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Titanium and Zirconium Hydride-Catalyzed Regioselective Isomerization of 1,4-Dihydrofulvenes: Access to 1-Substituted 1,2-Dihydrofulvenes

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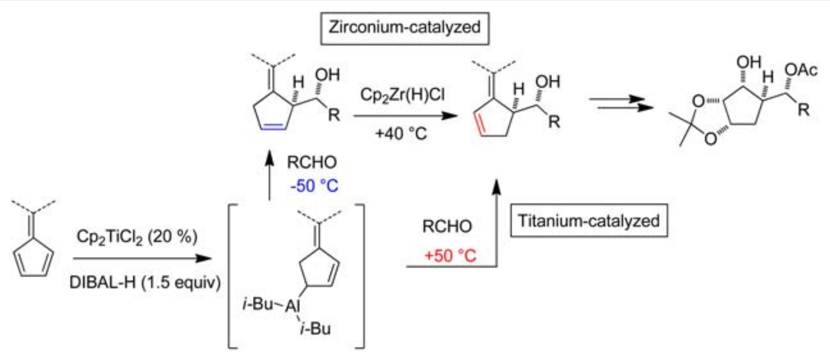
Supporting Information



ABSTRACT: Zirconium hydride-catalyzed C=C double bond migration from nonconjugated to conjugated dienes is described. Applied to 1-substituted 1,4-dihydrofulvenes, the migration leads selectively to 1-substituted 1,2-dihydrofulvenes. The C=C double bond migration can also be catalyzed by titanium hydride, allowing a one-pot procedure to provide 1-substituted 1,2-dihydrofulvenes from pentafulvenes via two titanium-catalyzed steps. This sequence was proven to be temperature-dependent, allowing the selective access to a conjugated or nonconjugated adduct by a simple temperature tuning. The synthetic potential of the methodology was illustrated by the diastereoselective synthesis of a polyhydroxycyclopentane.

Among polyunsaturated systems, conjugated dienes constitute a highly important class of building blocks with a widespread set of applications in organic synthesis,[1] as well as biological chemistry and materials science.[2] However, the direct access to conjugated dienes sometimes remains difficult.[3,4] In this context, Negishi reported an elegant low-valent zirconocene-mediated conversion of nonconjugated to conjugated dienes through a selective migration of the less sterically hindered unsaturated fragment (Figure 1a).[5] Additionally, isomerization of 1-alkene to 2-alkene could also be performed using a catalytic amount of zirconocene in the specific case of allylbenzene (Figure 1b).[5a]

Due to its reversible behavior at room temperature, the hydrozirconation of alkenes stands out from hydroboration and hydroalumination.[6] Implying successive hydrometalation/dehydrometalation/rehydrometalation, this process could be depicted as a C=C bond migration along an alkyl chain.[7] This so-called "zirconium promenade" produces a terminal alkene which undergoes a regioselective hydrozirconation, leading to the sterically least hindered alkylzirconium complex (Figure 1c). In comparison, the selectivity of the C=C migration in the case of cyclic alkenes still needs to be investigated.

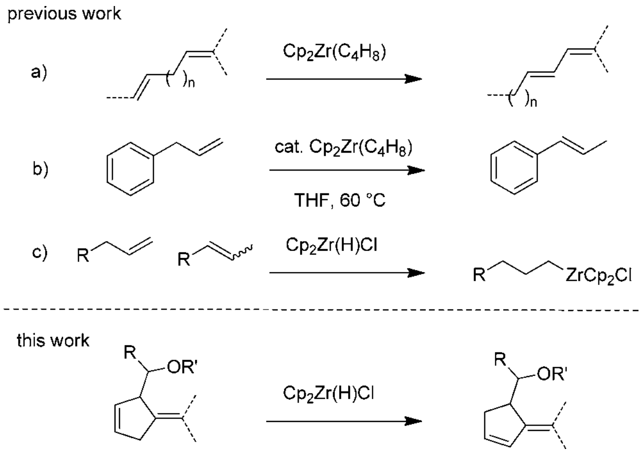


Figure 1. Zirconium-mediated C=C double bond migration.

Zirconocene complexes are known for their efficient binding to conjugated dienes, particularly those allowing the *s-trans* conformation.[8] Thus, driving the C=C migration toward the formation of a conjugated dienic system using a zirconium hydride complex may be envisioned in the typical case of cyclic

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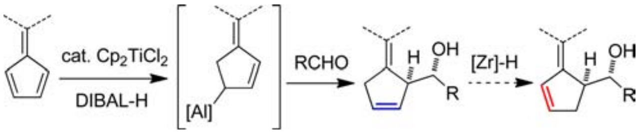
alkenes bearing a nonconjugated exocyclic C=C double bond (Figure 1).[9]

In this communication, we disclose the zirconium- and titanium-catalyzed C=C double bond migration from nonconjugated to conjugated dienes applied to dihydrofulvenes.

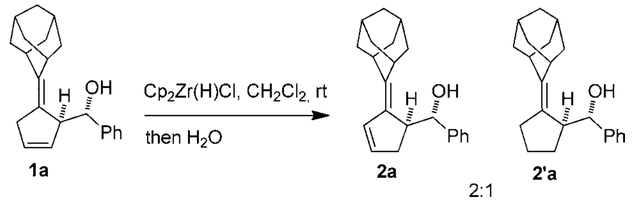
Recently, we described a sequential titanium-catalyzed hydroalumination of dienes/addition to aldehydes or ketones.[10] Applied to pentafulvenes, this method leads to dienic alcohols which are suitable substrates for testing such C=C double bond migration (Scheme 1).

Scheme 1. Zirconium Hydride-Mediated C=C Double Bond Migration



Our initial studies concerned hydrozirconation with model substrate **1a**. In a first experiment, the Schwartz reagent (2 equiv) was added to a solution of **1a** until complete dissolution (~2 h), then water was added. Under these conditions, a mixture of two new products, **2a** and **2′a**, was obtained in a 2:1 ratio (Scheme 2).

Scheme 2. Initial Experiment

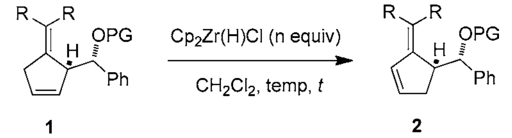


This encouraging result prompted us to optimize the formation of the conjugated diene **2a**. First, we observed a complete conversion after a prolonged reaction time (12 h) (Table 1, entry 1) or by heating at 40 °C for 2 h (entry 2). It was also noticed that the substituents of the exocyclic double bond impact the kinetics of the reaction (entries 3 and 4 vs entry 5). More interestingly, when the analogous methyl ether **1d** was used as the substrate, the Schwartz reagent loading could be reduced to 20% to promote a complete conversion, therefore indicating a catalytic process (entries 7−10).

To account for the catalytic activity of the zirconium hydride, we tentatively propose the following process in which stereoselectivity aspects are not considered for simplification (Figure 2). Initially, the hydrozirconation of **1** would reversibly lead to zirconocene **I**. In a first approximation, one may assume that, due to steric hindrance considerations, **I** is the major adduct; however, the reversible formation of the regioisomer may also be considered. At this stage, **I** would competitively evolve irreversibly toward complex **II**. Finally, hydride transfer from **II** to **1** would give the conjugated diene **2** and zirconocene **I** to complete the catalytic cycle.

With these new conditions in hand, a series of adamantylfulvene-derived dienic alcohols were tested (Table 2). The reaction appears to be quite general, allowing the formation of dienic alcohols or ethers containing aryl (entries 1−4), heteroaryl (entry 5), linear alkyl (entry 8), bulky alkyl (entry 9), or even a chain incorporating a protected hydroxy group (entry 10). The only limitation concerns substrates bearing a pyridine unit (entries 6 and 7), which may trap the catalyst by coordination. Finally, the reaction conditions are also compatible with an unprotected secondary amine (entry 11). It is further remarkable that the reaction proceeds chemoselectively in the presence of a cinnamyl unit (entry 12).

Table 1. Optimization of the Reaction Conditions



entry	R	R	PG	temp (°C)	t (h)	n	2	conversion (%) (yield,[a] %)
1	2-adamantyl		H	20	12	2	**2a**	>95 (70)
2[b]	2-adamantyl		H	20	12	2	**2a**	40
3	2-adamantyl		H	40	2	2	**2a**	>95 (85)
4	$(CH_2)_5$		H	40	2	2	**2b**	92 (83)
5	Ph	Ph	H	20	24	2	**2c**	60
6	Ph	Ph	H	40	40	2	**2c**	85
7	2-adamantyl		Me	40	2	1	**2d**	>95 (78)
8	2-adamantyl		Me	40	2	0.3	**2d**	>95 (75)
9	2-adamantyl		Me	40	2	0.2	**2d**	>95 (77)
10	2-adamantyl		Me	40	2	0.1	**2d**	84

[a]Isolated yield. [b]THF was used as the solvent.

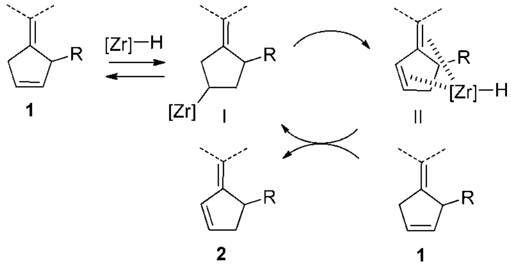
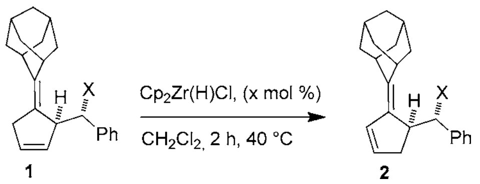


Figure 2. Proposed mechanism.

Although the C=C double bond migration requires only a catalytic amount of zirconium hydride, it is necessary to protect the hydroxy group of **1a**, unless 1 equiv of the Schwartz reagent must be sacrificed. A possible alternative is to achieve the C=C double bond migration from the crude allylation mixture, thus avoiding the hydroxy protection. Reconsidering the titanium-catalyzed hydroalumination of pentafulvene/addition onto aldehyde, one may assume that titanium hydride species remain in the reaction media and could eventually promote a similar migration.[11]

Thus, model compound **1a** was first treated with DIBAL-H (1equiv) to mimic the allylalumination adduct; then Cp_2TiCl_2 (0.2 equiv) and DIBAL-H (0.5 equiv) were added, and the resulting mixture was stirred at 40 °C for 2 h.[12] Pleasingly, the desired conjugated diene **2a** was obtained along with reduced product **2′a** (Scheme 3).

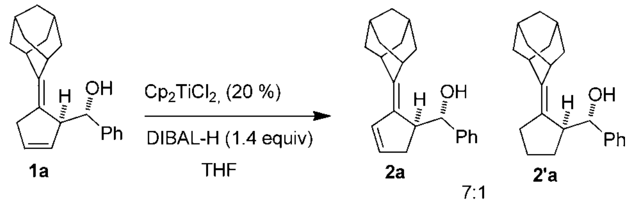
Table 2. Scope of the Reaction



entry	R	X	*x*	**2**	conversion (%) (yield,[a] %)
1	Ph	OH	1.25	**2a**	95 (86)
2	Ph	OMe	0.25	**2d**	95 (75)
3	Ph	OTBS	0.25	**2e**	95 (83)
4	4-Br-C_6H_4	OH	1.25	**2f**	95 (79)
5	2-furyl	OMe	0.25	**2g**	95 (73)
6	3-pyridyl	OMe	0.25	**2h**	10
7	3-pyridyl	OMe	1.25	**2h**	60
8	*n*-Bu	OH	1.25	**2i**	95 (69)
9	*t*-Bu	OH	1.25	**2j**	95 (77)
10	$(CH_2)_4OBn$	OH	1.25	**2k**	95 (74)
11[b]	Ph	NHBn	0.25	**2l**	95 (87)
12	CH=CHPh	OMe	0.25	**2m**	95 (85)

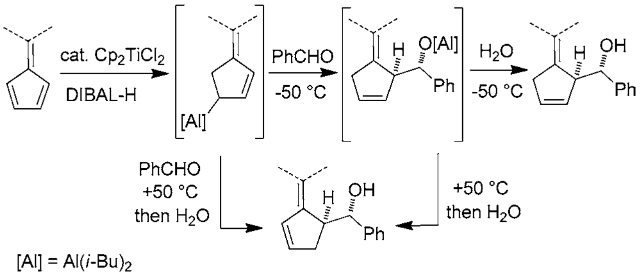
[a] Isolated yield. [b] The *anti* diastereomer was used as the starting material.

Scheme 3. Titanium-Catalyzed C=C Double Bond Migration



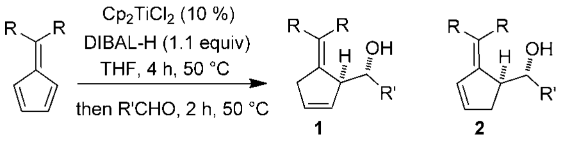
Because the C=C migration could also be catalyzed by titanium hydride, the exact nature of the hydride remains difficult to identify. We therefore reinvestigated the whole process. In a first experiment, the titanium-mediated hydroalumination, which was initially performed with 10% of Cp_2TiCl_2, was now performed using a catalyst loading of 20%. The resulting allylaluminum was allowed to react with benzaldehyde at −50 °C for 1 h and was then warmed to 50 °C and stirred for 2 h. In a second experiment, the allylaluminum generated in the first place was allowed to react with the aldehyde at 50 °C for 2 h. In both cases, the expected C=C double bond migration was observed, and the conjugated dienic alcohol was obtained as the major product (Scheme 4). This example shows that regioisomeric compounds could be obtained by simply adjusting the addition temperature of the aldehyde.

Scheme 4. Temperature Influence upon Titanium-Mediated C=C Double Bond Migration



This sequence, involving two titanium-catalyzed tranformations (i.e., the fulvene hydroalumination and the C=C double migration), was next applied to various aldehydes (Table 3). At first, the C=C double bond migration did not proceed in the case of diphenylfulvene (entry 1), as anticipated from the experiment using the Schwartz reagent (vide supra, Table 1, entries 5 and 6). In contrast, conjugated dienic alcohols derived from aromatic (entries 2 and 3) and linear alkyl (entry 4) aldehydes could be efficiently obtained from adamantylfulvene. Unfortunately, limitations to this process still remain with aldehydes containing bulky alkyl groups or extra coordinating fragments (entries 5 and 6).

Table 3. One-Pot Allylation/C=C Double Bond Migration



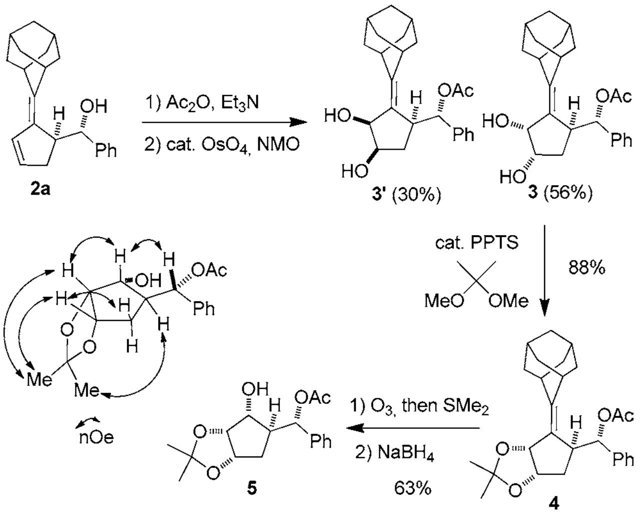
entry	R	R	R′	**1** or **2**	yield (%)[a]
1	Ph	Ph	Ph	**1x**	65
2	2-adamantyl		Ph	**2a**	65
3	2-adamantyl		4-MeO-C_6H_4	**2o**	89
4	2-adamantyl		*n*-Bu	**2i**	74
5	2-adamantyl		*t*-Bu	**1j**	77
6	2-adamantyl		2-NH_2-C_6H_4	**1n**	86

[a] Isolated yield.

Alcohols **2** were characterized by different degrees of substitution within the dienic system; therefore, selective transformations were envisioned to illustrate the synthetic potential of the methodology. Thus, alcohol **2a** was acylated and selectively dihydroxylated to afford the corresponding diols **3** and **3′**. Although a low diastereoselectivity was observed, the major isomer **3** could be isolated in the pure form. Subsequent protection and ozonolysis gave the corresponding ketone,[13] which was immediately reduced using $NaBH_4$ to provide the cyclopentanol **5** as a single diastereoisomer in 63% yield (Scheme 5).

In summary, an efficient zirconium and titanium hydride-catalyzed C=C double bond migration is described. Applied to

Scheme 5. Synthetic Application



nonconjugated dienic systems derived from pentafulvenes, this method allows the selective formation of the corresponding conjugated dienes. Combined with our previously described titanium-catalyzed hydroalumination of pentafulvenes, a divergent access to regioisomeric dienic alcohols could be achieved by simply adjusting the temperature of addition of the aldehyde. The synthetic interest of this method was illustrated by the diastereoselective synthesis of polyhydroxycyclopentane. Investigations regarding an extension of this method to other dienic systems are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03195.

Experimental procedures, characterization, and copies of ^{1}H and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(12) **1a** was recovered when using DIBAL-H without additive.

(13) Attempts to purify the ketone by flash column chromatography led to elimination product.