Iridium-Catalyzed Enantioselective Formal [4+2] Cycloaddition of Biphenylene and Alkynes for the Construction of Axial Chirality

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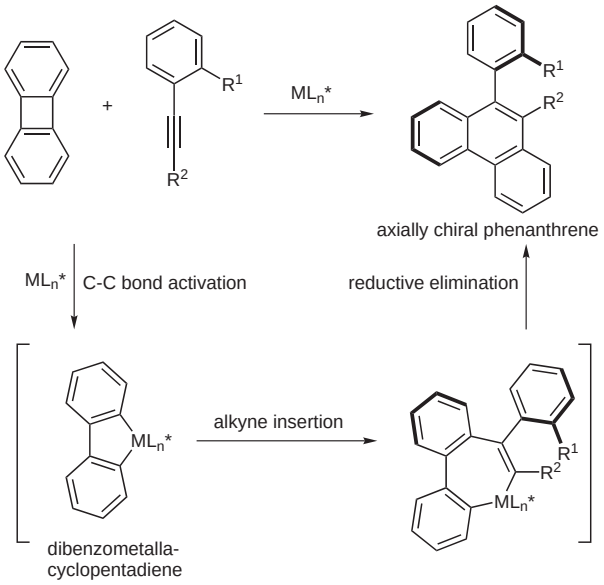
Abstract: Chiral iridium complex catalyzed a formal [4+2] cycloaddition of biphenylene with disubstituted alkynes, which was initiated by carbon–carbon bond cleavage. Axially chiral 9,10-disubstituted phenanthrenes were enantiomerically obtained.

Key words: alkynes, asymmetric catalysis, cycloadditions, iridium, rhodium

In general, a carbon–carbon single bond is inert and intact in organic reactions. However, carbon–carbon bond cleavage in strained molecules with small ring systems, such as cyclopropane and cyclobutane, could be possible.[1] Transition-metal complexes facilitate the bond cleavage, and catalytic and unique synthetic transformations have been reported, which were initiated by carbon–carbon bond cleavage (they are named carbon–carbon bond activation or functionalization).[2] Biphenylene, namely dibenzocyclobutadiene, which has a severely strained 4-membered ring, underwent carbon–carbon bond cleavage: the reaction of biphenylene with transition-metal complexes,[3] including Ni,[4] Ir,[5] Rh,[6] Co,[7] Pt,[8] Fe,[9] and Pd ones,[10] gave dibenzometallacyclopentadienes. However, it was not utilized in the catalytic organic syntheses until Jones and a co-worker reported a Rh-catalyzed reaction of biphenylene with alkynes.[11]

Here we assumed that, if the formal [4+2] cycloaddition of biphenylene with a monoalkyne with *ortho*-substituted aryl group (R^1) on its terminus proceeds, an axial chirality is generated in the substituted phenanthrene as a cycloadduct (Scheme 1).

We chose 1-(3-methoxyprop-1-ynyl)-2-methylbenzene (**1a**) as a model alkyne and examined the reaction with biphenylene using chiral catalysts, which were prepared in situ from $[RhCl(cod)]_2$ or $[IrCl(cod)]_2$ and chiral diphosphine ligands (Table 1).[12] When BINAP was used, the reaction proceeded sluggishly but the desired substituted phenanthrene **2a** was obtained in low yield, and the generation of axial chirality in the product was ascertained by the HPLC analysis using a chiral column. However, its enantiomeric excess was below 5% for both the Rh- and Ir-catalyzed reactions (entries 1 and 2). 1,2-Bis(2,5-dimethylphospholano)benzene (Me-DUPHOS) was a better



Scheme 1 Strategy for the construction of an axial chirality initiated by carbon–carbon bond activation of biphenylene

ligand; in particular, in the Ir-catalyzed reaction, alkyne **1a** was completely consumed within two hours, and moderate yield and enantiomeric excess were achieved (entries 3 and 4). 1,2-Bis(2,5-dimethylphospholano)ethane (Me-BPE) further improved both yield and enantioselectivity (entry 6), but iridium–1,2-bis(2,5-diphenylphospholano)ethane (Ir–Ph-BPE) catalyst showed almost no catalytic activity. In the present enantioselective cycloaddition, Ir complexes generally operated as more efficient chiral catalysts than Rh ones, and we used Ir–Me-BPE catalyst for further investigation.

We next examined various alkynes under the best reaction conditions, and the results are summarized in Table 2.[13] When a methyl group was introduced into the alkyne terminus in place of methoxymethyl one, enantiomeric excess of corresponding product **2b** was significantly increased (entry 1). The substituents on the *ortho* position of the aryl group drastically influenced the enantioselectivity: in the case of the 2-methoxyphenyl group, the enantiomeric excess of cycloadduct **2c** was miserable (entry 2);[14] in contrast, in the case of 2-trifluoromethylphenyl group, the enantiomeric excess of cycloadduct **2d** exceeded 90% (entry 3).[15] From alkyne **1e** with a bulkier siloxy group, corresponding cycloadduct **2e** with slightly lower enantiomeric excess was obtained (entry 4). These results

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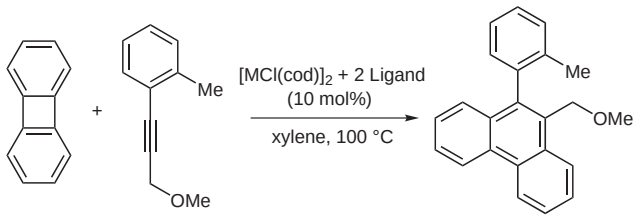
Table 1 Screening of Reaction Conditions Using Various Chiral Rh or Ir Complexes[a]



1a **2a**

Entry	M	Ligand[b]	Time (h)	Yield (%)	ee (%)
1	Rh	BINAP	24	23	<5
2	Ir	BINAP	10	31	<5
3	Rh	Me-DUPHOS	24	45	37
4	Ir	Me-DUPHOS	2	63	58
5	Rh	Me-BPE	24	57	47
6	**Ir**	**Me-BPE**	**2**	**65**	**65**
7	Ir	Ph-BPE	10	N.R.	–

[a] Reaction conditions: biphenylene (0.12 mmol), alkyne (0.10 mmol), $[MCl(cod)]_2$ (0.010 mmol), ligand (0.020 mmol), xylene (1.0 mL).
[b] The *S*- or *S*,*S*-isomer was used.

mean that the use of polarized alkynes, which have an electron-donating group at one side and an electron-withdrawing one at another side, is very important for high enantioselectivity. Actually, alkyne **1f** with methyl and 2-trifluoromethylphenyl groups realized the best enantioselectivity (entry 5).[16] Diaryl-substituted alkynes also reacted with biphenylene and corresponding chiral 9,10-diarylphenanthrenes **2g** and **2h** were obtained (entries 6 and 7). Also in these cases, alkyne **1g** with the electron-donating methoxy group on the benzene ring surely gave better results than the electron-withdrawing methoxycarbonyl group.

The methoxy group of cycloadduct **2g** was transformed into a hydroxy, and the absolute configuration was ascertained as its ferrocenyl ester (Figure 1).

In summary, we developed an Ir-catalyzed enantioselective formal [4+2] cycloaddition of biphenylene and alkynes, which gave 9,10-disubstituted phenanthrenes with an axial chirality. The two substituents on the alkynes played a pivotal role for asymmetric induction. We have already published Ir-catalyzed enantioselective [2+2+2] cycloaddition of alkynes, which induced axially chirality(ies) along with benzannulation.[17] Therefore, the present reaction is another new approach to the construction of axial chirality, which is initiated by carbon–carbon bond cleavage.

Table 2 Ir-Catalyzed Formal [4+2] Cycloaddition of Biphenylene with Various Alkynes[a]

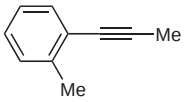
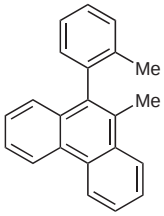
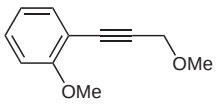
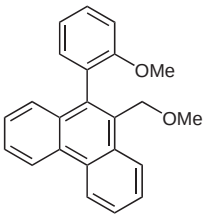
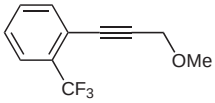
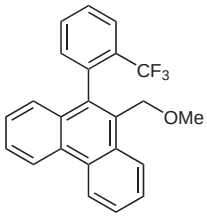
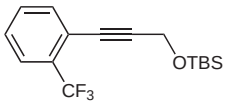
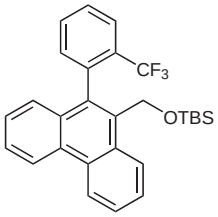
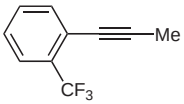
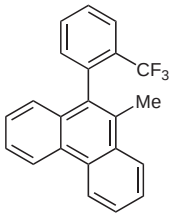
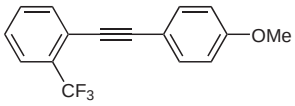
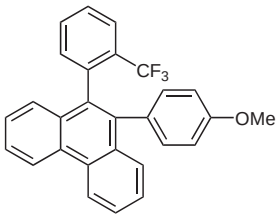
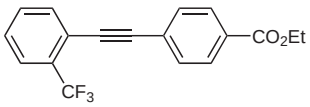
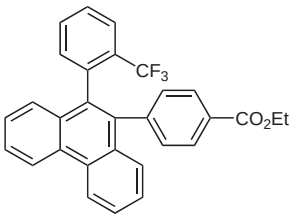
Entry	Alkyne		Time (h)	Product		Yield (%)	ee (%)
1	**1b**		2	**2b**		77	76
2	**1c**		18	**2c**		54	9
3	**1d**		11	**2d**		71	92

Table 2 Ir-Catalyzed Formal [4+2] Cycloaddition of Biphenylene with Various Alkynes[a] (continued)

Entry	Alkyne	Time (h)	Product	Yield (%)	ee (%)
4	**1e** 	3	**2e** 	78	85
5	**1f** 	2	**2f** 	74	95
6[b]	**1g** 	24	**2g** 	55	89
7[b]	**1h** 	24	**2h** 	23	62

[a] Reaction conditions: [IrCl(cod)$_2$] (0.010 mmol), (*S*,*S*)-Me-BPE (0.020 mmol), biphenylene (0.12 mmol), alkyne (0.10 mmol), xylene (1.0 mL).
[b] Alkynes **1** were not completely consumed.

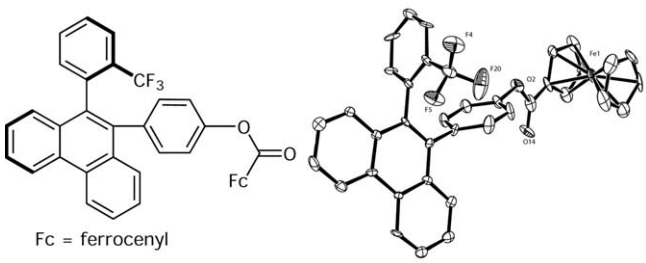


Figure 1 The ORTEP diagram of the ferrocenyl ester derived from cycloadduct **2g**

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(12) In the presence of $[IrCl(cod)]_2$ without diphosphine ligand, alkyne **1a** was consumed within 2 h, but the yield of **2a** was low (28%).
(13) **General Experimental Procedure**
$[IrCl(cod)]_2$ (6.7 mg, 0.010 mmol) was placed in a 30 mL two-neck flask under an argon atmosphere, and a xylene solution (0.4 mL) of (*S*,*S*)-Me-BPE (5.2 mg, 0.020 mmol) was added. After the mixture was stirred for 5 min at r.t., a xylene solution (0.6 mL) of biphenylene (18.3 mg, 0.12 mmol) and an alkyne (0.10 mmol) was added. The mixture was stirred at 100 °C, then the solvent was evaporated under reduced pressure, and the resulting crude products were purified by TLC to afford a pure cycloadduct.
(14) After being stirred for 4 h, cycloadduct **2c** was obtained in higher ee of 27% ee. Actually, gradual racemization of **2c** was ascertained at 100 °C.
(15) **9-Methoxymethyl-10-[(2-trifluoromethyl)phenyl]phenanthrene (2d)**
White solid; mp 151–152 °C. IR (CH_2Cl_2): 1315, 1130, 1110, 1097 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.25 (s, 3 H), 4.22 (d, *J* = 11.0 Hz, 1 H), 4.89 (d, *J* = 11.0 Hz, 1 H), 7.13 (d, *J* = 8.0 Hz, 1 H), 7.40–7.44 (m, 2 H), 7.60–7.72 (m, 5 H), 7.88 (d, *J* = 7.5 Hz, 1 H), 8.28–8.31 (m, 1 H), 8.73–8.78 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 58.2, 70.4, 122.4, 122.8, 125.2, 126.1, 126.2, 126.4, 126.7, 126.8, 127.1, 128.0, 128.1, 129.7, 130.0, 130.2, 130.3, 130.6, 130.7, 131.6, 132.7, 135.6, 138.0. Anal. Calcd for $C_{23}H_{17}F_3O$: C, 75.40; H, 4.68. Found: C, 75.47; H, 4.58. HRMS–FAB (positive): *m/z* calcd for $C_{23}H_{17}F_3O$: 366.1232 $[M]^+$; found: 366.1198 $[M]^+$; $[\alpha]_D^{36}$ 32.0 (*c* 1.00, $CHCl_3$, 99% ee after recrystallization). The ee was determined by chiral HPLC analysis using a chiral column (Daicel Chiralpak IA-H: 4 × 250 mm, 254 nm UV detector, r.t., eluent: 0.5% 2-PrOH in hexane, flow rate: 0.5 mL/min, t_R = 20 min for major isomer and 23 min for minor isomer).
(16) **9-Methyl-10-[(2-trifluoromethyl)phenyl]phenanthrene (2f)**
White solid; mp 109–111 °C. IR (CH_2Cl_2): 1315 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 7.09 (d, *J* = 8.4 Hz, 1 H), 7.25 (d, *J* = 2.4 Hz, 1 H), 7.38–7.43 (m, 1 H), 7.55–7.73 (m, 5 H), 7.89 (d, *J* = 8.4 Hz, 1 H), 8.13–8.16 (m, 1 H), 8.72 (d, *J* = 8.4 Hz, 1 H), 8.77–8.80 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7, 122.3, 122.9, 125.1, 125.3, 125.7, 126.2, 126.3, 126.3, 126.5, 126.8, 127.2, 127.7, 129.1, 130.2, 130.7, 131.6, 131.9, 132.2, 132.4, 133.8, 139.5. Anal. Calcd for $C_{22}H_{15}F_3$: C, 78.56; H, 4.50. Found: C, 78.50; H, 4.40. HRMS–FAB (positive): *m/z* calcd for $C_{22}H_{15}F_3$: 336.1126 $[M]^+$; found: 336.1105 $[M]^+$; $[\alpha]_D^{26}$ –28.1 (*c* 1.00, toluene, 98% ee after recrystallization). The ee was determined by chiral HPLC analysis using a chiral column (Daicel Chiralcel OD-H: 4 × 250 mm, 254 nm UV detector, r.t., eluent: 1% 2-PrOH in hexane, flow rate: 1.0 mL/min, t_R = 8 min for minor isomer and 14 min for major isomer).
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