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Stereoselective sp^2–sp^2 bond formation via Negishi cross-coupling of vinylic tellurides and 2-heteroarylzinc chlorides

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Abstract—The Negishi cross-coupling reaction of vinylic- and aryltellurides with heteroarylzinc chlorides catalyzed by $PdCl_2$/CuI is described. This cross-coupling reaction is general and permits the formation of a new sp^2–sp^2 carbon bond in good yields and high stereoselectivity.

Vinylic tellurides are of importance due to their useful behavior as intermediates in organic synthesis, including the synthesis of natural products.[1] Of the two isomers, the *Z*-vinylic tellurides have been employed more frequently as intermediates because of easy availability of these species.[2] Recently a new application of *Z*-vinylic tellurides utilizing palladium-catalyzed cross-coupling has been described.[3] In this cross-coupling reaction they react as aryl or vinyl carbocations in a manner similar to vinyl halides or triflates in the Sonogashira et al.,[4] Heck and Dieck,[5] Suzuki,[6] and Stille and co-workers[7] cross-coupling reactions with palladium as catalyst.

In the last decade, there have been developments in Pd-catalyzed coupling systems as a consequence of great interest in the development of coupling substrates that are more economic, more easily accessible, and reactive even under mild conditions. In this way, the Negishi cross-coupling is a powerful and versatile method for the construction of new carbon–carbon bond that can be applied to alkyl, alkenyl, and alkynyl substrates.[8] To the best of our knowledge, however, no Negishi cross-coupling reaction using aryl or vinyl tellurides as substrate in the preparation of sp^2–sp^2 carbon–carbon bond has been described so far. Our continuing interest in the palladium-catalyzed cross-coupling of vinylic tellurides prompted us to examine the cross-coupling reaction of *Z*-, *E*-vinyl, and aryl tellurides **1a–c** with heteroarylzinc chlorides **2a–c** to obtain 2-vinyl- or aryl-heterocycles **3a–i** (Scheme 1).

Our initial efforts were focused on the reactivity of *Z*-vinylic telluride **1a** in the cross-coupling reaction with 2-furylzinc chloride **2a**, using Negishi conditions.[9] Thus, treatment of *Z*-vinylic telluride **1a** (1 equiv) with 2-furylzinc chloride **2a** (2 equiv) (prepared in situ by reaction of furan with *n*-BuLi in THF followed by addition of $ZnCl_2$), in THF/DMF at room temperature and using $Pd(PPh_3)_4$ (10 mol %) as catalyst, in presence of CuI (1 equiv), affords the corresponding 2-(*Z*-styryl)-furan **3a** only in low yield (42%) (Scheme 2).

In view of this disappointing result, we decided to investigate the best experimental conditions for this cross-coupling reaction. Firstly, we investigated the influence of the ligands in the palladium complex. As shown in Table 1, both Pd(0) and Pd(II) with different ligands, exhibit catalytic activity in this reaction (Table

$$R^1TeBu \; (\mathbf{1a\text{-}c}) + R^2ZnCl \; (\mathbf{2a\text{-}c}) \xrightarrow[\text{THF}]{\text{cat. } PdCl_2,\ CuI} R^1\text{–}R^2 \; (\mathbf{3a\text{-}i})$$

1a R^1 = (*Z*)-PhC=CH **2a** - R^2 = 2-furyl
1b R^1 = (*E*)-PhC=CH **2b** - R^2 = 2-thienyl
1c R^1 = Ph **2c** - R^2 = 2-pyridyl

Scheme 1.

Keywords: Vinylic tellurides; Palladium; Negishi cross-coupling.
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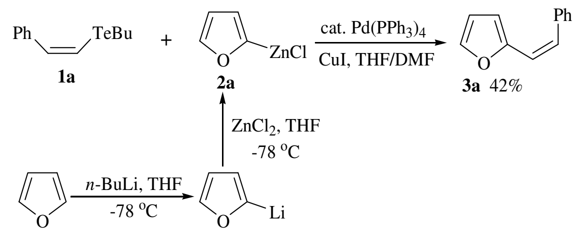


Scheme 2.

Table 1. Influence of catalyst in the reaction[a]

#	Catalyst (mol %)	Yield **3a** (%)[b]
1	$Pd(PPh_3)_4$ (20)	51
2	$Pd(PPh_3)_2Cl_2$ (20)	52
3	$Pd(OAc)_2$ (20)	45
4	$PdCl_2(dppe)$ (20)	47
5	$Pd(dba)_2$ (20)	54
6	$PdCl_2(PhCN)_2$ (20)	52
7	$PdCl_2$ (1)	17
8	$PdCl_2$ (5)	26
9	$PdCl_2$ (10)	35
10	$PdCl_2$ (20)	58

[a] All reactions were performed in presence of **2a** (2 equiv), **1a** (1 equiv), CuI (1 equiv), using THF/DMF as solvent, at room temperature for 24 h.
[b] Yields are given for isolated products.

1; entries 1–6) however, they gave unsatisfactory yields of the desired product **3a**.

The best yield in the preparation of 2-(*Z*-styryl)furan **3a** was obtained using $PdCl_2$ in absence of ligands (Table 1; entry 10) but this result was considered insufficient. We also observed that the cross-coupling reaction was greatly affected by increasing the amount of $PdCl_2$ from 1% to 20% (Table 1; entries 7–10).

The influence of other parameters such as the presence of copper salt, solvent, and base in the reaction was also investigated. When the reaction of *Z*-vinylic telluride **1a** (1 equiv) with 2-furylzinc chloride **2a** (3 equiv) using $PdCl_2$ as catalyst, was carried out in presence of CuI and using THF instead THF/DMF, **3a** was obtained in satisfactory yield (Table 2; entry 7).

On the other hand, the addition of bases such as Et_3N, Cs_2CO_3, K_2CO_3, and K_3PO_4 in the reaction did not improve the yields (Table 2; entries 1–4).

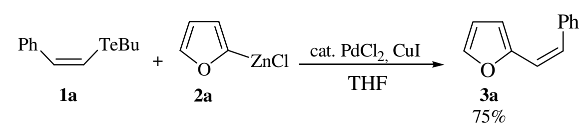
When the reaction was achieved with catalytic amount (Table 2; entry 8) or in absence of CuI (Table 2; entry 9), the desired product **3a** was also obtained in lower yield.

We observed that this cross-coupling reaction required the use of an excess of organozinc reagent (3 equiv). When 1 or 2 equiv of organozinc reagent were used unsatisfactory yields of **3a** were obtained (Table 2; entries 5 and 6). Thus, the careful analysis of the optimized reactions revealed that the optimum conditions for the coupling were found to be the use of *Z*-vinylic telluride **1a** (1 mmol) and 2-furylzinc chloride **2a** (3 equiv), $PdCl_2$ (20 mol %), CuI (1 mmol), in THF (7 mL), at room temperature. Using this reaction condition we are able to prepare the 2-(*Z*-styryl)furan **3a** in 75% (Scheme 3).

Table 2. Optimization of cross-coupling reaction of vinylic telluride **1a** with 2-furylzinc chloride **2a**

#	Condition	Yield **3a** (%)[a]
1	$PdCl_2$ (20%)/CuI (1 equiv) Et_3N (2 equiv)[b]	57
2	$PdCl_2$ (20%)/CuI (1 equiv) Cs_2CO_3 (2 equiv)[b]	57
3	$PdCl_2$ (20%)/CuI (1 equiv) K_2CO_3 (2 equiv)[b]	55
4	$PdCl_2$ (20%)/CuI (1 equiv) K_3PO4 (2 equiv)[b]	56
5	$PdCl_2$ (20%)/CuI (1 equiv) **2a** (1 equiv)	42
6	$PdCl_2$ (20%)/CuI (1 equiv) **2a** (2 equiv)	58
7	$PdCl_2$ (20%)/CuI (1 equiv) **2a** (3 equiv)	75
8	$PdCl_2$ (20%)/CuI (20%)	22
9	$PdCl_2$ (20%)	20

[a] Yields are given for isolated products.
[b] The reactions were performed in presence of **2a** (2 equiv).



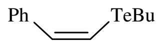
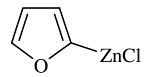
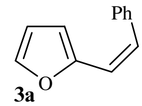
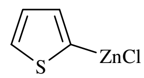
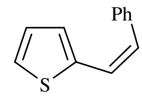
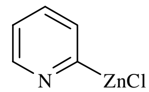
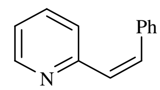
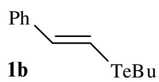
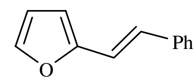
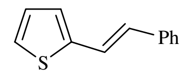
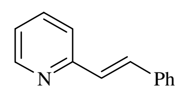
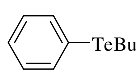
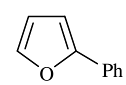
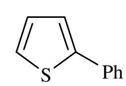
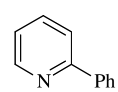
Scheme 3.

In order to demonstrate the efficiency of this cross-coupling reaction, we explored the generality of our method extending the coupling reaction to other vinyl or aryl tellurides as well as other heteroarylzinc chlorides and the results are summarized in Table 3.[10] It is worth mentioning that the reaction was carried out smoothly at room temperature with high selectivity, and **3a–i** were obtained in good yields.

Analysis of the ^1H and ^{13}C NMR spectra showed that all the obtained products presented data in full agreement with their assigned structures. The stereochemistry of the double bond was easily established. As an example, the ^1H spectrum of compound **3a** showed a doublet centered at 6.46 ppm with coupling constant of 12.6 Hz. The other vinylic hydrogen resonates at 6.35 ppm as a doublet, with a coupling constant of 12.6 Hz attributed to the *cis*-related olefinic hydrogens. The stereoisomeric purities of the product formed were identical to that of starting vinylic tellurides, proving the complete retention of configuration in this coupling.

In summary, we have explored the Negishi cross-coupling reaction of vinyl- and aryltellurides with heteroarylzinc chlorides catalyzed by $PdCl_2$/CuI and established a new stereoselective route to 2-vinyl- or aryl-heterocycles in good yields. The reaction proceeded cleanly

Table 3. Cross-coupling products obtained using vinylic tellurides **1a**–**c** and heteroarylzinc chlorides **2a**–**c**

#	Telluride	Heteroaylzinc chloride	Product	Time (h)	Yield (%)
1	 **1a**	 **2a**	 **3a**	32	75
2	**1a**	 **2a**	 **3b**	28	77
3	**1a**	 **2c**	 **3c**	36	72
4	 **1b**	**2a**	 **3d**	34	73
5	**1b**	**2b**	 **3e**	26	79
6	**1b**	**2c**	 **3f**	34	73
7	 **1c**	**2a**	 **3g**	30	69
8	**1c**	**2b**	 **3h**	28	74
9	**1c**	**2c**	 **3i**	32	71

under mild reaction conditions (room temperature) and was sensitive to nature of catalyst and solvent. We expect that these findings would be useful to assist in the choice to introduce a vinyl or aryl group at position 2 of the heterocycles.

Acknowledgements

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try for Organic Synthesis; Wiley and Sons: New York, 2002; Vols. 1 and 2; (c) Dabdoub, M. J.; Dabdoub, V. B.; Marino, J. P. *Tetrahedron Lett.* **2000**, *41*, 433–436; (d) Dabdoub, M. J.; Dabdoub, V. B.; Marino, J. P. *Tetrahedron Lett.* **2000**, *41*, 437–440.

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10. *Typical procedure for cross-coupling reaction*: A 25 mL, two-necked, round-bottom flask equipped with a magnetic stir bar, rubber septum, and argon was charged sequentially with $PdCl_2$ (0.035 g, 0.2 mmol), CuI (0.19 g, 1 mmol), THF (1 mL), and the appropriate aryl or vinyl tellurides **1a**–**c** (1 mmol). The mixture was stirred at room temperature for 10 min; then heteroarylzinc chloride **2a**–**c** (3.0 mmol) was transferred from other flask and added dropwise. The dark solution was stirred at room temperature for the time indicated in Table 3. After this time, the mixture was treated with aqueous ammonium chloride (30 mL) and CH_2Cl_2 (3×20 mL). The organic phase was separated and dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography. *Selected spectral and analytical data for:* **3a**-(Z)-2-styryl-furan: Yield: 0.127 g (75%). NMR ^{1}H: $CDCl_3$, 400 MHz, δ (ppm): 7.44–7.42 (m, 2H); 7.33–7.24 (m, 4H); 6.46 (d, $J = 12.60$ Hz, 1H); 6.35 (d, $J = 12.60$ Hz, 1H); 6.29 (dd, $J = 1.9$; 3.20 Hz, 1H); 6.23 (d, $J = 3.2$ Hz, 1H); NMR ^{13}C: $CDCl_3$, 100 MHz, δ (ppm): 152.10, 141.51, 137.39, 128.64, 128.08, 127.96, 127.30, 118.04, 111.15, 109.88. MS m/z (%) 170 (100), 93 (50), 77 (29), 67 (73). IR (KBr, film) ν 2927, 2860, 1742, 1479, 1435, 963. HRMS Calcd for $C_{12}H_{10}O$: 170.07316. Found: 170.07358. *Typical procedure for the preparation of heteroarylzinc chloride* **2a** and **2b**: *n*-Buthyllithium (3 mmol, 1.6 M in hexane, 1.87 mL) was added to a solution of the appropriated heterocycle (3 mmol) in THF (3 mL) at −75 °C and stirred for 45 min. After this time, a solution of anhydrous $ZnCl_2$ (3 mmol, in THF, 3 mL) was added and the mixture was warmed up to room temperature. After 10 min the compound **2a** or **2b** was used. *Typical procedure for the preparation of heteroarylzinc chloride* **2c**: *n*-Buthyllithium (3 mmol, 1.6 M in hexane, 1.87 mL) was added to a solution of 2-bromo pyridine (3 mmol, 0.29 mL) at −75 °C and stirred for 1 h. After this time the mixture was warmed up to room temperature and a solution of anhydrous $ZnCl_2$ (3 mmol, in THF, 3 mL) was added. After 15 min this compound was used.