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New Approach to the Stereoselective Synthesis of Metalated Dienes via an Isomerization−Elimination Sequence

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The carbometalation of a carbon−carbon multiple bond is one of the most fundamental and straightforward methodologies for the preparation of new organometallics.[1] Particularly interesting, the carbometalation of unactivated alkynes is a practical method for the preparation of vinylmetals, which have great versatility as building blocks in organic synthesis.[2] However, despite these extensive investigations, there are very few reports on vinylmetalation of alkynes since it gives new vinyl organometallics,[3] which may exhibit a reactivity similar to that of the starting vinyl organometallic compounds. This type of carbometalation results in oligomerization or polymerization reactions. Several pathway alternatives have been recently described in the literature, but the stereoselectivity for the preparation of these metalated dienes is the major problem.[4]

We have recently reported that vinyl enol ethers,[5] vinyl alkyl(aryl) sulfides, vinyl sulfoxides, and vinyl sulfones[6] smoothly react with the zirconocene derivative **1**[7] to give stereoselectively the corresponding vinylic organometallic derivatives. Moreover, it has also been described that **1** can induce in some cases, multipositional regioisomerization of unconjugated dienes.[8]

So, we reasoned that unconjugated dienes bearing an enol ether moiety such as **3**−**8** should undergo a new tandem *isomerization−elimination* reaction to give, in a single-pot operation, the corresponding metalated dienyl zirconocene derivatives **9** (Scheme 1).

Scheme 1. Synthesis of Conjugated Dienyl Zirconocene Derivatives

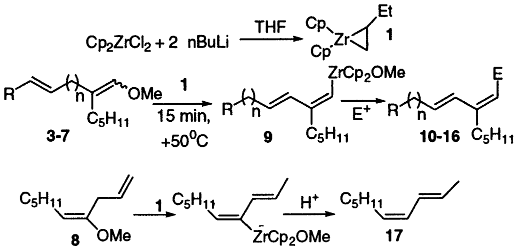

Table 1. Preparation of Isomerically Pure Dienes and Trienes

entry	comp	n	R	E⁺	pdts	yield[a] (%)
1	**3*Z***	1	H	H_3O^+	**10**	80
2	**3*Z***	1	H	I_2 [b]	**11**	75
3	**3*Z***	1	H	allylCl[c]	**12**	70
4	**3*E***	1	H	allylCl[c]	**12**	72
5	**4**	2	H	allylCl[c]	**13**	70
6	**5**	3	H	allylCl[c]	**14**	71
7	**6**	6	H	H	**15**	70
8	**7**	1	Me	allylCl[c]	**16**	80
9	**8**	1	/	H_3O^+	**17**	75
10	**23cCu**	/	/	H_3O^+	**24E**	70
11	**23cCu**	/	/	NBS	**25**	61
12	**23cCu**	/	/	1-iodohexyne[c,d]	**26**	61
13	**23cCu**	/	/	*p*-iodotoluene[c,d]	**27**	59
14	**23cCu**	/	/	methylvinyl ketone[e]	**28**	75
15	**23cCu**	/	/	allylCl[c]	**29**	76
16	**23cCu**	/	/	cyclohexenone[e]	**30**	59

[a] Isolated yield after purification by chromatography on silica gel. [b] Iododiene is unstable at room temperature and isomerized with time. [c] Obtained after a transmetalation step with 10% CuCl·2LiCl. [d] Obtained after a transmetalation step with 5% $Pd(PPh_3)_4$. [e] In the presence of 1 equiv of TMSCl.

All the starting materials **3**−**8** either of *E* or *Z* stereochemistry were easily prepared in a single-pot operation by carbocupration reaction[9] of alkoxyallene[10] (as the unique common starting material) followed by reaction with the appropriate electrophiles.[2] When **3***Z* is treated with **1** in THF for 15 min at +50 °C, the corresponding *E* conjugated diene **10** is isolated in 80% yield after hydrolysis (entry 1, Table 1). The formation of a discrete organometallic species was checked by iodinolysis (entry 2, Table 1), but the resulting iodo diene **11** was found to be unstable and rapidly isomerized to a mixture of ***(****E*)- and (*Z*)-isomers. Thus, the presence of the organometallic was classically checked by reaction with allylic halide after transmetalation of the dienyl zirconocene **9** into organocopper reagent[11] (entry 3). An (*E*,*Z*)-triene **12** is obtained in good overall yield with an isomeric ratio always higher than 95 to 5 as determined by NMR and gas chromatography analyses of the crude reaction mixture. When the reaction is performed on the enol ether **3***E*, the same (*E*,*Z*)-dienylmetal is obtained as determined after reaction with allyl chloride (entry 4, Table 1). In both cases, the stereochemistry was determined on the basis of differential nuclear Overhauser effect spectra. Thus, whatever the stereochemistry of the starting enol ether, the reaction is stereoselective and leads to the (*E*,*Z*)-dienyl zirconium derivative **9** (Scheme 1). The diene isomerization−elimination is not limited to those dienes with a one-carbon tether. Thus **4**, **5**, and **6** (with 2, 3, and 6 carbon tethers respectively) also underwent this tandem reaction (Table 1, entries 5−7). Moreover, the migrating group can be a 1,2-disubstituted alkenyl group since **7** (entry 8, R = Me, Table 1) undergoes similarly the isomerization−elimination process to give the corresponding (*E*,*Z*)-dienyl zirconocene derivative.

Finally, we were also interested to investigate the effect of the position of the unsaturated chain on the isomerization−elimination reaction. For this purpose **8**[9] was submitted to our isomerization−elimination conditions as described in Scheme 1. After hydrolysis of the dienyl zirconocene complex, **17** was isolated as unique (*E*,*Z*)-isomer in 75% yield. To gain more insight into the reaction mechanism, we have repeated this isomerization−elimination reaction on the dideuterated enol ether **18**.

When **18** was treated with **1** for 15 min at +55 °C, **19** was obtained in 62% yield after hydrolysis. The examination of the ^1H- and ^{13}C NMR of **19** indicates that the two deuterium atoms are

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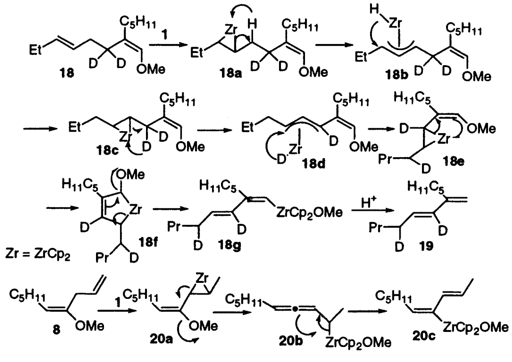
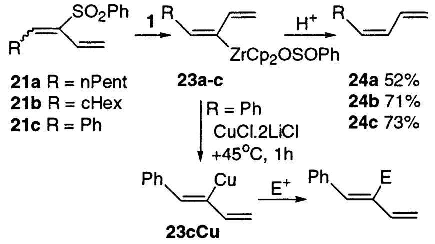
Scheme 2. Mechanistic Hypotheses for the Isomerization−Elimination Sequence



Scheme 3. Preparation and Reactivity of Dienylzirconocene Complexes from 2-Arylsulfonyl-1,3-dienes



now at the vinylic and allylic positions (Scheme 2). This migration−elimination reaction can be explained by the following mechanism (Scheme 2): **1** reacts first with the remote double bond of **18** to form a zirconacyclopropane derivative **18a**. Then, via a C−H allylic activation,[12] the η^3-allyl intermediate **18b** is formed, and after hydrogen migration, the new zirconacyclopropane **18c** is produced. By the same sequence, but with the deuterium atom instead of the hydrogen (**18c** into **18d**), the zirconacyclopropane **18e** is finally obtained before its rearrangement into the zirconacyclopentene intermediate **18f**. Then, by an elimination reaction, the metalated dideuteriodiene **18g** is obtained as determined by its hydrolyzed product **19**.

From this mechanistic pathway, we can rationalize not only the stereochemistry of the (*E*,*Z*)-dienyl zirconocene derivative but also that the stereochemistry of the initial enol ether has no effect on the stereochemical outcome of the reaction since the carbon-heteroatom bond of the sp^3-metalated center **18f** is free to isomerize before the elimination.

When the migrating group is now geminated to the leaving group such as in **8**, the isomerization reaction occurs similarly to give the zirconacyclopropane **20a** but is followed by a β-elimination reaction to lead to the β-metalated allenyl intermediate **20b** (Scheme 2). Then, **20b** is isomerized into its more stable dienyl form **20c**,[13] in which the alkyl and the organometallic groups are anti to each other. After hydrolysis, a unique isomer is observed (determined by NOE effects). This last approach where the leaving group is geminated to the zirconacyclopropane led us also to investigate the case of sulfonyl 1,3-dienyls derivatives **21a**−**c**.[14] As for the enol ether methodology, the major advantage of this approach is the very easy preparation of acyclic 2-arylsulfonyl 1,3-dienes from allylic sulfones and aldehydes in a one-pot procedure.[15] Then, the treatment of **21a**−**c** with 1.5 equiv of **1** at room temperature lead to the cis isomer **24a**−**c** (cis/trans > 95/5), whatever the stereochemistry of the starting material (Scheme 3). By analogy with the mechanistic pathway described for the enol ether **8**, we believe that the transformation of **21a**−**c** also occurs via the formation of the β-metalated allenyl intermediate generated from the β-elimination of the corresponding zirconacyclopropane and subsequent rearrangement. To further increase the scope of the reaction, transmetalation of vinyl zirconiums **23a**−**c** into several different vinylic organometallic derivatives was performed.[11] To our surprise, when these metalated dienes were transmetalated to copper derivative by addition of CuCl•2LiCl for 1 h at +45 °C, a complete isomerization of the dienyl system was found; that is, *trans*-**23cZr** is transmetalated into *cis*-**23cCu**, and then after hydrolysis, only the *(E)*-isomer of **24** is formed in 70% yield.[16]

Although we must await further investigations to elucidate completely the mechanism of this transmetalation, the synthetic use of this reaction is underlined in Table 1 (entries 10−16). For example, **23cCu** reacts either via a S$_N$2′ process with allyl chloride (Table 1, entry 15) or in a 1,4-addition manner with methyl vinyl ketone and cyclohexenone in the presence of TMSCl in 75 and 59% yields, respectively (Table 1, entries 14 and 16). Finally, the palladium-catalyzed cross-coupling reaction of **23cCu** with iodoalkyne or *p*-tolyl iodide, opens new routes for further functionalization as shown by the formation of **26** and **27** in Table 1 (entries 12 and 13).[17] In summary, we have reported an easy and straightforward new preparation of various metalated dienes in only two chemical steps from common starting materials. The study of the scope of this new methodology is underway and will be reported in due course.

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

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