Transition Metal-Catalyzed Synthesis of Optically Active Amino Acids and Heteroatom-Containing Polycyclic Compounds

遷移金属触媒を用いた光学活性アミノ酸および含ヘテロ元素多環式化合物の合成

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Research on Reaction Organic Chemistry

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Abstract

Organic compounds consisting of main group elements, such as oxygen, nitrogen, sulfur and phosphorus atoms, in addition to carbon and hydrogen atoms, are diverse. They exhibit various biological and/or pharmaceutical activities in life science field or functional activities in material science field. For example, natural amino acids, which construct peptides and proteins, support life and vital functions. On the other hand, unnatural amino acids are used as intermediates of medicines and chiral building blocks, and sometimes show biological activities by themselves. A number of functional materials are heteroatom-containing polycyclic compounds, such as organic light emitting diodes (OLED), organic electronics and thin solar cells. A variety of organic compounds have been synthesized and disclosed their functions. Therefore, the synthesis of new compounds has an infinite of possibilities for the creation of unknown functionalities.

Transition metal complexes prepared from metals and ligands play a key role for the development of novel catalytic reactions. In this thesis, the author developed synthetic methods for optically active amino acids and heteroatom-containing polycyclic compounds by using iridium-catalyzed C-H bond activation and rhodium-catalyzed cycloaddition.

This thesis comprises 9 chapters.

In chapter 1, general introduction of amino acids was described.

In chapter 2 through 4, transition metal-catalyzed synthesis of optically active amino acids was described. In chapter 2, the synthesis of 4-substituted tryptophan derivatives via iridium catalyzed sp^2 C-H bond activation and the total synthesis of *cis*-clavicipitic acid by using a 4-substituted tryptophan derivative as a key intermediate were described. This strategy for the synthesis of *cis*-clavicipitic acid started from natural amino acid asparagine and realized high atom efficiency with minimum use of protecting groups.

In chapter 3, enantioselective synthesis of aminoindan carboxylic acid derivatives by rhodium-catalyzed intramolecular cycloaddition was described. The reaction using originally designed amino acid-tethered triynes proceeded, and various tethered aminoindan carboxylic acid derivatives were obtained in good to high ee. In addition, Cbz-protected, free aminoindan carboxylic acid, and its dimethyl ester were obtained by further synthetic transformations.

In chapter 4, enantioselective synthesis of 4-substituted γ-amino acids via iridium catalyzed sp^3 C-H bond activation was described. Highly enantioselective iridium-catalyzed sp^3 C-H alkylation of γ-butyrolactam proceeded, and the corresponding chiral γ-amino acids were synthesized by removal of

directing group and hydrolysis. In addition, enantioselective formal total synthesis of pyrrolam A was achieved.

In chapter 5, general introduction of heteroatom-containing polycyclic compounds was described.

In chapter 6 through 8, transition metal-catalyzed synthesis of heteroatom-containing polycyclic compounds was described. In chapter 6, multi-substituted dibenzothiophene and dibenzophosphole oxide derivative synthesis by rhodium-catalyzed intermolecular cycloaddition was described. The reaction of sulfanyl and phosphoryl benzene-tethered diynes with monoalkynes proceeded to give multi-substituted dibenzothiophene and dibenzophosphole oxide derivatives in good to high yield. Enantioselective reaction could also be achieved, and an axial chiral compound possessing a bi-dibenzothiophene skeleton and a P-chiral dibenzophosphole oxide derivative were obtained in high ee.

In chapter 7, the synthesis of sulfur-containing condensed polycyclic compounds by rhodium-catalyzed intermolecular cycloaddition was described. Catalytic reaction of benzothiophene dioxide derivatives with diynes gave 4-11 ring condensed polycyclic compounds in one pot. This is the first catalytic example, where the 2,3-double bond of benzoheterole was used as an en moiety in [2+2+2] cycloaddition.

In chapter 8, enantioselective synthesis of multi-substituted tribenzothiepin derivatives by rhodium-catalyzed intermolecular cycloaddition was described. Chiral tribenzothiepin derivatives were synthesized by intermolecular reaction of diphenyl sulfide-tethered diynes and 2-phenyl sulfanylbenzene-tethered diynes with a monoalkyne. This is the first catalytic enantioselective synthesis of tribenzothiepin derivatives.

In chapter 9, summary of this thesis was described.

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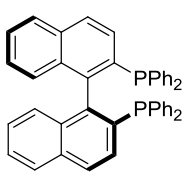
List of Abbreviations

Å	angstrom
Ac	acetyl
Aic	aminoindan carboxylic acid
AcOH	acetic acid
Alloc	allyloxycarbonyl
aPC	activated protein C
Ar	aryl
Asn	asparagine
Asp	aspartic acid
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAM	2,2'-bis(diphenylphosphinoamino)-1,1'-binaphthyl
Bn	benzyl
Bpin	4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl
br	broad
Boc	*tert*-butoxycarbonyl
Bu	butyl
°C	degree centigrade
ca.	circa
Cbz	benzyloxycarbonyl
CD	circular dichroism
C-H	carbon-hydrogen
C-P	carbon-phosphorus
CNS	central nervous system
cod	1,5-cyclooctadiene
conc	concentrated
Cy	cyclohexyl group
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBT	dibenzothiophene
DBP	dibenzophosphole
DBU	1,8-diazabicyclo[5.4.0]-7-undecene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DCU	dicyclohexylurea
dd	doublet of doublets
ddd	doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DG	directing group
DMA	*N,N*-dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	*N,N*-dimethyl-4-aminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide

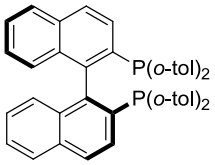
dppf	1,1'-bis(diphenylphosphino)ferrocene
dt	doublet of triplets
ECD	electronic circular dichroism
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
ee	enantiomeric excess
EP	Prostaglandin E receptor
equiv	equivalent
ESI	electro spray ionization
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
GABA	γ-aminobutyric acid
h	hour(s)
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectra
Hz	hertz
i	iso
J	coupling constant
LDA	lithium diisopropylamide
LFA-1	lymphocyte function-associated antigen 1
M	molar, mol/L
m	multiplet
m	meta
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
Mes	mesityl
mp	melting point
N	normality
n	normal
hNK_2	human neurokinin-2
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	NOE correlated spectroscopy
o	ortho
OLED	organic light-emitting diodes
p	para
PG	protecting group
Ph	phenyl
Phe	phenylalanine
PHMS	poly(methylhydrosiloxane)
Pr	propyl
PTC	phase transfer catalyst
PTLC	preparative thin layer chromatography
Py	2-pyridyl
q	quartet
rac	racemic
ref	reference

rt	room temperature
s	singlet
t	triplet
t	tertiary
TACE	tumor necrosis factor-alpha converting enzyme
TEA	triethylamine
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
temp	temperature
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl (as a functional group), tetramethylsilane (as a standard material)
tol	tolyl
Trp	tryptophan
Ts	*p*-toluenesulfonyl
UV	ultraviolet
VCD	vibrational circular dichroism

List of Ligands



(*S*)-BINAP



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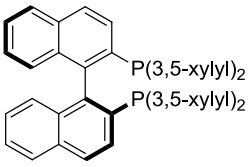

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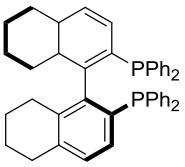

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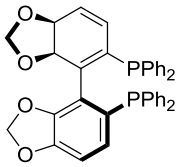

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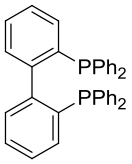
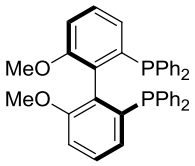
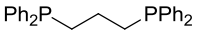


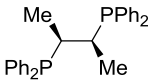
BIPHEP



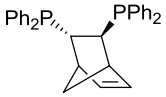
(*S*)-MeO-BIPHEP



DPPP



(*S*,*S*)-CHIRAPHOS



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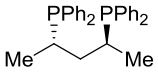

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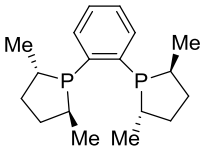
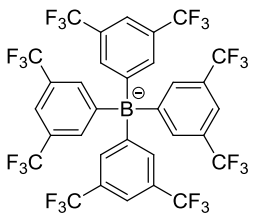


(*S*,*S*)-Me-DUPHOS



BARF

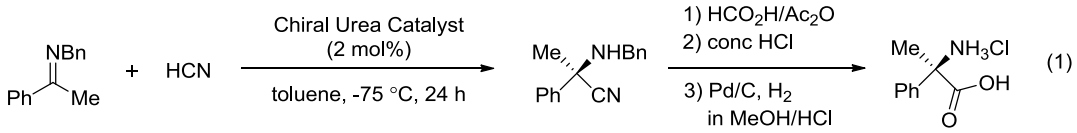
Chapter 1

General Introduction of Amino Acids

Backgrounds

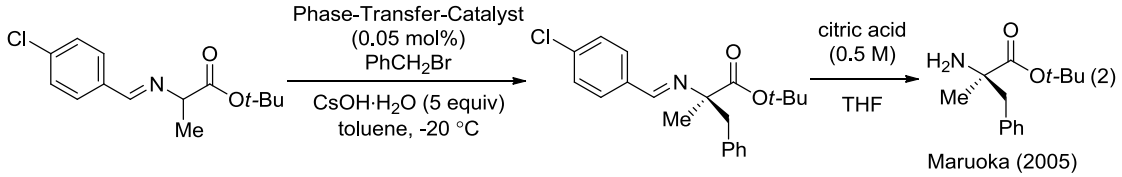
Natural amino acids are essential for the construction of peptides and proteins, the control of vital function, and the basis of life-support. On the other hand, unnatural amino acids are used as intermediates of medicine and chiral building blocks,[1] and sometimes show biological activities by themselves.[2]

Various methods for the synthesis of unnatural amino acids have been reported. Strecker reaction is a conventional approach to the synthesis of α-amino acid derivatives.[3] Vachal and Jacobsen reported an enantioselective Strecker reaction using a chiral urea catalyst, and quaternary amino acids were synthesized (eq. 1).[4]



Jacobsen (2000)

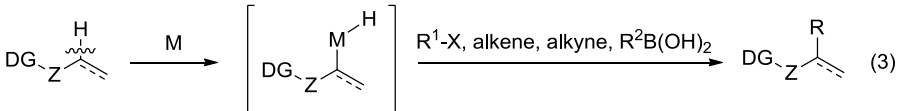
As another approach to the synthesis of chiral amino acids, phase-transfer-catalyzed reaction was developed.[5] Maruoka and co-workers reported enantioselective synthesis of α-alkyl- and α,α-dialkyl-α-amino acids by chiral phase-transfer-catalysts (eq. 2).[6]



Maruoka (2005)

Transition Metal-Catalyzed C-H Bond Activation

Transition metal-catalyzed C-H bond activation, where mainly sp^2 or sp^3 C-H bonds are cleaved and react with various coupling partners, has attracted synthetic chemists, because shorter and more atom-economical syntheses of complex and/or useful molecules can be realized (eq. 3).[7]



DG = Directing Group
Z = carbon or heteroatom

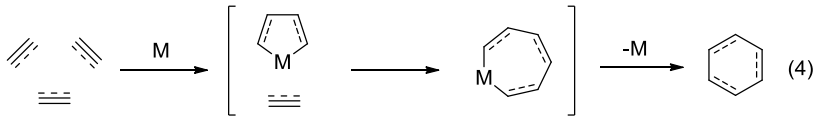
To date, direct C-H bond activation strategy has been used in key steps for the total synthesis of natural products and pharmaceuticals.[8] In particular, enantioselective activation of sp^3 C-H bond is an ideal transformation, but is still a challenging topic.[9]

In Shibata group, Rh- and Ir-catalyzed C-H bond activations have been comprehensively studied for

the carbon-carbon bond forming reaction, and useful synthetic building blocks were synthesized via sp^2 C-H bond activation.[10,11] Furthermore, activation of sp^3 C-H bond was also achieved[12] including an enantioselective variant.[13]

Transition Metal-Catalyzed Cycloaddition

Transition metal-catalyzed [2+2+2] cycloaddition of alkynes and/or alkenes, is a reliable and atom economical method for the synthesis of multi-substituted six-membered ring derivatives, and various types of substrates have been subjected to the cycloaddition (eq. 4).[14]



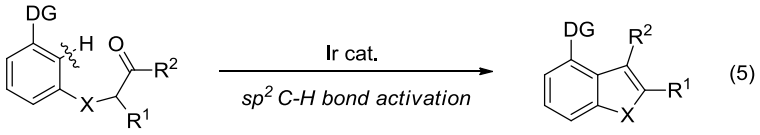
(4)

In Shibata group, intra-[15,16] and intermolecular[17,18] [2+2+2] cycloadditions of various types of unsaturated compounds by Rh- and Ir-catalysts have been extensively studied, and diverse compounds possessing six-membered ring system were synthesized.

Purpose of This Thesis (Chapter 2 through 4)

Purpose of chapter 2 through 4 in this thesis is the synthesis of amino acid derivatives by using iridium-catalyzed C-H bond activation and rhodium-catalyzed cycloaddition. 4-Substituted tryptophan (Trp) derivatives and aminoindan carboxylic acid (Aic) derivatives were synthesized as α-amino acids, and 4-substituted aminobutyric acid derivatives were synthesized as γ-amino acids.

Chapter 2 describes the synthesis of 4-substituted tryptophan derivatives and the total synthesis of *cis*-clavicipitic acid via iridium-catalyzed sp^2 C-H bond activation. Shibata and co-workers reported intramolecular cyclodehydration via sp^2 C-H bond activation for the synthesis of 4-substituted benzofuran and indole derivatives (eq. 5).[11b,11d]



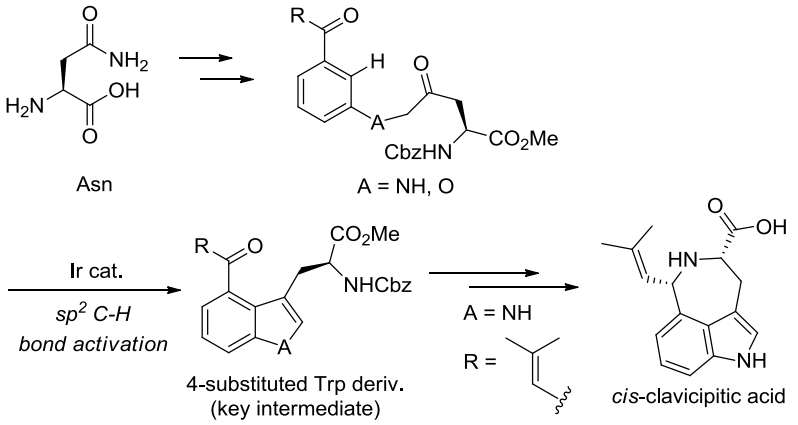
(5)

X = O, NH
DG = Ac, CO_2Me, NHAc

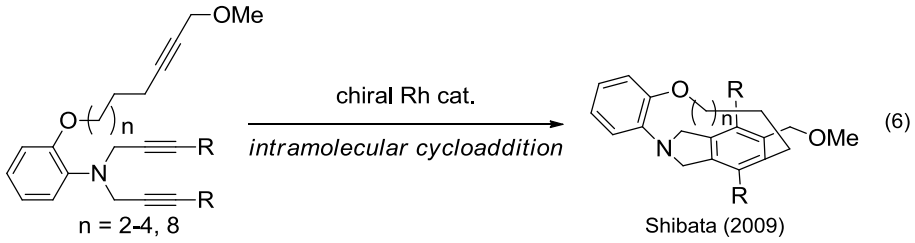
Shibata (2009)

This reaction was applied to the synthesis of 4-substituted Trp derivatives (Scheme 1). In addition, the total synthesis of *cis*-clavicipitic acid by using a 4-substituted Trp as a key intermediate and asparagine as a starting material was achieved.

Scheme 1. Synthesis of 4-substituted tryptophan derivatives and *cis*-clavicipitic acid

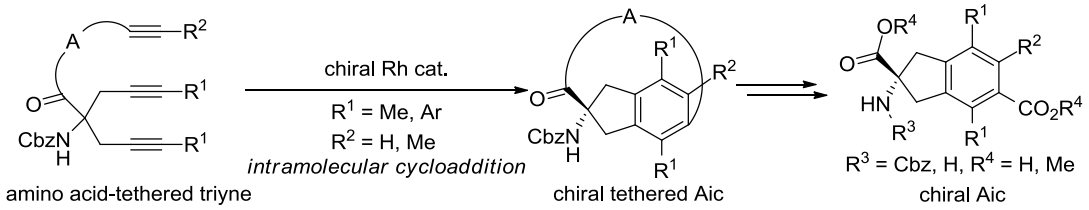


Chapter 3 describes the enantioselective synthesis of Aic derivatives by rhodium-catalyzed intramolecular cycloaddition. Shibata and co-workers reported enantioselective synthesis of chiral tripodal cage compounds by intramolecular cycloaddition of branched triynes (eq. 6).[15b,15c,15e]



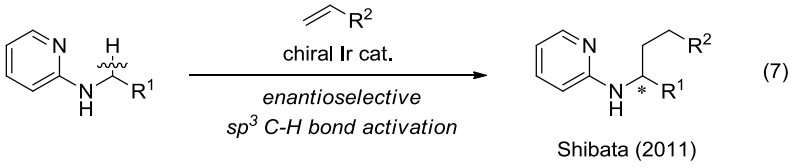
This reaction gave inspiration to the enantioselective intramolecular cycloaddition of amino acid-tethered triynes for the synthesis of Aic derivatives (Scheme 2). The enantioselective reaction proceeded, and chiral tethered Aic derivatives were obtained in good ee. Further synthetic transformation gave chiral Aic derivatives.

Scheme 2. Enantioselective synthesis of aminoindan carboxylic acid derivatives



Chapter 4 describes enantioselective synthesis of 4-substituted γ-amino acids and formal total synthesis of pyrrolam A via iridium-catalyzed sp^3 C-H bond activation. Shibata and co-workers reported iridium-catalyzed enantioselective secondary sp^3 C-H bond activation of 2-(alkylamino)pyridines: the

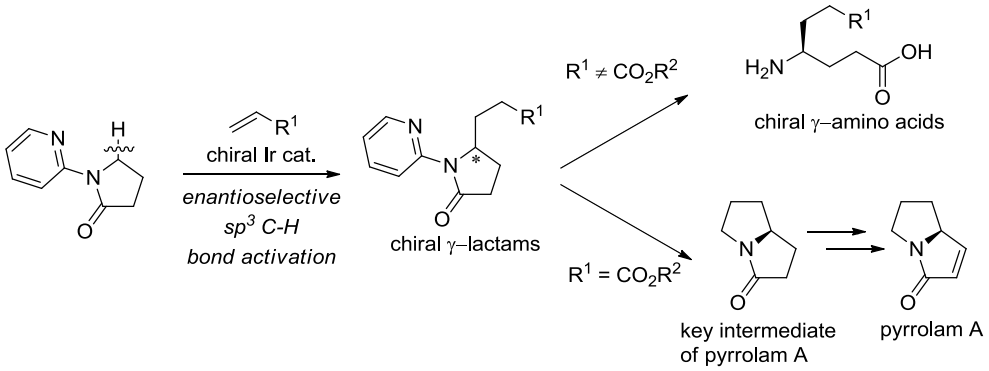
reaction of *N*-alkyl-2-aminopyridine with various alkenes gave chiral amines (eq. 7).[13]



(7)

This reaction was used for the enantioselective sp^3 C-H alkylation of γ-butyrolactam (Scheme 3). The obtained alkylated γ-lactams were transferred into 4-substituted aminobutyric acid derivatives. In addition, formal total synthesis of pyrrolam A was achieved using this reaction as a key step.

Scheme 3. Enantioselective synthesis of 4-substituted γ-amino acids and pyrrolam A



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(2) For selected examples, see: (a) Moriya, T.; Hagio, K.; Yoneda, N. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2217. (b) Albert, R.; Hinterding, K.; Brinkmann, V.; Guerini, D.; Müller-Hartwieg, C.; Knecht, H.; Simeon, C.; Streiff, M.; Wagner, T.; Welzenbach, K.; Zécri, F.; Zollinger, M.; Cooke, N.; Francotte, E. *J. Med. Chem.* **2005**, *48*, 5373.

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Chapter 2

Synthesis of 4-Substituted Tryptophan Derivatives and Total Synthesis of *cis*-Clavicipitic Acid via Iridium-Catalyzed sp^2 C-H Bond Activation

Backgrounds

Clavicipitic acid (**1**) is an ergot alkaloid that has been isolated from *Claviceps* Strain SD-58 and *Claviceps fusiformis* as a mixture of *cis*- and *trans*-isomers.[1] The unique tricyclic azepinoindole system has attracted synthetic chemists, and various strategies have been developed for its total syntheses.[3,4] 4-Substituted tryptophan skeleton was used as the key intermediate for the total synthesis of clavicipitic acid (1)[1-3] and other alkaloids such as aurantioclavine[4], lysergic acid[5], indolactam V[6] and rugulovasine A[7] (Figure 1). Tryptophan (Trp) is a natural and proteinogenic amino acid, but substituted tryptophan derivatives are unnatural and synthesized by chemical or enzymatic methods. Various synthetic methods for substituted Trp derivatives were developed. In particular, the introduction of substituents to C4-position is strongly desired (Figure 2),[8] because the introduction of substituents to C4-position is generally difficult compared with other positions.

Figure 1. Structures of alkaloids synthesized from 4-substituted Trp derivatives

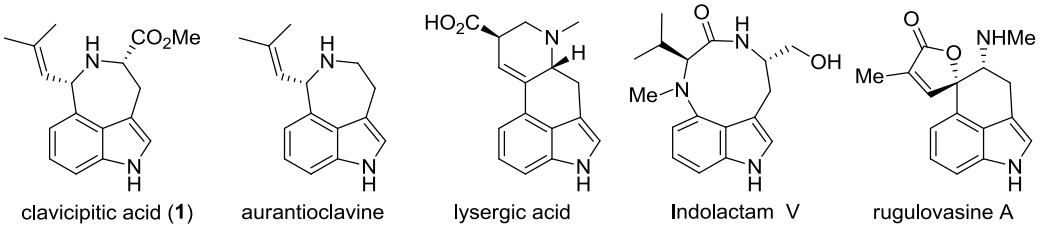
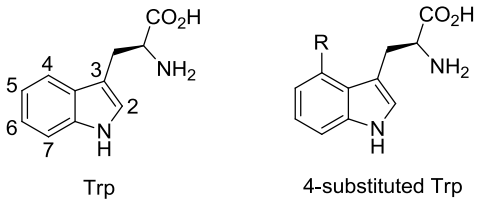
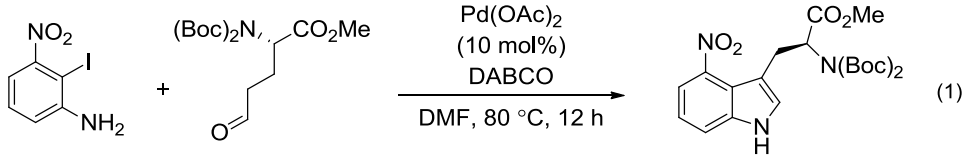


Figure 2. Structures of Trp and 4-substituted Trp derivative



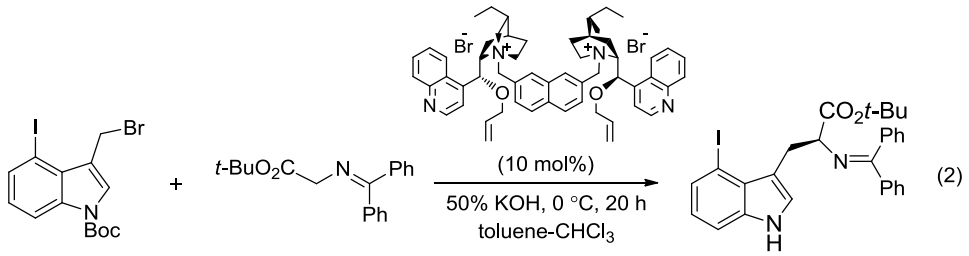
The author shows three typical approaches to chiral 4-substituted Trp derivatives: Jia and co-workers reported Pd-catalyzed indole synthesis by the coupling of 2-iodo-3-nitroaniline with an aldehyde having chiral amino acid moiety and obtained the chiral 4-nitro Trp derivative (eq. 1).[4]



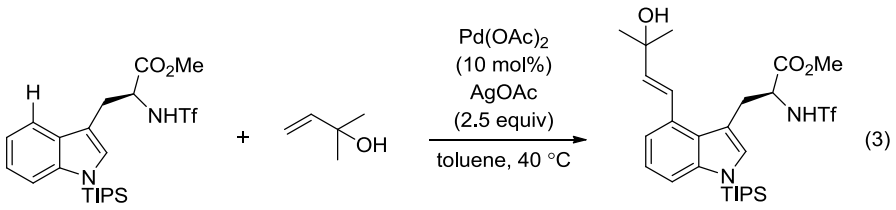
(1)

Jew and co-workers developed asymmetric synthesis of 4-iodo Trp derivative by the enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with 3-(bromomethyl)indole using a chiral

phase-transfer-catalyst (eq. 2).[3e]



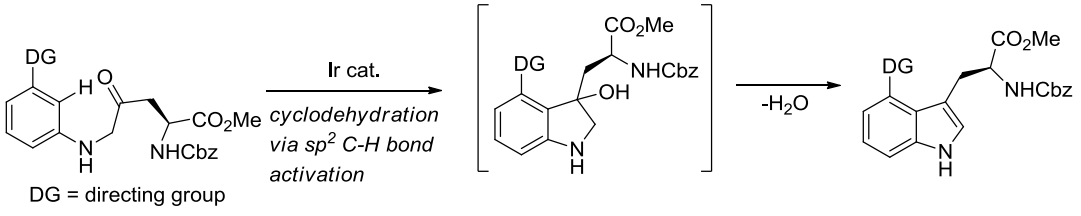
Yu group and Jia group developed Pd-catalyzed C-H alkenylation at the C-4 position of Trp using trifluoromethylsulfonamide as a directing group (eq. 3).[9]



Results and Discussion

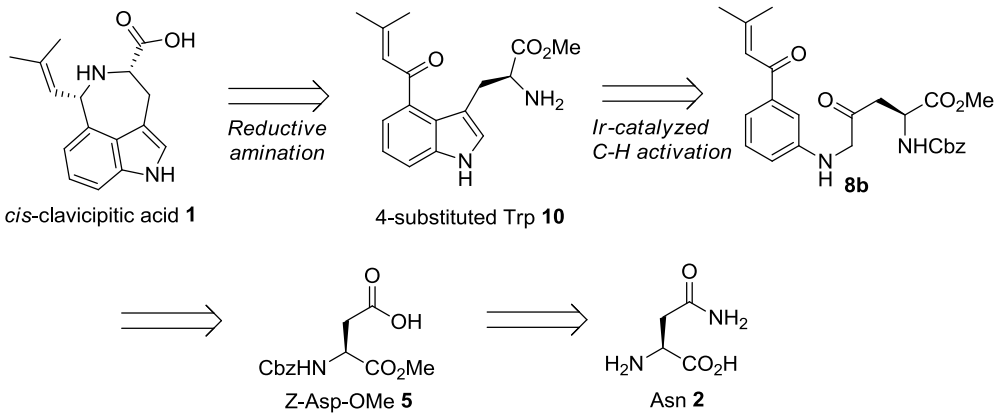
The author considered a new synthetic approach via intramolecular cyclodehydration initiated by the C-H bond activation of β-keto aniline possessing an α-amino acid moiety for the synthesis of chiral 4-substituted Trp derivatives (Scheme 1).[10] In addition, this protocol can be applied to the total synthesis of clavicipitic acid. Here, synthesis of 4-substituted Trp derivatives and total synthesis of clavicipitic acid via iridium catalyzed C-H bond activation were described.

Scheme 1. Synthetic strategy for 4-substituted Trp derivatives



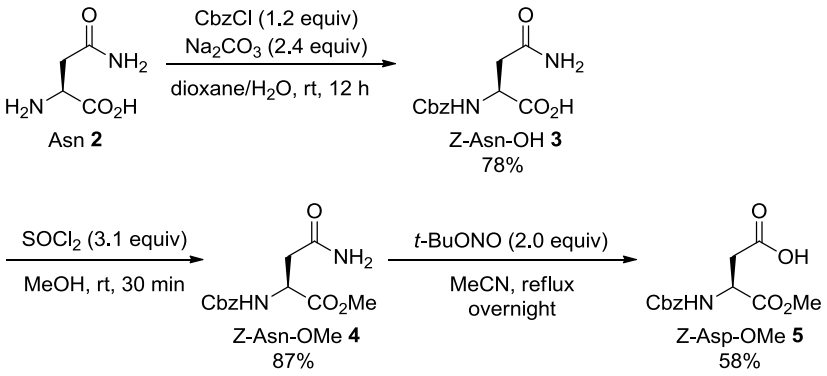
Retrosynthetic analysis of *cis*-clavicipitic acid **1** is shown in Scheme 2. The target compound would be accessible from the 4-substituted Trp derivative **10** by intramolecular reductive amination. Compound **10** would be converted from aniline derivative **8b** by originally developed intramolecular cyclodehydration. The substrate **8b** could be readily prepared from commercially available Cbz-L-Aspartic acid α–methyl ester **5** (Z-Asp-OMe), or cheaper asparagine **2** (Asn), which is a natural and protein amino acid.

Scheme 2. Retrosynthetic analysis of *cis*-clavicipitic acid



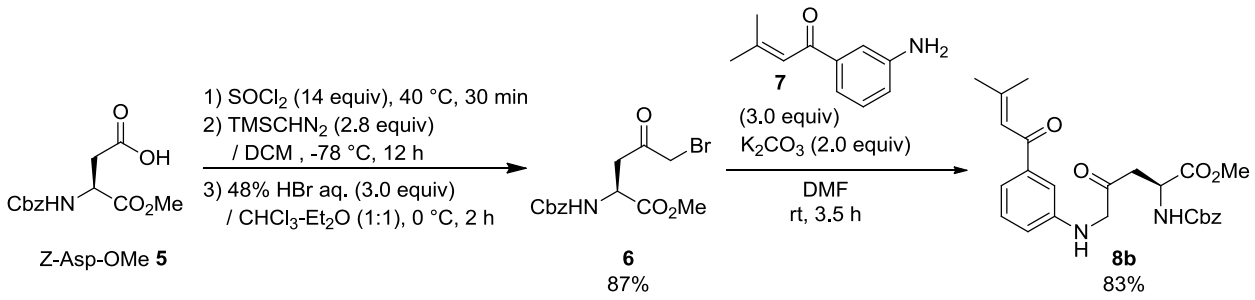
This synthetic strategy was initiated by the transformation of commercially available Asn **2** to Z-Asp-OMe **5** (Scheme 3). The carbobenzoxylation of Asn **2** with benzyl chloroformate (CbzCl) and sodium carbonate gave Z-Asn-OH **3**.[11a] Subsequent methyl esterification proceeded in the presence of thionyl chloride in methanol.[11b] Transformation from amide to carboxylic acid using *tert*-butyl nitrite afforded Z-Asp-OMe **5**.[11c,d]

Scheme 3. Synthesis of Z-Asp-OMe **5** from Asn **2**



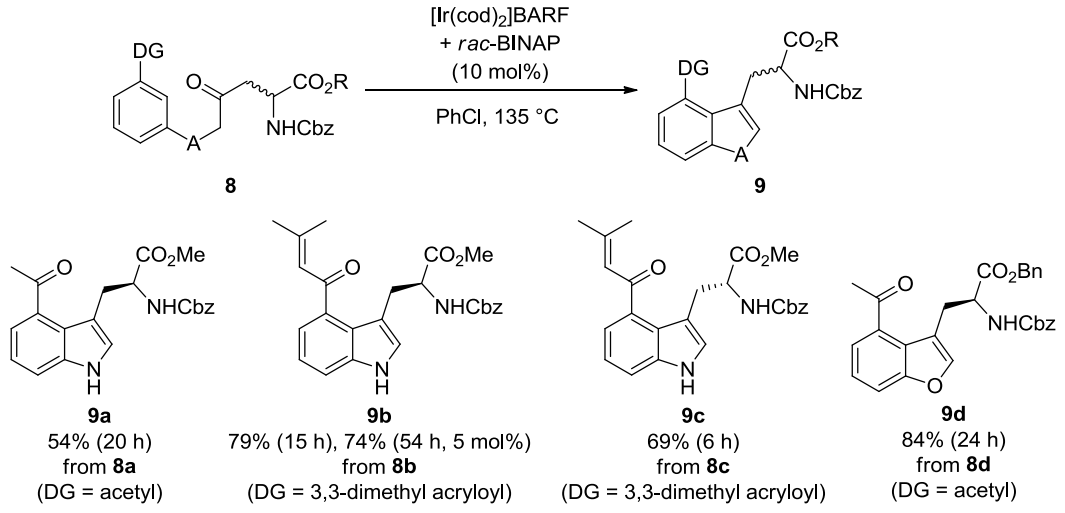
The synthesis of aniline derivative **8b**, which is a substrate of the key reaction, is depicted in Scheme 4. α-Ketobromide **6** was prepared by Arndt-Eistert synthesis from Z-Asp-OMe **5** using thionyl chloride, trimethylsilyldiazomethane, and aqueous hydrobromic acid in 87% yield. Subsequent nucleophilic substitution of α-ketobromide **6** with 1-(3-aminophenyl)-3-methylbut-2-en-1-one **7**[12] in the presence of potassium carbonate gave aniline derivative **8b** in 83% yield.

Scheme 4. Synthesis of β-keto aniline **8b**



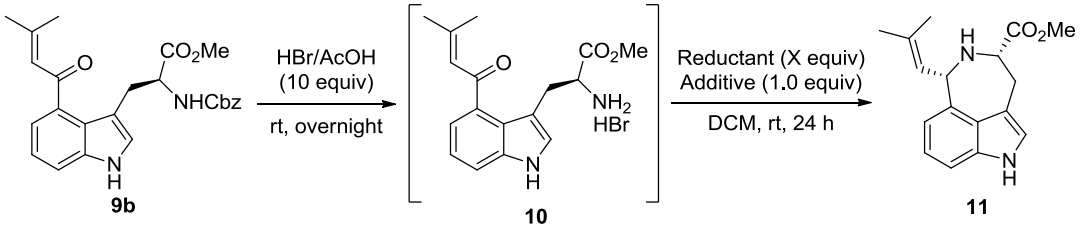
Next, the Ir-catalyzed cyclodehydration of β-keto aniline **8** via C-H bond activation for the synthesis of 4-substituted Trp derivatives **9** was examined (Table 1). First, the aniline derivative **8a** was chosen as a model substrate which has acetyl group as a directing group (DG), and submitted it to an intramolecular reaction in the presence of an Ir catalyst prepared from $[Ir(cod)_2]$BARF and *rac*-BINAP at 135 °C in chlorobenzene (PhCl).[10] The desired 4-substituted Trp **9a** was obtained in moderate yield. When aniline derivative **8b**, which has 3,3-dimethyl acryloyl group as a directing group, was used, the corresponding 4-substituted Trp **9b** was obtained in 79% yield. The high yield was also achieved even by using less amount of the catalyst, albeit in longer reaction time. The reaction of aniline derivative **8c** derived from D-form of amino acid also proceeded smoothly to give 4-substituted D-tryptophan derivative **9c**, which is the opposite enantiomer of **9b**. Phenylether derivative could be also used in the present transformation, and the reaction of **8d** afforded 4-substituted (3-benzofuranyl) alanine derivative **9d** in 84% (Entry 4). These results mean that Ir-catalyzed cyclodehydration is a versatile protocol for the synthesis of 4-functionalized tryptophan derivatives including its oxygen analogue.

Table 1. Cyclodehydration via Ir-catalyzed C-H bond activation for the synthesis of 4-substituted Trp derivatives **9**



The construction of tricyclic azepinoindole skeleton was examined by an intramolecular reductive amination, where ketimine would be formed between the carbonyl moiety of 3,3-dimethyl acryloyl group and amino moiety of amino acid (Table 2).[2f] First, Cbz group was deprotected in **9b** by using hydrogen bromide in acetic acid, and the obtained free amine **10** was submitted to the several conditions for the intramolecular reductive amination without isolation. When sodium triacetoxyborohydride was used as a reductant in dichloromethane, desired cyclic amine **11** could not be detected at all (Entry 1). In contrast, amine **11** was obtained by the addition of a stoichiometric amount of triethylamine, albeit in low yield because of low conversion of the ketamine, but it is noteworthy that the reductive amination proceeded with perfect diastereoselectivity (Entry 2). Next sodium cyanoborohydride was examined as a stronger reductant in the presence of triethylamine, and the formation of tricyclic azepinoindole could be ascertained. However, alkene reduction of isopropylidene moiety also proceeded and desired **11** was not detected (Entry 3). When the author increased the amount of sodium triacetoxyborohydride, moderate yield of 53% was achieved by using 4.2 equivalent amount of the reductant (Entries 4 and 5). However, significant decrease of ee of compound **11** was observed (13% ee). When the reduction was conducted at 0 °C, the ee of **11** was slightly improved to 29% ee, but the yield was decreased to 29%. The racemization proceeded even with other organic and inorganic bases, such as *N,N*-diisopropylethylamine, $NaHCO_3$, K_2CO_3, and Cs_2CO_3. In the absence of the bases, the formation of the cyclic imine could not be observed.

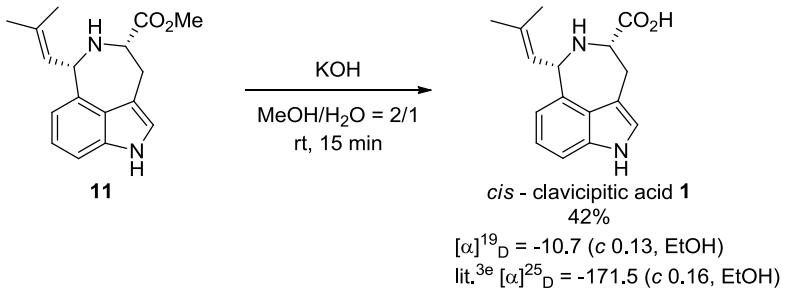
Table 2. Intramolecular reductive amination for the synthesis of *cis*-clavicipitic acid methyl ester **11**



Entry	Reductant	X / equiv	Additive	Yield / %
1	$NaBH(OAc)_3$	1.4	none	Not detected
2	$NaBH(OAc)_3$	1.4	Et_3N	21
3	$NaBH_3CN$	1.4	Et_3N	Not detected
4	$NaBH(OAc)_3$	2.8	Et_3N	46
5	$NaBH(OAc)_3$	4.2	Et_3N	53

Finally, hydrolysis of **11** by potassium hydroxide was examined in a mixed solvent of methanol and water (2:1),[9b] and the *cis*-clavicipitic acid **1** was obtained (Scheme 5).

Scheme 5. Synthesis of *cis*-clavicipitic acid



Conclusion

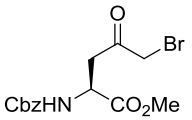
A new approach for the synthesis of 4-substituted Trp derivatives **9** by the cyclodehydration via Ir-catalyzed C-H bond activation was developed. In addition, the total synthesis of the *cis*-clavicipitic acid **1** from asparagine **2** by this original Ir-catalyzed reaction and intramolecular reductive amination was achieved in short steps. Racemization was observed in intramolecular reductive amination step, but this strategy started from commercially available and cheap compound, and realized higher atom efficiency with minimum use of protecting groups.

Experimental Section

General

^{1}H NMR spectra were recorded on JEOL AL-500 (500 MHz) spectrometers. The chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) for $CDCl_3$. The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). ^{13}C NMR spectra were obtained by JEOL AL-400 (125 MHz) spectrometers and referenced to the internal solvent signals (central peak is 77.16 ppm in $CDCl_3$). $CDCl_3$ was used as a NMR solvent. High-resolution mass spectra (HRMS) were measured on ESI (Electro Spray Ionization) – orbitrap mass spectrometer. Optical rotations were measured on a JASCO DIP-1000 polarimeter. Preparative thin-layer chromatography (PTLC) was performed with silica gel-precoated glass plates (Merck 60 GF254) prepared in the author's laboratory, Flash column chromatography was performed over silica gel 200-300. All reagents were weighed and handled in air and backfilled under argon at room temperature. Unless otherwise noted, all reactions were performed under an argon atmosphere. All reagents were purchased from Wako, Kanto, Aldrich and TCI and used without further purification. Compounds **S1**~**S3** were known. Compound **S1** was synthesized by the literature protocol.[13] Compounds **S2** and **S3** were synthesized by the modified protocols.[14]

Characterization of new compounds

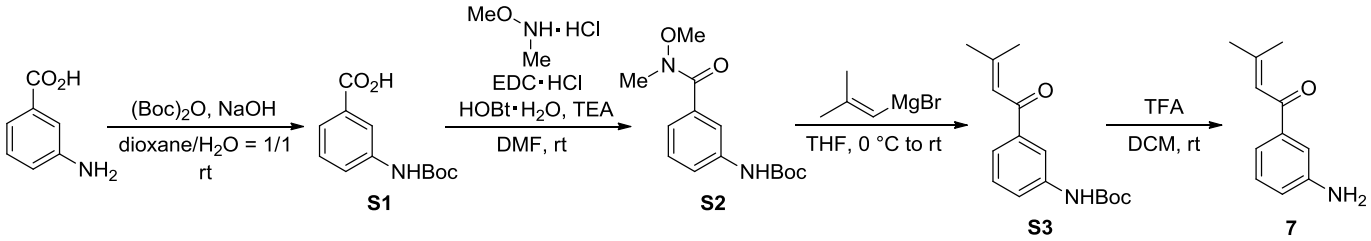


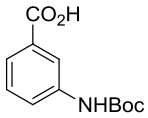
(*S*)-5-Bromo-2-(carbobenzoxyamino)-4-oxopentanoic acid methyl ester (**6**)

A 30 mL dry two-necked pear-shaped flask equipped with a rubber septum and argon balloon was charged with Z-Asp-OMe **5** (565.0 mg, 2.0 mmol) and $SOCl_2$ (2.0 mL). The solution was stirred at 40 °C for 30 min. After removal of $SOCl_2$ under reduced pressure, anhydrous CH_2Cl_2 (4.0 mL) was added, and the resulting solution was cooled to -78 °C. To the cooled solution, 0.6 M solution of trimethylsilyldiazomethane in hexane (9.6 mL) was added slowly. The reaction mixture was stirred at -78 °C for 12 h, and warmed to room temperature gradually. After removal of the solvent, 2.0 mL of $CHCl_3$-Et_2O (1:1) was added, and the resulting solution was cooled to 0 °C. To the cooled solution, 48% aqueous solution of HBr (0.68 mL, 6.0 mmol) was added slowly. The reaction mixture was stirred at 0 °C for 3 h, and quenched with sat. $NaHCO_3$ solution. The solution was extracted with EtOAc, and the organic layer was washed with sat. $NaHCO_3$ solution. (× 2) and brine (× 2). The organic extract was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the title compound **6** (626.2 mg,

87%) as an off-white solid that was used without further purification. Mp 89 °C. ^{1}H NMR δ 7.37-7.31 (m, 5H), 5.72 (d, *J* = 7.8 Hz, 1H), 5.12 (s, 2H), 4.67-4.58 (m, 1H), 3.88 (s, 2H), 3.74 (s, 3H), 3.38 (dd, *J* = 4.3, 18.1 Hz, 1H), 3.26 (dd, *J* = 4.3, 18.1 Hz, 1H); ^{13}C NMR δ 200.3, 171.2, 156.1, 136.2, 128.7, 128.4, 128.3, 67.3, 53.1, 50.2, 41.2, 33.7. HRMS(ESI) calcd for $C_{14}H_{16}O_5NBrNa$ (M+Na): 380.0104; found: 380.0106. $[\alpha]^{23}_{D}$ = +22.0 (c 1.0, $CHCl_3$).

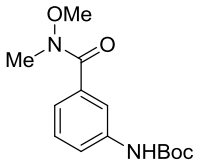
Synthetic scheme of 7





4-(*tert*-Butoxycarbonylamino)benzoic acid (S1)[13]

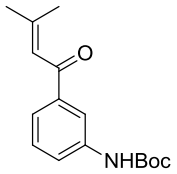
To a stirred solution of 4-aminobenzoic acid (5.00 g, 36.5 mmol) and sodium hydroxide (1.56 g, 39.3 mmol) in 60 mL of water-dioxane (1:1) at 0 °C was added di-*tert*-butyl dicarbonate (14.3 g, 65.4 mmol). The resulting mixture was stirred for 3 h, then warmed to room temperature and stirred overnight. The aqueous mixture was then washed with EtOAc (60 mL) before further EtOAc (60 mL) was added and the resulting mixture neutralized with 1 M aqueous $KHSO_4$. The organic layer was separated, washed with water (60 mL), dried (Na_2SO_4) and the solvent removed in vacuo to give the title product **S1** (7.53 g, 87%) as a white solid, which was used without further purification.



***tert*-Butyl *N*-(3-(methoxy-methylcarbamoyl)phenyl)carbamate (S2)**[14]

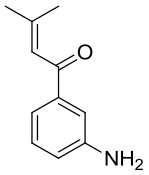
A 100 mL dry two-necked pear-shaped flask equipped with a rubber septum was charged with **S1** (2135.9 mg, 9.0 mmol), 1-hydroxybenzotriazole monohydrate (1404.5 mg, 9.0 mmol), and DMF (45 mL) under argon atmosphere. To the resulting solution were added *N*,*O*-dimethylhydroxylamine hydrochloride (2054.3 mg, 20 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3180.9 mg, 16 mmol), and triethylamine (7.1 mL, 51 mmol). The reaction mixture was stirred overnight at room temperature. To the reaction mixture was added EtOAc. The organic layer was washed with 5% citric acid

solution (× 2), 5% $NaHCO_3$ solution. (× 2), and brine (× 2). The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give **S2** (2362.1 mg, 94%) as a white solid that was used without further purification.



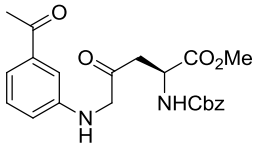
***tert*-Butyl *N*-(3-(3-methyl-1-oxo-2-buten-1-yl)phenyl)carbamate (S3)**[14]

To a solution of **S2** (2327.5 mg, 8.3 mmol) in THF (13.3 mL) at 0 °C under argon atmosphere was dropwised 2-methyl-1-propenylmagnesium bromide (0.5 M in THF, 41.5 mL, 20.8 mmol). The reaction mixture was stirred at 0 °C for 30 min. The cooling bath was removed and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C and quenched with 5% citric acid solution. The aqueous layer was extracted with ether (× 2) and the combined organic layers were washed with water and brine. The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give **S3** quantitatively as a light yellow solid that was used without further purification.



1-(3-Aminophenyl)-3-methylbut-2-en-1-one (7)[14]

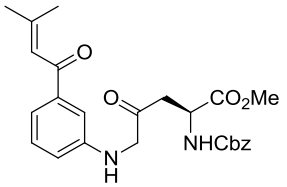
To a solution of **S3** (2277.2 mg, 8.1 mmol) in CH_2Cl_2 (6.4 mL) at room temperature was added trifluoroacetic acid (19.3 mL, 252.2 mmol). The reaction mixture was stirred at room temperature for 15 minutes. The solvents were removed under reduced pressure. The residue was redissolved in CH_2Cl_2 and re-evaporated three times. To the residue were added CH_2Cl_2, the solution was washed with sat. $NaHCO_3$ solution. The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (gradient elution: hexane/EtOAc = 100/0 to 60/40) to give **7** (902.0 mg, 63%) as a yellow solid.



(*S*)-5-(3-Acetylphenylamino)-2-(carbobenzoxyamino)-4-oxopentanoic acid methyl ester (8a)

A dry Schlenk tube equipped with a rubber septum was charged with 3'-aminocetophenone (202.7 mg,

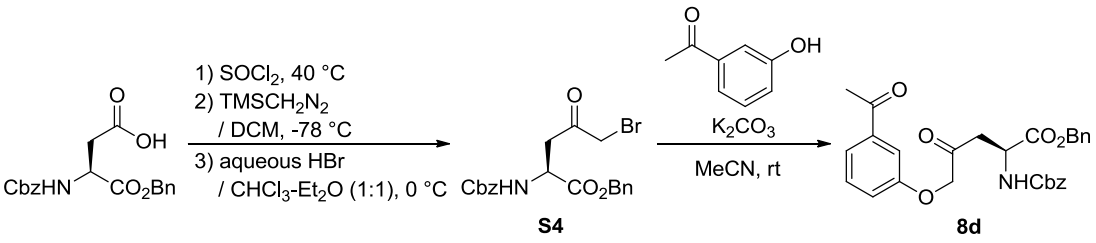
1.5 mmol), K_2CO_3 (137.7 mg, 1.0 mmol), and DMF (0.7 mL) under argon atmosphere. The resulting solution was stirred at room temperature for 30 min. To the reaction mixture was added **6** (179.1 mg, 0.50 mmol), and the solution was stirred for 2.5 h. To the reaction mixture was added water, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by preparative TLC (elution: hexane/EtOAc = 3/2) to give the title compound **8a** (142.3 mg, 69%) as a yellow oil. ^{1}H NMR δ 7.36-7.24 (m, 7H), 7.12 (s, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 5.76 (d, *J* = 8.0 Hz, 1H), 5.11 (s, 2H), 4.70-4.53 (m, 2H), 4.06 (dd, *J* = 20.1, 25.0 Hz, 2H), 3.74 (s, 3H), 3.24 (dd, *J* = 4.0, 17.5 Hz, 1H), 3.11 (dd, *J* = 4.0, 17.5 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR δ 204.4, 198.6, 171.3, 156.1, 147.0, 138.4, 136.2, 129.6, 128.7, 128.4, 128.3, 118.8, 118.2, 111.2, 67.3, 53.6, 53.1, 50.0, 42.2, 26.8. HRMS(ESI) calcd for $C_{22}H_{24}O_6N_2Na$ (M+Na): 435.1527; found: 435.1532. $[\alpha]^{24}_D$ = +16.7 (*c* 2.0, $CHCl_3$).

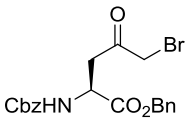


(*S*)-2-(Carbobenzoxyamino)-4-oxo-5-(3-(1-oxo-3-methylbut-2-en-1-yl)phenylamino)pentanoic acid methyl ester (**8b**)

A dry Schlenk tube equipped with a rubber septum was charged with **7** (314.8 mg, 1.8 mmol), K_2CO_3 (166.0 mg, 1.2 mmol), and DMF (0.84 mL) under argon atmosphere. The resulting solution was stirred at room temperature for 30 min. To the reaction mixture was added **6** (215.0 mg, 0.60 mmol), and the solution was stirred for 3 h. To the reaction mixture was added water, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (gradient elution: hexane/EtOAc = 3/2 to 2/1) to give the title compound **8b** (226.7 mg, 83%) as a yellow oil. ^{1}H NMR δ 7.37-7.21 (m, 7H), 7.11 (s, 1H), 6.74 (d, *J* = 7.5 Hz, 1H), 6.71 (s, 1H), 5.77 (d, *J* = 7.9 Hz, 1H), 5.11 (s, 2H), 4.71-4.54 (m, 2H), 4.06 (dd, *J* = 19.8, 25.2 Hz, 2H), 3.74 (s, 3H), 3.24 (dd, *J* = 4.3, 17.9 Hz, 1H), 3.11 (dd, *J* = 4.3, 17.9 Hz, 1H), 2.19 (s, 3H), 2.01 (s, 3H); ^{13}C NMR δ 204.6, 191.8, 171.3, 156.5, 156.1, 146.9, 140.5, 136.2, 129.4, 128.7, 128.4, 128.3, 121.5, 118.4, 117.4, 111.6, 67.3, 53.7, 53.0, 50.0, 42.2, 28.1, 21.3. HRMS(ESI) calcd for $C_{25}H_{28}O_6N_2Na$ (M+Na): 475.1840; found: 475.1840. $[\alpha]^{23}_D$ = +16.2 (*c* 1.3, $CHCl_3$).

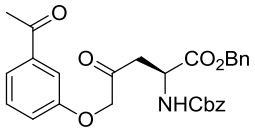
Synthetic scheme of 8d





(*S*)-5-Bromo-2-(carbobenzoxyamino)-4-oxopentanoic acid benzyl ester (S4)

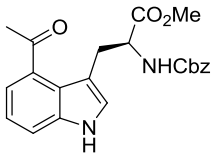
A 30 mL dry two-necked pear-shaped flask equipped with a rubber septum and argon balloon was charged with *N*-(benzyloxycarbonyl)-L-aspartic acid benzyl ester[15] (714.6 mg, 2.0 mmol) and $SOCl_2$ (2.0 mL). The solution was stirred at 40 °C for 30 min. After removal of $SOCl_2$ under reduced pressure, anhydrous Et_2O (4.0 mL) was added, and the resulting solution was cooled to -78 °C. To the cooled solution, 2.0 M solution of trimethylsilyldiazomethane in Et_2O (2.8 mL) was added slowly. The reaction mixture was stirred at -78 °C for 12 h, and warmed to room temperature gradually. After removal of the solvent, 2.0 mL of $CHCl_3$-Et_2O (1:1) was added, and the resulting solution was cooled to 0 °C. To the cooled solution, 48% aqueous solution of HBr (0.68 mL, 6.0 mmol) was added slowly. The reaction mixture was stirred at 0 °C for 3 h, and quenched with sat. $NaHCO_3$ solution. The solution was extracted with CH_2Cl_2, and the organic layer was washed with brine. The organic extract was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (elution: hexane/EtOAc = 3/1) to give **S4** (463.4 mg, 53%) as an off-white solid. Mp 94 °C. ^{1}H NMR δ 7.36-7.29 (m, 10H), 5.74 (d, *J* = 7.8 Hz, 1H), 5.16 (s, 2H), 5.10 (s, 2H), 4.71-4.62 (m, 1H), 3.81 (s, 2H), 3.38 (dd, *J* = 4.3, 18.2 Hz, 1H), 3.25 (dd, *J* = 4.3, 18.2 Hz, 1H); ^{13}C NMR δ 200.2, 170.5, 156.1, 136.2, 135.2, 128.8, 128.7, 128.5, 128.4, 128.3, 67.9, 67.3, 50.3, 41.9, 33.7 (A signal is overlapped with an aromatic peak). HRMS(ESI) calcd for $C_{20}H_{20}O_5NBrNa$ (M+Na): 456.0417; found: 456.0420. $[\alpha]^{20}_D$ = +11.6 (*c* 1.0, $CHCl_3$).



(*S*)-5-(3-Acetylphenoxy)-2-(carbobenzoxyamino)-4-oxopentanoic acid benzyl ester (8d)

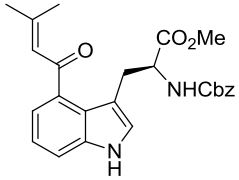
A dry Schlenk tube equipped with a rubber septum was charged with 3'-hydroxyacetophenone (68.2 mg, 0.50 mmol), K_2CO_3 (76.3 mg, 0.55 mmol), and **S4** (260.9 mg, 0.60 mmol) under argon atmosphere. To

the reaction vessel was added MeCN (0.70 mL), and the resulting solution was stirred at room temperature for 5.5 h. To the reaction mixture was added water, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (elution: hexane/EtOAc = 3/1) to give the title compound **8d** (234.2 mg, 96%) as a white solid. Mp 88 °C. ^{1}H NMR δ 7.59 (d, *J* = 7.9 Hz, 1H), 7.44-7.27 (m, 12H), 7.06 (d, *J* = 7.9 Hz, 1H), 5.78 (d, *J* = 8.0 Hz, 1H), 5.17 (s, 2H), 5.10 (s, 2H), 4.78-4.66 (m, 1H), 4.56 (dd, *J* = 16.7, 22.5 Hz, 2H), 3.35 (dd, *J* = 4.5, 18.4 Hz, 1H), 3.22 (dd, *J* = 4.5, 18.4 Hz, 1H), 2.58 (s, 3H); ^{13}C NMR δ 205.1, 197.6, 170.7, 157.9, 156.1, 138.8, 136.2, 135.3, 130.1, 128.8, 128.7, 128.6, 128.4, 128.4, 128.2, 122.4, 119.9, 113.4, 72.7, 67.8, 67.3, 49.9, 41.6, 26.8. HRMS(ESI) calcd for $C_{28}H_{27}O_7NNa$ (M+Na): 512.1680; found: 512.1680. $[\alpha]^{22}_D$ = +6.01 (*c* 1.1, $CHCl_3$).



(*S*)-3-(4-Acetylindol-3-yl)-2-(carbobenzoxyamino)propanoic acid methyl ester (9a)

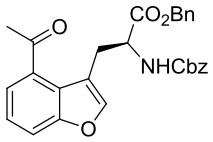
A dry Schlenk tube equipped with a rubber septum was charged with [Ir(cod)$_2$]BARF (57.4 mg, 0.045 mmol), *rac*-BINAP (27.9 mg, 0.045 mmol), and **8a** (186.3 mg, 0.45 mmol) under argon atmosphere. To the reaction vessel was added PhCl (0.90 mL), and the vessel was capped with a glass stopper. The reaction mixture was stirred at 135 °C for 20 h, and cooled to room temperature. The solvent was removed, and the crude product was purified by flash column chromatography (elution: hexane/EtOAc = 3/2) to give the title compound **9a** (96.7 mg, 54%) as a yellow oil. ^{1}H NMR δ 8.67 (s, 1H), 7.56 (d, *J* = 7.3 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.35-7.05 (m, 7H), 5.98 (d, *J* = 8.0 Hz, 1H), 4.98 (s, 2H), 4.55-4.46 (m, 1H), 3.71 (s, 3H), 3.41 (dd, *J* = 5.2, 14.7 Hz, 1H), 3.29 (dd, *J* = 9.3, 14.7 Hz, 1H), 2.70 (s, 3H); ^{13}C NMR δ 202.5, 173.3, 156.4, 137.9, 136.6, 132.6, 128.5, 128.1, 128.0, 126.8, 123.9, 123.1, 120.9, 116.3, 112.2, 66.8, 56.2, 52.4, 29.5, 29.2. HRMS(ESI) calcd for $C_{22}H_{22}O_5N_2Na$ (M+Na): 417.1421; found: 417.1419. $[\alpha]^{25}_D$ = -23.4 (*c* 1.2, $CHCl_3$)



(*S*)-2-(Carbobenzoxyamino)-3-(4-(1-oxo-3-methylbut-2-en-1-yl)indol-3-yl)propanoic acid methyl ester (9b)

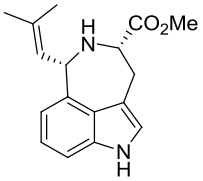
A dry Schlenk tube equipped with a rubber septum was charged with [Ir(cod)$_2$]BARF (112.4 mg, 0.089

mmol), *rac*-BINAP (55.0 mg, 0.089 mmol), and **8b** (400.7 mg, 0.89 mmol) under argon atmosphere. To the reaction vessel was added PhCl (1.8 mL), and the vessel was capped with a glass stopper. The reaction mixture was stirred at 135 °C for 24 h, and cooled to room temperature. The solvent was removed, and the crude product was purified by flash column chromatography (gradient elution: hexane/EtOAc = 100/0 to 55/45) to give the title compound **9b** (303.6 mg, 79%) as a yellow solid. Mp 55 °C. ^{1}H NMR δ 8.51 (s, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 7.1 Hz, 1H), 7.28-7.07 (m, 7H), 6.62 (s, 1H), 6.13 (d, *J* = 7.8 Hz, 1H), 4.97 (s, 2H), 4.55-4.44 (m, 1H), 3.71 (s, 3H), 3.36 (dd, *J* = 4.9, 14.8 Hz, 1H), 3.22 (dd, *J* = 9.5, 14.8 Hz, 1H), 2.21 (s, 3H), 1.98 (s, 3H); ^{13}C NMR δ 195.7, 173.2, 156.8, 156.4, 137.6, 136.7, 134.6, 128.5, 128.0, 127.9, 125.8, 124.9, 124.1, 121.8, 121.0, 114.9, 111.9, 66.7, 56.0, 52.4, 29.0, 28.1, 21.3. HRMS(ESI) calcd for $C_{25}H_{26}O_5N_2Na$ (M+Na): 457.1734; found: 457.1737. $[\alpha]^{24}_D$ = -21.1 (*c* 1.0, $CHCl_3$).



(*S*)-3-(4-Acetylbenzofuran-3-yl)-2-(carbobenzoxyamino)propanoic acid benzyl ester (**9d**)

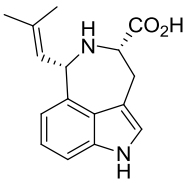
A dry Schlenk tube equipped with a rubber septum was charged with [Ir(cod)$_2$]BARF (6.8 mg, 5.0 μmol), *rac*-BINAP (3.2 mg, 5.0 μmol), and **8d** (24.5 mg, 0.050 mmol) under argon atmosphere. To the reaction vessel was added PhCl (0.10 mL), and the vessel was capped with a glass stopper. The reaction mixture was stirred at 135 °C for 24 h, and cooled to room temperature. The solvent was removed, and the crude product was purified directly by preparative TLC (elution: hexane/EtOAc = 3/1) to give the title compound **9d** (18.6 mg, 79%) as an off-white solid. Mp 112 °C. ^{1}H NMR δ 7.67 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.49 (s, 1H), 7.36-7.20 (m, 11H), 5.62 (d, *J* = 8.4 Hz, 1H), 5.13 (s, 2H), 5.00 (s, 2H), 4.66-4.58 (m, 1H), 3.43 (dd, *J* = 5.7, 14.7 Hz, 1H), 3.28 (dd, *J* = 8.5, 14.7 Hz, 1H), 2.66 (s, 3H); ^{13}C NMR δ 200.6, 172.1, 156.7, 156.1, 146.0, 136.4, 135.5, 133.4, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 125.6, 125.3, 123.7, 116.8, 116.2, 67.2, 66.9, 55.2, 28.8, 28.5. HRMS(ESI) calcd for $C_{28}H_{25}O_6NNa$ (M+Na): 494.1574; found: 494.1574. $[\alpha]^{22}_D$ = -8.04 (*c* 1.2, $CHCl_3$).



***cis*-Clavicipitic acid methyl ester** (**11**)

A dry Schlenk tube equipped with a rubber septum was charged with **9b** (21.7 mg, 0.050 mmol) under argon atmosphere. To the reaction vessel were added AcOH (0.13 mL) and HBr (30% in AcOH, 0.10 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* for 2

h. To the reaction vessel were added CH_2Cl_2 and triethylamine (7.0 μL, 0.050 mmol). To the resulting mixture was added $NaBH(OAc)_3$ (45.1 mg, 0.21 mmol), then the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution. The aqueous layer was extracted with ether (× 3). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by preparative TLC (elution: hexane/EtOAc = 2/1) to give *cis*-clavicipitic acid methyl ester **11** (7.5 mg, 53%) as a light yellow solid. Ee was determined by HPLC analysis using a chiral column (Daicel Chiralcel OD-3: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 0.1% diethylamine in MeOH, flow rate: 0.8 mL/min, retention time: 5.61 min for major isomer and 6.63 min for minor isomer).[15]



***cis*-Clavicipitic acid (1)**[15]

A solution of *cis*-clavicipitic acid methyl ester (16.2 mg, 0.055 mmol) in 1.8 ml of 4% KOH in MeOH-H_2O (2:1) was stirred for 15 min at room temperature. Ion-exchange resin (Amberlist 15 hydrogen form) was added to the reaction mixture until the pH of the solution became neutral. The resin was filtered and washed with MeOH. The filtrate was evaporated to give *cis*-clavicipitic acid (6.5 mg, 42%).

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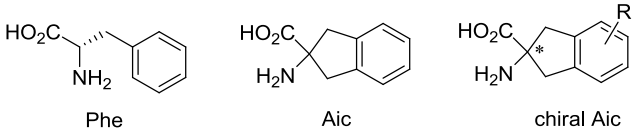
Chapter 3

Enantioselective Synthesis of Aminoindan Carboxylic Acid Derivatives by Rhodium-Catalyzed Intramolecular Cycloaddition

Backgrounds

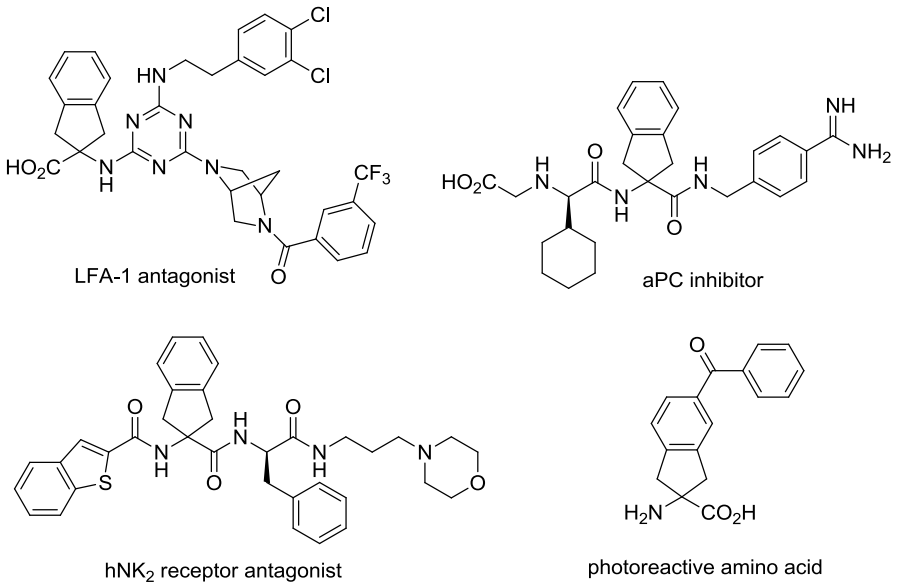
Aminoindan carboxylic acid (Aic) is a phenylalanine (Phe) analogue, which has conformationally constrained bicyclic skeleton, and an achiral amino acid. When a substituent (R) is introduced on the benzene ring, it becomes a chiral amino acid (Figure 1).

Figure 1. Structures of Phe, Aic, and chiral Aic



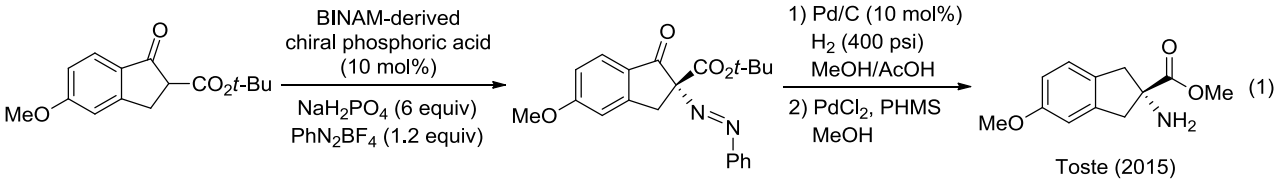
Aic skeleton is found in biologically active molecules, for example, activated protein C (aPC) inhibitors,[1] neurokinin NK_2 receptor antagonists,[2] and lymphocyte function-associated antigen 1 (LFA-1) antagonists were recently reported (Figure 2).[3] In addition, over the past few years, Aic-containing molecules have attracted much attention as amino acids for the photoaffinity labelling.[4]

Figure 2. Aic-containing functional molecules



Against this background, various synthetic methods of Aic derivatives have been developed. For example, as the synthesis of achiral Aic derivatives, Ru-catalyzed cascade reaction,[5] phase-transfer-catalyzed alkylation,[6] and alkyne trimerization[7] have been reported. With regard to asymmetric synthesis of Aic derivatives, resolution of diastereomers had been only one protocol, where

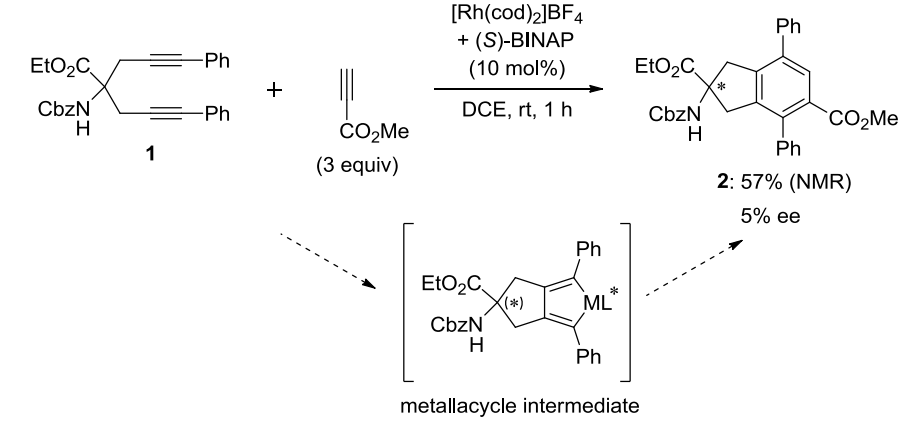
Aic derivatives were condensed with other chiral amino acid derivatives.[8] Quite recently, Toste and co-workers reported an enantioselective amination of 2-alkoxycarbonyl-1-indanones and transformed one of them into a chiral Aic (eq. 1).[9] This is only an example of enantioselective approach to Aic derivative synthesis. To the best of my knowledge, there has been no report of widely applicable enantioselective synthesis of Aic derivatives.

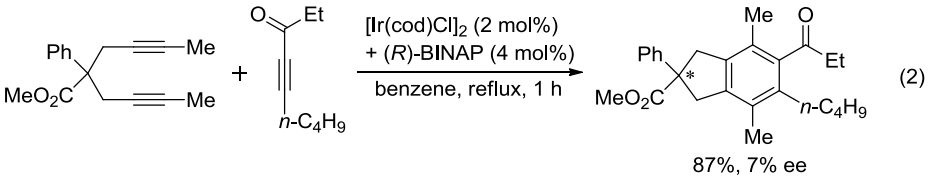


Results and Discussion

First, the author considered that enantioselective synthesis of Aic derivatives by intermolecular cycloaddition: when the reaction of amino acid-tethered diyne **1** with methyl propiolate was examined in the presence of a chiral Rh catalyst using (*S*)-BINAP as a chiral ligand, the desired Aic derivative **2** was obtained in moderate NMR yield (Scheme 1). However, its enantiomeric excess was very low as expected, because the stereogenic center is far from chiral metal catalyst. Actually, Takeuchi and co-workers reported that the generation of chiral center at the C4-position of 1,6-diynes by the intermolecular cycloaddition with alkynes, but the enantiomeric excess of the cycloadduct was very low (eq. 2).[10]

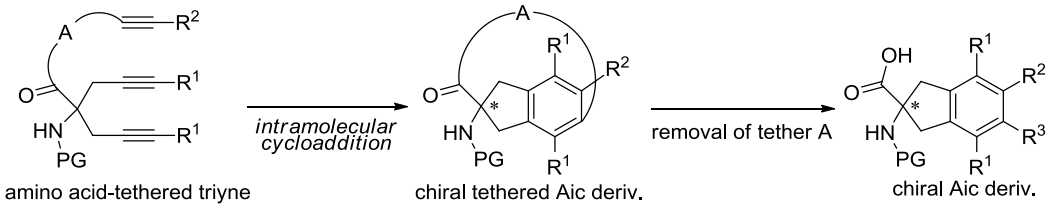
Scheme 1. Intermolecular cycloaddition of amino acid-tethered diyne **1** with methyl propiolate





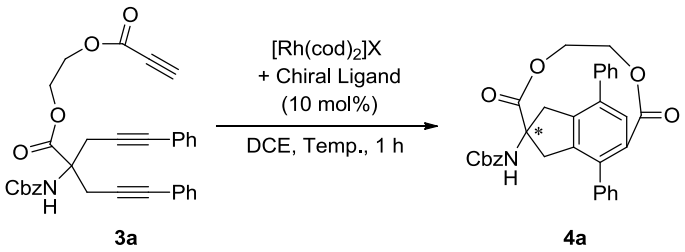
To improve the enantioselectivity, the author considered that intramolecular cycloaddition of amino acid-tethered triynes could realize high enantioselectivity in the generation of chiral center on the tether and give chiral tethered Aic derivatives. Subsequent removal of the tether readily gives chiral Aic derivatives (Scheme 2).

Scheme 2. Intramolecular approach for the enantioselective synthesis of Aic derivatives



As a model substrate, the author designed and synthesized amino acid-tethered triyne **3a** possessing a 1,6-diyne moiety and propiolate, which are connected by ethylene glycol chain. Three advantages of the tethered triyne **3a** is anticipated: (1) selective oxidative coupling of 1,6-diyne moiety with a metal catalyst, (2) high asymmetric induction because enantioselectivity is incidentally determined only by the orientation of alkyne insertion to metallacycle intermediate, and (3) easily removal of the ethylene glycol chain by hydrolysis. First, the intramolecular reaction using cationic rhodium complexes and various chiral ligands was examined in 1,2-dichloroethane (DCE) (Table 1). As the chiral ligand, (*S*,*S*)-Me-DUPHOS was used (Entries 1-3).[11] Although excellent enantioselectivity was achieved, the reaction proceeded sluggishly and the yields of desired tethered Aic derivative **4a** were miserable. When the Rh catalyst consisting of BARF as a counter anion and (*S*)-BINAP as a chiral ligand was used, the reaction proceeded smoothly even at room temperature, and the yield was drastically improved with decreased ee (Entry 4). Various BINAP derivatives were further examined: while H_8-BINAP and xylBINAP did not give better results than BINAP (Entries 5 and 6), higher enantioselectivity was achieved by tolBINAP (Entry 7). When the reaction was performed at 40 °C, the yield was improved to 80%, and the desired Aic **4a** was obtained without the decrease of ee (Entry 8). In addition, when the author examined recrystallization of cycloadduct **4a** (82% ee), recovery yield from mother liquid following recrystallization of **4a** was 87% and ee of **4a** was increased to 97% ee.

Table 1. Screening of chiral rhodium catalysts for the synthesis of chiral tethered Aic derivative



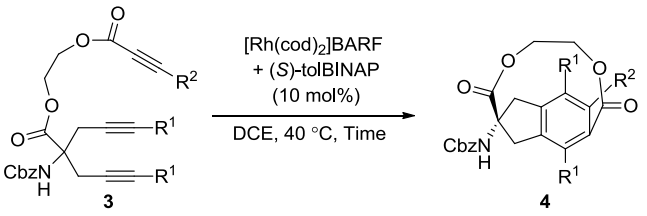
Entry[a]	Y	Chiral Ligand	Temp. / °C	Yield / %	Ee / %
1	BF_4	(*S,S*)-Me-DUPHOS	80	trace	96
2[b]	OTf	(*S,S*)-Me-DUPHOS	80	trace	93
3	BARF	(*S,S*)-Me-DUPHOS	40	17	90
4	BARF	(*S*)-BINAP	rt	76	75
5	BARF	(*S*)-H_8-BINAP	rt	62	72
6	BARF	(*S*)-xylBINAP	rt	55	47
7	BARF	(*S*)-tolBINAP	rt	38	82
8	BARF	(*S*)-tolBINAP	40	80	82 (97)[c]

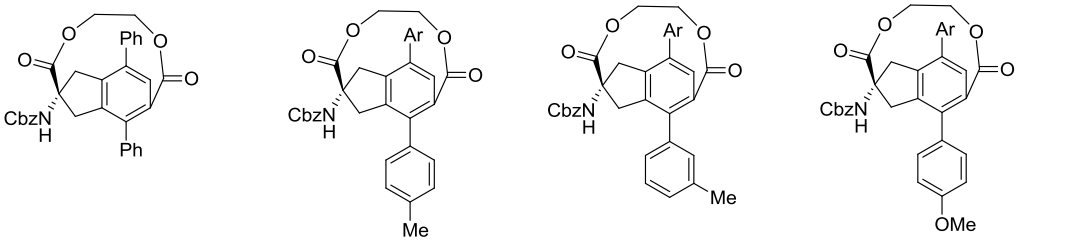
[*a*] Triyne **3a** was added dropwise to a DCE solution of the Rh catalyst over 1 h. [*b*] The reaction mixture was further stirred for 2.5 h after the dropwise addition. [*c*] Ee of the sample recovered from the mother liquid of recrystallization.

Under the optimum conditions (Table 1, Entry 8), various triynes were subjected to the intramolecular [2+2+2] cycloaddition (Table 2). The reaction of triynes **3b** and **3c** having 4- or 3-tolyl group on their respective diyne termini proceeded to give desired tethered Aic derivatives **4b** and **4c** in good yields and ee. The reaction of triyne **3d** possessing electron-rich aryl groups gave **4d** in moderate yield with good ee, but those of triynes **3e** and **3f** possessing electron-deficient aryl groups sluggishly proceeded, and the yields were low, but ee was still good. When triynes **3g** and **3h**, which have halogenated phenyl groups on their respective diyne termini, were used, the corresponding cycloaducts **4g** and **4h** were obtained in moderate to good yield. A single crystal was obtained as a racemic mixture by recrystallization of tethered Aic **4h**, and its structure was ascertained by X-ray crystallographic analysis (Figure 3). The reaction of triyne **3i** possessing a 2-naphthyl group on diyne termini as a bulky substituent also proceeded smoothly to give the corresponding cycloadduct **4i** in high yield and ee. The cycloaddition of triyne **3j** with methyl group on its diyne termini also proceeded, and desired product **4j** was obtained in good yield, but significant decrease of ee was observed. The reaction of triyne **3k** possessing but-2-ynoate as a monoalkyne moiety was examined. The reaction gave desired cycloadduct **4k** in good yield, but ee decreased. Notably, the ee of all these cycloadducts **4b**-**4k** was improved to more than 95% by recrystallization and recovery from mother liquid. These various chiral Aic derivatives have a terphenyl scaffold, and it is very attractive. Terphenyl scaffold mimics α-helix and interact with protein,[12] and a

fluorescent terphenyl unnatural amino acid was reported.[13] Absolute configuration of **4** was determined by VCD/ECD analysis and their calculation in Scheme 3 and Figure 4 in experimental section, and that of other cycloadducts was relatively determined.

Table 2. Intramolecular cycloaddition of various triynes[*a*]



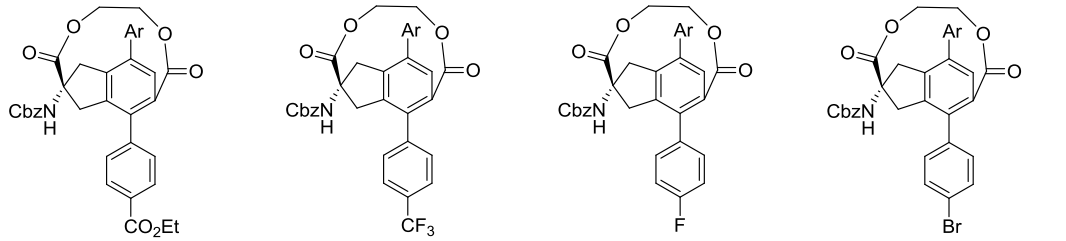


4a
80%, 82% ee (87%, 97% ee)
from **3a** (1 h)
(R^1 = Ph, R^2 = H)

4b
73%, 76% ee (90%, 96% ee)
from **3b** (1 h)
(R^1 = Ar = 4-MeC_6H_4, R^2 = H)

4c
70%, 76% ee (69%, 96% ee)
from **3c** (1 h)
(R^1 = Ar = 3-MeC_6H_4, R^2 = H)

4d
67%, 74% ee (89%, 97% ee)
from **3d** (1 h)
(R^1 = Ar = 4-$MeOC_6H_4$, R^2 = H)

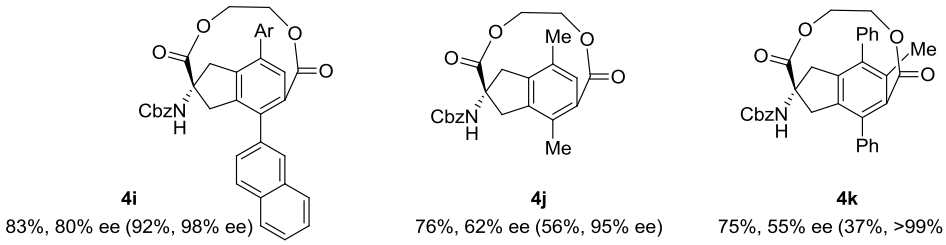


4e
36%, 75% ee (75%, >99% ee)
from **3e** (4 h)
(R^1 = Ar = 4-$EtO_2CC_6H_4$, R^2 = H)

4f
37%, 72% ee (72%, 97% ee)
from **3f** (2.5 h)
(R^1 = Ar = 4-$CF_3C_6H_4$, R^2 = H)

4g
74%, 77% ee (87%, 98% ee)
from **3g** (1.5 h)
(R^1 = Ar = 4-FC_6H_4, R^2 = H)

4h
58%, 82% ee (91%, 98% ee)
from **3h** (1 h)
(R^1 = Ar = 4-BrC_6H_4, R^2 = H)



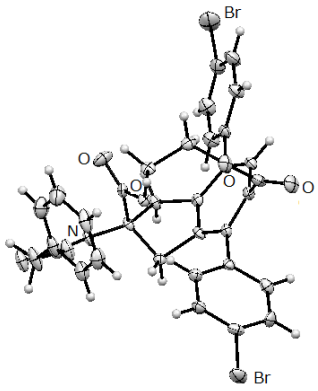
4i
83%, 80% ee (92%, 98% ee)
from **3i** (1.5 h)
(R^1 = Ar = 2-naphthyl, R^2 = H)

4j
76%, 62% ee (56%, 95% ee)
from **3j** (1 h)
(R^1 = Me, R^2 = H)

4k
75%, 55% ee (37%, >99% ee)
from **3k** (1 h)
(R^1 = Ph, R^2 = Me)

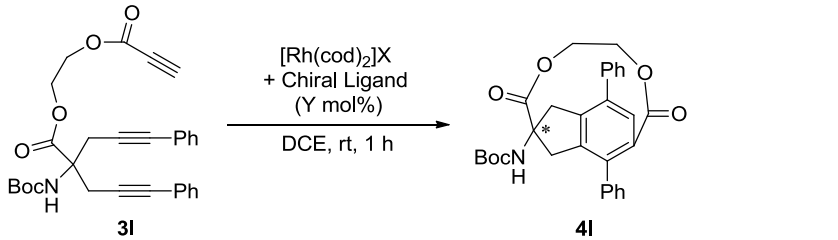
[*a*] The triyne was added dropwise to a DCE solution of the Rh catalyst over 1 h. Total time of dropwise addition (1 h) and additional reaction time was described. Recovery yield and ee in the mother liquid following recrystallization is listed in the parentheses.

Figure 3. Ortep diagram of **4h**



Next, the reaction of triyne **3l** possessing *tert*-butyloxycarbonyl group as a protecting group on nitrogen was examined (Scheme 3). Boc group has little affect on present reaction, and cycloaddition of **3l** proceeded enantioselectively in moderate yield (vs Table1, Entry 4). In addition, the enantiomers **4l** were subjected to VCD/ECD analysis and their calculation to determine absolute configuration of tethered Aic **4**. VCD and ECD spectra and their calculations for elucidation of absolute configuration of **4** were shown in experimental section. As a result, measured and calculated spectra of the enantiomers **4l** were quite similar to one another, and absolute configuration ((*R*)-form) of tethered Aic derivative **4** prepared by Rh-(*S*)-BINAP catalyst was elucidated by their analysis and calculation.

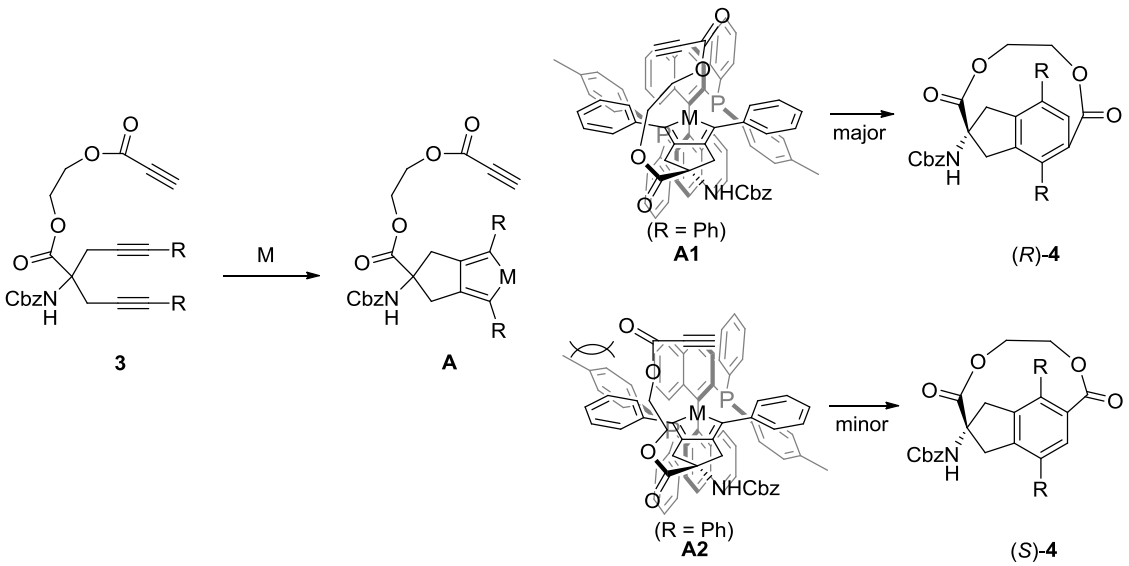
Scheme 3. Synthesis of Boc-protected tethered Aic **4l**



A possible explanation for enantioselective induction of chiral tethered Aic derivatives **4** was shown in Scheme 4. The first step is oxidative coupling of 1,6-diyne moiety with the square planar metal catalyst, and metallacyclopentadiene **A** is generated. Next step is insertion of the remaining alkyne moiety to metallacyclopentadiene moiety. Metallacyclopentadiene **A** can go through **A1** or **A2**, but steric hindrance

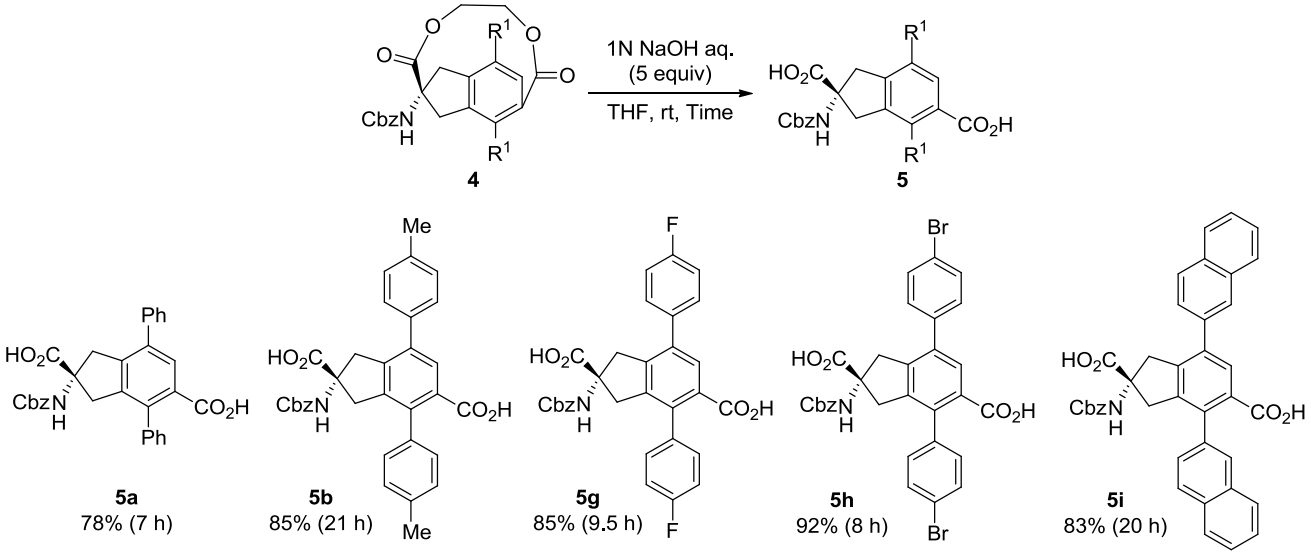
is occurred carbonyl group on propiolate metallacyclopentadiene and aryl group on ligand in **A2**. As a result, **A1** is preferred and (*R*)-**4** is obtained mainly after reductive elimination of metal catalyst.

Scheme 4. Possible explanation for enantioselective induction of **4**



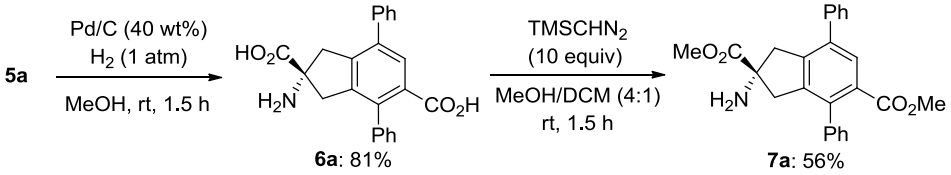
Next, hydrolysis of chiral tethered Aic **4** for the synthesis of chiral Cbz-protected Aic derivatives was examined by removal of ethylene glycol moiety (Table 3). When tethered Aic derivatives **4a, b, g, h, i** selected from Table 2 were treated with aqueous sodium hydroxide at room temperature, chiral Aic derivatives **5a, b, g, h, i** were obtained in good to high yield.

Table 3. Chiral Aic derivatives synthesis by hydrolysis of **4**



Finally, free Aic and its dimethyl ester was synthesized by deprotection of Cbz group and subsequent esterification (Scheme 5). First, the Cbz-protected Aic **5a** was treated with palladium on carbon under hydrogen atmosphere, and desired 5-carboxylated free Aic **6a** was obtained in good yield. Then, the reaction of **6a** with trimethylsilyldiazomethane gave dimethyl ester of Aic **7a** in moderate yield.

Scheme 5. Synthetic transformation to free Aic and its dimethyl ester.



Conclusion

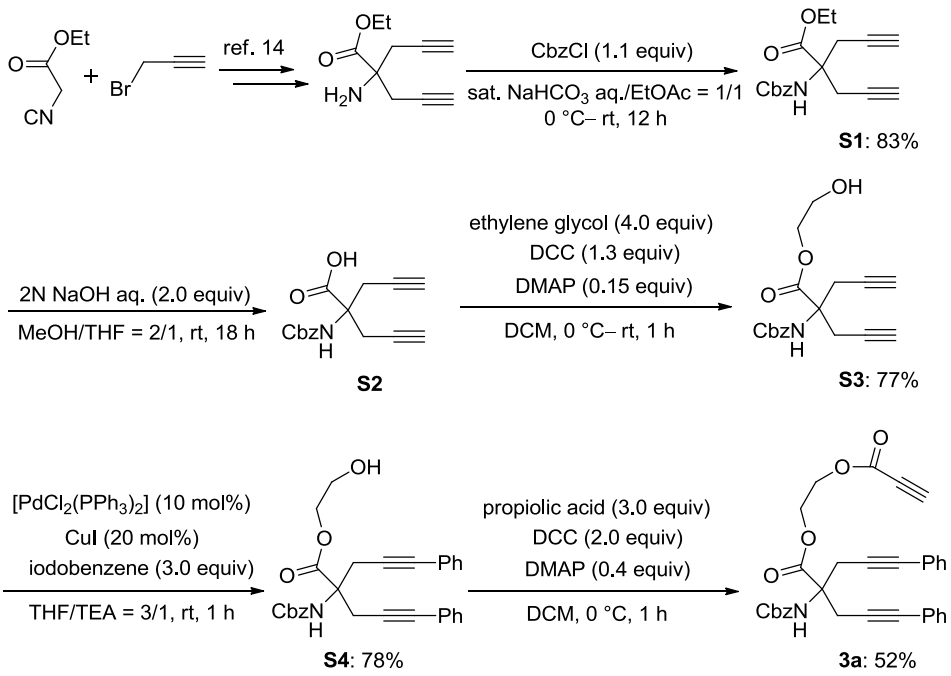
The author developed enantioselective intramolecular [2+2+2] cycloaddition of amino acid-tethered triynes. The present reaction provides a new and widely applicable protocol for the synthesis of chiral Aic derivatives.

Experimental Section

General

^{1}H NMR spectra were recorded on JEOL JNM-ECX500 (500 MHz) spectrometers. The chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) for $CDCl_3$, or external standard TMS (0 ppm) for CD_3OD. The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; q, quartet; br, broad. The coupling constants, *J*, are reported in Hertz (Hz). ^{13}C NMR spectra were obtained by JEOL JNM-ECX500 (125 MHz) spectrometers and referenced to the internal solvent signals (central peaks are 77.0 ppm in $CDCl_3$ and 49.9 ppm in CD_3OD), or external standard TMS (0 ppm) for CD_3OD. $CDCl_3$ and CD_3OD were used as NMR solvents. High-resolution mass spectra (HRMS) were measured on ESI (Electro Spray Ionization) – orbitrap mass spectrometer. Optical rotations were measured on a JASCO DIP-1000 polarimeter. IR and VCD spectra were measured on a Jasco JV-2001M spectrophotometer at a resolution of ca. 4 cm^{-1} under ambient temperature for 16 and 4000 scans, respectively. The samples were dissolved in $CDCl_3$ at a concentration of 0.05 M, and the solutions were placed in a 100-μm CaF_2 cell. UV and ECD spectra were measured on a JASCO J-820 spectropolarimeter using MeCN as solvent at 20 ºC. A path length of 1 mm was used and the concentrations were set to 0.228 and 0.212 mM, respectively. All spectral data were corrected by a solvent spectrum obtained under identical experimental conditions. Both VCD and ECD data were corrected with ee values and also enantiomeric correction was performed for VCD. Preparative thin-layer chromatography (PTLC) was performed with silica gel-precoated glass plates (Merck 60 GF254) prepared in the author's laboratory, Flash column chromatography was performed over silica gel 200-300. All reagents were weighed and handled in air and backfilled under Argon at room temperature. Unless otherwise noted, all reactions were performed under an argon atmosphere. All reagents were purchased from Wako, Kanto, Aldrich and TCI and used without further purification. Ethyl 2-amino-2-propargyl-4-pentynoate was prepared using the method in the literature.[14]

Synthetic scheme of triyne 3a



Experimental procedure for the synthesis of ethyl

2-(((benzyloxy)carbonyl)amino)-2-(prop-2-yn-1-yl)pent-4-ynoate (S1)

Ethyl 2-amino-2-propargyl-4-pentynoate[14] (2.6 g, 14.3 mmol), EtOAc (36.0 mL), and saturated aqueous sodium bicarbonate (36.0 mL) was added to a flask and it was cooled to 0-5 °C (ice bath). Benzyl chloroformate (2.3 mL, 15.7 mmol) was dropwisely added to the stirred mixture over 5 min. Stirring was continued for 18 h as the temperature rose to room temperature then the layers were separated. The aqueous phase was further extracted with EtOAc then combined extracts were washed with 1N HCl, dried by Na_2SO_4 and evaporated to dryness. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 4/1) to give diyne **S1** as pale yellow oil (3.7 g, 83%). ^{1}H NMR ($CDCl_3$) δ 7.44-7.26 (m, 5H), 5.93 (s, 1H), 5.11 (s, 2H), 4.28 (d, *J* = 6.9 Hz, 2H), 3.19 (d, *J* = 16.6 Hz, 2H), 2.80 (dd, *J* = 16.6, 2.6 Hz, 2H), 2.02 (t, *J* = 2.6 Hz, 2H), 1.29 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.6, 154.6, 136.4, 128.6, 128.2, 128.0, 78.3, 71.8, 66.8, 62.6, 61.7, 25.7, 14.2; HRMS(ESI) calcd for $C_{18}H_{19}NNaO_4$ (M+Na): 336.1206; found: 336.1206.

Experimental procedure for the synthesis of

2-(((benzyloxy)carbonyl)amino)-2-(prop-2-yn-1-yl)pent-4-ynoic acid (S2)

To diyne **S1** (2.8 g, 9.0 mmol) in a stirred mixture of MeOH (14.0 mL) and THF (7.0 mL), cooled to 0-5

°C (ice bath), was dropwisely added 2N NaOH aq. (9.0 mL, 18.0 mmol) over 5 min. Stirring was continued for 12 h at room temperature. After the reaction was finished, 1N HCl was added and the organic layer was extracted with EtOAc. The organic extracts were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure to afford diyne **S2**, which was used in the next step without further purification.

Experimental procedure for the synthesis of 2-hydroxyethyl 2-(((benzyloxy)carbonyl)amino)-2-(prop-2-yn-1-yl)pent-4-ynoate (S3)[15]

Diyne **S2** (854.7 mg, 3.0 mmol), a catalytic amount of DMAP (56.3 mg, 0.45 mmol) and ethylene glycol (0.68 mL, 12.0 mmol) were dissolved in dry DCM (6.0 mL) in a dried two necked 30 mL flask, then *N*,*N*'-dicyclohexylcarbodiimide (DCC) (804.3 mg, 3.9 mmol) in DCM (6.0 mL) was slowly added to the solution with stirring at 0-5 °C (ice bath). The reaction was conducted at room temperature for 1 h. The by-product dicyclohexylurea (DCU) precipitate was removed by filtration. Then, the filtrate was evaporated and the residue was diluted with EtOAc. The solution was washed with 1N HCl, saturated aqueous sodium bicarbonate and brine, dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 4/1) to give diyne **S3** as white solid (762.6 mg, 77%). Mp 72 °C; ^{1}H NMR ($CDCl_3$) δ 7.43-7.27 (m, 5H), 5.81 (s, 1H), 5.10 (s, 2H), 4.35 (s, 2H), 3.77 (s, 2H), 3.11 (d, *J* = 16.9 Hz, 2H), 2.89 (dd, *J* = 16.9, 2.6 Hz, 2H), 2.53 (s, 1H), 2.08 (t, *J* = 2.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 170.7, 155.1, 136.0, 128.7, 128.4, 128.1, 78.2, 72.3, 67.9, 67.2, 61.3, 60.7, 25.8; HRMS(ESI) calcd for $C_{18}H_{19}NNaO_5$ (M+Na): 352.1153; found: 352.1155.

Experimental procedure for the synthesis of 2-hydroxyethyl 2-(((benzyloxy)carbonyl)amino)-5-phenyl-2-(3-phenylprop-2-yn-1-yl)pent-4-ynoate (S4)[16]

$[PdCl_2(PPh_3)_2]$ (10 mol%), CuI (20 mol%), diyne **S3** (488.6 mg, 1.5 mmol) and iodobenzene (0.5 mL, 4.5 mmol) were dissolved in dry THF (17.0 mL) and NEt_3 (5.7 mL). The reaction mixture was stirred at room temperature for 1 h. When the completion of the reaction was judged by TLC, the solution was diluted with EtOAc and filtered. The solvents were removed in vacuo and the crude product was purified by column chromatography on silica gel (hexane/EtOAc = 5/1) to give diyne **S4** as yellow oil (559.2 mg, 78%). ^{1}H NMR ($CDCl_3$) δ 7.40-7.24 (m, 15H), 5.90 (s, 1H), 5.14 (s, 2H), 4.40 (s, 2H), 3.79 (s, 2H), 3.39 (d, *J* = 16.9 Hz, 2H), 3.18 (d, *J* = 16.9 Hz, 2H), 2.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 171.1, 155.3, 136.2, 131.8, 128.7, 128.5, 128.4, 128.3, 128.0, 122.9, 84.3, 83.6, 67.9, 67.1, 62.0, 60.9, 27.0; HRMS(ESI) calcd for $C_{30}H_{27}NNaO_5$ (M+Na): 504.1782; found: 504.1781.

Experimental procedure for the synthesis of triyne 3a[17]

Diyne **S4** (238.5 mg, 0.5 mmol), a catalytic amount of DMAP (25.1 mg, 0.20 mmol) and DCC (212.3 mg, 1.0 mmol) were dissolved in dry DCM (3.0 mL) in a dried two necked 30 mL flask, then propiolic acid (106.9 mg, 1.5 mmol) in DCM (2.0 mL) was slowly added to the solution with stirring at 0-5 °C (ice bath). The reaction was conducted at 0-5 °C for 1 h. The by-product dicyclohexylurea (DCU) precipitate was removed by filtration. Then, the filtrate was evaporated and the residue was diluted with EtOAc. The solution was washed with 1N HCl, saturated aqueous sodium bicarbonate and brine, dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 4/1) to give triyne **3a** (136.8 mg, 52%).

General procedure for the enantioselective [2+2+2] cycloaddition of triyne 3

(*S*)-tol-BINAP (10 mol%, 3.4 mg) and $[Rh(cod)_2]BARF$ (10 mol%, 5.9 mg) were placed in a dried schlenk tube, which was then evacuated and backfilled with argon (×3). To the reaction vessel was added 1,2-dichloromethane (0.5 mL). While stirring the solution at room temperature for 5 min, hydrogen gas was introduced, and the solution was further stirred for 30 min at room temperature. After removal of the solvent and hydrogen gas under reduced pressure, argon gas was introduced. 1,2-Dichloroethane (0.5 mL) was added and the reaction vessel was immersed in an oil bath of 40 °C for 5 min. Then, triyne **3** (0.05 mmol) in 1,2-dichloroethane (2.5 mL) was added dropwise via syringe pump over 1 h. After the reaction mixture was stirred at the temperature for 0-3 h, the solvent was removed under reduced pressure, and the crude product was purified by preparative TLC to give pure cycloadduct **4**. The enantiomeric excess was determined by HPLC analysis using a chiral column.

Synthetic procedure for the transformation of tethered Aic derivative 4a to Cbz-protected Aic derivative 5a

To a dried 50 mL flask tethered Aic **4a** (0.1 mmol) was added. The reaction vessel was evacuated and backfilled with argon (×3), then 1N NaOH aq. (0.5 mL, 0.5 mmol) and THF (5.0 mL) were added. After the reaction mixture was stirred at room temperature for 5 h, 1N HCl aq. was added to the solution. The mixture was extracted with EtOAc and resulting solution was dried with Na_2SO_4. After evaporation of the solution, the residue was purified by crystallization (hexane/EtOAc) and the desired solid **5a** was afforded (38.9 mg, 78%).

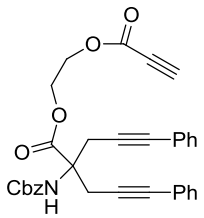
Experimental procedure for the synthesis of free Aic derivative 6a

To a dried two necked 50 mL flask Cbz-protected Aic derivative **5a** (38.9 mg, 0.08 mmol) was dissolved in MeOH (5.0 mL) and 40 wt% Pd/C (16.0 mg) was added. The resulting mixture was stirred under hydrogen atmosphere at room temperature for 1.5 h. After the reaction mixture was filtered and evaporated in vacuo, the residue was purified by crystallization (EtOAc/MeOH) and the desire solid **6a** was afforded (23.2 mg, 81%).

Experimental procedure for the synthesis of dimethylester Aic derivative 7a from 6a

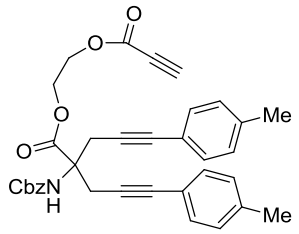
Aic derivative **6a** (20.6 mg, 0.06 mmol) was dissolved in MeOH (0.3 mL) and dry DCM (0.07 mL). Then TMS-diazomethane (2.0 M solution in diethyl ether, 0.25 mL) was added slowly to the solution with stirring at 0-5 °C (ice bath). After the reaction mixture was stirred at room temperature for 1.5 h, the solvent was removed under reduced pressure and the crude product was purified by preparative TLC (hexane/EtOAc = 3/2) to give pure dimethylester Aic **7a** (12.4 mg, 56%).

Characterization of new compounds



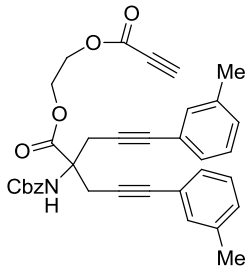
2-(Propioloyloxy)ethyl 2-(((benzyloxy)carbonyl)amino)-5-phenyl-2-(3-phenylprop-2-yn-1-yl)pent-4-ynoate (3a)

Isolated by column chromatography on silica gel (hexane/EtOAc = 4/1). The title compound was obtained as yellow solid (52%). Mp 93 °C; ^{1}H NMR ($CDCl_3$) δ 7.41-7.20 (m, 15H), 5.94 (s, 1H), 5.15 (s, 2H), 4.47 (br, 2H), 4.40 (br, 2H), 3.43 (d, *J* = 16.8 Hz, 2H), 3.15 (d, *J* = 16.8 Hz, 2H), 2.79 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 170.8, 154.8, 152.4, 136.4, 131.9, 128.6, 128.3, 128.2, 128.2, 127.9, 123.1, 84.2, 83.6, 75.7, 74.3, 66.8, 63.5, 63.3, 62.3, 26.8; HRMS(ESI) calcd for $C_{33}H_{27}NNaO_6$ (M+Na): 556.1730; found: 556.1731.



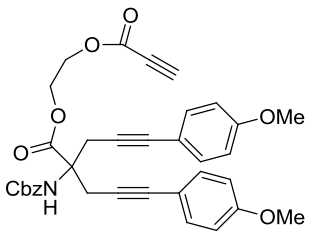
2-(Propioloyloxy)ethyl 2-(((benzyloxy)carbonyl)amino)-5-(*p*-tolyl)-2-(3-(*p*-tolyl)prop-2-yn-1-yl)pent-4-ynoate (3b)

Isolated by column chromatography on silica gel (hexane/EtOAc = 4/1). The title compound was obtained as yellow solid (70%). Mp 95 °C; ^{1}H NMR ($CDCl_3$) δ 7.43-6.98 (m, 13H), 5.91 (s, 1H), 5.14 (s, 2H), 4.46 (br, 2H), 4.40 (br, 2H), 3.40 (d, *J* = 16.8 Hz, 2H), 3.13 (d, *J* = 16.8 Hz, 2H), 2.80 (s, 1H), 2.32 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 170.9, 154.8, 152.4, 138.3, 136.4, 131.8, 129.1, 128.6, 128.2, 127.9, 120.0, 84.2, 82.8, 75.6, 74.3, 66.8, 63.5, 63.2, 62.3, 26.8, 21.5; HRMS(ESI) calcd for $C_{35}H_{31}NNaO_6$ (M+Na): 584.2043; found: 584.2044.



2-(Propioloyloxy)ethyl 2-(((benzyloxy)carbonyl)amino)-5-(*m*-tolyl)-2-(3-(*m*-tolyl)prop-2-yn-1-yl)pent-4-ynoate (3c)

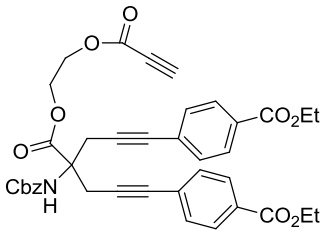
Isolated by column chromatography on silica gel (hexane/EtOAc = 4/1). The title compound was obtained as yellow oil (62%). ^{1}H NMR ($CDCl_3$) δ 7.39-7.27 (m, 5H), 7.22-7.06 (m, 8H), 5.90 (s, 1H), 5.15 (s, 2H), 4.48 (br, 2H), 4.41 (br, 2H), 3.41 (d, *J* = 16.8 Hz, 2H), 3.14 (d, *J* = 16.8 Hz, 2H), 2.79 (s, 1H), 2.30 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 170.8, 154.8, 152.4, 138.0, 136.4, 132.4, 129.1, 129.0, 128.6, 128.2, 128.2, 127.9, 122.9, 84.3, 83.2, 75.6, 74.3, 66.8, 63.5, 63.3, 62.3, 26.8, 21.3; HRMS(ESI) calcd for $C_{35}H_{31}NNaO_6$ (M+Na): 584.2043; found: 584.2044.



2-(Propioloyloxy)ethyl 2-(((benzyloxy)carbonyl)amino)-5-(4-methoxyphenyl)-2-(3-(4-methoxyphenyl)prop-2-yn-1-yl)pent-4-ynoate (3d)

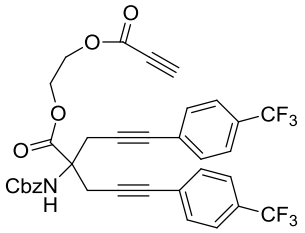
Isolated by column chromatography on silica gel (hexane/EtOAc = 4/1). The title compound was

obtained as yellow oil (60%). ^{1}H NMR ($CDCl_3$) δ 7.38-7.26 (m, 9H), 6.83-6.76 (m, 4H), 5.89 (s, 1H), 5.14 (s, 2H), 4.46 (br, 2H), 4.40 (br, 2H), 3.79 (s, 6H), 3.38 (d, *J* = 16.9 Hz, 2H), 3.12 (d, *J* = 16.9 Hz, 2H), 2.81 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 170.9, 159.5, 154.8, 152.4, 136.5, 133.3, 128.6, 128.2, 127.9, 115.2, 113.9, 83.9, 82.0, 75.6, 74.3, 66.8, 63.5, 63.2, 62.4, 55.4, 26.8; HRMS(ESI) calcd for $C_{35}H_{31}NNaO_8$ (M+Na): 616.1942; found: 616.1942.



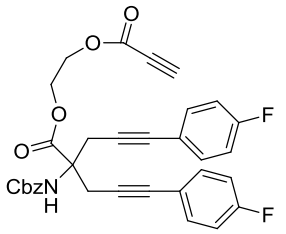
Diethyl 4,4'-(4-(((benzyloxy)carbonyl)amino)-4-((2-(propioloyloxy)ethoxy)carbonyl)hepta-1,6-diyne -1,7-diyl)dibenzoate (3e)

Isolated by column chromatography on silica gel (hexane/EtOAc = 4/1). The title compound was obtained as yellow oil (50%). ^{1}H NMR ($CDCl_3$) δ 7.96-7.92 (m, 4H), 7.42-7.28 (m, 9H), 5.94 (s, 1H), 5.15 (s, 2H), 4.64-4.17 (m, 8H), 3.47 (d, *J* = 16.9 Hz, 2H), 3.16 (d, *J* = 16.9 Hz, 2H), 2.80 (s, 1H), 1.38 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 170.6, 166.1, 154.7, 152.3, 136.3, 131.7, 130.0, 129.5, 128.6, 128.3, 128.0, 127.5, 86.6, 83.6, 75.7, 74.2, 66.9, 63.5, 63.4, 62.2, 61.2, 26.9, 14.4; HRMS(ESI) calcd for $C_{39}H_{35}NNaO_{10}$ (M+Na): 700.2150; found: 700.2153.



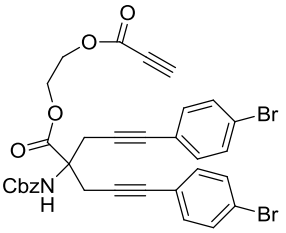
2-(Propioloyloxy)ethyl 2-(((benzyloxy)carbonyl)amino)-5-(4-(trifluoromethyl)phenyl)-2-(3-(4-(trifluoro-methyl)phenyl)prop-2-yn-1-yl)pent-4-ynoate (3f)

Isolated by column chromatography on silica gel (hexane/EtOAc = 4/1). The title compound was obtained as yellow oil (43%). ^{1}H NMR ($CDCl_3$) δ 7.52 (d, *J* = 8.2 Hz, 4H), 7.44 (d, *J* = 8.2 Hz, 4H), 7.38-7.26 (m, 5H), 5.96 (s, 1H), 5.15 (s, 2H), 4.49 (br, 2H), 4.42 (br, 2H), 3.48 (d, *J* = 16.9 Hz, 2H), 3.15 (d, *J* = 16.9 Hz, 2H), 2.80 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 170.6, 154.7, 152.3, 136.2, 132.1, 130.1 (d, *J* = 32.6 Hz), 128.6, 128.2 (d, *J* = 36.8 Hz), 126.7, 125.3 (q, *J* = 3.8 Hz), 125.1, 122.9, 86.1, 83.0, 75.7, 74.2, 67.0, 63.6, 63.4, 62.2, 26.8; HRMS(ESI) calcd for $C_{35}H_{25}F_6NNaO_6$ (M+Na): 692.1476; found: 692.1478.



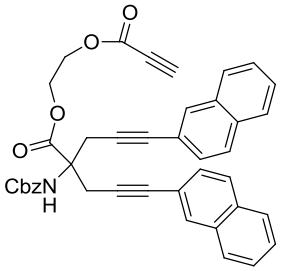
2-(Propioloyloxy)ethyl 2-(((benzyloxy)carbonyl)amino)-5-(4-fluorophenyl)-2-(3-(4-fluorophenyl)-prop-2-yn-1-yl)pent-4-ynoate (3g)

Isolated by column chromatography on silica gel (hexane/EtOAc = 4/1). The title compound was obtained as yellow oil (52%). ^{1}H NMR ($CDCl_3$) δ 7.38-7.27 (m, 9H), 7.00-6.92 (m, 4H), 5.92 (s, 1H), 5.15 (s, 2H), 4.47 (br, 2H), 4.41 (br, 2H), 3.41 (d, *J* = 16.8 Hz, 2H), 3.12 (d, *J* = 16.8 Hz, 2H), 2.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 170.8, 163.5, 161.5, 154.7, 152.4, 136.4, 133.7 (d, *J* = 8.3 Hz), 128.6, 128.1 (d, *J* = 32.7 Hz), 119.1 (d, *J* = 3.5 Hz), 115.6 (d, *J* = 22.0 Hz), 83.2, 83.1, 75.7, 74.2, 66.8, 63.5, 63.4, 62.3, 26.8, HRMS(ESI) calcd for $C_{33}H_{25}F_2NNaO_6$ (M+Na): 592.1541; found: 592.1542.



2-(Propioloyloxy)ethyl 2-(((benzyloxy)carbonyl)amino)-5-(4-bromophenyl)-2-(3-(4-bromophenyl)-prop-2-yn-1-yl)pent-4-ynoate (3h)

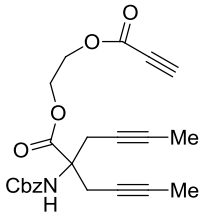
Isolated by column chromatography on silica gel (hexane/EtOAc = 4/1). The title compound was obtained as yellow solid (54%). Mp 97 °C; ^{1}H NMR ($CDCl_3$) δ 7.45-7.14 (m, 13H), 5.92 (s, 1H), 5.14 (s, 2H), 4.46 (br, 2H), 4.40 (br, 2H), 3.41 (d, *J* = 16.9 Hz, 2H), 3.11 (d, *J* = 16.9 Hz, 2H), 2.82 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 170.7, 154.7, 152.4, 136.3, 133.3, 131.6, 128.7, 128.3, 128.0, 122.5, 121.9, 84.8, 83.2, 75.7, 74.2, 66.9, 63.5, 63.4, 62.2, 26.8; HRMS(ESI) calcd for $C_{33}H_{25}Br_2NNaO_6$ (M+Na): 711.9940; found: 711.9941.



2-(Propioloyloxy)ethyl 2-(((benzyloxy)carbonyl)amino)-5-(naphthalen-2-yl)-2-(3-(naphthalen-2-yl)-prop-2-yn-1-yl)pent-4-ynoate (3i)

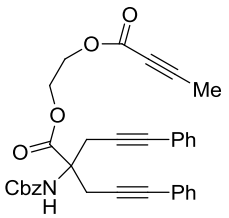
Isolated by column chromatography on silica gel (hexane/ EtOAc = 4/1). The title compound was

obtained as yellow solid (73%). Mp 117 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (s, 2H), 7.80-7.70 (m, 6H), 7.50-7.26 (m, 11H), 6.01 (s, 1H), 5.18 (s, 2H), 4.52 (br, 2H), 4.44 (br, 2H), 3.51 (d, *J* = 16.8 Hz, 2H), 3.24 (d, *J* = 16.8 Hz, 2H), 2.70 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 170.9, 154.9, 152.4, 136.4, 133.0, 132.8, 131.7, 128.7, 128.6, 128.2, 128.0, 127.8, 127.8, 126.7, 126.6, 120.4, 84.6, 83.9, 75.6, 74.2, 66.9, 63.5, 63.4, 62.4, 27.0 (a pair of peaks at the aromatic region is overlapped); HRMS(ESI) calcd for $C_{41}H_{31}NNaO_6$ (M+Na): 656.2039; found: 656.2044.



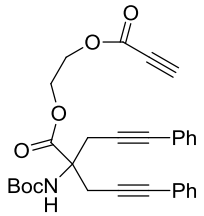
2-(Propioloyloxy)ethyl 2-(((benzyloxy)carbonyl)amino)-2-(but-2-yn-1-yl)hex-4-ynoate (3j)

Isolated by column chromatography on silica gel (hexane/EtOAc = 4/1). The title compound was obtained as yellow oil (52%). ^{1}H NMR ($CDCl_3$) δ 7.50-7.26 (m, 5H), 5.70 (s, 1H), 5.12 (s, 2H), 4.41 (br, 4H), 3.03 (br, 2H), 2.92 (s, 1H), 2.78 (d, *J* = 16.3 Hz, 2H), 1.75 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.1, 154.7, 152.4, 136.5, 128.6, 128.2, 128.0, 79.4, 75.5, 74.4, 72.9, 66.7, 63.6, 62.9, 62.1, 26.1, 3.6; HRMS(ESI) calcd for $C_{23}H_{23}NNaO_6$ (M+Na): 432.1417; found: 432.1418.



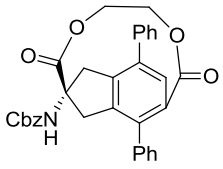
2-(But-2-ynoyloxy)ethyl 2-(((benzyloxy)carbonyl)amino)-5-phenyl-2-(3-phenylprop-2-yn-1-yl)pent-4-ynoate (3k)

Isolated by column chromatography on silica gel (hexane/EtOAc = 4/1). The title compound was obtained as yellow oil (91%). ^{1}H NMR ($CDCl_3$) δ 7.46-7.17 (m, 15H), 5.97 (s, 1H), 5.15 (s, 2H), 4.46 (br, 2H), 4.37 (br, 2H), 3.44 (d, *J* = 16.8 Hz, 2H), 3.14 (d, *J* = 16.8 Hz, 2H), 1.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.8, 154.8, 153.4, 136.5, 131.9, 128.6, 128.3, 128.2, 128.2, 127.9, 123.1, 86.7, 84.1, 83.6, 72.1, 66.8, 63.6, 63.0, 62.4, 26.8, 3.8; HRMS(ESI) calcd for $C_{34}H_{29}NNaO_6$ (M+Na): 570.1895; found: 570.1887.



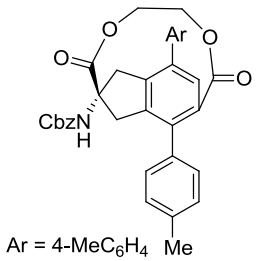
2-(Propioloyloxy)ethyl 5-phenyl-2-(3-phenylprop-2-yn-1-yl)pent-2-(((tertiarybutoxy)carbonyl)-amino)-4-ynoate (3l)

Isolated by column chromatography on silica gel (hexane/EtOAc = 4/1). The title compound was obtained as yellow oil (59%). ^{1}H NMR ($CDCl_3$) δ 7.43-7.35 (m, 4H), 7.33-7.26 (m, 6H), 5.54 (s, 1H), 4.52-4.44 (m, 2H), 4.44-4.39 (m, 2H), 3.44-3.25 (m, 2H), 3.15 (d, *J* = 16.8 Hz, 2H), 2.82 (s, 1H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$) δ171.1, 154.4, 152.4, 131.9, 128.3, 128.2, 123.2, 84.0, 83.8, 75.6, 74.3, 63.7, 63.1, 61.8, 33.6, 28.4, 26.8; HRMS(ESI) calcd for $C_{30}H_{29}NNaO_6$ (M+Na): 522.1888; found: 522.1887.



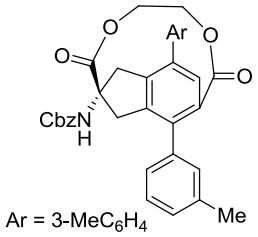
2-(((Benzyloxy)carbonyl)amino)-2,5-(2,5-dioxa-1,6-dioxohexano)-4,7-diphenyl-indan (4a)

Isolated by preparative TLC (hexane/EtOAc = 3/2, Rf = 0.6). The title compound was obtained as white solid (80%). Mp 255 °C; ^{1}H NMR ($CDCl_3$) δ 7.52-7.20 (m, 16H), 5.60 (s, 1H), 5.07-4.93 (m, 2H), 4.49 (br, 1H), 4.16 (br, 1H), 3.89 (br, 1H), 3.75-3.58 (m, 2H), 3.31 (br, 2H), 3.01 (dd, *J* = 13.7, 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 173.2, 168.6, 149.4, 140.6, 139.3, 137.4, 136.6, 131.0, 129.2, 128.9, 128.9, 128.8, 128.8, 128.7, 128.5, 128.5, 128.3, 128.2, 121.6, 71.5, 70.9, 67.3, 42.9, 29.8, 23.1 (two pairs of peaks at the aromatic region are overlapped); HRMS(ESI) calcd for $C_{33}H_{27}NNaO_6$ (M+Na): 556.1732; found: 556.1731. $[\alpha]^{34}_{D}$ = +4.6 (*c* 1.0, $CHCl_3$, 97% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/dichloromethane = 1/1, flow rate: 1.0 mL/min, retention time: 10.8 min for major isomer and 13.6 min for minor isomer). HPLC charts of racemic sample, chiral sample prepared by enantioselective [2+2+2] cycloaddition, and chiral sample after recrystallization, respectively, were listed. The same hereinafter.



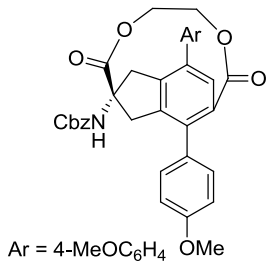
2-(((Benzyloxy)carbonyl)amino)-2,5-(2,5-dioxa-1,6-dioxohexano)-4,7-di(*p*-tolyl)-indan (4b)

Isolated by preparative TLC (hexane/EtOAc = 3/2, Rf = 0.6). The title compound was obtained as white solid (73%). Mp 175 °C; ^{1}H NMR ($CDCl_3$) δ 7.40-7.19 (m, 14H), 5.60 (s, 1H), 5.08-4.91 (m, 2H), 4.47 (br, 1H), 4.12 (br, 1H), 3.85 (br, 1H), 3.74-3.57 (m, 2H), 3.28 (br, 2H), 3.01 (dd, *J* = 13.6, 2.0 Hz, 1H), 2.40 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 178.4, 172.9, 155.6, 142.3, 140.8, 138.8, 137.8, 137.6, 137.5, 137.0, 136.3, 136.0, 130.9, 129.4, 129.1, 128.9, 128.6, 128.4, 128.3, 128.3, 128.2, 67.2, 66.7, 65.6, 60.8, 60.7, 43.8, 21.4, 21.3; HRMS(ESI) calcd for $C_{35}H_{31}NNaO_6$ (M+Na): 584.2046; found: 584.2044. $[\alpha]^{28}_D$ = +11.1 (*c* 0.9, $CHCl_3$, 96% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/dichloromethane = 1/1, flow rate: 1.0 mL/min, retention time: 9.5 min for major isomer and 11.4 min for minor isomer).



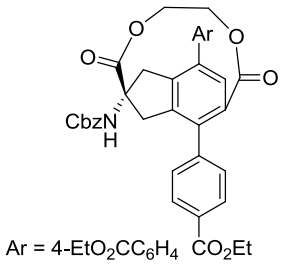
2-(((Benzyloxy)carbonyl)amino)-2,5-(2,5-dioxa-1,6-dioxohexano)-4,7-di(*m*-tolyl)-indan (4c)

Isolated by preparative TLC (hexane/EtOAc = 3/2, Rf = 0.6). The title compound was obtained as white solid (70%). Mp 140 °C; ^{1}H NMR ($CDCl_3$) δ 7.38-7.17 (m, 14H), 5.58 (s, 1H), 5.11-4.93 (m, 2H), 4.49 (s, 1H), 4.17 (br, 1H), 3.89 (br, 1H), 3.70 (br, 1H), 3.59 (dd, *J* = 13.4, 2.3 Hz, 1H), 3.47-3.14 (m, 2H), 3.02 (dd, *J* = 13.4, 2.3 Hz, 1H), 2.43 (s, 3H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.2, 168.7, 149.3, 140.7, 139.4, 138.8, 138.4, 137.4, 136.6, 130.0, 129.5, 129.3, 129.0, 128.8, 128.8, 128.7, 128.6, 128.4, 128.2, 125.5, 121.5, 71.5, 70.9, 67.3, 46.1, 43.0, 21.7, 21.6, 13.4 (four pairs of peaks at the aromatic region are overlapped); HRMS(ESI) calcd for $C_{35}H_{31}NNaO_6$ (M+Na): 584.2045; found: 584.2044. $[\alpha]^{31}_D$ = +8.8 (*c* 0.7, $CHCl_3$, 96% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/dichloromethane = 1/1, flow rate: 1.0 mL/min, retention time: 7.7 min for major isomer and 8.6 min for minor isomer).



2-(((Benzyloxy)carbonyl)amino)-4,7-bis(4-methoxyphenyl)-2,5-(2,5-dioxa-1,6-dioxohexano)-indan (4d)

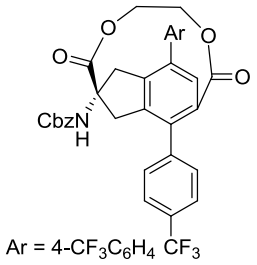
Isolated by preparative TLC (hexane/EtOAc = 3/2, Rf = 0.6). The title compound was obtained as white solid (67%). Mp 141 °C; ^{1}H NMR ($CDCl_3$) δ 7.43-7.23 (m, 10H), 7.02-6.89 (m, 4H), 5.60 (s, 1H), 5.09-4.94 (m, 2H), 4.48 (br, 1H), 4.20-4.02 (m, 1H), 3.93-3.77 (m, 7H), 3.72-3.58 (m, 2H), 3.27 (br, 2H), 3.02 (dd, *J* = 13.6, 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 173.3, 169.0, 160.1, 159.7, 155.4, 149.3, 139.8, 138.6, 130.3, 130.0, 129.4, 129.0, 128.7, 128.6, 128.5, 128.2, 121.0, 114.6, 114.3, 71.5, 70.8, 67.3, 64.0, 55.5, 55.4, 46.4, 42.8 (two pairs of peaks at the aromatic region are overlapped); HRMS(ESI) calcd for $C_{35}H_{31}NNaO_8$ (M+Na): 616.1940; found: 616.1942. $[\alpha]^{32}_D$ = +14.5 (*c* 1.0, $CHCl_3$, 97% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/2-propanol = 1/1, flow rate: 1.0 mL/min, retention time: 25.4 min for major isomer and 20.4 min for minor isomer).



2-(((Benzyloxy)carbonyl)amino)-4,7-bis(4-(ethoxycarbonyl)phenyl)-2,5-(2,5-dioxa-1,6-dioxohexano)-indan (4e)

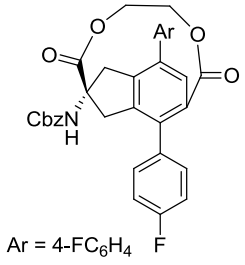
Isolated by preparative TLC (hexane/EtOAc = 3/2, Rf = 0.4). The title compound was obtained as white solid (36%). Mp 142 °C; ^{1}H NMR ($CDCl_3$) δ 8.22-8.06 (m, 4H), 7.62-7.20 (m, 10H), 5.72 (s, 1H), 5.01 (m, 2H), 4.53 (br, 1H), 4.42 (q, *J* = 6.3 Hz, 4H), 4.20 (br, 1H), 3.97-3.65 (m, 2H), 3.59 (d, *J* = 13.4 Hz, 1H), 3.31 (br, 2H), 2.99 (d, *J* = 13.4 Hz, 1H), 1.42 (t, *J* = 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 172.9, 168.0, 166.2, 166.1, 149.7, 141.3, 140.9, 140.3, 138.7, 130.8, 130.6, 130.4, 130.1, 128.9, 128.7, 128.5, 128.3, 128.2, 121.9, 71.7, 71.0, 67.5, 61.4, 61.2, 46.0, 42.8, 29.7, 14.4, 14.4 (four pairs of peaks at the aromatic region are overlapped); HRMS(ESI) calcd for $C_{39}H_{35}NNaO_{10}$ (M+Na): 700.2151; found: 700.2153. $[\alpha]^{37}_D$

= +8.0 (*c* 0.5, $CHCl_3$, >99% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/dichloromethane = 2/3, flow rate: 1.0 mL/min, retention time: 20.1 min for major isomer and 17.2 min for minor isomer).



2-(((Benzyloxy)carbonyl)amino)-4,7-bis(4-trifluoromethylphenyl)-2,5-(2,5-dioxa-1,6-dioxohexano)-indan (4f)

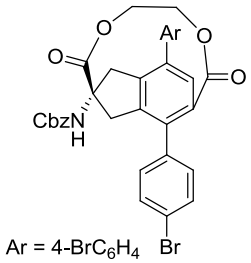
Isolated by preparative TLC (hexane/EtOAc = 3/2, Rf = 0.6). The title compound was obtained as white solid (37%). Mp 140 °C; ^{1}H NMR ($CDCl_3$) δ 7.81-7.13 (m, 14H), 5.61 (s, 1H), 5.09-4.90 (m, 2H), 4.53 (br, 1H), 4.19 (br, 1H), 3.99-3.63 (m, 2H), 3.59 (d, *J* = 13.4 Hz, 1H), 3.31 (br, 2H), 2.98 (d, *J* = 13.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 172.8, 167.8, 157.5, 149.8, 140.6, 140.0, 139.9, 138.5, 131.2, 130.9, 129.3, 129.2, 128.8, 128.7, 128.6, 128.6, 128.3, 126.2 (q, *J* = 7.7, 4.1 Hz), 126.0, 121.9, 71.6, 71.1, 67.5, 42.7, 29.8, 29.7 (two pairs of peaks at the aromatic region are overlapped); HRMS(ESI) calcd for $C_{35}H_{25}F_6NNaO_6$ (M+Na): 692.1476; found: 692.1478. $[\alpha]^{37}_D$ = +2.4 (*c* 0.5, $CHCl_3$, 97% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IC: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/dichloromethane = 1/1, flow rate: 1.0 mL/min, retention time: 5.9 min for major isomer and 7.8 min for minor isomer).



2-(((Benzyloxy)carbonyl)amino)-4,7-bis(4-fluorophenyl)-2,5-(2,5-dioxa-1,6-dioxohexano)-indan (4g)

Isolated by preparative TLC (hexane/EtOAc = 3/2, Rf = 0.6). The title compound was obtained as white solid (74%). Mp 148 °C; ^{1}H NMR ($CDCl_3$) δ 7.52-7.06 (m, 14H), 5.62 (s, 1H), 5.09-4.92 (m, 2H), 4.50 (br, 1H), 4.20-4.03 (m, 1H), 3.85 (br, 1H), 3.65 (br, 2H), 3.25 (br, 2H), 2.98 (dd, *J* = 13.6, 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 173.1, 168.4, 164.0 (d, *J* = 34.2 Hz), 162.0 (d, *J* = 33.6 Hz), 149.5, 139.7, 138.4, 133.5, 132.5 (d, *J* = 3.4 Hz), 130.8 (d, *J* = 8.3 Hz), 130.0 (d, *J* = 8.3 Hz), 129.0, 128.7, 128.5, 128.2, 121.5, 116.3 (d, *J* = 21.7 Hz), 116.0 (d, *J* = 21.5 Hz), 71.6, 70.9, 67.4, 63.9, 46.1, 42.6 (three pairs of

peaks at the aromatic region are overlapped); HRMS(ESI) calcd for $C_{33}H_{25}F_2NNaO_6$ (M+Na): 592.1541; found: 592.1542. $[\alpha]^{32}_D$ = +1.9 (*c* 0.9, $CHCl_3$, 98% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/dichloromethane = 1/1, flow rate: 1.0 mL/min, retention time: 13.2 min for major isomer and 19.1 min for minor isomer).



2-(((Benzyloxy)carbonyl)amino)-4,7-bis(4-bromophenyl)-2,5-(2,5-dioxa-1,6-dioxohexano)-indan (4h)

Isolated by preparative TLC (hexane/EtOAc = 3/2, Rf = 0.6). The title compound was obtained as white solid (58%). Mp 235 °C; ^{1}H NMR ($CDCl_3$) δ 7.66-7.52 (m, 4H), 7.42-7.23 (m, 10H), 5.57 (s, 1H), 5.09-4.95 (m, 2H), 4.51 (br, 1H), 4.14 (br, 1H), 3.94-3.52 (m, 3H), 3.26 (br, 2H), 2.98 (dd, *J* = 13.6, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 172.9, 168.1, 149.6, 139.8, 138.4, 136.1, 135.3, 132.4, 132.2, 130.5, 129.7, 128.9, 128.7, 128.6, 128.3, 123.3, 123.2, 121.5, 71.6, 71.0, 67.4, 64.0, 46.1, 42.7 (three pairs of peaks at the aromatic region are overlapped); HRMS(ESI) calcd for $C_{33}H_{25}Br_2NNaO_6$ (M+Na): 711.9940; found: 711.9941. $[\alpha]^{32}_D$ = +3.0 (*c* 0.9, $CHCl_3$, 98% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/dichloromethane = 1/1, flow rate: 1.0 mL/min, retention time: 23.3 min for major isomer and 25.2 min for minor isomer).

Crystal data of *racemic* **4h**; $C_{34}H_{25}Br_2Cl_2NO_6$, *M* = 774.29, triclinic, Space Group P-1 (#2), *a* = 11.0137(4) Å, *b* = 12.2025(4) Å, *c* = 13.0342(3) Å, *V* = 1564.39(9) Å^3, *T* = 292.0 K, *Z* = 2, μ(Cu-Ka) = 52.642 cm^{-1}; Number of Reflections Measures: Total 12321, Unique: 5297 (R_{int} = 0.0598), *R1* = 0.0560, *wR2* = 0.1597.

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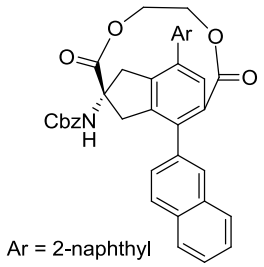
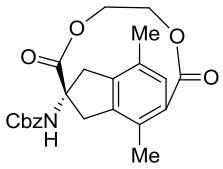


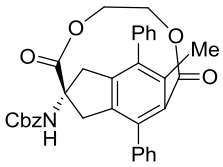
2-(((Benzyloxy)carbonyl)amino)-4,7-di(naphthalen-2-yl)-2,5-(2,5-dioxa-1,6-dioxohexano)-indan (4i)

Isolated by preparative TLC (hexane/EtOAc = 3/2, Rf = 0.6). The title compound was obtained as white solid (83%). Mp 157 °C; ^{1}H NMR ($CDCl_3$) δ 7.99-7.83 (m, 8H), 7.67-7.47 (m, 7H), 7.27 (br, 5H), 5.62 (s, 1H), 5.05-4.89 (m, 2H), 4.53 (br, 1H), 4.22 (br, 1H), 3.97 (br, 1H), 3.78 (br, 1H), 3.64 (d, *J* = 13.4 Hz, 1H), 3.48 (br, 1H), 3.35 (br, 1H), 3.05 (dd, *J* = 13.4, 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 173.1, 168.7, 155.3, 149.8, 140.6, 139.4, 135.7, 134.8, 134.1, 133.5, 133.4, 133.3, 133.1, 129.0, 128.9, 128.7, 128.6, 128.6, 128.4, 128.4, 128.2, 127.9, 127.8, 127.7, 126.9, 126.8, 126.6, 126.4, 125.8, 121.8, 71.7, 71.0, 67.3, 64.1, 46.2, 43.1 (three pairs of peaks at the aromatic region are overlapped); HRMS(ESI) calcd for $C_{41}H_{31}NNaO_6$ (M+Na): 656.2043; found: 656.2044. $[\alpha]^{26}_D$ = -2.9 (*c* 1.2, $CHCl_3$, 98% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IC: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/dichloromethane = 1/1, flow rate: 1.0 mL/min, retention time: 14.0 min for major isomer and 21.5 min for minor isomer).



2-(((Benzyloxy)carbonyl)amino)-4,7-dimethyl-2,5-(2,5-dioxa-1,6-dioxohexano)-indan (4j)

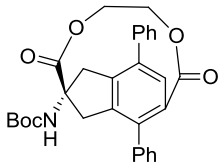
Isolated by preparative TLC (hexane/EtOAc = 3/2, Rf = 0.7). The title compound was obtained as white solid (76%). Mp 193 °C; ^{1}H NMR ($CDCl_3$) δ 7.46-7.29 (m, 5H), 6.83 (s, 1H), 5.68 (br, 1H), 5.17-5.02 (m, 2H), 4.48 (br, 1H), 3.88 (br, 2H), 3.66 (br, 1H), 3.33 (d, *J* = 13.1 Hz, 1H), 3.09 (d, *J* = 13.1 Hz, 1H), 3.01 (d, *J* = 12.7 Hz, 1H), 2.76-2.62 (m, 1H), 2.30 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.5, 170.1, 155.4, 148.9, 139.7, 135.8, 135.4, 133.3, 130.6, 128.7, 128.5, 128.3, 124.8, 71.4, 70.9, 67.5, 64.0, 44.7, 41.0, 18.8, 16.9; HRMS(ESI) calcd for $C_{23}H_{23}NNaO_6$ (M+Na): 432.1420; found: 432.1418. $[\alpha]^{35}_D$ = -7.4 (*c* 0.4, $CHCl_3$, 95% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/dichloromethane = 3/7, flow rate: 1.0 mL/min, retention time: 6.1 min for major isomer and 15.1 min for minor isomer).



2-(((Benzyloxy)carbonyl)amino)-6-methyl-2,5-(2,5-dioxa-1,6-dioxohexano)-4,7-diphenyl-indan (4k)

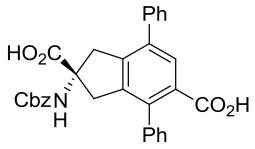
Isolated by preparative TLC (hexane/EtOAc = 3/2, Rf = 0.6). The title compound was obtained as white solid (75%). Mp 231 °C; ^{1}H NMR ($CDCl_3$) δ 7.56-7.13 (m, 15H), 5.52 (s, 1H), 5.08-4.90 (m, 2H), 4.64 (s, 1H), 4.16 (br, 1H), 3.94 (br, 1H), 3.69 (br, 1H), 3.21 (br, 1H), 3.10 (br, 1H), 3.04 (br, 1H), 2.87 (dd, *J* =

13.4, 2.3 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.6, 168.7, 155.4, 145.4, 140.8, 139.3, 137.8, 137.0, 130.4, 129.5, 129.1, 129.1, 128.9, 128.7, 128.7, 128.5, 128.4, 128.2, 128.0, 71.0, 70.8, 67.3, 64.2, 45.2, 42.1, 16.9 (two pairs of peaks at the aromatic region are overlapped); HRMS(ESI) calcd for $C_{34}H_{29}NNaO_6$ (M+Na): 570.1887; found: 570.1887. $[\alpha]^{36}_D$ = +27.6 (*c* 0.4, $CHCl_3$, >99% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/dichloromethane = 1/1, flow rate: 1.0 mL/min, retention time: 20.3 min for major isomer and 8.2 min for minor isomer).



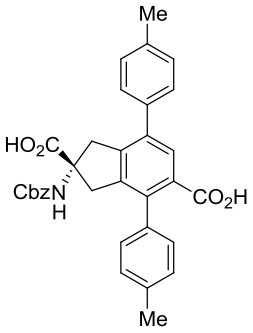
2,5-(2,5-Dioxa-1,6-dioxohexano)-4,7-diphenyl-2-(((tertiarybutoxy)carbonyl)amino)-indan (4l)

Isolated by preparative TLC (hexane/EtOAc = 3/2, Rf = 0.5). The title compound was obtained as white solid (66%). Mp 145 °C; ^{1}H NMR ($CDCl_3$) δ 7.51-7.38 (m, 10H), 5.31 (s, 1H), 4.53 (br, 1H), 4.16 (d, *J* = 14.7 Hz, 1H), 3.88 (br, 1H), 3.71-3.57 (m, 2H), 3.33 (br, 1H), 3.22 (br, 1H), 3.01 (d, *J* = 13.7 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.5, 168.7, 149.6, 140.5, 139.2, 137.4, 136.7, 129.1, 129.0, 128.9, 128.8, 128.7, 128.5, 128.3, 121.5, 71.6, 70.9, 63.8, 46.4, 43.0, 29.8, 28.3 (two pairs of peaks at the aromatic region are overlapped); HRMS(ESI) calcd for $C_{30}H_{29}NNaO_6$ (M+Na): 522.1890; found: 522.1887. $[\alpha]^{29}_D$ = +5.8 (*c* 0.9, $CHCl_3$, 66% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/dichloromethane = 1/1, flow rate: 1.0 mL/min, retention time: 8.0 min for major isomer and 11.4 min for minor isomer).



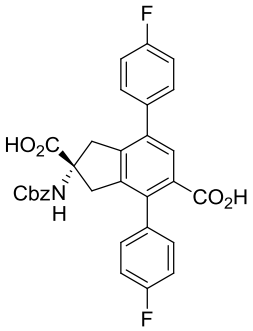
2-(((Benzyloxy)carbonyl)amino)-4,7-diphenyl-indan-2,5-dicarboxylic acid (5a)

Isolated by crystallization (hexane/EtOAc). The title compound was obtained as white solid (78%). Mp 138 °C; ^{1}H NMR ($CDCl_3$) δ 9.20 (br, 2H), 7.89 (s, 1H), 7.44-7.09 (m, 15H), 5.31 (s, 1H), 4.97 (s, 2H), 3.80 (br, 1H), 3.40 (br, 2H), 2.98 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 178.3, 172.6, 155.6, 142.5, 140.7, 140.2, 139.1, 139.0, 139.0, 138.0, 137.7, 135.9, 131.1, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 127.8, 127.4, 67.2, 65.5, 60.8, 43.6; HRMS(ESI) calcd for $C_{31}H_{25}NNaO_6$ (M+Na): 530.1576; found: 530.1574. $[\alpha]^{30}_D$ = -38.6 (*c* 1.6, $CHCl_3$).



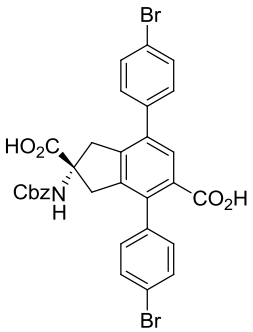
2-(((Benzyloxy)carbonyl)amino)-4,7-di(*p*-tolyl)-indan-2,5-dicarboxylic acid (5b)

Isolated by crystallization (hexane/EtOAc). The title compound was obtained as white solid (85%). Mp 141 °C; ^{1}H NMR ($CDCl_3$) δ 9.37 (br, 2H), 7.87 (s, 1H), 7.35-6.97 (m, 13H), 5.31 (br, 1H), 4.98 (s, 2H), 3.81 (br, 1H), 3.42 (br, 2H), 3.14-2.86 (m, 1H), 2.47-2.23 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 178.4, 172.9, 155.6, 142.3, 140.8, 138.8, 137.6, 137.5, 137.0, 136.3, 136.0, 130.9, 129.4, 129.2, 129.1, 128.9, 128.6, 128.4, 128.3, 128.3, 128.2, 67.2, 65.6, 43.8, 21.4, 21.3, 14.3; HRMS(ESI) calcd for $C_{33}H_{29}NNaO_6$ (M+Na): 558.1889; found: 558.1887. $[\alpha]^{36}_{D}$ = -20.9 (*c* 3.3, $CHCl_3$).



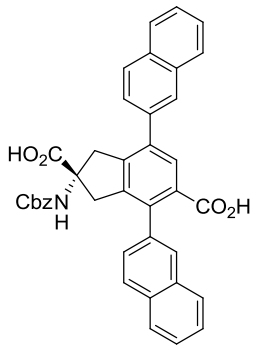
2-(((Benzyloxy)carbonyl)amino)-4,7-bis(4-fluorophenyl)-indan-2,5-dicarboxylic acid (5g)

Isolated by crystallization (hexane/EtOAc). The title compound was obtained as white solid (85%). Mp 135 °C; ^{1}H NMR ($CDCl_3$) δ 9.42 (br, 2H), 7.83 (s, 1H), 7.42-6.81 (m, 13H), 5.41 (br, 1H), 4.98 (s, 2H), 3.74 (br, 1H), 3.38 (br, 2H), 2.99 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 178.2, 172.3, 163.4 (d, J = 44.1 Hz), 161.4 (d, J = 43.6 Hz), 155.6, 142.6, 141.1, 138.1, 136.9, 135.8, 135.0, 134.8, 131.1, 130.2 (d, J = 7.0 Hz), 130.0, 128.8, 128.6, 128.4, 128.1, 115.7 (d, J = 21.6 Hz), 115.3 (d, J = 20.2 Hz), 67.3, 67.2, 65.4, 43.6; HRMS(ESI) calcd for $C_{31}H_{23}F_2NNaO_6$ (M+Na): 566.1386; found: 566.1386. $[\alpha]^{36}_{D}$ = -17.6 (*c* 2.2, $CHCl_3$).



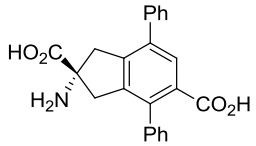
2-(((Benzyloxy)carbonyl)amino)-4,7-bis(4-bromophenyl)-indan-2,5-dicarboxylic acid (5h)

Isolated by crystallization (hexane/EtOAc). The title compound was obtained as white solid (92%). Mp 158 °C; ^{1}H NMR ($CDCl_3$) δ 9.15 (br, 2H), 7.84 (s, 1H), 7.59-6.90 (m, 13H), 5.50 (br, 1H), 4.98 (s, 2H), 3.74 (br, 1H), 3.56-3.12 (m, 2H), 3.00 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 178.0, 171.9, 155.6, 142.6, 141.0, 138.2, 137.9, 137.8, 136.8, 135.8, 132.0, 131.5, 131.0, 130.1, 128.6, 128.4, 128.2, 122.3, 121.6, 68.0, 67.3, 65.4, 43.5 (two pairs of peaks at the aromatic region are overlapped); HRMS(ESI) calcd for $C_{31}H_{22}Br_2NO_6$ (M-H): 661.9838; found: 661.9819. $[\alpha]^{36}_D$ = -20.7 (*c* 3.6, $CHCl_3$).



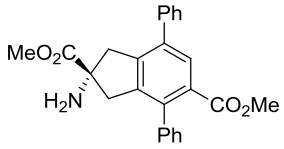
2-(((Benzyloxy)carbonyl)amino)-4,7-di(naphthalen-2-yl)-indan-2,5-dicarboxylic acid (5i)

Isolated by crystallization (hexane/EtOAc). The title compound was obtained as white solid (83%). Mp 153 °C; ^{1}H NMR ($CDCl_3$) δ 9.30 (br, 2H), 8.09-6.76 (m, 20H), 5.30 (br, 1H), 4.85 (s, 2H), 3.83 (br, 1H), 3.37 (br, 2H), 2.92 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 178.3, 172.5, 155.5, 142.8, 141.1, 139.0, 137.7, 136.7, 136.5, 135.8, 133.4, 133.2, 132.7, 132.6, 131.4, 128.9, 128.5, 128.4, 128.4, 128.3, 128.3, 128.1, 127.8, 127.6, 126.9, 126.5, 126.5, 126.2, 126.1, 72.3, 67.2, 65.6, 43.7 (four pairs of peaks at the aromatic region are overlapped). HRMS(ESI) calcd for $C_{39}H_{28}NO_6$ (M-H): 606.1935; found: 606.1922. $[\alpha]^{36}_D$ = -21.1 (*c* 4.0, $CHCl_3$).



2-Amino-4,7-diphenyl-indan-2,5-dicarboxylic acid (6a)

Isolated by crystallization (EtOAc/MeOH). The title compound was obtained as white solid (81%). Mp 233 °C (decomposition); ^{1}H NMR (CD_3OD) δ 7.64 (s, 1H), 7.53-7.22 (m, 10H), 3.93 (d, *J* = 17.4 Hz, 1H), 3.62 (d, *J* = 17.4 Hz, 1H), 3.17 (d, *J* = 17.4 Hz, 1H), 2.90 (d, *J* = 17.4 Hz, 1H); ^{13}C NMR (CD_3OD) δ 174.4, 172.2, 139.9, 139.7, 139.5, 139.3, 137.7, 137.1, 134.6, 128.6, 128.4, 128.4, 128.2, 127.8, 127.4, 126.9, 66.7, 43.0, 42.8; HRMS(ESI) calcd for $C_{23}H_{19}NNaO_4$ (M+Na): 396.1207; found: 396.1206. $[\alpha]^{30}_D$ = -38.6 (*c* 1.6, MeOH).



Dimethyl 2-amino-4,7-diphenyl-indan-2,5-dicarboxylate (7a)

Isolated by preparative TLC (hexane/EtOAc = 3/2, Rf = 0.6). The title compound was obtained as white solid (56%). Mp 153 °C; ^{1}H NMR (CD_3OD) δ 7.74 (s, 1H), 7.52-7.20 (m, 10H), 3.77-3.68 (m, 4H), 3.56 (s, 3H), 3.42 (d, *J* = 16.7 Hz, 1H), 3.03 (d, *J* = 16.7 Hz, 1H), 2.73 (d, *J* = 16.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 176.8, 168.4, 142.2, 141.4, 139.8, 139.7, 138.5, 137.8, 130.1, 129.9, 128.6, 128.6, 128.4, 128.1, 127.6, 127.2, 64.7, 52.6, 51.9, 46.2, 45.9; HRMS(ESI) calcd for $C_{25}H_{23}NNaO_4$ (M+Na): 424.1519; found: 424.1519. $[\alpha]^{36}_D$ = -6.3 (*c* 0.6, $CHCl_3$).

Determination of absolute configuration of tethered Aic 4

The following results were collaborated with Monde group at Hokkaido University.

VCD and ECD spectra of the two samples were measured in $CDCl_3$ and MeCN, respectively, giving nice mirror-image spectra.

To elucidate the absolute configuration of **4l**, conformational analysis, VCD and ECD calculations were performed on the *R* enantiomer. The MMFF94S search resulted in 25 conformers within a 21 kJ/mol energy window indicating moderate flexibility of the molecule. DFT reoptimization at B3LYP/TZVP in gas-phase yielded 3 low-energy conformers above 2% (96.4% overall population), see Figure 4. Low-energy conformers differ mainly in the orientation of the Boc group and one phenyl group. These conformers give more-or less similar VCD spectra differing mainly in the intensity of some transitions. Boltzmann-averaged B3LYP/TZVP level VCD spectrum resembles the main transitions of the experimental VCD spectrum of **4l** (Figure 5). Although in solution the Boltzmann-weights may be somewhat different from the B3LYP/TZVP *in vacuo* computed ones, due to the consistent VCD spectra of all low-energy conformers, absolute configuration can be elucidated with confidence.

ECD calculations gave similar results. Calculated ECD spectra at various levels (B3LYP/TZVP, BH&HLYP/TZVP and PBE0/TZVP) for the low-energy conformers resemble all three experimental transitions and differ only in relative intensities. Consequently, Boltzmann-weighted ECD spectra at all level give nice agreement with **4l**. Upon the good agreement both in VCD and ECD, the absolute configuration of the two enantiomers can be unambiguously elucidated, *i.e.* **4l** (sample A; from

$[Rh(cod)_2]BF_4$+(*S*)-BINAP) is the *R* enantiomer and **4l** (sample B; from $[Rh(cod)_2]BF_4$+(*R*)-BINAP) is the *S*.

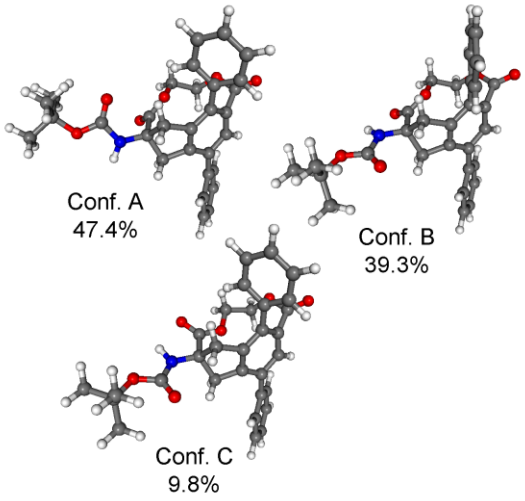


Figure 4. Low-energy conformers (≥2%) of (*R*)-**4l** obtained by optimization of the MMFF94S conformers at B3LYP/TZVP level *in vacuo*.

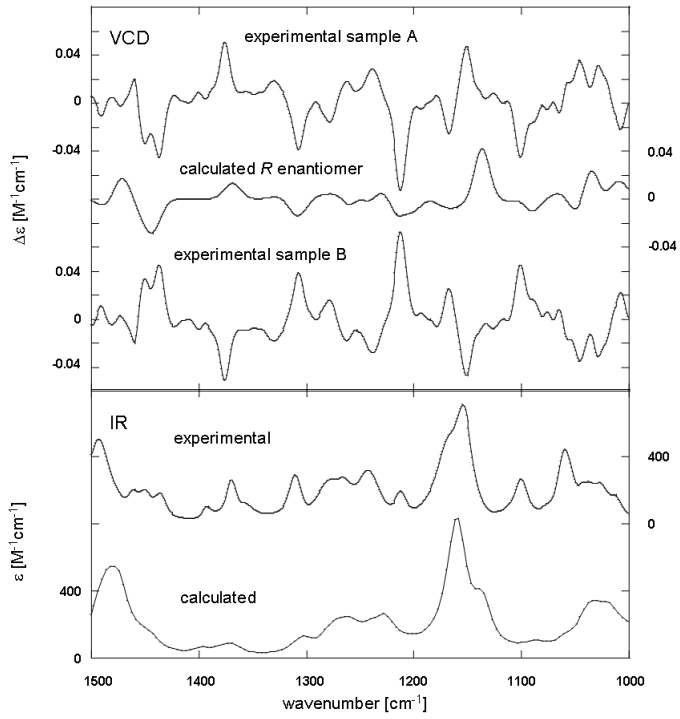


Figure 5. Comparison of experimental spectra of **4l** measured in $CDCl_3$ (c = 0.05 M, l = 100 μm) and Boltzmann-averaged calculated spectra for the low-energy conformers of (*R*)-**4l** at B3LYP/TZVP level.

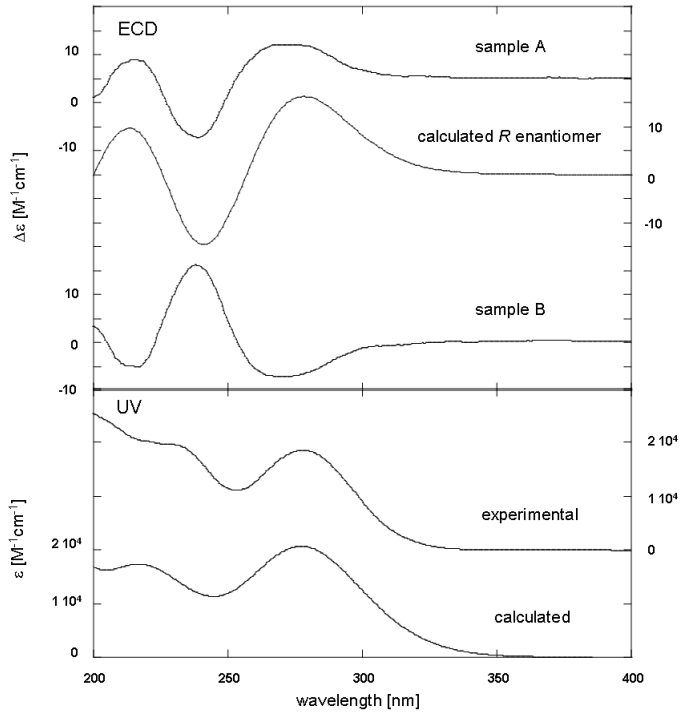


Figure 6. Comparison of experimental spectra of **4l** measured in MeCN (c = 0.228 (sample A) and 0.212 mM (sample B), l = 1 mm) and calculated spectra for the low-energy conformers of (*R*)-**9l** at B3LYP/TZVP in gas-phase.

Computational details:

Conformational search was carried out by means of the Conflex software at MMFF94S level.[18] Geometry reoptimizations, VCD and ECD calculations were performed with the Gaussian 09 package.[19] Geometry reoptimizations and VCD calculations were carried out at B3LYP/TZVP level in gas-phase. For ECD calculations various functionals (B3LYP, BH&HLYP, PBE0) and TZVP basis set were applied.[20] ECD spectra were generated as the sum of Gaussians[21] with 3000 cm^{-1} half-height width (corresponding to ca. 17 nm at 240 nm), using dipole-velocity computed rotational strengths, while VCD spectra were calculated with 10 cm^{-1} half-height width. Computed VCD and IR data were scaled by a factor of 0.975. Boltzmann distributions were estimated from the B3LYP/TZVP energies of the low-energy conformers. The MOLEKEL[22] software package was used for visualization of the results.

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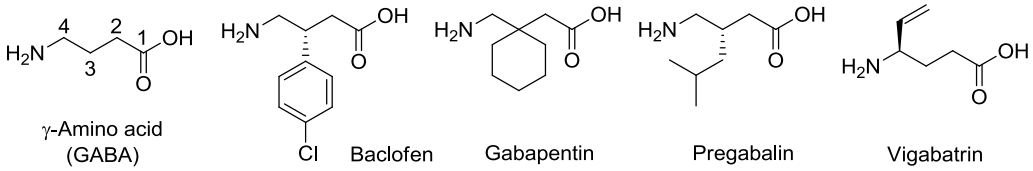
Chapter 4

Enantioselective Synthesis of 4-Substituted γ-Amino Acids and Formal Total Synthesis of Pyrrolam A via Iridium-Catalyzed sp^3 C-H Bond Activation

Backgrounds

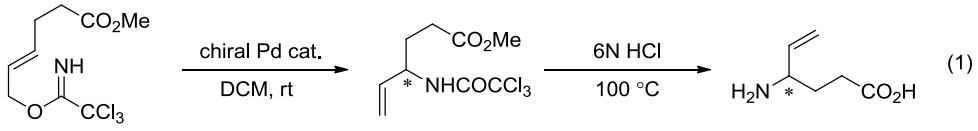
γ-Amino acid derivatives have attracted much attention as biologically active compounds in relation to γ-aminobutyric acid (GABA), which has a function as major inhibitory neurotransmitter in the central nervous system (CNS) of mammals.[1] Several γ-aminobutyric acid derivatives with substituent(s) on the carbon chain are known as pharmaceutical agents such as anticonvulsant drug, anti-seizure drug, and anti-epilepsy drug. For example, Baclofen,[2] Gabapentin,[3] Pregabalin[4] and Vigabatrin[5] were commercialized pharmaceutical agents.

Figure 1. γ-Amino acids known as pharmaceutical agents

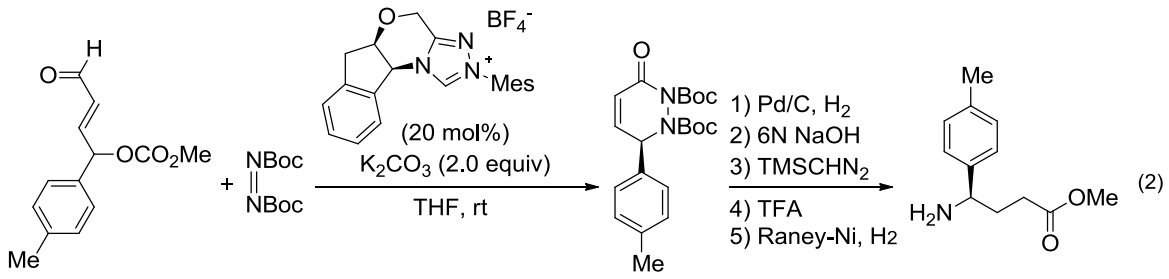


On the other hand, structural functions of γ-amino acid derivatives have been also recently reported: peptidic foldamers including γ-amino acids form novel helical structure[6] and self-assembling peptide nanotubes.[7]

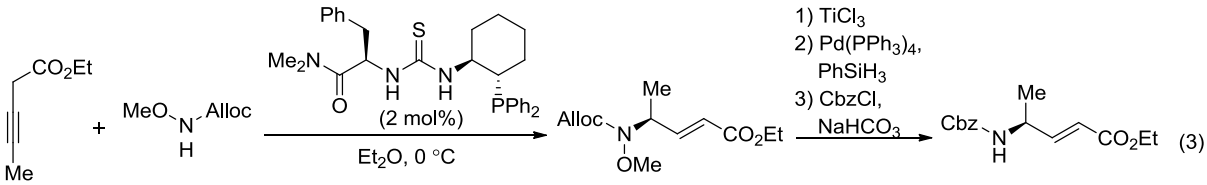
Against this background, various asymmetric syntheses of γ-amino acid derivatives have been developed.[8] In particular, a great deal of effort has been devoted to the enantioselective synthesis.[9] While there are many synthetic approaches to multi-substituted γ-aminobutyric acid including the 4-position, the enantioselective synthesis of γ-aminobutyric acids substituted only at the 4-position is limited. Anderson and Overman reported Pd-catalyzed rearrangement of allylic trichloroacetamidates, which gave 4-vinyl-γ-aminobutyric acid (eq. 1).[9a]



Ye and co-workers developed chiral NHC-catalyzed [4+2] annulation of enals possessing a leaving group at the γ-position with azodicarboxylates. The reaction gave γ-aminated products, which were derived into 4-aryl-γ-aminobutyric acid in 5 steps (eq. 2).[9i]



Jacobsen and co-workers reported chiral thiourea-catalyzed hydroamination of *in situ* generated allenyl esters from propargyl esters with *N*-methoxy carbamate. This reaction is a potentially efficient protocol but reduction of double bond, deprotection of Cbz group, and hydrolysis of ester moiety were further required for the preparation of free amino acids (eq. 3).[9j]

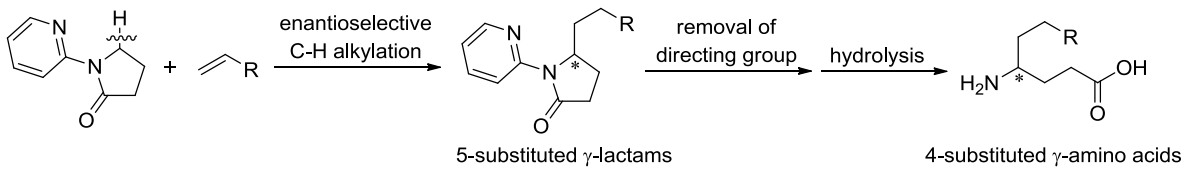


As described above, these methods have limited scope of substituent and/or require multiple steps for the transformation into γ-amino acids. Therefore, more broadly applicable protocols of chiral 4-substituted γ-aminobutyric acid synthesis are strongly desired.

Results and Discussion

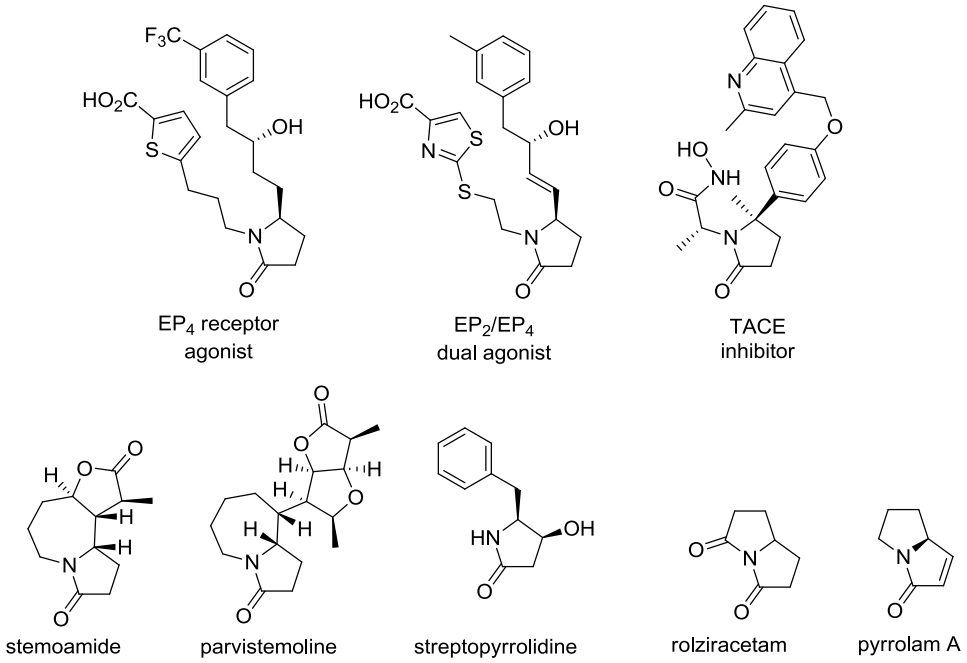
The author considered enantioselective C-H alkylation of γ-butyrolactam as a key strategy for the creation of the stereogenic center of the γ-amino acids. The obtained 5-substituted γ-butyrolactams can be readily transformed into free 4-substituted γ-aminobutyric acid after removal of the directing group and hydrolysis (Scheme 1).

Scheme 1. Approach to the enantioselective synthesis of γ-amino acids



Chiral γ-lactam skeleton is also found in various biologically active compounds[10] and natural products[11], and asymmetric synthesis of γ-lactam derivatives is also important (Figure 2).[12]

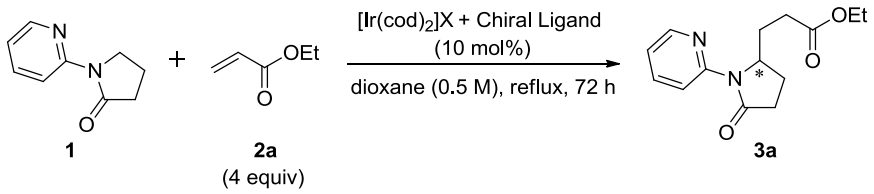
Figure 2. Selected examples of biologically active compounds and natural products include γ-lactam



Herein, a new approach to the efficient asymmetric synthesis of 5-alkylated γ-lactams and 4-substituted γ-amino acid derivatives initiated by Ir-catalyzed enantioselective sp^3 C-H bond activation is described.

The author chose *N*-(2-pyridyl)-γ-butyrolactam (**1**) as a model substrate and examined C-H alkylation using ethyl acrylate (**2a**) in the presence of various chiral iridium catalysts (Table 1). When Ir catalyst consisting of tetrafluoroborate (BF_4) as a counter anion and (*S*)-tolBINAP as a chiral ligand was used, the reaction proceeded in high yield with high enantioselectivity (Entry 1). When other Ir catalysts consisting of other counter anions and BINAP derivatives were examined, alkylated lactam **2a** was obtained in high ee but yields were decreased in all entries (Entries 2-5). The author further ascertained the tolerability of one-gram scale by Ir-tolBINAP catalyst (Entry 6).

Table 1. Screening of catalysts

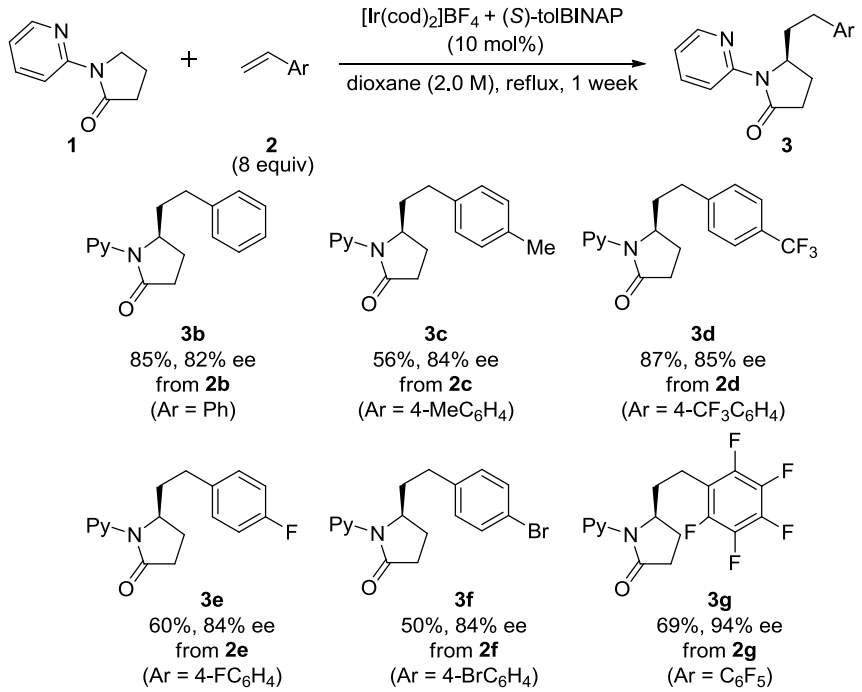


Entry	X	Chiral Ligand	Yield / %	Ee / %
1	BF_4	(*S*)-tolBINAP	87	91
2	BARF	(*S*)-tolBINAP	36	90
3	OTf	(*S*)-tolBINAP	trace	-
4	BF_4	(*S*)-xylBINAP	15	91
5	BF_4	(*S*)-H_8-BINAP	2	91
6[a]	BF_4	(*S*)-tolBINAP	85	94

[*a*] The reaction was performed on a one-gram scale.

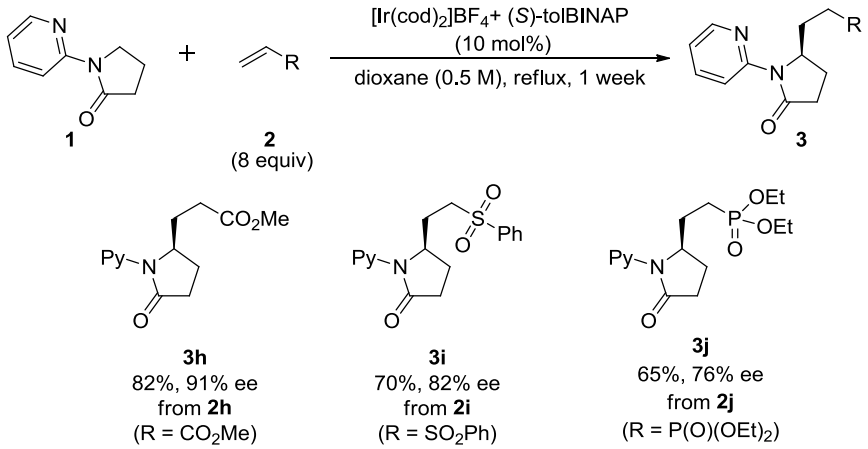
In the presence of the optimal chiral catalyst (Table 1, Entry 1), scope of styrenes was examined (Table 2). The reaction with styrene **2b** proceeded to give desired chiral lactam **3b** in high yield and ee. When styrenes with methyl or trifluoromethyl group on its *para*-position were used, the corresponding alkylated lactams **3c** and **3d** were obtained with the same ee as that of **3b**. Halogenated styrenes were also good coupling partners, and chiral γ-lactams **3e** and **3f** were obtained in moderate yield with high ee. In the reaction with pentafluorostyrene, the enantioselectivity was well above 90%. Absolute configuration of alkylated lactams **3** was determined by the comparison with that of non-protected lactam **4b** in Table 4, which is known compound.

Table 2. Enantioselective alkylation of γ-lactam **1** with styrenes



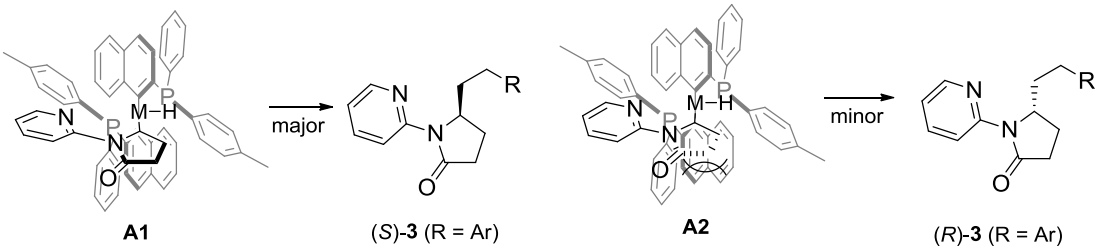
The reactions with a few functionalized alkenes using Ir-tolBINAP catalyst were examined (Table 3). Methyl acrylate was also a good coupling partner, and alkylated γ-lactam **3h** was obtained in high yield and high ee. Vinyl sulfone **2i** and vinyl phosphonate group **2j** were also accepted in this reaction, and the desired chiral γ-lactams **3i** and **3j** were obtained.

Table 3. Enantioselective alkylation of γ-lactam **1** with functionalized alkenes



A possible explanation for enantioselective induction of chiral alkylated lactams **3** was shown in Scheme 2. Intermediate **A1** or **A2** can be passed through after C-H bond cleavage by the square planar chiral Ir catalyst. Due to the steric hindrance between carbonyl group and methylene on lactam skeleton with aryl group on ligand in **A2**, **A1** is preferred and (*S*)-**3** was the major product.

Scheme 2. Possible explanation for enantioselective induction of **3**

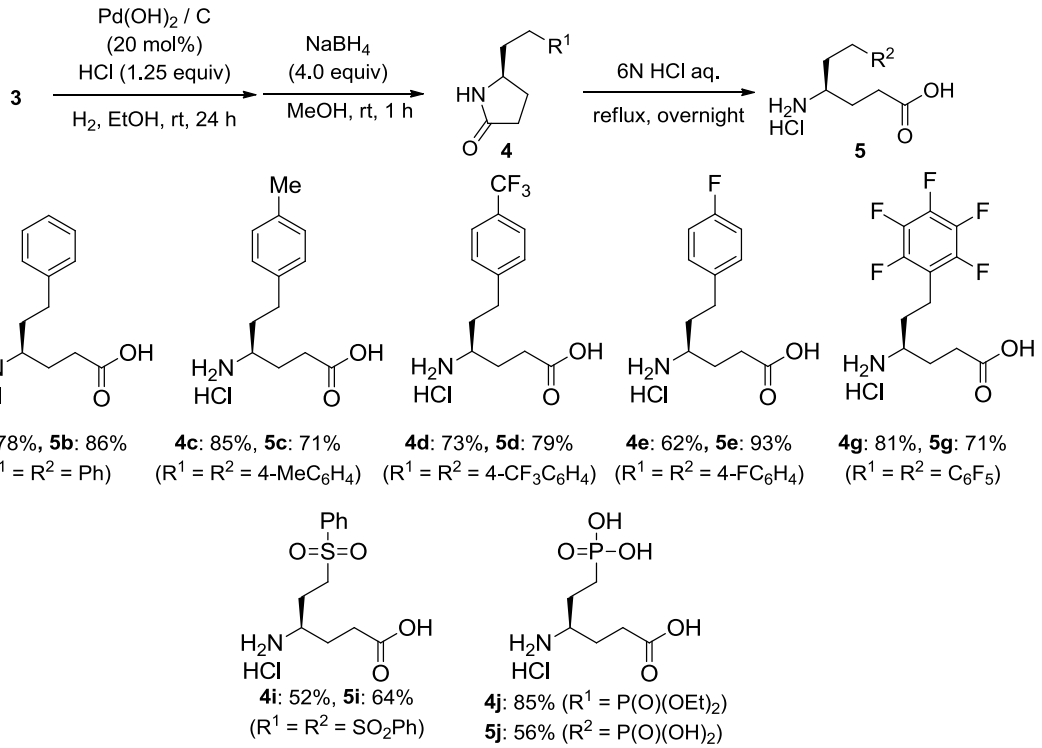


Next, the transformation of the obtained alkylated products into *N*-unprotected γ-lactams **4** and free γ-amino acids **5** was examined (Table 4). The author first submitted γ-lactam **3b** (82% ee) to hydrogenation using a catalytic amount of $Pd(OH)_2/C$ under the acidic conditions, then to reduction using sodium borohydride for removal of the pyridyl group.[13] γ-Lactam **4b** was obtained in 78% yield without loss ee (82% ee) and its absolute configuration was determined to be *S* enantiomer by the comparison of the sign of optical rotation in the literature.[14] Other

alkylated products **3c-3j** were also converted to non-protected lactams **4c-4j** in moderate to high yield under the same conditions.

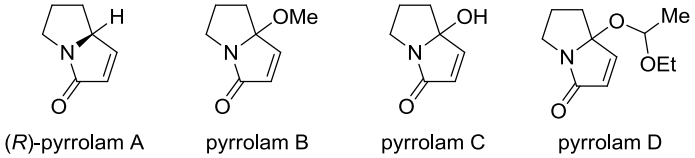
The second step was hydrolysis of lactam: the acidic hydrolysis of γ-lactam **4b** gave phenethyl substituted γ-amino acid hydrochloride salt **5b** in 86% yield without loss of ee (82% ee). Other aryl- and sulfonylethyl-substituted γ-lactams **4c-4i** were also transformed into the corresponding free γ-amino acid hydrochloride salts **5c-5i** in good to high yield. In the case of γ-lactam **4j**, phosphate moiety also underwent hydrolysis, and phosphono amino acid **5j** was obtained in moderate yield.

Table 4. Removal of pyridyl group and hydrolysis of lactams



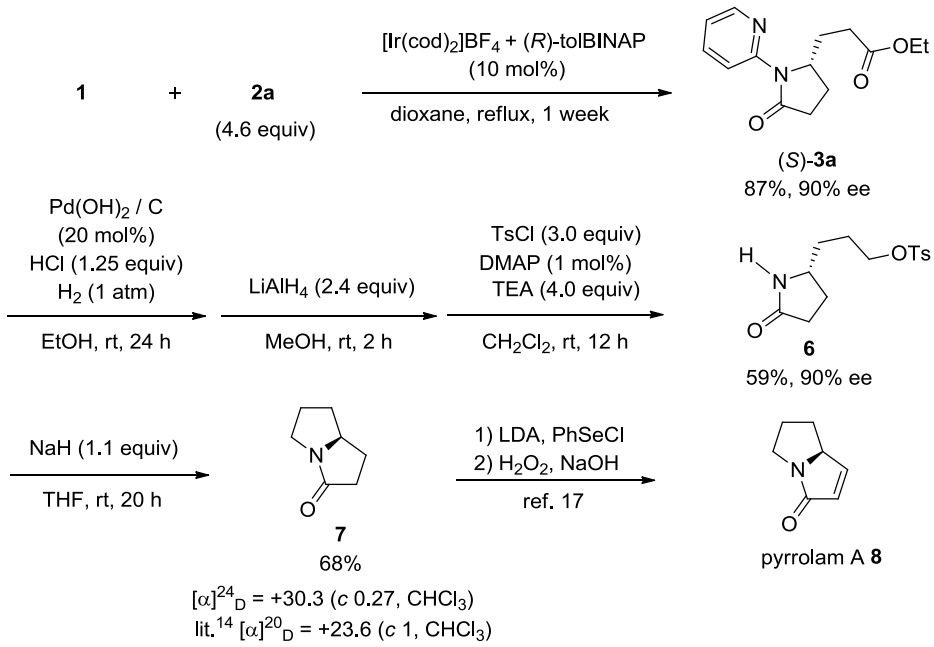
As synthetic application of the obtained alkylated γ-lactam, the author considered the preparation of a known synthetic precursor of pyrrolam A. Pyrrolam A **8** has been isolated from the bacterial strain *Streptomyces olivaceus* along with the related bicyclic lactams pyrrolam B-D (Figure 3).[15]

Figure 3. Structures of pyrrolam A-D



The chiral bicyclic lactam have attracted synthetic chemists, and various synthetic strategies have been developed.[16] The author tried to use the present enantioselective C-H alkylation of γ-lactam as a key reaction in the synthesis of dihydro-pyrrolam A **7**. The Ir-catalyzed C-H alkylation with ethyl acrylate (**2a**) using (*R*)-tolBINAP was examined for the synthesis of naturally type pyrrolam A, and (*S*)-**3a** was obtained in good yield with high ee. The next three steps, which include removal of the pyridyl group, reduction of ester moiety, and tosylation of the primary alcohol, were examined without purification. The tosylate **6** was afforded in 59% yield.[17] Then, the cyclization of **6** using sodium hydride gave desired bicyclic lactam **7** in 68% yield,[17] whose sign of optical rotation accorded with that in the literature.[14] The final step to pyrrolam A **8** is a known procedure.[18]

Scheme 4. Formal asymmetric synthesis of pyrrolam A



Conclusions

Enantioselective Ir-catalyzed sp^3 C-H bond activation of the γ-butyrolactam with various alkenes was developed. The present reaction provides a new simple protocol for the synthesis of chiral 5-alkylated γ-lactams and 4-alkylated γ-amino acid derivatives. This protocol would be used for the efficient enantioselective synthesis of bicyclic lactam **7**, a precursor of pyrrolam A.

Experimental Section

General

^{1}H NMR spectra were recorded on JEOL JNM-ECX500 (500 MHz) spectrometer. The chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) for $CDCl_3$, or external standard TMS (0 ppm) for D_2O. The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). ^{13}C NMR spectra were obtained by JEOL JNM-ECX500 (125 MHz) spectrometers and referenced to the internal solvent signals (central peak is 77.0 ppm in $CDCl_3$), or external standard TMS (0 ppm) for D_2O. $CDCl_3$ and D_2O were used as NMR solvents. High-resolution mass spectra (HRMS) were measured on ESI (Electro Spray Ionization) – orbitrap mass spectrometer. Optical rotations were measured on a JASCO DIP-1000 polarimeter. Preparative thin-layer chromatography (PTLC) was performed with silica gel-precoated glass plates (Merck 60 GF254) prepared in the author's laboratory, Flash column chromatography was performed over silica gel 200-300. All reagents were weighed and handled in air and backfilled under Argon at room temperature. Unless otherwise noted, all reactions were performed under an argon atmosphere. All reagents were purchased from Wako, Kanto, Aldrich and TCI and used without further purification.

Experimental procedure for the synthesis of γ-lactam 1[19,20]

To a dried two necked 50 mL flask CuI (2.0 mol%, 0.20 mmol, 38.1 mg) and K_2CO_3 (2.0 eq., 20 mmol, 2.8 g) were added. The reaction vessel was evacuated and backfilled with argon (×3), then 2-pyrrolidone (10.0 mmol, 851.1 mg), *N*,*N*'-dimethylethylenediamine (10 mol%, 1.0 mmol, 88.2 mg), 2-bromopyridine (1.5 eq., 15 mmol, 2.4 g) and toluene (20 mL) were added. The reaction mixture was refluxed for 24 h. After the reaction was completed, the solids were removed by celite filtration and washed with CH_2Cl_2 (5 × 5 mL). Then the solvent was evaporated, and the crude product was purified by column chromatography on silica gel (hexane/ EtOAc = 3/1 to 2/1) to give pure γ-Lactam **1** (1.62 g, quant.).

General procedure for the enantioselective C-H alkylation of γ-lactams 1

γ-Lactam **1** (0.20 mmol, 32.4 mg), (*S*)-tolBINAP (10 mol%, 13.6 mg) and $[Ir(cod)_2]BF_4$ (10 mol%, 10.0 mg) were placed in a dried sealed tube, then capped with a rubber septum. The reaction vessel was evacuated and backfilled with argon (×3), then alkene **2** (8.0 eq., 1.60 mmol) and degassed 1,4-dioxane

(0.1 mL) was added, unless otherwise noted (entry 2 in Table 2). The rubber septum was rapidly changed with a screw cap flowing argon, and then refluxed. After the reaction was complete, the reaction mixture was cooled to room temperature and the crude product was purified by preparative TLC to give pure product **3**.

General procedure for the transformation of γ-lactam derivatives to γ-amino acid derivatives[13]

γ-Lactam derivatives **3** (0.20 mmol) and $Pd(OH)_2/C$ (20% Pd, wetted with ca.50% water, 20 mol%, 56.2 mg) were placed in a dried Schlenk tube capped with a rubber septum, then EtOH (1.8 mL) and 1.25 M HCl in EtOH (0.2 mL) were added. The reaction vessel was flushed H_2 (× 3), then the mixture was stirred at room temperature for 24 h under H_2. The solids were removed by celite filtration and washed with CH_2Cl_2 (5 × 2 mL). Then the solvent was evaporated, and the crude product was obtained.

The crude product was placed in a dried two necked 30 mL flask. The reaction vessel was evacuated and backfilled with argon (× 3), then $NaBH_4$ (4.0 eq., 0.80 mmol, 30.4 mg) and MeOH (2.0 mL) were added carefully. The mixture was stirred at room temperature for 1 h. After the reaction was complete, the solvent was evaporated. The residue was purified by preparative TLC and the desired product **4** was obtained. Next, a round-bottom 30 mL flask was charged with the γ-lactam **4** (0.1 mmol) and 6 N HCl (2.0 mL). The solution was heated to 100 °C and stirred overnight. After cooled at room temperature, the solvent was removed in vacuo. EtOAc (2.0 mL) was added to the reaction vessel, then the mixture was suspended by sonication and stirred at room temperature. After 1 h, the mixture was filtered and washed by EtOAc (3 × 1 mL). The solid product **5** was obtained by filter paper washed with MeOH (5 × 1 mL) and dried.

Experimental procedure for the synthesis of dihydro-pyrrolam A 7[13,15,17]

γ-Lactam derivative (*S*)-**3a** (0.20 mmol, 52.4 mg) and $Pd(OH)_2/C$ (20% Pd, wetted with ca.50% water, 20 mol%, 56.2 mg) were placed in a dried Schlenk tube capped with a rubber septum, then EtOH (1.8 mL) and 1.25 M HCl in EtOH (0.2 mL) were added. The reaction vessel was flushed H_2 (× 3), then the mixture was stirred at room temperature for 24 h under H_2. The residue was removed by celite filtration and washed with CH_2Cl_2 (5 × 2 mL). The solvent was evaporated, and the crude product was obtained.

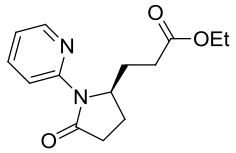
The crude product was placed in a dried two necked 30 mL flask. The reaction vessel was evacuated and backfilled with argon (× 3), the reaction vessel was cooled at 0 °C. $LiAlH_4$ (2.4 eq., 0.48 mmol, 18.2 mg) and THF (1.0 mL) was added carefully. Then the mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of $Na_2SO_4 \cdot 10H_2O$, then the solids were filtered and washed by CH_2Cl_2

(8 × 2 mL). The solvent was evaporated to give the crude solid products.

A dried Schlenk tube was charged with the crude solids and anhydrous CH_2Cl_2 (2.0 mL). Triethylamine (4.0 eq., 0.8 mmol) and *N, N*-dimethyl-4-aminopyridine (3 mol%, 2.1 mg) were added in sequence to the solution. After cooled to 0 °C, *p*-toluenesulfonyl chloride (3.0 eq., 0.6 mmol, 114.4 mg) was added instantly. The mixture was stirred at 0 °C for 15 min, and then warmed to room temperature overnight. After the reaction was completed, saturated $NaHCO_3$ aq. was added to the solution. The mixture was extracted with CH_2Cl_2 (4 × 2 mL) and the resulting solution was dried with Na_2SO_4. After evaporation of the solution, the residue was purified by preparative TLC (CH_2Cl_2/MeOH = 95/5, Rf = 0.5) and the desire solid **6** was afforded (35.1 mg, 59%).

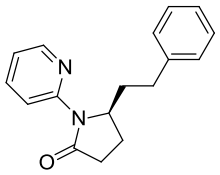
γ-Lactam derivative **6** (0.10 mmol, 29.7 mg) in THF (2.0 mL) was placed in a dried Schlenk tube. After the solution was cooled to 0 °C, Sodium hydride (1.1 eq., 0.11 mmol, 4.4 mg, 60 % dispersion in mineral oil) was added instantly under stirred. The reaction mixture was stirred at room temperature overnight. After the reaction was completed, the solution was cooled to 0 °C and quenched with saturated NH_4Cl aq. Solution. The mixture was extracted with EtOAc (5 × 2 mL) and the organic layer was dried over Na_2SO_4. After concentration under reduced pressure, the product was isolated by column chromatography on silica gel (EtOAc only) to give dihydro-pyrrolam A **7** (8.0 mg, 68%).

Characterization of new compounds



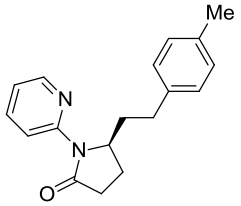
Ethyl 3-(5-oxo-1-(pyridin-2-yl)pyrrolidin-2-yl)propanoate (3a)

Isolated by preparative TLC (hexane/EtOAc = 2/1, Rf = 0.3). The title compound was obtained as yellow oil (87%). ^{1}H NMR δ 8.36-8.35 (m, 1H), 8.24-8.22 (m, 1H), 7.71-7.67 (m, 1H), 7.04-7.02 (m, 1H), 4.87-4.83 (m, 1H), 4.13-4.09 (m, 2H), 2.79-2.72 (m, 1H), 2.59-2.52 (m, 1H), 2.39-2.16 (m, 4H), 1.92-1.85 (m, 2H), 1.26-1.22 (m, 3H); ^{13}C NMR δ 174.8, 173.1, 151.3, 147.8, 137.8, 119.9, 116.4, 60.7, 57.3, 32.2, 30.7, 28.6, 23.0, 14.3. HRMS(ESI) calcd for $C_{14}H_{18}N_2NaO_3$ (M+Na): 285.1210; found: 285.1208. $[\alpha]^{27}_D$ = +63.4 (*c* 1.9, $CHCl_3$, 91% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/2-propanol = 19/1, flow rate: 1.0 mL/min, retention time: 18.4 min for major isomer and 15.7 min for minor isomer).



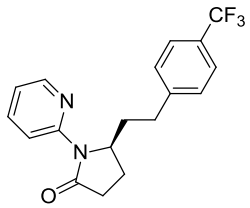
5-Phenethyl-1-(pyridin-2-yl)pyrrolidin-2-one (3b)

Isolated by preparative TLC (hexane/EtOAc = 2/1, Rf = 0.5). The title compound was obtained as yellow oil (85%). ^{1}H NMR δ 8.37-8.35 (m, 1H), 8.21-8.19 (m, 1H), 7.69-7.66 (m, 1H), 7.27-7.24 (m, 2H, overlap with $CHCl_3$), 7.18-7.14 (m, 3H), 7.03-7.01 (m, 1H), 4.87-4.82 (m, 1H), 2.79-2.65 (m, 3H), 2.60-2.53 (m, 1H), 2.32-2.19 (m, 2H), 1.97-1.91 (m, 1H), 1.84-1.76 (m, 1H); ^{13}C NMR δ 174.7, 151.1, 147.6, 141.3, 137.5, 128.3, 128.2, 125.9, 119.6, 116.4, 57.8, 34.5, 32.1, 31.6, 22.9. HRMS(ESI) calcd for $C_{17}H_{18}N_2NaO$ (M+Na): 289.1311; found: 289.1309. $[\alpha]^{31}_{D}$ = +64.9 (*c* 1.0, $CHCl_3$, 82% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/2-propanol = 19/1, flow rate: 1.0 mL/min, retention time: 12.0 min for major isomer and 10.5 min for minor isomer).



5-(4-Methylphenethyl)-1-(pyridin-2-yl)pyrrolidin-2-one (3c)

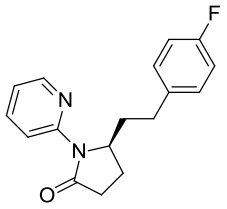
Isolated by preparative TLC (hexane/EtOAc = 2/1, Rf = 0.6). The title compound was obtained as white solid (56%). Mp 66 °C, ^{1}H NMR δ 8.37-8.35 (m, 1H), 8.20-8.18 (m, 1H), 7.69-7.66 (m, 1H), 7.07-6.97 (m, 5H), 4.86-4.81 (m, 1H), 2.79-2.71 (m, 1H), 2.64-2.53 (m, 3H), 2.32-2.26 (m, 4H), 2.24-2.16 (m, 1H), 1.96-1.90 (m, 1H), 1.81-1.75 (m, 1H); ^{13}C NMR δ 174.5, 150.9, 147.4, 138.0, 137.3, 135.1, 128.8, 127.8, 119.4, 116.3, 57.6, 34.4, 31.9, 30.9, 22.7, 20.7. HRMS(ESI) calcd for $C_{18}H_{20}N_2NaO$ (M+Na): 303.1468; found: 303.1467. $[\alpha]^{29}_{D}$ = +45.5 (*c* 1.4, $CHCl_3$, 84% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/2-propanol = 19/1, flow rate: 1.0 mL/min, retention time: 10.7 min for major isomer and 9.3 min for minor isomer).



5-(4-(Trifluoromethyl)phenethyl)-1-(pyridin-2-yl)pyrrolidin-2-one (3d)

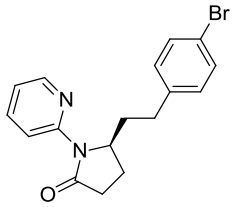
Isolated by twice preparative TLC (hexane/EtOAc = 2/1, Rf = 0.6). The title compound was obtained as yellow oil (87%). ^{1}H NMR δ 8.35-8.34 (m, 1H), 8.22-8.20 (m, 1H), 7.70-7.66 (m, 1H), 7.52-7.50 (m, 2H),

7.28-7.26 (m, 2H), 7.04-7.02 (m, 1H), 4.87-4.82 (m, 1H), 2.81-2.72 (m, 3H), 2.62-2.55 (m, 1H), 2.34-2.21 (m, 2H), 1.97-1.92 (m, 1H), 1.88-1,80 (m, 1H); ^{13}C NMR δ 174.6, 151.1, 147.6, 145.4, 137.6, 128.6, 128.3 (d, J_{C-F} = 32.2 Hz, 1C) , 125.3 (q, J_{C-F} = 3.6 Hz, 1C), 119.7, 116.3, 57.6, 34.2, 32.1, 31.5, 22.9 (A pair of peaks at the aromatic religion was overlapped). HRMS(ESI) calcd for $C_{18}H_{17}F_3N_2NaO$ (M+Na): 357.1185; found: 357.1191. $[\alpha]^{30}_D$ = +54.2 (*c* 2.7, $CHCl_3$, 85% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/2-propanol = 19/1, flow rate: 1.0 mL/min, retention time: 13.0 min for major isomer and 12.1 min for minor isomer).



5-(4-Fluorophenethyl)-1-(pyridin-2-yl)pyrrolidin-2-one (3e)

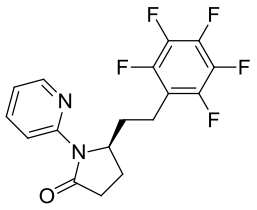
Isolated by twice preparative TLC (hexane/EtOAc = 2/1, Rf = 0.6). The title compound was obtained as white solid (60%). Mp 64 °C, ^{1}H NMR δ 8.36-8.35 (m, 1H), 8.22-8.20 (m, 1H), 7.70-7.66 (m, 1H), 7.12-7.09 (m, 2H), 7.04-7.01 (m, 1H), 6.96-6.91 (m, 2H), 4.85-4.80 (m, 1H), 2.80-2.71 (m, 1H), 2.66-2.53 (m, 3H), 2.33-2.16 (m, 2H), 1.96-1.89 (m, 1H), 1.83-1,73 (m, 1H); ^{13}C NMR δ 174.7, 160.3, 151.2, 147.6, 137.6, 136.9 (d, J_{C-F} = 2.4 Hz, 1C), 129.5 (d, J_{C-F} = 7.2 Hz, 1C), 119.7, 116.4, 115.0 (d, J_{C-F} = 21.5 Hz, 1C) 57.7, 34.6, 32.1, 30.8, 22.9. HRMS(ESI) calcd for $C_{17}H_{17}FN_2NaO$ (M+Na): 307.1217; found: 307.1217. $[\alpha]^{30}_D$ = +60.7 (*c* 1.3, $CHCl_3$, 83% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/2-propanol = 19/1, flow rate: 1.0 mL/min, retention time: 14.4 min for major isomer and 12.9 min for minor isomer).



5-(4-Bromophenethyl)-1-(pyridin-2-yl)pyrrolidin-2-one (3f)

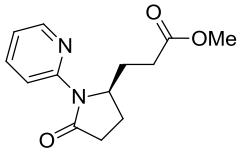
Isolated by twice preparative TLC (After hexane/EtOAc = 3/1, Rf = 0.6, EtOAc only, Rf = 0.7). The title compound was obtained as yellow oil (50%). ^{1}H NMR δ 8.35-8.34 (m, 1H), 8.21-8.20 (m, 1H), 7.69-7.66 (m, 1H), 7.37-7.35 (m, 2H), 7.03-7.01 (m, 3H), 4.84-4.79 (m, 1H), 2.79-2.71 (m, 1H), 2.64-2.53 (m, 3H), 2.32-2.16 (m, 2H), 1.95-1.89 (m, 1H), 1.82-1.74 (m, 1H); ^{13}C NMR δ 174.6, 151.1, 147.5, 140.2, 137.6, 131.4, 130.0, 119.6, 116.3, 57.6, 34.3, 32.1, 31.0, 22.9 (A pair of peaks at the aromatic religion was overlapped). HRMS(ESI) calcd for $C_{17}H_{17}BrN_2NaO$ (M+Na): 367.0421; found: 367.0416. $[\alpha]^{32}_D$ = +48.6

(*c* 1.4, $CHCl_3$, 84% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/2-propanol = 19/1, flow rate: 1.0 mL/min, retention time: 14.9 min for major isomer and 13.3 min for minor isomer).



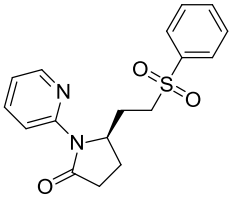
5-(2-(Pentafluorophenyl)ethyl)-1-(pyridin-2-yl)pyrrolidin-2-one (3g)

Isolated by preparative TLC (hexane/EtOAc = 2/1, Rf = 0.7). The title compound was obtained as white solid (69%). Mp 94 °C, ^{1}H NMR δ 8.29-8.28 (m, 1H), 8.23-8.21 (m, 1H), 7.70-7.66 (m, 1H), 7.04-7.01 (m, 1H), 4.79-4.74 (m, 1H), 2.82-2.71 (m, 3H), 2.64-2.57 (m, 1H), 2.38-2.30 (m, 1H), 2.20-2.14 (m, 1H), 2.01-1.96 (m, 1H), 1.84-1.77 (m, 1H); ^{13}C NMR δ 174.5, 150.9, 147.5, 146.0, 144.0, 137.6, 136.4, 119.7, 116.0, 114.2, 57.1, 32.1, 32.0, 22.6, 18.4. HRMS(ESI) calcd for $C_{17}H_{13}F_5N_2NaO$ (M+Na): 379.0840; found: 379.0841. $[\alpha]^{28}_D$ = +58.7 (*c* 2.3, $CHCl_3$, 94% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/2-propanol = 19/1, flow rate: 1.0 mL/min, retention time: 11.1 min for major isomer and 10.0 min for minor isomer).



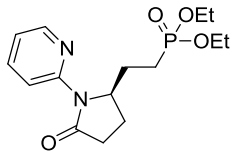
Methyl 3-(5-oxo-1-(pyridin-2-yl)pyrrolidin-2-yl)propanoate (3h)

Isolated by preparative TLC (hexane/EtOAc = 1/1, Rf = 0.3). The title compound was obtained as yellow oil (82%). ^{1}H NMR δ 8.36-8.34 (m, 1H), 8.24-8.22 (m, 1H), 7.70-7.67 (m, 1H), 7.04-7.02 (m, 1H), 4.86-4.82 (m, 1H), 3.65 (s, 3H), 2.79-2.72 (m, 1H), 2.58-2.52 (m, 1H), 2.42-2.15 (m, 4H), 1.93-1.83 (m, 2H); ^{13}C NMR δ 174.7, 173.4, 151.2, 147.7, 137.7, 119.8, 116.3, 57.2, 51.8, 32.1, 30.3, 28.5, 23.0. HRMS(ESI) calcd for $C_{13}H_{16}N_2NaO_3$ (M+Na): 271.1053; found: 271.1053. $[\alpha]^{24}_D$ = +55.9 (*c* 1.7, $CHCl_3$, 91% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/2-propanol = 19/1, flow rate: 1.0 mL/min, retention time: 23.9 min for major isomer and 19.1 min for minor isomer).



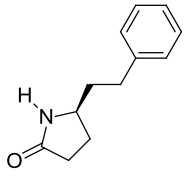
5-(2-(Phenylsulfonyl)ethyl)-1-(pyridin-2-yl)pyrrolidin-2-one (3i)

Isolated by preparative TLC (hexane/EtOAc = 1/2, Rf = 0.5). The title compound was obtained as yellow oil (70%). ^{1}H NMR δ 8.22-8.18 (m, 2H), 7.87-7.85 (m, 2H), 7.68-7.62 (m, 2H), 7.55-7.52 (m, 2H), 7.02-6.99 (m, 1H), 4.83-4.80 (m, 1H), 3.21-3.07 (m, 2H), 2.72-2.65 (m, 1H), 2.57-2.51 (m, 1H), 2.32-2.22 (m, 2H), 2.03-1.96 (m, 1H), 1.83-1.77 (m, 1H); ^{13}C NMR δ 174.3, 150.6, 147.4, 138.6, 137.7, 133.7, 129.2, 128.0, 119.8, 115.9, 56.1, 52.6, 31.7, 26.5, 22.8. HRMS(ESI) calcd for $C_{17}H_{18}N_2NaO_3S$ (M+Na): 353.0930; found: 353.0926. $[\alpha]^{29}_D$ = +53.4 (*c* 2.0, $CHCl_3$, 82% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IC: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/DCM = 1/1, flow rate: 4.0 mL/min, retention time: 12.7 min for major isomer and 9.8 min for minor isomer).



Diethyl 2-(5-oxo-1-(pyridin-2-yl)pyrrolidin-2-yl)ethylphosphonate (3j)

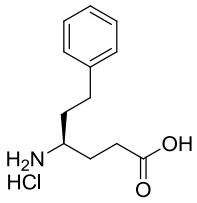
Isolated by preparative TLC (MeOH/EtOAc = 1/9, Rf = 0.4). The title compound was obtained as yellow oil (65%). ^{1}H NMR δ 8.36-8.34 (m, 1H), 8.23-8.22 (m, 1H), 7.72-7.68 (m, 1H), 7.06-7.03 (m, 1H), 4.85-4.80 (m, 1H), 4.12-3.96 (m, 4H), 2.78-2.70 (m, 1H), 2.60-2.54 (m, 1H), 2.32-2.24 (m, 1H), 2.19-2.13 (m, 1H), 1.91-1.69 (m, 4H), 1.30-1.26 (q, *J* = 7.2 Hz, 6H); ^{13}C NMR δ 174.5, 150.9, 147.5, 137.6, 119.7, 116.2, 61.6, 61.5, 57.8, 57.7, 31.9, 25.9, 25.8, 22.3, 22.1, 20.9, 16.3, 16.3, 16.3, 16.3. HRMS(ESI) calcd for $C_{15}H_{23}N_2NaO_4P$ (M+Na): 349.1288; found: 349.1291. $[\alpha]^{30}_D$ = +32.2 (*c* 1.7, $CHCl_3$, 76% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/2-propanol = 1/1, flow rate: 0.5 mL/min, retention time: 13.4 min for major isomer and 11.9 min for minor isomer).



(*S*)-5-phenethylpyrrolidin-2-one (4b)

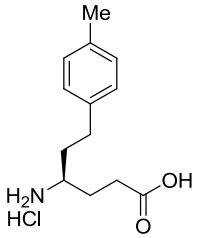
The title compound was obtained as white solid (86%). Mp 66 °C, ^{1}H NMR δ 7.31-7.17 (m, 5H, overlap with $CHCl_3$), 6.49 (br, 1H), 3.68-3.62 (m, 1H), 2.69-2.65 (m, 2H), 2.39-2.23 (m, 3H), 1.91-1.71 (m, 3H); ^{13}C NMR δ 178.3, 141.0, 128.6, 128.3, 126.2, 54.0, 38.4, 32.3, 30.1, 27.4. HRMS(ESI) calcd for $C_{12}H_{15}NNaO$ (M+Na): 212.1046; found: 212.1046. $[\alpha]^{21}_D$ = -22.2 (*c* 1.4, $CHCl_3$, 82% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/2-propanol = 19/1, flow rate: 1.0 mL/min, retention time: 17.9 min for major

isomer and 15.9 min for minor isomer).



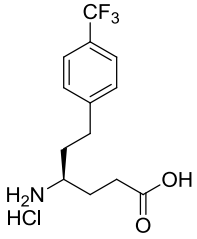
4-Amino-6-phenylhexanoic acid (5b)

The title compound was obtained as white solid (86%). Mp 157 °C, ^{1}H NMR δ 7.37-7.34 (m, 2H), 7.29-7.25 (m, 3H), 3.32-3.28 (m, 1H), 2.74-2.69 (m, 2H), 2.50-2.47 (m, 2H), 2.04-1.93 (m, 4H); ^{13}C NMR δ 176.9, 140.7, 128.8, 128.4, 126.5, 50.6, 33.4, 30.5, 29.5, 26.8. HRMS(ESI) calcd for $C_{12}H_{18}NO_2$ (M+H): 208.1332; found: 208.1333. $[\alpha]^{27}_{D}$ = -4.3 (*c* 1.2, H_2O, 82% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak ZWIX(+): 4.6 x 250 mm, 254 nm UV detector, rt, eluent: MeOH/CH_3CN/H_2O = 49/49/2, flow rate: 1.0 mL/min, retention time: 15.9 min for major isomer and 17.5 min for minor isomer).



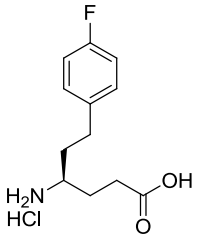
4-Amino-6-*p*-tolylhexanoic acid (5c)

The title compound was obtained as white solid (71%). Mp 146 °C, ^{1}H NMR δ 7.22-7.21 (m, 4H), 3.33-3.30 (m, 1H), 2.72-2.68 (m, 2H), 2.52-2.49 (m, 2H), 2.31 (s, 3H), 2.03-1.94 (m, 4H); ^{13}C NMR δ 177.0, 137.6, 136.4, 129.3, 128.4, 50.6, 33.5, 30.0, 29.6, 26.8, 20.0. HRMS(ESI) calcd for $C_{13}H_{20}NO_2$ (M+H): 222.1489; found: 222.1490. $[\alpha]^{25}_{D}$ = -5.2 (*c* 0.6, H_2O).



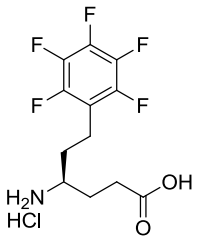
4-Amino-6-(4-(trifluoromethyl)phenyl)hexanoic acid (5d)

The title compound was obtained as white solid (79%). Mp 174 °C, ^{1}H NMR δ 7.49-7.47 (d, *J* = 8.2 Hz, 2H), 7.29-7.27 (d, *J* = 8.0 Hz, 2H), 3.27-3.24 (m, 1H), 2.74-2.62 (m, 2H), 2.42-2.39 (t, *J* = 7.5 Hz, 2H), 1.94-1.84 (m, 4H); ^{13}C NMR δ 176.6, 144.8, 128.7, 127.8, 125.3 (q, $J_{C\text{-}F}$ = 3.9 Hz, 1C), 123.2, 33.1, 30.4, 29.4, 26.7. HRMS(ESI) calcd for $C_{13}H_{17}F_3NO_2$ (M+H): 276.1207; found: 276.1206. $[\alpha]^{28}_{D}$ = -5.0 (*c* 2.2, H_2O).



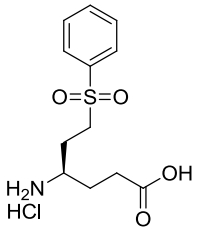
4-Amino-6-(4-fluorophenyl)hexanoic acid (5e)

The title compound was obtained as white solid (93%). Mp 161 °C, ^{1}H NMR δ 7.28-7.25 (m, 2H), 7.09-7.06 (m, 2H), 3.33-3.27 (m, 1H), 2.77-2.66 (m, 2H), 2.48 (t, J = 7.5 Hz, 2H), 2.04-1.87 (m, 4H); ^{13}C NMR δ 177.1, 162.2, 160.3, 136.4, 136.3, 129.9, 129.9, 115.2 (d, $J_{C\text{-}F}$ = 10.7 Hz, 1C), 50.6, 33.5, 29.7, 29.6, 26.8. HRMS(ESI) calcd for $C_{12}H_{17}FNO_2$ (M+H): 226.1238; found: 226.1239. $[\alpha]^{30}_{D}$ = -3.7 (*c* 0.6, H_2O).



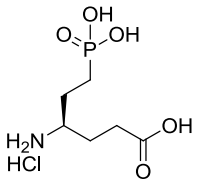
4-Amino-6-(pentafluorophenyl)hexanoic acid (5g)

The title compound was obtained as yellow paste (71%). Mp decomp (> 210 °C). ^{1}H NMR δ 3.42-3.39 (m, 1H), 2.91-2.87 (m, 2H), 2.58-2.55 (t, J = 7.5 Hz, 2H), 2.12-1.96 (m, 4H); ^{13}C NMR δ 176.8, 145.9, 143.9, 138.2, 136.3, 113.2, 50.6, 31.0, 29.5, 26.7, 17.7. HRMS(ESI) calcd for $C_{12}H_{13}F_5NO_2$ (M+H): 298.0861; found: 298.0860. $[\alpha]^{29}_{D}$ = -2.3 (*c* 0.8, H_2O)..



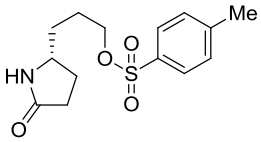
4-Amino-6-(phenylsulfonyl)hexanoic acid (5i)

The title compound was obtained as brown paste (64%). Mp decomp (> 210 °C). ^{1}H NMR δ 7.81 (d, J = 7.8 Hz, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.7 Hz, 2H), 3.41-3.38 (m, 2H), 3.31-3.29 (m, 1H), 2.31-2.29 (m, 2H), 1.92-1.88 (m, 2H), 1.79-1.73 (m, 2H); ^{13}C NMR δ 176.5, 136.2, 135.0, 129.8, 127.8, 51.0, 49.5, 29.2, 26.4, 25.0. HRMS(ESI) calcd for $C_{12}H_{18}NO_4S$ (M+H): 272.0951; found: 272.0951. $[\alpha]^{32}_{D}$ = -3.1 (*c* 2.4, H_2O).



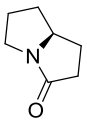
4-Amino-6-phosphonohexanoic acid (5j)

The title compound was obtained as yellow paste (56%). Mp decomp (> 210 °C). ^{1}H NMR δ 3.38-3.35 (m, 1H), 2.53-2.50 (m, 2H), 2.01-1.84 (m, 4H), 1.70-1.65 (m, 2H); ^{13}C NMR δ 176.8, 51.6, 29.5, 28.7, 26.6, 25.8. HRMS(ESI) calcd for $C_6H_{14}NO_5P$ (M+H): 212.0682; found: 212.0683. $[\alpha]^{32}_{D}$ = -1.2 (*c* 1.1, H_2O).



3-(5-Oxopyrrolidin-2-yl)propyl-4-methylbenzenesulfonate (6)

The title compound was obtained as white solid (59%). Mp 86 °C, ^{1}H NMR δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.50 (br, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 4.05-4.02 (m, 2H), 3.61-3.57 (m, 1H), 2.45-2.42 (m, 3H), 2.34-2.19 (m, 3H), 1.75-1.61 (m, 3H), 1.56-1.51 (m, 1H); ^{13}C NMR δ 178.6, 144.8, 132.8, 129.8, 127.7, 70.0, 53.9, 32.5, 30.1, 26.8, 25.2, 21.5. HRMS(ESI) calcd for $C_{14}H_{19}NNaO_4S$ (M+Na): 320.0927; found: 320.0926. $[\alpha]^{28}_{D}$ = -23.7 (*c* 4.20, $CHCl_3$, 90% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IB: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane/2-propanol = 1/1, flow rate: 0.5 mL/min, retention time: 17.2 min for major isomer and 19.4 min for minor isomer).



Pyrrolizidin-3-one (7)

The title compound was obtained as pale yellow oil (68%). ^{1}H NMR δ 3.95-3.83 (m, 1H), 3.61-3.49 (m, 1H), 3.11-3.00 (m, 1H), 2.81-2.67 (m, 1H), 2.51-2.39 (m, 1H), 2.35-2.24 (m, 1H), 2.19-1.96 (m, 3H), 1.83-1.66 (m, 1H), 1.40-1.25 (m, 1H); ^{13}C NMR δ 174.7, 62.0, 40.9, 35.3, 32.1, 27.1, 26.9. $[\alpha]^{24}_{D}$ = +30.3 (*c* 0.3, $CHCl_3$).

References

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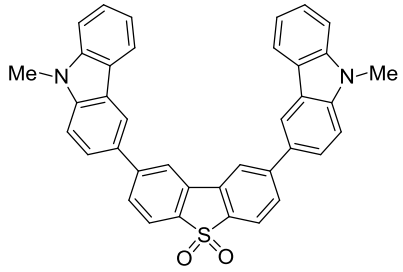
Chapter 5

General Introduction of Heteroatom-Containing Polycyclic Compounds

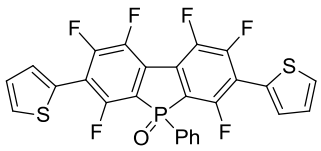
Backgrounds

Heteroatom-containing condensed polycyclic compounds perform as functional molecules, in particular, dibenzothiophene (DBT) and dibenzophosphole (DBP) oxide derivatives have attracted much attention such as organic molecular devices (Figure 1).[1,2] For example, a DBT dioxide derivative was reported a monodispersed molecular materials for efficient blue-electroluminescence[1f], a DBP oxide derivative was disclosed as a potential building block for electron transporting material[2e], and a ladder-type compound containing DBT was readily self-assembled and showed various electronic properties[1d].

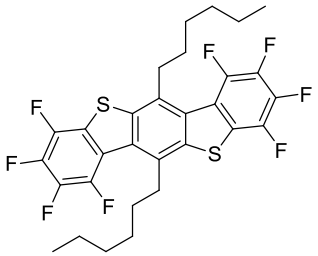
Figure 1. DBT and DBP oxide derivatives as functional organic molecules



DBT dioxide derivative



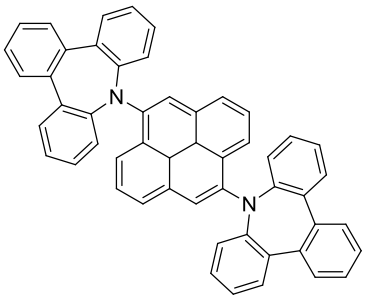
DBP oxide derivative



Ladder-type compound containing DBT skeleton

Recently, a tribenzazepin-containing compound was also reported as organic light-emitting diode (Figure 2).[3]

Figure 2. Functional organic molecule including tribenzazepin skeleton



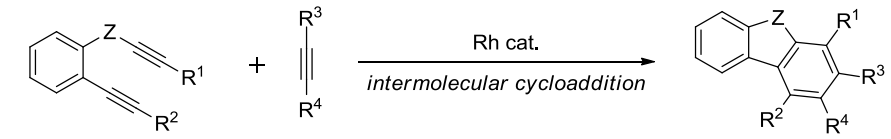
tribenzazepin-containing compound for OLED

Purpose of This Thesis (Chapter 6 through 8)

Purpose of chapter 6 through 8 in this thesis is the synthesis of heteroatom-containing condensed polycyclic compounds by rhodium-catalyzed cycloaddition. In particular, multi-substituted DBT and DBP oxide derivatives, sulfur-containing condensed polycyclic compounds were focused. In addition, the synthesis of tribenzothiepin derivatives was also examined. Various strategies for the synthesis of heteroatom-containing polycyclic compounds have been reported. However, there are some limitations in the previous methods. Development for the catalytic synthesis of variety multi-substituted heteroatom-containing polycyclic compounds under mild conditions is strongly desired.

Chapter 6 describes the multi-substituted DBT and DBP oxide derivatives synthesis by rhodium-catalyzed intermolecular cycloaddition (Scheme 1). The reaction of sulfanyl, sulfinyl, sulfonyl and phosphoryl benzene-tethered 1,6-diynes with monoalkynes proceeded to give various DBT and DBP oxide derivatives. The author further examined enantioselective reaction for the synthesis of an axially chiral compound possessing bi-dibenzothiophene skeleton and a P-chiral dibenzophosphole oxide derivative with high ee.

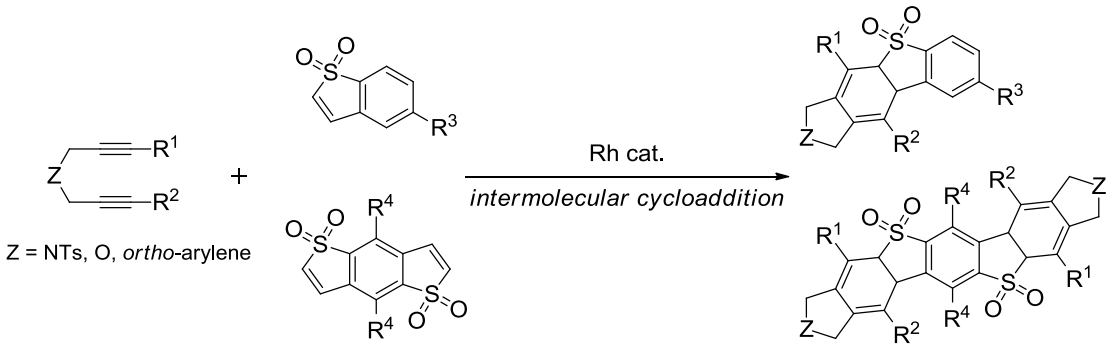
Scheme 1. Synthesis of multi-substituted DBT and DBP oxide derivatives



Z = S, S(O), SO_2, P(O)Ph

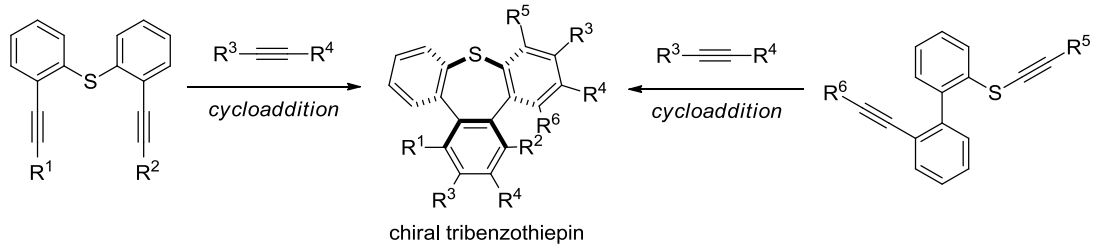
Chapter 7 describes the synthesis of sulfur-containing condensed polycyclic compounds by rhodium-catalyzed intermolecular cycloaddition (Scheme 2). The reaction of α,ω-diynes with benzothiophene dioxides was achieved, which gave dihydrodibenzothiophene dioxide derivatives. This is the first example of a catalytic [2+2+2] cycloaddition, where the 2,3-double bond of a benzoheterole was used as an ene moiety. The consecutive reaction using benzodithiophene tetraoxide gave an 11-ring condensed polycyclic compound in one pot.

Scheme 2. Synthesis of sulfur-containing condensed polycyclic compounds



Chapter 8 describes the enantioselective synthesis of multi-substituted tribenzothiepin derivatives by rhodium-catalyzed intermolecular cycloaddition (Scheme 3). Two types of reactions of diphenyl sulfide-tethered diynes and 2-phenyl sulfanylbenzene-tethered diynes with alkynes proceeded, and chiral tribenzothiepin derivatives were obtained in high ee. This is the first catalytic enantioselective synthesis of tribenzothiepin derivatives.

Scheme 3. Enantioselective synthesis of multi-substituted tribenzothiepin derivatives



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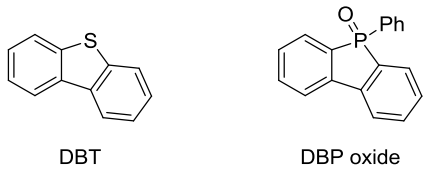
Chapter 6

Multi-Substituted Dibenzothiophene and Dibenzophosphole Oxide Derivatives Synthesis by Rhodium-Catalyzed Intermolecular Cycloaddition

Backgrounds

Dibenzothiophene (DBT) and dibenzophosphole (DBP) oxide are tricyclic compounds that have two benzene rings condensed with thiophene and phosphole oxide, respectively (Figure 1).

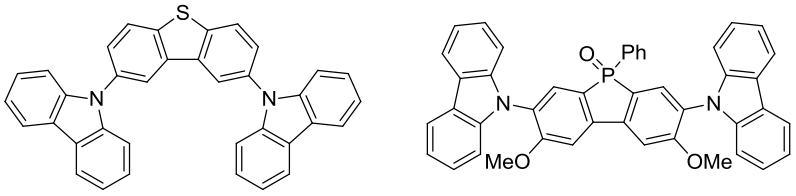
Figure 1. Structures of DBT and DBP oxide



DBT DBP oxide

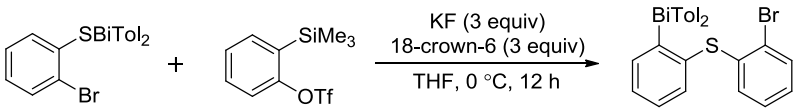
These skeletons have attracted much attention as organic electronics and materials in recent years. For example, DBT-containing compounds show optoelectronic and redox properties, and electrochemical characteristics such as organic light-emitting diodes (OLED).[1] DBP oxide-containing compounds also perform as organic molecular devices due to their highly electron-accepting character.[2-4] Polymers,[5] helical[6] and ladder-type[7] compounds containing DBP skeleton have been also synthesized, and their physical properties were investigated. For example, the carbazole-linking DBT and DBP oxide derivatives are known as host materials for phosphorescent organic light-emitting diodes (Figure 2).[4d]

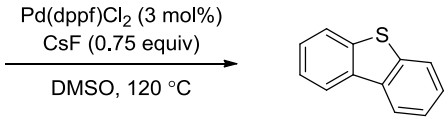
Figure 2. Structures of DBT- and DBP oxide-containing compounds



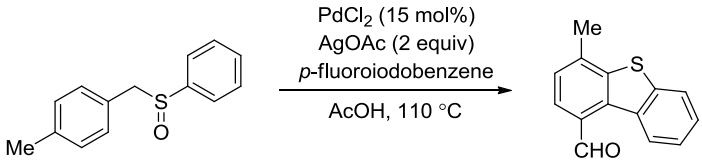
DBT- and DBP oxide-containing compounds for OLED

Due to these wide applicabilities of DBT and DBP oxide derivatives, there are many methods for the construction of their skeletons. As for DBT synthesis, intramolecular cyclization,[8] anionic cyclization,[9] radical cyclization,[10] photocyclization[11] and C-S bond formations[12] were successful examples. The protocols using cross-coupling (eq. 1),[13] C-H bond activation (eq. 2),[14] ring-closing metathesis (eq. 3)[15] and C-S bond formations (eq. 4),[16] were recently disclosed as catalytic approaches. But some of these transformations required harsh reaction conditions, such as high temperature, and/or basic or acidic condition.

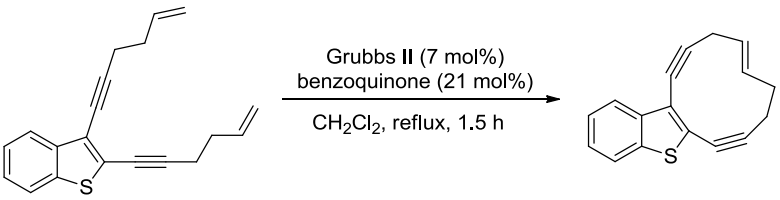


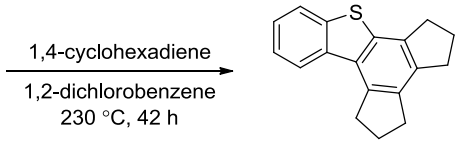


(1)

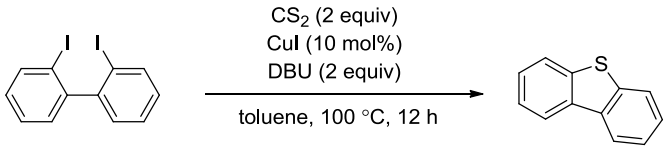


(2)



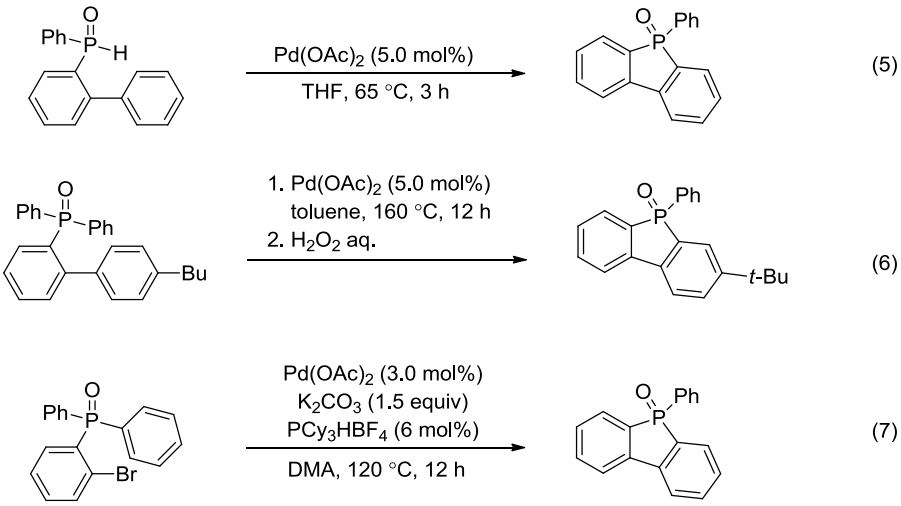


(3)



(4)

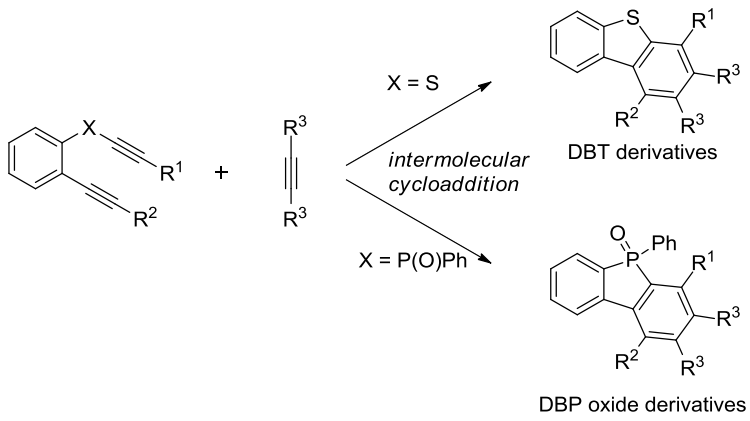
With regard to DBP oxide synthesis, several synthetic approaches have been developed. For example, radical phosphanylation using $(Me_3Sn)_2PPh$ and 1,1'-azobis(cyclohexane-1-carbonitrile (V-40),[4f] and radical cyclization with triethylborane and oxygen[7b] were reported. As for catalytic approaches, Pd-catalyzed direct arylation initiated by C-H and/or C-P bond cleavage (eqs. 5 and 6)[17] and Pd-catalyzed dehydrogenative cyclization (eq. 7)[18] were recently disclosed. However, most of these examples are the synthesis of mono- or disubstituted DBP oxides. Therefore, alternative approaches for the synthesis of multi-substituted DBT and DBP oxide derivatives in mild reaction conditions are strongly desired.



Results and Discussion

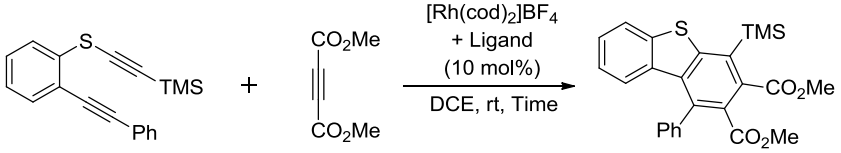
The author considered that intermolecular cycloaddition of sulfanylbenzene-tethered 1,6-diynes and phosphorylbenzene-tethered 1,6-diynes with alkynes could be another approach to the synthesis of multi-substituted DBT and DBP oxide derivatives (Scheme 1). It was already used for the syntheses of dibenzoheteroles, such as carbazoles,[19] dibenzofurans,[20] and dibenzosiloles.[21] Tanaka and co-workers developed Rh-catalyzed [2+2+2] cycloaddition of dialkynyl phosphorus compound with tetraynes for the synthesis of helical compounds containing DBP skeleton.[6a,b] However, to the best of our knowledge, intermolecular cycloaddition of 1,6-diynes and alkynes for the construction of DBT and DBP oxide skeletons has never been reported.

Scheme 1. Synthetic approach for DBT and DBP oxide derivatives



1,6-Diyne **1a** and dimethyl acetylenedicarboxylate (DMAD) (**2a**) were chosen as a model diyne and alkyne, and an intermolecular cycloaddition was examined using $[Rh(cod)_2]BF_4$ with several phosphine ligands. The desired cycloaddition proceeded at room temperature, and multi-substituted DBT **3aa** was obtained (Table 1). Triphenylphosphine gave a poor result, but DPPP, alkylene-tethered diphosphine, achieved moderate yield (Entries 1 and 2). Diphosphines possessing a biaryl scaffold facilitated the reaction and diyne **1a** was completely consumed within 1 h. In particular, BIPHEP gave the best result (Entries 3 and 4).

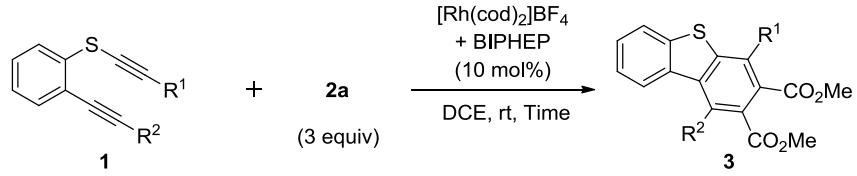
Table 1. Effect of ligands on the cycloaddition of diyne **1a** with **2a**

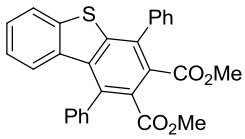


Entry	Ligand	Time / h	Yield / %
1	PPh_3	8	27
2	DPPP	8	61
3	*rac*-BINAP	1	84
4	BIPHEP	1	92

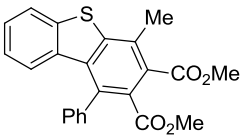
Under the optimum conditions (Table 1, Entry 4), various diynes were subjected to the intermolecular cycloaddition (Table 2). The reaction of diyne **1b**, which has phenyl groups on its alkyne termini, proceeded to give cycloadduct **3ba** in moderate yield. The reaction of diynes **1c** and **1d**, which have an alkyl group and phenyl group on its alkyne termini, proceeded sluggishly, and a higher reaction temperature was needed. Diynes **1e** and **1f**, which possess pentyl-substituted and unsubstituted alkyne terminus R^1, respectively, were very reactive and the dropwise addition of diynes to a solution of DMAD over 30 min was needed. These yields of the cross-cycloadducts **3ea** and **3fa** were moderate due to the formation of self-cycloadducts of diynes **1e** and **1f**. The reaction of diynes **1g** and **1h**, which have trimethylsilyl group on its alkyne terminus R^1, proceeded to give cycloadduct **3ga** and **3ha** in good yield. The reactivity of diynes **1i** and **1j**, which have trimethylsilyl groups or *tert*-butyl groups, respectively, on both of alkyne termini R^1 and R^2 was poor and no reaction proceeded. Diynes **1k** and **1l** with unsubstituted alkyne terminus(i) were too reactive, and the yields of cross-cycloadducts were low, because self-cycloadducts of the diynes were major products. On the other hand, diynes **1m** and **1n**, which have a phenyl- and pentyl- groups, respectively, along with unsubstituted alkyne terminus, were good substrates. In particular, the reaction of diyne **1n** realized the best yield of 94%.

Table 2. Cycloaddition of various diynes **1** with **2a**

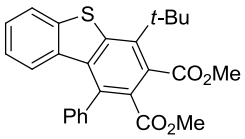




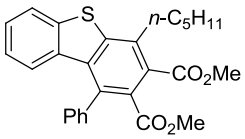
3ba
52% (1 h)
from **1b**
(R^1 = Ph, R^2 = Ph)



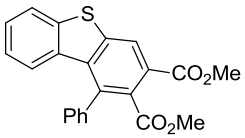
3ca[a]
30% (1 h)
from **1c**
(R^1 = Me, R^2 = Ph)



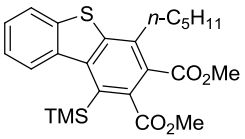
3da[a]
47% (6 h)
from **1d**
(R^1 = *t*-Bu, R^2 = Ph)



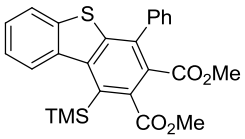
3ea[b]
28% (0.5 h)
from **1e**
(R^1 = *n*-C_5H_{11}, R^2 = Ph)



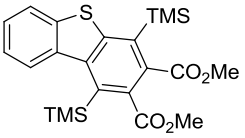
3fa[b]
33% (0.5 h)
from **1f**
(R^1 = H, R^2 = Ph)



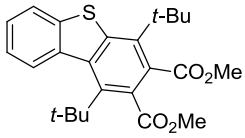
3ga[b]
67% (0.5 h)
from **1g**
(R^1 = *n*-C_5H_{11}, R^2 = TMS)



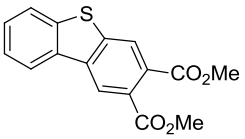
3ha
89% (1 h)
from **1h**
(R^1 = Ph, R^2 = TMS)



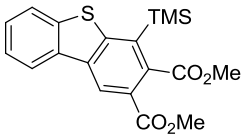
3ia
no reaction
from **1i**
(R^1 = TMS, R^2 = TMS)



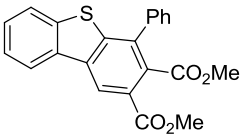
3ja
no reaction
from **1j**
(R^1 = *t*-Bu, R^2 = *t*-Bu)



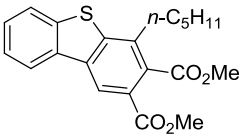
3ka[b]
38% (0.5 h)
from **1k**
(R^1 = H, R^2 = H)



3la
24% (1 h)
from **1l**
(R^1 = TMS, R^2 = H)



3ma
61% (1 h)
from **1m**
(R^1 = Ph, R^2 = H)

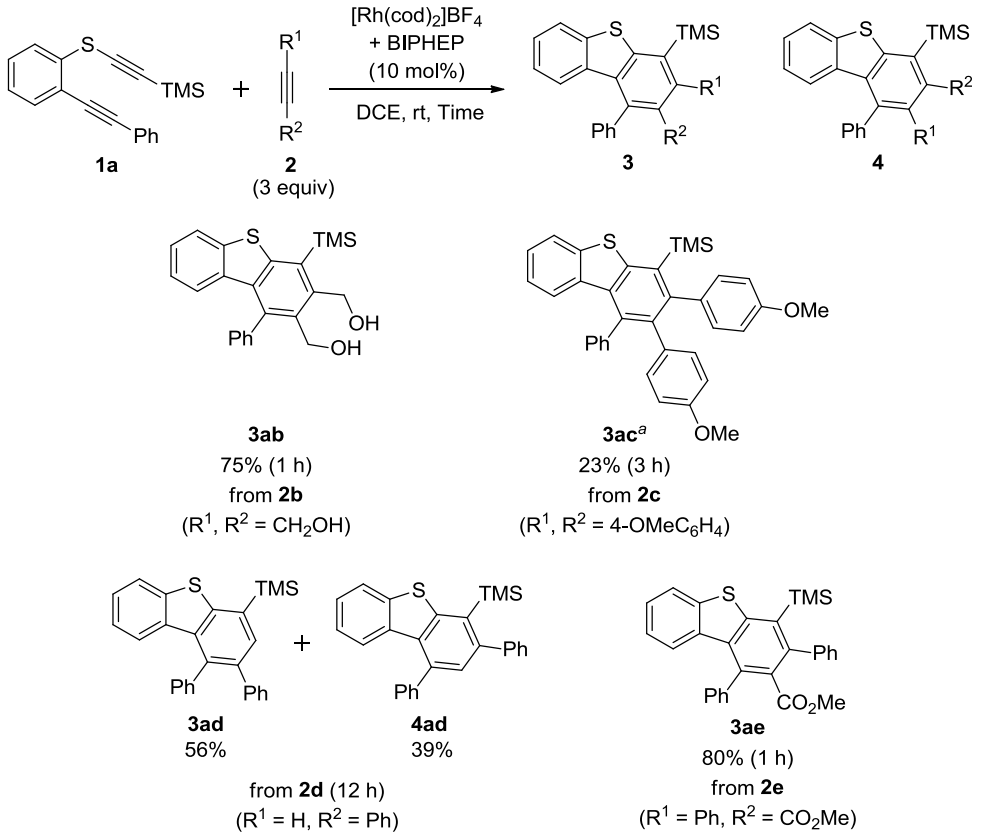


3na[b]
94% (0.5 h)
from **1n**
(R^1 = *n*-C_5H_{11}, R^2 = H)

[*a*] The reaction was examined at 80 °C. [*b*] Diyne was dropwisely added to a solution of Rh catalyst and DMAD over 30 min.

Next, the author ascertained the scope of symmetrical and unsymmetrical alkynes (Table 3). Diol **2b** could be used as a coupling partner, and the corresponding DBT derivative **3ab** was obtained in good yield. Diarylacetyelene was less reactive and the polyarylated DBT **3ac** was obtained, but in low yield even at a higher temperature. The cycloaddition of unsymmetrical alkynes also proceeded under the same reaction conditions. While the reaction of phenylacetylene (**2d**) gave a regioisomeric mixture of cycloadducts **3ad** and **4ad**, the reaction of methyl phenylpropiolate (**2e**) regioselectively proceeded to give **3ae** as a sole cycloadduct.

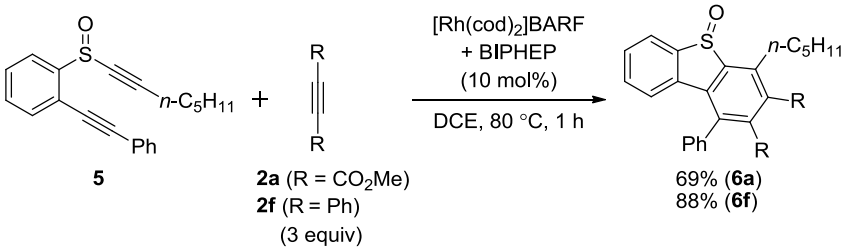
Table 3. Cycloaddition of diyne **1a** and various alkynes



[*a*] The reactions was examined at 80 °C.

As oxidized analogue of sulfanylbenzene-tethered 1,6-diyne, the cycloaddition with sulfinylbenzene-tethered diyne **5** was examined for the synthesis of dibenzothiophene 5-oxide derivatives (Scheme 2). The reaction with DMAD (**2a**) afforded desired multi-substituted DBT 5-oxide **6a** in 69% yield. Different from the sulfanylbenzene-tethered 1,6-diyne, phenylacetylene (**2f**) was also a good coupling partner, and the reaction gave polyaryl-substituted cycloadduct **6f** in high yield.

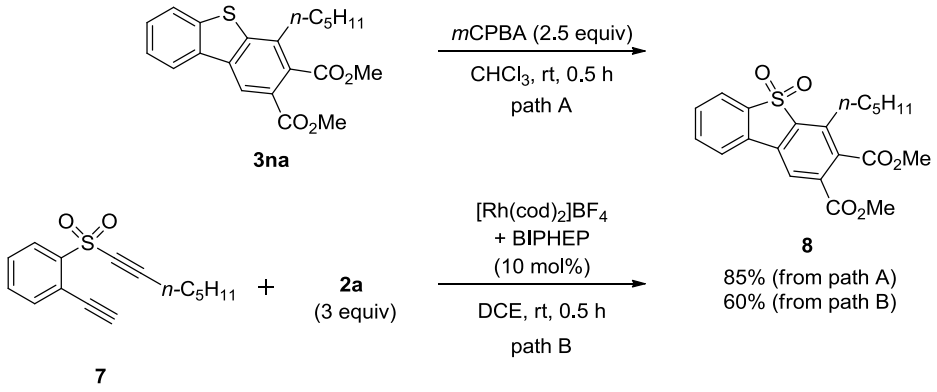
Scheme 2. Synthesis of DBT 5-oxide derivatives



Next, the synthesis of dibenzothiophene-5,5-dioxide (DBT-dioxide) derivatives was examined, because they have attracted attention as electronic materials.[22] Two methods were examined for the preparation of

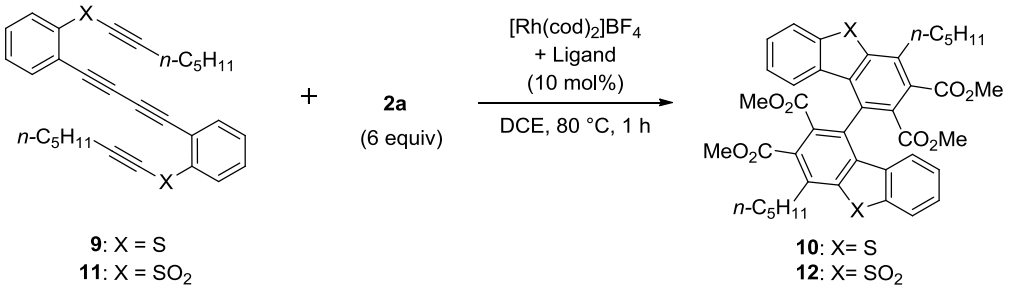
DBT-dioxide (Scheme 3). Oxidation of the obtained DBT **3na** readily proceeded by using *m*CPBA at room temperature to give DBT-dioxide **8** (path A). As another approach, intermolecular cycloaddition of sufonylbenzene-tethered diyne **7** with **2a** was examined. The reaction smoothly proceeded under the same conditions and DBT-dioxide **8** was obtained in moderate yield (path B).

Scheme 3. Synthesis of a DBT dioxide by two methods



The author further examined consecutive cycloaddition of tetraynes **9** and **11** possessing a 1,3-diyne moiety for the synthesis of bi-DBT derivatives (Table 4). When BIPHEP was used as an achiral diphosphine ligand, doubly-cyclized product **10** was obtained in low yield (Entry 1). The generation of axial chirality in **10** was ascertained by the HPLC analysis using a chiral column, and then several chiral diphosphine ligands were screened (Entries 2-5). BINAP and its derivatives achieved good enantioselectivity, but the yield was miserable, because many unidentified by-products were formed. When Me-DUPHOS was used, the yield was significantly improved, but ee was low (Entry 5). In contrast, the reaction of sulfonylbenzene-tethered tetrayne **11** using Rh-Me-DUPHOS catalyst realized the almost perfect ee along with moderate yield (Entry 6). Bi-DBT tetraoxide **12** could be prepared as a single crystal by recrystallization, and its structure and absolute configuration ((*R*)-form) were ascertained by X-ray crystallographic analysis (Figure 3).

Table 4. Consecutive cycloaddition for the synthesis of bi-DBT derivatives



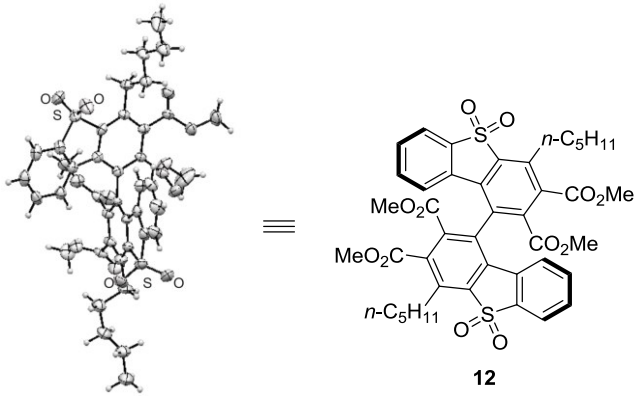
9: X = S
11: X = SO_2

10: X= S
12: X= SO_2

Entry	Tetrayne	Ligand	Yield / %	Ee / %
1	**9**	BIPHEP	19 (**10**)	-
2	**9**	(*R*)-BINAP	5 (**10**)	78
3	**9**	(*S*)-tolBINAP	7 (**10**)	73
4	**9**	(*S*)-H_8-BINAP	16 (**10**)	82
5	**9**	(*S,S*)-Me-DUPHOS	49 (**10**)	21
6[a]	**11**	(*S,S*)-Me-DUPHOS	65 (**12**)	97

[*a*] The reaction time was 8 h.

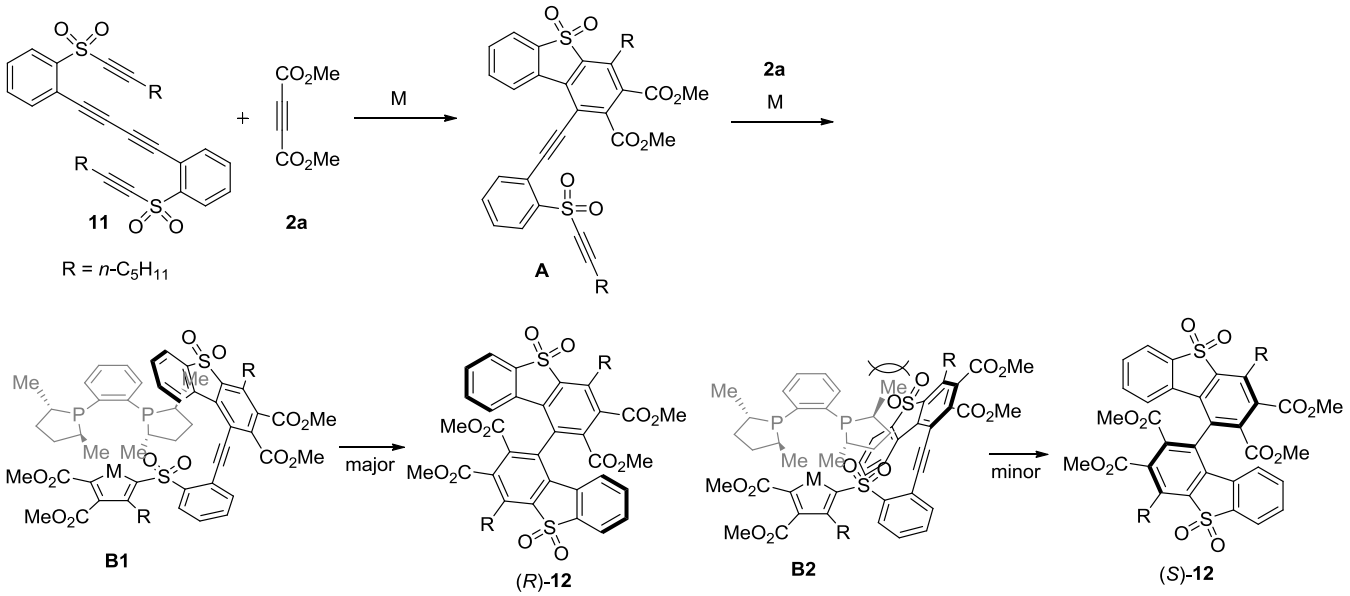
Figure 3. ORTEP diagram of **12**



12

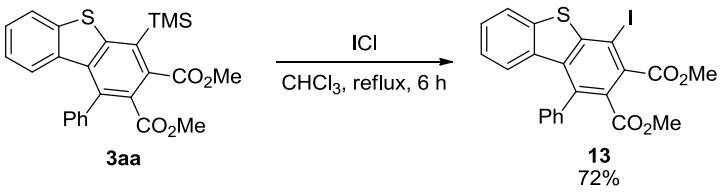
A possible explanation for enantioselective induction of **12** was shown in Scheme 4. The first intermolecular cycloaddition of 1,6-diyne moiety on tetrayne with **2a** gave intermediate **A**. The oxidative coupling of **A** with DMAD can give the square planar coordinated metallacyclopentadiene **B1** or **B2**. Due to steric hindrance of DBT skeleton and methyl group on ligand in **B2**, the formation of **B1** would prefer, and (*R*)-**12** was obtained as a major product.

Scheme 4. Possible explanation for enantioselective induction of **12**



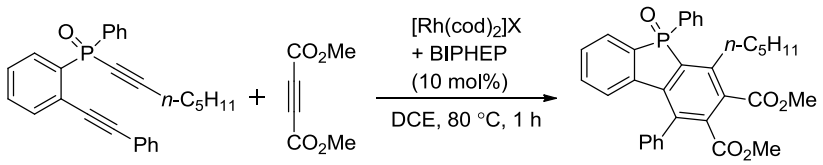
In addition, synthetic transformation of cycloadduct **3aa** was examined by iodine monochloride, and iodinated DBT **13** was obtained in good yield (Scheme 5).

Scheme 5. Synthetic application of cycloadduct **3aa**



In place of sulfanyl-tethered diynes, the author examined the cycloaddition of phosphorylbenzene-tethered 1,6-diyne **14a** with DMAD (**2a**) in the presence of a cationic rhodium catalyst using BIPHEP as a diphosphine ligand. The reaction conditions were reinvestigated, and Table 5 shows the effect of the counter anion of cationic rhodium complex: in each entry, diyne **14a** was completely consumed within 1 h, and the desired tetra-substituted DBP oxide **15aa** was obtained. Tetrafluoroborate (BF_4) and hexafluorophosphate (PF_6) gave the comparable yield (Entries 1 and 2). Trifluoromethanesulfonate (OTf) and hexafluoroantimonate (SbF_6) gave poor results, because the significant amounts of dimer of **14a** were formed by self-cycloaddition (Entries 3 and 4). In contrast, BARF gave the best yield of 85% by almost complete suppression of self-cycloaddition (Entry 5).

Table 5. Effect of counter anion on the cycloaddition of diyne **14a** with **2a**

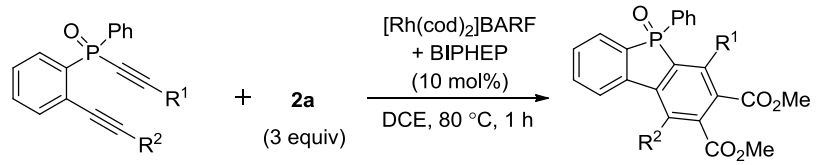


Entry[a]	X	Yield / %
1	BF_4	78
2	PF_6	73
3	OTf	42
4	SbF_6	46
5	BARF	85

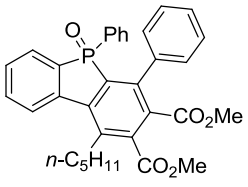
[*a*] The diyne was added dropwise to a DCE solution of the Rh catalyst and alkyne **2a**.

Under the reaction conditions of entry 5 in Table 5, various phosphorylbenzene-tethered diynes were subjected to the intermolecular cycloaddition (Table 6). When diyne **14b**, which has phenyl and pentyl groups on its alkyne termini of R^1 and R^2 respectively, was used, almost no reaction proceeded. The reaction of diyne **14c** having two phenyl groups on its alkyne termini proceeded, but the yield of the desired cycloadduct **15ca** was low. Diynes **14b** and **14c** were inappropriate substrates due to the formation of self-cycloadducts. The introduction of an alkyl group as R^1 was critical for high yield: diyne **14d**, which has pentyl and 4-methylphenyl groups, proceeded to give desired cycloadduct **15da** in 86% yield. The cycloaddition of diynes **14e** and **14f**, which have methoxyphenyl and chlorophenyl group, respectively as R^1, also proceeded to afford the corresponding products **15ea** and **15fa** in good yields. Diyne **14g** possessing a biphenyl group was also a good substrate, and the desired cycloadduct **15ga** was obtained in 86% yield. In addition, thienyl substituent could be also installed by the reaction of diyne **14h**.

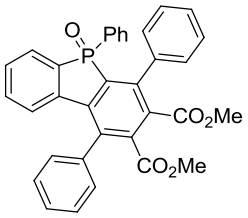
Table 6. Cycloaddition of various diynes **14** with **2a**[*a*]



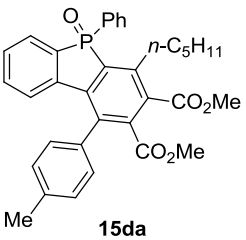
14 **15**



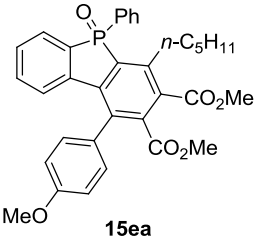
15ba
trace
from **14b**
(R^1 = Ph, R^2 = *n*-C_5H_{11})



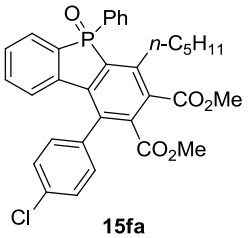
15ca
27%
from **14c**
(R^1 = Ph, R^2 = Ph)



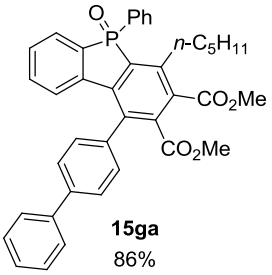
15da
86%
from **14d**
(R^1 = *n*-C_5H_{11}, R^2 = 4-MeC_6H_4)



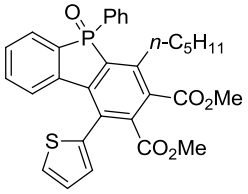
15ea
84%
from **14e**
(R^1 = *n*-C_5H_{11}, R^2 = 4-$OMeC_6H_4$)



15fa
80%
from **14f**
(R^1 = *n*-C_5H_{11}, R^2 = 4-ClC_6H_4)



15ga
86%
from **14g**
(R^1 = *n*-C_5H_{11}, R^2 = 4-PhC_6H_4)

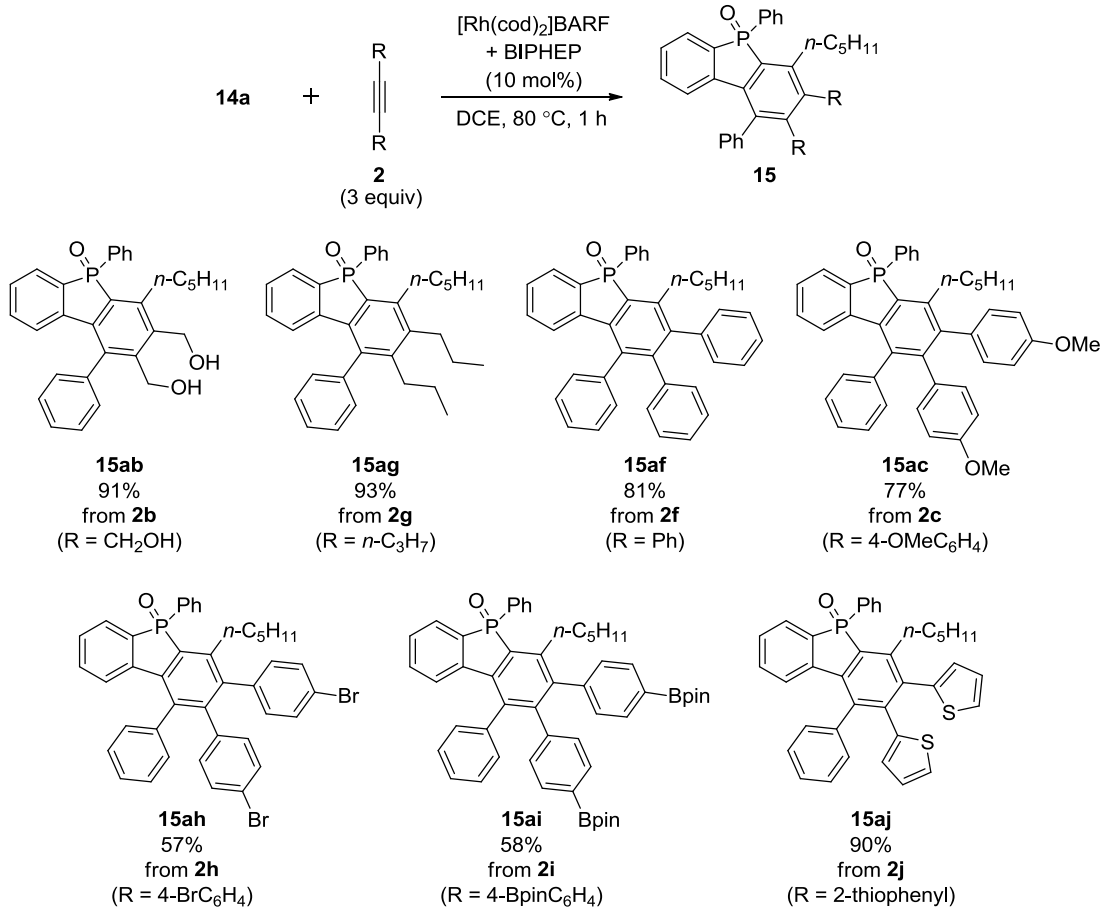


15ha
91%
from **14h**
(R^1 = *n*-C_5H_{11}, R^2 = 2-thienyl)

[*a*] Diyne was added dropwise to a solution of the Rh catalyst and alkyne.

Next, the reaction of diyne **14a** with various symmetrical alkynes was examined (Table 7). 2-Butyne-1,4-diol (**2b**) could be used, and the corresponding DBP oxide derivative **15ab** was obtained in high yield. Dialkyl-substituted alkyne **2g** could be also allowed as a coupling partner, and the desired cycloadduct **15ag** was obtained in 93% yield. The reaction using diphenylacetylene (**2f**) also proceeded, and polyarylated DBP oxide derivative **15af** was obtained in 81% yield. The cycloaddition using other diarylacetylenes **2c** and **2h**, which have electron-donating and -withdrawing groups, respectively gave the corresponding products **15ac** and **15ah**. The reaction of boryl-substituted diarylacetylene **2i** also proceeded and the obtained DBP oxide derivative **15ai** can be used for further transformation. In addition, 1,2-di(thiophene-2-yl)ethyne (**2j**) was also a good coupling partner, and the desired cycloadduct **15aj** substituted by two thienyl groups was obtained in 90% yield.

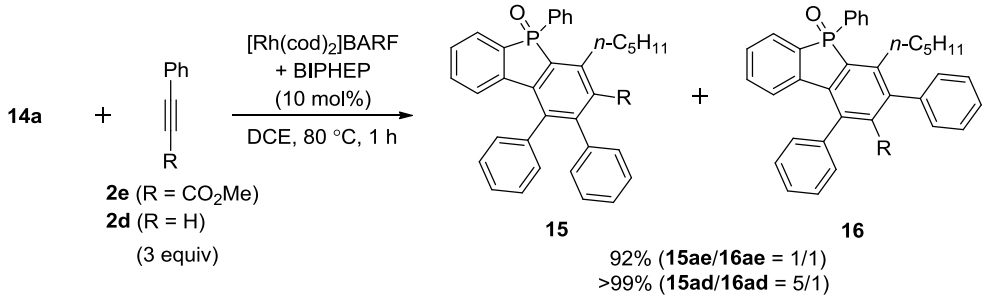
Table 7. Cycloaddition of diyne **14a** and various symmetrical alkynes **2**[*a*]



[*a*] Diyne was added dropwise to a solution of the Rh catalyst and alkyne.

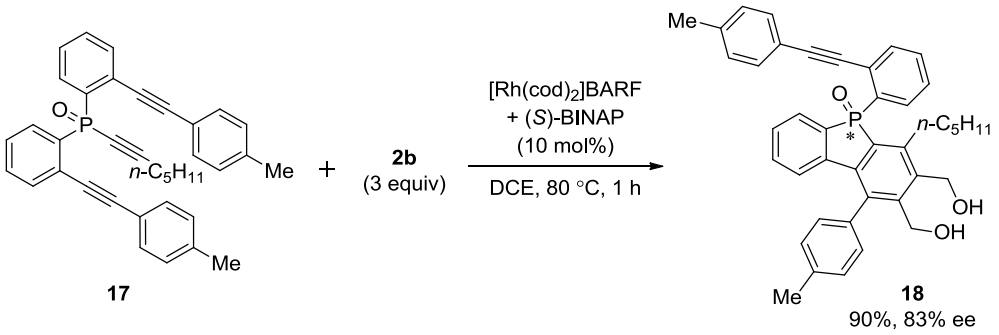
The cycloaddition using unsymmetrical alkynes also proceeded under the same reaction conditions (Scheme 6). The reaction of **14a** with ethyl phenylpropiolate (**2e**) gave the desired products in 92% total yield as a mixture of **15ae** and **16ae** without selectivity. In the case of ethynylbenzene (**2d**), almost quantitative yield was achieved, and cycloadduct **15ad** was a major product.

Scheme 6. Cycloaddition of diyne **14a** with unsymmetrical alkynes **2e** and **2d**



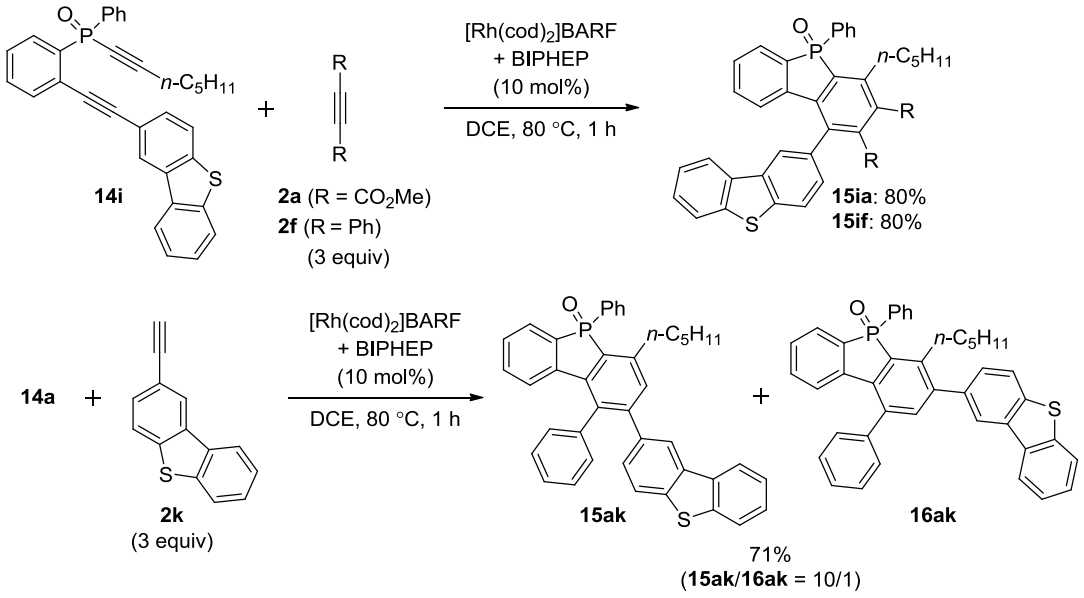
The asymmetric desymmetrization using [2+2+2] cycloaddition has been already reported: the reaction of symmetrical dialkynyl alcohol[23] or dialkynylphosphine oxide[24] with diynes gave chiral cycloadducts. Recently, the [2+2+2] cycloaddition of prochiral silicon-tethered triyne with monoalkyne has been developed for the enantioselective synthesis of Si-chiral dibenzosiloles.[25] Against this background, the author examined the asymmetric desymmetrization using phosphorylbenzene-tethered triyne (Scheme 7). When the cycloaddition of prochiral triyne **17** with 2-butyne-1,4-diol (**2b**) using Rh-(*S*)-BINAP catalyst, the desired P-chiral DBP oxide **18** was obtained in high yield with good ee.[26] With regard to asymmetric synthesis of chiral DBP oxides, optical resolution was only a protocol,[27] therefore, this is the first example of enantioselective synthesis.

Scheme 7. Enantioselective desymmetrization of **17** by the cycloaddition



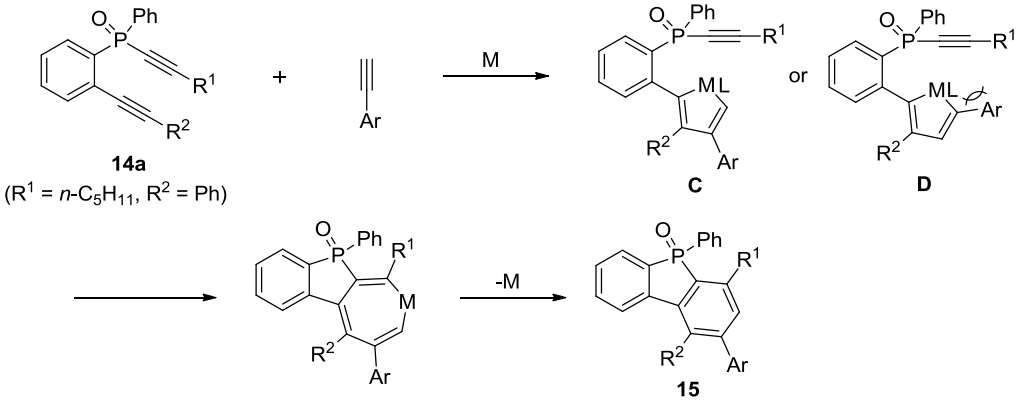
With a view to the synthesis of functional organic molecules, the author synthesized the DBP oxides possessing dibenzothiophene(s) (DBT) as substituent(s) (Scheme 8). The reaction of diyne **14i**, which has dibenzo[*b*,*d*]thiophen-2-yl group on one of its alkyne termini, proceeded to give the desired DBP oxide **15ia** in 80% yield. Diphenylacetylene (**2f**) could also be acceptable, and the polyarylated DBP oxide derivative **15if** was afforded in high yield. Furthermore, the cycloaddition of dibenzothiophene-containing alkyne **2k** with diyne **14a** was examined, and the reaction gave DBP oxide derivative **15ak** as a major regioisomer.

Scheme 8. Synthesis of bi-dibenzoheteroles



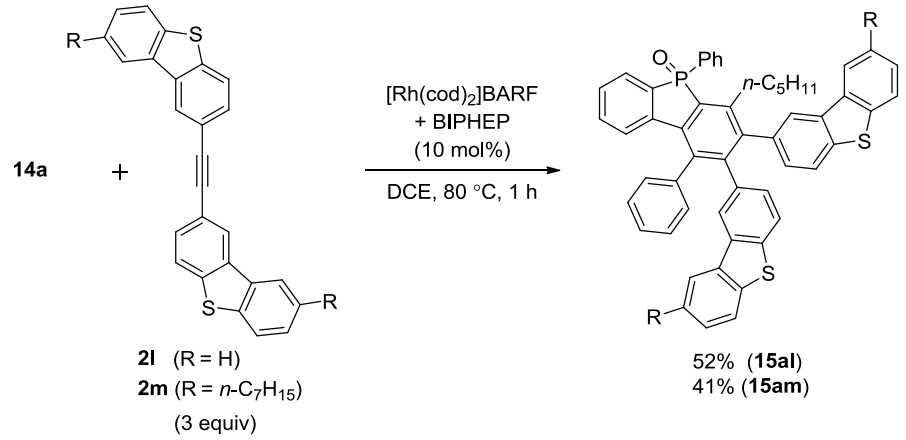
A possible explanation for regioselective reaction was shown in Scheme 9. The first step is oxidative coupling of diyne **14a** with metal catalyst, and metallacyclopentadiene **C** or **D** can be generated. Due to the steric repulsion of metal on the ligand with aryl group, the generation of metallacyclopentadiene **C** is preferred to **D**. The next step is insertion of remaining alkyne moiety of **14a** to **C**. Subsequent reductive elimination of metal catalyst, cycloadduct **15** is regioselectively obtained.

Scheme 9. Possible explanation for regioselective reaction



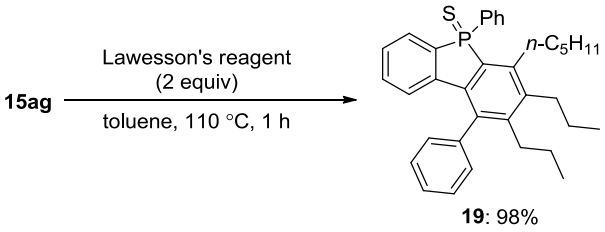
In addition, the cycloadditions using alkyne **2l** and **2m**, which have dibenzothiophenyl groups on its both termini, were examined (Scheme 10). The desired cycloadducts **15al** and **15am** consisting of a DBP oxide and two DBTs were obtained in moderate yield. Cycloadduct **15al** possessed high crystallinity and purification of its product was difficult, but solubility of dialkylated compound **15am** was improved.

Scheme 10. Synthesis of ter(dibenzoheterolyl)s



In addition, the synthetic transformation of cycloadduct **15ag** by using Lawesson's reagent gave dibenzophosphole sulfide **19** in excellent yield (Scheme 11).

Scheme 11. Synthesis of a dibenzophosphole sulfide derivative



As investigation of physical properties, the UV-vis spectra of the obtained DBT derivatives **3na** and **10**, the DBT-dioxide derivatives **8** and **12**, and DBP-oxide derivatives **15af**, **15if**, **15ak**, and **15al** were measured (Table 8). In the case of DBT derivatives, the λ_{max} of these compounds were observed at 294.5-330.5 nm. The DBT-dioxide derivatives were red-shifted compared with the DBT derivatives (Entry 1 vs Entry 2 and Entry 3 vs Entry 4). In the case of DBT-dioxide derivatives, significant blue-shift of bi-DBT-tetraoxide was unexpectedly observed compared with mono-DBT-dioxide (Entry 2 vs Entry 4). With regard to DBP oxide derivatives, the UV-vis spectra were measured to investigate the effect of DBT substituent(s) (Entries 5-8). The λ_{max} of these compounds were observed at 317.6-338.0 nm. There is no significant difference in the value of λ_{max} among **15af**, **15if** and **15al**. In the case of DBT substituent(s) derivatives, obvious red-shift of disubstituted **15al** was observed compared with monosubstituted **15ak** (Entry 7 vs Entry 8).

Table 8. UV-vis date of DBT and DBP oxide derivatives

Entry	Compound	UV-vis λ_{max} (nm) / logε
1	**3na**	294.5 / 3.84
2	**8**	330.5 / 3.57
3	**10**	297.5 / 4.03
4	**12**	304.0 / 4.07
5	**15af**	338.0 / 3.45
6	**15if**	332.0 / 3.21
7	**15ak**	317.6 / 3.65
8	**15al**	332.2 / 3.09

Conclusion

The author develooped Rh-catalyzed intermolecular cycloaddition of sulfanylbenzene-, sulfinylbenzene-, sulfonylbenzene-, and phosphorylbenzene-tethered 1,6-diynes with alkynes. The present reaction provides a new protocol for the synthesis of multi-substituted DBT and DBP oxide derivatives. As catalytic enantioselective reaction, a bi-dibenzothiophene tetraoxide derivative was synthesized by consecutive cycloaddition of a tetrayne. In addition, the first and highly enantioselective synthesis of a P-chiral DBP oxide by desymmetrization was achieved.

Experimental Section

General

All reactions were examined under an argon atmosphere in oven-dried glassware with a magnetic stirring bar. A hexane solution of *n*-butyllithium (1.58 or 1.60 M) was purchased from Kanto Chemical Co., Inc. Dehydrated diethyl ether and tetrahydrofuran (THF) Dehydrated dichloromethane and 1,2-dichloroethane were purchased from Wako Pure Chemical Industries Ltd. (Wako) and degassed by argon bubbling before use. Other reagents were purchased from Wako, Kanto, TCI, or Aldrich and were used without further purification. Flash column chromatography was performed with silica gel (Kanto Chemical Co., Inc. 60 N). Preparative thin-layer chromatography (PTLC) was performed with silica gel-precoated glass plates (Merck 60 GF254) prepared in the author's laboratory. FT-IR spectra were recorded with Horiba FT/IR-4200 spectrophotometer. NMR spectra were measured with JEOL AL-400 (400 MHz), JEOL ECS400 (400 MHz), JEOL Lambda 500 (500 MHz), or JEOL ECX500 (^{1}H NMR, 495.13 MHz; ^{13}C NMR, 124.5 MHz; ^{31}P NMR, 200.43 MHz) using TMS as an internal standard, $CDCl_3$ and C_2D_6OS were used as a solvent. High-resolution mass spectra (HRMS) were measured on ESI (Electro Spray Ionization) – orbitrap mass spectrometer. Optical rotations were measured with Jasco DIP-1000 polarimeter. Physical properties of 1,2-bis(2-bromophenyl)disulfane and 2,3-bis(methoxycarbonyl)dibenzothiophene **(3ka)** were omitted, because it was already reported.[28,29] Diynes **1** were prepared by Sonogashira coupling of the corresponding alkynes and (hept-1-ynyl)(2-iodephenyl)sulfane or (2-iodephenyl)(trimethylsilylethynyl)sulfane, which was prepared by the literature protocol.[30,31] Diyne **5** was prepared by oxidation using *m*CPBA.[32] Tetrayne **9** was prepared by CuCl-TMEDA-mediated oxidative coupling[33] of (2-ethynylphenyl)(hept-1-ynyl)sulfane (**1n**). The following oxidation using *m*CPBA[34] gave tetrayne tetraoxide **11**. Diynes **14** were prepared by iodination of diphenylphosphinic acid,[35] chlorination of phosphinic acid moiety,[36] alkynylation,[37] and Sonogashira coupling. Alkyne **2l**[1b] and **2m**[38] were prepared by the literature protocol.

Typical Procedure for the Rh-catalyzed cycloaddition for the synthesis of DBT derivatives

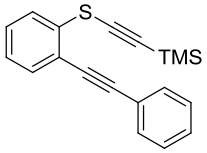
$[Rh(cod)_2]BF_4$ (2.0 mg, 0.005 mmol) and BIPHEP (2.6 mg, 0.005 mmol) were placed in Schlenk tube, which was then evacuated and backfilled with argon (3 ×). To the reaction vessel was added CH_2Cl_2 (1.0 mL). Then it was filled with H_2, and the mixture was stirred at r.t. for 30 min under H_2. After removal of the solvent and H_2 under reduced pressure, the reaction vessel was filled with argon. 1,2-Dichloroethane (0.2 mL) was added to the flask and the mixture was stirred to give a reddish soln. Then, a

1,2-dichloroethane solution (0.3 mL) of diyne (0.05 mmol) and DMAD (21.3 mg, 0.15 mmol) was added and the mixture was stirred at room temperature for 1 h. The volatiles were removed under reduced pressure, and the crude products were purified by PTLC.

Typical procedure for the Rh-catalyzed cycloaddition for the synthesis of DBP oxide derivatives

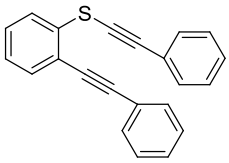
$[Rh(cod)_2]$BARF (5.9 mg, 0.005 mmol) and BIPHEP (2.6 mg, 0.005 mmol) were placed in Schlenk tube, which was then evacuated and backfilled with argon three times. 1,2-Dichloroethane (0.15 mL) and an alkyne (21.3 mg, 0.15 mmol) was added and the mixture was stirred at 80 °C. Then, a 1,2-dichloroethane solution (1.85 mL) of diyne (0.05 mmol) was added dropwise for 1 h. Solvent was excluded from the reaction mixture under reduced pressure, and the obtained crude products were purified by PTLC to give a pure cycloadduct.

Characterization of new compounds



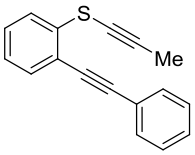
(2-(Phenylethynyl)phenyl)(trimethylsilylethynyl)sulfane (1a)

A pale brown solid; mp 43 °C; IR (CH_2Cl_2) 2892, 2097, 879, 843, 753 cm^{-1}; ^1H NMR δ 0.27 (s, 9H), 7.20 (ddd, *J* = 1.1, 7.6, 7.6 Hz, 1H), 7.34-7.39 (m, 4H), 7.47 (dd, *J* = 1.3, 7.6 Hz, 1H), 7.55-7.57 (m, 2H), 7.73 (dd, *J* = 0.6, 8.0 Hz, 1H); ^{13}C NMR δ -0.1, 85.4, 89.8, 96.8, 107.8, 120.3, 122.7, 125.4, 126.0, 128.4, 128.7, 129.2, 131.6, 132.0, 135.9; HRMS (ESI positive) m/z calcd for $C_{19}H_{19}SSi$ ($[M+H]^+$): 307.0971 Found: 307.0971.



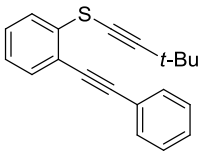
(Phenylethynyl)(2-(phenylethynyl)phenyl)sulfane (1b)

A brown oil; IR (CH_2Cl_2) 2850, 2170, 752, 688 cm^{-1}; ^1H NMR δ 7.20 (ddd, *J* = 1.1, 7.5, 7.5 Hz, 1H), 7.34-7.39 (m, 7H), 7.49 (dd, *J* = 1.2, 7.7 Hz, 1H), 7.53-7.55 (m, 2H), 7.58-7.60 (m, 2H), 7.77 (dd, *J* = 0.6, 8.1 Hz, 1H); ^{13}C NMR δ 70.5, 85.5, 96.9, 99.3, 120.3, 122.7, 122.8, 125.5, 125.9, 128.4, 128.4, 128.7, 128.8, 129.2, 131.7, 131.9, 132.1, 136.5; HRMS (ESI positive) m/z calcd for $C_{22}H_{15}S$ ($[M+H]^+$): 311.0889. Found: 311.0889.



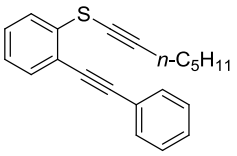
(2-(Phenylethynyl)phenyl)(prop-1-ynyl)sulfane (1c)

A brown oil; IR (CH_2Cl_2) 2913, 1057, 752, 689 cm^{-1}; ^1H NMR δ 2.14 (s, 3H), 7.17 (ddd, *J* = 1.1, 7.5, 7.5 Hz, 1H), 7.32-7.36 (m, 4H), 7.45 (dd, *J* = 1.3, 7.7 Hz, 1H), 7.56-7.57 (m, 2H), 7.70 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR δ 5.3, 63.5, 85.6, 96.6, 96.8, 119.9, 122.8, 125.2, 125.5, 128.4, 128.6, 129.0, 131.6, 131.9, 137.3; HRMS (ESI positive) m/z calcd for $C_{17}H_{13}S$ ($[M+H]^+$): 249.0732. Found: 249.0773.



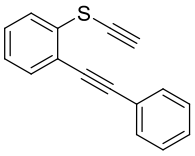
(3,3-Dimethylbut-1-ynyl)(2-(phenylethynyl)phenyl)sulfane (1d)

A pale yellow oil; IR (CH_2Cl_2) 2865, 2215, 1058, 754, 689 cm^{-1}; ^1H NMR δ 1.35 (s, 9H), 7.16 (ddd, *J* = 1.2, 7.6, 7.6 Hz, 1H), 7.34-7.37 (m, 4H), 7.45 (dd, *J* = 1.3, 7.7 Hz, 1H), 7.55-7.57 (m, 2H), 7.66 (dd, *J* = 0.9, 8.1 Hz, 1H); ^{13}C NMR δ 29.1, 30.9, 65.2, 85.6, 96.6, 109.2, 119.8, 122.8, 124.8, 125.4, 128.3, 128.6, 129.0, 131.6, 131.8, 137.5; HRMS (ESI positive) m/z calcd for $C_{20}H_{19}S$ ($[M+H]^+$): 291.1202. Found: 291.1202.



(Hept-1-ynyl)(2-(phenylethynyl)phenyl)sulfane (1e)

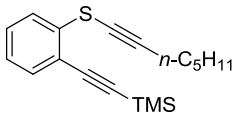
A pale brown oil; IR (CH_2Cl_2) 2859, 2215, 1491, 753, 689 cm^{-1}; ^1H NMR δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.32-1.47 (m, 4H), 1.63 (quint, *J* = 7.1 Hz, 2H), 2.03 (t, *J* = 7.1 Hz, 2H), 7.16 (ddd, *J* = 1.1, 7.5, 7.5 Hz, 1H), 7.33-7.37 (m, 4H), 7.45 (dd, *J* = 1.1, 7.7 Hz, 1H), 7.56-7.57 (m, 2H), 7.70 (dd, *J* = 0.7, 8.1 Hz, 1H); ^{13}C NMR δ 14.0, 20.3, 22.2, 28.3, 31.1, 64.2, 85.6, 96.6, 101.5, 119.8, 122.8, 125.1, 125.5, 128.4, 128.6, 129.0, 131.6, 131.9, 137.5; HRMS (ESI positive) m/z calcd for $C_{21}H_{21}S$ ($[M+H]^+$): 305.1358. Found: 305.1358.



Ethynyl(2-(phenylethynyl)phenyl)sulfane (1f)

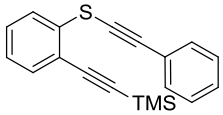
A pale brown oil; IR (CH_2Cl_2) 3287, 3057, 2219, 753, 688 cm^{-1}; ^1H NMR δ 3.35 (s, 1H), 7.20 (ddd, *J* = 1.0, 7.6, 7.6 Hz, 1H), 7.35-7.38 (m, 4H), 7.48 (dd, *J* = 1.1, 7.6 Hz, 1H), 7.56-7.57 (m, 2H), 7.73 (d, *J* =

8.1 Hz, 1H); ^{13}C NMR δ 70.5, 85.3, 88.5, 96.9, 120.5, 122.6, 125.6, 126.1, 128.4, 128.8, 129.2, 131.6, 132.0, 135.0; HRMS (ESI positive) m/z calcd for $C_{16}H_{11}S$ ([M+H]$^+$): 235.0576. Found: 235.0578.



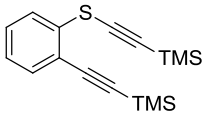
(Hept-1-ynyl)(2-(trimethylsilylethynyl)phenyl)sulfane (1g)

A pale yellow oil; IR (CH_2Cl_2) 2860, 2157, 1250, 864, 753 cm^{-1}; ^{1}H NMR δ 0.27 (s, 9H), 0.91 (t, *J* = 7.3 Hz, 3H), 1.33-1.45 (m, 4H), 1.62 (quint, *J* = 7.2 Hz, 2H), 2.47 (t, *J* = 7.1 Hz, 2H), 7.10 (ddd, *J* = 1.1, 7.5, 7.5 Hz, 1H), 7.32 (ddd, *J* = 1.3, 7.6, 7.6 Hz, 1H), 7.38 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.66 (dd, *J* = 0.7, 8.1 Hz, 1H); ^{13}C NMR δ -0.2, 14.0, 20.3, 22.2, 28.3, 31.1, 64.3, 100.7, 101.6, 102.5, 119.6, 124.8, 125.2, 129.2, 132.2, 137.9; HRMS (ESI positive) m/z calcd for $C_{18}H_{25}SSi$ ([M+H]$^+$): 301.1441. Found: 301.1426.



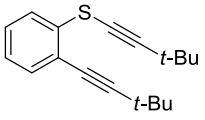
Phenylethynyl(2-(trimethylsilylethynyl)phenyl)sulfane (1h)

A yellow solid; mp 67 °C; IR (CH_2Cl_2) 2854, 2157, 862, 844 cm^{-1}; ^{1}H NMR δ 0.29 (s, 9H), 7.15 (ddd, *J* = 0.9, 7.5, 7.5 Hz, 1H), 7.33-7.36 (m, 4H), 7.41 (dd, *J* = 1.1, 7.6 Hz, 1H), 7.52-7.54 (m, 2H), 7.73 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR δ 0.9, 76.1, 100.4, 101.7, 103.8, 121.0, 123.9, 126.3, 126.8, 129.5, 129.8, 130.4, 132.8, 133.4, 138.0; HRMS (ESI positive) m/z calcd for $C_{19}H_{18}NaSSi$ ([M+Na]$^+$): 329.0791. Found: 329.0793.



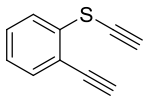
(Trimethylsilylethynyl)(2-(trimethylsilylethynyl)phenyl)sulfane (1i)

A pale brown oil; IR (CH_2Cl_2) 2898, 2098, 863, 842, 756 cm^{-1}; ^{1}H NMR δ 0.32 (s, 9H), 0.33 (s, 9H), 7.19 (ddd, *J* = 1.0, 7.5, 7.5 Hz, 1H), 7.41 (dddt, *J* = 1.3, 7.5, 7.5 Hz, 1H), 7.45 (dd, *J* = 1.0, 7.6 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR δ -0.2, -0.1, 89.3, 100.6, 102.7, 107.9, 120.0, 125.1, 125.7, 129.3, 132.2, 136.3; HRMS (ESI positive) m/z calcd for $C_{16}H_{23}SSi_2$ ([M+H]$^+$): 303.1054. Found: 303.1054.



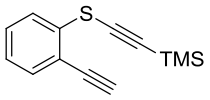
(3,3-Dimethylbut-1-ynyl)(2-(3,3-dimethylbut-1-ynyl)phenyl)sulfane (1j)

A yellow oil; IR (CH_2Cl_2) 2863, 2240, 1033, 752 cm^{-1}; ^{1}H NMR δ 1.34 (s, 18H), 7.09 (ddd, *J* = 1.1, 7.5, 7.5 Hz, 1H), 7.27-7.30 (m, 2H), 7.59 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR δ 28.3, 29.1, 30.9, 30.9, 63.5, 75.5, 106.4, 109.0, 120.5, 124.4, 125.2, 128.2, 131.5, 137.2; HRMS (ESI positive) m/z calcd for $C_{18}H_{23}S$ ([M+H]$^+$): 271.1515. Found: 271.1515.



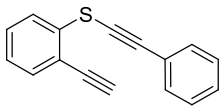
Ethynyl(2-ethynylphenyl)sulfane (1k)

A black oil; IR (CH_2Cl_2) 3288, 3059, 754 cm^{-1}; ^1H NMR δ 3.35 (s, 1H), 3.48 (s, 1H), 7.18 (ddd, *J* = 1.1, 7.6, 7.6 Hz, 1H), 7.38 (ddd, *J* = 1.4, 7.7, 7.7 Hz, 1H), 7.45 (dd, *J* = 1.3, 7.7 Hz, 1H), 7.71 (dd, *J* = 0.8, 8.1 Hz, 1H); ^{13}C NMR δ 70.2, 79.5, 84.8, 88.7, 119.3, 125.8, 126.1, 129.8, 133.0, 135.4; HRMS (ESI positive) m/z calcd for $C_{10}H_7S$ ($[M+H]^+$): 159.0263. Found: 159.0264.



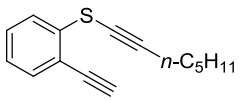
(2-Ethynylphenyl)(trimethylsilylethynyl)sulfane (1l)

A brown oil; IR (CH_2Cl_2) 3291, 2898, 2097, 862, 754 cm^{-1}; ^1H NMR δ 0.27 (s, 9H), 3.47 (s, 1H), 7.17 (ddd, *J* = 1.1, 7.6, 7.6 Hz, 1H), 7.39 (ddd, *J* = 1.4, 7.6, 7.6 Hz, 1H), 7.45 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.67 (dd, *J* = 0.6, 8.1 Hz, 1H); ^{13}C NMR δ 0.9, 80.6, 85.6, 90.4, 109.1, 120.1, 126.5, 126.9, 130.8, 134.0, 137.3; HRMS (ESI positive) m/z calcd for $C_{13}H_{15}SSi$ ($[M+H]^+$): 231.0658. Found: 231.0656.



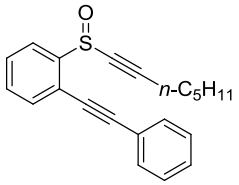
(2-Ethynylphenyl)(phenylethynyl)sulfane (1m)

A a pale brown oil; IR (CH_2Cl_2) 3287, 3020, 2170, 752, 688 cm^{-1}; ^1H NMR δ 3.51 (s, 1H), 7.18 (ddd, *J* = 1.1, 7.6, 7.6 Hz, 1H), 7.33-7.37 (m, 4H), 7.39 (ddd = 1.5, 7.6, 7.6 Hz, 1H), 7.52-7.55 (m, 2H), 7.76 (dd, *J* = 0.7, 8.1 Hz, 1H); ^{13}C NMR δ 75.6, 80.7, 85.7, 100.5, 120.1, 123.8, 126.6, 126.9, 129.5, 129.9, 130.8, 132.9, 134.1, 137.9; HRMS (ESI positive) m/z calcd for $C_{16}H_{10}S$ ($[M]^+$): 234.0498. Found: 234.0498.



(2-Ethynylphenyl)(hept-1-ynyl)sulfane (1n)

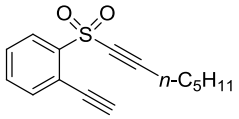
A pale brown oil; IR (CH_2Cl_2) 3290, 2859, 1461, 753 cm^{-1}; ^1H NMR δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.31-1.46 (m, 4H), 1.62 (quint, *J* = 7.1 Hz, 2H), 2.47 (t, *J* = 7.1 Hz, 2H), 3.46 (s, 1H), 7.14 (ddd, *J* = 1.1, 7.6, 7.6 Hz, 1H), 7.36 (ddd, *J* = 1.4, 7.7, 7.7 Hz, 1H), 7.42 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.68 (dd, *J* = 0.8, 8.1 Hz, 1H); ^{13}C NMR δ 13.9, 20.3, 22.2, 28.3, 31.1, 63.4, 79.7, 84.4, 101.8, 118.6, 125.2, 125.4, 129.5, 132.8, 137.8; HRMS (ESI positive) m/z calcd for $C_{15}H_{17}S$ ($[M+H]^+$): 229.1046. Found: 229.1045.



(Hept-1-yn-1-yl)(2-(phenylethynyl)phenyl)sulfoxide (5)

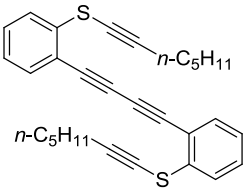
Sulfoxide **5** was prepared by the oxidation of the corresponding sulfide[14] using *m*CPBA**.**

A pale yellow oil; IR (CH_2Cl_2) 2955, 2350, 2312, 1492, 1463, 1081 cm^{-1}; ^1H NMR δ 0.78 (t, J = 7.3 Hz, 3H), 1.15-1.29 (m, 4H), 1.44-1.50 (m, 2H), 2.34 (dt, J_d = 2.6 Hz, J_t = 7.2 Hz, 2H), 7.37-7.40 (m, 3H), 7.50 (ddd, J = 1.2, 7.5, 7.5 Hz, 1H), 7.55-7.61 (m, 4H), 8.05 (dd, J = 1.6, 7.9 Hz, 1H); ^{13}C NMR δ 13.8, 19.8, 22.1, 27.3, 30.9, 77.7, 84.3, 98.6, 104.8, 120.4, 122.5, 124.1, 128.6, 129.2, 129.4, 130.9, 131.7, 132.6, 145.5; HRMS (ESI positive) m/z calcd for $C_{21}H_{20}NaOS$ ($[M+Na]^+$): 343.1127. Found: 343.1126.



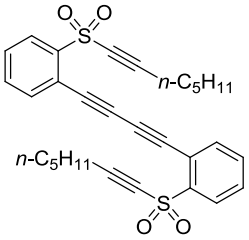
(2-Ethynylphenyl)(hept-1-ynyl)sulfone (7)

A brown oil; IR (CH_2Cl_2) 3267, 2200, 1163, 1126, 792 cm^{-1}; ^1H NMR δ 0.87 (t, J = 7.2 Hz, 3H), 1.25-1.38 (m, 4H), 1.55-1.61 (m, 2H), 2.40 (t, J = 7.1 Hz, 2H), 3.66 (s, 1H), 7.54 (ddd, J = 1.3, 7.8, 7.8 Hz, 1H), 7.61 (ddd, J = 1.3, 7.8, 7.8 Hz, 1H), 7.72 (dd, J = 1.2, 7.6 Hz, 1H), 8.10 (dd, J = 1.1, 7.9 Hz, 1H); ^{13}C NMR δ 14.8, 20.0, 23.0, 27.7, 31.9, 78.2, 79.9, 88.3, 98.7, 122.3, 129.2, 130.0, 134.3, 136.6, 143.7; HRMS (ESI positive) m/z calcd for $C_{15}H_{16}O_2NaS$ ($[M+Na]^+$): 283.0763. Found: 283.0762.



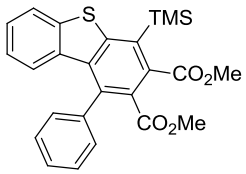
1,4-Bis(2-(hept-1-ynylsulfanyl)phenyl)buta-1,3-diyne (9)

A brown solid; mp 35 °C; IR (CH_2Cl_2) 2858, 2359, 1434, 752 cm^{-1}; ^1H NMR δ 0.92 (t, J = 7.4 Hz, 6H), 1.32-1.46 (m, 8H), 1.62 (quint, 7.3 Hz, 4H), 2.48 (t, J = 7.0 Hz, 4H), 7.15 (ddd, J = 1.0, 7.4, 7.4 Hz, 2H), 7.38 (ddd, J = 1.1, 7.7, 7.7 Hz, 2H), 7.47 (dd, J = 1.3, 7.8 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 13.9, 20.3, 22.1, 28.2, 31.0, 63.6, 79.6, 80.3, 101.9, 118.2, 125.3, 125.5, 129.9, 133.3, 139.1; HRMS (ESI positive) m/z calcd for $C_{30}H_{30}NaS_2$ ($[M+Na]^+$): 477.1681. Found: 477.1682.



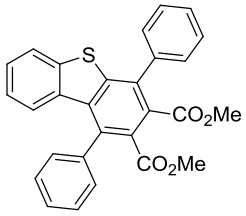
1,4-Bis(2-(hept-1-ynylsulfonyl)phenyl)buta-1,3-diyne (11)

A brown solid; mp 115 °C; IR (CH_2Cl_2) 2198, 1331, 1160, 766 cm^{-1}; ^1H NMR δ 0.83 (t, *J* = 7.3 Hz, 6H), 1.24-1.38 (m, 8H), 1.64 (quint, 7.1 Hz, 4H), 2.52 (t, *J* = 7.2 Hz, 4H), 7.57 (ddd, *J* = 1.3, 7.8, 7.8 Hz, 2H), 7.64 (ddd, *J* = 1.3, 7.6, 7.6 Hz, 2H), 7.76 (dd, *J* = 1.0, 7.7 Hz, 2H), 8.12 (dd, *J* = 1.0, 7.9 Hz, 2H); ^{13}C NMR δ 14.8, 20.0, 23.0, 27.8, 32.0, 77.9, 80.3, 83.8, 99.9, 121.7, 129.3, 130.5, 134.3, 136.7, 144.5; HRMS (ESI positive) m/z calcd for $C_{30}H_{30}O_4NaS_2$ ($[M+Na]^+$): 541.1478. Found: 541.1478.



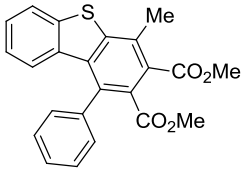
2,3-Bis(methoxycarbonyl)-1-phenyl-4-(trimethylsilyl)dibenzothiophene (3aa)

A brown solid; mp 135 °C; IR (CH_2Cl_2) 2849, 1734, 885, 841, 701 cm^{-1}; ^1H NMR δ 0.56 (s, 9H), 3.47 (s, 3H), 3.88 (s, 3H), 6.67 (d, *J* = 8.4 Hz, 1H), 7.02 (ddd, *J* = 1.0, 8.3, 8.3 Hz, 1H), 7.33-7.37 (m, 3H), 7.50-7.51 (m, 3H), 7.81 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR δ 0.8, 52.0, 52.6, 121.9, 124.0, 125.4, 126.9, 128.3, 128.7, 129.0, 129.9, 132.2, 133.5, 134.3, 135.4, 137.3, 137.8, 140.1, 148.0, 168.9, 169.8; HRMS (ESI positive) m/z calcd for $C_{25}H_{24}O_4NaSSi$ ($[M+Na]^+$): 471.1057. Found: 471.1055.



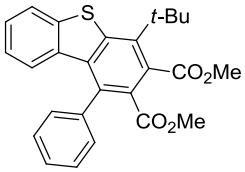
2,3-Bis(methoxycarbonyl)-1,4-diphenyldibenzothiophene (3ba)

A yellow solid; mp 178 °C; IR (CH_2Cl_2) 2849, 1739, 744, 701 cm^{-1}; ^1H NMR δ 3.52 (s, 3H), 3.56 (s, 3H), 6.72 (d, *J* = 8.4 Hz, 1H), 7.05 (ddd, *J* = 1.1, 7.8, 7.8 Hz, 1H), 7.33 (ddd, *J* = 1.1, 7.3, 7.3 Hz, 1H) 7.42-7.54 (m, 10H), 7.72 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR δ 52.2, 52.3, 122.5, 124.3, 125.6, 127.1, 128.4, 128.5, 128.6, 128.6, 128.7, 128.7, 129.3, 130.6, 134.7, 135.3, 135.4, 136.4, 137.6, 138.4, 141.2, 143.2, 168.1, 168.4; HRMS (ESI positive) m/z calcd for $C_{28}H_{20}NaO_4S$ ($[M+Na]^+$): 475.0975. Found: 475.0974.



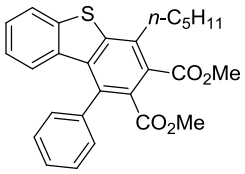
2,3-Bis(methoxycarbonyl)-4-methyl-1-phenyldibenzothiophene (3ca)

A yellow solid; mp 150 °C; IR (CH_2Cl_2) 2850, 1732, 1216, 742, 701 cm^{-1}; ^1H NMR δ 2.74 (s, 3H), 3.50 (s, 3H), 3.93 (s, 3H), 6.68 (d, *J* = 8.3 Hz, 1H), 7.06 (ddd, *J* = 1.1, 7.8, 7.8 Hz, 1H), 7.35-7.39 (m, 3H), 7.50-7.52 (m, 3H), 7.85 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR δ 19.9, 53.1, 53.7, 123.7, 125.4, 126.6, 128.0, 129.0, 129.3, 129.7, 130.4, 131.6, 131.9, 135.4, 136.2, 136.8, 138.8, 141.3, 143.9, 169.3, 169.7; HRMS (ESI positive) m/z calcd for $C_{23}H_{18}NaO_4SSi$ ($[M+Na]^+$): 413.0818. Found: 413.0818.



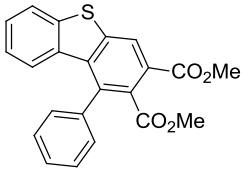
4-(1,1-Dimethylethyl)-2,3-bis(methoxycarbonyl)-1-phenyldibenzothiophene (3da)

A yellow solid; mp 170 °C; IR (CH_2Cl_2) 2951, 1734, 1216, 750, 708 cm^{-1}; ^1H NMR δ 1.30 (s, 9H), 3.91 (s, 3H), 4.04 (s, 3H), 5.74 (d, *J* = 8.5 Hz, 1H), 6.90 (ddd, *J* = 1.2, 7.8, 7.8 Hz, 1H), 7.28 (ddd, *J* =1.1, 7.6, 7.6 Hz, 1H), 7.35-7.36 (m, 2H), 7.50-7.56 (m, 3H), 7.74 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR δ 35.1, 40.1, 53.7, 53.9, 123.1, 124.8, 125.8, 127.0, 127.6, 129.4, 129.8, 131.8, 134.2, 136.4, 138.0, 138.8, 142.0, 142.7, 143.4, 144.5, 168.8, 172.1; HRMS (ESI positive) m/z calcd for $C_{26}H_{24}NaO_4SSi$ ($[M+Na]^+$): 455.1288. Found: 455.1285.



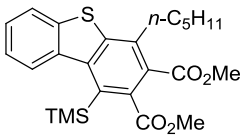
2,3-Bis(methoxycarbonyl)-4-pentyl-1-phenyldibenzothiophene (3ea)

A yellow oil; IR (CH_2Cl_2) 2853, 1101, 741, 701 cm^{-1}; ^1H NMR δ 0.94 (t, *J* = 7.1 Hz, 3H), 1.39-1.50 (m, 4H), 1.79-1.86 (m, 2H), 2.89 (t, *J* = 8.1 Hz, 2H), 3.49 (s, 3H), 3.91 (s, 3H), 6.67 (d, *J* = 8.4 Hz, 1H), 7.04 (ddd, *J* = 1.0, 8.3, 8.3 Hz, 1H), 7.35-7.38 (m, 3H), 7.50-7.51 (m, 3H), 7.83 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR δ 13.9, 22.3, 29.2, 32.1, 33.5, 52.0, 52.5, 122.5, 124.2, 125.4, 126.9, 127.7, 128.2, 128.5, 129.3, 130.6, 134.5, 135.2, 135.6, 135.7, 137.8, 140.1, 142.4, 168.3, 168.6; HRMS (ESI positive) m/z calcd for $C_{27}H_{26}NaO_4S$ ($[M+Na]^+$): 469.1444. Found: 469.1443.



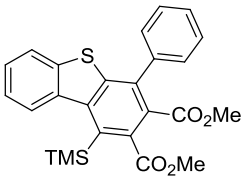
2,3-Bis(methoxycarbonyl)-1-phenyldibenzothiophene (3fa)

A brown solid; mp 175 °C; IR (CH_2Cl_2) 2851, 1726, 770, 701 cm^{-1}; ^1H NMR δ 3.57 (s, 3H), 3.95 (s, 3H), 6.60 (d, *J* = 8.3 Hz, 1H), 7.70 (ddd, *J* = 0.9, 7.7, 7.7 Hz, 1H), 7.37-7.40 (m, 3H), 7.51-7.53 (m, 3H), 7.83 (d, *J* = 8.0 Hz, 1H), 8.57 (s, 1H); ^{13}C NMR δ 52.0, 52.6, 122.6, 124.1, 124.3, 124.6, 125.6, 127.4, 128.5, 128.6, 129.4, 132.5, 134.6, 136.5, 136.7, 136.8, 140.1, 141.3, 165.7, 168.8; HRMS (ESI positive) m/z calcd for $C_{22}H_{16}NaO_4S$ ($[M+Na]^+$): 399.0662. Found: 399.0660.



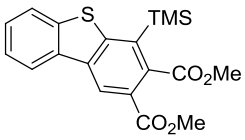
2,3-Bis(methoxycarbonyl)-4-pentyl-1-(trimethylsilyl)dibenzothiophene (3ga)

A yellow oil; IR (CH_2Cl_2) 2859, 1726, 1436, 842, 763 cm^{-1}; ^1H NMR δ 0.46 (s, 9H), 0.92 (t, *J* = 7.2 Hz, 3H), 1.36-1.47 (m, 4H), 1.72-1.79 (m, 2H), 2.94 (t, *J* = 8.2 Hz, 2H), 3.89 (s, 3H), 3.91 (s, 3H), 7.41 (ddd, *J* = 1.1, 7.1, 7.1 Hz, 1H), 7.45 (ddd, *J* = 1.1, 7.2, 7.2 Hz, 1H), 7.84 (d, *J* = 7.5 Hz, 1H), 8.32 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR δ 2.2, 14.0, 22.3, 29.1, 32.1, 33.6, 52.5, 52.5, 122.7, 123.3, 127.0, 127.3, 129.3, 134.8, 135.8, 136.5, 136.6, 140.0, 142.3, 142.4, 169.4, 170.0; HRMS (ESI positive) m/z calcd for $C_{24}H_{30}NaO_4SSi$ ($[M+Na]^+$): 465.1526. Found: 465.1527.



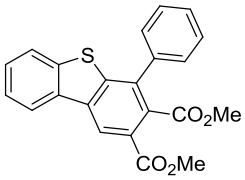
2,3-Bis(methoxycarbonyl)-4-phenyl-1-(trimethylsilyl)dibenzothiophene (3ha)

A white solid; mp 171 °C; IR (CH_2Cl_2) 2899, 1730, 882, 850, 847 cm^{-1}; ^1H NMR δ 0.52 (s, 9H), 3.58 (s, 3H), 3.91 (s, 3H), 7.43-7.50 (m, 7H), 7.75-7.77 (m, 1H), 8.36-8.38 (m, 1H); ^{13}C NMR δ 2.1, 52.3, 52.6, 122.6, 123.4, 127.1, 127.4, 128.6, 128.6, 128.7, 129.7, 135.7, 136.2, 136.3, 136.4, 138.0, 141.1, 142.3, 143.2, 169.0, 169.8; HRMS (ESI positive) m/z calcd for $C_{25}H_{24}NaO_4SSi$ ($[M+Na]^+$): 471.1057. Found: 471.1056.



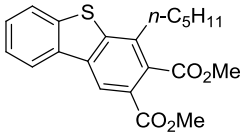
2,3-Bis(methoxycarbonyl)-4-(trimethylsilyl)dibenzothiophene (3la)

A brown oil; IR (CH_2Cl_2) 2850, 1727, 861, 843 cm^{-1}; ^1H NMR δ 0.53 (s, 9H), 3.96 (s, 3H), 3.96 (s, 3H), 7.49-7.54 (m, 2H), 7.88 (dd, *J* = 1.7, 7.7 Hz, 1H), 8.23 (dd, *J* = 1.7, 5.8 Hz, 1H), 8.78 (s, 1H); ^{13}C NMR δ 0.0, 52.1, 52.1, 121.4, 121.8, 123.7, 123.8, 124.4, 127.2, 131.6, 133.6, 134.7, 138.2, 139.3, 149.7, 166.2, 170.0; HRMS (ESI positive) m/z calcd for $C_{19}H_{20}NaO_4SSi$ ($[M+Na]^+$): 395.0744. Found: 395.0745.



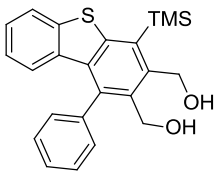
2,3-Bis(methoxycarbonyl)-4-phenyldibenzothiophene (3ma)

A yellow solid; mp 128 °C; IR (CH_2Cl_2) 2851, 1727, 741, 701 cm^{-1}; ^1H NMR δ 3.66 (s, 3H), 3.99 (s, 3H), 7.46-7.54 (m, 7H), 7.80 (dd, *J* = 2.6, 8.3 Hz, 1H), 8.27 (dd, *J* = 1.9, 6.1 Hz, 1H), 8.80 (s, 1H); ^{13}C NMR δ 52.4, 52.7, 122.7, 122.5, 122.8, 124.8, 125.1, 127.8, 128.7, 128.8, 128.9, 132.4, 135.1, 135.2, 135.8, 137.2, 140.6, 145.5, 166.4, 168.9; HRMS (ESI positive) m/z calcd for $C_{22}H_{16}NaO_4S$ ($[M+Na]^+$): 399.0662. Found: 399.0662.



2,3-Bis(methoxycarbonyl)-4-pentyldibenzothiophene (3na)

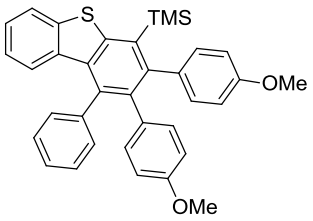
A yellow oil; IR (CH_2Cl_2) 2860, 1725, 1110, 741 cm^{-1}; ^1H NMR δ 0.92 (t, *J* = 7.1 Hz, 3H), 1.36-1.45 (m, 4H), 1.74-1.80 (m, 2H), 2.89 (t, *J* = 8.3 Hz, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 7.50-7.54 (m, 2H), 7.88-7.90 (m, 1H), 8.21-8.23 (m, 1H), 8.66 (s, 1H); ^{13}C NMR δ 13.9, 22.2, 28.8, 32.0, 33.3, 52.5, 52.5, 121.3, 122.2, 122.8, 124.7, 124.9, 127.6, 131.9, 134.9, 135.2, 135.7, 139.7, 144.4, 166.4, 169.6; HRMS (ESI positive) m/z calcd for $C_{21}H_{22}NaO_4S$ ($[M+Na]^+$): 393.1131. Found: 393.1131.



2,3-Bis(hydroxymethyl)-1-phenyl-4-(trimethylsilyl)dibenzothiophene (3ab)

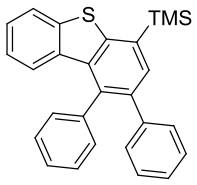
A white solid; mp 181 °C; IR (CH_2Cl_2) 3341, 2853, 840, 736, 703 cm^{-1}; ^1H NMR δ 0.67 (s, 9H), 2.96 (brs, 1H), 3.44 (brs, 1H), 4.65 (s, 2H), 5.08 (s, 2H), 6.39 (d, *J* = 8.3 Hz, 1H), 6.96 (ddd, *J* = 1.1, 7.8, 7.8 Hz, 1H), 7.29 (ddd, *J* = 1.1, 7.5, 7.5 Hz, 1H), 7.32-7.34 (m, 2H), 7.55-7.56 (m, 3H), 7.78 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR δ 3.1, 60.0, 62.8, 121.8, 123.6, 124.8, 125.9, 128.0, 129.1, 129.2, 132.8, 133.8, 134.8, 134.8,

139.4, 139.7, 140.6, 144.2, 146.4; HRMS (ESI positive) m/z calcd for $C_{23}H_{24}NaO_2SSi$ ($[M+Na]^+$): 415.1158. Found: 415.1157.



2,3-Bis(4-methoxyphenyl)-1-phenyl-4-(trimethylsilyl)dibenzothiophene (3ac)

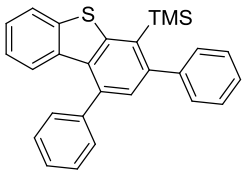
A brown solid; mp 210 °C; IR (CH_2Cl_2) 2853, 1245, 756, 734 cm^{-1}; ^1H NMR δ 0.18 (s, 9H), 3.61 (s, 3H), 3.74 (s, 3H), 6.39 (d, *J* = 8.2 Hz, 2H), 6.49 (d, *J* = 8.2 Hz, 1H), 6.63 (ddd, *J* = 0.6, 8.9, 8.9 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.96 (ddd, *J* = 1.1, 7.2, 7.2 Hz, 1H), 7.12 (dd, *J* = 1.7, 7.9 Hz, 2H), 7.22-7.26 (m, 3H), 7.29 (ddd, *J* = 0.9, 7.6, 7.6 Hz, 1H), 7.82 (d, 7.7 Hz, 1H); ^{13}C NMR δ 2.6, 55.9, 56.2, 113.0, 113.4, 122.8, 124.5, 126.0, 126.7, 127.8, 129.3, 131.0, 133.0, 133.2, 133.3, 133.4, 136.4, 136.7, 139.6, 140.0, 140.7, 141.3, 146.4, 147.9, 157.9, 159.2 (a pair of peaks at the aromatic region was overlapped); HRMS (ESI positive) m/z calcd for $C_{35}H_{32}NaO_2SSi$ ($[M+Na]^+$): 567.1784. Found: 567.1785.



1,2-Diphenyl-4-(trimethylsilyl)dibenzothiophene (3ad)

NOESY correlation was observed between TMS and C-H on dibenzothiophene ring (Figure 4).

A white solid; mp 160 °C; IR (CH_2Cl_2) 2853, 884, 839, 743, 699 cm^{-1}; ^1H NMR δ 0.53 (s, 9H), 6.67 (d, *J* = 8.3 Hz, 1H), 6.99 (ddd, *J* = 1.1, 7.7, 7.7 Hz, 1H), 7.13-7.18 (m, 5H), 7.21-7.23 (m, 2H), 7.29-7.34 (m, 4H) 7.60 (s, 1H), 7.82 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR δ 0.0, 123.3, 124.7, 126.3, 126.9, 127.2, 128.4, 128.5, 129.5, 131.3, 133.7, 133.8, 135.3, 136.7, 138.9, 139.2, 140.6, 141.0, 142.6, 145.7 (a pair of peaks at the aromatic region was overlapped); HRMS (ESI positive) m/z calcd for $C_{27}H_{24}NaSSi$ ($[M+Na]^+$): 431.1260. Found: 431.1262.



1,3-Diphenyl-4-(trimethylsilyl)dibenzothiophene (4ad)

NOESY correlation was observed between TMS and C-H on benzene ring (Figure 4).

A white solid; mp 214 °C; IR (CH_2Cl_2) 2850, 839, 742, 701, 699 cm^{-1}; ^1H NMR δ 0.21 (s, 9H), 7.05 (ddd, *J* = 1.1, 7.6, 7.6 Hz, 1H), 7.14-7.16 (m, 2H), 7.32 (ddd, *J* = 1.1, 7.6, 7.6 Hz, 1H), 7.33-7.37 (m, 5H), 7.48-7.49 (m, 5H), 7.83 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR δ 1.4, 121.9, 123.5, 124.8, 125.9, 127.2, 127.7, 128.6, 129.0, 129.4, 129.6, 130.6, 131.0, 134.7, 139.0, 139.4, 141.1, 144.5, 147.1, 147.5 (a pair of peaks at the aromatic region was overlapped); HRMS (ESI positive) m/z calcd for $C_{27}H_{25}SSi$ ($[M+H]^+$): 409.1441. Found: 409.1438.

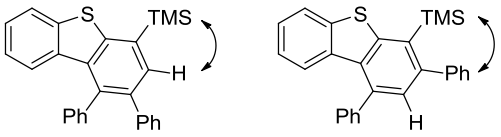
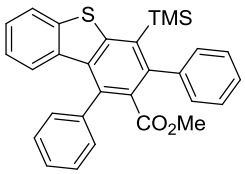


Figure 4. NOESY experiment on **3ad** and **4ad**



2-(Methoxycarbonyl)-1,3-diphenyl-4-(trimethylsilyl)dibenzothiophene (3ae)

NOESY correlation was observed between TMS and C-H on benzene ring, which is not observed in regioisomer (Figure 5).

A white solid; mp 174 °C; IR (CH_2Cl_2) 2852, 1733, 884, 840, 763, 701 cm^{-1}; ^1H NMR δ 0.17 (s, 9H), 3.09 (s, 3H), 6.60 (d, *J* = 8.3 Hz, 1H), 7.02 (ddd, *J* = 1.1, 7.7, 7.7 Hz, 1H), 7.32-7.34 (m, 6H), 7.41-7.43 (m, 2H), 7.47-7.49 (m, 3H) 7.82 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR δ 1.2, 51.2, 121.9, 123.7, 124.9, 126.2, 127.4, 127.7, 128.2, 128.6, 129.3, 130.3, 131.3, 132.1, 133.3, 134.7, 135.7, 138.1, 139.6, 141.0, 143.3, 147.2, 169.3; HRMS (ESI positive) m/z calcd for $C_{29}H_{26}NaO_2SSi$ ($[M+Na]^+$): 489.1315. Found: 489.1316.

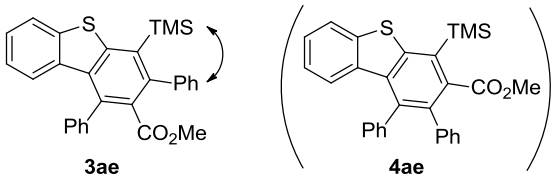
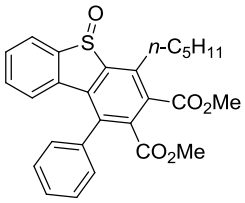
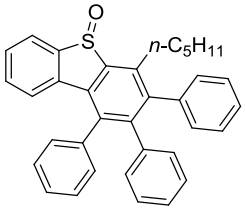


Figure 5. NOESY experiment on **3ea** and the structure of regioisomer **4ae**



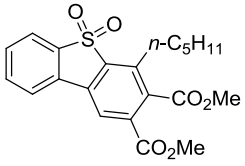
2,3-Bis(methoxycarbonyl)-4-pentyl-1-phenyldibenzothiophene-5-oxide (6a)

A yellow oil; IR (CH_2Cl_2) 2925, 2853, 1737, 1436, 1038, 702 cm^{-1}; ^1H NMR δ 0.93 (t, *J* = 7.3 Hz, 3H), 1.37-1.52 (m, 4H), 1.74-1.90 (m, 2H), 3.17-3.23 (m, 1H), 3.37-3.43 (m, 1H), 3.48 (s, 3H), 3.90 (s, 3H), 6.35 (d, *J* = 8.0 Hz, 1H), 7.18 (ddd, *J* = 1.0, 8.2, 8.2 Hz, 1H), 7.26-7.28 (m, 1H), 7.31-7.33 (m, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.47-7.52 (m, 3H), 7.94 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR δ 14.0, 22.4, 31.2, 31.4, 32.2, 52.4, 52.9, 126.0, 127.4, 128.9, 129.0, 129.1, 129.2, 129.9, 131.5, 132.4, 135.3, 136.2, 136.3, 137.2, 139.0, 143.1, 145.3, 145.9, 167.1, 167.5; HRMS (ESI positive) m/z calcd for $C_{27}H_{26}NaO_5S$ ($[M+Na]^+$): 485.1393. Found: 485.1395.



4-Pentyl-1,2,3-triphenyldibenzothiophene-5-oxide (6f)

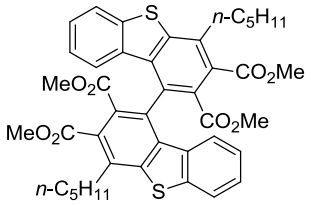
A white solid; mp 150 °C; IR (CH_2Cl_2) 2926, 1465, 1442, 1033 cm^{-1}; ^1H NMR δ 0.77 (t, *J* = 7.1 Hz, 3H), 1.15-1.25 (m, 4H), 1.61-1.67 (m, 2H), 2.79-2.85 (m, 1H), 3.10-3.16 (m, 1H), 6.23 (d, *J* = 7.9 Hz, 1H), 6.71-6.75 (m, 2H), 6.79-6.87 (m, 3H), 7.01-7.03 (m, 1H), 7.06-7.18 (m, 7H), 7.20-7.25 (m, 3H), 7.35 (ddd, *J* = 0.5, 7.5, 7.5 Hz, 1H), 7.83 (dd, *J* = 0.6, 7.7 Hz, 1H); ^{13}C NMR δ 13.9, 22.1, 30.7, 31.3, 32.1, 125.5, 125.9, 126.7, 126.8, 126.8, 127.3, 127.5, 127.5, 127.6, 128.4, 128.6, 128.7, 130.0, 130.0, 130.2, 130.5, 130.5, 130.6, 132.0, 134.3, 136.8, 138.0, 138.6, 138.6, 138.9, 142.2, 143.0, 143.1, 145.1, 146.9; HRMS (ESI positive) m/z calcd for $C_{35}H_{30}NaOS$ ($[M+Na]^+$): 521.1910. Found: 521.1915.



2,3-Bis(methoxycarbonyl)-4-pentyldibenzothiophene-5,5-dioxide (8)

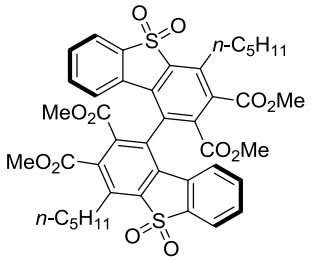
A white solid; mp 140 °C; IR (CH_2Cl_2) 1733, 1151, 1101, 819 cm^{-1}; ^1H NMR δ 0.93 (t, *J* = 7.2 Hz, 3H), 1.36-1.49 (m, 4H), 1.76-1.82 (m, 2H), 3.00 (t, *J* = 8.5 Hz, 2H), 3.96 (s, 3H), 3.97 (s, 3H), 7.57 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.66 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 8.19 (s, 1H); ^{13}C NMR δ 14.9, 23.2, 30.9, 32.0, 33.2, 53.9, 54.2, 121.6, 123.1, 123.1, 130.8, 132.2, 133.8, 134.3,

135.2, 138.5, 139.1, 140.4, 140.6, 165.9, 168.7; HRMS (ESI positive) m/z calcd for $C_{21}H_{22}NaO_6S$ ($[M+Na]^+$): 425.1029. Found: 425.1028.



2,2',3,3'-Tetrakis(methoxycarbonyl)-4,4'-dipentyl-1,1'-bidibenzothiophene (10)

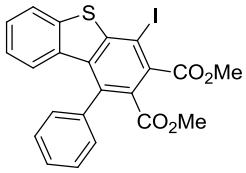
A brown solid; mp 115 ℃; IR (CH_2Cl_2) 2857, 1736, 1116, 739 cm^{-1}; ^1H NMR δ 0.97 (t, *J* = 7.2 Hz, 6H), 1.43-1.54 (m, 8H), 1.87-1.96 (m, 4H), 3.09-3.15 (m, 2H), 3.21-3.27 (m, 2H), 3.39 (s, 6H), 3.88 (s, 6H), 6.30 (d, *J* = 8.3 Hz, 2H), 6.88 (ddd, *J* = 1.1, 7.8, 7.8 Hz, 2H), 7.25 (ddd, *J* = 1.1, 7.6, 7.6 Hz, 2H), 7.75 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR δ 14.0, 22.4, 29.3, 31.9, 33.6, 52.0, 52.5, 122.4, 124.4, 124.8, 127.0, 129.2, 129.4, 131.5, 135.0, 135.2, 136.5, 139.9, 143.3, 167.2, 168.2; HRMS (ESI positive) m/z calcd for $C_{42}H_{42}NaO_8S_2$ ($[M+Na]^+$): 761.2213. Found: 761.2205. $[\alpha]^{26}_D$ 6.3 (*c* 0.2, CHCl3, 82% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4 x 250 mm, 254 nm UV detector, rt, eluent: 1% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 26.3 min for major isomer and 22.1 min for minor isomer).



2,2',3,3'-Tetrakis(methoxycarbonyl)-4,4'-dipentyl-1,1'-bidibenzothiophene-5,5,5',5'-tetraoxide (12)

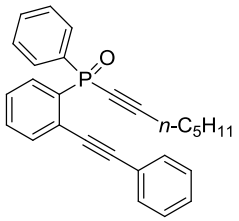
A brown solid; mp 204 °C; IR (CH_2Cl_2) 1739, 1310, 1162, 739 cm^{-1}; ^1H NMR δ 0.96 (t, *J* = 7.2 Hz, 6H), 1.39-1.53 (m, 8H), 1.82-1.87 (m, 4H), 3.22-3.31 (m, 2H), 3.33-3.37 (m, 2H), 3.51 (s, 6H), 3.89 (s, 6H), 6.42 (d, *J* = 8.1 Hz, 2H), 7.31 (ddd, *J* = 1.2, 7.8, 7.8 Hz, 2H), 7.64 (ddd, *J* = 0.8, 7.6, 7.6 Hz, 2H), 7.79 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR δ 15.0, 23.3, 30.8, 32.3, 33.1, 53.9, 54.1, 123.2, 125.1, 130.1, 130.2, 132.3, 133.9, 135.7, 136.2, 139.1, 139.2, 140.1, 142.7, 166.4, 167.1; HRMS (ESI positive) m/z calcd for $C_{42}H_{42}NaO_{12}S_2$ ($[M+Na]^+$): 825.2010. Found: 825.2002. $[\alpha]^{26}_D$ -52.1 (*c* 0.5, CHCl3, 97% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4 x 250 mm, 254 nm UV detector, rt, eluent: 10% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 17.7 min for major isomer and 21.7 min for minor isomer). The crystal data of **12**: $C_{42}H_{42}O_{12}S_2$, *M*=802.91, triclinic, space group P1 (#1), a = 9.4846(3) Å, b = 11.7163(3) Å, c = 18.1232(5) Å, α = 82.456(2) °, β = 80.977(2) °, γ = 85.287(2) °, V = 1967.89(9) $Å^3$, *T*=173 K, *Z*=2, μ(Cu Kα) 17.688 cm^{-1}; number of reflections measured:

total 23163 and unique 11998, *R1*=0.0552, *wR2*=0.1385, Flack parameter (Friedel pairs = 4945) 0.030(13). CCDC 1010885.



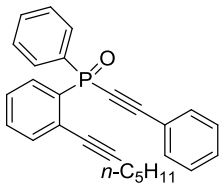
4-Iodo-2,3-bis(methoxycarbonyl)-1-phenyldibenzothiophene (13)

A chloroform solution (0.25 mL) of 2,3-bis(methoxycarbonyl)-1-phenyl-4-trimethylsilyldibenzothiophene (**3aa**) (22.4 mg, 0.05 mmol) and ICl (9.0 mg, 0.06 mmol) was stirred under reflux for 6 h. The resulting mixture was concentrated under reduced pressure. Diethyl ether was added and the solution was treated with sat. $Na_2S_2O_3$. The almost colourless organic phase was separated. The solvent was removed in vacuo to afford crude products which were purified by flash column chromatography on silica gel to give 4-iodo-2,3-bis(methoxycarbonyl)-1-phenyldibenzothiophene (**13**) (18 mg, 72 %): a white solid; mp 172 °C; IR (CH_2Cl_2) 2850, 1735, 1206, 701 cm^{-1}; ^1H NMR δ 3.49 (s, 3H), 3.97 (s, 3H), 6.61 (d, J = 8.4 Hz, 1H), 7.07 (dt, J_d = 1.0 Hz, J_t = 7.7 Hz, 1H), 7.34-7.36 (m, 2H), 7.40 (ddd, J = 0.8, 7.2, 7.2 Hz, 1H), 7.49-7.55 (m, 3H), 7.84 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ 51.8, 52.5, 86.7, 122.0, 124.1, 125.8, 126.9, 128.1, 128.3, 128.5, 129.7, 133.2, 134.6, 135.8, 136.7, 137.0, 139.3, 149.4, 166.6, 167.3; HRMS (ESI positive) m/z calcd for $C_{22}H_{15}INaO_4S$ ($[M+Na]^+$): 524.9628. Found: 524.9628.



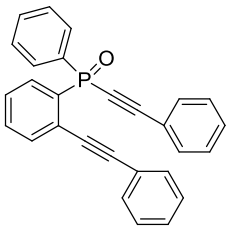
Hept-1-yn-1-yl(phenyl)(2-(phenylethynyl)phenyl)phosphine oxide (14a)

A pale yellow oil; IR (CH_2Cl_2) 2924, 2193, 1438, 1201, 758, 691 cm^{-1}; ^1H NMR δ 0.80 (t, J = 7.3 Hz, 3H), 1.17-1.30 (m, 4H), 1.45-1.50 (m, 2H), 2.34 (dt, J_d = 3.6 Hz, J_t = 7.2 Hz, 2H), 7.22-7.61 (m, 11H), 7.81-7.85 (m, 2H), 8.26-8.31 (m, 1H); ^{13}C NMR δ 13.9, 19.9, 19.9, 22.1, 27.3, 27.3, 31.1, 73.8, 75.2, 87.7, 87.7, 97.5, 109.2, 109.5, 122.8, 125.6, 125.6, 128.0, 128.1, 128.3, 128.3, 128.4, 128.7, 131.0, 131.1, 131.4, 131.9, 131.9, 132.0, 132.0, 132.7, 133.1, 133.4, 133.4, 133.6, 133.7, 133.7, 134.1; ^{31}P NMR δ 5.9; HRMS (ESI positive) m/z calcd for $C_{27}H_{25}NaOP$ ($[M+Na]^+$): 419.1535. Found: 419.1527.



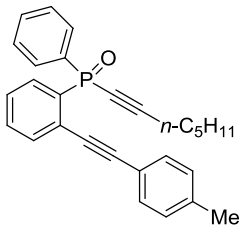
(2-(Hept-1-yn-1-yl)phenyl)(phenyl)(phenylethynyl)phosphine oxide (14b)

A yellow oil; IR (CH_2Cl_2) 2924, 2175, 1436, 846, 691, 436 cm^{-1}; ^1H NMR δ 0.80-0.82 (m, 3H), 1.17-1.18 (m, 4H), 1.28-1.30 (m, 2H), 2.12 (t, J = 7.2 Hz, 2H), 7.35-7.60 (m, 11H), 7.84-7.88 (m, 2H), 8.26-8.31 (m, 1H); ^{13}C NMR δ 13.8, 19.6, 22.1, 27.7, 31.1, 78.7, 78.8, 82.0, 83.4, 100.0, 104.3, 104.5, 120.4, 120.4, 126.5, 126.6, 127.3, 127.4, 128.2, 128.3, 128.5, 130.4, 130.8, 130.9, 131.8, 131.9, 132.1, 132.5, 132.9, 132.9, 133.2, 133.2, 133.6, 133.7, 133.9; ^{31}P NMR δ 7.3; HRMS (ESI positive) m/z calcd for $C_{27}H_{25}NaOP$ ($[M+Na]^+$): 419.1535. Found: 419.1533.



Phenyl(phenylethynyl)(2-(phenylethynyl)phenyl)phosphine oxide (14c)

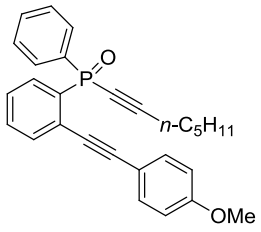
A pale yellow oil; IR (CH_2Cl_2) 2922, 2359, 1739, 1202, 690, 407 cm^{-1}; ^1H NMR δ 7.04-7.17 (m, 4H), 7.20-7.45 (m, 13H), 7.75-7.78 (m, 1H), 7.82-7.85 (m, 1H); ^{13}C NMR δ 81.9, 83.3, 87.6, 87.7, 88.9, 88.9, 97.2, 97.8, 120.2, 120.2, 122.3, 122.6, 122.7, 125.6, 125.7, 127.6, 128.1, 128.2, 128.2, 128.3, 128.4, 128.4, 128.5, 128.7, 128.7, 129.1, 129.2, 129.2, 130.4, 131.0, 131.0, 131.1, 131.4, 131.5, 131.9, 132.1, 132.2, 132.2, 132.6, 133.2, 133.3, 133.4, 133.4, 133.5, 133.6, 133.7, 133.7, 133.8, 133.8, 134.2, 134.6, 136.3; ^{31}P NMR δ 6.7; HRMS (ESI positive) m/z calcd for $C_{28}H_{19}NaOP$ ($[M+Na]^+$): 425.1066. Found: 425.1064.



Hept-1-yn-1-yl(phenyl)(2-(4-tolylethynyl)phenyl)phosphine oxide (14d)

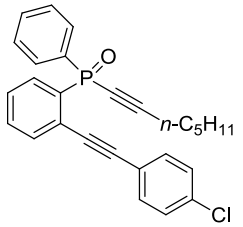
A pale yellow oil; IR (CH_2Cl_2) 2924, 2852, 2194, 1465, 1200, 538 cm^{-1}; ^1H NMR δ 0.81 (t, J = 7.1 Hz, 3H), 1.16-1.31 (m, 4H), 1.45-1.51 (m, 2H), 2.32-2.35 (m, 5H), 7.08-7.13 (m, 4H), 7.37-7.41 (m, 4H), 7.46-7.60 (m, 2H), 7.81-7.85 (m, 2H), 8.26-8.30 (m, 1H); ^{13}C NMR δ 13.9, 14.2, 19.9, 19.9, 21.6, 22.1, 27.3, 27.3, 29.8, 31.1, 68.1, 73.2, 80.3, 97.9, 119.8, 125.8, 127.0, 127.7, 127.9, 128.0, 128.2, 128.3, 128.4, 128.8, 129.0, 129.8, 130.6, 131.0, 131.1, 131.3, 131.9, 131.9, 132.0, 132.0, 133.3, 133.4, 133.6, 133.6,

134.1, 135.5, 138.9; ^{31}P NMR δ 5.9; HRMS (ESI positive) m/z calcd for $C_{28}H_{27}NaOP$ ($[M+Na]^+$): 433.1692. Found: 433.1692.



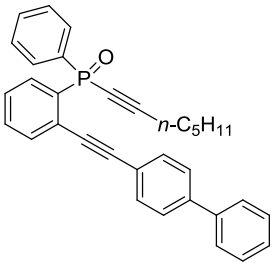
Hept-1-yn-1-yl(2-(4-methoxyphenylethynyl)phenyl)(phenyl)phosphine oxide (14e)

A pale yellow oil; IR (CH_2Cl_2) 2927, 2193, 1605, 1511, 1251, 1200 cm^{-1}; ^{1}H NMR δ 0.81 (t, J = 7.2 Hz, 3H), 1.19-1.50 (m, 6H), 2.33 (dt, J_d = 3.5 Hz, J_t = 7.2 Hz, 2H), 3.81 (s, 3H), 6.80-6.82 (m, 2H), 7.15-7.18 (m, 2H), 7.38-7.58 (m, 6H), 7.80-7.85 (m, 2H), 8.24-8.29 (m, 1H); ^{13}C NMR δ 13.9, 19.9, 19.9, 22.1, 27.3, 27.3, 31.1, 55.4, 55.4, 55.4, 55.4, 55.4, 73.8, 75.3, 86.6, 86.6, 97.8, 109.1, 109.3, 113.9, 114.0, 115.0, 126.0, 126.0, 127.7, 127.8, 128.3, 128.4, 131.0, 131.1, 131.9, 131.9, 132.0, 132.0, 132.4, 132.9, 133.1, 133.2, 133.3, 133.3, 133.4, 133.4, 133.5, 134.2, 160.0; ^{31}P NMR δ 6.1; HRMS (ESI positive) m/z calcd for $C_{28}H_{27}NaO_2P$ ($[M+Na]^+$): 449.1641. Found: 449.1641.



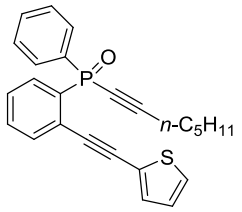
(2-(4-Chlorophenylethynyl)phenyl)(hept-1-yn-1-yl)(phenyl)phosphine oxide (14f)

A yellow oil; IR (CH_2Cl_2) 2928, 2193, 1583, 1491, 1201, 693, 535 cm^{-1}; ^{1}H NMR δ 0.82 (t, J = 7.1 Hz, 3H), 1.17-1.32 (m, 4H), 1.46-1.52 (m, 2H), 2.34 (dt, J_d = 3.5 Hz, J_t = 6.9 Hz, 2H), 7.13-7.16 (m, 2H), 7.25-7.27 (m, 2H), 7.38-7.42 (m, 2H), 7.47-7.61 (m, 4H), 7.78-7.83 (m, 2H), 8.22-8.27 (m, 1H); ^{13}C NMR δ 13.8, 19.8, 19.8, 22.0, 27.2, 30.9, 73.7, 88.5, 88.5, 96.2, 109.2, 109.5, 121.2, 125.1, 125.2, 128.1, 128.2, 128.3, 128.5, 130.9, 131.0, 131.9, 131.9, 132.0, 132.0, 132.5, 132.7, 132.9, 133.3, 133.4, 133.5, 133.5, 133.7, 133.9, 134.7; ^{31}P NMR δ 6.0; HRMS (ESI positive) m/z calcd for $C_{27}H_{24}ClNaOP$ ($[M+Na]^+$): 453.1146. Found: 453.1139.



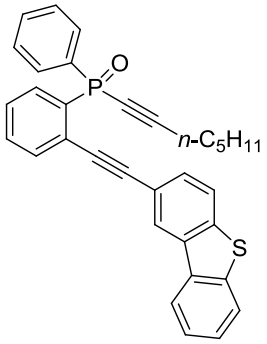
Hept-1-yn-1-yl(phenyl)(2-(4-phenylphenylethynyl)phenyl)phosphine oxide (14g)

A pale yellow oil; IR (CH_2Cl_2) 2928, 2193, 1488, 1200, 764, 697, 529 cm^{-1}; ^1H NMR δ 0.79 (t, J = 7.4 Hz, 3H), 1.15-1.32 (m, 4H), 1.47-1.53 (m, 2H), 2.36 (dt, J_d = 3.7 Hz, J_t = 7.2 Hz, 2H), 7.29-7.30 (m, 2H), 7.36-7.63 (m, 13H), 7.83-7.88 (m, 2H), 8.26-8.31 (m, 1H); ^{13}C NMR δ 13.8, 19.8, 19.9, 22.0, 27.3, 31.0, 73.8, 75.2, 88.4, 97.4, 109.2, 109.4, 121.6, 126.9, 127.0, 127.8, 128.0, 128.1, 128.3, 128.4, 128.9, 131.0, 131.1, 131.8, 131.9, 131.9, 132.0, 132.0, 132.6, 133.1, 133.3, 133.4, 133.6, 133.6, 133.6, 140.2, 141.4; ^{31}P NMR δ 6.0; HRMS (ESI positive) m/z calcd for $C_{33}H_{29}NaOP$ ($[M+Na]^+$): 495.1848. Found: 495.1852.



Hept-1-yn-1-yl(phenyl)(2-(thiophen-2-ylethynyl)phenyl)phosphine oxide (14h)

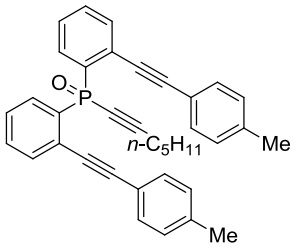
A pale yellow oil; IR (CH_2Cl_2) 2923, 2360, 2192, 1738, 1200, 694, 526 cm^{-1}; ^1H NMR δ 0.82 (t, J = 6.9 Hz, 3H), 1.19-1.26 (m, 2H), 1.28-1.34 (m, 2H), 1.48-1.56 (m, 2H), 2.38 (dt, J_d = 3.5 Hz, J_t = 7.2 Hz, 2H), 6.96-6.98 (m, 1H), 7.05-7.06 (m, 1H), 7.29-7.30 (m, 1H), 7.39-7.58 (m, 6H), 7.82-7.87 (m, 2H), 8.29-8.34 (m, 1H); ^{13}C NMR δ 13.8, 19.9, 19.9, 22.0, 27.2, 31.0, 73.4, 74.8, 90.9, 91.2, 91.3, 109.4, 109.7, 122.7, 125.0, 125.1, 127.1, 127.3, 127.9, 128.1, 128.2, 128.3, 128.4, 128.4, 128.6, 130.9, 131.0, 131.0, 131.1, 131.9, 131.9, 132.1, 132.1, 132.2, 132.6, 132.7, 132.9, 133.2, 133.3, 133.4, 133.6, 133.9; ^{31}P NMR δ 5.6; HRMS (ESI positive) m/z calcd for $C_{25}H_{23}NaOPS$ ($[M+Na]^+$): 425.1099. Found: 425.1098.



(2-(Dibenzo[*b,d*]thiophen-2-yl-ethynyl)phenyl)(hept-1-yn-1-yl)phenylphosphine oxide (14i)

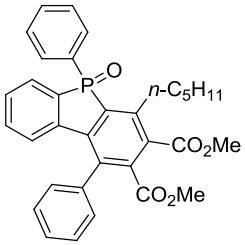
A pale yellow oil; IR (CH_2Cl_2) 2925, 2193, 1474, 1200, 764, 529 cm^{-1}; ^1H NMR δ 0.71 (t, J = 7.3 Hz, 3H), 1.07-1.14 (m, 2H), 1.20-1.26 (m, 2H), 1.43-1.49 (m, 2H), 2.31-2.35 (m, 2H), 7.31 (dd, J = 1.5, 8.3 Hz, 1H), 7.42-7.46 (m, 2H), 7.48-7.61 (m, 5H), 7.64-7.67 (m, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.84-7.90 (m, 3H), 7.94 (d, J = 1.0 Hz, 1H), 8.09-8.13 (m, 1H), 8.28-8.33 (m, 1H); ^{13}C NMR δ 13.8, 19.9, 19.9, 22.0, 27.3, 27.4, 31.0, 73.9, 75.4, 87.7, 87.8, 97.8, 109.3, 109.5, 118.9, 121.7, 122.7, 123.0, 124.7, 124.8, 125.6, 125.7, 127.3, 128.1, 128.2, 128.4, 128.5, 129.4, 131.1, 131.1, 132.0, 132.0, 132.1, 132.1, 132.6, 133.3, 133.5, 133.5, 133.6, 133.6, 134.3, 134.9, 135.6, 139.8, 140.0; ^{31}P NMR δ 6.0; HRMS (ESI positive) m/z

calcd for $C_{33}H_{27}NaOPS$ ($[M+Na]^+$): 525.1412. Found: 525.1414.



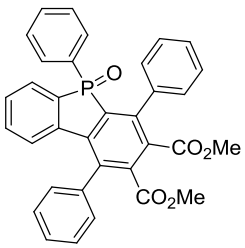
Hept-1-yn-1-yl-bis(2-(4-tolylethynyl)phenyl)phosphine oxide (17)

A yellow solid; mp 127 °C; IR (CH_2Cl_2) 2954, 2925, 2193, 1510, 1202, 817 cm^{-1}; ^1H NMR δ 0.77 (t, J = 7.0 Hz, 3H), 1.10-1.28 (m, 4H), 1.40-1.48 (m, 2H), 2.31 (dt, J_d = 3.6 Hz, J_t = 7.0 Hz, 2H), 2.35 (s, 6H), 7.08 (d, J = 8.1 Hz, 4H), 7.15 (d, J = 8.1 Hz, 4H), 7.28-7.32 (m, 2H), 7.41-7.45 (m, 2H), 7.53-7.56 (m, 2H), 8.23-8.28 (m, 2H); ^{13}C NMR δ 13.8, 19.9, 20.0, 21.6, 22.1, 27.3, 27.3, 31.1, 74.1, 75.6, 87.0, 87.0, 97.2, 108.7, 109.0, 119.9, 125.3, 125.4, 127.5, 127.6, 128.9, 131.5, 131.5, 131.6, 133.2, 133.5, 133.6, 133.8, 133.9, 134.2, 138.7; ^{31}P NMR δ 4.9; HRMS (ESI positive) m/z calcd for $C_{37}H_{33}NaOP$ ($[M+Na]^+$): 547.2161. Found: 547.2162.



Dimethyl 4-pentyl-1,5-diphenyl-5*H*-dibenzo[*b,d*]phosphole-2,3-dicarboxylate 5-oxide (15aa)

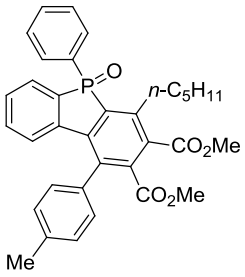
A pale yellow solid; mp 68 °C; IR (CH_2Cl_2) 2925, 1737, 1437, 1216, 1206, 704, 550 cm^{-1}; ^1H NMR δ 0.76-0.90 (m, 4H), 1.07-1.22 (m, 4H), 1.44-1.52 (m, 1H), 2.93-3.06 (m, 2H), 3.46 (s, 3H), 3.83 (s, 3H), 6.38-6.40 (m, 1H), 7.12-7.15 (m, 1H), 7.24-7.28 (m, 1H), 7.30-7.32 (m, 1H), 7.37-7.40 (m, 1H), 7.41-7.44 (m, 2H), 7.50-7.54 (m, 4H), 7.60-7.69 (m, 3H); ^{13}C NMR δ 5.0, 13.8, 22.2, 31.0, 32.1, 50.5, 52.2, 52.6, 52.6, 125.8, 128.7, 128.8, 128.8, 128.9, 129.1, 129.2, 129.4, 129.6, 129.6, 129.7, 129.9, 130.7, 131.2, 131.3, 132.3, 132.3, 133.0, 133.1, 133.9, 134.6, 134.8, 136.1, 137.1, 140.0, 140.5, 140.7, 145.6, 167.4, 167.8; ^{31}P NMR δ 31.8; HRMS (ESI positive) m/z calcd for $C_{33}H_{31}NaO_5P$ ($[M+Na]^+$): 561.1801. Found: 561.1801.



Dimethyl 1,4,5-triphenyl-5*H*-dibenzo[*b,d*]phosphole-2,3-dicarboxylate 5-oxide (15ca)

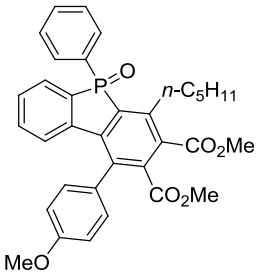
A white solid; mp 223 °C; IR (CH_2Cl_2) 2920, 2365, 1740, 1238, 700, 528 cm^{-1}; ^1H NMR δ 3.41 (s, 3H),

3.49 (s, 3H), 6.43-6.46 (m, 2H), 6.92-6.95 (m, 1H), 7.00-7.04 (m, 2H), 7.13-7.18 (m, 3H), 7.26-7.38 (m, 4H), 7.44-7.47 (m, 1H), 7.53-7.61 (m, 5H), 7.81-7.83 (m, 1H); ^{13}C NMR δ 52.3, 52.4, 66.2, 115.0, 116.1, 116.4, 119.0, 121.5, 126.0, 127.1, 127.3, 127.8, 127.9, 127.9, 127.9, 128.0, 128.1, 128.2, 128.2, 128.8, 128.8, 128.8, 128.9, 129.0, 129.3, 129.6, 129.7, 129.8, 130.8, 130.8, 130.9, 131.1, 131.2, 131.8, 131.9, 132.4, 133.0, 134.6, 135.7, 135.7, 137.0, 137.7, 154.4, 160.2; ^{31}P NMR δ 31.3; HRMS (ESI positive) m/z calcd for $C_{34}H_{25}NaO_5P$ ($[M+Na]^+$): 567.1332. Found: 567.1329.



Dimethyl 4-pentyl-5-phenyl-1-(4-tolyl)-5*H*-dibenzo[*b,d*]phosphole-2,3-dicarboxylate 5-oxide (15da)

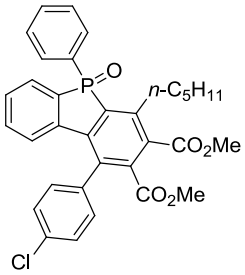
A pale brown solid; mp 63 °C; IR (CH_2Cl_2) 2925, 1736, 1437, 1244, 1207, 731 cm^{-1}; ^{1}H NMR δ 0.77 (t, *J* = 7.0 Hz, 3H), 0.81-0.89 (m, 1H), 1.08-1.21 (m, 4H), 1.42-1.51 (m, 1H), 2.48 (s, 3H), 2.93-3.05 (m, 2H), 3.49 (s, 3H), 3.83 (s, 3H), 6.46-6.48 (m, 1H), 7.14-7.18 (m, 2H), 7.25-7.31 (m, 4H), 7.40-7.44 (m, 2H), 7.51-7.54 (m, 1H), 7.60-7.68 (m, 3H); ^{13}C NMR δ 13.8, 21.5, 22.2, 31.0, 32.1, 32.2, 32.3, 40.2, 52.2, 52.6, 125.8, 125.9, 127.0, 128.7, 128.8, 129.0, 129.2, 129.5, 129.5, 129.5, 129.6, 129.8, 130.0, 131.0, 131.2, 131.3, 132.3, 132.3, 133.0, 133.9, 133.9, 134.7, 134.7, 138.4, 140.2, 140.2, 140.8, 141.8, 142.0, 143.0, 145.3, 145.4, 167.4, 167.8; ^{31}P NMR δ 31.7; HRMS (ESI positive) m/z calcd for $C_{34}H_{33}NaO_5P$ ($[M+Na]^+$): 575.1958. Found: 575.1956.



Dimethyl 1-(4-methoxyphenyl)-4-pentyl-5-phenyl-5*H*-dibenzo[*b,d*]phosphole-2,3-dicarboxylate 5-oxide (15ea)

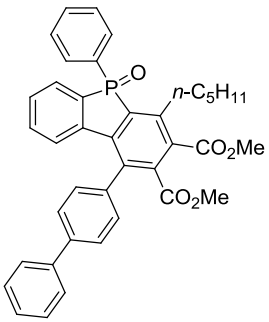
A white solid; mp 102 °C; IR (CH_2Cl_2) 2925, 1736, 1610, 1247, 1205, 733 cm^{-1}; ^{1}H NMR δ 0.77 (t, *J* = 7.0 Hz, 3H), 0.83-0.89 (m, 1H), 1.08-1.22 (m, 4H), 1.43-1.50 (m, 1H), 2.93-3.05 (m, 2H), 3.51 (s, 3H), 3.83 (s, 3H), 3.92 (s, 3H), 6.51 (dd, *J* = 3.1, 8.2 Hz, 1H), 7.02-7.05 (m, 2H), 7.16-7.22 (m, 2H), 7.25-7.30 (m, 2H), 7.40-7.44 (m, 2H), 7.51-7.54 (m, 1H), 7.60-7.68 (m, 3H); ^{13}C NMR δ 13.9, 22.2, 31.1, 32.1, 32.3, 52.3, 52.6, 52.6, 55.3, 114.3, 114.5, 125.8, 125.9, 128.8, 128.8, 128.9, 129.1, 129.6, 129.6, 129.7,

129.7, 130.5, 130.6, 130.8, 131.0, 131.3, 131.3, 132.3, 132.4, 133.1, 133.1, 134.7, 134.9, 142.2, 142.3, 144.5, 145.4, 159.8, 168.0; ^{31}P NMR δ 31.8; HRMS (ESI positive) m/z calcd for $C_{34}H_{33}NaO_6P$ ($[M+Na]^+$): 591.1907. Found: 591.1904.



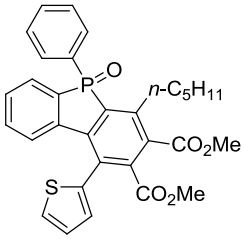
Dimethyl 1-(4-chlorophenyl)-4-pentyl-5-phenyl-5*H*-dibenzo[*b,d*]phosphole-2,3-dicarboxylate 5-oxide (15fa)

A pale yellow solid; mp 151 °C; IR (CH_2Cl_2) 2955, 1734, 1444, 1229, 986, 737 cm^{-1}; ^{1}H NMR δ 0.78 (t, *J* = 6.9 Hz, 3H), 0.81-0.88 (m, 1H), 1.08-1.22 (m, 4H), 1.43-1.49 (m, 1H), 2.93-3.05 (m, 2H), 3.51 (s, 3H), 3.83 (s, 3H), 6.47 (dd, *J* = 3.3, 8.0 Hz, 1H), 7.19-7.22 (m, 1H), 7.25-7.35 (m, 3H), 7.41-7.45 (m, 2H), 7.49-7.55 (m, 3H), 7.62-7.68 (m, 3H); ^{13}C NMR δ 13.9, 22.2, 31.0, 32.1, 36.9, 53.5, 69.4, 69.6, 105.9, 109.3, 109.3, 109.7, 115.6, 120.8, 122.1, 125.3, 125.6, 127.5, 127.6, 128.9, 129.0, 129.2, 129.4, 129.9, 129.9, 130.1, 131.0, 131.3, 131.3, 131.3, 131.6, 132.4, 132.7, 133.9, 134.9, 136.1, 165.2, 165.2; ^{31}P NMR δ 31.6; HRMS (ESI positive) m/z calcd for $C_{33}H_{30}ClNaO_5P$ ($[M+Na]^+$): 595.1412 . Found: 595.1407.



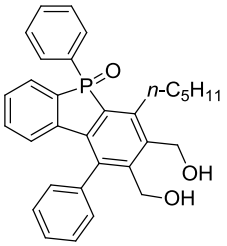
Dimethyl 4-pentyl-5-phenyl-1-(4-phenylphenyl)-5*H*-dibenzo[*b,d*]phosphole-2,3-dicarboxylate 5-oxide (15ga)

A white solid; mp 146 °C; IR (CH_2Cl_2) 2924, 1737, 1216, 1205, 694, 506 cm^{-1}; ^{1}H NMR δ 0.78 (t, *J* = 6.9 Hz, 3H), 0.83-0.90 (m, 1H), 1.08-1.22 (m, 4H), 1.45-1.52 (m, 1H), 2.94-3.07 (m, 2H), 3.49 (s, 3H), 3.84 (s, 3H), 6.56 (dd, *J* = 3.3, 8.3 Hz, 1H), 7.13-7.17 (m, 1H), 7.25-7.29 (m, 1H), 7.38-7.47 (m, 5H), 7.50-7.55 (m, 3H), 7.61-7.70 (m, 3H), 7.74-7.78 (m, 4H); ^{13}C NMR δ 13.9, 22.3, 31.1, 32.1, 32.3, 32.4, 52.3, 52.7, 125.8, 125.9, 127.1, 127.3, 127.6, 127.9, 128.8, 128.9, 129.0, 129.7, 129.7, 129.8, 129.8, 130.0, 130.8, 131.2, 131.3, 131.4, 132.4, 132.4, 133.1, 133.1, 134.0, 134.2, 134.3, 134.8, 134.9, 135.7, 136.1, 140.1, 140.2, 140.2, 140.6, 140.7, 141.2, 141.8, 142.0, 145.6, 145.7, 167.4, 167.4, 167.9; ^{31}P NMR δ 31.7; HRMS (ESI positive) m/z calcd for $C_{39}H_{35}NaO_5P$ ($[M+Na]^+$): 637.2114. Found: 637.2110.



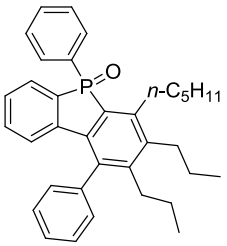
Dimethyl 4-pentyl-5-phenyl-1-thienyl-5*H*-dibenzo[*b,d*]phosphole-2,3-dicarboxylate 5-oxide (15ha)

A pale yellow oil; IR (CH_2Cl_2) 2924, 2360, 1737, 1437, 1205, 695 cm^{-1}; ^1H NMR δ 0.76-0.84 (m, 4H), 1.07-1.18 (m, 4H), 1.45 (br, 1H), 3.00-3.05 (m, 2H), 3.60 (s, 3H), 3.84 (s, 3H), 6.51 (dd, J = 3.1, 8.0 Hz, 1H), 7.07 (br, 1H), 7.18-7.20 (m, 1H), 7.24-7.27 (m, 1H), 7.30-7.33 (m, 1H), 7.41-7.45 (m, 2H), 7.51-7.56 (m, 2H), 7.62-7.68 (m, 3H); ^{13}C NMR δ 13.9, 22.2, 30.1, 32.1, 32.3, 32.4, 52.5, 52.7, 125.7, 126.8, 126.9, 127.6, 127.6, 127.9, 127.9, 128.8, 128.8, 128.9, 129.6, 129.7, 130.0, 130.0, 131.3, 131.4, 132.4, 132.5, 133.3, 133.3, 134.9, 140.1, 140.3, 141.6, 141.6, 146.8, 146.9, 167.1, 167.2, 167.5; ^{31}P NMR δ 31.7; HRMS (ESI positive) m/z calcd for $C_{31}H_{29}NaO_5PS$ ($[M+Na]^+$): 567.1366. Found: 567.1365.



2,3-Bis(hydroxymethyl)-4-pentyl-1,5-diphenyl-5*H*-dibenzo[*b,d*]phosphole 5-oxide (15ab)

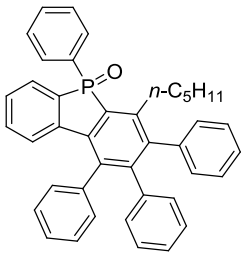
A colorless solid; mp 178 °C; IR (CH_2Cl_2) 3298, 2926, 1439, 1183, 1010, 704, 553 cm^{-1}; ^1H NMR δ 0.58 (br, 1H), 0.69-0.72 (m, 3H), 0.99-1.15 (m, 4H), 1.24-1.28 (m, 2H), 1.79 (br, 1H), 2.80-2.86 (m, 1H), 2.93-2.98 (m, 1H), 4.36-4.40 (m, 1H), 4.48-4.50 (m, 1H), 4.71-4.79 (m, 2H), 6.13 (dd, J = 3.0, 8.0 Hz, 1H), 7.08 (t, J = 7.7 Hz, 1H), 7.18 (dt, J_d = 3.2 Hz, J_t = 7.3 Hz, 1H), 7.30-7.31 (m, 2H), 7.38-7.41 (m, 2H), 7.48-7.55 (m, 5H), 7.64-7.68 (m, 2H); ^{13}C NMR δ 13.9, 22.4, 29.7, 31.6, 32.2, 58.2, 58.3, 59.7, 125.3, 125.4, 128.3, 128.6, 128.7, 128.7, 128.8, 129.2, 129.3, 129.4, 129.4, 129.5, 129.6, 131.2, 131.3, 131.4, 132.2, 132.9, 137.9, 138.0, 139.0, 139.6, 140.1, 140.2, 142.0, 142.2, 145.4, 145.5; ^{31}P NMR δ 33.6; HRMS (ESI positive) m/z calcd for $C_{31}H_{31}NaO_3P$ ($[M+Na]^+$): 505.1903. Found: 505.1903.



4-Pentyl-1,5-diphenyl-2,3-dipropyl-5*H*-dibenzo[*b,d*]phosphole 5-oxide (15ag)

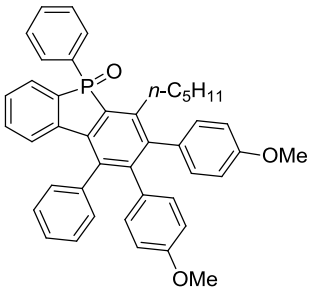
A white solid; mp 86 °C; IR (CH_2Cl_2) 2924, 2853, 1457, 1204, 706 cm^{-1}; ^1H NMR δ 0.63-0.75 (m, 4H), 0.79 (t, J = 6.9 Hz, 3H), 1.01-1.18 (m, 8H), 1.31-1.62 (m, 4H), 2.32-2.36 (m, 2H), 2.56 (t, J = 8.4 Hz, 2H),

2.68 (dt, J_d = 4.5 Hz, J_t = 12.9 Hz, 1H), 2.96 (dt, J_d = 4.5 Hz, J_t = 12.9 Hz, 1H), 5.99 (dd, J = 3.2, 8.1, 1H), 6.99-7.04 (m, 1H), 7.08-7.13 (m, 1H), 7.24-7.27 (m, 1H), 7.31-7.33 (m, 1H), 7.38-7.42 (m, 2H), 7.47-7.55 (m, 5H), 7.68-7.74 (m, 2H); ^{13}C NMR δ 10.9, 14.0, 14.8, 15.0, 22.4, 23.5, 24.5, 24.9, 29.7, 32.3, 32.5, 32.7, 33.4, 48.6, 98.4, 101.8, 106.9, 111.3, 111.5, 115.3, 118.7, 120.0, 124.0, 124.7, 125.9, 127.3, 127.7, 128.3, 128.5, 128.5, 128.6, 128.6, 128.9, 129.2, 129.3, 129.5, 129.7, 131.5, 146.2, 147.3, 148.5; ^{31}P NMR δ 33.0; HRMS (ESI positive) m/z calcd for $C_{35}H_{39}NaOP$ ($[M+Na]^+$): 529.2631. Found: 529.2632.



4-Pentyl-1,2,3,5-tetraphenyl-5*H*-dibenzo[*b,d*]phosphole 5-oxide (15af)

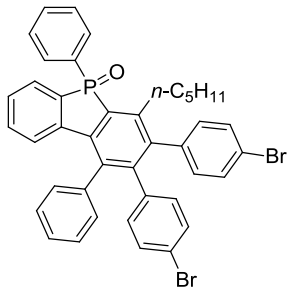
A white solid; mp >300 °C; IR (CH_2Cl_2) 2923, 2359, 1738, 1204, 700, 436 cm^{-1}; ^{1}H NMR δ 0.48-0.57 (m, 4H), 0.72-0.88 (m, 4H), 1.13-1.22 (m, 1H), 2.58 (dt, J_d = 4.5 Hz, J_t = 12.7 Hz, 1H), 2.84 (dt, J_d = 4.5 Hz, J_t = 12.7 Hz, 1H), 6.26 (dd, J = 3.3, 8.0 Hz, 1H), 6.64-6.66 (m, 1H), 6.77-6.90 (m, 5H), 7.00-7.15 (m, 6H), 7.17-7.22 (m, 4H), 7.25-7.28 (m, 1H), 7.43-7.47 (m, 2H), 7.51-7.54 (m, 1H), 7.59-7.62 (m, 1H), 7.79-7.83 (m, 2H); ^{13}C NMR δ 13.6, 21.8, 30.0, 31.9, 32.5, 32.6, 125.2, 125.3, 125.6, 126.3, 126.4, 126.6, 127.1, 127.1, 127.3, 128.2, 128.4, 128.5, 128.5, 128.6, 129.4, 129.5, 130.1, 130.2, 130.4, 130.5, 131.2, 131.2, 131.5, 131.6, 131.9, 131.9, 132.0, 132.1, 132.7, 132.7, 133.9, 134.8, 136.4, 136.4, 138.7, 138.7, 138.9, 139.2, 139.5, 142.4, 142.5, 142.7, 142.8, 144.8, 144.9, 147.6; ^{31}P NMR δ 32.9; HRMS (ESI positive) m/z calcd for $C_{41}H_{35}NaOP$ ($[M+Na]^+$): 597.2318. Found: 597.2318.



2,3-Bis(4-methoxyphenyl)-4-pentyl-1,5-diphenyl-5*H*-dibenzo[*b,d*]phosphole 5-oxide (15ac)

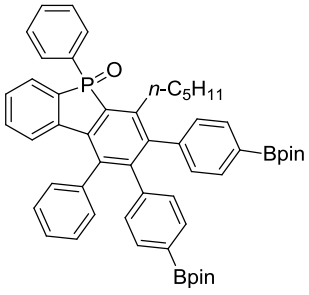
A white solid; mp 228 °C; IR (CH_2Cl_2) 2925, 2360, 1608, 1514, 1246, 1203, 703 cm^{-1}; ^{1}H NMR δ 0.45-0.54 (m, 1H), 0.56 (t, J = 6.5 Hz, 3H), 0.73-0.88 (m, 4H), 1.11-1.21 (m, 1H), 2.58 (dt, J_d = 4.6 Hz, J_t = 12.6 Hz, 1H), 2.82 (dt, J_d = 4.6 Hz, J_t = 12.6 Hz, 1H), 3.59 (s, 3H), 3.70 (s, 3H), 6.22 (dd, J = 3.4, 8.1 Hz, 1H), 6.36-6.41 (m, 2H), 6.53-6.58 (m, 2H), 6.67-6.70 (m, 2H), 6.77 (dd, J = 2.1, 8.4 Hz, 1H), 6.97 (dd, J = 2.1, 6.4 Hz, 1H), 6.99-7.01 (m, 1H), 7.05-7.09 (m, 1H), 7.16-7.22 (m, 4H), 7.26-7.29 (m, 1H),

7.42-7.46 (m, 2H), 7.50-7.53 (m, 1H), 7.59 (dd, J = 3.7, 7.1 Hz, 1H), 7.78-7.82 (m, 2H); ^{13}C NMR δ 13.7, 21.9, 30.0, 31.9, 32.6, 54.8, 55.0, 55.0, 112.0, 112.1, 112.6, 112.9, 113.9, 125.2, 125.3, 127.0, 128.1, 128.3, 128.4, 128.5, 128.6, 128.6, 128.7, 129.3, 129.4, 130.1, 130.2, 131.1, 131.2, 131.3, 131.4, 131.5, 131.5, 131.6, 131.8, 131.8, 131.9, 132.1, 132.6, 132.6, 133.9, 134.7, 136.8, 136.9, 138.5, 139.8, 142.4, 142.8, 142.9, 145.2, 157.1, 157.8; ^{31}P NMR δ 33.0; HRMS (ESI positive) m/z calcd for $C_{43}H_{39}NaO_3P$ ($[M+Na]^+$): 657.2529. Found: 657.2526.



2,3-Bis(4-bromophenyl)-4-pentyl-1,5-diphenyl-5*H*-dibenzo[*b,d*]phosphole 5-oxide (15ah)

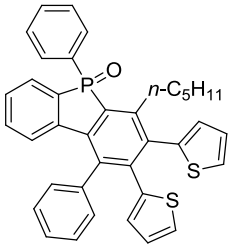
A white solid; mp 237 °C; IR (CH_2Cl_2) 2928, 1489, 1201, 1011, 704, 527 cm^{-1}; ^{1}H NMR δ 0.46-0.52 (m, 1H), 0.59 (t, J = 6.8 Hz, 3H), 0.76-0.89 (m, 4H), 1.09-1.16 (m, 1H), 2.49-2.55 (m, 1H), 2.79-2.85 (m, 1H), 6.23-6.26 (m, 1H), 6.50-6.52 (m, 1H), 6.65-6.67 (m, 1H), 6.75-6.77 (m, 1H), 6.93-6.95 (m, 1H), 6.98-7.02 (m, 3H), 7.07-7.11 (m, 1H), 7.15-7.32 (m, 7H), 7.43-7.47 (m, 2H), 7.52-7.55 (m, 1H), 7.59-7.62 (m, 1H), 7.76-7.81 (m, 2H); ^{13}C NMR δ 13.7, 22.0, 25.7, 30.2, 32.0, 32.5, 32.6, 120.3, 121.0, 125.4, 125.5, 127.6, 128.6, 128.7, 128.8, 128.8, 128.9, 129.0, 129.6, 129.7, 130.0, 130.0, 130.1, 130.3, 130.7, 131.0, 131.0, 131.6, 131.7, 131.9, 132.0, 132.0, 132.0, 132.1, 132.2, 132.2, 132.8, 132.9, 132.9, 134.0, 134.8, 136.5, 136.5, 137.6, 137.6, 138.0, 139.1, 139.3, 139.5, 141.3, 141.4, 142.1, 142.3, 144.9, 144.9, 146.2, 146.2; ^{31}P NMR δ 32.7; HRMS (ESI positive) m/z calcd for $C_{41}H_{33}Br_2NaOP$ ($[M+Na]^+$): 753.0528. Found: 753.0522.



2,3-Bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-pentyl-1,5-diphenyl-5*H*-dibenzo[*b, d*]phosphole 5-oxide (15ai)

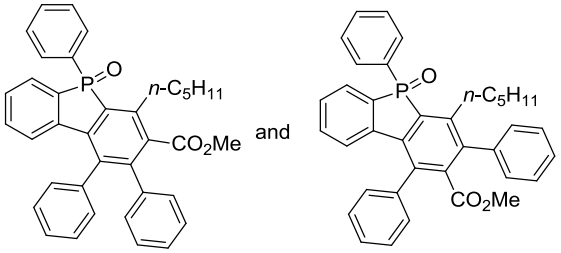
A white solid; mp 96 °C; IR (CH_2Cl_2) 2927, 2360, 2189, 1359, 1202, 1144, 417 cm^{-1}; ^{1}H NMR δ 0.44-0.56 (m, 4H), 0.71-0.94 (m, 5H), 1.27 (s, 12H), 1.31 (s, 12H), 2.49-2.55 (m, 1H), 2.76-2.82 (m, 1H), 6.18 (dd, J = 3.4, 8.2 Hz, 1H), 6.67-6.68 (m, 1H), 6.81-6.83 (m, 1H), 6.88-6.90 (m, 1H), 6.99-7.01 (m,

1H), 7.05-7.09 (m, 1H), 7.16-7.27 (m, 6H), 7.40-7.47 (m, 3H), 7.49-7.61 (m, 4H), 7.76-7.81 (m, 3H); ^{13}C NMR δ 13.8, 22.0, 25.0, 29.7, 29.8, 30.3, 30.7, 38.4, 39.7, 41.9, 51.1, 51.5, 59.7, 67.8, 83.7, 83.8, 97.2, 97.3, 98.8, 100.0, 102.9, 103.8, 110.7, 116.4, 118.1, 127.3, 128.4, 128.5, 128.5, 128.6, 128.7, 128.8, 129.3, 129.4, 129.5, 129.6, 129.7, 129.7, 129.9, 130.1, 130.1, 130.9, 131.2, 131.5, 131.6, 131.6, 131.9, 132.1, 132.8, 133.1, 133.4, 133.7, 133.9, 134.7, 139.5; ^{31}P NMR δ 33.0; HRMS (ESI positive) m/z calcd for $C_{53}H_{57}B_2NaO_5P$ ($[M+Na]^+$): 847.4088. Found: 847.4095.



4-Pentyl-1,5-diphenyl-2,3-bis(thien-2-yl)-5*H*-dibenzo[*b,d*]phosphole 5-oxide (15aj)

A brown oil; IR (CH_2Cl_2) 2925, 1738, 1458, 1203, 701, 520 cm^{-1}; ^{1}H NMR δ 0.60-0.66 (m, 4H), 0.84-0.95 (m, 3H), 1.17-1.37 (m, 2H), 2.72 (dt, J_d = 4.7 Hz, J_t = 12.9 Hz, 1H), 2.91 (dt, J_d = 4.7 Hz, J_t = 12.9 Hz, 1H), 6.26 (dd, J = 3.3, 8.2 Hz, 1H), 6.41 (dd, J = 1.1, 3.4 Hz, 1H), 6.57 (dd, J = 3.4, 5.1 Hz, 1H), 6.75 (dd, J = 1.1, 3.5 Hz, 1H), 6.83 (dd, J = 3.5, 5.2 Hz, 1H), 6.96 (dd, J = 0.9, 5.0 Hz, 1H), 7.08-7.12 (m, 2H), 7.17 (dd, J = 1.1, 5.1 Hz, 1H), 7.20-7.35 (m, 5H), 7.43-7.47 (m, 2H), 7.52-7.55 (m, 1H), 7.59-7.63 (m, 1H), 7.76-7.80 (m, 2H); ^{13}C NMR δ 13.8, 22.0, 22.4, 30.8, 32.1, 43.8, 123.1, 123.9, 124.2, 125.5, 125.6, 126.0, 126.0, 126.0, 126.2, 127.6, 127.8, 128.3, 128.4, 128.5, 128.7, 128.7, 128.8, 128.8, 128.8, 128.9, 128.9, 129.3, 129.6, 129.8, 129.9, 130.0, 130.9, 131.2, 131.4, 131.5, 131.6, 131.9, 132.1, 132.1, 132.8, 134.0, 137.8, 139.2, 139.5, 139.8, 146.4, 146.7; ^{31}P NMR δ 32.5; HRMS (ESI positive) m/z calcd for $C_{37}H_{31}NaOPS_2$ ($[M+Na]^+$): 609.1446. Found: 609.1445.

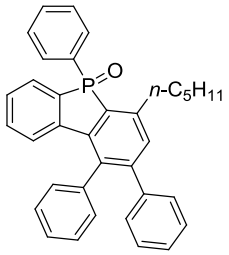


Methyl 4-pentyl-1,2,5-triphenyl-5*H*-dibenzo[*b,d*]phosphole-3-carboxylate 5-oxide (15ae)

and Methyl 4-pentyl-1,3,5-triphenyl-5*H*-dibenzo[*b,d*]phosphole-2-carboxylate 5-oxide (16ae)

A pale yellow solid; mp 131 °C; IR (CH_2Cl_2) 2925, 1733, 1206, 701, 444 cm^{-1}; ^{1}H NMR δ 0.46-0.59 (m, 4H), 0.76-0.95 (m, 8H), 1.06-1.23 (m, 5H), 1.53-1.62 (m, 1H), 2.55-2.61 (m, 1H), 2.73-2.90 (m, 2H), 2.90-2.96 (m, 1H), 3.09 (s, 3H), 3.37 (s, 3H), 6.30 (dd, J = 3.4, 7.9 Hz, 1H), 6.43 (dd, J = 3.2, 7.9 Hz, 1H), 6.99-7.15 (m, 8H), 7.20-7.31 (m, 9H), 7.37-7.38 (m, 2H), 7.41-7.55 (m, 11H), 7.59-7.63 (m, 2H),

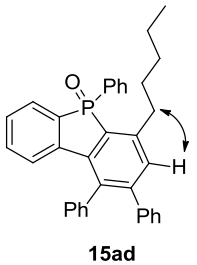
7.70-7.77 (m, 4H); ^{13}C NMR δ 13.6, 13.7, 13.9, 21.8, 22.2, 29.9, 31.0, 31.8, 31.8, 31.9, 31.9, 32.3, 32.6, 32.6, 51.4, 51.7, 125.2, 125.3, 125.6, 127.0, 127.1, 127.3, 127.6, 127.7, 127.8, 127.9, 128.5, 128.5, 128.7, 128.7, 128.8, 128.8, 128.8, 128.8, 128.9, 129.0, 129.0, 129.1, 129.5, 129.5, 129.6, 129.7, 129.7, 130.1, 130.1, 130.6, 130.7, 131.4, 131.4, 131.5, 131.5, 131.5, 131.7, 132.1, 131.2, 132.2, 132.6, 132.8, 132.9, 132.9, 133.3, 133.3, 133.4, 133.7, 134.1, 134.5, 135.7, 136.4, 136.9, 137.6, 137.8, 138.4, 138.8, 139.0, 139.8, 140.7, 141.4, 141.4, 141.6, 141.6, 141.8, 143.1, 145.2, 145.3, 145.6, 145.6, 168.3, 169.0, 169.0; ^{31}P NMR δ 32.0, 32.5; HRMS (ESI positive) m/z calcd for $C_{37}H_{33}NaO_3P$ ($[M+Na]^+$): 579.2060. Found: 579.2059.



4-Pentyl-1,2,5-triphenyl-5*H*-dibenzo[*b,d*]phosphole 5-oxide (15ad)

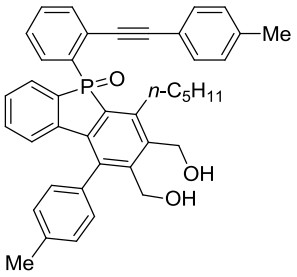
HMBC correlation was observed between carbon atom on pentyl group and hydrogen atom on benzene ring (Figure 6).

A white solid; mp 88 °C; IR (CH_2Cl_2) 2922, 2359, 1739, 1466, 1365, 1204 cm^{-1}; ^{1}H NMR δ 0.76-0.79 (m, 3H), 1.13-1.18 (m, 5H), 1.50-1.56 (m, 1H), 2.82-2.85 (m, 2H), 6.34 (dd, *J* = 3.3, 8.2 Hz, 1H), 7.04-7.08 (m, 3H), 7.13-7.20 (m, 7H), 7.29-7.32 (m, 3H), 7.42-7.46 (m, 2H), 7.50-7.54 (m, 1H), 7.59-7.63 (m, 1H), 7.74-7.78 (m, 2H); ^{13}C NMR δ 13.9, 22.4, 30.6, 31.7, 33.6, 33.7, 125.4, 125.5, 126.7, 127.5, 127.5, 128.5, 128.5, 128.5, 128.8, 129.5, 129.6, 130.4, 130.5, 130.6, 131.1, 131.3, 131.3, 131.3, 131.4, 131.4, 132.0, 132.0, 132.6, 132.7, 133.9, 134.8, 135.5, 135.6, 139.0, 139.7, 139.9, 140.7, 145.9, 146.0, 147.8, 147.8; ^{31}P NMR δ 31.9; HRMS (ESI positive) m/z calcd for $C_{35}H_{31}NaOP$ ($[M+Na]^+$): 521.2005. Found: 521.2007.



15ad

Figure 6. HMBC experiment on **15ad**



2,3-Bis(hydroxymethyl)-4-pentyl-1-(4-tolyl)-5-(2-(4-tolylethynyl)phenyl)-5*H*-dibenzo[*b*,*d*]phosphole 5-oxide (18)

A white solid; mp 124 °C; IR (CH_2Cl_2) 3369, 2922, 2852, 2360, 1634, 1465, 721 cm^{-1}; ^1H NMR δ 0.69 (t, *J* = 7.2 Hz, 3H), 0.78-1.13 (m, 6H), 1.37-1.47 (m, 1H), 1.76 (br, 1H), 2.40 (s, 6H), 2.85-2.88 (m, 2H), 4.27-4.35 (m, 2H), 4.73-4.80 (m, 2H), 5.95 (d, *J* = 7.4 Hz, 1H), 6.03-6.05 (m, 1H), 6.70-6.72 (m, 2H), 6.90 (d, *J* = 7.4 Hz, 1H), 6.95-6.97 (m, 1H), 7.02-7.06 (m, 3H), 7.14-7.20 (m, 2H), 7.45-7.50 (m, 2H), 7.53-7.56 (m, 1H), 7.62-7.65 (m, 1H), 8.64-8.68 (m, 1H); ^{13}C NMR δ 13.9, 21.3, 21.5, 22.4, 31.7, 32.2, 32.5, 58.4, 59.7, 85.2, 85.2, 96.4, 119.2, 125.3, 125.3, 125.5, 125.6, 128.2, 128.3, 128.3, 128.4, 128.8, 128.8, 128.9, 128.9, 129.1, 129.3, 129.8, 130.6, 130.8, 131.4, 131.7, 132.0, 132.4, 133.4, 134.0, 134.1, 135.0, 135.6, 137.3, 137.7, 137.8, 138.8, 139.5, 139.5, 140.6, 140.8, 143.5, 143.6, 144.8, 144.9; ^{31}P NMR δ 31.0; HRMS (ESI positive) m/z calcd for $C_{41}H_{39}NaO_3P$ ($[M+Na]^+$): 633.2529. Found: 633.2525. $[\alpha]^{28}_D$ -10.4 (*c* 0.2, $CHCl_3$, 83% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IC: 4 x 250 mm, 254 nm UV detector, rt, eluent: 2-propanol:hexane = 40:60, flow rate: 0.25 mL/min, retention time: 40.1 min for minor isomer and 54.9 min for major isomer). Crystal data of **18**; $C_{41}H_{39}O_3P$, *M* = 610.72, triclinic, Space Group P-1 (#2), *a* = 9.5271(6) Å, *b* = 13.1477(8) Å, *c* = 15.738(1) Å, α = 101.815(8) °, β = 90.675(6) °, γ = 94.821(6) °, *V* = 1921.9 Å3, *T* = 173.0 K, *Z* = 2, μ(CuKα) = 1.54187 cm-1, Number of Reflections Measures: Total 20458, Unique: 6820 (R*int* = 0.1758), *R1* = 0.1249, *wR2* = 0.3565

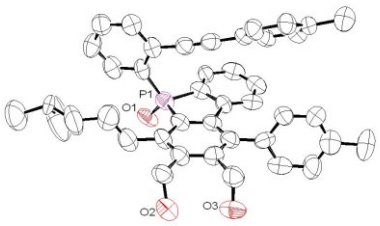
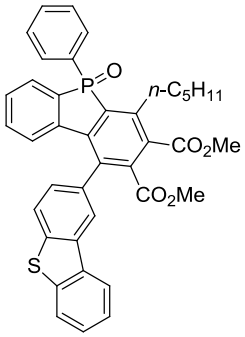
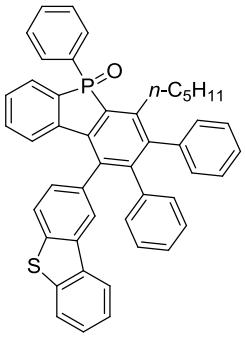


Figure 7. Ortep diagram of **18**



Dimethyl 1-(dibenzo[*b,d*]thiophen-2-yl)-4-pentyl-5-phenyl-5*H*-dibenzo[*b,d*]phosphole-2,3-dicarboxylate 5-oxide (15ia)

A white solid; mp 131 °C; IR (CH_2Cl_2) 2953, 1737, 1437, 1206, 736, 520 cm^{-1}; ^1H NMR δ 0.78-0.81 (m, 3H), 0.84-0.92 (m, 1H), 1.09-1.24 (m, 4H), 1.44-1.57 (m, 1H), 2.95-3.10 (m, 2H), 3.40 (d, *J* = 2.3 Hz, 3H), 3.84 (d, *J* = 1.6 Hz, 3H), 6.41-6.43 (m, 1H), 7.02-7.06 (m, 1H), 7.21-7.25 (m, 1H), 7.40-7.57 (m, 6H), 7.61-7.64 (m, 1H), 7.67-7.73 (m, 2H), 7.91-7.94 (m, 1H), 7.99-8.01 (m, 1H), 8.10-8.18 (m, 2H); ^{13}C NMR δ 13.8, 22.2, 31.0, 32.1, 32.3, 52.3, 52.6, 121.9, 122.0, 121.1, 122.3, 122.9, 123.0, 123.2, 123.5, 124.6, 124.8, 125.7, 125.8, 125.8, 125.9, 127.3, 127.3, 127.8, 127.9, 128.8, 128.9, 129.7, 129.7, 129.8, 129.8, 129.9, 130.7, 130.7, 131.2, 131.2, 131.3, 131.3, 131.3, 132.4, 133.2, 133.2, 133.3, 133.9, 133.9, 133.9, 134.2, 134.3, 134.8, 134.8, 134.9, 135.1, 135.2, 135.6, 135.7, 136.0, 136.2, 139.8, 139.8, 139.9, 140.0, 140.4, 140.4, 140.5, 140.5, 140.6, 140.7, 141.9, 142.0, 142.1, 142.1, 145.7, 145.7, 145.8, 145.8, 167.3, 167.3, 167.4, 167.4, 167.8; ^{31}P NMR δ 31.7; HRMS (ESI positive) m/z calcd for $C_{39}H_{33}NaO_5PS$ ($[M+Na]^+$): 667.1679. Found: 667.1678.



1-(Dibenzo[*b,d*]thiophen-2-yl)-4-pentyl-2,3,5-triphenyl-5*H*-dibenzo[*b,d*]phosphole 5-oxide (15if)

A white solid; mp 259 °C; IR (CH_2Cl_2) 2926, 1458, 1200, 729, 701, 527 cm^{-1}; ^1H NMR δ 0.53-0.59 (m, 4H), 0.72-0.86 (m, 4H), 1.16-1.24 (m, 1H), 2.57-2.64 (m, 1H), 2.82-2.90 (m, 1H), 6.26-6.29 (m, 1H), 6.66-7.17 (m, 13H), 7.29-7.56 (m, 5H), 7.58-7.63 (m, 1H), 7.68-7.75 (m, 1H), 7.81-8.07 (m, 5H); ^{13}C NMR δ 13.8, 13.8, 21.1, 30.2, 30.2, 32.0, 32.0, 32.7, 32.7, 118.2, 121.7, 121.9, 122.7, 122.9, 123.0, 123.1, 123.3, 123.4, 124.5, 124.6, 125.3, 125.4, 125.4, 125.4, 125.4, 125.4, 125.8, 125.8, 126.5, 126.6, 126.6, 126.9, 126.9, 126.9, 127.0, 127.2, 127.2, 127.5, 128.6, 128.6, 128.6, 128.7, 128.7, 128.8, 129.0, 129.0,

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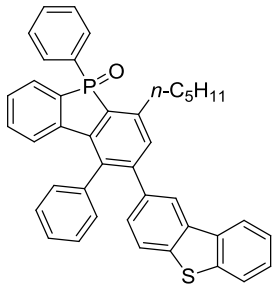
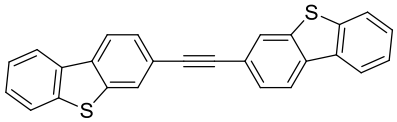


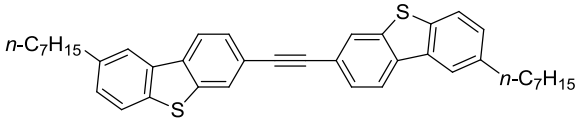
2-Dibenzo[*b,d*]thiophen-2-yl-4-pentyl-1,5-diphenyl-5*H*-dibenzo[*b,d*]phosphole 5-oxide (15ak)

A white solid; mp 104 °C; IR (CH_2Cl_2) 3054, 2927, 1463, 1198, 703, 418 cm^{-1}; ^{1}H NMR δ 0.73-0.80 (m, 4H), 1.12-1.22 (m, 4H), 1.56-1.60 (m, 1H), 2.86-2.89 (m, 2H), 6.38 (dd, *J* = 3.2, 8.0 Hz, 2H), 7.08-7.15 (m, 2H), 7.19-7.31 (m, 6H), 7.45-7.55 (m, 5H), 7.59-7.65 (m, 2H), 7.76-7.83 (m, 3H), 7.86 (s, 1H), 7.98-8.00 (m, 1H); ^{13}C NMR δ 14.0, 22.4, 22.4, 30.7, 30.7, 31.7, 33.7, 33.7, 121.5, 121.8, 122.6, 122.9, 123.5, 124.4, 125.4, 125.5, 126.8, 126.8, 127.0, 127.7, 128.4, 128.4, 128.5, 128.6, 128.8, 128.9, 129.5, 129.6, 130.4, 130.5, 130.7, 130.8, 131.1, 131.4, 131.5, 131.6, 131.7, 131.9, 131.9, 132.0, 132.0, 132.0, 132.7, 134.8, 135.0, 135.4, 135.7, 135.8, 137.1, 138.0, 138.9, 139.7, 142.5, 142.5, 145.9, 146.0, 146.1, 146.1, 147.5; ^{31}P NMR δ 31.9; HRMS (ESI positive) m/z calcd for $C_{41}H_{33}NaOPS$ ($[M+Na]^+$): 627.1882. Found: 627.1879.



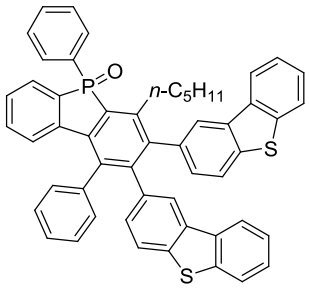
1,2-Bis(dibenzo[*b,d*]thiophen-2-yl)ethyne (2l)

A pale grey solid; mp 283 °C; IR (CH_2Cl_2) 1739, 1364, 1217, 417 cm^{-1}; ^{1}H NMR (C_2D_6OS, 495.13 MHz) δ 7.47-7.51 (m, 4H), 7.65 (dd, *J* = 1.6, 8.4 Hz, 2H), 7.92-7.95 (m, 2H), 7.98 (d, *J* = 8.3 Hz, 2H), 8.34-8.38 (m, 2H), 8.48 (d, *J* = 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$ in CS_2, 124.5 MHz) δ 113.8, 113.8, 113.9, 115.1, 127.8, 128.0, 128.5, 133.1, 136.3, 152.3, 154.7, 159.4, 170.8; HRMS (ESI positive) m/z calcd for $C_{26}H_{15}S_2$ ($[M+H]^+$): 361.0610. Found: 361.0605.



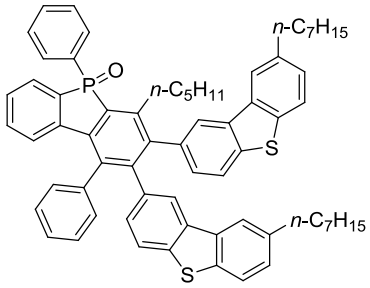
1,2-Bis(8-(hept-1-yl)-dibenzo[*b,d*]thiophen-2-yl)ethyne (2m)

A pale yellow solid; mp 83 °C; IR (CH_2Cl_2) 2924, 2852, 1736, 1457, 811 cm^{-1}; ^1H NMR δ 0.89 (t, *J* = 7.2 Hz, 6H), 1.25-1.42 (m, 16H), 1.70-1.76 (m, 4H), 2.80 (t, *J* = 7.8 Hz, 4H), 7.33 (dd, *J* = 1.5, 8.2 Hz, 2H), 7.64 (dd, *J* = 1.5, 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.83 (d, *J* = 8.2 Hz, 2H), 8.00 (s, 2H), 8.38 (s, 2H); ^{13}C NMR δ 14.1, 22.7, 29.2, 29.3, 31.8, 31.9, 36.0, 89.6, 119.3, 121.3, 122.5, 122.9, 124.8, 128.2, 129.5, 135.2, 135.8, 137.0, 139.8, 139.9; HRMS (ESI positive) m/z calcd for $C_{40}H_{43}S_2$ ($[M+H]^+$): 587.2801. Found: 587.2801.



2,3-Bis(dibenzo[*b,d*]thiophen-2-yl)-4-pentyl-1,5-diphenyl-5*H*-dibenzo[*b,d*]phosphole 5-oxide (15al)

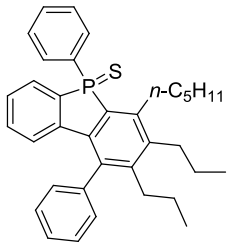
A pale yellow solid; mp 175 °C; IR (CH_2Cl_2) 2924, 1737, 1216, 1204, 703 cm^{-1}; ^1H NMR δ 0.44-0.55 (m, 4H), 0.65-0.88 (m, 4H), 0.92-1.00 (m, 1H), 2.65-2.78 (m, 1H), 2.84-2.97 (m, 1H), 6.27-6.34 (m, 1H), 6.95-7.05 (m, 1H), 7.07-7.15 (m, 2H), 7.18-7.30 (m, 6H), 7.35-7.39 (m, 10H), 7.63-7.72 (m, 3H), 7.79-7.94 (m, 5H); ^{13}C NMR δ 13.6, 17.0, 21.9, 30.0, 37.6, 121.4, 121.5, 121.8, 122.5, 122.7, 122.9, 122.9, 123.0, 123.3, 123.5, 123.7, 124.1, 124.1, 124.2, 124.4, 124.5, 124.7, 124.8, 125.4, 125.5, 126.4, 126.5, 126.9, 126.9, 127.3, 127.4, 128.6, 128.6, 128.7, 128.7, 128.8, 128.8, 128.8, 128.9, 129.0, 129.2, 129.6, 129.8, 129.8, 130.0, 130.1, 130.2, 131.5, 131.6, 131.7, 131.7, 131.9, 132.0, 132.1, 132.1, 133.2, 134.0, 134.4, 134.8, 134.9, 135.0, 135.2, 135.4, 135.8, 136.9, 137.7, 137.7, 139.3, 139.4, 139.4, 139.7, 142.3, 143.0; ^{31}P NMR δ 32.8; HRMS (ESI positive) m/z calcd for $C_{53}H_{39}NaOPS_2$ ($[M+Na]^+$): 809.2072. Found: 809.2070.



2,3-Bis(8-(hept-1-yl)dibenzo[*b,d*]thiophen-2-yl)-4-pentyl-1,5-diphenyl-5*H*-dibenzo[*b,d*]phosphole 5-oxide (15am)

A colorless solid; mp 61 °C; IR (CH_2Cl_2) 2953, 2925, 2853, 1438, 1278, 1202, 703, 418 cm^{-1}; ^1H NMR δ 0.43-0.51 (m, 4H), 0.65-0.94 (m, 16H), 1.21-1.38 (m, 12H), 1.64-1.74 (m, 3H), 2.47-2.65 (m, 1H), 2.65-2.69 (m, 4H), 2.84-2.97 (m, 1H), 6.27-6.33 (m, 1H), 6.92-6.97 (m, 1H), 7.00-7.31 (m, 10H),

7.45-7.90 (m, 13H), 7.90-8.00 (m, 1H); ^{13}C NMR δ 5.8, 9.1, 10.1, 10.8, 12.6, 14.1, 14.1, 14.1, 21.9, 22.6, 22.7, 22.7, 25.4, 25.8, 28.9, 29.2, 29.2, 29.2, 29.2, 29.3, 29.3, 29.3, 31.0, 31.8, 31.9, 33.4, 35.7, 35.9, 36.0, 36.0, 39.2, 41.0, 53.4, 55.7, 63.9, 67.0, 69.0, 83.2, 106.3, 107.6, 111.7, 114.5, 121.5, 122.6, 124.8, 124.8, 126.1, 127.7, 128.9, 129.6, 130.1, 131.6, 135.8, 135.9, 137.0, 140.0, 140.7, 143.0, 143.8, 148.0, 148.4, 148.7, 153.6, 158.3, 159.1, 165.7, 168.6, 168.8, 172.1, 172.8, 176.6, 176.7, 177.6, 179.0; ^{31}P NMR δ 33.1; HRMS (ESI positive) m/z calcd for $C_{67}H_{67}NaOPS_2$ ([M+Na]$^+$): 1005.4263. Found: 1005.4260.



Synthesis of 4-Pentyl-1,5-diphenyl-2,3-dipropyl-5*H*-dibenzo[*b,d*]phosphole 5-sulfide (19).

Dibenzophosphole oxide **3ac** (33.8 mg, 0.068 mmol) and Lawesson's reagent (54.9 mg, 0.136 mmol, 2 equiv) were dissolved in toluene (4.9 mL), and the mixture was heated under reflux for 1 h. After removal of solvent under reduced pressure, the product was purified by silica gel column (Hexane:Acetone = 5:1) to give **19** (34.8 mg, 0.067 mmol, 98%) as a white solid; mp 147 °C; IR (CH_2Cl_2) 2922, 2851, 1634, 1463, 703, 418 cm^{-1}; ^{1}H NMR δ 0.60-0.67 (m, 1H), 0.74 (t, J = 7.3 Hz, 3H), 0.80 (t, J = 7.1 Hz, 3H), 1.03 (t, J = 7.3 Hz, 3H), 1.06-1.18 (m, 3H), 1.24-1.28 (m, 1H), 1.32-1.40 (m, 2H), 1.44-1.62 (m, 3H), 2.34-2.37 (m, 2H), 2.56-2.59 (m, 2H), 2.68 (dt, J_d = 4.4 Hz, J_t = 13.0 Hz, 1H), 3.15 (dt, J_d = 4.4 Hz, J_t = 13.0 Hz, 1H), 5.99-6.01 (m, 1H), 6.98-7.01 (m, 1H), 7.11-7.15 (m, 1H), 7.29-7.33 (m, 2H), 7.35-7.39 (m, 2H), 7.43-7.55 (m, 5H), 7.77-7.82 (m, 2H); ^{13}C NMR δ 14.1, 14.9, 15.1, 22.5, 24.6, 25.1, 30.9, 31.2, 32.0, 32.1, 32.5, 32.8, 125.0, 125.1, 127.8, 128.3, 128.4, 128.5, 128.6, 128.8, 129.0, 129.3, 129.6, 129.8, 131.4, 131.5, 131.5, 131.6, 131.7, 131.9, 131.9, 132.1, 132.1, 136.7, 137.4, 137.4, 137.5, 137.5, 137.7, 140.5, 141.3, 141.4, 142.3, 142.4, 144.6, 144.7, 145.8, 145.8; ^{31}P NMR δ 39.0; HRMS (ESI positive) m/z calcd for $C_{35}H_{39}NaPS$ ([M+Na]$^+$): 545.2402. Found: 545.2404.

References

(1) (a) Wex, B.; Kaafarani, B.; Kirschbaum, K.; Neckers, D. *J. Org. Chem*. **2005**, *70*, 4502. (b) Lo, P.; Li, K.; Wong, M.; Cheah, K. *J. Org. Chem*. **2007**, *72*, 6672. (c) Ebata, H.; Miyazaki, E.; Yamamoto, T.; Takimiya, K. *Org. Lett.* **2007**, *9*, 4499. (d) Du, C.; Ye, S.; Chen, J.; Guo, Y.; Liu, Y.; Lu, K.; Liu, Y.; Qi, T.; Gao, X.; Shuai, Z.; Yu, G. *Chem. Eur. J*. **2009**, *15*, 8275. (e) Black, H.; Liu, S.; Ashby, V. *Org. Lett.* **2011**, *13*, 6492.

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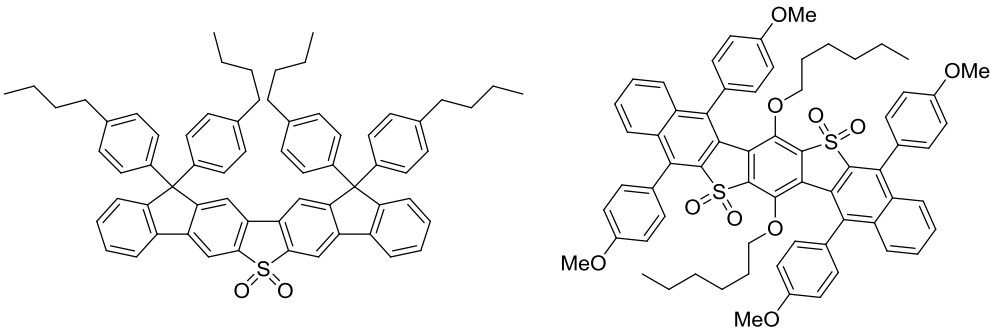
Chapter 7

Synthesis of Sulfur-Containing Condensed Polycyclic Compounds by Rhodium-Catalyzed Intermolecular Cycloaddition

Backgrounds

Recently, various polycyclic compounds including sulfone moieties have attracted much attention, because of their unique photophysical properties (Figure 1).[1] For example, Bryce and co-workers reported deep-blue fluorescent compounds containing dibenzothiophene dioxide skeleton.[1a] Mohanakrishnan and co-workers reported an anisyl substituted benzodithiophene tetraoxide-containing derivative, which showed the light-blue emission color in acetonitrile upon illumination at 365 nm.[1g]

Figure 1. Structures of compounds containing dibenzothiophene dioxide skeleton



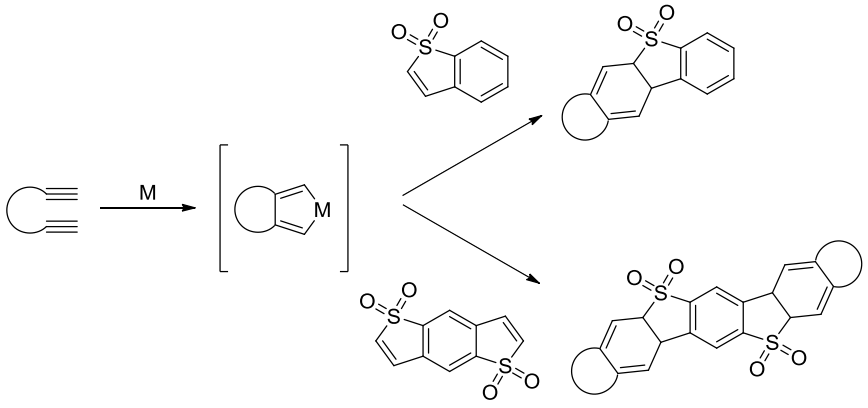
deep-blue fluorescent compound including dibenzothiophene dioxide skeleton

light-blue fluorescent compound including benzodithiophene tetraoxide skeleton

Results and Discussion

The author considered that catalytic intermolecular cycloaddition of α,ω-diynes with 2,3-double bond of benzothiophene dioxide provides various dibenzothiophene-dioxide-containing polycyclic compounds (Scheme 1).

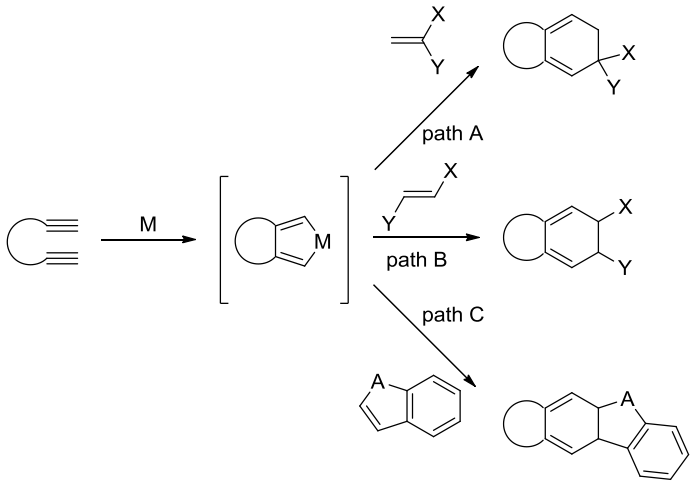
Scheme 1. Cycloaddition of α,ω-diyne with the 2,3-double bond of benzothiophene dioxide



Intermolecular cycloaddition of α,ω-diynes with 1,1-disubstituted alkenes[2] for the synthesis of bicyclic 5,5-disubstituted cyclohexa-1,3-dienes and that with 1,2-disubstituted alkenes[3] for the synthesis of

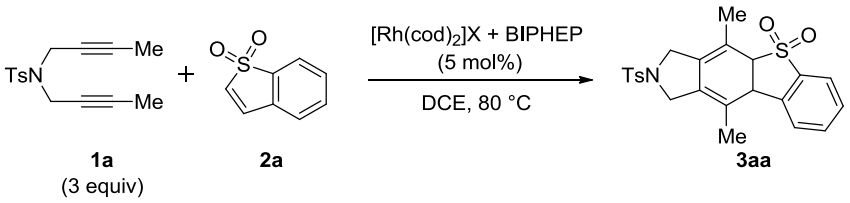
5,6-disubstituted cyclohexa-1,3-dienes were reported (paths A and B in Scheme 2). However, there had been no report of catalytic cycloaddition, where 2,3-double bond of benzoheterole was involved as an alkene moiety (path C in Scheme 2). This protocol is attractive because heteroatom-containing condensed polycyclic system can be readily constructed.[4]

Scheme 2. Intermolecular cycloaddition of α,ω-diynes with three types of ene moieties



Nitrogen-tethered 1,6-diyne **1a** and benzothiophene 1,1-dioxide (**2a**) were used as a model diyne and benzoheterole, and an intermolecular cycloaddition was examined in the presence of Rh-BIPHEP catalyst at 80 °C in 1,2-dichloroethane (DCE) (Table 1).[5] The desired cycloadduct **3aa** was obtained, but the yield was moderate due to the formation of self-cycloadduct of diyne **1a** (Entry 1). When diyne **1a** was added dropwisely to a heated solution of the Rh catalyst and dioxide **2a** over 1 h, the yield was dramatically improved to 90% (Entry 2). Slower dropwise addition (1.5 h) realized an excellent yield of 95% (Entry 3). This reaction was little affected by counter anions of cationic rhodium catalyst, and the author used tetrafluoroborate (BF_4) for further investigation (Entries 4 and 5).

Table 1. Screening of reaction conditions



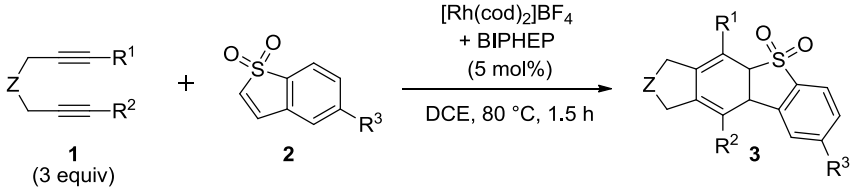
1a (3 equiv) **2a** **3aa**

Entry	X	Time / h	Yield / %
1	BF_4	1.0	48
2	BF_4	1.0[a]	90
3	BF_4	1.5[a]	95
4	BARF	1.5[a]	93
5	OTf	1.5[a]	95

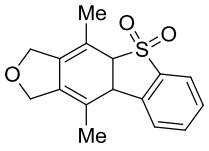
[*a*] Time taken for the dropwise addition of diyne **1a**.

Under the optimal conditions (Table 1, entry 3), various diynes and benzothiophene dioxides were screened in the intermolecular cycloaddition (Table 2). The reaction of oxygen-tethered diyne **1b** also proceeded, and the cycloadduct **3ba** was obtained in good yield. When unsymmetrical diynes, which have methyl or phenyl group on one of its alkyne termini, were examined, the corresponding cycloadducts **3ca** and **3da** were obtained with almost perfect regioselectivity.[6] The author examined the reaction of *ortho*-phenylene-tethered diyne **1e** with **2a** and pentacyclic compound **3ea** was obtained quantitatively. The reaction of substituted benzothiophene dioxide derivatives **2b**-**2d**, which have halogens or methoxy group, also proceeded to give functionalized cycloadducts **3eb**-**3ed** in good yield. Notably, benzothiophene dioxide **2e** with pinacolboryl group could also be used: the obtained cycloadduct **3ee** can be used for further transformation. 2,3-Naphtylene-tethered diyne **1f** was also an excellent substrate, and hexacyclic product **3fa** was obtained quantitatively.

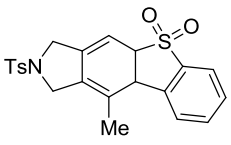
Table 2. Cycloaddition of various diynes **1** with substituted benzothiophene dioxides **2**[a]



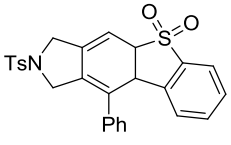
1 (3 equiv) + **2** → **3**



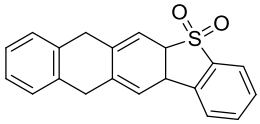
3ba
70% from **1b** and **2a**
(Z = O, R^1, R^2 = Me, R^3 = H)



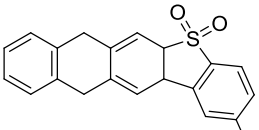
3ca
85% (>20:1) from **1c** and **2a**
(Z = NTs, R^1 = H, R^2 = Me, R^3 = H)



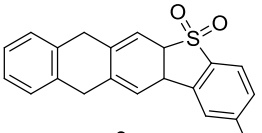
3da
89% (>20:1) from **1d** and **2a**
(Z = NTs, R^1 = H, R^2 = Ph, R^3 = H)



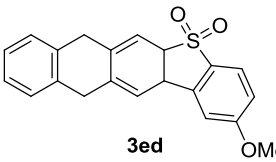
3ea
>99% from **1e** and **2a**
(Z = 1,2-C_6H_4, R^1, R^2 , R^3 = H)



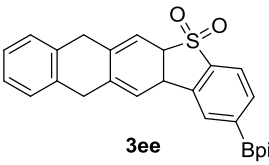
3eb
73% from **1e** and **2b**
(Z = 1,2-C_6H_4, R^1, R^2 = H, R^3 = Cl)



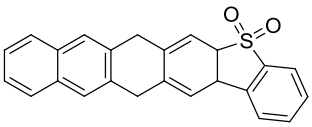
3ec
76% from **1e** and **2c**
(Z = 1,2-C_6H_4, R^1, R^2 = H, R^3 = Br)



3ed
77% from **1e** and **2d**
(Z = 1,2-C_6H_4, R^1, R^2 = H, R^3 = OMe)



3ee
73% from **1e** and **2e**
(Z = 1,2-C_6H_4, R^1, R^2 = H, R^3 = Bpin)

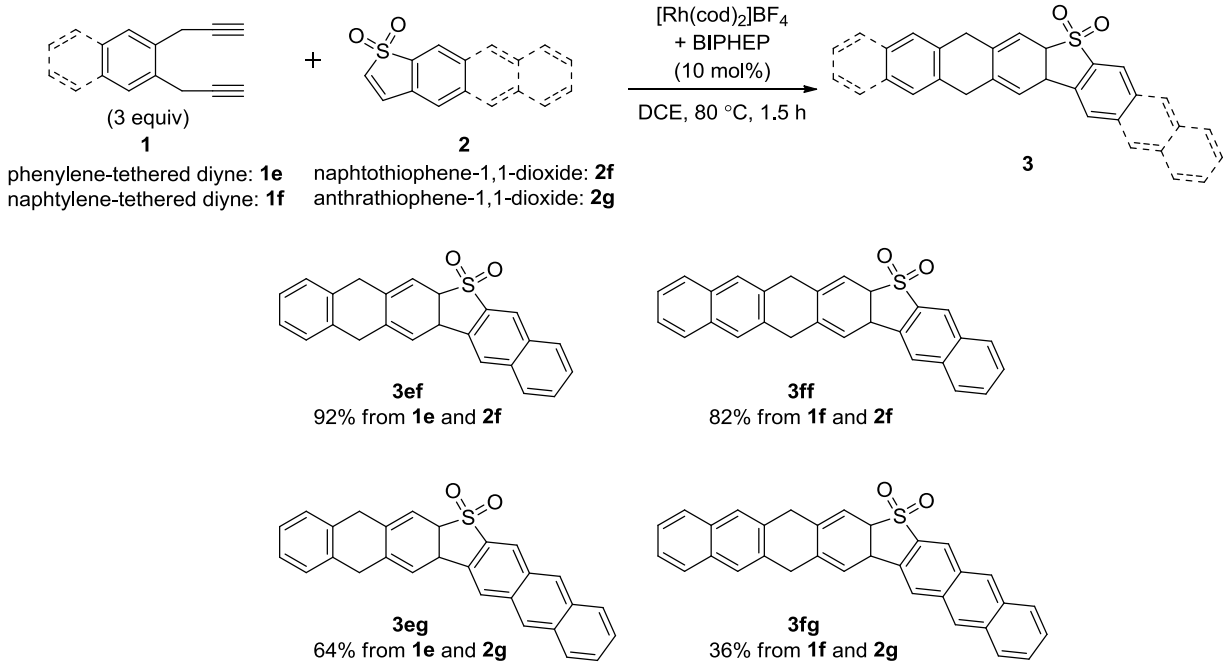


3fa
>99% from **1f** and **2a**
(Z = 2,3-$C_{10}H_6$, R^1, R^2, R^3 = H)

[*a*] Diyne was added dropwise to a solution of the Rh catalyst and benzothiophene dioxide over 1.5 h.

Next, the reaction of thiophene dioxides condensed with polycyclic aromatic hydrocarbons as ene moieties were examined (Table 3). Naphtothiophene-1,1-dioxide **2f** worked well, and the reaction with diynes **1e** and **1f** proceeded to give polycyclic compounds **3ef** and **3ff**, respectively in high yields. Furthermore, the reaction of anthrathiophene-1,1-dioxide **2g** also proceeded, but the yields of the corresponding cycloadducts **3eg** and **3fg** were moderate due to its poorer reactivity than **2f**, and **2g** was not completely consumed in these reactions.

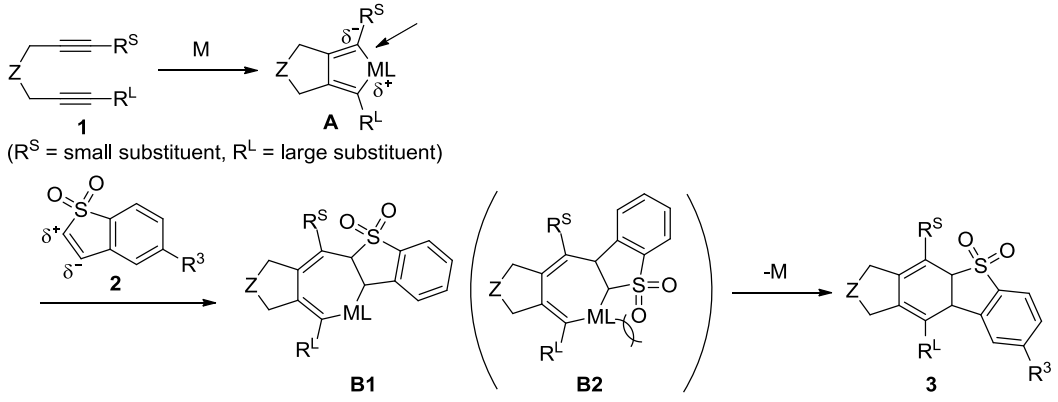
Table 3. Cycloaddition of arylene-tethered diynes **1** with naphto- and anthrathiophene dioxide derivatives **2**[*a*]



[*a*] Diyne was added dropwise to a solution of the Rh catalyst and benzothiophene dioxide over 1.5 h.

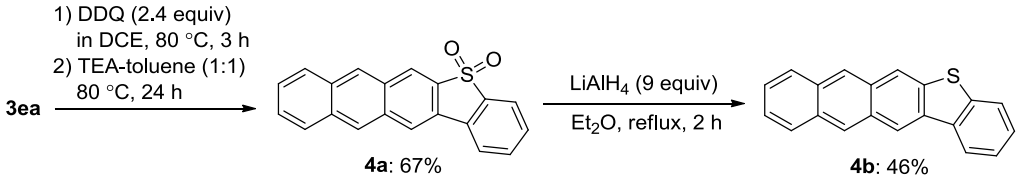
A possible explanation for regioselective reaction was shown in Scheme 3. The first step is oxidative coupling of diyne **1** and metal catalyst, and metallacyclopentadiene **A** is generated. The next step is insertion of 2,3-double bond of benzothiophene dioxide **2** to intermediate **A**. When unsymmetrical diyne ($R^L \neq R^S$) is used, benzothiophene dioxide **2** inserts to less hindered C-M bond. Due to the steric repulsion of metal on the ligand with sulfonyl group, the generation of metallacycloheptadiene **B1** is preferred to **B2**. Subsequent reductive elimination of metal catalyst, cycloadduct **3** is regioselectively obtained. Electronic factor with sulfonyl group is also conceivable, electrostatic interaction between intermediate **A** and benzothiophene dioxide **2** supported its regioselectivity.

Scheme 3. Possible explanation for regioselective reaction



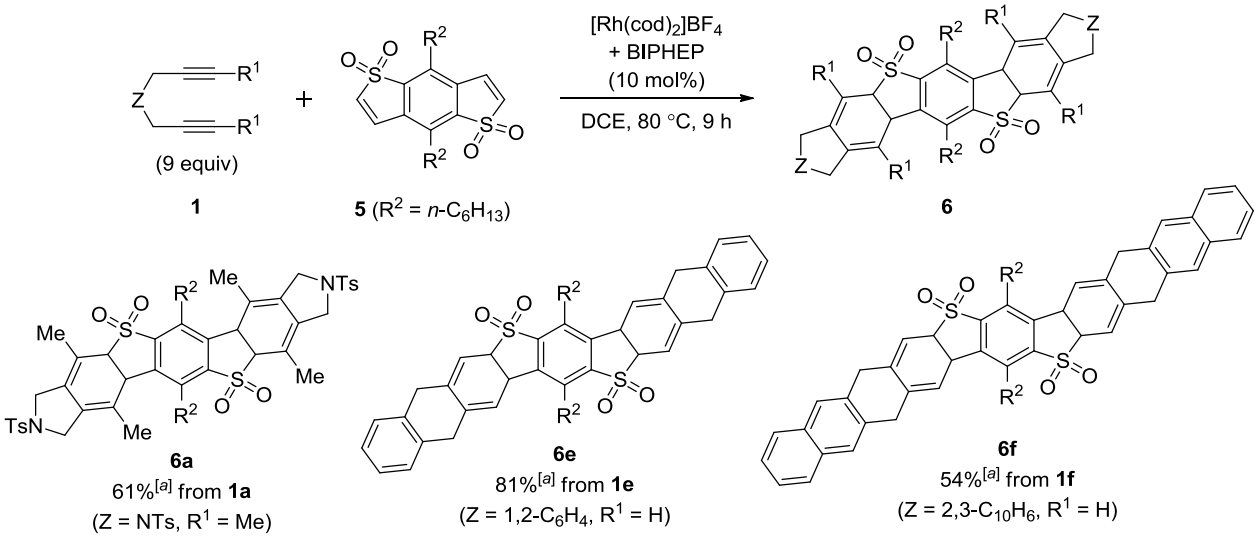
Next, the author examined the oxidative aromatization of the obtained cycloadducts. As an initial study, cycloadduct **3ea** was treated with *o*-chloranil, but desired fully aromatized product was not obtained. When 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) was used and treated with triethylamine (TEA) to induce the retro-Diels-Alder reaction of DDQ adduct with **3ea** as an intermediate,[7] desired **4a** was obtained in moderate yield (Scheme 4). Subsequent reduction gave anthra[2,3-*b*]benzo[*d*]thiophene (**4b**).

Scheme 4. Aromatization of cycloadduct **3ea** and subsequent reduction



The author further examined the consecutive cycloaddition using benzodithiophene tetraoxide (Table 4). Hexyl groups were introduced into 4 and 8 positions, respectively to increase the solubility and subjected to the reaction with diynes **1** (Table 4).[8] Excess amounts of diynes and much slower dropwise addition of them were required, but the reaction of nitrogen-tethered diyne **1a**, phenylene- and naphthylene-tethered diynes **1e** and **1f** proceeded to give polycyclic compounds. However, double bond isomerization of cyclohexadiene motif occurred under the reaction conditions, and the corresponding cycloadducts **6a**, **6e** and **6f** could not be completely isolated or fully characterized.

Table 4. Consecutive [2+2+2] cycloaddition of diynes **1** with benzodithiophene tetraoxide **5**

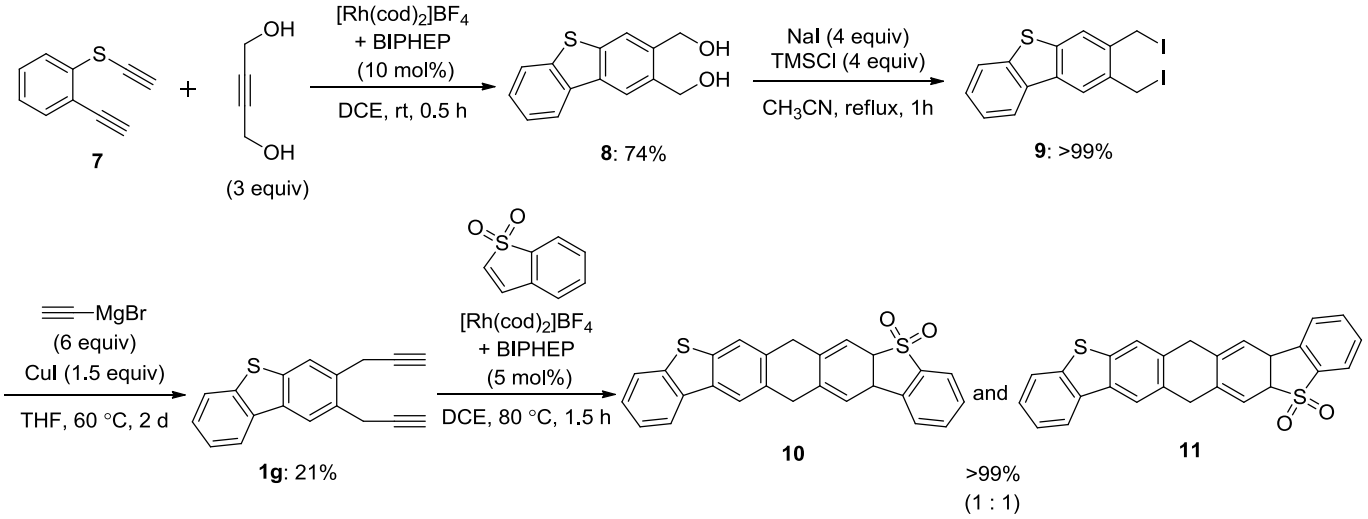


[*a*] The value is the total yield of cycloadducts **6** and their double bond isomers of 1,3-cyclohexadiene motif.

Finally, the author synthesized a condensed polycyclic compound containing two sulfur atoms, which

differ in the degree of oxidation by twice cycloadditions (Scheme 5). Rh-catalyzed intermolecular cycloaddition of sulfanylbenezene-tethered diyne **7** with 2-butyne-1,4-diol gave dibenzothiophene (DBT) derivative **8** in good yield. Subsequent iodination and ethynylation of two hydroxyl groups gave DBT-tethered diyne **1g**. The second intermolecular [2+2+2] cycloaddition of diyne **1g** with benzothiophene 1,1-dioxide **2a** proceeded to give a regioisomeric mixture of cycloadducts **10** and **11** in excellent yield. The chemical structure of **10** and **11** was determined as the mixture, because separation of their cycloadducts by using PTLC purification was impossible.

Scheme 5. Synthesis of polycyclic compounds with sulfide and sulfone moieties via two types of cycloaddition



Conclusion

The author developed Rh-catalyzed intermolecular cycloaddition of benzothiophene dioxides and benzodithiophene tetraoxide with α,ω-diynes. This is the first example of catalytic cycloaddition, where the 2,3-double bond of a benzoheterole was used as an ene moiety. The present reaction provides a new protocol for the synthesis of condensed polycyclic compounds containing sulfone moieties.

Experimental Section

General

All the reactions dealing with air or moisture sensitive compounds were carried out in a dry reaction vessel under positive pressure of argon. Air- and moisture-sensitive liquids and solutions were transferred via a syringe or a stainless steel cannula. Dehydrated 1,2-dichloroethane (DCE) is commercially available, which was dried over molecular sieves 4A (MS 4A) before use. Thin layer chromatography plates were visualized by exposure to ultraviolet light (254 nm). Organic solutions were concentrated by rotary evaporation at ca. 30 mmHg. Preparative thin-layer chromatography (PTLC) was performed with silica gel-precoated glass plates (Merck 60 GF_{254}) prepared in the author's laboratory. Flash column chromatography was performed over silica gel 200-300. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a JEOL ECX-400 (400 MHz) or ECX-500 (500 MHz) NMR spectrometer. Chemical shift values for protons are reported in parts per million (δ) relative to internal standard TMS (0 ppm) for $CDCl_3$. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 MHz: chemical shifts for carbons are reported in parts per million (δ) relative to internal standard TMS (77 ppm) for $CDCl_3$. Data are presented as following space: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad signal), coupling constant in hertz (Hz), and signal area integration in natural numbers, assignment (*italic*). High-resolution mass spectra (HRMS) were measured on ESI (Electro Spray Ionization) – orbitrap mass spectrometer. Unless otherwise noted, materials were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were used without further purification. Diynes **1a**[9], **1b**[10], **1c**[11], **1d**[12], **1e**[13] and **1f**[14] are known compounds. Benzothiphene dioxide derivatives **2a-2d**, **2f**, and **5** were synthesized by *m*CPBA oxidation of the corresponding benzothiphene derivatives, which were prepared by the reported protocols.[15-20]

Preparation of 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzothiophene *S,S*-dioxide 2e

A suspension of 5-bromo-benzothiophene *S,S*-dioxide **2c** (223.9 mg, 1.0 mmol), bis(pinacolato)diboron (305.0 mg, 1.2 mmol) and KOAc (294.0 mg, 3.0 mmol) in DMF (4.0 mL) was added to $PdCl_2$(dppf) (36.0 mg, 0.05 mmol), and the mixture was stirred at 100 °C for 3 hours. After cooling to room temperature, the mixture was diluted with brine. After separating the organic layer, the aqueous layer was extracted three times with AcOEt. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=1/1, then AcOEt only), and further purified by recrystallization from DCM/hexane to

give analytically pure product as pale yellow solid (143.1 mg, 49%).

General procedure for the cycloaddition in Table 2, 3 and the preparation of 10, 11 in Scheme 5

$[Rh(cod)_2]BF_4$ (2.0 mg, 0.005 mmol) and BIPHEP (2.6 mg, 0.005 mmol) were stirred in DCE (0.3 mL) at room temperature for 10 min, and then benzothiophene *S,S*-dioxide derivative (0.1 mmol) was added. To the yellowish orange solution, diyne (0.3 mmol) in DCE (0.7 mL) was added dropwise over 1.5 h at 80 ºC and the reaction mixture was further stirred for 5 min. After completion of the reaction, the solvent was removed under reduced pressure, and the crude product was purified by PTLC to give analytically pure compound.

General procedure for the cycloaddition in Table 4

$[Rh(cod)_2]BF_4$ (2.0 mg, 0.005 mmol) and BIPHEP (2.6 mg, 0.005 mmol) were stirred in DCE (0.3 mL) at room temperature for 10 minutes, and 4,8-bishexylbenzo[1,2-*b*:4,5-*b'*]dithiophene-*S,S,S',S*'-tetraoxide (**5**) (21.1 mg, 0.05 mmol) was added. To the yellow-orange solution, diyne (0.45 mmol) in DCE (1.0 mL) was added dropwise over 9 h at 80 ºC and the mixture was stirred for 5 min. After completion of the reaction, the solvent was removed under reduced pressure, and the crude product was purified by PTLC to give analytically pure compound.

Procedure for the oxidation in Scheme 4

DDQ (81.6mg, 0.36mmol) and 7,12,5a,13a-tetrahydro-anthra[2,3-*b*]-benzo[4,5-*d*]thiophene-*S,S*-dioxide (**3ea**) (47.7mg, 0.15 mmol) in DCE (6 ml) were stirred at 80 ºC. After completion of the reaction, the solvent was removed under reduced pressure, and triethylamine (TEA, 1.1 mL) and toluene (1.1 mL) was added.[21] The solution was heated to 80 ºC for 24 h. The solvent was removed under reduced pressure, the crude product was purified by PTLC (toluene: DCM=1:1, then DCM only) to give analytically pure **4** (18.8 mg, 0.06 mmol 40%).

Procedure for the cycloaddition in the preparation of 8 in Scheme 5

$[Rh(cod)_2]BF_4$ (2.0 mg, 0.005 mmol) and BIPHEP (2.6 mg, 0.005 mmol) were placed in Schlenk tube, which was then evacuated and backfilled with argon. To the reaction vessel was added CH_2Cl_2 (1.0 mL). Then it was filled with H_2, and the mixture was stirred at rt for 30 min under H_2. After removal of the solvent and H_2 under reduced pressure, the reaction vessel was filled with argon. DCE (0.2 mL) was added to the flask and the mixture was stirred to give a reddish solution. Then, 2-butyne-1,4-diol (12.9 mg,

0.15 mmol) was added and 1,2-dichloroethane solution (0.3 mL) of the compound **7** (0.05 mmol) was added dropwise for 0.5 h. The volatiles were removed under reduced pressure, and the crude product was purified by PTLC to afford the compound **8** (8.9 mg, 0.037 mmol, 74 %)

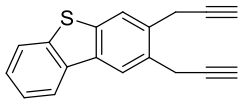
Procedure for iodination in the preparation of 9 in Scheme 5

A mixture of compound **8** (29.0 mg, 0.11 mmol) and NaI (66.0 g, 0.44 mmol) was dissolved in acetonitrile (1.2 mL). Chlorotrimethylsilane (0.055 mL, 0.44 mmol) was added to the solution and it was stirred at 70 °C for 1 h. After cooling to room temperature, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic phase was washed with brine and dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was washed with MeOH and dried in vacuo to afford the compound **9** (51.1 mg, 0.11 mmol, >99%).

Procedure for ethynylation in the preparation of 1g in Scheme 5

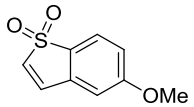
A mixture of compound **9** (46.4 mg, 0.1 mmol), copper iodide (28.6 mg, 0.15 mmol) and a THF solution of ethynyl magnesium bromide (0.50 M, 1.20 mL 0.6 mmol) are heated at 60-65 °C in 1.2 mL of THF for 48 h. After acid hydrolysis, organic materials were extracted with diethyl ether, washed several times with a 0.1 M solution of hydrochloric acid, then with sat. aqueous ammonium chloride solution and finally with brine, then dried over Na_2SO_4. The solvent is evaporated and the crude product was purified by preparative TLC to afford analytically pure compound **1g** (5.5 mg, 0.021mmol, 21 %).

Characterization of new compounds



2,3-Di(prop-2-ynyl)dibenzothiophene (1g)

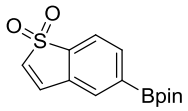
Pale yellow solid; mp 112 °C; ^{1}H NMR δ 2.28-2.29 (m, 2H), 3.77-3.78 (m, 4H), 7.43-7.47 (m, 2H), 7.83-7.86 (m, 1H), 7.99 (s, 1H), 8.14-8.17 (m, 1H), 8.24 (s, 1H); ^{13}C NMR δ 23.7, 23.8, 72.4, 72.6, 81.7, 82.0, 122.5, 122.6, 123.6, 123.8, 125.3, 127.6, 131.4, 133.9, 135.7, 136.2, 139.5, 140.7; HRMS (ESI, positive): *m/z* calcd. for $C_{18}H_{13}S^+$ $[M + H]^+$ 261.0732, found 261.0732.



5-Methoxybenzothiophene-*S,S*-dioxide (2d)

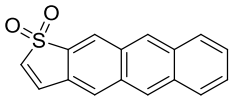
White solid; mp 98-99 °C; ^{1}H NMR δ 3.88 (s, 3H), 6.72 (d, *J* = 6.7 Hz, 1H), 6.85 (d, *J* = 2.5 Hz, 1H),

6.94-6.97 (m, 1H), 7.14 (d, *J* = 6.7 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR δ 55.9, 111.9, 114.5, 123.0, 128.4, 131.8, 132.1, 133.6, 163.9; HRMS (ESI, positive): *m/z* calcd. for $C_9H_8O_3NaS^+$ $[M + Na]^+$ 219.0086, found 219.0087.



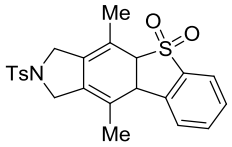
5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzothiophene-*S*,*S*-dioxide (2e)

Brown solid; mp 193-193.5 °C; ^{1}H NMR δ 1.36 (s, 12H), 6.71 (d, *J* = 6.9 Hz, 1H), 7.22 (d, *J* = 6.9 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.78 (s, 1H), 7.97 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 24.8, 84.6, 120.5, 130.2, 130.3, 131.2, 132.5, 137.3, 138.9 (a pair of peaks at the aromatic region is overlapped); HRMS (ESI, positive): *m/z* calcd. for $C_{14}H_{17}O_4BNaS^+$ $[M + Na]^+$ 315.0833, found 315.0831.



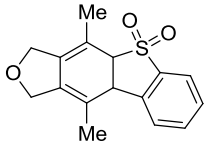
Anthra[2,3-*b*]thiophene-*S*,*S*-dioxide (2g)

Brown solid; mp 254-256 °C (decomp.); ^{1}H NMR δ 6.85 (d, *J* = 6.7 Hz, 1H), 7.41 (d, *J* = 6.7 Hz, 1H), 7.58-7.61 (m, 2H), 7.91 (s, 1H), 8.02-8.08 (m, 2H), 8.37 (s, 1H), 8.46 (s, 1H), 8.54 (s,1H); ^{13}C NMR δ 123.9, 125.9, 127.2, 127.3, 127.5, 128.3, 128.4, 128.5, 129.5, 130.1, 131.2, 131.8, 132.9, 133.4, 133.4, 134.0; HRMS (ESI, positive): *m/z* calcd. for $C_{16}H_{10}O_2NaS^+$ $[M + Na]^+$ 289.0294, found 289.0293.



2-Tosyl-4,10-dimethyl-2,3,4a,9b-tetrahydro-1H-benzo[4,5]-thieno[2,3-*f*]isoindole-*S*,*S*-dioxide (3aa)

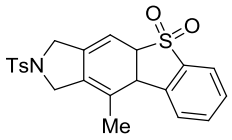
Pale brown solid; mp 201-202 °C (decomp.); ^{1}H NMR δ 1.65 (s, 3H), 1.99 (s, 3H), 2.43 (s, 3H), 3.75 (d, *J* = 13.2 Hz, 1H), 4.00 (d, *J* = 13.2 Hz, 1H), 4.10-4.30 (m, 4H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.50-7.54 (m, 2H), 7.62 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR δ 17.4, 18.6, 21.4, 44.4, 50.9, 68.5, 114.4, 120.9, 121.8, 127.7, 128.9, 129.2, 129.3, 129.9, 132.6, 133.0, 134.1, 137.7, 138.0, 144.0 (a pair of peaks at the aliphatic region is overlapped); HRMS (ESI, positive): *m/z* calcd. for $C_{23}H_{23}O_4NNaS_2^+$ $[M + Na]^+$ 464.0961, found 464.0958.



4,10-Dimethyl-2,3,4a,9b-tetrahydro-1H-benzo[4,5]-thieno[2,3-*f*]isobenzofuran-*S*,*S*-dioxide (3ba)

Pale brown solid; mp 132-133 °C; ^{1}H NMR δ 1.67 (s, 3H), 2.02 (s, 3H), 4.19 (d, *J* = 10.4 Hz, 1H), 4.30 (d,

J = 9.6 Hz, 1H), 4.45 (d, *J* = 12.8 Hz, 1H), 4.57 (d, *J* = 12.8 Hz, 1H), 4.60-4.74 (m, 2H), 7.51-7.55 (m, 2H), 7.63 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR δ 17.4, 18.8, 45.0, 69,1, 70.6, 70.7, 111.8, 118.2, 121.8, 129.1, 129.3, 132.3, 132.9, 137.3, 138.0, 138.1; HRMS (ESI, positive): *m/z* calcd. for $C_{16}H_{16}O_3NaS^+$ $[M + Na]^+$ 311.0712, found 311.0711.



2-Tosyl-10-methyl-2,3,4a,9b-tetrahydro-1H-benzo[4,5]-thieno[2,3-*f*]isoindole-*S*,*S*-dioxide (3ca)

The regioisomeric structure was determined by NOESY experiment (Figure 2). Pale brown solid; mp 160-164 °C; ^{1}H NMR δ 1.85 (s, 3H), 2.42 (s, 3H), 3.84 (d, *J* = 9.2 Hz, 1H), 3.96 (d, *J* = 9.2 Hz, 1H), 4.12-4.18 (m, 3H), 4.32 (br, 1H), 5.65 (d, *J* = 2.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.51 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.60 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR δ 18.8, 21.5, 42.8, 50.2, 51.6, 63.9, 105.0, 121.6, 124.9, 127.7, 128.0, 129.1, 129.2 129.9, 132.4, 133.3, 137.5, 138.1, 139.8, 144.0; HRMS (ESI, positive): *m/z* calcd. for $C_{22}H_{21}NO_4NaS_2^+$ $[M + Na]^+$ 450.0804, found 450.0804.

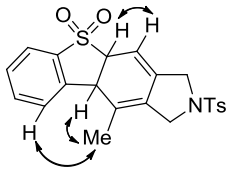
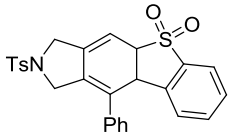


Figure 2. NOESY experiment of **3ca**



2-Tosyl-10-phenyl-2,3,4a,9b-tetrahydro-1H-benzo[4,5]-thieno[2,3-*f*]isoindole-*S*,*S*-dioxide (3da)

The regioisomeric structure was determined by NOESY experiment (Figure 3). Pale brown solid; mp 132-132.5 °C; ^{1}H NMR δ 2.43 (s, 3H), 3.85-3.89 (m, 1H), 4.06 (s, 2H), 4.13 (d, *J* = 9.9 Hz, 1H), 4.45 (br, 1H), 4.73 (d, *J* = 8.9 Hz, 1H), 5.78 (d, *J* = 2.5 Hz, 1H), 6.87 (d, *J* = 7.4 Hz, 1H), 7.22-7.46 (m, 9H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.72 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 21.5, 40.9, 51.2, 51.4, 64.3, 108.5, 121.2, 127.1, 127.4, 127.8, 128.6, 129.0, 129.0, 129.1, 129.8, 130.4, 132.4, 133.4, 136.8, 137.8, 138.5, 138.8, 144.1; HRMS (ESI, positive): *m/z* calcd. for $C_{27}H_{23}O_4NNaS_2^+$ $[M + Na]^+$ 512.0961, found 512.0962.

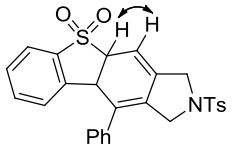
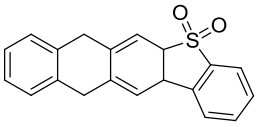
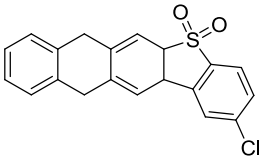


Figure 3. NOESY experiment of **3da**



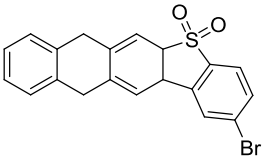
7,12,5a,13a-Tetrahydroanthra[2,3-*b*]-benzo[*d*]thiophene-*S*,*S*-dioxide (3ea)

Pale yellow solid; mp 99-100 °C; ^{1}H NMR δ 3.38-3.64 (m, 4H), 4.34 (br, 2H), 5.77 (s, 1H), 5.86 (s, 1H), 7.14-7.18 (m, 4H), 7.46–7.48 (m, 2H), 7.62 (t, *J* = 6.6 Hz, 1H), 7.81 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR δ 36.5, 36.7, 38.0, 61.7, 109.8, 119.1, 121.9, 126.6, 126.6, 126.7, 126.8, 127.0, 128.7, 132.9, 133.8, 135.7, 136.1 138.1, 138.6, 139.6; HRMS (ESI, positive): *m/z* calcd. for $C_{20}H_{16}O_2NaS^+$ $[M + Na]^+$ 343.0763, found 343.0763.



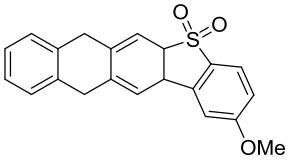
2-Chloro-7,12,5a,13a-tetrahydroanthra[2,3-*b*]-benzo[2,3-*d*]thiophene-*S*,*S*-dioxide (3eb)

White solid; mp 155-157 °C; ^{1}H NMR δ 3.39-3.63 (m, 4H), 4.33 (s, 2H), 5.76 (s, 1H), 5.83 (s, 1H), 7.16-7.18 (m, 4H), 7.42-7.44 (m, 2H), 7.72 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ 36.5, 36.7, 37.5, 62.1, 109.9, 118.1, 123.0, 126.7, 126.8, 126.8, 127.0, 129.3, 133.6, 135.6, 135.9, 136.6, 138.6, 140.1, 141.7 (a pair of peaks at the aromatic region is overlapped); HRMS (ESI, positive): *m/z* calcd. for $C_{20}H_{15}O_2ClNaS^+$ $[M + Na]^+$ 377.0373, found 377.0374.



2-Bromo-7,12,5a,13a-tetrahydroanthra[2,3-*b*]-benzo[2,3-*d*]thiophene-*S*,*S*-dioxide (3ec)

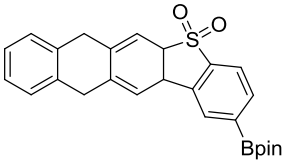
White solid; mp 152-153 °C; ^{1}H NMR δ 3.40-3.62 (m, 4H), 4.32 (s, 2H), 5.76 (s, 1H), 5.83 (s, 1H), 7.14-7.20 (m, 4H), 7.59–7.61 (m, 2H), 7.66 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR δ 36.5, 36.7, 37.5, 62.0, 109.9, 118.1, 123.2, 126.7, 126.8, 126.9, 127.0, 128.4, 129.7, 132.2, 133.7, 135.6, 135.9, 137.2, 138.7, 141.8; HRMS (ESI, positive): *m/z* calcd. for $C_{20}H_{15}O_2BrNaS^+$ $[M + Na]^+$ 420.9868, found 420.9869.



2-Methoxy-7,12,5a,13a-tetrahydroanthra[2,3-*b*]-benzo[2,3-*d*]thiophene-*S*,*S*-dioxide (3ed)

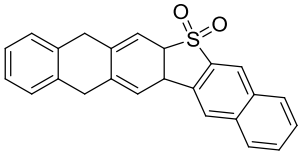
Pale yellow solid; mp 165-165.5 °C; ^{1}H NMR δ 3.37-3.63 (m, 4H), 3.87 (s, 3H), 4.30 (s, 2H), 5.74 (s, 1H), 5.84 (s, 1H), 6.88 (d, *J* = 1.6 Hz, 1H), 6.95-7.18 (m, 5H), 7.70 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR δ 36.5, 36.7, 37.9, 55.8, 62.1, 110.1, 110.7, 115.3, 118.9, 123.3, 126.6, 126.7, 126.8, 127.0, 130.1, 133.0, 135.8, 136.1,

138.4, 142.4, 164.1; HRMS (ESI, positive): *m/z* calcd. for $C_{21}H_{18}O_3NaS^+$ $[M + Na]^+$ 373.0869, found 373.0867.



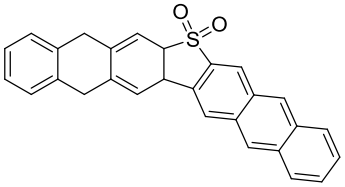
2-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-7,12,5a,13a-tetrahydroanthra[2,3-*b*]-benzo[2,3-*d*]thiophene-*S*,*S*-dioxide (3ee)

Brown solid; mp 84-85 °C; ^{1}H NMR δ 1.37 (d, *J* = 3.0 Hz, 12H), 3.37-3.64 (m, 4H), 4.30-4.35 (m, 2H), 5.83 (d, *J* = 8.4 Hz, 2H), 7.12-7.19 (m, 4H), 7.79-7.81 (m, 1H), 7.88-7.90 (m, 2H); ^{13}C NMR δ 24.8, 24.8, 24.9, 36.5, 36.8, 38.0, 61.7, 75.0, 84.5, 109.7, 119.3, 121.0, 126.6, 126.7, 126.8, 127.0, 132.8, 132.9, 134.9, 135.8, 136.2, 138.6, 138.7, 140.4; HRMS (ESI, positive): *m/z* calcd. for $C_{26}H_{27}O_4BNaS^+$ $[M + Na]^+$ 469.1615, found 469.1615.



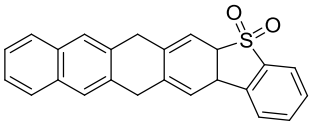
8,13,6a,14a-Tetrahydroanthra[2,3-*b*]-naphtho[2,3-*d*]thiophene-*S*,*S*-dioxide (3ef)

Pale yellow solid; mp 160-160.5 °C; ^{1}H NMR δ 3.39-3.59 (m, 4H), 4.37 (d, *J* = 9.8 Hz, 1H), 4.47 (d, *J* = 9.8 Hz, 1H), 5.86 (s, 1H), 5.93 (s, 1H), 7.12-7.18 (m, 4H), 7.52–7.61 (m, 2H), 7.86-7.93 (m, 1H), 8.30 (s, 1H); ^{13}C NMR δ 36.5, 36.7, 37.5, 62.4, 110.0, 119.7, 122.3, 125.6, 126.6, 126.7, 126.8, 127.0, 127.2, 127.9, 128.6, 129.2, 132.4, 133.1, 135.5, 135.7, 135.7, 135.9, 136.1, 138.8; HRMS (ESI, positive): *m/z* calcd. for $C_{24}H_{18}O_2NaS^+$ $[M + Na]^+$ 393.0921, found 393.0920.



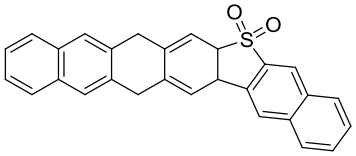
9,14,7a,15a-Tetrahydroanthra[2,3-*b*]-anthra[2,3-*d*]thiophene-*S*,*S*-dioxide (3eg)

Brown solid; mp 184-185 °C , ^{1}H NMR δ 3.43-3.60 (m, 4H), 4.38-4.41 (m, 1H), 4.49-4.52 (m, 1H), 5.89 (d, *J* = 3.7 Hz, 1H), 5.99 (d, *J* = 3.7 Hz, 1H), 7.13-7.18 (m, 4H), 7.49-7.56 (m, 2H), 8.00-8.04 (m, 3H), 8.43 (s, 1H), 8.50 (s, 1H), 8.55 (s, 1H); ^{13}C NMR δ 36.5, 36.8, 37.6, 62.5, 110.1, 120.0, 123.4, 125.7, 126.3, 126.6, 126.7, 126.7, 126.8, 127.0, 127.0, 128.1, 128.4, 128.6, 130.0, 132.2, 132.8, 133.2, 133.4, 134.4, 135.5, 135.8, 136.1, 139.0; HRMS (ESI, positive): *m/z* calcd. for $C_{28}H_{20}O_2NaS^+$ $[M+Na]^+$ 443.1076, found 443.1076.



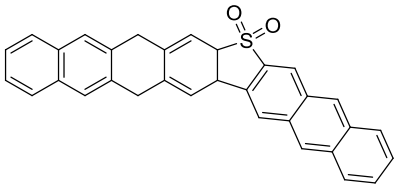
6,14,4a,14a-Tetrahydrotetraceno[2,3-*b*]-benzo[2,3-*d*]thiophene-*S*,*S*-dioxide (3fa)

Pale yellow solid; mp 121 °C; ^{1}H NMR δ 3.57-3.82 (m, 4H), 4.32-4.39 (m, 2H), 5.81 (d, *J* = 3.9 Hz, 1H), 5.91 (d, *J* = 3.9 Hz, 1H), 7.40-7.44 (m, 2H), 7.47-7.50 (m, 2H), 7.61-7.64 (m, 3H), 7.74-7.79 (m, 2H), 7.83 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR δ 38.4, 38.6, 39.4, 63.1, 111.4, 120.7, 123.3, 126.2, 126.5, 126.9, 126.9, 128.0, 128.6, 128.7, 130.2, 134.0, 134.1, 134.4, 135.3, 135.7, 136.1, 139.6, 140.1, 141.0; HRMS (ESI, positive): *m/z* calcd. for $C_{24}H_{18}O_2NaS^+$ $[M + Na]^+$ 393.0920, found 393.0917.



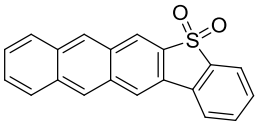
7,14,5a,15a-Tetrahydrotetraceno[2,3-*b*]-naphtho[2,3-*d*]thiophene-*S*,*S*-dioxide (3ff)

Pale yellow solid; mp 146 °C; ^{1}H NMR δ 3.60-3.78 (m, 4H), 4.39-4.52 (m, 2H), 5.93 (d, *J* = 4.0 Hz, 1H), 5.99 (d, *J* = 4.0 Hz, 1H), 7.39-7.43 (m, 2H), 7.55-7.61 (m, 4H), 7.75-7.76 (m, 2H), 7.88 (d, *J* = 6.6 Hz, 2H), 7.96 (d, *J* = 8.1 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR δ 37.9, 38.1, 38.5, 63.4, 111.2, 120.8, 123.4, 125.8, 126.0, 126.4, 126.4, 126.5, 128.1, 128.2, 128.3, 128.9, 129.6, 130.2, 133.5, 133.6, 133.6, 134.3, 135.2, 135.6, 136.4, 136.7, 136.9, 139.8; HRMS (ESI, positive): *m/z* calcd. for $C_{28}H_{20}O_2NaS^+$ $[M + Na]^+$ 443.1076, found 443.1076.



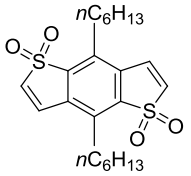
8,15,6a,16a-Tetrahydrotetraceno[2,3-*b*]-anthra[2,3-*d*]thiophene-*S*,*S*-dioxide (3fg)

Yellow solid; mp 152 °C; ^{1}H NMR δ 3.63-3.79 (m, 4H), 4.42-4.56 (m, 2H), 5.95 (d, *J* = 4.1 Hz, 1H), 6.06 (d, *J* = 4.1 Hz, 1H), 7.40-7.43 (m, 2H), 7.52-7.56 (m, 2H), 7.62 (d, *J* = 3.2 Hz, 2H), 7.75-7.77 (m, 2H), 8.00-8.05 (m, 3H), 8.47 (s, 1H), 8.54 (s, 1H), 8.59 (s, 1H); ^{13}C NMR δ 37.9, 38.1, 38.5, 63.5, 111.1, 121.0, 124.4, 125.8, 126.0, 126.4, 126.4, 126.6, 127.3, 127.6, 127.9, 128.1, 128.2, 129.0, 129.3, 129.6, 130.9, 133.2, 133.6, 133.6, 133.7, 134.1, 134.4, 135.2, 135.3, 135.6, 136.4, 140.0; HRMS (ESI, positive): *m/z* calcd. for $C_{32}H_{22}O_2NaS^+$ $[M + Na]^+$ 493.1233, found 493.1233.



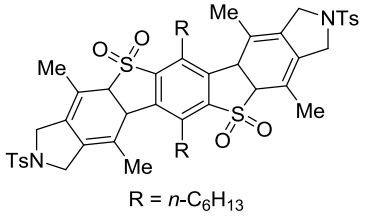
Anthra[2,3-*b*]-benzo[2,3-*d*]thiophene-*S*,*S*-dioxide (4a)

Yellow solid; mp 293-294 °C; ^{1}H NMR δ 7.54-7.62 (m, 3H), 7.68-7.75 (m, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 8.00-8.06 (m, 3H), 8.36 (s, 1H), 8.52 (s, 1H), 8.53 (s, 1H), 8.55 (s, 1H) ; ^{13}C NMR δ 121.2, 121.9, 122.3, 124.4, 126.5, 126.9, 127.4, 127.9, 128.2, 128.5, 129.3, 130.3, 130.4, 132.2, 132.3, 132.7, 133.5, 134.0, 135.4, 138.5; HRMS (ESI, positive): *m/z* calcd. for $C_{20}H_{12}O_2NaS^+$ $[M + Na]^+$ 339.0450, found 339.0450.



4,8-Dihexylbenzo[1,2-*b*:4,5-*b*']dithiophene-*S*,*S*,*S*',*S*'-tetraoxide (5)

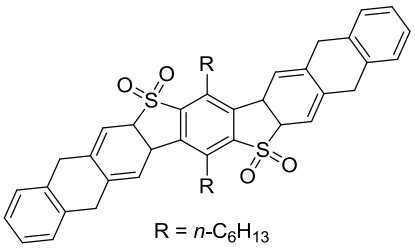
Yellow solid; mp 172-172.5 °C; ^{1}H NMR δ 0.90 (t, *J* = 6.9 Hz, 6H), 1.32-1.35 (m, 8H), 1.44 - 1.47 (m, 4H), 1.64-1.67 (m, 4H), 3.00 (t, *J* = 8.4 Hz, 4H), 6.80 (d, *J* = 7.2 Hz, 2H), 7.33 (d, *J* = 7.2 Hz, 2H) ; ^{13}C NMR δ 14.0, 22.5, 27.4, 29.4, 31.4, 31.8, 128.4, 131.8, 132.8, 134.0, 139.4; HRMS (ESI, positive): *m/z* calcd. for $C_{22}H_{30}O_4NaS_2^+$ $[M + Na]^+$ 445.1478, found 445.1478.



R = *n*-C_6H_{13}

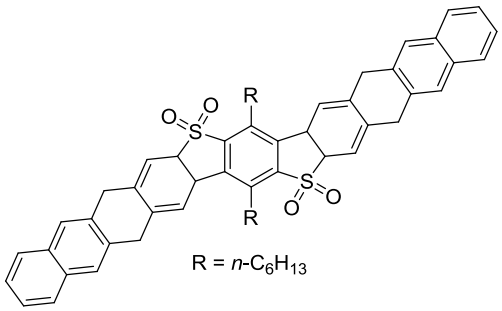
2,3,9,10,4a,7a',11a',13a-Octahydro-6,13-dihexyldi[2,3-*f*:2',3'-*f*]isoindolebenzo[1,2-*b*:4,5-*b*']-dithiophene-*S*,*S*,*S*',*S*'-tetraoxide (6a)

Pale yellow solid; mp 138-139 °C; ^{1}H NMR δ 0.87 (t, *J* = 6.8 Hz, 6H), 1.22-1.53 (m, 22H), 1.99 (s, 6H), 2.43 (s, 6H), 2.66-2.84 (m, 2H), 3.06-3.23 (m, 2H), 3.73-4.60 (m, 12H), 7.34 (d, *J* = 8.1 Hz, 4H), 7.72 (d, *J* = 8,1 Hz, 4H);^{13}C NMR δ 14.0, 16.8, 18.8, 21.6, 22.5, 22.6, 29.7, 29.9, 31.4, 40.8, 50.7, 50.8, 70.2, 114.1, 120.5, 127.8, 130.0, 130.5, 132.8, 135.1, 136.8, 139.3, 141.0, 144.1; HRMS (ESI, positive): *m/z* cald. for $C_{52}H_{64}N_2O_8NaS_4^+$[M+Na]$^+$995.3438, found 995.3436.



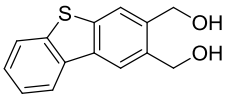
5,10,15,20,6a,9a',16a',18a-Ocatahydro-7,17-dihexyldianthra[2,3-*d*:2',3'-*d*]benzo[1,2-*b*:4,5-*b*']-dithiophene-*S*,*S*,*S'*,*S'*-tetraoxide (6e)

Pale yellow solid; mp 183-184 °C; ^{1}H NMR δ 0.87 (t, *J* = 14.4 Hz, 6H), 1.24-1.81 (m, 16H), 2.89-2.97 (m, 2H), 3.06-3.14 (m, 2H), 3.34 (d, *J* = 16.1 Hz, 2H), 3.42 (d, *J* = 16.1 Hz, 2H), 3.45 (d, *J* = 17.3 Hz, 2H), 3.77 (d, *J* = 17.3 Hz, 2H), 4.23 (dd, *J* = 4.1, 4.1 Hz, 2H), 4.50 (d, *J* = 5.0 Hz, 2H), 5.46 (br, 2H), 5.88 (d, *J* = 5.4 Hz, 2H), 7.16-7.25 (m, 8H);^{13}C NMR δ 13.9, 14.0, 22.4, 27.9, 29.8, 31.1, 31.3, 36.5, 36.6, 62.1, 108.1, 118.0, 126.7, 126.8, 126.8, 127.0, 134.0, 135.4, 136.1, 136.7, 138.9, 141.4, 142.5; HRMS (ESI, positive): *m/z* cald. for $C_{46}H_{50}O_4NaS_2^+$[M+Na]$^+$753.3043, found 753.3038.



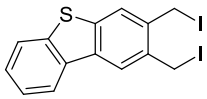
6,11,17,22,7a,9a',18a',20a-Ocatahydro-8,19-dihexyldianthra[2,3-*d*:2',3'-*d*]benzo[1,2-*b*:4,5-*b*']-dithiophene-*S*,*S*,*S'*,*S'*-tetraoxide (6f)

Pale yellow solid; mp 214 °C; ^{1}H NMR δ 0.81-0.88 (m, 6H), 1.25-1.31 (m, 10H), 1.43-1.51 (m, 3H), 1.64-1.68 (m,1H), 1.74-1.86 (m, 2H), 2.71-2.77 (m, 1H), 2.90-2.96 (m, 1H), 3.08-3.14 (m, 1H), 3.46-3.52 (m, 1H), 3.52 (d, *J* = 15.8 Hz, 2H), 3.68 (d, *J* = 15.8 Hz, 2H), 3.79 (d, *J* = 16.7 Hz, 2H), 3.94 (dd, *J* = 6.7, 16.7 Hz, 2H), 4.22-4.27 (m, 2H), 4.49 (t, *J* = 10.2 Hz, 2H), 5.52 (d, *J* = 15.1 Hz, 2H), 5.93-5.95 (m, 2H), 7.42-7.44 (m, 4H), 7.63 (br, 2H),7.67(s, 2H), 7.76-7.79 (m, 4H); ^{13}C NMR δ 14.0, 14.0, 22.5, 27.2, 28.0, 29.9, 29.9, 31.2, 31.3, 31.4, 31.7, 36.5, 36.6, 37.2, 37.2, 62.2, 62.3, 108.4, 118.3, 125.0, 125.0, 125.2, 125.2, 125.6, 125.6, 127.3, 127.3, 127.3, 132.7, 132.8, 134.0, 134.0, 134.2, 134.2, 134.7, 134.7, 136.8, 137.2, 139.0, 139.1, 141.6, 141.6, 142.5, 142.7; HRMS (ESI, positive): *m/z* cald. for $C_{54}H_{54}O_4NaS_2^+$[M+Na]$^+$853.3356, found 853.3354.



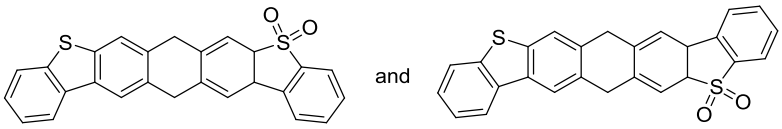
2,3-Di(hydroxymethyl)dibenzothiophene (8)

White solid; mp 163 °C; ^{1}H NMR δ 2.87 (br, 2H), 4.90 (s, 2H), 4.94 (s, 2H), 7.46-7.48 (m, 2H), 7.85-7.86 (m, 1H), 7.87 (s, 1H), 8.15-8.16 (m, 1H), 8.16 (s, 2H); ^{13}C NMR (Acetone-d_6) δ 63.0, 63.2, 121.9, 122.5, 122.6, 123.9, 125.6, 127.6, 135.4, 136.6, 137.9, 139.0, 140.5, 140.7; HRMS (ESI, positive): *m/z* calcd. for $C_{14}H_{12}O_2NaS^+$ $[M + Na]^+$ 267.0450, found 267.0450.



2,3-Di(iodomethyl)dibenzothiophene (9)

Yellow solid; mp 145 °C; ^{1}H NMR δ 4.75 (s, 2H), 4.79 (s, 2H), 7.46-7.47 (m, 2H), 7.80 (s, 1H), 7.81-7.83 (m, 1H), 8.09 (s, 1H), 8.10-8.12 (m, 1H); ^{13}C NMR δ 2.2, 2.7, 121.8, 122.9, 123.6, 124.8, 124.8, 127.3, 133.9, 134.7, 136.0, 136.2, 139.9, 140.1; HRMS (ESI, positive): *m/z* calcd. for $C_{14}H_{11}S^+$ $[M + H]^+$ 211.0576, found 211.0575. Iodine was eliminated.



7a, 12a-Dihydro((6, 11-dihydroanthra[2,3-*b*]-benzo[2,3-*d*]thiopheno)) [2,3-*b*]-benzo[2,3-*d*]-thiophene-12, 12-dioxide (10), and 7a, 12a-Dihydro((6,11-dihydroanthra[2,3-*b*]-benzo[2,3-*d*]-thiopheno)) [2,3-*b*]-benzo[2,3-*d*]-thiophene-8, 8-dioxide (11)

^{1}H NMR δ 3.53-3.81 (m, 8H), 4.33-4.40 (m, 4H), 5.82 (br, 2H), 5.92 (br, 2H), 7.42-7.45 (m, 4H), 7.47-7.50 (m, 4H), 7.61-7.64 (m, 3H), 7.66 (s, 1H), 7.81-7.83 (m, 4H), 7.92 (s, 1H), 7.96 (s, 1H), 8.08-8.11 (m, 2H); ^{13}C NMR δ 37.0, 37.1, 37.2, 37.3, 38.1, 61.7, 110.1, 110.2, 119.3, 119.4, 119.6, 119.8, 120.7, 120.9, 121.2, 121.3, 122.0, 122.8, 122.9, 124.3, 124.4, 126.4, 126.4, 126.6, 128.8, 132.6, 132.8, 133.0, 133.0, 133.9, 134.3, 134.4, 135.1, 135.4, 135.4, 135.5, 137.8, 137.9, 138.2, 138.3, 138.5, 138.6, 139.4, 139.5, 139.6, 139.6; HRMS (ESI, positive): *m/z* calcd. for $C_{26}H_{18}O_2NaS^+$ $[M + Na]^+$ 449.0640, found 449.0640.

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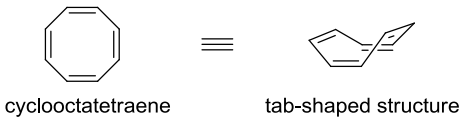
Chapter 8

Enantioselective Synthesis of Multi-Substituted Tribenzothiepin Derivatives by Rhodium-Catalyzed Intermolecular Cycloaddition

Backgrounds

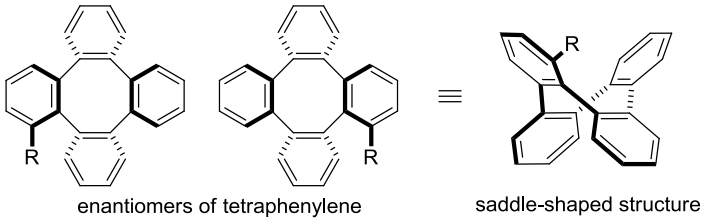
Cyclooctatetraene is a non-aromatic compound possessing an 8π electron system with non-planar, and tub-shaped sturucture (Figure 1). Its cyclic skeleton gives a unique flexible π-conjugated system. For example, an aryleno[*a*,*e*]cyclooctatetraene derivative, in which two aromatic fragments are fused to a cyclooctatetraene core, has shown to exhibit a dynamic conformational change, and perturbs the π-conjugation.[1]

Figure 1. Structure of cyclooctatetraene



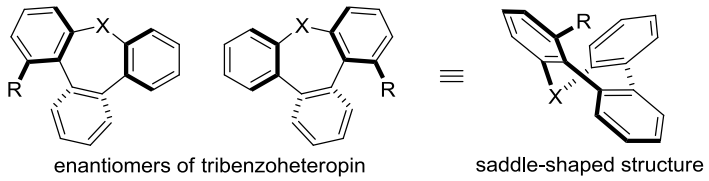
In contrast, tetrabenzo[*a,c,e,g*]cyclooctatetraene, called *o,o,o,o*-tetraphenylene, is a very rigid molecule possessing a saddle-shaped structure and scarcely undergoes flipping.[2] As a result, the introduction of at least one substituent can generate chirality, and the asymmetric synthesis of multi-substituted *o,o,o,o*-tetraphenylenes and their applications have been studied comprehensively (Figure 2).[3]

Figure 2. Structure of tetraphenylene

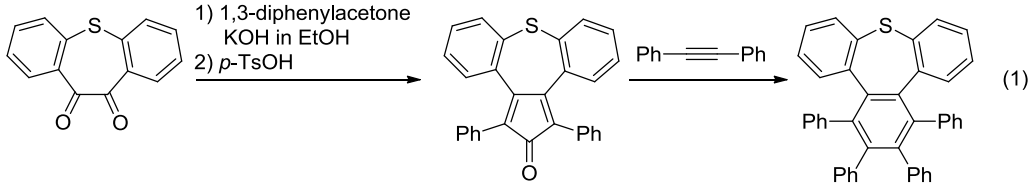


Heteropin is a seven-membered heterocyclic compound, which is considered to be a hetero-analogue of cyclooctatetraene, but little is known about its derivatives, probably because of their instability. In fact, thiepin itself is unstable[4] and can be isolated by converting to an iron complex[5]. On the other hand, tribenzoheteropin, a hetero-analogue of *o,o,o,o*-tetraphenylene, is expected to be a more stable and unique saddle-shaped molecule.[6] The introduction of even a single substituent can generate chirality (Figure 3).

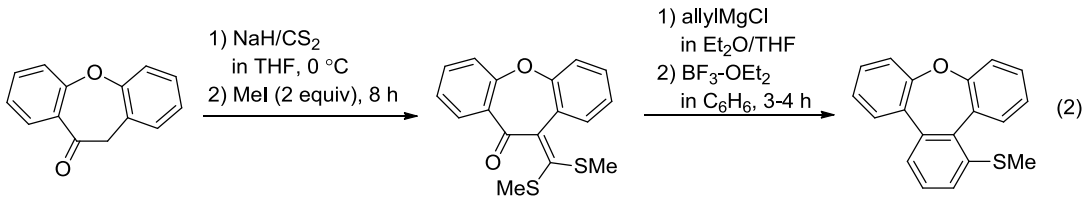
Figure 3. Enantiomes of tribenzoheteropin



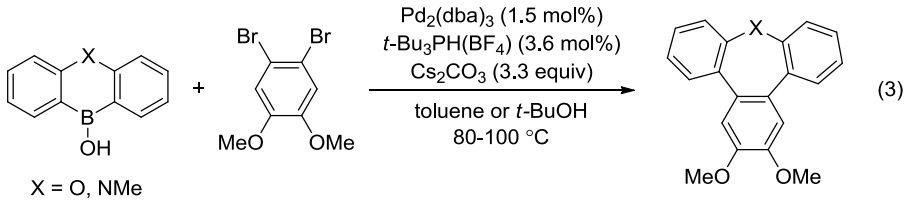
However, the synthetic methods for substituted tribenzoheteropin are quite limited. Substituted tribenzazepin and tribenzothiepin have been obtained by a photo-stimulated reaction, but in low yield.[7] As a classical protocol, Hori and co-workers reported the synthesis of substituted tribenzothiepin derivatives via [4+2] cycloaddition of cyclopentadienone-fused dibenzothiepin with alkynes (eq. 1).[8]



Ila and co-workers reported the synthesis of substituted tribenzoxepin derivatives via the cycloaromatization of ketene dithioacetal with allyl magnesium chloride (eq. 2).[9] These two methods are stoichiometric protocols where dibenzoheteropins were used as substrates.



With regard to catalytic protocol that includes the construction of a heteropin core, only one example of consecutive Suzuki-Miyaura coupling was recently reported by Taylor and co-workers, and both tribenzoxepin and tribenzazepin derivatives could be obtained (eq. 3).[10]

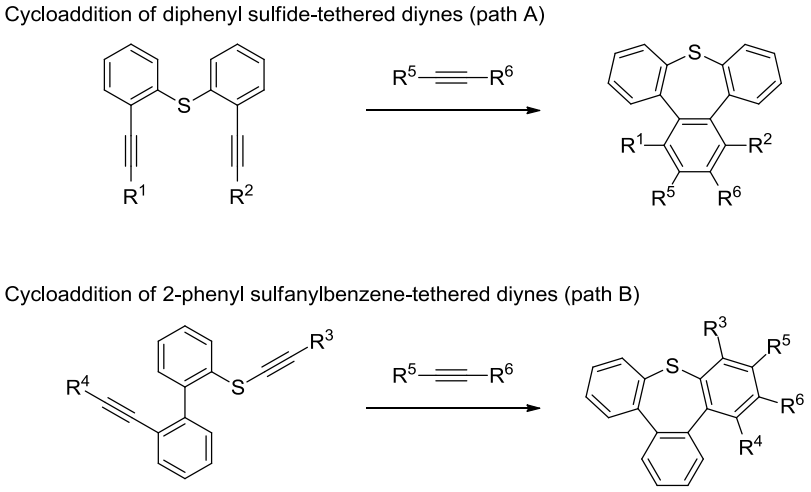


As only an example of asymmetric synthesis, chiral tribenzothiepin-2-carboxylic acid *S*,*S*-dioxide was prepared by optical resolution using brucine,[11] however, there has been no report of an enantioselective synthesis of substituted tribenzoheteropins.

Results and Discussion

The author considered that transition metal-catalyzed cycloaddition can be used for the construction of tribenzothiepin skeleton. There are two types of intermolecular cycloaddition for multi-substituted tribenzothiepin derivatives (Scheme 1). A cycloaddition of diphenyl sulfide-tethered diynes with alkynes gives 1,2,3,4-substituted tribenzothiepins (path A) and that of 2-phenyl sulfanylbenzene-tethered diynes with alkynes gives chiral 5,6,7,8-substituted tribenzothiepins (path B). The author describes the first catalytic and enantioselective synthesis of multi-substituted tribenzothiepin derivatives under mild conditions.

Scheme 1. Two types of intermolecular cycloaddition for the construction of tribenzothiepin skeleton



First, the intermolecular cycloaddition of unsymmetrical diphenyl sulfide-tethered diynes ($R^1 \neq R^2$) with dimethyl acetylenedicarboxylate (DMAD) was examined (path A in Scheme 1). The author chose diyne **1a** possessing an *n*-pentyl group on one of the alkyne termini as a model substrate and investigated various chiral rhodium catalysts in 1,2-dichloroethane (DCE) (Table 1). When a rhodium catalyst consisting of tetrafluoroborate (BF_4) as a counter anion and (*S*)-BINAP as a chiral ligand was used, desired 1,2,3-tribenzothiepin derivative **3aa** was obtained in moderate yield, but in low ee (Entry 1). When (*S*,*S*)-Me-DUPHOS was examined as a chiral ligand, the reaction proceeded smoothly, and the yield and ee were improved slightly (Entry 2). When (*S*,*S*)-CHIRAPHOS was used, the ee was drastically improved (Entry 3). (*S*,*S*)-BDPP gave higher ee than (*S*,*S*)-NORPHOS (Entries 4 and 5). Lower concentration of the diyne improved the yield because the formation of self-cycloadduct of **1a** was suppressed (Entry 6). When counter anions were examined, trifluoromethanesulfonate (OTf) was the best, and chiral tribenzothiepin **3aa** was obtained in high yield with high ee (Entry 8).

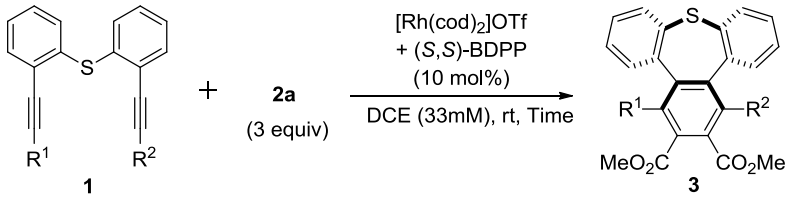
Table 1. Screening of chiral rhodium catalysts for the reaction of **1a**

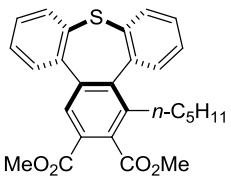
Entry	X	Chiral Ligand	Time / h	Yield / %	Ee / %
1[a]	BF_4	(*S*)-BINAP	15	52	6
2[a]	BF_4	(*S,S*)-Me-DUPHOS	2	70	17
3[a]	BF_4	(*S,S*)-CHIRAPHOS	4.5	74	79
4[a]	BF_4	(*S,S*)-NORPHOS	6	70	78
5[a]	BF_4	(*S,S*)-BDPP	3.5	54	89
6[b]	BF_4	(*S,S*)-BDPP	12	74	88
7[b]	BARF	(*S,S*)-BDPP	12	67	90
8[b]	OTf	(*S,S*)-BDPP	12	77	93

[*a*] The concentration of diyne **1a** was 100 mM. [*b*] The concentration of diyne **1a** was 33 mM.

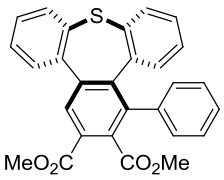
Next, various diphenyl sulfide-tethered diynes were screened under the optimal reaction conditions (Table 2). The reaction using diyne **1b** possessing a phenyl group proceeded, and the corresponding tribenzothiepin **3ba** was obtained in high yield and ee. When diynes **1c-1f**, which have a methoxy group as an electron-donating group or a bromo group as an electron-withdrawing group on the benzene ring, were used, the desired reaction proceeded efficiently to give tribenzothiepins **3ca-3fa**. Thiophene could also be installed by the reaction of **1g** and **1h**, and tribenzothiepins possessing a thienyl group **3ga** and **3ha** were obtained in high ee. Diyne **1i** possessing a naphthyl group on the alkyne termini was also a good substrate, and chiral tribenzothiepin **3ia** was obtained in high yield with 93% ee. When diynes **1j** and **1k**, which have substituents on both alkyne termini, were accepted in the reaction, but heating conditions were required for high conversion. In these cases, (*S,S*)-CHIRAPHOS gave better results than (*S,S*)-BDPP, and the reactions gave tetrasubstituted tribenzothiepins **3ja** and **3ka**. While the enantioselectivity of the reaction of trimethylsilyl (TMS), pentyl-substituted diyne **1j** decreased, the reaction of phenyl and pentyl-substituted diyne **1k** proceeded almost quantitatively with high enantioselectivity. Absolute configuration of cycloadduct **3ga** was determined by X-ray crystallographic analysis in Figure 4, and that of other cycloadducts were relatively determined.

Table 2. Intermolecular cycloaddition of diphenyl sulfide-tethered diynes with DMAD (path A).

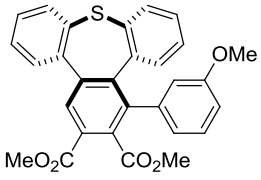




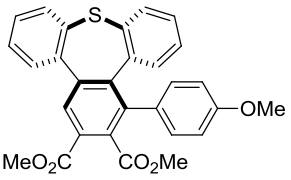
3aa
77%, 93% ee (12 h)
from **1a**
(R^1 = H, R^2 = *n*-C_5H_{11})



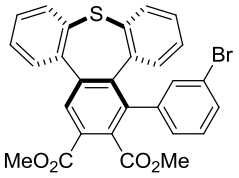
3ba
80%, 86% ee (24 h)
from **1b**
(R^1 = H, R^2 = Ph)



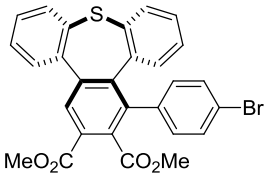
3ca
90%, 75% ee (4 h)
from **1c**
(R^1 = H, R^2 = 3-OMeC_6H_4)



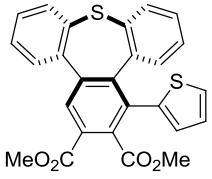
3da
89%, 92% ee (6 h)
from **1d**
(R^1 = H, R^2 = 4-OMeC_6H_4)



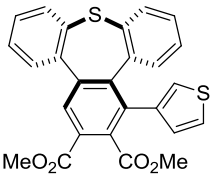
3ea
70%, 91% ee (8 h)
from **1e**
(R^1 = H, R^2 = 3-BrC_6H_4)



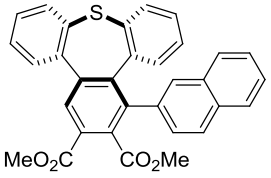
3fa
83%, 86% ee (4 h)
from **1f**
(R^1 = H, R^2 = 4-BrC_6H_4)



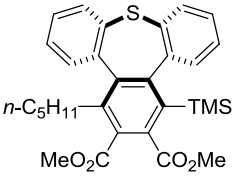
3ga
45%, 95% ee (4 h)
from **1g**
(R^1 = H, R^2 = 2-thienyl)



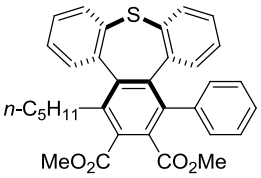
3ha
83%, 94% ee (6 h)
from **1h**
(R^1 = H, R^2 = 3-thienyl)



3ia
76%, 93% ee (5 h)
from **1i**
(R^1 = H, R^2 = 2-naphthyl)



3ja[a]
78%, 68% ee (24 h)
from **1j**
(R^1 = *n*-C_5H_{11}, R^2 = TMS)

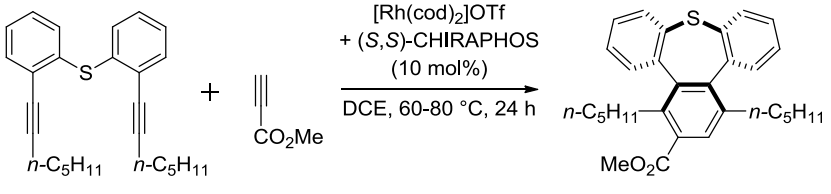


3ka[a]
98%, 87% ee (24 h)
from **1k**
(R^1 = *n*-C_5H_{11}, R^2 = Ph)

[*a*] (*S*,*S*)-CHIRAPHOS was used as a chiral ligand, and the reaction was examined at rt to 60 °C.

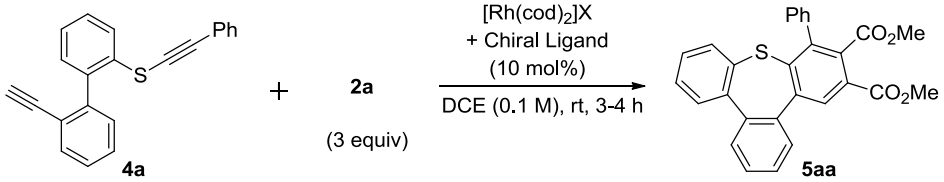
Furthermore, the reaction of a symmetrical diyne **1l** possessing pentyl groups on both alkyne termini with methyl propiolate (**2b**) as an unsymmetrical alkyne was examined (Scheme 2). The reaction required heating conditions and excess amounts of alkyne **2b**, but chiral 1,2,4-trisubstituted tribenzothiepin derivative **3lb** was obtained in moderate yield with good ee.

Scheme 2. Cycloaddition of symmetrical diphenyl sulfide-tethered diyne with methyl propiolate



Next, the intermolecular cycloaddition of 2-phenyl sulfanylbenzene-tethered diynes with DMAD for the synthesis of multi-substituted tribenzothiepin derivatives was examined (path B in Scheme 2). The author determined **4a**, possessing a phenyl group on one of the alkyne termini as a model substrate and investigated chiral catalysts (Table 3). A rhodium catalyst consisting of BARF as a counter anion and (*S*,*S*)-Me-DUPHOS as a chiral ligand was used, but the desired cycloadduct **5aa** was not obtained (Entry 1). When (*S*)-BINAP was examined, desired 6,7,8-trisubstituted tribenzothiepin **5aa** was obtained in low yield, but with good ee (Entry 2). BINAP derivatives were further examined, but both yield and ee did not exceed those by BINAP (Entries 3-5). When (*S*)-MeO-BIPHEP was examined, the highest yield and ee were achieved (Entry 6). After counter anion screening, BARF was the best (Entries 6-8).

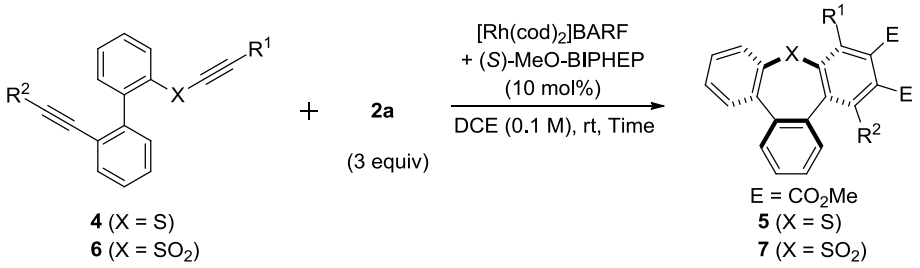
Table 3. Screening of chiral rhodium catalysts for path B



Entry	X	Chiral Ligand	Yield / %	Ee / %
1	BARF	(*S*,*S*)-Me-DUPHOS	not obtained	-
2	BARF	(*S*)-BINAP	36	66
3	BARF	(*S*)-tol-BINAP	27	8
4	BARF	(*S*)-H_8-BINAP	27	72
5	BARF	(*S*)-SEGPHOS	57	60
6	BARF	(*S*)-OMe-BIPHEP	58	81
7	BF_4	(*S*)-OMe-BIPHEP	50	62
8	OTf	(*S*)-OMe-BIPHEP	32	63

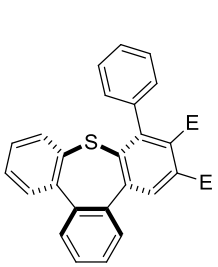
Substrate scope of diynes **4** was shown in Table 4. The reaction of diyne **4b**, which has a 4-methoxyphenyl group on the alkyne terminus, also proceeded to give cycloadduct **5ba**. Alkyl-substituted diyne **4c** was also transformed into the corresponding cycloadduct **5ca** with good ee. The cycloaddition of diynes possessing substituents on both alkyne termini was examined: diynes **4d** and **4e** having phenyl or pentyl groups on both alkyne termini, and diynes **4f** and **4g** having phenyl and pentyl groups on the respective alkyne termini were accepted in the reaction. While the yields of 5,6,7,8-tetrasubstituted tribenzothiepins **5da**-**5ga** were low to moderate, good enantioselectivity was achieved. In addition, sulfoxide-tethered diyne **6** was also a good substrate, and tribenzothiepin *S*,*S*-dioxide **7** was obtained with good ee. Absolute configuration of cycloadduct **5da** was determined by X-ray crystallographic analysis in Figure 5, and that of other products were relatively determined.

Table 4. Cycloaddition of 2-phenyl sulfanylbenzene-tethered diynes with DMAD (path B).

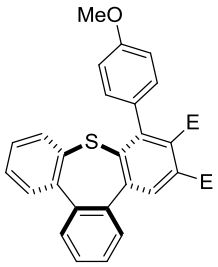


4 (X = S)
6 (X = SO_2)

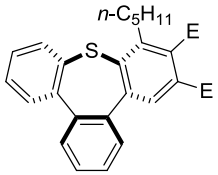
5 (X = S)
7 (X = SO_2)



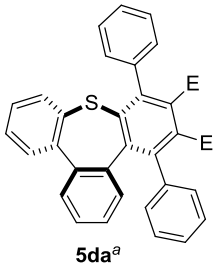
5aa
58%, 81% ee (4 h)
from **4a**
(R^1 = Ph, R^2 = H)



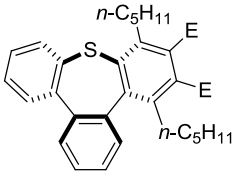
5ba
59%, 71% ee (1 h)
from **4b**
(R^1 = 4-$OMeC_6H_4$, R^2 = H)



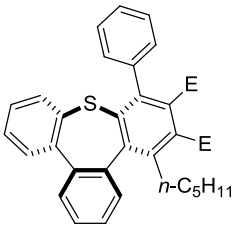
5ca
64%, 80% ee (4 h)
from **4c**
(R^1 = *n*-C_5H_{11}, R^2 = H)



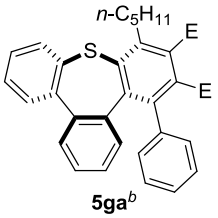
5da[a]
36%, 75% ee (4 h)
from **4d**
(R^1 = Ph, R^2 = Ph)



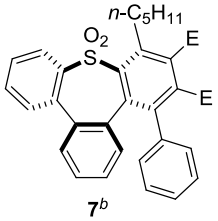
5ea[a]
52%, 73% ee (4 h)
from **4e**
(R^1 = *n*-C_5H_{11}, R^2 = *n*-C_5H_{11})



5fa
52%, 65% ee (4 h)
from **4f**
(R^1 = Ph, R^2 = *n*-C_5H_{11})



5ga[b]
42%, 74% ee (1 h)
from **4g**
(R^1 = *n*-C_5H_{11}, R^2 = Ph)



7[b]
50%, 80% ee (5 h)
from **6**
(R^1 = *n*-C_5H_{11}, R^2 = Ph)

[*a*] The reaction was examined at 40 °C. [*b*] The reaction was examined at 60 °C.

Cycloadduct **3ga** in Table 2 and cycloadduct **5da** in Table 4 could be prepared as a single crystal by recrystallization, and its structure and absolute configuration were ascertained by X-ray crystallographic analysis. Tribenzothiepins **3ga** and **5da** had a saddle-shaped structure as expected, and the sulfur atom and the trisubstituted benzene ring across from it were arranged upward, while the two other benzene rings were arranged downward (Figures 4 and 5).

Figure 4. ORTEP diagram of **3ga**

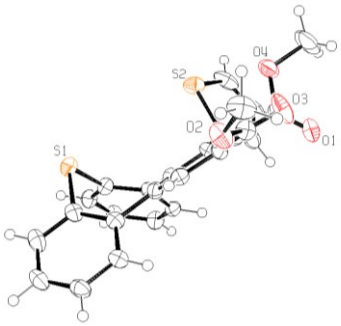
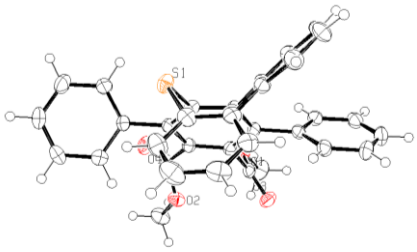
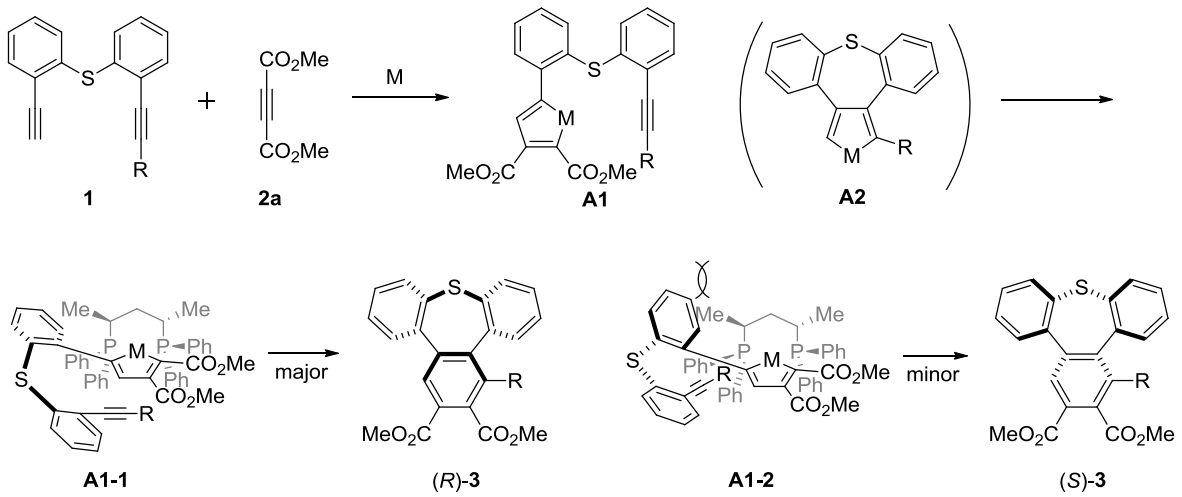


Figure 5. ORTEP diagram of **5da**



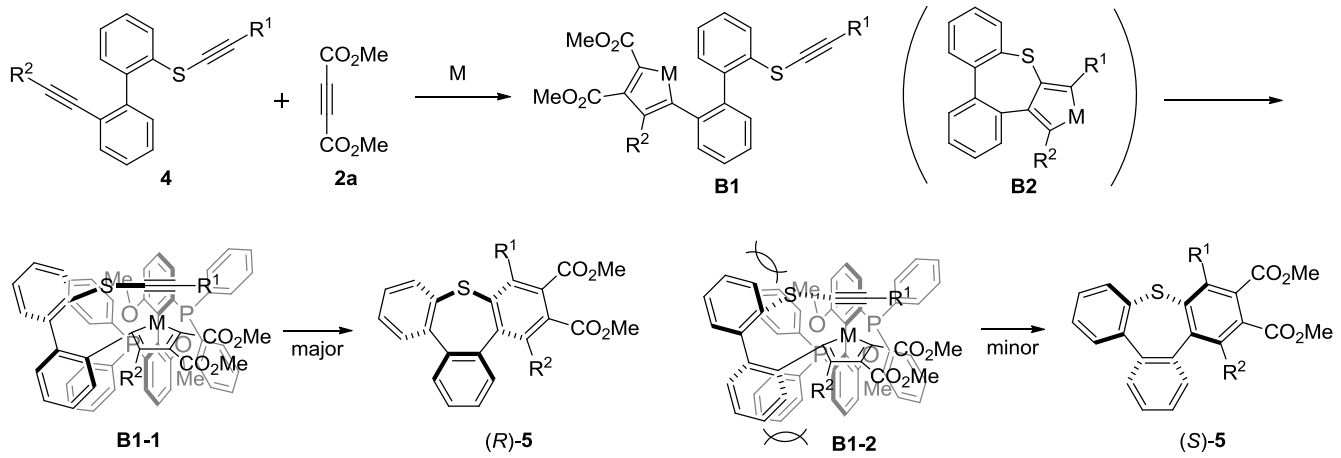
A possible explanation for enantioselective induction of **3** (path A) was shown in Scheme 3. The first step is oxidative coupling of metal catalyst and unsubstituted alkyne moiety of diyne **1** with DMAD, and metallacyclopentadiene **A1** is generated, because intermolecular coupling is more likely to proceed than intramolecular coupling, which gives seven-membered intermediate **A2**. The next step is insertion of remaining alkyne moiety of diyne **1** to intermediate **A1**. Metallacyclopentadiene **A1** can go through the square planar coodinated **A1-1** or **A1-2**, but steric hindrance occurred between aryl group on metallacyclopentadiene and methyl group on ligand in **A1-2**. Therefore **A1-1** is preferred to **A1-2**, and (*R*)-**3** is obtained predominantly.

Scheme 3. Possible explanation for enantioselective induction of **3**



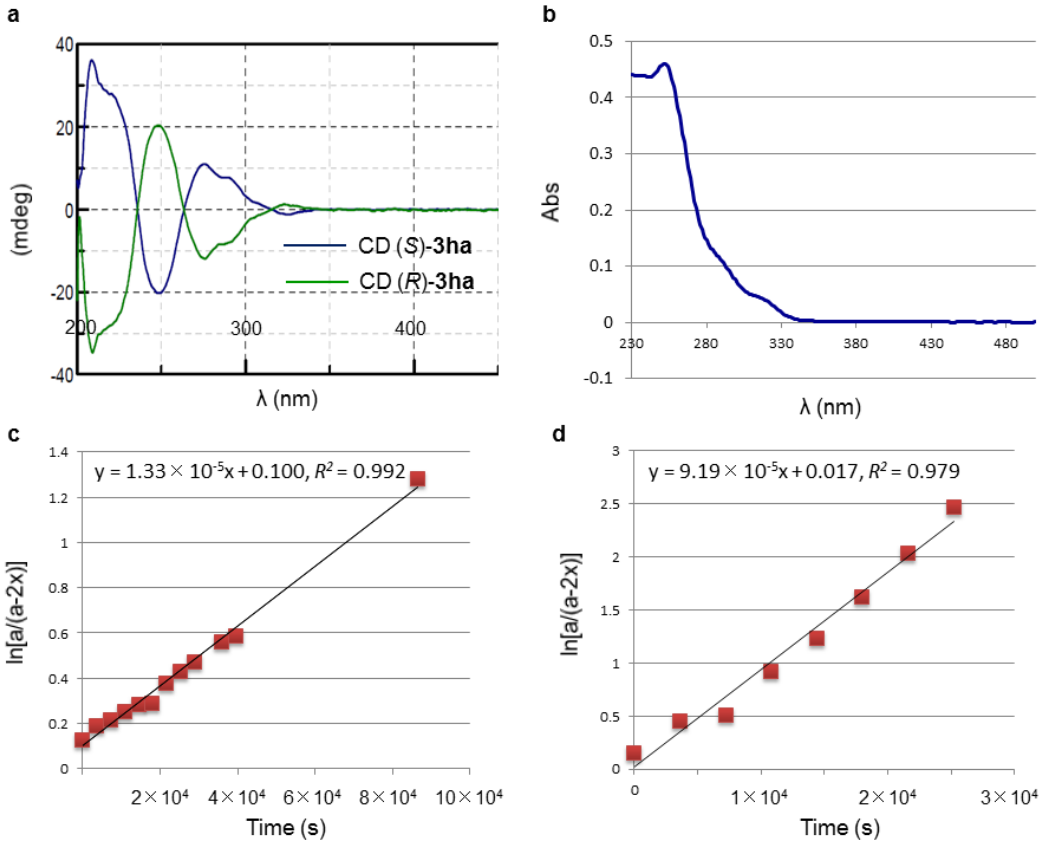
On the other hand, a possible explanation for enantioselective induction of **5** was shown in Scheme 4. The first step is oxidative coupling, and metallacyclopentadiene **B1** can be generated because intermolecular coupling is more likely to proceed than intramolecular coupling, which gives seven-membered intermediate **B2**. The next step is insertion of remaining alkyne moiety of diyne **4** to intermediate **B1**. Metallacyclopentadiene **B1** can go through the square planar coodinated **B1-1** or **B1-2**, but steric hindrance occurred between sulfur atom/aryl group on metallacyclopentadiene and phenyl group on ligand in **B1-2**. Therefore **B1-1** is preferred to **B1-2**, and (*R*)-**5** is obtained mainly.

Scheme 4. Possible explanation for enantioselective induction of **5**



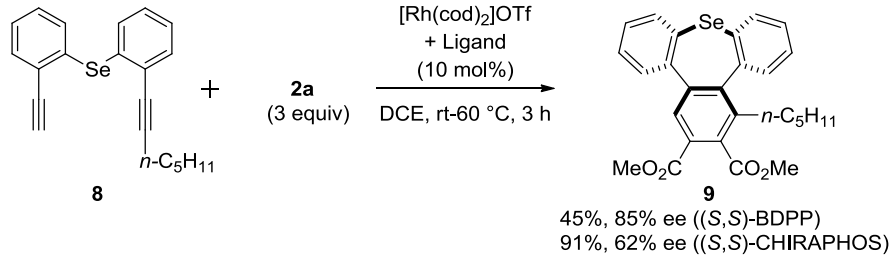
Next, the circular dichroism (CD) and ultraviolet-visible (UV-vis) spectra of **3ha** (Figures 6a and 6b) and the inversion energy of saddle-shaped compounds **3aa** and **3ka** in terms of their rates of racemization were measured (Figures 6c and 6d). Trisubstituted tribenzothiepin **3aa** was stable at 60 °C for 2 h, but racemization was observed at 80 °C. The rate constant of racemization for **3aa** at (353 K) was determined to be 6.63×10^{-6} s^{-1}, and the inversion energy ($\Delta G^{\ddagger}$) was calculated to be 29.1 kcal per mole according to the Eyring equation, which means that the half-life of **3aa** at 20 °C is 9.2 years. On the other hand, tetrasubstituted tribenzothiepin **3ka** was more stable, as expected, and racemization was observed at 120 °C for 2 h. The rate constant of racemization and the inversion energy ($\Delta G^{\ddagger}$) were calculated to be 4.59×10^{-5} s^{-1} (393 K) and 31.0 kcal per mole, respectively, which means that the half-life of **3ka** at 20 °C is 230 years.

Figure 6. CD and UV spectra, chirality and rate constant of racemization.[12] (**a**) CD spectra of compound (*S*)- and (*R*)-**3ha** in 1,2-dichloroethane solution (3.75×10^{-3} M). Blue line and Green line are CD spectra of (*S*)-**3ha** and (*R*)-**3ha**. Maximum values of (*S*)- and (*R*)-**3ha** are 209, 248 and 276 nm. (**b**) UV-vis spectra of (*R*)-**3ha** in dichloromethane solution (1.43×10^{-5} M), λ_{max} and log ε are 252 nm and 4.51. (**c**) Plot of ln[a/(a-2x)] versus t (s), a is the concentration of (*R*)-**3aa** (a = 0.944) and x is the concentration of newly generated (*S*)-**3aa** at time t. A linear curve fitting equation: $y = 1.33\times10^{-5}x + 0.100$, $R^2 = 0.992$. Rate constant $k_{3aa} = 6.63\times10^{-6}$ s^{-1} (353 K). Saddle inversion energy $\Delta G^{\ddagger} = 29.1$ kcal mol^{-1}. (**d**) Plot of ln[a/(a-2x)] versus t (s), a is the concentration of (*R*)-**3ka** (a = 0.933) and x is the concentration of newly generated (*S*)-**3ka** at time t. A linear curve fitting equation: $y = 9.19\times10^{-5}x + 0.017$, $R^2 = 0.979$. Rate constant $k_{3ka} = 4.59\times10^{-5}$ s^{-1} (393 K). Saddle inversion energy $\Delta G^{\ddagger} = 31.0$ kcal mol^{-1}.



In addition, the cycloaddition of selenium-tethered diyne **8** was examined (Scheme 5). The reaction of **8** with DMAD **2a** proceeded to give tribenzoselenepin **9** with high ee using (*S*,*S*)-BDPP as a chiral ligand and in high yield using (*S*,*S*)-CHIRAPHOS. Notably, this is the first example of the synthesis of tribenzoselenepin skeleton.

Scheme 5. Enantioselective synthesis of tribenzoselenepin



Conclusion

The author developed two-type intermolecular cycloadditions of diphenyl sulfide-tethered diynes and 2-phenyl sulfanylbenzene-tethered diynes with alkynes. The present reaction realized the first catalytic and enantioselective synthesis of multi-substituted tribenzoheteropins including tribenzothiepins, tribenzothiepin *S*,*S*-dioxide, and tribenzoselenepin.

Experimental Section

General

^{1}H NMR spectra were recorded on JEOL ECX-500 (500 MHz) spectrometers. The chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm) for $CDCl_3$. The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; dt, doublet of triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). ^{13}C NMR spectra were obtained by JEOL ECX-500 (125 MHz) spectrometers and referenced to the internal solvent signals (central peak is 77.16 ppm in $CDCl_3$). $CDCl_3$ was used as a NMR solvent. High-resolution mass spectra (HRMS) were measured on an ESI (Electro Spray Ionization) – Orbitrap mass spectrometer method. Optical rotations were measured on a JASCO DIP-1000 polarimeter. Ultraviolet spectrum was measured on a JASCO V-630 spectrometer. CD spectra were recorded on a JASCO J-820 (420W Xe) spectropolarimeter. X-ray structures were obtained by a Rigaku R-AXIS RAPID diffractometer. Preparative thin-layer chromatography (PTLC) was performed with silica gel-precoated glass plates (Merck 60 GF254) prepared in the author's laboratory, Flash column chromatography was performed over silica gel 200-300. All reagents were weighed and handled in air and backfilled under argon at room temperature. Unless otherwise noted, all reactions were performed under an argon atmosphere. All reagents were purchased from Wako, Kanto, Aldrich and TCI and used without further purification.

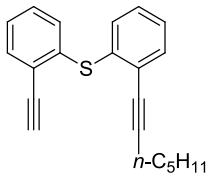
General procedure for the synthesis of tribenzothiepin derivatives by the intermolecular cycloaddition of diphenyl sulfide-tethered diynes with DMAD (path A)

$[Rh(cod)_2]OTf$ (2.3 mg, 0.005 mmol) and (*S,S*)-BDPP (2.2 mg, 0.005 mmol) were placed in Schlenk tube, which was then evacuated and backfilled with argon (3×). To the reaction vessel was added CH_2Cl_2 (1.0 mL). Then it was filled with H_2, and the mixture was stirred at room temperature for 30 min under H_2. After removal of the solvent and H_2 under reduced pressure, the reaction vessel was filled with argon. 1,2-Dichloroethane (0.6 mL) was added to the flask and the mixture was stirred to give a yellowish solution. Then, a 1,2-dichloroethane solution (0.9 mL) of diyne (0.05 mmol) and dimethyl acetylenedicarboxylate (21.3 mg, 0.15 mmol) was added and the mixture was stirred at room temperature. The volatiles were removed under reduced pressure, and the crude product was purified by preparative TLC to give a tribenzothiepin derivative.

General procedure for the synthesis of tribenzothiepin derivatives by the intermolecular cycloaddition of 2-phenyl sulfanylbenzene-tethered diynes with DMAD (path B)

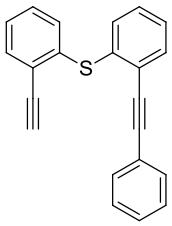
$[Rh(cod)_2]BARF$ (5.9 mg, 0.005 mmol) and (*S*)-OMe-BIPHEP (2.9 mg, 0.005 mmol) were placed in Schlenk tube. The following protocol is the same as above.

Characterization of new compounds



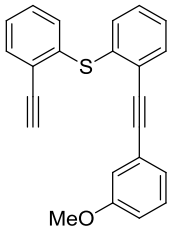
(2-Ethynylphenyl)(2-(hept-1-ynyl)phenyl)sulfane (1a)

Prepared Sonogashira coupling conditions were used.[13] Tetrahydrofuran (3.1 mL) and diisopropylamine (0.3 mL) were added to a mixture of (2-iodophenyl)(2-(hept-1-ynyl)phenyl)sulfane (165.0 mg, 0.4 mmol), $Pd(PPh_3)Cl_2$ (69.8 mg, 0.1 mmol) and CuI (38.1 mg, 0.2 mmol) under an Ar atmosphere. Trimetylsilylacetylene (0.2 ml, 1.2 mmol) was added, and the resulting mixture was stirred at room temperature. After 2 h, the solvents were removed, and the residue was purified by column chromatography on silica gel (hexane/CH_2Cl_2 = 3/1) to give (2-(hept-1-ynyl)phenyl)(2-trimethylsilylethynylphenyl)sulfane **1j** (102.3 mg, 67%) as a yellow oil. **1j** was dissolved in methanol (1.3 ml). After addition of KOH (30.5 mg, 0.5 mmol) and water (0.13 ml), the mixture was stirred overnight at room temperature. The reaction mixture was concentrated via rotary evaporation and diluted with brine. The solution was extracted with three portions of ethyl acetate. The combined organic fractions were dried over Na_2SO_4, filtered and concentrated via rotary evaporation. The crude product was purified by column chromatography on silica gel (hexane/CH_2Cl_2 = 3/1) to give diyne **1a** (44.0 mg, 53%) as a brown oil. ^{1}H NMR δ 7.53 (dd, *J* = 1.4, 7.5 Hz, 1H), 7.46-7.45 (m, 1H), 7.24-7.16 (m, 5H), 7.09-7.07 (m, 1H), 3.37 (s, 1H), 2.35 (t, *J* = 7.2 Hz, 2H), 1.50-1.46 (m, 2H), 1.36-1.26 (m, 4H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 139.2, 136.6, 133.6, 133.1, 132.1, 130.4, 129.5, 128.3, 127.5, 126.8, 126.5, 123.2, 97.4, 83.2, 81.5, 78.7, 31.2, 28.4, 22.4, 19.8, 14.2; HRMS(ESI) calcd for $C_{21}H_{20}NaS$ (M+Na): 327.1178; found: 327.1178.



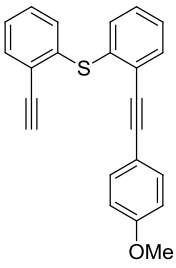
(2-Ethynylphenyl)(2-(phenylethynyl)phenyl)sulfane (1b)

Isolated by column chromatography on silica gel (hexane/EtOAc = 20/1). The title compound was obtained as a pale yellow solid (35%). Mp 70 °C; ^{1}H NMR δ 7.60-7.58 (m, 1H), 7.55 (dd, *J* = 1.1, 7.3 Hz, 1H), 7.44-7.42 (m, 2H), 7.31-7.26 (m, 6H), 7.23 (dd, *J* = 1.4, 7.5 Hz, 1H), 7.20 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.18-7.16 (m, 1H), 3.38 (s, 1H); ^{13}C NMR δ 138.8, 137.3, 133.8, 133.1, 132.0, 131.9, 130.8, 129.6, 129.1, 128.6, 128.4, 127.5, 126.8, 125.7, 123.5, 123.5, 95.5, 87.6, 83.4, 81.5; HRMS(ESI) calcd for $C_{22}H_{14}NaS$ (M+Na): 333.0708; found: 333.0708.



(2-Ethynylphenyl)(2-(3-methoxyphenylethynyl)phenyl)sulfane (1c)

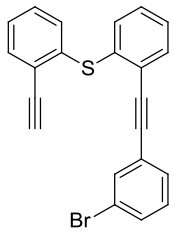
Isolated by column chromatography on silica gel (hexane/EtOAc = 10/1). The title compound was obtained as a yellow oil (57%). ^{1}H NMR δ 7.60-7.58 (m, 1H), 7.54 (dd, *J* = 1.4, 7.5 Hz, 1H), 7.32-7.17 (m, 6H), 7.16-7.13 (m, 1H), 7.04-7.03 (m, 1H), 6.93-6.92 (m, 1H), 6.87-6.85 (m, 1H), 3.79 (s, 3H), 3.39 (s, 1H); ^{13}C NMR δ 159.4, 138.9, 136.9, 133.6, 133.1, 132.2, 130.3, 129.5, 129.4, 129.0, 127.6, 126.6, 125.8, 124.4, 124.1, 123.1, 116.2, 115.6, 95.6, 87.3, 83.4, 81.4, 55.4; HRMS(ESI) calcd for $C_{23}H_{16}NaOS$ (M+Na): 363.0814; found: 363.0814.



(2-Ethynylphenyl)(2-(4-methoxyphenylethynyl)phenyl)sulfane (1d)

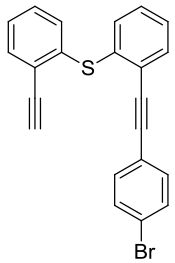
Isolated by column chromatography on silica gel (hexane/EtOAc = 10/1). The title compound was obtained as a pale yellow solid (82%). Mp 85 °C; ^{1}H NMR δ 7.57-7.53 (m, 2H), 7.37-7.34 (m, 2H), 7.28-7.21 (m, 4H), 7.19 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.16-7.14 (m, 1H), 6.82 (dd, *J* = 2.1, 6.9 Hz, 2H), 3.81 (s, 3H), 3.39 (s, 1H); ^{13}C NMR δ 159.9, 138.9, 136.7, 133.6, 133.3, 132.8, 132.1, 130.5, 129.5, 128.6,

127.5, 126.6, 126.1, 123.2, 115.3, 114.0, 95.8, 86.3, 83.3, 81.4, 55.4; HRMS(ESI) calcd for $C_{23}H_{16}NaOS$ (M+Na): 363.0814; found: 363.0814.



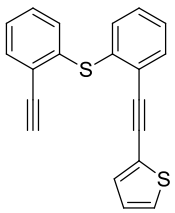
(2-(3-Bromophenylethynyl)phenyl)(2-ethynylphenyl)sulfane (1e)

Isolated by column chromatography on silica gel (hexane/EtOAc = 10/1). The title compound was obtained as a yellow oil (40%). ^{1}H NMR δ 7.58-7.54 (m, 3H), 7.43-7.42 (m, 1H), 7.35-7.33 (m, 1H), 7.30-7.27 (m, 3H), 7.23 (dd, *J* = 1.7, 7.5 Hz, 1H), 7.21 (dd, *J* = 1.7, 7.5 Hz, 1H), 7.18-7.14 (m, 2H), 3.39 (s, 1H); ^{13}C NMR δ 138.6, 137.4, 134.5, 133.8, 133.1, 132.1, 131.6, 130.6, 130.3, 129.8, 129.6, 129.3, 127.5, 126.8, 125.2, 125.1, 123.4, 122.2, 94.0, 88.7, 83.4, 81.3; HRMS(ESI) calcd for $C_{22}H_{13}BrNaS$ (M+Na): 410.9814; found: 410.9815.



(2-(4-Bromophenylethynyl)phenyl)(2-ethynylphenyl)sulfane (1f)

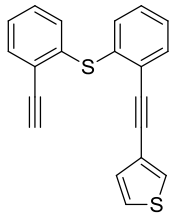
Isolated by column chromatography on silica gel (hexane/EtOAc = 10/1). The title compound was obtained as an orange solid (66%). Mp 62 °C; ^{1}H NMR δ 7.58-7.56 (m, 1H), 7.54 (dd, *J* = 1.3, 7.4 Hz, 1H), 7.43-7.42 (m, 2H), 7.30-7.25 (m, 5H), 7.25-7.21 (m, 1H), 7.20-7.17 (m, 1H), 7.14 (dd, *J* = 1.2, 7.9 Hz, 1H), 3.39 (s, 1H); ^{13}C NMR δ 138.8, 137.3, 133.8, 133.3, 133.1, 132.2, 131.7, 130.7, 129.7, 129.3, 127.6, 126.9, 125.5, 123.4, 122.9, 122.2, 94.6, 88.7, 83.5, 81.4; HRMS(ESI) calcd for $C_{22}H_{13}BrNaS$ (M+Na): 410.9814; found: 410.9815.



(2-Ethynylphenyl)(2-(thiophen-2-ylethynyl)phenyl)sulfane (1g)

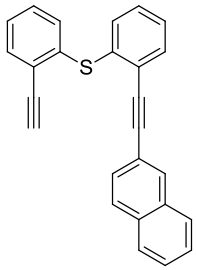
Isolated by column chromatography on silica gel (hexane/EtOAc = 10/1). The title compound was

obtained as a yellow solid (64%). Mp 64 °C; ^{1}H NMR δ 7.57-7.54 (m, 2H), 7.30-7.25 (m, 4H), 7.23 (dd, *J* = 1.8, 7.6 Hz, 1H), 7.21-7.18 (m, 2H), 7.18-7.15 (m, 1H), 6.97 (dd, *J* = 3.7, 5.2 Hz, 1H), 3.38 (s, 1H); ^{13}C NMR δ 138.6, 137.0, 133.7, 132.8, 132.4, 132.1, 130.7, 129.5, 129.0, 127.8, 127.4, 127.2, 126.8, 125.4, 123.5, 123.1, 91.1, 88.9, 83.3, 81.4; HRMS(ESI) calcd for $C_{20}H_{12}NaS_2$ (M+Na): 339.0273; found: 339.0272.



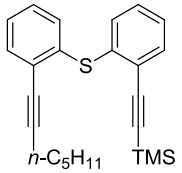
(2-Ethynylphenyl)(2-(thiophen-3-ylethynyl)phenyl)sulfane (1h)

Isolated by column chromatography on silica gel (hexane/EtOAc = 10/1). The title compound was obtained as a brown oil (63%). ^{1}H NMR δ 7.57-7.53 (m, 2H), 7.42 (dd, *J* = 1.1, 3.0 Hz, 1H), 7.31-7.23 (m, 5H), 7.22-7.18 (m, 1H), 7.17-7.13 (m, 1H), 7.08 (dd, *J* = 1.1, 5.0 Hz, 1H), 3.39 (s, 1H); ^{13}C NMR δ 139.0, 137.0, 133.7, 133.0, 132.3, 130.3, 130.1, 129.6, 129.3, 129.0, 127.6, 126.8, 125.9, 125.4, 123.3, 122.3, 90.9, 87.1, 83.4, 81.5; HRMS(ESI) calcd for $C_{20}H_{12}NaS_2$ (M+Na): 339.0273; found: 339.0272.



(2-Ethynylphenyl)(2-(naphth-2-ylethynyl)phenyl)sulfane (1i)

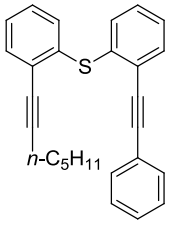
Isolated by column chromatography on silica gel (hexane/EtOAc = 10/1). The title compound was obtained as a pale yellow solid (73%). Mp 88 °C; ^{1}H NMR δ 7.93 (s, 1H), 7.80-7.74 (m, 3H), 7.64-7.62 (m, 1H), 7.57-7.56 (m, 1H), 7.48-7.46 (m, 3H), 7.32-7.22 (m, 4H), 7.20-7.17 (m, 2H), 3.42 (s, 1H); ^{13}C NMR δ 138.9, 137.1, 133.7, 133.1, 133.0, 133.0, 132.2, 131.8, 130.6, 129.6, 129.0, 128.5, 128.0, 128.0, 127.9, 127.5, 126.8, 126.7, 126.6, 125.8, 123.3, 120.5, 96.2, 87.9, 83.4, 81.4; HRMS(ESI) calcd for $C_{26}H_{16}NaS$ (M+Na): 383.0865; found: 383.0865.



(2-(Hept-1-ynyl)phenyl)(2-trimethylsilylethynylphenyl)sulfane (1j)

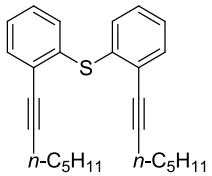
A brown oil; ^{1}H NMR δ 7.49-7.48 (m, 1H), 7.44-7.42 (m, 1H), 7.20-7.12 (m, 6H), 2.38 (t, *J* = 7.1 Hz, 2H),

1.55-1.51 (m, 2H), 1.39-1.30 (m, 4H), 0.88 (t, J = 7.1 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR δ 138.5, 137.6, 133.3, 132.9, 131.1, 131.0, 129.1, 128.2, 126.9, 126.8, 125.9, 124.9, 102.7, 101.2, 97.3, 78.8, 31.2, 28.5, 22.4, 19.8, 14.2, 0.0; HRMS(ESI) calcd for $C_{24}H_{28}NaSSi$ (M+Na): 399.1573; found: 399.1571.



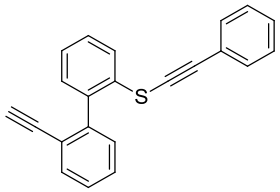
(2-(Hept-1-ynyl)phenyl)(2-(phenylethynyl)phenyl)sulfane (1k)

Isolated by column chromatography on silica gel (hexane/EtOAc = 20/1). The title compound was obtained as a yellow oil (80%). ^{1}H NMR δ 7.56 (dd, J = 3.3, 5.8 Hz, 1H), 7.47-7.44 (m, 3H), 7.31-7.30 (m, 3H), 7.23-7.16 (m, 6H), 2.37 (t, J = 7.1 Hz, 2H), 1.53-1.50 (m, 2H), 1.37-1.25 (m, 4H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 138.3, 137.3, 133.0, 132.8, 131.8, 131.4, 131.0, 128.8, 128.5, 128.3, 128.2, 127.0, 126.7, 126.1, 124.8, 123.4, 97.3, 95.6, 87.6, 78.8, 31.2, 28.4, 22.3, 19.8, 14.1; HRMS(ESI) calcd for $C_{27}H_{24}NaS$ (M+Na): 403.1491; found: 403.1492.



Bis(2-(hept-1-ynyl)phenyl)sulfane (1l)

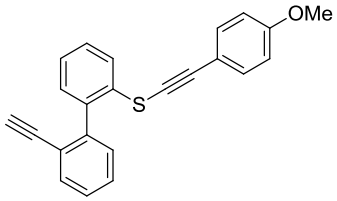
Isolated by column chromatography on silica gel (hexane/EtOAc = 20/1). The title compound was obtained as a yellow oil (69%). ^{1}H NMR δ 7.44-7.42 (m, 2H), 7.17-7.12 (m, 6H), 2.37 (t, J = 7.2 Hz, 4H), 1.55-1.49 (m, 4H), 1.40-1.28 (m, 8H), 0.88 (t, J = 7.1 Hz, 6H); ^{13}C NMR δ 137.5, 132.6, 130.8, 127.9, 126.6, 125.7, 97.0, 78.6, 31.0, 28.2, 22.2, 19.6, 14.0; HRMS(ESI) calcd for $C_{26}H_{30}NaS$ (M+Na): 397.1960; found: 397.1958.



(2-((2-Ethynyl)phenyl)phenyl)(phenylethynyl)sulfane (4a)

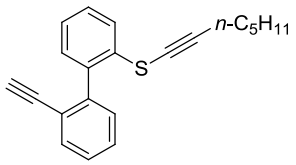
Prepared Suzuki-Miyaura coupling conditions were used.[14] (2-Iodophenyl)(2-phenylethynyl)sulfane (628.1 mg, 1.9 mmol), 2-(2-ethynyl)phenylboronic acid (327.3 mg, 2.2 mmol), K_2CO_3 (775.1 mg, 5.6 mmol), toluene (19.3 mL), ethanol (5.9 mL), and water (5.9 mL) were degassed and added to a 50 mL dry two-necked pear-shaped flask equipped with a rubber septum. $Pd(PPh_3)_4$ (53.7 mg, 0.05 mmol, 0.03

equiv) was added as a solid with a counterflow of argon. The reaction vessel was then placed in an oil bath preheated to 65 °C. After stirring for 24 h, the reaction mixture was allowed to cool to room temperature, concentrated via rotary evaporation and diluted with H_2O. The solution was extracted with three portions of CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4, filtered and concentrated via rotary evaporation. The crude product was purified by column chromatography on silica gel (hexane only) to give diyne **4a** (195.4 mg, 34%) as a yellow oil. ^{1}H NMR δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.63 (dd, *J* = 1.1, 7.6 Hz, 1H), 7.49-7.47 (m, 2H), 7.45-7.36 (m, 3H), 7.34-7.25 (m, 6H), 2.97 (s, 1H); ^{13}C NMR δ 141.8, 138.4, 133.2, 132.5, 131.7, 130.3, 129.9, 128.8, 128.7, 128.5, 128.3, 128.1, 126.4, 126.1, 123.0, 122.0, 98.0, 82.0, 80.7, 76.0; HRMS(ESI) calcd for $C_{22}H_{14}NaS$ (M+Na): 333.0708; found: 333.0708.



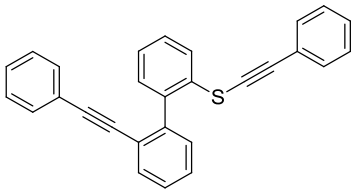
(2-(2-Ethynylphenyl)phenyl)(4-methoxyphenylethynyl)sulfane (4b)

Isolated by column chromatography on silica gel (hexane/EtOAc = 10/1). The title compound was obtained as a white solid (33%). Mp 113 °C; ^{1}H NMR δ 7.85 (dd, *J* = 0.7, 8.1 Hz, 1H), 7.63 (dd, *J* = 1.5, 7.4 Hz, 1H), 7.45-7.36 (m, 5H), 7.33-7.24 (m, 3H), 6.87-6.84 (m, 2H), 3.82 (s, 3H), 2.69 (s, 1H); ^{13}C NMR δ 160.2, 142.0, 138.3, 133.9, 133.4, 133.1, 130.4, 130.1, 128.9, 128.8, 128.2, 126.4, 126.0, 122.1, 115.2, 111.4, 98.2, 82.1, 80.7, 74.1, 55.5; HRMS(ESI) calcd for $C_{23}H_{16}NaOS$ (M+Na): 363.0814; found: 363.0814.



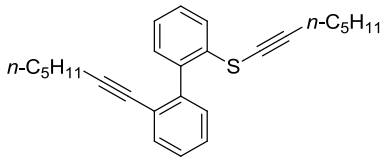
(2-((2-Ethynyl)phenyl)phenyl)(hept-1-ynyl)sulfane (4c)

Isolated by column chromatography on silica gel (hexane only). The title compound was obtained as a yellow oil (32%). ^{1}H NMR δ 7.79 (dd, *J* = 0.6, 8.0 Hz, 1H), 7.61 (dd, *J* = 1.4, 7.6 Hz, 1H), 7.42-7.34 (m, 4H), 7.29-7.27 (m, 1H), 7.24-7.21 (m, 1H), 2.94 (s, 1H), 2.42 (t, *J* = 7.2 Hz, 2H), 1.61-1.54 (m, 2H), 1.44-1.30 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 142.0, 137.9, 133.3, 133.2, 130.1, 129.9, 128.6, 128.6, 128.0, 125.9, 125.6, 122.0, 100.3, 82.0, 80.5, 65.0, 31.1, 28.4, 22.2, 20.3, 14.0; HRMS(ESI) calcd for $C_{21}H_{20}NaS$ (M+Na): 327.1178; found: 327.1178.



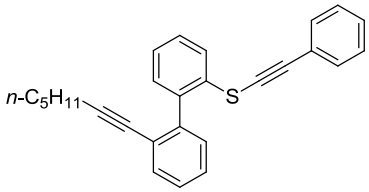
(Phenylethynyl)(2-((2-phenylethynyl)phenyl)phenyl)sulfane (4d)

Isolated by column chromatography on silica gel (hexane only). The title compound was obtained as a yellow oil (33%). ^{1}H NMR δ 7.90 (d, J = 7.9 Hz, 1H), 7.66-7.64 (m, 1H), 7.47-7.43 (m, 3H), 7.42-7.36 (m, 3H), 7.34-7.29 (m, 5H), 7.24-7.17 (m, 5H); ^{13}C NMR δ 141.6, 138.9, 132.8, 132.1, 131.7, 131.5, 130.6, 129.8, 128.7, 128.5, 128.3, 128.2, 128.1, 128.1, 126.6, 126.1, 123.2, 123.2, 123.1, 97.6, 93.2, 88.3, 76.4 (a pair of peaks at the aromatic region is overlapped); HRMS(ESI) calcd for $C_{28}H_{18}NaS$ (M+Na): 409.1021; found: 409.1022.



(Hept-1-ynyl)(2-(2-(hept-1-ynyl)phenyl)phenyl)sulfane (4e)

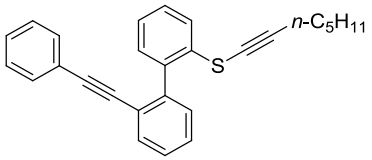
Isolated by column chromatography on silica gel (hexane only). The title compound was obtained as a pale brown oil (60%). ^{1}H NMR δ 7.89 (dd, J = 0.9, 7.9 Hz, 1H), 7.62-7.59 (m, 1H), 7.50-7.47 (m, 1H), 7.44-7.41 (m, 2H), 7.37-7.31 (m, 3H), 2.54 (t, J = 7.1 Hz, 2H), 2.30 (dt, J_d = 2.3 Hz, J_t = 6.9 Hz, 2H), 1.73-1.67 (m, 2H), 1.56-1.49 (m, 2H), 1.48-1.40 (m, 4H), 1.34-1.28 (m, 2H), 1.27-1.21 (m, 2H), 1.02 (t, J = 7.2 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 141.4, 138.7, 133.4, 132.1, 130.1, 129.6, 128.2, 127.9, 127.3, 125.8, 125.4, 123.9, 99.9, 94.3, 79.2, 65.4, 31.1, 30.6, 28.4, 28.0, 22.2, 22.2, 20.3, 19.3, 13.9, 13.9; HRMS(ESI) calcd for $C_{26}H_{30}NaS$ (M+Na): 397.1960; found: 397.1957.



(2-(2-(Hept-1-ynyl)phenyl)phenyl)(phenylethynyl)sulfane (4f)

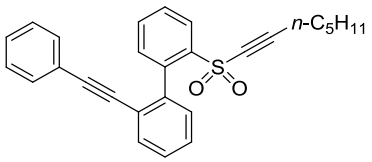
Isolated by column chromatography on silica gel (hexane only). The title compound was obtained as a brown oil (30%). ^{1}H NMR δ 7.85 (d, J = 8.0 Hz, 1H), 7.52-7.46 (m, 3H), 7.41-7.38 (m, 1H), 7.35-7.31 (m, 5H), 7.29-7.23 (m, 3H), 2.40 (dt, J_d = 3.1 Hz, J_t = 6.9 Hz, 2H), 1.35-1.29 (m, 2H), 1.22-1.10 (m, 4H), 0.84 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 141.3, 139.2, 132.6, 132.2, 131.7, 130.4, 129.6, 128.4, 128.3, 128.0, 127.4, 126.3, 125.9, 124.0, 123.1, 97.7, 94.5, 79.2, 76.5, 30.7, 28.1, 22.2, 19.3, 13.9 (a pair of peaks at the

aromatic region is overlapped); HRMS(ESI) calcd for $C_{27}H_{24}NaS$ (M+Na): 403.1491; found: 403.1492.



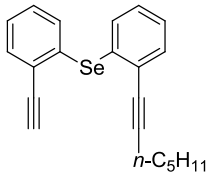
(Hept-1-ynyl)(2-((2-phenylethynyl)phenyl)phenyl)sulfane (4g)

Isolated by column chromatography on silica gel (hexane only). The title compound was obtained as a brown oil (60%). ^{1}H NMR δ 7.83 (d, *J* = 7.9 Hz, 1H), 7.64-7.61 (m, 1H), 7.44-7.41 (m, 1H), 7.40-7.36 (m, 2H), 7.35-7.33 (m, 1H), 7.30-7.28 (m, 2H), 7.23-7.20 (m, 3H), 7.18-7.16 (m, 2H), 2.40 (t, *J* = 7.1 Hz, 2H), 1.59-1.53 (m, 2H), 1.42-1.28 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 141.7, 138.4, 133.6, 132.0, 131.5, 130.4, 129.7, 128.5, 128.1, 128.1, 128.0, 128.0, 126.1, 125.5, 123.3, 123.2, 100.0, 93.0, 88.3, 65.3, 31.0, 28.3, 22.2, 20.3, 14.0; HRMS(ESI) calcd for $C_{27}H_{24}NaS$ (M+Na): 403.1491; found: 403.1490.



(Hept-1-ynyl)(2-((2-phenylethynyl)phenyl)phenyl)sulfone (6)

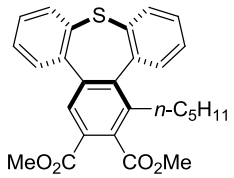
m-Chloroperoxybenzoic acid 30 % water (308.2 mg, 1.3 mmol, 2.5 equiv) was added to the solution of **4g** (190.3 mg, 0.5 mmol, 1 equiv) in $CHCl_3$ (3.5 mL) for 1 h at 25 °C. The residue was added to $NaHCO_3$, and the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and the solvent removed under vacuum. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 10/1) to give diyne **6** (134.1 mg, 65%) as a white solid. Mp 95 °C; ^{1}H NMR δ 8.27 (d, *J* = 7.8 Hz, 1H), 7.69 (dt, J_d = 1.2 Hz, J_t = 7.4 Hz, 1H), 7.63-7.58 (m, 2H), 7.55-7.53 (m, 1H), 7.49 (dd, *J* = 1.0, 7.6 Hz, 1H), 7.44-7.39 (m, 2H), 7.24-7.19 (m, 3H), 7.02 (dd, *J* = 1.2, 7.3 Hz, 2H), 2.10 (t, *J* = 7.2 Hz, 2H), 1.39-1.32 (m, 2H), 1.17-1.13 (m, 4H), 0.80 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 140.5, 140.1, 140.0, 133.5, 132.9, 131.4, 131.2, 131.1, 128.2, 128.1, 128.1, 127.4, 123.3, 122.9, 97.5, 93.4, 88.6, 77.3, 30.9, 26.4, 21.9, 19.0, 13.7 (two pairs of peaks at the aromatic region are overlapped); HRMS(ESI) calcd for $C_{27}H_{24}Na\ O_2S$ (M+Na): 435.1389; found: 435.1390.



(2-Ethynylphenyl)(2-(hept-1-ynyl)phenyl)selenium (8)

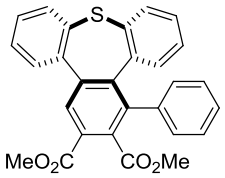
Isolated by column chromatography on silica gel (hexane only). The title compound was obtained as a brown oil (87%). ^{1}H NMR δ 7.55-7.53 (m, 1H), 7.44 (dd, *J* = 1.4, 7.6 Hz, 1H), 7.30-7.27 (m, 2H),

7.25-7.18 (m, 3H), 7.16-7.12 (m, 1H), 3.35 (s, 1H), 2.38 (t, J = 7.0 Hz, 2H), 1.54-1.48 (m, 2H), 1.41-1.25 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 134.8, 133.7, 133.4, 132.8, 132.6, 129.4, 128.2, 127.2, 127.1, 127.0, 124.8, 96.4, 82.3, 82.2, 79.5, 31.0, 28.2, 22.2, 19.5, 14.0 (a pair of peaks at the aromatic region is overlapped); HRMS(ESI) calcd for $C_{21}H_{20}NaSe$ (M+Na): 375.0622; found: 375.0623.



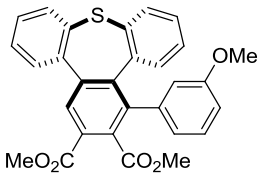
2,3-Bis(methoxycarbonyl)-1-heptyltribenzo[*b,d,f*]thiepin (3aa)

Isolated by preparative TLC (toluene/CH_2Cl_2 = 1/7). The title compound was obtained as a yellow oil (77%). ^{1}H NMR δ 7.97 (s, 1H), 7.66-7.64 (m, 1H), 7.60-7.57 (m, 2H), 7.37-7.32 (m, 2H), 7.28-7.23 (m, 3H), 3.99 (s, 3H), 3.92 (s, 3H), 3.00-2.94 (m, 1H), 2.48-2.42 (m, 1H), 1.36-1.26 (m, 1H), 1.18-0.98 (m, 5H), 0.70 (t, J = 6.7 Hz, 3H); ^{13}C NMR δ 170.1, 166.0, 144.6, 142.0, 141.9, 141.1, 140.6, 139.4, 138.8, 134.9, 132.8, 132.1, 131.4, 130.1, 129.8, 128.7, 128.4, 127.7, 126.4, 85.6, 52.6, 52.6, 31.5, 31.1, 29.7, 21.9, 13.8; HRMS(ESI) calcd for $C_{27}H_{26}NaO_4S$ (M+Na): 469.1444; found: 469.1445; $[\alpha]^{25}_D$ = +12.4 (*c* 0.9, $CHCl_3$, 74% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IB: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 5.9 min for major isomer and 7.2 min for minor isomer).



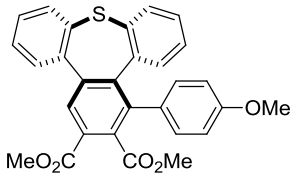
2,3-Bis(methoxycarbonyl)-1-phenyltribenzo[*b,d,f*]thiepin (3ba)

Isolated by preparative TLC (toluene/CH_2Cl_2 = 1/3). The title compound was obtained as a white solid (80%). Mp 82 ℃; ^{1}H NMR δ 8.16 (s, 1H), 7.64-7.62 (m, 2H), 7.53-7.50 (m, 2H), 7.39 (dt, J_d = 1.2 Hz, J_t = 7.5 Hz, 1H), 7.34-7.27 (m, 2H), 7.16-7.13 (m, 1H), 7.01-6.96 (m, 2H), 6.76-6.68 (m, 3H), 3.94 (s, 3H), 3.60 (s, 3H); ^{13}C NMR δ 169.3, 166.0, 144.3, 142.4, 142.0, 140.7, 140.6, 140.1, 139.8, 138.4, 135.6, 133.4, 132.3, 132.2, 131.5, 131.0, 130.6, 130.4, 129.0, 128.7, 128.1, 128.0, 127.5, 127.4, 127.3, 126.2, 52.9, 52.5; HRMS(ESI) calcd for $C_{28}H_{20}Na\ O_4S$ (M+Na): 475.0975; found: 475.0976; $[\alpha]^{25}_D$ = −108.8 (*c* 0.9, $CHCl_3$, 82% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 2% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 35.6 min for major isomer and 31.5 min for minor isomer).



2,3-Bis(methoxycarbonyl)-1-(3-methoxyphenyl)tribenzo[*b,d,f*]thiepin (3ca)

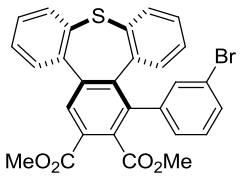
Isolated by column chromatography on silica gel (hexane/EtOAc = 5/1). The title compound was obtained as a white solid (90%). Mp 214 ℃; ^{1}H NMR showed the presence of two conformers in a ratio of 1/1.3, δ 8.15 (s, 2H (both)), 7.64-7.62 (m, 4H (both)), 7.53-7.51 (m, 2H (both)), 7.40-7.37 (m, 2H (both)), 7.30-7.27 (m, 2H (both)), 7.22 (dd, *J* = 7.7, 7.7 Hz, 1H (major)), 7.11-7.09 (m, 2H (both)), 7.03-6.99 (m, 2H (both)), 6.89 (dd, *J* = 7.8, 7.8 Hz, 1H (minor)), 6.80-6.75 (m, 4H (both)), 6.71-6.68 (m, 2H (both)), 6.28 (d, *J* = 7.7 Hz, 1H (minor)), 6.21-6.20 (m, 1H (major)), 3.94 (s, 6H (both)), 3.83 (s, 3H (minor)), 3.66 (s, 3H (major)), 3.64 (s, 3H (minor)), 3.44 (s, 3H (major)); ^{13}C NMR both conformers shown δ 169.3, 166.0, 165.9, 159.2, 159.1, 144.2, 142.5, 142.5, 142.0, 142.0, 140.7, 140.6, 140.6, 140.6, 140.0, 139.9, 139.7, 139.6, 135.5, 135.4, 133.2, 133.1, 132.4, 132.3, 132.2, 132.0, 131.5, 131.5, 130.6, 130.6, 129.1, 129.0, 129.0, 128.7, 128.1, 128.1, 127.5, 127.4, 126.3, 126.3, 123.6, 123.0, 116.4, 115.4, 114.6, 112.9, 55.5, 55.2, 52.9, 52.6; HRMS(ESI) calcd for $C_{29}H_{22}NaO_5S$ (M+Na): 505.1080; found: 505.1073; $[\alpha]^{25}_D$ = −67.9 (*c* 1.1, $CHCl_3$, 75% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 1% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 27.7 min for major isomer and 30.9 min for minor isomer).



2,3-Bis(methoxycarbonyl)-1-(4-methoxyphenyl)tribenzo[*b,d,f*]thiepin (3da)

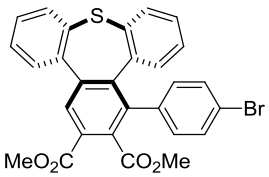
Isolated by column chromatography on silica gel (hexane/EtOAc = 5/1). The title compound was obtained as a pale yellow solid (89%). Mp 177 ℃; ^{1}H NMR δ 8.15 (s, 1H), 7.65-7.62 (m, 2H), 7.53 (dd, *J* = 1.1, 7.8 Hz, 1H), 7.44-7.37 (m, 2H), 7.30-7.27 (m, 1H), 7.00 (dt, J_d = 1.6 Hz, J_t = 7.1 Hz, 1H), 6.86 (dd, *J* = 2.6, 8.4 Hz, 1H), 6.81-6.78 (m, 1H), 6.75-6.73 (m, 1H), 6.61-6.59 (m, 1H), 6.54-6.51 (m, 1H), 3.94 (s, 3H), 3.75 (s, 3H), 3.66 (s, 3H); ^{13}C NMR δ 169.5, 166.0, 158.8, 144.5, 142.4, 142.1, 140.6, 140.6, 140.0, 139.8, 135.8, 133.4, 132.3, 132.3, 132.2, 131.4, 131.3, 130.6, 130.6, 129.0, 128.6, 127.9, 127.4, 126.1, 113.8, 112.8, 55.3, 52.9, 52.5; HRMS(ESI) calcd for $C_{29}H_{22}NaO_5S$ (M+Na): 505.1080; found: 505.1072; $[\alpha]^{25}_D$ = −156.3 (*c* 0.9, $CHCl_3$, 92% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 2.5% 2-propanol in hexane, flow

rate: 1.0 mL/min, retention time: 17.5 min for major isomer and 27.5 min for minor isomer).



1-(3-Bromophenyl)-2,3-bis(methoxycarbonyl)tribenzo[*b,d,f*]thiepin (3ea)

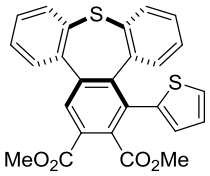
Isolated by preparative TLC (hexane/EtOAc = 5/1). The title compound was obtained as a yellow oil (70%). ^{1}H NMR showed the presence of two conformers in a ratio of 1/1.3, δ 8.18 (s, 1H (major)), 8.17 (s, 1H (minor)), 7.71 (dd, *J* = 1.8, 1.8 Hz, 1H (major)), 7.64-7.62 (m, 4H (both)), 7.57 (dd, *J* =1.0, 7.8 Hz, 1H (minor)), 7.53 (dd, *J* = 1.0, 7.7 Hz, 1H (major)), 7.47-7.45 (m, 1H (minor)), 7.39 (dd, *J* = 7.6, 7.6 Hz, 2H (both)), 7.31-7.28 (m, 4H (both)), 7.20 (dd, *J* = 7.8, 7.8 Hz, 1H (minor)), 7.06-7.00 (m, 2H (both)), 6.87-6.80 (m, 2H (both) + 1H (major)), 6.78 (dd, *J* = 1.2, 7.5 Hz, 1H (minor)), 6.74 (dd, *J* = 1.3, 7.9 Hz, 1H (major)), 6.68 (dd, *J* = 1.2, 7.8 Hz, 1H (minor)), 6.63-6.62 (m, 1H (major)), 3.94 (s, 6H (both)), 3.72 (s, 3H (major)), 3.63(s, 3H (minor)); ^{13}C NMR both conformers shown δ 168.9, 168.8, 165.6, 165.6, 144.0, 144.0, 142.4, 142.4, 141.6, 141.6, 140.7, 140.6, 140.4, 140.4, 140.3, 140.2, 139.3, 139.0, 138.3, 138.2, 135.3, 135.2, 133.7, 133.1, 132.9, 132.8, 132.3, 132.2, 132.2, 131.7, 131.6, 130.5, 130.4, 130.3, 129.6, 129.4, 128.9, 128.9, 128.9, 128.9, 128.6, 128.2, 128.1, 127.4, 127.2, 126.2, 126.2, 121.8, 124.5, 52.8, 52.4, 52.4; HRMS(ESI) calcd for $C_{28}H_{19}BrNaO_4S$ (M+Na): 553.0080; found: 553.0075; $[\alpha]^{25}_{D}$ = −64.0 (*c* 1.2, $CHCl_3$, 51% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 1% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 41.3 min for major isomer and 44.7 min for minor isomer).



1-(4-Bromophenyl)-2,3-bis(methoxycarbonyl)tribenzo[*b,d,f*]thiepin (3fa)

Isolated by preparative TLC (hexane/EtOAc = 5/1). The title compound was obtained as a pale yellow solid (83%). Mp 102 ℃; ^{1}H NMR δ 8.17 (s, 1H), 7.63-7.62 (m, 2H), 7.53 (dd, *J* = 1.1, 7.8 Hz, 1H), 7.48-7.46 (m, 1H), 7.41-7.37 (m, 2H), 7.29 (dt, J_d = 1.4 Hz, J_t = 7.4 Hz, 1H), 7.11 (dd, *J* = 2.1, 8.3 Hz, 1H), 7.03 (dt, J_d = 1.5 Hz, J_t = 7.6 Hz, 1H), 6.80 (dt, J_d = 1.2 Hz, J_t = 7.7 Hz, 1H), 6.69 (dd, *J* = 2.1, 8.3 Hz, 1H), 6.56 (dd, *J* = 2.1, 8.3 Hz, 1H), 3.94 (s, 3H), 3.65 (s, 3H); ^{13}C NMR δ 169.9, 165.6, 144.0, 142.4, 141.6, 140.5, 140.3, 139.3, 138.6, 137.2, 135.2, 133.1, 132.5, 132.2, 132.2, 131.7, 131.6, 131.1, 130.6, 130.3, 128.9, 128.6, 128.1, 127.4, 126.2, 121.7, 52.8, 52.5; HRMS(ESI) calcd for $C_{28}H_{19}BrNaO_4S$

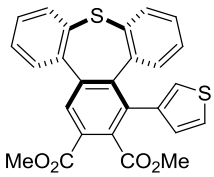
(M+Na): 553.0080; found: 553.0076; $[\alpha]^{29}_{D}$ = −130.9 (*c* 0.5, $CHCl_3$, 86% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 2.5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 13.4 min for major isomer and 16.1 min for minor isomer).



2,3-Bis(methoxycarbonyl)-1-(thiophen-2-yl)tribenzo[*b,d,f*]thiepin (3ga)

Isolated by preparative TLC (hexane/EtOAc = 5/1). The title compound was obtained as a white solid (45%). Mp 163 ℃; ^{1}H NMR δ 8.18 (s, 1H), 7.63-7.61 (m, 2H), 7.55 (dd, *J* = 1.1, 7.8 Hz, 1H), 7.38 (dt, J_d = 1.4 Hz, J_t = 7.7 Hz, 1H), 7.29 (dt, J_d = 1.4 Hz, J_t = 7.6 Hz, 1H), 7.19 (dd, *J* = 1.1, 5.0 Hz, 1H), 7.07 (dt, J_d = 1.5 Hz, J_t = 7.8 Hz, 1H), 6.95-6.93 (m, 2H), 6.88-6.85 (m, 2H), 3.94 (s, 3H), 3.72 (s, 3H); ^{13}C NMR δ 168.9, 165.5, 145.2, 142.2, 141.6, 140.6, 140.5, 139.6, 139.0, 136.5, 132.6, 132.2, 132.1, 132.0, 132.0, 130.3, 129.7, 128.8, 128.5, 128.1, 127.7, 127.3, 126.2, 126.0, 52.7, 52.4; HRMS(ESI) calcd for $C_{26}H_{18}NaO_4S_2$ (M+Na): 481.0539; found: 481.0536; $[\alpha]^{25}_{D}$ = −95.2 (*c* 0.6, $CHCl_3$, 95% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IC-3: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 2.5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 43.6 min for major isomer and 40.5 min for minor isomer).

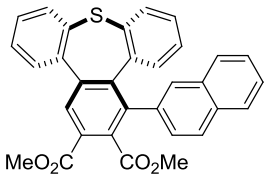
Crystal data of **3ga**; C26H18O4S2, *M* = 458.55, monoclinic, Space Group C2/c, *a* = 37.625(2) Å, *b* = 8.0468(3) Å, *c* = 14.9241(7) Å, β = 103.5446(17) °, *V* = 4392.8(4) Å3, *T* = 173.0 K, *Z* = 8, μ(MoKα) = 2.737 cm-1, Number of Reflections Measures: Total 20796, Unique: 9937 (R*int* = 0.0576), *R1* = 0.0592, *wR2* = 0.2019. Flack parameter = 0.08(4)



2,3-Bis(methoxycarbonyl)-1-(thiophen-3-yl)tribenzo[*b,d,f*]thiepin (3ha)

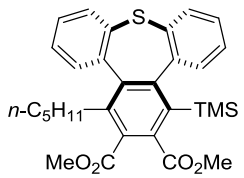
Isolated by preparative TLC (hexane/EtOAc = 3/1). The title compound was obtained as a pale yellow solid (83%). Mp 147 ℃; ^{1}H NMR δ 8.16 (s, 1H), 7.63-7.61 (m, 2H), 7.55-7.54 (m, 1H), 7.39 (dt, J_d = 1.4 Hz, J_t = 7.4 Hz, 1H), 7.29 (dt, J_d = 1.4 Hz, J_t = 7.7 Hz, 2H), 7.08-7.04 (m, 3H), 6.86-6.80 (m, 2H), 3.94 (s, 3H), 3.70 (s, 3H); ^{13}C NMR δ 169.5, 165.8, 142.3, 141.9, 140.6, 140.5, 139.9, 138.3, 135.8, 135.2, 132.7, 132.4, 132.3, 131.6, 130.6, 129.9, 129.1, 128.7, 128.2, 127.5, 126.2, 125.4, 125.4, 124.7, 52.9, 52.7;

HRMS(ESI) calcd for $C_{26}H_{18}NaO_4S_2$ (M+Na): 481.0539; found: 481.0539; $[\alpha]^{25}_D = -115.0$ (*c* 0.6, $CHCl_3$, 94% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak ID-3: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 2.5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 35.1 min for major isomer and 43.6 min for minor isomer).



2,3-Bis(methoxycarbonyl)-1-(naphth-2-yl)tribenzo[*b,d,f*]thiepin (3ia)

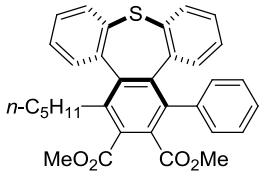
Isolated by preparative TLC (hexane/EtOAc = 3/1). The title compound was obtained as a white solid (76%). Mp 120 ℃; ^{1}H NMR showed the presence of two conformers in a ratio of 1/2, δ 8.19 (s, 2H (both)), 8.00 (s, 1H (major)), 7.86 (d, *J* = 7.7 Hz, 1H (major)), 7.81 (d, *J* = 8.3 Hz, 1H (minor)), 7.77 (d, *J* = 8.2 Hz, 1H (minor)), 7.70 (d, *J* = 8.2 Hz, 1H (major)), 7.67-7.63 (m, 4H (both)), 7.53 (d, *J* = 8.6 Hz, 1H (major)), 7.50-7.38 (m, 8H (both) + 1H (major)), 7.34-7.28 (m, 2H (both) + 1H (minor)), 7.19 (s, 1H (minor)), 6.95-6.92 (m, 1H (major)), 6.85-6.82 (m, 1H (minor)), 6.79-6.78 (m, 2H (both)), 6.74-6.72 (m, 1H (minor)), 6.60-6.57 (m, 2H (both)), 3.94 (s, 6H (both)), 3.54 (s, 3H (minor)), 3.51 (s, 3H (major)); ^{13}C NMR both conformers shown δ 169.3, 169.3, 166.0, 166.0, 144.8, 144.2, 142.5, 142.5, 142.1, 142.0, 140.7, 140.5, 140.1, 139.9, 139.9, 139.6, 136.2, 135.9, 135.8, 135.4, 133.5, 133.1, 132.9, 132.4, 132.4, 132.4, 132.3, 132.2, 131.7, 131.5, 130.6, 130.5, 129.4, 129.1, 129.1, 128.7, 128.7, 128.5, 128.5, 128.4, 128.2, 128.1, 128.1, 127.9, 127.7, 127.5, 127.5, 127.4, 127.1, 126.5, 126.4, 126.4, 126.3, 126.3, 126.1, 52.9, 52.6, 52.5; HRMS(ESI) calcd for $C_{32}H_{22}NaO_4S$ (M+Na): 525.1131; found: 525.1127; $[\alpha]^{25}_D$ = −156.0 (*c* 0.7, $CHCl_3$, 93% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 2.5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 15.1 min for major isomer and 18.6 min for minor isomer).



2,3-Bis(methoxycarbonyl)-1-pentyl-4-trimethylsilyltribenzo[*b,d,f*]thiepin (3ja)

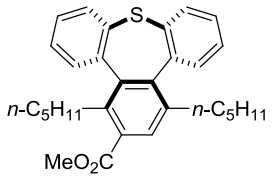
Isolated by preparative TLC (hexane/EtOAc = 5/1). The title compound was obtained as a pale yellow oil (78%). ^{1}H NMR δ 7.64-7.61 (m, 1H), 7.55-7.51 (m, 1H), 7.36-7.32 (m, 1H), 7.29-7.27 (m, 1H), 7.25-7.17 (m, 4H), 3.93 (s, 3H), 3.89 (s, 3H), 2.99-2.93 (m, 1H), 2.29-2.17 (m, 1H), 1.60-1.23 (m, 2H), 1.09-1.00 (m, 4H), 0.73 (t, *J* = 6.3 Hz, 3H), −0.14 (s, 9H); ^{13}C NMR δ 170.4, 169.8, 149.6, 143.6, 142.7, 142.7,

141.9, 139.1, 138.7, 138.3, 137.5, 133.2, 133,2, 132.7, 132.2, 132.0, 128.8, 128.2, 128.1, 127.5, 52,7, 52.6, 32.1, 31.6, 30.1, 22.1, 14.1, 1.8; HRMS(ESI) calcd for $C_{30}H_{34}NaO_4SSi$ (M+Na): 541.1839; found: 541.1841; $[\alpha]^{25}_D$ = −81.0 (*c* 1.0, $CHCl_3$, 68% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IB: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 2% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 10.6 min for major isomer and 12.0 min for minor isomer).



2,3-Bis(methoxycarbonyl)-4-pentyl-1-phenyltribenzo[*b,d,f*]thiepin (3ka)

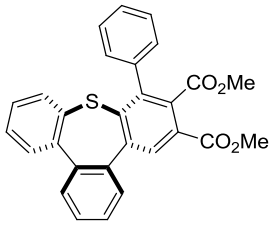
Isolated by preparative TLC (hexane/EtOAc = 5/1). The title compound was obtained as a white oil (98%). ^{1}H NMR δ 7.62 (dd, *J* = 1.4, 7.5 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.40 (dd, *J* = 1.6, 7.5 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.30-7.23 (m, 2H), 7.21-7.18 (m, 1H), 7.13-7.09 (m, 1H), 6.94-6.90 (m, 2H), 6.67-6.63 (m, 2H), 6.50 (d, *J* = 7.9 Hz, 1H), 3.90 (s, 3H), 3.47 (s, 3H), 2.97-2.90 (m, 1H), 2.83-2.74 (m, 1H), 1.28-1.20 (m, 2H), 1.12-0.95 (m, 4H), 0.71 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 169.2, 169.1, 142.8, 142.7, 142.4, 141.7, 139.3, 139.3, 139.1, 138.3, 137.0, 133.1, 133.0, 132.4, 132.0, 131.9, 131.6, 130.3, 129.6, 128.0, 127.6, 127.5, 127.5, 127.1, 126.7, 126.7, 52.6, 52.2, 31.4, 30.6, 30.1, 21.9, 13.8; HRMS(ESI) calcd for $C_{33}H_{30}NaO_4S$ (M+Na): 545.1757; found: 545.1757; $[\alpha]^{25}_D$ = −62.4 (*c* 0.6, $CHCl_3$, 74% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 11.4 min for major isomer and 13.1 min for minor isomer).



2-Methoxycarbonyl-1,4-dipentyltribenzo[*b,d,f*]thiepin (3lb)

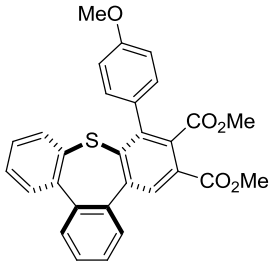
Isolated by preparative TLC (hexane/EtOAc = 10/1). The title compound was obtained as a yellow oil (50%). ^{1}H NMR δ 7.69 (s, 1H), 7.60-7.59 (m, 2H), 7.35-7.33 (m, 2H), 7.23-7.19 (m, 2H), 7.17-7.14 (m, 2H), 3.92 (s, 3H), 2.92-2.79 (m, 2H), 2.70-2.64 (m, 1H), 2.46-2.39 (m, 1H), 1.56-1.30 (m, 3H), 1.15-1.02 (m, 9H), 0.78 (t, *J* = 6.7 Hz, 3H), 0.73 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR δ 169.7, 143.0, 142.9, 142.9, 141.4, 140.4, 140.0, 138.4, 137.7, 132.5, 132.4, 132.1, 131.5, 131.0, 130.8, 127.7, 127.6, 127.4, 127.4, 52.4, 33.9, 31.9, 31.7, 31.0, 30.8, 30.2, 22.4, 22.3, 14.2, 14.1; HRMS(ESI) calcd for $C_{30}H_{34}NaO_2S$ (M+Na): 481.2172; found: 481.2174; $[\alpha]^{25}_D$ = +35.2 (*c* 1.1, $CHCl_3$, 75% ee). Ee was determined by HPLC analysis

using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: hexane, flow rate: 1.0 mL/min, retention time: 18.7 min for major isomer and 15.4 min for minor isomer).



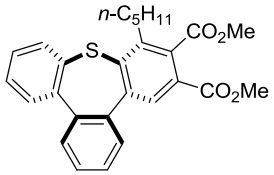
6,7-Bis(methoxycarbonyl)-8-phenyltribenzo[*b,d,f*]thiepin (5aa)

Isolated by preparative TLC (toluene/CH_2Cl_2 = 1/3). The title compound was obtained as a pale yellow solid (58%). Mp 222 °C; ^{1}H NMR δ 8.13 (s, 1H), 7.58-7.49 (m, 6H), 7.46-7.44 (m, 2H), 7.39 (dt, J_d = 1.5 Hz, J_t = 7.4 Hz, 1H), 7.32-7.26 (m, 3H), 7.23-7.21 (m, 1H), 3.87 (s, 3H), 3.52 (s, 3H); ^{13}C NMR δ 168.5, 165.5, 144.7, 144.5, 143.2, 142.2, 140.5, 139.6, 137.8, 137.5, 135.0, 132.7, 131.3, 130.5, 130.3, 130.0, 129.3, 129.1, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 126.6, 52.7, 52.2 (a pair of peaks at the aromatic region is overlapped); HRMS(ESI) calcd for $C_{28}H_{20}NaO_4S$ (M+Na): 475.0975; found: 475.0972; $[\alpha]^{25}_D$ = +98.6 (*c* 0.6, $CHCl_3$, 81% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 2% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 13.2 min for major isomer and 16.3 min for minor isomer).



6,7-Bis(methoxycarbonyl)-8-(4-methoxyphenyl)tribenzo[*b,d,f*]thiepin (5ba)

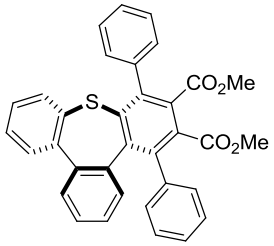
Isolated by preparative TLC (toluene/CH_2Cl_2 = 1/3). The title compound was obtained as a yellow solid (59%). Mp 193 °C; ^{1}H NMR δ 8.12 (s, 1H), 7.58-7.51 (m, 5H), 7.39 (dt, J_d = 1.4 Hz, J_t = 7.4 Hz, 1H), 7.34 (dd, *J* = 1.3, 7.7 Hz, 1H), 7.27 (dd, *J* = 1.4, 7.5 Hz, 1H), 7.23 (dd, *J* = 2.2, 8.5 Hz, 1H), 7.23 (dd, *J* = 2.2, 8.4 Hz, 1H), 7.04 (dd, *J* = 2.7, 8.5 Hz, 1H), 6.97 (dd, *J* = 2.7, 8.4 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.57 (s, 3H); ^{13}C NMR δ 168.6, 165.5, 159.3, 145.0, 144.6, 143.2, 141.9, 140.5, 139.7, 137.5, 135.2, 132.7, 131.5, 131.1, 130.5, 130.3, 130.3, 130.0, 129.9, 129.2, 128.4, 128.3, 127.8, 126.4, 113.4, 112.9, 55.2, 52.6, 52.3; HRMS(ESI) calcd for $C_{29}H_{22}NaO_5S$ (M+Na): 505.1080; found: 505.1082; $[\alpha]^{25}_D$ = +199 (*c* 0.7, $CHCl_3$, 71% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 1% 2-propanol in hexane, flow rate: 2.0 mL/min, retention time: 23.6 min for major isomer and 35.1 min for minor isomer).



6,7-Bis(methoxycarbonyl)-8-pentyltribenzo[*b,d,f*]thiepin (5ca)

Isolated by preparative TLC (toluene/CH_2Cl_2 = 3/1). The title compound was obtained as a yellow solid (64%). Mp 140 °C; ^{1}H NMR δ 7.96 (s, 1H), 7.63 (dd, J = 1.1, 7.7 Hz, 1H), 7.53-7.48 (m, 5H), 7.39 (dt, J_d = 1.3 Hz, J_t = 7.5 Hz, 1H), 7.29 (dt, J_d = 1.4, J_t = 7.6 Hz, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 3.12 (dt, J_d = 5.0 Hz, J_t = 12.0 Hz, 1H), 2.88 (dt, J_d = 4.8 Hz, J_t = 11.6 Hz, 1H), 1.76-1.67 (m, 1H), 1.61-1.52 (m, 1H), 1.51-1.38 (m, 4H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 169.5, 165.7, 145.0, 144.9, 143.4, 141.6, 140.4, 140.1, 137.5, 134.3, 132.9, 130.5, 130.2, 130.0, 129.9, 129.3, 128.2, 128.2, 127.7, 127.0, 52.6, 52.5, 32.8, 32.2, 31.3, 22.4, 14.0; HRMS(ESI) calcd for $C_{27}H_{26}NaO_4S$ (M+Na): 469.1444; found: 469.1445; $[\alpha]^{25}_D$ = +149 (*c* 0.7, $CHCl_3$, 80% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 2.5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 7.8 min for major isomer and 8.9 min for minor isomer).

Crystal data of **5ca**; $C_{34}H_{24}O4S$, M = 528.62, monoclinic, Space Group C2/c, a = 11.0057(6) Å, b = 14.3571(8) Å, c = 17.4259(9) Å, β = 94.5351(17) °, V = 2744.9(2) Å3, T = 173.0 K, Z = 4, μ(MoKα) = 1.555 cm-1, Number of Reflections Measures: Total 25663, Unique: 12232 (R*int* = 0.0227), *R1* = 0.0342, *wR2* = 0.0908. Flack parameter = 0.01(15)

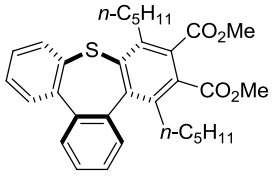


6,7-Bis(methoxycarbonyl)-5,8-diphenyltribenzo[*b,d,f*]thiepin (5da)

Isolated by preparative TLC (toluene/CH_2Cl_2 = 1/2). The title compound was obtained as a yellow oil (37%). ^{1}H NMR δ 7.63 (d, J = 7.5 Hz, 1H), 7.51-7.42 (m, 4H), 7.38-7.30 (m, 4H), 7.24-7.19 (m, 4H), 7.14 (dd, J = 7.4, 7.4 Hz, 1H), 6.98 (br, 1H), 6.94 (dt, J_d = 1.4 Hz, J_t = 7.7 Hz, 1H), 6.81 (dd, J = 1.1, 7.9 Hz, 1H), 6.43 (br, 1H), 3.46 (s, 3H), 3.43 (s, 3H); ^{13}C NMR δ 168.5, 168.0, 144.4, 143.9, 143.4, 141.6, 141.4, 140.4, 139.0, 138.7, 138.6, 138.6, 132.8, 132.8, 131.8, 131.7, 130.9, 129.5, 129.2, 128.9, 128.0, 128.0, 127.9, 127.8, 127.8, 127.4, 127.1, 126.0, 77.2, 52.3 (four pairs of peaks at the aromatic region are overlapped); HRMS(ESI) calcd for $C_{34}H_{24}NaO_4S$ (M+Na): 551.1288; found: 551.01288 $[\alpha]^{25}_D$ = +24.3 (*c* 0.7, $CHCl_3$, 75% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA:

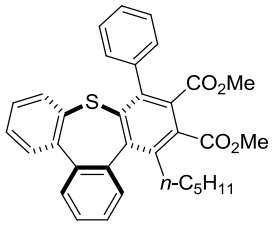
4.6 x 250 mm, 254 nm UV detector, rt, eluent: 1% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 16.4 min for major isomer and 28.3 min for minor isomer).

Crystal data of **5da**; $C_{34}H_{24}O4S$, M = 528.62, monoclinic, Space Group C2/c, a = 11.0057(6) Å, b = 14.3571(8) Å, c = 17.4259(9) Å, β = 94.5351(17) °, V = 2744.9(2) Å3, T = 173.0 K, Z = 4, μ(MoKα) = 1.555 cm-1, Number of Reflections Measures: Total 25663, Unique: 12232 (R*int* = 0.0227), *R1* = 0.0342, *wR2* = 0.0908. Flack parameter = 0.01(15)



6,7-Bis(methoxycarbonyl)-5,8-dipentyltribenzo[*b,d,f*]thiepin (5ea)

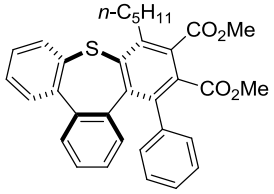
Isolated by preparative TLC (toluene/CH_2Cl_2 = 3/1). The title compound was obtained as a pale yellow oil (52%). ^{1}H NMR δ 7.58 (dd, J = 1.1, 7.8 Hz, 1H), 7.55 (dd, J = 1.4, 7.7 Hz, 1H), 7.50-7.46 (m, 2H), 7.42-7.38 (m, 2H), 7.30 (d, J = 7.5 Hz, 1H), 7.24 (dd, J = 1.4, 7.6 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.14 (dt, J_d = 5.1 Hz, J_t = 13.0 Hz, 1H), 2.90 (dt, J_d = 4.8 Hz, J_t = 12.8 Hz, 1H), 2.79-2.73 (m, 1H), 2.43-2.37 (m, 1H), 1.76-1.67 (m, 1H), 1.54-1.50 (m, 1H), 1.48-1.36 (m, 4H), 1.21-1.12 (m, 1H), 0.99-0.93 (m, 5H), 0.90-0.77 (m, 3H), 0.66 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 169.1, 168.9, 145.0, 144.8, 143.5, 141.4, 139.5, 139.4, 139.0, 138.6, 132.7, 132.6, 131.1, 130.2, 129.6, 129.4, 128.9, 127.8, 127.8, 126.4, 52.5, 52.4, 32.4, 32.1, 31.4, 31.4, 30.1, 22.5, 21.9, 14.1, 13.7 (a pair of peaks at the aliphatic region is overlapped); HRMS(ESI) calcd for $C_{32}H_{36}NaO_4S$ (M+Na): 539.2227; found: 539.2227; $[\alpha]^{25}_D$ = +153 (*c* 0.8, $CHCl_3$, 73% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 1% 2-propanol in hexane, flow rate: 0.5 mL/min, retention time: 17.6 min for major isomer and 15.3 min for minor isomer).



6,7-Bis(methoxycarbonyl)-5-pentyl-8-phenyltribenzo[*b,d,f*]thiepin (5fa)

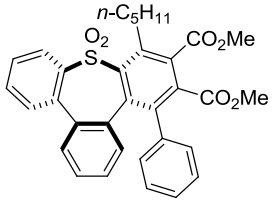
Isolated by preparative TLC (toluene/CH_2Cl_2 = 3/1). The title compound was obtained as a pale yellow oil (52%). ^{1}H NMR δ 7.54 (dd, J = 1.3, 7.7 Hz, 1H), 7.52-7.36 (m, 8H), 7.26-7.18 (m, 4H), 3.83 (s, 3H), 3.43 (s, 3H), 2.91-2.85 (m, 1H), 2.48-2.42 (m, 1H), 1.32-1.23 (m, 2H), 1.03-0.86 (m, 4H), 0.70 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 168.8, 168.3, 144.5, 144.3, 143.2, 141.5, 140.3, 139.8, 138.9, 138.8, 138.8, 132.6,

132.3, 131.7, 130.5, 130.1, 129.6, 129.3, 129.0, 128.5, 128.0, 127.9, 127.8, 127.7, 126.4, 52.6, 52.2, 31.6, 31.5, 30.1, 22.0, 13.7 (a pair of peaks at the aromatic region is overlapped); HRMS(ESI) calcd for $C_{33}H_{30}NaO_4S$ (M+Na): 545.1757; found: 545.1757; $[\alpha]^{25}_D$ = +142 (*c* 0.3, $CHCl_3$, 65% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 1% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 14.2 min for major isomer and 12.2 min for minor isomer).



6,7-Bis(methoxycarbonyl)-8-pentyl-5-phenyltribenzo[*b*,*d*,*f*]thiepin (5ga)

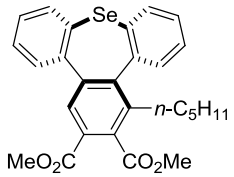
Isolated by preparative TLC (toluene/CH_2Cl_2 = 1/3). The title compound was obtained as a pale yellow oil (42%). ^{1}H NMR δ 7.66-7.63 (m, 2H), 7.46 (dt, J_d = 1.1 Hz, J_t = 7.5 Hz, 1H), 7.37 (dd, *J* = 1.1, 7.7 Hz, 1H), 7.30 (dt, J_d = 1.4 Hz, J_t = 7.7 Hz, 1H), 7.28 (br, 2H), 7.22 (dt, J_d = 1.2 Hz, J_t = 7.5 Hz, 1H), 7.11-7.08 (m, 1H), 6.94 (br, 1H), 6.90 (dt, J_d = 1.2 Hz, J_t = 7.7 Hz, 1H), 6.72 (dd, *J* = 1.1, 7.9 Hz, 1H), 6.37 (br, 1H), 3.87 (s, 3H), 3.40 (s, 3H), 3.28 (dt, J_d = 4.3 Hz, J_t = 12.3 Hz, 1H), 2.92-2.86 (m, 1H), 1.86-1.78 (m, 1H), 1.60-1.40 (m, 5H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 168.9, 168.6, 145.0, 144.1, 143.7, 141.6, 141.1, 139.3, 139.2, 139.0, 138.7, 133.1, 132.9, 131.9, 131.2, 130.1, 129.5, 129.2, 129.2, 128.9, 128.0, 127.8, 127.3, 126.9, 125.9, 52.6, 52.2, 32.8, 32.2, 31.5, 22.5, 14.1 (a pair of peaks at the aromatic region is overlapped); HRMS(ESI) calcd for $C_{33}H_{30}NaO_4S$ (M+Na): 545.1757; found: 545.1758; $[\alpha]^{25}_D$ = +28.9 (*c* 0.4, $CHCl_3$, 74% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 2.5% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 6.5 min for major isomer and 8.7 min for minor isomer).



6,7-Bis(methoxycarbonyl)-8-pentyl-5-phenyltribenzo[*b*,*d*,*f*]thiepin-*S*,*S*-dioxide (7)

Isolated by preparative TLC (toluene/CH_2Cl_2 = 1/1). The title compound was obtained as a white solid (50%). Mp 176 °C; ^{1}H NMR δ 8.17 (d, *J* = 7.7 Hz, 1H), 7.76-7.71 (m, 2H), 7.58-7.54 (m, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.28-7.25 (m, 3H), 7.14-7.10 (m, 1H), 6.96-6.92 (m, 2H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.21 (d, *J* = 7.6 Hz, 1H), 3.91 (s, 3H), 3.57 (dt, J_d = 4.8 Hz, J_t = 12.6 Hz, 1H), 3.40 (s, 3H), 3.08 (dt, J_d = 4.6 Hz, J_t = 12.4 Hz, 1H), 1.90-1.80 (m, 1H), 1.76-1.68 (m, 1H), 1.54-1.37 (m, 4H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C

NMR δ 167.9, 167.8, 145.1, 143.6, 140.8, 140.4, 138.7, 138.2, 138.0, 137.7, 137.0, 136.6, 134.2, 134.0, 132.5, 129.9, 129.6, 129.3, 128.2, 128.2, 128.2, 127.9, 127.3, 127.2, 127.1, 52.9, 52.5, 33.1, 32.4, 30.3, 22.3, 14.0 (a pair of peaks at the aromatic region is overlapped); HRMS(ESI) calcd for $C_{33}H_{30}NaO_6S$ (M+Na): 577.1655; found: 577.1655; $[\alpha]^{25}_D$ = −7.3 (*c* 0.7, $CHCl_3$, 65% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 1% 2-propanol in hexane, flow rate: 1.5 mL/min, retention time: 23.7 min for major isomer and 29.6 min for minor isomer).



2,3-Bis(methoxycarbonyl)-1-heptyltribenzo[*b*,*d*,*f*]selenepin (9)

Isolated by preparative TLC (hexane/EtOAc = 5/1). The title compound was obtained as a white solid (91%). Mp 108 °C; ^{1}H NMR δ 7.92 (s, 1H), 7.77 (dd, *J* = 0.9, 7.5 Hz, 1H), 7.72 (dd, *J* = 1.0, 7.7 Hz, 1H), 7.55 (dd, *J* = 1.2, 7.7 Hz, 1H), 7.35 (dt, J_d = 0.9 Hz, J_t = 7.5 Hz, 1H), 7.31-7.27 (m, 1H), 7.24-7.16 (m, 2H), 3.99 (s, 3H), 3.91 (s, 3H), 2.92-2.85 (m, 1H), 2.43-2.36 (m, 1H), 1.39-1.27 (m, 1H), 1.19-0.92 (m, 5H), 0.70 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR δ 170.1, 165.9, 145.6, 143.3, 142.4, 139.7, 138.6, 136.7, 136.6, 134.8, 134.3, 133.7, 131.3, 130.2, 129.8, 128.7, 128.1, 127.9, 127.7, 126.1, 52.6, 52.5, 31.6, 31.1, 29.4, 21.8, 13.8; HRMS(ESI) calcd for $C_{27}H_{26}NaO_4Se$ (M+Na): 517.0889; found: 517.0889; $[\alpha]^{25}_D$ = −13.1 (*c* 1.1, $CHCl_3$, 62% ee). Ee was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 2% 2-propanol in hexane, flow rate: 1.0 mL/min, retention time: 10.3 min for minor isomer and 12.1 min for major isomer).

Chirality and saddle inversion energy measurement[12]

In Schlenk tubes, each sample (**3aa**, **3ka**) was dissolved in xylene under Ar atmosphere. The solutions were then degassed and sealed. The solutions were immersed into a digital controlled oil bath preheated to 353 K or 393 K. During heating, **3aa** was taken out for chiral HPLC analysis at 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 10 h, 11 h and 24 h (HPLC conditions: Daicel Chiralpak IA, 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 1.0 mL/min), **3ka** was taken out for chiral HPLC analysis at 1 h, 2 h, 3 h, 4 h, 5 h, 6 h and 7 h (HPLC conditions: Daicel Chiralpak IA: 4.6 x 250 mm, 254 nm UV detector, rt, eluent: 5% 2-propanol in hexane, flow rate: 0.5 mL/min). Bowl inversion process follows the equation (1):

$$\ln[a/(a-2x)] = 2kt \qquad (1)$$

where a is the initial concentration of (*R*)-**3aa** or **3ka**, x is the concentration of gradually generated (*S*)-**3aa** or **3ka** at time t, and k is the inversion rate constant.

k_{3aa} = 6.63×10^{-6} s^{-1}. Saddle inversion energy $\Delta G^{\ddagger} = RT\ln(k_B T h^{-1} k^{-1})$ = 29.1 kcal mol^{-1}. Half-lifetime at 353 K : $t_{1/2} = (\ln 2)/2k$ = 14.5 h; Half-lifetime at 293 K : $t_{1/2}$ = 9.2 years.

k_{3ka} = 4.59×10^{-5} s^{-1}. Saddle inversion energy $\Delta G^{\ddagger}$ = 31.0 kcal mol^{-1}. Half-lifetime at 393 K : $t_{1/2}$ = 2.1 h; Half-lifetime at 293 K : $t_{1/2}$ = 230 years.

References

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Chapter 9

Concluding Remarks

In this thesis, the author disclosed that synthesis of optically active amino acids and heteroatom-containing polycyclic compounds using iridium-catalyzed C-H bond activation and rhodium-catalyzed cycloaddition. As α-amino acids, 4-substituted Trp derivatives were synthesized by iridium-catalyzed cyclodehydration via sp^2 C-H activation, and total synthesis of *cis*-clavicipitic acid was achieved using the transformation as a key step (Chapter 2). Chiral tethered Aic derivatives were synthesized by rhodium-catalyzed enantioselective intramolecular cycloaddition of amino acid-tethered triynes, and the synthetic transformation gave chiral Aic derivatives (Chapter 3). In addition, 4-substituted γ-amino acid derivatives were synthesized via iridium-catalyzed sp^3 C-H bond activation of γ-butyrolactam and subsequent synthetic transformation. Enantioselective formal total synthesis of pyrrolam A was also achieved by using the sp^3 C-H alkylation as a key step (Chapter 4).

With regard to the synthesis of heteroatom-containing polycyclic compounds, multi-substituted DBT and DBP oxide derivatives were prepared by rhodium-catalyzed intermolecular cycloaddition. These protocols were expanded to enantioselective reaction, and axially chiral bi-dibenzothiophene skeleton and chiral dibenzophosphole oxide skeleton were constructed in high ee (Chapter 6). The first catalytic intermolecular cycloaddition of α,ω-diynes with benzothiophene dioxide derivatives was achieved by a rhodium complex. The reaction gave sulfur-containing condensed polycyclic compounds (Chapter 7). The first catalytic and enantioselective synthesis of multi-substituted tribenzothiepin derivatives was accomplished by rhodium-catalyzed intermolecular cycloaddition of two types of sulfur-containing diynes (Chapter 8).

The catalytic and enantioselective synthesis of various chiral amino acids create a new library of potentially biologically important compounds. The synthesis of various heterocycles by cycloaddition affords a facile protocol for the preparation of multi-substituted condensed polycyclic compounds with high tolerability of functional groups. Therefore, these achievements virtually contribute to the synthesis of diverse compounds oriented toward life science and material science fields.

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論文	“Enantioselective Intramolecular [2+2+2] Cycloaddition of 1,4-Diene-ynes: A New Approach to the Construction of Quaternary Carbon Stereocenters” *J. Am. Chem. Soc.* **2006**, *128*, 11766-11767. Takanori Shibata, Yu-ki Tahara “Enantioselective Construction of Quaternary Carbon Centers by Catalytic [2+2+2] Cycloaddition of 1,6-Enynes and Alkynes” *Org. Lett.* **2005**, *7*, 4955-4957. Takanori Shibata, Yoshikazu Arai, Yu-ki Tahara
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