Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c5ob00452g

Received 6th March 2015,
Accepted 17th March 2015

DOI: 10.1039/c5ob00452g

www.rsc.org/obc

Synthesis of planar chiral [2.2]paracyclophane-based bisoxazoline ligands bearing no central chirality and application to Cu-catalyzed asymmetric O–H insertion reaction†

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C_2-symmetric planar chiral [2.2]paracyclophane-based bisoxazoline ligands, characterized by the inserted benzene spacer, which has a sterically demanding substituent, were synthesized and it was shown that up to 80% ee was obtained for the Cu-catalyzed O–H insertion reaction of α-diazo esters without the aid of the central chirality.

Chiral bisoxazoline (BOX) compounds are one of the most prevalent ligands that could be applied to diverse metal-catalyzed asymmetric reactions due to their easy preparation from the readily available chiral amino alcohols and high reliability for asymmetric induction.[1] Besides BOX ligands containing only the central chirality, such as simple *t*-Bu-BOX (**1**: R = *t*-Bu, Fig. 1), Ph-BOX (**1**: R = Ph), and PyBOX (**2**), the ligands made by combining the central and axial chiralities (**3**[2] and **4**[3,4]) or central and planar ones (**5**)[5] have been developed. To the best of our knowledge, however, no BOX ligands possessing only a planar chirality have so far been reported.[6,7]

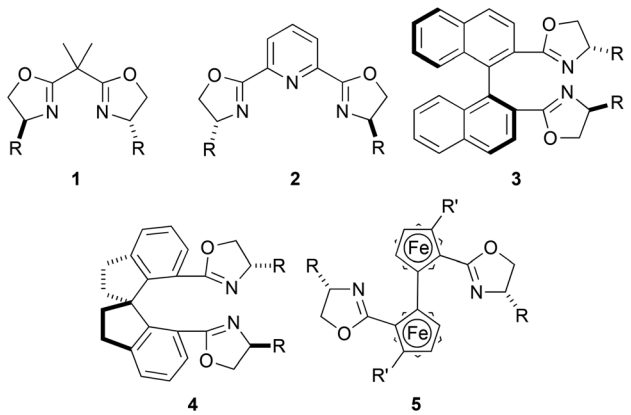
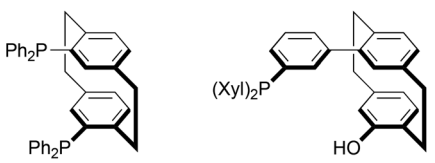


Fig. 1 Box ligands.

Substituted [2.2]paracyclophanes have been used as the planar chiral ligands in a variety of asymmetric reactions[8,9] since the emergence of [2.2]PHANEPHOS, 4,12-bis(diphenylphosphono)[2.2]paracyclophane (Fig. 2, left), which shows excellent enantioselectivities during the Rh-catalyzed hydrogenation of dehydroamino acids.[10] Although [2.2]paracyclophanes (pCps) possess many characteristic features such as configurational stability and diversity of possible chiral structures, the potential ability of this planar chiral backbone for asymmetric induction has not yet been sufficiently demonstrated. We now report the development of the pCp-based BOX, characterized by the inserted benzene spacer, which enabled the planar chirality to effectively control the asymmetric induction during the Cu-catalyzed O–H insertion reaction of α-diazo esters.

We have been interested in the pseudo-*ortho*-substituted aryl-pCp as a catalyst scaffold that has no additional chiral source and that is expected to provide an efficient asymmetric environment different from the known functionalized pCps. Our design concept is as follows: (1) one or two spacer aryl groups are connected to the pseudo-*ortho* position of the pCp backbone and two functionalized groups are located on the spacer at the *meta* position or directly on the backbone, (2) the backbone would provide the inherent conformational rigidity,[8,9,11] and (3) the spacer would offer not only the



[2.2]PHANEPHOS

our phosphine-phenol catalyst

Fig. 2 Pseudo-*ortho*-substituted pCp ligand and catalyst.

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†Electronic supplementary information (ESI) available: Experimental details, ^{1}H and ^{13}C NMR spectra, and HPLC data. See DOI: 10.1039/c5ob00452g

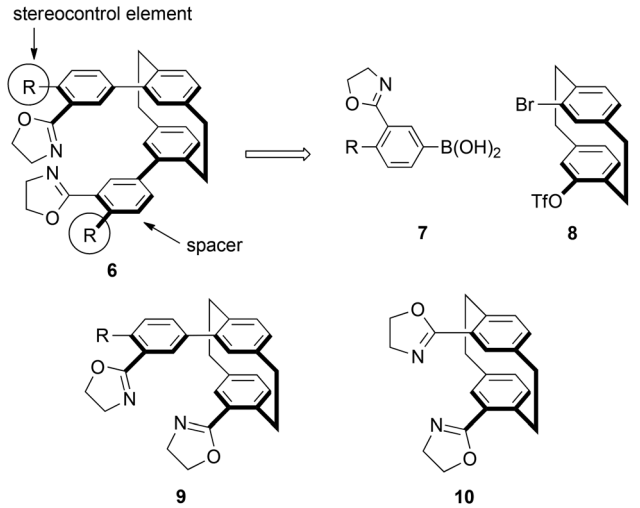
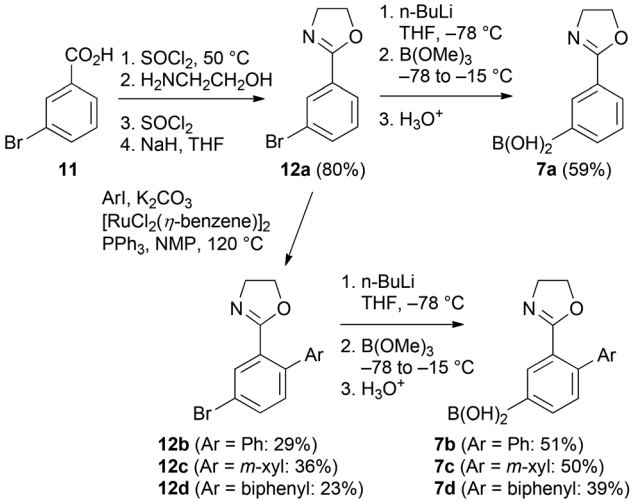


Fig. 3 [2.2]Paracyclophane-based BOXs.

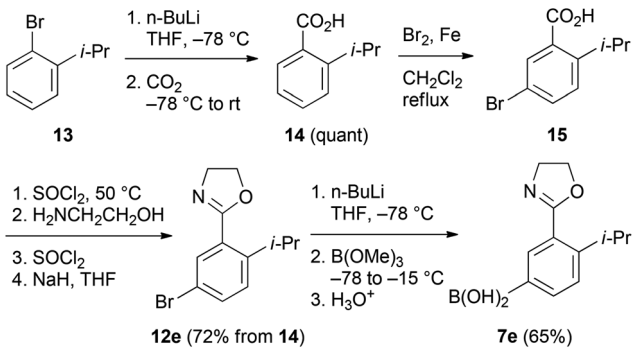


Scheme 1

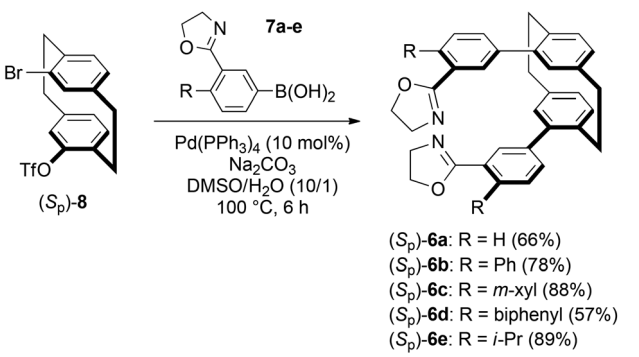
conformational flexibility that makes the distance between the two functional groups suitable for performing, but also a steric or electronic element based on the aryl group itself and/or its characteristic substituent, which interacts with the substrate and/or the reactant. In a previous paper, we reported that the single spacer in the pCp-based a phosphine-phenol catalyst (Fig. 2, right) was crucial for higher efficiency and enantioselectivity of the aza-Morita–Baylis–Hillman reaction.[12] Next, we envisaged that the planar chirality of the BOX ligand bearing the pCp backbone could highly control the enantioselection of the metal-catalyzed asymmetric reaction without the aid of the central chirality. Thus, we designed the C_2-symmetric BOX **6** in which two achiral oxazoline units were located at the *meta*-position of the spacer aryl group at whose *para*-position a bulky substituent R as the stereocontrol element was present, along with **9** having a single spacer and **10** bearing no spacer (Fig. 3).

The synthesis of BOX ligands **6** having different steric features was conducted based on the Suzuki–Miyaura coupling of bromocyclophanyl triflate **8**[13] with arylboronic acid **7** bearing an oxazolinyl group and a stereocontrol element R (Fig. 3). The preparation of **7** started with the oxazoline ring formation from *m*-bromobenzoic acid (**11**) (Scheme 1). Borylation *via* the lithium–bromine exchange of the resulting **12a** produced the unsubstituted *m*-oxazolinylphenylboronic acid **7a**. The aryl-substituted boronic acids **7b–d** were obtained by the Ru-catalyzed arylation[14] of **12a** and subsequent borylation. The isopropyl-substituted **7e** was prepared from 2-bromocumene (**13**) as shown in Scheme 2. The carboxylation of **13** followed by bromination produced the benzoic acid derivative **15**, which was converted into **7e** according to the aforementioned procedure for the preparation of **7a** from **11**. The coupling of **7a–e** and (S_p)-**8** under the influence of $Pd(PPh_3)_4$ afforded the desired bisoxazolines (S_p)-**6a–e** in good yields (Scheme 3).

With the designed ligands in hand, our endeavors turned to their application to the catalytic asymmetric reaction. The Cu-catalyzed O–H insertion reaction of α-diazo esters is useful



Scheme 2



Scheme 3

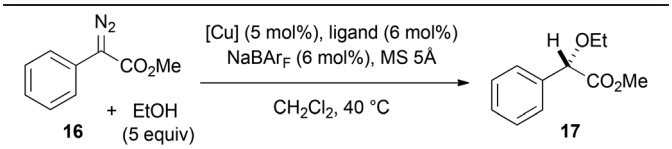
for the construction of α-alkoxycarbonyl compounds.[15] The highly enantioselective version of this reaction has recently been accomplished using bisazaferrocene,[16] the spiro-BOX **4**,[6b,17] or an imidazoindolephosphine ligand.[18] The development of an alternative ligand, however, is still desirable for this type of reaction, as more versatile BOXs **1–3** are not

suitable at all.[16,17] In this context, we first chose the insertion reaction of methyl α-diazophenylacetate (**16**) into the O–H bond of ethanol as a benchmark reaction for our ligands. The use of 5 mol% of a Cu salt, 6 mol% of the BOX ligand, 6 mol% of $NaBAr_F$ as an additive, and MS 5 Å in dichloromethane was set as the standard conditions with reference to Zhou's procedure using **4**.[17a] After mixing them at room temperature for 4 h, ethanol and α-diazo ester **16** were successively added at 40 °C to the mixture, which was stirred until **16** was completely consumed. When the phenyl-substituted ligand (S_p)-**6b** and $CuPF_6(CH_3CN)_4$ as a copper source were used, the desired methyl α-ethoxyphenylacetate (**17**) was obtained in 87% yield and 67% ee with the *S* configuration being preferred, although the absence of MS 5 Å dramatically decreased the enantioselectivity (Table 1, entries 1 and 2). Other copper sources were examined for the reaction using (S_p)-**6b**, and it turned out that $Cu(OTf)_2$ was the best source among those examined (entries 2–5). Surprisingly, the use of both MS 4 Å and 3 Å instead of 5 Å resulted in a significant decrease in enantioselectivity (entries 6 and 7).[19] The reaction in chloroform or dichloroethane gave the insertion product **17** in lower yield and ee (entries 8 and 9).

Under the conditions established for the Cu-catalyzed O–H insertion using ligand (S_p)-**6b**, the application of other BOX ligands was explored. When the unsubstituted ligand (S_p)-**6a** was used, the enantioselectivity of the product dramatically decreased as expected (entry 10). Ligands (S_p)-**6c** and (S_p)-**6e**, characterized by the horizontal extension of the substituent on the spacer, showed a lower selectivity while the vertically extended ligand (S_p)-**6d** exhibited an ee similar to (S_p)-**6b** (entries 11–13). The significance of the two-spacer benzene rings was confirmed as follows. The removal of one of the two spacers from (S_p)-**6b** led to a decrease in the enantioselectivity with the opposite sense (entry 5 *vs.* 15). The use of ligand (S_p)-**10**, whose oxazoline functionality was directly connected to the pCp backbone, also resulted in a lower level of asymmetric induction (46% ee) in the opposite sense (entry 16). These results suggest that the lack of spacer(s) leads to the construction of the asymmetric environment quite different from that of (S_p)-**6** having two spacers.

We next turned our attention to the applicability of the present protocol to systems other than the intermolecular aliphatic O–H insertion. As with the intermolecular version, the phenyl-substituted ligand (S_p)-**6b** showed a higher selectivity than the *m*-xylyl-substituted (S_p)-**6c** and isopropyl-substituted (S_p)-**6e** for the intramolecular aliphatic O–H insertion using α-diazo ester **18**[17d] (Table 2). On the other hand, for the inter-

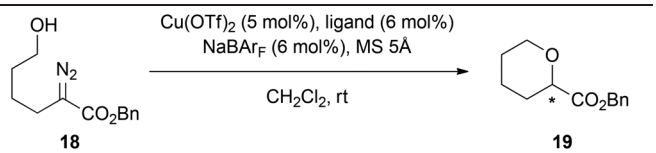
Table 1 BOX (S_p)-**6**-Cu-catalyzed intermolecular aliphatic O–H insertion of **16**[a]



Entry	Ligand	[Cu]	Time (h)	Yield[b] (%)	ee[c] (%)
1[d]	(S_p)-**6b**	$CuPF_6(MeCN)_4$	7	81	14
2	(S_p)-**6b**	$CuPF_6(MeCN)_4$	7	87	67
3	(S_p)-**6b**	CuCl	2	85	57
4	(S_p)-**6b**	$CuCl_2$	3	92	54
5	(S_p)-**6b**	$Cu(OTf)_2$	1.5	86	76
6[e]	(S_p)-**6b**	$Cu(OTf)_2$	3.5	83	5
7[f]	(S_p)-**6b**	$Cu(OTf)_2$	2	89	7
8[g]	(S_p)-**6b**	$Cu(OTf)_2$	2	71	60
9[h]	(S_p)-**6b**	$Cu(OTf)_2$	3	53	44
10	(S_p)-**6a**	$Cu(OTf)_2$	6	76	15
11	(S_p)-**6c**	$Cu(OTf)_2$	2	84	40
12	(S_p)-**6d**	$Cu(OTf)_2$	4	88	72
13	(S_p)-**6e**	$Cu(OTf)_2$	2	87	48
14	(S_p)-**9a** (R = H)	$Cu(OTf)_2$	0.75	91	18
15	(S_p)-**9b** (R = Ph)	$Cu(OTf)_2$	0.5	85	−54
16	(S_p)-**10**	$Cu(OTf)_2$	9	77	−46

[a] All reactions were performed with ligand (0.012 mmol), [Cu] (0.010 mmol), $NaBAr_F$ (0.012 mmol), MS 5 Å (300 mg), EtOH (1.0 mmol), and diazo ester (0.20 mmol) in CH_2Cl_2 (total 2 mL) unless otherwise noted. [b] Isolated yield. [c] Determined by HPLC analysis (Daicel CHIRALCEL OD-H). [d] Without MS 5 Å. [e] MS 4 Å was used instead of MS 5 Å. [f] MS 3 Å was used instead of MS 5 Å. [g] Performed in $CHCl_3$. [h] Performed in $(CH_2Cl)_2$.

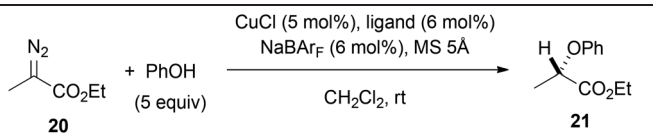
Table 2 BOX (S_p)-**6**-Cu-catalyzed intramolecular aliphatic O–H insertion of **18**[a]



Entry	Ligand	Time (h)	Yield[b] (%)	ee[c] (%)
1	(S_p)-**6b**	4.5	63	61
2	(S_p)-**6c**	4.5	63	55
3	(S_p)-**6e**	2.5	83	32

[a] All reactions were performed with ligand (0.012 mmol), $Cu(OTf)_2$ (0.010 mmol), $NaBAr_F$ (0.012 mmol), MS 5 Å (300 mg), and diazo ester (0.20 mmol) in CH_2Cl_2 (total 2 mL) unless otherwise noted. [b] Isolated yield. [c] Determined by HPLC analysis (Daicel CHIRALPAK AS-H).

Table 3 BOX (S_p)-**6**-Cu-catalyzed intermolecular aromatic O–H insertion of **20**[a]



Entry	Ligand	Time (h)	Yield[b] (%)	ee[c] (%)
1	(S_p)-**6b**	2	73	61
2	(S_p)-**6c**	2	65	39
3	(S_p)-**6e**	1	66	80

[a] All reactions were performed with ligand (0.012 mmol), CuCl (0.010 mmol), $NaBAr_F$ (0.012 mmol), MS 5 Å (300 mg), PhOH (1.0 mmol), and diazo ester (0.20 mmol) in CH_2Cl_2 (total 2 mL) unless otherwise noted. CuCl was used as a Cu source, according to Zhou's procedure.[17a] [b] Isolated yield. [c] Determined by HPLC analysis (Daicel CHIRALCEL OD-H).

molecular phenolic O–H insertion reaction of ethyl α-diazopropionate (**20**),[17a] (S_p)-**6e** was superior to (S_p)-**6b** during the enantioselection, achieving an 80% ee (Table 3).

Conclusions

In summary, we synthesized novel C_2-symmetric planar chiral BOX ligands based on the pCp bearing no central chirality and demonstrated that the bulky substituent on the spacer benzene ring played an important role to realize a high level of single planar chirality-controlled asymmetric induction (up to 80% ee). Further investigation of the scope and limitation of this Cu-catalyzed insertion reaction and application of the planar chiral ligands in other catalytic asymmetric reactions are currently underway.

Acknowledgements

This work was supported by JSPS KAKENHI grant number 24590006. The authors thank Dr Naoko Takenaga for technical support.

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