

Selective Co/Ti Cooperatively Catalyzed Biaryl Couplings of Aryl Halides with Aryl Metal Reagents

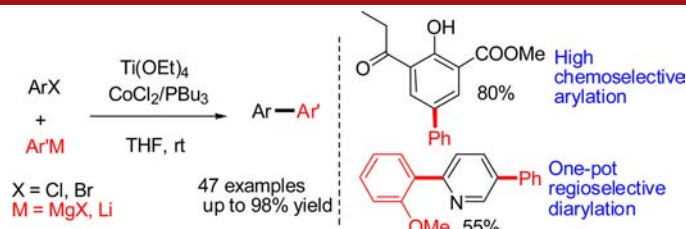
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ABSTRACT



Various aryl bromides or chlorides, including those bearing a free COOH, OH, CONHR, and SO₂NHR group, coupled with aryl magnesium or lithium reagents in the presence of 7.5 mol % CoCl₂/15 mol % PBu₃ and substoichiometric Ti(OEt)₄ (40 mol % to ArM) at room temperature in high yields with high chemo- and regioselectivity. This simple reaction represents the first example of Co/Ti cooperative catalysis which plays a key role in suppressing undesired homocouplings.

Transition-metal-catalyzed cross-coupling reactions are one of the most powerful tools for the construction C–C bonds in organic synthesis.^{1,2} In this field, the catalysts are largely dominated by palladium and nickel complexes due to their high catalytic activity for a wide range of substrates and high functional group tolerance.³ However, these common catalysts have some disadvantages, such as

the high cost of palladium and the high toxicity of nickel catalysts, which limit their use in industrial applications. In this context, relatively low-cost and low-toxic iron and cobalt complexes are viable alternatives.^{4,5} Although there has been much progress in Co-catalyzed coupling reactions between C(sp²) and C(sp³) centers,⁶ the corresponding biaryl cross-couplings have remained a considerable challenge due to undesired homocoupling reactions.⁷ To date,

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only a few Co-catalyzed biaryl cross-couplings with good selectivity have been documented.⁸ However, most of the reported examples are sensitive to the structure of substrate halides (i.e., heteroaryl halides, halophenones, chlorostyrenes) or require a special catalyst/ligand system (CoF₂/N-heterocyclic carbene).

Herein, we report a novel cobalt/titanium cocatalyzed biaryl cross-coupling reaction between aryl magnesium or lithium reagents and aryl chlorides or bromides. This general coupling reaction proceeds smoothly in the presence of 40 mol % Ti(OEt)₄ (based on the amount of ArMgX or ArLi) and 7.5 mol % CoCl₂/15 mol % PBu₃. Attractive features include the use of a simple and readily available cobalt catalyst system and substoichiometric nontoxic titanate, broad generality, mild conditions (room temperature), and high chemo- and regioselectivity. Importantly, the present reaction can also take place with high yields in the presence of free COOH, OH, CONHR, and SO₂NHR. We expect that the reaction presented here will add to the repertoire of transition-metal-catalyzed biaryl cross-coupling reactions.

Our research started with an investigation into the Co-catalyzed cross-coupling reaction of 4-bromobenzophenone with titanium ate-complexes [ArTi(OR)₄M], which are often used as a simple means to adjust the reactivity and selectivity of organomagnesium and lithium reagents.^{9,10} As illustrated in Table 1, various representative ligands or additives were examined using the model reaction between **1a** and the phenyl titanium ate-complex. To our delight, a high yield cross-coupling could be achieved by using a simple trialkylphosphine ligand with a low excess of Grignard reagent (0.15 equiv of 1.4 equiv of PhMgBr was needed to reduce CoCl₂) in a short reaction time (Table 1, entries 7–9). Tributylphosphine, being the cheapest and most easily handled among the three tested trialkylphosphines, was chosen for further investigation. Under the same conditions, Co(acac)₂ could also promote the cross-coupling equally well, yet with a prolonged reaction time

Table 1. Optimization for Co-Catalyzed Biaryl Cross-Coupling Reaction of Titanium Ate-Complex^a

entry	X	ligand ^b (solvent)	n ^c [mol %]	R	t [h]	yield ^d [%]
1	Br	– (THF)	100	Et	12	19
2	Br	– (NMP/THF)	100	Et	12	29
3	Br	TMEDA (THF)	100	Et	12	23
4	Br	PPh ₃ (THF)	100	Et	12	27
5	Br	dmadpp ^e (THF)	100	Et	12	42
6	Br	dppp ^f (THF)	100	Et	12	63
7	Br	PCy ₃ (THF)	100	Et	4	86
8	Br	PMe ₃ (THF)	100	Et	4	84
9	Br	PBu ₃ (THF)	100	Et	4	85
10 ^g	Br	PBu ₃ (THF)	100	Et	12	84
11 ^h	Br	PBu ₃ (THF)	100	Et	4	81
12	Br	PBu ₃ (ether)	100	Et	8	41
13	Br	PBu ₃ (DME)	100	Et	8	49
14	Br	PBu ₃ (toluene)	100	Et	8	44
15	Br	PBu ₃ (THF)	100	<i>i</i> -Pr	4	79
16	Br	PBu ₃ (THF)	100	R ⁱ	8	34
17	Br	PBu ₃ (THF)	80	Et	4	85
18	Br	PBu ₃ (THF)	60	Et	4	85
19	Br	PBu₃ (THF)	40	Et	4	84
20	Br	PBu ₃ (THF)	20	Et	8	46
21^h	Br	PBu₃ (THF)	40	Et	4	81
22	F	PBu ₃ (THF)	40	Et	12	--
23	Cl	PBu ₃ (THF)	40	Et	8	21
24	I	PBu ₃ (THF)	40	Et	2	55 ^j
25	OTs	PBu ₃ (THF)	40	Et	4	21
26	OTf	PBu ₃ (THF)	40	Et	4	45

^a PhMgBr (1.4 equiv) was used unless otherwise noted. ^b TMEDA was used at 40 mol % and 100 mol %, and other ligands, at 15 mol %.

^c Based on the amount of PhMgBr or PhLi. ^d Isolated yield. ^e Me₂N-(CH₂)₃PPh₂. ^f Ph₂P(CH₂)₃PPh₂. ^g Co(acac)₂ was used instead of CoCl₂.

^h PhLi (1.4 equiv) was used instead of PhMgBr. ⁱ Me₂CHCHMe₂.

^j Benzophenone was isolated in 34% yield.

(entry 10). Also, phenyllithium showed a comparable yield (Table 1, entries 11 and 21). THF proved to be an ideal solvent, for the reactions carried out in ether, DME, or toluene gave remarkably lower yields than in THF (Table 1, entries 12–14). Titanates with high-steric-hindrance ligands gave relatively lower yields (Table 1, entries 15 and 16). Very importantly, when a substoichiometric amount of Ti(OEt)₄ was applied (as low as 40 mol % to Grignard or lithium reagents), the reaction occurred equally well (Table 1, entries 17–21). To the best of our knowledge, the reaction described herein represents the first example where only 40 mol % titanate was used in the reactions involving titanium ate-complexes formed from Grignard or lithium reagents.^{10h} Therefore, this procedure can be regarded as a cobalt/titanium cooperatively catalyzed cross-coupling reaction between aryl magnesium or lithium reagents and aryl halides.

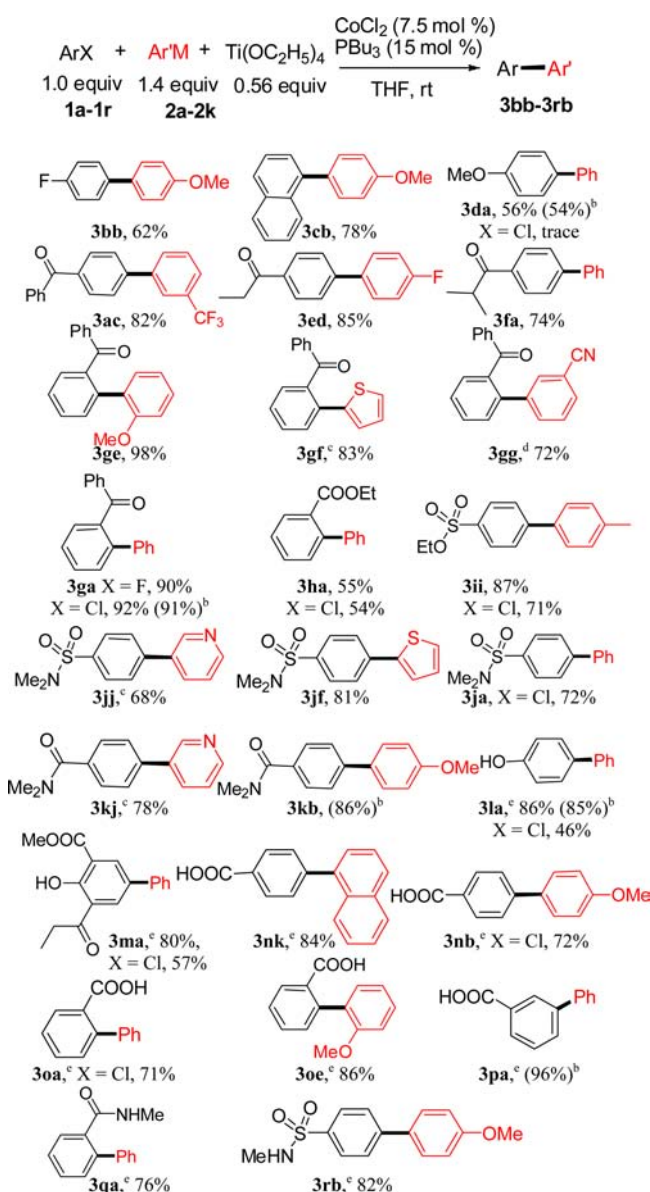
The above cross-coupling reaction was found to be sensitive to the nature of the leaving group of the electrophile (Table 1, entries 22–26). The corresponding chloride, tosylate, and triflate showed relatively poor conversions, while fluoride did not react in this case. 4-Iodobenzophenone could be consumed within a short period to give an

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Scheme 1. Cobalt/Titanium Catalyzed Cross-Couplings between Aryl Halides and Aryl Grignard or Lithium Reagents^a



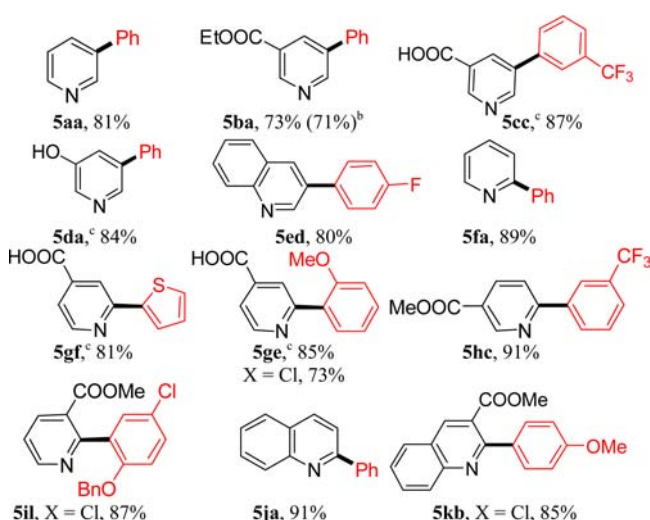
^a The reaction temperature was rt, X = Br unless otherwise indicated, and all yields are isolated yields. ^b The yield in parentheses was obtained using PhLi. ^c The reaction was carried out at 60 °C. ^d This Grignard reagent was prepared via bromine/magnesium exchange using *i*-PrMgCl·LiCl. ^e 2.4 equiv of Ar'M and 0.96 equiv of Ti(OEt)₄ were used.

acceptable yield of cross-coupling product. However a remarkable amount of benzophenone resulting from the reduction of the starting iodide was observed (Table 1, entry 24).

With optimized reaction conditions in hand, we then investigated the scope of this biaryl cross-coupling reaction between various aryl halides with aryl Grignard reagents or aryl lithium reagents. The results are summarized in Scheme 1. This cross-coupling reaction showed a broad scope with remarkable functional-group tolerance. Various aryl bromides underwent smooth cross-couplings in

55–98% within 4 h, while aryl chlorides with an electron-withdrawing group reacted to afford the biaryl products in 54–92% yield within 11 h (**3bb**–**3kb**). In addition to ester, phenyl ketone, amide, sulfonate, and sulfonamide groups (**3ac**–**3kb**), an ethyl or isopropyl ketone group could be well tolerated without competitive deprotonation (**3ed** and **3fa**). It was noticed that an *ortho*-ketone group could facilitate the cross-coupling where aryl bromide, chloride, and fluoride could undergo the reaction equally well (**3ge**–**3ga**).^{8a,b} Remarkably, functionalized aryl and heteroaryl Grignard reagents could also react well to furnish the biaryl products (**3gf**, **3gg**, **3jj**, and **3jf**), and the use of aryl lithium reagents gave comparable yields to those with Grignard reagents (**3da**, **3ga**, **3kb**, **3la**, **3pa**). Particularly important is that this cross-coupling proceeded very well in the presence of free COOH, OH, CONHR, and SO₂NHR (**3la**–**3rb**).¹¹ By comparing the results of **3da** and **3ha** with those of **3la**–**3rb**, it can be seen that the presence of such functional groups could promote the cross-couplings even more effectively. For example, the cross-coupling of 4-MeOC₆H₄Cl could not occur and that of 4-MeOC₆H₄Br only gave 56% yield; conversely, 4-HOC₆H₄Cl and 4-HOC₆H₄Br could couple in 46% and 86% yield respectively. Noteworthy is that this reaction can thus allow the simple and efficient arylation of highly functionalized aryl halides (i.e., **3ma**) without a protection/deprotection sequence.

Scheme 2. Cobalt/Titanium Catalyzed Cross-Couplings between *N*-Heteroaryl Halides and Aryl Grignard or Lithium Reagents^{a–c}

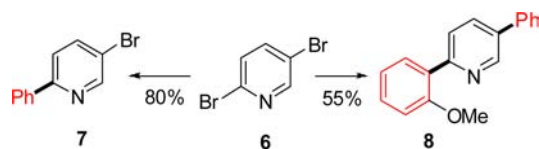


^a Conditions were the same as those in Scheme 2. ^b The yield in parentheses was obtained using PhLi. ^c 2.4 equiv of Ar'M and 0.96 equiv of Ti(OEt)₄ were used.

To further demonstrate the broad generality of this cross-coupling reaction, we subsequently investigated the cross-couplings between *N*-heteroaryl halides and aryl

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Scheme 3. Regioselective Arylation and One-Pot Iterative Diarylation^a



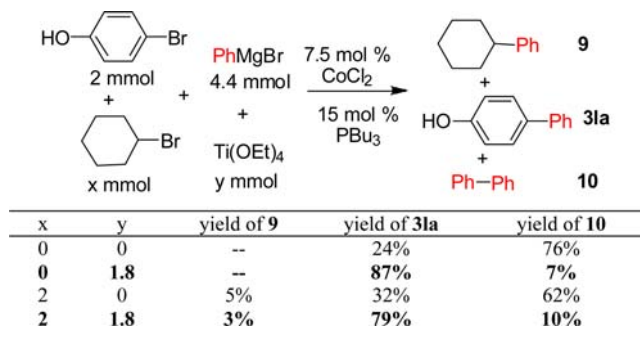
^a See Supporting Information for experimental details.

Grignard or lithium reagents. The results are summarized in Scheme 2. Notably, this Co-catalyzed cross-coupling reaction was also applicable to various *N*-heteroaryl halides. In sharp contrast to the fact that 3-pyridyl bromides could hardly couple with aryl Grignard reagents using the reported cobalt catalys system,^{8d} in this case 3-pyridyl bromides as well as 3-quinolynyl bromide underwent smooth cross-couplings based on the present procedure (**5aa–5ed**). Besides, 2-bromo or chloro pyridines or quinolines could also couple well with aryl Grignard reagents as expected (**5fa–5kb**). Once again, the cross-coupling occurred smoothly in the presence of a free carboxyl and phenolic hydroxyl group (**5cc**, **5da**, **5gf**, and **5ge**).

This Co-catalyzed biaryl cross-coupling reaction also exhibited high regioselectivity. As illustrated in Scheme 3, 2,5-dibromopyridine (**6**) could be arylated at C2 with high regioselectivity. Taking advantage of this high regioselectivity, dibromopyridine **6** could be iteratively diarylated in a one-pot manner.

To probe the selectivity between this biaryl cross-coupling and those of C(sp²) and C(sp³) centers,⁶ competition and control experiments were performed (Scheme 4). The results clearly indicated that the present biaryl cross-coupling had remarkable selectivity over the couplings between C(sp²) and C(sp³) centers. Moreover, the homocoupling occurred as a main reaction in the absence of titanate, clearly demonstrating that the synergetic effect of titanium played a key role in suppressing the undesired homocouplings. We assume that the cobalt–titanium bimetallic cooperativity suppresses the formation of the symmetrical diaryl cobalt complex [Co(Ar)₂ or Co(Ar')₂] and the consequent undesired homocouplings. It should be noted that this bimetallic cooperativity may be significantly enhanced when the groups such as OH, COOH, *etc.*, are presented, for the salts of these groups have a

Scheme 4. Competition and Control Experiments



strong tendency to complex with titanium and thus facilitate the formation of the bimetallic complex.

In summary, we have developed general and high chemo- and regioselective biaryl cobalt/titanium cocatalyzed cross-coupling reactions. With a simple catalyst system and substoichiometric nontoxic titanate, a broad range of reactants, particularly those bearing a free COOH, OH, CONHR, or SO₂NHR group, can be efficiently cross-coupled in a single solvent at room temperature. Since the present easy-handling reaction takes full advantage of the ready availability of organolithium and organomagnesium reagents and at the same time overcomes many of the limitations of previously reported cross-couplings (such as low functional group tolerance, undesired homocoupling, *etc.*), we believe that our discovery would enrich the repertoire of transition-metal-catalyzed biaryl cross-coupling reactions. Furthermore, the cobalt/titanium cooperativity provides a practical and eco-friendly protocol for developing efficient transition-metal-catalyzed cross-couplings using classic reagents. Further cooperative cross-couplings using titanium are being investigated in our laboratories.

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Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.