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Synthesis of 2-acylindoles via Ag- and Cu-catalyzed anti-Michael hydroamination of β–(2-aminophenyl)-α,β-ynones: experimental results and DFT calculation.

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ABSTRACT. β-(2-aminophenyl)-α,β-ynones afforded 3-unsubstituted 2-acylindoles in good yields in the presence of 20 mol% of AgOTf under MW heating. The use CuOTf as catalyst resulted in a similar reaction outcome, generally with a lower efficiency. This transformation represents the first example of *5-endo-dig* cyclization of 2-alkynylanilines bearing an acyl group linked to the triple bond. By contrast with the previously reported gold-catalyzed reaction of β-(2-aminophenyl)-α,β-ynones, that resulted in the formation of dibenzo[1,5]diazocines through a sequential process triggered by an intermolecular hydroamination, a selective intramolecular anti-Michael hydroamination was observed in the present study by mean of silver/copper catalysis. Density Functional Theory calculation on the Ag-catalyzed reaction revealed that the catalyst induces an electrostatic arrangement in the TS coherent with the experimentally observed cyclization.

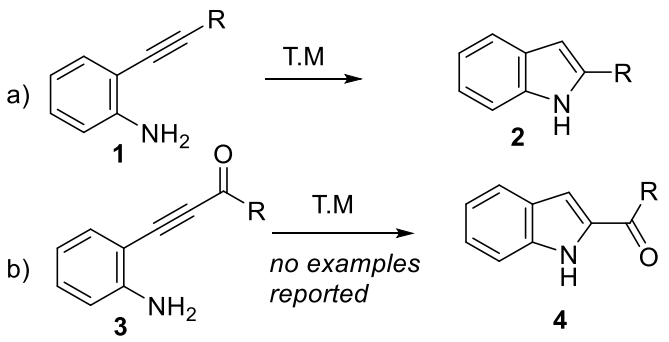
Introduction

The indole substructure is a near-ubiquitous component in many bioactive natural products,[1] and indole scaffold occurs in a large number of commercial drugs, as well as in molecules currently under clinical trial.[2] 2-Acylindoles constitute a particularly interesting class of indole derivatives, owing to their specific pharmacological properties. For instance, 2-(4-phenoxybenzoyl)indole derivatives have been identified as a novel structural class of calmodulin-dependent protein kinases (CaMKII) inhibitors.[3] Moreover, 2-aroyltrimethoxyindoles have been tested as analogues of the naturally-occurring drug Combretastatin A4, and resulted active as inhibitors of the tubulin polymerization.[4] In addition, 2-aroylindoles constitute a class of potent Histone deacetylase inhibitors for targeted cancer therapy.[5] Besides, hydrazone derivatives of acylindoles have been evaluated as inhibitors of methicillin-resistant Staphylococcus aureus growth. [6] Furthermore, 2-acylindoles have been recently used as useful building-blocks for the synthesis of pyrrolo[1,2-a]indoles and pyrroloquinolines.[7] Therefore, the development of practical and efficient routes

towards this useful indole derivatives is of great current interest.[8] Recently, the preparation of 3-unsubstituted 2-acylindoles has been accomplished by transition metals mediated coupling of a preformed indole ring with aldehydes,[9] α−oxocarboxylic acids,[10] α-diketones[11] and with toluene derivatives in the presence of *tert*-butyl hydroperoxide as oxidant.[12] These procedures, although efficient, require the presence of a directing group linked to the N_1 atom of the indole, that allows activation of C_2-H bond by cyclometalation; hydrolytic cleavage is then necessaty to obtain free N-H indole. Other recent routes towards 3-unsubstituted 2-acylindoles include the reaction of sulfur ylides and N-(orthochloromethyl) aryl amides in the presence of cesium carbonate,[13] rhodium (I) catalyzed reductive N-cyclization of 2-vinylnitroarenes using CO as a reducing agent,[14] reaction of 2-aminobenzaldehyde equivalents with α−bromoketones,[15] Cu (I) mediated cyclization of o-bromochalcones,[16] I_2-mediated intramolecular α-amination of ketones[17] and domino Pd-catalyzed cyclization of 2-*gem*-dibromovinylanilines-carbonylative Suzuki coupling. [18]

5-endo-dig cyclization of 2-alkynylaniniles **1** through transition-metals (T.M.) catalyzed hydroamination represents an efficient and atom-economical tool for the preparation of 2-substituted indole derivatives **2** (Scheme 1, a).[19] Over the years, this simple and straightforward methodology has been applied to the cyclization of alkynylanilines bearing a wide range of substituents R (aryl, alkyl, vinyl and other) linked to the C_{sp} carbon. However, no examples of *5-endo-dig* cyclization of 2-alkynylanilines with R = acyl (i.e. β-(2-aminophenyl)-α,β-ynones **3**, Scheme 1, b) have been reported so far. Only one example of TBAF-assisted cyclization of a propiolic ester (analogue of **1** with R = COOMe) has been described.[20]

Scheme 1. Cyclization of 2-alkynylanilines



T.M.: transition metal catalyst.

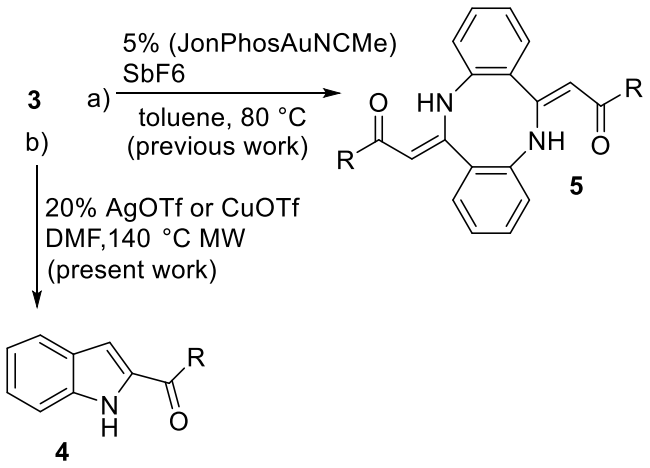
Substrates **3** can be readily obtained via a three-step procedure consisting of (i) reaction of aldehydes with ethynylmagnesium bromide, (ii) Sonogashira coupling of the resulting terminal propargylic alcohol with 2-iodoaniline derivatives, (iii) oxidation;[21] alternatively, carbonylative coupling of 2-ethynylaniline with aryl iodides or vinyl triflates can be used.[22] Therefore, the development of an efficient procedure for the *5-endo-dig* cyclization of **3** would nicely complement the existing procedures for the synthesis of 2-acylindoles, with the advantage of being fully atom-economical, without the need of protection/deprotection of the N-1 atom.

In fact, the reaction outlined in Scheme 2, b) requires a difficult anti-Michael nucleophilic addition of the amino group to the conjugated triple bond. To the best of our knowledge, only one example of anti-Michael *5-endo-dig* hydroamination of an alkynoate ester has been reported,[23] and in that case the cyclization was favored by the particular structure of the substrate, possessing a crowded quaternary center (*gem*-dimethyl effect). Alternative Michael-type cyclization of **3**, affording strained benzazetine ring,[24] could also be possible, at least in principle: one example of *4-exo-dig* Pd-catalyzed intramolecular hydroamination of gem-difluoropropargylamides has been described,[25] and the formation of β-lactam ring was driven by the polarization of the triple bond induced by fluorine substituents. Moreover we have recently reported that, in the presence of cationic Au(I) complex (JonPhosAuNCMe)SbF_6, substrates **3** underwent a sequential reaction, affording eight-membered dibenzo[1,5]diazocines **5** (Scheme 2, a).[26] In this case, an initial Michael-type

intermolecular hydroamination between two molecules of **3** took place preferentially, followed by cyclization of the resulting adduct.

Consequently, development of a selective intramolecular hydroamination of substrates **3** represents a challenging result. We wish to report here our investigation on the efficient conversion of β−(2-aminophenyl)-α,β−ynones **3** into the corresponding 2-acylindoles **4** , catalyzed by AgOTf or CuOTf (Scheme 2, b).

Scheme 2. Cyclization of β−(2-aminophenyl)-α,β−ynones **3**

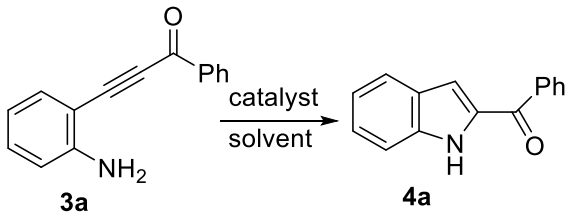


Results and Discussion

Ynone **3a** was selected as model substrate, and its cyclization under different catalyst/solvent/temperature combination was examined (Table 1). The anti-Michael hydroamination failed to occur by using well-estabilished methodologies for the cyclization of 2-alkynylaniline derivatives. For example, the formation of acylindole was not observed using $PdCl_2$ in MeCN at 80 °C,[27] (entry 1). Analogously, we failed to obtain **4a** when $NaAuCl_4$ (5 mol%) was employed as the catalyst in EtOH at room temperature[28] (entry 2), while at 80 °C (entry 3) the

nucleophilic addition of EtOH to the unsaturated alkynone took place to some extent, to give the 4-ethoxy-2-phenylquinoline **6a** in 26% yield. [29] During the optimization of our previous work,[26] we observed the formation of a small amount (12%) of acylindole **4a** (together with dibenzo[1,5]diazocine **5a)**, when AgOTf was used as the catalyst in toluene at 80 °C; consequently, we attempted the use of such catalyst.[30] Interestingly, partial formation of **4a** occurred in the presence of AgOTf in DMF at 100 °C, without formation of **5a** (entry 4), and this solvent resulted more effective respect to MeCN and EtOH (Table 1, entries 5-6). A better yield of **4a** was observed in dioxane (entry 7), but the ynone **3a** was not recovered in this case.

Table 1. Optimization of the cyclization of **3a** to give **4a**[a]



Entry	Catalyst (%)	Solvent	T(°C)	Time	**4a** (Yield %)[b]	**3a** (Recover %)[b]
1	$PdCl_2$ (10)	MeCN	80	24h	-	15
2	$NaAuCl_4$ (5)	EtOH	r.t.	24h	-	72
3	$NaAuCl_4$ (5)	EtOH	80	24h	-	31[c]
4	AgOTf (20)	DMF	100	8h	20	65
5	AgOTf (20)	MeCN	100	8h	9	88
6	AgOTf (20)	EtOH	100	8h	7	26
7	AgOTf (20)	Dioxane	100	8h	38	-
8	AgOTf (20)	DMF	100	16h	32	59
9	**AgOTf (20)**	**DMF**	**140[d]**	**15'**	**84[e]**	**-**
10	AgOTf (15)	DMF	140[d]	20'	82	-
11	AgOTf (10)	DMF	140[d]	30'	66	13

12	$AgSbF_6$ (20)	DMF	140[d]	20’	58	18
13	$AgNO_3$(20)	DMF	140[d]	20’	29	10
14	CuOTf (20)	DMF	140[d]	20’	74	-
15	CuCl (20)	DMF	140[d]	20’	60	-
16	$CuCl_2 \cdot 2H_2O$ (20)	DMF	140[d]	20’	16	20
17	$Cu(NO_3)_2 \cdot 3H_2O$ (20)	DMF	140[d]	20’	16	-
18	$Cu(OAc)_2 \cdot H_2O$ (20)	DMF	140[d]	20’	6	48
19	PPh_3AuNTf (5)	DMF	140[d]	20’	-	81
20	PPh_3AuCl(20) + AgOTf (15)	DMF	140[d]	20’	3	42
21	AuCl(20) + AgOTf (15)	DMF	140[d]	20’	-	51
22	(JonPhosAuNCMe) SbF_6 (5)	DMF	80	24h	-[f]	28
23	(JonPhosAuNCMe) SbF_6 (5)	DMF	140[d]	15’	3[g]	12
24	none	DMF	140[d]	15’	-	95
25	none[h]	THF	70	6h	-	-
26	none[h]	THF	140[d]	15’	-	-

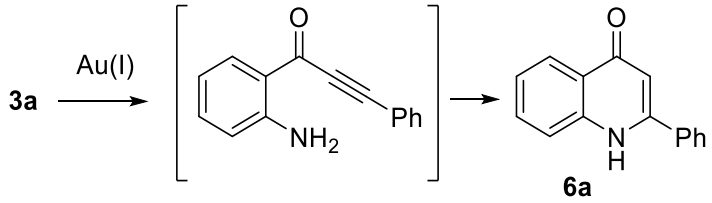
[a] Reactions were carried out on a 0.2 mmol scale in 1.2 mL of solvent. [b] NMR yields. [c] 4-ethoxy-2-phenylquinoline **6a** was obtained in 26% yield. [d] MW heating. [e] Isolated yield. [f]Dibenzo[1,5]diazocine **5a** was formed in 9% yield. [g]Dibenzo[1,5]diazocine **5a** was formed in 25% yield and quinolone **6a** was formed in 16% yield. [h] In the presence of 2 equiv. of 1.0 M solution of TBAF in THF, using 1 mL of solvent.

After prolonged time in DMF (entry 8), **4a** was isolated in 32% yield, and the starting material **3a** was recovered in 59% yield. Very pleasingly, after microwave heating at 140 °C for 15 minutes, we observed the complete conversion of **3a** into the acylindole **4a** as the sole product in high yield (entry 9). The influence of the AgOTf loading on the reaction outcome was also tested: with 15% of catalyst the yield was still good, while a further decrease gave worse results (entries 10-11). $AgSbF_6$ resulted less effective than AgOTf (entry 12), and AgNO3 afforded only a scarce amount of product (entry 13).

Then, we explored the use of other coinage metals. Cu(OTf) resulted quite effective in promoting the desired *anti*-Michael hydroamination (entry 14). Also CuCl afforded the product **4a** in moderate

yield (entry 15). By contrast, Cu(II) salts gave worse results (entries 16-18). Au(I) based catalysts were completely uneffective (entries 19-23). While the catalyst showed in entries 19-21 were previously found scarcely active also in the conversion of substrates **3** into **5**, (JonPhosAuNCMe)SbF_6 in toluene at 80 °C gave good results in such transformation (as stated also in the Introduction section and in Scheme 2).[26] Surprisingly, when we used this latter catalyst DMF at 80 °C (entry 22) and at 140 °C (entry 23) scarce formation of **5a** (R = Ph) was observed, and 2-acylindole **4a** was detected in trace amounts. At 140°C quinolone **6a** was also formed, likely via Au(I)-catalyzed rearrangement[31] of **3a**, followed by cyclization (Scheme 3).

Scheme 3. Formation of quinolone **6a** through Au(I)-catalyzed rearrangement

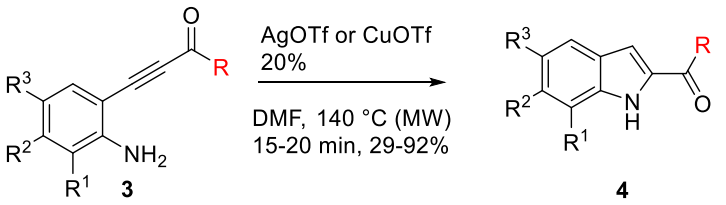


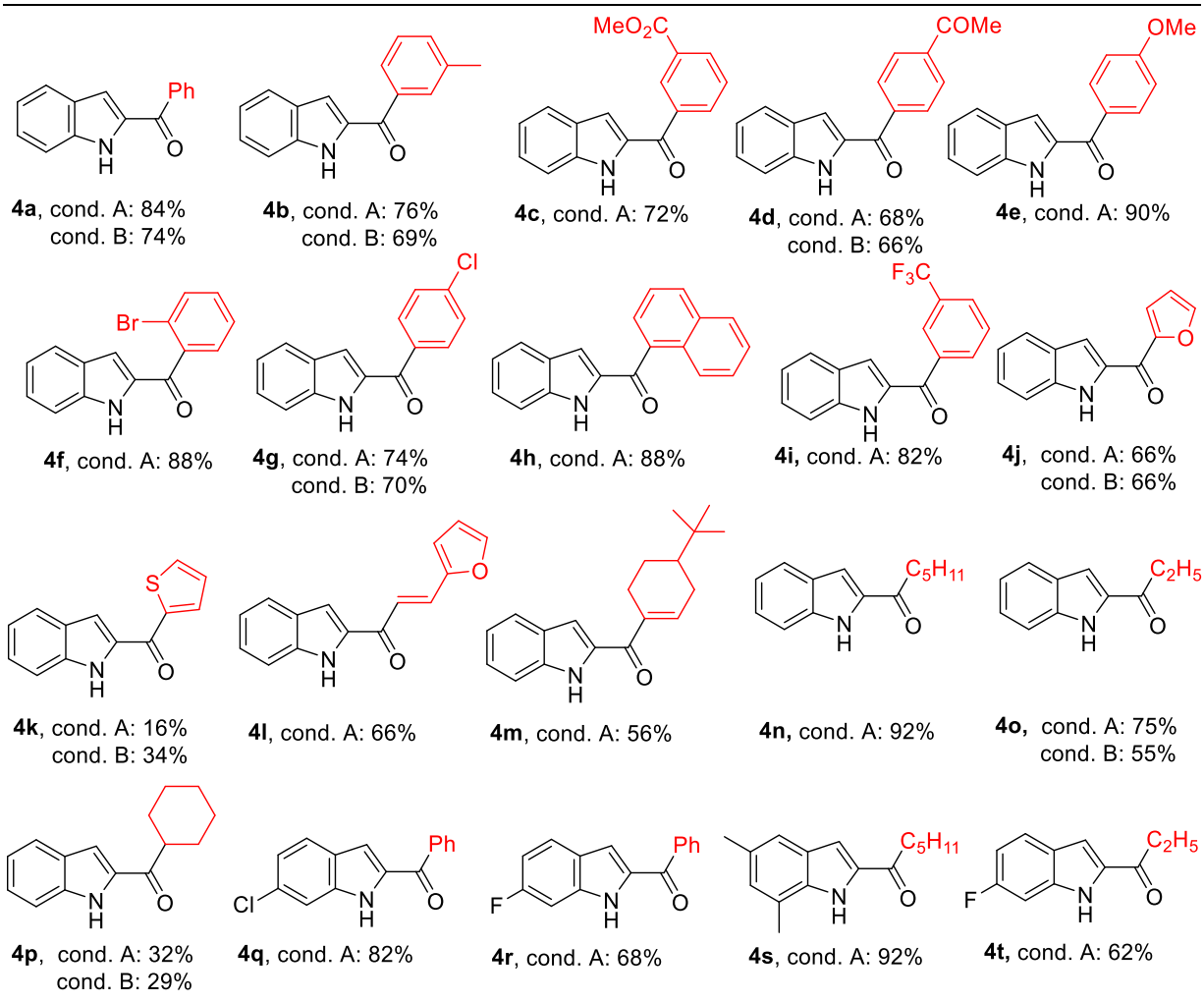
These results demonstrates that the reactivity of (JonPhosAuNCMe)SbF_6 with substrates **3** is dramatically influenced by the reaction medium. Finally, the near quantitative recovery of **3a** omitting the catalyst (entry 24) highlights the key role of the Ag(I) and Cu(I) catalysis in the formation of products. We also attempted the cyclization of **3a** in the presence of 1.0 M solution of TBAF [20] using normal or MW heating (entries 25, 26); in both cases complex reaction mixtures were obtained, without detectable formation of **4a**.

Optimized conditions of entry 9 were subsequently used for exploring the scope of the reaction. As reported in Table 2, a variety of 2-acylindoles **4** bearing aryl, heteroaryl, vinyl and alkyl group were quickly prepared usually in good to excellent yields by AgOTf catalyzed cyclization of ynones **3a-t**,[32] and only thienyl and cyclohexyl substituted products **4k** and **4p** were obtained in low yields.

Polysubstituted acylindoles **4q-t** were also prepared starting from ynones **3q-t**. We also explored the use of CuOTf.[33] Generally this catalyst resulted slightly less active respect to Ag(I) analogue, but still produced the acylindoles **4a**,**b**,**d**,**g**,**j**,**o**,**p** in synthetically useful yields. Interestingly, CuOTf afforded the thienoyl indole **4k** in better yield respect to AgOTf. It is worth noting that acylindoles **4** were obtained as sole products in all the case examined, without the formation of dibenzodiazocines **5**. Moreover, we did not observe the formation of products deriving from a Michael-type *4-exo-dig* process.

Table 2. Scope of the preparation of 2-acylindoles 4 from β−(2-aminophenyl)-α,β-ynones 3.[a,b]

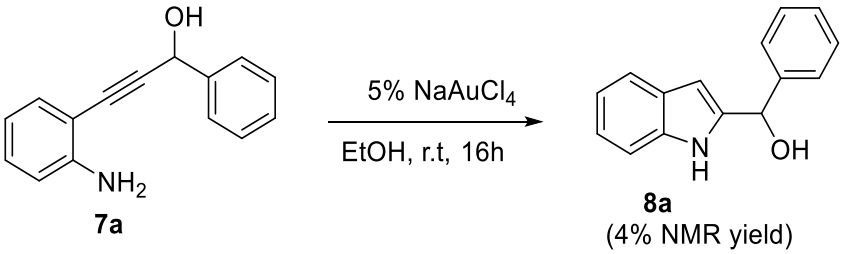




[a] Reaction conditions A: **3** (0.2 mmol), AgOTf (0.04 mmol), DMF (1.2 mL), 140 °C (MW), 15 min. B: **3** (0.2 mmol), CuOTf (0.04 mmol), DMF (1.2 mL), 140 °C (MW), 20 min. [b] Isolated yields are reported in %

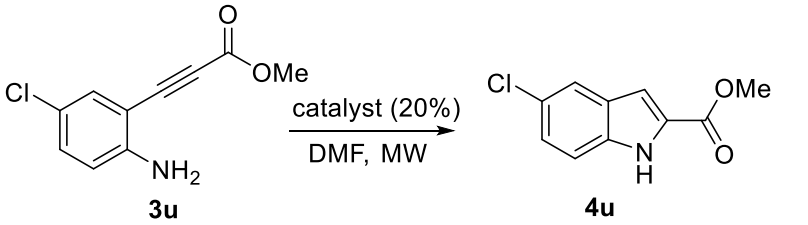
Cyclization of alkynylanilines bearing a secondary alcoholic group, followed by oxidation, could be also considered as a possible alternative route to acylindoles **4**. However, cyclization of **7a** resulted difficult: reaction with $NaAuCl_4$ at r.t[28] resulted in in a very little formation of product (Scheme 4), while the use of $PdCl_2$ in refluxing MeCN[27] resulted in the formation of a complex reaction mixture. Also reaction of **7a** with 20 mol% of AgOTf in refluxing MeCN failed: we obtained only 8% of **8a** after 4h; a similar result was obtained with 20 mol% of CuOTf (9% after 6h). These observations further demonstrate the usefulness of the present methodology.

Scheme 4. Attempts to cyclization of **7a**



We also attempted the cyclization of alkynoate ester **3u** (Scheme 5) but the indole **4t** was obtained in low yield using both AgOTf or CuOTf at 140 °C (condition A or B of Table 2); in both cases starting material was not recovered. Decreasing the reaction temperature to 120 °C with AgOTf, under otherwise identical reaction conditions, led to a similar result (21% yield). A further reduction to 100 °C afforded **4u** in 19% yield, together with recovered **3u** (10% yield)

Scheme 5. Attempts to cyclization of alkynoate ester **3u**.



catalyst	T (C°)	time	yield%
AgOTf	140	15'	18
CuOTf	140	15'	14
AgOTf	120	15'	21
AgOTf	100	30'	19

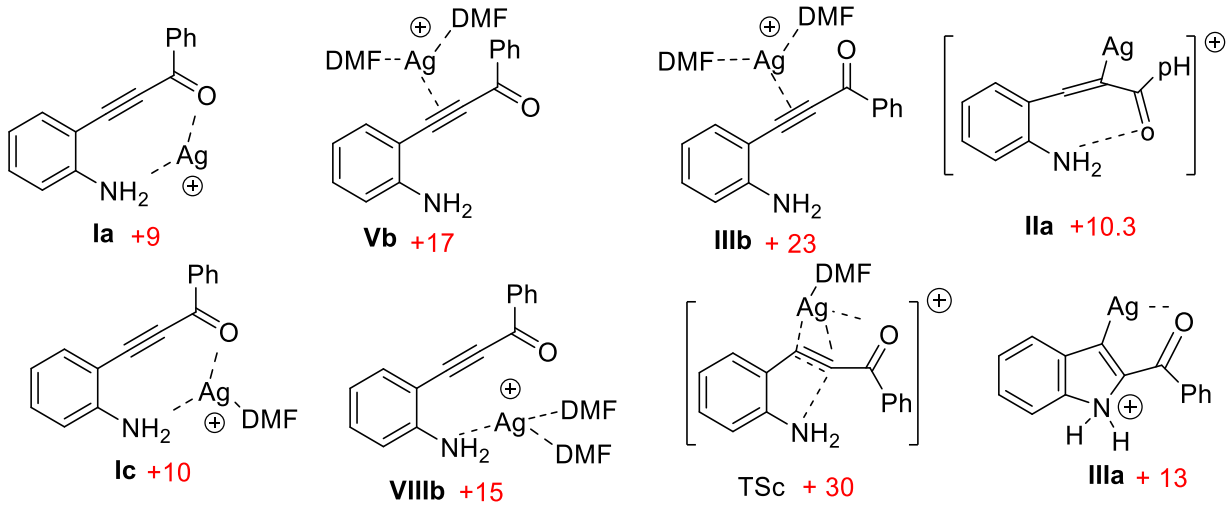
In order to try to shed some light onto the mechanism of the Ag-catalyzed cyclization of **3** and on the factors determining the highly selective 5-exo-dig anti Michael hydroamination pathway, we carried out quantum-chemical calculations in the framework of Density Functional Theory.[34] All

the related details are reported in the Supplementary information section. In this respect the first question to address is as to what is the actual reactant when silver triflate (AgTf) is solubilized in dimethylformamide. We have then studied the free energy of the reaction (1)

$$AgTf_{(sol)} + n\ DMF_{(l)} \rightarrow Ag(DMF)_n^+{}_{(sol)} + Tf_{(sol)} \quad (1)$$

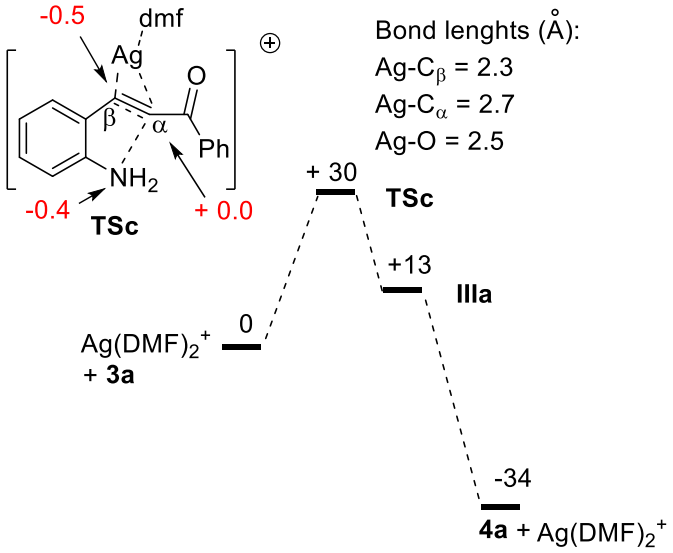
and we obtained, at 140°C, the value of -57.0 kJ/mole for n= 2 and -61 kJ/mole for n=4 indicating that, in DMF solution silver acts as a bi-solvated cation and that Tf⁻ does not play any relevant role, at least in the non-highly concentrated solutions utilized in the present study. At lower temperature (25°C) the free-energy difference becomes rather small suggesting that in this condition the tetra-coordinated $Ag(DMF)_4^+$ cluster is significantly populated as experimentally observed.[35] It is important to note that DMF preferentially binds to Ag^+ with carbonyl oxygen, i.e. all the investigated species obtained through N-Ag interaction have revealed much less stable. The main question, however, deals with the stability and the chemical structure of the complexes between solvated silver cation and **3a** in DMF solution under the experimental conditions. There are, obviously, different possibilities depending on the preferential binding site of Ag^+ with the **3a**, (NH_2, oxygen or C-C triple bond) and on the number of solvating DMF molecules possibly bound to Ag^+. Some of the relevant structures of [**3a**-Ag-DMF_n]$^+$ systems (with n=0, 1 and 2) are reported in Figure 1. In the same Figure we have also schematically reported the most accessible Transition Structures (see below).

Figure 1. Schematic view of of [**3a**-Ag-DMF_n]$^+$ systems (n=0, 1 and 2) and standard free energy of formation at 140°C in dmf solution with respect to $Ag(DMF)_2^+$ + **3a** species.



It is interesting to note that the affinity of silver cations toward **3a** is not outstanding and hence it would be rather difficult to isolate stable complexes at significant concentrations in the experimental conditions. At the same time the most stable intermediates turned out to be the structure **Ia** with the silver cation coordinated to nitrogen and oxygen. We also localized all the plausible TS structures, with a different number of explicit DMF molecules bound to silver cation. Thermochemical calculations (showing standard free energy barriers of +35 kcal/mole with n=0, +33 kcal/mole with n=2 and +30 kcal/mol with n=1 with respect to the free reactants $Ag(DMF)_2^+$ and **3a**) clearly indicate that only the TS with one DMF molecule (**TSc** in Figure 1) may play a kinetic role in the present conditions. On the basis of the above results we can conclude that $Ag(DMF)_2^+$ and **3a**, in pre-equilibrium with rather unstable intermediate complexes, evolve to the cyclic structure **IIIa** through a single-step path schematically depicted in Figure 2, and subsequent exoergonic protodemetallation affords the final products. In the same Figure we have also reported the atomic charges and bond lengths in the transition state **TSc** in which we observe that the presence of silver cation induces a correct electrostatic arrangement for the observed cyclization.[36]

Figure 2. Lowest energy reaction path, with atomic charges (in red) and selected bond lengths in the transition state TSa



To confirm the validity of the proposed model we also estimated the half-life of **3a** at the experimental initial concentration (0.2 M) and using a pseudo-first order rate constant (silver concentration of 0.1M). calculated according to the standard Eyring theory with transmission coefficient equal to 1. We obtained a calculated half-life of about 6400 s which, although higher than the experimental value, reveals rather satisfactory considering all the unavoidable systematic errors present in our calculations.

Conclusions

We have reported here the first example of *5-exo-dig* cyclization of 2-alkynylanilines bearing an acyl group on the triple bond, through a selective anti-Michael intramolecular hydroamination. Free N-H indoles were obtained, and derivatization of nitrogen was unnecessary in this alternative approach to 2-acylindoles. The use of silver and copper triflates *vs.* (JonPhosAuNCMe)SbF_6 resulted in divergent cyclization paths starting from substrates **3**. DFT calculations, carried out for the Ag-catalyzed reaction, have shown that the process is characterized by a very strong thermodynamic driving force and that it takes place in two steps by overcoming a barrier

characterized by a TS in which Ag^+ is coordinated by both carbon atom of the alkyne moiety, with different bond lengths, and by a single DMF molecule. Analysis of the atomic charges at the TS reveals that the presence of Ag(I) induces an electrostatic arrangement coherent with the experimentally observed anti-Michael hydroamination. A similar result was also obtained with Cu(I), whose details are also reported in the Supplementary Information.

Experimental Section

General remarks

Unless otherwise stated, all starting materials, catalysts, and solvents were commercially available and were used as purchased. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz in $CDCl_3$ (unless otherwise stated). Chemical shifts are reported in ppm relative to tetramethylsilane or referenced to the chemical shifts of residual solvent resonances ($CDCl_3$ at 77.04 ppm for ^{13}C). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dt = doublet of triplet, td = triplet of doublet, bs = broad signal. HRMS spectra were recorded using a MALDI-TOF spectrometer. β-(2-aminophenyl)-α,β-ynones **3a**[37], **3b-c**,[21] **3d**,[38] **3e**,[29] **3f**,[21] **3g-i**,[29] **3j-k**,[21] **3m**,[22] **3n-r**,[21] **3s-t**[26] and β-(2-aminophenyl)-α,β-ynoate **3u**[26] are known compounds and were prepared as reported (see Supporting Information for the related structures). Ynone **3l** was prepared using a reported procedure,[21] through Sonogashira coupling of 2-iodoaniline with (*E*)-1-(furan-2-yl)pent-1-en-4-yn-3-ol **9l** (obtained from the corresponding aldehyde via Grignard reaction) to give **7l** and subsequent oxidation. Compounds **7a** was prepared as reported.[37] Compound **8a** was not isolated, and its yield was determined by ^{1}H NMR of the reaction mixture (1,3,5-trimethoxybenzene as internal standard) through comparison with reported spectrum.[39] Indoles **4a**, **4b**, **4e**, **4f**, **4g**, **4h**, **4j**, **4k**, **4o**, **4q**, **4u** and quinolone **6a** are known compounds.

Computational details.

All the calculations were performed in the framework of Density Functional Theory (DFT) using the CAM-B3LYP functional[40] in conjunction with 6-31+G* basis set and with the Los Alamos National Laboratory Effective Core Potential with a double-zeta basis set (lanl2dz)[41] for silver. Larger basis set, 6-311+G*, was utilized for performing single point calculations onto the structures

more significant (i.e. showing lower formation free energies at the CAM-B3LYP/6-31+G* level). All the structures were first optimized and then characterized as minima or first order saddle points calculating the harmonic frequencies. Free energy calculations were finally obtained at the temperature of interest by calculating for each structure the partition function in the ideal-gas approximation, at the temperatures of interest, using the geometries, the associated frequencies and considering as reference state the concentration of 1.0 mole/liter at the pressure of 1.0 bar. The excess free energy, i.e. the effect of the solvent, was taken into account using a mean-field approach according to the Polarizable Continuum Model (PCM)[42] as implemented in the Gaussian 09 software.[43] On the purpose, the experimental dielectric constant[44] and density[45] of DMF were utilized at 140°C. The atomic charges were evaluated through standard fitting procedures.[46] All the details concerning the optimized structures and the free-energy calculations are reported in the Supplementary Information section.

(*E*)-1-(furan-2-yl)pent-1-en-4-yn-3-ol 9l. Yield: 1.15 g, 95 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.36 (m, 1H), 6.64 (d, *J* = 15.7 Hz, 1H), 6.40–6.24 (m, 3H), 5.05 (d, *J* = 5.5 Hz, 1H), 2.64 (dd, *J* = 2.2, 0.5 Hz, 1H), 2.44 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 151.7, 142.5, 125.9, 120.3, 111.4, 109.4, 82.6, 74.6, 62.3. HRMS m/z (ESI) positive ion, calculated for $C_9H_8KO_2$: $[M+K]^+$ 187.0161, Found: 187.0159

(*E*)-5-(2-aminophenyl)-1-(furan-2-yl)pent-1-en-4-yn-3-ol 7l. Yield: 415 mg, 87 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 2.0 Hz, 1H), 7.30 (dd, *J* = 6.4, 1.5 Hz, 1H), 7.17–7.13 (m, 1H), 6.72–6.66 (m, 3H), 6.41–6.33 (m, 3H), 5.32 (*J* = 4.7, 1.2 Hz, 1H), 3.50 (br s, 2H, NH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 151.8, 148.0, 142.5, 132.3, 130.0, 126.5, 120.0, 118.0, 114.5, 111.45, 111.42, 109.4, 93.2, 83.1, 63.1. HRMS m/z (ESI) positive ion, calculated for $C_{15}H_{13}KNO_2$: $[M+K]^+$ 278.0583, Found: 278.0583.

(*E*)-5-(2-aminophenyl)-1-(furan-2-yl)pent-1-en-4-yn-3-one 3l. Yield: 250 mg, 63 %; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 15.8 Hz, 1H), 7.57–7.56 (m, 1H), 7.43 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.26–7.22 (m, 1H), 6.79–6.70 (m, 4H), 6.55-6.53 (m, 1H), 4.45 (br s, 2H, NH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 177.3, 150.7, 150.1, 145.8, 133.6, 133.2, 132.4, 126.1, 118.0,

116.9, 114.7, 112.9, 104.0, 93.1, 89.1. HRMS m/z (ESI) positive ion, calculated for $C_{15}H_{11}KNO_2$: $[M+K]^+$ 276.0427, Found: 276.0422.

General procedure for the synthesis of 2-acylindoles 4

A sealed microwave vial was charged with β-(2-aminophenyl)-α,β−ynone **3** (0.22 mmol) and AgOTf (20 mol%) in anhydrous DMF (1.2 mL). After prestirring for 1 min at room temperature, the reaction mixture was irradiated with microwaves at 140 ^{0}C for 15 min. After completion of the reaction (as monitored by TLC), the reaction mixture was diluted with a H_2O (10 mL), and extracted with ethyl acetate (3x15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexanes/ ethyl acetate 90:10 v/v) to obtain 2-acylindole **4**.

(1*H*-indol-2-yl)(phenyl)methanone 4a.[18] Yield (Procedure A): 42 mg, 84%; (Procedure B): 37 mg, 74%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (br s, 1H), 8.00 (d, *J* = 8.3 Hz, 2H), 7.72 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.65–7.60 (m, 1H), 7.59–7.56 (m, 3H), 7.37 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H), 7.18–7.14 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 187.3, 138.0, 137.7, 134.3, 132.4, 129.3, 128.5, 127.8, 126.5, 123.2, 121.0, 112.9, 112.3.

(1*H*-indol-2-yl)(*m*-tolyl)methanone 4b.[47] Yield (Procedure A): 38 mg, 76 %; (Procedure B): 34.5 mg, 69%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (br s, 1H), 7.81–7.47 (m, 3H), 7.43–7.38 (m, 4H), 7.19–7.15 (m, 2H), 2.47 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 187.4, 138.4, 138.0, 137.5, 134.5, 133.2, 129.7, 128.3, 127.8, 126.49, 126.48, 123.2, 121.0, 112.7, 112.2, 21.5.

Ethyl 3-(1*H*-indole-2-carbonyl)benzoate 4c. Yield (Procedure A): 36 mg, 72 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (br s, 1H), 8.67–8.66 (m, 1H), 8.30 (dt, *J* = 7.9, 1.6 Hz, 1H), 8.18 (dt, *J* = 8.00, 1.6 Hz, 1H), 7.74 (dd, *J* = 8.00, 1.1 Hz, 1H), 7.64 (ddd, *J* = 7.8, 7.2, 0.9 Hz, 1H), 7.51 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.40 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H), 7.20–7.16 (m, 2H), 3.98 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 186.2, 166.3, 138.2, 137.7, 134.0, 133.3, 133.2, 130.5, 130.3, 128.8, 127.7,

126.9, 123.4, 121.2, 113.2, 112.3, 52.5. HRMS m/z (ESI) positive ion, calculated for $C_{17}H_{13}KNO_3$: $[M+K]^+$ 318.0533, Found: 318.0530.

1-(4-(1*H*-indole-2-carbonyl)phenyl)ethan-1-one 4d. Yield (Procedure A): 34 mg, 68 %; (Procedure B): 33 mg, 66 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (br s, 1H), 8.09 (dd, *J* = 8.7 Hz, 4H), 7.74–7.71 (m, 1H), 7.52–7.49 (m, 1H), 7.40 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.20–7.15 (m, 2H), 2.69 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 197.6, 186.4, 141.7, 139.6, 137.9, 134.1, 129.4, 128.4, 127.7, 127.0, 123.4, 121.3, 113.4, 112.3, 26.9. HRMS m/z (ESI) positive ion, calculated for $C_{17}H_{13}KNO_2$: $[M+K]^+$ 302.0583, Found: 302.0582.

(1*H*-indol-2-yl)(4-methoxyphenyl)methanone 4e.[18] Yield (Procedure A): 45 mg, 90 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (br s, 1H), 8.05 (dd, *J* = 8.6, 1.8 Hz, 2H), 7.72 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.49 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.36 (td, *J* = 8.2, 0.9 Hz, 1H), 7.18–7.14 (m, 2H), 7.03 (dd, *J* = 8.6, 1.8, 2H), 3.91 (s, 3H); ^{13}CNMR (100.6 MHz, $CDCl_3$): δ 185.9, 163.2, 137.3, 134.5, 131.6, 130.7, 127.8, 126.2, 123.1, 120.9, 113.8, 112.2, 111.9, 55.5.

(2-Bromophenyl)(1*H*-indol-2-yl)methanone 4f.[48] Yield (Procedure A): 44 mg, 88 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.38 (br s, 1H), 7.71–7.65 (m, 2H), 7.54–7.37 (m, 5H), 7.15 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.88 (dd, *J* = 2.1, 1.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 187.0, 139.7, 138.2, 134.5, 133.5, 131.4, 129.4, 127.5, 127.1, 126.9, 123.4, 121.2, 120.0, 114.4, 112.4.

(4-Chlorophenyl)(1*H*-indol-2-yl)methanone 4g.[18] Yield (Procedure A): 37 mg, 74 %; (Procedure B): 35 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54 (br s, 1H), 7.96 (dd, *J* = 8.6, 1.8 Hz, 2H), 7.72 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.59–7.45 (m, 3H), 7.39 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.20–7.14 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 185.8, 138.8, 137.6, 136.3, 134.0, 130.6, 128.8, 127.7, 126.8, 123.3, 121.2, 112.8, 112.2.

(1*H*-indol-2-yl)(naphthalen-1-yl)methanone 4h.[16] Yield (Procedure A): 44 mg, 88 %;^{1}H NMR (400 MHz, $CDCl_3$): δ 10.07 (br s, 1H), 8.34–8.24 (m, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.96–7.85 (m, 2H), 7.66–7.61 (m, 1H), 7.60–7.48 (m, 4H), 7.34 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.96 (dd, *J* = 2.1, 1.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 188.9, 138.2, 136.0, 135.7, 133.8, 131.5, 130.8, 128.4, 127.9, 127.6, 127.3, 126.8, 126.5, 125.5, 124.3, 123.3, 121.0, 113.9, 112.5.

(1*H*-indol-2-yl)(3-(trifluoromethyl)phenyl)methanone 4i. Yield (Procedure A): 41 mg, 82 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.39 (br s, 1H), 8.25 (s, 1H), 8.18 (d, *J* = 7.6 Hz, 1H), 7.89-7.87 (m, 1H), 7.75–7.66 (m, 2H), 7.50 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.41 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.21–

7.15 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 185.6, 138.6, 137.8, 133.8, 132.3 (q, *J* = 1.2 Hz), 130.1 (q, *J* = 33 Hz), 129.1 , 128.8 (q, *J* = 3.8 Hz), 127.7, 127.1, 126.0 (q, *J* = 3.9 Hz), 124.7 (q, *J* = 272 Hz), 123.4, 121.4, 113.3, 112.3. HRMS m/z (ESI) positive ion, calculated for $C_{16}H_{10}F_3NNaO$: $[M+Na]^+$ 312.0612, Found: 312.0613.

Furan-2-yl(1*H*-indol-2-yl)methanone 4j.[47] Yield (Procedure A): 33 mg, 66 %; (Procedure B): 33 mg, 66 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.31 (br s, 1H), 7.82–7.69 (m, 3H), 7.51–7.44 (m, 2H), 7.37 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.18 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.65 (dd, *J* = 3.6, 1.7 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 172.6, 152.7, 146.5, 137.2, 133.5, 128.0, 126.5, 123.4, 121.0, 118.6, 112.5, 112.1, 111.4.

(1*H*-indol-2-yl)(thiophen-2-yl)methanone 4k.[47] Yield (Procedure A): 8 mg, 16 %; (Procedure B): 17 mg, 34 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (br s, 1H), 8.06 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.74 (ddd, *J* = 6.5, 6.1, 1.0 Hz, 2H), 7.50 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.45 (dd, *J* = 2.2, 1.0 Hz, 1H), 7.38 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H), 7.24 (dd, *J* = 4.9, 3.8 Hz, 1H), 7.19 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 177.9, 142.5, 137.4, 134.1, 133.2, 133.0, 128.1, 127.8, 126.4, 123.2, 121.1, 112.2, 110.7.

(*E*)-3-(furan-2-yl)-1-(1*H*-indol-2-yl)prop-2-en-1-one 4l. Yield (Procedure A): 33 mg, 66 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (br s, 1H), 7.75–7.65 (m, 2H), 7.56 (d, *J* = 1.7 Hz, 1H), 7.48–7.42 (m, 2H), 7.38–7.36 (m, 2H), 7.16 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.74 (d, *J* = 3.6 Hz, 1H), 6.53 (dd, *J* = 3.3, 2.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 180.9, 151.7, 145.0, 137.8, 136.6, 129.2, 127.8, 126.4, 123.2, 121.0, 119.3, 116.3, 112.7, 112.2, 109.4. HRMS m/z (ESI) positive ion, calculated for $C_{15}H_{11}KNO_2$: $[M+K]^+$ 276.0427, Found: 276.0429.

(4-(*tert*-butyl)cyclohex-1-en-1-yl)(1*H*-indol-2-yl)methanone 4m. Yield (Procedure A): 28 mg, 56 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.38 (br s, 1H), 7.71–7.68 (m, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.33 (ddd, *J* = 8.3, 7.1, 1.1 Hz, 1H), 7.14 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 7.08 (dd, *J* = 1.2, 1.1 Hz, 1H), 7.02–6.99 (m, 1H), 2.76–2.70 (m, 1H), 2.43–2.29 (m, 2H), 2.13–1.99 (m, 2H), 1.45–1.37 (m, 1H), 1.30–1.19 (m, 1H), 0.94 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 188.3, 140.7, 138.4, 137.2, 134.4, 127.6, 125.8, 122.9, 120.7, 112.1, 110.6, 43.6, 32.3, 27.8, 27.2, 25.9, 23.5. HRMS m/z (ESI) positive ion, calculated for $C_{19}H_{24}NO$: $[M+H]^+$ 282.1858, Found: 282.1857.

1-(1*H*-indol-2-yl)hexan-1-one 4n. Yield (Procedure A): 46 mg, 92%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (br s, 1H), 7.71 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.46–7.44 (m, 1H), 7.34 (ddd, *J* = 8.3, 7.1, 1.1 Hz, 1H), 7.21 (dd, *J* = 1.1 Hz, 1H), 7.15 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 2.95 (t, *J* = 7.6 Hz, 2H), 1.85–1.77 (m, 2H), 1.42–1.35 (m, 4H), 0.92 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 193.9,

137.4, 135.3, 127.6, 126.2, 123.0, 120.9, 112.3, 109.2, 38.4, 31.6, 24.9, 22.5, 14.0. HRMS m/z (ESI) positive ion, calculated for $C_{14}H_{17}KNO$: $[M+K]^+$ 254.0947, Found: 254.0940.

(1*H*-indol-2-yl)(thiophen-2-yl)methanone 4o.[17] Yield (Procedure A): 37.5 mg, 75 %; (Procedure B): 27.5 mg, 55 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48 (br s, 1H), 7.70 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.45 (dt, *J* = 2.7, 0.9 Hz, 1H), 7.34 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H), 7.21 (dd, *J* = 2.1, 0.9 Hz, 1H), 7.15 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 3.01 (q, *J* = 7.4 Hz, 2H), 1.29 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 194.1, 137.3, 134.9, 127.6, 126.2, 123.0, 120.9, 112.3, 108.9, 31.5, 8.8.

cyclohexyl(1*H*-indol-2-yl)methanone 4p. Yield (Procedure A): 16 mg, 32%; (Procedure B): 14.5 mg, 29 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (br s, 1H), 7.71 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.34 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.26–7.24 (m, 1H), 7.15 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 3.24–3.16 (m, 1H), 1.96–1.89 (m, 4H), 1.64–1.54 (m, 4H), 1.46–1.24 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 197.1, 137.3, 134.4, 127.6, 126.2, 123.0, 120.9, 112.3, 108.9, 46.5, 29.8, 25.9. HRMS m/z (ESI) positive ion, calculated for $C_{15}H_{17}KNO$: $[M+K]^+$ 266.0947, Found: 266.0947.

(6-chloro-1*H*-indol-2-yl)(phenyl)methanone 4q.[48] Yield (Procedure A): 41 mg, 82 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (br s, 1H), 7.99 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.69–7.59 (m, 2H), 7.59–7.51 (m, 2H), 7.51–7.48 (m, 1H), 7.15–7.13 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 187.0, 137.7, 135.0, 132.6, 132.5, 129.2, 128.6, 126.3, 124.2, 122.2, 112.6, 112.0.

(6-fluoro-1*H*-indol-2-yl)(phenyl)methanone 4r. Yield (Procedure A): 34 mg, 68 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.41 (br s, 1H), 7.98 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.68–7.63 (m, 2H), 7.56–7.52 (m, 2H), 7.16–7.14 (m, 2H), 6.96 (ddd, *J* = 8.8, 6.7, 2.3 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 186.9, 162.4 (d, $J_{C\text{-}F}$ = 244 Hz), 137.8, 135.08 (d, $J_{C\text{-}F}$ = 3.7 Hz), 132.5, 129.2, 128.6, 124.6 (d, $J_{C\text{-}F}$ = 10.5 Hz), 124.4 (d, $J_{C\text{-}F}$ = 1.1 Hz), 113.08, 113.06, 110.9 (d, $J_{C\text{-}F}$ = 27.6 Hz), 98.1 (d, $J_{C\text{-}F}$ = 27.6 Hz). HRMS m/z (ESI) positive ion, calculated for $C_{15}H_{10}FKNO$: $[M+K]^+$ 278.0383, Found: 278.0381.

1-(5,7-dimethyl-1*H*-indol-2-yl)hexan-1-one 4s. Yield (Procedure A): 46 mg, 92 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 (br s, 1H), 7.32 (s, 1H), 7.13 (d, *J* = 2.2 Hz, 1H), 6.98 (s, 1H), 2.92 (t, *J* = 7.7 Hz, 2H), 2.47 (s, 3H), 2.41 (s, 3H), 1.82–1.74 (m, 2H), 1.39–1.34 (m, 4H), 0.91 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 193.8, 135.6, 135.1, 130.5, 128.6, 127.4, 121.2, 119.7, 109.2, 38.3, 31.6, 25.1, 22.5, 21.4, 16.7, 14.0. HRMS m/z (ESI) positive ion, calculated for $C_{16}H_{21}KNO$: $[M+K]^+$ 282.1260, Found: 282.1259.

1-(6-fluoro-1*H*-indol-2-yl)propan-1-one 4t. Yield (Procedure A): 31 mg, 62 %; ^{1}H NMR (400

MHz, $CDCl_3$): δ 9.46 (br s, 1H), 7.40 (dd, J = 9.0, 4.3 Hz, 1H), 7.34 (dd, J = 6.8, 2.3, 1H), 7.17 (dd, J = 2.2, 1.3 Hz, 1H), 7.11 (dt, J = 9.0, 6.7, 2.3 Hz, 1H), 3.01 (q, J = 7.4 Hz, 2H), 1.29 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 194.0, 158.1 (d, J_{C-F} = 236 Hz), 136.3, 133.8, 127.7 (d, J_{C-F} = 10.3 Hz), 115.3 (d, J_{C-F} = 26.9 Hz), 113.2 (d, J_{C-F} = 9.7 Hz), 108.6 (d, J_{C-F} = 5.9 Hz), 107.3 (d, J_{C-F} = 23.4 Hz), 31.6, 8.6. HRMS m/z (ESI) positive ion, calculated for $C_{11}H_{10}FKNO$: $[M+K]^+$ 230.0383, Found: 230.0384.

Methyl 5-chloro-1*H*-indole-2-carboxylate 4u.[49]

Yield (Procedure A): 9 mg, 18 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (br s, 1H), 7.67 (s, 1H), 7.35 (d, J = 8.7 Hz, 1H), 7.31–7.25 (m, 2H), 7.15 (d, J = 1.5 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (100.6MHz, $CDCl_3$): δ 162.1, 135.1, 128.4, 126.6, 126.0, 121.8, 112.98, 112.93, 108.1, 52.2.

2-phenylquinolin-4(1*H*)-one 6a.[50]

Yield: 8 mg, 16 %; ^{1}H NMR (400 MHz, DMSO): δ 11.75 (br s, 1H), 8.11 (dd, J = 8.1, 1.1 Hz, 1H), 7.84–7.77 (m, 3H), 7.67 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.61–7.53 (m, 3H), 7.34 (t, J = 7.5 Hz, 1H), 6.34 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO): δ 177.0, 150.0, 140.5, 134.2, 131.8, 130.4, 129.0, 127.4, 124.9, 124.7, 123.2, 118.7, 107.3.

Supporting Information Available. a) Structure of **3a-t**, copies of ^{1}H and ^{13}C NMR spectra of all new compounds and copies of ^{1}H spectra of known acylindoles and quinolone **6a**. b) Details of DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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