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Synthesis of 1,3-disubstituted cyclohexenes from dienylethers *via* sequential hydrozirconation/deoxygenative cyclisation†

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Access to 1,3-disubstituted cyclohexenes from zirconocenes containing a latent electrophilic allylic fragment is described. Requiring a specific conformation, 6-*endo*-trig cyclisation is based on the TMSOTf-mediated generation of a stabilized carbocation.

Although structurally simple, 1,3-disubstituted cyclohexenes remain synthetically useful precursors for accessing functionalized molecules owing to the plethora of methods dedicated to C=C double bound transformations. While the ring-closure metathesis appears as an obvious approach to access 1,3-disubstituted cyclohexenes,[1] the preparation of the relevant diene is not always trivial. As a consequence, most alternative methods rely on the functionalization of carbocyclic skeletons.

Among them, a regioselective allylic C–H activation, combining organic and photoredox catalysis, which may be applied to 1-arylcyclohexenes, was recently reported.[2]

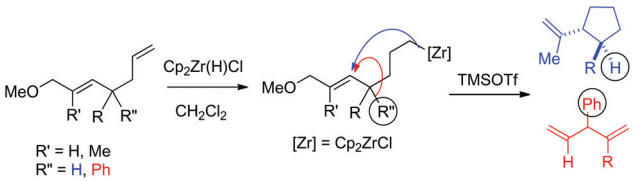
Typically, methods based on the generation of electrophilic cyclohexenyl fragments from allylic alcohols are predominant. Thus, by using silyl enol ethers,[3] allylsilanes[4] or ketoesters[5] as nucleophilic partners, 1,3-disubstituted cyclohexenes can be efficiently prepared. In Friedel–Crafts couplings, both allylic alcohols[6] and acetates[7] were used.

Transition metal-catalyzed reactions also turn out to be attractive tools for providing 1,3-disubstituted cyclohexenes. Thus, an enantioselective approach from enones, combining two consecutive transition metal-catalyzed reactions, was described.[8] The first reaction involves a tandem copper-catalyzed addition of dialkylzincs in the presence of phosphoramidite/trapping with Tf_2O, and the second, the palladium-catalyzed cross coupling of the resulting vinyltriflates. Interestingly, this strategy can also be simplified to a single step procedure.

Additionally, transition-metal-mediated allylic additions applied to cyclic substrates[9,10] can also be successfully applied to 1,3-disubstituted cyclohexenes using soft[11] and hard nucleophiles.[12] Ultimately, a regioselective transition metal-free version, involving the association of Grignard reagents with cyclic allylic phosphorothioate esters, was achieved.[13]

In contrast, strategies based on the construction of the cyclic skeleton are less exploited, and are restricted to malonic entities as the internal nucleophilic entity in palladium-catalyzed allylic substitution.[14] In this context, a methodology based on the intramolecular allylic coupling with a formally hard organometallic counter-part would provide a complementary approach to the existing ones.

Generating an electrophilic fragment within the structure of an organometallic species constitutes an attractive approach for the synthesis of carbocyclic skeletons. Lewis acid-mediated activation of zirconocenes bearing a latent electrophilic fragment has previously been reported, allowing the preparation of cyclopropanes,[15] pyrrolidines,[16] cyclopentylamines[17] and cyclopentanes.[18] Recently, we described the synthesis of vinylcyclopentanes from 7-methoxy-1,5-dienes *via* a sequential hydrozirconation/TMSOTf-mediated activation of the allylic ether.[19] Occurring through a 5-*exo*-trig mode, the ring-closure proceeds in a highly diastereoselective manner when R′ = Me and R″ = H (Scheme 1). Noticeably, the cyclization may be disrupted by steric congestions (R″ = Ph, Scheme 1) resulting in a different evolution of the zirconocene. In this case, the migration of a Ph group to the allylic fragment was observed instead, along with the loss of a molecule of ethylene.[20]



Scheme 1 Sequential activation of dienes.

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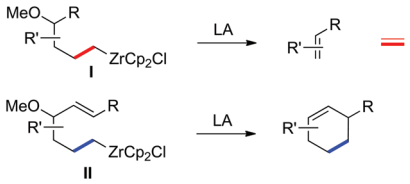


Fig. 1 Plausible compared evolution of zirconocenes **I** and **II**.

In the case of 4-methoxybutylzirconocene **I** (Fig. 1), we anticipated that a similar scenario may occur, instead of the competitive cyclobutane formation, providing an olefin. In contrast, we envisaged that vinylogous substrates **II** might favorably produce cyclohexenes according to a 6-*endo* mode of cyclization.

In this paper, we disclose a general method allowing access to 1,3-disubstituted cyclohexenes through an internal Csp^3-allylation reaction.

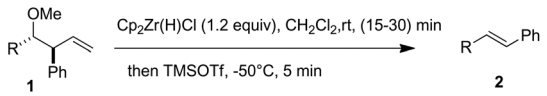
The study was initiated by first studying the evolution of zirconocenes **I** under Lewis acid conditions. As model substrates, homoallylic ethers **1** were prepared by allylation of aldehydes followed by methylation of the resulting alcohols. Compounds **1** were obtained with variable diastereoselectivities, strongly subordinated to the allyl metal used. While a moderate diastereoselectivity was observed from cinnamylzinc, an analogous aluminum reagent[21] provided a single isomer.

Thus, zirconocenes, derived from diastereomerically pure **1a–e**, were generated by hydrozirconation using 1.2 equiv. of the Schwartz reagent at rt, and subsequently treated with TMSOTf at −50 °C. While **1a** and **1b** were efficiently converted into olefins **2a** and **2b**, respectively (entries 1 and 2), only hydrolysis of the corresponding zirconocenes was observed using **1c** and **1e** as the substrates (entries 3 and 5) even after a prolonged reaction time. Moreover, degradation occurred in the case of **1d** (entry 4). Interestingly, when diastereomeric mixtures of **1a,f–g** were reacted under the same conditions, identical levels of stereoselectivity (entries 6–8) were achieved. Although the reaction is diastereospecific, these preliminary results indicate that only substrates bearing an activable benzylic position are involved, and therefore the method cannot be generalized to diversely substituted alkenes (Table 1).

Among deoxygenative processes involving alkylzirconocenes bearing an alkoxide fragment, the synthesis of cyclopropanes reported by Szymoniak[15b] was studied in-depth by Casey.[22] Using deuterium-labeled substrates, the ring-closure was shown to proceed *via* a concerted mechanism. In the present case, the nearly exclusive formation of the E isomer, from a mixture of diastereoisomers, may originate from a transient carbocation (Fig. 2). Accordingly, substrates bearing a stabilizing fragment would be more prone to favor the formation of the olefin, which is validated by the observed results.

Thus, we next focused our attention towards vinylogous substrates which are further prone to undergo an electrophilic activation, and displayed two potential sites of cyclisation,

Table 1 Stereoselective access to *E*-olefins from 4-methoxybutylzirconocenes



Entry	R	**1** dr	**2** yield[a] (%)	$E:Z^b$
1	Ph	**1a** 99 : 1	**2a** (76)	>20 : 1
2	4-MeO-C_6H_4	**1b** 99 : 1	**2b** (73)	>20 : 1
3	4-Br-C_6H_4	**1c** 99 : 1	NR[c]	—
4	2-Furyl	**1d** 96 : 4	Degradation	—
5	$CH(Et)_2$	**1e** 99 : 1	NR[c]	—
6	Ph	**1a** 80 : 20	**2a** (67)	>20 : 1
7	2-MeO-C_6H_4	**1f** 84 : 16	**2f** (64)	>20 : 1
8	2-Thiophenyl	**1g** 77 : 23	**2g** (62)	>20 : 1
9	3-Br-C_6H_4	**1h** 62 : 38	NR[c]	—

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] The unreacted zirconocene was hydrolyzed during work-up.

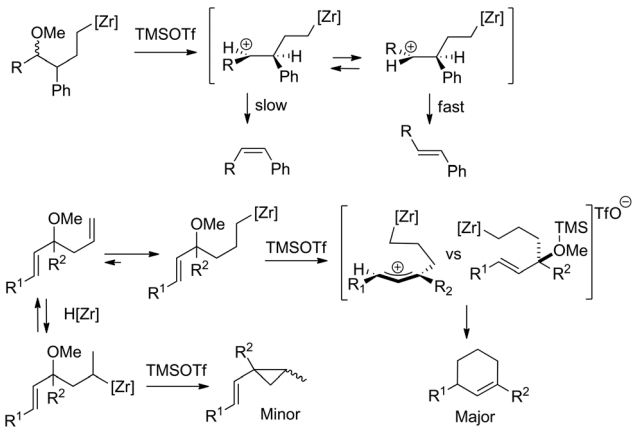


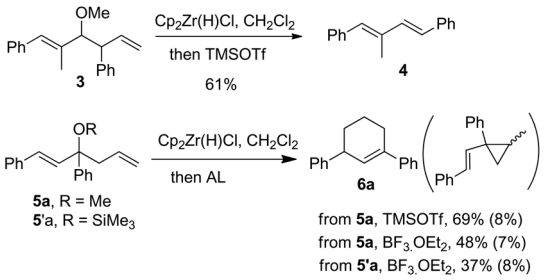
Fig. 2 Possible simplified transition states accounting for the *syn* selective olefination and the formation of cyclohexenes **6**.

thus making possible the formation of cyclohexenes. As model substrates, compound **3**, **5** and **5′** were tested under the above conditions.

Similarly, the zirconocene derived from **3** underwent an abstraction of ethylene upon addition of TMSOTf, providing the diene **4** as the single *E*,*E* isomer. In contrast, the cyclohexene **6a** was obtained in 69% isolated yield when **5a** was used as the substrate using TMSOTf as the Lewis acid. Along with **6a**, we detected the presence of cyclopropane (11% with respect to **6a**) which is assumed to originate from the coexisting regioisomeric zirconocene which arises from the reversible hydrozirconation of **5a**. $BF_3{\cdot}OEt_2$ can also be used to induce cyclization, starting from both **5a** and **5′a**, albeit with a lower conversion (Scheme 2).

In order to extend the scope of the reaction, substrates bearing diverse combinations of substituents were next tested.

The reaction appears to be general allowing the preparation of 1,3-disubstituted cyclohexenes with different combinations of substituents. Among them, diaryl (entries 1–5), 1-aryl-3-

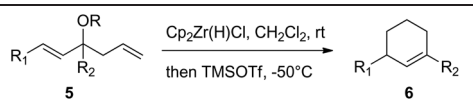


Scheme 2 Towards disubstituted cyclohexenes.

heteroaryl (entry 6), 1-aryl-3-alkyl (entries 8 and 9), and 1-alkyl-3-aryl (entries 10 and 11) products were obtained in moderate to good yields. Interestingly, cyclohexene **6l** bearing a vinylic unit at the 3-position can also be obtained from a substrate containing a conjugated dienic fragment (entry 12). Finally, the reaction conditions are compatible with the use of substrates bearing a protected alcohol chain (entry 13). In the specific case of **6g**, we were not able to prepare the corresponding homoallylic ether precursor with satisfactory purity. Nevertheless, by using the trimethylsilylether in combination with $BF_3{\cdot}OEt_2$, the expected cyclohexene **6g** can be prepared, albeit in a moderate yield (entry 7) (Table 2).

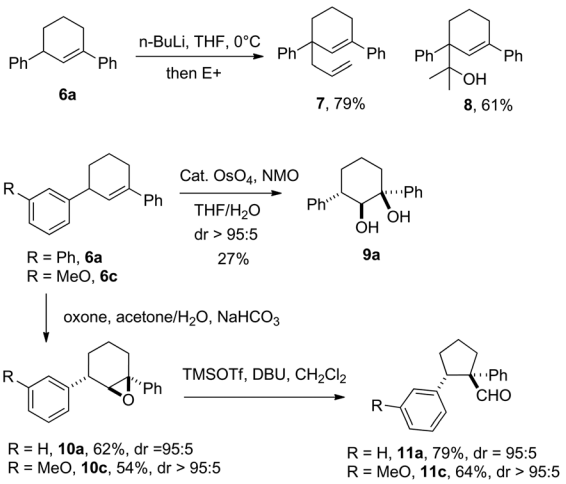
To account for the formation of cyclohexenes **6**, two selective steps are required. While the regioselective hydrozirconation of the terminal alkene, providing the less hindered zirconocene, is likely to result from steric considerations,[17,23] the origin of the selective formation of cyclohexenes from **5** may be attributed to the adequate positioning of the R^2 substituent. This specific localization is assumed to concomitantly (i) further enhance the carbocation generation, or more accurately a π-allyl electrophilic fragment, localizing the zirconocene side chain perpendicularly to the π-allyl system, to minimize the steric interactions, and (ii) induce a compression

Table 2 Scope of the reaction



Entry	R^1	R^2	R	LA	**6** yield[a] (%)
1	Ph	Ph	Me	TMSOTf	**6a** (69)
2	4-MeO-C_6H_4	Ph	Me	TMSOTf	**6b** (48)
3	3-MeO-C_6H_4	Ph	Me	TMSOTf	**6c** (46)
4	4-Br-C_6H_4	Ph	Me	TMSOTf	**6d** (62)
5	Ph	4-Br-C_6H_4	Me	TMSOTf	**6e** (68)
6	2-Thiophenyl	Ph	Me	TMSOTf	**6f** (66)
7	Ph	2-Pyridyl	$SiMe_3$	$BF_3{\cdot}OEt_2$	**6g** (32)
8	*n*-C_5H_{11}	Ph	Me	TMSOTf	**6h** (46)
9	^{i}Pr	Ph	Me	TMSOTf	**6i** (52)
10	Ph	^{i}Pr	Me	TMSOTf	**6j** (48)
11	Ph	Me	Me	TMSOTf	**6k** (30)
12	Ph-CH=CH	Ph	Me	TMSOTf	**6l** (56)
13	TBSO-CH_2-CH_2	Ph	Me	TMSOTf	**6m** (72)

[a] Isolated yield.



Scheme 3 Synthetic applications.

angle that allows the adoption of the suitable conformation for promoting the cyclohexene formation and preventing the competitive olefination and cyclobutane reactions (Fig. 2). While such a general mechanism involving a transient cationic entity is consistent with the experimental results, an alternative concerted S_N2'-like pathway cannot be ruled out at this stage.[24]

To illustrate the usefulness of this series of alkenes, conventional methods of alkene functionalization were applied to prepare valuable building blocks.

Firstly, the deprotonation[25] of symmetrical **6a** using *n*-BuLi followed by the addition of an allylbromide or acetone afforded 1,3,3-trisubstituted cyclohexenes **7** and **8**, respectively (Scheme 3).

Secondly, compounds **6** appear as ideal substrates for undergoing a diastereoselective dihydroxylation reaction, and the resulting diols would constitute candidates in pinacolic rearrangement. Thus, dihydroxylation of **6a** was attempted under standard conditions. The diol **9a** was obtained as a single isomer according to the accurate NMR spectroscopy results, however in a low yield. Epoxidation of **6a,c** using *in situ* generated DMDO was next investigated. **10a,c** were obtained in a highly diastereoselective manner and isolated with a satisfactory yield. Subsequent treatment with TMSOTf in the presence of DBU afforded aldehydes **11a,c** with a nearly complete transfer of chirality (Scheme 3).[26]

Conclusions

In summary, a sequential hydrozirconation/TMSOTf-mediated cyclisation, applied to 4-methoxy-1,5-dienes, providing 1,3-disubstituted cyclohexenes is described. This method is assumed to rely on the generation of a stabilized carbocationic intermediate together with a crucial positioning of the substituent to promote 6-*endo*-cyclization over the competitive olefination reaction. Involving simple substrates, this flexible syn-

thetic method provides access to diversely substituted 1,3-disubstituted cyclohexenes, and may potentially be applied to a larger range of substrates, including naphthalenic and quinolinic fragments, which constitute valuable building blocks. Particularly, carbocycles containing an all carbonated quaternary center can be targeted. Complementary experimental work is required to elucidate the exact mechanism of the reaction and will be presented in due course.

Conflicts of interest

There are no conflicts to declare.

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