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Indium(III)-catalyzed Aza-Conia-Ene Reaction for the Synthesis of Indolizines

Marta Meazza,[a] Lars A. Leth,[a] Jeremy D. Erickson[a] and Karl Anker Jørgensen*[a]

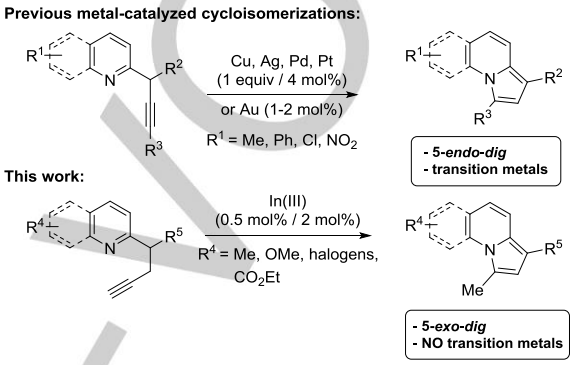
Abstract: A novel indium(III)-catalyzed reaction for the synthesis of a series of indolizine scaffolds has been developed. This methodology is highly efficient, allowing a low catalyst loading of 2 mol% (down to 0.5 mol%) and rendering the products in high yields through a 5-exo-dig aza-Conia-ene reaction. Furthermore, the possibility of incorporating an electrophile to the generated pyrrolidine-ring in a one-pot synergistic fashion is demonstrated. Finally, based on experimental observations, a mechanism proposal is outlined.

Indolizines represent the core structures of many natural products and pharmacologically active compounds such as anticancer, antibacterial, antifungal, anticholinergic, antihistaminic, antitubercular, calcium-entry blockers and antinflammatory agents. Indolizines also have applications in material science as organic light-emitting devices, biological markers and dyes.[1] Thus, the development of synthetic methodologies to access these valuable scaffolds has attracted a lot of attention.

Various methodologies have been reported starting from pyridine or pyrrole frameworks.[2] The classical synthesis is based on the venerable Scholtz and Chichibabin reactions.[3] More recently, new methodologies based on dipolar cycloadditions of pyridinium ylides and cyclization with alkenyldiazoacetates have been reported.[3] Another approach to synthesize indolizines is through cycloisomerization reactions, based on the activation of an alkyne by a metal. These reactions require the use of transition metals such as Cu, Ag, Pd, Pt or Au as catalysts, and sometimes the combination of more than one metal.[4] The loading of the metal varies from 1 equiv to 4 mol% and in only two methodologies employing Au[5] was the loading decreased to 1-2 mol%, providing the final products in good to moderate yields.

The aforementioned metal-catalyzed cycloisomerizations proceed *via* a 5-*endo-dig* cyclization, in which the nucleophilic pyridine attacks the alkyne coordinated to the metal. Surprisingly, there are, to the best of our knowledge, no metal-catalyzed 5-*exo-dig* cycloisomerization reactions for the synthesis of indolizines and pyrrolo-quinolines. Inspired by the success of 5-*exo-dig* cyclizations, such as the Conia-ene reaction,[6] we envisioned a novel approach for the synthesis of indolizines and related/fused heterocycles through an aza-Conia-ene type reaction that would be complementary to the previous methodologies (Scheme 1, top).

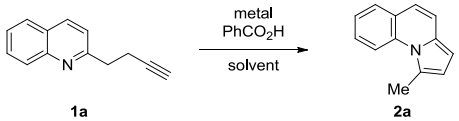
In the following, we will present a reaction concept for the formation of indolizines and pyrrolo-quinolines based on an 5-*exo-dig* indium(III)-catalyzed aza-Conia-ene cyclization reaction (Scheme 1, bottom).[7]



Scheme 1. Previous works and current indium(III)-catalyzed synthesis of indolizines.

Initially, we tested the cycloisomerization of 2-(but-3-yn-1-yl)quinoline **1a** under $InCl_3$ catalysis and in the presence of 0.5 equiv benzoic acid (BA) in dichloroethane and to our delight product **2a** was obtained in 66% yield after 3 d (Table 1, entry 1) When the loading of BA was increased to 1 equiv, product **2a** was obtained in 92% yield in 2 h (entry 2). The use of CH_3CN as the solvent gave only low conversion (entry 3). We then tested another indium(III) source, $In(OAc)_3$, that has the advantage of being cheaper and less hygroscopic compared to $InCl_3$. When 10 mol% of $In(OAc)_3$ was used, >90% conversion was obtained after 30 min (entry 4), and with 2 mol% of $In(OAc)_3$ full conversion was reached in 1 h with an excellent quantitative yield (entry 5). The reaction run at room temperature gave full conversion after 4 d, albeit with some byproducts present in the ^{1}H NMR spectrum of the crude reaction mixture (entry 6). To demonstrate the synergistic need for both acid and indium(III), the reaction performed in the absence of the acid did not afford any product (entry 7), nor did the reaction performed in the absence of indium(III) (entry 8). Finally, other metals were tested in dichloroethane with 1 equiv of BA: $Sc(OTf)_3$ did not give any conversion (entry 9), AgOTf, AuCl and $Pd(OAc)_2$ showed very low conversion to the final product, based on the ^{1}H NMR spectrum of the crude reaction mixture (entries 10-12). In contrast, $Cu(OAc)_2$ gave full conversion; however, a series of byproducts were formed along with low yield of **2a** (entry 13). Based on the screening results, $In(OAc)_3$ (2 mol%) and 1 equiv of BA in dichloroethane was chosen as the best catalytic system.

Table 1. Screening results for the reaction of 2-methyl quinoline **1a** with α,β-unsaturated aldehydes **2a** or **2b**.[a]



1a **2a**

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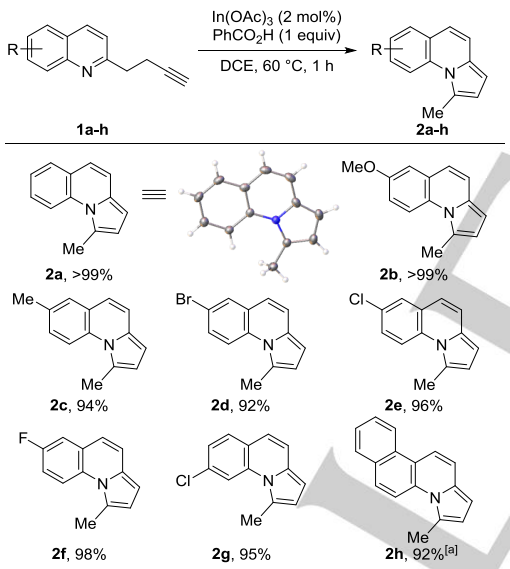
Entry	Metal	Metal loading (%)	Temp (°C)	Time	Conv (%)[b]
1[c]	$InCl_3$	20	60	3 d	full (66)[d]
2	$InCl_3$	10	70	2 h	full (92)[d]
3[e]	$InCl_3$	10	70	2 h	<20
4	$In(OAc)_3$	10	60	30 m	>90
5	$In(OAc)_3$	2	60	1 h	full (>99)[d]
6	$In(OAc)_3$	10	rt	4 d	full
7[f]	$InCl_3$	10	60	2 h	-
8	-	-	60	2 h	-
9	$Sc(OTf)_3$	10	60	2 h	-
10	AgOTf	10	60	2 h	<20
11	AuCl	10	60	2 h	<10
12	$Pd(OAc)_2$	10	60	2 h	<10
13	$Cu(OAc)_2$	10	60	2 h	full (68)[g]

[a] The reactions were performed, unless indicated otherwise, on a 0.05 mmol scale using 1 equiv of **1a**, 1 equiv of BA and 0.5 mL of 1,2-dichloroethane. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] The reaction was performed with 50 mol% of BA. [d] Isolated yield after FC. [e] The reaction was performed in CH_3CN. [f] The reaction was performed without BA. [g] The yield was determined by ^{1}H NMR analysis of the crude reaction mixture.

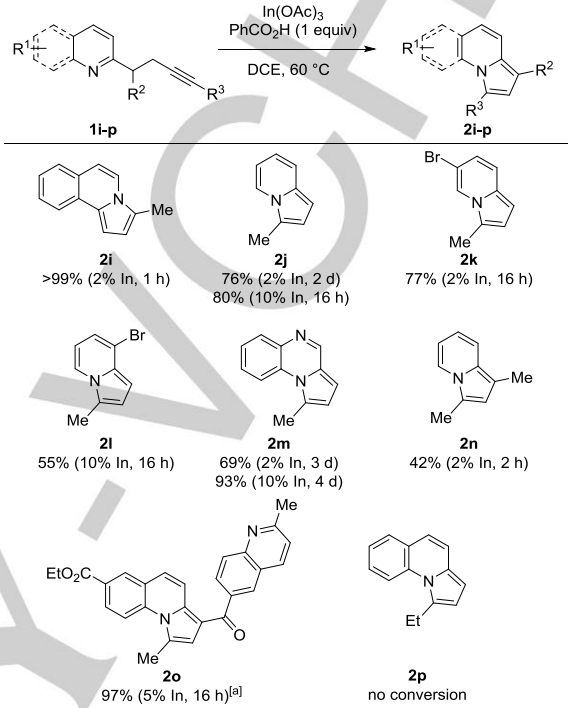
With the optimized conditions in hand, we started to explore the scope of the reaction of 2-(but-3-yn-1-yl)quinolines with different substituents on the aromatic ring (Scheme 2).



Scheme 2. Scope of the reaction of quinolines 1a-h bearing different substituents on the aromatic ring. The reactions were performed on a 0.2 mmol scale. [a] Reaction time 16 h.

The reaction with the quinoline **1a** gave pyrrolo[1,2-α]quinoline **2a** in >99% yield. The structure of **2a** was confirmed by X-ray crystallography (see Supporting Information (SI)). Substrates having electron-donating groups (-OMe and -Me) provided the products **2b** and **2c** in high yields. For substrates having halogens, the pyrrolo[1,2-α]quinolines **2d**-**f** were formed in 92-98% yield. Moving the chloro-substituent to position 7 of the aromatic ring gave 95% yield of **2g**. The scope can be extended to also include a benzoquinoline as demonstrated for **2h** which was obtained in 92% yield. The substituent pattern can also include an electron-withdrawing group such as CO_2Et (**2o** Scheme 3, *vide infra*). The results in Scheme 2 show that the reaction is very robust, giving the pyrrolo[1,2-α]quinolines in high yields, independent of the substituents on the aromatic ring.

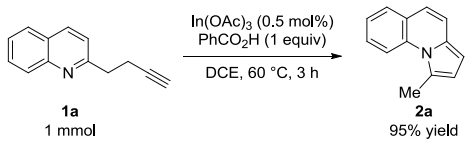
The cycloisomerization was also tested with different heterocycles and substrates having substituents on the alkyl chain and the results are reported in Scheme 3.



Scheme 3. Scope of the reaction of isoquinoline 1i, pyridines 1j-l,n, quinoxaline 1l and quinolines 1o,p. The reactions were performed on a 0.2 mmol scale. [a] The reactions were performed on a 0.1 mmol scale.

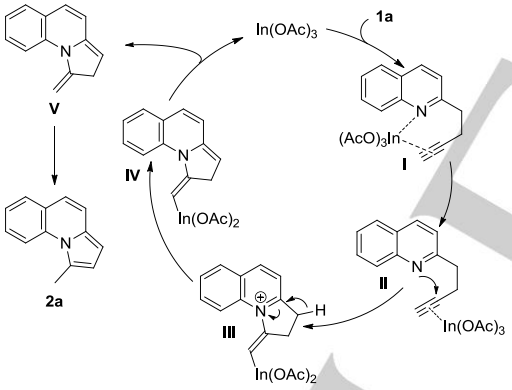
When an isoquinoline scaffold was employed, the pyrrolo[2,1-α]isoquinoline **2i** was obtained in quantitative yield in 1 h. The pyridine scaffold gave the product **2j** in 76% yield in 2 d with 2 mol% of $In(OAc)_3$. The time required to obtain full conversion decreased when the indium(III) loading was increased to 10 mol%. Pyridine substitutions in positions 3 and 5 have been tested and the corresponding products **2k** and **2l** were obtained in 77% and 55% yield, respectively. We were pleased to observe that a quinoxaline scaffold also reacted smoothly to afford **2m** in good to excellent yield depending on the catalyst loading. This occurs despite the presence of a competing nitrogen-coordination site complicating the activation of the alkyne. Then we tested different substituents attached to the first carbon atom of the alkyl chain in both the pyridine and quinoline scaffold. In the case of the pyridine having a methyl substituent, the desired product **2n** was obtained in moderate yields. However, for the quinoline moiety, a more complex starting material, bearing a ketone with another quinoline moiety as substituent provided the product **2o** in 97% yield in 16 h. This example shows that for **2o**, the quinoline moiety can be substituted in the first carbon atom of the alkyl chain without a decrease in the yield. Furthermore, the presence of an electron-withdrawing group on the aromatic ring is tolerated. In accordance with previous observations,[6,8] product **2p** could not be obtained from a non-terminal alkyne under the present reaction conditions (*vide infra*). We were pleased to observe that

a scale-up of the cycloisomerization of **1a** on a 1 mmol scale with 0.5 mol% of $In(OAc)_3$ afforded **2a** in 95% yield in 3 h (Scheme 4). To the best of our knowledge, this is the lowest loading of a metal used in cycloisomerizations for the synthesis of indolizines.



Scheme 4. Scale-up of the reaction and decrease of $In(OAc)_3$ loading.

A proposed reaction mechanism is outlined in Scheme 5. We suggest that there is an equilibrium between the indium(III) catalyst coordinating to **1** (outlined for **1a**) *via* the nitrogen atom and/or the alkyne (intermediate **I**). In order for the reaction to proceed, only the alkyne is coordinated to the indium(III) catalyst (**II**) thereby being activated as an electrophile to be attacked by the nucleophilic nitrogen atom forming the vinylindium intermediate **III**. Then **III** undergoes deprotonation leading to intermediate **IV** followed by a protodemetalation to **V** and aromatization to product **2a**.[8] The role of BA is crucial for the reactivity. We propose that BA coordinates to the acetate substituent of the In(III) catalyst, increasing the Lewis acidity of the indium center and its solubility, enhancing the reaction rate. This activation corresponds to Brønsted acid-assisted Lewis acid catalysis (see SI).[9]



Scheme 5. Proposed mechanism of the 5-*exo*-*dig* aza-Conia-ene reaction

Based on the proposed mechanism in Scheme 5, it is possible to explain why the reaction works only for terminal alkynes. Toste *et al.* have proposed that coordination of the metal to a terminally substituted alkyne is sterically unfavorable.[10] Moreover, as shown in Figure 1, due to a 1,3-allylic strain of the intermediate **VI**, the reaction would not occur with a substituted alkyne.

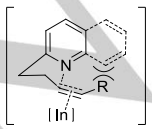
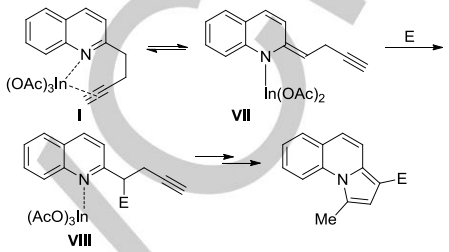


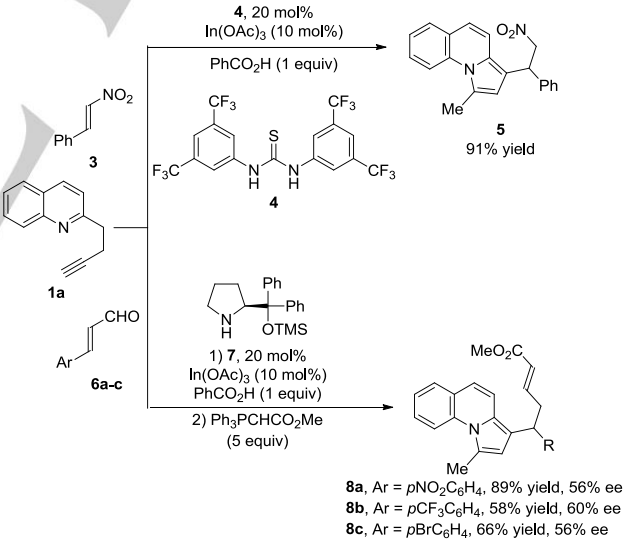
Figure 1. Proposed transition state with 1,3-allylic strain when using non-terminal alkynes.

Based on synergistic catalysis combining metal- and organocatalysis,[11] we envisioned the possibility to add an electrophile in position 3 of the final indolizine in a one-pot procedure. Our working hypothesis for the reaction is outlined in Scheme 6, where the intermediate **I** is in equilibrium with intermediate **VII**, in which indium(III) acts as a Lewis acid. This makes the methylene protons more acidic and, after deprotonation, the nucleophilic intermediate **VII** is formed.[12] This intermediate can attack an electrophile (**E**) forming intermediate **VIII** that will then follow the same mechanism reported in Scheme 5 (intermediate **II** to **V**).



Scheme 6. Proposed mechanism of the one-pot reaction.

A series of electrophiles have been tested for the reaction concept outlined in Scheme 6 and we have found that the reaction for electron-deficient olefins requires activation by an organocatalyst in order to proceed. Two different activation concepts are herein presented: non-covalent and covalent activation. The reaction between quinoline **1a**, activated by $In(OAc)_3$, and *trans*-β-nitrostyrene **3**, activated by a thiourea co-catalyst **4**, afforded **5** in 91% yield after 2 h (Scheme 7, top).



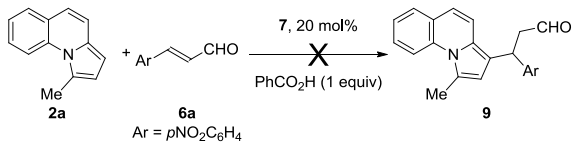
Scheme 7. One-pot aldehyde addition/ring closure by synergistic catalysis. scale. The reactions between 1a and 6a-c were performed on a 0.1 mmol scale and the enantiomeric excess was determined by chiral UPC^2.

To expand the scope of electrophiles that can be used in the present one-pot reaction, quinoline **1a** was also reacted with a series of α,β-unsaturated aldehydes **6a**-**c** activated by a secondary amine catalyst **7** (Scheme 7, bottom). We were pleased to discover that product **8a** was obtained in 89% yield and moderate enantioselectivity (see SI for a screening and optimization of the reaction). The reaction also tolerates different substituents on the aromatic ring of the aldehyde **6** as the products **8b** and **8c** were obtained in good yields and moderate

enantioselectivities. Product **8b** also contains a CF_3-group, an important functional group in medicinal chemistry.

To demonstrate the need for a synergistic process, the reaction between the indolizine **2a** and α,β-unsaturated aldehyde **6a**, catalyzed by the secondary amine catalyst **7**, was tested and no conversion was observed in the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 8). Moreover, while the normal ring closure takes 1 h, in the presence of the secondary amine catalyst it takes 20 h, as the In(III) catalyst coordinates with the nitrogen atom of the organocatalyst and of the quinoline. This makes it possible to have first the attack of the nucleophile intermediate to the aldehyde followed by activation of the alkyne to promote the ring closure.

The reaction outlined in Scheme 7 is the first example of a synergistic catalysis reaction followed by a cascade reaction, where the metal acts first as a Lewis acid followed by a metal activation of the alkyne.



Scheme 8. Control experiment.

In conclusion, we have disclosed a novel $In(OAc)_3$-catalyzed reaction for the synthesis of indolizines and pyrrolo-quinolines through a 5-*exo-dig* aza-Conia-ene reaction. The reaction is highly efficient, providing heterocyclic scaffolds in high to quantitative yields and with a catalyst loading as low as 0.5 mol%. Furthermore, a one-pot electrophile addition followed by a ring-closure reaction is presented. This is the first example of a double indium catalyst activation in concert with an organocatalyzed reaction –three activations in total.

Acknowledgements

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Keywords: indium • heterocycles • indolizines • synergistic catalysis

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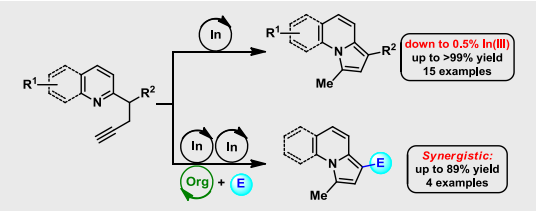

A novel indium(III)-catalyzed reaction for the synthesis of a series of indolizine scaffolds has been developed. This methodology is highly efficient, allowing a low catalyst loading of 2 mol% (down to 0.5 mol%) and rendering the products in high yields through a 5-exo-dig aza-Conia-ene reaction. Further-more, the possibility of incorporating an electrophile to the generated pyrrolidine-ring, in a one-pot synergistic fashion, is demonstrated. Finally, based on experimental observations, a mechanism proposal is outlined.

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