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Transmetalation of *Z*-Telluroenynes: Stereoselective Synthesis of *Z*-Enynols and Their Application in Palladium-Catalyzed Cyclization

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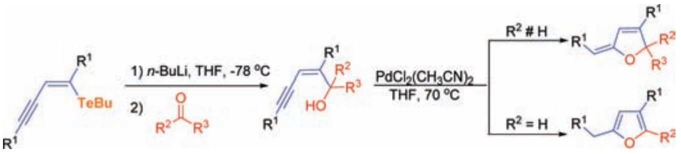
ABSTRACT



The synthesis of various *Z*-enynols via reaction of vinyllithium intermediate with aldehydes and ketones is described. The subsequent cyclization of a wide variety of *Z*-enynols afforded substituted furans and dihydrofurans with high regioselectivity under mild reaction conditions.

The stereospecific synthesis of conjugated enynes is of great interest to organic chemists. They are considered to be some of the most potent antitumoral agents known to date and have other interesting biological activities as well.[1] In this context, *Z*-enynols are extremely versatile structural units for drug lead discovery due to their wide range of activity against different families of targets.[2] Although considerable efforts have been devoted to the development of efficient methods for the synthesis of *Z*-enynols, the majority are focused on (1) zirconium-mediated cross-coupling,[3] (2) titanium complexes,[4] and (3) catalytic synthesis via Pd/Cu cross-coupling of the terminal alkynes with vinylic halides.[5] To the best of our knowledge, the preparation of *Z*-enynols using vinylic tellurides as substrate still remains an unexplored area.[6] The chemistry of organotellurium compounds has developed in the past years, being the subject of many review articles[7] as well as books.[8] From the many classes of tellurium compounds, vinylic tellurides constitute one of the most useful. Several methods have been developed

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(1) (a) Nicolaou, K. C.; Smith, A. L. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995. (b) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453. (c) Nicolaou, K. C.; Daí, W. M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (d) Nicolaou, K. C.; Daý, W.-D.; Hong, Y. P.; Tsay, S.-C.; Baldridge, J. S.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 7944. (e) Danishefsky, S. J.; Shair, M. D. *J. Org. Chem.* **1996**, *61*, 16. (f) Yang, C.; Nolan, S. P. *J. Org. Chem.* **2002**, *67*, 591, and references cited therein.

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(3) (a) Guo, S.; Zhang, H.; Song, F.; Liu, Y. *Tetrahedron Lett.* **2007**, *63*, 2009. (b) Liu, Y.; Song, F.; Cong, L. *J. Org. Chem.* **2005**, *70*, 6999. (c) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409.

(4) (a) Chen, J.; Liu, Y. *Tetrahedron Lett.* **2008**, *49*, 6655. (b) Liu, Y.; Gao, H. *Org. Lett.* **2006**, *8*, 309.

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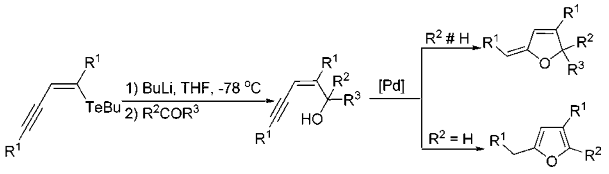
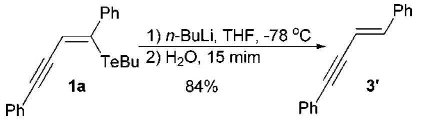
for their preparation;[7,8] among them, one of the most important is the hydrotelluration reaction of alkynes,[9] which furnishes exclusively the (*Z*)-vinylic telluride. These species can be transmetalated with many organometallic reagents to generate the corresponding (*Z*)-vinyl organometallics with retention of the double-bond geometry, which can react with several electrophiles like carbonyl compounds,[10] enones,[11] and epoxides.[12] These and especially the knowledge that *Z*-enynols are promising candidates for palladium-catalyzed cyclization to form substituted furans prompted us to develop a complete investigation on the synthesis of *Z*-enynols from vinylic tellurides as the sequence showed in Scheme 1.

Scheme 1



The generation of the (*Z*)-vinyllithium reagent from vinylic tellurides was attempted under a variety of reaction conditions by changing the medium, temperature, and amount of *n*-BuLi used for the transmetalation. On the basis of these experiments, we concluded that the best condition for the transmetalation was as follows: addition of *n*-BuLi (1.1 equiv) to a solution of *Z*-vinylic tellurides **1a** (0.5 mmol) in THF (3 mL) at −78 °C. After 15 min, the reaction was quenched by H_2O producing the corresponding *Z*-enyne **3′** in 84% yields (Scheme 2). Since we obtained **3′** as a single isomer and its stereochemistry is clearly indicated by coupling constant (*J* = 16 Hz) of the doublets attributed to the vinylic hydrogens, which is characteristic of trans vinyl coupling, we conclude that the Te/Li exchange proceeded with highly stereospecific retention of configuration.

Scheme 2



After standardizing the conditions of the transmetalation, the reaction of the (*Z*)-vinyllithium intermediate with ketones and aldehydes was extensively screened in order to determine the scope and limitations of our method. Table 1 summarizes the reaction of various aryl and alkyl ketones used as electrophile. Interestingly, all entries provided the corresponding *Z*-enynols in acceptable yields. Aromatic ketones having a neutral (Table 1, entry 6), an electron-donating (Table 1, entry 3), or an electron-withdrawing group (Table 1, entries 1, 2 and 4, 5) formed the desired products in similar yields. These results revealed that the reaction does not significantly depend on the electronic effects of substituents in the aromatic ring of ketones. In addition to aromatic ketones, the reaction with alkyl ketones also led to the formation of the desired products; however, a decrease in the yields was observed (Table 1, entries 7−9). A significant decrease in yields of enynols was also observed when the reaction was performed with bulky ketones (Table 1, entries 10 and 11). It is also worth noting that this reaction can be performed using aldehydes as the electrophile source. Most importantly, this method turned out to be general with respect to a diverse array of functionality in the aromatic ring at aryl aldehydes (Table 1, entries 20−23). In addition, alkyl aldehydes were effective in the preparation of the corresponding enynols (Table 1, entry 24).[13]

Since functionalized heterocycles containing oxygen exhibit a broad range of biological activities such as anticancer, antiviral, antioxidative, insecticidal, anti-inflammatory, and antifungal,[14] their preparation becomes a major challenge to organic chemists. During the past years, numerous protocols have been reported in the literature describing the synthesis of this class of compounds based on gold- or iodo-catalyzed cyclization of enynols.[15] Nevertheless, only a few methods involving palladium cyclization of enynols to furans have been reported to the present.[16] Here, we wish to report a new approach to the synthesis of furan and 2,5-dihydrofuran from enynols. Consequently, we investigated several synthetic strategies to facilitate the synthesis.[17] Thus, the reaction of (*Z*)-enynols **3** (Table 2, entries 1−6) with

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(7) (a) Zeni, G.; Ludtke, D. S.; Panatieri, R. B.; Braga, A. L. *Chem. Rev.* **2006**, *106*, 1032. (b) Vieira, M. L.; Zinn, F. K.; Comasseto, J. V. *J. Braz. Chem. Soc.* **2001**, *12*, 586. (c) Comasseto, J. V.; Barrientos-Astigarraga, R. E. *Aldrichim. Acta* **2000**, *33*, 66. (d) Comasseto, J. V.; Ling, L. W.; Petragnani, N.; Stefani, H. A. *Synthesis* **1997**, 373.

(8) (a) Petragnani, N. Tellurium in Organic Synthesis. *Best Synthetic Methods*; Academic Press: London, UK, 1994. (b) Petragnani, N. In *Organotellurium Compounds in Organic Synthesis*; McKillop, A., Ed.; Pergamon Press: New York, 1994; Vol. 11, Chapter 14.

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(13) The enynol stereochemistry was determined by the NOESY NMR experiment; see the Supporting Information.

(14) (a) Navarro, E.; Alonso, S. J.; Trujillo, J.; Jorge, E.; Perez, C. *J. Nat. Prod.* **2001**, *64*, 134. (b) Lambert, J. D.; Meyers, R. O.; Timmermann, B. N.; Dorr, R. T. *Cancer Lett.* **2001**, *171*, 47.

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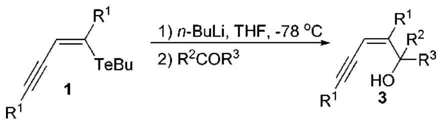
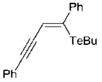
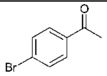
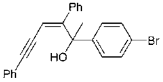
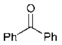
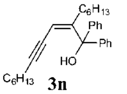
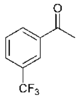
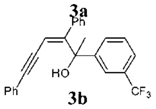
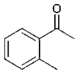
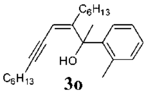
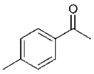
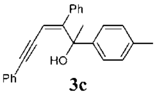
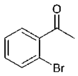
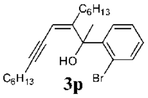
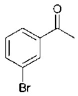
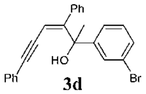
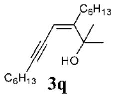
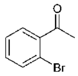
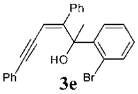
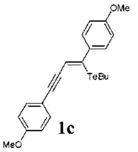
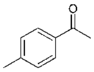
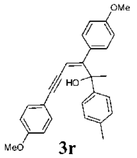
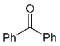
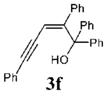
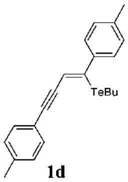
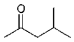
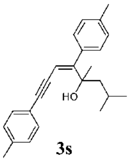
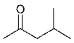
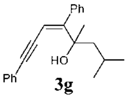
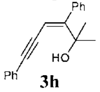
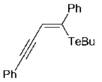
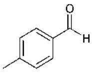
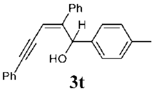
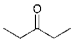
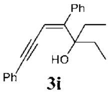
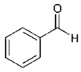
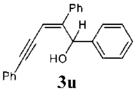
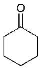
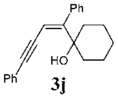
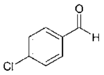
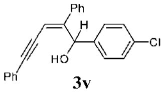
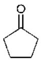
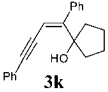
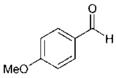
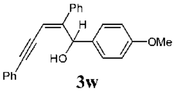
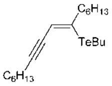
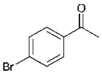
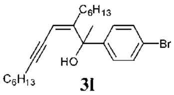
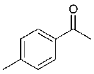
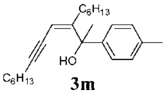
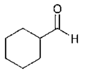
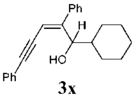
(16) (a) Larock, R. C.; Doty, M. J.; Han, X. *Tetrahedron Lett.* **1998**, *39*, 5143. (b) Gabriele, B.; Salerno, G. *Chem. Commun.* **1997**, 1083. (c) Wakabayashi, Y.; Fukuda, Y.; Shiragami, H.; Utimoto, K. *Tetrahedron* **1985**, *41*, 3655. (d) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816. (e) Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7687.

(17) Qing, F. L.; Gao, W. Z. *Tetrahedron Lett.* **2000**, *41*, 7727.

Table 1. Synthesis of (*Z*)-Enynols[b]

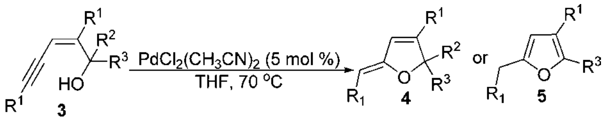


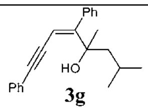
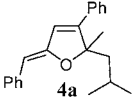
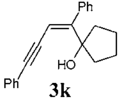
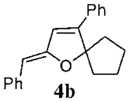
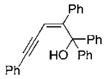
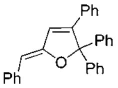
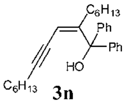
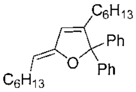
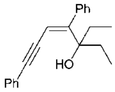
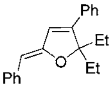
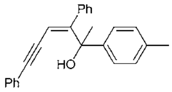
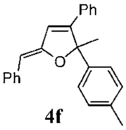
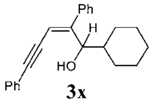
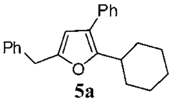
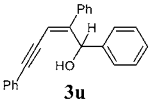
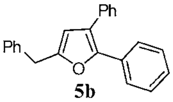
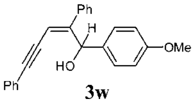
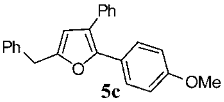
no.	tellurides	aldehydes/ ketones	product	yield (%)[a]	no.	tellurides	aldehydes/ ketones	product	yield (%)[a]
1	 **1a**	 **2a**	 **3a**	84	14		 **2f**	 **3n**	46
2		 **2b**	 **3b**	82	15		 **2l**	 **3o**	40
3		 **2c**	 **3c**	95	16		 **2e**	 **3p**	54
4		 **2d**	 **3d**	82	17		 **2h**	 **3q**	30
5		 **2e**	 **3e**	86	18	 **1c**	 **2c**	 **3r**	42
6		 **2f**	 **3f**	75	19	 **1d**	 **2g**	 **3s**	45[c]
7		 **2g**	 **3g**	65					
8		 **2h**	 **3h**	57	20	 **1a**	 **2m**	 **3t**	60
9		 **2i**	 **3i**	70[c]	21		 **2n**	 **3u**	63
10		 **2j**	 **3j**	49	22		 **2o**	 **3v**	30
11		 **2k**	 **3k**	34	23		 **2p**	 **3w**	85[c]
12	 **1b**	 **2a**	 **3l**	60					
13		 **2c**	 **3m**	30	24		 **2q**	 **3x**	50

[a] Yields are given for isolated products. [b] Reaction performed in the presence of **1** (0.5 mmol), *n*-BuLi (1.1 equiv) in THF at −78 °C followed by aldehydes or ketones addition (2.5 equiv). [c] These products were easily purified by column chromatography; however, they were unstable to obtain reliable elemental analysis or HRMS.

PdCl$_2$(CH$_3$CN)$_2$ (5 mol %) in THF at reflux for 30 min produced the corresponding 2,5-dihydrofurans **4a**−**c**,**e**−**f** in good isolated yields. Concerning the group directly bonded at the double or triple bond of enynols, we found some limitations in this methodology. For example no reaction was observed with enynol bearing an alkyl group at double and triple bonds (Table 2, entry 4). Finally, when this reaction condition was repeated with Z-enynols with

Table 2. Synthesis of Furans or Dihydrofurans[b]



no.	alcohol	product	yield(%)[a]
1	 **3g**	 **4a**	72
2	 **3k**	 **4b**	78
3	 **3f**	 **4c**	64
4	 **3n**	 **4d**	N.R.
5	 **3i**	 **4e**	67
6	 **3c**	 **4f**	75
7	 **3x**	 **5a**	74[c]
8	 **3u**	 **5b**	75[c]
9	 **3w**	 **5c**	72[c]

[a] Isolated yields. [b] Reaction performed in the presence of **3** (0.5 mmol) and $PdCl_2(CH_3CN)_2$ (5 mol %) in THF. [c] These products were easily purified by column chromatography; however, they were unstable to obtain reliable elemental analysis or HRMS.

an hydrogen in the allylic position, furans **5a**−**c** were obtained, instead of 2,5-dihydrofuran (Table 2, entries 7−9). These results strongly suggest that the cyclization was significantly influenced by nature of *Z*-enynols, becoming our methodology highly regioselective.[18] Regarding the five- versus six-membered ring, it is important to point out that the unique product obtained during the curse of this cyclization was the five-membered furan derivatives, which were determined by X-ray diffraction analysis (see the Supporting Information).

In summary, we showed the synthesis of various *Z*-enynols via reaction of the tellurium−lithium exchange and the reaction of these vinyllithium intermediates with aldehydes and ketones. Various aryl and alkyl groups directly bonded to the carbonyl group were successfully used as electrophiles. These enynols, bearing a hydroxyl group, underwent highly selective intramolecular cyclizations when treated with palladium salt affording 2,5-dihydrofuran or furan. The results demonstrated that the selectivity in the cyclization was significantly influenced by the presence of a substituent in the allylic position. *Z*-Enynols having a hydrogen at the allylic position gave 2,5-dihydronfurans, while *Z*-enynols without hydrogen in this position gave furan derivatives. In this way, there are some advantages to use vinylic tellurides instead of other methods, such as easy access by stereoselective reactions to (*Z*)-vinyllithium intermediate, low cost, and ease of availability, which are crucial for commercial applications.

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Supporting Information Available: Spectroscopic data for all new compounds, X-ray results, and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) For differentiation in the mechanism, see the Supporting Information.