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A Stereoselective Synthesis of *syn*-β-Amino Alcohols *via* Iodocyclization

Sung Ho Kang* and Do Hyun Ryu

Department of Chemistry,
Korea Advanced Institute of Science and Technology,
Taejon 305-701, Korea

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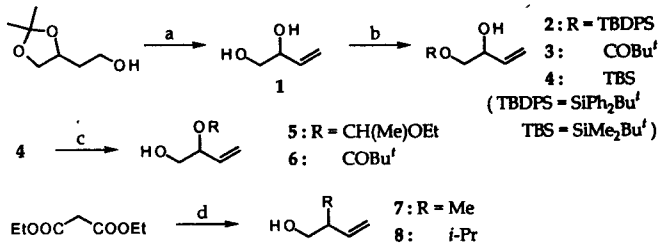
In recent years the stereoselective synthesis of β-amino alcohols is an increasingly important area in organic synthesis. They are indispensable peptide isosteres for the development of HIV protease,[1] renin[2] and ACE inhibitors.[3] Besides their utility as such therapeutic agents, β-amino alcohols have been employed as chiral auxiliaries,[4] and they are also expected to serve as chiral building blocks for the construction of glycosidase inhibitors.[5]

Several approaches to optically active β-amino alcohols have been explored such as the addition reaction of organometallics to α-amino aldehydes,[6] the reduction of α-amino ketones,[7] nitroaldol reaction,[8] the hydroboration of enamines[9] and the ring opening of epoxy alcohols with amine.[10] Alternatively we sought to exploit a practical asymmetric synthetic route to them, based on the electrophile promoted cyclization of allylic or homoallylic alcohols which comprise a nucleophilic nitrogen tethered through the alcoholic oxygen. Although Cardillo *et al.* pioneered this strategy,[11] we elected to reinvestigate the cyclization reaction in a more systematic manner to attain a facile procedure to β-amino alcohols with superior stereoinduction. This paper describes our stereocontrolled pathway to *syn*-β-amino alcohols *via* iodocyclization of homoallylic trichloroacetimidates derived from 3-buten-1,2-diols.



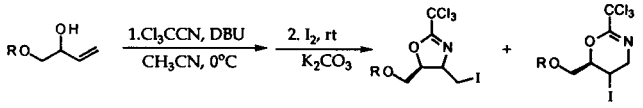
Scheme 1. Reagents: a. I_2/Ph_3P/imidazole/THF/0 ℃; *t*-BuOK/DMSO/rt; 6 N HCl/MeOH/rt. b. For **2**: TBDPSCl/imidazole/DMF/−60 ℃. For **3**: *t*-BuCOCl/Et_3N/CH_2Cl_2/0 ℃. For **4**: TBSCl/imidazole/DMF/−60 ℃. c. For **5**: CH_2=CHOEt/PPTS/CH_2Cl_2/0 ℃; *n*-Bu_4NF/aq. THF/rt. For **6**: *t*-BuCOCl/Py/CH_2Cl_2/0 ℃; 40% HF/CH_3CN/0 ℃. d. For **8**: NaH/*i*-PrI/18-crown-6/THF/65 ℃; LAH/Et_2O/0 ℃; TBSCl/imidazole/DMF/−55 ℃; Swern ox.; $Ph_3P^+CH_3I^-$/*n*-BuLi/THF/0 ℃; 40% HF/CH_3CN/0 ℃.

Allylic and homoallylic substrates **1-6** were prepared from 1,2-isopropylidenebutane-1,2,4-triol,[12] which was converted into iodide, eliminated and deprotected in sequence to furnish 3-buten-1,2-diol **1** in 71% overall yield (Scheme 1). Diol **1** reacted with TBDPSCl, pivaloyl chloride and TBSCl to produce TBDPS ether **2** (90%), pivalate **3** (57%) and TBS ether **4** (81%), respectively. The hydroxyl group of **4** was protected with ethyl vinyl ether and pivaloyl chloride, and then desilylated to yield ethoxyethyl ether **5** (82%) and pivalate **6** (86%), respectively. While 2-methyl-3-buten-1-ol **7** is commercially available, 2-isopropyl-3-buten-1-ol **8** was obtained from diethyl malonate over 6 steps in 40% overall yield.

After treatment of allylic alcohols **2** and **3** with trichloroacetonitrile in the presence of DBU in acetonitrile at 0 ℃, the resulting trichloroacetimidates were cyclized *in situ* using iodine and potassium carbonate at room temperature. The results are summarized in Table 1. While a 1 : 1 mixture of oxazolines **9** and dihydro-1,3-oxazines **10** was formed from TBDPS ether **2**, only oxazolines **11** could be isolated from pivalate **3**. Although stereochemical outcomes were not so excellent, it was noted that the identical aziridine could be generated from *trans*-**9**, *trans*-**10** and *trans*-**11** (*vide infra*). In addition better stereoselectivity was observed from **2** in favor of *trans*-isomers.

Homoallylic alcohols **1, 5-8**, containing a chiral substituent at the allylic position, were functionalized into trichloroacetimidates, of which *in situ* iodoamination was performed with iodine and sodium bicarbonate at 0 ℃. The experimental data are shown in Table 2. A relatively low stereoselectivity was resulted from **7** (entry 1). Although satisfactory stereoin-

Table 1. Iodocyclization of trichloroacetimidates from allylic alcohols **2** and **3**



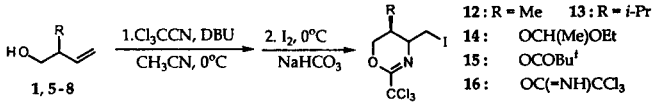
2: R = TBDPS
3: COBu^t

9: R = TBDPS
11: COBu^t

10: R = TBDPS

entry	substrate	isomeric ratio	% yield
1	**2**	*trans*-**9** : *cis*-**9** = 7 : 1	48
		trans-**10** : *cis*-**10** = 7 : 1	46
2	**3**	*trans*-**11** : *cis*-**11** = 4 : 1	87

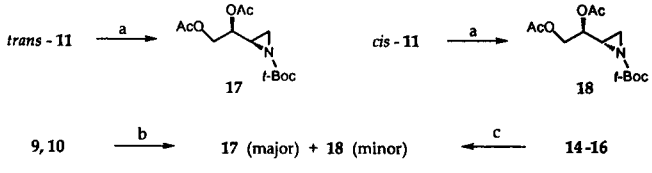
Table 2. Iodocyclization of trichloroacetimidates from homoallylic alcohols **1, 5-8**



1, 5-8

12: R = Me **13**: R = *i*-Pr
14: OCH(Me)OEt
15: OCOBu^t
16: OC(=NH)CCl$_3$

entry	substrate	isomeric ratio	% yield
1	**7**	*cis*-**12** : *trans*-**12** = 4 : 1	94
2	**8**	*cis*-**13** : *trans*-**13** = >100 : 1	85
3	**5**	*cis*-**14** : *trans*-**14** = 9 : 1	85
4	**6**	*cis*-**15** : *trans*-**15** = 25 : 1	93
5	**1**	*cis*-**16** : *trans*-**16** = 28 : 1	91

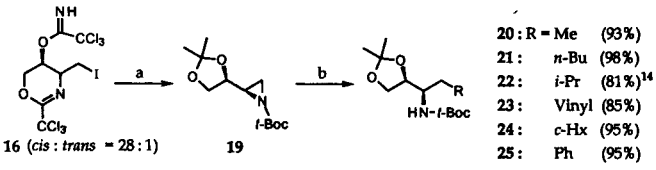


Scheme 2. **Reagents**: a. conc. HCl/MeOH/60 ℃; *t*-Boc$_2$O/NaHCO$_3$/MeOH/rt; Ac$_2$O/Et$_3$N/CH$_2$Cl$_2$/rt. b. CF$_3$COOH/aq. MeOH/rt; *t*-Boc$_2$O/aq. NaHCO$_3$/MeOH/rt; *n*-Bu$_4$NF/aq. THF/rt; Ac$_2$O/Et$_3$N/CH$_2$Cl$_2$/rt (66% from **9** and **10**, respectively). c. 6 N HCl/MeOH/rt (60 ℃ for **15**); *t*-Boc$_2$O/NaHCO$_3$/MeOH/rt; Ac$_2$O/Et$_3$N/CH$_2$Cl$_2$/rt (72% from **14**, 65% from **15** and 72% from **16**).

duction was achieved from the other substrates (entries 1-5), evidently the formation of *cis*-**16** from **1** is the most efficient process for a precursor of *syn*-β-amino alcohols (entry 5).

It is apposite to mention how the stereochemistries of **9-16** were determined. The stereochemistries of **9, 11-13** were assigned by nOe experiments. However, those of **10, 14-16** could not be corroborated unambiguously. Accordingly *trans*-**11** and *cis*-**11** were converted into the corresponding aziridines **17** and **18**, respectively. Also **9, 10, 14-16** were derivatized into a mixture of the aziridines respectively (Scheme 2). The spectroscopic comparison of the mixtures with **17** and **18** identified their stereochemistries as depicted in Table 1 and 2.[13]

Finally, as an effort to elaborate **16** (*cis* : *trans* = 28 : 1) to



20: R = Me (93%)
21: *n*-Bu (98%)
22: *i*-Pr (81%)[14]
23: Vinyl (85%)
24: *c*-Hx (95%)
25: Ph (95%)

Scheme 3. **Reagents**: a. CF$_3$COOH/aq. MeOH/rt; *t*-Boc$_2$O/NaHCO$_3$/MeOH/−15 ℃; Me$_2$C(OMe)$_2$/*p*-TsOH/acetone/0 ℃; NaH/THF/0 ℃/chromatographic separation. b. For **20**: Me$_2$CuLi/THF/−30~−20 ℃. For **21**: *n*-BuMgBr/CuCN/THF/−60~−20 ℃. For **22**: *i*-PrMgCl/CuCN/THF/Et$_2$O/−60~−20 ℃. For **23**: CH$_2$=CHMgBr/CuI/THF/−60~−30 ℃. For **24**: *c*-Hx-MgBr/CuCN/THF/−60~−20 ℃. For **25**: PhMgBr/CuBr·SMe$_2$/PhCH$_3$/−30~−20 ℃.

syn-β-amino alcohols, they were deprotected completely, and the generated amino and dihydroxyl groups were protected as *t*-butyl carbamate and acetonide sequentially (Scheme 3). The resulting iodides were cyclized and separated to furnish aziridine **19** in 80% overall yield from **16**. Further subjection of **19** to various cuprate reagents completed a facile stereoselective synthesis of *syn*-β-amino alcohols **20-25**.[15]

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13. The isomeric ratios of oxazolines and dihydro-1,3-oxazines were the same as those of aziridines.
14. The product generated from the hydride attack to aziridine **19** was formed in 10% yield (*i.e.* R=H).
15. All new compounds showed satisfactory spectral data.

Chemoselective Reduction of Carbonyl Compounds with Diisobutylethoxyalane

Jin Soon Cha*, Oh Oun Kwon, Sang Yong Kwon, Jong Mi Kim, Wone Woo Seo, and Seok Won Chang

Department of Chemistry, Yeungnam University, Kyongsan 712-749, Korea

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Very recently, we reported that diisobutylchloroalane (*i*-Bu_2AlCl) is a highly selective reducing agent for the competitive reduction between carbonyl compounds[1] and for the 1,2-reduction of α,β-unsaturated carbonyl compounds.[2] In continuation of our efforts to explore new reducing systems for such transformations, we prepared a series of diisobutylalkoxyalane (*i*-Bu_2AlOR) and examined the reducing action toward general organic functional groups. In the course of this systematic investigation, we found that the ethoxy derivative, diisobutylethoxyalane (*i*-Bu_2AlOEt), reduces aldehydes in a fast rate but ketones only slowly. Accordingly, we applied this reagent for the competitive reduction between carbonyl compounds. Herein, we report the results for such selective reduction by *i*-Bu_2AlOEt in ethyl ether.

The reagent can be readily prepared by alcoholysis of diisobutylaluminum hydride (*i*-Bu_2AlH) in ether solution (Eq. 1). The reagent is effective for the reduction of aldehydes and ketones at 25°. As in the case of *i*-Bu_2AlCl,[1,2] the reduction with *i*-Bu_2AlOEt involves hydride shift from the β-carbon atom of isobutyl group.

$$i\text{-Bu}_2\text{AlH} + \text{EtOH} \xrightarrow[0°]{\text{Et}_2\text{O}} i\text{-Bu}_2\text{AlOEt} + \text{H}_2\uparrow \quad (1)$$

The reduction of representative aldehydes and ketones with 10% excess reagent at 25° in ethyl ether is listed in Table 1. Aldehydes are reduced readily in less than 1 or 3 h, while ketones are reduced slowly requiring 48 hrs for completion.

The chemoselectivity of this reagent was tested with twenty-four representative pairs in competition experiments. Equimolar amounts of two compounds were allowed to compete for a limited quantity of *i*-Bu_2AlOEt (1 equivalent). A standard solution of the reagent (*ca.* 1 M) in ethyl ether was added to the equimolar mixture of two compounds (*ca.* 1 M in each compound) in ethyl ether maintained at 25°.

Table 1. Reduction of Representative Aldehydes and Ketones with Diisobutylethoxyalane in Ethyl Ether at 25 °C[a]

Compound	Product	Time (h)	Yield (%)[b]
Butanal	1-Butanol	1.0	96
		3.0	100
Benzaldehyde	Benzyl alcohol	0.5	98
		1.0	100
2-Butanone	2-Butanol	24	90
		48	100
Acetophenone	1-Phenyl ethanol	24	95
		48	100

[a] Ten % excess reagent was utilized. Reaction mixtures were *ca.* 1 M in substrates. [b] Determined by GC using internal standard.

Table 2. Chemoselective Reduction of Carbonyl Compounds with Diisobutylethoxyalane in Ethyl Ether at 25 °C[a]

Entry	Starting mixture	Time (h)	Ratio of redn products[b]
1	Butanal/Hexanal	12	60 : 40
2	Butanal/Benzaldehyde	3	5 : 95
3	Butanal/Anisaldehyde	6	95 : 5
4	Hexanal/Benzaldehyde	3	2 : 98
5	Hexanal/Anisaldehyde	6	92 : 8
6	Benzaldehyde/Anisaldehyde	3	99.5 : 0.5
7	Butanal/Cyclohexanone	6	100 : 0
8	Hexanal/Cyclohexanone	6	100 : 0
9	Hexanal/2-Heptanone	6	100 : 0
10	Hexanal/Acetophenone	6	100 : 0
11	Hexanal/Benzophenone	6	100 : 0
12	Anisaldehyde/Cyclohexanone	12	99 : 1
13	Cyclohexanone/2-Heptanone	24	100 : 0
14	Cyclohexanone/Acetophenone	24	95 : 5
15	Cyclohexanone/Benzophenone	24	100 : 0
16	Acetophenone/2-Heptanone	48	100 : 0
17	2-Heptanone/Benzophenone	96	95 : 5
18	Acetophenone/Benzophenone	48	100 : 0
19	Cyclohexanone/Cyclopentanone	24	90 : 10
20	Hexanal/Hexanoyl Chloride	6	100 : 0
21	Hexanal/Benzoyl Chloride	6	100 : 0
22	2-Heptanone/Benzoyl Chloride	96	99 : 1
23	Hexanal/Hexanenitrile	6	100 : 0
24	Hexanal/Ethyl Hexanoate	6	100 : 0

[a] Reaction mixtures were *ca.* 1 M in substrates. One equivalent of reagent was utilized for competitive reduction of equimolar mixture of two carbonyl compounds. [b] Normalized ratio determined by GC with appropriate internal standard; the total yields of product alcohols were ≥ 99%.

After appropriate time intervals, the mixture was hydrolyzed with 3 N HCl. The results obtained by GC analysis of the reaction mixture with an internal standard are summarized in Table 2.

Both aliphatic and aromatic aldehydes examined are selec-