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Sequential Hydrozirconation/Cyclization of Dienes, a New Route toward *Trans* 2-Substituted Vinylcyclopentanes

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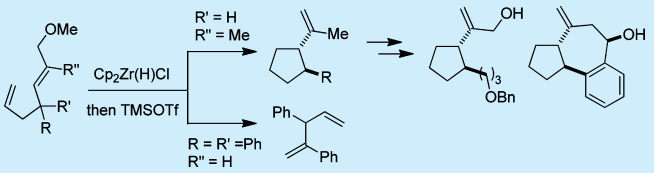
Supporting Information

ABSTRACT: The diastereoselective synthesis of *trans*-2-substituted vinylcyclopentanes is described. The method is based on the intramolecular coupling of 7-methoxy-1,5-dienes involving a sequential activation of the C=C double bonds *via* hydrozirconation and TMSOTf-promoted allylation.



Owing to the ubiquity of the cyclopentane skeleton in a number of biologically active and naturally occurring molecules, the development of methodologies allowing access to functionalized cyclopentanes remains important. In this context, 2-substituted vinylcyclopentanes, which are amenable to a wide range of synthetic transformations, may constitute valuable building blocks.

Several methodologies leading to vinylcyclopentanes are reported in the literature. Among them, Ti(III)-,[1] Ti(II)-, Zr(II)-,[2] Pd-,[3] and Au[4]-mediated coupling of dienes and a Ti/Ni multimetallic intramolecular Heck-type[5] and SmI_2-promoted[6] coupling of iodoalkane/alkene are emerging. Alternatively, vinylcyclopentanes could be prepared via an intramolecular allylic substitution.[7] This strategy relies on the generation of a C−metal bond onto substrates containing a reactive allylic fragment and could also be applied to vinylpyrrolidine synthesis.[8]

The hydrozirconation of alkenes is a powerful method for generating functionalized zirconocenes. Moreover, the hydrozirconation of alkenes is highly sensitive to steric hindrance, rendering possible the chemoselective hydrometalation of substrates containing two C=C double bonds with a different degree of substitution. This high chemoselectivity allows the development of intramolecular processes from dienes through a sequential activation of the two C=C double bonds.[9]

According to this approach, access to vinylcarbocycles from dienes could be envisioned by combining a chemoselective hydrozirconation to an intramolecular allylic addition. Such a strategy could be developed from dienes combining a terminal alkene to an internal allylic fragment.

Two activation modes could be considered to promote the cyclization: (i) by a Zr → Cu transmetalation, zirconocenes being known for acting as alkyl or vinyl promotors in Cu-catalyzed allyllic addition[10] or (ii) by a Lewis acid activation of the residual allylic fragment (Figure 1).

In this paper, we disclose a new access to 2-substituted vinylcyclopentanes from dienes *via* a sequential activation of the two C=C double bonds.

The present study began by checking the chemoselectivity of the hydrozirconation reaction toward dienes. Thus, model substrate **1a** was put in a reaction with the Schwartz reagent (1.2 equiv) until complete dissolution. Hydrolytic treatment gave the expected allylbromide, exclusively.[11] The cyclization conditions under Cu catalysis were first investigated (Table 1, entries 1 and 2). Whereas a low conversion was observed with CuI, the use of $CuBr{\cdot}Me_2S$ gave an encouraging result. In parallel, the electrophilic activation strategy was also tested, with the analogous methyl ether **1b**. This approach was proven to be more efficient.[12] However, the choice of the Lewis acid is crucial

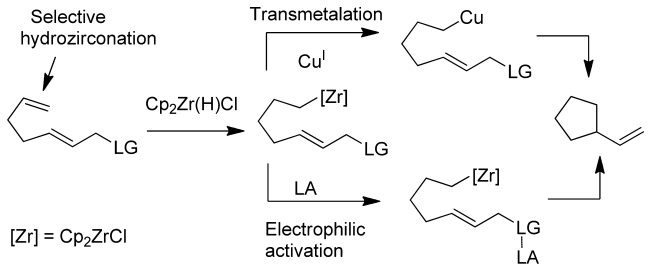
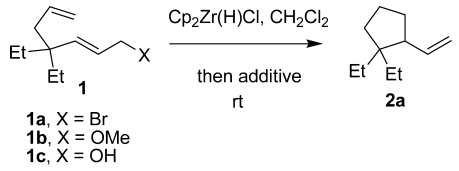


Figure 1. Approach toward vinylcyclopentanes.

Table 1. Optimization of the Cyclization



1a, X = Br
1b, X = OMe
1c, X = OH

entry	1	additive	convertion[a]
1	**1a**	$CuBr{\cdot}SMe_2$	56%
2	**1a**	CuI	20%
3	**1b**	$BF_3{\cdot}OEt_2$	–
4	**1b**	TMSOTf	78% (52%)[b]
5	**1c**[c]	TMSOTf	47%

[a]Determined from the ^1H NMR spectrum of the crude reaction mixture. [b]Isolated yield. [c]2 equiv of $Cp_2Zr(H)Cl$ were used.

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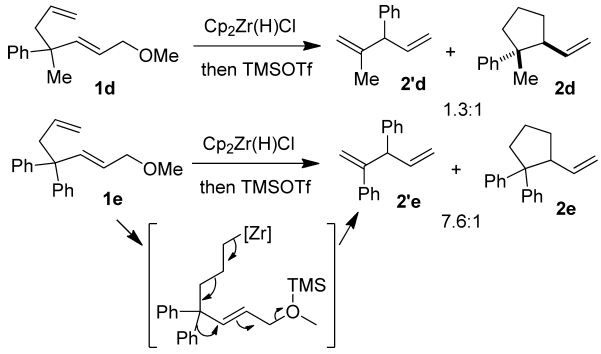
Scheme 1. Diene vs Vinylcyclopentane Formation



to promote the cyclization. While the use of a stoichiometric amount of TMSOTf gave the expected product, polymerization was observed when using $BF_3{\cdot}OEt_2$. Finally, the allylic alcohol **1c** was also tested but did not give satisfactory results.

These optimal conditions were next applied to analogous substrates bearing one or two phenyl groups. In these cases, a diene was obtained along with the desired cyclopentane (Scheme 1). By using **1d** as the substrate, a 1:1.3 mixture of cyclopentane and diene, which could not be separated, was obtained.[13] In the case of **1e**, the proportion of diene increased to 7.6:1.

Interestingly, cyclopentane **2d** was obtained as a 13:1 mixture of diastereomers in favor of the *trans*-isomer.[14]

The competitive diene formation may be due to steric congestion located at the proximity of the cyclization site. The diene is assumed to result from a [1,2]-phenyl shift onto the activated allylic ether, concerted with domino metallo-abstraction and ethylene exclusion. Similar metallo-abstraction and ethylene exclusion leading to alkenes have been previously observed from 4-trimethylstannylbutan-1-ol upon Lewis acid treatment.[15]

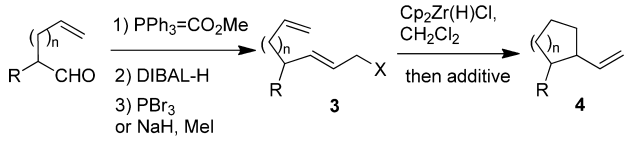
The possibility of performing a diastereoselective cyclization, from substrates incorporating a single substituant closely located with respect to the ring-closure site, was next examined. For that purpose, a series of dienes **3**[16] were prepared from known aldehydes[17] and tested. In a typical experiment, the Schwartz reagent (1.2 equiv) was added to a solution of **3** in CH_2Cl_2 and stirred until complete dissolution, and then TMSOTf (1 equiv) was added. The mixture was stirred for 1 h at rt and quenched with water.

From this series of substrates, vinylcyclopentanes **4** were the only identified products (Table 2). The method could be applied to the synthesis of vinylcyclopentanes bearing, at the 2-position, an aromatic (Table 2, entries 1−4), an alkyl substituent (entry 6), or a chain including a protected alcohol (Table 2, entry 7). Compound **4d**, bearing a thiophene group (Table 2, entry 5), was also obtained, however in low yield, even after a prolonged reaction time. Identical diastereoselectivities were observed independently of the cyclization strategy employed (Table 2, entries 1 and 2) and remained poor (Table 2). Extension of this methodology to vinylcyclohexanes was initiated; however, a complex mixture of vinylcyclopentanes and vinylcyclohexanes was obtained (Table 2, entry 8).

In order to improve the stereoselectivity of the cyclization, we decided to modify the allylether fragment.

The incorporation of a methyl group onto the allylic fragment afforded cyclopentene **4′g** by applying the above conditions. Nevertheless, it was pleasantly found that the addition of TMSOTf at 0 °C prevents the C═C migration and ensures a

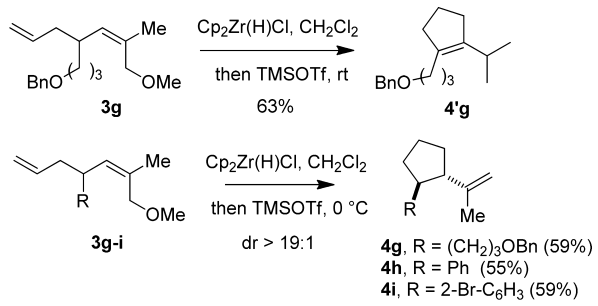
Table 2. Substrate Scope



entry	*n*	R	X	additive	**4** (yield)[a]	dr
1	1	Ph	OMe	TMSOTf	**4a** (72%)	4:1
2	1	Ph	Br	$CuBr{\cdot}SMe_2$	**4a** (36%)	4:1
3	1	2-Br-C_6H_4	OMe	TMSOTf	**4b** (60%)	3.8:1
4	1	PMP	OMe	TMSOTf	**4c** (68%)	4:1
5	1	2-thiophenyl	OMe	TMSOTf	**4d** (25%)[b]	4:1
6	1	CH_2Ph	OMe	TMSOTf	**4e** (51%)	2.8:1
7	1	BnO-$(CH_2)_3$	OMe	TMSOTf	**4f** (61%)	2.9:1
8	2	Ph	OMe	TMSOTf	–	–

[a]Isolated product. [b]Obtained after 12 h of stirring.

Scheme 2. Diastereoselective Synthesis of 2-Substituted Vinylcyclopentanes



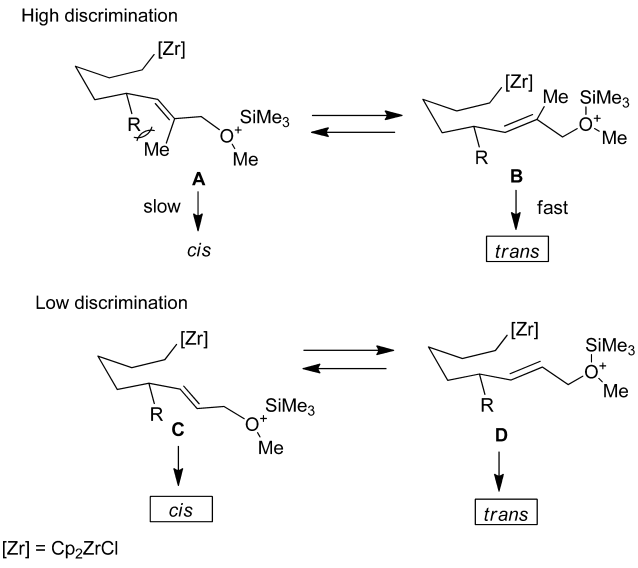


Figure 2. Diastereoselectivity rationale.

totally diastereoselective process, affording the *trans*-isomer.[18] Thus, *trans*-2-substituted vinylcyclopentanes with an aromatic or an alcohol protected chain could be obtained (Scheme 2).

Considering that the cyclization might proceed through a pseudochair-like transition state, the high diastereoselectivity observed in the case of **4g−i** would originate from a marked difference in the relative rates of cyclization of the two possible reactive rotameric forms **A** and **B** (Curtin−Hammett principle) (Figure 2). Assuming that the R substituent adopts a quasi-equatorial orientation, **A** would suffer from severe steric

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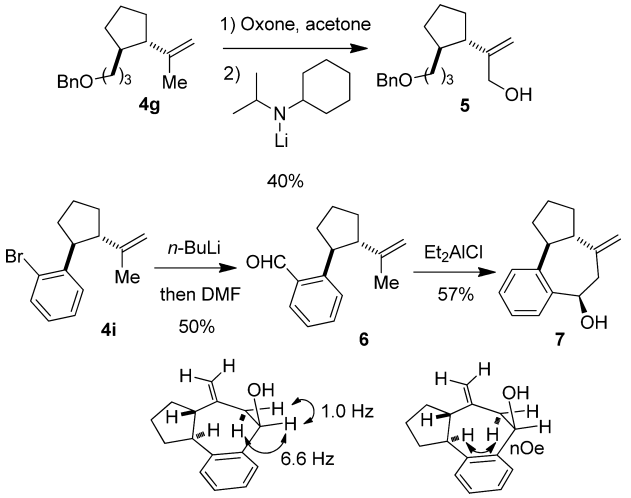
repulsions. The cyclization would thus favorably occur from **B** to give the *trans* isomer. In contrast, it is likely that the relative rates of cyclization of **C** and **D**, precursors of **4a−f**, are less contrasted, leading to a *cis*/*trans* mixture of isomers.

The synthetic interest of this approach relies on the possibility of functionalizing the C═C double bond to generate valuable building blocks. It was exemplified by converting cyclopentane **4g** into the allylic alcohol **5** in a two step sequence involving the formation of an epoxide,[19] followed by treatment with a base[20] (Scheme 3).

Scheme 3. Synthetic Applications



Additionally, access to polycyclic skeletons could be envisioned by coupling together the two branches of the cyclopentane. As an example, a seven-membered ring could be annulated to the cyclopentane through an ene reaction. The required aldehyde **6** was prepared from **4i**.[21] Subsequent Et_2AlCl-promoted cyclization[22] provided **7** as a single diastereoisomer (Scheme 3). This tricyclic skeleton constitutes the framework of naturally occurring presphaerene, isolated from the red alga *sphaerococcus coronopifolius*.[23]

In summary, an efficient diastereoselective method for the construction of 2-substituted vinylcyclopentanes is described. The method involves the successive activation of the two C═C double bonds of dienes via chemoselective hydrozirconation, followed by the electrophilic activation of an allylic ether which was preserved during the hydrozirconation stage.

Trans 2-substituted vinylcyclopentanes could be obtained in a highly diastereoselective manner by adequately substituting the allylic ether fragment. The synthetic potential of the method was illustrated by the preparation of 1,2-substituted cyclopentane bearing two functional groups and by the diastereoselective synthesis of an original tricyclic skeleton which opens the way to the synthesis of a presphaerene analogue.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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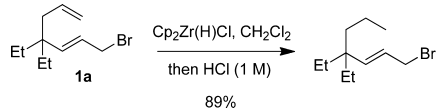
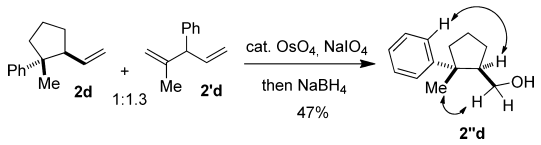
(11) Hydrolytic reaction providing an allylbromide:



(12) For a related hydrozirconation/cyclization sequence, see: Harada, S.; Kowase, N.; Tabuchi, N.; Taguchi, T.; Dobashi, Y.; Dobashi, A.; Hanzawa, Y. *Tetrahedron* **1998**, *54*, 753−766.

(13) Performing the addition of TMSOTf at different temperatures did not signifcantly affect the ratio of products.

(14) The relative configuration of **2d** was deduced from alcohol **2′′d** obtained by OsO_4-catalyzed oxidation of the mixture of **2d** and **2′d** followed by $NaBH_4$ reduction. The *trans* configuration in **2′′d** was determined by NOESY experiments.



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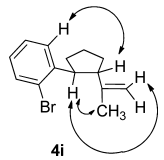
(18) The *trans* configuration was determined by NOESY experiments.



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