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Dual reaction pathways in the magnesium-mediated synthesis of aziridines from benzal halides and imines

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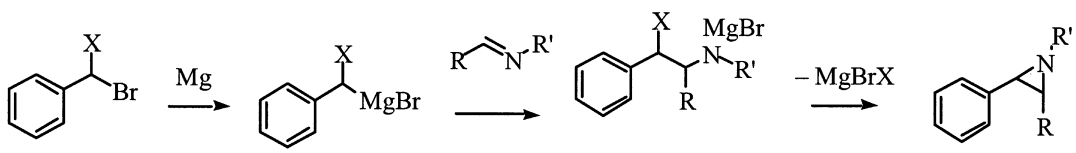
Abstract—Reaction between benzal dihalides, benzaldehyde imines, and magnesium in ether affords aziridines in modest yields. Two mechanistic pathways for aziridine formation are discerned. One path involves nucleophilic attack by an alpha-halo Grignard species on the imine; the other involves electrophilic attack on imine by phenylcarbene to afford an azomethine ylide. © 2001 Elsevier Science Ltd. All rights reserved.

A variety of methods for the preparation of aziridines have been reported.[1–4] Some, such as the thermolysis of β-haloamines,[5] involve transformation of a pre-existing C–C–N chain. Others can be characterized as of [1+2] type; they involve (a) addition of a nitrogen species to an alkene or (b) a carbon species to an imino (C=N) linkage. Type (a) processes include the copper-catalyzed addition of chloramine to alkenes[6] and the addition of carboethoxynitrene to activated esters.[7] Type (b) processes include the addition of diazo compounds or sulfur ylides to imines.[8–11] Another [1+2] sequence could be envisioned in which a benzal dihalide (**1**) first reacts with magnesium to form an alpha-halo Grignard reagent (**2**), the latter adds to an imine component of the solution, and the resulting adduct (**4**) then cyclizes to the aziridine (Scheme 1). We report successful implementation of this synthetic route and the surprising discovery that there are in fact *two* mechanistic paths to aziridine using this protocol.

Benzal chlorobromide (**1b**) and benzal bromide (**1a**) were allowed to react with varying molar ratios of benzaldehyde *n*-propyl imine (**3a**) and magnesium under ultrasonic irradiation. The products isolated (flash chromatography) were a mixture of aziridine **5**, reductive dimers of the starting imine (**6**), the imidazolidine **7**, and a mixture of *cis*- and *trans*-stilbenes (**8**) (Scheme 2, Table 1). Initial experiments in THF afforded low yields of aziridines, but ether was found to afford better yields and was used for the experiments in Table 1. A few experiments were carried out with substituted imines **3b**,**c** (runs 9–12). Authentic samples of *cis*- and *trans*-**5** were prepared by reaction between the appropriate stilbene oxide and propylamine to afford the appropriate β-aminoethanol (**9**), followed by cyclization of **9** with triphenylphosphine/diethyl azodicarboxylate.[12,13] Dimers **6** are produced by reaction of **3** with magnesium. They were formed in significant amounts only in those reactions in which the reaction of **1** with magnesium appeared to be slow. Only stilbenes were produced if imine **3** was omitted from the solution. Imidazolines **7** hydrolyzed to a mixture of benzaldehyde and **6** during chromatography and were characterized only by mass spectrometry.[14]



1a, X = Br
b, X = Cl

2

4

Scheme 1.

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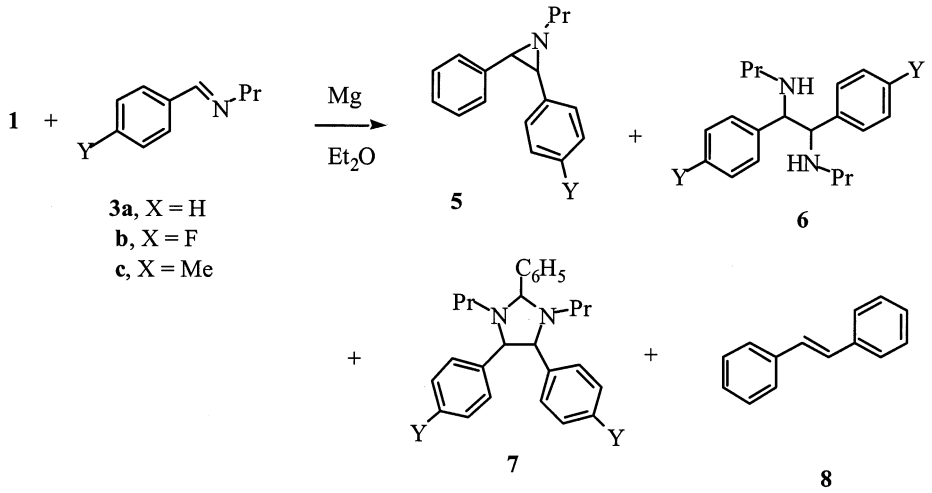


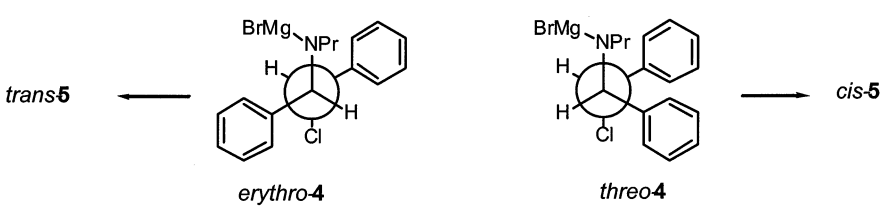
Scheme 2.

Table 1. Magnesium-promoted reaction between benzal dihalides with imines

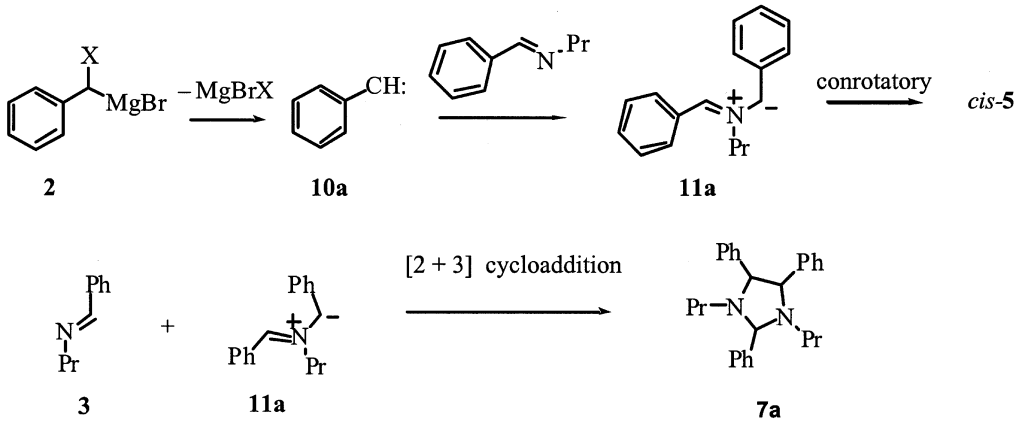
Run	Halide	Imine	Ratio of **3** to **1**	**5** (%)	*cis*:*trans* Ratio	**7** (%)
1	**1a**	**3a**	1:1	24	72:28	9
2	**1a**	**3a**	3:1	39	67:33	12
3	**1a**	**3a**	6:1	60	61:39	17
4	**1b**	**3a**	1:1	10	29:71	3
5	**1b**	**3a**	3:1	19	19:81	4
6	**1b**	**3a**	6:1	21	17:83	4
7	**1a**	**3b**	1:1	23	75:25	12
8	**1a**	**3b**	3:1	35	65:35	18
9	**1a**	**3c**	1:1	21	58:42	8
10	**1a**	**3c**	3:1	32	49:51	11

The dibromide (**1a**) and chlorobromide (**1b**) were found to differ in several significant respects in this reaction. First and most striking, the *cis*-aziridine (*cis*-**5**) is the major isomer produced with **1a**, while *trans*-**5** predominates in the reactions carried out with **1b**. Secondly, substantial quantities of imidazolidine **7** are produced when halide **1a** is used, whereas the amount of **7** produced is very low with **1b** as reactant. Finally, the yields of **5** and **7** are substantially dependent upon the concentration of imine with dibromide **1a** but much less so with chlorobromide **1b**. We conclude from these results that there are two paths to aziridine **5** in this system. Path A produces all or mostly *trans*-**5**, is less sensitive to the concentration of imine, and does not produce imidazolidine **7**. Path B affords *cis*-**5** as the major or exclusive product, is quite sensitive to the concentration of imine, and can lead to **7** as a side product. We propose that path A involves the mechanism of Scheme 1, i.e. nucleophilic attack of the initially-generated α-halomagnesium species **2** upon **3** to form a β-chloro nitrogen species (**4**), which then cyclizes to **5**. The preferred stereochemistry of addition of **2** to **3** should be such that the two phenyl rings are as far apart as possible in the transition state. This suggests that the major diastereomer of **4** produced should be the *erythro* diastereomer, which would then be expected to cyclize to *trans*-**5** (Scheme 3). A minor pathway would involve formation of *threo*-**4** and ultimately *cis*-**5**.

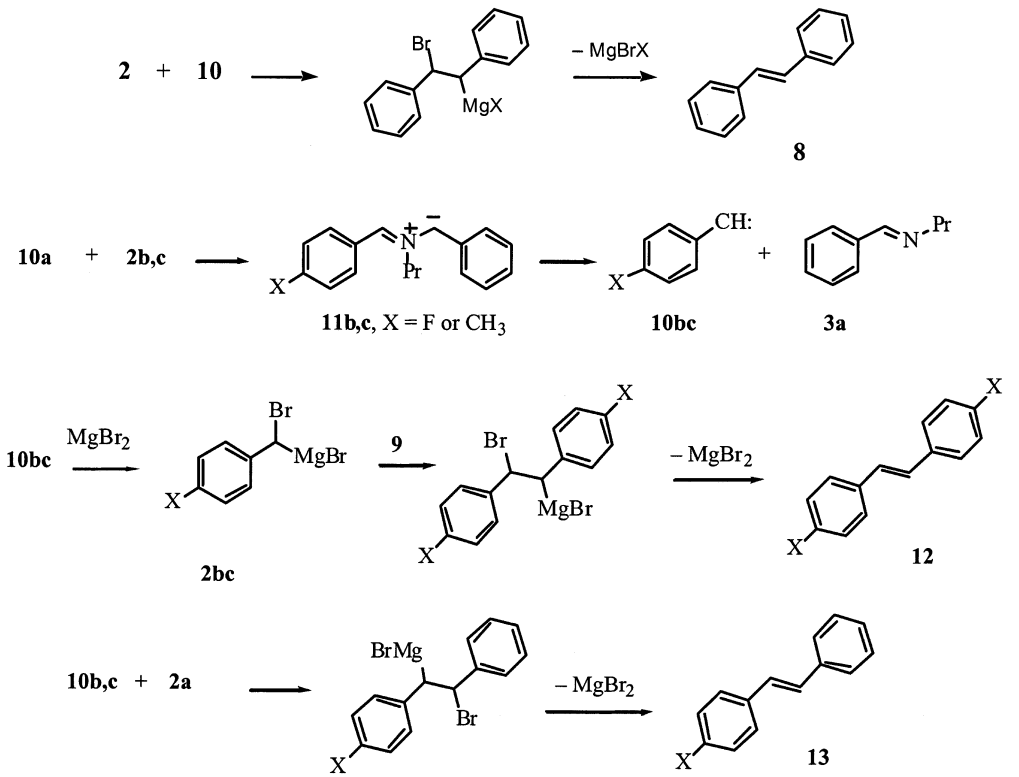
We suggest that path B involves loss of magnesium halide from **2** to afford phenylcarbene (**10**) (Scheme 4). Nucleophilic attack on **10** by imine **3** would produce the azomethine ylide **11**. Molecular mechanics calculations[15] on **11** predict that the s-*cis*/s-*trans* struc-



Scheme 3.



Scheme 4.



Scheme 5.

ture shown is lower energy than the all s-*trans* or all s-*cis* stereoisomers. Orbital symmetry-controlled cyclization of this stereoisomer should proceed in conrotatory fashion to afford *cis*-**3**, and **7** would be formed by [2+3] cycloaddition of **11a** to starting imine **3**.[16,17] This path would be favored for **1a** because of the better leaving group ability of bromide, though it is unlikely that either dihalide reacts exclusively by just one path.

A final unexpected result must be mentioned here. As mentioned above, *cis*- and *trans*-stilbenes **8** are produced as side products in these reactions. These are presumably formed by reaction of carbene **10** with **2**, followed by loss of magnesium halide (Eq. (1)).[18] Both aryl groups therefore originate from the geminal halide **1**. For this reason we were surprised to find the substituted stilbenes **12** (from **3b**) and **13** (from both **3b** and **3c**) among the reaction products in runs 7–10 (total yields of **12** and **13** ca. 5–10%).

We believe that this constitutes evidence that azomethine ylide formation is reversible (Scheme 5). Because carbenes are electrophilic, both methyl and fluorine should stabilize the substituted carbene (**10b**,**c**) resulting from decomposition of mixed ylide **11b**,**c**.[19] Trapping of **10b**,**c** by MgBrX or **2a** would then lead on to **12** and **13**. As Scheme 5 would predict, runs 7–10 also produced the unsubstituted imine **3a** as well as aziridines and imidazolidines containing varying degrees of substitution.

Acknowledgements

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References

1. Deyrup, J. A. In *The Chemistry of Heterocyclic Compounds*; Hassner, A., Ed.; Wiley: New York, 1983; Vol. 42, pp. 11–83.
2. Kametani, T.; Honda, T. *Adv. Heterocycl. Chem.* **1986**, *39*, 181.
3. Padwa, A.; Woolhouse, A. D. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon: Oxford, 1984; Vol. 7, pp. 80–93.
4. Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.
5. Bartnik, R.; Mloston, G.; Lesniak, S. *Pol. J. Chem.* **1979**, *53*, 537.
6. Ando, T.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 309.
7. Carducci, M.; Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Tetrahedron Lett.* **1996**, *37*, 3777.
8. Gunnoe, T. B.; White, P. S.; Templeton, J. L.; Cassarrubios, L. *J. Am. Chem. Soc.* **1997**, *119*, 3171.
9. Gyenes, F.; Bergmann, K. E.; Welch, J. T. *J. Org. Chem.* **1998**, *63*, 2824.
10. Mohan, J. M.; Uphade, B. S.; Choudhary, V. R.; Ravindranathan, T.; Sudalai, A. *Chem. Commun.* **1997**, 1429.
11. Wang, D.-K.; Dai, L.-X.; Hou, X.-L. *Chem. Commun.* **1997**, 1231.
12. Carlock, J. T.; Mack, M. P. *Tetrahedron Lett.* **1978**, 5153.
13. Stereochemical inversion at nitrogen is fairly slow at room temperature for **5**; comparison of experimental NMR spectra with computed spectra (Quantum Chemistry Program Exchange program DNMR5) indicated a rate of $\sim 35\ s^{-1}$ at 25°C.
14. Spectroscopic properties for new substances (^{1}H COSY NMR spectra were carried out on all new substances and were consistent with the assigned structures): (a) *trans*-**5a**: ^{1}H NMR (300 MHz): δ 0.95 (t, 3H), 1.6 (m, 2H), 2.05 (m, 1H), 2.5 (m, 1H), 3.1 (br s, 1H), 3.35 (br s, 1H), 7.3–7.6 (m, 10H); MS (EI): 237 (26), 236 (61), 194 (100), 165 (29); exact mass (CI) calcd for M+1: 238.1596, found: 238.1594; (b) *cis*-**5a**: ^{1}H NMR: δ 1.05 (t, 3H), 1.75 (m, 2H), 2.65 (t, 2H), 2.85 (s, 2H), 7.1–7.4 (m, 10H); MS (EI): 237 (20), 236 (53), 194 (100), 165 (27); exact mass (CI) calcd for M+1: 238.1596, found: 238.1590; (c) *erythro*-**9**: ^{1}H NMR: δ 0.9 (t, 3H), 1.35 (s, 1H), 1.5 (m, 2H), 2.5 (m, 2H), 3.25 (br s, 1H), 3.9 (d, 1H), 4.85 (d, 1H), 7.15 (m, 4H), 7.25–7.35 (m, 6H); ^{13}C NMR: 141, 140, 128.4, 128.3, 128.1, 127.8, 127.7, 127, 77, 69, 49, 23, 12; MS (EI): 254 (0.3), 237 (0.2), 236 (0.3), 208 (0.4), 194 (0.4), 148 (100), 106 (23); (d) *threo*-**9**: ^{1}H NMR: δ 0.9 (t, 3H), 1.35 (s, 1H), 1.5 (m, 2H), 2.5 (m, 2H), 3.3 (br s, 1H), 3.85 (d, 2H), 4.85 (d, 2H), 7.3–7.6 (m, 10H); MS (EI): 254 (0.3), 237 (0.2), 236 (0.3), 208 (0.4), 194 (0.4), 148 (100), 106 (23); (e) **3b**: ^{1}H NMR: δ 0.95 (t, 3H), 1.72 (m, 2H), 3.56 (t, 2H), 7.1 (dt, 2H), 7.75 (m, 2H), 8.24 (s, 1H); ^{13}C NMR: 164.3 (d, $J=249$ Hz), 159.4, 132.79 (doublet, $J=3$ Hz), 129.95 (d, $J=8$ Hz), 115.65 (d, $J=23$ Hz), 63.5, 24.2, 11.9; MS (EI): 165 (5), 164 (17), 136 (57), 109 (100); (f) *trans*-**5b**: ^{1}H NMR: δ 0.85 (t, 3H), 1.6 (m, 2H), 2.45 (m, 2H), 3.0 (br s, 1H), 3.25 (br s, 1H), 7–7.8 (m, 9H) MS (EI): 254 (20), 212 (100), 165 (15); (g) *cis*-**5b**: MS (EI): 254 (21), 212 (100), 165 (15): ^{1}H NMR: δ 0.95 (t, 3H), 1.75 (m, 2H), 3.55 (t, 2H), 7.10 (m, 2H), 7.7 (m, 2H), 8.24 (s, 1H); ^{13}C NMR: 166, 162.5, 159.5, 132.7 (doublet), 130, 116, 62, 24, 12; (h) **6b**: ^{1}H NMR: δ 0.8 (t, 3H), 1.35 (m, 2H), 1.55 (br s, 2H; disappears in the presence of D_2O), 2.2 (t, 2H), 3.7 (s, 2H), 6.85 (m, 4H), 7.3 (m, 6H); MS (EI): 274 (0.5), 166 (M/2) (100), 148 (13), 124 (13); (i) **7b**: MS (EI): 325 ($M-C_6H_4F$) (25), 273 (85), 255 (100), 230 (85%); (j) **7a**: MS (EI): 383 (M−1) (31), 355 (5), 341 (4), 307 (79), 237 (100), 236 (67), 194 (58).
15. PCMODEL7, Serena Software: Bloomington, IN.
16. Hall, J.; Huisgen, R. *J. Chem. Soc. D* **1971**, 1187.
17. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984.
18. Kirmse, W. *Carbene Chemistry*; Academic: New York, 1964.
19. Hine, J. *Divalent Carbon*; Ronald Press: New York, 1964.