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Diastereoselective titanium-mediated construction of *cis*-2,3-ring annelated 1-(2′-chloroethyl)cyclopropanols†

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Titanium(IV)-mediated cyclopropanation induced by reaction of cycloalkylmagnesium bromides 1a–e in the presence of titanium tetraisopropoxide with ethyl β-chloropropionate 2 yielded *cis*-fused 1-(2′-chloroethyl)cyclopropanols 3b–e with diastereoselectivity highly depending on the ring size. Unexpected rearrangement products 5d,e were isolated in some cases.

1-Vinylcyclopropanols and their derivatives (esters, trimethylsilylethers, *etc.*) are smoothly and efficiently prepared from 1-(2′-chloroethyl)cyclopropanols.[1] They constitute very useful intermediates for numerous transformations including $C_3 \rightarrow C_{4-8}$ ring expansions[2] and $C_3 \rightarrow C_{10,15,20}$ ring enlargements.[3] Moreover, the corresponding sulfonic esters undergo regio- and diastereoselective nucleophilic or electrophilic substitution *via* σ- or π-1,1-ethyleneallylmetal complexes[4] allowing large synthetic applications recently reported.

The titanium(IV)-promoted Kulinkovich cyclopropanation,[5] to now, appears to be the most efficient method for the preparation of substituted cyclopropanols; however, this procedure has not been applied to the direct synthesis of various *cis*-fused cyclopropane derivatives. In fact, cycloalkylmagnesium halides (cyclopentyl and cyclohexyl) have been used for hydroxycyclopropanation of alkenes involving ligand exchange.[5a,6] Surprisingly, Cha *et al.*[6a] claimed that such Grignard reagents did not yield any cyclopropanation products in reaction with esters under the Kulinkovich conditions, but de Meijere *et al.*[7] reported one reaction of formation in low yield of a fused cyclopropanol from ethyl acetate and cyclohexylmagnesium halide with titanium tetraisopropoxide. We decided to extend this reaction by the study of the reactivity of various cycloalkylmagnesium bromides (from three to seven-membered ring sizes) with ethyl β-chloropropionate **2** promoted by Ti(OiPr)$_4$ thus allowing the synthesis of 1,2,3-trisubstituted cyclopropanols.

Formation of products **3a–e** and by-products **4a**, **5d–e** as well as the relationship between diastereoselectivity and ring size are summarized in Table 1.

The reaction of cyclopropylmagnesium bromide **1a** (entry 1) according to the Kulinkovich protocol did not give the expected fused cyclopropanol **3a** (n = 3), but led only to the product **4a** (n = 3), resulting from the classical addition of the Grignard reagent to the ester **2**.

From cyclobutylmagnesium bromide **1b** (entry 2), cyclopropanol **3b** (n = 4) was isolated; only the *exo* diastereomer was detected. To our knowledge, such easy formation of 5-alkylbicyclo[2.1.0]pentan-5-ol has never been reported in the literature.

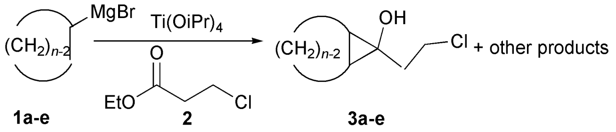
With cyclopentylmagnesium bromide **1c** (entry 3), the reaction led to a mixture of (*exo*/*endo*: 63/37) 6-(2′-chloroethyl) bicyclo[3.1.0]hexan-6-ol **3c** (n = 5).[8] The two diastereomers were separated by chromatography on silica gel; however, even on varying the experimental conditions (temperature, equivalents of titanium and Grignard species,…), the stereoselectivity was not significantly modified; the *exo* isomer was always observed as the major product.

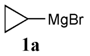
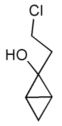
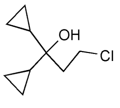
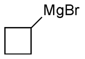
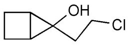
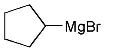
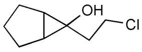
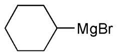
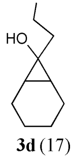
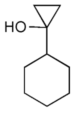
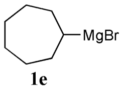
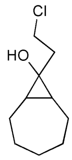
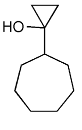
Unexpected results were obtained with cyclohexylmagnesium bromide **1d** (entry 4). In fact, although the expected cyclopropanol **3d** (n = 6) was isolated as a single *exo*-diastereomer, the main product surprisingly was 1-cyclohexylcyclopropanol **5d** (n = 6).

Competing routes could explain the formation of these two products. The first path (Scheme 1, path A) would proceed through the classical Kulinkovich reaction to lead to the fused cyclopropanol **3d**. In this case, formation of the intermediate titanafurane **A** (on the cyclohexyl moiety) could be slower than nucleophilic attack of the cyclohexylmagnesium bromide[9] on the ester function, leading to the anionic intermediate **B** (path B).

We suggest that intermediate **B** undergoes an internal S_N2 reaction on the terminal chloride (probably assisted by the

Table 1 Reaction of cycloalkylmagnesium bromides[a] **1a–e** with ethyl β-chloropropionate **2** and Ti(OiPr)$_4$



Entry	n	Grignard reagent	eq. Ti(OiPr)$_4$	Products (%)
1	3	 **1a**	1	 **3a** (0)  **4a** (38)
2	4	 **1b**	0.2	 [b] **3b** (46)
3	5	 **1c**	1	 [c] **3c** (63)
4	6	 **1d**	1	 [b] **3d** (17)  **5d** (46)
5	7	 **1e**	0.2	 [b] **3e** (56)  **5e** (2)

[a] Reactions were optimized with 4 eq. of Grignard reagents at room temperature in Et_2O–THF. [b] Pure *exo*. [c] Mixure *exo*/*endo* 63 : 37.

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† Electronic supplementary information (ESI) available: NMR, IR, MS and HRMS data. See http://www.rsc.org/suppdata/cc/b2/b211642a/

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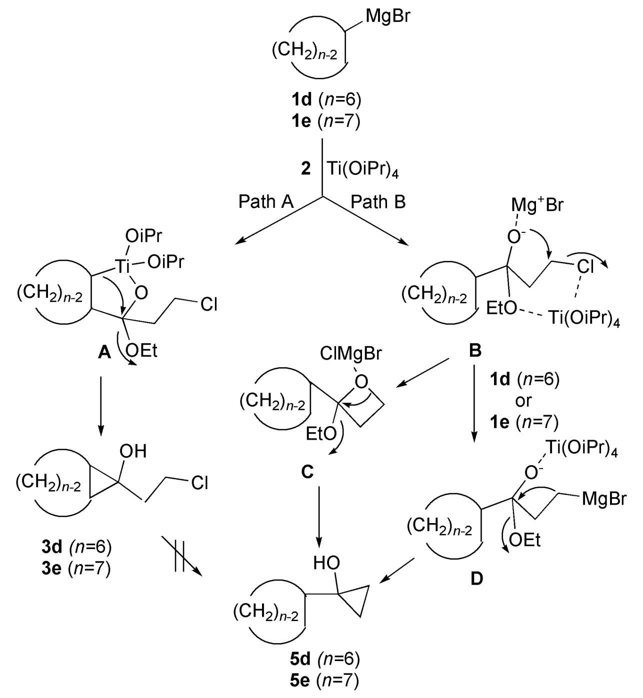


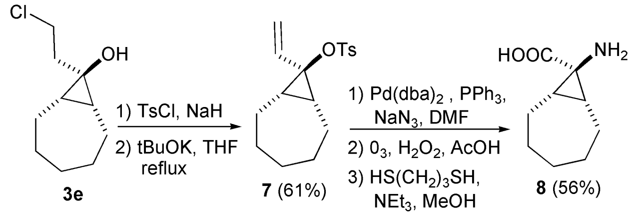
Scheme 1

presence of a titanium species) generating an unstable oxetane intermediate **C** which would afford the 1-cyclohexylcyclopropanol **5d** after ring contraction and hydrolysis. Such ring contraction of oxetane to cyclopropyl moiety has never been reported previously. However, another mechanism could also involve intermediate **B**, which in the presence of $Ti(OiPr)_4$, would undergo a known halogen metal exchange with the Grignard reagent[10] leading to the intermediate **D** capable of undergoing cyclization[11] to the cyclopropanol **5d**. Moreover, in using only 0.2 equivalents of $Ti(OiPr)_4$, the yield was hardly decreased (20%), but the ratio **3d**/**5d** reached 50:50. It must be underlined that when the reaction was carried out without $Ti(OiPr)_4$, only tertiary alcohol **4d** (n = 6) was isolated; furthermore, treatment of the cyclopropanol **3d** by $Ti(OiPr)_4$ and cyclohexylmagnesium bromide did not yield alcohol **5d** (n = 6).

To endorse the formation of the intermediate **D**, we treated chloroketone **6** (Scheme 2), which was prepared independently by known procedures, by 4 equivalents of cyclohexylmagnesium bromide **1d** in the presence of titanium tetraisopropoxide. Surprisingly, with 1 equivalent of $Ti(OiPr)_4$, only cyclopropanol **5d** was isolated. Such formation of cyclopropanol from β-haloketone has previously been reported in the literature, but using SmI_2.[12]

Cycloheptylmagnesium bromide **1e** (entry 5) gave almost exclusively the expected *exo* fused cyclopropanol **3e** (n = 7); only traces (2%) of 1-cycloheptylcyclopropanol **5e** (n = 5) were detected, suggesting the same mechanism previously proposed for the six-membered ring, but in this case, use of one equivalent of titanium tetraisopropoxide gave an unexploitable mixture.

Scheme 2



Scheme 3

The interest of this new strategy was exemplified by the total synthesis of the unknown 8-*exo*-amino bicyclo[5.1.0]octane-8-carboxylic acid **8**. Thus, after tosylation and dehydrochlorination of the alcohol **3e**, the resulting 1-vinylcyclopropyltosylate **7** successively underwent palladium(0)-catalyzed azidation, oxidation of the double bond and reduction of the azide function following a previously reported procedure[13] to give the required fused aminoacid **8** in 56% yield (Scheme 3).

In conclusion, we have developed a new and concise diastereoselective construction of fused 1-alkylcyclopropanols. The ability of such compounds to yield 1-vinylcyclopropanols opens a wide range of other useful applications which are under current investigation.

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