Copper-catalyzed hydride transfer from $LiAlH_4$ for the formation of alkylidenecyclopropane derivatives†

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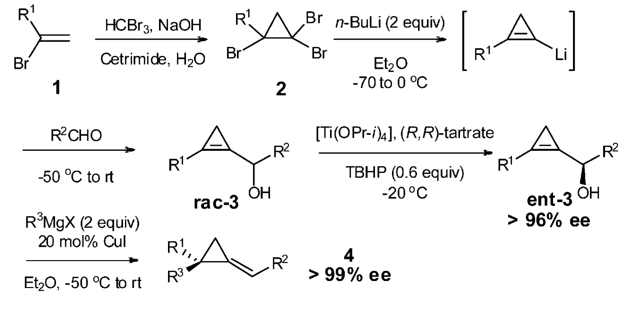
The copper-catalyzed addition of $LiAlH_4$ to cyclopropenylcarbinol leads to an easy and straightforward preparation of alkylidenecyclopropane derivative.

Over the past few decades, racemic cyclopropene and alkylidenecyclopropane (ACP) derivatives have been established as powerful tools in synthetic chemistry. Indeed, on one hand, cyclopropene derivatives can easily be transformed into more complex molecules by hydro- or carbometallation reactions[1] of the internal strained double bond[2] whereas alkylidenecyclopropane derivatives have proved their usefulness by their unique reactivity with transition-metal catalysts.[3] These catalyzed transformations, also based on the release of the high level of strain, can be performed either on the distal or proximal bonds of the three-membered ring as well as on the exoalkylidene moiety.[4] However, in the last few years, using strain as design principle for asymmetric reaction led to a complete renaissance of the field.[5] In this context, we have recently reported the straightforward preparation of enantiomerically pure cyclopropenylcarbinols **3** in excellent yields for a kinetic resolution upon Sharpless epoxidation (Scheme 1).[6] Racemic **3** is easily prepared by a two step sequence: reaction of substituted vinyl bromide derivatives **1** with bromoform in the presence of cetrimide as phase-transfer catalyst,[7] followed by treatment of the resulting 1,1,2-tribromocyclopropanes **2** with *n*-BuLi and reaction with various aldehydes. Then, starting from enantiomerically pure **3**, the synthesis of alkylidenecyclopropanes **4** was readily achieved by a simple combined copper-catalyzed carbomagnesiation followed by a *syn*-β-elimination reaction in excellent yields and enantiomeric excess.

Secondary allyl alcohol derivatives **3** led to alkylidenecyclopropanes **4** with a quaternary all-carbon stereocenter with a complete transfer of chirality, regardless of the nature of the alkylmagnesium halide. Moreover, in all these experiments, the unique or major isomer detected had *E*-configuration.



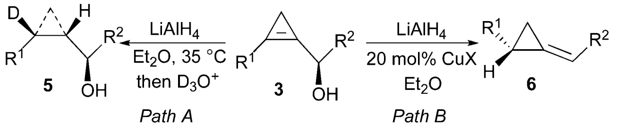
1 2 4

Scheme 1

To extend this methodology, and particularly if aiming to prepare alkylidenecyclopropanes **4** possessing a tertiary stereocenter (R^1 = H, R^3 = alkyl, aryl), the more challenging gaseous bromoethene **1** (R^1 = H) has to be used to obtain **2**. Despite many attempts, the reaction of bromoform to bromoethene in the presence of phase transfer catalyst, as described in Scheme 1, constantly led to very low yields of tribromocyclopropane **2** (R^1 = H). Therefore, we thought to develop an alternative strategy for the obtention of **4** (R^1 = H) using our easily prepared precursor **3** (R^1 = alkyl). In such case, the formal S_N2' addition of a hydride to the cyclopropenylcarbinol **3** should be the relevant strategy for the formation of the expected alkylidenecyclopropane derivative. The copper (I)-catalyzed hydride transfer is known to be a mild and often selective reducing agent, and among the most extensively studied and routinely used is the phosphine-stabilized hexameric complex $[\{CuH(PPh_3)\}_6]$, commonly referred to as Stryker's reagent.[8] It smoothly effects conjugate reductions of various α,β-unsaturated compounds.[9] More recently, alternatives such as stannanes,[10] boranes,[11] and in particular silanes[12] have been developed as hydrogen equivalents in CuH chemistry. Interestingly, since the initial report of Whitesides that reported the preparation of copper hydride *via* treatment of $i\text{-}Bu_2AlH$ with CuBr,[13] the use of HCu generated from aluminium species has never been really developed.

We have recently reported that $LiAlH_4$ could be successfully used to reduce cyclopropenylcarbinols **3** into the corresponding *anti*-cyclopropylcarbinols **5** in excellent yield and diastereoselectivity (Scheme 2, Path A).[14]

Although the regiochemistry of the hydroalumination reaction leads to the carbon–aluminium bond in a γ-position (as determined by treatment with D_3O^+ and exemplified in the formation of the deuteriocyclopropane derivative **5**), we envisaged that the addition of a catalytic amount of copper(I) salt to $LiAlH_4$ should reverse the chemical outcome of the reaction *via* a postulated copper hydride species. Thus, a



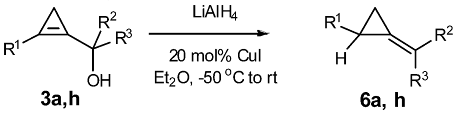
5 3 6

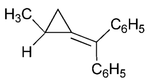
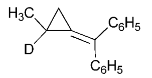
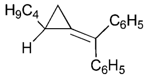
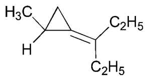
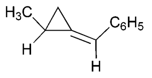
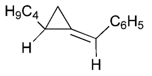
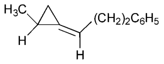
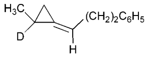
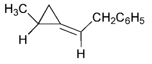
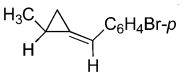
Scheme 2

The Mallat Family Laboratory of Organic Chemistry, Schulich Faculty of Chemistry and the Lise Meitner-Minerva Center for Computational Quantum Chemistry, Technion-Israel Institute of Technology, Haifa, 32000, Israel. E-mail: chilanm@tx.technion.ac.il; Fax: (+972)4 829 3709

† Electronic supplementary information (ESI) available: Experimental details; characterization data and NMR spectra for compounds **6a–h**. See DOI: 10.1039/b817710d

Table 1 Formal S_N2' addition of HCu on **3a–h**



Entry	R^1	R^2	R^3	Products		Yield (%)[a]
1 (**3a**)	CH_3	C_6H_5	C_6H_5		**6a**	87
2 (**3a**)	CH_3	C_6H_5	C_6H_5		**6a(D)**	85[b]
3 (**3b**)	C_4H_9	C_6H_5	C_6H_5		**6b**	82
4 (**3c**)	CH_3	C_2H_5	C_2H_5		**6c**	40[c]
5 (**3d**)	CH_3	C_6H_5	H		**6d**	60[d]
6 (**3e**)	C_4H_9	C_6H_5	H		**6e**	61[e]
7 (**3f**)	CH_3	$(CH_2)_2C_6H_5$	H		**6f**	68[e]
8 (**3f**)	CH_3	$(CH_2)_2C_6H_5$	H		**6f(D)**	70[b]
9 (**3g**)	CH_3	$CH_2C_6H_5$	H		**6g**	76[d]
10 (**3h**)	CH_3	*p*-BrH_4C_6	H		**6h**	83[f,g]

[a] Yields of isolated pure products after purification by column chromatography. [b] $LiAlD_4$ was used as reducing agent. [c] Volatile product. [d] Isolated as *E*/*Z* isomers in a 93 : 7 ratio. [e] Isolated as *E*/*Z* isomers in a 85 : 15 ratio. [f] Isolated as *E*/*Z* isomers in a 90 : 10 ratio. [g] ACP **6h** was directly transformed into its corresponding carboxylic acid *via* treatment with *t*-BuLi followed by CO_2.

formal S_N2' reaction should now be expected and lead to new alkylidenecyclopropane derivatives **6** possessing the desired hydrogen atom in the allylic position. We were pleased to find that indeed the addition of $LiAlH_4$ in Et_2O to a solution of 20 mol% of CuI and cyclopropenylcarbinol **3** at −50 °C and slow warming to room temperature overnight gives the expected alkylidenecyclopropanes **6** in very good yield as described in Table 1.

Tertiary and secondary alcohol derivatives (Table 1, entries 1 to 4 and 5 to 9 respectively) led similarly to alkylidenecyclopropane derivatives *via* the formal S_N2' reaction (the low yield observed for **6c** is most probably due to the volatile nature of the final product, Table, entry 4). When commercially available $LiAlD_4$ was used as reducing agent, the alkylidenecyclopropane deuterated in the allylic position was obtained in good yields with >95% deuterium incorporation (Table 1, entries 2 and 8). Substituents on the double bond of the cyclopropenyl ring (R^1) can be either methyl or butyl. Substituents R^2 and R^3 can be either alkyl, aryl or hydrogen groups. When secondary alcohols are used (R^2 = alkyl or aryl, R^3 = H, Table 1, entries 5 to 9), the fate of the stereochemistry of the double bond is raised and in all the tested experiments, we always found that the major isomer was of (*E*)-configuration.

In conclusion, the addition of a catalytic amount of copper salt such CuI to cyclopropenylcarbinol and $LiAlH_4$ reverses the chemical outcome of the reaction and a formal S_N2' reaction proceeds without any trace of hydroalumination reaction of the strained double bond. It is interesting to note that the rarely used lithium aluminium hydride could be an excellent source of copper hydride.

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