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#### **Diastereomeric Biaryl Diols Derived from Estrone**

Jie Feng, Xin-Bin Yang, Shuai Liang, Ji Zhang,\* Xiao-Qi Yu\*



# An Efficient Oxidative Coupling Method for Synthesis of Novel Diastereomeric Biaryl Diols Derived from Estrone

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#### Abstract:

An efficient oxidative coupling of estrogen derivatives was developed. Several 2-substitutent-17-deoxyestrones were applied to the aerobic oxidative coupling reactions catalyzed by CuCl<sub>2</sub>/TMEDA. The products were obtained as the diastereoisomers with moderate to good yields. As chiral ligands, three couples of diastereoisomers were applied to the asymmetric HDA reaction to investigate their chemical properties.

Keywords: oxidative coupling, estrogen derivatives, substituent, diastereoisomers

Axially chiral biaryl diols play important roles in asymmetric synthesis since the diols or their derivatives can induce high enantioselectivity.<sup>1</sup> In the past several decades, much attentions have been paid to the effective synthesis of these axially chiral diols, especially binaphthol and its derivatives.<sup>2</sup> Oxidative coupling of 2-naphthol derivatives represents a well established method for the preparation of binaphthols. Various oxidizing metal salts such as Fe,<sup>3</sup> Cu,<sup>4</sup> V,<sup>5</sup> Ru<sup>6</sup> or Re<sup>7</sup> have been used for the coupling of 2-naphthol derivatives to give binaphthols with high yields or enatioselectivities. However, limited researches were focused on the oxidative coupling of tetrahydronaphthalen-2-ol and its analogues, which have been proved to be inactive in oxidative coupling reactions.

In 1977, Ius and co-workers firstly reported that  $K_3Fe(CN)_6$  could catalyze the coupling reaction of 17 $\beta$ -estradiol,<sup>8</sup> which is a typical analogue of tetrahydronaphthalen-2-ol. The mixed *ortho*-coupled products were obtained with low yields and low selectivity. In 2004, Riva and co-workers applied a copper-containing enzymatic catalyst laccase to the oxidative coupling

reactions of tetrahydronaphthalen-2-ol and  $17\beta$ -estradiol.<sup>9</sup> Both of the substrates converted to dimeric products with low yields and improved selectivity. Afterwards, another peroxidase-H<sub>2</sub>O<sub>2</sub>-MnO<sub>2</sub> catalytic system was developed to catalyze the dimerization of  $17\beta$ -estradiol by Pezalla.<sup>10</sup> The dimeric product with axial symmetry was isolated only with 2% yield from eight different dimeric or trimeric products. To our knowledge, there was rare successful synthesis of axially symmetric dimmers through the coupling reaction from H<sub>4</sub>-naphthol's derivatives with high reactivity and selectivity. Herein, we report an efficient method of the oxidative coupling reactions of a series of chiral estrogen derivatives. These chiral substrates (*S*-**2**) as precursors of axially chiral biaryl diols are attractive because the diol products (*S*, *S*-**3**) could be easier for separation due to their diastereoisomerism.

The original challenge was the competition of reactive positions between C-2 and C-4 of estrogen in oxidative coupling reaction. Taylor and co-workers have used the *tert*-butyl as protecting group at C-2 of estrogen for the purpose of selective functionalization at C-4 position.<sup>11</sup> Inspired by this report, to block C-2 position of estrogen, a series of 2-alkyl or 2-aryl-17-deoxyestrones (**2a-2h**) were synthesized starting from estrone through different pathways (Scheme 1).<sup>12</sup>



Scheme 1. Synthesis of a series of 2-alkyl or aryl substituted 17-deoxyestrones

2-ethyl-17-deoxyestrone (**2a**) was then chosen as model substrate to optimize the aerobic oxidative coupling conditions, and the results are summarized in Table 1. Firstly, the use of three common oxidative metal salts exhibited no activity in the coupling reactions (Entries 1-3), and only trace target product could be observed when the reaction was catalyzed by copper salt. Then several ligands were investigated to improve the efficiency of metal catalyst used in the model reaction (Entries 4-6). To our delight, the dimeric product was obtained in 57 % yield in

the reaction catalyzed by  $CuCl_2$  in the presence of tetramethylethylenediamine (TMEDA, entry 5). This is the highest yield of estrogen's dimerization ever studied. Any changes of copper salts or solvents led to no reaction (Entries 7-11), and slightly decreased yield was obtained by using anhydrous  $CuCl_2$  instead of  $CuCl_2 2H_2O$  as catalyst (Entry 12). Neither the increase of catalyst loading nor reaction temperature could increase the yield (Entries 13, 14). In addition, the special aerobic oxidative method is vital for the reaction, and the desired product could only be obtained in the reaction with atmosphere bubbling through the reaction mixture (Entry 15). However, pure oxygen bubbling did not improve the yield of reaction.

**Table 1.** Optimization of the reaction conditions.



[a] Reaction conditions: **2a** (1 mmol), metal salt (20 mol %), ligand (20 mol %), solvent (15 mL), atmosphere was bubbled through the mixture at room temperature for 72h. [b] Reaction was performed with  $MnO_2$  (100 mol %). [c] Reaction was performed with  $CuCl_2 \cdot 2H_2O$  (40 mol %) and TMEDA (40 mol %). [d] Reaction was performed at 40 °C. [e] Reaction was performed not with bubbling atmosphere.

Substrates 2a-2h were then employed for the oxidative coupling under optimized conditions (Table 2). It's notable that the catalytic activities were strongly depended on the substituents at C-2 of estrogen. For example, the substrates with 2-ethyl and 2-methyl substituent (2a and 2b) gave the dimeric products with moderate yields, comparing with no product in the reaction involving 2-t-butyl-17-deoxyestrone 2c (Entries 1-3). Not only the alkyl groups but also several aryl substituents have different effects on the oxidative coupling. Electron-withdrawing deoxyestrones substituted by group might benefit the reaction, and the 3. 5-di(trifluromethyl)-phenyl at C-2 could give the dimeric product 3e smoothly with up to 75% yield (Entry 5), which was distinctly higher than that obtained by using phenyl substituted substrate 2d (58%, entry 4). In contrast, there was no reaction when the electron-donating aryl groups were introduced to the substrates (Entries 6, 7). Further, substrate with more bulky naphthalene group (2h) could also convert to the desired product with 22% yield (Entry 8). These results demonstrate that both electronic effect and steric effect of the substituents influence the oxidative coupling reaction remarkably.

 Table 2. Oxidative reactions of several 2-substituted-17-deoxyestrone.

		HO S-2	$ \begin{array}{c}                                     $	S, S-3
PC	Entry	Substrate	R	Isolated yield of $3 (\%)^{[b]}$
	1	2a	ethyl	57
	2	<b>2b</b>	methyl	68
	3	2c	<i>t</i> -butyl	N.R.
	4	2d	phenyl	58
	5	2e	3,5-di(trifluromethyl)-phenyl	75
	6	<b>2f</b>	4-methoxyphenyl	N.R.
	7	2g	2,4,6-trimethoxyphenyl	N.R.
	8	2h	1-naphthyl	22

[a] Reaction conditions: substrate **2** (1 mmol), CuCl<sub>2</sub>·2H<sub>2</sub>O (34 mg, 0.2 mmol), TMEDA (30 mg, 0.2 mmol), CH<sub>2</sub>Cl<sub>2</sub> (15 mL), atmosphere was bubbled through the mixture at room temperature for 72h. [b] Diastereoisomers ( $R_{av}$  S, S- and  $S_{av}$  S, S-) were obtained in 1 : 1 ratio.

The 4, 4'-linked biaryl diols *S*, *S*-**3a-3h** were obtained as 1 : 1 mixtures of two diastereoisomers ( $R_{ax}$ , *S*, *S*- and  $S_{ax}$ , *S*, *S*-, Figure 1). Among these diastereoisomers, **3a**, **3b** and **3d** could respectively be separated to a couple of axially chiral biaryl diols (**3a**<sub>1</sub> and **3a**<sub>2</sub>, **3b**<sub>1</sub> and **3b**<sub>2</sub>, **3d**<sub>1</sub> and **3d**<sub>2</sub>) by column chromatography. The pure diastereoisomers were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR and HRMS respectively, and the results for each couple were almost the same. However, every couple of compounds displayed mirror image on CD spectra (Figure 2). The CD spectra supported our assumption that the chiral properties of these diastereoisomers are mainly determined by the bis-estrogenic axis.



Figure 1. The axially chiral structure of the diastereoisomers



Figure 2. CD spectra of diastereoisomers of 3a, 3b and 3d

Subsequently, asymmetric hetero-Diels-Alder (HDA) reaction was chosen for examining the chemical properties of the diastereoisomers. As shown in Table 3, three couples of ligands exhibited different catalytic activities in the model HDA reaction between *trans*-1-methoxy-2-methyl-3-trimethylsiloxybuta-1, 3-diene and 4-nitrobenzaldehyde.<sup>13</sup> The reactions were carried out in the presence of diastereomeric ligand (25 mol %) and  $Ti(O^iPr)_4$  (20 mol %) in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C for 72 h. Interestingly, the HDA reactions involving

ethyl-containing **3a** and afforded 5-Methyl-2-(4-nitrophenyl)-2, 3-dihydro-4H-pyran-4-one with much higher yields and *ee* values than those using other two couples of ligands **3b** and **3d**. Meanwhile, the absolute configurations of the products were confirmed, and the opposite enantiomers were given in the reactions catalyzed by the ligands with different axial chirality.

	$4 \qquad 5 \qquad $	<u>Ti(O/Pr)₄</u> /ligand TFA		NO <sub>2</sub>
Entry	Ligand	Yield $(\%)^{[b]}$	ee (%) <sup>[c]</sup>	Product Configuration
1	3a <sub>1</sub>	99	93	S
2	3a <sub>2</sub>	98	96	R
3	3b <sub>1</sub>	75	57	S
4	$3b_2$	82	48	R
5	3d <sub>1</sub>	74	25	S
6	$3d_2$	77	32	R

Table 3. Investigation of chemical properties of several diastereometric ligands.<sup>[a]</sup>

[a] Reaction conditions: 4-nitrobenzaldehyde 0.2 mmol, diene 4 (2 mmol),  $Ti(O^{i}Pr)_{4}$  0.04 mmol, ligand 0.05 mmol at 0 °C for 72 h, then added TFA 0.1 mL at R.T. overnight. [b] Isolated yields. [c] The ee values were determined by HPLC using chiralcel OD-H column.

In summary, we described an oxidative coupling of estrogen derivatives catalyzed by CuCl<sub>2</sub>/TMEDA system. Key to the high selectivity and activity was the introduction of substituted groups with suitable steric and electronic properties at 2-position of estrogen. The catalytic products **3a**, **3b** and **3d** were separated to three couples of diastereoisomers. All of them were examined as chiral ligands in asymmetric HDA reaction. Further studies to find widespread application in asymmetric catalytic reactions are currently under investigation.

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