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# Rhodium-Catalyzed Atroposelective [2 + 2 + 2] Cycloaddition of *Ortho*-Substituted Phenyl Diynes with Nitriles: Effect of *Ortho* Substituents on Regio- and Enantioselectivity

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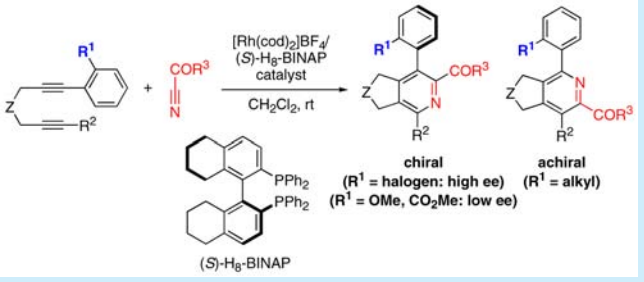
Supporting Information

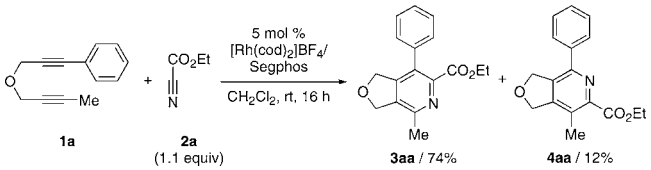
**ABSTRACT:** Axially chiral 3-(2-halophenyl)pyridines were successfully synthesized in high yields with excellent enantioselectivity by the cationic rhodium(I)/(*S*)-$H_8$–BINAP complex-catalyzed atroposelective [2 + 2 + 2] cycloaddition of (*o*-halophenyl)diynes with nitriles. Interestingly, regio- and enantioselectivity highly depend on *ortho* substituents on the phenyl group of diynes. When the *ortho* substituents were methoxy and methoxycarbonyl groups, axially chiral 3-arylpyridines were obtained as a major product, while enantioselectivity was lowered significantly. On the other hand, when the *ortho* substituents were alkyl groups, regioselectivity was switched to give achiral 6-arylpyridines in high yields.



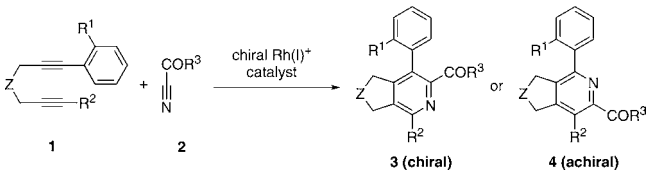

Atroposelective syntheses of axially chiral biaryls have been extensively studied by many research groups because of their high utility.[1] As a conceptually new approach, in 2004, three research groups independently reported the transition-metal-catalyzed atroposelective [2 + 2 + 2] cycloaddition using chiral cobalt(I),[2] iridium(I),[3] and rhodium(I)[4] catalysts.[5] The rhodium(I)- and iridium(I)-catalyzed reactions of aryl and diaryl diynes with monoynes afforded axially chiral biaryls[4] and teraryls,[3] respectively, with high enatioselectivity. On the other hand, the cobalt(I)-catalyzed reactions between aryl diynes with nitriles afforded axially chiral arylpyridines with high enantioselectivity.[2] After the above pioneering works, numbers of successful examples of the transition-metal-catalyzed atroposelective [2 + 2 + 2] cycloaddition reactions of alkynes giving axially chiral biaryls and teraryls have been reported by using cobalt(I),[6] iridium(I),[7] and rhodium(I)[8] catalysts. However, the transition-metal-catalyzed atroposelective [2 + 2 + 2] cycloaddition reactions of alkynes with nitriles[9] giving axially chiral arylpyridine have been largely limited to the cobalt(I) catalysis.[2,10] Although a single report of the rhodium(I) catalysis giving only two specific axially chiral arylpyridines has been reported,[8b] a systematic study of the rhodium(I)-catalyzed atroposelective [2 + 2 + 2] cycloaddition of alkynes with nitriles has not been reported.[11,12]

Previously, we reported that a cationic rhodium(I)/Segphos complex catalyzes the [2 + 2 + 2] cycloaddition of diyne **1a** with ethyl cyanoformate (**2a**) to give 3-arylpyridine **3aa** as a major product and 6-arylpyridine **4aa** as a minor product (Scheme 1).[11k] This result prompted us to investigate the rhodium(I)-catalyzed atroposelective [2 + 2 + 2] cycloaddition of *ortho*-substituted phenyl diyne **1** with nitrile **2**, which would afford axially chiral 3-arylpyridine **3** as a major product and 6-arylpyridine **4** as a minor product (Scheme 2). We report herein the regio- and enantioselective synthesis of axially chiral 3-arylpyridines by the rhodium(I)-catalyzed [2 + 2 + 2] cycloaddition. Interestingly, *ortho* substituents on the phenyl group significantly affected regio- and enantioselectivity.

**Scheme 1**




**Scheme 2**

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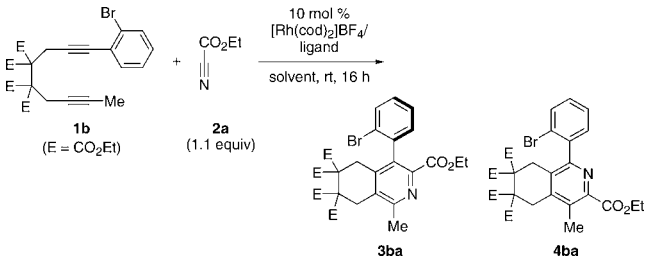
We first examined the reaction of ethane-1,1,2,2-tetracarboxylate-linked and 2-bromophenyl-substituted 1,7-diyne **1b** with ethyl cyanoformate (**2a**, 1.1 equiv) in $(CH_2Cl)_2$ in the presence of the cationic rhodium(I)/(*S*)-Segphos complex (10 mol %). Pleasingly, the reaction proceeded at room temperature to give the desired axially chiral 3-arylpyridine **3ba** as a sole product with moderate yield and enantioselectivity (Table 1, entry 1). The

**Table 1. Optimization of Reaction Conditions for Rh-Catalyzed Atroposelective [2 + 2 + 2] Cycloaddition of Diyne 1b with Nitrile 2a**[a]




| | | | | % yield[b] (% ee) | |
|---|---|---|---|---|---|
| entry | ligand | solvent | conv of **1b** (%) | **3ba** | **4ba** |
| 1 | (*S*)-Segphos | $(CH_2Cl)_2$ | 57 | 43 (66) | 0 |
| 2 | (*S*)-BINAP | $(CH_2Cl)_2$ | 57 | 46 (92) | 0 |
| 3 | (*S*)-$H_8$–BINAP | $(CH_2Cl)_2$ | 74 | 64 (99) | 0 |
| 4[c] | (*S*)-$H_8$–BINAP | $(CH_2Cl)_2$ | 69 | 59 (99) | 0 |
| 5 | (*S*)-$H_8$–BINAP | $CH_2Cl_2$ | 100 | 80 (99) | 0 |

[a]$[Rh(cod)_2]BF_4$ (0.010 mmol), ligand (0.010 mmol), **1b** (0.10 mmol), **2a** (0.11 mmol), and $(CH_2Cl)_2$ (2.0 mL) were used. [b]Isolated yield. [c]**2a** (0.20 mmol) was used.

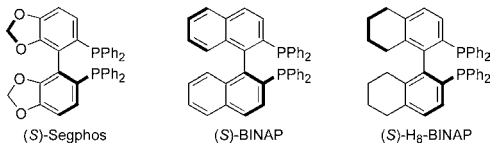



**Figure 1.** Structures of axially chiral biaryl bisphospnine ligands.

effect of axially chiral biaryl bisphosphine ligands (Figure 1) on yield and enantioselectivity was then examined (entries 1–3), which revealed that the use of (*S*)-$H_8$–BINAP furnished **3ba** with the highest yield and enantioselectivity (entry 3). In order to increase the conversion of **1b**, further optimization was conducted. Increasing the amount of **2a** to 2.0 equiv decreased the yield of **3ba** (entry 4). Gratifyingly, full conversion of **1b** was achieved by using $CH_2Cl_2$ in place of $(CH_2Cl)_2$ as a solvent to give **3ba** in high yield with excellent enantioselectivity (entry 5). Importantly, 6-arylpyridine **4ba** was not generated at all in all entries.

Thus, we tested the generality of the reaction with respect to both cycloaddition partners as shown in Table 2. With respect to the *ortho* substituents on the phenyl group, the reactions of bromo- and chloro-substituted diynes **1b** and **1c** with **2a** afforded axially chiral 3-arylpyridines **3ba** and **3ca**, respectively, as a sole product with high yield and enantioselectivity (entries 1 and 2). The absolute configuration of the 3-arylpyridine (−)-**3ca** was unambiguously determined to be *S* by an X-ray crystallographic analysis. Methoxycarbonyl-substituted diyne **1d** reacted with **2a** to give axially chiral 3-arylpyridine **3da** as a major product in high yield, while enantioselectivity was lowered dramatically (entry 3). Methoxy-substituted diyne **1e** reacted with **2a** to give axially chiral 3-arylpyridine **3ea** as a major product with low ee value along with 6-arylpyridine **4ea** as a minor product (entry 4). Surprisingly, when methyl-, trifluoromethyl-, and methoxymethyl-substituted diynes **1f–h** were used, complete regioselectivity switches were observed to give 6-arylpyridines **4fa–ha** in high yields (entries 5–7). With respect to the substituents on the diyne terminus, 2-chlorophenyl-substituted terminal diyne **1i** reacted with **2a** to give 3-arylpyridine **3ia** and 6-arylpyridine **4ia** in a ratio of 2:1 (entry 8), which is in sharp contrast to the reaction of 2-chlorophenyl-substituted internal diyne **1c** with **2a** giving 3-arylpyridine **3ca** as a sole product (entry 2). On the other hand, the reaction of 2-methylphenyl-substituted terminal diyne **1j** with **2a** afforded 6-arylpyridine **4ja** as a sole product (entry 9). With respect to the tether length, malonate-linked 1,6-diynes **1k** and **1l** reacted with **2a** to give axially chiral 3-arylpyridine **3ka** and 6-arylpyridine **3la**, respectively, as a major product (entries 10 and 11), which is consistent with the results using ethane-1,1,2,2-tetracarboxylate-linked 1,7-diynes **1c** and **1f** (entries 2 and 5).[13] With respect to the tether atom, the reaction of tosylamide-linked 1,6-diyne **1m** with **2a** also afforded axially chiral 3-arylpyridine **3ma** as a sole product (entry 12). However, the ee values of thus obtained 3-arylpyridines **3ka** and **3ma** were significantly lower than that obtained from 1,7-diyne **1c** (entries 10 and 12 vs entry 2). With respect to nitriles,[14] not only ethyl cyanoformate (**2a**) but also methyl cyanoformate (**2b**), acetyl cyanide (**2c**), and malononitrile (**2d**) were able to react with 2-chlorophenyl-substituted diyne **1c** to give axially chiral 3-arylpyridines **3cb–cd** with excellent enantioselectivity (entries 13–15), while in the case of **2d** the product yield was low even with the high loading of the catalyst (entry 15). Finally, the reaction of **1c** with diethyl phosphorocyanidate (**2e**) was examined. Interestingly, a significant amount of 6-arylpyridine **4ce** was generated, although 3-arylpyridine **3ce** was generated as a major product with high ee value (entry 16).

The reaction of diyne **1n**, possessing both the coordinating and less coordinating groups (chloro and methyl, respectively), with **2a** is of interest. As shown in Scheme 3, this reaction proceeded at room temperature to give 6-arylpyridine **4na** as a sole product in low yield and ee value.

Scheme 4 depicts a possible explanation of the effect of the *ortho* substituents on regio- and enantioselectivity. When the *ortho* substituent ($R^2$) is the coordinating group (Br, Cl, $CO_2Me$, and OMe), diyne **1** coordinates the cationic rhodium(I) center in a bidentate fashion through one alkyne and $R^2$ or two alkyne moieties, forming equilibrium intermediates **A** and **B**, respectively. Oxidative cyclization from intermediate **B** affords rhodacycle **C**, in which *ortho*-hydrogen (blue) avoids steric repulsion toward the equatorial phenyl group (red), and thus, axial chirality is determined. When $R^2$ is the highly coordinating methoxycarbonyl or methoxy group, enantioselectivity decreases as a result of partial contribution of intermediate **C′**, which gives the opposite enantiomer of **3** through coordination of $R^2$ to rhodium. In addition, the rhodacycle is not 5–6 ring fusion but 5–5 ring fusion in intermediate **C**, and **3** was obtained in low ee value as a result of gradual rotation around the C–C axis (green). Subsequent insertion of nitrile **2a** affords rhodacycle **D**. Formation of rhodacycle **D′** is unfavorable due to steric repulsion between the ethoxycarbonyl group and $R^1$. Indeed, when $R^1$ is sterically less demanding hydrogen, a mixture of 3- and 6-arylpyridines **3** and **4** were generated presumably from rhodacycles **D** and **D′**, respectively (Table 2, entry 8). Reductive



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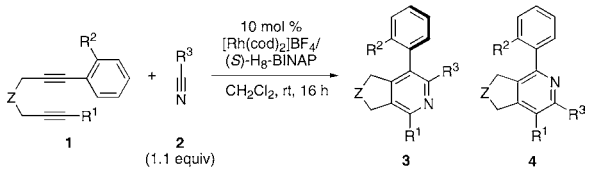
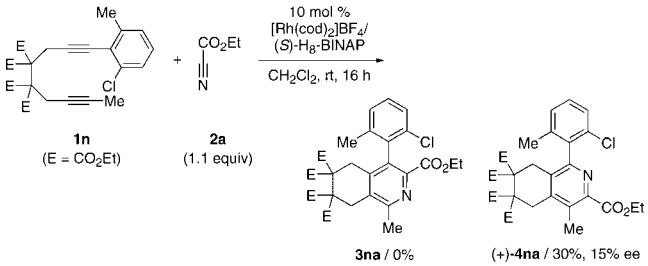
**Table 2. Rh-Catalyzed [2 + 2 + 2] Cycloaddition of Diynes 1 with Nitriles 2 Leading to Arylpyridines 3 and 4**[a]



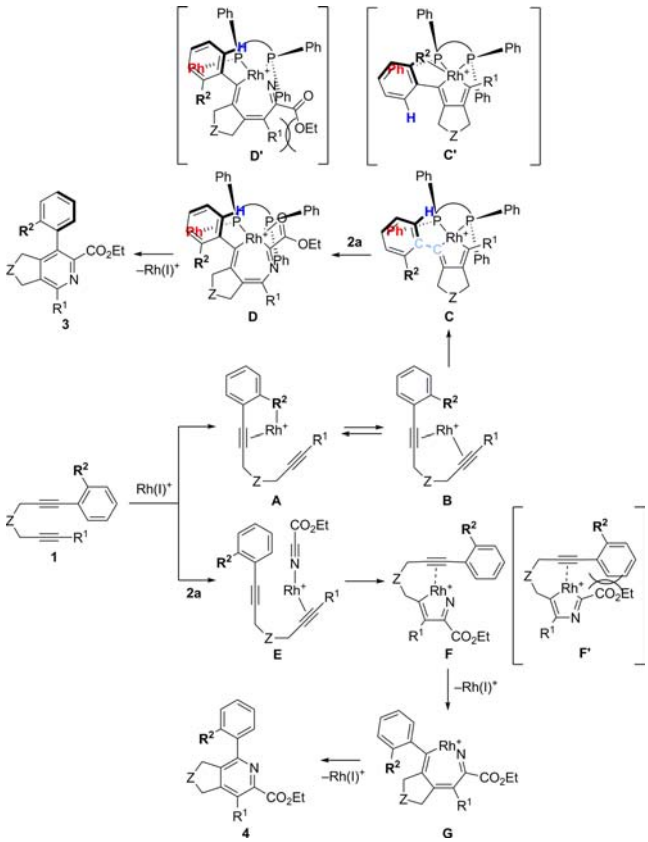

| entry | 1 | Z | $R^1$ | $R^2$ | 2 | $R^3$ | 3/% yield[b] (% ee) | 4/% yield[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | **1b** | $[C(CO_2Et)_2]_2$ | Me | Br | **2a** | $CO_2Et$ | (−)-**3ba**/80 (99) | **3ba**/0 |
| 2 | **1c** | $[C(CO_2Et)_2]_2$ | Me | Cl | **2a** | $CO_2Et$ | (*S*)-(−)-**3ca**/93 (98) | **4ca**/0 |
| 3 | **1d** | $[C(CO_2Et)_2]_2$ | Me | $CO_2Me$ | **2a** | $CO_2Et$ | (−)-**3da**/97 (9) | **4da**/3 |
| 4 | **1e** | $[C(CO_2Et)_2]_2$ | Me | OMe | **2a** | $CO_2Et$ | (−)-**3ea**/68 (24) | **4ea**/28 |
| 5 | **1f** | $[C(CO_2Et)_2]_2$ | Me | Me | **2a** | $CO_2Et$ | **3fa**/0 | **4fa**/98 |
| 6 | **1g** | $[C(CO_2Et)_2]_2$ | Me | $CF_3$ | **2a** | $CO_2Et$ | **3ga**/0 | **4ga**/96 |
| 7 | **1h** | $[C(CO_2Et)_2]_2$ | Me | $CH_2OMe$ | **2a** | $CO_2Et$ | **3ha**/ < 3 | **4ha**/97 |
| 8[c] | **1i** | $[C(CO_2Et)_2]_2$ | H | Cl | **2a** | $CO_2Et$ | (−)-**3ia**/21 (93) | **4ia**/10 |
| 9 | **1j** | $[C(CO_2Et)_2]_2$ | H | Me | **2a** | $CO_2Et$ | **3ja**/0 | **4ja**/85 |
| 10 | **1k** | $C(CO_2Me)_2$ | Me | Cl | **2a** | $CO_2Et$ | (−)-**3ka**/85 (76) | **4ka**/0 |
| 11 | **1l** | $C(CO_2Me)_2$ | Me | Me | **2a** | $CO_2Et$ | (−)-**3la**/8 (90) | **4la**/87 |
| 12 | **1m** | NTs | Me | Cl | **2a** | $CO_2Et$ | (+)-**3ma**/83 (63) | **4ma**/0 |
| 13 | **1c** | $[C(CO_2Et)_2]_2$ | Me | Cl | **2b** | $CO_2Me$ | (+)-**3cb**/89 (98) | **4cb**/0 |
| 14 | **1c** | $[C(CO_2Et)_2]_2$ | Me | Cl | **2c** | COMe | (−)-**3cc**/74 (94) | **4cc**/7 |
| 15[c] | **1c** | $[C(CO_2Et)_2]_2$ | Me | Cl | **2d** | $CH_2CN$ | (−)-**3cd**/41 (95) | **4cd**/4 |
| 16[c] | **1c** | $[C(CO_2Et)_2]_2$ | Me | Cl | **2e** | $P(O)(OEt)_2$ | (−)-**3ce**/41 (89) | **4ce**/24 |

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol), (*S*)-$H_8$−BINAP (0.010 mmol), **1** (0.10 mmol), **2** (0.11 mmol), and $CH_2Cl_2$ (2.0 mL) were used. [b] Isolated yield. [c] $[Rh(cod)_2]BF_4$ (0.020 mmol) and (*S*)-$H_8$−BINAP (0.020 mmol) were used.

**Scheme 3**




**Scheme 4**




elimination affords axially chiral 3-arylpyridine **3** and regenerates the cationic rhodium(I) catalyst. On the other hand, when the *ortho* substituent ($R^2$) is the less coordinating group (Me, $CF_3$, and $CH_2OMe$), the sterically less demanding alkyne moiety of diyne **1** and nitrile **2a** coordinates the cationic rhodium(I) center, forming intermediate **E**. Oxidative cyclization affords rhodacycle **F**, and subsequent insertion of the pendant alkyne affords rhodacycle **G**. Formation of rhodacycle **F′** is unfavorable due to steric repulsion between the ethoxycarbonyl and aryl groups. Reductive elimination affords 6-arylpyridine **4** and regenerates the cationic rhodium(I) catalyst. It has been demonstrated in the computational study of the $RhCl(PPh_3)_3$-catalyzed [2 + 2 + 2] cycloaddition of two acetylenes and a nitrile to form pyiridines that the formation of the rhodacyclopentadiene is more facile than that of the azarhodacyclopentadiene.[15] However, the lower reactivity of 1,7-diynes compared to 1,6-diynes and steric hindrance of *ortho*-substituted phenyl groups may deter the formation of the rhodacyclopentadiene **C**. In the case of diethyl phosphorocyanidate (**2e**), a significant amount of 6-arylpyridine **4ce** was generated (Table 2, entry 16). The higher coordination ability of **2e** than **2a** might facilitate the formation of rhodacycle **F**. The formation of 6-arylpyridine **4na** from (2-chloro-6-methylphenyl)diyne **1n** (Scheme 3) can be explained by contribution of steric hindrance rather than chloro coordination to form an azarhodacyclopentadiene like intermediate **F**.

In conclusion, axially chiral 3-(2-halophenyl)pyridines were successfully synthesized in high yields with excellent enantiose-



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lectivity by the cationic rhodium(I)/(*S*)-$H_8$–BINAP complex-catalyzed atroposelective [2 + 2 + 2] cycloaddition of (*o*-halophenyl)diynes with nitriles. Interestingly, regio- and enantioselectivity highly depend on *ortho* substituents on the phenyl group of diynes. When the *ortho* substituents were methoxy and methoxycarbonyl groups, axially chiral 3-arylpyridines were obtained as a major product, while enantioselectivity was lowered significantly. On the other hand, when the *ortho* substituents were alkyl groups, regioselectivity was switched to give achiral 6-arylpyridines in high yields.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00791.

Experimental procedures and compound characterization data (PDF)

X-ray crystallographic data for (−)-**3ca** (CIF)

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### Notes

The authors declare no competing financial interest.

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