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Synthesis of a novel spiro bisphosphinamidite ligand for highly enantioselective hydrogenation

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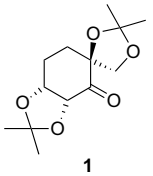
Abstract—A novel chiral bisphosphinamidite ligand SpiroNP has been synthesized. The rhodium complex of this ligand has been found to be highly active and enantioselective in the asymmetric hydrogenation of (*Z*)-2-acetamidoacrylic acid derivatives and α,β-unsaturated carboxylic acid derivatives.

Ligands containing chiral bisphosphorus donors are the most sought-after targets in asymmetric catalysis due to the relative ease of manipulation of both the electronic and steric properties about the phosphorus centre and the extensive range of reactions in which they can be employed.[1] Whilst bidentate phosphorus ligands possessing stereogenic biaryl linkages have attracted much attention, the study of chiral ligands composed of other forms of axial chirality, namely spiral compounds, is relatively rare. Notable seminal reports in recent years include the use of fructose-derived ketone **1** in epoxidation,[2] chiral spiro ammonium salts **3** in phase transfer catalysis,[3] SPRIXs **4** in tandem Wacker-type cyclization,[4] Siphos **5** in the hydrogenation of prochiral enamides,[5] and SDP **6** in the hydrogenation of unsymmetrical ketones.[6] We have also contributed in this area by demonstrating that bisphosphinite (*R*)-SpirOP **2** is highly efficient in transferring stereochemical information to enamides and (*Z*)-dehydroamino acid derivatives in catalytic hydrogenation to give the corresponding amides and α-amino acid derivatives, respectively, with good to excellent enantioselectivities.[7] We contended that the potency of ligand **2** arises from the highly skewed and a rigid conformation, a property which is also considered important to give rise to the effectiveness of BINAP and related systems,[8] of the spiro backbone.



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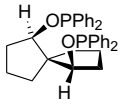

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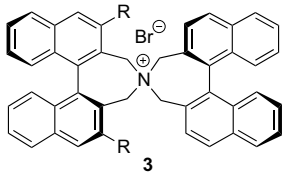

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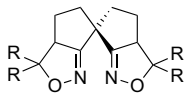
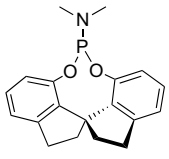


SPRIXs **4**



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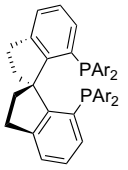

SDP **6**

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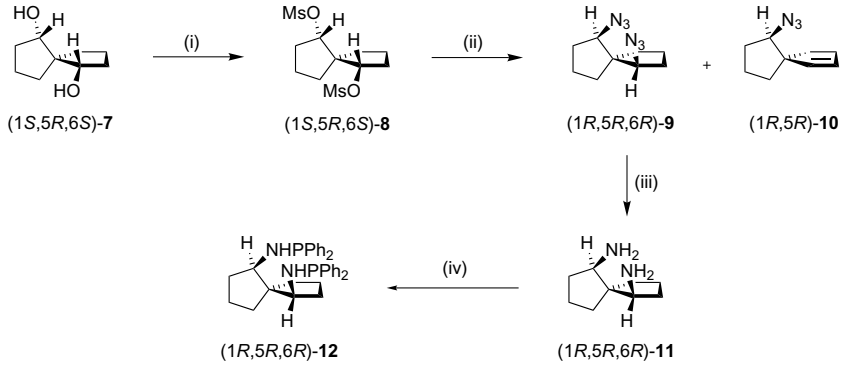


Scheme 1. Reagents and conditions: (i) MsCl, pyridine, 0 °C—rt, 5 h, 94%; (ii) NaN_3, DMF, 80 °C, 36 h, 55%; (iii) Pd/C, H_2, EtOH, RT, 2 h, 98%; (iv) (a) *n*-BuLi, THF −40 °C; (b) Ph_2PCl, −40 °C—rt; (c) saturated $NH_4Cl_{(aq)}$, 73%.

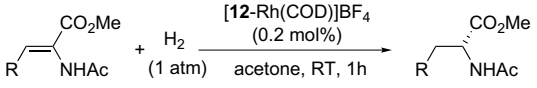
In search of a novel bisphosphinamidite ligand and further exploiting the use of the enantiopure spiro[4.4]nonane skeleton, herein, we wish to report a short-route synthesis of **12** (abbreviated (*R*)-SpiroNP) and its applications in the asymmetric hydrogenation of various olefinic substrates as a testing ground for its effectiveness.

The overall synthesis for bisphosphinamidite **12** is illustrated in Scheme 1. The requisite (1*S*,5*R*,6*S*)-diol **7** was first prepared according to our previously reported method,[9] which was then converted to the dimesylate **8**. Treatment of **8** with sodium azide gave the (1*R*,5*R*,6*R*)-diazide **9** (in a maximum of 55% yield) and the mono-azido product **10**. Several attempts were made to eliminate the formation of **10** but were not successful. The two products, however, could be readily separated by flash chromatography. The spirodiazide **9** was transformed to the corresponding spirodiamine **11** via Pd/C reduction with molecular hydrogen. Subsequent lithiation of **11** followed by the addition of chlorodiphenylphosphine afforded (1*R*,5*R*,6*R*)-**12** in a good yield.

The active cationic rhodium complex [**12**-Rh(COD)]BF_4 for hydrogenation was prepared directly by mixing [$Rh(COD)_2$]BF_4 and (1*R*,5*R*,6*R*)-**12** in dichloromethane at room temperature, followed by solvent removal once the complex was formed as judged by ^{31}P NMR. Routine screening of solvents for the enantioselective hydrogenation of methyl (*Z*)-acetamidocinnamate revealed that the best solvent was acetone.

In the ensuing investigation, a number of methyl esters of (*Z*)-2-acetamidoacrylic acid were hydrogenated with 0.2 mol% [**12**-Rh(COD)]BF_4 catalyst (Table 1) at room temperature under 1 atm H_2. Quantitative conversion was achieved within 1 h for all the substrates studied (Table 1) with enantioselectivities reaching over 99% (Table 1: entries 2, 4–8). Various substitutions on the phenyl ring of the acetamidocinnamate had almost

Table 1. The hydrogenation of various methyl esters of 2-acetamidoacrylic acid and (*Z*)-2-acetamido-3-arylacrylic acids with [**12**-Rh(COD)]BF_4

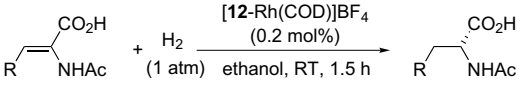


Entry	R	ee (%)[a,b]
1	H	95 (>99.9)
2	Ph	>99 (96)
3	*o*-Chloro-phenyl	96
4	*m*-Chloro-phenyl	>99
5	*p*-Chloro-phenyl	>99 (94)
6	*p*-Bromo-phenyl	>99 (96)
7	*p*-Fluoro-phenyl	>99 (96)
8	*p*-Methoxy-phenyl	>99 (96)
9	*p*-Methyl-phenyl	>98 (96)
10	*p*-Nitro-phenyl	94
11	3,4-Methylene-dioxyphenyl	>98 (95)
12	2-Furfuryl	>99 (97)

[a] The ee values were determined by GC using a Chrompack Chiralsil-L-Val capillary column. (*R*) product configuration was observed in all cases.

[b] The number in parenthesis is the enantioselectivity obtained using [(*R*)-**2**-Rh(COD)]BF_4 catalyst under otherwise identical conditions.

Table 2. The hydrogenation of various 2-acetamidoacrylic acid and (*Z*)-2-acetamido-3-arylacrylic acids with [**12**-Rh(COD)]BF_4

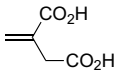
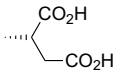
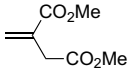
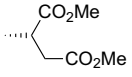
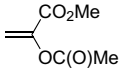
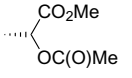
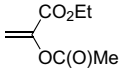
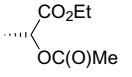


Entry	R	ee (%)[a,b]
1	H	78
2	Ph	>98 (98)
3	*o*-Chloro-phenyl	96 (97)
4	*m*-Chloro-phenyl	95 (97)
5	*o*-Methoxy-phenyl	84
6	3,4-Methylene-dioxyphenyl	92
7	3-Methoxy-4-acetophenyl	94

[a] The ee values were determined by GC using a Chrompack Chiralsil-L-Val capillary column. (*R*) product configuration was observed in all cases.

[b] The number in parenthesis is the enantioselectivity obtained using [(*R*)-**2**-Rh(COD)]BF_4 catalyst under otherwise identical conditions.

Table 3. Asymmetric hydrogenations of α,β-unsaturated carboxylic acid derivatives by [**12**-Rh(COD)]BF_4[a]

Entry	Substrate	Product	ee (%), configuration
1			68, *S*
2			93, *S*
3			96, *R*
4			97, *R*

[a] S/C = 250; [Sub] = 0.2 M; pressure of H_2 = 1 atm; 1.5 h; room temperature; solvent = THF.

negligible effect on the resulting enantioselectivities. It should be noted that the enantioselectivities obtained in this study were observed to be even higher than those obtained by using the highly effective SpirOP-Rh(I) catalyst.[7]

Direct catalytic asymmetric conversion of (*Z*)-2-acetamido-3-acrylic acids into their corresponding amino acids is also feasible with [**12**-Rh(COD)]BF_4 (Table 2). In this case, the protic solvent ethanol was the optimal solvent furnishing the hydrogenation products in excellent conversion with good to excellent enantioselectivity, except for 2-acetamidoacrylic acid (entry 1).

To further probe the effectiveness of **12**, the hydrogenation of another class of substrates was also investigated. Again, the rhodium complex of **12** was sufficiently active to promote the complete hydrogenation of α,β-unsaturated carboxylic acid derivatives (Table 3) under atmospheric hydrogen pressure within 1.5 h. The enantioselectivity ranged from moderate to excellent.

In conclusion, a new chiral bisphosphinamidite ligand, SpiroNP, based on a spiro backbone has been developed via a short-path synthesis. The cationic rhodium complex of SpiroNP was found to be an excellent catalyst for the synthesis of chiral amino acid and acrylic acid derivatives under mild conditions, giving products of up to >99% ee.

Acknowledgements

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