

Carbon–Carbon Bond Formation of α -Alkynylzirconacyclopentenes via Cyclization or a Cu/Pd-Mediated Cyclization/Cross-Coupling Sequence with Aryl Iodides

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The cyclization of α -alkynylzirconacyclopentenes in the presence of CuCl was achieved cleanly to afford stereodefined 3-ylidenecyclopentenes. Coupling of the copper intermediates with a variety of aryl iodides catalyzed by Pd(PPh₃)₄ afforded bis-arylated ylidenecyclopentenes; however, in the absence of copper salts, the coupling reaction of the same zirconacycles with aryl iodides was efficiently promoted by Pd(OAc)₂/PPh₃ in toluene to afford the monoarylated products. Activation of the central double bond of the cumulenic intermediate by a Pd(II) complex followed by nucleophilic attack of the Zr–sp³ carbon bond to form an alkenylpalladium intermediate accounting for this novel cyclization is suggested.

Group 4 metal complexes are attractive intermediates in an impressive array of synthetic methodologies and have received much attention in recent years.¹ One of the most extensively studied areas has been the chemistry of diynes R(C≡C)₂R and polyynes R(C≡C)_nR with group 4 metallocenes.^{2–4} The organometallic complexes of these conjugated alkynes are potentially

useful for building up carbon-rich networks and for materials science.⁵ A thorough investigation by Rosenthal et al.² was performed using the metallocene sources Cp₂M(L)(η^2 -Me₃SiC≡CSiMe₃) (M = Ti, L = none; M = Zr, L = THF) as low-valent metal equivalents. The resulting metal-containing products strongly depended on the diyne or polyyne substituent, the metal, the nature of the Cp ligands associated with the metal, and the stoichiometry employed. However, the utilization of these complexes in organic synthesis has not been amply highlighted. Recently we investigated the intermolecular cross-coupling reaction of α -alkynylated zirconacyclopentenes based on 1,4-bis(trimethylsilyl)-1,3-butadiyne with unsaturated compounds, which afforded an efficient regio- and stereocontrollable synthesis of *trans*-enediynes.^{6a} Soon after this study, we found a completely different new reaction mode of α -alkynylzirconacyclopentenes toward aldehydes. In a preliminary communication,^{6b} we have shown that zirconium-mediated coupling of 1,3-butadiynes with aldehydes or ketones provides access to an efficient, general, and one-pot method for tetrasubstituted [3]cumulenols with excellent *cis* stereoselectivity. We now report the cyclizing C–C bond formation of α -alkynylzirconacyclopentenes in the presence of CuCl and the selective coupling reactions of the same zirconacycles with various aryl iodides. This reaction provides an efficient, controllable synthesis of 3-ylidene 1-substituted or 1,2-disubstituted cyclopentenes in a highly regio- and stereoselective manner (Scheme 1).

It is known that zirconacyclopentene **2** is prepared by the reaction of a butadiyne and Cp₂Zr(CH₂=CH₂),³ which is generated from Cp₂ZrCl₂ and 2 equiv of EtMgBr with high yields. Here we found that treatment of zirconacycle **2** with an excess amount (2.5 equiv) of CuCl at 50 °C for 1 h followed by hydrolysis with saturated NaHCO₃ selectively afforded 3-alkylidene 1-substituted cyclopentenes **4** in generally good yields (Table 1). It is interesting to note that only the stereoisomerically pure compounds (*Z*)-**4** were

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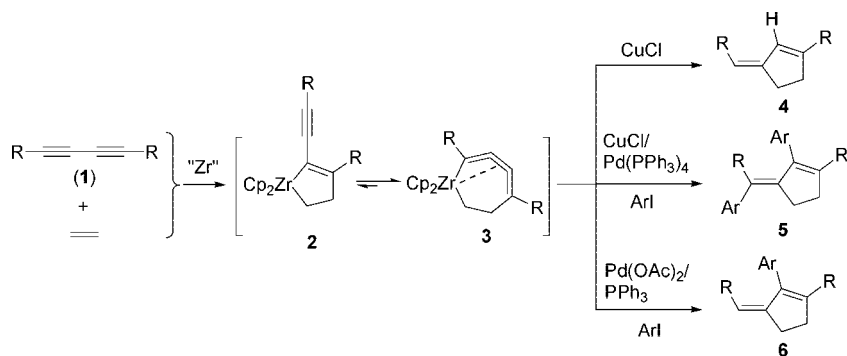
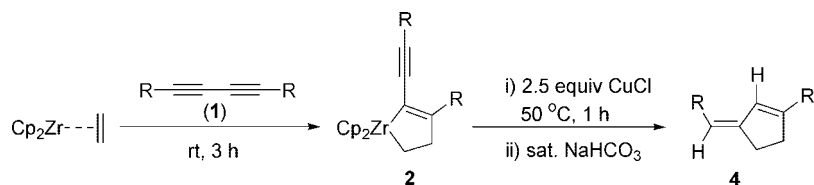
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Scheme 1

Table 1. Formation of 3-Alkylidenecyclopentenes from α -Alkynylzirconacyclopentenes

entry	R—C≡C—R	product	yield (%) ^a
1	ⁿ C ₄ H ₉ —C≡C—C≡C— ⁿ C ₄ H ₉ 1a		4a 74
2	ⁿ C ₅ H ₁₁ —C≡C—C≡C— ⁿ C ₅ H ₁₁ 1b		4b 76
3	ⁿ C ₆ H ₁₃ —C≡C—C≡C— ⁿ C ₆ H ₁₃ 1c		4c 52
4	PhMeNCH ₂ —C≡C—C≡C—CH ₂ NMePh 1d		4d 63
5	Ph ₂ NCH ₂ —C≡C—C≡C—CH ₂ NPh ₂ 1e		4e 63
6	MeO(H ₂ C) ₂ —C≡C—C≡C—(CH ₂) ₂ OMe 1f		4f 64
7	MeOCH ₂ —C≡C—C≡C—CH ₂ OMe 1g		4g 20

^a Isolated yields.

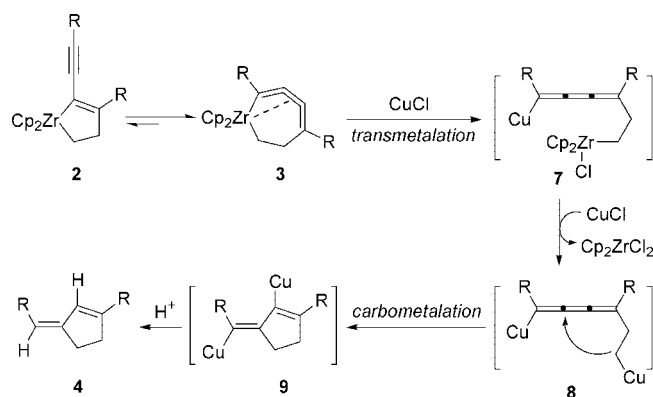
obtained. The geometry of the exocyclic double bond was unambiguously confirmed by the X-ray single-crystal analysis of **4e**.⁷ These results suggested that the cyclization of the copper intermediate was highly stereoselective. Decreasing the amount of CuCl or employing CuCN, CuBr, CuI, CuCl(PPh₃)₃, or [Cu(bipy)-(PPh₃)Br] did not afford good results. The representative results are given in Table 1. The cyclization of zirconacycles derived from bis-alkyl-substituted butadiynes afforded the corresponding products **4a–c** in 52–76% yields (Table 1, entries 1–3). Introduction of the functional groups —NMePh and —NPh₂ to the alkyl chain did

not influence the efficiency of this reaction, in which **4d,e** were isolated in the same yields of 63% (Table 1, entries 4 and 5). However, for methoxyalkyl-substituted butadiynes **1f,g**, the yields of the products were highly dependent on the length of the alkyl chain; while the methoxyethyl-substituted **1f** could afford **4f** in 64% yield (Table 1, entry 6), the cyclization using the methoxymethyl-substituted butadiyne **1g** only resulted in a low yield (20%) of the desired cyclopentene (Table 1, entry 7).

We propose the following reaction mechanism for the above reactions (Scheme 2): first, the five-membered α -alkynylzirconacyclopentene is produced in the reaction mixture, which is assumed to be in equilibrium with the seven-membered zirconacyclocumu-

(7) See the Supporting Information.

Scheme 2

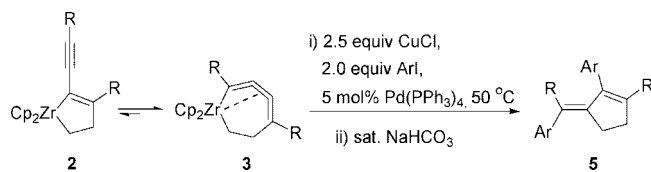


lene **3**. Actually, according to NMR analysis of the zirconium intermediate, it was suggested that the structure of the major zirconium intermediate might be best described as the seven-membered zirconacycle **3**.⁷ Theoretical calculations have shown that zirconacyclocumulenes **3** are thermodynamically more stable than the isomeric zirconacyclopentenes **2**.⁷ The cumulenic structure of zirconacycles was also frequently observed in the chemistry of diynes $R(C\equiv C)_2R$ and polyynes $R(C\equiv C)_nR$ with group 4 metallocenes.² Then, transmetalation of **3** with CuCl affords the monocopper intermediate **7**: in this step, selective transmetalation of the $Zr-sp^2$ bond may occur preferentially, as observed in the cases of alkyl- or aryl-substituted zirconacyclopentenes.⁸ This is followed by a second transmetalation to afford the dicopper species **8**. The intermediate **8** undergoes intramolecular carbometalation to give **9**,⁹ which affords the five-membered-ring product **4** after hydrolysis. It should be noted that the *cis* geometry of the cumulenic double bond was not changed during the transmetalation of **3** to **7** or **8**, thus resulting in (*Z*)-**4**.

The dicopper species **9** formed in situ are valuable intermediates for further transformations. To demonstrate the utility of **9**, we tested the coupling reaction with various aryl iodides to pursue the C–C bond formation reaction under the optimized reaction conditions. As shown in Table 2, all of the reactions proceeded smoothly in THF using a CuCl/ArI/Pd(PPh₃)₄ system. A wide range of aryl iodides with electron-donating groups (–Me, –MeO) or electron-deficient groups (–Cl, –Br, –CO₂Et) could be used, furnishing the corresponding bis-arylated products **5g–k** in 52–65% yields (Table 2, entries 7–11). The reaction could be conveniently carried out by addition of CuCl, ArI, and Pd(PPh₃)₄ successively to the reaction mixture of **2** and **3** followed by stirring at 50 °C for 1 h. There was no need to prepare the dicopper species **9** first in this coupling reaction. In all cases, only one stereoisomer of carbocycles **5** was isolated, and its stereochemistry was assigned on the basis of the NOESY spectra of **5h**. The structure of the ylidene-cyclopentenes was further confirmed by an X-ray crystal analysis of **5e**.⁷

Next we observed, surprisingly, the monocoupling reaction of zirconacycle **2** with aryl iodide in the presence only of the Pd catalyst (without addition of CuCl). As is already known, zirconacycles themselves are unreactive toward coupling reactions with aryl halides; to increase the reactivity of the $Zr-C$ bond, it is always necessary to transmetalate with other metal salts such as copper salts to form a new metal–carbon bond.¹⁰ There is no report of coupling reactions with aryl halides directly from zirconacycles,

Table 2. Formation of Bis-Arylated Ylidene-cyclopentenes through Cyclization/Coupling Sequence



entry	R–C≡C–R	ArI	product	yield (%) ^a
1	ⁿ C ₅ H ₁₁ –C≡C– ⁿ C ₅ H ₁₁ 1b	PhI	5a	59
2	ⁿ C ₆ H ₁₃ –C≡C– ⁿ C ₆ H ₁₃ 1c	PhI	5b	66
3	PhMeNCH ₂ –C≡C–CH ₂ NMePh 1d	PhI	5c	58
4	Ph ₂ NCH ₂ –C≡C–CH ₂ NPh ₂ 1e	PhI	5d	61
5	Ph–C≡C–Ph 1i	PhI	5e	38
6	MeO(H ₂ C) ₂ –C≡C–(CH ₂) ₂ OMe 1f	PhI	5f	64
7	1f	<i>p</i> -MeC ₆ H ₄ I	5g	58
8	1f	<i>p</i> -MeOC ₆ H ₄ I	5h	65
9	1f	<i>p</i> -ClC ₆ H ₄ I	5i	57
10	1f	<i>p</i> -BrC ₆ H ₄ I	5j	52
11	1f	<i>p</i> -EtO ₂ CC ₆ H ₄ I	5k	59

^a Isolated yields.

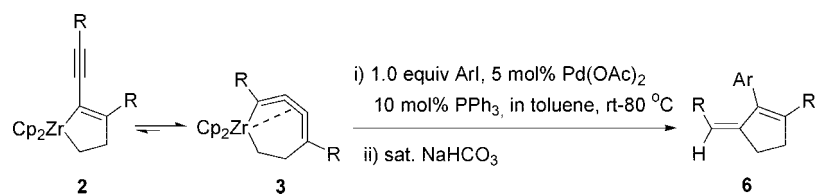
to the best of our knowledge. After a great deal of effort, we found that the best conditions for this monoarylation reaction were to use 5% Pd(OAc)₂ and 10% PPh₃ in toluene solvent with stirring at room temperature for 1 h and then at 80 °C for 1–4 h. The representative results are shown in Table 3.

Under the optimized reaction conditions, the coupling of butadiynes with various aryl iodides afforded the compounds **6a–k** in 41–68% yields. Both electron-deficient and electron-rich aromatic halides have been employed successfully in this reaction. Interestingly, in the cases of 1-chloro- and 1-bromo-4-iodobenzenes, the reaction selectively occurred with the iodo substituent, while the –Cl or –Br group remained intact. The heterocyclic group was also easily introduced to the cyclopentene ring by employing heteroaromatic iodide (Table 3, entry 7). The stereochemistry of the exocyclic double bond was confirmed by a NOESY spectrum of **6h**. It should be noted that **6b** was unstable upon isolation; it could be observed only in the hydrolyzed crude reaction mixture. We propose the following mechanism for this reaction (Scheme 3): in this novel process, the electrophilic arylpalladium complex **10**, generated

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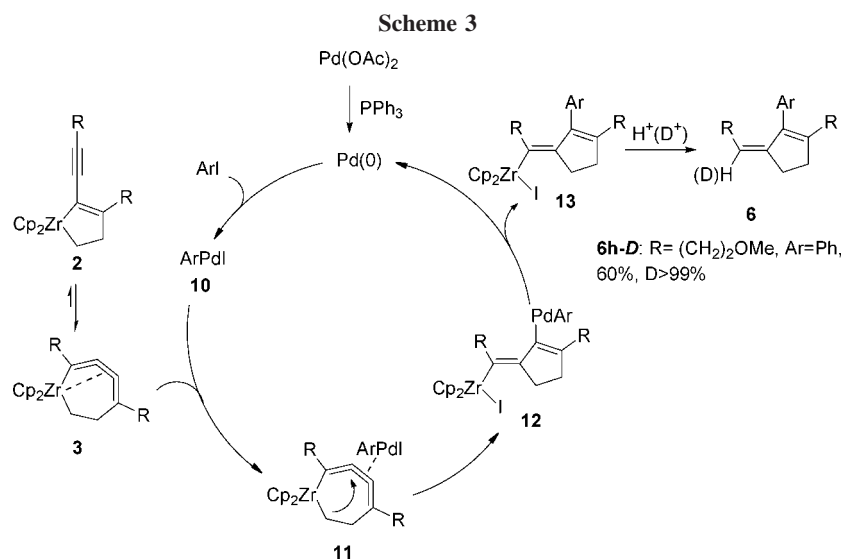
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Table 3. Formation of Mono-Arylated Ylidenecyclopentenes through Pd-Catalyzed Cyclization

entry	R—≡≡≡—R	ArI	product	yield (%) ^a
1	ⁿ C ₄ H ₉ —≡≡≡— ⁿ C ₄ H ₉ 1a	PhI	6a	47
2	1a	<i>p</i> -MeOC ₆ H ₄ I	6b	68 ^b
3	PhMeNCH ₂ —≡≡≡—CH ₂ NMePh 1d	PhI	6c	63
4	1d	<i>p</i> -ClC ₆ H ₄ I	6d	51
5	1d	<i>p</i> -BrC ₆ H ₄ I	6e	41
6	1d	<i>p</i> -MeOC ₆ H ₄ I	6f	53
7	1d	2-iodothiophene	6g	45
8	MeO(CH ₂) ₂ —≡≡≡—(CH ₂) ₂ OMe 1f	PhI	6h	60
9	1f	<i>p</i> -MeC ₆ H ₄ I	6i	62
10	1f	<i>p</i> -MeOC ₆ H ₄ I	6j	57
11	1f	<i>p</i> -EtO ₂ CC ₆ H ₄ I	6k	52

^a Isolated yields. All of the reactions were carried out at room temperature for 1 h and then at 80 °C for 1–4 h. ^b NMR yield.



from ArI and a Pd(0) catalyst, is suggested to activate the central double bond of the cumulenic structure of **3**, which enables facile nucleophilic attack by the Zr–sp³ carbon bond to form the alkenylpalladium intermediate **12**. Reductive elimination of **12** generates the vinylzirconium species **13**; hydrolysis of **13** affords the desired product **6**. The results also indicate the remaining Zr–C(sp²) bond does not easily undergo transmetalation with ArPdI to furnish the second arylation. To support the mechanism, a deuteration experiment was carried out. The deuterated compound **6h-D** was obtained in 60% yield with high deuterium incorporation (D > 99%; Scheme 3). In fact, in recent

years several papers have described the Pd(II)-promoted addition of oxygen-based functionalities to the triene central double bond in a number of cumulenic intermediates to substituted furans.¹¹ However, analogous reactions using carbon nucleophiles are rare.

In summary, we have succeeded in developing an efficient, one-pot procedure for the synthesis of stereodefined 3-ylidenecyclopentenes through CuCl-mediated cyclization of α -alkynylzirconium

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conacyclopentenes. Coupling of the copper intermediate by a variety of aryl iodides afforded bis-arylated ylidenecyclopentenes; however, in the absence of copper salts, coupling reactions of the zirconacycles with aryl iodides were efficiently promoted by Pd(OAc)₂/PPh₃ to afford the monoarylated products.

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07JC14063), and the Major State Basic Research Development Program (Grant No. 2006CB806105) for financial support.

Supporting Information Available: Text and figures giving experimental details and spectroscopic characterization data for all new compounds and CIF files giving crystallographic data for **4e** and **5e**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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