Highly Enantioselective Synthesis of Pseudo-C_2-Symmetric Axially Chiral Biaryl Diphosphines via Rhodium-Catalyzed Double [2 + 2 + 2] Cycloaddition

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Summary: Cationic rhodium complexes based on (R)-BINAP catalyze the sequential double [2 + 2 + 2] cycloaddition between 1,4-bis(diphenylphosphinoyl)buta-1,3-diyne and an internal 2,n-diyne followed by its terminal counterpart in an operationally straightforward procedure to afford pseudo-C_2-symmetric axially chiral biaryl diphosphines in good yield and with exceptionally high enantioselectivity.

Atropos biaryl diphosphines have evolved into a highly versatile class of ligand for a host of important carbon−carbon and carbon−heteroatom bond-forming reactions.[1] Since its introduction in the 1980s, the basic biaryl framework of BINAP has been used as a template for the synthesis of a wide range of derivatives, some with quite elaborate architectures (Chart 1).[2] However, the synthesis of these diphosphines is often a nontrivial multistep process that most commonly either starts from *rac* or enantiopure BINOL and involves a palladium- or nickel-catalyzed cross-coupling between a biaryl ditriflate and a secondary phosphine[3a,b] or requires construction of the biaryl unit via Ullmann coupling of a 3-substituted 2-iodophenyl phosphonic acid dialkyl ester, resolution, and transformation of the phosphonates into diarylphosphino groups.[3c] Moreover, modification of BINAP to facilitate catalyst immobilization or to improve solubility in nonconventional solvents also presents a significant synthetic challenge.[4] Even though both approaches are used by industry,[5] the need either to start from an enantiopure precursor or to perform a resolution, the use of high-temperature C−C or P−C coupling reactions, and the handling of hazardous pyrophoric diphenylphosphine severely limit their scope in reaction development and optimization. Thus, there will be immense potential benefits to developing a more efficient, cost-effective, operationally practical synthesis of biaryl-based diphosphines, particularly if it can be conducted under mild conditions, does not require an enantiopure starting material or involve resolution, and enables the level and nature of the substitution pattern on the biaryl unit to be varied in a systematic and straightforward manner.

Transition-metal-catalyzed [2 + 2 + 2] cycloaddition is evolving into an extremely powerful tool for the construction of axially chiral biaryls, spirocycles, and helical polyaryls, with some of the most recent and noteworthy developments originating from the research groups of Tanaka,[7] Shibata,[8] and Heller.[9] As part of our ongoing program to develop new, atom-economical, and efficient approaches for the synthesis of atropos and tropos biaryl and biaryl-like diphosphines,[10] we have recently demonstrated that the biaryl framework of BIPHEP-based diphosphines can be constructed in a single pot and with remarkable efficiency via rhodium-catalyzed [2 + 2 + 2] cycloaddition between 1,4-bis(diphenylphosphinoyl)buta-1,3-diyne and 2 equiv of a terminal 1,*n*-diyne.[11] Platinum metal complexes of these diphosphines can be resolved, and the

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(1) (a) Shimizu, H.; Nagasaki, I.; Sayo, N.; Saito, T. In *Phosphorus Ligands in Asymmetric Catalysis*; Borner, A., Ed.; Wiley-VCH: Weinheim, Germany, 2008; p 207. (b) Li, Y.-M.; Yu, W.-Y.; Chan, A. S. C. *Phosphorus Ligands in Asymmetric Catalysis*; Borner, A., Ed.; Wiley-VCH: Weinheim, Germany, 2008; p 260. (c) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Catalysis*; Wiley: New York, 1995. (d) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.

(2) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405.

(3) (a) Cai, D.; Payack, J. F.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. *J. Org. Synth.* **1998**, *76*, 6. (b) Ager, D. J.; East, M. B.; Esienstadt, A.; Laneman, S. A. *Chem. Commun.* **1997**, 2369. (c) Foricher, J.; Heiser, B.; Schmid, R. (Hoffmann-La Roche AG) PCT Int. Appl. WO 9216535, 1992.

(4) Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* **2005**, *105*, 1801.

(5) Kumobayashi, H.; Miura, T.; Sayo, N.; Saito, T.; Zhang, X. *Synlett* **2001**, 1055.

(6) For comprehensive and informative reviews see: (a) Tanaka, K. *Synlett* **2007**, 1977. (b) Shibata, T.; Tsuchikama, K. *Org. Biomol. Chem.* **2008**, *6*, 1317. For other reviews on transition-metal-catalyzed [2 + 2 + 2] cycloadditions see: (c) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307. (d) Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* **2006**, 2209. (e) Robinson, J. E. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; p 129.

(7) (a) Tanaka, K.; Nishida, G.; Wada, A.; Noguchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 6510. (b) Tanaka, K.; Nishida, G.; Ogino, M.; Hirano, M.; Noguchi, K. *Org. Lett.* **2005**, *7*, 3119. (c) Tanaka, K.; Kamisawa, A.; Suda, T.; Noguchi, K.; Hirano, M. *J. Am. Chem. Soc.* **2007**, *129*, 12078. (d) Tanaka, K.; Suda, T.; Noguchi, K.; Hirano, M. *Org. Lett.* **2007**, *72*, 2243. (e) Nishida, G.; Suzuki, N.; Noguchi, K.; Tanaka, K. *Org. Lett.* **2006**, *8*, 3489. (f) Wada, A.; Noguchi, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2007**, *9*, 1295.

(8) For selected examples see: (a) Tsuchikama, K; Kuwata, Y.; Shibata, T. *J. Am. Chem. Soc.* **2006**, *128*, 13686. (b) Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* **2004**, *126*, 8382. (c) Shibata, T.; Tsuchikama, K.; Otsuka, M. *Tetrahedron: Asymmetry* **2006**, *17*, 614. (d) Shibata, T.; Yoshida, S.; Arai, Y.; Otsuka, M.; Endo, K. *Tetrahedron* **2008**, *64*, 821.

(9) Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3745.

(10) (a) Doherty, S.; Knight, J. G.; Robins, E. G.; Scanlan, T. H.; Champkin, P. A.; Clegg, W. *J. Am. Chem. Soc.* **2001**, *123*, 5110. (b) Doherty, S.; Robins, E. G.; Nieuwenhuyzen, M.; Knight, J. G.; Champkin, P. A.; Clegg, W. *Organometallics* **2002**, *21*, 1383. (c) Doherty, S.; Newman, C. R.; Rath, R. K.; van den Berg, J.-A.; Hardacre, C.; Nieuwenhuyzen, M.; Knight, J. G. *Organometallics* **2004**, *23*, 1055. (d) Doherty, S.; Newman, C. R.; Rath, R. K.; Luo, K.-K.; Nieuwenhuyzen, M.; Knight, J. G. *Org. Lett.* **2003**, *5*, 3863. (e) Doherty, S.; Goodrich, P.; Hardacre, C.; Luo, H.-K.; Rooney, D. W.; Seddon, K.; Styring, P. *Green Chem.* **2004**, *6*, 63. (f) Doherty, S.; Knight, J. G.; Hardacre, C.; Luo, H.-K.; Newman, C. R.; Rath, R. K.; Campbell, S.; Nieuwenhuyzen, M. *Organometallics* **2004**, *23*, 6127. (g) Doherty, S.; Goodrich, P.; Hardacre, C.; Luo, H.-K.; Nieuwenhuyzen, M.; Rath, R. K. *Organometallics* **2005**, *24*, 5945. (h) Doherty, S.; Knight, J. G.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *J. Org. Chem.* **2006**, *71*, 9751. (i) Doherty, S.; Knight, J. G.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *Organometallics* **2007**, *26*, 6453. (j) Doherty, S.; Knight, J. G.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *Organometallics* **2007**, *26*, 5961.

(11) Doherty, S.; Knight, J. G.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *Org. Lett.* **2007**, *9*, 4925.

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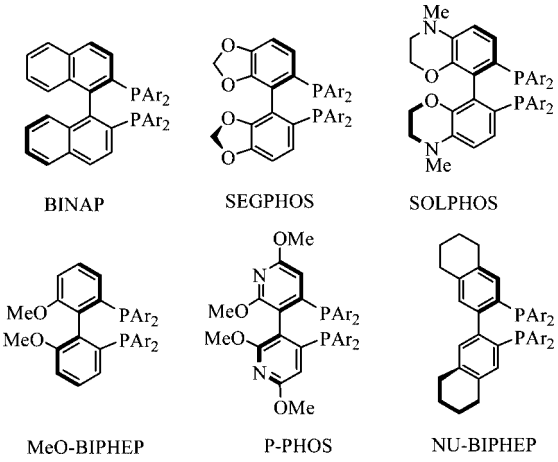
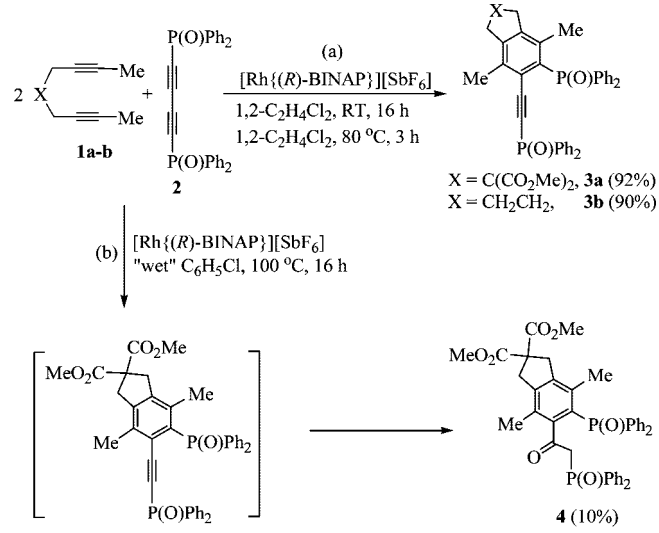
Chart 1



resulting enantiopure complexes form highly efficient catalysts for a range of asymmetric reactions. In a natural extension of this work, we have been investigating the corresponding reaction with internal 2,*n*-diynes, reasoning that the use of an enantiopure Rh/BINAP-based catalyst would generate nonracemic atropos 6,6′-substituted biaryl diphosphines. Herein we report the first examples of the use of asymmetric rhodium-catalyzed [2 + 2 + 2] cycloaddition to prepare axially chiral biaryl diphosphines, in good yield and with exceptionally high enantioselectivity. In related studies, rhodium-catalyzed [2 + 2 + 2] cycloaddition has been used to prepare biaryl monophosphines,[12,13] axially chiral monophosphonates,[14−16] and most recently biaryl-based P-stereogenic alkynylphosphine oxides via desymmetrization of symmetrical dialkynylphosphine oxides.[17]

Our initial attempt to prepare atropisomeric biaryl diphosphines via [2 + 2 + 2] cycloaddition followed the same protocol as that described earlier for the synthesis of tropos NU-BIPHEP diphosphines.[11] Addition of the dimethyl malonate derived 2,*n*-diyne **1a** and 1,4-bis(diphenylphosphinoyl)buta-1,3-diyne **2** to a dichloromethane solution containing [Rh(COD){(*R*)-BINAP}][SbF_6] resulted in selective monocycloaddition to afford adduct **3a** in near-quantitative yield after stirring at room temperature for 16 h, with no evidence for the desired C_2-symmetric biaryl diphosphine even after stirring for a further 24 h (Scheme 1a). The same reaction conducted in 1,2-dichloroethane at 80 °C gave a comparable yield of **3a** after only 3 h. The presence of two distinct, well-separated signals at δ 32.1 and 7.5 in the ^{31}P NMR spectrum provided the first indication that the product was not the desired biaryl diphosphine; the singlet at δ 32.1 is close to the region expected for a biaryl phosphine oxide, while that at δ 7.5 is characteristic of an alkynylphosphine oxide. Similarly, the corresponding reaction between 2,8-decadiyne and **2** in 1,2-dichloroethane at 80 °C for

Scheme 1



3 h gave **3b** in excellent yield as an analytically pure solid after purification by column chromatography. The identity of **3a**,**b** as monocycloadducts was firmly established by NMR spectroscopy and IR spectroscopy (ν(C≡C) 2173 cm^{-1}) together with electrospray mass spectrometry and, in the case of **3b**, was ultimately confirmed by a single-crystal X-ray study, the resulting structure being shown in Figure 1. The C(13)−C(14) bond length of 1.199(2) Å is close to that expected for a carbon−carbon triple bond and is similar to those found in related monocycloaddition adducts generated from **2** and substituted cyclopentadiene[18] and anthracene[19] derivatives. The P(2)−C(14)−C(13) and C(10)−C(13)−C(14) bond angles of 173.16(14) and 172.60(16)° also lie within the ranges of 172.25 and 177.31° for the corresponding angles in these monocycloadducts.

As double cycloaddition of an internal 2,*n*-diyne with **2** is clearly markedly more challenging than the corresponding reaction with its terminal counterpart, we next investigated the reaction between monoadduct **3a** and a further 1 equiv of **1a** in chlorobenzene at 100 °C, in the presence of the same Rh/(*R*)-BINAP catalyst. However, under these conditions **3a** underwent slow hydrolysis to afford **4** as the sole product, again with no evidence for cycloaddition (Scheme 1b). The identity of **4** was initially based on a number of distinctive features in the ^{31}P,

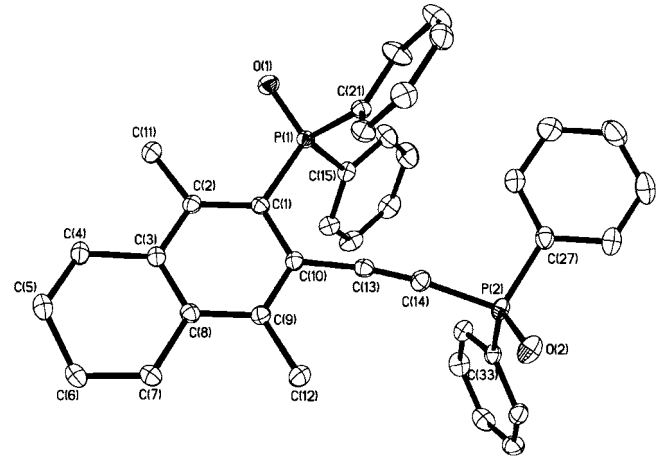


Figure 1. Molecular structure of cycloaddition adduct **3b**. Hydrogen atoms have been omitted for clarity. Ellipsoids are at the 40% probability level.

(12) Kondoh, A.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 6996.

(13) For the synthesis of racemic biaryl monophosphines via Diels−Alder cycloaddition see: (a) Ashburn, B. O.; Carter, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6737. (b) Ashburn, B. O.; Carter, R. G. *J. Am. Chem. Soc.* **2007**, *129*, 9109.

(14) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3951.

(15) Heller, B.; Gutnov, A.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Redkin, D.; Sundermann, C.; Sundermann, B. *Chem. Eur. J.* **2007**, *13*, 1117.

(16) For the synthesis of axially chiral biaryl monophosphonates via asymmetric Suzuki−Miyaura cross coupling see: Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051.

(17) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3410.

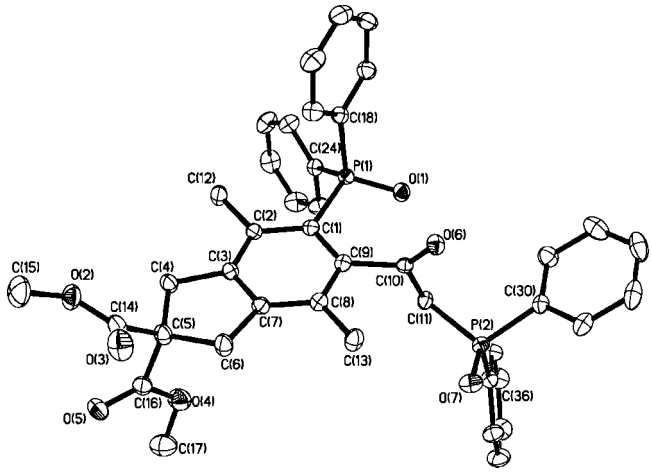
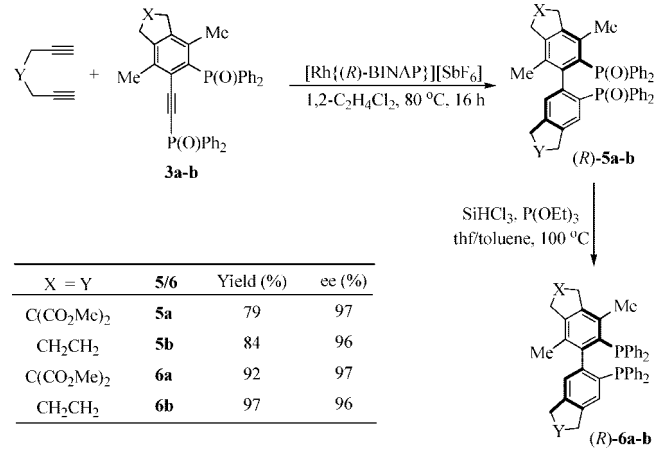


Figure 2. Molecular structure of **4** showing the β-keto phosphinoyl fragment and confirming the regioselectivity of hydrolysis. Hydrogen atoms as well as the toluene and water molecules of crystallization have been omitted for clarity. Ellipsoids are at the 40% probability level.

^{1}H, and ^{13}C NMR spectra, an intense band at 1732 cm^{-1} in the IR spectrum, and a molecular ion peak at 687 amu in the electrospray mass spectrum. Even though the presence of two signals at δ 31.1 and 28.9 in the ^{31}P NMR spectrum of **4** was clear evidence that double cycloaddition had not occurred, both appear in the region expected for a biaryl phosphine oxide, which suggested that both triple bonds had reacted. The ^{13}C NMR spectrum of **4** contains a characteristic low-field multiplet at δ 198.1, associated with the carbonyl adjacent to the aromatic ring, and two broad triplets at δ 4.51 and 3.99 in the ^{1}H NMR spectrum, each of intensity 1H, are indicative of the diastereotopic methylene protons sandwiched between the carbonyl and diphenylphosphinoyl fragments. The identity of **4** was conclusively established by a single-crystal X-ray study, and a perspective view of the molecular structure is shown in Figure 2. The structure clearly shows that **4** contains one arylphosphine oxide fragment, derived from a [2 + 2 + 2] cycloaddition to one of the triple bonds of **2**, and a β-keto phosphinoyl group that arises from regioselective hydrolysis of the triple bond in **3a**, presumably by adventitious water in the chlorobenzene. At this stage we are confident that **4** is the result of rhodium-catalyzed hydrolysis of adduct **3a**, primarily founded on the following observations: (i) a chlorobenzene solution containing 10 mol % of the cationic rhodium catalyst, 2 equiv of water, and **2** showed no evidence of hydrolysis even after heating at 100 °C for 16 h, (ii) **3a** did not undergo hydrolysis in chlorobenzene in the absence of catalyst, and (iii) addition of **3a** to a solution of the catalyst in chlorobenzene resulted in near-quantitative conversion to **4** after repeated cycles of replacing the solvent and heating at 100 °C.

As terminal 1,*n*-diynes readily undergo double cycloaddition with **2** at room temperature in the presence of cationic Rh/BINAP catalyst, the reluctance of **3a** to undergo a second cycloaddition is most likely due to unfavorable steric interactions between the methyl substituents of the metallacyclopentadiene intermediate and the alkynyldiphenylphosphinoyl fragment of **3a** during coordination and carborhodation of the triple bond. On this basis, we reasoned that **3a** would be more likely to undergo a second [2 + 2 + 2] cycloaddition with the dimethyl malonate derived terminal 1,6-diyne to afford the corresponding pseudo-C_2-symmetric biaryl diphosphine. Gratifyingly, addition of a slight excess of the malonate-derived 1,6-diyne to a solution of Rh/(*R*)-BINAP catalyst and **3a** in 1,2-dichloroethane at 80 °C

Scheme 2



X = Y	5/6	Yield (%)	ee (%)
$C(CO_2Me)_2$	**5a**	79	97
CH_2CH_2	**5b**	84	96
$C(CO_2Me)_2$	**6a**	92	97
CH_2CH_2	**6b**	97	96

resulted in complete consumption of the monoadduct within 16 h to afford diphosphine oxide **5a** in 97% ee and excellent yield, after purification by column chromatography (Scheme 2). The same rhodium-catalyzed protocol was also successfully applied to the cycloaddition between **3b** and 1,7-octadiyne to afford **5b** in 96% ee, also in good yield. The ^{31}P NMR spectra of **5a**,**b** both contain two singlets in the region associated with a biaryl diphosphine oxide, and the ^{1}H NMR spectrum of **5a** contains four distinctive well-separated signals between δ 3.82 and 3.70 associated with the two sets of diastereotopic methyl esters, while the diastereotopic protons of the methylene groups in **5b** appear as complex multiplets between δ 1.75 and 2.68. Although these are the first examples of the use of rhodium-catalyzed cycloaddition to prepare biaryl diphosphines, during the course of this study, Tanaka and co-workers reported that a cationic rhodium/(*R*)-SEGPHOS complex catalyzed the [2 + 2 + 2] cycloaddition between internal 2,*n*-diynes and the 1,4-bis(phosphonic acid diethyl ester) of 1,3-butadiyne to afford C_2-symmetric axially chiral biaryl diphosphonates in high yield and excellent enantioselectivity; the absolute configuration of one of these was determined to be *R*.[20]

Reduction of **5a**,**b** was achieved in high yield by heating a THF/toluene solution of the oxide, trichlorosilane, and triethyl phosphite at 100 °C for 5 days to afford the corresponding biaryl diphosphines **6a**,**b**. Even though **6a**,**b** are trisubstituted biaryls and as such are expected to be atropos in nature,[21] it was necessary to demonstrate that the stereochemical integrity of the axial chirality was retained during the reduction. This was achieved by reoxidizing small samples of **6a**,**b** and analyzing the resulting oxides by HPLC against authentic racemic mixtures. In both cases the ee's matched those obtained before reduction, confirming that **6a**,**b** are atropos diphosphines. In addition, the platinum metal complex [(**6a**)Pt{(*S*,*S*)-DPEN}]Cl_2 was isolated as a 98.5:1.5 mixture of diastereoisomers from the reaction between [(**6a**)$PtCl_2$] (**7**) and (*S*,*S*)-DPEN, which is entirely consistent with the enantioselectivity determined by HPLC. The absolute configuration of **6a** has tentatively been assigned as *R* by analysis of the products obtained from the carbonyl-ene reaction between allylbenzene and ethyl trifluo-

(18) Huang, Y.-D.; Yu, H.-T.; Meng, J.-B.; Wang, Y.-M. *Chin. J. Struct. Chem.* **2002**, *149*, 21.
(19) Huang, Y.-D.; Yu, H.-T.; Meng, J.-B.; Metsuura, T.; Wang, Y.-M. *J. Mol. Struct.* **2002**, *610*, 247.
(20) Nishida, G.; Ogaki, S.; Yusa, Y.; Yokozawa, T.; Noguchi, K.; Tanaka, K. *Org. Lett.* **2008**, *10*, 2849.
(21) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384.

ropyruvate catalyzed by [(**6a**)Pt][SbF_6]$_2$ and comparison with those obtained using the corresponding Lewis acid platinum complex of (*R*)-BINAP.[22] Reassuringly, the stereochemistry assigned to (*R*)-**6a** corresponds to the same sense of asymmetric induction obtained for the synthesis of biaryl diphosphonates with Rh/(*R*)-SEGPHOS, which was unequivocally established by single-crystal X-ray crystallography.[20]

In conclusion, [Rh{(*R*)-BINAP}][SbF_6] catalyzes the sequential double [2 + 2 + 2] cycloaddition of 1,4-bis(diphenylphosphinoyl)buta-1,3-diyne with an internal 2,6-diyne followed by its terminal counterpart to afford the corresponding pseudo-C_2-symmetric biaryl diphosphine in good yield and exceptional enantioselectivity. The construction of nonracemic axially chiral biaryl diphosphines from readily available alkyne-based building blocks is a significant development that could provide an advanced methodology for the synthesis of an important class of diphosphine. This approach also offers a number of potential benefits/improvements over existing multistep procedures in that it is operationally straightforward to perform and markedly more atom economical, the biaryl architecture is constructed in high yield via catalytic cycloaddition, which avoids the high-temperature Ullmann couplings often associated with the synthesis of biaryl diphosphines, it does not involve the use of a hazardous secondary phosphine in a Pd/Ni-catalyzed P−C bond forming reaction, and the second rhodium-catalyzed cycloaddition occurs with excellent enantioselectivity, which eliminates the need for resolution. The full potential of this protocol will only be realized if the synthesis can be extended to include atropos C_2-symmetric diphosphines, and studies are currently underway to address this challenge, as well as to explore the range of alkynylphosphines that undergo cycloaddition and obtain the performance data required to undertake a critical and comprehensive evaluation of these diphosphines in a range of asymmetric transformations.

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Supporting Information Available: Full details of experimental procedures and characterization data for all compounds, and for compounds **3a** and **4**, tables and CIF files giving details of crystal data, structure solution and refinement, atomic coordinates, bond distances, bond angles, and anisotropic displacement parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) The carbonyl-ene reaction between allylbenzene and ethyl trifluoropyruvate catalyzed by 10 mol % [(**6a**)Pt][SbF_6]$_2$ in CH_2Cl_2 gave the α-hydroxy ester in 58% ee and with *S* absolute configuration, which corresponds to the stereochemistry obtained with catalysts based on (*R*)-BINAP, (*R*)-SEGPHOS, and (*R*)-NU-BIPHEP[11] and related axially chiral biaryl diphosphines: (a) Mikami, K.; Aikawa, K.; Kainuma, S.; Kawakami, Y.; Saito, T; Sayo, N.; Kumobayashi, H. *Tetrahedron: Asymmetry* **2004**, *15*, 3885. (b) Aikawa, K.; Kainuma, S.; Hatano, M.; Mikami, K. *Tetrahedron Lett.* **2004**, *45*, 183.