Benzazepine formation by the 1.7 electrocyclisations of diene-conjugated nitrile ylides: studies on relative rates of cyclisation *via* intramolecular competition reactions[1]

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A series of reactions has been carried out using reactants of the type **19** in which nitrile ylide cyclisation on to the substituent at the 6 position is in competition with cyclisation on to the unsubstituted phenyl group at the 2 position. The relative reactivity of the two groups, determined by measuring the product ratio **20**:**21**, was determined for a series of 6-substituents as shown in Table 8. This is the first collection of such data for the electrocyclisation of 1,3-dipolar intermediates. Alkenyl groups and the thiophene ring were found to be > 100 × more reactive than phenyl. In cases where the 6-substituent was a substituted aryl group it was found that *all* aromatic substituents at the 3′ and 4′ positions, irrespective of their electronic nature, increased the reactivity of the ring relative to that of the unsubstituted phenyl group. In contrast, a methyl group at the 2′ position produced strong deactivation. The results are discussed in terms of the steric and electronic effects of the substituents.

Introduction

This paper is concerned with the reaction rates of 1.7 electrocyclisations of diene-conjugated 1,3-dipolar intermediates **1**. The synthetic utility of reactions of this type has been studied for several 1,3-dipoles and many different types of diene and it has been found that they provide a versatile and effective general route to monocyclic and fused seven-membered heterocycles **2**.[2] Their use is illustrated in Scheme 1 for the cyclisation of various types of unsaturated nitrile ylides **3**, **5**, **7** and **10**, to give the azepines **4**, **6**, **8**, **9** and **11**, respectively. Most of the earlier work on these and related reactions has been primarily concerned with their development as preparative routes to unsaturated seven-membered heterocyclic systems[3–6] and with the determination of the structural factors which control 1.5 *vs.* 1.7 periselectivity. These reactions are thought to follow a general reaction mechanism which involves, as a first step, an 8π electron electrocyclisation reaction taking place *via* a helical transition state **12**,[3] followed in the cases shown by a [1,5] hydrogen migration. The helical nature of the transition state is supported by theoretical calculations where the 1,3-dipole is a diazo compound.[7] However, although the basic reaction mechanism is known there are still major gaps in our understanding of the factors controlling these reactions. The major deficiency is that for electrocyclisation reactions in general there is no simple theoretical model comparable to the Sustmann treatment of concerted cycloaddition reactions[8] which can be used to predict the effect of substituents or other structural changes on the rate of reaction. Thus, in our earlier work, there was no way of predicting the effects of electron-withdrawing or -donating ring substituents **R** on the efficacy of the cyclisation of **7**;[5] or of predicting whether the cyclisation would be effective on electron-rich or -poor heterocyclic rings, *e.g.* **10** (hetaryl = thienyl) and **10** (hetaryl = pyridyl), respectively.[6] Not only is there no simple predictive theoretical model, but, for most electrocyclisations, including the ones discussed above, there is no body of experimental data on substituent effects on which to draw.

This paper reports the first attempt to obtain such data for the cyclisation of nitrile ylides. The objective was to study the effects of substituents of various types close to the cyclisation site and also the effect of varying the olefinic/aromatic nature of the γ,δ double bond. The need for some quantitative work in the latter area was first appreciated during synthetic studies on the nitrile ylides **3**, **5** and **7** when it was found that their apparent rates of cyclisation, as indicated by the disappearance of the red–brown colour taken to be due to the nitrile ylide, was inconsistent with what was expected.[5]

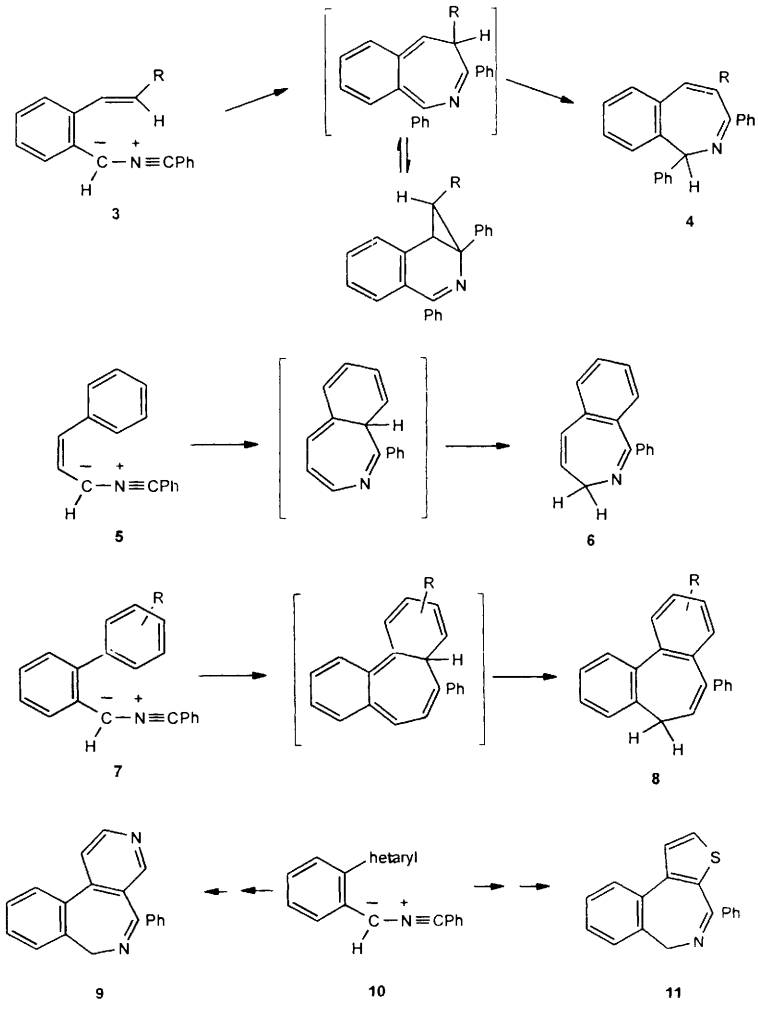
1 **2**

Results and discussion

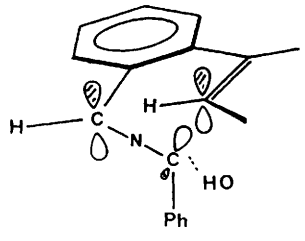
Choice of experimental method

The most satisfactory method would be to determine absolute rate constants by measuring directly the rates of cyclisation of the nitrile ylides. However, this is difficult to achieve in practice as the latter are highly reactive, transient species which have to be generated *in situ* and which cyclise very rapidly even at 0 °C. One of the most versatile routes to nitrile ylides, the one used in all of our earlier synthetic work, is *via* the base-induced dehydrochlorination of imidoyl chlorides (Scheme 2). Measuring the rate of product formation in this system is not useful since the rate of cyclisation of the nitrile ylides is generally as fast or faster than their rate of generation from the imidoyl chlorides. Instead we elected to determine relative reactivities by the use of competition reactions. Two distinct approaches are possible and are illustrated in Schemes 3 and 4.

The first is the 'external' competition, shown in Scheme 3, in which a series of substituted nitrile ylides **15** would be generated in turn in the presence of some appropriate trapping reagent **16**. From the relative yields of **17** and **18** for a range of substituents R it would be possible to obtain a measure of the effects of the substituents on the rate of the electrocyclisation reaction. The assumption would have to be made that the rate of the reaction used as comparator, the cycloaddition to **16**, was approximately constant, *i.e.* little affected by the nature of R in **15**. Earlier work by Padwa *et al.*[9] has shown this to be a reasonable assumption. A preliminary exploration of this method, however, revealed some severe practical problems. The major difficulty was in



Scheme 1



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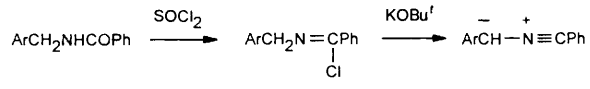
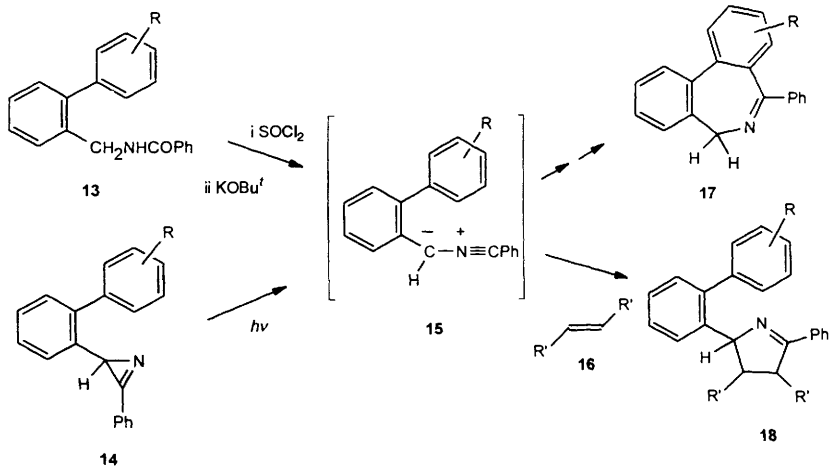


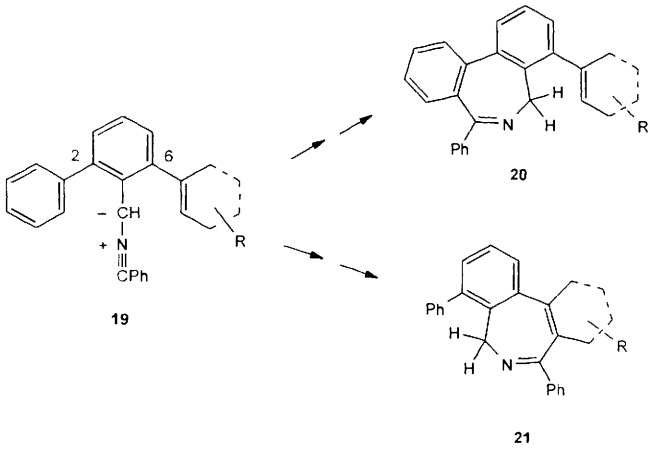
Scheme 2

identifying a dipolarophile **16** which (*a*) was reactive enough to compete with the electrocyclisation, (*b*) was itself stable to the reaction conditions required to generate the nitrile ylide and (*c*) gave a cycloadduct which was also stable. Thus, in the route to nitrile ylides from the amides **13**, both the dipolarophile **16** and the cycloadduct **18** would have to be stable to the base, usually potassium *tert*-butoxide, at 0 °C. Simple hydrocarbon dipolarophiles such as styrene and *E*-stilbene and even the more reactive strained alkene norbornene in 50-fold excess gave no cycloadduct but only the electrocyclisation product **17**. The more reactive 'activated' alkenes diethyl fumarate and maleate gave complex mixtures of products, not including **17**, indicating that they or their adducts were unstable under the reaction conditions. An alternative, less agressive, route to the nitrile ylides *via* the azirine **14** was also attempted. Although the azirine was synthesised in an impure state *via* the modified Neber reaction,[10] it proved impossible to purify by either distillation or chromatography.

Because of these difficulties it was decided to use the alternative 'internal' competition method shown in Scheme 4. Here the electrocyclisation on to the 6-substituent in structure **19** is in competition with another intramolecular reaction of the nitrile ylide. This could in principle be any type of reaction, but in order to ensure a comparable reaction rate, the electrocyclisation on to an unsubstituted phenyl ring at the 2 position to give compound **20** was selected. The intention was therefore to generate a range of intermediates of the type **19** with a variety of different unsaturated substituents, *e.g.* alkenyl, aryl and hetaryl groups, at the 6 position and to measure the product ratio **21**:**20** in each case by NMR spectroscopy or HPLC. As in the previous case the validity of these results as a measure of the relative rate of cyclisation on to the substituent at the 6 position depends on the assumption that the rate of the reaction used as comparator to give compound **20** is not much affected by the nature of the group at the 6 position. This seems likely to be true since model studies show that, in the helical transition state for electrocyclisation on to the phenyl ring at



Scheme 3



Scheme 4

the 2 position, the 6-substituent is twisted out of the plane of the central benzene ring by non-bonded interactions and is therefore largely out of conjugation with the nitrile ylide, thus minimising any electronic effect on its reactivity in the cyclisation on to the phenyl ring. As part of this work it was intended to test the validity of this assumption *via* a cyclic series of competition experiments. Consideration of molecular models also indicated that the two alternative transition states are equally accessible and that substituents on a benzene ring at the 6 position would not have any steric effect which might impede the competing cyclisation. Earlier work[4] had shown that the cyclisation step is irreversible for a closely related reaction and we make the assumption that it is also true in this case.

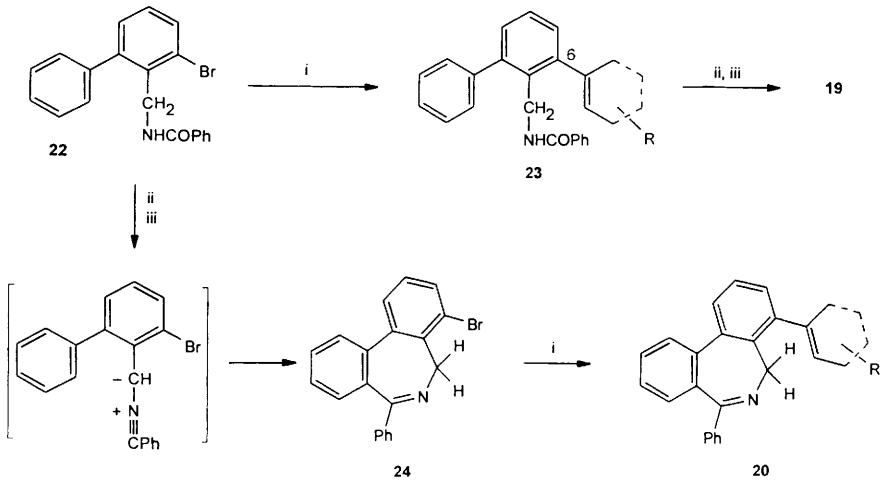
Synthesis of the amides 23a–m and the dibenz[*c,e*]azepines 20a–m

An intrinsic disadvantage of the 'internal competition' method in practical terms is that the synthesis of 1,2,3-trisubstituted compounds of the type **19** is necessarily more complicated than for those of type **13**. This work thus required the development of a route to the amides **23**, as precursors to the nitrile ylides **19**, which should ideally be capable of accommodating a wide range of functionalities in the substituent at the 6 position. 'Authentic' samples of one or both of the products **20** and **21** were also required for their identification in the NMR or HPLC analysis of the product mixtures. It seemed likely that the

Table 1 Identification of substituents in compounds **19**, **20**, **23**

Compd. **19**, **20**, **23**	6-Substituent in **19**, **23** 8-substituent in **20**
a	*E*-2-Phenylethenyl
b	2-Thienyl
c	3,5-Dimethylphenyl
d	3,5-Bis(trifluoromethyl)phenyl
e	3-Nitrophenyl
f	3-Methoxyphenyl
g	4-Methylphenyl
h	4-Trifluoromethylphenyl
i	4-Dimethylaminophenyl
j	4-Methoxyphenyl
k	4-Chlorophenyl
l	4-Fluorophenyl
m	2-Methylphenyl

mixture of these products formed by the cyclisation of **19** would not easily be separable by chromatography on a preparative scale for spectroscopic identification and so it was also necessary to develop an unambiguous synthetic route to one or both of them. These objectives were achieved as shown in Scheme 5. In this scheme the bromo amide **22** is coupled in a Suzuki reaction[11,12] with a range of vinyl, aryl or hetaryl boronic acids to give the amides **23** required as precursors for **19**. This Pd^0 catalysed coupling reaction is tolerant of a wide range of functional groups. The same compound **22** was also used to prepare 'authentic' samples of the dibenz[*c,e*]azepines **20** *via* cyclisation to give the 8-bromodibenz[*c,e*]azepine **24** and the Suzuki coupling of this compound with the same boronic acid used to prepare the amide **23**. The range of amides prepared, **23a–m**, and the corresponding 'authentic' benzazepines, **20a–m**, are shown in Table 1. The amides **26a,b** and the corresponding 'authentic' dibenz[*c,e*]azepines **27a,b** for use in the cyclic set of competition reactions (see below) were prepared by analogous routes from the bromo amide **25**. The physical and spectroscopic data on the amides **23a–m** and **26a,b** are given in Tables 2 and 3, respectively, and that of the 'authentic' dibenz[*c,e*]azepines **20a–m** and **27a,b** in Tables 4 and 5, respectively. The preparation of the bromo amides **22** and **25** required for these reactions was carried out as shown in Scheme 6. All of the steps were achieved in high yield (> 75%) except for step iv (65%), which always gave some 2-methyl-3-hydroxybiaryl as a by-product. Rigorous removal of the latter was necessary before the next step as, even in small amounts, it strongly inhibited the NBS bromination of the methyl group, presumably by serving as an effective radical trap.



Scheme 5 *Reagents:* i, $ArB(OH)_2$ or $vinylB(OH)_2$, Pd^0; ii, $SOCl_2$; iii, $KOBu^t$

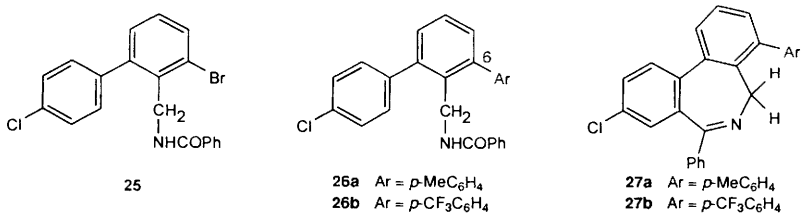


Table 2 Yields and physical data for the amides **23a–m**[a] and **26a,b**

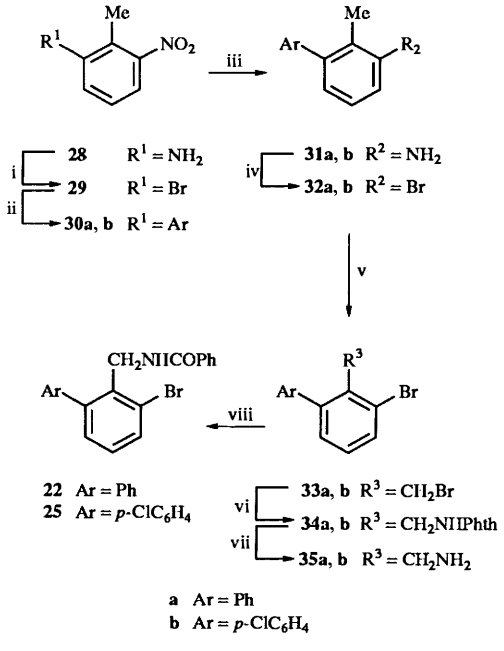
Compd.	Time (min)	Yield (%)	Cryst. solvent[b]	Mp (°C)	Molecular formula	C (%) Found / Calc.	H (%) Found / Calc.	N (%) Found / Calc.	m/z (M^+) Found / Calc.
23a	20	81	E–T	200–202	$C_{28}H_{23}NO$	86.1 / 86.3	6.0 / 6.0	3.5 / 3.6	389.1775 / 389.1779
23b	120	98	CH–E	153–155	$C_{24}H_{19}NOS$	78.0 / 78.0	5.0 / 5.2	3.6 / 3.8	369.1204 / 369.1187
23c	15	99	H–E	170–172	$C_{28}H_{25}NO$	85.7 / 85.9	6.4 / 6.4	3.6 / 3.6	391.1943 / 391.1936
23d	15	85	T–E	233–234	$C_{28}H_{19}FO$	67.4 / 67.3	3.8 / 3.8	3.0 / 2.8	499.1372 / 499.1371
23e	30	86	T–E	181–183	$C_{26}H_{20}N_2O_3$	76.5 / 76.4	4.8 / 4.9	6.9 / 6.9	408.1467 / 408.1474
23f	30	91	T–E	162.5–164	$C_{27}H_{23}NO_2$	81.9 / 82.4	5.8 / 5.9	3.7 / 3.6	393.1734 / 393.1729
23g	30	90	H–E	137–138.5	$C_{27}H_{23}NO$	86.0 / 85.9	6.1 / 6.15	3.7 / 3.7	377.1788 / 377.1780
23h	30	93	H–E	157–159	$C_{27}H_{20}F_3NO$	75.2 / 75.15	4.7 / 4.7	3.3 / 3.25	— / —
23i	45	78	H–E	161–163	$C_{28}H_{26}N_2O$	82.5 / 82.7	6.2 / 6.45	6.9 / 6.9	406.2039 / 406.2045
23j	15	88	H–E	151–152.5	$C_{27}H_{23}NO_2$	82.2 / 82.4	5.9 / 5.9	3.6 / 3.6	393.1721 / 393.1729
23k	20	61	H–E	163–165	$C_{26}H_{20}ClNO$	78.1 / 78.6	5.0 / 5.1	3.5 / 3.5	399.1212 / 399.1233
23l	45	87	H–E	178–180	$C_{26}H_{20}FNO$	81.8 / 81.9	5.3 / 5.3	3.7 / 3.7	381.1529 / 381.1529
23m	45	100	CH–E	126–128	$C_{27}H_{23}NO$	85.8 / 85.9	6.2 / 6.15	3.8 / 3.7	377.1779 / 377.1780
26a	30	85	CH–E	180–181	$C_{27}H_{22}ClNO$	78.3 / 78.7	5.3 / 5.4	3.3 / 3.4	411.1393 / 411.1390
26b	60	73	CH–E	175–177	$C_{27}H_{19}ClF_3NO$	69.7 / 69.7	3.9 / 4.1	3.3 / 3.0	465.1104 / 465.1107

[a] Compounds identified in Table 1. [b] CH = cyclohexane; H = hexane; E = ethanol; T = toluene; EA = ethyl acetate; P = light petroleum (bp 60–80 °C).

Table 3 Spectroscopic data for the amides **23a–m**[a] and **26a,b**

Compd.	Spectroscopic data[b] δ_H	m/z	ν_{max}
23a	4.73 (d, *J* 5.0, CH_2), 6.05 (br s, NH), 7.06 (d, *J* 16.0, 1 H), 7.20–7.34 (m, 19 H)	389 (22%), 268 (100), 105 (31), 77 (22)	3240 (NH), 1620 (C=O)
23b	4.67 (d, *J* 4.9, CH_2), 5.92 (br s, NH), 7.07–7.49 (m, 16 H, Ar-H)	369 (48%), 249 (21), 248 (100), 247 (35)	3290 (NH), 1625 (C=O)
23c	2.33 (s, 2 × CH_3), 4.59 (d, *J* 5.1, CH_2), 5.80 (br s, NH), 7.019 (s, 1 H), 7.023 (s, 2 H), 7.25–7.44 (m, 13 H)	391 (41%), 270 (100), 255 (23), 122 (50)	3310 (NH), 1625 (C=O)
23d	4.49 (d, *J* 5.2, CH_2), 6.78 (br s, NH), 7.25–7.49 (m, 13 H), 7.88 (s, 3 H)	499 (12%), 480 (16), 378 (21), 143 (100)	3280 (NH), 1620 (C=O)
23e	4.53 (d, *J* 5.2, CH_2), 5.79 (br s, NH), 7.25–7.63 (m, 14 H), 7.75–7.80 (m, 1 H), 8.17–8.27 (m, 2 H)	391 (10%), 287 (34), 270 (83), 105 (100)	3280 (NH), 1625 (C=O)
23f	3.78 (s, OMe), 4.62 (d, *J* 5.1, CH_2), 5.83 (br s, NH), 6.88–7.03 (m, 3 H), 7.25–7.45 (m, 14 H)	393 (30%), 392 (23), 272 (100), 143 (44)	3365 (NH), 1620 (C=O)
23g	1.67 (s, CH_3), 4.61 (d, *J* 5.1, CH_2), 5.78 (br s, NH), 7.21–7.44 (m, 17 H)	377 (49%), 256 (100), 122 (32), 69 (99)	3290 (NH), 1620 (C=O)
23h	4.58 (d, *J* 5.1, CH_2), 5.88 (br s, NH), 7.24–7.47 (m, 13 H), 7.54 (d, *J* 8.1, 2 H), 7.68 (d, *J* 8.1, 2 H)	431 (40%), 310 (100), 122 (85), 105 (72)	3310 (NH), 1625 (C=O)
23i	2.97 (s, 2 × CH_3), 4.65 (d, *J* 5.1, CH_2), 5.85 (br s, NH), 6.81 (d, *J* 8.7, 2 H), 7.24–7.43 (m, 15 H)	406 (3%), 285 (3.5), 269 (4), 131 (100)	3400 (NH), 1620 (C=O)
23j	3.82 (s, OCH_3), 4.61 (d, *J* 5.1, CH_2), 5.80 (br s, NH), 6.96 (d, *J* 8.8, 2 H), 7.25–7.44 (m, 15 H)	393 (31%), 272 (100), 122 (24), 77 (32)	3250 (NH), 1635 (C=O)
23k	4.57 (d, *J* 5.2, CH_2), 7.80 (br s, NH), 7.24–7.45 (m, 17 H)	399 (2%), 397 (6), 276 (7), 241 (6), 122 (100)	3310 (NH), 1635 (C=O)
23l	4.58 (d, *J* 5.1, CH_2), 5.81 (br s, NH), 7.06–7.15 (m, 2 H), 7.25–7.45 (m, 15 H)	381 (33%), 260 (100), 122 (60), 77 (77)	3290 (NH), 1620 (C=O)
23m	2.13 (s, CH_3), 4.28 (dd, *J* 14.8 and 4.9, CH), 4.56 (dd, *J* 14.8 and 5.5, CH), 5.73 (br s, NH), 7.18–7.45 (m, 17 H, Ar-H)	377 (66%), 256 (100), 241 (31), 122 (39)	3370 (NH), 1640 (C=O)
26a	2.39 (s, CH_3), 4.58 (d, *J* 5.1, CH_2), 6.80 (br s, NH), 7.22–7.44 (m, 16 H, Ar-H)	413 (17%), 411 (46), 290 (100), 255 (46), 122 (82)	3290 (NH), 1635 (C=O)
26b	4.58 (d, *J* 5.2, CH_2), 5.70 (br s, NH), 7.24–7.55 (m, 14 H, Ar-H), 7.67 (d, *J* 8.2, 2 H)	467 (8%), 465 (22), 309 (39), 122 (76), 105 (100)	3310 (NH), 1625 (C=O)

[a] Compounds identified in Table 1. [b] NMR spectra at 200 MHz, *J* values given in Hz; IR spectra as Nujol mulls, absorptions as cm^{-1}; mass spectra using EI source.



Scheme 6 *Reagents:* i, $NaNO_2$/HBr, CuBr; ii, $ArB(OH)_2/Pd^0$; iii, H_2, Pd/C; iv, $NaNO_2$/HBr, CuBr; v, NBS/Bz_2O_2; vi, potassium phthalimide; vii, NH_2NH_2/MeOH; viii, PhCOCl

Competitive cyclisation reactions of the nitrile ylides 19a–m

The overall course of the competition reactions for the general case is shown in Scheme 4. The methods used are discussed in general in (1) below and in more detail in the Experimental section. The results are discussed in (2) and (3) below.

(1) Experimental methods. The nitrile ylides **19a–m** were generated from the amides **23a–m** *via* the corresponding imidoyl chlorides as shown for the general case in Scheme 2. The imidoyl chlorides were prepared by reaction of the amides with thionyl chloride and were converted into the nitrile ylides in either THF or DMF as solvent at 0 °C by reaction with potassium *tert*-butoxide. Each competition reaction was carried out on a 0.5 mmol scale in THF and worked up to give the product or product mixture, and then a duplicate was carried out on an NMR scale (50 mg of amide) as a check on the results. In several cases the cyclisations were also carried out on an NMR scale (in duplicate) in DMF as solvent to determine the effect of a change in solvent polarity. In most cases the isomeric products **20** and **21** could not be separated by chromatography. Analysis of the crude product mixtures for the product ratios **21**:**20** was carried out by ^1H NMR (360 MHz) spectroscopy, generally using the characteristic pair of doublets due to the methylene protons of the azepine ring. Wherever possible, alternative peaks, *e.g.* those for methyl or methoxy groups, were also used as a check. It was shown by the use of synthetic mixtures that the presence of 1% of the minor isomer could be detected using this method of analysis. The reactions were generally very clean and the product mixtures contained only

Table 4 Yields and physical data for the 8-substituted dibenz[*c*,*e*]azepines **20a–m**[a] and **27a,b**

Compd.	Time (min)	Yield (%)	Cryst. solvent[b]	Mp (°C)	Molecular formula	C (%) Found Calc.	H (%) Found Calc.	N (%) Found Calc.	*m/z* (M^+) Found Calc.
20a	35	97	CH–T	159–161	$C_{28}H_{21}N$	90.6 90.5	5.7 5.7	3.9 3.8	371.1676 371.1674
20b	60	97	CH	144–145	$C_{24}H_{17}NS$	81.4 82.0	4.7 4.9	3.7 4.0	351.1089 351.1082
20c	10	91	—	oil	$C_{28}H_{23}N$	—	—	—	373.1829 373.1830
20d	20	87	CH	160–162	$C_{28}H_{17}F_6N$	69.6 69.8	3.5 3.6	3.0 2.9	481.1264 481.1265
20e	15	70	CH	157–158.5	$C_{26}H_{18}N_2O_2$	80.2 80.0	4.5 4.65	7.4 7.2	390.1377 390.1368
20f	20	100	CH	166–168	$C_{27}H_{21}NO$	86.3 86.4	5.6 5.6	3.8 3.7	375.1613 375.1623
20g	45	56	CH	158–160	$C_{27}H_{21}N$	90.1 90.2	5.9 5.9	3.9 3.9	359.1676 359.1674
20h	30	77	CH	187–189	$C_{27}H_{18}NF_3$	78.5 78.4	4.4 4.4	3.4 3.4	— —
20i	60	88	CH–E	197–198	$C_{28}H_{24}N_2$	86.7 86.55	6.3 6.2	7.1 7.2	388.1928 388.1939
20j	60	85	CH	156–157	$C_{27}H_{21}NO$	86.3 86.4	5.6 5.6	3.8 3.7	375.1631 375.1623
20k	30	79	CH	173.5–175.5	$C_{26}H_{18}ClN$	81.9 82.3	4.7 4.8	3.6 3.7	— —
20l	30	99	CH	153–154.5	$C_{26}H_{18}FN$	85.6 85.9	5.0 5.0	4.0 3.9	— —
20m	120	83	H	131–133	$C_{27}H_{21}N$	90.1 90.2	6.0 5.9	3.8 3.9	359.1677 359.1674
27a	30	94	CH	155–156.5	$C_{27}H_{20}ClN$	—	—	—	393.1254 393.1284
27b	30	86	—	oil	$C_{27}H_{17}ClF_3N$	—	—	—	447.1001 447.1002

[a] Compounds identified in Table 1. [b] CH = cyclohexane; H = hexane; E = ethanol; T = toluene.

compounds **21** and/or **20** and traces of the unchanged amide **23**. In each case the ^{1}H NMR peaks due to the product **20** in the mixture were identified by the peak enhancement method *via* the addition of a small amount of an 'authentic' sample prepared as in Scheme 5. The NMR data of the products are given in Table 6 with the enhanced peaks shown in italics. The mass spectrometry data of the products or product mixtures are given in Table 7. The reactivity ratios are shown in Table 8 and are discussed below. In several cases control experiments were carried out on product mixtures to which an additional amount of the product **20** had been added. These mixtures were dissolved in THF and treated with 2 equiv. of potassium *tert*-butoxide at 0 °C under the conditions of the cyclisation reaction, worked-up and again analysed by ^{1}H NMR spectroscopy. In all cases the relative amounts of the two products were unchanged showing that they were stable and not interconvertible under the conditions of the reaction.

(2) The relative reaction rates. (*i*) *Phenyl* vs. E-2-*phenylethenyl* **19a** (*Scheme* 7).—It was the apparently anomalous cyclisation rates observed in the synthetic work [3–5] on the two systems **3** and **7** which first led to this study of relative reaction rates. In all these cyclisations the addition of the base to the imidoyl chloride produces an immediate deep coloration which fades as the reaction proceeds. It was thought that this colour was due to the transitory presence of the nitrile ylide itself and that its duration gave a rough indication of the rate of reaction. For both **3** and **5** the colour persisted for several minutes at 0 °C, but, unexpectedly, for **7** the colour was hardly seen at 0 °C but its lifetime was prolonged when the reaction was carried out at −10 °C. That **7** should cyclise faster than **3** and **5** was highly unexpected since its cyclisation should have a higher activation energy as it involves the loss of aromatic stabilisation in *two* benzene rings compared to one only for **3** and **5**.

The competitive cyclisation of **19a**, Scheme 7, addressed this problem directly. In the event it was found that the only product detectable by NMR was the dihydrocyclopropa[*c*]isoquinoline **36** which gave a characteristic [3] ^{1}H NMR spectrum. No peaks were seen corresponding to those of the 'authentic' sample of the dibenzazepine **20a** prepared as shown in Scheme 5. The identity of the dihydrocyclopropa[*c*]isoquinoline **36** was confirmed by its characteristic [3] thermal isomerisation at 80 °C to give the benzazepine **37** in virtually quantitative yield. Thus, as expected from the arguments above, the olefinic double bond in **19a** was found to be much more reactive (at least 100 ×) than the aromatic double bond in the benzene ring. It must therefore be concluded that the colour changes seen in the synthetic work are not indicative of the rate of cyclisation. It seems likely therefore that the transient dark colours in these reactions are not due to the nitrile ylides at all but are possibly due to the highly conjugated quinonoid intermediates or the benzylic anions formed by the deprotonation of the imidoyl chloride.

(*ii*) *Phenyl* vs. 2-*thienyl* **19b** (*Scheme* 8).—The preference observed in **19a** for cyclisation on to the double bond of higher olefinic character was further tested in the cyclisation of **19b**. The 2,3 double bond in thiophene, although 'aromatic', has a higher olefinic character than the fully delocalised system in benzene and by the same argument should provide the preferred path. The cyclisation, Scheme 8, gave a product which by NMR analysis contained only **38** and no detectable amount of **20b**. Thus, like the alkene, the thiophene ring is at least 100 × more reactive than the benzene ring.

(*iii*) *Phenyl* vs. *substituted aryl groups* **19c–m**.—In the synthetic work on the cyclisation of nitrile ylides of type **7** it had been found [5] that high yields of product were obtained irrespective of the nature of the aromatic substituent **R**. The reaction is overall an aromatic substitution process and this

Table 5 Spectroscopic data for 8-substituted dibenz[*c*,*e*]azepines **20a–m**[a] and **27a,b**

Compd.	Spectroscopic data[b] δ_H	*m/z*	ν_{max}
20a	3.75 (d, *J* 10.7, 7-H), 5.41 (d, *J* 10.7, 7′-H), 7.08 (d, *J* 16.0, H–C=C), 7.30–7.89 (m, 18 H, Ar-H and H–C=C)	371 (99%), 370 (100), 269 (63), 143 (30)	1610 (C=N)
20b	3.71 (d, *J* 10.3, 7-H), 5.32 (d, *J* 10.3, 7′-H), 7.16–7.80 (m, 15 H, Ar-H)	351 (100%), 350 (37), 318 (37), 281 (95)	1605 (C=N)
20c	2.43 (s, 2 × CH_3), 3.69 (d, *J* 10.2, 7-H), 5.15 (d, *J* 10.2, 7′-H), 7.08 (s, 1 H), 7.25–7.69 (m, 13 H, Ar-H), 7.79–7.81 (m, 1 H)	373 (17%), 372 (16), 210 (64), 84 (100)	1605 (C=N)
20d	3.75 (d, *J* 10.5, 7-H), 4.89 (d, *J* 10.5, 7′-H), 7.33–7.65 (m, 12 H, Ar-H), 7.77 (d, *J* 7.7, 1 H), 7.79 (d, *J* 7.7, 1 H), 7.96 (s, 1 H)	481 (97%), 480 (100), 149 (37), 143 (33)	1605 (C=N)
20e	3.71 (d, *J* 10.5, 7-H), 4.90 (d, *J* 10.5, 7′-H), 7.31–7.81 (m, 13 H, Ar-H), 8.08 (d, *J* 6.6, 1 H), 8.27 (dd, *J* 5.9 and 2.3, 1 H), 8.48 (s, 1 H)	390 (100%), 389 (83), 281 (47), 239 (29)	1605 (C=N)
20f	3.90 (s, OCH_3), 3.69 (d, *J* 10.3, 7-H), 5.11 (d, *J* 10.3, 7′-H), 6.96–6.99 (m, 1 H), 7.22–7.68 (m, 14 H, Ar-H), 7.80 (d, *J* 7.6, 1 H)	375 (65%), 374 (100), 360 (15), 188 (9)	1660 (C=N)
20g	2.45 (s, CH_3), 3.65 (d, *J* 10.2, 7-H), 5.07 (d, *J* 10.2, 7′-H), 7.25–7.77 (m, 15 H, Ar-H), 7.80–7.83 (m, 1 H)	359 (47%), 358 (57), 182 (10), 69 (100)	1605 (C=N)
20h	3.67 (d, *J* 10.4, 7-H), 4.93 (d, *J* 10.4, 7′-H), 7.25–7.80 (m, 16 H, Ar-H)	413 (86%), 412 (100), 310 (14), 239 (17), 32 (61)	1610 (C=N)
20i	3.01 (s, NMe_2), 3.65 (d, *J* 10.2, 7-H), 5.15 (d, *J* 10.2, 7′-H), 6.87 (d, *J* 9.0, 2 H), 7.25–7.63 (m, 13 H, Ar-H), 7.77–7.80 (m, 1 H)	388 (100%), 387 (59), 194 (14), 142 (13)	1615 (C=N)
20j	3.89 (s, OMe), 3.67 (d, *J* 10.3, 7-H), 5.09 (d, *J* 10.3, 7′-H), 7.05 (d, *J* 8.9, 2 H), 7.29–7.67 (m, 13 H, Ar-H), 7.79–7.81 (m, 1 H)	375 (100%), 374 (92), 272 (14), 188 (10), 143 (18)	1605 (C=N)
20k	3.66 (d, *J* 10.3, 7-H), 4.98 (d, *J* 10.3, 7′-H), 7.31–7.70 (m, 15 H, Ar-H), 7.78–7.82 (m, 1 H)	381 (34%), 379 (100), 239 (22), 170 (14)	1605 (C=N)
20l	(200 MHz) 3.69 (d, *J* 10.3, 7-H), 5.02 (d, *J* 10.3, 7′-H), 7.16–7.20 (m, 2 H), 7.25–7.71 (m, 13 H, Ar-H), 7.78–7.81 (m, 1 H)	(FAB, glycerol) 364 (100%), 363 (20), 362 (21), 259 (8), 165 (10)	1605 (C=N)
20m	2.12 (s, 0.6 × CH_3), 2.23 (s, 0.4 × CH_3), 3.63 (d, *J* 10.5, 0.4 × 7-H), 3.68 (d, *J* 10.3, 0.6 × 7-H), 4.73 (d, *J* 10.3, 0.6 × 7′-H), 4.76 (d, *J* 10.5, 0.4 × 7′-H), 7.11–7.83 (m, 16 H, Ar-H)	359 (100%), 358 (60), 344 (33), 143 (23)	1610 (C=N)
27a	2.45 (s, CH_3), 3.64 (d, *J* 10.3, 7-H), 5.10 (d, *J* 10.3, 7′-H), 7.25–7.75 (m, 15 H, Ar-H)	395 (33%), 394 (53), 393 (100), 392 (98), 381 (59), 143 (52)	1610 (C=N)
27b	3.65 (d, *J* 10.5, 7-H), 4.98 (d, *J* 10.5, 7′-H), 7.33–7.60 (m, 15 H)	449 (35%), 448 (56), 447 (100), 446 (99), 412 (35), 309 (17)	1610 (C=N)

[a] Compounds identified in Table 1. [b] Except where stated: NMR spectra at 360 MHz, *J* values given in Hz; IR spectra as Nujol mulls, absorptions as cm^{-1}; mass spectra using EI source.

lack of sensitivity to electronic effects contrasts strongly with electrophilic cyclisations, *e.g.* the Bischler–Napieralski reactions of amides, which work well for cyclisation on to electron-rich rings but give low yields when electron-withdrawing groups are present. It was therefore of interest to find out in a more quantitative sense how the reactivity of the ring was affected by various types of substituents in the positions *ortho*, *meta* and *para* to the cyclisation site.

meta-*Substituents* (*cases* **19c–f**) (*Schemes* 9 *and* 10).—The first pair of reactions in this series, Scheme 9, involved the competition of the phenyl group against an aryl group symmetrically *meta*-disubstituted with methyl groups, **19c**, and with trifluoromethyl groups, **19d**. These groups were chosen as being of similar size but inductively of opposite electron demand. In both cases the substituted ring proved to be the more reactive, the trifluoromethyl groups enhanced the reactivity by a factor of 32 and the methyl groups by *ca.* 8. Similar results were obtained in both THF and DMF as solvents.

The next pair of reactants, **19e** and **19f** in Scheme 10, each contained a single *meta* substituent—the nitro and methoxy groups which have opposite and powerful capabilities for electron withdrawal and donation, respectively, *via* the conjugative effect. The presence of a single *meta* substituent introduces further complexity in that cyclisation can occur at either the position *ortho* to the substituent to give **40** or at the *para* position to give **41**. Earlier work in a related system[4] showed that the *ortho* position was slightly favoured (1.5–2.5 ×) for all the substituents studied (Me, OMe, Cl, CF_3). Cyclisation of **19e** gave *only* compounds **40** (R = NO_2) and **41** (R = NO_2), the two products formed by attack on the ring containing the nitro group. This was the case for both THF and DMF as reaction solvents. In this case it proved possible to separate the two isomers by chromatography and to identify them by their ^1H NMR spectra. The spectrum of compound **41** (R = NO_2) showed the absorption for the bay-region proton (1-H) as a doublet at δ 8.68, coupled only to the 3-H, whereas for isomer **40** (R = NO_2) it was a doublet of doublets at δ 8.08. The **40**:**41** ratio was 2.5 with THF as reaction solvent and 4.3 with DMF, *i.e.* '*ortho*' attack was favoured as in the earlier work.[4] The absence of compound **20e** in the product mixture was as usual confirmed by the addition of *ca.* 1% of the authentic material to the NMR sample. This result confirms that the benzene ring is activated to electrocyclic attack by the presence of an electron-withdrawing group either *ortho* or *para* to the cyclisation site and it is notable that the single nitro group had an overall activating effect (>100) much greater than the pair of trifluoromethyl groups in **19d** (32 ×). The effect of the single methoxy group in **19f**, Scheme 10, was less dramatic and all three isomers, **20f**, **40** (R = OMe) and **41** (R = OMe), were formed in the ratios shown (Table 8). They could not be separated by chromatography and were identified *via* the

Table 6 ^{1}H NMR data[a] on the products of the cyclisation of the nitrile ylides **19b–m**[b] and **43a,b**

Reactant	Product(s)	^{1}H NMR data (360 MHz) [δ(*J*/Hz)] 7-H	7′-H	Aromatic	R
19b	**38**	3.83 (10.6)	5.39 (10.6)	7.09–7.87	—
19c	**39** (R = Me)[c]	3.71 (10.0)	5.04 (10.0)	7.06–7.10, 7.25–7.81	Me: 1.98 (s), 2.49 (s)
	20c	*3.69* (10.2)	*5.14* (10.2)		Me: *2.43* (s)
19d	**39** (R = CF_3)[c]	3.65 (10.3)	5.15 (10.3)	7.25–7.79 (m), *7.96* (s,) 8.00 (s), 8.25 (s)	
	20d	*3.75* (10.5)	*4.89* (10.5)		
19e	**40** (R = NO_2)	3.81 (10.3)	5.22 (10.3)	7.23–7.76 (14 H), 7.99 (dd, 8/1.3, 1 H), 8.08 (dd, 8/1.3, 1 H)	
	41 (R = NO_2)	3.63 (10.5)	5.16 (10.5)	7.12–7.85 (14 H), 8.21 (dd, 8.6/2.3, 1 H), 8.68 (d, 2.3, 1 H)	
19f	**40/41** (R = OMe), **20f**[c]	3.69–3.87	5.10–5.28	6.98–7.01 (m), 7.25–7.77 (m), *7.80* (d, 7.7, 1 H)	MeO: 3.54 (s), *3.91* (s), 3.96 (s)
19g	**42** (R = Me)[c]	3.75 (10.2)	5.15 (10.2)	7.09–7.86 (m)	Me: 2.44 (s)
	20g	*3.74* (10.2)	*5.18* (10.2)		Me: *2.51* (s)
19h	**42** (R = CF_3)[c]	3.64 (10.4)	5.12 (10.4)	7.31–7.86 (m), 7.92–7.94 (m)	
	20h	*3.69* (10.4)	*4.96* (10.4)		
19i	**42** (R = NMe_2)[c]	3.72 (10.2)	5.03 (10.2)	6.65 (d, 2.8), *6.87* (d, 9), 6.98 (dd, 8.8/2.8), 7.24–7.67 (m)	NMe_2: 2.92 (s)
	20i	*3.65* (10.2)	*5.15* (10.2)	*7.70–7.80* (m)	NMe_2: *2.01* (s)
19j	**42** (R = OMe)[c]	3.69 (10.2)	5.07 (10.2)	6.91 (d, 2.7), *7.05* (d, 8.9), 7.08–7.67 (m), 7.73 (d, 8.7)	MeO: 3.79 (s)
	20j	*3.67* (10.2)	*5.09* (10.2)	*7.79–7.81* (m)	MeO: *3.89* (s)
19k	**42** (R = Cl)[c]	3.64 (10.3)	5.08 (10.3)	7.31–7.77 (m), *7.72–7.82* (m)	
	20k	*3.66* (10.3)	*4.98* (10.3)		
19l	**42** (R = F)[c]	3.67 (10.3)	5.11 (10.3)	7.12–7.77 (m), 7.76–7.81 (m)	
	20l	*3.69* (10.3)	*5.02* (10.3)		
19m	**20m**	identical with that of **20m** (Table 5)			
43a	**44a**[c]	3.68 (10.3)	5.03 (10.4)	7.25–7.76 (m)	Me: 2.40 (s)
	27a	*3.64* (10.3)	*5.14* (10.3)		Me: *2.45* (s)
43b	**44b**[c]	3.65 (10.5)	4.96 (10.5)	7.25–7.93 (m)	
	27b	*3.63* (10.5)	*5.02* (10.5)		

[a] Enhanced peaks shown in italics. [b] Substituents identified in Table 1. [c] As a mixture.

Table 7 Mass spectrometry data on the products of the cyclisation of the nitrile ylides **19a–m**[a] and **43a,b**

Reactant	Product(s)	Molecular formula	*m/z* (M^+) Found	Calc.	*m/z* (%)
19a	**36**	$C_{28}H_{21}N$	371.1666	371.1674	371 (65), 370 (100), 281 (12), 268 (39), 189 (10), 178 (10), 165 (13)
	37		371.1666		371 (43), 370 (71), 268 (24), 105 (100), 77 (54), 51 (28)
19b	**38**	$C_{24}H_{17}NS$	351.1075	351.1082	351 (100), 350 (71), 318 (22), 281 (76)
19c	**39** (R = Me), **20c**[b]	$C_{28}H_{23}N$	373.1817	373.1830	373 (69), 271 (58), 119 (74), 57 (100)
19d	**39** (R = CF_3), **20d**[b]	$C_{28}H_{17}F_6N$	481.1267	481.1265	481 (100), 480 (90), 378 (18), 69 (33)
19e	**40** (R = NO_2)	$C_{26}H_{18}N_2O_2$	390.1366	390.1368	390 (100), 389 (75), 381 (83), 143 (88)
	41 (R = NO_2)		390.1366		390 (100), 389 (65), 285 (43), 239 (42), 105 (51)
19f	**40/41** (R = OMe), **20f**[b]	$C_{27}H_{21}NO$	375.1637	375.1623	375 (100), 374 (83), 281 (38), 272 (60)
19g	**42** (R = Me), **20g**[b]	$C_{27}H_{21}N$	359.1667	359.1674	359 (70), 358 (72), 119 (74), 57 (100)
19h	**42** (R = CF_3), **20h**[b]	$C_{27}H_{18}F_6N$	413.1396	413.1391	413 (92), 412 (100), 344 (11), 69 (70)
19i	**42** (R = NMe_2), **20i**[b]	$C_{28}H_{24}N_2$	388.1942	388.1939	388 (2), 355 (6), 281 (22), 207 (33), 69 (100)
19j	**42** (R = OMe), **20j**[b]	$C_{27}H_{21}NO$	375.1621	375.1623	375 (36), 374 (34), 119 (49), 105 (85), 57 (100)
19k	**42** (R = Cl), **20k**[b]	$C_{26}H_{18}ClN$	381.1079	381.1098	381 (15), 380 (24), 379 (44), 378 (43), 69 (100)
19l	**42** (R = F), **20l**[b]	$C_{26}H_{18}FN$	363.1428	363.1423	363 (92), 362 (100), 260 (13), 257 (13)
19m	**20m**	$C_{27}H_{21}N$	359.1622	359.1674	359 (100), 358 (59), 344 (33), 143 (21)
43a	**27a**, **44a**[b]	$C_{27}H_{20}ClN$	393.1283	393.1284[c]	395 (33), 394 (55), 393 (99), 392 (100), 381 (24), 143 (23)
43b	**27b**, **44b**[b]	$C_{27}H_{17}ClF_3N$	447.0989	447.1002[c]	449 (33), 448 (54), 447 (99), 446 (100), 412 (17), 309 (15)

[a] Compounds identified in Table 1. [b] As a mixture. [c] For ^{35}Cl isotope.

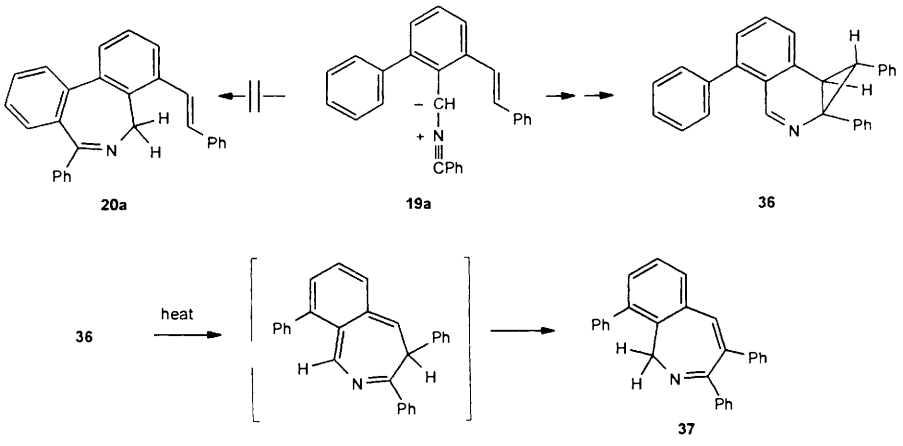
^{1}H NMR spectrum of the mixture. The methylene signals in the δ 7.25–7.80 region were not well resolved but the peaks due to the methoxy groups (Table 6) were well separated and served both for the identification of the isomers and for the measurement of their ratios. The methoxy peak due to **20f** was identified by the addition of authentic material and those due to **40** and **41** by their characteristic chemical shifts. It was shown in earlier work[4] that the methoxy group in compounds of the type **40** (R = OMe) is shielded relative to that in **41** (R = OMe) due to its proximity to the face of the phenyl substituent at the 5 position. The effect of the methoxy group on reactivity was much less than that of the nitro group in **19e**, again the overall effect was to activate the ring but the effect was only moderate (× 6) in THF as solvent and smaller (× 2) in DMF. The activation was concentrated at the *ortho* position and the reactivity at the *para* position was actually lower than for the unsubstituted ring.

para-*Substituents* (*cases* **19g–l**) (*Scheme* 11).—Since the *meta* substituents in **19c–f** had all activated the ring to electrocyclic substitution it was of interest to find out whether substituents in

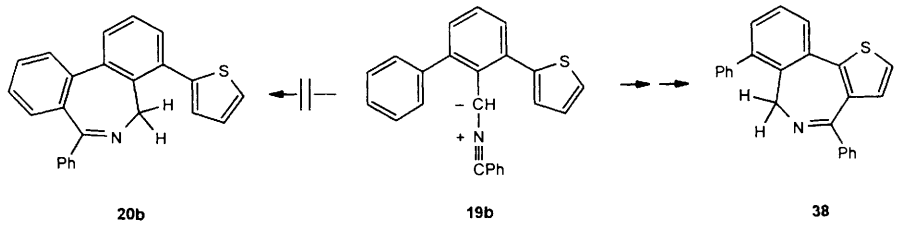
Table 8 Product ratios from the cyclisation of the nitrile ylides **19a–m** and **43a,b**

Reactant	Substituent	Yield[a] (%)	Product ratios: Products	Reaction in THF	Reaction in DMF
19a	*E*-2-Phenylethenyl	97	**36/20a**	> 100	> 100
19b	2-Thienyl	97	**38/20b**	> 100	> 100
19c	3,5-Dimethylphenyl	96	**39** (R = CH_3)/**20c**	8.3 ± 0.1	7.6 ± 0.1
19d	3,5-Bis(trifluoromethyl)phenyl	87	**39** (R = CF_3)/**20d**	32.0 ± 0.1	
19e	3-Nitrophenyl	quant.	**40** (R = NO_2) + **41** (R = NO_2)/**20e**	> 100	> 100
			40 (R = NO_2)/**41** (R = NO_2)	2.5	4.3
19f	3-Methoxyphenyl	99	**40** (R = OMe)/**41** (R = OMe)/**20f**	5.6 ± 0.2:0.8 ± 0.1:1	1.4 ± 0.1:0.3 ± 0.1:1
19g	4-Methylphenyl	93	**42** (R = CH_3)/**20g**	1.5 ± 0.1	
19h	4-Trifluoromethylphenyl	82	**42** (R = CF_3)/**20h**	2.8 ± 0.1	2.1 ± 0.1
19i	4-Dimethylaminophenyl	52	**42** (R = NMe_2)/**20i**	1.3 ± 0.2	
19j	4-Methoxyphenyl	96	**42** (R = OMe)/**20j**	1.6 ± 0.1	
19k	4-Chlorophenyl	97	**42** (R = Cl)/**20k**	2.2 ± 0.2	1.6 ± 0.1
19l	4-Fluorophenyl	94	**42** (R = F)/**20l**	1.2 ± 0.1	1.0 ± 0.1
19m	2-Methylphenyl	60	**20m/45**	> 100	> 100
43a	R = CH_3	quant.	**27a/44a**	1.4 ± 0.1	1.3 ± 0.1
43b	R = CF_3	quant.	**44b/27b**	1.1 ± 0.1	

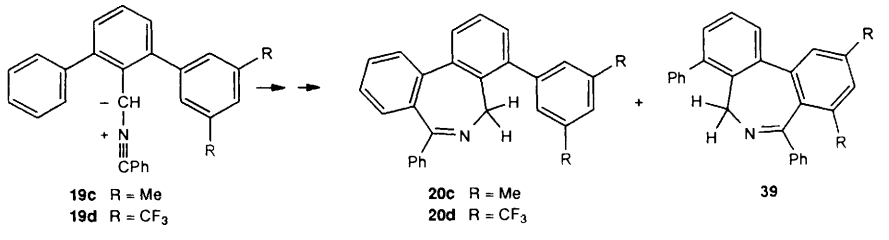
[a] After isolation by chromatography.



Scheme 7



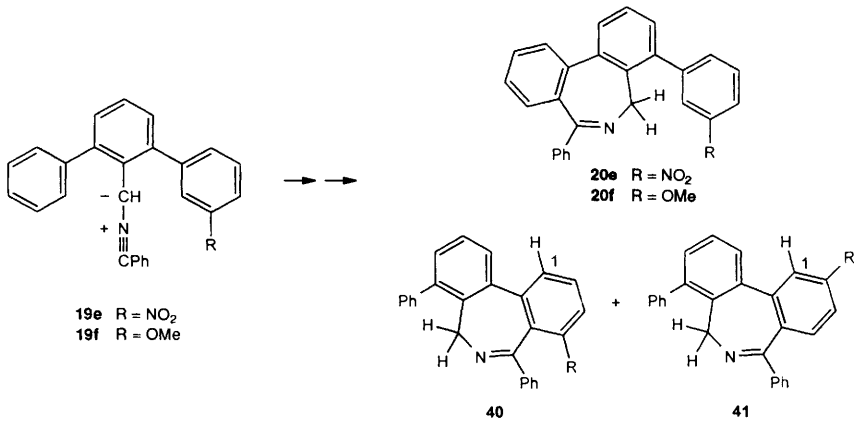
Scheme 8



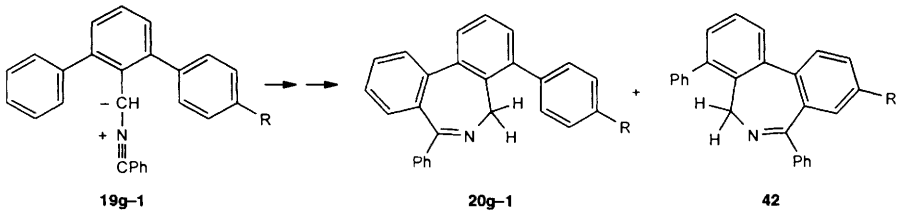
Scheme 9

the *para* position as in **19g–l**, Scheme 11, would have a similar effect. A wide range of substituents with both electron-donating and -withdrawing effects were studied and the results are shown in Table 8. Again all substituents were found to have an activating effect but it was small in magnitude (< 3) in THF and again even smaller in DMF.

Competition cycles.—In this work each individual competition experiment shows the relative rate of cyclisation of the



Scheme 10

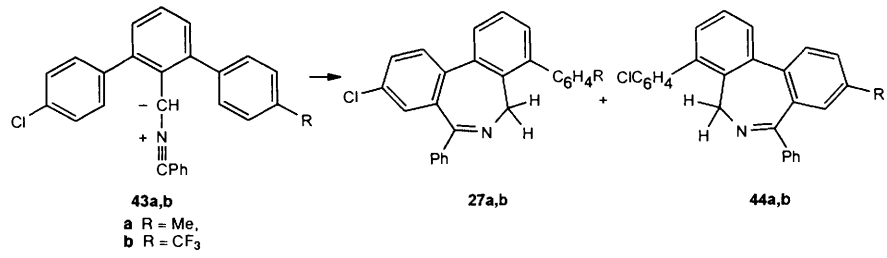


Scheme 11

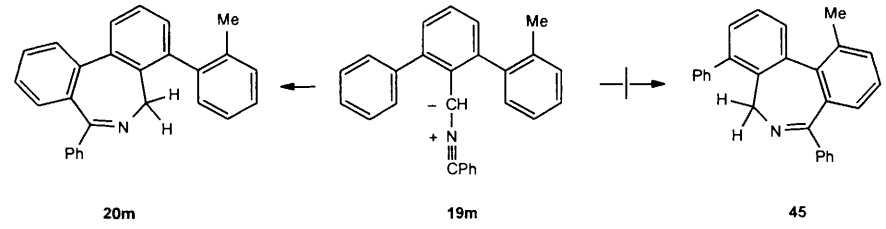
double bond/ring system concerned compared to the unsubstituted phenyl group. For these results to be a self-consistent set of relative reactivity data the rate of the reaction used as comparator must be independent of the nature of the competition partner, *i.e.* the two competing reactions must be effectively uncoupled in a reactivity sense. This is unlikely to be completely true for any pair of intramolecular competition reactions, but, as discussed earlier, it was hoped that in this case any interaction between the two reactions would be small because of the nature of the system. We have tested whether this is true by carrying out two cyclic sets of competition reactions involving the *p*-chloro-, *p*-methyl- and *p*-trifluoromethylphenyl groups. The additional reactions required were the direct competitions between *p*-chlorophenyl and the other two groups, Scheme 12. As in the previous work one component of each product mixture, compounds **27a** and **b**, was identified by comparison with an authentic sample. The first example was based on the cyclisations of **19g** and **19k** from which the *p*-methylphenyl and *p*-chlorophenyl rings were found to be 1.5 ± 0.1 and 2.2 ± 0.2 times more reactive respectively, than the unsubstituted phenyl group (each result the average of two experiments). If the reactivity of the phenyl group is unaffected by its competition partners then in a direct competition between *p*-chlorophenyl and *p*-methylphenyl the relative reactivity should be in the range 1.5 ± 0.2. In fact the result was 1.4 ± 0.1, *i.e.* within the expected range. In the second case involving *p*-chlorophenyl and *p*-trifluoromethylphenyl which were 2.2 ± 0.2 and 2.8 ± 0.1 times more reactive respectively, than phenyl, the predicted ratio for the direct competition is 1.3 ± 0.2 and the experimental result was 1.1 ± 0.1. These results show that, at least within the limited range of reactivity examined, the rates of the competing processes are independent of the nature of the competition partner.

ortho-*Substituents* (**19m**).—The only example studied was **19m**, Scheme 13, in which the *ortho* substituent was a methyl group. This was done to complement an earlier synthetic study on the cyclisation of compound **7** (R = *o*-Me) in which it was found unexpectedly that it failed to cyclise at the free *ortho* position and instead reacted *via* dimerisation.[5] It was suggested that this failure to cyclise was due to a steric interaction of the methyl group with the *ortho* hydrogen atom on the adjacent ring which inhibited the conjugation between the two benzene rings required by the electrocyclisation process. The alternative explanation that the *ortho* methyl group in some way facilitated the competing dimerisation pathway was thought less likely. The cyclisation of **19m** gave *only* the product **20m**, identical with an authentic sample, and no detectable amount of the alternative cyclisation product **45**. This in combination with the earlier work supports the rationalisation that the *ortho*-methyl group is serving to deactivate the ring to electrocyclic attack not by an electronic effect but rather by a steric effect which disrupts the electrocyclisation transition state leading to **45**. The effect of the methyl group in restricting rotation about the biphenyl bond was also nicely illustrated in the ^{1}H NMR spectra of both the amide **23m** (precursor to the nitrile ylide) (Table 3) and the product dibenz[*c*,*e*]azepine **20m** (Table 5). In both cases the restricted rotation on the NMR timescale produced 'biphenyl' type chirality which in the case of the amide **23m** caused the prochiral methylene protons to be diastereotopic and thus to give a ABX system coupling to each other and to the adjacent NH. A VT-NMR study showed that the ABX pattern collapsed to a doublet at *ca.* 125 °C which corresponds to a $\Delta G^{\ddagger}$ for the biphenyl rotation of 83 kJ mol^{-1}. In the room temperature spectrum of the dibenzazepine **20m** the same effect, in combination with the usual slow inversion of the azepine ring, produced two sets of AB doublets for the methylene protons and two well separated peaks for the methyl group. The latter had a coalescence temperature of *ca.* 130 °C corresponding to a $\Delta G^{\ddagger}$ of 87 kJ mol^{-1} for the biphenyl rotation, slightly higher than for the amide **23m** as would be expected from the increased steric interaction.

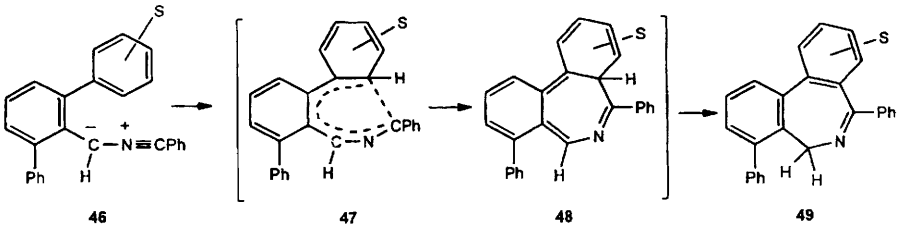
(3) Summary and discussion. The first two cases, *i.e.* the cyclisations involving the olefinic double bond (**19a**) and the thiophene ring (**19b**), confirm the reactivity order expected on the basis of the electrocyclisation mechanism (Scheme 14), *i.e.* that the activation energy increases with the aromatic character of the γ,δ-double bond. The remainder of the results, *i.e.* those concerning the effects of substituents in the aromatic ring, show



Scheme 12



Scheme 13

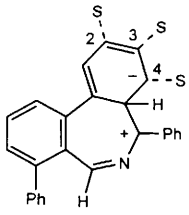


Scheme 14

a distinct pattern of reactivity but one which cannot be explained with any degree of certainty at present. With the exception of the *ortho* substituted case **19m**, where the effect is steric in origin as discussed above, the overall pattern observed is that the reactivity of the ring is at a minimum when it is unsubstituted and is increased by both electron-donating and -withdrawing substituents. Thus the results for this electrocyclic aromatic substitution process are quite different to those observed for either electrophilic or nucleophilic substitution. The nearest parallel is with free-radical substitution by a non-polar radical in that the effects of the substituents are relatively small and that all types of substituents serve to increase the reaction rate.[13] However, there are significant differences from radical substitution, *e.g.* the rate-enhancing effect of the single nitro group in **19e** (> 100 ×) is much larger than anything seen in free-radical substitution (2.94 × for the phenylation of nitrobenzene) and the *o*/*p* ratios in the cyclisation of **19e,f** are also higher (F_o/F_p for phenylation: $PhNO_2$, 1.12; PhOMe, 1.58).

In this work the *meta* substituents (cases **19c–f**) have the strongest effect, particularly for substitution at the ring position adjacent to the substituent. The rate enhancement is most notable for electron-withdrawing groups (NO_2, > 100; 2 × CF_3, 32) but is also produced in lesser degree (8 ×) by the modest electron release of the two methyl groups in **19c**. The *para* substituents in **19g–l** similarly all produce a rate enhancement but one which is smaller in all cases (< 3), much closer to typical values observed in radical substitution. The importance of the *polar* effects of the substituents is supported by the fact that there is an approximate correlation between the effect on reaction rate and the substituent σ values for both *meta* and *para* substituents. Thus, for the former, the order of reactivity is the same as the absolute values of σ_m (NO_2, 0.71; CF_3, 0.43; OMe, 0.12; CH_3, −0.07); and for the latter the order is similar to that of the absolute values of σ_p with the notable exception of the dimethylamino group (CF_3, 0.54; Cl, 0.23; MeO, −0.27, CH_3, −0.17; NMe_2, −0.83; F, 0.06). The biphilic nature of the cyclisation, *i.e.* the U-shaped dependence of reactivity on substituent polarity is similar to that seen in the cycloadditions of Sustmann Type II 1,3-dipoles with substituted alkenes. However nitrile ylides are Type I not Type II dipoles and the reactivity seen here is quite different from their behaviour in cycloadditions where the reaction rate is increased by electron-withdrawing groups on the alkene but is reduced by electron-donating groups. Hence, it appears that the behaviour of 1,3-dipoles in electrocyclisation does not necessarily follow their reactivity pattern in cycloadditions although both are concerted pericyclic processes of a formally similar type.

The mechanism for these cyclisations is shown in Scheme 14. We make the assumptions that the reaction proceeds through a transition state **47** which is helical in form (*cf.* structure **12**) and which leads to the intermediate **48**; and also that the cyclisation step is irreversible as shown for a closely related reaction.[4] The common effect of all the substituents S in reducing the activation energy may be achieved by any or all of the following effects: (i) by increasing the coefficients of the orbital lobes at the two terminii of the π-system (*cf.* structure **12**) and so increasing overlap in the transition state; (ii) by stabilising the transition state by enhancing or extending the electron delocalisation; or (iii) by polarising the molecule so as to produce a coulombic attraction between the reacting centres. In the absence of MO calculations on the system the influence of (i) is uncertain at present; but (ii) seems likely to be important, since by the nature of electrocyclisation reactions, the geometry



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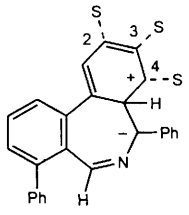

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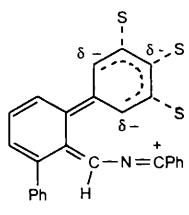

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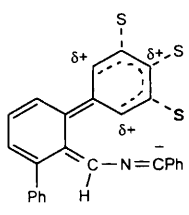

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of the transition state must be such that there is the maximum possible p-orbital overlap throughout the reacting π-system. We have no MO calculations on the transition state geometry for this reaction but the transition state for the cyclisation of the unsubstituted diazo compound **1** (a = CH; b = c = N) has been calculated[7] and it has been found that bond formation is quite well advanced (new partial σ bond = 2.061 Å) and that there is considerable pyramidalisation of the geometry of the terminal methylene group. The nitrile ylide is a similar type of propargyl-allenyl 1,3-dipole and therefore it does not seem unreasonable to assume that the transition state in this cyclisation is similar and therefore has some of the character of the intermediate **48**. In the following discussion we take the intermediate as a model for the transition state and assume that the latter is subject to similar stabilising/destabilising effects by substituents. For the intermediate **48** it might be expected that dipolar canonical forms such as **50** and **51** would make a significant contribution to the resonance stabilisation since both contain an intact benzene ring. These structures would be further stabilised by aromatic substituents in the upper ring with electron-donating or -withdrawing properties, respectively. The substituents would similarly serve to stabilise the transition state, assuming it is product-like, and so enhance the reactivity of the ring. Such substituents would have a maximum effect when directly conjugated with the charge to be delocalised, *i.e.* in the 4-position, or cross-conjugated in the 2-position (as for the cyclisation of the *meta*-substituted cases **19c–f**) and a lesser effect when in the 3-position (as for the cyclisation of the *para*-substituted cases **19g–l**). Since it will also affect the activation energy, the effect of the substituents on the stability of the nitrile ylide reactants must also be considered, *e.g.*, *via* delocalisation of the positive or negative charges of the 1,3-dipole, structures **52**, **53**. These would not be expected to make a major contribution since they involve loss of the aromatic stabilisation of both rings but any effect the substituents do have is different to that in the intermediates **50**, **51** since the pattern of conjugation has changed. Thus the *meta* substituents would be expected to have a minor effect on the stabilisation of the reactant and a major effect in the intermediate, while the opposite is true for the *para* substituents. The third factor may also be important, *i.e.* that the presence of any polar substituent in the target ring will stablilise the extended dipolar canonical structures **52**, **53** and thus favour the development of opposite charges at the two atoms between which the new σ bond will form. This coulombic attraction would also lower the activation energy. The effect of the polar solvent DMF in diminishing the rate enhancing effect of the substituents is probably due to the formation of a solvation shell around the polarised reactant which hinders the cyclisation.

The above rationalisation is speculative, since, at present, there is no way of knowing the relative importance of the three factors discussed, but it does fit with most of the results for this particular 1,3-dipolar intermediate. However, caution must be exercised in extrapolating these results and rationalisations to other systems since current work[14] has shown that the same pattern of reactivity is not exhibited by some other 1,3-dipoles.

Experimental

NMR spectra were run as solutions in deuteriochloroform unless otherwise stated. Chemical shifts are recorded as δ values. J Values are given in Hz. In the ^{13}C spectra carbon multiplicity was established by single frequency off-resonance decoupling or by DEPT. Mass spectra were obtained using electron ionisation at 70 eV unless otherwise stated. Preparative chromatography was carried out by the 'dry-column flash' technique[15] using silica gel (15 μm, Fluka Kieselgel GF_{254}) and eluting solvents based on light petroleum bp 40–60 °C (referred to as 'petrol') admixed with diethyl ether (referred to as ether) or ethyl acetate. Evaporation of solvents indicates evaporation under reduced pressure using a rotary evaporator. Solutions were dried over anhydrous magnesium sulfate.

Solvents, reagents and starting materials

Tetrahydrofuran (THF) was distilled from sodium and benzophenone as required. Cyclohexane, hexane and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride as required. 1,2-Dimethoxyethane (DME) was passed through a column of activated alumina and stored over 4 Å molecular sieves. Phenylboronic acid, 3-nitrophenylboronic acid, 3,5-bis(trifluoromethyl)phenylboronic acid, 4-methylphenylboronic acid, 4-methoxyphenylboronic acid, 4-fluorophenylboronic acid and 4-chlorophenylboronic acid were obtained from Lancaster Synthesis and used without further purification. (*E*)-2-Phenylethenylboronic acid was prepared by the method of Brown and Gupta.[16] 2-Bromo-6-nitrotoluene was prepared (88%) by the method of Harrington and Hegedus[17] from 2-methyl-3-nitroaniline (Aldrich Chemical Company).

Preparation of boronic acids†

2-Thienylboronic acid. General procedure. Butyllithium (26.25 cm^3 of a 2.0 mol dm^{-3} solution in hexanes) was added dropwise with stirring to a solution of 2-bromothiophene (8.15 g, 0.05 mol) in THF (30 cm^3) at −78 °C under dry nitrogen. The mixture was stirred at −78 °C for 30 min and then triisopropyl borate (9.41 g, 0.05 mol) was added dropwise. The mixture was stirred at −78 °C for 1 h and then allowed to warm to room temperature. The mixture was neutralised with 2 mol dm^{-3} hydrochloric acid and extracted with ether (50 cm^3). The ether layer was washed with chilled water (30 cm^3), dried and

† Boronic acids normally exist as mixed anhydrides which means that characterisation by combustion analysis is not possible. In most cases they do not give parent ions in EI mass spectrometry. All the examples prepared were characterised by their mp and IR spectra.

the solvent was evaporated. The product was crystallised from water to give 2-thienylboronic acid as a white crystalline solid (3.90 g, 61%), mp 128–130 °C (lit.,[18] 132–133 °C); ν_{max}(Nujol)/cm^{-1} 3270 (br, OH).

3-Methoxyphenylboronic acid (48%), mp 145–147 °C from cyclohexane (lit.,[19] 147 °C); ν_{max}(Nujol)/cm^{-1} 3320 (br, OH).

3,5-Dimethylphenylboronic acid (31%), mp 235–238 °C (from benzene); ν_{max}(Nujol)/cm^{-1} 3220 (br, OH).

4-Trifluoromethylphenylboronic acid (51%), mp 233–235 °C (from benzene); ν_{max}(Nujol)/cm^{-1} 3290 (br, OH) (Found: *m/z* 190.0412. $C_7H_6{}^{11}BF_3O_2$ requires 190.0413); *m/z* 190 (82%), 189 (14), 126 (79) and 45 (100).

4-Dimethylaminophenylboronic acid (47%), mp 268–272 °C (from benzene) (lit.,[20] 270–275 °C); ν_{max}(Nujol)/cm^{-1} 3400 (br, OH).

2-Methylphenylboronic acid (21%), mp 166–168 °C (from hexane) (lit.,[19] 168 °C); ν_{max}(Nujol)/cm^{-1} 3210 (br, OH).

Preparation of *N*-(2-bromo-6-phenylbenzyl)benzamide 22 and *N*-[2-Bromo-6-(4-chlorophenyl)benzyl]benzamide 25

These compounds were prepared by the route shown in Scheme 6.

2-Nitro-6-phenyltoluene 30a. 2-Bromo-6-nitrotoluene[17] (10.80 g, 0.05 mol) and tetrakis(triphenylphosphine)-palladium(0) (0.56 g, 0.5 × 10^{-3} mol, 1% catalyst) were stirred in 1,2-dimethoxyethane (75 cm^3) under dry nitrogen for 20 min. A solution of phenylboronic acid (6.70 g, 0.055 mol) and sodium carbonate (5.53 g, 0.05 mol) in water (30 cm^3) was added to it and the mixture was heated to reflux under dry nitrogen overnight. After evaporation of the 1,2-dimethoxyethane, methylene dichloride (50 cm^3) was added to the residue. The organic layer was separated and filtered through a thick pad of activated alumina. Evaporation gave a brown solid which was crystallised from hexane to give 2-nitro-6-phenyltoluene as a pale brown crystalline solid (9.32 g, 87%), mp 69–71 °C (Found: C, 73.0; H, 5.1; N, 6.4. $C_{13}H_{11}NO_2$ requires C, 73.2; H, 5.2; N, 6.6%); δ_H(200 MHz) 2.36 (s, CH_3), 7.25–7.51 (m, 7 H, Ar-H) and 7.77–7.82 (m, 1 H); *m/z* 213 (78%), 196 (70), 165 (100) and 152 (57); ν_{max}(Nujol)/cm^{-1} 1530 and 1360 (NO_2).

2-(4-Chlorophenyl)-6-nitrotoluene 30b. A similar reaction using 4-chlorophenylboronic acid gave 2-(4-chlorophenyl)-6-nitrotoluene as a pale brown crystalline solid (95%), mp 55–56 °C from hexane (Found: C, 63.3; H, 4.0; N, 5.7. $C_{13}H_{10}ClNO_2$ requires C, 63.0; H, 4.1; N, 5.7%); δ_H(200 MHz) 2.33 (s, CH_3), 7.20–7.44 (m, 6 H) and 7.79 (dd, *J* 7.6 and 2.0, 1 H); *m/z* 249 (24%), 247 (70), 230 (38), 212 (50) and 165 (100); ν_{max}(Nujol)/cm^{-1} 1530 and 1360 (NO_2).

2-Methyl-3-phenylaniline 31a. A solution of 2-nitro-6-phenyltoluene (21.32 g, 0.10 mol) in ethanol (250 cm^3) was hydrogenated using palladium on charcoal (10% Pd/C, 1.07 g) under 35 psi of hydrogen overnight. The mixture was filtered through Celite and the solvent was evaporated to give 2-methyl-3-phenylaniline as a white crystalline solid (18.33 g, 100%), mp 64–65.5 °C (from cyclohexane) (Found: C, 85.2; H, 6.9; N, 7.6. $C_{13}H_{13}N$ requires C, 85.2; H, 7.1; N, 7.6%); δ_H(200 MHz) 2.10 (s, CH_3), 3.64 (br s, NH_2), 6.72–6.78 (m, 2 H), 7.08–7.16 (m, 1 H) and 7.32–7.49 (m, 5 H); *m/z* 183 (100%), 182 (40), 165 (22) and 32 (55); ν_{max}(Nujol)/cm^{-1} 3410 and 3340 (NH_2).

3-(4-Chlorophenyl)-2-methylaniline 31b. A similar reaction using 2-(4-chlorophenyl)-6-nitrotoluene gave 3-(4-chlorophenyl)-2-methylaniline as a colourless oil (9.47 g, 97%) (Found: *m/z* 219.0626. $C_{13}H_{12}{}^{37}ClN$ requires 219.0629); *m/z* 219 (33%), 218 (20), 217 (100), 216 (20), 180 (18) and 69 (87); δ_H(200 MHz) 2.05 (s, CH_3), 3.70 (br s, NH_2), 6.65–6.73 (m, 2 H), 7.07 (t, *J* 7.5, 1 H) and 7.21–7.39 (m, 4 H); ν_{max}(film)/cm^{-1} 3470 and 3380 (NH_2).

2-Bromo-6-phenyltoluene 32a. This was made following the method of Harrington and Hegedus.[17] 2-Methyl-3-phenylaniline (5.13 g, 0.028 mol) in water (50 cm^3) was heated to reflux and hydrobromic acid (48%, 15 cm^3) was added to it; the mixture was maintained at reflux for 20 min and then cooled to 0 °C. Sodium nitrite (1.93 g, 0.028 mol) in water (15 cm^3) was added to it with rapid stirring and the resultant diazonium salt solution was stirred at 0 °C for 30 min. This was added slowly, while cold, to a rapidly stirred mixture of copper(I) bromide (20.08 g, 0.14 mol) in hydrobromic acid (48%, 12 cm^3) and water (30 cm^3) at 0 °C. The thick suspension was stirred at room temperature overnight then heated on a steam bath for 1 h. Extraction with ether (3 × 50 cm^3), drying, evaporation and dry-flash chromatography of the residue (silica, petrol–ether, 100:0 to 24:1) gave 2-bromo-6-phenyltoluene as a colourless oil (4.17 g, 60%) (Found: *m/z* 248.0029. $C_{13}H_{11}{}^{81}Br$ requires 248.0025); δ_H(200 MHz) 2.36 (s, CH_3) and 7.07–7.62 (m, 8 H); *m/z* 248 (13%); 246 (13), 167 (11), 131 (21) and 69 (100).

2-Bromo-6-(4-chlorophenyl)toluene 32b. A similar reaction using 3-(4-chlorophenyl)-2-methylaniline (9.14 g, 0.042 mol) gave 2-bromo-6-(4-chlorophenyl)toluene as a colourless oil (6.59 g, 56%) (Found: *m/z* 279.9654. $C_{13}H_{10}{}^{79}Br^{35}Cl$ requires 279.9654); δ_H(360 MHz) 2.30 (s, CH_3) and 7.06–7.58 (m, 7 H, Ar-H); *m/z* 284 (19%), 283 (14), 282 (84), 281 (49), 280 (64), 279 (4), 166 (100) and 165 (75).

2-Bromo-6-phenylbenzyl bromide 33a. A mixture of 2-bromo-6-phenyltoluene (11.86 g, 0.048 mol), *N*-bromosuccinimide (13.01 g, 0.072 mol) and benzoyl peroxide (0.4 g) in carbon tetrachloride (60 cm^3) was heated at reflux for 2 h and then allowed to cool to room temperature. Methylene dichloride (50 cm^3) was added and the mixture was washed with 2% w/v aqueous sodium carbonate (2 × 50 cm^3) then water (50 cm^3). Evaporation of the solvent and dry-flash chromatography (silica, petrol–ether, 19:1) of the residue gave 2-bromo-6-phenylbenzyl bromide as a yellow oil (15.54 g, 99%) (Found: *m/z* (FAB, glycerol) 325.9131. $C_{13}H_{10}{}^{79}Br^{81}Br$ requires 325.9131); δ_H(200 MHz) 4.53 (s, CH_2), 7.19–7.22 (m, 2 H) and 7.64–7.46 (m, 6 H); *m/z* (FAB, glycerol) 329 (M + 1, 9%), 327 (9), 325 (4), 245 (48) and 166 (100).

2-Bromo-6-(4-chlorophenyl)benzyl bromide 33b. In a similar reaction a mixture of 2-bromo-6-(4-chlorophenyl)toluene (6.19 g, 0.022 mol), carbon tetrachloride (30 cm^3), *N*-bromosuccinimide (4.77 g, 0.026 mol) and benzoyl peroxide (0.2 g) was heated at reflux for 1 h and worked up as above. After evaporation of the solvent the residue was crystallised from hexane to give 2-bromo-6-(4-chlorophenyl)benzyl bromide as a white crystalline solid (6.89 g, 87%), mp 75–76 °C (Found: C, 43.0; H, 2.4. $C_{13}H_9Br_2Cl$ requires C, 43.3; H, 2.5%); δ_H(360 MHz) 4.47 (s, CH_2), 7.14–7.25 (m, 2 H, Ar-H), 7.37–7.44 (m, 2 H, Ar-H) and 7.62 (dd, *J* 7.6 and 1.7, 1 H); *m/z* (FAB, glycerol) 365 (M + 1, 3%), 363 (8), 361 (2), 359 (12), 355 (43), 299 (39) and 32 (100).

3-Phenyl-2-(phthalimidomethyl)bromobenzene 34a. A mixture of potassium phthalimide (9.25 g, 0.05 mol) and 2-bromo-6-phenylbenzylbromide (14.67 g, 0.045 mol) in DMF (60 cm^3) was stirred at room temperature overnight. The solvent was evaporated under high vacuum and methylene dichloride (50 cm^3) was added to the residue. The mixture was washed with aqueous sodium hydroxide (2 mol dm^{-3}, 50 cm^3) and water (50 cm^3) and the organic layer was dried and the solvent was evaporated. The residue was crystallised from toluene–ethanol to give 3-phenyl-2-(phthalimidomethyl)bromobenzene as a white crystalline solid (14.09 g, 80%) mp 104–105 °C (Found: C, 64.2; H, 3.5; N, 3.6. $C_{21}H_{14}BrNO_2$ requires C, 64.45; H, 3.6; N, 3.6%); δ_H(200 MHz) 4.93 (s, CH_2), 7.16–7.34 (m, 8 H) and 7.54–7.72 (m, 4 H); *m/z* (FAB, glycerol) 394 (M + 1, 30%), 392 (30), 312 (36) and 160 (100); ν_{max}(Nujol)/cm^{-1} 1720 (C=O).

3-(4-Chlorophenyl)-2-(phthalimidomethyl)bromobenzene 34b. A similar reaction using 2-bromo-6-(4-chlorophenyl)benzyl bromide gave 3-(4-chlorophenyl)-2-(phthalimidomethyl)-bromobenzene as a white crystalline solid from toluene–ethanol (5.95 g, 77%), mp 101–103 °C (Found: C, 58.9; H, 2.9; N, 2.9. $C_{21}H_{13}BrClNO_2$ requires C, 59.1; H, 3.1; N, 3.3); δ_H(360 MHz) 4.90 (s, CH_2), 7.14–7.25 (m, 6 H, Ar-H) and 7.64–7.72 (m, 5 H, Ar-H); *m/z* (FAB, glycerol) 430 (M + 1, 25%), 428 (40), 426 (31), 274 (50) and 257 (100); ν_{max}(Nujol)/cm^{-1} 1720 (C=O).

2-Bromo-6-phenylbenzylamine 35a. A solution of 3-phenyl-2-(phthalimidomethyl)bromobenzene (13.73 g, 0.035 mol) and hydrazine hydrate (100% solution, 2.63 g, 0.053 mol) in methanol (150 cm^3) was heated at reflux for 1 h. The solvent was evaporated and ether (30 cm^3) was added to the residue. The insoluble phthaloyl hydrazide was filtered off and then the ether was evaporated to give 2-bromo-6-phenylbenzylamine as a yellow oil (8.44 g, 92%). This product was used without further purification (Found: *m/z* 263.0112. $C_{13}H_{12}{}^{81}BrN$ requires 263.0133); δ_H(200 MHz) 1.88 (br s, NH_2), 3.82 (s, CH_2) and 7.08–7.60 (m, 8 H); *m/z* 262 (7%), 244 (18), 182 (39), 165 (100) and 152 (26); ν_{max}(film) 3370 (NH).

2-Bromo-6-(4-chlorophenyl)benzylamine 35b. A similar reaction using 3-(4-chlorophenyl)-2-(phthalimidomethyl)bromobenzene (5.55 g, 0.013 mol) gave 2-bromo-6-(4-chlorophenyl)-benzylamine as a yellow oil (3.86 g, 100%). This product was used without further purification (Found: *m/z* 294.9773. $C_{13}H_{11}{}^{79}Br^{35}ClN$ requires 294.9764); δ_H(360 MHz) 1.79 (br s, NH_2), 3.80 (s, CH_2) and 7.09–7.56 (m, 7 H, Ar-H); *m/z* 299 (7%), 298 (10), 297 (9), 296 (21), 295 (22), 294 (16), 216 (100) and 152 (49); ν_{max}(film)/cm^{-1} 3360 and 3280 (NH_2).

***N*-(2-Bromo-6-phenylbenzyl)benzamide 22.** A mixture of 2-bromo-6-phenylbenzylamine (9.17 g, 0.035 mol), sodium carbonate (5.6 g, 0.053 mol) and benzoyl chloride (10.19 g, 0.07 mol) in methylene dichloride (100 cm^3) was stirred at room temperature under nitrogen overnight. Water (100 cm^3) was added to it and the mixture was stirred for 1 h. The organic layer was separated, washed with water (2 × 50 cm^3), dried and the solvent was evaporated. The oily residue was crystallised from ethanol to give *N*-(2-bromo-6-phenylbenzyl)benzamide as a white crystalline solid (9.38 g, 73%), mp 177–178 °C (Found: C, 65.6; H, 4.4; N, 3.8. $C_{20}H_{16}BrNO$ requires C, 65.75; H, 4.4; N, 3.8%) (Found: *m/z* 365.0392. $C_{20}H_{16}{}^{79}BrNO$ requires 365.0415); δ_H(200 MHz) 4.66 (d, *J* 5, CH_2), 6.23 (br s, NH), 7.17–7.50 (m, 10 H) and 7.59–7.71 (m, 3 H); *m/z* 286 (100%), 165 (38), 105 (30) and 77 (33); ν_{max}(Nujol)/cm^{-1} 3270 (NH) and 1625 (C=O).

***N*-[2-Bromo-6-(4-chlorophenyl)benzyl]benzamide 25.** A similar reaction using 2-bromo-6-(4-chlorophenyl)benzylamine gave *N*-[2-bromo-6-(4-chlorophenyl)benzyl]benzamide as a white crystalline solid (1.95 g, 75%), mp 170–172 °C (Found: C, 59.8; H, 3.6; N, 3.5. $C_{20}H_{15}BrClNO$ requires C, 60.15; H, 3.8; N, 3.5%) (Found: *m/z* 399.0016. $C_{20}H_{15}{}^{79}Br^{35}ClNO$ requires 399.0026); δ_H(200 MHz) 4.63 (d, *J* 5.1, CH_2), 6.40 (br s, NH) and 7.19–7.72 (m, 12 H, Ar-H); *m/z* 403 (1%), 401 (1), 399 (1), 322 (32) and 320 (100); ν_{max}(Nujol)/cm^{-1} 2290 (NH) and 1630 (C=O).

Preparation of *N*-(6-substituted-2-phenylbenzyl)benzamides 23a–m and *N*-[6-substituted-2-(4-chlorophenyl)benzyl]benzamides 26a,b

Compounds **23a–m** were prepared from the bromo amide **22** as shown in Scheme 5 using the appropriate arylboronic acid *via* the general method given in detail below for the compound **23a**. Compounds **26a,b** were prepared by a similar route from the bromo amide **25**. In most cases the isolation of the product required separation by dry-flash chromatography (on silica, with ethyl acetate–petrol as eluent usually in an initial ratio of 1:6) before purification by crystallisation. Reaction times, yields and physical properties of the products are given in Table 2 and their spectroscopic properties in Table 3.

***N*-[2-Phenyl-6-(*E*-2-phenylethenyl)benzyl]benzamide 23a. General procedure.** *N*-(2-Bromo-6-phenylbenzyl)benzamide (0.76 g, 2.1 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.07 g, 6 × 10^{-5} mol, 3% catalyst) were stirred in 1,2-dimethoxyethane (10 cm^3) under nitrogen for 20 min. A solution of *E*-2-phenylethenylboronic acid (0.37 g, 2.5 mmol) and sodium carbonate (0.22 g, 2.1 mmol) in water (6 cm^3) was added to it and the mixture was heated to reflux under dry nitrogen for 20 min. The 1,2-dimethoxyethane was evaporated and the residue was extracted with methylene dichloride (10 cm^3). The organic layer was separated, dried and evaporated to give the crude product which was crystallised from ethanol–toluene to give *N*-[2-phenyl-6-(*E*-2-phenylethenyl)benzyl]benzamide as a white crystalline solid (0.66 g, 81%), mp 200–202 °C.

Preparation of dibenz[*c,e*]azepines 20a–m and 27a,b

8-Bromo-5-phenyl-7*H*-dibenz[*c,e*]azepine 24. *N*-(2-Bromo-6-phenylbenzyl)benzamide (1.12 g, 3 mmol), dry ether (50 cm^3) and thionyl chloride (10 cm^3) were heated at reflux under dry nitrogen overnight. The solvent was evaporated and the residue was dried under high vacuum for 2 h. Dry THF (50 cm^3) was added to it and the mixture cooled to 0 °C. Solid potassium *tert*-butoxide (0.67 g, 6 mmol) was added to it in one portion with rapid stirring under dry nitrogen. The mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature and stirred for a further 1 h. Aqueous ammonium chloride (25% w/v, 50 cm^3) was added to it and the mixture was stirred vigorously for 5 min. Methylene dichloride (50 cm^3) was added to the mixture, the organic layer separated and the aqueous layer extracted with methylene dichloride (2 × 20 cm^3). The combined organic layers were dried and the solvent was evaporated. Dry-flash chromatography of the residue (silica, ethyl acetate–petrol, 1:19 to 1:9) gave 8-bromo-5-phenyl-7*H*-dibenz[*c,e*]azepine as a white crystalline solid (0.97 g, 93%), mp 142–143 °C (from cyclohexane–ethanol) (Found: C, 68.7; H, 4.0; N, 4.0. $C_{20}H_{14}BrN$ requires C, 69.2; H, 4.1; N, 4.0%) (Found: *m/z* 349.0295. $C_{20}H_{14}{}^{81}BrN$ requires 349.0290); δ_H(200 MHz) 3.76 (d, *J* 10.7, 7-H), 5.53 (d, *J* 10.7, 7'-H) and 7.17–7.74 (m, 12 H); *m/z* 349 (77%), 347 (79), 267 (18), 239 (15) and 165 (60); ν_{max}(Nujol)/cm^{-1} 1610 (C=N).

8-Bromo-3-chloro-5-phenyl-7*H*-dibenz[*c,e*]azepine. A similar reaction using *N*-[2-bromo-6-(4-chlorophenyl)benzyl]benzamide gave 8-bromo-3-chloro-5-phenyl-7*H*-dibenz[*c,e*]azepine as a colourless oil (0.44 g, 86%) (Found: *m/z* 380.9903. $C_{20}H_{13}{}^{79}Br^{35}ClN$ requires 380.9920); δ_H(360 MHz) 3.72 (d, *J* 10.7, 7-H), 5.54 (d, *J* 10.7, 7'-H) and 7.19–7.66 (m, 11 H, Ar-H); *m/z* 385 (22%), 384 (38), 383 (90), 382 (98), 381 (100), 380 (68), 346 (51) and 163 (49); ν_{max}(Nujol)/cm^{-1} 1610 (C=N).

Compounds **20a–m** were prepared from 8-bromo-5-phenyl-7*H*-dibenz[*c,e*]azepine **24** and the appropriate boronic acid as shown in Scheme 5 *via* the general method given in detail below for compound **20a**. Compounds **27a,b** were prepared by a similar route from 8-bromo-3-chloro-5-phenyl-7*H*-dibenz[*c,e*]-azepine. Reaction times, yields and physical properties of the products are given in Table 4 and their spectroscopic properties in Table 5.

5-Phenyl-8-(*E*-2-phenylethenyl)-7*H*-dibenz[*c,e*]azepine 20a. 8-Bromo-5-phenyl-7*H*-dibenz[*c,e*]azepine (0.17 g, 0.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.018 g, 1.5 × 10^{-5} mol; 3% catalyst) in 1,2-dimethoxyethane (3 cm^3) were stirred under nitrogen for 20 min. (*E*)-2-Phenylethenyl boronic acid (0.092 g, 0.63 mmol) and sodium carbonate (0.055 g, 0.53 mmol) in water (2 cm^3) were added to it and the mixture heated to reflux under dry nitrogen for 35 min. After evaporation of the dimethoxyethane the mixture was extracted with methylene dichloride (3 × 3 cm^3). The organic layer was separated, dried and evaporated to give the crude product which was purified by dry-flash chromatography (silica, ethyl

acetate–petrol, 1:49 to 1:19) to give 5-phenyl-8-(*E*-2-phenylethenyl)-7*H*-dibenz[*c*,*e*]azepine as a white crystalline solid (0.18 g, 97%), mp 159–161 °C (from cyclohexane–toluene).

Intramolecular competition reactions of the nitrile ylides 19a–m and 43a,b derived from the amides 23a–m and 26a,b, respectively

General method. The imidoyl chlorides of the amides **23a–h**, **j–m** were prepared by reaction of the amides with an excess of thionyl chloride in ether overnight and, after removal of the excess of solvent and reagent by evaporation, were used without further purification. The use of this method for the *p*-dimethylamino substituted amide **23i** gave only intractable mixtures, but a clean conversion (as shown by ^{1}H NMR spectroscopy) was obtained by the use of the more powerful reagent chlorodimethylformiminium chloride;[5] details are given in (*b*) below. The nitrile ylides **19a–m** were generated from the imidoyl chlorides in THF or DMF as solvent at 0 °C by reaction with solid potassium *tert*-butoxide; the reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 1 h. After quenching with aqueous ammonium chloride the crude reaction product was obtained by extraction with methylene dichloride. Each competition reaction was carried out twice, first on a 0.5 mmol scale and then on an NMR scale (50 mg of amide). Dry-column flash chromatography of the product of the larger scale reaction was used to separate the products from any residual starting material and by-products but in most cases the isomeric products **20** and **21** could not be separated. The products were identified and the crude product mixtures were analysed for the product ratio by ^{1}H NMR spectroscopy as discussed in the Results and Discussion section above. It was shown by NMR spectroscopy that the product ratio was not changed by chromatography. Mass spectra and parent-ion accurate mass measurements were obtained for the products or product mixtures. The NMR data are given in Table 6, the mass spectrometry data in Table 7, and the reactivity ratios in Table 8 as the average for two reactions. Typical reaction details are given in (*a*) below.

(*a*) **Benzonitrilio[2-phenyl-6-(*E*-2-phenylethenyl)phenyl]-methanide 19a from 23a.** *N*-[2-Phenyl-6-(*E*-2-phenylethenyl)-benzyl]benzamide (0.19 g, 0.5 mmol), dry ether (10 cm^3) and thionyl chloride (3 cm^3) were heated at reflux under dry nitrogen overnight. The solvent was evaporated and the residue was dried under high vacuum at room temperature for 3 h. Dry THF (10 cm^3) was added to the residue and the solution cooled to 0 °C. Solid potassium *tert*-butoxide (0.112 g, 1 mmol) was added in one portion with rapid stirring under dry nitrogen. The mixture was stirred at 0 °C for 2 h, allowed to warm to room temperature and stirred for 1 h. Aqueous ammonium chloride (25% w/v, 10 cm^3) was added to it and the mixture was stirred vigorously for 15 min and worked up as described above to give 1*H*-1,1a,4-triphenyl-1a,7b-dihydrocyclopropa[*c*]isoquinoline **36** (0.18 g, 97%) as a pale brown foam (Found: *m*/*z* 371.1666. $C_{27}H_{21}N$ requires 371.1674); δ_H(360 MHz) 1.86 (d, *J* 6.0, 1 H), 3.54 (d, *J* 6.0, 1 H), 6.94–7.61 (m, 18 H, ArH) and 8.33 (s, H–C=N); *m*/*z* 371 (65%), 370 (100), 81 (12), 268 (39), 189 (10), 178 (10) and 165 (13).

A duplicate experiment on a smaller scale using the amide (0.05 g, 1.3 × 10^{-4} mol) gave the same result. Two further reactions of the same kind on this scale using DMF as the cyclisation solvent gave the same result. Thermolysis of 1*H*-1,1a,4-triphenyl-1a,7b-dihydrocyclopropa[*c*]isoquinoline **36** (0.10 g) in refluxing cyclohexane for 4 h gave a brown oil. Dry-column flash chromatography (silica, ether–petrol, 1:19) gave 1*H*-3,4,9-triphenyl-2-benzazepine **37** as a yellow oil (0.08 g, 80%) (Found: *m*/*z* 371.1666. $C_{27}H_{21}N$ requires 371.1674); δ_H(360 MHz) 3.79 (d, *J* 10.0, 1 H), 5.31 (d, *J* 10.0, 1 H), 7.05–7.68 (m, 18 H, Ar-H) and 7.91 (s, H–C=N); *m*/*z* 371 (43%), 370 (71), 268 (24), 105 (100), 77 (54) and 51 (28).

(*b*) ***N*-[2-(4-Dimethylaminophenyl)-6-phenylbenzyl]benzimidoyl chloride.** A mixture of *N*-[2-(4-dimethylaminophenyl)-6-phenylbenzyl]benzamide **23i** (0.05 g, 1.3 × 10^{-4} mol) and dry DMF (0.019 g, 2.6 × 10^{-4} mol) in thionyl chloride (0.5 cm^3) was stirred at room temperature under nitrogen overnight. The excess of DMF and thionyl chloride was removed by evaporation under high vacuum at room temperature and the resulting imidoyl chloride was converted into the nitrile ylide as in the general method.

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