Organic LETTERS

Letter

pubs.acs.org/OrgLett

Rhodium-Catalyzed Asymmetric [2 + 2 + 2] Cycloaddition of α,ω-Diynes with Unsymmetrical 1,2-Disubstituted Alkenes

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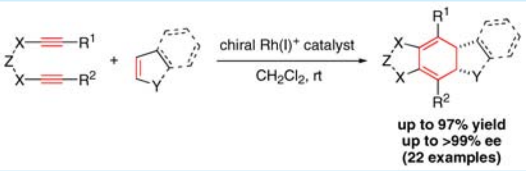
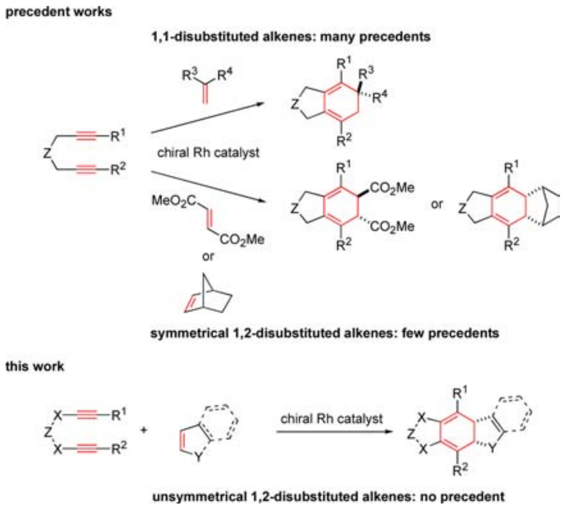
Supporting Information

ABSTRACT: It has been established that a cationic rhodium(I)/axially chiral biaryl bisphosphine complex catalyzes the asymmetric [2 + 2 + 2] cycloaddition of α,ω-diynes with electron-rich and unstrained unsymmetrical 1,2-disubstituted alkenes to give chiral multicyclic compounds with good yields and ee values. Interestingly, enantioselectivity highly depends on the structures of α,ω-diynes used presumably due to the presence of two distinct reaction pathways.

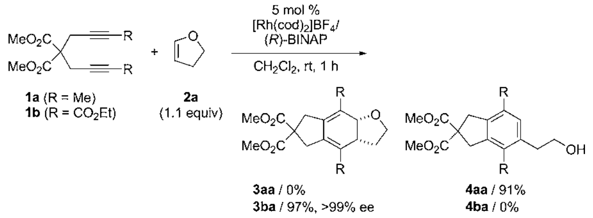


The transition-metal-catalyzed asymmetric [2 + 2 + 2] cycloaddition of α,ω-diynes with alkenes is one of the most convenient methods for the synthesis of chiral bicyclic 1,3-cyclohexadienes.[1−8] In 2006, Shibata reported the first example of this transformation in which a cationic rhodium(I)/axially chiral biaryl bisphosphine complex[9] catalyzes the asymmetric [2 + 2 + 2] cycloaddition of 1,6-diynes with electron-deficient mono- and 1,1-disubstituted alkenes (acrylate and methacrylate derivatives, respectively: Scheme 1, top).[2] After this report, our research group also reported similar transformations using functionalized 1,1-disubstituted alkenes possessing amide moieties (methacrylamide,[3,4] enamide,[3,4] and protected dehydroamino acid derivatives:[3] Scheme 1, top). Shibata reported that not only functionalized 1,1-disubstituted alkenes but also unfunctionalized ones could be employed in this transformation (Scheme 1, top).[5] On the other hand, the successful use of 1,2-disubstituted alkenes in the transition-metal-catalyzed asymmetric [2 + 2 + 2] cycloaddition with α,ω-diynes has been limited to the electron-deficient or strained symmetrical one (dimethyl fumarate[6] or norbornene,[5] respectively: Scheme 1, middle),[7] though our research group recently reported the rhodium(I)/(*R*)-BINAP complex-catalyzed [2 + 2 + 2] cycloaddition−aromatization of 1,6-diyne **1a** with an electron-rich and unstrained unsymmetrical 1,2-disubstituted alkene, 2,3-dihydrofuran (**2a**), to produce aryl alkanol **4aa** (Scheme 2).[10,11] In this paper, we have established that the cationic rhodium(I)/axially chiral biaryl bisphosphine complex is capable of catalyzing the asymmetric [2 + 2 + 2] cycloaddition of α,ω-diynes with electron-rich and unstrained unsymmetrical 1,2-disubstituted alkenes [2,3-dihydrofuran, indene, and (*Z*)-phenylpropene] with good yields and ee values (Scheme 1, bottom).

Scheme 1



Scheme 2



In sharp contrast to the above-mentioned reaction of electron-rich 1,6-diyne **1a** with **2a**, when using electron-deficient 1,6-diyne **1b**, possessing two ethoxycarbonyl groups at the alkyne termini, not the corresponding aromatized product **4ba** but the corresponding cyclohexadiene **3ba** was obtained in high yield with excellent ee value (Scheme 2).

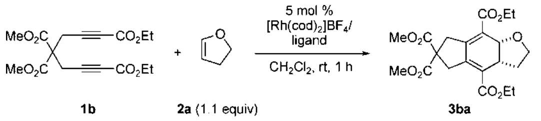
For the synthesis of **3ba**, (*R*)-BINAP was found to be the best ligand (Table 1, entry 1). The use of H_8−BINAP and Segphos

Received: April 18, 2016
Published: May 23, 2016

DOI: 10.1021/acs.orglett.6b01116
Org. Lett. 2016, 18, 2672−2675

(Figure 1) significantly lowered the product yields (entries 2 and 3).

Table 1. Screening of Ligands for Rh-Catalyzed Asymmetric [2 + 2 + 2] Cycloaddition of 1,6-Diyne 1b with 2,3-Dihydrofuran (2a)[a]



entry	ligand	yield[b] (%)	ee (%)
1	(*R*)-BINAP	97	>99 (+)
2	(*R*)-H$_8$–BINAP	76	98 (+)
3	(*R*)-Segphos	ca. 30[c]	ca. 98 (+)[c]

[a] [Rh(cod)$_2$]BF$_4$ (0.010 mmol), ligand (0.010 mmol), **1b** (0.20 mmol), **2a** (0.22 mmol), and CH$_2$Cl$_2$ (2.0 mL) were used. [b] Isolated yield. [c] The product could not be isolated in a pure form.

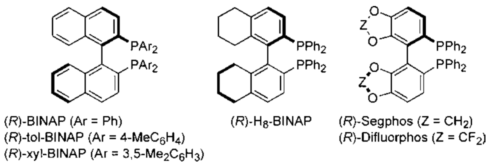
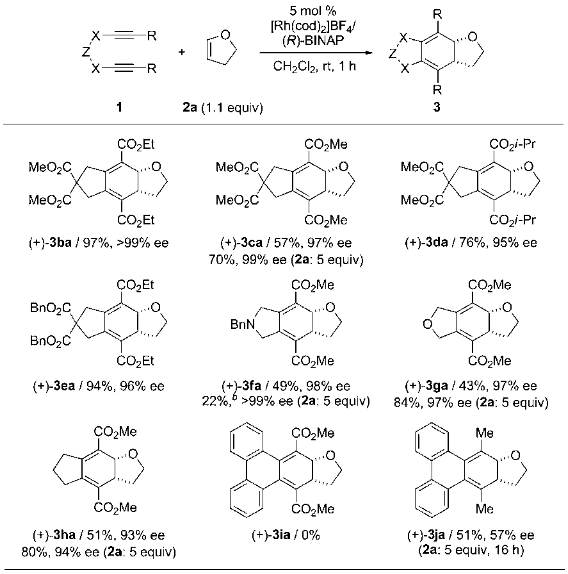


Figure 1. Structures of axially chiral biaryl bisphosphine ligands.

The scope of α,ω-diynes **1** was then examined by using the cationic rhodium(I)/(*R*)-BINAP catalyst (5 mol %) and **2a** (1.1 equiv) at room temperature (Scheme 3).[12] With respect to the alkoxycarbonyl groups at the alkyne termini, the reaction of sterically less demanding methoxycarbonyl-substituted 1,6-diyne **1c** afforded the corresponding tricyclic cyclohexadiene **3ca** in lower yield than **3ba** and **3da** obtained from ethoxycarbonyl- and isopropoxycarbonyl-substituted 1,6-diynes **1b** and **1d**, respectively, due to the rapid homo-[2 + 2 + 2] cycloaddition of **1c**. With respect to tethers of diynes, not only malonates **1b–e** but also nitrogen-, oxygen-, and methylene-linked 1,6-diynes **1f–h** were capable of participating in this transformation, while the yields of the products **3fa–ha** were moderate. Importantly, all these reactions were highly enantioselective and the products were obtained with excellent ee values (93→99% ees). In the cases of the low-yielding reactions (**3ca**, **3fa**, **3ga**, and **3ha**), increasing the amount of **2a** to 5 equiv significantly increased the product yields, though the undesired Diels–Alder adduct was generated from **3fa**. Various 1,7-diynes were also tested, which revealed that although electron-deficient biphenyl-linked diyne **1i** fails to react with **2a**, electron-rich diyne **1j** reacts with **2a** to give the corresponding pentacyclic compound **3ja** with moderate yield and ee value. In this reaction, cyclohexadiene product **3ja** could be isolated presumably due to stabilization of the diene moiety through conjugation with two phenyl groups.[13]

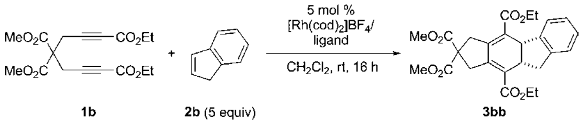
Scheme 3[a]



[a] [Rh(cod)$_2$]BF$_4$ (0.010 mmol), ligand (0.010 mmol), **1** (0.20 mmol), **2a** (0.22 mmol), and CH$_2$Cl$_2$ (2.0 mL) were used. The cited yields are of the isolated products. [b] The undesired Diels–Alder adduct between **3fa** and **2a** was generated in 49% yield.

Next, we attempted to use indene (**2b**) as an electron-rich and unstrained unsymmetrical 1,2-disubstituted alkene.[14] Pleasingly, 1,6-diyne **1b** reacted with **2b** (5 equiv) at room temperature in the presence of the cationic rhodium(I)/(*R*)-BINAP catalyst to give the corresponding tetracyclic cyclohexadiene **3bb** with moderate yield and ee value (Table 2, entry 1). Increasing the steric bulk of the aryl groups on the phosphorus atom (Figure 1) significantly decreased the yields of **3bb** (entries 2 and 3). Screening of axially chiral biaryl bisphosphine ligands (Figure 1) revealed that the use of (*R*)-Difluorphos affords **3bb** with the highest yield and ee value (entry 6).

Table 2. Screening of Ligands for Rh-Catalyzed Asymmetric [2 + 2 + 2] Cycloaddition of 1,6-Diyne 1b with Indene (2b)[a]



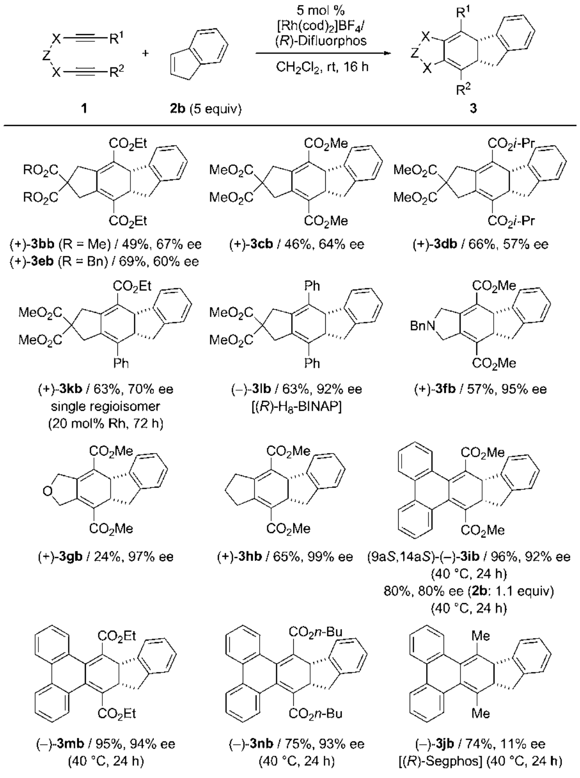
entry	ligand	yield[b] (%)	ee (%)
1	(*R*)-BINAP	38	56 (+)
2	(*R*)-tol-BINAP	22	36 (+)
3	(*R*)-xyl-BINAP	11	59 (+)
4	(*R*)-H$_8$–BINAP	40	65 (+)
5	(*R*)-Segphos	34	67 (+)
6	(*R*)-Difluorphos	49	67 (+)

[a] [Rh(cod)$_2$]BF$_4$ (0.010 mmol), ligand (0.010 mmol), **1b** (0.20 mmol), **2b** (0.22 mmol), and CH$_2$Cl$_2$ (2.0 mL) were used. [b] Isolated yield.

With the optimized conditions in hand, the scope of α,ω-diynes was examined (Scheme 4). With respect to the diyne termini, malonate-linked 1,6-diynes **1b–e**, possessing two alkoxycarbonyl groups, reacted with **2b** to give the corresponding cyclohexadienes **3bb–eb** with moderate yields and ee values. This cycloaddition is highly regioselective, and the reaction of unsymmetrical diyne **1k**,[15] possessing the ethoxycarbonyl and phenyl groups, with **2b** afforded the corresponding cyclohexadiene **3kb** as a single regioisomer. Not only diyne esters but also diphenyl-substituted 1,6-diyne **1l** were capable of reacting with **2b** to give the corresponding cyclohexadiene **3lb** in moderate yield.[16] Importantly, the ee value of **3lb** was significantly higher than those of **3bb–eb**. With respect to tethers of diynes, not only malonates but also nitrogen-, oxygen-, methylene-, and biphenyl-linked 1,6-diynes **1f–j** and **1m,n** were capable of participating in this transformation. The ee values of

DOI: 10.1021/acs.orglett.6b01116
Org. Lett. 2016, 18, 2672–2675

Scheme 4[a]

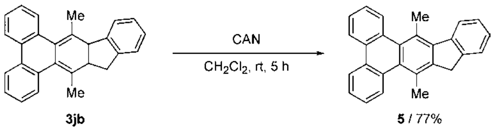


[a] $[Rh(cod)_2]BF_4$ (0.010 mmol), ligand (0.010 mmol), **1** (0.20 mmol), **2b** (1.00 mmol), and CH_2Cl_2 (2.0 mL) were used. The cited yields are of the isolated products.

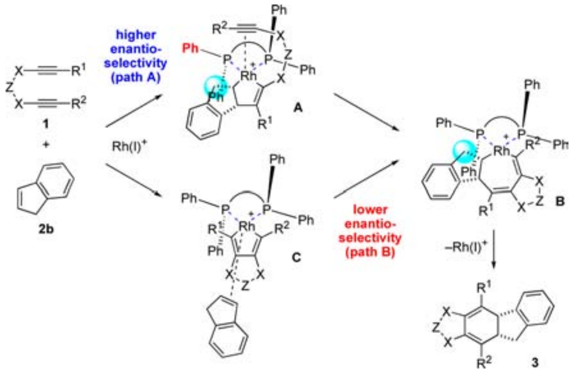
cyclohexadienes **3fb–ib** and **3mb,nb** were very high (92–99% ees); on the contrary, the ee value of cyclohexadiene **3jb** was very low (11% ee). Importantly, decreasing the amount of **2b** to 1.1 equiv decreased not only the yield but also the ee value of **3ib** (5 equiv: 92% ee, 1.1 equiv: 80% ee). The relative and absolute configurations of (−)-**3ib** were determined by X-ray crystallographic analysis.

Although **3jb** was obtained with low ee value, dehydrogenation of **3jb** by treatment with cerium(IV) ammonium nitrate (CAN)[5] afforded hexacyclic planar conjugated aromatic **5**, possessing photophysically important triphenylene and fluorene cores, in good yield (Scheme 5).

Scheme 5



Scheme 6



Scheme 6 depicts a possible explanation of the effect of the diyne substituents on enantioselectivity in the reactions with indene (**2b**).[17] When using diynes **1** in the absence of the Thorpe–Ingold effect (**1f–h** and **1i,m,n**), the reaction of **1** and **2b** with rhodium generates rhodacyclopentene intermediate **A** (path A), in which enantioselectivity is determined by avoidance of steric repulsion between the methylene group (blue) derived from **2b** and the equatorial phenyl group (red) of the bisphosphine ligand. Electron-deficient nature of **1** may also facilitate the reaction with electron-rich alkene **2b**. Subsequent insertion of the pendant alkyne affords rhodacycle **B**. Reductive elimination furnishes cyclohexadiene **3**. On the other hand, when using diynes **1** in the presence of the Thorpe–Ingold effect (**1b–e** and **1k**), the reaction of **1** and **2b** with rhodium generates not only rhodacyclopentene intermediate **A** but also rhodacyclopentadiene intermediate **C** (path B). Subsequent insertion of **2b** into intermediate **C** affords the rhodacycle **B**. The regioselective synthesis of cyclohexadiene **3kb** from diyne **1k** and **2b** can be rationalized by the regioselective formation of rhodacyclopentene **A** through oxidative coupling between the electron-deficient alkyne moiety (R^1 = CO_2Et) of **1k** and **2b**. In path A, the formation of intermediate **A** is the enantiodetermining step. In path B, the formation of intermediate **B** is the enantiodetermining step. Lower enantioselectivity of the latter (path B) than the former (path A) may explain the observed lower ee values of the products from diynes **1b–e** and **1k**. The observed high ee value for **3 lb** and low ee value for **3jb** may be explained by difficulty of forming rhodacyclopentadiene **C** due to steric hindrance of **1l** and rhodacyclopentene **A** due to electron-rich nature of **1j**, respectively. Based on the mechanism shown in Scheme 6, decreasing the amount of **2b** would lower the enantioselectivity as a result of increasing contribution of the less enantioselective path B. Indeed, the ee value of **3ib** using 1.1 equiv of **2b** was lower than that using 5 equiv of **2b** (Scheme 4).

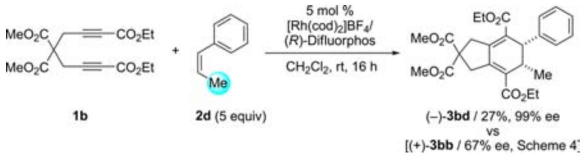
According to the mechanism shown in Scheme 6, no interaction can be seen between the phenyl moiety of indene (**2b**) and the equatorial phenyl group of the bisphosphine ligand (red). Therefore, the reaction of unsymmetrical diyne **1k** with cyclopentene (**2c**),[18] possessing the methylene group (blue) and no phenyl moiety, would afford the product with the same level of enantioselectivity as **3kb** derived from **1k** and **2b**. Indeed, the corresponding product **3kc** was obtained with 67% ee, which is close to that (70% ee) of **3kb** (Scheme 7).

In addition, the use of (Z)-1-phenylpropene (**2d**), which has not been employed for the transition-metal-mediated [2 + 2 + 2] cycloaddition, would improve the enantioselectivity due to the larger angle between the C═C bond and the methyl group (blue) in **2d** than that and the methylene group in **2b**, which results in larger steric hindrance toward the bisphosphine ligand.

Scheme 7

Indeed, the corresponding product **3bd** was obtained with 99% ee, although the product yield was low (Scheme 8).[19] This ee value is significantly higher than that (67% ee) of **3bb** obtained from **1b** and **2b**.

Scheme 8



In conclusion, we have established that a cationic rhodium(I)/axially chiral biaryl bisphosphine complex catalyzes the asymmetric [2 + 2 + 2] cycloaddition of α,ω-diynes with electron-rich and unstrained unsymmetrical 1,2-disubstituted alkenes [2,3-dihydrofuran, indene, and (*Z*)-1-phenylpropene] to give chiral multicyclic compounds with good yields and ee values. Interestingly, the enantioselectivity highly depends on the structures of α,ω-diynes used presumably due to the presence of two distinct reaction pathways. Further exploration and application of the rhodium-catalyzed asymmetric [2 + 2 + 2] cycloaddition reactions involving alkene units are underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01116.

Experimental procedures and characterization data (PDF)
X-ray crystallographic data for (−)-**3ib** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported in part by the ACT-C from JST (Japan) and Grants-in-Aids for Scientific Research (Nos. 15H03775 and 26102004) from MEXT (Japan). We thank Takasago International Corp. for the gift of Segphos and H_8–BINAP and Umicore for generous support in supplying the rhodium complex.

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(12) Unfortunately, 3,4-dihydro-2*H*-pyran failed to react with **1b**.

(13) The corresponding THF-protected aromatized arylalkanol was also generated in 28% yield.

(14) Although a catalytic nonasymmetric [2 + 2 + 2] cycloaddition involving indene (**2b**) has not been reported, the cobalt(I)-mediated reaction was reported. See: Geny, A.; Leboeuf, D.; Rouquié, G.; Vollhardt, K. P. C.; Malacria, M.; Gandon, V.; Aubert, C. *Chem. - Eur. J.* **2007**, *13*, 5408. See also ref 11b.

(15) The reaction of **1k** with **2a** afforded a complex mixture involving the corresponding aromatized and nonaromatized products.

(16) The reaction of **1l** with **2a** afforded a mixture of the corresponding aromatized products. The reaction of **1a** with **2b** was also examined, while the corresponding cyclohexadiene **3ab** was found to be unstable.

(17) As the absolute configuration of the product could not be determined, a mechanism for the reactions of α,ω-diynes **1** with 2,3-dihydrofuran (**2a**) is not clear at the present stage.

(18) For examples of the transition-metal-catalyzed nonasymmetric [2 + 2 + 2] cycloaddition involving cyclopentene (**2c**), see: (a) Varela, J. A.; Rubín, S. G.; González-Rodríguez, C.; Castedo, L.; Saá, C. *J. Am. Chem. Soc.* **2006**, *128*, 9262. (b) Varela, J. A.; Rubín, S. G.; Castedo, L.; Saá, C. *J. Org. Chem.* **2008**, *73*, 1320. (c) Satoh, Y.; Obora, Y. *J. Org. Chem.* **2011**, *76*, 8569. For an example using a stoichiometric amount of a cobalt(I) complex, see: Aubert, C.; Gandon, V.; Han, S.; Johnson, B. M.; Malacria, M.; Schömenauer, S.; Vollhardt, K. P. C.; Whitener, G. D. *Synthesis* **2010**, 2179.

(19) The reaction of (*E*)-1-phenylpropene (**2e**) with **1b** was also attempted. Unfortunately, however, cycloadduct **3be** was obtained in very low yield and could not be isolated in a pure form.