Conjugated Enyne Synthesis by Rearrangement of Acetylenic Epoxides Mediated by Low-Valence Organotitanium and Organozirconium Reagents

Aurélien Denichoux, Mathieu Cyklinsky, Fabrice Chemla,* Franck Ferreira,* Alejandro Pérez-Luna

Université Pierre et Marie Curie-Paris 6, UMR CNRS 7201, Institut Parisien de Chimie Moléculaire, Institut de Chimie Moléculaire (FR 2769), Case 183, 4 place Jussieu, 75252 Paris Cedex 05, France
Fax +33(144)277567; E-mail: fabrice.chemla@upmc.fr; E-mail: franck.ferreira@upmc.fr

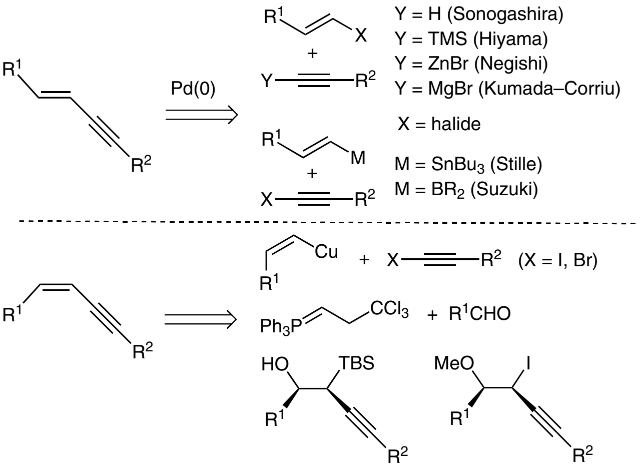
Received: 10.01.2013; Accepted after revision: 17.03.2013

Abstract: The rearrangement of acetylenic epoxides mediated by low-valence organotitanium and organozirconium reagents is reported to give conjugated enynes. Moderate to good yields and high selectivities are obtained when using the organozirconium(II) Negishi reagent in toluene at 20 °C; whereas only poor yields and low selectivities are achieved with the organotitanium(II) Sato reagent. The process is stereospecific and involves formation of titana- and zirconacyclopropenes by oxidative insertion of the low-valence titanium and zirconium reagents into the carbon–carbon triple bond of the acetylenic epoxides. These metallacyclopropenes then rearrange to afford stereodefined propargylmetals through the epoxide ring-opening. Conjugated enynes are finally produced by β-elimination of metal oxide.

Key words: elimination, enynes, rearrangement, titanium, zirconium

The conjugated enyne motif is largely widespread in natural products and has been intensively exploited in synthesis. The methods most commonly used for its synthesis utilize palladium(0)-catalyzed C(sp^2)–C(sp) cross-couplings between vinylic and acetylenic partners (Scheme 1). All these methods generally involve the cross-coupling of a vinyl halide with a terminal alkyne (Sonogashira coupling),[1,2] an alkynylsilane (Hiyama coupling),[3] an alkynylzinc (Negishi coupling),[1] or an alkynyl Grignard reagent (Kumada–Corriu coupling).[1,4] The cross-couplings of a vinylstannane (Stille coupling)[5] or a vinylborane (Suzuki coupling)[6] with an alkynyl halide are also efficient means to access conjugated enynes. Other less employed metal-catalyzed cross-coupling reactions are also described in the literature.[7–10]

All these metal-catalyzed cross-couplings require the use of stereomerically pure vinylic precursors, constituting the main obstacle to their application in the stereoselective synthesis of *Z* conjugated enynes. Alternative methods include the reaction of a *Z*-alkenylcopper reagent with an alkynyl iodide or bromide,[11] a sequence that combines the Wittig olefination reaction using 3,3,3-trichloropropylidene-1-triphenylphosphorane with the Corey–Fuchs rearrangement,[12] Peterson *syn* β-elimination of propargylic β-hydoxysilanes,[13] and *n*-BuLi-induced *syn* β-elimination of propargylic iodohydrin derivatives.[14]

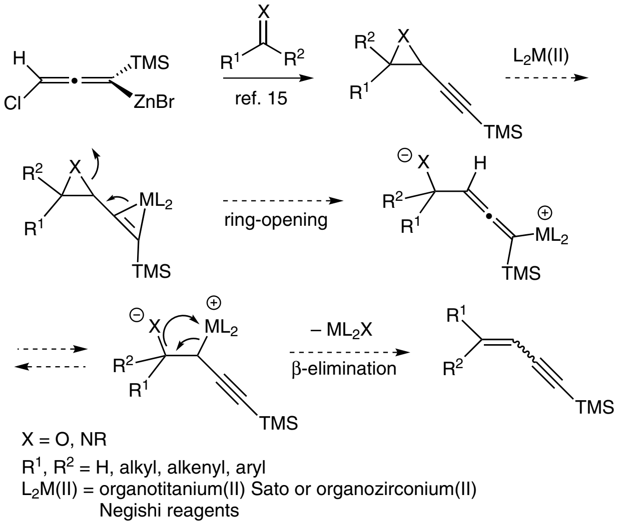


Scheme 1 Common syntheses of conjugated enynes

During the past decade, we have developed a stereoselective route to acetylenic epoxides and aziridines by reaction of allenylzinc reagents with carbonyl derivatives and imines, respectively.[15] Inspired by previous work on the preparation of conjugated dienes by zirconocene-mediated deoxygenation of vinyl epoxides,[16] we reasoned that acetylenic epoxides and aziridines could be precursors to conjugated enynes by reaction with low-valence metals such as the organotitanium(II) Sato reagent [formally a (i-PrO)$_2$Ti·propylene complex][17] or the organozirconium(II) Negishi reagent [formally a Cp$_2$Zr·(1-butene) complex].[18] The oxidative insertion of these low-valence metallic complexes into the carbon–carbon triple bond of acetylenic epoxides and aziridines was anticipated to give titana- and zirconacyclopropenes that could undergo heterocycle ring-opening.[19] This would result in the formation of allenyltitanium and allenylzirconium species that are in equilibrium with their respective propargylic forms.[20] Finally, β-elimination of metal oxo or imido complexes was expected to afford the corresponding conjugated enynes (Scheme 2).

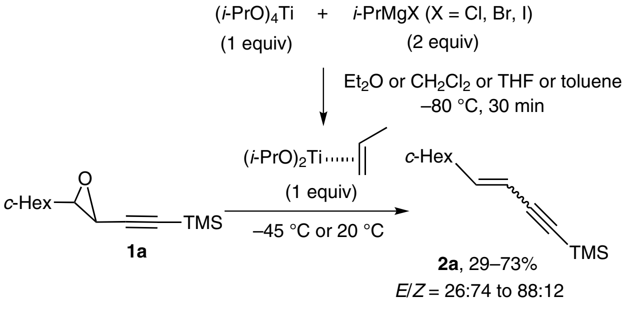
We initiated our studies with prototypical *trans*-acetylenic epoxide **1a** that was reacted with Sato reagent generated in situ from (i-PrO)$_4$Ti (1 equiv) and i-PrMgX (2 equiv) for 30 minutes at –80 °C. Gratifyingly, regardless of the reaction conditions employed, conjugated enyne **2a** was formed, albeit in moderate yields with poor *E*/*Z* selectivities (Scheme 3). In all cases, unidentified by-products were observed. Their formation was explained by the re-

SYNLETT 2013, 24, 1001–1005
Advanced online publication: 28.03.2013
DOI: 10.1055/s-0032-1316894; Art ID: ST-2013-D0034-L



Scheme 2 Our work

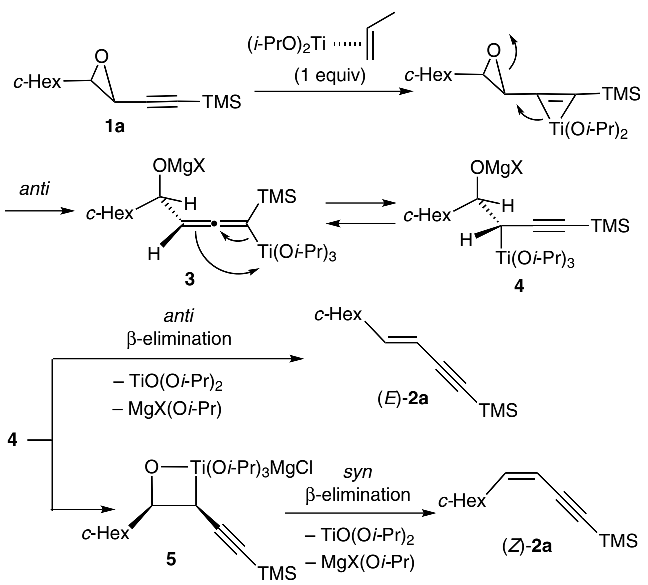
action of enyne **2a** with the Sato reagent that is indeed reported to be prone to react with conjugated enynes through the formation of enyne–titanium complexes.[21]



Scheme 3 Reaction of **1a** with Sato reagent

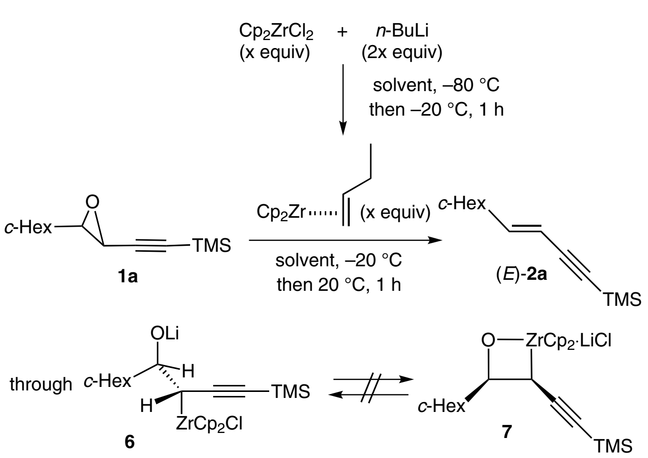
Although unsatisfactory both in terms of yield and selectivity, the results obtained with the Sato reagent validated our approach to conjugated enynes based on the rearrangement of acetylenic epoxides mediated by low-valence metal species. The epoxide ring-opening thus should occur in an *anti* manner subsequently to oxidative addition of the organotitanium(II) reagent. This could afford allenyltitanium **3** stereoselectively in equilibrium with the propargylic isomer **4** (Scheme 4).

The organotitanium species so formed should be configurationally stable as previously reported in the analogous reaction of substrates bearing leaving groups at the propargylic position.[22] At this point, the direct *anti* β-elimination of titanium oxide could take place giving conjugated enyne (*E*)-**2a**. The β-elimination could be favored in the presence of magnesium salts (MgX_2) produced in situ that could coordinate to the oxygen atom of the alkoxide moiety. On the other hand, because of the high oxophilicity of the titanium(IV) species, cyclic magnesium organotitanate **5** may be produced through free rotation around the σ carbon–carbon bond. Intermediate **5** could thus undergo the *syn* β-elimination of titanium oxide to afford conjugated enyne (*Z*)-**2a**.



Scheme 4 Mechanism of the reaction of **1a** with Sato reagent

Encouraged by the results obtained with the Sato reagent, we next examined the use of the Negishi reagent. Under optimized conditions, this reagent is preformed by adding *n*-BuLi (2 equiv) at –80 °C to a solution of Cp_2ZrCl_2 (1 equiv). This first leads to $Cp_2Zr(n\text{-Bu})_2$ then finally gives the desired organozirconium(II) reagent after an additional one hour stirring at –20 °C (Scheme 5).[23]



Scheme 5 Reaction of **1a** with Negishi reagent (see Table 1)

Thus, when reacting **1a** with the preformed Negishi reagent (1 equiv) at 0 °C or below, conjugated enyne **2a** was isolated in very low yields regardless the solvent, even though excellent stereoselectivities were achieved in favor of the *E*-isomer (Table 1, entries 1–3). Under these conditions, degradation was observed to some extent. By contrast, carrying out the reaction at 20 °C allowed **2a** to be produced in reasonable yields within one hour (Table 1, entries 4–6). Although in all cases excellent *E*/*Z* ratios were attained, only the use of toluene as solvent afforded

Table 1 Reaction of **1a** with Negishi Reagent (See Scheme 5)

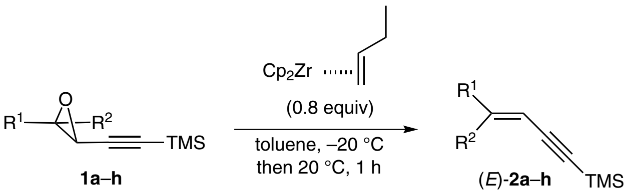
Entry	Solvent	Temp (°C)	Equiv (x)	*E*/*Z*[a]	Yield (%)[b]
1	THF	–20	1.0	92:08	9 (23)
2	Et_2O	0	1.0	–	0 (47)
3	toluene	–20	1.0	>98:02	6 (16)
4	THF	20	1.0	86:14	55 (83)
5	Et_2O	20	1.0	89:11	64 (97)
6	toluene	20	1.0	>98:02	48 (96)
7	toluene	20	1.2	>98:02	25 (62)
8	toluene	20	0.8	>98:02	64 (84)[c]
9	Et_2O[d]	20	1.0	87:13	63 (86)

[a] Selectivities were determined by ^1H NMR analysis at 400 MHz of the crude materials.
[b] Isolated yields. In parenthesis are given the conversions into **2a** based upon recovered **1a**.
[c] Isolated yield and conversion relative to 0.8 equiv of Negishi reagent.
[d] Reaction was conducted with Cp_2TiCl_2.

complete selectivity in favor of the *E*-isomer. Increasing the amount of Negishi reagent to 1.2 equivalents relative to **1a** resulted in a significantly lower yield (Table 1, entry 6 vs. entry 7). This result can be explained by the polymerization of **2a** by the excess organozirconium(II) species via carbozirconation of the carbon–carbon triple bond of **2a** giving zirconacyclopentenes.[24] Conversely, employing only 0.8 equivalent of Negishi reagent furnished *E*-conjugated enyne **2a** as the sole product and with an improved isolated yield of 64% (Table 1, entry 8).

Interestingly, in all cases better selectivities were observed with the Negishi reagent than with the Sato reagent. This could be first rationalized by comparing the hardness of the acidic metallic(IV) centers in **4** and **6**. Titanium(IV) is intrinsically a harder Lewis acid than zirconium(IV).[25] Accordingly, zirconium(IV) in **6** could be less likely to coordinate to the alkoxide (a hard base) as titanium(IV) in **4**. As a consequence **6** should be less prone to give the *Z*-isomer through cyclic zirconium intermediate **7**. However, the nature of the ligands on the metals could also play a role in these reactions.[26] To gain insight on the influence of both the metal and the ligand on the stereochemical outcome of the rearrangement, the reaction was thus performed with the titanium analogue of the Negishi reagent [formally the Cp_2Ti·(1-butene) complex] generated from Cp_2TiCl_2. At 20 °C in Et_2O the conjugated enyne **2a** was isolated in 63% yield and with an *E*/*Z* ratio of 87:13 (Table 1, entry 9). This result was significantly different from the ratio of 67:33 obtained with the Sato reagent under the same conditions, but very close to the 89:11 ratio obtained with the Negishi reagent. This result suggests that it is not the metal as such, but the nature of the ligand which is important in the stereochemical outcome of the rearrangement.

The optimized conditions in Table 1 [i.e., Negishi reagent (0.8 equiv), toluene, 20 °C, 1 h], were next applied to a variety of readily available *trans*-acetylenic epoxides **1** (Scheme 6).[15]



Scheme 6 Synthesis of (*E*)-**2a**–**h** from **1a**–**h** (see Table 2)

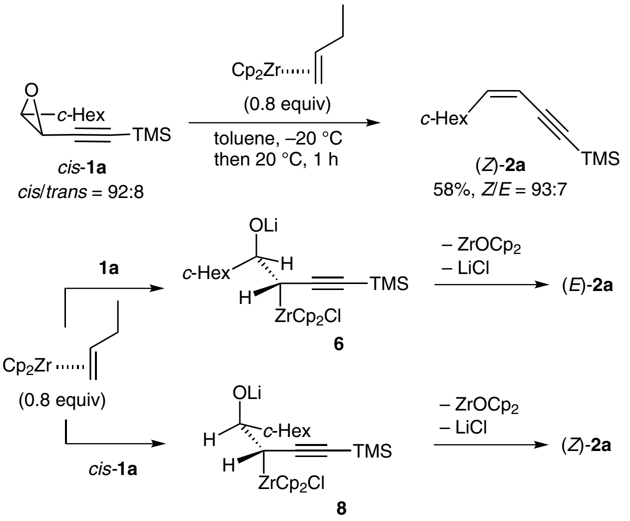
With all disubstituted epoxides, excellent *E*-selectivities were observed. Yields of conjugated enynes **2** were good with epoxides possessing alkyl substituents even though a low yield was obtained in the case of the *tert*-butyl group mainly due to the volatility of the product (Table 2, entries 1–4). Epoxides bearing ethenyl or aromatic substituents afforded the corresponding conjugated enynes in slightly lower yields (Table 2, entries 5 and 6). In contrast, when trisubstituted epoxides were used, significantly lower isolated yields were obtained (Table 2, entries 7 and 8).

Table 2 Synthesis of (*E*)-**2a**–**h** from **1a**–**h** (See Scheme 6)[27]

Entry	Epoxide	R^1	R^2	Enyne	*E*/*Z*[a]	Yield (%)[b]
1	**1a**	*c*-Hex	H	**2a**	>98:02	62
2	**1b**[c]	*n*-Bu	H	**2b**	93:07	67
3	**1c**	$Ph(CH_2)_2$	H	**2c**	>98:02	68
4	**1d**	*t*-Bu	H	**2d**	>98:02	30[d]
5	**1e**	PhCH=CH	H	**2e**	>98:02	55
6	**1f**	Ph	H	**2f**	>98:02	45
7	**1g**	*n*-Pent	*n*-Pent	**2g**	–	37
8	**1h**	Ph	Ph	**2h**	–	30

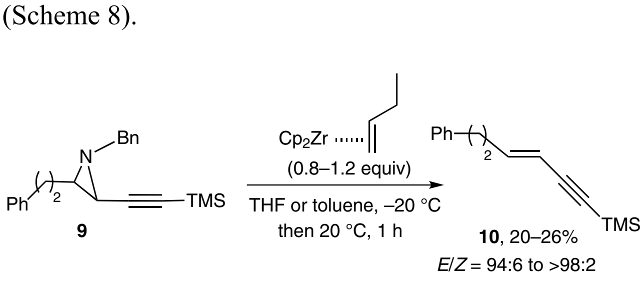
[a] Selectivities were determined by ^1H NMR analysis at 400 MHz of the crude materials.
[b] Isolated yields relative to 0.8 equiv of Negishi reagent.
[c] Ratio (*trans*/*cis*) = 92:08.
[d] Volatile product.

In order to gain further insight into the stereochemical outcome of the rearrangement mediated by the Negishi reagent, we carried out the reaction starting from epoxide *cis*-**1a**. Interestingly, under the optimized conditions, conjugated enyne (*Z*)-**2a** was isolated in good yield and with a high selectivity of 93:7 perfectly reflecting the initial 92:8 *cis*/*trans* ratio of **1a** (Scheme 7). All these results suggest that the zirconium(II)-mediated rearrangement is stereospecific, with acetylenic *trans*- and *cis*-epoxides giving *E*- and *Z*-isomers, respectively. As in the case of the Sato reagent, the ring-opening of the epoxide moiety should thus occur in an *anti*-fashion affording configurationally stable propargylzirconiums **6** and **8** that undergo the *anti* β-elimination of zirconium oxide.



Scheme 7 Stereospecificity of the rearrangement

The method was next applied to acetylenic aziridines. Using *N*-H or *N*-Bz aziridines with the Sato or Negishi reagents failed to produce conjugated enynes. With *N-tert*-butylsulfinyl and *N-tert*-butylsulfonyl aziridines, the desired products were isolated in moderate 32–39% yields and with low *E*-selectivities of ≤70:30. In fact, only *N*-Bn aziridines were found to give *E*-conjugated enynes with high selectivities, albeit in very poor isolated yields, as illustrated with **9** that furnished **10** in 20–26% yield and with a selectivity of ≥94:6 under optimized conditions (Scheme 8).



Scheme 8 Reaction of **9** with Negishi reagent

In conclusion, the synthesis of conjugated enynes by the reaction of acetylenic epoxides and aziridines with low-valence organotitanium(II) and organozirconium(II) reagents has been investigated. Only the reaction employing the Cp_2Zr·(1-butene) complex (Negishi reagent) and acetylenic epoxides has been fully satisfactory in producing di- and trisubstituted aliphatic and aromatic conjugated enynes, both in terms of reactivity and stereoselectivity. Using 0.8 equivalent of the Negishi reagent for one hour in toluene at 20 °C permitted stereospecific access to *E*- or *Z*- conjugated enynes from *trans*- and *cis*-acetylenic epoxides, respectively, in good yields and with complete selectivities.

Acknowledgment

The authors kindly thank the MESR for PhD grants to A.D. and M.C.

References and Notes

(1) For a review, see: Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.
(2) For examples, see: (a) Shao, L.-X.; Shi, M. *J. Org. Chem.* **2005**, *70*, 8635. (b) Saha, D.; Chatterjee, T.; Mukherjee, M.; Ranu, B. C. *J. Org. Chem.* **2012**, *77*, 9379.
(3) (a) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918. (b) Hatanaka, Y.; Matsui, K.; Hiyama, T. *Tetrahedron Lett.* **1989**, *30*, 2403.
(4) (a) Uemura, M.; Takayama, Y.; Sato, F. *Org. Lett.* **2004**, *6*, 5001. (b) Braun, M.; Hohmann, A.; Rahematpura, J.; Bühne, C.; Grimme, S. *Chem. Eur. J.* **2004**, *10*, 4584.
(5) For examples, see: (a) Rudisill, D. E.; Castonguay, L. A.; Stille, J. K. *Tetrahedron Lett.* **1988**, *29*, 1509. (b) Beaudet, I.; Parrain, J.-L.; Quintard, J.-P. *Tetrahedron Lett.* **1992**, *33*, 3647.
(6) (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, 3437. (b) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866.
(7) For palladium(0)- and nickel(0)-catalyzed cross-couplings of zinc reagents with 1,2-vinylic tellurides, see: (a) Raminelli, C.; da Silva, N. C.; Dos Santos, A. A.; Porto, A. L. M.; Andrade, L. H.; Comasseto, J. V. *Tetrahedron* **2005**, *61*, 409. (b) Raminelli, C.; Gargalaka, J. Jr.; Silveira, C. C.; Comasseto, J. V. *Tetrahedron* **2007**, *63*, 8801.
(8) For examples of palladium(0)-catalyzed cross-coupling of vinylboranes with alkynyllithiums, see: Negishi, E.; Yoshida, T.; Abramovich, A.; Lew, G.; Williams, R. M. *Tetrahedron* **1991**, *47*, 343.
(9) For examples of copper(I)-catalyzed cross-couplings of vinyl iodides with terminal alkynes, see: (a) Marshall, J. A.; Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2001**, *3*, 4107. (b) Bates, C. G.; Saejueng, P.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 1441. (c) Saejeung, P.; Bates, C. G.; Venkataraman, D. *Synthesis* **2005**, 1706.
(10) For cobalt(II)-catalyzed cross-couplings of vinyltriflates with alkynyl Grignard reagents, see: Shirakawa, E.; Sato, T.; Imazaki, Y.; Kimura, T.; Hayashi, T. *Chem. Commun.* **2007**, 4513.
(11) Commerçon, A.; Normant, J. F.; Villieras, J. *Tetrahedron* **1980**, *36*, 1215.
(12) For examples, see: (a) Wang, Z.; Campagna, S.; Yang, K.; Xu, G.; Pierce, M. E.; Fortunak, J. M.; Confalone, P. N. *J. Org. Chem.* **2000**, *65*, 1889. (b) Karatholuvhu, M. S.; Fuchs, P. L. *J. Am. Chem. Soc.* **2004**, *126*, 14314.
(13) For examples, see: (a) Wang, K. K.; Shi, C.; Petersen, J. L. *J. Org. Chem.* **1998**, *63*, 4413. (b) Badudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* **2001**, *51*, 549.
(14) For examples, see: (a) Inoue, A.; Maeda, K.; Shinokubo, H.; Oshima, K. *Tetrahedron* **1999**, *55*, 665. (b) Shinokubo, H.; Oshima, K. *Synlett* **2001**, 322.
(15) (a) Ferreira, F.; Denichoux, A.; Chemla, F.; Bejjani, J. *Synlett* **2004**, 2051. (b) Botuha, C.; Chemla, F.; Ferreira, F.; Pérez-Luna, A.; Roy, B. *New J. Chem.* **2007**, *31*, 1552. (c) Botuha, C.; Chemla, F.; Ferreira, F.; Louvel, J.; Pérez-Luna, A. *Tetrahedron: Asymmetry* **2010**, *21*, 1147.
(16) Kim, S.; Kim, K. H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1095.
(17) (a) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835. (b) Sato, F.; Okamoto, S. *Adv. Synth. Catal.* **2001**, *343*, 759.

(18) (a) Negishi, E.; Huo, S. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Chap. 1; Wiley-VCH: Weinheim, **2002**, 1. (b) Negishi, E. *Dalton Trans.* **2005**, 827.

(19) For examples of insertion of low-valence titanium and zirconium complexes into the carbon–carbon triple bond of propargylic derivatives bearing leaving groups at the propargylic position, see: (a) An, D. K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 4555. (b) Okamoto, S.; An, D. K.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 4551. (c) An, D. K.; Hirakawa, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1999**, *40*, 3737. (d) Okamoto, S.; Matsuda, S.; An, D. K.; Sato, F. *Tetrahedron Lett.* **2001**, *42*, 6323.

(20) For a discussion on the metallotropic equilibrium between allenyl and propargyl metals, see: Bejjani, J.; Botuha, C.; Chemla, F.; Ferreira, F.; Magnus, S.; Pérez-Luna, A. *Organometallics* **2012**, *31*, 4876.

(21) Hamada, T.; Mizojiri, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2000**, *122*, 7138.

(22) (a) Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 3769. (b) Nakagawa, T.; Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3207. (c) Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron* **1995**, *51*, 4507. (d) Yoshida, Y.; Nakagawa, T.; Sato, F. *Synlett* **1996**, 437. (e) An, D. K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 4861. (f) Hanazawa, T.; Okamoto, S.; Sato, F. *Org. Lett.* **2000**, *2*, 2369. (g) Yang, F.; Zhao, G.; Ding, Y. *Tetrahedron Lett.* **2001**, *42*, 2839.

(23) Dioumaev, V. K.; Harrod, J. F. *Organometallics* **1997**, *16*, 1452.

(24) Zhou, Y.; Chen, J.; Zhao, C.; Wang, E.; Liu, Y.; Li, Y. *J. Org. Chem.* **2009**, *74*, 5326.

(25) Because the ionization potential of a reagent is usually substantially larger than its electron affinity, the value of the ionization potential makes the dominant contribution to the hardness. Ti^{4+} is thus a harder Lewis acid than Zr^{4+} due to its higher value of ionization potential (99 eV for $Ti^{4+}$and 80 eV for Zr^{4+}).

(26) The hardness of metallic(IV) centers in **4** and **6** can be influenced by the nature of their ligands, i.e. *i*-PrO$^-$ (a hard base) for titanium(IV) and and Cp$^-$ (a soft base) for zirconium(IV). The steric hindrance generated by Cp$^-$ could also decrease the oxophilicity of the zirconium in **6**. See: Ayers, R. G.; Pearson, R. G. *J. Chem. Phys.* **2006**, *124*, 194107.

(27) **Representative Procedure for the Preparation of 2a–h; Preparation of 2e**: To a solution of Cp_2ZrCl_2 (117 mg, 0.40 mmol) in anhyd toluene (4 mL) was added dropwise *n*-BuLi (2.20 M in hexanes, 0.36 mL, 0.80 mmol) at –80 °C. The resulting mixture was warmed to –20 °C and stirred for 1 h at this temperature. Epoxide **1e** (121 mg, 0.50 mmol) was then added and the mixture was immediately warmed to 20 °C. After 1 h of stirring at 20 °C, the reaction was quenched with aq 0.5 M HCl. The layers were separated, and the aqueous phase was extracted with Et_2O (2 ×). The combined organic layers were washed with H_2O, then brine, dried over anhyd $MgSO_4$ and filtered through a plug of silica gel. Removal of the solvent and purification by flash chromatography (silica gel, pentane) afforded conjugated enyne **2e** (50 mg, 55%) as a colorless oil. Analytical data were in agreement with those reported (see ref. 28).

(28) Ni, Z.-H.; Luh, T.-Y. *Org. Synth.* **1992**, *70*, 240.