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Catalytic Regioselective Oxidative Coupling of Furan-2-Carbonyls with Simple Arenes

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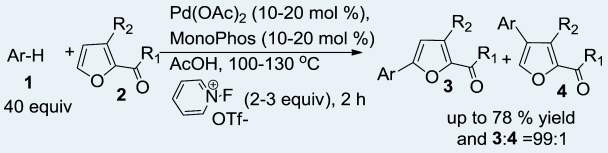
Supporting Information

ABSTRACT: Oxidative coupling of arenes by dual C−H activation, thereby avoiding prefunctionalization of coupling partners, is the ideal way to synthesize biaryls. This letter reports a palladium-catalyzed regioselective oxidative arylation of furan-2-carbonyl compounds with simple arenes to 5-arylfuran-2-carbonyls. The key for the high regioselectivity is the use of F^+ oxidants. The reaction is proposed to proceed through a Pd(II)−Pd(IV) catalytic cycle, wherein the substrates are activated by an electrophilic palladation mechanism, supported by preliminary mechanistic evidence.

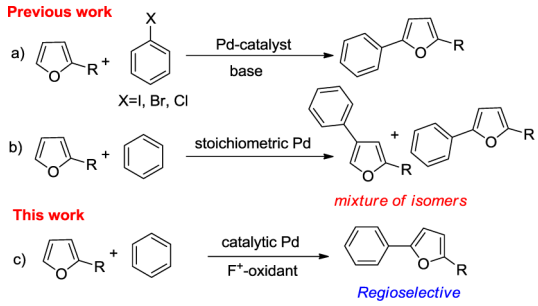


KEYWORDS: *C−H activation, oxidative coupling, furan, arenes, palladium, regioselective*

Biaryl scaffolds are ubiquitous in natural products and biologically active compounds.[1,2] Synthesis of these motifs by conventional transition metal-catalyzed cross-coupling reactions[3−9] entails the use of prefunctionalized coupling partners such as organometallics and organic halides or pseudohalides, which are synthesized by multistep transformations and generate organometallic salts as byproducts. Recently, more attractive direct arylation,[10−19] which requires only one preactivated substrate, while the other coupling partner is activated by C−H activation, has emerged. Ideal, but the most challenging, however, is the dehydrogenative coupling reactions[20−28] of two unactivated coupling partners with a net loss of two hydrogen atoms. Although several advances have been made in this emerging area recently, they are limited to certain classes of substrates, and complexity in controlling chemo- and regio- selectivity[29−32] has nevertheless been a major concern. In a green chemistry perspective, such methodologies based on direct oxidative coupling by C−H activation will not only improve the atom economy of the reaction, but also reduce the use and generation of environmentally hazardous reagents and wastes.[33]

5-Aryl furan derivatives are important intermediates in organic synthesis.[34−38] Direct arylation of furan-2-carbonyl compounds,[39−43] which are renewable building blocks available from biomass waste, with aryl bromides and chlorides was reported recently for the synthesis of these compounds (scheme 1a). Itahara et al.[44] demonstrated the first oxidative coupling of arenes with furan-2-carbonyl compounds mediated by $Pd(OAc)_2$, giving a mixture of the 4-aryl- and 5-arylfuran-2-carbonyls in a ratio of 2:1 (Scheme 1b); however, poor regioselectivity and the necessity of stoichiometric amounts of Pd were the major concerns. In this communication, we report a F^+ oxidant facilitated, palladium-catalyzed oxidative coupling of furan-2-carbonyl compounds with simple arenes forming 5-arylfuran-2-carbonyl derivatives with high regioselectivity.

Scheme 1. Arylation of 2-Substituted Furans



We initiated our investigation by studying the coupling of methyl furan-2-carboxylate with benzene by using different palladium catalysts in the presence of Ag or Cu oxidants.

Indeed, the combination of 20 mol % $Pd(OAc)_2$ in the presence of Ag_2CO_3 or AgOAc as oxidants in acetic acid as the solvent at 100 °C gave 42−48% yield of the mono arylated products with a regioisomeric ratio of nearly 1:1. During this period, Zhang and co-workers[45] reported the catalytic oxidative coupling of perfluoroarenes with thiophenes and furans selectively forming the 5-perfluoroarylated products using $Pd(OAc)_2$ and Ag_2CO_3 in DMSO−DMF−AcOH as the solvent system. To our surprise, there was no detectable heterocoupling when benzene and methyl furan-2-carboxylate were reacted under their conditions. However, intensive screening of solvents, ligands (see entries 5−11, Table 1 and Table S1 of the Supporting Information (SI)) and reaction conditions revealed that excellent yields (up to 79%) of the heterocoupled products could be achieved using bidentate ligands with wide bite angles, such as 4,6-bis-

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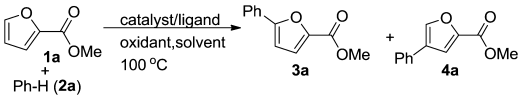
Table 1. Optimization Studies on the Oxidative Coupling of Methylfuran-2-carboxylate with Benzene[a]



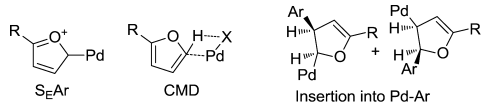
entry	catalyst/ligand	oxidant	solvent	*t*, h	yield[b], %	3a:4a
1	$Pd(OAc)_2$	Ag_2CO_3	AcOH	6	40	1:1.7
2	$Pd(OAc)_2$	$Cu(OAc)_2$	AcOH	6	0	
3	$Pd(TFA)_2$	Ag_2CO_3	AcOH	6	49	1:1.5
4	$Pd(OAc)_2$	AgOAc	AcOH	6	48	1:1,4
5	$Pd(OAc)_2$	Ag_2CO_3	PivOH	6	32	1:2.1
6	$Pd(OAc)_2$	Ag_2CO_3	DMF−AcOH[c]	6	0	
7	$Pd(OAc)_2$	Ag_2CO_3	DMSO−AcOH[c]	6	43	1:1
8	$Pd(OAc)_2$	Ag_2CO_3	dioxane−AcOH[c]	6	27	1:1.4
9	$Pd(OAc)_2$/**5**	Ag_2CO_3	AcOH	6	79	1:1.2
10	$Pd(OAc)_2$/**6**	Ag_2CO_3	AcOH	6	67	1:2.1
11	$Pd(OAc)_2$/**7**	Ag_2CO_3	AcOH	14	78	1:1
12	$Pd(MeCN)_4BF_4$	Ag_2CO_3	AcOH	6	21	2:1
13	$Pd(Phen)_2OTf_2$	Ag_2CO_3	AcOH	24	traces	
14	$Pd(OAc)_2$	O_2	AcOH	6	53	1:1
15	$Pd(OAc)_2$	$PhI(OAc)_2$	AcOH	6	traces	
16	$Pd(OAc)_2$	oxone	AcOH	6	18	2.3:1
17	$Pd(OAc)_2$	NFSI	AcOH	6	44	16:1
18	$Pd(OAc)_2$	NFPT	AcOH	6	50	19:1
19	$Pd(OAc)_2$	NFTMPT	AcOH	6	54	4:1
20	$Pd(OAc)_2$	SelectFluor	AcOH	6	54	3.3:1
21	$Pd(OAc)_2$	NFPTFB	AcOH	6	54	3.5:1
22	$Pd(OAc)_2$	NFPT	AcOH	6	45	12:1
23	$Pd(OAc)_2$/**7**[d]	NFPT	AcOH	6	38	9:1
24	$Pd(OAc)_2$/**5**[d]	NFPT	AcOH	6	55	8:1
25	$Pd(OAc)_2$/**8**[d]	NFPT	AcOH	6	57	16:1
26	$Pd(OAc)_2$/**8**[e]	NFPT	AcOH	6	29	10:1
27	$Pd(OAc)_2$/**8**	NFPT[f]	AcOH	6	65	15:1
28	$Pd(OAc)_2$/**8**	NFPT[f]	AcOH[g]	6	75	19:1
29	$Pd(OAc)_2$/**8**	NFPT[f]	AcOH[g]	2	80	20:1

[a]Conditions: 0.545 mmol of **1a**; 20 mol % catalyst; 20 mol % ligand; 30 equiv **2a** with regard to **1a**; 2 equiv of oxidant with regard to **1a**; reaction volume, 3.75 mL. [b]NMR yield determined using CH_2Br_2 as the internal standard. [c]3 equiv of AcOH with regard to **1a**. [d]10 mol % of $Pd(OAc)_2$ and ligand were used. [e]10 mol % of catalyst and 20 mol % of **8** was used. [f]3 equiv of NFPT with regard to **1a** was used. [g]40 equiv of **2a** with regard to **1a** was used.

(diphenylphosphino)-10*H*-phenoxazine (NiXantPhos, **5**), (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(di-*tert*-butylphosphine) (^{t}BuXantPhos, **6**), and (2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis-(methylene)) bis(diphenylphosphine) (DIOP, **7**), although, to our disappointment, with no regioselectivity.

Furan-2-carbonyls can be activated by palladium by different pathways (Scheme 2). The electrophilic palladation

Scheme 2. Different Modes of Palladation of Furan-2 Derivatives



(S_EAr)[46−48] or concerted metalation−deprotonation (CMD/σ-bond metathesis)[49−53] would prefer the C-5 over the C-4 position because of the resonance stability of the resulting cation by S_EAr and the higher acidity of the C−H at the C-5 than that at the C-4 position, respectively. On the contrary, a Heck type insertion of the furan to aryl palladium complexes could result in either C-4 or C-5 palladation.[44,54,55]

We reasoned that a highly electrophilic palladium would prefer the S_EAr pathway and result in the regioselective formation of 5-arylfuran-2-carbonyls. This prompted us to further examine various electrophilic cationic palladium(II) complexes as well as oxidants that could oxidize Pd(II) to highly electrophilic Pd(IV).[56−63] The dicationic palladium(II) complexes $[Pd(CH_3CN)_4](BF_4)$ and $Pd(Phen)_2(OTf)_2$ were examined but did not perform well under the aforementioned reaction conditions (entries 12 and 13, Table 1). $PhI(OAc)_2$ and oxone as the oxidants resulted in poor yields (entries 15 and 16, Table 1). Molecular oxygen as the oxidant gave a reasonable yield of heterocoupled products, but with no regioselectivity.

However, to our delight, electrophilic fluorine oxidants in the presence of $Pd(OAc)_2$ demonstrated a dramatic effect on regioselectivity. Thus, $Pd(OAc)_2$ in the presence *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide (NFSI, **9**) and *N*-fluoropyridin-1-ium triflate (NFPT, **10**) gave 5-phenylmethylfuran-2-carboxylate (**3a**) in high regioselectively (**3a**:**4a** = 16−19:1) and reasonable yields (44−50%). Screening of various F^+ oxidants indicated an influence of the steric bulk and counteranion on the regioselectivity, as demonstrated in the case of *N*-fluoro-2,4,6-trimethylpyridin-1-ium triflate

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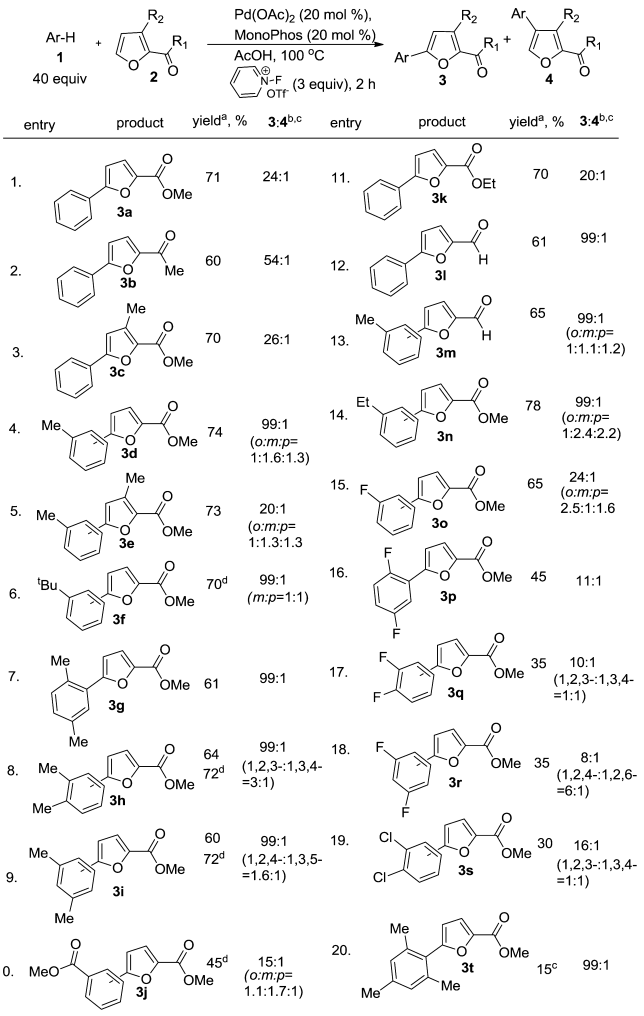
(NFTMPT, **12**) (entry 19, Table 1) and *N*-fluoropyridin-1-ium tetrafluoro borate (NFPTFB, **11**) (entry 21, Table 1), which resulted in lower **3a**:**4a** ratios. A control reaction in the absence of $Pd(OAc)_2$ and in the presence of the NFSI or NFPT gave no coupled products. Further screening of ligands (entries 23−25, Table 1) and optimization of reaction parameters (entries 25−29, Table 1) led to NMR yield as high as 80% with a **3a**:**4a** ratio of 20:1 in 2 h, using *N*,*N*-dimethyldinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]-dioxaphosphepin-4-amine (MonoPhos, **8**) as the ligand in the presence of 20 mol % of $Pd(OAc)_2$, 40 equiv of benzene, and 3 equiv of NFPT with respect to **1a**. Homocoupling of benzene to biphenyl was an unavoidable side reaction; nevertheless, it was minimized to <0.5% with regard to benzene under the optimized conditions. In addition, traces of homocoupled methyl furan-2-carboxylate and phenyl acetate were also detected by GC/MS under these conditions.

After attaining the optimized catalyst system and reaction conditions, we examined the scope of the reaction with respect to different arenes and furan-2-carbonyls. In general, excellent regioselectivity toward C-5 arylated products with moderate to high yields were obtained for the coupling of different functionalized arenes and furan-2-carbonyls. Unsymmetrically substituted arenes, however, gave the corresponding regioisomers in this case, unlike the recent report by Yu and co-workers, which demonstrated a highly para-selective C−H arylation of monosubstituted arenes with benzamides using $Pd(OAc)_2$ in the presence of similar F^+ oxidants.[31]

The total yield of the heterocoupled products and the **3**:**4** ratio were found to be influenced by the electronic as well as the steric characteristics of the arenes. Thus, arenes substituted with electron-donating groups gave high yield and an excellent **3**:**4** ratio, but arenes with electron-withdrawing groups formed the heterocoupled products in moderate yield and **3**:**4** ratio. For instance, in the case of the coupling of methyl furan-2-carboxylate with toluene and ethylbenzene, isolated yields of 74% (*o*/*m*/*p* = 1:1.6:1.3) and 78% (*o*/*m*/*p* = 1:2.4:2.2) of the C-5 arylated products **3d** and **3n**, respectively, were obtained with negligible C-4 arylation (entries 4 and 14, Table 2). In the case of xylenes, the C-5 arylated products **3g**−**3i** were formed almost regiospecifically, with slightly lower yield (61−65%), possibly due to the steric effects of the methyl substituents. Nonetheless, increased yields could be obtained in the case of sterically demanding alkyl arenes at a reaction temperature of 130 °C, as demonstrated in the case of *o*- and *m*-xylenes (72% yield) (entries 8 and 9, Table 2) and *tert*-butyl benzene (70% yield). The more sterically demanding 1,3,5-trimethyl benzene yielded the heterocoupled product **3t** in 15% yield under these conditions. In the case of benzene and fluorobenzene, 71% and 65% isolated yields of the corresponding heterocoupled products **3a** and **3o**, respectively, were obtained with a **3**:**4** ratio of 24:1.

Similar reactions of difluoro and dichlorobenzenes gave the corresponding heterocoupled products in 30−45% yields and **3**:**4** ratios of 8−16:1. In the case of methyl benzoate as the arene, an isolated yield of 45% was obtained (entry 10, Table 2). It is worth mentioning that under these conditions, there was no coupling reaction in the case of the highly electron deficient pentafluorobenzene with methyl furan-2-carboxylate. This methodology was also applied to other furan-2-carbonyl derivatives, as demonstrated in the coupling of ethyl furan-2-carboxylate (70% yield) (entry 11, Table 2), furan-2-carbaldehyde (60−65%) (entries 12 and 13, Table 2), methyl 3-methylfuran-2-carboxylate (70−73% yield, entries 3 and 5, Table 2), and 1-(furan-2-yl)ethanone (60% yield) (entry 2, Table 2) with benzene and toluene.

Table 2. Substrate Scope for the Regioselective Oxidative Coupling of Furan-2-carbonyls with Simple Arenes

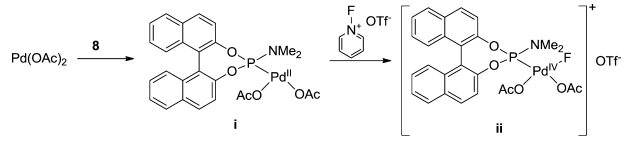


[a]Isolated yield. [b]Determined by NMR or GC/MS analysis. [c]Regioisomeric ratio with regard to the simple arene in parentheses determined by NMR or GC/MS analysis. [d]Reaction temperature was 130 °C.

In view of the strong influence of F^+ oxidants on the regioselective formation of 5-arylfuran-2-carbonyls, we suggest a mechanism that involves a Pd(II)−Pd(IV) catalytic cycle that could be initiated by an active Pd(IV)F species, **ii**, formed by the oxidation of Pd(II) complex **i** with NFPT (Scheme 3). Recently, fluorine oxidants have been demonstrated to oxidize Pd(II) complexes to form cationic and neutral Pd(IV) fluoro complexes.[56−63]

Our preliminary investigation to trace any such active catalytic species by ESI-MS/MS analysis suggested the likely formation of the species **i** and **ii** by the reaction of $Pd(OAc)_2$,

Scheme 3. Proposed Active Pd(IV) Species



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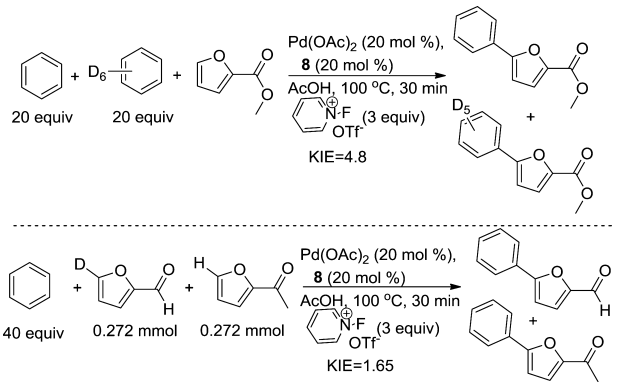
MonoPhos (**8**), and NFPT. Thus, the direct ESI(+)-MS analysis of a mixture of $Pd(OAc)_2$ and **8** in CH_2Cl_2 at room temperature, further diluted with CH_3CN, showed peaks ranging between m/z 523 and 527, corresponding to [**i**-OAc]$^+$(Figure S30, SI). Similarly, a mixture of $Pd(OAc)_2$, **8**, and 15 equiv of NFPT in CH_2Cl_2 at room temperature, diluted with CH_3CN, showed additional peaks at m/z of 603−609 (Figure S31, SI). The MS/MS analysis of the isotopologue at m/z 605 at a collision energy of 20 V showed daughter ion peaks at m/z of 559, 480, 437, 376, and 186 (Figure S32c in SI), which could be formed from a species of the type **ii**. However, this is not conclusive because there is a mass difference of 2 in the experimental vs predicted MS isotope pattern for [**ii**-OTf]$^+$ (Figure S32b, SI). In addition to these preliminary indications, detection of traces of aryl acetate as a side product in the coupling reactions also supports the possible involvement of high-valent Pd catalysis.[64−66] Nevertheless, further studies are necessary to determine the actual catalytic intermediates and understand the mechanism of the reaction.

To gain more insight into the mode of C−H activations under the catalytic conditions, we studied kinetic isotope effects (KIE)[67] on the simple arene as well as the furan-2-carbonyl substrates (Scheme 4). Interestingly, a primary KIE of 4.8 was

Scheme 4. Kinetic Isotope Effect Studies



observed for a competition reaction of benzene and benzene-d_6 with methyl furan-2-carboxylate. To study the kinetic isotope effect with respect to the furan-2-carbonyl coupling partner, we carried out a competition reaction between 2-acetylfuran and C5-*d*-2-furfural with benzene. However, no significant KIE (k_H/k_D = 1.65) was observed in this case. A competition reaction of 2-acetylfuran and 2-furfural was found to form the corresponding heterocoupled products in a ratio of 1:1.

Consequently, the lack of a significant kinetic isotope effect on the C-5 proton in the case of the furan-2-carbonyl derivative implies that C−H bond-breaking does not take place during the selectivity or the rate-determining step.[67] Instead, the activation of the furan-2-carbonyl substrate would be occurring by electrophilic palladation[68,69] at the C-5 carbon. However, C−H bond cleavage occurs in the case of the simple arene during the mechanism of the oxidative hetero coupling, as indicated by the high KIE (4.8). Nevertheless, the lower yields observed in the case of electron-deficient arenes compared with electron-rich arenes and the poor reactivity of pentafluorobenzene disagree with a CMD mechanism for the C−H cleavage, in which compounds with acidic C−H bonds are shown to be particularly more reactive.[49−53]

To confirm the electronic effects on the reaction rate, competition experiments of coupling of methyl furan-2-carboxylate with toluene, *p*-xylene, and *p*-difluorobenzene vs benzene were examined (Table S2, SI). These experiments further confirmed a higher reaction rate for toluene (k_{tol}:k_{ben} = 1.7:1) and lower reaction rate for difluorobenzene with respect to benzene ($k_{p\text{-diFben}}$:k_{ben} = 1:4). Benzene and *p*-xylene reacted at a similar rate, suggesting a role of steric effects on rate. These electronic effects on the reaction rate favor an electrophilic palladation mechanism rather than CMD. Hence, it is likely that under these conditions, the activation of the simple arene proceeds through electrophilic palladation, followed by a slow C−H cleavage.[70,71]

In conclusion, we have developed a regioselective oxidative arylation of furan-2-carbonyls with simple arenes to form 5-arylfuran-2-carbonyls using a catalyst system consisting of $Pd(OAc)_2$/MonoPhos/NFPT in acetic acid. This methodology is applicable to various functionalized arenes and furan-2-carbonyl compounds forming the corresponding 5-arylfuran-2-carbonyl compounds in good yields with high regioselectivity. Considering the major role of F^+ oxidants observed on selective C-5-arylation and preliminary mechanistic evidence, a plausible involvement of Pd(II)−Pd(IV) catalysis wherein the substrates are activated by an electrophilic palladation mechanism is proposed. Further studies directed toward expanding the substrate scope to the regioselective coupling of other heteroarenes and simple arenes and detailed mechanistic investigations are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data, NMR and ESI-MS/MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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