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[3+2]-Cycloaddition of Nonstabilized Azomethine Ylides, Part 9 #: A General Approach for the Construction of X-Azabicyclo[m.2.1]alkanes in Optically Pure form by Asymmetric 1,3-Dipolar Cycloaddition Reactions

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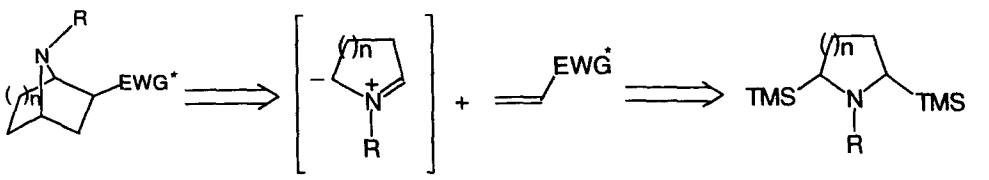
Abstract: *A general strategy for the construction of X-azabicyclo[m.2.1]alkane frameworks in optically pure form is reported by the asymmetric [3+2]-cycloaddition reaction of cyclic azomethine ylides with Oppolzer's acryloyl camphor sultam.*

Several compounds possessing X-azabicyclo[m.2.1]alkane frameworks (**1**) viz., epibatidine[1] (X=7, m= 2), cocaine alkaloids[2] (X=8, m=3) and anatoxins[3] (X=9, m=4) are known to exhibit a wide variety of biological activities. Therefore, their synthesis has occupied a prominent position as a target for organic chemists. Although, there are many excellent approaches for the construction of these frameworks in racemic form, the strategies related to their preparation in optically active forms are scarce.[4,5,6] As structure **1** encompasses an α,α'-fused pyrrolidine moiety, one attractive strategy for their preparation in optically active form may be considered by the asymmetric 1,3-dipolar cycloaddition reaction[7] of the azomethine ylides (AMY) **2**, which could be easily generated by the sequential double desilylation of **4** utilising Ag(I)F as one electron oxidant,[8] with a chiral dipolarophile. Asymmetric synthesis of highly substituted pyrrolidines in varying degrees of diastereomeric purity have been reported by 1,3-dipolar cycloaddition reactions utilising either chiral



1 **2** **3** **4**

Scheme-1

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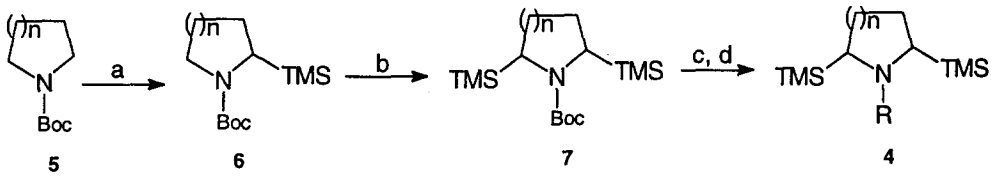
azomethine ylides[9] (dipoles) or chiral dipolarophiles.[10] The latter approaches, however, have invariably utilised N-metalated stabilised azomethine ylides to improve upon the diastereoselectivity.[9c] Since the control of absolute stereochemistry in the formation of **1** will mainly depend upon the facial and *exo/endo* selectivity of the cycloaddition reaction, we envisaged that the cycloaddition of **2**, known[8] to have excellent *exo/endo* selectivity with achiral dipolarophiles, with Oppolzer's chiral acryloyl sultam (**8**) which is established[11] to have facial selectivity, would provide an easy and general route for the synthesis of optically active X-azabicyclo[m.2.1]alkanes (**1**). We are pleased to disclose our success in this investigation.

The AMY precursors **4** were obtained by the sequential silylation of N-Boc derivatives of the corresponding cyclic amines **5** by following the steps as shown in **Scheme II**. The optimized reaction conditions and yields of **4** are also given in **Scheme II**.

Scheme-II



5 **6** **7** **4**

a	n = 1	68%	R = $PhCH_2$	75%
b	n = 2	71%	R = Me	80%
c	n = 3	62%	R = $PhCH_2$	65%

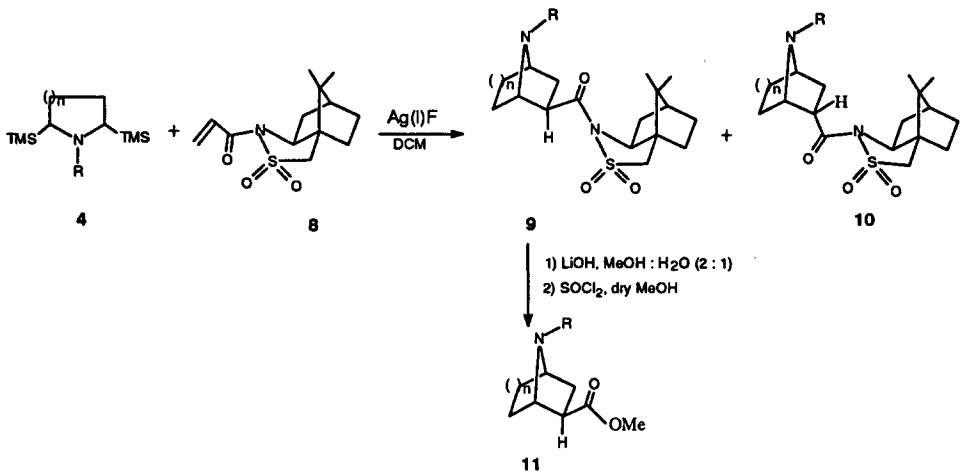
Reagents and conditions: *a*) TMEDA, *sec*-BuLi, TMSCl, -78 °C, 80-90%; *b)* 2 eq. TMEDA, 2 eq. *sec*-BuLi, TMSCl, -50 °C to -30 °C, 1 h (for n = 1 & 2) and -40 °C, 5 h (for n = 3); c) TFA, dry DCM; d) $PhCH_2Cl$, K_2CO_3, CH_3CN (for n = 1 & 3) and HCHO, $NaBH_3CN$, CH_3CN (for n = 2).

A typical cycloaddition reaction involved addition of **4** (4.1 mmol) to a stirring mixture of **8** (6.1 mmol) and Ag(I)F (10.2 mmol) in dry DCM. The color of the reaction mixture gradually turned to dark-brown with the concomitant deposition of silver on the surface of the flask in the form of a mirror. After stirring for 2 h, the reaction mixture was filtered through a small plug of celite and the solvent was evaporated under reduced pressure to give a crude brown residue which on careful column chromatography over silica-gel gave cycloadducts **9** and **10** in pure form. The cycloadducts were characterized by ^1H NMR, ^{13}C NMR and mass spectral analysis data.[12] The details of some physical data of the major diastereomers **9** are given in **Scheme-III**. The diasteromeric ratio of cycloadducts (**9**:**10**) was determined by comparing the integration values of the H-3 from their corresponding ^1H NMR spectra.

The *endo*-stereochemistry of H-3 in the major diastereomeric cycloadducts **9** was established by ^1H NMR decoupling and COSY experiments. It was found that in all cases H-3, appearing as a doublet of doublets, (J = 8-10, 4-6 Hz),[12] couples only with two adjacent protons and not with the bridgehead protons. It is known that in 7-azabicyclo[m.2.1]alkanes,[13] similar to norbornane frameworks,[14] no coupling is observed between bridgehead protons and adjacent *endo*-hydrogens due to a dihedral angle of 90° between them. Therefore, this observation is diagnostic for *exo*-substitution of amide functionality in all the major diastereomeric cycloadducts **9**.

To complete the chiral synthesis of X-azabicyclo[m.2.1]alkanes, it was mandatory to cleave the chiral auxiliary from the cycloadducts. This was achieved by hydrolysis carried out by warming **9** with LiOH in MeOH : H_2O (2:1) for 45 min. The acids thus obtained, were isolated as the corresponding methyl esters **11**, prepared by the reaction of $SOCl_2$ in dry methanol at 0 °C. The optical rotation of each ester is given in **Scheme-III.**

Scheme-III



4 8 9 10 11

Substrate (**9**)	R	yield (isolated)	**9 : 10**	m.p.of **9** (uncorrected)	Optical rotation of **11** $[\alpha_D]^{25}_{obs}$
a, n = 1	$PhCH_2$	62%	98 : 2	135-137 °C	+ 22.38 (c = 0.52, $CHCl_3$)
b, n = 2	Me	58%	80 : 20	165-167 °C	- 04.50 (c = 0.64, $CHCl_3$)
c, n = 3	$PhCH_2$	68%	95 : 5	205-207 °C	+ 15.69 (c = 0.54, $CHCl_3$)

In summary, we have developed an efficient strategy for the synthesis of X-azabicyclo[m.2.1]alkanes in enantiomerically pure form using a [3+2]-cycloaddition strategy of a cyclic azomethine ylide with Oppolzer's chiral acryloyl camphor sultam. The application of this methodology for the syntheses of optically active epibatidine and tropinone is in progress and will be discussed latter in a full paper.

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12. Spectroscopic data for the major cycloadducts (**9**): **9a:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (s, 3H), 1.09 (s, 3H), 1.23-1.56 (m, 4H), 1.67-1.80 (m, 4H),1.90- 2.06 (m, 5H), 3.30 (dd, *J* = 9.3, 4.9 Hz, 1H), 3.45 (d, *J* =13.2 Hz, 2H), 3.60 (d, *J* = 13.7 Hz, 2H), 3.75-3.82 (m, 2H), 3.90 (m, 1H), 7.20-7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.49, 20.29, 24.23,26.10, 28.26, 29.50, 32.25, 38.22, 44.19, 46.51, 47.34, 47.82, 51.27, 52.59, 60.06, 63.20, 64.92, 126.41,127.82, 127.94, 128.31, 139.39, 172.38; MS, *m/z* : 428 (M^+,12), 186 (74), 91(100). **9b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (s, 3H), 1.17 (s, 3H), 1.20-1.55 (m, 6H), 1.78-1.92 (m,5H), 1.98-2.40 (m, 4H), 2.36 (s, 3H), 3.15 (dd, *J* = 9.3, 5.6 Hz, 1H), 3.45 (d, *J* = 13.3 Hz, 2H), 3.62 (d, *J* = 6.5 Hz, 1H), 3.80-3.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$):δ 15.11, 19.88, 20.60, 26.48, 26.93, 28.36, 31.42, 32.77, 38.50, 41.13, 44.57, 46.44, 47.67, 47.97, 53.06, 61.77, 65.49, 65.74, 171.68; MS, m/z: 366 (M^+,8), 351 (0.4), 152 (23), 124 (43), 97 (100), 82 (62). **9c**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.92 (s, 3H), 1.06 (s, 3H), 1.23-1.5 (m, 4H), 1.60-1.90 (m, 8H), 2.01-2.40 (m, 5H), 2.75 (dd, *J* = 9.3, 4.5 Hz, 1H), 3.45 (d, *J* = 13.5 Hz, 2H), 3.75 (d, *J* = 13.5 Hz, 2H), 3.85-3.95 (m, 3H), 7.20-7.4 (m, 5H); ^{13}C NMR (50 MHz): δ 19.75, 20.65, 24.67, 26.36, 29.55, 31.52, 32.65, 34.89, 36.10, 38.60, 44.37, 47.48, 47.67, 48.15, 53.03, 61.23, 62.67, 65.51, 66.71, 126.44, 127.88, 128.18, 140.89, 172.33. MS, m/z: 456 (M^+,14), 214 (78), 91 (100), 55 (36).
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