Direct synthesis of tricyclic 5*H*-pyrido[3,2,1-ij]quinolin-3-one by domino palladium catalyzed reaction†

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Unexpectedly, the palladium catalyzed coupling reaction of acrolein with 8-bromoquinoline gave 5*H*-pyrido[3,2,1-ij]quinolin-3-one in a single step.

Tricyclic amides are important substructures of active compounds. Among them, some pyrrolo[3,2-ij] and [3,2,1-ij] quinolines exhibited antibacterial and antifungal activities for diseases of rice plants.[1] Tricyclic quinolinones were also evaluated as DNA intercalators[2] for their antitumor effects[3] or as acetylcholinesterase inhibitors.[4]

As a part of our study on the arylation of acrolein and acrolein derivatives[5] *via* the Heck reaction, we extended this reaction to several poly- and hetero-aromatic compounds.[6] Herrmann's palladacycle[7] exhibited very high activity for this coupling reaction towards the substituted α,β-unsaturated aldehydes (up to 87% yield) with almost all aromatic and heteroaromatic substrates. On the other hand, starting from acrolein diethyl acetal, the catalytic system dramatically affected the selectivity of the reaction: while the phosphine-free Cacchi's conditions led to the formation of the expected α,β-unsaturated aldehydes (up to 79% yield), the Herrmann's palladacycle gave mainly the corresponding saturated ester (up to complete selectivity). In that case, it was suggested that the palladium complex resulting from oxidative addition to the double bond interacted further with the aromatic ring and as a consequence, the *syn* β-hydrogen elimination occurred mainly *via* the H *gem* to the diacetal yielding thus the ester after hydrolysis. Similarly, palladium-catalyzed reactions between aryl halide and allylic alcohol provided either substituted allylic alcohol or ketone depending on the reaction conditions.[8] Such behaviour appears particularly interesting if the intermediate could be trapped by a complementary function at the desired position to perform synthesis of polycyclic compounds by the well documented palladium catalyzed cascade reactions.[9] In this paper, we report the specific reactivity of the 8-bromoquinoline that afforded tricyclic quinolinone in one step. For comparison, the reactivity of substrates synthesised from the corresponding alcohol was also studied.

Initially, the coupling reaction of acrolein and acrolein diethyl acetal with 8-bromoquinoline **1a** (Scheme 1) was performed using conditions reported by Cacchi *et al.* which were based on Jeffery's phase transfer reaction conditions[10] ($Pd(OAc)_2$, nBu_4NOAc, K_2CO_3, KCl, DMF, 90 °C). After 24 h, high conversions (>99%) were achieved with both reactants (Table 1). Moreover, the expected aldehyde **2**, corresponding to the classical Heck mechanism, was obtained as the major compound. Starting from acrolein, the aldehyde **2** was formed in 50% isolated yield together with dehalogenated quinoline **4** (8%). This can be attributed to the moderate activity of the substrate under these reaction conditions. After hydrolysis in the presence of dilute HCl, higher selectivity (90%) in coupling product **2** was achieved from diethyl acetal acrolein with small amount of propionic ester **5**.

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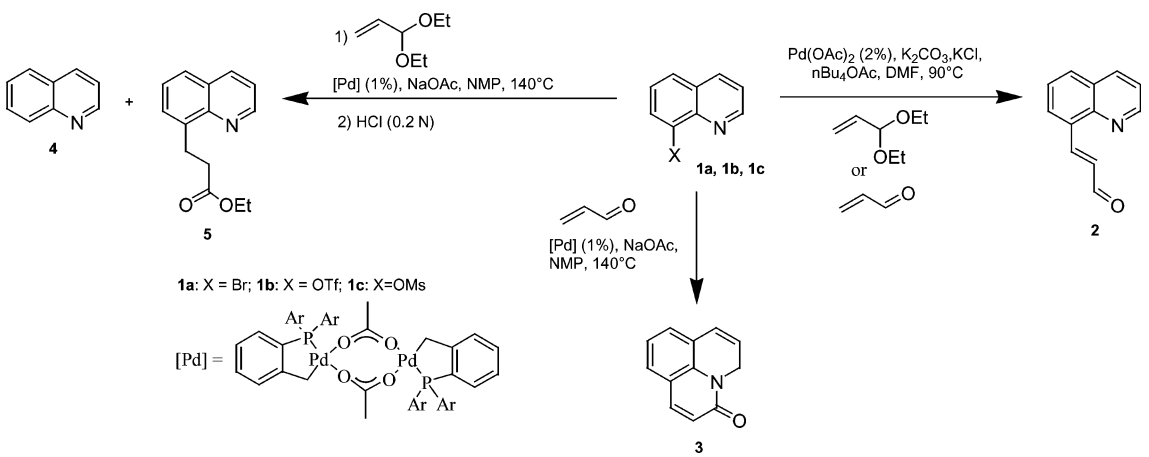

Scheme 1 Palladium-catalyzed reaction of acrolein and diethylacetal acrolein with 8-substituted quinolines.

Table 1 Palladium coupling of 8-bromoquinoline with acrolein and acrolein diethyl acetal. Influence of the reaction conditions

	Acrolein		Acrolein diethyl acetal	
Reaction conditions	Conversion (%)[a]	Selectivity (%)[a]	Conversion (%)[a]	Selectivity (%)[a]
$Pd(OAc)_2$, K_2CO_3, KCl, nBu_4NOAc, DMF, 90 °C, 24 h	100	**2**/67 (50)[b] **4**/8	>99	**2**/90 **5**/3
[Palladacycle] (1%), NaOAc, NMP, 140 °C, 24 h	93	**3**/56 (51)[b] **4**/7	67	**5**/61 (43)[b] **4**/<1

[a] Determined by GC analysis. [b] Isolated yield.

Then, the heteroarylation of acrolein diethyl acetal with 8-bromoquinoline **1a** was performed using the commercially available palladacyclic catalyst (1 mol% Herrmann's palladacycle, NMP, NaOAc, 140 °C) (Scheme 1).[5] Under these reaction conditions, lower conversion was achieved (67%) compared to the Cacchi's conditions (quantitative). This can be attributed to the rate acceleration effect of added halide ions as previously reported.[11] As expected from our previous work,[6] the ester **5**, resulting from a β-hydrogen elimination *via* the H *gem* to the diacetal, was the main product (61% selectivity, 43% isolated yield) together with traces of quinoline **4** (<1%) produced from direct dehalogenation of the substrate (Table 1). Under identical conditions, the reaction of 8-bromoquinoline with acrolein was studied. After 24 h reaction, high conversion (93%) was achieved (Table 1); however, the coupling compound **2** was not detected. After isolation and characterisation, it was established that 5*H*-pyrido[3,2,1-ij]quinolin-3-one **3** was synthesized preferentially (isolated yield 51%), the main by-product being quinoline **4** produced from dehalogenation (7%).

Mesylate and even more triflate derivatives are known to be efficient substrates for the palladium coupling reaction.[12] We synthesized the triflate derivative **1b** and the mesylate derivative **1c** from the commercially available 8-hydroxyquinoline in good yields according to reported literature procedures.[13] Under the same conditions, the cyclization of the mesylate substrate **1c** provided selectively the tricyclic compound **3** with moderate yield (30% conversion, Table 2). On the other hand, the triflate substrate **1b** yielded the tricyclic compound **3** (40% isolated yield, Table 2) after 24 h reaction time. It can be concluded that the leaving group has no influence on the selectivity of the reaction excepted that dehalogenation was avoided starting from activated alcohols.

In the literature, few reports were dealing with the synthesis of such tricyclic compounds that required usually many reaction steps. To our knowledge, no related mechanism to the formation of the tricyclic compound **3** *via* a palladium-catalyzed coupling reaction was reported in the literature.

Table 2 Palladium coupling of 8-substituted quinolines with acrolein. Influence of the leaving group

Substrate	Conversion (%)[a]	Isolated yield **3** (%)
1a	80	51
1b	100	40
1c	30	N.d.[b]

[a] Determined by GC analysis. [b] Not determined.

Due to the presence of the nitrogen in the quinoline, a small change in the reaction conditions exhibited a strong modification in the selectivity of the reaction. Considering the different results, the following mechanism is proposed that account to the one pot formation of the tricyclic compound (Scheme 2).

Starting from the acrolein diethyl acetal, the formation of the propionic ester results from a β-hydrogen elimination that occurs selectively at the H *gem* to diacetal group (Scheme 2). A strong interaction between the nitrogen of the heteroaromatic ring and the palladium center was proposed: this additional bond blocks the rotation along the Pd–**CH**–**CH**–Ar bond necessary to perform the *syn* β-hydrogen elimination of the benzylic hydrogen reported for the classical Heck coupling. As a consequence, after hydrolysis the resulting enol acetal yields the arylpropionic ester **5**.

Following the same initial idea, the existence of internal strong interactions should influence similarly the reactivity of the acrolein. After the initial steps of the expected Heck arylation of acrolein by the 8-bromoquinoline, we proposed that a relatively stable 6-membered palladacycle is formed by coordination of the quinoline ring through the nitrogen atom to the Pd(II)-center. As previously, this internal interaction prevents the internal rotation along the Pd–**CH**–**CH**–Ar bond. As a consequence, only hydrogen *gem* to the aldehyde may be abstracted, yielding intermediately the highly reactive ketene **6** together with a palladium hydride species still coordinated to the ketene moiety. Palladium intermediates are well known to undergo cascade transformations when adequate function is present at proximity.[9] In the considering reaction, we proposed that following the initial coupling and β-hydride elimination steps, a *syn* addition of [H–Pd] to the C=N of the quinoline ring occurs through the transition state **TS**. As the next step, the base attacks the acid benzylic proton of **7** to give the species **8** that undergoes reductive elimination to afford the tricyclic quinolinone **3**, regenerating the palladium catalyst.

In conclusion, starting from 8-substituted quinoline, three different compounds may be formed by small change in the reaction conditions. The specific reactivity of the Hermann's palladacycle allowed the one pot synthesis of a tricyclic quinolinone. To our knowledge, the single step procedure described in the communication is the shortest route to synthesize tricyclic fused quinolinones. Further works are under progress to extend the procedure to the synthesis of various benzoquinolizinones and to establish clearly the mechanism of formation of **3**.

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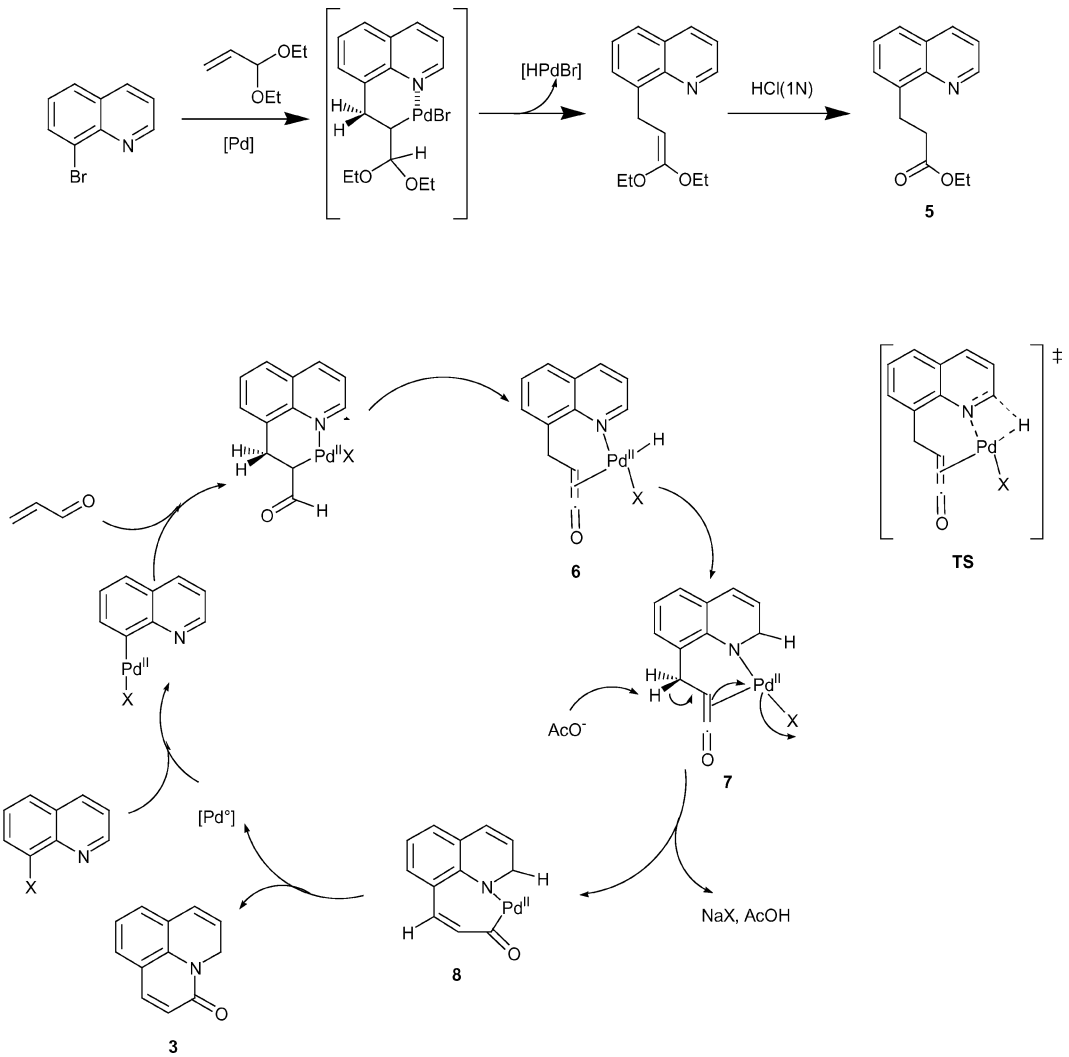

Scheme 2 Proposed mechanisms for the formation of **3** and **5** with palladacycle catalyst (ligands are omitted for the clarity).

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