Volume 1 | Number 1 | Jan 2013 | Pages 1–100

ChemComm

Chemical Communications
www.rsc.org/chemcomm

ROYAL SOCIETY OF CHEMISTRY

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

COMMUNICATION

Iron Catalyzed Oxidative Assembly of N-heteroaryl and Aryl Metal Reagents Using Oxygen as an Oxidant

Kun Ming Liu, Lian Yan Liao, and Xin Fang Duan*

An equivalent amount of N-heteroaryl and aryl Grignard or lithium reagents, after mediated by an equivalent of titanate, was facilely coupled to furnish N-heteroaryl-aryl compounds under the catalysis of FeCl₃/TMEDA at ambient temperature using oxygen as an oxidant. Most of common N-heteroaryls were all good candidates, and thus provided a general, green and pratical protocol for the flexible construction of various N-heteroaryl-aryl structures.

Biaryls, including those containing N-heteroaryl components occur ubiquitously in biologically active compounds, natural products and functional materials. Transition-metal catalyzed cross-coupling reactions of an organometallic reagent with an aryl halide or pseudohalide are among the most common methods for making these biaryls and heterobiaryls.[1] Recently, oxidative couplings of organometallics[2] have attracted much attention due to the advantages such as: (a) a wide variety of metal reagents can be used, and in particular the great advances in the direct metalation of arenes and heteroarenes enable this type of oxidative couplings using simple or functionalized arenes;[3] and (b) it can avoid the use of halides or halide equivalents as well as the process of their oxidative addition to a transition metal complex that usually requires special ligands for unreactive halides.[4] Actually, if molecular oxygen is used as an oxidant, an ideal oxidative coupling of this type will provide the desired products with peroxide inorganic salts as side products. These advantageous features are fully displayed in the Fe or Mn-catalyzed aerobic oxidative homocouplings of Grignard reagents reported by Cahiez, Lei and co-workers.[5,6] However, the cross-couplings of this type are very challenging because of the potential side homocoupling reactions of the two metal reagents. Only few examples of this oxidative cross-coupling have been described to date, most of which are achieved between different hybridized carbon atoms such as C(sp)—C(sp2);[7] C(sp)—C(sp3);[8] C(sp2)—C(sp3).[9] The examples of oxidative aryl-aryl cross couplings are very rare.[7b, 10] Obviously, the similar reactivity of the organometallic reagents makes the aryl-aryl oxidative cross couplings remarkably challenging.

Scheme 1. Iron-catalyzed oxidative cross-coupling of titanate mediated two aryl metal reagents.

Herein we wish to report a novel iron-catalyzed oxidative aryl-aryl cross-coupling of titanate-mediated two aryl Grignard or lithium reagents using oxygen as an oxidant (Scheme 1). Aryl magnesium halides (ArMgX, **1**) are transmetalated to the corresponding titanium reagents [ArTi(OR)₃, **2**] using ClTi(OR)₃.[11] Subsequent reaction in situ with *N*-heteroaryl metal reagents (ArᴺM, **3**) results in the formation of a mixed titanate of type **4** (Arᴺ[ArTi(OR)₃]M),[12] which is treated with FeCl₃/TMEDA/O₂ to provide the biaryl products through an iron-catalyzed oxidative cross-coupling (Scheme 1).

Because the pyridyl skeletons are prevalent in natural products, pharmaceuticals and functional materials,[13] and at the same time, the preparation of bench-stable 2-pyridyl metal reagents (such as boronic derivatives) and their cross couplings are usually a challenging task in organic synthesis,[14] our initial study focused on the model reaction between the 2-pyridyl and phenyl Grignard

Scheme 2. The influence of titanate mediation in the iron-catalyzed oxidative cross-couplings. Reaction conditions: 10 mol% FeCl₃ / 30 mol% TMEDA, RT. DCE = 1,2-dichloroethane.

reagents, hoping to find an alternative method for making *N*-heteroaryl structures using readily available 2-pyridyl Grignard or lithium reagents under mild conditions. As illustrated in Scheme 2, almost no cross-coupling product was observed without the mediation of a titanate. In this case the homocoupling of phenyl group took place rapidly with high yield. To our delight, after PhMgBr was transmetalated into $PhTi(OPr^i)_3$, and subsequently into **4aa** through the in-situ treatment with **3a**, the oxidative coupling generated the cross-coupling product (**5aa**) in a high yield. The comparison experiments in which the mixed titanate **4aa** were formed from the purified $PhTi(OPr^i)_3$ and 2-PyM (M = MgBr, Li) also gave similarly high yield of **5aa**, indicating that the formation of the mixed titanate (**4aa**) was crucial to the high selectivity of the oxidative cross-coupling while the influence of magnesium or lithium salts from **1a** or **3a** was not significant. Further attempts on the cross-coupling using the mixed titanate (**4′aa**, through transmetalation in a reverse sequence, Scheme 2) was unsuccessful because of the instability of $2-PyTi(OPr^i)_3$ (our experiments showed that a combination of 2-PyMgX and $ClTi(OPr^i)_3$ resulted in a black complex mixture).[11a] These observations showed that the formation of the mixed titanate of type **4aa** could adjust the reactivity of both ArMgX and 2-PyM in a suitable and combined manner (the Ph group through C—Ti bond and the 2-Py group through an ate-complex), which not only played a key role in the high selectivity of cross-coupling, but also provided a method to circumvent the problem of the instability of $2-PyTi(OPr^i)_3$.

Further optimization studies on the oxidative cross-coupling reaction of **1a** and **3a** were performed with the results being summarized in Table 1. Compared with iron catalysis, the Pd or Ni-catalyzed reactions gave rather low or no yields of cross-coupling product (entries 1 and 2), indicating a significant synergetic effect between iron and titanium.[15] While the simple phosphine ligands such as PBu_3, PCy_3, dppp, dmadpp can improve the cross-coupling, $FeCl_3$/TMEDA proved to be the most effective catalyst system, which promote the oxidative cross-couplings in a yield up to 92% (entries 3-8). Also, we examined the influence of different titanates (entries 9-11). It could be seen that most of tested titanates promoted the cross- coupling in high yields. To our delight, the cross-coupling occurred in a quantitative yield by using easily prepared and handling solid tbepc (entry 11). $Fe(acac)_3$ could also promote the cross coupling equally well, yet with prolonged reaction time (entry 12). Lowering the loading of catalyst to 8 mol % $FeCl_3$ / 20 mol % TMEDA did not affect the yield (entry 13). At this point, an equivalent amount of two different aryl Grignard reagents, after mediated with a titanate, was quantitatively coupled at room temperature under the catalysis of iron using DCE as an oxidant. Bearing in mind that atmospheric oxygen or oxygen is indeed the greenest candidate oxidant, we tried to use atmospheric oxygen or oxygen as an oxidant in this reaction (entries 14 and 15). It was observed that while dry air could give an acceptable yield (76%) in prolonged reaction time, the reaction using oxygen could proceed equally well with those using DCE.

The above reaction represents the first example of iron-catalyzed oxidative arylation of 2-pyridyl metal reagents, providing a very mild method for making 2-arylpyridines complementary to the existing methods.[14, 16] On the basis of these findings, we then investigated the scope of this oxidative cross-coupling reaction between various aryl and N-heteroaryl Grignard or lithium reagents. The results are summarized in Table 2. This cross-coupling reaction showed a very broad scope with remarkable functional-group tolerance. Aryl Grignard reagents functionalized with a sensitive ester and CN group could couple well in high yields (**5ac** and **5ad**). Various 2-pyridyl metal reagents also gave similarly good results (**5ba-5ea**). Notably, under the present iron-catalyzed coupling

Table 1. The optimization studies on the oxidative cross-coupling reaction of titanate-mediated **1a** and **3a**.[a]

entry	catalyst[b]	titanate	[O]	time (h)	yield (%)[c]
1	$PdCl_2$/dppp[d]	$ClTi(OPr^i)_3$	O_2	12	--
2	$NiCl_2$/dppp	$ClTi(OPr^i)_3$	DCE	12	16
3	$FeCl_3$	$ClTi(OPr^i)_3$	DCE	12	64
4	$FeCl_3$/PBu_3	$ClTi(OPr^i)_3$	DCE	4	87
5	$FeCl_3$/PCy_3	$ClTi(OPr^i)_3$	DCE	4	82
6	$FeCl_3$/dppp	$ClTi(OPr^i)_3$	DCE	4	78
7	$FeCl_3$/dmadpp[d]	$ClTi(OPr^i)_3$	DCE	4	72
8	$FeCl_3$/tmeda	$ClTi(OiPr)_3$	DCE	4	92
9	$FeCl_3$/tmeda	$ClTi(OEt)_3$	DCE	4	90
10	$FeCl_3$/tmeda	tmpc[d]	DCE	4	90
11	$FeCl_3$/tmeda	tbepc[d]	DCE	4	97
12	$Fe(acac)_3$/tmeda	tbepc	DCE	8	92
13	$FeCl_3$/tmeda[e]	tbepc	DCE	4	95
14	$FeCl_3$/tmeda[e]	tbepc	Dry air[f]	24	76
15	$FeCl_3$/tmeda[e]	tbepc	O_2[f]	8	96

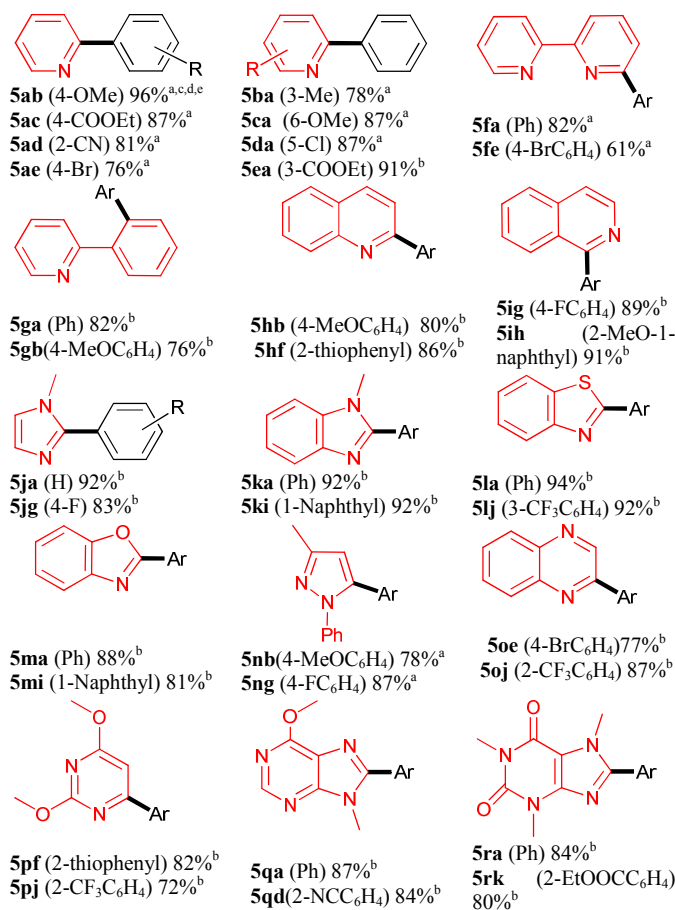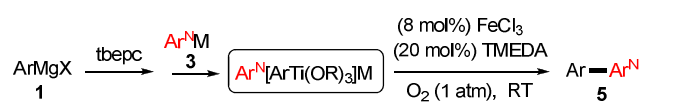[a]The reaction was carried out on a 1 mmol scale at room temperature. [b]Unless indicated otherwise, the catalyst metals were charged in 10 mol % with 20 mol % (monodentate), 10 mol % (bidentate) ligand or 30 mol % TMEDA. [c]Isolated yield. [d]Below are their structures [e]8 mol% $FeCl_3$ / 20 mol% TMEDA. [f]1 atm.
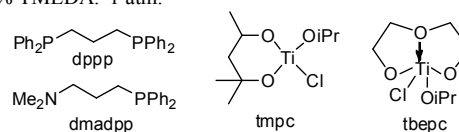
conditions, C—Br and C—Cl bonds were tolerated as well (**5ae**, **5da** and **5fe**). Other metal reagents of pyridine analogues such as 2-phenylpyridine, quinoline and isoquinoline also underwent the reaction quite well (**5fa-5ig**). Under Pd or Ni catalysis, the reactions giving biheteroaryls are often challenging due to the chelation of the product with the catalyst metal.[17] In contrast, the present coupling could assemble this type of biheteroaryls such as **5fa**, **5fe**, **5hf** and **5pf** in good yields. Besides, the coupling of isoquinoline metal reagent with a sterically hindered Grignard reagent could afford a useful axially chiral ligand (**5ih**)[18] in a high yield. Further studies on the scope of this oxidative biaryl cross-coupling reaction indicate that in addition to pyridine and (iso)quinoline derivatives, most of other common N-heteroarenes such as benzoimidazole, benzo-thiazole, benzoxazole, quinoxaline, pyrimidine, pyrazole, purine and caffeine could all undergo the reaction well (**5ja-5rk**).[3d, 19] Once again, various aryl Grignard reagents with functional groups were amenable to the coupling. Noticeably, lithiation of benzoxazole at C-2 and subsequent quenchment with electrophiles are often challenging due to the isomerization of this metal species to 2-(isocyano)phenolate.[20] Under our conditions, 2-benzoxazolyl lithium (lithiating benzoxazole using TMPLi at —40 °C), after mediated by tbepc, underwent the cross-coupling at ambient temperature to afford the product 5ma and 5mi in a 88% and 81% yield respectively. Since the methods for the direct metalation of a wide variety of N-heteroarenes have been well established,[3] taking full advantage of these achievements, this oxidative cross-coupling reaction can provide a general and very mild protocol for preparing various N-heteroaryl-aryl structures with various N-heteroarenes as starting materials.
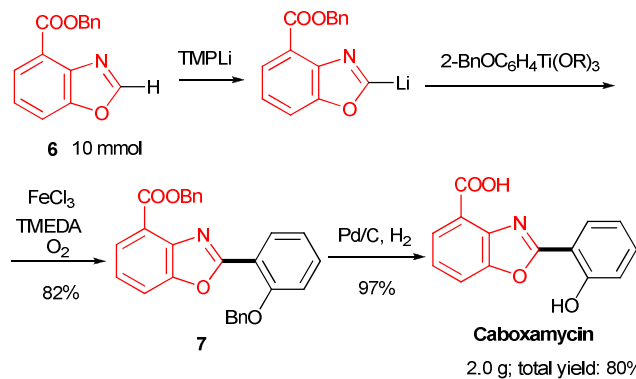
Since the present coupling allowed the flexible assembly of various aryl and N-heteroaryl metal reagents, we believe that it should find wide application in the rapid access to the biologically active compounds through the combination of two metal reagents of key structural units or by a late-stage functionalization of naturally occurring privileged structures. To demonstrate the feasibility of this
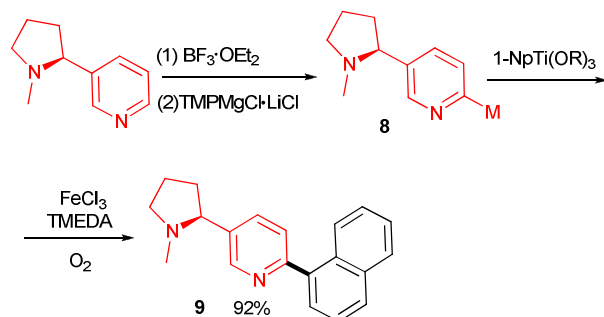
Table 2. Substrate Scope

$$ArMgX \xrightarrow{\text{tbepc}} \underset{3}{Ar^N M} \longrightarrow \boxed{Ar^N[ArTi(OR)_3]M} \xrightarrow[\text{O}_2 \text{ (1 atm), RT}]{\substack{(8 \text{ mol\%) FeCl}_3 \\ (20 \text{ mol\%) TMEDA}}} Ar-Ar^N$$

5ab (4-OMe) 96%[a,c,d,e]
5ac (4-COOEt) 87%[a]
5ad (2-CN) 81%[a]
5ae (4-Br) 76%[a]

5ba (3-Me) 78%[a]
5ca (6-OMe) 87%[a]
5da (5-Cl) 87%[a]
5ea (3-COOEt) 91%[b]

5fa (Ph) 82%[a]
5fe (4-BrC$_6$H$_4$) 61%[a]

5ga (Ph) 82%[b]
5gb (4-MeOC$_6$H$_4$) 76%[b]

5hb (4-MeOC$_6$H$_4$) 80%[b]
5hf (2-thiophenyl) 86%[b]

5ig (4-FC$_6$H$_4$) 89%[b]
5ih (2-MeO-1-naphthyl) 91%[b]

5ja (H) 92%[b]
5jg (4-F) 83%[b]

5ka (Ph) 92%[b]
5ki (1-Naphthyl) 92%[b]

5la (Ph) 94%[b]
5lj (3-CF$_3$C$_6$H$_4$) 92%[b]

5ma (Ph) 88%[b]
5mi (1-Naphthyl) 81%[b]

5nb (4-MeOC$_6$H$_4$) 78%[a]
5ng (4-FC$_6$H$_4$) 87%[a]

5oe (4-BrC$_6$H$_4$) 77%[b]
5oj (2-CF$_3$C$_6$H$_4$) 87%[b]

5pf (2-thiophenyl) 82%[b]
5pj (2-CF$_3$C$_6$H$_4$) 72%[b]

5qa (Ph) 87%[b]
5qd (2-NCC$_6$H$_4$) 84%[b]

5ra (Ph) 84%[b]
5rk (2-EtOOCC$_6$H$_4$) 80%[b]

[a] N-heteroaryl Grignard reagents were prepared via bromine or iodine-magnesium exchange using i-PrMgCl or i-PrMgCl·LiCl. [b] N-heteroaryl Grignard or lithium reagents were prepared through the metalation of heteroarenes using TMPMgCl or TMPLi (see Supporting Information for details). [c] Isolated yields. [d] 1 atm. [e] In most cases, no homodimers of Ar^{N}M were observed while 2~6% yields of homodimers of ArM was generated.

Scheme 3. Total Synthesis of Caboxamycin

Scheme 4. Direct Arylation of (S)-nicotine

approach, we investigated the total synthesis of caboxamycin (Scheme 4)[21] and the functionalization of (S)-nicotine (Scheme 5). The multi-gram scale total synthesis of caboxamycin involved an oxidative coupling of lithium reagent of **6** with a Grignard reagent as the key step, which furnished the intermidate (**7**) in 82% yield. The debenzylation of **7** through atmospheric pressure hydrogenation afforded caboxamycin in a 80% overall yield. Taking advantage of the regioslective metalation of (S)-nicotine,[22] the late-stage functionalization of (S)-nicotine also proceeded smoothly, giving the arylated nicotine (**9**) in a 92% yield (Scheme 5). Notably, the successful use of this mixed metal reagent of nicotine [Ar^{N}BF$_3$(MgCl)], (**8**)][22b,c] showed the generality in the types of metal reagents for this oxidative coupling. Overall, the above two examples fully demonstrate the flexibility and the potential of the present oxidative biaryl cross-coupling for further development and applications.

Conclusions

We have developed the first general iron-catalyzed oxidative aryl-aryl cross-coupling reaction of titanate-mediated N-heteroaryl and aryl Grignard or lithium reagents using oxygen as an oxidant. Under FeCl$_3$/TMEDA catalysis, an equivalent amount of a broad range of aryl and N-heteroaryl metal reagents, after simply sequentially combined with a titanate, can oxidatively couple well under mild reaction conditions in high yields. Since both iron and titanium are abundant, non-toxic metals (Titanium is the seventh most abundant metal on Earth, and the hydrolysis of a lot of titanium compounds will produce nontoxic and environmentally friendly TiO$_2$.[23]), and at the same time oxygen is the greenest oxidant, the present method proves to be eco-friendly and highly efficient for the flexible construction of various N-heteroaryl-aryl compounds. Furthermore, we also believe that the present way of using titanium centre to ligand and assemble two different anions as well as the synergetic effect between iron and titanium would provide guidance for the design of the other cross-coupling reactions between two nucleophiles. Preliminary mechanistic investigations showed that this oxidative coupling was not influenced by the addition of radical scavenger (TMPO), suggesting that a radical intermediate may not be involved. Further mechanistic studies and the development of the reactions with broader scope are being investigated in our laboratories.

Notes and references

College of Chemistry, Beijing Normal University, Beijing, 100875, China. E-mail: xinfangduan@vip.163.com

1   (a) F. Diederich and A. de Meijere, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, 2004; (b) J. F. Hartwig, *Organotransition Metal Chemistry*, University Science Books, Sausalito, California, 2010.

2   Selected reviews: (a) C. Liu, L. Jin and A. Lei, *Synlett*, 2010, 2527; (b) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780; (c) W. Shi, C. Liu and A. Lei, *Chem. Soc. Rev.*, 2011, **40**, 2761.

3   Selected reviews: (a) R. E. Mulvey, F. Mongin, M. Uchiyama and Y. Kondo, *Angew. Chem., Int. Ed.*, 2007, **46**, 3802; (b) B. Haag, M. Mosrin, H. Ila, V. Malakhov and P. Knochel, *Angew. Chem. Int. Ed.*, 2011, **50**, 9794; (c) F. Mongin and A. Harrison-Marchand, *Chem. Rev.*, 2013, **113**, 7563; (d) T. Klatt, J. T. Markiewicz, C. Sämann and P. Knochel, *J. Org. Chem.*, 2014, **79**, 4253.

4   Selected reviews: (a) A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176; (b) G. C. Fu, *Acc. Chem. Res.*, 2008, **41**, 1555; (c) R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461; (d) N. Marion and S. P. Nolan, *Acc. Chem. Res.*, 2008, **41**, 1440; (e) G. C. Fortman and S. P. Nolan, *Chem. Soc. Rev.*, 2011, **40**, 5151.

5   (a) G. Cahiez, A. Moyeux, J. Buendia and C. Duplais, *J. Am. Chem. Soc.*, 2007, **129**, 13788; (b) W. Liu and A. Lei, *Tetrahedron Lett.*, 2008, **49**, 610.

6   Selected examples of the oxidative homocouplings of organometallics: (a) T. Nagano and T. Hayashi, *Org. Lett.*, 2005, **7**, 491; (b) G. Cahiez, C. Chaboche, F. Mahuteau-Betzer and M. Ahr, *Org. Lett.*, 2005, **7**, 1943; (c) A. Krasovskiy, A. Tishkov, V. del Amo, H. Mayr and P. Knochel, *Angew. Chem. Int. Ed.*, 2006, **45**, 5010; (d) M. S. Maji, T. Pfeifer and A. Studer, *Angew. Chem. Int. Ed.*, 2008, **47**, 9547; (e) T. Truong, J. Alvarado, L. D. Tran and O. Daugulis, *Org. Lett.*, 2010, **12**, 1200.

7   (a) S. R. Dubbaka, M. Kienle, H. Mayr and P. Knochel, *Angew. Chem. Int. Ed.*, 2007, **46**, 9093. (b) G. Cahiez, C. Duplais and J. Buendia, *Angew. Chem. Int. Ed.*, 2009, **48**, 6731.

8   (a) Y. Zhao, H. Wang, X. Hou, Y. Hu, A. Lei, H. Zhang and L. Zhu, *J. Am. Chem. Soc.*, 2006, **128**, 15048; (b) M. Chen, X. Zheng, W. Li, J. He and A. Lei, *J. Am. Chem. Soc.*, 2010, **132**, 4101.

9   (a) G. Cahiez, L. Foulgoc, and A. Moyeux, *Angew. Chem. Int. Ed.*, 2009, **48**, 2969; (b) L. Jin, Y. Zhao, L. Zhu, H. Zhang and A. Lei, *Adv. Synth. Catal.,* 2009, **351**, 630.

10 (a) B. H. Lipshutz, K. Siegmann, E. Garcia and F. Kayser, *J. Am. Chem. Soc.*, 1993, **115**, 9276; (b) H. Mizuno, H. Sakurai, T. Amaya and T. Hirao, *Chem. Commun.*, 2006, 5042.

11 Selected reviews: (a) B. Weidmann and D. Seebach, *Angew. Chem., Int. Ed.*, 1983, **12**, 31; (b) R. O. Duthaler and A. Hafner, *Chem. Rev.*, 1992, **92**, 807; For the structures of ArTi(OPr^i)$_3$, see: (c) H. T. Yang, S. Zhou, F. S. Chang, C. R. Chen and H. M. Gau, *Organometallics*, 2009, **28**, 5715.

12 For selected papers on the reactions of titanium ate-complex ArTi(OR)$_4$M: (a) A. Bernardi, M. Cavicchioli, C. Marchionni, D. Potenza and C. Scolastico, *J. Org. Chem.*, 1994, **59**, 3690; (b) R. Mahrwald, *Tetrahedron*, 1995, **51**, 9015; (c) T. Hayashi, N. Tokunaga and K. Inoue, *Org. Lett.*, 2004, **6**, 305; (d) K. Mikami, T. Murase and Y. Itoh, *J. Am. Chem. Soc.*, 2007, **129**, 11686; (e) G. Manolikakes, N. Dastbaravardeh and P. Knochel, *Synlett*, 2007, 2077; (f) J. Zeng, K. M. Liu, X. F. Duan, *Org. Lett.*, 2013, **15**, 5342 and references cited therein.

13 (a) J. A. Joule and K. Mills, *Heterocyclic Chemistry*, John Wiley & Sons, New York, 2010; (b) S. Zhang, L. Y. Liao, F. Zhang and X. F. Duan, *J. Org. Chem.*, 2013, **78**, 2720 and the references cited therein.

14 For 2-pyridyl cyclic triolborate: (a) Y. Yamamoto, M. Takizawa, X. Q. Yu and N. Miyaura, *Angew. Chem. Int. Ed.*, 2008, **47**, 928; For 2-pyridyl MIDA boronates: (b) D. M. Knapp, E. P. Gillis and M. D. Burke, *J. Am. Chem. Soc.*, 2009, **131**, 6961; (c) G. R. Dick, E. M. Woerly and M. D. Burke, *Angew. Chem. Int. Ed.*, 2012, **51**, 2667; For a new type of solid 2-pyridyl zinc reagents: (d) J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald and P. Knochel, *Org. Lett.*, 2013, **15**, 5754; (e) A. Hernán-Gómez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinowski, S. M. Manolikakes, R. E. Mulvey and C. Schnegelsberg, *Angew. Chem. Int. Ed.*, 2014, **53**, 2706.

15 For a cobalt-titanium co-catalyzed cross-coupling reaction, see 12f; for a palladium-titanium co-catalyzed reaction, see: Y. X. Li, Q. Q. Xuan, L. Liu, D. Wang, Y. J. Chen, and C. J. Li, *J. Am. Chem. Soc.*, 2013, **135**, 12536.

16 Review: (a) J. Magano and J. R. Dunetz, *Chem. Rev.*, 2011, **111**, 2177; Selected recent examples: (b) D.-H. Lee, Y. Qian, J.-H. Park, J.-S. Lee, S.-E. Shim and M.-J. Jin, *Adv. Synth. Catal.*, 2013, **355**, 1729; (c) O. M. Kuzmina, A. Steib, J. T. Markiewicz,; D. Flubacher and P. Knochel, *Angew. Chem. Int. Ed.*, 2013, **52**, 4945.

17 J. A. McCleverty and T. J. Meyer, *Comprehensive Coordination Chemistry II, Vol. 1*, Elsevier, Oxford, 2004.

18 A. Ros, B. Estepa, P. Ramirez-Lopez, E. Alvarez, R. Fernandez and J. M. Lassaletta, *J. Am. Chem. Soc.*, 2013, **135**, 15730.

19 Selected examples for the arylation of various N-heteroaryl compounds: (a) H.-Q. Do and O. Daugulis, *J. Am. Chem. Soc.*, 2007, 129, 12404; (b) H.-Q. Do, R. M. K. Khan and O. Daugulis, *J. Am. Chem. Soc.*, 2008, **130**, 15185; (c) M. Mosrin and P. Knochel, *Chem.–Eur. J.,* 2009, **15**, 1468; (d) L. D. Tran and O. Daugulis, *Org. Lett.*, 2010, **12**, 4277; (e) K. Groll, S. M. Manolikakes, X. M. du Jourdin, M. Jaric, A. Bredihhin, K. Karaghiosoff, T. Carell and P. Knochel, *Angew. Chem. Int. Ed.*, 2013, **52**, 6776.

20 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 and references cited therein.

21 C. Hohmann, K. Schneider, C. Bruntner, E. Irran, G. Nicholson, A. T. Bull, A. L. Jones, R. Brown, J. E. M. Stach, M. Goodfellow, W. Beil, M. Krämer, J. F. Imhoff, R. D. Süssmuth and H.-P. Fiedler, *J. Antibiotics,* 2009, **62**, 99.

22 (a) F. F. Wagner and D. L. Comins, *Tetrahedron*, 2007, **63**, 8065; (b) M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2010, **49**, 5451; (c) M. Jaric, B. A. Haag, S. M. Manolikakes and P. Knochel, *Org. Lett.*, 2011, **13**, 2306.

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

Graphical abstract

Iron Catalyzed Oxidative Assembly of N-heteroaryl and Aryl Metal Reagents Using Oxygen as an Oxidant
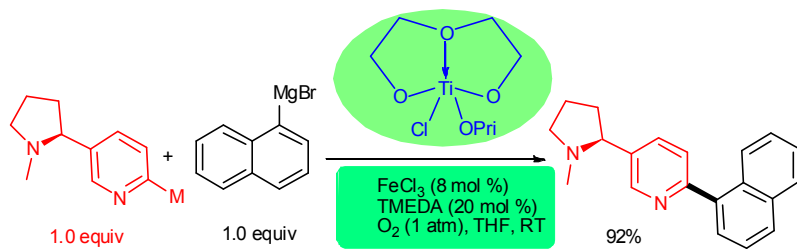
- nontoxic abundant TM
- RT and O_2 as oxidant
- broad substrate scope with high selectivity
- scalability (up to 10 mmol)

N-heteroaryl and aryl metal reagents, after mediated by a titanate, were cross-coupled under the catalysis of iron using oxygen.

ChemComm Accepted Manuscript