COMMUNICATION

JoyaPhos: An Atropisomeric Teraryl Monophosphine Ligand

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Abstract: A topologically well-defined atropisomeric teraryl monophosphine ligand system, prepared by a highly stereoselective arene-forming aldol condensation combined with a direct ester-to-anthracene transformation, is described herein. The ligands were evaluated for gold(I)-catalyzed [2+2] cycloaddition and cycloisomerization reactions as well as a unique intramolecular Pd-catalyzed C-N cross-coupling for the atroposelective synthesis of a *N*-arylindoline bearing a C-N stereogenic axis. The ligand structure induced up to 95:5 stereoselectivity in the asymmetric allylic alkylation reaction and features an interesting dynamic behavior as observed by X-ray crystallographic studies.

Introduction

A crucial requirement for ligands suitable for stereoselective, catalyst-controlled processes, is to organize the reactants within the coordination sphere of the metal in a spatially well-defined environment. An attractive but challenging setting is represented by Au(I) catalysts, whose linear coordination places the substrate opposite to the ancillary ligand, rendering enantioinduction particularly demanding.[1] Since the discovery of BINAP, atropisomeric binaphthyl bis- and monophosphines with their remarkably suitable topology, have become privileged scaffolds as supporting ligands in homogeneous catalysis, both in industry and academia.[2–4] While commonly obtained from inexpensive BINOL and successfully utilized in a vast number of transition metal catalyzed transformations, the binaphthyl core also presents several limitations when further tunability is required.[5] Higher structural variability is often achieved at the cost of tedious functionalizations, especially when accessing monophosphines with a binaphthyl skeleton as a core motif. Monodentate phosphorous ligands differ from their bidentate counterparts in many aspects, particularly as they allow the metal center to be coordinatively unsaturated in order to catalyze reactions that would otherwise be unfavored.[6–9] Methods for the *de novo* synthesis of monophosphines with increased structural variability are therefore highly desirable, particularly if a compact ligand design becomes feasible by straightforward and operationally simple synthetic approaches.

Based on our earlier work on the stereoselective construction of aromatic structures by catalytic aldol condensation reactions,[10] we thus synthesized atropisomeric teraryl ligands featuring a rotationally restricted *ortho*-substituted phenyl-naphthyl-anthracenyl scaffold, which we named JoyaPhos. Their activity and selectivity were evaluated by gold(I)-catalyzed enyne cycloisomerization and [2+2] cycloaddition of a terminal alkyne using methylstyrene. The atropisomeric ligands were also assessed in an atroposelective Pd-catalyzed C-N cross-coupling for the formation of *N*-arylindolines and a Pd-catalyzed asymmetric allylic alkylation (AAA), the latter serving to benchmark the ligands' capability to control stereocenter configuration using palladium catalysis. The synthesis of JoyaPhos ligands was envisaged by employing a *de novo* construction of the naphthalene core, followed by the installation of the side anthracenyl substituent, and a modular installation of phosphine moieties with distinct properties (Figure 1a). We thereby envisioned that the introduction of an all-carbon aromatic shielding group would differentiate JoyaPhos from commonly used chiral biaryl monophosphines, where oxygen or nitrogen substituents typically impact the electronic and steric properties of the ligand (Figure 1b).

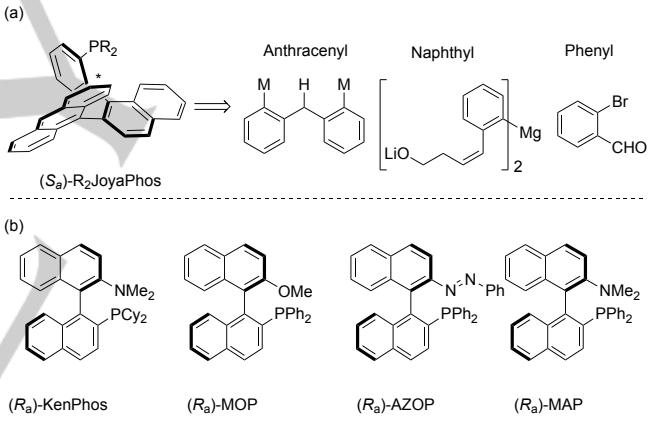
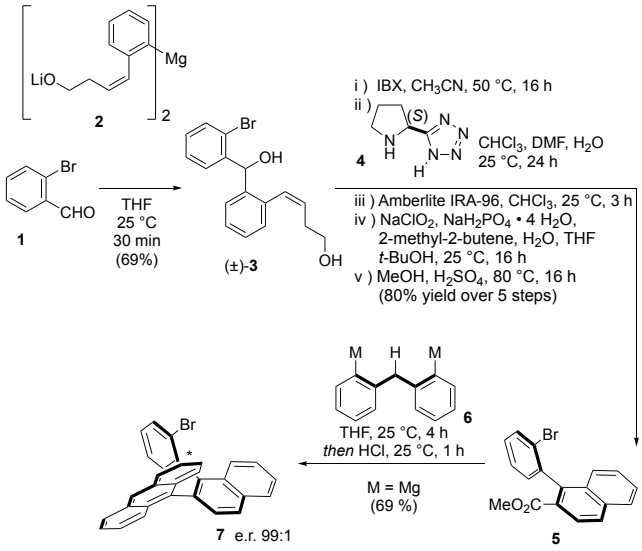


Figure 1. (**a**) Synthetic approach for JoyaPhos ligands by the *de novo* construction of the naphthyl backbone by a stereoselective aldol condensation. (**b**) Atropisomeric binaphthyl monophosphines commonly feature an oxygen- or nitrogen-containing functionality at the 2'-naphthyl position.

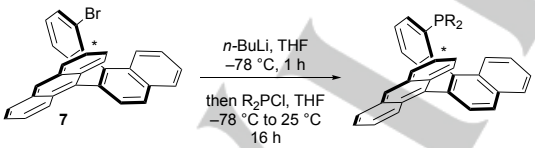
Results and Discussion

The synthesis of the ligands began with the addition of metalated building block **2**[10b,10c] to 2-bromobenzaldehyde **1**, affording the corresponding diol (±)-**3** in 69% yield (Scheme 1). An ensuing double oxidation with IBX yields the ketoaldehyde intermediate, which is a suitable starting material for the stereoselective aldol addition that occurs in presence of tetrazole-derived catalyst **4**. A subsequent arene-formation is readily achieved by treatment with Amberlite IRA-96, yielding the atropisomeric naphthaldehyde intermediate. The aldehyde functionality was next converted to a carboxylic acid by a Lindgren-Kraus oxidation and a subsequent esterification at 80°C (16 h) delivered the corresponding methyl ester **5** in 80% overall yield over five expeditious steps.



Scheme 1. Synthesis of the ligand backbone via a stereoselective aldol condensation and direct ester-to-arene transformation from inexpensive 2-bromobenzaldehyde.

With the ester functionality established on the naphthalene moiety, we employed a methodology developed in our group for the direct conversion of esters to arenes.[11] The introduction of the anthracenyl functionality by using the corresponding bifunctional organomagnesium reagent **6** thereby represents a chain termination strategy for the oligo-1,2-arylene synthesis,[10b] which smoothly delivers the halogenated intermediate **7** in 69% yield with 99:1 enantiomeric purity. The obtained anthracenyl-naphthyl-phenyl bromide **7** suitably serves as precursor for the atropisomeric monodentate diarylteraryl- and dialkylteraryl-phosphines with different steric and electronic properties. Halogen-metal exchange of the brominated substrate, followed by treatment of the lithiated species with the corresponding chlorophosphine, hence delivered the teraryl phosphines **8**, **9** and **10** as white solids after crystallization from MeOH in satisfactory yields (Scheme 2).



Scheme 2. Divergent installation of different phosphine moieties via halogen-metal exchange and nucleophilic addition to the corresponding chlorophosphine.

X-Ray analyses of **8** and **9** (Figure 2) highlight the structurally defined scaffold of JoyaPhos with the sterically protected phosphine moiety, providing sufficient inertness towards molecular oxygen.[12] The ligands can therefore be handled and stored on the bench at ambient temperature over extended periods of time without the need of inert conditions.

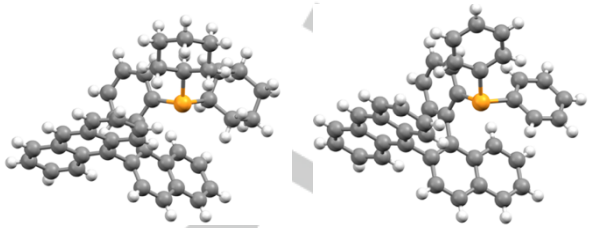
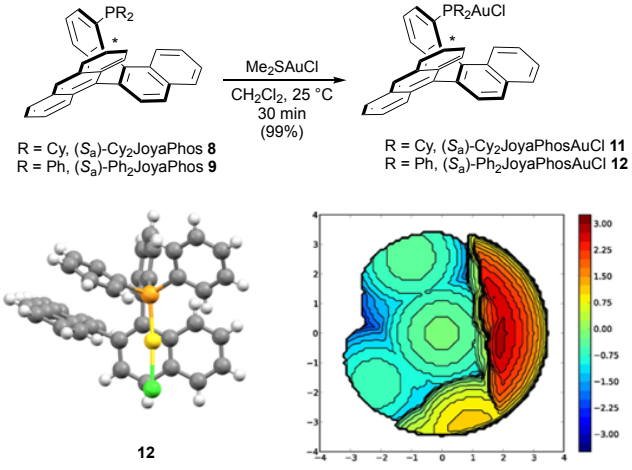


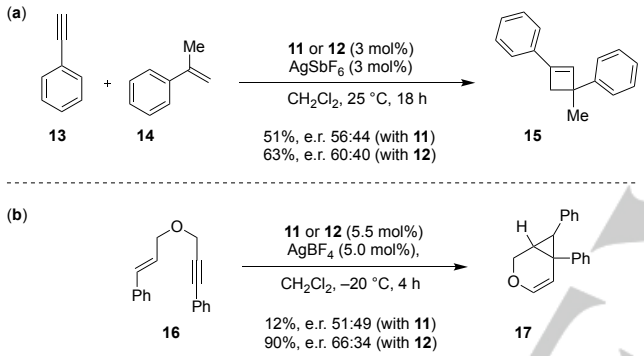
Figure 2. The X-ray structures of (S_a)-Cy$_2$JoyaPhos **8** (left) and (S_a)-Ph$_2$JoyaPhos **9** (right) highlight the P atom orienting the lone pair into the pocket defined by the scaffold, preventing oxidation by atmospheric oxygen. (±)-**8** was utilized to obtain single crystals suitable for X-ray crystallographic analysis (structure of (R_a)-**8** is omitted for clarity).

Given the topological features of JoyaPhos, we hypothesized that its well-defined structure and configurational stability might be suitable to accommodate the linear coordinating gold(I), creating the appropriate ligand environment for enantioselective catalysis. (S_a)-Ph$_2$JoyaPhos and (S_a)-Cy$_2$JoyaPhos were consequently treated with Me$_2$SAuCl in CH$_2$Cl$_2$ at 25 °C for 30 minutes to obtain the corresponding Au(I) complexes in quantitative yields (Scheme 3, top). Gratifyingly, the X-ray crystallographic analysis of (S_a)-Ph$_2$JoyaPhosAuCl **11** confirmed the short distances between the gold center and the naphthyl face as well as the anthracenyl edge (Scheme 3, bottom left).[1a] With a P-Au bond length of 2.24 Å and as highlighted by the steric map[13] (Scheme 3, bottom right), the substituents on the phosphorous provide hindrance on the upper part of the scaffold, whereas the naphthyl and anthracenyl moiety shield the back and lateral part of the metal center. Overall, a sterically demanding ligand, with a differentiated quadrant occupation and a buried volume of 52% was observed for (S_a)-Ph$_2$JoyaPhos **11**, providing a ligand distinct from previous structures.[14] The activity and selectivity of the newly formed gold complexes were next tested by the [2+2] cycloaddition of phenylacetylene **13** with α-methylstyrene **14** and the cycloisomerization of enyne **16** (Scheme 4). After generating



Scheme 3. Synthesis of (S_a)-Cy$_2$JoyaPhosAuCl **11** and (S_a)-Ph$_2$JoyaPhosAuCl **12** (top). As shown by the X-Ray structure of (S_a)-Ph$_2$JoyaPhosAuCl **12** (bottom left), the Au atom is accommodated in a well-defined ligand structure. The steric profile corresponds to a buried volume of 52% (bottom right).[13]

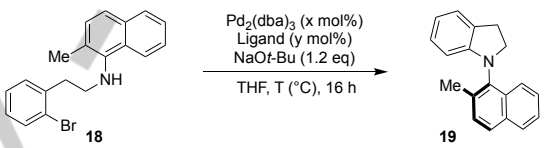
active cationic Au(I) catalysts with $AgSbF_6$, (S_a)-Cy_2JoyaPhos-AuCl **11** provided the corresponding cyclobutene **15** in 51% yield and 56:44 e.r., whereas (S_a)-Ph_2JoyaPhosAuCl **12** delivered the cycloaddition product in slightly higher yield and selectivity (63% yield, 60:40 e.r.). Interestingly, (S_a)-Ph_2JoyaPhos **12** provided a markedly improved yield in the cycloisomerization of enyne **16**, delivering the cycloisomerization product **17** in 66:34 e.r. (90% yield), whereas (S_a)-Cy_2JoyaPhos **11** gave only 12% of the desired product with an e.r. of 51:49. The observed selectivity trends therefore suggest that the smaller steric bulk of the phenyl groups of (S_a)-Ph_2JoyaPhos **12** might reduce both the front and back strain,[15] whereas the cyclohexyl substituents could lead to an elongated P-Au bond of the linear complex, placing the reactants farther away from the environment, thus affecting stereoinduction. Therefore, further functionalization of the backbone towards the incoming substrates, together with the suitable choice of phosphine substituents, might improve the stereoselectivity for gold-catalyzed processes[1] using JoyaPhos ligands.



Scheme 4. (**a**) Gold(I)-catalyzed [2+2] cycloaddition of phenylacetylene **13** with methylstyrene **14**. (**b**) Gold(I)-catalyzed cycloisomerization of enyne **16**.

To further evaluate the present ligand generation beyond gold catalysis, we next investigated the activity and selectivity with Pd(0), which adopts a square planar geometry in its catalytic cycle. Since electron rich dialkylbiaryl and dialkylteraryl mono-phosphines are routinely employed to catalyze a variety of transformations for the construction of C-O, C-B, C-C, C-F and in particular of C-N bonds,[16–19] we became interested in exploring a unique atroposelective C-N cross-coupling of indolines bearing a C-N stereogenic axis. Atropisomers with rotationally restricted C-N bonds are potential targets or intermediates for the synthesis of biologically active molecules, such as compounds of medicinal interest or pest-control agents.[20–22] Synthetic methodologies to control C-N stereogenic axes employing cross-coupling strategies are therefore currently investigated utilizing several notably elegant approaches.[23–27] While the inherent steric bulk of the JoyaPhos ligand would favor the formation of catalytically active monoligated LPd(0) species,[28] the naphthyl backbone and the side anthracenyl group likely prevent cyclometalative pathways that often result in a decreased catalytic activity.[29] *N*-Alkylaniline **18** was thus subjected to an intramolecular Buchwald-Hartwig amination reaction in presence of $Pd_2(dba)_3$, (S_a)-Cy_2JoyaPhos **8** and NaO*t*-Bu in THF at 85 °C, affording the atropisomeric indoline **19** with a conversion of 40% after 16 h and an enantiomeric ratio of 56:44 (Table 1, entry 1). The activity and selectivity of (S_a)-Cy_2JoyaPhos **8** were next compared to Josiphos SL-J003-1 (Entry 2, 40%, 47:53 e.r.) and SL-J009-1 (Entry 3, 10%, 50:50 e.r.). A conversion of 10% and an e.r. of 52:48 was observed with the monodentate binaphthyl phosphine (R_a)-MOP (Entry 4) and with (S_a)-SEGPHOS, no conversion could be detected (Entry 5). After optimization of the reaction conditions, (S_a)-Cy_2JoyaPhos **8** delivered the atropisomeric indoline in 82% isolated yield, with an increased e.r. of 65:35 (Entry 6). Employing (S_a)-Ph_2JoyaPhos **9** was inconsequential for the selectivity (Entry 7) but interestingly, an inverted sense of enantioselectivity was found with the fluorinated (S_a)-(3,5-CF_3Ph)$_2$JoyaPhos **10** (Entry 8). In order to exclude the possibility of racemization over the course of the reaction, an enantiomerically pure sample of **19** was heated in THF for 16 h at 100 °C. As the enantioenrichment was not impacted indicates that the *N*-arylindoline **19** is configurationally stable under the reaction conditions.

Table 1. Atroposelective synthesis of *N*-arylindolines via Pd-catalyzed C-N cross-coupling using ligands **8**, **9** and **10**.

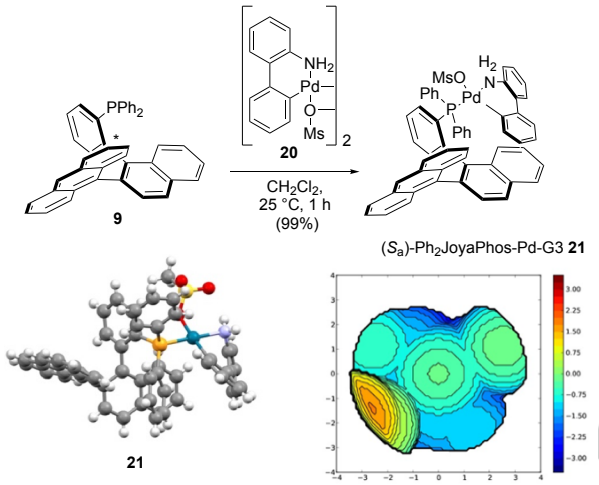


Entry	$Pd_2(dba)_3$ (mol%)	Ligand	T (°C)	Conversion %	e.r.[a]
1	1	**8** (3 mol%)	85	40	56:44
2	1	Josiphos SL-J003-1 (3 mol%)	85	40	47:53
3	1	Josiphos SL-J009-1 (3 mol%)	85	10	50:50
4	1	(R_a)-MOP (3 mol%)	85	10	52:48
5	1	(S_a)-SEGPHOS (3 mol%)	85	<1	-
6	2.5	**8** (12 mol%)	45	82[b]	65:35
7	2.5	**9** (12 mol%)	45	99	65:35
8	2.5	**10** (12 mol%)	45	99	35:65

[a] The enantiomeric ratios were determined using a *Chiralcel OJ-H* column (1.0 mLmin^{-1}, *n*-heptane:*i*-PrOH = 90:10). t_{R1} = 7.0 min and t_{R2} = 12.0 min. [b] Isolated yield.

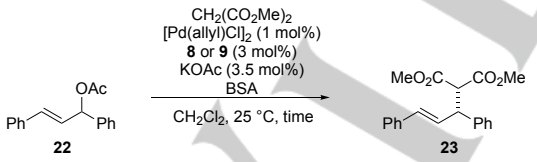
To better understand the unsatisfactory stereoselectivity for the atroposelective synthesis of *N*-arylindoline **19**, we synthesized the corresponding (S_a)-Ph_2JoyaPhos-Pd-G3 precatalyst **21** (Scheme 5),[30] which resembles the oxidative addition complex of the reaction in Table 1. A secondary Pd-arene interaction with the

lower ring, which would orient the metal within the ligand sphere, was not observed.[31–33] Instead, a rotation about the C-P bond places the coupling partners towards the outer sphere of the ligand, resulting in a buried volume of 37% and a P-Pd bond length of 2.27 Å. The rigidity of the ligand and the consequential repulsive interactions with bulky substrates such as **18** might hinder structural reorganizations that favor attractive non-covalent interactions. The ligand's flexibility that minimizes repulsive and maximizes attractive interactions for an optimal enantioinduction,[34,35] is therefore strongly impacted in the case of atroposelective C-N cross-coupling reactions, which require a high degree of substitution for sufficient configurational stability of the products.



Scheme 5. Synthesis of (S_a)-Ph$_2$JoyaPhos-Pd-G3 precatalyst **21** (top), X-ray structure of **21** (bottom left), showing the rotation about the C-P bond and the resulting steric map with a buried volume of 37% (bottom right).[13]

A high degree of enantioinduction was accordingly observed in the benchmarking asymmetric allylic alkylation reaction (AAA) of (*E*)-1,3-diphenylallyl acetate **22** with dimethyl malonate under standard conditions (Scheme 6).[36] (S_a)-Ph$_2$JoyaPhos **8** provided the alkylation product after 1 h at ambient temperature in 99% yield and 95:5 e.r., while (S_a)-Cy$_2$JoyaPhos **9** required 4 h reaction time for a comparable enantiomeric ratio of 93:7.[37]



Scheme 6. Pd-catalyzed asymmetric allylic alkylation of (*E*)-1,3-diphenylallyl acetate **22** with dimethyl malonate.

Conclusion

Three topologically well-defined atropisomeric ligands were efficiently prepared in high yields and selectivity using an atroposelective aldol condensation combined with a direct ester-to-antracene transformation with a suitable bifunctional organo-magnesium reagent. The ligands were structurally examined[38] and their catalytic performance tested for two gold(I)- and two Pd(0)-catalyzed reactions. It was observed that further extension of the ligand backbone is required for Au(I) catalysis and that high enantioselectivity is induced by the ligands in benchmarking palladium-catalyzed AAA reactions which allow the required structural arrangement of the ligands. We currently explore methods enabled by the unique structure of the atropisomeric teraryl monophosphine ligands and the modular synthesis of extended and specifically suited ligand structures using the straightforward synthetic approach presented herein.

Acknowledgements

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Keywords: Atroposelective synthesis • C-N cross-coupling • Gold catalysis • Monophosphine ligands • Palladium catalysis

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[37] These selectivities further indicate the high enantiomeric purity of the ligands, as based on an expected linear correlation.
[38] CCDC 1989919 ((*Sa*)-**9**), 1989920 ((*Sa*)-**21**), 1989921 ((±)-**8**) and 1989922 ((*Sa*)-**12**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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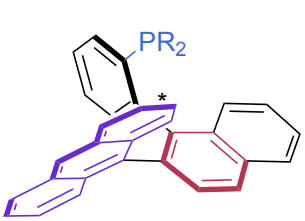

- Direct Ester to Arene Transformation
- Stereoselective Arene-Forming Aldol Condensation
- Modular Introduction of Dialkyl or Diaryl Phosphine Residues

JoyaPhos: A new atropisomeric monophosphine (JoyaPhos) was prepared by the sequential *de novo* introduction of aromatic units, resulting in a configurationally stable teraryl structure with a well-defined topology. The ligand scaffold differs from canonical binaphthyl structures and can accommodate transition metals in a dense ligand sphere, suitable for stereoselective transformations.

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