Asymmetric Synthesis of Axially Chiral Compounds by Rhodium(I)-Catalyzed [2+2+2] Cycloaddition

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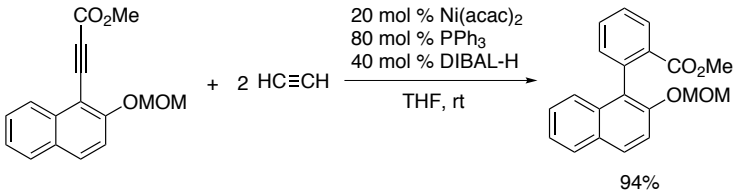
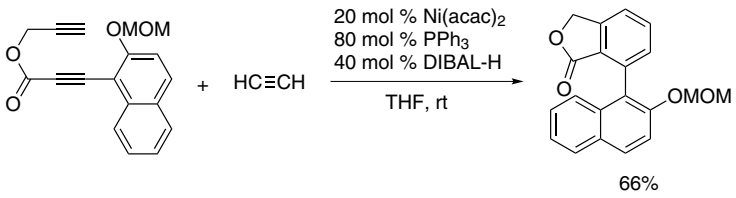
Abstract: This research article discloses rhodium(I)-catalyzed enantioselective [2+2+2] cycloaddition reactions to produce axially chiral biaryls, developed by our research group. The use of cationic rhodium(I)/axially biaryl bisphosphine complexes as catalysts realized the highly efficient enantioselective biaryl synthesis. Additionally, the enantioselective synthesis of axially chiral compounds with non-biaryl axial chirality and the diastereoselective biaryl synthesis are also disclosed.
Keywords: asymmetric catalysis, axial chirality, biaryls, rhodium, [2+2+2] cycloaddition

1. Introduction

Axially chiral biaryls are the important key structures of useful chiral ligands and catalysts,[1] and biologically active compounds.[2] Asymmetric cross-coupling reactions have been investigated for their catalytic enantioselective synthesis, but this approach suffers from low efficiency due to the difficulty of the sterically demanding aryl-aryl bond formation.[3] As a conceptually new approach, the asymmetric aromatic ring construction by the transition-metal-catalyzed [2+2+2] cycloaddition reactions[4] has been reported since seminal three reports in 2004.[5,6] In 1999, Sato, Mori, and co-worker reported two types of the nickel-catalyzed non-asymmetric [2+2+2] cycloaddition



Scheme 1. Nickel-catalyzed [2+2+2] cycloaddition of an aryl monoyne with two acetylenes



Scheme 2. Nickel-catalyzed [2+2+2] cycloaddition of an aryl diyne with acetylene

to produce functionalized biaryls.[7] One was the [2+2+2] cycloaddition of an aryl-substituted monoyne with two acetylenes, leading to a biaryl ester (Scheme 1), and the other was the [2+2+2] cycloaddition of an aryl-substituted and ester-linked 1,6-diyne with acetylene, leading to a biaryl lactone (Scheme 2).[7]

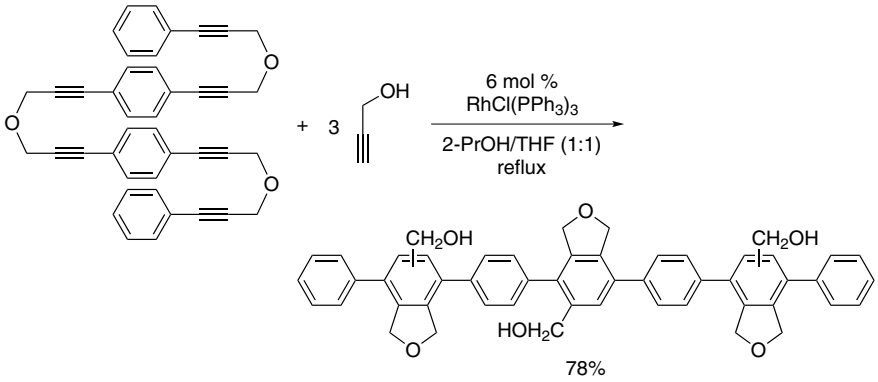
In 2002, McDonald and Smolentsev reported the novel synthesis of an oligo-*p*-phenylene by the $RhCl(PPh_3)_3$-catalyzed [2+2+2] cycloaddition of a hexayne with three propargyl alcohols (Scheme 3). The thus introduced dihydrofuran and alcohol functional groups increased the solubility of the oligo-*p*-phenylene.[8]

These pioneering works clearly demonstrated the utility of the transition-metal-catalyzed [2+2+2] cycloaddition for the synthesis of the functionalized biaryls, while asymmetric variants of these reactions were not accomplished.[9]

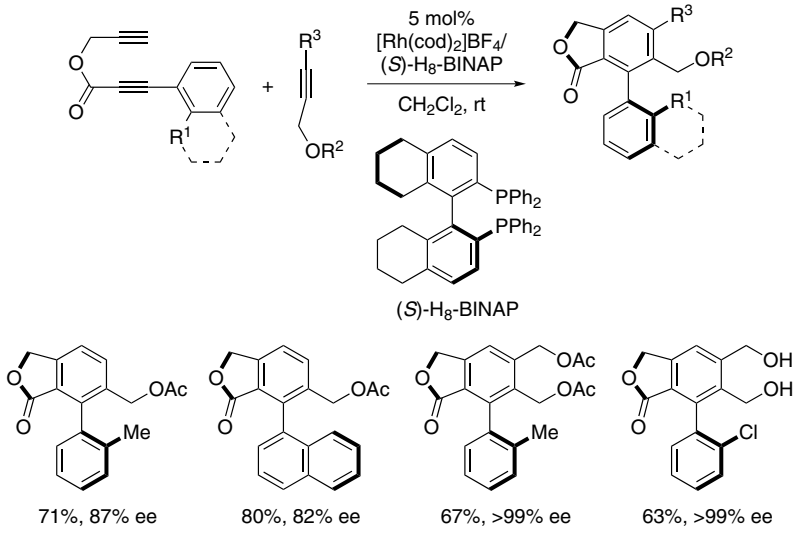
2. Enantioselective Synthesis of Axially Chiral Biaryls

2.1. Reactions Involving Aryl Diynes

In 2003, our research group discovered that cationic rhodium(I) complexes with axially chiral biaryl bisphosphine ligands, especially H_8-BINAP, exhibit remarkably high catalytic activity for chemo- and regioselective [2+2+2] cycloaddition of two different monoynes.[10,11] In 2004, this new chiral catalyst was successfully applied to the asymmetric aromatic ring construction by the [2+2+2] cycloaddition.[5c] A cationic rhodium(I)/(*S*)-H_8-BINAP complex catalyzed the enantioselective [2+2+2] cycloaddition of electron-deficient ester-linked 1,6-diynes, possessing *ortho*-substituted phenyl at an alkyne terminus, with propargyl acetate at room temperature to give axially chiral biaryl lactones with high yields and ee values (Scheme 4). In this reaction, sterically demanding regioisomers were generated with high regioselectivity. Interestingly, the reactions of symmetrical internal monoynes, 1,4-diacetoxy-2-butyne and 2-butyne-1,4-diol, afforded the corresponding biaryls with perfect ee values, although the product yields decreased (Scheme 4).



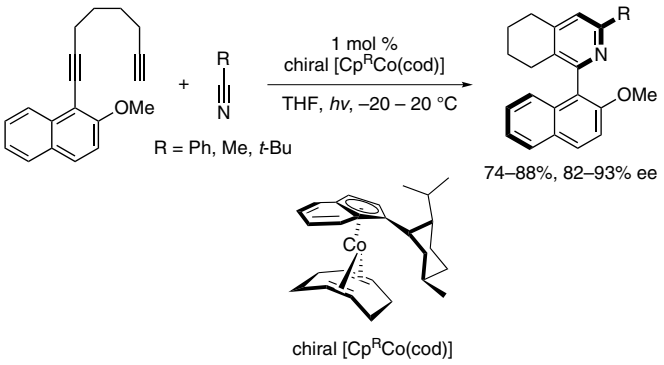
Scheme 3. Oligo-*p*-phenylene synthesis by $RhCl(PPh_3)_3$-catalyzed [2+2+2] cycloaddition



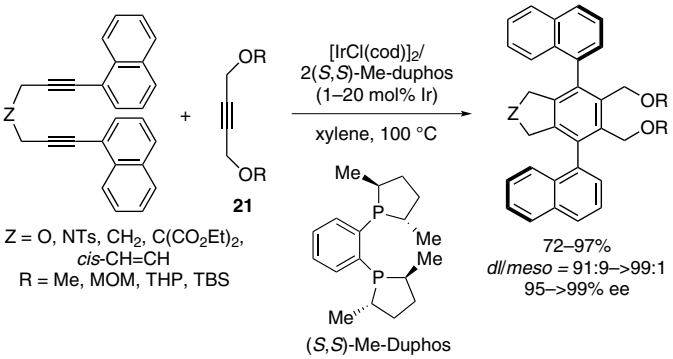
Scheme 4. Rhodium-catalyzed atroposelective [2+2+2] cycloaddition of aryl diynes with monoynes

Unfortunately, the above our report was the third example of the atroposelective [2+2+2] cycloaddition. In 2004, Gutnov, Heller, and co-workers reported the first example of the atroposelective biaryl synthesis by the transition-metal-catalyzed [2+2+2] cycloaddition.[5a] They reported that a cobalt(I)/chiral cyclopentadiene complex is able to catalyze the enantioselective [2+2+2] cycloaddition of an aryl-substituted 1,7-diyne with nitriles, leading to axially chiral aryl pyridines (Scheme 5).

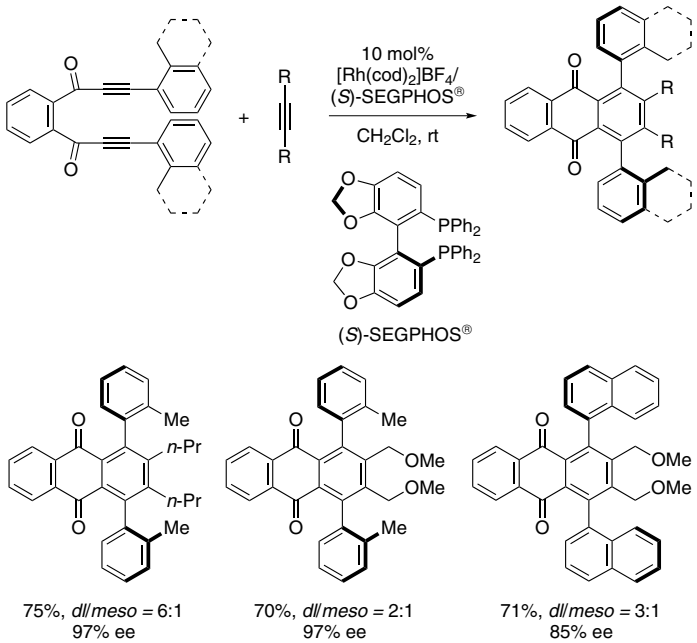
In 2004, Shibata and co-workers reported the second example of the atroposelective biaryl synthesis by using an iridium(I)/chiral bisphosphine complex as a catalyst.[5b] They reported that a neutral iridium(I)/(*S*,*S*)-



Scheme 5. Cobalt-catalyzed atroposelective [2+2+2] cycloaddition of an aryl diyne with nitriles



Scheme 6. Iridium-catalyzed atroposelective [2+2+2] cycloaddition of diaryl diynes with monoynes



Scheme 7. Rhodium-catalyzed atroposelective [2+2+2] cycloaddition of diaryl diynes with monoynes

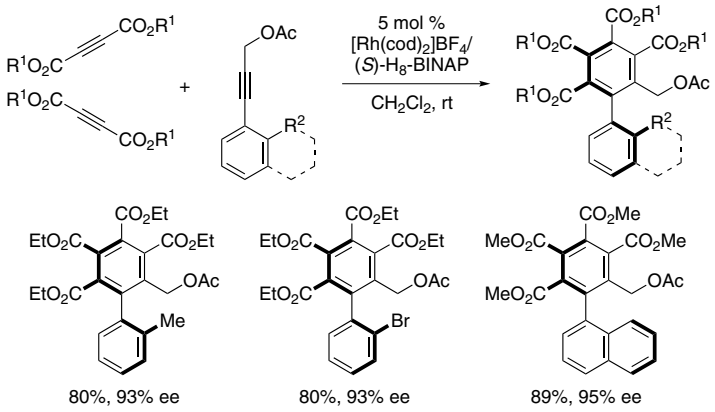
Me-Duphos complex is able to catalyze the diastereo- and enantioselective [2+2+2] cycloaddition of 1,6-diynes, possessing two *ortho*-substituted aryl groups at alkyne termini, with monoynes, leading to axially chiral 1,4-teraryls (Scheme 6). It should be noted that the desired axially chiral 1,4-teraryls are obtained with near-perfect diastereo- and enantioselectivity.

The atroposelective synthesis of axially chiral 1,4-teraryls having anthraquinone structures was achieved by using a cationic rhodium(I)/(*S*)-SEGPHOS® complex as a catalyst.[12] The reactions of electron-deficient 1,2-bis(arylpropiolyl)benzenes and various electron-rich monoynes proceeded at room temperature to give 1,4-teraryls in good yields with good diastereo- and enantioselectivity (Scheme 7).

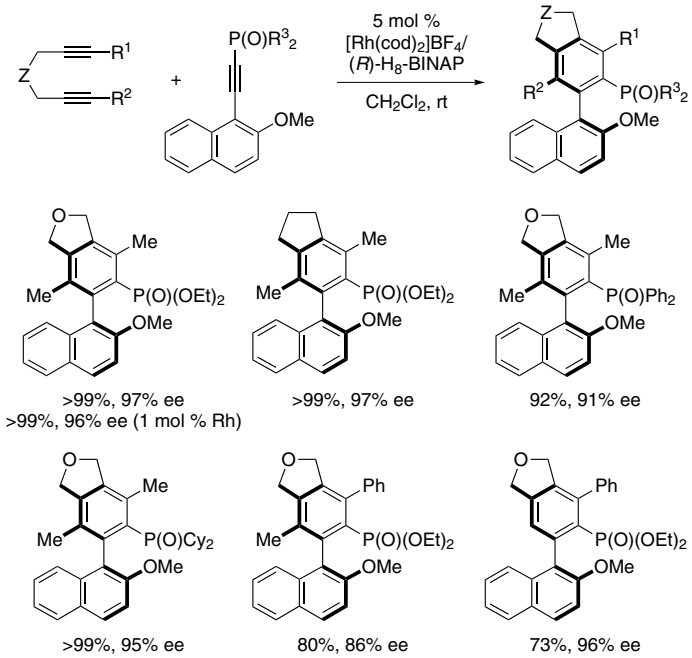
2.2. Reactions Involving Aryl Monoynes

The high catalytic activity of the cationic rhodium(I)/axially biaryl bisphosphine catalysts allowed the use of sterically demanding and less reactive aryl monoynes instead of aryl diynes in the atroposelective [2+2+2] cycloaddition. The cationic rhodium(I)/(*S*)-H_8-BINAP complex was able to catalyze the atroposelective [2+2+2] cycloaddition of acetyloxymethyl substituted aryl monoynes with two dialkyl acetylenedicarboxylates at room temperature to give the corresponding axially chiral biaryls with high yields and ee values (Scheme 8).[13]

Not only acetyloxymethyl substituted aryl monoynes but also phosphorus substituted aryl monoynes could be employed for the rhodium(I)-catalyzed atroposelective [2+2+2] cycloaddition. The reactions of electron-rich 1,6-diynes with electron-deficient alkynylphosphonates or alkynylphosphine oxides proceeded at room temperature



Scheme 8. Rhodium-catalyzed atroposelective [2+2+2] cycloaddition of two monoynes with aryl monoynes



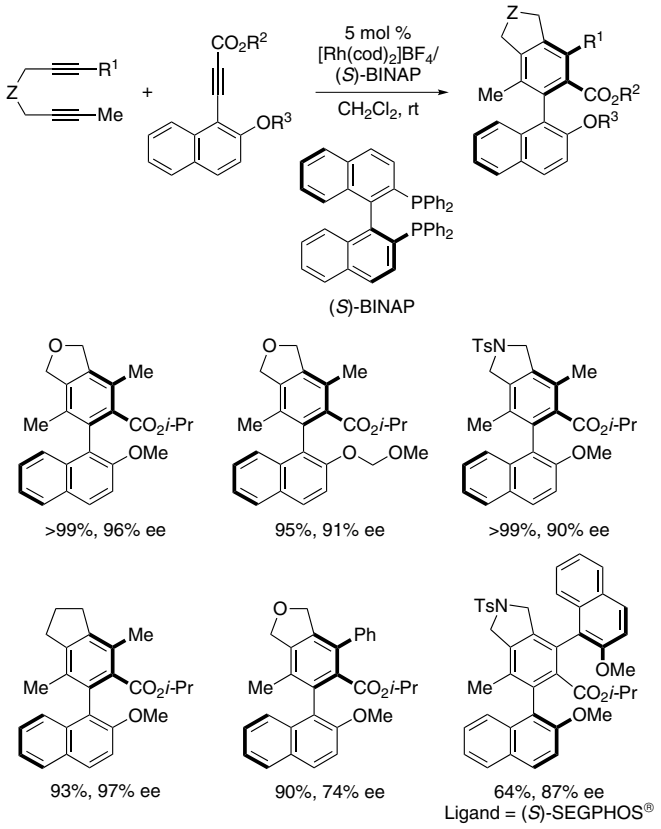
Scheme 9. Rhodium-catalyzed atroposelective synthesis of biaryl phosphorus compounds

to give the corresponding biaryl phosphorus compounds with high yields and ee values (Scheme 9).[14,15] Furthermore, excellent regioselectivity was observed when using unsymmetrical 1,6-diynes (Scheme 9).[14] As the catalytic activity of this rhodium catalyst is very high, the reaction could be carried out even with 1 mol % of the catalyst without erosion of the product yield and ee value (Scheme 9).[14]

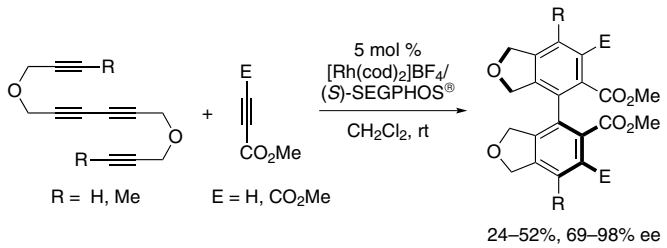
The atroposelective synthesis of axially chiral hydroxycarboxylic acid derivatives was also accomplished with high yields and ee values by the cationic rhodium(I)/(*S*)-BINAP complex-catalyzed [2+2+2] cycloaddition of α,ω-diynes with 2-alkoxynaphthalene-derived alkynylesters (Scheme 10).[16] Additionally, an axially chiral 1,3-teraryl was synthesized with good ee value by using (*S*)-SEGPHOS® as a ligand (Scheme 10).[16]

2.3. Double Cycloaddition Leading to C_2-Symmetric Biaryls

C_2-symmetric axially chiral biaryls are more important than unsymmetric chiral biaryls as basic skeletons of chiral ligands and catalysts. For the atroposelective synthesis of the C_2-symmetric axially chiral biaryls, the rhodium(I)-catalyzed enantioselective double [2+2+2] cycloaddition of symmetric tetraynes with monoynes was examined. Pleasingly, the enantioselective double [2+2+2] cycloaddition of electron-rich tetraynes with two electron-deficient monoynes proceeded at room temperature to give the desired C_2-symmetric axially chiral biaryl diesters with varying yields and ee values by using a cationic rhodium(I)/(*S*)-SEGPHOS® complex as a catalyst (Scheme 11).[17]



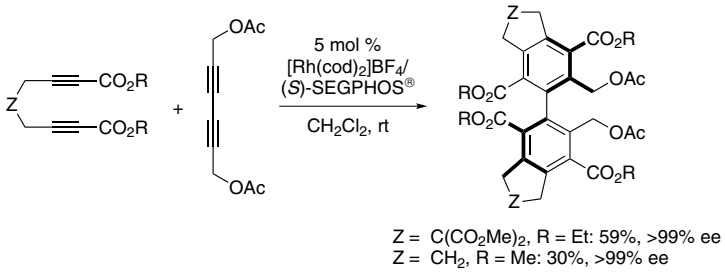
Scheme 10. Rhodium-catalyzed atroposelective synthesis of biaryl esters



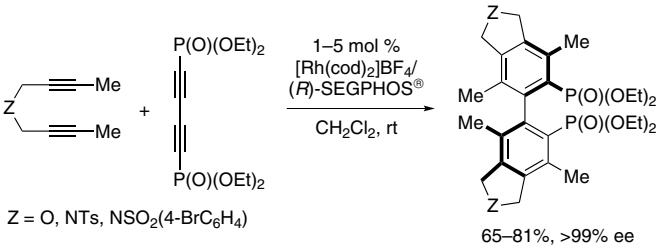
Scheme 11. Rhodium-catalyzed atroposelective [2+2+2] cycloaddition of tetraynes with two monoynes

The cationic rhodium(I)/(*S*)-SEGPHOS® catalyst was also capable of catalyzing the enantioselective double [2+2+2] cycloaddition of two electron-deficient 1,6-diynes with electron-rich 1,3-diynes. The corresponding C_2-symmetric axially chiral biaryls were obtained at room temperature with perfect enantioselectivity, although the yields were moderate (Scheme 12).[17]

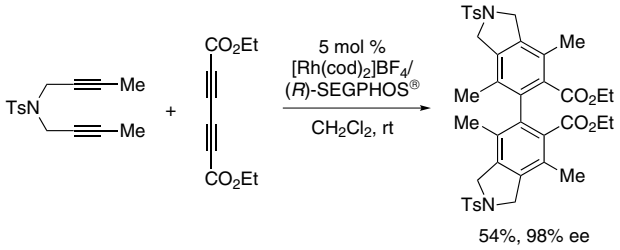
The synthetically very useful C_2-symmetric axially chiral biaryl phosphorus compounds could be synthesized by the rhodium(I)-catalyzed enantioselective double [2+2+2] cycloaddition. The [2+2+2] cycloaddition of 1,6-diynes with a phosphonate-substituted 1,3-butadiyne proceeded at room temperature by using the cationic rhodium(I)/(*R*)-SEGPHOS® catalyst to give C_2-symmetric axially chiral biaryl diphosphonates in good yields with perfect enantioselectivity (Scheme 13).[18–20] The catalytic activity of this rhodium catalyst is very high so that the reaction could be carried out even with 1 mol % of the catalyst. A C_2-symmetric axially chiral biaryl dicarboxylate could also be synthesized by using an ester-substituted 1,3-butadiyne instead of the phosphonate-substituted 1,3-butadiyne (Scheme 14).[18]



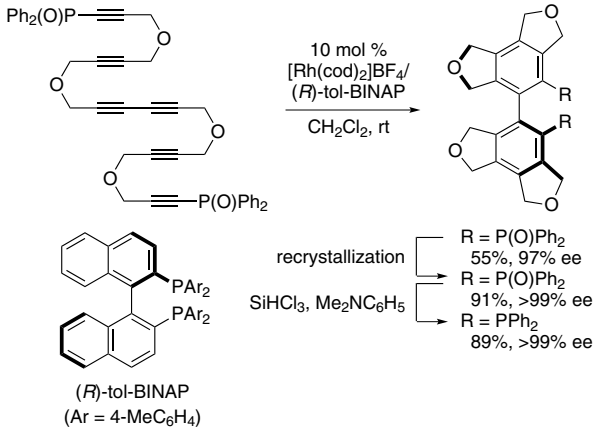
Scheme 12. Rhodium-catalyzed atroposelective [2+2+2] cycloaddition of two 1,6-diynes with a 1,3-diyne



Scheme 13. Rhodium-catalyzed atroposelective synthesis of biaryl diphosphorus compounds



Scheme 14. Rhodium-catalyzed atroposelective synthesis of biaryl diesters



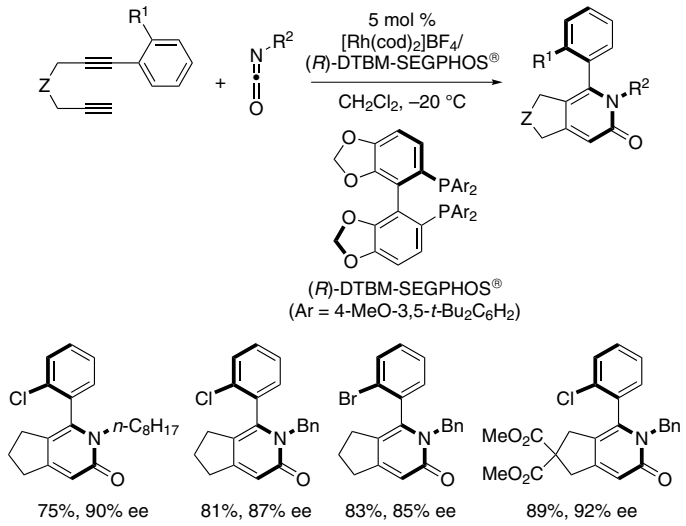
Scheme 15. Enantioselective synthesis of an axially chiral biaryl bisphosphine *via* the rhodium-catalyzed [2+2+2] cycloaddition of a hexayne

Unfortunately, in the above rhodium(I)-catalyzed enantioselective intermolecular double [2+2+2] cycloaddition, a phosphine oxide-substituted 1,3-butadiyne could not be employed. In order to overcome this limitation, we designed the entropically favorable completely intramolecular double [2+2+2] cycloaddition. The [2+2+2] cycloaddition of a diphenylphosphinoyl-substituted hexayne in the presence of the cationic rhodium(I)/(*R*)-tol-BINAP catalyst proceeded at room temperature to give a C_2-symmetric axially chiral biaryl bisphosphine oxide in moderate yield with high enantioselectivity (Scheme 15).[21,22] Subsequent recrystallization and reduction of this bisphosphine oxide furnished the corresponding enantiopure bisphosphine (Scheme 15), which could be used as an effective chiral ligand for the rhodium(I)-catalyzed asymmetric hydrogenation and cycloaddition.[21]

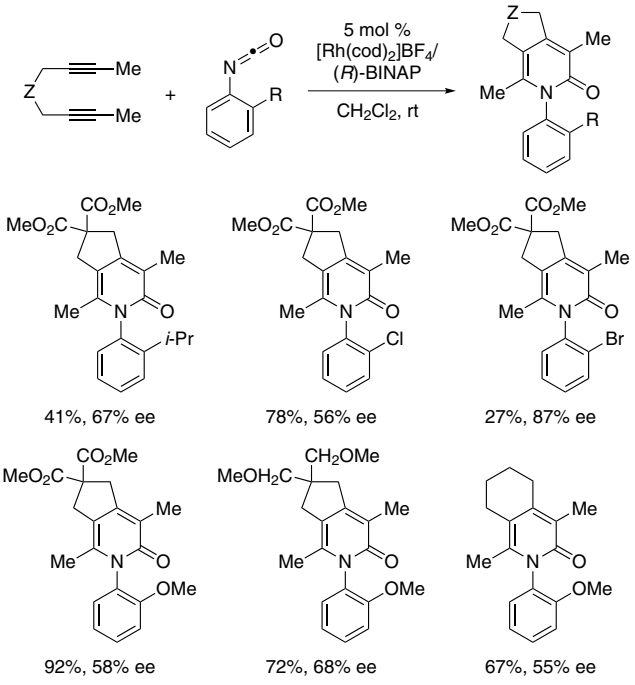
3. Enantioselective Synthesis of Axially Chiral Hetero Biaryls

In the axially chiral biaryl synthesis through the [2+2+2] cycloaddition between aryl-substituted α,ω-diynes and monoynes, the use of isocyanates instead of monoynes furnished axially chiral 6-aryl-2-pyridones in high yields with high regio- and enantioselectivity (Scheme 16).[23,24] In this reaction, the use of 2-halophenyl-substituted 1,6-diynes as a coupling partner and sterically demanding DTBM-SEGPHOS® as a ligand is crucial to attaining the high enantio- and regioselectivity.

On the other hand, the reactions of internal α,ω-diynes and *ortho*-substituted phenyl isocyanates in the presence of the cationic rhodium(I)/(*R*)-BINAP catalyst proceeded at room temperature to give enantioenriched *N*-aryl-2-



Scheme 16. Rhodium-catalyzed atroposelective [2+2+2] cycloaddition of aryl diynes with isocyanates

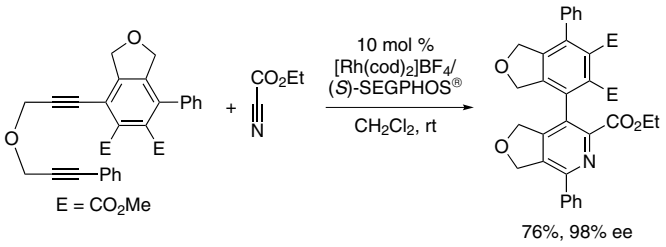


Scheme 17. Rhodium-catalyzed atroposelective [2+2+2] cycloaddition of diynes with aryl isocyanates

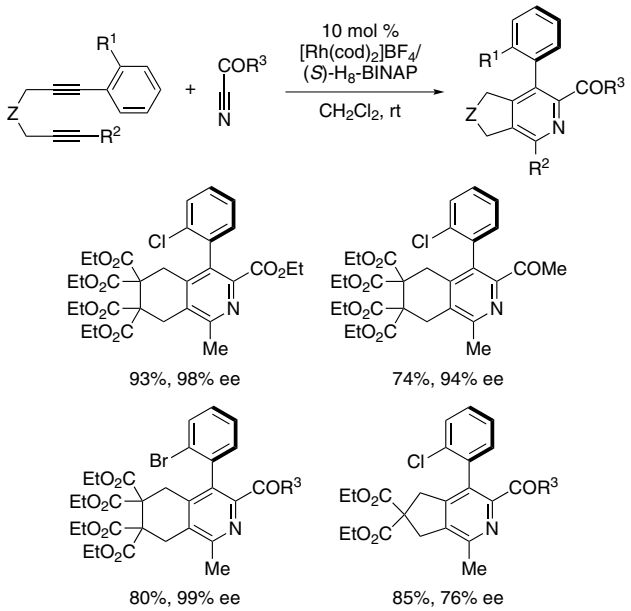
pyridones with axially chiral C–N bonds (Scheme 17).[25,26] Phenyl isocyanates bearing coordinating substituents such as 2-methoxy and 2-chloro groups smoothly reacted with α,ω-diynes to give the corresponding *N*-aryl-2-pyridones in high yields, while ee values were moderate. Although the reaction of sterically demanding and coordinating 2-bromophenyl isocyanate with a 1,6-diyne was sluggish, the highest enantioselectivity was observed.

Not only axially chiral 2-pyridones but also axially chiral pyridines could be synthesized atroposelectively by the rhodium(I)-catalyzed [2+2+2] cycloaddition. The reaction of a 1,6-diyne, possessing a pentasubstituted phenyl at an alkyne terminus, with ethyl cyanoacetate in the presence of the cationic rhodium(I)/(*S*)-SEGPHOS® catalyst afforded an axially chiral arylpyridine as a single regioisomer in good yield with excellent ee value (Scheme 18).[17]

Axially chiral 3-(2-halophenyl)pyridines were successfully synthesized at room temperature in high yields with excellent ee values by the cationic rhodium(I)/(*S*)-H_8-BINAP complex-catalyzed enantioselective [2+2+2] cycloaddition of *ortho*-halophenyl substituted α,ω-diynes with electron-deficient nitriles (Scheme 19).[27] The ee values of the products derived from 1,7-diynes were higher than that from a 1,6-diyne. As with the reactions of ary-substituted 1,6-diynes and isocyanates, the use of 2-halophenyl-substituted 1,6-diynes as a coupling partner is crucial to attaining the high enantio- and regioselectivity.



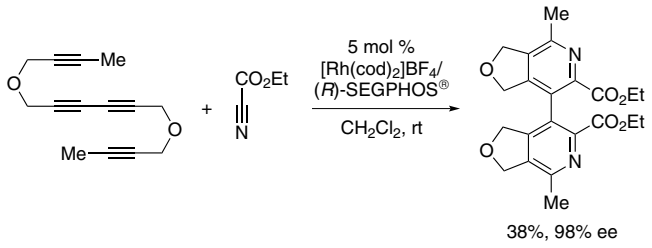
Scheme 18. Rhodium-catalyzed atroposelective [2+2+2] cycloaddition of an aryl diyne with a nitrile



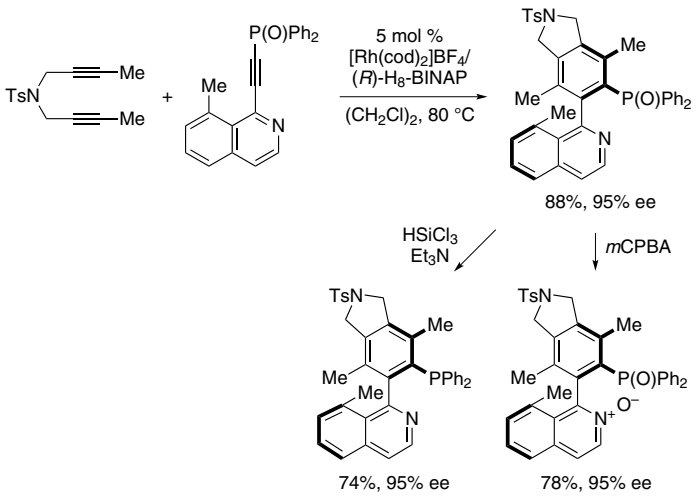
Scheme 19. Rhodium-catalyzed atroposelective [2+2+2] cycloaddition of haloaryl diynes with nitriles

In the axially chiral biaryl synthesis through the double [2+2+2] cycloaddition shown in Scheme 11, the use of ethyl cyanoacetate instead of monoynes furnished the corresponding C_2-symmetric axially chiral pyridine with excellent enantioselectivity, although the yield of the desired C_2-symmetric product was low due to the formation of undesired regioisomers (Scheme 20).[17]

Not only axially chiral P-P compounds but also axially chiral P-N compounds could be synthesized atroposelectively by the rhodium(I)-catalyzed [2+2+2] cycloaddition. The reaction of a 1,6-diyne with a diphenylphosphinoyl-substituted isoquinolinyl acetylene proceeded at 80 °C by using the cationic rhodium(I)/(*R*)-H_8-BINAP catalyst to give a diphenylphosphinoyl-substituted axially chiral 1-arylisoquinoline with high yield and ee value (Scheme 21).[28] This product was derivatized to the corresponding axially chiral P-N ligand and isoquinoline *N*-oxide without racemization (Scheme 21), which could be used in the rhodium(I)-catalyzed hydroboration and the Lewis base-catalyzed allylation, respectively.[28]



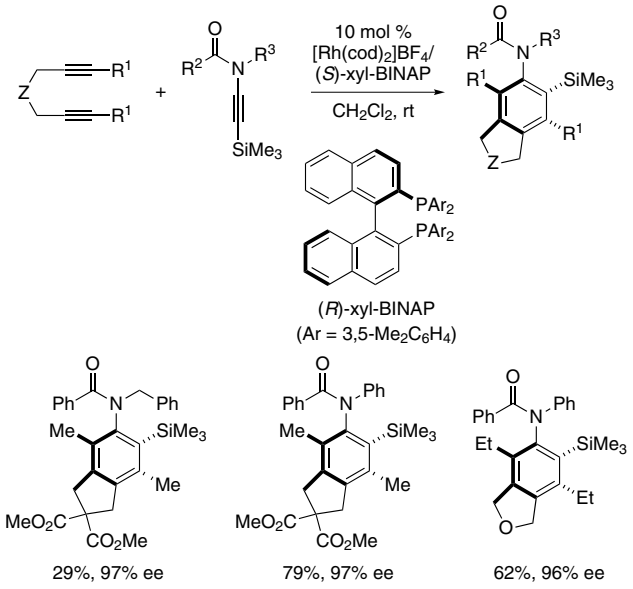
Scheme 20. Rhodium-catalyzed atroposelective [2+2+2] cycloaddition of a tetrayne with two nitriles



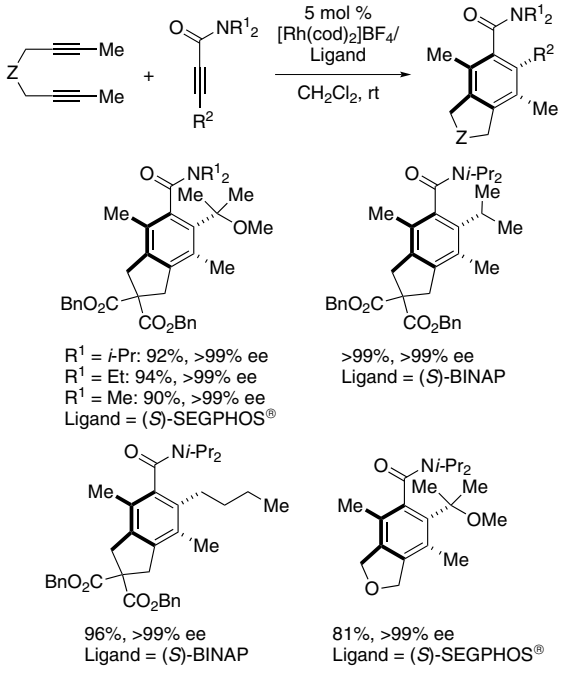
Scheme 21. Rhodium-catalyzed atroposelective synthesis of aryl isoquinoline derivatives

4. Enantioselective Synthesis of Axially Chiral Anilides and Benzamides

Anilides bearing a sterically demanding *ortho*-substituent are known to exist as atropisomers due to the high rotational barrier around the aryl-nitrogen single bond.[29] We anticipated that the [2+2+2] cycloaddition of internal 1,6-diynes with readily prepared trimethylsilylynamides would afford sterically demanding trimethylsilyl-substituted anilides having chiral C–N axis. Pleasingly, the desired axially chiral anilides were obtained at room temperature with high ee values by using a cationic rhodium(I)/(*S*)-xyl-BINAP complex as a catalyst, although the product yields highly depend on the substrates used (Scheme 22).[30,31]



Scheme 22. Rhodium-catalyzed atroposelective synthesis of anilides



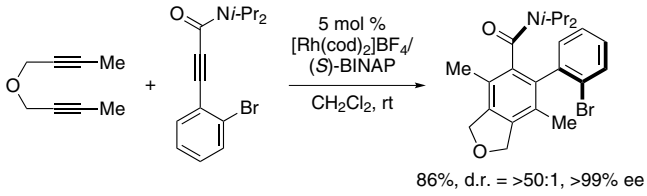
Scheme 23. Rhodium-catalyzed atroposelective synthesis of benzamides

2,6-Disubstituted *N*,*N*-dialkylbenzamides are also known to exist as atropisomers due to the high rotational barrier around the aryl-carbonyl single bond.[32] This non-biaryl axial chirality could also be constructed atroposelectively by the rhodium(I)-catalyzed [2+2+2] cycloaddition. The reaction of internal 1,6-diynes with *N*,*N*-dialkylalkynylamides in the presence of the cationic rhodium(I)/(*S*)-SEGPHOS® or (*S*)-BINAP catalyst proceeded at room temperature to give the desired axially chiral benzamides in excellent yields with perfect enantioselectivity (Scheme 23).[33]

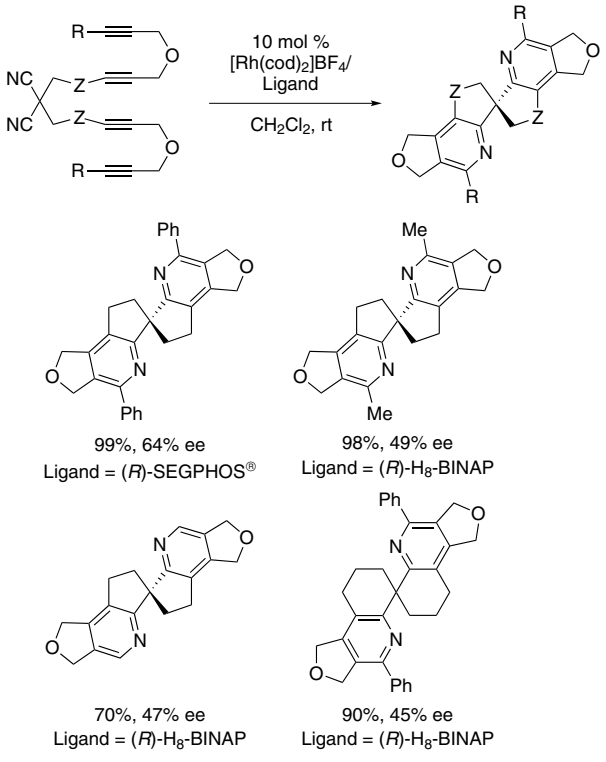
The simultaneous construction of both the aryl-carbonyl and aryl-aryl axial chirality was accomplished with excellent diastereo- and enantioselectivity by the cationic rhodium(I)/(*S*)-BINAP complex-catalyzed [2+2+2] cycloaddition of *N*,*N*-dialkylalkynylamide, bearing a 2-bromophenyl group at an alkyne terminus, with an internal 1,6-diyne (Scheme 24).[33]

5. Enantioselective Synthesis of Axially Chiral Spiranes

C_2-Symmetric heterospiranes with the stable axial chirality are valuable structures for efficient chiral ligands because heteroatoms containing chiral spiranes readily coordinate with many metals to form well-defined chiral chelate complexes.[34] The rhodium(I)-catalyzed [2+2+2] cycloaddition was successfully applied to the atroposelective spirane synthesis. The cationic rhodium(I)/(*R*)-SEGPHOS® or (*R*)-H_8-BINAP complex-catalyzed intramolecular double [2+2+2] cycloaddition of bis-diynenitriles afforded enantioenriched C_2-symmetric spirobipyridine ligands, although the product ee values were moderate (Scheme 25).[35]



Scheme 24. Rhodium-catalyzed diastereo- and enantioselective synthesis of a biarylamide



Scheme 25. Rhodium-catalyzed atroposelective synthesis of spirobipyridines

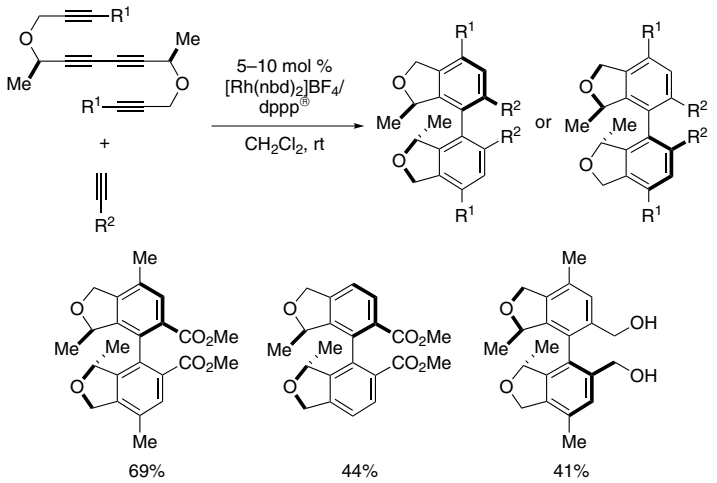
6. Diastereoselective Synthesis of Axially Chiral Biaryls

The chirality transfer from centrochirality to axial chirality is also an attractive strategy for the asymmetric synthesis of biaryls, if the chiral compounds with centrochirality are readily available. Thus, we designed the diastereoselective double [2+2+2] cycloaddition of chiral tetraynes, derived from commercially available (*R*)-3-butyn-2-ol, with functionalized monoynes as shown in Scheme 26.[36] Pleasingly, the desired reactions proceeded at room temperature by using a cationic rhodium(I)/dppp® complex as a catalyst to give the corresponding C_2-symmetric axially chiral biaryls with perfect diastereoselecivity. Interestingly, the reactions with methyl propiolate afforded biaryls, possessing large dihedral angles, exclusively. On the contrary, that with propargyl alcohol afforded a biaryl, possessing small dihedral angle, exclusively.

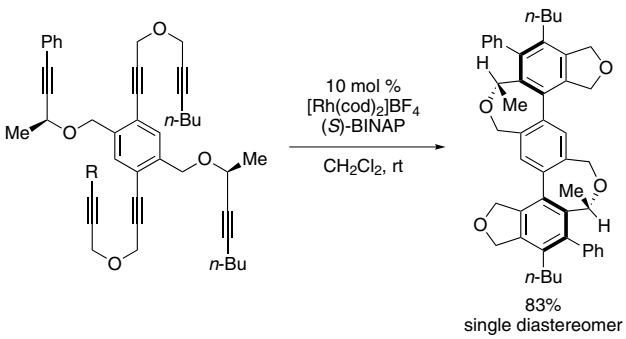
The asymmetric synthesis of a configurationally stable oxygen-linked Geländer-type *p*-terphenyl has also been achieved in the cationic rhodium(I)/BINAP complex-catalyzed diastereoselective intramolecular double [2+2+2] cycloaddition of a chiral hexayne, derived from commercially available (*R*)-3-butyn-2-ol (Scheme 27).[37] Centrochirality of the chiral hexayne perfectly induced the axial chirality to give the Geländer-type *p*-terphenyl as a single stereoisomer.

7. Conclusion

This research article disclosed the rhodium(I)-catalyzed atroposelective [2+2+2] cycloaddition, developed in our research group, for the synthesis of axially chiral compounds including biaryls, hetero biaryls, teraryls, anilides, benzamides, and spiranes.[38] We established that cationic rhodium(I)/axially chiral biaryl bisphosphine complexes are highly active and selective catalysts for a wide variety of the atroposelective [2+2+2] cycloaddition. In this catalyst system, the combination of electron-rich alkynes and electron-deficient unsaturated compounds (alkynes, nitriles, and isocyanates) is important to realize the highly chemoselective intermolecular cycloaddition. With respect to stereoselectivity, the introduction of the coordinating functional groups to the substrates is important. Especially, electron-deficient and highly coordinating alkynylphosphonates and alkynylamides are the best-suited coupling partners, the use of which realized excellent chemo- and stereoselectivity. The present rhodium(I) catalyst system allows in situ generation of active catalysts from stable and commercially available rhodium(I)/diene complexes and axially chiral bisphosphine ligands. This feature is advantageous for catalyst tuning and convenient handling. The further development of new catalysts and reactions are waiting for the application to the synthesis of novel functional molecules.



Scheme 26. Rhodium-catalyzed diastereoselective [2+2+2] cycloaddition of chiral tetraynes with two monoynes



Scheme 27. Rhodium-catalyzed diastereoselective [2+2+2] cycloaddition of a chiral hexayne

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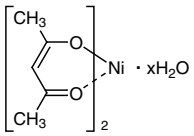
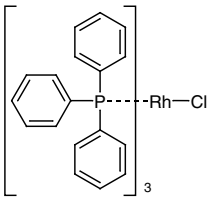
TCI Related Products

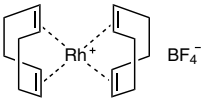
Metal Complexes



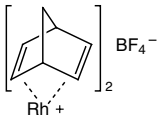
Bis(2,4-pentanedionato)nickel(II) Hydrate
(= $Ni(acac)_2$)
25g, 100g, 500g
[N0096]



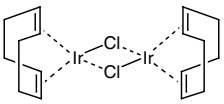
Tris(triphenylphosphine)rhodium(I) Chloride (= $RhCl(PPh_3)_3$)
1g, 5g
[T0931]



Bis(1,5-cyclooctadiene)rhodium(I) Tetrafluoroborate
(= $[Rh(cod)_2]BF_4$)
100mg, 1g
[B3961]

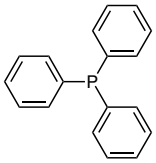


Bis[η-(2,5-norbornadiene)]rhodium(I) Tetrafluoroborate (= $[Rh(nbd)_2]BF_4$)
100mg
[B2091]

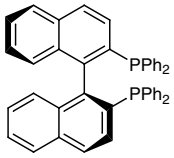


Chloro(1,5-cyclooctadiene)iridium(I) Dimer
(= $[IrCl(cod)_2]$)
250mg, 1g
[C1807]

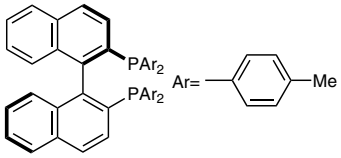
Phosphine Ligands



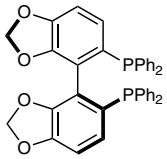
Triphenylphosphine
25g, 100g, 500g
[T0519]



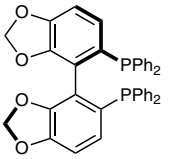
(*S*)-(-)-BINAP
1g, 5g
[B1405]



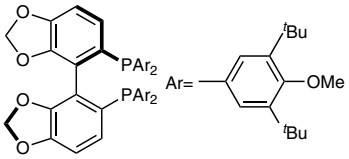
(*R*)-(+)-TolBINAP
1g, 5g
[T3152]



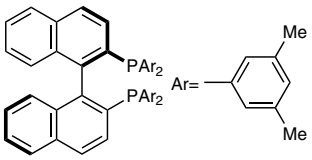
(*S*)-(-)-SEGPHOS®
200mg, 1g
[S0929]



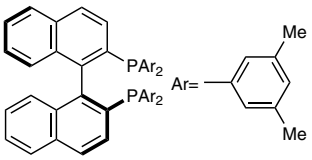
(*R*)-(+)-SEGPHOS®
200mg, 1g
[S0930]



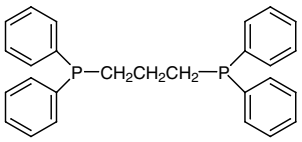
(*R*)-(-)-DTBM-SEGPHOS®
200mg, 1g
[D4501]



(*R*)-(+)-XylBINAP
200mg, 1g
[X0070]



(*S*)-(-)-XylBINAP
200mg, 1g
[X0071]



1,3-Bis(diphenylphosphino)propane (= dppp®)
5g, 25g
[B1138]