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ORIGINAL PAPER

A general palladium-catalyzed cross-coupling of aryl fluorides and organotitanium (IV) reagents

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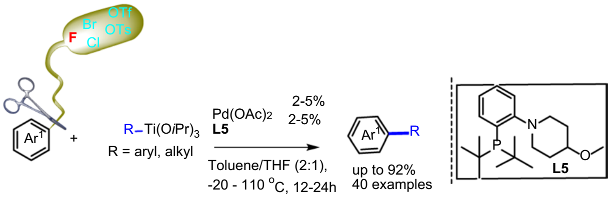
Abstract

$Pd(OAc)_2$/1-[2-(di-*tert*-butylphosphanyl)phenyl]-4-methoxy-piperidine was demonstrated to effectively catalyze cross-coupling of aryl fluoride and aryl(alkyl) titanium reagent. Both electron-deficient and electron-rich aryl fluoride can react effectively with nucleophile and provide extensive functional groups tolerance. 2-Arylated product was realized by selective activation of the C–F bond.

Graphic abstract



Keywords Transition metal catalyzed · Aryl sulfonates · C–C bond · Aryl titanium reagents

Introduction

Transition metal (TM) catalyzed cross-coupling reactions are widely used in pharmaceutical industry [1–3]. Aryl iodides, bromides, and chlorides have played a central role as electrophilic partners for carbon–carbon bond formations. Aryl sulfonates are promising candidates for coupling partners, since they can be obtained from inexpensive phenol derivatives and TsCl or MsCl. The recent dramatic advances in transition–metal catalysts have expanded the scope of electrophiles. With electron-rich transition–metal complexes that undergo smooth oxidative addition, the use of reactive aryl fluorides can be reduced [4–16]. Electrophiles, such as traditional halides (Cl, Br, and I) for TM-catalyzed cross-couplings have attracted much interest. In the early days, organotitanium was mainly used for their unique selectivity in the nucleophilic addition to carbonyl groups [17] as well as their use as carbotitanation of olefins, dienes, and alkynes [18]. In the past two decades, extensive efforts have been devoted to the development of organotitaniums in TM-catalyzed cross-coupling reactions. Several cross-coupling reactions with organotitaniums [19–27] have been reported, and most of them focused on reactions with organic bromides and chlorides. The first use of organotitaniums as the nucleophilic partners in TM-catalyzed cross-coupling reactions dated back to Hayashi's [19] (Fig. 1a) report in 2002. However, the substrates are limited to naphthyl triflates and those with electron-deficient aryl triflates, bromides, and chlorides. Nickel-catalyzed (as shown in Fig. 1b) [20] cross-coupling between aryl bromides and chlorides with aryl titanium reagents was reported by Paul Knochel, which extends the range of substrates that tolerated ketone carbonyl and ester group functional groups. Palladium-catalyzed (Fig. 1c) [21] reactions between aryl bromides and aryl titanium reagents ware reported for the preparation of biaryls. The carbon–carbon cross-couplings reaction of benzyl bromides

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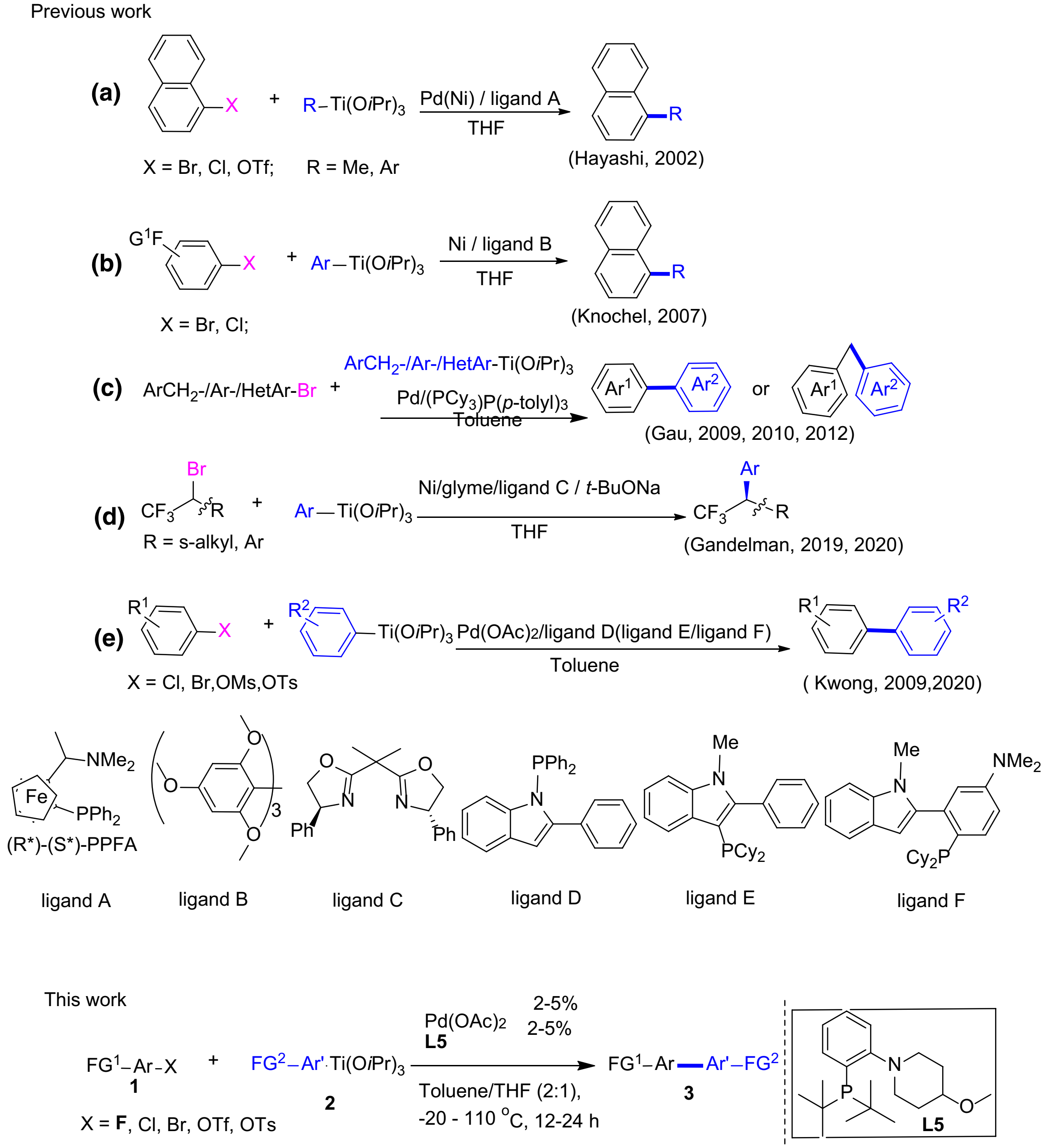


Fig. 1 Direct synthesis of organotitanium(IV) reagents

and chlorides and aryl titanium reagent were reported in 2010 [22]. The carbon–carbon coupling reaction of aryl halide and benzyl titanium reagent was realized in 2012 [23]. Although the substrate has been expanded from aromatic groups to benzyl groups, and titanium reagents have also expanded from aryl compounds to benzyl compounds, the functional group tolerance is still very poor and limit to cyano groups. Aryl titanium reagent was employed in non-asymmetric cross-coupling transformations (Fig. 1d) [24, 25] and achieved a better yield under low temperature. Recently, palladium-catalyzed cross-coupling between aryl tosylates, mesylates, and aryl titanium reagents was reported by Kwong (Fig. 1e) [27]. When compared with the previous reports [26], the reaction substrate has been expanded from aryl halides to aryl(alkenyl) tosylates, mesylates.

For the C–F bond cleavage cross-coupling, especially with organoboron (Suzuki) [11–13] and organozinc (Negishi) [14–16], reactions are limited to aryl fluorides with extremely electron-deficient nature or with ortho group assistance, and electron-rich aryl compounds are invariably less reactive. Therefore, efficient and versatile methods with broad substrate scope and high selectivity are needed. Here we report an efficient protocol for organotitanium-mediated cross-coupling reactions with a variety of organic fluorides providing a new methodology for carbon–carbon bond formation via C–F bond cleavage. In our exploration of C–F bond activation, we found that Pd(OAc)$_2$/**L5** is an effective catalyst. To the best of our knowledge, this is the first demonstration of cross-coupling of activated and deactivated aryl fluorides with organotitaniums and selective activation of C–F bonds in 2,5-dibromopyridine.

Results and discussion

At the outset of our research, the effects of twelve ligands on the catalytic activity were examined in the Pd(OAc)$_2$-catalyzed cross-coupling of *p*-CH$_3$OPhTi(O*i*Pr)$_3$ (**2a**) with *p*-fluorotoluene (**1a**) (Fig. 2), and the yields of the product after 1, 3, 6, and 12 h are summarized in Fig. 2. 1-[2-[Di-*tert*-butylphosphanyl)phenyl]-4-methoxypiperidine (**L5**) was highly active with yield over 80%. In comparison, **L2**, **L3**, **L6**, and **L7** were less active. **L1**, **L4**, and **L8** show poor coupling activity (Fig. 2) under the same condition. Simple monophosphane and bisphosphanes (**L9**–**L12**), such as

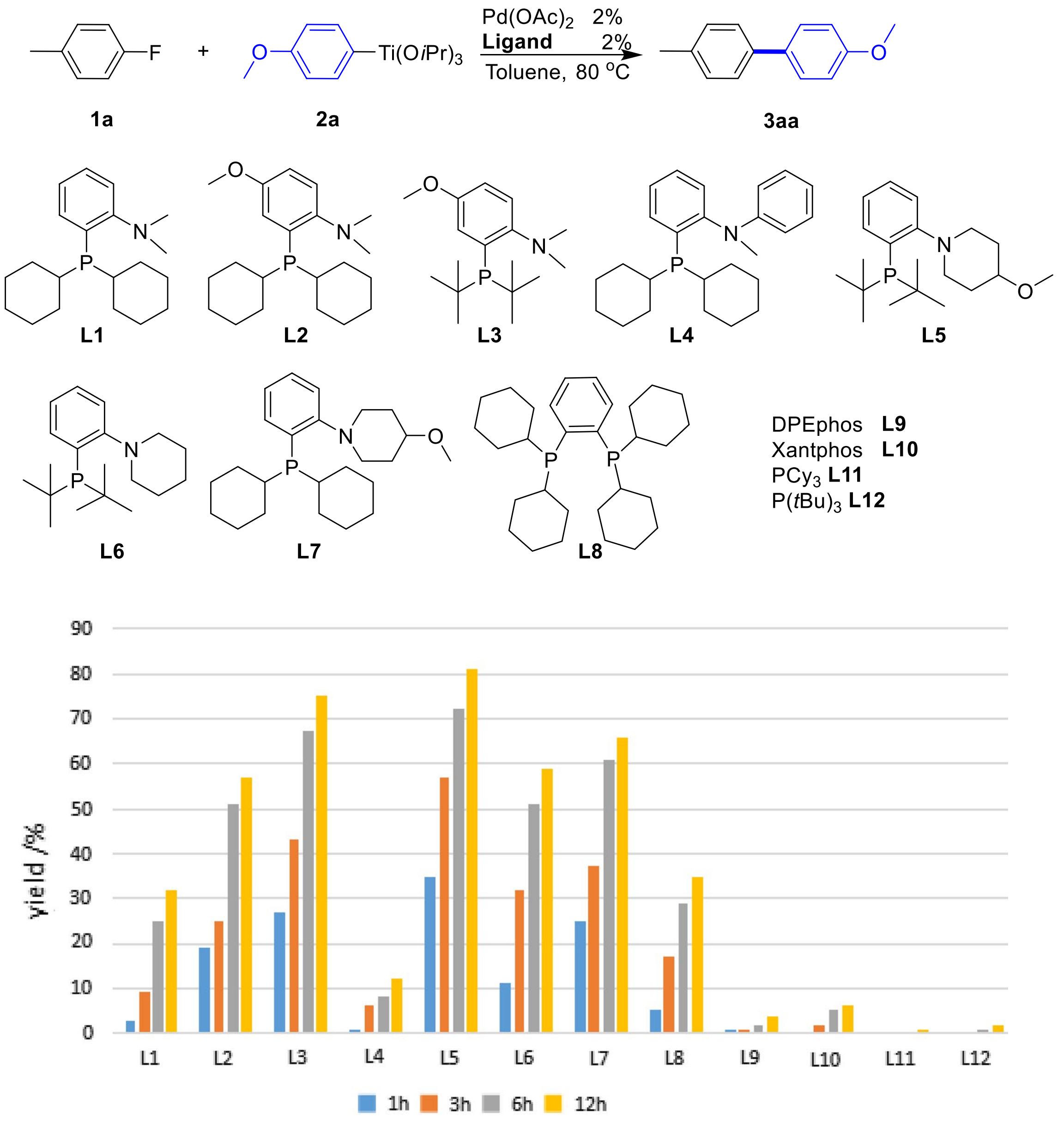
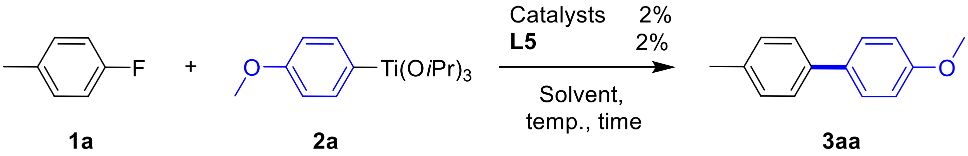


Fig. 2 Effect of ligands (yields after 1 h, 3 h, 6 h, and 12 h)

DPEphos, Xantphos, PCy_3, and $P(tBu)_3$, gave < 10% yield of the coupling product after 12 h.

We also studied the effect of catalyst source, the solvent, and other reaction conditions. The representative results are shown in Table 1. In the first round, toluene was chosen as the solvent to evaluate the catalysts (Table 1, entries 1–7). It is shown that nickel catalyst sources, such as $NiCl_2$, $Ni(OAc)_2$, $Ni(acac)_2$, and $NiCl_2$ • glyme gave the desired product **3aa** in low yield (Table 1, entries 1–4). $Pd(acac)_2$ and $Pd(dba)_2$ gave better results compared with those mentioned above (Table 1, entries 6 and 7). $Pd(OAc)_2$ was the best catalyst to give the corresponding coupling product in 81% yield (Table 1, entry 5). In the second round, using $Pd(OAc)_2$ as the catalyst, a variety of solvents was tested and it was found that the solvents used significantly affected the reaction. For example, almost no product was obtained when the reactions were performed in ether and CH_2Cl_2 (Table 1, entries 10, 12). We also tested other solvents (dioxane and glyme) for the reaction, which shown moderate yields (Table 1, entries 9, 11). The solvent THF gave good yields (Table 1, entry 8), while toluene resulted poor yields (Table 1, entry 5). Finally, we tested mixed solvent for this reaction, 2:1 mixture of toluene and THF is a suitable solvent for cross-coupling. Further improvement of the yield was carried out by changing the reaction temperature from 80 to 110 °C (Table 1, entry 16). It was noted that

Table 1 Screening of the reaction conditions[a]



Entry	Catalysts	Solvent	Temp./°C	Time/h	Conv.	Yield/%[b]
1	$NiCl_2$	Toluene	80	12	5	0
2	$Ni(OAc)_2$	Toluene	80	12	20	13
3	$Ni(acac)_2$	Toluene	80	12	15	9
4	$NiCl_2$ • glyme	Toluene	80	12	45	41
5	$Pd(OAc)_2$	Toluene	80	12	100	81
6	$Pd(acac)_2$	Toluene	80	12	80	68
7	$Pd(dba)_2$	Toluene	80	12	35	28
8	$Pd(OAc)_2$	THF	80	12	100	78
9	$Pd(OAc)_2$	Dioxane	80	12	70	45
10	$Pd(OAc)_2$	Ether	80	12	30	7
11	$Pd(OAc)_2$	Glyme	80	12	65	53
12	$Pd(OAc)_2$	CH_2Cl_2	80	12	< 5	2
13	$Pd(OAc)_2$	Toluene:THF (1:1)	80	12	100	80
14	$Pd(OAc)_2$	Toluene:THF (1:2)	80	12	100	71
15	$Pd(OAc)_2$	Toluene:THF (2:1)	80	12	100	85
16	$Pd(OAc)_2$	Toluene:THF (2:1)	110	12	100	89 (85)[c]
17	$Pd(OAc)_2$	Toluene:THF (2:1)	50	12	35	27
18[d]	$Pd(OAc)_2$	Toluene:THF (2:1)	50	12	100	83
19[d]	$Pd(OAc)_2$	Toluene:THF (2:1)	25	12	100	79
20[d]	$Pd(OAc)_2$	Toluene:THF (2:1)	0	12	89	72
21[d]	$Pd(OAc)_2$	Toluene:THF (2:1)	− 10	12	76	51
22[de]	$Pd(OAc)_2$	Toluene:THF (2:1)	− 10	12	100	75
23	$Pd(OAc)_2$	Toluene:THF (2:1)	110	24	100	90

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (2 mol%), **L5** (2 mol%), solvent (1.0 cm^3), under Ar

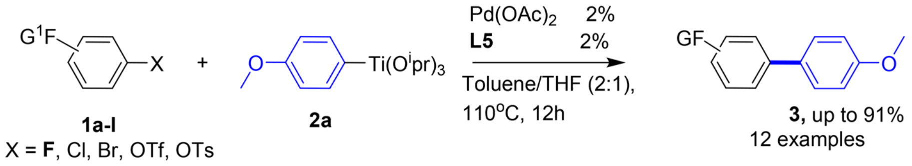
[b] GC yield using tridecane as an internal standard

[c] Isolated yields are given in parentheses

[d] LiCl 2.5 equiv

[e] $Pd(OAc)_2$ (5 mol%), **L5** (5 mol%)

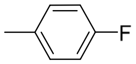
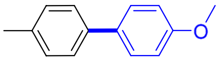
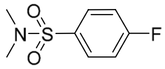
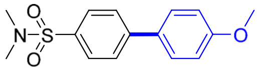
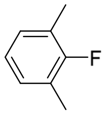
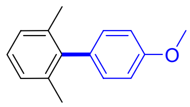
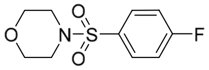
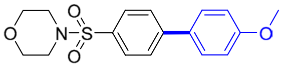
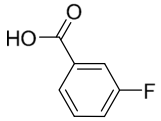
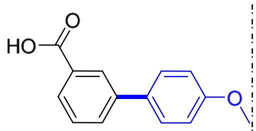
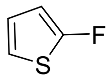
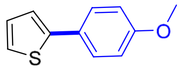
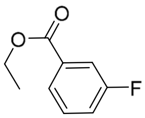
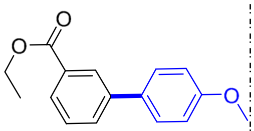
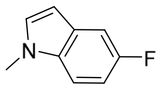
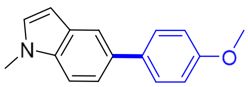
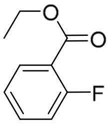
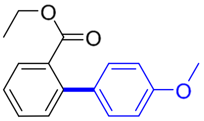
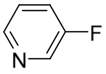
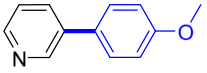
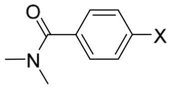
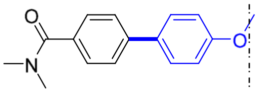
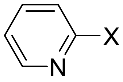
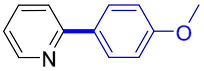
Table 2 Palladium-catalyzed cross-coupling of aryl or heteroaryl fluorides with *p*-$CH_3OPhTi(OiPr)_3$[a,b]



1a-l
X = **F**, Cl, Br, OTf, OTs

2a

3, up to 91%
12 examples

Entry	Ar(Het)-X	Product	Entry	Ar(Het)-X	Product
1	 **1a**	 **3aa**, 85%	7	 **1g**	 **3ga**, 82%
2	 **1b**	 **3ba**, 54% (72%)[e]	8	 **1h**	 **3ha**, 89%
3	 **1c**	 **3ca**, 83%[c]	9	 **1i**	 **3ia**,78%
4	 **1d**	 **3da**, 85%	10	 **1j**	 **3ja**, 91%
5	 **1e**	 **3ea**, 78%	11	 **1k**	 **3ka**, 86%
6	 **1f**	 **3fa**, 78% (X = F) 89% (X = Cl) 91% (X = Br)	12	 **1l**	 **3la**, 75% (X = F) 86% (X = OTf)[d] 81% (X = OTs)[d]

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Pd(OAc)_2$ (2 mol%), **L5** (2 mol%), toluene: THF = (2:1) (1.0 cm^3) were stirred at 110 °C for 12 h under Ar atmosphere

[b] Isolated yields

[c] 0.4 mmol of **2a**

[d] **L3** (2 mol%)

[e] $Pd(OAc)_2$ (5 mol%), **L5** (5 mol%)

decreasing the temperature led to yield decrease (Table 1, entry 17). However, the presence of lithium ion was important (Table 1, entries 18–22). 2.5 equiv. of LiCl additive improved the reaction result (Table 1, entry 18) significantly. A similar phenomenon was observed by other groups [28, 29], the role of LiCl additive might enhance the elimination ability of fluorine as Lewis acid and strong Li–F bond formation [16, 28–30]. The product yield cannot be further improved by extending the reaction time (Table 1, entry 23).

With the optimal reaction conditions, we set out to examine the scope of aryl fluorides using *p*-MeOPhTi(O*i*Pr)$_3$ as the nucleophilic reagent. Most reactions proceeded well to give the desired products **3** with moderate/high yields under identical conditions. Ortho-position substituted aryl fluorides have major effect on the reaction. For example, the reaction involving 2,6-dimethylphenyl fluoride (**1b**) gave the corresponding product **3ba** with 54% yield due to the steric hindrance (Table 2, entry 2). Increasing the amount of catalyst to 5%, the yield reached to 75%. On the other hand, sterically hindered substituents on the single substitution aryl fluorides have minor effect on the reactions (Table 2, entry 5). Functional groups, including COOH, COOEt, CONMe$_2$, and SO$_2$NMe$_2$, SO$_2$NO(CH$_2$)$_2$ can be tolerated. Reaction involving heteroaryl fluorides also gave moderate/high product yield (Table 2, entries 9–12). Under the same conditions, it can be seen that both aryl chloride and bromide gave higher yields (Table 2, entry 6). Aryl tosylates, mesylates also achieved good coupling yield (Table 2, entry 12).

Various titanium reagents were also tested for the couplings. Functionalized heteroaryl titanium reagents reacting with simple aryl fluorides or functionalized aryl fluorides resulted no product under the optimized conditions. Lowering the reaction temperature or increasing the amount of catalyst did not improve product results. In comparison, both aryl chloride and bromide can get higher yields under the same conditions (Table 3, entries **3mb**, **3mc**, **3md**, **3ul**, **3vm**). The reaction of the *o*-benzonitrile titanium reagent with *p*-fluorotoluene gives a more satisfactory yield (Table 3, entry **3al**). The *o*-benzonitrile titanium reagent is a stable compound at room temperature. The heterocyclic thienyl titanium reagent and *p*-methoxyphenyl fluoride, chloride, and bromide have all achieved good results. *p*-Methoxyphenyl tosylates and mesylates also achieved excellent results under the action of **L3** ligand (Table 3, entry **3me**). The easily enolizable ketone could be well tolerated and no notable by-products resulting from the addition of (hetero) aryl titanium reagents to this group (Table 3, entries **3ne**, **3nf**, and **3 ng**). Fluorinated benzoic acid and (hetero)aryl titanium reagents have achieved moderate results (Table 3, entries **3cf**, **3oh**, **3oi**, **3oj**, **3ck**, and **3pk**). The sterically hindered aryl titanium reagent at the ortho position has also achieved good results (81% and 73%) (Table 3, entries **3ck** and **3pk**), it can be explained that the sterically hindered substituents on the aryl titanium reagents have less effect on the reactions (Table 3, entries **3sk**, **3gk**, and **3tk**). On the other hand, ortho-position substituted hindered substituents on the aryl fluorides have ruling effect on the reactions (Table 3, entries **3qj** and **3rj**). Heteroaryl titanium reagents were well compatible with this biaryl coupling reaction and provided the heteroaryl-containing biaryls in good yields (Table 3, entries **3qe**, **3we**, **3xe**, **3oj**, **3qj**, and **3rj**). To our surprise, the alkyl titanium reagent have also achieved 61%, 53%, 39%, and 65% aryl–alkyl cross-coupling products, respectively (Table 3, entries **3wn**, **3 mn**, **3mo**, and **3vp**).

Finally, we have compared the reactivity of (hetero)aryl titanium compounds with the corresponding arylzinc halides (Negishi cross-coupling). The reaction of 2,5-difluoropyridine (**1y**) with arylTi(OEt)$_3$ (**2**) afforded the 2-position arylated products **3ya** (88%) and **3yq** (85%), respectively (Scheme 1a). The same reaction with the arylzinc halide **2** gave only **3ya** (23%) and **3yq** (19%), respectively, after 24 h. 5-Position arylated product or biarylated product were not found in the reaction system. Based on these findings, we then investigated the C–F bond activation in the presence of C–Cl bonds. The reaction of (4-chlorophenyl)(2-fluorophenyl)methanone with *p*-MeOPhTi(O*i*Pr)$_3$ selectively cleave a highly strong bond (C–F) over a relatively weak bond (C–Cl) afforded an ortho-arylated product (4-chlorophenyl)(4′-methoxy-[1,1′-biphenyl]-2-yl)methanone in 91% yield (Scheme 1b).

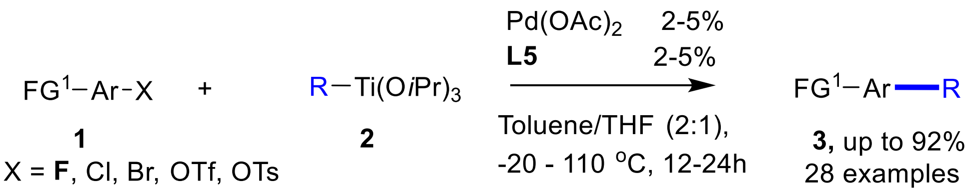
Conclusion

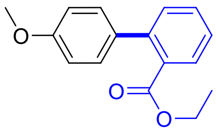
In conclusion, we have developed the first active and general system for the cross-coupling of aryl fluorides based on the Pd(OAc)$_2$/**L5**. Both activated and deactivated aryl fluorides can be efficiently coupled. Electron-rich and electron-deficient aryl(alkyl) titanium reagents were proven to be suitable nucleophiles. Notably, heteroaryl ring and various sensitive functional groups, including easily enolizable ketone, carboxylic acid, ester, nitrile, amide, sulfamide groups can be well tolerated. We also confirmed that the 2-position selective activation of C–F bonds in 2,5-difluoropyridine, with 2-arylated products being obtained.

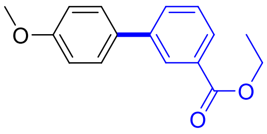
Experimental

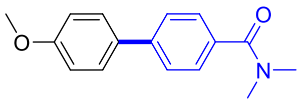
Lithium chloride anhydrous, Ni(acac)$_2$, NiCl$_2$, Ni(OAc)$_2$, NiCl$_2$·glyme, Pd(OAc)$_2$, Pd(acac)$_2$, and Pd(dba)$_2$ were purchased from Sigma-Aldrich. THF, dioxane were purchased from Alfa Aesar. Other reagents are available commercially and were used without further purification, unless otherwise indicated. All reactions were carried out under an argon

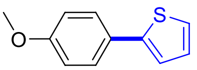
Table 3 Palladium-catalyzed cross-coupling of aryl or heteroaryl halides with various ArTi(O*i*Pr)$_3$^{a,b}

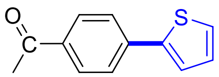


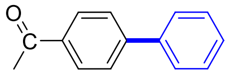

3mb^{e}, 11%
65% (X = Cl)
81% (X = Br)

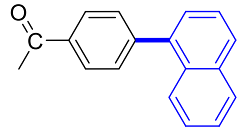

3mc^{e} , 25%
69% (X = Cl)
84% (X = Br)

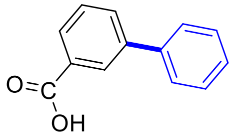

3md^{d} , 26%
71% (X = Cl)
87% (X = Br)

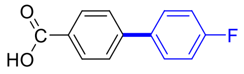

3me, 83%
89% (X = Cl)
92% (X = Br)
91% (X = OTf)^{f}
86% (X = OTs)^{f}

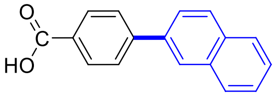

3ne^{e}, 29%
66% (X = Cl)
83% (X = Br)

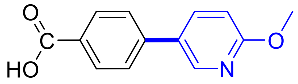

3nf^{e}, 32%
72% (X = Cl)
87% (X = Br)

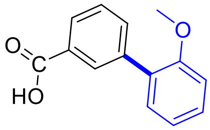

3ng^{e}, 34%
69% (X = Cl)
88% (X = Br)

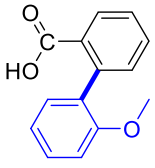

3cf, 92%^{c}

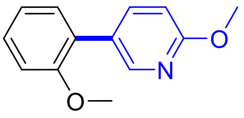

3oh, 89%^{c}

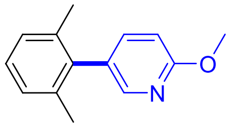

3oi, 88%^{c}

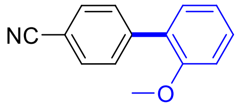

3oj, 85%^{c}

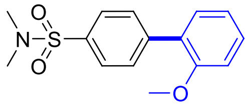

3ck, 81%^{c}

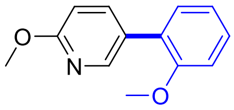

3pk, 73%^{c}

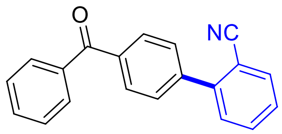

3qj, 86%

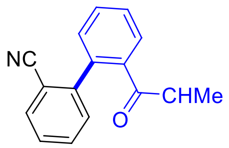

3rj, 57% (79%)

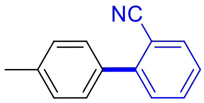

3sk, 82%

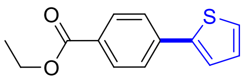

3gk, 88%

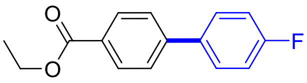

3tk, 89%

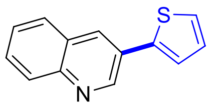

3ul^{d}, 23%
85% (X = Cl)
89% (X = Br)

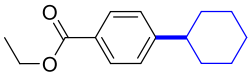

3vm^{d}, 15%
79% (X = Cl)
80% (X = Br)

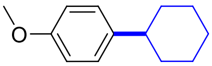

3al, 85%

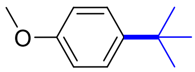

3we, 81%


3wh, 76%


3xe, 83%


3wn^{g}, 61%


3mn^{g}, 53%


3mo^{g}, 39%

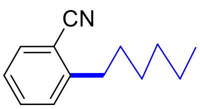

3vp^{g}, 65%

Table 3 (continued)

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), Pd(OAc)$_2$ (2 mol%, with respect to ArF), **L5** (2 mol%), toluene:THF = (2:1) (1.0 cm^3) were stirred at 110 °C for 12 h under Ar atmosphere

[b] Isolated yields

[c] 0.4 mmol of **2**

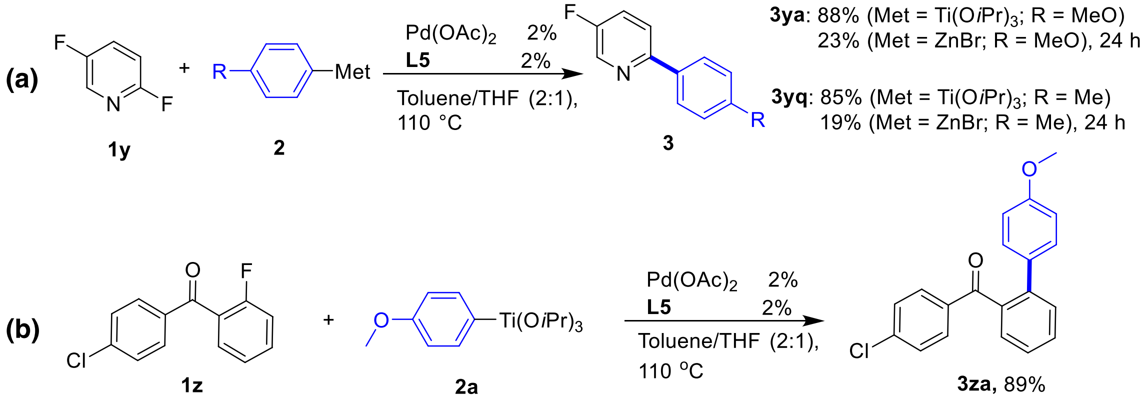
[d] Pd(OAc)$_2$ (5 mol%), **L5** (5 mol%),reaction performed at – 10 °C for 24 h

[e] Pd(OAc)$_2$ (5 mol%), **L5** (5 mol%), reaction performed at – 20 °C for 24 h

[f] **L3** (2 mol%)

[g] Pd(dba)$_2$ (2 mol%), **L5** (2 mol%)

Scheme 1



atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. THF was dried over alumina under N$_2$ using a Grubbs-type solvent purification system. All aryl titanium reagents were prepared from the corresponding arylmagnesium halides. **1f**, **1i**, **1j**, **1v** were prepared according to the literature procedures [31–34], and other aryl fluorides were purchased from Alfa Aesar. **L1**, **L2**, **L3**, **L4**, **L8** were prepared according to literature procedures [35–38], DPEphos, Xantphos, PCy$_3$ and P(^{t}Bu)$_3$ were purchased from Sigma-Aldrich, and **L5** (1-[2-(di-*tert*-butylphosphanyl)-phenyl]-4-methoxypiperidine), **L6**, **L7** were the new ligand reported by our research group [39]. Spectroscopy data of the known compounds matches with the data reported in the corresponding references. Reactions were monitored by Agilent GC Series 6890 N and GCMS 7890A. All new compounds were further characterized by HRMS (EI), and ^{1}H and ^{13}C NMR spectra were measured on a Bruker 400 M spectrometer. ^{1}H NMR and ^{13}C NMR were recorded using tetramethylsilane (TMS) in the solvent of deuterated chloroform (CDCl$_3$) and deuterium oxide as the internal standard. Chemical shifts were reported in parts per million. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; and m, multiplet. The coupling constant J is reported in hertz (Hz). The products were purified by column chromatography on silica gel 300–400 mesh under an argon atmosphere.

General procedure A: the formation of organo-titanium reagents

The corresponding glassware was oven-dried (100 °C) and cooled under a stream of argon gas. Aryl grignard reagents, such as phenylmagnesium or 4-methylphenyl magnesium were prepared according to the standard procedure. 2-Methoxypyridinyl grignard reagents were prepared via bromine–magnesium exchange using *i*-PrMgCl, other structure containing active hydrogen protons, such as *o*-amidophenyl reagents neutralized by 2 equiv *i*-PrMgCl firstly, while functionalized aryl Grignard reagents, such as 2-carboethoxyphenyl magnesium chloride were prepared via iodine–magnesium exchange using *i*-PrMgCl·LiCl according to Knochel's method [40]. All of the Grignard reagents were titrated before use [41].

The above Grignard reagents (20 mmol) were cooled to 0 °C (functionalized Grignard reagents were cooled to – 20 °C). In another two-necked 500 cm^3 round-bottomed flask under a nitrogen atmosphere, to a solution of 4.08 cm^3 Ti(O*i*Pr)$_4$ (15.0 mmol) in 50 cm^3 of THF at 0 °C was added 0.56 cm^3 TiCl$_4$ (5.0 mmol). The resulting solution was warmed to room temperature and stirred for 30 min, giving a ClTi(O*i*Pr)$_3$ solution (100 mmol). The ClTi(O*i*Pr)$_3$ solution was cooled to 0 °C or – 20 °C, and to this solution was transferred the cold Grignard solution via a cannula. The reaction mixture was warmed to room temperature and was allowed to react for 3 h (functionalized Grignard reagents direct reaction for 8 h without heating). The volatile material was removed completely under reduced pressure, and under a nitrogen atmosphere, the residue was extracted with n-hexane (3 × 40 cm^3). The combined hexane solution was concentrated and was cooled to − 20 °C, furnishing a solid product of the aryltris(2-propoxo)titanium species.

General procedure B: Palladium-catalyzed biaryl cross-coupling reaction of (hetero)aryl fluorides with (hetero)aryl titanium reagents

In a glovebox, solid aryl fluorides (0.20 mmol), Pd(OAc)$_2$ (2 mol%), and **L5** (2 mol%) were charged to a dried two-necked round-bottom reaction flask quipped with an addition funnel, and ArTi(O*i*Pr)$_3$ (0.30 mmol) in 1 cm^3 mixed solvents of toluene: THF (2:1) was added. The mixture was stirred at room temperature for 15 min and warmed to 110 °C and was allowed to react for 12 h and quenched with 10 cm^3 of water. The solution was extracted with dichloromethane (3 × 30 cm^3). The combined organic phase was dried over MgSO$_4$ and concentrated to dryness under reduced pressure. The residue was purified by column chromatography to give the coupling product.

General procedure C: Palladium-catalyzed biaryl cross-coupling reaction of fluorinated benzoic acid with (hetero)aryl titanium reagents

In a glovebox, fluorinated benzoic acid (0.20 mmol), Pd(OAc)$_2$ (2 mol%), and **L5** (2 mol%) were charged to a dried two-necked round-bottom reaction flask quipped with an addition funnel, and ArTi(O*i*Pr)$_3$ (0.40 mmol) in 1 cm^3 mixed solvents of toluene:THF (2:1) was added. The mixture was stirred at room temperature for 15 min and warmed to 110 °C and was allowed to react for 12 h and quenched with 10 cm^3 of water. The solution was extracted with dichloromethane (3 × 30 cm^3). The combined organic phase was dried over MgSO$_4$ and concentrated to dryness under reduced pressure. The residue was purified by column chromatography to give the coupling product.

General procedure D: Palladium-catalyzed biaryl cross-coupling reaction of (hetero)aryl fluorides with functionalized heteroaryl titanium reagents

In a glovebox, (hetero)aryl fluorides (0.20 mmol), Pd(OAc)$_2$ (5 mol%), LiCl (0.20 mmol), and **L5** (5 mol%) were charged to a dried two-necked round-bottom reaction flask quipped with an addition funnel, and ArTi(O*i*Pr)$_3$ (0.40 mmol) in 1 cm^3 mixed solvents of toluene:THF (2:1) was added. The mixture was stirred at − 10 °C for 24 h and quenched with 10 cm^3 of water. The solution was extracted with dichloromethane (3 × 30 cm^3). The combined organic phase was dried over MgSO$_4$ and concentrated to dryness under reduced pressure. The residue was purified by column chromatography to give the coupling product.

General procedure E: Palladium-catalyzed biaryl cross-coupling reaction of functionalized aryl fluorides with (hetero)aryl titanium reagents

In a glovebox, functionalized aryl fluorides (0.20 mmol), Pd(OAc)$_2$ (5 mol%), LiCl (0.20 mmol), and **L5** (5 mol%) were charged to a dried two-necked round-bottom reaction flask quipped with an addition funnel, and ArTi(O*i*Pr)$_3$ (0.30 mmol) in 1 cm^3 mixed solvents of toluene:THF (2:1) was added. The mixture was stirred at − 20 °C for 24 h and quenched with 10 cm^3 of water. The solution was extracted with dichloromethane (3 × 30 cm^3). The combined organic phase was dried over MgSO$_4$ and concentrated to dryness under reduced pressure. The residue was purified by column chromatography to give the coupling product.

5-(2,6-Dimethylphenyl)-2-methoxypyridine (3rj, $C_{14}H_{15}NO$) was obtained following the general procedure B. Purification via silica gel column chromatography (petroleum ether/ethyl acetate = 10/1, v/v) afforded the desired product. Yellow solid; m.p.: 44–47 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.99$ (dd, $J = 2.4$ Hz, $J = 0.8$ Hz, 1H), 7.39 (dd, $J = 8.4$ Hz, $J = 2.4$ Hz, 1H), 7.21–7.12 (m, 3H), 6.84 (dd, $J = 8.4$ Hz, $J = 0.7$ Hz, 1H), 4.01 (s, 3H), 2.07 (s, 6H) ppm; ^{13}C NMR (CDCl$_3$, 100 MHz): $\delta = 163.1$, 146.6, 139.7, 137.9, 136.9, 129.4, 127.5, 110.7, 53.4, 21.0 ppm; HRMS (ESI): *m/z* calc. for $C_{14}H_{16}NO$ ([M + H]$^+$) 214.1154, found 214.1229.

2′-Methoxy-*N*,*N*-dimethyl-[1,1′-biphenyl]-4-sulfonamide (3gk, $C_{15}H_{17}NO_3S$) was obtained following the general procedure B. Purification via silica gel column chromatography (petroleum ether/ethyl acetate = 10/1, v/v) afforded the desired product. Yellow solid; m.p.: 183–185 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.80$ (d, $J = 8.2$ Hz, 2H), 7.70 (d, $J = 8.2$ Hz, 2H), 7.40–7.32 (m, 2H), 7.08–7.01 (m, 2H), 3.84 (s, 3H), 2.77 (s, 6H) ppm; ^{13}C NMR (CDCl$_3$, 100 MHz): $\delta = 156.4$, 143.2, 133.7, 130.8, 130.1, 129.7, 128.7, 127.4, 121.0, 111.4, 55.5, 38.0 ppm; HRMS (ESI): *m/z* calc. for $C_{15}H_{18}NO_3S$ ([M + H]$^+$) 292.0929, found 292.1004.

4′-Benzoyl-[1,1′-biphenyl]-2-carbonitrile (3ul, $C_{20}H_{13}NO$) was obtained following the general procedure E. Purification via silica gel column chromatography (petroleum ether/ethyl acetate = 10/1, v/v) afforded the desired product. Yellow solid; m.p.: 104–106 °C; ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.93$ (dt, $J = 8.2$ Hz, $J = 1.7$ Hz, 2H), 7.87–7.85 (m, 2H), 7.82–7.81 (m, 1H), 7.70–7.67 (m, 3H), 7.62–7.56 (m, 2H), 7.54–7.49 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 196.2$, 144.4, 142.1, 137.7, 137.4, 134.0, 133.1, 132.8, 130.6, 130.2, 128.9, 128.5, 128.4, 118.5, 111.4 ppm; HRMS (ESI): *m/z* calc. for $C_{20}H_{14}NO$ ($[M+H]^+$) 284.0997, found 284.1075.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00706-021-02796-6.

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