# Generation of Allenic/Propargylic Zirconium Complexes and Subsequent Cross-Coupling Reactions: A Facile Synthesis of Multisubstituted Allenes

Hao Zhang,[†] Xiaoping Fu,[†] Jingjin Chen,[†] Erjuan Wang,[‡] Yuanhong Liu,*,[†] and Yuxue Li*,[†]

[†]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, People's Republic of China, and* [‡]*Department of Chemistry, East China Normal University, 3663 North Zhongshan Road, Shanghai 200062, People's Republic of China*

yhliu@mail.sioc.ac.cn

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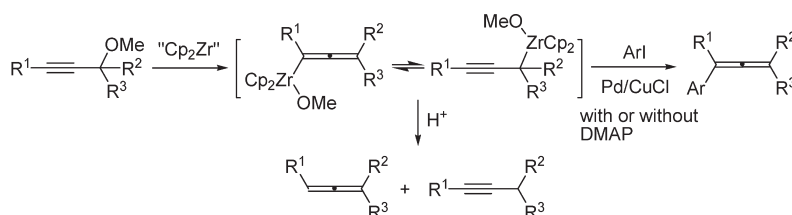
The β-alkoxide elimination reaction of propargylic ether with Negishi reagent leads to allenes and/or alkynes after hydrolysis. The product distribution is highly dependent on the substitution pattern of starting propargylic ethers; that is, aryl- or alkyl-substituted propargylic ethers favor the allene products, whereas TMS-substituted propargylic ethers afford alkynes. DFT calculations revealed that both the large steric effect and the β-effect of the TMS group favor the alkyne products, reversing the selectivity. Subsequent coupling reactions of the allenic/propargylic zirconium intermediates with aryl iodides in the presence of $Pd(PPh_3)_4$/CuCl provide a straightforward route for the synthesis of multisubstituted allenes.

Introduction

Organozirconium compounds are attractive intermediates in an impressive array of synthetic methodology and have received much attention in recent years.[1] Among various possibilities for the generation of organozirconium reagents, low-valent zirconium induced β-alkoxide elimination reaction is a particularly attractive protocol.[2] Due to the oxophilic nature of zirconium metal, it can cause the elimination of the alkoxy group at β-position of the zirconium metal to form useful organometals such as allylic,[3] γ-alkoxy allylic,[4] γ,γ-dialkoxy allylic,[5] allenic,[3b,6] and alkenyl[7] zirconium

*To whom correspondence should be addressed. Fax: (+86) 021-64166128.

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SCHEME 1
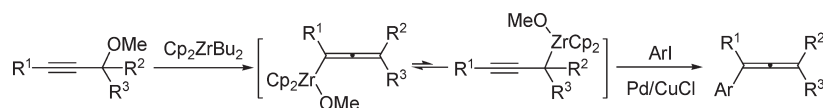
SCHEME 2
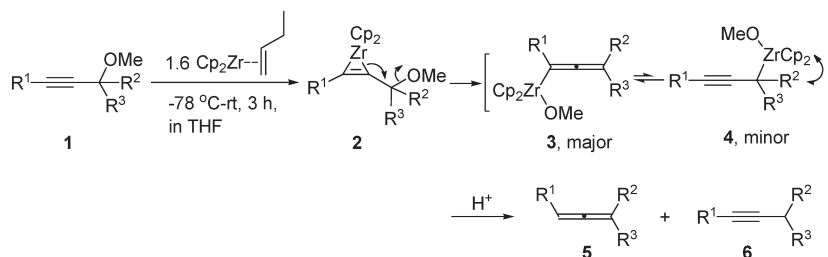
species. β-Alkoxide elimination from zirconacycles has also been reported for the construction of allenes.[8] Allenic/propargylic zirconium species can be conveniently prepared by treatment of propargylic ethers with dibutylzirconocene complex (Negishi reagent). However, the synthetic utility of these intermediates has only been described in the reaction with aldehydes, which affords mainly homopropargyl alcohols.[3b,6] Nevertheless, the development of new C−C bond formation reactions via these organometallic derivatives is still highly demanding. In this paper, we report the substituent-dependent generation of the allenic zirconium complexes and their coupling reactions with aryl halides (Scheme 1). The coupling reaction of aryl halides with organometals represents one of the most powerful methods for C−C bond formation. Although the coupling reactions of aryl iodides with various organozirconocenes such as vinyl zirconocenes, zirconacyclopentenes, or zirconacyclopentadienes are known,[9] there is no report for the coupling reactions with allenic/propargylic zirconium complexes to the best of our knowledge. The present method could be readily applied to the synthesis of multisubstituted allenes.

Results and Discussion

Hydrolysis of Allenic/Propargylic Zirconium Complexes Generated from Propargylic Ether. Our investigation began with an examination of the reaction between propargylic ether **1** with Negishi reagent "Cp$_2$ZrBu$_2$" (Scheme 2). In principle, both the allenic **3** and propargylic zirconium species **4** could be formed under the reaction conditions, and there exists an equilibrium between the two species. The latter is suggested to be produced through a 1,3-metallotropic rearrangement. As proposed by Taguchi et al.,[3b,6] when the propargylic ether contains a substituent at the propargylic position, the allenic zirconium will be formed preferentially due to the steric repulsion between R^2/R^3 substituent and the metal center. We envisioned that

hydrolysis of the reaction mixture might form allenes, which could also account for the existence of allenic zirconium species. However, there are no such results in their report. Here we found that quenching the reaction mixture by 3 N HCl aqueous solution in the case of propargyl methyl ether **1a** (R^1 = Ph) bearing a cyclic ring at C-1 selectively afforded allene **5a** in 87% yield without contamination of any alkyne **6a** (Scheme 2 and Table 1, entry 1). Alkyl-substituted propargylic ethers **1b**, **1d**, and **1e** afforded similar results, although with lower yield compared with the phenyl-substituted propargylic ether (entries 2, 4, and 5). The substrate of **1f** tethered with a phenyl group on the alkyne substituent afforded allene **5f** and alkyne **6f** in 81% and 6% yields, respectively (entry 6). C-1 substituted by two methyl groups gave exclusively allene **5g** in 64% yield (entry 7). C-1-monosubstituted propargylic ethers **1h−j** also gave rise to allenes as major products (entries 8−10). The above reactions also provided an efficient method for the synthesis of allenes by simply quenching the zirconium intermediates.[10] Interestingly, when R^1 was a TMS group, the reaction selectively generated alkynes **6k−n** in 55−70% yields (entries 11−14), whereas the allene products were not detected. It is noteworthy that bulky ^{t}Bu-substituted **1j** reacted completely differently with zirconocene−butene complex compared with TMS-substituted one, in which allene **5j** was obtained as a major product (entry 10). In addition to the steric effect caused by TMS group, the special

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TABLE 1. Formation of Allenes and/or Alkynes by the Reaction of Cp$_2$ZrBu$_2$ with Propargyl Ethers

entry	propargyl ether	product 5	yield(%)[a]	product 6	yield(%)[a]
1	1a	5a, R^1=Ph	87	-	
2	1b	5b, R^1=Bu	58	-	
3	1c	5c, R^1=Ph	92	-	
4	1d	5d, R^1=Pr	53	-	
5	1e	5e, R^1=Bu	62	-	
6	1f	5f, R^1= -CH$_2$CH$_2$Ph	81	6f	6
7	1g	5g	64	-	
8[b]	1h	5h	71	6h	9
9[b]	1i	5i	64	-	
10	1j	5j	72	6j	11
11[b]	1k	-		6k	69
12[b]	1l	-		6l	70
13[c]	1m	-		6m	60
14[c]	1n	-		6n	55

[a] Isolated yields. Unless noted, all the reactions were carried out using 1.6 equiv of Negishi reagent at room temperature for 3 h. [b] 1.25 equiv of Negishi reagent was used. [c] 2.0 equiv of Negishi reagent was used.

electronic effects of the TMS group might also be responsible for the observed experimental results. These unusual results prompted us to investigate the in situ NMR of the reaction with TMS-substituted propargylic ethers. Surprisingly, it was found that the allenic zirconium species **3n** (R^1 = TMS, R^2, R^3 = −(CH$_2$)$_5$−) was formed as a major zirconium species (90% NMR yield) according to ^{1}H and ^{13}C NMR spectra in the case of propargylic ether **1n**.[11] In ^{13}C NMR, the low-field signal (195.4 ppm) is characteristic for sp carbon in allene skeleton. The in situ NMR of allenic zirconium **3m** (R^1 = TMS, R^2, R^3 = ^{n}Pr) has also been investigated, which is similar to that of **3n**.[12]

To better understand the structure of intermediates **3** and **4**, density functional theory (DFT)[13] studies have been performed with the Gaussian03 program[14] using the B3LYP[15]

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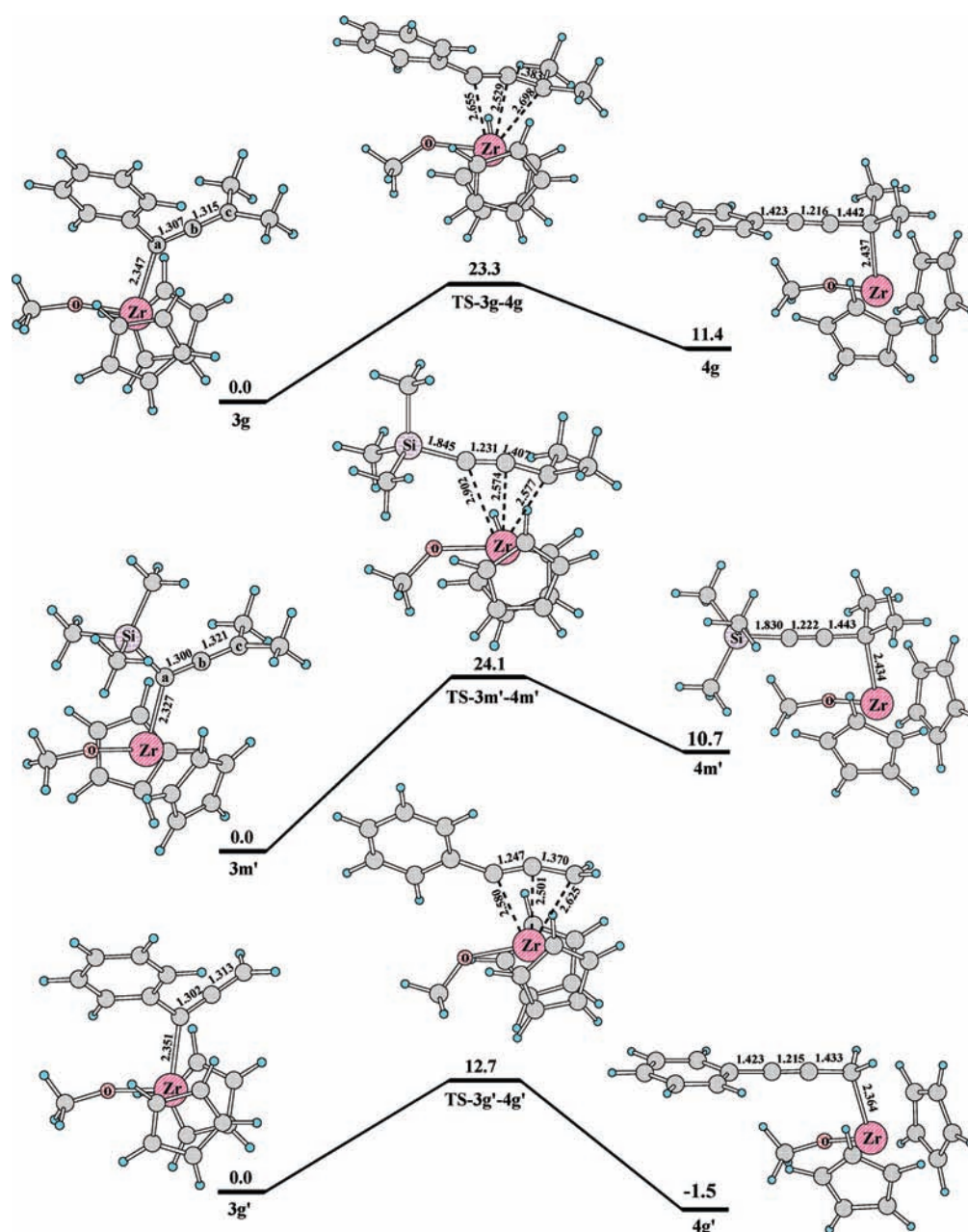
FIGURE 1. Optimized allenic structures **3g** (R^1 = Ph, R^2 = R^3 = Me), **3m′** (R^1 = TMS, R^2 = R^3 = Me) and **3g′** (R^1 = Ph, R^2 = R^3 = H), the propargylic structures **4g**, **4m′**, and **4g′**, the rearrangement transition states **TS-3g−4g**, **TS-3m′−4m′**, and **TS-3g′−4g′**. The selected bond lengths are in angstroms, and the relative free energies ΔG are in kcal/mol. Calculated at B3LYP/6-311+G**/Lanl2DZ level.

method. For C, H, O, Cl, and Si, the 6-311+G** basis set was used; for Zr the Lanl2DZ basis set with Effective Core Potential (ECP)[16] was used. The optimized structures were all checked with harmonic vibration frequency calculations. The structures of allenic zirconium species **3g** (R^1 = Ph, R^2 = R^3 = Me), propargylic zirconium species **4g** and the transition states for their rearrangement **TS-3g−4g** have been fully optimized with complete models (Figure 1). For the TMS

substituted propargylic ether **1m**, the simplified model **3m′** with R^2 = R^3 = Me was used. To find out the effect of the R^2 and R^3 group, the model **3g′** with R^1 = Ph and R^2 = R^3 = H was also studied.[17]

The results indicate that the allenic structure **3g** is more stable than the propargylic structure **4g** by about 11.4 kcal/mol. Therefore, the allenic structure **3g** should be dominant under room temperature. The barrier of the rearrangement from **3g** to **4g** (**TS-3g−4g**) is 23.3 kcal/mol. For **3m′**, the situation is similar. Therefore, R^1 has small effect on the equilibrium of **3** and **4**. The barriers of the rearrangement are over 23 kcal/mol, which indicates a reaction being completed within hours. Since the hydrolysis of **3g** and **3m** by 3 N HCl can be completed within minutes, the hydrolysis via the

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(17) For the reaction of propargyl ether without substituent at the C-1 carbon such as (3-(benzyloxy)prop-1-ynyl)benzene with 2 equiv of Negishi reagent, see ref 3b. The reaction produced (Z)-β-methylstyrene as a sole product, which was explained by addition of "Cp₂Zr" to propargyl zirconium species.
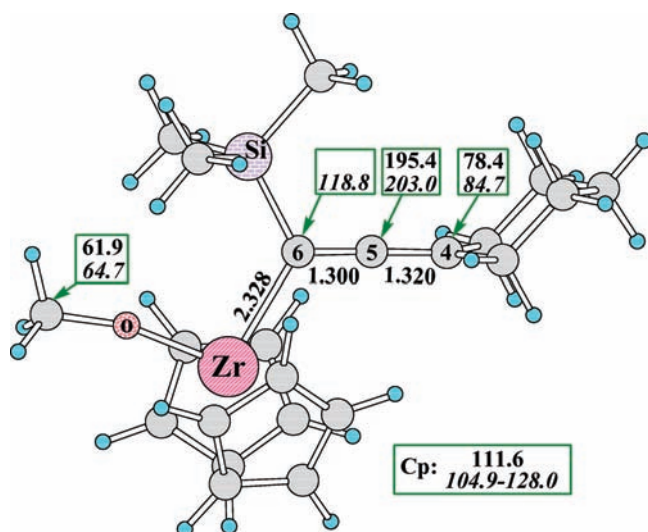
FIGURE 2. Optimized structure of **3n**, the selected ^{13}C chemical shifts (regular font for experimental values, and italic for calculated results), and bond lengths (in angstroms). Both the geometry optimization and the NMR studies were calculated at B3LYP/6-311+G**/Lanl2DZ level.

propargylic pathway can be excluded safely. Interestingly, the propargylic structure **4g′** is more stable than the allenic structure **3g′** by 1.5 kcal/mol, and the rearrangement barrier (**TS-3g′−4g′**) is also dropped to 12.7 kcal/mol, indicating that R^2 and R^3 have great effect on the relative stabilities of **3** and **4**. The C−Zr bond length in **4g** (2.437 Å) and **4m′** (2.434 Å) are much longer than those in **4 g′** (2.364 Å), **3g** (2.347 Å), and **3m′** (2.327 Å). This indicates that the large repulsion between the R^2/R^3 and the Cp rings decreases the interaction of the carbanion and the metal center. Consequently the energies of the propargylic structures are increased.[3b,6]

To further confirm that the allenic structure **3** is dominant under room temperature, the ^{13}C chemical shifts of **3n** were calculated by gauge including atomic orbital (GIAO) method.[18] The selected results are shown in Figure 2. The calculated NMR shifts are in good agreement with the experimental values.[19]

The mechanisms of the hydrolysis of **3g** and **3m′** by 3N HCl have been studied with the models shown in Figure 3. In these models, both the proton H^+ and the $Cl^−$ ion were solvated by an explicit water molecule. The long rang solvent effect was estimated with IEFPCM[20] (UAHF atomic radii) method in water ($\varepsilon = 78.39$) using the gas-phase optimized structures. The atomic charges were calculated by NBO natural bonding analysis.[21] As shown in Figure 3, in transition states **TS-3g-alkyne** and **TS-3m′-alkyne**, the protons attack C_c and lead to alkyne products, whereas in transition states **TS-3g-allene** and **TS-3m′-allene**, the protons attack C_a and lead to allene products. **TS-3g-allene** is 6.8 kcal/mol lower in energy than **TS-3g-alkyne**; however, **TS-3m′-allene** is 4.7 kcal/mol higher in energy than **TS-3m′-alkyne**, which is

well consistent with the experimental observations: **3g** favors the allenic product, whereas **3m′** favors the alkyne product.

Generally, in the allenic zirconium complexes **3g** and **3m′**, the carbon atom which is connected with the Zr center (C_a) possesses a greater negative charge. In **3g**, the NBO charges on C_a and C_c are −0.465 and −0.158, respectively; in **3m′**, the NBO charges on C_a and C_c are −0.901 and −0.198, respectively. Consequently, C_a is more easily attacked by the proton. This is the case for **3g**. However, the situation may be changed by the steric effect of R^1, R^2, and R^3. Obviously, in **TS-3g-allene** the flat phenyl group causes small steric energy on the attack of the proton, whereas in **TS-3m′-allene** the bulky TMS group will cause large steric repulsion. **3g** or **3m′** will be distorted on the attack of the proton. This distortion is to some extent caused by the steric effect of R^1, R^2, R^3, and the Cp rings. Therefore, the steric energies in the four transition states were estimated by the distortion energy (**DE**).[22] **DE** was calculated by this way: for the four transition states shown in Figure 3, the HCl and the two H_2O molecules were deleted with the rest part unchanged, and then the single-point energies were calculated. Using the undistorted **3g** and **3m′** as the zero-point references, the relative distortion energies for the four transition states were obtained. As shown in Figure 3, the **DE** of **TS-3m′-allene** is 3.3 kcal/mol higher than that of **TS-3m′-alkyne**, whereas the **DE** of **TS-3g-allene** is nearly the same as that of **TS-3g-alkyne**. Thus, the steric effect is one of the important factors to determine the selectivity.

On the other hand, for the transition states to form alkyne products, the attack of the proton on C_c will arouse positive charges on C_b. The calculated NBO atomic charges of C_b in **TS-3m′-alkyne** is 0.203. It is smaller than that of C_b in **TS-3g-alkyne** (0.257), indicating that TMS group can stabilize the positive charges on C_b. This can be explained by the well-known β-effect[23] of the TMS group; i.e., the hyperconjugation of the C_a-Si σ bond with the partially positive charged p orbital on the β position (C_b). Thus, both the large steric effect and the β-effect of the TMS group favor the alkyne product, reversing the selectivity.

Cross-Coupling Reactions of Allenic/Propargylic Zirconium Complexes with Aryl Halides. We next proceeded to investigate the coupling reactions of the allenic/propargylic zirconium species with aryl iodides. Here, we found that treatment of the reaction mixture of **1c** and Cp_2ZrBu_2 with 1.2 equiv of CuCl[9] and 1.2 equiv of PhI in the presence of 5 mol % of $Pd(PPh_3)_4$ at room temperature for 2 h afforded arylated allene **7a** in 72% yield (Scheme 3 and Table 2, entry 1). Aryl iodides bearing electron- donating or electron-withdrawing substituents could be used, furnishing the corresponding products **7b−d** in 64−71% yields (Table 2, entries 2−4). It should be noted that in some cases, addition of 2 equiv of DMAP and stirring for 1 h before coupling reactions would afford better yields of the desired products and also result in a cleaner reaction. For example, in the case of alkyl-substituted propargylic ether **1e**, the allene **7e** was formed in a higher yield of 79% in the presence of DMAP (Table 2, entry 5). DMAP was suggested to be coordinated with the excess amount of the low-valent zirconium species, which

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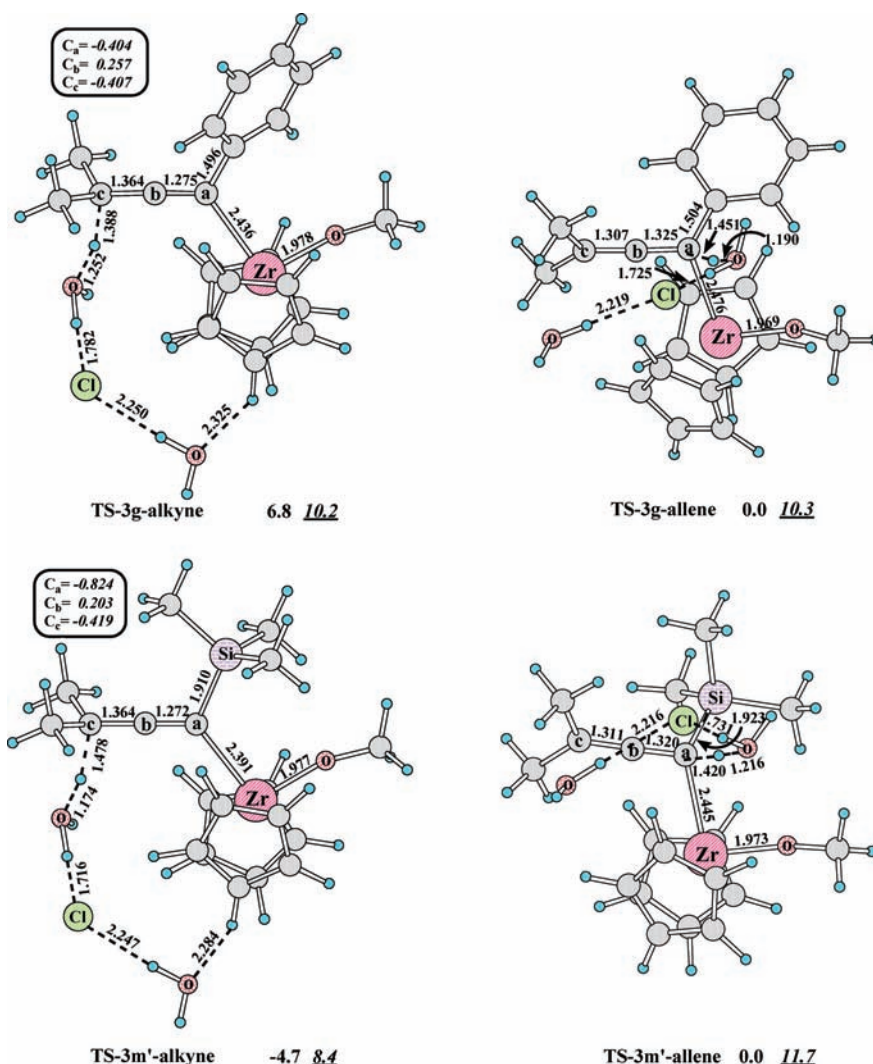
FIGURE 3. Optimized transition states for the hydrolysis reaction. The selected NBO charges for C_a, C_b, and C_c are given in the box. The selected bond lengths (bold) are in angstroms, and the relative free energies including solvent effect ΔG_{sol} (bold) and the relative distortion energies (**DE**, italic underlined) are in kcal/mol. Calculated at the B3LYP/6-311+G**/Lanl2DZ level.

may give a negative effect on the coupling process. When C-1-monosubstituted substrates **1h–j** were employed, the corresponding allenes **7i–k** were formed in good to high yields (entry 9–11). In these cases, DMAP had little influence on the reaction. Interestingly, in the cases of TMS-substituted propargylic ether **1k–n**, the coupling reactions with ArI still generated the allene type of products **7l–o** in 46–73% yields (entries 12–15). The results indicated that the coupling precursor of the metal intermediate was an allenic zirconium. These coupling reactions are also quite different with that of the Pd-catalyzed coupling reaction of allenic/propargylic zinc species with phenyl iodide,[24] in which a TMS substituent results in the formation of both arylated alkyne and allene.

A plausible reaction mechanism is shown in Scheme 4. First, an allenic zirconium **3** and propargylic zirconium **4** are formed in the reaction mixture through β-alkoxide elimination. In all of the cases, the allenic zirconium **3** is formed as a predominant zirconium species due to the steric interaction

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(24) Ma, S.; Zhang, A. *J. Org. Chem.* **2002**, *67*, 2287.

SCHEME 3
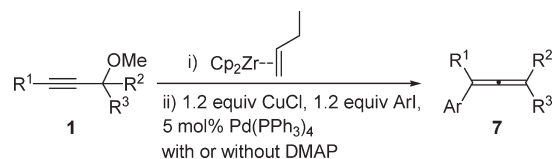
between the R^2/R^3 group and the zirconium atom in **4**. Transmetalation of both of the Zr–C bonds in **3** and **4** to a Cu–C bond affords allenic/propargylic copper species **8** and **9**; however, the equilibrium leaves largely on the side of allenic copper **8**. This is followed by transmetalation with an arylpalladium intermediate generated from ArI and a Pd(0) catalyst, and then reductive elimination to form the desired arylated products.

To further demonstrate the utility of allenic/propargylic zirconium species, the coupling reactions with allylic halides were carried out. The allylic allenes were obtained cleanly in 54–76% yields in the presence of CuCl (Table 3). Without CuCl, no allylation occurred.

TABLE 2. Coupling Reactions of Allenic/Propargylic Zirconium Species with Aryl Iodides

entry	substrate	ArI	condition	products		yields(%)[a]
1	**1c**	PhI	rt, 2 h	Ph / Ph (cyclohexylidene allene)	**7a**	72
2	**1c**	p-MeC$_6$H$_4$I	rt, 2 h		**7b**	71
3	**1c**	p-ClC$_6$H$_4$I	rt, 2 h		**7c**	64
4	**1c**	p-NO$_2$C$_6$H$_4$I	rt, 2 h		**7d**	64
5	**1e**	PhI	rt, 2 h	Bu / Ph	**7e**	55(79)
6	**1f**	p-NO$_2$C$_6$H$_4$I	rt, 2 h	Bn / p-NO$_2$C$_6$H$_4$	**7f**	(73)
7	**1g**	PhI	rt, 2 h	Ph / Ph	**7g**	(57)
8	**1g**	p-ClC$_6$H$_4$I	rt, 2 h	Ph / p-ClC$_6$H$_4$	**7h**	(64)
9[b]	**1h**	PhI	rt, 2 h	Ph / Ph / i-Pr	**7i**	70
10[b]	**1i**	PhI	rt, 2 h	Ph / Ph / n-Pr	**7j**	55(58)
11	**1j**	PhI	rt, 2 h	t-Bu / Ph / n-Hex	**7k**	87(82)
12[b]	**1k**	PhI	rt, 2 h	TMS / Ph / Hex	**7l**	73
13[b]	**1l**	PhI	rt, 2 h	TMS / Ph / Et / Bu	**7m**	61
14[c]	**1m**	PhI	50 °C, 24 h	TMS / Pr / Ph / Pr	**7n**	(46)
15[c]	**1n**	PhI	50 °C, overnight	TMS / Ph (cyclohexylidene)	**7o**	(65)

[a]Isolated yields. The yields with 2.0 equiv of DMAP are shown in parentheses. Unless noted, all the reactions were carried out using 1.6 equiv of Negishi reagent. [b]1.25 equiv of Negishi reagent was used. [c]2.0 equiv of Negishi reagent was used.

SCHEME 4
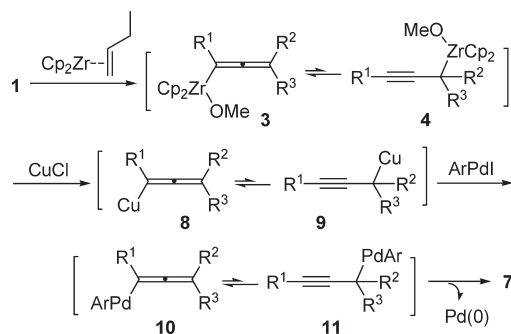
Conclusion

In summary, we have shown that the β-alkoxide elimination reaction of propargylic ether with Negishi reagent leads to allenes and/or alkynes after hydrolysis, which can be obtained selectively by tuning the substituents on the alkyne terminus of the propargylic ether. The subsequent coupling reactions with aryl iodides in the presence of Pd/CuCl provided a straightforward route for the synthesis of multisubstituted allenes.

Experimental Section

General Procedure for the Synthesis of Allenes 5 and/or Alkynes 6 via the β-Alkoxide Elimination Reaction of Propargylic Methyl Ethers with Negishi Reagent. To a solution of Cp$_2$ZrCl$_2$ (0.234 g, 0.8 mmol) in THF (5 mL) was added n-BuLi (1.6 M solution in hexanes, 1.0 mL, 1.6 mmol) at −78 °C. After the mixture was stirred for 1 h at the same temperature, propargylic methyl ether (0.5 mmol) was added, and then the mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was quenched with 3 N HCl aqueous solution and extracted with ethyl ether. The extract was washed with saturated NaHCO$_3$ solution and dried over MgSO$_4$. The solvent was evaporated in vacuo, and the residue was purified by chromatography on silica gel to afford allenes **5** and/or

TABLE 3. Reactions of Allenic Zirconium with Allyl Halides
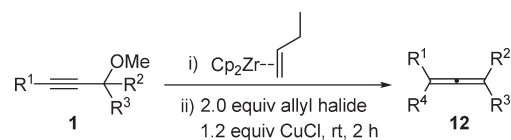
entry	substrate	allyl halide	product	yields(%)[a]
1	**1c**	Cl	**12a**	73
2	**1c**	Br	**12a**	76
3	**1c**	Cl	**12b**	67
4	**1g**	Cl	**12c**	54[b]

[a]Isolated yields. [b]2.0 equiv DMAP was added and the mixture stirred for 1 h before addition of allyl chloride.

alkynes **6**. (**2-Cyclopentylidenevinyl)benzene (5a).** Column chromatography on silica gel (petroleum ether) afforded the title product in 87% isolated yield: ^{1}H NMR (CDCl$_3$, Me$_4$Si) δ 1.69−1.79 (m, 4H), 2.40−2.57 (m, 4H), 6.06−6.11 (m, 1H), 7.11−7.18 (m, 1H), 7.26−7.30 (m, 4H); ^{13}C NMR (CDCl$_3$, Me$_4$Si) δ 27.2, 31.1, 94.8, 107.5, 126.3, 126.6, 128.4, 136.0, 198.6; HRMS (EI) for C$_{13}$H$_{14}$ calcd 170.1096, found 170.1104.

General Procedure for the Synthesis of Arylated Allenes 7 through the Coupling Reactions of Allenic Zirconium Complexes with Aryl Iodides. To a solution of Cp$_2$ZrCl$_2$ (0.234 g, 0.8 mmol) in THF (5 mL) was added *n*-BuLi (1.6 M solution in hexanes, 1.0 mL, 1.6 mmol) at −78 °C. After the mixture was stirred for 1 h at the same temperature, propargylic methyl ether (0.5 mmol) was added, and then the mixture was warmed to room temperature and stirred for 3 h. Aryl iodides (0.6 mmol), Pd(PPh$_3$)$_4$ (29 mg, 0.025 mmol), and CuCl (60 mg, 0.6 mmol) were added, and the mixture was stirred at room temperature for 2 h. In some cases, the addition of 2 equiv of DMAP and stirring for 1 h before coupling reactions was performed. The reaction mixture was quenched with 3 N HCl aqueous solution and extracted with ethyl ether. The extract was washed with saturated NaHCO$_3$ solution and dried over MgSO$_4$. The solvent was evaporated in vacuo, and the residue was purified by chromatography on silica gel to afford aryl-substituted allenes **7**. **1-(2-Cyclohexylidene-1-phenylvinyl)-4-methylbenzene (7b).** Column chromatography on silica gel (petroleum ether) afforded the title product in 71% isolated yield: ^{1}H NMR (CDCl$_3$, Me$_4$Si) δ 1.56−1.58 (m, 2H), 1.66−1.67 (m, 4H), 2.27−2.30 (m, 4H), 2.34 (s, 3H), 7.12 (d, J = 8.1 Hz, 2H), 7.19−7.25 (m, 3H), 7.27−7.36 (m, 4H); ^{13}C NMR (CDCl$_3$, Me$_4$Si) δ 21.1, 26.1, 27.6, 31.5, 105.4, 107.3, 126.5, 128.1, 128.4, 128.9, 135.2, 136.3, 138.4, 200.2; HRMS (EI) for C$_{21}$H$_{22}$ calcd 274.1722, found 274.1721.

Supporting Information Available: General methods and spectroscopic characterization of all new compounds calculated total energies and geometrical coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.