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# Iron-catalyzed oxidative biaryl cross-couplings via mixed diaryl titanates: significant influence of the order of combining aryl Grignard reagents with titanate†

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The mixed diaryl titanates were used for the first time to modify the reactivity of two aryl Grignard reagents. Two titanate intermediates,  $\text{Ar}[\text{Ar}'\text{Ti}(\text{OR})_3]\text{MgX}$  and  $\text{Ar}'[\text{ArTi}(\text{OR})_3]\text{MgX}$ , formed via alternating the sequence of combining Grignard reagents with  $\text{ClTi}(\text{OR})_3$  showed a significant reactivity difference. Taking advantage of such different reactivity, two highly structurally similar aryl groups could be facilely assembled through iron-catalyzed oxidative cross-couplings using oxygen as the oxidant.

Oxidative couplings of organometallics to construct C–C bond frameworks are attractive synthetic strategies in organic chemistry<sup>1</sup> because the preparation of a wide variety of organometallic reagents has been well established.<sup>2</sup> Great progress has been made in developing the synthetically valuable couplings of this type.<sup>1</sup> However, achieving an oxidative cross-coupling between two different organometallics would confront the problem of selectivity because of the side homocoupling reactions of the two metal reagents.<sup>3</sup> To date, most of the reported examples have been obtained between different hybridized carbon atoms such as  $\text{C}(\text{sp})\text{--}\text{C}(\text{sp}^2)$ ,<sup>4</sup>  $\text{C}(\text{sp})\text{--}\text{C}(\text{sp}^3)$ ,<sup>5</sup> and  $\text{C}(\text{sp}^2)\text{--}\text{C}(\text{sp}^3)$ .<sup>6</sup> The examples of biaryl oxidative cross couplings are very rare.<sup>7</sup> On the other hand, the high cost of palladium and the high toxicity of nickel catalysts prompt the search for practical alternatives, especially for industrial application. The cheap and nontoxic iron salts or complexes are thus desirable alternatives.<sup>8</sup> However, to the best of our knowledge, there has been no report on iron-catalyzed oxidative cross-couplings between two aryl metal reagents to date. We believe that the key to achieving a selective oxidative cross-coupling between two structurally similar organometallics is to establish a strategy to discriminate the reactivity of two participating groups. Herein we report an iron-catalyzed oxidative cross-coupling between two structurally similar aryl Grignard reagents. The mixed diaryl titanates were used for the first time



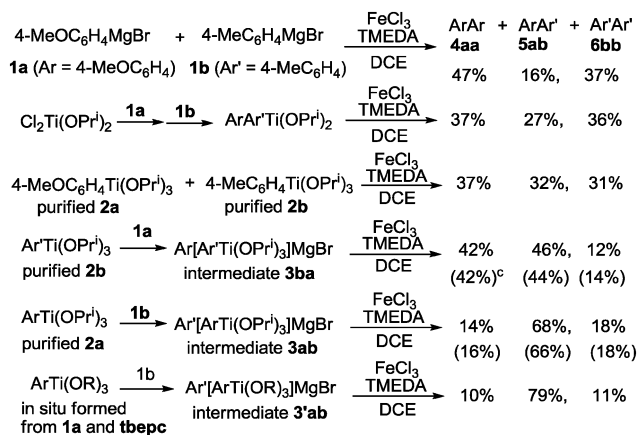
Scheme 1 Iron-catalyzed oxidative biaryl cross-couplings through the mixed diaryl titanates.

as a novel and simple means to modify and discriminate the reactivity of two aryl anions (Scheme 1). The two types of titanate intermediates,  $\text{Ar}[\text{Ar}'\text{Ti}(\text{OR})_3]\text{MgX}$  and  $\text{Ar}'[\text{ArTi}(\text{OR})_3]\text{MgX}$ , which can be formed just by alternating the order of combining aryl Grignard reagents with titanates showed a significant reactivity difference. Taking advantage of such different reactivity, two highly structurally similar aryl groups could be facilely assembled through iron-catalyzed oxidative cross-couplings using oxygen as the oxidant.

Recently we have achieved an iron-catalyzed oxidative cross-coupling of titanate-mediated *N*-heteroaryl and aryl metal reagents.<sup>9</sup> We postulated that the intrinsic reactivity difference between *N*-heteroaryl and aryl metal reagents and the strong affinity of the nitrogen atom to titanium or iron might help to promote the highly selective cross-couplings. Compared with those couplings, the oxidative cross-couplings between two aryl (non-azaheteroaryl) Grignard reagents should be even more challenging due to the high structural similarity and thereby homocoupling side reactions. Our preliminary experiments indicated that very low yield of the cross-coupling product was formed when a mixture of Grignard **1a** and **1b** was applied to iron-catalyzed oxidative coupling (Scheme 2). Similarly, the couplings using  $\text{ArAr}'\text{Ti}(\text{OPr}^i)_2$  (**2ab**) or a mixture of  $\text{ArTi}(\text{OPr}^i)_3$  and  $\text{Ar}'\text{Ti}(\text{OPr}^i)_3$  only generated a statistical mixture of three coupling products. To our delight, the reactions using the mixed diaryl titanates (Scheme 2) could improve the selectivity of the cross-coupling. For example, the reaction of **3ab** resulted in the selective cross-coupling in 68% yield. Furthermore, the use of easily prepared and easy to handle solid **thepec** instead of  $\text{ClTi}(\text{OPr}^i)_3$ <sup>9</sup> increased the yield of the cross-coupling product to 79%. We also noticed that the influence of magnesium salts

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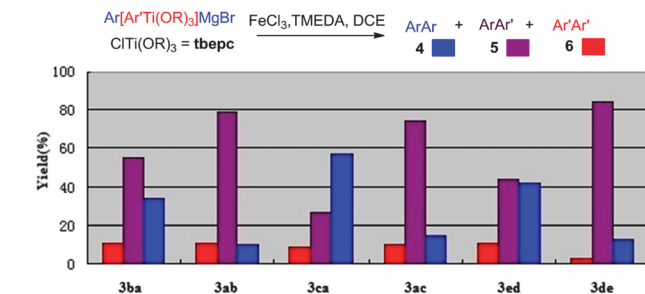
† Electronic supplementary information (ESI) available: Full experimental details and copies of the NMR spectra. See DOI: 10.1039/c5cc00514k



**Scheme 2** The influence of titanate mediation in the iron-catalyzed oxidative cross-couplings of two aryl Grignard reagents. <sup>a</sup> Reaction conditions: 10 mol%  $\text{FeCl}_3$ /30 mol% TMEDA; 0 °C. <sup>b</sup> Isolated yields. <sup>c</sup> The yields were obtained using *in situ* formed titanate **2a** or **2b**. DCE = 1,2-dichloroethane.

from **1a** or **1b** was not significant since the mixed titanate formed *in situ* from  $\text{Ar}(\text{Ar}')\text{MgX}$  and  $\text{ClTi}(\text{OPr}^i)_3$  also gave the similar results (the yields are given in parentheses in Scheme 2). These observations demonstrate that as expected, the application of the mixed diaryl titanates is a suitable strategy to modify and discriminate the reactivity of two aryl anions.

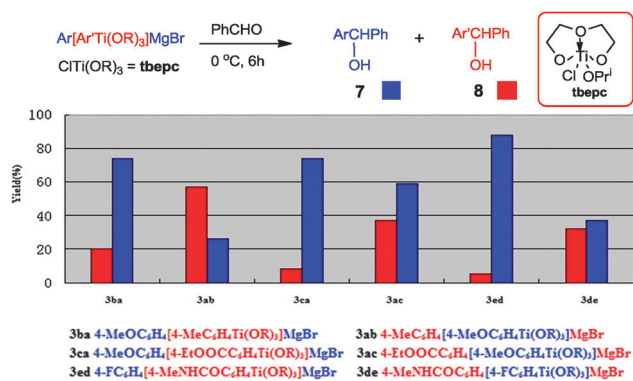
Although the ate-complexes  $[\text{ArTi}(\text{OR})_4\text{M}]$  have been known for a long time,<sup>10</sup> their precise structures have not been well proven. Thus, the nature of the new types of mixed titanate  $\text{Ar}[\text{Ar}'\text{Ti}(\text{OR})_3]\text{MgX}$  also waits for further studies, which are underway in our laboratory. Remarkably, the results in Scheme 2 clearly indicated a significant reactivity difference between  $\text{Ar}[\text{Ar}'\text{Ti}(\text{OR})_3]\text{MgX}$  and  $\text{Ar}'[\text{ArTi}(\text{OR})_3]\text{MgX}$  in the oxidative coupling reaction. Such reactivity difference which resulted only from the different order of combining two structurally similar aryl Grignard reagents with  $\text{ClTi}(\text{OR})_3$  was observed for the first time. We further compared the reactivity of three pairs of  $\text{Ar}[\text{Ar}'\text{Ti}(\text{OR})_3]\text{MgX}$  and  $\text{Ar}'[\text{ArTi}(\text{OR})_3]\text{MgX}$  through their reactions with PhCHO as well as their oxidative cross-couplings. The results are summarized in Fig. 1 and 2. It can be seen that an Ar



**Fig. 2** Comparison of the iron-catalyzed oxidative couplings of the mixed diaryl titanates  $\text{Ar}[\text{Ar}'\text{Ti}(\text{OR})_3]\text{MgX}$  and  $\text{Ar}'[\text{ArTi}(\text{OR})_3]\text{MgX}$ . Reaction conditions were the same as those given in Table 1.

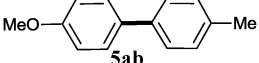
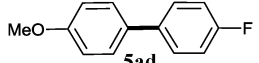
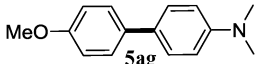
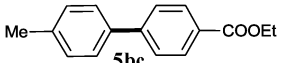
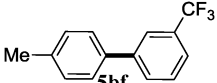
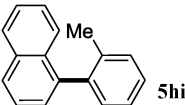
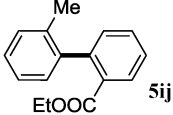
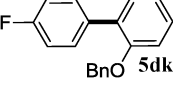
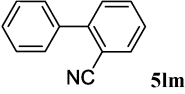
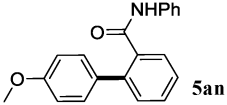
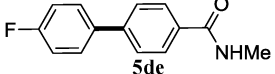
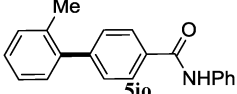
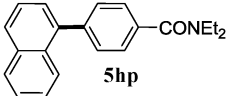
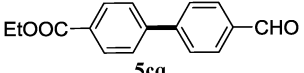
group in  $\text{Ar}'[\text{ArTi}(\text{OR})_3]\text{MgX}$  (through the first combination of  $\text{ArMgX}$  with  $\text{ClTi}(\text{OR})_3$ ) would show a remarkably lower reactivity than that in  $\text{Ar}[\text{Ar}'\text{Ti}(\text{OR})_3]\text{MgX}$  [through the second combination of  $\text{ArMgX}$  with  $\text{Ar}'\text{Ti}(\text{OR})_3$ ]. As illustrated in Fig. 1, the  $4\text{-CH}_3\text{OC}_6\text{H}_4$  group in **3ba** could add to PhCHO in a highly selective manner while its addition in **3ab** occurred with much more difficulty. Similar results were obtained with **3ca** vs. **3ac** and **3ed** vs. **3de**. Similar reactivity changes were also observed in the iron-catalyzed oxidative couplings (Fig. 2). We noticed that the coupling of unsubstituted aryl groups (Ph, Np) or those bearing an electron-donating substituent such as OMe or Me usually proceeded faster. Thus, bonding this type of Ar groups to titanium in the form of  $\text{ArTi}(\text{OR})_3$  could remarkably suppress their homocoupling side reactions. For instance, the homocoupling of  $4\text{-FC}_6\text{H}_4$  in **3ed** occurred up to 44% while it was suppressed to 11% in **3de** (Fig. 2, for specific data, see Tables S1 and S2 in the ESI†). These results clearly showed that the observed reactivity difference between  $\text{Ar}[\text{Ar}'\text{Ti}(\text{OR})_3]\text{MgX}$  and  $\text{Ar}'[\text{ArTi}(\text{OR})_3]\text{MgX}$  enabled the reactivity of two aryl groups to be modified in a combined and alternative manner. Taking advantage of these modifications, highly selective oxidative cross-couplings can be achieved between two structurally highly similar aryl Grignard reagents.

The optimization of the reaction conditions of the iron-catalyzed oxidative cross-couplings was also investigated using **1a** and **1b** (optimization studies in the ESI†). With optimized reaction conditions (8 mol%  $\text{FeCl}_3$ /20 mol% TMEDA as a catalyst and  $\text{O}_2$  as an oxidant) in hand, we then investigated the scope of this biaryl oxidative cross-coupling reaction between various aryl Grignard reagents. The results are summarized in Table 1. This oxidative cross-coupling reaction showed a broad scope with remarkable selectivity over homocouplings. The coupling was also chemoselective and various Grignard reagents functionalized with sensitive groups such as ester (entries 4 and 7), amide (entries 10–13), cyano (entry 9) and imine (entries 14 and 15) functions were used successfully. Notably, two highly structurally similar aryl Grignard reagents could undergo the cross-coupling in satisfactory yields (entries 1–6 and 14), and sterically hindered biaryls (entries 6–10) could also be prepared smoothly. Besides, not only the couplings between electronically different aryl Grignard reagents occurred with good yields (entries 2, 4, 5 and 7–13), the couplings between electronically similar aryl Grignard reagents

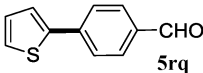


**Fig. 1** Comparison of the addition of the mixed diaryl titanates  $\text{Ar}[\text{Ar}'\text{Ti}(\text{OR})_3]\text{MgX}$  and  $\text{Ar}'[\text{ArTi}(\text{OR})_3]\text{MgX}$  to PhCHO. Reaction conditions: 2.5 mmol titanate, 2.5 mmol PhCHO, at 0 °C for 6 h with isolated yields.

**Table 1** Iron-catalyzed oxidative cross-couplings of titanate-mediated two aryl Grignard reagents using oxygen as the oxidant<sup>a</sup>

$\text{ArMgX} \xrightarrow{\text{tbepec}} \text{ArMgX} \xrightarrow{1} \text{Ar}[\text{ArTi}(\text{OR})_3]\text{MgX} \xrightarrow[\text{O}_2 (1 \text{ atm})]{(8 \text{ mol}\%) \text{ FeCl}_3, (20 \text{ mol}\%) \text{ TMEDA}} \text{Ar}-\text{Ar}'$				
Entry	ArMgX	Ar'MgX	Product (5)	Yield <sup>b</sup> (%)
1	1a	1b		79
2	1a	1d		80
3	1a	1g		79
4	1b	1c <sup>d</sup>		77
5	1b	1f		84
6	1h	1i		72
7	1i	1j <sup>d</sup>		76
8	1d	1k		67
9	1l	1m <sup>d</sup>		78
10 <sup>c</sup>	1a	1n <sup>d</sup>		79
11 <sup>c</sup>	1d	1e <sup>d</sup>		84
12 <sup>c</sup>	1i	1o <sup>d</sup>		76
13 <sup>c</sup>	1h	1p <sup>d</sup>		79
14	1c	1q <sup>d,e</sup>		72

**Table 1** (continued)

$\text{ArMgX} \xrightarrow{\text{tbepec}} \text{ArMgX} \xrightarrow{1} \text{Ar}[\text{ArTi}(\text{OR})_3]\text{MgX} \xrightarrow[\text{O}_2 (1 \text{ atm})]{(8 \text{ mol}\%) \text{ FeCl}_3, (20 \text{ mol}\%) \text{ TMEDA}} \text{Ar}-\text{Ar}'$				
Entry	ArMgX	Ar'MgX	Product (5)	Yield <sup>b</sup> (%)
15	1r	1q <sup>d,e</sup>		78

<sup>a</sup> The mixed titanates were formed in an *in situ* manner. <sup>b</sup> Yields of isolated products. <sup>c</sup> These reactions were conducted at 15 °C, and the other reactions were performed at 0 °C. <sup>d</sup> These Grignard reagents were prepared *via* iodine-magnesium exchange using *i*PrMgCl·LiCl. <sup>e</sup> 1q: PhN=CHC<sub>6</sub>H<sub>4</sub>MgI.

also proceeded equally well (entries 1, 3, 6, 14 and 15). Also, a heteroaryl Grignard reagent such as (1r) was readily amenable to this cross-coupling.

In conclusion, we have developed a novel and highly selective iron-catalyzed oxidative cross-coupling of two aryl Grignard reagents by using mixed diaryl titanates as a simple means to modify and discriminate the reactivity of two structurally similar aryl Grignard reagents. Since both iron and titanium are abundant non-toxic metals, and at the same time oxygen is the greenest oxidant, the present method proves to be simple, eco-friendly, and highly efficient for the flexible construction of various biaryl compounds. Compared with the known ate-complexes such as ArAr'Cu(CN)Li<sub>2</sub>,<sup>7a</sup> the fact that the different order of combining aryl Grignard reagents with ClTi(OR)<sub>3</sub> resulted in two diaryl mixed titanates with different reactivity is noteworthy. These findings would provide guidance for developing new types of mixed ate-complexes. Furthermore, we also believe that the undocumented reaction behaviours of the new mixed diaryl titanates and the synergetic effect between iron and titanium<sup>11</sup> would help in the further investigations on organo-titanium reagents and iron catalysis.

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