

Design, Synthesis and Application of Novel Chiral C₂-symmetric Spiroketal-containing Ligands in Transition Metal Catalysis**

Alonso J. Argüelles, Siyuan Sun, Brenna G. Budaitis, and Pavel Nagorny*

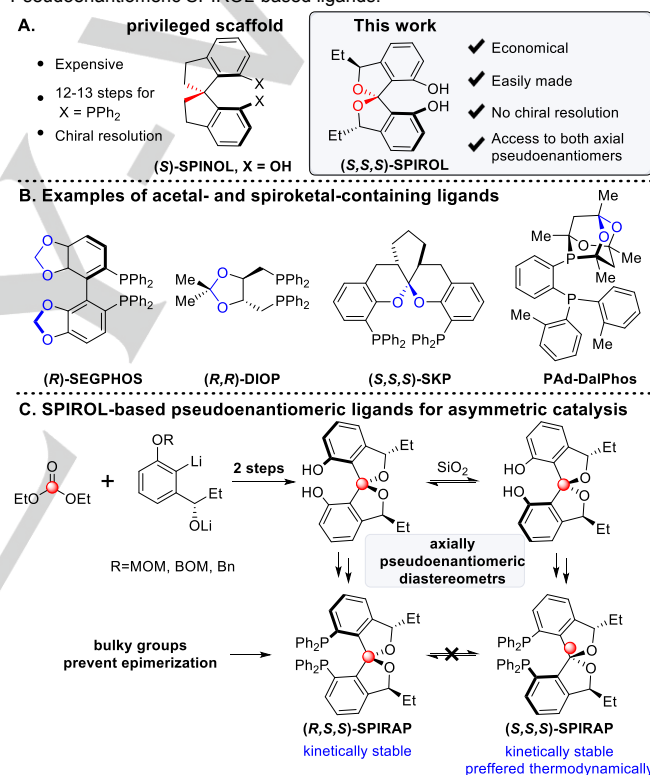
Abstract: We present an expedient and economical route to a new spiroketal-based C₂-symmetric chiral scaffold termed SPIROL. Based on this spirocyclic scaffold, several chiral ligands were generated and successfully employed in an array of stereoselective transformations including Ir-catalyzed hydroarylation (up to 95% ee), Pd-catalyzed allylic alkylation (up to 97% ee), intermolecular Pd-catalyzed Heck reaction (up to 95% ee), and Rh-catalyzed hydrogenations of dehydroalanine (up to 93% ee).

Asymmetric transition metal catalysis is one of the most practical and powerful tools to achieve stereocontrol.^[1] Its successful application heavily relies both on the powerful and enabling chemistry of transition metals and the versatility of chiral organic ligands to access stereoselective transformations. The generality and utility of this mode of activation has stressed the need for a wide variety of structurally diverse chiral ligands in order to fine-tune the stereocontrol in these reactions. Since the popularization of BINAP, chiral phosphine ligands have dominated the field of asymmetric transition metal catalysis,^[2,3] and organic chemists have strived to provide alternative chiral backbones with superior performance in catalysis.^[4] SPINOL-derived ligands, such as SDPs,^[5] have been used with great results in the past decades (Fig 1A, left).^[6] Although their performance is notable, high prices and tedious preparation pose severe limitations to the application of these ligands. The recent efforts of Tan and coworkers focused on addressing some of these problems by developing an optimized synthesis of SPINOL.^[7] However, this approach still suffers from the obligatory use of SPINOL-derived phosphoric acids that are expensive and commercially unavailable on a large scale.

Based on our prior work on the asymmetric formation of axially chiral spiroketals,^[8] we proposed a new easily accessible spiroketal-based C₂-symmetric chiral scaffold termed SPIROL (Fig 1A, right). While a spiroketal moiety is typically labile under strongly acidic conditions, the majority of the transition metal-catalyzed reactions are not carried out under highly acidic conditions. Due to these reasons as well as their high accessibility, acetal^[9] and spiroketal-containing^[10] ligands have proven to be of great value in asymmetric catalysis (Fig 1B). We surmised that the introduction of bulky 7,7'-substituents such as PPh₂, would render the both axial pseudoenantiomeric diastereomers kinetically stable under a variety of conditions (Fig. C). Moreover, the additional stereocenters at the benzylic 3,3'-positions would prevent the epimerization of the more stable (S,S,S)-diastereomer ($\Delta G^\circ = 2.3$ kcal/mol for SPIRAP) even under equilibrating conditions. This work describes the development of a novel reliable dimerizative condensation that enables rapid access to chiral SPIROL on large scale, and the

application of SPIROL-based ligands in various Pd-, Ir-, and Rh-catalyzed asymmetric reactions. These results along with the computational studies suggest that (S,S,S)-diastereomers are structurally and electronically similar to SPINOL-based ligands, whereas their axial pseudoenantiomeric, (R,S,S)-diastereomers represent a structurally different scaffold. We believe that these features coupled with the ease of preparation and higher level of tunability make SPIROL ligands of great value to asymmetric catalysis.

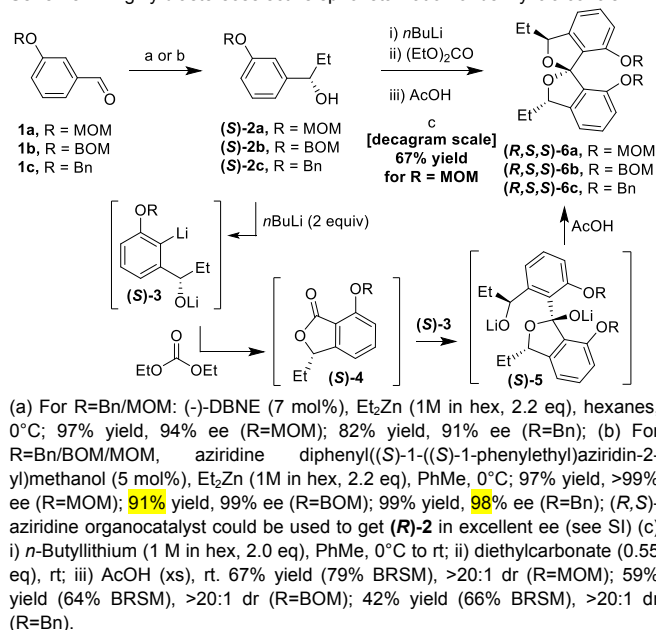
Figure 1. A. Privileged SPINOL scaffold (left) and our proposed scaffold (right). B. Acetal and spiroketal-containing commercial phosphine ligands. C. Pseudoenantiomeric SPIROL-based ligands.



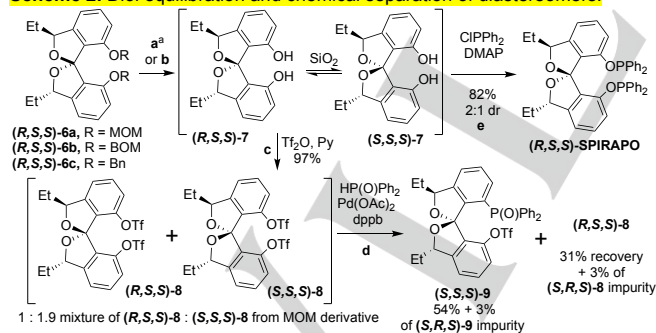
Our studies commenced with a highly enantioselective alkylation of protected 3-hydroxybenzaldehyde **1** (Scheme 1). Although commercially available DBNE could be used to catalyze a highly enantioselective additions to different protected aldehydes (R=MOM, BOM, Bn),^[11] readily available aziridine-based organocatalysts could also be used to attain the desired products **2** in a practically enantiopure form (*cf.* SI).^[12] The treatment of the resulting alcohol **2** with two equivalents of *n*-butyl lithium in toluene regioselectively afforded the dilithiated species **3** (*cf.* SI), which is then captured by diethyl carbonate to produce the desired spiroketal **6** in good yields and excellent diastereoselectivity. This transformation is proposed to proceed through the intermediacy of isobenzofuranone **4**, and then adduct **5** that subsequently collapses to **6** upon treatment with acetic acid. This unprecedented dimerization could be carried on a decagram scale and provides quick means for accessing protected SPIROL.

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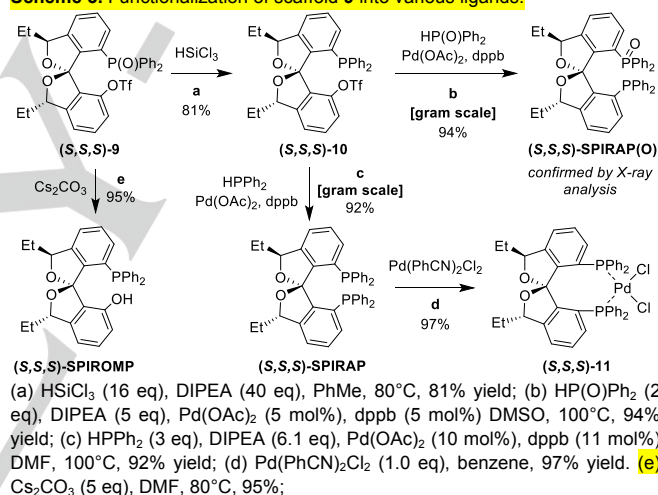
Scheme 1. Highly diastereoselective spiroketalization of benzylic alcohols 2.

Computational studies^[13] showed that the pseudoenantiomeric diol diastereomers (R,S,S)-7 and (S,S,S)-7 had near equal gas-phase energy (1.0 kcal/mol difference, favoring (S,S,S)-7), and we therefore surmised that we would be able to equilibrate them under mildly acidic conditions to obtain majorly (S,S,S)-7, or suppress the epimerization to favor (R,S,S)-7. To our delight, the deprotection of substrates 6a–c could be carried out with excellent yields and moderate selectivities for either diastereomer of SPIROL scaffold 7 (1:3.8 d.r. favoring (R,S,S)-7 to 1.9:1 favoring (S,S,S)-7, Scheme 2, cf. SI). During the acid deprotection of (R,S,S)-6a or (R,S,S)-6b, a small amount of undesired (S,R,S)-7 diol was also formed (~6% for R=MOM). The mixture of diastereomers were not separated at this stage as they were not configurationally stable and was converted to the corresponding configurationally stable ditriflates (R,S,S)-8 and (S,S,S)-8.

Scheme 2. Diol equilibration and chemical separation of diastereomers.

(a) AcCl (2 eq), MeOH, 0°C to rt; for R=MOM: 91% yield, 3.8:1 or 1:1.9 dr depending on conditions, + 6% (S,R,S)-8 impurity; for R=BOM, 87% yield, 1:1.3 dr, + 10% (S,R,S)-8 impurity, (b) For R=Bn, H₂ (balloon), NaHCO₃ (9 eq), MeOH, rt; 94% yield, 1:6.9 dr; (c) Tf₂O (2.4 eq), pyridine (5.3 eq), DCM, 0°C to rt; 97% yield, with conserved dr; (d) HP(O)Ph₂ (0.9 eq), Pd(OAc)₂ (4.1 mol%), dppb (4.1 mol%), DIPEA (2.3 eq), DMSO, 80°C. For 1:1.9 dr mixture with 6% (S,R,S)-8 impurity: 54% yield of (S,S,S)-9, with 3% of (S,R,S)-9; and 31% recovery of (R,S,S)-8 with 3% (S,R,S)-8 impurity. ⁹(R,S,S)-7 is the major diastereomer that is initially formed; however, a prolonged exposure to acids, including SiO₂, results in epimerization leading to (S,S,S)-7 as the major diastereomer (cf. SI). (e) PPh₂Cl (2.5 eq), DMAP (0.1 eq) NEt₃ (4 eq), DCM, 82% yield over 2 steps, 2:1 dr favoring (R,S,S)-SPIRAPO.

Despite their close R_f values, the ditriflates could be separated by the conventional chromatographic techniques. However, we have also identified a more convenient for the larger scale purification method that takes advantage of the difference in reactivity between these species. Thus, the mixture of ditriflates was subjected to a Pd-catalyzed coupling with diphenylphosphine oxide at 80°C. We observed that, at this temperature, (S,S,S)-8 diastereomer reacted in excellent yield to form (S,S,S)-9, while (R,S,S)-8 diastereomer was recovered almost quantitatively. The (S,R,S)-8 impurity reacted partially but was easily removed by recrystallization from cyclohexane. Afterwards, we were able to elaborate the triflate/phosphine oxide (S,S,S)-9 to the respective diphosphine. A reduction with trichlorosilane afforded triflate/phosphine (S,S,S)-10, which was then subjected to a second coupling with diphenyl phosphine oxide to obtain phosphine oxide/phosphine (S,S,S)-SPIRAP(O), the structure of which was confirmed by X-ray crystallography. In addition, a direct coupling of the phosphine/triflate (S,S,S)-10 with diphenyl phosphine provided (S,S,S)-SPIRAP in excellent yields (Scheme 3).

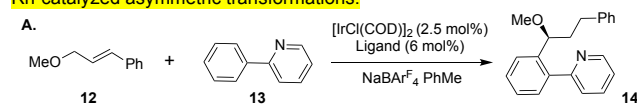
Scheme 3. Functionalization of scaffold 9 into various ligands.

In line with the aforementioned studies, the recovered ditriflate (R,S,S)-8 was recrystallized from cyclohexane and reacted in good yields with diphenyl phosphine oxide in similar coupling conditions, albeit at 100°C, to provide pure (R,S,S)-9, which was likewise elaborated to (R,S,S)-SPIRAP(O) and (R,S,S)-SPIRAP in good yields. The absolute stereochemistry of (S,R,R)-SPIRAP(O) obtained by an identical route using (R)-2a was confirmed by X-ray crystallography (cf. SI). All of the intermediates towards (R,S,S)-SPIRAP were found to be configurationally stable, which leads us to believe that epimerization is mostly impeded for steric reasons. In addition, other ligands such as diphosphinite (R,S,S)-SPIRAPO (Scheme 2) and catalysts such as (S,S,S)-SPIROMP as well PdCl₂ complexes 11 (Scheme 3) were conveniently generated. The SPIRAPO was obtained as a separable by chromatography 2:1 mixture of (R,S,S)- and (S,S,S)- diastereomers (82% yield), which is reflective of the dr of the initially used mixture of isomers 7.

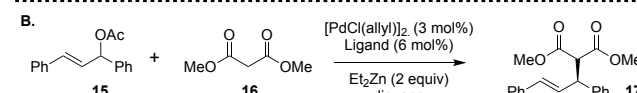
The ligands synthesized above were then tested in various reported asymmetric catalysis applications (cf. Scheme 4). We were pleased to find that (S,S,S)-SPIRAP is an exceptional

ligand in the Ir-catalyzed hydroarylation of methylated cinnamyl alcohol **12** and 2-phenyl pyridine **13**, which provided better enantiocontrol (entry 5) than the BINAP- (entries 1 and 3) and SEGPHOS-based

Scheme 4. Application of SPIRAP, SPIRAP(O), and SPIRAPO in Ir-, Pd- and Rh-catalyzed asymmetric transformations.



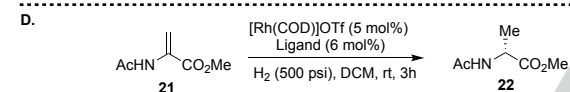
entry	ligand	temperature (°C)	yield (%)	ee (%)
1	(R)-BINAP	80	84	88
2	(R)-SEGPHOS	80	7	81
3	(R)-3,5-Xyl-BINAP	80	87	94
4	(R)-SDP	70	82	94
5	(S,S,S)-SPIRAP	70	91	95
6	(R,S,S)-SPIRAP	70	N.R.	–



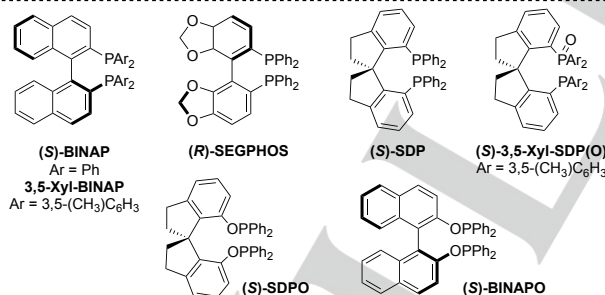
entry	ligand	yield (%)	ee (%)
7	(S)-SDP	97	97
8	(S,S,S)-SPIRAP	94	97
9	(R,S,S)-SPIRAP	98	-88



entry	ligand	yield (%)	ee (%)
10	(R)-3,5-Xyl-SDP(O)	96	99
11	(S,S,S)-SPIRAP(O)	99	-94
12	(R,S,S)-SPIRAP(O)	96	89



entry	ligand	yield (%)	ee (%)
13	(S)-BINAPO	84	89
14	(S)-SDPO	85	-93
15	(S,R,R)-SPIRAPO	87	-90
16	(R,R,R)-SPIRAPO	85	93



A) [IrCl(COD)]₂ (2.5 mol%), ligand (6 mol%), NaBARF₄ (10 mol%), 2-phenylpyridine (1.07 eq), PhMe; B) [PdCl(allyl)]₂ (2.5 mol%), Ligand (6 mol%), dimethyl malonate (2 eq), Et₂Zn (2 eq), rt, 1,4-dioxane; C) Pd(dba)₂ (2.5 mol%), ligand (3 mol%), norbornene (4 eq), DIPEA (2 eq), 1,4-dioxane, 70°C D) [Rh(COD)]OTf (5.0 mol%), ligand (6.0 mol%), H₂ (500 psi), DCM, rt.

(entry 2) ligands recently explored by the Nishimura group (Scheme 6A).^[14] Interestingly, its diastereomer, (R,S,S)-SPIRAP was not a viable ligand for this reaction, and no product was detected (entry 6). Similarly, excellent performance of (S,S,S)-SPIRAP was observed in the Pd-catalyzed allylic alkylation of chalcone derivative **15** with dimethyl malonate **16** to afford chiral diester **17** in 94% yield and 97% ee (entry 8, Scheme 6B), which is comparable to commercial (S)-SDP (entry 7).^[15] Remarkably, the pseudoenantiomeric ligand (R,S,S)-SPIRAP favored the

other enantiomer of the product in 88% ee (entry 9). The phosphine oxide/phosphine ligand (S,S,S)-SPIRAP(O) was also used with great success in a Pd-catalyzed Heck reaction of 2-vinylphenyl triflate **18** with norbornene **19** to afford tricycle **20** (entry 11, Scheme 4C).^[16] As before, the diastereomeric complex (R,S,S)-SPIRAP(O) favored an enantiomeric product albeit with somewhat lower selectivity (entry 12). Finally, diphosphinites (S,R,R)-SPIRAPO and (R,R,R)-SPIRAPO were applied in the Rh-catalyzed asymmetric hydrogenations of dehydroalanine derivative **21** with excellent results.^[17] The (R,R,R)-SPIRAPO performed similarly to SPINOL-based ligand (S)-SDPO (entries 16 and 14) while the use of the (S,R,R)-diastereomer resulted in reversal of enantioselectivity (entry 15). In addition, application of SPIROMP organocatalytic aza-Baylis Hillman reaction^[18] has been demonstrated (cf. SI).

Table 1. Comparison of 3D structures of SPIRAP diastereomers and SDP.^a

entry	complex	natural charge at Pd(II)	τ_4	τ_4'	bite angle (°)
1	(S,S,S)-11	0.425	0.113	0.125	94.4
2	(R,S,S)-11	0.425	0.086	0.092	95.3
3	(S)-23	0.427	0.112	0.129	94.2

^a τ_4 and τ_4' are geometry index parameters defined by two largest angles at Pd

The consistent similar performance of (S,S,S)-SPIRAP and (S)-SDP and different behavior of (R,S,S)-SPIRAP prompted us to do a more thorough comparison between the (S,S,S)- and (R,S,S)-diastereomers. The DFT^[13,19] analysis of diastereomeric Pd(II) complexes of SPIRAP (**11**), and commercial (S)-SDP, demonstrated that these complexes have similar natural charge at the metallic center. However, while the geometry index parameters τ_4 ^[20] and τ_4' ^[21] showed similar values for (S,S,S)-11 and (S)-23 (entries 1 and 3, Table 1), τ_4 and τ_4' for (R,S,S)-11 were found to be considerably different (entry 2, Table 1). This implied that, although these three complexes are electronically similar, the (R,S,S)-SPIRAP complex is structurally significantly different from (S)-SDP, while (S,S,S)-SPIRAP, although not identical, is much more similar. The calculated bite angles also demonstrated this trend, with (R,S,S)-SPIRAP showcasing a slightly larger angle. This explains the lower performance of (R,S,S)-SPIRAP in catalytic applications optimized for SDP. A closer inspection of the three-dimensional structures of these complexes reveals that the ethyl sidechain in (R,S,S)-SPIRAP disturbs the π -stacking between the aryl groups of the backbone, leading to a different overall geometry (Figure 2). The structural dissimilarities between our spiroketal manifold and the SPINOL core leads us to believe that our catalytic platform could provide a unique solution to new asymmetric methodologies of importance in current organic chemistry. This divergence is reflected in the performance of some of the reactions mentioned above. The ease of preparation,

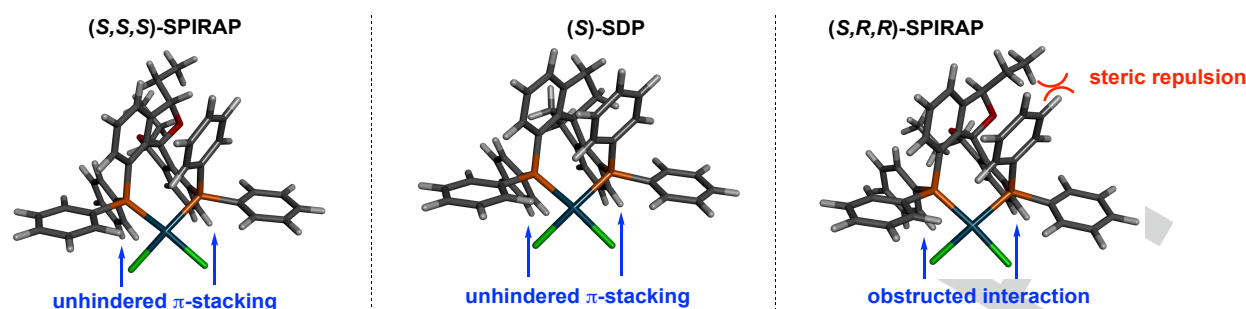


Figure 2. Comparison of (R,S,S) -SPIRAP, (S,S,S) -SPIRAP, and SDP complexes of PdCl_2 . The geometries of (S,S,S) -11, (R,S,S) -11 and (S) -25 were optimized using DFT with B97-D exchange functional and mixed bases sets (LanI2dz for Pd, P, Cl and 6-31G** for all of the other atoms).

stability, availability of new sites for tuning and outstanding performance of (S,S,S) -SPIRAP prompt us to suggest that it could be a widely used and successful ligand in asymmetric catalysis. In addition, (R,S,S) -ligands were easily accessible from the same chiral intermediate and could be used if reversed selectivity is desired. The results obtained with the (R,S,S) -ligands are particularly remarkable, as these thermodynamically less stable than (S,S,S) -diastereomers ligands were found to possess kinetic stability under a variety of reaction conditions. Further application of our new ligands to novel reactions and chemical processes that will help highlight the differences between these and established SDPs, as well as the preparation of other catalysts derived from the SPIROL core, are currently underway in our laboratory.

Acknowledgements

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Conflict of Interests

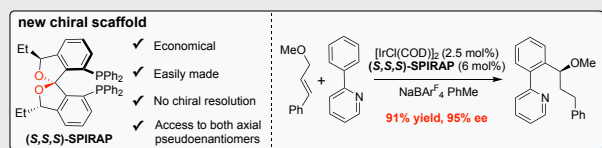
The authors declare no conflict of interest.

Keywords: ligand • spirocyclic • spiroketal • palladium • iridium • asymmetric catalysis • phosphine

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COMMUNICATION



Alonso J. Argüelles, Siyuan Sun, Brenna G. Budaitis, and Pavel Nagorny*

Design, Synthesis and Application of Novel Chiral C₂-symmetric Spiroketal-containing Ligands in Transition Metal Catalysis

This manuscript describes expedient synthesis of new spirocyclic C₂-symmetric spiroketal-based chiral scaffold (SPIROL) and its successful application in asymmetric catalysis.