Transition-Metal Catalysis

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Palladium-Catalyzed Intramolecular Nucleophilic Substitution at the Alkoxycarbonyl Group**

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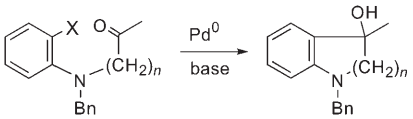
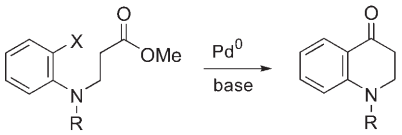
The widespread application of palladium catalysts in organic synthesis owes mainly to their tolerance of most important functional groups, largely as a result of the low nucleophilicity of organopalladium compounds.[1] Thus, aryl and vinyl palladium complexes are commonly used as electrophiles in C–C coupling reactions, and there are only a few examples of their use as nucleophiles in reactions with polar electrophilic multiple bonds.[2–5] Alkoxycarbonyl groups have long been considered inert toward organopalladium reagents. In many cases, substrates that bear an ester moiety can undergo palladium-mediated processes in which the alkoxycarbonyl group is not modified in any way.[6] For example, the palladium-catalyzed α arylation of esters,[7] which involves the nucleophilic attack of an enolate at a σ-aryl palladium complex, has emerged recently as a straightforward method for the preparation of α-aryl esters.[8,9]

We described recently the Pd^0-catalyzed intramolecular nucleophilic addition of aryl halides to amino-tethered ketones [Eq. (1); Bn = benzyl].[3c] This process appears to



(1)

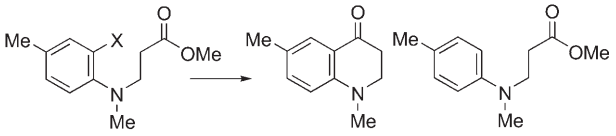
involve the formation of a four-membered azapalladacyclic intermediate, which strongly modifies the interaction of the metal center with the carbonyl group and forces the otherwise unexpected nucleophilic addition. Herein we report that we can take advantage of the formation of such transient intermediates to force nucleophilic attack at functional groups less electrophilic than the ketone carbonyl group, such as an alkoxycarbonyl group. In particular, we describe the Pd^0-catalyzed intramolecular coupling of β-(2-iodoanilino)esters to give dihydroquinolin-4-ones [Eq. (2)].[10]



(2)

Our initial efforts were focused on the Pd^0-catalyzed intramolecular coupling reaction of ester **1a** (Table 1). The use of $[Pd(PPh_3)_4]$ as the catalyst and Cs_2CO_3 as the base, a combination that was effective in promoting nucleophilic addition in β-(2-iodoanilino)ketones,[3c] resulted exclusively in the reduction of the aryl halide (Table 1, entry 1).[11] In contrast, when K_3PO_4 was used instead of Cs_2CO_3, a mixture of the reduction product **3** and ketone **2** was obtained. The latter compound results from nucleophilic substitution at the alkoxycarbonyl group (Table 1, entry 2). During our studies

Table 1: Optimization of the Pd^0-catalyzed intramolecular nucleophilic substitution of **1a**.



1a, X = I
1b, X = Br

Entry	Catalyst[a]	Additives ([equiv])	Solvent	*T* [°C][b]	*t* [h]	Products (yield [%])[c]
1	$[Pd(PPh_3)_4]$	Cs_2CO_3 (2)	THF	110	24	**1a** (40), **3** (40)
2	$[Pd(PPh_3)_4]$	K_3PO_4 (3)	THF	110	31	**2** (30), **3** (25)[d]
3	$[Pd(PPh_3)_4]$	K_3PO_4 (3), Et_3N (10)	toluene	110	72	**2** (65), **3** (30)
4	$[Pd(PPh_3)_4]$	K_3PO_4 (3), Et_3N (10)	toluene	130	48	**2** (45), **3** (45)
5	$[Pd(PPh_3)_4]$	K_3PO_4 (3), Et_3N (10)	toluene	90	100	**1a** (79), **2** (10), **3** (5)
6	$[Pd(PPh_3)_4]$	K_3PO_4 (2), Ag_3PO_4 (1), Et_3N (10)	toluene	110	72	**3** (36)[e]
7	$[Pd_2(dba)_3]$, $P(c\text{-}C_6H_{11})_3$[f]	K_3PO_4 (3), Et_3N (10)	toluene	110	72	**1a** (40), **3** (43)
8	$Pd(OAc)_2$, $P(o\text{-tolyl})_3$[f]	K_3PO_4 (3), Et_3N (10)	toluene	110	72	**1a** (72), **3** (15)
9[g]	$[Pd(PPh_3)_4]$	K_3PO_4 (3), Et_3N (10)	toluene	110	72	**2** (26), **3** (64)

[a] Catalyst loading: 0.2 equivalents of Pd with respect to **1a**. [b] All reactions were carried out in a sealed tube. [c] Yields of the isolated products. [d] Compound **1a** was also recovered (10%). [e] Methyl 3-(*N*-(4-methylphenyl)amino)propionate was also isolated in 5% yield. [f] Ligand/Pd 2:1. [g] Bromide **1b** was used instead of **1a**. dba = dibenzylideneacetone.

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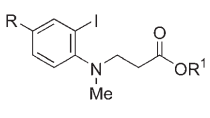
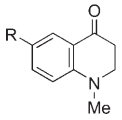
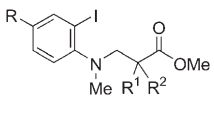
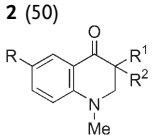
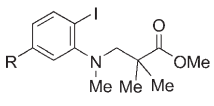
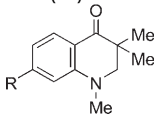
toward the optimization of the cyclization process, we found that the use of toluene in place of THF and in combination with Et_3N led to an increase in the yield of ketone **2** to 65% (Table 1, entry 3). The use of higher reaction temperatures resulted in an increase in the amount of the reduction product obtained (Table 1, entry 4), whereas low reaction rates were observed at lower reaction temperatures (Table 1, entry 5). The addition of Ag_3PO_4 to remove the iodide ligand and facilitate the coordination of the carbonyl group (Table 1, entry 6) resulted in the formation of reduction products only, as did the use of other ligands on the palladium catalyst (Table 1, entries 7 and 8). Finally, the substitution reaction was less efficient with bromide **1b** as the substrate: Under the same reaction conditions, **3** was obtained as the main product (Table 1, entry 9).

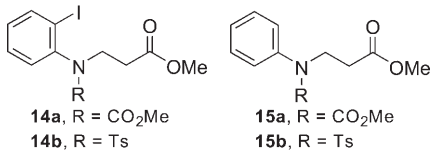
A range of differently substituted dihydroquinolin-4-ones were synthesized under the optimized reaction conditions (Table 2). In general, substituents on the aromatic ring were found to have little effect on the success of the carbopalladation reaction. Thus, the nucleophilicity of the aryl palladium species does not appear to be affected by the electronic properties of the substituent. The low yield of the acylation product derived from **4b** is mainly a consequence of an increase in the rate of the competitive retro-Michael fragmentation of the β-aminoester (Table 2, entry 2). We found that benzyl esters can also be used as substrates in the reaction, although the desired product was formed in slightly lower yield from the benzyl ester counterpart of **1a** than from the methyl ester **1a** itself (compare Table 2, entry 3 with Table 1, entry 3).

Table 2: Synthesis of substituted dihydroquinolin-4-ones.[a]

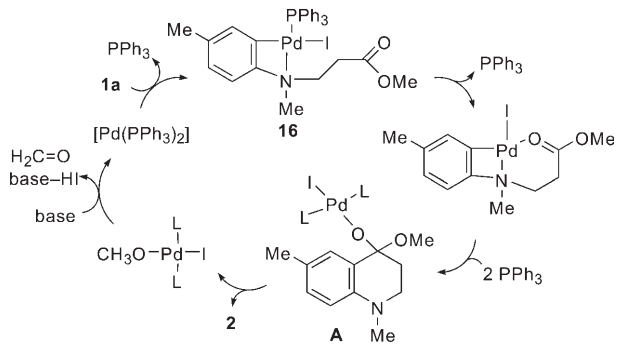
Entry	Ester	Quinolin-4-one[b] (yield [%])	ArH[c] (yield [%])
			
1	**4a**, R = OMe, R^1 = Me	**5a** (67)	**6a** (30)
2	**4b**, R = CO_2Me, R^1 = Me	**5b** (35)[d]	**6b** (28)
3	**4c**, R = Me, R^1 = Bn	**2** (50)	**6c** (25)
			
4	**7**, R = R^1 = Me, R^2 = H	**8** (49)	**9** (45)
5	**10a**, R = R^1 = R^2 = Me	**11a** (79)	–
6	**10b**, R = OMe, R^1 = R^2 = Me	**11b** (83)	–
7	**10b**, R = OMe, R^1 = R^2 = Me	**11b** (80)[e]	–
8	**10c**, R = CO_2Me, R^1 = R^2 = Me	**11c** (88)[f]	–
9	**11d**, R = R^1 = Me, R^2 = Ph	**11d** (74)[f]	–
			
10	**12a**, R = Me	**13a** (83)	–
11	**12b**, R = Cl	**13b** (83)	–

[a] Reaction conditions: $[Pd(PPh_3)_4]$ (0.2 equiv), K_3PO_4 (3 equiv), Et_3N (10 equiv), toluene, 72 h, 110°C (sealed tube). [b] Yield of the isolated product. [c] Product of hydrodehalogenation (for details, see the Supporting Information). [d] Methyl 4-(methylamino)benzoate was also isolated. [e] $[Pd(PPh_3)_4]$: 0.1 equivalents. [f] Reaction time: 40 h.

The reaction of amino esters without hydrogen atoms α to the carbonyl group proceeded smoothly to give the corresponding ketones in high yields (Table 2, entries 5–11), even when the amount of catalyst used was decreased to 0.1 equivalents (Table 2, entry 7). On the other hand, no competition between nucleophilic attack at the carbonyl group and α arylation was observed in the reactions of amino esters **1a**, **4a–c**, and **7**, which contain hydrogen atoms α to the carbonyl group. The Pd-catalyzed intramolecular α arylation of α-amino esters was described recently for substrates with (2-halobenzyl)amino or (2-(2-halophenyl)ethyl)amino moieties:[9] No interference from nucleophilic attack at the ester group was observed.[12] As the main difference between these amino esters and those examined in the present study is that there are no carbon atoms between the nitrogen atom and the aromatic ring, our initial assumption that the intermediacy of four-membered azapalladacycles could force otherwise unfavorable processes may be accurate. In fact, carbamate **14a** and sulphonamide **14b**, in which the coordination ability of the N atom has been suppressed, failed to undergo nucleophilic attack at the ester group, and the reduction products **15a** (87%) and **15b** (63%; Ts = *p*-toluenesulfonyl), respectively, were formed exclusively. Moreover, the treatment of **1a** with $[Pd_2(dba)_3]$ and PPh_3 in benzene at room temperature for 24 h afforded the four-membered azapalladacycle **16** (see Scheme 1), which was transformed into ketone **2** together with ester **3** when heated at 110°C in toluene in the presence of K_3PO_4.



A plausible mechanism for the observed Pd^0-catalyzed cyclization[13] is shown in Scheme 1. The oxidative addition of the aryl iodide to a Pd^0 species would give the four-membered azapalladacycle **16**. A carbopalladation reaction between the



Scheme 1. Proposed mechanism for the acylation reaction.

σ-aryl palladium moiety and the alkoxycarbonyl group would then lead to the Pd^{II} alkoxide **A**. The coordination of the N atom to the palladium center in **16** not only brings the carbonyl group nearer to the metal to facilitate the formation of a transient chelated intermediate in which the carbonyl group is coordinated to the palladium center,[14] but also increases the electron density on the palladium center to enable the otherwise unfavorable carbopalladation reaction to occur. β-Alkoxide elimination from **A** would afford ketone **2** and a Pd^{II} alkoxide, which would finally undergo β-hydride elimination to regenerate the Pd^0 catalyst. The isolation of significant amounts of benzaldehyde in the reaction of benzyl ester **4c** supports this reduction sequence.[15]

In summary, we have described the first examples of a palladium-catalyzed acylation of aryl iodides by alkoxycarbonyl groups. Further studies to expand the intramolecular reaction and provide deeper insight into the mechanism are under way.

Experimental Section

Typical procedure: A mixture of the amino ester (0.04 M), K_3PO_4 (3 equiv), Et_3N (10 equiv), and $[Pd(PPh_3)_4]$ (20 mmol %) in toluene was stirred at 110 °C in a sealed tube for 72 h. The reaction mixture was then poured into water, and the resulting mixture was extracted with Et_2O. The organic extracts were washed with brine, dried, and concentrated. The residue was purified by flash chromatography to give the corresponding dihydroquinolin-4-one.

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