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Synthesis of three-dimensionally arranged bis-biphenol ligand on hexaaryl benzene scaffold and its application for cross-pinacol coupling reaction

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ABSTRACT

The three-dimensionally arranged bis-biphenol ligand on a hexaaryl benzene scaffold for a dinuclear complex was synthesized by the Diels–Alder addition–decarbonylation reaction as a key step. Its preliminary studies on the titanium-induced cross-pinacol coupling reaction were performed based on step-by-step activation of two different aldehydes.

Dual reactive sites allow to position two substrates appropriately for the reaction, activate them, and induce electrically cooperating effect. Well-organized dinuclear transition metal complexes are considered to permit such a system, which is also found sometimes in active sites of enzymes to catalyze the reactions.[1] So far, many dinuclear catalysts have been developed and applied to organic reactions.[2] In this context, we envisioned that the controlled arrangement of two metals on the rigid scaffold can provide spatially regulated reaction sites. Based on this concept, the rigid bis-biphenol ligand **1** on a hexaphenyl benzene scaffold was designed (Scheme 1). The utility of our bis-biphenols depends on such conformationally regulated structure although there are various reports of ligands possessing two biphenol moieties.[2d,3] Here, we report the synthesis of the bis-biphenol ligand **1** and its preliminary studies on the ligand controlled cross-pinacol coupling reaction based on step-by-step activation of two different aldehydes.

Structural optimization of ligand **1a** was carried out using MM2 force field. The obtained structure showed the three-dimensionally controlled arrangement of biphenol ligand moieties (see Supplementary data, Fig. S1).

Our synthetic strategy for ligand **1** is outlined retrosynthetically in Scheme 1. We envisaged that **1** is constructed via the Diels–Alder addition–decarbonylation reaction[4] of tetraphenylcyclopentadienone (**2**) with the tolan **3** possessing two bis-biphenol moieties. Such tolan **3** would arise from the two biphenol derivatives **4** and acetylene spacer through the repetitive Sonogashira coupling reaction.

Scheme 2 shows the synthesis of **1**. The iodide **4** and the ethynyl derivative **5**[5] were coupled by the Sonogashira reaction to give **3a** and **3b** in 80% and 52% yields, respectively. The thus-obtained **3a** and **3b** were treated with **2** in diphenylether at 250 °C, followed by deprotection of the methoxy group with BBr_3 to give the bis-biphenol ligand **1a** and **1b** as a mixture of diastereomers (two steps 63% for **1a** and 57% for **1b**, Scheme 2). The *cis*/*trans* ratios for **1a** and **1b** are 35:65 and 32:68, respectively, the assignment of which is described in the next paragraph. Diastereomers were able to be separated by silica-gel chromatography. The gram scale synthesis was possible.

The structural assignment was studied by 1D ROESY experiments of the trimethylsilyl derivative $\mathbf{6}_{\mathit{cis}}$, which was prepared by the reaction of $\mathbf{3}_{\mathrm{TMS}}$[6] with **2**, followed by the separation of the *cis*/*trans* diastereomers by preparative thin-layer chromatography (Scheme 3). The isomer, in which ROEs were observed between the trimethylsilyl and methoxy groups, was assigned as a *cis*-isomer. The trimethylsilyl derivative $\mathbf{6}_{\mathit{cis}}$ was transformed to $\mathbf{1a}_{\mathit{cis}}$ by treatment with BBr_3 for the deprotection of the methoxy and trimethylsilyl groups. In this way, the structure of $\mathbf{1a}_{\mathit{cis}}$ was determined. Similarly, the *cis*/*trans* determination of $\mathbf{1b}_{\mathit{cis}}$ was carried out by the transformation to $\mathbf{1a}_{\mathit{cis}}$ by deiodation.

The desired *cis*-isomer is a minor product in the Diels–Alder addition–decarbonylation reaction, which made us investigate the isomerization equilibrium. The treatment of the demethylated compound $\mathbf{1a}_{\mathit{trans}}$ in diphenylether at 150 °C for 12 h resulted in the *trans*- and *cis*-isomers in 37:63 (Scheme 4). This finding

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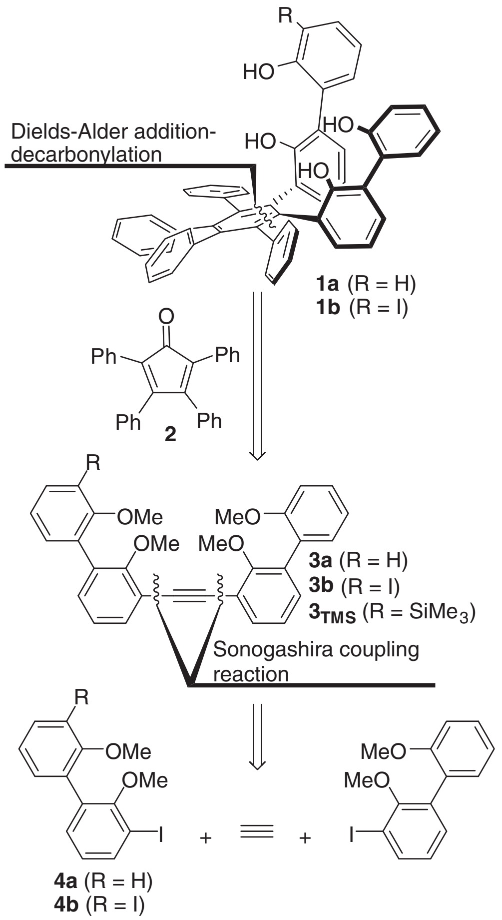
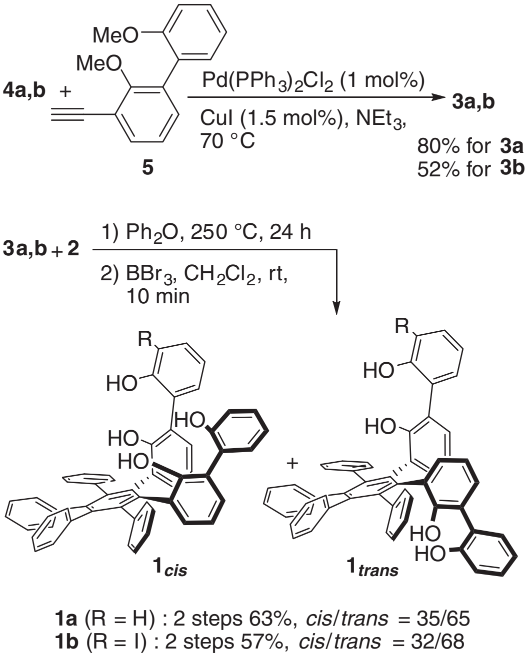
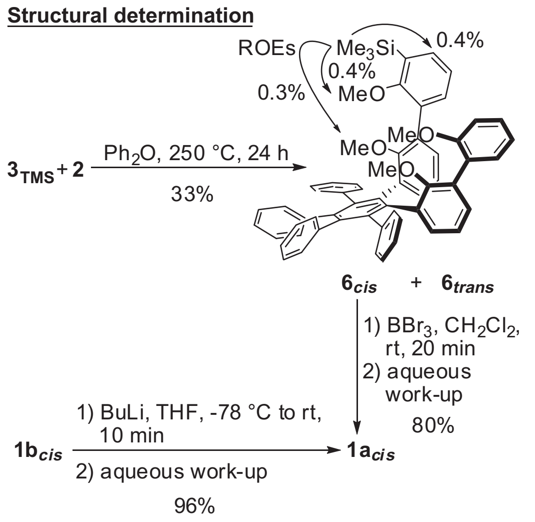


Scheme 1. Synthetic strategy for the ligand **1**.

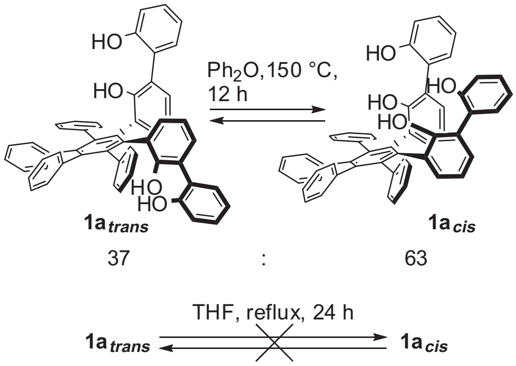


Scheme 2. Synthesis of **1a** and **1b**.

permits the better conversion to $\mathbf{1a}_{cis}$. On the other hand, this isomerization did not occur in THF at reflux temperature even after 24 h to indicate the conformational rigidity.



Scheme 3. Structural determination of **1** based on 1D ROESY experiments of $\mathbf{6}_{cis}$.

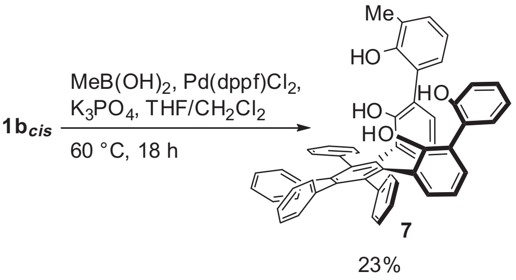


Scheme 4. *Trans*/*cis* isomerization of **1a**.

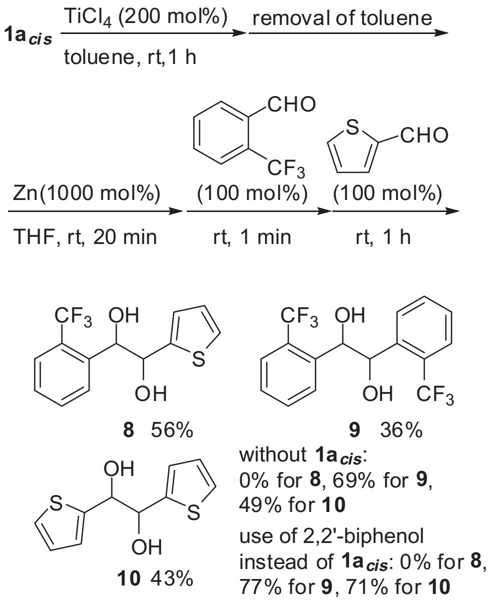
Furthermore, the derivatization is possible by using the iodo-substituent of $\mathbf{1b}_{cis}$. For example, the *B*-alkyl Suzuki–Miyaura cross-coupling reaction with $MeB(OH)_2$ allowed the introduction of the methyl group with the formation of **7** (Scheme 5).

Complexation of $\mathbf{1a}_{cis}$ with $TiCl_4$ was studied by ^1H NMR (see Supplementary data, Fig. S2). The integral ratio for the hydroxyl protons in the phenoxy group decreased by half by the addition of 1 equiv $TiCl_4$. On further addition of 1 equiv $TiCl_4$, the peaks disappeared, suggesting the formation of the corresponding dinuclear complex.

With such a complex in hand, the intermolecular cross-pinacol coupling reaction was studied using the stoichiometric amount of $\mathbf{1a}_{cis}$ (Scheme 6) because the sequential activation of two different aldehydes and subsequent cross-coupling is envisioned to be allowed due to the fixed bimetallic reactive sites. Although catalytic, diastereoselective, and/or enantioselective methods have been developed,[7,8] the intermolecular cross-pinacol coupling reaction is still a challenging issue due to the difficulty in the discrimination of two aldehydes in the reaction. So far, there are only few examples for the cross-pinacol-type coupling, which strongly depend on the combination of substrates.[9] First, the ligand (100 mol %) was mixed with 200 mol % of $TiCl_4$ for complexation in toluene under argon at room temperature. After 1 h, the solvent was changed to THF. Then, activated Zn (1000 mol %) was added to the mixture to generate a reduced Ti complex.[10] *o*-Trifluoromethyl benzaldehyde was added to the reaction mixture at room temperature. One minute later, 2-thienylaldehyde was added to the reaction mixture at the same temperature. The cross-coupling product **8** was obtained in 56% yield (*syn*/*anti* = 51:49)[11], where the



Scheme 5. Derivatization to **7**.



Scheme 6. Cross-pinacol coupling reaction based on step-by-step activation using the ligand **1a$_{cis}$**.

homo-coupling products **9** and **10** were also formed in 36% (*dl*/*meso* = 71:29)[12] and 43% (*dl*/*meso* = 76:24)[13] yields, respectively. Here, yield was calculated as follows: (mol of product)/(maximal mol of producible products)×100. On the other hand, the same reaction using 2,2′-biphenol instead of **1a$_{cis}$** gave only the homo-coupling products **9** and **10** in 77% (*dl*/*meso* = 48:52) and 71% (*dl*/*meso* = 55:45) yields,[14] respectively, without the formation of **8**. Similarly, the same reaction without **1a$_{cis}$** led to only the homo-coupling products **9** and **10** in 69% (*dl*/*meso* = 53:47) and 49% (*dl*/*meso* = 71:29) yields,[14] respectively. These results indicate a steric effect of the bis-biphenol ligand **1a$_{cis}$** toward the cross-pinacol reaction.

In summary, the three-dimensionally arranged bis-biphenol ligand on the hexaaryl scaffold for the dinuclear complex was synthesized to show the conformational stability. The formation of the dinuclear titanium complex permitted preliminary investigation on the cross-pinacol coupling reaction utilizing step-by-step activation of two different aldehydes by sterically controlled arrangement of the biphenol ligand moieties. Further increase of cross-selectivity is expected by the left–right asymmetric ligand as shown in the concept in Figure 1, which can be synthesized using the Pd-catalyzed cross-coupling reaction as demonstrated by the synthesis of **7**. Furthermore, such ligands will be applied to other reactions that need dual activation by metals.

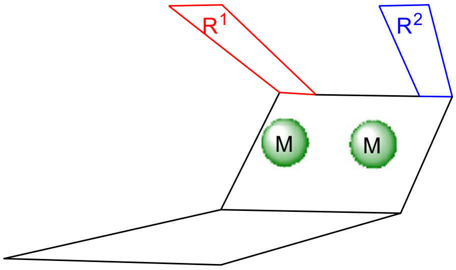


Figure 1. Concept of next generation ligands.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.113.

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