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Stereoselective oxymercuration of cyclopropylcarbinols with anchimeric assistance by aromatic groups

Janine Cossy,* Nicolas Blanchard and Christophe Meyer

Laboratoire de Chimie Organique, associé au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France

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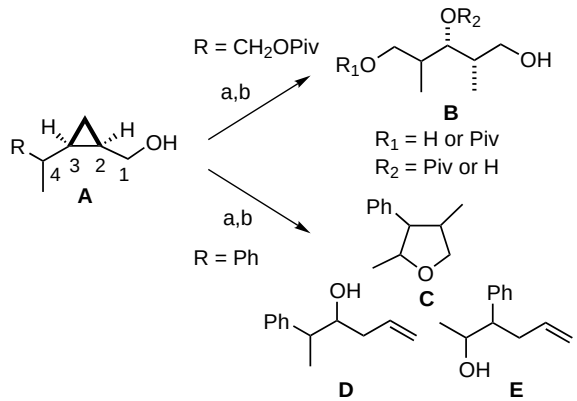
Abstract—Cyclopropylcarbinols bearing an adjacent stereocenter substituted by a phenyl group undergo anchimerically assisted mercurations, leading after reductive demercuration to oxygenated heterocycles or acyclic alcohols depending on the relative configurations.

Organomercurials are frequently encountered intermediates in organic synthesis.[1] The usual role of mercury is to introduce another associated nucleophilic reagent and in most cases, after having served its purpose, mercury is removed by reduction.[1,2] This strategy is exemplified by the oxymercuration of carbon–carbon double bonds[1] and by cyclopropane ring cleavage.[3] The stereocontrolled synthesis of cyclopropanes followed by inter- or intramolecular ring-opening is an attractive strategy for the preparation of acyclic and heterocyclic compounds bearing contiguous stereogenic centers.[4,5] We have recently shown that stereotriads **B** could be generated by oxymercuration–reduction of cyclopropylcarbinols of type **A** bearing an appropriately protected hydroxymethyl group at C-4 ($R = CH_2OPiv$).[6] Here, we would like to report that the mercuration–demercuration of cyclopropylcarbinols of type **A** with a phenyl group at C-4 ($R = Ph$) follows a different pathway and leads to cyclic products of type **C** and/or linear products of type **D** and **E**, due to anchimeric assistance by the aromatic substituent (Scheme 1).



Scheme 1. Oxymercuration of cyclopropylcarbinols of type **A**. *Reagents and conditions*: (a) $Hg(OCOCF_3)_2$, CH_2Cl_2; (b) reductive demercuration.

For this study, four cyclopropylcarbinols **1**–**4** were prepared. Cyclopropylcarbinols **1** and **2** were synthesized from 2-phenylpropanal **5**. The latter aldehyde was first transformed to the dibromoolefin **6** (85%).[7] After treatment of the dibromoolefin **6** with 2 equiv. of *n*-BuLi in THF at −100°C,[8] the resulting acetylide was quenched with paraformaldehyde and the propargylic alcohol **7** (95%) was isolated. Reduction of the triple bond with a zinc–copper couple afforded the corresponding (*Z*)-allylic alcohol **8** (79%),[9] which was subjected to Zn- or Sm-promoted cyclopropanations to give the diastereomeric cyclopropylcarbinols **1** and **2** (Scheme 2).[10,11]

Cyclopropylcarbinols **3** and **4** were synthesized in four steps from 3-phenylprop-1-yne **9**. Upon treatment of **9** with 2 equiv. of *n*-BuLi in THF at −20°C, the resulting dianion[12] was regioselectively alkylated with 3-bromo-1-benzyloxypropane. Subsequent addition of paraformaldehyde led to the propargylic alcohol **10** (85%). Since the (*Z*)-allylic alcohol **13** could not be obtained by reduction of **10** with the zinc–copper couple in refluxing isopropanol,[9] a two-step procedure was used. The *syn*-hydrostannation of propargylic alcohol **10** with $n\text{-}Bu_3SnH$ catalyzed by $Pd(PPh_3)_4$[13] afforded two regioisomeric vinylstannanes **11** and **12** in a ratio of

* Corresponding author. Tel.: +33.1.40.79.46.63; fax: +33.1.40.79.46.60; e-mail: janine.cossy@espci.fr

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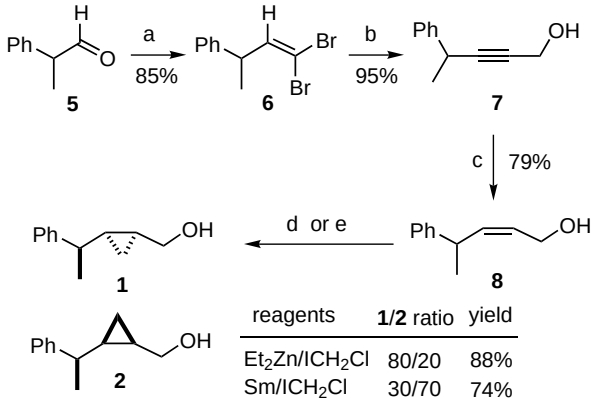
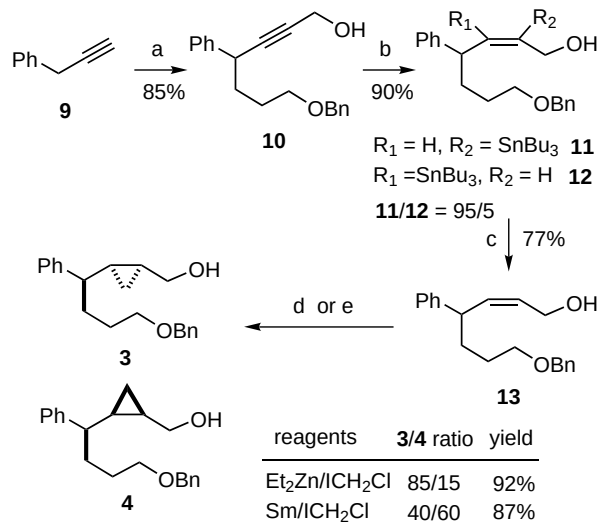


Scheme 2. Preparation of cyclopropylcarbinols **1** and **2**. *Reagents and conditions*: (a) PPh_3, CBr_4, CH_2Cl_2; (b) *n*-BuLi, THF, −100°C, $(CH_2O)_n$, −78°C to rt; (c) Zn, $Br(CH_2)_2Br$, CuBr, LiBr, THF/*i*-PrOH; (d) Et_2Zn, ICH_2Cl, DCE, −23°C; (e) Sm(Hg), ICH_2Cl, −50 to −20°C, THF.

95:5 in 90% overall yield. The allylic alcohol **13** was obtained by transmetallation of **11** and **12** with *n*-BuLi in THF followed by hydrolysis. Cyclopropanation of **13** according to the previously reported methods afforded cyclopropylcarbinols **3** and **4** (Scheme 3).[11]

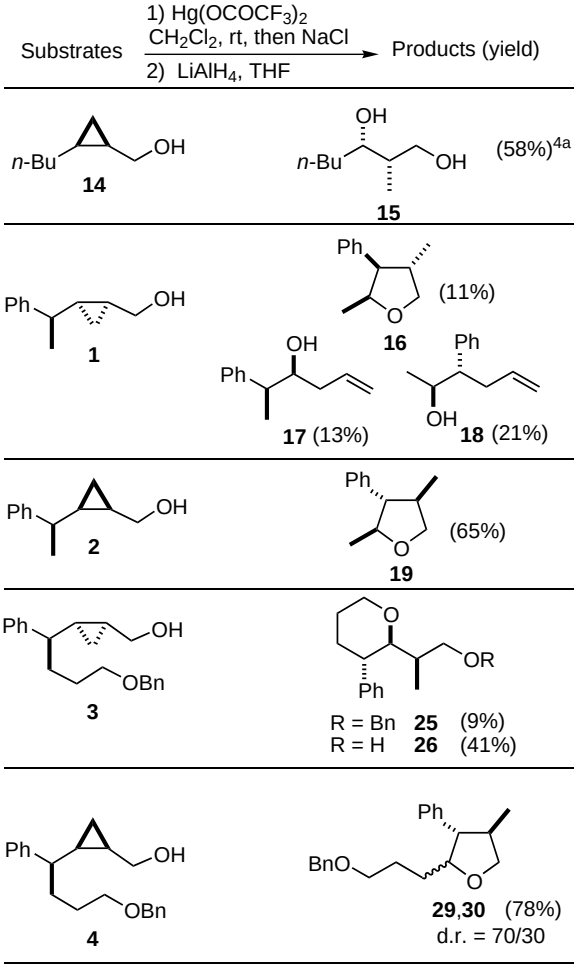
Cyclopropylcarbinols **1**–**4** were then treated with 2 equiv. of mercuric trifluoroacetate followed by an aqueous work-up with a saturated aqueous solution of NaCl. The resulting intermediate organomercuric chlorides were then subjected to reductive demercuration with $LiAlH_4$ in THF (Table 1).

The formation of diol **15** has been previously reported in the case of cyclopropylcarbinol **14**.[4a] The high



Scheme 3. Preparation of cyclopropylcarbinols **3** and **4**. *Reagents and conditions*: (a) *n*-BuLi (2 equiv.), THF, −20°C, then $Br(CH_2)_3OBn$, −20 to −10°C, $(CH_2O)_n$, −10°C to rt; (b) Bu_3SnH, cat. $Pd(PPh_3)_4$, THF, rt; (c) *n*-BuLi, THF, −78 to −60°C, then aq. NH_4Cl; (d) Et_2Zn, ICH_2Cl, DCE, −23°C; (e) Sm(Hg), ICH_2Cl, −50 to −20°C, THF.

Table 1. Mercuration–demercuration of cyclopropylcarbinols **1**–**4**



regioselectivity usually observed in the oxymercuration of substituted cyclopropylcarbinols has been explained by electrophilic ring-opening by Hg^{2+} of the most electron-rich bond of the three-membered ring, in consideration of the inductive effect of the neighboring electron-withdrawing hydroxymethyl moiety.[4a,5c]

When subjected to the mercuration–demercuration, the *anti*,*cis*-cyclopropylcarbinol **1** was converted to a mixture of products, from which three major components were isolated by flash chromatography: the trisubstituted tetrahydrofuran **16** (11%),[14] the known homoallylic alcohols **17**[15] (13%) and **18**[16] (21%). By contrast, the *syn*,*cis*-cyclopropylcarbinol **2** was exclusively converted to the trisubstituted tetrahydrofuran **19** (65%), obtained as a single diastereomer.[14]

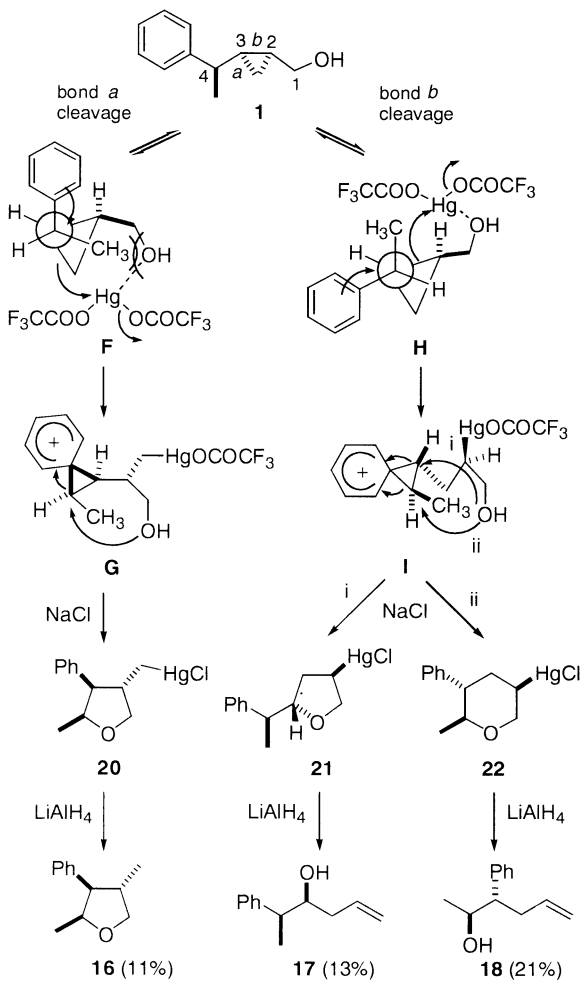
In the case of cyclopropylcarbinols **1** and **2**, the formation of tetrahydrofurans **16** and **19** as well as the acyclic homoallylic alcohols **17** and **18** is explained by the anchimeric assistance by the phenyl group adjacent to the cyclopropane ring. We note that electrophilic ring opening of the cyclopropane by Hg^{2+} with concomitant participation of the phenyl group can only occur in a conformation in which overlap of the aromatic π-sys-

tem and the developing empty p-orbital at C-3 is possible.[17]

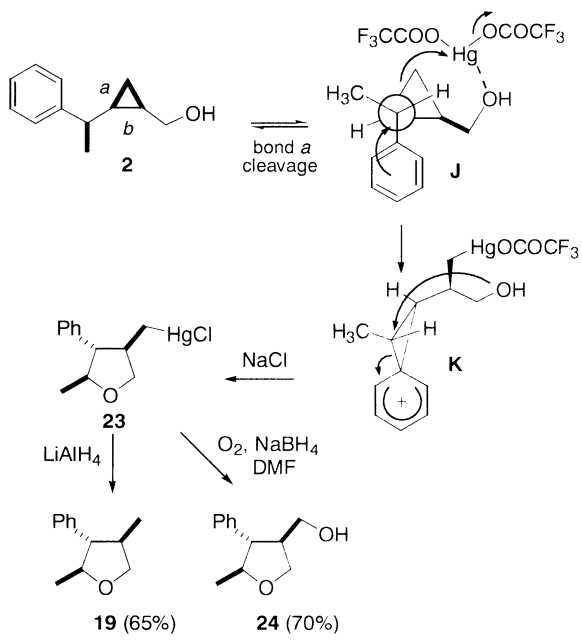
Thus for the *anti*,*cis*-cyclopropylcarbinol **1**, the phenyl group can assist in the cleavage of the most electron-rich bond of the cyclopropane (bond *a*) in conformer **F** leading to an intermediate phenonium ion[17] **G**. However conformer **F** is destabilized by a severe 1,3-interaction similar to $A^{1,3}$ strain.[18] Therefore, the phenyl group can also assist in the cleavage of bond *b* in conformer **H** leading to the phenonium ion **I**. The nucleophilic attack of the hydroxy group onto the intermediate phenonium ions **G** and **I** can lead to three organomercuric chlorides **20**–**22**, after treatment with NaCl. The reductive demercuration of **20** leads to the trisubstituted tetrahydrofuran **16** but, as reductive demercuration is a radical process, it can also initiate a β-fragmentation[19] for organomercurials **21** and **22** and generate the known homoallylic alcohols **17**[15] and **18**[16] (Scheme 4). The fact that these two homoallylic alcohols essentially derive from the reduction of the organomercuric compounds **21** and **22** with $LiAlH_4$ is also supported by examination of the ^1H NMR spectrum of the crude reaction mixture (compounds **20**–**22**) after mercuration of **1**, showing that only traces of olefinic compounds are formed at this stage. Therefore the formation of homoallylic alcohols **17** and **18** cannot be rationalized by a simple cyclopropylcarbinyl cationic ring-opening of cyclopropylcarbinol **1**.

By contrast, in the case of the *syn*,*cis*-cyclopropylcarbinol **2**, the phenyl group can assist in the cleavage of the most electron-rich bond of the cyclopropane (bond *a*) in conformer **J**, which does not suffer from 1,3-strain compared to **F**. After nucleophilic attack of the hydroxy group on the resulting intermediate phenonium **K**, the organomercuric chloride **23** is obtained exclusively. Reductive demercuration leads to the trisubstituted tetrahydrofuran **19** (65%). The structure of the intermediate organomercuric compound **23** was further confirmed by its conversion to alcohol **24** (70%) upon radical oxidation induced by $O_2/NaBH_4$ in DMF (Scheme 5).[20]

With the aim of studying the competition between anchimeric assistance by a phenyl group and assistance by an appropriately located heteroatom, the mercuration of cyclopropylcarbinols **3** and **4** was investigated. When the *anti*,*cis*-diastereomer **3** was treated with mercuric trifluoroacetate followed by reductive demercuration with $LiAlH_4$, two products were formed: the benzyl ether **25** and the alcohol **26** which were isolated in 9 and 41% yield, respectively. The formation of these products can be explained by a rapid intramolecular oxymercuration promoted by the benzyl ether in conformation **L**, involving the most electron-rich bond (bond *a*) of the cyclopropane, which leads to an intermediate oxonium ion **M**. The latter can react with the trifluoroacetate anion to give alcohol **28** or by nucleophilic attack of the hydroxy group to give benzyl ether **27**. Reductive demercuration then affords tetrahydropyrans **25** and **26**. In this case, anchimeric assistance by the phenyl group that would have involved



Scheme 4. Mercuration–demercuration of cyclopropylcarbinol **1**.

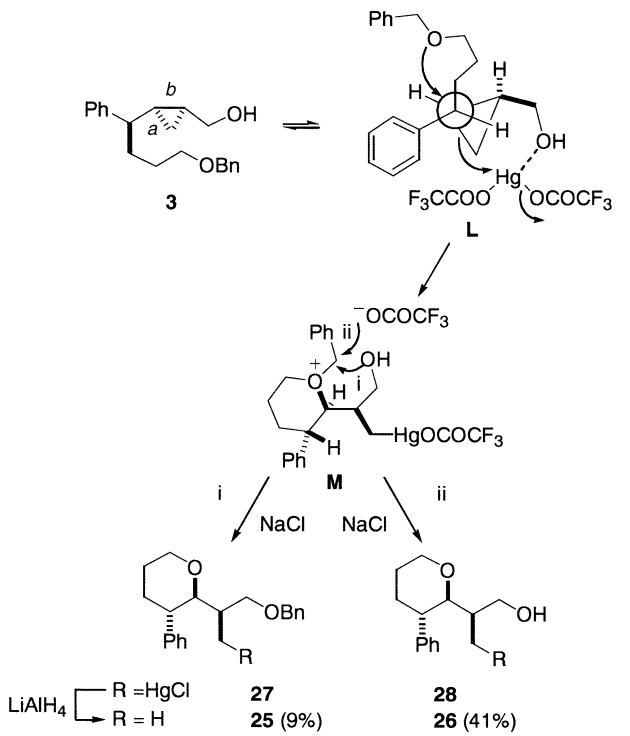


Scheme 5. Mercuration–demercuration of cyclopropylcarbinol **2**.

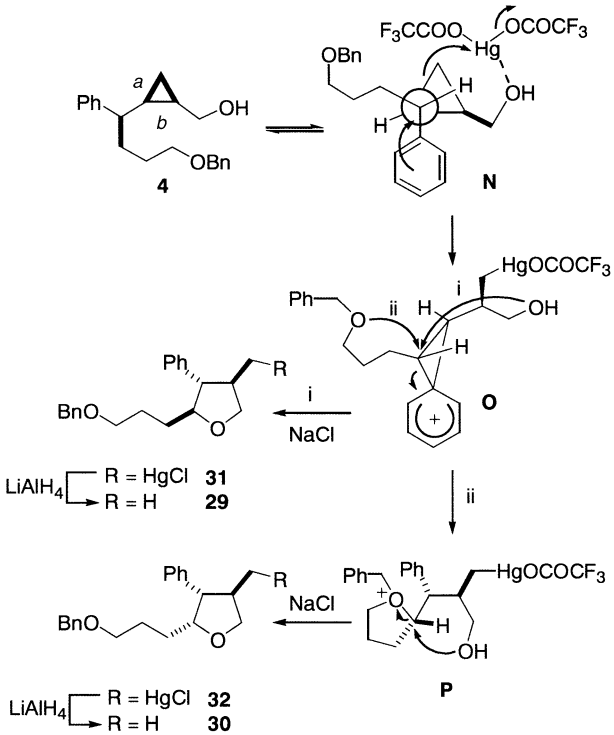
cleavage of the less reactive bond of the cyclopropane (bond *b*) is not observed (Scheme 6).

By contrast, mercuration–reductive demercuration of the *syn*,*cis*-cyclopropylcarbinol **4** afforded a 70/30 diastereomeric mixture of two tetrahydrofurans **29** and **30** (78%). The formation of these compounds is explained by anchimeric assistance by the phenyl group with cleavage of the most electron-rich bond of the cyclopropane (bond *a*) in conformer **N**, leading to an intermediate phenonium ion **O**. Intramolecular nucleophilic attack by the hydroxy group leads to the organomercuric compound **31**, which upon reductive demercuration affords tetrahydrofuran **29**. However, an epimeric tetrahydrofuran **30** was also formed during this reaction. Its formation can be attributed to the assistance by the benzyl ether moiety in the ring-opening of phenonium ion **O** leading to an intermediate oxonium ion **P**, which is then attacked by the hydroxy group to give the organomercuric compound **32**. Reductive demercuration affords the epimeric tetrahydrofuran **30**. Worthy of note is the fact that anchimeric assistance by the aromatic group in this reaction overrides intramolecular oxymercuration promoted by the benzyl ether (Scheme 7).

We have shown that cyclopropylcarbinols of type **A** bearing a phenyl group at C-4 undergo anchimerically assisted mercuration reactions which can lead in some cases to the formation of oxygenated heterocycles in good yields. This study highlights the dramatic influence of the relative configuration of the stereocenter substituted by the phenyl group on the course of the mercuration reaction.



Scheme 6. Mercuration–demercuration of cyclopropylcarbinol **3**.



Scheme 7. Mercuration–demercuration of cyclopropylcarbinol **4**.

Acknowledgements

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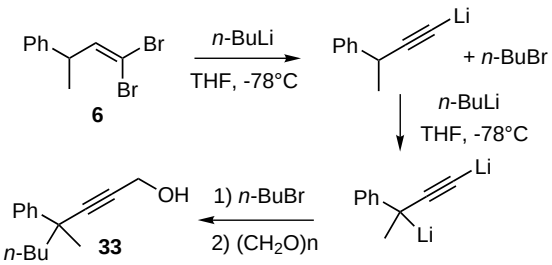
8. The reaction has to be performed at −100°C in order to avoid a second metallation at the propargylic position of the initially formed lithium acetylide.[12] Indeed, when the reaction was performed at −78°C, the alcohol **33** was obtained as a by-product. The greater acidity of the propargylic proton in this case is probably due to the presence of the phenyl group.



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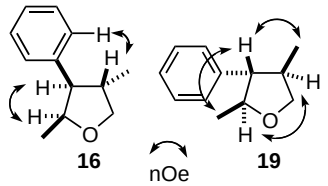
14. The relative configurations of tetrahydrofurans **16** and **19** were confirmed by ^{1}H NMR analysis on the basis of the observed differential nuclear Overhauser effects.



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