Zincate-mediated rearrangement reaction of 2-(1-hydroxyalkyl)-1-alkylcyclopropanol†

Kenichi Nomura and Seijiro Matsubara*

Received (in Cambridge, UK) 16th January 2009, Accepted 11th February 2009
First published as an Advance Article on the web 3rd March 2009
DOI: 10.1039/b901043b

A rearrangement of lithium alkoxide of 2-(1-hydroxyalkyl)-1-alkylcyclopropanol into lithium alkoxide of *vic*-diol was mediated with an organozincate complex.

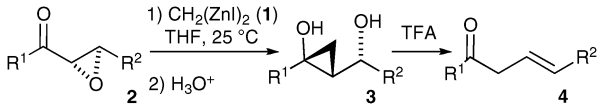
In 1960, Julia *et al.* reported the acid-catalyzed ring opening rearrangement of 2-hydroxyalkylcyclopropane, which affords *E*-homoallylic alcohol *via* a carbocation species on the cyclopropyl-substituted carbon.[1] When the reaction was applied to 2-(1-hydroxyalkyl)-1-alkylcyclopropanol **3**, the acid-mediated ring-opening reaction gave the corresponding α,β-unsaturated ketone **4** as shown in Scheme 1.[2]

We have reported that treatment of α,β-epoxyketones **2** with bis(iodozincio)methane (**1**) gave **3** stereoselectively and stereospecifically in good yields after aqueous work-up.[3,4] The corresponding zinc alkoxides were formed *in situ*. When the reaction mixture was heated to reflux in THF without aqueous work-up, *vic*-diol **5a** was obtained in 68% yield (Scheme 2).

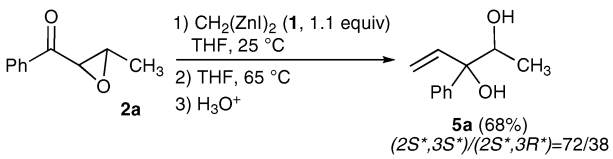
As shown in Table 1, the rearrangement reaction from 2-hydroxymethyl-1-phenylcyclopropanol (**3b**) was examined with various reagents. A simple heating of the zinc or lithium alkoxide of **3b** resulted in the recovery of **3b**.[5] While addition of 1 equiv. of zinc(II) chloride to the lithium alkoxide of **3b** gave a complex mixture (entry 3), a use of 1 equiv. of zinc(II) chloride and 3 equiv. of butyllithium gave the desired product in good yield (entry 4). The combination was expected to form a zincate-complex (*e.g.* $Bu(RO)_2Zn^-Li^+$). The pre-formed zincate $^tBu_3ZnLi$,[6] which can be prepared easily from $ZnCl_2$ and ^{t}BuLi, was also effective for this rearrangement (entry 6). Treatment of the prepared lithium alkoxide of **3b** with a catalytic amount of $^tBu_3ZnLi$ also gave **5b** (entries 7 and 8).

In order to study the wider applications of the rearrangement, we treated various lithium alkoxides of **6**, prepared *in situ* from **3**, with *t*-Bu_3ZnLi as a catalyst (Table 2). The substrates **6b–d** gave the corresponding 1,2-diols **5b–d** in good yields (entries 2–4). Cyclopropyl alkyl carbinol derivatives **6a,e,f** were also converted into the corresponding 1,2-diols **5a,e,f** in good yields with a low diastereoselectivity (entries 1,5,6). In the case of cyclopropyl dimethyl carbinol derivative **6g**, the corresponding diol **5g** was obtained in 57% yield (entry 7). It is notable that ethyl phenyl ketone was also obtained in this reaction in 30% yield.

We speculated that the reaction proceeded *via* a zincate intermediate. The working hypothesis of this rearrangement is shown in Fig. 1. The alkoxide **6a**, which was formed from **3a** by a deprotonation with BuLi, would form a zincate complex **7** *via* a ligand-exchange with *t*-Bu_3ZnLi. The high affinity between Zn and O atoms will benefit this reaction. The retro-allylation analog would afford acetaldehyde and an allylic anion that are connected with zinc atom **8**. The intermediate **8** reacts rapidly to give the product **9**. A hydrolysis of **8** would form acetaldehyde and 1-phenyl-2-propen-1-ol; the latter will tautomerize into ethyl phenyl ketone. In entry 1, neither acetaldehyde nor ethyl phenyl ketone were detected. Only in the case of entry 7 (Table 2), ethyl phenyl ketone was isolated in 30% yield. The results can be rationalized by considering that the addition of intermediary allylic anion to acetone is slow enough to break a pair of the allylic anion and acetone.

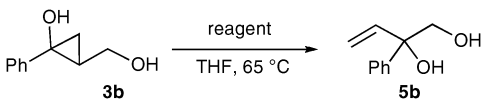


Scheme 1 Acid-mediated isomerization of 2-(1-hydroxyalkyl)-1-alkylcyclopropanol **3** into the β,α-unsaturated ketone.



Scheme 2 Formation of *vic*-diol **5a**.

Table 1 Rearrangement of 2-hydroxymethyl-1-phenylcyclopropanol (**3b**)



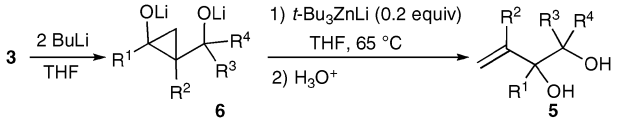
Entry	Reagent (equiv.)	Time/h	Yield of **5b** (%)[a]
1	Me_2Zn (2.0)	3	0[b]
2	BuLi (3.0)	3	0[b]
3	BuLi (2.0)/$ZnCl_2$ (1.0)	3	0[c]
4	BuLi (3.0)/$ZnCl_2$ (1.0)	3	88
5	BuLi (3.0)/$ZnCl_2$ (2.0)	3	53
6	*t*-Bu_3ZnLi (1.0)	3	70
7	*t*-Bu_3ZnLi (0.2)/BuLi (2.0)	6	88
8	*t*-Bu_3ZnLi (0.1)/BuLi (2.0)	12	65

[a] The yield was detemined by nmr using bromoform as an internal standard. [b] **3b** was recovered quantitatively. [c] Complex mixture was obtained.

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoutodaigaku-Katsura, Nishikyo, Kyoto, 615-8501, Japan. E-mail: matsubar@orgrxn.mbox.media.kyoto-u.ac.jp; Fax: (+81)75-3832461

† Electronic supplementary information (ESI) available: Experimental. See DOI: 10.1039/b901043b

Table 2 Rearrangement of lithium alkoxide of 2-(1-hydroxyalkyl)-1-alkylcyclopropanol (**3**) with *t*-Bu_3ZnLi



Entry	R^1	R^2	R^3	R^4	*T*/h	Yield (%)[a]	Product
1	Ph	H	CH_3	H	24	78 (3/2)[b]	**5a**
2	Ph	H	H	H	24	88	**5b**
3	Ph	CH_3	H	H	24	89	**5c**
4	Pentyl	H	H	H	24	89	**5d**
5	Ph	CH_3	CH_3	H	24	98 (2/1)[c]	**5e**
6	CH_3	H	Ph	H	24	86 (3/1)[d]	**5f**
7	Ph	H	CH_3	CH_3	1	57[e]	**5g**

[a] Isolated yields. [b] The diastereomer ratio was shown in parenthesis. The major product's stereochemistry was (2*S**, 3*S**). [c] The major product's stereochemistry was (2*S**, 3*S**). [d] The major product's stereochemistry was (2*S**, 3*R**). [e] Ethyl phenyl ketone was isolated in 30% yield.

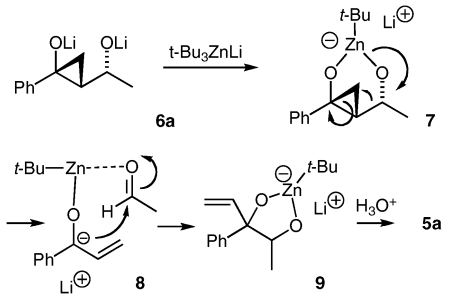
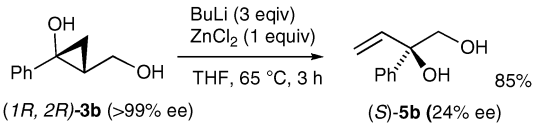


Fig. 1 Possible route for rearrangement.

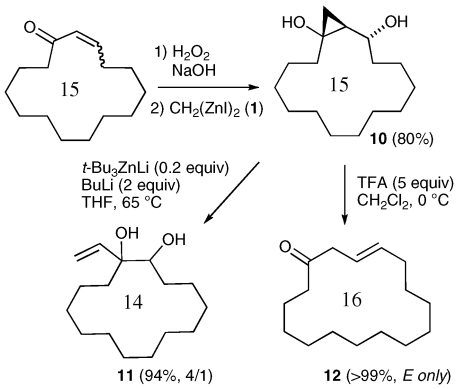
Starting from an optically pure (1*R*,2*R*)-**3b**, we examined the stereospecificity of the transformation (Scheme 3).[7,8] The obtained diol has an *S*-configuration with loss of optical purity. The low stereospecificity may be unavoidable, as the optical purity is based on the enantiofacial selectivity in the intermediary corresponding to **8**.

Although the low stereospecificity shown in Scheme 3 is disappointing, the skeletal rearrangement can be applied to ring-contraction starting from a bicyclo[n.1.0] compound such as **10** as shown in Scheme 4. Our previous method concerning acid-catalyzed rearrangement can be adapted to ring-expansion from **10** (Scheme 4).[2] Epoxidation of cyclopentadec-2-enone with basic hydrogenperoxide, followed by treatment with bis(iodozincio)methane (**1**), gave cyclopropanediol **10** in 80% yield. While treatment with TFA afforded *E*-cyclohexadec-3-enone (**12**) quantitatively, that with BuLi and *t*-Bu_3ZnLi gave 1-vinylcyclotetradecane-1,2-diol (**11**) in 94% yield.[9]

Thus we can show a novel rearrangement of the lithium alkoxide of cyclopropanediol, which is mediated with an organozincate catalyst. While the organozincate complex was shown as an efficient stoichiometric reagent for halogen–metal exchange,[6] its use for organic synthesis as a catalyst is not common. A study including the mechanistic details is now under way.



Scheme 3 Stereospecificity of the rearrangement of **3b**.



Scheme 4 Ring-expansion and -contraction *via* cyclopropanediol.

Notes and references

1 (*a*) M. Julia, S. Julia and R. Guegan, *Bull. Soc. Chim. Fr.*, 1960, 1072; (*b*) K. Sakaguchi, M. Fujita and Y. Ohfune, *Tetrahedron Lett.*, 1998, **39**, 4313; (*c*) M. Honda, Y. Yamamoto, H. Tsuchida, M. Segi and T. Nakajima, *Tetrahedron Lett.*, 2005, **46**, 6465; (*d*) S. R. Wilson, A. E. Davey and M. E. Guazzaroni, *J. Org. Chem.*, 1992, **57**, 2007; (*e*) C. Singh, S. Pandey, G. Saxena, N. Srivastava and M. Sharma, *J. Org. Chem.*, 2006, **71**, 9057.

2 K. Nomura and S. Matsubara, *Synlett*, 2008, 1412.

3 (*a*) K. Nomura, K. Oshima and S. Matsubara, *Angew. Chem., Int. Ed.*, 2005, **44**, 5860; (*b*) K. Nomura and S. Matsubara, *Chem. Lett.*, 2007, **36**, 164.

4 S. Matsubara, H. Yoshino, Y. Yamamoto, K. Oshima, H. Matsuoaka, K. Ishikawa and E. Matsubara, *J. Organomet. Chem.*, 2005, **690**, 5546.

5 Treatment of α,β-unsaturated ketone with aldehyde in the presence of chromium(II) affords 2-(1-hydroxyalky)-1-alkylcyclopropanol. Meanwhile the same reaction with the addition of TMSCl affords cross pinacol coupling product. See, (*a*) K. Takai, R. Morita and C. Toratsu, *Angew. Chem., Int. Ed.*, 2001, **40**, 1116; (*b*) K. Takai, R. Morita, H. Matsushita and C. Toratsu, *Chirality*, 2003, **15**, 17.

6 (*a*) T. Harada, T. Katsuhira, D. Hara, Y. Kotani, K. Maejima, R. Kaji and A. Oku, *J. Org. Chem.*, 1993, **58**, 4897; (*b*) M. Uchiyama, T. Furuyama, M. Kobayashi, Y. Matsumoto and K. Tanaka, *J. Am. Chem. Soc.*, 2006, **128**, 8404.

7 Compared with the result of specific rotation of the literature, it was found that the obtained **5b** has (*S*)-configuration. See: M. E. Vargas-Diaz, L. Chacon-Garcia, P. Velazquez, J. Tamariz, P. Joseph-Nathan and L. G. Zepeda, *Tetrahedron: Asymmetry*, 2003, **14**, 3225.

8 The enantiomeric purity of **5b** was determined by ^{1}H NMR after converting into the corresponding Mosher ester using (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The enantiomeric excess of the product was determined by ^{1}H NMR focused on methoxy group (the chemical shift at 3.40 ppm corresponds to (*S*)-isomer and that at 3.44 ppm, (*R*)-isomer).

9 The major product of **11** was (1*R**,2*S**) isomer.