

Article

Iron/Rhodium Bimetallic Lewis Acid/Transition Metal Relay Catalysis for Alkynylation/Cyclotrimerization Sequential Reactions Toward Isoindolinone 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 pyridinoisoindolinone derivatives were obtained under mild conditions from easily available *N*-(propargyl) hydroxy amins, as the simplest *N*-acyliminium ion precursors, and several alkynes.

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



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1. Introduction

The development of novel methodologies that enable the 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 [1,2].

Isoindolinone frameworks, which are referred to 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 [3], MDM2-p53 inhibitory [4], antimicrobial [5], antiviral [6], PARP-1-inhibitory [7], histone deacetylase inhibitory [8], antihyperglycemic [9], antioxidant [10], anti-inflammatory [11], antifungal [12], antiparkinsonian [13], selective Nav1.7 blocking [14], antipsychotic [15], antihypertensive [16], anticancer [17], anesthetic [18], vasodilatory [19], and survival motor neuron protein-production-regulating activities (Figure 1) [20].

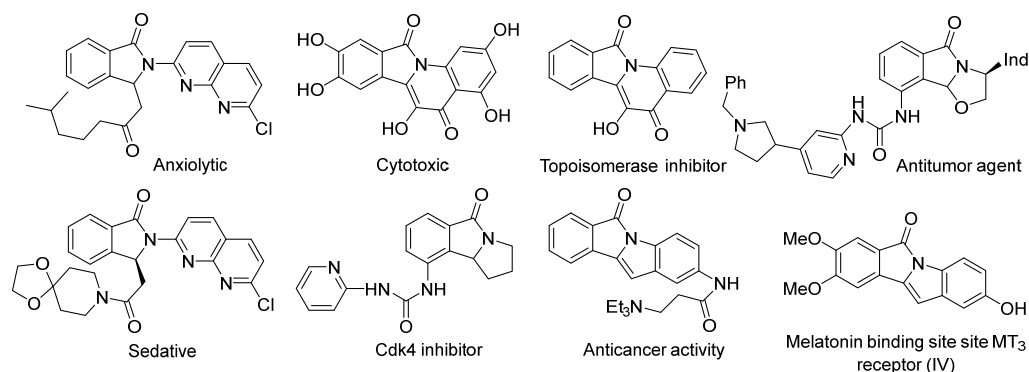
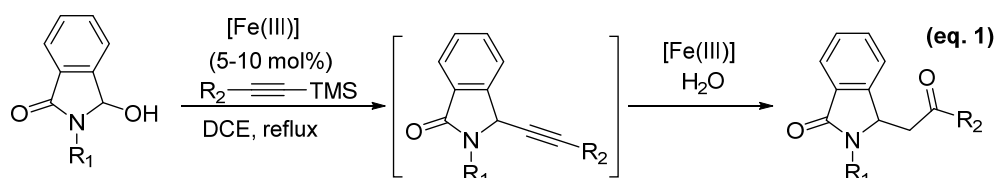


Figure 1. Examples of biologically active isoindolinone derivatives.

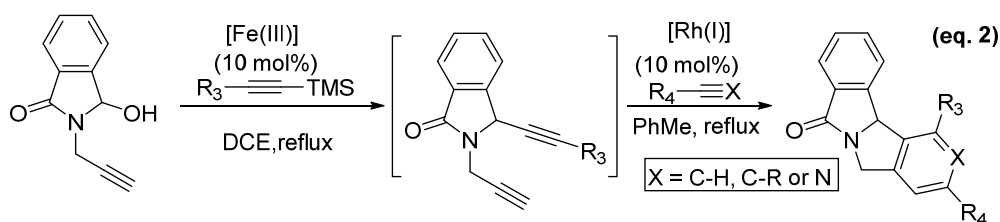
Owing to the wide spectrum of isoindolinone core biological activities, substantial efforts have been devoted to preparing this heterocyclic skeleton [21]. Among them are the functionalization of phthalimides or phthalimidines, and transition-metal-catalyzed C-C-bond-forming reactions involving, for example, C-H activation [22–24], cyclotrimerization [25], cross-coupling [26], and carbonylation [27] strategies. Despite the development of a plethora of methods, isoindolines [28]- and pyrrolopyridine [29]-fused isoindolinones were not yet reported.

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-economical source of electrophiles in comparison to the parent acetoxylactams, were used in these transformations (Scheme 1, eq. 1) [30].

a) Single Prior Example of Catalytic one-pot Alkynylation/Hydration sequences



b) This Work: Iron/Rhodium Catalytic one-pot Alkynylation/Cyclotrimerization sequences



Scheme 1. Current state-of-the-art C-alkynylation of *N*-acyliminium reactions (a, eq. 1) and this work (b, 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 [31]. Since Reppe's pioneering cyclotrimerization of alkynes in 1948, a myriad of efficient catalytic species (e.g., Rh [32], Ru [33], Ir [34], Co [35], Ni [36], Mo [37], Nb [38], Au [39], Pd [40], and Fe [41]) and coupling partners (e.g., olefins, nitriles, isocyanates, cyanamides, aldehydes, ketones, carbon dioxide, imines, and carbodiimides) were employed for this purpose.

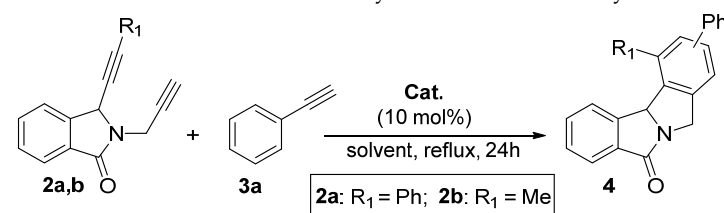
Inspired by our results on iron (III) *N,O*-cyclic acetal alkynylation, the advances and elegance of transition-metal-catalyzed [2+2+2] cyclotrimerization reactions, and the biological and synthetic importance of isoindolinone scaffolds, we became interested in developing a one-step synthetic route to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

2. Results

Cyclotrimerization of Dialkyne 2: 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, FeI₂, or Fe(OAc)₂ as precatalysts along with various ligands in the presence of Zn metal as a 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 N₂. ^[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(PPh₃)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 the Grubbs first-generation (Grubbs-I) catalyst (Table 1, entry 10) under Wilkinson conditions (**3a** (10 equiv.), PhMe reflux, argon) gave **4** in only 10% yield along with several side-products. Under the

Grubbs second-generation (Grubbs-II) catalyst (Table 1, 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, addition rates, numbers of equivalents of alkyne **3a**, and reaction times were examined. We found that the slow addition of alkyne **2b** to the reaction media for 2 h and then refluxing in PhMe for 1 h afforded the expected isoindolinones **4a/4a'** (**4a:4a'** = 60:40) in the highest yield (76%, entry 6).

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

The reaction scheme shows the cyclotrimerization of di-alkyne **2b** (a benzimidazole derivative with two terminal alkynes) and alkyne **3a** (phenylacetylene) in the presence of a Rhodium catalyst, $\text{RhCl(PPh}_3)_3$ (10 mol%), in a solvent at temperature T for time t . The products are two isomers of isoindolinones, **4a** and **4a'**, which are fused bicyclic systems with a benzimidazole core and a phenyl group.

Entry	Catalyst	Add of 3a (h)	t (h)	T (°C)	Yield (%) ^[b]	4a:4a' ^[c]
1	$\text{RhCl(PPh}_3)_3$	0.5	48	rt	29	55:45
2	$\text{RhCl(PPh}_3)_3$	0.5	0.3	reflux	47	60:40
3	$\text{RhCl(PPh}_3)_3$	1	0.5	reflux	55	58:42
4	$\text{RhCl(PPh}_3)_3$	2	2	reflux	68	60:40
5	$\text{RhCl(PPh}_3)_3$	3	2	reflux	60	57:43
6	$\text{RhCl(PPh}_3)_3$	2	1	reflux	76	60:40
7	$\text{RhCl(PPh}_3)_3$	2	1	80	64	57:43
8 ^[d]	$\text{RhCl(PPh}_3)_3$	2	1	reflux	20	60:40
9 ^[e]	$\text{RhCl(PPh}_3)_3$	2	1	reflux	43	60:40
10 ^[f]	$\text{RhCl(PPh}_3)_3$	2	1	reflux	55	58:42
11 ^[g]	$\text{RhCl(PPh}_3)_3$	2	1	reflux	60	56:44
12 ^[h]	$\text{RhCl(PPh}_3)_3$	2	1	reflux	52	57:43
13 ^[i]	$\text{RhCl(PPh}_3)_3$	2	1	reflux	45	57:43
14	Grubbs-I	2	1	reflux	20	60:40
15 ^[j]	Grubbs-I	2	1	reflux	15	58:42
16	Grubbs-II	2	1	reflux	30	60:40
17 ^[k]	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 (see Supplementary Materials). ^[d] Reaction was performed using 2 equiv. of alkyne **3a**. ^[e] Reaction was performed using 5 equiv. of alkyne **3a**. ^[f] Reaction was performed using 8 equiv. of alkyne **3a**. ^[g] Reaction was performed using 5 mmol% of the catalyst. ^[h] The reaction was tested in DCE. ^[i] The reaction was tested with $\text{RhCl(PPh}_3)_3$ in THF. ^[j] The reaction was tested with Grubbs-I in THF. ^[k] The reaction was tested with Grubbs-II in THF.

The use of the 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) catalysts (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, $\text{RhCl(PPh}_3)_3$ in DCE produced **4a/4a'** in 52% yield (Table 2, entry 10).

With the establishment of the optimized conditions, the substrate scope was examined (Table 3). 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 (Table 3, 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) (Table 3, entries 2 and 3). Substrates with an electron-withdrawing substituent on the aryl ring, such as *p*-NO₂ and *p*-Br, proved to also be suitable, furnishing **4d**/**4d'** and **4e**/**4e'** in 58% (**4d**:**4d'** = 61:39) and 75% (**4e**:**4e'** = 58:42) yields (Table 3, entries 4 and 5).

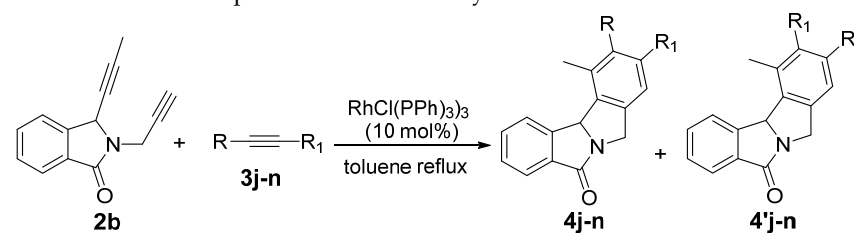
Table 3. Reaction scope of aromatic alkynes ^[a,b]

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(PPh₃)₃ (10 mol%) in PhMe (2 mL) for 2 h, and under reflux (monitored by TLC). ^[b] Ratio was determined by ¹H NMR of the crude materials (see Supplementary 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 (Table 3, entries 6 and 7). Heteroaryl-substituted alkyne (e.g., 2-thienyl-substituted) transformed to **4h**/**4h'** (**4h**:**4h'** = 54:46) successfully in 71% yield (Table 3, entry 8). The reaction was also applicable to internal aromatic alkynes, as exemplified by the synthesis of **4i**/**4i'** isoindolinone derivatives in 43% (**4i**:**4i'** = 63:37) isolated yield (Table 3, 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 Table 4.

Table 4. Reaction scope of non-aromatic alkynes ^[a].


Entry	Alkyne	t (h)	4:4' ^[b]	Yield (%) ^[c] of 4 + 4'
1	Bn- 3j	24	60:40	51
2	<i>t</i> -Bu- 3k	2	73:27	40
3	MeO ₂ C- 3l	8	55:45	54 ^[d]
4	MeO ₂ C- 3m -CO ₂ Me	10	100:00	45
5	3n	3	60:40	88 ^[d]

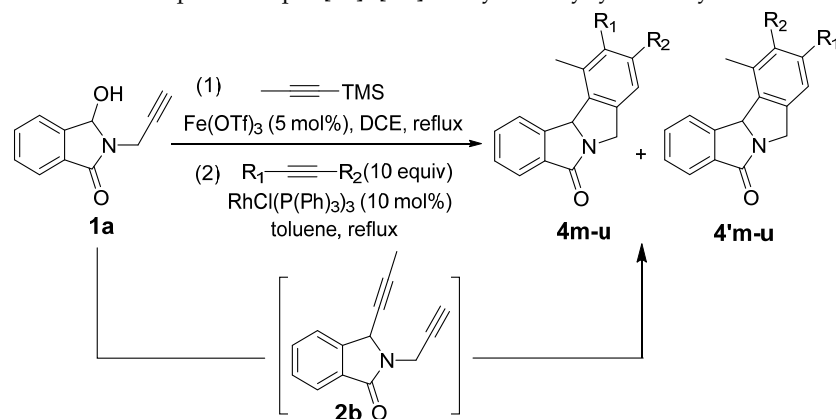
^[a] Standard reaction conditions: **2b** (0.5 mmol) in PhMe (1 mL), a portion-wise addition of a mixture of alkyne **3** (5 mmol) and RhCl(PPh₃)₃ (10 mol%) in PhMe (2 mL) for 2 h, and under reflux (monitored by TLC). ^[b] Ratio was determined by ¹H NMR of the crude materials (see Supplementary Materials). ^[c] Isolated product yield. ^[d] Separable through column chromatography.

The reaction with benzylacetylene **3j** provided isoindolinones **4j/4j'** in 51% (**4j:4j'** = 60:40) yield (Table 4, entry 1). Similarly, diyne **2b** reacted with *tert*-butylacetylene **3k** to produce **4k/4k'** (**4k:4k'** = 73:27) in 40% yield (Table 4, 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 (Table 4, entry 3). The reaction with dimethyl acetylenedicarboxylate (DMAD) **3m** gave isoindolinone **4m** in 45% yield (Table 4, 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) (Table 4, 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 (monitored by TLC)) followed by a portion-wise addition of a solution of alkyne **3b** (10 equiv.) and 10 mol% of RhCl(PPh₃)₃ in DCE (2 mL) for 2 h, isoindolinones **4a/4a'** were isolated after 1 h of reflux (monitored by 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.

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 (monitored by TLC), solvent removed in vacuo, a portion-wise addition of alkyne **2b** solution (10 equiv.) and 10 mol% of RhCl(PPh₃)₃ in 2 mL of PhMe (for 2 h), under reflux 1 h), produced isoindolinones **4a/4a'** in a 60% yield (Table 5, entry 1).

Table 5. 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 ^[d]
3		3	51:41	70
4		3	53:47	68 ^[d]
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 ^[d]
12		3	58:42	82 ^[d]
13		7	67:33	72 ^[d]

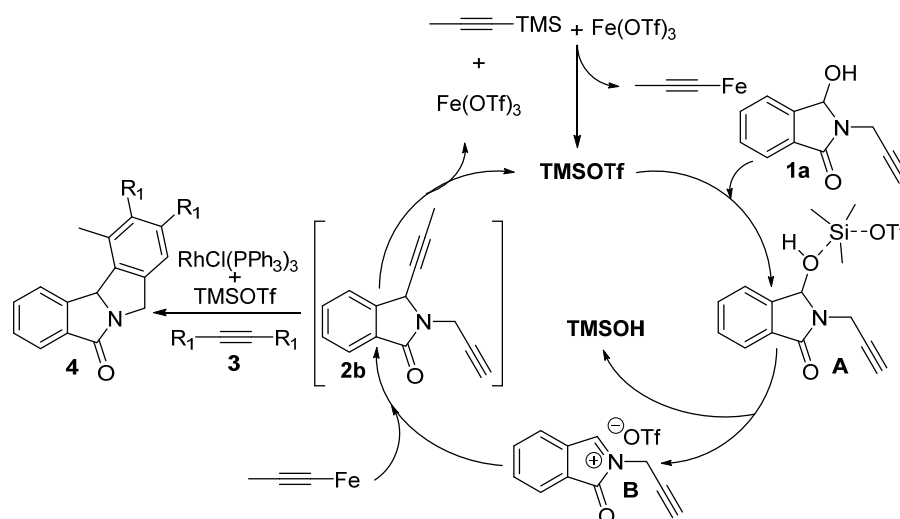
^[a] Standard reaction conditions: hydroxylactam **1a** (0.5 mmol), propyne-TMS (0.5 mmol), Fe(OTf)_3 (10 mmol%), DCE (2 mL), under reflux, 4 h, a portion-wise addition of a mixture of alkyne **3** (5 mmol) and RhCl(PPh)_3 (10 mol%) in PhMe (2 mL) for 2 h and refluxed (monitored by TLC). ^[b] The ratio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

Having established the optimal reaction conditions, we inspected the scope of the one-pot bimetallic sequence. As depicted in Table 5, 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, Table 5, 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 (Table 5, entries 6 and 7). Similarly, the reaction of **2b** with DMAD **3m** afforded the cyclotrimerization product **4m** in a moderate yield of 35% (Table 5, 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 (Table 5, 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 (Tables 3 and 4), demonstrating the formation of mixtures of *ortho* and *meta* isoindolinones in varying ratios.

3. Mechanistic Study

The use of $\text{Fe}(\text{OTf})_3$ and the 1-TMS-propyne in the alkynylation reactions may generate TMSOTf, TMSOH, or TfOH (generated by $\text{Fe}(\text{OTf})_3$ hydrolysis) (Scheme 2), highlighting the possibility that the in situ-generated TMSOTf, TMSOH, and TfOH may catalyze or co-catalyze the [2+2+2] reaction [42–44]. 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.

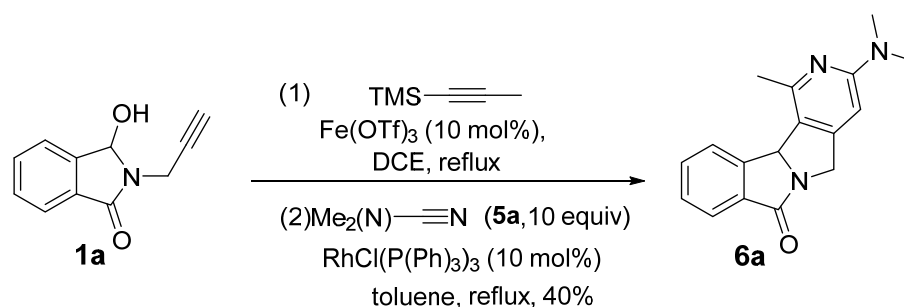


Scheme 2. Mechanistic study to reveal the identity of the catalytic species.

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 $\text{RhCl}(\text{PPh}_3)_3$ 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 + $\text{RhCl}(\text{PPh}_3)_3$. The treatment of **2b** with **3d** or **3g** under a mixture of 10 mol% of (TMSOTf + $\text{RhCl}(\text{PPh}_3)_3$) 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% (Table 3, entry 4) for **4d/4d'** and 81% vs. 83% (Scheme 2, entry 7) for **4g**), and 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 $\text{RhCl}(\text{PPh}_3)_3/\text{TMSOTf}$ 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 [45], we also evaluated the one-pot alkynylation/cyclotrimerization reaction in the construction of novel pyridine-fused isoindolinones [46–52]. A nitrile derivative **5a** was subjected to our protocol under the standard reaction conditions (Scheme 3). The pyridine derivative **6a** was obtained as a single regioisomer and isolated in an acceptable yield of 40%.



Scheme 3. Cyclotrimerization of nitriles and preparation of pyridine **6a**.

4. Conclusions

In conclusion, we took advantage of the different reactivities of iron and rhodium, and of 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 alkynylation step, and then, in a one-pot procedure, rhodium (I) was used to ensure the [2+2+2] cycloaddition reaction. Additional studies are currently under development in our laboratory to extend the scope and utility of this Fe/Rh-catalyzed cascade reaction.

5. Experimental Section

General Information. ^1H NMR spectra were recorded at 300 MHz with a Bruker AvanceTM 300 spectrometer and data are reported as chemical shift (δ) in ppm, multiplicity (s = singlet, d = doublet, t = triplet, b = broad, m = multiplet), and coupling constants J in Hz. ^{13}C NMR spectra were recorded at 75 MHz using broadband proton decoupling and the data are reported as chemical shift (δ) in ppm. High-resolution mass spectra (HRMS) were measured on the Agilent 6530 Q-ToF MS system (Les Ulis, France). FTIR spectra were recorded with a PerkinElmer Frontier (Waltham, MA, USA). The starting materials were purchased from commercial sources such as Sigma-Aldrich (Saint Louis MO, USA), Fisher scientific (Waltham, MA, USA), and TCI (Palo Alto, CA, USA). All solvents were dried and freshly distilled by refluxing over CaH_2 . Flash chromatography purifications were performed on an Interchim Puriflash (Puriflash columns 50 μ) (Montluçon, France) using a cyclohexane/ethyl acetate eluent system.

Representative Procedure for the Rhodium(I)-Catalyzed Cyclotrimerization of Di-alkynes: To a solution of alkynes **3a–w** (2.3 mmol, 10 eq) and $\text{RhCl}(\text{PPh}_3)_3$ (0.023 mmol, 0.1 eq) in toluene (4 mL), we slowly added 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**.

5.1. 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.

5.1.1. 2-((1-Methyl-7-oxo-7,11b-dihydro-5H-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 ($\nu_{\max}$ cm^{-1}): 1687; ^1H 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, m, 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, 168.1, 145.0, 142.6, 137.1, 136.5, 134.2, 133.9, 133.6, 132.2, 132.1, 130.0, 128.8, 125.1, 124.7, 123.5, 121.2, 69.4, 49.3, 41.3, 21.6 ppm. HRMS (+ESI) calculated for $\text{C}_{25}\text{H}_{18}\text{N}_2\text{O}_3$ $[\text{M} + \text{H}]^+$: 395.1390, found 395.1395.

5.1.2. 2-((1-Methyl-7-oxo-7,11b-dihydro-5H-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 ($\nu_{\max}$ cm^{-1}): 1687; ^1H 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, 168.2, 145.5, 141.3, 138.1, 134.2, 134.2, 134.1, 133.6, 132.2, 132.2, 132.1, 129.9, 128.8, 125.2, 124.7, 123.5, 121.0, 69.8, 49.5, 39.3, 18.5 ppm. HRMS (+ESI) calculated for $\text{C}_{25}\text{H}_{18}\text{N}_2\text{O}_3$ $[\text{M} + \text{H}]^+$: 395.1390, found 395.1395.

Representative Procedure for the Iron(III)/Rhodium(I)-Catalyzed One-Pot Alkynylation/Cyclotrimerization of *N,O*-Acetals: Commercially available $\text{Fe}(\text{OTf})_3$ (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 preheated oil bath at reflux and magnetically stirred. The progress of the reaction was monitored by TLC. The solvent was evaporated 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 $\text{RhCl}(\text{PPh}_3)_3$ (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).

5.2. Synthesis and Characterization of Compounds **4o/4o'**

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

5.2.1. 11-Methyl-9-(thiophen-3-yl)-7,11b-dihydro-5H-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 ($\nu_{\max}$ cm^{-1}): 1683; ^1H NMR (300 MHz,

CDCl₃): 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, CH₂), 4.49 (d, J = 15.0 Hz, 1H, CH₂), 2.70 (s, 3H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ_C 174.0, 145.2, 142.7, 141.7, 136.5, 135.7, 133.9, 133.7, 132.2, 128.8, 128.0, 126.5, 126.4, 125.2, 124.7, 120.8, 119.0, 69.5, 49.4, 21.8 ppm. HRMS (+ESI) calculated for C₂₀H₁₅NOS [M + H]⁺: 318.0947, found 318.0947.

5.2.2. 11-Methyl-10-(thiophen-3-yl)-7,11b-dihydro-5H-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 ($\nu_{\max}$ cm^{−1}): 1696; ¹H NMR (300 MHz, CDCl₃): 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, CH₂), 4.50 (d, J = 15.0 Hz, 1H, CH₂), 2.63 (s, 2H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ_C 174.1, 145.5, 141.5, 140.9, 138.1, 136.9, 133.7, 132.2, 131.7, 130.4, 129.1, 128.8, 125.4, 125.3, 124.7, 123.2, 120.8, 69.9, 49.5, 20.2 ppm. HRMS (+ESI) calculated for C₂₀H₁₅NOS [M + H]⁺: 318.0947, found 318.0947.

5.3. 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 ($\nu_{\max}$ cm^{−1}): 1695; ¹H NMR (300 MHz, CDCl₃): 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, CH₂), 4.34 (d, J = 15.5 Hz, 1H, CH₂), 3.05 (s, 6H, 2 × CH₃), 2.68 (s, 3H, CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ_C 174.2, 159.1, 152.8, 151.2, 145.9, 133.3, 132.3, 128.7, 124.7, 124.6, 120.1, 97.3, 67.8, 49.3, 38.3, 24.7 ppm. HRMS (+ESI) calculated for C₁₇H₁₇N₃O [M + H]⁺: 280.1450, found 280.1448.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/catal15020151/s1>.

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