



Negishi cross-coupling of organotellurium compounds: synthesis of biaryls, aryl-, and diaryl acetylenes

Hélio A. Stefani^{a,*}, Jesus M. Pena^a, Flávia Manarin^a, Rômulo A. Ando^b, Daiana M. Leal^a, Nicola Petragani^b

^a Departamento de Farmácia, Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, SP, Brazil

^b Instituto de Química, Universidade de São Paulo, São Paulo, SP, Brazil

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ABSTRACT

A functional group tolerant palladium-catalyzed Negishi coupling of diaryl tellurides with organozinc has been developed. This methodology permits efficient preparation of biaryls, aryl acetylenes and diaryl acetylenes in moderate to good yields. A preliminary study to gain further insight into the reaction was performed using in situ ReactIR technology.

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Introduction

Carbon–carbon bond formation is a major focus of research in organic synthesis. Tools for making such bonds are indispensable for the construction of complex molecules and intense efforts are continuously directed toward developing novel and selective bond-forming reactions.¹

The transition metal-catalyzed cross-coupling reaction of organometallics is a methodology widely used by many in the chemical community to produce products prevalent in pharmaceuticals, ligands, and materials. Extensive research has focused on a variety of ways to form C–C bonds using transition metal catalysts.²

The palladium-catalyzed Negishi cross-coupling, the reaction of aryl and vinyl halides/triflates with organozinc reagents, represents a powerful tool for the formation of carbon–carbon bonds in view of the ready availability and high functional group compatibility of organozinc compounds.³ Some particular examples of this type of cross-coupling reaction has been provided recently by a number of authors in the synthesis of tylocrebine,⁴ salmochelines,⁵ amythiamicin C and D,⁶ just to mention a few (Fig. 1).

On the other hand, organotellurium compounds have attained remarkable interest as synthons and intermediates in synthetic organic chemistry.⁷ In the current decade, organotellurium compounds have been identified as alternatives to halogens as electrophilic partners in some palladium-catalyzed cross-coupling

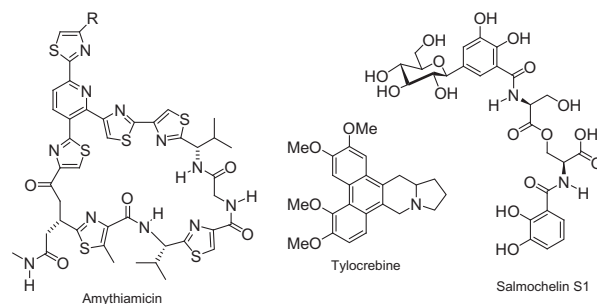


Figure 1. Structure of amythiamicin, tylocrebine and Salmocheline S1.

reactions, such as Heck,⁸ Negishi,⁹ Sonogashira¹⁰ and Suzuki–Miyaura.¹¹ Recently, we have reported the use of some organotellurium compounds in a Suzuki–Miyaura reaction employing potassium organotrifluoroborate salts as nucleophilic partners.¹¹ Until now, only a few studies on the coupling reaction of organozinc with organotellurides have been described.¹²

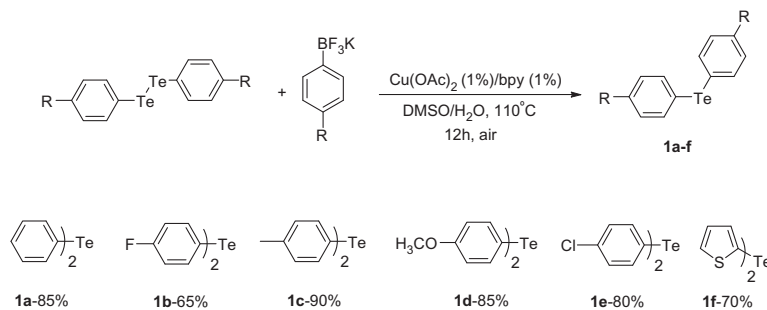
Herein, we report our success in accomplishing a sp^2 – sp^2 and sp^2 – sp Negishi coupling reaction between diaryl tellurides and organozinc reagents.

Results and discussion

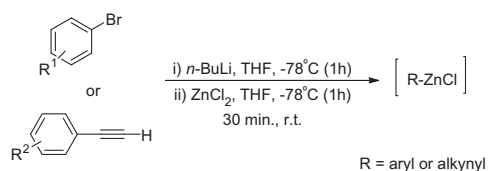
The diaryltelluride starting materials were prepared in good to excellent yields through the reaction of diarylditellurides¹³ with

* Corresponding author.

E-mail address: hstefani@usp.br (H.A. Stefani).



Scheme 1.



Scheme 2.

potassium aryltrifluoroborate salts bearing electron-withdrawing, electron-donating, and neutral substituents, using a catalytic amount of $\text{Cu}(\text{OAc})_2$ and bipyridine in $\text{DMSO}/\text{H}_2\text{O}$ in moderate to good yields^{14,15} (65–90%) (Scheme 1).

Following the Buchwald procedure,¹⁶ the organozinc reagent was prepared in situ from corresponding aryl bromides or arylalkynyl acetylene in dry THF. The resulting solution was cooled to -78°C , then *n*-butyllithium was added dropwise via a syringe through the septum, and the resulting solution was stirred at -78°C for 1 h. ZnCl_2 was added in one portion by removal of the septum (Scheme 2).

With the substrates in hand, we began our investigation on the optimization of the Pd source, additives and solvents.

Of the various palladium catalysts tested, $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ and $\text{PdCl}_2(\text{PPh}_3)_2$ proved to be most effective in terms of the

Table 1

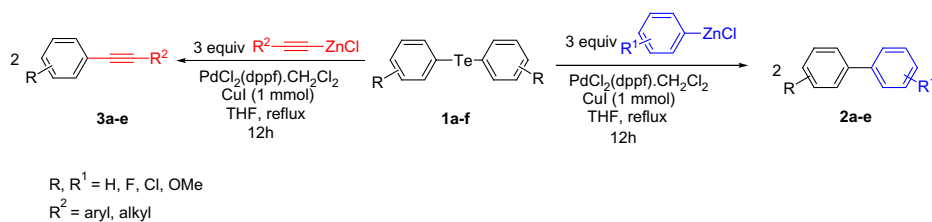
Screening of the catalyst in the Negishi reaction of diphenyltelluride with (4-methoxyphenyl)zinc(II) chloride

Entry	Pd Catalyst (10 mol %)	'Cu' (equiv)	Yield (%)
1	$\text{Pd}(\text{PEPPSI})$	CuI (1)	40
2	PdCl_2	CuI (1)	29
3	$\text{Pd}(\text{OAc})_2$	CuI (1)	15
4	$\text{Pd}(\text{PPh}_3)_4$	CuI (1)	45
5	$\text{PdCl}_2(\text{PPh}_3)_2$	CuI (1)	83
6	$\text{Pd}_2(\text{dba})_3$	CuI (1)	23
7	No catalyst	—	—
8	$\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$	CuI (1)	88
9	$\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$	CuI (0.5)	34
10	$\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$	$\text{Cu}(\text{OAc})_2$ (1)	29
12	$\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$	CuCN (1)	38
13	$\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$	CuCl (1)	56
14	$\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$	$\text{CuSO}_4\cdot 5\text{H}_2\text{O}$ (1)	27

product yield and reaction rate (88% and 83%, respectively). $\text{Pd}(\text{OAc})_2$, PdCl_2 , $\text{Pd}_2(\text{dba})_3$, $\text{Pd}(\text{PEPPSI})$, $\text{Pd}(\text{PPh}_3)_4$ were found to be less efficient, affording the coupled product in 15–45% yield. No reaction took place in the absence of a catalyst (Table 1).

Table 2


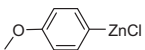
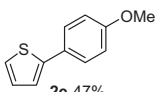
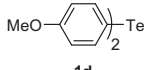
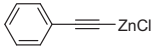
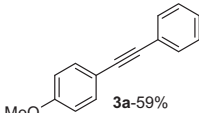
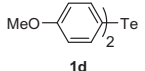
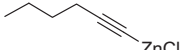
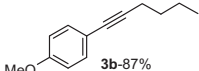

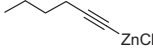
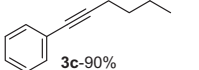
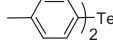
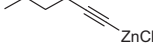
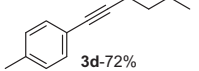
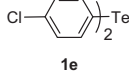
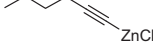
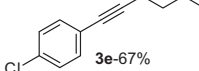
Negishi cross-coupling reaction of diaryltellurides and organozinc reagents



Entry	Telluride	Organozinc	Product/Yield (%)
1			 2a-88%
2			 2b-67%
3			 2c-72%
4			 2d-32%

(continued on next page)

Table 2 (continued)

Entry	Telluride	Organozinc	Product/Yield (%)
5	 1f		 2e-47%
6	 1d		 3a-59%
7	 1d		 3b-87%
8	 1a		 3c-90%
9	 1c		 3d-72%
10	 1e		 3e-67%

Catalyst loading was also studied, indicating that the use of 5 mol % of $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ was not very effective, affording 25% yield of the desired cross-coupled product in addition to a relatively small amount (>10%) of the homocoupled product. Once $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ was identified as the best catalyst, the influence of the copper salt employed on the cross-coupling reaction was examined. The next step, as shown in Table 1 (entries 8–14), was the determination of the best copper additive. Different copper(I) and copper(II) species were tested in the coupling reaction, displaying poor to high yields; the best result was obtained using CuI (1 mmol), giving the desired product in very good yield (Table 1, entry 8).

Copper loading was also analyzed. When the amount of CuI was dropped to 0.5 equiv, the product was formed in only 34% yield (Table 1, entry 9).

The influence of the reaction solvent was also investigated. The reaction occurred in poor to moderate yields in acetonitrile, DME and THF/DCM, giving the biaryl product in 46%, 63% and 66% yield, using $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ as the catalyst with copper iodide.

The highest yield was achieved using THF as the solvent, affording the cross-coupled product in 88% yield.

Thus, it was deemed that the optimum conditions for the cross-coupling reaction of interest involved the use of organotellurides (0.5 mmol), organozinc reagents (3.0 mmol), $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (10 mol %), and CuI (1.0 mmol) in THF solvent at reflux temperature (Table 2). Having established the viability of the presented methodology, the general applicability as well as the reactivity of various organozinc and aryl tellurides was also tested¹⁷ (Table 2).

The reaction demonstrated tolerance to common functional groups in aromatic rings like fluorine, methyl and methoxy with yields ranging from 32% to 88% (Table 2, entries 1–4). In the case of thiophene, the yield was very modest, only 47% (Table 2, entry 5). On the other hand, the aryl acetylenes (Table 2, entries 6–10) were accomplished in moderate to good yields.

In order to gain further insight into the reaction of interest, in situ ReactIR spectroscopy^{18,19} was employed to monitor the conversion of diphenyltelluride **1a**–**2a**. As can be observed in Figure 2, after the addition of diarylzinc to the diphenyltelluride, there is a rapid increase of a band at 1248 cm^{-1} that remains constant few minutes later, indicating that the reaction occurs quite fast. This intense band can be assigned to a vibrational mode involving the ring mode $\phi(14)$ and the methoxy group stretching, $\nu(\text{C}-\text{O})$. A detailed IR characterization was done for both the reactant and the product and to complement the vibrational assignment, density functional theory (DFT) calculations were performed for both species (the experimental and theoretical IR spectra, as well as the vibrational assignments are available in the Supplementary data).

Conclusion

The methodology was effective for obtaining asymmetric biaryl, biaryl acetylene and aryl acetylene compounds in moderate yields employing Negishi reaction conditions and symmetric diaryl tellurides catalyzed by palladium and copper. Also, the reaction allows the transference of both aromatic rings linked to tellurium atom.

A preliminary study to gain further insight into the reaction was performed using in situ ReactIR technology. Further studies on this methodology and the mechanism reaction are currently ongoing in our laboratory and will be reported in due course.

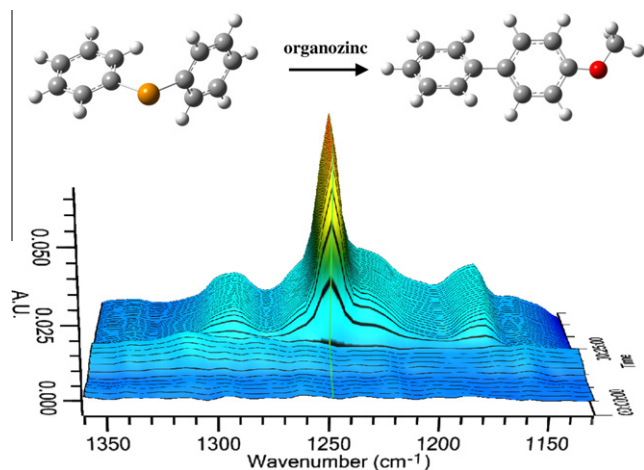


Figure 2. Reaction course (Table 2, entry 1) followed by in situ IR spectroscopy. The structures represented are the optimized geometries of the reactant and the product obtained by DFT calculations.

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.2011.06.025](https://doi.org/10.1016/j.tetlet.2011.06.025).

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- General procedure for the cross-coupling reaction of diaryl ditellurides with potassium aryltrifluoroborates*. To a round-bottom flask containing diaryl ditelluride (0.25 mmol), potassium aryltrifluoroborate salt (0.5 mmol), Cu(OAc)₂ (1 mol %) and bpy (1 mol %), DMSO (1 mL) and H₂O (0.5 mL) were added. The reaction mixture was allowed to stir at reflux for 12 h. After this time, the solution was cooled to room temperature, diluted with dichloromethane (20 mL) and washed with saturated aqueous NH₄Cl (3 × 20 mL). The organic phase was separated, dried over MgSO₄ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent. *Bis-(p-tolyl)-telluride (1c)*. The product was obtained in 94% yield. NMR ¹H (CDCl₃, 300 MHz) δ (ppm): 7.57 (d, *J* = 7.7 Hz, 4H), 7.01 (d, *J* = 7.7 Hz, 4H), 2.33 (s, 6H). NMR ¹³C (CDCl₃, 75 MHz) δ (ppm): 139.2(2C), 136.9 (4C), 131.4 (4C), 110.7 (2C), 22.0. ESI MS (relative intensity) *m/z* (%): 312 (34), 182 (100), 167 (72), 91 (59), 65 (36). HRMS calcd C₁₄H₁₄Te: 312.0157. found: 312.0169.
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- Representative procedure for the Negishi cross-coupling.¹⁵ A two-neck flask equipped with a rubber septum, a nitrogen inlet system and magnetic stirring was charged in sequence with PdCl₂(dppf)·CH₂Cl₂ (0.05 mmol, 40.8 mg), CuI (1 mmol, 190 mg), THF (3 mL) and the diaryl telluride (0.5 mmol). The organozinc chloride (3 mmol) was then transferred via cannula. The mixture became dark and was stirred under reflux. The reaction was monitored by TLC. Then the mixture was filtered under vacuum (silica), extracted with aqueous NH₄Cl (3 × 15 mL), washed with ethyl acetate (3 × 20 mL) and dried over MgSO₄. Finally, the solvent was evaporated under vacuum and the product purified by chromatography column with a mixture of hexane/dichloromethane (99:1). *1-(hex-1-ynyl)-4-methylbenzene (3d)*. The product was obtained as yellowish oil in 72% yield. NMR ¹H (300 MHz, CDCl₃) δ (ppm): 7.31 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 2.43 (t, *J* = 6.8 Hz, 2H), 2.35 (s, 3H), 1.66–1.47 (m, 4H), 0.98 (t, *J* = 6.9 Hz, 3H). NMR ¹³C (75 MHz, CDCl₃) δ (ppm): 137.3 (1C), 131.41 (2C), 128.92 (2C), 121.07 (1C), 89.56 (1C), 80.58 (1C), 30.95 (1C), 22.03 (1C), 21.37 (1C), 19.12 (1C), 13.64 (1C). IR cm⁻¹ (ethyl acetate solution): 2988, 1759, 1461, 1245, 1055, 755. ESI MS (relative intensity) *m/z* (%): 172 (36), 157 (48), 143 (48), 129 (100), 77 (18).
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