Palladium-Catalyzed Intramolecular Coupling of Amino-Tethered Vinyl Halides with Ketones, Esters, and Nitriles Using Potassium Phenoxide as the Base

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Abstract: Vinyl halides undergo intramolecular coupling with amino-tethered ketones, esters, and nitriles in the presence of a palladium catalyst and potassium phenoxide as the base. This reaction constitutes a useful methodology for the synthesis of monocyclic, bridged, and spirocyclic nitrogen-containing compounds.

Keywords: alkenylation; enolates; homogeneous catalysis; nitrogen heterocycles; palladium

During the past decade there has been a growing interest in the palladium-catalyzed coupling reactions of aryl and vinyl halides with enolates and related anions. However, while the reactions of aryl halides have been extensively studied, and it is now possible to introduce an aromatic unit to a broad range of enolate-type nucleophiles,[1] the coupling reactions involving vinyl halides have received little attention and deal almost exclusively with the α-alkenylation of ketone enolates.

The first examples of such palladium-catalyzed coupling reactions involving vinyl halides were reported by Piers at the beginning of the 1990s, when he described the intramolecular alkenylation of ketone enolates and then applied the reaction to the synthesis of the diterpenoid crinipellin B.[2] Some years later, another example of this coupling process was reported by Cook in the context of the total synthesis of the alkaloid (+)-vellosimine,[3] and we reported our studies on the synthesis of nitrogen heterocycles by the Pd(0)-catalyzed intramolecular coupling of amino-tethered vinyl halides and ketone enolates.[4] Later on, Buchwald described the intermolecular vinylation of ketone enolates.[5] Finally, it is worth mentioning that isolated examples of the alkenylation reaction have also been reported in the studies of the Pd(0)-catalyzed intermolecular arylation of ester[6] and alanine-derived azlactone[7] enolates.

In our previous work, we established that the use of $Pd(PPh_3)_4$ (0.2 equivs.) and KO-*t*-Bu (1.5 equivs.) in THF at reflux effectively promotes the intramolecular coupling of amino-tethered vinyl halides and ketones to afford bridged, condensed, and monocyclic nitrogen-containing compounds.[4] However, for some substrates side reactions such as the elimination of HX leading to alkynes which may undergo subsequent coupling with the starting vinyl halides to afford dimeric compounds, and dealkylation at the nitrogen, resulted in low or moderate yields of the cyclization products.[4b] As these side reactions can mainly be attributed to the use of a strong base, a more general protocol for the intramolecular α-alkenylation of ketones could be found if, instead of KO-*t*-Bu, a milder base was used. In this context, it should be noted that the intramolecular coupling of amino-tethered vinyl halides and ketones was also accomplished in some cases by using Cs_2CO_3 as the base, although these reaction conditions were only suitable for the construction of five-membered ring systems and afforded moderate or low yields.[4b]

Continuing our studies on this palladium chemistry,[8] we have recently reported that both vinyl and aryl halides undergo the intramolecular coupling with amino-tethered allylic nitro moieties in the presence of a palladium catalyst and a base, potassium phenoxide being the reagent of choice in these reactions.[9]

With these precedents in mind, we decided to look more closely at the coupling reactions of vinyl halides with ketones and test the use of PhOK in order to find a more efficient catalytic system. Table 1 shows that the intramolecular coupling of diverse amino-tethered vinyl halides and ketones can be successfully accomplished when using PhOK as the base (Method A). For the sake of comparison, the results obtained previously by using KO-*t*-Bu as the base[4b, c] (Method B) have also been included.

The examples depicted include intramolecular coupling processes from γ-amino, β-amino, and α-amino ketones leading to seven-, six-, and five-membered rings in generally good yields. It is noteworthy that the use of

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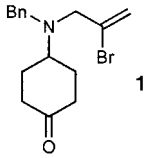
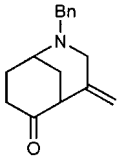
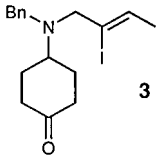
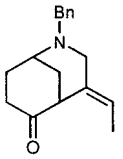
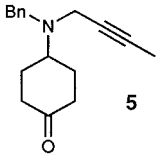
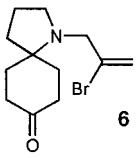
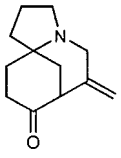
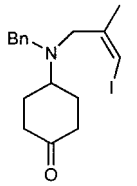
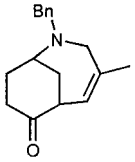
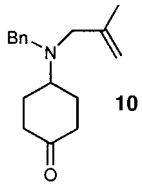
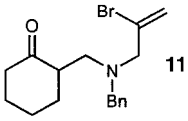
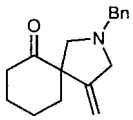
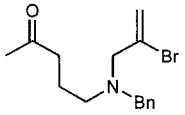
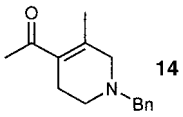
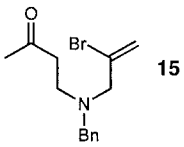
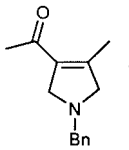
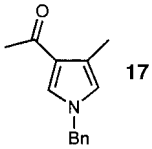
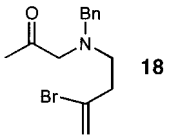
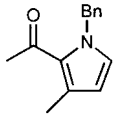
Table 1. Pd-catalyzed intramolecular coupling of vinyl halides and ketones using PhOK as the base.[a]

Entry	Substrate	Method[b]	Time	Products/yield[c]			
1	 **1**	A	3 h	 **2**		92%[d]	
2	**1**	B[e]	0.5 h	**2**		40–50%[f]	
3	 **3**	A	2.5 h	 **4**	82%	 **5**	
4	**3**	B[e]	0.75 h		41%		24%
5	 **6**	A	3 h	 **7**		77%	
6	**6**	B[g]	0.5 h	**7**		54%	
7	 **8**	A[h]	96 h	 **9**	48%	 **10**	5%
8	 **11**	A	5 h	 **12**		70%	
9	 **13**	A	1 h	 **14**	89%		
10	**13**	B[e]	4 h	**14**		41%[i]	
11	 **15**	A	3 h	 **16**	 **17**	83%, **16**/**17** ratio 2.8:1	
12	**15**	B[e]	4 h	**16**	**17**	32%, **16**/**17** ratio 1:1	
13	 **18**	A	3 h	 **19**		15%	

[a] For the preparation of substrates and NMR data of the cyclization products, see Supporting Information.
[b] Method A: KO-*t*-Bu (2.5 equivs.), PhOH (3 equivs.), $Pd(PPh_3)_4$ (0.05 equivs.), THF reflux. Method B: KO-*t*-Bu (1.5 equivs.), $Pd(PPh_3)_4$ (0.2 equivs.), THF reflux.
[c] Yields refer to pure isolated products of reactions on 0.15–0.25 mmol scale.
[d] When the reaction was carried out starting from 1.5 mmol of **1**, ketone **2** was isolated in 88% yield.
[e] See Ref.[4b] [f] Minor amounts (5%) of a dimeric compound were also isolated.
[g] See Ref.[4c] [h] $Pd(PPh_3)_4$ (0.2 equivs.).
[i] Minor amounts of a dimeric compound (5%) and of the corresponding alkyne (5%) were also isolated.

PhOK allowed the amount of the palladium catalyst to be reduced to 0.05 equivs., although longer reaction times were required in general. Compared to the reactions using KO-*t*-Bu as the base, both the yields and turnover numbers obtained with PhOK are higher. In fact, all substrates could be effectively coupled using 0.05 equivs. of $Pd(PPh_3)_4$, except for cyclohexanone **8** which required the use of 0.2 equivs. of catalyst for the reaction to reach completion within a reasonable amount of time (entry 7). Under these reaction conditions, **8** underwent cyclization to give **9** in 48% yield, together with small amounts of alkene **10**, formed by hydrodehalogenation of the starting material.[10]

A comparison of the reactions in entries 3 and 4 illustrates the dramatic influence of the base in these coupling processes. When KO-*t*-Bu was used as the base in the intramolecular coupling from **3**, considerable amounts of the elimination compound **5** were obtained (entry 4), but this side product was not observed when using PhOK in spite of the presence of a larger excess of base (entry 3).

As shown in entries 8 and 11, β-amino ketones **11** and **15**, which underwent retro-Michael fragmentation as the main reaction when KO-*t*-Bu was used, reacted under the new conditions to give the cyclization products in high yields. It is especially interesting to note that the cyclization reaction of β-amino ketone **11** takes place at a methine position to afford the azaspirocyclic ketone **12** in 70% yield (entry 8).

Additionally, even α-amino ketone **18** (entry 13), which failed to afford the cyclization product with KO-*t*-Bu, underwent the intramolecular coupling when using PhOK, although in low yield.

All reactions in Table 1 were conducted using an excess of PhOK, which was generated by reaction of 3 equivs. of PhOH and 2.5 equivs. of KO-*t*-Bu. However, it should be noted that no more than 1 equiv. of PhOK is required for these cyclization reactions. Thus, treatment of **1** with 5 mol % of $Pd(PPh_3)_4$, 1.3 equivs. of PhOH, and 1 equiv. of KO-*t*-Bu, gave the bridged ketone **2** in 95% yield.

On the other hand, neither the change of PhOK for PhONa nor the presence of water seems to have any significant effect on the course of the reaction. In fact, when using commercially available $PhONa \cdot 3\,H_2O$ (1.5 equivs.) instead of PhOK, under essentially the same reaction conditions, ketone **2** was obtained in 86% yield. On the contrary, the use of commercially available PhOLi (2.5 equivs.) resulted in long reaction times (48 h in refluxing THF) and afforded a lower yield (75%) of the cyclization product.

The alkenylation procedure reported here is easy to carry out and no special precautions need to be taken, although all cyclization reactions were conducted under an argon atmosphere. The protocol developed in this paper for the intramolecular α-alkenylation reactions of ketones is the most general with respect to the substrate scope. In this context, it should be noted that the reaction conditions developed by Cook for the intramolecular coupling of vinyl iodides and ketones [$Pd(OAc)_2$, PPh_3, Bu_4NBr, K_2CO_3, DMF-H_2O (9:1), 70 ^{0}C][3] were unsuccessful at promoting the coupling either from vinyl bromides **1** and **6**, which were recovered unchanged, or from vinyl iodide **3**, which afforded 4-(*N*-benzylamino)-cyclohexanone as the only reaction product.

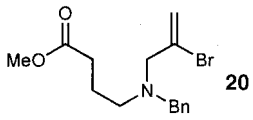
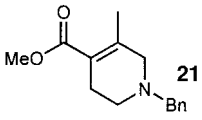
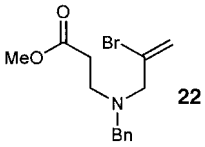
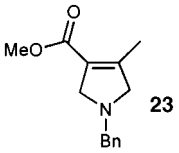
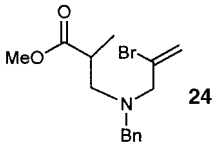
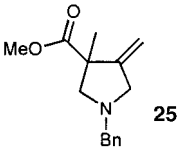
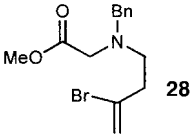
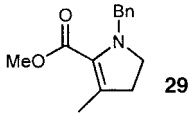
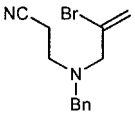
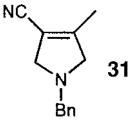
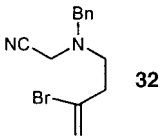
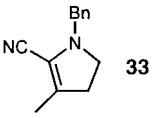
As PhOK was so effective in promoting the Pd-catalyzed intramolecular α-alkenylation of ketones, we decided to test its utility in the α-alkenylation of other enolate-type nucleophiles. As shown in Table 2, the intramolecular alkenylation process was extended to amino-esters[6,7,11–13] and aminonitriles.[14] Some examples of Pd-catalyzed intramolecular alkenylations involving cyclization at the α-methylene carbons of γ-, β-, and α-amino esters to afford six- and five-membered rings in moderate to good yields are reported (entries 1, 2, and 4). As already observed in the case of ketone alkenylations leading to monocyclic compounds (see entries 9–12 in Table 1), the initially formed annulation products underwent isomerization to the more stable conjugated enoates. However, in the ester series the oxidation of pyrrolines **23** and **29** to the corresponding pyrroles was not observed. Additionally, pyrrolidine **25** embodying a quaternary center was obtained, albeit in low yield, starting from an α-substituted ester (entry 3). It is worth mentioning that the use of KO-*t*-Bu as the base instead of PhOK in the case of amino esters always resulted in the decomposition of the starting material.

Finally, amino nitriles **30** and **32** underwent the Pd-catalyzed intramolecular α-alkenylation to give pyrrolines **31** and **33**, respectively, in moderate or good yields (entries 5 and 6), although longer reaction times were required. As in the ester series, no oxidation to the corresponding pyrroles was observed.

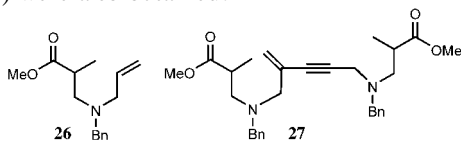
The effectiveness of PhOK in the Pd-catalyzed intramolecular alkenylation reactions presented herein is somewhat surprising since the pK_a of phenol is considerably lower than that of ketones, esters, and nitriles.[15] Although weak bases (e.g., K_3PO_4 and Cs_2CO_3) have been used in some Pd-catalyzed arylation[8,16,17] and alkenylation[3,4a,b] reactions, PhOK could play an additional role in these processes as can be seen in Buchwald's work, where phenol is used as a catalytic additive in some α-arylation reactions of ketone enolates. In line with Buchwald's proposal,[18] we thought that the intermediacy of a palladium phenoxide complex, which both stabilizes an otherwise unstable intermediate and facilitates the enolization by coordinating the carbonyl group, could be the most plausible explanation of the key role of phenoxide in these reactions.

Further studies directed to extend this methodology to the intramolecular alkenylation and arylation of other stabilized carbanions and to gain deeper insights into the role of phenoxide in these processes are in progress in our laboratory and will be reported in due course.

Table 2. Pd-catalyzed intramolecular coupling of vinyl halides with esters and nitriles.[a, b]

Entry	Substrate	Time	Products/yield[c]	
1	 **20**	15 h[d]	 **21**	42%[e]
2	 **22**	3 h	 **23**	74%
3	 **24**	24 h[d]	 **25**	24%[f]
4	 **28**	16 h	 **29**	79%
5	 **30**	8 h	 **31**	70%
6	 **32**	63 h[d]	 **33**	49%

[a] For the preparation of substrates and NMR data of the cyclization products, see Supporting Information.
[b] KO-*t*-Bu (2.5 equivs.), PhOH (3 equivs.), $Pd(PPh_3)_4$ (0.05 equivs.), THF reflux.
[c] Yields refer to pure isolated products of reactions on 0.15–0.25 mmol scale.
[d] $Pd(PPh_3)_4$ (0.1 equiv.).
[e] *N*-Benzyl-2-pyrrolidinone (19%) was also isolated.
[f] Allylamine **26** (3%) and dimer **27** (5%) were also obtained:



Experimental Section

Representative Procedure for the Pd-Catalyzed Intramolecular Coupling of Amino-Tethered Vinyl Halides with Ketones, Esters, and Nitriles

To a stirred solution of ketone **11** (51 mg, 0.15 mmol) and phenol (42 mg, 0.45 mmol) in freshly distilled THF (5 mL) were added under argon *t*-BuOK (0.37 mmol, 0.37 mL of 1 M solution in *tert*-butyl alcohol) and $Pd(PPh_3)_4$ (9 mg, 0.008 mmol). The solution was heated at reflux for 5 h. After being cooled to room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and 1 N aqueous NaOH. The organic layer was dried and concentrated. The residue was purified by flash chromatography (SiO_2, from CH_2Cl_2 to 98:2 CH_2Cl_2/MeOH) to give ketone **12**; yield: 27 mg (70%).

Acknowledgements

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References and Notes

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