Synthesis of 1-Substituted 7-Cyano-2,3-diphenylindolizines and Evaluation of Antioxidant Properties

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Protocols for the synthesis of novel 1-substituted 7-cyano-2,3-diphenylindolizines from the corresponding indolizinol have been developed, and the compounds' abilities to act as antioxidants, i.e. to inhibit lipid peroxidation in vitro, have been examined. 1-Bromo-7-cyano-2,3-diphenylindolizine **9** readily participates in Pd-catalysed coupling reactions with organotin, organozinc, and organoboron reagents. Similar treatment of the corresponding indolizinyl triflate **6**, on the other hand, resulted only in partial cleavage of the triflate back to the indolizinol, except in reaction with 1-ethoxyethenyl(tributyl)tin. Here, the unexpected acetal (1-ethoxyethoxy)indolizine **10** was formed. The structure of **10** was determined by single-crystal X-ray diffraction methods at 150 K. An alternative strategy for the introduction of substituents at C-1 is by lithiation of the bromide **9** followed by reaction with electrophiles. The ability of the indolizine derivatives to inhibit lipid peroxidation in vitro was examined. Lipid peroxidation of boiled rat liver microsomes was induced by ascorbic acid/$FeSO_4$ and peroxidation was determined by measuring the material reactive to thiobarbituric acid. In particular, the indolizinyl acetate **4** and the triflate **6** appear to be highly active antioxidants, with IC_{50} values below 1 μm in the bioassay.

Introduction

Compounds with antioxidant/radical-scavenging properties may have therapeutic potential, because free radicals have been implicated in major diseases such as, for instance, cancer, Parkinson's disease, Alzheimer's disease, stroke, heart infarction and rheumatoid arthritis.[1] Inspired by the fact that 1-indolizinols are easily oxidised to stable free radicals,[2] we have previously prepared a number of indolizinols *O*-protected as esters, ethers, carbonates, and carbamates (Figure 1). Several of these derivatives strongly inhibited lipid peroxidation in vitro.[3,4] Regardless of the nature of the *O*-substituent, otherwise identical indolizines exhibited comparable activities in the test system. This finding led us to infer that the indolizines themselves were acting as antioxidants and not as pro-drugs; cleavage of *O*-substituents (especially methyl ethers) to give the unprotected indolizinol in the test medium was highly unlikely. We proposed that the indolizines may inhibit lipid peroxidation by an electron donation mechanism. Cyclic voltammetry supported this hypothesis; reversible oxidation to the corresponding radical cation with $E°$ (vs. Fc/Fc^+) in the range of 0.4−0.7 V was found for acetates, ethers and carbonates.[4] Here we report the synthesis of a variety of novel 1-substituted indolizine derivatives, as well as their abilities to inhibit lipid peroxidation in vitro.

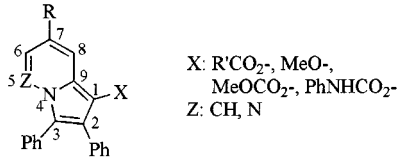

Figure 1. General structure for indolizine derivatives which inhibit lipid peroxidation. The numbering of the indolizine nucleus used throughout this paper is shown

Results and Discussion

We chose to prepare all of the indolizines reported here via the indolizinol **3**, which is readily generated in situ by cyclisation of cyanopyridine **1** with commercially available diphenylcyclopropenone **2**[2a] (Scheme 1). Previous results had led us to believe that an electron-withdrawing substituent in the indolizine 7-position was beneficial for lipid peroxidation inhibition.[4] The cyano group was chosen because: complete regioselectivity had been reported in the reaction between pyridine **1** and cyclopropenone **2**,[2a] the indolizinol **3** is reasonably stable,[2a] and the cyano substituent was expected to be compatible with a variety of reaction conditions.

Previously, we had reported high antioxidant activity for acetates and methyl ethers of other 1-indolizinols,[4] and so we first prepared the acetate **4**[2a] and the methoxy compound **5** (Scheme 1). We anticipated that conversion of the hydroxy substituent in compound **3** into halides or sulfonates would allow us to synthesise a number of 1-substituted indolizines. Compound **3** was easily converted into the tri-

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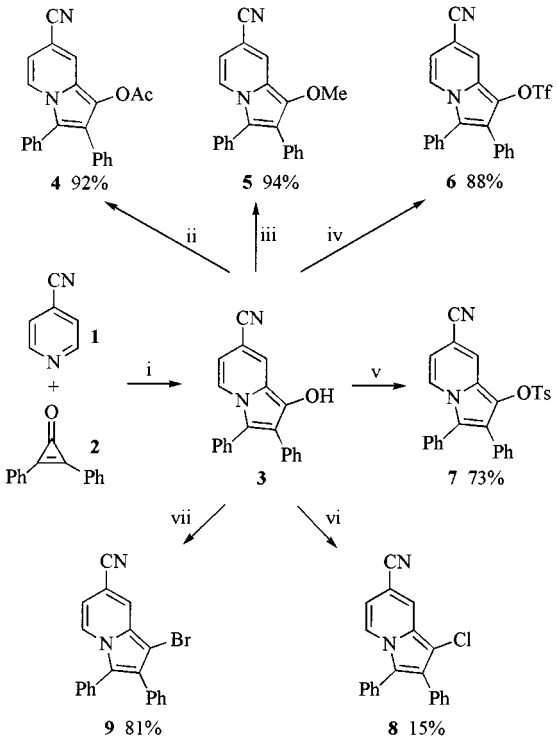
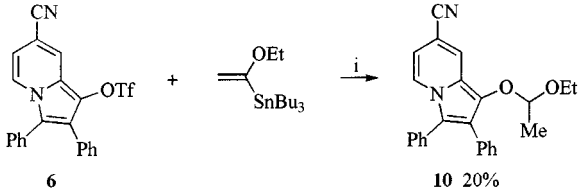


Scheme 1. Reagents and conditions: i, DCE, Δ; ii, DMAP, Ac_2O, DCE; iii, NaH, MeI, THF; iv, DMAP, Tf_2O, DCM, −78 °C; v, TsCl, DMAP, Et_3N, DCE, 0 °C; vi, $POCl_3$, Δ; vii, Br_2, PPh_3, MeCN, 70 °C

flate **6** and the tosylate **7** (Scheme 1). Conversion of a 5-azaindolizinol into the corresponding chloride has been achieved by refluxing the azaindolizinol with phosphorus oxychloride ($POCl_3$).[5,13] When the indolizinol **3** was subjected to refluxing $POCl_3$, the chloroindolizine **8** was indeed formed, but only in low yield (attempts to make the chloride **8** by treatment of the indolizinol with triphenylphosphane dichloride were unsuccessful, however). Hence, we transformed the indolizinol **3** into the more reactive bromide **9** with triphenylphosphane dibromide[6] in dry acetonitrile.

The indolizines **6**−**9** were subjected to palladium-catalysed cross coupling reaction conditions with organotin, organozinc or organoboron reagents. Tosylates are generally poor substrates for such couplings, and the tosylate **7**, not unexpectedly, was inert under the reaction conditions employed. Comparable reactivities are often reported for bromides and triflates in Pd-catalysed couplings,[7] but remarkable differences were observed when the triflate **6** and the bromide **9** were treated with organotin or organozinc reagents in the presence of a palladium catalyst. Pd-catalysed coupling with organozinc reagents can usually be conducted under mild reaction conditions, but when the triflate **6** was treated with methylzinc bromide in the presence of catalytic amounts of tetrakis(triphenylphosphane)palladium(0), only cleavage of the triflate **6** to the indolizinol **3** was observed[8] and compound **3** was isolated in 65% yield. The reactivity of the triflate **6** was essentially the same whether or not lithium chloride was added to the reaction mixture. All attempts to perform Stille coupling on the triflate **6** resulted in extensive decomposition of the starting material and no indolizine products could be detected, except in the coupling with 1-ethoxyethenyl(tributyl)tin where the unexpected acetal **10** was isolated in 20% yield (Scheme 2). The formation of compound **10** is not completely understood, but most probably the triflate is cleaved to give **3** during the reaction sequence. In the literature we can find no other examples describing acetal formation when 1-ethoxyethenyl(tributyl)tin is treated with phenols or triflates. The structure of compound **10** was confirmed by HMQC[9] and HMBC[10] NMR spectroscopy, as well as by X-ray crystallography (Figure 2, Table 1). The asymmetric unit of **10**, with partial atom numbering, is shown in Figure 2. Two positions for the methyl group bound to C22 were located in the difference electron density map calculated from the atoms in the indolizine and phenyl moieties. The side chain at C6 is disordered over two conformations. Except for O1, all non-H atoms in the side chain were refined over two positions. The two components, with occupancy factors 0.517(5) and 0.483(5), were restrained to the same 1−2 and 1−3 distances within an effective standard deviation of 0.03 Å. Further pairs of disordered atoms in each component share the same set of displacement parameters. Tables of geometric parameters, anisotropic displacement parameters, coordinates of hydrogen atoms and a listing of observed and calculated structure factors are available from the correspondence author upon request.



Scheme 2. Reagents and conditions: i, $(Ph_3P)_4Pd$, LiCl, THF, 50 °C

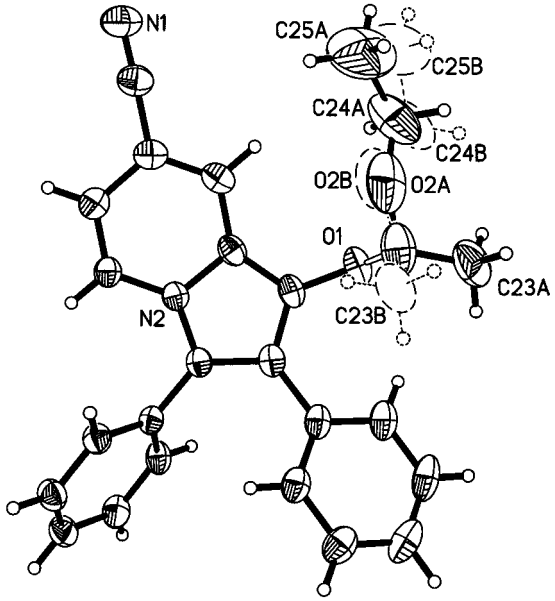


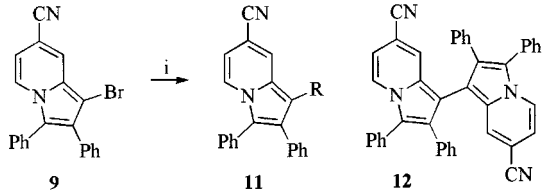
Figure 2. Molecular structure of **10** with partial atomic numbering. Displacement ellipsoids drawn at the 50% probability level. H-atoms arbitrarily scaled. Minor component of disordered side chain drawn using open ellipsoids and broken lines

Table 1. Crystal data, intensity collection and refinement data for **10**

Empirical formula	$C_{25}H_{22}N_2O_2$
Formula mass [g mol^{-1}]	382.45
Crystal size [mm]	1.20×0.35×0.05
Colour, habit	Yellow plates
Crystal system	Monoclinic
Space group	$P2_1/c$ (No. 14)
Cell dimensions [Å,°]	a = 15.2145(2) b = 5.9043(1) c = 23.2611(2) β = 103.644(1)
Volume [Å^3]	2030.6(1)
Z	4
$D_{calcd.}$ [g cm^{-3}]	1.251
Diffractometer	Siemens SMART[12]
Radiation	Mo-K_α (λ = 0.71073 Å)
T [K]	150
2θ range [°]	2.51…26.38
No. of reflections measured	16022
No. of reflections used in refinement	4144
No. of reflections with $I > 2\sigma(I)$ n	3395
Refinement	on F^2
No. of refined parameters p	282
$R = \Sigma\|\Delta F\|/\|F_o\|$[a] $[I > 2\sigma(I)]$	0.0658
$R_w = \{\Sigma[w(\Delta F)^2/w(F_o)^2]\}^{1/2}$[b] $[I > 2\sigma(I)]$	0.1519
$S = \{\Sigma[w(\Delta F)^2/(n\text{-}p)]\}^{1/2}$ $[I > 2\sigma(I)]$	1.040
Residual electron density [e Å^{-3}]	+0.452, −0.427

[a] $\Delta F = |F_o| - |F_c|$. — [b] $w = (\sigma^2(F_O^2) + (0.0572P)^2 + 2.2873P)^{-1}$, where $P=(F_o^2 + 2F_c)/3$.

On the other hand, the indolizinyl bromide **9** readily participated in Pd-catalysed couplings with organotin, organozinc and organoboron reagents to give the desired coupling products **11** (Scheme 3, Table 2). The choice of tin-zinc, or boron as the metal in the organometallic coupling partner was largely governed by the availability of the reagents. To the best of our knowledge, the examples reported here constitute the first examples of Pd-catalysed cross-couplings on 1-haloindolizines.



Scheme 3. Reagents and conditions: i, $(Ph_3P)_4Pd$, R-Met, see also Table 2

The yields of the coupling products **11** were generally high and even the hindered *o*-methoxyphenylzinc reagent participated in the coupling reaction to give compound **11g** in quite good yield. In several of the reactions, minor quantities of the dimer **12** and also the reduced indolizine **13** (Scheme 3) was formed, and the isolated yields of some coupling products (i.e. **11d** and **11f**) were somewhat reduced thanks to the necessary, tedious separation from the by-products. In the reaction with 1-ethoxyethenyl(tributyl)tin, the initially formed enol ether was cleaved during workup, and only the methyl ketone **11b** could be isolated.

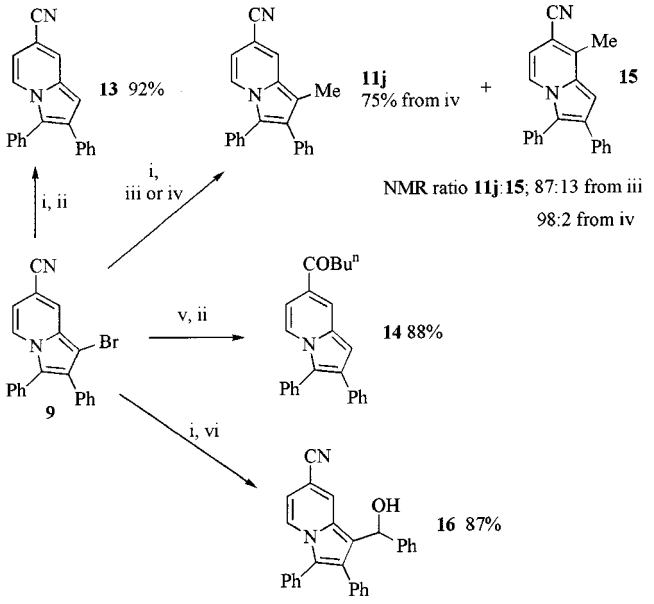
In order to evaluate the influence of the indolizine 1-substituent on antioxidant properties, we also needed the C-1 unsubstituted compound **13**. We prepared this compound in 92% yield by treatment of the bromoindolizine **9** with *n*-butyllithium (*n*BuLi), with subsequent quenching with aqueous ammonium chloride (Scheme 4). When only 1.0 equiv. of *n*BuLi was employed, the metal-halogen exchange was completely selective and no attack on the cyano substituent was observed. Increasing the amount of *n*BuLi resulted in mixtures of the cyanide **13** and the *n*-butyl ketone **14** after aqueous workup, and the ketone **14** was isolated in high yield when a large excess (10 equiv.) of *n*BuLi was employed.

When the lithiated indolizine described above was treated with methyl iodide, we found that partial rearrangement to the 8-lithioindolizine took place if the reaction mixture was allowed to reach ambient temperature during the trapping reaction; a minor amount of the 8-methyl isomer **15** was formed together with the expected product **11j**. We were not able to isolate the compound **15** in pure form and the proposed structure is based on the coupling pattern for the indolizine hydrogen resonances in the ^{1}H NMR spectrum. When the reaction temperature was kept at −78 °C during the methylation, the formation of compound **11j** was almost specific. The 1-lithioindolizine reacted readily with benzaldehyde at −78 °C to give the adduct **16**, and no regioisomers could be detected.

The ability of the indolizine derivatives to inhibit lipid peroxidation in vitro was examined and the results are summarised in Table 3. The testing was performed as we have described previously.[4] Lipid peroxidation of boiled rat liver microsomes was induced by ascorbic acid/$FeSO_4$ and

Table 2. Palladium-catalysed cross coupling between the bromide **9** and organometallic reagents

R-Met	Solvent	Temp. [°C]	Time [h]	R in **11**	Yield (%) **11**
CH_2=CHSnBu_3	DMF	100	23	CH_2=CH-	74, **11a**
CH_2=C(OEt)SnBu_3	DMF	100	24	MeCO-	68, **11b**
2-ThienylSnBu_3	DMF	90	48	2-Thienyl-	91, **11c**
3-ThienylB(OH)$_2$	Dioxane NaOH (aq)	Δ	0.5	3-Thienyl-	55, **11d**
2-FurylSnBu_3	DMF	90	48	2-Furyl	97, **11e**
PhZnBr	THF	60	42	Ph-	71, **11f**
o-MeOC$_6$H$_4$ZnBr	THF	60	50	*o*-MeOC$_6$H$_4$-	55, **11g**
m-MeOC$_6$H$_4$ZnBr	THF	60	23	*m*-MeOC$_6$H$_4$-	70, **11h**
p-MeOC$_6$H$_4$ZnBr	THF	60	18	*p*-MeOC$_6$H$_4$-	78, **11i**
MeZnBr	Dioxane	Δ	42	Me-	75, **11j**



Scheme 4. Reagents and conditions: i, *n*BuLi (1.1 equivs.), THF, −78 °C; ii, NH_4Cl (aq); iii, MeI, 9 h, −78 °C to room temp.; iv, MeI, 47 h, −78 °C; v, *n*BuLi (10 equivs.), THF, −78 °C; vi, PhCHO, 1.5 h, −78 °C

the peroxidation was determined by measuring the materials reactive to thiobarbituric acid. Compounds bearing an oxygen atom in the indolizine 1-position (acetate **4**, methyl ether **5**, triflate **6**, and tosylate **7**), and also the benzyl alcohol **16**, were all able to inhibit lipid peroxidation, while the unsubstituted compound **13**, the bromide **9** and the coupling products **11** were essentially inactive. The acetate **4** and the triflate **6** appear, especially, to be highly active antioxidants, with IC_{50} values below 1 μM in the bioassay. Further studies of the structure/activity relationships (SAR) of indolizines as antioxidants are in progress.

Table 3. Antioxidant properties of 1-substituted 7-cyano-2,3-diphenylindolizine derivatives

Compound	Substituent in the indolizine 1-position	IC_{50} values[a]
4	AcO−	0.15
5	MeO−	22.0
6	TfO−	0.60
7	TsO−	3.64
9	Br−	>100
11a	CH_2=CH−	>100
11b	MeCO−	>100
11c	2-Thienyl−	>100
11d	3-Thienyl−	>100
11e	2-Furyl−	>100
11f	Ph−	>100
11g	*o*-$MeOC_6H_4$−	>100
11h	*m*-$MeOC_6H_4$−	>100
11i	*p*-$MeOC_6H_4$−	>100
13	H−	>100
16	PhCH(OH)−	35.8

[a] IC_{50} (μM) is the concentration which causes 50% inhibition of lipid peroxidation after 30 min. The values are given as the mean of 3 separate experiments and the accuracy of the data is within 25%.

Conclusions

A variety of novel 1-substituted indolizines have been prepared from the corresponding 1-indolizinol. Treatment of the indolizinol with triphenylphosphane dibromide gives the corresponding bromoindolizine, which readily participates in Pd-catalysed cross-coupling reactions. An alternative strategy for the introduction of substituents at C-1 was also developed; this consisted of lithiation of the bromide **9** followed by completely regioselective reaction with electrophiles at low temperatures. At higher temperatures, some migration of lithium to the indolizine 8-position was observed; after further fine-tuning it may be possible to direct the lithiation reaction to give regioselective formation of either the 1- or the 8-substituted indolizine, depending on the reaction conditions. The antioxidant properties of the indolizines described here were examined and the acetate **4** and the triflate **6** in particular were found to be strong inhibitors of lipid peroxidation in vitro, with IC_{50} values below 1 μM.

Experimental Section

General Remarks: The ^1H NMR spectra were recorded at 500 MHz with a Bruker Avance DRX 500 instrument, at 300 MHz with a Bruker Avance DPX 300 instrument or at 200 MHz with a Bruker Avance DPX 200 instrument. The ^{13}C NMR spectra were recorded at 125, 75 or 50 MHz using the above-mentioned spectrometers, and the ^{19}F NMR spectra were recorded at 188 MHz on the Bruker Avance DPX 200 instrument. − Mass spectra were recorded at 70 eV ionising voltage with a VG Prospec instrument, and are presented as *m/z* (% rel. int.). Methane was used for chemical ionisation (CI). − Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany. − Melting points are uncorrected. − Silica gel for flash chromatography was purchased from Merck, Darmstadt, Germany (Merck No. 9385). − Analytical thin layer chromatography was performed using E. Merck silica gel $60F_{254}$ 0.25 mm plates (Merck No. 1.05554). − THF and 1,4-dioxane were distilled from sodium and benzophenone, and acetonitrile, DMF, DCE, DCM, pyridine, and triethylamine were distilled from calcium hydride. Methanol was distilled from magnesium and iodine. Zinc bromide was dried at 125 °C under high vacuum for 2−4 h, weighed out, and dissolved in dry THF to give a solution, which was stored under N_2. Benzaldehyde was distilled under N_2 prior to use. 7-Cyano-2,3-diphenylindolizin-1-yl acetate **4**[2a] was prepared as described before. All other reagents were commercially available and used as received.

1-Methoxy-2,3-diphenylindolizine-7-carbonitrile (5): A mixture of diphenylcyclopropenone (309 mg, 1.50 mmol) and 4-cyanopyridine (156 mg, 1.50 mmol) in dry DCE (20 mL) was refluxed under N_2 for 16 h, cooled and evaporated in vacuo. The residue was dissolved in dry THF (40 mL), and sodium hydride (79 mg, 3.3 mmol) was added. The resulting mixture was stirred under N_2 at ambient temperature for 1 h, after which iodomethane (468 mg, 3.30 mmol) was added. After stirring at ambient temperature for 1 h, the reaction mixture was evaporated in vacuo, the residue was dissolved in diethyl ether (300 mL) and washed with water (100 mL). The dried ($MgSO_4$) organic solution was evaporated in vacuo and the product was purified by flash chromatography, eluting with EtOAc/hexane (1:19). Yield 457 mg (94%) of yellow crystals, m.p. 178 °C. − ^1H

NMR (500 MHz, [D$_6$]acetone): δ = 3.80 (s, 3 H, Me), 6.55 (dd, 1 H, *J* = 7.4 and 1.8 Hz, 6-H), 7.2−7.4 (7 H, m, Ph), 7.4−7.5 (m, 3 H, Ph), 7.96 (dd, 1 H, *J* = 7.4 and 1.0 Hz, 5-H), 8.08 (dd, 1 H, *J* = 1.8 and 1.0 Hz, 8-H). − ^{13}C NMR (125 MHz, [D$_6$]acetone): δ = 62.8, 98.0, 110.7, 119.7, 121.4, 121.8, 122.8, 124.2, 125.0, 127.7, 129.0, 129.5, 130.0, 130.8, 130.8, 131.4, 133.2, 140.5. − MS (EI); *m*/*z* (%): 324 [M$^+$] (54), 309 (100), 149 (16), 131 (20), 122 (16), 103 (50), 81 (7), 68 (19). − $C_{22}H_{16}N_2O$ (324.38): calcd. C 81.46, H 4.97; found C 81.73, H, 5.08.

7-Cyano-2,3-diphenylindolizin-1-yl Triflate (6): A mixture of diphenylcyclopropenone (206 mg, 1.00 mmol) and 4-cyanopyridine (104 mg, 1.00 mmol) in dry DCE (40 mL) was refluxed under N_2 for 16 h and evaporated in vacuo. The residue was dissolved in dry DCM (120 mL) and DMAP (244 mg, 2.00 mmol) was added. The resulting mixture was stirred under N_2 at ambient temperature for 1.5 h and cooled to −78 °C, after which trifluoromethanesulfonic anhydride (0.164 mL, 1.00 mmol) was added. After stirring at −78 °C for 1 h, the reaction mixture was allowed to reach ambient temperature and evaporated in vacuo. The product was purified by flash chromatography, eluting with EtOAc/hexane (1:29). Yield 389 mg (88%) of yellow crystals, m.p. 158−160 °C (decomp.). − ^{1}H NMR (200 MHz, [D$_6$]acetone): δ = 6.87 (dd, 1 H, *J* = 7.4 and 1.8 Hz, 6-H), 7.2−7.5 (m, 10 H, Ph), 8.15 (m, 1 H, 8-H), 8.21 (dd, 1 H, *J* = 7.4 and 1.0 Hz, 5-H). − ^{13}C NMR (50 MHz, [D$_6$]acetone): δ = 103.1, 112.3, 118.6, 119.3 (q, J_{CF} 320 Hz, CF_3), 122.6, 123.2, 123.4, 124.2, 125.0, 126.1, 128.8, 129.3, 129.4, 130.1, 130.1, 130.8, 131.1, 131.6. − ^{19}F NMR (188 MHz, [D$_6$]acetone): δ = −73.6 (CF_3). − MS (CI); *m*/*z* (%): 443 [M + 1] (7), 339 (18), 325 (29), 310 (100), 295 (30), 279 (27), 178 (39), 165 (24), 105 (23), 65 (63). − $C_{22}H_{13}F_3N_2O_3S$ (442.42): calcd. C 59.73, H 2.97; found C 59.87, H, 2.85.

7-Cyano-2,3-diphenylindolizin-1-yl Tosylate (7): A mixture of diphenylcyclopropenone (516 mg, 2.50 mmol) and 4-cyanopyridine (260 mg, 2.50 mmol) in dry DCE (140 mL) was refluxed under N_2 for 24 h and cooled to 0 °C, after which DMAP (610 mg, 5.00 mmol) and toluene-4-sulfonyl chloride (953 mg, 5.00 mmol) were added. The resulting mixture was stirred at 0 °C for 30 min and at ambient temperature for 24 h. The reaction mixture was washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography, eluting with EtOAc/hexane (1:4). Yield 847 mg (73%) of yellow crystals, m.p. 201−202 °C. − ^{1}H NMR (200 MHz, [D$_6$]acetone): δ = 2.33 (s, 3 H, Me), 6.75 (dd, 1 H, *J* = 7.5 and 1.8 Hz, 6-H), 6.9−7.0 (m, 2 H, Ar), 7.1−7.5 (m, 2 H, Ar), 7.87 (dd, 1 H, *J* = 1.8 and 1.0 Hz, 8-H), 8.07 (dd, 1 H, *J* = 7.5 and 1.0 Hz, 5-H). − ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 21.6, 100.5, 110.8, 118.6, 122.0, 122.8, 123.0, 123.4, 124.6, 126.5, 126.9, 127.8, 128.4, 128.9, 129.2, 129.3, 129.9, 130.4, 130.5, 131.1, 145.3. − MS (EI); *m*/*z* (%): 464 [M$^+$] (3), 367 (7), 309 (100), 285 (46), 178 (7), 131 (11), 103 (29), 91 (12), 65 (6). − $C_{28}H_{20}N_2O_3S$ (464.55): calcd. C 72.40, H 4.34; found C 72.51, H, 4.25.

1-Chloro-2,3-diphenylindolizine-7-carbonitrile (8): A mixture of diphenylcyclopropenone (52 mg, 0.5 mmol) and 4-cyanopyridine (103 mg, 0.50 mmol) in methanol (3 mL) was refluxed under N_2 for 4 h and the resulting mixture was kept in the refrigerator for 24 h. The crystals formed were filtered off and refluxed in phosphorus oxychloride (2 mL) under N_2 for 24 h. After cooling to ambient temperature, chloroform (25 mL) and ice (25 g) were added to the reaction mixture and the phases were separated after the ice had melted. The organic extract was washed with saturated aqueous sodium carbonate solution (25 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography, eluting with EtOAc/hexane (1:9). Yield 25 mg (15%) of yellow crystals, m.p. 183−184 °C. − R_f = 0.34 (1:4, EtOAc/hexane). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.49 (dd, 1 H, *J* = 7.4 and 1.8 Hz, 6-H), 7.2−7.3 (7 H, m, Ph), 7.3−7.4 (m, 3 H, Ph) 7.87 (dd, 1 H, *J* = 1.8 and 0.8 Hz, 8-H), 7.90 (dd, 1 H, *J* = 7.4 and 0.8 Hz, 5-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 99.9, 106.6, 110.8, 118.8, 122.5, 124.3, 125.5, 127.0, 127.5, 127.8, 128.2, 128.9, 129.2, 129.2, 130.4, 130.4, 131.0. − MS (EI); *m*/*z* (%): 328 [M$^+$] (100), 293 (24), 292 (20), 264 (4), 253 (2), 239 (3), 225 (3), 211 (3), 146 (12), 85 (24). − HRMS $C_{21}H_{13}N_2Cl$: calcd. 328.0767; found 328.0780.

1-Bromo-2,3-diphenylindolizine-7-carbonitrile (9): A mixture of diphenylcyclopropenone (103 mg, 0.50 mmol) and 4-cyanopyridine (52 mg, 0.50 mmol) in dry DCE (10 mL) was refluxed under N_2 for 20 h, cooled and the solvent was removed under a stream of N_2. The residue was dissolved in dry acetonitrile (5 mL) and the mixture was stirred at ambient temperature under N_2. A mixture of triphenylphosphane dibromide in acetonitrile [generated in a separate flask from triphenylphosphane (393 mg, 1.50 mmol) and bromine (240 mg, 1.50 mmol) in acetonitrile (3 mL) at 0 °C] was added and the resulting mixture was stirred at 70 °C for 72 h, cooled and evaporated in vacuo. The product was purified by flash chromatography, eluting with EtOAc/hexane (1:29). Yield 151 mg (81%) of yellow crystals, m.p. 197−198 °C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.47 (dd, 1 H, *J* = 7.4 and 1.7 Hz, 6-H), 7.1−7.4 (m, 10 H, Ph), 7.82 (dd, 1 H, *J* = 1.7 and 0.9 Hz, 8-H), 7.89 (dd, 1 H, *J* = 7.4 and 0.9 Hz, 5-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 93.4, 110.4, 110.9, 118.7, 122.8, 125.1, 126.2, 127.5, 128.0, 128.5, 128.8, 129.1, 129.1, 129.6, 130.3, 130.5. 132.2. − MS (EI); *m*/*z* (%): 374/372 [M$^+$] (100/100), 293 (54), 264 (8), 189 (7), 146 (31), 132 (7). − $C_{21}H_{13}BrN_2$ (373.24): calcd. C 67.58, H 3.51; found C 67.21, H, 3.66.

(1-Ethoxyethoxy)-2,3-diphenylindolizine-7-carbonitrile (10): Tetrakis(triphenylphosphane)palladium(0) [generated from tris(dibenzylideneacetone)dipalladium chloroform adduct (26 mg, 0.025 mmol) and triphenylphosphane (52 mg, 0.20 mmol)] in dry DMF (2.5 mL) was added to a solution of 7-cyano-2,3-diphenylindolizin-1-yl triflate **6** (442 mg, 1.00 mmol), lithium chloride (85 mg, 2.0 mmol), and 1-ethoxyethenyl(tributyl)tin (0.439 mL, 1.30 mmol) in DMF (1.5 mL). The resulting mixture was stirred for 1 h under N_2 at 50 °C, cooled and evaporated in vacuo. The residue was dissolved in a saturated solution of KF in MeOH and stirred for 1 h. The mixture was evaporated in vacuo and the product was purified by flash chromatography, eluting with EtOAc/hexane (1:29). Yield 76 mg (20%) of yellow crystals, m.p. 105−110 °C (decomp.). − ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 1.01 (t, 3 H, *J* = 7.1 Hz, Me), 1.25 (3 H, d, *J* = 5.2 Hz, Me), 3.41 (m, 1 H, H_A in CH_2), 3.66 (m, 1 H, H_B in CH_2), 5.00 (1 H, q, *J* = 5.2 Hz, CH), 6.59 (dd, 1 H, *J* = 7.4 and 1.8 Hz, 6-H), 7.2−7.5 (m, 10 H, Ph), 8.01 (dd, 1 H, *J* = 7.4 and 0.9 Hz, 5-H), 8.05 (dd, 1 H, *J* = 1.8 and 0.9 Hz, 8-H). − ^{13}C NMR (50 MHz, [D$_6$]acetone): δ = 15.1, 20.5, 63.3, 98.0, 104.5, 110.4, 119.2, 122.5, 122.7, 122.8, 123.9, 125.0, 127.4, 128.5, 129.0, 129.5, 130.3, 130.7, 131.0, 133.0, 135.7. − MS (CI); *m*/*z* (%): 383 [M + 1] (1), 339 (4), 352 (6), 310 (100), 294 (18), 281 (2), 178 (7), 149 (5), 103 (4), 91 (4). − $C_{25}H_{22}N_2O_2$ (382.46): calcd. C 78.51, H 5.80; found C 78.75, H, 5.94.

1-Ethenyl-2,3-diphenylindolizine-7-carbonitrile (11a): Tetrakis(triphenylphosphane)palladium(0) [generated from tris(dibenzylideneacetone)dipalladium chloroform adduct (26 mg, 25 μmol) and triphenylphosphane (52 mg, 200 μmol)] in dry DMF (7 mL) was added to a solution of 1-bromo-7-cyano-2,3-diphenylindolizine **9** (373 mg, 1.00 mmol) and ethenyl(tributyl)tin (0.379 mL, 1.30 mmol) in DMF (3 mL). The resulting mixture was stirred for 23 h under N_2

at 100 °C, cooled and evaporated in vacuo. The residue was dissolved in a saturated solution of KF in MeOH and stirred for 2 h. The mixture was evaporated in vacuo and the product was purified by flash chromatography, eluting with EtOAc/hexane (1:49, 1:39, 1:29, 1:19 and finally 1:9). Yield 236 mg (74%) of yellow crystals, m.p. 156−157 °C. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.10 (dd, 1 H, *J* = 11.5 and 1.5 Hz, =CH_2), 5.30 (dd, 1 H, *J* = 17.8 and 1.5 Hz, =CH_2), 6.37 (dd, 1 H, *J* = 7.5 and 1.7 Hz, 6-H), 6.60 (dd, 1 H, *J* = 17.8 and 11.5 Hz, CH=), 7.0−7.1 (m, 2 H, Ph), 7.1−7.2 (m, 5 H, Ph), 7.2 (m, 3 H, Ph), 7.80 (dd, 1 H, *J* = 7.5 and 1.0 Hz, 5-H), 7.96 (dd, 1 H, *J* = 1.7 and 1.0 Hz, 8-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 100.3, 110.9, 115.0, 115.8, 119.5, 123.3, 125.8, 126.8, 127.4, 128.4, 128.4, 128.8, 129.3, 129.9, 130.0, 130.8, 131.1, 134.1, one signal was hidden. − MS (EI); *m*/*z* (%): 320 [M^+] (100), 319 (96), 242 (11), 215 (12), 159 (7), 152 (9). − $C_{23}H_{16}N_2$ (320.39): calcd. C 86.22, H 5.03; found C 85.96, H, 4.84.

1-Acetyl-2,3-diphenylindolizine-7-carbonitrile (11b): The title compound was prepared from 1-bromo-7-cyano-2,3-diphenylindolizine **9** (113 mg, 0.30 mmol) and 1-ethoxyethenyl(tributyl)tin (142 mg, 0.390 mmol) in DMF (4 mL) as described for compound **11a** above and in Table 2. The product was purified by flash chromatography, eluting with EtOAc/hexane (1:99, 1:39, 1:29, and finally 1:19). Yield 69 mg (68%) of yellow crystals, m.p. 187−189 °C. − ^{1}H NMR (300 MHz, [D_6]acetone): δ = 1.93 (s, 3 H, Me), 7.05 (dd, 1 H, *J* = 7.3 and 1.9 Hz, 6-H), 7.3−7.5 (m, 10 H, Ph), 8.21 (dd, 1 H, *J* = 7.3 and 1.0 Hz, 5-H), 8.84 (dd, 1 H, *J* = 1.9 and 1.0 Hz, 8-H). − ^{13}C NMR (75 MHz, [D_6]acetone): δ = 30.8, 106.2, 116.0, 117.1, 118.9, 124.9, 127.6, 128.6, 128.7, 128.9, 129.8, 129.8, 129.8, 131.6, 131.7, 132.7, 132.9, 135.5, 194.4. − MS (EI); *m*/*z* (%): 336 [M^+] (88), 321 (100), 299 (10), 293 (28), 264 (6), 203 (27), 168 (11), 146 (9), 129 (6). − $C_{23}H_{16}N_2O$ (336.39): calcd. C 82.12, H 4.79; found C 82.26, H, 4.93.

2,3-Diphenyl-1-(2-thienyl)indolizine-7-carbonitrile (11c): The title compound was prepared from 1-bromo-7-cyano-2,3-diphenylindolizine **9** (205 mg, 0.550 mmol) and 2-thienyl(tributyl)tin (0.227 mL, 0.720 mmol) in DMF (5 mL) as described for compound **11a** above and in Table 2. The product was purified by flash chromatography, eluting with EtOAc/hexane (1:99, 1:39, and finally 1:29). Yield 188 mg (91%) of yellow crystals, m.p. 217−218 °C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.43 (dd, 1 H, *J* = 7.4 and 1.7 Hz, 6-H), 6.79 (dd, 1 H, *J* = 3.5 and 1.1 Hz, 3-H in thienyl), 6.88 (dd, 1 H, *J* = 5.1 and 3.5 Hz, 4-H in thienyl), 6.9−7.0 (m, 2 H, Ph), 7.0−7.1 (m, 3 H, Ph), 7.1−7.2 (m, 3 H, Ph and 5-H in thienyl), 7.2−7.3 (m, 3 H, Ph), 7.85 (dd, 1 H, *J* = 7.4 and 0.9 Hz, 5-H), 7.99 (1 H, br s, 8-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 100.1, 110.7, 112.0, 119.1, 122.6, 125.4, 125.8, 126.7, 126.7, 127.0, 127.2, 127.9, 128.6, 128.7, 129.0, 129.5, 129.6, 130.4, 130.9, 133.1, 134.4. − MS (EI); *m*/*z* (%): 376 [M^+] (100), 342 (2), 331 (2), 329 (2), 298 (5), 273 (4), 271 (5), 239 (3), 149 (8). − $C_{25}H_{16}N_2S$ (376.49): calcd. C 79.76, H 4.28; found C 79.58, H, 4.46.

2,3-Diphenyl-1-(3-thienyl)indolizine-7-carbonitrile (11d): Tetrakis-(triphenylphosphane)palladium(0) [generated from tris(dibenzylideneacetone)dipalladium chloroform adduct (13 mg, 13 μmol) and triphenylphosphane (26 mg, 0.10 mmol)] in dry dioxane (3 mL) was added to a solution of 1-bromo-7-cyano-2,3-diphenylindolizine **9** (187 mg, 0.500 mmol) and 3-thiopheneboronic acid (83 mg, 0.65 mmol) in dioxane (2 mL). The resulting mixture was stirred at reflux for 20 min and cooled, after which diethyl ether (50 mL) and EtOAc (50 mL) were added. The mixture was washed with water (2× 50 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography, eluting with EtOAc/hexane (1:49, 1:29, and finally 1:9), and recrystallised from 2-propanol. Yield 103 mg (55%) of yellow crystals, m.p. 257 °C. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.46 (dd, 1 H, *J* = 7.4 and 1.8 Hz, 6-H), 6.78 (dd, 1 H, *J* = 5.0 and 1.3 Hz, 4-H in thienyl), 7.0 (m, 2 H, Ph), 7.03 (dd, 1 H, *J* = 3.0 and 1.3 Hz, 2-H in thienyl), 7.1−7.2 (m, 3 H, Ph), 7.2−7.3 (m, 3 H, Ph and 5-H in thienyl), 7.3−7.4 (m, 3 H, Ph), 7.91 (dd, 1 H, *J* = 7.4 and 0.9 Hz, 5-H), 7.92 (dd, 1 H, *J* = 1.8 and 0.9 Hz, 8-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 99.5, 110.5, 114.1, 119.3, 122.5, 122.7, 125.5, 125.8, 126.4, 126.9, 128.0, 128.4, 128.6, 128.9, 129.1, 129.1, 129.7, 130.4, 130.7, 133.3, 133.5. − MS (EI); *m*/*z* (%): 376 [M^+] (100), 342 (2), 339 (3), 298 (6), 271 (7), 239 (3), 188 (3), 166 (2). − $C_{25}H_{16}N_2S$ (376.49): calcd. C 79.76, H 4.28; found C 79.48, H, 4.24.

1-(2-Furyl)-2,3-diphenylindolizine-7-carbonitrile (11e): The title compound was prepared from 1-bromo-7-cyano-2,3-diphenylindolizine **9** (224 mg, 0.600 mmol) and 2-furyl(tributyl)tin (278 mg, 0.780 mmol) in DMF (5 mL) as described for compound **11a** above and in Table 2. The product was purified by flash chromatography, eluting with EtOAc/hexane (1:99, 1:29, and finally 1:19). Yield 209 mg (97%) of yellow crystals, m.p. 233−234 °C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.64 (dd, 1 H, *J* = 3.4 and 0.7 Hz, 3-H in furyl), 6.16 (dd, 1 H, *J* = 3.4 and 1.9 Hz, 4-H in furyl), 6.40 (dd, 1 H, *J* = 7.4 and 1.8 Hz, 6-H), 7.0−7.3 (m, 10 H, Ph), 7.30 (dd, 1 H, *J* = 1.9 and 0.7 Hz, 5-H in furyl), 7.80 (dd, 1 H, *J* = 7.4 and 1.0 Hz, 5-H), 8.36 (dd, 1 H, *J* = 1.8 and 1.0 Hz, 8-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 100.7, 106.8, 109.0, 110.7, 111.1, 119.2, 122.6, 127.2, 127.4, 127.5, 127.9, 128.2, 128.5, 128.9, 129.3, 130.2, 130.6, 133.8, 141.0, 149.3, 1 signal was hidden. − MS (EI); *m*/*z* (%): 360 [M^+] (100), 331 (28), 329 (19), 316 (3), 305 (4), 255 (8), 237 (3), 228 (3), 195 (4), 165 (6), 158 (7). − $C_{25}H_{16}N_2O$ (360.42): calcd. C 83.31, H 4.47; found C 83.18, H, 4.76.

1,2,3-Triphenylindolizine-7-carbonitrile (11f): A solution of phenylmagnesium bromide (1.11 M, 1.80 mL, 2.00 mmol) in THF was added dropwise to a stirred solution of zinc bromide (1.08 M, 2.04 mL, 2.20 mmol) in dry THF (6 mL) at −78 °C under N_2. When the addition was complete, the resulting mixture was stirred for 1 h at −78 °C and at ambient temperature for 30 min. Tetrakis(triphenylphosphane)palladium(0) [generated from tris(dibenzylideneacetone)dipalladium chloroform adduct (26 mg, 25 μmol) and triphenylphosphane (52 mg, 0.20 mmol)] and **9** (373 mg, 1.00 mmol) in dry THF (14 mL) were added and the reaction mixture was stirred for 42 h at 60 °C, cooled and evaporated in vacuo. The product was purified by flash chromatography, eluting with EtOAc/hexane (1:99, 1:39, 1:29, 1:19, 1:9, 1:4, and finally 1:1), and recrystallised from 2-propanol. Yield 263 mg (71%) of yellow crystals, m.p. 239−240 °C. − R_f = 0.30 (1:4, EtOAc/hexane). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.45 (dd, 1 H, *J* = 7.4 and 1.8 Hz, 6-H), 6.9−7.0 (m, 2 H, Ph), 7.0−7.1 (m, 3 H, Ph), 7.1−7.4 (m, 10 H, Ph), 7.86 (dd, 1 H, *J* = 7.4 and 1.0 Hz, 5-H), 7.90 (dd, 1 H, *J* = 1.8 and 1.0 Hz, 8-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 99.6, 110.5, 119.0, 119.2, 122.4, 125.7, 126.3, 126.6, 126.7, 127.9, 128.4, 128.5, 128.5, 129.0, 129.0, 129.8, 130.1, 130.5, 130.9, 133.2, 133.4. − MS (EI); *m*/*z* (%): 370 [M^+] (100), 292 (14), 291 (7), 267 (6), 265 (14), 177 (7), 176 (6), 165 (5), 146 (5). − HRMS $C_{27}H_{18}N_2$: calcd. 370.1470; found 370.1481.

1-(2-Methoxyphenyl)-2,3-diphenylindolizine-7-carbonitrile (11g): A solution of 2-methoxyphenylmagnesium bromide (0.95 M, 1.05 mL, 1.00 mmol) was added dropwise to a stirred solution of zinc bromide (1.23 M, 1.06 mL, 1.30 mmol) in dry THF (2 mL) at −78 °C under N_2. When the addition was complete, the resulting mixture was stirred for 1 h at −78 °C and at ambient temperature for 30 min. Tetrakis(triphenylphosphane)palladium(0) [generated from tris(dibenzylideneacetone)dipalladium chloroform adduct (13 mg,

13 μmol) and triphenylphosphane (26 mg, 0.10 mmol)] in dry THF (1 mL) and 1-bromo-7-cyano-2,3-diphenylindolizine **9** (187 mg, 0.500 mmol) in dry THF (3 mL) were added and the reaction mixture was stirred for 50 h at 60 °C. After cooling to ambient temperature, EtOAc (75 mL) and diethyl ether (75 mL) were added and the mixture was washed with saturated ammonium chloride solution (50 mL) and water (50 mL) and evaporated in vacuo. Traces of water were removed by azeotropic evaporation with a small quantity of acetone in vacuo. The product was purified by flash chromatography, eluting with EtOAc/hexane (1:49, 1:29, and finally 1:9). Yield 111 mg (55%) of yellow crystals, m.p. 200−202 °C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.48 (s, 3 H, Me), 6.58 (dd, 1 H, *J* = 7.4 and 1.7 Hz, 6-H), 6.9−7.0 (m, 1 H, Ph), 7.0−7.1 (m, 3 H, Ph), 7.1−7.2 (m, 3 H, Ph), 7.3 (m, 1 H, Ph), 7.4−7.5 (m, 6 H, Ph), 7.85 (dd, 1 H, *J* = 1.7 and 0.9 Hz, 8-H), 8.05 (dd, 1 H, *J* = 7.4 and 0.9 Hz, 5-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.9, 99.0, 110.1, 111.3, 115.2, 119.3, 120.6, 122.0, 122.3, 125.8, 126.0, 126.2, 127.6, 128.3, 128.6, 128.8, 128.9, 129.8, 129.9, 129.9, 130.5, 132.3, 134.4, 156.9. − MS (EI); *m*/*z* (%): 400 [M^+] (100), 385 (6), 357 (8), 292 (9), 280 (6), 252 (5), 177 (8). − $C_{28}H_{20}N_2O$ (400.48): calcd. C 83.98, H 5.03; found C 83.95, H, 4.94.

1-(3-Methoxyphenyl)-2,3-diphenylindolizine-7-carbonitrile (11h): The title compound was prepared from 1-bromo-7-cyano-2,3-diphenylindolizine **9** (93 mg, 0.25 mmol) and 3-methoxyphenylmagnesium bromide as described for compound **11g** above and in Table 2. The product was purified by flash chromatography, eluting with EtOAc/hexane (1:49, 1:29, 1:19, and finally 1:9). Yield 70 mg (70%) of yellow crystals, m.p. 244−245 °C. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.58 (s, 3 H, Me), 6.49 (dd, 1 H, *J* = 7.3 and 1.0 Hz, 6-H), 6.65 (dd, 1 H, *J* = 2.4 and 1.6 Hz, Ph), 6.8 (m, 2 H, Ph), 6.9−7.0 (m, 2 H, Ph), 7.1 (m, 3 H, Ph), 7.2 (m, 1 H, Ph), 7.2−7.3 (m, 2 H, Ph), 7.3−7.4 (m, 3 H, Ph), 7.9−8.0 (m, 2 H, 5-H and 8-H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 55.0, 99.7, 110.5, 112.6, 115.5, 118.9, 119.3, 122.5, 125.8, 126.4, 126.7, 128.0, 128.4, 128.5, 129.1, 129.1, 129.5, 129.8, 130.5, 130.9, 133.5, 134.6, 159.5. − MS (EI); *m*/*z* (%): 400 [M^+] (100), 355 (4), 279 (8), 252 (4), 103 (5), 77 (13). − $C_{28}H_{20}N_2O$ (400.48): calcd. C 83.98, H 5.03; found C 83.53, H, 4.85.

1-(4-Methoxyphenyl)-2,3-diphenylindolizine-7-carbonitrile (11i): The title compound was prepared from 1-bromo-7-cyano-2,3-diphenylindolizine **9** (93 mg, 0.25 mmol) and 4-methoxyphenylmagnesium bromide as described for compound **11g** above and in Table 2. The product was purified by flash chromatography, eluting with EtOAc/hexane (1:49, 1:29, and finally 1:9). Yield 78 mg (78%) of yellow crystals, m.p. 195−196 °C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.58 (s, 3 H, Me), 6.56 (dd, 1 H, *J* = 7.4 and 1.8 Hz, 6-H), 6.9−7.0 (m, 2 H, Ph), 7.1−7.2 (m, 2 H, Ph), 7.2−7.3 (m, 5 H, Ph), 7.4 (m, 2 H, Ph), 7.4−7.5 (m, 3 H, Ph), 7.99 (dd, 1 H, *J* = 1.8 and 0.9 Hz, 8-H), 8.04 (dd, 1 H, *J* = 7.4 and 0.9 Hz, 5-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.1, 99.1, 110.3, 113.9, 118.7, 119.2, 122.3, 125.4, 126.1, 126.5, 127.8, 128.3, 128.4, 128.8, 128.9, 129.8, 130.4, 130.8, 131.1, 133.4, 158.4. − MS (EI); *m*/*z* (%): 400 [M^+] (100), 385 (26), 355 (3), 279 (8), 252 (4), 77 (9). − $C_{28}H_{20}N_2O$ (400.48): calcd. C 83.98, H 5.03; found C 84.19, H, 5.43.

1-Methyl-2,3-diphenylindolizine-7-carbonitrile (11j). − Procedure A: The title compound was prepared from 1-bromo-7-cyano-2,3-diphenylindolizine **9** (93 mg, 0.25 mmol) and methylmagnesium chloride as described for compound **11g** above and in Table 2. The product was purified by flash chromatography, eluting with Et_3N/hexane (1:19). Yield 58 mg (75%) of yellow crystals, m.p. 185−186 °C. − R_f = 0.41 (1:4, EtOAc/hexane). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, Me), 6.37 (dd, 1 H, *J* = 7.4 and 1.7 Hz, 6-H), 7.1−7.3 (m, 10 H, Ph), 7.86 (dd, 1 H, *J* = 1.7 and 0.9 Hz, 8-H), 7.88 (dd, 1 H, *J* = 7.4 and 0.9 Hz, 5-H). − ^{13}C NMR (300 MHz, $CDCl_3$): δ = 9.4, 97.4, 109.7, 113.1, 119.6, 122.0, 124.9, 125.6, 126.7, 128.1, 128.2, 128.7, 128.9, 130.1, 130.2, 130.3, 130.4, 134.0. − MS (EI); *m*/*z* (%): 308 [M^+] (100), 307 (27), 292 (5), 231 (3), 229 (4), 223 (64), 154 (5), 146 (12). − HRMS ($C_{22}H_{16}N_2$): calcd. 308.1313; found 308.1301.

Procedure B: *n*-Butyllithium (0.340 mL of a 1.62 M solution in hexane, 0.550 mmol) was added dropwise to a stirred solution of 1-bromo-7-cyano-2,3-diphenylindolizine **9** (187 mg, 0.500 mmol) in dry THF (20 mL) at −78 °C under N_2, and the mixture was stirred at −78 °C for 1 h, after which iodomethane (0.093 mL, 1.50 mmol) was added. The resulting mixture was stirred at −78 °C for an additional 48 h. EtOAc (50 mL), diethyl ether (50 mL) and saturated aqueous ammonium chloride (30 mL) were added to the cold reaction mixture. The phases were separated and the organic layer was washed with water (30 mL), dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography, eluting with Et_3N/hexane (1:49), followed by crystallisation from 2-propanol to give the compound **11j** (116 mg, 75%). When the temperature of this reaction was allowed to reach ambient levels during methylation, flash chromatography of the crude product also gave fractions containing an 82:18 mixture of the 1-methylindolizine **11j** and 7-cyano-8-methyl-2,3-diphenylindolizine **15**. The ^{1}H NMR resonances belonging to compound **15** are given. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.74 (s, 3 H, Me), 6.54 (d, 1 H, *J* = 7.5 Hz, 6-H), 7.01 (1 H, br s, 1-H), 7.2−7.5 (m, 10 H, Ph), 7.82 (d, 1 H, *J* = 7.5 Hz, 5-H).

2,2′,3,3′-Tetraphenyl-1,1′-biindolizine-7,7′-dicarbonitrile (12): The title compound was formed in minor amounts in several of the coupling reactions described above and isolated as a yellow wax. R_f = 0.22 (1:4, EtOAc/hexane). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.59 (dd, 2 H, *J* = 7.4 and *J* = 1.7 Hz, 6-H and 6′-H), 6.7−6.8 (m, 4 H, Ph), 6.9−7.1 (m, 6 H, Ph), 7.3−7.5 (m, 10 H, Ph), 7.57 (dd, 2 H, *J* = 1.7 and *J* = 0.7 Hz, 8-H and 8′-H), 8.08 (dd, 2 H, *J* = 7.4 and *J* = 0.7 Hz, 5-H and 5′-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 99.4, 109.8, 110.5, 119.0, 122.6, 125.5, 126.2, 126.5, 127.7, 128.5, 129.1, 129.2, 129.8, 129.9, 130.5, 130.7, 133.5. − MS (EI); *m*/*z* (%): 586 [M^+] (100), 509 (3), 481 (3), 431 (2), 405 (5), 293 (20), 254 (5).

2,3-Diphenylindolizine-7-carbonitrile (13): *n*-Butyllithium (0.288 mL of a 1.7 M solution in hexane, 0.490 mmol) was added dropwise to a stirred solution of 1-bromo-7-cyano-2,3-diphenylindolizine **9** (183 mg, 0.490 mmol) in dry THF (20 mL) at −78 °C under N_2 and the resulting mixture was stirred at −78 °C for an additional 2 h before saturated aqueous ammonium chloride solution (1 mL) was added. The reaction mixture was allowed to reach ambient temperature, the phases were separated and the organic layer was evaporated in vacuo. The crude product was recrystallised from dichloromethane/hexane. Yield 133 mg (92%) of yellow crystals, m.p. 234−235 °C. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.38 (dd, 1 H, *J* = 7.4 and 1.8 Hz, 6-H), 6.83 (1 H, br s, 1-H), 7.1−7.4 (m, 10 H, Ph), 7.70 (1 H, br s, 8-H), 7.77 (1 H, br d, *J* = 7.4 Hz, 5-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 99.3, 104.6, 110.1, 119.2, 122.5, 125.4, 126.2, 126.9, 128.4, 128.8, 128.8, 129.4, 130.3, 130.5, 130.6, 134.5 one signal was hidden. − MS (EI); *m*/*z* (%): 294 [M^+] (100), 278 (2), 266 (3), 264 (3), 254 (3), 234 (3), 216 (3), 189 (7), 165 (5), 146 (12), 139 (6). − $C_{21}H_{14}N_2$ (294.35): calcd. C 85.69, H 4.79; found C 85.65, H, 4.83.

7-Pentanoyl-2,3-diphenylindolizine (14): *n*-Butyllithium (2.94 mL of a 1.70 M solution in hexane, 5.00 mmol) was added dropwise to a

stirred solution of 1-bromo-7-cyano-2,3-diphenylindolizine **9** (187 mg, 0.500 mmol) in dry THF (20 mL) at −78 °C under N_2 and the resulting mixture was stirred at −78 °C for an additional 2 h, after which saturated aqueous ammonium chloride solution (1 mL) was added. The reaction mixture was allowed to reach ambient temperature, the phases were separated and the organic layer was evaporated in vacuo. The product was purified by flash chromatography, eluting with EtOAc/hexane (1:29). Yield 156 mg (88%) of yellow crystals, m.p. 134−135 °C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (t, 3 H, *J* = 7.3 Hz, Me), 1.4−1.5 (m, 2 H, CH_2), 1.7−1.8 (m, 2 H, CH_2), 2.98 (t, 2 H, *J* = 7.5 Hz, CH_2CO), 7.04 (1 H, s, 1-H), 7.09 (dd, 1 H, *J* = 7.5 and 1.8 Hz, 6-H), 7.2−7.4 (m, 5 H, Ph), 7.4−7.6 (m, 5 H, Ph), 7.94 (1 H, br d, *J* = 7.5 Hz, 5-H), 8.15 (1 H, br s, 8-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 27.0, 37.4, 105.4, 108.4, 121.7, 121.9, 124.8, 126.2, 126.6, 128.3, 128.4, 128.7, 129.2, 130.0, 130.6, 130.8, 131.0, 135.1, 198.2. − MS (EI); *m*/*z* (%): 353 [M^+] (100), 311 (43), 296 (44), 268 (34), 267 (41), 239 (10), 191 (7), 165 (5), 155 (8), 133 (6). − $C_{25}H_{23}NO$ (353.47): calcd. C 84.95, H 6.56; found C 84.50, H 6.36.

1-(α-Hydroxybenzyl)-2,3-diphenylindolizine-7-carbonitrile (16): *n*-Butyllithium (0.170 mL of a 1.62 M solution in hexane, 0.280 mmol) was added dropwise to a stirred solution of 1-bromo-7-cyano-2,3-diphenylindolizine **9** (93 mg, 0.25 mmol) in dry THF (10 mL) at −78 °C under N_2 and the mixture was stirred at −78 °C for 30 min, after which benzaldehyde (0.076 mL, 0.75 mmol) was added. The resulting mixture was stirred at −78 °C for an additional 1.5 h. EtOAc (25 mL), diethyl ether (25 mL), and saturated aqueous ammonium chloride (30 mL) were added to the cold reaction mixture. The phases were separated and the organic layer was washed with water (2 × 30 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography, eluting with EtOAc/hexane (1:99, 1:29, and finally 1:9). Yield 87 mg (87%) of a yellow wax. R_f = 0.15 (1:4, EtOAc/hexane). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.18 (d, 1 H, *J* = 3.3 Hz, OH), 6.11 (d, 1 H, *J* = 3.3 Hz, CH), 6.47 (dd, 1 H, *J* = 7.4 and 1.8 Hz, 6-H), 7.1 (m, 2 H, Ph), 7.2−7.3 (m, 6 H, Ph), 7.3−7.4 (m, 7 H, Ph), 7.87 (dd, 1 H, *J* = 1.8 and 0.8 Hz, 8-H), 7.95 (dd, 1 H, *J* = 7.4 and 0.8 Hz, 5-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 69.5, 99.2, 110.5, 119.2, 119.3, 122.5, 125.8, 125.9, 126.8, 127.3, 127.5, 127.9, 128.2, 128.4, 128.5, 129.0, 129.7, 130.2, 130.7, 133.4, 143.5. − MS (EI); *m*/*z* (%): 400 [M^+] (100), 384 (9), 383 (28), 323 (52), 293 (7), 105 (9), 78 (57), 77 (94). − HRMS $C_{28}H_{20}N_2O$: calcd. 400.1576; found 400.1584.

X-ray Crystallographic Study: Single crystals for X-ray crystallography were obtained by slow evaporation of hexane into a dichloromethane solution of **10**. X-ray diffraction data were collected on a Siemens SMART diffractometer. Positional parameters for all heavy atoms were refined. Hydrogen atoms were kept in idealised positions, refining a single C−H bond length for all H atoms connected to the same C atom. Heavy atoms were refined anisotropically, whereas U_{iso} for the hydrogen atoms were fixed at $1.2\times U_{eq}$ (for −CH− and CH_2) and $1.5\times U_{eq}$ (for $-CH_3$) of the bonded C atom. The side chain at C6 is disordered over two conformations. Except for O1, all non-H atoms in the side chain were refined over two positions. The two components, with occupancy factors 0.517(5) and 0.483(5), where restrained to have the same 1−2 and 1−3 distances within an effective standard deviation of 0.03 Å, using the SAME command of *SHELXTL*.[11] Further pairs of disordered atoms in each component share the same set of displacement parameters. The crystal data and refinement results of the structure **10** are listed in Table 1. Reference number CCDC 142363.

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