Regio and Stereoselective Synthesis of (*E*)-4-Arylidene/alkenylidene-3-tosyloxazolidin-2-ones through Palladium-Catalyzed Reactions of Aryl Iodides/Vinyl Triflates with Propargyl Tosylcarbamates

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Abstract. The palladium-catalyzed reaction of aryl iodides/vinyl triflates with propargyl tosylcarbamates produces regio and stereoselectively (*E*)-4-Arylidene/alkenylidene-3-tosyloxazolidin-2-ones in moderate to good yields.

In recent years, synthetic approaches to functionalized N-substituted 4-methylene-2-oxazolidinones and (*Z*)-4-alkylidene-2-oxazolidinones have been reported.[1] Interest in these compounds arises from their importance as synthetic intermediates, since they are functionalized with enamine and allylic carbamate moieties.[2] Nevertheless, the stereoselective preparation of (E)-4-arylidene/alkenylidene-2-oxazolidinones **3** is still a challenge in organic chemistry.

As part of our ongoing interest in developing methods for the preparation of five-membered heterocycles[3] and based on the ability of the *in situ* generated σ-vinyl, σ-aryl, σ- acyl and σ-alkynylpalladium

Table 1. Preparation of (E)-4-Arylidene/alkenylidene-3-tosyloxazolidin-2-ones **3** from Aryl Iodides[a]/Vinyl Triflates[b] **2**

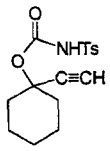
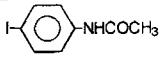
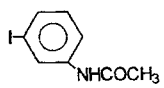
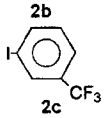
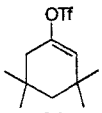
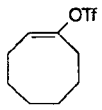
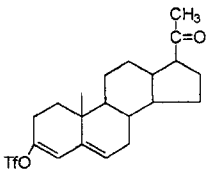
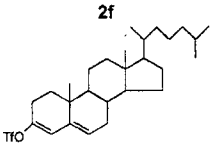
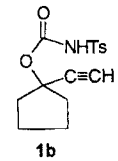
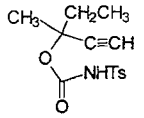
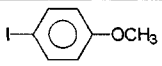
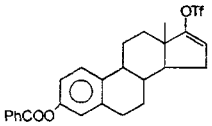
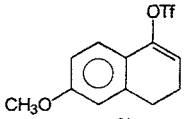
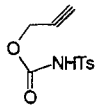
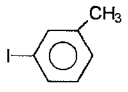
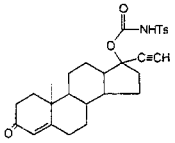
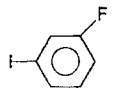
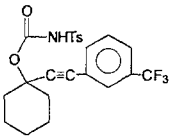
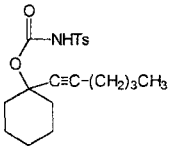
Entry	Compound 1	Compound 2	Reaction time h	2 :1 ratio	Recovered 3 (% yield)[c]
1	 **1a**	 **2a**	2	1	62 (10)[d] **3a**
2	"	 **2b**	4	1	50(30)[d] **3b**
3	"	 **2c**	2	2	70 (5)[d] **3c**
4	"	 **2d**	4	2	50 (14)[d] **3d**
5	"	 **2e**	3	2	65 (25)[d] **3e**
6	"	 **2f**	1	2	80 **3f**
7	"	 **2g**	2	2	68 **3g**
8	 **1b**	**2g**	2	2	58 **3h**

Table 1. (continued)

Entry	Compound 1	Compound 2	Reaction time h	2 :1 ratio	Recovered 3 (% yield)[c]
9	 **1c**	 **2h**	1	2.5	50 (18)[d] **3i**
10	"	 **2i**	0.5	2	64 **3j**
11	"	 **2j**	1	2	60 (30)[d] **3k**
12	 **1d**	 **2k**	1	3.5	65 **3l**
13	 **1e**	 **2l**	2.5	3	56 (7)[d] **3m**
14	 **1f**	**2h**	0.5	3	53 **3n**
15	 **1g**	**2k**	24	3	52 **3o**

[a]Unless otherwise stated, reactions were carried out at 60°C in DMF under a nitrogen atmosphere using the following molar ratios: **1**:K_2CO_3:$Pd(PPh_3)_4$= 1:5:0.02. [b]Unless otherwise stated, reactions were carried out at 60°C in DMF under nitrogen atmosphere using the following molar ratios: **1**:K_2CO_3:TBA^+Cl^- :$Pd(PPh_3)_4$=1:5:1:0.02. [c]Yields refer to single runs, are given for isolated products and are calculated on the basis of 1. All new products had satisfactory elemental analysis and spectral data were consistent with postulated structures. [d]Yield of 4.

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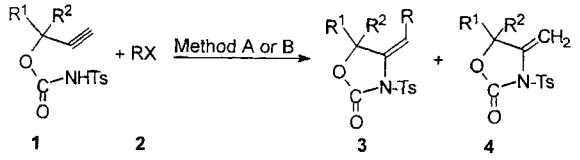
complexes to activate carbon-carbon triple bonds towards intramolecular nucleophilic attack[4], we decided to explore the use of propargyl tosylcarbamates **1** and aryl iodides/vinyl triflates[5] **2** as building blocks for the preparation of functionalized (*E*)-4-arylidene/alkenylidene-3-tosyloxazolidin-2-ones **3**.

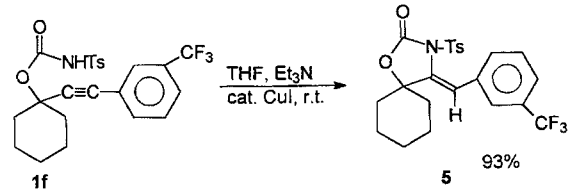
This transformation has now been achieved (Scheme 1) and the results obtained are summarized in Table 1.



R=Aryl, Vinyl; X=I, OTf
Method A: ArI, $Pd(PPh_3)_4$, K_2CO_3, DMF, 60°C
Method B: ROTf, TBA^+Cl^-, $Pd(PPh_3)_4$, K_2CO_3, DMF, 60°C

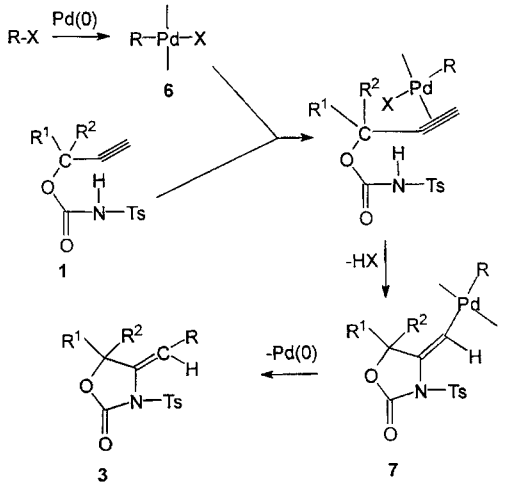
Scheme 1

A variety of aryl iodides (Method A) and vinyl triflates (Method B) were found to react with propargyl tosylcarbamates **1**, which undergo the palladium-catalyzed cycloamination to give regio and stereoselectively (*E*)-4-arylidene-3-tosyloxazolidin-2-ones **3**.[6] This reaction gave exclusively a single stereoisomer and the structure was assigned to be *E* on the basis of the chemical shifts of C-6 olefinic protons. Indeed, in order to clarify the stereochemical course for the cyclization of terminal acetylenic substrates, the (*Z*)- 4-arylidene-2-oxazolidinone **5** was prepared according to reference 1(Scheme 2). The vinylic proton in **3c** (δ 7.22, $CDCl_3$) is downfield from the vinylic proton in the *Z*-isomer **5** (δ 6.07,$CDCl_3$). Analogously, the vinylic proton of **3f** is downfield from the *Z*-isomer[7] (δ 6.50 vs 6.22, $CDCl_3$).



Scheme 2

The uniform (*E*)-selectivity might be as a consequence of *trans*-aminometallation across the triple bond thanks to the *in situ* generated σ-palladium complex **6**; the reductive elimination of Pd(0) from the σ-vinyl palladium complex **7** gave **3** (Scheme 3).



Scheme 3

Table 2. Palladium-catalyzed Reaction of Aryl Iodides/Vinyl Triflates **2** with Propargyl Tosylcarbamates **1**

Entry	1	2	Reaction time (h)	Ratio 2:1	Base	3 (%yield)[a]	4 (% yield)[a]
1	**1a**	**2a**	4	1	Et_3N	---	63
2	"	"	5	1	Na_2CO_3	7	50
3	"	"	6	1	KOAc	50	20
4	"	"	2	1	K_2CO_3	62	10
5	"	**2c**	2	2	Et_3N	---	quantitative[b]
6	"	"	2	2	K_2CO_3	70	5
7	**1e**	**2l**	3	1	K_2CO_3	30	20[c]
8	"	"	3	2.5	K_2CO_3	56	7[c]
9	**1a**	**2f**	1	1	K_2CO_3	45	35[d]
10	"	"	1	2	K_2CO_3	82[d]	---

[a]Unless otherwise stated, reactions were carried out in DMF, at 60°C; yields referred to single runs and are for pure, isolated products. [b]The reaction was carried out with and without the palladium-catalyst.[c] Method A; [d] Method B.

The regioisomeric six-membered cyclic carbamates were not obtained in any case: the preference of π-palladium complexes to produce five-*vs* six-membered rings has been reported[4] and IR spectral bands for compounds **3** were in agreement with reported frequencies for five-membered exocyclic derivatives. [1]

Best results were obtained using K_2CO_3 as base (Table 2).

In the presence of Et_3N, the 4-methylene-3-tosyloxazolidin-2-ones **4** represent the only products isolated (Table 2, entries 1, 5). To shed light on this point **1a** was treated with **2c** in DMF in the presence of the Et_3N, without the palladium catalyst, leading to the formation of **4a** in quantitative yield via a base-catalyzed addition[8] reaction of the nitrogen atom to the triple bond of the propargyl tosylcarbamate **1a**. The amounts of 4-methylene-3-tosyloxazolidin-2-ones **4**, usually obtained as side products even in the presence of K_2CO_3, could be reduced by increasing the **2:1** ratio (Table 2. entries 7-10). The regio and stereoselective preparation of (*E*)-4-alkenylidene-3-tosyloxazolidin-2-ones **3** from vinyl triflates and **1** was carried out by adding *n*-Bu_4NCl to the DMF/K_2CO_3/$Pd[P(Ph_3)]_4$ system. The triflate-chloride exchange has been reported to affect the reactivity and/or to enhance the reaction yield in a variety of palladium-catalyzed reactions of organotriflates.[9] In the present reaction, the involment of this mechanism along the reaction pathway is supported by the observation that in the absence of *n*-Bu_4NCl a more complex mixture is usually obtained. A reasonable working hypothesis envisions that, in the absence of chloride anions, the strongly electrophilic palladium of the σ-organopalladium triflate complex **6** could react with the nitrogen in the NHTos group[10] in **1** to give a σ-organopalladium complex that is prone to undergo side reactions.

Finally, the reaction of aryl iodides with internal acetylenic substrates **1f, g**, presumably does not change the stereoselective *trans*-aminopalladation pattern of the reaction, giving **3n,o** as the only steroisomers respectively. No attempts were made to determine their *E*-*Z* configuration.

In conclusion, the stereoselective heterocyclization described above provides an easy access to functionalised (*E*)-4-arylidene/alkenylidene-3-tosyloxazolidinon-2-ones. The utility of the present reaction may be apparent from the ready availability of the starting materials.

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(6) A typical procedure for (*E*)- 4- arylidene-3-tosyloxazolidin-2-ones **3** is as follows:a solution of **1a** (0.27 g, 0.84 mmol) in DMF (4 ml), 4-iodoacetanilide **2a** (0.22 g, 0.84 mmol), K_2CO_3 (0.58 g, 4.2 mmol) and $Pd[P(Ph)_3]_4$ (0.019 g, 0.017 mmol) was stirred at 60 °C for 2.0 h, under nitrogen atmosphere. Then the mixture was cooled, diluted with EtOAc and washed with water. The organic layer was dried over Na_2SO_4 and evaporated under vacuum. The residue was chromatographed on silica gel, eluting with *n*-hexane/ ethyl acetate (70/30 v/v) to afford 0.23 g of **3a** (62 % yield): mp 194-195 °C; IR (Kbr) 3310, 1805, 1670, 1600, 810, 670, 660 cm^{-1}; ^1H NMR δ 1.61-1.43 (m, 10 H), 2.18(s, 3H), 2.46 (s, 3H), 7.09(BB' part of an AA'BB' system, J=8.4 Hz), 7.15 (s, 1H), 7.40 (BB' part of an AA'BB' system, J=8.5 Hz), 7.56 (AA' part of AA'BB' system, J= 8.5 Hz), 7.97(AA' part of AA'BB' system, J= 8.4 Hz); ^{13}C NMR δ 21.1, 21.7, 24.0, 24.3, 35.1, 86.11, 111.2, 119.2, 127.9, 129.3, 129.4, 129.6, 134.3, 137.7, 138.4, 146.12, 150.4, 168.9; Ms, m/e (relative intensity) 454 (M^+, 4), 410 (4), 299 (74), 255(100), 91(75).

(7) The *Z*-isomer was prepared (90% yield) from the corresponding 3-substituted propargyl alcohol and *p*-toluenesulfonyl isocyanate using a CuI/Et_3N catalyst in dichloromethane at room temperature according to Ohe, K.; Ishihara, T.; Chatani, N.; Kawasaki, Y.; Murai, S. *J. Org. Chem.* **1991**, *56*, 2267. The 3-substituted propargyl alcohol derivatives (arylethynyl, dialkyl carbinols and dienylethynyl, dialkyl carbinols) can be easily prepared according to the previously described procedure (Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron* **1985**, *41*, 5121).

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