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ARTICLE *in* ORGANIC LETTERS · JULY 2010

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2009
Vol. 11, No. 1
141−144

Hiyama Cross-Coupling Reaction in the Stereospecific Synthesis of Retinoids

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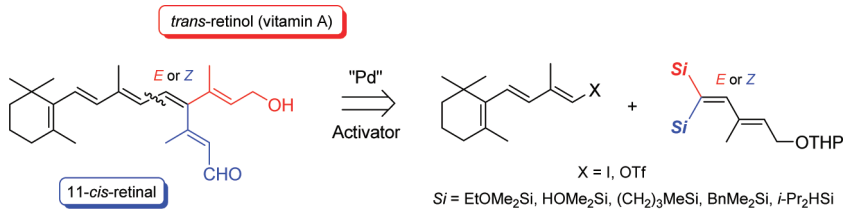
Received November 5, 2008

ABSTRACT



The first application of the Hiyama reaction to the synthesis of retinoids is reported. A range of organosilicon moieties (siloxanes, silanols and three kinds of "safety-catch" silanols) were successfully coupled, under activation, to obtain *trans*-retinol or 11-*cis*-retinol with high yield and stereoselectivity. The advantageous properties of the silicon-based coupling partners and the mild reaction conditions firmly establish the Hiyama reaction as a viable (even superior) alternative to the traditional Suzuki and Stille couplings in the retinoid field.

Retinoids—vitamin A (**1**), and its structural and functional analogues—have been the subject of intense research for decades because of their critical roles in a variety of biological processes, including vision, cell growth and differentiation, reproduction, embryonic development, and the immune response.[1] Synthetic studies also abound in this field, with the classical routes based on olefin elongation procedures (the Wittig, Horner-Emmons, and Julia reactions) being replaced in the last years by more stereoselective approaches.[2] In this respect, transition metal-catalyzed cross-coupling methods,[3] the well-established Stille and Suzuki reactions in particular, have been extensively applied to the synthesis of retinoids and related polyenes.[4] Nevertheless, significant drawbacks to these reactions, including the toxicity and high molecular weight of organostannanes and the limited stability of organoboranes still constitute serious limitations and, therefore, the development of more efficient approaches continues to be a major objective.

Organosilicon compounds have recently emerged as an attractive alternative to traditional organometallic donors because of their high chemical stability, low toxicity and ease of handling, and the availability and relatively low cost of the silicon-containing starting materials. Their inherent reluctance to undergo cross-coupling, as a result of the absence of a significant dipole associated with C−Si bond, has been successfully overcome, and a variety of heteroatom-containing silicon species (halosilanes, siloxanes, polysiloxanes, and silanols) have been shown to couple efficiently to organic electrophiles upon treatment with an appropriate

(1) *The Retinoids: Biology, Chemistry and Medicine*; Sporn, M. B., Roberts, A. B., Goodman, D. S., Eds.; Raven: New York, 1993.

(2) For a recent review of the synthesis of retinoids, see: Domínguez, B.; Alvarez, R.; de Lera, A. R. *Org. Prep. Proc. Int.* **2003**, *35*, 239.

(3) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998. (b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vols 1 and 2.

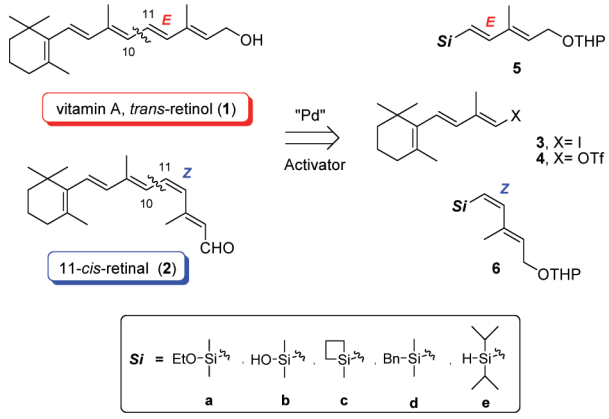
(4) Selected papers on the Suzuki reaction: (a) Torrado, A.; Iglesias, B.; López, S.; de Lera, A. R. *Tetrahedron* **1995**, *51*, 2435. (b) de Lera, A. R.; Iglesias, B.; Rodríguez, J.; Alvarez, R.; López, S.; Villanueva, X.; Padrós, E. *J. Am. Chem. Soc.* **1995**, *117*, 8220. (c) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Wada, A.; Ito, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 320. (d) Uenishi, J.; Matsui, K.; Wada, A. *Tetrahedron Lett.* **2003**, *44*, 3093. Selected papers on the Stille reaction: (e) Alvarez, R.; Iglesias, B.; López, S.; de Lera, A. R. *Tetrahedron Lett.* **1998**, *39*, 5659. (f) Thibonnet, J.; Prié, G.; Abarbri, M.; Duchêne, A.; Parrain, J.-L. *Tetrahedron Lett.* **1999**, *40*, 3151. (g) Domínguez, B.; Iglesias, B.; de Lera, A. R. *Tetrahedron* **1999**, *55*, 15071. (h) Wada, A.; Fukunaga, K.; Ito, M. *Synlett* **2001**, 800. (i) Wada, A.; Fukunaga, K.; Ito, M.; Mizuguchi, Y.; Nakagawa, K.; Okano, T. *Bioorg. Med. Chem.* **2004**, *12*, 3931. (j) Wada, A.; Matsuura, N.; Mizuguchi, Y.; Nakagawa, K.; Ito, M.; Okano, T. *Bioorg. Med. Chem.* **2008**, *16*, 8471.

10.1021/ol802551a CCC: $40.75
Published on Web 12/09/2008

palladium catalyst and a nucleophilic promoter (the Hiyama reaction).[5] Furthermore, the advent of several families of "safety-catch" silanols, that is, stable precursors that can be unmasked *in situ* to reveal the reactive silanol itself (siletanes, silyl hydrides, benzyl-, triallyl-, aryl-, 2-pyridyl-, and 2-thienylsilanes),[6] has raised the synthetic potential of the reaction and firmly established organosilicon cross-coupling as a viable alternative to the Suzuki and Stille protocols.

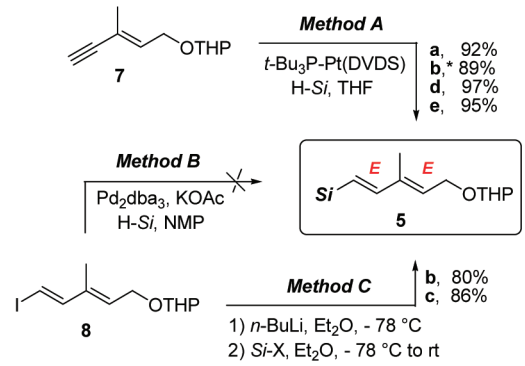
Encouraged by the growing significance of the silicon-based reagents, and as part of our ongoing research on the chemistry and biology of retinoids,[7] we decided to investigate the possibility of applying the Hiyama reaction to the synthesis of these highly conjugated polyenes. Here we describe its use to synthesize the parent metabolite *trans*-retinol (vitamin A, **1**) and the visual chromophore 11-*cis*-retinal (**2**).

Scheme 1. Retrosynthetic Analysis



In both cases we emulated previous Suzuki and Stille approaches[4a,7c] by employing the highly convergent "C14+C6" strategy, in which the key step is the construction of the central $C_{10}-C_{11}$ single bond. As the electrophilic 14-carbon fragment we planned to use trienyl iodide **3** or triflate **4** (both prepared as described previously),[4a,7c] and as the 6-carbon fragment we planned to use a range of *trans*- and *cis*-alkenyl moieties (dienyl compounds **5** and **6**) comprising two types of oxygen-substituted silanes (siloxanes **a** and silanols **b**) and three kinds of "safety-catch" silanols (siletanes **c**, benzylsilanes **d** and silyl hydrides **e**) (Scheme 1). To prepare dienylsilanes **5** and **6**, we initially considered three established one-step procedures starting from enyne **7** or a vinyl iodide (**8** or **10**) (Schemes 2 and 3): metal-catalyzed hydrosilylation (Method A), metal-catalyzed cross-coupling reaction of the halide to a silicon nucleophile (Method B), and lithium-halogen exchange followed by anion trapping with a silicon electrophile (Method C).

Scheme 2. Synthesis of (1*E*,3*E*)-Dienylsilanes **5**



	H-*Si*	*Si*-X
a	$HMe_2(OEt)Si$	---
b	$HMe_2(OEt)Si$*	D_3
c	---	$(CH_2)_3MeSiCl$
d	HMe_2BnSi	$BnMe_2SiCl$
e	$H_2i\text{-}Pr_2Si$	$i\text{-}Pr_2HSiCl$

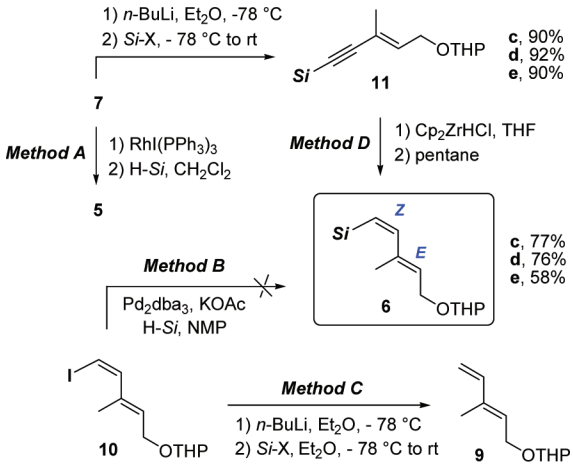
D_3 = hexamethylcyclotrisiloxane
DVDS = platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane
*Followed by acid hydrolysis: CH_3CN- 1.0 M HOAc/NaOAc buffer, pH = 5

The most direct and atom-economical way of synthesizing alkenylsilanes is hydrosilylation of terminal alkynes (Method A),[8] and a number of transition metal catalysts have been devised to perform this reaction regio- and stereoselectively. Cationic rhodium complexes and platinum catalysts generally afford the β-(*E*)-isomer through *syn*-addition;[9] neutral rhodium catalysts usually give the β-(*Z*)-vinylsilane as the major product;[9] and $[RhI(PPh_3)_3]$ can be used to obtain, at will, either (*E*)- or (*Z*)-alkenylsilanes, depending on the reaction conditions.[10] Unlike most other Rh catalysts, $[RhI(PPh_3)_3]$ also performs hydrosilylation with silane reagents containing heteroatoms.[11] However, in this work the synthesis of *E*-siloxane **5a** was significantly more efficient using Pt(DVDS) and *t*-Bu_3P,[12] which gave a 92% yield in 1 h at rt (Scheme 2), than with other platinum catalysts [Cl_2PtCOD, H_2PtCl_6] or $[RhI(PPh_3)_3]$ (data not shown); and hydrolysis of **5a** at optimal pH (pH = 5, CH_3CN 1.0 M HOAc/NaOAc buffer)[13] cleanly provided silanol **5b** in 89% overall yield for the one-pot silylation-hydrolysis procedure (Scheme 2). No attempt was made to prepare siletane **5c** by this procedure, because the required hydrosilane reagent is not commercially available; but the conditions optimized for **5a** gave even better results in the cases of benzylsilane **5d** and silyl hydride **5e**, which were obtained in almost quantitative yield (Scheme 2).

Unfortunately, attempts to prepare the *Z*-dienylsilanes **6** by formal *anti*-hydrosilylation of enyne **7**, under tunable $[(Cp^*RhCl_2)_2]$[9] or stereodivergent $[RhI(PPh_3)_3]$[10] conditions, afforded only the corresponding *E*-isomers **5** (Scheme 3).[14]

(5) (a) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471. (b) Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 10. (c) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835. (d) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531. (e) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61. (f) Denmark, S. E.; Ober, M. H. *Aldrichimica Acta* **2003**, *36*, 75. (g) Sahoo, A. K.; Oda, T.; Nakao, Y.; Hiyama, T. *Adv. Synth. Catal.* **2004**, *346*, 1715. (h) Denmark, S.; Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1, Chapter 4.

Scheme 3. Synthesis of (1*Z*,3*E*)-Dienylsilanes **6**



We therefore turned our attention to Method B. Although the cross-coupling reaction of organic halides to a silicon source (disilanes, monohydrosilanes, or dihydrosilanes), using Pd, Rh, or Pt complexes as catalysts, has proven to be a useful route to functionalized arylsilanes,[15] only two instances of its use for silicon-alkenyl-carbon bond formation have been reported to date:[16] Hiyama prepared vinyl- and dienylsilanes by coupling the corresponding halides to hexamethyldisilane under TASF-promoted Pd(0) catalysis; and Masuda reported the efficient coupling of alkenyl iodides to hydrosilanes using $Pd_2dba_3.CHCl_3$ as catalyst, KOAc as base, and amide solvents (NMP). Discourangingly, in the present work, neither of these protocols allowed the preparation of silanes **6** from iodide **10** or of silanes **5** from iodide **8** (Schemes 2 and 3), affording only starting materials or complex reaction mixtures.

The reaction of silicon electrophiles with organo-lithium or organomagnesium reagents (Method C) is a classical means of obtaining access to organosilicon compounds.[17] In this work, the metalation of *E*-vinyl iodide **8** with *n*-BuLi, followed by trapping of the resulting anion with hexamethylcyclotrisiloxane (D_3) or chloromethylsilacyclobutane, uneventfully afforded silanol **5b** and siletane **5c** in yields of 80% and 86%, respectively (Scheme 2). Surprisingly, however, failure met attempts to trap this vinyl anion with benzyldimethylchlorosilane or diisopropylchlorosilane to obtain silanes **5d** and **5e**, and it was similarly impossible to obtain any of the *cis*-silanes **6** by applying Method C to *cis*-vinyl iodide **10**. In all these cases of failure, the inability of the anions that were generated to trap the silicon electrophile resulted in the main reaction product after workup being the terminal alkene **9** (Scheme 3).

In view of the apparent impossibility of preparing *cis*-silanes **6** by means of one-step protocols, we turned to a two-step sequence based on the *cis*-selective reduction of the corresponding 1-alkynylsilane precursors (Method D).[18] Gratifyingly, the precursors required for **6c**−**e**, alkynylsilanes **11c**−**e** were obtained uneventfully by metalation of enyne **7** and anion trapping with chloromethylsilacyclobutane, benzyldimethylchlorosilane, or chlorodiisopropylsilane; subsequent reaction with $Cp_2Zr(H)Cl$[19] and pentane afforded the desired coupling partners **6c**−**e** in yields of 77, 76, and 58%, respectively (Scheme 3). Unfortunately, the method could not be applicable to the preparation of **6a**−**b** because of the unavailability of the required silicon electrophile and the instability of the alkynylsilane precursor, respectively.

With the organosilicon reagents **5a**−**e** and **6c**−**e** in hand, we investigated the Hiyama cross-coupling reactions. Addition of TBAF (1.0 M in THF, 2−3 equiv) to a solution of **5** or **6** (1.5−2.5 equiv) in THF, followed by stirring for 30 min at rt, sequential addition of trienyl iodide **3** and $Pd_2(dba)_3.CHCl_3$ (0.05−0.1 equiv) and stirring for a further 1−4 h, afforded retinyl ethers **12** and **13** as pure isomers in yields that in most cases were in the range 75−90% (Scheme

(6) Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P. *Curr. Org. Synth.* **2004**, *1*, 211.

(7) (a) López, S.; Rodríguez, V.; Montenegro, J.; Saá, C.; Alvarez, R.; López, C. S.; de Lera, A. R.; Simón, R.; Lazarova, T.; Padrós, E. *Chembiochem* **2005**, *6*, 2078. (b) Silva, C.; Nieto, O.; López, S.; de Lera, A. R. *J. Comput. Chem.* **2006**, *27*, 116. (c) López, S.; Montenegro, J.; Saá, C. *J. Org. Chem.* **2007**, *72*, 9572.

(8) (a) Ojima, I. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley: Chichester, 1989; p 1479. (b) Hiyama, T.; Kusumoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, p 763. (c) Ojima, I.; Li., Z.; Zhu, J. In *The Chemistry of Organic Silicon Compounds*; Rappoport, Z., Apeloig, Y., Eds.; Wiley: New York, 1998; p 1687.

(9) For a recent example of tunable selectivity using rhodium catalysts, see: Faller, J. W.; D'Alliessi, D. G. *Organometallics* **2002**, *21*, 1743.

(10) (a) Mori, A.; Takahisa, E.; Kajiro, H.; Hirabayashi, K.; Nishihara, Y.; Hiyama, T. *Chem. Lett.* **1998**, 443. (b) Mori, A.; Takahisa, E.; Kajiro, H.; Nishihara, Y.; Hiyama, T. *Polyhedron* **2000**, *19*, 567. (c) Mori, A.; Takahisa, E.; Kajiro, H.; Nishihara, Y.; Hiyama, T. *Macromolecules* **2000**, *33*, 1115. (d) Mori, A.; Takahisa, E.; Yamamura, Y.; Kato, T.; Mudalige, A. P.; Kajiro, H.; Hirabayashi, K.; Nishihara, Y.; Hiyama, T. *Organometallics* **2004**, *23*, 1755.

(11) Ru-catalyzed stereodivergent hydrosilylation has also been reported, but mainly in relation to arylvinylsilanes. See: Katayama, H.; Taniguchi, K.; Kobayashi, M.; Sagawa, T.; Minami, T.; Ozawa, F. *J. Organomet. Chem.* **2002**, *645*, 192.

(12) (a) Chandra, G.; Lo, P. Y.; Hitchcock, P. B.; Lappert, M. F. *Organometallics* **1987**, *6*, 191. (b) Denmark, S. E.; Wang, Z. *Org. Lett.* **2001**, *3*, 1073.

(13) Denmark, S. E.; Kallemeyn, J. M. *Org. Lett.* **2003**, *5*, 3483.

(14) Possibly through isomerization of initially produced *Z*-isomers, via an insertion-β-elimination mechanism, in the presence of a catalytic amount of hydrosilane and the Rh catalyst. See: Mori, A.; Takahisa, E.; Nishihara, Y.; Hiyama, T. *Can. J. Chem.* **2001**, *79*, 1522.

(15) Some significant references: Pd (hydrosilanes): (a) Murata, M.; Suzuki, K.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 8569. (b) Manoso, A. S.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 7449. (c) Yamanoi, Y. *J. Org. Chem.* **2005**, *70*, 9607. Pd (dihydrosilanes): (d) Yamanoi, Y.; Taira, T.; Sato, J.; Nakamula, I.; Nishihara, H. *Org. Lett.* **2007**, *9*, 4543. Pd (disilanes): (e) Matsumoto, H.; Nagashima, S.; Kato, T.; Nagai, Y. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 279. (f) See ref 13. Rh catalyst: (g) Murata, M.; Ishikura, M.; Nagata, M.; Watanabe, S.; Masuda, Y. *Org. Lett.* **2002**, *4*, 1843. (h) Yamanoi, Y.; Nishihara, H. *Tetrahedron Lett.* **2006**, *47*, 7157. (i) Murata, M.; Yamasaki, H.; Ueta, T.; Nagata, M.; Ishikura, M.; Watanabe, S.; Masuda, Y. *Tetrahedron* **2007**, *63*, 4087. Pt catalyst: (j) Hamze, A.; Provot, O.; Alami, M.; Brion, J.-D. *Org. Lett.* **2006**, *8*, 931.

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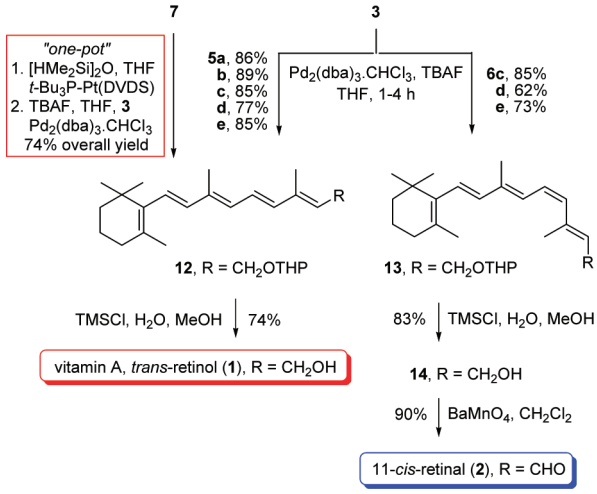
(17) (a) Sieburth, S. M.; Fensterbank, L. *J. Org. Chem.* **1993**, *58*, 6314. (b) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565. (c) Denmark, S. E.; Neuville, L. *Org. Lett.* **2000**, *2*, 3221. (d) Denmark, S. E.; Pan, W. *J. Organomet. Chem.* **2002**, *653*, 98. (e) Morrill, C.; Mani, N. S. *Org. Lett.* **2007**, *9*, 1505.

(18) (a) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821. (b) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc.* **2005**, *127*, 3666.

(19) Reduction of alkynylboronates and stannanes with Schwartz's reagent has been reported, for example, in ref 7c.

Scheme 4. Hiyama Cross-Coupling Reactions



4). Fluoride-free coupling of iodide **3** to silanol **5b** was also possible but was rather less efficient: under Ag_2O activation[20] [$Pd(PPh_3)_4$, 50 °C, 12 h], the yield of the retinyl ether **12** was 61%, while under TMSOK activation[21] (Pd_2dba_3, dioxane, 3 h), the reaction proceeded at rt but the yield was again lower than with TBAF (74% as against 89%).

We also found it possible to obtain compound **12** from **7** by an efficient one-pot hydrosilylation/cross-coupling sequence (Scheme 4). Following Denmark,[12,22] we hydrosilylated enyne **7** with tetramethyldisiloxane, under *t*-Bu_3P−Pt(DVDS) catalysis, and then coupled the resulting vinyldisiloxane *in situ* to trienyl iodide **3** under Pd catalysis with activation by fluoride, obtaining *trans*-retinyl ether **12** in a remarkable 74% overall yield.

By contrast with iodide **3**, triflate **4** failed to couple to **5** or **6**. Indeed, very few examples of triflate-organosilicon coupling have been reported in the literature,[23] although Hiyama described a pioneer coupling of fluorosilanes with aryl and alkenyl triflates using $Pd(PPh_3)_4$ and TBAF, and Denmark coupled alkenylsilanols with triflates and nonaflates using TBAF•$3H_2O$, $PdBr_2$ and (2-biphenyl)(*t*-Bu)$_2$P. In the present study, neither of these protocols worked, the only products isolated from the reaction mixtures being starting materials.

Finally, the synthesis of the target retinoids was completed by deprotection of retinyl ethers **12** and **13** [TMSCl, H_2O, MeOH, 5min], which afforded *trans*-retinol (**1**) and 11-*cis*-retinol (**14**) in 74 and 83% yield, respectively, and subsequent oxidation of **14** [$BaMnO_4$, CH_2Cl_2] to obtain 11-*cis*-retinal (**2**) in 90% yield (Scheme 4).

To sum up, the Hiyama cross-coupling reaction has been applied, for the first time, to the stereospecific synthesis of retinoids. The approach is inexpensive, harmless and highly efficient, and establishs a reliable (even superior) alternative to the traditional Suzuki and Stille couplings.

Acknowledgment. Support of this research by the Spanish Ministry of Science and Innovation under Project CTQ2008-06557BQU, and by the Xunta de Galicia under Projects 2007/XA084 and INCITE08PXIB209024PR, is gratefully acknowledged.

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(22) (a) Denmark, S. E.; Wang, Z. *Org. Synth.* **2005**, *81*, 54. (b) Thiot, C.; Schmutz, M.; Wagner, A.; Mioskowski, C. *Chem.−Eur. J.* **2007**, *13*, 971.

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