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Room-temperature cobalt-catalyzed arylation of aromatic acids: overriding the *ortho*-selectivity via the oxidative assembly of carboxylate and aryl titanate reagents using oxygen†

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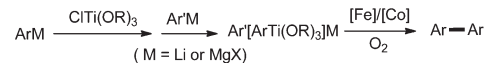
A room temperature phosphine or NHC ligand-free cobalt-catalyzed arylation of (hetero)aromatic acids has been developed. It involves an oxidative cross-coupling between carboxylate and aryl titanate reagents using oxygen as an oxidant, and the arylation at the position *ortho*, *meta* and *para* to the carboxylic acid group could all be achieved. As application, various (hetero)aromatic acids including xenalpin, tafamidis and the key intermediate for a cardioprotective compound have been efficiently synthesized.

Introduction

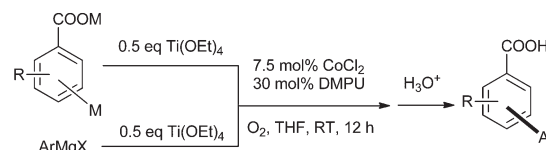
Biaryl acids and derivatives, including those containing heteroaryl components, are key structural units present in a vast number of pharmaceuticals (*e.g.*, telmisartan, tafamidis, xenalpin), agrochemicals and functional materials.¹ Besides, aromatic acids have nowadays become a class of important coupling substrates due to the remarkable advances in the Pd-catalyzed decarboxylic coupling reactions.² The great demand for these privileged compounds has been promoting the development of efficient synthetic methods to access them. Direct arylation of (substituted)benzoic acids through C–H activation represents a very attractive approach to synthesize biaryl acids, among which the Pd-catalyzed *ortho*-controlled arylation reactions have been well established by Daugulis,³ Yu⁴ and other groups.⁵ Despite these achievements, a more general approach that can override the *ortho*-selectivity and achieve *ortho*, *meta* and *para* (to the carboxylic acid group) arylation is still highly desired. Besides, using green oxidants such as oxygen (or air) to replace the common Ag salts as well as cheap iron or cobalt salts to replace the high cost palladium catalyst are also expected to make the arylation of aromatic acids more practical and environmentally friendly.

Recently we have developed mild iron and cobalt-catalyzed oxidative cross-couplings between two titanate-mediated aryl metal reagents (Scheme 1).⁶ In this context, we decided to develop an iron or cobalt-catalyzed arylation of aromatic acids

Our previous iron or cobalt-catalyzed oxidative cross-couplings



Cobalt-catalyzed oxidative arylation of aromatic acids in this work



Scheme 1 Cobalt-catalyzed oxidative arylation of aromatic acids.

through an oxidative coupling between titanate-mediated aryl carboxylate and aryl metal reagents. Since the preparations of various double lithium^{7,8} or magnesium⁹ reagents of unprotected (hetero)aromatic carboxylic acids have been well-established, we expected that this arylation protocol could overcome the limit of *ortho* selectivity by using lithium or magnesium metal reagents at various positions of aromatic carboxylates. Furthermore, using cheap, low-toxic iron or cobalt salts as desirable viable alternatives to noble palladium catalyst as well as oxygen as the greenest oxidant, this arylation could be developed into a more general and practical protocol to access various biaryl acids.

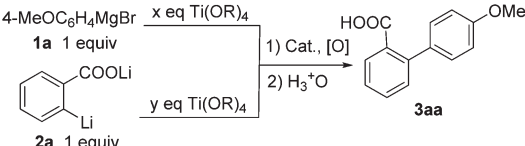
Compared with our previously developed Fe or Co-catalyzed oxidative cross-couplings⁶ (Scheme 1), Fe-catalyzed oxidative cross-couplings of a mixed titanate of $\text{MOOCa}^*\text{r}^*\text{M}$ (*e.g.*, $\text{MOOCa}^*\text{r}^*[\text{ArTi(OR)}_3]\text{M}$) could not give any arylated aromatic acid while the corresponding Co-catalyzed reaction only gave the desired product in rather low yield (Table 1). Instead, we finally developed a facile Co-catalyzed oxidative arylation of

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Table 1 Optimization studies^a


Entry	Catalyst ^b	Ti (x : y)	[O] ^{a,d}	Yield ^c (%)
1	NiCl ₂ /NHC ^a	Ti(OEt) ₄ (1 : 0)	DCE	None
2	PdCl ₂ /dppp ^a	Ti(OEt) ₄ (1 : 0)	DCE	None
3	FeCl ₃ /TMEDA	Ti(OEt) ₄ (1 : 0)	DCE	None
4	Co(acac) ₃ /PCy ₃	Ti(OEt) ₄ (1 : 0)	DCE	12
5	CoCl ₂ /PCy ₃	Ti(OEt) ₄ (1 : 0)	DCE	33
6	CoCl ₂ /PBU ₃	Ti(OEt) ₄ (1 : 0)	DCE	43
7	CoCl ₂ /dppp	Ti(OEt) ₄ (1 : 0)	DCE	16
8	CoCl ₂ /TMEDA	Ti(OEt) ₄ (1 : 0)	DCE	27
9	CoCl ₂ /DMPU ^e	Ti(OEt) ₄ (1 : 0)	DCE	38
10	CoCl ₂ /DMPU	Ti(OEt) ₄ (1 : 0)	DCE	44
11	CoCl ₂ /DMPU	Ti(OPr) ₄ (1 : 0)	DCE	27
12	CoCl ₂ /DMPU	tbepc ^a (1 : 0)	DCE	Trace
13	CoCl ₂ /DMPU	Ti(OEt) ₄ (0.5 : 0)	DCE	32
14	CoCl ₂ /DMPU	Ti(OEt) ₄ (2 : 0)	DCE	57
15	CoCl ₂ /DMPU	Ti(OEt) ₄ (0 : 1)	DCE	13
16	CoCl ₂ /DMPU	Ti(OEt) ₄ (1 : 1)	DCE	76
17	CoCl ₂ /DMPU	Ti(OEt) ₄ (0.5 : 0.5)	DCE	75
18	CoCl ₂ /DMPU	Ti(OEt) ₄ (0.5 : 0.5)	DBE	78
19	CoCl ₂ /DMPU	Ti(OEt) ₄ (0.5 : 0.5)	O ₂	75

^a The reaction was carried out at the 5 mmol scale in THF at room temperature. DCE: dichloroethane; DBE: dibromoethane; NHC: SIPr-HCl; dppp: Ph₂P(CH₂)₃PPh₂; DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone; tbepc: ClTi(OPr)₂(OCH₂CH₂OCH₂CH₂O). ^b Unless indicated otherwise, the catalyst metals were charged in 7.5 mol% with 15 mol% (monodentate), 7.5 mol% (bidentate) ligand or 20 mol% TMEDA. ^c Isolated yields. ^d DCE or DBE was charged at 1.2 equiv. and O₂ at 1 atm. ^e DMPU was charged at 15 mol%; in other cases at 30 mol%.

(hetero)aromatic carboxylic acids by modifying arylcarboxylate and aryl metal reagents with titanate in a new manner (Scheme 1), which we report herein. This arylation involves an oxidative assembly of arylcarboxylate and aryl titanate reagents using oxygen as an oxidant, where the arylation at the positions *ortho*, *meta* and *para* to the carboxylic acid group could all be achieved. The cross-couplings were catalyzed efficiently with a simple catalytic system (CoCl₂/DMPU; DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) in the absence of phosphine or NHC ligand at room temperature. Noteworthy, although recently Co-catalyzed cross-coupling reactions,¹⁰ especially the direct arylation of aromatic acid amides,¹¹ have been extensively studied, to the best of our knowledge, the present protocol is the first example of Co-catalyzed arylation of unprotected (hetero)aryl acids to date.

Results and discussion

Initially, we chose the oxidative coupling between 4-MeOC₆H₄MgBr (**1a**) and lithium (2-carboxylatophenyl)lithium (**2a**)^{8c,d} as the model reaction, and various parameters were

optimized. As illustrated in Table 1, Pd and Ni complexes failed to produce any cross-coupling products (Table 1, entries 1 and 2). Compared with our previously reported iron and cobalt-catalyzed oxidative cross-couplings,⁶ the presence of the acid group seemed to make the desired oxidative cross-coupling more challenging: upon FeCl₃/TMEDA catalysis (entry 3), the reaction did not afford any product of cross-coupling when two coupling metal reagents were transformed into a mixed titanate reagent (2-LiOOC₆H₄[4-CH₃OC₆H₄-Ti(OEt)₃Li]); whereas the corresponding Co-catalyzed reaction^{6c} only gave low yields (entries 4 and 5). Since the cobalt catalytic system often showed a higher activity than that of iron,⁶ we then focused on the cobalt catalytic system.¹²

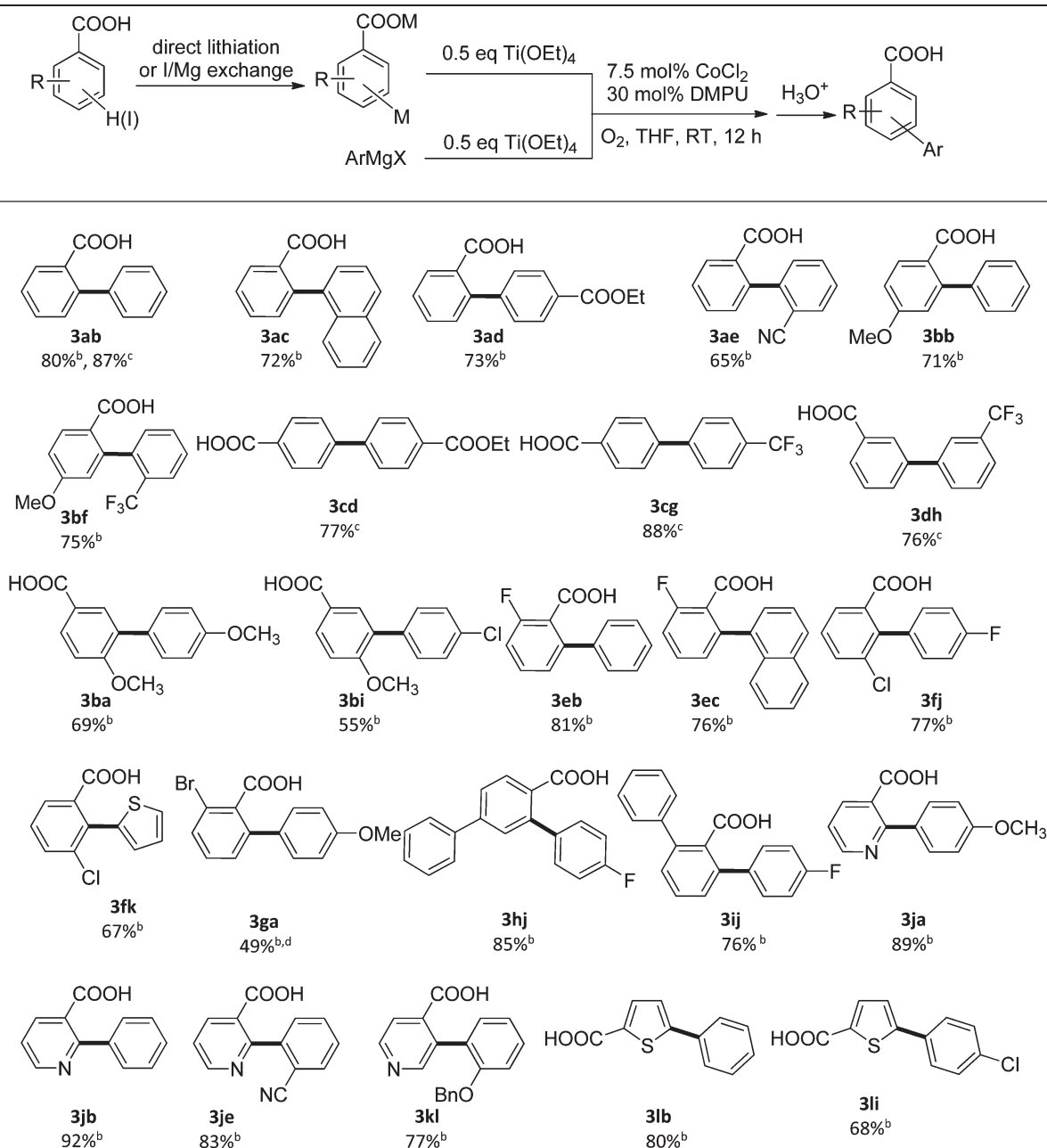
While Co(acac)₃/PCy₃ showed a rather low catalytic activity, CoCl₂/PCy₃ could promote the cross-coupling in 33% yield. The screening of ligands for cobalt catalysis indicated that simple PBU₃ was most effective (Table 1, entries 5–8).¹² To our delight, the use of 30 mol% DMPU could catalyze the cross-coupling with an equal effect to PBU₃ (Table 1, entries 9 and 10). The influence of the type of titanate was also examined, the other two titanates except for Ti(OEt)₄ gave disappointing results (Table 1, entries 10–12). Importantly, the combining manners of metal reagents with titanates showed a significant influence on the yields of the cross-coupling (Table 1, entries 13–18). Combining the two metal reagents with 1.0 or 0.5 equiv. of Ti(OEt)₄ respectively, namely the formation of two aryl titanate ate-complexes, [Ar₂Ti(OEt)₄M₂] and Ar'₂Ti(OEt)₄M₂, could improve the yield of **3aa** to 78%. This observation is in sharp contrast to our previously reported iron-catalyzed oxidative cross-couplings, where the formation of the mixed titanates [ArAr'Ti(OEt)₃M] was crucial to the selectivity of cross-couplings^{6a,b}. Thus, the present manner of combining the two metal reagents with titanates provided a new way to modulate the reactivity of the two metal reagents in oxidative cross-coupling. Noticeably, lithium (2-carboxylatophenyl)-lithium and its analogues are usually unstable at ambient temperature, the combination of lithium (2-carboxylatophenyl)lithium with Ti(OEt)₄ provided a very simple means to modify their reactivity, which enabled a facile arylation reaction at room temperature. The screening of oxidants showed that in addition to DCE and DBE, O₂ could also function as a green oxidant in this Co-catalyzed oxidative cross-coupling (Table 1, entries 17–19).

With the optimized reaction conditions in hand, we set out to test the generality of this reaction with the results being summarized in Table 2. This oxidative cross-coupling showed a broad scope with regard to both metal reagents, and had a high functional-group tolerance as well. Lithium (2-carboxylatophenyl)lithium could couple with a series of aryl Grignard reagents including those bearing a sensitive group such as ester and cyano groups to afford the desired products (**3ab–3ae**) under optimal conditions. Sterically hindered biaryl acids (**3ac** and **3ae**) could also be prepared based on the present procedure. On the other hand, the coupling also proceeded equally well (**3ab**, 87%) using the double-magnesiated species prepared from 2-iodobenzoic acid by halogen-magnesium exchange using *i*-PrMgCl-LiCl.⁹ Similarly, the

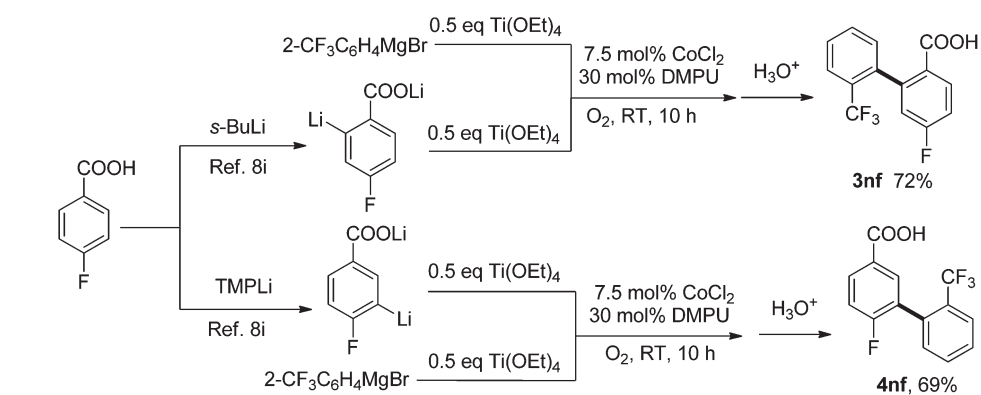
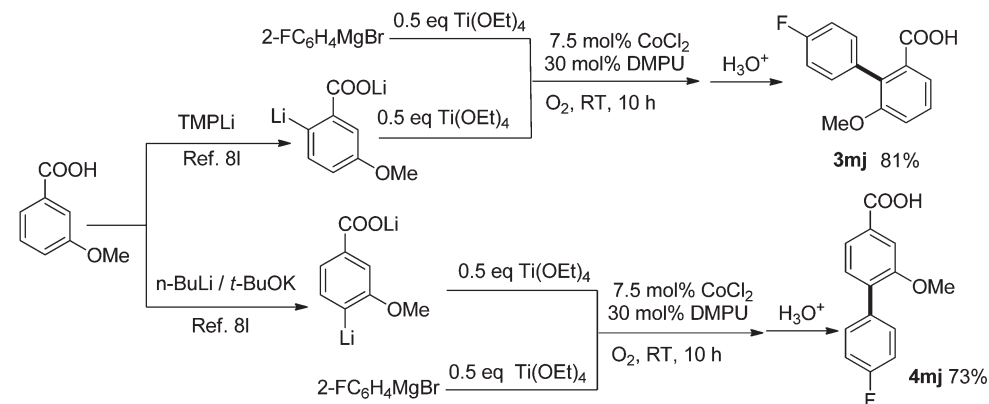
arylation at the *para* or *meta* position of benzoic acid could be achieved through this oxidative cross-coupling (**3cd**, **3cg** and **3dh**). The arylation at the *meta* position to COOH could also be implemented through a regioselectivity controlled lithiation (**3ba** and **3bi**). Notably, under the present cobalt-catalyzed coupling conditions, C–Cl and C–Br bonds were tolerated. For example, under the mediation of $\text{Ti}(\text{OEt})_4$, lithium (2-carboxy-

lato-6-chlorophenyl)lithium^{8g} coupled with 4-fluorophenyl-magnesium bromide and thiophen-2-yl magnesium bromide to afford the sterically congested products (**3fj** and **3fk**). With two handles, namely halogen chlorine and carboxylic acid groups (through decarboxylic coupling reactions), these products (**3fj**, **3fk** and **3ga**) can readily be derivatized to yield 1,2,3-trisubstituted benzene compounds. Besides, the present

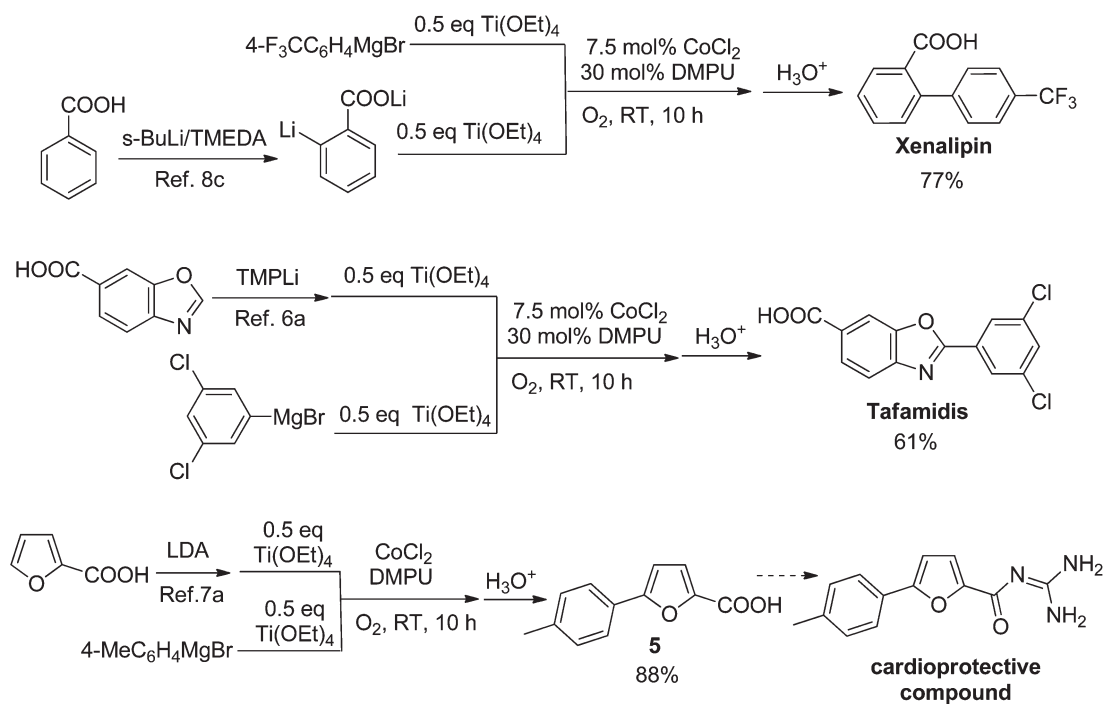
Table 2 Co-catalyzed oxidative arylation of unprotected (hetero)aromatic acids using O_2 as an oxidant^a



^a The oxidative cross-coupling reactions were carried out at the 5 mmol scale in THF at room temperature under the catalysis of 7.5 mol% CoCl_2 /30 mol% DMPU and the yields are all isolated ones. ^b Aryl carboxylate metal reagents were prepared through the deprotonative lithiation of unprotected acids. ^c Aryl carboxylate metal reagents were prepared through iodine-magnesium exchange using $i\text{-PrMgCl-LiCl}$. ^d Isolated and characterized as its methyl ester.



Scheme 2 Regioselectivity-switchable arylation of substituted benzoic acids.



Scheme 3 Syntheses of xenalipin, tafamidis and intermediate 5.

Co-catalyzed arylation was amenable to heteroaromatic acids such as (iso)nicotinic acid and thiophene-2-carboxylic acid, which provided a convenient protocol to access the corresponding biaryl acids starting from simple heteroaromatic acids (Table 2, **3ja–3li**).

Regioselective lithiation of substituted benzoic acids is a powerful tool to derivatize the acids in an alternative manner.⁸ Combining this process with the present oxidative cross-coupling, we developed a regioselectivity-switchable arylation of substituted benzoic acids. As illustrated in Scheme 2 (also see Scheme 1, **3bb** and **3bf** vs. **3ba** and **3bi**), 3-MeOC₆H₄COOH and 4-FC₆H₄COOH were regioselectively lithiated based on the reported procedure,^{8i,l} two couples of product regioisomers were obtained through subsequential oxidative cross-couplings, which respectively corresponded to the arylation *ortho*, *meta* and *para* to the carboxylic acid group.

To further demonstrate the synthetic potential of this Co-catalyzed arylation of unprotected aromatic acids, new syntheses of two market pharmaceuticals (xenalipin¹³ and tafamidis¹⁴) and a key intermediate (**5**) for a cardioprotective compound¹⁵ using this method as the key step are outlined in Scheme 3. While xenalipin was prepared through *ortho*-arylation of benzoic acid, tafamidis was synthesized *via* a cross-ring arylation to the carboxylic acid group, and the C–Cl bonds were tolerated as well. Noticeably, lithiation of benzoxazole at C-2 and subsequent quenching with electrophiles are often challenging due to the isomerization of this metal species to 2-(isocyano)phenolate,¹⁶ nevertheless, the present arylation occurred smoothly. In the synthesis of intermediate **5** for a cardioprotective compound, furan-2-carboxylic acid was facilely arylated at the C5 position in 88% yield. It could be seen that the reagents used in these syntheses are readily available, and the corresponding procedures were straightforward. Once again, the arylation beyond *ortho*-selectivity was achieved.

Conclusions

In summary, a room temperature cobalt-catalyzed arylation of (hetero)aromatic acids has been developed using oxygen as an oxidant, which represents a new complementary approach to the existing methods. Although the preparations of lithium reagents of (hetero)aryl carboxylates have been well established through direct deprotonative lithiation, their arylation used to be challenging due to their high reactivity. The mediation of Ti(OEt)₄ in the present reaction not only provides a new way to modulate the reaction behavior of sensitive lithium reagents of aryl carboxylate, but also facilitates a very mild Co-catalyzed oxidative arylation. Since both titanium¹⁷ and cobalt are abundant non(low)-toxic metals, and the modification of carboxylate and aryl metal reagents using titanates could be easily achieved by simple *in situ* mixing, this room temperature Co-catalyzed arylation protocol provides a mild and eco-friendly method to prepare various biaryl acids, which is amenable to scale up. Moreover, combined with regioselective deprotona-

tive lithiation, the present approach enables a regioselectivity-switchable arylation of unprotected substituted benzoic acids.

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