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Selectivity aspects of the ring opening reaction of 2-alkenyl aziridines by carbon nucleophiles

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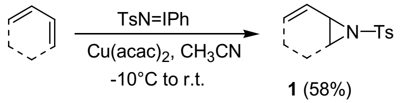
Abstract—A series of common organometallic reagents were used in the reaction with an acyclic and a cyclic activated 2-alkenyl aziridines and the selectivity aspects for each aziridine was addressed.

Aziridines have emerged as valuable synthetic intermediates in a plethora of useful transformations.[1] In this context the ring opening reactions of saturated aziridines have been intensively studied.[2] However, the ring opening of 2-alkenyl aziridines did not receive the same attention. Among the publications dedicated to this matter, only three deal with organometallic reagents.[3] None of them make a comparison between different organometallics, and only one use a structurally simple aziridine,[3d] so avoiding the interference of other groups in the reactivity and the selectivity of the 2-alkenyl aziridine system.

In this work, two structurally simple 2-alkenyl aziridines acyclic **1** and cyclic **2** were reacted with routinely used organometallic reagents, such as lithium, magnesium, copper and zinc species,[4] in order to establish the preference for a S_N2 or a S_N2' ring opening process, as well as the stereoselectivity of each reaction.

Aziridines **1** and **2** were prepared by the copper promoted aziridination of, respectively, butadiene and cyclohexadiene with TsN=IPh, using a variant[5] of the original published protocol (Scheme 1).[6]



1 (58%)
2 (54%)

Scheme 1. Synthesis of 2-alkenyl aziridines.[7]

Initially, the acyclic alkenyl aziridine **1** was reacted under several reaction conditions with *n*-butyl organometallics. As an ambident electrophile, it is expected that aziridine **1** would lead to a mixture of products due to S_N2 *like* (**3** and **4**) and S_N2' *like* (**5**) ring opening processes (Table 1).

Buthyllithium alone (Table 1, entry 1) or in combination with HMPA (Table 1, entry 2) did not afford the desired ring opening products, whereas in combination with 20 mol % of Cu(I) salts the reaction proceeded smoothly with a good S_N2' selectivity but with poor stereoselectivity of the double bond formation (Table 1, entries 3–5). Butyl magnesium bromide consumed the acyclic aziridine with low regioselectivity, favouring the S_N2 ring opening process (Table 1, entry 6). As observed for the lithium series, the combination of the Grignard reagent with Cu(I) salts highly improved the selectivity of the reaction in favour of the S_N2' process, with better *E*-stereoselectivity than for the organolithium series (Table 1, entries 7–9). Lithium and magnesium cyanocuprates reacted cleanly with **1** with very high S_N2' selectivity. The lower-order cyanocuprates were more selective than the Lipshutz cuprates, and the gegenion influenced the reaction stereoselectivity, favouring the formation of *E*-alkenes (Table 1, entries 10–13). When the gegenion was magnesium bromide the selectivities were lower

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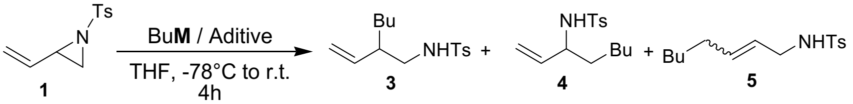
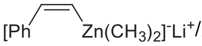
Table 1. Experimental conditions and selectivities obtained for the reactions with 2-alkenyl aziridine **1**[8]



Entry	*n*-BuM/additive	Conversion	S_N2':S_N2 ratio (*E*/*Z* ratio)[a]
1	BuLi	—	—[b]
2	BuLi/HMPA (1 equiv)	—[c]	—
3	BuLi/CuI (20 mol %)	57	11.5:1 (3:1)
4	BuLi/CuCN (20 mol %)	42	13.2:1 (2.6:1)
5	BuLi/Li_2CuCl_4 (20 mol %)	53	15.7:1 (2.0:1)
6	BuMgBr	98	1:1.4 (2.7:1)
7	BuMgBr/CuI (20 mol %)	98	12:1 (4.7:1)
8	BuMgBr/CuCN (20 mol %)	>99	>100:1 (1.7:1)
9	BuMgBr/Li_2CuCl_4 (20 mol %)	98	21:1 (3.7:1)
10	BuCuCNLi	96	183:1 (3.2:1)[d]
11	$Bu_2CuCNLi_2$	>99	19:1 (13.7:1)[e]
12	BuCuCN(MgBr)	>99	60:1 (1.6:1)[f]
13	$Bu_2CuCN(MgBr)_2$	>99	38:1 (1.6:1)
14	BuZnCl·LiCl	—	—[b]
15	BuZnBr·LiBr	—	—[b]
16	$[BuZn(CH_3)_2]^-Li^+$	—	—[b]
17	$[BuZn(CH_3)_2]^-Li^+$/MeCuCNLi (10 mol %)	97	>100:1 (5:1; Bu transfer) >100:1 (3.5:1; Me transfer)
18	 $[Ph$ $Zn(CH_3)_2]^-Li^+$/MeCuCNLi (10 mol %)	94	1:0 (3.8:1)

[a] The isomeric ratio was determined from the crude reaction mixture after work-up and comparison with pure (2*Z*)-(**5a**) and (2*E*)-1*N*-(*p*-toluenesulfonamido)-octene (**5b**) by GC–MS.

[b] The starting aziridine was recovered unchanged.

[c] A complex mixture of products was obtained.

[d] 84% isolated yield.

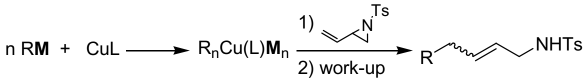
[e] 81% isolated yield (see also Ref. 10).

[f] 74% isolated yield, **5a** and **5b** were isolated and separated by flash chromatography (SiO_2) doped with $AgNO_3$ (Ref. 9) using a gradient of hexanes to AcOEt/hexanes (3:1).

than those observed for lithium gegenion. In the case of lithium cuprates, although the lower order cyanocuprates were more S_N2' selective than the Lipshutz cuprates, the latter led to the best *E*-stereoselectivity of the studied series (*E*:*Z* = 13.7:1, entry 11).[10]

The interaction of **1** with organozinc reagents was also evaluated. Chloro and bromobutylzinc were not reactive enough to consume **1**, which remained intact in the reaction media, even after 4 h (Table 1, entries 14 and 15). Recently, Lipshutz et al. reported the alkylation of 2-alkenyl epoxides by functionalized zincates by catalysis of a cyanocuprate.[11] Analogously, we converted chlorobutylzinc to lithium dimethylbutylzincate,[12] which also did not react with **1** (Table 1, entry 16) but, in the presence of a catalytic amount (10 mol %) of MeCuCNLi, **1** was consumed with low ligand transfer selectivity, despite the moderate *E*-stereoselectivity for both transfers (Table 1, entry 17). Under MeCuCNLi catalysis, lithium (*Z*)-styryldimethylzincate[13] transferred specifically the vinylic moiety only by a S_N2' process, but with low stereoselectivity (Table 1, entry 18).

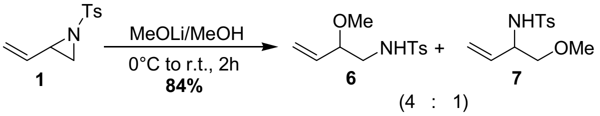
The above commented results show that the use of a Cu(I) salt changed the original reactivity of the organometallic (BuLi, BuMgBr or $[BuZn(CH_3)_2]^-$). This can be due to the in situ generation of more reactive cuprates of unknown stoichiometry, by transmetallation[14] (Scheme 2).



Scheme 2. The transmetallation of the organometallics led to more efficient ring opening process.

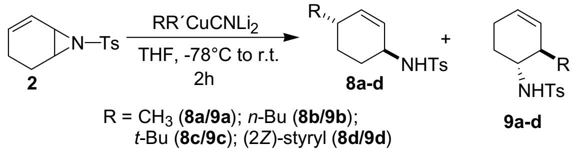
The used organometallics do not show an expressive variation on its hardness character.[15] In order to establish a comparison, **1** was reacted with MeOLi in MeOH and the reaction was S_N2 selective yielding ethers **6** and **7** in 84% yield with a preference for the nucleophilic attack at the allylic carbon (Scheme 3).[16]

These results indicated the preference of hard nucleophiles for a S_N2 *like* ring opening process, whereas softer nucleophiles led preferentially to a S_N2' *like* ring opening of **1**.



Scheme 3. Ring opening of **1** with MeOLi.

Table 2. Experimental conditions and S_N2'/S_N2 regioselectivity of the ring opening reaction of 2-alkenyl aziridine **2** with cyanocuprates ($RR'CuCNLi_2$)



2 **8a-d** **9a-d**

R = CH_3 (**8a/9a**); *n*-Bu (**8b/9b**); *t*-Bu (**8c/9c**); (2*Z*)-styryl (**8d/9d**)

Entry	R,R′	S_N2'/S_N2 ratio[a]	Isolated yield[b] (%)
1	R = R′ = CH_3	1.2:1	68
2	R = R′ = *n*-Bu	3:1	76
3	R = R′ = *t*-Bu	10:1	59[c]
4[d]	R = (2*Z*)-styryl R′ = CH_3	6.5:1 1:1 (CH_3/alkenyl)	82
5[d]	R = (2*Z*)-styryl R′ = 2-thienyl	6.5:1	92

[a] Determined by CG–MS and ^1H and ^{13}C data NMR analysis.

[b] After purification by flash chromatography (SiO_2) using a gradient of hexanes to AcOEt/hexanes (1:4) as eluent.

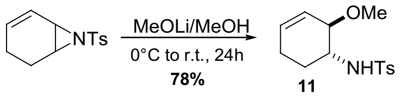
[c] Ref. 17.

[d] Prepared from the corresponding vinylic telluride (Ref. 18).

Since Lipshutz lithium cuprates led to the best selectivities, these reagents were used in the reaction with the cyclic alkenyl aziridine **2**. These reactions were all S_N2'-regioselective, resulting in a mixture of *trans* 3,6-disubstituted cyclohexenes **8a–d** as the major product and the S_N2 product **9a–d** (Table 2).

The regioselectivity increased with the steric demand of the alkyl group (Table 2, entries 1–3), and both products were confirmed by 2D NMR experiments, where the correlation of the (–C*H*NHTs) with the vicinal double bond hydrogen supports this assignment.

When the reaction was performed with a dilithium (*Z*)-styryl methylcyanocuprate (Table 2, entry 4) a 1:1 mixture of methyl and alkenyl transfer products was obtained. For this reason we used an alkenyl heterocuprate with a dummy ligand (2-thienyl)[17] to assure exclusive transfer of the alkenyl moiety in the ring opening reaction, keeping the regioselectivity unchanged (Table 2, entry 5).



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Scheme 4. MeOLi ring opening of cyclic aziridine.

The *anti*-selectivity of the S_N2' like ring opening of aziridine **2** is in agreement with the reaction with the related epoxide, which affords a high *anti*-stereoselectivity when reacted with organocopper reagents.[19] The alkylation of allylic electrophiles with organocopper reagents usually occurs by an *anti*-addition, unless in cases where the electrophiles have a group able to complex with copper.[20] Interestingly, it has been reported that in the ring opening of a Cbz-protected cyclic 2-alkenyl aziridine,[3d,21] the copper complexation with the aziridine nitrogen and the double bond may occur, and thus it could direct the ligand transfer to the same face of the aziridine ring (*syn* addition).

The *trans* stereochemistry proposed for the **8** series has been assumed by comparison of the ^{13}C chemical shifts for the hydrogenated compound **10** with previously published data of the phtalimido derivatives of 4-*tert*-butylcyclohexylamine (Fig. 1).[22]

The ring opening of **2** with lithium methoxide resulted only in the S_N2 product **11** in 78% yield (Scheme 4),[23] contrasting with the regioselectivity observed for carbon nucleophiles.

In summary, we performed the first systematic study of the ring opening reaction of two simple examples of 2-alkenyl aziridines with a variety of organometallic nucleophiles and also with lithium methoxide. The observed regio and stereoselectivities were influenced by the type of the organometallic and also by the Cu(I) additives used. Excellent regio- and stereoselectivities were obtained in the reaction of **1** using Lipshutz cyanocuprates. The ring opening of **2** led to poor to moderate S_N2' *anti*-addition. This regioselectivity increases with the steric demand of the organic moiety of the Lipshutz cuprates.

Acknowledgements

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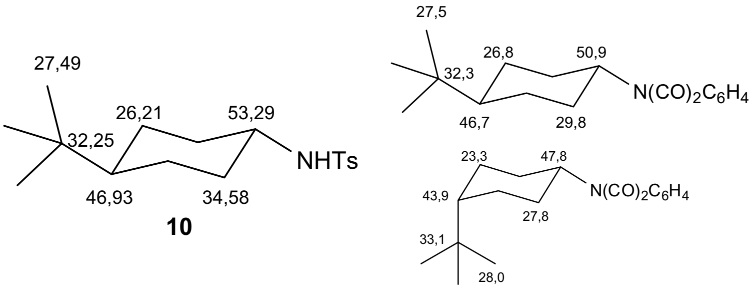

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Figure 1. ^{13}C Chemical shifts δ (ppm) comparision for compound **10**.

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7. Spectral data for 2-alkenyl aziridines. Aziridine **1** (white solid, mp: 55.6–55.9 °C): ^{1}H NMR (300 MHz, $CDCl_3$, J in Hz, δ in ppm) δ 7.83 (d, $^{3}J = 8.4$, 2H), 7.34 (d, $^{3}J = 8.4$, 2H), 5.57–5.39 (m, 2H), 5.24 (dd, $^{3}J = 9.0$, $^{4}J = 2.5$, 1H), 3.27 (ddd, $^{3}J = 7.2$ 4.8 $^{4}J = 2.5$, 1H), 2.78 (d, $^{3}J = 7.2$, 1H), 2.44 (s, 3H), 2.22 (d, $^{3}J = 4.8$, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm) δ 144.4, 134.9, 132.8, 129.6, 127.7, 120.1, 40.8, 34.0, 21.5. IR (KBr, cm^{-1}) 2586, 2471, 2409, 2311, 1596, 1494, 1325, 1305, 1161, 1092, 990, 935, 838, 794, 743, 672, 630, 562. Aziridine **2** (white solid, mp: 94.6–94.8 °C): ^{1}H NMR (300 MHz, $CDCl_3$, J in Hz, δ in ppm) δ 7.83 (d, $^{3}J = 8.1$, 2H), 7.34 (d, $^{3}J = 8.4$, 2H), 5.92–5.89 (m, 2H), 3.34–3.31 (m, 1H), 3.21–3.16 (m, 1H), 2.45 (s, 3H), 2.11–1.99 (m, 3H), 1.60–1.48 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm) δ 144.4, 135.8, 133.8, 129.9, 127.9, 120.6, 41.9, 36.8, 21.9, 20.7, 18.9. IR (KBr, cm^{-1}) 2940, 2845, 2590, 2464, 1595, 1492, 1319, 1292, 1158, 1091, 1027, 950, 865, 821, 810, 771, 705, 672, 598, 557, 534.
8. Typical procedure for ring opening with nucleophiles: *n*-Buthyllithium (1.2 mmol, 1.0 mL, 1.20 mol/L) was added dropwise to a suspension of CuCN (0.54 mg, 0.6 mmol) in THF (1.0 mL), at −78 °C, under stirring. After 20 min, a solution of the appropriate aziridine (0.5 mmol) in THF (1 mL) was added dropwise, and the mixture was allowed to warm to room temperature. The reaction was monitored by TLC. Anhydrous ethyl acetate was added to the solution and then washed with brine (3 × 15 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered and the solvent removed. The product was purified by chromatography on SiO_2, using hexanes/AcOEt mixture. The product was obtained as a colourless oil. Spectral data for ring opening products from aziridine **1**. **(5a)** ^{1}H NMR (300 MHz, $CDCl_3$, J in Hz, δ in ppm) δ 7.76 (d, $^{3}J = 8.3$, 2H), 7.30 (d, $^{3}J = 8.3$, 2H), 5.53 (dt, $^{3}J = 15$, 7.1, 1H), 5.28 (dt, $^{3}J = 15$, 7.1, 1H), 4.91 (t, $^{3}J = 5.9$, 1H), 3.51 (t, $^{3}J = 6.1$, 2H), 2.42 (s, 3H), 1.93–1.87 (m, 2H), 1.29–1.17 (m, 6H), 0.86 (t, $^{3}J = 7.1$, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm) δ: 143.1, 137.0, 134.8, 129.5, 127.1, 124.2, 45.2, 31.9, 31.2, 28.4, 22.3, 21.3, 13.9. IR (neat, cm^{-1}) 3282, 2926, 2857, 1599, 1428, 1327, 1161, 1095, 1046, 972, 815, 665, 552.
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10. The differences between the results obtained for the BuLi/CuCN (20 mol %) system (entry 4) and for the Lipshutz cuprate (entry 11) is probably due to the nature of the organometallic species present in each system. Albeit the reagents, a priori, could be considered as the same in both systems, excess of BuLi in combination with CuCN can generate organocuprates with several stoichiometries in solution, different from those present in the reaction media of the pre-formed Lipshutz cuprate. For a more detailed discussion, see: Nakamura, E.; Yoshikai, N. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1, and references cited therein.
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13. Procedure adapted from: Marshal, J. A.; Eidam, P. *Org. Lett.* **2004**, *6*, 445, In this work the authors used an alkenyl iodide as vinylic moiety source of vinyllithium, we used instead a vinylic telluride as a vinyl moiety source.
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16. Procedure for the ring opening with lithium methoxide. Buthyllithium solution (0.7 mmol, 0.54 mL, 1.3 mol/L) was added dropwise to absolute methanol (8 mL), under stirring at 0 °C. The obtained solution was stirred for 15 min and then the vinylic aziridine (0.6 mmol) in MeOH (2 mL) was added. The mixture was allowed to warm to room temperature and the reaction was monitored by TLC. Methanol was removed at reduced pressure and the residue was dissolved in AcOEt (20 mL) and washed with brine (3 × 15 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered and concentrated to afford a colourless oil.
17. NMR data for **9d**: ^{1}H NMR (500 MHz, $CDCl_3$, J in Hz, δ in ppm) δ 7.79 (d, $^{3}J = 8.1$, 2H), 7.30 (d, $^{3}J = 8.1$, 2H), 5.71 (ddd, $J = 2.0$, $J = 3.8$, $J = 10.4$, 1H), 5.38 (ddd, $J = 1.9$, $J = 4.3$, $J = 10.4$, 1H), 4.79 (d, $J = 8.7$, 1H), 3,80 (m, 1H), 2.42 (s, 3H), 1.94–1.98 (m, 1H), 1.78–1.82 (m, 1H), 1.70–1.74 (m, 1H), 1.26 (m, 2H), 0.81 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, δ in ppm) δ 143.2, 138.2, 134.5, 129.6, 126.9, 126.3, 47.3, 45.6, 32.5, 29.2, 28.4, 27.8, 27.2, 21.5, 18.6.
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23. NMR data for **11**: ^{1}H NMR (300 MHz, $CDCl_3$, J in Hz, δ in ppm) δ 7.81 (d, $^{3}J = 8.4$, 2H), 7.30 (d, $^{3}J = 8.4$, 2H), 5.85–5.79 (m, 1H), 5.66–5.61 (m, 1H), 5.33 (d, $^{3}J = 6.6$, 1H), 3.57–3.52 (m, 1H), 3.41–3.36 (m, 1H), 3.17 (s, 3H), 2.42 (s, 3H), 2.05–1.94 (m, 3H), 1.60–1.52 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm) δ 143.1, 137.7, 131.0, 129.4, 126.9, 124.3, 77.1, 55.6, 51.6, 25.1, 22.6, 21.4.