Ir-catalyzed almost perfect enantioselective synthesis of helical polyaryls based on an axially-chiral sequence†

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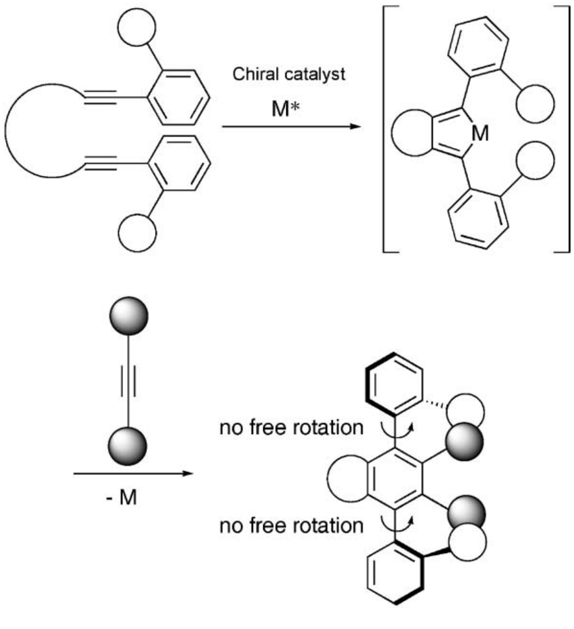
Ir-catalyzed enantioselective [2 + 2 + 2] cycloaddition of tetraynes or an octayne with monoalkynes proceeded to give helically-chiral quinquearyl and noviaryl compounds, which respectively have four and eight consecutive axial chiralities, in an almost enantiomerically pure form.

Chirality is found in various functionalized organic molecules, including pharmacologically-active compounds, and plays a pivotal role in the expression of various functionalities. Therefore, asymmetric synthesis, *i.e.* the development of new synthetic approaches for the generation of chirality, is an important topic in synthetic organic chemistry, and many efficient and general asymmetric reactions have been reported. In particular, catalytic asymmetric synthesis is a major subject of recent research.[1] Among asymmetric reactions, enantioselective carbon–carbon bond forming reactions are desirable because they generate new chirality along with the construction of a carbon skeleton. As a rival to chiral Lewis acid catalysts, whose coordination to heteroatoms such as oxygen and/or nitrogen induces chirality,[2] chiral transition metal catalysts, whose coordination to unsaturated motifs such as alkyne and/or alkene induces chirality, have attracted considerable attention.[3] In particular, cycloaddition *via* a metallacycle as a key intermediate, formed by the oxidative coupling of a transition metal catalyst with unsaturated moieties, is the most atom-economical,[4] and excellent enantiomeric excesses (>95% ee) have been achieved in various types of enantioselective cycloaddition using chiral transition metal catalysts.

Our group recently reported the chiral iridium complex-catalyzed enantioselective [2 + 2 + 2] cycloaddition of an α,ω-diyne, possessing ortho-substituted aryl groups on its alkyne termini, with a disubstituted alkyne;[5] trimerization of the alkyne moieties[6] gave a teraryl compound, which possesses two axial chiralities derived from rotational hindrance of the *ortho*-substituents on the aryl groups (eqn. (1)). In contrast to conventional approaches of enantioselective aryl–aryl coupling,[7] this is a new and practical approach for the catalytic and enantioselective synthesis of an axially-chiral biaryl skeleton.[8] This reaction gives C_2-symmetric compounds with extremely high enantio- and diastereoselectivities.[9,10] We now further examine the synthesis of helically-chiral polyaryl compounds based on an axially-chiral sequence by using the present excellent [2 + 2 + 2] cycloaddition. We examined the reaction of the oxygen and naphthalene ring-bridged tetrayne **1a** and 1,4-dimethoxybut-2-yne in the presence of a chiral iridium catalyst, which was prepared *in situ* from $[IrCl(cod)]_2$ and the chiral diphosphine ligand (*S*,*S*)-MeDUPHOS (1,2-bis(2,5-dimethylphospholano)benzene) (Table 1, entry 1)‡. As a result, asymmetric cycloaddition proceeded promptly (10 min) at 100 °C to give quinquearyl compound **2a** in high yield and almost perfect enantioselectivity (>99% ee).[11] In the case of but-2-yne-1,4-diol as the monoalkyne, it took a longer reaction time but the reaction proceeded even at room temperature, and the corresponding tetraol **2b** was obtained in almost enantiomerically pure form (Table 1, entry 2). This reaction could



(1)

Table 1 Iridium-catalyzed cycloaddition of tetraynes **1** with monoalkynes for the synthesis of chiral quinquearyl compounds **2**

Entry	Z	Tetrayne	R	Yield (%)	ee (%)
1[a]	O	**1a**	Me	89	>99 (**2a**)
2[a,b]	O	**1b**	H	75	>99 (**2b**)
3[c]	N–Ts	**1c**	Me	76	>99 (**2c**)
4[c,d]	*cis*-CH=CH	**1d**[e]	Me	55	>99 (**3d**)[f]

[a] Tetrayne/alkyne = 1 : 6. [b] The reaction was examined in 1,2-dimethoxyethane at room temperature for 5 h. [c] Tetrayne/alkyne = 1 : 20. [d] The reaction was examined at 140 °C. [e] (*Z*,*Z*) : (*Z*,*E*) : (*E*,*E*) = 40 : 10 : 1. [f] Aromatization of the obtained cycloadduct **2d** by DDQ gave quinquenaphthalene **3d**. The yield in 2 steps is based on the (*Z*,*Z*)-isomer of **1d**.

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† Electronic Supplementary Information (ESI) available: Analytical data for **2a–c**, **3d**, **4d** and **2e**. See DOI: 10.1039/b513124c

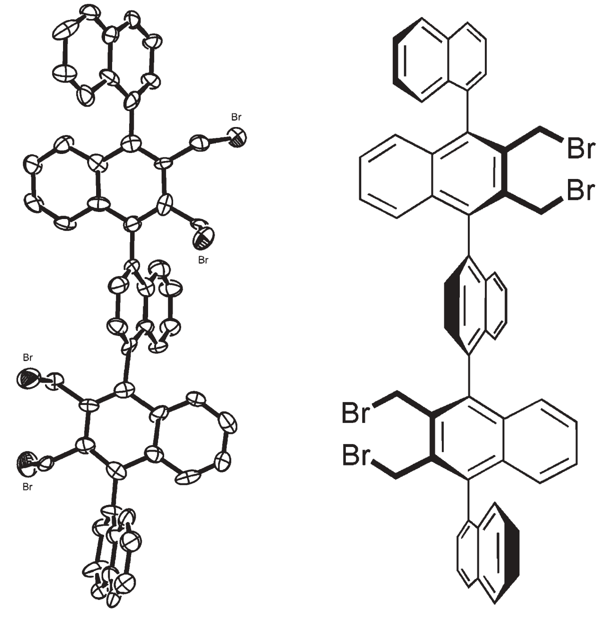
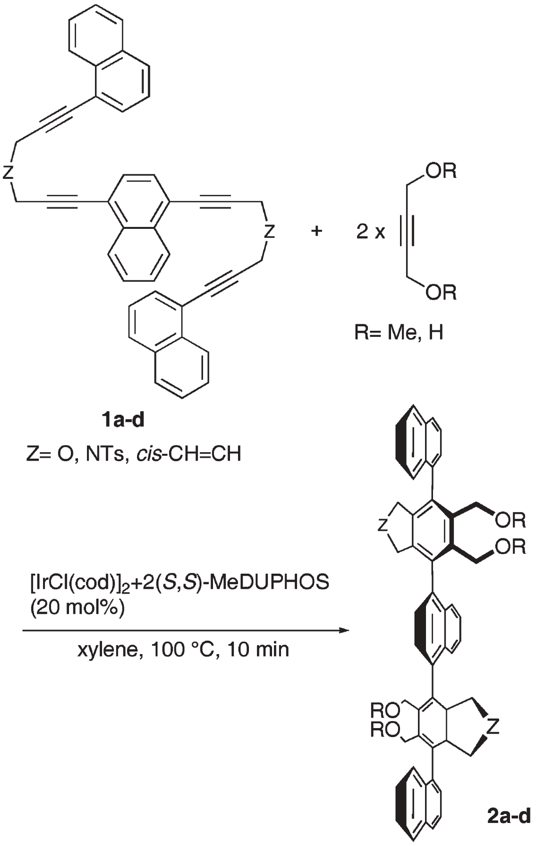


Fig. 1 Crystal structure of **4d** (CH_2Cl_2 and all hydrogen atoms are omitted from the ORTEP diagram for clarity).

tolerate not only oxygen, but also nitrogen on the tether of the tetrayne; again, good yield and almost perfect enantioselectivity were achieved (Table 1, entry 3). Tetrayne **1d**, with *cis*-olefinic tethers, also coupled with 1,4-dimethoxybut-2-yne, and subsequent aromatization of the obtained dihydronaphthalene rings by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave chiral quinquenaphthalene **3d** (Table 1, entry 4).[12] The methoxy groups in **3d** were transformed into bromides, and the structure of tetrabromide **4d** was ascertained by X-ray measurements (Fig. 1§). As we expected, the results show that the five naphthalene rings are helically-situated and that quinquearyl compounds **2** possess helical chirality derived from an axially-chiral sequence.

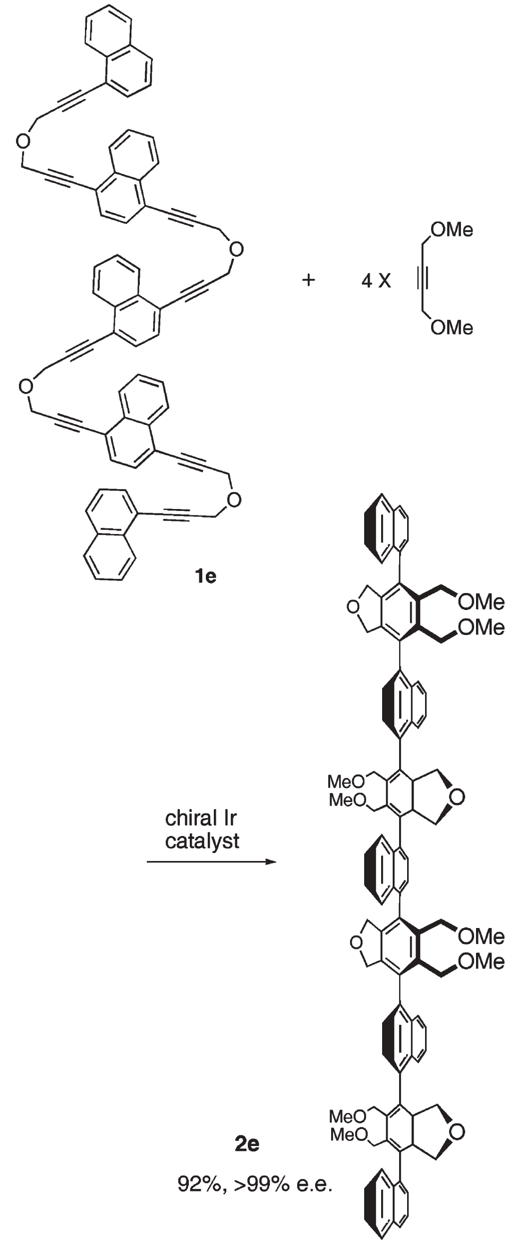


1a-d

Z= O, NTs, *cis*-CH=CH

2a-d

Next, we further examined octayne **1e**, which possesses four reaction sites as a diyne moiety; the asymmetric cycloaddition also proceeded with almost perfect enantioselectivity, and chiral noviaryl **2e**, which has nine consecutive aryl groups, was obtained in high yield (eqn. (2)).[11,12] This result means that eight consecutive axial chiralities were perfectly controlled. When we used (*R*,*R*)-MeDUPHOS, the opposite enantiomer of the chiral ligand, noviaryl **2e** with helically inverse winding, was obtained. When we use a further elongated poly-yne, helically-chiral polyaryl compounds derived from an axially-chiral sequence would be obtained.



1e

2e

92%, >99% e.e.

(2)

These results demonstrate the superiority of enantioselective cycloaddition using a chiral transition metal catalyst as a synthetic approach in asymmetric synthesis; a sequence of eight axial chiralities were generated in a single pot using a transition metal-catalyzed reaction with almost perfect enantio- and diastereoselectivities. Moreover, helical structures have been found in functionalized organic molecules including DNA and RNA, and helical chirality is indispensable for their operation.[13] The present helically-chiral polyaryl compounds may be useful for creating a new library of helically-chiral molecules.

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Notes and references

‡ Typical experimental procedure (Table 1, entry 1): (*S*,*S*)-MeDUPHOS (6.1 mg, 0.02 mmol) and $[IrCl(cod)]_2$ (6.7 mg, 0.01 mmol) were stirred in degassed xylene (1.0 mL) at room temperature to give a reddish-yellow solution. After the addition of a xylene solution (1.5 mL) of 1,4-dimethoxybut-2-yne (34.2 mg, 0.30 mmol) and a xylene solution (1.5 mL) of diyne **1a** (28.2 mg, 0.05 mmol), the resulting mixture was further stirred at 100 °C for 10 min. The solvent was removed under reduced pressure, and purification of the crude products by thin layer chromatography (hexane/AcOEt = 2 : 1) gave pure **2a** (35.4 mg, 89% yield). The ee was determined by HPLC analysis using a chiral column.

§ Crystal data for **4d**·CH_2Cl_2: $C_{55}H_{38}Br_4Cl_2$, M = 1089.43, monoclinic, space group $P2_1$ (no. 4), a = 8.028(3), b = 22.64(1), c = 13.025(8) Å, β = 100.99(2)°, V = 2323(1) Å^3, T = 123 K, Z = 2, μ(Mo-Kα) = 36.26 cm^{-1}; number of reflections measured: total 20814 and unique 9793 (R_{int} = 0.056), $R1$ = 0.064, $wR2$ = 0.161, Flack parameter (Friedel pairs = 4391) 0.03(2). CCDC 284721. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b513124c.

1 (*a*) *Comprehensive Asymmetric Catalysis I–III*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer-Verlag, Berlin, 1999; (*b*) *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Wiley-VCH, New York, 2nd edn, 2000; (*c*) *Comprehensive Asymmetric Catalysis: Supplement 1*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer-Verlag, Berlin, 2003; (*d*) *Methodologies in Asymmetric Catalysis*, ed. S. V. Malhotra, American Chemical Society, Washington, DC, 2004.

2 (*a*) *Lewis Acid Reagents: A Practical Approach*, ed. H. Yamamoto, Oxford University Press, New York., 1999; (*b*) *Lewis Acids in Organic Synthesis*, ed. H. Yamamoto, Wiley-VCH, Weinheim, 2000.

3 (*a*) *Transition Metals Catalyzed Reactions*, ed. S.-I. Murahashi and S. G. Davies, Blackwell Science, Oxford, 1999; (*b*) Tien-Yau Luh, Lectures presented at the 11th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-11), Taipei, Taiwan, 22–26 July 2001, *Pure Appl. Chem.*, 2002, **74**, 1, 1–186; (*c*) *Transition Metals for Organic Synthesis*, ed. M. Beller and C. Bolm, Wiley-VCH, Weinheim, 2004.

4 (*a*) B. M. Trost, *Science*, 1991, **254**, 1471; (*b*) B. M. Trost and M. J. Krische, *Synlett*, 1998, 1; (*c*) B. M. Trost, *Acc. Chem. Res.*, 2002, **35**, 695.

5 T. Shibata, T. Fujimoto, K. Yokota and K. Takagi, *J. Am. Chem. Soc.*, 2004, **126**, 8382.

6 (*a*) N. E. Schore, in *Comprehensive Organometallic Chemistry II*, ed. L. S. Hegedus, Pergamon Press, Oxford, 1999, vol. 12, pp. 703–739; (*b*) M. Lautens, W. Klute and W. Tam, *Chem. Rev.*, 1996, **96**, 49; (*c*) S. Saito and Y. Yamamoto, *Chem. Rev.*, 2000, **100**, 2901.

7 (*a*) T. Hayashi, K. Hayashizaki, T. Kiyoi and Y. Ito, *J. Am. Chem. Soc.*, 1988, **110**, 8153; (*b*) T. Hayashi, S. Niizuma, T. Kamikawa, N. Suzuki and Y. Uozumi, *J. Am. Chem. Soc.*, 1995, **117**, 9101; (*c*) M. Nakajima, K. Kanayama, I. Miyoshi and S.-I. Hashimoto, *Tetrahedron Lett.*, 1995, **36**, 9519; (*d*) S. Saito, T. Kano, H. Muto, M. Nakadai and H. Yamamoto, *J. Am. Chem. Soc.*, 1999, **121**, 8943; (*e*) J. Yin and S. L. Buchwald, *J. Am. Chem. Soc.*, 2000, **122**, 12051; (*f*) A. N. Cammidge and K. V. L. Crépy, *Chem. Commun.*, 2000, 1723; (*g*) C.-Y. Chu, D.-R. Hwang, S.-K. Wang and B.-J. Uang, *Chem. Commun.*, 2001, 980; (*h*) X. Li, J. B. Hewgley, C. A. Mulrooney, J. Yang and M. C. Kozlowski, *J. Org. Chem.*, 2003, **68**, 5500.

8 A recent review of the synthesis of atropoisomeric biaryl skeletons with axial chirality: G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner and M. Breuning, *Angew. Chem., Int. Ed.*, 2005, **44**, 5384.

9 The pioneering work on the enantioselective [2 + 2 + 2] cycloaddition of triynes for the synthesis of helicene derivatives: I. G. Stará, I. Stary, A. Kollárovic, F. Teply, S. Vyskocil and D. Saman, *Tetrahedron Lett.*, 1999, **40**, 1993.

10 Other than us, two groups independently reported cobalt and rhodium complex-catalyzed [2 + 2 + 2] cycloadditions for the synthesis of an atropoisomeric biaryl with an axial chirality. They used diynes with no substituent on one of two alkyne termini: (*a*) A. Gutnov, B. Heller, C. Fischer, H.-J. Drexler, A. Spannenberg, B. Sundermann and C. Sundermann, *Angew. Chem., Int. Ed.*, 2004, **43**, 3795; (*b*) K. Tanaka, G. Nishida, A. Wada and K. Noguchi, *Angew. Chem., Int. Ed.*, 2004, **43**, 6510.

11 Ee was determined by high-performance liquid chromatography (HPLC) using a chiral stationary phase column (see supporting information†). A >99% ee means that the minor enantiomer could not be detected.

12 In each reaction, diastereomers could not be detected during the purification of the products using thin layer chromatography on silica gel or by NMR measurement of cycloadducts **2**.

13 Teraryl compounds were used as a synthetic scaffold that mimics an α-helix, the key element of a protein surface in biochemical research: H. Yin, G. Lee, K. A. Sedey, O. Kutzki, H. S. Park, B. P. Orner, J. T. Ernst, H.-G. Wang, S. M. Sebti and A. D. Hamilton, *J. Am. Chem. Soc.*, 2005, **127**, 10191.