Synthesis and Reactivity of Functionalized Alkynyl Titanium Derivatives

Natalia Morlender-Vais, Julia Kaftanov, Ilan Marek*

Department of Chemistry and Institute of Catalysis Science and Technology, Technion-Israel Institute of Technology,Technion City, Haifa 32000 Israel

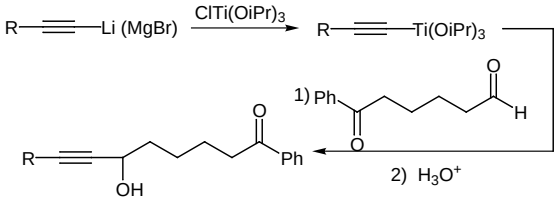
Fax (972)48233735; E-mail: chilanm@tx.technion.ac.il

Received 14 January 2000

Abstract: The in situ formation of Ti(II) and subsequent reaction with halogeno alkynes offer a new route to the preparation of functionalized alkynyl titanium derivatives, which can then react chemoselectively with functionalized electrophiles.

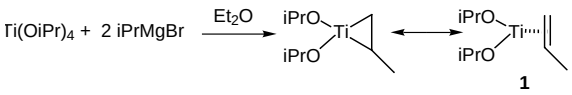
Key words: titanium, functionalized organometallic, halogeno alkynes, alkynes

Most organic molecules are polyfunctional compounds[1] requiring in the retrosynthetic analysis, the reaction between a functionalized carbon electrophile and a functionalized carbon nucleophile. Although a large part of the carbon nucleophiles are organometallic derivatives, the highly reactive nature of the carbon-metal bond precludes the presence of functional groups in the carbon skeleton of these reagents. Several elegant solutions to these problems were successfully developed in particular with the synthesis of functionalized nucleophiles as organozinc derivatives.[2] On the other hand, organotitanium reagents undergo chemoselective and stereoselective carbon-carbon bond forming reactions[3] with bifunctional electrophiles as shown in Scheme 1 (>99% reaction on the aldehyde).[4]



Scheme 1

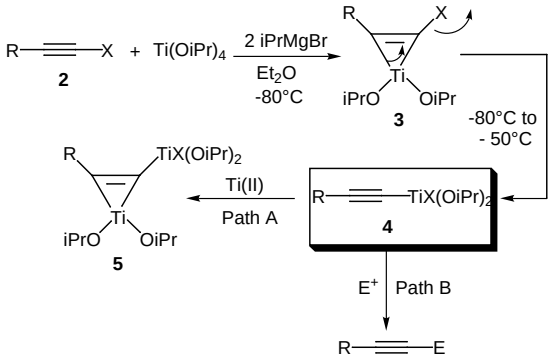
However, as these transition-metal organometallics were prepared from lithium or magnesium reagents, functionalized titanium organometallics are still in their infancy.[3] Indeed, few examples are described in the literature; mostly for the synthesis of trichloro- and alkoxytitanium homoenolates.[5] The recent chemistry based on Ti(II) derivatives have shown a high tolerance for oxygenated functional groups as in the enyne cyclocarbonylation reaction[6] involving "Cp_2Ti" (from Cp_2TiCl_2 and 2 equivalents of EtMgBr)[7] or in the intramolecular nucleophilic acyl substitution reactions[8] [Ti(II)[9] is prepared from $Ti(O^iPr)_4$ and 2 equivalents of *i*-PrMgBr as described in Equation 1].[10]



Equation 1

In these intramolecular nucleophilic acyl substitution reactions, the nucleophile must be generated in the presence of a carbonyl functional group, and at the same time this nucleophile is expected to react only with the carbonyl group in an intramolecular fashion but not intermolecularly.[8]

We have recently reported that treatment of 1-halogenoalkyne **2** (Scheme 2, R = alkyl, aryl X = I, Br, Cl, SPh) with 2.5 equivalents of the combination $Ti(O^iPr)_4$/2 *i*-PrMgBr (Sato's reagent as described in eq.1) gives, in a single-pot operation at −50 °C in 2 hours, the desired titano-titanacyclopropene **5** in high chemical yield (Scheme 2, path A).[11]



Scheme 2

The postulated mechanism for this reaction is that the in situ formed diisopropyloxy(η^2-propene) titanium **1**[10] (generated as described in Equation 1) reacts with halogenoalkyne **2**, via a ligand exchange, to give the unstable halogeno-titanacyclopropene **3** as intermediate.[12] Then, **3** undergoes a very fast β-elimination at low temperature[13] to give the alkynyltitanium derivative **4**, which reacts with the second equivalent of **1** to give the titano-titanacyclopropene **5** (an alternative possible mechanism for the formation of **4** is the oxidative addition of Ti(II) into the carbon-chlorine bond of **2**). Although the exact chemical pathway for the transformation of **2** into **4** is ambiguous,

Table Reactivity of the Alkynyl Titanium **4**

Entries	R	E	Pdt	Lewis Acid	Yield(%)[a]
1	Oct	MeOD	**6**	none	93
2	pTolyl	iPrCHO	**7**	none	70
3	pTolyl	iPrCHO	**7**	$ClTi(OiPr)_3$	85
4	pTolyl	PhCHO	**8**	none	70

[a] Isolated yields after hydrolysis.

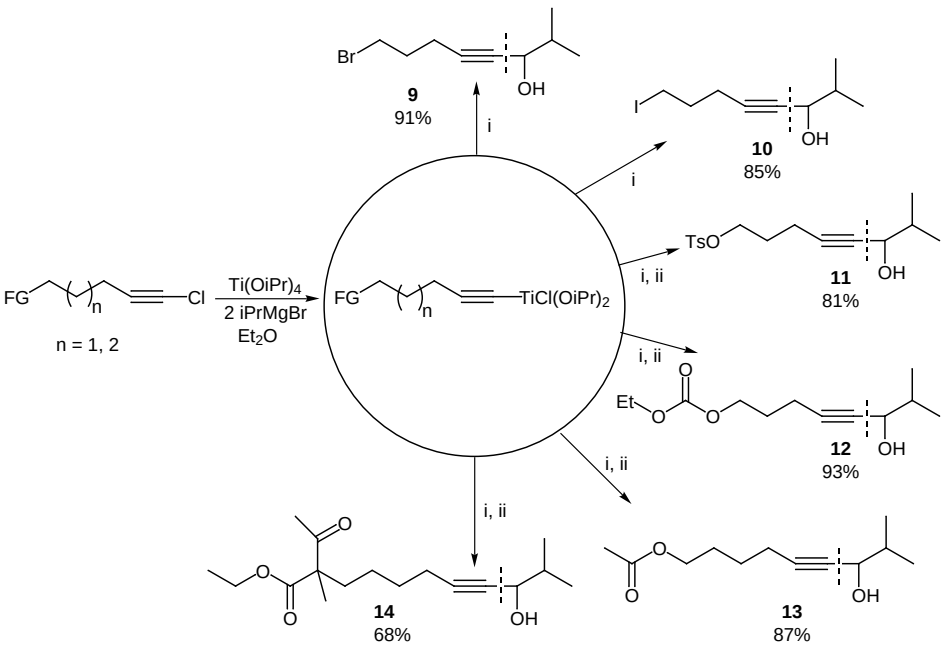
we would like to report here a general route to highly functionalized alkynyltitanium derivatives of type **4**. Indeed, since Grignard reagents are relatively unreactive towards many functional groups at low temperature in Et_2O,[14] the transmetallation reaction between titanium tetraisopropoxide and *i*-PrMgBr to give **1** should be faster than the reaction of *i*-PrMgBr with other functional groups. Firstly, we have checked the reactivity of **4** with aldehydes on model compounds (R = alkyl or *p*-Tolyl, X = Cl), Scheme 2 (path B) and Table.

Quenching the reaction with MeOD at −78 °C (Table, entry 1) proved the presence of the metalated alkyne **4** since the deuterioalkyne **6** (R = Octyl, %D>95, 93%) was obtained quantitatively. Addition of aldehydes to **4** led to the corresponding propargylic alcohols in good overall yields (entries 2, 3, 4). However, the co-addition of a mild Lewis acid as $ClTi(O^iPr)_3$ is beneficial for the reaction with an aldehyde (Table, compare entries 2 and 3). Once the experimental conditions were set up on the model substrates (as described in Scheme 2 and Table), we focussed our attention on the preparation of functionalized alkynes, readily prepared from ω-alkyn-1-ol, and their transformations into functionalized alkynyl titanium derivatives as described in Scheme 3. Thus, treatment of an ethereal solution of functionalized chloroalkynes and $Ti(O^iPr)_4$ (1.2 equivalents) with *i*-PrMgBr (2.4 equivalents) at −78 °C leads, by warming the reaction mixture up to −50 °C, to the desired functionalized alkynyl titanium derivatives in excellent yield. These derivatives tolerate a large variety of functional groups on its carbon skeleton. Halides like bromide or iodide (**9** and **10** in 91% and 85% yields respectively), tosylate **11** (81%), carbonate **12** (93%), ester **13** (87%) and β-keto ester **14** (68%) are compatible with the formation of the organometallic derivatives. They present a good reactivity with standard aldehyde even if, in some cases, the addition of Lewis acid is necessary in order to reach a good chemical yield. For example, **12** was obtained only in 50% yield without addition of $ClTi(O^iPr)_3$, whereas it was formed in 70% yield in the presence of a catalytic amount of $ClTi(O^iPr)_3$ (10%) and in 93% when an equimolar amount of Lewis acid was added.

Finally, the chemoselective reaction between a functionalized alkynyl titanium derivative and a functionalized electrophile has been performed in order to prepare, in a one-pot procedure, a polyfunctional compound (Scheme 4).

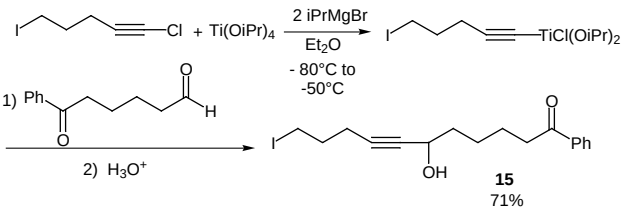
By applying the herein described strategy with Zr(II)[15] instead of Ti(II), we have also been able to prepare the corresponding functionalized alkynyl zirconium derivatives in good yield.

In conclusion, the in situ formation of Ti(II)[16] and subsequent reaction with halogeno alkynes offer a new route for the preparation of functionalized alkynyl titanium derivatives. These can further react chemoselectively with func-



i) *i*-PrCHO (1 equiv), −50 °C to −30 °C; ii) $ClTi(O^iPr)_3$ (1 equiv), −50 °C.

Scheme 3



Scheme 4

tionalized electrophiles. This strategy can be easily generalized to a large variety of alkynes since several mild methods are known for the transformation of alkynes into halogeno alkynes.[17]

^{1}H and ^{13}C NMR spectra were recorded on AM Bruker 200 MHz and 400 MHz spectrometers with $CDCl_3$ as the solvent. All reactions were carried out under an Ar atmosphere using flame-dried glassware. THF and Et_2O were distilled, prior to use, from Na/benzophenone ketyl. $Ti(O^iPr)_4$ was distilled and stored under Ar. Benzaldehyde and isobutyraldehyde were distilled immediately prior to use. $Ti(O^iPr)_3Cl$ was prepared from $Ti(O^iPr)_4$ and $TiCl_4$ according to the literature procedure.[3] Flash column chromatography was carried out on ICN Silica 63-200, 60Å.

1-Deuterio-1-decyne (6)
To a stirred solution of 1-chloro-1-decyne (166 mg, 0.96 mmol) and $Ti(O^iPr)_4$ (0.31 mL, 1.06 mmol) in Et_2O (25 mL) was added dropwise *i*-PrMgBr (1 M in Et_2O, 2.1 mL, 2.12 mmol) at −80 ºC. The mixture was warmed to −50 ºC and kept at this temperature for 2 h. MeOD (0.78 mL, 20 mmol) was added and the mixture was allowed to reach r.t. The reaction was quenched by addition of aq HCl (1 N, 20 mL) and extracted with Et_2O (3 × 20 mL). Combined organic phases were washed with sat. $NaHCO_3$, dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, pentane) to afford the deuteriated product (124 mg, 93%, %D>95) as a colorless oil.

^{1}H NMR (200 MHz): δ = 0.88 (t, *J* = 6.7 Hz, 3H), 1.18−1.62 (m, 12H), 2.14 (t, *J* = 6.7 Hz, 2H).

^{13}C NMR (50.3 MHz): δ = 13.27, 17.57, 21.84, 27.71, 27.96, 28.26, 28.35, 31.02, 66.93, 83.49.

Anal: $C_{10}H_{17}D$ (139.26): Calc C, 86.25; H, 12.30. Found: C, 86.41; H, 12.61.

2-Methyl-5-*p*-tolyl-4-pentyn-3-ol (7)
To a stirred solution of 1-chloro-2-*p*-tolylacetylene (275 mg, 1.83 mmol) and $Ti(O^iPr)_4$ (0.68 mL, 2.28 mmol) in Et_2O (25 mL) was added dropwise *i*-PrMgBr (1 M in Et_2O, 4.6 mL, 4.56 mmol) at −80 ºC. The reaction mixture was warmed to −50 ºC and kept at this temperature for 2 h. Freshly distilled isobutyraldehyde (0.25 mL, 2.7 mmol) was then added and the reaction mixture was stirred at −30 ºC for another 2 h. The reaction was quenched by an addition of aq HCl (1 N, 20 mL) and extracted with Et_2O (3 × 20 mL). Combined organic phases were washed with sat. $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 6:1) to afford the alcohol (240 mg, 85%) as a colorless oil.

^{1}H NMR (200 MHz): δ = 1.01 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 1.93 (m, 1H), 2.32 (s, 3H), 4.35 (d, *J* = 5.5 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H).

^{13}C NMR (50.3 MHz): δ = 17.51, 18.13, 21.35, 36.69, 68.37, 85.64, 88.21, 119.65, 128.96, 131.55, 138.35.

6-Hydroxy-7-methyl-4-octynylethoxycarbonate (12); Typical Procedure
To a stirred solution of the chloroacetylenic carbonate (216 mg, 1,13 mmol) and $Ti(O^iPr)_4$ (0.42 mL, 1.36 mmol) in Et_2O (25 mL) was added dropwise *i*-PrMgBr (1.08 M in Et_2O, 2.5 mL, 2.7 mmol) at −80 ºC. The reaction mixture was warmed to −50 ºC and kept at this temperature for 2 h. $Ti(O^iPr)_3Cl$ (2 M in Et_2O, 0.68 mL, 1.36 mmol) was introduced at −50 ºC and the mixture was stirred at this temperature for 30 min. Freshly distilled isobutyraldehyde (0.16 mL, 1.7 mmol) was then added and the reaction mixture was stirred at −35 ºC for another 2 h. The reaction was quenched by addition of aq HCl (1 N, 20 mL) and extracted with Et_2O (3 × 20 mL). Combined organic phases were washed with sat. $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 5:1) to afford the alcohol (240 mg, 93%) as a colorless oil.

^{1}H NMR (200 MHz): δ = 0.92 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 1,28 (t, *J* = 7.8 Hz, 3H), 1.74−1.93 (m, 3H), 2.33 (dt, *J* = 7.0, 1.8 Hz, 2H), 4.11−4.24 (m, 5H).

^{13}C NMR (50.3 MHz): δ = 14.22, 15.31, 17.43, 18.04, 27.81, 34.61, 63.94, 66.35, 68.03, 80.92, 84.31, 155.13.

Anal: $C_{12}H_{20}O_4$ (228.28): Calc C, 63.13; H, 8.83. Found: C, 63.21; H, 8.92.

1-Phenyl-3-*p*-tolyl-2-propyn-1-ol (8)
The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 5:1).

^{1}H NMR (200 MHz): δ = 2.35 (s, 3H), 5.68 (s, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.30−7.45 (m, 5H), 7.60 (d, *J* = 8.0 Hz, 2H).

^{13}C NMR (50.3 MHz): δ = 31.39, 65.1, 86.81, 88.13, 119.4, 126.7, 128.3, 128.56, 129.01, 131.64, 138.69, 140.84.

8-Bromo-2-methyl-4-octyn-3-ol (9)
The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 6:1).

^{1}H NMR (200 MHz): δ = 0.93 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 1.82 (m, 1H), 2.04 (q, 2H), 2.41 (dt, *J* = 6.7, 1.8 Hz, 2H), 3.49 (t, *J* = 6.3 Hz, 2H), 4.14 (br d, *J* = 5.6 Hz, 1H).

^{13}C NMR (50.3 MHz): δ = 17.43, 18.07, 29.67, 31.48, 32.20, 34.63, 68.06, 81.11, 83.88.

Anal: $C_9H_{15}BrO$ (219.12): Calc C, 49.33; H, 6.90. Found: C, 49.44; H, 6.98.

8-Iodo-2-methyl-4-octyn-3-ol (10)
The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 6:1).

^{1}H NMR (200 MHz): δ = 0.93 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 1.82 (m, 1H), 1.96 (q, *J* = 6.6 Hz, 2H), 2.36 (dt, *J* = 6.6, 1.8 Hz, 2H), 3.27 (t, *J* = 6.6 Hz, 2H), 4.14 (br d, *J* = 5.7 Hz, 1H).

^{13}C NMR (50.3 MHz): δ = 5.08, 17.46, 18.08, 29.67, 32.07, 34.64, 68.09, 81.18, 83.90.

Anal: $C_9H_{15}IO$ (266.12): Calc C, 40.62; H, 5.68. Found: C, 41.2; H, 5.96.

6-Hydroxy-7-methyl-4-octynyl *p*-Toluenesulfonate (11)
The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 5:1).

^{1}H NMR (200 MHz): δ = 0.89 (d, *J* = 5.2 Hz, 3H), 0.91 (d, *J* = 5.2 Hz, 3H), 1.66−1.88 (m, 3H), 2.33 (dt, *J* = 6.4, 1.8 Hz, 2H), 2.42 (s, 3H), 4.06 (br d, *J* = 5.8 Hz, 1H), 4.10 (t, *J* = 6.5 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 8.1 Hz, 2H).

^{13}C NMR (50.3 MHz): δ = 14.98, 17.40, 17.99, 27.92, 29.64, 34.50, 67.92, 68.88, 81.26, 83.60, 127.87, 129.82, 133.10, 144.75.

7-Hydroxy-8-methyl-5-nonynyl Acetate (13)
The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 5:1).

^{1}H NMR (200 MHz): δ = 0.93 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 1,52−1.85 (m, 5H), 2.03 (s, 3H), 2.25 (dt, *J* = 6.8, 1.9 Hz, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 4.14 (br d, *J* = 5.6 Hz, 1H).

^{13}C NMR (50.3 MHz): δ = 17.43, 18.05, 18.34, 20.90, 25.1, 27.77, 34.66, 63.94, 68.11, 99.83, 104.63, 190.43.

Anal: $C_{12}H_{20}O_3$ (212.28): Calc C, 67.89; H, 9.50. Found: C, 68.03; H, 9.84.

2-Methyl-2(8-methyl-5-nonyn-7-ol)ethyl Acetoacetate (14)
The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 5:1).

^{1}H NMR (400 MHz): δ = 0.92 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 1.23 (t, *J* = 7.4 Hz, 3H), 1.21−1.27 (m, 2H), 1.30 (s, 3H), 1.49 (m, 2H), 1.67−1.88 (m, 3H), 2.11 (s, 3H), 2.2 (br t, *J* = 6.3 Hz, 2H), 4.11 (br d, *J* = 5.4 Hz, 1H), 4.17 (q, *J* = 6.5 Hz, 2H).

^{13}C NMR (100.6 MHz): δ = 14.06, 17.46, 18.11, 18.35, 18.83, 23.36, 26.12, 28.89, 34.25, 34.67, 59.61, 61.27, 68.10, 80.40, 85.54, 172.96, 205.49.

Anal: $C_{17}H_{28}O_4$ (296.39): Calc C, 68.88; H, 9.52. Found: C, 68.97; H, 9.71.

6-Hydroxy-11-iodo-1-phenyl-7-undecyn-1-one (15)
The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 6:1).

^{1}H NMR (200 MHz): δ = 1.60−1.77 (m, 6H), 1.96 (q, *J* = 7.0 Hz, 2H), 2.34 (br t, *J* = 6.8 Hz, 2H), 2.99 (t, *J* = 7.3 Hz, 2H), 3.26 (t, *J* = 7.2 Hz, 2H), 4.48 (br t, *J* = 6.5 Hz, 1H), 7.44 (m, 3H), 7.92 (d, *J* = 8 Hz, 2H).

^{13}C NMR (50.3 MHz): δ = 5.12, 19.77, 24.95, 29.35, 31.44, 37.78, 38.42, 62.47, 82.42, 83.22, 128.02, 128.53, 132.90, 137.06, 200.09.

Anal: $C_{17}H_{21}IO_2$ (384.24): Calc C, 53.13; H, 5.51. Found: C, 53.48; H, 5.32.

Acknowledgement

I. M. is Holder of the Lawrence G. Horowitz Career Development Chair, is a Ygal Alon fellow and Evelyn and Salman Grand Academic Lectureship-USA. This research was supported in part by The Israel Science Foundation founded by The Academy of Sciences and Humanities (N° 060-471) and by Technion V.R.P. Fund- S. and N. Grand Research Fund. Acknowledgement is also made to the donors of The Petroleum Research Fund, administered by the ACS, for partial support of this research (PRF#33747-AC1). We also thank the ministry of Immigrant Absorption for financial support.

References

(1) Corey, E. J.; Cheng, X. *The Logic of Chemical Synthesis*; Wiley: New-York, 1989.
(2) For a recent review, see: Knochel, P. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH, 1998; p 387.
(3) For a recent review, see: Reetz, M. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: 1994; p 195.
(4) Krause, N.; Seebach. D. *Chem. Ber.* **1987**, *120*, 1845.
(5) Kuwajima, I.; Nakamura, E. In *Metal Homoenolates* In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: 1991; *2*, p 441.
(6) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S.L. *J. Am. Chem. Soc*. **1999**, *121*, 5881.
Grossman, R. B.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 5803.
(7) Buchwald, S. L.; Nielsen R. B. *Chem. Rev.* **1988**, *88*, 1047.
(8) Okamoto, S.; Iwakubo, M.; Kobayashi, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 6984.
Urabe H.; Suzuki, K.; Sato, F. *J. Am. Chem. Soc*. **1997**, *119*, 10014.
Urabe, H.; Hamada, T.; Sato, F. *J. Am. Chem. Soc*. **1999**, *121*, 2931.
Okamoto, S.; Kasatkin, A.; Zubaidha, P. K.; Sato, F. *J. Am. Chem. Soc.* **1996**, *118*, 2208.
(9) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, T. S.;. Pritskaya, T. S. *Zh. Org. Khim*. **1989**, *25*, 2245.
Kulinkovich, O. G; Pritskaya, T. S. *J. Org. Chem. USSR (Engl. Transl.)* **1990**, *25*, 2027.
Kulinkovitch, O. G.; Sviridov, S. V.; Vasilevski, D. A. *Synthesis* **1991**, 234, and references cited therein.
Williams, C. M.; Chaplinski, V.; Schreiner, P. R.; de Meijere, A. *Tetrahedron Lett*. **1998**, *39*, 7695.
(10) Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203.
(11) Averbuj, C.; Kaftanov, J.; Marek, I. *Synlett* **1999**, 1939.
(12) All attempts to trap the intermediate **3** at low temperature were unsuccessful.
(13) Equivalent reactions were described in the literature for the formation of vinylzirconium derivatives from zirconocenes and vinyl halides, see: Takahashi, T.; Kotora, M.; Fischer, R.; Nishihara, Y.; Nakajima, K. *J. Am. Chem. Soc.* **1995**, *117*, 11039.
(14) Boymond, L.; Rottlander, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed*. **1998,** *37*, 1701.
(15) For the use of dialkylzirconocenes in synthesis, see the last review: Neghishi, E. I.; Takahashi T. *Bull. Chem. Soc. Jpn*. **1998**, *71*, 755.
(16) Okamoto, S.; Kasatkin, A.; Zubaidha, P. K.; Sato, F. *J. Am. Chem. Soc.* **1996**, *118*, 2208.
Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 7342.
Frid, M.; Perez, D.; Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9469.
(17) Wagner, A.; Heitz, M. P.; Mioskowski, C. *Tetrahedron Lett.* **1990**, *31*, 3141.
Naskar, D.; Roy, S. *J. Org. Chem.* **1999**, *64*, 6896.
Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron Lett.* **1994**, *35*, 3529.
Kloster−Jenson, E. *Tetrahedron* **1971**, 27, 33.
Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 485.

Article Identifier:
1437-210X,E;2000,0,07,0917,0920,ftx,en;C00200SS.pdf