Carbenoids

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Mechanism-Driven Elaboration of an Enantioselective Bromocyclopropanation Reaction of Allylic Alcohols

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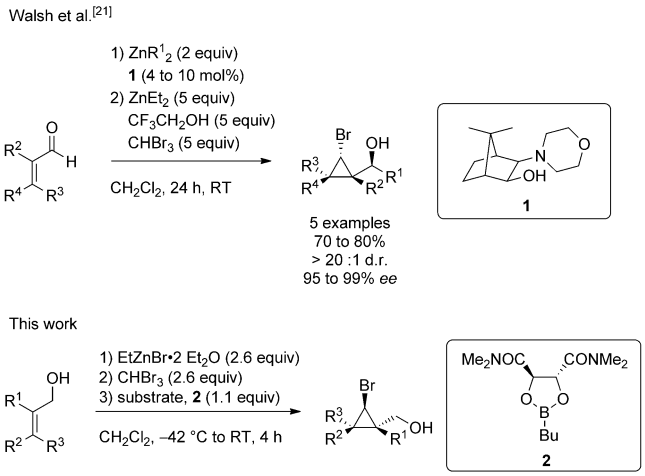
Abstract: *A stereoselective bromocyclopropanation of allylic alcohols using dibromomethylzinc bromide is described. Spectroscopic studies to monitor the formation of transient intermediates not only led to the development of a more-atom-economical halocyclopropanation reaction, but also highlighted the unique role of ether additives in the process. The desired bromo-substituted cyclopropanes were isolated in high yields and excellent diastereo- as well as enantioselectivities using readily available reagents.*

As one of the most used carbocycles for the development of new drugs,[1] the cyclopropane core is a key unit for the pharmaceutical industry.[2] Yet, the synthesis of highly substituted cyclopropanes remains challenging, and new methodologies to access them are needed.[3]

Among the different cyclopropanation approaches, one of the most straightforward methods involves the use of α-substituted zinc carbenoids.[4,5] For example, it has been shown that α-halocarbenoids can deliver enantiomerically pure chloro-[6] and fluorocyclopropanes,[7] which are valuable scaffolds present in numerous natural and synthetic bioactive molecules.[8,9] Iodocyclopropanes can also be obtained by this strategy, thus allowing further derivatization.[10] However, as any iodinated compound, their stability to light and air causes a major shelf-storage issue. In contrast, brominated compounds provide a good compromise between stability and reactivity,[11] and bromocyclopropanes are no exception. They proved to be usable in lithium–halogen exchange reactions,[12] Grignard-reagent formation,[13] elimination and formal substitution,[14] and even radical reactions.[15,16] Despite these broad applications, few efficient methodologies currently exist for the synthesis of enantioenriched bromocyclopropanes with good stereoselectivities. One of the earliest methods involves the selective dehalogenation of dibromocyclopropanes obtained by the reaction of dibromocarbene with various alkenes.[17] While this is a popular strategy, the dehalogenation process is rarely selective and a mixture of the *cis* and *trans* bromocyclopropanes is usually observed.[18,19] Miyano et al. reported the first Furukawa-type bromocyclopropanation of alkenes using what is presumed to be dibromomethyl(ethyl)zinc.[20] However, the reaction requires the presence of oxygen to catalyze the reagent formation as well as the mandatory use of the substrate as the solvent. More recently, Walsh and co-workers reported an elegant diastereoselective bromocyclopropanation of chiral allylic alcohols, generated in situ by an enantioselective MIB-catalyzed (MIB = (2*S*)-3-exo-(morpholino)isoborneol) dialkylzinc 1,2-addition to α,β-unsaturated aldehydes (Scheme 1).[21] In this work, (dibromomethyl)zinc 2,2,2-trifluoroethoxide in excess (5 equiv) was the optimal cyclopropanating reagent.



Scheme 1. Simmons–Smith-type bromocyclopropanations.

Herein, we report a comprehensive spectroscopic study and optimization of a dibromomethylzinc carbenoid formation from readily available reagents, which were employed in a new enantio- and diastereoselective bromocyclopropanation reaction of allylic alcohols. This method yields the desired halogenated carbocycles in unprecedented high yields and with excellent selectivities (Scheme 1).

The preparation of α-halozinc carbenoids (RZnCHIX) typically requires a diiodohalomethane precursor.[6,10a] For example, iodoform is used in the iodocyclopropanation and chlorodiiodomethane leads to chlorocyclopropanes. However, in an attempt to utilize bromodiiodomethane to generate bromocyclopropanes, we surprisingly found that significant amounts of the undesired iodocyclopropane were formed over the desired bromo-substituted product (Scheme 2).[6]

To rationalize these results, two possible scenarios were envisioned (Scheme 3): a) diethylzinc reacts with both the C–

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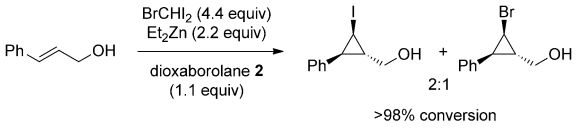
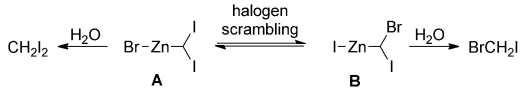


Scheme 2. Initial attempt of bromocyclopropanation with $CHBrI_2$.

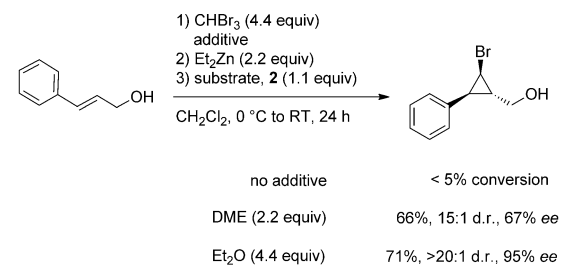


Scheme 3. Halogen scrambling possibly taking place on the (bromoiodomethyl)zinc carbenoid.

I and C–Br bonds leading to a mixture of the reagents **A** and **B**, respectively (thus forming both ethyl iodide and ethyl bromide as by-products); and/or b) the diethylzinc reacts preferentially with the C–I bond but a subsequent halogen scrambling allows the formation of both the (diiodomethyl)-zinc bromide **A** and (bromoiodomethyl)zinc iodide **B**.

To gain further insight into the reactive species generated when diethylzinc is mixed with bromodiiodomethane, we monitored the formation of the reagent by ^{1}H NMR spectroscopy. The first conclusion from this study is that iodoethane was formed exclusively (> 99 %) when diethylzinc was mixed with bromodiiodomethane.[22] This result indicated the strong preference for diethylzinc to react with the C–I bond of the haloform. These results are in agreement with the previous observation made by Nishimura and Furukawa.[23] When 1N HCl was added to this mixture, the signals corresponding to both bromoiodomethane and diiodomethane were detected by NMR spectroscopy. This result can only be obtained if there is a halogen scrambling between **A** and **B**.

To suppress the undesired iodocyclopropanation, bromoform, which is known to react with diethylzinc towards the formation of a reactive zinc carbenoid,[20] was used instead of bromodiiodomethane. We hoped that by modifying Miyano's reaction conditions, the requirement to introduce excess alkene and oxygen/air would be by-passed. The first experiment that was performed consisted of borrowing the previously optimized reaction conditions developed for the enantioselective iodocyclopropanation, but applying them to bromoform instead of iodoform (Scheme 4). Unfortunately, under these reaction conditions, only the starting material was recovered after 24 hours. However, we noted the formation of a thick precipitate upon mixing diethylzinc and bromoform, possibly indicating that the carbenoid was formed but it either completely precipitated in dichloromethane or rapidly decomposed into zinc bromide. To circumvent this issue, several coordinating additives were tested to solubilize and stabilize the zinc carbenoid. In sharp contrast, when 1.0 equivalent of dimethoxyethane (DME) was employed as an additive,[24] the desired bromocyclopropane was obtained in 66 % yield after 24 hours. Unfortunately, the level of stereocontrol was only moderate (15:1 d.r., 67 % *ee*) when using the ligand **2**. Gratifyingly, a subsequent screening of other coordinating solvents revealed that the addition of 2.0 equivalents of Et_2O per zinc atom was optimal, thus yielding the desired bromocyclopropane in 71 % yield, with greater than 20:1 d.r. and 95 % *ee*. Despite the fact that the desired bromocyclopropane product was obtained with high selectivity and yield, the minimization of the number of equivalents of the reagents was addressed to make this transformation more efficient. Under these reaction conditions, more than 4.0 equivalents of the haloform were needed for the reaction to proceed to completion.



Scheme 4. Effects of coordinating ethers on the reactivity and selectivity.

To improve the reaction efficiency, careful ^{1}H NMR monitoring of the reagent formation was undertaken. Figure 1 illustrates the ^{1}H NMR spectrum of a 2:1 mixture of $CHBr_3$ and diethylzinc in the presence of 2.0 equivalents of diethyl ether. The spectrum shows the presence of significant amounts of residual bromoform given the signal at $\delta =$ 6.90 ppm (0.65 equiv out of 2.0 equiv), the formation of bromoethane from the signals at $\delta = 3.43$ and 1.65 ppm (1.3 equiv instead of 2.0 equiv), and a new signal at $\delta =$ 5.22 ppm, which was attributed to the carbenoid C–H bond. The formation of the latter was supported by the disappearance of the C–H signal upon adding water, which gave rise to a new signal corresponding to dibromomethane. Intriguingly, about 30 % of the ethyl groups from the initial amount of diethylzinc used cannot be accounted for. A close look at the products indicated that propene was also formed in the process. To gain further insight about the formation of the reagent, its formation was monitored by ^{1}H NMR spectroscopy. Aliquots taken after 10, 15, and 20 minutes indicated

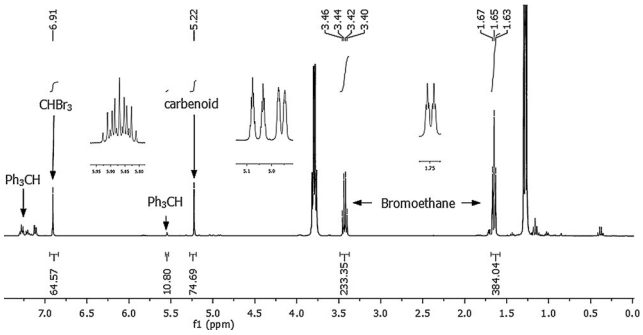
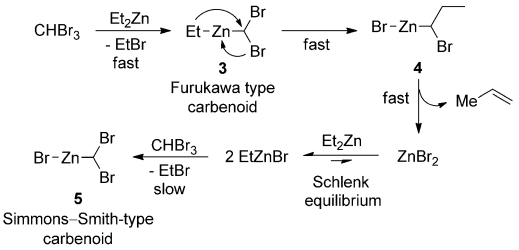


Figure 1. ^{1}H NMR spectrum of a 1:2:2 mixture of $Et_2Zn/CHBr_3/Et_2O$ in CD_2Cl_2 (0.4 M), −42 °C to RT, 10 min (0.1 equiv of triphenylmethane relative to the amount of Et_2Zn was added as the internal standard). Zooms represent propene signals.

that, as expected, the amount of zinc carbenoid increased over time. No formation of tetrabromoethylene or dibromomethane was observed, thus implying that the carbenoid was stable. However the ratio EtBr/$ZnCHBr_2$ decreased unexpectedly over time, thus indicating that EtBr was initially formed much faster than "$ZnCHBr_2$". Furthermore, a close look at the products formed in Figure 1 indicated that significant amounts of propene were also formed in the process. All these observations led to the conclusion that a significant amount of bromoform was initially wasted to form propene and zinc bromide by the 1,2-ethyl migration depicted in Scheme 5. α-Alkylzinc carbenoids are known to



Scheme 5. Proposed mechanism for the formation of the active dibromomethylzinc reagent.

be unstable and undergo rapid decomposition to the alkene by 1,2-alkyl shift. This decomposition pathway for the Furukawa carbenoid has already been spectroscopically established.[26] A subsequent Schlenk equilibration between zinc bromide and diethylzinc generated ethylzinc bromide, which could then react with the second equivalent of bromoform to generate the Simmons–Smith-type carbenoid (Scheme 5).

The formation of propene was highlighted if 1.0 equivalent of bromoform was slowly added to 1.0 equivalent of diethylzinc. Under these reaction conditions, a large amount (23%) of propene was detected by ^{1}H NMR spectroscopy along with less than 10% of the desired carbenoid signal.[27] This experiment clearly shows the instability of the Furukawa-type reagent and how fast the 1,2-ethyl migration is. On this basis, it was envisioned that the generation of the reagent using ethylzinc bromide instead of diethylzinc should lead to a more efficient way to access the active cyclopropanating reagent.

The simplest strategy for the formation of ethylzinc bromide in CH_2Cl_2 is the reaction of 1.0 equivalent of Et_2Zn with 1.0 equivalent of bromine. The subsequent addition of 1.0 equivalent of $CHBr_3$ should generate the desired Simmons–Smith-type carbenoid. Gratifyingly, ^{1}H NMR analysis showed this procedure yielded the desired carbenoid in about 80% yield, without the need for a large excess of bromoform (Figure 2). However, trace quantities of propene were still observed by this protocol and attempts to completely suppress it through reverse addition of reagents (ethylzinc bromide added to bromoform) were unfruitful. Further fine-tuning of the reaction conditions for the bromocyclopropanation of cinnamyl alcohol revealed that using 2.6 equivalents of Et_2Zn, Br_2, and $CHBr_3$ were optimal. Full conversion of the

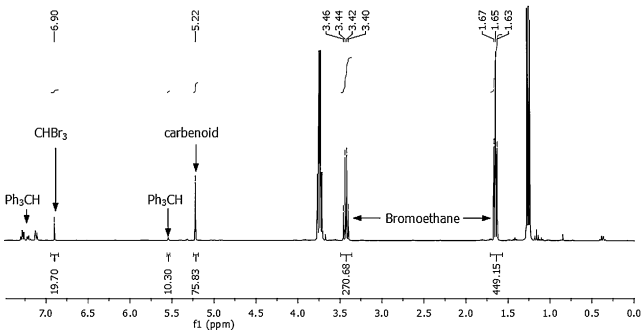
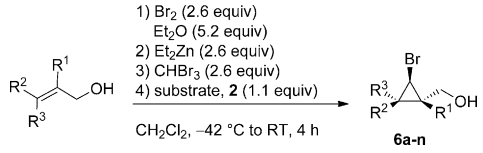


Figure 2. ^{1}H NMR spectrum of a 1:1:1:2 mixture of Br_2/Et_2Zn/$CHBr_3$/Et_2O in CD_2Cl_2 (0.4 M), −42 °C to RT, 10 min (0.1 equiv of triphenylmethane—relative to the amount of Et_2Zn—was added as the internal standard).

starting material was observed after only four hours of reaction time, thus giving the desired product in 88% yield with high stereoselectivities (>20:1 d.r., 95% *ee*).

With the optimal reaction conditions in hand, we next examined the scope of the allylic alcohol component in this new bromocyclopropanation reaction (Table 1). As illustrated, moderate to high yields, and excellent selectivities were achieved for all the substrates tested. It was observed that the presence of a methyl substituent on the aryl group of the cinnamyl alcohol substrate had little effect on either the yield or selectivity outcome of the reaction (entries 1–3). However, when the phenyl moiety is replaced by a more sterically demanding mesityl group, a marginal reduction in yield was obtained (81%), however enantioselectivity was slightly improved to 98% *ee* (entry 4). Importantly, both electron-withdrawing and electron-donating substituents are tolerated around the aryl ring, thus giving good yields and excellent selectivity in all cases (entries 5 to 9). Entries 10 and 12 show that alkyl substituents are tolerated as well, with only minor reductions of yields and still excellent stereoselectivities. As expected, a *cis* allylic alcohol is a more challenging substrate as opposed to a *trans*-allylic alcohols. Nonetheless a substrate of the former class still yields the desired bromocyclopropane in acceptable yield and stereoselectivity (54% yield, 5:1 d.r., 98% *ee*, entry 11). Exchange of the aromatic group for a cyclohexane moiety still allows access to the desired product with excellent stereoselectivity, although in reduced yield (57% yield, >20:1 d.r., 94% *ee*, entry 13). This reduced yield is reasoned to be due to steric effects in which the cyclohexane moiety inhibits approach of both the chiral auxiliary and the carbenoid in the transition state. Finally, entry 14 demonstrates that the newly developed protocol is not only limited to disubstituted alkenes, as trisubstituted alkenes are also viable substrates, thus giving rise to high yields and stereoselectivity for the corresponding bromocyclopropane under the optimized reaction conditions. To avoid the use of bromine, it would also be possible to exploit the Schlenk equilibrium between 1.0 equivalents of zinc bromide and 1.0 equivalent of diethylzinc to yield 2.0 equivalents of ethylzinc bromide. Using this protocol, the enantioselective bromocyclopropanation of cinnamyl alcohol yielded the desired compound in nearly quantitative

Table 1: Scope of the monobromocyclopropanation reaction.



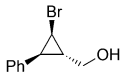
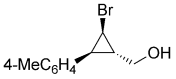
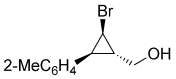
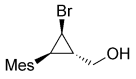
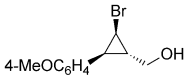
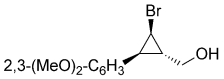
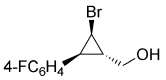
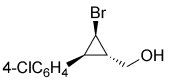
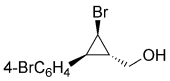
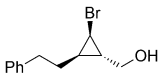
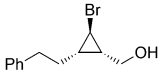
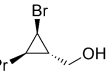
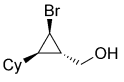
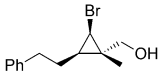
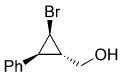
Entry	Product	Yield [%]	d.r.[a]	*ee* [%]
1	 **6a**	88	>20:1	95
2	 **6b**	85	>20:1	94
3	 **6c**	88	>20:1	96
4	 **6d**	81	>20:1	98
5	 **6e**	83	>20:1	95
6	 **6f**	66	>20:1	96
7	 **6g**	74	>20:1	94
8	 **6h**	80	>20:1	96
9	 **6i**	89	>20:1	96
10	 **6j**	79	>20:1	95
11	 **6k**	54	5:1	98
12	 **6l**	81	>20:1	98[b]
13	 **6m**	57	>20:1	94[c]
14		90	>20:1	94

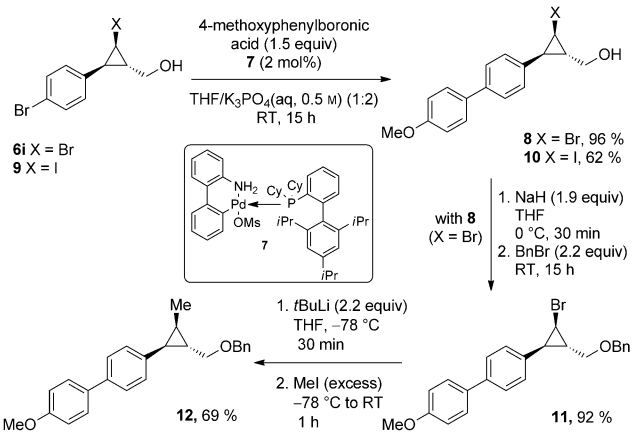
Table 1: (Continued)

Entry	Product	Yield [%]	d.r.[a]	*ee* [%]
15[d]	**6n**  **6a**	92	>20:1	98

[a] Determined by ^{1}H NMR analysis of the crude mixture. [b] Determined after benzylation of the alcohol. [c] Determined after benzoylation of the alcohol. [d] Procedure: 1. $ZnBr_2$ (1.3 equiv), Et_2O (5.2 equiv); 2. Et_2Zn (1.3 equiv); 3. $CHBr_3$ (2.6 equiv); 4. allylic alcohol, **2** (1.1 equiv); CH_2Cl_2, −42 °C to RT, 4 h.

yield and with excellent selectivities (entry 15). In addition, the mesityl-substituted bromocyclopropane **6d** furnished single crystals suitable for X-Ray analysis, thus confirming the absolute stereochemistry of the product.[28]

To illustrate the utility of bromocyclopropanes for late-stage diversification, the compound **6i** was engaged in a Suzuki cross-coupling reaction using Buchwald's G3-Xphos precatalyst **7** (Scheme 6).[29] This compound is an



Scheme 6. Derivatization of the bromocyclopropane **6i** and comparison with the iodinated analogue. THF = tetrahydrofuran.

interesting example because of the presence of two functionalization sites: the first one on the cyclopropane, the other on the phenyl substituent. We were glad to obtain selective cross-coupling on the arene, with the bromocyclopropane remaining untouched. Conversely, the iodinated analogue **9** led to **10** in only 62%. After protection of the free alcohol (**11**), we were able to perform the alkylation of the bromocyclopropane by a lithium–halogen exchange followed by a quench with methyl iodide (see **12**) as a simple proof of concept.

In conclusion, we have described a protocol for the efficient, enantioselective bromocyclopropanation of allylic alcohols. In all cases, unprecedentedly high yields and excellent stereoselectivities were obtained in a single step. A comprehensive study of the nature and formation mechanism of the reactive carbenoid allowed the elaboration of the fully optimized protocols and led to the development of more-atom-economic reaction conditions than previously de-

scribed, in a very short reaction time. Efforts are currently underway towards achieving full and irrefutable evidence concerning the identity of the active carbenoid. This work will be reported in due course.

Acknowledgements

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Keywords: cyclopropanes · carbenoids · NMR spectroscopy · reaction mechanisms · zinc

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