

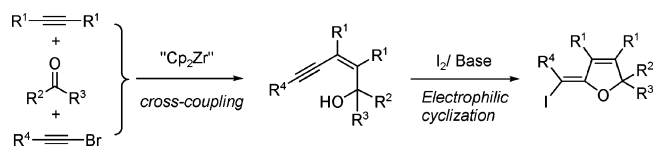
# A Facile Zr-Mediated Approach to (Z)-Enynols and Its Application to Regio- and Stereoselective Synthesis of Fully Substituted Dihydrofurans

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Efficient synthetic approaches to stereodefined (Z)-enynols have been developed through zirconium-mediated cross-coupling reactions of three different components involving alkyne, ketone, and alkynyl bromide in a one-pot procedure. The subsequent electrophilic cyclization of a wide variety of (Z)-enynols affords fully substituted (Z)-5-(1-iodoylidene)-2,5-dihydrofurans with high regio- and stereoselectivity under mild reaction conditions.

Oxygen-containing heterocycles and their analogues widely occur as structural subunits in numerous natural products, which have displayed interesting biological activities and find applications in pharmaceutical use.<sup>1</sup> Furthermore, substituted heterocycles, in particular, halogen-containing ones, are of significant interest since they are useful and versatile synthetic intermediates for further structural elaboration. Electrophile-promoted cycloaddition of unsaturated compounds has proven to be a powerful synthetic route to the wide variety of halogenated heterocyclic compounds.<sup>2</sup> However, the electrophilic cyclization performed on acetylenic compounds has been far less studied, although alkynes have been frequently employed in transition-metal-catalyzed inter- or intramolecular annulations to produce fruitful results for the synthesis of carbo- and heterocycles.<sup>3</sup> Most of the recent reports focused on arylalkynes bearing ortho-related heteroatomic nucleophiles, which provided ef-

ficient approaches to benzofused heterocycles such as benzothiophenes,<sup>4a,b</sup> benzo[b]furans,<sup>4c,d</sup> isoquinolines,<sup>4e</sup> quinolines,<sup>4f</sup> isochromenes,<sup>4g,h</sup> furopyridines,<sup>4i</sup> indoles,<sup>4j,k</sup> isoindolin-1-ones,<sup>4l</sup> and so on.<sup>4</sup> Enynes bearing nucleophilic substituents such as -OH, -NHR, and SR groups would represent an important class of suitable substrates for this strategy due to the structural analogy with arylalkynes; however, only limited reports concerning electrophilic cyclization have been presented in the literature by employing enyne derivatives.<sup>5</sup> It is known that (Z)-enynols undergo transition-metal-catalyzed transformations to form substituted furans.<sup>6</sup> The preparation of (Z)-enynols are usually achieved through multistep transformations involving Pd/Cu-catalyzed coupling of the terminal alkynes with vinylic halides, addition of alk-1-yne to vinyl ketones followed by acid-catalyzed allylic isomerization, reduction of methyl (Z)-2-en-4-ynoates etc.<sup>6a,c</sup> Nevertheless, enhancing the efficiency of the synthesis of these compounds is still highly attractive. In our ongoing efforts<sup>7</sup> to maximize the molecular complexity from simple building blocks using zirconium,<sup>8</sup> we found that (Z)-2-en-4-yn-1-ols were readily constructed by a one-pot, three-component reaction. This strategy offered the advantage of the efficient route for substituted

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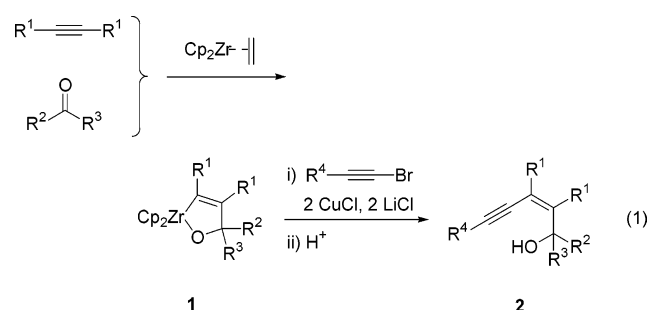
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(*Z*)-enynols with a tertiary alcoholic group, which enabled us to develop convenient protocol for the synthesis of highly substituted 5-(1-iodoylidene)-2,5-dihydrofurans with high regio- and stereoselectivity.

Alkynes undergo selective intermolecular coupling with aldehydes or ketones using zirconocenes.<sup>9</sup> The hydrolysis of the thus-formed oxazirconacyclopentene **1** with aqueous HCl solution affords allylic alcohols in good to excellent yields. Takahashi recently reported a new pathway for the formation of 2,5-dihydrofuran derivatives by the reaction of oxazirconacyclopentenones **1** with propynoates.<sup>9b</sup> We envisioned that the oxazirconacycles could be converted to (*Z*)-enynols by further applications of these cross-coupling reactions. The straightforward way is to develop a method for selective alkylation of Zr–C bond of oxazirconacyclopentenones **1**. This was solved by the coupling of zirconacycle **1** with an alkynyl bromide (eq 1).



It was found that **1** did not react with alkynyl bromide directly. Copper-catalyzed or -mediated carbon–carbon bond formation reactions of zirconacycles have been reported, and transmetalation of Zr–C bonds to Cu–C bonds has proven to be an effective methodology for activation of Zr–C bonds.<sup>10</sup> Treatment of oxazirconacycle **1e** ( $R^1 = \text{Ph}$ ,  $R^2 = o\text{-BrC}_6\text{H}_4$ ,  $R^3 = \text{Me}$ ) with 2 equiv of 1-hexynyl bromide and 2 equiv of CuCl at room temperature and stirring the mixture for 24 h afforded (*Z*)-enynols **2e** in 51% yield after hydrolysis. It should be noted that addition of 2 equiv of LiCl resulted in a cleaner reaction process and reduced reaction time (12 h). In the presence of LiCl, **2e** was obtained in higher isolated yield (69%). This result can be explained by the fact that the LiCl salt may facilitate the transmetalation of Zr–C bond to Cu–C bond and stabilize the organocopper species generated in the reaction solution.<sup>11</sup> The representative reactions with various alkynyl bromide are listed in Table 1. Alkynyl bromide bearing alkyl or aryl substituents

**TABLE 1. Formation of (*Z*)-Enynols from Three-Component Reactions Mediated by Zirconium**

Alkyne	Ketone	Alkynyl Bromide	Product	Yield (%) <sup>a</sup>
Ph—C≡C—Ph		Bu—C≡C—Br	<b>2a</b>	(60) <sup>b</sup>
Ph—C≡C—Ph		Ph—C≡C—Br	<b>2b</b>	71 (56)
C <sub>3</sub> H <sub>7</sub> —C≡C—C <sub>3</sub> H <sub>7</sub>		Ph—C≡C—Br	<b>2c</b>	85 (70)
Ph—C≡C—Ph		Bu—C≡C—Br	<b>2d</b>	70 (64) <sup>b</sup>
Ph—C≡C—Ph		Bu—C≡C—Br	<b>2e</b>	83 (69)
Ph—C≡C—Ph		Bu—C≡C—Br	<b>2f</b>	71 (51) <sup>c</sup>
Ph—C≡C—Ph		Ph—C≡C—Br	<b>2g</b>	(74) <sup>b,c</sup>
Ph—C≡C—Ph		Bu—C≡C—Br	<b>2h</b>	92 (76) <sup>b</sup>
Ph—C≡C—Ph		Bu—C≡C—Br	<b>2i</b>	(57)
Bu—C≡C—Bu		<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> —C≡C—Br	<b>2j</b>	(66)

<sup>a</sup> GC yields. Isolated yields are given in parentheses. Unless noted, all of the reactions were done at room temperature for 12 h using alkynyl bromide (2 equiv), CuCl (2 equiv), and LiCl (2 equiv). <sup>b</sup> Alkynyl bromide (1 equiv), CuCl (1 equiv), and LiCl (2 equiv) were used. <sup>c</sup> The reaction was performed for 24 h.

reacted very well with oxazirconacycles to afford enynols **2** in 57–92% yields. A wide range of aromatic ketones could be used, especially with halogenated aromatic ketones, affording the corresponding enynols in good to high yields. 2-Acetylthiophene could also be applied in this reaction to give **2i** in 57% isolated yield. When an aliphatic ketone such as 3-pentanone was subjected to the reaction, a prolonged reaction time was required (24 h) to afford **2f** in 71% yield.

With (*Z*)-enynols **2** in hand, we were interested in exploring the feasibility of using **2** in electrophilic cyclization reactions. We began our investigation with enynol **2a** ( $R^1 = \text{Ph}$ ,  $R^2 = \text{Ph}$ ,  $R^3 = \text{Me}$ ,  $R^4 = \text{Bu}$ ) bearing alkyl group at C-5 and a tertiary alcohol group at C-1. The reaction of **2a** with I<sub>2</sub> was done first in solvents such as CH<sub>2</sub>Cl<sub>2</sub> and CH<sub>3</sub>CN which were frequently used for iodocyclization in the presence of NaHCO<sub>3</sub> as base. However, only sluggish reaction mixture was observed. After many efforts, we were delighted to find that iodocyclization proceeded smoothly and provided a >99% NMR yield of the 5-ylidene-2,5-dihydrofuran derivative **3a** in THF solution with K<sub>3</sub>PO<sub>4</sub> as base. The results for

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**TABLE 2. Effect of Base for the Iodocyclization Reaction**

base	time (h)	yield <sup>a</sup> (%)	base	time (h)	yield <sup>a</sup> (%)
	6	24	K <sub>3</sub> PO <sub>4</sub>	1	>99
Na <sub>2</sub> CO <sub>3</sub>	8	71	NaOCO <sub>2</sub> CH <sub>3</sub>	4	>99
NaHCO <sub>3</sub>	6	75	KO <sup>t</sup> Bu	9	56
KHCO <sub>3</sub>	18	18	NEt <sub>3</sub>	20	10
KOH	3	37	pyridine	12	78

<sup>a</sup> NMR yields.

optimization of this electrophilic cyclization process are summarized in Table 2. When no base was employed, only 24% of product **3a** was obtained. The addition of carbonate bases such as Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, and KHCO<sub>3</sub> increased the yield of **3a** to 71, 75, and 79% NMR yields along with the formation of several side products, which was difficult to be separated from the main product. When a stronger base, KO<sup>t</sup>Bu was used, 56% yield of **3a** was observed. The use of organic base such as Et<sub>3</sub>N and pyridine resulted in the formation of **3a** in 10% and 78% yields, respectively. The presence of K<sub>3</sub>PO<sub>4</sub> was crucial for a clean, high-yielding reaction within short reaction time (1 h). It was suggested that K<sub>3</sub>PO<sub>4</sub> would neutralize the produced HI of iodocyclization and generate K<sub>2</sub>HPO<sub>4</sub>, while using carbonate bases would produce H<sub>2</sub>O. The H<sub>2</sub>O generated might lead to the formation of side products.<sup>4e</sup> Accordingly, using NaOCO<sub>2</sub>CH<sub>3</sub> as reported by Larock et al. in isoquinoline formation reaction<sup>4e</sup> also afforded the desired product in high yield (>99%).

Based on the above optimization results, we chose the following reaction conditions: 3 equiv of I<sub>2</sub> and 3 equiv of K<sub>3</sub>PO<sub>4</sub> or NaOCO<sub>2</sub>CH<sub>3</sub> in THF stirred at room temperature for an appropriate amount of time. The results are summarized in Table 3.

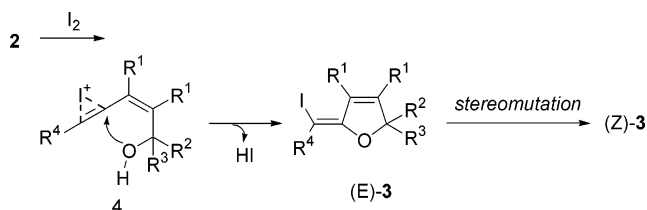
The alkyne moiety in enynols **2** bearing an aromatic ring as well as alkyl substituent all reacted very well to provide the 5-*exo-dig* cyclization product in 66–86% yields. The effect of substitution on α-carbon of alcoholic group in **2** has also been examined: enynol **2f** bearing two alkyl group on α-carbon of alcoholic group (entry 6) required increased amount of base (6 equiv) and a prolonged reaction time (12 h). Bulky substrates, such as **2g** bearing the *o*-chlorophenyl group at C-1 and phenyl group at the end of the alkyne moiety, tend to hinder cyclization. A stronger reaction condition involving 6 equiv of I<sub>2</sub> and 6 equiv of base was required, and the product of **3g** still could be formed in 73% yield within 3 h.

It is interesting to note that in all cases, only 5-*exo-dig* iodocyclization occurred and stereoisomerically pure compounds (*Z*)-**3** were found to be the only reaction products, while the regioisomers of pyran derivative derived from 6-endocyclization and the stereoisomer of (*E*)-**3** were not observed. The observed selectivity are rare in electrophilic cyclization reactions. The structure of dihydrofurans were unequivocally confirmed by single-crystal analysis of **3g** and **3h**. These results clearly showed five-membered oxygen heterocycles and the (*Z*)-

**TABLE 3. Synthesis of Highly Substituted Stereofined 5-Ylidene-2,5-2H-furans**

Entry	Enynols	Base/Time	Product	Yield (%) <sup>a</sup>
1	<b>2a</b>	K <sub>3</sub> PO <sub>4</sub> , 1h		( <b>3a</b> ) 74
2	<b>2b</b>	NaOCO <sub>2</sub> CH <sub>3</sub> , 1h		( <b>3b</b> ) 66
3	<b>2c</b>	K <sub>3</sub> PO <sub>4</sub> , 8h		( <b>3c</b> ) 85
4	<b>2d</b>	K <sub>3</sub> PO <sub>4</sub> , 1h		( <b>3d</b> ) 82
5	<b>2e</b>	K <sub>3</sub> PO <sub>4</sub> , 3h		( <b>3e</b> ) 66
6	<b>2f</b>	K <sub>3</sub> PO <sub>4</sub> , 12h		( <b>3f</b> ) 77 <sup>b</sup>
7	<b>2g</b>	NaOCO <sub>2</sub> CH <sub>3</sub> , 3h		( <b>3g</b> ) 73 <sup>c</sup>
8	<b>2h</b>	NaHCO <sub>3</sub> , 4h		( <b>3h</b> ) 86
9	<b>2i</b>	NaOCO <sub>2</sub> CH <sub>3</sub> , 3h		( <b>3i</b> ) 76 <sup>b</sup>

<sup>a</sup> Isolated yields. <sup>b</sup> 6 equiv of base was used. <sup>c</sup> 6 equiv of I<sub>2</sub> and 6 equiv of I<sub>2</sub> base were used.

**SCHEME 1**

configuration of **3**. On the basis of the above observations, a possible reaction mechanism is proposed in Scheme 1, which may involve the following steps: (i) Cyclic iodonium ion **4** was formed through coordination of the triple bond with iodine cation. (ii) Anti attack of the oxygen of alcohol group onto iodonium ion led to the formation of (*E*)-**3**. In intermediate **4**, more of the partial positive charge caused by iodine coordination is located on the alkyne carbon closed to the substituted double bond moiety, since it stabilizes a carbocation much better. Thus, a 5-*exo-dig* cyclization resulted. (iii) (*E*)-**3** underwent stereomutation in the presence of I<sub>2</sub> to give the thermodynamically more stable (*Z*)-product **3**. Similar iodine-promoted isomerization of vinyl iodide compounds was reported previously.<sup>12</sup>

In summary, we have succeeded in developing an efficient, general, and one-pot procedure to synthesize

stereodefined (*Z*)-enynols through zirconium-mediated cross-coupling of alkyne, ketone, and alkynyl bromide. The iodocyclization of a wide variety of (*Z*)-enynols affords fully substituted 5-ylidene-2,5-dihydrofurans with high regio- and stereoselectivity under mild reaction conditions. This methodology provided a highly efficient route to stereodefined oxygen heterocycles from common starting materials. We are currently exploring the new synthetic potential of electrophilic cyclization reactions.

## Experimental Section

**Typical Experimental Procedure for the Preparation of Enynol 2a.** To a solution of  $\text{Cp}_2\text{ZrCl}_2$  (0.365 g, 1.25 mmol) in THF (5 mL) was added  $\text{EtMgBr}$  (1.0 M THF solution, 2.5 mmol) at  $-50^\circ\text{C}$ . After the mixture was stirred for 1 h at the same temperature, diphenylacetylene (0.18 g, 1 mmol) was added, and the reaction mixture was warmed to  $0^\circ\text{C}$  and stirred for 3 h. Acetophenone (0.12 g, 1 mmol) was added, and the reaction mixture was heated to  $50^\circ\text{C}$  for 1 h. Then, to the above reaction solution containing oxazirconacyclopentene **1a** were added 1-hexynyl bromide (0.32 g, 2 mmol),  $\text{CuCl}$  (0.20 g, 2 mmol), and  $\text{LiCl}$  (0.08 g, 2 mmol) at room temperature. After being stirred at room temperature for 12 h, the reaction mixture was quenched with 3 N HCl solution and extracted with diethyl

ether. The extract was washed with  $\text{NaHCO}_3$ , water, and brine. The solvent was evaporated in vacuo, and the residue was purified by chromatography on a  $\text{Al}_2\text{O}_3$  column (petroleum ether/ethyl acetate = 15:1) to afford 245 mg (64%) of product as a yellow oil.

**General Procedure for Electrophilic Cyclization of Enynols 2.** To a solution of enynol **2** (0.2 mmol) in 1.5 mL of THF were added  $\text{K}_3\text{PO}_4$  (0.6 mmol) and  $\text{I}_2$  (0.6 mmol) at  $0^\circ\text{C}$ . After 5 min, the above suspension was warmed to room temperature and stirred for an appropriate amount of time. The reaction mixture was then diluted with ethyl acetate, washed with saturated  $\text{Na}_2\text{S}_2\text{O}_3$  solution, dried ( $\text{Na}_2\text{SO}_4$ ), and filtered. The solvent was evaporated under reduced pressure, and the product was isolated by chromatography on an  $\text{Al}_2\text{O}_3$  column.

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**Supporting Information Available:** Experimental details and characterization data of compounds **2a–j**, **3a–i**, and crystallographic data of **3g,h**. Copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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