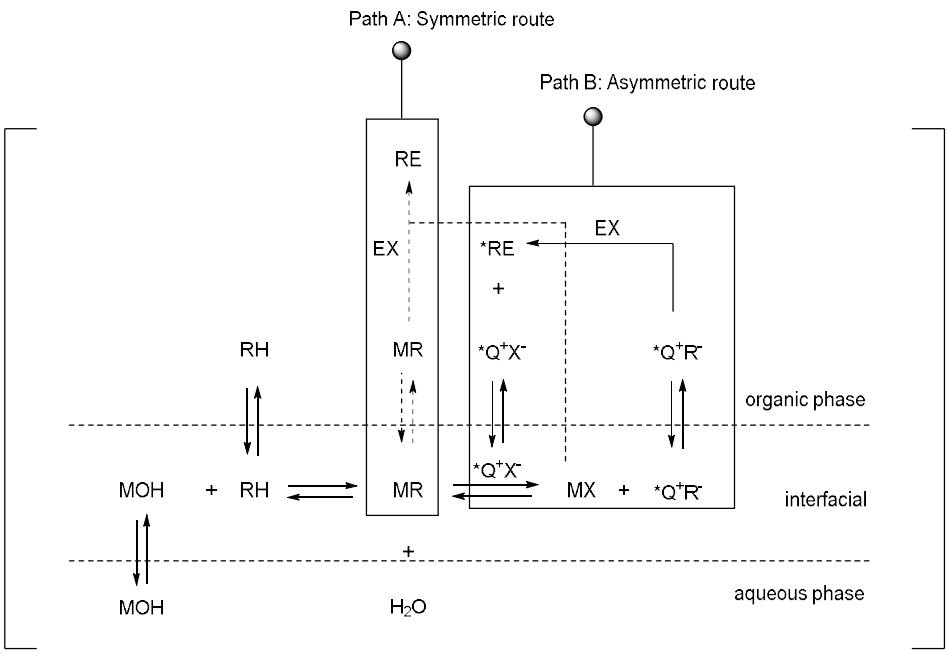


Figure 2. Makosza의 interfacial mechanism [2][3]

일반적으로 비대칭 PTC 반응은 chiral 촉매를 사용하며 새로운 stereogenic center가 만들어진다. 비대칭 PTC 반응의 mechanism은 **Figure 3** 과 같다. 비대칭 반응은 path B 과정에서 나타나며 먼저 interfacial에서 반응물(RH)가 염기(MOH)에 의해 수소가 제거되어 metal

enolate(MR) 형태로 존재하게 된다. 다음으로 chiral catalyst($*Q^+X^-$)의 음이온 교환이 일어나고 lipophilic한 chiral onium enolate($*Q^+R^-$)가 만들어진다. 이 물질은 organic 상으로 이동하여 친전자체와 반응하게 되는데 이 때 광학활성을 띄는 chiral prouduct(*RE)가 만들어진다 (**Figure 3**).



M = alkaline metal (Li, Na, K, Cs)
NuH = reactant (nucleophile)
EX = reactant (electrophile)
NuE = product (Nu-E bond formed)
Q+X- = phase-transfer catalyst
Q+Nu- = onium-carbanion complex

Figure 3. 일반적인 비대칭 PTC 반응의 mechanism

높은 enantioselectivity를 얻기 위해서는 이온 교환 과정이 충분한 속도로 진행되어야 하며 촉매의 quaternary onium salt($^*Q^+$)와 기질의 enolate(R^-) 간의 구조가 적합하여 이온쌍이 형성되어야 한다. 또한 빠른 이온교환을 위해 교반을 세게 해야 되며 적절한 반응조건을 얻는 것이 중요하다.

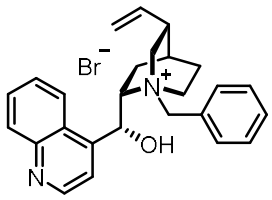
PTC 반응은 간단한 실험과정, mild한 반응조건, 비싸지 않고 친환경적인 시약과 용매를 사용한다는 장점이 있다. 오늘날 다양한 유기화학 분야에 중요한 합성방법 중 하나이며 산업현장에서 적용법이 널리 확산되고 있다. [4]

1-2. PTC 촉매 (Phase-transfer catalyst)

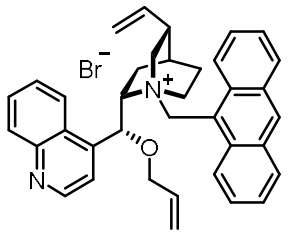
PTC 촉매(phase-transfer catalyst)는 **Figure 3**에서와 같이 반응염(MNu)과 onium-carbanion 복합체(*Q^+Nu^-)를 형성하여 organic 상과 aqueous 상 사이의 이동을 용이하게 함으로써 반응을 촉진시키는 역할을 한다. 이 때 onium-carbanium 복합체가 강하게 결합할수록 더 높은 입체 선택성을 얻을 수 있다. 따라서 광학적 수율이 높은 물질을 합성하기 위해 많은 chiral PTC 촉매들을 개발 및 응용하고 있다. 대표적인 촉매로 cinchona alkaloid 계열(**Figure 4)**과 non-cinchona 계열(**Figure 5**)이 있다.

1989년, M. J. O'Donnell이 cinchona alkaloid 계열의 촉매를 사용하여 α-alkyl-α-amino acid 류의 glycinate Schiff base를 substrate로 한 chiral PTC 반응을 최초로 성공하였다. [5]

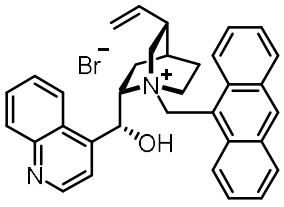
Cinchona 계열의 촉매는 cinchonine, cinchonidine, quinine, quinidine 등의 천연물에서 유래한 물질로서 값이 싸고 쉽게 구할 수 있다는 장점이 있다. [6] O'Donnell이 cinchona 계열의 촉매를 발명한 후에 Corey, Lygo 그리고 본 실험실에서도 cinchona 계열의 촉매를 변형하여 개발하고 있다 (**Figure 4**).



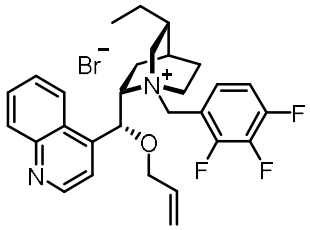
O'Donnell, M. J. et al.
J. Am. Chem. Soc. **1989,** 111, 2353.



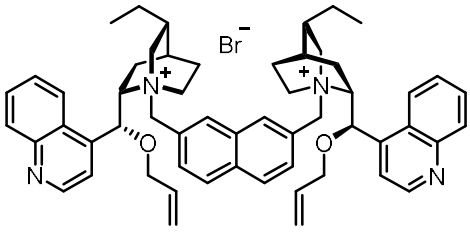
Corey, E. J. et al.
J. Am. Chem. Soc. **1997,** 119, 12414.



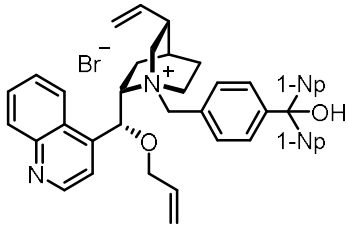
Lygo, B. et al.
Tetrahedron Lett. **1997,** 38,8595.



Park, H.-g. et al.
Org. Lett. **2002,** 4, 4245.



Park, H.-g. et al.
Angew. Chem. Int. Ed. **2002,** 41, 3036.



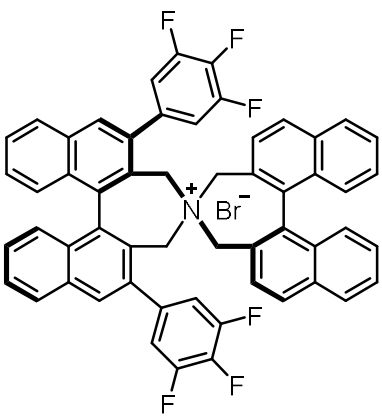
Ramachandran, U. et al.
Tetrahedron. **2005,** 61, 7022.

Figure 4. 대표적인 cinchona alkaloid 계열의 PTC 촉매

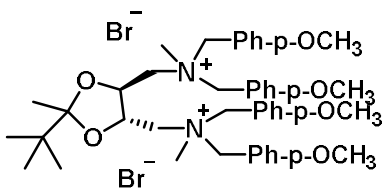
Maruoka 그룹[7]과 Shibasaki 그룹[8]은 non-cinchona 계열의 촉매를 개발하였다 (**Figure 5**). 특히 Maruoka그룹은 binaphthyl을 기본 골격으로 가지는 PTC 촉매를 개발하였다. [7] 이 PTC 촉매를 사용하여

asymmetric alkylations 을 진행하였을 때 높은 화학적 수율과 광학적 수율을 얻었다.

Cinchona alkaloid 계열의 PTC 촉매들은 β-수소의 Hoffmann elimination에 의해 분해될 수 있다. Non-cinchona 계열의 PTC 촉매들은 염기 조건 하에서 안정하며 이를 사용하면 높은 화학적 수율과 광학적 수율을 얻을 수 있다. 하지만 non-cinchona 계열의 PTC 촉매들은 대량으로 합성하기에 어려움이 존재하며, 값이 매우 비싸다는 단점이 있다.



Maruoka, K. et al.
J. Am. Chem. Soc. **1999**, *121*, 6519.



Shibuguchi, T. et al.
Tetrahedron Lett. **2002**, *43*, 9539.

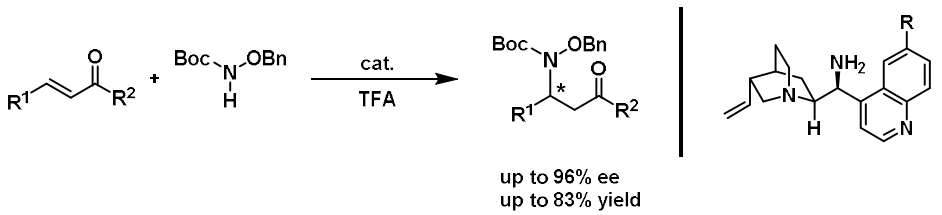
Figure 5. Non-cinchona 계열의 PTC 촉매

2. Chiral β–amino carbonyl 화합물

2-1. 중요성 및 입체 선택적인 합성 연구

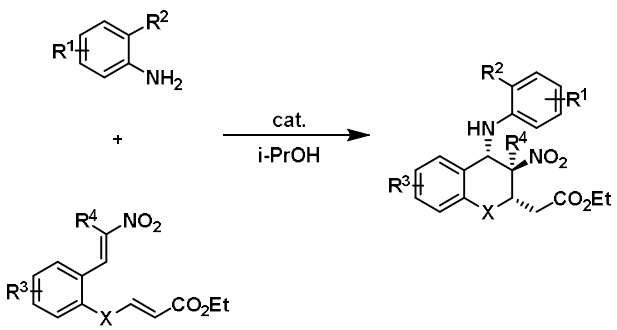
β–Amino carbonyl 골격은 β-lactams을 포함하여 amino alcohols, diamines, β-amino acids 등 다양한 질소 함유 중간체에서 중요한 구조를 차지하고 있다. [9] 따라서 β–amino carbonyl 골격은 유기합성 반응에 있어 중요한 building blocks 중 하나에 해당되며, 이 구조를 유기 촉매를 이용하여 chiral 하게 합성하기 위한 연구들이 진행되어왔다.

2008년, Li group은 유기 촉매를 사용하여 단순한 형태의 α,β-unsaturated ketone 을 기질로 한 입체 선택적인 aza-Michael reaction 을 최초로 보고한 바 있다 (**Scheme 1**). [10]



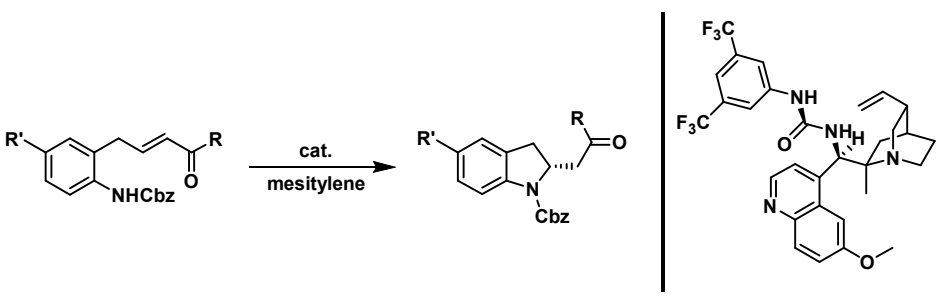
Scheme 1. Li group의 Asymmetric aza-Michael reactions [10]

2011년, Xiao group은 chiral bifunctional thiourea 촉매를 이용하여 anilines과 nitroolefin enoates 를 기질로 한 입체 선택적인 aza-Michael-Michael addition을 성공적으로 보고하였다 (**Scheme 2**). [11]



Scheme 2. Catalytic asymmetric aza-Michael-Michael addition cascade [11]

Miyaji group은 2013년에 bifunctional amino(thio)urea를 촉매로 intramolecular aza-Michael addition을 통해 2-substituted indolines의 입체 선택적인 합성법을 보고하였다 (**Scheme 3**). [12]



Scheme 3. Asymmetric Intramolecular aza-Michael addition [12]

2-2. Cyclic chiral β–amino carbonyl 화합물

Acyclic β-amino carbonyl 화합물을 입체 선택적으로 합성하는 연구는 위와 같이 많이 진행되어 있다. 하지만, aza-Michael reaction을 통해 cyclic β-amino carbonyl 골격을 입체 선택적으로 합성하는 연구는 아직까지 많이 진행되어 있지 않은 상태이다. Chiral cyclic β-amino carbonyl 골격은 생물학적으로 활성을 갖는 천연물과 chiral 약리활성물질의 building block으로 변형될 수 있으며, 이러한 골격을 포함하는 천연물에는 다음과 같은 것들이 있다 (**Figure 6**).

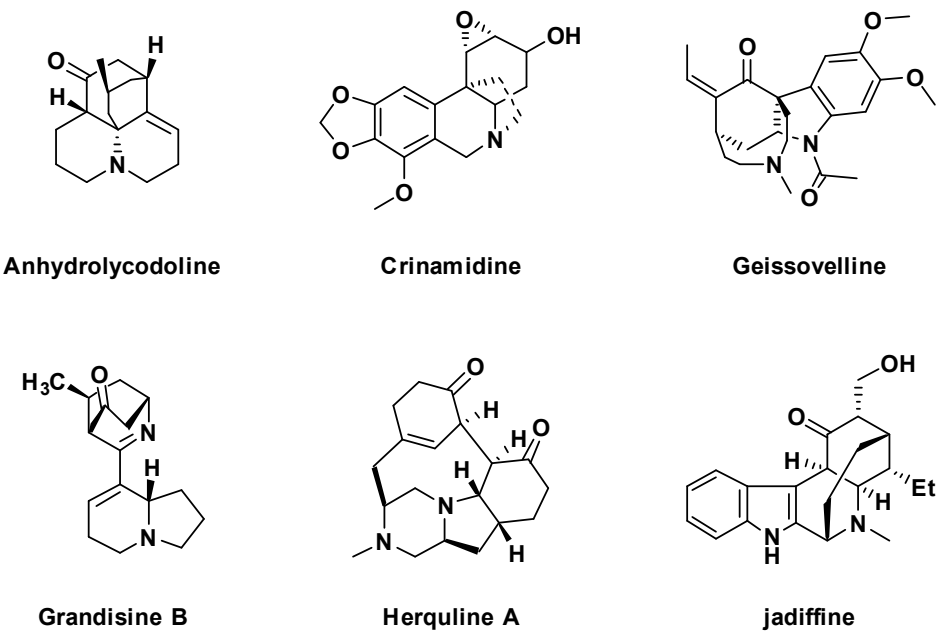
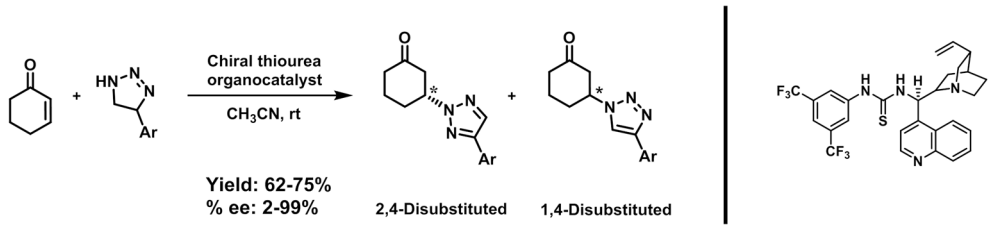


Figure 6. Chiral β-amino carbonyl structure 을 포함하는 천연물들

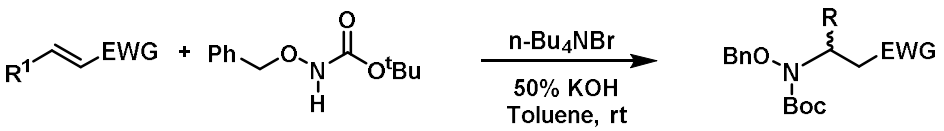
2018년, Peddinti group 은 chiral bifunctional thiourea 유기촉매들을 이용하여 4-aryl-NH-1,2,3,trizoles과 cyclic enones을 기질로 한 비대칭 aza-Michael addtion에 대한 결과를 보고하였다 (**Scheme 4**). [13]



Scheme 4. Peddinti group 의 asymmetric aza-Michael addition [13]

Peddinti group 의 연구에 의하면 β-amino carbonyl 골격이 포함된 물질을 최대 99% ee로 합성할 수 있다. 하지만 다음과 같은 한계점들이 여전히 존재하였다. 첫 번째로, aza-Michael reaction 결과 생성된 물질에 triazole 골격이 포함되어 있어 다른 물질로의 응용 가능성이 제한적이다. 두 번째로, aza-Michael reaction 결과 2,4-Disubstituted 생성물과 1,4-Disubstituted 생성물이 동시에 생성되어 최대 수율이 75% 라는 한계점이 존재하였다.

따라서, 본 연구에서는 cyclic enone 에 적용 가능하면서도 생성된 product 의 응용 가능성을 넓힐 수 있는 입체 선택적인 aza-Michael reaction 을 진행하기로 하였다. 2008 년에 본 연구실에서 *tert*-butyl benzyloxycarbmate 와 다양한 electron-deficient olefins 을 기질로 한 PTC aza-Michael reaction 에서 높은 수율 (>99%)을 보고한 바 있다 (**Scheme 5**). [14]



Scheme 5. Park group 의 PTC aza-Michael addition [14]

선행 연구[14] 결과를 토대로 PTC aza-Michael reaction 을 위한 Michael donor 로 *tert*-butyl benzyloxycarbmate 을 선정하였다. carbamates 내 Nitrogen anion 의 낮은 친핵성을 Oxygen moiety 를 도입함으로써 극복하였다.[14] Carbamate 내 Nitrogen 에 benzyloxy group 을 도입하여 α-effect 을 통한 친핵성을 부여하였고, 상업적으로 이용 가능하다는 점과 생성물의 selective deprotection 을 통해 다양한 작용기로 전환 가능하다는 점에서 *tert*-butyl benzyloxycarbmate 을 Michael Donor 로 최종 선정하였다.[14]

Michael acceptor 또한 선행 연구[14] 에 따라 2-cyclohexen-1-one 부터 다른 cyclic enone 까지 확장하였다. 이를 통해 *tert*-butyl oxycarbmates 와 cyclic enones 을 기질로 한 입체 선택적인 PTC aza-Michael reaction 결과를 확인하였다.

Ⅱ. 본　　론

1. *tert*-Butyl benzyloxycarbamate 의 PTC aza-Michael reaction

1-1. 상전이 촉매 탐색

상전이 촉매를 이용한 aza-Michael reaction을 최적화하기 위해, 선행 연구[14] 에서의 반응 조건을 채택하였다. 입체 선택성을 얻기 위해 탐색에 사용한 상전이 촉매들은 다음과 같다 (**Figure 7**).

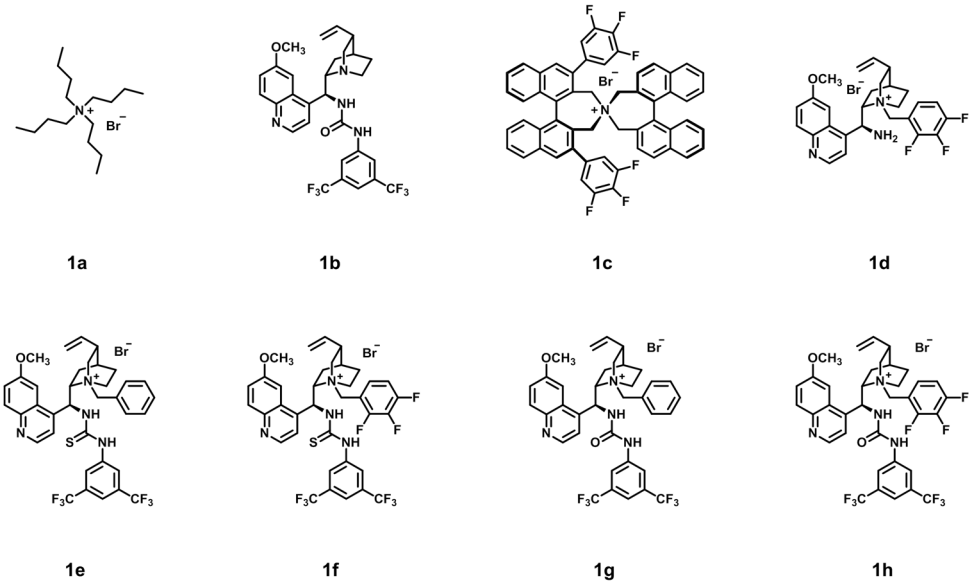
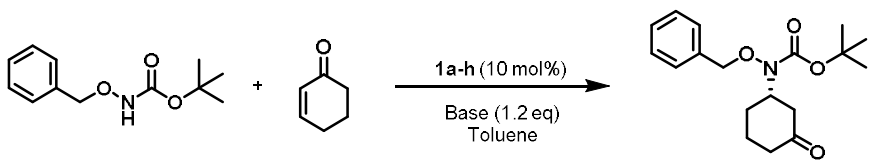


Figure 7. 반응 탐색에 사용한 상전이 촉매들

tert-Butyl benzyloxycarbamate와 2-cyclohexen-1-one을 기질로 사용하였으며, 대표적인 chiral 상전이 촉매를 통해 입체 선택적인 PTC aza-Michael reaction을 진행하였다 (**Table 1**).

Table 1. 상전이 촉매 탐색



2e 3b 4e

Entry	Temperature (°C)	Catalyst	Base	Time	Yield (%)	ee (%)
1	rt	**1a**	50% KOH	5 min	99	-
2	0	**1b**	-	N.R.	N.R.	N.R.
3	0	**1b**	TEA	N.R.	N.R.	N.R.
4	0	**1b**	DBU	N.R.	N.R.	N.R.
5	rt	**1c**	50% KOH	10 min	45	6
6	0	**1d**	50% KOH	2 h	79	9
7	0	**1e**	50% KOH	93 h	82	13
8	0	**1f**	50% KOH	93 h	67	19

9	0	**1g**	50% KOH	1.5 h	69	87
10	0	**1h**	50% KOH	1.5 h	99	87

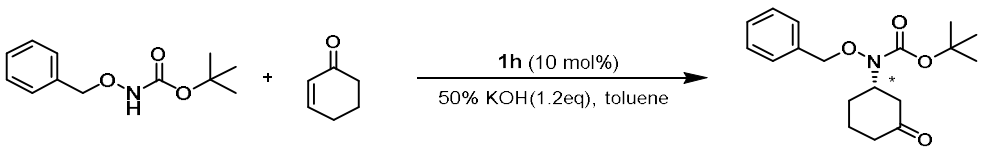
N.R. = No Reaction

라세미 화합물을 합성하기 위한 TBAB 을 포함하여 촉 8 가지 촉매를 반응에 사용하였다. 상전이 촉매가 아닌 일반적인 bifunctional 유기촉매 **1b** 의 경우, 촉매 내 자체적인 염기 역할을 고려하여 반응을 진행하였다. 하지만, 염기를 사용하지 않은 경우와 TEA, DBU 를 염기로 사용한 경우에서 모두 반응이 전혀 진행되지 않았다. 이를 통해 위 기질 및 조건에서의 입체선택적인 aza-Michael reaction 을 위해서는 상전이 촉매가 필요함을 간접적으로 확인하였다. 이외에 총 6 가지 비대칭성 상전이 촉매(**1c**-**1h**)를 사용한 결과, **1h** 촉매에서 높은 수율(99%)과 광학 활성(87% ee)을 얻었다. Maruoka 촉매(**1c**) 는 기질과 촉매의 입체 선택적인 배향을 만들어주지 못하여 낮은 수율과 광학적 수율을 보였다. Cinchona 촉매 내 Free amine 이 존재하는 경우(**1d**) 와 thio-urea 구조를 갖고 있는 촉매(**1e**-**1f**)에서 모두 낮은 광학적 수율을 보였고 이를 통해 기질과 입체 선택적인 결합이 제대로 이루어지지 않았음을 확인하였다. 반면, urea 구조를 포함하는 상전이 촉매(**1g**-**1h**) 에서는 높은 광학적 수율을 얻었고, 가장 높은 수율(99%) 과 광학 활성(87% ee) 을 보였던 **1h** 촉매를 추가적인 반응 탐색에 이용하기로 하였다.

1-2. 온도 탐색

앞서 확립한 **1h** 촉매를 이용하여 2-cyclohexen-1-one과 *tert*-butyl benzyloxycarbamate (2 eq), 50% KOH 수용액 (1.2 eq), toluene 조건에서 온도에 따른 탐색을 진행하였다 (**Table 2**).

Table 2. 온도 탐색 (I)



2e 3b 4e

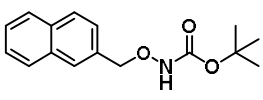
Entry	Temperature (°C)	Time	Yield (%)	ee (%)
1	rt	20 min	84	36
2	0	1.5 h	99	87
3	- 20	2.5 h	93	92
4	- 40	44 h	91	93

온도가 낮아짐에 따라 입체 선택성이 증가하였으나, 반응이 느려지고 화학적 수율이 감소하였다. 결과적으로 0 °C 에서 가장 높은 화학적 수율(99%) 을 얻은 반면, -40 °C 에서는 가장 높은 광학 수율(93% ee)을 얻을 수 있었다 (**Table 2**).

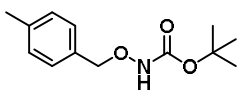
2. Michael donor

2-1. Michael donor 선정 및 합성

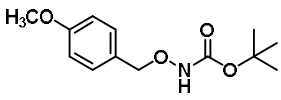
Michael Donor의 구조에 따른 입체 선택적인 PTC aza-Michael reaction의 화학적 수율과 광학 수율의 차이가 있는지를 확인하기 위해 다음과 같은 14 가지 *tert*-butyl oxycarbamates를 선정하였다 (**Figure 8**).



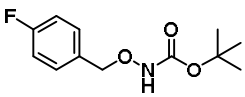
2a



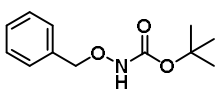
2b



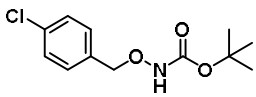
2c



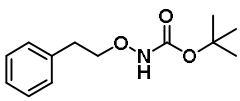
2d



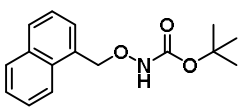
2e



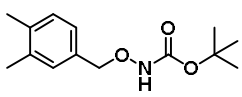
2f



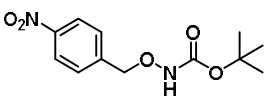
2g



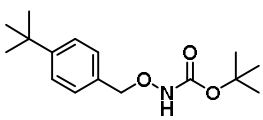
2h



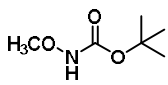
2i



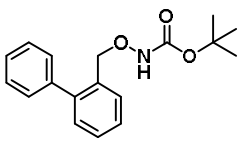
2j



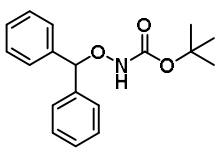
2k



2l



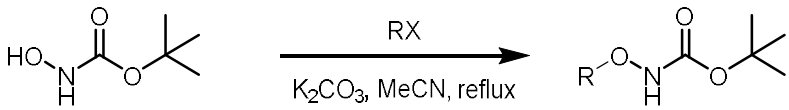
2m



2n

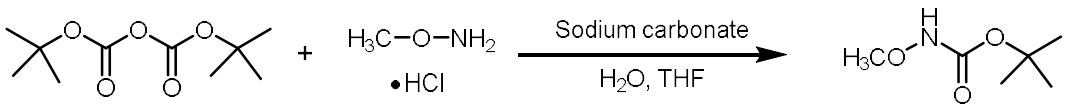
Figure 8. 14가지의 Michael donor

tert-Butyl oxycarbamates 의 oxygen에 다양한 치환기가 도입된 Michael donor는 다음과 같은 방법으로 합성하였다 (**Scheme 6**).



Scheme 6. Michael Donor 합성 방법 (Ⅰ)

tert-Butyl methoxycarbamate (**2l**) 는 Hydroxylamine hydrochloride 를 Disodium carbonate 염기 하에 Bon-anhydride 와 반응시켜 합성하였다 (**Scheme 7**).



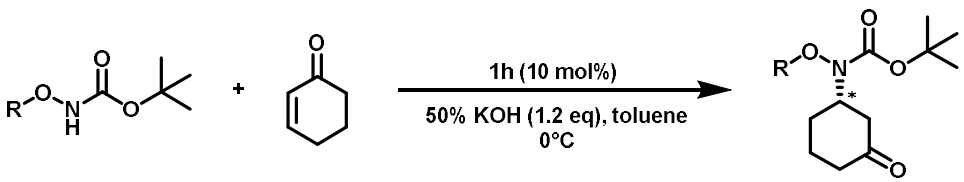
2l

Scheme 7. Michael Donor 합성 방법 (Ⅱ)

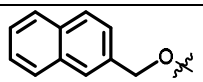
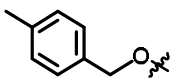
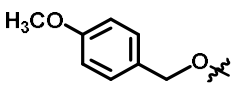
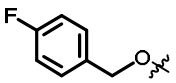
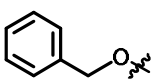
2-2. 다양한 Michael donor 탐색

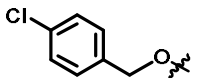
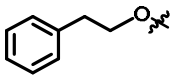
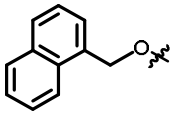
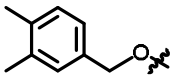
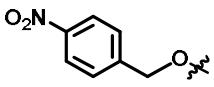
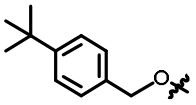
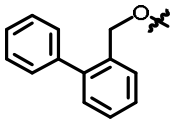
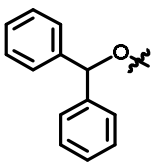
앞서 선정한 14가지 Michael donor (2eq.)와 2-cyclohexen-1-one (1eq.), 상전이 촉매 **1h** (10 mol %), 50% KOH 수용액 (1.2 eq.), toluene, 0°C 조건 하에서 PTC aza-Michael reaction을 진행하였다 (**Table 3**).

Table 3. 14가지 Michael donor 의 입체 선택적인 PTC aza-Michael reaction



2 3b 4

Entry	R-	Product	Time	Yield (%)	ee (%)
1	 2a	**4a**	4h	99	95
2	 2b	**4b**	2h	84	92
3	 2c	**4c**	4h	97	90
4	 2d	**4d**	3h	90	89
5	 2e	**4e**	1.5h	99	87

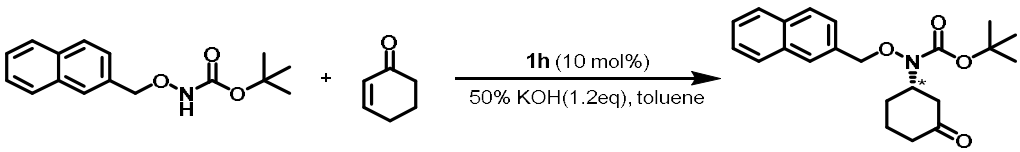
6	 2f	**4f**	2.5h	98	85
7	 2g	**4g**	4h	99	76
8	 2h	**4h**	7h	99	76
9	 2i	**4i**	2h	86	69
10	 2j	**4j**	4h	99	67
11	 2k	**4k**	4h	91	62
12	2l	**4l**	4h	97	58
13	 2m	**4m**	6h	94	19
14	 2n	**4n**	93h	64	4

tert-Butyl benzyloxycarbamate의 질소에 phenyl group이 붙어 있지 않은 경우(entry 12)를 보면 ee 값이 58%로 감소하였다. 뿐만 아니라 2-methyl naphthalene이 결합한 기질(entry 1)에서 가장 높은 광학 수율(95% ee)을 보였다는 점에서 기질과 촉매 간의 π-π 상호작용이 관여하고 있음을 간접적으로 생각해볼 수 있다. Steric hinderance가 크게 작용하는 기질(entry 9,11)에서는 phenyl group에 결합한 치환기의 방해 정도에 따라 ee값이 감소하였고 따라서 입체 장애 또한 중요한 요인임을 확인할 수 있었다. Phenyl group에 붙은 치환기의 electronic effect를 확인하기 위해 다양한 EDG(Electron Donating Group)와 EWG(Electron Withdrawing Group)을 결합한 기질을 선정하여 반응을 진행하였다(entry 2-6, 10). 일관된 경향성을 발견하지는 못했지만, 전반적으로 EDG가 결합한 기질에서 높은 광학 수율을 얻었고, 원자의 크기 등 다른 부차적인 요인이 같이 관여하고 있음을 생각할 수 있었다. 결론적으로 가장 중요한 요인은 입체 선택적으로 반응이 진행될 수 있도록 기질과 촉매간의 3차원적인 접근이 가능해야 한다는 점이다. Bi-phenyl이 있는 기질(entry 13-14)에서는 ee 값이 19%, 4%으로 현저하게 감소했다는 점에서 기질과 촉매의 3차원적 결합 모델의 중요성을 다시 한 번 확인할 수 있다.

2-3. *tert*-Butyl (naphthalene-2-ylmethoxy)carbamate

가장 높은 화학적 및 광학적 수율을 보인 *tert*-butyl (naphthalene-2-ylmethoxy)carbamate 을 기질로 온도에 따른 결과를 확인하였다. 반응 조건으로는 앞에서와 동일하게 **1h** 촉매, 50% KOH 수용액 (1.2 eq), toluene을 이용하였다 (**Table 4**).

Table 4. 온도 탐색 (Ⅱ)



2a 3b 4a

Entry	Temperature (°C)	Time	Yield (%)	ee (%)
1	0	2.5 h	99	95
2	- 20	4 h	97	97
3	- 40	44 h	99	98

온도가 낮아짐에 따라 입체 선택성이 증가하였고, 화학적 수율 또한 증가하였다. 결과적으로 -40 °C 에서 높은 화학적 수율(99%)과 광학적 수율(98% ee)을 얻을 수 있었다. 이를 토대로 추가적인 Michael acceptor 탐색을 위한 조건을 *tert*-butyl (naphthalene-2-ylmethoxy)carbamate 와 50% KOH 수용액(1.2 eq), toluene, -40 °C 으로 선정하였다.

3. Michael acceptor

3-1. Michael acceptor 선정

Michael acceptor 의 구조에 따른 입체 선택적인 PTC aza-Michael reaction의 화학적 수율과 광학 수율의 차이가 있는지를 확인하기 위해 다음과 같은 9가지 cyclic enone 을 선정하였다 (**Figure 9**).

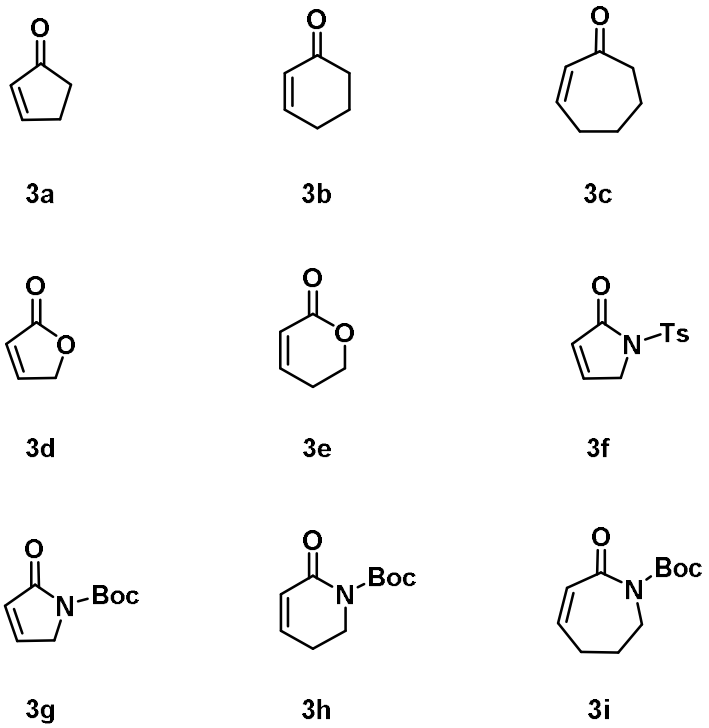
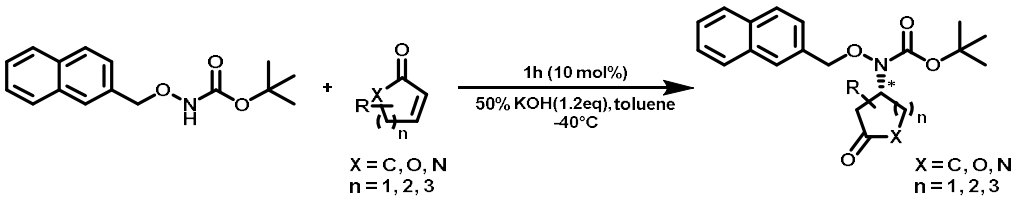


Figure 9. 9가지의 Michael acceptor [15]

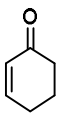
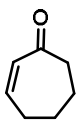
3-2. 다양한 Michael acceptor 탐색

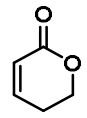
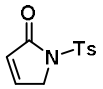
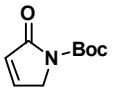
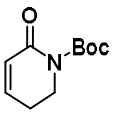
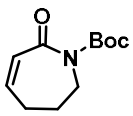
9가지 Michael acceptor (1eq.) 와 *tert*-butyl (naphthalene-2-ylmethoxy)carbamate (2eq.), 촉매 **1h** (10 mol %), 50% KOH 수용액 (1.2 eq.), toluene, -40°C 조건에서 반응을 진행하였다 (**Table 5**).

Table 5. 9가지 Michael acceptor 의 입체 선택적인 PTC aza-Michael reaction



2a 3 5

Entry	R-	Product	Time	Yield (%)	ee (%)
1	3a	**5a**	20 h	83	93
2	 3b	**5b**	44 h	99	98
3	 3c	**5c**	5 d	85	93
4	3d	**5d**	21 h	32	83

5[a]	 3e	**5e**	19 h	42	97
6	 3f	**5f**	20 h	35	30
7	 3g	**5g**	17 h	15	65
8	 3h	**5h**	85 h	68	97
9	 3i	**5i**	85 h	76	95

a. aza-Michael reaction 이후 가수분해 된 일부 생성물을 EDC coupling 까지 진행함

기질 **3a-3c** (entry 1-3) 을 사용하였을 때 모두 90% 이상의 광학적 수율을 얻었고, 그 중에서 Michael donor 탐색에 계속 사용했던 **3b** 에서 가장 높은 화학적 수율(99%)과 광학 수율(98% ee)을 얻었다. Lacton을 포함하고 있는 기질 **3d-3e** (entry 4-5) 은 KOH 조건 하에 가수분해에 취약하여 낮은 화학적 수율을 보였으나, **3e** 기질에서 높은 광학수율(97% ee)을 얻을 수 있었다. Lactam을 포함하고 있는 5각 고리 구조의 기질 **3d-3e** (entry 4-5). 또한, KOH에 대한 가수분해 취약성으로 인해 낮은 화학적 수율을 나타냈고, 기질과 촉매 간의 3차원적인 결합이 제대로 이루어지지 않아서 광학 수율도 감소하였다. 마지막으로, lactam을 포함하고

있는 6각 및 7각 고리 구조의 기질 **3h, 3i** (entry 8-9) 에서는 5각 고리의 기질 **3g** 에서보다 가수분해에 대한 저항성으로 인해 향상된 화학적 수율을 얻었다. 뿐만 아니라 높은 광학 수율까지 확인할 수 있었다.

4. 생성물의 절대 배열 및 Plausible Mechanism

생성물 **5h** 을 결정화시켜 X-ray crystallography 분석을 통해 절대 배열을 확인하였다. **5h** 는 X-ray 구조상 (S)-form 의 절대 배열을 갖고 있다 (**Figure 10**).

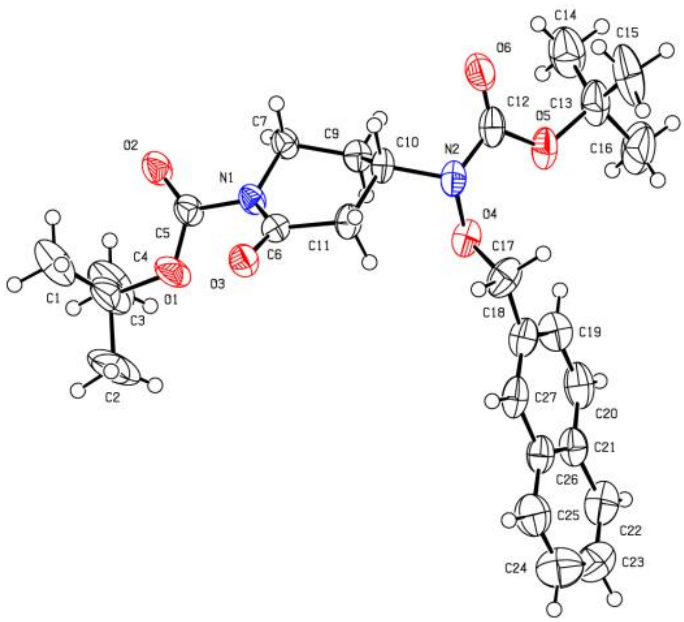


Figure 10. 5h 의 X-ray crystal 구조

이처럼 (S)-form 의 입체 선택적인 반응물이 생성되었다는 점에서 기질과 촉매 간의 3 가지 상호작용을 제안해보았다. 첫 번째로, 상전이 촉매의 quinuclidine 구조 내 질소 양전하와 염기 하에 생성된 Michael

donor 내 음전하 사이에 이온 쌍 상호작용이 형성될 수 있다. 두 번째로, Michael donor 내 aromatic 작용기와 상전이 촉매 내 quinoline 구조 간 π-π 상호작용이 존재할 수 있다. 이는 **Table 3** 에서 **4e** 기질과 비교하였을 때 aromatic 치환기가 사라진 **4l** 기질에서 ee 값이 58%로 감소하였다는 점에서 생각해볼 수 있다. 마지막으로, Michael acceptor 의 carbonyl 골격 내 oxygen 과 상전이 촉매의 urea 사이에 Hydrogen bonding 상호 작용이 있다. 이는 **Table 1** 에서 urea 골격이 없는 **1d** 촉매에서의 낮은 ee 값으로부터 알 수 있다. 결과적으로 위와 같은 3 가지 상호작용이 충분히 일어날 수 있도록 기질과 촉매 간의 3 차원적 배향이 유지된다면 Si face attack 을 통해 높은 입체 선택성을 보이는 (S)-form 의 생성물이 생겨날 수 있다 (**Figure 11**).

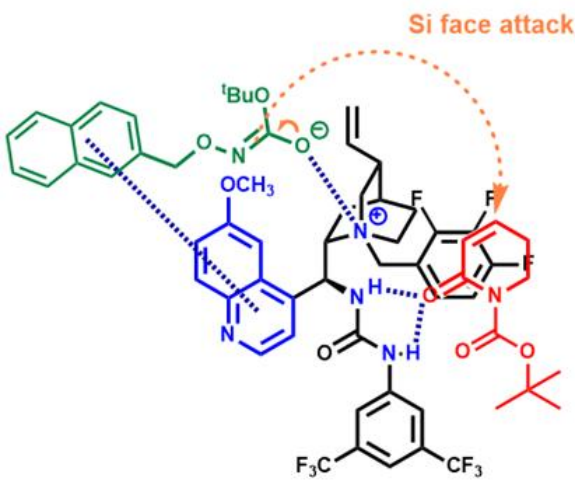
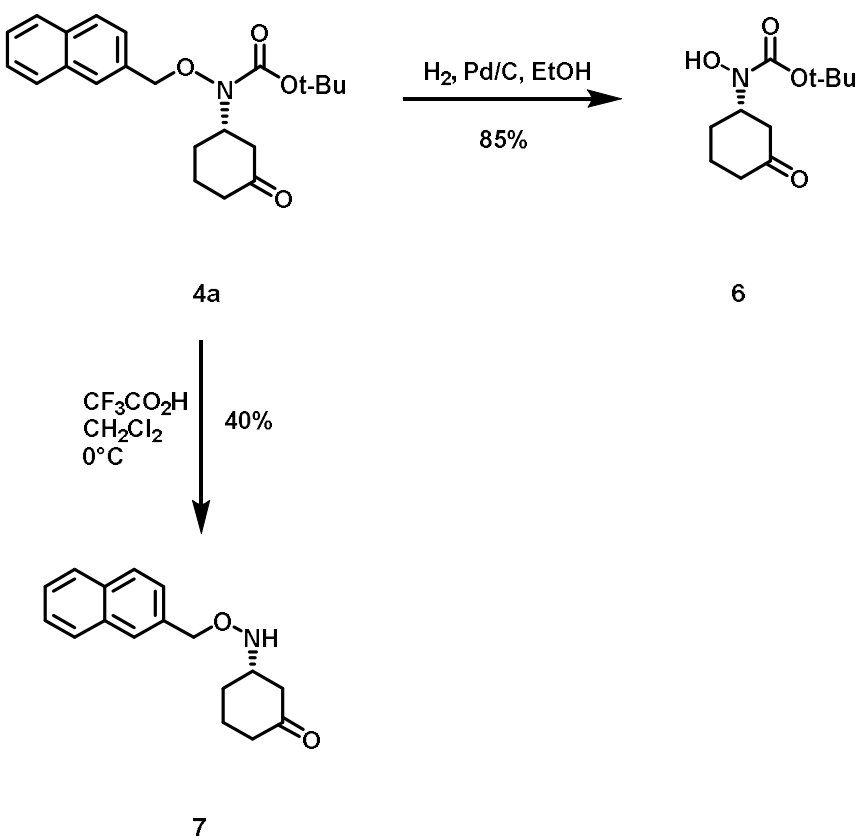


Figure 11. Plausible mechanism

5. Aza-Michael products 의 Selective Deprotection

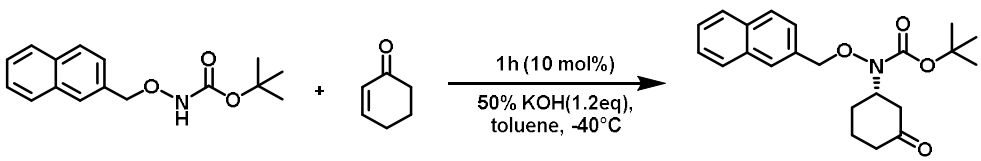
Aza-Michael reaction 을 통해 입체 선택적으로 합성한 물질을 각각 H_2, Pd/C 조건과 TFA 산 조건에서 선택적으로 deprotection 시켰다 (**Scheme 8**). EtOH 에 **4a** 와 Pd/C 을 넣고 Hydrogen 하에 반응시켜 carbamate 의 Oxygen 에 붙은 Alkyl group 을 선택적으로 떼어냈다. 또한, TFA 와 dichloromethane, 0°C 조건에서 Boc group 을 선택적으로 분리시켰다.



Scheme 8. 생성물 **4a** 의 Selective Deprotection

Ⅲ. 결　　론

본 연구실에서는 *tert*-butyl benzyloxycarbamate 와 다양한 electron-deficient olefins 을 기질로 한 PTC aza-Michael reaction 을 성공적으로 보고한 바 있다. 이를 토대로 본 연구에서는 cyclic β-amino carbonyl 골격을 입체 선택적으로 합성하는 방법을 설명하였다. 비대칭 cinchona 알칼로이드 계열의 촉매 **1h** 하에 *tert*-butyl (naphthalene-2-ylmethoxy)carbamate 와 2-cyclohexen-1-one 을 기질로 -40℃ 에서 높은 화학적 수율 (99%)과 광학 수율 (98% ee) 을 얻었다.



이렇게 합성한 물질은 각각 TFA 산 조건과 H_2, Pd/C 조건 하에 선택적으로 보호기를 떼어낼 수 있다. 입체 선택적인 생성물은 cyclic β-amino carbonyl 골격을 chiral 하게 포함하고 있는 천연물을 합성하는 데 유용한 도구가 될 것이다.

Ⅳ. 실 험

1. 일반적인 방법

1-1. Spectra 데이터

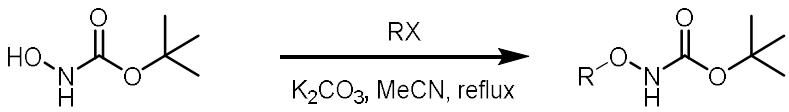
Infrared (IR) spectra 는 JASCO FT/IR-300E and Perkin-Elmer 1710 FT spectrometer 를 사용하였다. Nuclear magnetic resonance (^{1}H-NMR & ^{13}C-NMR) spectra 는 JEOL JNM-ECZ 400S/L [400 MHz (^{1}H), 100 MHz (^{13}C)] spectrometer 와 5-mm triple resonance inverse cryoprobe 가 있는 Bruker Avance Ⅲ HD [800 MHz (^{1}H), 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. 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.

1-2. 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 사용하였다. 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 OD-H, Chiralcel AS-H columns 그리고 Chiralcel OJ-H columns 을 사용하여 HPLC 기계로 측정하였다.

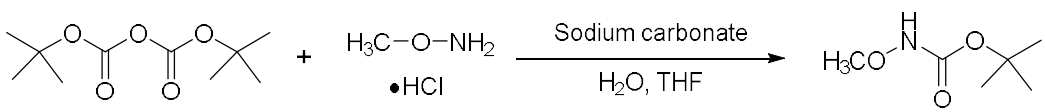
2. Michael donor

2-1. Michael donor 의 일반적인 합성법



실험과정 (A)

RBF 에 potassium carbonate (1.5 당량), *tert*-butyl hydroxycarbamate (1.25 당량), alkyl halide (1 당량)을 넣는다. 다음으로 acetonitrile 을 넣고 80 °C 에서 교반한다. 반응 종료 후, 반응 용매를 감압 농축시켜 제거한다. 물과 EtOAc 로 3 번 추출하고 유기층을 $MgSO_4$ 로 건조 및 필터한다. 이후 Medium pressure liquid chromatography 를 통해 정제하여 생성물을 얻는다.



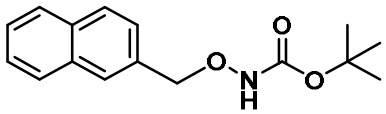
2l

실험과정 (B)

Boc anhydride (1200 mg, 5.498 mmol) 를 교반 중인 THF (4.5mL) 에 넣는다. DDW (10 mL) 에 녹인 Sodium carbonate (1748.3 mg, 16.495 mmol) 을 넣고 5 분간 교반한다. DDW (10 mL)에 녹인 Methoxyamine hydrochloride (1377.6 mg, 16.495 mmol)을 천천히 적가하고 교반시킨다.

반응 종료 후, 감압 농축시킨 물질을 물과 EtOAc 로 1 번 추출한다. 이후 유기층을 $MgSO_4$로 건조 및 필터한다. 생성 물질을 감압농축 시켜 colorless oil 형태로 생성물을 얻는다.

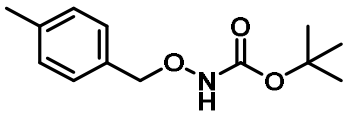
***tert*-Butyl (naphthalen-2-ylmethoxy)carbamate (2a)**



2-(Bromomethyl)naphthalene 을 출발물질로 하여 실험과정 (A) 로 합성하여 white caramel 형태의 물질 **2a**를 얻는다 (87% yield).

^{1}H-NMR (400 MHz, DMSO-D6) δ 10.08 (s, 1H), 7.85-7.90 (m, 4H), 7.46-7.50 (m, 3H), 4.86 (s, 2H), 1.36 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.93, 133.49, 133.39, 133.34, 128.52, 128.21, 127.90, 126.79, 126.49, 126.43, 81.99, 78.73, 28.40 ppm; IR (KBr) 3290, 3056, 2979, 2932, 2874, 1719, 1603, 1509, 1477, 1456, 1392, 1368, 1272, 1250, 1167, 1107, 1042, 1017, 951, 895, 855, 819, 773, 753 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{16}H_{20}NO_3]^+$($[M+H]^+$) 274.1443; found 274.1432.

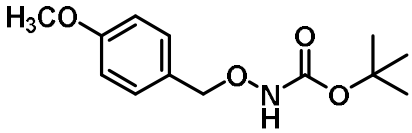
***tert*-Butyl ((4-methylbenzyl)oxy)carbamate (2b)**



α-Chloro-*p*-xylene 을 출발물질로 하여 실험과정 (A) 로 합성하여 colorless liquid 형태의 물질 **2b**를 얻는다 (81% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 7.8 Hz, 2H), 7.16 (d, J = 7.8 Hz, 2H), 7.04 (s, 1H), 4.80 (s, 2H), 2.34 (s, 3H), 1.46 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.90, 138.53, 132.86, 129.41, 129.36, 81.86, 78.44, 28.39, 21.43 ppm; IR (KBr) 3297, 2979, 2930, 2873, 1721, 1618, 1517, 1478, 1393, 1269, 1167, 1042, 1014, 937, 848, 807, 754 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{13}H_{20}NO_3]^+([M+H]^+)$ 238.1443; found 238.1453.

***tert*-Butyl ((4-methoxybenzyl)oxy)carbamate (2c)**

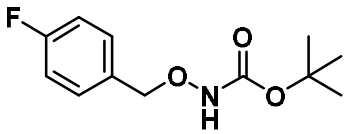


4-Methoxybenzyl chloride 을 출발물질로 하여 실험과정 (A) 로 합성하여 colorless liquid 형태의 물질 **2c** 를 얻는다 (50% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 (dt, J = 9.1, 2.4 Hz, 2H), 7.05 (s, 1H), 6.88 (dt, J = 9.1, 2.4 Hz, 2H), 4.77 (s, 2H), 3.80 (s, 3H), 1.47 (s, 9H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.02, 156.92, 131.05, 127.98, 114.04, 81.86, 78.24, 55.48, 28.41 ppm; IR (KBr) 3301, 2979, 2935, 2838, 1720, 1613, 1586, 1519, 1459, 1393, 1368, 1303, 1250, 1174, 1108, 1035, 927, 849, 824, 773 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{13}H_{20}NO_4]^+([M+H]^+)$ 254.1392; found 254.1401.

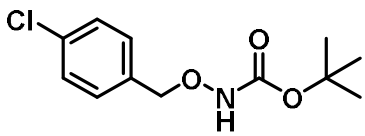
***tert*-Butyl ((4-fluorobenzyl)oxy)carbamate (2d)**



4-Fluorobenzyl bromide 를 출발물질로 하여 실험과정 (A) 로 합성하여 colorless liquid 형태의 물질 **2d** 를 얻는다 (59% yield).

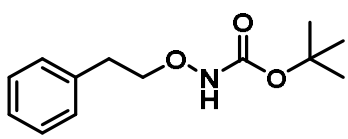
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (td, J = 6.1, 2.4 Hz, 2H), 7.07 (s, 1H), 7.01-7.06 (m, 2H), 4.80 (s, 2H), 1.46 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.30, 161.85, 156.95, 131.77, 131.75, 131.31, 131.23, 115.70, 115.48, 82.07, 77.90, 28.39 ppm; IR (KBr) 3296, 2980, 2934, 2350, 1720, 1604, 1511, 1477, 1457, 1394, 1369, 1251, 1226, 1159, 1108, 1015, 854, 828, 671 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{12}H_{17}FNO_3]^+([M+H]^+)$ 242.1192; found 242.1188.

***tert*-Butyl ((4-chlorobenzyl)oxy)carbamate (2f)**



1-(bromomethyl)-4-chlorobenzene 을 출발물질로 하여 실험과정 (A) 로 합성하여 white solid 형태의 물질 **2f** 를 얻는다 (mp 66.1°C, 71% yield). ^{1}H-NMR (400 MHz, DMSO-D6) δ 10.02 (s, 1H), 7.37 (ddd, J = 16.0, 6.4, 2.3 Hz, 4H), 4.67 (s, 2H), 1.36 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.93, 134.59, 134.45, 130.67, 128.87, 82.14, 77.82, 28.39 ppm; IR (KBr) 3290, 2979, 2933, 2879, 1890, 1719, 1600, 1579, 1492, 1456, 1408, 1393, 1271, 1251, 1166, 1091, 1043, 1016, 936, 844, 812, 802 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{12}H_{17}ClNO_3]^+([M+H]^+)$ 258.0897; found 258.0898.

***tert*-Butyl phenethoxycarbamate (2g)**

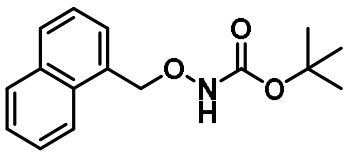


(2-Bromoethyl)benzene 을 출발물질로 하여 실험과정 (A) 로 합성하여 pale liquid 형태의 물질 **2g** 를 얻는다 (57% yield).

^{1}H-NMR (400 MHz $CDCl_3$) δ 7.27-7.30 (m, 2H), 7.21 (d, J = 6.9 Hz, 3H),

3.72 (t, J = 7.1 Hz, 2H), 2.93 (t, J = 7.4 Hz, 2H), 1.35 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.95, 139.12, 129.18, 128.67, 126.51, 81.89, 51.75, 33.48, 28.36 ppm; IR (KBr) 3238, 2978, 2932, 2310, 1692, 1604, 1477, 1455, 1395, 1367, 1252, 1219, 1165, 1106, 1073, 1031, 855, 772, 700 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{13}H_{20}NO_3]^+([M+H]^+)$ 238.1443; found 238.1442.

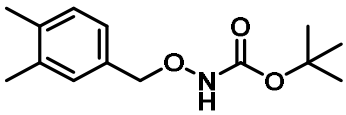
tert-Butyl (naphthalen-1-ylmethoxy)carbamate (2h)



1-(Chloromethyl)naphthalene 을 출발물질로 하여 실험과정 (A) 로 합성하여 pale yellow oil 형태의 물질 2h 를 얻는다 (81% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.3 Hz, 1H), 7.86 (dd, J = 8.3, 2.8 Hz, 2H), 7.41-7.59 (m, 4H), 7.12 (s, 1H), 5.32 (s, 2H), 1.47 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 157.02, 133.94, 132.38, 131.50, 129.84, 128.88, 128.69, 126.81, 126.18, 125.33, 124.53, 82.01, 77.55, 28.40 ppm; IR (KBr) 3298, 3048, 2979, 2932, 1718, 1599, 1512, 1477, 1456, 1393, 1368, 1249, 1220, 1165, 1108, 1012, 854, 802 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{16}H_{20}NO_3]^+([M+H]^+)$ 274.1443; found 274.1437.

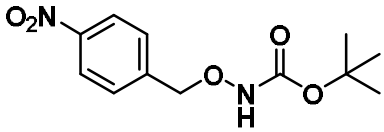
***tert*-Butyl ((3,4-dimethylbenzyl)oxy)carbamate (2i)**



3,4-Dimethylbenzyl chloride 을 출발물질로 하여 실험과정 (A) 로 합성하여 colorless oil 형태의 물질 **2i** 를 얻는다 (38% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 17.8 Hz, 3H), 7.05 (s, 1H), 4.78 (s, 2H), 2.25 (s, 6H), 1.47 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.90, 137.20, 136.94, 133.27, 130.70, 129.93, 126.88, 81.84, 78.51, 28.42, 19.90, 19.76 ppm; IR (KBr) 3299, 2978, 2310, 1717, 1456, 1393, 1368, 1249, 1220, 1168, 1107, 1017, 820, 772 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{14}H_{22}NO_3]^+$($[M+H]^+$) 252.1600; found 252.1605.

***tert*-Butyl ((4-nitrobenzyl)oxy)carbamate (2j)**

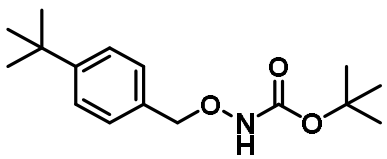


4-Nitrobenzyl bromide 을 출발물질로 하여 실험과정 (A) 로 합성하여 white solid 형태의 물질 **2j** 를 얻는다 (mp 64.4°C, 84% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.16-8.19 (m, 2H), 7.54 (d, J = 8.7 Hz, 2H),

7.35 (s, 1H), 4.93 (s, 2H), 1.44 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.98, 148.01, 143.39, 129.46, 123.83, 82.46, 77.43, 28.34 ppm; IR (KBr) 3294, 3114, 3082, 2980, 2934, 1722, 1607, 1524, 1477, 1457, 1393, 1347, 1272, 1220, 1164, 1109, 1016, 849, 822, 772, 741, 699 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{12}H_{17}N_2O_5]^+([M+H]^+)$ 269.1137; found 269.1138.

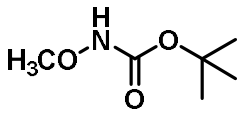
tert-Butyl ((4-(tert-butyl)benzyl)oxy)carbamate (2k)



4-*tert*-butyl benzyl bromide 을 출발물질로 하여 실험과정 (A) 로 합성하여 colorless oil 형태의 물질 **2k** 를 얻는다 (65% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37-7.39 (m, 2H), 7.32 (dd, J = 6.4, 2.3 Hz, 2H), 7.08 (s, 1H), 4.81 (s, 2H), 1.46 (s, 9H), 1.31 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.92, 151.77, 132.89, 129.23, 125.65, 81.89, 78.42, 34.83, 31.52, 28.42 ppm; IR (KBr) 3297, 2967, 2310, 1721, 1515, 1476, 1393, 1368, 1250, 1168, 1108, 1016, 835, 819, 772, 688 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{16}H_{26}NO_3]^+([M+H]^+)$ 280.1913; found 280.1903.

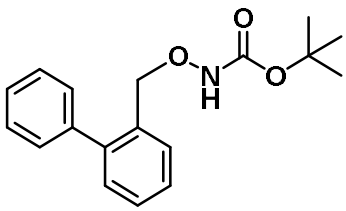
***tert*-Butyl methoxycarbamate (2l)**



실험과정 (B) 의 합성법을 이용하여 colorless oil 형태의 물질 **2l** 을 얻는다 (56% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 3.70 (t, J = 1.5 Hz, 3H), 1.47 (d, J = 2.3 Hz, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.03, 81.91, 64.62, 28.38 ppm; IR (KBr) 3296, 2975, 2349, 2310, 1715, 1508, 1368, 1250, 1169, 1113, 808 cm^{-1}; HRMS (FAB+) was unable to provide any molecular and fragmentation ions.

***tert*-Butyl ([1,1'-biphenyl]-2-ylmethoxy)carbamate (2m)**

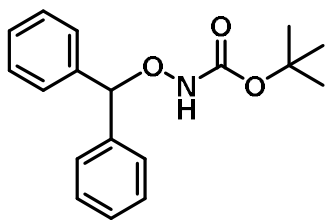


[1,1'-biphenyl]-2-ylmethyl methanesulfonate 을 출발물질로 실험과정 (A) 로 합성하여 yellow oil 형태의 물질 **2m**을 얻는다 (41% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.58-7.60 (m, 1H), 7.30-7.43 (m, 8H), 7.08 (s, 1H), 4.79 (s, 2H), 1.43 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.85,

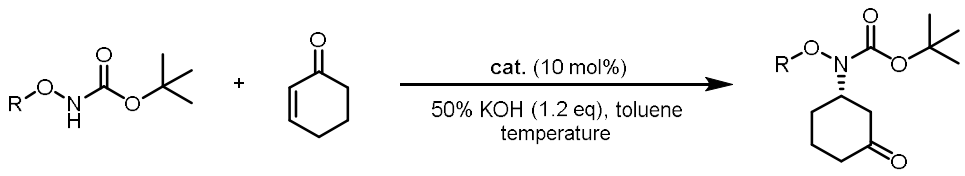
143.04, 140.67, 133.06, 130.97, 130.34, 129.60, 128.68, 128.33, 127.63, 127.42, 81.87, 76.31, 28.38 ppm; IR (KBr) 3297, 3064, 2979, 2350, 1716, 1599, 1480, 1454, 1393, 1368, 1249, 1220, 1167, 1102, 1010, 847, 772, 703 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{18}H_{22}NO_3]^+([M+H]^+)$ 300.1600; found 300.1593.

***tert*-Butyl (benzhydryloxy)carbamate (2n)**



α-Bromodiphenylmethane 을 출발물질로 하여 실험과정 (A) 로 합성하여 white solid 형태의 물질 **2n** 을 얻는다 (mp 128.2°C, 39% yield). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.25-7.36 (m, 10H), 5.81 (s, 1H), 1.42 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.65, 139.57, 128.68, 128.37, 128.08, 89.08, 81.99, 28.44 ppm; IR (KBr) 3566, 3306, 3032, 2979, 2349, 2310, 1746, 1495, 1455, 1393, 1368, 1247, 1220, 1147, 1103, 1011, 850, 772, 699, 654 cm^{-1} HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{18}H_{22}NO_3]^+([M+H]^+)$ 300.1600; found 300.1602.

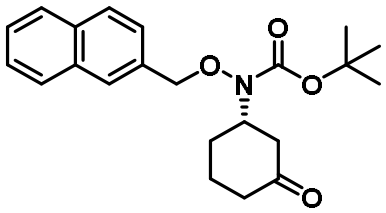
2-2. 입체 선택적인 PTC aza-Michael reaction



일반적인 방법

RBF 에 *tert*-butyl benzyloxycarbamates (2.0 당량) 와 상전이 촉매 (10 mol%) 을 넣고 toluene 용매 하에 교반한다. 2-cyclohexen-1-one (1 당량)을 넣고 정해진 온도에서 15 분 동안 교반한다. 정해진 온도에서 충분히 교반시킨 후, 유기층과 수층의 비율이 4:1 이 되도록 50% KOH 수용액 (1.2 당량)과 DDW 을 넣는다. TLC 상에서 기질이 모두 사라지면 반응을 종결시킨다. 물과 EtOAc 로 3 번 추출하고 유기층을 $MgSO_4$ 로 건조 및 필터한다. 이후 Medium pressure liquid chromatography 를 통해 정제하여 생성물을 얻는다.

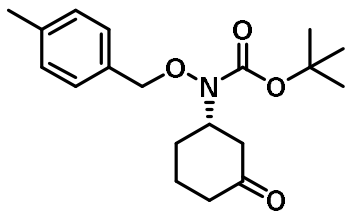
***tert*-Butyl (S)-(naphthalen-2-ylmethoxy)(3-oxocyclohexyl)carbamate (4a)**



물질 **2a** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 pale caramel 형태의 물질 **4a** 를 얻는다 (99% yield).

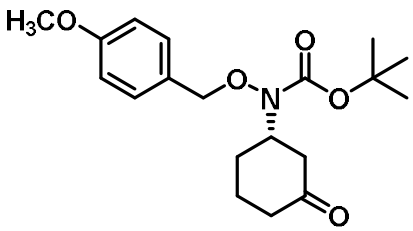
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82-7.85 (m, 4H), 7.46-7.55 (m, 3H), 4.97-5.02 (m, 2H), 4.19-4.26 (m, 1H), 2.72 (td, J = 12.6, 1.1 Hz, 1H), 2.54 (dd, J = 14.0, 4.4 Hz, 1H), 2.34 (d, J = 14.7 Hz, 1H), 2.22 (td, J = 13.4, 5.8 Hz, 1H), 1.90-2.09 (m, 3H), 1.57-1.62 (m, 1H), 1.53 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.38, 156.73, 133.52, 133.34, 132.82, 128.76, 128.43, 128.23, 127.89, 127.14, 126.53, 126.41, 82.35, 79.05, 58.54, 45.00, 40.67, 28.49, 28.23, 22.20 ppm; IR (KBr) 3056, 2973, 2871, 1712, 1508, 1473, 1456, 1423, 1368, 1339, 1319, 1301, 1255, 1220, 1165, 1113, 1092, 1067, 1034, 889, 854, 819, 772 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{22}H_{28}NO_4]^+$($[M+H]^+$) 370.2018; found 370.2017. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak OD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 250 nm) retention time: minor isomer 14.41 min, major isomer 11.19 min, 98% ee, $[\alpha]^{20}_D$ = -18.54 (*c* 1.0, $CHCl_3$).

***tert*-Butyl (S)-((4-methylbenzyl)oxy)(3-oxocyclohexyl)carbamate (4b)**



물질 **2b** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 pale yellow liquid 형태의 물질 **4b** 를 얻는다 (84% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, J = 48.5, 7.8 Hz, 4H), 4.76-4.81 (m, 2H), 4.15-4.23 (m, 1H), 2.67 (dd, J = 13.3, 11.9 Hz, 1H), 2.47-2.52 (m, 1H), 2.31 (s, 1H), 2.16-2.24 (m, 1H), 1.87-2.08 (m, 3H), 1.55-1.62 (m, 1H), 1.52 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.47, 156.74, 138.76, 132.39, 129.72, 129.39, 82.21, 78.78, 58.45, 45.00, 40.70, 28.51, 28.20, 22.23, 21.48 ppm; IR (KBr) 3724, 2975, 2349, 2308, 1712, 1518, 1456, 1369, 1320, 1256, 1225, 1165, 1114, 1068, 1006, 890, 854, 808, 752, 670, 649 cm^{-1} HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{19}H_{28}NO_4]^+([M+H]^+)$ 334.2018; found 334.2014. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 250 nm) retention time: minor isomer 43.49 min, major isomer 33.87 min, 92% ee, $[\alpha]^{20}_D$ = -16.2955 (*c* 1.0, $CHCl_3$).

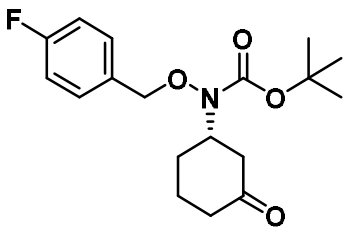
***tert*-Butyl (S)-((4-methoxybenzyl)oxy)(3-oxocyclohexyl)carbamate (4c)**



물질 **2c** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 pale yellow oil 형태의 물질 **4c** 를 얻는다 (97% yield).

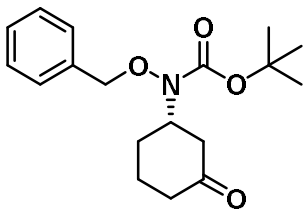
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.72-4.78 (m, 2H), 4.14-4.22 (m, 1H), 3.79 (s, 3H), 2.66 (dd, J = 13.3, 11.9 Hz, 1H), 2.48 (dd, J = 14.0, 4.4 Hz, 1H), 2.32 (d, J = 14.7 Hz, 1H), 2.20 (td, J = 13.6, 6.0 Hz, 1H), 1.85-2.07 (m, 3H), 1.59 (dd, J = 13.1, 4.4 Hz, 1H), 1.51 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.49, 160.16, 156.73, 131.33, 127.60, 114.08, 82.20, 78.51, 58.43, 55.50, 45.01, 40.70, 28.51, 28.21, 22.23 ppm; IR (KBr) 3725, 2973, 2349, 1712, 1613, 1586, 1456, 1369, 1320, 1253, 1165, 1113, 1067, 1034, 889, 854, 825, 678, 650 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{19}H_{28}NO_5]^+([M+H]^+)$ 350.1967; found 350.1961. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 13.19 min, major isomer 9.96 min, 90% ee, $[\alpha]^{20}_D$ = -19.4290 (*c* 1.0, $CHCl_3$).

***tert*-Butyl (S)-((4-fluorobenzyl)oxy)(3-oxocyclohexyl)carbamate (4d)**



물질 **2d** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 pale yellow liquid 형태의 물질 **4d** 를 얻는다 (90% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37 (ddd, J = 11.8, 5.1, 3.1 Hz, 2H), 7.03 (tt, J = 8.9, 2.3 Hz, 2H), 4.78 (t, J = 10.3 Hz, 2H), 4.16-4.23 (m, 1H), 2.62-2.68 (m, 1H), 2.48-2.52 (m, 1H), 2.34 (d, J = 15.1 Hz, 1H), 2.17-2.26 (m, 1H), 1.85-2.08 (m, 3H), 1.57-1.63 (m, 1H), 1.51 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.15, 164.24, 161.78, 156.53, 131.49, 131.40, 131.15, 115.60, 115.39, 82.25, 77.91, 58.39, 44.82, 40.55, 28.36, 28.10, 22.08 ppm; IR (KBr) 2974, 2350, 2308, 1713, 1604, 1512, 1456, 1417, 1369, 1320, 1302, 1256, 1226, 1164, 1114, 1095, 1068, 889, 854, 828, 670 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{18}H_{25}FNO_4]^+$($[M+H]^+$) 338.1768; found 338.1764. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 250 nm) retention time: minor isomer 43.17 min, major isomer 35.88 min, 89% ee, $[\alpha]^{20}_D$ = -15.83 (*c* 1.0, $CHCl_3$).

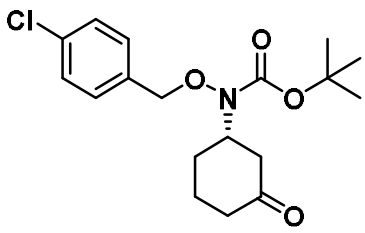
***tert*-Butyl (S)-(benzyloxy)(3-oxocyclohexyl)carbamate (4e)**



물질 **2e** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 colorless oil 형태의 물질 **4e** 를 얻는다 (99% yield).

^{1}H-NMR (400 MHz, DMSO -D6) δ 7.32-7.39 (m, 5H), 4.75 (s, 2H), 4.13 (s, 1H), 2.57-2.63 (m, 1H), 2.23-2.31 (m, 2H), 2.12 (d, J = 15.2 Hz, 1H), 1.80-1.86 (m, 3H), 1.54 (s, 1H), 1.42 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.51, 156.73, 135.36, 129.68, 128.92, 128.73, 82.33, 78.95, 58.48, 44.99, 40.71, 31.18, 28.50, 28.20, 22.23 ppm; IR (KBr) 2927, 1712, 1455, 1369, 1320, 1255, 1165, 1113, 1067, 1009, 915, 854, 748, 700 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{18}H_{26}NO_4]^+([M+H]^+)$ 320.1862; found 320.1866. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 ml/min, 23 °C, λ = 250 nm) retention time: minor isomer 14.81 min, major isomer 12.05 min, 93% ee, $[\alpha]^{20}_D$ = -8.7405 (*c* 1.0, $CHCl_3$).

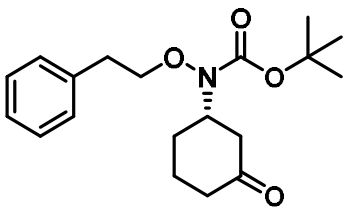
***tert*-Butyl (S)-((4-chlorobenzyl)oxy)(3-oxocyclohexyl)carbamate (4f)**



물질 **2f** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 white solid 형태의 물질 **4f** 를 얻는다 (98% yield).

^{1}H-NMR (400 MHz, CD_3OD) δ 7.33-7.41 (m, 4H), 4.80 (s, 2H), 4.17-4.24 (m, 1H), 2.68 (dd, J = 14.0, 10.8 Hz, 1H), 2.43 (dd, J = 13.8, 4.6 Hz, 1H), 2.28 (dd, J = 10.6, 6.0 Hz, 2H), 1.92-2.07 (m, 3H), 1.55-1.67 (m, 1H), 1.49 (s, 9H) ppm; ^{13}C-NMR (100 MHz, CD_3OD) δ 211.67, 158.34, 135.72, 135.65, 132.29, 132.18, 132.08, 129.70, 83.61, 83.15, 78.81, 60.04, 45.55, 41.33, 29.25, 28.70, 28.65, 23.23 ppm; IR (KBr) 3849, 3734, 3647, 3565, 2975, 1713, 1601, 1493, 1456, 1369, 1319, 1256, 1164, 1113, 1091, 1016, 813 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{18}H_{25}ClNO_4]^+([M+H]^+)$ 354.1472; found 354.1469. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane : 2-propanol = 99 : 1, flow rate = 1.0 ml/min, 23 °C, λ = 250 nm) retention time: minor isomer 28.57 min, major isomer 20.62 min, 86% ee, $[\alpha]^{20}_D$ = -12.6575 (*c* 1.0, $CHCl_3$).

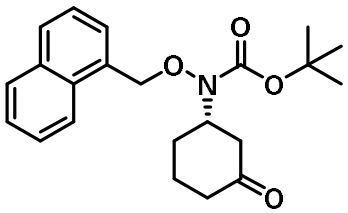
***tert*-Butyl (S)-(3-oxocyclohexyl)(phenethoxy)carbamate (4g)**



물질 **2g** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 pale liquid 형태의 물질 **4g** 를 얻는다 (99% yield).

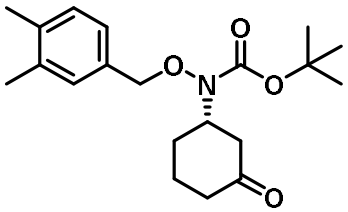
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.21-7.29 (m, 4H), 7.15-7.19 (m, 1H), 3.86-4.12 (m, 3H), 2.84-2.89 (m, 2H), 2.26-2.40 (m, 2H), 2.02-2.21 (m, 2H), 1.91 (qd, J = 9.3, 4.2 Hz, 1H), 1.77-1.81 (m, 1H), 1.48-1.68 (m, 2H), 1.44 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.53, 156.66, 138.61, 129.37, 128.56, 126.63, 82.15, 77.51, 58.39, 44.62, 40.54, 34.97, 28.43, 27.83, 22.12 ppm; IR (KBr) 3850, 3724, 3626, 2974, 2349, 2308, 1713, 1455, 1369, 1320, 1257, 1165, 1115, 1071, 1032, 854, 701, 648 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{19}H_{28}NO_4]^+$($[M+H]^+$) 334.2018; found 334.2018. 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 = 250 nm) retention time: minor isomer 15.54 min, major isomer 17.62 min, 76% ee, $[\alpha]^{20}_D$ = -11.4545 (*c* 1.0, $CHCl_3$).

***tert*-Butyl (S)-(naphthalen-1-ylmethoxy)(3-oxocyclohexyl)carbamate (4h)**



물질 **2h** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 pale yellow caramel 형태의 물질 **4h** 를 얻는다 (99% yield). ^{1}H-NMR (400 MHz, CD_3OD) δ 8.39 (dd, J = 18.4, 8.3 Hz, 1H), 7.83-7.88 (m, 2H), 7.42-7.56 (m, 4H), 5.18-5.30 (m, 2H), 4.14-4.21 (m, 1H), 2.64 (dd, J = 13.8, 11.5 Hz, 1H), 2.39 (dd, J = 13.8, 4.1 Hz, 1H), 2.17-2.21 (m, 2H), 1.85-2.03 (m, 3H), 1.54-1.76 (m, 1H), 1.50 (s, 9H) ppm; ^{13}C-NMR (100 MHz, CD_3OD) δ 211.65, 158.90, 158.87, 158.49, 135.36, 133.94, 133.29, 133.23, 133.06, 130.76, 130.66, 130.00, 129.88, 129.76, 129.56, 127.52, 127.17, 126.46, 126.11, 83.67, 77.88, 60.19, 45.63, 41.30, 28.79, 28.72, 23.21 ppm; IR (KBr) 3849, 3723, 3565, 2976, 1712, 1513, 1456, 1369, 1319, 1256, 1164, 1114, 1065, 851, 802 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{22}H_{28}NO4]^+([M+H]^+)$ 370.2018; found 370.2011. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak OD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 16.84 min, major isomer 13.92 min, 76% ee, $[\alpha]^{20}_{D}$ = -17.8155 (*c* 1.0, $CHCl_3$).

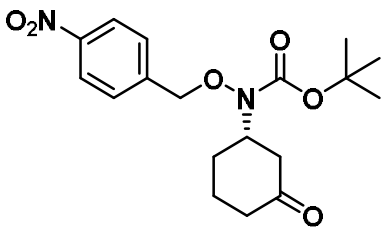
***tert*-Butyl (S)-((3,4-dimethylbenzyl)oxy)(3-oxocyclohexyl)carbamate (4i)**



물질 **2i** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 pale yellow oil 형태의 물질 **4i** 를 얻는다 (86% yield).

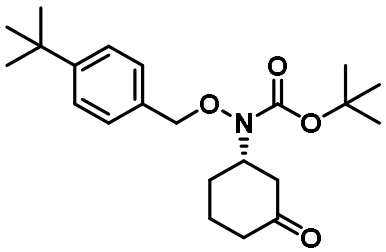
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 7.10-7.14 (m, 2H), 4.73-4.78 (m, 2H), 4.19 (tt, J = 11.0, 4.4 Hz, 1H), 2.65-2.72 (m, 1H), 2.51 (dt, J = 13.6, 2.3 Hz, 1H), 2.29-2.41 (m, 1H), 2.25 (d, J = 3.2 Hz, 6H), 2.21 (dd, J = 14.0, 7.6 Hz, 1H), 1.88-2.10 (m, 3H), 1.55-1.61 (m, 1H), 1.52 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.56, 156.73, 137.47, 136.95, 132.73, 131.06, 129.95, 127.23, 82.20, 78.95, 58.43, 45.03, 40.72, 28.52, 28.20, 22.24, 19.93, 19.81 ppm; IR (KBr) 3754, 3738, 3650, 2973, 2882, 1713, 1648, 1620, 1542, 1456, 1368, 1320, 1255, 1166, 1114, 1092, 1067, 1034, 1003, 889, 854, 818, 772 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{20}H_{30}NO_4]^+$($[M+H]^+$) 348.2175; found 348.2178. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 220 nm) retention time: minor isomer 8.72 min, major isomer 7.14 min, 69% ee, $[\alpha]^{20}_D$ = -19.2527 (*c* 1.0, $CHCl_3$).

***tert*-Butyl (S)-((4-nitrobenzyl)oxy)(3-oxocyclohexyl)carbamate (4j)**



물질 **2j** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 pale yellow caramel 형태의 물질 **4j** 를 얻는다 (99% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17-8.31 (m, 2H), 7.50-7.59 (m, 2H), 4.84-4.95 (m, 2H), 4.18-4.27 (m, 1H), 2.66 (ddd, J = 14.2, 10.6, 0.9 Hz, 1H), 2.51-2.56 (m, 1H), 2.35 (dt, J = 14.7, 4.4 Hz, 1H), 2.19-2.27 (m, 1H), 1.87-2.10 (m, 3H), 1.56-1.67 (m, 1H), 1.50 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.01, 156.54, 148.12, 142.57, 129.72, 123.89, 82.81, 77.36, 58.71, 44.88, 40.66, 31.16, 28.48, 28.26, 22.22 ppm; IR (KBr) 3725, 2976, 2381, 2349, 2308, 1712, 1607, 1523, 1456, 1370, 1319, 1257, 1225, 1163, 1113, 1071, 852, 742, 670, 648 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{18}H_{25}N_2O_6]^+$($[M+H]^+$) 365.1713; found 365.1709. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 28.84 min, major isomer 33.70 min, 67% ee, $[\alpha]^{20}_D$ = -10.0430 (*c* 1.0, $CHCl_3$).

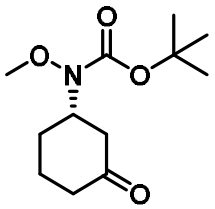
***tert*-Butyl (S)-((4-(tert-butyl)benzyl)oxy)(3-oxocyclohexyl)carbamate (4k)**



물질 **2k** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 pale yellow oil 형태의 물질 **4k** 를 얻는다 (91% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32-7.40 (m, 4H), 4.77-4.82 (m, 2H), 4.16-4.23 (m, 1H), 2.69 (dd, J = 14.0, 11.7 Hz, 1H), 2.51 (dd, J = 14.0, 4.3 Hz, 1H), 2.34 (d, J = 14.6 Hz, 1H), 2.17-2.25 (m, 1H), 1.91-2.07 (m, 3H), 1.56-1.61 (m, 1H), 1.51 (s, 9H), 1.30 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.48, 156.74, 151.99, 132.37, 129.52, 125.67, 82.20, 78.75, 58.47, 45.00, 40.71, 34.85, 31.50, 28.50, 28.21, 22.23 ppm; IR (KBr) 2964, 2871, 1713, 1518, 1458, 1368, 1320, 1302, 1256, 1223, 1166, 1111, 1067, 1034, 889, 855, 824 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{22}H_{34}NO_4]^+([M+H]^+)$ 376.2488; found 376.2480. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 250 nm) retention time: minor isomer 37.30 min, major isomer 31.24 min, 62% ee, $[\alpha]^{20}_D$ = -11.9285 (*c* 1.0, $CHCl_3$).

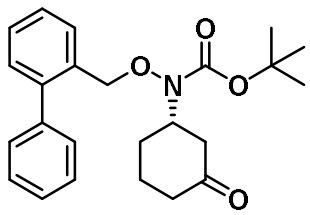
***tert*-Butyl (S)-methoxy(3-oxocyclohexyl)carbamate (4l)**



물질 **2l** 을 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 pale yellow oil 형태의 물질 **4l** 을 얻는다 (97% yield).

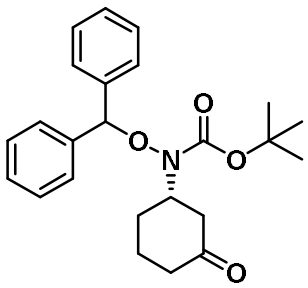
^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.07-4.22 (m, 1H), 3.60-3.74 (m, 3H), 2.64 (ddd, J = 14.0, 11.0, 1.1 Hz, 1H), 2.45-2.49 (m, 1H), 2.18-2.35 (m, 2H), 2.00-2.08 (m, 1H), 1.85-1.96 (m, 2H), 1.52-1.62 (m, 1H), 1.46 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.38, 156.52, 82.19, 64.42, 58.33, 44.74, 40.71, 28.45, 28.07, 22.24 ppm; IR (KBr) 2975, 2939, 1712, 1458, 1424, 1370, 1303, 1257, 1167, 1115, 1093, 1036, 1013, 964, 886, 855, 756 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{12}H_{22}NO_4]^+$($[M+H]^+$) 244.1549; found 244.1545. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AS-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 220 nm) retention time: minor isomer 11.57 min, major isomer 8.95 min, 58% ee, $[\alpha]^{20}_D$ = -5.4560 (*c* 1.0, $CHCl_3$).

***tert*-Butyl (S)-([1,1'-biphenyl]-2-ylmethoxy)(3-oxocyclohexyl)carbamate (4m)**



물질 **2m** 을 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 pale yellow caramel 형태의 물질 **4m** 을 얻는다 (94% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54-7.58 (m, 1H), 7.26-7.43 (m, 8H), 4.77-4.85 (m, 2H), 3.99 (tt, J = 11.7, 4.2 Hz, 1H), 2.23-2.27 (m, 2H), 2.01-2.17 (m, 2H), 1.86 (td, J = 6.2, 2.9 Hz, 1H), 1.62-1.72 (m, 1H), 1.46 (s, 9H), 1.36-1.44 (m, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.54, 156.48, 143.22, 141.09, 132.51, 131.55, 130.36, 129.61, 129.02, 128.39, 127.95, 127.52, 82.17, 76.36, 58.09, 44.67, 40.49, 28.45, 27.63, 22.13 ppm; IR (KBr) 3840, 3650, 2927, 2311, 1712, 1542, 1480, 1453, 1369, 1320, 1302, 1256, 1222, 1166, 1115, 1066, 1036, 890, 855, 754, 704 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{24}H_{30}NO_4]^+$($[M+H]^+$) 396.2175; found 396.2179. 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 27.84 min, major isomer 21.29 min, 19% ee, $[\alpha]^{20}_D$ = -2.5365 (*c* 1.0, $CHCl_3$).

***tert*-Butyl (S)-(benzhydryloxy)(3-oxocyclohexyl)carbamate (4n)**



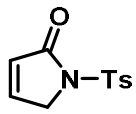
물질 **2n** 을 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 white caramel 형태의 물질 **4n** 을 얻는다 (64% yield).

^{1}H-NMR (400 MHz, CD_3OD) δ 7.25-7.37 (m, 10H), 5.81-5.87 (m, 1H), 3.90 (tt, J = 11.7, 4.1 Hz, 1H), 2.51 (t, J = 12.9 Hz, 1H), 2.13-2.17 (m, 2H), 2.01-2.08 (m, 1H), 1.85-1.92 (m, 1H), 1.72-1.80 (m, 1H), 1.61 (t, J = 6.4 Hz, 1H), 1.40-1.52 (m, 1H), 1.32-1.39 (m, 9n) ppm; ^{13}C-NMR (100 MHz, CD_3OD) δ 211.65, 158.90, 158.87, 158.49, 135.36, 133.94, 133.29, 133.23, 133.06, 130.76, 130.66, 130.00, 129.88, 129.76, 129.56, 127.52, 127.17, 126.46, 126.11, 83.67, 77.88, 60.19, 45.63, 41.30, 28.79, 28.72, 23.21 ppm; IR (KBr) 3840, 3738, 3614, 3032, 2975, 1712, 1648, 1604, 1542, 1508, 1497, 1452, 1369, 1317, 1299, 1255, 1221, 1164, 1114, 1063, 1032, 985, 892, 852, 771, 700 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{24}H_{30}NO_4]^+$($[M+H]^+$) 396.2175; found 396.2177. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AS-H, hexane : 2-propanol = 99 : 1,

flow rate = 1.0 ml/min, 23 ℃, λ = 250 nm) retention time: minor isomer 17.49 min, major isomer 14.14 min, 4% ee, $[\alpha]^{20}_{D}$ = -1.9915 (*c* 1.0, $CHCl_3$).

3. Michael aceeptor

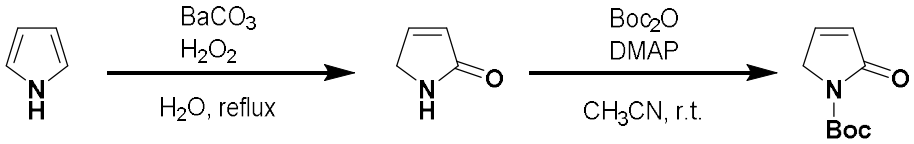
1-Tosyl-1,5-dihydro-2H-pyrrol-2-one (3f)



RBF에 **3j** (1.0 당량) 을 넣고 Ar 기체로 내부를 치환한 후 anhydrous THF에 녹인다. -78 ℃ 에서 5분 동안 교반한 후, n-BuLi (1.1 당량) 을 천천히 적가한다. 15분 동안 추가로 교반한 후, p-TsCl (1.1 당량)을 천천히 적가한다. 이후, 상온에서 약 2일 동안 교반한 후 반응을 종결시킨다. 물과 EtOAc 로 3번 추출하고 유기층을 $MgSO_4$로 건조 및 필터한다. 이후 Medium pressure liquid chromatography 를 통해 정제하여 dark yellow solid 형태의 물질 **3f** 를 얻는다 (mp 154-157℃, 16% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 7.22-7.24 (m, 1H), 6.06-6.08 (m, 1H), 4.49 (t, J = 1.8 Hz, 2H), 2.43 (d, J = 9.2 Hz, 3H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$) δ 168.30, 146.46, 145.17, 135.29, 129.75, 127.96, 127.12, 52.31, 21.65 ppm; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{11}H_{12}NO_3S]^+$($[M+H]^+$) 238.0538; found 238.0542.

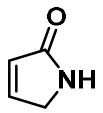
물질 **3g** 는 **ref 15** 의 합성법을 이용하여 아래와 같은 합성법과 동일하게 합성하였다.



RBF 에 pyrrole (1 당량), barium carbonate (0.1 당량) 을 넣고 증류수로 녹인 후 교반한다. 30% Hydrogen peroxide (10 당량)을 넣고 120 ˚C 에서 5 시간 동안 reflux 시킨다. 이후 반응 혼합물의 온도를 상온으로 낮추면서 hydrogen peroxide 를 quenching 하기 위해 lead dioxide 를 넣는다. 거품 생성이 멈출 때까지 lead dioxide 를 넣고, filter paper 로 걸러진 물질의 반응 용매를 감압 농축시켜 제거한다. 이후, Dioxane 을 넣고 filter paper 로 다시 한 번 여과하며 Dioxane 으로 씻어준다. 여과된 물질을 $MgSO_4$ 로 건조 및 필터한 후, 반응 용매를 감압 농축시켜 제거하여 dark orange liquid 형태의 물질 **3j** 를 얻는다.

RBF 에 물질 **3j** (1 당량)와 Boc_2O (1 당량) 을 넣고 상온에서 CH_3CN 으로 녹인다. DMAP (5 mol%) 을 넣고 상온에서 2 시간 동안 교반시킨다. 반응 종료 후, 감압 농축시킨 물질을 EtOAc 에 녹인 후, Silica gel 을 넣고 상온에서 20 분 동안 교반시킨다. Filter paper 을 이용하여 여과한 물질의 반응 용매를 감압 농축시켜 제거한 후, Medium pressure liquid chromatography 를 통해 정제하여 생성물 **3g** 을 얻는다

1,5-Dihydro-2H-pyrrol-2-one (3j)

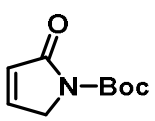


Dark orange liquid (Yield = 38%)

물질 **3j** 의 ^{1}H-NMR spectral data가 **ref 15** 에서와 일치함.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.14-7.16 (m, 1H), 6.14-6.16 (m, 1H), 4.05 (s, 2H) ppm; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_4H_6NO]^+([M+H]^+)$ 84.0449; found 84.0453.

***tert*-Butyl 2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (3g)**

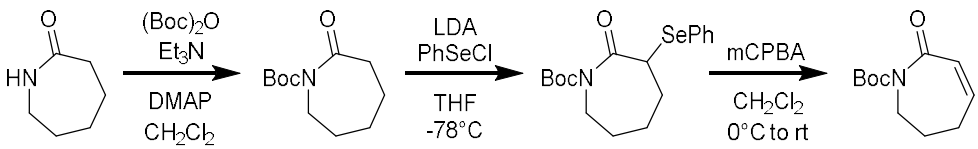


Dark yellow solid (Yield = 23%)

물질 **3g** 의 ^{1}H-NMR spectral data가 **ref 15** 에서와 일치함.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.17 (td, J = 4.1, 1.8 Hz, 1H), 6.15 (td, J = 4.1, 2.0 Hz, 1H), 4.33 (t, J = 2.1 Hz, 2H), 1.54 (s, 9H) ppm; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_9H_{14}NO_3]^+([M+H]^+)$ 184.0974; found 184.0974.

물질 **3i** 와 **3h** 는 **Ref 16** 의 합성법을 참고하여 아래와 같은 과정으로 합성하였다.



<u>실험과정 (C)</u>

RBF 에 ε-Caprolactam (1 당량), 4-(dimethylamino)pyridine (1 당량), Di-*tert*-butyl dicarbonate (2 당량) 을 넣고 무수 Dichloromethane 으로 녹인다. 이후 내부를 argon 가스로 치환한 후 상온에서 교반한다. 20 시간 동안 교반시킨 후, 반응이 종결되면 CH_2Cl_2 로 희석시키며 포화 $NaHCO_3$ 수용액으로 씻는다. 유기층을 물과 brine 을 이용하여 CH_2Cl_2 로 역추출한 후, $MgSO_4$ 로 건조 및 필터한다. 혼합물을 Medium pressure liquid chromatography 를 통해 정제하여 물질 **3k** 를 얻는다.

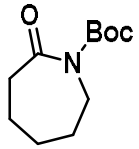
실험과정 (D)

RBF 에 물질 **3k** (1 당량) 와 LDA (2.0M in heptane/THF/ethylbenzene, 1.1 당량)를 anhydrous THF 에 녹인 후 -78 ˚C 에서 30 분 동안 교반시킨다. Phenylselenyl chloride (1.1 당량) 을 anhydrous THF 에 녹인 solution 을 dropwise 로 넣어준다. 3 시간 동안 -78 ˚C 에서 교반한 후, 반응 용매를 감압 농축하여 제거한다. 물로 quenching 하고, dichloromethane 으로 역추출하여 얻은 유기층을 $MgSO_4$ 로 건조 및 필터한다. 이후, Medium pressure liquid chromatography 를 통해 정제하여 물질 **3l** 을 얻는다.

실험과정 (E)

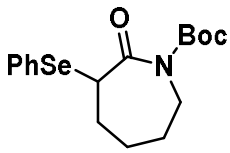
Anhydrous dichloromehtane 으로 물질 **3l** (1 당량) 을 녹인 후, 0 ˚C 에서 10 분 동안 교반시킨다. 3-Chloroperoxybenzoic acid(70-75%, balance 3-chlorobenzoic acid and water, 2 당량) 을 anhydrous dichloromethane 으로 녹인 solution 을 dropwise 로 넣어준다. 상온에서 3 시간 동안 교반시킨 후, 포화 $NaHCO_3$ 수용액으로 씻어준다. Dichloromethane 으로 역추출하여 얻은 유기층을 $MgSO_4$ 로 건조 및 필터한 후, Medium pressure liquid chromatography 를 통해 정제하여 물질 **3i** 를 얻는다.

***tert*-Butyl 2-oxoazepane-1-carboxylate (3k)**



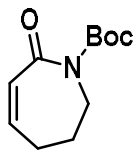
실험과정 (C) 로 합성하여 colorless liquid 형태의 물질 **3k** 를 얻는다 (Yield = 49%). 물질 **3k**의 ^{1}H-NMR spectral data가 **ref 16** 에서와 일치함. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.72-3.74 (m, 2H), 2.60-2.63 (m, 2H), 1.69-1.74 (m, 6H), 1.49 (s, 9H) ppm; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{11}H_{20}NO_3]^+([M+H]^+)$ 214.1443; found 214.1444.

***tert*-Butyl 2-oxo-3-(phenylselanyl)azepane-1-carboxylate (3l)**



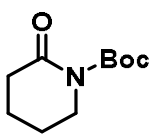
실험과정 (D) 로 합성하여 Light yellow solid 형태의 물질 **3l** 을 얻는다 (Yield = 19%). 물질 **3l**의 ^{1}H-NMR spectral data가 **ref 16** 에서와 일치함. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.17 (td, J = 4.1, 1.8 Hz, 1H), 6.15 (td, J = 4.1, 2.0 Hz, 1H), 4.33 (t, J = 2.1 Hz, 2H), 1.54 (s, 9H) ppm; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{17}H_{23}NO_3Se]^+([M+H]^+)$ 369.0844; found 369.0843.

***tert*-Butyl 7-oxo-2,3,4,7-tetrahydro-1H-azepine-1-carboxylate (3i)**



실험과정 (E) 로 합성하여 Pale yellow oil 형태의 물질 **3i** 를 얻는다 (Yield = 20%). 물질 **3i**의 ^{1}H-NMR spectral data가 **ref 16** 에서와 일치함. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.38 (dt, J = 12.4, 5.7 Hz, 1H), 5.99 (dt, J = 11.5, 1.1 Hz, 1H), 3.73 (t, J = 6.0 Hz, 2H), 2.31-2.37 (m, 2H), 1.90-1.96 (m, 2H), 1.51 (s, 9H) ppm; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{11}H_{18}NO_3]^+([M+H]^+)$ 212.1287; found 212.1285.

***tert*-Butyl 2-oxopiperidine-1-carboxylate (3m)**

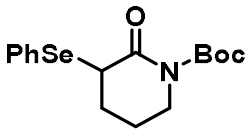


2-piperidone 을 출발물질로 하여 위의 실험과정 (C) 를 통해 yellow oil 형태의 물질 **3m** 을 얻는다 (72% yield, 반응 시간 = 20시간).

물질 **3m** 의 ^{1}H-NMR spectral data가 **ref 35** 에서와 일치함.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.59-3.62 (m, 2H), 2.42-2.54 (m, 2H), 1.73-1.82 (m, 4H), 1.48 (s, 9H) ppm; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{10}H_{18}NO_3]^+([M+H]^+)$ 200.1287; found 200.1286.

***tert*-Butyl 2-oxo-3-(phenylselanyl)piperidine-1-carboxylate (3n)**

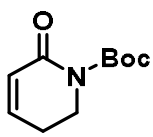


물질 **3m** 을 출발물질로 하여 위의 실험 과정 (D) 를 통해 yellow oil 형태의 물질 **3n** 을 얻는다 (18% yield, 반응 시간 = 3시간).

물질 **3n** 의 ^{1}H-NMR spectral data가 **ref 35** 에서와 일치함.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.65 (dq, J = 8.2, 2.3 Hz, 2H), 7.25-7.34 (m, 3H), 3.92-3.98 (m, 1H), 3.55-3.70 (m, 2H), 2.15-2.26 (m, 1H), 1.93-2.08 (m, 2H), 1.71-1.80 (m, 1H), 1.51 (s, 9H) ppm; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{16}H_{21}NO_3Se]^+$($[M+H]^+$) 355.0687; found 355.0690.

***tert*-Butyl 6-oxo-3,6-dihydropyridine-1(2H)-carboxylate (3h)**



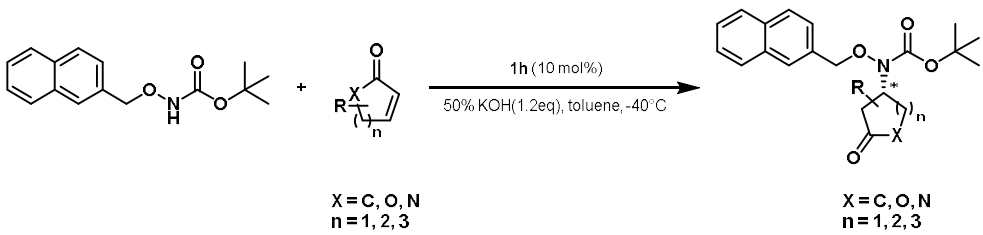
물질 **3n** 을 출발물질로 하여 위의 실험 과정 (E) 을 통해 yellow oil 형태의 물질 **3h** 를 얻는다 (57% yield, 반응 시간 = 3시간).

물질 **3h** 의 ^{1}H-NMR spectral data가 **ref 35** 에서와 일치함.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.75 (dt, J = 9.7, 4.1 Hz, 1H), 5.92 (dt, J = 9.7, 1.8 Hz, 1H), 3.82 (t, J = 6.4 Hz, 2H), 2.35-2.40 (m, 2H), 1.51 (s, 9H)

ppm; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{10}H_{16}NO_3]^+$($[M+H]^+$) 198.1130; found 198.1131.

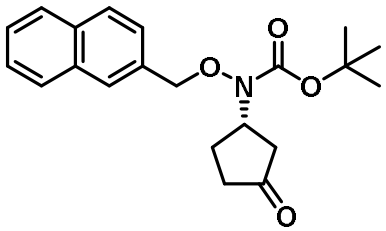
3-2. 입체 선택적인 PTC aza-Michael reaction



일반적인 방법

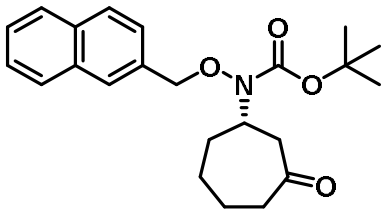
RBF에 *tert*-butyl (naphthalen-2-ylmethoxy)carbamate (2.0 당량) 와 상전이 촉매 (10 mol%) 을 넣고 toluene 용매 하에 교반한다. Michael acceptor (1당량) 을 넣고 -40 °C에서 15분 동안 교반한다. -40 °C 에서 충분히 교반시킨 후, 유기층과 수층의 비율이 4:1이 되도록 50% KOH 수용액 (1.2당량)과 DDW을 넣는다. TLC 상에서 기질이 모두 사라지면 반응을 종결시킨다. 물과 EtOAc 로 3번 추출하고 유기층을 $MgSO_4$로 건조 및 필터한다. 이후 Medium pressure liquid chromatography 를 통해 정제하여 생성물을 얻는다.

***tert*-Butyl (S)-(naphthalen-2-ylmethoxy)(3-oxocyclopentyl)carbamate (5a)**



물질 **3a** 를 출발물질로 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 white solid 형태의 물질 **5a** 를 얻는다 (mp 118°C, 83% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, J = 8.7, 5.9 Hz, 4H), 7.48 (td, J = 6.4, 3.4 Hz, 3H), 4.99 (dd, J = 24.2, 9.6 Hz, 2H), 4.67-4.74 (m, 1H), 2.35-2.46 (m, 3H), 2.09-2.29 (m, 3H), 1.55 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.48, 157.28, 133.59, 133.37, 132.55, 129.00, 128.55, 128.32, 127.92, 127.18, 126.62, 126.46, 82.52, 79.08, 57.32, 41.69, 37.43, 28.55, 26.87 ppm; IR (KBr) 3840, 3737, 3650, 3614, 2977, 2310, 1745, 1705, 1648, 1603, 1542, 1508, 1473, 1459, 1394, 1369, 1323, 1255, 1220, 1162, 1071, 1005, 904, 855, 820, 773, 672 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{21}H_{26}NO_4]^+$($[M+H]^+$) 354.1862; found 356.1859. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak OD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 14.68 min, major isomer 12.87 min, 93% ee, $[\alpha]^{20}_{D}$ = +1.0950 (*c* 1.0, $CHCl_3$).

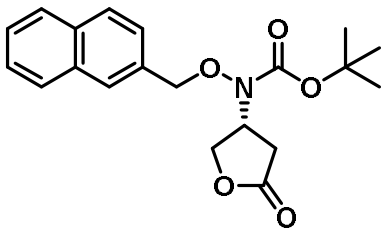
***tert*-Butyl (S)-(naphthalen-2-ylmethoxy)(3-oxocycloheptyl)carbamate (5c)**



물질 **3c** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 yellow caramel 형태의 물질 **5c** 를 얻는다 (85% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 8.7, 6.0 Hz, 4H), 7.46-7.54 (m, 3H), 4.99 (dd, J = 16.1, 9.7 Hz, 2H), 4.18 (tt, J = 11.0, 2.7 Hz, 1H), 3.05 (dd, J = 14.7, 11.5 Hz, 1H), 2.65 (d, J = 14.7 Hz, 1H), 2.51 (dt, J = 15.6, 4.1 Hz, 1H), 2.38-2.45 (m, 1H), 1.87-2.06 (m, 4H), 1.38-1.61 (m, 11H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.89, 157.09, 133.53, 133.38, 133.03, 128.61, 128.42, 128.25, 127.90, 127.09, 126.50, 126.40, 82.32, 78.94, 57.76, 47.98, 44.16, 34.71, 28.55, 27.39, 24.11 ppm; IR (KBr) 3903, 3840, 3756, 2975, 2310, 1704, 1603, 1473, 1369, 1255, 1163, 1069, 903, 856, 772, 673 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{23}H_{30}NO_4]^+$($[M+H]^+$) 384.2175; found 384.2173. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 11.84 min, major isomer 9.22 min, 93% ee, $[\alpha]^{20}_D$ = +16.4325 (*c* 1.0, $CHCl_3$).

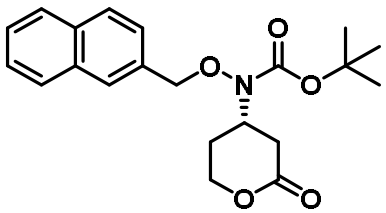
***tert*-Butyl (R)-(naphthalen-2-ylmethoxy)(5-oxotetrahydrofuran-3-yl)-carbamate (5d)**



물질 **3d** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 white caramel 형태의 물질 **5d** 를 얻는다 (32% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.81-7.86 (m, 4H), 7.47-7.51 (m, 3H), 5.00-5.08 (m, 2H), 4.81-4.87 (m, 1H), 4.40 (dd, J = 10.1, 7.3 Hz, 1H), 4.28 (dd, J = 9.8, 3.9 Hz, 1H), 2.59-2.71 (m, 2H), 1.55 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.35, 157.04, 133.64, 133.31, 132.19, 129.26, 128.67, 128.34, 127.93, 127.19, 126.74, 126.53, 83.41, 79.21, 71.23, 55.95, 31.86, 28.44 ppm; IR (KBr) 3840, 3738, 3649, 3566, 2977, 2929, 2310, 1783, 1708, 1648, 1603, 1508, 1473, 1369, 1318, 1257, 1220, 1169, 1101, 1027, 946, 852, 821, 772, 686 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{20}H_{24}NO_5]^+$($[M+H]^+$) 358.1654; found 358.1649. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OD-H, hexane : 2-propanol = 90 : 10, flow rate = 1.0 ml/min, 23 °C, λ = 254 nm) retention time: minor isomer 24.77 min, major isomer 21.77 min, 83% ee, $[\alpha]^{20}_D$ = -36.3050 (*c* 1.0, $CHCl_3$).

***tert*-Butyl (S)-(naphthalen-2-ylmethoxy)(2-oxotetrahydro-2H-pyran-4-yl)-carbamate (5e)**

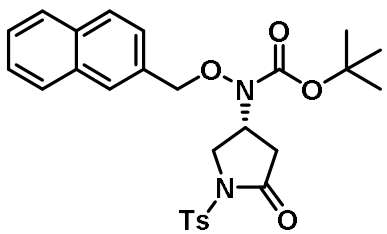


물질 **3e** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 white solid 형태의 물질 **5e** 를 얻는다. 일부 가수분해 된 물질을 coupling 시키기 위해 추가 반응을 진행하였다. 가수분해 된 물질을 Dichloromethane으로 녹인 후, EDC·HCl (1.1 당량), Triethylamine (1.1 당량)을 넣고 상온에서 반응시킨다. 20 시간 후, 포화 $NaHCO_3$ 수용액으로 2번, 물로 1번 추출하고 유기층을 $MgSO_4$로 건조 및 필터한다. 이후 정제하여 얻은 생성물을 **5e** 에 합산하였다 (mp 89.4°C, 42% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.84 (t, J = 4.3 Hz, 4H), 7.47-7.52 (m, 3H), 5.02 (t, J = 9.8 Hz, 2H), 4.44-4.51 (m, 1H), 4.38 (dt, J = 11.6, 4.9 Hz, 1H), 4.15-4.21 (m, 1H), 2.74-2.87 (m, 2H), 1.97-2.11 (m, 2H), 1.55 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.68, 157.04, 133.60, 133.33, 132.46, 129.05, 128.56, 128.30, 127.91, 127.17, 126.67, 126.49, 82.95, 79.17, 66.74, 52.65, 33.56, 28.48, 26.37 ppm; IR (KBr) 3903, 3840, 3757, 3736, 3649, 3526, 2977, 2931, 2310, 1731, 1707, 1648, 1603, 1542, 1508, 1457, 1369, 1338, 1256, 1220, 1165, 1098, 901, 856, 820, 772, 673 cm^{-1}; HRMS (FAB)

m/z: $[M+H]^+$ Calcd for $[C_{21}H_{26}NO_5]^+([M+H]^+)$ 372.1811; found 372.1802. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane : 2-propanol = 90 : 10, flow rate = 1.0 ml/min, 23 °C, λ = 250 nm) retention time: minor isomer 31.38 min, major isomer 25.12 min, 97% ee, $[\alpha]^{20}_D$ = +5.1485 (*c* 1.0, $CHCl_3$).

tert-Butyl (R)-(naphthalen-2-ylmethoxy)(5-oxo-1-tosylpyrrolidin-3-yl)-carbamate (5f)

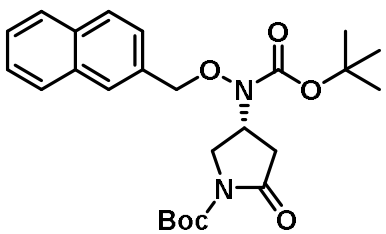


물질 **3f** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 colorless oil 형태의 물질 **5f** 를 얻는다 (35% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76-7.85 (m, 5H), 7.72 (d, J = 9.7 Hz, 1H), 7.47-7.55 (m, 2H), 7.34-7.38 (m, 1H), 6.99-7.05 (m, 2H), 4.89-5.01 (m, 2H), 4.69-4.78 (m, 1H), 4.08-4.13 (m, 1H), 3.87-3.93 (m, 1H), 2.54-2.72 (m, 2H), 2.13-2.21 (m, 3H), 1.53 (s, 9H) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 170.773, 156.689, 145.008, 134.930, 133.379, 133.111, 131.943, 129.420, 128.879, 128.242, 128.175, 127.917, 127.677, 126.921, 126.495, 126.275, 83.193, 79.062, 51.663, 50.577, 35.626, 29.685, 28.239, 21.426, 14.092

ppm; IR (KBr) 2927, 2350, 2310, 1742, 1708, 1598, 1508, 1473, 1368, 1318, 1219, 1170, 1090, 963, 817, 772, 707, 664, 607 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{27}H_{31}N_2O_6S]^+([M+H]^+)$ 511.1903; found 511.1914. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 ml/min, 23 °C, λ = 250 nm) retention time: minor isomer 13.35 min, major isomer 18.14 min, 30% ee, $[\alpha]^{20}_D$ = -3.2575 (*c* 1.0, $CHCl_3$).

<u>*tert*-Butyl (R)-4-((tert-butoxycarbonyl)(naphthalen-2-ylmethoxy)-amino)-2-oxopyrrolidine-1-carboxylate (5g)</u>



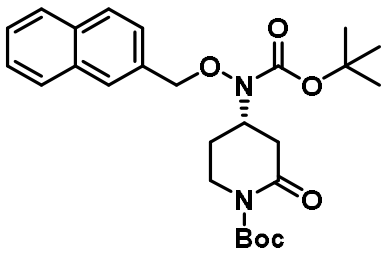
물질 **3g** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 pale liquid 형태의 물질 **5g** 를 얻는다 (15% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.80-7.84 (m, 4H), 7.47-7.49 (m, 3H), 5.02 (t, J = 10.5 Hz, 2H), 4.63-4.70 (m, 1H), 3.72-3.90 (m, 2H), 2.70-2.75 (m, 2H), 1.55 (s, 9H), 1.47 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 171.500, 156.869, 149.643, 133.425, 133.154, 132.114, 128.877, 128.426, 128.144, 127.704, 126.893, 126.478, 126.283, 83.096, 82.974, 78.988, 51.225,

49.417, 36.287, 29.698, 28.265, 27.946 ppm; IR (KBr) 2979, 2927, 1788, 1712, 1508, 1475, 1369, 1318, 1256, 1219, 1155, 1092, 1023, 952, 899, 855, 820, 774 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{25}H_{33}N_2O_6]^+([M+H]^+)$ 457.2339; found 457.2353. 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 = 250 nm) retention time: minor isomer 22.72 min, major isomer 82.31 min, 65% ee, $[\alpha]^{20}_D$ = +2.31 (*c* 1.0, $CHCl_3$)

.

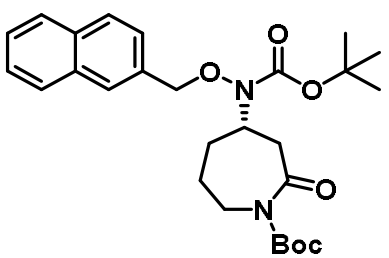
<u>*tert*-Butyl (S)-4-((tert-butoxycarbonyl)(naphthalen-2-ylmethoxy)-amino)-2-oxopiperidine-1-carboxylate (5h)</u>



물질 **3h** 를 출발물질로 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 white solid 형태의 물질 **5h** 를 얻는다 (mp 111°C, 68% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.32-7.40 (m, 4H), 4.77-4.82 (m, 2H), 4.16-4.23 (m, 1H), 2.69 (dd, J = 14.0, 11.7 Hz, 1H), 2.51 (dd, J = 14.0, 4.3 Hz, 1H), 2.34 (d, J = 14.6 Hz, 1H), 2.17-2.25 (m, 1H), 1.91-2.07 (m, 3H), 1.56-

1.61 (m, 1H), 1.51 (s, 9H), 1.30 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.84, 156.99, 152.41, 133.57, 133.34, 132.57, 128.96, 128.49, 128.30, 127.89, 127.18, 126.58, 126.42, 83.36, 82.68, 79.14, 53.60, 43.83, 37.92, 28.50, 28.15, 26.60 ppm; IR (KBr) 3840, 3757, 3738, 3649, 3614, 2978, 2933, 2310, 1772, 1715, 1648, 1603, 1542, 1508, 1474, 1457, 1368, 1292, 1254, 1220, 1159, 1096, 903, 854, 819, 772, 673 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{26}H_{35}N_2O_6]^+([M+H]^+)$ 471.2495; found 471.2502. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane : 2-propanol = 95 : 5, flow rate = 1.0 ml/min, 23 °C, λ = 250 nm) retention time: minor isomer 19.20 min, major isomer 14.23 min, 97% ee, $[\alpha]^{20}_D$ = +15.5645 (*c* 1.0, $CHCl_3$).

tert-Butyl (S)-4-((tert-butoxycarbonyl)(naphthalen-2-ylmethoxy)-amino)-2-oxoazepane-1-carboxylate (5i)

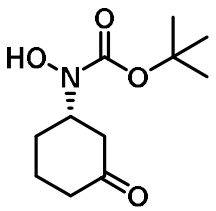


물질 **3i** 를 출발물질로 하여 일반적인 입체 선택적 PTC aza-Michael 실험과정으로 colorless caramel 형태의 물질 **5i** 를 얻는다 (76% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 7.8 Hz, 4H), 7.46-7.54 (m, 3H), 5.01 (dd, J = 16.3, 9.9 Hz, 2H), 4.10-4.24 (m, 2H), 3.25 (dd, J = 15.2, 10.6 Hz, 1H), 3.14 (dd, J = 13.8, 11.0 Hz, 1H), 2.77 (d, J = 13.8 Hz, 1H), 1.96-2.03 (m, 3H), 1.54 (d, J = 8.3 Hz, 10H), 1.50 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.55, 156.84, 152.80, 133.54, 133.36, 132.95, 128.70, 128.48, 128.26, 127.92, 127.13, 126.56, 126.45, 83.39, 82.60, 79.03, 56.27, 45.44, 44.91, 32.30, 28.54, 28.28, 28.20, 27.02 ppm; IR (KBr) 3898, 3836, 3742, 3686, 3655, 3626, 2978, 2372, 2322, 1768, 1714, 1553, 1459, 1368, 1331, 1274, 1205, 1154, 1088, 1014, 855, 819, 748, 670, 661 cm^{-1}; HRMS (FAB) m/z: $[M+Na]^+$ Calcd for $[C_{27}H_{37}N_2O_6Na]^+$($[M+Na]^+$) 507.2471; found 507.2458. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel AD-H, hexane : 2-propanol = 80 : 20, flow rate = 1.0 ml/min, 23 °C, λ = 250 nm) retention time: minor isomer 13.35 min, major isomer 18.14 min, 30% ee, $[\alpha]^{20}_D$ = -0.82 (*c* 1.0, $CHCl_3$).

3. Deprotection of the Aza-Michael Adduct

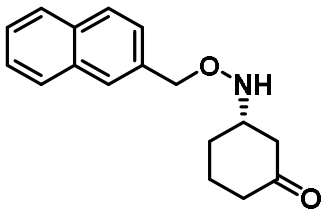
***tert*-Butyl (S)-hydroxy(3-oxocyclohexyl)carbamate (6)**



Two-neck RBF에 **4a** (1.0 당량) 와 촉매량의 Pd/C (10% on activated carbon)을 넣고 EtOH 용매 하에 교반한다. 수소 가스로 내부를 치환한 후, 상온에서 16시간 교반한다. TLC 상에서 기질이 모두 사라진 것을 확인하면 반응을 종결시킨다. 반응 혼합물을 Celite Pad을 통해 필터한 후, EtOH로 씻어준다. 여과물 내 반응 용매를 감압 농축시켜 제거한 후, Medium pressure liquid chromatography 를 통해 정제하여 colorless oil 형태의 물질 **6** 을 얻는다 (82% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.45 (s, 1H), 4.18 (tt, J = 11.0, 4.6 Hz, 1H), 2.74-2.81 (m, 1H), 2.43-2.49 (m, 1H), 2.34-2.38 (m, 1H), 2.21-2.30 (m, 1H), 1.92-2.13 (m, 3H), 1.61-1.65 (m, 1H), 1.47 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.00, 156.73, 82.74, 57.54, 44.74, 40.71, 28.47, 28.02, 22.15 ppm; IR (KBr) 3849, 3298, 2975, 2350, 2310, 1692, 1454, 1394, 1340, 1258, 1168, 1079, 973, 887, 772 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{11}H_{20}NO_4]^+$($[M+H]^+$) 230.1392; found 230.1398. $[\alpha]^{20}_D$ = +10.3185 (*c* 1.0, $CHCl_3$).

(S)-3-((naphthalen-2-ylmethoxy)amino)cyclohexan-1-one (7)



CH_2Cl_2에 **4a** (1.0 당량) 을 녹인 후, 0 °C에서 trifluoroacetic acid (30 당량)을 넣는다. 1시간 동안 교반시킨 후 반응이 종결되면 CH_2Cl_2 로 희석시키고 CH_2Cl_2를 이용하여 역추출한다. 유기층을 $MgSO_4$로 건조 및 필터하고, Medium pressure liquid chromatography 를 통해 정제하여 white oil 형태의 물질 **7** 을 얻는다. (40% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.78-7.83 (m, 4H), 7.46 (td, J = 4.9, 3.2 Hz, 3H), 5.45 (s, 1H), 4.84 (dd, J = 13.3, 11.9 Hz, 2H), 3.39 (s, 1H), 2.58 (dd, J = 14.2, 4.1 Hz, 1H), 2.25-2.42 (m, 3H), 2.00-2.09 (m, 2H), 1.64-1.70 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.17, 135.25, 133.45, 133.28, 128.38, 128.15, 127.90, 127.60, 126.56, 126.34, 126.22, 77.38, 59.36, 45.73, 41.36, 28.71, 22.19 ppm; IR (KBr) 3250, 2929, 2865, 1711, 1636, 1602, 1508, 1450, 1366, 1319, 1270, 1221, 1173, 1124, 1034, 951, 901, 858, 819, 772, 673 cm^{-1}; HRMS (FAB) m/z: $[M+H]^+$ Calcd for $[C_{17}H_{20}NO_2]^+$($[M+H]^+$) 270.1494; found 270.1497. $[\alpha]^{20}_D$ = -19.24 (*c* 1.0, $CHCl_3$).

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Abstract

β-Amino carbonyl is an important structure in various nitrogen-containing intermediates, including β-lactams, amino alcohols, diamines, β-amino acids etc. In this lab, we have successfully reported aza-Michael reaction with *tert*-butyl benzyloxylcarbamate and electro-deficient olefins with a phase-transfer catalyst. High chemical yield (99%) was achieved via phase-transfer catalysis using 50% aqueous potassium hydroxide as base and toluene as solvent.

In our research, we firstly conducted phase-transfer catalytic aza-Michael reaction with *tert*-butyl benzyloxylcarbamate and 2-cyclohexen-1-one. We could find specific phase-transfer catalyst that shows a high optical yield (87% ee) at 0 ^{o}C. This established phase-transfer catalyst was used to carry out phase-transfer catalytic aza-Michael reactions with 14 types of *tert*-butyl oxycarbamates and 9 cyclic enones.

Finally, high yields (>99%) and high optical yields (98% ee) were obtained when the *tert*-butyl(naphthalene-2-ylmethyl)carbamate and 2-cyclohexen-1-one were used. This is due to the interactions between catalysts and substrates. And we suggest that the following three interactions are involved (Ion-pair interaction, π-π interaction, Hydrogen-bonding interaction).

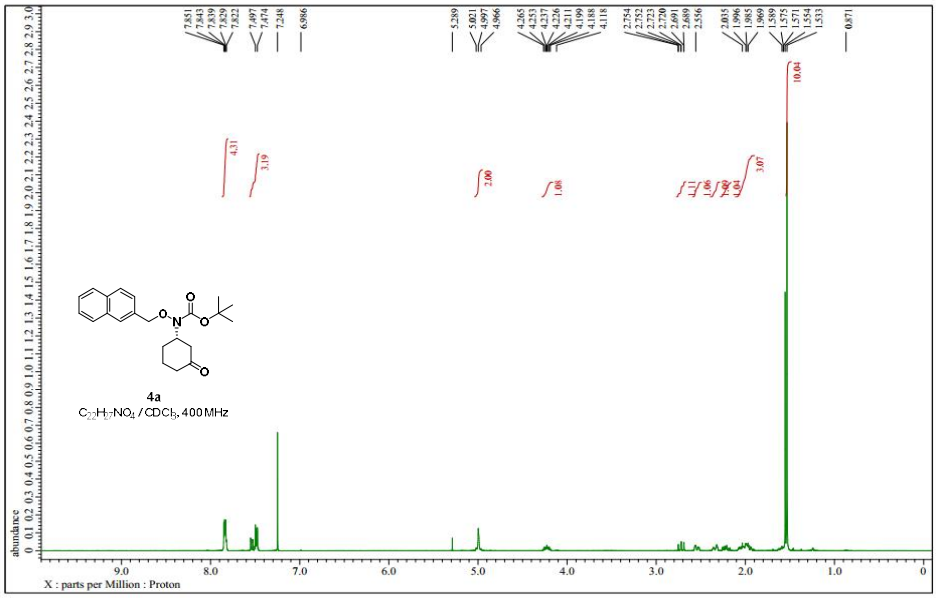
In addition, the selective deprotection, the objective of designing the cyclic chiral β-amino carbonyl structure, in TFA acidic and Pd/C conditions was confirmed. We suggest that it is available as a precursor to natural substances that contain β-amino carbonyl structure.

Key words : asymmetric aza-Michael reaction, chiral cyclic *β*-amino carbonyl-functionality, *tert*-butyl oxycarbamates, Phase-transfer catalysis

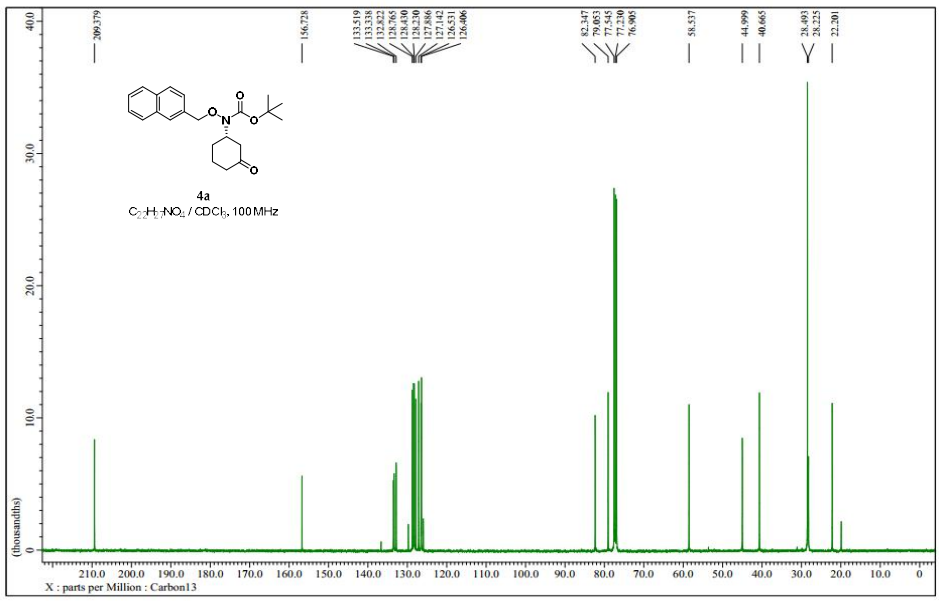
Student Identification Number : 2018-26663

Ⅶ. 부　　록

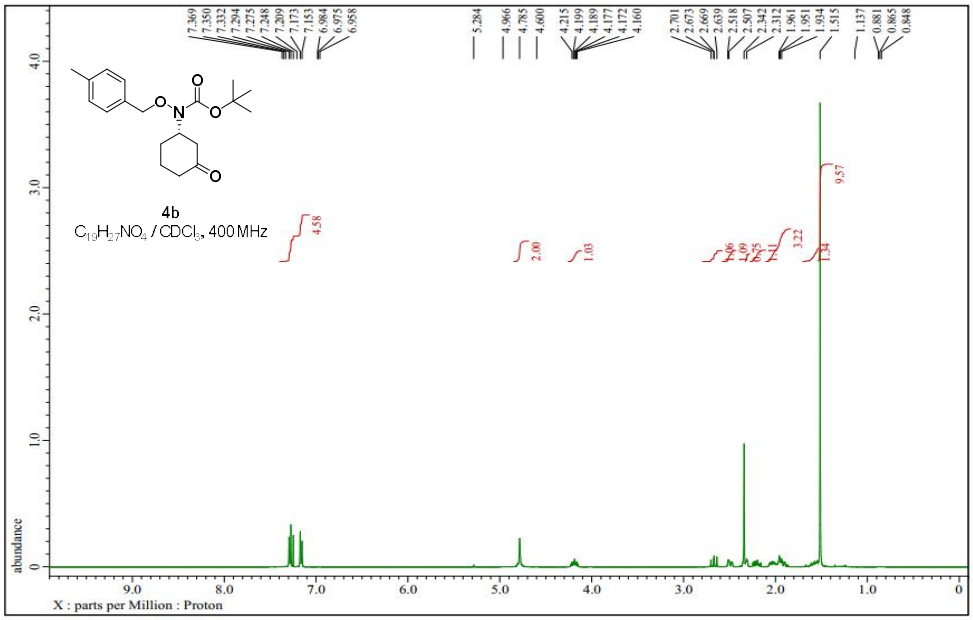
^{1}H-NMR of compound **4a** (400 MHz, $CDCl_3$)



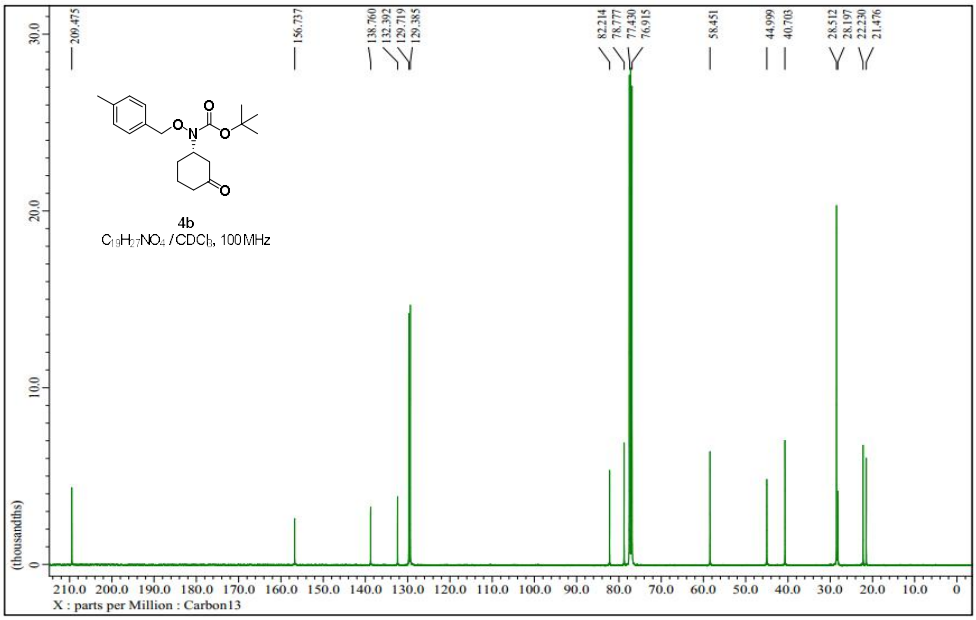
^{13}C-NMR of compound **4a** (100 MHz, $CDCl_3$)



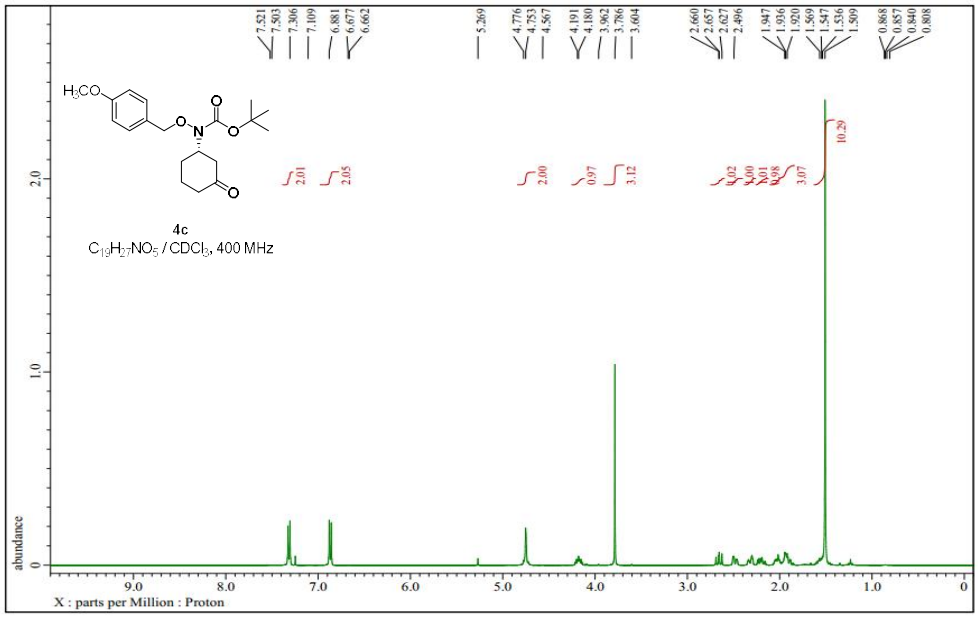
^{1}H-NMR of compound **4b** (400 MHz, $CDCl_3$)



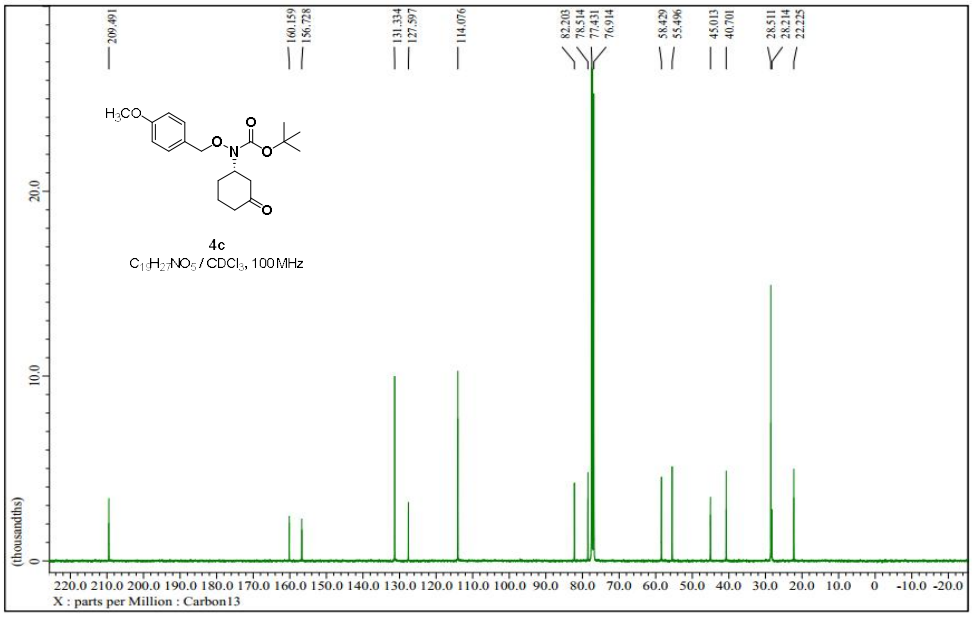
^{13}C-NMR of compound **4b** (100 MHz, $CDCl_3$)



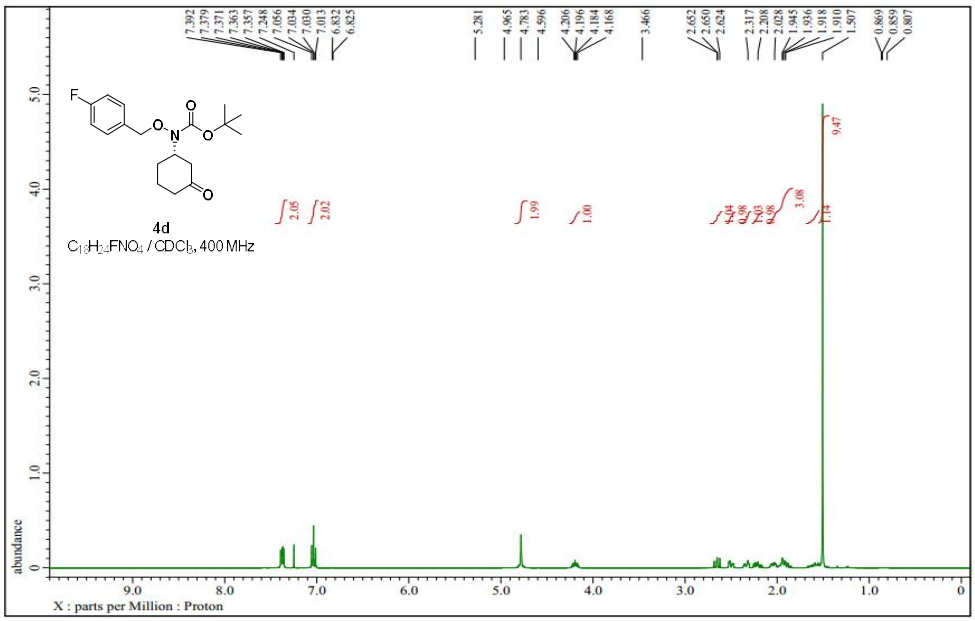
^{1}H-NMR of compound **4c** (400 MHz, $CDCl_3$)



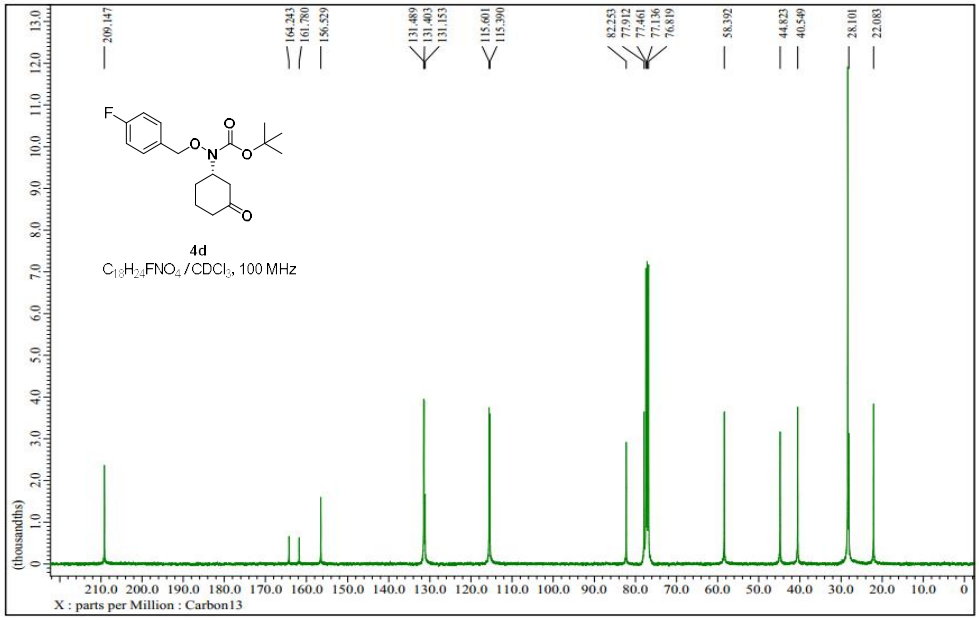
^{13}C-NMR of compound **4c** (100 MHz, $CDCl_3$)



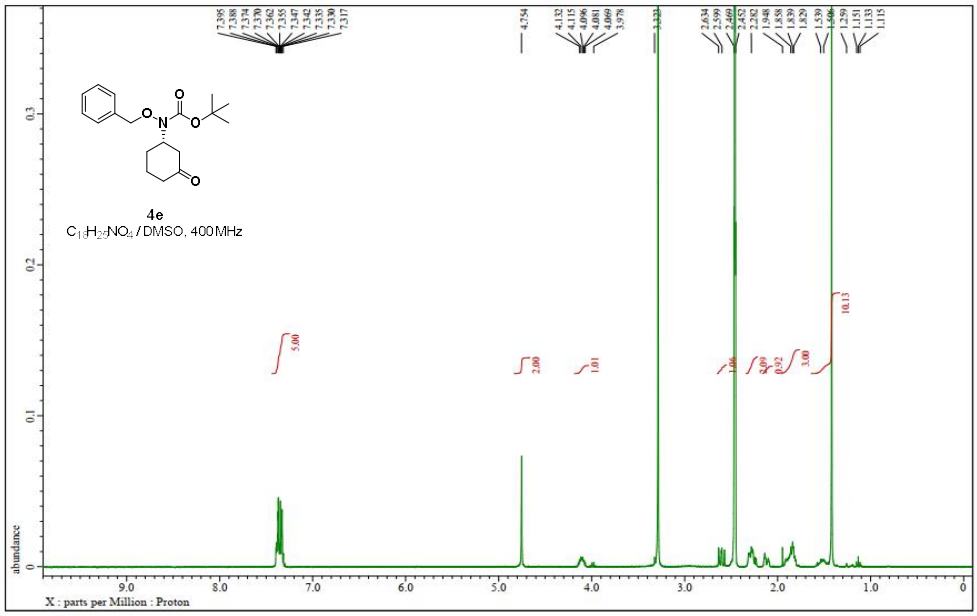
^{1}H-NMR of compound **4d** (400 MHz, $CDCl_3$)



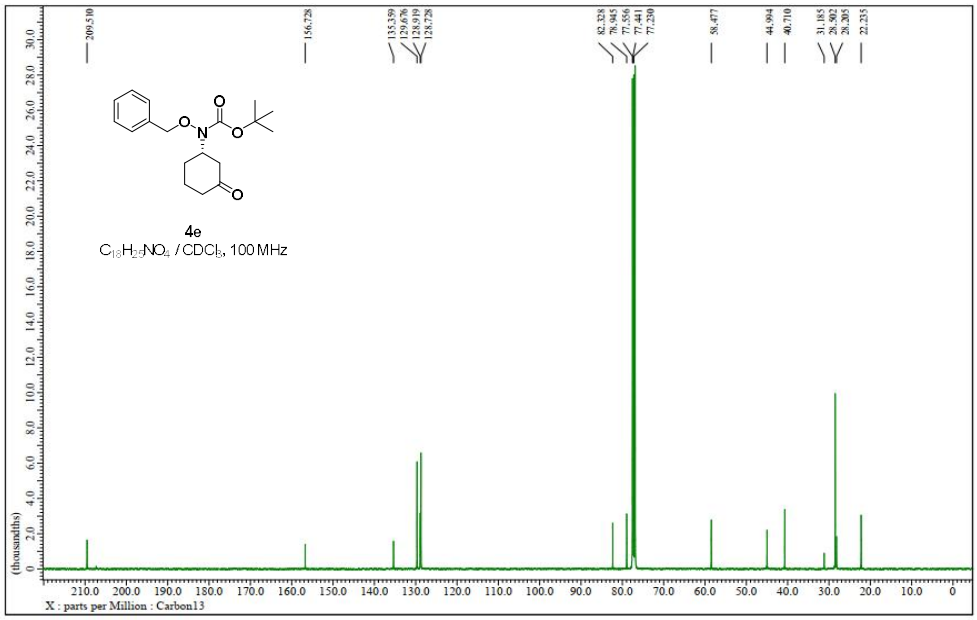
^{13}C-NMR of compound **4d** (100 MHz, $CDCl_3$)



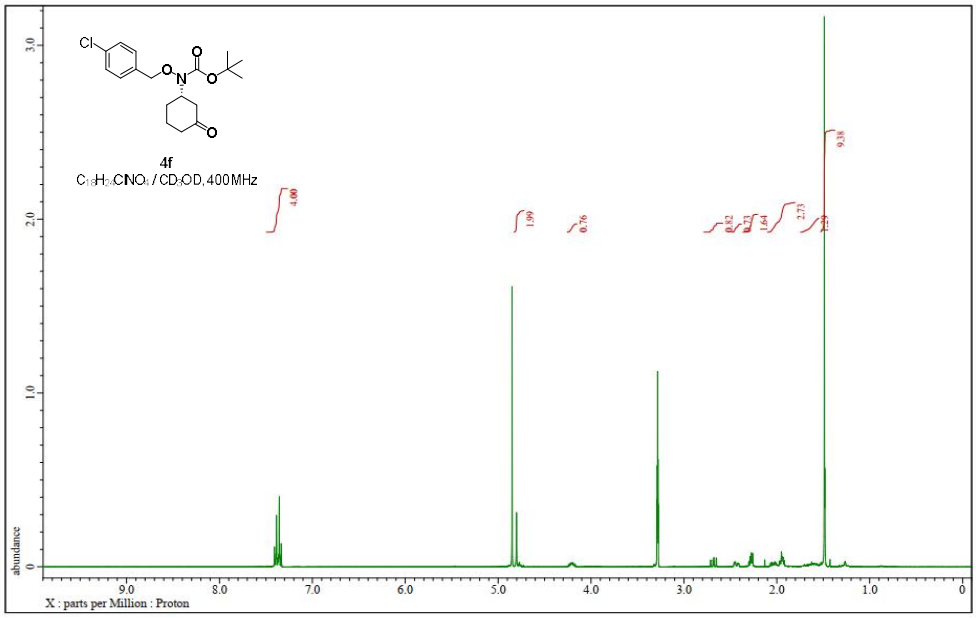
^{1}H-NMR of compound **4e** (400 MHz, DMSO)



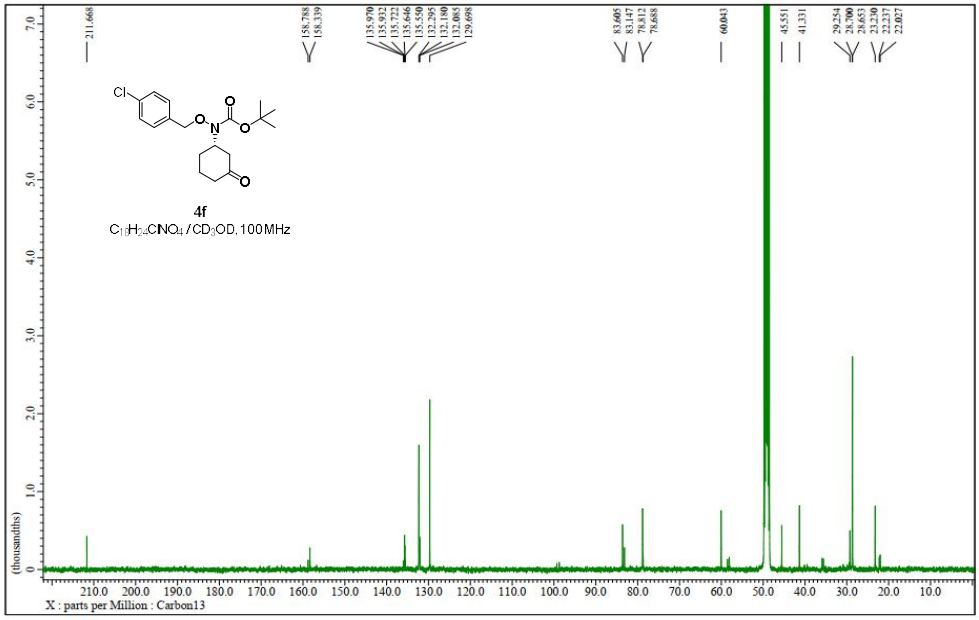
^{13}C-NMR of compound **4e** (100 MHz, $CDCl_3$)



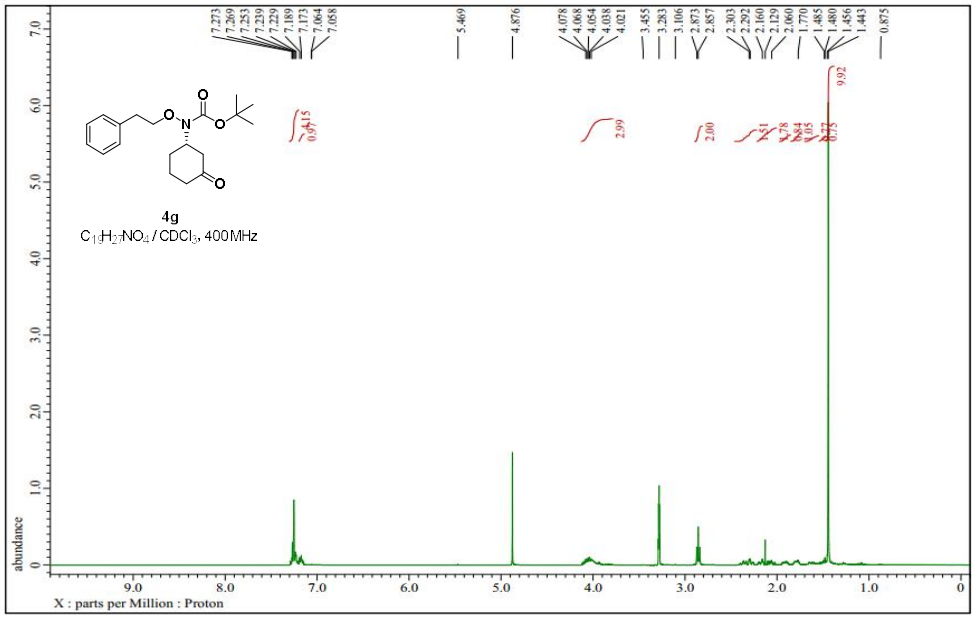
^{1}H-NMR of compound **4f** (400 MHz, CD_3OD)



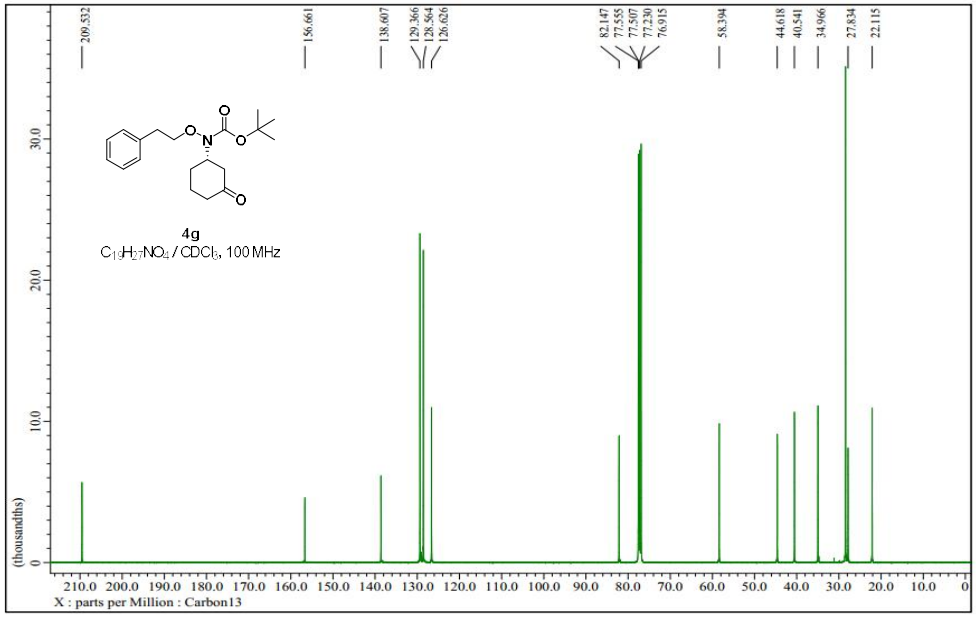
^{13}C-NMR of compound **4f** (100 MHz, CD_3OD)



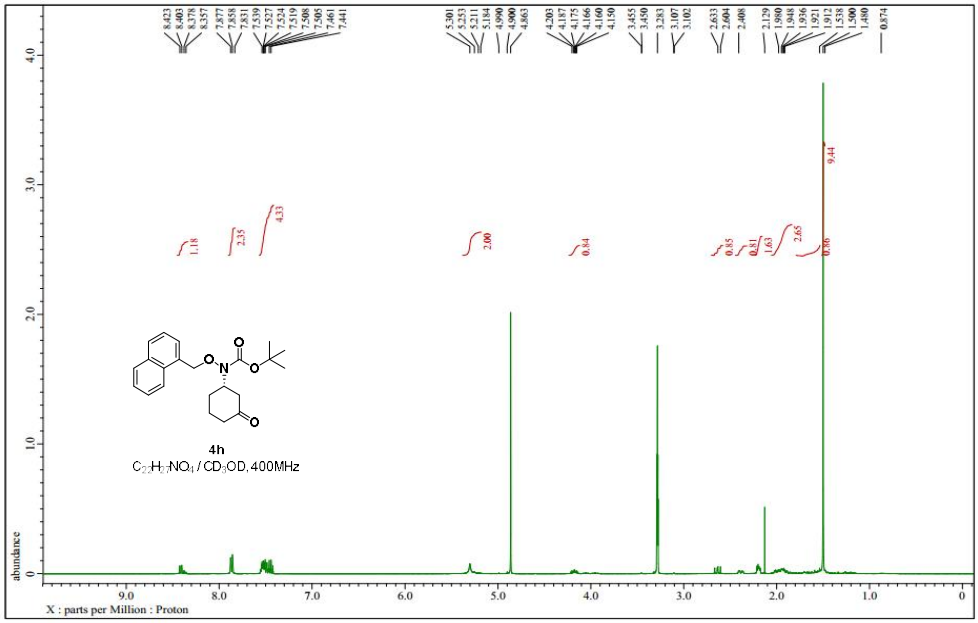
^{1}H-NMR of compound **4g** (400 MHz, $CDCl_3$)



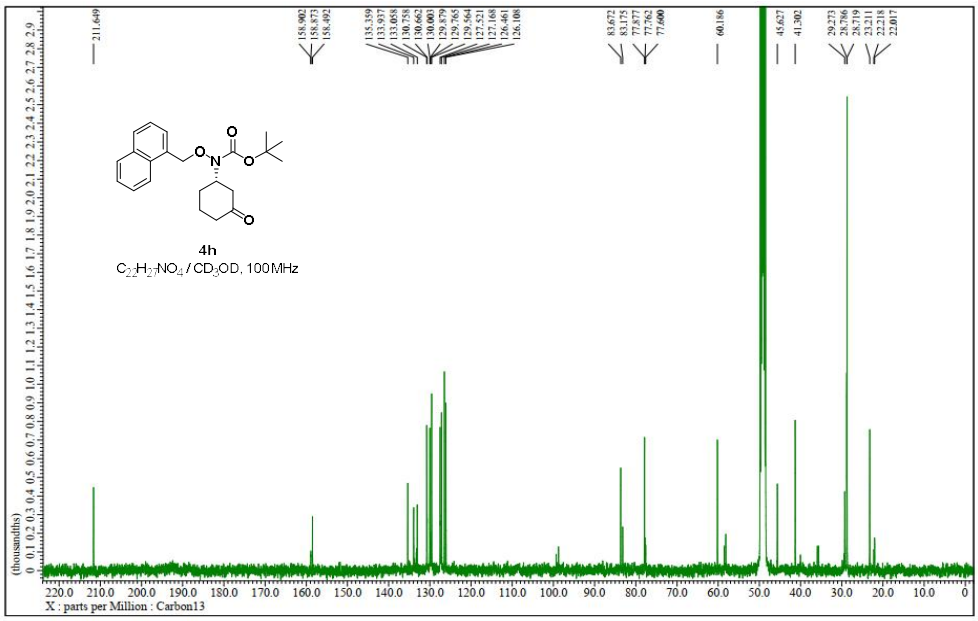
^{13}C-NMR of compound **4g** (100 MHz, $CDCl_3$)



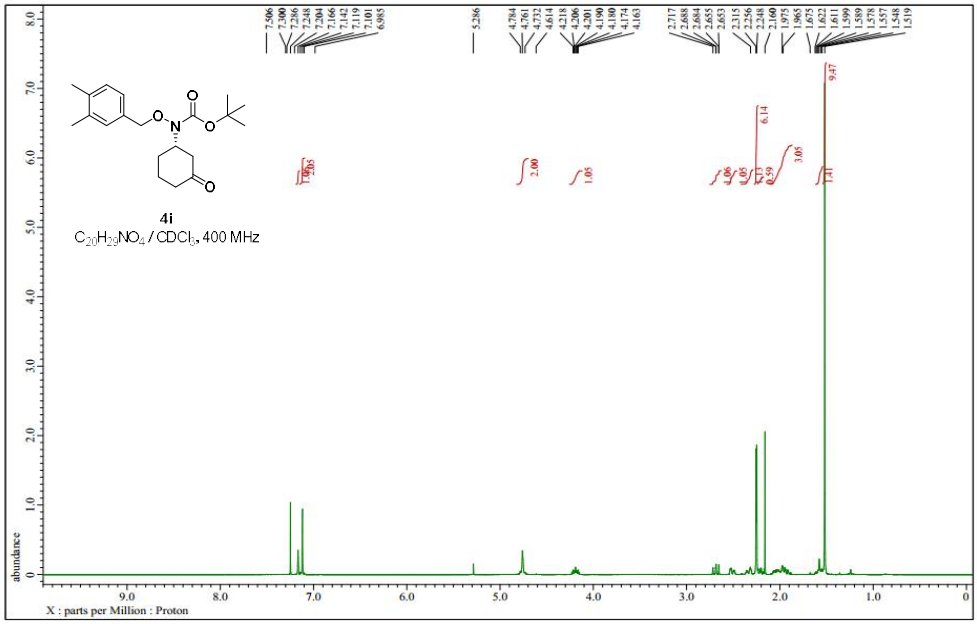
^{1}H-NMR of compound **4h** (400 MHz, CD_3OD)



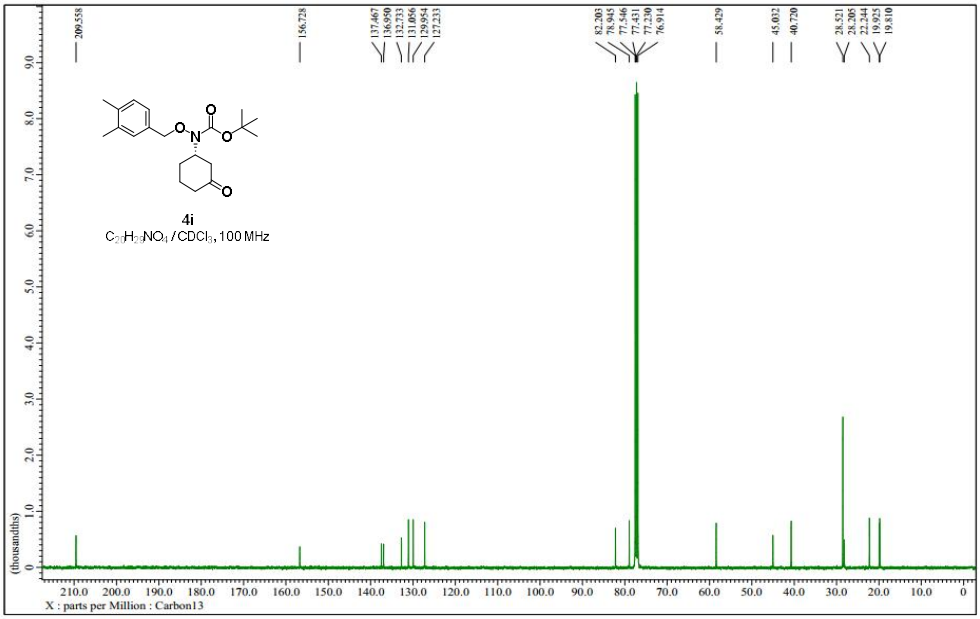
^{13}C-NMR of compound **4h** (100 MHz, CD_3OD)



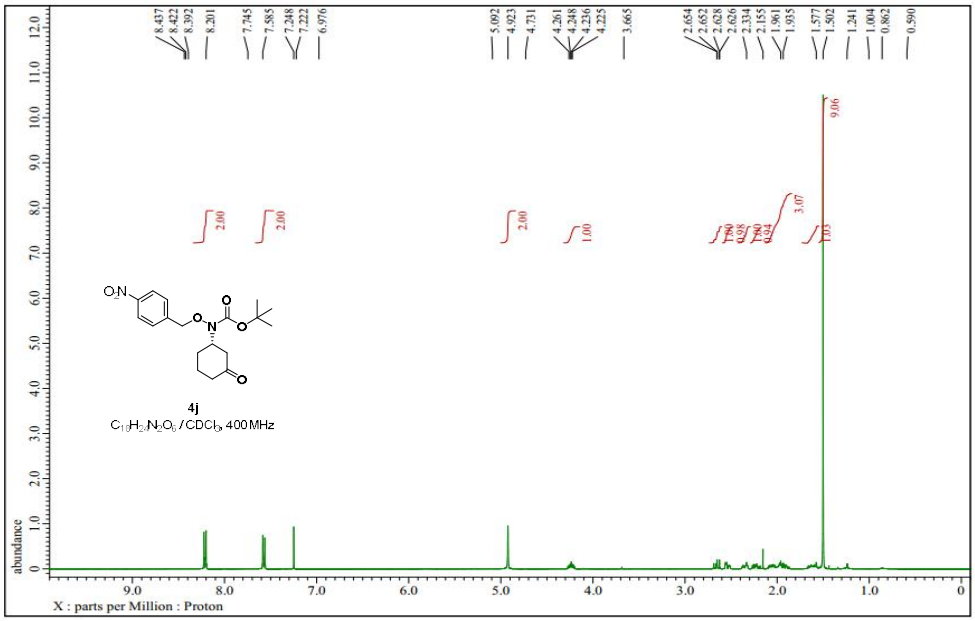
^{1}H-NMR of compound **4i** (400 MHz, $CDCl_3$)



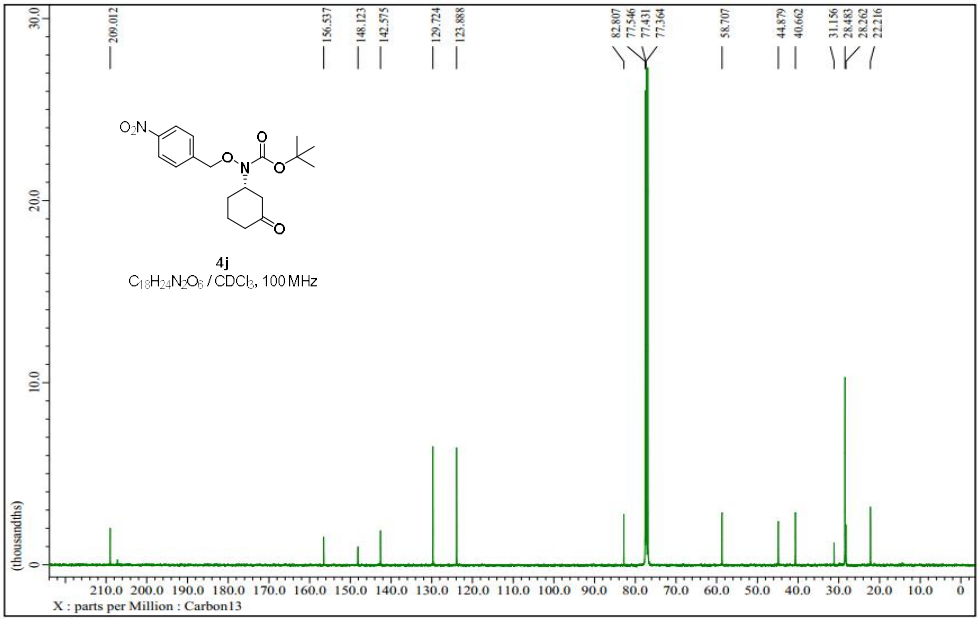
^{13}C-NMR of compound **4i** (100 MHz, $CDCl_3$)



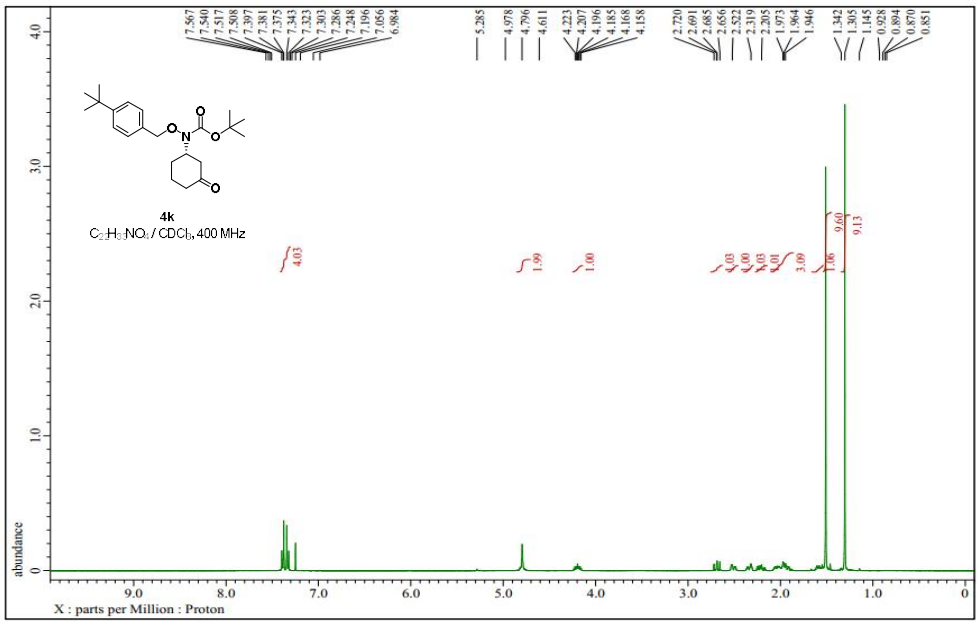
^{1}H-NMR of compound **4j** (400 MHz, $CDCl_3$)



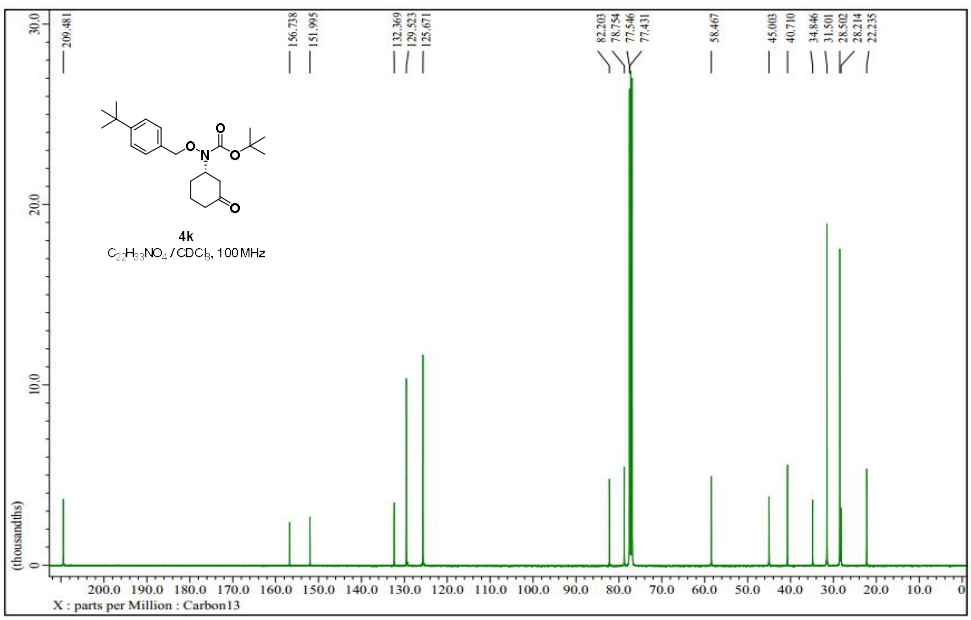
^{13}C-NMR of compound **4j** (100 MHz, $CDCl_3$)



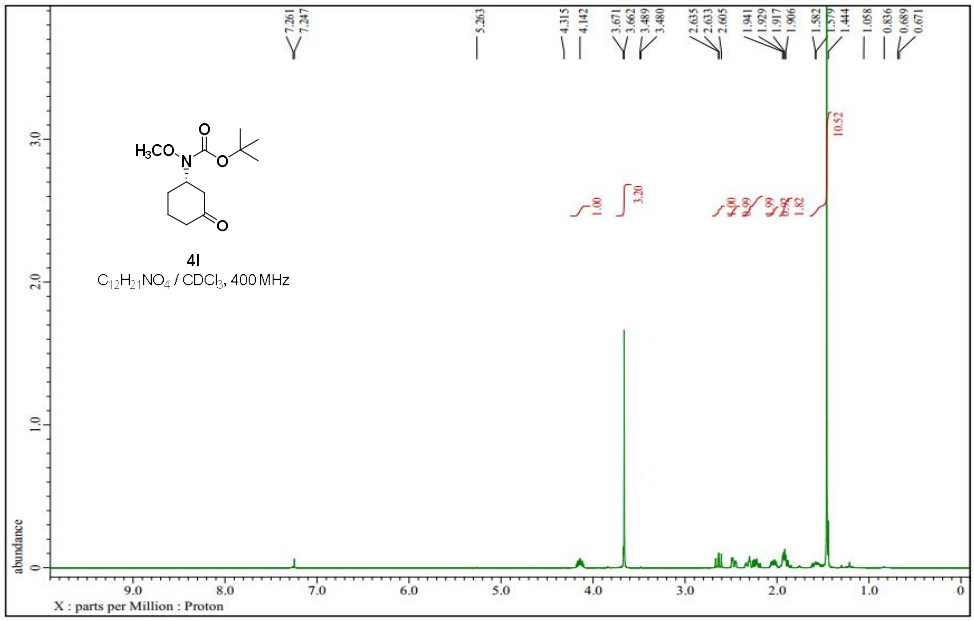
^{1}H-NMR of compound **4k** (400 MHz, $CDCl_3$)



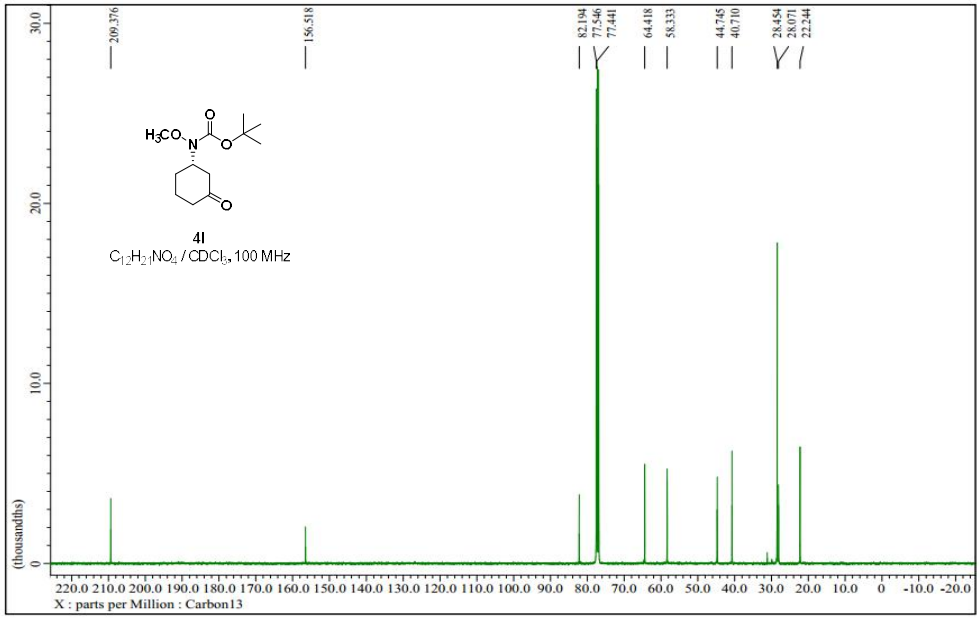
^{13}C-NMR of compound **4k** (100 MHz, $CDCl_3$)



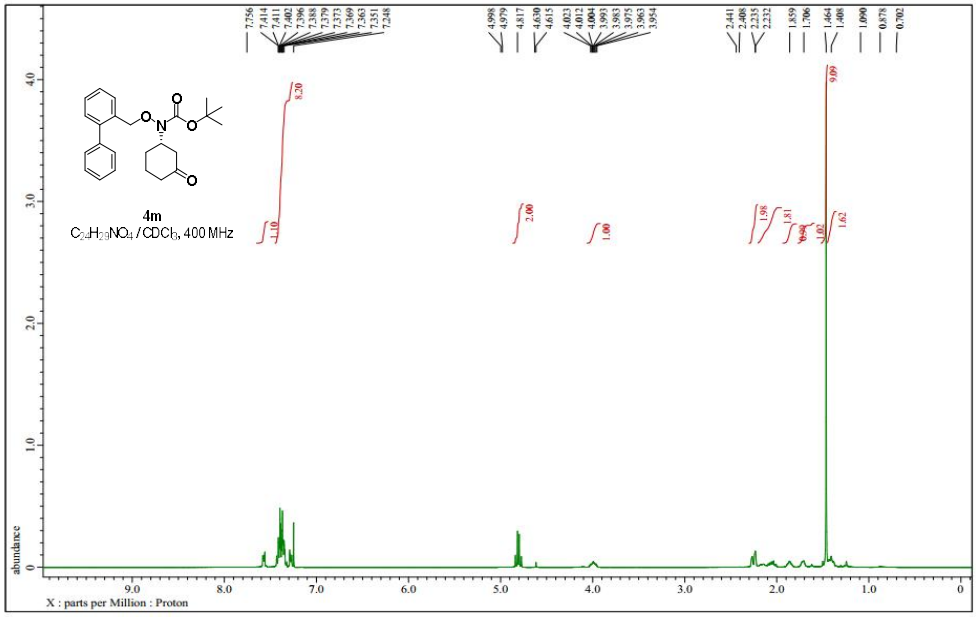
^{1}H-NMR of compound **4l** (400 MHz, $CDCl_3$)



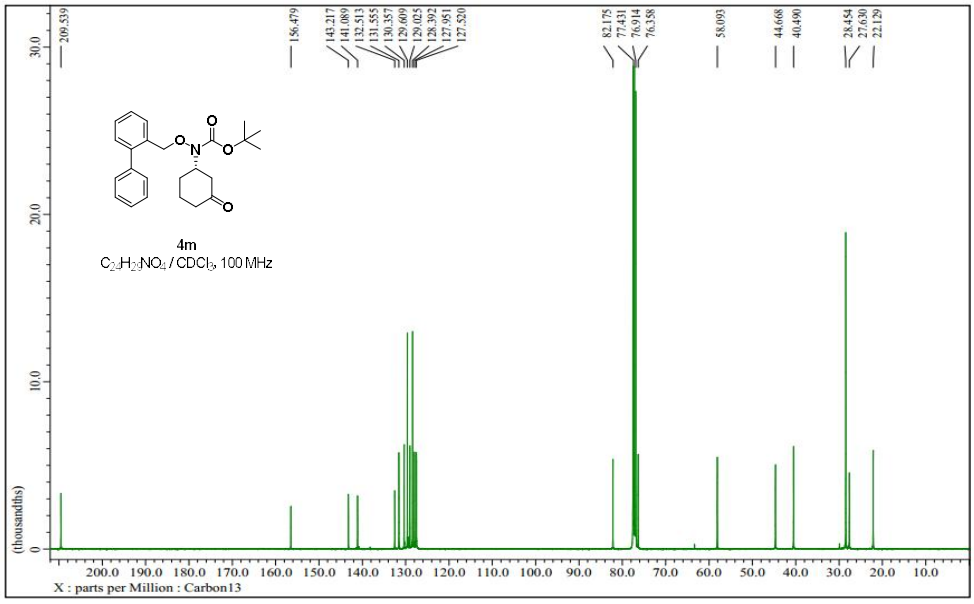
^{13}C-NMR of compound **4l** (100 MHz, $CDCl_3$)



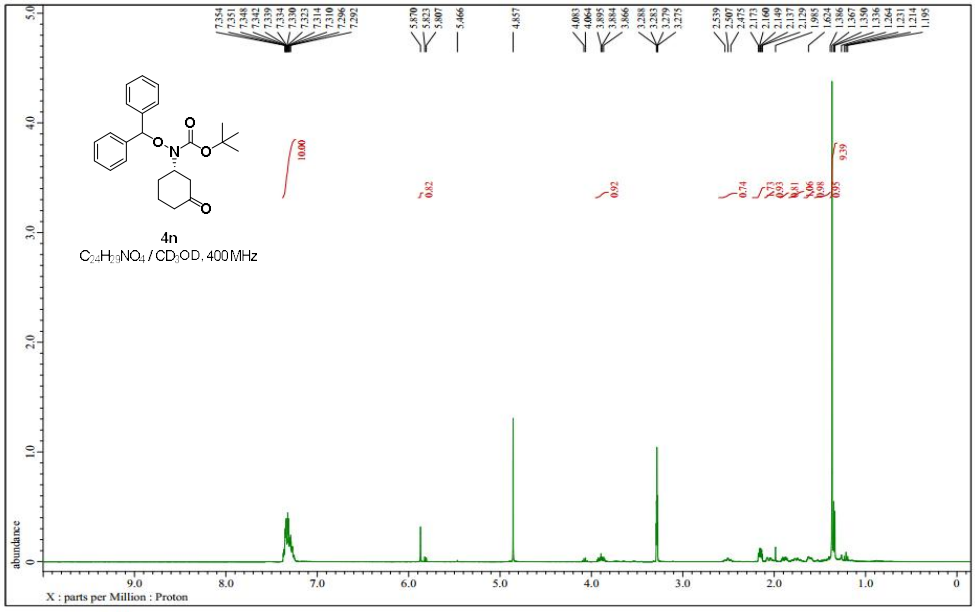
^{1}H-NMR of compound **4m** (400 MHz, $CDCl_3$)



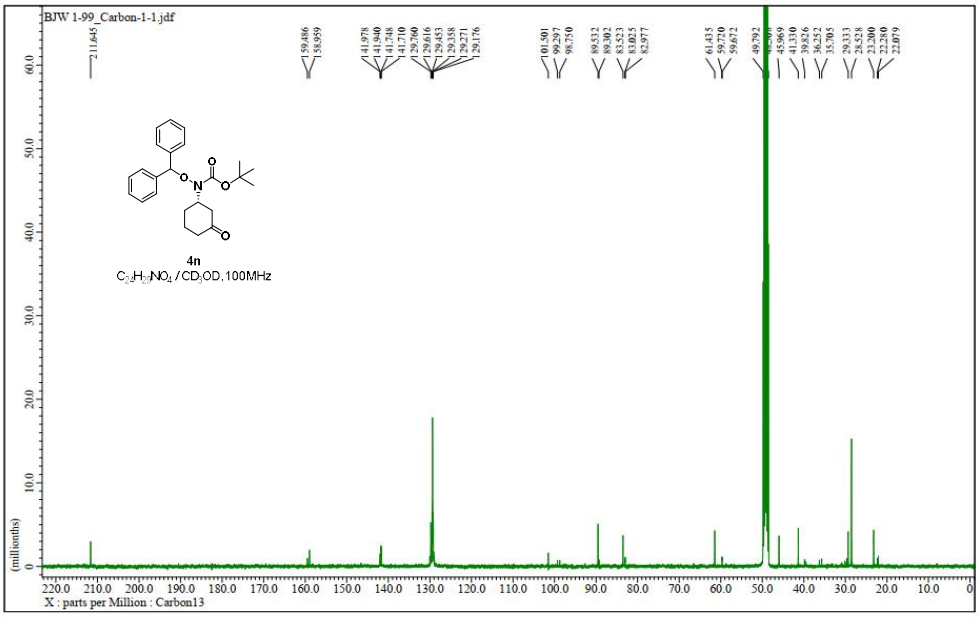
^{13}C-NMR of compound **4m** (100 MHz, $CDCl_3$)



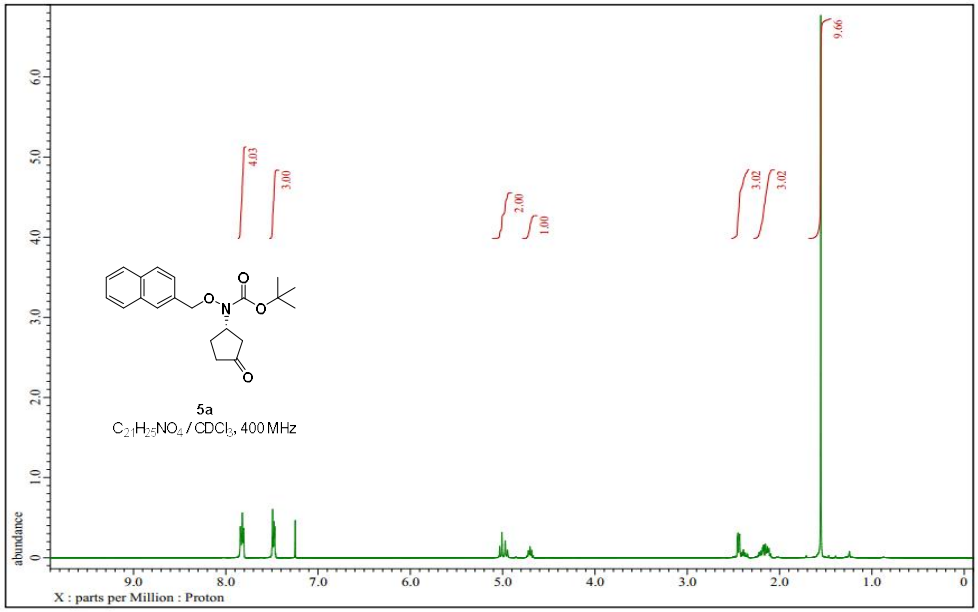
^{1}H-NMR of compound **4n** (400 MHz, CD_3OD)



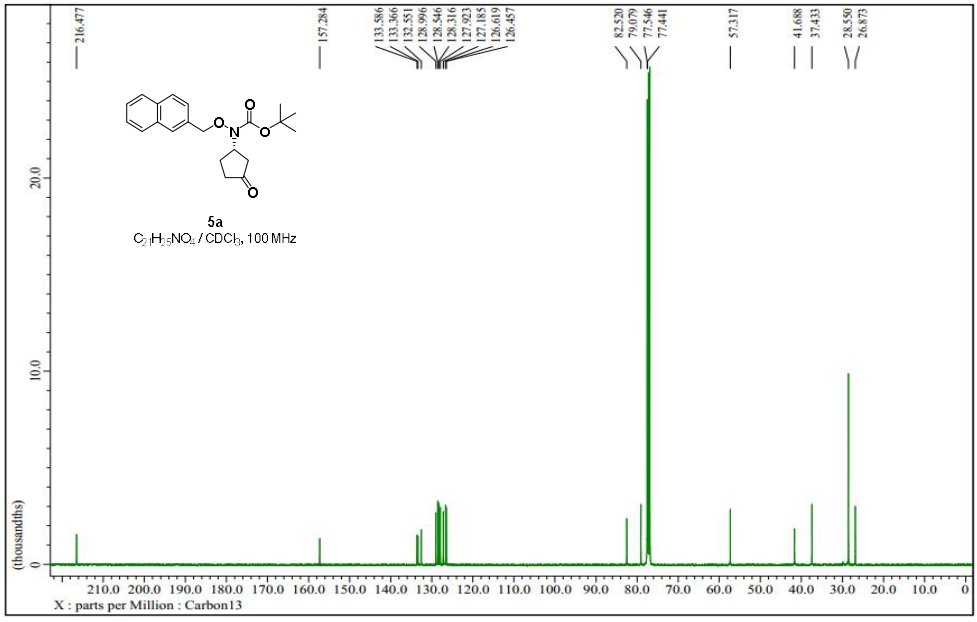
^{13}C-NMR of compound **4n** (100 MHz, CD_3OD)



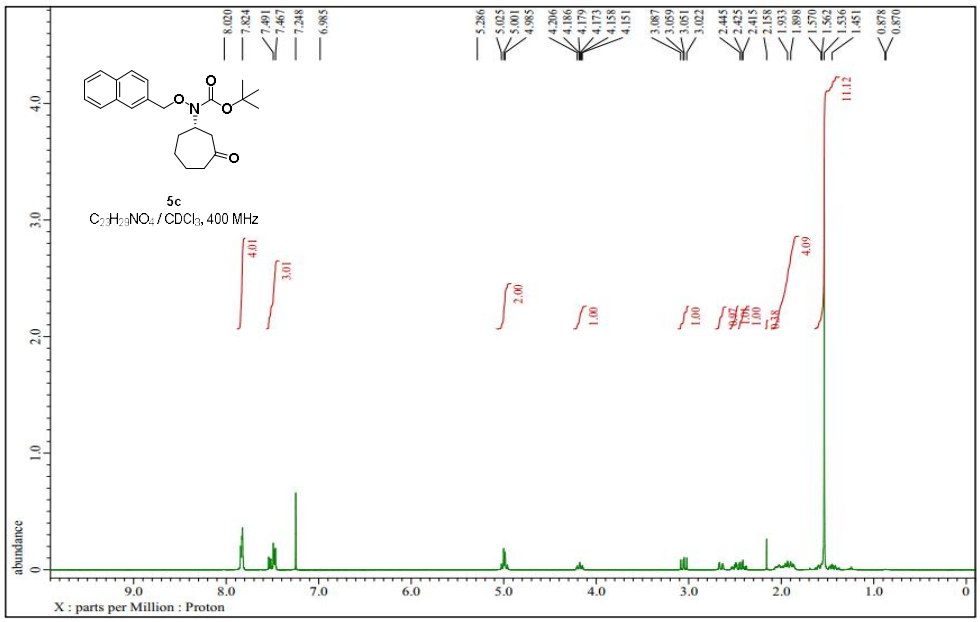
^{1}H-NMR of compound **5a** (400 MHz, $CDCl_3$)



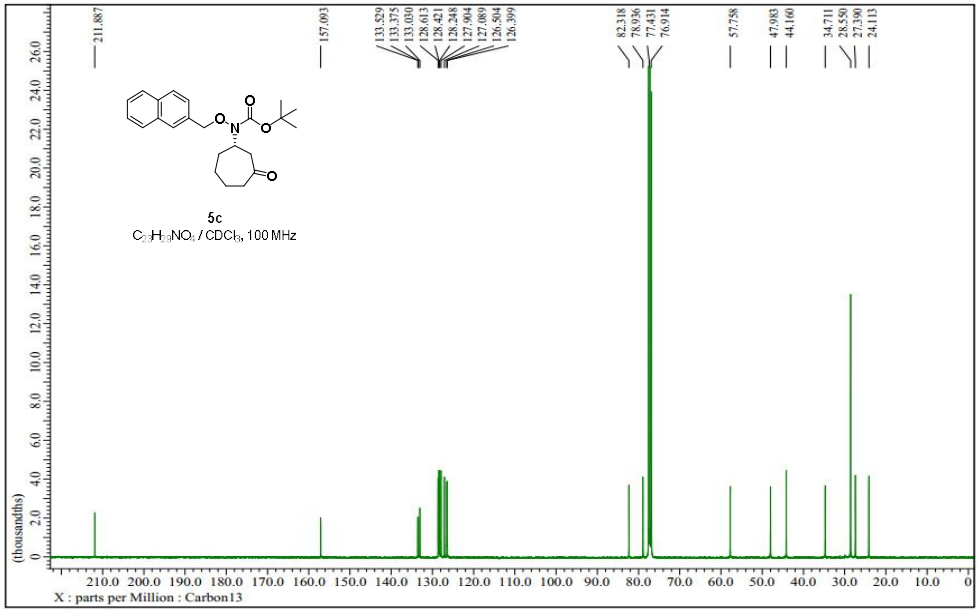
^{13}C-NMR of compound **5a** (100 MHz, $CDCl_3$)



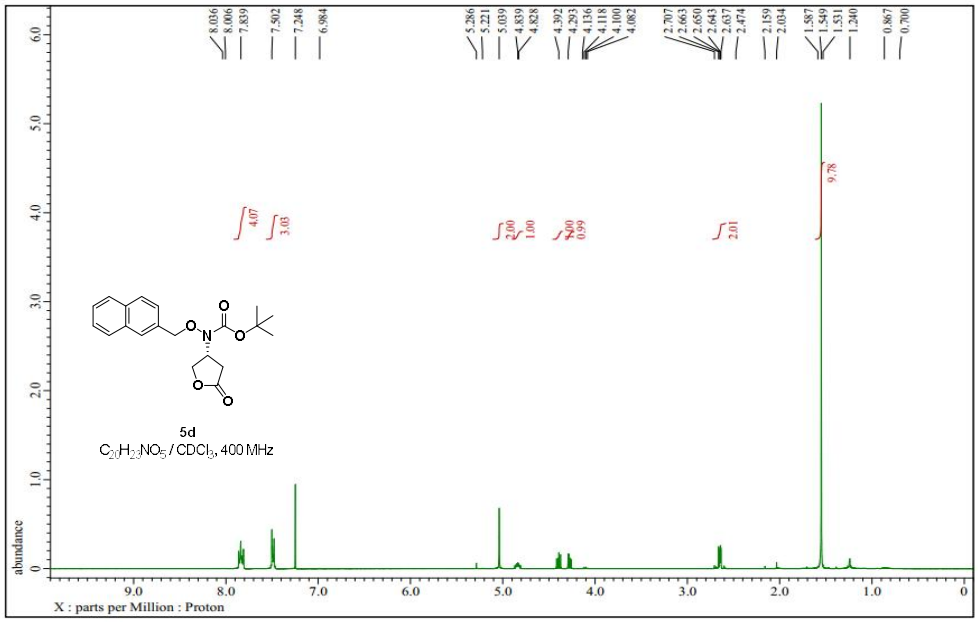
^{1}H-NMR of compound **5c** (400 MHz, $CDCl_3$)



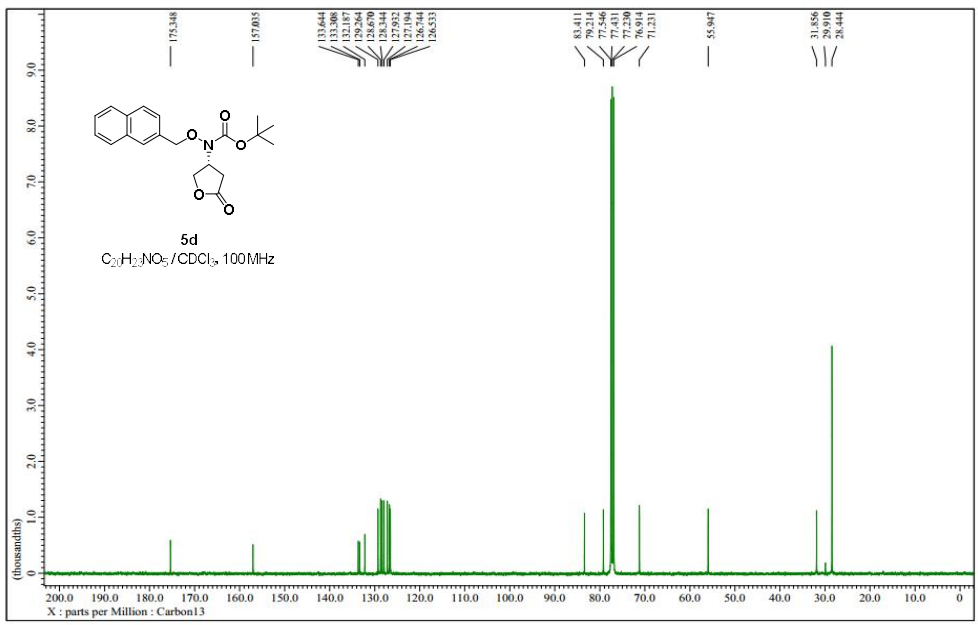
^{13}C-NMR of compound **5c** (100 MHz, $CDCl_3$)



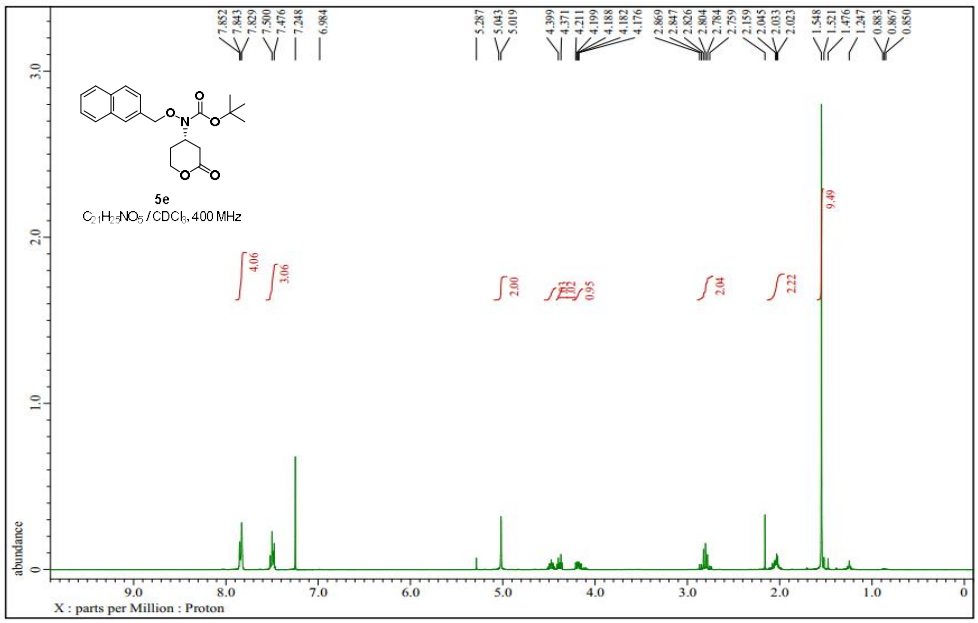
^{1}H-NMR of compound **5d** (400 MHz, $CDCl_3$)



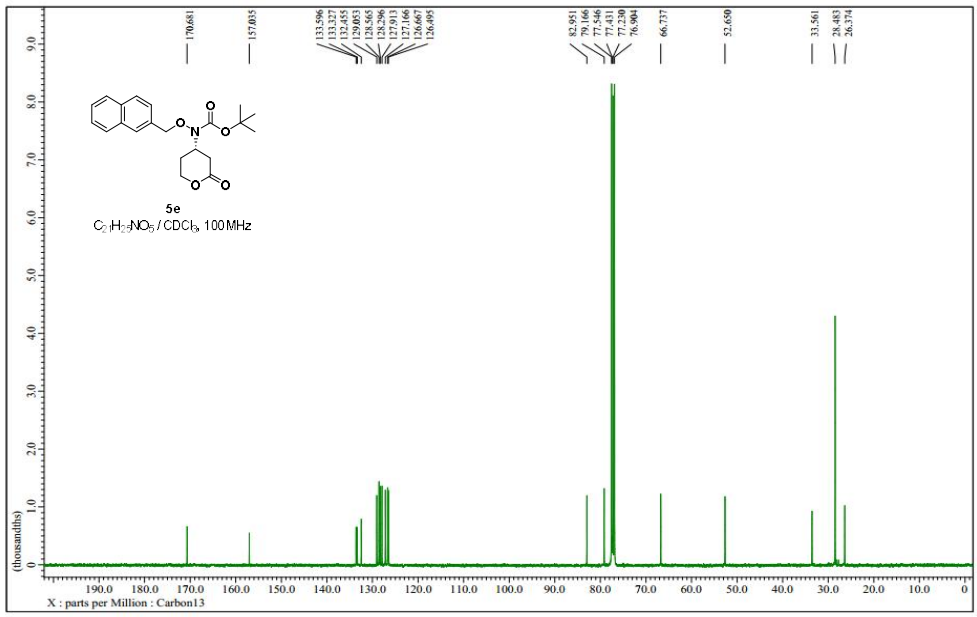
^{13}C-NMR of compound **5d** (100 MHz, $CDCl_3$)



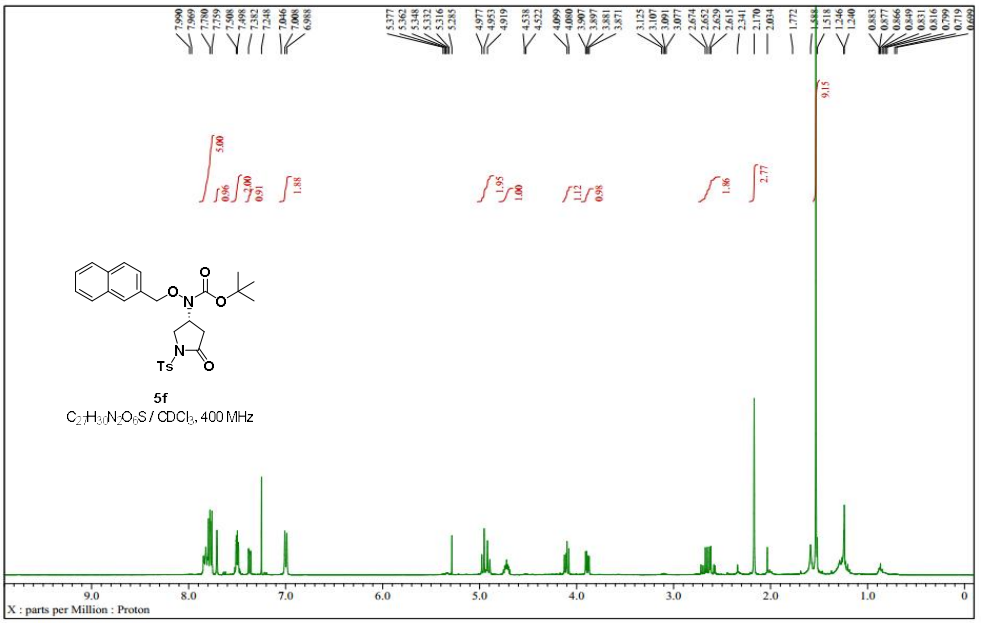
^{1}H-NMR of compound **5e** (400 MHz, $CDCl_3$)



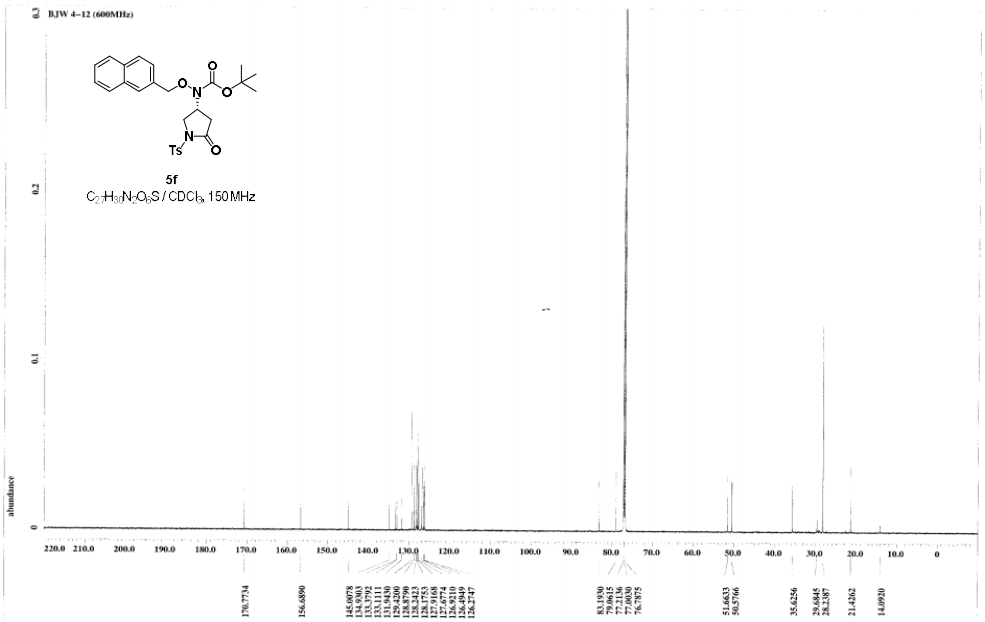
^{13}C-NMR of compound **5e** (100 MHz, $CDCl_3$)



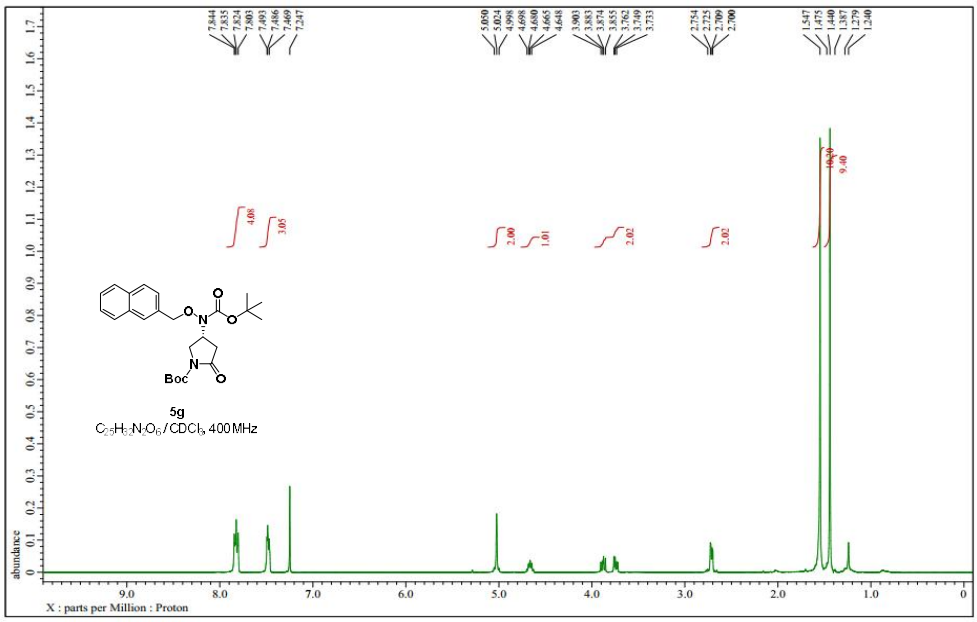
^{1}H-NMR of compound **5f** (400 MHz, $CDCl_3$)



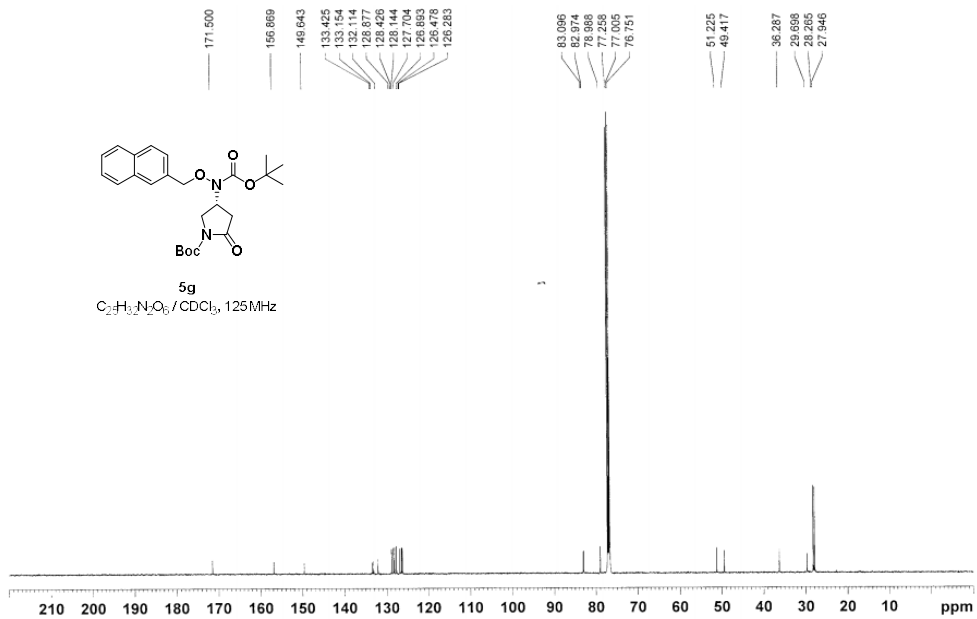
^{13}C-NMR of compound **5f** (150 MHz, $CDCl_3$)



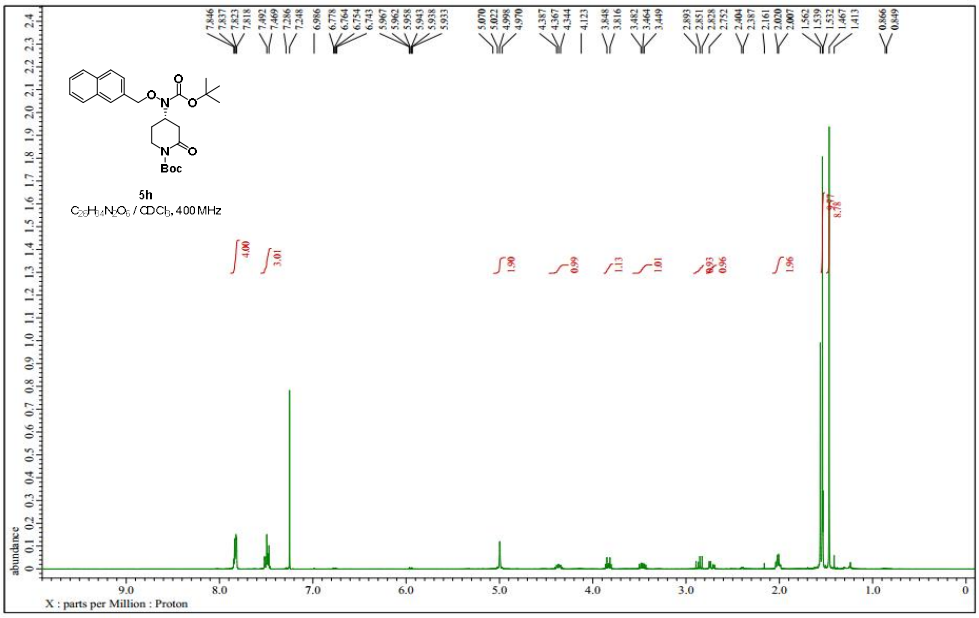
^{1}H-NMR of compound **5g** (400 MHz, $CDCl_3$)



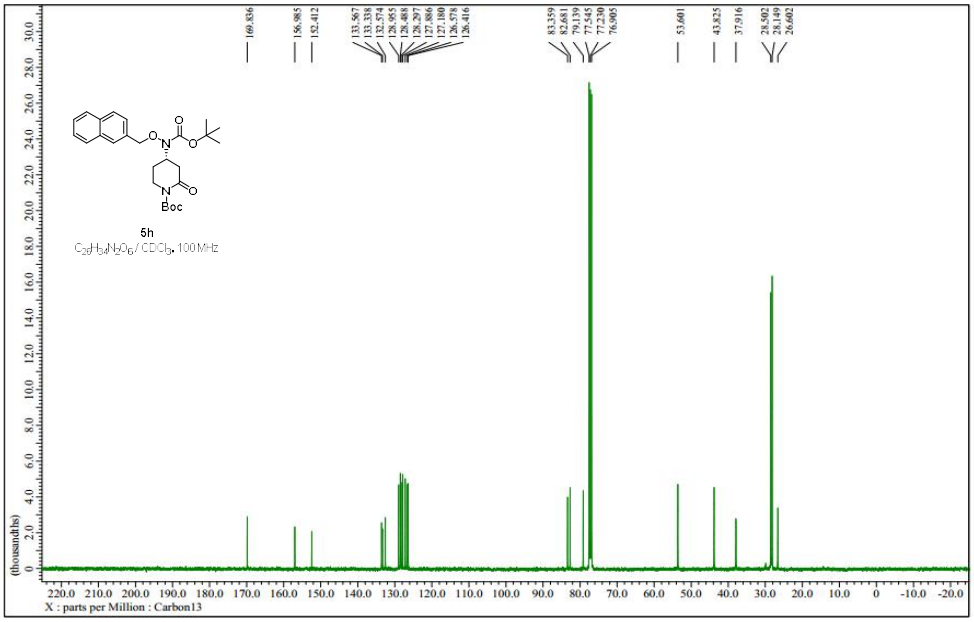
^{13}C-NMR of compound **5g** (125 MHz, $CDCl_3$)



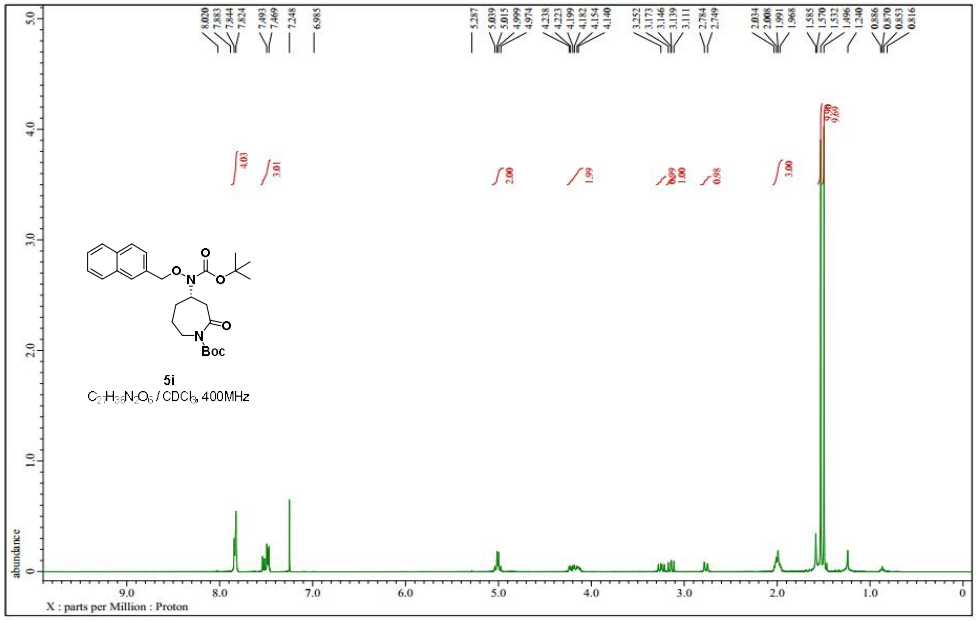
^{1}H-NMR of compound **5h** (400 MHz, $CDCl_3$)



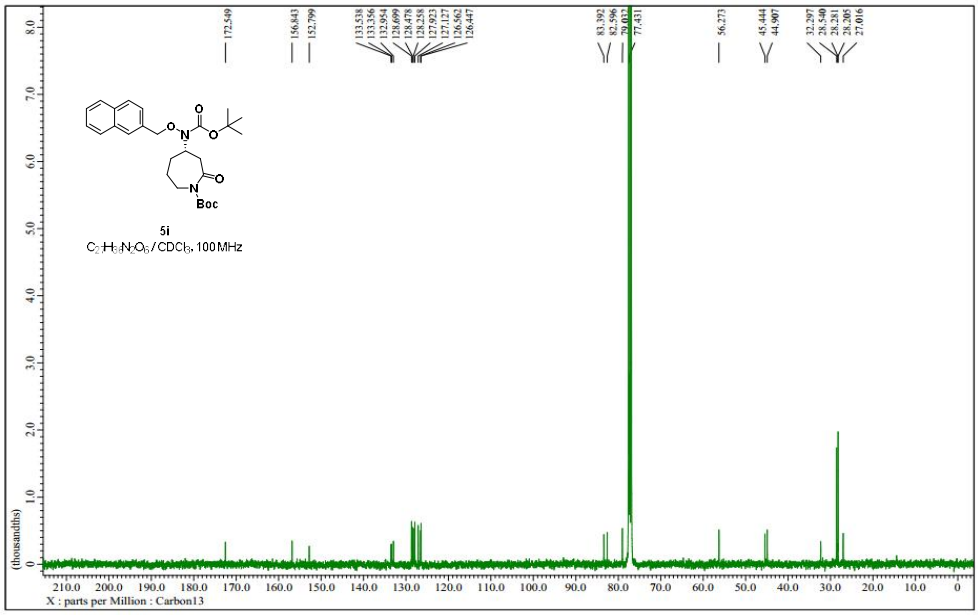
^{13}C-NMR of compound **5h** (100 MHz, $CDCl_3$)



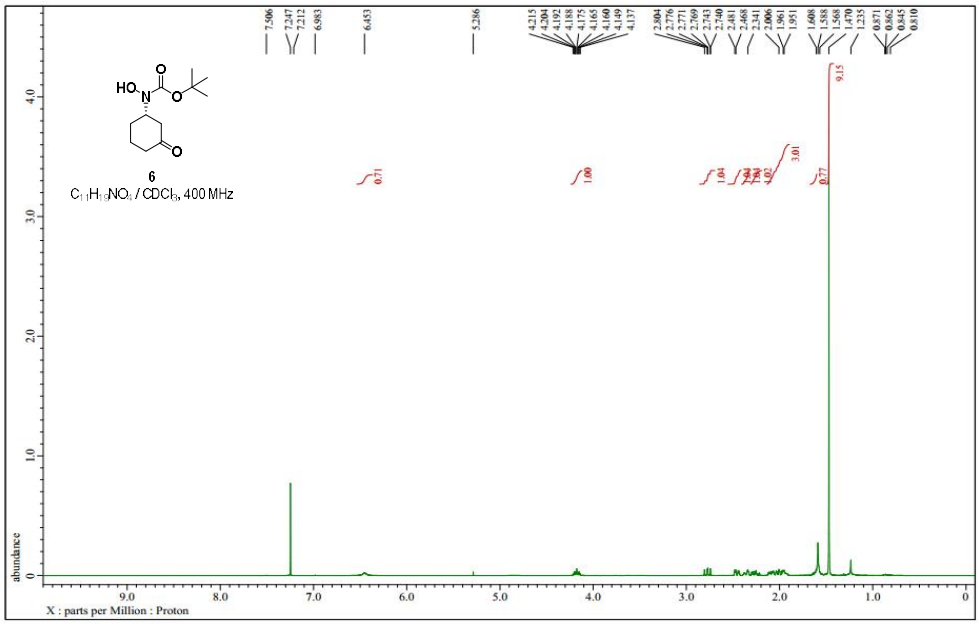
^{1}H-NMR of compound **5i** (400 MHz, $CDCl_3$)



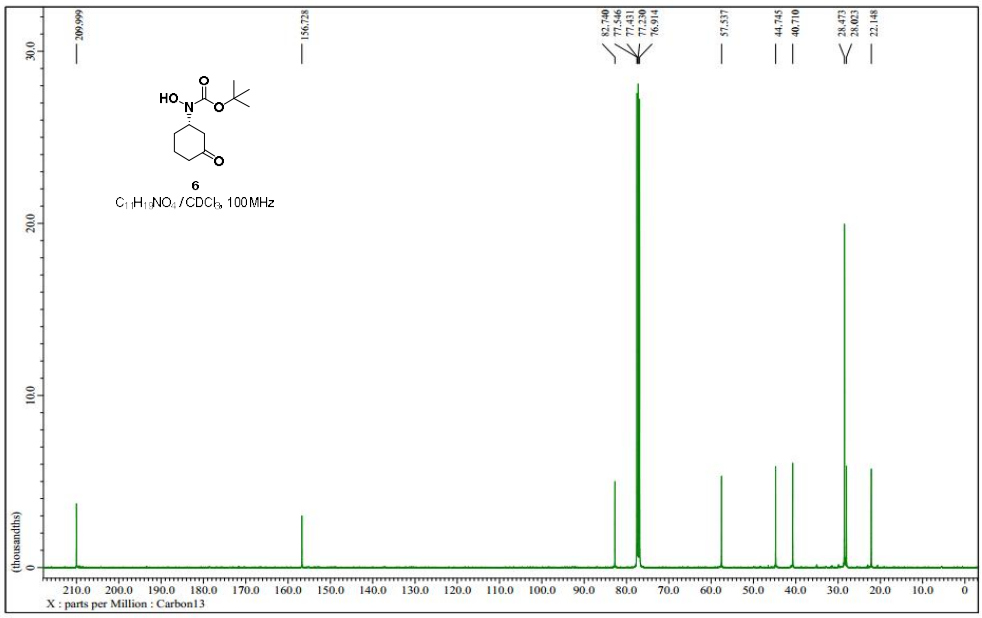
^{13}C-NMR of compound **5i** (100 MHz, $CDCl_3$)



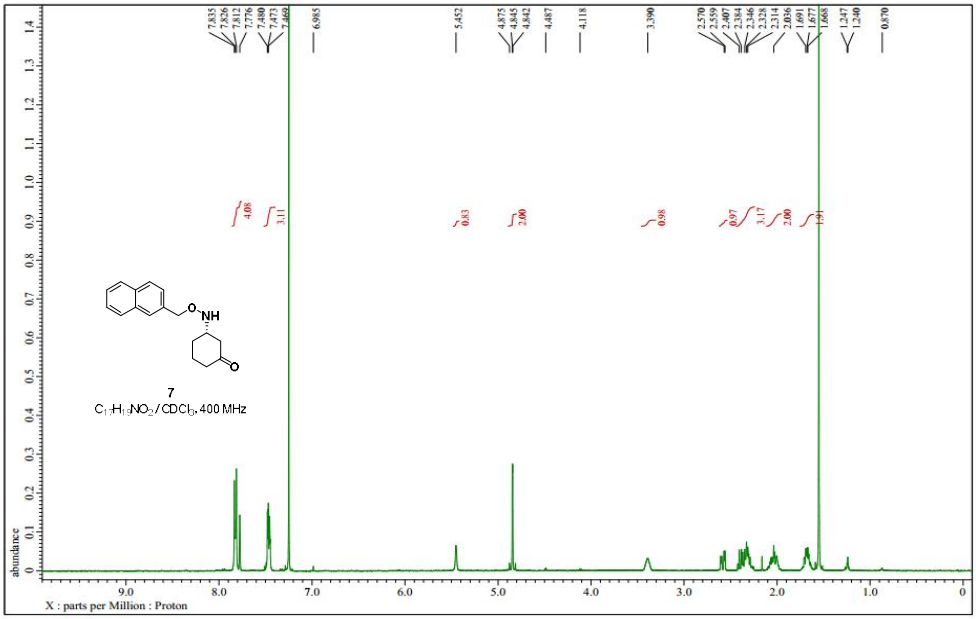
^{1}H-NMR of compound **6** (400 MHz, $CDCl_3$)



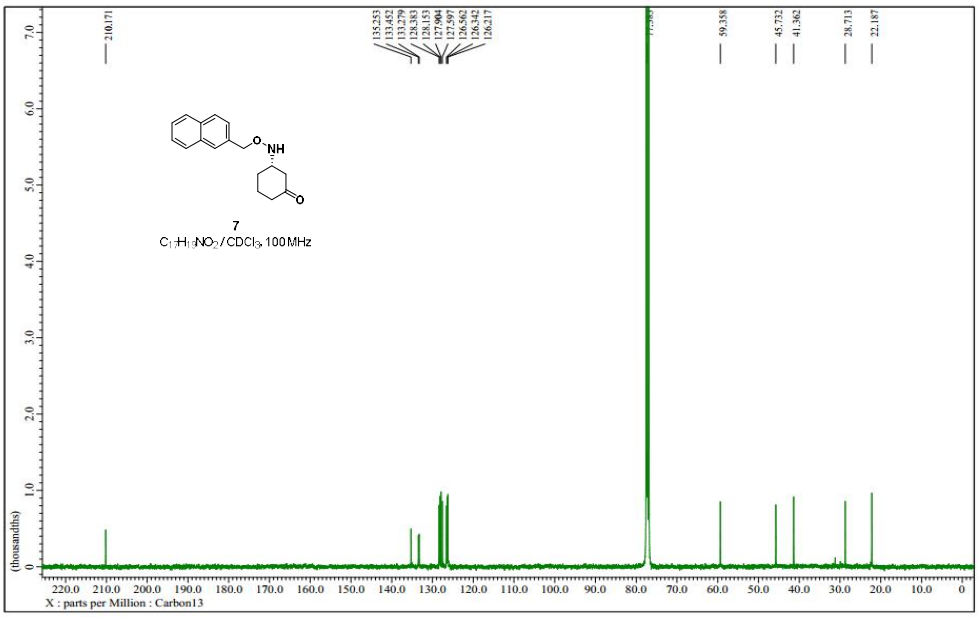
^{13}C-NMR of compound **6** (100 MHz, $CDCl_3$)



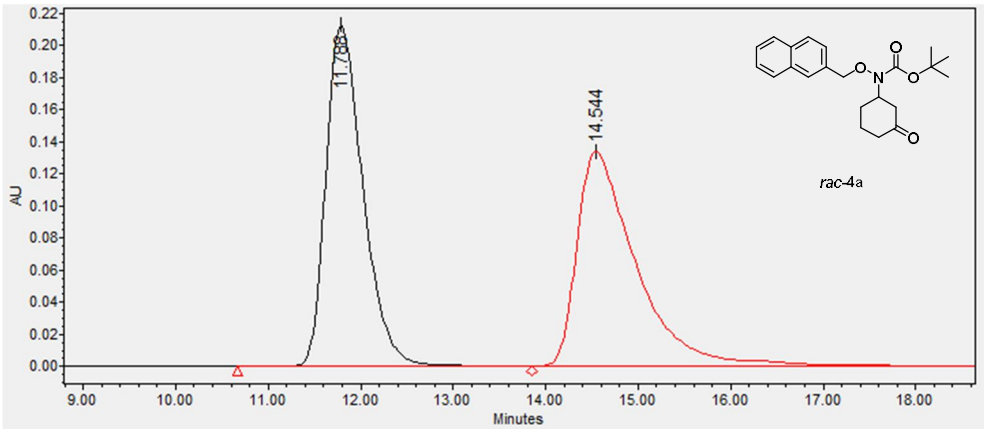
^{1}H-NMR of compound **7** (400 MHz, $CDCl_3$)



^{13}C-NMR of compound **7** (100 MHz, $CDCl_3$)

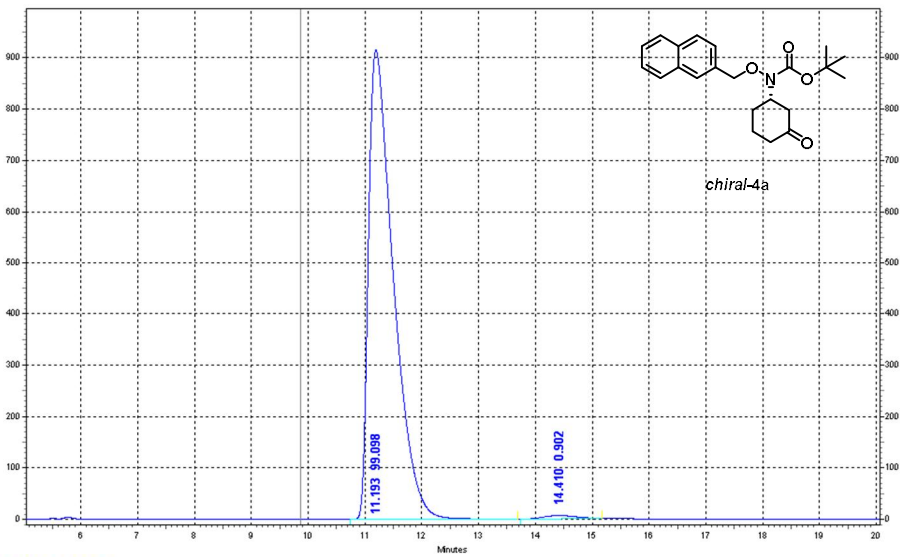


HPLC Graph of ***rac*-4a**



	RT	Area	% Area	Height
1	11.613	5119609	50.02	192377
2	14.297	5116413	49.98	119642

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

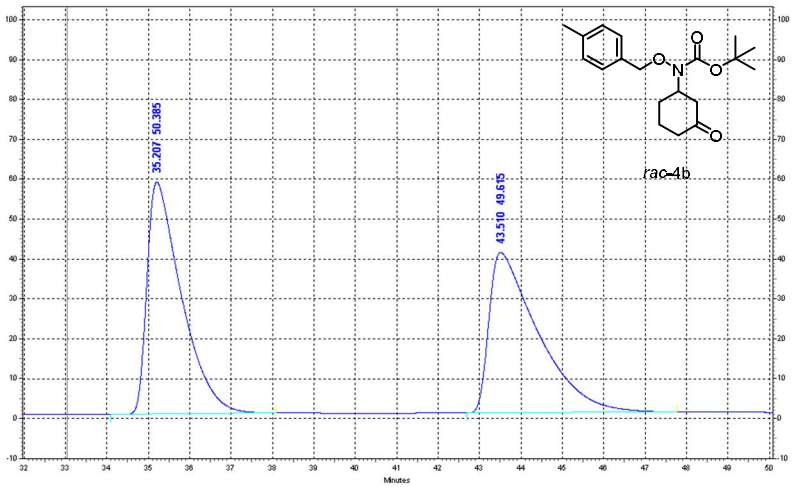


UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	11.193	110793655	99.098	BB
	14.410	1008122	0.902	BI

Totals		111801777	100.000

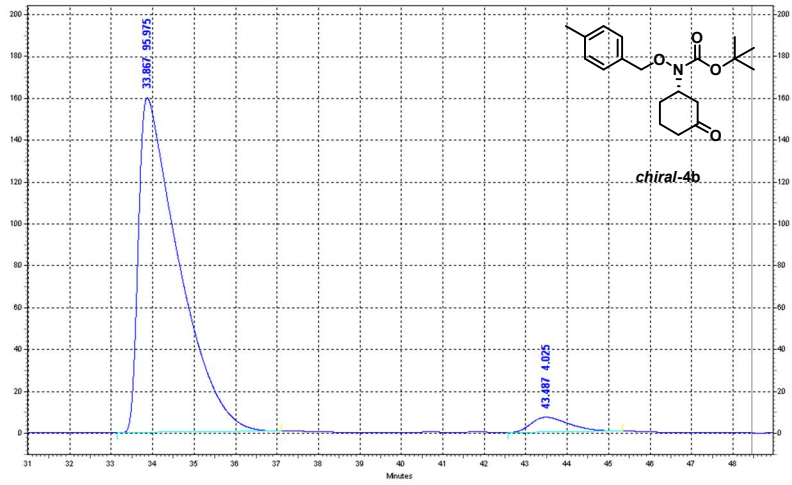
HPLC Graph of ***rac*-4b**



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	35.207	13457719	50.385	MM
	43.510	13251834	49.615	MM
Totals		26709553	100.000	

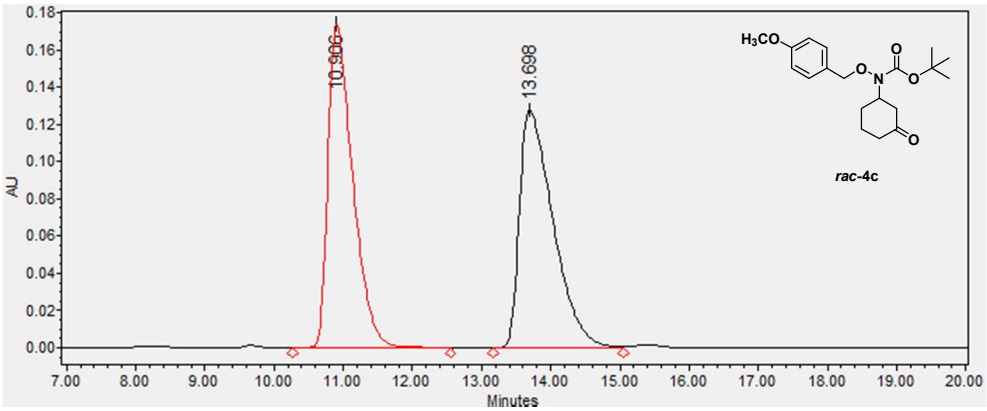
HPLC Graph of ***chiral*-4b**



UV Results

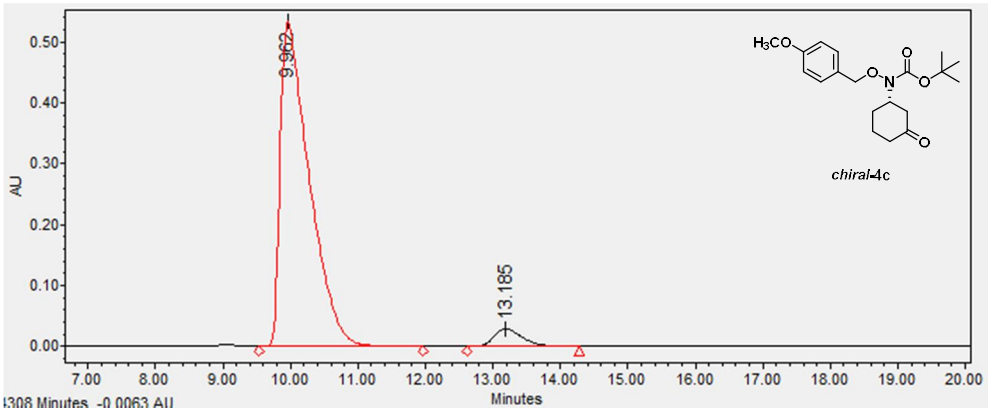
Name	Retention Time	Area	Area Percent	Integration Codes
	33.867	43016181	95.975	MM
	43.487	1804218	4.025	MM
Totals		44820399	100.000	

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



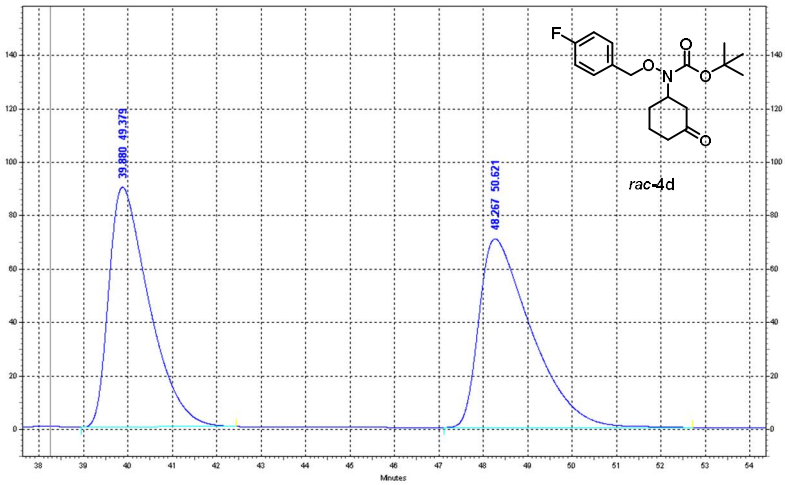
	RT	Area	% Area	Height
1	10.906	4320554	49.98	173895
2	13.698	4323365	50.02	128205

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



	RT	Area	% Area	Height
1	9.962	15841323	95.10	532368
2	13.185	815922	4.90	28704

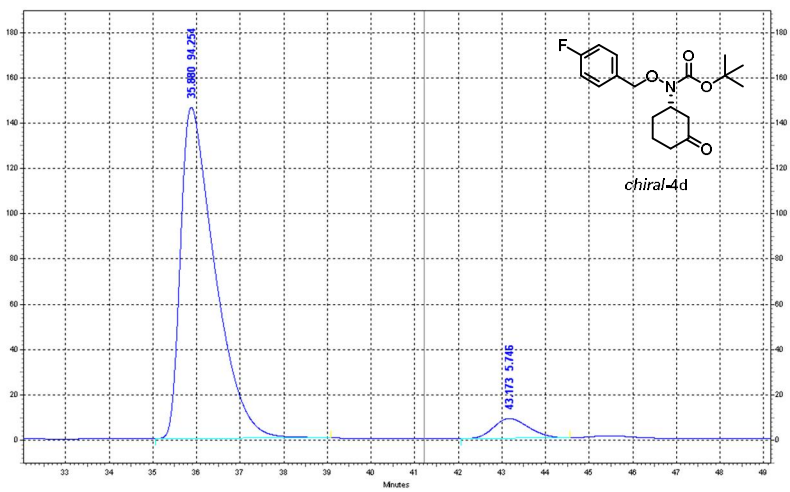
HPLC Graph of ***rac*-4d**



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	39.880	22605019	49.379	MM
	48.267	23173309	50.621	II
Totals		45778328	100.000	

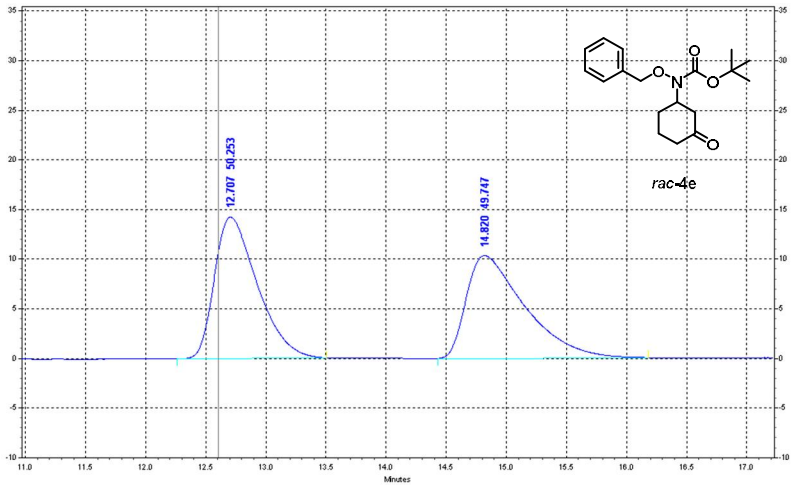
HPLC Graph of ***chiral*-4d**



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	35.880	31881972	94.254	MM
	43.173	1943707	5.746	MM
Totals		33825679	100.000	

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

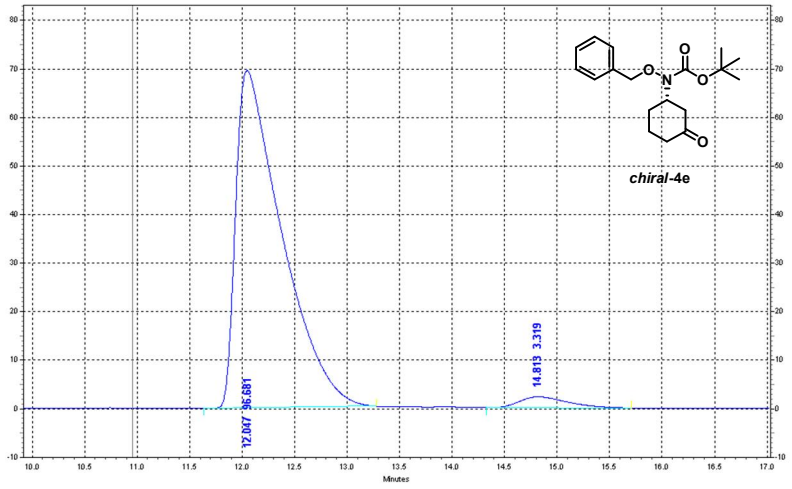


UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	12.707	1407287	50.253	BI
	14.820	1393128	49.747	II

Totals			
		2800415	100.000

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

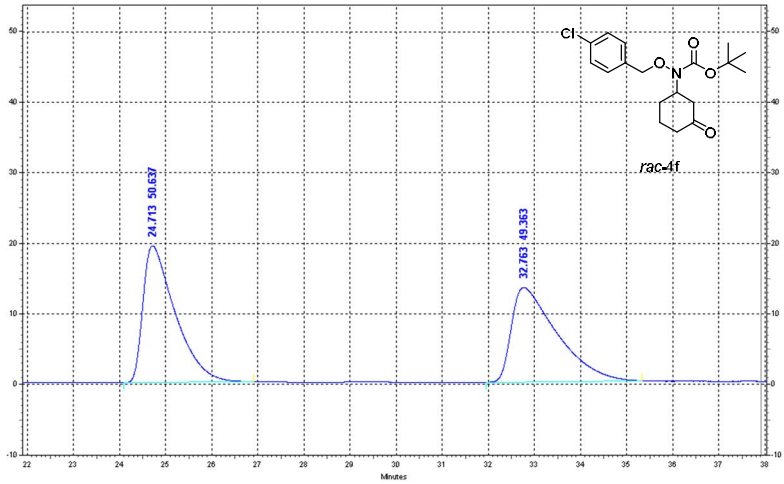


UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	12.047	8476125	96.681	BI
	14.813	290985	3.319	BI

Totals			
		8767110	100.000

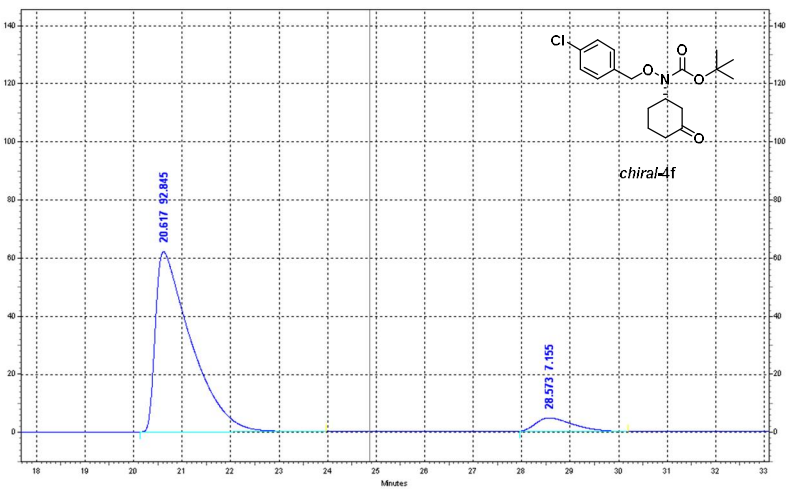
HPLC Graph of ***rac*-4f**



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	24.713	3750239	50.637	MM
	32.763	3655918	49.363	BI
Totals		7406157	100.000	

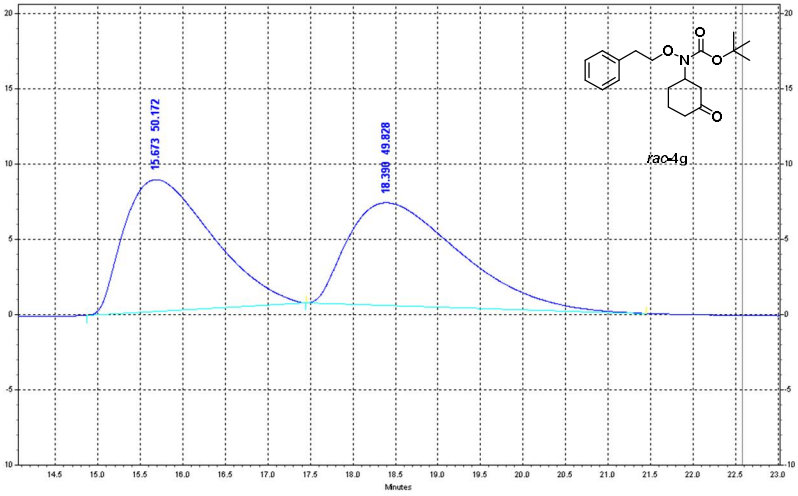
HPLC Graph of ***chiral*-4f**



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	20.617	12605175	92.845	MM
	28.573	971438	7.155	mm
Totals		13576613	100.000	

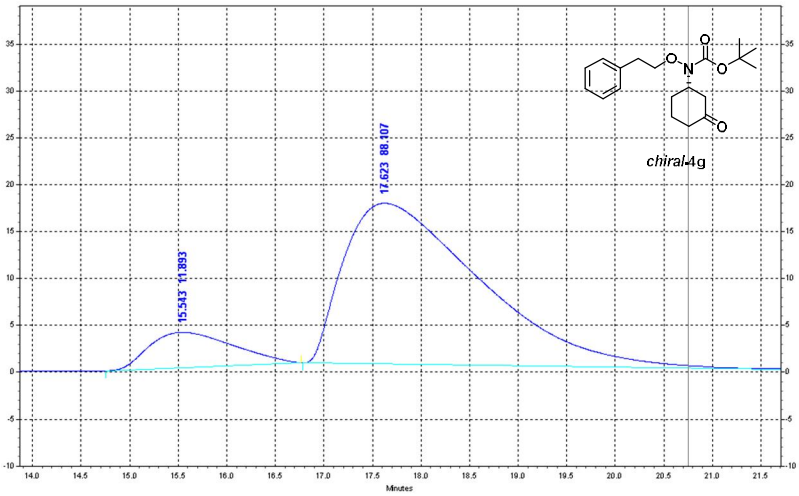
HPLC Graph of ***rac*-4g**



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	15.673	2522815	50.172	MM
	18.390	2505482	49.828	MM
Totals		5028297	100.000	

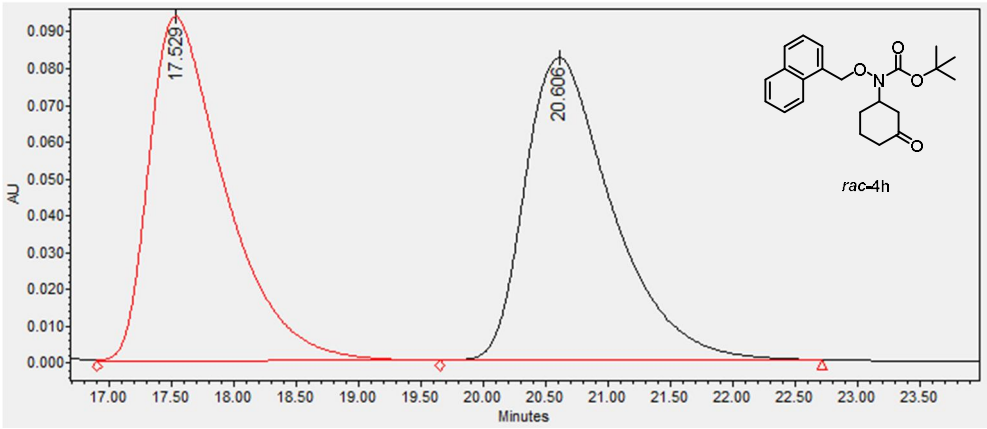
HPLC Graph of ***chiral*-4g**



UV Results

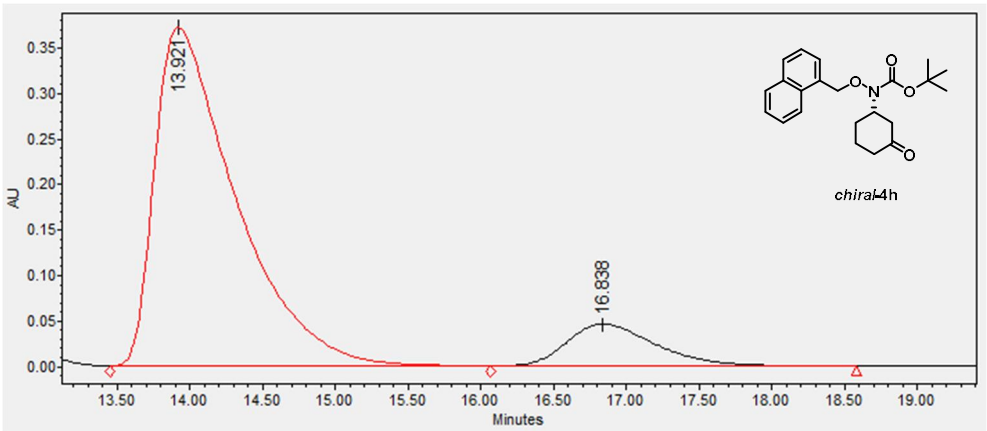
Name	Retention Time	Area	Area Percent	Integration Codes
	15.543	911044	11.893	MM
	17.623	6749590	88.107	MM
Totals		7660634	100.000	

HPLC Graph of ***rac*-4h**



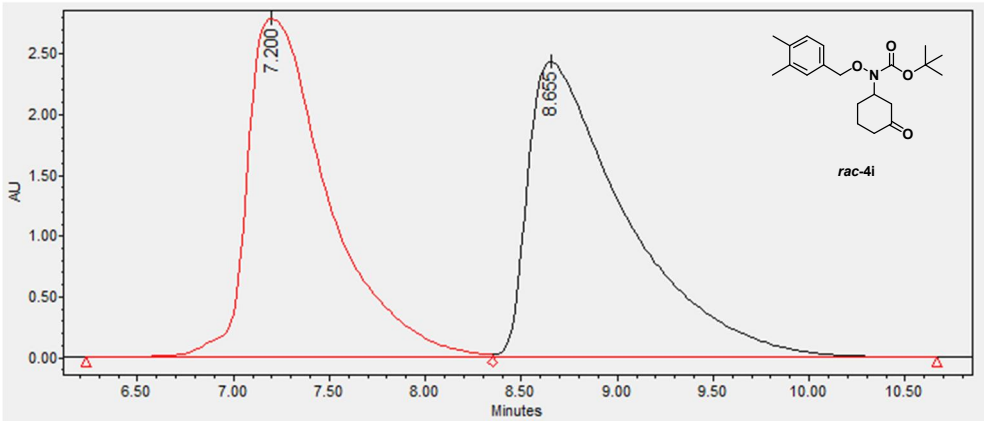
	RT	Area	% Area	Height
1	17.529	3982926	49.82	93628
2	20.606	4011310	50.18	82190

HPLC Graph of ***chiral*-4h**



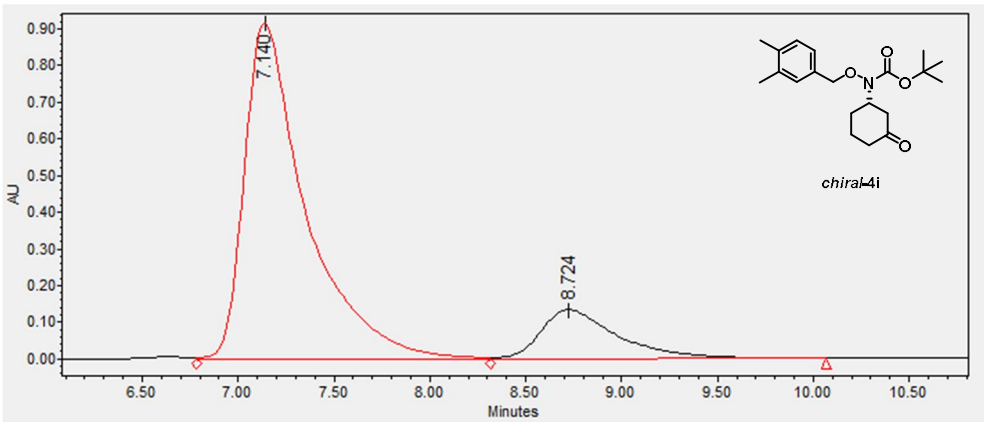
	RT	Area	% Area	Height
1	13.921	14445551	87.96	372446
2	16.838	1978166	12.04	46359

HPLC Graph of ***rac*-4i**



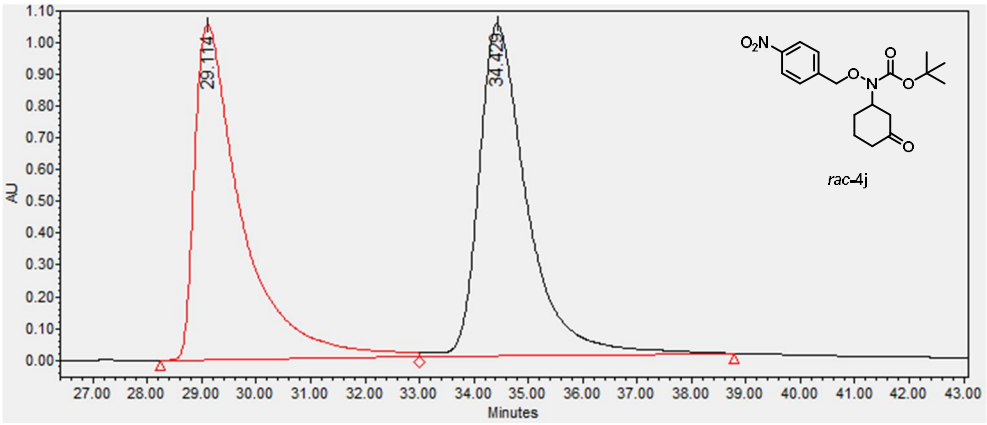
	RT	Area	% Area	Height
1	7.200	81844646	48.69	2784501
2	8.655	86264928	51.31	2432214

HPLC Graph of ***chiral*-4i**



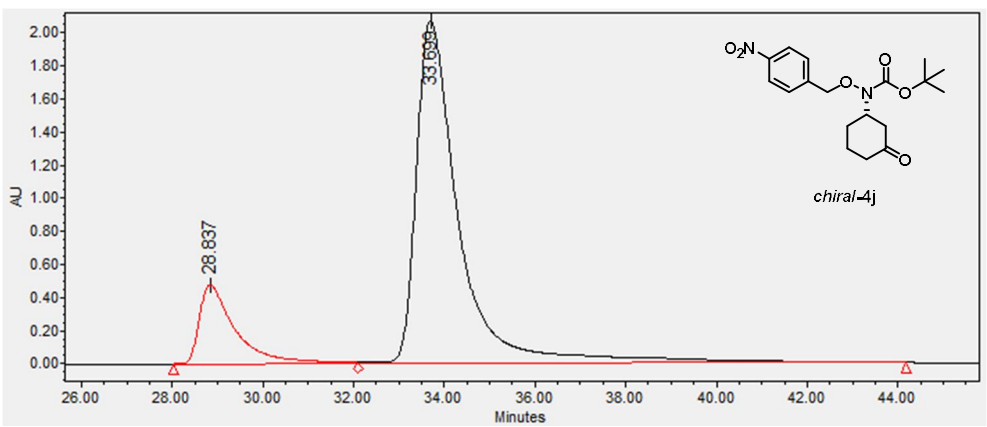
	RT	Area	% Area	Height
1	7.140	20309394	84.68	916784
2	8.724	3673393	15.32	133709

HPLC Graph of ***rac*-4j**



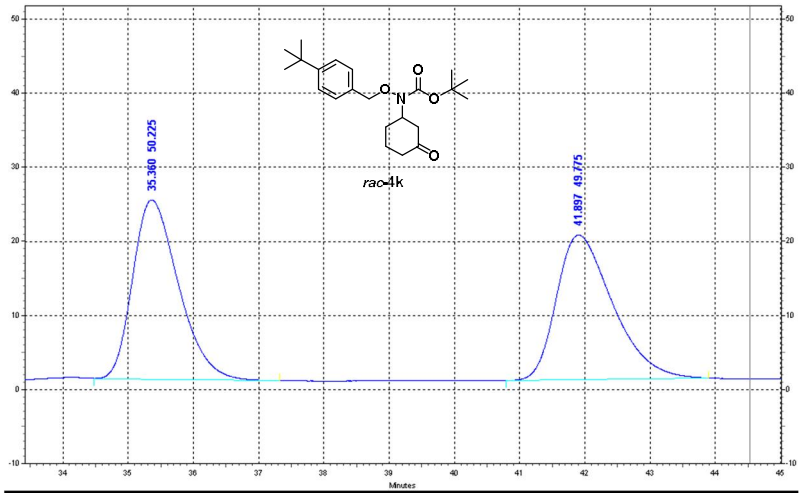
	RT	Area	% Area	Height
1	29.114	63612239	49.62	1052715
2	34.429	64580543	50.38	1047796

HPLC Graph of ***chiral*-4j**



	RT	Area	% Area	Height
1	28.837	26536068	16.26	478089
2	33.699	136633066	83.74	2066731

HPLC Graph of ***rac*-4k**

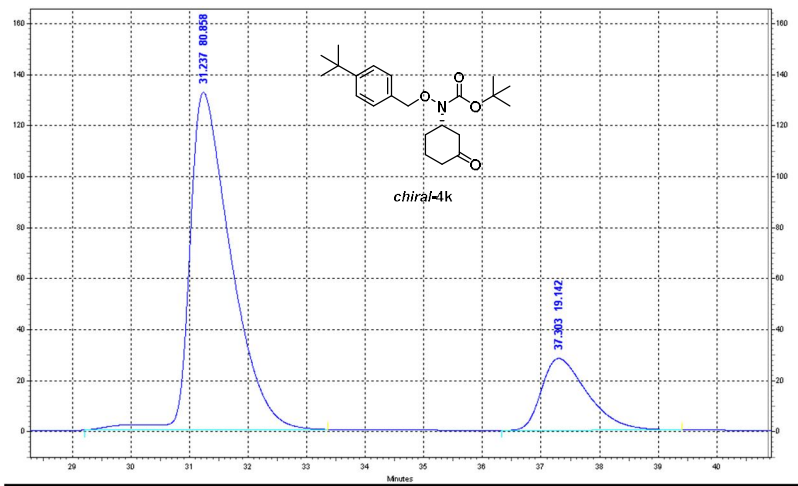


UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	35.360	4719566	50.225	MM
	41.897	4677193	49.775	MM

Totals			
		9396759	100.000

HPLC Graph of ***chiral*-4k**

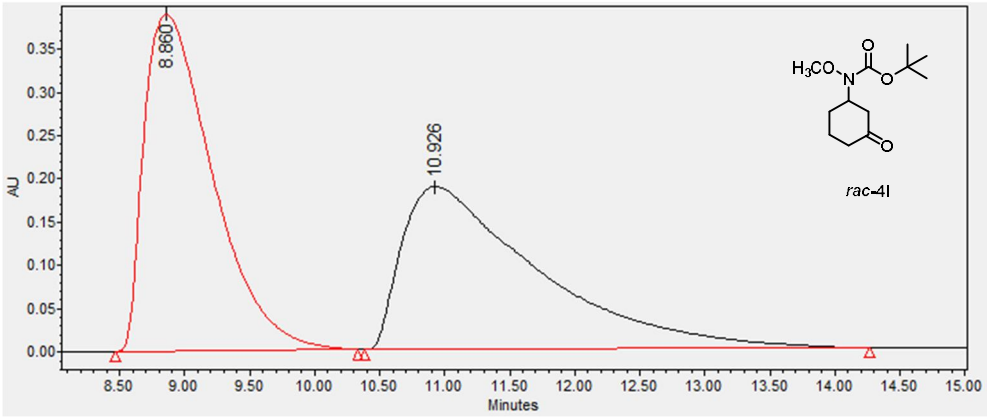


UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	31.237	25782921	80.858	MM
	37.303	6103887	19.142	MM

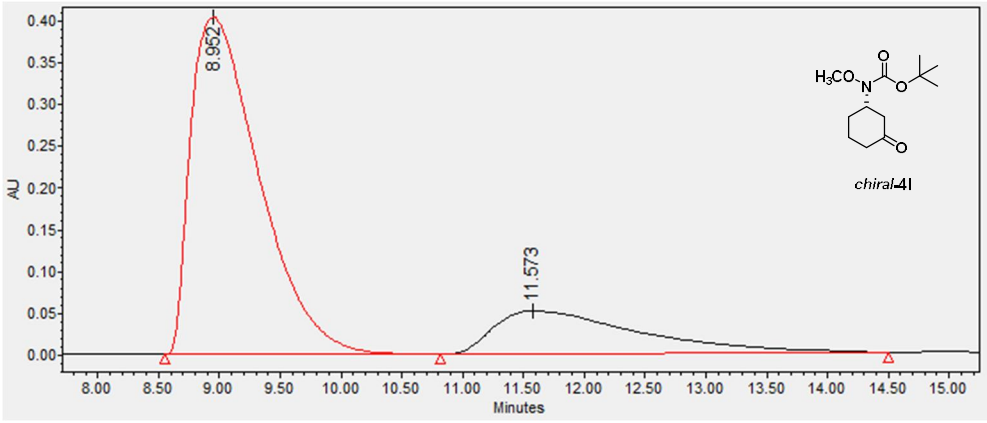
Totals			
		31886808	100.000

HPLC Graph of ***rac*-4l**



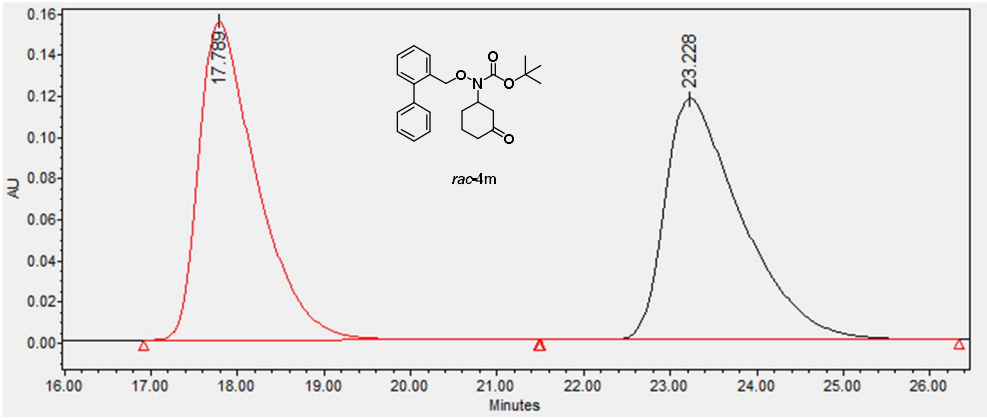
	RT	Area	% Area	Height
1	8.860	14255261	50.97	388453
2	10.926	13710610	49.03	187965

HPLC Graph of ***chiral*-4l**



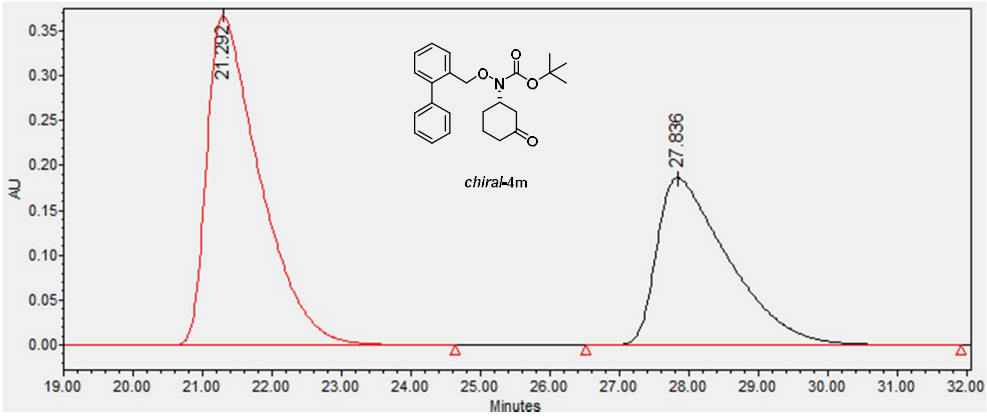
	RT	Area	% Area	Height
1	8.952	15898172	78.99	404889
2	11.573	4229369	21.01	51414

HPLC Graph of ***rac*-4m**



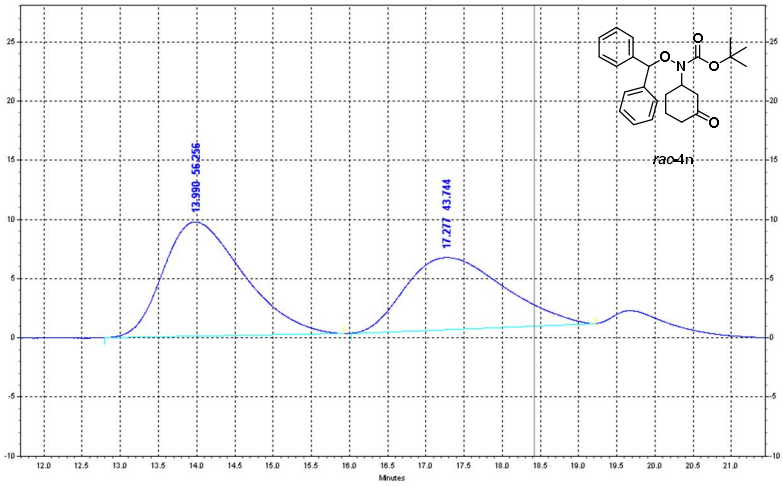
	RT	Area	% Area	Height
1	17.789	7211415	49.99	154868
2	23.228	7214351	50.01	117410

HPLC Graph of ***chiral*-4m**



	RT	Area	% Area	Height
1	21.292	19464028	59.39	367375
2	27.836	13310801	40.61	186134

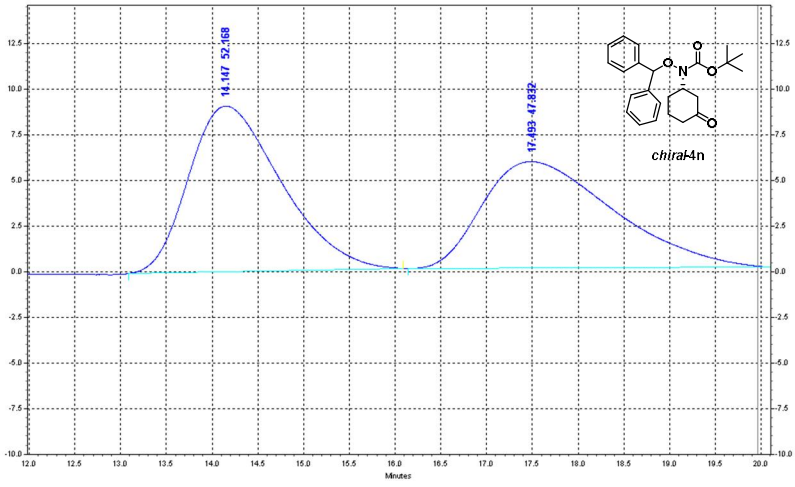
HPLC Graph of ***rac*-4n**



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	13.990	2814773	56.256	MM
	17.277	2188729	43.744	MM
Totals		5003502	100.000	

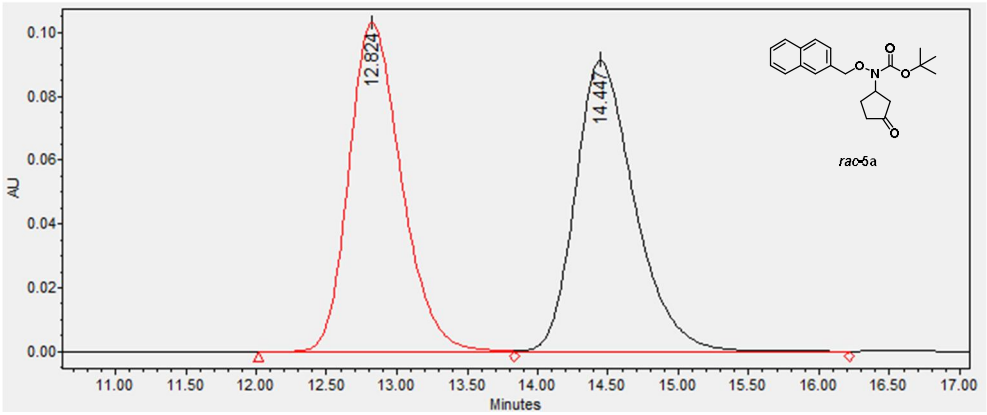
HPLC Graph of ***chiral*-4n**



UV Results

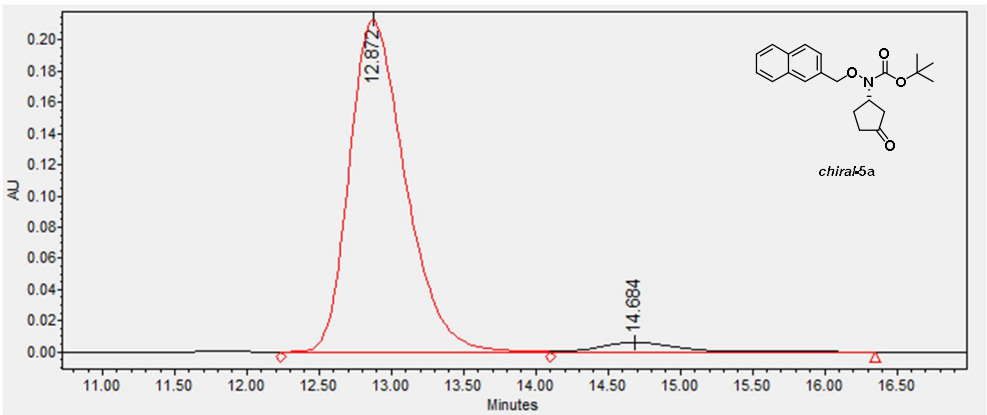
Name	Retention Time	Area	Area Percent	Integration Codes
	14.147	2540048	52.168	MM
	17.493	2328954	47.832	MM
Totals		4869002	100.000	

HPLC Graph of ***rac*-5a**



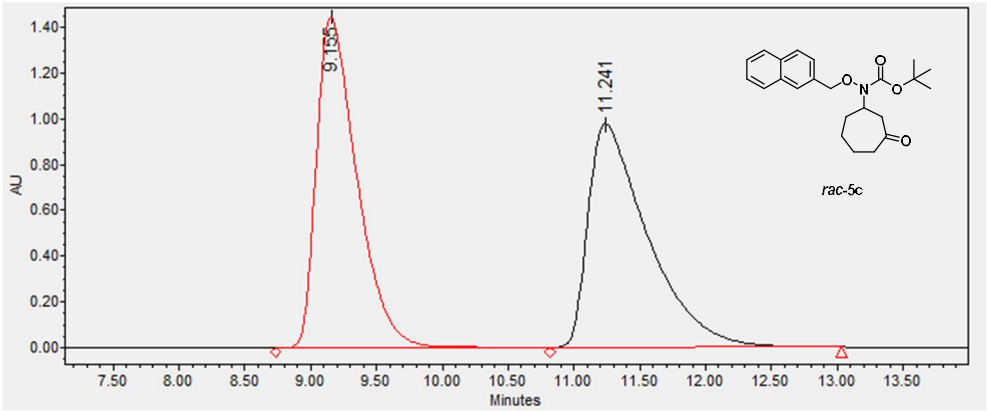
	RT	Area	% Area	Height
1	12.824	2667723	49.95	103170
2	14.447	2673126	50.05	91382

HPLC Graph of ***chiral*-5a**



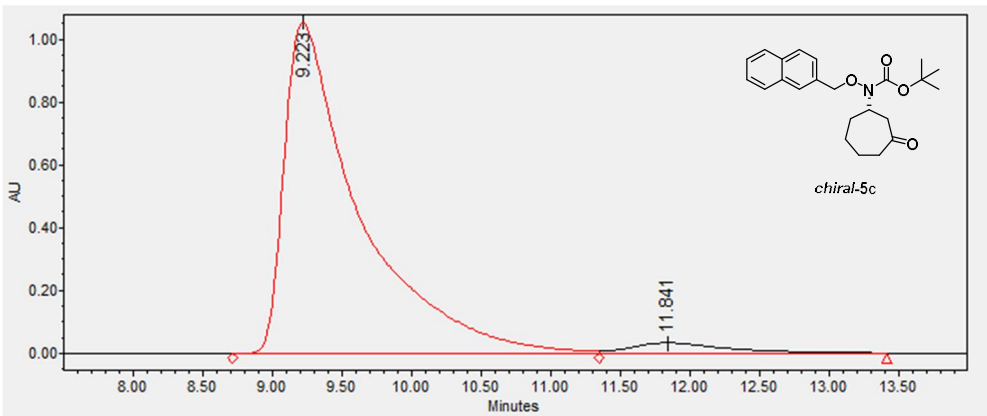
	RT	Area	% Area	Height
1	12.872	5716045	96.50	213169
2	14.684	207373	3.50	5936

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



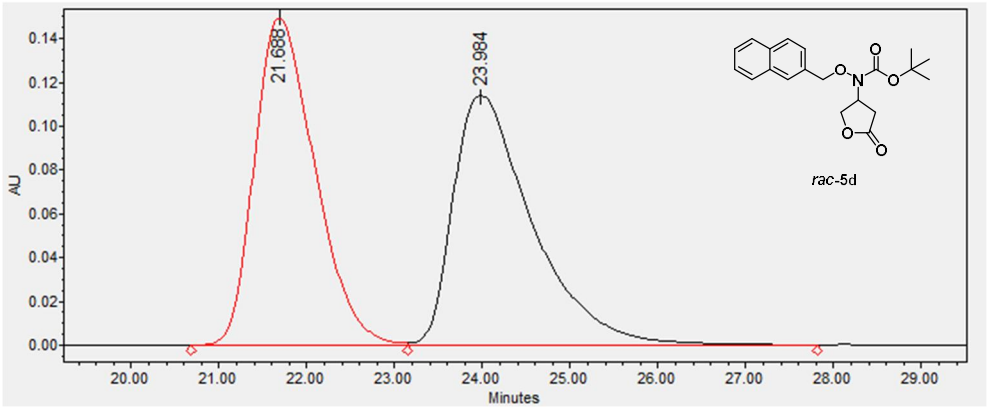
	RT	Area	% Area	Height
1	9.155	30632668	49.96	1444237
2	11.241	30681613	50.04	976340

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



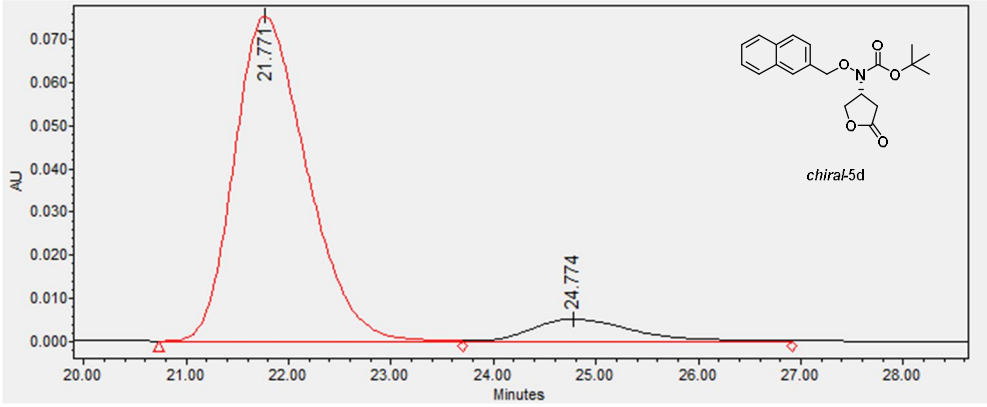
	RT	Area	% Area	Height
1	9.223	39448996	96.28	1053164
2	11.841	1525403	3.72	32811

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



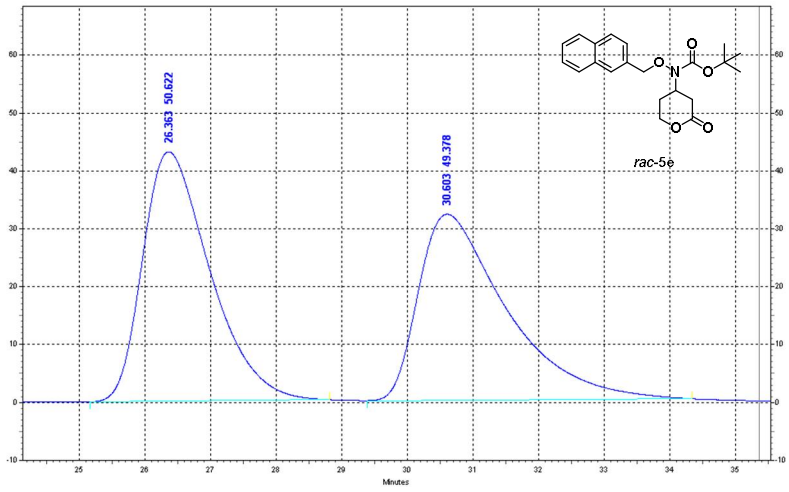
	RT	Area	% Area	Height
1	21.688	7140532	49.90	149231
2	23.984	7168914	50.10	113910

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



	RT	Area	% Area	Height
1	21.771	3687817	91.30	75222
2	24.774	351327	8.70	5147

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

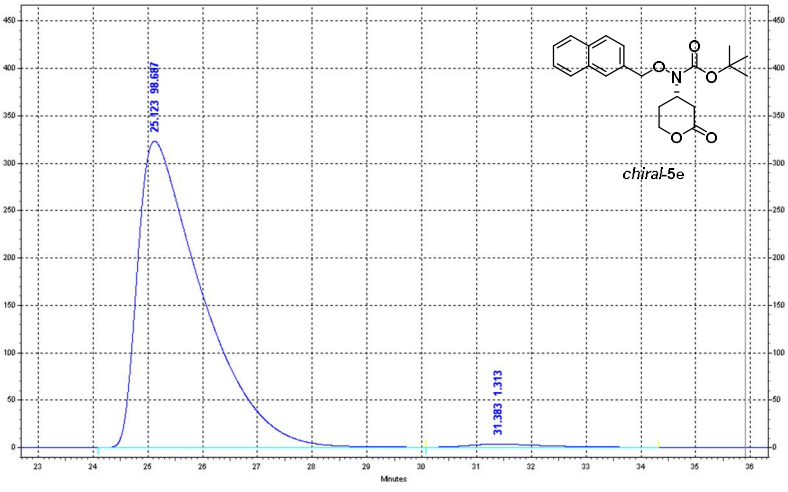


UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	26.363	12269256	50.622	II
	30.603	11967679	49.378	BI

Totals			
		24236935	100.000

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

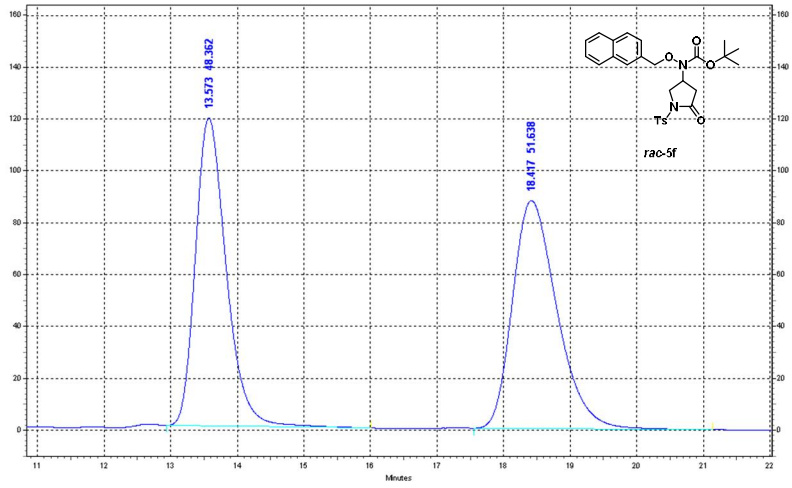


UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	25.123	105716384	98.687	BV
	31.383	1406054	1.313	VI

Totals			
		107122438	100.000

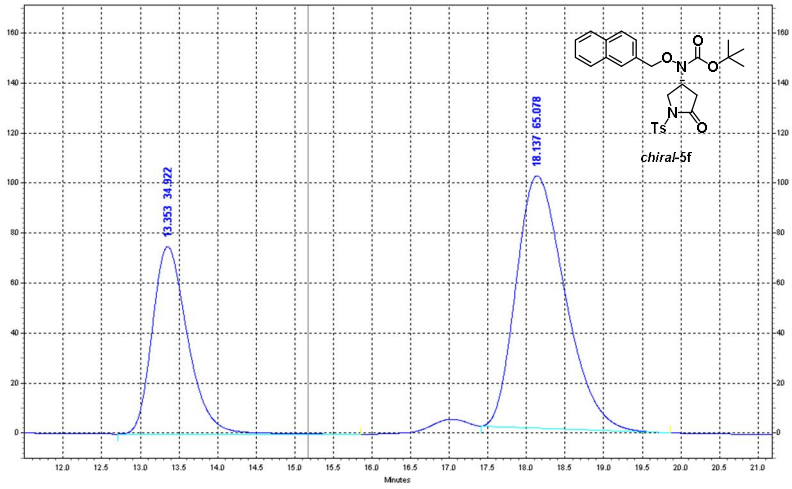
HPLC Graph of ***rac*-5f**



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	13.573	15265217	48.362	BI
	18.417	16299323	51.638	BI
Totals		31564540	100.000	

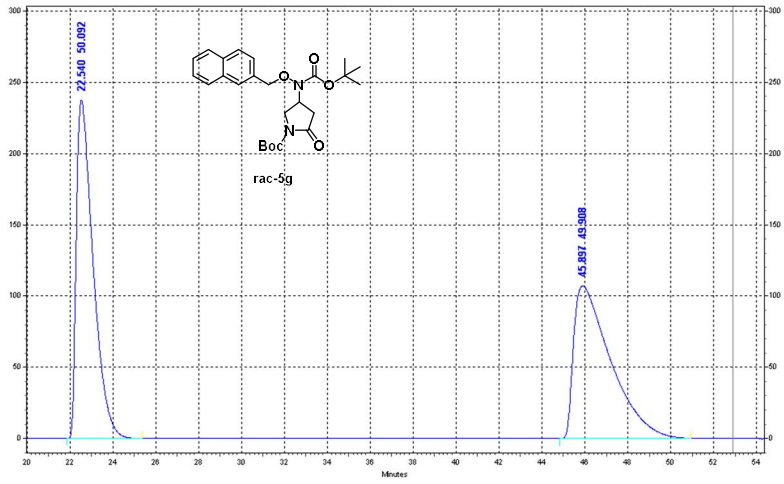
HPLC Graph of ***chiral*-5f**



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	13.353	9566993	34.922	BB
	18.137	17828201	65.078	mm
Totals		27395194	100.000	

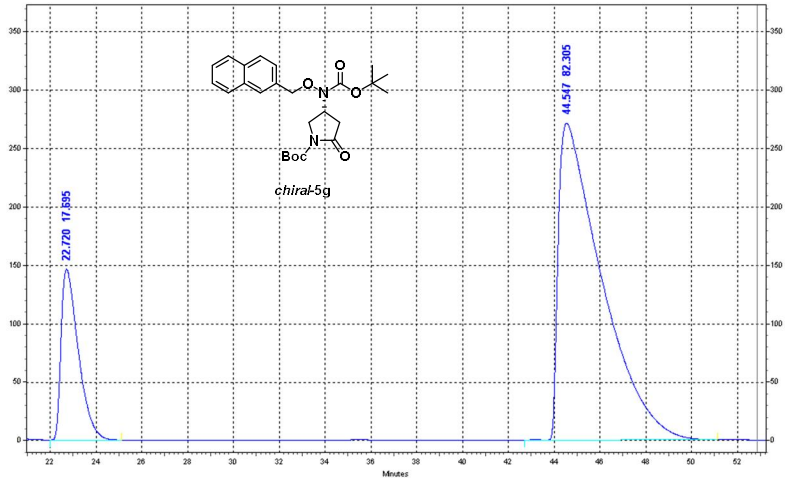
HPLC Graph of ***rac*-5g**



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	22.540	51512455	50.092	II
	45.897	51323917	49.908	MM
Totals		102836372	100.000	

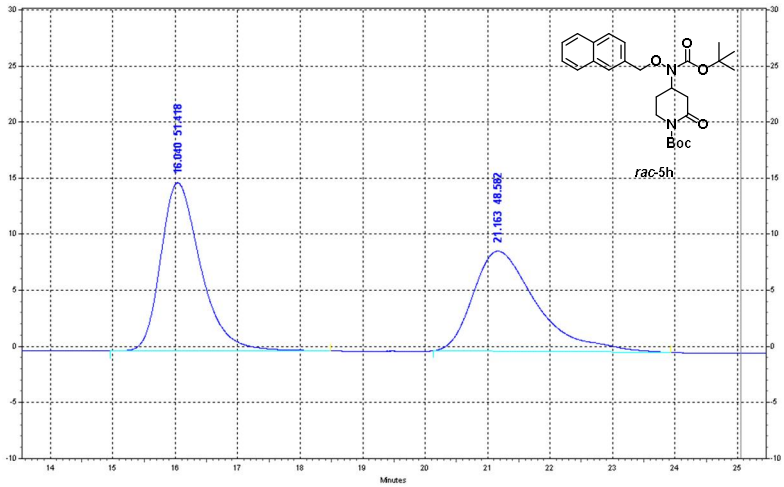
HPLC Graph of ***chiral*-5g**



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	22.720	30645517	17.695	BI
	44.547	142537544	82.305	MM
Totals		173183061	100.000	

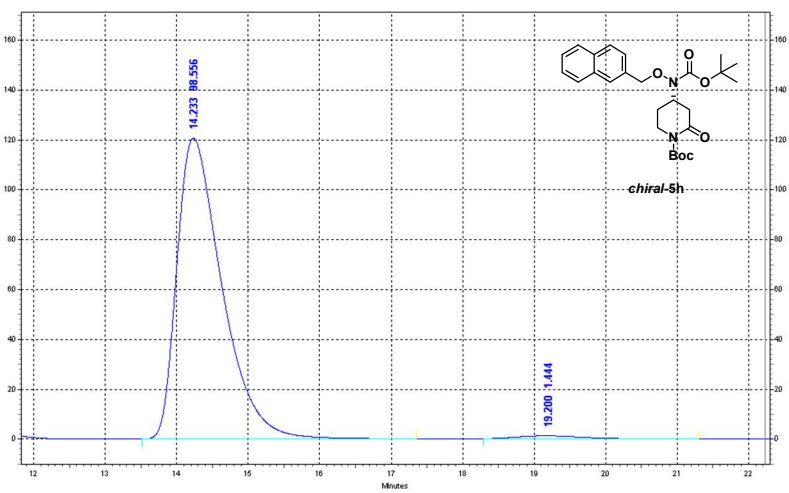
HPLC Graph of ***rac*-5h**



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	16.040	2663421	51.418	MM
	21.163	2516539	48.582	II
Totals		5179960	100.000	

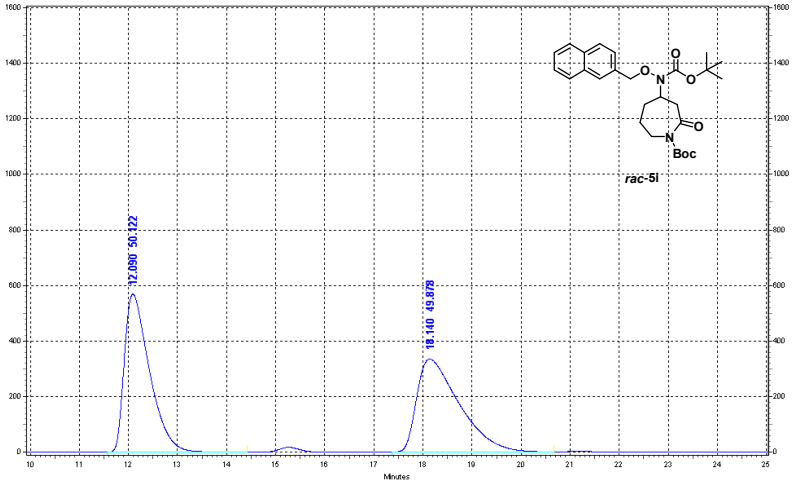
HPLC Graph of ***chiral*-5h**



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	14.233	21112100	98.556	mm
	19.200	309229	1.444	mm
Totals		21421329	100.000	

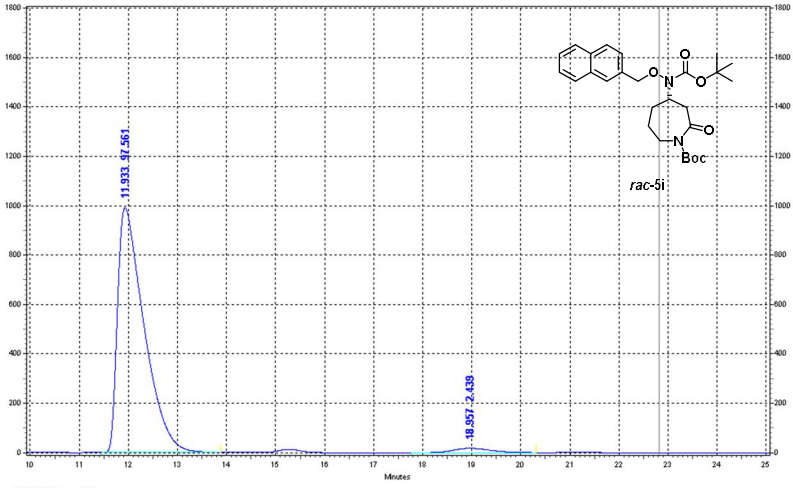
HPLC Graph of ***rac*-5i**



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	12.090	80486301	50.122	MM
	18.140	80094450	49.878	mm
Totals		160580751	100.000	

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



UV Results

Name	Retention Time	Area	Area Percent	Integration Codes
	11.933	147866919	97.561	MM
	18.957	3697095	2.439	II
Totals		151564014	100.000	