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Totally regio- and stereoselective synthesis of (*E*)-3-arylidene-3,4-dihydro-2*H*-1,4-benzoxazines under palladium catalyst

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ABSTRACT

A new, one-pot palladium catalyzed reaction has been developed for the general synthesis of (*E*)-3-arylidene-3,4-dihydro-2*H*-1,4-benzoxazines at room temperature. The reaction procedure tolerates various functional groups. The method is characterized by regio- and stereoselectivity, operational simplicity, mild reaction conditions, and short reaction time.

The development of simplified and efficient reaction protocol using palladium catalysts for the synthesis of various heterocyclic scaffolds has attracted a great deal of attention in recent years. Towards this end, selection of appropriate catalyst and reaction conditions are two challenging tasks. Heterocyclic compounds, possessing heteroatoms at C1 and C4 and fused with an aromatic ring, are important targets because of their wide range of biological and therapeutical properties.[1] Notably, 2*H*-1,4-benzoxazine represents an important heterocyclic core, as several of its derivatives are shown to display a wide range of activities such as anticancer,[2a] antihypertensive,[2b] antirheumatic,[2c] serotonin-3(5-HT_3) receptor antagonist,[2d] neuroprotective antioxidant[2e] and other activities.[2f,g] 1,4-Benzoxazine structural motif is also found in the secondary metabolites of gramineous plants and plays a key role in the defense of the germinating stage of maize, wheat and rye against the attack of insects, fungi, bacteria and other pathogens.[3]

In particular, the 3-substituted-3,4-dihydro-2*H*-1,4-benzoxazines have been integral parts of bioactive natural products,[4a] potent drugs,[4b] and important building blocks[4c,d] which are used in the synthesis of fascinating molecules of therapeutic interests. The substitution and stereochemistry at C3 position of 3,4-dihydro-2*H*-1,4-benzoxazines play important role in pharmacological activities.[5] In recent past, a 3-(ylidene)-1,4-benzoxazine derivative **1** (Fig. 1) have been reported as a potential useful agent for treating the infections caused by *Mycobacterium* species.[6]

Emergence of such promising results has stimulated investigations into the synthesis of 1,4-benzoxazines and their various derivatives, using mostly conventional methods[7] and few modern palladium catalyzed reactions.[8] Although there are many reports about the synthesis of 2*H*-1,4-benzoxazines, the stereoselective synthesis of 2- or 3-ylidene-3,4-dihydro-2*H*-1,4-benzoxazines **2** (Fig. 1), which could provide biologically attractive chiral analogs (upon asymmetric hydrogenation[9a]) and other important building blocks, are only few in numbers.[9] Among these, the palladium catalyzed synthesis of the *Z*-isomers of compound **2** was demonstrated recently by Kundu[9b] followed by Zhou[9a] under multi-step reactions. However, to the best of our knowledge there is no report on the general synthesis of the *E*-isomers of 3-arylidene-3,4-dihydro-2*H*-1,4-benzoxazines **2** in one-pot under palladium catalyst.

As part of our efforts in the field of palladium catalyzed reactions[10] for the development of efficient strategies for accessing privileged heterocycles, we have reported very recently the synthesis of 1,4-benzoxazine fused with triazoles.[10b] We envisaged that the development of straightforward and general method for the stereoselective synthesis of the (*E*)-3-arylidene-3,4-dihydro-

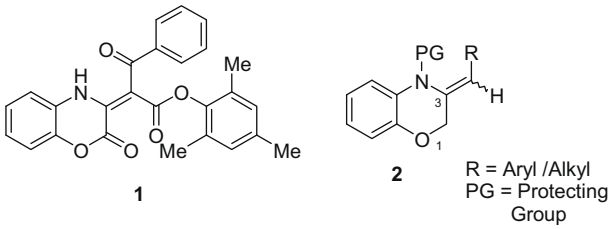

Figure 1.

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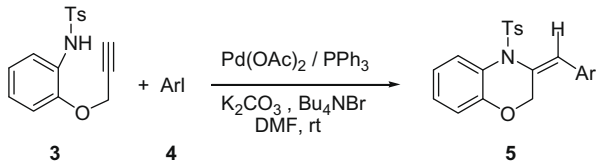
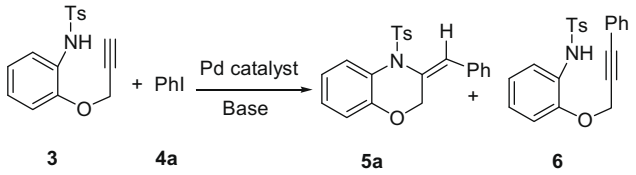


Scheme 1. Palladium catalyzed synthesis of (*E*)-3-arylidene-3,4-dihydro-2*H*-1,4-benzoxazines.

2*H*-1,4-benzoxazine **5** could be realized through the palladium catalyzed reaction of *N*-tosyl-2-(prop-2′-ynyloxy)aniline **3** and aryl iodide **4**. The strategy appeared to be viable by choosing appropriate catalyst and reaction conditions (Scheme 1). We are reporting herein the preliminary results obtained so far towards this goal.

Encouraged by the remarkable advancement of Sonogashira coupling[11a,b] and its spectacular applications in various heteroannulation strategies,[11c,d] we initially studied the reaction of the readily available acetylenic substrate **3** with phenyl iodide (**4a**) under Sonogashira's catalyst system [$Pd(PPh_3)_2Cl_2$/CuI], targeting the heteroannulated product **5a** (Table 1). However, it furnished the desired product **5a** only in low yield (14%) along with the acyclic product **6** with 35% yield (Table 1, entry 1). In order to obtain more appropriate reaction conditions, we examined a variety of conditions for the reactions of acetylene **3** with phenyl iodide (**4a**) by employing different palladium catalysts, bases, solvents and other parameters. Some selected data are presented in Table 1. Towards this endeavor, replacing $Pd(PPh_3)_2Cl_2$ by $Pd(OAc)_2/PPh_3$ (Table 1, entry 2) afforded (56%) only the acyclic product **6**, which could not be converted to the cyclized product **5a** even after heating the reaction mixture at 90 °C for several hours. Realizing that the formation of acyclic product **6** is occurring through Sonogashira's pathway,[11a,b] we decided to eliminate the CuI from the reaction mixture. Indeed removal of CuI and also employment of Et_3N as base, suppressed the formation of product **6** but the desired product **5a** was still isolated with poor (15%) yield (Table 1, entry 3). Gratifyingly, changing the base to K_2CO_3 along with phase-transfer catalyst (Bu_4NBr) furnished exclusively the cyclized product **5a** with 69% yield (Table 1, entry 4). However, removal of PPh_3 dropped the product yield to 22% (Table 1, entry 5), indicating its importance in the product formation. Further change of catalyst to $Pd(PPh_3)_4$ diminished the product yield to 50% (Table 1, entry 6). Employment of $PdCl_2/PPh_3$ as catalytic system furnished the product **5a** (61%) at elevated temperature (80 °C) only (Table 1, entry 7). Substituting $PdCl_2$ with Pd/C, used frequently in various heteroannulations,[12] gave low yield of the product **5a** (Table 1, entry 8). Thus, combination of $Pd(OAc)_2$ and PPh_3 appeared to be the catalyst of choice. Screening of a wide range of bases (all are not shown in Table 1) led to identification of K_2CO_3 as the best option. Among the different solvent systems examined, DMF appeared to be superior to the others. The aforementioned heteroannulation proceeded well at room temperature. The tosyl group attached with amine functionality of **3** was found to be essential for the reaction to proceed. Neither free nor otherwise protected

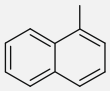
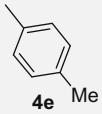
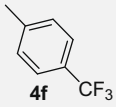
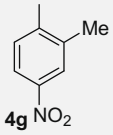
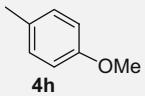
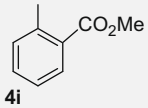
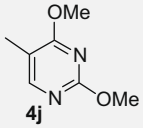
Table 1
Optimization of reaction conditions for the synthesis of **3a**[a,b]



Entry	Catalyst	Co-catalyst	Base	Time (h)	Yield (%)	
					5a	**6**
1	$Pd(PPh_3)_2Cl_2$	CuI	K_2CO_3	8	14	35
2	$Pd(OAc)_2/PPh_3$	CuI	K_2CO_3	2	0	56
3	$Pd(OAc)_2/PPh_3$	—	Et_3N	16	15	30
4	**$Pd(OAc)_2/PPh_3$**	**—**	**K_2CO_3**	**2**	**69**	**0**
5	$Pd(OAc)_2$	—	K_2CO_3	4	22	0
6	$Pd(PPh_3)_4$	—	K_2CO_3	3	50	0
7[c]	$PdCl_2/PPh_3$	—	K_2CO_3	5	61	0
8[c]	Pd/C, PPh_3	—	K_2CO_3	5	14	0

[a] *N*-Tosyl-2-(prop-2′-ynyloxy)aniline **3** (1.0 equiv), phenyl iodide **4a** (1.15 equiv), palladium catalyst (0.05 equiv), PPh_3 (0.2 equiv), CuI (0.1 equiv, entries 1 and 2 only), Bu_4NBr (0.1 equiv), base (4.0 equiv) in dry DMF at rt (except entries 7 and 8).
[b] Rt represents the temperature between 35 and 40 °C.
[c] Reaction was heated at 80 °C.

Table 2
Substrate scope for the palladium catalyzed synthesis of 3-arylidene-2*H*-1,4-benzoxazines **5**[a]

Entry	Iodide (ArI) Ar	Time[b]	Products[c] **5**	Yield (%)
1	 **4a**	2 h	**5a**	69
2	 **4b**	3 h	**5b**	71
3	 **4c**	2.5 h	**5c**	70
4	 **4d**	2 h	**5d**	78
5	 **4e**	2.5 h	**5e**	38
6	 **4f**	5 h	**5f**	51
7	 **4g**	2.5 h	**5g**	55
8	 **4h**	5 h	**5h**	58
9	 **4i**	3.5 h	**5i**	74
10	 **4j**	5.5 h	**5j**	68

[a] Acetylene **3** (0.5 mmol), iodide **4** (0.57 mmol), $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.1 mmol), K_2CO_3 (2.0 mmol), Bu_4NBr (0.05 mmol) in DMF (4 ml) at room temperature (35–40 °C).
[b] Time indicated the completion of the reaction as monitored through TLC.
[c] Satisfactory spectroscopic and analytical data were obtained for all new products.

(Boc, $COCF_3$, Me etc.) amine did respond to the reaction. Tetrabutylammonium bromide (Bu_4NBr) was necessary for this reaction.

Having demonstrated the optimum reaction conditions and catalyst (Table 1, entry 4), we next turned our attention to explore the scope and generality of this transformation (Table 2). To assess the impact of different structural motifs on the reaction, we examined various iodides **4** having different functional groups (e.g., nitro, ester, methyl, trifluoromethyl, methoxy, etc.) which were found to be tolerant to the reaction conditions. Apparently, heteroaryl iodides afforded better product yields compared to simple aryl iodides. Similarly, electron-withdrawing groups present in aryl iodide **4** facilitated the reactions compared to electron-donating groups. This method was found to be completely regio- and stereoselective. No formation of seven membered ring product via 7-*endo-dig* mode or of products with *Z*-stereochemistry was observed. The spectral and analytical data[13] of products **5** were in accordance with the assigned structures. In ^1H NMR, the olefinic proton appeared in downfield (δ_H >7 ppm) due to the deshielding effect of the *N*-tosyl group, indicating the *E*-stereochemistry of the exocyclic double bond. The chemical shifts (δ_H) of the olefinic proton in the *Z*-isomers of **5** have earlier been reported[9b] in the range between 6 and 7 ppm. Further evidence in favor of *E*-stereochemistry came from NOE experiments and $^3J_{CH}$ coupling constant value between the vinylic proton and methylenic carbon (OCH_2) of 1,4-oxazine ring. In literature,[14] $^3J_{CH}$ values less than 5 Hz or more than 7 Hz were attributed to *Z*- or *E*-isomer, respectively. In our case, $^3J_{CH}$ values of the isolated products were between 7 and 8 Hz, supporting *E*-stereochemistry. Finally, single crystal X-ray analysis[15] of product **5d** (for ORTEP diagram see Supplementary data) confirmed the stereochemistry and structure simultaneously.

The reaction proceeded through activation of the triple bond of substrate **3** followed by concurrent cyclization leading to the product **5** with *E*-stereochemistry.[16]

In conclusion, we have developed a general and practical methodology that provides rapid access to a variety of (*E*)-3-arylidene-1,4-benzoxazines with moderate to excellent yields at room temperature. The methodology uses readily available inexpensive starting materials and is characterized by regio- and stereoselectivity, operational simplicity, mild reaction conditions and short reaction time. This method may find applications in synthetic organic chemistry and medicinal chemistry as well.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.081.

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13. *General procedure for the synthesis of (E)-3-arylidene-4-tosyl-3,4-dihydro-2H-[1,4]benzoxazine* (**5**): $Pd(OAc)_2$ (4 mg, 5 mol %) and PPh_3 (20 mg, 20 mol %) were dissolved in dry DMF (3 mL) under argon atmosphere and stirred magnetically for 10 min. Then aryl iodide **4** (0.382 mmol) dissolved in dry DMF (2 mL) was added slowly to the reaction mixture followed by the addition of K_2CO_3 (183 mg, 1.329 mmol) and *n*-Bu_4NBr (11 mg, 0.033 mmol). After stirring of another 10 min, the acetylenic compound **3** (0.332 mmol) was added and the whole reaction mixture was allowed to stir at room temperature (35–40 °C) under argon atmosphere. After completion of the reaction (monitored by TLC), the solvent was removed in vacuum; the crude residue was diluted with water (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100–200 mesh) column chromatography using ethyl acetate-petroleum ether (2:98 to 30:70, v/v) as eluent to furnish the desired product **5**. *(E)-3-[(Naphthalen-1-yl)methylidene]-4-tosyl-3,4-dihydro-2H-1,4-benzoxazine* (**5b**): Yield: 71%; white solid, mp: 154–156 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 4.05 (s, 2H), 6.77 (d, *J* = 8.1 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.18–7.25 (m, 3H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.53–7.61 (m, 4H), 7.75 (s, 1H), 7.86 (t, *J* = 9.1 Hz, 2H), 7.96 (d, *J* = 7.8 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.58, 61.98, 117.08, 121.16, 124.93, 124.99, 125.16, 125.89, 126.36, 126.44, 126.72, 126.75, 127.71, 128.36, 128.84, 129.78, 129.96, 130.56, 131.42, 131.84, 133.38, 134.51, 144.58, 147.29; IR (KBr, cm^{-1}) 3056, 1591, 1360, 1165; ESI-MS *m*/*z* 450.18 $[M+Na]^+$; Anal. Calcd for $C_{26}H_{21}NO_3S$: C, 73.04; H, 4.95; N, 3.28. Found: C, 73.09; H, 5.01; N, 3.24.
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15. Product **5d** was crystallized by slow evaporation from petroleum ether (bp. 60–80 °C); Crystal data: $C_{20}H_{17}NO_3S_2$, *M* = 383.47, orthorhombic P, space group P2(1)2(1)2(1), *a* = 6.2186(7) Å, *b* = 14.4311(19) Å, *c* = 20.025(2) Å, *V* = 1797.1(4) $Å^3$, *Z* = 4, D_{calcd} = 1.417 mg m^{-3}, *T* = 296(2) K, μ = 0.316 mm^{-1}, *F*(000) = 800, λ = 0.71073 Å, processed reflections 4426 and unique reflections 2282, Final *R* factor = 0.0463. The crystal data has been deposited at Cambridge Crystallographic Data Centre [CCDC No. 745154]. Copies of the data can be obtained free of charge via www.ccdc.ac.uk/conts/retrieving.html or CCDC, 12 union Road, Cambridge CB2 1EZ, UK.
16. *Mechanistically, the stereoselective (E) formation of product* **5** *can be explained as described in the following steps*: (a) generation of σ-arylpalladium(II) iodide ($ArPd^{II}I$) through oxidative addition of aryl iodide **3** to palladium(0) which is formed in situ from $Pd(OAc)_2$ and PPh_3; (b) activation of the triple bond of substrate **5** through the palladium of $ArPd^{II}I$; (c) intramolecular nucleophilic attack of NH-Ts on activated alkyne via *6-exo-dig* mode resulting in the formation of 1,4-benzoxazine ring with exo-methylene (at C3) attached with Pd^{II}-Ar moiety; (d) reductive elimination of palladium regenerates Pd(0) and affords the product **5** with *E*-stereochemistry.