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ARTICLE

Room-Temperature Cobalt-Catalyzed Arylation of Aromatic Acid: Overriding *Ortho*-Selectivity via Oxidative Assembly of Carboxylate and Aryl Titanate Reagents Using Oxygen

Kun-Ming Liu,[a,b] Rui Zhang[a,b] and Xin-Fang Duan[a]*

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 Xenalepin, Tafamidis and key intermediate for cardioprotective compound have been efficiently synthesized.

Introduction

Biaryl acids and derivatives, including those containing heteroaryl components, are key structural units presented in a vast number of pharmaceuticals (e.g., Telmisartan, Tafamidis, Xenalepin), agrochemicals and functional materials.[1] Besides, aromatic acids have nowadays become a class of important coupling substrates due to the remarkable advances of the Pd-catalyzed decarboxylic coupling reactions.[2] The great demand for these privileged compounds have 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 make biaryl acids, among which the Pd-catalyzed *ortho*-controlled arylation reactions have been well established by Daugulis,[3] Yu[4] 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 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 titanate-mediated two aryl metal reagents (Scheme 1).[6] In this context, we decide to develop an iron or cobalt-catalyzed arylation of aromatic acid through an oxidative coupling between titanate-mediated aryl

Our previous iron or cobalt-catalyzed oxidative cross-couplings

$$ArM \xrightarrow{ClTi(OR)_3} Ar'M \xrightarrow{} Ar'[ArTi(OR)_3]M \xrightarrow[O_2]{[Fe]/[Co]} Ar\text{---}Ar'$$
$$(\ M = Li\ or\ MgX)$$
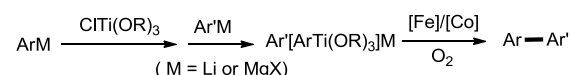
Cobalt-catalyzed oxidative arylation of aromatic acids in this work
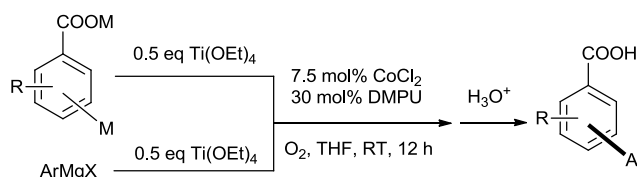
Scheme 1 Cobalt-catalyzed oxidative arylation of aromatic acids

carboxylate and aryl metal reagents. Since the preparations of various double lithium[7,8] or magnesium[9] 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 a 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-couplings[6] (Scheme 1), Fe-catalyzed oxidative cross-couplings of mixed titanate of MOOCAr'M (e.g., MOOCAr'[ArTi(OR)$_3$]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 (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

[a.] *College of Chemistry, Beijing Normal University, Beijing, 100875, P. R. China. E-mail: xinfangduan@vip.163.com*
[b.] *K. M. Liu and R. Zhang contributed equally to this paper.*
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oxidative assembly of arylcarboxylate and aryl titanate reagents using oxygen as an oxidant, where the arylation at the position *ortho*, *meta* and *para* to the carboxylic acid group could all be achieved. The cross-couplings were catalyzed efficiently with simple catalyst system (CoCl$_2$/DMPU; DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) in the absence of phosphine or NHC ligand at room temperature. Noteworthily, 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-MeOC$_6$H$_4$MgBr (**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 acid group seemed to make the desired oxidative cross-coupling more challenging: upon FeCl$_3$/TMEDA catalysis (entry 3), the reaction did not afford any product of the cross-coupling when two coupling metal reagents were transformed into mixed titanate reagent (2-LiOOCC$_6$H$_4$[4-CH$_3$OC$_6$H$_4$Ti(OEt)$_3$]Li); 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)$_2$/PCy$_3$ showed a rather low catalytic activity, CoCl$_2$/PCy$_3$ could promote the cross-coupling in a 33% yield. The screening of ligands for cobalt catalysis indicated that simple PBu$_3$ was most effective (Table 1, entries 5-8).[12] To our delight, the use of 30 mol% DMPU could catalyze the cross-coupling with equal effect to PBu$_3$ (Table 1, entries 9 and 10). The influence of the type of titanates was also examined, the other two titanates except Ti(OEt)$_4$ gave disappointing results (Table 1, entries 10-12). Importantly, the combining manners of metal reagents with titanates showed a significant influence in 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, [Ar$_2$Ti(OEt)$_4$M$_2$ and Ar'$_2$Ti(OEt)$_4$M$_2$], could improve the yield of **3aa** to 78%. This observation is in sharp contrast with our previously reported iron-catalyzed oxidative cross-couplings, where the formation of the mixed titanates [ArAr'Ti(OEt)$_3$M] 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 two metal reagents in an 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

Table 1 Optimization studies[a]
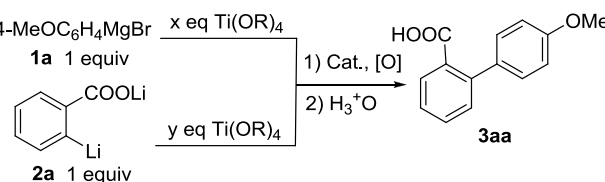
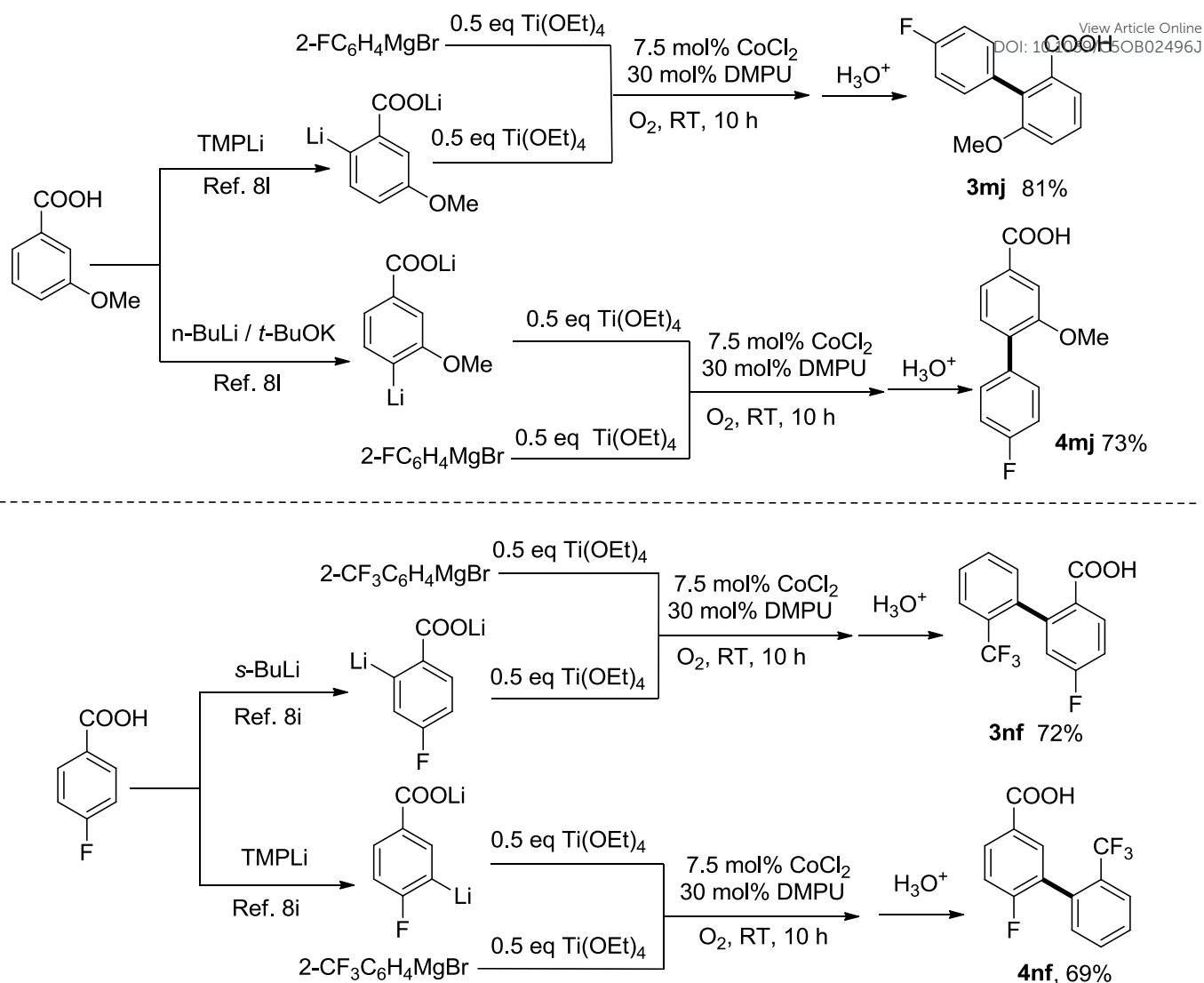| Entry	Catalyst[b]	Ti (x:y)	[O][a,d]	Yield(%)[c]
1	NiCl$_2$/NHC[a] A	Ti(OEt)$_4$ (1:0)	DCE	none
2	PdCl$_2$/dppp[a]	Ti(OEt)$_4$ (1:0)	DCE	none
3	FeCl$_3$/TMED	Ti(OEt)$_4$ (1:0)	DCE	none
4	Co(acac)$_2$/PCy$_3$	Ti(OEt)$_4$ (1:0)	DCE	12
5	CoCl$_2$/PCy$_3$	Ti(OEt)$_4$ (1:0)	DCE	33
6	CoCl$_2$/PBu$_3$	Ti(OEt)$_4$ (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^j)$_4$ (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 5 mmol scale in THF at room temperature. DCE: dichloroethane; DBE: dibromoethane; NHC: SIPr·HCl; dppp: Ph$_2$P(CH$_2$)$_3$PPh$_2$; DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; tbepc: ClTi(OPr^j)-(OCH$_2$CH$_2$OCH$_2$CH$_2$O). [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 O$_2$ at 1 atm. [e] DMPU was charged at 15 mol%; in other cases at 30 mol%.

reactivity, which enabled a facile arylation reaction at room temperature. The screening of oxidants showed that in addition to DCE and DBE, O$_2$ 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 Scheme 1. 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, cyano group to afford the desired products (**3ab**-**3ae**) under the 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,

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

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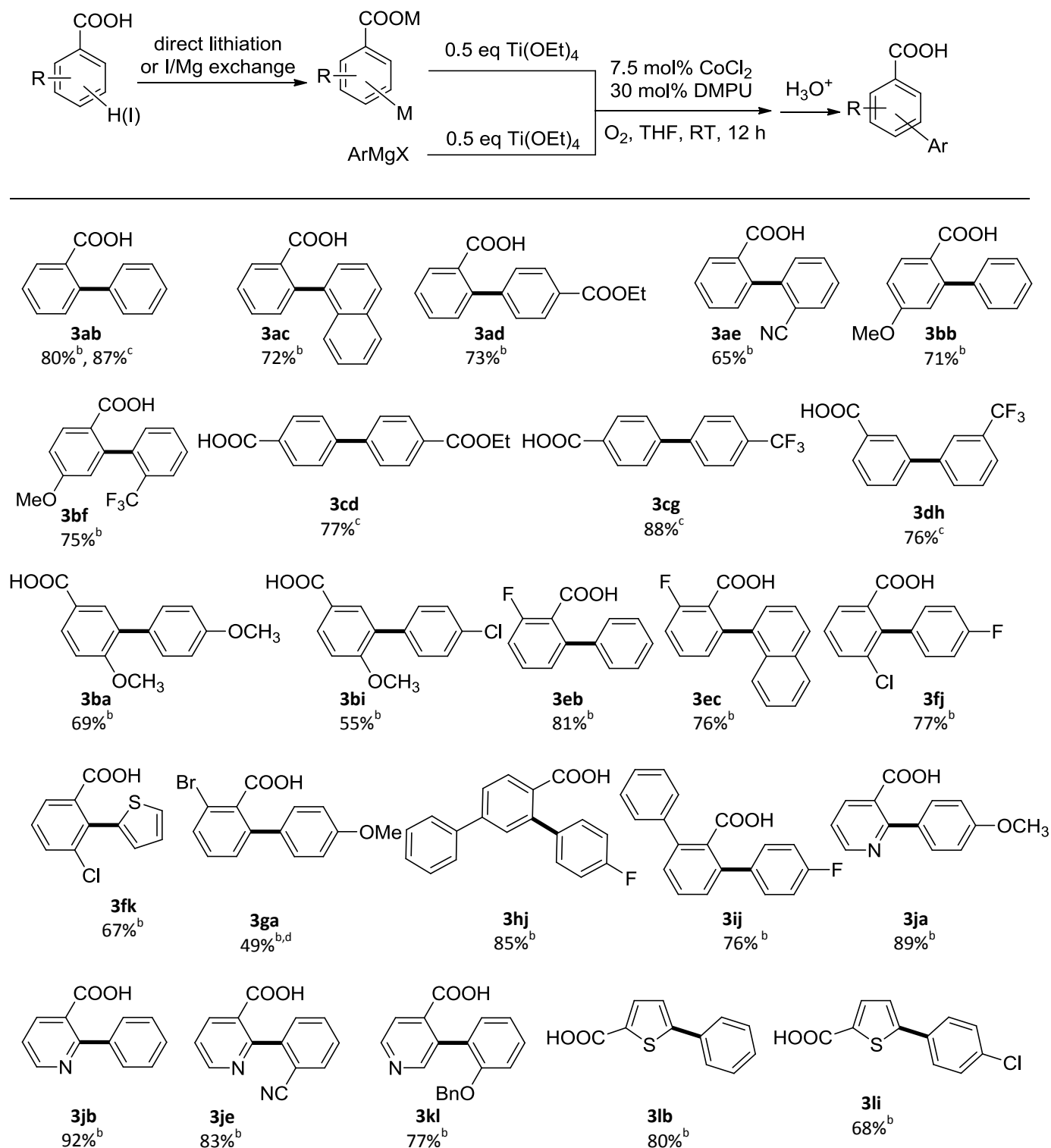
[a] The oxidative cross-coupling reactions were carried out at 5 mmol scale in THF at room temperature under the catalysis of 7.5 mol% $CoCl_2$ / 30 mol% DMPU and the yields are all isolated ones. [b] Aryl carboxylate metal reagents were prepared through the deprotonative lithiation of unprotected acids.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

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2-FC$_6$H$_4$MgBr — 0.5 eq Ti(OEt)$_4$

COOLi · 0.5 eq Ti(OEt)$_4$ (Li, OMe)

TMPLi / Ref. 8l

COOH / OMe

7.5 mol% CoCl$_2$
30 mol% DMPU
O$_2$, RT, 10 h

H$_3$O$^+$

3mj 81% (F, COOH, MeO)

n-BuLi / t-BuOK / Ref. 8l

COOLi / OMe / Li

2-FC$_6$H$_4$MgBr — 0.5 eq Ti(OEt)$_4$
0.5 eq Ti(OEt)$_4$

7.5 mol% CoCl$_2$
30 mol% DMPU
O$_2$, RT, 10 h

H$_3$O$^+$

4mj 73% (COOH, OMe, F)

2-CF$_3$C$_6$H$_4$MgBr — 0.5 eq Ti(OEt)$_4$

COOLi / Li / F · 0.5 eq Ti(OEt)$_4$

s-BuLi / Ref. 8i

COOH / F

7.5 mol% CoCl$_2$
30 mol% DMPU
O$_2$, RT, 10 h

H$_3$O$^+$

3nf 72% (COOH, CF$_3$, F)

TMPLi / Ref. 8i

COOLi / F / Li

2-CF$_3$C$_6$H$_4$MgBr — 0.5 eq Ti(OEt)$_4$
0.5 eq Ti(OEt)$_4$

7.5 mol% CoCl$_2$
30 mol% DMPU
O$_2$, RT, 10 h

H$_3$O$^+$

4nf, 69% (COOH, CF$_3$, F)

Scheme 2 Regioselectivity-switchable arylation of substituted benzoic acids

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 Ti(OEt)$_4$, lithium (2-carboxylato-6-chlorophenyl)lithium[8g] coupled with 4-fluorophenylmagnesium 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 group (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 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.

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-MeOC$_6$H$_4$COOH and 4-FC$_6$H$_4$COOH were regioselectively lithiated based on the reported procedure,[8i,l] two couples of product regioisomers were afforded through subsequential oxidative cross-couplings, which respectively corresponded to the arylation *ortho*, *meta* and *para* to carboxylic acid group.

To further demonstrate the synthetic potentials of this Co-catalyzed arylation of unprotected aromatic acid, new syntheses of two market pharmaceuticals (Xenalipin[13] and Tafamidis[14]) and a key intermediate (**5**) for cardioprotective

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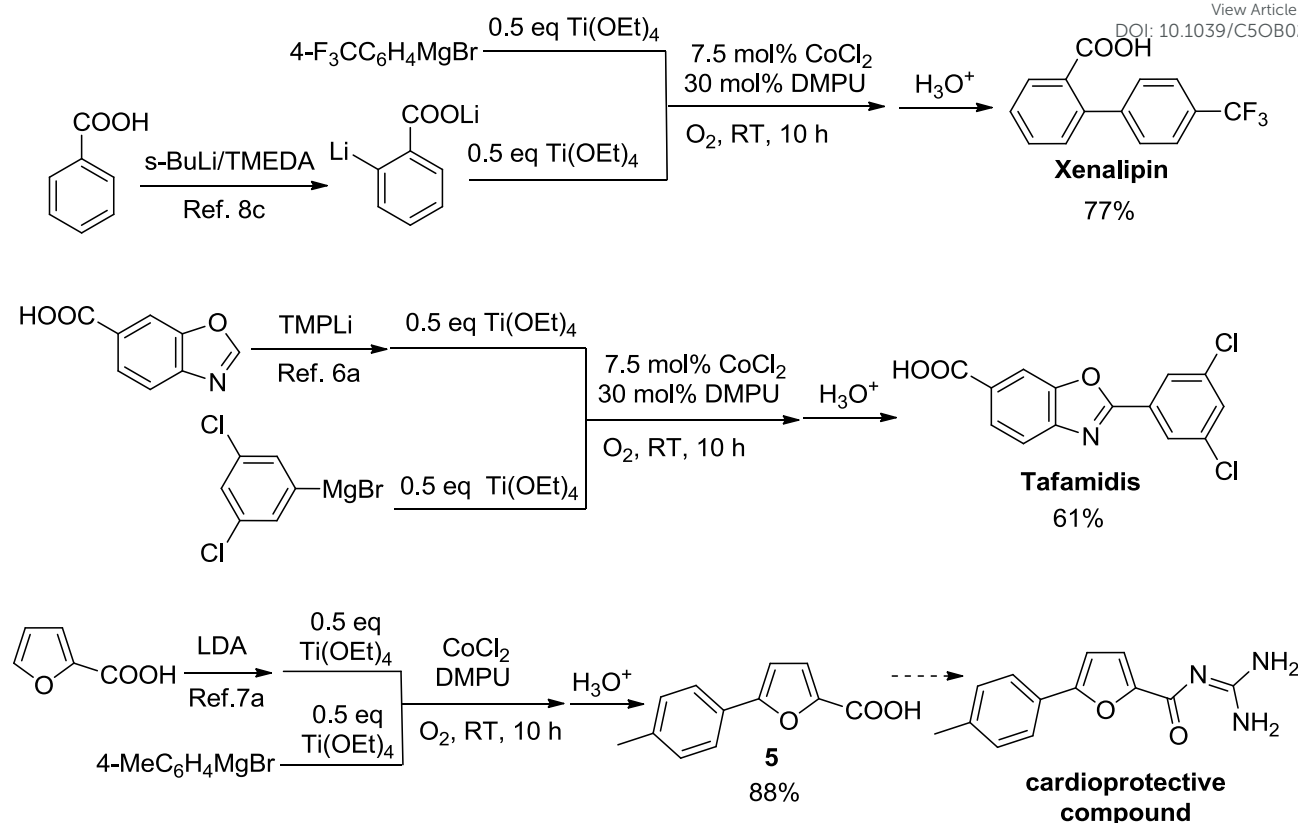
Scheme 3 Syntheses of Xenalipin, Tafamidis and intermediate 5

compound[15] using the method as the key step were outlined in Scheme 3. While Xenalepin was prepared through *ortho*-arylation of benzoic acid, Tafamidis was synthesized via a cross-ring arylation to 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 cardioprotective compound, furan-2-carboxylic acid was facilely arylated at C5 position in a 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 titanium[17] 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 deprotonative lithiation, the present approach enables a regioselectivity-switchable arylation of unprotected substituted benzoic acids.

Acknowledgements

Notes and references

1   (a) P. J. Hajduk, M. Bures, J. Praestgaard and S. W. Fesik, *J. Med. Chem.,* 2000, **43**, 3443; (b) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner and M. Breuning, *Angew. Chem., Int. Ed.,* 2005, **44**, 5384.
2   For selected reviews, see: (a) O. Baudoin, *Angew. Chem., Int. Ed.,* 2007, **46**, 1373; (b) L. J. Goossen, N. Rodriguez, and K.

Goossen, *Angew. Chem., Int. Ed.,* 2008, **47**, 3100; (c) S. M. Bonesi, and M. Fagnoni, *Chem. — Eur. J.,* 2010, **16**, 13572.

3   H. A. Chiong, Q.-N. Pham and O. Daugulis, *J. Am. Chem. Soc.,* 2007, **129**, 9879.

4   (a) R. Giri, N. Maugel, J. J. Li, D. H. Wang, S. P. Breazzano, L. B. Saunders and J. Q. Yu, *J. Am. Chem. Soc.,* 2007, **129**, 3510; (b) D. H. Wang, T. S. Mei and J. Q. Yu, *J. Am. Chem. Soc.,* 2008, **130**, 17676.

5   (a) K. Ueura, T. Satoh, M. Miura, *J. Org. Chem.,* 2007, **72**, 5362; (b) C. Arroniz, A. Ironmonger, G. Rassias and I. Larrosa, *Org. Lett.,* 2013, **15**, 910; (c) C. Zhu, Y. Zhang, J. Kan, H. Zhao and W. Su, *Org. Lett.,* 2015, **17**, 3418.

6   For Fe-catalyzed couplings, see: (a) K. M. Liu, L. Y. Liao, and X. F. Duan, *Chem. Commun.,* 2015, **51**, 1124; (b) K. M. Liu, J. Wei and X. F. Duan, *Chem. Commun.,* 2015, **51**, 4655; for Co-catalyzed couplings, see: (c) L. Y. Liao, K. M. Liu, and X. F. Duan, *J. Org. Chem.,* 2015, **80**, 9856.

7   For selected reviews, see: (a) J. Mortier in *Recent Research Developments in Organic Chemistry*, *vol. 2* (Ed. S. G. Pandalai), Transworld Research Network, Trivandrum, India, USA, 1998; p. 269; (b) M. C. Whisler, S. MacNeil, V. Snieckus, and P. Beak, *Angew. Chem., Int. Ed.*, 2004, **43**, 2206.

8   For representative papers on lithiation of unprotected (hetero)aromatic acids, see: (a) D. W. Knight and A. P. Nott, *J. Chem. Soc., Perkin Trans. 1*, 1981*,* 1125; (b) D. W. Knight and A. P. Nott, *J. Chem. Soc., Perkin Trans. 1,* 1983*,* 791; (c) J. Mortier and J. Moyroud, *J. Org. Chem.,* 1994, **59**, 4042; (d) B. Bennetau, J. Mortier, J. Moyroud, and J.-L. Guesnet, *J. Chem. Soc., Perkin Trans. 1,* **1995**, 1265; (e) F. Mongin, F. Trécourt, and G. Quéguiner, *Tetrahedron Lett.,* 1999, **40**, 5483; (f) J. Lazaar, A.-S. Rebstock, F. Mongin, A. Godard, F. Trécourt, F. Marsais, and G. Quéguiner, *Tetrahedron,* 2002, **58**, 6723; (g) F. Gohier, and J. Mortier, *J. Org. Chem.,* 2003, **68**, 2030; (h) F. Gohier, A.-S. Castanet, and J. Mortier, *Org. Lett.,* 2003, **5**, 1919; (i) F. Gohier, A.-S. Castanet, and J. Mortier, *J. Org. Chem.,* 2005, **70**, 1501; (j) D. Tilly, S. S. Samanta, A.-S. Castanet, A. De, and J. Mortier, *Eur. J. Org. Chem*., 2006, 174; (k) T. H. Nguyen, A.-S. Castanet, and J. Mortier, *Org. Lett.,* 2006, **8**, 765; (1) T. H. Nguyen, N. T. T. Chau, A.-S. Castanet, K. P. P. Nguyen, and J. Mortier, *J. Org. Chem.,* 2007, **72**, 3419.

9   F. Kopp, S. Wunderlich, and P. Knochel, *Chem. Commun.,* 2007, 2075.

10 For selected reviews on cobalt-catalyzed reactions, see: (a) C. Gosmini, J.-M. Bégouin, and A. Moncomble, *Chem. Commun.,* 2008, **28**, 3221; (b) G. Cahiez, and A. Moyeux, *Chem. Rev.,* 2010, **110**, 1435; (c) K. Gao, and N. Yoshikai, *Acc. Chem. Res.,* 2014, **47**, 1208; (d) L. Ackermann, *J. Org. Chem.,* 2014, **79**, 8948.

11 For selected recent examples of cobalt-catalyzed direct alkylation or arylation of amides, see: a) Q. Chen, L. Ilies, and E. Nakamura, *J. Am. Chem. Soc.,* 2011, **133**, 428; (b) L. Ilies, Q. Chen, X. Zeng, and E. Nakamura, *J. Am. Chem. Soc.,* 2011, **133**, 5221; (c) L. Grigorjeva, and O. Daugulis, *Angew. Chem., Int. Ed.,* 2014, **53**, 10209; (d) L. Grigorjeva, and O. Daugulis, *Org. Lett.,* 2014, **16**, 4684; (e) J. Li and L. Ackermann, *Chem. — Eur. J.,* 2015, **21**, 5718; (f) L. Grigorjeva, and O. Daugulis, *Org. Lett.,* 2015, **17**, 1204.

12 J. Zeng, K. M. Liu and X. F. Duan, *Org. Lett.,* 2013, **15**, 5342.

13 C. Dupuis, K. Adiey, L. Charruault, V. Michelet, M. Savignac, and J.-P. Genet, *Tetrahedron Lett.,* 2001, **42**, 6523.

14 T. Yamamoto, K. Muto, M. Komiyama, J. Canivet, J. Yamaguchi, and K. Itami, *Chem. — Eur. J.,* 2011, **17**, 10113.

15 S. Lee, K. Y. Yi, S. K. Hwang, B. H. Lee, S. Yoo, and K. Lee, *J. Med. Chem.* 2005, **48**, 2882.

16 O. Bayh, H. Awad, F. Mongin, C. Hoarau, L. Bischoff, F. Trécourt, G. Quéguiner, F. Marsais, F. Blanco, B. Abarca and R. Ballesteros, *J. Org. Chem.,* 2005, **70**, 5190.

17 D. J. Ramón and M. Yus, *Chem. Rev.,* 2006, **106**, 2126.