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Bridged amides and anilines display interesting properties owing to perturbation of conjugation of the nitrogen lone-pair with the adjacent π -system. A convergent approach to diazabicyclic scaffolds which contain either twisted amides or anilines is described, based on the photocatalysed hydroamination of cyclic enecarbamates and subsequent cyclisation. The modular nature of the synthesis allows for variation of the degree of 'twist' and hence the properties of the amides and anilines.

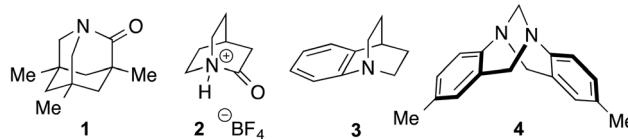
The impact of resonance upon both the structure and chemical properties of amides has been recognised since Pauling's seminal treatise on the nature of the chemical bond.¹ Maximisation of this resonance requires planarity of the amide, and while small departures from this may be tolerated without significant energetic penalty (e.g. in many peptidic structures),² larger deviations lead to a significant reduction in n_N to $\pi^*_{C=O}$ conjugation, and hence unusual structural and chemical properties. Twisted amides have therefore received significant attention as chemists seek to understand and exploit their unique characteristics and reactivity profiles.³ A prominent example is Kirby's most-twisted amide **1** (Fig. 1, panel a), in which the nitrogen lone pair is perpendicular to the carbonyl π -bond: the resulting lack of resonance manifests in 'aminoketone'-like behaviour structurally (lengthened C–N and shortened C=O bonds), spectroscopically ($\delta_C = 200$ ppm for C=O), and in reactivity (rapid hydrolysis at room temperature).⁴ More recently, the landmark synthesis of 2-quinuclidonium salts such as **2** by Stoltz⁵ has enabled experimental quantification of the high basicity of the

nitrogen lone pair,^{5b} which contrasts with the greater basicity on oxygen exhibited by simple amides. While compounds such as **1** and **2** represent the extremes of behaviour of twisted amides, the ability to tune molecular properties such as the relative basicities⁶ and hydrogen-bonding capabilities of the oxygen and nitrogen atoms across families of homologous amides is a source of fascination and utility to chemists.

While less widely studied than amides, similar effects are observed with twisted anilines such as benzoquinuclidine **3**⁷ and Tröger's base **4**,⁸ in which conjugation between the nitrogen lone pair and aromatic group are disrupted. The orthogonality of the nitrogen lone-pair with the arene in **3** manifests itself, for example, in the anomalous basicity of the amine ($pK_a = 7.8$, *c.f.* 5.2 for dimethylaminobenzene),⁹ the observation of *meta*-substitution in $S_{E}Ar$ reactions under acidic conditions,¹⁰ and in anomalous photophysical behaviour of donor-acceptor compounds containing this motif.¹¹

Previously we reported the preparation of diazabicyclic twisted amides based on the bicyclo[3.3.1]nonane and bicyclo[4.3.1]decane scaffolds.¹² Our synthesis employed reductive amination of 3-ketoazacycles with α - and β -aminoesters to convergently prepare precursors for Bu_2SnO -mediated lactamisation. Although

(a) bicyclic twisted amides and anilines



(b) modular approach to diverse bicyclic twisted amides and anilines

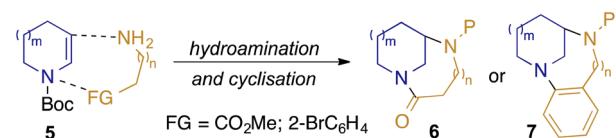


Fig. 1 Bicyclic twisted amides and anilines, and a proposed modular approach to congeners.

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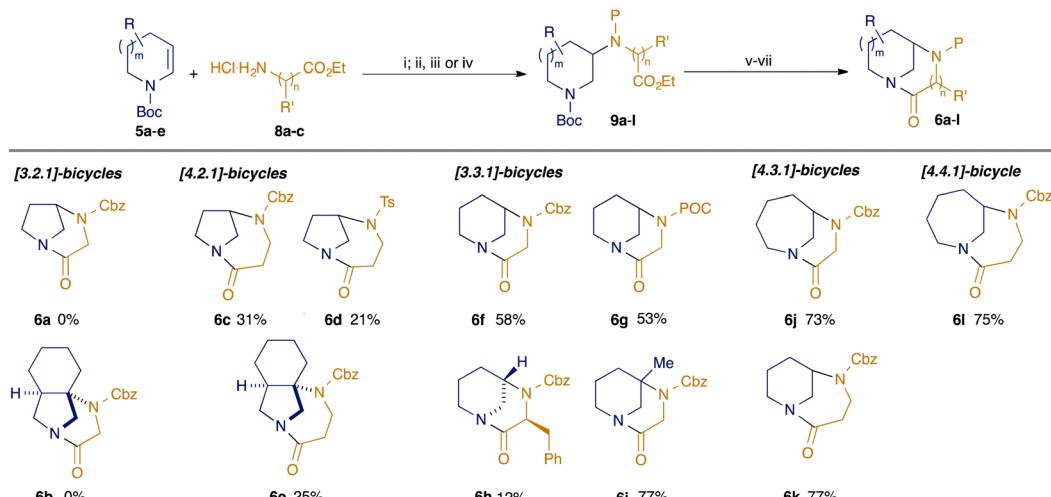
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† Electronic supplementary information (ESI) available. CCDC 2192693. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3cc01470c>





Scheme 1 Modular synthesis of bicyclic twisted amides. (i) $[\text{Ir}(\text{dF}(\text{Me})\text{ppy})_2(\text{dtbbpy})\text{PF}_6]$ (2 mol%), TRIP thiol (50 mol%), toluene, blue LEDs; (ii) CbzCl , NaHCO_3 , DCM; (iii) TsCl , DIPEA, DMAP (5 mol%), DCM; (iv) POCCl (= propargyl chloroformate), NaHCO_3 , DCM; (v) NaOH , $\text{MeOH}/\text{H}_2\text{O}$, 70°C ; (vi) 6M HCl , EtOAc ; (vii) $^7\text{Bu}_2\text{SnO}$, toluene, reflux. Yields shown are for the sequence from **9** to **6** (steps v–vii) only; for full details see ESI[†]

successful, this approach limited exploration *e.g.* of alternative ring-sizes and substitution patterns. We describe herein a complementary and more general approach, based upon coupling of key building blocks through photoredox-mediated hydroamination^{13,14} of readily-available¹⁵ enecarbamates **5** (Scheme 1, panel b). Cyclisation either through lactamisation or Buchwald–Hartwig amination gives a broad range of bicyclic twisted amides **6** and anilines **7** wherein the impact of subtle changes in structure upon properties can be probed.

Our studies commenced by exploiting our previously reported conditions¹³ for the photoredox-catalysed hydroamination of enecarbamates (Scheme 1). Hence, coupling of substrates **5a–e** (prepared from the corresponding saturated amines through electrochemical oxidation and elimination¹⁵) with aminoesters **8a–c** proceeded in generally good yield (see ESI[†] for full details). Protection of the resulting secondary amines variously as carbamates ($\text{P} = \text{Cbz}$, POC) or sulfonamides ($\text{P} = \text{Ts}$) enabled the preparation of a library of cyclisation precursors **9a–l**. Conversion to the desired diazabicyclic scaffolds was effected by basic ester hydrolysis, removal of the Boc protecting group from the azacycle under acidic conditions, and finally cyclisation using Bu_2SnO .¹² Attempts to form the [3.2.1]-diazabicyclic products **6a,b** derived from hydroamination of dihydropyrroles **5a,b** with ethyl glycinate **8a** failed at the cyclisation step, presumably owing to the high degree of strain in the products: we are unaware of any successful approaches to twisted amides with the [3.2.1]-bicyclic skeleton *via* amide bond formation. However, we were delighted to find that the use of ethyl aminopropionate **8b** as the hydroamination partner led successfully to the formation of the diazabicyclo[4.2.1]nonanes **6c–e** in moderate yield. Most notably, the formation of the unprecedented tricyclic system **6e**, which contains a fully-substituted carbon, could not have been achieved through our previous reductive amination approach.¹² Cyclisations of substrates based on hydroamination of Boc-tetrahydropyridine **5c** with glycine ester **6a** were also successful, in line with our previous construction of diazabicyclo[3.3.1]nonanes:¹² the simple

Cbz and **POC**-protected scaffolds **6f/g** were returned in higher yield than the corresponding [4.2.1] products **6c–e**, which may be indicative of the relative degrees of strain in the products (*vide infra*). The incorporation of backbone substituents on the coupling partners **5** and **8** was also probed: use of an α -substituted amino ester (ethyl phenylalaninate **8c**) led to a mixture of diastereomers in the hydroamination step, only one of which cyclised to give a poor yield of the desired bicyclic product **6h** (relative configuration determined by NOE studies, ESI[†]). Pleasingly, hydroamination using Boc 3-methyltetrahydropyridine **5d** led ultimately to bridgehead-substituted bicycle **6i** in a notably higher yield than for **6f**, perhaps reflecting a lower energy penalty to access the reactive conformation for lactamisation: again, this substitution pattern would not be available through routes based upon reductive amination chemistry.

Larger ring systems containing diazabicyclo[4.3.1]decanes could be accessed either through hydroamination of Boc tetrahydropyridine **5c** with ethyl aminopropionate **8b**, or as an isomeric lactam through the coupling of the dehydroazepine **5e** with ethyl glycinate **8a**. Regardless of the location of the amide (in the six- or seven-membered ring in **6j** and **6k** respectively), the cyclisations occurred in good yield, as was also seen in the cyclisation to give the homologous diazabicyclo[4.4.1]undecane **6l**.

Our new synthetic strategy had enabled us to prepare five distinct diazabicyclic bridged amides (and substituted/fused variants) varying systematically in the size of each ring, enabling interrogation of the impact on molecular properties (Fig. 2; data for ‘parent’ scaffolds shown, for all data see ESI[†]). The reduced contribution from resonance forms with $\text{C}=\text{N}$ character manifests itself in a greater degree of electron-deficiency at the carbonyl carbon, and hence higher ^{13}C NMR chemical shifts^{3a} (for example in the [4.n.1] series **6c/k/l**, $\delta_{\text{C}} = 182.1$, 176.8, 172.8 ppm for $n = 2, 3, 4$). Similarly, the greater overall contribution of the $\text{C}=\text{O}$ resonance form^{3a} can be seen in the IR stretches (*e.g.* for the [4.n.1] series **6c/k/l**, $\nu_{\text{max}} = 1680$, 1657, 1647 for $n = 2, 3, 4$).

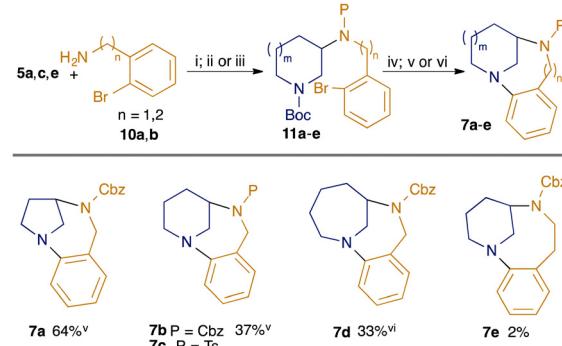
	6c	6f	6k	6l	6j
δ_c/ppm	182.1 ^a	180.2	176.8	172.8 ^a	170.9
$\nu_{\text{C}-\text{O}/\text{cm}^{-1}}$	1680	1686	1657	1647	1667
$\Sigma_{\text{angles}}/^\circ$	333.7 ^b	348.8 ^b	357.8		
$\tau/^\circ$	23.5 ^b	8.9 ^b	3.6		
N-C/Å	1.380 ^b	1.360 ^b	1.355		

Fig. 2 Influence of ring-size on structural and spectroscopic features. ^a two signals visible owing to Cbz rotamers, $\Delta\delta < 0.1$ ppm; P = Cbz except for ^bvalues for P = Bn.¹²

Single crystal X-ray analysis of compound **6l** also permits comparison with our previously reported structures of the *N*-Bn analogues of **6f/k**.¹² The significant pyramidalisation at nitrogen can be seen as a sum of the bond angles at that atom:¹⁶ while the [4.4.1] compound **6l** shows near planarity ($\Sigma_{\text{angles}} = 357.8^\circ$ vs. ideal $\text{sp}^2 = 360^\circ$), the smaller homologues show significant pyramidalisation, with the diazabicyclo[3.3.1]nonane skeleton much closer to sp^3 hybridisation ($\Sigma_{\text{angles}} = 333.7^\circ$ vs. ideal $\text{sp}^3 = 328.4^\circ$). Amide distortion can also be measured through the Winkler–Dunitz parameters:¹⁷ for example, the ‘twist angle’ τ (0° for a planar amide and 90° for a perpendicular arrangement) varies from 3.6–23.5° across the series (for additional parameters, see ESI†). Finally, as expected, the N-C bond shortens with increased conjugation of the nitrogen lone pair: the relatively long bond of 1.380 Å in the N-Bn analogue of **6f** shortens to 1.355 Å in **6l** (cf. 1.475 Å in the most-twisted amide **1^a** and 1.325 Å for *N*-methylpiperidone^{4b}). We considered that the twist-induced destabilisation of (particularly) the smaller diazabicycles could make them competent acylating agents and hence they might have the potential to act as anti-microbial agents. Screening of a panel of compounds **6** was therefore carried out against *Staphylococcus Aureus* ATCC29213, with the strained tricyclic structure **6e** showing activity at 32 µg mL⁻¹ (see ESI† for full details).

The modular nature of our synthetic approach meant that it could be readily adapted to the synthesis of related twisted anilines (Scheme 2). Hence, photoredox-catalysed hydroamination of enecarbamates **5a, c** and **e** with 2-bromobenzylamine **10a,b** followed by suitable amine protection gave adducts **11a–d**. Removal of the Boc-group was followed by intramolecular amine arylation under Buchwald–Hartwig conditions, giving the desired homologous diazabicycles **7a–d**. We also attempted to investigate homologues in the diazacyclic ring, but although the desired cyclisation precursor **11e** could be readily prepared by reaction of **5c** with 2-(2-bromophenyl)ethan-1-amine **10b**, the Buchwald–Hartwig cyclisation gave only a trace amount of the desired product **7e**, reflecting the challenging nature of medium-ring formation.¹⁸

Products **7a–e** were oils and so crystallographic structural data could not be obtained. However, the enforced non-planarity of the anilinic nitrogen with the aromatic ring may be inferred from the ¹³C NMR shift of the *para*-carbon to the nitrogen, as demonstrated by Zakrzewska.¹⁹ The values for **7a, b**



Scheme 2 Modular synthesis of twisted bicyclic anilines. (i) $[\text{Ir}(\text{dF}(\text{Me})\text{ppy})_2(\text{dtbbpy})\text{PF}_6]$ (2 mol%), TRIP thiol (50 mol%), toluene, blue LEDs; (ii) CbzCl, NaHCO_3 , DCM; (iii) TsCl, DIPEA, DMAP (5 mol%), DCM; (iv) 6M HCl, EtOAc; (v) $\text{Pd}_2(\text{dba})_3$ (4 mol%), BINAP (8 mol%), NaOtBu, toluene, reflux; (vi) $\text{Pd}(\text{OAc})_2$ (10 mol%), BINAP (20 mol%), Cs_2CO_3 , toluene, reflux. Yields shown for steps from **11** to **7** (steps iv plus v/vi) only: for full details see ESI.†

and **d** are shown in Fig. 3: the value of 118.1 ppm for the largest ring system **7d** indicates a largely planar structure (cf. 115.1 ppm for *N,N*-dibutylaminobenzene and 118.9 ppm for *N*-phenylpiperidine¹⁹); the higher value of 121.4 for the dehomologous **7b** suggests a departure from planarity, while the value of ca. 129 ppm for **7a** indicates significant disruption of resonance (cf. 127.0 ppm for benzoquinuclidine **3**,¹⁹ which features a completely orthogonal lone pair). As expected, the value for the relevant carbon in the benzodiazacene-containing **7e** (119.2 ppm) indicates strong lone pair overlap.

The different degrees of lone-pair overlap ought also to be reflected in the basicity of the nitrogen. Compounds **7** are poorly water soluble, and determination of pK_a values in non-aqueous solvents is non-trivial. We recently developed an NMR-based assay using pH gradients in a single sample and chemical shift imaging to determine pK_a values in DMSO.^{20,21} Using this method, a significant variation in pK_a was observed: over 3 units separate the three compounds **7a,b,d** in the homologous series, with the most strained variant **7a** being the most basic as expected. This trend in relative basicity was also confirmed computationally in water using the Jaguar pK_a prediction method.^{22,23} Inspection of the calculated structures²³ (gas phase and solvated in DMSO or water; see ESI†) also revealed the expected trend in pyramidalisation at nitrogen

	7a	7b	7d
Measured pK_a (DMSO)	3.85	2.10	0.81
Calculated pK_a (water)	5.64	3.56	1.27
$\Sigma_{\text{angles}}/^\circ$	331.5	342.6	350.5
$\delta^{13}\text{C}$ NMR (ppm)	130–128 ^b	121.4	118.1

Fig. 3 Influence of ring-size on ¹³C NMR shift and pK_a of bicyclic anilines **7**. ^a calculated values (DMSO solvation); ^b unambiguous assignment not possible.



(measured by sum of bond angles): **7a** shows values close to that for ideal sp^3 -hybridisation, whereas **7d** is much closer to that for sp^2 .

In summary, we have developed a modular approach to the synthesis of diazabicyclic amides and anilines, in which independent variation of the ring sizes allows interrogation of the effect on molecular structures and properties. The ability to tune molecular properties (e.g. pK_a) by variation of scaffold size rather than substituents or functional groups may find application in the design of functional organic molecules.

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Conflicts of interest

Redbrick Molecular marketed diverse building blocks for applications in drug discovery.

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