Synthesis of cyclohepta[*b*]indoles by (4+3) cycloaddition of 2-vinylindoles or 4*H*-furo[3,2-*b*]indoles with oxyallyl cations

Valentina Pirovano,[†*] Elisa Brambilla,[†] Andrea Moretti,[†] Silvia Rizzato,[∫]
Giorgio Abbiati,[†] Donatella Nava[†] and Elisabetta Rossi[†*]

[†] Dipartimento di Scienze Farmaceutiche - Sezione di Chimica Generale e Organica "A. Marchesini", Università degli Studi di Milano, Via Venezian 21, 20133 Milano, Italy

[∫] Dipartimento di Chimica, Università degli Studi di Milano, Via Golgi 19, 20133, Milano, Italy

e-mail: valentina.pirovano@unimi.it or elisabetta.rossi@unimi.it

ABSTRACT

The synthesis of cyclohepta[*b*]indole derivatives through dearomative (4+3) cycloaddition reaction of 2-vinylindoles or 4*H*-furo[3,2-*b*]indoles with *in situ* generated oxyallyl cations is reported. Oxyallyl cations are generated from α-bromoketones in the presence of a base and a perfluorinated solvent. Cyclohepta[*b*]indole scaffolds are obtained under mild reaction conditions, in the absence of expensive catalysts, starting from simple reagents, in good to excellent yields and with complete diasteroselectivity. Preliminary expansion of the scope to 3-vinylindoles and to aza-oxyallyl cations is reported.

KEY WORDS

Indoles, oxyallyl cations, perfluorinated solvents, (4+3) cycloadditions

INTRODUCTION

The cyclohepta[*b*]indole is the core privileged structure of a variety of natural as well as non-natural compounds owing different degrees of structural complexity in addition to a great variety of biological activities. Gaich and Stempel have recently organized all of these features in an exhaustive review.[1] In particular, they describe the structural geography of the different families of cyclohepta[*b*]indoles alkaloids ranging from the simplest exotines and ervitsine-ervatamine alkaloids to the more complex actinophyllic acid and ambiguines (Figure 1).

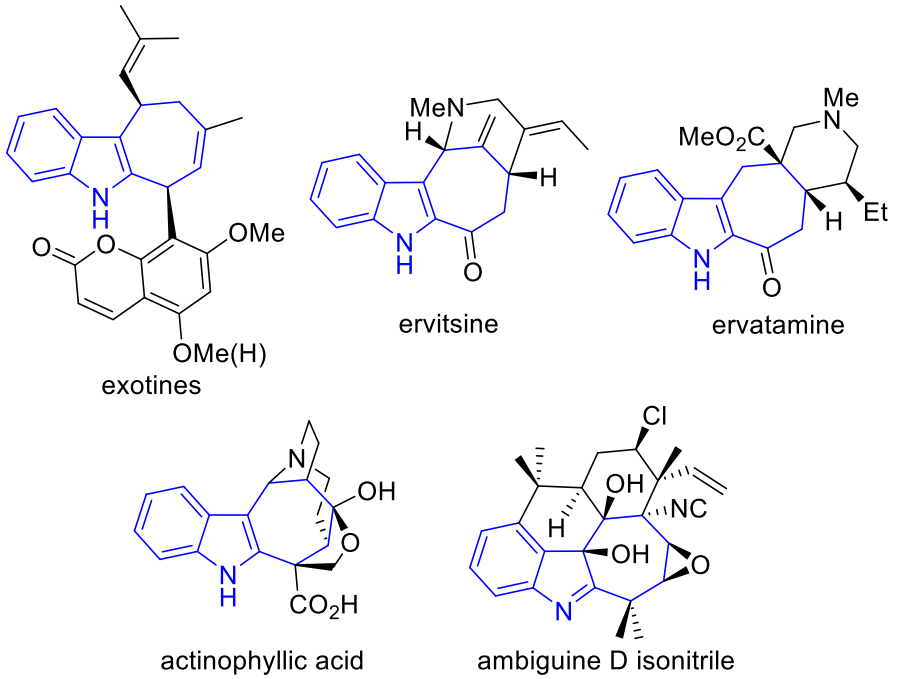


Figure 1. Natural products containing the cyclohepta[*b*]indoles scaffold.

Moreover, as is often the case, the reported biological activities attracted the interest of both medicinal and synthetic chemists for the rational design of new therapeutic agents (Figure 2) and for the development of efficient synthetic methods.

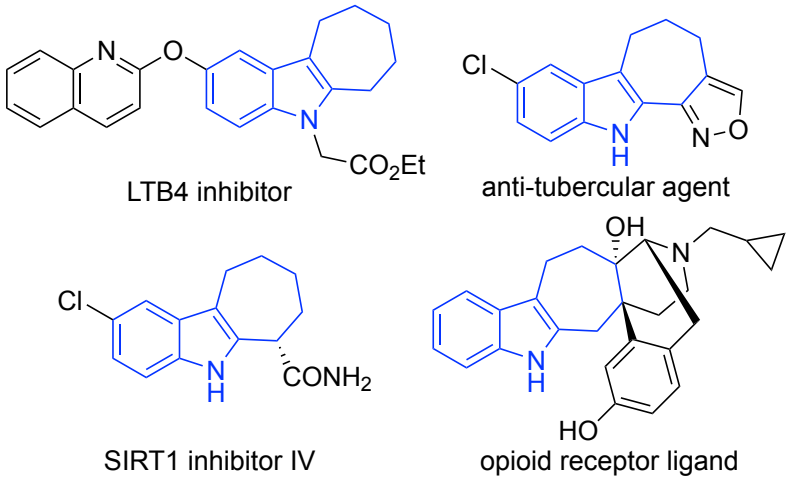
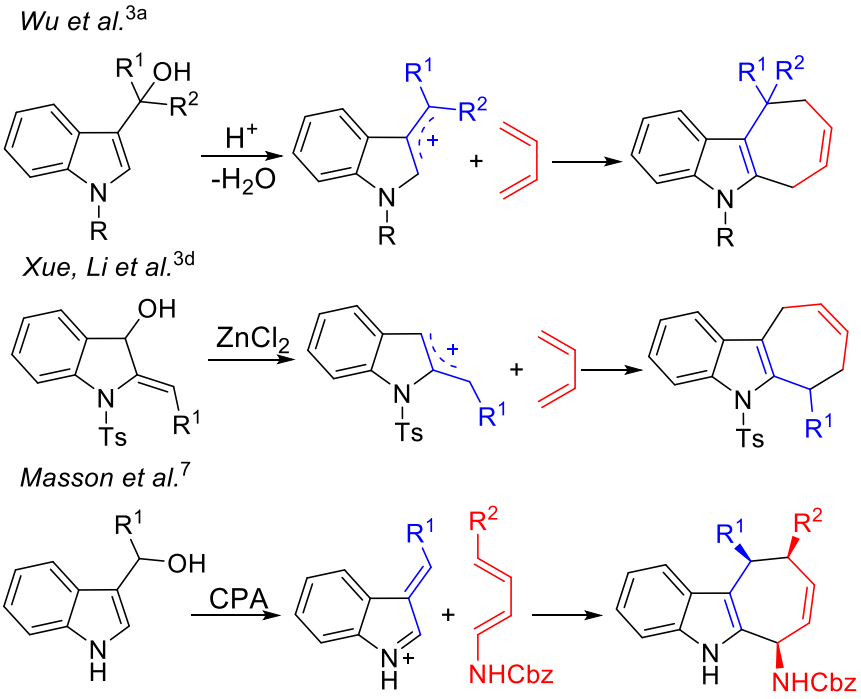


Figure 2. Non-natural cyclohepta[*b*]indoles derivatives.

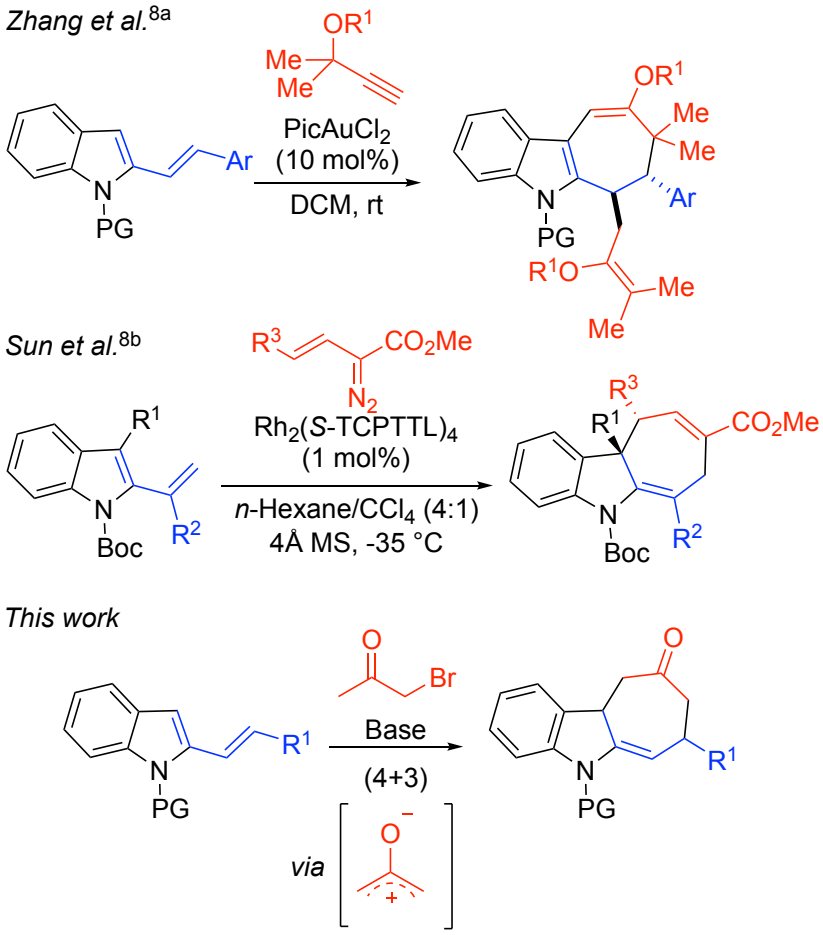
It is about this last aspect that Gaich and Stempel have made several useful points. Notably, apart from the well-known Fischer indole synthesis, limited to the synthesis of symmetrically substituted cyclohepta[*b*]indoles,[2] most reported methodologies involve the use of cycloaddition reactions,[3] sigmatropic rearrangements,[4] and palladium-catalyzed cyclizations.[5] The most representative and versatile protocols involve (4+3)[6] cycloadditions (Scheme 1) and were developed, beyond the examples reported by Gaich and Stempel, also in their enantioselective version.[7]



Scheme 1. Indolyl derivatives as 3C partners in (4+3) cycloadditions with dienes. CPA = Chiral Phosphoric Acid.

In these cycloaddition reactions, the indolyl moiety functions as the 3C partner, whereas (4+3) cycloaddition reactions having indoles as 4C component have become operative only more recently (Scheme 2).[8]

For example, in 2017 Zhang and co-workers reported a regioselective gold-catalyzed (4+3) cascade cycloaddition/CH functionalization of 2-vinylindoles and propargylic esters leading to highly substituted derivatives.[8a] In 2018, Sun described an enantioselective rhodium-catalyzed (4+3) cycloaddition of both 2- and 3-vinylindoles with vinyldiazoesters leading to dearomatized cyclohepta[*b*]indolines in high yields and enantiomeric excesses.[8b] A 3-alkenylindole was also considered as the reactive intermediate in the iron(III)-catalyzed reaction between simple indoles and o-hydroxychalcone.[8c] Taking into account these precedents and our interest in the synthesis of complex indole derivatives through cycloaddition reactions of 2-vinylindoles,[9] we decided to test the reactivity of 2-vinylindoles with oxyallyl cations in order to synthetize cyclohepta[*b*]indoles through (4+3) cycloaddition reactions. The use of oxyallyl cations as three-carbon partners in [3+*n*] cycloadditions has been widely studied and includes both (3+2)[10] and (4+3)[11] cycloaddition reactions. Oxyallyl cations can be generated from α-haloketones, α,α'-dihaloketones, allene oxides and by Nazarov cyclization,[12] among other precursors. We chose to focus our attention on the base-mediated dehydrohalogenation of α-haloketones. This approach, in fact, employs simple and easy-accessible starting materials allowing for the easy generation of diversely substituted oxyallyl cations. In this paper, we report a full account of the obtained results.

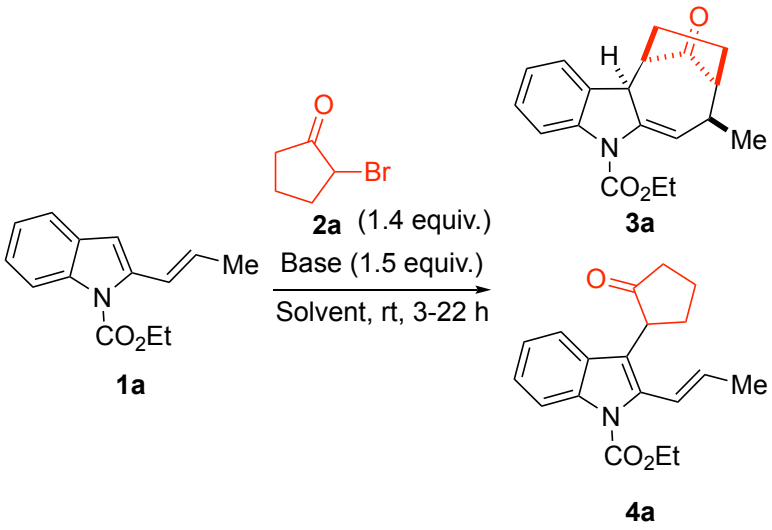


Scheme 2. Previous and present works using indoles as 4C components. $PicAuCl_2$ = dichloro(2-pyridinecarboxylato) gold. Rh_2(*S*-TCPTTL)$_4$ = Tetrakis[*N*-tetrachlorophthaloyl-(*S*)-tert-leucinato]dirhodium bis(ethyl acetate) adduct.

RESULTS AND DISCUSSION

In order to test the viability of our idea, 2-vinylindole **1a** and 2-bromocyclopentan-1-one **2a** were selected as model substrates and reacted in the presence of different bases and/or fluorinated solvents. These solvents, in fact, possess unique qualities, including the capability to activate carbonyl groups and stabilize cationic intermediates, and were reported as solvents of choice in related reactions.[13] The results obtained during the optimization of the reaction conditions are summarized in Table 1.

Table 1. Optimization of reaction conditions for the synthesis of **3a**.[a,c]



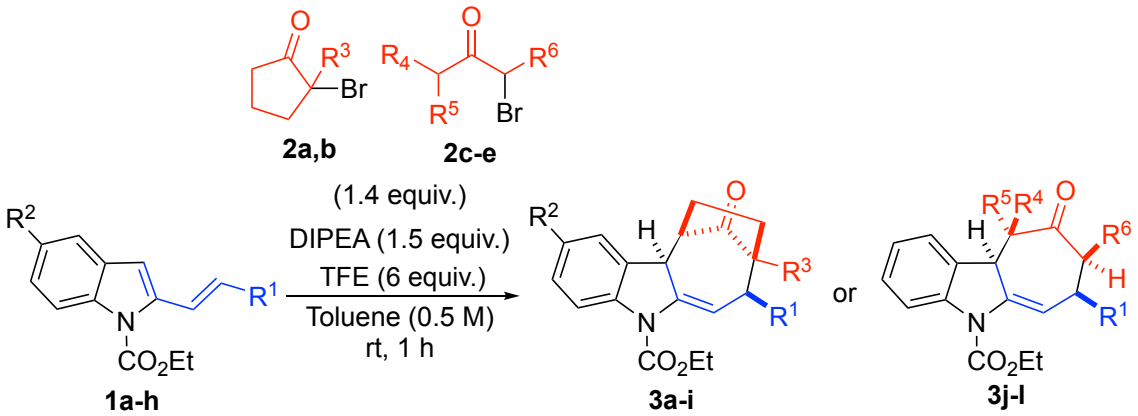
Entry	Base	Solvent	Time, h	3a[b] (%)	4a[b] (%)
1	Na_2CO_3	TFE (1 M)	3	67	17
2	Et_3N	TFE (1 M)	1	56	26
3	DIPEA	TFE (1 M)	1	75	17
4	DBU	TFE (1 M)	3	50	15
5[c]	DIPEA	TFE (1 M)	2	53	32
6	DIPEA	HFIP (1 M)	1	53	47
7	DIPEA	TFE (1 eq.), Toluene (0.5 M)	22	32	<5
8	DIPEA	TFE (3 eq.), Toluene (0.5 M)	6	53	<5
9	DIPEA	TFE (6 eq.), Toluene (0.5 M)	1	88	<5
10	DIPEA	TFE (6 eq.), CH_2Cl_2 (0.5 M)	1	74	13
11	DIPEA	$LiClO_4$ (1 eq.), Et_2O (0.5 M)	22	27	<5

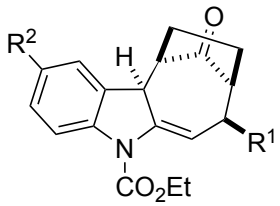
[a] *Reaction conditions:* **1a** (0.2 mmol), **2a** (0.28 mmol), base (0.3 mmol) in the stated solvent or in TFE/solvent mixture at rt for 1-22 h. [b] Isolated yield. [c] Reaction performed at -20 °C.

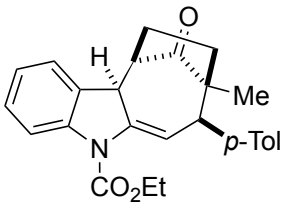
At the outset, we focused our attention on the influence of different bases on the reaction outcome using 2,2,2-trifluoroethanol (TFE) as solvent. Both inorganic, (Na_2CO_3, entry 1) and organic bases, (Et_3N, DIPEA and DBU, entries 2-4), led to the formation of desired dearomatized cycloadduct **3a** together with a minor amount of product **4a** arising from the nucleophilic addition of C3 of the indole nucleus on the *in situ* generated oxyallyl cation.[14] Better results in terms of the **3a**/**4a** ratio were achieved with DIPEA, which was selected as the best base for the following optimization steps. Then, in order to reduce the competitive formation of **4a**, we modified both reaction temperature and solvent. However, the reduction of reaction temperature down to -20 °C (entry 5), as well as the use of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (entry 6), had a negative impact on the formation of **3a**, increasing the formation of **4a**. Taking into accounts these results, we decided to verify the influence of TFE in promoting the formation of the desired cycloadduct **3a**, by a progressive increase of its

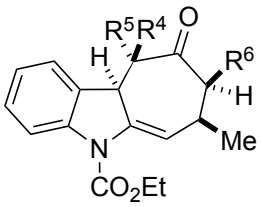
concentration from 1 to 6 equivalents in a 0.5 M solution of the reactants in toluene. As a result, we observed that the use of an equimolar amount of TFE (entry 7) significantly reduced the reaction rate but strongly inhibited the formation of **4a**. A better yield and faster reaction time were obtained using 3 equivalents of TFE (entry 8). The optimal 88% yield of **3a** was finally achieved employing 6 equivalents of fluorinated alcohol (entry 9). Switching from toluene to dichloromethane slightly worsened the reaction outcome in both terms of yield and selectivity (entry 10), while the use of a classical Lewis acid such as $LiClO_4$ in diethyl ether led to a significantly lower yield (entry 11).[11f] Notably, in all tested reactions, **3a** was isolated as a single diastereoisomer, the structure of which was fully elucidated by 1D- and 2D-NMR analyses (see ESI).

With the best conditions in hand, we then explored the scope of the reaction with different substituted 2-vinylindoles and α-bromoketones (Scheme 3).









3a: R^1 = Me, R^2 = H, 88%
3b: R^1 = *n*-Pr, R^2 = H, 58%
3c: R^1 = Cy, R^2 = H, 69%
3d: R^1 = 4-Me-C_6H_4, R^2 = H, 80%
3e: R^1 = 4-F-C_6H_4, R^2 = H, 70%
3f: R^1 = 4-OMe-C_6H_4, R^2 = H, 79%
3g: R^1 = 4-Me-C_6H_4, R^2 = F, 68%
3h: R^1 = 4-Me-C_6H_4, R^2 = OMe, 70%

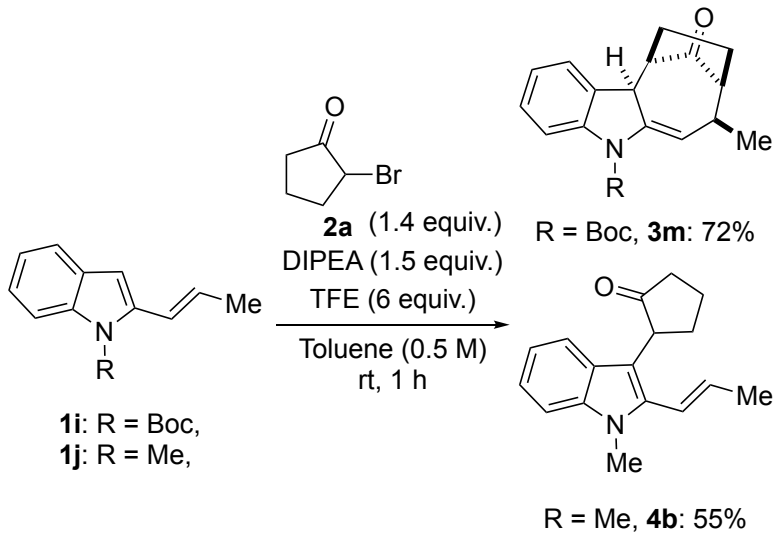
3i: 72%[b]

3j: R^5 = H, R^4 = R^6 = Me, 78%[b]
3k: R^5 = H, R^4 = R^6 = Ph, 55%[b]
3l: R^4 = R^5 = Me, R^6 = H, 37%[c]

Scheme 3.[a] Scope of the reaction between **1a-h** and **2a-e**. [a]*Reaction conditions:* **1a-h** (0.2 mmol), **2a-e** (0.28 mmol), DIPEA (0.3 mmol), TFE (1.2 mmol) in toluene (0.4 ml) for 1 h at rt. [b]TFE (1 M) was used as solvent for 24 h at rt. [c]Na_2CO_3 (0.3 mmol) was used as base in TFE (1 M) for 48 h at 40 °C.

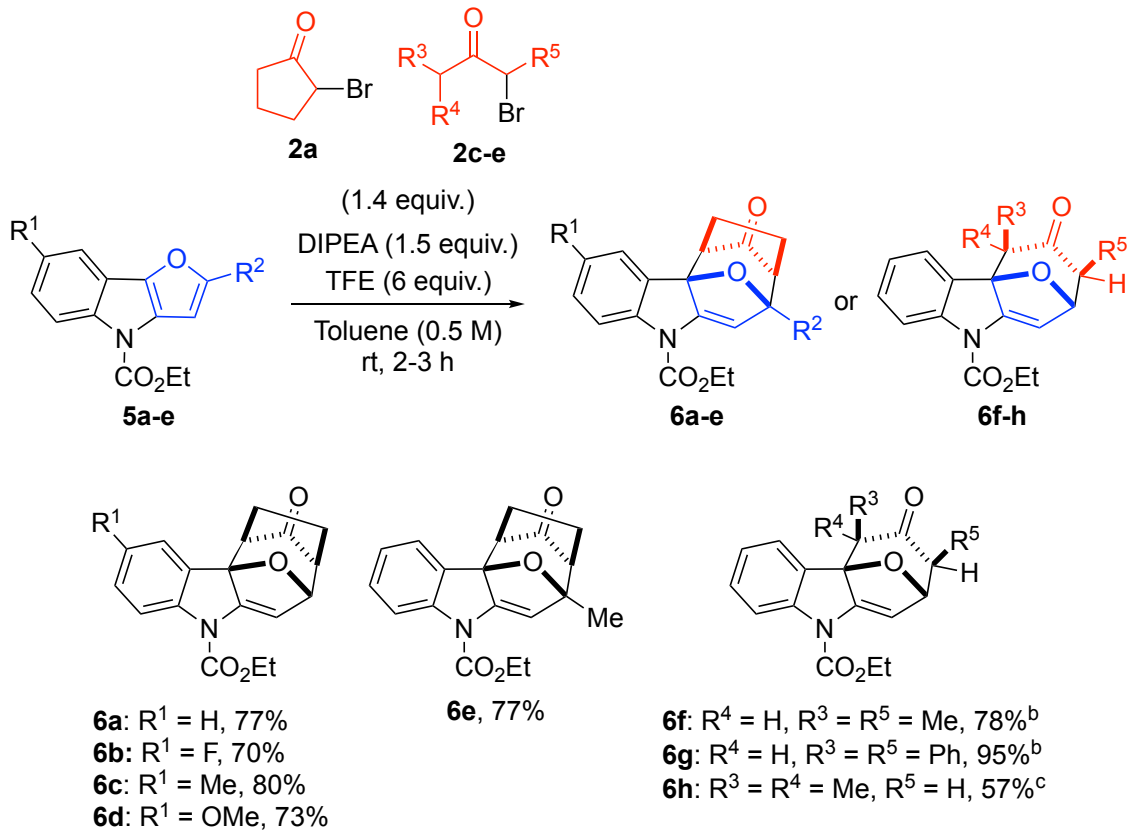
We first focused on the modification of the indole vinyl moiety by using different β-alkyl and β-aryl substituted 2-vinylindoles. The substitution of the methyl group with a longer alkyl chain or with a cyclohexyl ring was well tolerated and the corresponding indolines **3b** and **3c** were isolated in 58%

and 69% yield, respectively, in addition to residual amounts of starting vinylindoles, nucleophilic substitution products (less than <10%) and traces of other unidentified side products. Aryl-substituted 2-vinylindoles reacted efficiently as well. In particular, 4-methylstyrylvinylindole (**1d**) afforded **3d** in a satisfying 80% yield, while related vinylindoles bearing electron-withdrawing (**1e**) or electron-donating (**1f**) substituents led to cycloadducts **3e-f** in comparable 70 and 79% yields. Next, we introduced different substituents on 5-position of the indole skeleton in order to evaluate variation in the reactivity of the vinylindole due to a reduced or augmented nucleophilicity of the carbon in position 3. As a result, we observed that 5-fluoro derivative **1g** smoothly reacted with **2a** to give **3g** in 68% yield, while 5-methoxy-substituted **1h** led to **3h** in 70% yield. We then evaluated the influence of ketones other than 2-bromocyclopentan-1-one on the reaction course. The employment of 2-bromo-2-methylcyclopentan-1-one (**2b**) was tolerated, however, the reaction performed under optimized conditions resulted in a significantly lower conversion of starting materials even after prolonged reaction times (less than 10% after 96 h at rt). Surprisingly, with this more substituted ketone the use of TFE as sole solvent (1 M) permitted the isolation of **3i** in a satisfying 72% yield. Similarly, symmetrically substituted acyclic ketones **2c** and **2d** led to the corresponding products **3j** and **3k** in 78% and 55% yields, respectively, only when TFE was used as solvent. In all the last cases a residual amount of unreacted vinylindole was recovered along with traces of unidentified by-products. On the other hand, the reaction between **1a** and non-symmetrically disubstituted ketone **2e** was more challenging and did not proceed even in TFE at 40 °C. In this case, after a brief screening of reactions conditions, we were able to isolate **3l** as single isomer in moderate 37% yield, only by using Na_2CO_3 in TFE (1 M) for 48 h at 40 °C. Finally, we verified the influence of the substituent on vinylindole nitrogen employing *N*-Boc and *N*-methyl 2-vinylindoles **1i** and **1j** under optimized reaction conditions. The use of Boc-derivative **1i**, led to results comparable to those obtained with **1a**, affording **3m** in 72% yield. On the other hand, the presence of a mild electron-donating group on the indole nitrogen gave the nucleophilic addition product **4b** as exclusive reaction product in 55% yield beside a small amount of unreacted **1j**, confirming the pivotal presence of an electron-withdrawing protecting group on vinylindole nitrogen in order to support the cycloaddition pathway (Scheme 4).[15]



Scheme 4. Reaction between **1i-j** and **2a**.

Moreover, in the context of our studies on the metal-catalyzed functionalization of indoles,[16] we recently reported the synthesis of ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylates, an interesting class of heterocyclic compounds, which could be employed in gold-catalyzed reactions to give indolin-3-one derivatives.[17] Taking a look into the structure of these substrates, we observed that they could be considered as an attractive alternative to 2-vinylindoles, in which the diene system is embedded in the furan ring and constrained in a *s*-cis conformation. Thus, we decided to test their reactivity in these (4+3) cycloadditions under the previously optimized conditions in order to expand the scope of our transformation (Scheme 5).



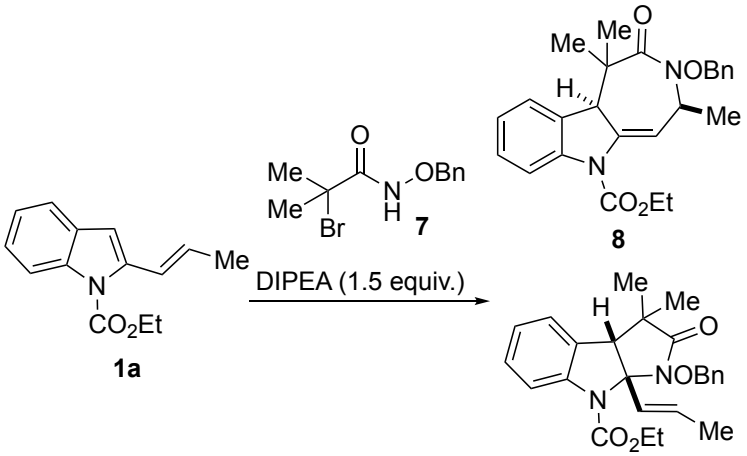
Scheme 5.[a] Scope of the reaction between **5a-e** and **2a-e**. [a]*Reaction conditions:* **5a-e** (0.2 mmol), **2a**, **c-e** (0.28 mmol), DIPEA (0.3 mmol), TFE (1.2 mmol) in toluene (0.4 ml) for 2-3 h at rt. [b] TFE (1 M) was used as solvent for 24 h at rt. [c] Na_2CO_3 (0.3 mmol) was used as base in TFE (1 M) for 48 h at 40 °C.

As supposed, when we reacted 4*H*-furo[3,2-*b*]indole-4-carboxylate **5a** with cyclopentyl oxyallyl cation generated *in situ* with TFE and DIPEA, we were able to isolate 7,8-dihydro-5*H*-7,10a-epoxycyclohepta[*b*]indole derivative **6a** as single product in high yield (77%) after 2 h. Notably, in this case no product arising from nucleophilic substitution on furan moiety was observed or isolated. As for **3a**, the structure of indoline **6a** was confirmed by 2D-NMR spectra and by X-Ray diffraction analysis on a single crystal (see Supporting Information for details).

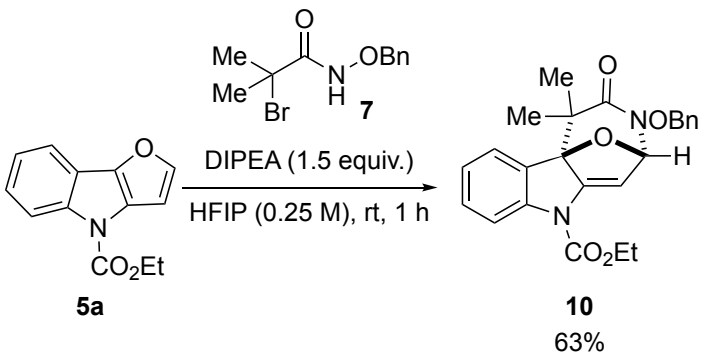
Similarly, 5-substituted furoindoles **5b-d** were efficiently transformed into the corresponding cycloaddition products **6b-d**, suggesting that the presence of both electron-withdrawing and electron-donating groups on this position does not affect the reaction outcome. We also employed furoindoles

substituted on the furan moiety. In this case, methyl-substituted **5e** afforded **6e** in 77% yield after 3 h. Finally, as for 2-vinylindoles, 2-bromopentan-3-one (**2c**) and 1-bromo-1,3-diphenylpropan-2-one (**2d**) were used instead than **2a**. The reaction of these haloketones required the use of TFE as solvent and resulted in the isolation of **6f** and **6g** in 78% and 95% yield, respectively. In addition, 1-bromo-3-methylbutan-2-one (**2e**) reacted with **5a** to give **6h** as single isomer in 57% yield, but only when Na_2CO_3 was used as base in TFE at 40 °C for 48 h.

Further, considering the great number of reports on cycloaddition reactions with aza-oxyallylcations[18] we decided to examine whether these substrates could be suitable partners in the (4+3) cycloaddition with vinylindole **1a** under our optimized conditions (Scheme 6). However, in this case, the reactions were extremely slow and only traces of products were observed after 24 h. Using pure TFE as solvent, we were able to isolate a 14% yield of **8** after 24 h, while the switch to other fluorinated alcohols such as 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) led to rapid and full conversion of starting material to give a separable 1:1 mixture of (4+3) and (3+2) cycloaddition products, **8** and **9**,[19] in overall 82% yield. Further studies to improve the selectivity towards (4+3) cycloadducts are now in progress in our laboratory. In addition, we tested the reactivity of furoindole **5a** and, in this case, we were able to isolate cycloadduct **10** as single product in 63% yield.

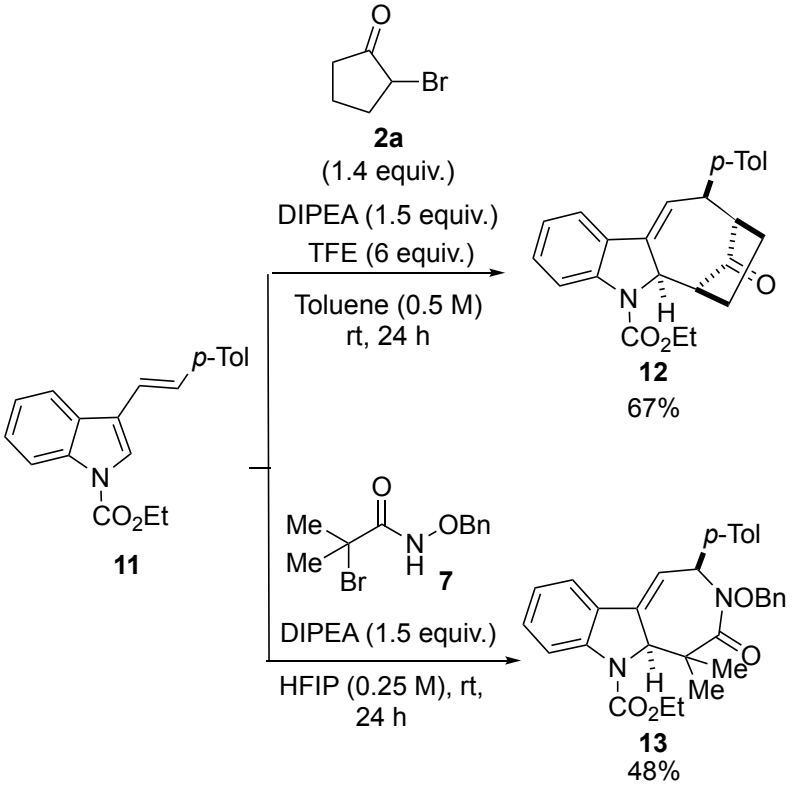


	8	9
TFE (6 equiv.), Toluene (0.5 M), rt, 24 h:	<10%	-
TFE (1 M), rt, 24 h:	14%	-
HFIP (0.25 M), rt, 1 h:	42%	40%



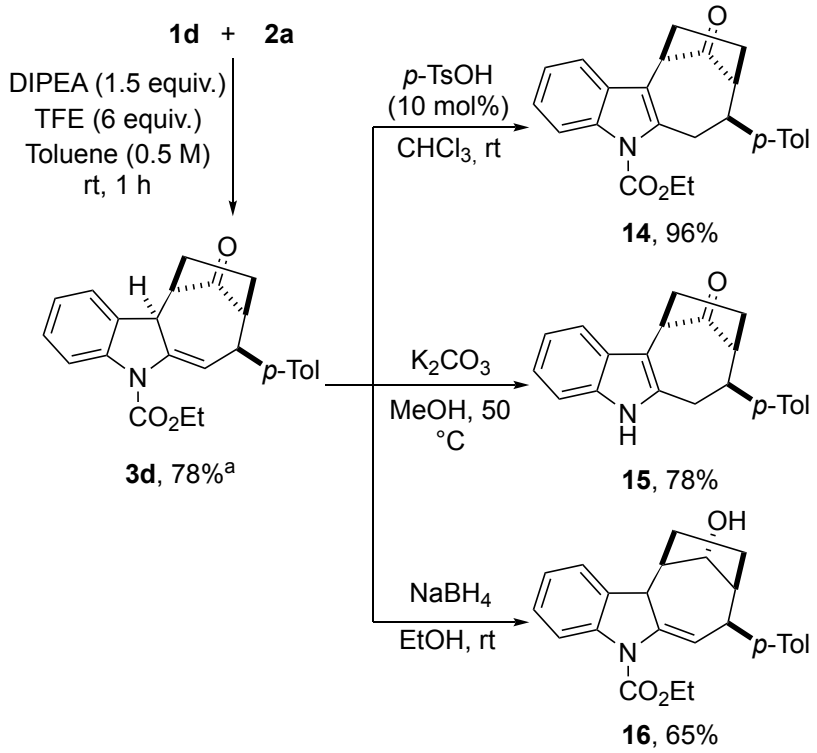
Scheme 6. Extension of the scope to aza-oxyallylcations.

Subsequently, we studied the behavior of 3-vinylindoles by reacting **11** and **2a** under the optimized conditions. Substrate **11** was less reactive than the isomeric 2-vinylindole **3d** and the reaction required 24 h to afford cycloadduct **12** in 67% yield (Scheme 7). In addition, the same substrate reacted with azaoxyallyl cation generated from **7** to give (4+3) derivative **13** as single product using HFIP as solvent. In this case the reaction was also slow and required 24 h to provide **13**, in addition to unreacted 3-vinylindole.



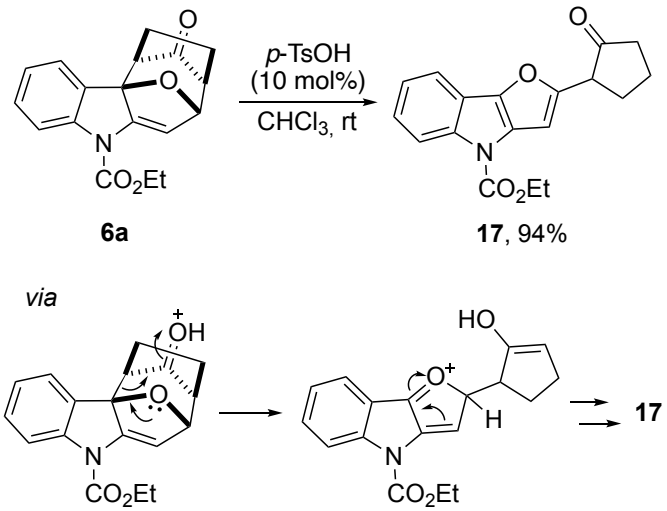
Scheme 7. Reaction between 3-vinylindole **11** and **2a** or **7**.

Having synthesized a series of cyclohepta[*b*]indoles **3a-l**, we finally focussed our attention in proposing simple and effective modifications of these scaffolds. To this end, **3d** was prepared on a gram scale and it was subjected to selected transformations (Scheme 8). Thus, we observed that **3d** quantitatively aromatized to give **14** up on treatment with catalytic amounts of *p*-TsOH, while under basic hydrolytic conditions, NH-free aromatic cycloheptaindole **15** was isolated in 78% yield. Moreover, the cycloheptanone ring of **3d** was effectively and selectively reduced with sodium borohydride to give the corresponding alcohol **16** in 65% yield.



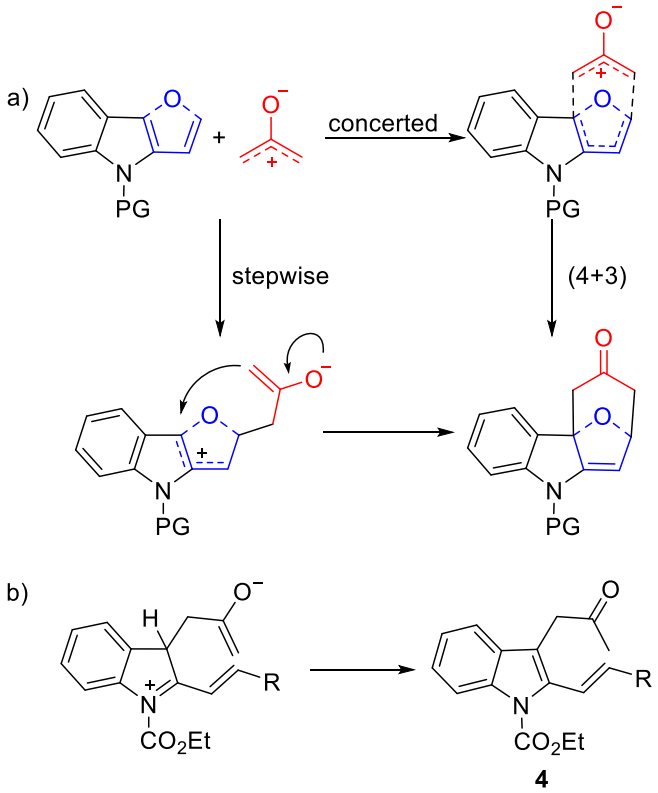
Scheme 8. Selective functional group transformations on product **3d**. [a]Reaction performed on 1.64 mmol scale.

As above mentioned, aromatization of **3d** easily occurred under acid conditions affording the corresponding product almost quantitatively. For this reason, we became interested in verifying the behavior of **6a** under the same reaction conditions, considering that aromatization of such a product would probably require the ring-opening of the epoxy ring. Nevertheless, when we treated **6a** with catalytic amounts of *p*-TsOH in chloroform, we isolated the sole 2-(2-oxocyclopentyl)-4*H*-furo[3,2-*b*]indole derivative **17** in high 94% yield (Scheme 9). This result was not unexpected and a similar behavior has already been described by Harmata for the acidic treatment of cycloadducts synthetized starting from 2-chloro-cyclopentanones and furans.[20] Additionally, the conversion of **6a** to substituted furan **17** could be mechanistically ascribed to a Grob fragmentation[21] of protonated **6a**, followed by the re-aromatization of the furan moiety and keto-enol tautomerism to regenerate the cyclopentanone ring (Scheme 9).



Scheme 9. Behavior of **6a** under acid conditions.

A plausible reaction mechanism for the (4+3)-cycloaddition reactions is not easy to describe nor to predict. In general, the reaction can be viewed as a (4+3) cycloaddition that relies on the use of α-haloketones as oxyallyl cation precursors (C3 fragment) and 2-vinylindoles or furoindoles as dienes (C4 fragment). Moreover, based on the IUPAC convention, the process is a homologue of the Diels-Alder reaction, a standard [4+2] cycloaddition considering the numbers of electrons involved. As reported in the literature,[11b,c,f] these reactions occur through pathways ranging from a classical pure concerted process to processes that are stepwise (Scheme 10).



Scheme 10. a) Plausible reaction mechanism for (4+3) cycloaddition with oxyallyl cations; b) formation of nucleophilic substitution compound **4**.

The nature of the substrates involved as well as the reaction conditions employed affect the mechanism and in turn the chemical and stereochemical outcome of the reaction. In our cycloadditions, we observed complete regio- and diastereoselectivity. The stereochemistry of the isolated compounds arose from an *endo* approach between the diene and the dienophile (Figure 3).

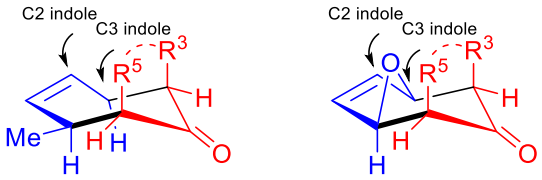


Figure 3. Stereochemical outcome derived from endo approach.

Both open chain internal-external ring dienes (vinylindoles) and dienes embedded in a furan ring (furoindoles) gave analogous results. The same occurred using both cyclic and acyclic oxyallyl cation precursors. Based on these results, our reactions could be viewed as proceeding via a concerted mechanism. However, looking at the electronic features of the reacting dienes (polarized, electron rich) and dienophiles (electrophilic, TFE-stabilized), a pseudoconcerted or fast stepwise process cannot be excluded. In this context, Cramer[22] and coworkers recently reported the results of their computational studies on the mechanism of related reactions. In particular, they demonstrated that stepwise processes are more favored for electron-rich dienes and electrophilic oxyallyl cations. Furthermore, a mechanism involving cationic intermediates is plausibly operating in the reaction of 2-vinylindoles as demonstrated by the isolation of compound **4a**, arising from the first intermediate of the stepwise process by a proton elimination/re-aromatization reaction (Scheme 10).

Finally, several remarks on the role of TFE on the reaction outcome can be made. The role of TFE in these reactions is to assist and accelerate the deprotonation of α-haloketones and their subsequent ionization, via hydrogen bond formation. Cyclic ketones require low amounts of TFE probably because they are sufficiently reactive to participate in the cycloaddition. Indeed, an excess of TFE lowers the reaction selectivity favoring the formation of undesired nucleophilic substitution compounds. However, when open chain and hindered substrates were involved pure TFE must be used as solvent, in some case in the presence of a base stronger than DIPEA in order to facilitate both the enolization and the abstraction steps.

CONCLUSION

In conclusion, we developed a selective and efficient synthesis of complex cyclohepta[*b*]indole derivatives through dearomative (4+3) cycloaddition reaction of vinylindoles or 4*H*-furo[3,2-*b*]indoles with oxyallyl cations. Oxyallyl cations were efficiently generated *in situ* starting from the corresponding α-haloketones using DIPEA and TFE under mild reaction conditions.

Differently from the well-known methods for synthetizing cyclohepta[*b*]indoles, in which the indolyl moiety contributes to the (4+3) cycloaddition as 3C unit, our approach exploits the ability of vinylindoles to react as 4C partner in these cycloaddition reactions. It is worth noting that the use of

these latter substrates in (4+3) cycloaddition reactions has been scarcely described in literature. Moreover, the existing methodologies require the intermediacy of a metal vinylcarbene intermediate as 3C partner, generated from propargyl esters or vinyldiazoacetates under gold and rhodium catalysis, respectively.[8] Thus, the results obtained herein represent an expansion of the reactivity of vinylindoles as 4C partner with C3 counterparts such as oxyallyl cations and demonstrate their utility as building blocks to create complex molecular architectures. Finally, clear advantage resides in the use of simple and inexpensive starting materials, solvents, and additives that do not require the use of strictly controlled reaction conditions. The extension of the scope to other substrates such as 3-vinylindoles and aza-oxyallylcations was also briefly explored as were further transformations of the obtained products.

EXPERIMENTAL SECTION

All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Silica gel F254 thin-layer plates were employed for thin-layer chromatography (TLC). Silica gel 40–63 micron/60 Å was employed for flash column chromatography. Melting points were measured with a Perkin- Elmer DSC 6 calorimeter at a heating rate of 5 °C/min and are uncorrected. ^{1}H and ^{13}C-NMR spectra were determined with a Varian-Gemini 300, a Bruker 300, 500 Avance or 600 Bruker spectrometers at room temperature in $CDCl_3$, CD_2Cl_2 C_6D_6 or acetone-d_6 with residual solvent peaks as the internal reference. The APT sequences were used to distinguish the methine and methyl carbon signals from those arising from methylene and quaternary carbon atoms. Two-dimensional NMR experiments were performed for products **3a, 3d, 3i, 3j, 3l, 6a, 6f, 6h, 8, 9, 10, 12, 16** and **17** to aid the assignment of structures. Low-resolution MS spectra were recorded with a Thermo-Finnigan LCQ advantage AP electrospray/ion trap equipped instrument using a syringe pump device to directly inject sample solutions.

2-Vinylindoles **1a-j**,[23] ethyl 4H-furo[3,2-b]indole-4-carboxylates **5a-e**,[17] ethyl (*E*)-3-(4-methylstyryl)-1*H*-indole-1-carboxylate **11**,[24] α-haloketones **2a-e**[25] and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **7**[19] are known compounds and were prepared according to literature procedures.

General procedure for the reaction between 2-vinylindoles 1a-i and α-haloketones 2a-e

To a stirring solution of 2-vinylindole **1a-i** (0.2 mmol, 1.0 equiv.), α-haloketone **2a-e** (0.28 mmol, 1.4 equiv.) TFE (86.4 µl, 1.2 mmol, 6.0 equiv.) in toluene (0.4 ml, 0.5 M), DIPEA (52.3 µl, 0.3 mmol, 1.5 equiv.) was added and the mixture was stirred for 1 h at room temperature. Solvent was then removed and the crude was purified by column chromatography to yield the corresponding cyclohepta[*b*]indole **3a-m.**

*Ethyl 7-methyl-12-oxo-7,8,9,10,11,11a-hexahydro-5H-8,11-methanocycloocta[b]indole-5-carboxylate (**3a**).* General procedure was followed using ethyl (*E*)-2-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate **1a** (46.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **2a** (46.0 mg, 0.28 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **3a** (55 mg, 88%) as a yellow thick wax. ^{1}H NMR (300 MHz, C_6D_6): 7.91 (d, J = 8.2 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 6.84 (t, J = 7.4 Hz, 1H), 6.76 (d, J = 7.7 Hz, 1H), 6.70 (t, J = 3.1 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 3.69 (m, 1H), 2.69 (m, 1H), 2.49 (m, 1H), 2.14 (m, 1H), 1.41 – 1.28 (m, 3H), 1.10 (m,

1H), 1.02 – 0.90 (m, 6H). $^{13}C\{^{1}H\}$ NMR (126 MHz, C_6D_6): 219.3 (C), 152.5 (C), 142.7 (C), 141.1 (C), 130.1 (C), 127.9 (CH), 123.5 (CH), 123.2 (CH), 116.7 (CH), 116.2 (CH), 61.7 (CH_2), 54.3 (CH), 49.4 (CH), 47.6 (CH), 36.6 (CH), 22.7 (CH_3), 21.1 (CH_2), 20.4 (CH_2), 13.9 (CH_3). ESI(+)-MS: m/z(%) = 312 (100) $[M+H]^+$. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found C, 73.44; H, 6.77; N, 4.51.

*Ethyl 12-oxo-7-propyl-7,8,9,10,11,11a-hexahydro-5H-8,11-methanocycloocta[b]indole-5-carboxylate (**3b**)*. General procedure was followed using ethyl (*E*)-2-(pent-1-en-1-yl)-1*H*-indole-1-carboxylate **1b** (51.5 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **2a** (46.0 mg, 0.28 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **3b** (39 mg, 58%) as a yellow thick wax. ^{1}H NMR (300 MHz, $CDCl_3$): 7.76 (d, *J* = 8.2 Hz, 1H), 7.26 (m, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.60 (t, *J* = 3.1 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 1H), 2.86 (m, 1H), 2.44 (d, *J* = 7.0 Hz, 1H), 2.31 (s, 1H), 1.85 – 1.76 (m, 2H), 1.66 – 1.48 (m, 2H), 1.44 (m, 6H), 1.29 (m, 1H), 0.96 (t, *J* = 6.9 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, C_6D_6): 219.5 (C), 152.5 (C), 142.7 (C), 141.5 (C), 130.2 (C), 128.0 (CH), 123.5 (CH), 123.3 (CH), 116.2 (CH), 115.5 (CH), 61.7 (CH_2), 52.6 (CH), 50.1 (CH), 47.5 (CH), 41.9 (CH), 38.9 (CH_2), 21.2 (CH_2), 20.9 (CH_2), 20.7 (CH_2), 13.9 (CH_3), 13.7 (CH_3). ESI(+)-MS: m/z(%) = 393 (100) $[M+CH_3ONa]^+$. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found C, 74.23; H, 7.45; N, 4.12.

*Ethyl 7-cyclohexyl-12-oxo-7,8,9,10,11,11a-hexahydro-5H-8,11-methanocycloocta[b]indole-5-carboxylate (**3c**)*. General procedure was followed using ethyl (*E*)-2-(2-cyclohexylvinyl)-1*H*-indole-1-carboxylate **1c** (59.5 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **2a** (46.0 mg, 0.28 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **3c** (52 mg, 69%) as a white thick wax. ^{1}H NMR (500 MHz, C_6D_6): 7.97 (d, *J* = 8.2 Hz, 1H), 7.09 (m, 1H), 6.97 (t, *J* = 3.6 Hz, 1H), 6.85 (td, *J* = 7.4, 1.0 Hz, 1H), 6.81 (m, 1H), 4.06 (m, 2H), 3.66 (m, 1H), 2.69 (dq, *J* = 7.9, 1.8 Hz, 1H), 2.45 (m, 1H), 2.17 (m, 1H), 1.74 – 1.59 (m, 4H), 1.56 (m, 1H), 1.48-1.39 (m, 3H), 1.33 (m, 1H), 1.18 – 1.05 (m, 6H), 0.99 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, C_6D_6): 219.4 (C), 152.6 (C), 142.7 (C), 141.9 (C), 130.3 (C), 128.0 (CH), 123.5 (CH), 123.5 (CH), 116.2 (CH), 113.9 (CH), 61.7 (CH_2), 51.6 (CH), 50.4 (CH), 48.1 (CH), 47.4 (CH), 44.3 (CH), 30.7 (CH_2), 30.2 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 22.3 (CH_2), 21.3 (CH_2), 13.9 (CH_3). ESI(+)-MS: m/z(%) = 380 (100) $[M+H]^+$. Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69. Found C, 75.84; H, 7.73; N, 3.70.

*Ethyl 12-oxo-7-(p-tolyl)-7,8,9,10,11,11a-hexahydro-5H-8,11-methanocycloocta[b]indole-5-carboxylate (**3d**)*. General procedure was followed using ethyl 2-(4-methylstyryl)-1*H*-indole-1-carboxylate **1d** (61.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **2a** (46.0 mg, 0.28 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **3d** (60 mg 80%) as a yellow solid (m.p. 94-99° C). ^{1}H NMR (300 MHz, C_6D_6): 8.13 (d, *J* = 8.2 Hz, 1H), 7.41 (m, 1H), 7.31 – 7.18 (m, 3H overlapped with C_6D_6), 7.07 (d, *J* = 7.9 Hz, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 4.12 (m, 2H), 3.87 (s, 2H), 2.87 (m, 1H), 2.71 (m, 1H), 2.21 (s, 3H), 1.78 (m, 1H), 1.44 (m, 2H), 1.34 (m, 1H), 1.03 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, C_6D_6): 218.2 (C), 152.6 (C), 143.0 (C), 142.9 (C), 142.0 (C), 135.8 (C), 130.1 (C), 129.5 (2xCH), 128.2 (CH), 127.6 (2xCH), 123.6 (CH), 123.3 (CH), 116.3 (CH), 115.1 (CH), 61.9 (CH_2), 56.0 (CH), 49.8 (CH), 48.1 (CH), 47.6 (CH), 21.2 (CH_2), 21.0 (CH_2), 20.7 (CH_3), 14.0 (CH_3). ESI(+)-MS: m/z(%) = 388

(100) $[M+H]^+$. Anal. Calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61. Found C, 77.63; H, 6.52; N, 3.60.

*Ethyl 7-(4-fluorophenyl)-12-oxo-7,8,9,10,11,11a-hexahydro-5H-8,11-methanocycloocta[b]indole-5-carboxylate (**3e**)*. General procedure was followed using ethyl (*E*)-2-(4-fluorostyryl)-1*H*-indole-1-carboxylate **1e** (62.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **2a** (46.0 mg, 0.28 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **3e** (55 mg, 70%) as a white solid (m.p. 108-112° C). ^{1}H NMR (300 MHz, C_6D_6): 8.08 (d, J = 8.2 Hz, 1H), 7.27 (m, 1H, overlapped with C_6D_6), 7.23 (m, 1H), 7.04 (m, 2H), 6.98 (m, 1H), 6.93 – 6.82 (m, 3H), 4.13 (q, J = 7.1 Hz, 2H), 3.84 (m, 1H), 3.73 (m 1H), 2.86 (m, 1H), 2.55 (d, J = 6.8 Hz, 1H), 1.71 – 1.56 (m, 1H), 1.50 – 1.19 (m, 3H), 1.03 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, C_6D_6): 218.0 (C), 161.6 (d, J = 240.2 Hz, C), 152.6 (C), 142.8 (C), 142.2 (C), 141.6 (d, J = 3,1 Hz, C), 129.9 (C), 129.1 (d, J = 8,1 Hz, 2xCH), 128.3 (CH), 123.7 (CH), 123.3 (CH), 116.3 (CH), 115.5 (d, J = 20.6 Hz, 2xCH), 114.6 (CH), 62.0 (CH_2), 55.7 (CH), 49.7 (CH), 48.1 (CH), 47.1 (CH), 21.2 (CH_2), 20.8 (CH_2), 14.0 (CH_3). ESI(+)-MS: m/z(%) = 392 (100) $[M+H]^+$. Anal. Calcd for $C_{24}H_{22}FNO_3$: C, 73.64; H, 5.67; N, 3.58. Found C, 73.71 H, 5.69; N, 3.59.

*Ethyl 7-(4-methoxyphenyl)-12-oxo-7,8,9,10,11,11a-hexahydro-5H-8,11-methanocycloocta[b]indole-5-carboxylate (**3f**)*. General procedure was followed using ethyl 2-(4-methoxystyryl)-1*H*-indole-1-carboxylate **1f** (64.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **2a** (46.0 mg, 0.28 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **3f** (64 mg, 79%) as a yellow solid (m.p. 135-138° C). ^{1}H NMR (300 MHz, C_6D_6): 8.12 (d, J = 8.2 Hz, 1H), 7.41 (s, 1H), 7.26 (m, 1H, overlapped with C_6D_6), 7.22 (m, 2H), 6.98 (td, J = 7.4, 0.9 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 6.89 – 6,84 (m, 2H), 4.17 – 4.10 (m, 2H), 3.86 (m, 2H), 3.42 (s, 3H), 2.88 (m, 1H), 2.71 (d, J = 7.5 Hz, 1H), 1.80 (m, 1H), 1.51 – 1.28 (m, 3H), 1.04 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, C_6D_6): 218.3 (C), 158.7 (C), 152.7 (C), 142.9 (C), 141.9 (C), 138.0 (C), 130.1 (C), 128.6 (2xCH), 127.2 (CH), 123.6 (CH), 123.3 (CH), 116.3 (CH), 115.3 (CH), 114.3 (2xCH), 61.9 (CH_2), 56.2 (CH_3),54.6 (CH), 49.8 (CH), 48.1 (CH), 47.3 (CH), 21.3 (CH_2), 21.0 (CH_2), 14.0 (CH_3). ESI(+)-MS: m/z(%) = 404 (100) $[M+H]^+$. Anal. Calcd for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found C, 74.35; H, 6.27; N, 3.48.

*Ethyl 2-fluoro-12-oxo-7-(p-tolyl)-7,8,9,10,11,11a-hexahydro-5H-8,11-methanocycloocta[b]indole-5-carboxylate (**3g**)*. General procedure was followed using ethyl 5-fluoro-2-(4-methylstyryl)-1*H*-indole-1-carboxylate **1g** (64.6 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **2a** (46.0 mg, 0.28 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **3g** (59 mg, 68%) as a yellow solid (m.p. 151-153° C). ^{1}H NMR (300 MHz, C_6D_6): 7.77 (dd, J = 9.0, 4.6 Hz, 1H), 7.18 (t, J = 3.2 Hz, 1H), 7.11 (m, 2H, overlapped with C_6D_6), 6.91 (m, 2H), 6.71 (m, 1H), 6.44 (m, 1H), 3.94 (m, 2H), 3.69 (m, 1H), 3.58 (m, 1H), 2.53 (m, 2H), 2.06 (s, 3H), 1.61 (m, 1H), 1.27 (m, 2H), 1.08 (m, 1H), 0.86 (t, J = 7.1, 3H). ^{13}C{^{1}H} NMR (75 MHz, C_6D_6): 217.6 (C), 158.5 (d, J = 242,2 Hz, C), 152.3 (C), 142.7 (C), 141.6 (C), 138.7 (C), 135.8 (C), 131.9 (d, J = 8,4 Hz, C), 129.4 (2xCH), 127.4 (2xCH), 117.1 (d, J = 7,8 Hz, CH), 115.3 (CH), 114.4 (d, J = 22,8 Hz, CH), 110.4 (d, J = 24,3 Hz, CH), 61.8 (CH_2), 55.7 (CH), 49.2 (CH), 47.8 (CH), 47.4 (CH), 21.0 (CH_2), 20.8 (CH_2), 20.5 (CH_3), 13.8 (CH_3). ESI(+)-MS: m/z(%) = 428 (100) $[M+Na]^+$. Anal. Calcd for $C_{25}H_{24}FNO_3$: C, 74.06; H, 5.97; N, 3.45. Found C, 73.88; H, 5.99; N, 3.44.

*Ethyl 2-methoxy-12-oxo-7-(p-tolyl)-7,8,9,10,11,11a-hexahydro-5H-8,11-methanocycloocta[b] indole-5-carboxylate (**3h**)*. General procedure was followed using ethyl 5-methoxy-2-(4-methylstyryl)-1*H*-indole-1-carboxylate **1h** (67.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **2a** (46.0 mg, 0.28 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **3h** (57 mg, 70%) as a white solid (m.p. 83-85° C). ^{1}H NMR (300 MHz, C_6D_6): 7.91 (d, *J* = 8.9 Hz, 1H), 7.28 (m, 1H), 7.12 (m, 2H overlapped with C_6D_6), 6.92 (d, *J* = 7.8 Hz, 2H), 6.69 (m, 1H), 6.59 (m, 1H), 4.00 (m, 2H), 3.73 (m, 2H), 3.26 (s, 3H), 2.72 (m, 1H), 2.56 (m, 1H), 2.06 (s, 3H), 1.66 (dt, *J* = 10.6, 4.7 Hz, 1H), 1.38 – 1.17 (m, 3H), 0.91 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, C_6D_6): 218.0 (C), 156.7 (C), 152.4 (C), 142.9 (C), 142.1 (C), 136.3 (C), 135.7 (C), 131.3 (C), 129.3 (2xCH), 127.4 (2xCH), 116.9 (CH), 114.9 (CH), 113.3 (CH), 109.0 (CH), 61.6 (CH_2), 55.8 (CH), 54.8 (CH), 49.7 (CH), 48.2 (CH), 47.5 (CH_3), 21.1 (CH_2), 20.9 (CH_2), 20.5 (CH_3), 13.9 (CH_3). ESI(+)-MS: m/z(%) = 418 (100) $[M+H]^+$. Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found C, 74.92; H, 6.51; N, 3.34.

*Ethyl 7,8,10-trimethyl-9-oxo-8,9,10,10a-tetrahydrocyclohepta[b]indole-5(7H)-carboxylate (**3i**)*. General procedure was followed using ethyl 2-(4-methylstyryl)-1*H*-indole-1-carboxylate **1d** (61.0 mg, 0.2 mmol) and 2-bromo-5-methylcyclopentan-1-one **2b** (49.5 mg, 0.28 mmol) for 24 at rt. TFE (0.2 ml, 1 M) was used as solvent instead than toluene. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **3i** (58 mg 72%) as white thick wax. ^{1}H NMR (500 MHz, C_6D_6): 8.02 (d, *J* = 8.2 Hz, 1H), 7.22 (t, *J* = 3.2 Hz, 1H), 7.12(m, 1H), 7.03 (bs, 2H), 6.93 (d, *J* = 7.9 Hz, 2H), 6.89 – 6.86 (m, 2H), 3.98 (m, 2H), 3.86 (d, *J* = 2.6 Hz, 1H), 3.23 (t, *J* = 3.1 Hz, 1H), 2.91 (m, 1H), 2.15 (m, 1H), 2.11 (s, 3H), 1.35 (m, 1H), 1.22 (m, 1H), 1.10 (m, 1H), 0.92 – 0.86 (m, *J* = 12.4, 5.2 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, C_6D_6): 220.4 (C), 152.5 (C), 142.9 (C), 141.6 (C), 140.8 (C), 135.9 (C), 130.1 (C), 128.9 (2xCH), 128.1 (2xCH), 128.0 (CH), 123.5 (CH), 123.1 (CH), 117.4 (CH), 116.2 (CH), 61.7 (CH_2), 53.8 (C), 52.2 (CH), 50.6 (CH), 48.1 (CH), 30.0 (CH_2), 21.7 (CH_3), 20.6 (CH_3), 19.6 (CH_2), 13.8 (CH_3). ESI(+)-MS: m/z(%) = 402 (100) $[M+H]^+$. Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found C, 77.62; H, 6.76; N, 3.50.

*Ethyl 7,8,10-trimethyl-9-oxo-8,9,10,10a-tetrahydrocyclohepta[b]indole-5(7H)-carboxylate (**3j**)*. General procedure was followed using ethyl (*E*)-2-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate **1a** (51.5 mg, 0.2 mmol) and 2-bromopentan-3-one **2c** (46.0 mg, 0.28 mmol) for 24 h at rt. TFE (0.2 ml, 1 M) was used as solvent instead than toluene. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **3j** (49 mg 78%) as white thick wax. ^{1}H NMR (300 MHz, C_6D_6): 8.12 (d, *J* = 8.3 Hz, 1H), 7.24 (m, 1H overlapped with C_6D_6), 7.09 (d, *J* = 7.4 Hz, 1H), 6.96 (td, *J* = 7.4, 0.8 Hz, 1H), 6.74 (dd, *J* = 5.8, 2.2 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.51 (m, 1H), 2.48 – 2.28 (m, 2H), 2.06 (m, 1H), 1.25 (d, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.19 – 1.05 (m, 6H).

^{13}C{^{1}H} NMR (75 MHz, C_6D_6): 212.2 (C), 152.3 (C), 143.8 (C), 142.7 (C), 130.0 (C), 128.2 (CH), 125.8 (CH), 122.8 (CH), 117.1 (CH), 116.3 (CH), 61.9 (CH_2), 55.5 (CH), 53.2 (CH), 46.2 (CH), 35.9 (CH), 19.5 (CH_3), 15.6 (CH_3), 14.8 (CH_3), 14.0 (CH_3). ESI(+)-MS: m/z(%) = 314 (100) $[M+H]^+$. Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found C, 72.69; H, 7.38; N, 4.46.

*Ethyl 7-methyl-9-oxo-8,10-diphenyl-8,9,10,10a-tetrahydrocyclohepta[b]indole-5(7H)-carboxylate (**3k**)*. General procedure was followed using ethyl (*E*)-2-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate **1a** (46.0 mg, 0.2 mmol) and 1-chloro-1,3-diphenylpropan-2-one **2d** (63.0 mg, 0.28 mmol) for 24 h at rt.

TFE (0.2 ml, 1 M) was used as solvent instead than toluene. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **3k** (48 mg 55%) as a yellow thick wax.

^{1}H NMR (300 MHz, C_6D_6): 7.99 (d, *J* = 8.3 Hz, 1H), 7.09 – 6.97 (m, 6H), 6.93 – 6.82 (m, 5H), 6.68 (dd, *J* = 5.8, 2.4 Hz, 1H), 6.55 (td, *J* = 7.5, 1.0 Hz, 1H), 6.46 (dd, *J* = 6.9, 0.7 Hz, 1H), 4.74 (dd, *J* = 11.0, 2.1 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.80 (d, *J* = 11.0 Hz, 1H), 3.69 (d, *J* = 11.3 Hz, 1H), 3.16 (m, 1H), 1.06 – 0.91 (m, 6H). ^{13}C{^{1}H} NMR (75 MHz, C_6D_6): 205.8 (C), 152.3 (C), 142.5 (C), 142.3 (C), 136.8 (C), 136.2 (C), 130.9 (C), 129.1 (2xCH), 128.6 (4xCH), 128.1 (CH), 128.0 (2xCH), 126.9 (CH), 126.5 (CH), 124.1 (CH), 123.0 (CH), 116.0 (CH), 115.0 (CH), 66.8 (CH), 65.2 (CH), 61.9 (CH_2), 43.1 (CH), 32.5 (CH), 20.1 (CH_3), 13.9 (CH_3). ESI(+)-MS: m/z(%) = 438 (100) $[M+H]^+$. Anal. Calcd for $C_{29}H_{27}NO_3$: C, 79.61; H, 6.22; N, 3.20. Found C, 79.75; H, 6.23; N, 3.21.

*Ethyl 7,10,10-trimethyl-9-oxo-8,9,10,10a-tetrahydrocyclohepta[b]indole-5(7H)-carboxylate (**3l**)*. General procedure was followed using ethyl (*E*)-2-(pent-1-en-1-yl)-1*H*-indole-1-carboxylate **1a** (46.0 mg, 0.2 mmol) and 1-bromo-3-methylbutan-2-one **2e** (46.0 mg, 0.28 mmol) for 24 h at 40 °C. TFE (0.2 ml, 1 M) was used as solvent instead than toluene, while Na_2CO_3 (32.0 mg, 0.3 mmol) was used as base. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **3l** (23 mg, 37%) as a yellow thick wax. ^{1}H NMR (300 MHz, C_6D_6): 8.11 (d, *J* = 8.3 Hz, 1H), 7.25 (m, 1H, overlapped with C_6D_6), 7.09 (d, *J* = 7.6 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.70 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.93 (s, 1H), 2.98 (dd, *J* = 11.7, 5.7 Hz, 1H), 2.62 (bs, 1H), 2.22 (dd, *J* = 11.8, 5.3 Hz, 1H), 1.30 – 1.14 (m, 6H), 1.06 (t, *J* = 7.1 Hz, 3H), 0.92 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, C_6D_6): 211.0 (C), 152.4 (C), 143.5 (C), 141.0 (C), 128.6 (C), 128.2 (CH), 125.7 (CH), 122.7 (CH), 116.4 (CH), 115.7 (CH), 61.8 (CH_2), 54.5 (C), 49.0 (CH), 45.1 (CH_2), 31.2 (CH), 23.6 (CH_3), 23.6 (CH_3), 17.4 (CH_3), 13.9 (CH_3). ESI(+)-MS: m/z(%) = 314 (100) $[M+H]^+$. Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found C, 72.63; H, 7.38; N, 4.48.

*Tert-butyl 7-methyl-12-oxo-7,8,9,10,11,11a-hexahydro-5H-8,11-methanocycloocta[b]indole-5-carboxylate (**3m**)*. General procedure was followed using tert-butyl (*E*)-2-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate **1i** (51.5 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **2a** (46.0 mg, 0.28 mmol). Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **3m** (49 mg, 72%) as a white solid (m.p. 149-154° C). ^{1}H NMR (300 MHz, C_6D_6): 8.08 (d, *J* = 8.2 Hz, 1H), 7.22 (m, 1H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.83 (t, *J* = 3.1 Hz, 1H), 3.79 (s, 1H), 2.80 (m, 1H), 2.62 (m, 1H), 2.24 (s, 1H), 1.53 (s, 9H), 1.43 (m, 4H), 1.09 (d, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, C_6D_6): 219.3 (C), 151.5 (C), 143.1 (C), 141.5 (C), 130.3 (C), 128.0 (CH), 123.4 (CH), 123.3 (CH), 116.7 (CH), 116.3 (CH), 81.9, (C) 54.4 (CH), 49.5 (CH), 47.7 (CH), 36.8 (CH), 27.9 (3xCH_3), 22.9 (CH_3), 21.2 (CH_2), 20.5 (CH_2). ESI(+)-MS: m/z(%) = 361 (65) $[M+Na]^+$. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found C, 74.57; H, 7.44; N, 4.15.

Preparation and characterization data for compounds 4a-b

*Ethyl (E)-3-(2-oxocyclopentyl)-2-(prop-1-en-1-yl)-1H-indole-1-carboxylate (**4a**)*. **4a** was isolated during the screening of reaction conditions (see Table 1) as secondary product by reacting ethyl (*E*)-2-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate **1a** (46.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **2a** (46.0 mg, 0.28 mmol) in a fluorinated alcohol (TFE or HFIP, 0.2 ml, 1 M) and in the presence of a base (1.5 equiv.) at the temperature and for the time stated in Table 1. Removal of the solvent and purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded

progressively **3a** (see previous section for characterization) and **4a**. ^{1}H NMR (300 MHz, CD_2Cl_2): 8.18 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.30 (m, 1H), 7.23 – 7.18 (m, 2H), 6.66 (dq, *J* = 15.8, 1.8 Hz, 1H), 5.86 (dq, *J* = 15.8, 6.6 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 3.70 (m, 1H), 2.62 – 2.22 (m, 5H), 2.04 (m, 1H), 1.97 (dd, *J* = 6.6, 1.8 Hz, 3H), 1.49 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2): 218.2 (C), 151.7 (C), 137.5 (C), 135.6 (C), 130.8 (CH), 128.0 (C), 124.1 (CH), 122.8 (CH), 122.4 (CH), 119.2 (CH), 116.4 (C), 115.9 (CH), 63.1 (CH_2), 47.8 (CH), 38.5 (CH_2), 30.9 (CH_2), 21.3 (CH_2), 18.3 (CH_3), 14.1 (CH_3). ESI(+)-MS: m/z(%) = 334 (100) $[M+Na]^+$. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found C, 73.17; H, 6.78; N, 4.52.

*(E)-2-(1-methyl-2-(prop-1-en-1-yl)-1H-indol-3-yl)cyclopentan-1-one (**4b**)*. General procedure employed for the synthesis of **3a-m** was followed using (*E*)-1-methyl-2-(prop-1-en-1-yl)-1*H*-indole **1j** (34 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **2a** (46 mg, 0.28 mmol). Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **4b** (28 mg, 55%) as a thick wax. ^{1}H NMR (300 MHz, $CDCl_3$): 7.28 – 7.22 (dd, *J* = 7.5, 4.1 Hz, 2H), 7.17 (m, 1H), 7.02 (m, 1H), 6.39 (dd, *J* = 15.9, 1.7 Hz, 1H), 6.00 (dq, *J* = 15.8, 6.6 Hz, 1H), 3.75 – 3.54 (m, 4H), 2.63 – 2.47 (m, 2H), 2.42 – 2.31 (m, 2H), 2.25 (m, 1H), 2.06 – 1.88 (m, 4H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): 219.6 (C), 137.2 (C), 137.0 (C), 132.9 (CH), 125.8 (C), 121.5 (CH), 120.2 (CH), 119.1 (CH), 119.0 (CH), 109.4 (CH), 109.0 (C), 48.1 (CH), 38.6 (CH_2), 31.6 (CH_2), 30.4 (CH_3), 21.4 (CH_2), 19.1 (CH_3). ESI(+)-MS: m/z(%) = 252 (65) $[M-H]^-$. Anal. Calcd. for $C_{17}H_{19}NO$: calcd. for C, 80.60; H, 7.56; N, 5.53. Found C, 80.83; H, 7.58; N, 5.54.

General procedure for the reaction between 4*H*-furo[3,2-*b*]indole 5a-e and α-haloketones 2a,c-e

To a stirring solution of 4*H*-furo[3,2-*b*]indole **5a-e** (0.2 mmol, 1.0 equiv.), α-haloketone **2a,c-e** (0.28 mmol, 1.4 equiv.) TFE (86.4 µl, 1.2 mmol, 6.0 equiv.) in toluene (0.4 ml, 0.5 M), DIPEA (52.3 µl, 0.3 mmol, 1.5 equiv.) was added and the mixture was stirred for 2-3 h at room temperature. Solvent was then removed and the crude was purified by column chromatography to yield the corresponding cyclohepta[*b*]indoline **6a-h.**

*Ethyl 13-oxo-8,9,10,11-tetrahydro-7,11a-epoxy-8,11-methanocycloocta[b]indole-5(7H)-carboxylate (**6a**)*. General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **5a** (46.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **2a** (46.0 mg, 0.28 mmol) for 3 h at rt. Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **6a** (48 mg, 77%) as a yellow solid (m.p. 116-118° C). ^{1}H NMR (300 MHz, $CDCl_3$): 7.98 (d, *J* = 6.4 Hz, 1H), 7.48 (m, 1H), 7.41 (td, *J* = 8.2, 1.2 Hz, 1H), 7.14 (td, *J* = 7.5, 0.6 Hz, 1H), 5.81 (s, 1H), 4.99 (dd, *J* = 4.2, 2.2 Hz, 1H), 4.40 (m, 2H), 2.67 (m, 1H), 2.42 – 2.27 (m, 2H), 2.15 (m, 1H), 1.98 – 1.87 (m, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): 208.2 (C), 151.3 (C), 150.6 (C), 145.3 (C), 130.6 (CH), 128.4 (C), 124.2 (CH), 123.3 (CH), 116.3 (CH), 107.3 (CH), 91.9 (C), 87.4 (CH), 62.9 (CH_2), 56.7 (CH), 51.0 (CH), 22.4 (CH_2), 21.1 (CH_2), 14.4 (CH_3). ESI(+)-MS: m/z(%) = 312 (100) $[M+H]^+$. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found C, 69.34; H, 5.48; N, 4.52.

*Ethyl 2-fluoro-13-oxo-8,9,10,11-tetrahydro-7,11a-epoxy-8,11-methanocycloocta[b]indole-5(7H)-carboxylate (**6b**)*. General procedure was followed using ethyl 7-fluoro-4*H*-furo[3,2-*b*]indole-4-carboxylate **5b** (50.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **2a** (46.0 mg, 0.28 mmol) for 2 h at rt. Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded

6b (46 mg, 70%) as a yellow solid (m.p. 136-140° C). ^{1}H NMR (300 MHz, C_6D_6): 7.99 (bs, 1H), 6.88 (dd, *J* = 7.5, 2.7 Hz, 1H), 6.66 (td, *J* = 9.0, 2.8 Hz, 1H), 5.45 (bs, 1H), 4.33 (dd, *J* = 4.3, 2.2 Hz, 1H), 3.81 (m, 2H), 2.19 (m, 1H), 2.04 (m, 1H), 1.80 (m, 1H), 1.65 (m, 1H), 1.50 – 1.23 (m, 2H), 0.79 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, C_6D_6): 205.0 (C), 159.3 (d, *J* = 243.6 Hz, C), 150.8 (C), 150.6 (C), 141.4 (C), 130.3 (d, *J* = 7.7 Hz, C), 117.3 (d, *J* = 8.1 Hz, CH), 116.5 (d, *J* = 23.2 Hz, CH), 110.8 (d, *J* = 24.5 Hz, CH), 107.3 (CH), 91.19 (C), 87.0 (CH), 62.31 (CH_2), 56.1 (CH), 50.7 (CH), 22.2 (CH_2), 20.8 (CH_2), 13.7 (CH_3). ESI(+)-MS: m/z(%) = 328 (100) $[M-H]^-$. Anal. Calcd for $C_{18}H_{16}FNO_4$: C, 65.65; H, 4.90; N, 4.25. Found C, 65.82; H, 4.92; N, 4.24.

*Ethyl 2-methyl-13-oxo-8,9,10,11-tetrahydro-7,11a-epoxy-8,11-methanocycloocta[b]indole-5(7H)-carboxylate (**6c**)*. General procedure was followed using ethyl 7-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **5c** (49.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **2a** (46.0 mg, 0.28 mmol) for 2 h at rt. Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 95:5 to 9:1) yielded **6c** (52 mg, 80%) as an orange solid (m.p. 114-117° C). ^{1}H NMR (300 MHz, C_6D_6): 8.16 (bs, 1H), 7.07 (m, 1H), 6.85 (m, 1H), 5.53 (bs, 1H), 4.42 (dd, *J* = 4.2, 2.2 Hz, 1H), 3.84 (m, 2H), 2.31 – 2.13 (m, 2H), 2.04 (m, 1H), 1.93 (s, 3H), 1.75 (m, 1H), 1.54 – 1.34 (m, 2H), 0.81 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (75 MHz, C_6D_6): 205.5 (C), 150.98 (C), 143.5 (C), 133.4 (C), 130.7 (CH), 129.1 (C), 126.7 (C), 123.9 (CH), 116.0 (CH), 106.9 (CH), 91.8 (C), 87.0 (CH), 62.2 (CH_2), 56.5 (CH), 50.7 (CH), 22.3 (CH_2), 21.0(CH_2), 20.4 (CH_3), 13.7 (CH_3). ESI(+)-MS: m/z(%) = 326 (100) $[M+H]^+$. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found C, 69.92; H, 5.90; N, 4.29.

*Ethyl 2-methoxy-13-oxo-8,9,10,11-tetrahydro-7,11a-epoxy-8,11-methanocycloocta[b]indole-5(7H)-carboxylate (**6d**)*. General procedure was followed using ethyl 7-methoxy-4*H*-furo[3,2-*b*]indole-4-carboxylate **5d** (52.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **2a** (46.0 mg, 0.28 mmol) for 2 h at rt. Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 9:1 to 8:2) yielded **6d** (50 mg, 73%) as a white solid (m.p. 118-122° C). ^{1}H NMR (300 MHz, $CDCl_3$): 7.86 (bs, 1H), 6.99 (d, *J* = 2.7 Hz, 1H), 6.90 (dd, *J* = 9.0, 2.7 Hz, 1H), 5.74 (bs, 1H), 4.96 (dd, *J* = 4.2, 2.2 Hz, 1H), 4.36 (m, 2H), 3.80 (s, 3H), 2.64 (m, 1H), 2.36 (m, 1H), 2.27 (m, 1H), 2.09 (m, 1H), 2.02 – 1.82 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): 208.0 (C), 156.5 (C), 151.3 (C), 150.8 (C), 138.8 (C), 129.4 (C), 116.9 (CH), 115.4 (CH), 109.3 (CH), 106.9 (CH), 91.7 (C), 87.4 (CH), 62.7 (CH_2), 56.5 (CH_3), 55.7 (CH), 50.9 (CH), 22.3 (CH_2), 21.1 (CH_2), 14.4 (CH_3). ESI(+)-MS: m/z(%) = 363 (100) $[M+Na]^+$. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found C, 66.76; H, 5.63; N, 4.11.

*Ethyl 7-methyl-13-oxo-8,9,10,11-tetrahydro-7,11a-epoxy-8,11-methanocycloocta[b]indole-5(7H)-carboxylate (**6e**)*. General procedure was followed using ethyl 2-methyl-4*H*-furo[3,2-*b*]indole-4-carboxylate **5e** (49.0 mg, 0.2 mmol) and 2-bromocyclopentan-1-one **2a** (46.0 mg, 0.28 mmol) for 3 h at rt. Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 9:1 to 8:2) yielded **6e** (50 mg, 77%) as a white solid (m.p. 155-160° C). ^{1}H NMR (300 MHz, $CDCl_3$): 7.95 (bs, 1H), 7.43 (m, 1H), 7.37 (m, 1H), 7.10 (td, *J* = 7.5, 0.9 Hz, 1H), 5.63 (bs, 1H), 4.36 (m, 2H), 2.45 (m, 1H), 2.30 (m, 1H), 2.21 (m, 1H), 2.10 (m, 1H), 1.95 – 1.80 (m, 2H), 1.50 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): 208.6 (C), 151.3 (C), 150.0 (C), 145.0 (C), 130.5 (CH), 128.6 (C), 124.2 (CH), 123.2 (CH), 116.2 (CH), 110.6 (CH), 93.5 (C), 91.3 (C), 62.8 (CH_2), 55.4 (CH),

54.5 (CH), 21.3 (CH_2), 21.1 (CH_3), 19.8 (CH_2), 14.4 (CH_3). ESI(+)-MS: m/z(%) = 348 (100) $[M+Na]^+$. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found C, 70.33; H, 5.88; N, 4.30.

Ethyl 8,10-dimethyl-9-oxo-7,8,9,10-tetrahydro-5H-7,10a-epoxycyclohepta[b]indole-5-carboxylate ***(6f)***. General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **5a** (46.0 mg, 0.2 mmol) and 2-bromopentan-3-one **2c** (46 mg, 0.28 mmol) for 24 at rt. TFE (0.2 ml, 1 M) was used as solvent instead than toluene. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **6f** (49 mg 78%) as an orange solid (m.p. 102-105° C). ^{1}H NMR (300 MHz, $CDCl_3$): 7.89 (d, *J* = 7.0 Hz, 1H), 7.52 – 7.33 (m, 2H), 7.17 (td, *J* = 7.5, 0.8 Hz, 1H), 5.83 (bs, 1H), 5.13 (dd, *J* = 4.8, 2.5 Hz, 1H), 4.37 (m, 2H), 3.28 – 2.86 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.62 (d, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) 207.8 (C), 151.3 (C), 150.3 (C), 145.9 (C), 130.4 (CH), 127.3 (C), 124.5 (CH), 123.8 (CH), 115.8 (CH), 107.6 (CH), 92.4 (C), 88.3 (CH), 62.9 (CH_2), 54.7 (CH), 49.9 (CH), 14.4 (CH_3), 11.0 (CH_3), 8.7 (CH_3). ESI(+)-MS: m/z(%) = 314 (100) $[M+H]^+$. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47. Found C, 68.86; H, 6.12; N, 4.45.

Ethyl 9-oxo-8,10-diphenyl-7,8,9,10-tetrahydro-5H-7,10a-epoxycyclohepta[b]indole-5-carboxylate ***(6g)***. General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **5a** (46.0 mg, 0.2 mmol) and 1-chloro-1,3-diphenylpropan-2-one **2d** (63 mg, 0.28 mmol) for 24 h at rt. TFE (0.2 ml, 1 M) was used as solvent instead than toluene. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **6g** (83 mg 95%) as a yellow solid (m.p. 202-204° C). ^{1}H NMR (300 MHz, $CDCl_3$): 7.50 (m, 1H), 7.45 – 7.28 (m, 6H), 7.19 – 6.95 (m, 5H), 6.85 – 6.75 (m, 2H), 5.97 (bs, 1H), 5.39 (dd, *J* = 4.9, 2.5 Hz, 1H), 4.44 (d, *J* = 4.9 Hz, 1H), 4.38 (qd, *J* = 7.1, 2.2 Hz, 2H), 4.24 (s, 1H), 1.41 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$): 205.3 (C), 150.7 (C), 150.1 (C), 145.1 (C), 135.4 (C), 133.3 (C), 130.3 (CH), 129.9 (2xCH), 129.8 (CH), 128.6 (2xCH), 127.6 (CH), 127.4 (2xCH), 127.1 (CH), 126.9 (C), 123.9 (CH), 123.9 (CH), 115.3 (CH), 108.9 (CH), 92.6 (C), 88.6 (CH), 65.8 (CH), 62.7 (CH_2), 61.5 (CH), 14.5 (CH_3). CH_{sp2} is overlapped with another CH_{sp2}. ESI(-)-MS: m/z(%) = 436 (50) $[M+H]^+$. Anal. Calcd for $C_{28}H_{23}NO_4$: C, 76.87; H, 5.30; N, 3.20. Found C, 77.05; H, 5.31; N, 3.21.

Ethyl 10,10-dimethyl-9-oxo-7,8,9,10-tetrahydro-5H-7,10a-epoxycyclohepta[b]indole-5-carboxylate ***(6h)***. General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **5a** (46.0 mg, 0.2 mmol) and 1-bromo-3-methylbutan-2-one **2e** (46 mg, 0.28 mmol) for 48 h at 40 °C. TFE (0.2 ml, 1 M) was used as solvent instead than toluene, while Na_2CO_3 (32 mg, 0.3 mmol) was used as base. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 95:5) yielded **6h** (36 mg 57%) as a yellow thick wax. ^{1}H NMR (300 MHz, $CDCl_3$): 7.94 (d, *J* = 7.9 Hz, 1H), 7.49 – 7.35 (m, 2H), 7.15 (td, *J* = 7.5, 0.6 Hz, 1H), 5.84 (s, 1H), 5.28 (m, 1H), 4.39 (m, 2H), 3.24 (dd, *J* = 16.2, 4.9 Hz, 1H), 2.58 (dd, *J* = 16.2, 0.8 Hz, 1H), 1.47 – 1.37 (m, 6H), 0.71 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$): 210.0 (C), 151.3 (C), 150.4 (C), 146.2 (C), 130.4 (CH), 126.0 (C), 124.8 (CH), 123.8 (CH), 115.6 (CH), 109.6 (CH), 92.8 (C), 83.2 (CH), 62.8 (CH_2), 56.5 (C), 44.2 (CH_2), 21.0 (CH_3), 17.4 (CH_3), 14.4 (CH_3). ESI(+)-MS: m/z(%) = 314 (100) $[M+H]^+$. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47. Found C, 68.87; H, 6.09; N, 4.47.

General procedure for the reaction between 1a or 5a and *N*- (benzyloxy)-2-bromo-2-methylpropanamide 7.

To a stirring solution of 2-vinylindole **1a** or 4*H*-furo[3,2-*b*]indole **5a** (0.2 mmol, 1.0 equiv.) and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **7** (82 mg, 0.3 mmol, 1.5 equiv.) in HFIP (0.84 ml, 0.25 M), DIPEA (52.3 µl, 0.3 mmol, 1.5 equiv.) was added and the mixture was stirred for 1 at room temperature. Solvent was then removed and the crude was purified by column chromatography to yield the corresponding products **8-10.**

*Ethyl 3-(benzyloxy)-1,1,4-trimethyl-2-oxo-2,3,4,10b-tetrahydroazepino[4,5-b]indole-6(1H)-carboxylate (**8**) and ethyl (E)-1-(benzyloxy)-3,3-dimethyl-2-oxo-8a-(prop-1-en-1-yl)-2,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-8(1H)-carboxylate (**9**)*. General procedure was followed using ethyl (*E*)-2-(prop-1-en-1-yl)-1*H*-indole-1-carboxylate **1a** (46.0 mg, 0.2. mmol) and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **7** (82.0 mg, 0.3 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded progressively **9** (34 mg, 40%) and **8** (35 mg, 42%) as clear thick oils. **8:** ^{1}H NMR (300 MHz, C_6D_6): 8.08 (d, *J* = 8.3 Hz, 1H), 7.60 – 7.47 (m, 2H), 7.32 – 7.18 (m, 4H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.96 (td, *J* = 7.5, 1.0 Hz, 1H), 6.68 (dd, *J* = 4.6, 2.1 Hz, 1H), 4.96 (d, *J* = 10.5 Hz, 1H), 4.84 (d, *J* = 10.5 Hz, 1H), 4.41 (m, 1H), 4.26 – 4.00 (m, 3H), 1.57 (s, 3H), 1.46 (d, *J* = 6.7 Hz, 3H), 1.05 (dd, *J* = 8.9, 5.3 Hz, 6H). ^{13}C{^{1}H} (75 MHz, C_6D_6): 179.3 (C), 152.2 (C), 143.5 (C), 143.2 (C) 136.8 (C), 129.4 (2xCH), 128.3 (C), 128.3 (CH), 128.3 (2xCH), 128.2 (CH), 126.5 (CH), 122.9 (CH), 116.0 (CH), 110.8 (CH), 76.2 (CH_2), 62.1 (CH_2), 57.6 (CH), 51.2 (C), 48.7 (CH), 26.2 (CH_3), 19.9 (CH_3), 19.8 (CH_3), 13.9 (CH_3). ESI(+)-MS: m/z(%) = 421 (100) $[M+H]^+$. Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found C, 71.34; H, 6.73; N, 6.64.

9: ^{1}H NMR (300 MHz, C_6D_6): 8.29 (d, *J* = 8.2 Hz, 1H), 7.30 (m, 1H), 7.14 – 6.94 (m, 5H), 6.82 – 6.68 (m, 2H), 5.68 (dq, *J* = 15.5, 6.2 Hz, 1H), 5.56 (dd, *J* = 15.5, 1.2 Hz, 1H), 5.03 (d, *J* = 2.9 Hz, 2H), 4.15 – 3.86 (m, 2H), 3.14 (s, 1H), 1.35 (dd, *J* = 6.3, 1.3 Hz, 3H), 1.19 (s, 3H), 0.99 – 0.85 (m, 6H). ^{13}C{^{1}H} (75 MHz, C_6D_6): 162.5 (C), 152.4 (C), 142.8 (C), 138.7 (C), 131.0 (CH), 129.0 (CH), 127.2 (CH), 126.0 (CH), 126.0 (C), 125.5 (CH), 122.3 (CH), 115.3 (CH), 103.6 (C), 75.9 (CH_2), 61.2 (CH_2), 61.2 (CH), 43.4 (C), 29.5 (CH_3), 24.4 (CH_3), 16.8 (CH_3), 14.0 (CH_3). 4xCH_{sp2} are overlapped with C_6D_6. ESI(+)-MS: m/z(%) = 421 (100) $[M+H]^+$. Anal. Calcd for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66. Found C, 71.68; H, 6.72; N, 6.67.

*Ethyl 3-(benzyloxy)-1,1-dimethyl-2-oxo-1,2,3,4-tetrahydro-6H-4,10b-epoxyazepino[4,5-b]indole-6-carboxylate (**10**)*. General procedure was followed using ethyl 4*H*-furo[3,2-*b*]indole-4-carboxylate **5a** (46.0 mg, 0.2 mmol) and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **7** (82.0 mg, 0.3 mmol). Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 8:2) yielded **10** (53 mg, 63%) as a transparent oil. ^{1}H NMR (300 MHz, C_6D_6): 8.27 (bs, 1H), 7.49 (m, 2H), 7.37 – 7.08 (m, 5H), 6.86 (td, *J* = 7.6, 0.8 Hz, 1H), 6.01 (bs, 1H), 5.54 (d, *J* = 1.8 Hz, 1H), 5.21 (d, *J* = 10.6 Hz, 1H), 4.97 (d, *J* = 10.6 Hz, 1H), 3.97 (m, 2H), 1.69 (s, 3H), 1.02 (s, 3H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} (75 MHz, C_6D_6): 174.2 (C), 153.7 (C), 150.8 (C), 146.8 (C), 136.2 (C), 130.6 (CH), 129.6 (2xCH), 128.5 (CH), 128.4 (2xCH), 125.6 (CH), 125.3 (C), 123.6 (CH), 115.7 (CH), 110.5 (CH), 96.3 (CH), 94.7 (C), 77.8 (CH_2), 62.5 (CH_2), 52.4 (CH_2), 22.9 (CH_3), 18.7 (CH_3), 13.8 (CH_3). ESI(+)-MS: m/z(%) = 421 (100) $[M+H]^+$. Anal. Calcd for $C_{24}H_{24}N_2O_5$: C, 68.56; H, 5.75; N, 6.66. Found C, 68.38; H, 5.77; N, 6.68.

Reaction between 3-vinylindole 11 and 2a or 7.

*Ethyl (12-oxo-10-(p-tolyl)-5a,6,7,8,9,10-hexahydro-5H-6,9-methanocycloocta[b]indole-5-carboxylate (**12**).* General procedure employed for the synthesis of **3a-m** was followed using ethyl (*E*)-3-(4-methylstyryl)-1*H*-indole-1-carboxylate **11** (61.1 mg, 0.2 mmol), and 2-bromocyclopentan-1-one **2a** (46.0 mg, 0.28 mmol) for 24 h at rt. Purification of the crude by column chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **12** (52 mg, 67%) as a white solid (m.p. 85-90° C). ^{1}H NMR (300 MHz, C_6D_6): 8.35 (bs, 1H), 7.25 – 7.16 (m, 2H), 7.15 – 7.10 (m, 4H), 6.92 (t, *J* = 7.2 Hz, 1H), 6.47 (t, *J* = 3.5, 1H), 4.73 (s, 1H), 4.20 (m, 2H), 3.75 – 3.64 (m, 2H), 2.65 (m, 1H), 2.25 (s, 3H), 1.70 (m, 1H), 1.51 – 1.33 (m, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} (75 MHz, C_6D_6): 217.0 (C), 152.8 (C), 144.9 (C), 142.4 (C), 138.1 (C), 136.2 (C), 129.6 (2xCH), 129.5 (CH), 129.3 (C), 127.6 (2xCH), 123.0 (CH), 121.2 (CH), 119.4 (CH), 116.1 (CH), 66.0 (CH), 61.8 (CH_2), 56.9 (CH), 50.3 (CH), 48.2 (CH), 21.3 (CH_2), 20.7 (CH), 20.2 (CH_2), 14.2 (CH_3). ESI(+)-MS: m/z(%) = 388 (100) $[M+H]^+$. Anal. Calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61; found C, 77.24; H, 6.52; N, 3.60.

*Ethyl -3-(benzyloxy)-5,5-dimethyl-4-oxo-2-(p-tolyl)-3,4,5,5a-tetrahydroazepino[4,5-b]indole-6(2H)-carboxylate (**13**).* General procedure employed for the synthesis of **8-10** was followed using ethyl (*E*)-3-(4-methylstyryl)-1*H*-indole-1-carboxylate **11** (61.1 mg, 0.2 mmol) and and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **7** (82.0 mg, 0.3 mmol) for 24 h. Purification of the crude by flash chromatography (SiO_2, hexane/ethyl acetate 9:1) yielded **13** (48 mg, 48%) as a clear thick oil. ^{1}H NMR (500 MHz, C_6D_6): 7.94 (bs, 1H), 7.37 – 7.30 (m, 2H), 7.15 (ddt, *J* = 10.1, 8.4, 1.8 Hz, 4H), 7.11 – 7.03 (m, 2H), 6.97 (d, *J* = 7.8 Hz, 2H), 6.83 (dd, *J* = 4.1, 3.6 Hz, 1H), 6.73 (td, *J* = 7.5, 1.0 Hz, 1H), 5.75 (m, 1H), 5.63 (bs, 1H), 5.27 (t, *J* = 3.1 Hz, 1H), 4.64 (s, 2H), 4.03 (m, 2H), 2.06 (s, 3H), 1.65 (s, 3H), 1.11 (s, 3H), 1.00 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} (126 MHz, C_6D_6): 181.7 (C), 154.2 (C), 145.6 (C), 137.8 (C), 137.7 (C), 137.2 (C), 136.9 (C), 129.6 (CH), 129.4 (2xCH), 129.1 (2xCH), 128.8 (C), 128.2 (2xCH), 128.0 (2xCH), 127.7 (CH), 123.3 (CH), 119.8 (CH), 117.4 (CH), 114.6 (CH), 74.9 (CH_2), 69.2 (CH), 64.9 (CH), 61.8 (CH_2), 54.3 (C), 26.6 (CH_3), 20.6 (CH_3), 19.0 (CH_3), 14.0 (CH_3). ESI(+)-MS: m/z(%) = 497 (100) $[M+H]^+$. Anal. Calcd for $C_{31}H_{32}N_2O_4$: C, 74.98; H, 6.50; N, 5.64; found C, 75.14; H, 6.51; N, 5.63.

Preparation and characterization data for compounds 14-17

*Ethyl 12-oxo-7-(p-tolyl)-6,7,8,9,10,11-hexahydro-5H-8,11-methanocycloocta[b]indole-5-carboxylate (**14**).* To a stirring solution of **3d** (38.7 mg, 0.1 mmol) in $CHCl_3$ (0.5 ml, 0.2 M), *p*-TSOH (1.90 mg, 0.01 mmol) was added and the mixture was stirred for 2 h at room temperature. The reaction mixture was then quenched with $NaHCO_3$ saturated solution (5 ml) and extracted with ethyl acetate (3 x 5 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to yield **14** (37 mg, 96%) as a brownish solid (m.p. 177-180° C). ^{1}H NMR (300 MHz, $CDCl_3$): 8.00 (m, 1H), 7.53 (m, 1H), 7.30 – 7.23 (m, 4H), 7.16 (m, 2H), 4.45 (q, *J* = 7.14, 2H), 4.11 (m, 1H), 3.69 – 3.51 (m, 3H), 2.85 (m, 1H), 2.50 (m, 1H), 2.35 (m, 4H), 2.23 – 2.11 (m, 2H), 1.45 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$): 216.8 (C), 152.2 (C), 141.5 (C), 136.4 (C), 135.4 (C), 135.4 (C), 129.3 (2xCH), 128.1 (C), 126.8 (2xCH), 124.4 (CH), 123.0 (CH), 119.8 (C), 117.8 (CH), 115.4 (CH), 63.3 (CH_2), 53.7 (CH), 49.0 (CH), 43.5 (CH), 28.4 (CH_2), 28.1 (CH_2), 21.0 (CH_3), 20.2 (CH_2), 14.3 (CH_3). ESI(+)-MS: m/z(%) = 388 (100) $[M+H]^+$. Anal. Calcd. for $C_{25}H_{25}NO_3$: calcd. for C, 77.49; H, 6.50; N, 3.61. Found C, 77.74; H, 6.52; N, 3.61.

*7-(p-tolyl)-6,7,8,9,10,11-hexahydro-5H-8,11-methanocycloocta[b]indol-12-one (**15**).* To a stirring solution of **3d** (50.0 mg, 0.13 mmol) in MeOH (1.4 ml, 0.01 M), K_2CO_3 (17.8 mg, 0.13 mmol) was added and the mixture was stirred for 5 h at 50°C. Solvent was then removed and the crude was diluted with water (5 ml) and extracted with ethyl acetate (3 x 5 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by column chromatography (SiO_2, hexane/ethyl acetate 9:1) to yield **15** (32 mg, 78%) as a white solid (m.p. 186-190° C). ^{1}H NMR (300 MHz, acetone-d_6): 10.04 (bs, 1H), 7.54 (m, 1H), 7.33 – 7.26 (m, 3H), 7.18 (m, 2H), 7.09 – 7.00 (m, 2H), 3.73 – 3.57 (m, 3H), 3.10 (m, 1H), 2.84 (s, 1H), 2.71 (m, 1H), 2.50 – 2.36 (m, 2H), 2.32 (s, 3H), 2.21 (m, 1H). ^{13}C{^{1}H} (75 MHz, acetone-d_6): 215.7 (C), 142.0 (C), 136.0 (C), 134.8 (C), 133.5 (C), 129.2 (2xCH), 127.3 (C), 126.7 (2xCH), 121.1 (CH), 119.0 (CH), 117.3 (CH), 110.5 (CH), 110.5 (C), 52.8 (CH), 48.4 (CH), 44.0 (CH), 30.1 (CH_2), 29.0 (CH_2), 20.1 (CH_3) 19.5 (CH_2). ESI(+)-MS: m/z(%) = 316 (100) $[M+H]^+$. Anal. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found C, 83.53; H, 6.70; N , 4.46.

*Ethyl 12-hydroxy-7-(p-tolyl)-7,8,9,10,11,11a-hexahydro-5H-8,11-methanocycloocta[b]indole-5-carboxylate (**16**).* To a stirring solution of **3d** (50.0 mg, 0.13 mmol) in EtOH (1.3 ml, 0.1 M), $NaBH_4$ (4.90 mg, 0.13 mmol) was added and the mixture was stirred for 2 h at room temperature. The reaction mixture was then quenched with NH_4Cl saturated solution (5 ml) and extracted with ethyl acetate (3 x 5 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified by column chromatography (SiO_2, hexane/ethyl acetate 9:1) to yield **16** (33 mg 65%) as a white solid (m.p. 135-139° C). ^{1}H NMR (300 MHz, C_6D_6): 8.21 (d, J = 8.2 Hz, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.26 (m, 2H overlapped with C_6D_6), 7.16 – 7.04 (m, 4H), 4.73 (m, 1H), 4.53 (m 1H), 4.17 – 4.09 (m, 2H), 4.0o (t, J = 6.9 Hz, 1H) 2.50 (bs, 1H), 2.27 (m, 4H), 1.99 (m, 1H), 1.55 – 1.45 (m, 3H), 1.35 (bs, 1H), 1.04 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} (75 MHz, C_6D_6): 152.9 (C), 145.8 (C), 143.6 (C), 142.5 (C), 135.0 (C), 132.8 (C), 129.3 (2xCH), 128.9 (CH), 127.9 (2xCH), 123.4 (CH), 122.9 (CH), 116.3 (CH), 115.4 (CH), 75.6 (CH), 61.7 (CH_2), 49.5 (CH), 44.0 (CH), 43.2 (CH), 40.3 (CH), 23.5 (CH_2), 23.4 (CH_2), 20.8 (CH_3), 14.0 (CH_3). ESI(+)-MS: m/z(%) = 390 (100) $[M+H]^+$. Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found C, 76.91; H, 7.01; N, 3.61.

*Ethyl 2-(2-oxocyclopentyl)-4H-furo[3,2-b]indole-4-carboxylate (**17**).* To a stirring solution of **6a** (47.0 mg, 0.15 mmol) in $CHCl_3$ (0.75 ml, 0.2 M), *p*TSOH (3.00 mg, 0.015 mmol) was added and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was concentrated and the crude was purified by column chromatography (SiO_2, hexane/ethyl acetate 8:2) to yield **17** (44 mg 94%) as a pink sold (117-119° C). ^{1}H NMR (500 MHz, $CDCl_3$): 8.33 (bs, 1H), 7.63 (m, 1H), 7.34 – 7.25 (m, 2H), 6.68 (s, 1H), 4.53 (q, J = 7.1 Hz, 2H), 3.59 (dd, J = 10.6, 8.5 Hz, 1H), 2.57 (m, 1H), 2.50 (ddd, J = 18.8, 8.5, 3.5 Hz, 1H), 2.44 (dd, J = 10.1, 8.5 Hz, 1H), 2.36 (m, 1H), 2.25 (m, 1H), 2.00 (m, 1H), 1.52 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} (151 MHz, $CDCl_3$): 214.8 (C), 155.3 (C), 151.0 (C), 142.7 (C), 138.2 (C), 129.7 (C), 123.6 (CH), 123.3 (CH), 118.1 (C), 116.3 (CH), 116.1 (CH), 100.8 (CH), 63.0 (CH_2), 49.8 (CH), 37.9 (CH_2), 29.6 (CH_2), 21.0 (CH_2), 14.5 (CH_3).

ESI(+)-MS: m/z(%) = 312 (100) $[M+H]^+$. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found C, 69.21; H, 5.52; N, 4.48.

ASSOCIATED CONTENTS

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:. NMR spectra of all synthesized compounds, 2D-NMR spectra of compound products **3a, 3d, 3i 3j, 3l, 6a, 6f, 6h, 8, 9, 10, 12, 16** and **17** and crystallographic data for **6a** (CCDC No. 1964975).

AUTHOR INFORMATION

Corresponding Author

*E-mail: valentina.pirovano@unimi.it and elisabetta.rossi@unimi.it

ORCID

Valentina Pirovano: 0000-0003-3113-6579

Elisa Brambilla: 0000-0001-5992-4361

Silvia Rizzato: 0000-0001-9893-0238

Giorgio Abbiati: 0000-0002-2502-4127

Elisabetta Rossi: 0000-0003-0397-6175

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank MIUR-Italy (Ph.D. fellowship to E.B) for financial support. G. Celentano (University of Milan) is acknowledged for some mass analyses.

REFERENCES

(1) Stempel, E.; Gaich, T. Cyclohepta[*b*]indoles: A Privileged Structure Motif in Natural Products and Drug Design. *Acc. Chem. Res*. **2016**, *49*, 2390-2402.

(2) Robinson, B. Studies on the Fischer indole synthesis. *Chem. Rev.* **1969**, *69*, 227-250.

(3) a) Han, X.; Li, H.; Hughes, R. P.; Wu, J. Gallium(III)-Catalyzed Three-Component (4+3) Cycloaddition Reactions. *Angew. Chem. Int. Ed.* **2012**, *51*, 10390-10393; b) Shu, D.; Song, W.; Li, X.; Tang, W. Rhodium- and Platinum-Catalyzed [4+3] Cycloaddition with Concomitant Indole Annulation: Synthesis of Cyclohepta[*b*]indoles. *Angew. Chem. Int. Ed*. **2013**, *52*, 3237-3240; c) Kusama, H.; Sogo, H.; Saito, K.; Suga, T.; Iwasawa, N. Construction of Cyclohepta[*b*]indoles via

Platinum-Catalyzed Intermolecular Formal [4+3]-Cycloaddition Reaction of α,β-Unsaturated Carbene Complex Intermediates with Siloxydienes. *Synlett* **2013**, *24*, 1364-1370; d) Zhang, J.; Shao, J.; Xue, J.; Wang, Y.; Li, Y. One pot hydroamination/[4+3] cycloaddition: synthesis towards the cyclohepta[*b*]indole core of silicine and ervatamine. *RSC Adv*. **2014**, *4*, 63850-63854;

e) He, S.; Hsung, R. P.; Presser, W. R.; Ma, Z. -X.; Haugen, B. J. An Approach to Cyclohepta[*b*]indoles through an Allenamide (4+3) Cycloaddition–Grignard Cyclization–Chugaev Elimination Sequence. *Org. Lett.* **2014**, *16*, 2180-2183; f) Zhang, H. -H.; Zhu, Z. -Q.; Fan, T.; Liang, J.; Shi, F. Intermediate-Dependent Unusual [4+3], [3+2] and Cascade Reactions of 3-Indolylmethanols: Controllable Chemodivergent and Stereoselective Synthesis of Diverse Indole Derivatives. *Adv. Synth. Catal*. **2016**, *358*, 1259-1288.

(4) Chakraborty, A.; Goswami, K.; Adiyala, A.; Sinha, S. Syntheses of Spiro[cyclopent[3]ene-1,3′-indole]s and Tetrahydrocyclohepta[*b*]indoles from 2,3-Disubstituted Indoles through Sigmatropic Rearrangement. *Eur. J. Org. Chem.* **2013**, 7117-7127.

(5) a) Ishikura, M.; Kato, H. A Synthetic use of the intramolecular alkyl migration process in indolylborates for intramolecular cyclization: a novel construction of carbazole derivatives. *Tetrahedron* **2002**, *58*, 9827-9838; b) Ferreira, E. M.; Stoltz, B. M. Catalytic C−H Bond Functionalization with Palladium(II): Aerobic Oxidative Annulations of Indoles. *J. Am. Chem. Soc.* **2003**, *125*, 9578-9579; c) Liu, C.; Widenhoefer, R. A. Palladium-Catalyzed Cyclization/Carboalkoxylation of Alkenyl Indoles. *J. Am. Chem. Soc.* **2004**, *126*, 10250-10251.

(6) In all this manuscript (4+3) and (3+2) notation indicate to the number of atoms involved in the cycloaddition reaction.

(7) Gelis, C.; Levitre, G.; Merad, J.; Retailleau, P.; Neuville, L.; Masson, G. Highly Diastereo- and Enantioselective Synthesis of Cyclohepta[*b*]indoles by Chiral-Phosphoric-Acid-Catalyzed (4+3) Cycloaddition. *Angew. Chem. Int. Ed*. **2018**, *57*, 12121-12125.

(8) a) Li, Y.; Zhu, C. -Z.; Zhang, J. Gold-Catalyzed [4+3] Cycloaddition/C–H Functionalization Cascade: Regio- and Diastereoselective Route to Cyclohepta[*b*]indoles. *Eur. J. Org. Chem.* **2017**, 6609-6613; b) Xu, G.; Chen, L.; Sun, J. Rhodium-Catalyzed Asymmetric Dearomative [4+3]-Cycloaddition of Vinylindoles with Vinyldiazoacetates: Access to Cyclohepta[*b*]indoles. *Org. Lett.* **2018**, *20*, 3408-3412; c) Wang, W.; Bai, X.; Jin, S.; Guo, J.; Zhao, Y.; Miao, H.; Zhu, Y.; Wang, Q.; Bu, Z. An Unexpected $FeCl_3$-Catalyzed Cascade Reaction of Indoles and o-Hydroxychalcones for the Assembly of Chromane-Bridged Polycyclic Indoles. *Org. Lett.* **2018**, *20*, 3451-3454.

(9) a) Pirovano, V.; Abbiati, G.; Dell'Acqua, M.; Facoetti, D.; Giordano, M.; Rossi, E. Diels–Alder reactions of 2-vinylindoles with cyclic dienophiles: synthesis of [*c*]-annulated tetrahydrocarbazoles. *Synlett* **2012**, *23*, 2913-2918; b) Pirovano, V.; Dell'Acqua, M.; Facoetti, D.; Nava, D.; Rizzato, S.; Abbiati, G.; Rossi, E. Cycloaddition vs alkylation reactions of 2-vinylindoles with α,β-unsaturated carbonyl compounds under gold catalysis. *Eur. J. Org. Chem*. **2013**, 6267-6279; c) Pirovano, V.; Decataldo, L.; Rossi, E.; Vicente, R. Gold-catalyzed synthesis of tetrahydrocarbazole derivatives through an intermolecular cycloaddition of vinyl indoles and *N*-allenamides. *Chem. Commun*. **2013**, *49*, 3594-3596; d) Rossi, E.; Pirovano, V.; Negrato, M.; Abbiati, G.; Dell'Acqua, M. Synthesis of constrained analogues of tryptophan. *Beilstein J. Org. Chem.* **2015**, *11*, 199-2006; e) Pirovano, V.;

Arpini, E.; Dell'Acqua, M.; Vicente, R.; Abbiati, G.; Rossi, E. Gold(I) catalyzed synthesis of tetrahydrocarbazoles via cascade [3,3]-propargylic rearrangement/[4+2]-cycloaddition of vinylindoles and propargylic esters. *Adv. Synth. Catal.* **2016**, *358*, 403-409; f) Pirovano, V.; Borri, M.; Abbiati, G.; Rizzato, S.; Rossi, E. Gold(I)-catalyzed enantioselective synthesis of tetrahydrocarbazoles through dearomative [4+2] cycloadditions of 3/2-substituted 2/3-vinylindoles. *Adv. Synth. Catal.* **2017**, *359*, 1912-1918.

(10) For a review on this topic see: Li, H.; Wu, J. (3+2)-Cycloaddition Reactions of Oxyallyl Cations. *Synthesis* **2015**, *47*, 22-33.

(11) For reviews on this topic see: a) Harmata, M. Asymmetric Catalytic [4+3] Cycloaddition Reactions. *Adv. Synth. Catal.* **2006**, *348*, 2297-2306; b) Harmata, M. The (4+3)-cycloaddition reaction: simple allylic cations as dienophiles. *Chem. Commun*. **2010**, *46*, 8886-8903; c) Harmata, M. The (4+3)-cycloaddition reaction: heteroatom-substituted allylic cations as dienophiles. *Chem. Commun.* **2010**, *46*, 8904-8922; d) Lohse, A. G.; Hsung, R. P. (4+3) Cycloaddition Reactions of Nitrogen-Stabilized Oxyallyl Cations. *Chem. Eur. J.* **2011**, *17*, 3812-3822; e) Fernández, I.; Mascareñas, J. L. Transition metal-catalysed (4+3) cycloaddition reactions involving allyl cations. *Org. Biomol. Chem*. **2012**, *10*, 699-704. In addition see: f) Mascareñas, J. L.; Gulías, M.; López, F. in *Comprehensive Organic Synthesis*, *2nd ed.,* (Eds. Knochel, P.; Molander, G. A.), Elsevier, Amsterdam, **2014**, pp. 595-655.

(12) a) See ref 11b-c; b) Grant, T. N.; Rieder, C. J.; West, F. G. Interrupting the Nazarov reaction: domino and cascade processes utilizing cyclopentenyl cations. *Chem. Commun.* **2009**, 5676-5688.

(13) For recent reviews on fluorinated solvents, see: a) Bégué, J. P.; Bonnet-Delpon, D.; Crousse, B. Fluorinated Alcohols: A New Medium for Selective and Clean Reaction. *Synlett* **2004**, *1*, 18-29; b) Shuklov, I. A.; Dubrovina, N. V.; Börne, A. Fluorinated Alcohols as Solvents, Cosolvents and Additives in Homogeneous Catalysis. *Synthesis* **2007**, *19*, 2925-2943. For examples of (4+3) cycloadditions involving oxyallyl cations in TFE, see: c) Föhlisch, B.; Gehrlach, E.; Herter, R. Efficient Synthesis of 8-Oxabicyclo[3.2.1]oct-6-en-3-ones, Preparatively Useful [4+3]-Cycloadducts. *Angew. Chem. Int. Ed.* **1982**, *21*, 137; d) Walters, M. A.; Arcand, H. R.; Lawrie, D. J. The first example of a nitrogen-substituted oxyallyl cation cycloaddition. *Tetrahedron Lett.* **1995**, *36*, 23-26; e) Grainger, R. S.; Owoare, R. B.; Tisselli, P.; Steed, J. W. A Synthetic Alternative to the Type-II Intramolecular 4 + 3 Cycloaddition Reaction. *J. Org. Chem*. **2003**, *68*, 7899-7902.

(14) For some examples of nucleophilic addition to oxyally cations, see: a) Tang, Q.; Chen, X.; Tiwari, B.; Chi, Y. R. Addition of Indoles to Oxyallyl Cations for Facile Access to α-Indole Carbonyl Compounds. *Org. Lett*. **2012**, *14*, 1922-1925; b) Vander Wal, M. N.; Dilger, A. K.; MacMillan, D. W. C. Development of a generic activation mode: nucleophilic α-substitution of ketones via oxy-allyl cations. *Chem. Sci*. **2013**, *4*, 3075-3079; c) Liu, C.; Oblak, E. Z.; Vander Wal, M. N; Dilger, A. K.; Almstead, D. K.; MacMillan, D. W. C. Oxy-Allyl Cation Catalysis: An Enantioselective Electrophilic Activation Mode. *J. Am. Chem. Soc.* **2016**, *138*, 2134-2137.

(15) A similar behavior was observed also in a) Ref. 9c; b) Jia, M.; Monari, M.; Yang, Q. -Q.; Bandini, M. Enantioselective gold catalyzed dearomative [2+2]-cycloaddition between indoles and allenamides. *Chem. Commun.* **2015**, *51*, 2320-2323; c) Pirovano, V.; Brambilla, E.; Tserberlidis, G.

[Copper(I)(Pyridine-Containing Ligand)] Catalyzed Regio- and Steroselective Synthesis of 2-Vinylcyclopropa[*b*]indolines from 2-Vinylindoles. *Org. Lett.* **2018**, *20*, 405-408.

(16) For recent reports see: a) Rossi, E.; Abbiati, G.; Dell'Acqua, M.; Negrato, M.; Paganoni, A.; Pirovano, V. Exploiting the σ-phylic properties of cationic gold(I) catalysts in the ring opening reactions of aziridines with indoles. *Org. Biomol. Chem.* **2016**, *14*, 6095-6110; b) Pirovano, V.; Negrato, M.; Abbiati, G.; Dell'Acqua, M.; Rossi, E. Gold-catalyzed cis-hydroarylation of ynamides with indoles: regio- and stereoselective synthesis of a class of 2-vinylindoles. *Org. Lett.* **2016**, *18*, 4798-4801.

(17) a) Pirovano, V.; Brambilla, E.; Rizzato, S.; Abbiati, G.; Bozzi, M.; Rossi, E. Gold-Catalyzed Cascade Reactions of 4*H*-Furo[3,2-*b*]indoles with Allenamides: Synthesis of Indolin-3-one Derivatives. *J. Org. Chem*. **2019**, *84*, 5150-5166; b) Brambilla, E.; Pirovano, V.; Giannangeli, M.; Abbiati, G.; Caselli, A.; Rossi, E. Gold-catalyzed cascade reactions of 4*H*-furo[3,2-*b*] indoles with propargyl esters: Synthesis of 2-alkenylidene-3-oxoindolines. *Org. Chem. Front.* **2019**, *6*, 3078-3084.

(18) See a) Ref. 11c-d; b) Barnes, K. L.; Koster, A. K.; Jeffrey, C. S. Trapping the elusive aza-oxyallylic cation: new opportunities in heterocycloaddition chemistry. *Tetrahedron Letters* **2014**, *55*, 4690-4696; c) Acharya, A.; Anumandla, D.; Jeffrey, C. S. Dearomative Indole Cycloaddition Reactions of Aza-Oxyallyl Cationic Intermediates: Modular Access to Pyrroloindolines. *J. Am. Chem. Soc.* **2015**, *137*, 14858-14860; d) DiPoto, M. C.; Hughes, R. P.; Wu, J. Dearomative Indole (3 + 2) Reactions with Azaoxyallyl Cations - New Method for the Synthesis of Pyrroloindolines. *J. Am. Chem. Soc*. **2015**, *137*, 14861-14864; e) Ji, W.; Yao, L.; Liao, X. Access to the Pyrroloindoline Core via [3 + 2] Annulation as well as the Application in the Synthetic Approach to (±)-Minfiensine. *Org. Lett.* **2016**, *18*, 628-630.

(19) Stereochemistry of **9** was assigned according to ref. 18d.

(20) Gao, X.; Harmata, M. Formation and ring-opening of 8-oxabicyclo[3.2.1]oct-6-en-3-ones from (4+3)-cycloaddition of furan and chlorocyclopentanone derivatives. *Tetrahedron* **2013**, *69*, 7675-7682.

(21) Prantz, K.; Mulzer, J. Synthetic Applications of the Carbonyl Generating Grob Fragmentation. *Chem. Rev.* **2010**, *110*, 3741-3766.

(22) a) Cramer, C. J.; Barrows, S. E. Quantum Chemical Characterization of Cycloaddition Reactions between the Hydroxyallyl Cation and Dienes of Varying Nucleophilicity. *J. Org. Chem*. **1998**, *63*, 5523-5532; b) Cramer, C. J.; Barrows, S. E. Quantum chemical characterization of cycloaddition reactions between 1,3-butadiene and oxyallyl cations of varying electrophilicity. *J. Phys. Org. Chem*. **2000**, *13*, 176-186; c) Cramer, C. J.; Harmata, M.; Rashatasakhon, P. Intramolecular 4+3 Cycloadditions. Theoretical and Experimental Evaluation of Endo/Exo Preferences of a Cyclopentenyl Cation. *J. Org. Chem.* **2001**, *66*, 5641-5644.

(23) Rossi, E.; Abbiati, G.; Canevari, V.; Celentano, G. 2-Trifluoromethanesulfonyloxyindole-1-carboxylic Acid Ethyl Ester: A Practical Intermediate for the Synthesis of 2-Carbosubstituted Indoles. Synthesis **2006**, 299-304; b) Abbiati, G.; Canevari, V.; Facoetti, D.; Rossi, E. Diels-Alder Reactions of 2-Vinylindoles with Open-Chain C=C Dienophiles. E. *Eur. J. Org. Chem*. **2007**, 517-525; c) see ref 9c and 15c.

(24) Wang, Y.; Zhang, P.; Liu, Y.; Xia, F.; Zhang, J. Enantioselective gold-catalyzed intermolecular [2+2] versus [4+2]-cycloadditions of 3-styrylindoles with *N*-allenamides: observation of interesting substituent effects. *Chem Sci.* **2015**, *6*, 5564-5570.

(25) a) Hirano, K.; Urban, S.; Wang, C.; Glorius, F. A Modular Synthesis of Highly Substituted Imidazolium Salts. *Org. Lett.* **2009**, *11*, 1019-1022; b) Lou, S.; Fu, G. C. Nickel/Bis(oxazoline)-Catalyzed Asymmetric Kumada Reactions of Alkyl Electrophiles: Cross-Couplings of Racemic α-Bromoketones. *J. Am. Chem. Soc.* **2010**, *9*, 1264-1266; c) Fraser, R. R.; Kong. The Chlorination of Ketones Using Trimeihylchlorosilane and Dimethylsulfoxide With Bromide Ion Catalysis. *Synth. Commun.* **1988**, *18*, 1071-1077.

Graphical abstract