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Iron-catalyzed Pinacol Coupling of Aryl Ketones with a Phenyltitanium Reagent: A New Type of Catalytic Reaction

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A reaction of aryl ketones with phenyltitanium triisopropoxide ([PhTi(O*i*-Pr)$_3$]) in the presence of [Fe(acac)$_3$] as a catalyst (1 mol %) gave the corresponding pinacols in high yields. The catalytic cycle of this process involves an iron-catalyzed disproportionation of [PhTi(O*i*-Pr)$_3$] into biphenyl and a low-valent titanium species.

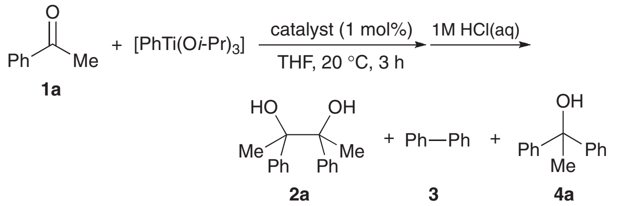
Since iron is one of the most abundant metals on earth and consequently is one of the most inexpensive and environmentally friendly, there have recently been extensive studies on the use of iron salts and complexes as catalysts for organic transformations.[1] During the course of our studies on iron-catalyzed carbon–carbon bond forming reactions,[2] we found that a new type of iron-catalyzed transformation takes place for the reaction of aryl ketones with phenyltitanium triisopropoxide[3–5] ([PhTi(O*i*-Pr)$_3$]), which gives high yields of the pinacol coupling products.

Table 1 demonstrates the unique catalysis by iron salt to promote pinacol coupling. Thus, to a solution of [Fe(acac)$_3$] (0.01 mmol, 1 mol %) in THF (2.0 mL) were added a solution of [PhTi(O*i*-Pr)$_3$], which was generated in a separate flask from [ClTi(O*i*-Pr)$_3$] (1.5 mmol) and PhLi in cyclohexane/Et$_2$O (1.6 mmol), and acetophenone (**1a**, 1.0 mmol) successively, and the mixture was stirred at 20 °C for 3 h. Acidic hydrolysis with 1 M HCl followed by silica gel chromatography gave 0.40 mmol (80% yield) of pinacol coupling product, 2,3-diphenylbutane-2,3-diol (**2a**, *dl*/*meso* = 8/2), together with 0.485 mmol (97% based on **1a**) of biphenyl (**3**) and 0.19 mmol (19%) of 1,1-diphenylethanol (**4a**) (Entry 1). In the absence of [Fe(acac)$_3$], the pinacol **2a** or biphenyl (**3**) was not formed under otherwise the same conditions. Instead, the reaction gave 64% yield of alcohol **4a** which should result from nucleophilic attack of the phenyltitanium reagent on ketone **1a** (Entry 2). Thus, the present pinacol coupling is clearly demonstrated to be catalyzed by the small amount of [Fe(acac)$_3$]. The yield of pinacol **2a** was slightly enhanced by increasing the amount of [Fe(acac)$_3$] catalyst to 5 mol % (Entry 3). The use of isolated [PhTi(O*i*-Pr)$_3$] in place of the in situ generated phenyltitanium also gave pinacol **2a** albeit in a little lower yield (Entry 4). The pinacol coupling was also observed with FeCl$_3$ as a catalyst (Entry 5). Of other metal complexes examined, [Co(acac)$_3$] was catalytically as active as [Fe(acac)$_3$] to give a high yield of **2a** (Entry 6). [Ni(acac)$_2$] also catalyzed the present pinacol coupling although its activity is lower than that of [Fe(acac)$_3$] or [Co(acac)$_3$] (Entry 7). Ruthenium, rhodium, or palladium acac complex did not catalyze the pinacol coupling (Entries 8, 9, and 10).

It has been well-documented that trivalent titanium species, generated by reduction of tetravalent titanium complexes with magnesium or zinc metal, function as one-electron reducing reagents of carbonyl compounds to lead to pinacol coupling.[6,7] Some organometallic reagents such as Grignard reagents have also been used to reduce titanium(IV) complexes for the pinacol coupling. For example, "[Ti(O*i*-Pr)$_3$]" generated by treatment of [Ti(O*i*-Pr)$_4$] with EtMgBr is reported to be an effective reagent for the coupling of aromatic aldehydes and ketones.[8] It is interesting that [PhTi(O*i*-Pr)$_3$], which is a stable titanium(IV) complex, promotes the pinacol coupling in the presence of an iron catalyst in our system. The formation of biphenyl (**3**) observed in the iron-catalyzed pinacol coupling suggests that [PhTi(O*i*-Pr)$_3$] undergoes disproportionation in the presence of an iron catalyst to give biphenyl (**3**) and a low-valent titanium species, most likely "[Ti(O*i*-Pr)$_3$]," which will bring about the pinacol coupling of ketones (Scheme 1).

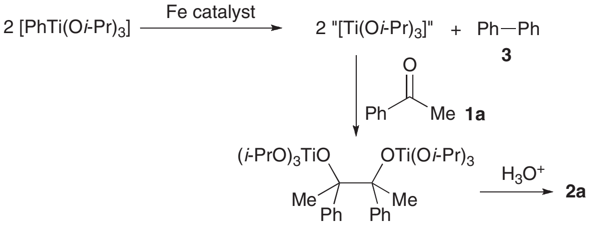
The reaction pathway proposed in Scheme 1 is supported in part by control experiments shown in Scheme 2. Thus, to a solution of [PhTi(O*i*-Pr)$_3$] (1.0 mmol) in THF, [Fe(acac)$_3$] (0.10 mmol) was added at 20 °C, and the mixture was stirred at the same temperature for 10 min. Acidic hydrolysis of the reaction mixture gave 0.29 mmol (58% yield) of biphenyl (**3**),

Table 1. Pinacol coupling of acetophenone (**1a**) with [PhTi(O*i*-Pr)$_3$] in the presence of transition-metal catalysts[a]

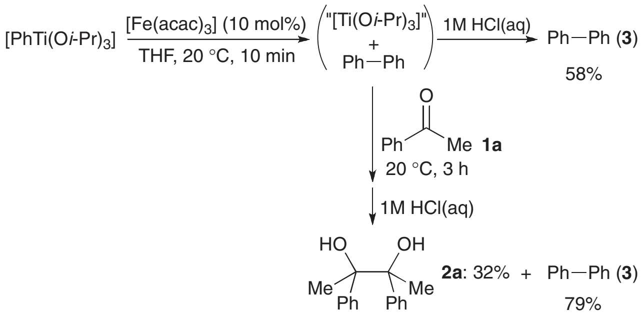


Entry	Catalyst	Yield/%[b] **2a**[c]	Yield/%[b] **4a**	Recovered/%[b] **1a**
1[d]	[Fe(acac)$_3$]	81 (80)	19	<1
2[d]	none	0	64	36
3[e]	[Fe(acac)$_3$]	83 (80)	17	<1
4[f]	[Fe(acac)$_3$]	63	32	<1
5	FeCl$_3$	75 (73)	25	<1
6	[Co(acac)$_3$]	83	17	<1
7	[Ni(acac)$_2$]	36	38	3
8	[Ru(acac)$_3$]	4	53	43
9	[Rh(acac)$_3$]	4	51	40
10	[Pd(acac)$_2$]	3	50	43

[a]The reaction was carried out with **1a** (1.0 mmol), [PhTi(O*i*-Pr)$_3$] (1.5 mmol, generated from [ClTi(O*i*-Pr)$_3$] and PhLi), catalyst (0.01 mmol, 1 mol %) in THF at 20 °C for 3 h. [b]Determined by ^{1}H NMR. The numbers in parentheses are isolated yield. [c]The ratio of *dl*/*meso* **2a** is 8/2 for all the Entries 1 and 3–10. [d]The yields of biphenyl (**3**) are 97% and <2% for Entries 1 and 2, respectively. [e]The reaction with 5 mol % of [Fe(acac)$_3$]. [f]The reaction with isolated [PhTi(O*i*-Pr)$_3$].



Scheme 1. Proposed reaction pathway for the iron-catalyzed pinacol coupling of ketone **1a** with [PhTi(O*i*-Pr)$_3$].

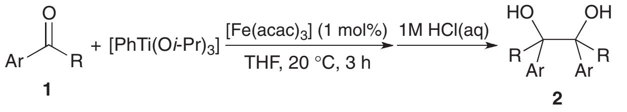


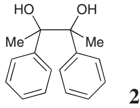
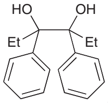
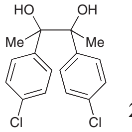
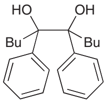
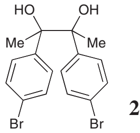
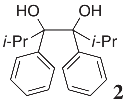
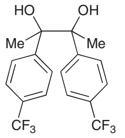
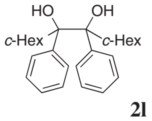
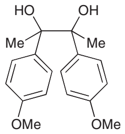
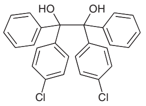
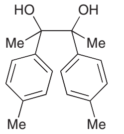
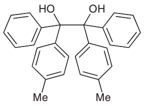
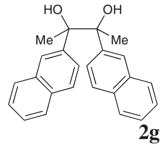
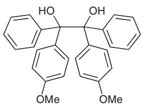
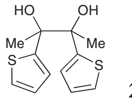
Scheme 2. Reaction of [PhTi(O*i*-Pr)$_3$] with [Fe(acac)$_3$] as a catalyst to generate "[Ti(O*i*-Pr)$_3$]" and biphenyl (**3**).

which demonstrates that the iron catalyzed the disproportionation. Addition of acetophenone (**1a**, 1.0 mmol) to the reaction mixture resulting from [PhTi(O*i*-Pr)$_3$] (1.0 mmol) and [Fe(acac)$_3$] (0.10 mmol) in THF for 10 min followed by stirring for 3 h gave 32% yield of pinacol **2a** together with 79% of biphenyl (**3**). The low yield of pinacol compared with that observed in Table 1 (Entries 1 and 3), where ketone **1a** was mixed with others ([PhTi(O*i*-Pr)$_3$] and [Fe(acac)$_3$]) immediately, may be caused by low stability of "[Ti(O*i*-Pr)$_3$]" in the presence of iron catalyst. Alternatively, the ketone is involved in the iron-catalyzed reaction of [PhTi(O*i*-Pr)$_3$] to accelerate the generation of a low-valent titanium species.

A study of scope for the present iron-catalyzed pinacol coupling is summarized in Table 2. Acetophenone derivatives substituted with electron-withdrawing groups (Cl, Br, and CF$_3$) at para position gave the corresponding pinacols **2b**–**2d** in the yields of 77%–78% (Entries 2–4), while the yields of pinacols were lower for those substituted with electron-donating groups (MeO and Me) (Entries 5 and 6). The low yield of pinacols is attributed mainly to the competing phenylation of the ketones giving tertiary alcohols **4**. Phenyl alkyl ketones where alkyl group is ethyl, butyl, isopropyl, and cyclohexyl also underwent the pinacol coupling reaction giving the corresponding pinacols **2i**–**2l**. It is remarkable that the *dl*/*meso* ratio of the products is higher with the more sterically demanding alkyl groups on the ketones (Entries 9–12).[9] The *dl* structure of pinacol **2l** was confirmed by X-ray crystal analysis.[10] The yields are high for diaryl ketones under the present reaction conditions (Entries 13–15). Unfortunately, aldehydes did not produce their pinacols because the phenylation of aldehyde carbonyl with [PhTi(O*i*-Pr)$_3$] giving secondary alkyl alcohols is faster than the pinacol coupling.

Table 2. Iron-catalyzed pinacol coupling of ketones **1** with [PhTi(O*i*-Pr)$_3$]: scope[a]



Entry	Product **2**	Yield/%[b] (*dl*/*meso*)[c]	Entry	Product **2**	Yield/%[b] (*dl*/*meso*)[c]
1	 **2a**	80 (8/2)	9[d]	 **2i**	71 (8/2)
2	 **2b**	78 (7/3)	10[d]	 **2j**	69 (8/2)
3	 **2c**	77 (7/3)	11[d]	 **2k**	71[e] (9/1)
4	 **2d**	77 (6/4)	12[d]	 **2l**	78[e] (>9/1)
5	 **2e**	56 (7/3)	13[d]	 **2m**	93 (1/1)
6	 **2f**	69 (8/2)	14[d]	 **2n**	86 (1/1)
7[d]	 **2g**	62 (8/2)	15[d]	 **2o**	81 (1/1)
8[d]	 **2h**	66 (8/2)			

[a]The reaction was carried out with ketone **1** (1.0 mmol), [PhTi(O*i*-Pr)$_3$] (1.5 mmol, generated from [ClTi(O*i*-Pr)$_3$] and PhLi), catalyst (0.01 mmol, 1 mol %) in THF at 20 °C for 3 h. [b]Isolated yield of a mixture of *dl* and *meso* isomers. [c]The ratio of *dl*/*meso* was determined by ^{1}H NMR analysis of crude products. [d]The reaction was conducted with 2.0 mmol of [PhTi(O*i*-Pr)$_3$] for 12 h. [e]Isolated yield of *dl* isomer.

In summary, we found a new type of iron-catalyzed reaction where an iron complex catalyzes disproportionation of [PhTi(O*i*-Pr)$_3$] into biphenyl and a low-valent titanium species "[Ti(O*i*-Pr)$_3$]," which then promotes the reductive coupling of aryl ketones giving the corresponding pinacols in 56–93% yield.[11]

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11 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.