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Regioselective Opening of Substituted (Cyclopropylmethyl)lithiums Derived From Cyclopropylmethyl Iodides.

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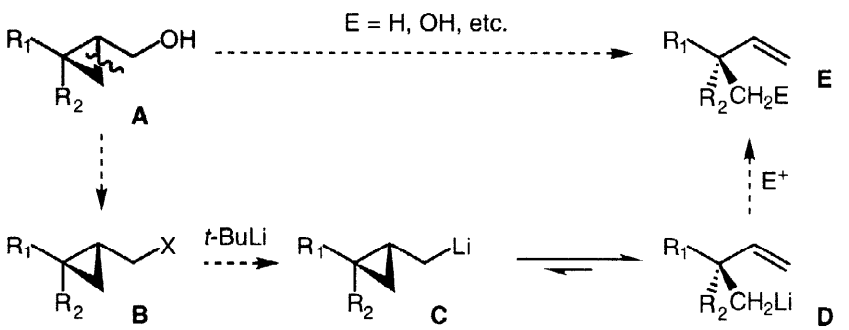
Abstract: Substituted cyclopropylmethanol derivatives were successfully opened with excellent regiocontrol by a three-step protocol. The resulting homoallylic carbanion could be trapped with a variety of electrophiles.

The number of efficient methods available for the enantioselective conversion of allylic alcohols into the corresponding enantiomerically enriched cyclopropylmethanol derivatives is constantly increasing.[1] The products are becoming increasingly useful precursors to other chiral acyclic compounds.[2] Although the regioselective reductive ring opening of cyclopropanes is a classical approach to generate *gem*-dimethyl centers, very few methods are available for the efficient opening of chiral cyclopropylmethanol derivatives such as **A**.[3] In this communication, we describe a new efficient method for the conversion of chiral allylic alcohols **A** into acyclic derivatives **E** (Scheme 1). Our strategy relies on the conversion of alcohols **A** into various cyclopropylmethyllithium species **C**. The energy gained by the release of the ring strain upon opening of the cyclopropane should produce the more stable homoallylic alkyllithium (species **D**).[4] Furthermore, the regioselectivity of the opening should also be controlled by the relative stability of the alkyllithium produced. Subsequent trapping of the homoallylic anion with a variety of electrophiles should produce adducts **E**.

Scheme 1



Several substituted cyclopropylmethanol derivatives were converted into their corresponding halides. We found that the most efficient way to achieve this transformation was to initially convert the alcohol into its corresponding mesylate. The crude mesylate was then rapidly treated with the desired halide[5] to produce the

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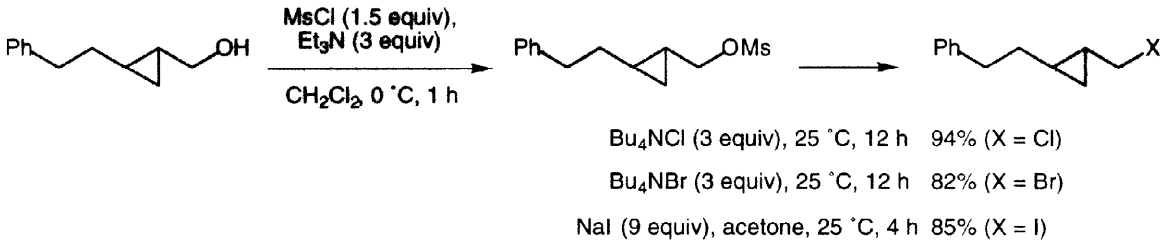
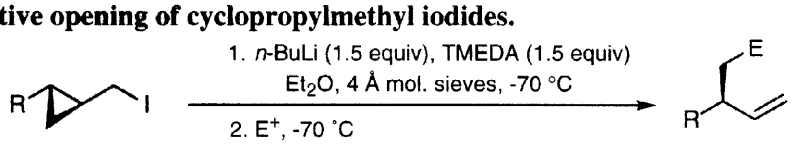
sensitive precursor in high yields (Scheme 2). In most cases, it was better to use the cyclopropylmethyl halides immediately since any adventitious traces of acid led to rapid decomposition.

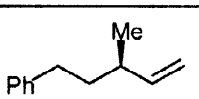
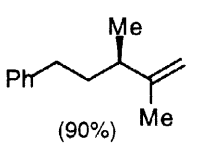
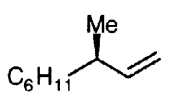
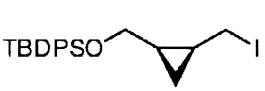
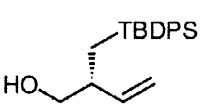
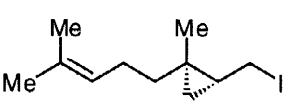
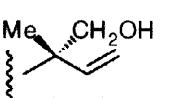
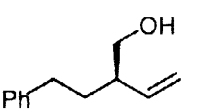
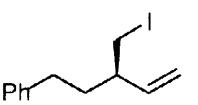
Scheme 2



All three halides were treated with either *t*-BuLi, *n*-BuLi or Mg[6] in various solvents and additives. Although, several other reaction conditions produced the desired ring opened product, we found that the optimal conditions involve the treatment of the iodide with *n*-BuLi at –70 °C in ether in the presence of TMEDA and molecular sieves (Table 1).[7] In all the cases, excellent regiocontrol (>20:1) was observed.[8] A variety of electrophiles could be added to produce the desired ring-opened product with outstanding regiocontrol. For example, the use of H_2O as the electrophile produces the methyl-substituted acyclic chain in excellent yields (Table 1, entries 1-3).

Table 1. Regioselective opening of cyclopropylmethyl iodides.



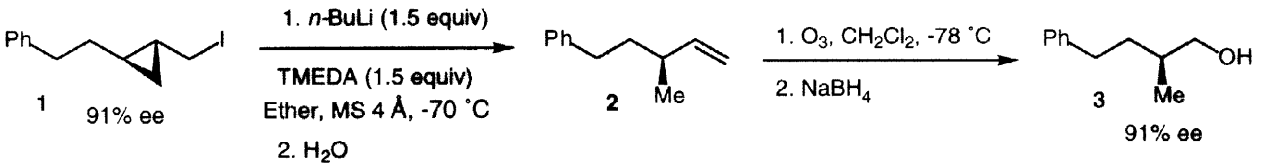
Entry	Starting iodide	E^+	Product (Yield)
1		H_2O	 (>95%)
2		H_2O	 (90%)
3		H_2O	 (90%)
4		H_2O	 (67%)
5		O_2[a]	 (47%)
6		O_2[a]	 (52%)
7		I_2	 (50%)

[a]In this case, the crude reaction mixture was quenched with sat. aq. $NaHSO_3$ to reduce the hydroperoxide.

In cases where a silyl ether can act as an internal electrophile, silyl transfer occurs to produce the corresponding silane derivative (Table 1, entry 4).[9] Alternatively, oxygen or iodine can be used as electrophiles to produce high yields of the addition product (Table 1, entries 5-7).

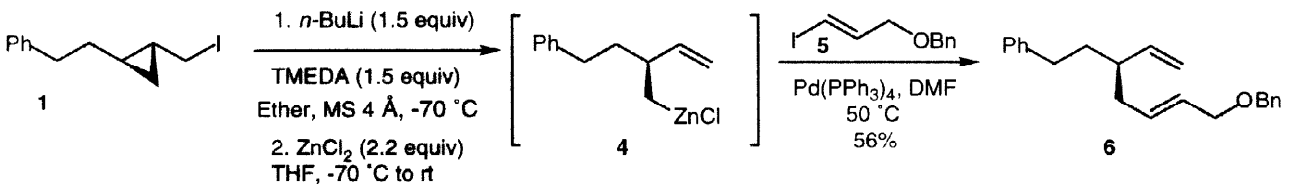
The stereochemical integrity of the ring opening process was checked by the conversion of cyclopropyl iodide **1** into alcohol **3** (Scheme 2). Both compounds had the same enantiomeric excess which implies that no stereochemical scrambling occurred in the ring opening process.

Scheme 2



Finally, the intermediate organolithium could also be transmetallated with zinc chloride to produce organozinc **4** which could undergo Negishi-type, palladium-catalyzed cross-coupling reaction[10] with vinyl iodide **5**. The diene **6** was obtained in 56% unoptimized yield.

Scheme 3



In conclusion, substituted cyclopropyl iodide derivatives undergo regioselective ring opening reaction to produce acyclic organolithium derivatives that can be efficiently trapped with several electrophiles. More importantly, the stereochemical integrity of the cyclopropane precursor is maintained in the opening process and no racemization is observed. Applications of this methodology to the synthesis of natural products is underway and will be reported in due course.

Typical Procedure: To a solution of iodide **1** (200 mg, 0.70 mmol) in ether (7 mL) was added TMEDA (158 µL, 1.05 mmol) and 4 Å molecular sieves (400 mg). The reaction mixture was cooled to –78 °C (internal temperature –70 °C) and a 1.7 M solution of *n*-BuLi in hexane (618 µL, 1.05 mmol) was added dropwise over 2 min. The reaction mixture was stirred at that temperature for 30 min and H_2O (3 mL) was added. The cold bath was removed and the temperature of the mixture was allowed to warm to room temperature. Ether (20 mL) was added and the organic layer was successively washed with 10% aqueous HCl (5 mL), with saturated aqueous $NaHCO_3$ (5 mL), with saturated aqueous NaCl (5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to produce the desired opened product **2**. The crude product was purified by chromatography on silica gel using hexanes to produce alkene **2**[11] (112 mg, 100%) as a colorless oil: R*f* 0.54 (hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.20 (m, 5H), 5.80-5.70 (m, 1H), 5.12-4.93 (m, 2H), 2.70-2.61 (m, 2H), 2.33-2.10 (m, 1H), 1.70-1.60 (m, 2H), 1.03 (d, *J* = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 144.3, 129.2, 128.5, 125.5, 112.9, 38.3, 37.3, 33.5, 29.6, 20.2.

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