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Efficient bimetallic titanium catalyst for carbonyl-ene reaction

Fang Fang, Fang Xie, Han Yu, Hui Zhang, Bo Yang, Wanbin Zhang *

School of Chemistry and Chemical Technology, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, PR China

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ABSTRACT

A new family of achiral 3,3′,5,5′-tetrasubstituted-2,2′,6,6′-tetrahydroxy biphenyl ligand **4** was developed. The axial chirality of the ligand could be induced by the chelation of 2,2′,6,6′-tetrahydroxy groups with (*R*)-BINOL-Ti(O^{i}Pr)$_2$ to form an axially chiral bimetallic titanium catalyst **9**. Compared with (*R*)-BINOL-Ti(O^{i}Pr)$_2$ catalyst, this novel catalyst **9** exhibited excellent activity and enantioselectivity for the carbonyl-ene reaction of methylstyrene and ethyl glyoxylate. 3,3′,5,5′-Tetrasubstituted groups showed a remarkable effect on both enantioselectivity and yield. With **9d** prepared from 3,3′,5,5′-tetramethyl-2,2′,6,6′-tetrahydroxy biphenyl **4d** as the catalyst, the best result, up to 97.6% ee and 99% yield, was obtained. Additionally, the bimetallic catalyst **9** also showed better catalytic capability than the corresponding monometallic catalyst.

The design and development of novel and effective chiral ligands for enantioselective reactions are of the fundamental aspects in asymmetric catalysis, and have attracted a great deal of attention from both academic research and industry. Thousands of ligands with various chiral elements have been developed and applied in many catalytic asymmetric reactions to produce enantiomerically pure compounds.[1]

Among them, axial chirality is one of the important stereogenic elements used for the development of chiral ligands.[2] In general, there are two necessary preconditions for axial chirality in biaryl molecules, that is, a rotationally stable biaryl axis and the presence of different *ortho* substituents on both sides of the biaryl axis.

Recently, we are interested in a new family of axially achiral biaryl, which has four constitutionally identical substituents groups at the *ortho* positions of the biphenyl axis. This type of molecule has three C_2 symmetric factors in its structure, but no axial chirality due to the molecular symmetry. However, when the four identical substituents are linked pairwise by two bridges, the axial chirality of the molecule is induced, so a pair of enantiomers is formed, which is different from traditional axially chiral molecules (Fig. 1, **1**).[3] If the four substituents are of the coordination group and coordinated to metal ions, one pair of enantiomeric complexes would be formed. If we introduce a chiral element in the four coordination groups (Fig. 1, **2**) or an additional chiral ligand (Fig. 1, **3**) to the metal ions, one of the two possible diastereomeric bimetallic complexes with different axial chirality in biphenyl backbone should be formed in preference to the other, and in some cases, only one of the two bimetallic diastereomers might be formed because of the different energies of the two diastereomers. These chiral bimetallic complexes would provide new reactivity patterns and physical properties that could not be achieved with similar monometallic complexes, and neighboring metal ions would be expected to cooperate in promoting the reaction.[4]

With this axial chiral catalyst design concept of the former case (Fig. 1, **2**), we have successfully developed a new family of tetraoxazolinyl biphenyl ligands, in which a chiral element was introduced in the oxazoline coordination group. When they chelated with Pd(II), a stable axial chirality of the biphenyl backbone was induced and only one of the two diastereomer complexes was formed. This chelation-induced axially chiral Palladium complex system with tetraoxazoline ligands showed excellent catalytic activities and enantioselectivities in the Wacker-type cyclizations.[5]

Herein, using our axial chiral catalyst design concept of the later case mentioned above (Fig. 1, **3**), we would like to report a new family of achiral *ortho*-tetrahydroxy biphenyl ligand **4** (Fig. 2) and its complexation and application to the enantioselective carbonyl-ene reactions. Since four substituted groups at 3,3′,5,5′-positions are near the metal reaction center, when **4** is complexed to metal ion, the bimetallic catalyst so formed (Fig. 1, **3**) is expected to have a better effect on catalytic activities and enantioselectivities.

Achiral ligand **4** can be readily prepared. **4a**, **4b,** and **4e** were prepared as reported methods.[6] 3,3′,5,5′-Tetrabromo-2,2′,6,6′-tetrahydroxy biphenyl **4c** was readily synthesized as following (Scheme 1): bromation of 2,2′,6,6′-tetramethoxy biphenyl with Br_2 (4.4 equiv) in the presence of HOAc (0.3 equiv) gave bromized compound **5**[7] in quantitative yield. Then, 3,3′,5,5′-tetrabromo-2,2′,6,6′-tetrahydroxy biphenyl **4c**[8] was obtained by the deprotection of **5** with BBr_3 (4.4 equiv) in quantitative yield.

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* Corresponding author. Tel./fax: +86 21 5474 3265.
E-mail address: wanbin@sjtu.edu.cn (W. Zhang).

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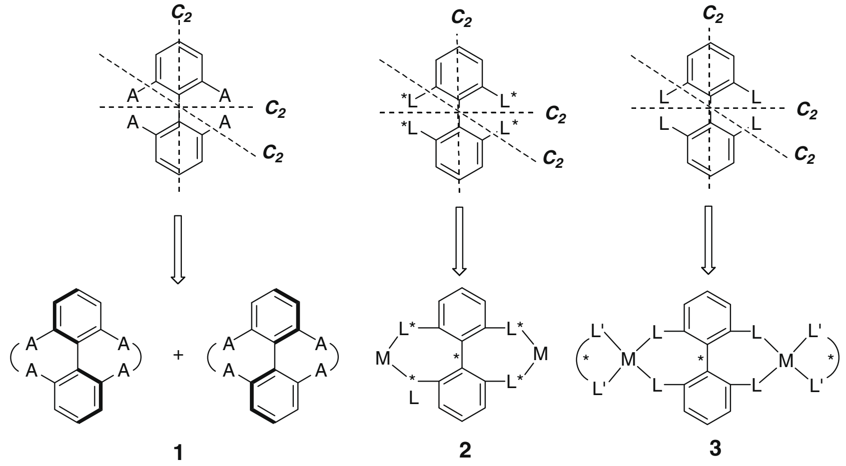


Figure 1. The inducement of the axial chirality of the axially achiral biaryl.

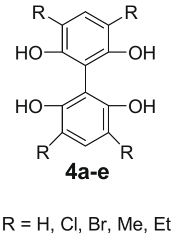
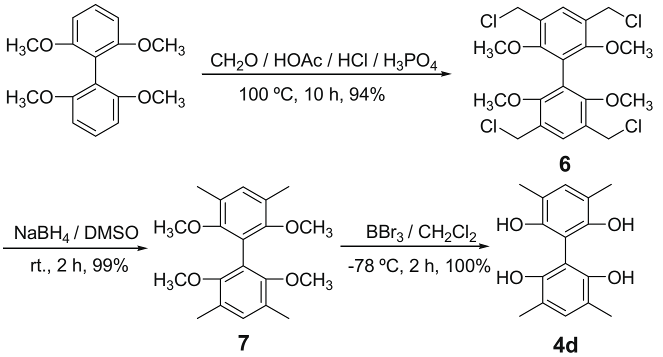


Figure 2. Axially achiral *ortho*-tetrahydroxy biphenyl ligands **4a**–**e**.



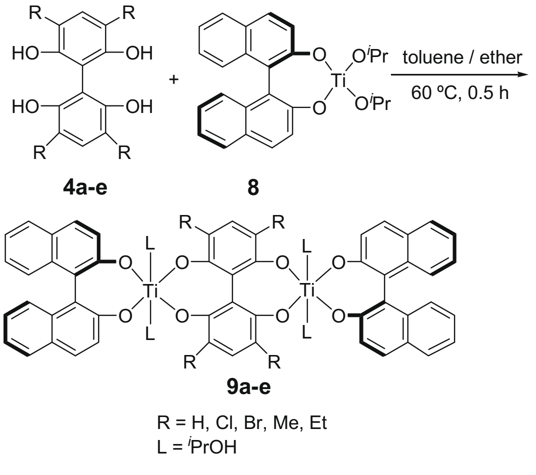
Scheme 2. The synthesis of ligand **4d**.

Preparation of the 3,3′,5,5′-tetramethyl-2,2′,6,6′-tetrahydroxy biphenyl **4d** was as following (Scheme 2): firstly, chloromethylation of 2,2′,6,6′-tetramethoxy biphenyl with paraformaldehyde (30 equiv) in the mixture acid of phosphoric acid, concentrated hydrochloric acid, and acetic acid ($V = 1{:}1{:}1$, 0.01 M) afforded product **6**[9] with 94% isolated yield. Then, reduction of **6** by NaBH$_4$ gave 3,3′,5,5′-tetramethylated compound **7**[10] in 99% yield. After the deprotection of **7** with BBr$_3$ (4.4 equiv), **4d**[11] was obtained in quantitative yield.

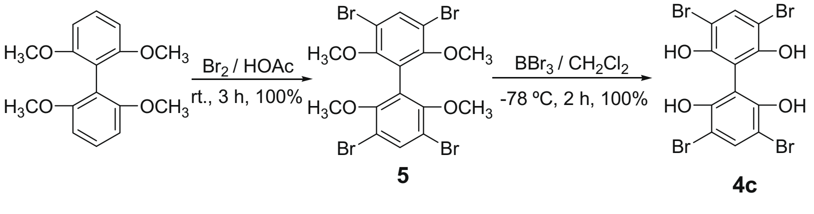
Then we investigated the complexation of **4** with Ti(IV). When **4** was added to 2 equiv (*R*)-BINOL-Ti(O^{i}Pr)$_2$ and stirred at 60 °C for 0.5 h, 2,2′,6,6′-tetrahydroxy groups were linked pairwise by chelation with metal Ti to give the compound **9** with bimetallic structure (Scheme 3).[12]

Then this new catalyst **9** prepared from the addition of axial achiral biphenyl **4** to (*R*)-BINOL-Ti(O^{i}Pr)$_2$ was evaluated by the carbonyl-ene reaction (Scheme 4),[13] since it was reported by Mikami that dramatic increases in both yields and the ees could be obtained by the addition of optically active ligands such as (*R*)-BINOL to the (*R*)-BINOL-Ti(O^{i}Pr)$_2$ catalyst compared with no addition or addition of racemic ligands such as (±)-BINOL.[14]

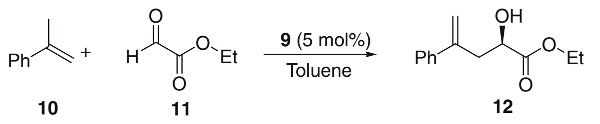
Thus, (*R*)-BINOL and Ti(O^{i}Pr)$_4$ (molar ratio = 1:1) were stirred in dry toluene at rt for 30 min, and then, to this mixture 2,2′,6,6′-tet-



Scheme 3. The synthesis of the axially chiral bimetallic titanium catalysts **9a**–**e**.



Scheme 1. The synthesis of ligand **4c**.



Scheme 4. The carbonyl-ene reaction catalyzed by the axially chiral bimetallic titanium catalyst **9a**–**e**.

rahydroxy biphenyl **4** (0.5 equiv) resolved in dry ether was added, and stirred for another 0.5 h at 60 °C. At 0 °C, α-methylstyrene **10** (10 equiv) and freshly distilled ethyl glyoxylate **11** (20 equiv) were added and stirred at 0 °C for 30 h. The results of the experiment showed that bimetallic catalyst **9** showed higher enantioselectivity and activity than catalyst (*R*)-BINOL-Ti(O^{i}Pr)$_2$ (Table 1, entries 1–6), and the introduction of sterically bulky 3,3′,5,5′-tetrasubstituents had a remarkable effect on enantioselectivity or/and yield (Table 1, entries 2–6). The yields of the reaction were advanced dramatically except **9c** and **9e**, which were presumed to be too bulky in 3,3′,5,5′-positions and decreased the activity of the reaction. When **9d** containing 3,3′,5,5′-tetramethyl groups was used, **12** was obtained with the best result in 97.6% ee and 99% yield (Table 1, entry 5).

Furthermore, addition of (*R*)-BINOL-Ti(O^{i}Pr)$_2$ to **4d** with the molar ratio of 1:1 formed the monometallic catalyst **13d** (Fig. 3), with which catalyst, 96.1% ee and 90% yield were obtained (Table 1, entry 7). This result was slightly inferior to the corresponding bimetallic catalyst **9d** in both ee and yield (Table 1, entry 5).

Though there was not much direct information to prove the inducement of axial chirality in biphenyl skeleton of bimetallic catalyst **9**, comparing our results with those of Mikami,[14] it was suggested that the *R* axial chirality of the biphenyl backbone was induced in the complex **9**, which resulted in more catalytic activity and higher enantioselectivity than (*R*)-BINOL-Ti(O^{i}Pr)$_2$.

The *R* axial chirality inducement process in complex **9** could be suggested as follows: *R* axial chirality in biphenyl skeleton was induced by (*R*)-BINOL when achiral tetrahydroxy biphenyl **4** was chelated with 1 equiv (*R*)-BINOL-Ti(O^{i}Pr)$_2$ to form monometallic catalyst *R*,*R*-**13** (Scheme 5), since **13** showed much better activity and enantioselectivity compared with (*R*)-BINOL-Ti(O^{i}Pr)$_2$ (Table 1, entry 7).[14] The similar phenomenon was also reported by Vallée and co-workers in the case of conformationally flexible biphenols, of which the axial chirality was induced by a chiral activator, (*R*)-BINOL-Ti(O^{i}Pr)$_2$.[17] *R*,*R*-**13** was then chelated with another 1 equiv (*R*)-BINOL-Ti(O^{i}Pr)$_2$ to form bimetallic catalyst *R*,*R*,*R*-**9** (Scheme 5), which showed better catalytic behavior than the corresponding monometallic one.

Table 1
The carbonyl-ene reaction catalyzed by **9** and **13d** complex[a,15]

Entry	R (cat.)	Yield[b] (%)	Ee[c] (%)
1[d]	–	74	90.0
2	H (**9a**)	99	93.1
3	Cl (**9b**)	99	91.3
4	Br (**9c**)	89	94.1
5	CH_3 (**9d**)	99	97.6
6	CH_3CH_2 (**9e**)	91	96.8
7[e]	CH_3 (**13d**)	90	96.1

[a] The reaction was carried out with the molar ratio of 1/2/0.05 (**10**/**11**/**9**).

[b] Isolated yield.

[c] The ee was determined by HPLC on a chiral OJ column and absolute configuration was assigned to be *R* by comparing with the literature.[16]

[d] Using (*R*)-BINOL-Ti(O^{i}Pr)$_2$ as the catalyst.

[e] The catalyst **13d** was formed by mixing (*R*)-BINOL-Ti(O^{i}Pr)$_2$ and **4d** with the molar ratio of 1:1, the reaction was carried out with the molar ratio of 1/2/0.1 (**10**/**11**/**13d**).

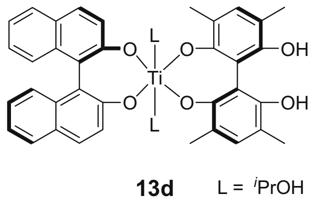
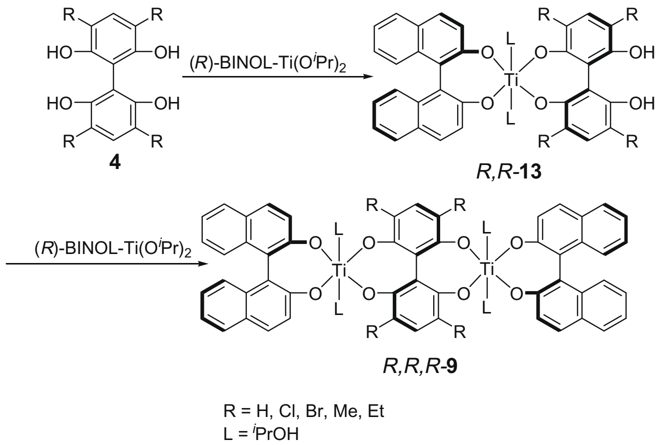


Figure 3. The axially chiral monometallic titanium catalyst **13d**.



Scheme 5. The suggested inducement process of the complex **9** to form the *R* configuration.

In conclusion, we have developed a new family of achiral 3,3′,5,5′-tetrasubstituted-2,2′,6,6′-tetrahydroxy biphenyl ligand **4**. The axial chirality of the ligand could be induced by the chelation of 2,2′,6,6′-tetrahydroxy groups with (*R*)-BINOL-Ti(O^{i}Pr)$_2$ to form an axially chiral bimetallic titanium catalyst **9**. And this novel catalyst **9** exhibited excellent activity and enantioselectivity for carbonyl-ene reaction of methylstyrene and ethyl glyoxylate compared with (*R*)-BINOL-Ti(O^{i}Pr)$_2$ catalyst system. 3,3′,5,5′-Tetrasubstituted groups showed remarkable effect on both enantio selectivity and yield. With **9d** prepared from 3,3′,5,5′-tetramethyl-2,2′,6,6′-tetrahydroxy biphenyl **4d** as the catalyst, 97.6% ee was obtained with 99% yield. Additionally, the bimetallic catalyst **9** also showed better catalytic capability than the corresponding monometallic one.

Acknowledgments

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7. *3,3′,5,5′-Tetrabromo-2,2′,6,6′-tramethoxy biphenyl* **5**. Yield: 100%. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.84 (s, 2H, Ar*H*), 3.64 (s, 12H, OC*H*$_3$); ^{13}C NMR (100 MHz, CDCl$_3$): δ 156.37, 136.69, 125.91, 112.81, 61.18; HRMS calcd for $C_{16}H_{14}Br_4O_4$, 589.7585, found 589.7540.
8. *3,3′,5,5′-Tetrabromo-2,2′,6,6′-tetrahydroxy biphenyl* **4c**. Yield: 100%. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.69 (s, 2H, Ar*H*), 5.56 (s, 4H, O*H*); ^{13}C NMR: (100 MHz, DMSO-d_6) δ 153.16, 134.59, 112.59, 101.43; HRMS calcd for $C_{12}H_6Br_4O_4$, 533.6959, found 533.6938.
9. *3,3′,5,5′-Tetrachloromethyl-2,2′,6,6′-tetramethoxy biphenyl* **6**. Yield: 94%.^{1}H NMR (400 MHz, CDCl$_3$): δ 7.57 (s, 2H, Ar*H*), 4.67 (s, 8H, C*H*$_2$), 3.61 (s, 12H, OC*H*$_3$); ^{13}C NMR (100 MHz, CDCl$_3$): δ 157.87, 133.41, 127.58, 122.95, 61.88, 41.20; HRMS calcd for $C_{20}H_{22}Cl_4O_4$ 468.0243, found 468.0228.
10. *3,3′,5,5′-Tetramethyl-2,2″,6,6’-tetramethoxy biphenyl* **7**. Yield: 100%. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.03 (s, 2H, Ar*H*), 3.49 (s, 4H, OC*H*$_3$), 2.27 (s, 12H, C*H*$_3$); ^{13}C NMR (100 MHz, CDCl$_3$): δ 156.23, 132.65, 126.04, 122.97, 60.17, 16.28; HRMS calcd for $C_{20}H_{26}O_4$ 330.1831, found 330.1798.
11. *3,3′,5,5′-Tetramethyl-2,2′,6,6′-tetrahydroxy biphenyl* **4d**. Yield: 100%. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.04 (s, 2H, Ar*H*), 4.71 (s, 4H, O*H*), 2.21 (s, 12H, C*H*$_3$); ^{13}C NMR (100 MHz, CDCl$_3$): δ 156.81, 136.58, 119.99, 115.30, 21.56; HRMS calcd for $C_{16}H_{18}O_4$, 274.1205, found 274.1200.
12. Bimetallic catalyst **9** can be confirmed by Mass, for example **9d**: ES+: *m*/*z*: 958 [*M*+23].
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15. *A general procedure for carbonyl-ene reaction*: Under an atmosphere of argon, (*R*)-BINOL 14.3 mg (0.05 mmol) and Ti(O^{i}Pr)$_4$ 14.8 µl (0.05 mmol) were stirred in dry toluene 1 ml at rt for 30 min, and then to this mixture, 3,3′,5,5′-tetramethyl-2,2′,6,6′-tetrahydroxy biphenyl **4d** 6.8 mg (0.025 mmol) resolved in 0.5 ml dry ether was added, and stirred for another 0.5 h at 60 °C. At 0 °C, α-methylstyrene 65 µl (0.5 mmol) and freshly distilled ethyl glyoxylate 117 µl (1.0 mmol) were added and stirred at 0 °C for another 30 h. Pure product **12** was obtained by column chromatography over silica gel eluted with petroleum/ethyl acetate (10:1). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.44–7.28 (m, 5H, Ar*H*), 5.44 (s, 1H, C=C*H*$_2$), 5.25 (s, 1H, C=C*H*$_2$), 4.30–4.24 (m, 1H, C*H*OH), 4.15–4.00 (m, 2H, OC*H*$_2$), 3.07 (dd, *J* = 4.5 Hz, 13.5 Hz, 1H, CC*H*$_2$CH), 2.84 (dd, *J* = 8.1 Hz, 13.5 Hz, 1H, CC*H*$_2$CH), 2.73 (d, *J* = 6.0 Hz, 1H, O*H*), 1.24 (t, *J* = 7.2 Hz, 3H, C*H*$_3$). Enantiomeric excesses were determined by HPLC using a Daicel Chiralpak OJ column, eluent, hexane/^{i}PrOH = 90/10, flow rate: 0.5 ml/min, λ = 254 nm, t_R = 18.46 min (minor), 25.05 min (major), respectively, the absolute configuration of the homoallylic alcohol is *R*, based on literature data.
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