Iodine(III)-Mediated Selective Intermolecular C-H Amination for the Chemical Diversification of Tryptamines

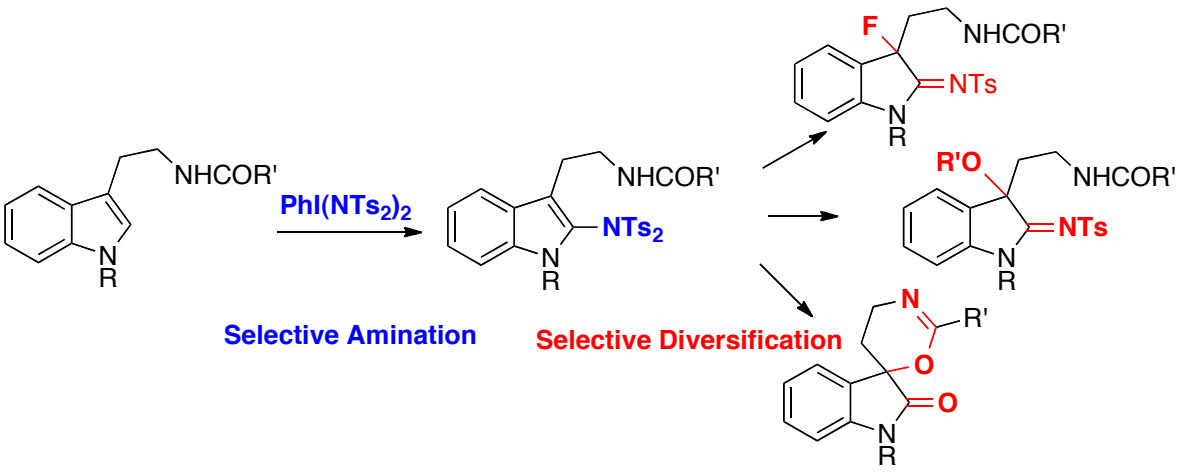
Alexandra E. Bosnidou,[†] Alba Millán,[†] Javier Ceballos,[†] Claudio Martínez[†] and Kilian Muñiz*[†‡]

Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, Av. Països Catalans 16, E-43007 Tarragona (Spain)

ICREA, Pg. Lluís Companys 23, 08010 Barcelona (Spain)

Corresponding Autor. Email: kmuniz@iciq.es

Abstract Graphic/ToC



Abstract

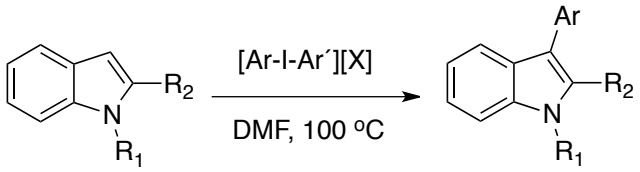
Defined hypervalent iodine reagents of the general structure $PhI[N(SO_2R)SO_2R')]_2$ promote the selective direct C-H-amination of the indole core of various tryptamines. Starting from a general C2-amination strategy, subsequent transformations enable a variety of site-selective functionalizations, which proceed with noteworthy high chemoselectivity and provide an overall access to structurally diversified products.

Introduction

Hypervalent iodine(III) reagents have emerged as versatile tools in modern organic oxidation, where they have contributed to the realization of new chemical transformations.[1,2] The ability of hypervalent iodine(III) reagents to expand synthetic possibilities and their benign reactivity without requirement for metal promoters have stirred particular interest from fields such as pharmaceutical and medicinal chemistry. In these cases, the supply of suitable molecules for biological studies prefers transformations that do not lead to potential contamination by metal-traces.

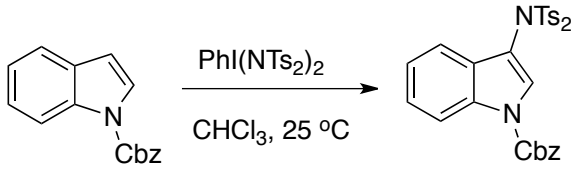
We have recently been interested in the application of iodine(III) compounds as reagents or catalysts for the synthesis of indoles.[3] Within the quest for new oxidative functionalization of indoles, hypervalent iodine reagents have also been employed with certain success in recent years. In particular, (diacetoxy)iodosobenzene ($PhI(OAc)_2$) has enabled interesting transformations such as the direct C3-oxygenation[4] and *trans*-diacetoxylation[5] of N-protected indoles, respectively. Application of alternative hypervalent iodine(III) reagents should provide access to complementary substitution at the indole core. Within this concept, Ackermann disclosed the direct C3-arylation of indoles with diaryliodonium salts (Scheme 1, eq. 1).[6]

Iodine-Mediated Direct 3-Arylation of Indoles:



(1)

Iodine-Mediated Direct 3-Amination of Indoles:



(2)

Scheme 1. Iodine(III)-reagents for the selective 3-functionalization of indoles.

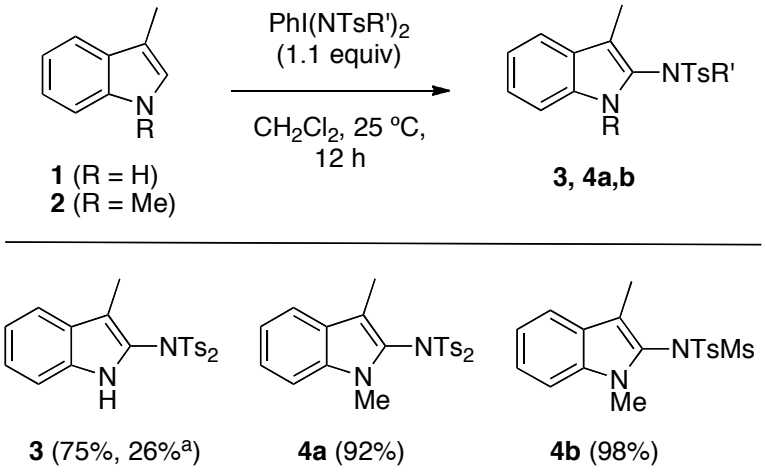
We recently became interested in the application of hypervalent iodine(III) reagents such as $PhI(NTs_2)_2$[7] with preformed iodine-nitrogen bonds as uniquely active promoters for the selective amination of hydrocarbon molecules.[8,9] This chemistry can either be carried out with preformed reagents or through their *in situ* generation, and greatly surpasses the chemistry of related reagents bearing nitrogen groups such as phthalimide and saccharin,[10] which require the presence of metal promoters for amination reactions. It has resulted in the development of direct amination reactions such as allylic,[11,12] acetylenylic,[13] allenylic,[14] and aromatic[15] amination reactions, and the diamination of alkenes[16] and butadienes.[17,18] These reagents also enable the position-selective 3-amination of indoles under metal-free conditions (eq. 2).[3a] A related process was reported using NFSI as aminating agent.[19] Amination of indoles should be considered a particularly interesting topic given the inherent biological diversification that arises from amine incorporation into the aromatic indole core. Consequently, investigation on protocols for additional selective C-N bond formation is highly desirable. We herein report our general results on this topic and

demonstrate that the conceived products can be selectively further diversified into higher-functionalized molecules.

Results and Discussion

For indoles with a substituted 3-position, as demonstrated by the introduction of a methyl substituent, the amination reaction with $PhI(NTs_2)_2$ takes place selectively at the 2-position (Table 1).

Table 1. Selective 2-amination of 3-methyl indoles **1** and **2**.



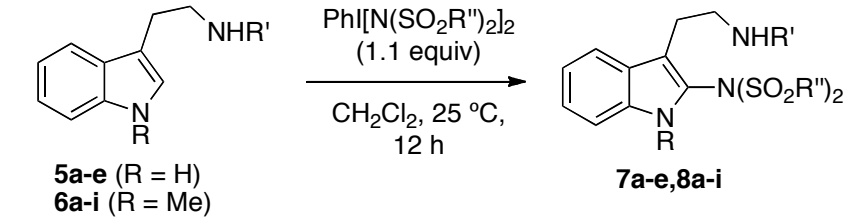
[a] Reaction with $PhI(OAc)_2$/2 $HNTs_2$

The reaction was explored for free 3-methyl indole **1** and its N-methylated derivative **2**, both of which underwent 2-bistosylimidation to the corresponding products **3** and **4a** in good yields. Changing the bissulfonimide group in the hypervalent iodine reagent to mesyltosylimide led to formation of **4b** in excellent yield. As demonstrated for **3** as substrate, a reagent combination of (diacetoxy)iodosobenzene and bistosylimide for *in situ*

formation of $PhI(NTs_2)_2$ gives inferior results, which is due to the high reactivity of the indole core. It also appears that N-protected indoles give higher yields, possibly due to non-productive reactivity of the N-H bond in **1**, while **2** reacts with complete selectivity. The successful formation of **3** and **4a,b** add to recent work on iodine-mediated 2-amination of indoles[19] and to a recent non-related 2-selective amination at the free indole core by Togo, who employed our $PhI(OAc)_2/HNTs_2$ reagent combination.[20-22]

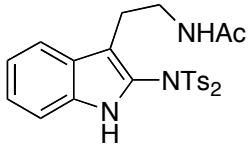
Aiming for a higher functional derivatization, we turned attention to tryptamines as the starting point for structural diversification within amination with hypervalent iodine reagents. In the field of tryptamine alkaloids, the hexahydropyrroloindole derivatives derived from intramolecular 2-amination represent common entities that constitute a fascinating class of natural products.[24] Tryptamine and derivatives thereof have therefore been of interest for the exploration of oxidative transformations. Interestingly, the parent oxidant (diacetoxy)iodosobenzene is known to enable aminooxygenation of *N*-acetyl tryptamine to form the corresponding 2-acetoxylated fused pyrrolidine products.[25] In another reaction, we had reported a single example that unlike this reagent, $PhI(NTs_2)_2$ does not provide the corresponding diamination reaction, but rather provides access to the corresponding 2-aminated tryptamine product.[7]

Table 2. Intermolecular 2-amination of tryptamines: scope

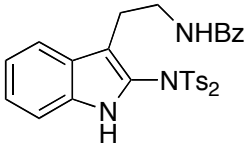


5a-e (R = H)
6a-i (R = Me)

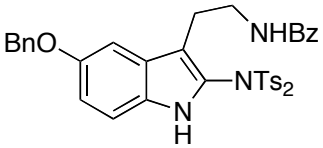
7a-e,8a-i



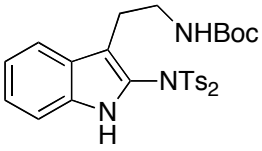
7a (88%)



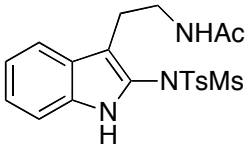
7b (63%)



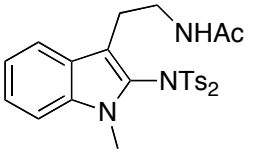
7c (79%)



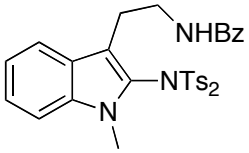
7d (50%)



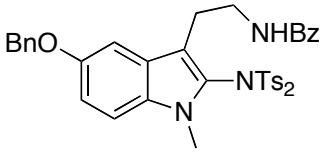
7e (62%)



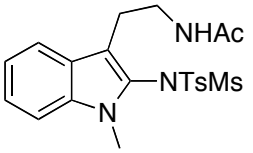
8a (99%)



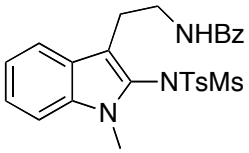
8b (92%)



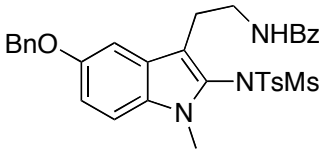
8c (95%)



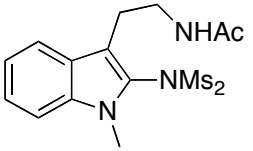
8d (87%)



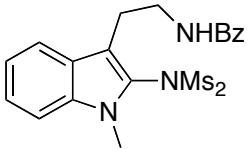
8e (90%)



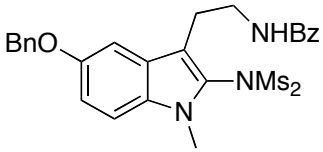
8f (92%)



8g (71%)



8h (77%)

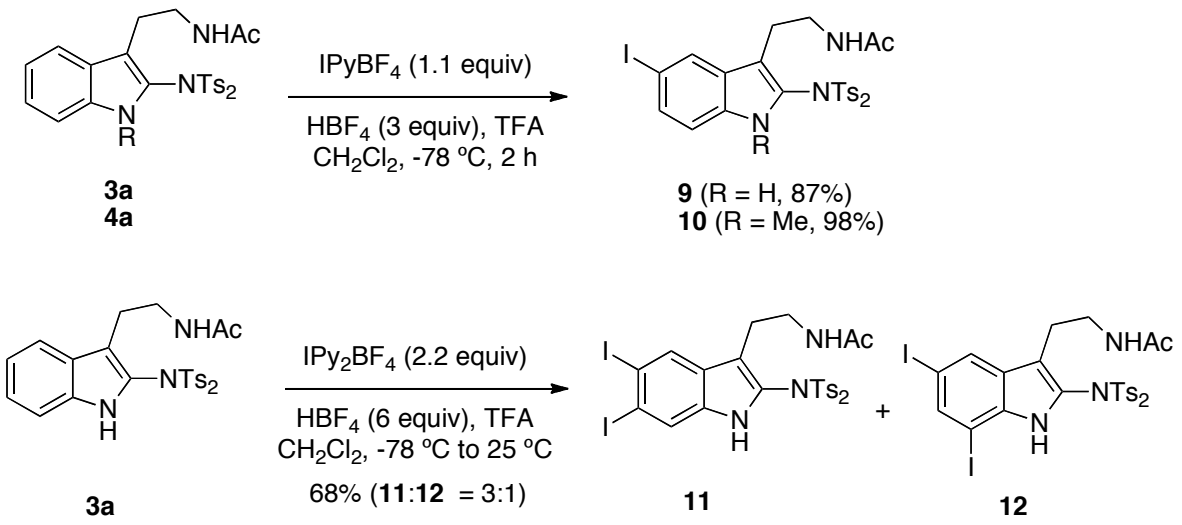


8i (80%)

Efficient reactions for intermolecular 2-aminations of tryptamines are apparently rare, since they require overriding the intramolecular cyclization event. We therefore investigated the scope of such a transformation and discovered that the reaction is of general applicability.

As outlined in Table 2 for 14 examples, differently substituted tryptamines, either free (**5a-e**) or methylated (**6a-i**) at the aromatic nitrogen, underwent clean 2-amination with complete selectivity in favor of the intermolecular pathway. Transferred nitrogen groups include bistosylimide, bismesylimide and mesyltosylimide alike and the reaction follows the feature from Table 1 that N-protected tryptamines (71-99% isolated yield) give higher yields that the one with free N-H group (50-88% isolated yield).

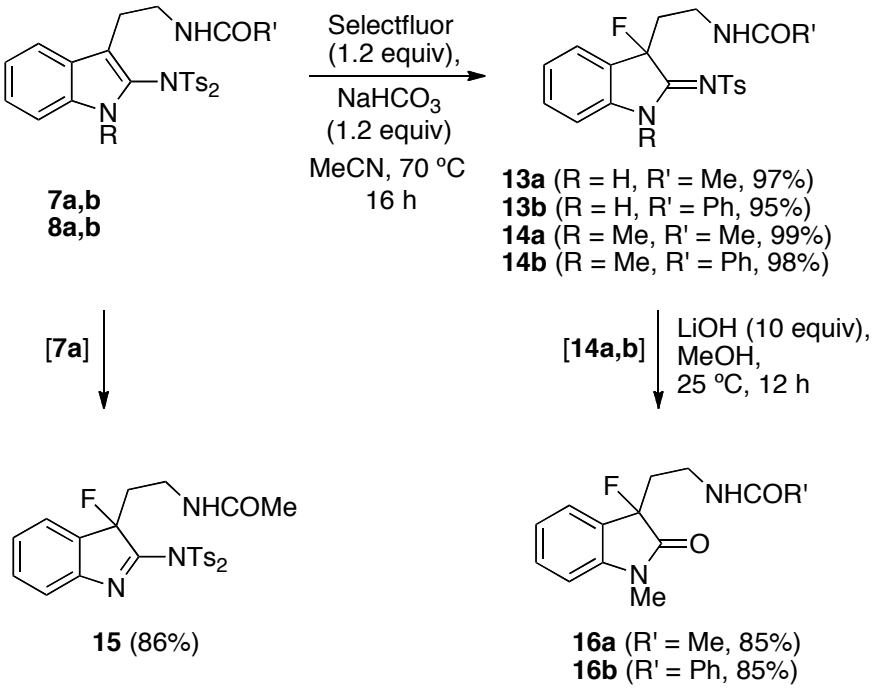
The formed 2-aminated tryptamine derivatives should represent interesting starting points for additional amination/cyclization under electrophilic conditions.[24] Such a process appeared of interest and was briefly addressed experimentally. At the outset, electrophilic iodonium generated from established IPy_2BF_4[26] was investigated. Despite experimental variation, the desired iodoamination was never accomplished. Obviously, the size of the bissulfonylimido group at the 2-position of the substrate exercises significant steric shielding of both faces of the C2-C3-double bond of the indole thus preventing electrophilic activation, even with an iodonium of enhanced electrophilicity. Instead, position-selective iodination of the arene core was observed as demonstrated for the reactions of **7a** and **8a** yielding **9** and **10** in very good to quantitative yield, respectively (Scheme 2).[27] Forcing the reaction with higher amounts of reagent, additional arene iodination took place at the 6- and the 7-position of **7a**, respectively.[27] Particularly the latter is an interesting outcome, since functionalization at the 7-position of the indole is usually complicated.[28] Other common iodonium precursors such as NIS or hypervalent iodine reagents such as bis(trifluoroacetoxy)iodosobenzene[10a,b] led to no conversion.



Scheme 2. Iodination of 2-aminated tryptamines **7a**, **8a**.

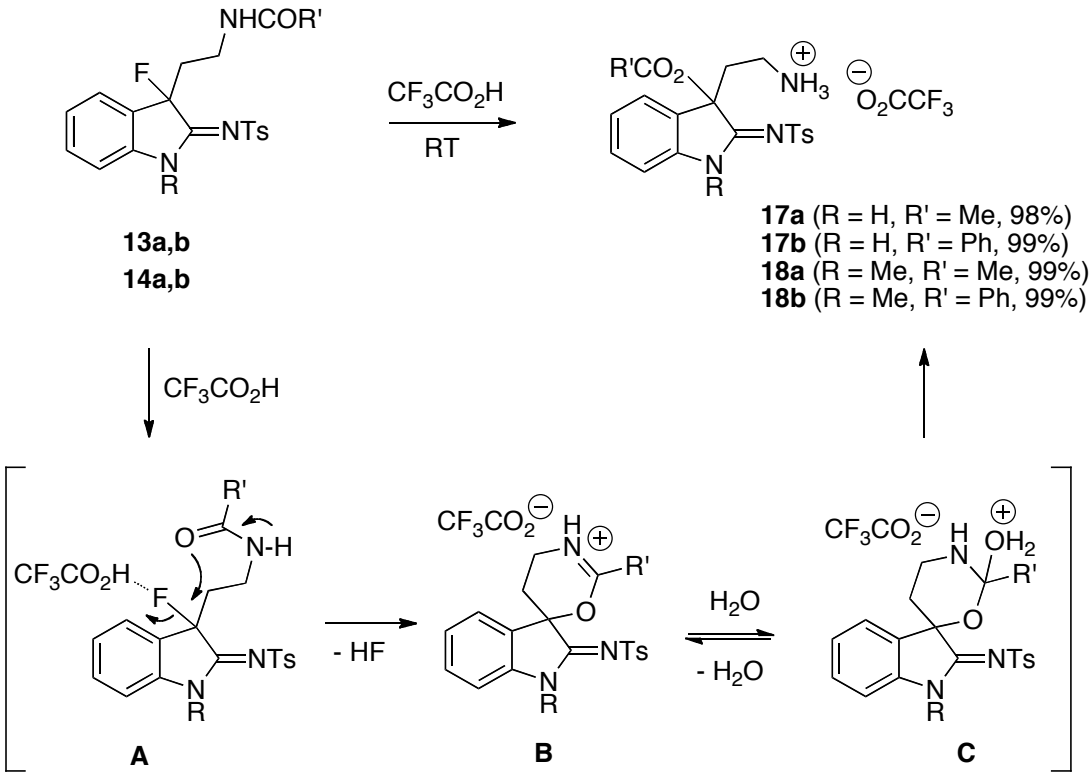
In order to investigate a smaller electrophile, attention was turned to electrophilic fluorination. To this end, a recent report from Gouvernor on fluoroamination of tryptamines using Selectfluor set the basis to investigate a possible cyclization.[29a] Although the reported requirement for cinchona alkaloids shut down any reactivity for the present cases, exposing compounds **7a,b** and **8a,b**, respectively, to the presence of Selectfluor and base, resulted in clean fluorination.[29] However, despite several attempts no accompanying cyclization could be accomplished, but rather detosylation to result in an imino group at C2 to produce the so far unknown amidine products **13a,b** and **14a,b** (Scheme 3). Under these conditions, products **13a,b** and **14a,b** were obtained in almost quantitative yields. These transformations were considered to involve an initial participation of the lone pair of the nitrogen of the indole core. This assumption could be confirmed when the reaction of **7a** was conducted for a shorter period of time, which led to the isolation of compound **15** as

the major product in 86% yield. Exposure of **15** to an additional period of heating in acetonitrile led to unprecedented detosylation and formation of **13a** as the only product.



Scheme 3. Chemical transformation of compounds **7a,b** and **8a,b** upon electrophilic fluorination.

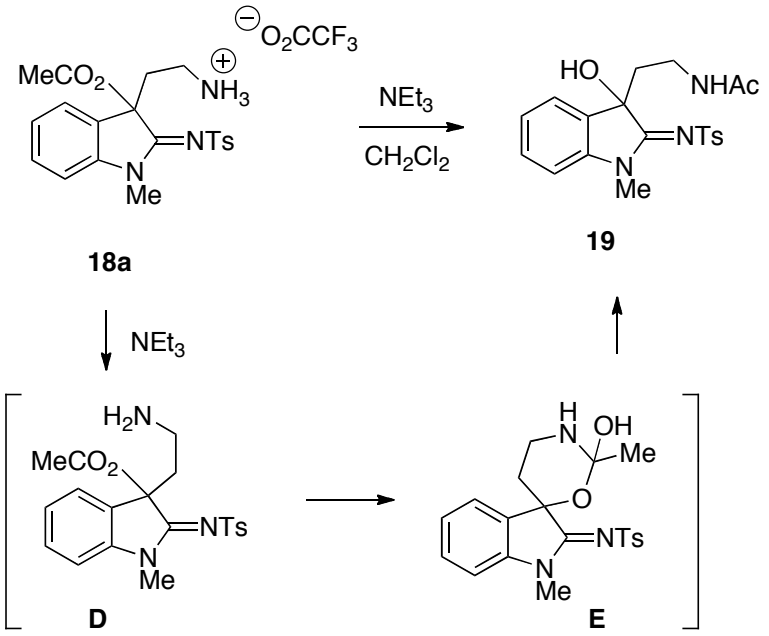
The treatment of **14a,b** with lithium hydroxide in methanol provided conditions for a clean hydrolysis of their tosylimido groups leading to their conversion into the corresponding new oxindole derivatives **16a,b**. Again, this transformation is of complete selectivity and the two compounds are isolated as the only products in 85% yield each. When fluorinated compounds **13a,b** and **14a,b** were exposed to acidic conditions with neat trifluoroacetic acid (TFA), clean defluorination was observed (Scheme 4).



Scheme 4. Chemical transformation of compounds **13a,b** and **14a,b**.

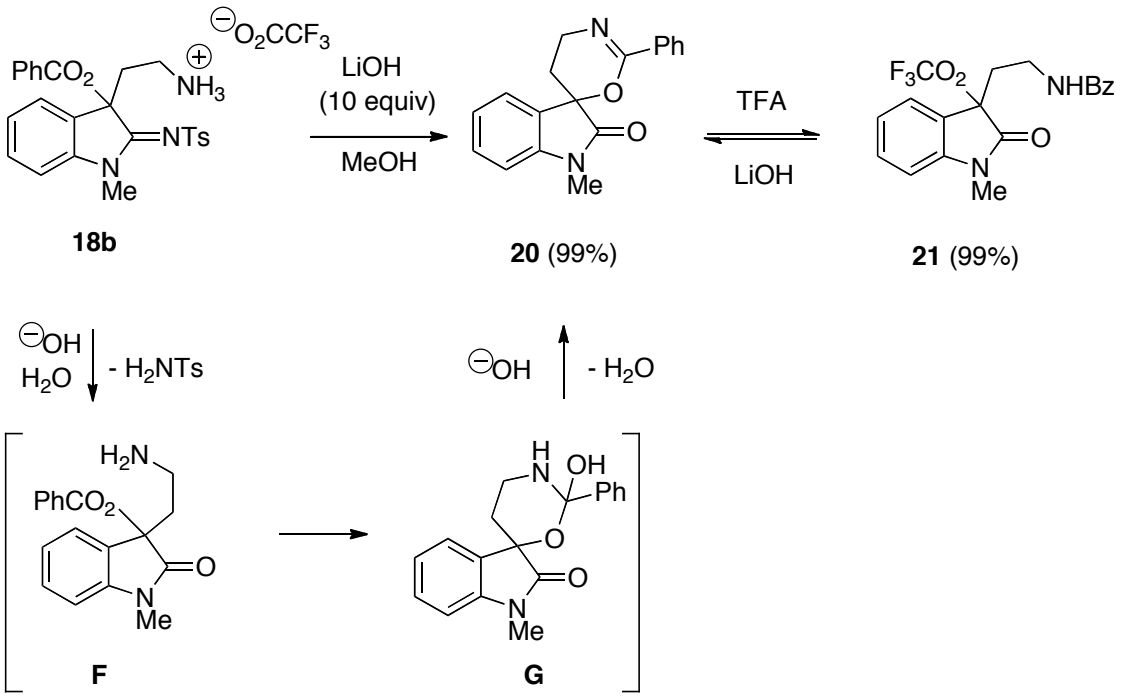
These conditions led to nucleophilic substitution by the *N*-acetyl and *N*-benzoyl groups from the ethylenylamine side chain at the benzylic position. Upon exposure to moisture during crystallization, they converted in quantitative yields into the benzylic esters **17a,b** and **18a,b**, respectively, bearing an ammonium trifluoroacetate group in the side chain.[16] This overall transformation initiates from **A** upon activation of the benzylic fluoride in the presence of TFA as a strong acid, thereby greatly enhancing its leaving group quality. Subsequently, intermediate **B** forms via intramolecular nucleophilic substitution followed by reversible addition of water to **C**, from which an intramolecular proton shift afford the products. Note that in the presence of basic conditions, compounds **13a,b** and **14a**,**b** retain the benzylic fluoride moiety. Exposure of products **17a,b** and **18a,b** to basic conditions

affords additional diversification (Scheme 5). Treatment with triethylamine generates a free primary amine **D** from **17a**, which initiates quantitative intramolecular acetyl transfer via the tetrahedral intermediate **E** to reestablish the acetamide side chain and provides a benzylic hydroxyl group in **19**.[27]



Scheme 5. Chemical transformation of compound **18a** to **19**.

In contrast, treatment with stronger LiOH base promotes the expected oxindole formation together with the installment of a *spiro*-dihydrooxazine functionality in **20**.[27] Again, this multiple transformation starts from liberation of the free primary amine **F** and proceeds through the corresponding tetrahedral intermediate **G** with complete selectivity and in quantitative isolated yield (Scheme 6).



Scheme 6. Chemical transformation of compound **18b** to **21**.

In the presence of TFA, compound **20** undergoes quantitative opening of the spiro-cyclic arrangement upon concomitant addition of one molecule of TFA to furnish **21** with its benzoylamide side chain and a benzylic trifluoroacetate ester. Exposure to LiOH reverts **21** back to **20** in essentially quantitative manner. These transformations provide access to a unique number of new tryptamine derivatives. In view of the general occurrence of the 3-(aminoethyl)-3-hydroxyoxindole motif (Figure 1),[30] our new methodology provides unique access to derivatives of this core, and to the additional, yet biologically unexplored classes of 2-imido and allosteric 3-fluoro[30] derivatives.

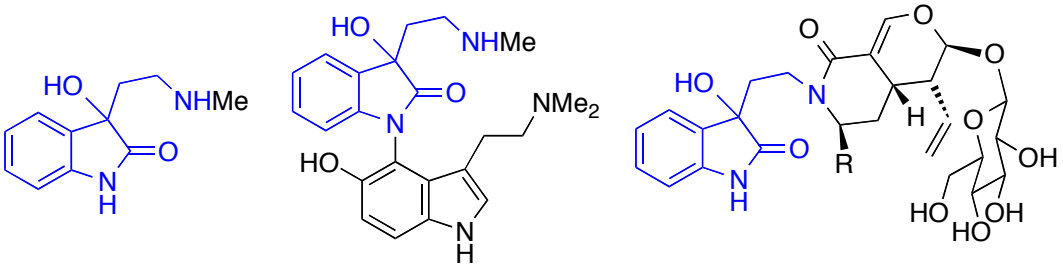


Figure 1. Examples for naturally occurring 3-(aminoethyl)-3-hydroxyoxindoles.

In summary, we have developed a general strategy to intermolecular C2-amination of indoles and tryptamines. This transformation proceeds selectively in the presence of hypervalent iodine reagents of the general formula PhI[N(SO_2R)(SO_2R')]. The corresponding products undergo oxidative fluorination under parallel desulfonylation to provide a new class of tryptamine derivatives. These compounds initiate a number of remarkable transformations, with and without interplay by the ethylenamine side chain. As a result, a higher degree of structural variation is now available for tryptamine derivatives providing building blocks for future exploration.

Experimental Section

General Remarks

Chemicals and solvents for chromatography were used as received. Solvents were obtained from a solvent purification system. Reactions that were monitored by TLC were visualized by a dual short wave/long wave UV lamp. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded using an internal deuterium lock on a 300 or a 500 MHz spectrometer. All chemical shifts

in NMR experiments are reported as ppm downfield from TMS. *J* couplings are reported in hertz. The following calibrations were used: $CDCl_3$ δ = 7.26 and 77.0 ppm, CD_2Cl_2 δ = 5.32 and 54.00 ppm, MeOD δ = 3.31 and 49.0 ppm. Infrared spectra were taken in the solid state and were recorded on a FT-IR fitted with an ATR accessory. Absorptions are given in wavenumbers (cm^{-1}). High resolution mass spectra were obtained on a HRMS-TOF spectrometer.

The following compounds were purchased form commercial suppliers and used as received: tryptamine, 5-benzyloxytryptamine, tosyl chloride, mesyl chloride, triethylamine, acetyl chloride, benzoyl chloride, methyl iodide, trifluoroacetic acid, lithium hydroxide, di(acetoxy)iodobenzene, bis(pyridine)iodonium tetrafluoroborate, tetrafluoroboric acid diethyletherate, Selectfluor® and 3-methylindole (**1**). The following compounds were synthesized according to literature procedures: **2**,[32] **5a**,[33] **5b**,[7] **5c**,[34] **5d**,[35] **6a**,[33] and **6b**.[33]

***N*-(2-(5-(Benzyloxy)-1-methyl-1*H*-indol-3-yl)ethyl)benzamide 6c.** A mixture of the indole **5c**[33] (0.18 g, 0.5 mmol, 1.0 equiv), NaOH (0.06 g, 1.5 mmol, 3 equiv) and Bu_4NOH (8 mg, 0.025 mmol, 5% mol) in CH_2Cl_2 (5 mL), was stirred at 25 ^oC for 10 min. MeI (0.08 g, 0.55 mmol, 1.1 equiv) was added into the reaction mixture at 25 ^oC. The reaction mixture was stirred for 12h. The reaction mixture was quenched with aqueous solution of 10% HCl and then with aqueous saturated solution of $NaHCO_3$ and was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, MeOH/CH_2Cl_2, 0.2/10, v/v) to afford the pure product (0.096 g, 50% yield, colorless oil). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.95 (t, *J* = 6.6 Hz, 2H), 3.63-3.70 (m, 5H), 3.79 (td, *J* = 6.8, 6.1 Hz,

2H), 4.91 (s, 2H), 6.22 (s, 1H), 6.80 (s, 1H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.22-7.36 (m, 8H), 7.58-7.61 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 25.3 (CH_2), 32.8 (CH_3), 40.7 (CH_2), 71.0 (CH_2), 102.3, 110.2, 111.2, 112.8, 126.9, 127.5, 127.7, 127.8, 128.1, 128.5, 128.6, 131.3, 132.7, 134.7, 137.6, 153.1, 167.4 (C=O). IR ν(cm^{-1}): 3316 (N-H), 3029 (Ar-H), 2926 (Ar-H), 2860 (Ar-H), 1625 (C=O), 1542, 1488, 1462, 1317, 1218, 1198, 1021, 795, 695. HRMS (ESI-TOF): calcd. for $C_{25}H_{25}N_2O_2$: 385.1911; found: 385.1914.

General procedure for amination reaction indoles and tryptamines. To a solution of the corresponding starting material (0.2 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added the corresponding iodine(III) reagent (0.22 mmol, 1.1 equiv) and the mixture was stirred at 25 ºC for 12 h. After that time, the solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (silica gel, MeOH/CH_2Cl_2, 0.2/10, v/v) to obtain the pure product.

4-Ethyl-*N*-(3-methyl-1*H*-indol-2-yl)-*N*-tosylbenzenesulfonamide 3. 70 mg, 75% yield, white solid. m.p. = 164-165 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (s, 3H), 2.48 (s, 6H), 7.14 (m, 1H), 7.28-7.31 (m, 2H), 7.34 (d, *J* = 7.7 Hz, 4H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.82 (brs, 1H), 7.86 (d, *J* = 8.4 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.0 (CH_3), 21.8 (CH_3), 111.4, 115.6, 119.9, 120.0, 122.7, 124.1, 127.5, 128.6, 129.7, 135.0, 136.4, 145.3. IR ν(cm^{-1}): 3385 (N-H), 2956 (Ar-H), 2923 (Ar-H), 2851 (Ar-H), 1595, 1372, 1345, 1169, 1082, 881, 657, 549. HRMS (ESI-TOF): calcd. for $C_{23}H_{21}N_2O_4S_2$: 453.0943; found: 453.0927.

***N*-(1,3-Dimethyl-1*H*-indol-2-yl)-4-methyl-*N*-tosylbenzenesulfonamide 4a.** 85 mg, 92% yield, brown solid. m.p. = 194-196 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 3H), 2.40 (s, 6H), 3.19 (s, 3H), 7.03-7.08 (m, 1H), 7.15-7.23 (m, 2H), 7.26 (d, *J* = 7.7 Hz, 4H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 8.7 (CH_3), 21.8 (CH_3), 29.5 (CH_3), 109.8, 113.8, 119.4, 120.0, 123.7, 124.6, 126.4, 129.0, 129.7, 136.0, 136.4, 145.5. IR ν(cm^{-1}): 3055 (Ar-H), 2922 (Ar-H), 1594, 1469, 1372, 1357, 1166, 1084, 878, 738. HRMS (ESI-TOF): calcd. for $C_{24}H_{24}N_2NaO_4S_2$: 491.1070; found 491.1065.

***N*-(1,3-dimethyl-1*H*-indol-2-yl)-4-methyl-*N*-(methylsulfonyl)benzenesulfonamide 4b.** 76 mg, 98% yield, yellow solid. m.p. = 189-191 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01 (s, 3H), 2.49 (s, 3H), 3.44 (s, 3H), 3.61 (s, 3H), 7.14-7.19 (m, 1H), 7.24-7.32 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 8.8 (CH_3), 21.8 (CH_3), 29.4 (CH_3), 44.4 (CH_3), 109.8, 113.5, 119.5, 120.0, 123.8, 126.3, 129.2, 129.7, 135.1, 135.9, 145.9. IR ν(cm^{-1}): 3055 (Ar-H), 2931 (Ar-H), 1469, 1369, 1354, 1163, 1121, 1087, 966, 872, 737. HRMS (ESI-TOF): calcd. for $C_{18}H_{20}N_2NaO_4S_2$: 415.0757; found 415.0743.

***N*-(2-(2-(4-Methyl-N-tosylphenylsulfonamido)-1*H*-indol-3-yl)ethyl)acetamide 7a**. 87 mg, 83% yield, white solid. m.p. = 170-171 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79 (s, 3H), 2.16-2.20 (t, *J* = 6.7, 2H), 2.48 (s, 6H), 3.53 (td, *J* = 6.2, 5.8 Hz, 2H), 6.24 (brs, 1H), 7.13-7.17 (m, 1H), 7.28-7.35 (m, 2H), 7.36 (d, *J* = 8.1 Hz, 4H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 4H), 8.30 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 22.9

(CH_3), 23.0 (CH_2), 38.6 (CH_2), 111.8, 116.2, 120.3, 120.4, 123.4, 124.5, 126.4, 128.7, 129.9, 135.2, 135.8, 145.9, 170.4 (C=O). IR ν(cm^{-1}): 3376 (N-H), 3257 (N-H), 2922 (Ar-H), 1659 (C=O), 1536, 1377, 1353, 1167, 876, 773, 659, 540. HRMS (ESI-TOF): calcd. for $C_{26}H_{27}N_3O_5NaS_2$: 548.1290, found: 548.1277.

***N*-(2-(2-(4-Methyl-*N*-tosylphenylsulfonamido)-1*H*-indol-3-yl)ethyl)benzamide 7b**.[7] 74 mg, 63% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (t, *J* = 6.7 Hz, 2H), 2.47 (s, 6H), 3.73 (td, *J* = 6.7, 5.1 Hz, 2H), 6.67 (brs, 1H), 7.10-7.15 (m, 1H), 7.28-7.39 (m, 9H), 7.66-7.69 (m, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 4H), 8.02 (brs, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.2 (CH_2), 39.3 (CH_2), 111.7, 116.3, 120.4, 120.7, 123.2, 124.5, 126.6, 127.1, 128.2, 128.7, 129.9, 131.1, 134.4, 135.1, 135.9, 145.8, 167.7 (C=O).

***N*-(2-(5-(Benzyloxy)-2-(4-methyl-*N*-tosylphenylsulfonamido)-1*H*-indol-3-yl)ethyl)benzamide 7c**. 110 mg, 80% yield, brown solid. m.p. = 109-111 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (t, *J* = 6.6 Hz, 2H), 2.48 (s, 6H), 3.70 (td, *J* = 6.6, 5.2 Hz, 2H), 4.94 (s, 2H), 6.65 (t, *J* = 5.2 Hz, 1H), 7.00 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 8.9 Hz, 1H), 7.30-7.43 (m, 12H), 7.68-7.70 (m, 2H), 7.85-7.88 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.2 (CH_2), 39.2 (CH_2), 70.6 (CH_2), 103.0, 112.6, 116.0, 116.2, 123.6, 127.1, 127.8, 127.8, 128.3, 128.5, 128.7, 130.0, 130.2, 130.3, 131.1, 134.4, 135.9, 137.2, 137.5, 145.8, 153.6, 167.6 (C=O). IR ν(cm^{-1}): 3384 (N-H), 3191 (Ar-H), 3059 (Ar-H), 2922 (Ar-H), 1640 (C=O), 1579, 1485, 1376, 1187, 1165, 1083, 882. HRMS (ESI-TOF): calcd. for $C_{38}H_{35}N_3NaO_6S_2$: 716.1859; found: 716.1863.

***tert*-Butyl(2-(2-(4-methyl-*N*-tosylphenylsulfonamido)-1*H*-indol-3-yl)ethyl)carbamate 7d.** 58 mg, 50% yield, yellow solid. m.p. = 102-107 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 2.26 (t, *J* = 7.2 Hz, 2H), 2.48 (s, 6H), 3.24-3.29 (m, 2H), 4.73 (brs, 1H), 7.12-7.16 (m, 1H), 7.28-7.30 (m, 2H), 7.35 (d, *J* = 7.9 Hz, 4H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 4H), 7.99 (brs, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.7 (CH_3), 24.2 (CH_2), 28.4 (CH_3), 39.8 (CH_2), 78.8, 111.5, 116.6, 120.1, 120.7, 122.9, 124.2, 126.7, 128.7, 129.8, 135.0, 136.0, 145.6, 155.9 (C=O). IR ν(cm^{-1}): 3294 (N-H), 2927 (Ar-H), 1632 (C=O), 1580, 1470, 1282, 1145, 1082, 770, 751, 671, 545, 461. HRMS (ESI-TOF): calcd. for $C_{29}H_{33}N_3O_6NaS_2$: 606.1708, found: 606.1690.

***N*-(2-(2-(4-Methyl-*N*-(methylsulfonyl)phenylsulfonamido)-1*H*-indol-3-yl)ethyl)acetamide 7e.** 52 mg, 58% yield, yellow solid. m.p. = 166-172 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.83 (s, 3H), 2.28-2.36 (m, 1H), 2.48 (s, 3H), 2.58-2.64 (m, 1H), 3.57 (td, *J* = 6.1, 5.5 Hz, 2H), 3.64 (s, 3H), 6.02 (s, 1H), 7.15-7.18 (m, 1H), 7.31-7.35 (m, 4H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 8.10 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.0 (CH_2), 23.3 (CH_3), 38.6 (CH_2), 44.2 (CH_3), 111.8, 115.3, 120.2, 120.3 122.8, 124.4, 126.2, 128.9, 129.9, 134.6, 135.1, 146.2, 170.7 (C=O). IR ν(cm^{-1}): 3358 (N-H), 2928 (Ar-H), 2880 (Ar-H), 1646 (C=O), 1550, 1369, 1347, 1165, 976, 877, 744, 664, 520. HRMS (ESI-TOF): calcd. for $C_{20}H_{23}N_3O_5NaS_2$: 472.0966, found: 472.0977.

***N*-(2-(1-Methyl-2-((4-methyl-*N*-tosylphenyl)sulfonamido)-1*H*-indol-3-yl)ethyl)acetamide 8a.** 107 mg, 99% yield, yellow solid. m.p. = 189-190 ºC. ^{1}H NMR (400

MHz, $CDCl_3$): δ = 1.82 (s, 3H), 2.25 (t, *J* = 6.5 Hz, 2H), 2.53 (s, 6H), 3.36 (s, 3H), 3.57-3.61 (m, 2H), 6.20 (brs, 1H), 7.17-7.20 (m, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.36-7.39 (m, 1H), 7.40 (d, *J* = 7.8 Hz, 4H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.0 (CH_3), 23.7 (CH_2), 30.0 (CH_3), 38.8 (CH_2), 110.2, 114.7, 120.0, 120.6, 124.1, 125.1, 125.5, 129.2, 129.8, 135.8, 136.3, 146.0, 170.3 (C=O). IR ν(cm^{-1}): 3399 (N-H), 3059 (Ar-H), 2928 (Ar-H), 1652 (C=O), 1595, 1534, 1471, 1431, 1373, 1358, 1166, 1083, 1017. HRMS (ESI-TOF): calcd. for $C_{27}H_{30}N_3O_5S_2$: 540.1621; found: 540.1630.

***N*-(2-(1-Methyl-2-(4-methyl-*N*-tosylphenyl)sulfonamido)-1*H*-indol-3-yl)ethyl)benzamide 8b.** 110 mg, 92% yield, yellow solid. m.p. = 178-180 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46 (t, *J* = 6.9 Hz, 2H), 2.51 (s, 6H), 3.28 (s, 3H), 3.83 (td, *J* = 6.9, 5.1 Hz, 2H), 6.70 (t, *J* = 5.0 Hz, 1H), 7.15-7.18 (m, 1H), 7.28-7.30 (m, 1H), 7.33-7.36 (m, 3H), 7.39-7.44 (m, 5H), 7.70-7.73 (m, 2H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.9 (CH_2), 29.8 (CH_3), 39.5 (CH_2), 110.1, 114.6, 120.0, 120.9, 124.0, 125.1, 125.6, 127.0, 128.2, 129.1, 129.8, 131.0, 134.5, 135.9, 136.2, 145.9, 167.6 (C=O). IR ν(cm^{-1}): 3242 (N-H), 3069 (Ar-H), 2923 (Ar-H), 1630 (C=O), 1549, 1492, 1470, 1386, 1357, 1334, 1169, 1084, 1016. HRMS (ESI-TOF): calcd. for $C_{33}H_{27}N_7NaOS_2$: 624.1611; found: 624.1612.

***N*-(2-(5-(Benzyloxy)-1-methyl-2-(4-methyl-*N*-tosylphenylsulfonamido)-1*H*-indol-3-yl)ethyl)benzamide 8c**. 133 mg, 95% yield, orange solid. m.p. = 168-170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (t, *J* = 6.7 Hz, 2H), 2.51 (s, 6H), 3.26 (s, 3H), 3.80 (td, *J* = 6.8,

5.2 Hz, 2H), 5.02 (s, 2H), 6.68 (t, *J* = 5.2 Hz, 1H), 7.08 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.20 (d, *J* = 8.9 Hz, 1H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.33-7.42 (m, 10H), 7.46-7.48 (m, 2H), 7.71-7.73 (m, 2H), 7.91-7.93 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.9 (CH_2), 29.9 (CH_3), 39.4 (CH_2), 70.7 (CH_2), 103.1, 111.1, 114.2, 125.2, 125.8, 127.0, 127.1, 127.7, 127.8, 128.3, 128.4, 128.5, 129.1, 129.8, 129.9, 131.1, 131.6, 134.5, 135.9, 137.3, 145.9, 153.4, 167.6 (C=O). IR ν(cm^{-1}): 3395 (N-H), 3032 (Ar-H), 2924 (Ar-H), 1645 (C=O), 1596, 1487, 1374, 1166, 1083, 1019, 872. HRMS (ESI-TOF): calcd. for $C_{39}H_{37}N_3NaO_6S_2$: 730.2016; found: 730.2048.

***N*-(2-(1-Methyl-2-((4-methyl-*N*-(methylsulfonyl)phenyl)sulfonamido)-1*H*-indol-3-yl)ethyl)acetamide 8d**. 80 mg, 87% yield, yellow solid. m.p. = 119-121 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (s, 3H), 2.39-2.44 (m, 1H), 2.50 (s, 3H), 2.68-2.73 (m, 1H), 3.39 (s, 3H), 3.54-3.60 (m, 1H), 3.62-3.68 (m, 1H), 3.73 (s, 3H), 5.95 (s, 1H), 7.17-7.20 (m, 1H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.35-7.37 (m, 3H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.0 (CH_3), 24.1 (CH_2), 29.5 (CH_3), 38.9 (CH_2), 44.6 (CH_3), 110.2, 114.4, 120.1, 120.4, 124.2, 124.6, 125.3, 129.2, 129.9, 134.5, 136.2, 146.3, 170.4 (C=O). IR ν(cm^{-1}): 3316 (N-H), 3017 (Ar-H), 2982 (Ar-H), 2936 (Ar-H), 1642 (C=O), 1549, 1448, 1368, 1355, 1345, 1295, 1167, 1087. HRMS (ESI-TOF): calcd. for $C_{21}H_{25}N_3NaO_5S_2$: 486.1128; found: 486.1135.

***N*-(2-(1-Methyl-2-(4-methyl-*N*-(methylsulfonyl)phenyl)sulfonamido)-1*H*-indol-3-yl)ethyl)benzamide 8e**. 94 mg, 90% yield, yellow solid. m.p. = 182-184 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48 (s, 3H), 2.57-2.67 (m, 1H), 2.81-2.90 (m, 1H), 3.36 (s, 3H), 3.66 (s,

3H), 3.81-3.89 (m, 2H), 6.55 (s, 1H), 7.14-7.19 (m, 2H), 7.30-7.39 (m, 5H), 7.42-7.45 (m, 1H), 7.68-7.71 (m, 2H), 7.75-7.80 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 24.4 (CH_2), 29.4 (CH_3), 39.6 (CH_2), 44.5 (CH_3), 110.1, 114.4, 120.1, 120.6, 124.1, 124.5, 125.4, 127.1, 128.3, 129.2, 129.9, 131.2, 134.4, 134.6, 136.2, 146.3, 167.7 (C=O). IR ν(cm^{-1}): 3300 (N-H), 3043 (Ar-H), 2929 (Ar-H), 1636 (C=O), 1598, 1579, 1538, 1488, 1470, 1429, 1356, 1309, 1165, 1086. HRMS (ESI-TOF): calcd. for $C_{26}H_{27}N_3NaO_5S_2$: 548.1284; found: 548.1291.

***N*-(2-(5-(Benzyloxy)-1-methyl-2-(4-methyl-*N*-(methylsulfonyl)phenyl sulfonamido)-1*H*-indol-3-yl)ethyl)benzamide 8f**. 115 mg, 92% yield, orange solid. m.p. = 146-148 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.49 (s, 3H), 2.52-2.62 (m, 1H), 2.77-2.87 (m, 1H), 3.34 (s, 3H), 3.66 (s, 3H), 3.83 (td, *J* = 6.6, 6.0 Hz, 2H), 5.04 (q, *J* = 11.4 Hz, 2H), 6.53 (t, *J* = 5.5 Hz, 1H), 7.07 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.20 (d, *J* = 8.9 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.34-7.47(m, 10H), 7.69-7.72 (m, 2H), 7.80 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 24.4 (CH_2), 29.6 (CH_3), 39.6 (CH_2), 44.5 (CH_3), 70.7 (CH_2), 103.0, 111.1, 113.9, 115.7, 124.6, 125.6, 127.1, 127.7, 128.4, 128.5, 129.2, 129.9, 131.2, 131.6, 134.4, 134.6, 136.2, 137.2, 146.3, 167.6 (C=O). IR ν(cm^{-1}): 3410 (N-H), 3033 (Ar-H), 2928 (Ar-H), 1648 (C=O), 1486, 1370, 1353, 1163, 1086, 1025, 966, 873. HRMS (ESI-TOF): calcd. for $C_{33}H_{33}N_3NaO_6S_2$: 654.1703; found: 654.1709.

***N*-(2-(1-Methyl-2-(*N*-(methylsulfonyl)methylsulfonamido)-1*H*-indol-3-yl)ethyl)acetamide 8g**. 54 mg, 71% yield, white solid. m.p. = 209-210 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (s, 3H), 3.06 (t, *J* = 7.1 Hz, 2H), 3.55 (s, 6H), 3.74-3.78 (m, 5H),

5.99 (s, 1H), 7.19-7.23 (m, 1H), 7.36-7.41 (m, 2H), 7.73 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.1 (CH_3), 25.1 (CH_2), 29.8 (CH_3), 38.9 (CH_2), 43.3 (CH_3), 110.2, 114.0, 120.3, 120.4, 124.1, 124.4, 125.3, 136.3, 170.4 (C=O). IR ν(cm^{-1}): 3425 (N-H), 3023 (Ar-H), 3002 (Ar-H), 2942 (Ar-H), 2923 (Ar-H), 1663 (C=O), 1531, 1469, 1361, 1347, 1290, 1225, 1158, 1101. HRMS (ESI-TOF): calcd. for $C_{15}H_{21}N_3NaO_5S_2$: 410.0815; found: 410.0815.

***N*-(2-(1-Methyl-2-(*N*-(methylsulfonyl)methylsulfonamido)-1*H*-indol-3-yl)ethyl)benzamide 8h.** 69 mg, 77% yield, white solid. m.p. = 166-168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.19 (t, *J* = 7.0 Hz, 2H), 3.53 (s, 6H), 3.76 (s, 3H), 3.99 (td, *J* = 7.0, 5.6 Hz, 2H), 6.59 (s, 1H), 7.18-7.22 (m, 1H), 7.36-7.42 (m, 4H), 7.46-7.50 (m, 1H), 7.72-7.75 (m, 2H), 7.82 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 25.3 (CH_2), 29.8 (CH_3), 39.6 (CH_2), 43.2 (CH_3), 110.1, 114.0, 120.4, 120.6, 124.0, 124.4, 125.4, 127.0, 128.4, 131.3, 134.3, 136.3, 167.7 (C=O). IR ν(cm^{-1}): 3308 (N-H), 2932 (Ar-H), 1630 (C=O), 1543, 1472, 1355, 1311, 1164, 962, 874, 748. HRMS (ESI-TOF): calcd. for $C_{20}H_{23}N_3NaO_5S_2$: 472.0971; found: 472.0979.

***N*-(2-(5-(Benzyloxy)-1-methyl-2-(*N*-(methylsulfonyl)methylsulfonamido)-1*H*-indol-3-yl)ethyl)benzamide 8i.** 89 mg, 80% yield, brown solid. m.p. = 157-159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.12 (t, *J* = 6.9 Hz, 2H), 3.50 (s, 6H), 3.70 (s, 3H), 3.89-3.94 (m, 2H), 5.03 (s, 2H), 6.55 (t, *J* = 5.5 Hz, 1H), 7.08 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.23-7.27 (m, 2H), 7.31-7.45 (m, 8H), 7.70-7.72 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 25.1 (CH_2), 30.0 (CH_3), 39.5 (CH_2), 43.2 (CH_3), 70.8 (CH_2), 103.2, 111.2, 113.5, 115.9, 124.1, 125.6, 127.1,

127.7, 127.9, 128.4, 128.5, 131.4, 131.7, 134.3, 137.2, 153.6, 167.7 (C=O). IR ν(cm^{-1}): 3341 (N-H), 3062 (Ar-H), 3033 (Ar-H), 2930 (Ar-H), 1711 (C=O), 1651, 1532, 1488, 1451, 1366, 1279, 1162, 1128, 1022, 875, 727, 694. HRMS (ESI-TOF): calcd. for $C_{27}H_{29}N_3NaO_6S_2$: 578.1390; found: 578.1403.

***N*-(2-(5-Iodo-2-(4-methyl-*N*-tosylphenylsulfonamido)-1*H*-indol-3-yl)ethyl)acetamide 9.** To a stirred solution of acetamide **7a** (47.8 mg, 0.091 mmol, 1equiv) and TFA (2 mL) in CH_2Cl_2 (20 mL) at -78 ºC, $HBF_4{\cdot}Et_2O$ (0.038 mL, 0.3 mmol, 3 equiv) and bis(pyridine)iodonium tetrafluoroborate (0.034 g, 0.091 mmol, 1 equiv) were added. The brown solution was stirred for 2 h. The reaction was quenched with cold water. The two phases were separated and the organic layer was washed with water and an aqueous saturated solution of sodium thiosulfate. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure to obtain a crude product, which was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 1/1, v/v) to afford the pure product (46 mg, 78% yield, white solid). m.p. = 187-191 ºC. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.79 (s, 3H), 2.15 (t, *J* = 6.7 Hz, 2H), 2.48 (s, 6H), 3.35 (td, *J* = 6.2, 5.7 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 4H), 7.52 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 4H), 7.96 (s, 1H). ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 21.9 (CH_3), 22.9 (CH_3), 23.4 (CH_2), 39.1 (CH_2), 83.4 (C-I), 114.3, 115.0, 124.2, 129.0, 129.1, 129.4, 130.3, 132.8, 134.6, 136.1, 146.7, 171.6 (C=O). IR ν(cm^{-1}): 3379 (N-H), 3170 (Ar-H), 2921 (Ar-H), 2582 (Ar-H), 2366 (Ar-H), 1643 (C=O), 1596, 1376, 1353, 1165, 879, 660, 542. HRMS (ESI-TOF): calcd. for $C_{26}H_{26}IN_3O_5NaS_2$: 674.0256, found: 674.0279.

***N*-(2-(5-Iodo-1-methyl-2-(4-methyl-*N*-tosylphenylsulfonamido)-1*H*-indol-3-yl)ethyl)acetamide 10.** Synthesized from **4a** through an identical procedure as described for compound **9**. 59 mg, 98% yield, white solid. m.p. = 196-197 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.82 (s, 3H), 2.15 (t, *J* = 6.4 Hz, 2H), 2.50 (s, 6H), 3.31 (s, 3H), 3.48-3.52 (m, 2H), 6.11 (t, *J* = 6.1 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 4H), 7.58 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 4H), 7.98 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.0 (CH_3), 23.5 (CH_2), 30.0 (CH_3), 38.9 (CH_2), 83.4 (C-I), 112.2, 114.1, 125.7, 127.8, 129.1, 129.3, 129.9, 132.4, 135.2, 135.5, 146.13, 170.3 (C=O). IR ν (cm^{-1}): 3290 (N-H), 2923 (Ar-H), 2853 (Ar-H), 1651 (C=O), 1372, 1166, 873, 659, 542, 478. HRMS (ESI-TOF): calcd. for $C_{27}H_{28}IN_3O_5NaS_2$: 688.0413, found: 688.0437.

***N*-(2-(5,6-Diiodo-2-(4-methyl-*N*-tosylphenylsulfonamido)-1*H*-indol-3-yl)ethyl)acetamide 11** and ***N*-(2-(5,7-Diiodo-2-(4-methyl-N-tosylphenylsulfonamido)-1*H*-indol-3-yl)ethyl)acetamide 12**. To a stirred solution of the acetamide **7a** (0.052 g, 0.1mmol, 1 equiv) and TFA (2 mL) in CH_2Cl_2 (20 mL) at -78 ºC, $HBF_4{\cdot}Et_2O$ (0.086 mL, 0.6 mmol, 6 equiv) and bis(pyridine)iodonium tetrafluoroborate (0.082 g, 0.22 mmol, 2.2 equiv) were added. The brown solution was allowed to stir for 2 h. The reaction was quenched with cold water, after extraction the organic layer was washed with an aqueous saturated solution of $Na_2S_2O_4$. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, CH_2Cl_2/EtOAc, 1/1, v/v) to afford a mixture of the two regioisomers in 1:3-ratio. (53 mg, 68% yield, white solids. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86 (s, 6H), 2.12-2.15 (m, 2H), 2.19-2.22 (m, 2H), 2.52 (s, 6H), 2.53 (s, 6H), 3.43-3.48

(m, 2H), 3.64-3.68 (m, 2H), 6.12 (s, 2H), 7.39-7.44 (m, 8H), 7.84-7.89 (m, 8H), 7.93 (s, 1H), 7.95 (s, 1H), 8.17 (s, 1H), 8.18 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 22.7 (CH_2), 22.8 (CH_2), 23.0 (CH_3), 31.9 (CH_2), 38.7 (CH_2), 96.9 (C-I), 101.7 (C-I), 115.4, 122.4, 124.5, 128.5, 128.7, 128.8, 130.0, 130.1, 130.5, 135.4, 135.5, 146.1, 146.3, 170.5 (C=O). IR ν (cm^{-1}): 3387 (N-H), 2919 (Ar-H), 2850 (Ar-H), 1657 (C=O), 1597, 1540, 1375, 1351, 1164, 1083, 876, 754, 659, 541. HRMS (ESI-TOF): calcd. for $C_{26}H_{26}I_2N_3O_5S_2$, 777.9398, found: 777.9418.

General procedure for fluorination. Selectfluor® (0.019 g, 0.06 mmol, 1.2 equiv) was added to a stirred solution of the corresponding starting material (0.027 g, 0.05 mmol, 1.0 equiv) and $NaHCO_3$ (0.005 g, 0.06 mmol, 1.2 equiv) in acetonitrile at 70 ºC. The reaction was allowed to stir at 70 ºC for 16 h. The solvent was removed under reduced pressure and an aqueous saturated solution of $NaHCO_3$ was added. The residue was extracted with ethyl acetate and the combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc, 2/3, v/v). The products were obtained as solids in 95-99% isolated yield.

***N*-(2-(3-Fluoro-2-(tosylimino)indolin-3-yl)ethyl)acetamide 13a**. 19 mg, 98% yield, yellow solid. m.p. = 230-232 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.87 (s, 3H), 2.27-2.50 (m, 5H), 3.33 (m, 2H), 5.93 (brs, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.31-7.37 (m, 3H), 7.42 (d, *J* = 7.5 Hz, 1H) 7.88 (d, *J* = 8.3 Hz, 2H), 9.82 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6 (CH_3), 23.1 (CH_3), 33.7 (d, J_{C-F} = 9.8 Hz, CH_2), 35.8 (d, J_{C-F} = 27.9 Hz, CH_2), 97.3 (d, J_{C-F} = 192.2 Hz, C-F), 111.8, 124.6 (d, J_{C-F} = 2.7 Hz), 124.8, 125.6

(d, $J_{C\text{-}F}$ = 18.7 Hz), 126.8, 129.7, 131.9 (d, J = 3.1 Hz), 137.5, 141.0, 144.2, 165.1 (d, $J_{C\text{-}F}$ = 19.7 Hz), 170.3 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -150.3. IR ν (cm^{-1}): 3303 (N-H), 2921 (Ar-H), 2851 (Ar-H), 1615 (C=O), 1469, 1284, 1143, 1082, 752, 665, 546. HRMS (ESI-TOF): calcd. for $C_{19}H_{19}FN_3O_3S$: 388.1137, found: 388.1137.

***N*-(2-(3-Fluoro-2-(tosylimino)indolin-3-yl)ethyl)benzamide 13b.** 21 mg, 95% yield, yellow solid. m.p. = 202-204 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33-2.64 (m, 5H), 3.62 (td, J = 6.4, 6.2 Hz, 2H), 6.52 (t, J = 5.8 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 7.16-7.19 (m, 1H), 7.30 (d, J = 8.2 Hz, 2H), 7.36-7.49 (m, 5H), 7.69-7.72 (m, 2H), 7.86 (d, J = 8.3 Hz, 2H), 9.82 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.6 (CH_3), 34.2 (d, $J_{C\text{-}F}$ = 10.1 Hz, CH_2), 35.6 (d, $J_{C\text{-}F}$ = 27.2 Hz, CH_2), 99.2 (d, $J_{C\text{-}F}$ = 194.5 Hz, C-F) 111.8, 124.7 (d, $J_{C\text{-}F}$ = 2.7 Hz), 124.9, 126.8 (d, $J_{C\text{-}F}$ = 16.7 Hz), 129.7, 131.5, 131.9, 132.0, 134.0, 137.6, 141.0, 144.1, 164.9 (d, $J_{C\text{-}F}$ = 24.3 Hz), 167.3 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -149.8. IR ν (cm^{-1}): 3295 (N-H), 2851 (Ar-H), 1616 (C=O), 1532, 1470, 1284, 1142, 1082, 669, 547. HRMS (ESI-TOF): calcd. for $C_{24}H_{22}FN_3NaO_3S$: 474.1264, found: 474.1260.

***N*-(2-(3-Fluoro-1-methyl-2-(tosylimino)indolin-3-yl)ethyl)acetamide 14a.** 20 mg, 99% yield, yellow solid. m.p. = 47-53 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.87 (s, 3H), 2.44 (s, 3H), 2.64-2.70 (m, 1H), 3.08-3.13 (m, 1H), 3.20-3.38 (m, 5H), 6.32 (s, 1H), 6.90-6.92 (m, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.41-7.44 (m, 2H), 7.92 (d, J = 8.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6 (CH_3), 23.1 (CH_3), 29.0 (CH_3), 33.9 (d, $J_{C\text{-}F}$ = 9.8 Hz, CH_2), 35.6 (d, $J_{C\text{-}F}$ = 27.1 Hz, CH_2), 96.9 (d, $J_{C\text{-}F}$ = 194.3 Hz, C-I), 110.0, 124.1, 124.7 (d, $J_{C\text{-}F}$ = 2.7 Hz), 126.7, 127.1 (d, $J_{C\text{-}F}$ = 19.0 Hz), 129.4, 131.8 (d, $J_{C\text{-}F}$ = 2.7

Hz), 140.0, 143.0, 143.3 (d, J_{C-F} = 5.1 Hz), 164.8 (d, J_{C-F} = 23.5 Hz), 170.1(C=O). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -153.0. IR ν(cm^{-1}): 3294 (N-H), 2927 (Ar-H), 1632 (C=O), 1580, 1470, 1282, 1145, 1082, 770, 751, 671, 545, 461. HRMS (ESI-TOF): calcd. for $C_{20}H_{22}FN_3O_3NaS$: 426.1258; found: 426.1261.

***N*-(2-(3-Fluoro-1-methyl-2-(tosylimino)indolin-3-yl)ethyl)benzamide 14b.** 22 mg, 98% yield, orange solid. m.p. = 128-129 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.46 (s, 3H), 2.73-2.80 (m, 1H), 3.02 (s, 3H), 3.30-3.36 (m, 1H), 3.50-3.71 (m, 2H), 6.90 (d, *J* = 7.9 Hz, 1H), 7.12-7.14 (m, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.29-7.32 (m, 2H), 7.38-7.52 (m, 5H), 7.84-7.88 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 21.5 (CH_3), 28.7 (CH_3), 34.5 (d, J_{C-F} = 10.1 Hz, CH_2), 35.3 (d, J_{C-F} = 27.4 Hz, CH_2), 96.9 (d, J_{C-F} = 193.6 Hz, C-I), 110.0, 124.0, 124.7 (d, *J* = 2.7 Hz), 126.6, 126.8, 127.0, 127.2, 128.4, 129.3, 131.4, 131.8 (d, J_{C-F} = 2.8 Hz), 133.8, 140.0, 142.9, 143.3 (d, J_{C-F} = 5.2 Hz), 165.3 (d, J_{C-F} = 23.5 Hz), 166.8 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$) δ = -152.8. IR ν (cm^{-1}): 3253 (N-H), 3068 (Ar-H), 2920 (Ar-H), 1627 (C=O), 1550, 1381, 1167, 876, 657, 540. HRMS (ESI-TOF): calcd for $C_{25}H_{24}FN_3NaO_3S$: 488.1415; found: 488.1422.

***N*-(2-(3-Fluoro-2-(4-methyl-*N*-tosylphenylsulfonamido)-3*H*-indol-3-yl)ethyl)acetamide 15.** 23 mg, 86% yield, yellow solid. m.p. = 132-134 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (s, 3H), 2.13-2.25 (m, 1H), 2.26-2.40 (m, 1H), 2.51 (s, 6H), 3.15-3.23 (m, 1H), 3.34-3.43 (m, 1H), 5.51 (t, *J* = 6.0, 1H), 7.36-7.41 (m, 5H), 7.44-7.52 (m, 2H), 7.57 (d, *J* = 7.6 Hz, 1H), 8.11 (d, *J* = 8.4, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.2 (CH_3), 33.5 (d, J_{C-F} = 26.0 Hz, CH_2), 34.0 (d, J_{C-F} = 6.9 Hz, CH_2), 100.4 (d, J_{C-F} = 197.0 Hz, C-F),

101.4, 122.9, 123.9, 128.8 (d, J_{C-F} = 1.6 Hz), 129.5, 129.7 (d, J_{C-F} = 1.9 Hz), 131.2, 134.4 (d, J_{C-F} = 18.5 Hz), 136.2, 145.8, 149.7 (d, J_{C-F} = 6.3 Hz), 165.4 (d, J_{C-F} = 18.8 Hz), 169.8 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -166.6. IR ν (cm^{-1}): 3282 (N-H), 2919 (Ar-H), 2850 (Ar-H), 1650 (C=O), 1563, 1381, 1167, 1082, 886, 659, 538. HRMS (ESI-TOF): calcd. for $C_{26}H_{25}FN_3O_5S_2$: 542.1225, found: 542.1221.

***N*-(2-(3-Fluoro-1-methyl-2-oxoindolin-3-yl)ethyl)acetamide 16a.** Compound **14a** (0.045 g, 0.11 mmol, 1 equiv) was dissolved in MeOH (2 mL) and LiOH (0.027, 1.1 mmol, 10 equiv) was added. The reaction mixture was stirred at 25 ºC for 16 h. The solvent was removed under reduced pressure. The residue was quenched with water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, MeOH/CH_2Cl_2, 0.2:10, v/v) to afford the pure product in 85% yield (0.023 g) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94 (s, 3H), 2.14-2.27 (m, 1H), 2.41-2.52 (m, 1H), 3.22 (s, 3H), 3.43-3.60 (m, 2H), 6.15 (brs, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.40-7.44 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.2 (CH_3), 26.3 (CH_3), 33.9 (d, J_{C-F} = 5.9 Hz, CH_2), 34.8 (d, J_{C-F} = 26.8 Hz), 92.4 (d, J_{C-F} = 186.9 Hz, CH_2-F), 108.9, 123.6 (d, J_{C-F} = 2.8 Hz), 124.5, 125.9 (d, J_{C-F} = 18.2 Hz), 126.4, 129.7, 131.5 (d, J_{C-F} = 3.0 Hz), 143.7 (d, J_{C-F} = 5.4 Hz), 170.0 (C=O), 172.8 (d, J_{C-F} = 22.0 Hz, C=O). ^{19}F NMR (101 MHz, $CDCl_3$): δ = -158.5. IR ν(cm^{-1}): 3294 (N-H), 3065 (Ar-H), 2927 (Ar-H), 1724 (C=O), 1615 (C=O), 1470, 1372, 1246, 1113, 750. HRMS (ESI-TOF): calcd. for $C_{13}H_{15}FN_2NaO_2$: 273.1010, found: 273.1013.

***N*-(2-(3-Fluoro-1-methyl-2-oxoindolin-3-yl)ethyl)benzamide 16b.** Synthesized in an analogous manner to compound **16a** as described above. 29 mg, 85% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.23-2.36 (m, 1H), 2.57-2.67 (m, 1H), 3.18 (s, 3H), 3.63-3.71 (m, 1H), 3.78-3.87 (m, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 7.02 (brs, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.39-7.52 (m, 5H), 7.76-7.82 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 26.3 (CH_3), 34.3 (d, J_{C-F} = 5.8 Hz, CH_2), 34.8 (d, J_{C-F} = 27.0 Hz, CH_2), 92.5 (d, J_{C-F} = 186.8 Hz, C-F), 109.0, 123.7 (d, J_{C-F} = 2.7 Hz), 124.5, 125.9 (d, J_{C-F} = 18.3 Hz), 126.9, 128.5, 131.4, 131.6 (d, J_{C-F} = 3.2 Hz), 134.3, 143.6 (d, J_{C-F} = 5.4 Hz), 167.0 (C=O), 173.0 (d, J_{C-F} = 22.0 Hz, C=O). ^{19}F NMR (101 MHz, $CDCl_3$): δ = -158.3. IR ν (cm^{-1}): 3327 (N-H), 2923 (Ar-H), 2852 (Ar-H), 1725 (C=O), 1639 (C=O), 1616, 1537, 1491, 1470, 1376, 1306, 1092, 751, 694. HRMS (ESI-TOF): calcd. for $C_{18}H_{17}FN_2NaO_2$: 335.1166, found: 335.1169.

General procedure for treatment of 13a,b and 14a,b with TFA. The corresponding starting material (0.12 mmol, 1 equiv) was dissolved in TFA (4 mL) and the reaction mixture was allowed to stir for 12 h under an atmosphere of argon. The solvent was removed under reduced pressure and the pure product was isolated in quantitative yield.

2-(3-Acetoxy-2-(tosylimino)indolin-3-yl)ethanaminium trifluoroacetate 17a. 59 mg, 98% yield, brown solid. m.p. = 112-115 ºC. ^{1}H NMR (400 MHz, MeOD): δ = 2.43 (s, 3H), 2.51 (s, 3H), 2.55-2.56 (m, 1H), 2.73-2.81 (m, 1H), 3.77-3.83 (m, 1H), 4.09-4.18 (m, 1H), 7.29-7.35 (m, 2H), 7.49 (d, *J* = 7.7 Hz, 2H), 7.56-7.62 (m, 2H), 7.93 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (101 MHz, MeOD): δ = 21.5 (CH_3), 22.5 (CH_3), 33.8 (CH_2), 37.5 (CH_2), 81.0, 83.5, 87.4, 113.4, 125.0, 125.4, 127.8, 130.6, 130.6, 131.7, 140.0, 142.6, 143.4, 145.2, 170.1 (C=O). ^{19}F NMR (376 MHz, MeOD): δ = -77.5. IR ν (cm^{-1}): 3306 (N-H), 2921 (Ar-

H), 2851 (Ar-H), 1599 (C=O), 1469, 1279, 1138, 1082, 753, 666, 547. HRMS (ESI-TOF): calcd. for $C_{19}H_{22}N_3O_4S$: 388.1326; found: 388.1311.

2-(3-(Benzoyloxy)-2-(tosylimino)indolin-3-yl)ethanaminium 2,2,2-trifluoroacetate 17b. 67 mg, 99% yield, yellow solid. m.p. = 131-135 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.19-2.23 (m, 1H), 2.43 (s, 3H), 3.61-3.64 (m, 1H), 3.74 (td, *J* = 7.1, 6.9, 2H), 5.38 (s, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 7.18-7.54 (m, 8H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.6 (CH_3), 34.8 (CH_2), 37.4 (CH_2), 86.6, 111.7, 124.6, 126.5, 126.6, 127.0, 128.5, 128.6, 129.3, 129.7, 130.8, 131.8, 138.0, 144.0, 168.2 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -76.0. IR ν (cm^{-1}): 3253 (N-H), 3068 (Ar-H), 2920 (Ar-H), 1627 (C=O), 1550, 1381, 1167, 876, 657, 540. HRMS (ESI-TOF): calcd. for $C_{24}H_{24}N_3O_4S$: 450.1482; found: 450.1476.

2-(3-Acetoxy-1-methyl-2-(tosylimino)indolin-3-yl)ethanaminium 2,2,2-trifluoroacetate 18a. 61 mg, 99% yield, yellow solid. m.p. = 129-132 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.19-2.23 (m, 1H), 2.46 (s, 3H), 2.55 (s, 3H), 3.20-3.28 (m, 1H), 3.48 (s, 3H), 3.84-3.95 (m, 1H), 4.04-4.11 (m, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 7.26-7.30 (m, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.44 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.55 (td, *J* = 7.9, 1.1 Hz, 1H), 7.83-7.96 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.0 (CH_3), 21.5 (CH_3), 25.1 (CH_3), 30.4 (CH_2), 34.5 (CH_2), 84.3, 110.5, 123.7, 125.3, 126.3, 127.1, 129.6, 132.9, 138.9, 142.5, 143.8, 162.5, 172.8 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -75.9. IR ν (cm^{-1}): 3383 (N-H), 2919 (Ar-H), 1678 (C=O), 1572, 1190, 1148, 1132, 1083, 948, 777, 760, 680. HRMS (ESI-TOF): calcd. for $C_{20}H_{24}N_3O_4S$: 402.1488; found: 402.1485.

2-(3-(Benzoyloxy)-1-methyl-2-(tosylimino)indolin-3-yl)ethanaminium 2,2,2-trifluoroacetate 18b. 89 mg, 99% yield, yellow solid. m.p. = 56-58 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31-2.34 (m, 1H), 2.39 (s, 3H), 3.27-3.34 (m, 1H), 3.53 (s, 3H), 4.09-4.14 (m, 1H), 4.21-4.28 (m, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.21-7.28 (m, 3H), 7.50-7.55 (m, 4H), 7.70-7.71 (m, 3H), 8.00-8.08 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.5 (CH_3), 25.4 (CH_3), 30.7 (CH_2), 35.1 (CH_2), 84.7, 110.6, 124.0, 124.9, 125.4, 126.3, 127.0, 128.9, 129.4, 129.5, 132.5, 135.9, 138.8, 142.6, 143.7, 162.2, 167.6 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -75.9. IR ν (cm^{-1}): 3067 (N-H), 2929 (Ar-H), 1783 (C=O), 1588, 1138, 1084. HRMS (ESI-TOF): calcd. for $C_{25}H_{25}N_3NaO_4S$: 486.1463; found: 486.1458.

***N*-(3-(2-Acetamidoethyl)-3-hydroxy-1-methylindolin-2-ylidene)-4-methylbenzenesulfonamide 19**

Compound **18a** (46 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (0.25 mL) and Et_3N (0.5 mL) was added dropwise. After 16 hours, additional CH_2Cl_2 (5 mL) and water were added, and the resulting mixture was extracted with diluted HCl (1 M in water). The organic phase was separated and the solvent was removed under reduced pressure. The title compound was isolated as a yellowish solid (40 mg, 0.1 mmol, 99% yield). m.p. = 135-138 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (s, 3H), 2.45 (s, 3H), 3.19 (s, 3H), 2.45-2.55 (m, 1H), 2.94-3.17 (m, 3H), 3.19 (s, 3H), 6.31 (brs, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 7.19-7.23 (m, 1H), 7.32-7.34 (m, 2H), 7.35 -7.41 (m, 2H), 7.88-7.90 (m, 2H), 8.08-8.10 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.6 (CH_3), 23.1 (CH_3), 28.4 (CH_3), 34.5 (CH_2), 38.8 (CH_2), 80.2 (C-O), 109.8, 123.4, 125.0, 126.4, 129.4, 129.7, 130.4, 130.5, 139.1, 142.7, 143.3, 169.9, 171.2 (C=O). IR ν (cm^{-1}): 3411 (O-H), 3376 (N-H), 2921 (Ar-H), 2852 (Ar-H), 1665

(C=O), 1548, 1073, 961, 778, 752, 689, 553. HRMS (ESI-TOF): calcd. for $C_{20}H_{23}N_3NaO_4S$: 424.1301; found: 424.1307.

8-Methyl-2,3,3a,8-tetrahydropyrrolo[2,3-*b*]indol-3a-yl benzoate 20. Compound **18b** (0.372 g, 0.64 mmol, 1 equiv) was dissolved in MeOH (10 mL) and LiOH (0.154 g, 6.4 mmol, 10 equiv) was added. The reaction mixture was allowed to stir at 25 ^{o}C for 16 h. The solvent was removed under reduced pressure. The residue was quenched with water and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure affording compound **20** in quantitative yield (185 mg, 99%) as a brownish solid. m.p. = 45-46 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.07 (ddd, *J* = 14.0, 7.1, 5.3 Hz, 1H), 2.23 (ddd, *J* = 14.0, 6.5, 5.3 Hz, 1H), 3.27 (s, 3H), 3.90 (ddd, *J* = 17.2, 6.5, 5.3 Hz, 1H), 4.17 (ddd, *J* = 17.2, 7.1, 5.3 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.34-7.44 (m, 5H), 7.91-7.94 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.4 (CH_3), 27.5 (CH_2), 38.7 (CH_2), 76.7, 108.7, 123.4, 124.1, 127.2, 128.0, 129.1, 130.4, 130.5, 133.5, 143.2, 154.3, 174.2 (C=O). IR ν(cm^{-1}): 3060 (Ar-H), 2924 (Ar-H), 1715 (C=O), 1653, 1613, 1156, 1120, 1091. HRMS (ESI-TOF): calcd. for $C_{18}H_{17}N_2O_2$: 293.1285; found: 293.1284.

Trifluoromethyl 3-(2-benzamidoethyl)-1-methyl-2-oxoindoline-3-carboxylate 21. Compound **20** (58 mg, 0.20 mmol, 1 equiv) was dissolved in CH_2Cl_2 (2 mL) and TFA (0.05 mL, 0.60 mmol, 3 equiv) was added. The reaction mixture was stirred for 16 h at 25 ºC. After 16 hours, the solvent was removed under reduced pressure to afford the pure product as a yellow oil in 80 mg (99% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45-2.50 (m, 1H), 2.68-2.74 (m, 1H), 3.29 (s, 3H), 4.09-4.14 (m, 1H), 4.40-4.47 (m, 1H), 7.04 (d, *J* = 7.9,

1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.36-7.59 (m, 3H), 7.74 (t, *J* = 7.4 Hz, 1H), 7.67-7.77 (m, 1H), 7.98 (d, *J* = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 25.0 (CH_3), 26.7 (CH_2), 35.8 (CH_2), 81.4, 109.9, 112.0, 114.3, 116.5, 118.8, 123.7, 124.0, 125.0, 128.4, 129.5, 132.8, 136.2, 143.5, 161.3 (q, CF_3C=O), 168.4 (C=O), 170.8 (C=O). ^{19}F NMR (101 MHz, $CDCl_3$): δ = -76.0. IR ν (cm^{-1}): 3325 (N-H), 2926 (Ar-H), 1697 (C=O), 1638 (C=O), 1611 (C=O), 1537, 1490, 1347, 1301, 1128, 1091, 749, 695. HRMS (ESI-TOF): calcd. for $C_{20}H_{17}F_3N_2NaO_2$: 429.1038, found: 429.1026.

Supporting Information

Reproduction of NMR spectra for new compounds and ORTEP plots from X-ray analyses (pdf format), and individual X-ray crystallographic data for compounds **9**, **11**/**12**, **14a**, **18a**, **19**, and **20**, respectively (cif). This material is available free of charge via the Internet at http://pubs.acs.org.

Acknowledgements

Financial support for this project was provided from the Spanish Ministry for Economy and Competitiveness and FEDER (CTQ2014-56474R grant to K. M., and Severo Ochoa Excellence Accreditation 2014-2018 to ICIQ, SEV-2013-0319). A.E.B. acknowledges a FPI fellowship and C. M. support from Cellex Foundation. The authors thank E. Escudero-Adán for the X-ray structural analyses.

References

(1) Zhdankin, V. V. *Hypervalent Iodine Chemistry Preparation, Structure and Synthetic Applications of Polyvalent Iodine Compounds*, Wiley, Chichester 2013.

(2) (a) *Hypervalent Iodine Chemistry. Modern Developments in Organic Synthesis*, Wirth, T. (Ed.), *Top. Curr. Chem*. 224, Springer, Berlin, 2003. (b) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328. (c) Richardson, R. D.; Wirth, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4402. (d) Ochiai, M. *Chem. Rec.* **2007**, *7*, 12. (e) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073. (f) Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, 2086.

(3) (a) Fra, L.; Millán, A.; Souto, J. A.; K. Muñiz, K. *Angew. Chem. Int. Ed*. **2014**, *53*, 7349. (b) Fra, L.; Muñiz, K. *Chem. Eur. J.* **2016**, *22*, 4351.

(4) (a) Liu, K.; Wen, P.; Liu, J.; Huang, G. *Synthesis* **2010**, 3623. (b) Liu, Q.; Li, G.; Yi, H.; Wu, P.; Liu, J.; Lei, A. *Chem. Eur. J.* **2011**, *17,* 2353. (c) Soni, V.; Patel, U. N.; Punji, B. *RSC Adv.* **2015**, *5*, 57472.

(5) Liu, Q.; Zhao, Q. Y.; Liu, J.; Wu, P.; Yi, H.; Lei, A. *Chem. Commun.* **2012**, *48*, 3239.

(6) Ackermann, L.; Dell'Acqua, M.; Fenner, S.; Vicente, R.; Sandmann, R. *Org. Lett.* **2011**, *13*, 2358.

(7) Souto, J. A.; Martínez, C.; Velilla, I.; Muñiz, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 1324.

(8) For related bromine(III) reagents incorporating transferable nitrogen groups: (a) Ochiai, M.; Kaneaki, T.; Tada, N.; Miyamoto, K.; Chuman, H.; Shiro, M.; Hayashi, S.; Nakanishi, W. *J. Am. Chem. Soc.* **2007**, *129*, 12938. (b) Ochiai, M.; Miyamoto, K.; Kaneaki, T.; Hayashi, S.; Nakanishi, W. *Science* **2011**, *332*, 448.

(9) For the alternative concept of electrophilic amination with hypervalent iodine reagents: (a) Tellitu, I.; Domínguez, E. *Trends Heterocycl. Chem.* **2011**, *15*, 23. (b) Narayan, R.; Manna, S.; Antonchick, A. P. *Synlett* **2015**, *26*, 1785. (c) Samanta, R.; Matcha, K.; Antonchick, A. P. *Eur. J. Org. Chem.* **2013**, 5769.

(10) (a) Yoshimura, A.; Koski, S. R.; Fuchs, J. M.; Saito, A.; Nemykin, V. N.; Zhdankin, V. V. *Chem. Eur. J.* **2015**, *21*, 5328. (b) Kiyokawa, K.; Kosaka, T.; Kojima, T.; Minakata,

S. *Angew. Chem. Int. Ed.* **2015**, *54*, 13719. (c) Hadjiarapoglou, L.; Spyroudis, S.; Varvoglis, A. *Synthesis* **1983**, 207. (d) Papadopoulou, M.; Varvoglis, A. *Chem. Res. Synop.* **1983**, 66. (e) Papadopoulou, M.; Varvoglis, A. *Chem. Res. Synop.* **1984**, 166.

(11) Souto, J. A.; Zian, D.; Muñiz, K. *J. Am. Chem. Soc.* **2012**, *134*, 7242.

(12) Kiyokawa, K.; Yahata, S.; Kojima, T.; Minakata, S. *Org. Lett.* **2014**, *16*, 4646.

(13) Souto, J. A.; Becker, P.; Iglesias, A.; Muñiz, K. *J. Am. Chem. Soc.* **2012**, *134*, 15505.

(14) Purkait, N.; Okamura, S.; Souto, J. A.; Muñiz, K. *Org. Lett.* **2014**, *16*, 4750.

(15) Moriyama, K.; Ishid, K.; Togo, H. *Chem. Commun.* **2015**, *51*, 2273.

(16) (a) Souto, J. A.; González, Y.; Iglesias, Á.; Zian, D.; Lishchynskyi, A.; Muñiz, K. *Chem. Asian J.* **2012**, *7*, 1103. (b) Röben, C.; Souto, J. A.; González, Y.; Lishchynskyi, A.; Muñiz, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 9478. (c) Röben, C.; Souto, J. A.; Escudero-Adán, E. C. Muñiz, K. *Org. Lett*. **2013**, *15*, 1008.

(17) Lishchynskyi, A.; Muñiz, K. *Chem. Eur. J.* **2012**, *18*, 2213.

(18) For an overview on alkene difunctionalization with hypervalent iodine(III) reagents: Romero, R. M.; Wöste, T. H.; Muñiz, K. *Chem. Asian J.* **2014**, *9*, 972.

(19) Liu, H.-H.; Wang, Y.; Deng, G.; Yang, L. *Adv. Synth. Catal.* **2013**, *355*, 3369.

(20) (a) Li, Y.-X.; Ji, K.-G.; Wang, H.-X.; Ali, S.; Liang, Y.-M. *J. Org. Chem*. **2011**, *76*, 744. (b) Li, Y.-X.; Wang, H.-X.; Ali, S.; Xia, X.-F.; Liang, Y.-M. *Chem. Commun*. **2012**, *48*, 2343. (c) Wu, W.-B.; Huang, J.-M. *Org. Lett*. **2012**, *14*, 5832. (d) Ali, A.; Li, Y.-X.; Anwar, S.; Yang, F.; Chen, Z.-S.; Liang, Y.-M. *J. Org. Chem*. **2012**, *77*, 424. (e) Prasad, B.; Sreenivas, B. Y.; Rambabu, D.; Krishna, G. R.; Reddy, C. M.; Kumar, K. L.; Pal, M. *Chem. Commun*. **2013**, *49*, 3970.

(21) Moriyama, K.; Ishid, K.; Togo, H. *Chem. Commun.* **2015**, *51*, 2273.

(22) For the same concept using subsequent copper catalysis for 3-amination of indoles: (a) Sokolovs, I.; Lubriks, D.; Suna, E. *J. Am. Chem. Soc.* **2012**, *134*, 15436. (b) Lubriks, D.; Sokolovs, I.; Suna, E. *J. Am. Chem. Soc.* **2014**, *136*, 6920.

(23) For recent other, mechanistically non-related 2-amination reactions, see: (a) Shi, J.; Zhou, B.; Yang, Y.; Li, Y. *Org. Biomol. Chem*. **2012**, *10*, 8953. (b) Qin, Q.; Yu, S. *Org. Lett*. **2014**, *16*, 3504. (c) Greulich, T. W.; Daniliuc, C. G.; Studer, A. *Org. Lett*. **2015**, *17*, 254. (d) Brachet, E.; Ghosh, T.; Ghosh, I.; König, B. *Chem. Sci*. **2015**, *6*, 987.

(24) (a) Steven, A.; Overman, L. E. *Angew. Chem. Int. Ed.* **2007**, *46*, 5488. (b) Crich, D.; Banerjee, A. *Acc. Chem. Res*. **2007,** *40***,** 151. (c) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Álvarez, M. *Chem. Eur. J*. **2011**, *17*, 1388.

(25) (a) Kajiyama, D.; Saitoh, T.; Yamaguchi, S.; Nishiyama, S. *Synthesis* **2012**, *44*, 1667. (b) Yang, Y.; Jiang, X.; Qing, F.-L. *J. Org. Chem*. **2012**, 77, 7538.

(26) (a) Barluenga, J. *Pure Appl. Chem*. **1999**, *71*, 431. (b) Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem. Int. Ed.* **1985**, *24*, 319. (c) Barluenga, J.; González-Bobes, F.; Murguía, M. C.; Ananthoju, S. R.; González, J. M. *Chem. Eur. J.* **2004**, *10*, 4206. (d) Espuña, G.; Ananthoju, S. R.; Andreu, D.; Barluenga, J.; Pérez, X.; Planas, A.; Arsequell, G.; Valencia, G. *Biochem.* **2006**, *45*, 5957. (e) Barluenga, J.; González, J. M.; García-Martín, M. A.; Campos, P. J.; Asensio, G. *J. Org. Chem.* **1993**, *58*, 2058.

(27) See Supporting Information for details and X-ray analyses.

(28) (a) Loach, R. P.; Fenton, O. S.; Amaike, K.; Siegel, D. S.; Movassaghi, M. *J. Org. Chem.* **2014**, *79*, 11254 and cited literature. For enzymatic approaches: (b) Wiesner, W.; Vanpee, K. H.; Lingens, F. *FEBS Lett*. **1986**, *209*, 321. (c) Dong, C. J.; Flecks, S.; Unversucht, S.; Haupt, C.; van Pee, K. H.; Naismith, J. H. *Science* **2005**, *309*, 2216.

(29) (a) Lozano, O.; Blessley, G.; Martínez del Campo, T.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2011**, *50*, 8105. (b) Tréguier, B.; Roche, S. P. *Org. Lett*. **2014**, *16*, 278.

(30) (a) Peddibhotla, S. *Curr. Bioact. Comp.* **2009**, *5*, 20. (b) Yan, T.; Wang, X.; Sun, H.; Liu, J.; Xie, Y. *Molecules* **2013**, *18*, 14505.

(31) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.

(32) Anumadla, D.; Jeffrey, C. S. *J. Am. Chem. Soc.* **2015**, *137*, 14858.

(33) Song, H.; Yang, J.; Chen, W.; Gin, Y. *Org. Lett.* **2006**, *8*, 6011.

(34) Desaty, D.; Keglevic, D. *Croatica Chem. Acta* **1965**, *37*, 25.

(35) Nicolaou, K. C.; Krasovskiy, A.; Majumder, Trepanier, V. E.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2009**, *131*, 3690.