(50 mL) at room temperature and an ethylene pressure of 1 bar. After 8 min, the reaction mixture was transferred to another flask containing a slurry of dried silica (1.5 g) in toluene (10 mL) and MAO (1 mL). After stirring at room temperature for 15 min, the mixture was filtered into another flask containing $[Ni(acac)_2]$ (90 mg, 0.35 mmol) in toluene. After the mixture had been stirred at room temperature for 30 min under an ethylene pressure of 1 bar, the reaction was quenched by the addition of dilute HCl (50 mL of a 1M solution). After separation of the phases, the organic layer was dried over $MgSO_4$ and the product was analyzed by GC.

Received: September 14, 2001 [Z17904]

[1] K. Ziegler, H. G. Gellert, H. Kühlhorn, H. Martin, K. Meyer, K. Nagel, H. Sauer, K. Zosel, *Angew. Chem.* **1952**, *64*, 323 – 329.

[2] a) D. Vogt in *Applied Homogeneous Catalysis with Organometallic Compounds*, *Vol. 1* (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**, p. 245 – 258. b) J. D. Wagner, G. R. Lappin, J. R. Zietz in *Kirk-Othmer Encyclopedia of Chemical Technology*, *Vol. 1*, Wiley, NY, **1991**, pp. 865 – 913.

[3] K. Ziegler, H. G. Gellert, E. Holzkamp, G. Wilke, *Brennstoff-Chem.* **1954**, *35*, 321 – 352.

[4] K. Ziegler, E. Holzkamp, H. Breil, H. Martin, *Angew. Chem.* **1955**, *67*, 541 – 547.

[5] J. D. Scollard, D. H. McConville, J. J. Vittal, N. C. Payne, *J. Mol. Catal.* **1998**, *128*, 201 – 214.

[6] A.-L. Mogstad, R. M. Waymouth, *Macromolecules* **1992**, *25*, 2282 – 2284.

[7] R. Leino, H. J. G. Luttikhedde, P. Lehmus, C.-E. Wilén, R. Sjöholm, A. Lehtonen, J. V. Seppälä, J. H. Näsman, *Macromolecules* **1997**, *30*, 3477 – 3483.

[8] D.-J. Byun, S. Y. Kim, *Macromolecules* **2000**, *33*, 1921 – 1923.

[9] G. J. P. Britovsek, M. Bruce, V. C. Gibson, B. S. Kimberley, P. J. Maddox, S. Mastroianni, S. J. McTavish, C. Redshaw, G. A. Solan, S. Strömberg, A. J. P. White, D. J. Williams, *J. Am. Chem. Soc.* **1999**, *121*, 8728 – 8740.

[10] H. Wesslau, *Liebigs Ann. Chem.* **1960**, *629*, 198 – 206.

[11] E. G. Samsel, (Ethyl Corporation), EP 0539876, **1993** [*Chem. Abstr.* **1993**, *119*, 95815].

[12] E. G. Samsel, D. C. Eisenberg, (Ethyl Corporation), EP 0574854, **1993** [*Chem. Abstr.* **1994**, *121*, 86240].

[13] J. F. Pelletier, A. Mortreux, X. Olonde, K. Bujadoux, *Angew. Chem.* **1996**, *108*, 1980 – 1982; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1854 – 1856.

[14] J. F. Pelletier, K. Bujadoux, X. Olonde, E. Adisson, A. Mortreux, T. Chenal, (Enichem S. p. A.), US 5779942, **1998** [*Chem. Abstr.* **1998**, *125*, 301844].

[15] G. C. Bazan, J. S. Rogers, C. C. Fang, *Organometallics* **2001**, *20*, 2059 – 2064.

[16] H. Lehmkuhl, O. Olbrysch, *Liebigs Ann. Chem.* **1975**, 1162 – 1175.

[17] H. Lehmkuhl, I. Döring, H. Nehl, *J. Organomet. Chem.* **1981**, *221*, 123 – 130.

[18] S. Gagneur, J.-L. Montchamp, E. Negishi, *Organometallics* **2000**, *19*, 2417 – 2419.

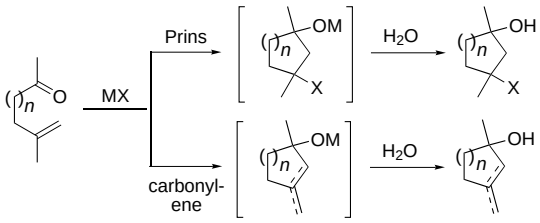
[19] H. Stadtmüller, R. Lentz, C. E. Tucker, T. Stüdemann, W. Dörner, P. Knochel, *J. Am. Chem. Soc.* **1993**, *115*, 7027 – 7028.

[20] S. Vettel, A. Vaupel, P. Knochel, *J. Org. Chem.* **1996**, *61*, 7473 – 7481.

Stereoselective Prins Cyclizations of δ,ε-Unsaturated Ketones to *cis*-3-Chlorocyclohexanols with $TiCl_4$**

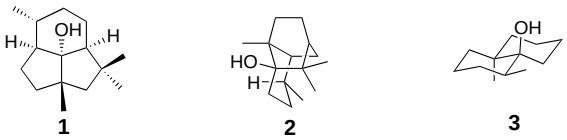
Chad E. Davis and Robert M. Coates*

The closely related Prins and carbonyl-ene cyclizations have proven to be useful transformations for forming five-membered, six-membered, and larger rings in the synthesis of carbocyclic natural products.[1, 2] These similar annulation methods both involve initial electrophilic attack of an activated carbonyl group onto an olefin, followed by either nucleophilic capture or proton elimination (Scheme 1, MX = Lewis acid).



Scheme 1. Lewis acid mediated Prins and carbonyl-ene cyclizations of unsaturated ketones.

Although Lewis acid mediated Prins cyclizations of aldehydes[1, 3] and trifluoromethyl ketones[4, 5] are rather well documented in the literature, to our knowledge only a few examples of nucleophilic capture products from non-fluorinated ketones have been reported.[6] This transformation would afford an attractive synthetic approach for the construction of hindered tertiary alcohols, a structural motif common in terpene natural products such as presilphiperfolan-8-ol (**1**), patchouli alcohol (**2**), and geosmin (**3**).[7] Here we report $TiCl_4$-mediated stereoselective Prins cyclizations of δ,ε- and ε,ζ-unsaturated ketones[8] to *cis*-3-chlorocyclohexanols as well as comparisons with the corresponding reactions in which HCl is used.



1 **2** **3**

A series of δ,ε-unsaturated ketones prepared by the Sakurai[9] addition of allyl- or methallylsilanes to the requisite enone underwent cyclization in the presence of $TiCl_4$ (1.0 equiv) or HCl (0.9 equiv to large excess) in CH_2Cl_2 at

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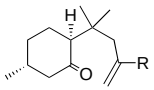
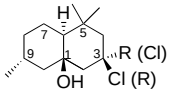
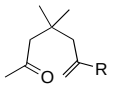
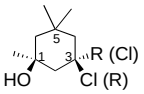
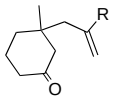
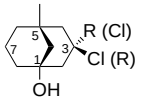
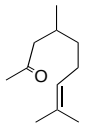
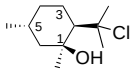
[**] This research was supported in part by the National Institutes of Health (GM 13952).

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

  1433-7851/02/4103-0491 $ 17.50+.50/0

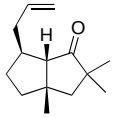
Table 1. Conditions and isomeric chlorohydrin products formed in Prins-type cyclizations of allyl and methallyl ketones with $TiCl_4$ and HCl.

Entry	Keto Olefins: Structure	R	No.	Conditions[a]: Reagent, *t* [min]	Chlorohydrin Products[b,c]: Structure	*cis*	*trans*	Ratio	Yield [%]	Olefin Products: Yield [%]
1		H	**4a**	$TiCl_4$, 0.5		**5a**	**6a**	7:1	62	–
2				15				8:1	72	–
3				HCl, 5				< 1:99	64	–
4		Me	**4b**	$TiCl_4$, 0.25		**5b**	**6b**	13:1	55	12
5				0.5[d]				4:1	65	28
6				HCl, 0.5				< 1:99	50	41
7		H	**7a**	$TiCl_4$, 5		**8a**	**9a**	6:1	59	–
8				15				5:1	66	–
9				HCl, 22[e]					(no reaction)	
10		Me	**7b**	$TiCl_4$, 0.5		**8b**	**9b**	12:1	93	–
11				0.5[d]				10:1	91	3
12				HCl, 45				1:3	51	33
13				60[f]				1:4	68	32
14		H	**10a**	$TiCl_4$, 45		**11**	**12**	1.3:1	63	8
15		Me	**10b**	0.5						48
16			**13**	$TiCl_4$, 0.5		**14**			69	11
17				0.5[d]					87	11

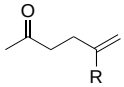
[a] CH_2Cl_2 at $-78\,^{\circ}C$ unless otherwise noted. [b] *cis* and *trans* refer to Cl–OH relationship. [c] Ratios and yields of unstable tertiary chlorohydrins determined by ^1H NMR analysis of the crude product. [d] Toluene, $-78\,^{\circ}C$. [e] $-20\,^{\circ}C$, 15 min; RT, 7 min. [f] Et_2O, RT.

$-78\,^{\circ}C$ (Table 1). The product distributions were determined by quantitative ^1H NMR analysis prior to chromatographic purification. The structure and stereochemistry of the cyclization products were established by a combination of NMR analysis, X-ray crystallography,[10] and chemical conversions.[11] Reductive dechlorination (Bu_3SnH, AIBN, PhH, reflux) of secondary epimeric chlorohydrins afforded the same tertiary alcohol whereas base-induced elimination of epimeric tertiary chlorides provided correlation to olefins.

The results indicate that the $TiCl_4$-mediated cyclizations are selective for the formation of *cis*-chlorohydrins, whereas the use of HCl gave the *trans*-chlorohydrin with variable selectivity and higher proportions of cyclic olefins. Higher yields and increased selectivities were obtained in dichloromethane or toluene than in pentane. The yields and isomer ratios from cyclizations of ketones **4a** and **7a** did not vary appreciably with prolonged reaction times, which indicates the stability of the products under the reaction conditions. Interestingly, keto olefins **15**, **16a** and **16b** were all inert to the $TiCl_4$ conditions. The failure of the allyl bicyclo[3.3.0]octanone (**15**) to undergo cyclization may be a reflection of the high degree of strain associated with the tricyclo[5.3.1.$0^{4,11}$]undecane ring system.

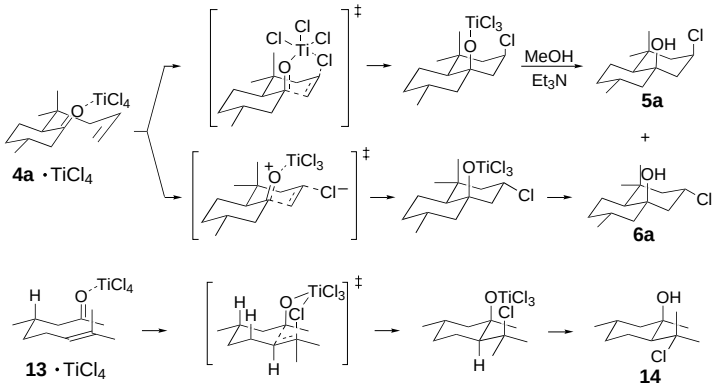


15



16a R = H
16b R = CH_3

The *cis* selectivity observed in the $TiCl_4$-mediated cyclizations may be rationalized either by a pericyclic mechanism that proceeds through a six-membered cyclic transition state (Scheme 2) or by suprafacial ion pair formation and collapse. In the former model, a ketone–$TiCl_4$ complex could undergo



Scheme 2. Pericyclic mechanisms proposed for *cis* selective Prins cyclizations with $TiCl_4$.

concerted suprafacial addition across the proximal double bond by way of a highly polarized boatlike or chairlike array. Alternatively the predominant formation of *cis*-chlorohydrin could be explained by a nonconcerted mechanism in which intramolecular alkylation of the double bond generates transient carbocation ion pairs such as $R^+/ROTiCl_4^-$ or R^+/Cl^- that collapse to the covalent *cis*-chlorotitanate products

  1433-7851/02/4103-0492 $ 17.50+.50/0

faster than rearrangement to the *trans* ion pair stereoisomers occurs. The much faster rates ($\geq 10-20$ times) of the methallyl ketones reveals substantial carbocation character in either case.

This hydroxyalkylation transformation constitutes a *syn* addition to the C–C double bond. Although this *syn* selectivity is not without precedent,[12] it contrasts with the predominant *anti* selectivity observed in cyclodecenone cyclizations.[6a,b] The *trans*-chlorohydrins formed in the $TiCl_4$-mediated reactions may arise from a competing pathway in which the chloride is delivered from the opposite face of the C–C double bond in an antiperiplanar fashion. The erosion of *cis* selectivity (1.3:1) in the $TiCl_4$-mediated cyclization of **10a** and increased amounts of olefinic products from the cyclization of **10b** may be attributed to the strain and deformation of a bridged cyclic transition state in this bicyclic structure.

The stereoselectivity of the $TiCl_4$-mediated cyclization of citronellyl ketone **13** may be rationalized via a chair–chair cyclic transition state (Scheme 2). The mechanism shown should be favored over the alternative path with an equatorially positioned titanate which suffers from apparently more severe 1,3-diaxial CH_3-H and CH_3-CH_3 steric interactions.

The *trans* selectivity observed in the HCl-induced cyclizations is consistent with the usual stereoelectronic bias in favor of antiperiplanar transition states for electrophilic additions to C–C double bonds. Moreover, the transition state for the *syn* addition of HCl might be disfavored by the necessary angular distortions from a presumably linear oxygen $\cdots$ H–Cl geometry in the ketone $\cdot$ HCl complex.

The $TiCl_4$-mediated Prins cyclization of δ,ε- and ε,ζ-unsaturated ketones offers a simple stereoselective annulation method for construction of thermodynamically stable, tertiary cyclohexanols with incorporation of a *cis*-chloro substituent. Many questions remain about the scope of nucleophile options, mechanism, and role of the metal ion in this *syn* hydroxyalkylation reaction. The reasons for the predominance of elimination to ene products with alkylaluminum halide reagents[3] are unclear. However, this reaction should find application in syntheses of halogenated terpenes[13] and various types of functionalized cyclohexanols.

Experimental Section

5a: Representative procedure with $TiCl_4$ (Table 1, entry 2): The conditions were based on those described in ref. [1a] except that neutralization was done at low temperature. A solution of ketone **4a** (0.80 g, 4.12 mmol) in CH_2Cl_2 (30 mL) was stirred and cooled at $-78\,^{\circ}C$ as 1.0 M $TiCl_4$ in CH_2Cl_2 (4.12 mL, 4.12 mmol) was added dropwise over 3 min. After 15 min, a solution of Et_3N (2.9 mL, 20.6 mmol) and MeOH (0.92 mL, 20.6 mmol) was added dropwise over 2 min. After 5 min at $-78\,^{\circ}C$, the orange suspension was warmed to RT, diethyl ether (100 mL) was added, and the salts were hydrolyzed by two extractions with 10% HCl (30 mL each). The ethereal solution was washed with saturated $NaHCO_3$ (30 mL) and saturated NaCl, dried ($MgSO_4$) and concentrated by rotary evaporation to give 0.91 g of crude product composed mainly of chlorohydrins **5a** and **6a** (8:1 ratio by ^1H NMR analysis). Purification and separation by flash chromatography on silica gel (98:2 hexane–diethyl ether) gave 0.60 g (63%) of *cis*-chlorohydrin **5a** and 103 mg that was a 5:1 mixture (^1H NMR analysis) of *trans*-chlorohydrin **6a** (9%) and (1*R*,6*S*,9*R*)-5,5,9-trimethylbicyclo[4.4.0]dec-2(or 3)-en-1-ol (2%) as colorless oils. The major product (**5a**) solidified upon standing: mp 63–65 °C; anal. calcd for $C_{13}H_{23}ClO$ (230.78): C 67.66, H 10.05, Cl 15.36; found: C 67.74, H 10.35, Cl 15.67. See Supporting Information for IR, ^1H NMR, ^{13}C NMR, COSY, HMQC, HMBC, and NOE data.

Received: August 3, 2001
Revised: November 19, 2001 [Z17663]

[1] a) N. D. Willmore, R. Goodman, H. H. Lee, R. M. Kennedy, *J. Org. Chem.* **1992**, *57*, 1216–1219; b) T. G. LaCour, C. Guo, S. Bhandaru, M. R. Boyd, P. L. Fuchs, *J. Am. Chem. Soc.* **1998**, *120*, 692–707.

[2] a) L. A. Paquette, Y. K. Han, *J. Org. Chem.* **1979**, *44*, 4014–4016; b) K. Mikami, M. Shimizu, *Chem. Rev.* **1992**, *92*, 1021–1050; c) A. C. Jackson, B. E. Goldman, B. B. Snider, *J. Org. Chem.* **1984**, *49*, 3988–3994.

[3] a) B. B. Snider, *Comprehensive Organic Synthesis*, *Vol. 2* (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon Press, Oxford, **1991**, pp. 527–561; b) N. H. Anderson, S. W. Hadley, J. D. Kelly, E. R. Bacon, *J. Org. Chem.* **1985**, *50*, 4144–4151.

[4] a) D. Bonnet-Delpon, A. Abouabdellah, J. P. Begue, *Recent Res. Dev. Org. Bioorg. Chem.* **1998**, *2*, 1–16; b) A. Abouabdellah, J. P. Begue, D. Bonnet-Delpon, T. Lequeux, *J. Org. Chem.* **1991**, *56*, 5800–5808.

[5] a) C. Aubert, J. P. Begue, *Tetrahedron Lett.* **1988**, *29*, 1011–1014; b) J. Guilhem, *J. Chem. Soc. Perkin Trans. 1* **1991**, 1397–1403.

[6] a) Y. Chu, J. B. White, B. A. Duclos, *Tetrahedron Lett.* **2001**, *42*, 3815–3817; b) D. Colclough, J. B. White, W. B. Smith, Y. Chu, *J. Org. Chem.* **1993**, *58*, 6303–6313; c) J. Li, C.-J. Li, *Heterocycles* **2000**, *53*, 1691–1695; d) G. L. N. Peron, J. Kitteringham, J. D. Kilburn, *Tetrahedron Lett.* **1999**, *40*, 3045–3048; e) Amini, R. Bishop, G. Burgess, D. C. Craig, I. G. Dance, M. L. Scudder, *Aust. J. Chem.* **1989**, *42*, 1919–1928; f) H. Stetter, J. Gartner, P. Tacke, *Chem. Ber.* **1965**, *98*, 3888–3891.

[7] a) F. Bohlmann, C. Zdero, J. Jakupovic, H. Robinson, R. M. King, *Phytochemistry* **1981**, *20*, 2239–2244; b) G. Büchi, R. E. Erickson, N. Wakabayashi, *J. Am. Chem. Soc.* **1961**, *83*, 927–938; c) N. N. Gerber, H. A. Lechevalier, *Appl. Microbiol.* **1965**, *13*, 935–938.

[8] The tendency of $TiCl_4$ to produce tertiary chloroalkyl cyclopentanols in electrophilic cyclizations of δ,ε- and ε,ζ-unsaturated aldehydes at the expense of the corresponding alkenyl cyclopentanols has been noted.[1a, 3b]

[9] a) H. Sakurai, A. Hosomi, J. Hayashi, *Org. Synth. Coll.* **1990**, *VII*, 443–446; b) A. Hosomi, H. Sakurai, *J. Am. Chem. Soc.* **1977**, *99*, 1673–1675.

[10] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-167996 (**5b**), 167997 (**8b**), and 167998 (**11**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[11] See supporting information for a discussion of structure elucidation.

[12] B. B. Snider, D. J. Rodini, T. C. Kirk, R. Cordova, *J. Am. Chem. Soc.* **1982**, *104*, 555–563.

[13] D. J. Faulkner, *Nat. Prod. Rep.* **2001**, *18*, 1–49.

  1433-7851/02/4103-0493 $ 17.50+.50/0