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Exploration of chiral diastereomeric spiroketal (SPIROL)-based phosphinite ligands in asymmetric hydrogenation of heterocycles†

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New and readily available chiral SPIROL-based diphosphinite ligands (SPIRAPO) have been prepared and employed for iridium-catalyzed asymmetric hydrogenations of quinolines, quinoxalines and 2*H*-1,4-bezoxazin-2-ones. While the structurally similar (*R*,*R*,*R*)-SPIRAPO and (*R*)-SPINOL-based phosphinites were not the best ligands for these transformations, the (*S*,*R*,*R*)-diastereomer of SPIRAPO was found to be highly effective ligand for the reduction of 20 different heterocyclic systems with loadings as low as S/C = 10 000. This dearomatizative hydrogenation provided direct access to optically active tetrahydroquinolines in high enantioselectivities (up to 94% ee) and excellent yields (up to 99%), and was used to generate 1.75 g of natural alkaloid (−)-(*R*)-angustureine. This protocol was subsequently extended to achieve asymmetric hydrogenation of quinoxalines and 2*H*-1,4-benzoxazin-2-ones in good to excellent enantioselectivities.

In the recent decade, spirocyclic ligands of the 1,1′-*bis*-spiroindane (SPINOL) family have received significant attention in asymmetric catalysis.[1] SPINOL scaffold possesses many unique features such as higher rigidity, different dihedral angle, greater distance between hydroxyls with a more confined binding cavity. Due to these characteristics, SPINOL has emmerged as a privileged scaffold, and there are thousands of recent studies that describe the use of SPINOL ligands and catalysts (SDP,[2a] SIPHOS-PE,[2b] CPA,[1c] SITCP,[2c] *etc.*) in asymmetric synthesis or catalysis. Following the original synthesis by the Birman group,[3] several studies focused on improving the accessibility of SPINOL and its derivatives;[4] however, unlike the preparation of BINOL derivatives, this is still challenging and expensive. There have been several efforts focused on addressing this challenge. The recent efforts of Tan and coworkers focused on eliminating the resolution step by executing a chiral phosphoric acid-catalyzed enantioselective spirocyclization that leads to enantioenriched SPINOL derivatives.[4] Other approaches have focused on making structural modifications that may simplify access to SPINOLs and may improve/enhance the characteristics of the ligands and catalysts. Being aware of the studies on SKP ligands[5] and based on our own work on CPA-catalyzed enantioselective spiroketalizations,[6] our group in 2018 reported the development of spiroketal-based ligands (SPIROLs), synthesis of which features only 3 steps from commercially available starting materials and does not require chiral resolution (Fig. 1B).[7] Subsequently, several reports on modified SPINOL ligands (OSPINOL[8] and **1**–**3**[9–11]) as well as some studies of modified SPIROL[12] and Si-SPINOL[13] scaffolds appeared in literature (*cf.* Fig. 1A).

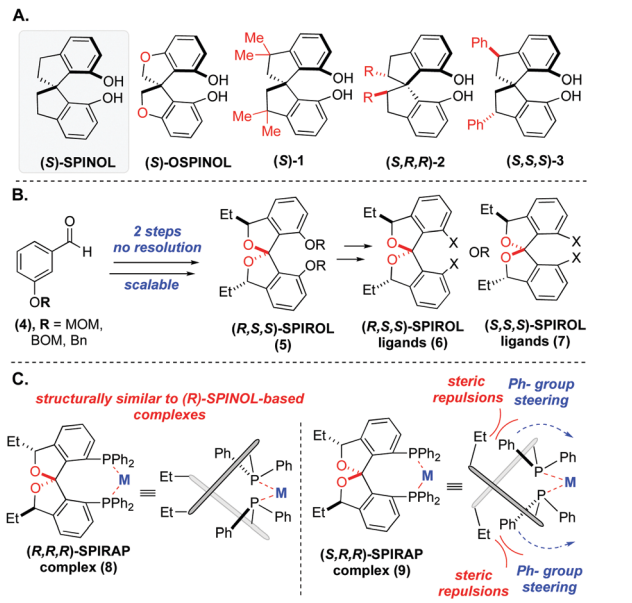

Fig. 1 (A) SPINOL and related scaffolds. (B) Pseudoenantiomeric SPIROL-based ligands. (C) Effect of spiroketal and substituent configuration on (*R*,*R*,*R*)- and (*S*,*R*,*R*)-SPIROL ligands.

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Previously,[7] we observed that SPIROL scaffolds are almost unmatched in terms of their ease of preparation and unique structural features that allow the ligand properties to be tuned.[6] These ligands could be easily generated from inexpensive aldehydes **4** through a two-step protocol that gives rise to the protected (*R*,*S*,*S*)-diastereomer **5** (or its (*S*,*R*,*R*)-counterpart) in good yields and selectivities. The (*R*,*S*,*S*)-**5** was further elaborated to various (*R*,*S*,*S*)- and (*S*,*S*,*S*)- (or enantiomeric (*S*,*R*,*R*)- and (*R*,*R*,*R*)-) ligands **6** and **7**.[7] The subsequent experimental evaluation of both diastereomeric scaffolds demonstrated that ligands with (*S*,*S*,*S*)-SPIROL configuration **7** are similar to (*S*)-SPINOL-based ligands in terms of their performance and structural parameters. In contrary, diastereomeric (*R*,*S*,*S*)-SPIROL ligands behaved as pseudoenantiomers of (*S*,*S*,*S*)-SPIROL and provided opposite enantiomers with lower enantioselectivities. The computational studies were consistent with these observations and indicated that (*R*,*S*,*S*)-SPIROL ligands **8** and **9** possessed considerably different geometry index parameters τ_4[26] and τ_4' and the calculated bite angles. The subsequent analysis of the computed three-dimensional structures indicated that the Et-sidechain in (*R*,*S*,*S*)-complexes disturbs the π-stacking between the aryl groups of the backbone, leading to a different overall geometry (Fig. 1C). The structural dissimilarities between the (*R*,*S*,*S*)-spiroketal manifold and the SPINOL core lead us to believe that the (*R*,*S*,*S*)-based catalytic platform could provide a unique solution to new asymmetric methodologies of importance while the (*S*,*S*,*S*)-based platform provides a more readily available alternative to SPINOL. This manuscript describes our studies focused on the use of (*R*,*S*,*S*)-SPIROL phosphinites in asymmetric dearomatizative hydrogenation reactions leading to the formation of chiral heterocyclic frameworks (*cf.* Fig. 2). It is noteworthy that (*R*,*S*,*S*)-SPIROL phosphinites outperform (*S*,*S*,*S*)-SPIROL and (*S*)-SPINOL-based ligands, and demonstrate great substrate tolerance to the changes in the heterocycle substitutions and frameworks.

Synthesis of chiral nitrogen-containing heterocyclic compounds is of great importance to natural product synthesis and drug discovery (Fig. 2).[14] Among various methods, asymmetric transition metal-catalyzed reduction of aromatic heterocycles represents one of the most robust, and inexpensive methods available.[15] Due to their high catalytic activity,[16] Ir-based catalysts have been extensively used for the dearomatizative hydrogenations of many nitrogen-containing heterocyclic systems including pyridines, quinolines, quinoxalines and benzoxazinones.[15]

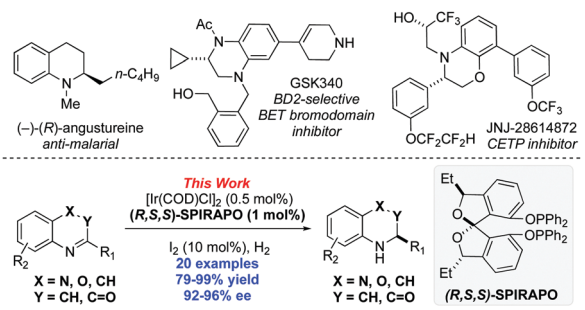
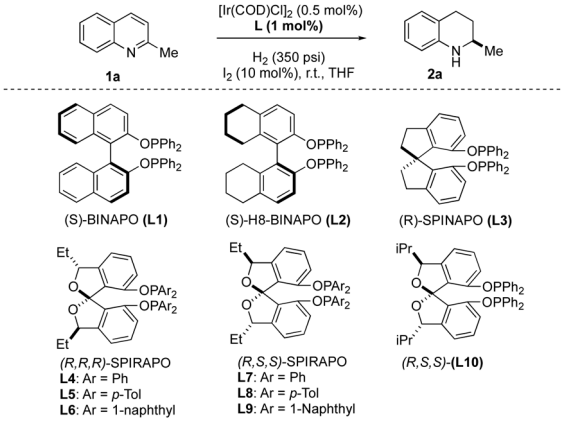


Fig. 2 Application of SPIRAP-based ligands to Ir(I)-catalyzed asymmetric hydrogenation of heterocycles (this work).

Table 1 Evaluation of SPIRAPO ligands for the Ir(I)-catalyzed reduction of quinaldine (**1a**)[ab]



Entry	Ligand	H_2 (psi)	Time (h)	Conv. (%)	ee (%)
1[c]	**L1**	700	20	99	81
2	**L1**	350	10	99	42
3	**L2**	350	10	99	87
4	**L3**	350	10	99	90
5	**L4**	350	10	99	88
6	**L5**	350	10	99	33
7	**L6**	350	10	99	12
8	**L7**	350	10	99	94
9[d]	**L7**	600	3	99	96
10[e]	**L7**	350	10	93	91
11	**L7**	350	1	95	94
12	**L8**	350	10	99	87
13	**L9**	350	10	99	55
14	**L10**	350	10	99	90

[a] Reactions were carried out at r.t. with 0.1 mmol quinaldine **1a** using Ir(I) complex generated *in situ* from $[Ir(COD)Cl]_2$ (0.5 mol%), ligand **L1** to **L10** (1.1 mol%), and I_2 (10 mol%) under pressurized H_2 in 1 mL of solvent. [b] The conversion was determined by ^1H NMR and the enantioselectivity was determined by HPLC analysis with a Chiralpak OJ–H column. [c] Described in ref. 18*a*. [d] Performed at 0 °C and 600 psi for 3 h. [e] Performed with 0.01 mol% of catalyst (S/C = 10 000).

These powerful transformations may result in highly selective formation of chiral heterocyclic products;[17,18] however, they often suffer from limited substrate scope and high pressures required to achieve good conversions. Recently, Chan and coworkers demonstrated that SPINOL-based diphosphinites may serve as excellent ligands for the Ir-catalyzed hydrogenation allowing to achieve high S/C ratios and excellent enantioselectivities for narrow range of isoquinolines as substrates.[18a] Surmising that SPIROL-based diphosphinites are more accessible (3 steps from commercially available materials), have higher degree of tunability, and might result in significantly broader substrate scope than SPINOL-based ligands, we investigated the asymmetric Ir-catalyzed reductions of quinaldine (**1a**) using (*R*,*R*,*R*)-SPIROL and (*R*,*S*,*S*)-SPIROL-derived diphosphinites (**L4–L10**, Table 1). As it was observed by Chan and coworkers,[18a] BINAPO ligand (**L1**) may serve as good ligand for the reduction of **1a** providing **2a** in 81% ee; however, high pressures (700 psi) and long reaction times (20 h) were required to achieve full conversion and selectivity (entry 1).

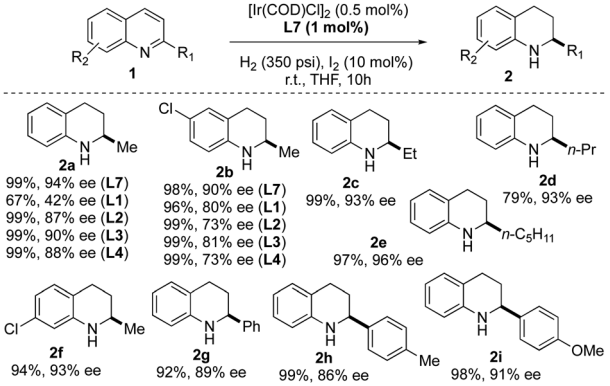
In our studies, we decided to optimize these conditions so that the reduction of **1a** could be carried at lower and safer pressure (350 psi) and shorter reaction time (10 h). However, when **L1** was used under such conditions, **2a** was formed in only 42% ee (entry 2). At the same time, the reaction with related (*S*)-*H*8-BINAPO ligand **L2** (entry 3) resulted in 87% ee and full conversion, and SPINAPO ligand (**L3**) demonstrated even better performance (99% conversion, 90% ee, entry 4).

Having this as a benchmark for our further studies, we subsequently evaluated various SPIRAPO ligands **L4–L10** (entries 5–11). These ligands were generated through a 3-step sequence starting with commercially available MOM-protected 3-benzyloxybenzaldehyde.[7] As expected, (*R*,*R*,*R*)-SPIRAPO ligand **L4** (Ar═Ph), performed similarly to SPINAPO affording **2a** in 88% ee. The increase of the sterics of the Ar group on phosphorus(III) in **L5** and **L6** resulted in inferior enantioselectivities (33% ee and 12% ee correspondingly, entries 6 and 7). At the same time, the diastereomeric counterparts of ligands **L4**, (*R*,*S*,*S*)-ligand **L7** demonstrated significantly better performance affording **2a** in 94% ee (entry 8), and could be further raised to 96% ee if run at higher pressure (600 psi) and 0 °C (entry 9). Remarkably, this transformation could be run for the same period of time with only 0.01 mol% of the catalyst (S/C = 10 000) without significant reduction in conversion and selectivity (93%, 91% ee, entry 9). In addition, we observed that the reduction time could be cut tenfold (1 h instead of 10 h) without significant impact on conversion (entry 10).

In further attempts to optimize the selectivity using (*R*,*S*,*S*)-counterparts of **L5** and **L6**, (*R*,*S*,*S*)-ligands **L8**, and **L9**, were tested (entries 11 and 12). Although these ligands demonstrated significantly better performance then **L5** and **L6** affording **2a** in 87% ee and 55% ee, correspondingly, they were inferior to **L7**. Finally, an i-Pr, rather than Et-group substituted (*R*,*S*,*S*)-SPIRAPO ligand **L10** was synthesized and tested (entry 13). This ligand demonstrated performance comparable to (*R*,*R*,*R*)-SPIRAPO ligand **L4**, but inferior to (*R*,*S*,*S*)-SPIRAPO ligand **L7**.

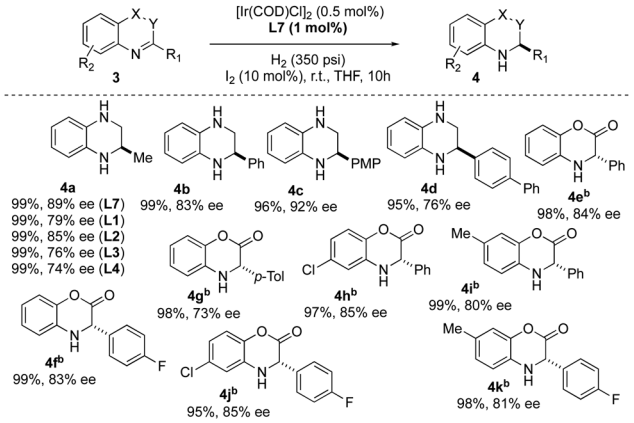
The studies in Table 1 identified **L7** as the best ligand for the lower pressure (350 psi) hydrogenation of **2a**. In addition, the generally better performance of **L7** relative to ligands **L1–L4** was tested and observed for other substrates such as **2b** and **4a**. Thus, **L7** was selected and used for the reduction of other substituted quinolines (Scheme 1). The changes in the size of the C2-substituent were well tolerated, and chiral products **2c–2e** were obtained in excellent yields and selectivities (93–96% ee). In addition, the substitution in the benzene ring was tolerated, and chlorinated products **2b** and **2f** were produced in 90% ee and 93% ee, correspondingly. While the C2-alkyl to C2-aromatic substituent switch often results in significant erosion of selectivity and necessity to re-optimize the ligand,[16–18] (*R*,*S*,*S*)-SPIROL-based ligand **L7** demonstrated great performance for the reduction of 2-aryl substituted quinolines resulting in products **2g**, **2h** and **2i** in 89% ee, 86% ee and 91% ee, correspondingly.

Finally, to demonstrate that these transformations are amenable to scale up, the reduction of quinoline **1d** was performed on 2.0 g scale. The resultant product **2d** was obtained without erosion in the yield and selectivity (97%, 94% ee). This compound was subsequently methylated to provide natural alkaloid (−)-(*R*)-angustureine in 81% yield (*cf.* ESI†).



Scheme 1 Asymmetric reduction of substituted quinolines using optimized conditions. All reactions were carried out at room temperature with 0.1 mmol of substrates **1** (with the exception of **1d** that was run on 10 mmol scale) using Ir(I) complex generated *in situ* from $[Ir(COD)Cl]_2$ (0.5 mol%), ligand (*R*,*S*,*S*)-**L7** or **L1–L4** (1.1 mol%), and I_2 (10 mol%) under pressurized H_2 (350 psi) in THF.

Our subsequence studies were focused on evaluating the scope of other related heterocyclic systems that could be reduced by iridium complexes with **L7** (*cf.* Scheme 2). In particular, we were interested in examining the reduction of 2-substituted quinoxalines and 3-substituted 2*H*-1,4-bezoxazin-2-ones.[18b,c] The products arising from the reduction of these heterocyclic compounds often display bioactivity and are of great importance to drug discovery (*cf.* Fig. 2). Using the optimized conditions from Table 1, the reduction of 2-substituted quinoxalines was accomplished in good enantioselectivities and resulted in chiral products **4a–4d** (Scheme 2). This transformation was tolerant to the nature of the C2-substituent, and Me-substituted product **4a** and Ph-substituted product **4b** were obtained in 89% ee and 83% ee, correspondingly. Importantly, when tested, other common ligands **L1–L3**[18d] demonstrated inferior performance relative to **L7**.



Scheme 2 Asymmetric reduction of substituted quinolines using optimized conditions. [a]All reactions were carried out at room temperature with 0.1 mmol of substrates **1** using Ir(I) complex generated *in situ* from $[Ir(COD)Cl]_2$ (0.5 mol%), ligand (*R*,*S*,*S*)-**L7** (1.1 mol%), and I_2 (10 mol%) under pressurized H_2 (350 psi) in THF. [b]Substrates **4e–4k** were obtained using (*S*,*R*,*R*)-**L7**.

The substitution at the Ph ring was found to affect the selectivities as the 4-methoxyphenyl-substituted substrate **4c** was obtained in 92% ee and 4-biphenyl-substituted substrate **4d** was obtained in 76% ee.

The reactions of 3-aryl substituted 2*H*-1,4-bezoxazin-2-ones were examined next (**4e–4k**, Scheme 2) using (*S*,*R*,*R*)-enantiomer of ligand **L7**. These substrates were hydrogenated with good levels of enantiocontrol. As for quinoxalines, additional substitution at the C4 position of the aromatic group was found to affect the stereoselectivity of the reduction. While the C2-phenyl-substituted product **4e** was obtained in 84% ee, the reduction of 4-fluorophenyl- and 4-tolyl-substituted substrates lead to products **4f** and **4g** in 83% ee and 73% ee, correspondingly. At the same time, substitution at the 6- or 7-positions of the heterocyclic skeleton did not lead to significant changes in selectivity, and products **4h** and **4i** were obtained in 85% ee and 80% ee, correspondingly. Similarly, additional substitution at both the C2-aryl group or the 6- or 7-positions of the heterocyclic skeleton could be tolerated as substrates **4j** and **4k** were obtained in 85% ee and 81% ee.

In summary, this work showcases the use of readily available by a 3 step synthesis chiral SPIROL-based diphosphinite ligands (SPIRAPO) for iridium-catalyzed asymmetric hydrogenations of quinolines, quinoxalines and 2*H*-1,4-bezoxazin-2-ones. The asymmetric hydrogenations with (*R*,*S*,*S*)-SPIRAPO ligand **L7** were accomplished at reduced pressures (350 psi), and could be run for the reaction times as short as 1–10 h with the S/C ratio as low as 10 000. Under these conditions, the (*R*,*S*,*S*)-diastereomer of SPIRAPO **L7** was found to be highly effective ligand with generally better performance then more common ligands **L1–L3** or (*R*,*R*,*R*)-SPIRAPO diastereomer **L4**. This dearomatizative hydrogenation provided direct access to optically active tetrahydroquinolines in high enantioselectivities (up to 94% ee) and excellent yields (up to 99%) and was used to carry a 2 step synthesis of natural alkaloid (−)-(*R*)-angustureine on a 2.0 gram scale. This protocol was subsequently extended to achieve an asymmetric hydrogenation of quinoxalines and 2*H*-1,4-bezoxazin-2-ones in good to excellent enantioselectivities.

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Conflicts of interest

(*R*,*R*,*R*)- and (*S*,*S*,*S*)-SPIROL based diphosphine ligands have been commercialized through Sigma Aldrich.

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