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One-Pot Trimetallic Relay Catalysis: A Unified Approach for the Synthesis of β-Carbolines and Other [*c*]-Fused Pyridines

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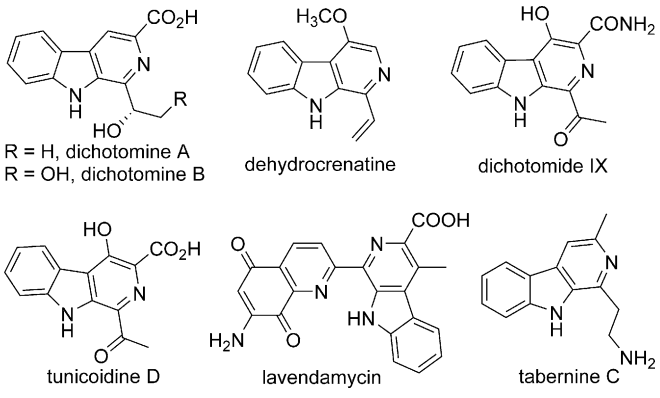
Dedicated to Professor N. Sathyamurthy

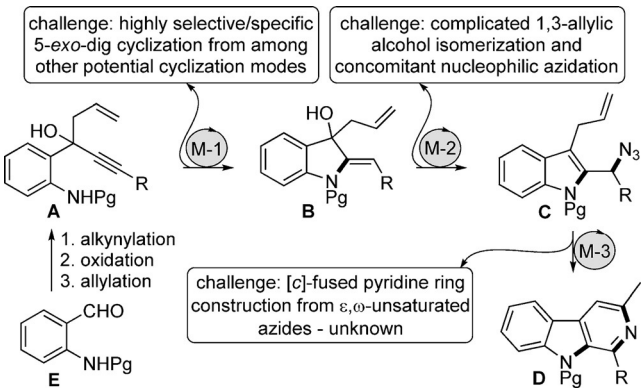
Abstract: *A divergent strategy is presented for the synthesis of 1,3-di- and 1,3,4-trisubstituted β-carbolines through an unprecedented one-pot triple-orthogonal-metal relay catalysis, and 1,3-disubstituted 4-hydroxy-β-carbolines through a one-pot bimetallic relay catalysis from readily accessible 3-(2-aminophenyl)-5-hexenyn-3-ols. These strategies were elaborated to enable the synthesis of benzofuro[2,3-c]pyridines, benzothieno[2,3-c]pyridines, and isoquinolines, which otherwise require multistep synthesis.*

Pyridine-fused indoles, commonly known as carbolines, are one of the most important and abundant heterocycles. In particular, the privileged pyrido[3,4-*b*]indole (β-carboline) scaffold is a significant substructure prevalent in a variety of bioactive natural products and druglike molecules (Scheme 1).[1] Consequently, many protocols have been developed for the synthesis of β-carboline derivatives. Among them, approaches based on the Pictet–Spengler (P-S) and Bischler–Napieralski (B-N) reactions are the most widely used.[2] A few eminent contributions independent of P-S or B-N reactions have also emerged.[3]



Scheme 1. A few representative bioactive β-carboline natural products.

Orthogonal relay catalytic approaches have received tremendous attention owing to their potential to create intricate molecular architectures from simple starting materials in a rapid and efficient manner.[4] However, the development of such processes is not always straightforward. Compatibility issues between the catalytic systems, further hampered by chemoselectivity aspects, complicate the evolution of such methods. Significant advances have been made in the development of novel cascade processes facilitated by two distinct metal catalysts.[5] However, to the best of our knowledge, reactions promoted by *three* orthogonal relay metal-catalytic systems have not been reported so far. Herein, we report an example of triple relay catalysis[6] that integrates silver, bismuth, and palladium catalysts towards the synthesis of β-carbolines through a one-pot cascade involving intramolecular hydroamination, Friedel–Crafts-type dehydrative azidation, and an unprecedented annulation of the resulting ε,ω-unsaturated azide to generate a pyridine ring (Scheme 2).



Scheme 2. Hypothesis based on triple relay catalysis. Pg = protecting group, M-1, M-2, and M-3 are metal-based catalysts.

The foremost challenge was to address the synthesis of the desired indolines **B** (Scheme 2). We envisioned that an intramolecular hydroamination of alkynols **A** promoted by an appropriate metal catalyst M-1 could provide indolines **B**. However, the promotion of a 5-*exo*-dig cyclization[7] over other competing cyclization pathways could be a challenge.[8] A M-2-promoted acid-catalyzed 1,3-allylic alcohol isomerization (1,3-AAI) and dehydrative nucleophilic azidation cascade of **B** was considered for the synthesis of ε,ω-unsaturated azides **C**.[9] It was further hypothesized that a thermal or metal-catalyzed intramolecular azide–alkene

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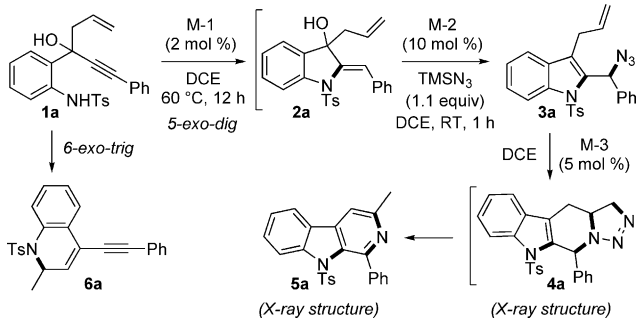
[3+2] cycloaddition, or a metal-catalyzed nitrene insertion into the side-chain olefin in **C** and subsequent bond reorganization, could afford β-carbolines **D**.[10] Since modular access to enynols **A** from amino benzaldehydes **E** is possible in three simple steps, this method serves as a short and efficient alternative to existing synthetic approaches to β-carbolines.

We began our investigation towards identifying an efficient catalytic system to substantiate our hypothesis in Scheme 2 by evaluating the gold(I)-catalyzed intramolecular hydroamination conditions reported earlier by our research group[9d,e] with the enynol **1a** as the model substrate.[11] However, only the 6-*exo*-trig product **6a** was isolated (Table 1, entry 1).[8a,12] Among a few other variations attempted, AgOAc successfully produced the desired 5-*exo*-dig product **2a** with excellent chemo- and regioselectivity.[9c] During the screening of different Lewis acids for the cascade 1,3-AAI/nucleophilic azidation, to our surprise, $Yb(OTf)_3$, $BiCl_3$, and certain other Lewis acids[13] delivered the β-carboline **5a** directly in good yield, plausibly via the azide **3a** and the triazole **4a** (Table 1, entries 2 and 3).[14] To improve the yield, we carried out further optimization studies with copper- and palladium-based catalysts.[10] Although **5a** was isolated in only moderate yield in the presence of Cu catalysts (Table 1, entries 4 and 5), our attempts to improve the yield with Pd catalysts were met with success (entries 6–12). Notably, the yield could be improved by increasing the temperature, especially with $Pd(OAc)_2$ as the catalyst (Table 1, entries 6–8).

Table 1: Optimization of the reaction parameters.[a]

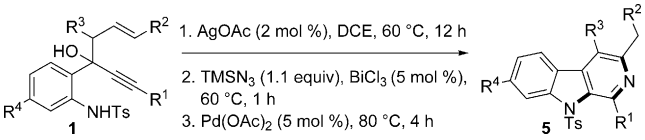


Entry	M-1/M-2	M-3, conditions	Yield of **5a** [%][b]
1	$AuCl,K_2CO_3$/–	–	–[c]
2	$AgOAc/Yb(OTf)_3$	–	54
3	$AgOAc/BiCl_3$	–	62
4	$AgOAc/BiCl_3$	$CuCl_2$, 24 h, 80 °C	23
5	$AgOAc/BiCl_3$	$Cu(OTf)_2$, 24 h, 80 °C	47
6	$AgOAc/BiCl_3$	$Pd(OAc)_2$, RT, 48 h	68
7	$AgOAc/BiCl_3$	$Pd(OAc)_2$, 60 °C, 48 h	70
8	$AgOAc/BiCl_3$	$Pd(OAc)_2$, 80 °C, 4 h	78
9	$AgOAc/BiCl_3$	$Pd_2(dba)_3$, 80 °C, 6 h	73
10	$AgOAc/FeCl_3$	$Pd(OAc)_2$, 80 °C, 4 h	74
11	$AgOAc/Sc(OTf)_3$	$Pd(OAc)_2$, 80 °C, 16 h	63
12[d]	$AgOAc/BiCl_3$	$Pd(OAc)_2$, 80 °C, 4 h	82

[a] See the Supporting Information for details of the reaction conditions. [b] Yield of the isolated product after column chromatography. [c] Product **6a** formed exclusively. [d] The reaction was carried out with 5 mol% of $BiCl_3$ at 60 °C. DCE = 1,2-dichloroethane, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl.

Having optimized the reaction conditions, we next evaluated the scope of the reaction with respect to the substitution of the substrate and product (Table 2).[15] A wide range of 1,3-disubstituted β-carbolines (Table 2, entries 1–6, **5b–g**) and 1,3,4-trisubstituted β-carbolines (entries 7–12, **5h–m**) were assembled in a one-pot process in good to excellent yield. Thus, the alkyne substituent R^1 can be aromatic (products **5b–k**), heteroaromatic (product **5l**), and even aliphatic (product **5m**). However, a slight substitution dependence was observed. Enynols **1n** and **1o** did not yield the respective carbolines **5n** and **5o**, despite our repeated attempts. Apparent decomposition of the azide **3n** under the reaction conditions could possibly be due to its inability to undergo the azide–alkene [3+2] cycloaddition, whereas in the case of **3o**, it is most likely due to instability or insufficient activation of the primary azide functionality.

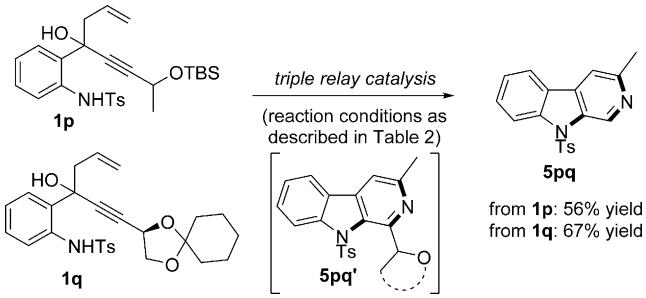
Table 2: Synthesis of 1,3-di- and 1,3,4-trisubstituted β-carbolines.[a]



Entry	**1**	**5**, R^1, R^2, R^3, R^4	Yield of **5** [%][b]
1	**1b**	**5b**, *p*-$(CH_3)C_6H_4$, H, H, H	80
2	**1c**	**5c**, *m*-FC_6H_4, H, H, H	78
3	**1d**	**5d**, *p*-$(C_6H_5)C_6H_4$, H, H, H	71
4	**1e**	**5e**, *p*-$(OMe)C_6H_4$, H, H, H	71
5	**1f**	**5f**, *p*-OH-*m*-$(OMe)C_6H_3$, H, H, Cl	65
6	**1g**	**5g**, 2-naphthyl, H, H, OMe	68
7	**1h**	**5h**, C_6H_5, H, Me, H	81
8	**1i**	**5i**, *m*-FC_6H_4, H, Me, H	76
9	**1j**	**5j**, *p*-$(C_6H_5)C_6H_4$, H, Me, H	74
10	**1k**	**5k**, *p*-$(OMe)C_6H_4$, H, Me, H	78
11	**1l**	**5l**, 3-thienyl, H, Me, H	79
12	**1m**	**5m**, *n*Bu, H, Me, H	67
13	**1n**	**5n**, C_6H_5, C_4H_9, H, H	0[c]
14	**1o**	**5o**, H, H, H, H	0[c]

[a] See the Supporting Information for details of the reaction conditions. [b] Yield of the isolated product after column chromatography. [c] Azide **3** formed but decomposed under the reaction conditions.

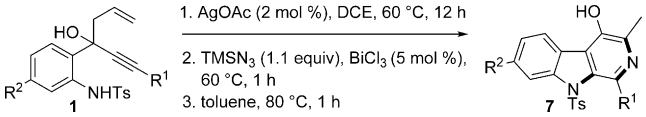
We prepared enynols **1p** and **1q** (Scheme 3) with the intention to attempt the total synthesis of β-carboline natural products dichotomine A and dichotomine B (see Scheme 1).[1] However, surprisingly, the reaction of **1p** or **1q** under the optimized conditions generated only the β-carboline **5pq**. This observation led to the conjecture that substrates containing propargylic ethers undergo a domino sequence involving benzylic ether deprotection, benzylic alcohol oxidation, and retro-Claisen condensation of the intermediate **5pq′** (see the Supporting Information for further details). Nevertheless, a new method for the synthesis of medicinally pertinent 3-substituted β-carbolines was established.[16]



Scheme 3. Unusual formation of 3-substituted β-carbolines. TBS = *tert*-butyldimethylsilyl.

During our efforts to isolate the azide **3a**, we made a remarkable observation. The isolated sample of the azide **3a** was found to be unstable under ambient conditions[14] and underwent slow transformation into a crystalline material, which was characterized to be the 1,3-disubstituted 4-hydroxy-β-carboline **7a**.[17] Prompted by the occurrence of several bioactive 4-hydroxy-β-carboline natural products (for representative examples, see Scheme 1),[1,18] we explored the generality of the observation (Table 3).

Table 3: Synthesis of 1,3-disubstituted 4-hydroxy-β-carbolines.[a]

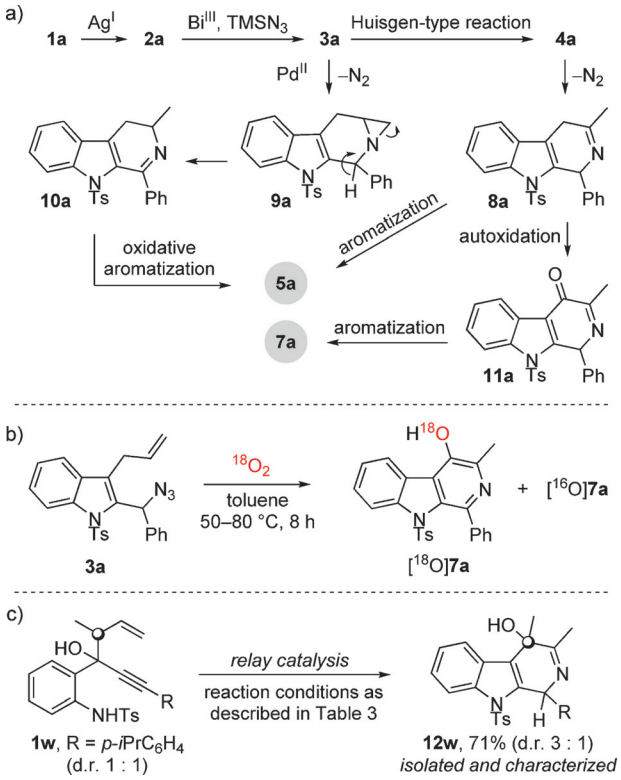


Entry	1	7, R^1, R^2	Yield of 7 [%][b]
1	**1a**	**7a**, C_6H_5, H (X-ray crystal structure)	89
2	**1c**	**7b**, *m*-FC_6H_4, H	81
3	**1d**	**7c**, *p*-$(C_6H_5)C_6H_4$, H	79
4	**1e**	**7d**, *p*-$(OMe)C_6H_4$, H	78
5	**1r**	**7e**, *p*-*i*PrC_6H_4, H	86
6	**1s**	**7f**, 2-naphthyl, H	81
7	**1t**	**7g**, 3-thienyl, H	87
8	**1u**	**7h**, C_6H_5, Cl	84
9	**1v**	**7i**, *n*Bu, H	78
10	**1p**	**7j**, $CH_3CH(OTBS)$, H	76

[a] See the Supporting Information for details of the reaction conditions. [b] Yield of the isolated product after column chromatography.

It can be inferred from Table 3 that the scope of this procedure is significant.[19] All 4-hydroxy-β-carbolines **7a–j** were obtained in consistent turnaround times and excellent yields. Notably, electronically diverse substituents R^1 and R^2, both aromatic and aliphatic, were tolerated well under the reaction conditions. As a substantial advancement, the enynol **1p** with a propargylic *tert*-butyldimethylsilyl ether moiety was converted into the expected product **7j** (in contrast to the reaction of **1p** in Scheme 3). Compound **7j** possesses the complete carbon framework present in the β-carboline natural products dichotomide IX and tunicoidine D (see Scheme 1).[1]

On the basis of our experimental observations and in conjunction with previous reports,[10,20] a plausible mechanism that explains the formation of **5a** and **7a** from **1a** is proposed



Scheme 4. Plausible mechanism of formation of the β-carbolines **5a** and **7a**.

in Scheme 4a.[21] Thus, silver(I)-catalyzed 5-*exo*-dig cyclization and protodemetalation of **1a** generates the indoline intermediate **2a**. A bismuth(III)-promoted cascade involving 1,3-allylic alcohol isomerization (1,3-AAI) and nucleophilic azidation then provides the azide **3a**, which undergoes a Huisgen-type intramolecular azide–alkene [3+2] cycloaddition to form **4a**. Transformation of the triazole **4a** into **8a** and aromatization provides **5a**.

On the other hand, the azide **3a** is converted into the aziridine intermediate **9a** in the presence of a Pd^{II} complex.[20] Aziridine **9a** undergoes deprotonation followed by ring opening to generate **10a**, which upon aromatization delivers **5a**. Thus, the Pd^{II} complex plays a remarkable role in the exclusive formation of **5a**. This mechanism also explains the marked yield enhancement in the presence of Pd^{II} complexes (see Table 1).[15] In the absence of a Pd^{II} complex, **3a** forms **8a**, and the reaction takes an interesting detour. Presumably, **8a** undergoes an autoxidation and aromatization sequence to generate the 4-hydroxy-β-carboline **7a** (Scheme 4a).

To establish the role of atmospheric oxygen during the conversion of **8a** into **7a**, we conducted an isotopic labeling experiment with $^{18}O_2$ (Scheme 4b). The HRMS spectrum of the product showed a distinct [*M*+H] peak for ^{18}O-containing **7a**.[21]

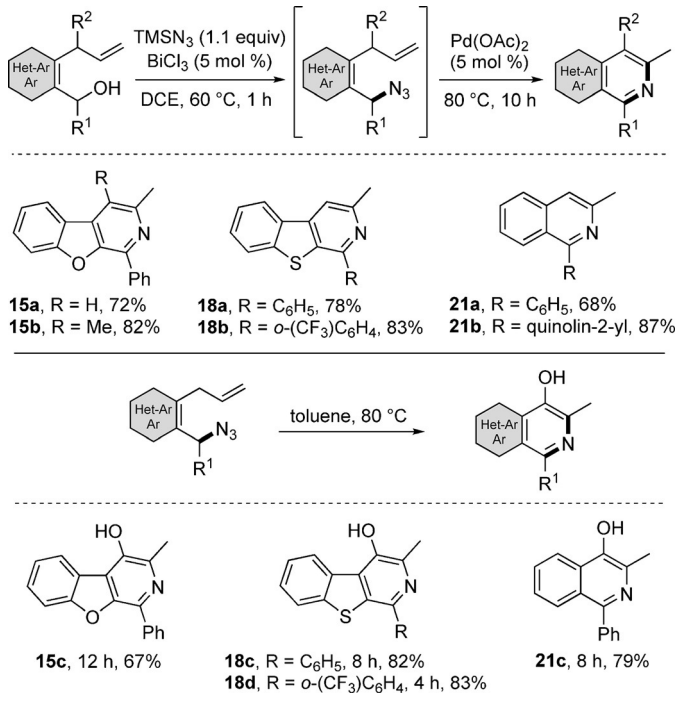
In an attempt to interrupt and detect the proposed autoxidation of **8a** to **11a**, we designed the enynol **1w** with a methyl group positioned at the allylic position (Scheme 4c). The role of the methyl group is to restrict the formation of the ketone. Indeed, we were able to isolate and characterize the tertiary alcohol **12w**.[21] Besides supporting an autoxidation

process, this result also provides valuable information about the triazole decomposition pathway.

After successfully establishing one-pot relay processes for the facile synthesis of unusual β-carbolines by effectively accommodating orthogonal metal-catalytic cycles, we extended this strategy to the synthesis of other important [*c*]-fused pyridines. Accordingly, a variety of ε,ω-unsaturated azides were prepared and subjected to the optimized conditions to demonstrate the versatility of the current approach (Scheme 5). An interesting array of 1,3-disubstituted and 1,3,4-trisubstituted benzofuro[2,3-*c*]pyridines (products **15a–c**) and benzothieno[2,3-*c*]pyridines (products **18a–d**) were efficiently assembled. Benzofuro- and benzothienopyridines are the primary molecular architectures of many biologically active compounds and drug candidates,[22] and find application in materials science as well.[23]

The versatility of this method was furthered by setting up new approaches to isoquinolines (product **21a**), 2-(isoquinolin-1-yl)quinolones (product **21b**),[24] and 4-hydroxyisoquinolines (product **21c**), which otherwise require multistep synthesis. Isoquinolines are the key structural scaffolds of several naturally occurring alkaloids; they are also the principal components of numerous therapeutics and can provide the backbone for chiral ligands.[25]

In conclusion, we have presented unprecedented examples of relay catalysis through the sequential use of silver, bismuth, and palladium catalysts to access an array of distinct β-carbolines. The method was subsequently extended to the synthesis of intriguing [*c*]-fused pyridines, such as benzofuro- and benzothieno[2,3-*c*]pyridines, and isoquinolines. Intriguing mechanistic details governing these processes were elucidated. This methodology has demonstrated great potential and will stimulate further research in the synthesis of new heterocycles.



Scheme 5. Benzofuro[2,3-*c*]pyridines, benzothieno[2,3-*c*]pyridines, and isoquinolines prepared by this approach.

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Keywords: azides · β-carbolines · Lewis acids · relay catalysis · transition metals

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[11] See the Supporting Information for the synthesis of enynols **1** employed in this study.

[12] This result establishes a new gold(I)-catalyzed approach for the synthesis of 1,2-dihydroquinolines of the type **6a**.

[13] See Supporting Information for detailed screening results.

[14] The intermediates **2a** and **3a** are isolable (but have short lifetimes), and preliminary screening was performed with the isolated samples.

[15] $Pd(OAc)_2$ was crucial for the synthesis of the products in good yield. Use of the $Ag^{I}/Bi^{III}/Pd^{II}$ system rather than the Ag^{I}/Bi^{III} system alone led to a yield enhancement of at least 20–30%.

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