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Hydrozirconation of Stannylacetylenes: A Novel and Highly Efficient Synthesis of 1,1-Diiodo-, 1,1-Dibromo-, and Mixed (*Z*)- or (*E*)-1-Iodo-1-bromo-1-alkenes Using 1,1-Hetero-Bimetallic Reagents

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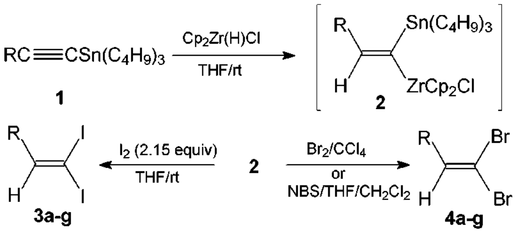
In the past three decades 1,1-dibromo alkenes have been largely employed as important intermediates in organic synthesis. Alkenyl bromides of *Z* or *E* configuration and 1,1-dibromo-1-alkenes are subunits present in the chemical structure of some natural products isolated from marine sponges.[1] Uenishi and co-workers[2] described the stereoselective transformation of 1,1-dibromo-1-alkenes **4** into the (*Z*)-vinylbromides by hydrogenolysis using Bu_3SnH and Pd-$(PPh_3)_4$ as catalyst. Grandjean and Pale,[3] obtained the *E*-isomers as the major products by reaction of **4** with 1 equiv of organolithium followed by hydrolysis. It is well established that the stereospecific palladium-catalyzed cross-coupling of 1,1-dibromo-1-alkenes **4** in a sequential manner provides access to configurationally defined trisubstituted alkenes.[4−6] In these processes, monosubstitution of the bromide at the *E*-position occurs exclusively as demonstrated by several authors employing Negishi,[4,5] Suzuki,[6] and Stille[7] reactions. Corey and Fuchs reported in 1972 the use of dibromoalkene compounds as intermediates in the transformation of aldehydes to terminal alkynes.[8] Although a wide series of 1,1-dibromo-1-alkenes or 1,1-diiodo-1-alkenes are easily prepared,[8,9] certain functionalized dibromides and diiodides cannot be synthesized in an efficient manner while other types of 1,1-dihalovinyl compounds such as mixed (*Z*)- or (*E*)-1-iodo-1-bromo alkenes are not accessible at all. The most useful procedures for the synthesis of compounds **3** and **4** are all conceptually similar because they use Wittig or related approaches. The need for phosphorus reagents limits the appeal of these methodologies as a result of toxicity, and the tedious purification due to the voluminous waste streams particularly is another drawback.[10] Two other different routes that use homobimetallic species of Sn[11] or In[12] obtained from alkynes have been described for **3** and **4**.

Scheme 1



However, these routes are not efficient or general. Only specific alkynes (oxygenated) were used because no general methods for the regioespecific synthesis of the bimetallic starting materials are known.[11,12] Therefore, new, alternative and efficient processes for the synthesis of 1,1-dihaloalkenes would be of considerable value in organic chemistry.

To solve all of these problems and inspired by the work of Lipschutz[13] who has shown that stannylacetylenes undergo the regiocontrolled hydrozirconation with $Cp_2Zr(H)Cl$, and also based on our previous work,[14] we would like to disclose in this report, the first successful, seemingly general, halogenolysis of regio- and stereochemically pure hetero 1,1-bimetallic species for the synthesis of 1,1-diiodo, 1,1-dibromo, and the previously unknown (*E*)- and (*Z*)-1-iodo-1-bromo-1-alkenes that can be difficult to prepare in a stereospecific sense using existing methodologies. The treatment of stannylacetylenes with 1.4 equiv of $Cp_2Zr(H)$-Cl generated the corresponding 1,1-heterobimetallic species of tin and zirconium **2** that by iodinolysis (I_2; 2.15 equiv) gave the 1,1-diiodoalkenes **3a**−**g** in very good yields. The use of 2.5 equiv of Br_2 in CCl_4 or 3.0 equiv of NBS gave the corresponding dibromides **4a**−**g** in 53−83% isolated yield (Scheme 1, Table 1).

The hydrozirconation and the halogenolysis steps were carried out at room temperature in THF, under a nitrogen atmosphere. It is noteworthy that the developed route is compatible with various functionalities such as hydroxylic groups or alkyl halides which cannot be present when phosphorus ylides are used. For the unprotected hydroxylic compounds **3f** and **4f** it was necessary the use of 2.8 equiv of the Schwartz's reagent[15] ($Cp_2Zr(H)Cl$). The reactions were clean, and no alkynyl halides nor over-halogenated products, for example, $RCHICI_3$ or $RCHBrCBr_3$, were detected.

The results summarized in Table 1 and Scheme 1 show the generality of the new route to trisubstituted 1,1-dihalo-alkenes, in which the two carbon−halogen bonds are formed in a one-pot reaction, yet expected to be stepwise (Schemes 1 and 2), because the reactions of the C−Zr bond with electrophiles,[13,14] are normally much faster than the reactions of the C−Sn bond. In accordance with these previous results, we isolated the new compounds **5a**−**c** as exclusive products by the iodinolysis of the C−Zr bond using I_2 (1.07 equiv) in THF at room temperature. By contrast, our attempts to induce similar reactions of zirconated vinylstannane intermediates with Br_2 did not produce clean and useful results. Reactions of **2** with 1.1 equiv of Br_2/CCl_4 show no chemospecificity, with the halogenolysis of the C−Zr (in **2**) and C−Sn (in **6**) bonds being competitive in their respective reactions with Br_2. Even the treatment of intermediates **2** with 0.9 equiv of Br_2 in CCl_4 at −78 °C afforded a mixture of products

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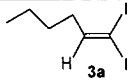
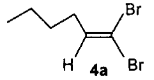
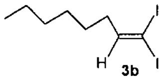
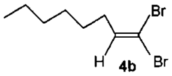
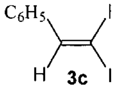
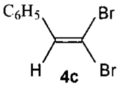
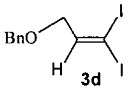
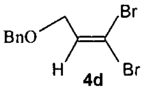
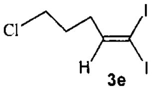
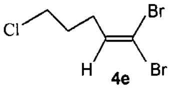
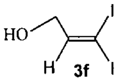
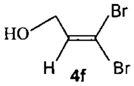
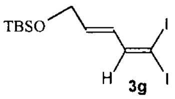
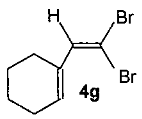
Table 1. 1,1-Dihaloalkenes Obtained Using Bimetallic Species

Diiodide[a]	Yield (%)[b]	Dibromide[a]	Yield (%)[b]
 3a	78[c]	 4a	53[d]
 3b	84[c]	 4b	83[d]
 3c	87[c]	 4c	78[d]
 3d	84[c]	 4d	81[e]
 3e	77[c]	 4e	73[d]
 3f	72[c]	 4f	55[d]
 3g	63[c]	 4g	70[e]

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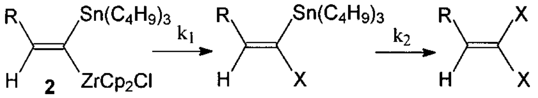
[a] Fully characterized by NMR, MS, HRMS, and IR data. [b] Isolated yields. [c] I_2/THF. [d] Br_2/CCl_4. [e] NBS/THF/CH_2Cl_2.

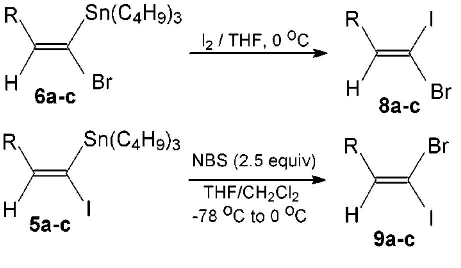
Scheme 2



X = H		7	-
X = I (I_2)	$k_1 >> k_2$	5	3
X = Br (Br_2)	$k_2 > k_1$	6	4
X = Br (NBS)	$k_1 >> k_2$	6	4

Reaction conditions	5 : 6 : 4 : 7
1.1 equiv of Br_2/CCl_4, rt	- : 49 : 36 : 15
0.9 equiv Br_2/CCl_4, -78 °C	- : 62 : 30 : 8
1.05 equiv NBS/THF, -78 °C to rt	- : 100 : - : -
1.07 equiv I_2/ THF, rt.	100 : - : - : -

Scheme 3



which contained the desired (*Z*)-**6**, their *E*-isomer, the 1,1-dibromo-1-alkene **4**, and the (*Z*)-vinyl stannane **7** (Scheme 2). Compound **7** is formed by the proton trap during the aqueous workup.

The observed results (Scheme 2) allowed us to conclude that somehow the Sn/Br exchange in **6** is faster than the Zr/Br exchange in **2** ($k_2 > k_1$), while in **2** the Zr/halogen exchange is always exclusive (the (*Z*)-vinyl bromide was never obtained). Using NBS (1.05 equiv) in THF/CH_2Cl_2 at −78 °C to room temperature, it was possible to overcome these problems, and compounds **6a**−**c** were isolated in excellent yields (Table 2, Scheme 2).

With compounds **5** and **6** in hand we decided to perform the halogenolysis of the C−Sn bond using a halogenating agent differing from that used in the first step so that we could synthesize compounds of type **8** and **9** with complete stereocontrol. Performing the reactions of **6a**−**c** with I_2/THF 0 °C, it was possible to obtain the isomerically pure (*Z*)-1-iodo-1-bromo alkenes **8a**−**c** in very high yields after column chromatography. In our first attempts to prepare the isomers of *E*-configuration, reactions of **5** with Br_2/CCl_4 at room temperature, 0 °C, or −78 °C were carried out. Mixtures of (*E*)-**9** and (Z)-**8** isomers and the dibromo compound **4** were obtained under any of these conditions. The observed results were rationalized on the basis of an addition−elimination process in compound **9** initially formed. This side reaction was completely suppressed by performing brominolysis with NBS in a mixture of THF/CH_2Cl_2. Under these conditions, the isomers of *E*-configuration **9a**−**c** were exclusively obtained and were isolated by PTLC in the yields indicated in Table 3. Independent of mechanistics assumptions about stereochemistry of halogenations of alkenylmetal compounds, the stereochemistry of **5**, **6**, **8**, and **9** could be assigned by ^{1}H and ^{13}C NMR (chemical shifts, NOESY and $J_{\text{Hvinyl-Sn}}$). For compounds **8a**−**b** the vinylic hydrogen appears at 6.45 ppm, and for **8c**, at 7.65 ppm, while for isomers **9a**−**b** it appears at 6.79−6.81 ppm and at 7.87 for **9c**.

Table 2. 1-Halo-1-tributyltin-1-alkenes Obtained

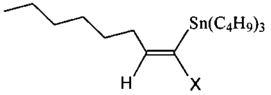
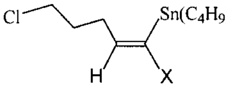
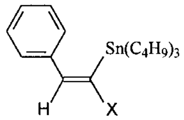
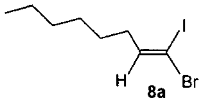
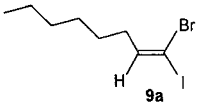
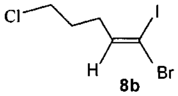
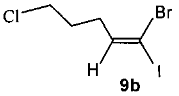
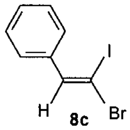
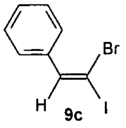
1-Stannyl-1-halo-1-alkene	Yield(%) X = Br	Yield (%) X = I
	(**6a**) 98	(**5a**) 94
	(**6b**) 96	(**5b**) 93
	(**6c**) 97	(**5c**) 97

Table 3. (*Z*)- or (*E*)-1-Iodo-1-bromo-1-alkenes Obtained

(*Z*)-product	Yield (%)[a]	(*E*)-product	Yield (%)[b]
 8a	90	 9a	76
 8b	93	 9b	72
 8c	87	 9c	79

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[a] Isolated yield(column chromatography). [b] Isolated yield(PTLC).

In conclusion, the first synthesis of potentially useful 1-iodo-1-bromo-1-alkenes was developed with complete stereocontrol. Our methods were proven also to be highly efficient for the preparation of 1,1-diiodo-1-alkenes and 1,1-dibromo-1-alkenes, which are highly useful synthetic intermediates. Further work examining the selective reactivity of the halogen atoms in **3**, **4**, **8**, and **9** and also between halogens and tributyltin group in **5** and **6** is in progress.

Acknowledgement is due to FAPESP for financial support of this work. Professor Joseph P. Marino (University of Michigan) is acknowledged for high-resolution mass spectra.

Supporting Information Available: Experimental procedures, analytical data, and spectra for all prepared compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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