Highly Diastereoselective Addition of Phenyllithium on *cis*-Substituted *C*-Cyclopropylaldimines

Damien Belotti, Nadim Noujeim, Janine Cossy*

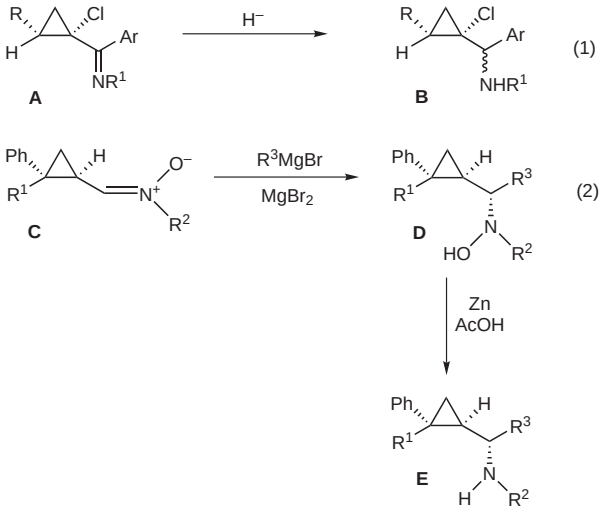
Laboratoire de Chimie Organique associé au CNRS, ESPCI, 10 Rue Vauquelin, 75231 Paris Cedex 05, France
E-mail: janine.cossy@espci.fr

Received 19 September 2006

Abstract: The addition of phenyllithium to *cis*-substituted *C*-cyclopropylaldimines produces in high diastereoselectivity and in good yields *anti*-(1-aminoalkyl)cyclopropanes as the major isomers.

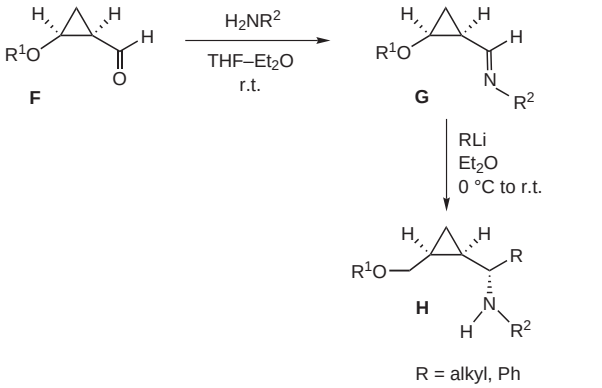
Key words: cyclopropylaldimines, (1-aminoalkyl)cyclopropanes, phenyllithium

The stereochemical course of the addition of nucleophiles to acyclic α-chiral aldehydes and imines has been extensively studied and predictions can be made on the basis of the Felkin–Anh and Cram chelate model. In general, selectivities obtained by Felkin–Anh control are moderate while high selectivities are observed if a chelation occurs.[1] The addition of nucleophiles to cyclopropylketones or cyclopropanecarboxaldehydes has found considerable attention but only a few cases have been reported to proceed with high diastereoselectivity.[2] As (1-aminoalkyl)cyclopropanes can be used as potent NMDA receptor antagonists,[3] it is of interest to develop highly diastereoselective methods for obtaining these products from simple starting materials. Recently, (1-aminoalkyl)cyclopropanes of type **B** were obtained by reduction of imidoylcyclopropanes of type **A** but, the reduction was not stereoselective[4] [Scheme 1, (1)]. (1-Aminoalkyl)cyclopropanes were also synthesized by stereoselective addition of Grignard reagents to *cis*-substituted *C*-cyclopropylaldonitrones of type **C** in the presence of a Lewis acid.[5] However, a reduction step is necessary to transform the obtained *anti*-(1-hydroxylaminoalkyl)cyclopropanes of type **D** to the desired (1-aminoalkyl)cyclopropanes of type **E** [Scheme 1, (2)].



Scheme 1

Here, we would like to report an efficient, direct and highly diastereoselective synthesis of *cis*-substituted (1-aminobenzyl)cyclopropanes of type **H** (R = Ph) from *cis*-substituted *C*-cyclopropylaldimines of type **G** by using phenyllithium (PhLi) without any additives (Scheme 2).



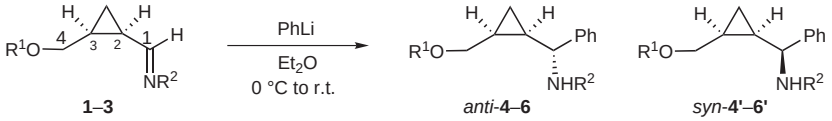
Scheme 2

The cyclopropylaldimines of type **G** were prepared from the corresponding cyclopropanecarboxaldehydes of type **F**[6] by treatment with primary amines in a mixture of dry Et_2O–THF (5:1) overnight at room temperature. After evaporation of the solvent, the cyclopropylaldimines of type **G** were dried by azeotropic removal of water and treated, without purification, with alkyllithium such as MeLi, *n*-BuLi, *s*-BuLi as well as aryllithium such as PhLi in Et_2O at 0 °C in order to obtain substituted cyclopropanes of type **H**[7] (Scheme 2). At first, compound **1** was treated with MeLi, *n*-BuLi and *s*-BuLi. By using these alkyllithium reagents in Et_2O, from 0 °C to room temperature, a complex mixture of products was obtained and the expected substituted cyclopropanes of type **H** were only detected by GC-MS.

As PhLi is more nucleophilic than alkyllithium reagents, compounds **1** and **2** were treated with phenyllithium [2 M in Bu_2O (1.5 equiv)] in Et_2O from 0 °C to room temperature. Under these conditions compound **1** was transformed to **4**[7] and **4′** in a 98:2 ratio (87% overall yield starting from

SYNLETT 2007, No. 2, pp 0259–0262
Advanced online publication: 24.01.2007
DOI: 10.1055/s-2007-967988; Art ID: G25606ST

Table 1 Reaction of Compounds **1**–**3** with PhLi/Bu_2O



Entry	Starting material R^1, R^2	*anti*:*syn*	Yield *syn* + *anti* (%)
1	R^1 = Bn, R^2 = *p*-Tol **1**	**4**/**4′** (98:2)	87
2	R^1 = Me, R^2 = *i*-Pr **2**	**5**/**5′** (98:2)	71
3	R^1 = Bn, R^2 = *i*-Pr **3**	**6**/**6′** (97:3)	72

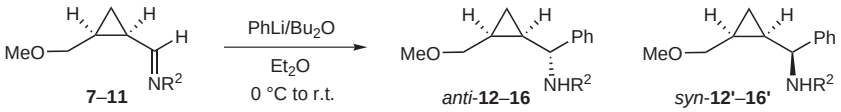
the aldehyde), in favor of the *anti*-isomer **4**. Furthermore, the addition of phenyllithium to **2** (R^1 = methyl) occurred stereoselectively to give compound **5** and **5′** (71% yield) in a 98:2 ratio in favor of the *anti*-compound **5**. The stereoselectivity does not depend on the alkoxy group at C4 as the treatment of **3** (R^1 = Bn) with PhLi led to **6** and **6′** in 72% yield in a 97:3 ratio always in favor of the *anti*-isomer, the (1-aminobenzyl)cyclopropane **6** (Table 1).

The reaction is general and the *anti*-(1-aminobenzyl)cyclopropanes **12**–**16** were obtained, as the major isomers, from the corresponding cyclopropylaldimines derivatives **7**–**11**. The *anti*/*syn*-(1-aminobenzyl)cyclopropanes were formed in a ratio of 98:2 in favor of the *anti*-products in moderate to good yields (45–96%), whatever the amino substituent. The results are reported in Table 2.

As the stereoselectivity may be due to either a chelating effect of the OR group present at C4 or to steric hindrance, compounds **17**–**20** were synthesized and treated with PhLi. The results are reported in Table 3. When the addition of PhLi to compounds **17** and **18** possessing a *tert*-butyl-dimethylsilyloxy was achieved, the *anti*/*syn* ratio was decreased relative to that observed previously as, compounds **21**/**21′** were obtained from **17** in a ratio of 90:10 and **22**/**22′** were obtained from **18** in a 75:25 ratio. Compounds **23**/**23′** were formed in a ratio of 89:11 when **19**, which possess a sterically hindered group (R^1 = *t*-Bu), was treated with PhLi. It is worth noting that **24**/**24′** were obtained in a 50:50 *anti*/*syn* ratio from the cyclopropylaldimine **20**, substituted by the sterically less hindered *n*-propyl group. The diastereoselectivity of the addition of PhLi to cyclopropylaldimines of type **G** seems sensitive to steric hindrance (Table 3).

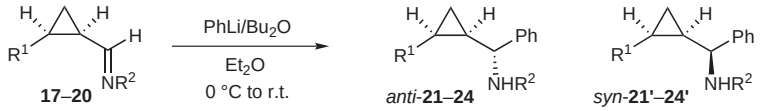
In order to establish the relative stereochemistry between the amino group and the cyclopropane, the bicyclo[3.1.0] compounds **25** and **25′** were synthesized from compounds **22** (*anti*, major) and **22′** (*syn*, minor), respectively. After separation of **22** and **22′**, treatment of these compounds with TBAF (THF, r.t.) and oxidation using PDC (CH_2Cl_2, r.t.), **25** (69% for the 2 steps) and **25′** (53% for the 2 steps) were isolated, respectively. Based on previous results,[4,8] and by analyzing the ^{1}H NMR spectrum of **25** and **25′**, we found that a coupling constant $J_{H4–H5}$ = 1 Hz for **25**

Table 2 Reaction of Compounds **7**–**11** with PhLi/Bu_2O

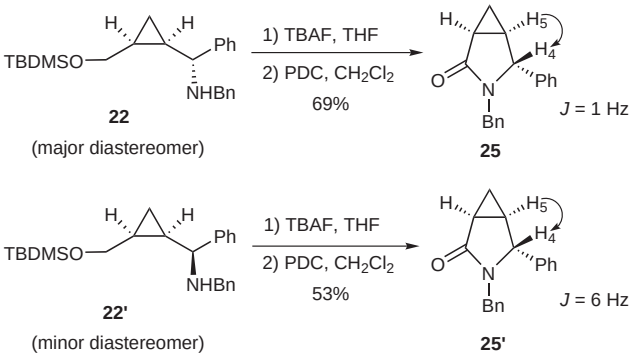


Entry	Starting material R^2	*anti*:*syn*	Yield *syn* + *anti* (%)
1	R^2 = *p*-Tol **7**	**12**/**12′** (98:2)	96
2	R^2 = Bn **8**	**13**/**13′** (98:2)	61
3	R^2 = Cy **9**	**14**/**14′** (98:2)	80
4	R^2 = *n*-Pr **10**	**15**/**15′** (98:2)	45
5	R^2 = *t*-Bu **11**	**16**/**16′** (98:2)	45

Table 3 Reaction of Compounds **17**–**20** with PhLi/Bu_2O



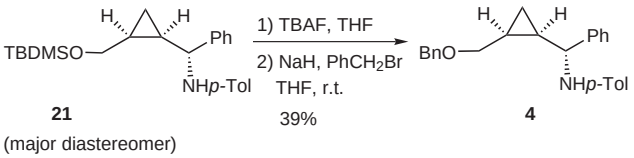
Entry	Starting material R^1, R^2	(Aminoalkyl)cyclopropane *anti*:*syn*	Yield *syn* + *anti* (%)
1	R^1 = $CH_2OTBDMS$, R^2 = *p*-Tol **17**	**21**/**21′** (90:10)	90
2	R^1 = $CH_2OTBDMS$, R^2 = Bn **18**	**22**/**22′** (75:25)	90
3	R^1 = *t*-Bu, R^2 = *p*-Tol **19**	**23**/**23′** (89:11)	97
4	R^1 = *n*-Pr, R^2 = *p*-Tol **20**	**24**/**24′** (50:50)	90



Scheme 3

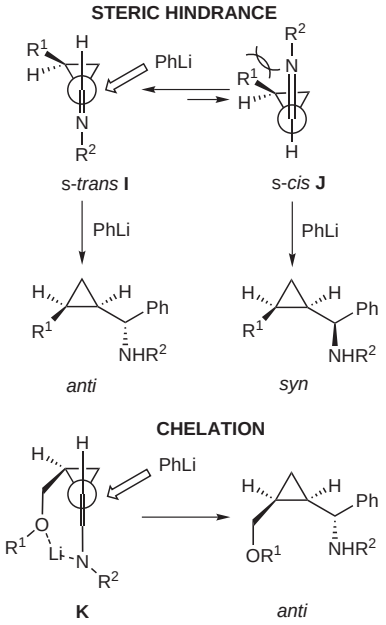
and $J_{H4–H5}$ = 6 Hz for **25′**. These values allowed us to determine that the major compound was the *anti*-isomer (Scheme 3).

We were also able to transform compound **21** to **4** in 2 steps (TBAF, THF, r.t.; then NaH, $PhCH_2Br$, THF, r.t.) and this compound corresponds to the major isomer which was obtained from the addition of PhLi to **1** (Scheme 4). Thus, whatever the protecting group of the hydroxy group present at C4, in the *C*-cyclopropylaldimines of type **G**, with chelating or non-chelating properties, the *anti*-(1-aminophenyl)cyclopropanes were always obtained as the major isomers.



Scheme 4

The addition of phenyllithium to cyclopropylaldimines of type **G** was highly stereoselective and led to the *anti*-(1-aminobenzyl)cyclopropanes. Based on previous results[5] of the two possibilities, the s-*trans*-conformation **I** is preferred to the s-*cis*-conformation **J**, because in the latter one, the imine group is oriented in the cyclopropyl moiety which increases the steric hindrance. The stereochemical outcome of the reaction could then be understood by the attack of the PhLi on the less hindered face of the stereoelectronically stabilized bisected s-*trans*-conformer **I** (Scheme 5). When the alkoxy group at C4 can chelate the organometallic, the addition of phenyllithium to cyclopropylaldimines is highly stereoselective and led also to the *anti*-(1-aminobenzyl)cyclopropanes via intermediate **K** (Scheme 5).



Scheme 5

We have shown that *cis*-substituted (1-aminobenzyl)cyclopropanes can be obtained with high diastereoselectivity from *cis*-substituted *C*-cyclopropylaldimines by addition of PhLi and that chelation effects have more influence on the diastereoselectivity of the addition of PhLi than steric effects.

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(6) Cyclopropanecarboxaldehydes of type **F** have been synthesized by PCC oxidation of the corresponding alcohols, which have to be prepared by Simmons–Smith–Furukawa cyclopropanation[9] of the corresponding *cis*-alkenes.

(7) **Synthesis of 4 as Representative Procedure.**
All the reactions were performed under an argon atmosphere. To a stirred solution of *cis*-2-benzyloxymethylcyclopropanecarboxaldehyde (0.38 g, 2 mmol) in a 5:1 mixture of dry Et_2O (20 mL) and dry THF (4 mL), was added *p*-toluidine (0.214 g, 2 mmol). The resulting solution was stirred at r.t. for 4 h. The solvents were removed in vacuo and the residue was dried by azeotropic evaporation to give the pure crude imine **1** which was solubilized in dry Et_2O (15 mL). To this solution, stirred at 0 °C, was added PhLi (2 M in Bu_2O, 1.5 mL, 3 mmol). The resulting light brown solution was stirred from 0 °C to r.t. overnight and then diluted carefully with H_2O (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The solvents were removed in vacuo and the residue, which was mainly constituted by one diastereomer (GC-MS analysis showed a ratio *anti*/*syn* > 98:2), was purified by flash column chromatography on silica gel (90:10 PE–EtOAc) to provide *anti*-(1-aminobenzyl)cyclopropane **4** as a yellow oil (0.615 g, 86% yield). IR: 3367 (br), 1615, 1516, 1071, 809, 735, 697 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.50–7.20 (10 H), 6.82 (d, *J* = 8.3 Hz, 2 H), 6.30 (m, 2 H), 4.78 (br s, 1 H), 4.43 (s, 2 H), 3.80 (dd, *J* = 10.2, 5.2 Hz, 1 H), 3.65 (d, *J* = 9.8 Hz, 1 H), 3.27 (t, *J* = 10.2 Hz, 1 H), 2.17 (s, 3 H), 1.45–1.20 (2 H), 0.82 (m, 1 H), 0.48 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ = 145.9 (C), 144.6 (C), 138.1 (C), 129.3 (2 CH), 128.7 (2 CH), 128.4 (2 CH), 127.8 (2 CH), 127.6 (CH), 126.9 (CH), 126.5 (C), 126.1 (2 CH), 114.2 (2 CH), 73.3 (CH_2), 70.2 (CH_2), 60.5 (CH), 26.1 (CH), 20.4 (CH_3), 17.1 (CH), 9.0 (CH_2). MS (EI): *m/z* (rel. int.) = 357 (10) [M^+], 196 (10), 129 (10), 107 (55), 91 (100).

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