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Palladium-Catalyzed [4+2] and [5+2] Annulation for the Synthesis of Tetrahydroquinolines and 1,4-Benzoxazepines

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Abstract: Palladium-catalyzed [4+2] and [5+2] annulations of propargyl carbonates with malonate-tethered anilines and 2-aminobenzylic alcohols were developed, giving the corresponding tetrahydroquinolines and 1,4-benzoxazepines, respectively, in good to excellent yields.

Tetrahydroquinoline and benzoxazepine derivatives are ubiquitous structural motifs in numerous bioactive products and pharmaceuticals (Figure 1).[1] Consequently, significant attention has been devoted to the synthesis of these molecules. Many synthetic methods for tetrahydroquinolines have been developed, including hydrogenation of quinolines,[2] aza-Diels-Alder reactions,[3] and Reissert-type reactions.[4] Benzoxazepines can be accessed by Beckmann or Schmidt rearrangements,[5] transition-metal catalyzed cross-coupling.[6]

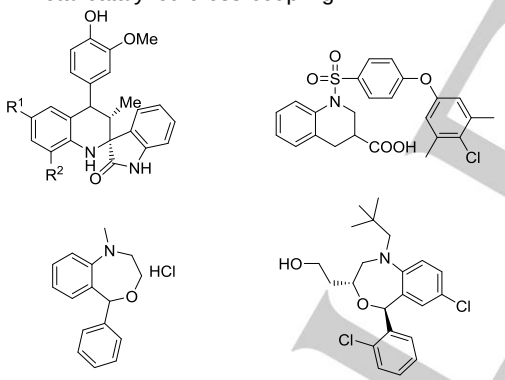
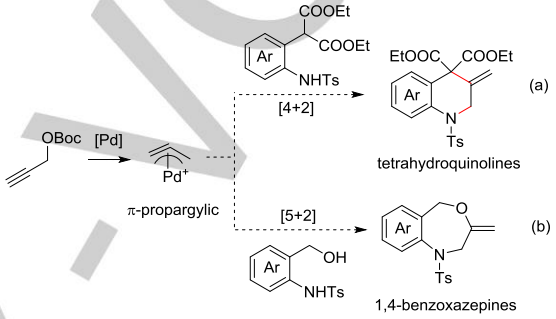


Figure 1. Selected biologically active tetrahydroquinolines and 1,4-benzazepines.

The palladium-catalyzed cyclization of propargylic compound,[7] particularly of propargylic carbonates,[8] via the key intermediate of π-propargyl palladium has been well developed for the synthesis of various cyclic compounds. In this paper, we reported a palladium-catalyzed [4+2] annulation of propargylic carbonates with malonate-tethered anilines[9] to give tetrahydroquinoline (Scheme 1, reaction a). The corresponding [5+2] annulation of propargylic carbonates with 2-aminobenzylic alcohols to give 1,4-benzoxazepines was also realized (Scheme 1, reaction b).



Scheme 1. Palladium catalyzed annulations for the synthesis of tetrahydroquiolines and 1,4-benzoxazepines.

The model reaction of malonate-tethered aniline **1a** and propargyl carbonate **2a** was investigated under palladium catalysis (Table 1). We were happy to find the desired [4+2] annulation product **3a** was formed in 62% NMR yield when the reaction was carried out using 10 mol% Pd_2dba_3•$CHCl_3$ and 20 mol% DPPF as the catalyst and ligand at 80 °C in toluene (entry 1). A series of bisphophine ligands were then screened (entries 2-7) and DPPP performed best to give **3a** in 92% yield (entry 3). Lowering the reaction temperature to 40 °C decreased the yield (entry 8). Screening of the solvent revealed that 1,4-dioxane was the best of choice, giving **3a** in near-quantitative yield (entries 8-10). The excellent yield (99%) was kept when the loading of palladium catalyst was reduced to 3 mol% (entry 11). Further reducing of the loading of Pd catalyst to 1 mol% resulted in decreased yield (70%, entry12). Other typical metal complex, such as $Pd(OAc)_2$, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and $Ni(cod)_2$ could not give better results (entries 13-15). Control experiments revealed that the reaction did not occur in the absence of palladium or ligand (entries 16-17).

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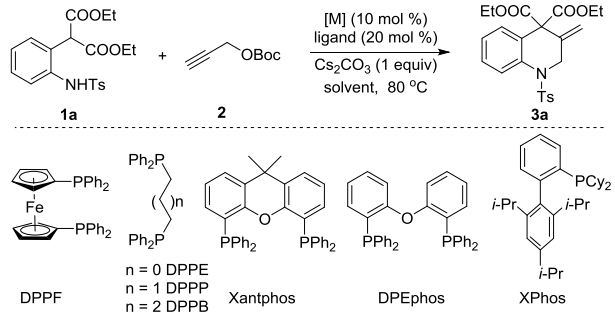
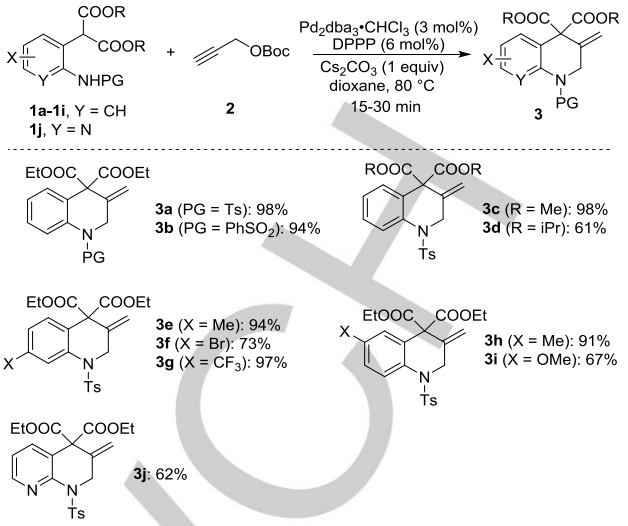
Table 1. Optimization of the Reaction Conditions. [a]



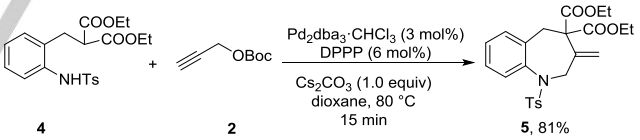
Entry	[M]	Ligand	Solvent	Yield (%)[b]
1	$Pd_2dba_3{\cdot}CHCl_3$	DPPF	toluene	62
2	$Pd_2dba_3{\cdot}CHCl_3$	DPPE	toluene	89
3	$Pd_2dba_3{\cdot}CHCl_3$	DPPP	toluene	92
4	$Pd_2dba_3{\cdot}CHCl_3$	DPPB	toluene	80
5	$Pd_2dba_3{\cdot}CHCl_3$	Xantphos	toluene	24
6	$Pd_2dba_3{\cdot}CHCl_3$	DPEphos	toluene	31
7	$Pd_2dba_3{\cdot}CHCl_3$	XPhos	toluene	24
8[c]	$Pd_2dba_3{\cdot}CHCl_3$	DPPP	toluene	70
9	$Pd_2dba_3{\cdot}CHCl_3$	DPPP	THF	98
10	$Pd_2dba_3{\cdot}CHCl_3$	DPPP	dioxane	>99
11[d]	$Pd_2dba_3{\cdot}CHCl_3$	DPPP	dioxane	>99 (98[e])
12[f]	$Pd_2dba_3{\cdot}CHCl_3$	DPPP	dioxane	70[e]
13[d]	$Pd(OAc)_2$	DPPP	dioxane	37
14[d]	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	DPPP	dioxane	70
15[d]	$Ni(cod)_2$	DPPP	dioxane	10
16	/	DPPP	dioxane	0
17	$Pd_2dba_3{\cdot}CHCl_3$	/	dioxane	0

[a] Reaction condition: **1a** (0.2 mmol, 83.0 mg), **2a** (0.26 mmol, 40 μL), Cs_2CO_3 (0.2 mmol), $Pd_2dba_3{\bullet}CHCl_3$ (0.02 mmol), ligand (0.04 mmol), N_2 atmosphere. [b] NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [c] The reaction was conducted at 40 °C. [d] 3 mol % [M] and 6 mol % ligand were used. [e] Isolated yield. [f] 1 mol% [M] and 2 mol% ligand were used.



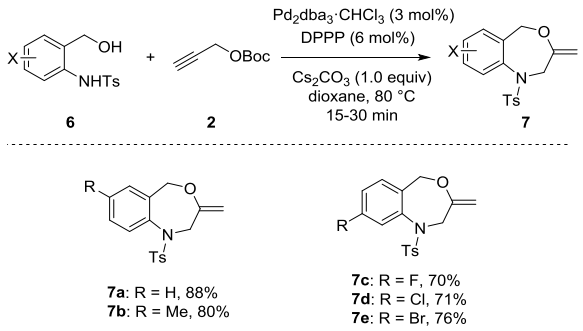
Scheme 2. Synthesis of tetrahydroquinolines **3**.

With the optimized condition in hand, a series of malonate-tethered anilines was then tested for the palladium catalyzed [4+2] annulation reaction (Scheme 2). It was found that the N-benzenesulfonyl group worked as well as the *N*-tosyl group, giving the corresponding tetrahydroquinoline (**3b**) in high yield. Besides diethyl, dimethyl malonate-tethered anilines worked as well (**3c**), while diisopropyl malonate resulted in some decreased yield (**3d**). Both electron-donating groups and electron-withdrawing groups were well tolerated on the anilines, giving the corresponding products (**3e**-**3i**) in good to high yields. Interestingly, the malonate-tethered 2-aminopyridine (**1j**) worked as well to give the corresponding tetrahydronaphthyridine **3j** in good yield, which is a core structure for various bioactive compounds.[10]



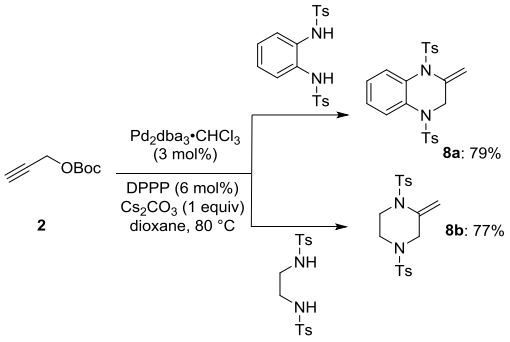
Scheme 3. Synthesis of benzazepine **5**.

The [5+2] annulation of malonate-tethered aniline **4** with one more carbon linkage was also carried out in the standard conditions, which afforded the desired benzazepine **5** in 81% yield (Scheme 3).



Scheme 4. Synthesis of 1,4-benzoxazepines **7**.

The investigation was continued by using 2-amino benzyl alcohol **6** as the 1,5-bisnucleophile for the reaction, which led to synthesis of the corresponding 1,4-benzoxazepines (**7a**-**7e**) in good yields (Scheme 4).[11]



Scheme 5 Synthesis of piperazines

In addition, the reaction of benzene-1,2-diamine and ethane-1,2-diamine worked well for the reaction, giving the corresponding piperazines **8a** and **8b**, respectively, in good yields (Scheme 5).[8h]

The structure of compound **3c** was determined by X-ray analysis of its single crystal (Figure 2).[12]

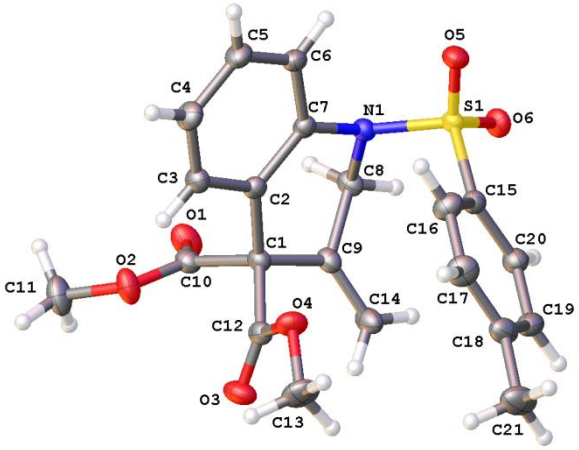
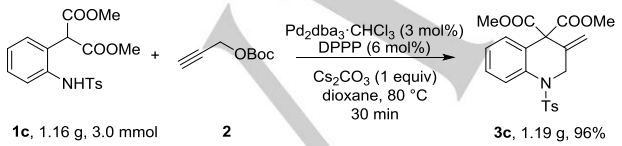
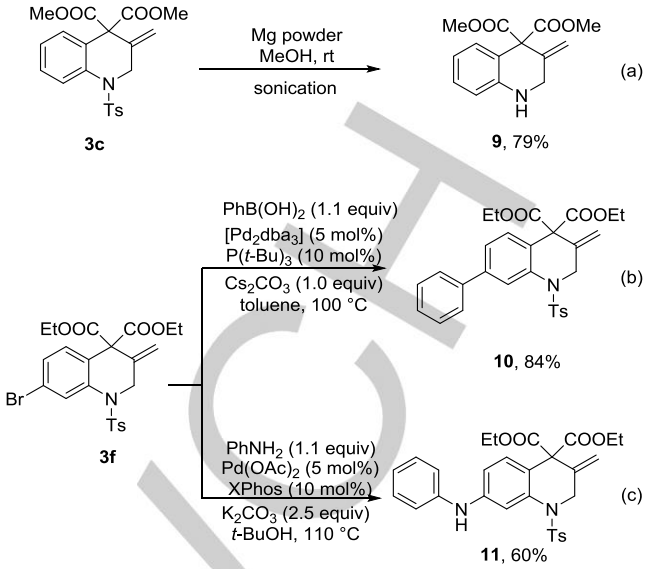


Figure 2. X-ray structure of **3c**



Scheme 6. Scale up reaction.

The reaction could be easily scaled up to 3.0 mmol, giving the tetrahedroquinoline **3c** in 1.19 g, 96% yield (Scheme 6).



Scheme 6. Further chemical transformations.

The resulted highly functionalized tetrahydroquinolines affords many possible further chemical transformations. For example, the *N*-tosyl group in compound **3c** could be removed by Mg/MeOH (Scheme 6, reaction a). Compound **3f** could readily undergo the cross-coupling reactions with phenylboronic acid and aniline to give the corresponding products **10** and **11**, respectively, in good to high yields.[13]

In summary, the palladium-catalyzed [4+2] and [5+2] annulations of propargyl carbonate with malonate-tethered anilines and 2-aminobenzylic alcohol were developed, giving the corresponding tetrahydroquinolines and 1,4-benzoxazepines, respectively, in good to high yields. The reaction features ready available starting materials, efficient construction of six- and seven-membered heterocycles with potential bioactivities.

Acknowledgements ((optional))

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Keywords: Tetrahydroquinolines • 1,4-Benzoxazepines • Annulation • Palladium Catalysis • Propargyl carbonates

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[12] CCDC 1994587 (**3c**) contains the supplementary crystallographic data for this paper.

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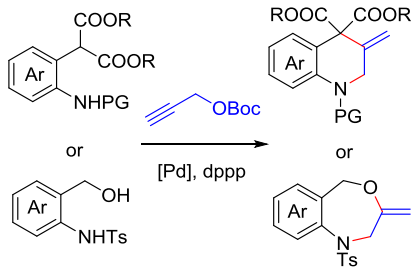
Entry for the Table of Contents

Key Topic: N-heterocycles Synthesis



A general strategy for the synthesis of tetrahydroquinolines and 1,4-benzoxazepines has been developed via palladium-catalyzed [4+2] and [5+2] annulations of propargyl carbonates with malonate-tethered anilines and 2-aminobenzylic alcohols. A series of six- and seven-membered heterocycles with potential bioactivities was obtained in good to excellent yields.

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