Palladium-Catalyzed Direct Arylation of Furans via C−H Functionalization at Low Catalyst Loadings

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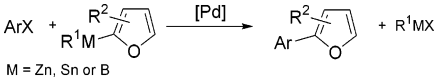
Summary: A system combining the tetraphosphine cis,cis,cis-1,2,3,4-tetrakis((diphenylphosphino)methyl)cyclopentane (Tedicyp) and [Pd(C$_3$H$_5$)Cl]$_2$ was found to promote the direct arylation of furans via C−H functionalization in good yields using very low catalyst loadings.

The coupling reaction of furan derivatives with aryl halides provides an efficient method for the preparation of arylfurans. The classical method to perform this reaction is to employ an aryl halide with an organometallic derivative of furan (metal = ZnX,[1] SnR$_3$[2] B(OR)$_2$[3]) using a palladium catalyst (Scheme 1). However, these reactions require preparation of the furan organometallic derivative and provide either an organometallic or a salt (MX) as a byproduct.

In the last few years, very interesting results for the coupling of aryl halides with aryl derivatives via C−H activation have been reported: for example, Fagnou has used simple palladium salts or Pd associated with monodentate ligands.[4] The direct coupling of furans with aryl halides via C−H activation/functionalization of furans at low catalyst loadings would provide an economically and environmentally attractive procedure for the preparation of such compounds. A few results have already been reported for this coupling. To our knowledge, the first coupling of furans with aryl halides via C−H activation was described by Ohta et al. using tetrakis(triphenylphosphine)-palladium (5 mol %) and potassium acetate as base.[5a] However, in general low to moderate yields of arylated products (0−60%) were obtained using this catalyst. This procedure was applied in a few syntheses of furan derivatives to give the arylated or biarylated furans in 13−73% yields.[5b,d,e] The sterically hindered and electron-rich phosphine P(Cy)$_3$ (10 mol %) associated to PdCl$_2$ (5 mol %) also catalyzes the coupling of 2-furaldehyde with a variety of aryl iodides in good yields.[5c] Finally, the coupling of 2-furaldehyde with bromobenzene using 10 mol % of Pd(OH)$_2$/C as catalyst gave the coupling product in 75% yield.[5f]

Scheme 1



Although monophosphine ligands have been successfully used for the coupling of furan derivatives with aryl halides via C−H activation, to the best of our knowledge, the efficiency of polydentate ligands for such couplings has not been demonstrated. Moreover, all of the reactions employing monophosphines as ligands were performed using high catalyst loadings (5−10 mol %). Therefore, an effective and selective method allowing high substrate/catalyst ratios for the coupling of these challenging substrates is still subject to significant improvement.

The nature of phosphine ligands on complexes has an important influence on the rate of catalyzed reactions. In order to find more efficient palladium catalysts, we have prepared the tetrapodal phosphine ligand *cis,cis,cis*-1,2,3,4-tetrakis-((diphenylphosphino)methyl)cyclopentane (Tedicyp; Scheme 2),[6] in which the four diphenylphosphino groups are stereospecifically bound to the same face of the cyclopentane ring. A very high efficiency has been observed for Suzuki, Heck, Sonogashira, or Negishi cross-coupling reactions using Tedicyp

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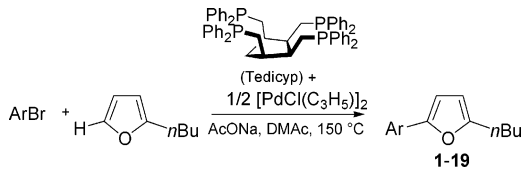
Scheme 2



1-19

as the ligand.[7,8] The presence of four phosphines close to the metal center seems to increase the stability of the catalyst. The palladium is shown by NMR to circulate around the four phosphorus atoms under the "pressure to coordinate" of the four phosphino groups maintained in a half-space. This "pressure to coordinate" in a half-space might be responsible for the easy reductive elimination step for several cross-coupling reactions. In this paper, we wish to report on the efficiency of this ligand for the chalenging coupling reaction of aryl halides with furan derivatives via C−H activation/functionalization.

Our first objective was to determine the most suitable reaction conditions using our tetraphosphine ligand. We observed that the coupling of 4-bromoacetophenone with 2-*n*-butylfuran in the presence of AcONa and the catalytic system [PdCl(η^3-C_3H_5)]$_2$/Tedicyp (0.1 mol %) in DMAc at 150 °C gave a high yield of arylated product (Table 1, Scheme 2). Moreover, this reaction is very selective in favor of the 5-arylation of 2-*n*-butylfuran. The 3- or 4-arylated furans were not observed by GC or NMR analysis of the crude mixtures. Using other bases ($NaHCO_3$, Na_2CO_3, K_2CO_3, KOH, and NaOH) and solvents such as NMP, DMF, and xylene led to lower conversions.

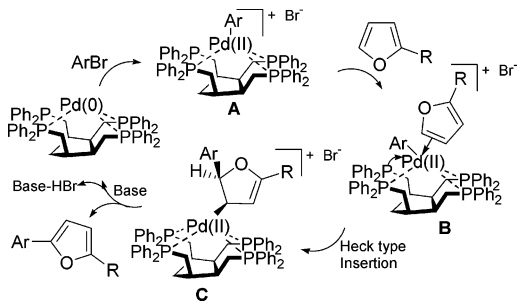
Then, we tried to evaluate the scope and limitations of the Tedicyp−palladium complex for this reaction. A survey of coupling of aryl halides with 2-*n*-butylfuran is provided in Table 1. A variety of functional groups on aryl bromide are tolerated. Quite similar turnover numbers (TONs) were obtained using electron-poor aryl bromides such as 4-bromobenzaldehyde, 4-bromobenzonitrile, and 4-bromonitrobenzene (590, 280, and 940) and the electron-rich 4-bromoanisole and 4-bromotoluene (480 and 660) (Table 1, entries 1−17). As expected, very similar results were obtained using the meta-substituted aryl bromides 3-bromoacetophenone and 3-bromobenzaldehyde (Table 1, entries 18 and 19). The coupling of 2-*n*-butylfuran with ortho-substituted aryl bromides also proceeds nicely. 2-Bromobenzotrifluoride or 1-bromonaphthalene gave the arylated furan with TONs of 360 and 330, respectively (Table 1, entries 20−23). With this catalyst, even the di-ortho-substituted 9-bromoanthracene or 2,4,6-triisopropylbromobenzene led to the expected coupling products, however, in lower TONs (Table 1, entries 24−27). Then, we examined the reactivity of three heteroaryl bromides with 2-*n*-butylfuran. 4-Bromoisoquinoline was found to be less reactive than 3-bromopyridine or 3-bromoquinoline, and TONs of 70, 720, and 550 were obtained, respectively (Table 1, entries 28−32). This lower reactivity of 4-bromoisoquinoline is probably due to steric factors.

Table 1. Palladium-Catalyzed Reactions[a] of Aryl Bromides with 2-*n*-Butylfuran (Scheme 1)[9]

entry	aryl bromide	subst/cat. ratio	product	yield (%)
1	4-bromoacetophenone	100	**1**	100 (90)
2	4-bromoacetophenone	1000	**1**	88
3	4-bromobenzophenone	100	**2**	100 (91)
4	4-bromobenzophenone	1000	**2**	90
5	4-bromobenzaldehyde	100	**3**	100 (91)
6	4-bromobenzaldehyde	1000	**3**	59
7	methyl 4-bromobenzoate	250	**4**	100 (92)
8	4-bromobenzonitrile	100	**5**	100 (90)
9	4-bromobenzonitrile	1000	**5**	28
10	4-bromo-1-nitrobenzene	100	**6**	100
11	4-bromo-1-nitrobenzene	1000	**6**	94 (82)
12	4-fluoro-1-bromobenzene	100	**7**	100 (92)
13	4-fluoro-1-bromobenzene	1000	**7**	74
14	4-bromotoluene	100	**8**	100 (89)
15	4-bromotoluene	1000	**8**	66
16	4-bromoanisole	100	**9**	94 (84)[b−d]
17	4-bromoanisole	1000	**9**	48
18	3-bromoacetophenone	1000	**10**	100 (91)
19	3-bromobenzaldehyde	1000	**11**	100 (90)
20	2-(trifluoromethyl)-1-bromobenzene	100	**12**	100 (92)
21	2-(trifluoromethyl)-1-bromobenzene	1000	**12**	36
22	1-bromonaphthalene	250	**13**	89 (80)
23	1-bromonaphthalene	1000	**13**	33
24	bromomesitylene	50	**14**	61 (57)
25	9-bromoanthracene	100	**15**	82 (74)[b−d]
26	9-bromoanthracene	1000	**15**	56
27	2,4,6-triisopropyl-1-bromobenzene	50	**16**	45 (42)
28	3-bromopyridine	250	**17**	100 (87)
29	3-bromopyridine	1000	**17**	72
30	3-bromoquinoline	250	**18**	100 (88)
31	3-bromoquinoline	1000	**18**	55
32	4-bromoisoquinoline	100	**19**	70 (66)

[a] Conditions: catalyst, 1/2 [Pd(C_3H_5)Cl]$_2$/Tedicyp;[6] aryl bromide, 1 mmol; 2-*n*-butylfuran, 2 mmol; AcONa, 2 mmol; DMAc; 20 h; 150 °C; Yields were determined by GC and NMR; yields given in parentheses are isolated yields. [b] The reaction using 1% Pd(PPh_3)$_4$ and AcONa in DMF at 110 °C gave no product **9** and 5% of **15**. [c] The reaction using 1% Pd(OH)$_2$/C and AcOK in DMAc at 140 °C gave 40% of product **9** and 78% of **15**. [d] The reaction using 1% $PdCl_2$, 2% PCy_3, KOAc, DMF, and 1 mmol of Bu_4NBr at 110 °C gave 14% of **9** and 0% of **15**.

Scheme 3



In order to have a more accurate idea of the efficiency of the Pd/Tedicyp system vs other catalysts, we also performed a few reactions using more classical palladium catalysts for the reaction of 2-*n*-butylfuran with 4-bromoanisole or 9-bromoanthracene (Table 1, entries 16 and 25). Using 1% of Pd(PPh_3)$_4$ or $PdCl_2$ associated with PCy_3, very low yields of **9** and **15** were obtained. On the other hand, medium to high yields were obtained using 1% of Pd(OH)$_2$/C (Pearlman's catalyst).[5f]

The mechanism of this reaction might proceed via an oxidative addition of the aryl bromide followed by a Heck type insertion of furan to give the cis intermediate **C**. Then, a migration of the palladium to the 5-position of the furan and a β-elimination into the side-alkyl chain would give the arylfuran derivative. When 3-furaldehyde was used, the β-elimination might occur via the formation of an enolate of the aldehyde.

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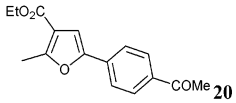
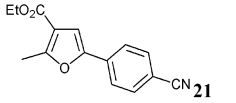
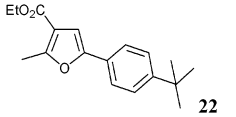
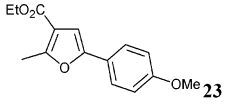
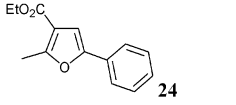
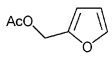
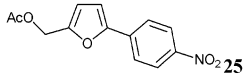
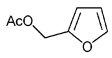
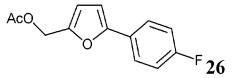
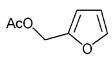
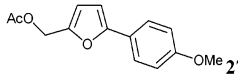
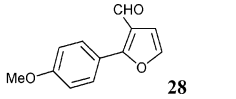
(9) In a typical experiment, the aryl bromide (1 mmol), furan derivative (2 mmol), and AcONa (2 mmol) were dissolved in DMAc (3 mL) under an argon atmosphere. The prepared Pd−Tedicyp catalyst complex[6] was then transferred to the reaction flask via cannula. The reaction mixture was stirred at 150 °C for 20 h. The solution was diluted with H_2O (5 mL), and then the product was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography.

Table 2. Tedicyp−Pd-Catalyzed Reaction[b] of Aryl Halides with Furan Derivatives[9]

Entry	Aryl halide	Furan	Ratio Substrate/catalyst	Product	Yield (%)
1	4-Bromoacetophenone		1000	 **20**	100 (88)
2	4-Bromoacetophenone		10000		51
3	4-Bromobenzonitrile		1000	 **21**	100 (90)
4	4-Bromobenzonitrile		10000		98
5	4-*t*-Butylbromobenzene		100	 **22**	100 (91)
6	4-*t*-Butylbromobenzene		1000		75
7	4-Bromoanisole		100	 **23**	100 (84)
8	4-Bromoanisole		250		78
9	Iodobenzene		1000	 **24**	100
10	Iodobenzene		10000		95 (87)
11	4-Bromonitrobenzene		1000	 **25**	100 (83)
12	4-Bromonitrobenzene		10000		40
13	4-Fluorobromobenzene		100	 **26**	100 (89)
14	4-Fluorobromobenzene		1000		53
15	4-Bromoanisole		100	 **27**	75 (70)
16	4-Bromoanisole		100	 **28**	80 (74)[a]

[a] This reaction gave a mixture of 2- and 5-arylated furaldehydes in a 90/10 ratio. [b] Conditions: catalyst, 1/2 $[Pd(C_3H_5)Cl]_2$/Tedicyp;[6] aryl bromide, 1 mmol; furan derivative, 2 mmol; AcONa, 2 mmol; DMAc; 20 h; 150 °C. Yields were determined by GC and NMR, yields given in parentheses are isolated yields.

Then, a reductive elimination assisted by the base regenerates the Pd(0) (Scheme 3). This mechanism seems to be supported by the results obtained with 2-methoxyfuran. With this substrate the β-elimination into a side-alkyl chain or via the formation of an enolate is not possible, and as expected, using 4-bromoacetophenone or 4-bromoanisole and 2-methoxyfuran, no formation of product was observed even in the presence of 2 mol % of the catalyst.

The presence of a polydentate ligand should not accelerate the oxidative addition of the aryl bromide and the coordination of the furan derivative to palladium for steric reasons, and this is also due to the competition with phosphines for the coordination sites on palladium. On the other hand, the insertion of the furan derivative in the Ar−Pd bond, the β-elimination, and/or the reductive elimination of HBr to regenerate the Pd(0) complex might be accelerated by the steric factors and recoordination pressure of the phosphines.

The reactivity of a few other furan derivatives has also been examined (Table 2). 2-Methylfuran-3-carboxylic acid ethyl ester reacted with activated aryl bromides such as 4-bromoacetophenone and 4-bromobenzonitrile to give the coupling products in very high TONs of 5100 and 9800, respectively (Table 2, entries 1−4). The electron-rich aryl bromides 4-*tert*-butylbromobenzene and 4-bromoanisole led to lower TONs of 750 and 195, respectively (Table 2, entries 5−8). Protected furfuryl alcohol also led to the 5-arylated compounds with high TONs and good yields using electron-deficient aryl bromides and to a TON of 75 with an electron-rich aryl bromide (Table 2, entries 11−15). Finally, 3-furaldehyde reacting with 4-bromoanisole led to the 2-arylated 3-furaldehyde with 90% selectivity (Table 2, entry 16). This arylation at the more hindered 2-position rather than at the 5-position also argues against a C−H activation (palladation) mechanism.

In conclusion, the use of the tetradentate ligand Tedicyp associated to a palladium complex provides a very powerful catalyst for the coupling of aryl bromides with furan derivatives. This catalyst is much more efficient than the complex formed with monodentate ligands. The reaction can be performed with as little as 0.01 mol % catalyst, with the most reactive substrates instead of 5−10 mol % with the reported procedures. Moreover, a wide range of functional groups such as methoxy, fluoro, trifluoromethyl, acetyl, formyl, benzoyl, carboxylate, nitro, and nitrile on the aryl bromide are tolerated. It should be noted that electron-deficient furans are more reactive than electron-neutral furans. The efficiency of this catalyst probably comes from the presence of the four (diphenylphosphino)alkyl groups stereospecifically bound to the same face of the cyclopentane ring, which probably increases the coordination of the ligand to the metal, prevents the precipitation of the catalyst, and could also accelerate the insertion, the β-elimination, or the reductive elimination steps in the catalytic cycle.

Supporting Information Available: Text giving experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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