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Iridium-Catalyzed Enantioselective [2+2+2] Cycloaddition of Diynes and Monoalkynes for the Generation of Axial Chiralities

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Abstract: A highly enantioselective intermolecular [2+2+2] cycloaddition of alkynes was catalyzed by a chiral iridium complex. Symmetrical and unsymmetrical diynes, and monoalkynes possessing functional group(s) were subjected to the reaction and various types of axially chiral compounds possessing biaryl skeletons were obtained in good to excellent enantiomeric excesses.

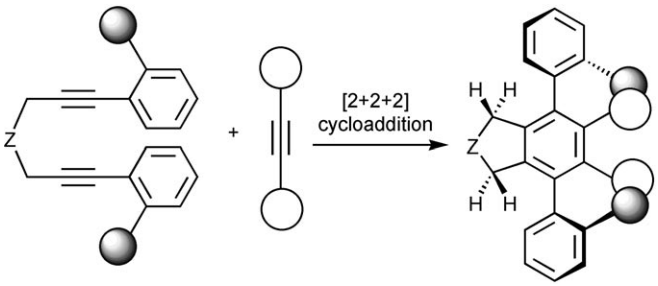
Keywords: asymmetric catalysis; chirality; cycloaddition; enantioselectivity; iridium

Introduction

The transition metal-catalyzed [2+2+2] cycloaddition of alkynes is an atom-economical and reliable protocol for the synthesis of highly substituted arenes.[1] It started with Reppe's report, in which a Ni complex-mediated acetylene oligomerization gave benzene among several cycloadducts.[2] Yamazaki's report on the Co-mediated trimerization of diphenylacetylene can be recognized as a pioneering work on [2+2+2] cycloaddition in organic synthesis.[3] And since Vollhardt used a Co-catalyzed coupling of diynes and monoalkynes for natural product syntheses,[4] [2+2+2] cycloaddition has become a powerful synthetic method. However, an enantioselective [2+2+2] cycloaddition of alkynes has not been developed yet and, to the best of our knowledge, there have been only two practical examples: Mori reported an Ni-catalyzed enantiotopic group-selective [2+2+2] cycloaddition of a triyne and acetylene for the construction of an asymmetric carbon center at the benzylic position[5] while Stará and Starý disclosed an Ni-catalyzed intramolecular [2+2+2] cycloaddition of a triyne for the construction of helical chirality.[6] We considered a new concept for an enantioselective [2+2+2] cycloaddition of alkynes (Scheme 1): when the cycloaddition of a diyne, possessing *ortho*-substituted aryl groups on its termini, and a disubstituted monoalkyne proceeds, a C_2-symmetrical teraryl compound is obtained, which has two axial chiralities derived from steric repulsion between, on the one hand, substituents on the monoalkynes or hydrogens on the tether of the diyne and, on the other, the *ortho*-substituents on the aryl groups.[7]

We have found that a chiral Ir catalyst realizes the new concept for the construction of axial chiralities, and we have already reported a preliminary communication.[8] Quite independently, two groups reported an enantioselective [2+2+2] cycloaddition based on the same concept: Gutnov and Heller used a chiral Co catalyst under the photoirradiation conditions,[9] and Tanaka used a chiral Rh catalyst.[10] Related papers using enantioselective [2+2+2] cycloaddition of alkynes were published by the two groups.[11]

This manuscript discloses the full details of the Ir-catalyzed enantioselective [2+2+2] cycloaddition of



Scheme 1. A novel approach to the generation of axial chiralities.

diynes and monoalkynes including its scope and limitation.

Results and Discussion

Further Optimization of the Reaction Conditions

In our preceding communication,[8] the [2+2+2] cycloaddition of α,ω-diynes and monoalkynes was examined at 100 °C using Ir-MeDUPHOS catalyst, which was prepared in situ from $[IrCl(cod)]_2$ and (*S*,*S*)-MeDUPHOS. In the case of the reaction of the oxygen-tethered diyne **1a** with 1,4-dimethoxybut-2-yne (**2a**), diyne **1a** was consumed promptly and only a *dl* isomer of the teraryl compound **3aa** was obtained in almost perfect enantioselectivity (Table 1, Entry 1) and (*R*,*R*)-MeDUPHOS surely induced the opposite enantiomer (Entry 2). However, the yield did not exceed 90% because an intramolecular [4+2] cycloaddition of the alkyne moiety with arylyne moiety of diyne **1a** proceeded at the high reaction temperature.[12] In order to prevent the side reaction, the cycloaddition was examined at lower temperature. As a result, cycloadduct **3aa** was obtained in excellent *ee*, but diyne **1a** was recovered after stirring the reaction mixture for 24 h (Entry 3). When the concentration of the catalyst was quadrupled, diyne **1a** was consumed within 1 h even at room temperature, and an excellent yield of 97% was achieved without formation of the by-product (Entry 4).

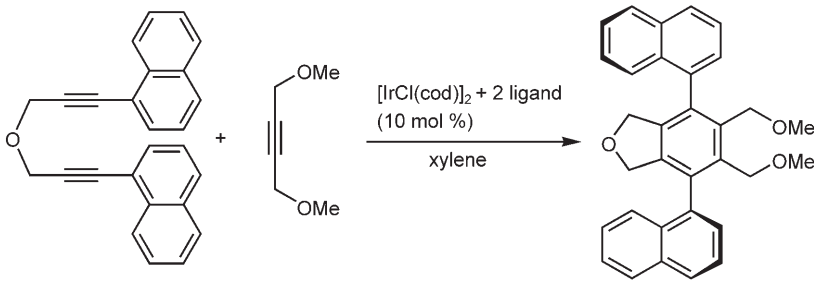
Diol or Monool as a Coupling Partner

In our preceding communication,[8] symmetrical and protected diols, such as 1,4-dimethoxybut-2-yne (**2a**), were used as coupling partners for diynes. We further examined but-2-yne-1,4-diol (**2b**), a symmetrical but non-protected diol using the same chiral catalyst {henceforth, the catalyst, which was prepared *in situ* from $[IrCl(cod)]_2$ and (*S*,*S*)-MeDUPHOS, is described as "chiral Ir catalyst"} (Table 2). Here we found that a exchange of the solvent from xylene to 1,2-dimethoxyethane (DME) was needed due to the solubility of diol **2b**; almost perfect diastereoselectivity and enantioselectivity were achieved and axially chiral diols were directly obtained. In the case of oxygen-tethered diyne **1a**, the reaction at room temperature gave a better yield than at the reflux condition (Entries 1 and 2). On the other hand, nitrogen- and carbon-tethered diynes **1b** and **1c** were not consumed completely at room temperature after stirring the reaction mixture even for three days, and teraryls **3bb** and **3cb** were obtained in better yields under the reflux condition (Entries 3–6).

The ferrocenyl diester of teraryl diol **3bb** was obtained as a single crystal, and its absolute configuration was determined by X-ray measurements (Figure 1).[13]

Scheme 2 shows a possible explanation for the generation of axial chirality: oxidative coupling of the Ir-MeDUPHOS complex to a diyne gives an iridacyclopentadiene. At this stage, two axial chiralities were generated by steric repulsion between a naphthyl group of the diyne and a methyl group of MeDUPHOS. The following metalla-[4+2] cycloaddition with alkyne **2b** or alkyne insertion along with reduc-

Table 1. Further optimization of the reaction conditions.

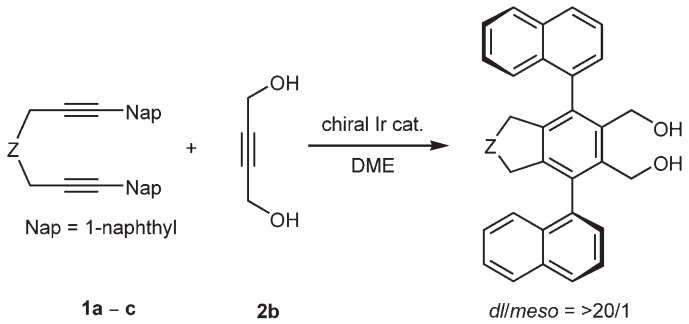


1a **2a** **3aa** *dl*/*meso* = >20/1

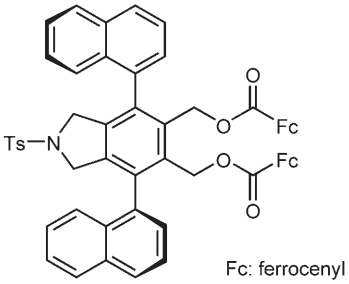
Entry	Ligand	[M][a]	Temperature [°C]	Time [h]	Yield [%]	*ee* [%]
1	(*S*,*S*)-MeDUPHOS	0.5	100	1	83	>99 (+)
2	(*R*,*R*)-MeDUPHOS	0.5	100	1	88	>99 (−)
3	(*S*,*S*)-MeDUPHOS	0.5	r.t.	24	62	99 (+)
4	(*S*,*S*)-MeDUPHOS	2.0	r.t.	1	97	>99 (+)

[a] The concentration of the Ir catalyst [10^{-2} mol/L].

Table 2. But-2-yne-1,4-diol as a coupling partner for diynes.



Entry	Z	Diyne	Temperature [°C]	Time [h]	Yield [%]	*ee* [%]
1	O	**1a**	reflux	2	62 (**3ab**)	>99 (+)
2	O	**1a**	r.t.	5	98 (**3ab**)	>99 (+)
3	NTs	**1b**	reflux	4	84 (**3bb**)	>99 (+)
4	NTs	**1b**	r.t.	72	67 (**3bb**)	99 (+)
5	CH_2	**1c**	reflux	2	87 (**3cb**)	>99 (+)
6	CH_2	**1c**	r.t.	72	43 (**3cb**)	>99 (+)



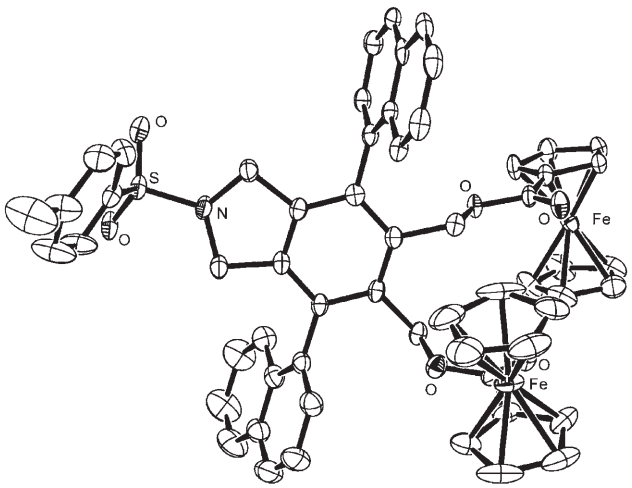
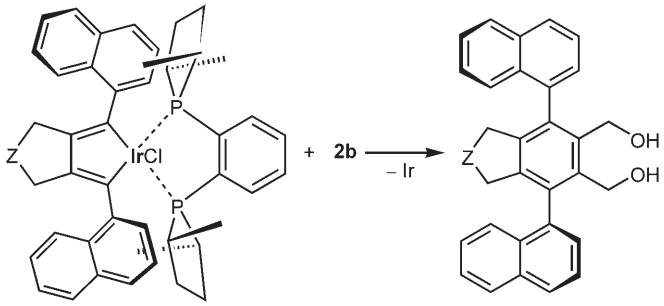


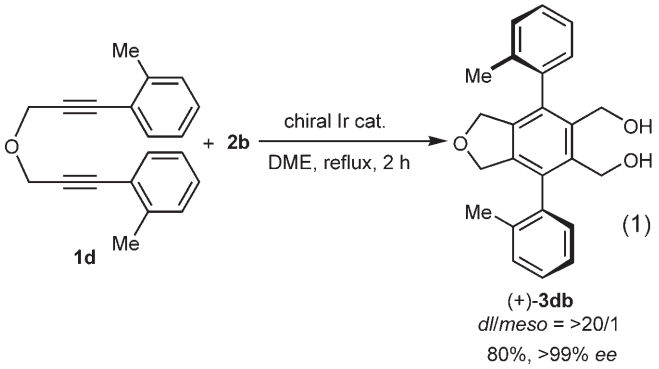
Figure 1. ORTEP diagram of ferrocenyl diester of teraryl diol **3bb**.



Scheme 2. A possible explanation for the generation of axial chirality.

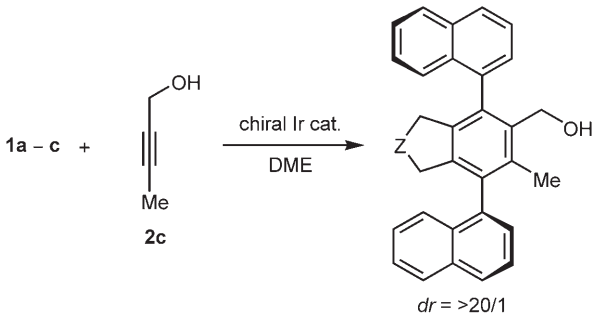
tive elimination gives the corresponding axially chiral teraryl compound.

In place of the naphthyl-substituted diyne **1a**, *o*-tolyl-substituted diyne **1d** was also a good substrate, and the corresponding teraryl **3db** was obtained in enantiomerically pure form under the same reaction conditions [Eq. (1)].



We next chose but-2-yn-1-ol (**2c**) as an unsymmetrical alkyne, which possesses an oxygen functionality at the propargylic position (Table 3). Under reflux con-

Table 3. But-2-yn-1-ol as a coupling partner for diynes.



Entry	Z	Diyne	Temperature [°C]	[M][a]	Time [h]	Yield [%]	*ee* [%]
1	O	**1a**	reflux	0.5	3	89 (**3ac**)	89 (+)
2	O	**1a**	r.t.	0.5	24	43 (**3ac**)	98 (+)
3	O	**1a**	r.t.	2.0	72	84 (**3ac**)	>99 (+)
4	NTs	**1b**	r.t.	0.5	72	77 (**3bc**)	97 (+)
5	CH_2	**1c**	reflux	0.5	2	87 (**3cc**)	99 (+)

[a] The concentration of the catalyst [10^{-2} mol/L].

ditions in DME, the [2+2+2] cycloaddition of diyne **1a** efficiently proceeded, and axially chiral monool **3ac** was obtained in almost perfect diastereoselectivity; however the *ee* was below 90% (Entry 1). When the reaction was examined at room temperature, the *ee* increased to 98% but the yield was moderate because of low conversion of diyne **1a** (Entry 2). A higher concentration of catalyst worked well again and a high yield and almost perfect enantioselectivity were achieved (Entry 3). The reaction of nitrogen-tethered diyne **1b** proceeded at room temperature, and monool **3bc** was obtained as a single diastereomer with excellent *ee* (Entry 4), and its structure and absolute configuration were determined by X-ray measurements (Figure 2). Carbon-tethered diyne **1c** needed a high reaction temperature for high conversion (Entry 5). When hex-3-yne was subjected to the [2+2+2] cycloaddition as a coupling partner for diyne **1a** under the reflux conditions, no cross-cycloadduct was detected. These results imply that at least one oxygen functionality at the propargylic position of monoalkyne is indispensable for the cross coupling with the diyne.

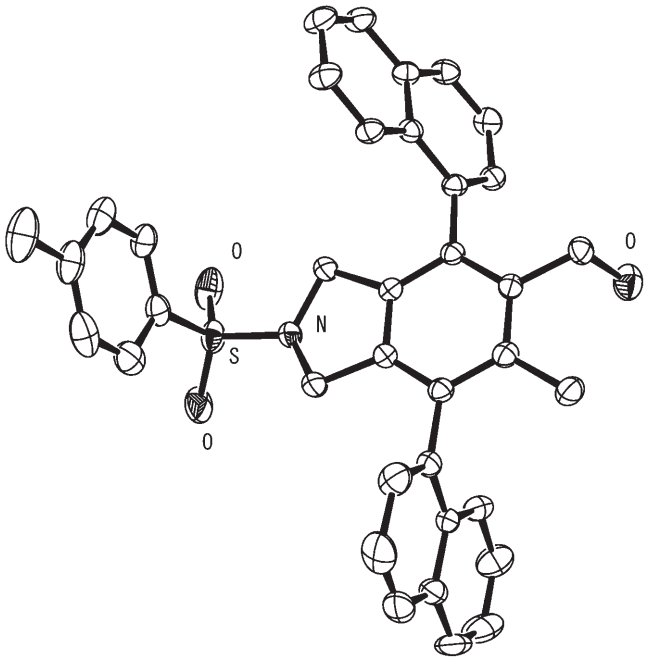
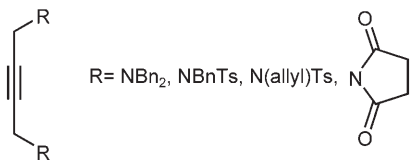


Figure 2. ORTEP diagram of teraryl monool **3bc**.

Alkynes with Nitrogen Functionalities as a Coupling Partner

An alkyne possessing nitrogen functionalities at the propargylic positions is the next candidate as a coupling partner. The substituents on the nitrogen atoms were found to be very important. Here, in the reaction of diyne **1a** with diamines, which is shown in Scheme 3, almost no cross-cycloadduct could be isolated. Alkyne **2d** with acetyl and benzyl groups on its



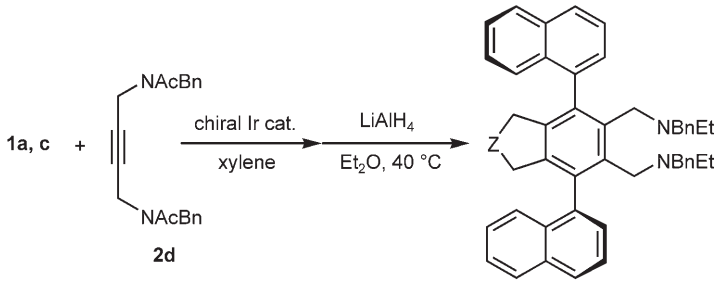
Scheme 3. Inappropriate nitrogen functionalities for alkyne.

nitrogen atoms successfully reacted with diyne **1a**, and the corresponding teraryl compound was ob-

tained. In order to determine the enantiomeric excess, the amides were reduced to amines and the axially chiral diamine **3ad** was fully characterized (Table 4). At 100 °C, the yield was moderate and the *meso* isomer was a major product; however, the enantiomeric excess of the *dl* isomer was over 99% (Entry 1). At room temperature, the yield was drastically improved, and the ratio of *dl* isomer also increased (Entry 2). In the case of carbon-tethered diyne **1c**, the *dl* isomer was a major product even under reflux conditions and enantioselectivity was again almost perfect (Entry 3).

Unsymmetrical alkynes, possessing an acetylbenzylamino group at its propargylic position, were subjected to the cycloaddition (Table 5): in the reaction of alkyne **2e** with diyne **1a** and **1c**, diastereoselectivity was not high, however, both diastereomers were obtained in excellent *ee* (Entries 1 and 2). Exchange of the substituents on the nitrogen gave dramatically better results. Here, in the case of alkyne **2f**, possessing a methyltosylamino group at its propargylic position, the reaction of diyne **1a** proceeded at room temperature and teraryl **3af** was obtained in excellent yield as a single diastereomer and the minor enantiomer could not be detected by NMR analysis after the

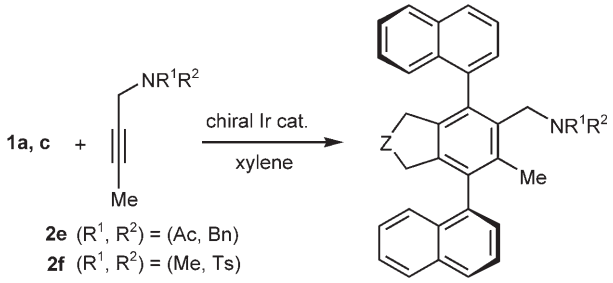
Table 4. An alkyne with two nitrogen functionalities at its propargylic positions as a coupling partner for diynes.



Entry	Z	Diyne	Temperature[°C]	Time [h]	Yield [%][a]	*dl*/*meso*	*ee* [%][b]
1	O	**1a**	100	2	64 (**3ad**)	1/2	>99 (−)
2	O	**1a**	r.t.	4	95 (**3ad**)	1/1	>99 (−)
3	CH_2	**1c**	100	1	75 (**3cd**)	4/1	>99 (−)

[a] Yield of two steps.
[b] The *ee* of *dl* isomer.

Table 5. Alkynes with a nitrogen functionality at the propargylic position as a coupling partner for diynes.

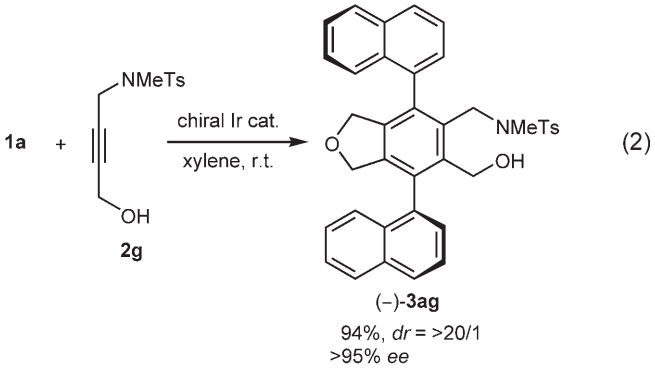


Entry	Diyne	Alkyne	Temperature [°C]	Time [h]	Yield [%]	*dr*	*ee* [%][c]	*ee* [%][d]
1[a]	**1a**	**2e**	r.t.	2	99[b] (**3ae**)	4/1	>99 (−)	97 (+)
2[a]	**1c**	**2e**	100	0.3	95[b] (**3ce**)	5/1	>99 (−)	>99 (+)
3	**1a**	**2f**	r.t.	4	94 (**3af**)	>20/1	>95 (−)[e]	–
4	**1c**	**2f**	100	0.3	quant. (**3cf**)	>20/1	>99 (+)	–

[a] The cycloadduct was reduced by $LiAlH_4$.
[b] Yield in two steps.
[c] The *ee* of major diastereomer.
[d] The *ee* of minor diastereomer.
[e] The *ee* was determined using ^1H NMR after the tosyl amide had been transformed into the camphorsulfonyl amide.

transformation of tosyl amide into camphorsulfonyl amide (Entry 3). Alkyne **2f** was a better coupling partner also for diyne **1c**: at 100 °C, the [2+2+2] cycloaddition proceeded quantitatively, and the corresponding axially chiral monoamine **3cf** was obtained in diastereomerically and enantiomerically pure form[14] (Entry 4).

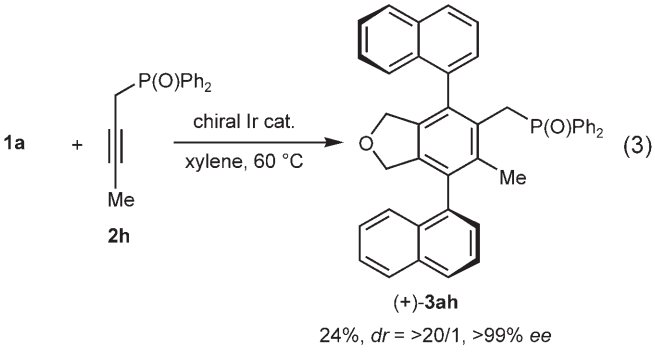
Alkyne **2g** with both oxygen and nitrogen functionalities at its propargylic positions was the next coupling partner [Eq. (2)]. The [2+2+2] cycloaddition



(2)

smoothly proceeded at room temperature in xylene and axially chiral amino alcohol **3ag** was obtained as a single diastereomer with excellent enantiomeric excess, which was determined by NMR analysis after alcohol **3ag** was transformed into the camphorsulfonate. The structure and absolute configuration of amino alcohol **3ag** was determined by X-ray measurements after the transformation of the hydroxy group into ferrocenyl ester (Figure 3).

Alkyne **2h** with a phosphorus functionality at its propargylic position was subjected to the reaction [Eq. (3)]. After screening of the reaction temperature,



(3)

concentration, and amounts of the chiral iridium catalyst, the yield was unfortunately low; however, the diastereo- and enantioselectivities were almost perfect.

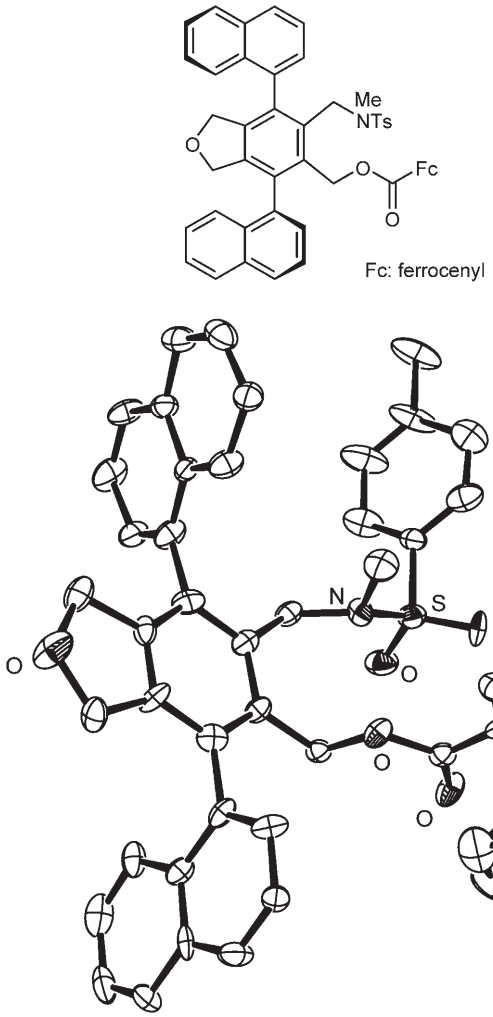
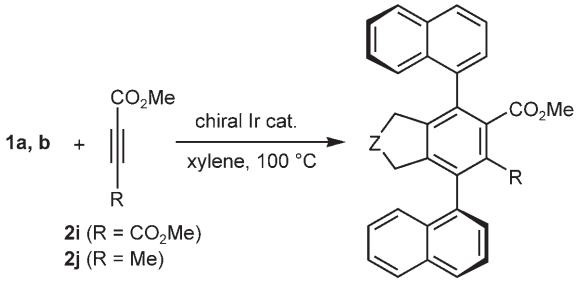


Figure 3. ORTEP diagram of ferrocenyl ester of teraryl amino alcohol **3ag**.

Alkynes with Ester Functionalities as a Coupling Partner

We assumed that electron-withdrawing group(s) on an alkyne are necessary to facilitate the cycloaddition with diynes and thus alkynyl esters were examined (Table 6). The [2+2+2] cycloaddition of oxygen- and nitrogen-tethered diynes **1a**, **1b** with alkyne **2i** possessing two ester functionalities efficiently proceeded and the corresponding axially chiral diesters **3ai**, **3bi** were obtained in excellent *ee* (Entries 1 and 2). Dimethyl acetylenedicarboxylate (**2i**) was very reactive; its self-coupling proceeded and the yield did not exceed 90%. Actually, methyl propiolate (**2j**) was a better coupling partner, and axially chiral monoesters **3aj**, **3bj**[15] were obtained quantitatively with almost perfect enantiomeric excess (Entries 3 and 4). The absolute configuration of **3bi** was determined by X-ray measurements (Figure 4).

Table 6. Alkynyl esters as a coupling partner for diynes.



Entry	Diyne	Alkyne	Time [h]	Yield [%]	*ee* [%]
1	**1a**	**2i**	2	81[a] (**3ai**)	>99 (−)
2	**1b**	**2i**	1	86[b] (**3bi**)	99 (+)
3	**1a**	**2j**	1	quant.[c] (**3aj**)	>99 (−)
4	**1b**	**2j**	1	quant.[c] (**3bj**)	99 (+)

[a] *dl*/*meso* = 5/1.
[b] *dl*/*meso* = > 20/1.
[c] A sole diastereomer was detected.

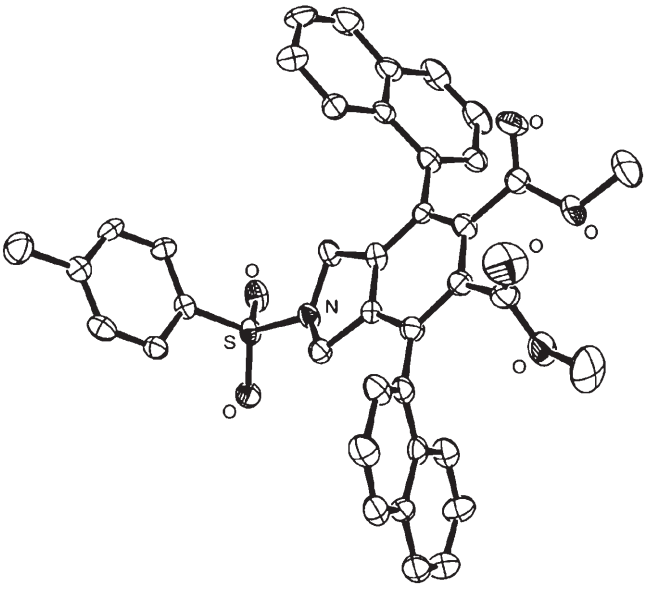
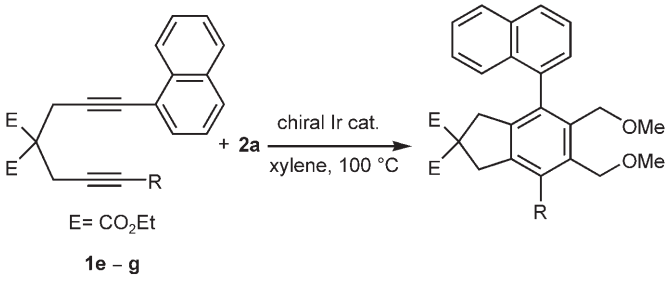


Figure 4. ORTEP diagram of axially chiral diester **3bi**.

Unsymmetrical Diynes with Symmetrical Monoalkynes

Thus far, the [2+2+2] cycloaddition of symmetrical diynes with symmetrical or unsymmetrical monoalkynes was examined using the chiral Ir catalyst, and various teraryl compounds with two axial chiralities were obtained. We next examined the coupling of unsymmetrical diyne **1e**, possessing methyl and naphthyl groups on its termini, and symmetrical monoalkyne **2a** under the same reaction conditions as symmetrical diynes (Table 7, Entry 1). The yield of cross-cycloadduct **3ea** was moderate because of the formation of self-cycloadduct of diyne **1e**. Moreover, the *ee* of biaryl compound **3ea** with an only axial chirality was moderate. The bulkiness of the substituent on the alkyne terminus was very important, and trimethylsilyl and phenyl groups in place of the methyl group improved both yield and enantioselectivity (Entries 2 and 3).

Table 7. The reaction of unsymmetrical diynes and symmetrical alkyne **2a**.

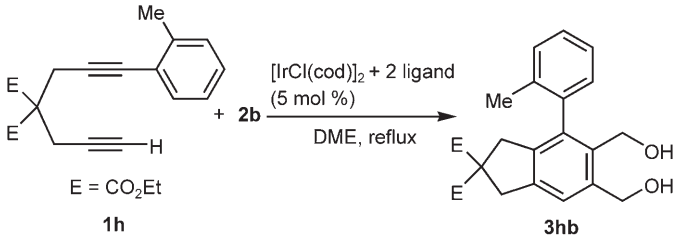


Entry	R	Diyne	Time [h]	Yield [%]	*ee* [%]
1	Me	**1e**	2	49 (**3ea**)	41 (+)
2	TMS	**1f**	1	78 (**3fa**)	89 (+)
3	Ph	**1g**	1	99 (**3ga**)	94 (+)

In the case of diyne **1h** with an unsubstituted alkyne terminus, the Ir-MeDUPHOS catalyst did not work well and biaryl compound **3hb** with an axial chirality was obtained in moderate yield with low *ee* (Table 8, Entry 1). After screening of several chiral ligands (Entries 2–5), BINAP realized good enantioselectivity of 83% (Entry 2).

Diynes **1i–1m** with *ortho*-substituted phenyl or naphthyl groups were subjected to the [2+2+2] cycloaddition using the Ir-BINAP catalyst, and the cor-

Table 8. Screening of the chiral ligands for an unsymmetrical diyne with unsubstituted alkyne terminus.

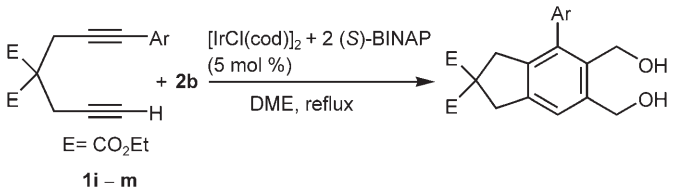


Entry	Ligand[a]	Time [h]	Yield [%]	*ee* [%]
1	MeDUPHOS	10	43	23 (+)
2	BINAP	12	38	83 (−)
3	tolBINAP	12	48	78 (−)
4	BDPP	3	36	62 (+)
5	DIOP	2	43	74 (−)

[a] (*S*,*S*) or (*S*)-isomer was used.

responding axially chiral biaryl compounds **3ib**–**3mb** were obtained (Table 9). In each reaction, the self-cycloaddition of the diyne and the alkyne moiety of the diyne decreased the yield of cross-cycloadduct; however, the enantioselectivity was generally high.

Table 9. The reaction of unsymmetrical diynes with unsubstituted alkyne terminus.



Entry	Ar	Diyne	Time [h]	Yield [%]	*ee* [%]
1[a]	2-MeOC$_6$H$_4$	**1i**	24	47 (**3ib**)	65 (−)
2	2-ClC$_6$H$_4$	**1j**	6	52 (**3jb**)	92 (+)
3	1-Naphthyl	**1k**	2	50 (**3kb**)	90 (+)
4	4-Me-1-Naphthyl	**1l**	1	34 (**3lb**)	92 (+)
5	4-MeO-1-Naphthyl	**1m**	1	46 (**3mb**)	87 (+)

[a] The reaction was examined at 50 °C.

Conclusions

Enantioselective [2+2+2] cycloadditions of diynes and monoalkynes have been comprehensively studied using the Ir-MeDUPHOS catalyst, and various types of cycloadducts possessing axially chiral biaryl skeleton(s) were obtained. As coupling partners for symmetrical diynes, symmetrical monoalkynes possessing two oxygen- or nitrogen-functionalities on their propargylic positions, or ester functionalities gave C_2-symmetrical teraryl compounds with two axial chiralities. In most examples, the *meso* isomer could not be detected, and excellent to almost perfect enantioselectivity was achieved. An only oxygen, nitrogen, or ester functionality on the monoalkynes is sufficient for undergoing the cycloaddition with diynes, and unsymmetrical teraryl compounds with two axial chiralities were obtained in almost perfect diastereo- and enantioselectivities. In the case of the cycloaddition of unsymmetrical diynes with an unsubstituted alkyne terminus, the Ir-BINAP complex was an efficient catalyst, and biaryl compounds with an axial chirality were obtained in high enantiomeric excess. These results proved that the Ir-catalyzed enantioselective [2+2+2] cycloaddition of diynes and monoalkynes is a facile and general protocol for the construction of axial chiralities in biaryl skeletons.

Experimental Section

General Remarks

Dehydrated xylene and 1,2-dimethoxyethane (DME) are commercially available, and they were dried over molecular sieves 4 Å (MS 4 A) and degassed by argon bubbling before use. All reactions were performed under an argon atmosphere. IR spectra were recorded with Horiba FT730 spectrophotometer. NMR spectra were measured with JEOL AL-400 and Lambda500 spectrometers using tetramethylsilane as an internal standard and $CDCl_3$ was used as a solvent. Mass spectra were measured with a JEOL JMS-SX102 A and elemental analyses with a Perkin–Elmer PE2400II. Optical rotation was measured with a Jasco DIP-1000 polarimeter.

Typical Procedure for the Enantioselective [2+2+2] Cycloaddition of a Diyne and a Monoalkyne (Table 2)[16]

(*S*,*S*)-MeDUPHOS (6.2 mg, 0.020 mmol) and $[IrCl(cod)]_2$ (6.7 mg, 0.010 mmol) were stirred in DME (1.0 mL) at room temperature to give a yellow solution. After the addition of a DME solution (1.5 mL) of but-2-yne-1,4-diol (25.8 mg, 0.30 mmol) and a DME solution (1.5 mL) of diyne (0.10 mmol), the resulting mixture was further stirred under reflux or at room temperature. After completion of the reaction, the solvent was removed under reduced pressure, and purification of the crude products by thin layer chromatography gave pure teraryl compounds. The ratio of *dl*/*meso* isomers was determined by ^{1}H NMR spectroscopy and the *ee* was determined by HPLC analysis using a chiral column.

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[13] The absolute configuration determined by the circular dichroism exciton method (Ref.[8]) was opposite.

[14] Characterization of chiral monoamine **3cf** was ascertained by the transformation of monool **3cc** (Entry 5 in Table 3): bromination of the hydroxy group along with the substitution reaction by a methyl(tosyl)amino group gave monoamine **3cf** and its NMR spectrum and the sign of its optical rotation were in accord with those of monoamine **3cf**, which was obtained by the reaction of alkyne **2f**.

[15] Characterization of chiral monoester **3bj** was ascertained by the transformation into monool **3bc**: reduction of ester group gave monool **3bc** and its NMR spectrum and the sign of optical rotation were in accord with those of monool **3bc**, which was obtained by the reaction of alkyne **2c** (Entry 4 in Table 3).

[16] See the Supporting Information for characterization data of diynes, monoalkynes, and axially chiral compounds.

