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Indium(III)-Catalyzed Stereoselective Synthesis of Tricyclic Frameworks by Cascade Cycloisomerization Reactions of Aryl 1,5-Enynes

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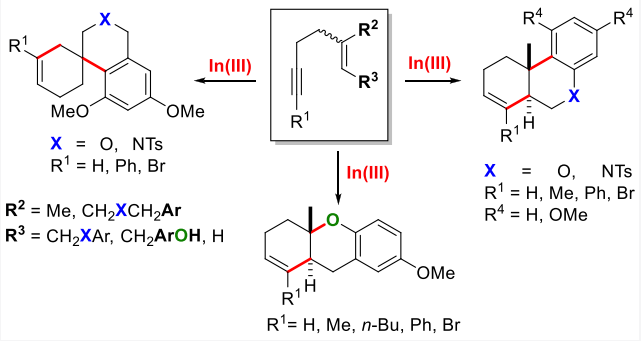
ABSTRACT: The indium(III)-catalyzed cascade cycloisomerization reaction of 1,5-enynes with pendant aryl nucleophiles is reported. The reaction proceeds in cascade under mild reaction conditions, using InI_3 (5 mol %) as a catalyst with a range of 1,5-enynes furnished with aryl groups (phenyl and phenol) at alkene (*E* and Z isomers) and with terminal and internal alkynes. Using 1-bromo-1,5-enynes, a one-pot sequential indium-catalyzed cycloisomerization and palladium-catalyzed cross-coupling with triorganoindium reagents were developed. The double cyclization is stereospecific and operates *via* a biomimetic cascade cation-olefin through 1,5-enyne cyclization (*6-endo-dig*) and subsequent C−C hydroarylation or C−O phenoxycyclization. Density functional theory (DFT) computational studies on 1,5-enynyl aryl ethers support a two-step mechanism where the first stereoselective 1,5-enyne cyclization produces a nonclassical carbocation intermediate that evolves to the tricyclic reaction product through a S_EAr mechanism. Using this approach, a variety of tricyclic heterocycles such as benzo[*b*]chromenes, phenanthridines, xanthenes, and spiroheterocyclic compounds are efficiently synthesized with high atom economy.



INTRODUCTION

The design of synthetic methodologies based on catalytic cascade reactions constitutes an ideal tool for the construction of complex molecules with high chemo-, regio-, and stereoselectivity.[1] In particular, catalytic cascade cycloisomerization reactions allow the synthesis of a large structural diversity of molecules under complete atom economy and mild reaction conditions. As an example, cascade polyene cyclizations are one of the most impressive biosynthetic transformations known, and their chemical emulation represents a major challenge in modern synthetic chemistry.[2] Usually, these transformations involve the epoxide activation in a polyenic compound using oxophilic Lewis acids under stoichiometric or catalytic conditions.[3] Alternatively, electrophilic alkyne activation under metal catalysis has been recently envisaged as a different synthetic approach to promote catalytic cascade polyenynic π-cyclizations.[4] The catalytic electrophilic activation of alkynes promotes the addition of nucleophiles and allows the formation of new carbon−carbon and carbon−heteroatom bonds in an intermolecular and intramolecular manner. Although this methodology has been associated with the use of carbophilic late precious transition metals such as platinum[5] or gold[6] as catalysts, main group metals such as gallium[7] or indium[8] have been shown as valuable alternatives (Scheme 1a).

Indium(III) is a soft Lewis acid that exhibits a dual-mode catalytic activity as σ-acid and π-acid, enabling both the electrophilic activation of carbon−heteroatom and to carbon−carbon unsaturated bonds.[9] In addition, reactions involving indium are used to provide high chemoselectivity and substantial economical, environmental, and safety advantages.[10] Along the years, these attractive chemical properties have been exploited in classical synthetic transformations as oxophilic Lewis acid either by using stoichiometric or catalytic conditions.[11] Recent contributions have demonstrated the synthetic utility of indium(III) salts as carbophilic π-acid catalysts in the electrophilic activation of alkynes.[12]

Metal-catalyzed 1,*n*-enyne cycloisomerization reactions constitute a straightforward methodology for the synthesis of polycyclic structures.[13] In particular, gold(I)-catalyzed cycloisomerization reactions of functionalized 1,5- and 1,6-enynes

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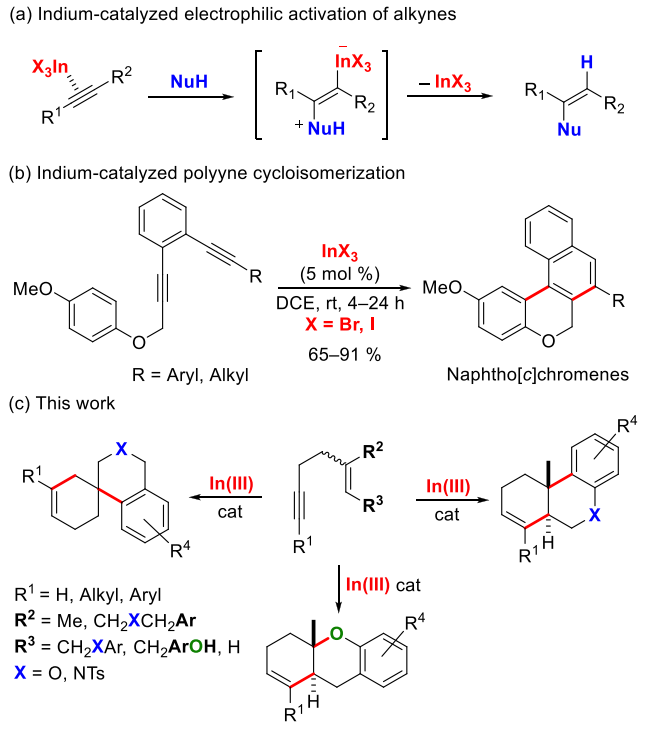
Scheme 1. Indium(III)-Catalyzed Electrophilic Activation of Alkynes



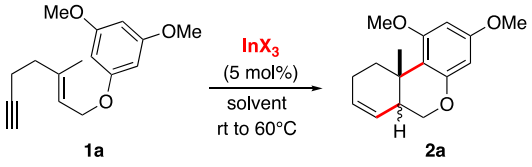
have been widely explored for the synthesis of polycyclic organic compounds.[14] On the other hand, indium(III)-catalyzed enyne cycloisomerization reactions were first reported by Chatani,[15] and more recently, Corey described the stereoselective synthesis of complex chiral polycyclic molecules by cascade cycloisomerization of chiral aryl polyenynes under indium(III) catalysis.[16a] In this contribution, the catalytic activity of In(III) as π-acid for the electrophilic activation of alkynes is remarked and attributed to the vacant 5s and 5p orbitals, which might lead to coordinate the C−C triple bond by bidentate complexation. Later on, Corey also reported the superior catalytic activity of diiodoindium(III) cation (InI_2^+), generated by the addition of Ag(I) salts to InI_3.[16b]

As part of a long-term research on indium chemistry,[17] our group has recently reported intramolecular hydroarylation and hydroalkoxylation reactions and sequential indium-catalyzed polyyne reactions under indium(III) catalysis (Scheme 1b).[18] Herein, we report the In(III)-catalyzed cascade cycloisomerization reactions of 1,5-enynes (*E* and *Z* isomers) furnished with aryl nucleophiles and density functional theory (DFT) studies about the mechanism of the reaction and the nature of the organoindium intermediates involved (Scheme 1c).

RESULTS AND DISCUSSION

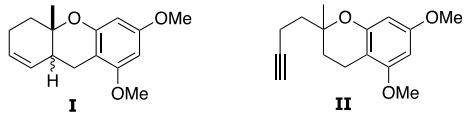
Our investigation started with the cycloisomerization reaction of (*E*)-1,5-enynyl aryl ether **1a** under In(III) catalysis. This substrate was chosen to measure the indium alkynophilicity, the regioselectivity of the reaction (*6-endo* vs *5-exo*), and to establish comparisons with other metal catalysts.[14a] In our first experiments, we found that the treatment of (*E*)-**1a** with 5 mol % InI_3 in 1,2-dichloroethane (DCE) at 60 °C resulted in the stereoselective formation of the tricyclic compound **2a** in 58% yield after 5 h as the only isolated product as a separable mixture of diastereoisomers (*cis*/*trans* = 25:75, Table 1, entry 1).

Table 1. Indium-Catalyzed Reactions with (*E*)-1,3-Dimethoxy-5-[(3-methylhept-2-en-6-yn-1-yl)oxy]benzene (1a)



entry	InX_3	solvent	T (°C)	t (h)[a]	yield (%)[b]	**2a** (cis/trans)[c]
1	InI_3	DCE	60	5	58	25:75
2	$InBr_3$	DCE	60	20	53	33:67
3	$InCl_3$	DCE	60	48	[d]	
4	InI_3[e]	DCE	60	24	55	31:69
5	InI_3	toluene	60	2	65	11:89
6	InI_3[f]	toluene	rt	6	62	20:80
7	InI_3[f]	DCM	rt	7	63	19:81
8	InI_3[f]	DCM	−20	24	[d]	
9	InI_3[g]	DCE	60	5	72[h]	
10	$In(NTf_2)_3$	DCE	60	5	63[i]	
11	$In(OTf)_3$	DCE	60	24	[j]	
12	$In(acac)_3$	DCE	60	48	[d]	

[a]Monitored by thin-layer chromatography (TLC). [b]Isolated yield. [c]Determined by gas chromatography−mass spectrometry (GCMS). [d]No reaction observed. [e]2 mol %. [f]20 mol %. [g]$AgSbF_6$ (5 mol %) as a cocatalyst. [h]Mixture of products **I**:**2a** (4:1 ratio). [i]Compound **II** was isolated. [j]Decomposition.



Alternatively, the use of $InBr_3$ (5 mol %) also provided **2a** in similar yield and diastereoselectivity, whilst $InCl_3$ (5 mol %) resulted to be ineffective (entries 2 and 3, respectively). In all cases, *trans*-fused **2a** was identified as the major diastereoisomer and its formation can be explained by a double regioselective *6-endo-dig*/*endo-trig* cyclization in cascade.

The stereoselectivity of this In(III)-catalyzed 1,5-enyne cycloisomerization was then studied under different reaction conditions. In this endeavor, we found that the reaction also takes place with 2 mol % of InI_3 in similar stereoselectivity but longer reaction times (55%, *cis*/*trans* = 31:69, entry 4). Interestingly, the yield, stereoselectivity, and reaction time were slightly improved using toluene as a solvent (65%, *cis*/*trans* = 11:89, entry 5). The reaction also proceeds at room temperature using 20 mol % of InI_3 in toluene or dichloromethane (DCM) with similar results (entries 6 and 7), but no reaction was observed at −20 °C (entry 8). Surprisingly, the combination of InI_3 (5 mol %) with the halide abstractor $AgSbF_6$ (5 mol %) to generate the diiodonium cation (InI_2^+) gave a new major tricyclic product (**I**) concomitant with **2a** (**I**:**2a** = 4:1 ratio) as a separable mixture in a combined 72% isolated yield (entry 9). The formation of compound **I**, as a mixture of *cis*/*trans* (11:89) diastereoisomers, can be explained by ether cleavage, Friedel−Crafts *C*-alkylation, and 1,5-enyne phenoxycyclization reaction. In a similar pathway, treatment with $In(NTf_2)_3$ (5 mol %) resulted in the formation of the bicyclic compound **II** (63% yield, entry 10) with an alkene phenoxycyclization as the last step. The use of $In(OTf)_3$ as a catalyst resulted in decomposition (entry 11). No reaction was observed employing $In(acac)_3$ as the catalyst, recovering the starting 1,5-enyne **1a** (entry 12). In

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this optimization process, the important role of the catalyst counteranion is noteworthy, confirming InI_3 as the most efficient π-catalyst. Although different solvents can be used, toluene was the solvent of choice for this 1,5-enyne cyclization. The high chemoselectivity of InI_3 in the electrophilic activation of the alkyne over the ether cleavage is remarkable.

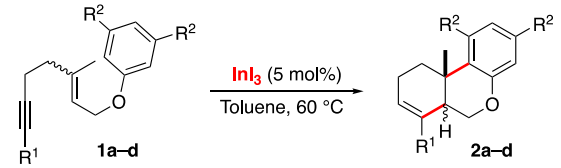
To further study the chemo-, regio-, and stereoselectivity and access to novel functionalized benzo[*b*]chromenes, our investigation was extended to 1,5-enynes functionalized at the arene and alkyne units and with different alkene geometries. Under the previously optimized reaction conditions, we were pleased to find that the reaction of 1,5-enyne (*E*)-**1b** furnished with a methyl group at the terminal alkyne proceeded successfully to give *trans*-**2b** in 68% yield as a separable diastereoisomeric mixture (*cis*/*trans* = 22:78, Table 2, entry 2). This synthetic transformation was more efficient and selective than using Hg(II), probably due to the softer Lewis acid character of In(III).[14a] Interestingly, the reaction using 1-bromo-1,5-enyne (*E*)-**1c** also provided 7-bromobenzo[*b*]-chromene *trans*-**2c** diastereoselectively in good yield (62%, *cis*/*trans* = 27:73, entry 3). The synthesis of *trans*-**2c** should allow access to a variety of substituted benzo[*b*]chromenes by metal-catalyzed cross-coupling reactions.[17]

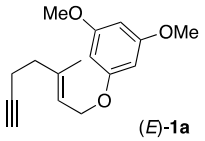
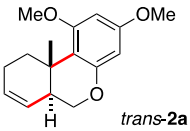
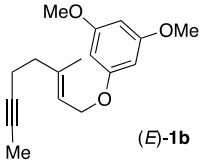
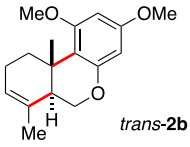
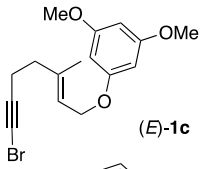
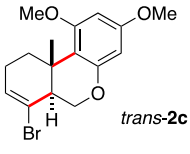
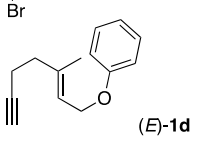
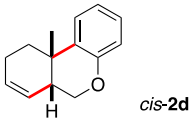
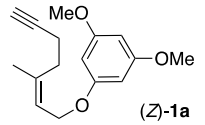
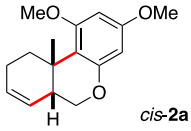
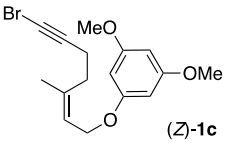
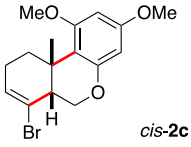
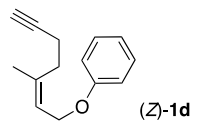
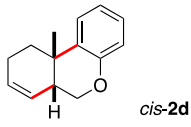
The role of electronic effects was examined using phenyl 1,5-enynyl ether (*E*)-**1d**. Interestingly, under the previously developed reaction conditions, the double cycloisomerization proceeded with complete stereochemical inversion giving rise to the *cis*-benzo[*b*]chromene *cis*-**2d** as a single diastereoisomer by ^{1}H NMR (61% yield, Table 2, entry 4). The isomerization suggests a two-step mechanism, where the lower nucleophilicity of the phenyl group facilitates the stereochemical inversion after the first *6-endo-dig* cycloisomerization reaction to produce the most thermodynamically stable diastereoisomer.

Prompted by these interesting results, we studied the influence of alkene stereochemistry on the reactivity, regio-, and stereoselectivity. Previous metal-catalyzed 1,5-enyne cycloisomerization reactions have shown a divergent outcome based on the alkene geometry.[14c] In our case, the In(III)-catalyzed cycloisomerization with (*Z*)-**1a** also proceeded with *6-endo* regioselectivity without isomerization providing the *cis*-**2a** as a single diastereoisomer as determined by ^{1}H NMR in 64% yield (Table 2, entry 5). The same regiochemistry and stereochemical outcomes were observed using 1-bromo-1,5-enyne (*Z*)-**1c** (entry 6). Interestingly, the reaction with 1,5-enyne (*Z*)-**1d** also proceeded with full retention of the stereochemistry to obtain *cis*-**2d** as the only diastereoisomer as established by ^{1}H NMR (entry 7). These results point out at least three reactivity patterns: the reaction is stereospecific through a two-step mechanism; electronic effects affect the stereochemical outcome; and the cis stereoisomer is thermodynamically more favorable.

After these interesting results, we explored the reaction with 1,5-enynyl phenyl *N*-tosylamines, substrates of interest for the synthesis of nitrogen heterocycles such as phenanthridines or indoles. In this venture, we found that the reaction of 3,5-dimethoxyphenyl 1,5-enynyl *N*-tosylamine (*E*)-**3a** with InI_3 (5 mol %) in toluene at 60 °C gave the phenanthridine *trans*-**4a** in 90% yield in just 2 h as the only diastereoisomer detected by ^{1}H NMR (Table 3, entry 1). Analogously, the reaction with 1,5-enynes (*E*)-**3b** and (*E*)-**3c** furnished with a methyl and a phenyl group at the alkyne afforded phenanthridines *trans*-**4b** and *trans*-**4c** stereoselectively as the only isolated products in 85 and 82% yield (Table 3, entries 2 and 3, respectively). Furthermore, the

Table 2. Indium-Catalyzed Reactions with 1,5-Enynyl Aryl Ethers 1a−d[c]



Entry	Enyne	Product[a]	Yield (%)[b]	*cis*:*trans*[c]
1	 (*E*)-**1a**	 *trans*-**2a**	65	11:89
2	 (*E*)-**1b**	 *trans*-**2b**	68	22:78
3	 (*E*)-**1c**	 *trans*-**2c**	62	27:73
4	 (*E*)-**1d**	 *cis*-**2d**	61	> 95:5
5	 (*Z*)-**1a**	 *cis*-**2a**	64	> 95:5
6	 (*Z*)-**1c**	 *cis*-**2c**	57	> 95:5
7	 (*Z*)-**1d**	 *cis*-**2d**	65	> 95:5

[a]Major isolated diastereomer. [b]Isolated yield. [c]Measured by ^{1}H NMR.

reaction with 1-bromo-1,5-enyne (*E*)-**3d** led to the 7-bromo-hexahydrophenanthridine *trans*-**4d** in 73% yield (entry 4). Although no isomerization was detected with these 1,5-enynes, the reaction of (*E*)-1,5-enyne **3e**, furnished with an unsubstituted phenyl group, proceeded with complete inversion and the *cis*-**4e** was obtained as a single diastereoisomer (49% yield, entry 5). As previously reported, the isomerization can be explained by a stepwise mechanism where after the first *6-endo-dig* cyclization, the synthetic intermediate could isomerize toward the most thermodynamically stable polycyclic compound. Therefore, we can conclude that aryl 1,5-enynes **3a−d** furnished with the *N*-tosylamine moiety are more reactive than

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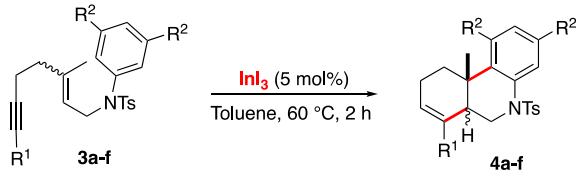
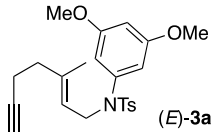
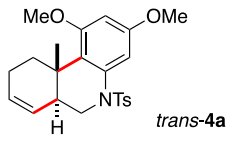
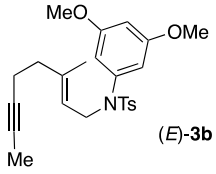
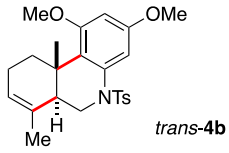
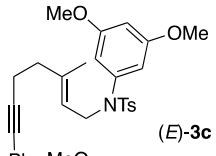
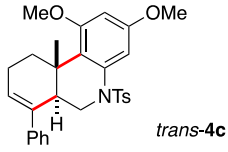
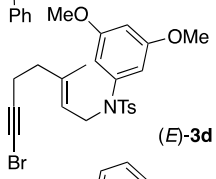
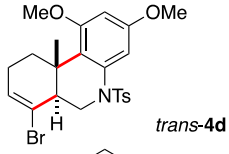
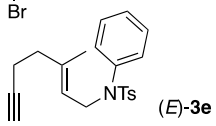
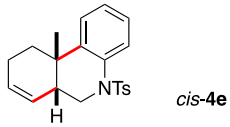
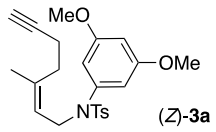
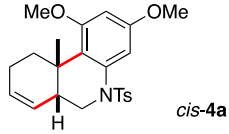
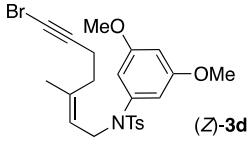
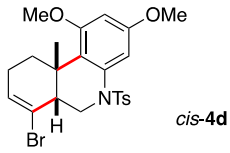
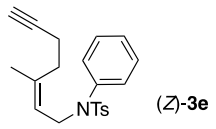
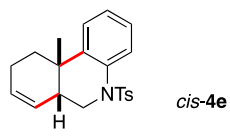
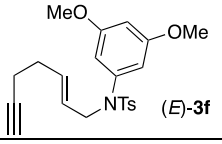
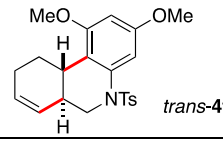
Table 3. Indium-Catalyzed Reactions of 1,5-Enynyl Aryl *N*-Tosylamines 3a−f



Entry	Enyne	Product	Yield (%)[a]
1	 (*E*)-**3a**	 *trans*-**4a**	90
2	 (*E*)-**3b**	 *trans*-**4b**	85
3	 (*E*)-**3c**	 *trans*-**4c**	82
4	 (*E*)-**3d**	 *trans*-**4d**	73
5	 (*E*)-**3e**	 *cis*-**4e**	49
6	 (*Z*)-**3a**	 *cis*-**4a**	88
7	 (*Z*)-**3d**	 *cis*-**4d**	72
8	 (*Z*)-**3e**	 *cis*-**4e**	63
9	 (*E*)-**3f**	 *trans*-**4f**	79

[a]Isolated yield.

the ethers **1a−d** and the cycloisomerization reaction takes place with complete retention of the alkene configuration.

The stereospecificity of the cycloisomerization reaction was also explored with the *Z*-alkene analogues. In this case, we observed that the reaction with 1,5-enyne (*Z*)-**3a** afforded phenanthridine *cis*-**4a** as a single diastereoisomer in 88% yield (entry 6). Analogously, the reaction with bromoalkyne (*Z*)-**3d** provided phenanthridine *cis*-**4d** in 72% yield (entry 7) and the reaction with 1,5-enyne (*Z*)-**3e** without methoxy groups at the phenyl unit gave *cis*-**4e** in 63% yield (entry 8). As previously observed with the 1,5-enynyl ether (*Z*)-**1d**, in this case, the reaction proceeded with full retention of the alkene stereochemistry. Finally, we also explored the reaction with (*E*)-1,5-enyne **3f**, where the alkene moiety is disubstituted. Gratifyingly, the cascade cycloisomerization proceeded with complete regio- and stereospecificity to afford *trans*-**4f** in 79% yield as the only detected and isolated product.[19] This result demonstrates that the cascade cycloisomerization reaction is not limited to trisubstituted alkenes and resembles a biomimetic cascade olefin process.

The synthetic utility of the In(III)-catalyzed double cycloisomerization was then explored using 1,5-enynes equipped with a phenol moiety. Although InI_3 showed as an efficient catalyst for the synthesis of benzo[*b*]furans from *ortho*-alkynylphenols,[18d] this cascade cycloisomerization process found some synthetic limitations using other transition metal catalysts.[20] In addition, the regioselective phenoxycyclization should provide access to xanthenes, a tricyclic skeleton of a relevant class of natural products.[21]

Using 1,5-enyne (*E*)-**5a** as a model substrate,[20] we found that InI_3 (5 mol %) catalyzes the double cycloisomerization reaction in toluene at room temperature to afford the tricyclic *6-endo-dig/endo-trig* product *trans*-**6a** in 86% isolated yield as a single diastereoisomer in 5 h (Table 4, entry 1). It is interesting to note the higher reactivity exhibited compared to the previous aryl 1,5-enynyl ethers **1a−d** and *N*-tosylamines **3a−f** as well as the chemical compatibility of the In(III) catalysis with the free hydroxyl group of the phenol. Furthermore, the reaction with (*Z*)-**5a** provided the cis-fused xanthene *cis*-**6a** in an excellent yield of 87% as the only isolated product (entry 2). These experimental results could be explained either by a stereospecific concerted or by a stepwise mechanism.

As the next step, we also tested the reaction of aryl 1,5-enynes **5** substituted at the alkyne. However, the complex synthesis of these substrates led us to consider a sequential procedure based on indium-catalyzed cascade cycloisomerization of the 1-bromo-1,5-enyne (*E*)-**5b**[14c] and subsequent functionalization by the cross-coupling reaction. With this approach in mind, we found that the reaction of 1-bromo-1,5-enyne (*E*)-**5b** and (*Z*)-**5b** with InI_3 (5 mol %) results in a stereospecific manner, affording the expected 1-bromo-tetrahydroxanthenes *trans*-**6b** and *cis*-**6b** in 89 and 92% yield, respectively, as the only isolated products (Table 4, entries 3 and 4).

Having demonstrated the feasibility of both alkene isomers of 1-bromo-1,5-enyne **5b** in the double cycloisomerization reaction, we assayed the one-pot sequential indium(III)-catalyzed 1,5-enyne cyclization and palladium-catalyzed cross-coupling reaction using triorganoindium reagents.[17,22] Gratifyingly, the treatment of (*E*)-**5b** with InI_3 (5 mol %) in toluene at room temperature followed by addition of a solution of Ph_3In (70 mol %) and $Pd(PPh_3)_4$ (5 mol %) in tetrahydrofuran (THF) at 80 °C afforded the 4-phenyltetrahydroxhantene *trans*-**6c** in 76% yield (Scheme 2). The sequential protocol using Me_3In and *n*-Bu_3In also gave the xanthene derivatives *trans*-**6d** and *trans*-**6e** in 83 and 81% yield, respectively. These results show the versatility of the In-catalyzed cascade cycloisomerization

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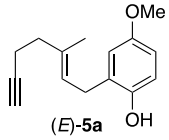
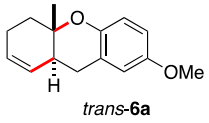
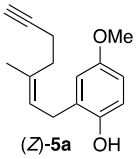
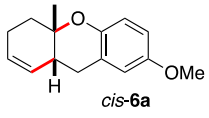
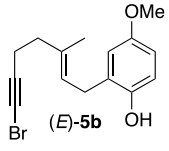
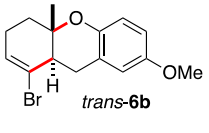
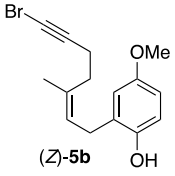
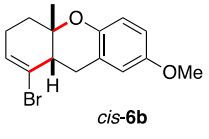
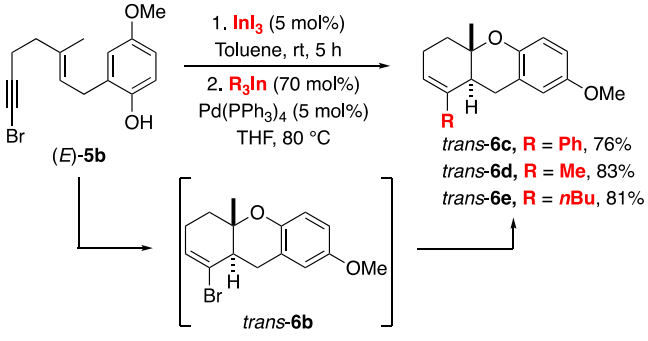
Table 4. Indium-Catalyzed Phenoxycyclization of 1,5-Enynes 5a–b

Entry	1,5-enyne	Product	Yield (%)[a]
1	 (*E*)-**5a**	 *trans*-**6a**	86
2	 (*Z*)-**5a**	 *cis*-**6a**	87
3	 (*E*)-**5b**	 *trans*-**6b**	89
4	 (*Z*)-**5b**	 *cis*-**6b**	92

[a]Isolated yield.

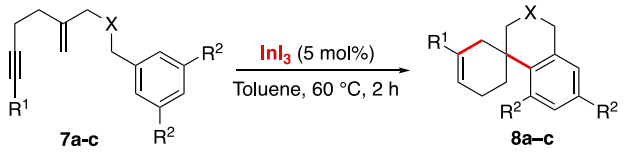
Scheme 2. Sequential One-Pot In-Catalyzed 1,5-Enyne Cycloisomerization and Pd-Catalyzed Cross-Coupling Reaction with (*E*)-5b

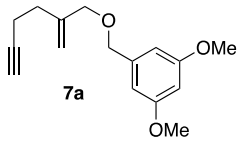
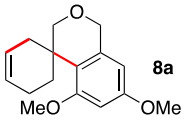
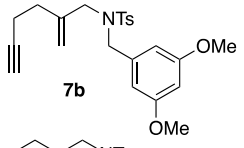
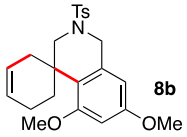
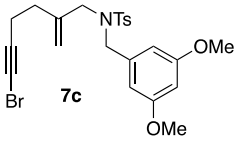
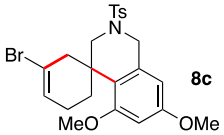
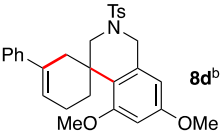


reaction using aryl 1,5-enynes and its chemical compatibility with Pd-catalyzed cross-coupling reactions.

Finally, the indium-catalyzed cycloisomerization reaction of 1,5-enynes with aryl nucleophiles at the C-5 alkene unit (**7a–c**) was also briefly studied (Table 5). These substrates should allow the synthesis of spiroheterocycles if the cycloisomerization proceeds with *6-endo* regioselectivity according to the previously described cation-olefin mechanism.[14a] Interestingly, the treatment of 1,5-enyne **7a** with InI_3 (5 mol %) in toluene at 60 °C afforded oxaspirane **8a** as the only isolated product in an excellent yield of 84% (Table 5, entry 1). As expected, the cascade cycloisomerization reaction proceeded with *6-endo-dig/endo-trig* regioselectivity to afford the Markovnikov product

Table 5. Synthesis of Spiroheterocycles by Indium-Catalyzed Reaction with 1,5-Enynes 7a–c[c]



Entry	1,5-enyne	Product	Yield (%)[a]
1	 **7a**	 **8a**	84
2	 **7b**	 **8b**	92
3	 **7c**	 **8c**	76
4	**7c**	 **8d**[b]	61[c]

[a]Isolated yield. [b]Obtained from **7c** by sequential In-catalyzed cycloisomerization and Pd-catalyzed cross-coupling. [c]Overall yield (two steps).

exclusively. Analogously, the reaction using 1,5-enynyl benzyl *N*-tosylamine **7b** provided the azaspirane **8b** in 92% yield (entry 2). The reaction with 1-bromo-1,5-enyne **7c** afforded the corresponding spirane **8c** in 76% yield (entry 3). In addition, the one-pot sequential indium-catalyzed cycloisomerization of **7c** followed by the cross-coupling reaction with Ph_3In using $Pd(PPh_3)_4$ as the catalyst provided the phenyl-substituted azaspirane **8d** in 61% overall yield (two steps, entry 4).

Mechanistic Studies. According to the experimental results, we postulate that the course of the indium(III)-catalyzed double cascade cycloisomerization could be viewed as either a *concerted* process or a *stepwise* route depending on the arene nucleophilicity (Scheme 3). In a two-step mechanism, we postulate that the initial η^2 coordination of the indium(III) halide with the alkyne moiety (**C**) would trigger 1,5-enyne cyclization to form the intermediate **D**.[2] This intermediate should not be a pure carbocation and could be seen as a resonance hybrid of two resonance structures, an indium-stabilized homoallylic carbocation (**D**) and a cyclopropylindium ylide. Once there, the second cyclization should proceed through a Friedel–Crafts type alkylation reaction, subsequent aromatization and protodemetallation should provide the corresponding tricyclic compound, regenerating the catalytic species (Scheme 3). The mechanistic pathway and the nature of the transition states and synthetic intermediates should also depend on the substituents at the alkene, alkyne, or arene units.

Our experimental data show that the In(III)-catalyzed double cycloisomerization reaction of aryl-substituted (*Z*)-1,5-enynes is stereoselective, yielding in all cases the cis adducts with

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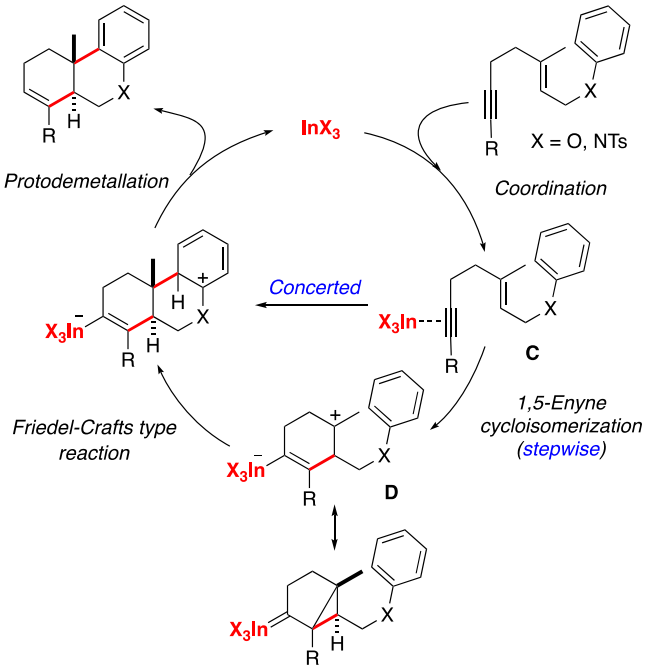
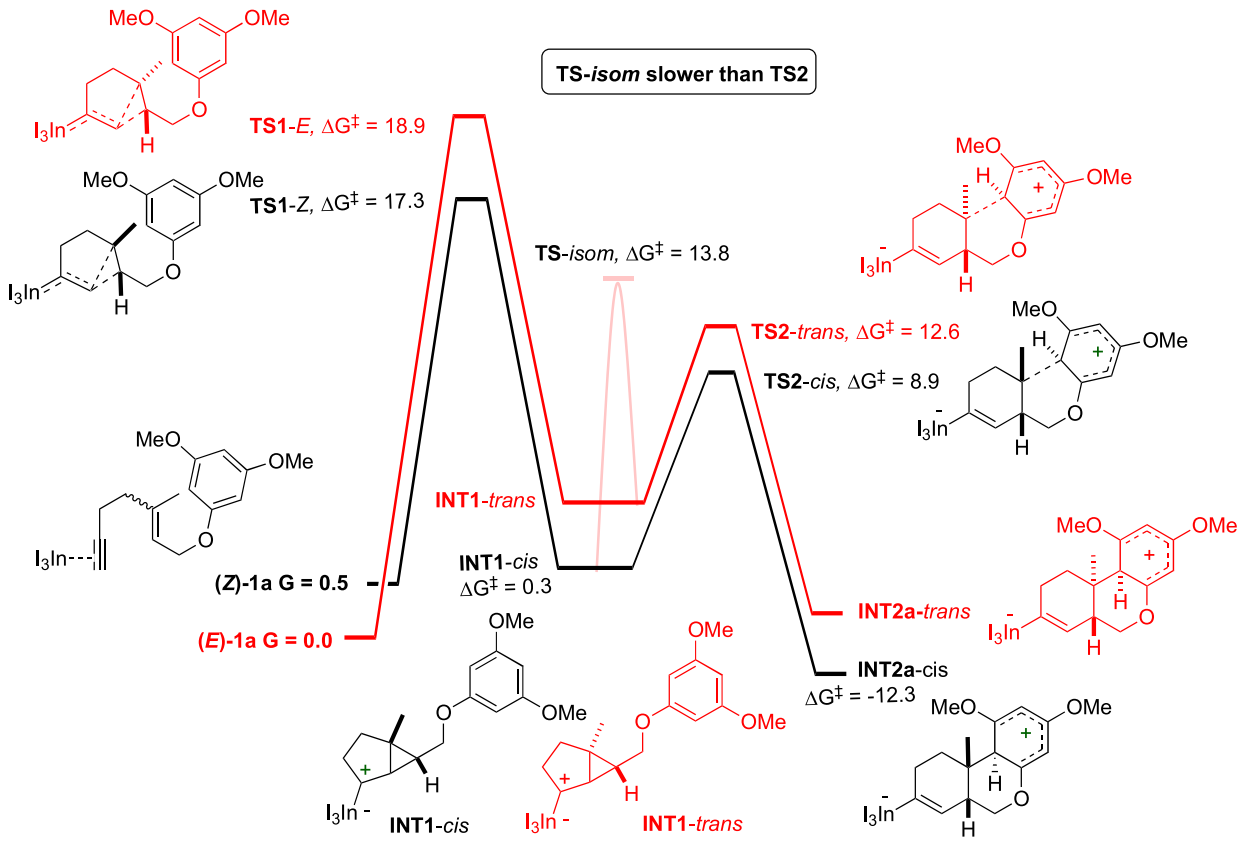
Scheme 3. General Plausible Mechanism for the In(III)-Catalyzed Cascade Cycloisomerization Reaction of 1,5-Enynes 1a−d and 3a−f



complete selectivity. For example, independently of the electronic nature of the aromatic ring, the final *cis*-products are obtained, *cis*-**2a**, *cis*-**2c**, and *cis*-**2d** from (*Z*)-**1a**, (*Z*)-**1c**, and (*Z*)-**1d**, respectively (Table 2, entries 5−7), as for the 1,5-enyne cycloisomerizations of Table 3 (entries 6−8) and Table 4. Accordingly, one would expect that using (*E*)-1,5-enynes, the tricyclic products would belong to the *trans* series. In fact, this is true for all of the dimethoxyphenyl, electron-rich arenes, 1,5-enynes like (*E*)-**1a** (Table 2, entry 1, *cis*/*trans* = 11:89), and others (Table 2, entries 1−3; Table 3, entries 1−4; Table 4). However, surprisingly, the unsubstituted phenyl 1,5-enynes (*E*)-**1d** and (*E*)-**3e** break this rule, affording the opposite cis diastereoisomers of the final adduct *cis*-**2d** (Table 2, entry 4) and *cis*-**4e** (Table 3, entry 5). In other words, phenyl ether 1,5-enynes **1d** and **3e** lead diastereoselectively to the *cis* final adducts, regardless of the *E* or *Z* configuration of the initial double bonds. To gain insights into the intriguing behavior of aryl 1,5-enynyl ethers (*E*)-**1d** and (*E*)-**3e**, we set out to study the reaction theoretically.[23]

Computational studies[24] for (*Z*)- and (*E*)-1,5-enynyl aryl ether **1a** (Scheme 4) showed that the formation of the first cycle occurs *via* **TS1**-*Z* or **TS1**-*E*, two transition states originated by the nucleophilic *6-endo-dig* alkene attack to the indium-activated electrophilic triple bond. The activation energy is very similar for the two compounds, 17.3 and 18.9 kcal/mol, respectively. As expected, the aromatic ring does not participate in the formation of the first ring, which affords intermediates **INT1** stereospecifically, **INT1**-*cis* from *Z*, and **INT1**-*trans* from *E* starting materials. These intermediates are low in energy, 0.3−1.8 kcal/mol, presenting a bicyclic structure [4.1.0] and a partial indium carbene character. The computational data shows that the first step (**TS1**) is rate limiting since the formation of the second cycle by an electrophilic aromatic substitution in **TS2**-type transition states proceeds with lower activation energies, 8.9 for **TS2**-*cis* and 12.6 kcal/mol for **TS2**-*trans*. As expected for this

Scheme 4. DFT-Calculated Mechanism of the Reaction of (*Z*)-1a and (*E*)-1a for the Selective Formation of INT2-*cis* and -*trans*



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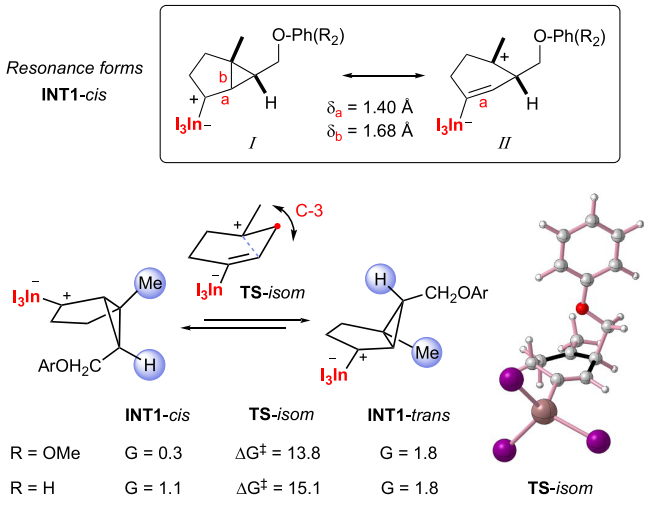
Scheme 5. DFT-Calculated Isomerization Process between the Intermediates INT1-*cis* and INT1-*trans*

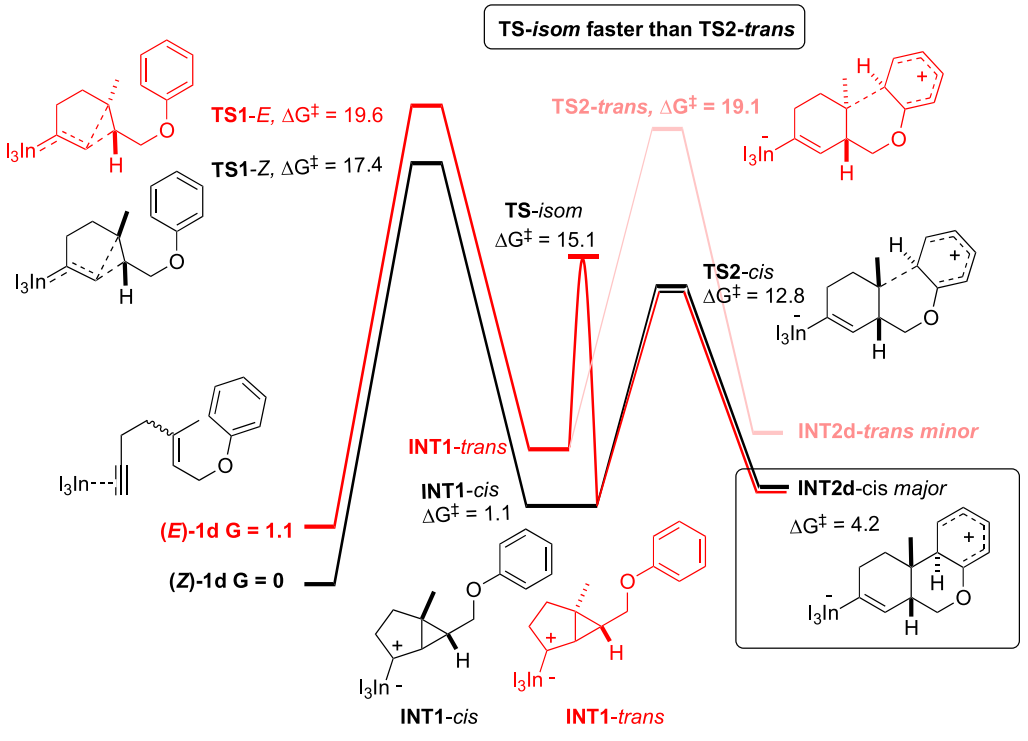


type of reaction (S_EAr), electron-rich arenes are positively affected by the stabilization of the incipient positive charge in the aryl ring by the electron-releasing methoxy groups. For the same reason, the arenium intermediates **INT2a** (*cis* and *trans*) are very stable in the presence of methoxy substituents (−12.3 and −7.6 kcal/mol). Although we did not compute them, the easy final deprotonation and hydrolysis (protodemetallation) of the C−In bond after **INT2a** intermediates would render exclusive adducts *cis*-**2a** (from *Z*-**1a**, black pathway in Scheme 4) and *trans*-**2a** (from *E*-**1a**, red line), in complete agreement with the experimental results.

Intermediate **INT1** presents very interesting structures, as they can be described by two resonance forms, *I* and *II* (Scheme 5, top). The former is a fused bicyclic skeleton with a polarized C−In bond, whilst *II* shows the zwitterionic character, with the positive charge on the methylated tertiary carbon and an anionic alkenyl-indium motif. The NBO analysis of **INT1**(OMe) and **INT1**(H) affords Wiberg bond orders showing the mixed character of both structures, slightly more akin to structure *I*, since the internal C−C bond *b* is advanced but not completely formed (BO = 0.67−0.81), and the C−C bond *a* presents slight but not complete double bond character (BO = 1.33−1.43). The bonding distances also show mixed characteristics of both resonance forms, with computed values of δ_a = 1.40 Å and δ_b = 1.68 Å. Thus, resonance form *II* also has a significant participation in the actual structure of these intermediates. We rationalized that, given the weakness of bond *b* and the partial carbocationic character at the C-3 position (Scheme 5, bottom), the bicyclic species **INT1**-*cis* and **INT1**-*trans* could potentially interconvert by an isomerization equilibrium. Indeed, a transition state was located (**TS**-*isom*) bearing an almost planar tertiary carbocation, where the adjacent carbon (labeled as C-3) is flipping between the upper and lower faces of the cyclohexene plane (Scheme 5). The activation energy of this process is quite low, *ca.* 13.5−15.1 kcal/mol, making the isomerization plausible, at least in some circumstances. However, as mentioned before for, the **1a** starting materials, the second step (**TS2**) is low enough in energy (8.9 and 12.6 kcal/mol, Scheme 4) to outcompete the isomerization, providing a complete selectivity (experimental > 95:5) for the cis and trans final products.

The scenario is quite different for 1,5-enynes (*E*)- and (*Z*)-**1d** without methoxy groups (Scheme 6). The initial cyclization through **TS1** is also rate limiting, with values of 17.4 and 19.6 kcal/mol. After the first transition state, the structure and energies of **INT1** intermediates are very similar to the previous ones. However, due to the absence of stabilizing methoxy groups in the aromatic ring, the second cyclization (**TS2**) increases its energy significantly in *ca.* 5−7 kcal/mol (12.8 and 19.1 kcal/mol, Scheme 6) above the values noted for **1a**. This fact is

Scheme 6. DFT-Calculated Mechanism of the Reaction of (*Z*)-1d and (*E*)-1d under Curtin−Hammett Conditions



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especially important in the case of the *trans* cyclization, which also shows larger ring strain, producing a sluggish cyclization (19.1 kcal/mol), which becomes slower than the isomerization (15.1 kcal/mol) between the two **INT1** isomers. Therefore, intermediate **INT1**-*trans* prefers to isomerize to **INT1**-*cis* rather than cyclize, and the reaction follows the red line in Scheme 6 to cis isomer. Meanwhile, the double cyclization of the *Z* isomer proceeds *via* the black line to lead stereospecifically to the *cis* isomer. These observations can explain how both starting materials converge in **INT1**-*cis* to give the same *cis* final isomer under Curtin−Hammett conditions.

CONCLUSIONS

Indium(III) iodide is an efficient catalyst to promote a double cycloisomerization reaction of 1,5-enynes with pendant aryl nucleophiles. The reaction can be performed under mild reaction conditions using 5 mol % of catalyst and proceeds in cascade through alkyne electrophilic activation with complete 6-*endo* regioselectivity *via* a biomimetic cascade cation-olefin process. In some cases, the double cycloisomerization is stereospecific with the retention of the alkene configuration. In addition, the synthetic transformation is highly versatile, allowing 1,5-enynes substituted at the alkyne and alkene units and phenyl groups and phenol derivatives as nucleophiles. Accordingly, a diverse group of polycyclic heterocycles such as benzo[*b*]chromenes, phenanthridines, xanthenes, and spiroheterocyclic compounds was synthesized. Computational studies on aryl 1,5-enynyl ethers support a mechanism consisting of two consecutive cyclizations: the first one is a *6-endo-dig* process catalyzed by a regioselective alkyne electrophilic activation and a second cyclization through a nonstereospecific S_EAr process.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out in flame-dried glassware under argon using standard gastight syringes, cannulae, and septa. Toluene and THF were distilled from sodium/benzophenone. Dry MeOH, DCE, Et_3N, and other commercially available reagents were used as received. Reaction temperatures refer to external bath temperatures. Butyllithium was titrated prior to use. Indium(III) iodide (99.998%) and indium(III) bromide (99.999%) were purchased from Aldrich and used as received under argon. The reactions were monitored by TLC using precoated silica gel plates (Alugram Xtra SIL G/UV254, 0.20 mm thick), UV light as the visualizing agent, and ethanolic phosphomolybdic acid as the developing agent. Flash column chromatography was performed with 230−400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 K using a Bruker Advance 300 MHz, 400 MHz or a Bruker Advance 500 MHz spectrometer and calibrated to the solvent peak. Mass spectra were obtained with a MAT 95XP Magnetic Sector EI spectrometer or with a QSTAR Elite hybrid quadrupole time-of-flight (TOF) ESI mass spectrometer, both operating in the positive ionization mode. Gas chromatography (GC) was performed on a Trace 1300 autosampling GC with a TG-5SILMS capillary column and equipped with an ISQ QD mass spectrometer.

(*E*)-1,3-Dimethoxy-5-[(3-methyloct-2-en-6-yn-1-yl)oxy]-benzene [(*E*)-1b].[14a] To a cooled solution of enyne (*E*)-**1a**[14c] (202.8 mg, 0.78 mmol) in dry THF (10 mL) at 0 °C, *n*-BuLi (0.38 mL, 0.82 mmol, 2.19 M in hexanes) was added dropwise. After 30 min, MeI (0,06 mL, 0.94 mmol) was added, and the reaction mixture was stirred for 2 h. The reaction was quenched with EtOH (1 mL), the solvent was evaporated, and the corresponding residue was purified by flash chromatography (2% EtOAc/hexanes) to afford (*E*)-**1b** (162.6 mg, 76%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11−6.09 (m, 3H), 5.54−5.50 (m, 1H), 4.51 (d, J = 6.5 Hz, 2H), 3.77 (s, 6H), 2.26 (m, 4H), 1.77 (s, 3H), 1.74 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 161.6, 160.9, 139.9, 120.5, 93.7, 93.1, 78.6, 76.2, 65.0, 55.5, 39.0, 17.7, 16.7, 3.6; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{17}H_{22}O_3Na$ 297.1461; found 297.1458.

(*E*)-1-[(7-Bromo-3-methylhept-2-en-6-yn-1-yl)oxy]-3,5-dimethoxybenzene [(*E*)-1c]. To a room temperature solution of (*E*)-3-methylhept-2-en-6-yn-1-ol[25] (105.7 mg, 0.85 mmol) in acetone (5 mL), *N*-bromosuccinimide (NBS) (166.7 mg, 0.93 mmol) and $AgNO_3$ (15.8 mg, 0.09 mmol) were added and the reaction mixture was stirred for 1 h. The reaction mixture was diluted with Et_2O (10 mL), washed with H_2O (10 mL) and brine (10 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford (*E*)-7-bromo-3-methylhept-2-en-6-yn-1-ol as an orange oil, which was used in the next step without further purification. The crude product was added to a solution of triphenylphosphine (329.4 mg, 1.25 mmol) and 3,5-dimethoxyphenol (193.2 mg, 1.25 mmol) in THF (10 mL). To this solution at 0 °C, diisopropyl azodicarboxylate (DIAD) (0.25 mL, 1.25 mmol) was added dropwise and the reaction mixture was stirred for 5 h at 60 °C. Then, the solvent was evaporated *in vacuo* and the corresponding residue was purified by flash chromatography (5% EtOAc/hexanes) to afford (*E*)-**1c** (161.0 mg, 56% in two steps) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (m, 3H), 5.54−5.50 (m, 1H), 4.50 (d, J = 6.6 Hz, 2H), 3.76 (s, 6H), 2.36−2.29 (m, 4H), 1.74 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 161.6, 160.8, 139.1, 120.9, 93.7, 93.1, 79.6, 64.8, 55.4, 38.6, 38.0, 18.6, 16.6; IR (neat) ν_{max} 2929, 2841, 1594, 1460, 1204, 1150, 1062, 819 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{16}H_{19}BrO_3Na$ 361.0409; found 361.0416.

(*E*)-[(3-Methylhept-2-en-6-yn-1-yl)oxy]benzene [(*E*)-1d]. To a 0°C solution of (*E*)-3-methylhept-2-en-6-yn-1-ol[25] (201.9 mg, 1.63 mmol), triphenylphosphine (640.0 mg, 2.44 mmol) and phenol (229.6 mg, 2.44 mmol) in THF (10 mL), DIAD (0.48 mL, 2.44 mmol) was added dropwise. The reaction mixture was stirred for 5 h at 60 °C in an oil bath and the solvent was evaporated *in vacuo*. Then, the corresponding residue was purified by flash chromatography (5% EtOAc/hexanes) to afford (*E*)-**1d** (251.4 mg, 77%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.28 (m, 2H), 6.94−6.93 (m, 3H), 5.58−5.53 (m, 1H), 4.56 (d, J = 6.5 Hz, 2H), 2.35−2.31 (m, 4H), 1.95 (t, J = 2.3 Hz, 1H), 1.75 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.9, 139.1, 129.5, 121.1, 120.8, 114.8, 83.9, 68.9, 64.7, 38.3, 17.3, 16.6; HRMS (EI) m/z: [M]$^+$ calcd for $C_{14}H_{16}O$ 200.1201; found 200.1196.

(*Z*)-1,3-Dimethoxy-5-[(3-methylhept-2-en-6-yn-1-yl)oxy]-benzene [(*Z*)-1a]. DIAD (0.51 mL, 2.57 mmol) was added dropwise at 0 °C to a solution of (*Z*)-3-methylhept-2-en-6-yn-1-ol[26] (212.6 mg, 1.71 mmol), triphenylphosphine (674.1 mg, 2.57 mmol), and 3,5-dimethoxyphenol (396.2 mg, 2.57 mmol) in THF (10 mL). The reaction mixture was stirred for 3 h at 60 °C in an oil bath and the solvent was evaporated *in vacuo*. Then, the corresponding residue was purified by flash chromatography (5% EtOAc/hexanes) to afford (*Z*)-**1a** (227.3 mg, 51%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11−6.09 (m, 3H), 5.60 (td, J = 6.8, 1.6 Hz, 1H), 4.51 (d, J = 6.8 Hz, 2H), 3.76 (s, 6H), 2.36−2.34 (m, 4H), 1.97 (t, J = 2.4 Hz, 1H), 1.81 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 161.6, 160.7, 139.7, 122.0, 93.6, 93.0, 83.7, 69.0, 64.5, 55.4, 31.2, 23.3, 17.5; IR (neat) ν_{max} 3289, 2935, 2840, 1593, 1474, 1204, 1147, 1060, 818 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{16}H_{20}O_3Na$ 283.1304; found 283.1313.

(*Z*)-1-[(7-Bromo-3-methylhept-2-en-6-yn-1-yl)oxy]-3,5-dimethoxybenzene [(*Z*)-1c]. To a room temperature solution of (*Z*)-3-methylhept-2-en-6-yn-1-ol[26] (115.7 mg, 0.93 mmol) in acetone (5 mL), NBS (182.4 mg, 1.02 mmol) and $AgNO_3$ (17.3 mg, 0.10 mmol) were added and the reaction mixture was stirred for 1 h. The reaction mixture was diluted with Et_2O (10 mL) and washed with H_2O (10 mL) and brine (10 mL), dried with $MgSO_4$ (anhydrous), filtered, and concentrated *in vacuo* to afford (*Z*)-7-bromo-3-methylhept-2-en-6-yn-1-ol as an orange oil, which was used in the next step without further purification. The crude product was added to a solution of triphenylphosphine (354.0 mg, 1.35 mmol) and 3,5-dimethoxyphenol (208.9 mg, 1.35 mmol) in THF (10 mL), DIAD (0.26 mL, 1.35 mmol) at 0 °C was added dropwise, and the reaction mixture was heated at 60 °C for 5 h. Then, the solvent was evaporated *in vacuo* and the corresponding residue was purified by flash chromatography (5% EtOAc/hexanes) to afford (*Z*)-**1c** (149.9 mg, 47% in two steps) as a

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yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11−6.09 (m, 3H), 5.61 (m, 1H), 4.49 (d, J = 6.7 Hz, 2H), 3.77 (s, 6H), 2.34 (m, 4H), 1.80 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 161.5, 160.7, 139.5, 122.0, 93.6, 93.1, 79.5, 64.4, 55.4, 38.8, 31.0, 23.3, 18.8; IR (neat) ν_{max} 2927, 2840, 1593, 1474, 1204, 1148, 1061, 818 cm^{-1}; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{19}BrO_3Na$ 361.0409; found 361.0403.

(*Z*)-[(3-Methylhept-2-en-6-yn-1-yl)oxy]benzene [(*Z*)-1d]. To a cooled solution of (*Z*)-3-methylhept-2-en-6-yn-1-ol[26] (215.8 mg, 1.74 mmol), triphenylphosphine (684.6 mg, 2.61 mmol) and phenol (245.6 mg, 2.61 mmol) in THF (10 mL) at 0 °C, DIAD (0.52 mL, 2.61 mmol) was added dropwise and the reaction mixture was stirred for 5 h at 60 °C in an oil bath. The solvent was evaporated *in vacuo* and the corresponding residue was purified by flash chromatography (5% EtOAc/hexanes) to afford (*Z*)-**1d** (236.7 mg, 68%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.25 (m, 2H), 6.95−6.91 (m, 3H), 5.62−5.60 (m, 1H), 4.55 (d, J = 6.8, 2H), 2.38−2.33 (m, 4H), 1.98−1.96 (m, 1H), 1.82 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 158.8, 139.5, 129.5, 122.2, 120.8, 114.8, 83.8, 69.0, 64.3, 31.3, 23.3, 17.5; IR (neat) ν_{max} 3292, 2917, 2868, 1598, 1494, 1235, 1172, 1006, 752 cm^{-1}; HRMS (EI) m/z: $[M]^+$ calcd for $C_{14}H_{16}O$ 200.1201; found 200.1197.

(*E*)-*N*-(3,5-Dimethoxyphenyl)-4-methyl-*N*-(3-methyloct-2-en-6-yn-1-yl)benzenesulfonamide [(*E*)-3b]. To a 0 °C solution of 1,5-enyne (*E*)-**3a**[14c] (205.6 mg, 0.50 mmol) in dry THF (10 mL), *n*-BuLi (0.21 mL, 0.52 mmol, 2.5 M in hexanes) was added dropwise. After 30 min, MeI (0,04 mL, 0.60 mmol) was added and the reaction mixture was left stirring for 2 h. The reaction was quenched with EtOH (3 mL), the solvent was evaporated, and the corresponding residue was purified by flash chromatography (10% EtOAc/hexanes) to afford (*E*)-**3b** (108.4 mg, 51%) as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 8.4 Hz, 2H), 7.28−7.25 (m, 2H), 6.36 (d, J = 2.1 Hz, 1H), 6.20 (d, J = 2.1 Hz, 2H), 5.15 (t, J = 7.0 Hz, 1H), 4.13 (d, J = 6.9 Hz, 2H), 3.71 (s, 6H), 2.42 (s, 3H), 2.07 (m, 4H), 1.72 (s, 3H), 1.52 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.5, 143.4, 141.3, 139.1, 135.8, 129.4, 127.9, 119.7, 107.0, 100.1, 78.5, 76.0, 55.5, 48.7, 38.8, 21.6, 17.7, 16.2, 3.5; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{30}NO_4S$ 428.1890; found 428.1893.

(*E*)-*N*-(3,5-Dimethoxyphenyl)-4-methyl-*N*-(3-methyl-7-phenylhept-2-en-6-yn-1-yl)benzenesulfonamide [(*E*)-3c]. To a solution of 1,5-enyne (*E*)-**3a**[14c] (163.0 mg, 0.39 mmol) in Et_3N (4 mL), CuI (3.75 mg, 0.02 mmol), $Pd(PPh_3)_2Cl_2$ (13.83 mg, 0.02 mmol), and iodobenzene (103.4 mg, 0.51 mmol) were added and the reaction mixture was stirred overnight at room temperature. Then, the reaction was quenched with H_2O (15 mL) and the aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic phase was washed with brine (50 mL), dried with $MgSO_4$ (anhyd.), filtered, and concentrated *in vacuo* to afford (*E*)-**3c** (107.9 g, 57%) as an amorphous white solid after purification by column chromatography (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 8.2 Hz, 2H), 7.34 (dd, J = 6.7, 3.1 Hz, 2H), 7.27−7.24 (m, 5H), 6.35 (t, J = 2.3 Hz, 1H), 6.20 (d, J = 2.3 Hz, 2H), 5.22 (t, J = 6.7 Hz, 1H), 4.15 (d, J = 6.8 Hz, 2H), 3.68 (s, 6H), 2.42 (s, 3H), 2.36 (t, J = 7.5 Hz, 2H), 2.20 (t, J = 7.5 Hz, 2H), 1.58 (s, J = 1.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.6, 143.5, 141.3, 138.9, 135.8, 131.6, 129.5, 128.3, 127.9, 127.7, 123.9, 120.1, 107.1, 100.2, 89.6, 82.2, 81.1, 55.5, 48.7, 38.5, 21.7, 18.6, 16.4; IR (neat) ν_{max} 2925, 2841, 1596, 1458, 1346, 1205, 1154, 1066, 663 cm^{-1}; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{29}H_{31}NO_4SNa$: 512.1866; found 512.1853.

(*E*)-*N*-(7-Bromo-3-methylhept-2-en-6-yn-1-yl)-*N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide [(*E*)-3d].[14c] NBS (125.0 mg, 0.70 mmol) and $AgNO_3$ (12.0 mg, 0.07 mmol) were added to a solution of the enyne (*E*)-**3a** (266.3 mg, 0.64 mmol) in acetone (6 mL), and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with Et_2O (10 mL), the organic phase was washed with H_2O (10 mL) and brine (10 mL), dried with $MgSO_4$ (anhyd.), filtered, and concentrated *in vacuo* to afford, after purification by column chromatography (15% EtOAc/hexanes), (*E*)-**3d** (198.0 mg, 74%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 2H), 7.28 (m, 2H), 6.37 (m, J = 2.3 Hz, 1H), 6.20 (d, J = 2.3 Hz, 2H), 5.16 (t, J = 6.7 Hz, 1H), 4.13 (d, J = 6.9 Hz, 2H), 3.71 (s, 6H), 2.42 (s, 3H), 2.16−2.10 (m, 4H), 1.55 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.6, 143.5, 141.3, 138.5, 135.9, 129.5, 127.9, 120.2, 107.1, 100.2, 79.6, 55.5, 48.6, 38.4, 38.0, 21.7, 18.7, 16.3; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{23}H_{26}BrNO_4SNa$ 514.0658; found: 514.0645.

(*E*)-4-Methyl-*N*-(3-methylhept-2-en-6-yn-1-yl)-*N*-phenylbenzenesulfonamide [(*E*)-3e]. DIAD (0.36 mL, 1.81 mmol) was added dropwise at 0 °C to a solution of (*E*)-3-methylhept-2-en-6-yn-1-ol[25] (150.0 mg, 1.21 mmol), triphenylphosphine (474.7 mg, 1.81 mmol), and *p*-toluenesulfonanilide (447.6 mg, 1.81 mmol) in THF (10 mL). The reaction mixture was stirred for 5 h at 60 °C in an oil bath and the solvent was evaporated *in vacuo*. The corresponding residue was purified by flash chromatography (20% EtOAc/hexanes) to afford (*E*)-**3e** (303.7 mg, 71%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 8.3 Hz, 2H), 7.27−7.24 (m, 5H), 7.06−7.04 (m, 2H), 5.18 (ddt, J = 8.2, 6.9, 1.3 Hz, 1H), 4.19 (d, J = 7.0 Hz, 2H), 2.42 (s, 3H), 2.10 (m, 4H), 1.84 (m, 1H), 1.49 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 143.4, 139.4, 138.7, 135.8, 129.5, 129.0, 128.9, 127.9, 127.8, 120.1, 83.7, 68.8, 48.5, 38.1, 21.7, 17.3, 16.1; IR (neat) ν_{max} 3295, 2972, 2922, 1598, 1494, 1345, 1156, 1091, 654 cm^{-1}; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{21}H_{23}NO_2SNa$: 376.1341; found: 376.1338.

(*Z*)-*N*-(3,5-Dimethoxyphenyl)-4-methyl-*N*-(3-methylhept-2-en-6-yn-1-yl)benzenesulfonamide [(*Z*)-3a]. DIAD (0.34 mL, 1.74 mmol) was added dropwise at 0 °C to a solution of (*Z*)-3-methylhept-2-en-6-yn-1-ol[26] (144.2 mg, 1.16 mmol), triphenylphosphine (456.4 mg, 1.74 mmol), and *N*-(3,5-dimethoxybenzyl)-4-methylbenzenesulfonamide[27] (534.4 mg, 1.74 mmol) in THF (10 mL). The reaction mixture was stirred for 5 h at 60 °C in an oil bath and the solvent was evaporated *in vacuo*. The corresponding crude reaction product was purified by flash chromatography (15% EtOAc/hexanes) to afford (*Z*)-**3a** (359.8 mg, 75%) as a white solid; mp 100−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.3 Hz, 2H), 7.28−7.25 (m, 2H), 6.37 (t, J = 2.3 Hz, 1H), 6.20 (d, J = 2.3 Hz, 2H), 5.24−5.20 (m, 1H), 4.15 (dd, J = 7.0, 1.2 Hz, 2H), 3.71 (s, 6H), 2.43 (s, 3H), 2.14−2.09 (m, 4H), 1.90 (m, 1H), 1.63 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.6, 143.4, 141.2, 138.2, 135.7, 129.4, 127.8, 121.4, 107.1, 100.1, 83.8, 68.8, 55.4, 48.5, 30.7, 23.0, 21.6, 17.1; IR (neat) ν_{max} 3294, 2927, 2840, 1594, 1459, 1348, 1154, 1065, 663 cm^{-1}; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{23}H_{27}NO_4SNa$ 436.1553; found 436.1555.

(*Z*)-*N*-(7-Bromo-3-methylhept-2-en-6-yn-1-yl)-*N*-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide [(*Z*)-3d]. NBS (75.0 mg, 0.42 mmol) and $AgNO_3$ (7.1 mg, 0.04 mmol) were added to a solution of 1,5-enyne (*Z*)-**3a** (158.3 mg, 0.38 mmol) in acetone (5 mL), and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with Et_2O (10 mL), the organic phase was washed with H_2O (10 mL) and brine (10 mL), dried with $MgSO_4$ (anhyd.), filtered, and concentrated *in vacuo*. After purification by column chromatography (15% EtOAc/hexanes), (*Z*)-**3d** was obtained (128.9 mg, 69%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 2H), 7.28−7.25 (m, 2H), 6.37 (t, J = 2.3 Hz, 1H), 6.19 (dt, J = 2.3, 1.3 Hz, 2H), 5.24−5.20 (m, 1H), 4.13 (d, J = 7.0 Hz, 2H), 3.71 (s, 6H), 2.42 (s, 3H), 2.10 (m, 4H), 1.62 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.7, 143.5, 141.2, 138.2, 135.8, 129.5, 127.9, 121.5, 107.1, 100.2, 79.7, 55.5, 48.6, 38.5, 30.6, 23.2, 21.7, 18.5; IR (neat) ν_{max} 2925, 2839, 1592, 1457, 1347, 1204, 1152, 1065, 662 cm^{-1}; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{23}H_{26}BrNO_4SNa$ 514.0658; found 514.0651.

(*Z*)-4-Methyl-*N*-(3-methylhept-2-en-6-yn-1-yl)-*N*-phenylbenzenesulfonamide [(*Z*)-3e]. To a 0 °C solution of (*Z*)-3-methylhept-2-en-6-yn-1-ol[26] (151.4 mg, 1.21 mmol), triphenylphosphine (479.2 mg, 1.81 mmol) and *p*-toluene-sulfonanilide (451.8 mg, 1.81 mmol) in THF (15 mL), DIAD (0.36 mL, 1.81 mmol) was added dropwise. The reaction mixture was stirred for 5 h at 60 °C in an oil bath and the solvent was evaporated *in vacuo*. The corresponding residue was purified by flash chromatography (10% EtOAc/hexanes) to afford (*Z*)-**3e** as a colorless oil (329.3 mg, 77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 8.3 Hz, 2H), 7.29−7.25 (m, 5H), 7.05−7.02 (m, 2H), 5.24−5.19 (m, 1H), 4.19 (d, J = 7.0 Hz, 2H), 2.43 (s, 3H), 2.10−2.05 (m, 4H), 1.89 (t, J = 2.4 Hz, 1H), 1.61 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 143.4, 139.4, 138.3, 135.8, 129.5, 129.0, 129.0, 127.9,

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127.8, 121.4, 83.8, 68.8, 48.5, 30.7, 23.0, 21.6, 17.1; IR (neat) ν_{max} 3290, 2920, 2869, 1596, 1493, 1345, 1162, 1092, 656 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{21}H_{23}NO_2SNa$ 376.1341; found 376.1334.

(*E*)-*N*-(3,5-Dimethoxyphenyl)-*N*-(hept-2-en-6-yn-1-yl)-4-methylbenzenesulfonamide [(*E*)-3f]. To a 0 °C solution of (*E*)-hept-2-en-6-yn-1-ol[28] (150.0 mg, 1.36 mmol), triphenylphosphine (535.1 mg, 2.04 mmol), and *N*-(3,5-dimethoxybenzyl)-4-methylbenzenesulfonamide[27] (627.0 mg, 2.04 mmol) in THF (10 mL), DIAD (0.40 mL, 2.04 mmol) was added dropwise and the reaction mixture was stirred for 5 h at 60 °C in an oil bath. The solvent was evaporated *in vacuo* and the corresponding residue was purified by flash chromatography (20% EtOAc/hexanes) to afford (*E*)-**3f** (396.6 g, 73%) as a white solid; mp 90−92 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 6.35 (t, *J* = 2.3 Hz, 1H), 6.18 (d, *J* = 2.3 Hz, 2H), 5.56−5.40 (m, 2H), 4.07 (d, *J* = 5.9 Hz, 2H), 3.68 (s, 6H), 2.40 (s, 3H), 2.10 (m, *J* = 3.1, 2.6 Hz, 4H), 1.87 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.5, 143.5, 140.9, 135.6, 133.2, 129.4, 127.8, 125.8, 107.2, 100.1, 83.5, 68.8, 55.4, 52.9, 31.0, 21.6, 18.3; IR (neat) ν_{max} 3289, 2934, 2840, 1593, 1458, 1345, 1153, 1090, 662 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{25}NO_4SNa$ 422.1396; found 422.1385.

(*Z*)-4-Methoxy-2-(3-methylhept-2-en-6-yn-1-yl)phenol [(*Z*)-5a]. PBr_3 (162.4 mg, 0.60 mmol) was added dropwise to a solution of (*Z*)-3-methylhept-2-en-6-yn-1-ol[26] (150.2 mg, 1.21 mmol) in Et_2O (10 mL) at 0 °C and was stirred for 30 min. The reaction was quenched with H_2O (10 mL) and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with H_2O (30 mL), $NaHCO_3$ (30 mL, satd. sol.), and brine (10 mL), dried with $MgSO_4$ (anhyd.), filtered, and concentrated *in vacuo* to afford (*Z*)-7-bromo-5-methylhept-5-en-1-yne as an orange oil, which was used in the next step without further purification. The crude product was dissolved in toluene (10 mL) and NaH 95% (35.5 mg, 1.33 mmol) and 4-methoxyphenol (165.2 mg, 1.33 mmol) was added. The reaction mixture was stirred overnight at room temperature, quenched with a NH_4Cl saturated solution, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The resulting organic phase was washed with H_2O (30 mL) and brine (30 mL), dried with $MgSO_4$ (anhyd.), filtered, and concentrated *in vacuo* to yield, after purification by column chromatography (10% EtOAc/hexanes), (*Z*)-**5a** (158.8 mg, 57%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (d, *J* = 8.5 Hz, 1H), 6.68−6.64 (m, 2H), 5.41−5.36 (m, 1H), 4.68 (s, 1H), 3.75 (s, 3H), 3.37 (d, *J* = 7.1 Hz, 2H), 2.42−2.40 (m, 2H), 2.38−2.35 (m, 2H), 1.99 (t, *J* = 2.5 Hz, 1H), 1.78 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 153.7, 148.1, 136.2, 128.2, 124.2, 116.3, 115.9, 112.1, 84.1, 68.9, 55.9, 30.8, 29.6, 23.1, 17.2; IR (neat) ν_{max} 3405, 3290, 2913, 2834, 1497, 1430, 1199, 1039, 803 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{15}H_{18}O_2$ 230.1301; found 230.1296.

(*Z*)-2-(7-Bromo-3-methylhept-2-en-6-yn-1-yl)-4-methoxyphenol [(*Z*)-5b]. To a room temperature solution of (*Z*)-3-methylhept-2-en-6-yn-1-ol[26] (84.8 mg, 0.68 mmol) in acetone (5 mL), NBS (133.8 mg, 0.75 mmol) and $AgNO_3$ (12.7 mg, 0.07 mmol) were added, and the reaction mixture was stirred for 1 h. The reaction mixture was diluted with Et_2O (10 mL), washed with H_2O (10 mL) and brine (10 mL), dried with $MgSO_4$ (anhyd.), filtered, and concentrated *in vacuo* to afford (*Z*)-7-bromo-3-methylhept-2-en-6-yn-1-ol as an orange oil, which was used in the next step without further purification. The crude product was dissolved in Et_2O (10 mL) and cooled at 0 °C, PBr_3 (92.4 mg, 0.34 mmol) was then added dropwise, and the reaction mixture was stirred for 30 min. The reaction was quenched with H_2O (10 mL), and the aqueous phase was extracted with Et_2O (3 × 10 mL). The resulting organic phase was washed with H_2O (30 mL), a $NaHCO_3$ saturated solution (30 mL), and brine (10 mL), dried with $MgSO_4$ (anhyd.), filtered, and concentrated *in vacuo* to afford (*Z*)-1,7-dibromo-5-methylhept-5-en-1-yne as an orange oil, which was used in the next step without further purification.

The crude product in toluene (10 mL) was added to a solution of NaH 95% (20.0 mg, 0.75 mmol) and 4-methoxyphenol (92.9 mg, 0.75 mmol) at room temperature, and the reaction mixture was stirred overnight. The reaction mixture was quenched with a NH_4Cl saturated solution (2 mL) and was extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with H_2O (30 mL) and brine (30 mL), dried with $MgSO_4$ (anhyd.), filtered, and concentrated *in vacuo* to afford, after purification by column chromatography (10% EtOAc/hexanes), (*Z*)-**5b** (90.4 mg, 43%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 6.74−6.63 (m, 3H), 5.42−5.38 (m, 1H), 4.89 (s, 1H), 3.76 (s, 3H), 3.36 (d, *J* = 7.2 Hz, 2H), 2.40−2.35 (m, 4H), 1.77 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 153.7, 148.0, 135.9, 128.3, 124.2, 116.2, 115.8, 112.1, 79.9, 55.9, 38.5, 30.7, 29.3, 23.3, 18.6; IR (neat) ν_{max} 3408, 2915, 2835, 1504, 1432, 1201, 1041, 805 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{17}BrO_2Na$: 331.0304; found 331.0315.

General Procedure for In(III)-Catalyzed Cascade Cycloisomerization Reactions of 1,5-Enynes. In a Schlenk tube filled with argon, InI_3 (5 mol %) was placed and a solution of the corresponding 1,5-enyne (~0.07 M) in toluene was added. The reaction mixture was stirred at 60 °C in an oil bath (for **1a−d**, **3a−f**, and **7a−c**) or at room temperature (for **5a−b**) until the starting material is consumed (TLC). The reaction was quenched with NH_4Cl (10 mL, satd. sol.), poured into a separatory funnel, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The resulting combined organic phase was washed with brine (15 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford, after purification by column chromatography, the corresponding tricyclic product.

(6a*S,10a*S**)-1,3-Dimethoxy-10a-methyl-6a,9,10,10a-tetrahydro-6*H*-benzo[*c*]chromene [*trans*-2a].**[14c] According to the general procedure, the reaction of 1,5-enyne (*E*)-**1a** (87.4 mg, 0.34 mmol) with InI_3 (8.5 mg, 0.017 mmol) gave **2a** (56.8 mg, 65%; cis/trans = 11:89) as a colorless oil. Purification by column chromatography (2% EtOAc/hexanes) provided pure *trans*-**2a**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.05−6.02 (m, 2H), 5.82−5.76 (m, 1H), 5.36 (dq, *J* = 9.8, 2.1 Hz, 1H), 4.08 (dd, *J* = 10.3, 4.1 Hz, 1H), 3.99 (dd, *J* = 12.4, 10.3 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.07−3.00 (m, 1H), 2.71−2.67 (m, 1H), 2.22 (m, 2H), 1.57−1.53 (m, 1H), 1.17 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.3, 159.3, 155.8, 129.3, 123.8, 113.8, 94.1, 92.3, 66.4, 55.3, 55.3, 41.7, 33.3, 32.0, 24.4, 18.1. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{20}O_3Na$ 283.1304; found 283.1317.

Scale-Up Experiment for (*trans*)-2a. In a Schlenk tube filled with argon, InI_3 (38.1 mg, 0.077 mmol) was placed and a solution of the enyne (*E*)-**1a** (400.5 mg, 1.54 mmol) in toluene (22 mL) was added. The reaction mixture was stirred at 60 °C in an oil bath for 2 h, quenched with a NH_4Cl (30 mL, satd. sol.), poured into a separatory funnel, and extracted with Et_2O (3 × 30 mL). The combined organic phase was washed with brine (35 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (2% EtOAc/hexanes) to afford **2a** (252.4 mg, 63%; cis/trans = 16:84) as a colorless oil.

(4a*S,9a*S**)-6,8-Dimethoxy-4a-methyl-4,4a,9,9a-tetrahydro-3*H*-xanthene (I).** According to the general procedure, the reaction of 1,5-enyne (*E*)-**1a** (150.2 mg, 0.58 mmol) with InI_3 (14.3 mg, 0.029 mmol) in the presence of $AgSbF_6$ (10.0 mg, 0.029 mmol) afforded a mixture of **I**:**2a** (4:1) by ^1H NMR. After purification by column chromatography (1% EtOAc/hexanes), compound **I** was isolated as a colorless oil (81.1 mg, 54%, cis/trans = 19:81); ^1H NMR (500 MHz, $CDCl_3$) δ 6.05 (d, *J* = 0.9 Hz, 2H), 5.66−5.64 (m, 1H), 5.52 (ddt, *J* = 9.7, 2.5, 1.7 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 2.72 (dd, *J* = 16.2, 5.5 Hz, 1H), 2.50−2.42 (m, 1H), 2.35−2.28 (m, 1H), 2.27−2.18 (m, 1H), 2.11 (dd, *J* = 16.2, 13.7 Hz, 1H), 1.98−1.92 (m, 1H), 1.86 (td, *J* = 12.0, 6.9 Hz, 1H), 1.11 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.5, 158.5, 154.9, 128.8, 126.5, 104.0, 93.8, 91.0, 75.9, 55.4, 55.3, 38.6, 35.2, 25.1, 22.3, 15.9. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{21}O_3$ 261.1491; found 261.1486.

2-(But-3-yn-1-yl)-5,7-dimethoxy-2-methylchromane (II). According to the general procedure, the reaction of 1,5-enyne (*E*)-**1a** (90.1 mg, 0.35 mmol) with $In(NTf_2)_3$ (16.7 mg, 0.018 mmol) in DCE (5 mL) at 60 °C in an oil bath for 5 h afforded, after purification by column chromatography (5% EtOAc/hexanes), compound **II** (56.7 mg, 63%) as a yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 6.03 (d, *J* = 2.4 Hz, 1H), 5.99 (d, *J* = 2.4 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 2.64−2.49 (m, 2H), 2.37−2.32 (m, 2H), 1.97−1.91 (m, 2H), 1.86−1.82 (m, 1H), 1.79−1.73 (m, 2H), 1.28 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ

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159.6, 158.6, 154.8, 102.5, 93.8, 91.1, 84.8, 75.3, 68.3, 55.5, 55.4, 38.4, 30.8, 23.8, 16.3, 13.1; IR (neat) ν_{max} 3289, 2926, 2853, 1616, 1590, 1202, 1143, 1105, 811 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{20}NaO_3$ 283.1304; found 283.1317.

(6a*S*,10a*S***)-1,3-Dimethoxy-7,10a-dimethyl-6a,9,10,10a-tetrahydro-6*H*-benzo[*c*]chromene [*trans*-2b].**[14a] According to the general procedure, the reaction of 1,5-enyne (*E*)-**1b** (99.2 mg, 0.36 mmol) with InI_3 (8.9 mg, 0.018 mmol) afforded **2b** (67.5 mg, 68%; cis/trans = 22:78) as a colorless oil. Purification by column chromatography (2% EtOAc/hexanes) afforded pure *trans*-**2b**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.04−6.01 (m, 2H), 5.46 (m, 1H), 4.38 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.01−3.94 (m, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.00 (dd, *J* = 13.1, 6.1 Hz, 1H), 2.66 (d, *J* = 12.1 Hz, 1H), 2.14 (m, 2H), 1.67 (s, 3H), 1.49−1.41 (m, 1H) 1.18 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.3, 159.3, 155.7, 130.0, 123.5, 113.8, 93.9, 92.4, 64.4, 55.3, 55.3, 44.7, 33.7, 31.9, 23.7, 20.8, 18.4; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{22}O_3Na$ 297.1461; found 297.1454.

(6a*S*,10a*S***)-7-Bromo-1,3-dimethoxy-10a-methyl-6a,9,10,10a-tetrahydro-6*H*-benzo[*c*]chromene [*trans*-2c].** According to the general procedure, the reaction of 1,5-enyne (*E*)-**1c** (68.6 mg, 0.20 mmol) with InI_3 (5.0 mg, 0.010 mmol) afforded **2c** (42.5 mg, 62%; cis/trans = 27:73) as a white solid. Purification by column chromatography (2% EtOAc/hexanes) afforded pure *trans*-**2c**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.18−6.16 (m, 1H), 6.05−6.02 (m, 2H), 4.57 (dd, *J* = 10.4, 3.5 Hz, 1H), 3.95 (dd, J = 11.8, 10.4 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.14−3.07 (m, 1H), 2.99−2.93 (m, 1H), 2.26−2.22 (m, 2H), 1.49 (m, 1H), 1.25 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.9, 159.5, 155.8, 131.1, 119.7, 112.4, 93.9, 92.5, 66.2, 55.4, 55.3, 46.8, 36.3, 31.3, 26.2, 18.5; IR (neat) ν_{max} 2933, 2837, 1612, 1583, 1463, 1201, 1151, 1104, 814 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{19}BrO_3Na$ 361.0409; found 361.0418.

(6a*R*,10a*S***)-10a-Methyl-6a,9,10,10a-tetrahydro-6*H*-benzo[*c*]chromene [*cis*-2d].** According to the general procedure, the reaction of 1,5-enyne (*E*)-**1d** (105.4 mg, 0.53 mmol) with InI_3 (13.0 mg, 0.027 mmol) or 1,5-enyne (*Z*)-**1d** (99.2 mg, 0.49) with InI_3 (11.8 mg, 0.025 mmol) afforded *cis*-**2d** [64.3 mg, 61% from (*E*)-**1d** and 64.5 mg, 65% from (*Z*)-**1d**] as a yellow oil after purification by column chromatography (2% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.08 (ddd, *J* = 8.0, 7.2, 1.7 Hz, 1H), 6.90 (td, *J* = 7.5, 1.3 Hz, 1H), 6.79 (dd, *J* = 8.1, 1.4 Hz, 1H), 5.82−5.79 (m, 1H), 5.59 (ddt, *J* = 10.0, 3.8, 2.0 Hz, 1H), 4.22 (dd, *J* = 11.0, 3.0 Hz, 1H), 3.90 (dd, *J* = 11.0, 6.6 Hz, 1H), 2.34 (m, 1H), 2.02−1.98 (m, 2H), 1.88−1.68 (m, 2H), 1.35 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 154.3, 130.4, 129.9, 127.3, 127.1, 126.1, 120.9, 117.0, 66.8, 41.3, 33.9, 32.9, 29.1, 22.6; IR (neat) ν_{max} 2922, 2855, 1579, 1488, 1447, 1218, 751 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{14}H_{16}O$ 200.1201; found 200.1182.

(6a*R*,10a*S***)-1,3-Dimethoxy-10a-methyl-6a,9,10,10a-tetrahydro-6*H*-benzo[*c*]chromene [*cis*-2a].** According to the general procedure, the reaction of 1,5-enyne (*Z*)-**1a** (91.5 mg, 0.35 mmol) with InI_3 (9.1 mg, 0.018 mmol) afforded *cis*-**2a** (58.6 mg, 64%) as a colorless oil after purification by column chromatography (2% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.07 (d, *J* = 2.6 Hz, 1H), 6.01 (d, *J* = 2.6 Hz, 1H), 5.84−5.81 (m, 1H), 5.51 (ddt, *J* = 9.9, 3.6, 1.8 Hz, 1H), 4.13 (dd, *J* = 10.7, 2.8 Hz, 1H), 3.84 (dd, *J* = 10.7, 6.8 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 2.26−2.24 (m, 1H), 2.22−2.18 (m, 1H), 1.99−1.78 (m, 3H), 1.39 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.7, 159.0, 156.5, 130.5, 125.9, 111.0, 93.7, 92.9, 66.8, 55.3, 55.3, 43.4, 33.2, 30.8, 25.7, 23.0; IR (neat) ν_{max} 2922, 2837, 1612, 1583, 1463, 1200, 1153, 814 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{16}H_{20}O_3$ 260.1407; found 260.1402.

(6a*R*,10a*S***)-7-Bromo-1,3-dimethoxy-10a-methyl-6a,9,10,10a-tetrahydro-6*H*-benzo[*c*]chromene [*cis*-2c].** According to the general procedure, the reaction of 1,5-enyne (*Z*)-**1c** (84.0 mg, 0.25 mmol) with InI_3 (6.1 mg, 0.012 mmol) afforded *cis*-**2c** (47.9 mg, 57%) as a yellow oil after purification by column chromatography (2% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 6.21(m, 1H), 6.07 (d, *J* = 2.6 Hz, 1H), 6.05 (d, *J* = 2.6 Hz, 1H), 4.32 (dd, *J* = 10.9, 2.9 Hz, 1H), 4.06 (dd, *J* = 10.9, 8.0 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 2.52−2.49 (m, 1H), 2.03 (m, 3H), 1.89 (m, 1H), 1.44 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.3, 159.4, 156.7, 132.5, 121.6, 110.9, 93.9, 93.3, 65.8, 55.3, 51.3, 36.2, 29.2, 25.1, 24.8; IR (neat) ν_{max} 2935, 2837, 1612, 1584, 1464, 1201, 1153, 815 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{16}H_{19}BrO_3$ 338.0512; found 338.0511.

(6a*S*,10a*S***)-1,3-Dimethoxy-10a-methyl-5-tosyl-5,6,6a,9,10,10a-hexahydrophenanthridine [*trans*-4a].**[14c] According to the general procedure, the reaction of 1,5-enyne (*E*)-**3a** (120.0 mg, 0.29 mmol) with InI_3 (7.2 mg, 0.015 mmol) afforded, after purification by column chromatography (5% EtOAc/hexanes), *trans*-**4a** (108.1 mg, 90%) as a white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.3, 2H), 7.21−7.17 (m, 3H), 6.22 (d, *J* = 2.5, 1H), 5.71 (dq, *J* = 9.9, 3.3 Hz, 1H), 5.33 (dq, *J* = 9.8, 2.1 Hz, 1H), 4.00 (dd, *J* = 11.9, 4.2 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.22 (dd, *J* = 13.6, 11.8 Hz, 1H), 2.99 (dt, *J* = 13.3, 4.1 Hz, 1H), 2.36 (s, 3H), 2.30 (m, 1H), 2.10−2.05 (m, 2H), 1.30−1.29 (m, 1H), 0.66 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.3, 158.2, 143.8, 137.9, 135.8, 129.6, 128.8, 127.4, 125.0, 120.4, 100.4, 96.3, 55.5, 55.4, 47.9, 41.0, 35.2, 31.9, 23.9, 21.6, 16.4; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{27}NO_4SNa$ 436.1553; found 436.1559.

(6a*S*,10a*S***)-1,3-Dimethoxy-7,10a-dimethyl-5-tosyl-5,6,6a,9,10,10a-hexahydrophenanthridine [*trans*-4b].** According to the general procedure, the reaction of 1,5-enyne (*E*)-**3b** (48.8 mg, 0.11 mmol) with InI_3 (2.8 mg, 0.006 mmol) afforded, after purification by column chromatography (5% EtOAc/hexanes), *trans*-**4b** (41.5 mg, 85%) as a white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.3 Hz, 2H), 7.21−7.17 (m, 3H), 6.24 (d, *J* = 2.5 Hz, 1H), 5.39 (m, 1H), 4.38 (dd, *J* = 12.6, 3.6 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.20 (t, *J* = 12.8 Hz, 1H), 2.93 (dd, *J* = 13.1, 6.2 Hz, 1H), 2.36 (s, 3H), 2.22−2.18 (m, 1H), 2.05−1.98 (m, 2H), 1.70 (s, 3H), 1.15−1.07 (m, 1H), 0.80 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.5, 158.1, 143.8, 137.7, 136.3, 130.8, 129.6, 127.4, 123.3, 120.4, 100.4, 96.6, 55.5, 55.4, 45.2, 44.1, 35.9, 31.9, 23.5, 21.7, 21.2, 17.1; IR (neat) ν_{max} 2926, 2839, 1606, 1581, 1455, 1350, 1187, 1164, 671 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{24}H_{29}NO_4SNa$ 450.1709; found 450.1705.

(6a*R*,10a*S***)-1,3-Dimethoxy-10a-methyl-7-phenyl-5-tosyl-5,6,6a,9,10,10a-hexahydrophenanthridine [*trans*-4c].** According to the general procedure, the reaction of 1,5-enyne (*E*)-**3c** (80.9 mg, 0.17 mmol) with InI_3 (4.2 mg, 0.008 mmol) afforded *trans*-**4c** (66.3 mg, 82%) as a white solid after purification by column chromatography (5% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.3 Hz, 2H), 7.36−7.28 (m, 3H), 7.21−7.11 (m, 4H), 7.13 (d, *J* = 2.5 Hz, 1H), 6.26 (d, *J* = 2.5 Hz, 1H), 5.67 (q, *J* = 3.4 Hz, 1H), 4.09 (dd, *J* = 12.7, 3.4 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.09−3.04 (m, 1H), 2.98 (t, *J* = 12.8 Hz, 1H), 2.79 (dq, *J* = 12.9, 3.1 Hz, 1H), 2.37 (s, 3H), 2.23−2.21 (m, 2H), 1.41−1.30 (m, 1H), 0.94 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.4, 158.2, 143.7, 141.6, 137.9, 137.5, 136.6, 129.6, 128.3, 127.9, 127.5, 127.3, 126.9, 120.3, 100.5, 96.5, 55.5, 45.7, 43.4, 36.2, 31.7, 23.9, 21.7, 17.3; IR (neat) ν_{max} 2935, 2837, 1604, 1579, 1418, 1349, 1201, 1163, 1152, 664 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{29}H_{31}NO_4SNa$ 512.1866; found: 512.1860.

(6a*S*,10a*S***)-7-Bromo-1,3-dimethoxy-10a-methyl-5-tosyl-5,6,6a,9,10,10a-hexahydrophenanthridine [*trans*-4d].**[14c] According to the general procedure, the reaction of 1,5-enyne (*E*)-**3d** (79.8 mg, 0.17 mmol) with InI_3 (4.1 mg, 0.008 mg) afforded, after purification by column chromatography (5% EtOAc/hexanes), *trans*-**4d** (58.3 mg, 73%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60−7.57 (m, 2H), 7.24−7.21 (m, 2H), 7.20 (d, *J* = 2.5 Hz, 1H), 6.25 (d, *J* = 2.5 Hz, 1H), 6.08 (dd, *J* = 4.8, 2.8 Hz, 1H), 4.65 (dd, *J* = 13.0, 3.5 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.24 (t, *J* = 12.8 Hz, 1H), 3.00 (dd, *J* = 13.3, 6.0 Hz, 1H), 2.41 (m, 1H), 2.38 (s, 3H), 2.14−2.05 (m, 2H), 1.20−1.12 (m, 1H), 0.93 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.2, 158.5, 143.9, 137.9, 136.3, 130.8, 129.8, 127.5, 121.0, 119.1, 100.8, 96.8, 55.5, 55.4, 47.2, 46.3, 38.2, 31.4, 25.9, 21.7, 17.3; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{27}BrNO_4S$ 492.0838; found 492.0839.

(6a*R*,10a*S***)-10a-Methyl-5-tosyl-5,6,6a,9,10,10a-hexahydrophenanthridine [*cis*-4e].** According to the general procedure, reactions of 1,5-enyne (*E*)-**3e** (85.5 mg, 0.24 mmol) with InI_3 (5.9 mg, 0.012 mmol) or 1,5-enyne (*Z*)-**3e** (89.0 mg, 0.25) with InI_3 (6.3 mg, 0.013 mmol) afforded, after purification by column chromatography

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(5% EtOAc/hexanes), *cis*-**4e** [41.9 mg, 49% from (*E*)-**3e** and 56.1 mg, 63% from (*Z*)-**3e**] as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75−7.72 (m, 1H), 7.51−7.48 (m, 2H), 7.26−7.13 (m, 5H), 5.75 (ddd, J = 9.4, 4.7, 2.4 Hz, 1H), 5.45 (ddt, J = 9.2, 4.9, 2.3 Hz, 1H), 4.16 (dd, J = 14.1, 3.4 Hz, 1H), 3.23 (ddd, J = 15.2, 10.8, 4.4 Hz, 1H), 2.37 (s, 3H), 1.99−1.93 (m, 2H), 1.81 (d, J = 11.3 Hz, 1H), 1.57 (dt, J = 9.4, 2.3 Hz, 2H), 0.91 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.7, 139.0, 137.4, 135.7, 129.7, 128.9, 127.6, 127.3, 126.4, 125.7, 125.5, 124.5, 48.4, 39.3, 34.7, 33.3, 25.7, 22.4, 21.6; IR (neat) ν_{max} 2925, 1486, 1447, 1347, 1163, 1090, 658 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{21}H_{23}NO_2SNa$: 376.1341; found: 376.1348.

(6a*R,10a*S**)-1,3-Dimethoxy-10a-methyl-5-tosyl-5,6,6a,9,10,10a-hexahydrophenanthridine [*cis*-4a].** According to the general procedure, the reaction of 1,5-enyne (*Z*)-**3a** (95.3 mg, 0.23 mmol) with InI_3 (5.7 mg, 0.011 mmol) afforded, after purification by column chromatography (5% EtOAc/hexanes), *cis*-**4a** (83.9 mg, 88%) as a white solid; mp 101−103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 2.6 Hz, 1H), 6.31 (d, J = 2.6 Hz, 1H), 5.79−5.75 (m, 1H), 5.41−5.38 (m, 1H), 4.14 (dd, J = 14.0, 3.2 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.17 (dd, J = 14.0, 11.2 Hz, 1H), 2.37 (s, 3H), 2.15 (dt, J = 13.2, 4.2 Hz, 1H), 1.93−1.87 (m, 2H), 1.74 (d, J = 11.0 Hz, 1H), 1.42 (ddd, J = 13.1, 10.6, 5.4 Hz, 1H), 0.95 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.9, 158.0, 143.7, 137.9, 137.6, 129.7, 129.5, 127.3, 125.6, 120.2, 101.2, 97.8, 55.5, 55.3, 48.3, 41.5, 34.9, 28.0, 22.6, 22.3, 21.6; IR (neat) ν_{max} 2928, 2837, 1607, 1579, 1460, 1349, 1161, 672 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{23}H_{27}NO_4SNa$ 436.1553; found 436.1555.

(6a*R,10a*S**)-7-Bromo-1,3-dimethoxy-10a-methyl-5-tosyl-5,6,6a,9,10,10a-hexahydrophenanthridine [*cis*-4d].** According to the general procedure, the reaction of 1,5-enyne (*Z*)-**3d** (90.2 mg, 0.18 mmol) with InI_3 (4.6 mg, 0.009 mmol) afforded, after purification by column chromatography (5% EtOAc/hexanes), *cis*-**4d** (64.9 mg, 72%) as a white solid; mp 144−146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 2.6 Hz, 1H), 6.34 (d, J = 2.6 Hz, 1H), 6.12 (t, J = 4.0 Hz, 1H), 4.65 (dd, J = 14.3, 3.2 Hz, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 3.06 (dd, J = 14.3, 11.9 Hz, 1H), 2.37 (s, 3H), 2.30−2.24 (m, 1H), 1.99−1.95 (m, 2H), 1.79−1.75 (m, 1H), 1.25 (ddd, J = 13.6, 10.6, 6.7 Hz, 1H), 0.92 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.4, 158.3, 143.9, 137.8, 136.8, 131.1, 129.7, 127.7, 121.5, 120.1, 102.1, 98.3, 55.6, 55.3, 49.0, 47.4, 37.3, 26.1, 24.7, 21.7, 21.4; IR (neat) ν_{max} 2932, 1608, 1579, 1461, 1352, 1203, 1164, 672 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{23}H_{26}BrNO_4SNa$ 514.0658; found: 514.0657.

(6a*S,10a*S**)-1,3-Dimethoxy-5-tosyl-5,6,6a,9,10,10a-hexahydrophenanthridine [*trans*-4f].** According to the general procedure, the reaction of 1,5-enyne (*E*)-**3f** (85.0 mg, 0.22 mmol) with InI_3 (5.5 mg, 0.011 mmol) afforded, after purification by column chromatography (5% EtOAc/hexanes), *trans*-**4f** (67.2 mg, 79%,) as a white solid; mp 101−103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H), 7.07 (d, J = 2.5 Hz, 1H), 6.26 (d, J = 2.5 Hz, 1H), 5.66−5.63 (m, 1H), 5.52 (dq, J = 9.7, 2.0 Hz, 1H), 4.22 (dd, J = 12.8, 3.7 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.05 (dd, J = 12.8, 12.1 Hz, 1H), 2.82 (ddt, J = 13.0, 5.5, 2.5 Hz, 1H), 2.38 (s, 3H), 2.21 (td, J = 11.2, 11.2, 2.2 Hz, 1H), 2.19−1.99 (m, 2H), 2.02 (bt, J = 11.5 Hz, 1H), 1.03−0.96 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.6, 158.5, 143.7, 139.1, 137.0, 129.7, 128.8, 127.7, 127.3, 114.8, 101.3, 96.6, 55.6, 55.4, 51.2, 39.2, 38.6, 27.2, 27.1, 21.7; IR (neat) ν_{max} 2929, 2836, 1607, 1579, 1455, 1346, 1185, 1162, 665 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{22}H_{25}NO_4SNa$ 422.1396; found 422.1397.

(4S*,9S*)-7-Methoxy-4-methyl-4,9-tetrahydro-3*H*-xanthene [*trans*-6a].[20] According to the general procedure, the reaction of 1,5-enyne (*E*)-**5a**[20] (97.6 mg, 0.42 mmol) with InI_3 (10.5 mg, 0.021 mmol) afforded, after purification by column chromatography (5% EtOAc/hexanes), *trans*-**6a** (83.9 mg, 86%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, J = 8.8 Hz, 1H), 6.70 (dd, J = 8.9, 2.9 Hz, 1H), 6.63 (d, J = 2.9 Hz, 1H), 5.68−5.65 (m, 1H), 5.49 (ddt, J = 9.7, 2.9, 1.6 Hz, 1H), 3.76 (s, 3H), 2.69 (dd, J = 13.9, 3.4 Hz, 1H), 2.67−2.47 (m, 2H), 2.34−2.29 (m, 1H), 2.26−2.22 (m, 1H), 1.98−1.93 (m, 1H), 1.86 (td, J = 11.9, 6.9 Hz, 1H), 1.10 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.1, 148.0, 128.5, 127.0, 123.1, 118.1, 114.5, 113.7, 75.5, 55.8, 39.1, 35.4, 28.5, 25.2, 16.0; HRMS (EI) m/z: [M]$^+$ calcd for $C_{15}H_{18}O_2$ [M]$^+$: 230.1301; found: 230.1294.

(4S*,9R*)-1-Bromo-7-methoxy-4-methyl-4,9-tetrahydro-3*H*-xanthene [*trans*-6b].[14c] According to the general procedure, the reaction of 1,5-enyne (*E*)-**5b**[14c] (105.4 mg, 0.31 mmol) with InI_3 (7.7 mg, 0.016 mmol) afforded, after purification by column chromatography (5% EtOAc/hexanes), *trans*-**6b** (93.8 mg, 89%) as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78−6.67 (m, 3H), 6.11−6.08 (m, 1H), 3.76 (s, 3H), 3.05 (dd, J = 16.1, 5.2 Hz, 1H), 2.86−2.82 (m, 1H), 2.57 (ddt, J = 16.1, 13.4, 1.0 Hz, 1H), 2.29−2.24 (m, 2H), 1.99−1.89 (m, 2H), 1.15 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.4, 147.2, 129.2, 123.8, 122.6, 117.9, 114.3, 114.1, 76.1, 55.8, 45.1, 34.9, 29.0, 25.9, 16.5; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{15}H_{18}BrO_2$ 309.0484; found: 309.0481.

(4S*,9R*)-7-Methoxy-4-methyl-4,9-tetrahydro-3*H*-xanthene [*cis*-6a]. According to the general procedure, the reaction of 1,5-enyne (*Z*)-**5a** (82.7 mg, 0.35 mmol) with InI_3 (8.9 mg, 0.017 mmol) afforded, after purification by column chromatography (5% EtOAc/hexanes), *cis*-**6a** (71.9 mg, 87%) as a white solid; mp 75−77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69−6.67 (m, 2H), 6.58 (d, J = 2.6 Hz, 1H), 5.72−5.68 (m, 1H), 5.35 (dq, J = 9.9, 2.2 Hz, 1H), 3.74 (s, 3H), 3.08 (dd, J = 16.3, 6.1 Hz, 1H), 2.52 (dd, J = 16.3, 3.7 Hz, 1H), 2.43 (dt, J = 5.6, 2.8 Hz, 1H), 2.31 (ddq, J = 15.7, 9.5, 2.9 Hz, 1H), 2.06−1.95 (m, 2H), 1.70 (ddd, J = 13.4, 9.6, 6.6 Hz, 1H), 1.33 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 152.9, 148.1, 128.8, 128.5, 120.0, 117.2, 114.1, 113.5, 73.7, 55.8, 36.8, 33.8, 29.7, 26.0, 22.9; IR (neat) ν_{max} 2921, 2832, 1494, 1236, 1213, 1101, 1041 cm^{-1}; HRMS (EI) m/z: [M]$^+$ calcd for $C_{15}H_{18}O_2$ 230.1301; found 230.1293.

(4S*,9S*)-1-Bromo-7-methoxy-4-methyl-4,9-tetrahydro-3*H*-xanthene [*cis*-6b]. According to the general procedure, the reaction of 1,5-enyne (*Z*)-**5b** (76.0 mg, 0.25 mmol) with InI_3 (6.1 mg, 0.012 mmol) afforded, after purification by column chromatography (5% EtOAc/hexanes), *cis*-**6b** (69.9 mg, 92%) as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70−6.69 (m, 2H), 6.61 (d, J = 2.6 Hz, 1H), 6.05 (td, J = 4.1, 1.6 Hz, 1H), 3.76 (s, 3H), 3.13 (dd, J = 16.6, 6.0 Hz, 1H), 2.94 (dd, J = 16.6, 6.0 Hz, 1H), 2.62 (m, 1H), 2.36−2.30 (m, 1H), 2.11−2.02 (m, 1H), 1.94 (dt, J = 12.4, 6.1 Hz, 1H), 1.74−1.65 (m, 1H), 1.42 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 153.3, 147.6, 129.9, 124.4, 120.2, 117.1, 113.8, 113.7, 75.9, 55.9, 45.5, 31.6, 29.1, 26.4, 25.0; HRMS (EI) m/z: [M]$^+$ calcd for $C_{15}H_{17}BrO_2$ 308.0406; found: 308.0395.

5′,7′-Dimethoxyspiro[cyclohexane-1,4′-isochroman]-3-ene (8a).[14c] According to the general procedure, the reaction of 1,5-enyne **7a** (98.3 mg, 0.38 mmol) with InI_3 (9.5 mg, 0.019 mmol) afforded, after purification by column chromatography (5% EtOAc/hexanes), **8a** (82.6 mg, 84%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (d, J = 2.5 Hz, 1H), 6.12 (d, J = 2.5 Hz, 1H), 5.70 (d, J = 2.6 Hz, 2H), 4.69 (d, J = 0.8 Hz, 2H), 3.92 (d, J = 11.4 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.59 (dd, J = 11.4, 1.3 Hz, 1H), 2.88−2.68 (m, 2H), 2.08−2.01 (m, 3H), 1.46−1.42 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.8, 158.6, 137.5, 126.4, 125.5, 122.5, 99.9, 98.1, 73.9, 70.0, 55.3, 55.1, 34.5, 31.6, 27.5, 22.1; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{16}H_{21}O_3$ 261.1485; found: 261.1479.

5′,7′-Dimethoxy-2′-tosyl-2′,3′-dihydro-1′*H*-spiro-[cyclohexane-1,4′-isoquinolin]-3-ene (8b).[14c] According to the general procedure, the reaction of 1,5-enyne **7b** (88.5 mg, 0.21 mmol) with InI_3 (5.3 mg, 0.011 mmol) afforded, after purification by column chromatography (10% EtOAc/hexanes), **8b** (81.4, 92%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 6.32 (d, J = 2.5 Hz, 1H), 6.15 (d, J = 2.5 Hz, 1H), 5.76−5.65 (m, 2H), 4.16 (d, J = 14.5 Hz, 1H), 4.00 (d, J = 14.5 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.16 (d, J = 11.7 Hz, 1H), 3.00−2.93 (m, 2H), 2.69 (td, J = 13.1, 12.4, 6.8 Hz, 1H), 2.44 (s, 3H), 2.12 (m, 2H), 1.90 (d, J = 18.2 Hz, 1H), 1.45 (dd, J = 13.5, 5.5 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.8, 158.7, 143.7, 134.4, 133.0, 129.8, 128.0, 126.0, 125.5, 122.9, 102.1, 98.5, 55.4, 55.2, 52.5, 50.1, 37.0, 31.9, 27.8, 22.0, 21.7; HRMS (EI) m/z: [M]$^+$ calcd for $C_{23}H_{27}NO_4S$ 413.1655; found 413.1643.

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3-Bromo-5′,7′-dimethoxy-2′-tosyl-2′,3′-dihydro-1′*H*-spiro-[cyclohexane-1,4′-isoquinolin]-3-ene (8c).[14c] According to the general procedure, the reaction of 1,5-enyne **7c** (95.0 mg, 0.19 mmol) with InI_3 (4.8 mg, 0.010 mmol) afforded, after purification by column chromatography (10% EtOAc/hexanes), **8c** (72.2 mg, 76%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 6.35 (d, J = 2.5 Hz, 1H), 6.15 (d, J = 2.5 Hz, 1H), 6.08 (m, 1H), 4.10 (q, J = 14.6 Hz, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.51−3.44 (m, 1H), 3.19 (d, J = 12.0 Hz, 1H), 2.95 (d, J = 11.9 Hz, 1H), 2.55 (td, J = 12.3, 6.5 Hz, 1H), 2.44 (s, 3H), 2.26−2.09 (m, 3H), 1.64−1.53 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.4, 159.0, 143.8, 134.4, 132.9, 129.8, 127.8, 127.0, 121.0, 120.8, 102.2, 98.4, 55.3, 55.2, 52.2, 49.8, 41.3, 39.6, 26.3, 24.0, 21.6; HRMS (EI) m/z: [M]$^+$ calcd for $C_{23}H_{26}BrNO_4S$: 491.0760; found 491.0770.

General Procedure for the One-Pot Sequential Indium-Catalyzed Cycloisomerization and Palladium-Catalyzed Cross-Coupling Reactions of (*E*)-5b and 7c. In a Schlenk tube filled with argon, InI_3 (5 mol %) was placed and a solution of 1,5-enyne (*E*)-**5b** or **7c** (~0.07 M) in toluene was stirred at room temperature (for **5b**) or 60°C in an oil bath (for **7c**) until the starting material was consumed (TLC). Then, $Pd(PPh_3)_4$ (5 mol %) and a solution of R_3In (70 mol %, 0.45 M in dry THF) were added and the mixture was stirred at 80 °C in an oil bath for 10 h. The reaction was quenched by the addition of a few drops of MeOH and the mixture was concentrated *in vacuo*. H_2O (10 mL) was added and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine (15 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography to afford, after concentration and high vacuo drying, the corresponding products *trans*-**6c−e** and **8d**.

(4*S,9*S**)-7-Methoxy-4-methyl-1-phenyl-4,9-tetrahydro-3*H*-xanthene [*trans*-6c].**[20] According to the general procedure, the reaction of 1,5-enyne (*E*)-**5b**[14c] (96.0 mg, 0.31 mmol) with InI_3 (7.1 mg, 0.016 mmol), triphenylindium (0.217 mmol), and $Pd(PPh_3)_4$ (17.5 mg, 0.016 mmol) afforded, after purification by column chromatography (5% EtOAc/hexanes), *trans*-**6c** (72.2 mg, 76% in two steps) as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.28 (m, 3H), 7.26−7.20 (m, 2H), 6.78 (d, J = 8.9 Hz, 1H), 6.69 (dd, J = 8.9, 2.9 Hz, 1H), 6.51 (d, J = 3.0 Hz, 1H), 5.73 (dt, J = 5.1, 2.7 Hz, 1H), 3.70 (s, 3H), 3.08−3.03 (m, 1H), 2.70 (dd, J = 16.7, 5.2 Hz, 1H), 2.45−2.35 (m, 2H), 2.27−2.16 (m, 1H), 2.03−1.99 (m, 2H), 1.19 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.1, 147.5, 141.4, 140.0, 128.2, 127.5, 126.9, 126.1, 123.3, 118.0, 114.2, 114.0, 76.0, 55.8, 40.6, 35.3, 27.3, 24.7, 16.6; HRMS (EI) m/z: [M]$^+$ calcd for $C_{21}H_{22}O_2$ 306.1614; found: 306.1587.

(4*S,9*S**)-7-Methoxy-1,4-dimethyl-4,9-tetrahydro-3*H*-xanthene [*trans*-6d].**[20] According to the general procedure, the reaction of 1,5-enyne (*E*)-**5b** (96.3 mg, 0.31 mmol) with InI_3 (7.1 mg, 0.016 mmol), trimethylindium (0.217 mmol), and $Pd(PPh_3)_4$ (17.5 mg, 0.016 mmol) afforded, after purification by column chromatography (5% EtOAc/hexanes), *trans*-**6d** (62.9 mg, 83% in two steps) as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77−6.65 (m, 3H), 5.39 (m, 1H), 3.76 (s, 3H), 2.87−2.79 (m, 1H), 2.53−2.50 (m, 2H), 2.21−2.18 (m, 2H), 1.92−1.82 (m, 2H), 1.72 (s, 3H), 1.09 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.1, 147.7, 133.7, 123.1, 121.7, 117.9, 114.5, 113.7, 75.9, 55.8, 42.1, 35.6, 26.4, 24.2, 20.1, 16.5; HRMS (EI) m/z: [M]$^+$ calcd for $C_{16}H_{20}O_2$ 244.1458; found 244.1439.

(4*S,9*S**)-1-Butyl-7-methoxy-4-methyl-4,9-tetrahydro-3*H*-xanthene [*trans*-6e].** According to the general procedure, the reaction of 1,5-enyne (*E*)-**5b**[14c] (95.7 mg, 0.31 mmol) with InI_3 (7.1 mg, 0.016 mmol), tributylindium (0.217 mmol), and $Pd(PPh_3)_4$ (17.5 mg, 0.016 mmol) afforded, after purification by column chromatography (5% EtOAc/hexanes), *trans*-**6e** (71.9 mg, 81% two steps) as a white solid; mp 48−50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78−6.72 (m, 2H), 6.66 (d, J = 2.7 Hz, 1H), 5.39 (m, 1H), 3.76 (s, 3H), 2.85 (d, J = 11.0 Hz, 1H), 2.54−2.50 (m, 2H), 2.21 (m, 2H), 2.06−1.81 (m, 4H), 1.41−1.26 (m, 4H), 1.09 (s, 3H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.0, 147.7, 137.7, 123.1, 120.8, 117.9, 114.4, 113.8, 76.1, 55.8, 40.7, 35.6, 33.5, 30.7, 26.2, 24.2, 22.6, 16.6, 14.2; IR (neat) ν_{max} 2929, 2856, 1493, 1224, 1148, 1081, 1041 cm^{-1}; HRMS (EI) m/z: [M]$^+$ calcd for $C_{19}H_{26}O_2$ 286.1927; found: 286.1923.

5′,7′-Dimethoxy-3-phenyl-2′-tosyl-2′,3′-dihydro-1′*H*-spiro-[cyclohexane-1,4′-isoquinolin]-3-ene (8d). According to the general procedure, the reaction of 1,5-enyne **7c** (95.2 mg, 0.19 mmol) with InI_3 (4.9 mg, 0.010 mmol), triphenylindium (0.13 mmol), and $Pd(PPh_3)_4$ (11.0 mg, 0.010 mmol) afforded, after purification by column chromatography (5% EtOAc/hexanes), **8d** (56.7 mg, 61% in two steps) as a white solid; mp 125−127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.67 (m, 2H), 7.41−7.39 (m, 2H), 7.32−7.21 (m, 5H), 6.35 (d, J = 2.5 Hz, 1H), 6.18 (d, J = 2.5 Hz, 1H), 6.13 (q, J = 3.4, 2.4 Hz, 1H), 4.21−4.08 (m, 2H), 3.76 (s, 6H), 3.37 (dd, J = 17.2, 3.3 Hz, 1H), 3.12 (q, J = 11.9 Hz, 2H), 2.73−2.67 (m, 1H), 2.39 (s, 3H), 2.30 (d, J = 17.3 Hz, 3H), 1.26 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.8, 158.9, 143.7, 142.6, 135.7, 134.6, 133.2, 129.8, 128.3, 127.9, 126.8, 125.5, 123.0, 122.6, 102.2, 98.6, 55.4, 55.3, 52.5, 50.0, 37.7, 34.0, 27.2, 22.8, 21.7; IR (neat) ν_{max} 2932, 2841, 1608, 1460, 1340, 1164, 1055, 831 cm^{-1}; HRMS (EI) m/z: [M]$^+$ calcd for $C_{29}H_{31}NO_4S$ 489.1968; found 489.1976.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00825.

Copies of ^{1}H and ^{13}C{^{1}H} NMR spectra (PDF)

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Notes

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