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Optically active *trans*-4-(*tert*-butyldimethylsiloxymethyl)-5-(*tert*-butyldimethylsiloxy)-2-cyclohexenone as a useful chiral building block for preparation of substituted cyclohexane rings: synthesis and its highly stereoselective reaction with RCu(CN)Li

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Abstract

Optically active *trans*-4-(*tert*-butyldimethylsiloxymethyl)-5-(*tert*-butyldimethylsiloxy)-2-cyclohexenone (**2**) has been synthesized in 25% overall yield starting from easily available 1,4-bis(benzyloxy)-2,3-epoxy butane (**3**). The enone **2** reacts with excellent stereoselectivity with RCu(CN)Li thus working as an efficient chiral building block for preparation of substituted cyclohexane compounds. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: asymmetric synthesis; copper; copper compounds; cyclohexenones; cyclohexanes.

Many biologically important compounds have a chiral cyclohexane ring in their structure as the main or a subunit. One attractive method to synthesize these skeletons involves the use of naturally occurring or man-made non-racemic 2-cyclohexenone compounds as the starting material, taking advantage of their versatile reactivity. Recently, we have developed an efficient and practical method for preparation of optically active 5-(*tert*-butyldimethylsiloxy)-2-cyclohexenone (**1**) and have shown that it can be effectively used as a chiral building block for synthesizing a variety of substituted 2-cyclohexenone and cyclohexanone derivatives.[1]

However, it is not an easy task to prepare 2-cyclohexenone or cyclohexanone derivatives having a substituent at the 4-position starting from **1**. Optically active 5-(*tert*-butyldimethylsiloxy)-2-cyclohexenone having a siloxymethyl group at the 4-position seems to be an attractive chiral building block for the preparation of a variety of these types of compounds, since the siloxymethyl group can be potentially used as a handle for further functionalization. We report here the synthesis of 4-(*tert*-butyldimethylsiloxymethyl)-5-(*tert*-butyldimethylsiloxy)-2-cyclohexenone with *trans* configuration, **2**, starting from 1,4-bis(benzyloxy)-2,3-epoxy butane (**3**), both enantiomers of which can be readily pre-

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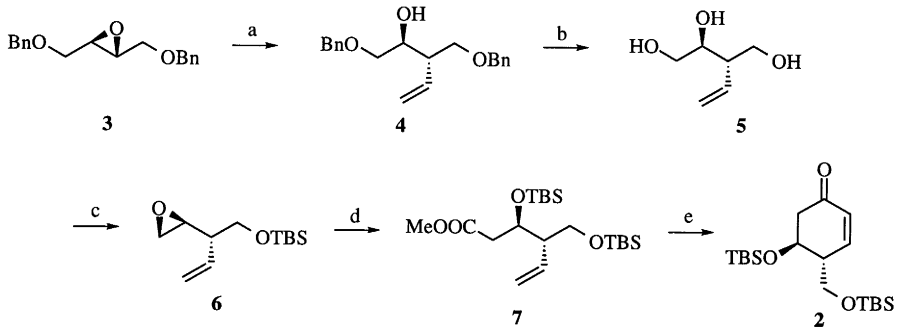
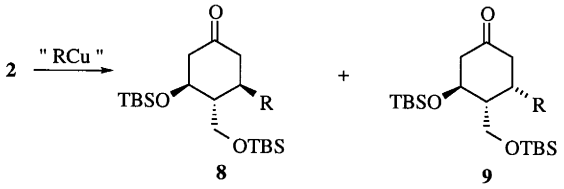
pared from diethyl D- or L-tartrate, respectively, according to the protocol of Nicolaou et al.,[2] and its highly diastereoselective conjugate addition reaction with an organocopper compound.

The preparation of **2** from **3** was carried out according to the procedure shown in Scheme 1. Reaction of (*R*,*R*)-**3** with vinylmagnesium bromide in the presence of CuI gave the vinylalcohol **4** (94% yield),[3] which in turn was converted to the triol **5** under the Birch reduction conditions (88% yield). From **5**, epoxide **6** was prepared via a four-step sequence according to the procedure developed by Sharpless in 64% overall yield.[4] Compound **6** was then converted to the ester **7** in 62% overall yield by conventional reaction sequences which involve ring opening with the CN anion using Et_2AlCN, protection of the resulting hydroxy group as a TBS-ether, and the following conversion of the CN moiety to a methylester group. The ester **7** could then be converted to the expected **2** in 72% overall yield according to the procedure used previously for the synthesis of **1**, i.e., the intramolecular nucleophilic acyl substitution reaction mediated by a Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl reagent[5] and $FeCl_3$-induced ring enlargement reaction.[6] In conclusion, the enone **2** was prepared from **3** in 25% overall yield.



Scheme 1. (a) CuI, CH_2=CHMgBr, Et_2O; (b) Li/NH_3, THF; (c) (i) MeC(OMe)$_3$, cat. PPTS, CH_2Cl_2, (ii) CH_3COBr, CH_2Cl_2, (iii) K_2CO_3, MeOH, (iv) TBSCl, imidazole, DMF; (d) (i) Et_2AlCN, THF, (ii) TBSCl, imidazole, DMF, (iii) DIBAL-H, C_6H_{14}, (iv) $NaClO_2$, $NaH_2PO_4 \cdot 2H_2O$, H_2O, ^{t}BuOH, 2-methyl-2-butene, (v) MeI, K_2CO_3, acetone; (e) (i) Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl, Et_2O, (ii) $FeCl_3$, pyr, DMF, (iii) AcONa, MeOH

With **2** in hand, our next concern was the diastereoselectivity of the conjugated addition of organocopper compounds to it. It had been reported that 1,4-addition of organocopper compounds to 4- or 5-substituted 2-cyclohexenones proceeds highly selectively via an *anti*-addition pathway, respectively. Thus, at first glance, it seemed difficult to get high diastereoselectivity for the reaction of **2** with organocopper compounds. However, we had previously found that, while the reaction of **1** with the Gillman cuprates R_2CuLi or higher-order cyanocuprates $R_2Cu(CN)Li_2$ proceeded via an *anti*-addition pathway, the reaction with lower-order cyanocuprates RCu(CN)Li, exceptionally, afforded *syn*-addition products highly selectively owing to the ligating effect of the alkoxy group.[1a,b] We, therefore, expected that this *syn*-addition tendency by the reaction with RCu(CN)Li might be applicable to the reaction with **2** irrespective of the presence of the *tert*-butyldimethylsiloxymethyl substituent at the C-4 position, thus affording highly selectively the 1,4-addition product **8** having the structure where the R group introduced is *cis* to the *tert*-butyldimethylsiloxy group and *trans* to the *tert*-butyldimethylsiloxymethyl group. As expected, the reaction of RCu(CN)Li where R is a methyl and primary-, secondary-, and tertiary-alkyl group afforded the 1,4-addition product **8** with the anticipated structure almost exclusively. The phenyl derivative, however, proceeded with lower selectivity and lower yield; this observation is in accord with our earlier result observed for the reaction with **1**.[1b] We also confirmed that the reaction of **2** with $R_2Cu(CN)Li_2$ provided the mixture of two possible diastereomers, **8** and **9**, in a variable ratio dependent on the R group (Table 1); it is noteworthy, however, that the reaction with $Ph_2Cu(CN)Li_2$ proceeded with exceptionally high selectivity to afford the corresponding **8** exclusively.[7]



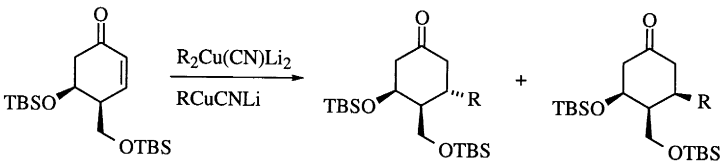
(1)

Table 1
1,4-Addition of lower-order and higher-order cyanocuprates onto **2**

Entry	R	RCu(CN)Li		$R_2Cu(CN)Li_2$	
		8 : 9[a]	Yield(%)	**8 : 9**[a]	Yield(%)
1	Me	**>95 : <5**	**88**	3 : 1	93[b]
2	Bu	**>99 : <1**[c]	**86**	58 : 42[c]	83[b]
3	*sec*-Bu	**>95 : <5**	**83**	5.5 : 1	88[b]
4	*tert*-Bu	**>95 : <5**	**84**	7 : 1	69[b]
5	Ph	2 : 1	32[b]	**>95 : <5**	**84**

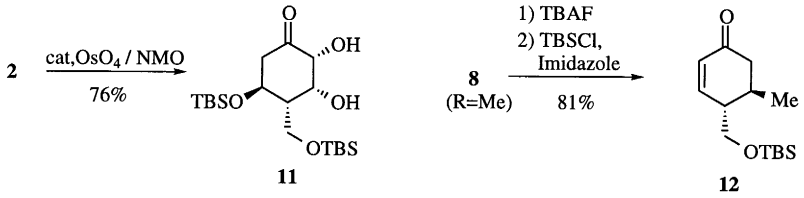
a: NMR measurement unless otherwise noted. <5 : >95 means that the other diastereomer was not detected *b:* NMR yield. *c:* GC measurement.

At this point, we were interested in the diastereoselectivity of the reaction of organocopper compounds with 4-(*tert*-butyldimethylsiloxymethyl)-5-(*tert*-butyldimethylsiloxy)-2-cyclohexenone having *cis* configuration, **10**, i.e., the diastereomer of **2**. We assumed that the reaction with $R_2Cu(CN)Li_2$ would proceed highly selectively to introduce the R group at the *trans* position to both the *tert*-butyldimethylsiloxymethyl and *tert*-butyldimethylsiloxy groups, while the reaction with RCu(CN)Li might occur with low stereoselectivity. Our assumption turned out to be valid: thus, as shown in Eq. (2), the reaction of *rac*-**10** with $Me_2Cu(CN)Li_2$ or $Bu_2Cu(CN)Li_2$ provided the 1,4-addition product with the expected stereochemistry almost exclusivly(<5:>95), but the reaction with BuCu(CN)Li afforded a mixture of the two possible adducts in a ratio of 56:44. Thus, it may safely be said that the 1,4-addition reaction of organocopper compounds to 5-(*tert*-butyldimethylsiloxy)-2-cyclohexenone having a substituent at the 4-position can be carried out with excellent selectivity irrespective of the stereochemistry of the enone by using either RCu(CN)Li or $R_2Cu(CN)Li_2$.



(2)

Further synthetic utility of **2** and **8** (obtained from **2** and RCu(CN)Li) in organic syntheses is currently under study in our laboratory. We have so far found that the osmylation of **2** proceeds in a stereoselective way to afford the diol **11** exclusively.[8] The treatment of **8** (R=Me) with TBAF resulted in β-elimination to give **12**. The relative configuration of **12** was confirmed by converting to *trans*-3-methyl-4-(*tert*-butyldimethylsiloxymethyl)-cyclohexanone[9] by hydrogenation of the double bond of **12**.



Acknowledgements

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