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Domino or Single-Step Tsuji–Trost/Heck Reactions and Their Application in the Synthesis of 3-Benzazepines and Azepino[4,5-*b*]indole Ring Systems

Scott G. Stewart,*[a] Charles H. Heath,[a] and Emilio L. Ghisalberti[a]

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A series of methods for palladium-mediated single-step and domino Tsuji–Trost/Heck reactions are described. These methods are applied to the synthesis of both 3-benzazepines and azepino[4,5-*b*]indoles in the category of complex 6-7-6 and 6-5-7 ring heterocycles. In addition, a domino Heck/Heck sequence of reactions that produces the azepinobenzindolizine tetracyclic ring system from *N*-diallylated precursors is described.
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Introduction

Alkaloids containing seven-membered rings have been isolated from several natural sources and form a significant series of medicinal agents. One class, the substituted 3-benzazepines, have been explored as potential medicinal agents in many instances such as the dopamine agonist SCH23390 (**1**)[1] and the 5-HT_{2C} agonist/anti-obesity compound **2**.[2] The use of 3-benzazepines as *N*-methyl-D-aspartate (NMDA) antagonists has also recently been highlighted in the literature.[3] The azepino[4,5-*b*]indole ring system, containing a seven-membered C ring, has recently been found in several natural products such as arboflorine (**3**) and subincanadine F (**4**).[4,5] These natural products have attracted our interest because of their unique molecular architecture and unexplored biological properties (Figure 1). The preparation of both of these classes of compounds could, in theory, come from the same retrosynthetic disconnection. Historically, 3-benzazepines have been prepared through various methods including Friedel–Crafts-type approaches,[6] thermal-rearrangement-promoted cyclisations[7] and radical cyclisations,[8] among others.[3,9]

Also within these methodologies, the palladium-catalyzed intramolecular Heck reaction provides an efficient route to the 3-benzazepine ring system from halogenated aromatic precursors.[10] However, exploitation of this methodology to incorporate additional non-aromatic rings has yet to be fully explored.

To increase the efficiency of this ring-forming process, we initially envisioned the synthesis of these seven-membered systems through a domino cross-coupling reaction, where the *N*-allylated Heck precursor is prepared in situ through an initial Tsuji–Trost reaction. Domino reactions are defined as "the execution of two or more bond-forming transformations under identical reaction conditions, in which the latter transformations take place at the functionalities formed by the preceding transformation".[11] Domino reactions are attractive to industry and research laboratories because of their potential to save solvents, reagents, time and energy.[11,12] Palladium-mediated domino reactions have been used in a host of important total syntheses including various alkaloids, the steroid ring system, vitamin E, xestoquinone and scopadulcic acid.[13] The single-pot combination of a Tsuji–Trost[14] and Heck[15] reaction, falling in the category of a palladium-mediated domino reaction,[11] has advantages over other domino-type processes because of the similar conditions, in which the two reactions can be carried out. Domino Tsuji–Trost/Heck reactions have been

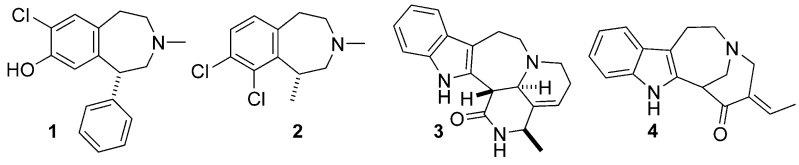

Figure 1. Structures of interesting 3-benzazepines and azepino[4,5-*b*]indoles natural products.

[a] The School of Biomedical, Biomolecular & Chemical Sciences, The University of Western Australia,
Crawley, WA 6009, Australia
Fax: +61-8-6488-1005
E-mail: sgs@cyllene.uwa.edu.au
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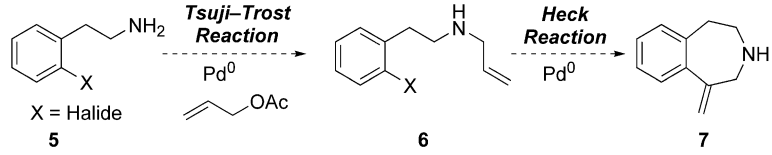


Scheme 1. Proposed domino Tsuji–Trost/Heck reaction.

used to construct complex ring systems, being more commonly applied when both the initial Tsuji–Trost and Heck reactions are carried out intramolecularly.[16] Examples, where the Tsuji–Trost reaction is intermolecular and the Heck reaction is intramolecular, are extremely rare in the literature,[17] and to the best of our knowledge none have been reported with a free amine or amide as the nucleophilic species. Because these domino reactions are assumed to go through two catalytic cycles they have also been described as pseudo-domino reactions.[16c]

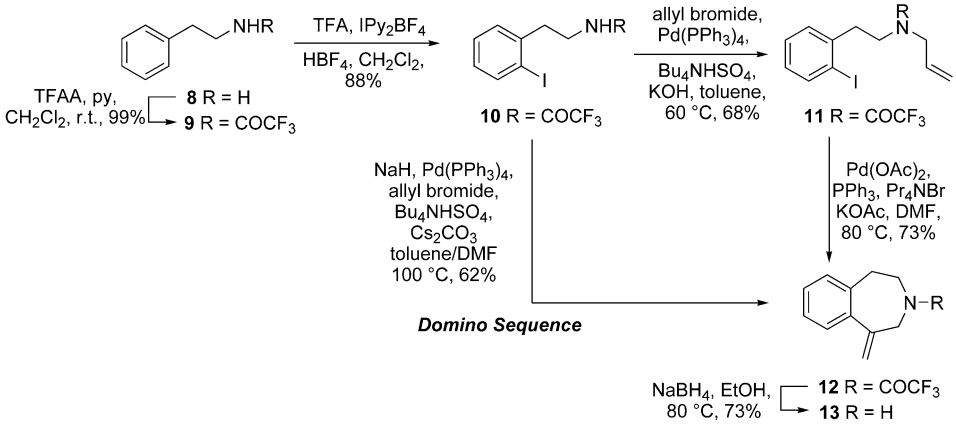
The intermolecular Tsuji–Trost reaction planned between a tethered alkylamine **5** and a π-allylpalladium complex provides the olefin **6** (Scheme 1). A palladium(0) oxidative addition to the aryl–halide bond initiates the Heck cross-coupling reaction process, and an increase in temperature should promote the ring-forming process.

Results and Discussion

The 3-benzazepine ring system was first targeted to examine the possibility of a domino intermolecular Tsuji–Trost reaction followed by an intramolecular Heck reaction. Trifluoroacetate was chosen as a protecting group because of its ability as a directing group for aryl iodination reactions and its application in intramolecular Heck reactions.[18,19] Thus, treatment of the arylamine **8** with trifluoroacetic anhydride furnished the protected amine **9** in excellent yield (99%, Scheme 2). Treatment of this compound with IPy_2BF_4 following the *ortho*-directing iodination procedure of Barluenga et al.[19] afforded the aryl iodide **10** in good yields (88%). This substrate was subsequently set up for a domino Tsuji–Trost/Heck reaction; however, the allylated intermediate **11** was prepared so later domino reactions could be more closely monitored and optimised. Thus, treatment of the amide **10** with allyl acetate and a series of palladium catalysts afforded **11** in moderate yields. To improve this transformation,[20] allyl bromide was investigated as a reagent with and without a palladium catalyst present. The reactions mediated by palladium(0) and allyl bromide were faster than their uncatalysed counterparts. It thus appears that the more favoured pathway involved a preformed π-allylpalladium species as opposed to a simple S_N2'-type reaction, although the S_N2' pathway could not be completely ruled out as a possible mechanistic pathway.

In these allylation reactions, the combination of $Pd(PPh_3)_4$ (8 mol-%), KOH and a phase-transfer catalyst consistently produced the most reliable yields (68%). With the allyl product **11** in hand, we set about optimising the intramolecular Heck reaction, which in turn could also be applied in the domino process. In this case, the combination of $Pd(OAc)_2$ (10 mol-%), PPh_3 (20 mol-%) was optimum, affording the exocyclic double-bond Heck product in 73% yield and none of the product resulting from the sterically more encumbered 8-*endo*-*trig* cyclisation.[21] Similar results have been observed in pioneering work completed by the Tietze group.[10d]

Having completed the single-step approach in good yields, we investigated the domino reaction with several combinations of catalysts, bases and additives. The most efficient conversion to the 3-benzazepine **12** involved the use of $Pd(PPh_3)_4$, NaH, Cs_2CO_3 and Bu_4NHSO_3 starting the reaction at 60 °C and increasing the temperature to 100 °C. Fittingly, under these conditions the desired domino product **12** was isolated in good yields (62%). In all of the attempted domino reactions the choice of conditions depended on the use of a strong base (i.e. NaH or KOH) for the deprotonation of the amide and a mild base (K_2CO_3



Scheme 2. Construction of the 3-benzazepine ring system through single-step or domino Tsuji–Trost/Heck reaction.

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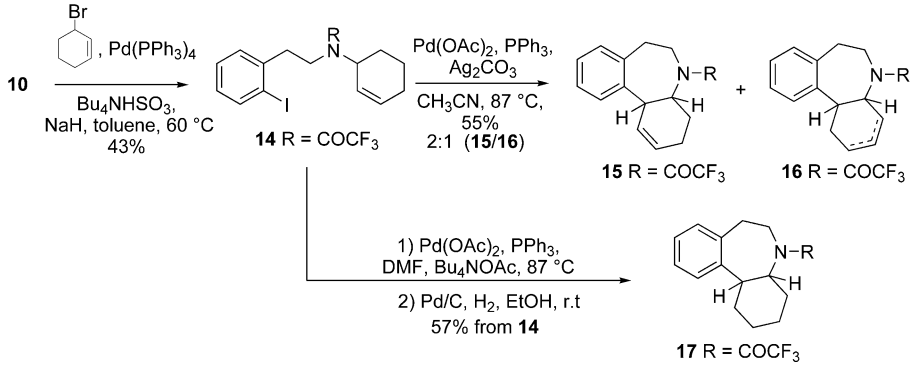
or Cs_2CO_3) for an efficient turnover of the Heck catalytic cycle. Furthermore, the use of a toluene/DMF (9:1) mixture was essential for consistently high yields. As expected, additional attempts to exclude either of these aforementioned bases resulted in either the Heck or Tsuji–Trost reaction not functioning. Treatment of compound **12** with $NaBH_4$ in EtOH resulted in the formation of the unprotected 3-benzazepine **13** (73%).

To test the effectiveness of this series of reactions in the formation of other 3-benzazepines, an alternative pathway containing a cyclohexene attachment was also tried. This procedure would provide the extremely rare 6-7-6 ABC-ring-fused alkaloid.[22] In the single-step procedure amide **10** was treated with 3-bromocyclohexene[23] to afford the cyclohexene-tethered amide **14** in moderate yields (Scheme 3). Under conditions that facilitated the intramolecular Heck reaction described earlier, the required tetrahydrodibenzazepine ring system was produced as found in the regioisomers **15** (37%) and **16** (18%).[24] In all reactions the major regioisomer **15** resulting from initial β-hydride elimination could be isolated by using standard chromatography conditions, whereas **16** was isolated as a mixture of regioisomers. The mixture **16** was presumed to be a result of additional hydropalladation followed by β-hydride elimination. Several alternative catalytic conditions with and without silver salts were tried, the best conditions being $Pd(OAc)_2$, PPh_3 and Ag_2CO_3 in acetonitrile. As reported by others,[25] in our example the addition of silver salts suppressed some of the double-bond migration; however, in all instances the mixture **16** was obtained. Clean chromatographic separation in many of the methods tried proved difficult. However, to fully gauge how successful the intramolecular Heck cyclisation was, a reaction mixture of **15** and **16** was hydrogenated (Pd/C under H_2) to afford compound **17** with the overall yield from compound **14** being a respectable 57%. Given the moderate yields of the initial allylation and the complex double-bond migration products of the intramolecular Heck reaction, the domino reaction was not attempted in this series.

To further explore the utility of this reaction and form precursors that could be used in the construction of a seven-membered ring within compounds like arbiflorine (**3**) or subincanadine F (**4**), we investigated the possibility of intramolecular Heck reactions through the C-2 position of the indole ring system. Functionalisation at this position, through intermolecular cross coupling, has recently been observed by Hsung[26] and Chu,[27] and compound **20**, bearing a bromine atom at C-2, was considered an ideal precursor for such cross couplings. This compound was prepared from tryptamine (**18**) through protection and bromination,[27] in 70 and 83% yield, respectively (Scheme 4). Unfortunately, iodination following the previously described procedure with IPy_2BF_4 failed to produce any of the equivalent 2-iodo derivative. The indole nitrogen atom within compound **20** was initially protected, to stop unwanted allylation of this group. Thus, treatment of **20** with $(Boc)_2O$ under standard conditions afforded the *tert*-butyl carbamate **21** in 78% yield. Indole **21** was subjected to similar Tsuji–Trost and Heck reaction conditions as outlined in Scheme 4. In the stepwise procedure with allyl bromide, $Pd(PPh_3)_4$ and base, the allylated **22** was produced in 69% yield. Treatment of this compound, under similar Heck reaction conditions described previously [$Pd(PPh_3)_4$, K_2CO_3 in DMF], provided the desired product, compound **23** resulting from 7-*exo*-*trig* cyclisation. Such a ring system is rare in the literature, and compounds similar to tricycle **23**, containing a double bond at C-5, are yet undescribed. Again, no endocyclic product was isolated as seen in other intramolecular Heck reactions in the literature. Once again subjecting the Boc-protected amine **21** to conditions, which favour the domino Tsuji–Trost/Heck reaction sequence, $Pd(PPh_3)_4$, NaH, Cs_2CO_3 in DMF, returned the desired product **23** in 69% yield. A careful choice of bases allows the domino reaction to proceed.

We also investigated the reactivity and behaviour of compounds unprotected at the indole nitrogen atom with the intention of also allylating in this position and later functionalising to produce more complex ring systems. Thus, treatment of amide **20** with allyl bromide, under Tsuji–Trost conditions as described before, afforded the diallylated product in 56% yield.

Interestingly, when compound **24** is subjected to palladium-mediated catalysis, $Pd(PPh_3)_4$ and K_2CO_3, the azepinobenzindolizine derivative **25** resulting from a second Heck-type cross coupling is produced in 24% yield (Scheme 5).



Scheme 3. Construction of the octahydrodibenzazepine ring system through single-step Tsuji–Trost and Heck reactions.

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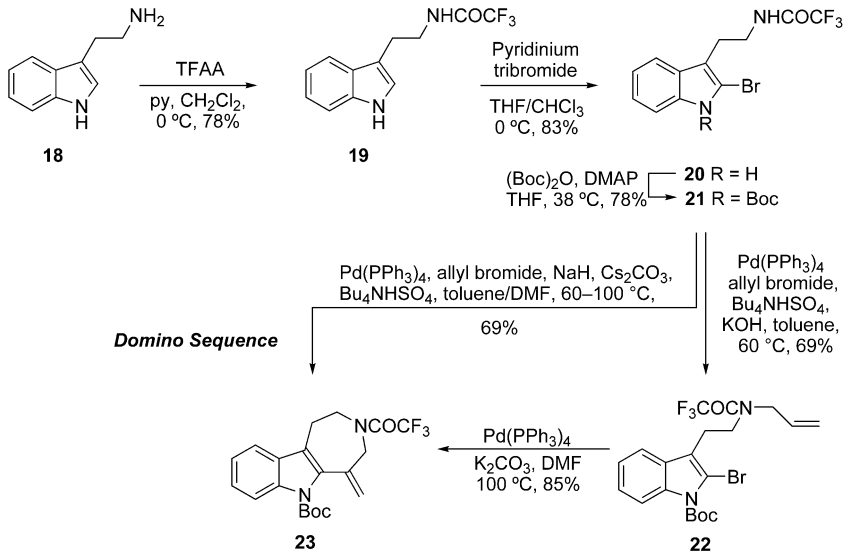
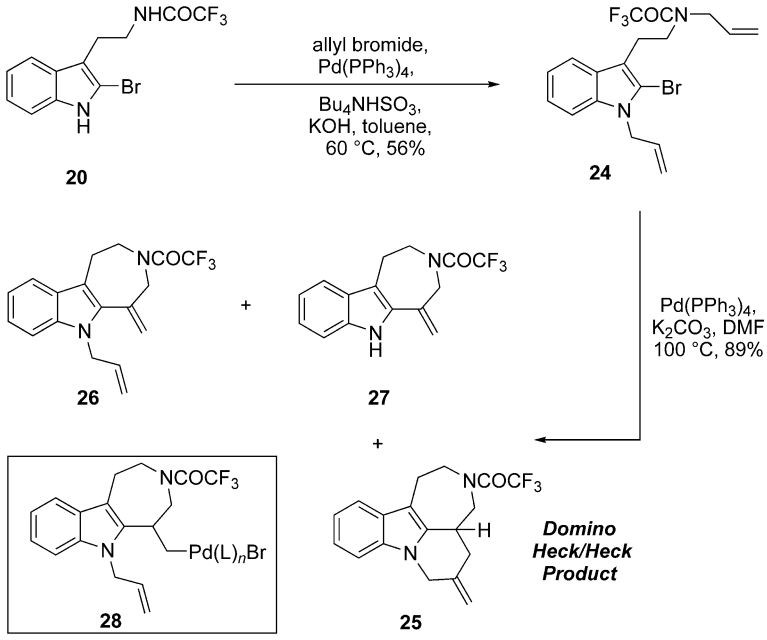


Scheme 4. Construction of the azepino[4,5-*b*]indole ring system through single-step or domino Tsuji–Trost/Heck reactions.



Scheme 5. Synthesis of allylazepino[4,5-*b*]indoles and azepinobenzindolizine ring systems through a Heck and domino Heck/Heck reaction.

Two other compounds, **26** (24%) and **27** (40%), resulting from Heck reactions were also isolated providing excellent overall mass conversion. Compound **27** resulted from a concomitant deallylation of the secondary amine.[28] To the best of our knowledge, derivative **25**, containing a 6-5-7-6-membered ring system, has not been reported in the literature, although some natural products, e.g. dippinine A, partially contain this ring framework.[29] It is assumed this product **25** arises from an intermediate such as alkylpalladium bromide **28** prior to β-hydride elimination. The stabilisation of such intermediates through a nitrogen atom within close proximity may enhance the chance of a second Heck reaction over dehydropalladation.[30] The domino-Heck-type pathway has been explored by several groups towards the synthesis of complex natural products.[13d,31] The formation of the tetracycle **25** is extremely interesting, and further examination of this series of reactions with indole precursors and substituted allyl halides are currently underway in our laboratories.

As in the previous series, we investigated the treatment of compound **20** under the domino Tsuji–Trost/Heck reaction. Treatment of the indole **20** with $Pd(PPh_3)_4$, allyl bromide, KOH and K_2CO_3 resulted in a mixture of allylated and Heck-reaction product, compounds **24**, **25**, **26** and **29** (Scheme 6) in a 1:1:3:1 ratio, respectively. Unfortunately, at this stage conditions that favoured significant amounts of

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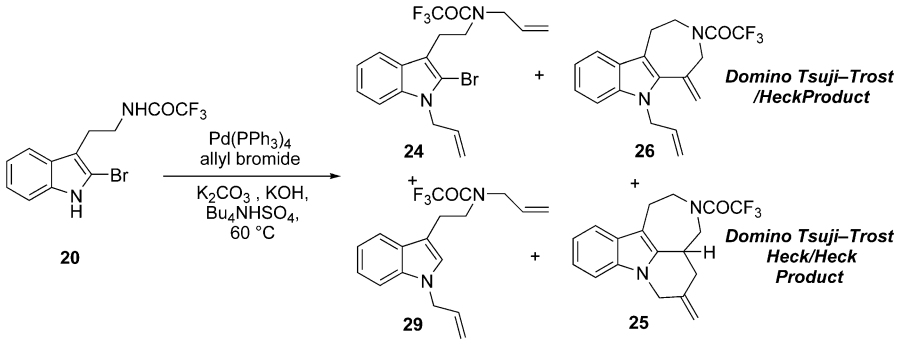

Scheme 6. Domino Tsuji–Trost/Heck cross-coupling to produce tricycle **26** and accompanying domino Tsuji–Trost/Heck/Heck reaction to produce tetracycle **25**.

only tricycle **26** and tetracycle **25** were not found. Investigation into a series of alkylation and Heck reactions in more substituted substrates to extend this domino process will be undertaken.

Conclusions

The results of this paper highlight the use of Tsuji–Trost and Heck reactions as key steps to create seven-membered-ring nitrogen heterocycles. In particular, we have reported the application of this method to the synthesis of novel 3-benzazepines and azepino[4,5-*b*]indole ring systems. In this study we have also developed a new method for a single-pot domino Tsuji–Trost/Heck reaction involving an initial intermolecular amide allylation. We have also highlighted the need for a particular specific set of palladium cross-coupling conditions for these reactions with particular emphasis on the choice of base. In further exploration of *N*-diallylated compounds, formed in the initial study, we have discovered a domino Tsuji–Trost/Heck/Heck reaction process, which leads to the preparation of the azepinobenzindolizines.

Experimental Section

General: All reactions were performed in flame-dried glassware under argon unless stated otherwise. Solvents were dried and purified according to the method defined by Armarego and Chai.[32] All reactions involving heating were carried out by immediately placing reaction vessel in an oil bath preheated to the specified temperature. All palladium-mediated cross-coupling reactions were carried out by using degassed solvents or by degassing according to the freeze-pump-thaw method. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} pre-coated aluminium sheets. Visualisation of developed plates was achieved through the use of a 254-nm or 365-nm UV lamp or staining with phosphomolybdic acid. Column chromatography was performed by using silica gel 60 (0.063–0.200 mm), as supplied by Merck, with the eluents indicated. HPLC was performed with a Grace-Apollo 250 × 10 mm, 5 micron, C18 semi-preparative column coupled to a UV detector. ^{1}H and ^{13}C NMR spectra were acquired with either a Bruker Avance (AV) 500 spectrometer (500.13 MHz, 125.8 MHz, for ^{1}H and ^{13}C, respectively) at 25 °C or a Bruker Avance (AV) 600 spectrometer (600.1 MHz and 150.9 MHz for ^{1}H and ^{13}C, respectively) at 25 °C. For ^{1}H and ^{13}C NMR spectra, $CDCl_3$ and [D_6]-acetone were used as solvents. Chemical shifts are reported on a δ scale. Signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br. (broad). ^{13}C NMR assignments were aided by the use of DEPT135 analysis. Mass spectra were acquired with a VG AutoSpec instrument through electron-impact ionisation (EI). HRMS was performed with a resolution of approximately 10000. IR spectra were recorded with a Perkin-Elmer Spectrum One Spectrometer FT-IR spectrometer. Samples were analysed as thin films on NaCl discs, $CHCl_3$ solution between NaCl plates or pressed KBr plates.

2,2,2-Trifluoro-*N*-(2-phenylethyl)acetamide (9): The preparation of trifluoroacetamide **9** was carried out according to that described by Barluenga et al.[19] All spectroscopic data matched those acquired previously.

2,2,2-Trifluoro-*N*-[2-(2-iodophenyl)ethyl]acetamide (10): The preparation of trifluoroacetamide **10** was carried out according to that described by Barluenga et al.[19] All spectroscopic data matched those acquired previously.

***N*-Allyl-2,2,2-trifluoro-*N*-[2-(2-iodophenyl)ethyl]acetamide (11):** Amide **10** (200 mg, 0.58 mmol) was added to a magnetically stirred suspension of powdered KOH (100 mg, 1.8 mmol) and Bu_4NHSO_4 (20 mg, 0.06 mmol) in toluene (6 mL), and the solution was stirred at room temperature for 10 min. The resulting mixture was treated with allyl bromide (50 μL, 70 mg, 0.58 mmol) followed immediately by $Pd(PPh_3)_4$ (54 mg, 8 mol-%) and the yellow suspension heated at 60 °C for 5 min. The mixture was cooled to 0 °C and treated dropwise with water (ca. 5 mL) with stirring. The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the organic fractions were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting crude oil was subjected to flash chromatography (hexane → toluene/hexane, 3:7) to afford compound **11** (150 mg, 68% yield) as a colourless oil (R_f = 0.6, in EtOAc/hexane, 1:4). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84–7.81 (m, 1 H, HAr), 7.33–7.28 (m, 1 H, HAr), 7.26–7.20 (m, 1 H, HAr), 6.97–6.92 (m, 1 H, HAr), 5.87–5.79 (m, 0.36 H, C*H*=CH_2), 5.74–5.67 (m, 0.64 H, C*H*=CH_2), 5.32–5.22 (m, 2 H, CH=CH_2), 4.11 (d, J = 6.0 Hz, 0.36 H, CH_2), 3.85 (d, J = 6.0 Hz, 0.64 H, CH_2), 3.57–3.54 (m, 2 H, CH_2), 3.07–3.03 (m, 2 H, CH_2) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 157.1, 156.9 (q, J = 35.9 Hz, *C*OCF_3), 140.9, 140.3 (C), 139.9, 139.8 (CH), 131.8, 131.2 (CH), 130.6, 130.2 (CH), 129.1, 128.9, 128.8 (CH), 119.6, 119.1 (CH_2), 116.5, 116.7 (q, J = 288.0 Hz, CF_3), 50.8 (q, J = 3.3 Hz), 49.6, 47.2 (q, J = 3.0 Hz), 46.8 (2 × CH_2), 40.2, 37.7 (CH_2) ppm. HR-EIMS: calcd. for $C_{13}H_{13}IF_3NO$ 382.9994; found 382.9996. IR (neat): $\tilde{\nu}$ = 2941, 1693, 1467, 1204, 1145, 1008, 932, 754 cm^{-1}.

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1-Methylene-3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (12). Method A (Single-Step Procedure from Compound 11): A mixture of iodide **11** (154 mg, 0.40 mmol), $Pd(OAc)_2$ (9 mg, 10 mol-%), triphenylphosphane (21 mg, 20 mol-%), Pr_4NBr (117 mg, 0.44 mmol), KOAc (126 mg, 1.28 mmol) in DMF (8 mL) was degassed. The resulting mixture was stirred and heated to 80 °C for 1.75 h. The resulting solution was cooled and then poured directly into a separatory funnel containing water and diethyl ether (1:1, 40 mL). The ensuing solution was extracted with diethyl ether (3× 10 mL), the combined organic extracts dried ($MgSO_4$) and concentrated under reduced pressure to afford a pale oil. The crude oil was subjected to flash chromatography (hexane → toluene/hexane, 1:1) to afford compound **12** (75 mg, 73%) as colourless oil (R_f = 0.45, in EtOAc/hexane, 1:4). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 1 H, HAr), 7.29–7.23 (m, 2 H, HAr), 7.16–7.12 (m, 1 H, HAr), 5.44 (s, 0.55 H, C=CH_2), 5.42 (s, 0.55 H, C=CH_2), 5.39 (s, 0.45 H, C=CH_2), 5.31 (s, 0.45 H, C=CH_2), 4.46 (s, 0.9 H, CH_2), 4.42 (s, 1.1 H, CH_2), 3.88 (t, J = 6.1 Hz, 0.9 H, CH_2), 3.83 (t, J = 5.7 Hz, 1.1 H, CH_2), 3.05 (m, 2 H, CH_2) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 156.9, 156.5 (q, J = 35.8 Hz, *C*OCF$_3$), 145.8, 145.2 (C), 140.0, 139.1 (C), 136.0, 135.4 (C), 129.5, 129.4 (CH-Ar), 128.8, 128.7, 128.7, 128.3 (CH-Ar), 127.6, 127.5 (CH-Ar), 118.1, 116.1 (C=*C*H$_2$), 116.6, 116.5 (q, J = 288.0 Hz, CF_3), 51.1 (q, J = 3.4 Hz), 51.0, 46.9 (q, J = 3.3 Hz), 45.8 (2× CH_2), 35.5, 33.3 (CH_2) ppm. HR-EIMS: calcd. for $C_{13}H_{12}F_3NO$ 255.0871; found 255.0872. IR (neat): $\tilde{\nu}$ = 2931, 1693, 1460, 1202, 1144, 754 cm^{-1}.

2,2,2-Trifluoro-1-(1-methylidene-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)ethanone (12). Method B (Domino Procedure from Compound 10): Amide **10** (200 mg, 0.58 mmol) was added to a magnetically stirred mixture of Cs_2CO_3 (575 mg, 1.76 mmol) and Bu_4NHSO_4 (60 mg, 0.18 mmol) in toluene/DMF (9:1) (4 mL). NaH (36 mg, 60% in oil, 0.9 mmol) was then added and the reaction mixture stirred for 10 min. $Pd(PPh_3)_4$ (65 mg, 0.06 mmol, 10 mol-%) was added followed by allyl bromide (0.1 mL, 140 mg, 1.15 mmol), and the mixture was heated to 60 °C for 30 min, after which time additional NaH (11 mg, 60% in oil, 0.3 mmol) was added, and the reaction mixture was heated to 100 °C for 22 h. The reaction mixture was cooled to 0 °C, and water (4 mL) was added with stirring. The phases were separated, and the aqueous phase was extracted with dichloromethane (4× 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated. The crude oil was subjected to flash chromatography (toluene/hexane, 2:3 → toluene/hexane, 45:55) to afford compound **12** (93 mg, 62%) as a yellow oil.

1-Methylene-2,3,4,5-tetrahydro-1*H*-3-benzazepine (13): $NaBH_4$ (57 mg, 1.50 mmol) was added to a solution containing amide **12** (95 mg, 0.37 mmol) in EtOH (7 mL) maintained at room temperature. The mixture was heated to 80 °C with stirring for 45 min before being cooled to room temperature and concentrated in vacuo. The crude residue was dissolved in diethyl ether (10 mL), and 2 M HCl was added slowly with stirring. The layers were separated, and the organic phase was extracted with HCl (4× 5 mL of 2 M solution). The combined aqueous phases were basified with NaOH (2.5 M) and extracted with dichloromethane (5× 10 mL). The combined organic extracts were concentrated, the resulting oil was redissolved in toluene (10 mL) and concentrated to remove any residual water. Amine **13** was obtained as a faint yellow oil (43 mg, 73%). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 7.27–7.24 (m, 1 H, HAr), 7.22–7.18 (m, 2 H, HAr), 7.12–7.08 (m, 1 H, HAr), 5.2 (m, 1 H, C=CH_2), 5.13 (d, J = 1.6 Hz, 1 H, C=CH_2), 3.57 (s, 2 H, CH_2C=CH_2), 3.05 (m, 2 H, CH_2), 2.90 (m, 2 H, CH_2), 1.9 (br. s, 1 H, NH) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 153.2 (C), 142.6 (C), 138.6 (C), 129.1 (CH-Ar), 128.4 (CH-Ar), 127.7 (CH-Ar), 126.6 (CH-Ar), 114.6 (C=*C*H$_2$), 53.4 (CH_2), 47.5 (CH_2), 39.3 (CH_2) ppm. HR-EIMS: calcd. for $C_{11}H_{13}N$ 159.1048; found 159.1053. IR (neat): $\tilde{\nu}$ = 3271, 2927, 2855, 1626, 1484, 1431, 1316, 1135, 909, 752 cm^{-1}.

***N*-(Cyclohex-2-en-1-yl)-2,2,2-trifluoro-*N*-[2-(2-iodophenyl)ethyl]-acetamide (14):** Amide **10** (1.00 g, 2.91 mmol) was added to a magnetically stirred suspension of Bu_4NHSO_4 (200 mg, 0.60 mmol) in toluene (20 mL). NaH (154 mg, 60% in paraffin oil, 3.85 mmol) was added and the solution stirred at ambient temperature for 10 min. $Pd(PPh_3)_4$ (200 mg, 6 mol-%) was added followed by 3-bromocyclohexene (1.0 mL, 8.7 mmol) and the mixture heated to 65 °C for 4.5 h. The ensuing solution was cooled to 0 °C and treated dropwise with water (20 mL) and the mixture stirred rapidly. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (4× 15 mL) and the organic fractions were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude oil was subjected to flash chromatography (hexane → toluene/hexane, 1:1) to afford compound **14** (540 mg, 43% yield) as a colourless oil (R_f = 0.63, in EtOAc/hexane, 3:7). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.0 Hz, 1 H, HAr), 7.31–7.2 (m, 2 H, HAr), 6.93–6.90 (m, 1 H, HAr), 6.05–5.96 (m, 1 H, C*H*=CH), 5.58 (d, J = 10.2 Hz, 0.1 H, C*H*=CH), 5.31 (d, J = 10.2 Hz, 0.9 H, C*H*=CH), 4.96 (br. s, 0.1 H, CH=C*H*), 4.55 (br. s, 0.9 H, CH=C*H*), 3.54 (t, J = 8.6 Hz, 0.2 H, CH_2), 3.46–3.38 (m, 1.8 H, CH_2), 3.16–2.99 (m, 2 H, CH_2), 2.08–1.55 (m, 6 H, 3× CH_2) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 157.4 (q, J = 35.3 Hz, *C*OCF$_3$), 142.0, 141.2 (C), 139.9, 139.6 (CH), 133.6, 132.2 (CH), 130.6, 130.0 (CH), 129.0, 128.9, 128.8, 128.6 (2× CH), 126.9, 126.5 (CH), 116.7 (q, J = 287.5 Hz, CF_3), 100.5, 100.1 (ArCI), 55.2 (q, J = 3.6 Hz, CH), 45.5 (q, J = 3.1 Hz) 44.5, (CH_2), 41.9, 38.5 (CH_2), 28.6, 26.7 (CH_2), 24.7, 24.4 (CH_2), 21.8, 21.6 (CH_2) ppm. HR-EIMS: calcd. for $C_{16}H_{17}F_3INO$ 423.0307; found 423.0301. IR (neat): $\tilde{\nu}$ = 2936, 1685, 1434, 1211, 1181, 1143, 748, 696 cm^{-1}.

5-(Trifluoroacetyl)-4,4a,5,6,7,11b-hexahydro-3*H*-dibenzo[*b*,*d*]-azepine (15): Aryl iodide **14** (119 mg, 0.28 mmol) was transferred to a flask equipped with a reflux condenser. Ag_2CO_3 (155 mg, 0.56 mmol), PPh_3 (15 mg, 0.057 mmol, 30 mol-%) and $Pd(OAc)_2$ (6.0 mg, 0.026 mmol, 30 mol-%) were transferred to this flask, and the flask was backfilled with argon. Acetonitrile (5 mL) was added, and the resulting mixture was heated at reflux for 2.5 h. The mixture was cooled to room temperature and then concentrated under reduced pressure. The crude material was subjected to flash chromatography (toluene/hexane, 2:3 → toluene/hexane, 1:1) to afford compound **15** (31 mg, 37% yield) as a colourless oil (R_f = 0.63, in acetone/toluene, 5:95). This material is sufficiently pure for most purposes; however, an analytical sample may be obtained by semi-preparative HPLC (MeOH/H_2O, 4:1, 4 mL/min). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.27 (m, 1 H, HAr), 7.23–7.16 (m, 2 H, HAr), 7.14–7.08 (m, 1 H, HAr), 6.00–5.88 (m, 2 H, C*H*=C*H*), 5.10–5.05 (m, 0.6 H, CH), 4.65–4.55 (m, 0.4 H, CH), 4.47–4.41 (m, 0.4 H, CH_2), 4.03–3.06 (m, 0.6 H, CH_2), 3.77 (br. s, 0.6 H, CH) 3.74 (br. s, 0.4 H, CH), 3.5–3.41 (m, 0.6 H, CH_2), 3.10–2.92 (m, 2.4 H, CH_2), 2.45–2.20 (m, 2 H, CH_2), 1.93–1.82 (m, 1 H, CH_2), 1.66–1.58 (m, 1 H, CH_2) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 156.8, 156.7, (q, J = 34.8 Hz, *C*OCF$_3$), 140.3, 139.2, 139.1, 138.7 (2× C), 131.8, 131.7 (CH) 130.2, 130.0 (CH), 129.72, 129.70, (CH), 128.0 (CH), 127.3, 127.2 (CH), 127.0, 126.8 (CH), 116.9, 117.1 (q, J = 288.5 Hz, CF_3), 55.5 (q, J = 3.6 Hz), 52.9 (CH), 44.9, 44.1 (CH), 43.0 (q, J = 3.3 Hz), 41.2 (CH_2), 36.4, 35.7 (CH_2), 25.8, 24.9 (CH_2), 24.3, 23.5 (CH_2) ppm. HR-EIMS: calcd. for $C_{16}H_{16}F_3NO$ 295.1184; found 295.1179. IR ($CHCl_3$): $\tilde{\nu}$ = 3024, 2952, 1682, 1450, 1204, 1148 cm^{-1}. The second fraction collected from the chomatog-

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raphy column contained an inseparable mixture of regioisomers **16** (15 mg) as indicated by ^{1}H NMR spectroscopy.

5-(Trifluoroacetyl)-2,3,4,4a,5,6,7,11b-octahydro-1*H*-dibenzo[*b*,*d*]-azepine (17): Iodide **14** (396 mg, 0.93 mmol) was transferred to a flask equipped with a reflux condenser and stirrer bar. $Pd(OAc)_2$ (21.0 mg, 0.09 mmol, 10 mol-%) was added followed by PPh_3 (24.0 mg, 0.09 mmol, 10 mol-%) and Bu_4NOAc (845 mg, 2.80 mmol). The apparatus was evacuated and thrice backfilled with argon. DMF (15 mL) was added via syringe, and the mixture was heated to 86 °C for 45 min. The black reaction mixture was cooled to room temperature and concentrated in vacuo. The crude material was subjected to flash chromatography (toluene/hexane, 2:3 → toluene/hexane, 7:3), fractions from $R_f \approx 0.6$ to 0.5 (acetone/toluene, 5:95) were combined to afford crude regioisomers **15** and **16** (237 mg). This material was dissolved in EtOH (20 mL), Pd/C (35 mg) was added and the mixture stirred under H_2 from a balloon at room temperature for 18 h. The mixture was concentrated under reduced pressure. Flash chromatography (toluene/hexane, 3:7 → toluene/hexane, 1:1) afforded **17** (158 mg, 57%) as a colorless oil (R_f = 0.73, in acetone/toluene, 5:95). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 7.45 (d, J = 7.9 Hz, 1 H, ArH), 7.25 (m, 1 H, ArH), 7.2–7.1 (m, 2 H, ArH), 4.92–4.97 (m, 0.6 H, CH), 4.60–4.55 (m, 0.4 H, CH_2), 4.25–4.20 (m, 0.4 H, CH), 4.05–3.95 (m, 0.6 H, CH_2), 3.35–3.30 (m, 1.6 H, CH, CH_2), 3.05–2.85 (m, 2.4 H, CH_2), 2.6–2.45 (m, 1 H, CH_2), 2.05–1.6 (m, 6 H, 3 × CH_2), 1.5–1.35 (m, 1 H, CH_2) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 156.2, 156.1 (q, J = 34.8 Hz, *C*OCF_3), 141.2, 140.2, 138.7, 138 (2 × C), 130.5, 130.3, 130.2, 130.0 (2 × CH-Ar), 127.0, 126.8, 126.78, 126.7 (2 × CH-Ar), 117.3, 117.1 (q, J = 288.4 Hz, CF_3), 59.7 (q, J = 3.4 Hz), 56.5 (CH), 44.2, 43.0 (CH), 42.7 (q, J = 3.3 Hz), 40.5 (CH_2), 38.7, 37.8 (CH_2), 30.38, 30.37 (CH_2), 27.5, 26.8, 26.7, 26.2 (2 × CH_2), 21.2, 20.7 (CH_2) ppm. HR-EIMS: calcd. for $C_{16}H_{18}F_3NO$ 297.1340; found 297.1338. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2945, 1679, 1449, 1215, 1145 cm^{-1}.

***N*-[2-(2-Bromo-1*H*-indol-3-yl)ethyl]-2,2,2-trifluoroacetamide (20):** Pyridinium tribromide (5.35 g, 0.016 mol) was added portionwise to a magnetically stirred solution of amide **19** (3.96 g, 0.015 mol) in THF/$CHCl_3$ (1:1, 180 mL) at 0 °C over 1.25 h. The resulting mixture was then stirred at this temperature for an additional 15 min and then treated with aqueous $Na_2S_2O_3$ (100 mL, 0.5 M) under continuous stirring. The resulting mixture was treated with $NaHCO_3$ (50 mL, saturated), water (50 mL) and CH_2Cl_2 (50 mL) and stirred. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material was subjected to flash chromatography (toluene → acetone/toluene, 1:49) to afford compound **20** (4.43 g, 83%) as an off-white solid (R_f = 0.35, in acetone/toluene, 5:95). M.p. 101–103 °C. ^{1}H NMR (500 MHz, [D_6]acetone): δ = 10.6 (br. s, 1 H, NH), 8.6 (br. s, 1 H, NH), 7.56 (d, J = 8.0 Hz, 1 H, ArH), 7.35 (d, J = 8.0 Hz, 1 H, ArH), 7.12 (t, J = 7.7 Hz, 1 H, ArH), 7.05 (t, J = 7.5 Hz, 1 H, ArH), 3.61 (q, J = 6.6 Hz, 2 H, CH_2), 3.03 (t, J = 7.2 Hz, 2 H, CH_2) ppm. ^{13}C NMR (125.8 MHz, [D_6]acetone): δ = 157.7 (q, J = 36.2 Hz, *C*OCF_3), 137.5 (C), 128.5 (C), 122.8 (CH), 120.5 (CH), 118.6 (CH), 117.1 (q, J = 287.7 Hz, CF_3), 112.1 (C), 111.6 (CH), 109.6 (C), 40.4 (CH_2), 24.9 (CH_2) ppm. HR-EIMS: calcd. for $C_{12}H_{10}BrF_3N_2O$ 335.9908 and 333.9929; found 335.9898 and 333.9925. IR ($CHCl_3$): $\tilde{\nu}$ = 3387, 3308, 1707, 1553, 1450, 1337, 1211, 1177, 746 cm^{-1}.

2-Bromo-*tert*-butyl-3-{2-[(trifluoroacetyl)amino]ethyl}-1*H*-indole-1-carboxylate (21): Di-*tert*-butyl dicarbonate (357 mg, 1.63 mmol) was added in one portion to a magnetically stirred solution of indole **19** (500 mg, 1.49 mmol) and DMAP (20 mg, 0.16 mmol) in THF (14 mL). The resulting solution was heated to 38 °C for 40 min. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was re-dissolved in CH_2Cl_2 (15 mL), and water (10 mL) was added. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was subjected to flash chromatography (hexane → EtOAc/hexane, 1:9) to afford compound **21** (553 mg, 85%) as a colourless solid (R_f = 0.55, in acetone/toluene, 1:19). M.p. 115–116 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.1 (d, J = 8.1 Hz, 1 H, ArH), 7.48 (d, J = 7.7 Hz, 1 H, ArH), 7.32 (t, J = 7.7 Hz, 1 H, ArH), 7.25 (t, J = 7.2 Hz, 1 H, ArH), 6.50 (s, 1 H, NH), 3.64 (q, J = 6.3 Hz, 2 H, 1′-H), 3.05 (t, J = 6.7 Hz, 2 H, 2′-H), 1.71 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 157.5 (q, J = 37.1 Hz, *C*OCF_3), 149.1 (C=O), 136.7 (C-Ar), 128.6 (C-Ar), 125.0 (CH-Ar), 123.4 (CH-Ar), 119.2 (C-Ar), 117.8 (CH-Ar), 115.8 (q, J = 287.9 Hz, CF_3), 115.6 (CH-Ar), 110.0 (C-Ar), 85.4 (C), 39.3 (CH_2), 28.3 (CH_3), 24.8 (CH_2) ppm. HR-EIMS: calcd. for $C_{17}H_{18}BrF_3N_2O_3$ 434.0453 and 436.0432; found 434.0463 and 436.0438. IR (KBr): $\tilde{\nu}$ = 3296, 2988, 1730, 1701, 1561, 1453, 1354, 1165, 1153, 1100, 749 cm^{-1}.

***tert*-Butyl 3-{2-[Allyl(trifluoroacetyl)amino]ethyl}-2-bromo-1*H*-indole-1-carboxylate (22):** Amide **21** (195 mg, 0.45 mmol) was added to a magnetically stirred suspension of powdered KOH (101 mg, 1.8 mmol) and Bu_4NHSO_4 (30 mg, 0.09 mmol) in toluene (4 mL), and the solution was stirred at room temperature for 10 min. The resulting mixture was treated with allyl bromide (97 μL, 135 mg, 1.12 mmol) followed immediately by $Pd(PPh_3)_4$ (58 mg, 11 mol-%) and the resulting yellow suspension heated at 60 °C for 1 h. The mixture was cooled to 0 °C and treated dropwise with water (ca.4 mL) with stirring. The phases were separated, and the aqueous phase was extracted with dichloromethane (4 × 2 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was subjected to flash chromatography (toluene/hexane, 1:1 → toluene/hexane, 4:1) to afford compound **22** (148 mg, 69%) as a colourless oil (R_f = 0.6, in acetone/toluene, 1:19). ^{1}H NMR (500 MHz, [D_6]acetone): δ = 8.11 (t, J = 7.9 Hz, HAr), 7.67, (d, J = 7.7 Hz, 0.66 H, HAr), 7.59 (d, J = 7.7 Hz, 0.33 H, HAr), 7.35–7.27 (m, 2 H, ArH), 5.92–5.78 (m, 1 H, C*H*=CH_2), 5.33–5.24 (m, 2 H, CH=C*H*$_2$), 4.21 (d, J = 5.9 Hz, 0.33 H, CH_2), 4.05 (d, J = 5.9 Hz, 0.66 H, CH_2), 3.68–3.58 (m, 2 H, CH_2), 3.17–3.05 (m, 2 H, CH_2), 1.71 (m, 9 H, *t*Bu) ppm. ^{13}C NMR (125.8 MHz, [D_6]acetone): δ = 156.8, 157.1 (q, J = 35.5 Hz, *C*OCF_3), 149.6, 149.5 (C=O), 137.5 (C), 133.4, 132.7 (CH), 129.5, 129.2 (C), 125.6, 125.5 (CH), 124.0, 123.9 (CH), 120.6, 119.7 (C), 119.3, 118.9 (C=*C*H_2), 119.1, 118.7 (CH), 117.7, 117.5 (q, J = 287.8 Hz, CF_3), 116.2, 116.0 (CH-Ar), 110.6, 110.3 (C-Ar), 85.9, 85.8 (C), 51.4 (q, J = 3.3 Hz), 50.0, 46.6, 46.4 (q, J = 3.0 Hz, 2 × CH_2), 28.2 (CH_3), 25.3, 23.3 (CH_2) ppm. HR-EIMS: calcd. for $C_{20}H_{22}BrF_3N_2O_3$ 474.0766 and 476.0745; found 474.0757 and 476.0747. IR (neat): $\tilde{\nu}$ = 2982, 1736, 1692, 1448, 1351, 1253, 1152, 757 cm^{-1}.

***tert*-Butyl-5-methylene-3-(trifluoroacetyl)-2,3,4,5-tetrahydro-azepino[4,5-*b*]indole-6(1*H*)-carboxylate (23). Method A (Single-Step Procedure from Compound 22):** Bromide **22** (150 mg, 0.31 mmol) was transferred to a flask equipped with a reflux condenser and stirrer bar. DMF (9 mL) was added followed by K_2CO_3 (88 mg, 0.63 mmol) and $Pd(PPh_3)_4$ (45 mg, 0.04 mmol, 12 mol-%). The flask was evacuated briefly with stirring and backfilled thrice with argon and heated to 100 °C for 1.75 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude material was subjected to flash chromatography

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(toluene/hexane, 7:3 → toluene/hexane, 9:1) to afford compound **23** (107 mg, 85%) as a light pink oil (R_f = 0.5, in acetone/toluene, 1:19). ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 8.05 (dd, J = 8.3 and 4.8 Hz, 1 H, HAr), 7.50 (t, J = 7.2 Hz, 1 H, HAr), 7.34 (t, J = 8.2 Hz, 1 H, HAr), 7.26–7.23 (m, 1 H, HAr), 5.72 (d, J = 0.9 Hz, 0.5 H, C=CH_2), 5.68 (s, 0.5 H, C=CH_2), 5.32 (s, 0.5 H, C=CH_2), 5.28 (s, 0.5 H, C=CH_2), 4.65 (s, 1 H, CH$_2$), 4.53 (s, 1 H, CH$_2$), 4.05 (t, J = 5.6 Hz, 1 H, CH$_2$), 3.99 (t, J = 5.8 Hz, 1 H, CH$_2$), 3.09 (m, 2 H, CH$_2$), 1.58 (m, 9 H, *t*Bu) ppm. ^{13}C NMR (125.8 MHz, [D$_6$]-acetone): δ = 156.8, 156.7 (q, J = 35.6 Hz, *C*OCF$_3$), 150.8, 150.7 (C=O), 138.2, 138.1 (C), 136.6, 136.2 (C), 135.0, 133.2 (C), 130.0, 129.9 (C), 125.9, 125.8 (CH-Ar), 123.7, 123.6 (CH-Ar), 122.3, 120.78 (C=*C*H$_2$), 119.7, 119.6 (CH-Ar), 119.65, 118.9 (C), 117.5, 117.7 (q, J = 288.0 Hz, CF$_3$), 115.14, 115.1 (CH-Ar), 84.5, 84.4 (C), 55.4 (q, J = 3.7 Hz), 55.3, 45.5 (q, J = 3.0 Hz), 44.7 (2× CH$_2$), 28.3, 28.0 (CH$_3$), 27.0, 24.1 (CH$_2$) ppm. HR-EIMS: calcd. for $C_{20}H_{21}F_3N_2O_3$ 394.1504; found 394.1490. IR (CHCl$_3$): $\tilde{\nu}$ = 3021, 1731, 1689, 1456, 1370, 1323, 1215, 1153 cm^{-1}.

***tert*-Butyl-5-methylene-3-(trifluoroacetyl)-2,3,4,5-tetrahydroazepino[4,5-*b*]indole-6(1*H*)-carboxylate (23). Method B (Domino Procedure from Compound 21):** Amide **21** (200 mg, 0.46) was added to a magnetically stirred mixture of Cs_2CO_3 (475 mg, 1.45 mmol) and Bu_4NHSO_4 (50 mg, 0.15 mmol) in toluene/DMF (9:1; 4 mL). NaH (60% in oil; 30.0 mg, 0.75 mmol) was then added and the reaction mixture allowed stirred for 10 min. Pd(PPh$_3$)$_4$ (55 mg, 0.05 mmol, 10 mol-%) was added followed by allyl bromide (84 μL, 117 mg, 0.97 mmol), and the resulting mixture was heated to 60 °C for 30 min, after which time additional NaH (60% in oil; 12 mg, 0.3 mmol) was added, and the reaction mixture was heated to 100 °C for 19 h. The reaction mixture was cooled to 0 °C, and water (4 mL) was added with stirring. The phases were separated, and the aqueous phase was extracted with dichloromethane (4× 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated. The crude oil was subjected to flash chromatography (toluene/hexane, 1:1 → toluene/hexane, 65:35) to afford compound **22** (132 mg, 69%) as yellow oil.

***N*-Allyl-*N*-[2-(1-allyl-2-bromo-1*H*-indol-3-yl)ethyl]-2,2,2-trifluoroacetamide (24):** Amide **20** (500 mg, 1.49 mmol) was added to a magnetically stirred suspension of powdered KOH (675 mg, 12 mmol) and Bu_4NHSO_4 (75 mg, 0.22 mmol) in toluene (10 mL), and the solution was stirred at room temperature for 10 min. The resulting mixture was treated with allyl bromide (650 μL, 908 mg, 7.51 mmol) followed immediately by Pd(PPh$_3$)$_4$ (175 mg, 10 mol-%) and the resulting yellow suspension heated at 60 °C for 2.5 h. The mixture was cooled to 0 °C and treated dropwise with water (ca.10 mL) with stirring. The phases were separated, the aqueous phase was extracted with dichloromethane (3× 10 mL), and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was subjected to flash chromatography (toluene/hexane, 1:1 → toluene/hexane, 4:1) to afford compound **24** (348 mg, 56%) as a colourless oil (R_f = 0.7, in acetone/toluene, 1:19). ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 7.65 (d, J = 7.7 Hz, 0.6 H, HAr), 7.58 (d, J = 7.7 Hz, 0.4 H, HAr), 7.18 (m, 1 H, HAr), 7.11 (m, 1 H, HAr), 7.40 (m, 1 H, HAr), 6.00–5.90 (m, 1 H, C*H*=CH$_2$), 5.90–5.73 (m, 1 H, C*H*=CH$_2$), 5.30–5.17 (m, 2 H, CH=CH_2), 5.13–5.07 (m, 1 H, CH=CH_2), 4.92–4.80 (m, 3 H, CH$_2$ and CH=CH_2), 4.87 (d, J = 6.0 Hz, 0.8 H, CH$_2$), 3.95 (d, J = 6.0 Hz, 1.2 H, CH$_2$), 3.64 (m, 2 H, CH$_2$), 3.17–3.06 (m, 2 H, CH$_2$) ppm. ^{13}C NMR (125.8 MHz, [D$_6$]acetone): δ = 157.0, 156.8 (q, J = 35.4 Hz, *C*OCF$_3$), 137.4, (C) 134.1, 134.0, 133.4, 132.7 (CH), 128.1, 127.8 (C), 123.1, 123.0 (CH), 121.0, 120.8 (CH), 119.1, 118.8 (CH=CH_2), 118.9, 118.6 (CH), 117.8, 117.6 (q, J = 287.0 Hz, CF$_3$), 116.8, 116.7 (CH=CH_2), 113.9, 113.7 (C), 112.3, 111.4 (C), 111.1, 110.9 (CH), 51.4 (q, J = 3.3 Hz), 50.0, 47.6, 47.5, 47.3, 47.2 (q, J = 3.1 Hz, 3× CH$_2$), 25.4, 23.4 (CH$_2$) ppm. HR-EIMS: calcd. for $C_{18}H_{18}BrF_3N_2O$ 414.0588 and 416.0534; found 414.0575 and 416.0529. IR (neat): $\tilde{\nu}$ = 2929, 1692, 1457, 1333, 1203, 1146, 929, 742 cm^{-1}.

6-Allyl-5-methylene-3-(trifluoroacetyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (26), 6-Methylene-3-(trifluoroacetyl)-2,3,4,4a,5,6-hexahydroazepino[3,4,5-*hi*]benz[*b*]indolizine (25), 5-Methylene-3-trifluoroacetyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (27): Bromide **24** (345 mg, 0.83 mmol) was transferred to a flask equipped with a reflux condenser and stirrer bar. K_2CO_3 (115 mg, 0.83 mmol) and Pd(PPh$_3$)$_4$ (95 mg, 0.08 mmol, 10 mol-%) were added, and the flask was backfilled thrice with argon. DMF (15 mL) was added and the mixture heated to 100 °C for 3 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude material was subjected to flash chromatography (toluene/hexane, 1:1 → toluene). First to elute was an otherwise pure 1:1 (by ^{1}H NMR) mixture of compounds **26**/**25** (135 mg, 49% combined, R_f = 0.6, in acetone/toluene, 1:19). Next to elute (R_f = 0.4, in acetone/toluene, 1:19) was the tricycle **27** (98 mg, 40% yield) as an off-white solid. M.p. 131–134 °C. The 1:1 mixture of tricycle **25** and tetracycle **26** was separated by using semi-preparative HLPC (MeOH/H$_2$O, 4:1, 4 mL/min) to give pure samples of both compounds.

6-Allyl-5-methylene-3-(trifluoroacetyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (26): Colorless oil (31 mg). R_t = 18.3 min. ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 7.54 (d, J = 7.9 Hz, 1 H, HAr), 7.34 (d, J = 8.3 Hz, 1 H, HAr), 7.20 (t, J = 7.6 Hz, 1 H, HAr), 7.09 (t, J = 7.0 Hz, 1 H, HAr), 6.07–5.96 (m, 1 H, C*H*=CH$_2$), 5.74 (s, 0.6 H, C=CH_2), 5.68 (s, 0.4 H, C=CH_2), 5.45 (s, 0.6 H, C=CH_2), 5.41 (s, 0.4 H, C=CH_2), 5.15–5.10 (m, 1 H, CH=CH_2), 4.87–4.78 (m, 3 H, CH$_2$ and CH=CH_2), 4.60 (s, 0.8 H, CH$_2$), 4.45 (s, 1.2 H, CH$_2$), 4.02–3.96 (m, 2 H, CH$_2$), 3.17 (t, J = 5.8 Hz, CH$_2$) ppm. ^{13}C NMR (125.8 MHz, [D$_6$]acetone): δ = 156.7, 156.6 (q, J = 35.2 Hz, *C*OCF$_3$), 139.1, 138.8 (C), 136.5, 136.3 (C), 135.8, 135.1 (C), 135.65, 135.6 (CH), 128.4, 128.3 (C), 123.5, 123.4 (CH), 121.0, 119.6 (C=*C*H$_2$), 120.5 (CH), 119.5, 119.3 (CH), 117.7, 117.5 (q, J = 287.7 Hz, CF$_3$), 116.2, 116.1 (=*C*H$_2$), 113.3, 112.4 (C-Ar), 111.35, 111.3 (CH), 55.3, 55.0 (q, J = 3.5 Hz), 47.6 (q, J = 3.5 Hz), 46.9, 46.8, 46.3 (3× CH$_2$) 26.6, 23.9 (CH$_2$) ppm. HR-EIMS: calcd. for $C_{18}H_{17}F_3N_2O$ 334.1293; found 334.1288. IR (CHCl$_3$): $\tilde{\nu}$ = 3019, 1686, 1463, 1215, 1149, 927 cm^{-1}.

6-Methylene-3-(trifluoroacetyl)-2,3,4,4a,5,6-hexahydroazepino-[3,4,5-*hi*]benz[*b*]indolizine (25): Colorless oil (31 mg). R_t = 23 min. ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 7.48 (t, J = 8.8 Hz, 1 H, HAr), 7.33, (d, J = 8.1 Hz, 1 H, HAr), 7.15 (t, J = 7.1 Hz, 1 H, HAr), 7.06 (t, J = 7.1 Hz, 1 H, HAr), 5.24–5.20 (m, 2 H, C=CH_2), 4.76 (m, 1 H, 7-H), 4.69 (dt, J = 13.2 and 3.3 Hz, 0.4 H, 2-H), 4.63 (m, 1 H, 7-H), 4.50 (dd, J = 13.0 and 3.1 Hz, 0.6 H, 4-H), 4.33 (m, 0.6 H, 2-H), 4.16 (m, 0.4 H, 4-H), 3.55–3.48 (m, 0.6 H, 2-H), 3.45–3.39 (m, 0.4 H, 4-H), 3.29–3.02 (m, 3 H, 1-H, 4a-H, 2-H, 4-H), 2.92–2.74 (m, 1 H, 1-H), 2.76–2.73 (m, 1 H, 5-H), 2.37–2.29 (m, 1 H, 5-H) ppm. ^{13}C NMR (125.8 MHz, [D$_6$]acetone): δ = 156.6 (q, J = 35.4 Hz, *C*OCF$_3$), 140.8, 140.7 (C), 136.2, 135.8, 135.5 (2× C), 129.0, 128.9 (C), 122.0, 121.9 (CH-Ar), 120.2 (CH-Ar), 118.7, 118.6 (CH-Ar), 117.8 (q, J = 287.7 Hz, CF$_3$), 112.4, 112.3 (C=*C*H$_2$), 110.6, 109.4 (C), 109.65, 109.60 (CH-Ar), 54.7 (q, J = 2.7 Hz), 54.5 (C-4), 50.4 (q, J = 2.8 Hz), 50.1 (C-2), 48.7, 48.6 (C-7), 40.6, 38.2 (C-4a), 35.0, 34.7 (C-5), 27.1, 24.9 (C-1) ppm. HR-EIMS: calcd. for $C_{18}H_{17}F_3N_2O$ 334.1293; found 334.1296. IR (CHCl$_3$): $\tilde{\nu}$ = 3020, 1687, 1472, 1458, 1215, 1168, 1147 cm^{-1}.

5-Methylene-3-(trifluoroacetyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (27): ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 10.30 (s, 1 H,

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NH), 7.54 (dd, J = 4.2 and 8.0 Hz, 1 H, HAr), 7.33 (m, 1 H, HAr), 7.14 (m, 1 H, HAr), 7.03, (t, J = 8.0 Hz, 1 H, HAr), 5.62 (m, 1 H, C=CH_2), 5.32 (s, 1 H, C=CH_2), 5.27 (s, 1 H, C=CH_2), 4.64 (s, 1 H, CH_2), 4.58 (s, 1 H, CH_2), 4.02 (t, J = 5.8 Hz, 1 H, CH_2), 3.95 (t, J = 6.1 Hz, 1 H, CH_2), 3.28 (t, J = 6.1 Hz, 1 H, CH_2), 3.24 (t, J = 6.1 Hz, 1 H, CH_2) ppm. ^{13}C NMR (125.8 MHz, [D$_6$]acetone): δ = 156.9, 156.8 (q, J = 35.3 Hz, COCF$_3$), 138.2, 137.9, 137.6, 137.4 (2 × C), 134.2, 133.4 (C), 129.35, 129.3 (C) 123.8, 123.7 (CH), 120.05, 120.02 (CH) 117.7, 117.5 (q, J = 287.8 Hz, CF_3), 113.7, 112.3 (C), 112.8, 111.7 (C=CH$_2$), 111.8, 111.7 (CH), 52.6 (q, J = 3.5 Hz), 52.0, 50.0, 49.0 (q, J = 3.4 Hz, 2 × CH$_2$), 24.5, 22.8 (CH$_2$) ppm. HR-EIMS: calcd. for $C_{15}H_{13}F_3N_2O$ 294.0980; found 294.0984. IR (KBr): $\tilde{\nu}$ = 3357, 2936, 1668, 1453, 1329, 1207, 1188, 1142, 736 cm^{-1}.

***N*-Allyl-*N*-[2-(1-allyl-2-bromo-1*H*-indol-3-yl)ethyl]-2,2,2-trifluoroacetamide (24), 6-Allyl-5-methylene-3-(trifluoroacetyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (26), 6-Methylene-3-(trifluoroacetyl)-2,3,4,4a,5,6-hexahydroazepino[3,4,5-*hi*]benz[*b*]indolizine (25); *N*-Allyl-*N*-[2-(1-allyl-1*H*-indol-3-yl)ethyl]-2,2,2-trifluoroacetamide (29):** Amide **20** (200 mg, 0.59 mmol) was added to a magnetically stirred suspension of powdered KOH (267 mg, 4.76 mmol), K_2CO_3 (245 mg, 1.77 mmol) and Bu_4NHSO_4 (33 mg, 0.1 mmol) in toluene (6 mL), and the solution was stirred at room temperature for 10 min. The resulting mixture was treated with allyl bromide (320 μL, 447 mg, 3.7 mmol) followed immediately by Pd(PPh$_3$)$_4$ (104 mg, 0.09 mmol, 15 mol-%) and the resulting yellow suspension heated at 60 °C for 40 min. The mixture was cooled to 0 °C and treated dropwise with water (ca. 6 mL) with stirring. The phases were separated, the aqueous phase was extracted with dichloromethane (4 × 4 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was subjected to flash chromatography (toluene/hexane, 2:3 → toluene/hexane, 55:45). First to elute was amide **24** (12 mg, 5% yield). Second to elute was a mixture of compounds **26/25/29** (61 mg) in a ratio (by ^{1}H NMR) of 63:20:17 (colourless oil). Compound **25** was separated by HPLC (MeOH/H_2O, 4:1). R_t = 23 min. Compounds **26** and **29** were separated by HPLC (CH_3CN/H_2O, 7:3). Spectroscopic data for compounds **25**, **26**, and **24** matched those reported previously. Amide **29** (colourless oil): ^{1}H NMR (600.1 MHz, [D$_6$]acetone): δ = 7.67 (d, J = 7.8 Hz, 0.6 H, HAr), 7.59 (d, J = 7.9 Hz, 0.4 H, HAr), 7.38 (t, J = 8.2 Hz, 1 H, HAr), 7.19–7.15 (m, 1.4 H, HAr), 7.11 (s, 0.6 H, HAr), 7.09–7.05 (m, 1 H, HAr), 6.05–5.97 (m, 1 H, CH=CHR$_2$R), 5.90–5.80 (m, 1 H, CH=CH$_2$), 5.30–5.21 (m, 2 H, CH=CH_2), 5.15–5.12 (m, 1 H, CH=CH_2), 5.07–5.02 (m, 1 H, CH=CH_2), 4.80–4.76 (m, 2 H, CH_2), 4.19 (d, J = 5.9 Hz, 0.8 H, CH_2), 4.01 (d, J = 5.9 Hz, 1.2 H, CH_2), 3.73–3.65 (m, 2 H, CH_2), 3.15–3.05 (m, 2 H, CH_2) ppm. ^{13}C NMR (125.8 MHz, [D$_6$]acetone): δ = 156.9, 156.8 (q, J = 35.3 Hz, COCF$_3$), 137.53, 137.50 (C) 135.22, 135.18, 133.6, 132.9 (CH), 128.9, 128.7 (C), 127.2, 127.1 (CH), 122.4, 122.35 (CH), 119.8, 119.7, 119.6, 119.3 (2×CH), 118.8, 118.5 (CH=CH_2), 117.8, 117.6 (q, J = 287.6 Hz, CF_3), 117.0, 116.9 (CH=CH_2), 112.0, 111.3 (C), 110.8, 110.7 (CH), 111.1, 110.9 (CH), 51.0 (q, J = 3.2 Hz), 49.9, 49.05, 49.00, 48.8 (q, J = 3.1 Hz), 48.6 (3 × CH_2), 25.4, 23.2 (CH_2) ppm. HR-EIMS: calcd. for $C_{18}H_{19}F_3N_2O$ 336.1449; found 336.1443. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 1686, 1467, 1215, 1148, 930 cm^{-1}.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for new compounds.

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[23] 3-Bromocyclohexene (technical grade) was purchased from Sigma–Aldrich Australia, https://www.sigmaaldrich.com/australia.html
[24] Compounds **11**, **12**, **14**, **15**, **17**, **22**, **23**, **24**, **25**, **26** and **27** have hindered rotation about the C–N bond due to the partial double-bond character within the amide protecting group. Due to slow site exchange at room temperature a doubling of signals in both the ^{1}H and ^{13}C NMR spectra were observed.
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