Heterocycles

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Catalytic and Enantioselective Synthesis of Chiral Multisubstituted Tribenzothiepins by Intermolecular Cycloadditions

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Abstract: *The first catalytic and highly enantioselective synthesis of tribenzothiepin derivatives was achieved. Two types of intermolecular cycloadditions using either diphenyl-sulfide-tethered diynes or 2-phenyl sulfanylbenzene-tethered diynes with a monoalkyne successfully gave chiral multisubstituted tribenzothiepins in good to excellent ee values under mild conditions. The inversion energy of this saddle-shaped molecule was calculated by measurement of the racemization rate of chiral tribenzothiepins using the Eyring kinetic equation under heating conditions. The present protocol could also be used to prepare a chiral tribenzoselenepin.*

Cyclooctatetraene is a nonaromatic compound possessing an 8π electron system with a nonplanar, tub-shaped structure. Its cyclic skeleton gives a unique flexible π-conjugated system. For example, diaryleno[*a*,*e*]cyclooctatetraenes, in which two aromatic moieties are fused to a cyclooctatetraene core, have been shown to exhibit a dynamic conformational change.[1] In contrast, tetrabenzo[*a*,*c*,*e*,*g*]cyclooctatetraene, namely *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 create chirality, and the asymmetric synthesis of multisubstituted *o*,*o*,*o*,*o*-tetraphenylenes and their applications have been studied extensively.[3] Heteropin, a seven-membered heterocycle, is considered to be a heteroanalogue of cyclooctatetraene. Little is known about its derivatives, probably because of their instability. For example, thiepin itself is unstable[4] and can be isolated as an iron complex.[5] Tribenzoheteropin, a heteroanalogue of *o*,*o*,*o*,*o*-tetraphenylene, is expected to be a more stable and a unique saddle-shaped molecule.[6] The introduction of a single substituent can create chirality (Figure 1), but the reports of substituted tribenzoheteropin syntheses are quite limited.

Substituted tribenzazepin and tribenzothiepin have been prepared by a photostimulated reaction, but in low yield.[7] As a classical protocol, the [4+2] cycloaddition of cyclopentadienone-fused dibenzothiepin with alkynes gives substituted tribenzothiepin derivatives (Scheme 1 a).[8] The cycloaromatization of ketene dithioacetal was reported for the synthesis of tribenzoxepin derivatives (Scheme 1 b).[9] These are stoichiometric protocols which use dibenzoheteropins as substrates. With regard to a catalytic protocol which includes the construction of a heteropin core, only one example of consecutive Suzuki–Miyaura couplings was recently reported, and was used for the preparation of both tribenzoxepin and tribenzazepin derivatives (Scheme 1 c).[10] Chiral tribenzothiepin-2-carboxylic acid *S*,*S*-dioxide was prepared by resolution using brucine.[11] However, to the best of our knowledge, there has been no report of an enantioselective synthesis of substituted tribenzoheteropins. We describe herein the catalytic and enantioselective synthesis of multisubstituted tribenzoheteropin derivatives.

We chose a transition-metal-catalyzed cycloaddition as a key strategy for construction of the tribenzoheteropin skeleton since the cycloaddition of unsaturated motifs such as alkynes and/or alkenes is a powerful and atom-economical method for the synthesis of multisubstituted six-membered-

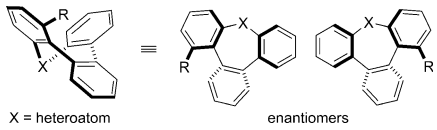
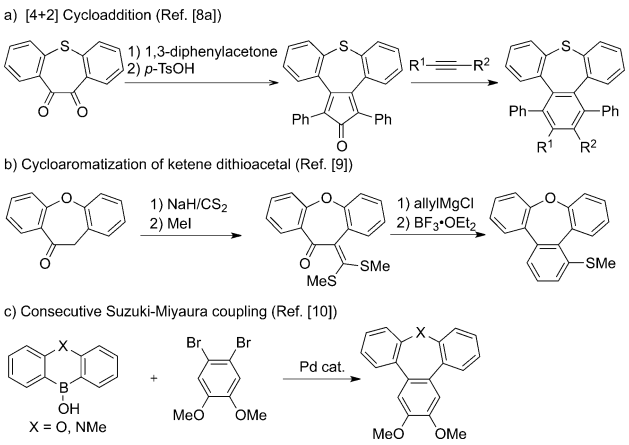


Figure 1. Structure and enantiomers of tribenzoheteropins.



Scheme 1. Approaches to the synthesis to tribenzoheteropins. *p*-Ts = *p*-toluenesulfonyl.

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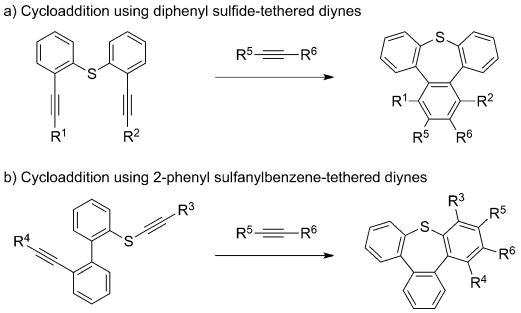
ring compounds.[12] We comprehensively studied the inter-[13] and intramolecular[14] cycloaddition of various substances, including three alkyne motifs. Recently, we focused on the construction of sulfur-containing cyclic systems by cycloaddition.[13g,15] In addition, we achieved a highly enantioselective synthesis of saddle-shaped tetraphenylene derivatives by consecutive inter- and intramolecular cycloadditions.[3i,k,l] Against this background, we considered two types of reactions which could be used to construct chiral tribenzoheteropin skeletons (Scheme 2). An intermolecular cycloaddition

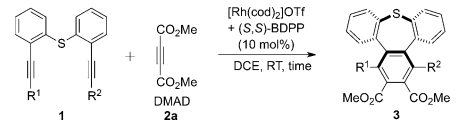


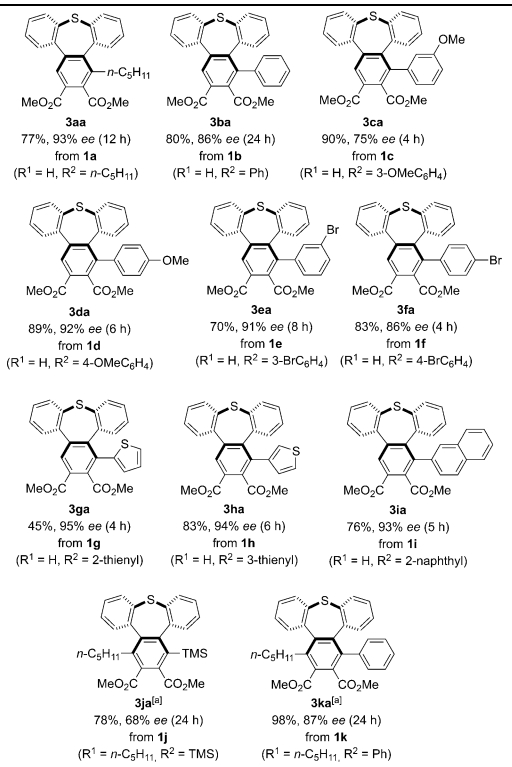
Scheme 2. Two types of intermolecular cycloaddition for the synthesis to tribenzothiepins.

of diphenyl-sulfide-tethered diynes with alkynes gives chiral tribenzoheteropins possessing a substituted benzene ring fused at the 4,5-position of thiepin (Scheme 2a). An intermolecular cycloaddition of 2-phenyl sulfanylbenzene tethered diynes with alkynes gives chiral tribenzoheteropins possessing a substituted benzene ring fused at the 2,3-position (Scheme 2b). Herein we describe the first catalytic and enantioselective synthesis of multisubstituted tribenzoheteropin derivatives under mild reaction conditions.

We first examined the intermolecular cycloaddition of unsymmetrical diphenyl-sulfide-tethered diynes ($R^1 \neq R^2$) with dimethyl acetylenedicarboxylate (DMAD) (Scheme 2a). We chose the diyne **1a** ($R^1 = H$, $R^2 = n$-pentyl) as a model substrate, and investigated the results with various chiral rhodium catalysts.[16] When a rhodium catalyst consisting of trifluoromethanesulfonate (OTf) as a counter anion and (2*S*,4*S*)-bis(diphenylphosphino)pentane [(*S*,*S*)-BDPP] as a chiral ligand were used, the desired reaction proceeded smoothly at room temperature in 1,2-dichloroethane (DCE), and the chiral tribenzothiepin **3aa** was obtained in high yield and with an excellent *ee* value. Various diynes were screened under the optimal reaction conditions (Table 1). The reaction using the diyne **1b**, possessing a phenyl group, also proceeded, and the corresponding tribenzothiepin **3ba** was obtained in high yield and *ee* value. When the diynes **1c–f**, which have either 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 the tribenzothiepins **3ca–fa**. Thiophene could also be installed by the reaction of **1g** and **1h**, and the thienylated tribenzothiepins **3ga** and **3ha**, respectively, were obtained with well over 90% *ee*. The enantiomerically pure cycloadduct **3ga** was prepared as a single crystal by recrystal-

Table 1: Enantioselective synthesis of tri- and tetrasubstituted tribenzothiepins by intermolecular cycloaddition of diphenyl sulfide-tethered diynes with DMAD (**2a**).





Diyne/alkyne was 1:3. The concentration of the diyne was 33 mM. Yield is that of the isolated product. The *ee* value was determined by chiral-phase HPLC analysis. [a] (*S*,*S*)-CHIRAPHOS was used as a chiral ligand, and the reaction was run at RT→60°C. BDPP = 2,4-bis(diphenylphosphine)pentane, cod = cycloocta-1,5-diene, DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

lization, and its structure and absolute configuration of the axial chirality (*R*-form) were ascertained by X-ray crystallographic analysis. This molecule had a saddle-shaped structure, as expected. The sulfur atom and the trisubstituted benzene ring across from it are situated above the plane, while the two other benzene rings are below the plane (Figure 2). The diyne **1i**, possessing a naphthyl group on one of the alkyne termini, was also a good substrate, and the chiral tribenzothiepin **3ia** was obtained in high yield with 93% *ee*. When the diynes **1j** and **1k**, which have substituents on both alkyne termini, were used in the reaction, heating was required to achieve high conversion. The reactions with (2*S*,3*S*)-2,3-bis(diphenylphosphino)butane [(*S*,*S*)-CHIRAPHOS] gave better results than did (*S*,*S*)-BDPP, and the tetrasubstituted tribenzothiepins were obtained. While the enantioselectivity of the reaction of **1j** decreased, the reaction of **1k** proceeded almost quantitatively with high enantioselectivity.

We further examined the reaction of the symmetrical diyne **1l**, having pentyl groups on both alkyne termini, with methyl propiolate (**2b**) as an unsymmetrical alkyne

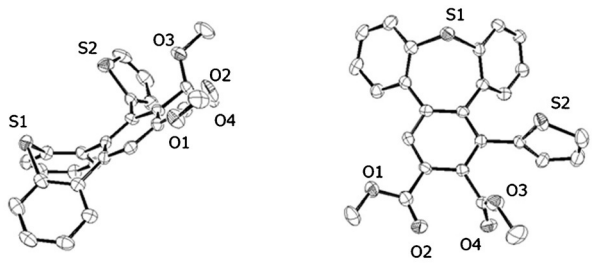
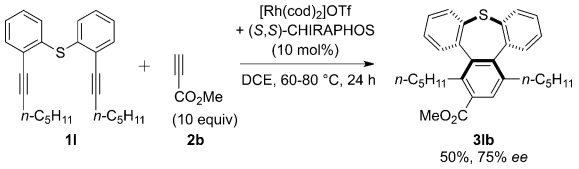


Figure 2. ORTEP diagram of **3ga**. Thermal ellipsoids shown at 50% probability.[20]

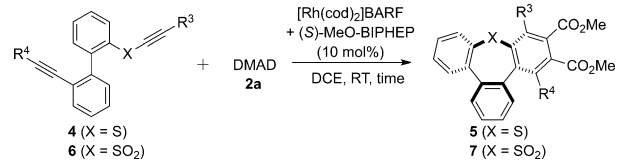
(Scheme 3). The reaction required heating and excess amounts of **2b**. However, the chiral tribenzothiepin derivative **3lb** was obtained in moderate yield with a good *ee* value.

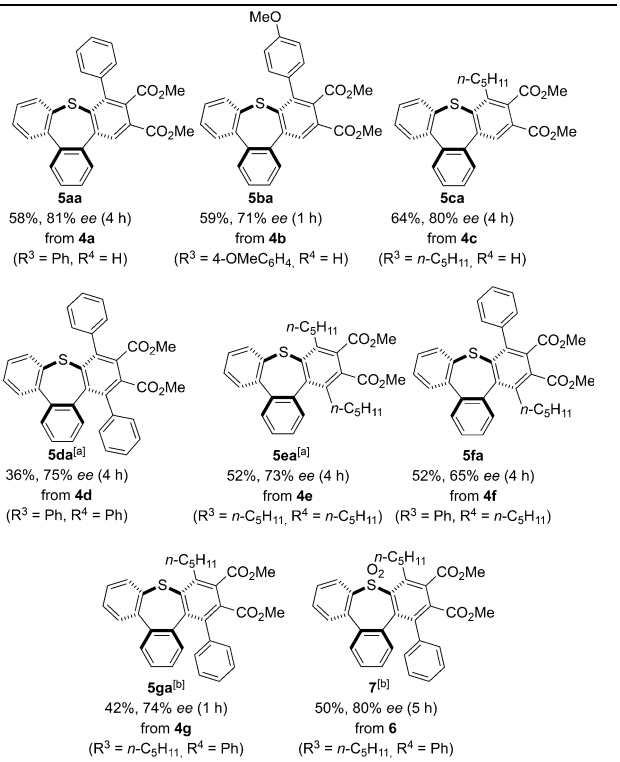


Scheme 3. Intermolecular cycloaddition of symmetrical diyne with methyl propiolate (**2b**). CHIRAPHOS = 2,3-bis(diphenylphosphino)-butane.

Next, we examined the intermolecular cycloaddition of 2-phenyl sulfanylbenzene tethered diynes with DMAD for the synthesis of multisubstituted tribenzothiepin derivatives (Scheme 2b). We first chose Rh/BDPP, which was an optimal catalyst the reaction in Scheme 2a, but the desired cycloadduct could not be obtained. Therefore, we reinvestigated the use of the chiral catalysts,[17] and the combination of a rhodium catalyst consisting of tetrakis(3,5-bistrifluoromethylphenyl)borate (BARF) as a counter anion and (*S*)-2,2′-bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl [(*S*)-MeO-BIPHEP] as a chiral ligand gave the best results: the intermolecular cycloaddition of the diyne **4a**, possessing a phenyl group on one of the alkyne termini, with DMAD proceeded at room temperature to give the 6,7,8-trisubstituted tribenzothiepin **5aa** with a good *ee* value (Table 2). The substrate scope of the diynes **4** is also shown. The reaction of **4b**, which has a 4-methoxyphenyl group on the alkyne terminus, proceeded to afford cycloadduct **5ba**. The alkyl-substituted diyne **4c** was also transformed into the corresponding cycloadduct **5ca** with a good *ee* value. The cycloaddition of diynes possessing substituents on both alkyne termini was examined: **4d** and **4e**, possessing phenyl and pentyl groups, respectively, on both alkyne termini, and diynes **4f** and **4g**, each possessing a phenyl and pentyl group at the alkyne termini were used in the reaction. While the yields of tetrasubstituted the tribenzothiepins **5da–ga** were low to moderate, good enantioselectivity was achieved. In particular, enantiomerically pure **5da** could be prepared as a single crystal by recrystallization. Its structure and the absolute configuration of the axial chirality (*S*-form) were ascertained by X-ray crystallographic analysis, and the saddle-shaped structure was also recognized (Figure 3). In addition, the sulfoxide-tethered diyne **6** was also a good substrate, and the tribenzothiepin *S,S*-dioxide **7** was obtained with good *ee* value (Table 2).

Table 2: Enantioselective synthesis of tri- and tetrasubstituted tribenzothiepins by intermolecular cycloaddition of 2-phenyl sulfanylbenzene-tethered diynes with DMAD.





Diyne/alkyne was 1:3. The concentration of the diyne was 0.1 M. Yield is that of the isolated product.The *ee* value was determined by chiral-phase HPLC analysis. [a] The reaction was run at 40 °C. [b] The reaction was run at 60 °C.

Next, we measured the circular dichroism (CD), ultraviolet-visible (UV-vis), and fluorescence spectra to study the photophysical properties of **3ha** (Figure 4a and b), and the barrier to saddle inversion of the compounds **3aa** and **3ka** in terms of their rates of racemization.[18,19] The trisubstituted tribenzothiepin **3aa** was stable at 60 °C for 2 hours, but racemization was observed at 80 °C. The rate constant of racemization for **3aa** at (353 K) was determined to be $6.63 \times 10^{-6}\ s^{-1}$, and the barrier to saddle inversion ($\Delta G^{\neq}$) 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. In contrast, the tetrasubstituted tribenzothiepin **3ka** was more stable, as we expected, and racemization was observed at 120 °C after 2 hours. The rate constant of racemization and the barrier to saddle inversion ($\Delta G^{\neq}$) were calculated to be $4.59 \times 10^{-5}\ s^{-1}$ (393 K) and 31.0 kcal per

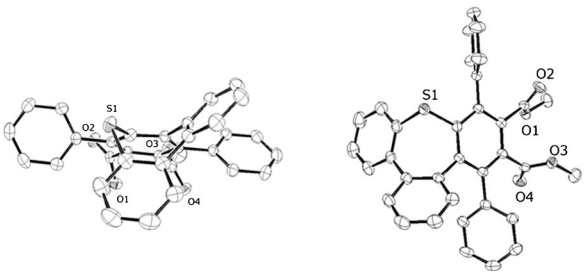


Figure 3. ORTEP diagram of **5da**. Thermal ellipsoids shown at 50% probability.[20]

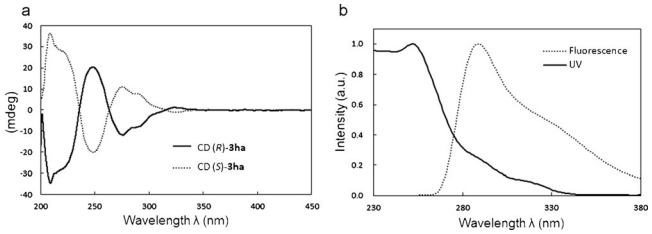
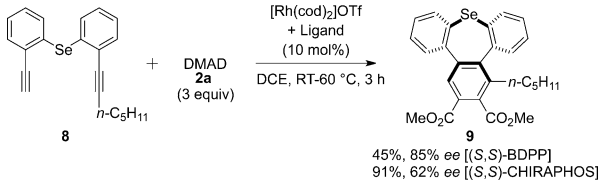


Figure 4. CD, UV, and fluorescence spectra. a) CD spectra of (*S*)-**3ha** and (*R*)-**3ha** in 1,2-dichloroethane solution (3.75×10^{-3} M). Maximum values for (*S*)-**3ha** and (*R*)-**3ha** are $\lambda = 209$, 248, and 276 nm. b) Black line is UV-vis spectrum of (*R*)-**3ha** in dichloromethane solution (1.43×10^{-5} M), λ_{max} (absorption) and log ε are $\lambda = 252$ nm and 4.51, respectively. Dotted line is fluorescence spectrum of (*R*)-**3ha** in dichloromethane solution (1.36×10^{-4} M), λ_{max}(emission) is 289 nm.

mole, respectively, which means that the half-life of **3ka** at 20 °C is 230 years.

In addition to sulfur-tethered diynes, the selenium-tethered diyne **8** could also be used in the present cycloaddition (Scheme 4). The reaction of **8** with **2a** proceeded to give the tribenzoselenepin **9** with a high *ee* value by using (*S*,*S*)-BDPP as a chiral ligand, and in high yield using (*S*,*S*)-CHIRAPHOS. Notably, this report is the first example of the synthesis of tribenzoselenepin skeleton.



Scheme 4. Enantioselective synthesis of tribenzoselenepin.

In summary, we have successfully developed two types of intermolecular cycloadditions, that of diphenyl-sulfide-tethered diynes and 2-phenyl sulfanylbenzene tethered diynes with alkynes. We report the first catalytic and enantioselective synthesis of multisubstituted tribenzoheteropins including tribenzothiepins, tribenzothiepin *S*,*S*-dioxide, and tribenzoselenepin. Further studies on the enantioselective synthesis of other tribenzoheteropin derivatives, and their applications in material science are underway in our laboratory.

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Keywords: chirality · cycloaddition · enantioselectivity · rhodium · synthetic methods

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[16] Optimization of the catalyst for the intermolecular cycloaddition using **1a** with DMAD is listed in the Supporting Information.

[17] Optimization of the catalyst for the intermolecular cycloaddition using **4** with DMAD is listed in the Supporting Information.

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[19] Examination for the racemization of tribenzothiepin derivatives is shown in the Supporting Information.

[20] CCDC CCDC 1441339 (**3ga**) and 1441340 (**5da**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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