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A one-pot access to cyclopropanes from allylic ethers *via* hydrozirconation–deoxygenative ring formation

Vincent Gandon and Jan Szymoniak*

Réactions Sélectives et Applications, CNRS (UMR 6519) and Université de Reims Champagne Ardenne, 51687 Reims cedex 2, France. E-mail: jan.szymoniak@univ-reims.fr; Fax: +33 3 26 91 31 66

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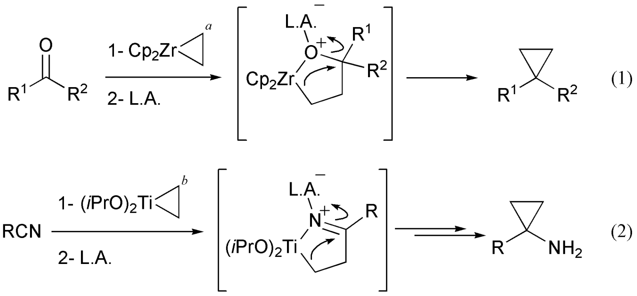
A synthetic method for the direct transformation of allylic ethers into mono-, di- and trisubstituted cyclopropanes is presented.

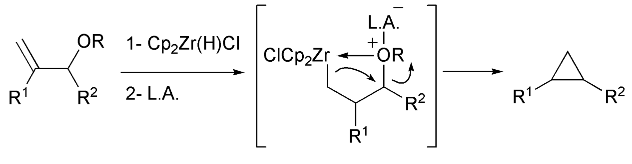
Among the known methods employed for constructing three-membered rings, a large number are based upon the direct cyclopropanation of alkenes.[1] We recently reported a new approach to cyclopropanes from carbonyl compounds and Grignard reagents through $Cp_2Zr(II)$ chemistry.[2,3] The described reaction involves a deoxygenative contraction of an intermediate oxazirconacycle under Lewis acid activation conditions [Scheme 1, eqn. (1)]. An analogous process was next applied for developing a new synthesis of primary cyclopropylamines from nitriles [(eqn. (2)].[4]



Scheme 1 [a] Generated from Cp_2ZrCl_2 and EtMgBr. [b] Generated from $Ti(OiPr)_4$ and EtMgBr. L.A. = $TiCl_4$ or $BF_3\cdot OEt_2$.

We envisioned that a Lewis acid-mediated contraction of heterozirconacycles might be a more general reaction leading to carbocycles and especially cyclopropanes. For this purpose, the zirconium intermediate could be formed indifferently, not only by employing $Cp_2Zr(II)$ chemistry. This idea led us to explore the feasibility of converting allylic ethers in cyclopropanes following Scheme 2.[5]

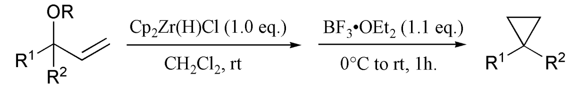
Hydrozirconation of the C=C double bond in allylic ethers has been reported.[6] In several cases, alkenes and alkanes were formed as side-products in these reactions, due to a β-elimination of the alkoxy group from the hydrozirconated intermediate, and a possible second hydrozirconation. Furthermore, complex reaction mixtures were often obtained starting from the allylic trimethylsilyl ethers, because of the reductive cleavage of the O–Si bond. In order to avoid such secondary reactions and favour the cyclopropanation, we examined various reaction conditions. The hydrozirconation was carried out with Schwartz reagent ($Cp_2Zr(H)Cl$), but also with $Cp_2Zr(H)OTf$ in some cases.[7] The reactions were carried out in THF, CH_2Cl_2 or C_6H_6 as solvents, at room temperature or by heating the reaction mixture up to 60 °C (in C_6H_6). Several Lewis acids, namely $TiCl_4$, $BF_3\cdot OEt_2$, $ZrCl_4$ and Me_3SiOTf were tested to induce the cyclopropanation step. When using allylic ethers with a terminal C=C double bond, mild reaction conditions made it possible to avoid undesirable side-products. Thus, hydrozirconation cleanly occurred in CH_2Cl_2 at room temperature. As expected, the deoxygenative cyclopropanation step next proceeded by adding $BF_3\cdot OEt_2$[8] to afford the corresponding cyclopropanes in good to excellent yields (Table 1), systematically better than those obtained starting from aldehydes.[2]

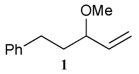
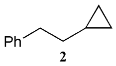
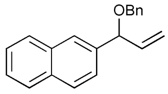
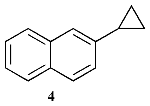
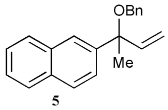
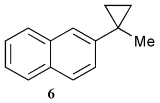
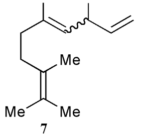
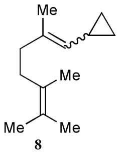
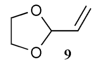
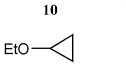
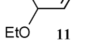
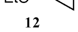


Scheme 2

The reaction proceeded smoothly from the methyl or benzyl allylic ethers bearing both alkyl and aryl substituents (entries 1 and 2). It also took place starting from the ether **5** with a quaternary C3 atom (entry 3). Additional substituted C=C double bonds can be present in the substrate and tolerated by an equivalent of Schwartz reagent (entry 4). The reactions employing the allylic acetals **9** and **11** could also be accomplished leading to the cyclopropyl ethers **10** and **12** (entries 5 and 6).

Table 1 Synthesis of cyclopropanes from allylic ethers with a terminal C=C double bond.



Entry	Substrate	Product	Time (h)	Yield (%)[a]
1	 **1**	 **2**	1	80
2	 **3**	 **4**	0.5	89
3[b]	 **5**	 **6**	6	79
4	 **7**	 **8**	0.6	78
5	 **9**	 **10**	0.5	65
6	 **11**	 **12**	0.25	92[c]

[a] Yields of isolated products after hydrolytic workup ($NaHCO_3$ aq) and flash chromatography. [b] Requires 1.5 eq. of $Cp_2Zr(H)Cl$ and 1.6 eq. of $BF_3\cdot OEt_2$. [c] Estimated by ^1H NMR.

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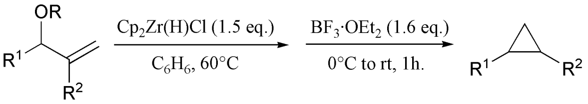
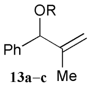
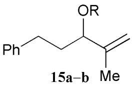
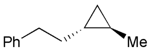
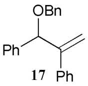
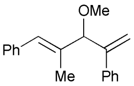
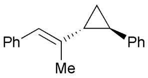
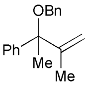
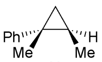
We next employed 2-substituted allylic ethers as substrates. When using CH_2Cl_2 as solvent, the reaction times were long at 20 to 40 °C, undesirable side-products were formed and the yields of cyclopropanes were moderate or low. However, synthetically useful yields were achieved after modifying the reaction conditions. The hydrozirconation step was typically carried out at 60 °C in C_6H_6 instead of CH_2Cl_2. The cyclopropanation step was promoted as before with $BF_3{\cdot}OEt_2$.

Table 2 summarizes the results of reactions employing various allylic ethers.[9,10] Both 1,2-disubstituted and 1,1,2-trisubstituted cyclopropanes having alkyl and aryl groups could be obtained. The *trans* configuration was assigned to the major or unique diastereomers of compounds **14**, **16**, **18**, **20** and **22** from the vicinal coupling constants and on the basis of NOE measurements. We noticed that not only yields but also stereoselectivity increased when using C_6H_6 as solvent in place of CH_2Cl_2.[11] The degree of *trans* stereoselectivity in entry 1 appears to be dependent on the nature of the –OR group, and increases with decreasing of steric demand from R = Bn (*trans*:*cis* = 71:29) to R = Me (*trans*:*cis* = 97:3). A similar stereochemical trend is observed in entry 2. The influence of the –OR group on stereoselectivity possibly indicates a concerted process for the ring formation.

Table 2 Synthesis of cyclopropanes from 2-substituted allylic ethers



Entry	Substrate		Product	Time (h)	Yield (%)[a] (*trans*:*cis*)[b]
1	 **13a–c**	**a**: Bn **b**: MOM **c**: Me	 **14**	1 1 1	76 (71:29) 80 (85:15) 86 (97:3)
2	 **15a–b**	**a**: Bn **b**: Me	 **16**	2 2	75 (83:17) 72 (90:10)
3	 **17**		 **18**	1.5	60 (100:0)
4	 **19**		 **20**	2	75 (90:10)
5	 **21**		 **22**	2	42 (100:0)

[a] Yields of isolated products after hydrolytic workup ($NaHCO_3$ aq) and flash chromatography. [b] ^{1}H-NMR ratios.

In summary, cyclopropanes can be prepared directly from allylic ethers by combining hydrozirconation and the Lewis acid-promoted deoxygenative ring formation. Since several functional groups can be tolerated by an equivalent of Schwartz reagent,[12] the described procedure should be synthetically useful. Studies are underway to further explore the reaction.

Notes and references

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3 For reviews of ′Cp_2Zr′ Chemistry, see E. Negishi and T. Takahashi, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 755; E. Negishi and D. Y. Kondakov, *Chem. Soc. Rev.*, 1996, **26**, 417; E. Negishi and T. Takahashi, *Acc. Chem. Res.*, 1994, **27**, 124; E. Negishi, *Chem. Scr.*, 1989, **29**, 457.

4 (*a*) P. Bertus and J. Szymoniak, *Chem. Commun.*, 2001, 1792; (*b*) P. Bertus and J. Szymoniak, *J. Org. Chem.*, 2002, **67**, 3965.

5 Allylic ethers or acetals have only rarely been used as 3 C-components for the construction of the cyclopropane ring. For some particular transformations, see: monosubstituted cyclopropanes *via* hydroalumination and thermolysis, L. I. Zakharkin and L. A. Savina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1963, **9**, 1693; cyclopropylmethanols *via* hydrozirconation of 1-butenyl- and vinyloxiranes; S. Harada, N. Kowase, N. Tabuchi, T. Taguchi, Y. Dobashi, A. Dobashi and Y. Hanzawa, *Tetrahedron*, 1998, **54**, 753; chiral phenyl- and vinylcyclopropanes *via* carbolithiation of the mixed acetals of acetone with cinnamyl or dienyl alcohols, I. Marek, *J. Chem. Soc., Perkin Trans. 1*, 1999, 535; S. Majumdar, A. de Meijere and I. Marek, *Synlett*, 2002, 423; vinylcyclopropylcarbinols *via* carbozincation of γ-lithiated allylic ethers, F. Ferreira, C. Herse, E. Riguet and J. F. Normant, *Tetrahedron lett.*, 2000, **41**, 1733.

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7 For the preparation of $Cp_2Zr(H)Cl$ and $Cp_2Zr(H)OTf$, see respectively: (*a*) S. L. Buchwald, S. J. LaMaire, R. B. Nielsen, B. T. Watson and S. M. King, *Org. Synth., Coll. Vol. IX*, 1998, 162; (*b*) P. Wipf, H. Takahashi and N. Zhuang, *Pure Appl. Chem.*, 1998, **70**, 1077.

8 No cyclopropanes were obtained when using THF as solvent. Among the Lewis acid tested the distinctly best yields were observed with $BF_3{\cdot}OEt_2$.

9 Selected data for **16**: R_f (Petroleum ether) 0.80; ^{1}H-NMR (250 MHz; $CDCl_3$) *cis* isomer: δ −0.27 (q, J = 5.2 Hz, 1 H), 0.64 (td, J = 8.2, J = 5.2 Hz, 1 H), 0.69–0.83 (m, 2 H), 1.05 (d, J = 6.1 Hz, 3 H), 1.58–1.70 (m, 2 H), 2.65–2.76 (m, 2 H), 7.15–7.30 (m, 5 H), *trans* isomer: δ 0.17 (dt, J = 7.9, J = 4.3 Hz, 1 H), 0.22 (dt, J = 7.8, J = 4.3 Hz, 1 H), 0.37–0.48 (m, 2 H), 1.02 (d, J = 5.5 Hz, 3 H), 1.50–1.60 (m, 2 H), 2.65–2.76 (m, 2 H), 7.15–7.30 (m, 5 H); ^{13}C-NMR (63 MHz; $CDCl_3$) *cis* isomer: δ 9.5, 12.0, 13.2, 15.4, 30.7, 36.5, 125.6, 128.2, 128.4, 142.8, *trans* isomer: δ 12.8, 12.9, 19.0, 19.6, 36.0, 36.3, 125.5, 128.2, 128.5, 142.7; IR (neat) ν (cm^{-1}) 2925, 1453; MS (70eV) m/z 160 ($M^{+\cdot}$, 20), 117 (36), 104 (40), 91 (100); Analysis calculated for $C_{12}H_{16}$: C, 89,94; H, 10,06; found C, 89,63; H, 10,36%.

10 Allylic ethers having exocyclic or internal disubstituted C=C double bond did not give cyclopropanes, even when using $Cp_2Zr(H)OTf$ for hydrozirconation.

11 Comparatively, **14** was obtained from **13c** in 50% yield (*trans*:*cis* = 75:25) with CH_2Cl_2.

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