3276 J. Org. Chem. **1995**, *60*, 3276-3277

Stereospecific Synthesis of Temarotene, Its Structural Isomers, and Mixed Triaryl Alkenes from *gem*-Borazirconocene Alkenes

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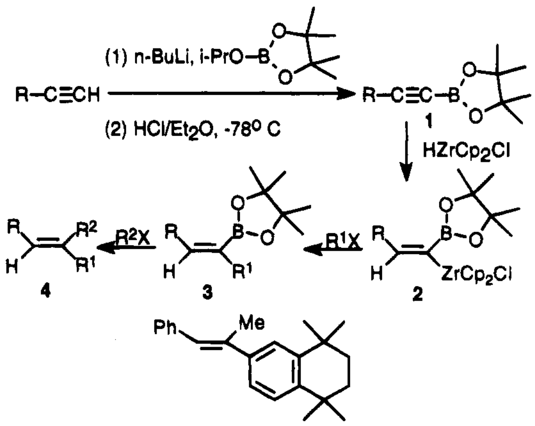
Received February 2, 1995

The ability to form carbon–carbon bonds rationally around an alkene is the object of continuing vigorous research.[1] Our contribution to this area involves the use of *gem*-borazirconocene alkenes, **2**, readily available from 1-alkynylboronates by hydrozirconation.[2] These compounds are stabile and due to the considerably different reactivities of the C–Zr and C–B bonds, enable selective and sequential reactions with a variety of electrophiles. As a demonstration of the scope of this emerging methodology we selected to synthesize temarotene, **4a**, several of its structural isomers, and totally mixed triaryl alkenes.

Temarotene,[3] **4a**, is a retinoid[4] and is of interest because it shows no sign of hypervitaminosis A and it is not teratogenic, presumably due to lack of a polar group.[5] The published synthesis of temarotene-type compounds is long and leads to mixtures of diastereomers from which the desired product is isolated.[6,7] The synthesis of temarotene by our methodology is straightforward and is outlined in Scheme 1.

Scheme 1



Temarotene 4a

Coupling of **2a**[2a] with 6-bromo-2,2,3,3,-tetrahydro-1,1,4,4-tetramethylnaphthalene[8] in THF at 0 °C in the presence of 5 mol % $Pd(PPh_3)_4$ cleanly gave **3a** (68%). As has been our experience to date, the C–Zr bond reacts exclusively. Suzuki coupling[9] with MeI then gave temarotene, **4a** (69%), as the only detectable stereoisomer. Using our methodology we also synthesized two additional isomers of temarotene by changing the sequence of electrophiles (Table 1, entries b and c). Noteworthy here is the hitherto unreported alkylation of alkenylzirconocenes with MeI (Table 1, entry b).[10] While we found that the reaction with MeI occurs readily under palladium catalysis,[11] EtI and higher analogs gave complex reaction mixtures, with only low yields of the desired coupling products.

Various biaryls are of importance in the synthesis of natural products and pharmaceuticals as well as providing possible entries into ligands for asymmetric synthesis.[12] As a further demonstration of our methodology we therefore synthesized several mixed trisubstituted aryl alkenes (Table 1, entries d–h). Instead of EtONa, we used CsF (method B) in the Suzuki coupling of aryl aldehydes (Table 1, footnote d). Under these conditions, either aryl bromides or iodides may be used, and the sequence is compatible with important functional groups such as esters, trifluoromethyl, nitro, ethers, and aldehydes.

Assignment of structure is consistent with ^1H NMR, ^{13}C NMR, and MS. A single crystal X-ray analysis of one compound, **4d**, corroborated that the stereochemistry of the *gem*-borazirconocenes was retained during the sequential alklyations.[13]

Acknowledgment. We thank the University of Toledo for support of this work, and the State of Ohio Academic Challenges Program for providing funds for a high field NMR spectrometer. Thanks to Dr. Ewa

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[1] Some recent examples are: (a) Creton, I.; Marek, I.; Brasseur, D.; Jestin, J.-L.; Normant, J.-F. *Tetrahedron Lett.* **1994**, 35, 6873. (b) Lipshutz, B. H.; Keil, r. *Inorg. Chim. Acta* **1994**, *220*, 41. (c) Hinkle, R. J.; Poulter, G. T.; Stang, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 11626. (d) Moriya, T.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1993**, 1429. (e) Cahiez, G.; Venegas, P.; Tucker, C. E.; Majid, T. N.; Knochel, P. *J. Chem. Soc. Chem. Commun.* **1992**, 1406.

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[10] For reviews of the chemistry of organozirconocenes, see: (a) Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1. (b) Schwartz, J.; Arvanitis, G. M.; Smegel, J. A.; Meier, I. K.; Clift, S. M.; Van Engen, D. *Pure Appl. Chem.* **1988**, *60*, 65. (c) Negishi, E.; Takahashi, T.; *Aldrichim. Acta*, **1985**, *18*, 31. (d) Dzhemilev, U. M.; Vostrikova, O. S.; Ibragimov, A. G. *Russ. Chem. Rev.* **1986**, *55*, 66. (e) Cardin, D. J.; Lappert, M. F.; Raston, C. L. *Chemistry of Organo-Zirconium and Hafnium Compounds;* Ellis Horwood Limited: Chichester, 1986.

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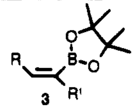
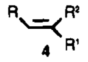
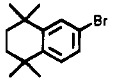
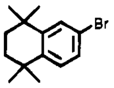
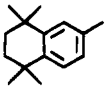
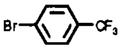
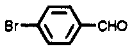
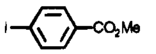
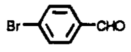
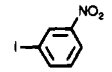
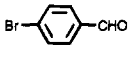
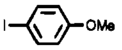
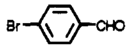
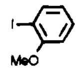
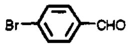
[13] Futher details of the crystal structure investigation are available on request from the Director of the Cambridge Crystallographic Data Centre,12 Union Road, GB-Cambridge CB2 1EZ (UK), on quoting the full journal citation.

0022-3263/95/1960-3276$09.00/0

Table 1. Sequential Alkylation of *gem*-Borazirconocene Alkenes 2

Entry	 3		Yield,%^{a}	 4	Method	Yield, %^{a}
	R	R^1X		R^2X		
a	Ph		68	MeI	A^c	69
b	Ph	MeI	63^b		A^c	79
c		PhI	72	MeI	A^c	65
d	Ph		80		B^d	82
e	Ph		78		B^d	77
f	Ph		70		B^d	78
g	Ph		74		B^d	75
h	Ph		68		B^d	71

^{a} Isolated yields based on halides. ^{b}Always accompanied by about 5 % formation of C-Zr hydrolysis product. ^{c} Conditions A : **3** (0.5 mmol), benzene (4 mL), R^2X (0.5 mmol), $Pd(PPh_3)_4$ (5 mol%), ETONa in ETOH (0.75 mmol), reflux 3 h, according to: Miyaura, N.; Satoh, M.; Suzuki, A. *Tetrahedron Lett.* **1986,** *27,* 3745. ^{d} Conditions B: **3** (0.6 mmol), DME (4 mL), R^2X (0.51 mmol), CsF (1.12 mmol), $Pd(PPh_3)_4$ (3 mol%), reflux 15 h, according to: Wright, S.W.; Hageman, D.Z.; McLure, L.D. *J. Org. Chem.* **1994,** *59,* 6095.

Skrzypczak-Jankun, Department of Chemistry, University of Toledo, for useful discussions. Special thanks to Boulder Scientific for a generous gift of zirconocene dichloride.

Supplementary Material Available: General experimental procedures (5 pages).

JO950206W