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COMMUNICATIONS

Published on Web 06/17/2004

# 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 enantioposition-selective cross-coupling using a chiral palladium catalyst[3] 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 copper[6] 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

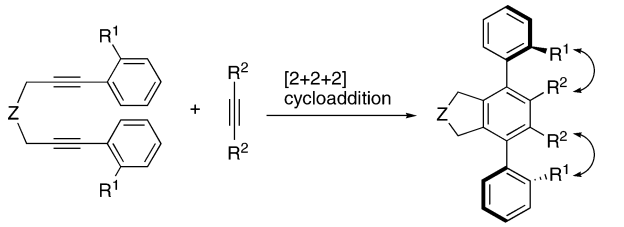
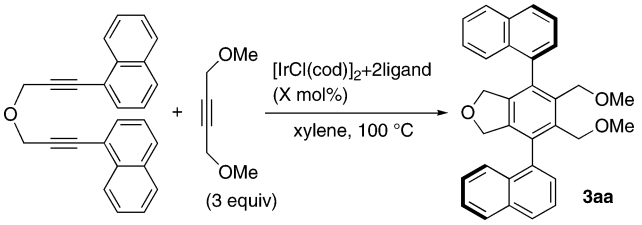



***Table 1.*** Asymmetric [2+2+2] Cycloaddition Using Chiral Iridium Complexes




**1a** **2a** **+ 3aa-*meso***

| entry | ligand | X/mol% | time/h | yield/% | *dl*/*meso* | ee/% |
|---|---|---|---|---|---|---|
| 1 | (*S*)-BINAP | 10 | 4 | 31 | 60/40 | 6 |
| 2 | (*S*,*S*)-BDPP | 10 | 6 | 39 | 45/55 | 51 |
| 3 | (*S*,*S*)-MeDUPHOS | 10 | 1 | 83 | >95/5 | 99.6 |
| 4 | (*S*,*S*)-EtDUPHOS | 10 | 1 | 75 | >95/5 | 99.8 |
| 5 | (*R*,*R*)-MeDUPHOS | 10 | 1 | 88 | >95/5 | 99.6[a] |
| 6 | (*S*,*S*)-MeDUPHOS | 5 | 1 | 83 | >95/5 | 99.0 |
| 7 | (*S*,*S*)-MeDUPHOS | 2 | 1 | 89 | >95/5 | 99.3 |
| 8 | (*S*,*S*)-MeDUPHOS | 0.5 | 3 | 84 | 98/2 | 99.1 |

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

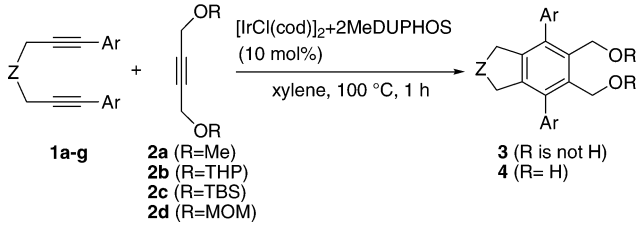
(entry 1). BDPP gave moderate enantioselectivity, but the diastereoselectivity was low (entry 2). We found that MeDUPHOS (1,2-bis-(2,5-dimethylphospholano)benzene) gave the best results: the *meso* isomer could not be detected in the NMR spectrum, and the enantioselectivity exceeded 99% (entry 3). EtDUPHOS 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-diynes 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.


10.1021/ja048131d CCC: $27.50 

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



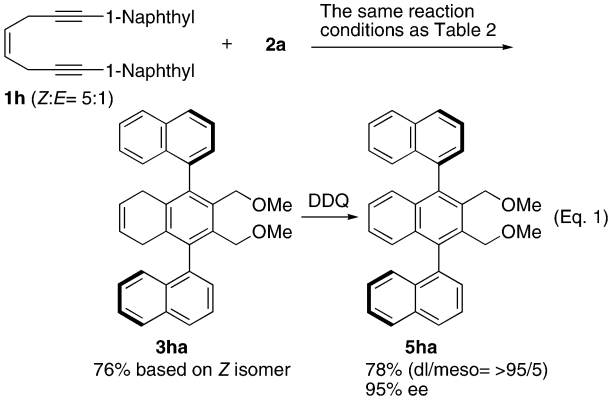

**1a-g** **2a** (R=Me) **2b** (R=THP) **2c** (R=TBS) **2d** (R=MOM) **3** (R is not H) **4** (R= H)

| 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-Me$C_6H_4$ | O | **1b** | Me | 85 (**3ba**) | 99.6 |
| 5 | 2-Cl $C_6H_4$ | 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 | $C(CO_2Et)_2$ | **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] |

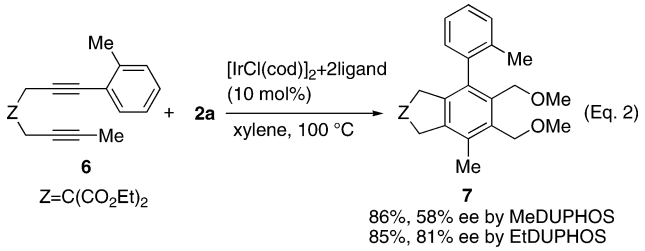
[a] Only *dl* isomer was detected by NMR spectrum, except entries 3 and 11. [b] Yield and ee were determined as diol **4a** or **4e** after deprotection using PPTS in EtOH. [c] Ee was determined as diol **4a** or **4g** after deprotection using TBAF in THF. [d] *dl*/*meso*= 93/7. [e] *dl*/*meso* = 91/9.

(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.

**Acknowledgment.** The authors thank Masaya Hirase for his experimental assistance. This research was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

**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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JA048131D