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Diastereoselective Synthesis of Polycyclic Indolizines with 2-(2-Enynyl)pyridines and Enamines

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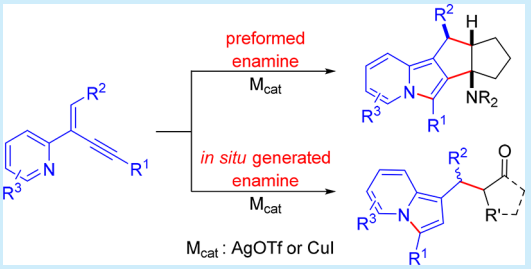
Supporting Information

ABSTRACT: A diastereoselective metal-catalyzed reaction of 2-(2-enynyl)pyridines and cyclic enamines is reported. The method provides access to a variety of substituted indolizine derivatives by variation of the enyne component and the reaction conditions. Performing the reaction using a preformed enamine led to the formation of polycyclic indolizines. With *in situ* generated enamines, ketone-containing indolizine derivatives were obtained. An asymmetric reaction of 2-(2-enynyl)pyridines and enamines generated from an aldehyde and a catalytic amount of amine is presented.



Indolizines are important motifs in both pharmaceutical and material sciences (Figure 1).[1] Because of their prevalence in

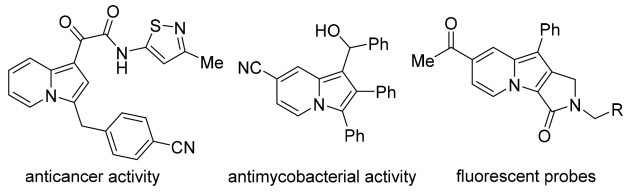


Figure 1. Examples of bioactive and fluorescent indolizines.[1j−l]

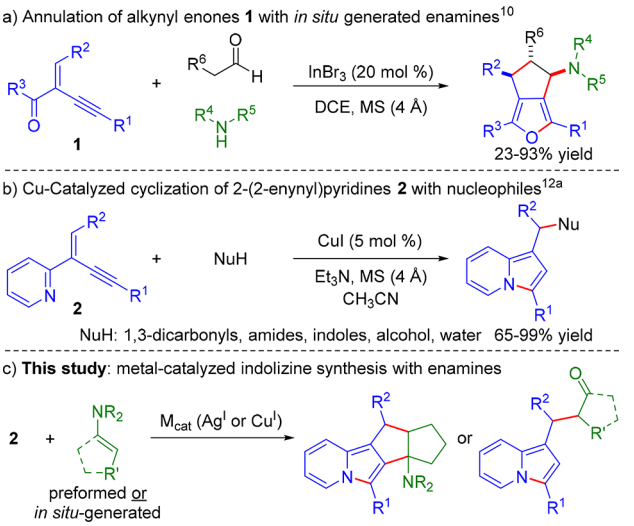
bioactive compounds, a variety of methods for the construction of indolizines have been developed. The classical approach for their synthesis is via the Scholtz[2] or Chichibabin[3] reaction. However, a range of other methods,[1b,4] including cycloadditions,[5] cycloisomerizations,[6] multicomponent reactions,[6c,7] and other metal-catalyzed reactions,[8] have been reported as well.

Recently, we reported on a diastereoselective synthesis of cyclopenta[*c*]furans from alkynyl enones[9] **1** and *in situ* generated enamines (Scheme 1a).[10] A range of enamines, formed from aldehydes and secondary amines, were found to be reactive in the transformation. However, enamines derived from cyclic ketones displayed a different reactivity.[11]

The structurally related 2-(2-enynyl)pyridines **2** have been employed by Jia[12] and others[13] for the synthesis of indolizines. With copper(I) catalysis, and in the presence of a nucleophile, the formation of the indolizine takes place with the concurrent introduction of a O-, C-, or N-nucleophile (Scheme 1b).[12a] With Pd catalysis, the protocol was extended to incorporate an allyl electrophile yielding 1,2,3-substituted indolizines.[12b]

We were interested in exploring enamines as C-centered nucleophiles in the metal-catalyzed synthesis of indolizine derivatives with 2-(2-enynyl)pyridines **2**. Herein we present the Ag- (or Cu-) catalyzed formation of polycyclic and ketone-containing indolizine derivatives using preformed and *in situ*

Scheme 1. Reaction of Alkynyl Enones 1 with Enamines, and Indolizine Synthesis with 2-(2-Enynyl)pyridines 2[10,12a]



generated enamines (Scheme 1c). Our method could provide access to novel and structurally diverse indolizine targets.

2-(2-Enynyl)pyridine **2a** and enamine **3a** were selected for the screening of reaction conditions (Table 1). In analogy with our work on alkynyl enones, $InBr_3$ (20 mol %) was investigated as a catalyst. Products **4a** and **5a** were observed in trace amounts, and the remaining starting materials were found to be unreacted (entry 1). When $Zn(OTf)_2$ was employed as a catalyst, polycyclic indolizine **4a** was observed in 27% yield with a dr of 93:7 (entry 2). Gratifyingly, the use of CuBr increased the yield of the reaction to 90%. However, a lower dr (72:28) was obtained (entry 3). AgOTf was found to be a superior

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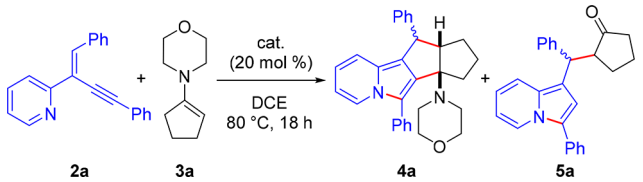
Table 1. Catalyst Screening[a]



entry	cat.	yield **4a** (%) (dr)[b]	yield **5a** (%) (dr)[b]
1	$InBr_3$	trace	4
2	$Zn(OTf)_2$	27 (93:7)	0
3	CuBr	90 (72:28)	5
4	AgOTf	92 (86:14)	7
5[c,d]	AgOTf	trace	71 (58:42)
6[c]	AgOTf	–	99 (59:41)
7[c]	CuI	–	93 (56:44)

[a]2-(2-Enynyl)pyridine **2a** (0.10 mmol), **3a** (0.15 mmol in 1.0 mL of dry DCE), and catalyst (20 mol %). [b]Yields and dr were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c]Cyclopentanone (1.1 equiv) and morpholine (1.1 equiv) were used instead of **3a**. [d]4 Å MS (450 mg) were added.

catalyst, providing polycyclic indolizine **4a** in 92% yield in an improved dr (86:14, entry 4).

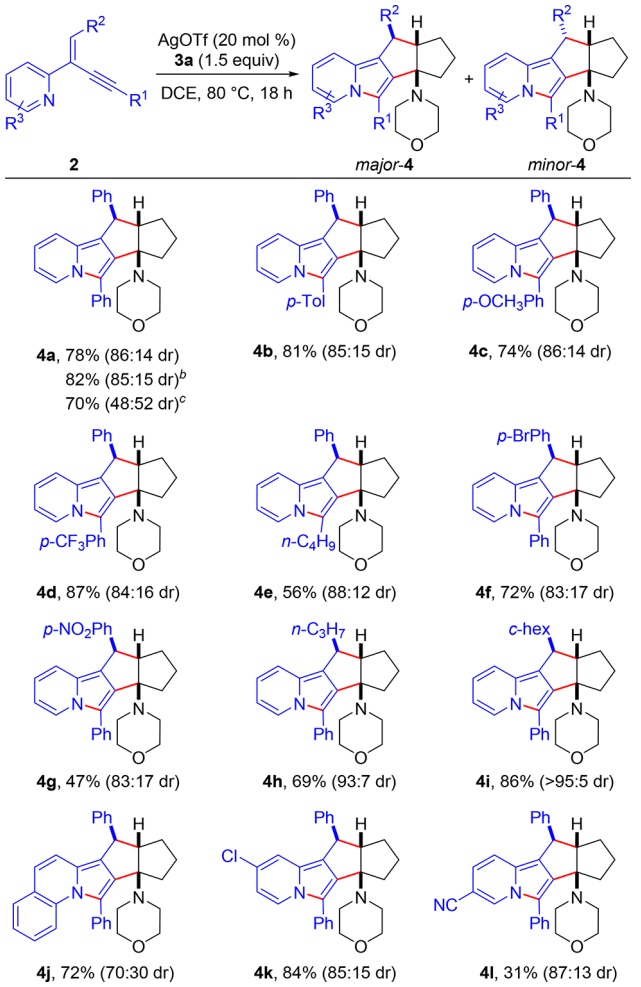
Next, we were interested in the *in situ* generation of cyclic enamine **3a** from cyclopentanone and morpholine. Interestingly, in the presence of molecular sieves, the desired product was obtained only in trace amounts. Instead, indolizine derivative **5a** was obtained in a good yield (71%, entry 5). Moreover, upon performing the reaction in the absence of molecular sieves, the *in situ* protocol afforded product **5a** in a near-quantitative yield, with both AgOTf and CuI as catalysts (entries 6–7).[14]

A broad range of 2-(2-enynyl)pyridines **2** were found to be suitable for the synthesis of polycyclic indolizines **4** (Scheme 2). Polycyclic indolizine **4a** was isolated in 78% yield (82% yield at a 1.0 mmol scale). Interestingly, the use of the *Z*-isomer of **2a**, instead of the *E*-isomer, provided product **4a** in a similar yield (70%) but in a much lower dr (48:52 instead of 86:14). Both electron-rich and -poor arenes were well tolerated at the alkyne position of **2**; indolizines **4a–d** were obtained in good yields (74–87%) in similar dr (~85:15). An alkyl substituent could also be introduced at this position, although a lower yield of **4e** was obtained (56%). 2-(2-Enynyl)pyridines with aromatic, as well as with aliphatic alkene substituents, were found to be reactive (**4f–i**). The *para*-bromo-substituted product **4f** was obtained in good yield in high dr (72%, 83:17). However, the *para*-nitro product **4g** was obtained in 47% yield only. The introduction of an aliphatic substituent greatly increased the diastereoselectivity of the reaction. The *n*-propyl-substituted product **4h** was formed in 69% yield and 93:7 dr. A single diastereomer was observed for the cyclohexyl-substituted product **4i** (86% yield). Substituents on the pyridine moiety of **2a** were investigated. Quinoline product **4j** was isolated in high yield, but in a relatively low dr. A high yield and dr was obtained with a 4-chloro substituent on the pyridine ring of **2** (**4k**). The cyano-substituted indolizine **4l** was obtained in a low yield (31%).

Next enamines formed from other amines were investigated in combination with 2-(2-enynyl)pyridine **2i** (Scheme 3).

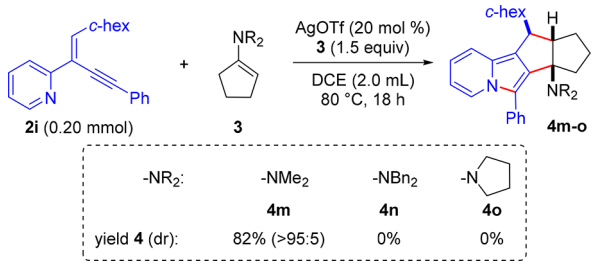
Gratifyingly, when morpholine was replaced with dimethylamine, **4m** was obtained as a single diastereomer in 82% yield. However, the use of dibenzylamine led to an unidentified

Scheme 2. Scope of Polycyclic Indolizines 4[a]



[a]2-(2-Enynyl)pyridine **2** (0.20 mmol), **3a** (0.30 mmol in 2.0 mL of dry DCE), and AgOTf (20 mol %). The dr was determined by ^{1}H NMR analysis of the crude reaction mixture. Isolated yields. The major diastereomers are shown. [b]1.0 mmol scale. [c]From the *Z*-isomer of **2a**.

Scheme 3. Reactions with Other Enamines[a]



[a]2-(2-Enynyl)pyridine **2i** (0.20 mmol), **3** (0.30 mmol in 2.0 mL of dry DCE), and AgOTf (20 mol %). The dr was determined by ^{1}H NMR analysis of the crude reaction mixture. Isolated yields.

decomposition of **2i**, and **2i** was recovered when pyrrolidine was employed.

Upon performing the reaction of **2a** with enamine **3a** at a higher reaction temperature (100 °C), elimination of morpholine was observed along with polycyclic indolizine product **4a** (Scheme 4). Elimination product **6** was obtained in 27% isolated yield as a single diastereomer, and a small decrease in the dr of product **4a** was observed. Unfortunately, a prolonged

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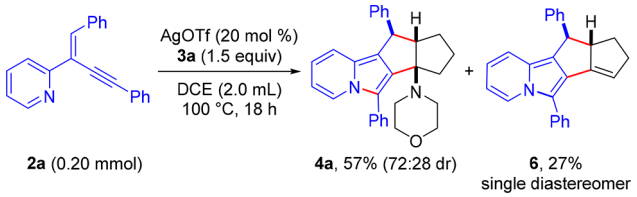
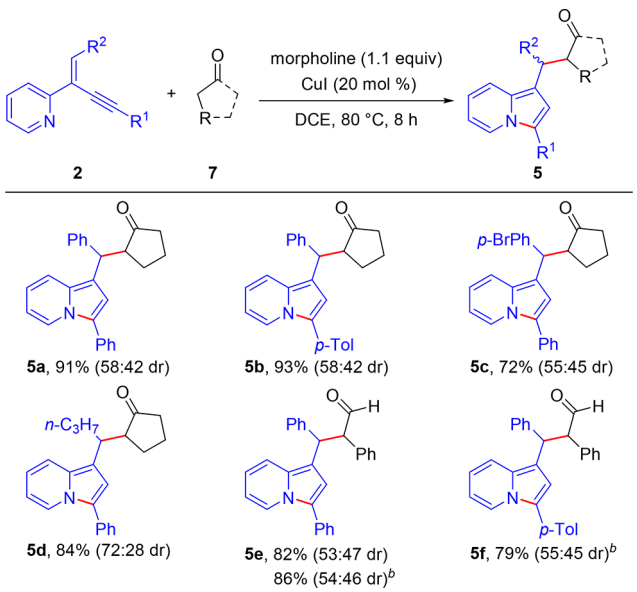
Scheme 4. Elimination at Higher Temperature



reaction time, or a higher temperature, did not improve the yield of **6**.

The three-component reaction yielding indolizine derivatives **5** was investigated next (*cf.*, Table 1, entries 5−7). Although AgOTf and CuI both led to high conversions to product **5**, slightly higher isolated yields were obtained with CuI.[14] Both aromatic and aliphatic substituents at the alkene position of **2** were well tolerated. Products **5a** and **5b** were isolated in high yields (Scheme 5, 91−93%).

Scheme 5. Scope of Indolizine Derivatives 5[a]



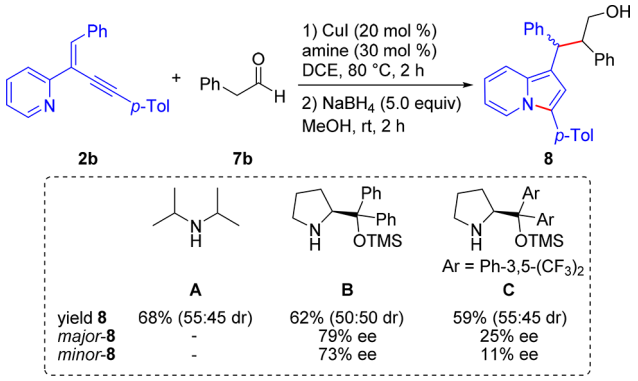
[a]2-(2-Enynyl)pyridine **2** (0.30 mmol), **7** (0.33 mmol), morpholine (0.33 mmol), CuI (20 mol %), and DCE (3.0 mL). The dr was determined by ^{1}H NMR analysis of the crude reaction mixture. Isolated yields. [b]30 mol % of morpholine, 2 h reaction time.

A *para*-bromo-phenyl substituent provided desired compound **5c** in 72% yield. For the aromatic alkene substituents, low diastereoselectivities were observed (near 1:1 dr), probably due to epimerization through reversible enamine formation. Interestingly, the dr was improved significantly (72:28 dr) when an aliphatic alkene substituent was introduced; **5d** was obtained in 84% yield. This is in line with the results obtained for the formation of polycyclic indolizines **4h** and **4i**.

Cyclopentanone could be replaced by phenylacetaldehyde, and the corresponding product **5e** was isolated in 82% yield (53:47 dr). Moreover, a catalytic amount (30 mol %) of morpholine could be used for this substrate, providing **5e** and **5f** in 86% and 79% yields, respectively.

Motivated by this result, enantioenriched amines were screened in the reaction of **2b** with phenylacetaldehyde (Scheme 6). The resulting indolizine was reduced to the corresponding alcohol **8** to facilitate analysis by HPLC.

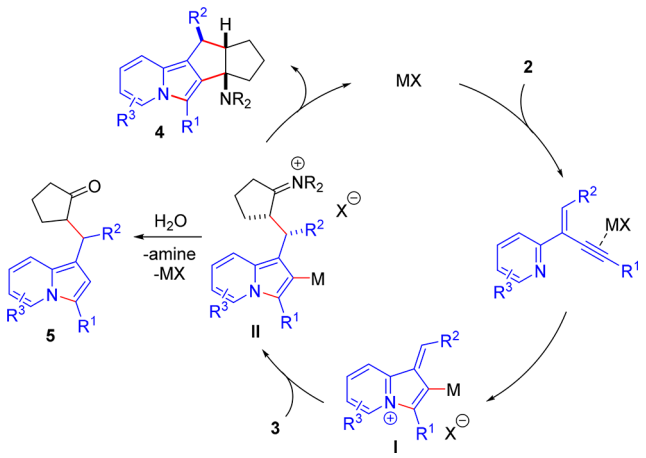
Scheme 6. Investigation of Asymmetric Catalysis



Diisopropylamine (**A**) provided product **8** in 68% yield and 55:45 dr. To our delight, the use of enantioenriched amine **B** resulted in the formation of **8** in 62% yield (50:50 dr) with an ee of 79% for one of the diastereomers and 73% for the other. Surprisingly, lower enantioselectivities were obtained when the structurally related amine **C** was employed (59% yield, 55:45 dr, ee: 11−25%).

The formation of polycyclic indolizines **4** and indolizine derivatives **5** is likely to proceed through a common intermediate (Scheme 7).

Scheme 7. Mechanistic Proposal



AgOTf (or CuI) can function as a π-Lewis acid, activating the alkyne of **2** toward nucleophilic attack by the pyridine nitrogen. The resulting intermediate **I** can subsequently undergo a, supposedly diastereoselective, nucleophilic attack by enamine **3**. Under dry conditions (using preformed enamines), intermediate **II** can subsequently ring-close to form polycyclic indolizine **4**. Although the origin of the diastereoselectivity is not understood, we propose that the reaction of **3** and **I** is selective, setting the stereochemistry of **II**. Partial epimerization of **II** or an *E*/*Z* isomerization of the alkene, and a difference in rate for the formation of the two diastereomers of **4** could explain the lower dr when the *Z*-isomer of **2a** was used.

When the enamine was generated *in situ*, product **5** was obtained in a high yield, with ∼1:1 dr. The water formed in the *in situ* generation of the enamine could hydrolyze the iminium moiety of intermediate **II** and/or protolyze the C−M bond, preventing the cyclization to **4** to take place. The lower dr of

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product **5** could be explained by a reversible enamine formation from intermediate **II**.

In summary, a diastereoselective, Ag- (or Cu)-catalyzed cyclization reaction of 2-(2-enynyl)pyridines and enamines was developed. With preformed enamines, high yields of polycyclic indolizines were obtained with high to excellent diastereoselectivities. When the enamine was formed *in situ*, indolizines **5** were formed in excellent yields. In this reaction, low diastereomeric ratios were generally observed, with the exception of alkyl-substituted 2-(2-enynyl)pyridine starting materials. An asymmetric organocatalyzed reaction of 2-(2-enynyl)pyridines, cyclopentanone, and enantioenriched amines was performed (ee up to 79%). The indolizine products are proposed to be formed from a common intermediate with the Ag (or Cu) catalyst functioning as a π-Lewis acid activating the alkyne moiety.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01498.

Detailed experimental data and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(14) See the Supporting Information for additional screening data.

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