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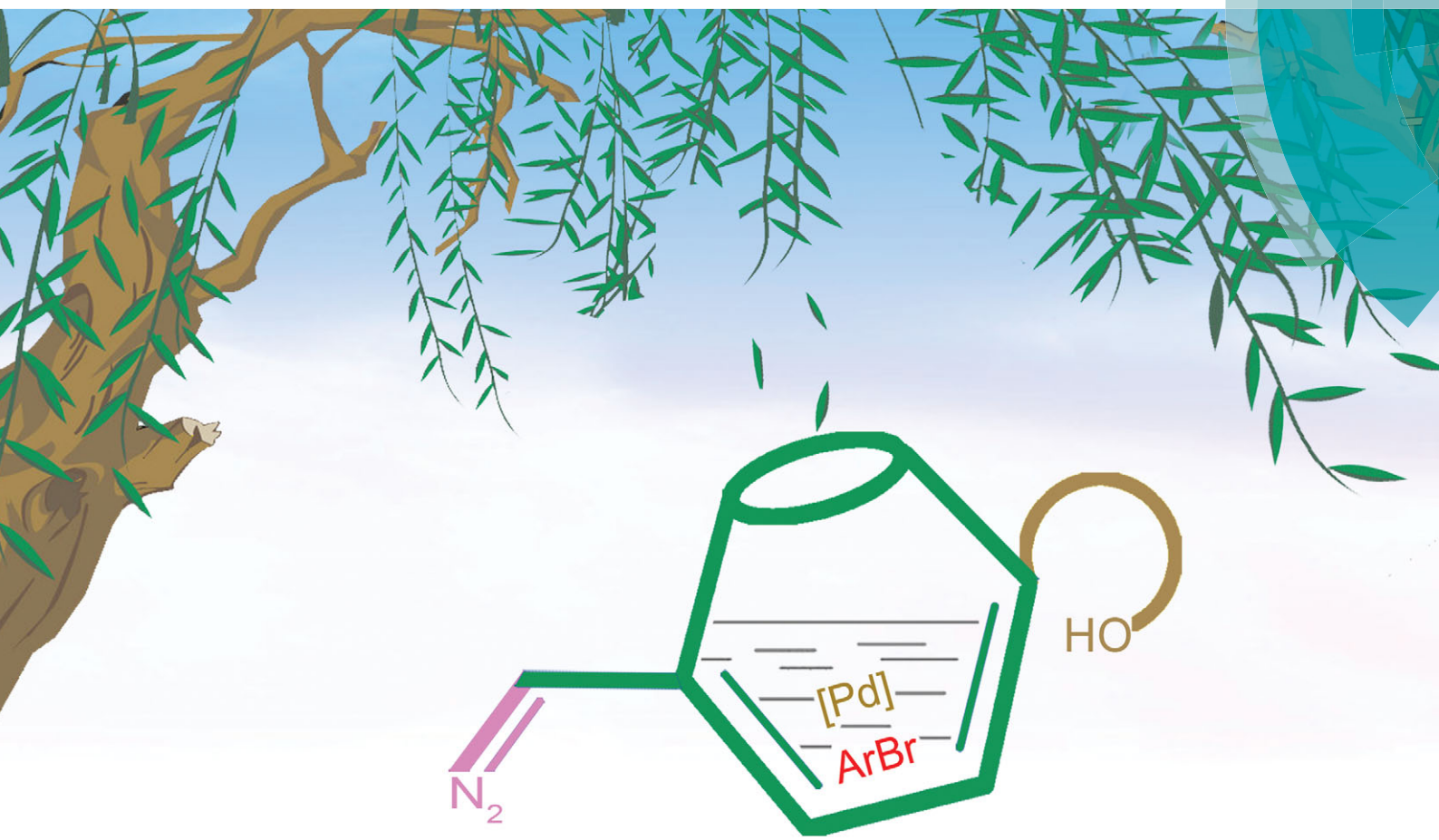

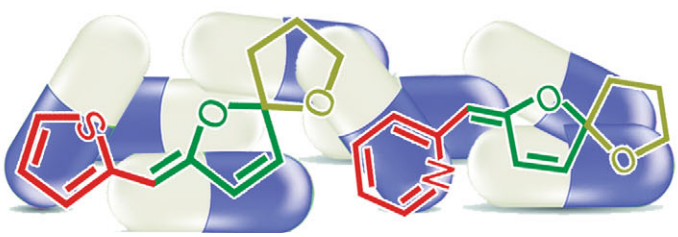

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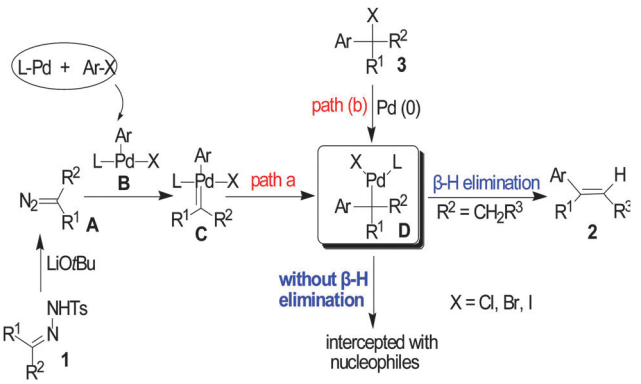
Practical access to spiroacetal enol ethers *via* nucleophilic dearomatization of 2-furylmethylene-palladium halides generated by Pd-catalyzed coupling of furfural tosylhydrazones with aryl halides†

Biaolin Yin,* Xiaoyu Zhang, Jianchao Liu, Xuehui Li and Huanfeng Jiang

Pd-catalyzed cross-coupling of furfural tosylhydrazones with aryl halides produces 2-furylmethylenepalladium halides, which can undergo intramolecular nucleophilic dearomatization to provide spiroacetal enol ethers. This is the first report on the formation of 2-furylmethylenepalladium halides from stable furfural hydrazones instead of from 2-furylmethyl halides, which are not readily accessible or are unstable.

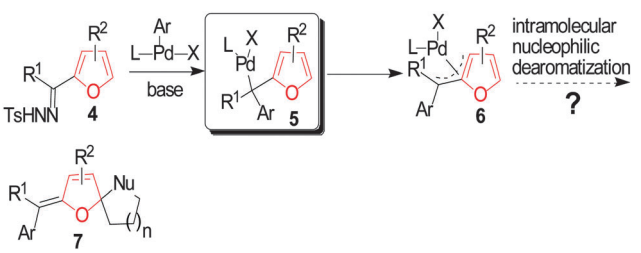
The Pd-catalyzed cross-coupling of tosylhydrazones with aryl halides is a very simple, powerful method to form C–C bonds using carbonyl compounds as the nucleophilic components without the need for a stoichiometric amount of an organometallic reagent.[1] This reaction is believed to occur *via* the mechanism outlined in Scheme 1. Oxidative addition of the aryl halide to the Pd^0 catalyst gives aryl Pd complex **B**, which reacts with diazo compound **A** (generated *in situ* from tosylhydrazone **1**) to afford Pd carbene complex **C**. This complex can undergo migratory insertion of the aryl group into the C–Pd bond to give arylmethylenepalladium halide **D** (path a), which then either undergoes β-hydrogen elimination to provide an olefin[2] or is intercepted by a nucleophile.[3] This cross-coupling is an alternative to the preparation of **D** *via* oxidative addition reactions between a Pd^0 catalyst and arylmethyl halides **3** (path b), which are not readily available or are unstable.[4] The development of new coupling reactions based on tosylhydrazones and exploration of their synthetic applications currently are attractive research topics.

Furan derivatives, such as furfurals, are readily available from a renewable feedstock such as biomass.[5] Furans demonstrate the typical arene reactivity of heteroaromatic compounds,[6] but owing to the low aromaticity of the furan ring, they can also behave as synthetic equivalents of alkenes, 1,3-dienes, alkynes, 1,4-diketones, and enol ethers.[7,8] Thus, furans are attractive four-carbon starting materials for various chemical transformations. Because of the electron richness of the furan ring, 2-furylmethyl



Scheme 1 Formation and transformation of arylmethylenepalladium **D**.

halides are usually unstable and prone to oligomerization even at room temperature. Accordingly, it is difficult to prepare and to investigate the chemical properties of the exceedingly reactive 2-furylmethylenepalladium halides generated *via* oxidative addition of 2-furylmethyl halides to Pd^0. On the basis of the pathway shown in Scheme 1, we envisioned that coupling of 2-furfural tosylhydrazone **4** with an aryl halide (Scheme 2) would produce 2-furylmethylenepalladium halide **5** or η^3-furylmethylene-palladium halide **6** (*via* σ–π isomerization of 5). Because the structure of **6** is similar to that of other η^3-arylmethylene-palladium halides, it could undergo intramolecular nucleophilic dearomatization[4d–g] if a suitable nucleophile was tethered at



Scheme 2 Formation and dearomatization of **5**.

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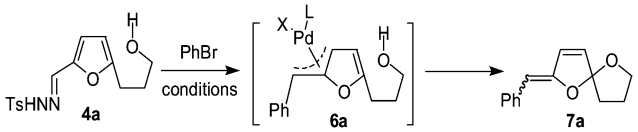
† Electronic supplementary information (ESI) available: Copies of ^{1}H NMR and ^{13}C NMR spectra of all the new compounds. See DOI: 10.1039/c4cc01725k

the 2-position of the furan ring (path c). As part of our ongoing studies on furan dearomatization[9] and the use of furans as building blocks,[10] we report herein the dearomatizing transformations of 2-furylmethylenepalladium halides generated by Pd-catalyzed coupling of aryl halides with furfural tosylhydrazones **4**, which have a hydroxypropyl group tethered at the 2-position of the furan ring, to prepare spiro dienyl ethers.[11,12]

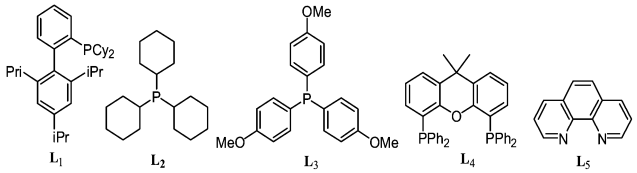
First, the reaction of **4a** with PhBr was employed as a model to optimize the reaction conditions (Table 1). Using $Pd(PPh_3)_4$ as the catalyst and LiO*t*Bu as the base, reaction in toluene at 90 °C for 2 h afforded **7a** in 31% yield as an inseparable *Z*/*E* mixture (*Z*/*E* = 4/1, entry 1). The stereochemistry of **7a** was unambiguously established by 2D-NMR spectroscopy (see the NOESY spectrum of **7a** in the ESI†). The *Z*-isomers demonstrated the NOEs between the olefinic protons of an enol ether and an endo-cyclic double bond. To improve the yield of **7a**, we screened various Pd catalysts, ligands, bases, and solvents. $Pd_2(dba)_3$ showed superior catalytic activity (entry 5), affording **7a** in 52% yield (entry 5). Among the ligands examined, tricyclohexyl phosphine $\mathbf{L_2}$ gave the highest yield of **7a** (74%, entry 8). Other bases, including KO*t*Bu, NaO*t*Bu, NaH, and K_2CO_3 did not improve the yield (entries 15–18), nor did other solvents, such as DMF, DCE, THF, and 1,4-dioxane (entries 19–22). The optimal yield was obtained using $Pd_2(dba)_3$ as the catalyst, $\mathbf{L_2}$ as the ligand, toluene as the solvent, and 90 °C as the reaction temperature.

Table 1 Optimization of reaction conditions for coupling of **4a** with PhBr[a,b]



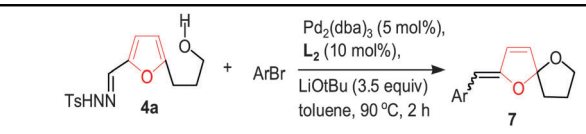
	Conditions			
Entry	Catalyst	Ligand	Base	Yield[c] [%]
1	$Pd(PPh_3)_4$	—	LiO*t*Bu	31
2	$Pd(MeCN)_2Cl_2$	PPh_3	LiO*t*Bu	40
3	$Pd(OAc)_2$	PPh_3	LiO*t*Bu	ND[d]
4	$Pd(PPh_3)_2Cl_2$	—	LiO*t*Bu	18
5	$Pd_2(dba)_3$	PPh_3	LiO*t*Bu	52
6	$Pd_2(dba)_3$	BINAP	LiO*t*Bu	22
7	$Pd_2(dba)_3$	$\mathbf{L_1}$	LiO*t*Bu	17
8	$Pd_2(dba)_3$	$\mathbf{L_2}$	LiO*t*Bu	74
9	$Pd_2(dba)_3$	$\mathbf{L_3}$	LiO*t*Bu	32
10	$Pd_2(dba)_3$	$\mathbf{L_4}$	LiO*t*Bu	25
11	$Pd_2(dba)_3$	dppp	LiO*t*Bu	Trace
12	$Pd_2(dba)_3$	dppf	LiO*t*Bu	18
13	$Pd_2(dba)_3$	dppe	LiO*t*Bu	Trace
14	$Pd_2(dba)_3$	$\mathbf{L_5}$	LiO*t*Bu	ND[d]
15	$Pd_2(dba)_3$	$\mathbf{L_2}$	KO*t*Bu	7
16	$Pd_2(dba)_3$	$\mathbf{L_2}$	NaO*t*Bu	28
17	$Pd_2(dba)_3$	$\mathbf{L_2}$	NaH	Trace
18	$Pd_2(dba)_3$	$\mathbf{L_2}$	K_2CO_3	Trace
19[e]	$Pd_2(dba)_3$	$\mathbf{L_2}$	LiO*t*Bu	ND
20[f]	$Pd_2(dba)_3$	$\mathbf{L_2}$	LiO*t*Bu	28
21[g]	$Pd_2(dba)_3$	$\mathbf{L_2}$	LiO*t*Bu	45
22[h]	$Pd_2(dba)_3$	$\mathbf{L_2}$	LiO*t*Bu	ND

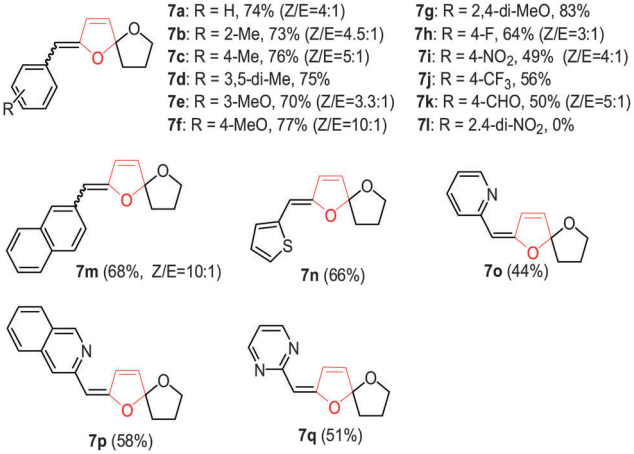
[a] Reaction conditions: **4a** (1.0 equiv.), PhBr (1.2 equiv.), Pd (5.0 mol%), ligand (10 mol%), base (3.5 equiv.), 90 °C for 2 h. [b] The solvent was toluene unless stated otherwise. All reactions were performed at a 0.3 mmol scale. [c] Yield determined by ^{1}H NMR analysis with mesitylene as an internal standard. The products were *Z*/*E* mixtures (approximately 4/1), as indicated by ^{1}H NMR analysis of the crude product. [d] Not detected. [e] DMF was the solvent. [f] DCE was the solvent. [g] THF was the solvent. [h] 1,4-Dioxane was the solvent.



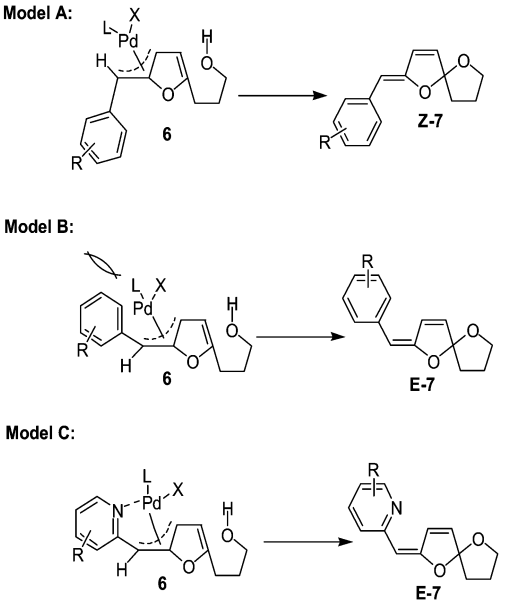
Next, we investigated the substrate scope of the transformation by reacting **4a** with various aryl bromides under the optimized conditions (Table 2). The substituent on the phenyl ring clearly influenced the reaction outcome. When R was electron-donating, the reaction gave the desired products (**7a–7g**) in moderate to good yields. Electron-withdrawing groups generally led to lower yields of the corresponding products (**7h–7l**). When R was a 2,4-dinitro group, none of the desired product (**7l**) was detected, implying that the electron-rich phenyl ring favored the formation of **6** and thus led to a higher yield of **7**. 2-Naphthyl bromide and 2-thienyl bromide gave **7m** and naturally occurring **7n**,[13] respectively, in good yields. The stereochemistry of **7b–7n** was assigned as shown in Table 2 in analogy with **7a**, with *Z*-isomer as the major or exclusive one. Nitrogen-containing aryl bromides, such as 2-pyridyl bromide, 2-quinolyl bromide, and 2-pyrimidyl bromide, also afforded the desired products (**7o–7q**), but in low yields, perhaps because of the electron-poor nature of the nitrogen-containing rings. Notably, **7o** was produced as exclusive *E*-isomer based on the NOESY spectrum (see ESI†). The stereochemistry of **7p** and **7q** was assigned as the exclusive

Table 2 Substrate scope of reaction of **4a**[a]





[a] All reactions were performed at a 0.3 mmol scale; percentages are isolated yields; ratios of *Z*/*E* isomers were determined by ^{1}H NMR analysis of the isolated product mixtures (the *Z*/*E* isomers are inseparable by flash chromatography).



Scheme 3 Stereochemical models for the formation of **7**.

E-isomer by comparison of their chemical shifts of three olefinic protons with those of **7o** and *Z*-**7a**.

To rationalize the stereoselectivities obtained, we proposed stereochemical models A, B and C (Scheme 3). For **7a–7n**, model A was preferred due to the absence of interaction between the phenyl group and the ligand (model A *vs.* model B). While for **7o–7q**, these reactions exclusively proceeded through model C due to the chelation between the nitrogen atom and palladium.

In summary, we have developed a simple, practical Pd-catalyzed coupling of furfural hydrazones with aryl halides, which proceeds *via* 2-furylmethylenepalladium halide intermediates to provide efficient access to spiroacetal enol ethers. This is the first report on the formation of 2-furylmethylenepalladium halides from stable furfural hydrazones instead of from unstable 2-furylmethyl halides. The 2-furylmethylenepalladium halides can undergo intramolecular nucleophilic dearomatization, and thus this protocol greatly expands the synthetic applications of furan derivatives, which can be obtained sustainably. Further exploration of the reaction scope, especially the variation of the dearomatizing aryl rings and nucleophiles, is currently underway in our laboratory, with the goal of synthesizing bioactive and natural products *via* this route.

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