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Rhodium-Catalyzed Double [2 + 2 + 2] Cycloaddition of 1,4-Bis(diphenylphosphinoyl)buta-1,3-diyne with Tethered Diynes: A Modular, Highly Versatile Single-Pot Synthesis of NU-BIPHEP Biaryl Diphosphines

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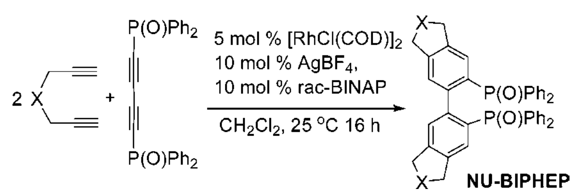
ABSTRACT



Rhodium-catalyzed double [2 + 2 + 2] cycloaddition of 1,4-bis(diphenylphosphinoyl)buta-1,3-diyne with tethered diynes provides a straightforward, single-pot procedure for the synthesis of a new class of *tropos* biaryl diphosphine, NU-BIPHEP. This methodology represents a significant improvement on existing multistep procedures. Enantiopure Lewis acid platinum complexes of these diphosphines are highly efficient catalysts for carbonyl-ene and Diels–Alder reactions, and ruthenium diphosphine-diamine complexes catalyze the asymmetric reduction of ketones to give ee's that rival those obtained with their BINAP counterpart.

Tropos and *atropos* biaryl diphosphines[1] are proving to be a highly versatile and indispensable class of ligand for platinum group metal asymmetric catalysis;[2] recent applications include the ruthenium-catalyzed asymmetric hydrogenation of ketones,[3] as well as numerous Lewis acid-catalyzed transformations such as ene cyclizations,[4] Diels−Alder,[5] hetero Diels−Alder,[6] carbonyl-ene reactions,[7] and Friedel−Crafts alkylations.[8] Phosphines of this type are typically prepared by multistep syntheses involving either a palladium- or nickel-catalyzed cross-coupling between a biaryl ditriflate and a secondary phosphine or Ullmann coupling of a 3-substituted-2-iodophenyl phosphonic acid dialkylester.[1] For use in asymmetric catalysis an *atropos* biaryl diphosphine must be either resolved or prepared from an enantiopure starting material. However, recent developments in enantioselective aryl−aryl cross-coupling method-

(1) *Tropos* meaning turn in Greek, refers to axial chiral conformations that interconvert with a half life of less than 1000 s. *Atropos* (a meaning not in Greek) refers to axial chiral conformations which intercovert with a half life of more than than 1000 s at a given temperature.
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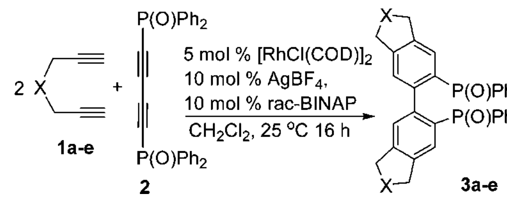
ology could present an alternative strategy for the synthesis of nonracemic biaryl diphosphines, although to date this approach has been limited to the Suzuki−Miyaura coupling of phosphonate-based aryl halides with aryl boronic acids.[9] In the case of *tropos* biaryl-based diphosphines, on-metal resolution and asymmetric activation/deactivation have both proven to be effective strategies for achieving efficient asymmetric catalysis.[10] In addition, *rac*-BINAP and BIPHEP-type diphosphines have also proven to be the ligand of choice for numerous achiral platinum group metal-catalyzed transformations such as iridium/rhodium-catalyzed C−C bond-forming hydrogenations,[11a] chemo- and regioselective intermolecular cyclotrimerization of terminal alkynes,[11b,c] cycloaddition and cycloisomerization of 1,6-enynes,[11d] intramolecular amination of aryl bromides.[11e] and rhodium-catalyzed isomerization of secondary propargylic alcohols,[11f] which further underpins the need to improve the synthesis of this ligand class. Thus, there is likely to be considerable interest in developing a more efficient, cost-effective, straightforward synthesis of biaryl diphosphines, particularly if it is amenable to the preparation of enantiopure derivatives and also enables the level and nature of substitution on the biaryl unit to be varied in a systematic and straighforward manner.

Herein we report a convenient, highly versatile, modular single-pot synthesis of *tropos* biaryl NU-BIPHEP diphosphines via chemoselective rhodium-catalyzed double [2 + 2 + 2] cycloaddition of 1,4-bis(diphenylphosphinoyl)-buta-1,3-diyne with tethered diynes. Platinum complexes of these diphosphines have been resolved, and the resulting enantiopure Lewis acids catalyze the Diels−Alder and carbonyl-ene reactions, giving excellent levels of enantiocontrol. Rhodium- and iridium-catalyzed [2 + 2 + 2] cycloadditions have recently evolved into a highly efficient strategy for the synthesis of axially chiral compounds, chiral spirocyclic structures, and helical polyaryls, with the majority of contributions originating from the research groups of Tanaka[12] and Shibata[13] and more recently Oshima and Yorimitsu.[14] As part of an ongoing program to develop the synthesis of four-carbon bridged *tropos* and *atropos* diphosphines for applications in platinum group asymmetric catalysis,[15] we reasoned that chemoselective double [2 + 2 + 2] cycloaddition between 1,4-bis(diphenylphosphinoyl)-buta-1,3-diyne (**2**) and an appropriate 1,*n*-diyne would afford substituted BIPHEP diphosphine oxides directly in a single-pot transformation. Gratifyingly, addition of 1,7-octadiyne **1a** (2 equiv) and **2** to a dichloromethane solution of the cationic rhodium complex generated by abstraction of chloride from $[RhCl(COD)]_2$ in the presence of *rac*-BINAP resulted in complete consumption of the starting material within 12 h to afford NU-BIPHEP diphosphine oxide **3a** in 95% yield, after purification by column chromatography (eq 1).



(1)

The same rhodium-catalyzed protocol was successfully applied to a range of tethered diynes, including those based on heteroatoms, to give **3a−d** in good to excellent yield as analytically pure off-white solids, after purification by column chromatography (Table 1). In contrast, the corresponding reaction with **1e** resulted in poor conversions (<5%) which we tentatively suggest to be due to competitive homo [2 + 2 + 2] cycloaddition of the 1,*n*-diyne, as previously described.[14] However, a near quantitative yield of **3e** was obtained by slow addition (syringe pump, 6 h) of a dichloromethane solution of **1e** to a catalyst mixture containing **2**. Reduction of the phosphine oxides was achieved in high yield by heating a THF/toluene solution of **3a−e**, trichlorosilane, and triethylphosphite at 100 °C for 48 h to afford the corresponding NU-BIPHEP phosphines **4a−e**.

Table 1. Rhodium-Catalyzed [2 + 2 + 2] Cycloaddition of 1,4-Bis(diphenylphosphinoyl)buta-1,3-diyne with 1,*n*-Diynes[a]

entry	1	X	time (h)	product	yield[b] (%)
1	**1a**	CH_2CH_2	14	**3a**	95
2	**1b**	CH_2	16	**3b**	93
3	**1c**	O	14	**3c**	90
4	**1d**	$C(CO_2Me)_2$	12	**3d**	96
5	**1e**	TsN	18	**3e**	93

[a] Reaction conditions: 5 mol % $[RhCl(COD)]_2$, 10 mol % *rac*-BINAP, 10 mol % $AgBF_4$, **1a−c** (3.6 mmol), **2** (1.5 mmol) in 20 mL of CH_2Cl_2, room temperature. [b] Isolated yield.

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X-ray quality crystals of **4a** were obtained by slow diffusion of a chloroform solution layered with methanol at room temperature, the structure of which is shown in Figure 1.[16]

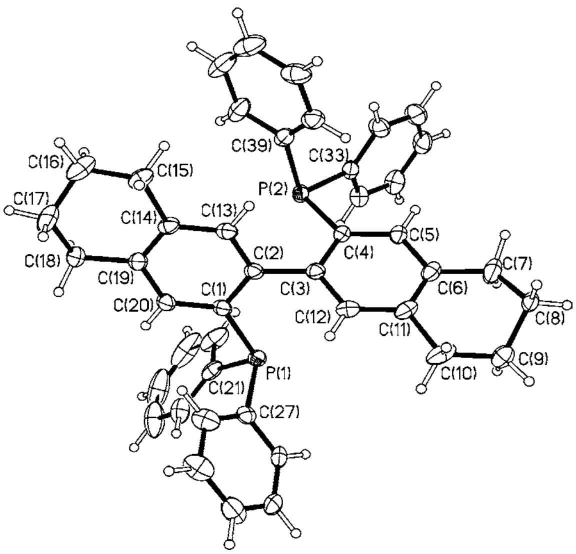
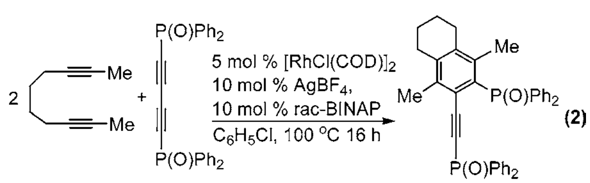


Figure 1. Structure of one of the two crystallographically inequivalent molecules of **4a** with 40% probability ellipsoids.

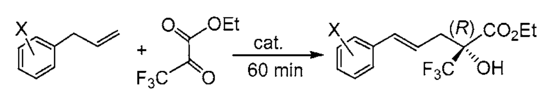
In an attempt to extend this methodology to include the synthesis of highly substituted NU-BIPHEP diphosphines from internal diynes, the reaction between 2,8-decadiyne and **2** was investigated. While there was no evidence for cycloaddition under the same conditions as those used to prepare **3a**−**e** even after 24 h at room temperature, the same reaction in chlorobenzene at 100 °C resulted in selective mono [2 + 2 + 2] cycloaddition to afford **5** in near quantitive yield, based on consumption of **2** (eq 2). The identity of **5** was initially established by a combination of ^{31}P, ^{1}H, and ^{13}C NMR spectropscopy and mass spectrometry and ultimately confirmed by a single-crystal X-ray study. Although this reaction clearly shows that double cycloaddition of internal diynes is a much more challenging transformation, the unreacted alkynyl phosphine oxide in adducts of type **5** could provide an ideal template for the synthesis of unsymmetrical biaryl diphosphines by reaction either with a terminal 1,*n*-diyne or an ynenitrile.



2 5 (2)

In order to evaluate the potential of these new biaryl diphosphines in platinum group metal asymmetric catalysis it was first necessary to identify an appropriate resolution procedure. In this regard, various ligands have emerged as effective resolving agents for platinum group metal complexes of *tropos* diphosphines, including enantiopure BINOL, 2,2′-diaminobinaphthyl (DABN) and its derivatives as well as 1,2-diphenylethylenediamine (DPEN). By analogy with early studies on BIPHEP,[17] we chose to prepare λ- and δ-[(**4a**)Pt{(*S*)-BINOL}] (**7a**) which was initially obtained as a near 1:1 mixture of diastereoisomers from the reaction between *rac*-[(**4a**)$PtCl_2$] (**6a**)[18] and (*S*)-Na_2-BINOLate in THF/toluene (1:1). Thermolysis of a toluene solution of this mixture resulted in diastereointerconversion and near quantitative precipitation of the thermodynamically favored diastereopure δ-[(**4a**)Pt{(*S*)-BINOL}], which was converted into the corresponding enantiopure dichloride δ-**6a**, by treatment of a dichloromethane solution with 2 equiv of HCl. The stereochemistry of δ-**6a** was assigned by analysis of the absolute configurations of the products obtained from the benchmark carbonyl-ene[19] and Diels−Alder reactions described below. In the first of these, the Lewis acid fragment generated by treatment of a dichloromethane solution of δ-**6a** with 2 equiv of silver hexafluoroantimonate catalyzes the carbonyl-ene reaction between a range of allylbenzene derivatives, **8a**−**f**, and ethyl trifluoropyruvate to give the corresponding α-hydroxy esters **9a**−**f** in good yield, complete *E*-selectivity, and exceptionally high enantioselectivity (Table 2). The absolute configuration of α-hydroxy ester **9a** was determined by comparison of the optical rotation with that reported in the literature,[20] and those of **9b**−**f** were assigned by analogy.

Table 2. Asymmetric Carbonyl-ene Reactions Catalyzed by δ-[(**4a**)Pt]$(SbF_6)_2$ in CH_2Cl_2 at Room Temperature[a]



8a-f 9a-f

entry	product	X	conversion (%)	% ee
1	**9a**	H	67	99
2	**9b**	4-Me	63	99
3	**9c**	2-Cl	71	99
4	**9d**	3-Cl	66	99
5	**9e**	4-Cl	60	>99
6[b]	**9f**	4-NO_2	98	99

[a] Reaction conditions: 5 mol % catalyst, allylbenzene (0.4 mmol), ethyl trifluoropyruvate (0.6 mmol) in 2.0 mL of CH_2Cl_2. [b] 24 h.

(16) Full details of the single-crystal X-ray analysis of **4a** are given in the Supporting Information.

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(18) Full details of the single-crystal X-ray analysis of *rac*-**6a** are given in the Supporting Information.

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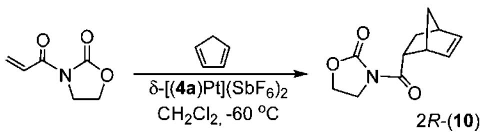
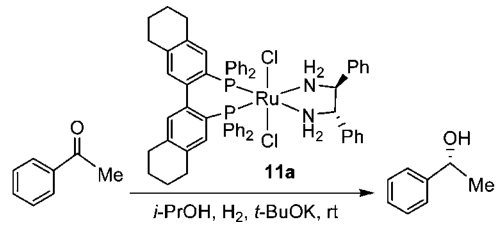
The same Lewis acid also catalyzes the Diels−Alder reaction between *N*-acryloyl-oxazolidinone and cyclopentadiene (eq 3) to afford cycloadduct 2*R*-(**10**) with high *endo* selectivity (93:7 *endo*:*exo*) and excellent endo enantioselectivity (99%). The absolute configuration of the products obtained from these benchmark reactions is the same as that obtained with (*S*)-BINAP and its derivatives, which was used as the basis for the assignment of a δ, *S*-like, stereochemistry to enantiopure **6a** (vide supra). Catalyst reaction mixtures were routinely quenched immediately prior to workup by addition of 1 equiv of (*S*,*S*)-DPEN. In each case the ^{31}P NMR spectrum showed the presence of a single diastereisomer ($^{1}J_{\mathrm{Pt-P}}$ = 3453 Hz), confirming that the stereochemical integrity of the Lewis acid remains intact under the reaction conditions.



(3)

Biaryl diphosphines have also been widely investigated for the ruthenium-catalyzed asymmetric hydrogenation of ketones,[21] which prompted us to investigate the efficiency of these new ligands in this transformation. A preliminary study revealed that the 1:1 diastereoisomeric mixture of [$RuCl_2$(**4a**){(*S*,*S*)-DPEN}] (**11a**) forms a highly active catalyst for the asymmetric hydrogenation of acetophenone (0.1 mol % catalyst, >99% conversion in 12 h), giving the corresponding alcohol with *R* absolute configuration in 58% ee (eq 4), a significant improvement on that of 46% obtained with the corresponding catalyst based on *rac*-BINAP and (*S*,*S*)-DPEN.[21]

In conclusion, [2 + 2 + 2] cycloaddition of 1,4-bis(diphenylphosphinoyl)buta-1,3-diyne with 1,*n*-diynes provides a versatile single-pot synthesis of NU-BIPHEP biaryl



(4)

diphosphines with a variety of substitution patterns and functionalities. This highly modular synthesis overcomes many of the limitations associated with the conventional methods of preparation such as the palladium- and nickel-catalyzed phosphination, which can result in monosubstitution, and low-yielding bromination−lithiation procedures. Studies are currently underway to explore the range of alkynylphosphines that undergo double [2 + 2 + 2] cycloaddition, develop this methodology to include the enantioselective synthesis of chiral NU-BIPHEP diphosphines from internal 1,*n*-diynes, prepare unsymmetrical derivatives, and to determine whether cycloaddition occurs via a seven-membered metalacycloheptatriene or a metalanorbornene intermediate.[22]

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Supporting Information Available: Experimental details and characterization data for compounds **3a**−**e**, **4a**−**e**, **5**, **6a**, **7a**, **9b**−**f**, and **11a**, details of catalyst testing, and for compounds **4a** and *rac*-**6a** details of crystal data, structure solution and refinement, atomic coordinates, bond distances and angles and anisotropic displacement parameters in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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