Cyclopropenyllithiums as a new source of 1,1-bismetalated cyclopropyl derivatives†

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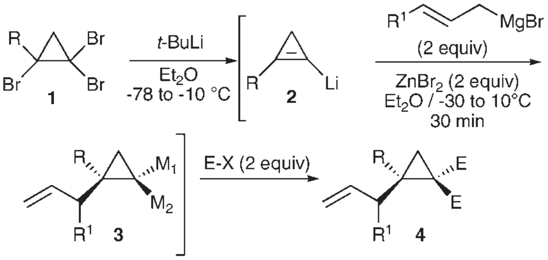
The allylmetalation of functionalised cyclopropenyllithium derivatives leads to the unique formation of 1,1-bismetalated cyclopropyl species that react selectively with different electrophiles.

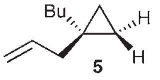
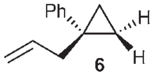
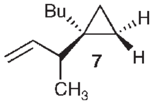
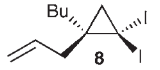
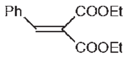
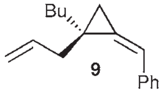
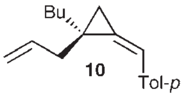
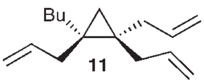
Cyclopropene derivatives are high-energy-possessing and, therefore, extremely reactive molecules with a large spectrum of remarkable activities that extend far beyond simple reactions typical of olefins.[1] Their chemistries have been the subject of numerous reviews and most of their racemic preparations were developed until the mid 1980s.[1] However, in the last few years, strain as a design principle for asymmetric reactions led to a complete renaissance of the field.[2] Indeed, upon breaking the π-bond, the trigonal ring carbons can pyramidalize, thus relieving the additional angle strain that results from the presence in the three-membered ring of carbons that are nominally sp^2, rather than sp^3, hybridized. If such operations can be performed diastereoselectively on already prepared chiral entities,[3] synthetic interests become obvious as a new entry to enantiomerically enriched products. In this context, diastereoselective hydro- and carbometalation on racemic or enantiomerically enriched cyclopropenes have been recently reported by us[4] and others[5] as a powerful and versatile approach to functionalised cyclopropanes. Moreover, carbometalation reaction[6] of unsaturated metal species[7] represents a mild and interesting approach to bismetalated alkane[8] or alkene[9] derivatives. In such a context, we would like to disclose our preliminary results for the first preparation of diastereoselective polysubstituted bismetalated cyclopropyl derivatives.[10] Cyclopropenyllithium **2** is obtained from 1,1,2-tribromocyclopropane **1** (easily prepared by reaction of the corresponding vinyl bromide derivative with bromoform in the presence of cetrimide as phase transfer catalyst)[11] by a successive 1,2-dehalogenation reaction followed by a halogen–lithium exchange as described in Scheme 1. Then, after addition of allylmagnesium bromide and zinc salt,[8] the corresponding bismetalated cyclopropyl species **3** is formed as a stable intermediate (Scheme 1 and Table 1).

As the exact nature of the bismetalated species is still not confirmed either by X-ray analysis (Mg, Zn or Zn, Zn) or by NMR, they will be represented as monomers with M_1 and M_2



Scheme 1

Table 1 Allylmetalation of cyclopropenyllithium **2**

Entry	R	R^1	E–X	Product	Yield[a] (%)
1	Bu	H	H^+		81
2	Ph	H	H^+		75
3	Bu	Me	H^+		65
4	Bu	H	I_2		68
5	Bu	H			60[b]
6	Bu	H	*p*-TolCHO		53[c]
7	Bu	H	allylBr[d]		60

[a] Yields of isolated pure products after purification by column chromatography. [b] Isolated as a mixture of geometrical isomers in a 85 : 15 *Z* : *E* ratio. [c] Isolated as a mixture of geometrical isomers in a 2 : 1 *Z* : *E* ratio. [d] After a transmetalation reaction with $Me_2CuCNLi_2$ in THF.

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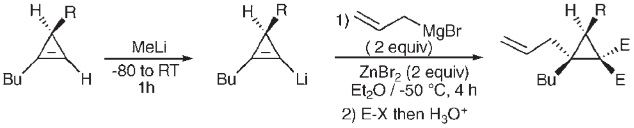
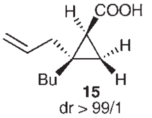
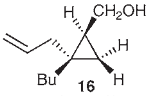
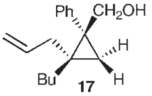
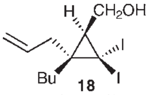
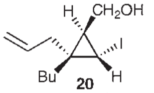
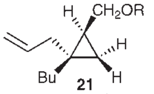
describing the presence of the bismetalated species throughout the manuscript.[12] The allylmetalation occurs rapidly under mild conditions (−30 to −10 °C, 30 min) due to the release of strain. The bismetalated species can be obtained in good yields when R is either an alkyl (Table 1, entry 1) or an aromatic group (Table 1, entry 2). Similarly, the reaction proceeds nicely for the introduction of allyl or crotyl nucleophiles (Table 1, entries 1 and 3, respectively). The presence of 1,1-dimetallic species has been proved by reaction of **3** with iodine (Table 1, entry 4) to lead to the 1,1-diiodo cyclopropane derivative **8**.[13] Alkylidenecyclopropane derivatives **9** and **10** are also obtained by reaction of the bismetalated species with either alkylidenemalonate[14] or aldehyde to give a 85 : 15 and 2 : 1 *Z* : *E* ratio, respectively. Finally, the transmetalation reaction of the bismetalated species **3** into an organocopper species was performed with the help of $Me_2CuCNLi_2$ and further S_N2' reaction with allyl bromide (Table 1, entry 7).[10]

As the diastereoselective allylzincation of substituted γ-heterosubstituted vinylmetal has been successfully performed on (*Z*)-γ-iodoallylic ethers, amines and thioethers,[15] we investigated the diastereoselectivity of the allylzincation of functionalised cyclopropenyllithium derivatives such as **11–14** (Table 2). It should be noted that the enantioselective cyclopropenation of terminal alkynes such as butyne with ethyl diazoacetate in the presence of chiral catalysts leads to 2-substituted-2-cyclopropene carboxylic acid ethyl esters (R = COOEt) in excellent enantiomeric excess.[3] However, the direct metalation of such ester-substituted cyclopropenes usually result in a rapid ring-opening[16] reaction and the solution to this problem was based on the formation of dianions of carboxylic acids **11** (R = COOH),[17] and extended to the formation of **12** and **13** (R = CH_2OH) or protected alcohol **14** [R = $CH_2OC(CH_3)_2OCH_3$], respectively (Table 2). The metalation of **11–14** occurs easily (with 1 and 2 equivalents of RLi[18] for **14** and **11**, **12**, **13**, respectively) and when **11Li** was treated with allylmagnesium bromide and zinc salt, the corresponding cyclopropane **15** was obtained after hydrolysis (see Table 2, entry 1). While the yield is only modest after acidic work up, the reaction is remarkable since it tolerates functionality on the cyclopropenyl ring (the addition specifically occurs on the vinyl lithium moiety and not on the carboxylate anions) and only one diastereoisomer is obtained during the carbometalation reaction.

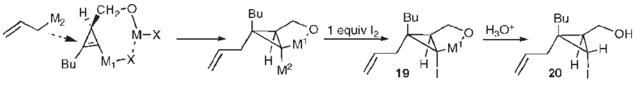
Table 2 Allylmetalation of functionalized cyclopropenyllithium **11**, **12**, **13**, **14**



Entry	R^1	R	E^1–X	E^2–X	Product	Yield[a] (%)
1 (**11**)	COOH	H	H^+	H^+	 **15** dr > 99/1	50
2 (**12**)	CH_2OH	H	H^+	H^+	 **16** dr > 99/1	72
3 (**13**)	CH_2OH	Ph	H^+	H^+	 **17** dr: 4/1	60[b]
4 (**12**)	CH_2OH	H	I_2	I_2	 **18** dr > 99/1	50[c]
5 (**12**)	CH_2OH	H	I_2	H^+	 **20** dr > 99/1	55[bc]
6 (**14**)	CH_2OR^d	H	H^+	H^+	 **21** dr > 99/1	90

[a] Yields of isolated pure products after purification by column chromatography. [b] Stereochemistry of major isomer not determined. [c] Unstable product and slowly decomposes. [d] R = $C(CH_3)_2OCH_3$.

Although the carbometalation reaction starting from the alcohol **12** takes place with a similar diastereoselection (>99 : 1), the reaction is giving a much better yield after treatment with an aqueous solution of HCl (formation of **16**, Table 2, entry 2). However, if the carbometalation is conducted at 0 °C instead of −50 °C, the diastereoisomeric ratio drops dramatically. The stereochemistry of the carbometalation reaction was confirmed by NOE and chemical correlations[19] and could be rationalized by an addition of the allylmetal anti to the metalacycle as described in Scheme 2. The anti-addition was verified when a quaternary stereocenter was present on the cyclopropenyllithium as for **13**. In such case, the allylmetalation is no more diastereoselective since both faces are shielded and the resulting cyclopropane **17** was obtained in a 4 : 1 ratio (Table 2, entry 3). The formation of the gem-bismetallic species has been proved by quenching the intermediate resulting from the carbometalation of **12Li** with I_2 to afford the unstable gem-diiodo cyclopropane product **18**. In the course of our previous studies on the formation of organo *gem*-bismetallic species *via* allylmetalation of metalated unsaturated systems, we have shown that an internal chelation (with a basic functional group) was able to differentiate the reactivity of the two metals of a 1,1-bimetaloalkane and alkene towards two electrophiles. The coordination (or chelation) of the oxygen atom to the metal M_1 decreases the reactivity of the latter towards the first electrophile and thus, the non-chelated metal M_2 reacts preferentially with this electrophile.[20] Therefore, the addition of one equivalent of I_2



Scheme 2

leads to the unique reaction of the non-chelated metal M_2 to give the corresponding cyclopropyl zinc carbenoid **19**[21] that subsequently reacts with the second electrophile such as H^+ to lead to **20** (Scheme 2). In such case, a single diastereoisomer is formed for the creation of three stereogenic centers in the reaction sequence (Scheme 2 and Table 2, entry 5). It should be noted that the selectivity of this reaction is reverse to that reported for the halogenation of cyclopropylmetal reagents, generated *via* allylmetalation of cyclopropenes.[17]

For the creation of carbon–carbon bonds from bismetalated species, a zinc to copper transmetalation is required as described in Table 1, entry 7; when applied to functionalized 1,1-bismetalated cyclopropyl species as generated in Table 2, low yields are obtained. Finally, the best chemical transformation was obtained when cyclopropyl ether **14** was subjected to our metalation/carbometalation conditions. The reaction leads to the corresponding cyclopropane **21** in excellent isolated yields after hydrolysis (Table 2, entry 6).

In conclusion, the allylmetalation of cyclopropenyllithium species is an easy and straightforward way to synthesize the 1,1-bismetalated cyclopropyl moiety. The reactive nature of such entities allows various chemical transformations that can even be diastereoselective when internal chelation is present.

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