Fused Tetracyclic Heterocycles by Thermally Initiated Intramolecular Criss-Cross Cycloaddition of 3-Substituted Homoallenylaldazines

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Dedicated to Professor Dr. Peter Stanetty on the occasion of his 60th birthday

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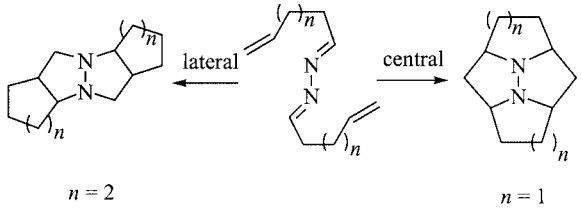
The thermally initiated intramolecular criss-cross cycloaddition of 3-substituted homoallenylaldazines **5** has been explored. Their cyclization led to interesting new fused heterocyclic systems **6** consisting of four five-membered rings with two nitrogen heteroatoms. The azines were prepared by the reaction of homoallenyl aldehydes **4** with hydrazine. The homoallenyl aldehydes **4** were synthesized by the Claisen rearrangement of new *N*,*N*-disubstituted 4-[(2-methylprop-1-en-1-yl)oxy]but-2-yn-1-amines **3a–f** prepared by Mannich reaction of 2-methylprop-1-en-1-yl prop-2-yn-1-yl ether (**2**). The success of the reaction was based on the improved solvent-free synthesis of 1-chloro-2-methylpropyl prop-2-yn-1-yl ether (**1**) and its conversion to isolable 2-methylprop-1-en-1-yl prop-2-yn-1-yl ether (**2**) in high yield.

Introduction

Criss-cross cycloaddition reactions provide a route to the "one-pot" synthesis of fused heterocyclic compounds. Most of these reactions are reported in the literature to occur by intermolecular processes to give two fused five-membered rings,[1,2] with only a few intramolecular reactions having been described. Thus, Marthur and Suschitzky[3] performed intramolecular reactions with benzaldehyde and naphthaldehyde azines bearing allyloxy and propargyloxy groups, respectively, *ortho* to the azine group. When the other *ortho* position to the alkenyloxy group was blocked by substitution in order to prevent Claisen rearrangement, the reaction led to the formation of cycloadducts in which the rings were connected laterally. We have found that bis(homoallenyl) azines undergo another type of intramolecular reaction.[4] During this reaction a completely new type of compound was formed having four centrally fused five-membered heterocyclic rings. Apparently, the distance between the azine group and the multiple bonds determines whether a "lateral"- or "central"-type cyclization is preferred (Scheme 1).



Scheme 1.

In this paper we would like to extend our knowledge of this central type of intramolecular criss-cross cycloaddition reactions and to investigate the effects of substitution upon the reaction.

To carry out this research we needed to synthesize substituted homoallenyl aldehydes. These compounds can be prepared by thermally initiated Claisen rearrangement of substituted propargyl vinyl ethers. Most of these transformations have been carried out at about 250 °C in a stream of nitrogen by using a vertically oriented pyrolytic electrically heated apparatus filled with glass wool[5,6] with the rearrangement product being collected in a cooled trap. Sometimes the reactions were carried out at reflux in unreactive high-boiling solvents.[5] Although homoallenyl aldehydes can be prepared in a single step starting from isobutyraldehyde and substituted propargyl alcohols in the presence of an acid catalyst,[7,8] we found the method using 2-methylprop-1-en-1-yl prop-2-yn-1-yl ether (**2**) as a starting compound was more convenient because it enabled us to use the appropriate substituents (including an amino func-

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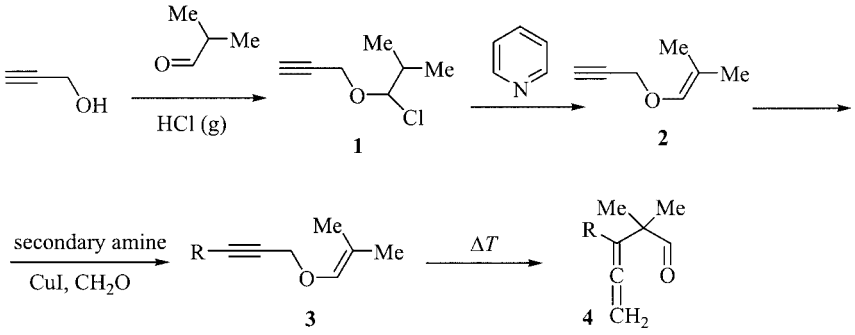


Scheme 2.

tion) and because the ether **2** can be stored in a refrigerator for almost an unlimited time.

The preparation of propargyl vinyl ethers has been reported in the literature. Two methods for the synthesis of chlorinated ether **1** and, consequently, ether **2** (Scheme 2) are also known. Both literature methods start from propargyl alcohol and isobutyraldehyde. The older procedure,[9] in some cases catalyzed by calcium chloride, afforded the corresponding acetal, which, when treated with boron trichloride, led to the chlorinated ether **1** in 47% yield. Ether **1** in diethyl ether, when treated overnight with trimethylamine at 0 °C, formed a hygroscopic solid. On heating under vacuum at a temperature of 160–170 °C, this solid afforded ether **2** in 75% yield. A more recent paper[10] describes the reaction in the presence of HCl at 0 °C, followed by the application of a huge excess of *N*,*N*-dimethylaniline at 75 °C. For our purposes we needed to be able to substitute the alkynic hydrogen atom of **2** to form substituted propargyl vinyl ethers **3** and therefore we had to find a procedure that would enable us to obtain ether **2** as a pure and easily isolable compound. We intended to subject the substituted propargyl vinyl ethers **3** to the Claisen rearrangement to give homoallenyl aldehydes **4**. However the isolation of pure ether **2** was difficult and we had to improve the literature procedure in order to obtain starting compounds for the preparation of substituted ethers **3**.

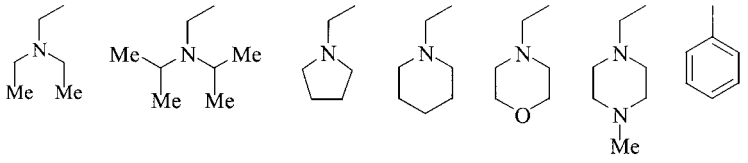
Results and Discussion

We started by preparing ethers **1** and **2**. When we applied the procedure described in the literature[10] to the preparation of ether **2** we were faced with two problems. At first we found that heating **1** for a long time at 75 °C caused Claisen rearrangement of the ether **2** to 2,2-dimethylpenta-3,4-dienal and that we could not isolate the expected ether **2** as a pure entity. Secondly, removal of the excess *N*,*N*-dimethylaniline after the reaction was difficult. Thus we modified the process and divided the procedure into two separate steps − the preparation of chlorinated ether **1** followed by the elimination of HCl to give ether **2** (Scheme 2).

The first step of the reaction can be realized without any solvent when the reagents are used in a ratio of 1:1.5 (propargyl alcohol/isobutyraldehyde) but the reaction mixture must be stirred well by a mechanical stirrer. At the beginning of the reaction, the mixture became rather viscous andif it was not stirred sufficiently local overheating was observed resulting in the formation of unwanted side-products. The end of the reaction was indicated by a reduction of the viscosity, no further absorption of gaseous HCl and finally by the formation of two layers. We changed the isolation procedure so that no water was used. The upper layer was separated and dried with magnesium sulfate. The more volatile components were removed on a rotary evaporator and the remainder by vacuum distillation. In this way a high yield (87%) of chlorinated ether **1** was obtained. Application of the purified ether **1** in the following procedure allowed us to test the efficacy of various nitrogen-containing bases in the elimination reaction and to avoid side-reactions with impurities and to remove unreacted amines at the end of the reaction. Besides *N*,*N*-dimethylaniline we tested *N*,*N*-diethylaniline, triethylamine, morpholine and pyridine; we found an equimolar amount of pyridine to be the best reagent. The reaction temperature had to be kept below 80 °C and under these conditions the reaction time was reduced from the recommended 24 h for the reaction with *N*,*N*-dimethylaniline to the time needed for the slow addition of chlorinated ether **1** to pyridine and the elimination of HCl (2–3 h). Although ether **2** may be isolated by ether extraction and, after drying, by distillation, we have found a more efficient procedure: direct distillation of the reaction mixture, purification of the distillate by charcoal absorption and finally by vacuum distillation. The first distillation process was shown to complete the elimination reaction and increase the yield. By following this procedure the product was isolated in a yield of 75% and was found to be very pure with a very low water content (less than 10^{-4} g of water per 1 g of product). Note here that the yield obtained by using this procedure depends on the precise reproduction of the experimental conditions.

Having developed an efficient synthesis of ether **2** we could concentrate on the preparation of its derivatives. We tried to prepare a set of derivatives by the Mannich reaction,[11] however when we followed the literature procedure[12] we could not obtain sufficient yields. We modified the reported reaction and because both our starting ether **2** and the products **3** were liquids we decided to carry out the reaction without any solvent. The components were mixed so that the corresponding secondary amine was added last.

Table 1. Structures of compounds **3**, **4**, **5** and **6** and their yields.

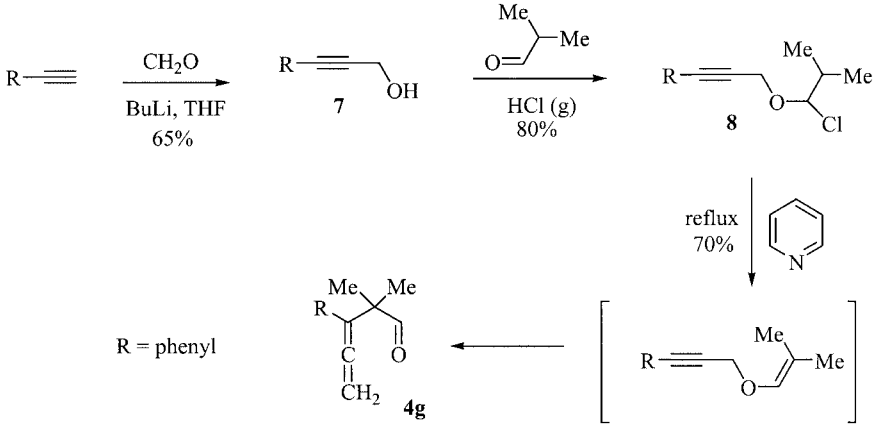
R 

Compounds	Yield [%]						
R	**a**	**b**	**c**	**d**	**e**	**f**	**g**
3	81	80	88	87	88	76	–
4	82	81	88	88	78	82	70
5	97	85	75	96	86	96	60
6	–	–	46	65	75	44	77

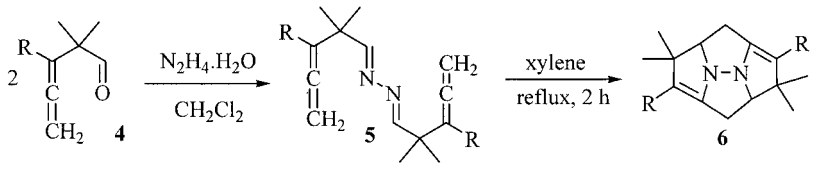
To avoid a vigorous exothermic reaction and side-product formation, the mixture had to be cooled during amine addition. After the reaction had ceased the reaction mixture was heated to 70 °C to complete the reaction. The water formed during the reaction was removed from the reaction mixture on a rotary evaporator and the product finally distilled under high vacuum on a kugelrohr apparatus. The structures of the products were proved by NMR spectroscopy (Table 1). In the next step we carried out Claisen rearrangement of ethers **3**, which gave homoallenyl aldehydes **4**. Although in most reports in the literature a pyrolytic oven was used at a temperature of over 250 °C, we have found that ether **2** rearranges easily, which led us to find some better conditions; after much experimentation we found 200 °C to be the best temperature. At this temperature the rearrangement was accomplished within 5–10 min depending on the substituent, after which it was necessary to cool the mixture rapidly. Pure compounds were obtained by kugelrohr distillation under high vacuum. The structures of compounds **4** were proved by IR and NMR spectroscopy.

The course of the reaction was followed by IR spectroscopy, which was found to be a good and very useful method for identification of the reaction course. All the products differ significantly in their characteristic bands. The chlorinated ether **1** is characterized by an intense vibration band at 2123 cm^{-1} belonging to the nonsymmetrically substituted triple bond and also by the vibration of the adjacent hydrogen atom at 3299 cm^{-1}. The ether **2** formed after elimination of the chlorine atom contained another characteristic band at 1693 cm^{-1} belonging to the double bond. Substitution of the alkynic hydrogen atom and formation of **3** is reflected by the disappearance of the corresponding vibration and because of its intensity it is a sufficient indicator of substitution. At the same time the vibration of the triple bond is shifted to 2256 cm^{-1} and its intensity is substantially reduced. The signal of the double-bond vibration 1693 cm^{-1} remains unchanged. The transformation from **3** to **4** is accompanied by the disappearance of the triple- and double-bond vibrations, but their disappearances are not significant owing to their low intensity and therefore they cannot be used to prove the transformation. In addition the double-bond vibration is overlapped by the appearance of a carbonyl-bond vibration (1720 cm^{-1}). However, a very significant and characteristic band appeared at 1952 cm^{-1} belonging to the allenyl system.

Another derivative **4g** with phenyl in the 3-position was prepared by the pathway shown in Scheme 3. Phenylacetylene was used as the starting compound, which was mixed



Scheme 3. Preparation of allenyl aldehyde **4g**.



Scheme 4. Intramolecular criss-cross cycloaddition of azines.

with paraformaldehyde and butyllithium as base. In this way phenylpropargyl alcohol **7** was prepared, which was treated with isobutyraldehyde and hydrogen chloride to produce chlorinated ether **8** with a chlorine atom in the 1-position. The elimination of hydrogen chloride was carried out in refluxing pyridine. After following the isolation procedure the product **4g** of a [3,3] sigmatropic Claisen rearrangement of propargyl vinyl ether was obtained showing that the product of the elimination reaction transformed immediately to aldehyde **4g**.

Symmetrical azines **5** were prepared from allenyl aldehydes **4** by reaction with hydrazine hydrate in a molar ratio of 2:1. In this way we prepared the azines **5a**–**g** with different substituents in the 3-position (Table 1 and Scheme 4).

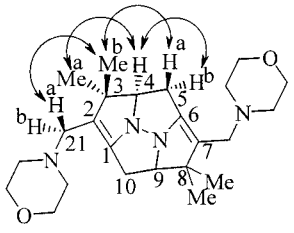
The course of this reaction was also monitored by infrared spectroscopy, by analysing the differences in the intensities of the characteristic signals. In the spectra of **5a**–**g** a new signal at 1640 cm^{-1} belonging to the C=N group appears and at the same time the signal at 1725 cm^{-1} due to the carbonyl group of **4** disappears. ^1H NMR spectroscopy was also used to monitor the reaction. The proton chemical shift of the aldehyde at about 9.5 ppm was replaced by a signal at 7.5 ppm belonging to the CH=N group. Of particular interest are the NMR spectra of allenyl aldehydes **4**, which reveal the pronounced interaction of hydrogen atoms over five bonds (hydrogen atoms on both sides of the allene cumulated double bonds) with coupling constants ranging between 2.4–2.9 Hz.

Having obtained symmetrical azines **5** we then used them in a thermally initiated intramolecular reaction. When refluxed in an inert solvent (xylene) they afforded in five cases centrally fused heterocyclic compounds **6c**–**g** consisting of four fused five-membered nitrogen-containing rings. The course of the reaction was again monitored by IR spectroscopy. During the reaction the peaks arising from the C=N group at 1640 cm^{-1} and the cumulated double bonds at 1955 cm^{-1} decreased in intensity and at the same time the signal at 1690 cm^{-1} belonging to C=C increased. When an aliphatic chain was bonded to the nitrogen atom of the aminomethyl group in the 3-position the cyclization reaction failed; it seems that some decomposition occurred.

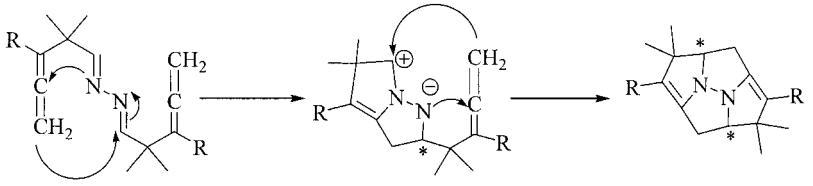
It is generally accepted that the reaction proceeds via a 1,3-dipole formed by the attack of one of the nitrogen atoms on the sp carbon atom of the allenyl skeleton. A successive attack of the dipole on the second allenyl moiety leads to the formation of a criss-cross adduct consisting of four five-membered rings. During the reaction two new stereogenic centres are formed (Scheme 5).

To assign the signals observed in the ^1H NMR spectra, 2D NMR NOESY experiments were performed and the resulting data are shown in Table 2 for compound **6e**.

Table 2. Chemical shifts, multiplicity and coupling constants of hydrogen atoms in compound **6e**.



Atom	δ [ppm]	multiplicity	*J* [Hz]
5a	2.47	dd	$J_{5a,\,4}$ = 3.0
			$J_{5a,\,5b}$ = 15.9
5b	2.30	dd	$J_{5b,\,4}$ = 9.8
			$J_{5b,\,5a}$ = 15.9
4	3.75	dd	$J_{4,\,5a}$=3.0
			$J_{4,\,5b}$ = 9.8
3a	1.10	s	–
3b	1.30	s	–
21a	2.87	d	$J_{21a,\,21b}$ = 12.9
21b	2.65	d	$J_{21b,\,21a}$ = 12.9



Scheme 5.

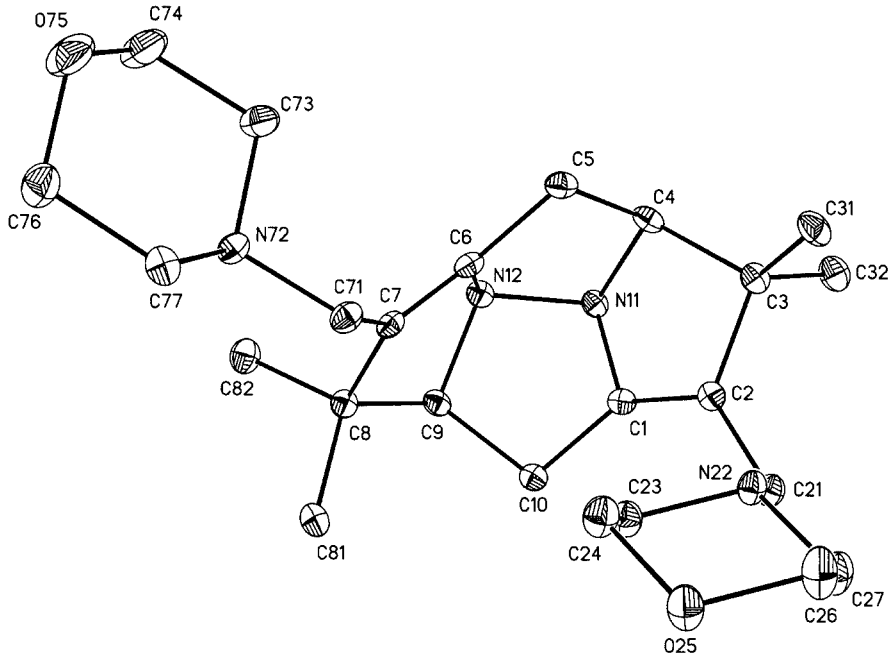


Figure 1. A perspective view of 3,3,8,8-tetramethyl-2,7-bis(morpholin-4-ylmethyl)-11,12-diazatetracyclo[4.4.2.$0^{4,11}$.$0^{9,12}$]dodeca-1,6-diene (**6e**).

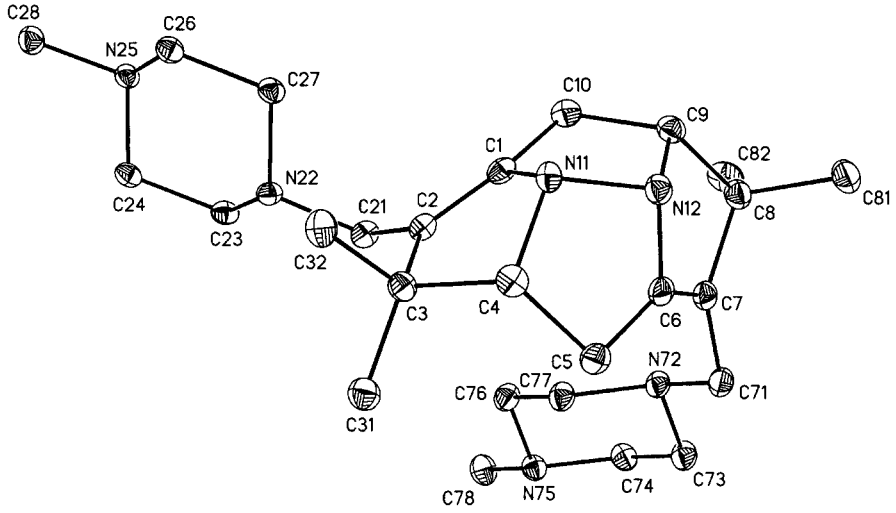


Figure 2. A perspective view of 3,3,8,8-tetramethyl-2,7-bis[(4-methylpiperazin-1-yl)methyl]-11,12-diazatetracyclo[4.4.2.$0^{4,11}$.$0^{9,12}$]dodeca-1,6-diene (**6f**).

Suitable crystals of the products **6e**, **6f** and **6g** were grown and analyzed by X-ray diffraction (Figures 1, 2, 3). The centrally fused four heterocyclic rings in each of the crystallographically characterized molecules have very similar bond lengths and angles. This is tantamount to saying that they form a very rigid structure that is not very sensitive to the nature of the attached substituents. The overall shape of the centrally fused structure might be most appropriately described as a "shallow dish" (Figure 3). The fusion of the four five-membered cycles has a significant impact on the internal bond angles, which are often less than their ideal values. The angles at the sp^3 carbon atoms are sometimes as low as 100.3°, similarly for the nitrogen atoms (angles of ca. 103° and less). The most important bond lengths and angles are listed in Table 3. The six-membered heterocyclic moieties in **6e** and **6f** adopt, as might be expected, typical chair conformations; configurations at the chiral carbons are (*R*,*R*) and (*S*,*S*), respectively.

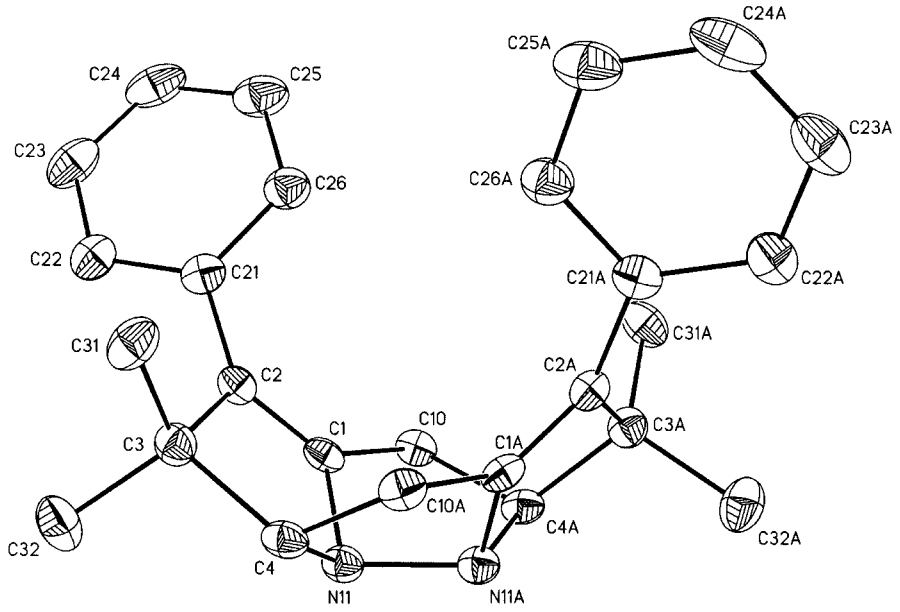


Figure 3. A perspective view of 3,3,8,8-tetramethyl-2,7-diphenyl-11,12-diazatetracyclo [4.4.2.$0^{4,11}$.$0^{9,12}$]dodeca-1,6-diene (**6g**) showing the dish-like shape of the central heterocyclic moiety. The atoms marked with the A suffix are generated by rotation through the two-fold symmetry axis that bisects the N11–N11A linkage and lies in the plane of paper.

Table 3. Crystal data and refinement parameters for compounds **6e**, **6f and 6g**.

	6e	**6f**	**6g**
Empirical formula	$C_{24}H_{38}N_4O_2$	$C_{26}H_{44}N_6$	$C_{26}H_{28}N_2$
Formula mass	414.58	440.67	368.50
Crystal system	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$	$C2/c$
a [Å]	10.400(2)	20.987(4)	19.947(3)
b [Å]	11.245(2)	15.098(3)	14.035(3)
c [Å]	19.525(4)	16.359(3)	7.2491(9)
α [°]	90	90	90
β [°]	95.58(3)	101.04(3)	91.75(2)
γ [°]	90	90	90
Volume [Å^3]	2272.6(8)	5087.5(18)	2028.5(5)
Z	4	8	4
Calculated density [Mg m^3]	1.212	1.151	1.207
Absorption coefficient [mm^{-1}]	0.078	0.070	0.070
F(000)	904	1936	792
Crystal size [mm]	0.30 × 0.30 × 0.15	0.30 × 0.20 × 0.20	0.40 × 0.40 × 0.30
Crystal colour	colourless	colourless	colourless
θ range [°]	3.52–25.00	2.88–25.00	3.39–25.00
Index range h	–12 → 7	–17 → 24	–23 → 23
Index range k	–13 → 13	–17 → 17	–16 → 9
Index range l	–23 → 23	–19 → 19	–8 → 8
Reflections collected/unique	13383/3981	30587/8899	6647/1772
Data/restraints/parameters	3981/0/271	8899/0/578	1772/0/128
GOF	1.132	1.017	1.114
Final R/wR_2 ($I > 2\sigma/I$)	0.0575/0.1223	0.0518/0.1318	0.0397/0.0971
Final R/wR_2 (all data)	0.0815/0.1329	0.0756/0.1458	0.0520/0.1022

Conclusions

We have succeeded in developing an efficient and reliable method for the preparation of chlorinated ether **1** and a procedure for the elimination of HCl from **1** to give 2-methylprop-1-en-1-yl prop-2-yn-1-yl ether (**2**). By applying the Mannich reaction we prepared a series of new ethers **3a**–**g** and these underwent Claisen rearrangement to homoallenyl aldehydes **4a**–**f**, both in good yields of around 80%. The ether **3g** was prepared in a different way and was not isolated but transformed immediately to aldehyde **4g**. All ethers **3** and homoallenyl aldehydes **4,** having an amino group, are unstable at ambient temperature even under argon and must be used immediately in subsequent transfor-

mations. Therefore compounds **4** were used in the preparation of stable symmetrical azines, which served as the starting materials in thermally initiated reactions that lead to substituted fused heterocycles. These fused heterocycles were formed by intramolecular criss-cross cycloaddition reactions that involve two successive 1,3-dipolar cycloaddition reactions within the same molecule. Two new stereogenic centres were formed through this reaction. The compounds thus formed exist as racemic mixtures of enantiomers with (*R*,*R*) and (*S*,*S*) configurations. Our experiments with the 3-substituted homoallenyl aldehyde azines have allowed us to formulate some conclusions about the role of substitution. Generally, electron-donating substituents in the 3-position increase the reactivity of azines **5** towards criss-cross cycloaddition, whereas bulky substituents cause steric hindrance reducing the reactivity of the azines. Finally the thermally initiated criss-cross reaction provides a route to interesting fused heterocyclic compounds consisting of four fused five-membered heterocycles.

Experimental Section

General Remarks: Melting points were measured on a Boetius Rapido PHMK 73/2106 (Wägetechnik) instrument with a TM-1300K thermometer. TLC was carried out on silica gel 60 F_{254} (Merck), and detection was carried out with a Fluotest Universal (Quarzlampen, Hanau) apparatus or in I_2 vapours. NMR spectra were recorded in chloroform with a Bruker Avance DRX 300 spectrometer. $CHCl_3$ and $CDCl_3$ were used as internal standards in the ^1H (δ = 7.27 ppm) and ^{13}C (triplet, δ = 77.23 ppm) NMR spectra. The ^{13}C and ^1H NMR spectra were correlated with those obtained by simulation (Advanced Chemistry Development, Inc., Toronto, Canada). FTIR spectra were measured at GENESIS ATI (Unicam) in a film between NaCl windows (wave numbers in cm^{-1}). Mass spectra (EI, 70 eV) were recorded with a FISONS TRIO 1000 instrument. Elemental analyses were performed with a FlashEA 1112, Thermo Finnigan instrument. Products **1**, **2** and **3** were kept under argon and refrigerated below –10 °C.

X-ray Crystallographic Study: Diffraction data were collected on a Kuma KM-4 four-circle single-crystal diffractometer (λ = 0.71073 Å) equipped with a CCD camera using ω scan mode and are corrected for Lorentz and polarization effects. Data collection was carried out at 120(2) K. The intensity data were corrected for Lorentz and polarization effects. All structures were solved by direct methods and refined by full-matrix least-squares methods using anisotropic thermal parameters for the non-hydrogen atoms. The positions of the hydrogen atoms were calculated from the geometry of the structures and refined by using a riding model. The software packages used were: Xcalibur CCD system for the data collection/reduction,[13] and SHELXTL for the structure solution, refinement and drawing preparation.[14] In Figures 1, 2, 3 the thermal ellipsoids are drawn at the 50% probability level and hydrogen atoms have been omitted for clarity. Details of the data collection and structure refinement are listed in Table 4.

CCDC-246503–246505 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 4. Selected bond lengths [Å] and angles [°] for compounds **6e**, **6f** and **6g**. For the two crystallographically independent molecules in **6f**, both values are given. Owing to the presence of symmetry equivalents in **6g**, the atoms N12 and C5 in **6e** and **6f** correspond to N11A and C10A in **6g**, in accord with the labeling scheme shown in Figure 3.

	6e	6f	6g
N11–N12	1.485(2)	1.479(2); 1.484(2)	1.497(2)
N11–C1	1.434(3)	1.435(2); 1.427(2)	1.430(2)
N12–C6	1.434(3)	1.433(2); 1.434(2)	
N11–C4	1.496(3)	1.492(2); 1.494(2)	1.502(2)
N12–C9	1.496(3)	1.493(2); 1.494(2)	
C1–C10	1.488(3)	1.492(2); 1.494(2)	1.490(2)
C5–C6	1.491(3)	1.496(2); 1.492(2)	
C9–C10	1.560(3)	1.558(2); 1.564(2)	1.560(2)
C4–C5	1.561(3)	1.562(2); 1.568(2)	
C1–C2	1.324(3)	1.327(2); 1.331(2)	1.329(2)
C6–C7	1.327(3)	1.326(2); 1.330(2)	
C2–C3	1.530(3)	1.533(2); 1.533(2)	1.535(2)
C7–C8	1.526(3)	1.530(2); 1.531(2)	
C3–C4	1.550(3)	1.561(2); 1.560(2)	1.563(2)
C8–C9	1.550(3)	1.553(2); 1.552(2)	
C2–C21	1.492(3)	1.491(2); 1.493(2)	1.483(2)
C7–C71	1.490(3)	1.498(2); 1.488(2)	
C1–N11–N12	102.8(1)	103.2(1); 103.5(1)	102.5(1)
C6–N12–N11	103.3(1)	103.0(1); 103.0(1)	
C4–N11–N12	106.2(2)	106.9(1); 106.9(1)	106.7(1)
C9–N12–N11	106.4(2)	106.5(1); 106.4(1)	
C1–N11–C4	103.2(2)	103.5(1); 103.5(1)	103.8(1)
C6–N12–C9	103.1(2)	103.4(1); 103.7(1)	

1-Chloro-2-methylpropyl Prop-2-yn-1-yl Ether (1): After cooling isobutyraldehyde (129 g, 1.8 mol) to –5 °C, a stream of HCl(g) was introduced for 5 s and then propargyl alcohol (67 g, 1.2 mol) was slowly added. The reaction temperature was kept between –5 and 0 °C, and the reaction mixture was vigorously agitated during the further introduction of HCl(g). At the beginning of the reaction, the reaction mixture became very viscous. After the viscosity of the reaction mixture had lowered and two phases had appeared, HCl(g) was slowly introduced into the mixture for another 30 min. Then the organic layer was separated, dried with $MgSO_4$ and after filtration the low boiling portions were removed under vacuum. The crude product was distilled under vacuum (≈20 Torr, 53–55 °C) to give ether **1** as a colourless liquid (87% yield). ^1H NMR ($CDCl_3$): δ = 1.02 (d, J = 6.7 Hz, 6 H, CH_3), 2.1 (sept d, J = 6.7, J = 4.2 Hz, 1 H, CH_3–C*H*–CH_3), 2.47 (t, J = 2.4 Hz, 1 H, H–C≡), 4.33 (dd, J = 15.9, J = 2.4 Hz, 1 H, CH_2–O), 4.39 (dd, J = 15.9, J = 2.4 Hz, 1 H, CH_2–O), 5.62 (d, J = 4.2 Hz, 1 H, O–CH–Cl) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.5, 17.6, 36.4, 56.9, 75.8, 78.0, 101.7 ppm. IR: $\tilde{\nu}$ = 1099, 1187, 1255, 1390, 1463, 2123 (C≡C), 2879, 2933, 2971, 3299 (H–C≡C) cm^{-1}. MS (EI, 70 eV): m/z (%) = 133 (100), 105 (28), 91 (13), 79 (37), 55 (40), 43 (93).

2-Methylprop-1-en-1-yl Prop-2-yn-1-yl Ether (2): Pyridine (79 g, 1.0 mol) was warmed to 75 °C and then ether **1** (146 g, 1.0 mol) was added dropwise. The temperature was kept between 75 and 80 °C during all the reaction steps. The reaction mixture was agitated for 20 minutes, and then the product was carefully distilled under vacuum. The crude product **2** was mixed with charcoal and left overnight at laboratory temperature, then filtered and distilled under vacuum (≈50 Torr; 55–58 °C). Colourless liquid (75% yield). IR: $\tilde{\nu}$ = 1024, 1147, 1274, 1367, 1446, 1693 (C=C), 2119 (C≡C), 2861, 2919, 2962, 3295 (H–C≡C) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.54 (m, 3 H, -CH_3), 1.60 (m, 3 H, -CH_3), 2.43 (t, J = 2.3 Hz, 1 H, H–C≡), 4.30 (d, J = 2.3 Hz, 2 H, CH_2), 5.90 (m, 1 H, =CH) ppm.

^{13}C NMR ($CDCl_3$): δ = 15.1, 19.5, 58.6, 74.7, 79.6, 113.0, 138.7 ppm. MS (EI, 70 eV): *m/z* (%) = 111 (19) $[M]^+$, 110 (38), 98 (17), 83 (31), 55 (52), 43 (100), 42 (57).

Preparation of Substituted Ethers 3a–f. General Procedure: Under argon, an appropriate amine (0.1 mol) was added to a mixture of CuI (100 mg), paraformaldehyde (3.0 g, equivalent of 0.1 mol CH_2O) and ether **2** (11.0 g, 0.1 mol). The reaction mixture was cooled under cold water bath for 10 minutes and then heated at 70 °C for 30 minutes. The water formed during the reaction was removed under vacuum and the product was separated by kugelrohr distillation under high vacuum (≈1 Torr). Ethers **3** were produced as colourless liquids.

***N*,*N*-Diethyl-4-[(2-methylprop-1-en-1-yl)oxy]but-2-yn-1-amine (3a):** ^{1}H NMR ($CDCl_3$): δ = 0.96 (m, 6 H, CH_3–CH_2–N), 1.47 (s, 3 H, CH_3–C=), 1.52 (s, 3 H, CH_3–C=), 2.44 (m, 4 H, CH_3–CH_2–N), 3.35 (t, *J* = 2.0 Hz, 2 H, N–CH_2–C≡), 4.22 (t, *J* = 2.0 Hz, 2 H, O–CH_2), 5.80 (m, 1 H, CH=) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.6, 15.0, 19.5, 40.9, 47.2, 58.9, 80.3, 81.5, 112.4, 138.7 ppm. IR: $\tilde{\nu}$ = 1016, 1101, 1146, 1321, 1384, 1454, 1693, 2256 (C≡C), 2821, 2927, 2972 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 196.9 (38) $[M + 2]^+$, 195.6 (100), 180.4 (30), 125.2 (57), 124.4 (30), 123.8 (73), 122.8 (29), 109.1 (49), 107.9 (31), 86.4 (10), 85.8 (21).

***N*,*N*-Diisopropyl-4-[(2-methylprop-1-en-1-yl)oxy]but-2-yn-1-amine (3b):** ^{1}H NMR ($CDCl_3$): δ = 1.09 (d, *J* = 6.6 Hz, 12 H, C*H*$_3$–CH–C*H*$_3$), 1.56 (s, 3 H, CH_3–C=), 1.61 (s, 3 H, CH_3–C=), 3.19 (sept, *J* = 6.6 Hz, 2 H, CH_3–CH–CH_3), 3.46 (t, *J* = 1.9 Hz, 2 H, N–CH_2–C≡), 4.30 (t, *J* = 1.9 Hz, 2 H, O–CH_2), 5.89 (m, 1 H, CH=) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.1, 19.6, 20.7, 34.4, 48.6, 59.3, 79.1, 86.2, 112.4, 138.9 ppm. IR: $\tilde{\nu}$ = 1014, 1144, 1269, 1340, 1383, 1464, 1693, 2256 (C≡C), 2828, 2927, 2966 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 225.0 (33) $[M + 2]^+$, 223.7 (76), 152.3 (19), 151.2 (15), 137.2 (17), 136.1 (17), 121.9 (15), 114.0 (8), 109.9 (8).

1-{4-[(2-Methylprop-1-en-1-yl)oxy]but-2-yn-1-yl}pyrrolidine (3c): ^{1}H NMR ($CDCl_3$): δ = 1.47 (s, 3 H, CH_3–C=), 1.52 (s, 3 H, CH_3–C=), 1.71 (m, 4 H, C*H*$_2$–CH_2–N), 2.52 (m, 4 H, CH_2–C*H*$_2$–N), 3.35 (t, *J* = 1.8 Hz, 2 H, N–CH_2–C≡), 4.23 (t, *J* = 1.8 Hz, 2 H, O–CH_2), 5.81 (m, 1 H, CH=) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.0, 19.5, 23.8, 43.2, 52.5, 58.9, 79.9, 82.5, 112.3, 138.7 ppm. IR: $\tilde{\nu}$ = 1014, 1146, 1272, 1322, 1346, 1448, 1693, 2256 (C≡C), 2789, 2910, 2962 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 194.3 (100) $[M + 1]^+$, 192.1 (13), 123.2 (37), 122.2 (40), 121.3 (33), 119.6 (20), 93.6 (16), 84.0 (14).

1-{4-[(2-Methylprop-1-en-1-yl)oxy]but-2-yn-1-yl}piperidine (3d): ^{1}H NMR ($CDCl_3$): δ = 1.42 (m, 2 H, C*H*$_2$–CH_2–CH_2–N), 1.5–1.7 (m, 4 H, C*H*$_2$–CH_2–N), 1.55 (s, 3 H, CH_3–C=), 1.60 (s, 3 H, CH_3–C=), 2.47 (t, *J* = 5.1 Hz, 4 H, CH_2–C*H*$_2$–N), 3.28 (t, *J* = 2.0 Hz, 2 H, N–CH_2–C≡), 4.32 (t, *J* = 2.0 Hz, 2 H, O–CH_2), 5.90 (m, 1 H, CH=) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.1, 19.5, 24.0, 26.0, 48.0, 53.3, 59.0, 80.5, 82.2, 112.4, 138.8 ppm. IR: $\tilde{\nu}$ = 1016, 1146, 1340, 1444, 1691, 2256 (C≡C), 2754, 2798, 2854, 2933 cm^{-1}.MS (EI, 70 eV): *m/z* (%) = 209.6 (13) $[M + 2]^+$, 208.3 (100), 206.2 (15), 137.3 (15), 136.0 (70), 134.0 (14), 108.0 (13), 98.0 (16).

4-{4-[(2-Methylprop-1-en-1-yl)oxy]but-2-yn-1-yl}morpholine (3e): ^{1}H NMR ($CDCl_3$): δ = 1.53 (s, 3 H, CH_3–C=), 1.59 (s, 3 H, CH_3–C=), 2.52 (t, *J* = 4.7 Hz, 4 H, O–CH_2–C*H*$_2$–N), 3.29 (t, *J* = 1.8 Hz, 2 H, N–CH_2–C≡), 3.70 (t, *J* = 4.7 Hz, 4 H, O–C*H*$_2$–CH_2–N), 4.30 (t, *J* = 1.8 Hz, 2 H, O–CH_2), 5.90 (m, 1 H, CH=) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.2, 19.6, 47.6, 52.4, 59.0, 67.0, 81.3, 81.4, 112.8, 138.8 ppm. IR: $\tilde{\nu}$ = 1004, 1117, 1147, 1288, 1346, 1452, 1693, 2256 (C≡C), 2762, 2814, 2856, 2914, 2960 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 211.6 (7) $[M + 2]^+$, 210.3 (95), 139.4 (13), 137.9 (100), 107.9 (20), 100.0 (22).

1-Methyl-4-{4-[(2-methylprop-1-en-1-yl)oxy]but-2-yn-1-yl}piperazine (3f): ^{1}H NMR ($CDCl_3$): δ = 1.40 (s, 3 H, CH_3–C=), 1.45 (s, 3 H, CH_3–C =), 2.14 (s, 3 H, CH_3–N), 2.2–2.5 (m, 8 H, CH_2–CH_2), 3.19 (t, *J* = 1.9 Hz, 2 H, N–CH_2–C≡), 4.16 (t, *J* = 1.9 Hz, 2 H, O–CH_2), 5.73 (m, 1 H, CH =) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.0, 19.4, 45.9, 47.0, 51.9, 54.9, 58.8, 80.8, 81.5, 112.3, 138.6 ppm. IR: $\tilde{\nu}$ = 1012, 1145, 1283, 1346, 1455, 1692, 2258 (C≡C), 2765, 2795, 2840, 2934 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 224.0 (52) $[M + 1]^+$, 223.0 (100), 221.6 (19), 152.4 (17), 150.9 (91), 112.8 (98), 107.7 (36), 98.9 (41).

Preparation of Homoallenyl Aldehydes 4a–f by Claisen Rearrangement. General Procedure: Ether **3** was heated under argon in an oil bath preheated to 200 °C for 5–10 minutes. The product, after rapid cooling in running tap water, was distilled under high vacuum (≈1 Torr) using a kugelrohr apparatus. Ethers **4** were produced as colourless liquids.

3-[(Diethylamino)methyl]-2,2-dimethylpenta-3,4-dienal (4a): ^{1}H NMR ($CDCl_3$): δ = 0.90 (t, *J* = 7.1 Hz, 6 H, C*H*$_3$–CH_2), 1.13 (s, 6 H, C*H*$_3$–C–C*H*$_3$), 2.44 (m, 4 H, CH_3–C*H*$_2$), 2.93 (t, *J* = 2.0 Hz, 2 H, N–CH_2–C=), 4.78 (t, *J* = 2.0 Hz, 2 H, CH_2=), 9.22 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.7, 21.4, 45.6, 46.8, 53.9, 76.7, 105.6, 200.7, 207.7 ppm. IR: $\tilde{\nu}$ = 845, 1090, 1387, 1456, 1718 (C=O), 1953 (C=C=C), 2708, 2808, 2933, 2970 cm^{-1}. GC–MS: *m/z* (%) = 196.2 (49) $[M + 1]^+$, 167.3 (13), 166.2 (16), 152.1 (11), 86.0 (100).

3-[(Diisopropylamino)methyl]-2,2-dimethylpenta-3,4-dienal (4b): ^{1}H NMR ($CDCl_3$): δ = 0.95 (d, *J* = 6.7 Hz, 12 H, C*H*$_3$–CH–C*H*$_3$), 1.18 (s, 6 H, C*H*$_3$–C–C*H*$_3$), 3.05 (sept, *J* = 6.7 Hz, 2 H, CH_3–C*H*–CH_3), 3.08 (t, *J* = 2.1 Hz, 2 H, N–CH_2–C=), 4.79 (t, *J* = 2.1 Hz, 2 H, CH_2=), 9.32 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.2, 21.4, 45.2, 47.0, 47.1, 76.6, 106.0, 201.8, 208.5 ppm. IR: $\tilde{\nu}$ = 843, 1174, 1363, 1390, 1462, 1720 (C=O), 1952 (C=C=C), 2707, 2834, 2872, 2933, 2966 cm^{-1}.GC–MS: *m/z* (%) = 224.6 (5) $[M + 1]^+$, 194.6 (8), 180.2 (16), 136.1 (13), 114.1 (100).

2,2-Dimethyl-3-(pyrrolidin-1-ylmethyl)penta-3,4-dienal (4c): ^{1}H NMR ($CDCl_3$): δ = 1.07 (s, 6 H, C*H*$_3$–C–C*H*$_3$), 1.59 (m, 4 H, C*H*$_2$–CH_2–N), 2.38 (m, 4 H, CH_2–C*H*$_2$–N), 2.95 (t, *J* = 2.4 Hz, 2 H, N–CH_2–C=), 4.75 (t, *J* = 2.4 Hz, 2 H, CH_2=), 9.13 (1 H, s, CH=O) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.2, 23.8, 46.8, 53.5, 55.2, 77.2, 105.8, 200.0, 206.6 ppm. IR: $\tilde{\nu}$ = 847, 1142, 1346, 1460, 1716 (C=O), 1954 (C=C=C), 2706, 2796, 2875, 2929, 2968 cm^{-1}. GC–MS: *m/z* (%) = 194.2 (17) $[M + 1]^+$, 164.7 (15), 150.1 (8), 84.0 (100).

2,2-Dimethyl-3-(piperidin-1-ylmethyl)penta-3,4-dienal (4d): ^{1}H NMR ($CDCl_3$): δ = 1.15 (s, 6 H, C*H*$_3$–C–C*H*$_3$), 1.3–1.5 (m, 6 H, C*H*$_2$–C*H*$_2$–CH_2–N), 2.33 (m, 4 H, CH_2–CH_2–C*H*$_2$–N), 2.83 (t, *J* = 2.1 Hz, 2 H, N–CH_2–C=), 4.80 (t, *J* = 2.1 Hz, 2 H, CH_2=), 9.28 (1 H, s, CH=O) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.4, 24.5, 25.7, 47.0, 54.3, 58.9, 76.8, 105.0, 201.0, 207.4 ppm. IR: $\tilde{\nu}$ = 844, 993, 1116, 1338, 1454, 1716 (C=O), 1954 (C=C=C), 2715, 2796, 2935 cm^{-1}. GC–MS: *m/z* (%) = 208.3 (20) $[M + 1]^+$, 178.2 (11), 98.0 (100).

2,2-Dimethyl-3-(morpholin-4-ylmethyl)penta-3,4-dienal (4e): ^{1}H NMR ($CDCl_3$): δ = 1.10 (s, 6 H, C*H*$_3$–C–C*H*$_3$), 2.36 (t, *J* = 4.5 Hz, 4 H, N–C*H*$_2$–CH_2–O), 2.84 (t, *J* = 2.0 Hz, 2 H, N–CH_2–C=), 3.52 (t, *J* = 4.5 Hz, 4 H, N–CH_2–C*H*$_2$–O), 4.77 (t, *J* = 2.0 Hz, 2 H, CH_2=), 9.27 (1 H, s, CH=O) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.6, 46.9, 53.1, 58.5, 66.7, 77.0, 103.6, 201.1, 207.7 ppm. IR: $\tilde{\nu}$ = 863, 1007, 1116, 1308, 1456, 1716 (C=O), 1954 (C=C=C), 2704, 2810, 2856, 2964 cm^{-1}. GC–MS: *m/z* (%) = 210.2 (20) $[M + 1]^+$, 181.4 (13), 179.9 (10), 166.1 (14), 122.7 (12), 99.9 (100).

2,2-Dimethyl-3-[(4-methylpiperazin-1-yl)methyl]penta-3,4-dienal-(4f): ^{1}H NMR ($CDCl_3$): δ = 1.13 (s, 6 H, C*H*$_3$–C–C*H*$_3$), 2.21 (s, 3

H, N–CH_3), 2.2–2.5 (m, 8 H, N–CH_2–CH_2–N), 2.86 (t, J = 2.0 Hz, 2 H, N–CH_2–C=), 4.80 (t, J = 2.0 Hz, 2 H, CH_2=), 9.28 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.4, 46.1, 47.0, 52.8, 54.9, 58.1, 77.0, 104.3, 201.4, 207.6 ppm. IR: $\tilde{\nu}$ = 822, 1011, 1163, 1282, 1456, 1716 (C=O), 1954 (C=C=C), 2694, 2796, 2935, 2966 cm^{-1}. GC–MS: *m/z* (%) = 221.2 (1) $[M]^+$, 193.2 (45), 113.0 (53). MS (EI, 70 eV): *m/z* (%) = 223.4 (100) $[M + 1]^+$, 221.7 (18), 220.6 (9), 194.7 (22), 193.2 (58), 113.0 (74).

2,2-Dimethyl-3-phenylpenta-3,4-dienal (4g):[15] Pyridine (6.82 g, 0.086 mol) was heated to reflux and then ether **8** (15.6 g, 0.070 mol) was added dropwise. The reaction mixture was refluxed for an hour whilst stirring. Then the mixture was mixed with water and extracted with diethyl ether. The ether layer was dried with $MgSO_4$. The solvent and the excess of the pyridine were removed under vacuum. The remainder was distilled under vacuum (≈1 Torr, 133–138 °C). Colourless liquid (9.2 g, 70% yield). ^{1}H NMR ($CDCl_3$): δ = 1.27 (s, 6 H, CH_3), 5.09 (s, 2 H, C=CH_2), 7.2–7.3 (m, 5 H, $H_{ar.}$), 9.60 (s, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.08, 48.71, 78.56, 108.48, 128.59, 135.36, 203.38, 209.24 ppm. IR (NaCl): $\tilde{\nu}$ = 1030, 1144, 1442, 1728 (C=O), 1940 (C=C=C), 2701, 2802, 2931, 3056 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 186 (33) $[M]^+$, 171 (96), 143 (40), 128 (55), 115 (100), 91 (30), 77 (32), 43 (58).

Synthesis of Azines 5a–g. General Procedure: Using a Dean–Stark apparatus, hydrazine hydrate was added dropwise to allenyl aldehyde **4** (in a hydrazine hydrate/allenylaldehyde molar ratio of 1:2) in dichloromethane (10 mL) in a flask fitted with a magnetic stirring. The reaction mixture was refluxed and water was removed by azeotropic distillation for 6 hours. Then the solvent was removed under vacuum and the residue was washed with petroleum ether, dried and identified.

3-[(Diethylamino)methyl]-2,2-dimethylpenta-3,4-dienal Azine (5a): Reaction mixture: aldehyde **4a** (2.47 g, 12.7 mmol), hydrazine hydrate (0.32 g, 6.3 mmol). Yield: 2.39 g (97%). Yellow liquid. ^{1}H NMR ($CDCl_3$): δ = 0.97 (m, 12 H, CH_3), 1.28 (s, 12 H, CH_3), 2.49 (m, 8 H, CH_2), 3.01 (t, J = 2.5 Hz, 4 H, C–CH_2–N), 4.80 (t, J = 2.5 Hz, 4 H, =CH_2), 7.67 (s, 2 H, CH=N) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.58, 25.04, 39.73, 46.46, 53.36, 77.16, 106.94, 168.16, 207.40 ppm. IR (NaCl): $\tilde{\nu}$ = 843, 1089, 1145, 1295, 1382, 1459, 1641 (C=N), 1951 (C=C=C), 2802, 2933, 2967 cm^{-1}.

3-[(Diisopropylamino)methyl]-2,2-dimethylpenta-3,4-dienal Azine (5b): Reaction mixture: aldehyde **4b** (2.00 g, 8.9 mmol), hydrazine hydrate (0.22 g, 4.5 mmol). Yield: 1.69 g (85%). Yellow solid, m.p. 44–48 °C. ^{1}H NMR ($CDCl_3$): δ = 0.98 (m, 24 H, CH_3), 1.27 (s, 12 H, CH_3), 3.0–3.1 (m, J = 2.7 Hz, 8 H, C–CH_2–N, CH), 4.76 (t, J = 2.7 Hz, 4 H, =CH_2), 7.71 (s, 2 H, CH=N) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.63, 25.24, 39.81, 44.89, 47.48, 77.12, 108.94, 168.70, 207.93 ppm. IR (KBr): $\tilde{\nu}$ = 840, 1041, 1139, 1380, 1461, 1641 (C=N), 1951 (C=C=C), 2823, 2869, 2966 cm^{-1}.

2,2-Dimethyl-3-(pyrrolidin-1-ylmethyl)penta-3,4-dienal Azine (5c): Reaction mixture: aldehyde **4c** (2,00 g, 10.4 mmol), hydrazine hydrate (0.26 g, 5.2 mmol). Yield: 1.49 g (75%). White solid, m.p. 23–26 °C. ^{1}H NMR ($CDCl_3$): δ = 1.24 (s, 12 H, CH_3), 1.69 (m, 8 H, CH_2–CH_2), 2.45 (m, 8 H, CH_2–N), 3.01 (t, J = 3.0 Hz, 4 H, C–CH_2–N), 4.82 (t, J = 3.0 Hz, 4 H, =CH_2), 7.54 (s, 2 H, CH=N) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.70, 24.78, 39.76, 54.23, 55.14, 78.07, 107.37, 167.31, 206.55 ppm. IR (KBr): $\tilde{\nu}$ = 842, 933, 1143, 1346, 1459, 1641 (C=N), 1953 (C=C=C), 2726, 2780, 2962 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 382 (9) $[M]^+$, 312 (15), 242 (14), 227 (12), 191 (53), 122 (30), 84 (100).

2,2-Dimethyl-3-(piperidin-1-ylmethyl)penta-3,4-dienal Azine (5d): Reaction mixture: aldehyde **4d** (2.28 g, 11.0 mmol), hydrazine hydrate (0.28 g, 5.5 mmol). Yield: 2.19 g (96%). Light yellow solid, m.p. 51–55 °C. ^{1}H NMR ($CDCl_3$): δ = 1.29 (s, 12 H, CH_3), 1.51 (m, 12 H, CH_2), 2.34 (m, 8 H, CH_2N), 2.88 (t, J = 2.4 Hz, 4 H, C–CH_2–N), 4.80 (t, J = 2.4 Hz, 4 H, =CH_2), 7.68 (s, 2 H, CH=N) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.77, 25.08, 26.16, 39.80, 54.69, 58.87, 77.15, 106.33, 168.24, 207.27 ppm. IR (KBr): $\tilde{\nu}$ = 842, 991, 1114, 1265, 1305, 1342, 1450, 1641 (C=N), 1951 (C=C=C), 2751, 2856, 2933 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 410 (52) $[M]^+$, 395 (14), 326 (100), 312 (46), 242 (89), 227 (35), 213 (18).

2,2-Dimethyl-3-(morpholin-4-ylmethyl)penta-3,4-dienal Azine (5e): Reaction mixture: aldehyde **4e** (4.06 g, 19.1 mmol), hydrazine hydrate (0.49 g, 9.6 mmol). Yield: 3.44 g (86%). Yellow solid, m.p. 56–58 °C. ^{1}H NMR ($CDCl_3$): δ = 1.29 (s, 12 H, CH_3), 2.41 (t, J = 4.5 Hz, 8 H, CH_2–N), 2.93 (t, J = 2.2 Hz, 4 H, C–CH_2–N), 3.65 (t, J = 4.5 Hz, 8 H, CH_2–O), 4.81 (t, J = 2.2 Hz, 4 H, =CH_2), 7.69 (s, 2 H, CH=N) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.98, 39.74, 53.57, 58.46, 67.09, 77.25, 105.38, 168.47, 207.46 ppm. IR (KBr): $\tilde{\nu}$ = 862, 1004, 1118, 1346, 1450, 1643 (C=N), 1951 (C=C=C), 2688, 2800, 2854, 2971 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 414 (16) $[M]^+$, 328 (20), 207 (80), 122 (28), 100 (100), 56 (20).

2,2-Dimethyl-3-[(4-methylpiperazin-1-yl)methyl]penta-3,4-dienal Azine (5f): Reaction mixture: aldehyde **4f** (3.00 g, 13.5 mmol), hydrazine hydrate (0.34 g, 6.8 mmol). Yield: 2.88 g (96%). Yellow solid, m.p. 61–66 °C. ^{1}H NMR ($CDCl_3$): δ = 1.27 (s, 12 H, CH_3), 2.3–2.5 (m, 22 H, CH_2, CH_3), 2.92 (t, J = 2.3 Hz, 4 H, C–CH_2–N), 4.79 (t, J = 2.3 Hz, 4 H, =CH_2), 7.66 (s, 2 H, CH=N) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.10, 39.80, 46.23, 53.11, 55.32, 58.03, 77.19, 105.88, 168.26, 207.38 ppm. IR (KBr): $\tilde{\nu}$ = 847, 1012, 1162, 1346, 1456, 1643 (C=N), 1952 (C=C=C), 2761, 2798, 2931 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 440 (43) $[M]^+$, 425 (12), 341 (31), 242 (100), 227 (20).

2,2-Dimethyl-3-phenylpenta-3,4-dienal Azine (5g): Reaction mixture: aldehyde **4g** (8.53 g, 45.8 mmol), hydrazine hydrate (1.15 g, 22.9 mmol). Yield: 5.08 g (60%). White solid, m.p. 73–83 °C. ^{1}H NMR ($CDCl_3$): δ = 1.37 (s, 12 H, CH_3), 5.01 (s, 4 H, =CH_2), 7.2–7.3 (m, 10 H, $H_{ar.}$), 7.78 (s, 2 H, CH=N) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.73, 40.68, 77.89, 111.20, 127.09, 128.25, 128.92, 130.52, 168.54, 208.39 ppm. IR (KBr): $\tilde{\nu}$ = 865, 948, 1124, 1155, 1446, 1490, 1633 (C=N), 1940 (C=C=C), 2865, 2929, 3077 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 368 (16) $[M]^+$, 353 (32), 184 (45), 141 (58), 128 (82), 115 (100), 77 (25).

Criss-Cross Cycloaddition to 6c–g. General Procedure: Azine **5** was refluxed in dry xylene under argon for 2 hours. Then the solvent was then removed under vacuum and the solid residue was washed with diethyl ether and then with acetonitrile. After filtration of the solid the compound was identified as a pure product.

3,3,8,8-Tetramethyl-2,7-bis(pyrrolidin-1-ylmethyl)-11,12-diazatetracyclo[4.4.2.0^{4,11}.0^{9,12}]dodeca-1,6-diene (6c): Reaction mixture: azine **5c** (256.3 mg, 0.67 mmol) in dry xylene (5 mL). Yield: 117 mg (46%). White solid, m.p. 115–119 °C. ^{1}H NMR ($CDCl_3$): δ = 1.10 (s, 6 H, CH_3), 1.30 (s, 6 H, CH_3), 1.70 (m, 8 H, CH_2), 2.21 (dd, J_1 = 9.8, J_2 = 15.9 Hz, 2 H, CH_2), 2.3–2.4 (m, 8 H, CH_2–N), 2.54 (dd, J_1 = 3.0, J_2 = 15.9 Hz, 2 H, CH_2), 2.73 (d, J = 12.9 Hz, 2 H, CH_2), 3.07 (d, J = 12.9 Hz, 2 H, CH_2), 3.73 (dd, J_1 = 3.0, J_2 = 9.8 Hz, 2 H, CH) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.89, 23.83, 25.06, 28.56, 51.49, 54.49, 77.54, 118.66, 149.21 ppm. IR (KBr): $\tilde{\nu}$ = 879, 1045, 1110, 1261, 1348, 1461, 1699 (C=C), 2728, 2775, 2960 cm^{-1}. MS (EI, 70 eV): *m/z* (%) 382 $[M^+, 9]$, 312 (9), 242 (20), 147 (11), 120 (24), 84 (88), 79 (33), 70 (100), 42 (84). $C_{24}H_{38}N_4$ (382.59): calcd. C 75.34, H 10.01, N 14.64; found C 75.00, H 10.33, N 14.50.

3,3,8,8-Tetramethyl-2,7-bis(piperidin-1-ylmethyl)-11,12-diazatetracyclo[4.4.2.0^{4,11}.0^{9,12}]dodeca-1,6-diene (6d): Reaction mixture: azine

5d (490 mg, 1.20 mmol) in dry xylene (5 mL). Yield: 0.32 g (65%). Light yellow solid, m.p. 118–122 °C. ^{1}H NMR ($CDCl_3$): δ = 1.10 (s, 6 H, CH_3), 1.30 (s, 6 H, CH_3), 1.47 (m, 12 H, CH_2), 2.1–2.3 (m, 10 H, CH_2), 2.51 (dd, J_1 = 3.3, J_2 = 15.9 Hz, 2 H, CH_2), 2.64 (d, J = 13.2 Hz, 2 H, CH_2), 2.83 (d, J = 13.2 Hz, 2 H, CH_2), 3.74 (dd, J_1 = 3.3, J_2 = 9.6 Hz, 2 H, CH) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.89, 24.91, 24.98, 26.40, 28.50, 51.50, 54.79, 77.56, 117.56, 149.88 ppm. IR (KBr): $\tilde{\nu}$ = 788, 985, 1041, 1105, 1342, 1440, 1698 (C=C), 2751, 2935 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 410 (32) $[M]^+$, 326 (48), 241 (63), 120 (26), 98 (100), 84 (43), 41 (29). $C_{26}H_{42}N_4$ (410.64): calcd. C 76.05, H 10.31, N 13.64; found C 76.00, H 10.53, N 13.60.

3,3,8,8-Tetramethyl-2,7-bis(morpholin-1-ylmethyl)-11,12-diazatetracyclo[4.4.2.0^{4,11}.0^{9,12}]dodeca-1,6-diene (6e): Reaction mixture: azine **5e** (2.00 g, 4.83 mmol) in dry xylene (5 mL). Yield: 1.49 g (75%). White solid, m.p. 160–165 °C. ^{1}H NMR ($CDCl_3$): δ = 1.10 (s, 6 H, CH_3), 1.30 (s, 6 H, CH_3), 2.2–2.4 (m, 8 H, CH_2–N; dd, J_1 = 9.8, J_2 = 15.9 Hz, 2 H, CH_2), 2.47 (dd, J_1 = 3.0, J_2 = 15.9 Hz, 2 H, CH_2), 2.65 (d, J = 12.9 Hz, 2 H, CH_2), 2.87 (d, J = 12.9 Hz, 2 H, CH_2), 3.65 (m, 8 H, CH_2–O), 3.75 (dd, J_1 = 3.0, J_2 = 9.8 Hz, 2 H, CH) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.85, 24.99, 28.48, 51.52, 53.89, 54.44, 67.33, 77.55, 116.34, 150.77 ppm. IR (KBr): $\tilde{\nu}$ = 864, 1002, 1116, 1272, 1346, 1450, 1698 (C=C), 2759, 2944 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 414 (21) $[M]^+$, 328 (31), 241 (53), 147 (59), 120 (28), 100 (100), 77 (44), 56 (75). $C_{24}H_{38}N_4O_2$ (414.58): calcd. C 69.53, H 9.24, N 13.51; found C 69.49, H 9.32, N 13.49.

3,3,8,8-Tetramethyl-2,7-bis[(4-methylpiperazin-1-yl)methyl]-11,12-diazatetracyclo[4.4.2.0^{4,11}.0^{9,12}]dodeca-1,6-diene (6f): Reaction mixture: azine **5f** (500 mg, 1.13 mmol) in dry xylene (5 mL). Yield: 218.7 mg (44%). Yellow solid, m.p. 135–140 °C. ^{1}H NMR ($CDCl_3$): δ = 1.09 (s, 6 H, CH_3), 1.29 (s, 6 H, CH_3), 2.1–2.4 (m, 24 H, CH_2, CH_3), 2.48 (dd, J_1 = 3.3, J_2 = 15.9 Hz, 2 H, CH_2), 2.68 (d, J = 12.9 Hz, 2 H, CH_2), 2.88 (d, J = 12.9 Hz, 2 H, CH_2), 3.72 (dd, J_1 = 3.3, J_2 = 9.8 Hz, 2 H, CH) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.88, 25.01, 28.52, 46.31, 51.53, 53.36, 53.97, 55.60, 77.58, 116.97, 150.39 ppm. IR (KBr): $\tilde{\nu}$ = 822, 1011, 1161, 1284, 1348, 1456, 1701 (C=C), 2759, 2933 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 440 (9) $[M]^+$, 340 (42), 241 (100), 147 (20), 120 (35), 99 (51), 70 (75), 58 (69), 42 (78). $C_{26}H_{44}N_6$ (440.67): calcd. C 70.86, H 10.06, N 19.07; found C 70.58, H 9.89, N 18.75.

3,3,8,8-Tetramethyl-2,7-diphenyl-11,12-diazatetracyclo[4.4.2.0^{4,11}.0^{9,12}]dodeca-1,6-diene (6g): Reaction mixture: azine **5g** (79.6 mg, 0.22 mmol) in dry xylene (5 mL). Yield: 61.4 mg (77%). White solid, m.p. 159–163 °C. ^{1}H NMR ($CDCl_3$): δ = 1.20 (s, 6 H, CH_3), 1.44 (s, 6 H, CH_3), 2.52 (dd, J_1 = 9.6, J_2 = 16.2 Hz, 2 H, CH_2), 2.69 (dd, J_1 = 3.6, J_2 = 16.2 Hz, 2 H, CH_2), 3.94 (dd, J_1 = 3.6, J_2 = 9.6 Hz, 2 H, CH), 7.2–7.3 (m, 10 H, $H_{ar.}$) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.58, 26.52, 29.05, 52.99, 77.55, 122.63, 126.53, 128.62, 135.70, 149.73 ppm. IR (KBr): $\tilde{\nu}$ = 806, 910, 1026, 1250, 1465, 1599, 1670 (C=C), 2859, 2966, 3059 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 368 (78) $[M]^+$, 353 (25), 312 (37), 184 (100), 170 (67), 141 (44), 128 (73), 115 (41), 91 (18), 77 (22), 41 (17). $C_{26}H_{28}N_2$ (368.51): calcd. C 84.74, H 7.66, N 7.60; found C 84.79, H 7.82, N 7.56.

3-Phenylprop-2-yn-1-ol (7): Phenylacetylene (9.0 g, 0.088 mol) was dissolved in dry tetrahydrofuran (60 mL) and cooled to –78 °C whilst stirring. Then 1.6 M butyllithium (51 mL, 0.092 mol) was added dropwise. After addition the reaction mixture was warmed to 0 °C and paraformaldehyde (5.2 g, 0.173 mol) was added in one portion. Then the reaction mixture was stirred overnight at room temperature. Finally the mixture was treated with H_2O (20 mL), extracted with diethyl ether (40 mL) and dried with $MgSO_4$. The solvent was removed under vacuum and the residue distilled under vacuum (≈7 Torr, 126–132 °C). Yield: 7.58 g (65%) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ = 2.6–2.7 (m, 1 H, OH), 4.52 (d, 2 H, CH_2), 7.3–7.4 (m, 5 H, $H_{ar.}$) ppm. ^{13}C NMR ($CDCl_3$): δ = 51.57, 85.73, 87.49, 122.73, 128.58, 131.82 ppm. IR (NaCl): $\tilde{\nu}$ = 1029, 1095, 1257, 1448, 1601, 2237, 2856, 2923, 3346 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 132 (65) $[M]^+$, 131 (100), 115 (33), 103 (60), 77 (70), 51 (40), 39 (15).

1-Chloro-2-methylpropyl 3-Phenylprop-2-yn-1-yl Ether (8): Isobutyraldehyde (19.8 g, 0.272 mol) was cooled to –5 °C, then HCl(g) was introduced into the flask and propargyl alcohol (12.0 g, 0.091 mol) was slowly added. The reaction temperature was kept between –5 and 0 °C and the reaction mixture was vigorously stirred. HCl(g) must be added as fast as possible. The end of the reaction was indicated by the formation of two layers. Then the organic layer was separated, dried with $MgSO_4$ and after filtration the low-boiling portions were removed under vacuum. The crude product was distilled under vacuum (≈1 Torr, 112–116 °C). Yield: 15.9 g (79%) as a colourless liquid. ^{1}H NMR ($CDCl_3$): δ = 1.0–1.1 (m, 6 H, CH_3), 2.1–2.2 (m, 1 H, CH), 4.52 (s, 2 H, CH_2), 5.73 (d, 1 H, CH), 7.3–7.5 (m, 5 H, $H_{ar.}$) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.68, 36.51, 57.81, 85.04, 86.50, 102.16, 122.70, 128.54 ppm. IR (NaCl): $\tilde{\nu}$ = 690, 1139, 1363, 1596, 1689, 2239, 2924, 2967, 3059 cm^{-1}.

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