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Graphical Abstract

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Rana Chatterjee, Satyajit Samanta, Anindita Mukherjee, Sougata Santra, Grigory V. Zyryanov, Adinath Majee*
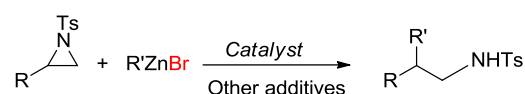
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Use of allylzinc halide as a source of halide: differential addition of nucleophiles to Ts-aziridines and aldehydes under similar reaction conditions
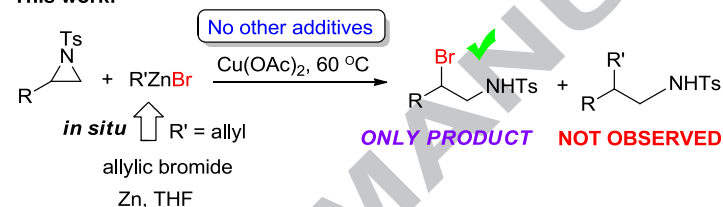
Rana Chatterjee,[a] Satyajit Samanta,[a] Anindita Mukherjee,[b] Sougata Santra,[b] Grigory V. Zyryanov,[b,c] and Adinath Majee[a], *

[a] *Department of Chemistry; Visva-Bharati (A Central University), Santiniketan 731235, India*

[b] *Department of Organic and Biomolecular Chemistry, Chemical Engineering Institute, Ural Federal University, 19 Mira Street, 620002, Yekaterinburg, Russian Federation*

[c] *I. Ya. Postovskiy Institute of Organic Synthesis, Ural Division of the Russian Academy of Sciences, 22 S. Kovalevskoy Street, 620219 Yekaterinburg, Russian Federation*

ARTICLE INFO

ABSTRACT

We have observed that the allylic zinc halide under identical reaction conditions acts in different modes for different electrophiles. For Ts-aziridines the halide part of the allylic halide has been introduced as a nucleophile and for the carbonyl compounds the simple allylation reaction occurs. To the best of our knowledge this is the first report where the allylic zinc halide is the source of halide acting as nucleophile. The main advantages of the present procedure are easy to handle, no need of inert atmosphere, mild reaction conditions, and applicability to a wide variety of substrates for aziridines and carbonyl compounds.

The basic difference between the Barbier [1] and the Grignard reaction [2] is that the former is a single step one-pot reaction whereas the later, composes of a two-step procedure that requires the formation of an alkyl metal in the first step followed by its reaction with a carbonyl or targeted compound in the second step. Both of these reactions are well studied since their innovation. Particularly, allylation reaction has been studied extensively in Barbier concept, due to the high reactivity of allylic halides towards many low valent metals like Li [3], Mg [4], Mn [5], Zn [6], Sn [7], Pb [8], Bi [9], Ce [10], In [11], and many others [12] and the characteristic features of each metal has been well documented. It is worthy to mention that both in Barbier and Grignard concept we use the alkyl part as a nucleophilic source for the addition reaction assuming the *in situ* formation of organometallic reagent. To the best of our knowledge there is no such report till date where the halide portion has been used as a source of nucleophile for addition reactions from an organometallic reagent by Barbier or Grignard concept.

Since two decades, our group is actively engaged in developing new methodologies for different useful reactions in organic synthesis and recently with aziridines giving special emphasis on green chemistry [13]. Herein, we wish to report a very much interesting and new finding of Ts-aziridine versus simple carbonyl compounds under similar reaction conditions. We have observed that in cases of Ts-aziridine the halide part of

the allylic halide has been added as a nucleophile while for the carbonyl compounds the simple allylation reaction has occurred (Scheme 1) under similar reaction conditions.
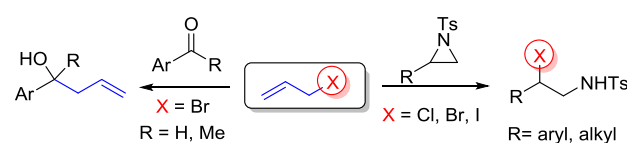

**Scheme 1** Allylation and halogenations reactions of carbonyl compounds and Ts-aziridines respectively.

Initially we were interested in the simple nucleophilic ring opening of aziridine by allylation for which, *N*-tosylaziridines **1a** (1 mmol) and allylic bromide **2a** (3 mmol) were taken as substrates in presence of zinc dust (1 mmol) as reported by Doyle *et al.* [14] at room temperature using Cu(OAc)$_2$ as an additive. We have observed in change of the starting material after 12 h. Afterwards we carried out the same reaction at 60 °C and observed a considerable conversion of aziridine to our expected ring opening product. After careful work up and purification, surprisingly we found that the corresponding ring opening product of aziridine under these conditions using the additive Cu(OAc)$_2$ is not the allylation product rather it is the ring opening product of aziridine by bromide as a nucleophile (Scheme 2).

* Corresponding author. e-mail: adinath.majee@visva-bharati.ac.in

A. G. Doyle's work:
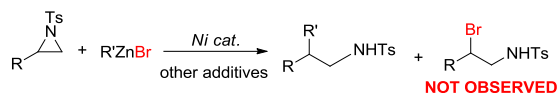
Our work:
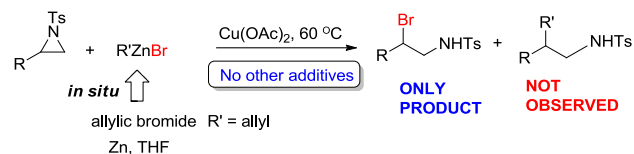
Scheme 2. Selectivity of nucleophile for aziridine ring-opening.

In view of complete understanding and optimizing this observation the reaction was carried out in various organic solvents such as THF, DMSO, DMF, acetonitrile, 1,2-DCE, toluene, 1,4-dioxane, ethanol, etc. at 60 °C temperature. The results are summarized in Table 1. Either moderate or trace amount of the desired product was observed in DMSO, DMF, acetonitrile, 1,2-DCE, toluene, 1,4-dioxane and ethanol (Table 1, entries 2-8) as the solvent. Whereas the targeted product was obtained with maximum yield (84%) in THF solvent at 60 °C for 6 h (Table 1, entry 1), no significant amount of the desired product was formed when the reaction was carried out at room temperature (Table 1, entry 10). The best effective reaction temperature was found to be 60 °C (Table 1, entry 1) and the yield of the reaction did not improve by increasing the reaction time from 6 h to 9 h (Table 1, entry 11). Increase of the temperature was not beneficial (Table 1, entry 12) while decreasing the reaction temperature decreased the yield of the reaction (Table 1, entries 13). The use of Cu(OAc)$_2$ (10 mol%) gave the best result with excellent yield. The reaction has also been carried out by using other copper salts (10 mol% each) such as CuCl$_2$, CuI, CuBr$_2$, Cu(OTf)$_2$, Cu$_2$O, CuO nano etc. (Table 2) but they were not so efficient as Cu(OAc)$_2$. Increasing the amount of Cu(OAc)$_2$ from 10 to 20 mol% resulted no significant change in the formation of product (Table 2, entry 8). On decreasing the amount from 10 mol% to 5 mol% there was notable decrease in product formation (Table 2, entry 9). The reaction did not proceed at all without any catalyst (Table 2, entry 10). In addition, Zn dust also made a vital contribution for the reaction to proceed (Table 3, entry 1,). There is no reaction without zinc dust (Table 3, entry 2) and use of indium powder instead of Zn dust did not afford any product (Table 3, entry 3). Use of other allylic bromides like crotyl bromide or cinnamyl bromide gave no response as a source of bromine (Table 4, entry 2, entry 3). Accordingly, our final optimized reaction condition was achieved using *N*-tosylaziridine (1 mmol) with allylic bromide (3 mmol) in the presence of 10 mol% copper acetate, Zn dust (1 mmol) and THF solvent at 60 °C temperature to give the corresponding halogenated product under ambient air.

Table 1 Screening of the solvent effects.[a]

Entry	Solvents (2 mL)	Yields[b] (%)
1	THF	84
2	DMSO	32
3	DMF	Trace
4	CH$_3$CN	29
5	1,2-DCE	51
6	Toluene	35
7	1,4-Dioxone	42
8	EtOH	18
9	-	0
10[c]	THF	Trace
11[d]	THF	83
12[e]	THF	80
13[f]	THF	62

[a] Reaction conditions: A mixture of **1a** (1 mmol) and **2a** (3 mmol) was heated at 60 °C for 6 h in presence of 10 mol% Cu(OAc)$_2$ and 1 mmol of Zn dust.

[b] Isolated yields.

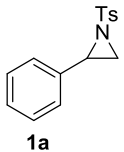[c] Reaction was carried out at room temperature.

[d] Reaction time 9 h.

[e] Reaction was carried out at 80 °C.

[f] Reaction was carried out at 50 °C.

Table 2. Effects of various copper catalysts.[a]

Entry	Catalyst (mol%)	Yields[b] (%)
1	Cu(OAc)$_2$ (10)	84
2	CuCl$_2$ (10)	67
3	CuI (10)	56
4	CuBr$_2$ (10)	69
5	Cu(OTf)$_2$ (10)	48
6	Cu$_2$O (10)	40
7	CuO nano (10)	62
8	Cu(OAc)$_2$ (20)	84
9	Cu(OAc)$_2$ (5)	65
10	-	0

[a] Reaction conditions: A mixture of **1a** (1 mmol) and **2a** (3 mmol) was heated in THF (2 mL) at 60 °C for 6 h in presence of different copper catalysts and 1 mmol of Zn dust.

[b] Isolated yields.

Table 3. Effects of other metal on the halogenation reaction.[a]

Entry	Metal	Yields[b] (%)
1	Zn dust	84
2	-	0
3	Indium dust	Trace

[a] Reaction conditions: A mixture of **1a** (1 mmol) and **2a** (3 mmol) was heated in THF (2 mL) at 60 °C for 6 h in presence of 10 mol% Cu(OAc)$_2$ and 1 mmol of different additives.
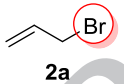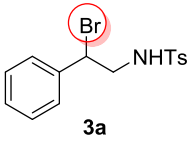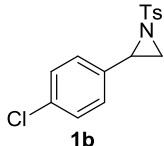
[b] Isolated yields.

Table 4 Effects of different allylic bromides on the halogenation reaction.[a]

Entry	R	Yields[b] (%)
1	H	84
2	CH$_3$	NR

| 3 | Ph | NR |
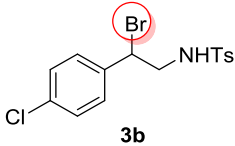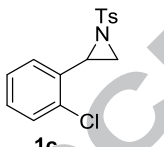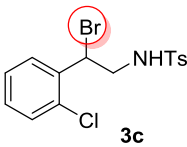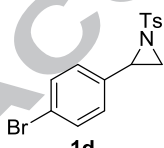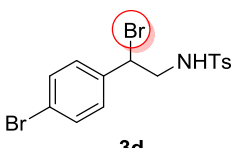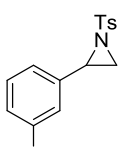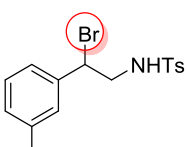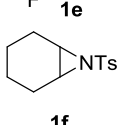
After optimizing the reaction conditions, we explored the scope of this reaction (Table 5). At first, our attention was focused on the use of different aziridine systems with various allylic halides to prove the general applicability of the reaction conditions and the results are summarized in Table 5. It was observed that allylic br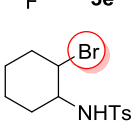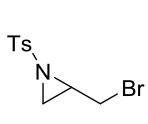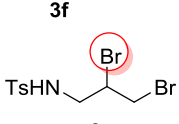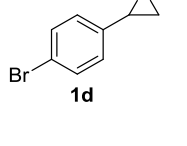omide, allylic chloride and allylic iodide reacted efficiently with various aziridines to afford the desired products with good yields under the present reaction conditions. Simple phenyl *N*-tosylaziridine (**1a**) reacted well with allylic bromide to give the desired product with good yield (**3a**). Similarly, aryl *N*-tosylaziridine substituted with chloro- in the benzene ring was found quite effective to afford the desired products (**3b** and **3c**) with excellent yield. Aziridines, substituted by other halogens (such as –Br, -F) underwent smooth reactions with allylic bromide which highlighted the general applicability of this reaction (**3d** and **3e**). In addition, the aliphatic aziridine systems were also investigated under the present reaction
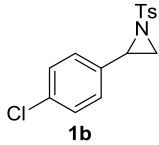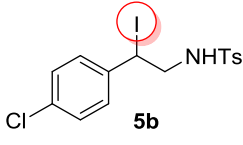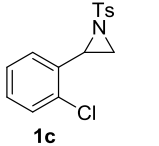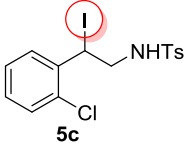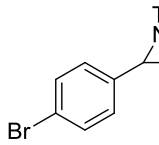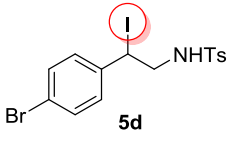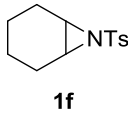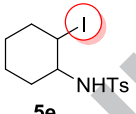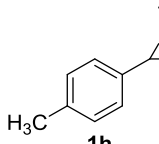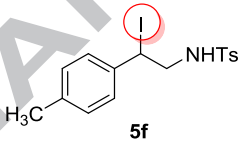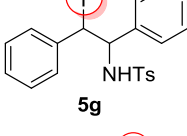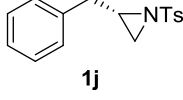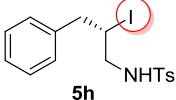
conditions and reacted smoothly with allylic bromide to afford the brominated amines (**3f** and **3g**). Next, we turned our attention using another allylic halide namely allylic chloride with various substituted aziridine systems. N-tosylaziridine substituted with various functionalities (such as –Cl, -Br) at the benzene ring underwent smooth reaction (**4a**-**4d**). Aliphatic aziridine also reacted smoothly with allylic chloride to give the desired chlorinated amine (**4e**) with good yield. We have successfully used allylic iodide to synthesize the corresponding compounds (**5a-5f**) which increases the scope of this transformation. Both aryl *N*-tosylaziridine (**1a**) and chloro- and bromo-substituted aryl *N*-tosylaziridine reacted smoothly with good yields (**5b-5d**). Aliphatic aziridine system also gave the desired product (**5e**). However, *N*-tosylaziridine with electron-donating group like methyl (**1h**) did not react with all three allylic halides under the optimized reaction conditions. Again, *N*-tosylziridines from *cis*-stilbene (**1i**) and another enantiomerically pure (*s*)-2-benzyl-1-tosylaziridine (**1j**) are also inert under the present reaction conditions.

The present protocol has also been examined for epoxides and it is worthy to mention that styrene epoxide (**1k**) reacted smoothly with these three allylic halides (Table 6); yielding the corresponding products **6a**, **6b** and **6c** in 77%, 69% and 80% yields, respectively.

Table 5 Scopes and limitations of the present protocol.[a]

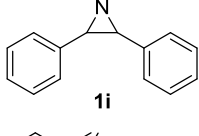| Entry	Aziridines (**1**)	Allylic halides (**2**)	Products	Yields[b] (%)
1	**1a**	**2a**	**3a**	84
2	**1b**	**2a**	**3b**	86
3	**1c**	**2a**	**3c**	79
4	**1d**	**2a**	**3d**	82
5	**1e**	**2a**	**3e**	80
6	**1f**	**2a**	**3f**	73
7	**1g**	**2a**	**3g**	70
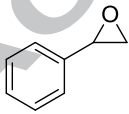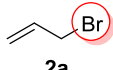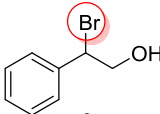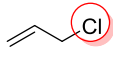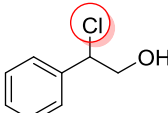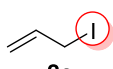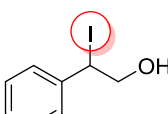
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8	**1h**	**2a** / **3h**	NR
9	**1i**	**2a** / **3i**	NR
10	**1j**	**2a** / **3j**	NR
11	**1a**	**2b** / **4a**	79
12	**1b**	**2b** / **4b**	80
13	**1c**	**2b** / **4c**	75
14	**1d**	**2b** / **4d**	77
15	**1f**	**2b** / **4e**	71
16	**1h**	**2b** / **4f**	NR
17	**1i**	**2b** / **4g**	NR
18	**1j**	**2b** / **4h**	NR
19	**1a**	**2c** / **5a**	86

Entry	Aziridine	Allylic Halide	Product	Yield (%)
20	**1b**	**2c**	**5b**	87
21	**1c**	**2c**	**5c**	82
22	**1d**	**2c**	**5d**	84
23	**1f**	**2c**	**5e**	76
24	**1h**	**2c**	**5f**	NR
25	**1i**	**2c**	**5g**	NR
26	**1j**	**2c**	**5h**	NR

[a] Reaction conditions: A mixture of aziridine (**1**, 1 mmol) and allylic halide (**2**, 3 mmol) was heated in THF (2 mL) at 60 °C for 6 h in presence of 10 mol% Cu(OAc)$_2$ and 1 mmol of Zn dust.

[b] Isolated yields.

Table 6 Scope of the epoxide in the reaction with allylic halides.[a]

Entry	Epoxide	Allylic Halides	Products	Yields[b] (%)
1	**1k**	**2a**	**6a**	77
2	**1k**	**2b**	**6b**	69
3	**1k**	**2c**	**6c**	80

[a] Reaction conditions: A mixture of epoxide (**1k**, 1 mmol) and allylic halide (**2**, 3 mmol) was heated in THF (2 mL) at 60 °C for 6 h in presence of 10 mol% Cu(OAc)$_2$ and 1 mmol of Zn dust.

[b] Isolated yields.

All of the known synthesized compounds have been characterized by spectral data and the new compounds by spectral and analytical data. X-ray crystallographic analysis of *N*-(2-chlorocyclohexyl)-4-methylbenzenesulfonamide (**4e**) was performed to confirm the structure of the product as shown in Figure 1 [15]. The reaction conditions were mild enough and gave no decomposition of the products or polymerization of the starting materials. We have not observed any by-products for all the reaction combinations giving rise to high yields of desire products and regioselectivity of the protocol. In all the cases the halide part has been introduced as a nucleophile.

Before coming to any conclusion based on the above observation, we thought to explore the same reaction conditions using the carbonyl compounds where the halide addition in the carbonyl functionality is not usual. To our delight we observed the expected result and got the homoallyllic alcohol as the sole product (Table 7). First, we have tested various aryl aldehydes substituted with various functionalities. Both electron-donating as well as electron-withdrawing substituents afforded the desired

allylation products (**7a-7e**) with excellent yields. Next we have also examined few acetophenone derivatives which underwent allylation reaction in very good yields (**7f-7h**).
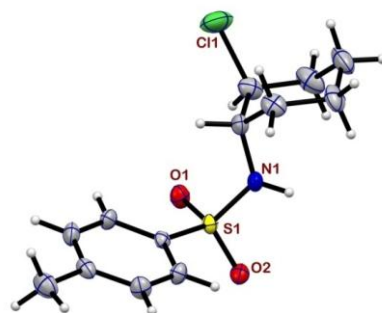
Figure 1. X-ray crystal structure of *N*-(2-chlorocyclohexyl)-4-methylbenzenesulfonamide (**4e**).

Table 7. Reaction of aldehydes and ketones with allylic bromide.[a]

Entry	Carbonyls	Allylic halide	Product	Time (h)	Yields[b] (%)
1	**1l**	**2a**	**7a**	2	88
2	**1m**	**2a**	**7b**	2	85
3	**1n**	**2a**	**7c**	2	86
4	**1o**	**2a**	**7d**	2	82
5	**1p**	**2a**	**7e**	2	85
6	**1q**	**2a**	**7f**	12	86
7	**1r**	**2a**	**7g**	12	83
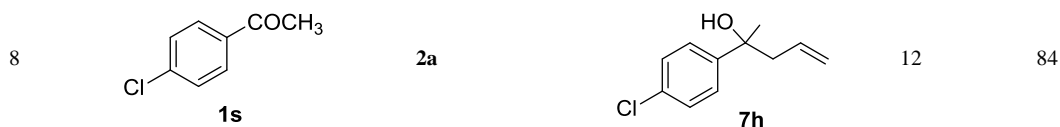
8   **1s** (4-chloroacetophenone)   **2a**   **7h** (1-(4-chlorophenyl)-1-methyl-3-buten-1-ol)   12   84

It is worthy to mention that we have optimized the reaction time (Table 1) using only allyl bromide and within 6 h the reaction completed. We have found the same reaction time for allyl chloride as well as iodide also. So, from this observation we may conclude that under the reaction conditions zinc allylic halide possesses ambident nucleophilic character where both the allylic and halide are active nucleophile which is not observed usually. The addition of the zinc allylic halide with these two-different species may be explained from a literature survey [6]. The zinc allylic halide is formed under the experimental conditions and the Cu(OAC)$_2$ acts as the catalysis to activate the carbonyl group as well as aziridine ring. In case of carbonyl compound two competitive nucleophiles may add but as the addition of halide is not thermodynamically favorable due to the elimination of hydrogen halide from the gem halohydrin, the resulting product is the homoallylic alcohol; whereas, in case of aziridines, the halide ion is better nucleophile. Thus, the halide ion readily attacks the available electrophilic carbon in the aziridine as the zinc allylic species is relatively bound and produce the corresponding nucleophilic ring-opening product of aziridine [16] in presence of Lewis acid. Thus, the probable mechanism of this observation is described in Scheme 3.
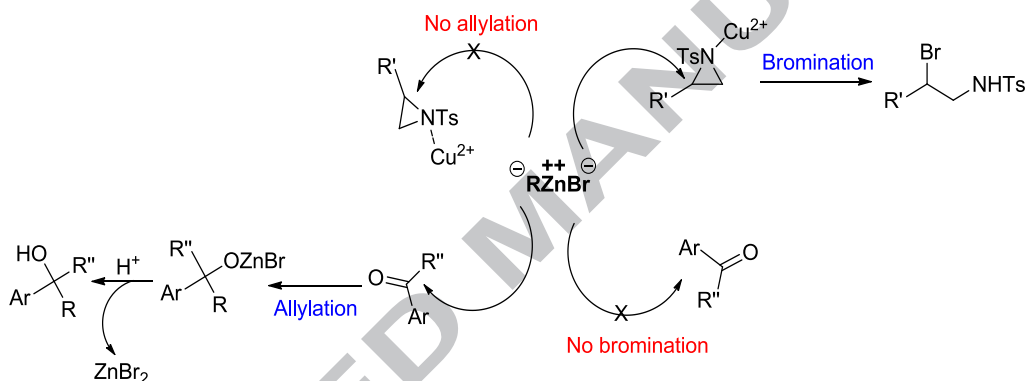
Scheme 3. Proposed reaction mechanism.

From the above observation we can conclude that the zinc allylic halide under identical reaction conditions may produce two effective nucleophiles which are very reactive and act in differential mode for different electrophiles. Usually, under these reaction conditions always the acting nucleophile is the allylic part as reported in the literature even in case of aziridines. To the best of our knowledge this is the first report where zinc allylic halide is the source of halide. The reaction procedure is very easy to handle there is no need of inert atmosphere, the condition is mild, and applicable for a wide variety of substrates for aziridines and carbonyl compounds. Thus, we hope that this observation will be very useful for synthetic organic communities.

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Highlights

- The allylic zinc halide acts in different modes for different electrophiles.
- Zinc alyllic halide is the source of halide in aziriding ring-opening.
- A probable reaction mechanism was proposed.
- This approach bears broad substrate scopes for aziridines and carbonyls.