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Umpolung-like Cross-coupling of Tosylhydrazones with 4-Hydroxy-2-pyridones under Palladium Catalysis

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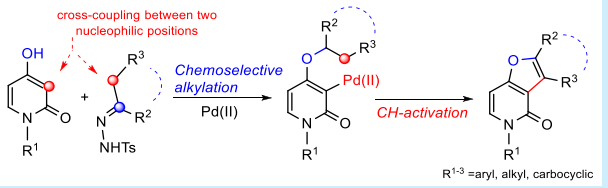
Supporting Information

ABSTRACT: Tosylhydrazones under palladium catalysis were found to perform cross-coupling reactions with 4-hydroxy-2-pyridones. The umpolung-like reactivity, between the α-carbon of tosylhydrazone and the 3-position of the heterocycle, which is observed in the obtained products, indicates the directed sp^3-CH-activation of an alkylated phenol intermediate by the pendant 3-palladated heterocycle. The reaction and its intercepted variants are surveyed in their scope, allowing the synthesis of inaccessible 3-carbocyclic pyridones in moderate to excellent yields.



CH-activation of 2-pyridone heteroaromatic ring has attracted considerable attention in recent years.[1] CH-functionalization at the 3-position is mainly relying on radical mediators, such as nickel, manganese, iron, and iridium complexes,[2] whereas the functionalization of the 5-position is almost exclusively dependent on palladium chemistry (Figure 1).[3] However, the electron deficient 6-position of the heteroaromatic core has been accessed by the aid of directing groups attached on the nitrogen atom,[4] or by cooperative catalysis between electrophilic activation employing Lewis acids and electron-rich metal complexes (Figure 1).[4] These methods render 2-pyridones as a reliable heteroaromatic template for CH-functionalization by a wide range of reagents, including electron-rich and -poor aromatics, alkenes, and alkyl groups. On the contrary, despite their well-established biological importance,[5] methods for the CH-activation of the related 4-hydroxy-2-pyridones are rather scarce[6] due to the nucleophilicity of the attached 4-phenol substituent that leads preferentially to dimerized products when metals are applied. Recently, our group revealed the ability of the 4-hydroxy-2-pyridone core to palladate at the 3-position with the aid of palladium acetate under mild conditions, enabling the application of Suzuki–Miyaura[7a] and Heck[7b] reactions to produce 3-aryl and 3-alkyl derivatives, respectively (Figure 1).

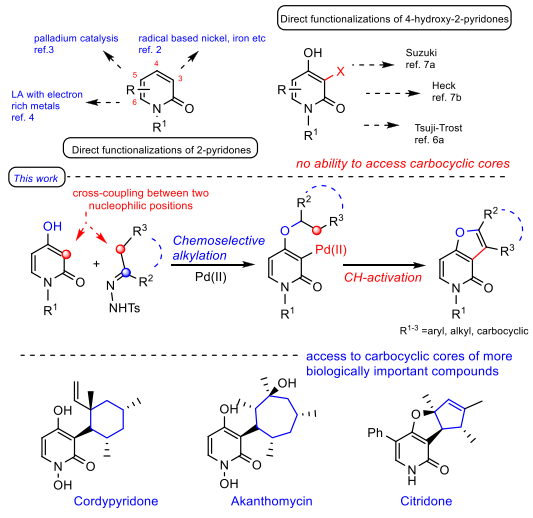


Figure 1. Existing methods for the CH-activation of 2-pyridone and 4-hydroxy-2-pyridone cores and the reported herein sequential alkylation-CH-activation of 4-hydroxy-2-pyridone heteroaromatic.

Despite the undeniable power of the latter method to easily provide 3-alkylated products, its inability to access more complex derivatives has been witnessed when endocyclic alkenes were utilized as coupling partners. The latter is especially unfortunate, due to the longstanding interest of our group in the total synthesis of 4-hydroxy-2-pyridone alkaloids (Figure 1),[8] where the direct C-3 selective alkylation is highly desirable to access these complex carbocyclic cores.

Tosylhydrazones have been well recognized the past decade as powerful cross-coupling partners for several transformations, including their application as alkylating agents and metal carbene precursors.[9] Based on these literature precedents, we quested whether tosylhydrazones can act as alkylating reagents for 4-hydroxy-2-pyridone heteroaromatic core allowing not only to access more complex members but also to trespass the regioselectivity issues posed by a typical Heck-type reaction.

To test this hypothesis, *N*-methyl-2-pyridone (**1**) and acetophenone-tosylhydrazone (**2**) were chosen as readily available materials to model the reaction. Based on our previous studies,[7] it was known that the addition of a base is advantageous for the formation of dipyridone as a byproduct. However, in the case of tosylhydrazones the use of a base was necessary for the formation of the diazo components. The first attempts, utilizing K_2CO_3 in different reaction sets (entries 1–5),

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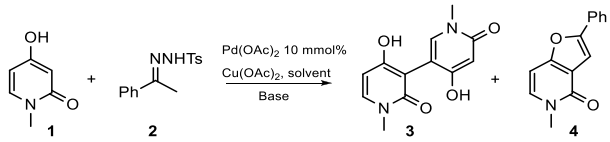
provided only traces of a cross-coupling product (5−20%), favoring, as expected, the production of dipyridone **3**. To our surprise, purification and characterization of the cross-coupling fraction led to the 5-methyl-2-phenylfuro[3,2*c*]-pyridin-4(5*H*)-one (**4**) as the sole product, identical to the one produced by the acidic Heck reaction of styrene with *N*-methyl-4-hydroxy-2-pyridone (**1**).[7b] Besides these unpredicted findings, the reaction sets reveal the expected enhancement of dipyridone byproduct under polar solvents at high temperatures (entries 1 and 6; Table 1).[7a] These effects were minimized by utilization

Table 1. Optimization of Reaction Parameters[a]



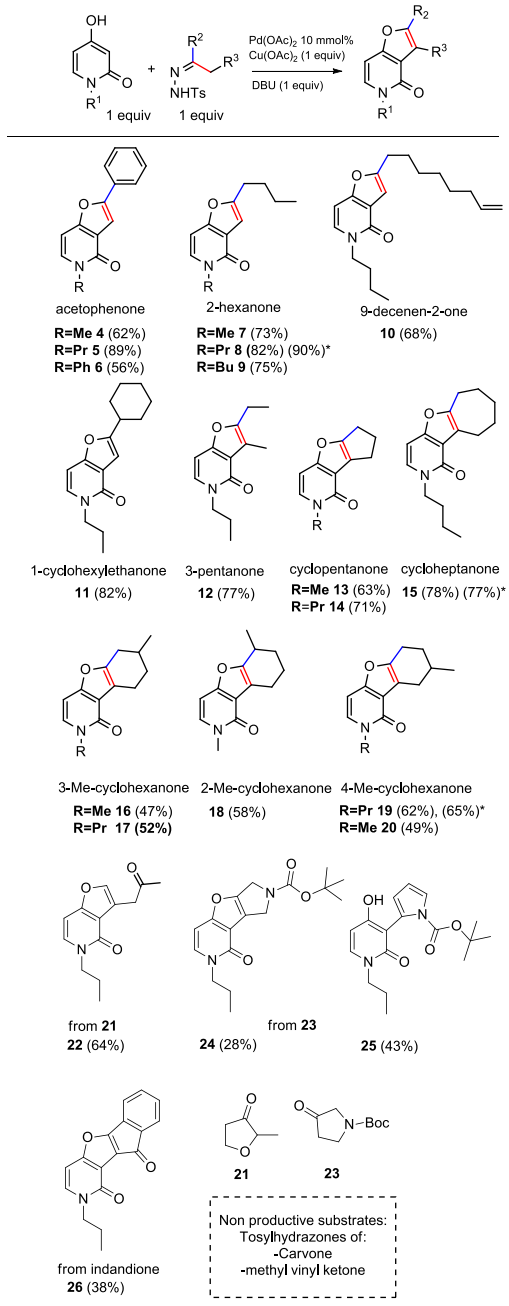
entry	base	solvent[b]	temp (°C)	conv (%)[b]	yield (%) (3/4)[c]
1	K_2CO_3 (2 equiv)	dioxane	130	100	70:10
2	K_2CO_3 (2 equiv)	dioxane	80	89	55:20
3	K_2CO_3 (2 equiv)	dioxane	60	29	20:5
4	K_2CO_3 (2 equiv)	AcOEt	80	50	30:10
5	K_2CO_3 (2 equiv)	acetonitrile	80	78	58:12
6	K_2CO_3 (2 equiv)	DMF	80	100	80:10
7	K_2CO_3 (3 equiv)	dioxane	80	85	70:10
8	LiOtBu (1 equiv)	dioxane	80	80	64:10
9	DBN (1 equiv)	dioxane	80	100	decomp
10	**DBU (1 equiv)**	**dioxane**	**80**	**94**	**26:64**
11	DBU (2 equiv)	dioxane	80	87	65:15
12	DBU (1 equiv)	DMF	80	100	63:22
13	DABCO (1 equiv)	DMF	80	100	65:20
14	DABCO (1 equiv)	dioxane	80	90	30:58
15[d]	DBU (1 equiv)	DMF	80	100	97:0
16[e]	DBU (1 equiv)	dioxane	80	100	decomp
17[f]	DBU (1 equiv)	dioxane	80	100 (based on **2**)	20:66
18[g]	DBU (2 equiv)	dioxane	80	100	55:35
19[h]	**DBU (1 equiv)**	**dioxane**	**80**	**93**	**20:70**

[a]Reaction conditions unless otherwise noticed: (a) 1 (0.16 mmol), 2 (0.16 mmol), solvent (1 mL), $Pd(OAc)_2$ (10 mmol %), $Cu(OAc)_2$ (0.16 mmol), base (indicated equivalents), 80 °C, 12 h in a 4 mL sealed screw capped vial. [b]Conversion as indicated by crude NMR using internal standard. [c]Yields referred to isolated products. [d]In the absence of $Cu(OAc)_2$; oxygen as oxidant. [e]Benzoquinone (1 equiv) was used as oxidant. [f]The ratio of pyridone/hydrazine was 2:1 (0.32 mmol: 0.16 mmol). [g]The ratio of pyridone/hydrazone was 1:2 (0.16 mmol: 0.32 mmol). [h]Premixing conditions of tosylhydrazone and the base were applied followed by heating at 40 °C for 10 min before pyridone **1**, $Cu(OAc)_2$, and $Pd(OAc)_2$ were introduced and heated to 80 °C.

of dioxane at 80 °C (entry 2; Table 1). The use of hindered bases in stoichiometric quantities, like DBU, improved the results, affording 64% yield of **4** (entry 10; Table 1). Premixing hydrazone **2** with DBU before the addition of the heteroaromatic substrate followed by the oxidant and the catalyst was found to be advantageous delivering **4** in 70% yield (entry 19). Attempts to further diminish dipyridone formation by screening oxidants (entries 15−16) or by altering the ratio of the reagents (entries 17−18; Table 1) did not allow any observable improvement.

Having in our hands the optimized conditions, we sought to test if diverse tosylhydrazone substrates lead to similar results. For this study, a range of linear and carbocyclic hydrazones were prepared and allowed to react under our optimized conditions with different *N*-protected 4-hydroxy-2-pyridones (Scheme 1).

Scheme 1. Reaction Scope[a]



[a]Reaction conditions of Table 1 utilizing tosylhydrazones obtained from the indicated ketones. The reported yields are after isolation; yields indicated with an (*) correspond to the *in situ* formation of tosylhydrazones in the reaction mixture.

In all tested cases, reactions proceeded smoothly to provide furo[3,2*c*]-pyridin-4(5*H*)-one in moderate to excellent yields. As expected, linear methyl alkyl or methyl phenyl hydrazones delivered products **4**−**11** (Scheme 1), which are identical to those obtained from the cross-coupling of the associated terminal alkenes.[7b] These results validate our initial assumption over a Heck-type mechanistic pathway resulting from the dissociation

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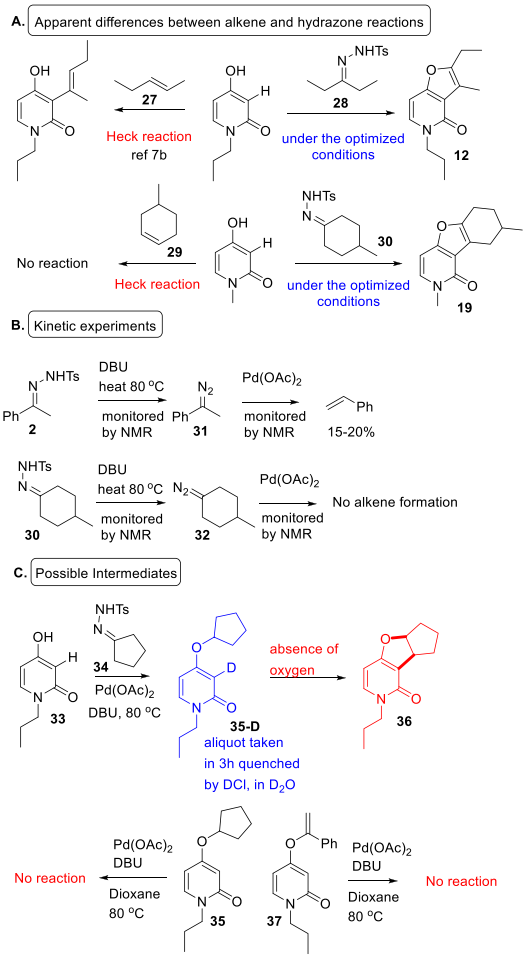
of tosylhydrazones to provide the most accessible alkenes. In sharp contrast to our previous observations,[7b] where internal alkenes (like compound **27**, Scheme 2) were unable to cyclize under Heck reaction conditions when tosylhydrazone of 3-pentanone **28** was applied in the reaction conditions, the formation of compound **12** was evidenced (Scheme 2). The latter inconsistency regarding Heck reaction pathway has also been demonstrated when several carbocyclic hydrazones have been utilized to deliver compounds **13**–**20** (Scheme 1). The cyclized products were obtained in moderate yields, whereas endocyclic alkenes under Heck conditions (see compound **29**, Scheme 2) did not provide any coupling products.

Scheme 2. Studies on Reaction Mechanism



More interestingly, the carbocyclic tosylhydrazones bearing substituents afforded exclusively one of the possible isomeric products that attributed solely to an initial chemoselective attack from the phenol group of the heterocycle to the sp^2 carbon atom of the hydrazone (**16**–**20**, Scheme 1). The latter clearly indicates the direct involvement of hydrazones, instead of alkenes, as the active partners of the umpolung-like coupling between its α-carbon and the 3-position of the heterocycle.

In an attempt to rationalize these results, an array of kinetic experiments was set up with the aid of NMR to establish the potential existence of *in situ* produced alkenes in the reaction mixture (Scheme 2). Tosylhydrazones **2** and **30** were allowed to react in NMR tubes under two different sets: (a) in the presence of 1 equiv of DBU at 80 °C and (b) in the presence of 1 equiv of DBU and 10 mol % of $Pd(OAc)_2$. Chloroform-*d* was used as the solvent in both cases. Both tosylhydrazone of acetophenone **2** and 4-methyl cyclohexanone **30** were transformed to diazo derivatives **31** and **32**, respectively, within 1 h of heating with DBU, without the evidence of any produced alkenes. The same was also apparent even after several hours of heating under the same conditions. Applying the same set of reactions in the presence of $Pd(OAc)_2$ afforded 15% of styrene within 1 h of heating and dimerization products as major components after extended hours of heating. However, no formation of alkene product was detected for hydrazone **30** in the same series of reactions (Scheme 2).

Taking into account this information, we next turned our attention to potential isolated intermediates from the reaction mixture. To this end, aliquots were taken from the reaction of *N*-propyl-4-hydroxy-2-pyridone **33** and cyclopentanone tosylhydrazone **34**, at different reaction times (Scheme 2). In all cases, the only observed coupling product, apart from **14**, was compound **35**[10] (or its deuterated form **35-d** depending on the quenching conditions). What is more, exclusion of dioxygen from the reaction mixture led to the isolation of dihydro component **36** (Scheme 2).

To further exclude reactive intermediates on the reaction pathway, we synthesized and tested compounds **35** and **37** for their ability to cyclize to **14** and **5**, respectively (Schemes 1 and 2). Heating, even for prolonged reaction times, compounds **35** and **37** in the presence of DBU and $Pd(OAc)_2$ did not provide any products. This corroborates our previous observations[7] for the necessity of a free phenol as mediator to deliver Pd(II) in the heterocycle for the formation of the cyclized products.

These preliminary studies on the reaction mechanism suggest a catalytic cycle that starts with the incorporation of palladium acetate into the pyridone-2 core to form **38** (Scheme 3). Then, the subsequent formation of diazo-compound **39** under the basic conditions allows the formation of palladium carbene **40**. Intramolecular phenol insertion on the carbene forms intermediate **41**, which bears both *O*-alkylation and palladium(II) in the 3-position of the heterocycle. We hypothesize that the latter is responsible for a directed CH-activation of the pendant sp^3 bond to produce intermediate **43** and then form the final products. As discussed earlier, an additional synergistic mechanism (Heck type reaction) might still be valid for the cases of methyl-tosylhydrazones where alkenes even in small quantities have been witnessed (Scheme 3).

In our attempts to make the described protocol more applicable, we tested the *in situ* preparation of tosylhydrazones in the reaction mixture. Thus, mixing the desired ketone with tosylhydrazide followed by stirring and sequential addition of DBU, *N*-protected 4-hydroxy-2-pyridone, copper acetate, and palladium acetate afforded the expected products in equal or better yields compared to the ordinary procedure (Scheme 1, yields with an *). Finally, reaction of 3-propyl-4-hydroxy-2-pyridone **33** with **34** in a 2 mmol scale under our optimized protocol provided a similar yield of **14** (67%), even by lowering the catalyst loading to 5 mol %.

The ability of furo[3,2*c*]-pyridin-4(5*H*)-ones to serve as excellent entry points for structural modifications[5i] is evidenced when these are treated with aqueous acid. Furo[3,2*c*]-pyridin-4(5*H*)-ones, especially those bearing substituents in both 2- and 3-positions of the furan moiety, were found to be prone to cationic cleavage of the furan ring under acidic conditions. The free phenol compounds that formed are in equilibrium with the cyclized form, which allows further transformations. Indicative examples for their ability to serve as excellent

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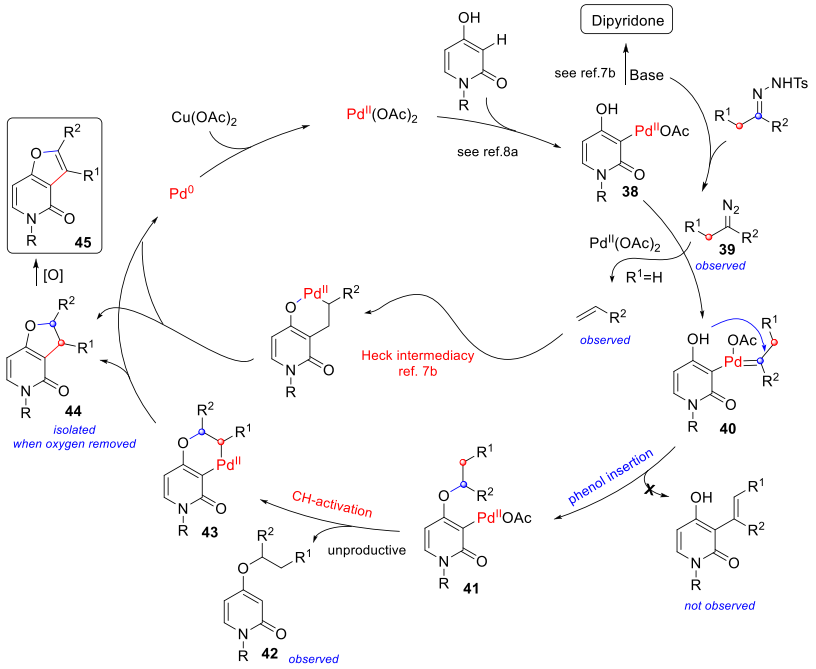
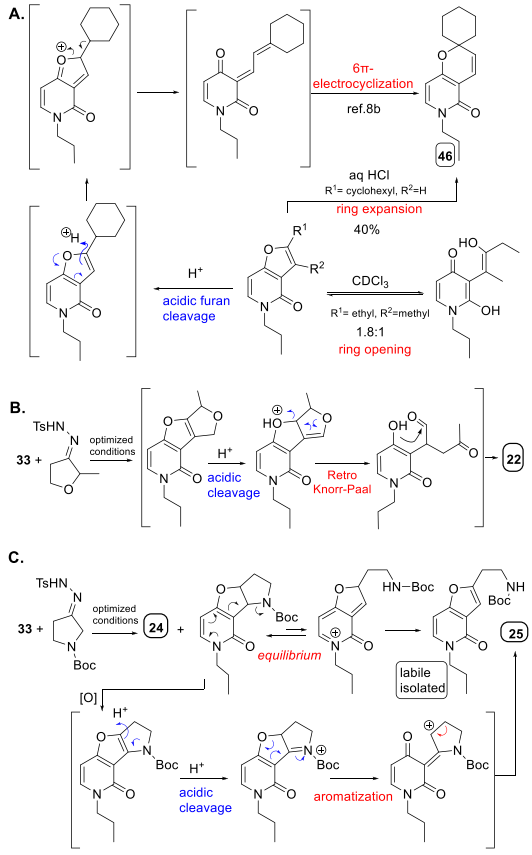
Scheme 3. Postulated Reaction Mechanism for the Cross-coupling of Tosylhydrazones with 4-Hydroxy-2-pyridones



Scheme 4. Indicative Transformations of Selected Furo[3,2*c*]-pyridin-4(5*H*)-ones under Acidic Conditions



precursors of diverse pyridone compounds are presented in Scheme 4.

In conclusion, we describe the cross-coupling of the 4-hydroxy-2-pyridones core by tosylhydrazones under palladium catalysis. The reaction is proposed to involve an initial alkylation of the phenol substituent of the heterocycle by tosylhydrazone, followed by directed CH-bond activation of the more unshielded sp^3-bond to deliver a formal umpolung coupling between the α-position of a ketone and the C-3 position of the heterocycle. The reaction allows the incorporation of carbocyclic substituents in the heterocycle permitting an easy access to natural and synthetic privileged structures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03119.

Experimental procedures, kinetic experiments, and full characterization of all newly prepared compounds (PDF)

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Notes

The authors declare no competing financial interest.

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