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NEW PREPARATION OF TRIDENTATE BIS-OXAZOLINE CARBAZOLE LIGAND EFFECTIVE FOR ENANTIOSELECTIVE NOZAKI-HIYAMA REACTION

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Abstract – A new preparation of the tridentate bis-oxazoline carbazole ligand **1** is described. This method features direct formation of the amide, which is a precursor of the ligand **1**, via the Pd-catalyzed amidation and following $BF_3 \cdot OEt_2$ mediated oxazoline formation. This method required only 2 steps from the aryl iodide to form the bis-oxazoline ligand; hence, it would be generally used for preparing other bis-oxazoline ligands.

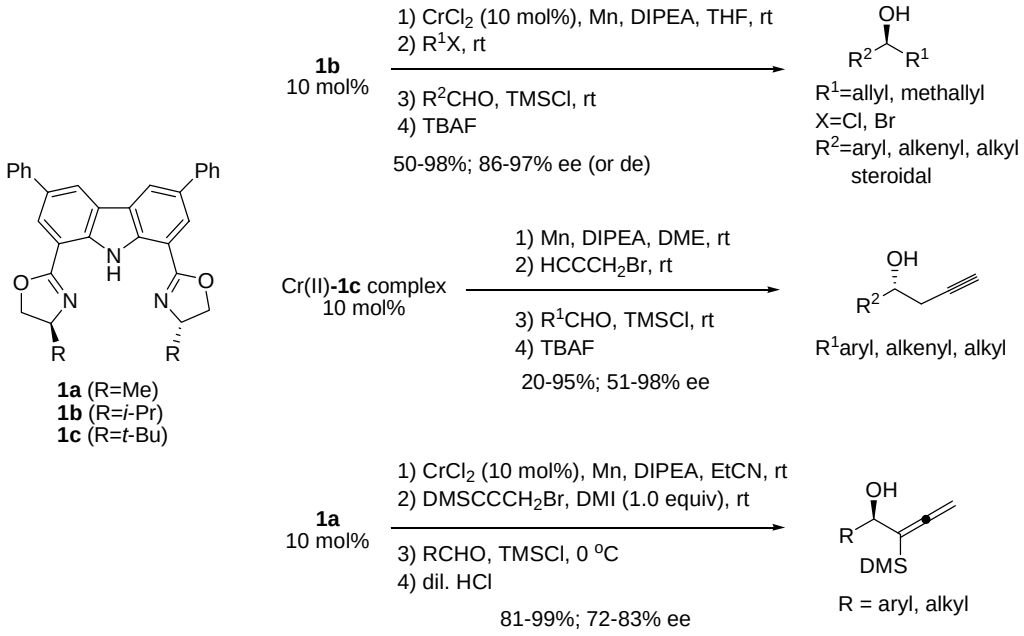
Nozaki-Hiyama reactions, Cr(II)-mediated C-C bond-forming reactions developed by Nozaki et al., have been well studied and developed by many research groups because of their potential utility.[1] Indeed, numerous total syntheses of complex natural products employed these reactions, proving their high chemoselectivity and excellent compatibility with various functional groups.[2]

However, because a large amount of chromium (II) salts must be used to complete these reactions,[2] a method for reducing this amount has been explored. In 1996, Fürstner et al. reported the catalytic redox system which successfully reduced the quantity of chromium salts, and since then, the Cr(II)-mediated C-C bond-forming reactions have been more valuable[3] and their asymmetric catalysis has drawn much attention.

Cozzi and Umani-Ronchi reported the first catalytic asymmetric Nozaki-Hiyama allylation using a commercially available salen ligand,[4] but the enantioselectivities and yields were not satisfactory. In addition, the formation of a considerable amount of the side-product derived from a pinacol coupling was also a problem.

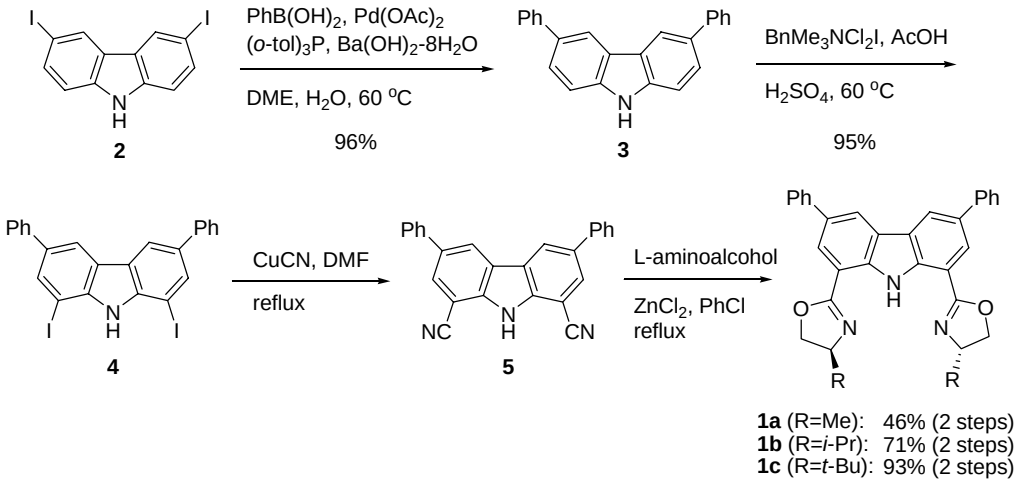
To overcome these difficulties new chiral ligands for Nozaki-Hiyama reaction have been developed by several research groups,[5] and we have independently reported a newly developed tridentate bis-oxazoline

carbazole ligand **1** that realized a highly enantioselective Nozaki-Hiyama allylation,[6] methallylation,[6] propargylation,[7] and allenylation[8] (Scheme 1).



Scheme 1 Catalytic asymmetric Nozaki-Hiyama allylation, methallylation, propargylation, and allenylation using a newly developed tridentate bis-oxazoline carbazole ligand **1a-c**

For further studies of the Nozaki-Hiyama reaction as well as other asymmetric catalysis, we required a new method for preparing the derivatives of ligand **1**, and herein we report an improved preparation and a new preparation of **1**.



Scheme 2 Improved preparation of ligand **1a-c**

We previously reported the synthetic route to **1** as shown in Scheme 2,[6] which started with Suzuki-Miyaura coupling reaction of **2** with phenylboronic acid (96%), followed by iodination to provide the iodide **4**. The yield of the iodination step from **3** to **4** was 67%, but this was improved to 95% under the modified conditions reported by Kajigaeshi.[9] The iodide **4** was converted to the nitrile **5** by reaction with CuCN, followed by reaction with amino alcohol to provide ligand **1** in 46-93% yield (2 steps).

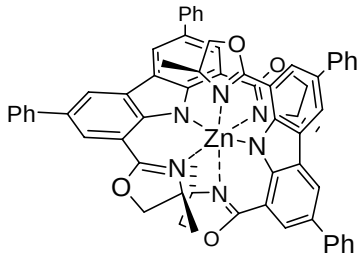


Figure 1 Structure of the initial product by the reaction of **5** with (*S*)-alaninol

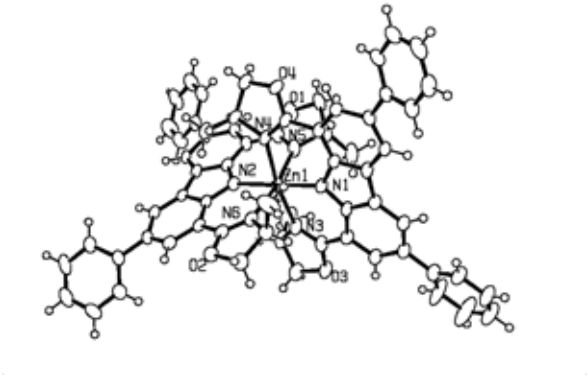
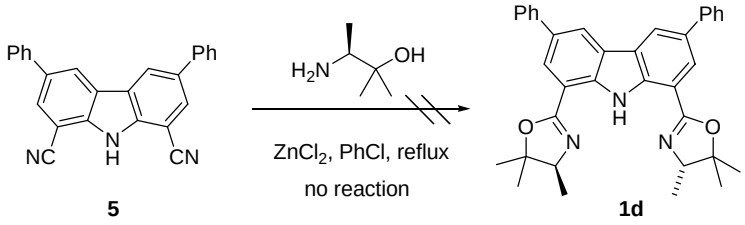


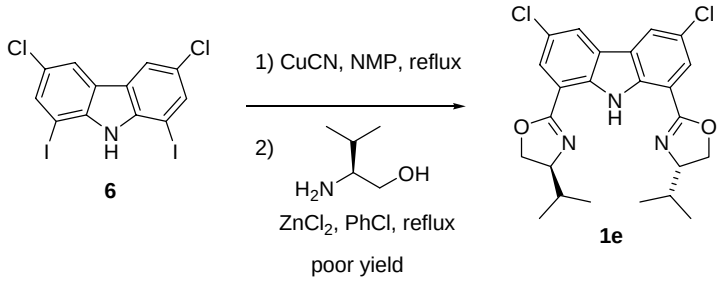
Figure 2 ORTEP of the Zn(II) complex shown in Figure 1

The yield of **1a** was rather low (46%) because the initial product obtained by reaction of **5** with (*S*)-alaninol was the Zn(II)-complex (Figure 1), which required rather strong acid conditions (AcOH, H_2SO_4, H_2O) to dissociate, providing **1a**. Unfortunately, this work-up resulted in decomposition of a large amount of acid labile **1a**. The structure of this Zn(II)-complex was determined by X-ray crystallographic analysis (Figure 2), clearly indicating that no coordination site was available around Zn^{2+} cation, which resulted in its high stability in dissociation.



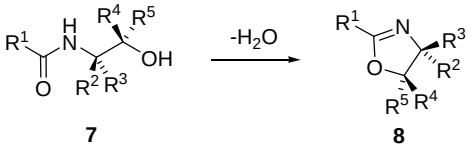
Scheme 3 Attempted preparation of ligand **1d**

In addition, although the method in Scheme 2 was successfully applied to preparing other carbazole bis-oxazoline ligands, we encountered its limitation as shown in Scheme 3. The reaction of nitrile **5** and (*S*)-3-amino-2-methylbutane-2-ol with $ZnCl_2$ afforded no desired product **1d**, probably due to the low reactivity of the bulky amino alcohol.



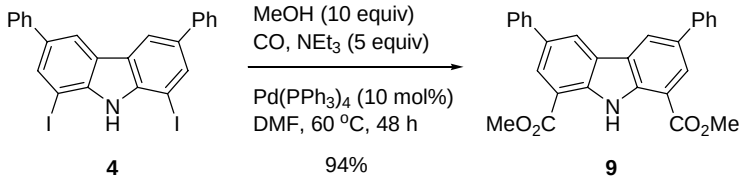
Scheme 4 Attempted preparation of ligand **1e**

Furthermore, we found another problem in preparing bis-oxazoline ligand **1e** (Scheme 4); that is, both reaction of the iodide **6** and the corresponding cyanide were too slow to provide a satisfactory amount of ligand **1e**. This result was surmised to arise from the low reactivity and insolubility of the both substrates under the conditions employed. Consequently, we decided to develop a new method for preparing the bis-oxazoline carbazole ligand **1**.



Scheme 5 General preparation of oxazoline **8** from amide **7**

Preparation of an oxazoline has been well studied, and most of the methods depend on cyclization of the amide **7** via dehydration, dehydrohalogenation, or dehydrosulfonation, and amide **7** has been prepared from the corresponding carboxylic acid or ester (Scheme 5);[10] however, the carbazole derived iodide **4** and **6** were highly crystalline and sparingly soluble in ether and THF, so that **4** and **6** were hardly converted to the corresponding carboxylic acids or esters by the usual method. Actually, halogen-metal exchange reactions of **4** and **6** failed to provide the corresponding organometallic reagents.



Scheme 6 Preparation of **9** from **7** by the Pd-mediated reaction

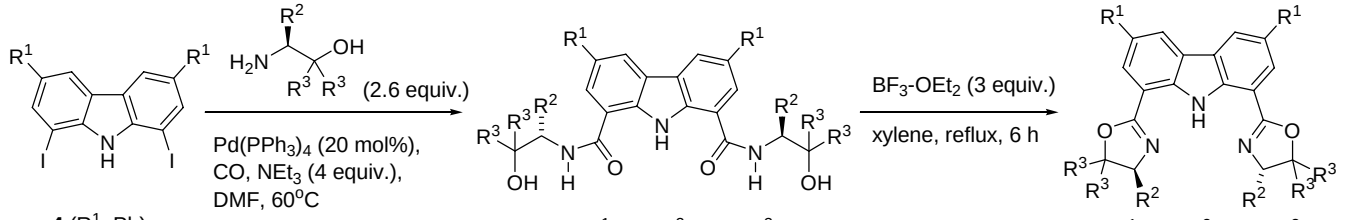
Thence, we turned our attention to the Pd-catalyzed amidation of the iodide **4** because this reaction was able to carry out in DMF which dissolved the iodide **4** well.[11] As a preliminary experiment, we carried out the Pd-catalyzed conversion of the iodide **4** to its methyl ester **9** (Scheme 6), and we found that the Pd-catalyzed reaction of **4** provided the methyl ester **9** in 94% yield under the conditions in Scheme 6.

Although the methyl ester **9** was expected to be a versatile intermediate for preparing various bis-oxazoline carbazole ligands, we next examined the Pd-catalyzed amidation of the iodide with amino alcohol under an atmosphere of CO because this reaction was expected to afford the desired amide

directly. Meyers reported the Pd-mediated reaction of aryl triflate, alkenyl triflate, aryl bromide, and alkenyl bromide with amino alcohol to prepare the amides for the oxazoline synthesis;[12] however, the reported reaction was carried out with $Pd(PPh_3)_4$ or $Pd(dba)_2$ and PPh_3 in THF in the presence of LiCl under 40 psi of CO, or alternatively, with $Pd(OAc)_2$, dppp ($PPh_2(CH_2)_3PPh_2$), and Et_3N in THF at 70 ºC under a balloon of CO.

Consequently, we optimized the reaction conditions for the Pd-catalyzed amidation of iodide **4** to form **10a** (Table 1), and finally found that this reaction proceeded smoothly using $Pd(PPh_3)_4$ in DMF under a balloon of CO, providing the desired amide **10** in high yield, which was subsequently treated with $BF_3 \cdot OEt_2$ in refluxing xylene to provide the bis-oxazoline carbazole ligand **1a** in 73% yield (2 steps, entry 1). This yield was greatly improved compared with 46% yield (2 steps) by the previous method in Scheme 2.

Table 1. Alternative synthetic route to the carbazole bis-oxazoline ligand **1**



4 (R^1=Ph)
6 (R^1=Cl)

10a (R^1=Ph, R^2=CH_3, R^3=H)
10b (R^1=Ph, R^2=*i*-Pr, R^3=H)
10c (R^1=Ph, R^2=CH_3, R^3=CH_3)
10d (R^1=Cl, R^2=*i*-Pr, R^3=H)

1a (R^1=Ph, R^2=CH_3, R^3=H)
1b (R^1=Ph, R^2=*i*-Pr, R^3=H)
1d (R^1=Ph, R^2=CH_3, R^3=CH_3)
1e (R^1=Cl, R^2=*i*-Pr, R^3=H)

Entry	R^1	R^2	R^3	Time (h)[a]	Product	Yield (%)[b]
1	Ph	CH_3	H	8	**1a**	73
2	Ph	*i*-Pr	H	8	**1b**	69
3	Ph	CH_3	CH_3	84[c]	**1d**	61
4	Cl	*i*-Pr	H	36	**1e**	82

[a]Time required for the Pd-catalyzed amidation. [b]Isolated yield. [c]Reaction at 80 ºC.

This new method was applied to prepare various bis-oxazoline carbazole ligands. For example, ligand **1b** was successfully prepared in 69% yield (entry 2), which was comparable to 71% yield by the previous method shown in Scheme 2. We also succeeded in preparing ligand **1c** and **1d** by this method in 61% (entry 3) and 82% yields (entry 4), respectively, which were inaccessible by the previous method (Scheme 3 and 4).

In summary, a new preparation method for the bis-oxazoline carbazole ligand **1** was developed. This method features direct formation of the amide, which is a precursor of the ligand **1**, via the Pd-catalyzed reaction and following $BF_3 \cdot OEt_2$ mediated dehydrative oxazoline formation. This method required only 2 steps from the aryl iodide to form the bis-oxazoline ligand; hence, it could be generally used for preparing other aryl oxazoline ligands.

ACKNOWLEDGEMENTS

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