이학석사 학위논문

Enantioselective Synthesis of Chiral Allenes through Tandem *S*-Propargylation and Sulfinyl Retro-Ene Reactions

프로파질 치환 및 설피닐 레트로-엔 연쇄반응을 통한 카이랄 알렌의 비대칭 합성법

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서울대학교 대학원

자연과학대학 화학부

유기화학 전공

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지도교수 이철범

이 논문을 이학석사 학위논문으로 제출함

2023년 1월

서울대학교 대학원

화학부 유기화학 전공

신웅식

신웅식의 이학석사 학위논문을 인준함

2023년 1월

위 원 장 이 홍 근 (인)

부위원장 이 철 범 (인)

위 원 홍 승 윤 (인)

Table of Contents

Abstract

Described in this dissertation are the studies directed toward the development of a new method for the enantioselective synthesis of chiral allenes that constitute an important structural unit in various bioactive natural products and compounds used in asymmetric synthesis. Starting with racemic propargylic carbonates derived from terminal alkynes, the method involves tandem propargylic sulfonylation, Sonogashira cross-coupling and sulfinyl retro-ene reactions. The copper-catalyzed *S*-propargylation of sodium *tert*-butyldimethylsilyloxymethylsulfinate (TBSOMS-Na) proceeds through the intermediacy of a copper-allenylidene complex which deracemizes the propargylic substrates and brings about asymmetric induction with chiral oxazoline-derived dinitrogen ligands. After the alkynyl C-H arylation of the propargylic sulfone of a terminal alkyne by a Sonogashira coupling, the resulting enantioenriched sulfone, upon deprotection of the TBSOMS group, undergoes a sulfinyl retro-ene reaction that removes sulfur dioxide (SO_2) to furnish the allene product with complete transfer of chirality from the propargylic center to the allene axis. The scope, limitations and prospect of the new method are described in detail.

Keywords: copper-allenylidene, propargylic substitution, sulfinyl retro-ene, allene, terminal alkynes

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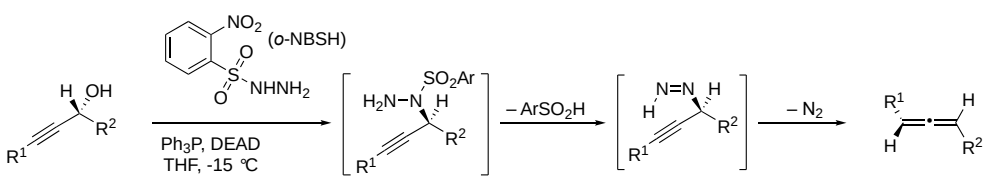
INTRODUCTION

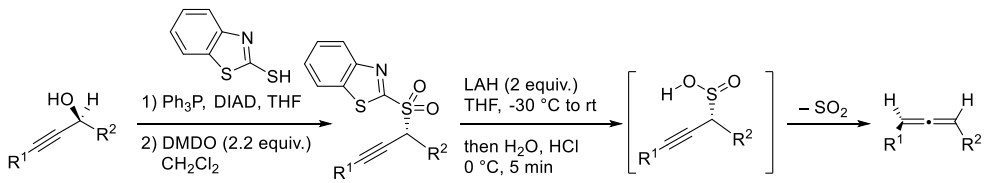
Over the past few decades, allenes have garnered increasing attention from synthetic chemists due to their pharmacological activity and occurrence as a key structural motif in natural products.[1] Since the first allene was synthesized in the late 19th century,[2] a diverse range of methods for the synthesis of allenes, including enantioselective variants,[3] have been developed, making use of various reactions such as prototropic rearrangement,[4,5] sigmatropic rearrangement,[6,7] nucleophilic substitution,[8,9] and 1,2-elimination.[10,11] Notable among these processes is the protocol based on a retro-ene reaction in which a propargylic carbon-heteroatom bond is broken with concomitant transposition of the alkyne to an allene pi-system. This reductive process, driven by the thermodynamically favorable gas evolution, has been well established by the work of Myers[12] (Scheme 1), Movassaghi[13] and Kocienski[14] (Scheme 2), demonstrating that the retro-ene reactions proceed in a stereospecific manner with chirality transfer.



Scheme 1. Myers' allene synthesis

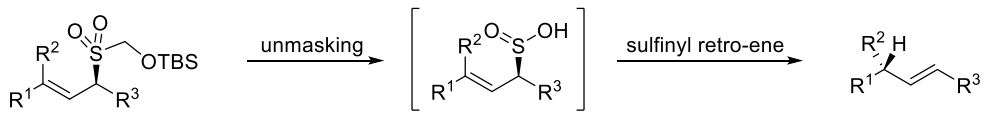
Hence, the sequence involving enantioselective construction of a propargylic carbon-heteroatom (e.g., C-N, C-S) bond and stereospecific removal of the heteroatom would enable asymmetric allene synthesis. However, asymmetric

induction approaches based on this notion are extremely rare,[23] and no example has been reported which employs the rearrangement of a propargylic sulfinic acid derived from an enantioenriched sulfone prepared via asymmetric sulfonylation.



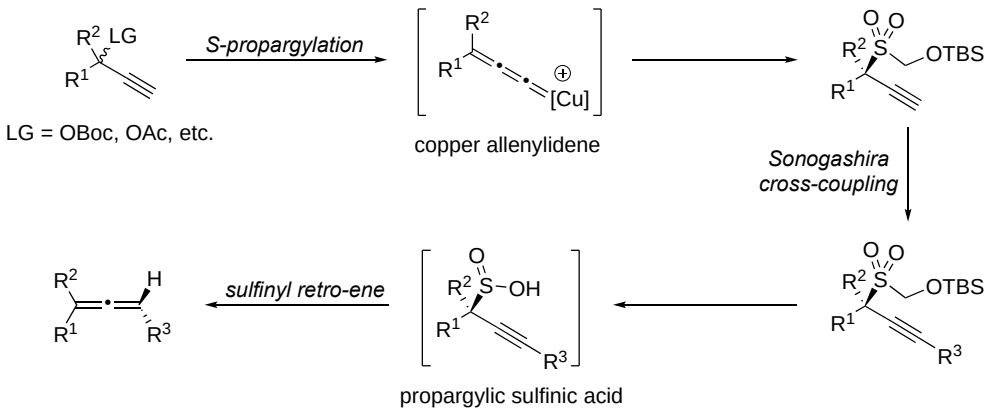
Scheme 2. Kocienski's allene synthesis

In accordance with the sulfinic acid rearrangement reactions first reported by Julia et al.,[15] a stereoselective method for allylic reduction has recently been developed in our laboratory using an allylic sulfinic acid rearrangement reaction (Scheme 3).[16] In this tandem process involving allylic sulfonylation and retro-ene reactions, sodium (*tert*-butyl)dimethylsilyloxymethanesulfinate (TBSOMS-Na), prepared from the commercially available reagent Rongalie™, serves as a nucleophile in the palladium-catalyzed Tsuji-Trost *S*-allylation to form the TBSOMS sulfone which undergoes a sulfinyl retro-ene reaction, upon deprotection under mild conditions, effecting reductive alkene transposition with removal of sulfur dioxide. It has also been shown that highly enantioselective allylic sulfonylation can be carried out in tandem with complete chirality transfer by the subsequent pericyclic rearrangement to construct a chiral allylic system.



Scheme 3. Stereoselective allylic reduction via retro-ene route

Based on the tandem approach to chiral allylic centers, we aimed to develop a new method for the enantioselective synthesis of chiral allenes from racemic propargylic alcohol derivatives (Scheme 4). Since the first copper-catalyzed propargylic substitution was reported in which heteroatom nucleophiles were used in the reaction with a copper-allenylidene electrophile,[17,18] asymmetric versions of propargylic amination,[19] etherification[20] and sulfonylation[21] have been reported. While the scope of propargylic sulfonylation is still limited, we envisaged to achieve asymmetric induction by an enantioconvergent sulfonylation of racemic propargylic substrates with the sulfonylation reagent TBSOMS-Na. In particular, it was anticipated that terminal alkyne-derived propargylic alcohol derivatives would undergo a deracemizing sulfonylation via transition metal allenylidene-mediated catalysis. Subsequently, the C-C bond formation at the terminal alkyne could be performed by a Sonogashira cross-coupling to generate a sulfone with an internal alkyne, poised for a sulfinyl retro-ene reaction producing the chiral allene product. As a result of the three-step sequence, polysubstituted chiral allenes are prepared in an enantioselective fashion from racemic propargylic alcohols.



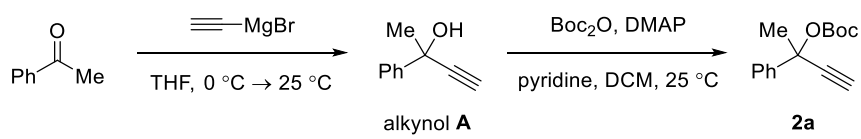
Scheme 4. Proposed tandem approach to chiral allene synthesis

RESULT AND DISCUSSION

1. Initial Discovery

1.1 Preparation of substrates

Our studies aimed at the development of an enantioselective protocol for chiral allene synthesis were started with preparation of a suitable model substrate containing an aromatic substituent and a leaving group at the propargylic position according to the report of Zhao (Scheme 5).[22] As we targeted a transition metal allenylidene complex as the electrophile for the *S*-propargylation of TBSOMS-Na, a carbonate such as **2a** was considered most suitable since a tertiary leaving group at a propargylic as well as benzylic position would facilitate the formation of the requisite metal-allenylidene intermediate. Thus, alkynol **A** was prepared by the addition of an ethynyl Grignard reagent to acetophenone, and the resulting alcohol was converted to carbonate **2a** by the reaction with di-*tert*-butyl dicarbonate.

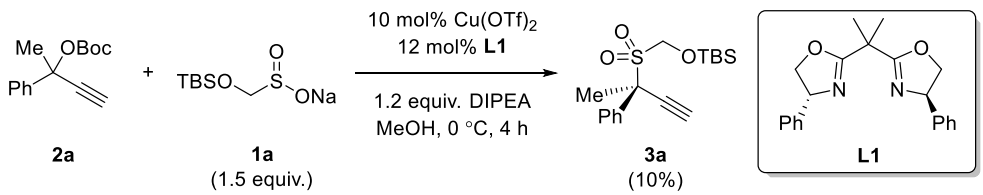


Scheme 5. Synthesis of a model substrate

1.2 Initial Survey

Our initial effort was focused on establishing the general reaction conditions for the *S*-propargylation following the protocols developed by van Maarseveen[19] and Nishibayashi[20] groups who studied related propargylic substitution reactions.

From a cursory study with several trials, we obtained the desired product **3a** in 10% yield from the reaction of **2a** with **1a** under the conditions employing catalytic $Cu(OTf)_2$ and the chiral bis-oxazoline ligand **L1** in MeOH solvent in the presence of DIPEA base (Scheme 6).

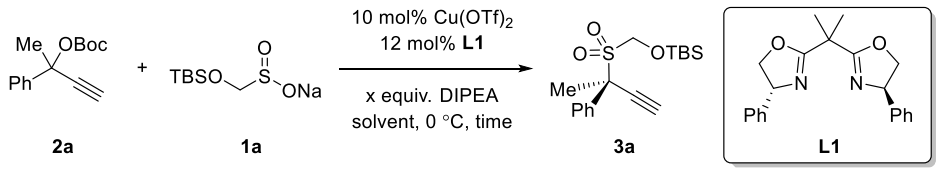


Scheme 6. Initial attempt of propargylic sulfonylation

1.3 Screening Experiment with sodium sulfinate **1a**

With the initial result, solvent screening studies were next conducted because it was known from previous studies[16] in our laboratory that nucleophile **1a** easily decomposes in MeOH (Table 1, entry 1-8). As expected, all other solvents gave better yields of the product than MeOH. In the case of DME solvent, the reaction generated sulfone **3a** in 49% yield while approximately 30% of the starting material remained unreacted (Table 1, entry 4).

Table 1. Screening of solvents and the amount of base using a nucleophile **1a**[a)]

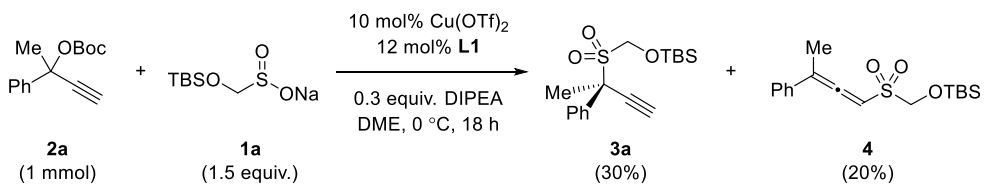


2a **1a** **3a** **L1**

entry	solvent	x (equiv.)	time (h)	yield (%)[b)]	**2a** (%)[b)]
1	toluene	1.2	15	23	7
2	ether	1.2	15	43	-
3	THF	1.2	3	45	-
4	DME	1.2	21	49	30
5	DMF	1.2	15	25	-
6[c)]	DMSO	1.2	3	18	-
7	^{i}PrOH	1.2	4	54	-
8	^{n}BuOH	1.2	4	42	-
9	DME	0	18	33	61
10	DME	0.1	18	53	16
11	DME	0.3	18	65	7
12	DME	0.6	18	59	8
13	DME	1	18	51	35
14	DME	2	18	38	55
15	DME	4.3	18	37	40

a) All reactions were performed with 0.2 mmol of **2a**, 0.02 mmol of $Cu(OTf)_2$, 0.024 mmol of **L1**, 0.3 mmol of TBSOMS-Na and x equivalent of DIPEA in 1 ml of solvent at 0 °C. b) Yield was determined by NMR using 1,3,5-trimethoxybenzene as an internal standard.c) Reaction was performed at 25 °C.

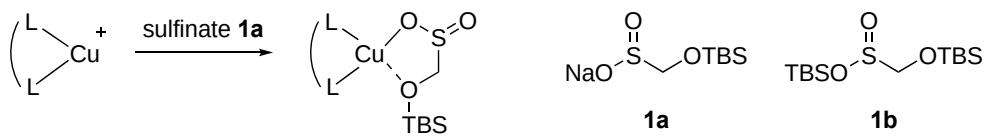
While an amine base is typically used in many metal-catalyzed reactions involving activation of the terminal alkynyl C-H bond, in theory, only a catalytic amount of base is needed to promote the formation of a copper alkynyl en route to an allenylidene complex. Therefore, we set out to examine the amount of base and its impact on the reaction yield (Table 1, entry 9-15). It was found from a series of experiments that more than one equivalent of DIPEA slowed down the reaction (Table 1, entry 13-15). When 0.3 equivalent of DIPEA was used, the product yield was improved to 65% (Table 1, entry 11). However, it was soon apparent that further optimization effort did not bring an improved result. Of particular note was a scale-up experiment conducted using 1 mmol of **2a** and sulfinate **1a** (Scheme 7). Compared to the results from screening experiments where only 0.2 mmol of **2a** was used, the yield of propargylic sulfone **3a** was drastically decreased and the formation of allenyl sulfone **4** became substantial.



Scheme 7. A byproduct formed from a scale-up reaction

We reasoned that the formation of the allenyl product **4** was due to a possible complexation[16] between the copper catalyst and sulfinate **1a** which might act as a ligand (Scheme 8). An alternative possibility was inhibition or impracticality of the catalytic cycle since the transformation would have to generate a strongly basic

tert-butoxide anion through substitution with a weakly basic sulfinate anion nucleophile. Based on this line of thought and the initial screening result, we decided to modify the nucleophile from the sodium sulfinate **1a** to the silyl sulfinate **1b**.

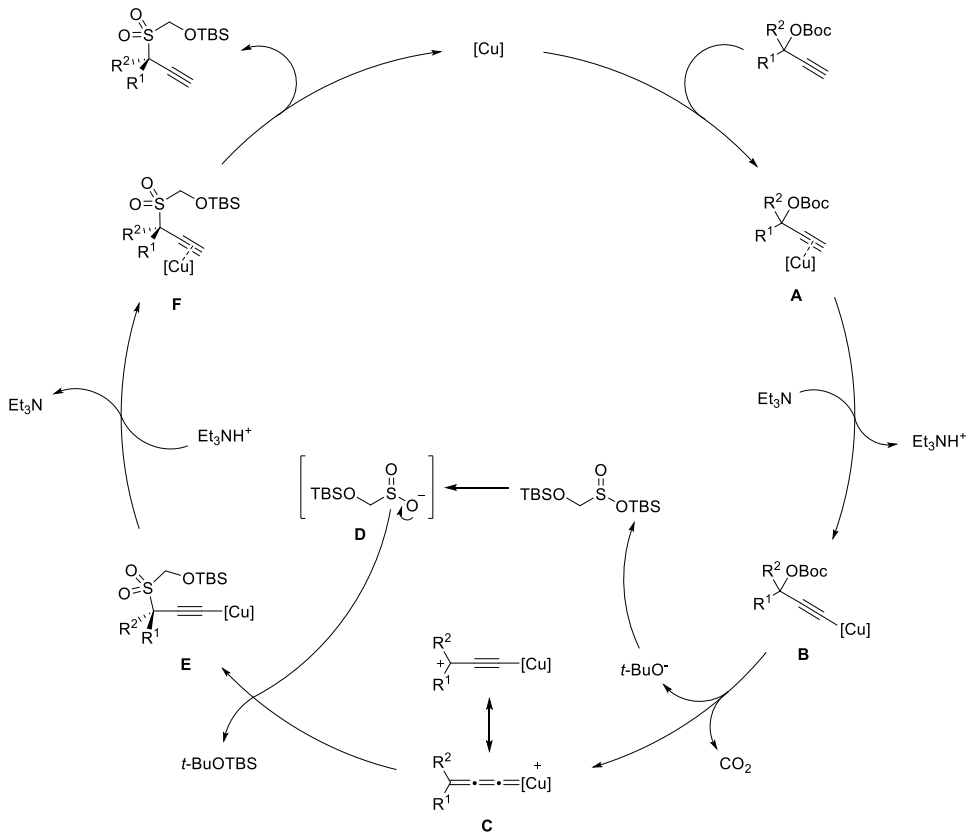


Scheme 8. Complexation of a sulfinate **1a** with copper catalyst

2. Design Plan Based on a Proposed Mechanism

The new design plan of our investigation was based on a proposed mechanism for the propargylic substitution using silyl sulfinate **1b** as shown in Scheme 9. In the first step of the catalytic cycle, the copper complex[19] binds to the alkynyl substrate to form π-complex **A**. The formation of this π-complex lowers the pK_a value of the acetylenic hydrogen atom, which can be deprotonated by an amine base[19] to form copper-alkynyl intermediate **B**. Then, the resonance-stabilized copper-allenylidene **C**[20,21] is formed in concomitant with ionization of a *tert*-butylcarbonate anion. While silyl sulfinate **1b** may directly undergo *S*-alkylation with the copper-complexed electrophile, an anionic sulfinate nucleophile such as **D** can be formed *in situ* with the help of a *tert*-butoxide anion, derived from the *tert*-butylcarbonate anion via decarboxylation, and attacks the γ-carbon of intermediate **C** to form intermediate **E**. The enantioselectivity is probably determined at this stage by the control of the chiral BOX-type ligand attached to the copper center.

Protonation of copper-alkynyl **E** generates **F**, from which dissociation of the copper complex gives rise to the product to complete the catalytic cycle.



Scheme 9. Proposed mechanism for *S*-propargylation

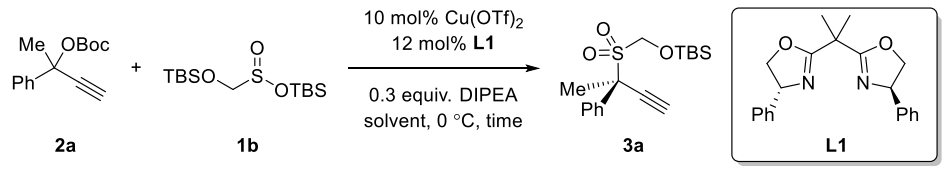
3. Optimization of the Reaction Condition

3.1 Screening Experiment with silylsulfinate **1b**

The new approach using a neutral sulfonylation nucleophile was examined by starting with solvent screening studies (Table 2). Among the four solvents screened, the best yield was obtained when the reaction of **2a** with **1b** was carried out in

^{i}PrOH. While the reaction gave **3a** in a yield of 41%, because a large portion of the unreacted **2a** was recovered, we sought to achieve full conversion by changing other factors in the reaction conditions.

Table 2. Screening of solvent using nucleophile **1b**[a)]



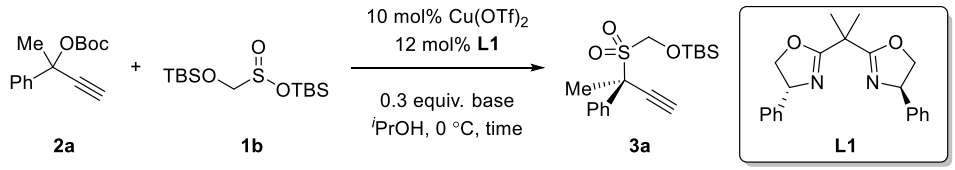
2a **1b** **3a** **L1**

entry	solvent	time (h)	yield (%)[b)]
1	toluene	22	17
2	THF	24	10[c)]
3	DME	24	27
4	^{i}PrOH	24	41[c)]

a) All reactions were performed with 0.2 mmol of **2a**, 0.02 mmol of $Cu(OTf)_2$, 0.024 mmol of **L1**, 0.3 mmol of TBSOMS-TBS and 0.06 mmol of DIPEA in 1 ml of solvent at 0 °C. b) Yield was determined by NMR using 1,3,5-trimethoxybenzene as an internal standard. c) Starting material remained.

To our delight, changing the base from DIPEA to TEA or DABCO led to full conversion of the starting material **2a** within 2 hours (Table 3, entry 1 and 3). Surprisingly, the use of DABCO gave the highest yield without forming any byproduct such as **4** (Table 3, entry 3).

Table 3. Screening of base[a)]



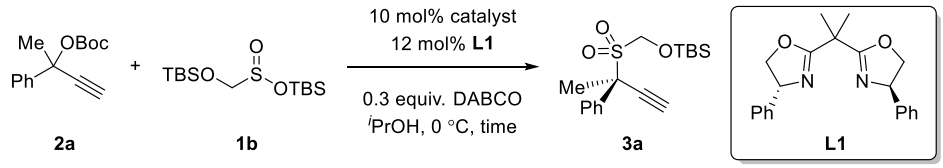
2a **1b** **3a** **L1**

entry	base	time (h)	yield (%)[b)]
1	TEA	2	65
2	DBU	20	50[c)]
3	DABCO	2	92
4	K_2CO_3	20	3[c)]

a) All reactions were performed with 0.2 mmol of **2a**, 0.02 mmol of $Cu(OTf)_2$, 0.024 mmol of **L1**, 0.3 mmol of TBSOMS-TBS and 0.06 mmol of base in 1 ml of ^{i}PrOH at 0 °C. b) Yield was determined by NMR using 1,3,5-trimethoxybenzene as an internal standard. c) Starting material remained.

We then focused on screening various copper catalyst systems known to form allenylidene complexes (Table 4). The use of $Cu(OAc)_2$ gave the highest reaction rate and yield of the product **3a** (Table 4, entry 3). When no copper catalyst was added to the reaction, most of the starting material was remained intact and none of the desired product **3a** was detected. This result of a control experiment established that copper catalyst was essential to the reaction.

Table 4. Screening of copper catalyst[a)]

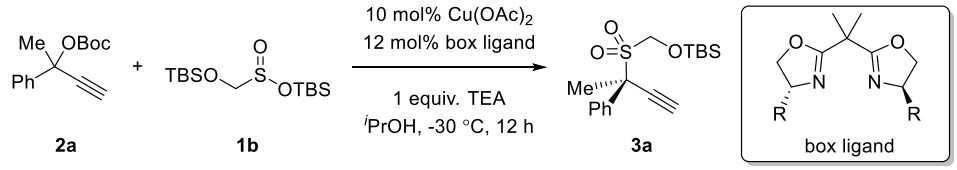


entry	catalyst	time (h)	yield (%)[b)]
1	none	24	0[c)]
2	Cu(OAc)	24	65
3	$Cu(OAc)_2$	4	99
4	CuI	24	60
5	$Cu(MeCN)_4PF_6$	24	92

a) All reactions were performed with 0.2 mmol of **2a**, 0.02 mmol of catalyst, 0.024 mmol of **L1**, 0.3 mmol of TBSOMS-TBS and 0.06 mmol of DABCO in 1 ml of ^{i}PrOH at 0 °C. b) Yield was determined by NMR using 1,3,5-trimethoxybenzene as an internal standard. c) Starting material remained.

With the promising results in hand, we then examined the enantioselectivity of the reaction. Unfortunately, it was found that a racemic mixture of sulfone **3a** was produced from the reaction conditions that gave the high yield. Therefore, we lowered the temperature to -30 °C to enhance stereoselectivity. At this temperature, the reaction using DABCO did give a nonzero enantiomeric excess, but TEA worked better by showing higher reaction rate and yield. By performing the ligand screening experiment, the reaction condition was optimized to obtain the product in 91% yield and 26% enantiomeric excess (Table 5).

Table 5. Screening of BOX-type ligand[a)]

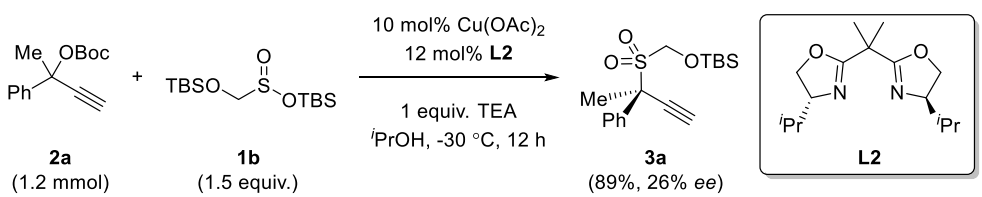


2a **1b** **3a**

entry	box ligand (R)	yield (%)[b)]	*ee* (%)
1	Ph	80[c)]	18
2	^{i}Pr	91[c)]	26
3	Bn	63[c)]	11

a) All reactions were performed with 0.2 mmol of **2a**, 0.02 mmol of catalyst, 0.024 mmol of box ligand, 0.3 mmol of TBSOMS-TBS and 0.2 mmol of TEA in 1 ml of ^{i}PrOH at -30 °C for 12 h. b) Yield was determined by NMR using 1,3,5-trimethoxybenzene as an internal standard. c) Starting material remained.

Fortunately, a large-scale reaction under these conditions also worked well (Scheme 10) without generating the allenyl side-product **4** that was formed in a sizable proportion when sulfinate sodium salt **1a** was used (Scheme 7). We reasoned that an active nucleophile was slowly generated from **1b** *in situ* by silyl transfer to a *tert*-butoxide anion or to isopropanol solvent.



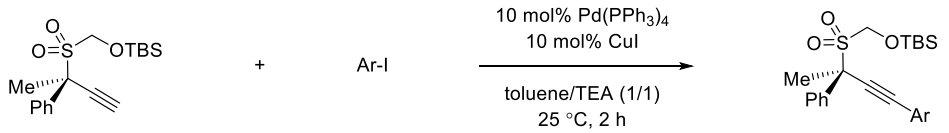
2a (1.2 mmol) **1b** (1.5 equiv.) **3a** (89%, 26% *ee*)

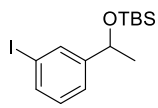
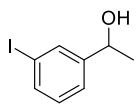
Scheme 10. Optimized condition for propargylic substitution reaction

3.2 Sonogashira Cross-Coupling Reaction

With the propargylic sulfone **3a** in hand, we then performed its Sonogashira cross-coupling reaction (Table 6). It was of importance to verify the feasibility of this C–C bond-forming reaction without compromising the enantioselectivity because CuI could regenerate a copper-allenylidene species by displacing the sulfonyl moiety as a leaving group, which might deteriorate the *ee*. Fortunately, it was observed that the stereochemical integrity of the propargylic quaternary carbon center remained intact. High yields of arylated products **5** were uniformly obtained from the reaction of **3a** with several aryl iodides. When iodobenzene was used, complete retention of chirality was observed (Table 6, entry 1). This result established that the Sonogashira reaction could be performed without potential complication arising from the involvement of a copper-allenylidene intermediate.

Table 6. Sonogashira cross-coupling reaction[a)]



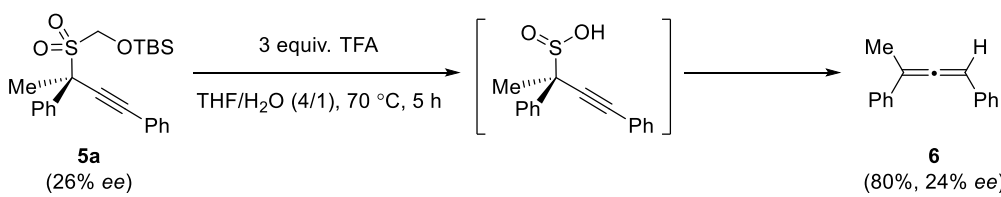
entry	Ar-I	product	yield (%)[b)]	*ee* (%)
1		**5a**	82	26
2		**5b**	82	-
3		**5c**	72	-

a) All reactions were performed with 0.2 mmol of **3a**, 0.02 mmol of $Pd(PPh_3)_4$, 0.02 mmol of CuI, 0.5 ml of toluene and 0.5 ml of TEA at 25 °C for 2 h. b) Isolated yield.

3.3 Sulfinyl Retro-Ene Reaction

As shown by a previous study in our group where a TBSOMS group adjacent to an alkene could be removed in preparation for a sulfinyl retro-ene reaction,[16] we next examined if the same protocol could be applied to the propargylic system. Among the various reaction conditions shown to be effective in our previous studies such as the use of hydrochloric acid, acetic acid and trifluoroacetic acid, treatment of **5a** with 3 equivalents of trifluoroacetic acid at 70 °C produced the chiral allene **6** in 80% yield (Scheme 11). Importantly, the 24% *ee* of the product from 26% *ee* of the reactant showed that the retro-ene reaction occurred with high conservation of enantiomeric excess (92% *cee*). Lowering the reaction temperature

to 50 °C still generated the product but in a decreased yield of 60%. Further lowering the temperature below 40 °C barely mediated the reaction. These results indicate that in the given solvent mixture (TFA-THF-H_2O), the sulfinyl retro-ene reaction requires a minimum temperature of approximately 50 °C. This finding casts doubt on the previous report by the Kocienski group (Scheme 2),[20] in which formation of an allenyl product from the LAH reduction of a benzothiazolyl propargylic sulfone was suggested to be the consequence of a propargylic sulfinic acid rearrangement. It appears highly unlikely that the rearrangement took place at 0 °C within 5 min as reported in the paper. Possible involvement of a direct S_N2' pathway should be carefully examined.



5a (26% *ee*) **6** (80%, 24% *ee*)

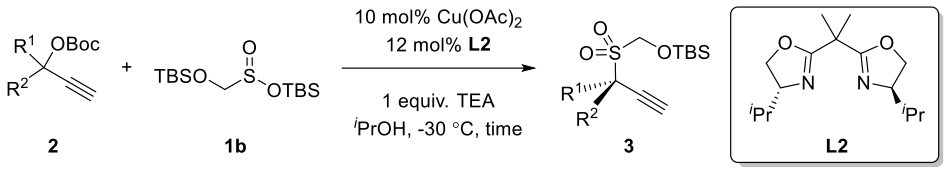
Scheme 11. Sulfinyl retro-ene reaction

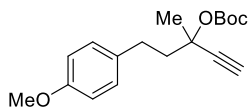
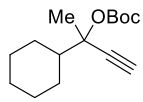
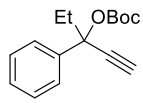
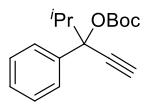
4. Substrate Scope

Using the reaction conditions producing **3a** in high yield, we investigated the scope of the propargylic substitution reaction. An aryl group at propargylic position is considered to be highly beneficial for this type of substitution reactions.[19] Nevertheless, alkyl groups were tolerated in the reaction under these optimized conditions though of slightly reduced yields (Table 7, entry 1 and 2). We also checked the reactivity of the substrates having longer and bulkier alkyl chains, rather than a methyl group, at the propargylic position. As the chains became

longer or bulkier, the yields tended to be reduced to 77% and 66%, respectively (Table 7, entry 3 and 4).

Table 7. Substrate scope of propargylic substitution reaction[a)]



entry		substrate	time (h)	product	yield (%)[b)]	*ee* (%)
1	**2b**		24	**3b**	75	8
2	**2c**		24	**3c**	80	8
3	**2d**		18	**3d**	77[c)]	33
4	**2e**		18	**3e**	66[c)]	8

a) All reactions were performed with 0.2 mmol of **2**, 0.02 mmol of catalyst, 0.024 mmol of **L1**, 0.3 mmol of TBSOMS-TBS and 0.2 mmol of TEA in 1 ml of ^{i}PrOH at -30 °C. b) Yield was determined by NMR using 1,3,5-trimethoxybenzene as an internal standard. c) Starting material remained.

CONCLUSION

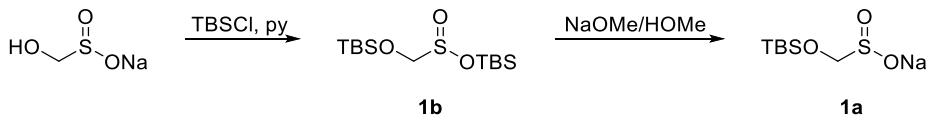
In summary, we have developed a novel method for the synthesis of chiral allenes by making use a tandem protocol involving copper-catalyzed asymmetric *S*-propargylation, Sonogashira cross-coupling and sulfinyl retro-ene reactions. The proof of concept has been established by converting racemic propargylic substrates to the propargyl sulfone products in up to 91% yield and 26% *ee* and eventually to the desired chiral 1,3-trisubstituted allene in high yield with up to 92% *cee*. This method employs two reactants, propargylic alcohol derivatives and sulfonylation reagents, that can be easily prepared, while taking advantage of an earth abundant inexpensive copper catalyst. It has also been corroborated that the TBSOMS reagent developed in our group can be used for *S*-propargylation and generation of a propargylic sulfinic acid. Although further studies are needed to achieve high selectivity in asymmetric induction, the protocol established in this investigation provides a reliable template for the development of an efficient synthetic route to various natural products and chemical compounds containing chiral allenes.

EXPERIMENTAL SECTION

General Information. NMR spectra were obtained on an Agilent 400-MR DD2 Magnetic Resonance System (400 MHz) and a Varian/Oxford As-500 (500 MHz) spectrophotometer. Chemical shift values were recorded as parts per million relative to tetramethylsilane as an internal standard unless otherwise indicated, and coupling constants in Hertz. The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad.

The progress of reaction was checked on thin layer chromatography (TLC) plates (Merck 5554 Kiesel gel 60 F254), and the spots were visualized under 254 nm UV and/or charring after dipping the TLC plate into a vanillin solution (15.0 g of vanillin and 2.5 ml of concentrated sulfuric acid in 250 ml of ethanol), a $KMnO_4$ solution (3.0 g of $KMnO_4$, 20.0 g of K_2CO_3, and 5.0 ml of 5% NaOH solution in 300 ml of water), or a ninhydrin solution (0.3 g ninhydrin, 3 ml of concentrated sulfuric acid in 100 ml of ^{n}butanol). Column chromatography was performed on silica gel (Merck 9385 Kiesel gel 60). All solvents were obtained by passing through activated alumina columns of solvent purification systems from Glass Contour.

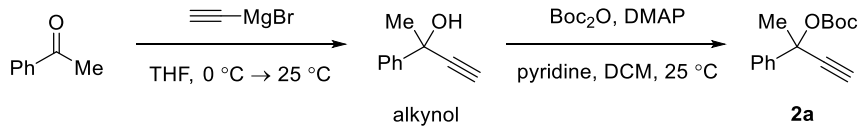
Preparation of TBSOMS-Na and TBSOMS-TBS



TBSOMS-Na was prepared according to the procedure described in the reference literature[15]: To a flame-dried and argon-purged round bottom flask containing a magnetic stirring bar were added TBSCl (12.1 g, 80 mmol) and Rongalite^{TM} (2.37 g, 20 mmol). The mixture was cooled to 0 °C before pyridine (20 ml) was slowly added over several minutes. The reaction mixture was stirred at an ambient temperature. The crude was evaporated *in vacuo* at 50 °C for 5 minutes, then filtered through a short pad of Celite washed with hexane to obtain a crude mixture of **1b** and TBS silanol. (To obtain a pure compound of **1b**, the crude was evaporated *in vacuo* at 70 °C for 10 minutes, white creamy liquid)

To a solution of **1a** in DCM (60 ml) was added sodium methoxide (3.6 ml, 19 mmol, 5.4 M in MeOH) slowly over 10 minutes. The reaction mixture was vigorously stirred for 1 h and turned into a heterogeneous white solution. After evaporation, the waxy precipitate was collected through washing and trituration with hexane. After dried for a day under vacumn, the pure compound **1a** was obtained (70% yield, white solid).

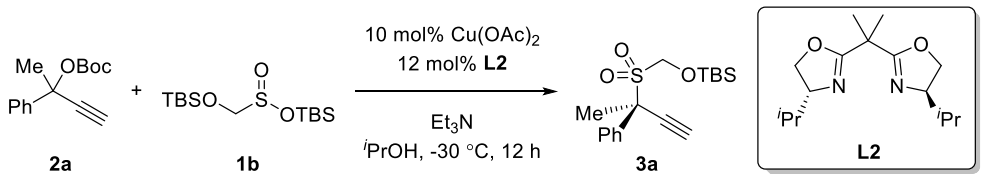
Preparation of propargylic *tert*-butyl carbonate substrates



The propargylic *tert*-butyl carbonate derivatives were prepared according to the procedure described in the reference literature[16]: To a flame-dried and argon-purged round bottom flask containing a magnetic stirring bar were added ethynyl magnesium bromide (96 ml, 48 mmol, 0.5M in THF) and hexane (100 ml). The solution was cooled to 0 °C, then acetophenone (4.71 ml, 40 mmol) was added dropwise. The mixture was stirred overnight at room temperature. The reaction was quenched with aq. NH_4Cl, extracted with EA, and dried over $MgSO_4$. After concentration, the pure alkynol was purified by flash column chromatography (R_f 0.28 in Hex:EA 10:1, 65% yield, light yellow liquid).

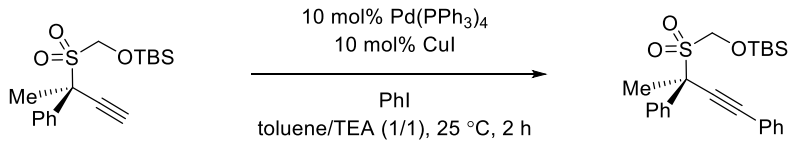
To a solution of alkynol (3.806 g, 26 mmol), DMAP (320 mg, 2.6 mmol), and pyridine (8.4 ml, 104 mmol) in DCM (30 ml) was added Boc_2O dropwise at 0 °C under inert atmosphere. The mixture was stirred overnight at room temperature. The reaction was quenched with water, extracted with DCM, and washed with brine. The crude mixture was dried over $MgSO_4$. After concentration, the pure product **2a** was purified by flash column chromatography (R_f 0.46 in Hex:EA 10:1, 90% yield, colorless sticky oil).

General procedure for copper-catalyzed propargylation



To a flame-dried and argon-purged vial, $Cu(OAc)_2$ (3.63 mg, 0.02 mmol) and chiral ligand **L2** (6.4 mg, 0.024 mmol) were added. Subsequently, ^{i}PrOH (1 ml) was added and stirred for 1 h at an ambient temperature for complexation. The mixture was cooled to -30 °C and the substrate **2a** (49.3 mg, 0.2 mmol) was added dropwise to the solution. Followingly, TBSOMS-TBS reagent **1b** (97.4 mg, 0.3 mmol) and Et_3N (0.028 ml, 0.2 mmol) were successively added at -30 °C. The reaction mixture was stirred until TLC analysis showed the complete consumption of substrate. The reaction was quenched with aq. NH_4Cl and extracted with DCM. The crude mixture was dried over $MgSO_4$. After concentration, the pure product **3a** was purified by flash column chromatography (R_f 0.21 in Hex:EA 10:1, 91% yield, 26% *ee*, yellow liquid).

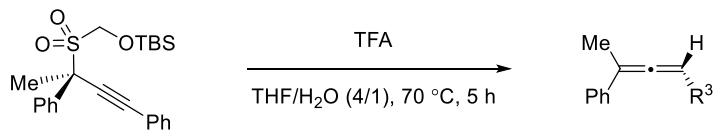
Procedure for the Sonogashira cross-coupling reaction



3a **5a**

To a flame-dried and argon-purged vial were successively added **3a** (67.7 mg, 0.2 mmol, 26% *ee*), iodobenzeene (0.0268 ml, 0.24 mmol), $Pd(PPh_3)_4$ (23.1 mg, 0.02 mmol) and CuI (3.8 mg, 0.02 mmol). The toluene (0.5 ml) and triethylamine (0.5 ml) were added by a syringe at an ambient temperature. Then, the resulting solution was stirred until TLC analysis showed the complete consumption of the starting material. The crude mixture was filtered through a short pad of silica gel by using EA. After concentration, the pure product **5a** was purified by flash column chromatography (R_f 0.41 in Hex:EA 10:1, 82% yield, 26% *ee*, light yellow liquid).

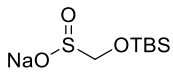
Procedure for sulfinyl retro-ene reaction



5a **6**

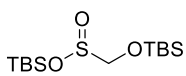
To a solution of **5a** (35.8 mg, 0.086 mmol, 26% *ee*) in THF (0.6 ml) and H_2O (0.15 ml) was slowly added a trifluoroacetic acid (0.02 ml, 0.26 mmol) at an ambient temperature. Then, the reaction mixture was warmed to 70 °C and stirred for 5 h. The mixture was washed with H_2O and extracted with DCM. The crude mixture was dried over $MgSO_4$. After concentration, the pure product **6** was purified by flash column chromatography (R_f 0.50 in Hex:EA 100:1, 80% yield, 23% *ee*, colorless oil).

Characterization of substrates



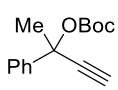
sodium ((*tert*-butyldimethylsilyl)oxy)methanesulfinate (1a)

^{1}H NMR (500 MHz, CD_3OD): δ 3.86 (s, 2H), 0.92 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (126 MHz, CD_3OD): δ 88.08, 26.35, 19.25, -4.92.



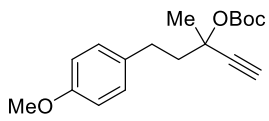
***tert*-butyldimethylsilyl((*tert*-butyldimethylsilyl)oxy)methanesulfinate (1b)**

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.31 (d, J = 9.5 Hz, 1H), 4.26 (d, J = 9.5 Hz, 1H), 0.96 (s, 9H), 0.92 (s, 9H), 0.28 (d, J = 6.9 Hz, 6H), 0.14 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 85.97, 25.64, 25.27, 18.25, 18.07, -3.92, -4.16, -5.16, -5.35.



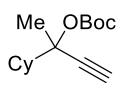
***tert*-butyl(2-phenylbut-3-yn-2-yl)carbonate (2a)**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, J = 7.5 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 2.82 (s, 1H), 1.88 (s, 1H), 1.40 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.84, 142.17, 128.33, 127.90, 124.65, 82.84, 82.59, 76.78, 75.60, 32.52, 27.68.



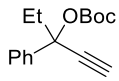
tert-butyl (5-(4-methoxyphenyl)-3-methylpent-1-yn-3-yl) carbonate (2b)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 3.77 (s, 3H), 2.77 (pd, J = 13.6 Hz, 5.2 Hz, 2H), 2.63 (s, 1H), 2.29 - 2.22 (m, 1H), 2.12 – 2.05 (m, 1H), 1.74 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.90, 151.37, 133.33, 129.26, 113.87, 83.46, 82.16, 77.28, 75.74, 73.79, 55.19, 55.17, 43.32, 29.65, 27.81, 26.54.



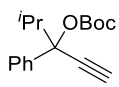
tert-butyl (2-cyclohexylbut-3-yn-2-yl) carbonate (2c)

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.52 (d, J = 2.8 Hz, 1H), 1.96 (d, J = 10.4 Hz, 1H), 1.91 – 1.82 (m, 1H), 1.77 (d, J = 10.1 Hz, 3H), 1.67 – 1.59 (m, 4H), 1.45 (d, J = 3.0 Hz 9H), 1.27 – 1.06 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 151.45, 83.06, 81.77, 79.36, 73.95, 46.65, 27.79, 27.43, 26.85, 26.18, 26.11, 26.06, 23.29.



***tert*-butyl (3-phenylpent-1-yn-3-yl) carbonate (2d)**

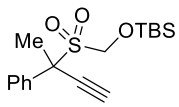
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, J = 7.6 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 7.3 Hz, 1H), 2.83 (s, 1H), 2.19 (dq, J = 14.7 Hz, 7.4 Hz, 1H), 1.96 (dq, J = 14.8 Hz, 7.4 Hz, 1H), 1.39 (s, 9H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.91, 140.97, 128.16, 127.80, 125.12, 82.46, 81.60, 80.91, 76.44, 37.64, 27.67, 8.62.



***tert*-butyl (4-methyl-3-phenylpent-1-yn-3-yl) carbonate (2e)**

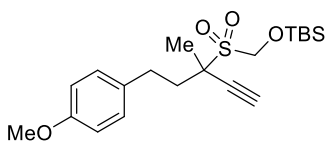
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, J = 7.5 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 7.1 Hz, 1H), 2.80 (s, 1H), 2.24 (hept, J = 6.7 Hz, 1H), 1.35 (s, 9H), 1.20 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.01, 140.68, 127.95, 127.74, 125.59, 84.23, 82.22, 79.90, 77.28, 40.18, 27.65, 17.93, 17.20.

Characterization of products



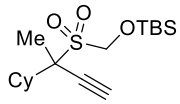
***tert*-butyldimethyl(((2-phenylbut-3-yn-2-yl)sulfonyl)methoxy)silane (3a)**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 – 7.76 (m, 2H), 7.45 – 7.38 (m, 3H), 4.92 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 2.87 (s, 1H), 2.14 (s, 3H), 0.87 (s, 9H), 0.14 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 133.39, 129.19, 128.65, 128.34, 80.83, 77.94, 76.54, 65.41, 25.48, 23.03, 18.20, -5.51, -5.67.



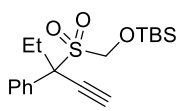
***tert*-butyl(((5-(4-methoxyphenyl)-3-methylpent-1-yn-3-yl)sulfonyl)methoxy) dimethylsilane (3b)**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 5.03 (d, *J* = 11.9 Hz, 1H), 4.90 (d, *J* = 11.9 Hz, 1H), 3.78 (s, 3H), 2.86 (td, *J* = 12.9 Hz, 4.6 Hz, 1H), 2.73 (td, *J* = 12.9 Hz, 5.2 Hz, 1H), 2.65 (s, 1H), 2.43 (td, *J* = 12.8 Hz, 4.6 Hz, 1H), 2.09 (td, *J* = 12.8 Hz, 5.3 Hz, 1H), 1.73 (s, 3H), 0.89 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.03, 132.62, 129.28, 113.89, 80.65, 76.58, 76.48, 61.88, 55.24, 36.43, 29.70, 25.46, 20.58, 18.16, -5.45, -5.52.



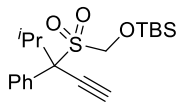
***tert*-butyl(((2-cyclohexylbut-3-yn-2-yl)sulfonyl)methoxy)dimethylsilane (3c)**

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.22 (d, J = 11.7 Hz, 1H), 4.65 (d, J = 11.7, 1H), 2.59 (s, 1H), 2.23 – 2.15 (m, 2H), 2.10 (d, J = 12.6 Hz, 1H), 1.80 (t, J = 14.1 Hz, 2H), 1.66 (d, J = 17.5 Hz, 4H), 1.37 – 1.07 (m, 5H), 0.92 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 81.43, 77.86, 77.82, 77.79, 76.57, 66.10, 41.82, 28.70, 27.64, 26.46, 26.19, 26.02, 25.53, 18.61, 18.24, -5.35, -5.57.



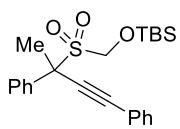
***tert*-butyldimethyl(((3-phenylpent-1-yn-3-yl)sulfonyl)methoxy)silane (3d)**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, J = 6.3 Hz, 2H), 7.42 – 7.36 (m, 3H), 4.82 (d, J = 11.5 Hz, 1H), 4.62 (d, J = 11.6 Hz, 1H), 2.90 (s, 1H), 2.64 – 2.50 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H), 0.85 (s, 9H), 0.11 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 131.22, 129.06, 128.39, 79.38, 79.24, 76.85, 76.81, 76.78, 71.10, 27.15, 25.45, 18.18, 8.41, -5.56, -5.69.



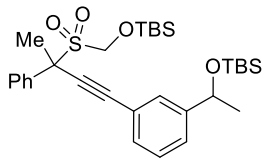
***tert*-butyldimethyl(((4-methyl-3-phenylpent-1-yn-3-yl)sulfonyl)methoxy) silane (3e)**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 – 7.84 (m, 2H), 7.41 – 7.34 (m, 3H), 4.20 (d, *J* = 11.1 Hz, 1H), 4.16 (d, *J* = 11.1 Hz, 1H), 3.07 (dt, *J* = 13.1 Hz, 6.6 Hz, 1H), 2.93 (s, 1H), 1.45 (d, *J* = 6.4 Hz, 3H), 0.81 (s, 9H), 0.72 (d, *J* = 6.7 Hz, 3H), 0.07 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 133.75, 129.04, 128.57, 128.50, 80.86, 78.37, 78.34, 78.31, 77.02. 75.07, 34.08, 25.42, 19.26, 18.62, 18.17, -5.61, -5.75.



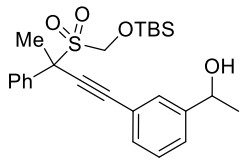
***tert*-butyl(((2,4-diphenylbut-3-yn-2-yl)sulfonyl)methoxy)dimethylsilane (5a)**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, *J* = 6.9 Hz, 2H), 7.55 (d, *J* = 6.1 Hz, 2H), 7.44 – 7.36 (m, 6H), 5.02 (d, *J* = 11.6 Hz, 1H), 4.69 (d, *J* = 11.6 Hz, 1H), 2.22 (s, 3H), 0.86 (s, 9H), 0.13 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 134.10, 131.89, 129.11, 129.05, 128.79, 128.39, 128.35, 121.93, 89.38, 85.93, 66.32, 25.49, 23.33, 18.25, -5.47, -5.66.



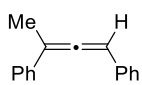
***tert*-butyl(((4-(3-(1-((*tert*-butyldimethylsilyl)oxy)ethyl)phenyl)-2-phenylbut-3-yn-2-yl)sulfonyl)methoxy)dimethylsilane (5b)**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, J = 7.2 Hz, 2H), 7.52 (s, 1H), 7.47 – 7.39 (m, 4H), 7.38 (d, J = 7.9 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 5.03 (d, J = 11.5 Hz, 1H), 4.87 (q, J = 6.0 Hz, 1H), 4.70 (d, J = 11.5 Hz, 1H), 2.23 (s, 3H), 1.42 (d, J = 6.2 Hz, 3H), 0.93 (s, 9H), 0.86 (s, 9H), 0.14 (s, 3H), 0.08 (s, 6H), 0.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.39, 134.18, 130.25, 129.08, 128.81, 128.69, 128.34, 128.26, 126.05, 121.59, 89.69, 85.52, 70.37, 66.32, 27.17, 25.85, 25.51, 23.36, 18.25, 18.22, -4.81, -5.45, -5.64.



1-(3-(3-((((*tert*-butyldimethylsilyl)oxy)methyl)sulfonyl)-3-phenylbut-1-yn-1-yl)phenyl)ethan-1-ol (5c)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, J = 6.8 Hz, 2H), 7.57 (s, 1H), 7.46 – 7.39 (m, 5H), 7.34 (t, J = 7.6 Hz, 1H), 5.00 (d, J = 11.6 Hz, 1H), 4.91 (q, J = 6.3 Hz, 1H), 4.69 (d, J = 11.6 Hz, 1H), 2.22 (s, 3H), 2.04 (br, -OH), 1.50 (d, J = 6.4 Hz, 3H), 0.86 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 146.27, 134.06, 130.89, 129.13, 128.86, 128.78, 128.56, 128.37, 126.20, 122.01, 89.38, 85.82, 69.86, 66.35, 25.50, 25.30, 23.32, 18.24, -5.46, -5.64.



buta-1,2-diene-1,3-diyldibenzene (6)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 – 7.44 (m, 2H), 7.36 – 7.28 (m, 6H), 7.26 – 7.18 (m, 2H), 6.48 (q, J = 2.8 Hz, 1H), 2.23 (d, J = 2.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 206.82, 136.37, 134.54, 128.66, 128.42, 127.00, 126.98, 126.87, 125.83, 104.52, 96.53, 16.74.

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국문 초록

카이랄 알렌은 다양한 생체활성을 띄는 천연물에서 발견되며 비대칭 합성에서 이용되는 중요한 화합물이다. 말단 알카인을 포함하는 라세미 혼합물의 기질로부터 프로파질 치환반응, 소노가시라 교차 짝지음 반응과 설피닐 레트로-엔 반응성을 이용한 카이랄 알렌의 비대칭 합성법을 개발하였다. 이 반응에서 말단 알카인이 구리에 의해 구리-알레닐리딘을 형성한 후, TBSOMS 친핵체의 첨가 반응이 진행되어 카이랄 옥사졸린 리간드의 존재 하에 프로파질 위치에 거울상선택적으로 설폰기가 도입된다. 프로파질 설폰 화합물은 산성 조건에서 이산화항이 이탈하는 과정을 통해 알렌을 형성한다. 이 반응을 통해 프로파질 위치의 카이랄성이 알렌구조로 이동하며 입체선택적인 알렌을 합성할 수 있다.

주요어: 구리-알레닐리딘, 프로파질 치환반응, 설피닐 레트로-엔, 알렌, 말단 알카인

학번: 2021-22407

감사의 글

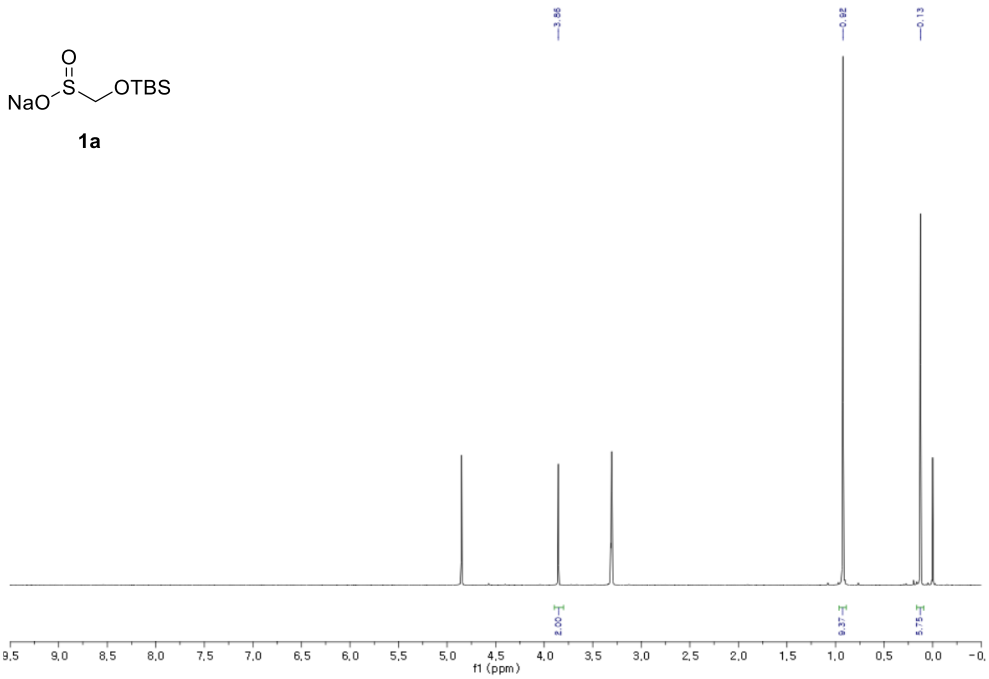
유기화학을 깊이 있게 배우고 싶다는 목표를 가지고 서울대학교 화학부에 들어와 실험실 생활을 시작한 지 어느덧 2년이 되었습니다. 교수님과 실험실 동료들을 비롯한 많은 분의 도움 덕분에 석사학위 과정을 무사히 마칠 수 있었습니다.

누구보다도 저를 믿고 열정적으로 지도해주신 이철범 교수님께 감사드립니다. 학부 졸업 후 학문적 공백으로 인해 두려움을 가지고 있던 저에게 배움의 기회를 주신 점에 대해 감사드리고, 올바른 연구자로서의 태도와 인생을 살아가는 방식에 대해 다시금 돌아볼 수 있게 해 주셔서 진심으로 감사하다는 말씀을 전하고 싶습니다.

또한 바쁜 대학원 생활 속에서도 활기를 유지할 수 있게 해준 실험실 동료들 덕분에 힘든 순간들을 헤쳐 나갈 수 있었습니다. 먼저 어려움이 있을 때 항상 도와주고 선배로서 의지할 수 있었던 혜지, 대권이, 태현이, 민철이에게 고맙다는 말을 전하고 싶습니다. 함께 프로젝트를 진행하며 정말 많은 도움을 준 현석이형, 세훈이, 규진이에게도 감사합니다. 그리고 항상 격려해준 민정누나, 열정적인 이삭이, 동윤이, 이환이 모두 그동안 감사했습니다. 실험실 동료분들 모두 많은 시간과 노력을 쏟는 만큼 하시는 일 잘되기를 진심으로 바랍니다.

마지막으로 제가 하는 일을 항상 응원해주고 믿어 주신 아버지 어머니를 포함한 우리 가족에게 감사의 말씀 전하고 싶습니다. 덕분에 더 성장하고 발전할 수 있었습니다. 이외에도 도움을 주신 고마운 분들이 많기에 항상 감사하는 마음을 가지고 열심히 살아가겠습니다.

SPECTRA



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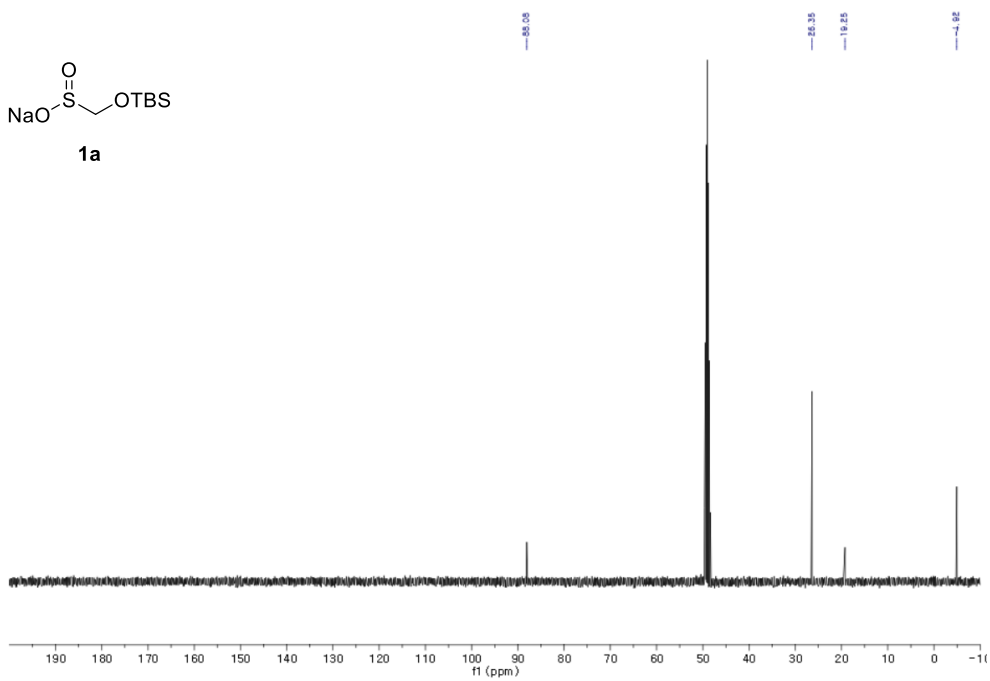

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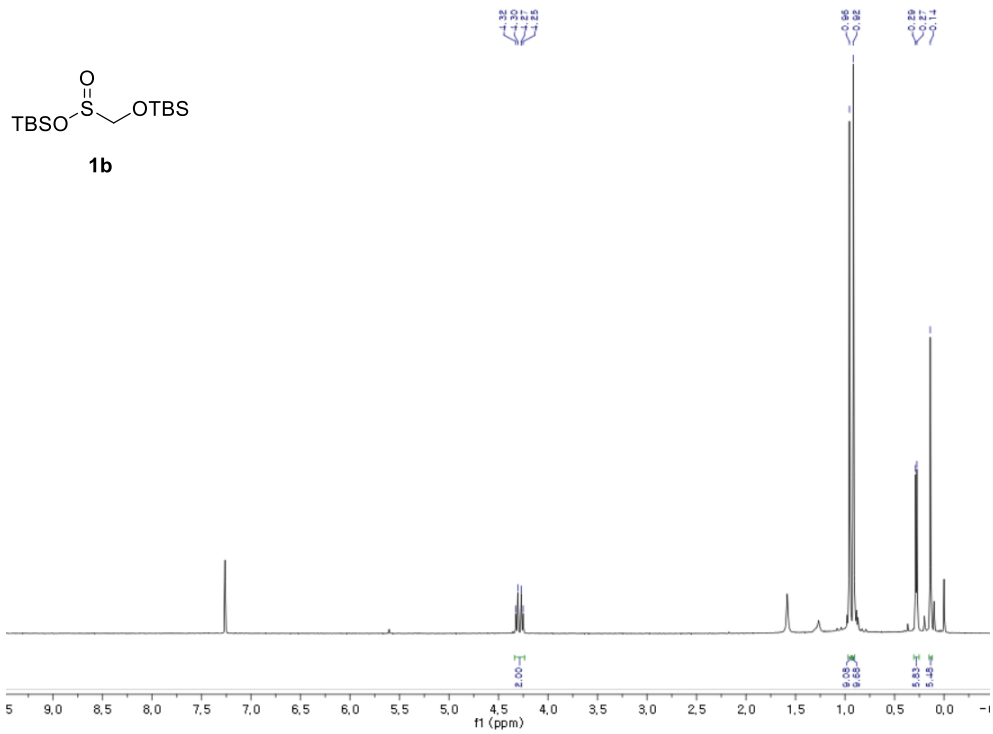

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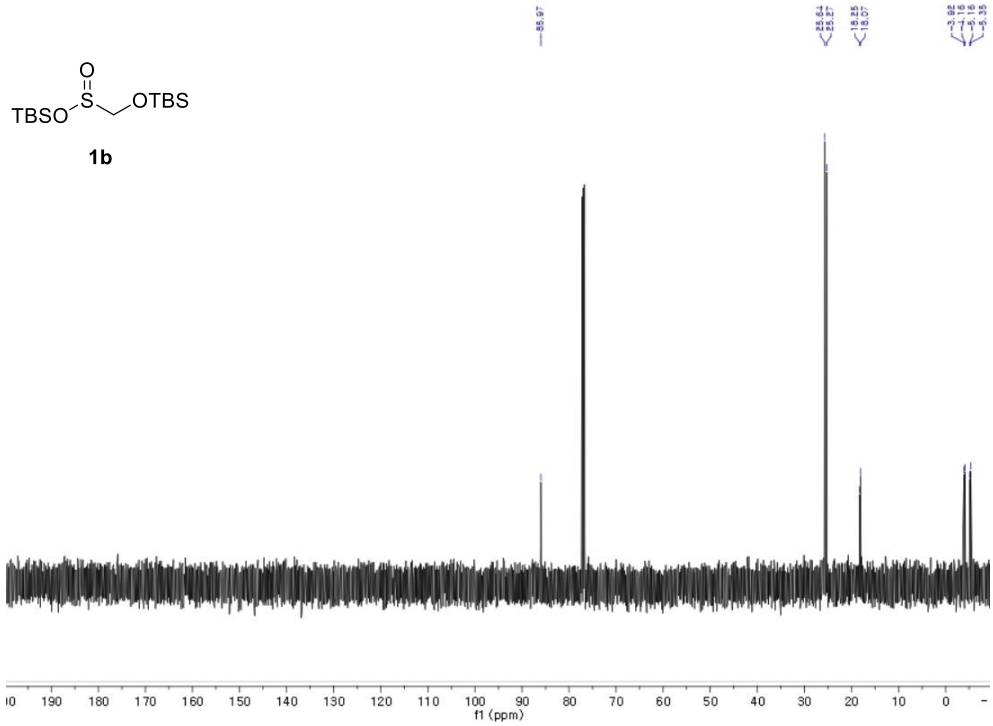

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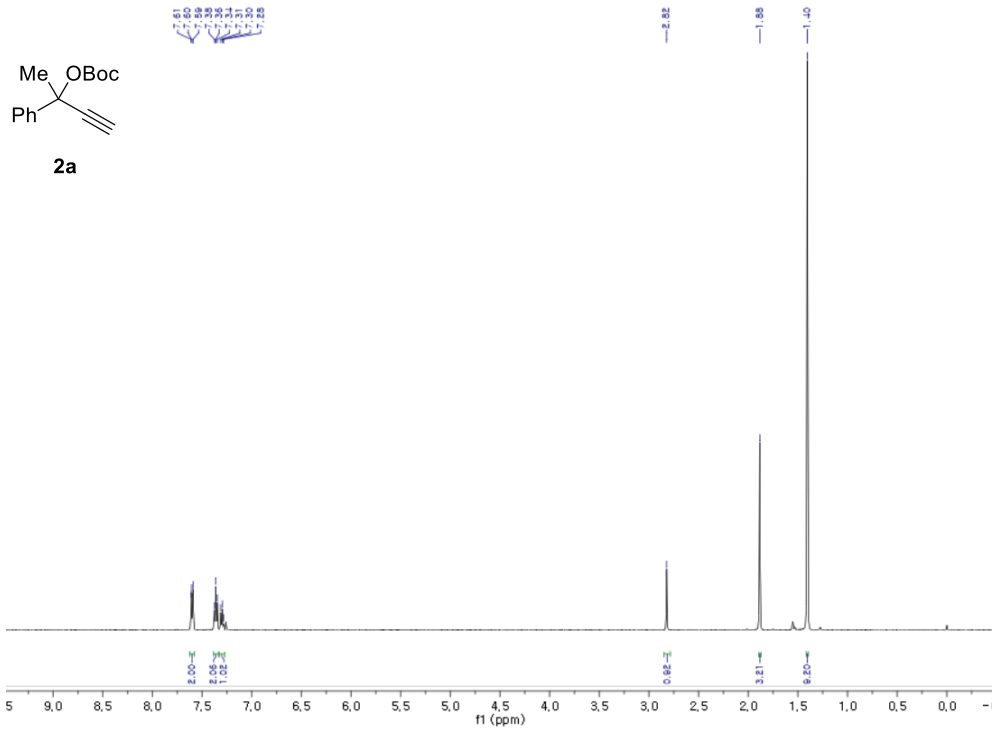

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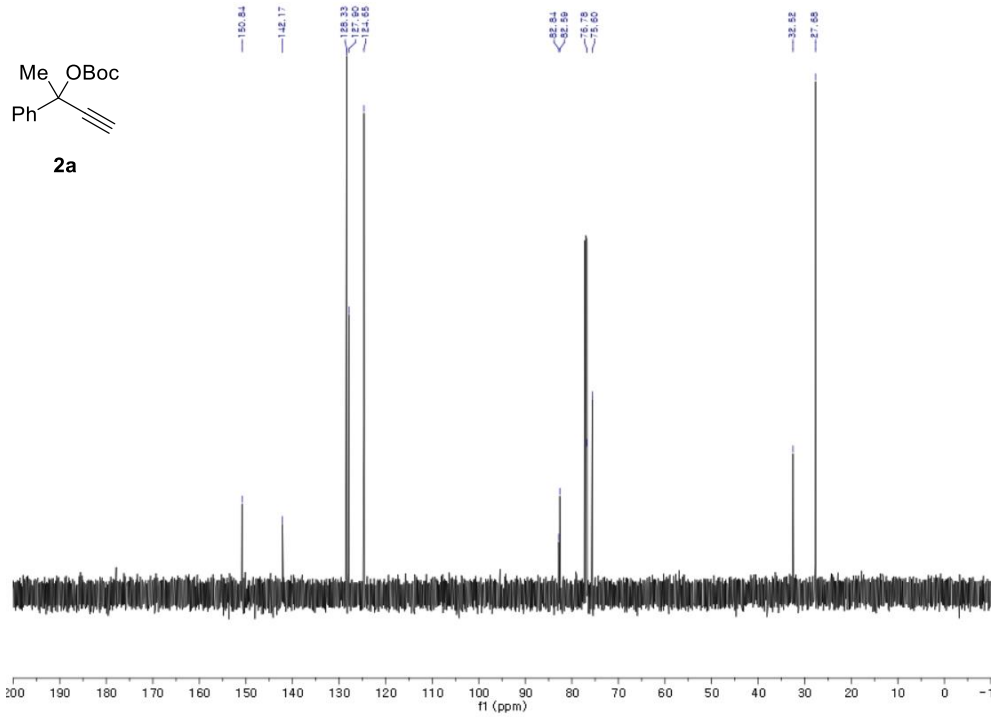

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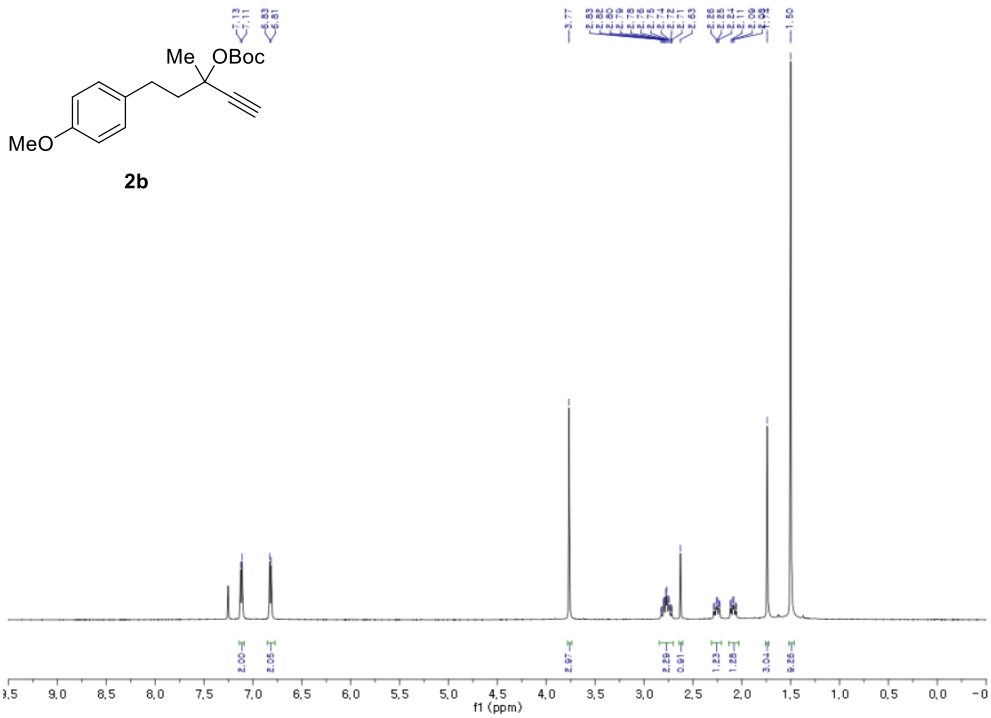

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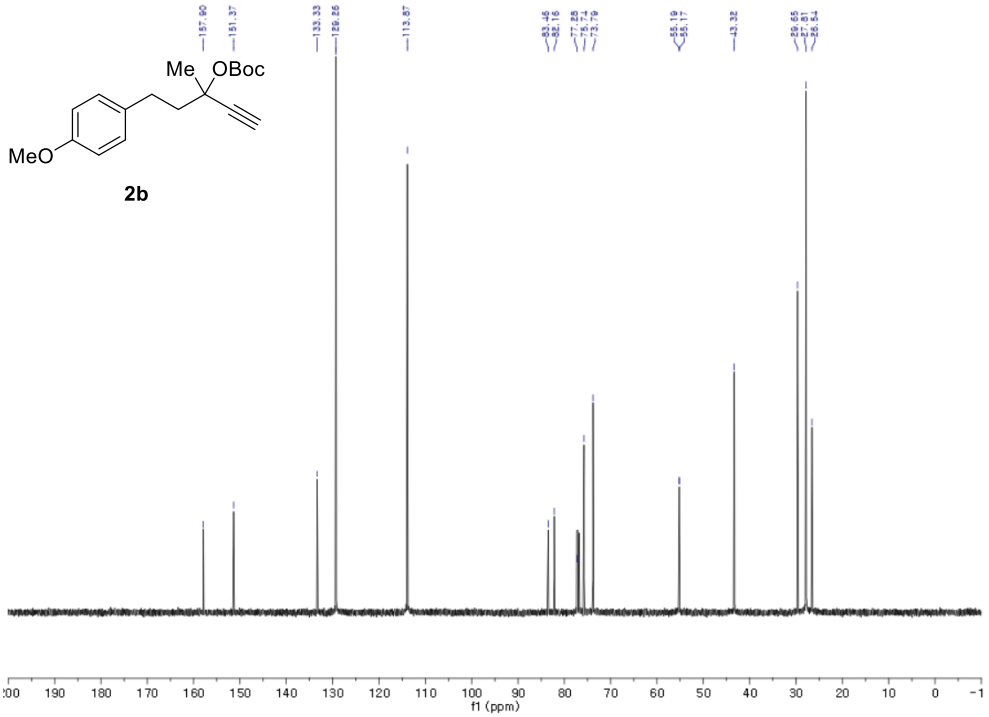

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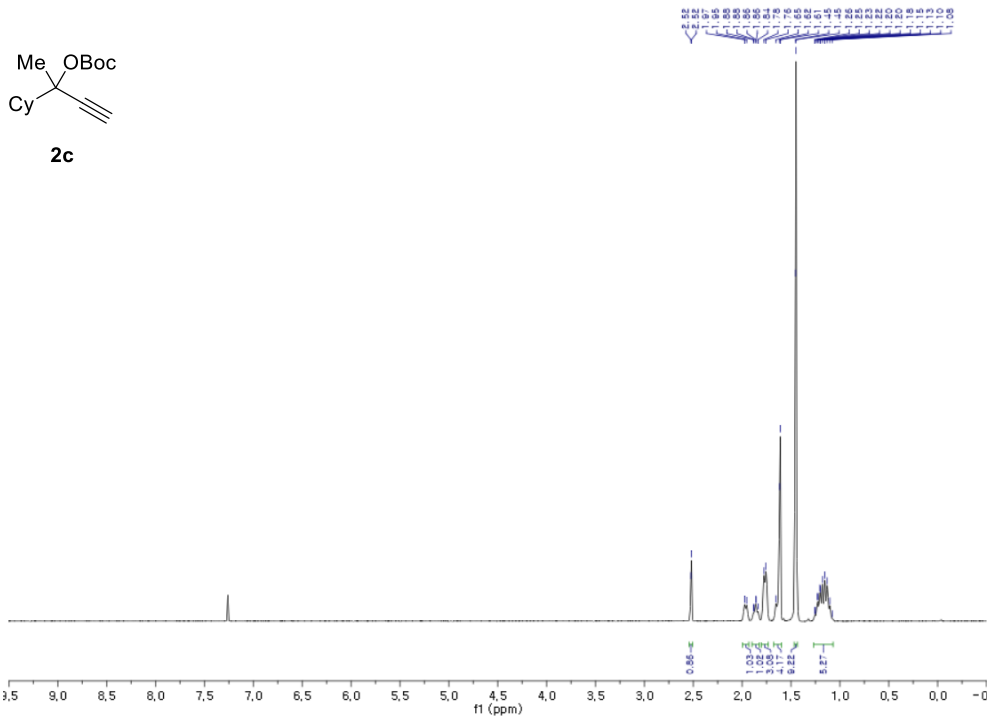

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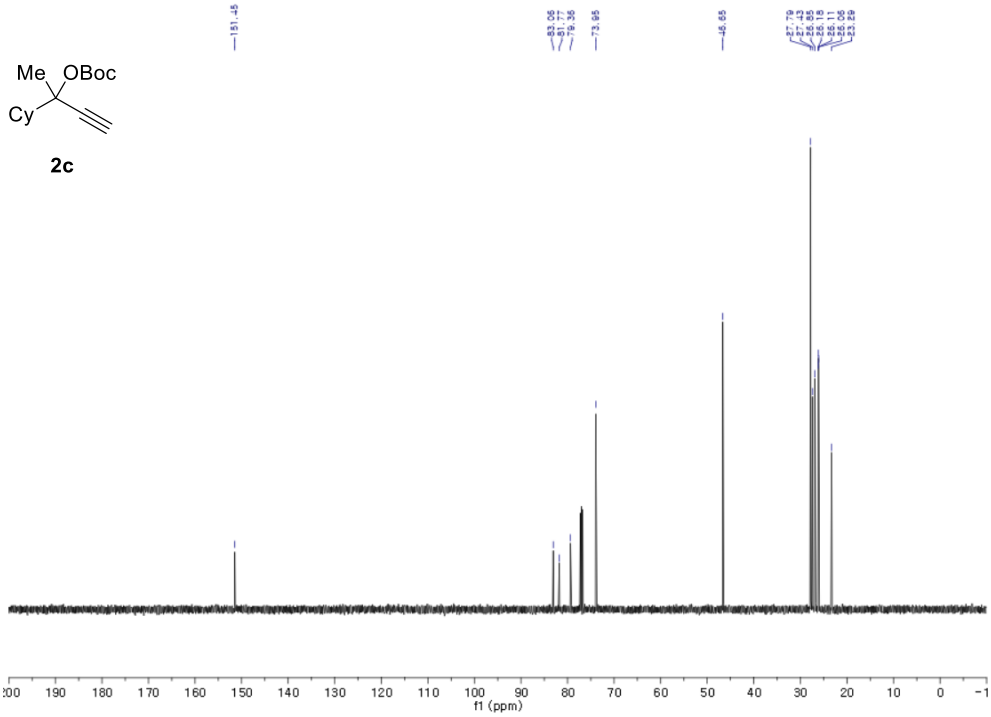

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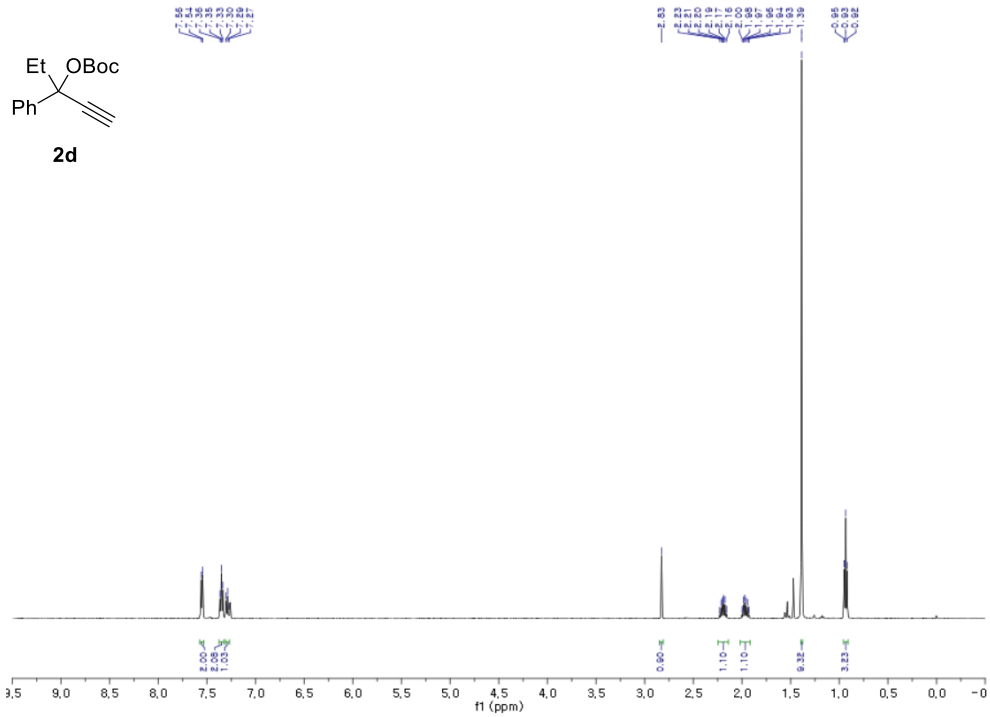

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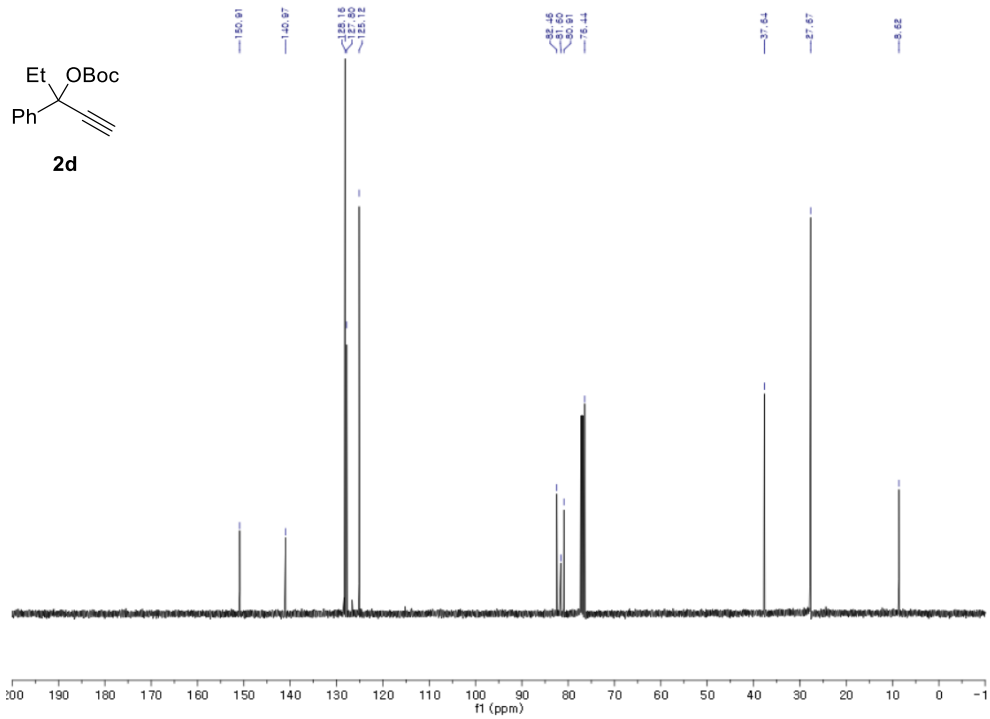

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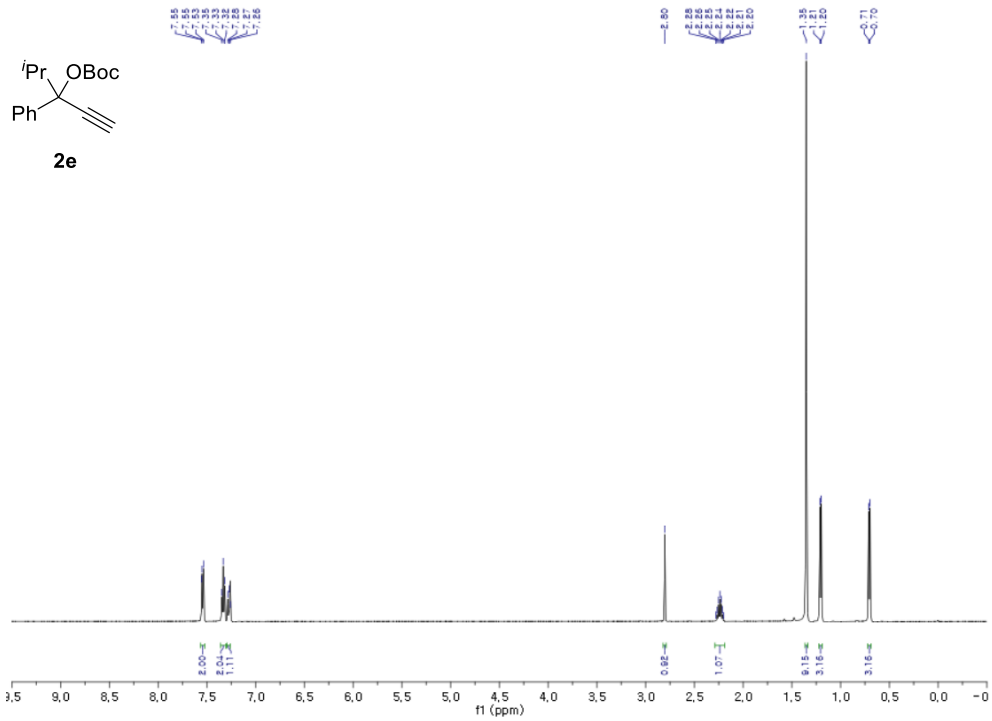

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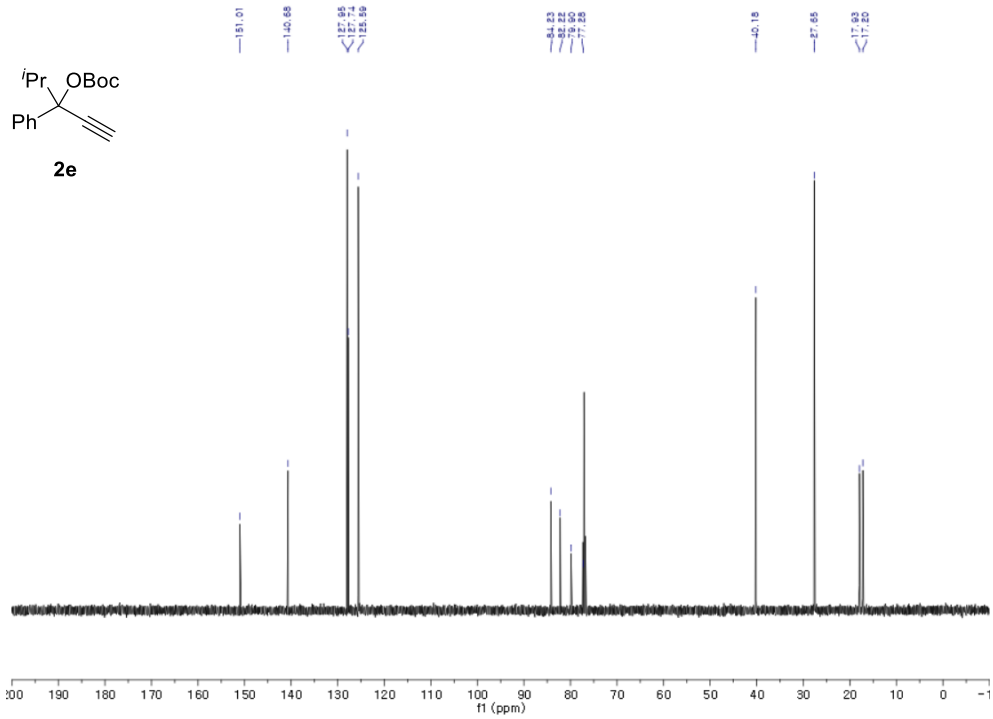

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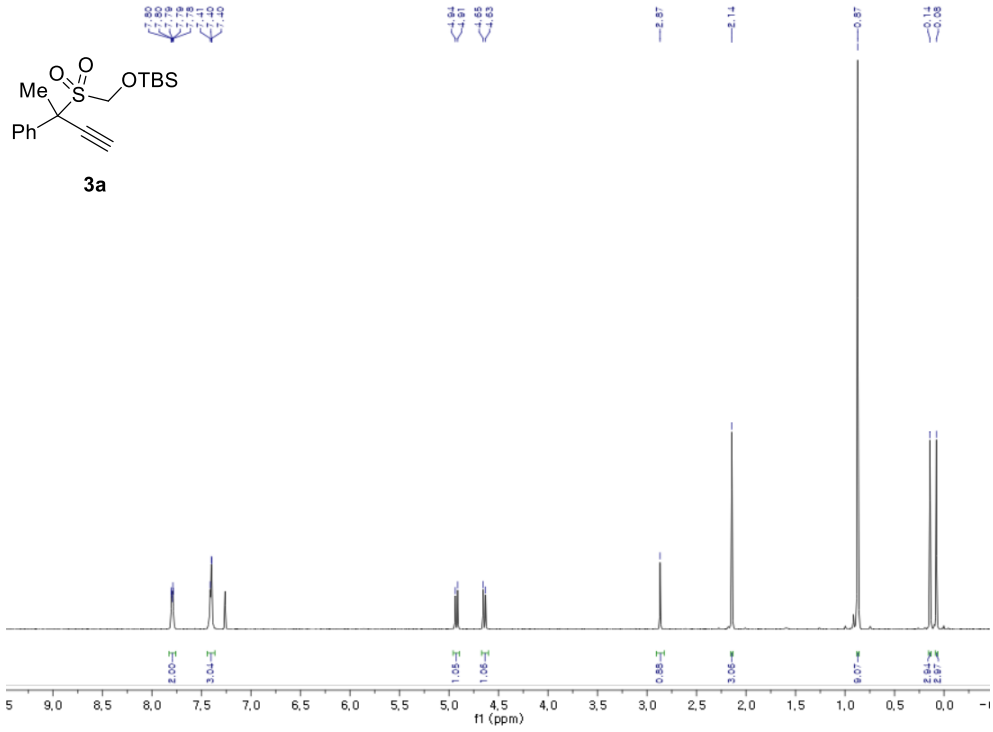

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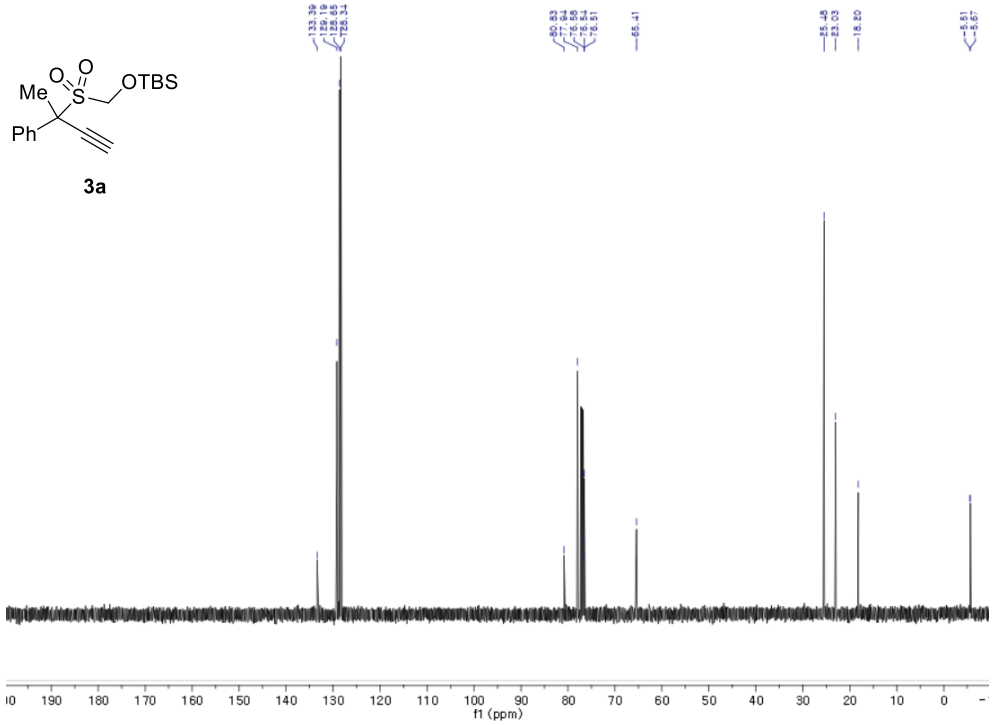

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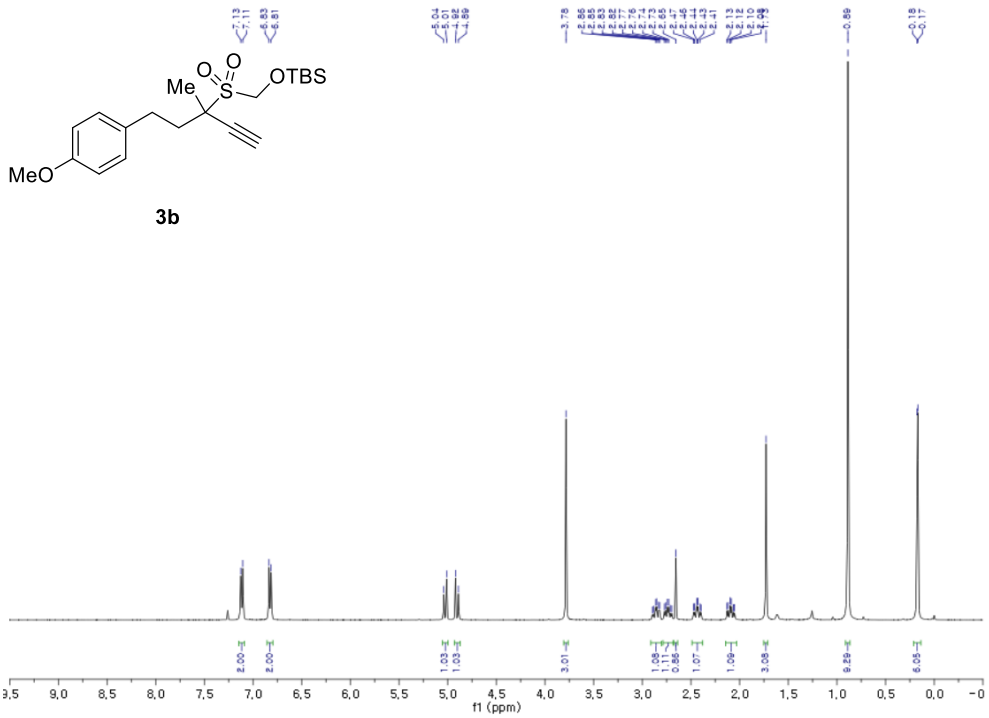

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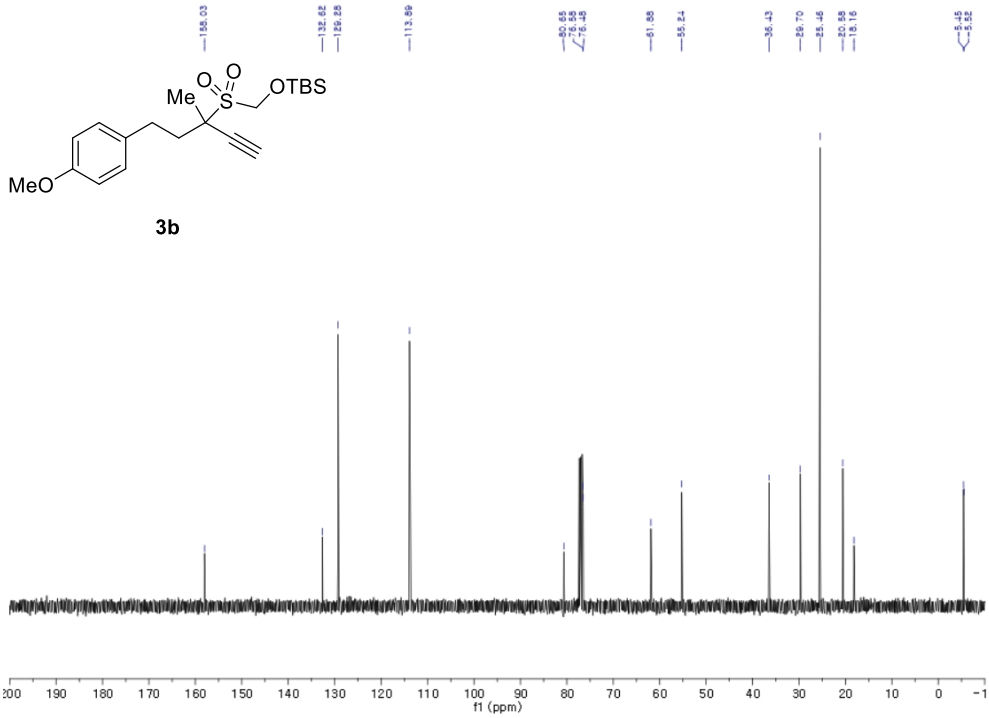

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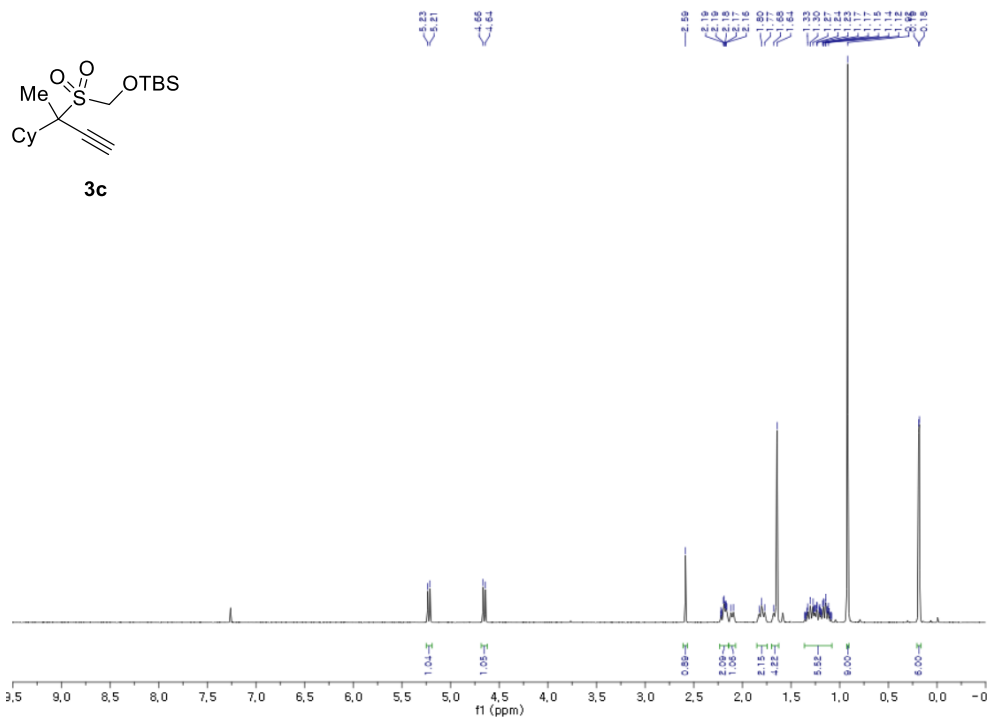
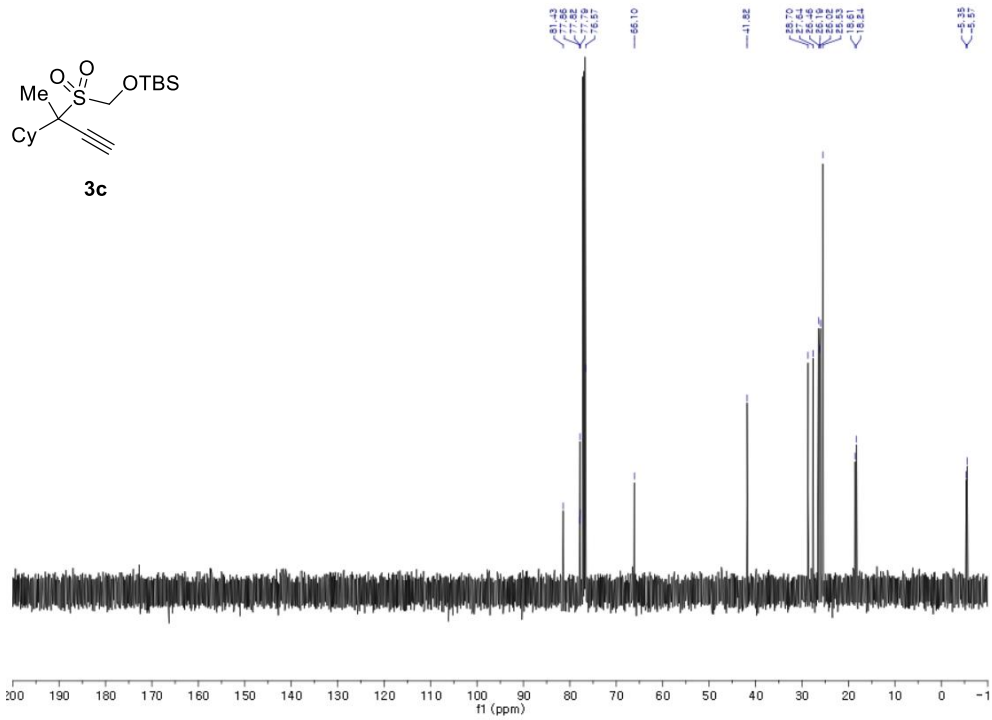
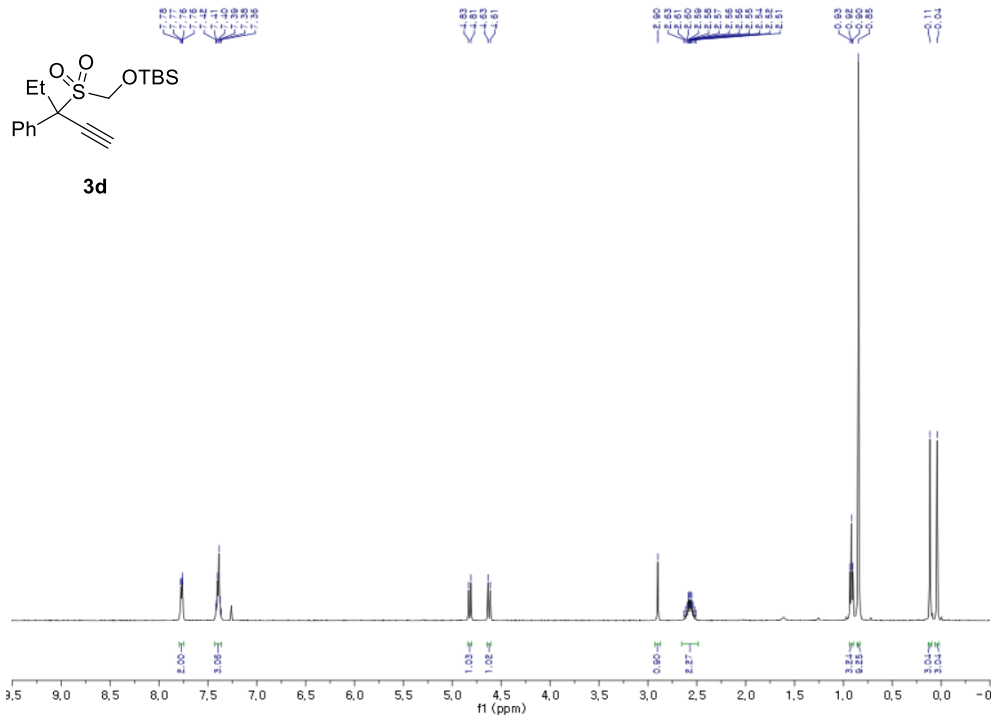


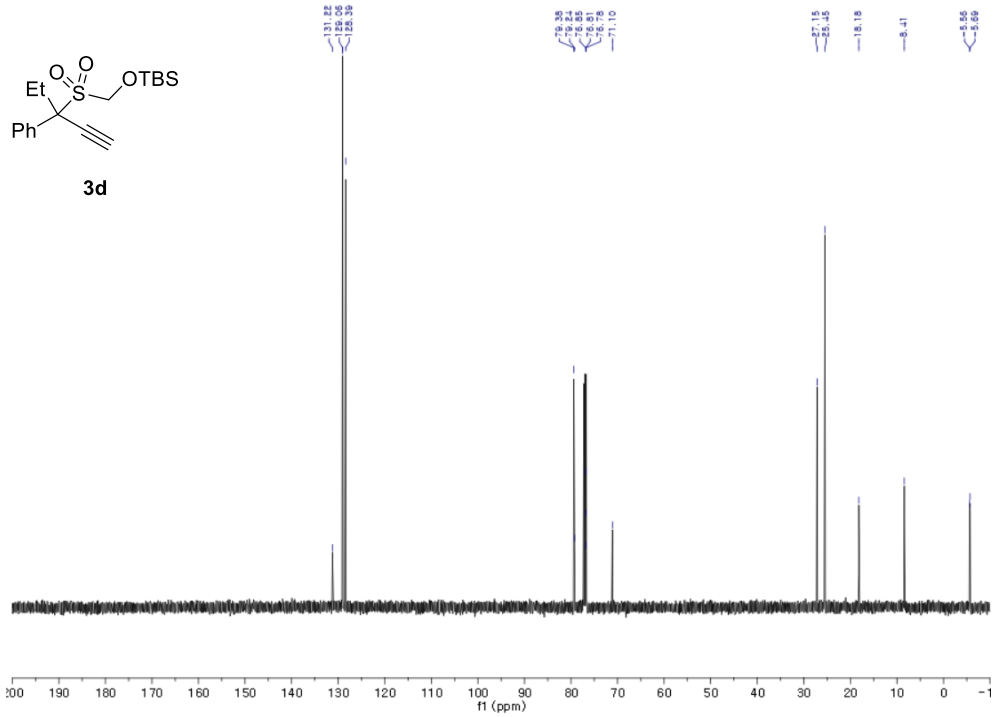
^{1}H NMR (500 MHz, $CDCl_3$) of **3c**



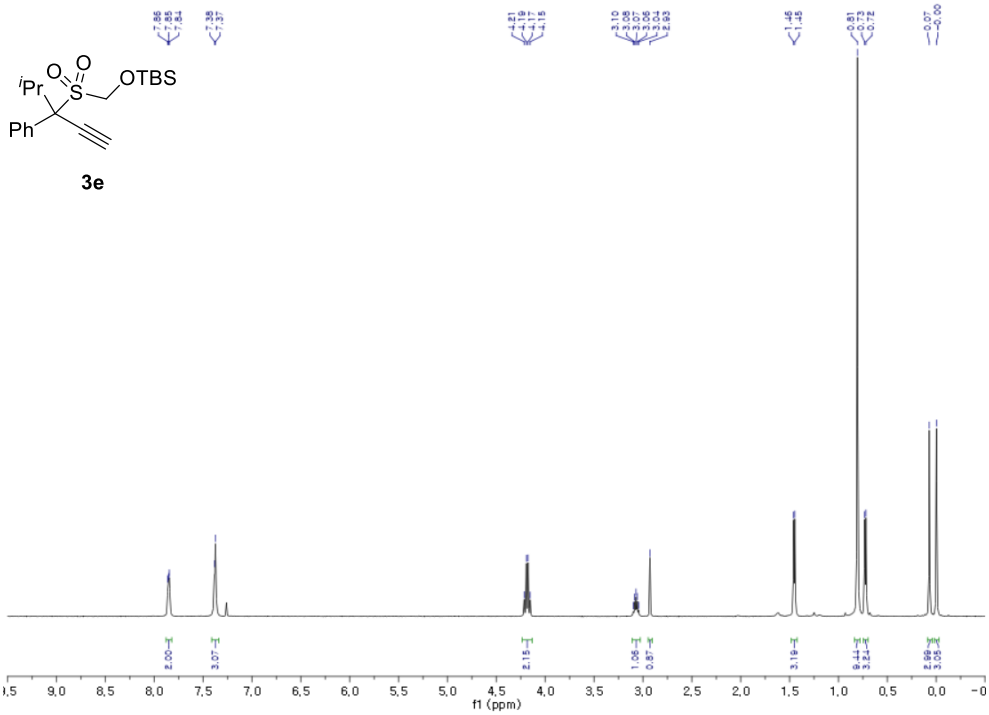
^{13}C NMR (126 MHz, $CDCl_3$) of **3c**



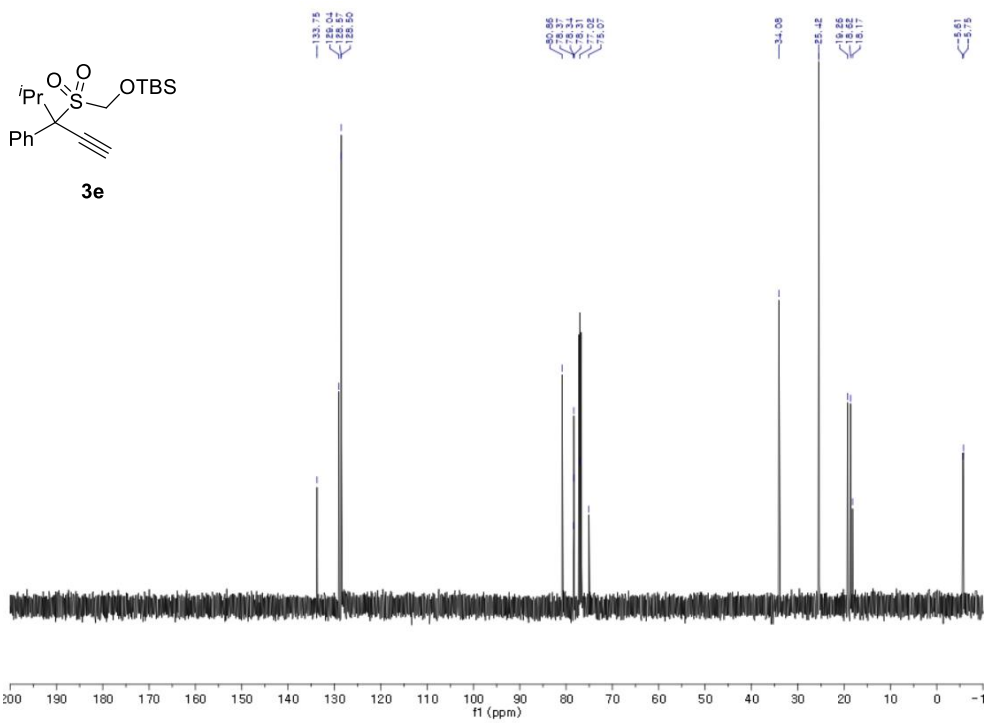
^{1}H NMR (500 MHz, $CDCl_3$) of **3d**



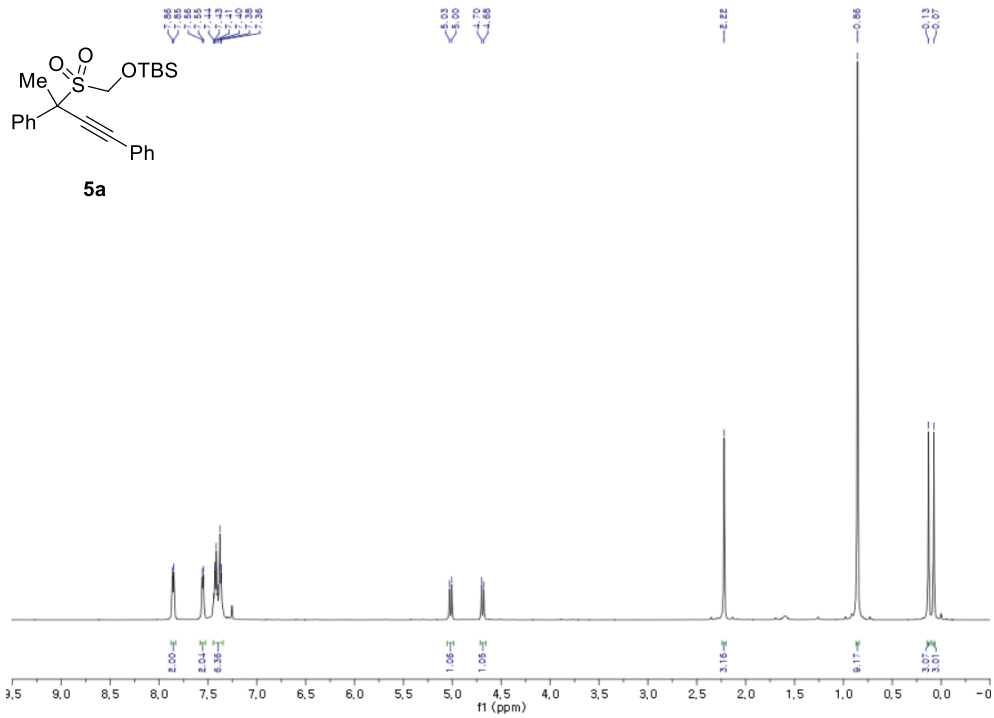
^{13}C NMR (126 MHz, $CDCl_3$) of **3d**



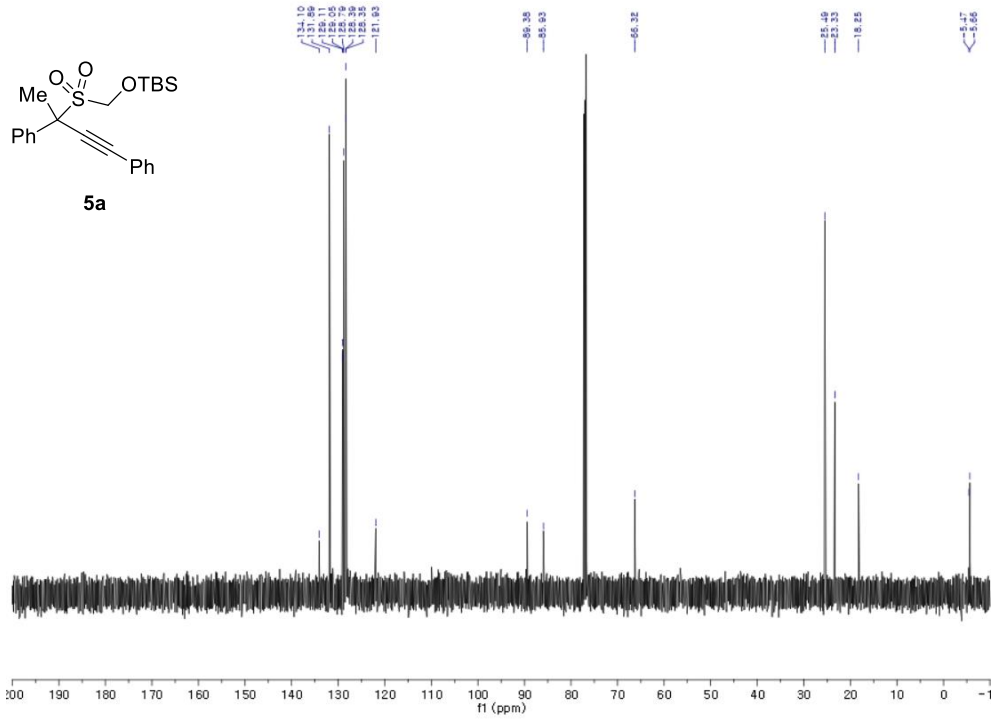
^{1}H NMR (500 MHz, $CDCl_3$) of **3e**



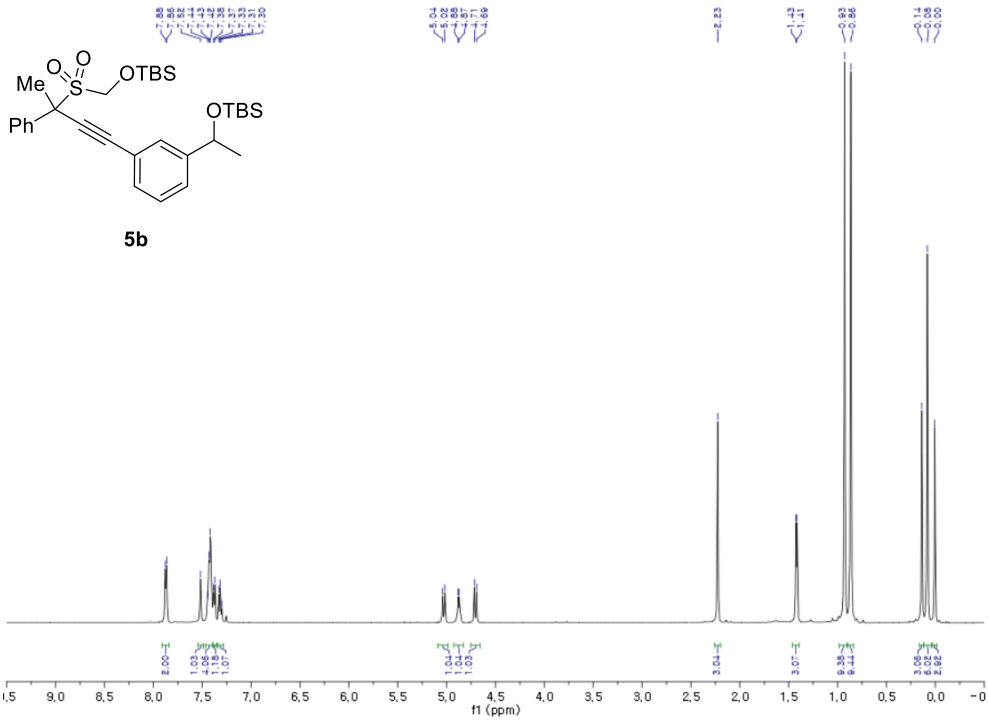
^{13}C NMR (126 MHz, $CDCl_3$) of **3e**



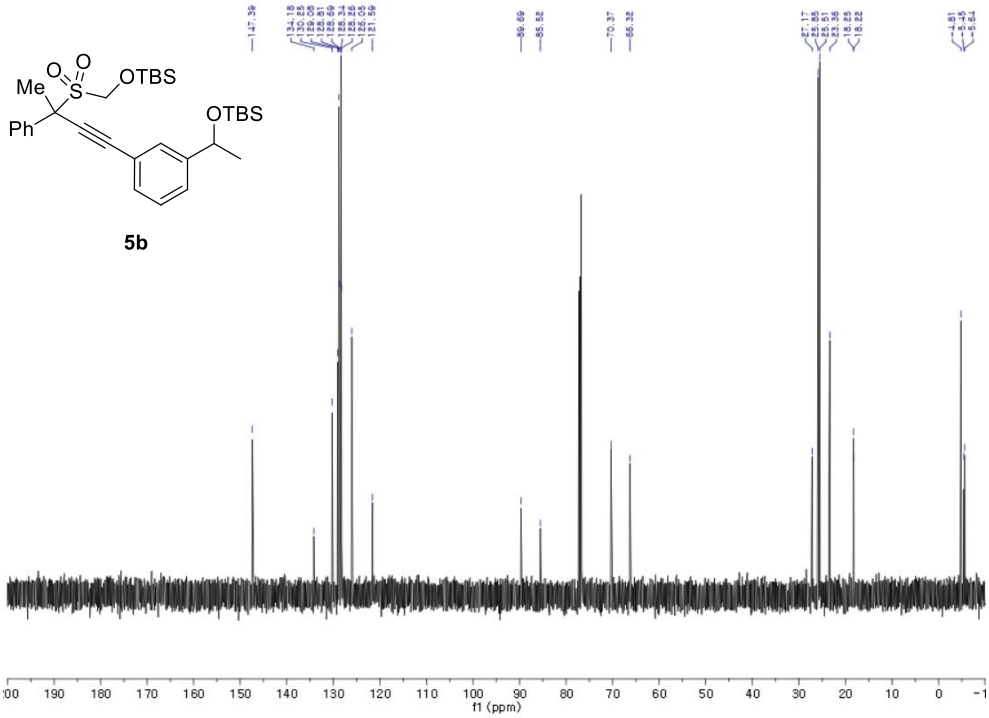
^{1}H NMR (500 MHz, $CDCl_3$) of **5a**



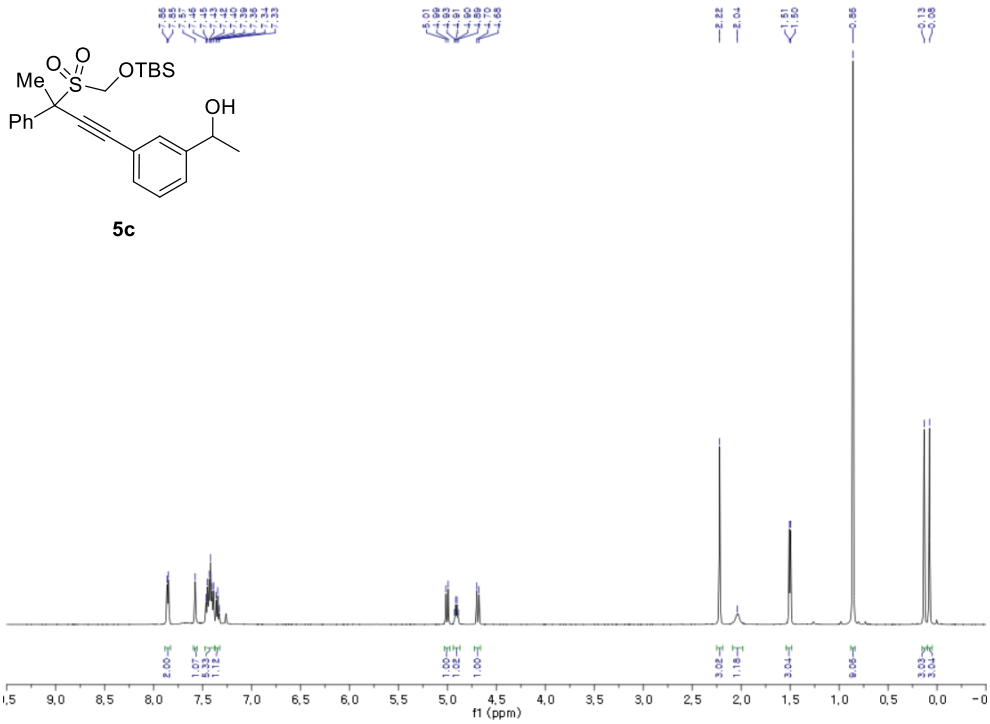
^{13}C NMR (126 MHz, $CDCl_3$) of **5a**



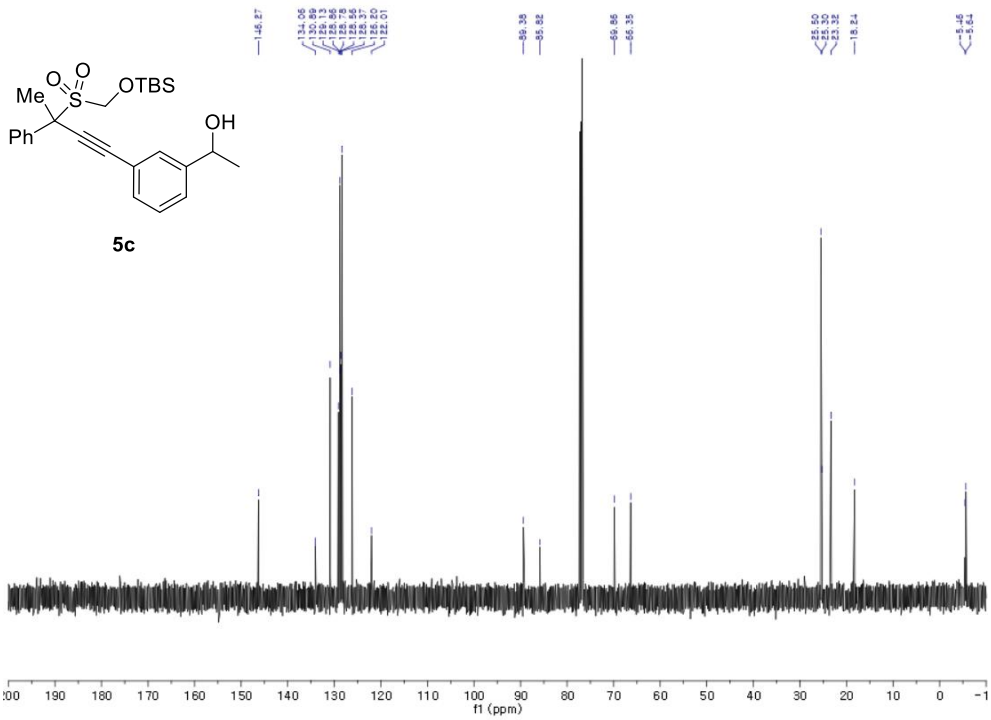
^{1}H NMR (500 MHz, $CDCl_3$) of **5b**



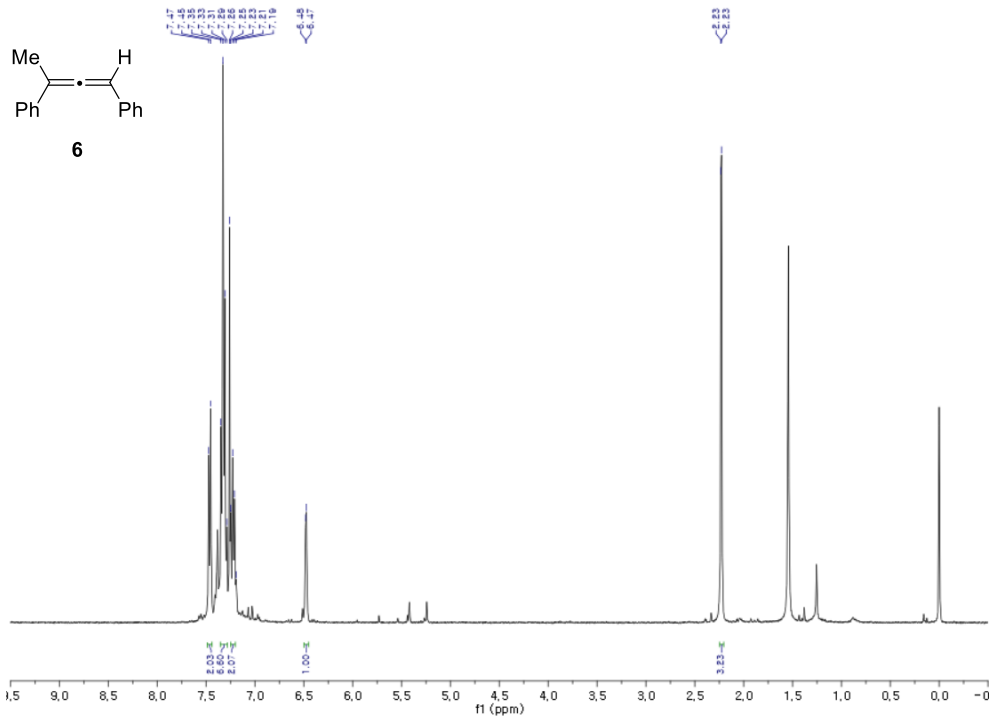
^{13}C NMR (126 MHz, $CDCl_3$) of **5b**



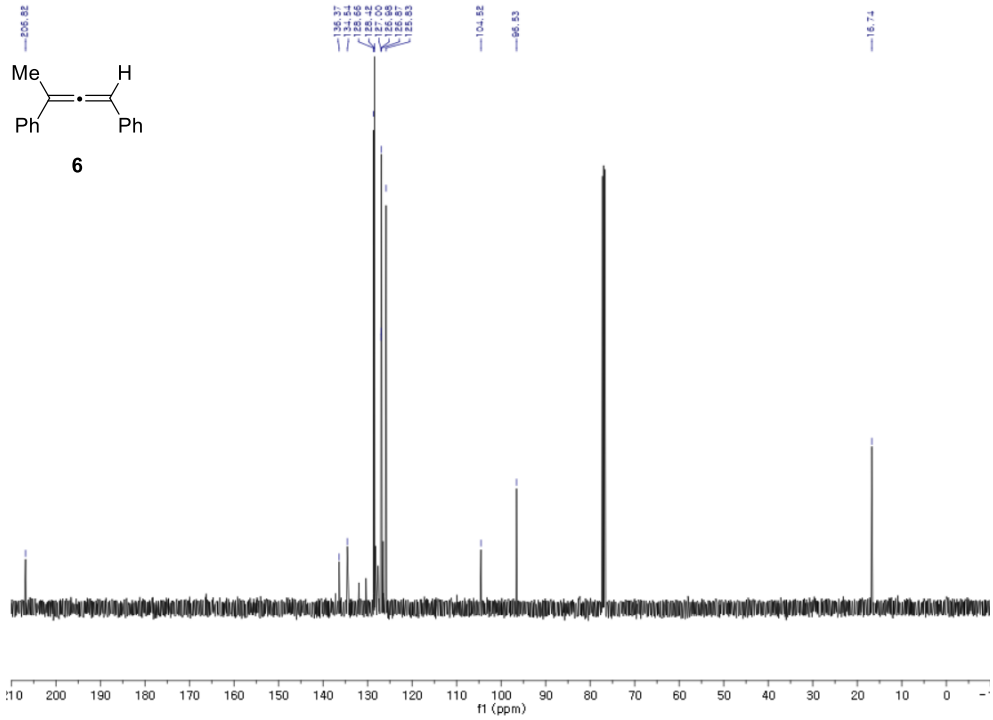
^{1}H NMR (500 MHz, $CDCl_3$) of **5c**



^{13}C NMR (126 MHz, $CDCl_3$) of **5c**



^{1}H NMR (500 MHz, $CDCl_3$) of **6**



^{13}C NMR (126 MHz, $CDCl_3$) of **6**

Chiral HPLC data

1. Analytical method for compound **3a**

Column: Chiralpak IA-3

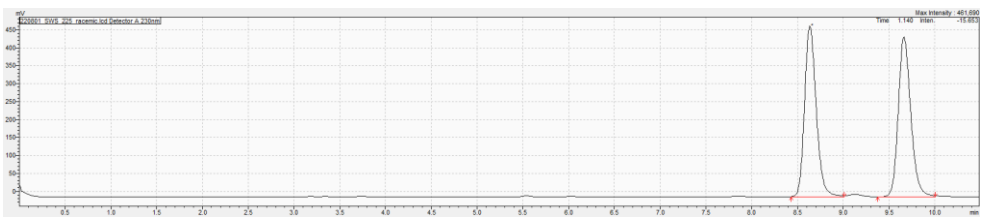
Eluent: Hexane/isopropyl alcohol = 98:2

Flow rate: 1.0 ml/min

Detection Wavelength: 230 nm

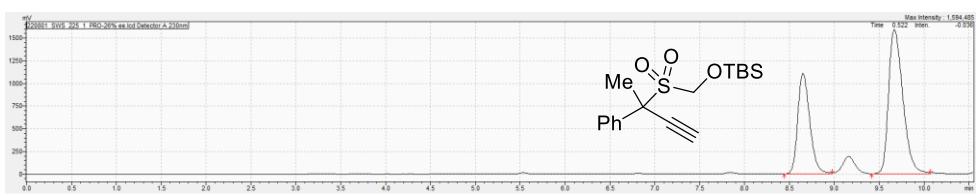
2. Chromatographic Traces of **3a**

2-1. A racemic sample



Peak#	Ret. Time	Mark	USP Width	Area	Height	Area%
1	8.635	M	0.237	4214849	477223	49.682
2	9.663	M	0.256	4268741	445242	50.318

2-2. A chiral sample (26% *ee*)



Peak#	Ret. Time	Mark	USP Width	Area	Height	Area%
1	8.651	M	0.251	10437378	1113566	37.094
2	9.669	M	0.297	17700326	1591973	62.906

3. Analytical method for compound **3b**

Column: Chiralpak IA-3

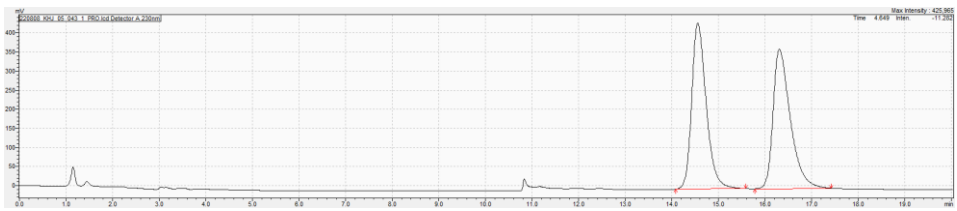
Eluent: Hexane/isopropyl alcohol = 98:2

Flow rate: 1.0 ml/min

Detection Wavelength: 230 nm

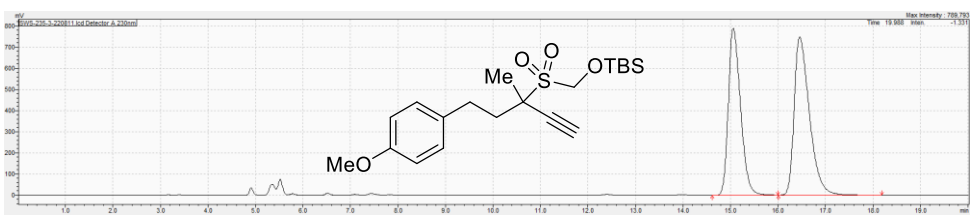
4. Chromatographic Traces of **3b**

4-1. A racemic sample



Peak#	Ret. Time	Mark	USP Width	Area	Height	Area%
1	14,553	M	0,557	9380128	434506	50,000
2	16,306	M	0,659	9380161	364803	50,000

4-2. A chiral sample (8% *ee*)



Peak#	Ret. Time	Mark	USP Width	Area	Height	Area%
1	15,059		0,475	14232409	791301	46,064
2	16,459	M	0,580	16664307	748789	53,936

5. Analytical method for compound **3c**

Column: Chiralpak IA-3

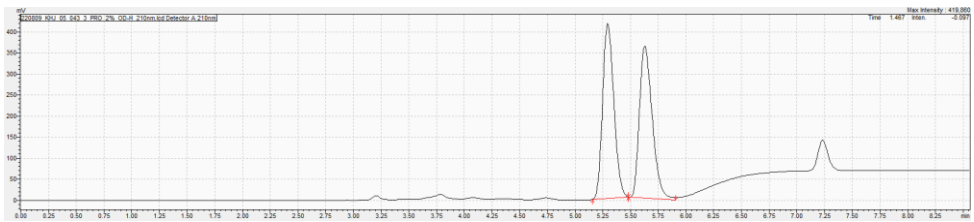
Eluent: Hexane/isopropyl alcohol = 98:2

Flow rate: 1.0 ml/min

Detection Wavelength: 210 nm

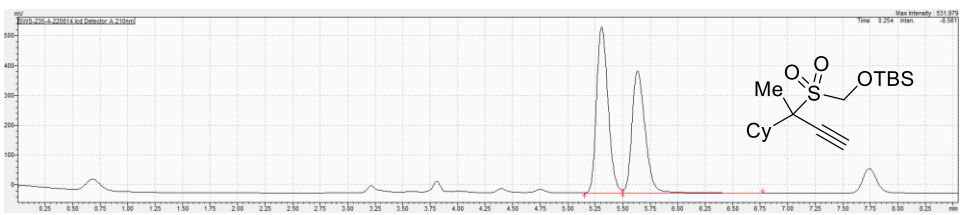
6. Chromatographic Traces of **3c**

6-1. A racemic sample



Peak#	Ret. Time	Mark	USP Width	Area	Height	Area%
1	5,294	M	0,199	2948995	415558	50,167
2	5,628	M	0,222	2929416	360753	49,833

6-2. A chiral sample (8% *ee*)



Peak#	Ret. Time	Mark	USP Width	Area	Height	Area%
1	5,310		0,202	4066141	559441	54,222
2	5,635	V	0,225	3432983	410255	45,778

7. Analytical method for compound **3d**

Column: Chiralpak IA-3

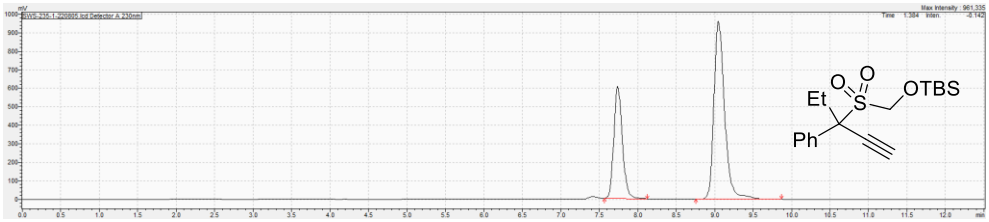
Eluent: Hexane/isopropyl alcohol = 98:2

Flow rate: 1.0 ml/min

Detection Wavelength: 230 nm

8. Chromatographic Traces of **3d**

8-1. A chiral sample (33% *ee*)



Peak#	Ret. Time	Mark	USP Width	Area	Height	Area%
1	7,739	M	0,212	4694910	604959	33,578
2	9,049	M	0,253	9287140	960658	66,422

9. Analytical method for compound **3e**

Column: Chiralpak IA-3

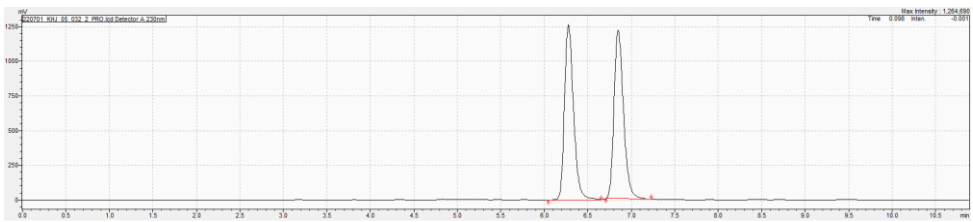
Eluent: Hexane/isopropyl alcohol = 98:2

Flow rate: 1.0 ml/min

Detection Wavelength: 230 nm

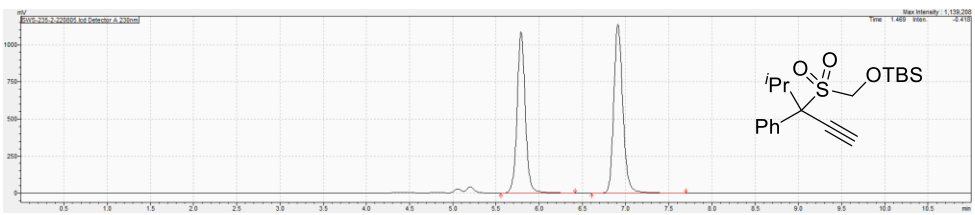
10. Chromatographic Traces of **3e**

10-1. A racemic sample



Peak#	Ret. Time	Mark	USP Width	Area	Height	Area%
1	6,278		0,197	9179086	1264751	49,844
2	6,849	M	0,208	9236419	1213287	50,156

10-2. A chiral sample (8% *ee*)



Peak#	Ret. Time	Mark	USP Width	Area	Height	Area%
1	5,791	M	0,180	7182250	1088911	46,182
2	6,911	M	0,199	8369949	1139093	53,818

11. Analytical method for compound **5a**

Column: Chiralpak IA-3

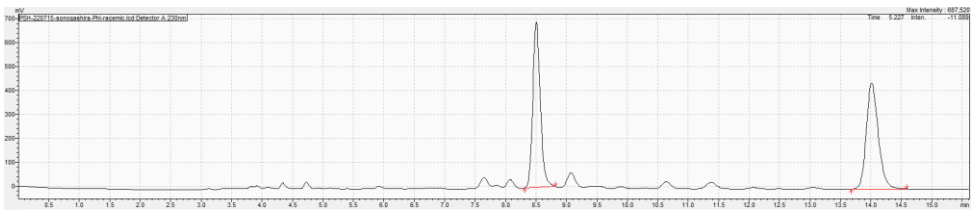
Eluent: Hexane/isopropyl alcohol = 98:2

Flow rate: 1.0 ml/min

Detection Wavelength: 230 nm

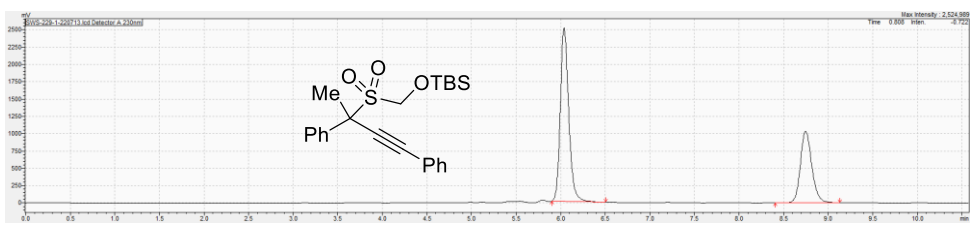
12. Chromatographic Traces of **5a**

12-1. A racemic sample



Peak#	Ret. Time	Mark	USP Width	Area	Height	Area%
1	8.505	M	0.233	5977358	693155	49.474
2	14.014	M	0.361	6104373	444578	50.526

12-2. A chiral sample (28% *ee*)



Peak#	Ret. Time	Mark	USP Width	Area	Height	Area%
1	6.039	M	0.181	16499555	2502898	64.237
2	8.747	M	0.240	9185763	1032486	35.763

13. Analytical method for compound **6**

Column: Chiralcel OD-H

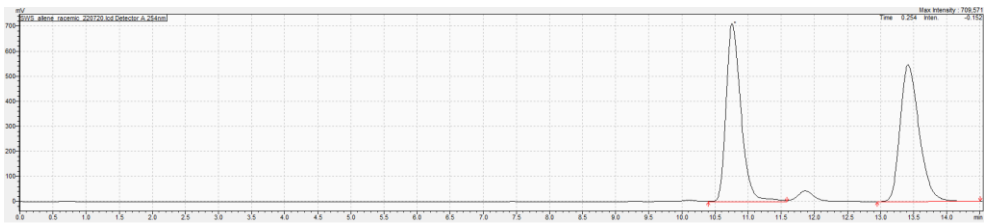
Eluent: Hexane = isocratic

Flow rate: 1.0 ml/min

Detection Wavelength: 254 nm

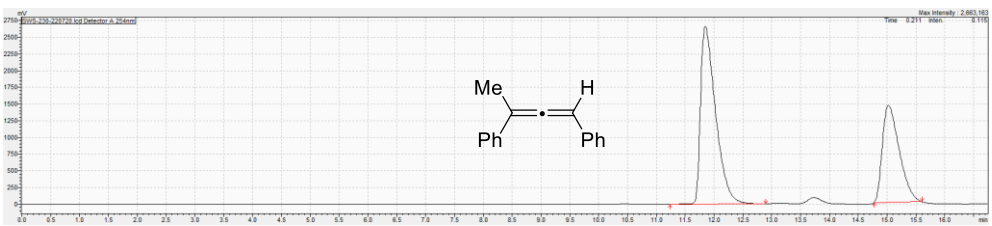
14. Chromatographic Traces of **6**

14-1. A racemic sample



Peak#	Ret. Time	Mark	USP Width	Area	Height	Area%
1	10,760		0,406	11078804	709900	50,379
2	13,417		0,526	10912327	545965	49,621

14-2. A chiral sample (24% *ee*)



Peak#	Ret. Time	Mark	USP Width	Area	Height	Area%
1	11,849	M	0,479	48331524	2661889	62,066
2	15,024	M	0,551	29539759	1452155	37,934