A direct conversion of α,β-unsaturated ketones to vinylcyclopropanes: new zirconium-mediated reaction†

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Various vinylcyclopropanes are synthesized from α,β-unsaturated ketones *via* a zirconium-mediated [1,2]-addition–deoxygenative cyclopropanation sequence; the latter step surprisingly proceeds under specific protic conditions.

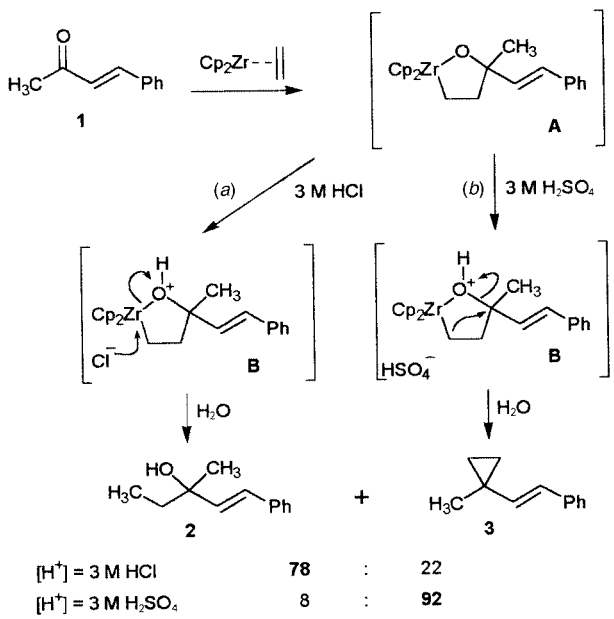
Vinylcyclopropane derivatives are useful intermediates for a wide variety of transformations including rearrangements and stereoselective ring expansions, nucleophilic and electrophilic ring opening, and transition metal catalyzed reactions.[1] On the other hand, many natural or synthetic biologically active molecules contain a vinylcyclopropane moiety. The latter can be constructed using procedures that involve direct formation of the cyclopropane ring.[1,2] The limitation of these methods lies in the necessary use of the carbon–carbon double bond entity as a precursor. Thus, it appears worthwhile to search for new synthetic procedures aimed at relating the vinylcyclopropane moiety to other frequently encountered structural subunits.

Here we present a new approach to vinylcyclopropane derivatives.[3] The described procedure makes it possible to obtain them directly from α,β-enones, by zirconium-assisted deoxygenative addition of an ethylene dianion equivalent (in a formal sense). In practice, zirconocene (ethylene) complex, formed from Cp_2ZrEt_2, was used as a reagent.[4] In the first experiment, Cp_2ZrEt_2 was formed from Cp_2ZrCl_2 and EtMgBr (2 equiv.) in THF at −78 °C, and Cp_2Zr (ethylene) generated by allowing the reaction mixture to warm to 0 °C. Afterwards, benzylideneacetone (**1**) was added, and the reaction carried out at room temperature for 2 h.[5] The hydrolysis of the reaction mixture with 3 M HCl afforded alcohol **2** and an unexpected minor vinylcyclopropane derivative **3** (**3**:**2** = 22:78) (Scheme 1).[6]

Deuterolysis of the reaction mixture with DCl in D_2O (3 M) gave [^{2}H]-**2**, namely 5-deuterio-3-methyl-1-phenylpent-1-en-3-ol, with > 98% D incorporation. This result suggested that the reaction had involved an intermediate oxazirconacyclopentane (**A**), similar to those postulated for the reactions employing saturated ketones.[6]

Using 3 M H_2SO_4 instead of 3 M HCl for hydrolysis, the course of the final reaction changed. Thus, quenching of the reaction with 3 M H_2SO_4 resulted in predominant formation of vinylcyclopropane derivative **3** (**3**:**2** = 92:8) which was isolated in 45% yield (Scheme 1). We next ascertained that the cyclization process had not occurred before protonolysis, under the reaction conditions. In fact, no trace of **3** was detected in THF at 0 °C or at room temperature even after prolonged reaction time (36 h). This observation confirmed the crucial role of H_2SO_4 for cyclization. Thus, the title reaction markedly differs from the somewhat similar Kulinkovich hydroxy-cyclopropanation, which allows the preparation of cyclopropanols or cyclopropylamines from esters (carbonates) or amides and a Grignard reagent, in the presence of $Ti(OPr^i)_4$.[7] Whereas the latter involves the spontaneous rearrangement of the intermediate oxatitanacycle, specific protic conditions proved to be necessary for our cyclization to occur. Finally, we noticed that no cyclization reaction occurred with H_2SO_4 starting from the saturated ketones, and only the corresponding alcohols were isolated in all cases.

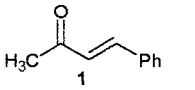
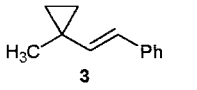
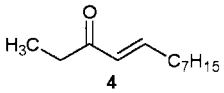
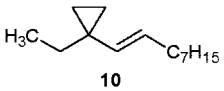
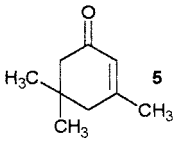
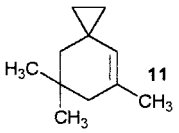
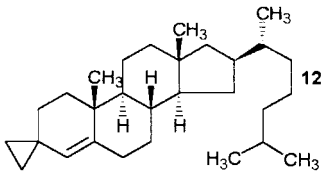
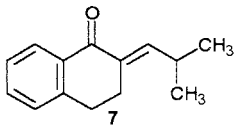
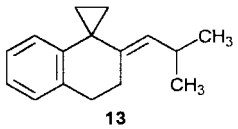
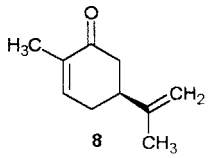
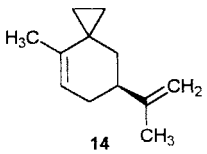
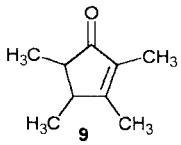
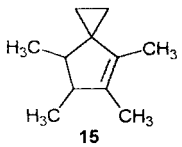
To further explore the scope of the title reaction other α,β-unsaturated ketones were tested. As shown in Table 1, the reaction can be applied to the synthesis of various vinylcyclopropane derivatives. Particularly, the spiro cyclopropane derivatives **11**–**15** (entries 3–7) could be prepared in moderate to excellent yields starting from the cyclic substrates. Thus, isophorone (**5**) and cholestenone (**6**) were transformed into the corresponding vinylcyclopropane derivatives **11** and **12**, respectively, in 75 and 91% yield (entries 3 and 4). The easily prepared **12** should be considered as a new potentially useful steroidal intermediate.[8] The carbonyl-conjugated C=C double bond may be in an exocyclic as well as endocyclic position, and even an additional isolated C=C double bond may be present in the substrate (entries 5 and 6). The reactions have also been accomplished starting from the relatively crowded tetramethylcyclopentenone (**9**) (entry 7). The absence of the corresponding alcohols using the cyclic substrates **5**–**9** is noteworthy. The less reactive acyclic enones **1** and **4** gave lower yields on average (entries 1 and 2). We thought that this might be due to the relative thermal instability of the Cp_2Zr(ethylene) complex,[4] performed *in situ* in the absence of the substrate. To overcome this limitation we tried to stabilize the complex by adding 1 equiv. of trimethylphosphine prior to increasing the temperature from −78 to 0 °C.[6] As a result, only slightly higher yields were observed (53 and 42% for **3** and **10**). Nevertheless, the phosphine-based procedure could also be applied to the preparation of substituted vinylcyclopropane derivatives, as exemplified by the synthesis of **16** (Scheme 2). This reaction did not proceed with a significant yield without PMe_3, possibly



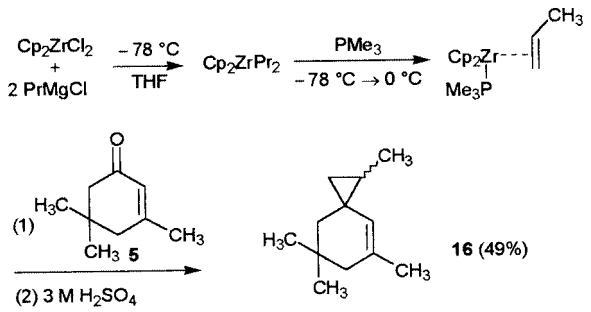
Scheme 1

† Dedicated to Professor Pierre Sinaÿ on the occasion of his 62nd birthday.

Table 1 Reaction of α,β-enones with Cp_2Zr/(ethylene), followed by hydrolysis with H_2SO_4

Entry	α,β-Enone	Product	Yield (%)[a,b]
1	 1	 3	45 (53)
2	 4	 10	31 (42)
3	 5	 11	75
4	6 (4-cholesten-3-one)	 12	91
5	 7	 13	47
6	 8	 14	40 (59)
7	 9	 15	55

[a] Yields of isolated products after column chromatography. [b] Yields for the reaction employing PMe_3 (1 equiv.) are given in parentheses.



Scheme 2

because of the generally more difficult incorporation of higher alkenes.[4]

Two aspects of the title reaction are remarkable: (i) the cyclopropanation (C–C bond formation) step occurs under protic conditions, and (ii) this selective reaction requires 3 M H_2SO_4, whereas the use of 3 M HCl leads to the predominant formation of the alcohol. Further studies are necessary to clarify the specific role of H_2SO_4 in the cyclization process. However, based on the dichotomous behavior of the two strong protic acids, 3 M HCl and 3 M H_2SO_4, a hypothetical rationale for the two different reaction modes can be proposed (Scheme 1). In the first step, oxazirconacyclopentane **A** must invariably be protonated under the strongly acidic conditions to give the oxonium intermediate **B**. Depending on whether HCl or H_2SO_4 is employed, strikingly different mechanistic pathways [(*a*) or (*b*)] can follow. The reasonably nucleophilic Cl^- apparently attacks at the Cp_2Zr residue with cleavage of the Zr–O bond, which is favourably accompanied by the formation of the relatively strong Zr–Cl bond. In contrast, the attack of the weakly nucleophilic HSO_4^- on Cp_2Zr is slower than the competing ring contraction, leading to a cyclopropane derivative. In this concerted process,[9] the partial positive charge developing on the allylic carbon atom is efficiently stabilized by the neighbouring double bond. Studies are underway to fully elucidate the cyclization step and to extend the synthetic scope of the reaction, and the results will be published in due course.

Notes and references

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2 T. Hudlicky, F. Rulin, T. C. Lovelace and J. W. Reed, *Studies in Natural Product Chemistry, Stereoselective Synthesis*, ed. Atta-ur-Rahman, Elsevier, Amsterdam, 1989, Part B, vol. 3, p. 3; T. Tsuji and S. Nishida, *The Chemistry of the Cyclopropyl Group*, ed. Z. Rappoport, Wiley, New York, 1987, p. 307.

3 A similar reaction involving allylindium reagents was reported; this reaction is restricted, however, to the synthesis of homoallyl-substituted vinylcyclopropanes, see H. A. Höppe, G. C. Lloyd-Jones, M. Murray, T. M. Peakman and K. E. Walsh, *Angew. Chem., Int. Ed.*, 1998, **37**, 1545.

4 E. Negishi and T. Takahashi, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 755 and references therein; E. Negishi and T. Takahashi, *Acc. Chem. Res.*, 1994, **27**, 124.

5 Usually, zirconocene (alkene) complexes are generated in the presence of a substrate. However, in our case, a complex mixture of products was formed using this procedure.

6 Cp_2Zr (ethylene) adds to saturated aldehydes and ketones to afford the corresponding alcohols, see T. Takahashi, N. Suzuki, M. Hasegawa, Y. Nitto, K. Aoyagi and M. Saburi, *Chem. Lett.*, 1992, 331; N. Suzuki, C. J. Rousset, K. Aoyagi, M. Kotora and T. Takahashi, *J. Organomet. Chem.*, 1994, **473**, 117.

7 O. L. Epstein, A. I. Savchenko and O. G. Kulinkovich, *Tetrahedron Lett.*, 1999, **40**, 5935 and references therein.

8 *Selected data* for **12**: δ_H(500 MHz, $CDCl_3$, TMS) 0.30–0.52 (m, 4 H), 0.70 (s, 3 H), 0.80–2.05 (m, 39 H), 2.15–2.25 (m, 1 H), 4.67 (s, 1 H); δ_C(125 MHz, $CDCl_3$) 12.0, 13.7, 15.1, 18.7, 19.1, 21.7, 22.6, 22.9, 23.9, 24.3, 28.0, 28.3, 30.0, 32.3, 33.2, 35.8, 36.0, 36.2, 37.0, 37.3, 39.5, 40.1, 42.5, 126.4, 144.1; *m/z* (70 eV) 397 (100%) [M^+], 382 (17) (calc. for $C_{29}H_{48}$: C, 87.80; H, 12.20; found: C, 87.56; H, 12.51%).

9 A concerted process for this ring contraction is in accordance with the fact that the double bond configuration in the acyclic products **3** and **10** is retained.

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