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Iron/Rhodium Bimetallic Lewis Acid/Transition Metal Relay Catalysis for Alkynylation/Cyclotrimerization Sequential Reactions Toward Isoindolinones Derivatives from *N,O*-Cyclic Acetals

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Abstract: A novel sequential one-pot bimetallic catalytic system combining Fe(III)-catalyzed alkynylation and a Rh(I)-catalyzed [2+2+2] reaction was successfully developed. The σ-Lewis acid properties of iron (III) and the π-Lewis acid properties of rhodium (I) catalysts were unified in an unprecedented intermolecular alkynylation/cyclotrimerization one-pot process. Using this unique Fe/Rh bimetallic relay catalytic system, a variety of benzo and pyrridinoisoindolinones derivatives were obtained under mild conditions from easily available N-(propargyl) hydroxy aminals, as the simplest *N*-acyliminium ion precursors, and several alkynes.

Keywords: Isoindolinones; alkynylation; cyclotrimerization; iron; rhodium; sequential tandem reactions

1. Introduction

The development of novel methodologies that enable rapid, practical, and economical construction of privileged small molecules in pharmaceutical sciences is highly desirable. In this context, sequential one-pot bimetallic catalysis is undoubtedly one of the most powerful strategies offering an efficient diversity-oriented, ecofriendly synthesis of these privileged scaffolds [1–15].

Isoindolinone frameworks, which are referred as phthalimidines or benzo fused γ-lactams, are common structural motifs in many synthetic and natural products that exhibit interesting biological activities. Many of these frameworks showed anxiolytic [16], MDM2-p53 inhibitory [17,18], antimicrobial [19–22], antiviral [23–26], PARP-1-inhibitory [27], histone deacetylase inhibitory [28,29], antihyperglycemic [30–33], antioxidant [34], anti-inflammatory [35], antifungal [36], antiparkinsonian [37], selective NaV1.7 blocking [38,39] antipsychotic [40–42], antihypertensive [43], anticancer [44–46], anesthetic [47], vasodilatory [48], and survival motor neuron protein production regulating activities (Figure 1) [49].

Owing to the wide spectrum of isoindolinone core biological activities, substantial efforts have been devoted to preparing this heterocyclic skeleton [50–57]. Among them are the functionalization of phthalimides or phthalimidines, transition-metal catalyzed C-C bond-forming reactions involving for example, C-H activation [58–69], cycloaddition [70,71], cross-coupling [72–81], carbonylation [82–84] strategies. Despite the development of a plethora of methods, the preparation of isoindolines [85–94] and pyrollopyrridine [95–97] fused isondolinones were not yet reported.

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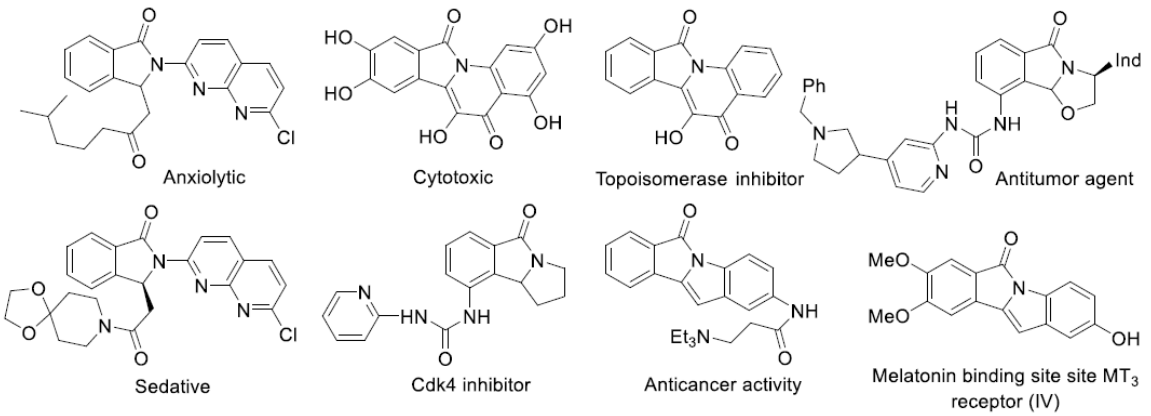
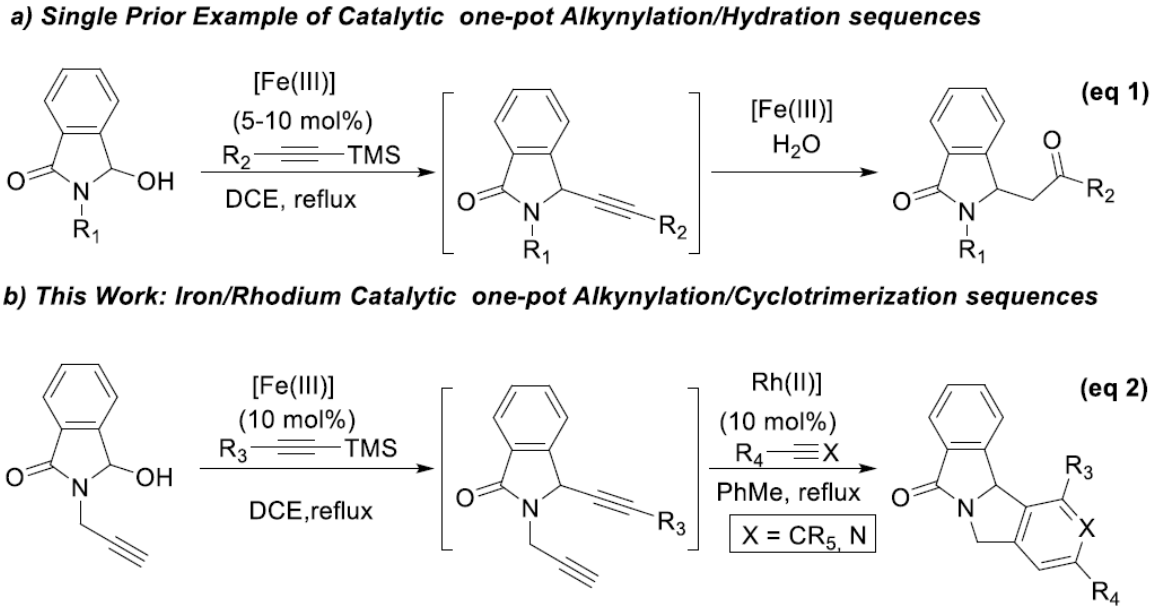


Figure 1. Examples of biologically active isoindolinone derivatives.

Recently, our group developed an unprecedented (ligand-free) iron (III) tandem intermolecular amidoalkynylation/intramolecular hydration sequence of several isoindolic cyclic *N,O*-acetals (acetoxylactams) allowing expedient access to new functionalized isoindolinone ketone motifs. Unprotected hydroxy *N,O*-acetals (hydroxylactams), a more atom-economic source of electrophile in comparison with the parent acetoxylactams, was used in these transformations (Scheme 1, eq. 1) [98].



Scheme 1. Current state-of-the-art C-alkynylation of *N*-acyliminium reactions (**eq. 1**) and this work (**eq. 2**).

Moreover, the transition-metal-catalyzed [2+2+2] cyclotrimerization reactions of alkynes constitute powerful methods for the synthesis of substituted six-membered aromatics in a one-step highly atom economic process [99–109]. Since Reppe's pioneering cyclotrimerization of alkynes in 1948, a myriad of efficient catalytic species (e.g., Rh [110–121], Ru [122–128], Ir [129–132], Co [133–137], Ni [138–143], Mo [144,145], Nb [146], Au [147], Pd [148], Fe [149–156]) and coupling partners (e.g., olefins, nitriles, isocyanates, cyanamides, aldehydes, ketones, carbon dioxide, imines, and carbodiimides), were employed for this purpose.

Inspired by our results on iron (III) *N,O*-cyclic acetals alkynylation, the advances and elegance of transition-metal-catalyzed [2+2+2] cyclotrimerization reactions, and the biological and synthetic importance of isondolinone scaffolds, we became interested in developing a one-step synthetic route to prepare novel isoindolines and pyrollopyrridines fused isoindolinones through bimetallic Fe(III) alkynylation/Rh(I) [2+2+2] cycloaddition relay catalysis (Scheme 1, eq. 2).

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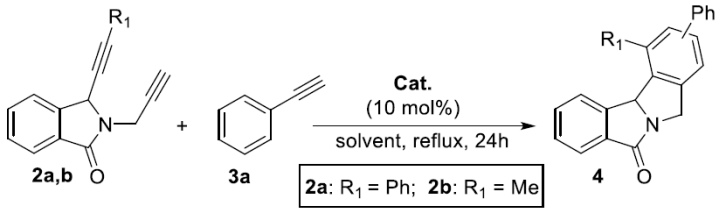
2. Results

2.1. Cyclotrimerization of Dialkyne (Optimization Study)

Based on our previous work on iron-catalyzed alkynylation and before exploring the one-pot procedure, we decided to test the feasibility of the cyclotrimerization reaction. We performed a catalyst screening for the [2+2+2] cycloaddition reaction. Based on recent successes in constructing highly substituted benzenes and pyridines via an iron cyclotrimerization reaction, we first applied a similar approach to diynes **2a,b,** and phenylacetylene **3a** as a model substrate. Unfortunately, all efforts to obtain the isoindolinones **4** using $Fe(OTf)_3$, FeI_2, or $Fe(OAc)_2$ as precatalysts along with various ligands in the presence of Zn metal as reducer were unsuccessful, and diynes **2a,b** were invariably partially regenerated (Table 1, entries 1-3). To overcome these limitations, we decided to move from a monometallic iron-based catalyst to a bimetallic sequence, using a hard Lewis acid (FeIII) catalyst for alkynylation and Rh or Ru catalyst for the [2+2+2] cycloaddition step (Table 1, entries 4-11).

Table 1. Identification of the best cyclotrimerization catalyst.[a]



entry	R1	catalyst	solvent	product	yield[b]
1	Ph/Me	$Fe(OTf)_3$	-[c,d]	**-**	ND
2	Ph/Me	$Fe(OAc)_2$/L/Zn	-[c,d]	**-**	ND
3	Ph/Me	FeI_2/dppp/Zn	-[c,d]	-	ND
4	Ph	$RhCl(PPh_3)_3$	PhMe	-[d]	ND
5	**Me**	**$RhCl(PPh_3)_3$**	**PhMe**	**4**	**35**
6	Me	$RhCl(PPh_3)_3$	PhMe	**4**	15
7	Me	$RhCl(PPh_3)_3$	THF	**4**	17
8	Me	$RhCl(PPh_3)_3$	DCE	**4**	25
9	Ph	Grubbs-I/II	-[c,d]	-[d]	ND
10	Me	Grubbs-I	PhMe	**4**	10
11	Me	Grubbs-II	PhMe	**4**	15

[a] Standard reaction conditions: All reactions were carried out using **2** (0.5 mmol), **3a** (5 mmol), 10 mol% catalyst, and 2 mL of solvent under N_2. [b] Isolated yield. [c] The reaction was tested in DCM, DCE, PhMe, or THF. [d] The reaction was tested at room temperature and under reflux. ND = not determined.

The results showed that **2b** and $RhCl(PPh_3)_3$ were the best substrate and the most effective catalyst for this reaction, respectively (Table 1, entries 4-8). Further assessment of the solvent effect indicated that PhMe was the best solvent for this cyclotrimerization reaction, providing a higher yield than other commonly used solvents (entry 5 vs. 7-8). Grubbs catalysts resulted in inferior results. The use of Grubbs first generation (Grubbs-I) catalyst (Table 1, entry 10) under the Wilkinson conditions (**3a** (10 equiv.), PhMe reflux, argon) gave **4** in only 10% yield along with several side-products. Under Grubbs second generation (Grubbs-II) catalyst (Table 2, entry 11), the same profile of the reaction was observed (**4**: 15%; several side-products) even after a prolonged reaction time (24 h). These findings highlighted the advantage of using Rhodium (I) in the cyclotrimerization reaction.

Encouraged by these results, we moved forward to optimizing the reaction conditions (Table 2). Different temperatures, the addition rate of alkyne **3a,** and reaction time were examined. It was found that the slow addition of alkyne **3a** to the reaction media for 2 h followed by reflux in PhMe for 1 h afforded the expected isoindolinones **4a/4a'** (**4a:4a' =** 60:40 in the highest yield (76%, entry 6).

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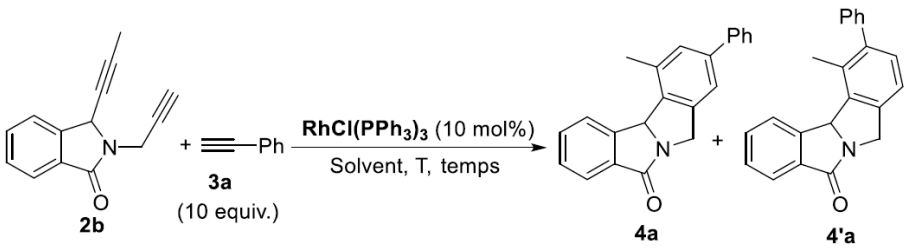
Table 2. Optimization of cyclotrimerization of di-alkyne 2b[a]



entry	catalyst	add of **3a** (h)	t (h)	T (°C)	yield (%) [b]	**4a:4a'**[c]
1	$RhCl(PPh_3)_3$	0.5	48	rt	29	55:45
2	$RhCl(PPh_3)_3$	0.5	0.3	reflux	47	60:40
3	$RhCl(PPh_3)_3$	1	0.5	reflux	55	58:42
4	$RhCl(PPh_3)_3$	2	2	reflux	68	60:40
5	$RhCl(PPh_3)_3$	3	2	reflux	60	57:43
6	**$RhCl(PPh_3)_3$**	**2**	**1**	**reflux**	**76**	**60:40**
7	$RhCl(PPh_3)_3$	2	1	80	64	57:43
8[d]	$RhCl(PPh_3)_3$	2	1	reflux	43	60:40
9[e]	$RhCl(PPh_3)_3$	2	1	reflux	60	56:44
10[f]	$RhCl(PPh_3)_3$	2	1	reflux	52	57:43
11[g]	$RhCl(PPh_3)_3$	2	1	reflux	45	57:43
12	Grubbs-I	2	1	reflux	20	60:40
13[g]	Grubbs-I	2	1	reflux	15	58:42
14	Grubbs-II	2	1	reflux	30	60:40
15[g]	Grubbs-II	2	1	reflux	12	60:40

[a] Standard reaction conditions: All reactions were carried out using **2b** (0.5 mmol), **3a** (5 mmol, 10 equiv.), 10 mol% catalyst, and 2 mL of solvent under N_2. [b] Isolated yield. [c] Ratio was determined by ^1H NMR of the crude materials. [d] Reaction was done using 5 equiv. of alkyne **3a** [e] Reaction was done using 5 mmol% of the catalyst. [f] The reaction was tested in DCE. [g] The reaction was tested in THF.

The use of Grubbs instead of Wilkinson catalyst under the above-optimized conditions did not improve the yield; isoindolinones **4** were obtained in 20% and 30% isolated yields, respectively, with Grubbs first generation (Grubbs-I) and Grubbs second generation (Grubbs-II) (Table 2, entries 12 and 14). Switching the solvent from PhMe to other solvents such as THF or DCE resulted in inferior results. For example, $RhCl(PPh_3)_3$ in DCE produced **4a/4a'** in 52% yield (Table 2, entry 10).

With the establishment of the optimized conditions, the substrate scope was examined (Scheme 2). The [2+2+2] cyclotrimerization proved to be quite general; a broad range of terminal aromatic alkynes served as suitable substrates for this reaction, leading to the desired isoindolinones in moderate to excellent yields (Scheme 2, entries 1–8). The reactions of alkynes bearing an electron-donating group such as *m*- or *p*-methyl on aryl rings resulted in high yields of isoindolinones **4b**/**4b'** (69% yield, **4b**:**4b'** = 54:46) and **4c**/**4c'** (68% yield, **4c:4c'** = 60:40) (Scheme 2, entries 2 and 3). Substrates with an electron-withdrawing substituent on the aryl ring, such as *p*-NO_2 and *p*-Br, proved to be also suitable, furnishing **4d**/**4d'**and **4e**/**4e'** in 58% (**4d:4d'** = 61:39) and 75% (**4e:4e'** = 58:42) yields (Scheme 2, entries 4 and 5).

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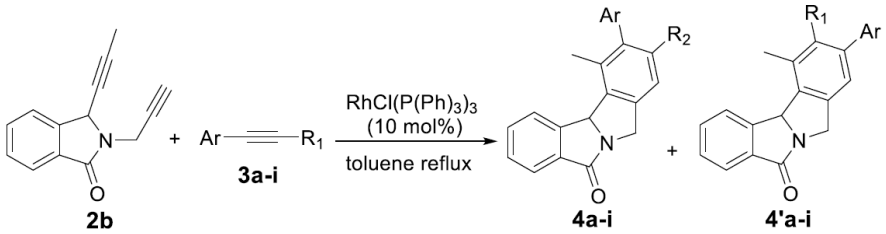
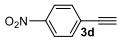
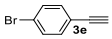
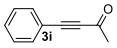
Scheme 2. Reaction scope of aromatic alkynes.[a,b]



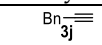
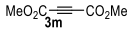
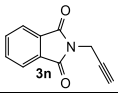
entry	Alkyne	t (h)	**4:4′**[b]	yield (%)[c] of **4** + **4′**
1		1	57:43	76
2		4	54:46	69
3		1	60:40	68
4		6	61:39	58
5		1	58:42	75
6		5	100:00	59
7		3	100:00	83
8		6	57:43	71[d]
9		8	63:37	43[d]

[a] Standard reaction conditions: **2b** (0.5 mmol) in PhMe (1 mL), a portion-wise addition of a mixture of alkyne **3** (5 mmol) and $RhCl(PPh_3)_3$ (10 mol%) in PhMe (2 mL) for 2h, and was refluxed (TLC). [b] The ratio was determined by ^1H NMR of the crude materials [c] Isolated product yield. [d] Separable through column chromatography.

Interestingly, with the *ortho*-substituted alkynes **3f** and **3g**, the reaction proceeded with complete regioselectivity. Isoindolinones **4f** and **4g** were obtained in 59% and 83% isolated yields, respectively (Scheme 2, entries 6 and 7). Heteroaryl-substituted alkyne (e.g., 2-thienyl-substituted) was transformed to **4h**/**4h′** (**4h**:**4h′** = 54:46) successfully in 71% yield (Scheme 2, entry 8). The reaction was also applicable to internal aromatic alkynes, as exemplified by the synthesis of **4i**/**4i′** isoindolinones derivatives in 43% (**4i**:**4i′** = 63:37) isolated yield (Scheme 2, entry 9).

Encouraged by the results with aromatic alkynes, we examined the [2+2+2] cyclotrimerization reaction with aliphatic alkynes. A wide range of aliphatic alkynes were used for our cycloaddition. The results are summarized in Scheme 3.

Scheme 3. Reaction scope of non-aromatic alkynes

entry	alkyne	t (h)	**4:4′**[b]	yield (%)[c] of **4** + **4′**
1		24	60/40	51
2		2	73:27	40
3		8	55/45	54 [a]
4		10	100:00	45
5		3	60/40	88[a]

[a] Standard reaction conditions: **2b** (0.5 mmol) in PhMe (1 mL), a portion-wise addition of a mixture of alkyne **3** (5 mmol) and $RhCl(PPh_3)_3$ (10 mol%) in PhMe (2 mL) for 2 h, and under reflux (TLC). [b] The ratio was determined by ^1H NMR of the crude materials [c] Isolated product yield. [d] Separable through column chromatography.

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The reaction with benzylacetylene **3j** provided isoindolinones **4j/4j'** in 51% (**4j**:**4j'** = 60:40) yield (Scheme 3, entry 1). Similarly, diyne **2b** reacted with *tert*-butylacetylene **3k** to produce **4k/4k'** (**4k**:**4k'** = 73:27) in 40% yield (Scheme 3, entry 2). Activated aliphatic alkynes were also good substrates for the reaction; diyne **2b** reacted smoothly with methyl propiolate **3l** to provide **4l/4l'** (**4l**:**4l'** = 55:45) in 54% yield (Scheme 3, entry 3). The reaction with dimethyl acetylenedicarboxylate (DMAD) **3m** gave regioselectively isoindolinone **4m** in 45% yield (Scheme 3, entry 5). An isoindole moiety was also introduced at the side chain of the benzene ring. When diyne **2b** was reacted with *N*-propargyl phthalimide **3n**, isoindolinones **4n/4n'** were obtained in an excellent yield of 88% (**4n**:**4n'** = 60:40) (Scheme 3, entry 5).

Having established the conditions for the two distinct catalytic (Fe(III)-catalyzed alkynylation and Rh(I)-catalyzed cycloaddition) reactions, we tried combining both catalytic systems into a one-pot bimetallic tandem alkynylation/[2+2+2] cycloaddition sequences to save time, labor, and resources and to avoid yield losses associated with the purification of dialkynes **2**.

When the one-pot/sequential procedure was carried out in DCE (hydroxylactam **1a** (1 equiv.), propyne-TMS (1 equiv.), $Fe(OTf)_3$ 10 mol%, 4 h at reflux (TLC)) followed by a portion-wise addition of a solution of alkyne **3b** (10 equiv.) and 10 mol% of $RhCl(PPh_3)_3$ in DCE (2 mL) for 2 h, isoindolinones **4a/4a'** were isolated after 1 h of reflux (TLC) in a 20% yield. Although the desired products were isolated in moderate yield after purification, this result validates our initial design plan. The choice of solvent was found to be critical. Switching from DCE to a mixture of solvents DCE/PhMe (2:1) gave the desired isoindolinones in a 27% yield. Increasing the ratio of PhMe to 50% (DCE:PhMe (1:1)) delivered **4a/4a'** in a 36% isolated yield (entry 11).

The replacement of DCE (removed under vacuum) after completion of the alkynylation step by PhMe, in the same above conditions ($Fe(OTf)_3$ 10 mol%, DCE (2 mL), 4 h under reflux (TLC), solvent removed *in vacuo*, a portion-wise addition of alkyne **2b** solution (10 equiv.) and 10 mol% of $RhCl(PPh_3)_3$ in 2 mL of PhMe (for 2 h), under reflux 1 h) produced isoindolinones **4a/4a'** in a 60% yield (Scheme 4, entry 1).

Having established the optimal reaction conditions, we inspected the scope of the one-pot bimetallic sequence. As depicted in scheme 4, electron-neutral (**3a**, **3o**, **3p**), electron-rich (**3q**), and electron-withdrawing (**3d**) substituents on the phenyl ring of alkyne **3**, such as *p*-methoxy or *p*-nitro, were well accommodated in this relay catalysis, delivering the isoindolinones **4** in moderate to high yields (51–70% yields, Scheme 4, entries 1-5). The *ortho*-bromo and *ortho*-methoxy-substituted alkynes **3f** and **3g** were also favorable for this one-pot bimetallic transformation, generating the corresponding products **4f** and **4g** in 51 and 73% yields, respectively and in total regioselectivity (Scheme 4, entries 6 and 7). Similarly, the reaction of **2b**, with DMAD **3m** afforded regioselectively the cyclotrimerization product **4m** in a moderate yield of 35% (Scheme 4, entry 10).

Isoindolic substrates alkynes **3n** and **3t**, and their non-aromatic analog succinimide **3u** were suitable substrates in producing isoindolinones **4n/4n'**, **4t**/**4t'** and **4u**/**4u'** in good yields of 70%, 82%, and 72%, respectively (Scheme 4, entries 11-13). It is worth mentioning that all the regiochemical profiles obtained throughout this exemplification study are in good agreement with the preliminary experiments obtained during the cyclotrimerization reactions (Schemes 2 and 3), demonstrating the formation of mixtures of *ortho* and *meta* isoindolinones in varying ratios.

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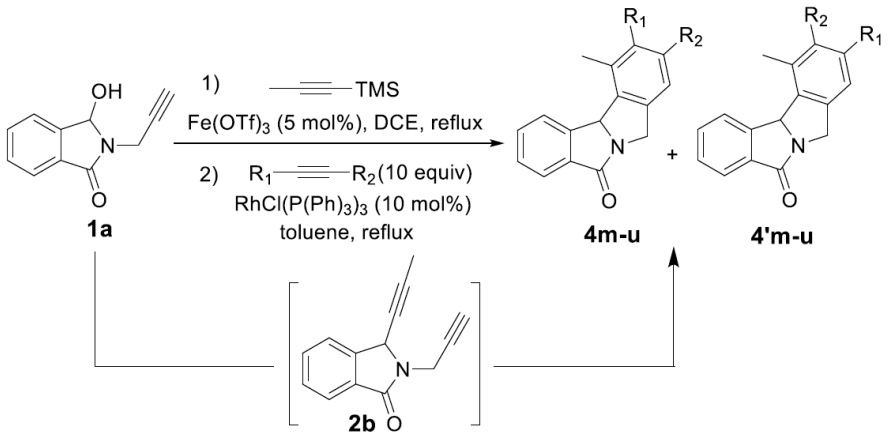
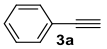
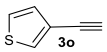
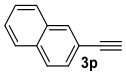
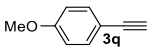
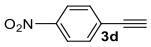
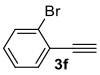
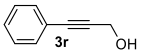
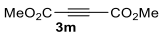
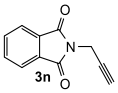
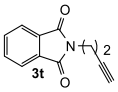
Scheme 4. The scope of one-pot [Fe]/[Rh]-catalyzed alkynylation/cyclotrimerization reaction. [a]



entry	alkyne	time (h)	**4:4′**[b]	yield (%)[c] of **4** + **4′**
1		1	60:40	60
2		4	58:42	59[a]
3		3	51:41	70
4		3	53:47	68[a]
5		4	61:39	51
6		3	100:00	51
7		2	100:00	73
8		1	70:30	69
9		2	63:37	55
10		8	100:00	35
11		2	60/40	70[a]
12		3	58/42	82[a]
13		7	67:33	72[a]

[a] Standard reaction conditions: Hydroxylactam **1a** (0.5 mmol), propyne-TMS (0.5 mmol), $Fe(OTf)_3$ (10 mmol%), DCE (2 mL), under reflux, 4 h, a portion-wise addition of a mixture of alkyne **3** (5 mmol) and $RhCl(PPh_3)_3$ (10 mol%) in PhMe (2 mL) for 2 h and was refluxed (TLC). [b] The ratio was determined by ^1H NMR of the crude materials [c] Isolated product yield. [d] Separable through column chromatography.

3. Mechanistic Study

The use of $Fe(OTf)_3$ and the 1-TMS-propyne in the alkynylation reactions may generate TMSOTf and TMSOH (Scheme 5), highlighting the possibility that the *in situ* generated TMSOTf and TMSOH may catalyze or co-catalyze the [2+2+2] reaction [157–159]. The following control experiments were performed. When 10 mol% of TMSOH was used as the catalyst under the described conditions for **2b**, no cyclotrimerization product was observed even after a prolonged reaction time (24 h). Only dialkyne **2b** was partially regenerated along with several side-products resulting from the hydration of alkyne functions, thus ruling out the possibility of TMSOH catalysis.

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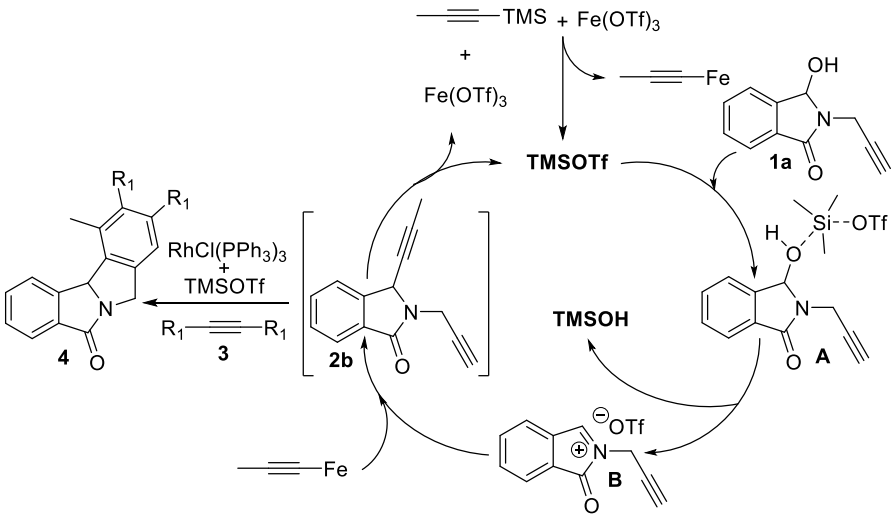
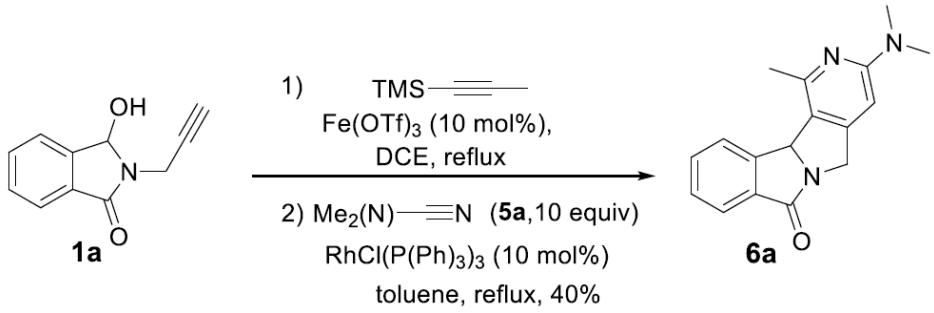
Scheme 5. Mechanistic study to reveal the identity of the catalytic species.



The reaction of **2b** with **3a** catalyzed by 10 mol% of TMSOTf afforded **4a/4a'** in trace amounts (< 10%). However, the addition of 10 mol% of $RhCl(PPh_3)_3$ to the reaction mixture led to the formation of **4a/4a'** in 67% yield. These results suggested that the cyclotrimerization reaction proceeded through rhodium-catalysis. These observations were confirmed by experiments performed with TMSOTf + $RhCl(PPh_3)_3$. The treatment of **2b** with **3d** or **3g** under a mixture of 10 mol% of (TMSOTf + $RhCl(PPh_3)_3$) provided isoindolinones **4d/4d'** and **4g** in 55% and 81% isolated yields, respectively, and in shorter reaction times (4 h for **4d/4d'** and 2 h for **4g**). Considering the cyclotrimerization reactions, the yields were not diminished (55% *vs* 58% (Scheme 2, entry 4) for **4d/4d'** and 81% *vs* 83% (Scheme 2, entry 7) for **4g**), combined with the fact that the higher rates were observed (4 h *vs* 6 h for **4d/4d'** and 2 h versus 3 h for **4g**), we believe that the reaction proceeded through rhodium-catalysis, although $RhCl(PPh_3)_3$/TMSOTf co-catalysis should not be excluded.

Encouraged by the efficiency and robustness of the current protocol in the construction of novel isoindolinone products and inspired by the fact that pyridines are privileged structures widely available in natural products, pharmaceuticals, and agrochemicals [160–164], we also evaluated the one-pot alkynylation/cyclotrimerization reaction in the construction of novel pyridines-fused isoindolinones [165–184]. A nitrile derivative **5a** was subjected to our protocol under the standard reaction conditions (Scheme 6). The pyridine derivative **6a** was obtained as a single regiosomer and isolated in an acceptable yield of 40%.

Scheme 6. Cyclotrimerization of nitriles, preparation of pyridines 6.[a,b]



4. Conclusions

We took advantage of the different reactivities of iron and rhodium, and their compatibility to develop an efficient sequential one-pot bimetallic iron-rhodium alkynylation/cyclotrimerization sequential reactions to synthesize novel fused benzene and pyridine isoindolinone derivatives from trivial starting materials. The σ-Lewis acid properties of iron (III) were implemented to promote the

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alkynylation step, and then, in a one-pot procedure, rhodium (I) was used to ensure the [2+2+2] cycloaddition reaction. This method can be applied for the synthesis of chemical scaffolds with potential applications in the chemical and pharmaceutical industries.

5. Experimental Section

General Information. Unless otherwise specified, the starting reagents and deuterated solvent were purchased from commercial sources and used without further purification (Sigma-Aldrich, Fisher scientific, TCI). All solvents were dried and freshly distilled before use, taking precautions to exclude moisture by refluxing over CaH_2. All reactions were performed under an argon-inert atmosphere. Thin layer chromatography (TLC) was performed on precoated sheets of silica gel 60 with fluorescent indicator UV254 (Merck). Detection was accomplished by exposure to a UV lamp and by heating after exposure to an ethanolic solution of *p*-anisaldehyde. Chromatographic separations were achieved on silica gel columns (Kieselgel 60, 40−63 μm, Merck) using a cyclohexane/ethyl acetate eluent system. Flash chromatography purifications were performed on Interchim Puriflash (Puriflash columns 50 μ) using a cyclohexane/ethyl acetate eluent system. In all cases, distilled solvents were used as eluents for column chromatography. NMR spectra were recorded on a Bruker AvanceTM 300 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz and data are reported as chemical shift (δ) in ppm, multiplicity (s = singlet, d = doublet, t = triplet, b = broad, m = multiplet), coupling constants *J* in Hz and integration. ^{13}C NMR spectra were recorded at 75 MHz using broadband proton decoupling and the data were reported as chemical shift (δ) in ppm. High-resolution mass spectra (HRMS) were measured on Agilent 6530 Q-Tof MS system. The Q-TOF MS instrument was operated under the following conditions: Ion source ESI$^+$ Agilent Jet Stream or APCI in positive ionization mode. FTIR spectra were recorded with a PerkinElmer Frontier.

Representative Procedure for the Rhodium(I)-Catalyzed Cyclotrimerization of Dialkynes: To a solution of alkynes **3a-w** (2.3 mmol, 10 eq) and $RhCl(PPh_3)_3$ (0.023 mmol, 0.1 eq) in toluene (4 mL) we slowly add the substrate **2b** (0.23 mmol, 1 equiv.), for 2 h, under argon. The reaction mixture was heated under reflux and monitored by TLC. After the total conversion of the starting material, the solvent was removed under reduced pressure. The crude product was then purified by flash chromatography on a silica gel column using a mixture of cyclohexane/AcOEt as the eluent or DCM/AcOEt to give the desired compounds **4**.

Synthesis and characterization of compounds 4a/4a'.

These products were obtained as a mixture of separable two regioisomers in 76% global yield, with a ratio of **4a:4a'**: 60:40.

11-Methyl-9-phenyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4a).

Major regioisomer-4a: This product was isolated as a white solid, R_f (cyclohexane/AcOEt: 9/1) = 0.24; m.p. = 174-176 °C; **IR (ν_{max} cm^{-1})**: 1687; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.99-7.89 (m, 1H, H_{aro}), 7.89 (d, *J* = 7.5 Hz, 1H, H_{aro}), 7.63 (td, *J* = 7.6, 1.3 Hz, 1H, H_{aro}), 7.56-7.49 (m, 3H, H_{aro}), 7.46-7.34 (m, 3H, H_{aro}), 7.33 (s, 1H, H_{aro}), 7.30 (s, 1H, H_{aro}), 6.14 (s, 1H, CH), 5.29 (d, *J* = 15.0 Hz, 1H, CH_2), 4.52 (d, *J* = 15.0 Hz, 1H, CH_2), 2.73 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.1 (C=O), 145.2 (C^q_{aro}), 142.7 (C^q_{aro}), 142.1 (C^q_{aro}), 140.6 (C^q_{aro}), 135.9 (C^q_{aro}), 133.8 (C^q_{aro}), 133.7 (C^q_{aro}), 132.2 (CH_{aro}), 129.0 (2 x CH_{aro}), 128.8 (CH_{aro}), 128.8 (CH_{aro}), 127.7 (CH_{aro}), 127.3 (2 x CH_{aro}), 125.2 (CH_{aro}), 124.8 (CH_{aro}), 119.7 (CH_{aro}), 69.5 (CH), 49.5 (CH_2), 21.8 (CH_3) ppm. HRMS (+ESI) calculated for $C_{22}H_{17}NO$ $[M+H]^+$: 312.1383, found 312.1404.

11-Methyl-10-phenyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4a').

Minor regioisomer-4a': This product was isolated as a white solid, R_f (cyclohexane/AcOEt: 9/1) = 0.23; m.p. = 173-175 °C; **IR (ν_{max} cm^{-1})**: 1687; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.97-7.93 (m, 1H, H_{aro}), 7.90 (d, *J* = 7.3 Hz, 1H, H_{aro}), 7.61 (td, *J* = 7.5, 1.3 Hz, 1H, H_{aro}), 7.51 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.42-7.35 (m, 3H, H_{aro}), 7.28 (d, *J* = 1.8 Hz, 2H, H_{aro}), 7.19 (d, *J* = 4.3 Hz, 2H, H_{aro}), 6.17 (s, 1H), 5.29 (d, *J* = 15.0 Hz, 1H, CH_2), 4.51 (d, *J* = 14.9 Hz, 1H, CH_2), 2.57 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.1 (C=O), 145.5 (C^q_{aro}), 142.3 (C^q_{aro}), 141.3 (C^q_{aro}), 140.9 (C^q_{aro}), 138.0 (C^q_{aro}), 133.8 (C^q_{aro}), 132.2 (CH_{aro}), 131.3 (C^q_{aro}), 130.5 (CH_{aro}), 129.5 (2 x CH_{aro}), 128.8 (CH_{aro}), 128.3 (2 x CH_{aro}), 127.2 (CH_{aro}), 125.4 (CH_{aro}), 124.7

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(CH_{aro}), 120.8 (CH_{aro}), 70.0 (CH), 49.5 (CH_2), 20.2 (CH_3) ppm. HRMS (+ESI) calculated for $C_{22}H_{17}NO$ $[M+H]^+$: 312.1383, found 312.1404.

Synthesis and characterization of compounds 4b/4b'.

This product was obtained as a mixture of inseparable two regioisomers and was isolated as a yellow oil in 69% global yield, with a ratio of **4b/4b'**: 54/46, R_f (cyclohexane/AcOEt: 7/3) = 0.22; **IR (ν_{max} cm^{-1})**: 1705.

11-Methyl-9-(m-tolyl)-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4b).

Major regioisomer-4b: The NMR characteristics of this product were extracted from the spectrum of the mixture; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.93 (d, *J* = 5.5 Hz, 1H, H_{aro}), 7.88 (d, *J* = 3.8 Hz, 1H, H_{aro}), 7.54-7.47 (m, 2H, H_{aro}), 7.37-7.27 (m, 6H, H_{aro}), 6.16 (s, 1H, CH), 5.29 (d, *J* = 14.9 Hz, 1H, CH_2), 4.51 (d, *J* = 14.9 Hz, 1H, CH_2), 2.58 (s, 3H, CH_3), 2.40 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.0 (C=O), 145.4 (C^q_{aro}), 142.3 (C^q_{aro}), 141.1 (C^q_{aro}), 140.4 (C^q_{aro}), 137.8 (C^q_{aro}), 135.6 (C^q_{aro}), 133.5 (C^q_{aro}), 132.0 (CH_{aro}), 131.2 (C^q_{aro}), 130.3 (CH_{aro}), 128.7 (CH_{aro}), 128.6 (CH_{aro}), 128.1 (CH_{aro}), 127.8 (CH_{aro}), 126.5 (CH_{aro}), 125.1 (CH_{aro}), 124.3 (CH_{aro}), 120.6 (CH_{aro}), 69.9 (CH), 49.3 (CH_2), 21.6 (CH_3), 21.5 (CH_3) ppm. HRMS (+ESI) calculated for $C_{23}H_{19}NO$ $[M+H]^+$: 326.1539, found 326.1560.

11-Methyl-10-(m-tolyl)-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4b').

Minor regioisomer-4b': The NMR characteristics of this product were extracted from the spectrum of the mixture; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.96 (d, *J* = 5.3 Hz, 1H, H_{aro}), 7.91 (d, *J* = 3.7 Hz, 1H, H_{aro}), 7.66-7.58 (m, 2H, H_{aro}), 7.22-7.14 (m, 4H, H_{aro}), 7.10-7.05 (m, 2H, H_{aro}), 6.13 (s, 1H, CH), 5.29 (d, *J* = 14.9 Hz, 1H, CH_2), 4.51 (d, *J* = 14.9 Hz, 1H, CH_2), 2.72 (s, 3H, CH_3), 2.42 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 74.0 (C=O), 145.1 (C^q_{aro}), 142.5 (C^q_{aro}), 142.1 (C^q_{aro}), 140.6 (C^q_{aro}), 138.4 (C^q_{aro}), 137.8 (C^q_{aro}), 133.6 (C^q_{aro}), 133.6 (C^q_{aro}), 132.0 (CH_{aro}), 130.1 (CH_{aro}), 128.7 (2 x CH_{aro}), 128.3 (CH_{aro}), 127.9 (CH_{aro}), 125.3 (CH_{aro}), 124.6 (CH_{aro}), 124.6 (CH_{aro}), 119.6 (CH_{aro}) 69.4 (CH), 49.3 (CH_2), 21.7 (CH_3), 20.1 (CH_3) ppm. HRMS (+ESI) calculated for $C_{23}H_{19}NO$ $[M+H]^+$: 326.1539, found 326.1560.

Synthesis and characterization of compounds 4c/4c'.

These products were obtained as a mixture of inseparable two regioisomers and were isolated as a yellow oil in 68% global yield, with a ratio of **4c/4c'**: 60/40, R_f (cyclohexane/AcOEt: 8/2) = 0.23; **IR (ν_{max} cm^{-1})**: 1697.

11-Methyl-9-(p-tolyl)-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4c).

Major regioisomer-4c: The NMR characteristics of this product were extracted from the spectrum of the mixture; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.98-7.86 (m, 2H, H_{aro}), 7.62 (t, *J* = 7.5 Hz, 1H, H_{aro}), 7.53-7.42 (m, 2H, H_{aro}), 7.32 (s, 1H, H_{aro}), 7.29 (s, 1H, H_{aro}), 7.26-7.13 (m, 3H, H_{aro}), 6.13 (s, 1H, CH), 5.28 (d, *J* = 14.9 Hz, 1H, CH_2), 4.51 (d, *J* = 15.0 Hz, 1H, CH_2), 2.72 (s, 3H, CH_3), 2.39 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.1(C=O), 145.2 (C^q_{aro}), 142.6 (C^q_{aro}), 142.0 (C^q_{aro}), 137.7 (C^q_{aro}), 137.5 (C^q_{aro}), 135.6 (C^q_{aro}), 133.7 (C^q_{aro}), 133.7 (C^q_{aro}), 132.1 (CH_{aro}), 129.7 (2 x CH_{aro}), 128.8 (CH_{aro}), 128.5 (CH_{aro}), 127.1 (2 x CH_{aro}), 125.2 (CH_{aro}), 124.7 (CH_{aro}), 119.5 (CH_{aro}), 69.5 (CH), 49.5 (CH_2), 21.8 (CH_3), 21.2 (CH_3) ppm. HRMS (+ESI) calculated for $C_{23}H_{19}NO$ $[M+H]^+$: 326.1539, found 326.1565.

11-Methyl-10-(*p*-tolyl)-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4c').

Minor regioisomer-4c'e: The NMR characteristics of this product were extracted from the spectrum of the mixture; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.95 (d, *J* = 7.7 Hz, 1H, H_{aro}), 7.90 (d, *J* = 7.5 Hz, 1H, H_{aro}), 7.61 (t, *J* = 7.5 Hz, 1H, H_{aro}), 7.50 (t, *J* = 7.5 Hz, 1H, H_{aro}), 7.25-7.14 (m, 6H, H_{aro}), 6.16 (s, 1H, CH), 5.28 (d, *J* = 14.5 Hz, 1H, CH_2), 4.51 (d, *J* = 15.0 Hz, 1H, CH_2), 2.58 (s, 3H, CH_3), 2.41 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.1 (C=O), 145.6 (C^q_{aro}), 142.2 (C^q_{aro}), 140.7 (C^q_{aro}), 138.3 (C^q_{aro}), 138.0 (C^q_{aro}), 136.9 (C^q_{aro}), 133.8 (C^q_{aro}), 132.2 (CH_{aro}), 131.3 (C^q_{aro}), 130.5 (CH_{aro}), 129.4 (2 x CH_{aro}), 129.0 (2 x CH_{aro}), 128.8 (CH_{aro}), 125.4 (CH_{aro}), 124.7 (CH_{aro}), 120.7 (CH_{aro}), 70.0 (CH), 49.5 (CH_2), 21.3 (CH_3), 20.2 (CH_3) ppm. HRMS (+ESI) calculated for $C_{23}H_{19}NO$ $[M+H]^+$: 326.1539, found 326.1565.

Synthesis and characterization of compounds 4d/4d'.

These products were obtained as a mixture of inseparable two regioisomers and were isolated as a yellow oil in 58% global yield, with a ratio of **4d/4d'**: 61/39, R_f (cyclohexane/AcOEt: 7/3) = 0.34; **IR (ν_{max} cm^{-1})**: 1690, 1511, 1339.

11-Methyl-9-(4-nitrophenyl)-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4d).

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Major regioisomer-4d: The NMR characteristics of this product were extracted from the spectrum of the mixture; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.30-8.24 (m, 2H, H_{aro}), 7.96-7.86 (m, 2H, H_{aro}), 7.71-7.60 (m, 2H, H_{aro}), 7.54-7.43 (m, 2H, H_{aro}), 7.36 (s, 1H, H_{aro}), 7.33 (s, 1H, H_{aro}), 6.17 (s, 1H, CH), 5.30 (d, *J* = 15.2, 2.6 Hz, 1H, CH_2), 4.51 (d, *J* = 15.3, 2.1 Hz, 1H, CH_2), 2.57 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.1 (C=O), 148.2 (C^q_{aro}), 147.1 (C^q_{aro}), 145.1 (C^q_{aro}), 142.2 (C^q_{aro}), 139.9 (C^q_{aro}), 138.5 (C^q_{aro}), 133.6 (C^q_{aro}), 132.3 (CH_{aro}), 131.1 (C^q_{aro}), 130.4 (CH_{aro}), 130.1 (CH_{aro}), 128.9 (CH_{aro}), 128.0 (CH_{aro}), 125.3 (CH_{aro}), 124.8 (CH_{aro}), 124.2 (CH_{aro}), 123.6 (CH_{aro}), 121.2 (CH_{aro}), 69.8 (CH), 49.4 (CH_2), 20.1 (CH_3) ppm. HRMS (+ESI) calculated for $C_{22}H_{16}N_2O_3$ $[M+H]^+$: 357.1234, found 357.1254.

11-Methyl-10-(4-nitrophenyl)-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4d').

Minor regioisomer-4d': The NMR characteristics of this product were extracted from the spectrum of the mixture; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.30-8.24 (m, 2H, CH_{aro}), 7.96-7.86 (m, 2H, CH_{aro}), 7.71-7.60 (m, 2H, CH_{aro}), 7.54-7.43 (m, 2H, CH_{aro}), 7.24-7.16 (m, 2H, CH_{aro}), 6.14 (s, 1H, CH), 5.30 (d, *J* = 15.2, 2.6 Hz, 1H, CH_2), 4.51 (d, *J* = 15.3, 2.1 Hz, 1H, CH_2), 2.75 (s, 1H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.0 (C=O), 147.3 (C^q_{aro}), 147.0 (C^q_{aro}), 144.8 (C^q_{aro}), 143.2 (C^q_{aro}), 139.5 (C^q_{aro}), 137.7 (C^q_{aro}), 134.4 (C^q_{aro}), 133.5 (C^q_{aro}), 132.3 (CH_{aro}), 130.4 (2 x CH_{aro}), 128.9 (2 x CH_{aro}), 125.2 (CH_{aro}), 124.8 (CH_{aro}), 123.6 (2 x CH_{aro}), 119.9 (CH_{aro}), 69.4 (CH), 49.3 (CH_2), 21.8 (CH_3) ppm. HRMS (+ESI) calculated for $C_{22}H_{16}N_2O_3$ $[M+H]^+$: 357.1234, found 357.1254.

Synthesis and characterization of compounds 4e/4e'.

This product was obtained as a mixture of inseparable two regioisomers and was isolated as a yellow oil, in 75% global yield, with a ratio of **4e/4e'**: 58/42, R_f (cyclohexane/AcOEt: 7/3) = 0.26; **IR (ν_{max} cm^{-1})**: 1688.

9-(4-Bromophenyl)-11-methyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-a]isoindol-5-one (4e):

Major regioisomer-4e: The NMR characteristics of this product were extracted from the spectrum of the mixture; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.04 (d, *J* = 7.9 Hz, 1H, H_{aro}), 8.00 (d, *J* = 7.7 Hz, 1H, H_{aro}), 7.71 (t, *J* = 7.6 and1.4 Hz, 1H, H_{aro}), 7.66-7.58 (m, 3H, H_{aro}), 7.36 (s, 2H, H_{aro}), 7.23 (d, *J* = 1.9 Hz, 2H, H_{aro}), 6.26 (s, 1H, CH), 5.38 (d, *J* = 15.1 Hz, 1H, CH_2), 4.60 (d, *J* = 15.1 and 1.6 Hz, 1H, CH_2), 2.65 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.1 (C=O), 145.4 (C^q_{aro}), 141.3 (2 x C^q_{aro}), 141.0 (C^q_{aro}), 140.2 (C^q_{aro}), 138.2 (C^q_{aro}), 133.7 (C^q_{aro}), 132.2 (CH_{aro}), 131.5 (2 x CH_{aro}), 131.2 (2 x CH_{aro}), 130.3 (CH_{aro}), 128.9 (CH_{aro}), 125.3 (CH_{aro}), 124.8 (CH_{aro}), 121.5 (C^q_{aro}), 120.9 (CH_{aro}), 69.9 (CH), 49.4 (CH_2), 20.1 (CH_3) ppm. HRMS (+ESI) calculated for $C_{22}H_{16}BrNO$ $[M+H]^+$: 390.0488, found 390.0508.

10-(4-Methoxyphenyl)-11-methyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4e').

Minor regioisomer-4e': The NMR characteristics of this product were extracted from the spectrum of the mixture; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 8.06-7.96 (m, 2H, H_{aro}), 7.75-7.68 (m, 1H, H_{aro}), 7.67 - 7.57 (m, 2H, H_{aro}), 7.50 (d, *J* = 8.5 Hz, 2H, H_{aro}), 7.40-7.32 (m, 3H, H_{aro}), 6.22 (s, 1H, CH), 5.38 (d, *J* = 15.1 Hz, 1H, CH_2), 4.60 (d, *J* = 15.1 Hz, 1H, CH_2), 2.82 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.1 (C=O), 145.1 (C^q_{aro}), 142.9 (C^q_{aro}), 140.8 (C^q_{aro}), 139.5 (C^q_{aro}), 136.3 (C^q_{aro}), 134.1 (C^q_{aro}), 133.6 (C^q_{aro}), 132.2 (CH_{aro}), 132.1 (2 x CH_{aro}), 128.9 (2 x CH_{aro}), 128.5 (CH_{aro}), 125.2 (CH_{aro}), 124.8 (CH_{aro}), 122.0 (C^q_{aro}), 120.9 (CH_{aro}), 119.5 (CH_{aro}), 69.5 (CH), 49.4 (CH_2), 21.8 (CH_3) ppm. HRMS (+ESI) calculated for $C_{22}H_{16}BrNO$ $[M+H]^+$: 390.0488, found 390.0508.

Synthesis and characterization of compound 4f.

10-(2-Bromophenyl)-11-methyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4f).

This product was obtained as a single regioisomer in 59% yield.

This compound was isolated as a yellow oil, R_f (cyclohexane/AcOEt: 7/3) = 0.24; **IR (ν_{max} cm^{-1})**: 1696; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.95 (d, *J* = 7.7 Hz, 1H, H_{aro}), 7.90 (d, *J* = 8.4 Hz, 1H, H_{aro}), 7.68-7.60 (m, 2H, H_{aro}), 7.51 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.34 (td, *J* = 7.5, 1.3 Hz, 1H, H_{aro}), 7.23 (dd, *J* = 3.8, 1.9 Hz, 1H, H_{aro}), 7.21-7.15 (m, 2H, H_{aro}), 7.12 (s, 1H, H_{aro}), 6.15 (s, 1H, CH), 5.28 (d, *J* = 15.0 Hz, 1H, CH_2), 4.52 (d, *J* = 15.0 Hz, 1H, CH_2), 2.72 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.1 (C=O), 145.1 (C^q_{aro}), 141.9 (C^q_{aro}), 141.9 (C^q_{aro}), 141.7 (C^q_{aro}), 136.2 (C^q_{aro}), 133.7 (C^q_{aro}), 133.3 (CH_{aro}), 133.2 (C^q_{aro}), 132.2 (CH_{aro}), 131.3 (CH_{aro}), 130.8 (CH_{aro}), 129.1 (CH_{aro}), 128.8 (CH_{aro}), 127.6 (CH_{aro}), 125.2 (CH_{aro}), 124.8 (CH_{aro}), 122.6 (C^q_{aro}), 122.0 (CH_{aro}), 69.6 (CH), 49.4 (CH_2), 21.8 (CH_3) ppm. HRMS (+ESI) calculated for $C_{22}H_{16}BrNO$ $[M+H]^+$: 390.0488, found 390.0482.

Synthesis and characterization of compound 4g.

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10-(2-Methoxyphenyl)-11-methyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4g).

This product was obtained as a single regioisomer in 83% yield.

This compound was isolated as a yellow oil, R_f (cyclohexane/AcOEt: 7/3) = 0.23; **IR (ν_{max} cm^{-1})**: 1696; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.93 (d, *J* = 7.8 Hz, 1H, H_{aro}), 7.88 (d, *J* = 7.5 Hz, 1H, H_{aro}), 7.62 (t, *J* = 7.5 Hz, 1H, H_{aro}), 7.49 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.38-7.28 (m, 2H, H_{aro}), 7.24-7.15 (m, 2H, H_{aro}), 7.08-6.91 (m, 2H, H_{aro}), 6.13 (s, 1H, CH), 5.27 (d, *J* = 14.9 Hz, 1H, CH_2), 4.51 (d, *J* = 14.8 Hz, 1H, CH_2), 3.80 (s, 3H, O-CH_3), 2.70 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.1 (C=O), 156.5 (C^q_{aro}), 145.3 (C^q_{aro}), 141.8 (C^q_{aro}), 139.2 (C^q_{aro}), 135.5 (C^q_{aro}), 133.7 (C^q_{aro}), 133.1 (C^q_{aro}), 132.1 (CH_{aro}), 130.9 (CH_{aro}), 130.9 (CH_{aro}), 130.0 (C^q_{aro}), 129.0 (CH_{aro}), 128.7 (CH_{aro}), 125.2 (CH_{aro}), 124.7 (CH_{aro}), 122.2 (CH_{aro}), 121.0 (CH_{aro}), 111.2 (CH_{aro}), 69.6 (CH), 55.7 (O-CH_3), 49.5 (CH_2), 21.8 (CH_3) ppm. HRMS (+ESI) calculated for $C_{23}H_{19}NO_2$ $[M+H]^+$: 342.1489, found 342.1513.

Synthesis and characterization of compounds 4h/4h'.

This product was obtained as a mixture of separable two regioisomers in 71% global yield, with a ratio of **4h**/**4h'**: 57/43.

11-Methyl-9-(thiophen-2-yl)-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4h).

Major regioisomer-4h: This compound was isolated as a yellow oil, R_f (cyclohexane/AcOEt: 8/2) = 0.25; **IR (ν_{max} cm^{-1})**: 1687; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.91 (d, *J* = 8.9 Hz, 1H, H_{aro}), 7.88 (d, *J* = 7.2 Hz, 1H, H_{aro}), 7.62 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.49 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.35 (s, 1H, H_{aro}), 7.32 (s, 1H, H_{aro}), 7.29-7.27 (m, 2H, H_{aro}), 7.08-7.06 (m, 1H, H_{aro}), 6.10 (s, 1H, CH), 5.26 (d, *J* = 15.0 Hz, 1H, CH_2), 4.48 (d, *J* = 14.9 Hz, 1H, CH_2), 2.69 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.0 (C=O), 145.1 (C^q_{aro}), 143.6 (C^q_{aro}), 142.8 (C^q_{aro}), 136.1 (C^q_{aro}), 135.0 (C^q_{aro}), 134.0 (C^q_{aro}), 133.6 (C^q_{aro}), 132.2 (CH_{aro}), 128.8 (CH_{aro}), 128.2 (CH_{aro}), 127.5 (CH_{aro}), 125.3 (CH_{aro}), 125.2 (CH_{aro}), 124.8 (CH_{aro}), 123.6 (CH_{aro}), 118.4 (CH_{aro}), 69.5 (CH), 49.4 (CH_2), 21.7 (CH_3) ppm. HRMS (+ESI) calculated for $C_{20}H_{15}NOS$ $[M+H]^+$: 318.0947, found 318.0977.

11-Methyl-10-(thiophen-2-yl)-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4h').

Minor regioisomer-4h': This compound was isolated as a yellow oil, R_f (cyclohexane/AcOEt: 8/2) = 0.21; **IR (ν_{max} cm^{-1})**: 1687; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.96 (d, *J* = 8.7 Hz, 1H, H_{aro}), 7.90 (d, *J* = 7.2 Hz, 1H, H_{aro}), 7.62 (td, *J* = 7.5, 1.3 Hz, 1H, H_{aro}), 7.51 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.37-7.31 (m, 2H, H_{aro}), 7.14 (d, *J* = 7.8 Hz, 1H, H_{aro}), 7.09 (dd, *J* = 5.1, 3.5 Hz, 1H, H_{aro}), 6.99 (dd, *J* = 3.5, 1.2 Hz, 1H, H_{aro}), 6.16 (s, 1H, CH), 5.27 (d, *J* = 15.2 Hz, 1H, CH_2), 4.50 (d, *J* = 15.1 Hz, 1H, CH_2), 2.71 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.2 (C=O), 145.5 (C^q_{aro}), 142.3 (C^q_{aro}), 141.5 (C^q_{aro}), 138.4 (C^q_{aro}), 134.5 (C^q_{aro}), 133.7 (C^q_{aro}), 132.3 (C^q_{aro}), 132.3 (CH_{aro}), 131.3 (CH_{aro}), 128.9 (CH_{aro}), 127.3 (CH_{aro}), 127.1 (CH_{aro}), 125.7 (CH_{aro}), 125.3 (CH_{aro}), 124.7 (CH_{aro}), 120.8 (CH_{aro}), 69.9 (CH), 49.5 (CH_2), 20.4 (CH_3) ppm. HRMS (+ESI) calculated for $C_{20}H_{15}NOS$ $[M+H]^+$: 318.0947, found 318.0977.

Synthesis and characterization of compounds 4i/4i'.

This product was obtained as a mixture of separable two regioisomers in 43% global yield, with a ratio of **4i**/**4i'**: 63/37.

10-Acetyl-11-methyl-9-phenyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4i).

Major regioisomer-4i: This product was isolated as a white solid, R_f (cyclohexane/AcOEt: 7/3) = 0.19; m.p. = 198-200 °C; **IR (ν_{max} cm^{-1})**: 1691; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.97-7.86 (m, 2H, H_{aro}), 7.68-7.56 (m, 1H, H_{aro}), 7.52 (t, *J* = 7.5 Hz, 1H, H_{aro}), 7.48-7.36 (m, 3H, H_{aro}), 7.31 (s, 1H, H_{aro}), 7.25-7.18 (m, 1H, H_{aro}), 7.17-7.08 (m, 1H, H_{aro}), 6.17 (s, 1H, CH), 5.31 (d, *J* = 15.2 Hz, 1H, CH_2), 4.51 (d, *J* = 15.1 Hz, 1H, CH_2), 2.48 (s, 3H, CH_3), 1.79 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 204.5 (C=O), 174.1 (C=O), 145.1 (C^q_{aro}), 142.7 (C^q_{aro}), 141.0 (C^q_{aro}), 140.3 (C^q_{aro}), 139.6 (C^q_{aro}), 138.9 (C^q_{aro}), 133.6 (C^q_{aro}), 132.5 (C^q_{aro}), 132.4 (CH_{aro}), 130.1 (CH_{aro}), 129.9 (CH_{aro}), 129.0 (CH_{aro}), 129.0 (CH_{aro}), 128.5 (CH_{aro}), 128.2 (CH_{aro}), 125.2 (CH_{aro}), 124.9 (CH_{aro}), 119.9 (CH_{aro}), 69.8 (CH), 49.4 (CH_2), 30.4 (CH_3), 20.1 (CH_3) ppm. HRMS (+ESI) calculated for $C_{24}H_{19}NO_2$ $[M+H]^+$: 354.1489, found 354.1515.

9-Acetyl-11-methyl-10-phenyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4i').

Minor regioisomer-4i': This product was isolated as a white solid, R_f (cyclohexane/AcOEt: 7/3) = 0.23; m.p. = 197-199 °C; **IR (ν_{max} cm^{-1})**: 1691; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.94 (d, *J* = 7.9 Hz, 1H, H_{aro}), 7.89 (d, *J* = 7.7 Hz, 1H, H_{aro}), 7.63 (t, 1H, H_{aro}), 7.52 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.43-7.34 (m, 3H, H_{aro}), 7.30 (m, *J* = 2.8 Hz, 2H, , H_{aro}), 7.15 (s, 1H, H_{aro}), 6.17 (s, 1H, CH), 5.30 (d, *J* = 15.3 Hz, 1H, CH_2),

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4.51 (d, *J* = 15.2 Hz, 1H, CH_2), 2.63 (s, 3H, CH_3), 1.92 (s, 3H, CH_3) ppm.**^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 207.5 (C=O), 174.2 (C=O), 145.1 (C^q_{aro}), 142.5 (C^q_{aro}), 141.7 (C^q_{aro}), 139.8 (C^q_{aro}), 139.5 (C^q_{aro}), 137.2 (C^q_{aro}), 133.5 (C^q_{aro}), 132.4 (CH_{aro}), 129.6 (C^q_{aro}), 129.0 (CH_{aro}), 129.0 (2 x CH_{aro}), 128.9 (2 x CH_{aro}), 128.2 (CH_{aro}), 125.3 (CH_{aro}), 124.8 (CH_{aro}), 122.5 (CH_{aro}), 69.6 (CH), 49.5 (CH_2), 32.5 (CH_3), 19.0 (CH_3) ppm. HRMS (+ESI) calculated for $C_{24}H_{19}NO_2$ $[M+H]^+$: 354.1489, found 354.1515.

Synthesis and characterization of compounds 4j/4j'.

These products were obtained as a mixture of inseparable two regioisomers and were isolated as a yellow oil in 51% global yield, with a ratio of **4j/4j'**: 60/40, R_f (cyclohexane/AcOEt: 8/2) = 0.22; **IR (ν_{max} cm^{-1})**: 1691.

9-Benzyl-11-methyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4j).

Major regioisomer-4j: The NMR characteristics of this product were extracted from the spectrum of the mixture; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.94-7.84 (m, 2H, H_{aro}), 7.64-7.54 (m, 1H, H_{aro}), 7.47 (t, *J* = 7.5 Hz, 1H, H_{aro}), 7.32-7.26 (m, 2H, H_{aro}), 7.23-7.15 (m, 3H, H_{aro}), 6.95 (s, 1H, H_{aro}), 6.92 (s, 1H, H_{aro}), 6.05 (s, 1H, CH), 5.32-5.12 (m, 1H, CH_2), 4.44 (t, *J* = 14.8 Hz, 1H, CH_2), 3.93 (s, 2H, CH_2), 2.62 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.0 (C=O), 145.3 (C^q_{aro}), 142.3 (C^q_{aro}), 140.8 (C^q_{aro}), 138.7 (C^q_{aro}), 134.6 (C^q_{aro}), 133.6 (C^q_{aro}), 133.4 (C^q_{aro}), 132.0 (CH_{aro}), 130.3 (CH_{aro}), 128.9 (3 x CH_{aro}), 128.6 (CH_{aro}), 128.6 (CH_{aro}), 126.3 (CH_{aro}), 125.1 (CH_{aro}), 124.6 (CH_{aro}), 121.4 (CH_{aro}), 69.4 (CH), 49.3 (CH_2), 41.6 (CH_2), 21.6 (CH_3) ppm. HRMS (+ESI) calculated for $C_{23}H_{19}NO$ $[M+H]^+$: 326.1539, found 326.1562.

Synthesis and characterization of compounds 4k/4k'.

These products were obtained as a mixture of inseparable two regioisomers and were isolated as a yellow oil in 40% global yield, with a ratio of **4k /4k'**: 73/27, R_f (cyclohexane/AcOEt: 7/3) = 0.42; **IR (ν_{max} cm^{-1})**: 1688.

9-(*tert*-Butyl)-11-methyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (**4k**).

Major regioisomer-4k: The NMR characteristics of this product were extracted from the spectrum of the mixture; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.93-7.83 (m, 2H, CH_{aro}), 7.60 (t, *J* = 7.5 Hz, 1H, CH_{aro}), 7.51-7.43 (m, 1H, CH_{aro}), 7.14 (s, 1H, CH_{aro}), 7.10 (s, 1H, CH_{aro}), 6.06 (s, 1H, CH), 5.22 (d, *J* = 14.9 Hz, 1H, CH_2), 4.44 (dd, *J* = 14.8, 7.8 Hz, 1H, CH_2), 2.66 (s, 3H, CH_3), 1.30 (s, 9H, 3 x CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.1 (C=O), 152.2 (C^q_{aro}), 145.4 (C^q_{aro}), 142.0 (C^q_{aro}), 134.0 (C^q_{aro}), 133.7 (C^q_{aro}), 132.9 (C^q_{aro}), 132.0 (CH_{aro}), 128.6 (CH_{aro}), 126.8 (CH_{aro}), 125.1 (CH_{aro}), 124.6 (CH_{aro}), 117.9 (CH_{aro}), 69.5 (CH), 49.6 (CH_2), 34.7 (C^q), 31.5 (3 x CH_3), 21.9 (CH_3) ppm. HRMS (+ESI) calculated for $C_{20}H_{21}NO$ $[M+H]^+$: 292.1696, found 292.1714.

10-(*tert*-Butyl)-11-methyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4k').

Minor regioisomer-4k': The NMR characteristics of this product were extracted from the spectrum of the mixture; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.98 (d, *J* = 7.9 Hz, 1H, H_{aro}), 7.93-7.83 (m, 1H, H_{aro}), 7.60 (t, *J* = 7.5 Hz, 1H, H_{aro}), 7.51-7.43 (m, 1H, H_{aro}), 7.36 (d, *J* = 8.1 Hz, 1H, H_{aro}), 7.05 (d, *J* = 8.1 Hz, 1H, H_{aro}), 6.16 (s, 1H, CH), 5.22 (d, *J* = 14.9 Hz, 1H, CH_2), 4.44 (dd, *J* = 14.8, 7.8 Hz, 1H, CH_2), 2.87 (s, 3H, CH_3), 1.42 (s, 9H, 3 x CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.0 (C=O), 147.7 (C^q_{aro}), 145.7 (C^q_{aro}), 139.5 (C^q_{aro}), 139.3 (C^q_{aro}), 133.9 (C^q_{aro}), 132.7 (C^q_{aro}), 132.0 (CH_{aro}), 128.7 (CH_{aro}), 126.8 (CH_{aro}), 125.7 (CH_{aro}), 124.6 (CH_{aro}), 120.5 (CH_{aro}), 70.4 (CH), 49.2 (CH_2), 36.0 (C^q), 31.4 (3 x CH_3), 22.3 (CH_3) ppm. HRMS (+ESI) calculated for $C_{20}H_{21}NO$ $[M+H]^+$: 292.1696, found 292.1714.

Synthesis and characterization of compounds 4l/4l'.

These products were obtained as a mixture of separable two regioisomers in 54% global yield, with a ratio of **4l/4l'**: 55/45.

Methyl 1-methyl-7-oxo-7, 11*b*-dihydro-5*H*-isoindolo [1,2-*a*]isoindole-3-carboxylate (4l).

Major regioisomer-4l: This compound was isolated as a yellow oil, R_f (cyclohexane/AcOEt: 8/2) = 0.14; **IR (ν_{max} cm^{-1})**: 1703 (2 x C=O); **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.92 (d, *J* = 7.9 Hz, 1H, H_{aro}), 7.88 (d, *J* = 7.7 Hz, 1H, H_{aro}), 7.78 (s, 2H, H_{aro}), 7.63 (td, *J* = 7.6, 1.3 Hz, 1H, H_{aro}), 7.54-7.47 (m, 1H, H_{aro}), 6.11 (s, 1H, CH), 5.26 (d, *J* = 15.2 Hz, 1H, CH_2), 4.47 (d, *J* = 15.2 Hz, 1H, CH_2), 3.90 (s, 3H , CH_3), 2.71 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 173.9 (C=O), 166.7 (C=O), 144.4 (C^q_{aro}), 142.4 (C^q_{aro}), 141.7 (C^q_{aro}), 133.8 (C^q_{aro}), 133.6 (C^q_{aro}), 132.3 (CH_{aro}), 131.1 (CH_{aro}), 130.7 (C^q_{aro}), 129.0 (CH_{aro}), 125.3 (CH_{aro}),

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124.8 (CH_{aro}), 122.2 (CH_{aro}), 69.6 (CH), 52.4 (O-CH_3), 49.2 (CH_2), 21.6 (CH_3) ppm. HRMS (+ESI) calculated for $C_{18}H_{15}NO_3$ $[M+H]^+$: 294.1125, found 294.1147.

Methyl 1-methyl-7-oxo-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindole-2-carboxylate (4l').

Minor regioisomer-4l': This compound was isolated as a yellow oil, R_f (cyclohexane/AcOEt: 8/2) = 0.12; **IR (ν_{max} cm^{-1})**: 1703 (2 x C=O). **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.98 (d, *J* = 7.8 Hz, 1H, H_{aro}), 7.87 (d, *J* = 7.6 Hz, 1H, H_{aro}), 7.83 (d, *J* = 7.9 Hz, 1H, H_{aro}), 7.62 (t, *J* = 7.5 Hz, 1H, H_{aro}), 7.50 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.16 (d, *J* = 7.9 Hz, 1H, H_{aro}), 6.17 (s, 1H, CH), 5.27 (d, *J* = 15.6 Hz, 1H , CH_2), 4.48 (d, *J* = 15.6 Hz, 1H, CH_2), 3.89 (s, 3H, CH_3), 2.90 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.3 (C=O), 168.0 (C=O), 145.4 (C^q_{aro}), 145.4 (C^q_{aro}), 139.1 (C^q_{aro}), 135.9 (C^q_{aro}), 133.4 (C^q_{aro}), 132.5 (CH_{aro}), 131.2 (CH_{aro}), 130.2 (C^q_{aro}), 129.0 (CH_{aro}), 125.3 (CH_{aro}), 124.7 (CH_{aro}), 120.7 (CH_{aro}), 69.7 (CH), 52.2 (O-CH_3), 49.7 (CH_2), 20.6 (CH_3) ppm. HRMS (+ESI) calculated for $C_{18}H_{15}NO_3$ $[M+H]^+$: 294.1125, found 294.1147.

Synthesis and characterization of compound 4m.

Dimethyl 1-methyl-7-oxo-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindole-2,3-dicarboxylate (4m).

This product was obtained as a single regioisomer in a 45% yield.

This product was isolated as a white solid in 45% yield, R_f (cyclohexane/AcOEt: 7/3) = 0.38; m.p. = 196-198 °C; **IR (ν_{max} cm^{-1})**: 1736, 1719, 1692; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.95-7.84 (m, 2H, H_{aro}), 7.77 (s, 1H, H_{aro}), 7.62 (t, *J* = 7.6, 1.4 Hz, 1H, H_{aro}), 7.51 (t, *J* = 7.4 Hz, 1H, H_{aro}), 6.13 (s, 1H, CH), 5.28 (d, *J* = 15.4 Hz, 1H, CH_2), 4.47 (d, *J* = 15.3 Hz, 1H , CH_2), 3.94 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 2.64 (s, 3H, CH_3) ppm.**^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.0 (C=O), 169.5 (C=O), 165.8 (C=O), 144.2 (C^q_{aro}), 142.8 (C^q_{aro}), 142.4 (C^q_{aro}), 135.9 (C^q_{aro}), 133.4 (C^q_{aro}), 132.5 (CH_{aro}), 131.5 (C^q_{aro}), 129.2 (CH_{aro}), 128.5 (C^q_{aro}), 125.3 (CH_{aro}), 124.9 (CH_{aro}), 122.7 (CH_{aro}), 69.6 (CH), 52.9 (CH_3), 52.8 (CH_3), 49.3 (CH_2), 18.7 (CH_3) ppm. HRMS (+ESI) calculated for $C_{24}H_{19}NO_2$ $[M+H]^+$: 352.1179, found 352.1203.

Synthesis and characterization of compounds 4n/4n'.

These products were obtained as a mixture of separable two regioisomers in 88% global yield, with a ratio of **4n**/**4n'**: 60/40.

2-((1-Methyl-7-oxo-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-3-yl)methyl)isoindoline-1,3-dione (4n).

Major regioisomer-4n: This product was isolated as a white solid, R_f (DCM/AcOEt: 9/1) = 0.24; m.p. = 174-176 °C; **IR (ν_{max} cm^{-1})**: 1687; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.89-7.80 (m, 4H, H_{aro}), 7.73-7.68 (m, 2H, H_{aro}), 7.58 (t, *J* = 7.5 Hz, 1H, H_{aro}), 7.46 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.18 (s, 1H, H_{aro}), 7.14 (s, 1H, H_{aro}), 6.03 (s, 1H, CH), 5.18 (d, *J* = 15.1 Hz, 1H, CH_2), 4.79 (s, 2H, CH_2), 4.41 (d, *J* = 15.1 Hz, 1H, CH_2), 2.63 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.0 (C=O), 168.1 (2 x C=O), 145.0 (C^q_{aro}), 142.6 (C^q_{aro}), 137.1 (C^q_{aro}), 136.5 (C^q_{aro}), 134.2 (2 x CH_{aro}), 133.9 (C^q_{aro}), 133.6 (C^q_{aro}), 132.2 (2 x C^q_{aro}), 132.1 (CH_{aro}), 130.0 (CH_{aro}), 128.8 (CH_{aro}), 125.1 (CH_{aro}), 124.7 (CH_{aro}), 123.5 (2 x CH_{aro}), 121.2 (CH_{aro}), 69.4 (CH), 49.3 (CH_2), 41.3 (CH_2), 21.6 (CH_3) ppm. HRMS (+ESI) calculated for $C_{25}H_{18}N_2O_3$ $[M+H]^+$: 395.1390, found 395.1395.

2-((1-Methyl-7-oxo-7,11*b*-dihydro-5*H*-isoindolo[1,2-a]isoindol-2-yl)methyl)isoindoline-1,3-dione (**4n'**).

Minor regioisomer-4n': This product was isolated as a white solid, R_f (DCM/AcOEt: 9/1) = 0.19; m.p. = 208-210 °C; **IR (ν_{max} cm^{-1})**: 1687; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.95 (d, *J* = 7.8 Hz, 1H, H_{aro}), 7.88-7.79 (m, 3H, H_{aro}), 7.74-7.69 (m, 2H, H_{aro}), 7.59 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.47 (t, *J* = 7.5 Hz, 1H, H_{aro}), 7.32 (d, *J* = 7.8 Hz, 1H, H_{aro}), 7.07 (d, *J* = 7.8 Hz, 1H, H_{aro}), 6.13 (s, 1H, CH), 5.19 (d, *J* = 15.1 Hz, 1H, CH_2), 4.98-4.75 (m, 2H, CH_2), 4.41 (d, *J* = 15.0 Hz, 1H, CH_2), 2.82 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.1 (C=O), 168.2 (2 x C=O), 145.5 (C^q_{aro}), 141.3 (C^q_{aro}), 138.1 (C^q_{aro}), 134.2 (2 x CH_{aro}), 134.2 (C^q_{aro}), 134.1 (C^q_{aro}), 133.6 (C^q_{aro}), 132.2 (CH_{aro}), 132.2 (C^q_{aro}), 132.1 (CH_{aro}), 129.9 (C^q_{aro}), 128.8 (CH_{aro}), 125.2 (CH_{aro}), 124.7 (CH_{aro}), 123.5 (2 x CH_{aro}), 121.0 (CH_{aro}), 69.8 (CH), 49.5 (CH_2), 39.3 (CH_2), 18.5 (CH_3) ppm. HRMS (+ESI) calculated for $C_{25}H_{18}N_2O_3$ $[M+H]^+$: 395.1390, found 395.1395.

Representative Procedure for the Iron(III)/Rhodium(I)-Catalyzed One-Pot Alkynylation/Cyclotrimerization of *N,O*-Acetals: Commercially available $Fe(OTf)_3$ (Aldrich, 5 mol%) was added to a solution of hydroxylactam **1** (0.5 mmol) and propyne-TMS **2** (1.1 equiv.) in 1,2-dichloroethane (2 mL) under argon. The mixture was placed in a pre-heated oil bath at reflux and magnetically stirred. The progress of the reaction was monitored by TLC. The solvent was evaporated

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under reduced pressure. The intermediate **2b** was solubilized without purification in 2 mL of toluene and was added dropwise over 2 h to a solution of **3a-t** alkynes (10 equiv.) and $RhCl(PPh_3)_3$ (10 mol%) in toluene (4 mL). The reaction mixture was heated under reflux. After the total conversion of the starting material as monitored by TLC, the solvent was removed under reduced pressure. The crude products were purified by flash chromatography (silica gel column, cyclohexane/AcOEt, or DCM/AcOEt as eluents).

Synthesis and characterization of compounds 4a/4a'.

These products were obtained as a mixture of separable two regioisomers in 60% global yield, with a ratio of **4a**/**4a'**: 60/40.

Data analyses were identical in all respects with cyclotrimerization step data.

Synthesis and characterization of compounds 4e/4e'.

These products were obtained as a mixture of separable two regioisomers in 51% global yield, with a ratio of **4e**/**4e'**: 60/40.

Data analyses were identical in all respects with cyclotrimerization step data.

Synthesis and characterization of compounds 4f.

This product was obtained as a single regioisomer in 51% global yield.

Data analyses were identical in all respects with cyclotrimerization step data.

Synthesis and characterization of compounds 4g.

This product was obtained as a single regioisomer in 73% global yield.

Data analyses were identical in all respects with cyclotrimerization step data.

Synthesis and characterization of compounds 4m.

This product was obtained as a single regioisomer in 35% global yield.

Data analyses were identical in all respects with cyclotrimerization step data.

Synthesis and characterization of compounds 4n/4n'.

These products were obtained as a mixture of separable two regioisomers in 70% global yield, with a ratio of **4n**/**4n'**: 60/40.

Data analyses were identical in all respects with cyclotrimerization step data.

Synthesis and characterization of compounds 4o/4o'.

These products were obtained as a mixture of separable two regioisomers in 59% global yield, with a ratio of **4o**/**4o'**: 58/42.

11-Methyl-9-(thiophen-3-yl)-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4o).

Major regioisomer-4o: This compound was isolated as a white solid, R_f (cyclohexane/AcOEt: 8/2) = 0.21; m.p. = 193-195 °C; **IR (ν_{max} cm^{-1})**: 1683; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.95-7.85 (m, 2H, H_{aro}), 7.68-7.57 (m, 1H, H_{aro}), 7.55-7.44 (m, 1H, H_{aro}), 7.41 (s, 1H, H_{aro}), 7.39-7.32 (m, 3H, H_{aro}), 7.31 (s, 1H, H_{aro}), 6.11 (s, 1H, CH), 5.27 (d, *J* = 15.7 Hz, 1H, CH_2), 4.49 (d, *J* = 15.0 Hz, 1H, CH_2), 2.70 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.0 (C=O), 145.2 (C^q_{aro}), 142.7 (C^q_{aro}), 141.7 (C^q_{aro}), 136.5 (C^q_{aro}), 135.7 (C^q_{aro}), 133.9 (C^q_{aro}), 133.7 (C^q_{aro}), 132.2 (CH_{aro}), 128.8 (CH_{aro}), 128.0 (CH_{aro}), 126.5 (CH_{aro}), 126.4 (CH_{aro}), 125.2 (CH_{aro}), 124.7 (CH_{aro}), 120.8 (CH_{aro}), 119.0 (CH_{aro}), 69.5 (CH), 49.4 (CH_2), 21.8 (CH_3) ppm. HRMS (+ESI) calculated for $C_{20}H_{15}NOS$ $[M+H]^+$: 318.0947, found 318.0947.

11-Methyl-10-(thiophen-3-yl)-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4o').

Minor regioisomer-4o': This compound was isolated as a white solid, R_f (cyclohexane/AcOEt: 8/2) = 0.18; m.p. = 191-193 °C; **IR (ν_{max} cm^{-1})**: 1696; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.96 (d, *J* = 7.7 Hz, 1H, H_{aro}), 7.90 (d, *J* = 7.6 Hz, 1H, H_{aro}), 7.62 (t, *J* = 7.1 Hz, 1H, H_{aro}), 7.50 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.42-7.33 (m, 1H, H_{aro}), 7.27-7.25 (m, 1H, H_{aro}), 7.20-7.10 (m, 2H, H_{aro}), 7.12 -7.04 (m, 1H, H_{aro}), 6.16 (s, 1H, CH), 5.27 (d, *J* = 15.2 Hz, 1H, CH_2), 4.50 (d, *J* = 15.0 Hz, 1H, CH_2), 2.63 (s, 2H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.1 (C=O), 145.5 (C^q_{aro}), 141.5 (C^q_{aro}), 140.9 (C^q_{aro}), 138.1 (C^q_{aro}), 136.9 (C^q_{aro}), 133.7 (C^q_{aro}), 132.2 (CH_{aro}), 131.7 (C^q_{aro}), 130.4 (CH_{aro}), 129.1 (CH_{aro}), 128.8 (CH_{aro}), 125.4 (CH_{aro}), 125.3 (CH_{aro}), 124.7 (CH_{aro}), 123.2 (CH_{aro}), 120.8 (CH_{aro}), 69.9 (CH), 49.5 (CH_2), 20.2 (CH_3) ppm. HRMS (+ESI) calculated for $C_{20}H_{15}NOS$ $[M+H]^+$: 318.0947, found 318.0947.

Synthesis and characterization of compounds 4p/4p'.

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These products were obtained as a mixture of inseparable two regioisomers and were isolated as a yellow oil in 70% global yield, with a ratio of **4p/4p'**: 51/49, R_f (cyclohexane/AcOEt: 7/3) = 0.35; **IR (ν_{max} cm^{-1})**: 1695.

11-Methyl-9-(naphthalen-2-yl)-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (**4p**).

The NMR characteristics of this product were extracted from the spectrum of the mixture; **^{1}H NMR (300 MHz, CDCl$_3$)**: δ_H 8.01-7.84 (m, 10H, H_{aro}) (**4p** or **4p'**), 7.72 (dd, *J* = 9.1, 1.8 Hz, 2H, H_{aro}) (**4p or 4p'**), 7.68-7.60 (m, 3H, H_{aro}) (**4p or 4p'**), 7.54-7.46 (m, 7H, H_{aro}) (**4p or 4p'**), 7.44-7.39 (m, 2H, H_{aro}) (**4p or 4p'**), 7.30 (d, *J* = 7.8 Hz, 1H, H_{aro}) (**4p or 4p'**), 7.21 (d, *J* = 7.8 Hz, 1H, H_{aro}) (**44p or 4p'**), 6.16 (s, 1H, CH), 5.32 (dd, *J* = 15.1, 3.5 Hz, 1H, CH_2), 4.54 (d, *J* = 15.0 Hz, 1H, CH_2), 2.76 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)**: δ_C 174.1 (C=O), 145.5 (C^q_{aro}) (**4p or 4p'**), 145.2 (C^q_{aro}) (**4p or 4p'**), 142.8 (C^q_{aro}) (**4p or 4p'**), 142.2 (C^q_{aro}) (**4p or 4p'**), 142.0 (C^q_{aro}) (**4p or 4p'**), 141.0 (C^q_{aro}) (**4p or 4p'**), 138.9 (C^q_{aro}) (**4p or 4p'**), 138.1 (C^q_{aro}) (**4p or 4p'**), 137.9 (C^q_{aro}) (**4p or 4p'**), 136.0 (C^q_{aro}) (**4p or 4p'**), 133.9 (C^q_{aro}) (**4p or 4p'**), 133.8 (C^q_{aro}) (**4p or 4p'**), 133.7 (C^q_{aro}) (**4p or 4p'**), 133.7 (C^q_{aro}) (**4p or 4p'**), 133.4 (C^q_{aro}) (**4p or 4p'**), 132.9 (C^q_{aro}) (**4p or 4p'**), 132.5 (C^q_{aro}) (**4p or 4p'**), 132.2 (CH_{aro}) (**4p or 4p'**), 132.2 (CH_{aro}) (**4p or 4p'**), 131.5 (C^q_{aro}) (**4p or 4p'**), 130.7 (CH_{aro}) (**4p or 4p'**), 129.0 (CH_{aro}) (**4p or 4p'**), 128.8 (2 x CH_{aro}) (**4p or 4p'**), 128.7 (CH_{aro}) (**4p or 4p'**), 128.3 (CH_{aro}) (**4p or 4p'**), 128.2 (CH_{aro}) (**4p or 4p'**), 128.1 (CH_{aro}) (**4p or 4p'**), 127.9 (3 x CH_{aro}) (**4p or 4p'**), 127.8 (CH_{aro}) (**4p or 4p'**), 126.6 (CH_{aro}) (**4p or 4p'**), 126.5 (CH_{aro}) (**4p or 4p'**), 126.2 (CH_{aro}) (**4p or 4p'**), 126.2 (CH_{aro}) (**4p or 4p'**), 126.0 (CH_{aro}) (**4p or 4p'**), 125.6 (CH_{aro}) (**4p or 4p'**), 125.4 (CH_{aro}) (**4p or 4p'**), 125.2 (CH_{aro}) (**4p or 4p'**), 124.8 (2 x CH_{aro}) (**4p or 4p'**), 120.8 (CH_{aro}) (**4p or 4p'**), 120.0 (CH_{aro}) (**4p or 4p'**), 69.5 (CH), 49.5 (CH_2), 21.8 (CH_3) ppm. HRMS (+ESI) calculated for $C_{26}H_{19}NO$ $[M+H]^+$: 362.1539, found 362.1562.

Synthesis and characterization of compounds 4q/4q'.

This product was obtained as a mixture of separable two regioisomers in 68% global yield, with a ratio of **4q/4q'**: 53/47.

9-(4-Methoxyphenyl)-11-methyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4q).

Major regioisomer-4q: This product was isolated as a white solid, R_f (cyclohexane/AcOEt: 7/3) = 0.24; m.p. = 181-183 °C; **IR (ν_{max} cm^{-1})**: 1691; **^{1}H NMR (300 MHz, CDCl$_3$)**: δ_H 7.93 (d, *J* = 7.8 Hz, 1H, H_{aro}), 7.88 (d, *J* = 7.5 Hz, 1H, H_{aro}), 7.62 (t, *J* = 7.2 Hz, 1H, H_{aro}), 7.53-7.44 (m, 3H, H_{aro}), 7.27 (d, *J* = 6.7 Hz, 2H, H_{aro}), 6.96 (d, *J* = 8.7 Hz, 2H, H_{aro}), 6.11 (s, 1H, CH), 5.27 (d, *J* = 15.0 Hz, 1H, CH_2), 4.50 (d, *J* = 14.9 Hz, 1H, CH_2), 3.84 (s, 3H, O-CH_3), 2.71 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)**: δc 174.1 (C=O), 159.5 (C^q_{aro}), 145.3 (C^q_{aro}), 142.7 (C^q_{aro}), 141.6 (C^q_{aro}), 135.2 (C^q_{aro}), 133.7 (C^q_{aro}), 133.6 (C^q_{aro}), 133.1 (C^q_{aro}), 132.1 (CH_{aro}), 128.8 (CH_{aro}), 128.3 (3 x CH_{aro}), 125.2 (CH_{aro}), 124.7 (CH_{aro}), 119.2 (CH_{aro}), 114.4 (2 x CH_{aro}), 69.5 (CH), 55.5 (O-CH_3), 49.5 (CH_2), 21.8 (CH_3) ppm. HRMS (+ESI) calculated for $C_{23}H_{19}NO_2$ $[M+H]^+$: 342.1489, found 342.1510.

10-(4-Methoxyphenyl)-11-methyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4q').

Minor regioisomer-4q': This product was isolated as a white solid, R_f (cyclohexane/AcOEt: 7/3) = 0.37; m.p. = 180-182 °C **IR (ν_{max} cm^{-1})**: 1691; **^{1}H NMR (300 MHz, CDCl$_3$)**: δ_H 7.95 (d, *J* = 7.8 Hz, 1H, H_{aro}), 7.90 (d, *J* = 7.5 Hz, 1H, H_{aro}), 7.61 (t, *J* = 7.6, 1.3 Hz, 1H, H_{aro}), 7.52 (t, *J* = 7.5 Hz, 1H, H_{aro}), 7.24-7.13 (m, *J* = 8.6, 6.3 Hz, 4H, H_{aro}), 7.01-6.90 (d, 2H, H_{aro}), 6.16 (s, 1H, CH), 5.28 (d, *J* = 15.0 Hz, 1H, CH_2), 4.51 (d, *J* = 15.0 Hz, 1H, CH_2), 3.86 (s, 3H, O-CH_3), 2.58 (s, 3H, CH_3). **^{13}C NMR (75 MHz, CDCl$_3$)**: δ_C 174.1 (C=O), 158.9 (C^q_{aro}), 145.6 (C^q_{aro}), 141.9 (C^q_{aro}), 140.6 (C^q_{aro}), 138.0 (C^q_{aro}), 133.8 (C^q_{aro}), 133.6 (C^q_{aro}), 132.2 (CH_{aro}), 131.4 (C^q_{aro}), 130.6 (2 x CH_{aro}), 130.5 (CH_{aro}), 128.8 (CH_{aro}), 125.3 (CH_{aro}), 124.7 (CH_{aro}), 120.7 (CH_{aro}), 113.7 (2 x CH_{aro}), 70.0 (CH), 55.5 (O-CH_3), 49.5 (CH_2), 20.3 (CH_3). HRMS (+ESI) calculated for $C_{23}H_{19}NO_2$ $[M+H]^+$: 342.1489, found 342.1510.

Synthesis and characterization of compounds 4r/4r'.

These products were obtained as a mixture of separable two regioisomers in 69% global yield, with a ratio of **4r/4r'**: 70/30.

10-(Hydroxymethyl)-11-methyl-9-phenyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4r).

Major regioisomer-4r: This compound was isolated as a yellow oil, R_f (cyclohexane/AcOEt: 5/5) = 0.11; **IR (ν_{max} cm^{-1})**: 3383, 1678; **^{1}H NMR (300 MHz, CDCl$_3$)**: δ_H 7.89 (d, *J* = 7.6 Hz, 2H, H_{aro}), 7.62-7.55 (m, 1H, H_{aro}), 7.53-7.37 (m, 4H, H_{aro}), 7.35 (s, 1H, H_{aro}), 7.19 (d, *J* = 7.4 Hz, 1H, H_{aro}), 7.05 (dd, *J* = 5.7, 3.3

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Hz, 1H, H_{aro}), 6.16 (s, 1H, CH), 5.30 (d, *J* = 15.0 Hz, 1H, CH_2), 4.51 (d, *J* = 15.0 Hz, 1H, CH_2), 4.33 (s, *J* = 2.2 Hz, 2H, CH_2), 2.34 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.2 (C=O), 145.5 (C^q_{aro}), 141.1 (C^q_{aro}), 140.6 (C^q_{aro}), 139.8 (C^q_{aro}), 139.1 (C^q_{aro}), 136.7 (C^q_{aro}), 133.7 (C^q_{aro}), 132.2 (CH_{aro}), 132.1 (C^q_{aro}), 129.5 (CH_{aro}), 129.2 (CH_{aro}), 128.9 (CH_{aro}), 128.8 (CH_{aro}), 128.8 (CH_{aro}), 127.6 (CH_{aro}), 125.3 (CH_{aro}), 124.7 (CH_{aro}), 119.9 (CH_{aro}), 69.9 (CH), 63.5 (CH_2OH), 49.6 (CH_2), 19.9 (CH_3) ppm. HRMS (+ESI) calculated for $C_{23}H_{19}NO_2$ $[M+H]^+$: 342.1489, found 342.1513.

9-(Hydroxymethyl)-11-methyl-10-phenyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4r').

Minor regioisomer-4r': This compound was isolated as a yellow oil, R_f (cyclohexane/AcOEt: 5/5) = 0.13; **IR (ν_{max} cm^{-1})**: 3383, 1678; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.98 (d, *J* = 7.8 Hz, 1H, H_{aro}), 7.86 (d, *J* = 7.5 Hz, 1H, H_{aro}), 7.61 (t, *J* = 7.6, 1.3 Hz, 1H, H_{aro}), 7.48 (t, *J* = 7.5 Hz, 1H, H_{aro}), 7.45-7.27 (m, 5H, H_{aro}), 7.04 (s, 1H, H_{aro}), 6.15 (s, 1H, CH), 5.22 (d, *J* = 15.1 Hz, 1H, CH_2), 4.59 (s, 2H, CH_2), 4.44 (d, *J* = 15.1 Hz, 1H, CH_2), 2.85 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.2 (C=O), 145.5 (C^q_{aro}), 143.9 (C^q_{aro}), 141.2 (C^q_{aro}), 141.1 (C^q_{aro}), 137.3 (C^q_{aro}), 135.7 (C^q_{aro}), 134.3 (C^q_{aro}), 133.6 (C^q_{aro}), 132.3 (CH_{aro}), 129.3 (2 x CH_{aro}), 128.8 (CH_{aro}), 128.3 (2 x CH_{aro}), 127.5 (CH_{aro}), 125.3 (CH_{aro}), 124.7 (CH_{aro}), 122.7 (CH_{aro}), 69.8 (CH), 59.8 (CH_2OH), 49.5 (CH_2), 18.6 (CH_3) ppm. HRMS (+ESI) calculated for $C_{23}H_{19}NO_2$ $[M+H]^+$: 342.1489, found 342.1513.

Synthesis and characterization of compounds 4s/4s'.

These products were obtained as a mixture of inseparable two regioisomers and were isolated as a yellow oil in 55% global yield, with a ratio of **4s/4s'**: 63/37, R_f (cyclohexane/AcOEt: 7/3) = 0.28; **IR (ν_{max} cm^{-1})**: 1694.

11-Methyl-9-propyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4s).

Major regioisomer-4s: The NMR characteristics of this product were extracted from the spectrum of the mixture; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.98-7.84 (m, 2H, H_{aro}), 7.60 (t, *J* = 7.5 Hz, 1H, H_{aro}), 7.47 (t, *J* = 7.4 Hz, 1H, H_{aro}), 6.93 (s, 1H, H_{aro}), 6.88 (s, 1H, H_{aro}), 6.05 (s, 1H, CH), 5.20 (d, *J* = 14.6 Hz, 1H, CH_2), 4.43 (d, *J* = 14.8 Hz, 1H, CH_2), 2.63 (s, 3H, CH_3), 2.58-2.49 (m, 2H, CH_2), 1.64-1.52 (m, 2H, CH_2), 0.99 -0.88 (m, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.1 (C=O), 145.4 (C^q_{aro}), 143.5 (C^q_{aro}), 142.0 (C^q_{aro}), 134.1 (C^q_{aro}), 133.7 (C^q_{aro}), 133.1 (C^q_{aro}), 132.0 (CH_{aro}), 129.9 (CH_{aro}), 128.6 (CH_{aro}), 125.1 (CH_{aro}), 124.6 (CH_{aro}), 120.9 (CH_{aro}), 69.5 (CH), 49.4 (CH_2), 37.7 (CH_2), 24.8 (CH_2), 21.6 (CH_3), 13.9 (CH_3) ppm. HRMS (+ESI) calculated for $C_{19}H_{19}NO$ $[M+H]^+$: 278.1539, found 278.1556.

11-Methyl-10-propyl-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-5-one (4s').

Minor regioisomer-4s': The NMR characteristics of this product were extracted from the spectrum of the mixture; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.98-7.84 (m, 2H, CH_{aro}), 7.60 (t, *J* = 7.5 Hz, 1H, CH_{aro}), 7.47 (t, *J* = 7.4 Hz, 1H, CH_{aro}), 7.09 (d, *J* = 7.7 Hz, 1H, CH_{aro}), 7.03 (d, *J* = 7.8 Hz, 1H, CH_{aro}), 6.13 (s, 1H, CH), 5.20 (d, *J* = 14.6 Hz, 1H, CH_2), 4.43 (d, *J* = 14.8 Hz, 1H, CH_2), 2.63 (s, 3H), 2.58-2.49 (m, 2H, CH_2), 1.64-1.52 (m, 2H, CH_2), 0.99-0.88 (m, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.1 (C=O), 145.8 (C^q_{aro}), 140.7 (C^q_{aro}), 139.2 (C^q_{aro}), 137.6 (C^q_{aro}), 133.8 (C^q_{aro}), 132.1 (CH_{aro}), 131.6 (C^q_{aro}), 129.7 (CH_{aro}), 128.6 (CH_{aro}), 125.1 (CH_{aro}), 125.2 (CH_{aro}), 120.6 (CH_{aro}), 69.9 (CH), 49.4 (CH_2), 35.5 (CH_2), 23.9 (CH_2), 18.2 (CH_3), 14.2 (CH_3) ppm. HRMS (+ESI) calculated for $C_{19}H_{19}NO$ $[M+H]^+$: 278.1539, found 278.1556.

Synthesis and characterization of compounds 4t/4t'.

These products were obtained as a mixture of separable two regioisomers in 82% global yield, with a ratio of **4t/4t'**: 52/48.

2-(2-(1-Methyl-7-oxo-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-3-yl)ethyl)isoindoline-1,3-dione (4t)

Major regioisomer-4t: This product was isolated as a white solid, R_f (DCM/AcOEt: 9/1) = 0.22; m.p. = 179-181 °C; **IR (ν_{max} cm^{-1})**: 1690; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.91-7.80 (m, 4H, H_{aro}), 7.74-7.68 (m, 2H, H_{aro}), 7.60 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.48 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.02 (s, 1H, H_{aro}), 6.99 (s, 1H, H_{aro}), 6.05 (s, 1H, CH), 5.17 (d, *J* = 15.0 Hz, 1H, CH_2), 4.41 (d, *J* = 14.9 Hz, 1H, CH_2), 3.913.79 (m, 2H, CH_2), 2.98-2.87 (m, 2H, CH_2), 2.62 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.0 (C=O), 168.3 (2 x C=O), 145.3 (C^q_{aro}), 142.4 (C^q_{aro}), 138.8 (C^q_{aro}), 135.3 (C^q_{aro}), 134.1 (2 x CH_{aro}), 133.7 (C^q_{aro}), 133.7 (C^q_{aro}), 132.2 (2 x C^q_{aro}), 132.1 (CH_{aro}), 130.3 (CH_{aro}), 128.7 (CH_{aro}), 125.2 (CH_{aro}), 124.7 (CH_{aro}), 123.4 (2

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x CH_{aro}), 121.4 (CH_{aro}), 69.5 (CH), 49.3 (CH_2), 39.3 (CH_2), 34.3 (CH_2), 21.6 (CH_3) ppm. HRMS (+ESI) calculated for $C_{26}H_{20}N_2O_3$ $[M+H]^+$: 409.1547, found 409.1548.

2-(2-(1-Methyl-7-oxo-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-2-yl)ethyl)isoindoline-1,3-dione (4t').

Minor regioisomer-4t': This product was isolated as a white solid, R_f (DCM/AcOEt: 9/1) = 0.15; m.p. = 178-180 °C; **IR (ν_{max} cm^{-1})**: 1690; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.96 (d, *J* = 7.8 Hz, 1H, H_{aro}), 7.88-7.79 (m, 3H, H_{aro}), 7.75-7.66 (m, 2H, H_{aro}), 7.60 (t, *J* = 7.7 Hz, 1H, H_{aro}), 7.48 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.17 (d, *J* = 7.7 Hz, 1H, H_{aro}), 7.04 (d, *J* = 7.7 Hz, 1H, H_{aro}), 6.13 (s, 1H, CH), 5.20 (d, *J* = 14.9 Hz, 1H, CH_2), 4.42 (d, *J* = 14.9 Hz, 1H, CH_2), 3.81 (t, *J* = 8.2 Hz, 2H, CH_2), 3.00 (t, *J* = 8.3 Hz, 2H, CH_2), 2.77 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.1 (C=O), 168.3 (2 x C=O), 145.6 (C^q_{aro}), 140.4 (C^q_{aro}), 138.1 (C^q_{aro}), 136.0 (C^q_{aro}), 134.1 (2 x CH_{aro}), 133.7 (C^q_{aro}), 132.4 (C^q_{aro}), 132.2 (2 x C^q_{aro}), 132.2 (CH_{aro}), 130.3 (CH_{aro}), 128.7 (CH_{aro}), 125.3 (CH_{aro}), 124.6 (CH_{aro}), 123.4 (2 x CH_{aro}), 121.0 (CH_{aro}), 69.9 (CH), 49.4 (CH_2), 38.3 (CH_2), 32.3 (CH_2), 18.2 (CH_3) ppm. HRMS (+ESI) calculated for $C_{26}H_{20}N_2O_3$ $[M+H]^+$: 409.1547, found 409.1548.

Synthesis and characterization of compounds 4u/4u'.

These products were obtained as a mixture of separable two regioisomers in 72% global yield, with a ratio of **4u**/**4u'**: 67/33.

1-((1-Methyl-7-oxo-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-3-yl)methyl)pyrrolidine 2,5-dione (4u).

Major regioisomer-4u: This product was isolated as a white solid, R_f (DCM/AcOEt: 9/1) = 0.22; m.p. = 208-210 °C; **IR (ν_{max} cm^{-1})**: 1705; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.86 (t, *J* = 8.4 Hz, 2H, H_{aro}), 7.59 (t, *J* = 7.5 Hz, 1H, H_{aro}), 7.47 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.14 (s, 1H, H_{aro}), 7.10 (s, 1H, H_{aro}), 6.04 (s, 1H, CH), 5.19 (d, *J* = 15.1 Hz, 1H, CH_2), 4.60 (d, *J* = 2.3 Hz, 2H, CH_2), 4.41 (d, *J* = 15.1 Hz, 1H, CH_2), 2.69 (s, 4H, 2 x CH_2), 2.63 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 176.9 (2 x C=O), 170.0 (C=O), 145.0 (C^q_{aro}), 142.6 (C^q_{aro}), 136.7 (C^q_{aro}), 136.4 (C^q_{aro}), 133.9 (C^q_{aro}), 133.6 (C^q_{aro}), 132.1 (CH_{aro}), 130.3 (CH_{aro}), 128.8 (CH_{aro}), 125.2 (CH_{aro}), 124.7 (CH_{aro}), 121.5 (CH_{aro}), 69.4 (CH), 49.3 (CH_2), 42.1 (CH_2), 28.3 (2 x CH_2), 21.6 (CH_3) ppm. HRMS (+ESI) calculated for $C_{21}H_{18}N_2O_3$ $[M+H]^+$: 347.1390, found 347.1410.

1-((1-Methyl-7-oxo-7,11*b*-dihydro-5*H*-isoindolo[1,2-*a*]isoindol-2-yl)methyl)pyrrolidine-2,5-dione (4u').

Minor regioisomer-4u': This product was isolated as a white solid, R_f (DCM/AcOEt: 9/1) = 0.17; m.p. = 197-199 °C; **IR (ν_{max} cm^{-1})**: 1705; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.95 (d, *J* = 7.8 Hz, 1H, H_{aro}), 7.86 (d, *J* = 7.5 Hz, 1H, H_{aro}), 7.60 (t, *J* = 7.5 Hz, 1H, H_{aro}), 7.48 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.27 (d, *J* = 8.6 Hz, 1H, H_{aro}), 7.07 (d, *J* = 7.9 Hz, 1H, H_{aro}), 6.13 (s, 1H, CH), 5.20 (d, *J* = 15.0 Hz, 1H, CH_2), 4.71 (d, *J* = 16.2 Hz, 2H, CH_2), 4.42 (d, *J* = 14.6 Hz, 1H, CH_2), 2.80-2.74 (m, 4H, 2 x CH_2), 2.72 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 177.1 (2 x C=O), 174.2 (C=O), 145.6 (C^q_{aro}), 141.5 (C^q_{aro}), 138.1 (C^q_{aro}), 133.6 (C^q_{aro}), 133.5 (C^q_{aro}), 132.5 (C^q_{aro}), 132.3 (CH_{aro}), 130.1 (CH_{aro}), 128.8 (CH_{aro}), 125.3 (CH_{aro}), 124.7 (CH_{aro}), 121.0 (CH_{aro}), 69.8 (CH), 49.5 (CH_2), 39.9 (CH_2), 28.3 (2 x CH_2), 18.6 (CH_3) ppm. HRMS (+ESI) calculated for $C_{21}H_{18}N_2O_3$ $[M+H]^+$: 347.1390, found 347.1410.

Synthesis and characterization of compound 6a.

3-(Dimethylamino)-1-methyl-5,11b-dihydro-7H-pyrido[3',4':3,4]pyrrolo[2,1-a]isoindol-7-one (6a).

This product was isolated as a yellow oil in 40% yield, R_f (cyclohexane/AcOEt: 7/3) = 0.5; IR (ν_{max} cm^{-1}): 1695; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.92-7.80 (m, 2H, H_{aro}), 7.61 (td, *J* = 7.5 and 1.4 Hz, 1H, H_{aro}), 7.48 (t, *J* = 7.4 Hz, 1H, H_{aro}), 6.23 (s, 1H, H_{aro}), 5.96 (s, 1H, CH), 5.12 (d, *J* = 15.6 Hz, 1H, CH_2), 4.34 (d, *J* = 15.5 Hz, 1H, CH_2), 3.05 (s, 6H, 2 x CH_3), 2.68 (s, 3H, CH_3) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 174.2 (C=O), 159.1 (C^q_{aro}), 152.8 (C^q_{aro}), 151.2 (C^q_{aro}), 145.9 (C^q_{aro}), 133.3 (C^q_{aro}), 132.3 (CH_{aro}), 128.7 (CH_{aro}), 124.7 (CH_{aro}), 124.6 (CH_{aro}), 120.1 (C^q_{aro}), 97.3 (CH_{aro}), 67.8 (CH), 49.3 (CH_2), 38.3 (2 x CH_3), 24.7 (CH_3) ppm. HRMS (+ESI) calculated for $C_{17}H_{17}N_3O$ $[M+H]^+$: 280,1450, found 280.1448.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Figure S1. ^{1}H NMR spectrum of compound **4a**; Figure S2. ^{13}C NMR spectrum of compound **4a**; Figure S3. ^{1}H NMR spectrum of compound **4a'**; Figure S4. ^{13}C NMR spectrum of compound **4a'**; Figure S5. ^{1}H NMR spectrum of compounds **4b** + **4b'**; Figure S6. ^{13}C NMR spectrum of compounds **4b** + **4b'**;

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Figure S7. ^{1}H NMR spectrum of compounds **4c** + **4c'**; Figure S8. ^{13}C NMR spectrum of compounds **4c** + **4c'**; Figure S9. ^{1}H NMR spectrum of compound **4c'**; Figure S10. ^{13}C NMR spectrum of compound **4c'**; Figure S11. ^{1}H NMR spectrum of compounds **4d** + **4d'**; Figure S12. ^{13}C NMR spectrum of compounds **4d** + **4d'**; Figure S13. ^{1}H NMR spectrum of compounds **4e** + **4e'**; Figure S14. ^{13}C NMR spectrum of compounds **4e** + **4e'**; Figure S15. ^{1}H NMR spectrum of compound **4e**; Figure S16. ^{13}C NMR spectrum of compound **4e**; Figure S17. ^{1}H NMR spectrum of compound **4f**; Figure S18. ^{13}C NMR spectrum of compound **4f**; Figure S19. ^{1}H NMR spectrum of compound **4g**; Figure S20. ^{13}C NMR spectrum of compound **4g**; Figure S21. ^{1}H NMR spectrum of compound **4h**; Figure S22. ^{13}C NMR spectrum of compound **4h**; Figure S23. ^{1}H NMR spectrum of compound **4h'**; Figure S24. ^{13}C NMR spectrum of compound **4h'**; Figure S25. ^{1}H NMR spectrum of compound **4i**; Figure S26. ^{13}C NMR spectrum of compound **4i**; Figure S27. ^{1}H NMR spectrum of compound **4i'**; Figure S28. ^{13}C NMR spectrum of compound **4i'**; Figure S29. ^{1}H NMR spectrum of compounds **4j** + **4j'**; Figure S30. ^{13}C NMR spectrum of compounds **4j** + **4j'**; Figure S31. ^{1}H NMR spectrum of compounds **4k** + **4k'**; Figure S32. ^{13}C NMR spectrum of compounds **4k** + **4k'**; Figure S33. ^{1}H NMR spectrum of compound **4l**; Figure S34. ^{13}C NMR spectrum of compound **4l**; Figure S35. ^{1}H NMR spectrum of compo und **4l'**; Figure S36. ^{13}C NMR spectrum of compound **4l'**; Figure S37. ^{1}H NMR spectrum of compound **4m**; Figure S38. ^{13}C NMR spectrum of compound **4m**; Figure S39. ^{1}H NMR spectrum of compound **4n**; Figure S40. ^{13}C NMR spectrum of compound **4n**; Figure S41. ^{1}H NMR spectrum of compound **4n'**; Figure S42. ^{13}C NMR spectrum of compound **4n'**; Figure S43. ^{1}H NMR spectrum of compound **4o**; Figure S44. ^{13}C NMR spectrum of compound **4o**; Figure S45. ^{1}H NMR spectrum of compound **4o'**; Figure S46. ^{13}C NMR spectrum of compound **4o'**; Figure S47. ^{1}H NMR spectrum of compounds **4p** + **4p'**; Figure S48. ^{13}C NMR spectrum of compounds **4p** + **4p'**; Figure S49. ^{1}H NMR spectrum of compound **4q**; Figure S50. ^{13}C NMR spectrum of compound **4q**; Figure S51. ^{1}H NMR spectrum of compound **4q'**; Figure S52. ^{13}C NMR spectrum of compound **4q'**; Figure S53. ^{1}H NMR spectrum of compound **4r**; Figure S54. ^{13}C NMR spectrum of compound **4r**; Figure S55. ^{1}H NMR spectrum of compound **4r'**; Figure S56. ^{13}C NMR spectrum of compound **4r'**; Figure S57. ^{1}H NMR spectrum of compounds **4s** + **4s'**; Figure S58. ^{13}C NMR spectrum of compounds **4s** + **4s'**; Figure S59. ^{1}H NMR spectrum of compound **4t**; Figure S60. ^{13}C NMR spectrum of compound **4t**; Figure S61. ^{1}H NMR spectrum of compound **4t'**; Figure S62. ^{13}C NMR spectrum of compound **4t'**; Figure S63. ^{1}H NMR spectrum of compound **4u**; Figure S64. ^{13}C NMR spectrum of compound **4u**; Figure S65. ^{1}H NMR spectrum of compound **4u'**; Figure S66. ^{13}C NMR spectrum of compound **4u'**; Figure S67. ^{1}H NMR spectrum for product **6a**; Figure S68. ^{13}C NMR spectrum for product **6a**.

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