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Iron-Catalyzed 1,5-Enyne Cycloisomerization via 5-*Endo-Dig* Cyclization for the Synthesis of 3-(Inden-1-yl)indole Derivatives

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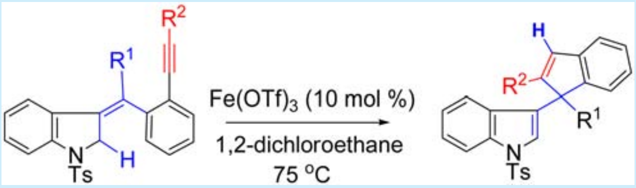
Supporting Information

ABSTRACT: An Fe(OTf)$_3$-catalyzed 1,5-enyne cycloisomerization via 5-*endo-dig* cyclization is described for the synthesis of 3-(1-indenyl)indole derivatives. Since a variety of 1,5-enynes are readily accessible via Heck–Suzuki coupling, this strategy provides a rapid and easy access to a wide range of highly substituted 3-(1-indenyl)indoles in good yields.

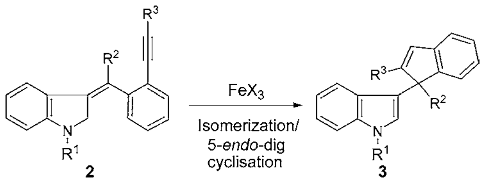


Transition-metal-catalyzed 1,5-enyne cycloisomerization is one of the most important strategies for the construction of complex carbocycles or heterocycles.[1] This process is attractive as wide structural complexity can be explored with compounds containing enyne subunits with high atom economy.[2] Depending on the catalyst, substrates, and reaction conditions, structurally diverse organic compounds are formed via this synthetic route, and a variety of enyne cycloisomerizations have been reported in the past few years. However, 1,5-enyne cycloisomerization processes involving 5-*endo-dig* cyclizations have been less explored, despite their potential synthetic utility.[3] Therefore, the design and development of new systems bearing 1,5-enynes and their application to the synthesis of pharmaceutically important molecules will be highly valuable.

In this regard, indole derivatives are ubiquitously found in natural products, agrochemicals, pharmaceuticals, and functional materials, and hence, considerable efforts have been made to construct or functionalize indoles.[4] In particular, C3-substituted indoles are a very important class of compounds because of their biological activities and medicinal application.[5] Similarly, the indene skeleton is also an important synthetic target in organic chemistry because it is often encountered in many natural products and biologically active pharmaceutical agents.[6] Consequently, numerous synthetic methods have been developed for the synthesis of both C3-substituted indoles[7] and indene derivatives.[8] On the other hand, hybrid molecules with two structural domains having different biological functions are currently an important research topic in the rational design and development of new drugs.[9] Therefore, due to the significance of C3-substituted indoles and substituted indenes, the synthesis of a hybrid structure containing these two classes of compounds would be very challenging. However, until now, only one report has been found in the literature for the synthesis of 3-(1-indenyl)indole derivatives involving Au(I)-catalyzed 1,2-indole migration/C–H insertion reactions of C3-propargylated indoles in moderate to good yields as a regioisomeric mixture.[10] For this reason, the establishment of new, efficient synthetic methods for the synthesis of 3-(1-indenyl)indole derivatives with selective control of substitution patterns from easily obtained starting materials would be highly desirable.

Very recently, we have reported a novel iron(III)-catalyzed strategy for the synthesis of polycyclic heterocycles via isomerization or isomerization/cyclization of 3-(methylene)-indoline derivatives under mild and neutral conditions.[11] Encouraged by these results, we reasonably anticipated that the 3-(methylene)indoline derivative **2** may undergo iron(III)-catalyzed 1,5-enyne cycloisomerization via 5-*endo-dig* cyclization (Scheme 1). In this paper, we report a new and flexible method for the synthesis of diversely substituted 3-(1-indenyl)indoles through Fe(OTf)$_3$-catalyzed 5-*endo-dig* cycloisomerization of 1,5-enynes in good yields. The synthesis of model substrate **2a** is shown in Scheme 3.

Scheme 1. Iron-Mediated Isomerization/Cyclization for the Synthesis of 3-(1-Indenyl)indole



The domino Heck–Suzuki coupling between substrate **1a** and phenylboronic acid was accomplished to afford the 1,5-enyne **2a** in 65% yield using 5 mol % of Pd(OAc)$_2$ and 10 mol % of tricyclohexylphosphine (PCy$_3$) in the presence of 2.5 M K$_2$CO$_3$ in ethanol and toluene at 70 °C (Scheme 2).[11] The *N*-propargylation of the tosylamide derivative of 2-iodoaniline **A** with diynyl bromide **B** was carried out in the presence of K$_2$CO$_3$ in CH$_3$CN at 70 °C to obtain **1a** in 80% yield.

With the desired 1,5-enyne substrate **2a** in hand, we set out to optimize the reaction conditions with respect to catalysts,

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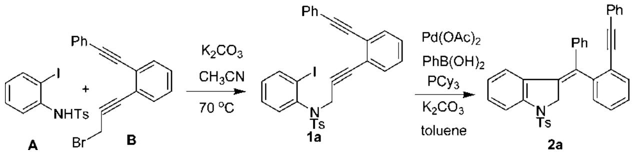
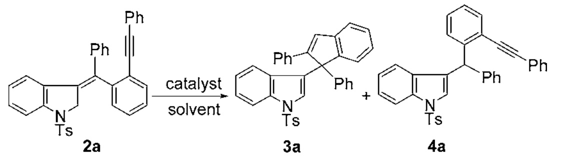
Scheme 2. Preparation of Substrate 2a



solvent, and temperature. We first examined the cycloisomerization of **2a** in the presence of Fe(OTf)$_3$ (10 mol %) in 1,2-dichloroethane at 65 °C. Under these reaction conditions, only isomerized product **4a** was obtained in 75% yield through the complexation of olefin with Fe(OTf)$_3$.[11a] When the reaction was carried out at 75−80 °C for 4 h, the desired 3-(1-indenyl)indole **3a** was obtained as a sole product in 85% yield (Table 1, entry 2) due to selective complexation of Fe(OTf)$_3$ with an alkyne unit. Switching the solvent from 1,2-dichloroethane to other solvents such as CH$_3$CN, THF, or MeNO$_2$ gave inferior results. For example, both CH$_3$CN and MeNO$_2$ produced **3a** in 50% yield, whereas the reaction did not initiate in THF and toluene (Table 1, entries 3−5). Other iron salts such as FeCl$_3$ failed to execute this transformation; instead, it produced a mixture of nonseparable products (Table 1, entry 6). Interestingly, FeBr$_3$ produced isomerized product **4a** in 40% yield without formation of any desired cyclized product **3a** (Table 1, entry 7). Next, other metal salts were investigated, such as In(OTf)$_3$, AgOTf, AgSbF$_6$, and AuCl, under similar reaction conditions. In(OTf)$_3$ did not give any products (Table 1, entry 8), AgOTf and AgSbF$_6$ afforded in 50% and 70% yields, respectively (Table 1, entries 9 and 10), and AuCl gave only 55% of the desired product **3a** (Table 1, entry 11). These results demonstrated that Fe(OTf)$_3$ (10 mol %) exhibited higher catalytic activity for this particular transformation. Thus, Fe(OTf)$_3$ (10 mol %) in 1,2-dichloroethane at 75−80 °C for 4 h was defined as the optimum reaction conditions. The structure of **3a** was characterized by ^{1}H, ^{13}CNMR and HRMS spectra and finally confirmed by X-ray diffraction (Figure 1, CCDC no. 1488890).

Table 1. Optimization of Reaction Conditions[a]



entry	catalysts	solvent	temp (°C)	time (h)	yield (%) 3a	yield (%) 4a
1	Fe(OTf)$_3$	DCE	65	4	0	75
2	Fe(OTf)$_3$	DCE	75	4	85	0
3	Fe(OTf)$_3$	CH$_3$CN	75	6	50	0
4	Fe(OTf)$_3$	THF	75	6	trace	0
5	Fe(OTf)$_3$	CH$_3$NO$_2$	75	4	50	0
6	FeCl$_3$	DCE	75	4	0	0
7	FeBr$_3$	DCE	75	4	0	40
8	In(OTf)$_3$	DCE	75	4	NR	NR
9	AgOTf	DCE	75	4	50	0
10	AgSbF$_6$	DCE	75	4	70	0
11	AuCl	DCE	75	4	55	0

[a] Reaction conditions: **2a** (0.5 mmol) and catalyst (0.05 mmol) in 3 mL of solvent under Ar atmosphere. [b] Isolated yield.

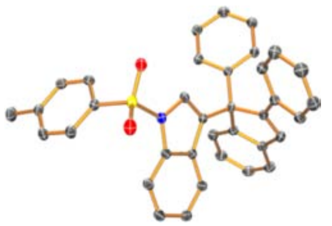
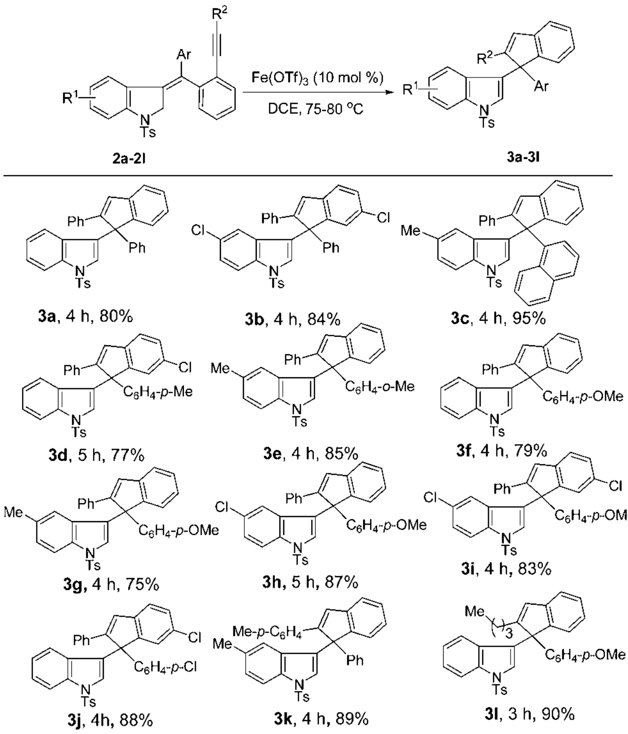


Figure 1. ORTEP diagram of **3a** (H atoms are omitted for clarity). Thermal ellipsoids are given at the 50% probability level.

Having successfully optimized the reaction conditions for the domino isomerization and cyclization process, we then wanted to explore the scope of the protocol with a variety of substrates. A series of substrates containing the 1,5-enyne motif **2b−j** have been prepared following the above strategy in good yields (56−86%) (see the Supporting Information).

After synthesizing substrates **2b−j**, we investigated any steric or electronic influence that the aryl group (Ar) at the olefin center might have, as this center of the alkene directly participated in the cyclization process. Both unsubstituted and substituted aryl groups were investigated; the results are summarized in Scheme 3. It was observed that the unsubstituted aryl rings, such as phenyl (Scheme 1, **3a** and **3b**) and *α*-naphthyl ring (Scheme 3, **3c**), were well tolerated, and the desired indole-tethered indene derivatives were obtained in excellent yields, such as 80%, 84%, and 95%, respectively. Introduction of aryl rings with electron-donating groups such as *o*-Me, *p*-Me, and *p*-OMe led to product formation in high yields of 75−87% (Scheme 3, **3d−i**). Similarly, introduction of electron-withdrawing groups such as a

Scheme 3. Fe(OTf)$_3$-Catalyzed 1,5-Enyne Cycloisomerization of (3-Methylene)indoline Derivatives[a]

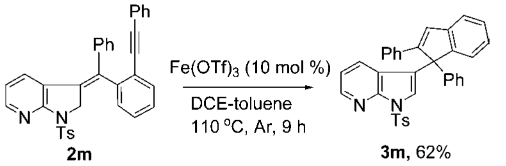


[a] Reaction conditions: **2a** (0.5 mmol) and Fe(OTf)$_3$ (0.05 mmol) in 3 mL of 1,2-DCE under inert atmosphere. [b] Isolated yield.

p-Cl group (Scheme 3, **3j**) also induced the Fe(OTf)$_3$-catalyzed 1,5-enyne cycloisomerization and furnished the desired product in high yields (88%). It appears that there was no pronounced stereoelectronic effect of the substituent on the olefinic aryl ring. A substrate (Scheme 3, **3c**) containing a highly congested α-naphthyl system was also smoothly transformed to the desired product with excellent yield. Moreover, the reaction was not markedly affected by the substituent on the aniline derivatives. Both an electron-donating −Me group (Scheme 3, **3c**, **3e**, **3g**) and an electron-withdrawing −Cl group (Scheme 3, entries **3b**, **3h−j**) prove fruitful in this context. Furthermore, the reaction could smoothly convert into the desired 3-(1-indenyl)indole derivatives in very good yields when *p*-tolyl- and butyl-substituted alkyne were installed at the alkyne terminus instead of a phenyl group (Scheme 3, **3k** and **3l**). Notably, the reaction was very clean and in all cases afforded the 5-*endo-dig*-cyclized products. Along this line, it is noteworthy that this strategy leads to 3-(1-indenyl)indole derivatives having all-carbon quaternary centers. Quaternary carbon centers are widely found in various natural products and pharmaceuticals, and hence, 3-substituted indole derivatives having all-carbon quaternary centers should be very attractive.

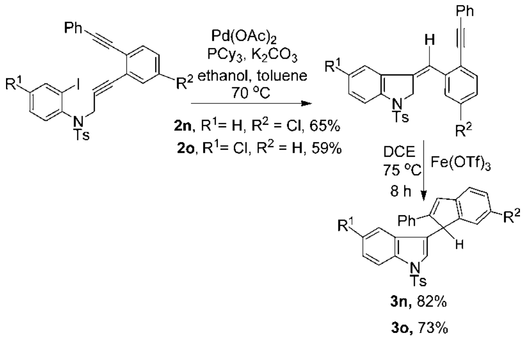
To broaden the scope of our strategy, we extended our iron-catalyzed reaction for the synthesis of 3-(1-indenyl)-7-azaindole derivative. First, we prepared the precursor of 1,5-enyne system **2k** using a Heck−Suzuki coupling reaction in 70% yield. But when the substrate **2m** was treated with Fe(OTf)$_3$ in 1,2-dichloroethane at 80 °C, no reaction took place. When compound **2m** was dissolved in a mixture of dichloroethane and toluene (2:1) and was heated to 110 °C, substrate **2m** smoothly converted to the desired 7-azaindole-tethered indene derivative **3m** with all-carbon quaternary centers in 62% yield (Scheme 4).

Scheme 4. Fe(OTf)$_3$-Catalyzed Synthesis of 7-Azaindole Derivative



Furthermore, we also investigated the reaction in the absence of aryl group (Ar = H) at the olefin center. The results are summarized in Scheme 5. To do so, we prepared 1,5-enyne substrates **2n** and **2o** in 65% and 59% yields through reductive carbopalladation of **1n** and **1o** in the presence of Pd(OAc)$_2$/PCy$_3$ and K$_2$CO$_3$ in the toluene−ethanol mixture at 70 °C. Presumably, ethanol acts as a hydride source for the reduction of intermediate carbopalladation complex in the presence of K$_2$CO$_3$.[11a,12] Pleasantly, the 1,5-enyne isomerization of **2n** and **2o** proceeded smoothly under similar reaction conditions, affording the corresponding 3-(1-indenyl)indole derivative in 82% and 73% yields, respectively.

Scheme 5. Fe(OTf)$_3$-Catalyzed 1,5-Enyne Cycloisomerization

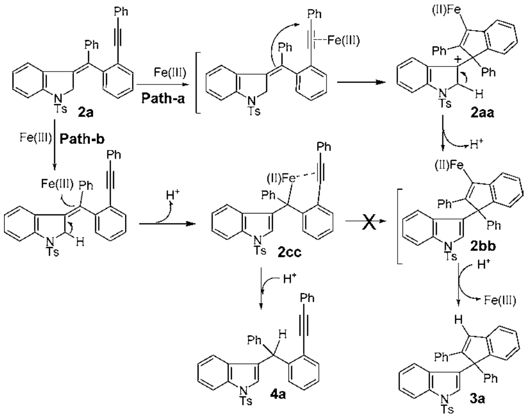


Therefore, this new transformation is quite general. All of the substrates were smoothly transformed to the 3-(1-indenyl)-indole derivatives via 5-*endo-dig* cyclization in high yields. Although iron is very popular in contemporary metal catalysis and modern organic synthesis due to its environmentally friendly characteristics, iron-mediated enyne cycloisomerizations are very limited. So far, only specially designed low-valent Fe(0)/Fe(-II) complexes have been reported to perform enyne cycloisomerization.[13]

The effect of temperature is very crucial in the case of Fe(OTf)$_3$-catalyzed 1,5-enyne cycloisomerization. The 1,5-enyne cycloisomerization of all of the above substrates readily took place at temperatures ≥75 °C; however, at lower temperature (65 °C), two tested tetrasubstituted olefins (Heck−Suzuki products) such as **2a** and **2g** gave only isomerized products via a hydrogen shift, similar to our previous report.[11a] In addition, in our previous report, we also proved that isomerization was not due to catalysis by the in situ generated TfOH; it was truly catalyzed by Fe(OTf)$_3$. We believed that in the present study the isomerization of 1,5-enyne substrate proceeded through complexation of olefin with Fe(OTf)$_3$ at a lower temperature. Interestingly, no isomerization was observed in the case of substrates (Ar = H) such as **2n** or **2o** at 60−70 °C, but on prolonged heating it gave a trace amount of the desired cyclized product. Furthermore, we also noticed that there was no temperature threshold in case of Ag salts and AuCl. They gave exclusively the desired cyclized product even at lower temperature, albeit in low yields.

On the basis of the aforementioned results a tentative mechanism is proposed to explain the formation of products (Scheme 6). It is noteworthy to mention that as the iron salt is a moderately soft Lewis acid it could coordinate and activate both triple bonds and double bonds.[14] If the alkyne π-bond is activated by Fe(OTf)$_3$ (path a) and triggers the cyclization through intramolecular nucleophilic attack of the *exo*-cyclic

Scheme 6. Plausible Mechanism for Iron-Catalyzed 1,5-Enyne Cycloisomerization



double bond, then it could produce an iron-bound five-membered intermediate **2aa**. Subsequently, isomerization of **2aa** followed by protonolysis of **2bb** produces the desired product **3a**. On the other hand, Fe(OTf)$_3$ may also coordinate to the double bond of compound **2a** (path b), which could trigger the aromatization leading to **2cc**. Protonolysis of **2cc** leads to simple isomerized product **4a** or may undergo cyclization with alkyne to furnish **2bb,** which is subsequently transformed to the desired product **3a**. However, we never obtained any 3-(1-indenyl)indole derivative under the isomerization conditions. In addition, a few experimental observations such as (i) trisubstituted olefins (reductive Heck coupling product) did not produce any isomerization product with Fe(OTf)$_3$, and (ii) gold and silver salts did not have any temperature threshold, proving that the 1,5-enyne cycloisomerization reaction was most likely initiated through the selective complexation of Fe(OTf)$_3$ with alkyne. Further investigations to understand the mechanism of this reaction are ongoing in our laboratory.

In conclusion, we have described a new Fe(OTf)$_3$-catalyzed 1,5-enyne cycloisomerization of (3-methylene)indoline-tethered alkyne derivatives to provide an efficient route to highly substituted 3-(1-indenyl)indole derivatives in very good yields. In addition, this reaction also proceeds efficiently for the synthesis of 7-azaindole derivative. The other advantages of this new reaction are the ease of preparation of substrates, high atom-economy, mild conditions, and use of inexpensive and environmentally friendly Fe(OTf)$_3$ (10 mol %) as the catalyst. Further investigation and synthetic application are in progress in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03544.

Crystallographic data collection and refinement data for **3a** (PDF)

X-ray crystallographic data for **3a** (CIF)

Experimental procedure, copies of NMR spectra and X-ray crystallographic structure of **3a** (PDF)

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Notes

The authors declare no competing financial interest.

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