

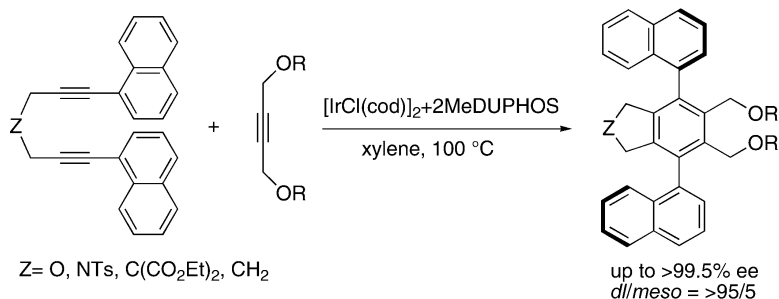
Communication

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Iridium Complex-Catalyzed Highly Enantio- and Diastereoselective [2+2+2] Cycloaddition for the Synthesis of Axially Chiral Teraryl Compounds

Takanori Shibata,^{*,†} Takayoshi Fujimoto,[‡] Kazuhisa Yokota,[‡] and Kentaro Takagi[‡]

Department of Chemistry, School of Science and Engineering, Waseda University, Shinjuku, Tokyo 169-8555, Japan, and Department of Chemistry, Faculty of Science, Okayama University, Tsushima, Okayama, 700-8530, Japan

Received April 1, 2004; E-mail: tshibata@waseda.jp

An axially chiral biaryl is an important structure among chiral ligands, and many catalytic and highly enantioselective reactions have been achieved by using axially chiral biaryl compounds possessing C_2 symmetry, as represented by BINOL and BINAP.¹ While various methods have been reported for the synthesis of axially chiral biaryl components, including optical resolution of racemic compounds and diastereoselective reactions using a stoichiometric amount of chiral auxiliaries, practical examples of the catalytic synthesis of axially chiral biaryls are limited. Hayashi and Ito reported a pioneering work on asymmetric Kumada coupling using a chiral nickel catalyst for the synthesis of 1,1'-binaphthyl compounds.² Hayashi further reported an enantioselective cross-coupling using a chiral palladium catalyst³ and an asymmetric Kumada coupling of dinaphthothiophene based on the concept of dynamic kinetic resolution.⁴ Asymmetric Suzuki coupling using a chiral palladium catalyst is another approach for the catalytic synthesis of axially chiral biaryls.⁵ Oxidative coupling of 2-naphthol derivatives has also been reported for the synthesis of BINOL derivatives using chiral copper⁶ or oxovanadium complexes.^{7,8} However, all of these procedures involve the asymmetric coupling of aryl compounds.⁹

We report here an asymmetric [2+2+2] cycloaddition of an α,ω -diyne and monoalkynes as a new approach for obtaining axially chiral compounds possessing C_2 symmetry.^{10,11} [2+2+2] Cycloaddition is a common protocol for the synthesis of substituted aromatic compounds, and various transition metal complexes, including those of cobalt, rhodium, and palladium, have been reported to be efficient catalysts.¹² We considered that the cycloaddition of an α,ω -diyne, possessing ortho-substituted aryls on its terminus, and a disubstituted alkyne would give an axially chiral teraryl compound due to steric hindrance between R^1 and R^2 (Scheme 1).¹³

We have previously reported an iridium complex-catalyzed [2+2+1] cycloaddition of an α,ω -diyne and carbon monoxide. As a minor product of this reaction, we obtained a polysubstituted benzene, which resulted from the [2+2+2] cycloaddition of the α,ω -diyne itself.^{14a} We anticipated that iridium complexes would show high catalytic activity in [2+2+2] cycloaddition for the synthesis of a congested polyaryl compound, and examined the cross-coupling of propargyl ether possessing naphthyl groups **1a** and methyl-protected 2-butyne-1,4-diol **2a** using an Ir-dppp complex.^{14,15} As a result, teraryl **3aa** was obtained as a mixture of *dl* and *meso* isomers, and the *dl* isomer was resolved by HPLC using a chiral column.

Next, we investigated the reaction conditions for asymmetric coupling (Table 1): while BINAP was the first choice as a chiral ligand, both the yield and the enantioselectivity of **3aa** were low

Scheme 1. Synthesis of Axially Chiral Teraryl Compound by [2+2+2] Cycloaddition

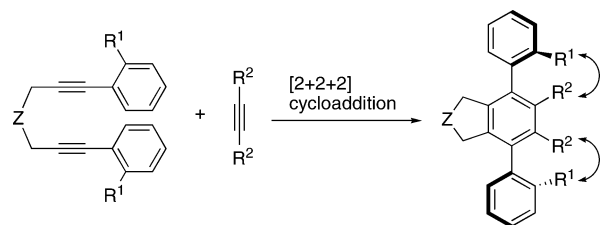
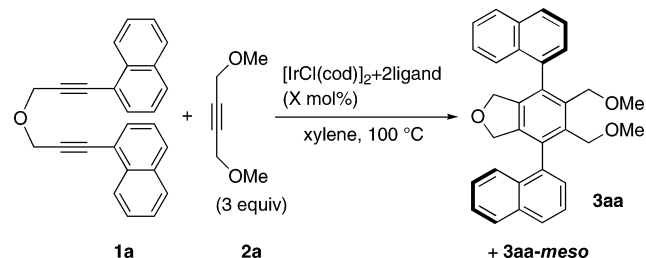


Table 1. Asymmetric [2+2+2] Cycloaddition Using Chiral Iridium Complexes



entry	ligand	X/mol%	time/h	yield/%	<i>dl</i> / <i>meso</i>	ee/%
1	(<i>S,S</i>)-BINAP	10	4	31	60/40	6
2	(<i>S,S</i>)-BDPP	10	6	39	45/55	51
3	(<i>S,S</i>)-MeDUPHOS	10	1	83	>95/5	99.6
4	(<i>S,S</i>)-EtDUPHOS	10	1	75	>95/5	99.8
5	(<i>R,R</i>)-MeDUPHOS	10	1	88	>95/5	99.6 ^a
6	(<i>S,S</i>)-MeDUPHOS	5	1	83	>95/5	99.6
7	(<i>S,S</i>)-MeDUPHOS	2	1	89	>95/5	99.3
8	(<i>S,S</i>)-MeDUPHOS	0.5	3	84	98/2	99.1

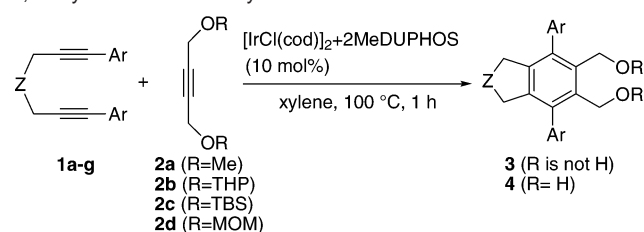
^a An opposite enantiomer to the above structure of **3aa** was obtained.

(entry 1). BDPP gave moderate enantioselectivity, but the diastereoselectivity was low (entry 2). We found that MeDUPHOS (1,2-bis-(2,5-dimethylphospholano)benzene) gave the best results: the *meso* isomer could not be detected in the NMR spectrum, and the enantioselectivity exceeded 99% (entry 3). EtDUPHOS gave almost the same results (entry 4), and (*R,R*)-MeDUPHOS provided the opposite enantiomer (entry 5).¹⁶ No decrease in selectivity was observed upon lowering the amount of catalyst to 2 mol %, and a high ee of 99.1% was achieved, even with 0.5 mol % catalyst (entries 6–8).

The asymmetric [2+2+2] cycloaddition of various α,ω -dienes and protected 2-butyne-1,4-diols (3 equiv) was examined using the Ir-MeDUPHOS catalyst, and extremely high enantio- and diastereoselectivities were achieved in each reaction (Table 2). THP- and TBS-protected diols **2b,c** were also good coupling partners, and the ee was extremely high after deprotection to diol **4a**

[†] Waseda University.

[‡] Okayama University.

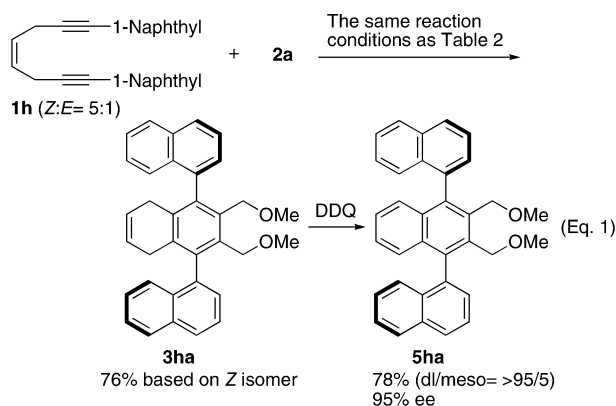
Table 2. Asymmetric [2+2+2] Cycloaddition of Various α,ω -Diynes and Monoalkynes

entry	Ar	Z	diyne	R	yield/% ^a	ee/%
1	1-naphthyl	O	1a	THP	76 (4a) ^b	99.5 ^b
2	1-naphthyl	O	1a	TBS	74 (3ac)	99.5 ^c
3	1-naphthyl	O	1a	MOM	76 (3ad) ^d	98.5
4	2-MeC ₆ H ₄	O	1b	Me	85 (3ba)	99.6
5	2-Cl C ₆ H ₄	O	1c	Me	85 (3ca)	97.7
6	4-MeO-1-naphthyl	O	1d	Me	72 (3da)	99.4
7	1-naphthyl	NTs	1e	Me	92 (3ea)	99.4
8	1-naphthyl	NTs	1e	THP	97 (4e) ^b	99.1 ^b
9	1-naphthyl	C(CO ₂ Et) ₂	1f	Me	77 (3fa)	>99.8
10	1-naphthyl	CH ₂	1g	Me	96 (3ga)	>99.8
11	1-naphthyl	CH ₂	1g	TBS	77 (3gc) ^e	98.6 ^c

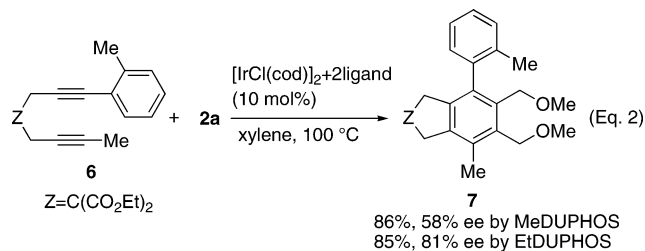
^a Only *dl* isomer was detected by NMR spectrum, except entries 3 and 11. ^b Yield and ee were determined as diol **4a** or **4e** after deprotection using PPTS in EtOH. ^c Ee was determined as diol **4a** or **4g** after deprotection using TBAF in THF. ^d *dl/meso* = 93/7. ^e *dl/meso* = 91/9.

(entries 1 and 2). 2-Methyl-, 2-chlorophenyl, and 4-methoxy-1-naphthyl were acceptable as substituents on the terminus of α,ω -diynes (entries 4–6). Nitrogen-bridged diynes also reacted with alkynes **2a,b** in high ee and de (entries 7 and 8). In the reaction of carbon-bridged diynes **1f,g** and methyl ether **2a**, almost perfect enantioselectivity was achieved, and the peak of the minor enantiomer was below the level of detection by HPLC analyses (entries 9 and 10).

With a *cis*-olefinic tether, octa-1,7-diyne **1h** also reacted with alkyne **2a** under the same reaction conditions, and the subsequent aromatization by DDQ oxidation gave chiral ternaphthyl **5ha** in high ee and de (eq 1).¹⁶



The present asymmetric [2+2+2] cycloaddition was applied to the unsymmetrical diyne **6**, and the chiral biaryl compound **7** was obtained (eq 2). In this reaction, EtDUPHOS gave a significantly better enantioselectivity than MeDUPHOS.



In conclusion, we have reported an asymmetric [2+2+2] cycloaddition of diynes and alkynes with oxygen functionalities. This reaction proceeds with extremely high enantio- and diastereoselectivity to give various axially chiral compounds. The present procedure provides access to a new chiral pool of diol compounds possessing C_2 symmetry.

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Supporting Information Available: Experimental details and spectral data for α,ω -diynes and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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