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The stereoselective addition of organocuprates to cyclopentenyl aziridine derivatives

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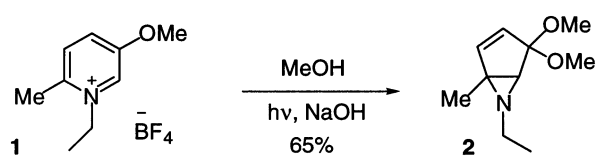
Abstract—Various organocopper reagents were added in the expected *anti*-S_N2' fashion to cyclopentenyl aziridines, which were derived from the photosolvolysis of pyridinium salts. © 2001 Elsevier Science Ltd. All rights reserved.

Recent publications from our group,[1] and others,[2,3] have shown that the photosolvolysis of *N*-alkylpyridinium salts in an alcohol solvent allows facile construction of bicyclic cyclopentenyl aziridines such as **2** (Scheme 1).

Such molecules offer a wealth of potential for elaboration into a wide range of highly substituted five-membered rings. Some interesting uses of these compounds have so far been reported, such as the total synthesis of mannostatin,[2b] however much of this potential remains untapped. In particular, the ring-opening of the aziridine moiety has so far only been reported with heteroatomic nucleophiles. We were interested in seeing how the formation of new carbon–carbon bonds could be effected on such a system.

A challenge was posed by the poor reactivity of unactivated aziridines (i.e. those lacking an electron-withdrawing group on nitrogen)[4] towards nucleophiles in the absence of Lewis acids. Indeed the aziridine **2** showed no sign of reaction upon prolonged exposure to MeLi. However, Ganem has reported that simple *N*-alkyl aziridines can be opened in an S_N2 fashion by organocuprates in the presence of $BF_3{\cdot}OEt_2$.[5] None of the substrates investigated were 2-alkenyl aziridines, and so no S_N2' reactions were observed. Indeed, the few examples of S_N2' reactions between cuprates and alkenyl aziridines so far reported have all involved activated[4] aziridines.[6–8]



Scheme 1.

Intrigued by this relatively unexplored area of chemistry we applied Ganem's conditions[5] to our substrates. To our delight the simple *N*-alkyl aziridine **2** underwent S_N2' reactions to allow the formation of new carbon–carbon bonds in a highly stereoselective manner. The *N*-ethyl and *N*-allyl cyclopentenyl aziridines[1] **2** and **5** were reacted with a range of cuprates to give the ring-opened products **3a**–**3f** in moderate to good yields.[9] Moreover, the stereoselectivity of the reactions was excellent, with only a single (*anti*-) diastereomer of each product being observed (Table 1).

S_N2' reactions of cuprates with a variety of leaving groups generally show predominantly *anti*-stereoselectivity, and Corey[12] has suggested that this is due to the fact that filled *d*-orbitals on the copper can interact with both the π* antibonding orbital of the olefin and the σ* orbital of the carbon-leaving group bond. However, the strong preference for *anti*- attack in this case may also be explained by the increased steric bulk introduced about the aziridinyl nitrogen as a result of coordination between the nitrogen lone pair and the Lewis acid.

In entry (a) the reaction between **2** and the dimethyl cuprate species produced a small amount of the by-product **4a**. Unfortunately we could not isolate it free from the product **3a**, hence its structure has only been tentatively assigned from NMR studies, and more rig-

Keywords: photosolvolysis; heterocycle; vinyl; alkenyl; cyclopentenyl; aziridine; organocuprate; stereoselective; S_N2'.

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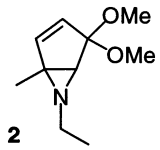
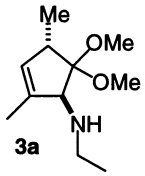
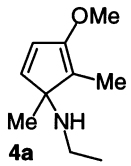
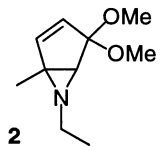
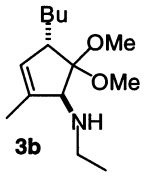
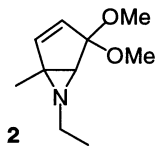
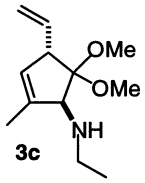
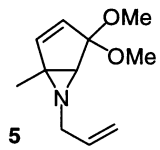
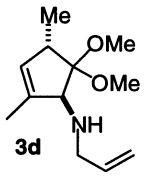
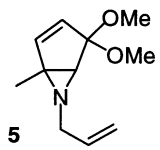
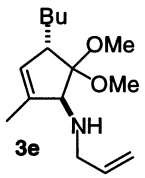
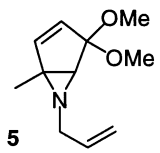
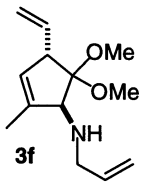
Table 1. Reaction of *N*-ethyl and *N*-allyl cyclopentenyl aziridines **2** and **5** with various organocopper reagents

Entry	Substrate	Reagents and conditions	Products	Yield (%)
a[10]	 **2**	Me_2CuLi $BF_3{\cdot}OEt_2$, THF, −78°C	 **3a** &  **4a**	40 and 13
b	 **2**	Bu_2CuLi $BF_3{\cdot}OEt_2$, THF, −78°C	 **3b**	39
c	 **2**	$(Vinyl)_2CuMgBr$ $BF_3{\cdot}OEt_2$, THF, −78°C	 **3c**	45
d[11]	 **5**	Me_2CuLi $BF_3{\cdot}OEt_2$, THF, −78°C	 **3d**	51
e	 **5**	Bu_2CuLi $BF_3{\cdot}OEt_2$, THF, −78°C	 **3e**	62
f	 **5**	$(Vinyl)_2CuMgBr$ $BF_3{\cdot}OEt_2$, THF, −78°C	 **3f**	35

orous characterisation has so far been prevented. It may be that **4a** arises from competing S_N2 opening of the aziridine (which would be more favourable for smaller cuprates), followed by elimination of MeOH (Scheme 2).

It is unclear why methanol should be eliminated in the case of S_N2 attack (i.e. in the formation of **4a**) and not in the case of S_N2' attack.

In conclusion, we have shown how organocuprates can be reacted with cyclopentenyl aziridines to incorporate new alkyl groups in a stereoselective fashion. These represent the first examples of S_N2' reactions between cuprates and unactivated alkenyl aziridines.

Acknowledgements

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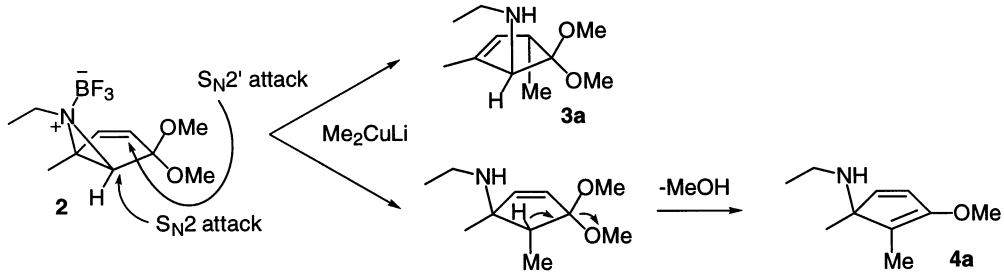
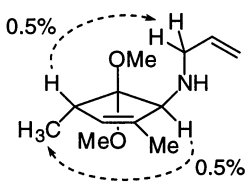


Scheme 2.

and the EPSRC Service Centre in Swansea for mass spectral analyses. Finally we thank Professor Philip Parsons for his advice and support.

References

1. (a) Penkett, C. S.; Simpson, I. D. *Synlett* **1999**, 93; (b) Penkett, C. S.; Simpson, I. D. *Tetrahedron* **1999**, *55*, 6183.
2. (a) Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439; (b) Ling, R.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 6072.
3. (a) Acar, E. A.; Glarner, F.; Burger, U. *Helv. Chim. Acta* **1998**, *81*, 1095; (b) Glarner, F.; Acar, B.; Etter, I.; Damiano, T.; Acar, E. A.; Bernardinelli, G.; Burger, U. *Tetrahedron* **2000**, *56*, 4311.
4. Ham, G. E. *J. Org. Chem.* **1964**, *29*, 3052.
5. Eis, M. J.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 1153.
6. Wipf, P.; Fritch, P. C. *J. Org. Chem.* **1994**, *59*, 4886.
7. (a) Fujii, N.; Nakai, K.; Tamamura, H.; Otaka, A.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1359; (b) Aoyama, H.; Mimura, N.; Ohno, H.; Ishii, K.; Toda, A.; Tamamura, H.; Otaka, A.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **1997**, *38*, 7383.
8. Cantrill, A. A.; Jarvis, A. N.; Osborn, H. M. I.; Ouadi, A.; Sweeney, J. B. *Synlett* **1996**, 847.
9. **Typical experimental procedure**: Vinyl magnesium bromide (6.5 ml, 1.0 M solution in THF) was added dropwise to a suspension of copper(I) iodide (625 mg, 3.27 mmol) in tetrahydrofuran (10 ml) at −50°C. After 15 minutes the solution was cooled to −78°C and the aziridine **2** (283 mg, 1.55 mmol) in THF (3 ml) was added, followed by boron trifluoride diethyl etherate (0.38 ml, 3.1 mmol). The reaction mixture was stirred at −78°C for 4 h, then allowed to warm gradually to room temperature over a further 4 h. The reaction mixture was quenched with 2 M sodium hydroxide solution (5 ml) and poured into concentrated ammonia (50 ml). The ammonia solution was extracted with ethyl acetate (3×50 ml) and the combined organic layers were washed with water (30 ml), dried ($MgSO_4$) and concentrated in vacuo to give the crude product as a red oil. This was purified by flash chromatography (SiO_2, DCM:EtOH:NH_3, 400:8:1) to give the amine **3c** as a colourless oil (148 mg, 0.70 mmol, 45%).
10. Ethyl-(5,5-dimethoxy-2,4-dimethylcyclopent-2-enyl)-amine **3a**: δ_H (500 MHz, $CDCl_3$) 1.02 (d, 3H, *J* 7.2 Hz, (C-4)CH_3), 1.08 (t, 3H, *J* 7.2 Hz, NCH_2CH_3), 1.7 (br s, 1H, N*H*), 1.71 (ddd, 1H, *J* 0.9, 1.5, 2.3 Hz, (C-2)CH_3), 2.61 (dq, 1H, *J* 7.2, 10.9 Hz, NC*H*HCH_3), 2.65 (dq, 1H, *J* 7.2, 10.9 Hz, NCH*H*CH_3), 2.82 (m, 1H, (C-4)*H*), 3.23 (s, 3H, (C-5)OCH_3), 3.26 (s, 3H, (C-5)OCH_3), 3.42 (m, 1H, (C-1)*H*), 5.22 (m, 1H, (C-3)*H*). If the proton signal at 1.71 ppm is selectively decoupled, the three proton signals on (C-1), (C-3) and (C-4) simplify to 2.82 (ddq, 1H, *J* 1.6, 2.0, 7.2 Hz, (C-4)*H*), 3.42 (dd, 1H, *J* 1.0, 1.6 Hz, (C-1)*H*), 5.22 (dd, 1H, *J* 1.0, 2.0 Hz, (C-3)C*H*). δ_C (125 MHz, $CDCl_3$) 15.15, 15.38, 15.78, 41.61, 45.08, 48.68, 49.77, 69.02, 107.61, 130.39, 138.11.
Ethyl-(3-methoxy-1,2-dimethyl-cyclopenta-2,4-dienyl)-amine **4a**: δ_H (500 MHz, $CDCl_3$) 1.01 (t, 3H, *J* 7.2 Hz, NCH_2CH_3), 1.16 (s, 3H, (C-1)CH_3), 1.61 (s, 3H, (C-2)CH_3), 1.7 (br s, 1H, N*H*), 2.22 (dq, 1H, *J* 7.2, 11.3 Hz, NC*H*HCH_3), 2.25 (dq, 1H, *J* 7.2, 11.3 Hz, NCH*H*CH_3), 3.71 (s, 3H, (C-3)OCH_3), 6.11 (br d, 1H, *J* 5.9 Hz, (C-5)*H*), 6.28 (d, 1H, *J* 5.9 Hz, (C-4)*H*). δ_C (125 MHz, $CDCl_3$) 7.00, 15.68, 22.44, 37.57, 57.40, 68.62, 119.05, 124.95, 141.62, 151.66.
11. Allyl-(5,5-dimethoxy-2,4-dimethyl-cyclopent-2-enyl)-amine **3d**: δ_H (500 MHz, C_6D_6) 1.18 (d, 3H, *J* 7.2 Hz, (C-4)CH_3), 1.6 (br s, 1H, N*H*), 1.82 (ddd, 3H, *J* 1.0, 1.5, 2.3 Hz, (C-2)CH_3), 2.79 (m, 1H, (C-4)*H*), 3.08 (s, 3H, (C-5)OCH_3), 3.14 (s, 3H, (C-5)OCH_3), 3.34 (ddt, 1H, *J* 1.7, 6.0, 14.1 Hz, NC*H*$HCH{=}CH_2$), 3.49 (ddt, 1H, *J* 1.7, 5.4, 14.1 Hz, NC*H*$HCH{=}CH_2$), 3.56 (br s, 1H, (C-1)*H*), 5.10 (ddt, 1H, *J* 1.7, 2.0, 10.2 Hz, $NCH_2CH{=}CHH$), 5.18 (m, 1H, (C-3)C*H*), 5.33 (ddt, 1H, *J* 1.7, 2.0, 17.2 Hz, $NCH_2CH{=}CHH$), 6.05 (dddd, 1H, *J* 5.4, 6.0, 10.3, 17.2 Hz, $NCH_2CH{=}CHH$). δ_C (125 MHz, $CDCl_3$) 15.19, 15.40, 45.07, 48.79, 49.77, 50.10, 68.28, 107.80, 115.29, 130.48, 137.86, 138.10.
The relative stereochemistry of compound **3d** was confirmed by the observation of the following NOE results.



12. Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063.