Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c8ob01785a

Received 25th July 2018,
Accepted 13th August 2018

DOI: 10.1039/c8ob01785a

rsc.li/obc

Synthesis and application of a new chiral monodentate spiro phosphoramidite ligand based on hexamethyl-1,1′-spirobiindane backbone in asymmetric hydroamination/arylation of alkenes†

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The design and synthesis of a new chiral monodentate spiro phosphoramidite ligand based on a hexamethyl-1,1′-spirobiindane scaffold has been accomplished. The ligand could serve as an elegant chiral monodentate ligand in the Pd-catalyzed asymmetric hydroamination/arylation of alkenes leading to chiral imidazolidin-2-ones with good enantioselectivities.

The development of highly efficient chiral ligands for transition-metal-catalyzed organic transformations has become one of the most challenging goals in chemical synthesis.[1] Research advances indicated that chiral monodentate phosphorus ligands can be effective for asymmetric catalysis.[2] A large number of monodentate ligands, especially those monodentate phosphoramidite ligands with C_2 symmetry, have been developed for highly efficient asymmetric catalysis. Ligand design based on a chiral backbone plays a crucial role and has remarkable influence on catalytic performance in some cases in this area. Notably, monodentate phosphoramidite ligands have been prepared from BINOL and SPINOL, and represented the great success of the promising class of ligands. These ligands have led to excellent enantioselectivities in many transition-metal-catalyzed asymmetric reactions.[3] Despite these achievements, there remains a significant need to develop novel monodentate phosphoramidite ligands with excellent catalytic activities in a diverse range of asymmetric transformations.

Substituted imidazolidin-2-ones is well-known for its significant biological and pharmacological properties.[4] However, over the past decade, only several asymmetric catalysis strategies have been developed for preparing chiral 4-substituted imidazolidin-2-ones.[5] For instance, Shi's group discovered Cu(I)-catalyzed asymmetric diamination of olefins as an efficient methodology to construct chiral imidazolidin-2-one moieties.[5a–c] Gong's group reported Pd-catalyzed asymmetric oxidative 1,2-diamination of conjugated dienes with ureas.[5d] Trost's group developed asymmetric Pd-catalyzed addition of vinylaziridines to isocyanates for direct synthesis of chiral imidazolinones.[5e] Recently, Wolfe's group described the first catalytic asymmetric hydroamination/arylation of alkenes for providing a simple route to enantiomerically enriched 4-substituted imidazolidin-2-ones.[5f]

Chiral spiro backbone has been recognized as one of the privileged structures for chiral ligands and catalysts in asymmetric calalysis.[6,7] During the past few years, our group has developed chiral spirocyclic phosphoric acids (SPAs) that derived from axially chiral 1,1′-spirobiindane-7,7′-diol (SPINOL) with conformational rigidity, and found good utility in over 100 asymmetric reactions.[8,9] In searching for new structural backbones, we found that hexamethyl-1,1′-spirobiindane-6,6′-diol **1** (6,6′-HMSIOL) was first reported in the 1936, and no further attempts had been made to synthesize chiral ligand.[10] More recently, we utilized 6,6′-HMSIOL as a precursor to develop new types of chiral phosphine-oxazoline ligands (HMSI-PHOX) and bisphosphine ligands (HMSI-PHOS), and demonstrated their successful application in asymmetric catalysis.[11] Herein we report the facile resolution of 6,6′-HMSIOL and the first synthesis of chiral monodentate spiro phosphoramidite ligand based on the hexamethyl-1,1′-spirobiindane backbone (HMSI-PPA). To demonstrate its potential role in asymmetric catalysis, chiral monodentate spiro phosphoramidite ligand **8** was prepared, and exhibited excellent enantioselectivity (up to 93% ee) in Pd-catalyzed asymmetric alkene carboamination reaction, as shown in Scheme 1.

The preparation of racemic 6,6′-HMSIOL was carried out by following the previous reported method by us in 92% yield from the commercially available Bisphenol C in one step by acid-catalyzed rearrangement.[11] Next, we attempted to resolve the racemic 6,6′-HMSIOL, and found the two optical spiro diols could be obtained in good yields through highly efficient chromatography resolution of the corresponding diastereomeric diester derived from *N*-tosyl-L-phenylalanine acid chlor-

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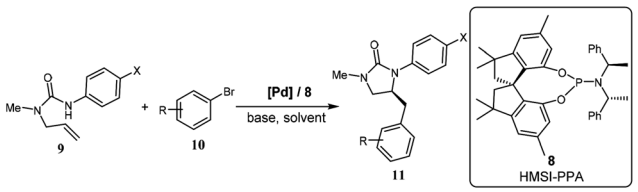
†Electronic supplementary information (ESI) available: Experimental details, characterization and analytical data, NMR and HPLC spectra. CCDC 1857510 [(*S*)-**1**]. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ob01785a



Scheme 1 Palladium-catalyzed asymmetric alkene carboamination reaction.

ide and then hydrolysis of each pure diastereomer with hydrazine hydrate under reflux in THF (Scheme 1). The absolute configuration of (*S*)-**1** was confirmed by its single-crystal X-ray diffraction structure analysis (Fig. 1 and Scheme 2).

With enantiopure **1** in hand, we extended its application to the synthesis of a new type of C_2-symmetric monodentate spiro phosphoramidite ligand **8**. As shown in Scheme 3, the chiral ligand (S_a,*R*,*R*)-**8** could be conveniently synthesized from (*S*)-**1**. The chiral spiro dibromides (*S*)-5 was obtained in high yield from (*S*)-**1** in three steps, including bromination with NBS, esterification with Tf_2O and the following Pd-catalyzed selective reduction with HCOOH.[11] Then, the spiro dialdehydes **6** was successfully accomplished in 92% yield by a simple Br/Li exchange followed treatment with DMF and hydrolysis. The subsequent Baeyer–Villiger oxidation rearrangement and subsequent hydrolysis provided chiral 7,7′-HMSIOL 7 in 82% yield. Finally, the desired chiral monodentate spiro phosphoramidite ligand (S_a,*R*,*R*)-**8** was prepared by substitution reaction of 7 with dichloro-phosphanamine. The different diastereomer (R_a,*R*,*R*)-**8** was also prepared by using another enantiomer (*R*)-**1**.

Next, the efficiency of new ligand was tested in the Pd-catalytic asymmetric hydroamination/arylation of alkenes between

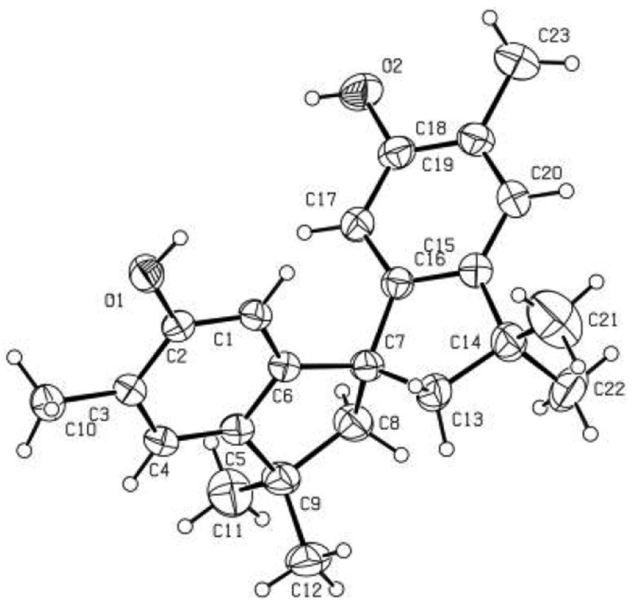
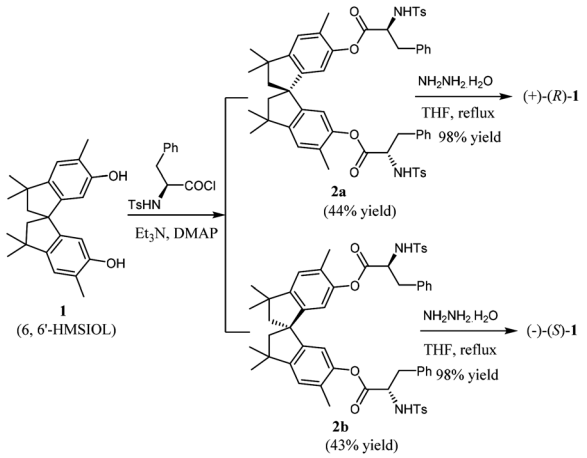
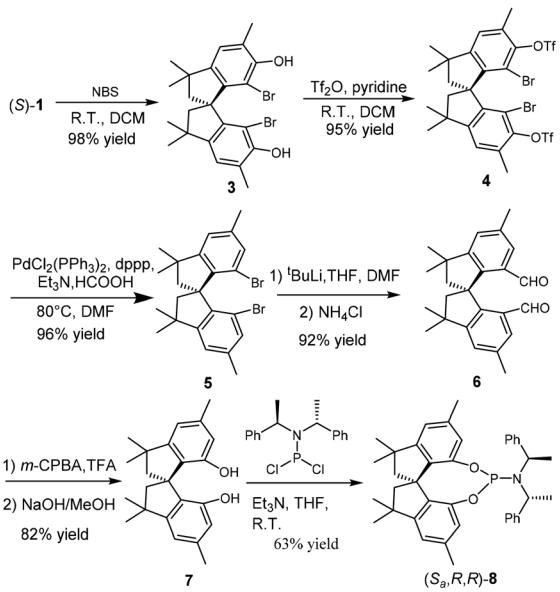


Fig. 1 X-ray crystal structure of (*S*)-**1**.



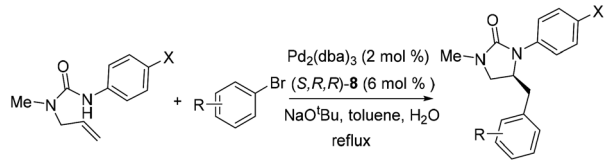
Scheme 2 Resolution of 6,6′-HMSIOL.



Scheme 3 Synthesis of spiro phosphoramidite ligand.

N-allyl urea derivatives and aryl halides using optimized conditions,[5f] as shown in Table 1. We initially examined the use of the chiral ligand (S_a,*R*,*R*)-**8** and [Pd_2(dba)$_3$] for the asymmetric reaction of 1-allyl-3-(4-methoxyphenyl)-1-methyl urea **9a** and 1-bromo-4-(*tert*-butyl)benzene **10a**, and found the desired imidazolidin-2-one **11a** could be obtained in 94% yield with 54% ee (Table 1, entry 1). The absolute configuration of (*S*)-**11a** was confirmed in comparation with the known data.[5f] The use of the diastereomeric ligand (R_a,*R*,*R*)-**8** gave poor result in 80% yield and −7% ee (Table 1, entry 2). The decrease of the phosphoramidite ligand loading of (S_a,*R*,*R*)-**8** to 4 mol% led to a significant drop in yield but did not compromise the enantioselectivity (Table 1, entry 3, 62% yield, 53% ee). Notably, nitrogen nucleophilicity of *N*-allyl urea derivatives **9** on asymmetric induction had remarkable effect. The increasing electron-withdrawing ability of the p-substituent on the *N*-aryl moiety of **9**

Table 1 Asymmetric hydroamination/arylation of alkenes[a]



Entry	X	R	11	Yield[b] (%)	ee[c] (%)
1	OMe	4-*t*Bu	**11a**	94	54
2[d]	OMe	4-*t*Bu	**11a**	80	−7
3[e]	OMe	4-*t*Bu	**11a**	62	53
4	H	4-*t*Bu	**11b**	91	66
5	Br	4-*t*Bu	**11c**	63	79
6	CN	4-*t*Bu	**11d**	89	83
7	CN	4-Me	**11e**	85	87
8	CN	4-MeO	**11f**	77	86
9	CN	4-CF_3	**11g**	63	87
10	NO_2	4-*t*Bu	**11h**	87	91
11	NO_2	H	**11i**	75	84
12	NO_2	4-CF_3	**11j**	75	93
13	NO_2	3-CF_3	**11k**	67	91
14	NO_2	4-F	**11l**	57	93
15	NO_2	4-Cl	**11m**	77	90
16	NO_2	4-PhCO	**11n**	62	83
17	NO_2	4-Morpholino	**11o**	83	91

[a] Reactions were performed with **9** (0.05 mmol), **10** (0.1 mmol), NaO^{t}Bu (0.1 mmol), 2 mol% [$Pd_2(dba)_3$], 6 mol% (*S*,*R*,*R*)-**8**, H_2O (0.1 mmol) in toluene (0.05 M) under reflux for 20 h. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] with 6 mol% (*R*,*R*,*R*)-**8**. [e] with 4 mol% (*S*,*R*,*R*)-**8**.

could increase with the level of asymmetric induction (Table 1, entries 1, 4–6 and 10). *p*-Cyanophenyl-substituted *N*-allyl urea derivative **9d** and *p*-nitrophenyl-substituted substrate **9e** could give the good results. Furthermore, a range of different aryl bromide electrophiles were tested to react with substrate **9d**, generating the corresponding imidazolidin-2-one products in 63–89% yields with 83–87% enantiomeric excesses (Table 1, entries 6–9). The reactions of **9e** with a series of different aryl bromides gave the corresponding imidazolidin-2-one products with excellent enantioselectivies in most cases (Table 1, entries 10–17). The electronic property of the substituents on the aromatic rings of **10** had a very limited effect on the enantioselectivity.

In summary, a new type of hexamethyl-1,1′-spirobiindane-based chiral monodentate spiro phosphoramidite (HMSI-PPA) ligand has been developed. The rigid and unique spiro core structure is the notable feature of HMSI-PPA. The new HMSI-PPA ligand (S_a,*R*,*R*)-8 was applied in Pd-catalyzed asymmetric hydroamination/arylation of alkenes of *N*-allyl urea derivatives with aryl bromides to afford chiral imidazolidin-2-ones in moderate to high yields with excellent enantioselectivities. Further investigations to expand this promising chiral monodentate spiro phosphoramidite ligand in transition-metal-catalyzed asymmetric reaction for constructing other chiral carbon–carbon and carbon–heteroatom bonds are currently under development.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We appreciate the National Natural Science Foundation of China (21572200) and the Fundamental Research Funds for the Central Universities (2017QNA3013) for financial support.

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