Article

Reversal of Regioselectivity in Catalytic Arene-Ynamide Cyclization: Direct Synthesis of Valuable Azepino[4,5-b]indoles and #–Carbolines and DFT Calculations

Long Li, Xiu-Mei Chen, Ze-Shu Wang, Bo Zhou, Xin Liu, Xin Lu, and Long-Wu Ye

ACS Catal., **Just Accepted Manuscript** • Publication Date (Web): 04 May 2017

Reversal of Regioselectivity in Catalytic Arene-Ynamide Cyclization: Direct Synthesis of Valuable Azepino[4,5-*b*]indoles and β − Carbolines and DFT Calculations

Long Li,[†] Xiu-Mei Chen,[‡] Ze-Shu Wang,[†] Bo Zhou,[†] Xin Liu,[†] Xin Lu,*[,‡] and Long-Wu Ye*[,†,§]

[†]Collaborative Innovation Center of Chemistry for Energy Material, State Key Laboratory of Physical Chemistry of Solid Surfaces, and Fujian Provincial Key Laboratory of Chemical Biology, Department of Chemistry, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China.

[‡]Collaborative Innovation Center of Chemistry for Energy Material, State Key Laboratory of Physical Chemistry of Solid Surfaces, and Fujian Provincial Key Laboratory of Theoretical and Computational Chemistry, Department of Chemistry, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China.

[§]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China.

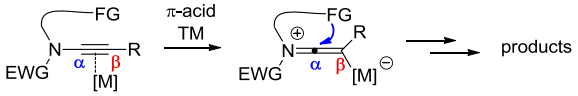
ABSTRACT: Ynamides are important building blocks in organic synthesis, and a variety of versatile synthetic methods have been developed in the past decade. Among these, catalytic cyclizations of π-tethered ynamides are particularly attractive since this approach enables facile access to a diverse array of synthetically useful nitrogen heterocycles. However, due to the fact that the nitrogen atom is able to impose an electronic bias, these cyclizations exclusively occur on the α position of ynamides. Herein, we report the reversal of regioselectivity in arene-ynamide cyclization by copper catalysis, which represents the first catalytic π-tethered ynamide cyclization involving the reversal of regioselectivity. This strategy allows the expedient and practical synthesis of valuable azepino[4,5-*b*]indoles and β − carbolines in generally high yields under mild conditions. Moreover, the relevant mechanistic rationale for this cyclization, especially for the observed high regioselectivity, is strongly supported by density functional theory (DFT) calculations. The synthetic utility of this chemistry is also indicated by the synthesis of several biologically active compounds and natural product bauerine A.

KEYWORDS : *copper, heterocycles, regioselectivity, homogeneous catalysis, synthetic methods*

INTRODUCTION

Ynamides have proven to be privileged precursors for regiospecific synthesis of synthetically highly versatile nitrogen-containing molecules, and various efficient synthetic methods have been established in the past decade.[1,2] Among these, cyclizations of π-tethered ynamide derivatives using either transition metal π-acids[3,4] or Brønsted acids[5] are particularly attractive as this approach enables facile access to a diverse array of structurally complex nitrogen heterocycles. Due to the fact that the nitrogen atom is able to impose an electronic bias, the initial nucleophilic attack of these cyclizations is highly regioselective and exclusively occurs on α position of ynamides (Scheme 1). For example, Hsung et al. demonstrated that the arene-ynamide cyclization via Brønsted acid catalysis could lead to efficient synthesis of various six-membered nitrogen heterocycles (Scheme 2a).[5a] Recently, Takasu et al. also reported an elegant protocol for the construction of the 3*H*-pyrrolo[2,3-*c*]quinolines involving a Brønsted acid-promoted arene−ynamide cyclization (Scheme 2a).[5b] Reversing the regioselectivity from α position to β for these π-tethered ynamide cyclizations not only greatly enrichs the ynamide chemistry, but also represents an attractive method to build complex cyclic compounds with high skeletal diversity. However, this is highly challenging due to the inherent polarization nature of ynamides. To our best knowledge, examples of catalytic π-tethered ynamide cyclizations involving the reversal of regioselectivity have not been reported.[6]

Scheme 1. Catalytic π-tethered Ynamide Cyclizations: Regioselective on α Position of Ynamides



FG: π-electron rich system (olefin, allene, arene, etc.)

In our recent study on the ynamide chemistry,[7] we realized the reversal of regioselectivity in the above arene-ynamide cyclization by copper catalysis, allowing the facile and practical synthesis of a wide range of azepino[4,5-*b*]indoles (Scheme 2b), which are important heterocyclic structural motifs found in an array of bioactive molecules and natural products (Fig. 1).[8] In addition, this copper-catalyzed arene-ynamide cyclization could also be extended to the highly efficient synthesis of valuable β-carbolines (Fig. 1). Furthermore,

a mechanistic rationale for the observed unique regioselectivity is also strongly supported by DFT calculations. In this paper, we wish to report the results of our detailed investigations of this copper-catalyzed reversal of regioselectivity in arene-ynamide cyclization, including substrate scope, synthetic applications and mechanistic studies.

Scheme 2. Catalytic Arene-Ynamide Cyclizations

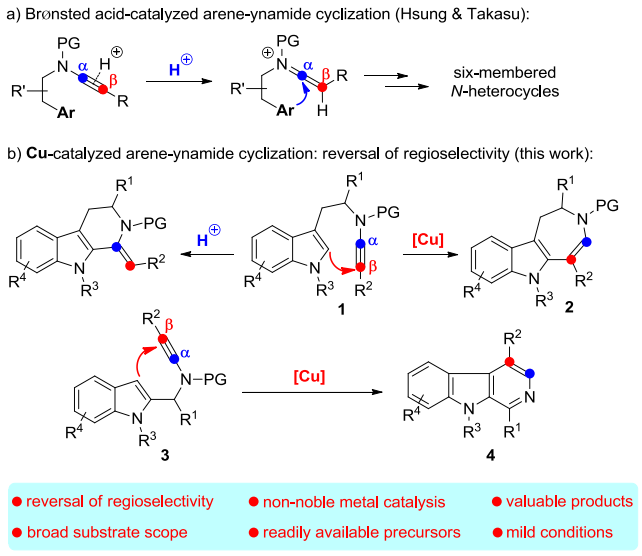
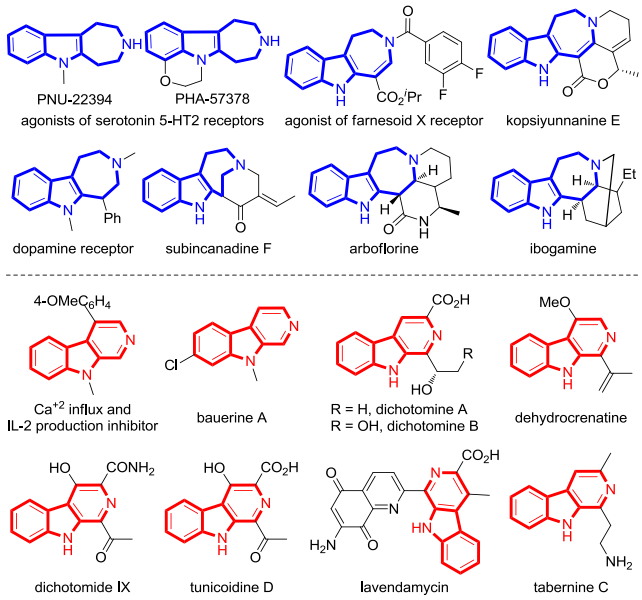


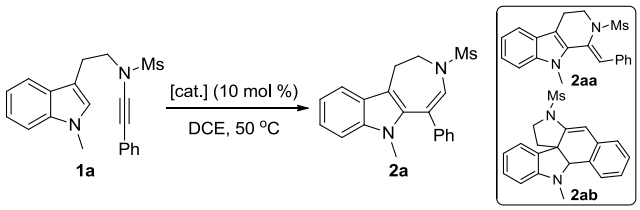
Figure 1. Representative biologically active molecules and natural products with Azepino[4,5-b]indole subunit and β-carboline subunit.



RESULTS AND DISCUSSION

1. Synthesis of Azepino[4,5-*b*]indoles through Copper-Catalyzed 7-*endo-dig* Cycloisomerization. At the outset, the 3-substituted indole-tethered ynamide **1a**, easily prepared from the commercially available tryptamine, was chosen as the model substrate and some of the results are outlined in Table 1. Similar to Hsung's protocol, enamide **2aa** was obtained as the main product via a keteniminium Pictet-Spengler cyclization in the presence of TsOH or MsOH (Table 1, entries 1-2). Notably, spirocyclic compound **2ab** was also detected in both cases presumably through an intramolecular formal [4+2] annulation.[3b,9] Gratifyingly, subsequent catalyst screening (Table 1, entries 3-7) revealed that the desired 7-*endo-dig* cyclization[10] could be observed by employing $Fe(OTf)_3$ or $Fe(OTf)_2$ as the catalyst albeit still along with the byproduct **2aa** and **2ab** (Table 1, entries 6-7). Finally, we were pleased to find that in the presence of $Cu(OTf)_2$ or CuOTf as catalyst, the desired azepino[4,5-*b*]indole **2a** could be achieved in 81% or 76% yield in only 1 h, and neither **2aa** nor **2ab** formation was observed (Table 1, entries 8-9). In addition, it was found that other Cu(II) and Cu(I) catalysts[9] and typical gold catalysts such as $Ph_3PAuNTf_2$ and $IPrAuNTf_2$ were not effective in promoting this reaction (Table 1, entries 10-11).

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	time (h)	NMR yield (%)[b] 2a	2aa	2ab
1	TsOH	20	<1	54	28
2	MsOH	20	<1	34	22
3	$In(OTf)_3$	20	<1	36	28
4[c]	$Sm(OTf)_3$	20	<1	14	29
5	$Zn(OTf)_2$	20	<1	11	34
6	$Fe(OTf)_3$	20	31	27	36
7[d]	$Fe(OTf)_2$	20	10	12	27
8	$Cu(OTf)_2$	1	81	<1	<1
9	CuOTf	1	76	<1	<1
10[e]	$Ph_3PAuNTf_2$	20	43	<5	<5
11[e]	$IPrAuNTf_2$	20	49	<5	9

[a]Reaction conditions: reactions run in vials; [**1a**] = 0.05 M; DCE = 1, 2-dichloroethane. [b]Measured by ^1H NMR using diethyl phthalate as the internal standard. [c]50% of **1a** remained unreacted. [d]20% of **1a** remained unreacted. [e]5 mol % gold catalyst was used.

With the best conditions in hand, we then examined the scope of this copper-catalyzed 7-*endo-dig* cycloisomerization reaction. A variety of indolyl ynamides **1**, readily prepared from the corresponding tryptamines, were employed to generate the desired azepino[4,5-*b*]indoles **2** in generally moderate to good yields. Notably, no 6-*exo-dig* cycloisomerization was detected in all cases. Initial investigation of *N*-protecting groups demonstrated that the Ts or Bs (*p*-bromobenzenesulfonyl) protected ynamides gave a slightly decreased yield (Table 2, entries 1-3). In the case of ynamides with different aryl groups (R^2 = aryl), the reaction worked well to deliver the desired **2d-2j** in 72-83% yields, and importantly, no spirocyclic byproduct was detected in these cases (Table 2, entries 4-10). This new reaction was also extended to het-

eroaryl-substituted ynamide **1k** and alkyl-substituted ynamide **1l**, affording the corresponding **2k** and **2l** in 71% and 63% yield, respectively (Table 2, entries 11-12). Moreover, this transformation was generally tolerant of various functional groups such as OAc, OBoc and Cl (Table 2, entries 13–15). In addition, ynamides containing different substituents or protecting groups on the indole ring could also undergo smooth cycloisomerization to produce the desired **2p**-**2s** in moderate to good yields (Table 2, entries 16-19). The molecular structure of **2a** was further confirmed by X-ray diffraction (Fig. 2).[11] To test the practicality of the current catalytic system, the reaction was carried out on a gram scale (5 mmol, 1.762 g) in the presence of 5 mol % of $Cu(OTf)_2$, and the desired product **2a** was afforded in 73% yield (1.286 g), highlighting the synthetic utility of this chemistry (Table 2, entry 1). Considering that the chiral indolyl ynamides **1** could be prepared with excellent enantiomeric excesses (95-99% ee)[9] by starting from readily available indolyl aldehydes and (*S*)-(+)-*tert*-butylsulfinamide according to Ellman's *tert*-butylsulfinimine chemistry,[12] we also investigated chiral indolyl ynamides **1t**-**w** and found that all of the reactions took place smoothly to afford the expected chiral azepino[4,5-*b*]indoles **2t**-**w** in moderate to good yields under the optimal reaction conditions (Table 2, entries 20-24). It should be mentioned that in these cases, it is necessary to add NaBARF as additive to generate in situ the corresponding $Cu(BARF)_2$ so as to promote this copper catalysis. Importantly, excellent enantioselectivities were achieved in all cases, and essentially no epimerization was observed. In addition, (*R*)-(+)-*tert*-butylsulfinamide-derived **1t′** could also undergo smooth cyclization to deliver **2t′** with the opposite enantioselectivity (Table 2, entry 24). Of note, attempts to prepare the indolyl ynamide tethered with one carbon (**1a′**) failed.[9]

Figure 2. Crystal structure of compound **2a**.

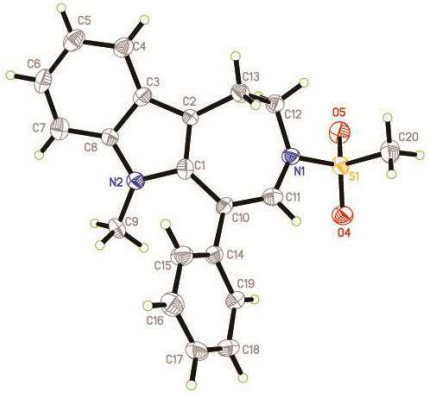
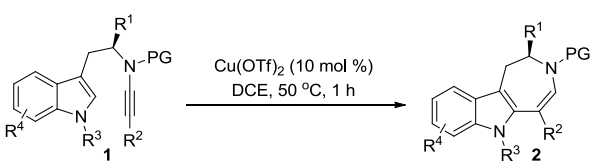
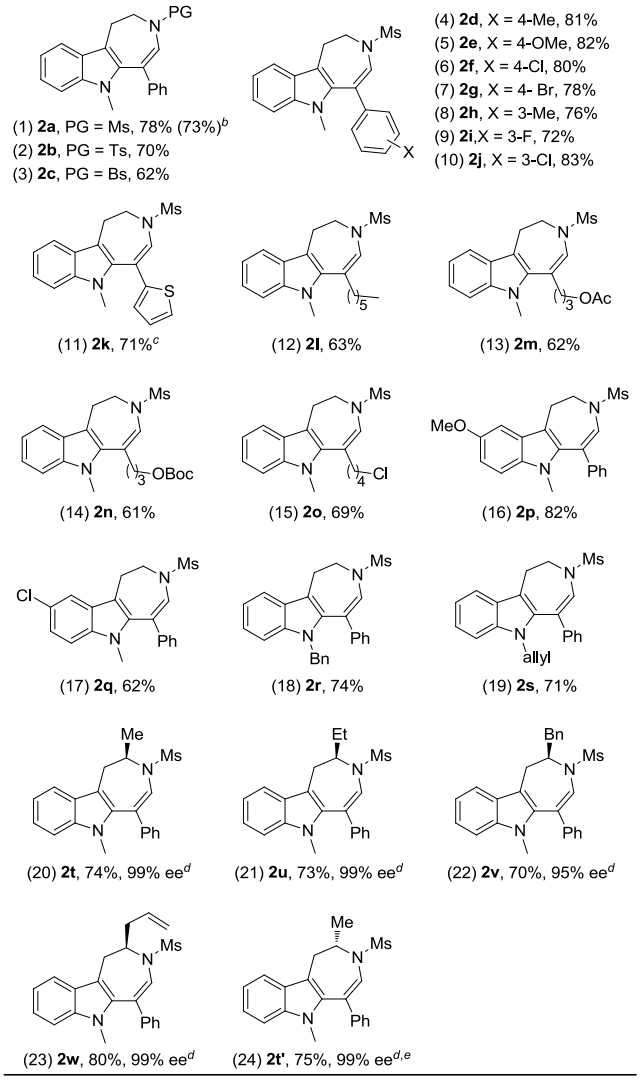


Table 2. Reaction Scope for the Formation of Azepino[4,5-*b*]indoles 2[a]





[a]Reactions run in vials; [**1**] = 0.05 M; yields are those for the isolated products. [b]5.0 mmol scale, 5 mol % $Cu(OTf)_2$ was used, 8 h. [c]80 °C, 1 h. [d]10 mol % $Cu(OTf)_2$ and 20 mol % NaBARF were used, 80 °C, 1 h; NaBARF = sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate. [e]Using (*R*)-(+)-*tert*-butylsulfinamide-derived indolyl ynamide **1t′** as the substrate.

Synthetic applications of this copper-catalyzed cycloisomerization reaction were also explored (Scheme 3). For example, **2a** could be readily oxidized into the indole-fused azepine **2ac** in 85% yield by DDQ. In addition, hydrogenation of **2a**, followed by deprotection and *N*-methylation, could afford the final **2ae** as dopamine receptor and potential neuroleptic agent (68% three-step overall yield).[13] Importantly, hexahydroazepino[4,5-*b*]indole is a ubiquitous heterocyclic structural motif found in an array of natural products and other biologically relevant molecules.[8] Of note, hydrogenation of chiral **2t** could lead to the formation of **2ta** in 72% yield with high diastereoselectivity and well-maintained enantioselectivity. The configuration of **2ta** was confirmed by X-ray diffraction (Fig. 3).[11]

Scheme 3. Synthetic Applications

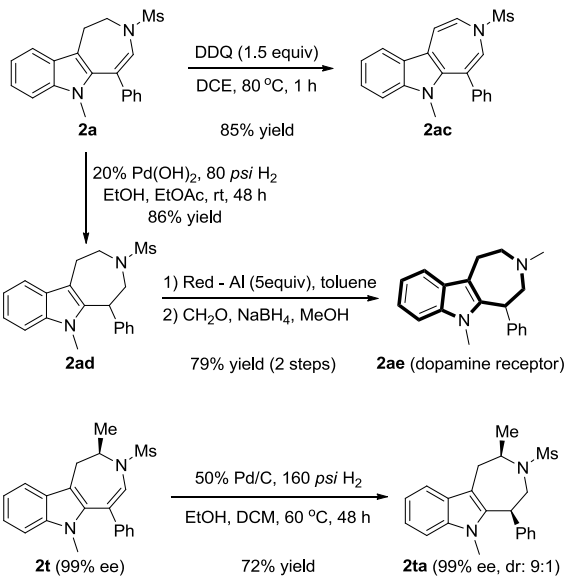
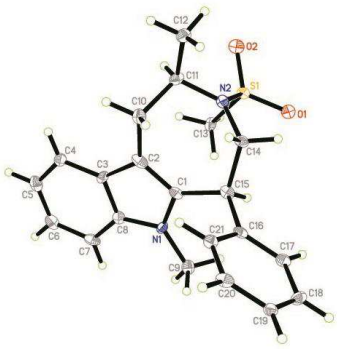
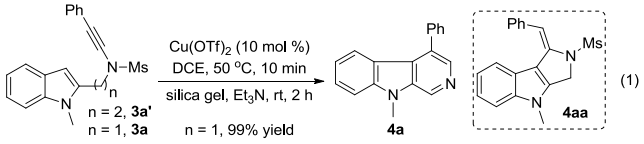


Figure 3. Crystal structure of compound **2ta**.

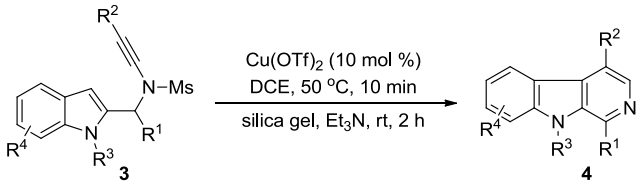


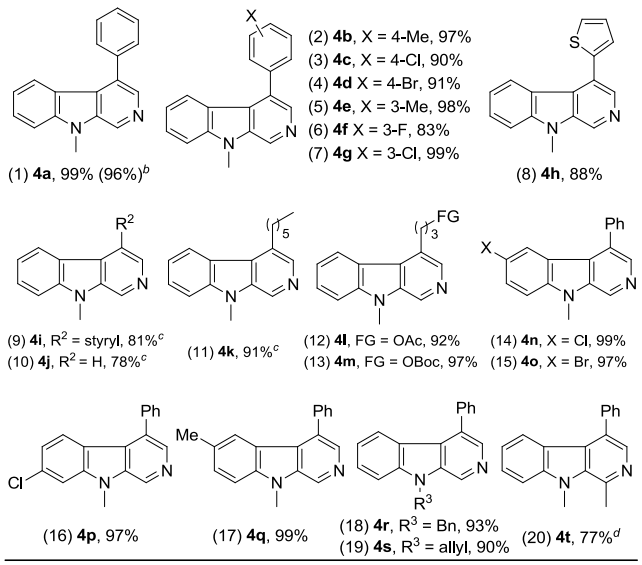
2. Synthesis of β-Carbolines through Copper-Catalyzed 6-*endo*-*dig* Cycloisomerization. We then considered the possibility of extending the above protocol to 2-substituted indole-tethered ynamides **3**. Although our attempts to expand this chemistry to indolyl ynamide **3a′** (n = 2) only led to the formation of complicated mixtures, indolyl ynamide **3a** (n = 1) could undergo the smooth 6-*endo*-*dig* cycloisomerization and the subsequent demesylation/aromatization to deliver the corresponding β-carboline **4a** in almost quantitative yield under the optimized reaction conditions (eq 1).[9] Again, no 5-*exo*-*dig* cycloisomerization was observed.



Next we also investigated the scope of this transformation. As summarized in Table 3, the reaction proceeded smoothly with various 2-substituted indole-tethered ynamides **3**, and the yields ranged from 78% to 99%. Ynamides with various aryl groups were first examined (R^2 = aryl), and the desired β–carbolines **4a**–**4g** could be formed in 83–99% yields (Table 3, entries 1−7). The reaction also worked satisfactorily with heteroaryl-substituted ynamide, providing the desired **4h** in 88% yield (Table 3, entry 8). In addition, styryl-substituted ynamide and even terminal ynamide turned out to be suitable substrates as well, leading to the corresponding **4i** (81%) and **4j** (78%) respectively (Table 3, entries 9-10). In particular, this chemistry worked well to convert alkyl-substituted ynamides to the desired **4k**-**4m** in excellent yields (Table 3, entries 11–13). It is noteworthy that the preparation of alkyl-substituted β–carbolines conventionally suffers from multistep tedious synthesis processes.[14] Furthermore, substituents with different electronic nature on the indole ring were also readily tolerated, thus allowing the facile synthesis of products **4n**−**4q** in almost quantitive yields (Table 3, entries 14−17). In the case of ynamides bearing different protecting groups, the reaction also worked well to deliver the anticipated **4r**-**4s** in excellent yields (Table 3, entries 18−19). Finally, it was found that the reaction also proceeded well with methyl substituted ynamide (R^1= Me) but requiring the use of NaOH instead of Et_3N as the base to facilitate the demesylation (Table 3, entry 20). Of note, slightly improved yields could be achieved in some cases by using 20 mol % NaBARF as the additive (Table 3, entries 9–11). Again, a gram scale synthesis was also feasible (Table 3, entry 1). Thus, this protocol provides a highly efficient and practical route for the construction of the synthetically useful β–carboline scaffold.

Table 3. Reaction Scope for the Formation of β − carbolines 4[a]

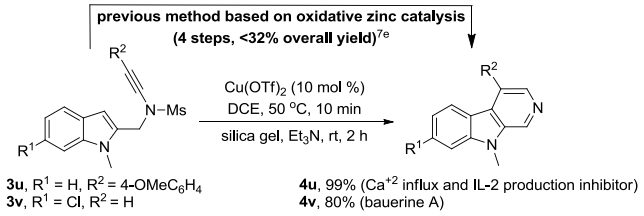




[a]Reactions run in vials; [**3**] = 0.05 M; silica gel (100 mg/0.1 mmol) and Et_3N (2 equiv) were added after 10 min; yields are those for the isolated products. [b]5.0 mmol scale, 5 mol % $Cu(OTf)_2$ was used, 30 min. [c]20 mol % NaBARF was used as the additive; NaBARF = sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate. [d]3 equiv of NaOH in DMSO/H_2O (1/1) was added and the reaction was stirred at 125 °C for another 3 h.

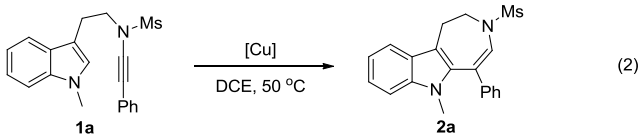
Further synthetic applications of this copper-catalyzed cycloisomerization reaction were demonstrated in the concise and efficient synthesis of the Ca^{+2} influx and IL-2 production inhibitor (**4u**)[14] and natural product bauerine A (**4v**).[15] Notably, starting from the same indolyl ynamides, these valuable β–carbolines previously demanded rather lengthy synthesis (4 steps), especially including the additional necessary deprotection and dehydrogenative stages of the sequence (Scheme 4).[7g]

Scheme 4. Synthetic Applications



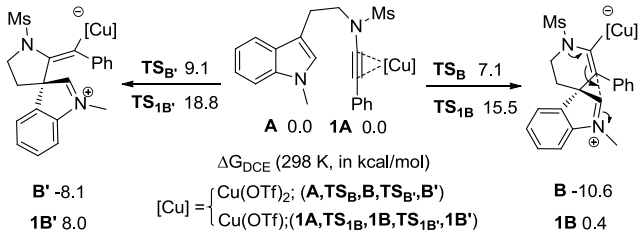
3. Mechanistic Study. To understand the mechanism of this novel cyclization, a radical trapping experiment was first conducted. It was found that the radical scavengers such as BHT (butylated hydroxytoluene) and TEMPO have no apparent inhibiting effect on this cyclization reaction (eq 2a-b),[9] indicating that a radical chain reaction mechanism can be ruled out.

We then studied the real catalytic species for this copper catalysis. Interestingly, when catalyst loading was reduced to 1 mol % or 2 mol %, yields of **2a** significantly decreased in the case of using CuOTf as catalyst, but remain to be high by employing $Cu(OTf)_2$ as catalyst (eq 2c-d). These results suggested that $Cu(OTf)_2$ was most likely the real catalytic species, and CuOTf could be slowly oxidized into the catalytically active $Cu(OTf)_2$ by the trace air in the reaction system. Indeed, preliminary DFT calculations revealed that the first step of the cyclization catalyzed by $Cu(OTf)_2$ or CuOTf tended to generate six-membered ring intermediate **B** or **1B**, and the Cu(II)-catalyzed one was favorable kinetically and thermodynamically over the Cu(I)-catalyzed one (Scheme 5).[9]



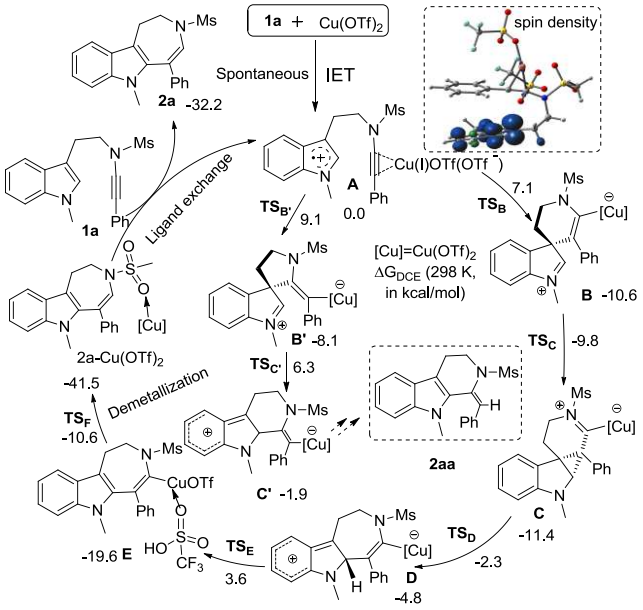
a) $Cu(OTf)_2$ (10 mol %), BHT (2 equiv), 2 h, 79%
b) $Cu(OTf)_2$ (10 mol %), TEMPO (2 equiv), 12 h, 82%
c) $Cu(OTf)_2$ (1 mol %), 20 h, 84%; CuOTf (1 mol %), 24 h, <1% (>95% **1a** left)
d) $Cu(OTf)_2$ (2 mol %), 15 h, 82%; CuOTf (2 mol %), 24 h, 24% (70% **1a** left)

Scheme 5. M06(SMD, DCE)/6-31G(d,p)/LanL2DZ Level Free Energies for the Formation of 2a by Comparing Cu(II)(OTf)2 with Cu(I)OTf



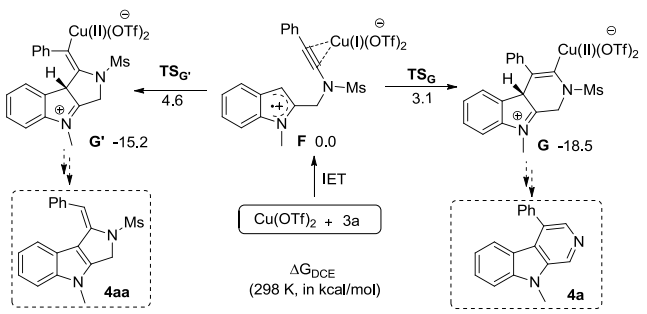
Further DFT computations, together with detailed analyses on the electronic structures of the precursors, intermediates and transition states involved in the cyclization processes,[9] disclosed a plausible mechanism (Scheme 6) to rationalize the formation of **2a** from ynamide **1a**. Ligation of ynamide **1a** to the Cu(II)-catalyst spontaneous triggers intramolecular electron transfer (IET). The as-formed Cu(I)-bound alkyne **A** is attacked by the electrophilic C-3 atom of the tethered indolium radical to form either a 6- or 5-membered ring intermediate **B** or **B′**, both resuming Cu(II).[16] Then both **B** and **B′** are subjected sequentially to 1,2-alkenyl migration (with ring expansion), 1,3-proton migration and demetallation to furnish **2a** and **2aa**, respectively. Clearly, the regioselectivity of the whole process is determined by the kinetics of the cyclization step; the DFT-predicted free energy barrier is 7.1 kcal/mol (at TS_B) for the pathway to **2a**, by 2.0 kcal/mol lower than that (at $TS_{B'}$) for the pathway to **2aa**, most likely due to smaller steric strain in 6-membered ring than in 5-membered ring. Accordingly, the whole process affords regioselectively **2a**, not **2aa**, with free energy release amounting to 32.2 kcal/mol. However, a Brønsted acid catalyzes ynamide **1a** to form 6-membered ring intermediate, which is attributed to the preferential formation of keteniminium precursor.[9]

Scheme 6. Free-Energy Profile for the Regioselective Formation of 2a in DCE Predicted at the SMD-M06/DZP Level of Theory



The origin of regioselectivity for 6-*endo-dig* cycloisomerization was also disclosed by DFT calculations.[9] As shown in Scheme 7, the formation of 6-membered ring intermediate **G** is kinetically and thermodynamically more favorable than that of 5-membered intermediate **G′**, likely due to smaller strain in 6-membered ring. The former passes through base-assisted demesylation/aromatization[17] to deliver the final β-carboline **4a**.

Scheme 7. M06(SMD, DCE)/6-31G(d,p)/LanL2DZ-Predicted Relative Free Energies for Precursors and Key Transition States Responsible for the Regioselective Formation of 4a in DCE



CONCLUSIONS

In summary, reversal of regioselectivity in arene-ynamide cyclization by copper catalysis has been achieved, providing straightforward and practical access to structurally diverse azepino[4,5-*b*]indoles and β-carbolines in generally good to excellent yields under mild reaction conditions. Importantly, this protocol represents the first catalytic π-tethered ynamide cyclization involving the reversal of regioselectivity. In addition, the synthetic utility of this methodology has also been demonstrated in the synthesis of several biologically active compounds and natural product bauerine A. Moreover, detailed theoretical calculations have been carried out to understand the experimentally observed regioselectivity. In other words, the unique π-acidic property of Cu(II) catalyst together with the dual ion precursor generated from intramolecular electron transfer (IET) plays a key role in such an exclusive cyclization. The development of novel catalytic reactions involving the reversal of ynamide regioselectivity and mechanistic investigations are the subjects of ongoing research in our laboratory.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedure, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

Crystallographic data (CIF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: longwuye@xmu.edu.cn

*E-mail: xinlu@xmu.edu.cn

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We are grateful for the financial support from the National Natural Science Foundation of China (21622204, 21572186, 91545105 and 21273177), the Natural Science Foundation of Fujian Province for Distinguished Young Scholars (2015J06003), the President Research Funds from Xiamen University (20720150045), XMU Training Program of Innovation and Enterpreneurship for Undergraduates (201410384055), PCSIRT, NFFTBS (J1310024) and SRFDP (20130121110004). We also thank Professor Dr. Yuanzhi Tan for assistance with X-ray crystallographic analysis.

REFERENCES

(1) For recent reviews on ynamide reactivity, see: (a) Pan, F.; Shu, C.; Ye, L.-W. *Org. Biomol. Chem.* **2016**, *14*, 9456−9465. (b) Evano, G.; Theunissen, C.; Lecomte, M. *Aldrichimica Acta* **2015**, *48*, 59−70. (c) Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* **2014**, *47*, 560−578. (d) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064−5016. (e) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840−2859.

(2) For recent selected examples, see: (a) Wang, T.; Hoye, T. R. *J. Am. Chem. Soc.* **2016**, *138*, 13870−13873. (b) Hu, L.; Xu, S.; Zhao, Z.; Yang, Y.; Peng, Z.; Yang, M.; Wang, C.; Zhao J. *J. Am. Chem. Soc.* **2016**, *138*, 13135−13138. (c) Wang, T.; Niu, D.; Hoye, T. R. *J. Am. Chem. Soc.* **2016**, *138*, 7832−7835. (d) Wang, Y.; Song, L.-J.; Zhang, X.; Sun, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 9704−9708. (e) Wezeman, T.; Zhong, S.; Nieger, M.; Bräse, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 3823−3827. (f) Jin, H.; Huang, L.; Xie, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 794−797. (g) Jadhav, A. M.; Pagar, V. V.; Huple, D. B.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2015**, *54*, 3812−3816. (h) Pawar, S. K.; Sahani, R. L.; Liu, R.-S. *Chem.-Eur. J.* **2015**, *21*, 10843−10850. (i) Liu, J.; Chen, M.; Zhang, L.; Liu, Y. *Chem.-Eur. J.* **2015**, *21*, 1009−1013. (j) Brioche, J.; Meyer, C.; Cossy, J. *Org. Lett.* **2015**, *17*, 2800−2803. (k) Fujino, D.; Yorimitsu, H.; Osuka, A. *J. Am. Chem. Soc.* **2014**, *136*, 6255−6258. (l) Gawade, S. A.; Huple, D. B.; Liu, R.-S. *J. Am. Chem. Soc.* **2014**, *136*, 2978−2981. (m) Romain, E.; Fopp, C.; Chemla, F.; Ferreira, F.; Jackowski, O.; Oestreich, M.; Perez-Luna, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 11333−11337. (n) Karad, S. N.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2014**, *53*, 9072−9076.

(3) For recent selected examples based on Au or Ag catalysis, see: (a) Heinrich, C. F.; Fabre, I.; Miesch, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 5170−5174. (b) Zheng, N.; Chang, Y.-Y.; Zhang, L.-J.; Gong, J.-X.; Yang, Z. *Chem. Asian J.* **2016**, *11*, 371−375. (c) Adcock, H. V.; Chatzopoulou, E.; Davies, P. W. *Angew. Chem., Int. Ed.* **2015**, *54*, 15525−15529. (d) Nayak, S.; Ghosh, N.; Prabagar, B.; Sahoo, A. K. *Org. Lett.* **2015**, *17*, 5662−5665. (e) Kiruthika, S. E.; Nandakumar, A.; Perumal, P. T. *Org. Lett.* **2014**, *16*, 4424−4427. (f) Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2014**, *16*, 3138−3141. (g) Ghosh, N.; Nayak, S.; Sahoo, A. K. *Chem.-Eur. J.* **2013**, *19*, 9428−9433. (h) Garcia, P.; Harrak, Y.; Diab, L.; Cordier, P.; Ollivier, C.; Gandon, V.; Malacria, M.; Fensterbank, L.; Aubert, C. *Org. Lett.* **2011**, *13*, 2952−2955. (i) Hashmi, A. S. K.; Pankajakshan, S.; Rudolph, M.; Enns, E.; Bander, T.; Rominger, F.; Frey, W. *Adv. Synth. Catal.* **2009**, *351*, 2855−2875.

(4) For recent selected examples based on other transition metal catalysis, see: (a) Straker, R. N.; Peng, Q.; Mekareeya, A.; Paton, R. S.; Anderson, E. A. *Nat. commun.* **2016**, *7*, 10109. (b) Reddy, A. S.; Kumara Swamy, K. C. K. *Org. Lett.* **2015**, *17*, 2996−2999. (c) Yeh, M.-C. P.; Liang, C.-J.; Chen, H.-F.; Weng, Y.-T. *Adv. Synth. Catal.* **2015**, *357*, 3242−3254.

(5) (a) Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A. *Org. Lett.* **2005**, *7*, 1047−1050. (b) Yamaoka, Y.; Yoshida, T.; Shinozaki, M.; Yamada, K.-i.; Takasu, K. *J. Org. Chem.* **2015**, *80*, 957−964. (c) Theunissen, C.; Métayer, B.; Henry, N.; Compain, G.; Marrot, J.; Martin-Mingot, A.; Thibaudeau, S.; Evano, G. *J. Am. Chem. Soc.* **2014**, *136*, 12528−12531. (d) Lecomte, M.; Evano, G. *Angew. Chem., Int. Ed.* **2016**, *55*, 4547−4551. (e) Xie, L.-G.; Shaaban, S.; Chen, X.; Maulide, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 12864−12867.

(6) Recent reports involving the reversal of regioselectivity in ynamide chemistry are mostly limited to radical reactions, and reactions governed by ring strain factor or metal-carbonyl chelation. For radical reactions, see: (a) Laroche, C.; Li, J.; Kerwin, S. M. *J. Med. Chem.* **2011**, *54*, 5059−5069. (b) Banerjee, B.; Litvinov, D. N.; Kang, J.; Bettale, J. D.; Castle, S. L. *Org. Lett.* **2010**, *12*, 2650−2652. (c) Sato, A.; Yorimitsu, H.; Oshima, K. *Synlett* **2009**, 28−31. For reactions governed by ring strain factor, see: (d) Tokimizu, Y.; Wieteck, M.; Rudolph, M.; Oishi, S.; Fujii, N.; Hashmi, A. S. K.; Ohno, H. *Org. Lett.* **2015**, *17*, 604−607. (e) Frischmuth, A.; Knochel, P. *Angew.*

Chem., Int. Ed. **2013**, *52*, 10084−10088. (f) Li, J.; Neuville, L. *Org. Lett.* **2013**, *15*, 1752−1755. (g) Istrate, F. M.; Buzas, A. K.; Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *Org. Lett.* **2008**, *10*, 925−928. (h) Hashmi, A. S. K.; Salathé, R.; Frey, W. *Synlett* **2007**, 1763−1766. For reactions governed by metal-carbonyl chelation, see: (i) He, G.; Qiu, S.; Huang, H.; Zhu, G.; Zhang, D.; Zhang, R.; Zhu, H. *Org. Lett.* **2016**, *18*, 1856−1859. (j) Gati, W.; Rammah, M. M.; Rammah, M. B.; Couty, F.; Evano, G. *J. Am. Chem. Soc.* **2012**, *134*, 9078−9081. (k) Gourdet, B.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 3802−3803. For other examples, see: (l) Hentz, A.; Retailleau, P.; Gandon, V.; Cariou, K.; Dodd, R. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 8333−8337. (m) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820−1821.

(7) For recent selected examples, see: (a) Zhou, B.; Li, L.; Zhu, X.-Q.; Yan, J.-Z.; Guo, Y.-L.; Ye, L.-W. *Angew. Chem., Int. Ed.* **2017**, *56*, 4015−4019. (b) Shen, W.-B.; Xiao, X.-Y.; Sun, Q.; Zhou, B.; Zhu, X.-Q.; Yan, J.-Z.; Lu, X.; Ye, L.-W. *Angew. Chem., Int. Ed.* **2017**, *56*, 605−609. (c) Pan, F.; Li, X.-L.; Chen, X.-M.; Shu, C.; Ruan, P.-P.; Shen, C.-H.; Lu, X.; Ye, L.-W. *ACS Catal.* **2016**, *6*, 6055−6062. (d) Shu, C.; Wang, Y.-H.; Shen, C.-H.; Ruan, P.-P.; Lu, X.; Ye, L.-W. *Org. Lett.* **2016**, *18*, 3254−3257. (e) Pan, Y.; Chen, G.-W.; Shen, C.-H.; He, W.; Ye, L.-W. *Org. Chem. Front.* **2016**, *3*, 491−495. (f) Shu, C.; Wang, Y.-H.; Zhou, B.; Li, X.-L.; Ping, Y.-F.; Lu, X.; Ye, L.-W. *J. Am. Chem. Soc.* **2015**, *137*, 9567−9570. (g) Li, L.; Zhou, B.; Wang, Y.-H.; Shu, C.; Pan, Y.-F.; Lu, X.; Ye, L.-W. *Angew. Chem., Int. Ed.* **2015**, *54*, 8245−8249. (h) Zhou, A.-H.; He, Q.; Shu, C.; Yu, Y.-F.; Liu, S.; Zhao, T.; Zhang, W.; Lu, X.; Ye, L.-W. *Chem. Sci.* **2015**, *6*, 1265−1271. (i) Li, L.; Shu, C.; Zhou, B.; Yu, Y.-F.; Xiao, X.-Y.; Ye, L.-W. *Chem. Sci.* **2014**, *5*, 4057−4064. (j) Pan, F.; Liu, S.; Shu, C.; Lin, R.-K.; Yu, Y.-F.; Zhou, J.-M.; Ye, L.-W. *Chem. Commun.* **2014**, *50*, 10726−10729.

(8) For recent selected examples, see: (a) Barve, I. J.; Dalvi, P. B.; Thikekar, T. U.; Chanda, K.; Liu, Y. L.; Fang, C. P.; Liu, C. C.; Sun, C. M. *RSC Adv.* **2015**, *5*, 73169−73179. (b) Zhu, P.-L.; Zhang, Z.; Tang, X.-Y.; Marek, I.; Shi, M. *ChemCatChem* **2015**, *7*, 595−600. (c) Mizoguchi, H.; Oikawa, H.; Oguri, H. *Nat. Chem.* **2014**, *6*, 57−64. (d) Kitajima, M.; Murakami, Y.; Takahashi, N.; Wu, Y.; Kogure, N.; Zhang, R.-P.; Takayama, H. *Org. Lett.* **2014**, *16*, 5000−5003. (e) Kargbo, R. B.; Sajjadi-Hashemi, Z.; Roy, S.; Jin, X.; Herr, R. J. *Tetrahedron Lett.* **2013**, *54*, 2018−2021. (f) Cheng, X.; Duhaime, C. M.; Waters, S. P. *J. Org. Chem.* **2010**, *75*, 7026−7028. (g) Garfield, A. S.; Heisler, L. K.; *J. Physiol.* **2009**, *587*, 49−60. (h) Gao, P.; Liu, Y.; Zhang, L.; Xu, P.; Wang, S.; Lu, Y.; He, M.; Zhai, H. *J. Org. Chem.* **2006**, *71*, 9495−9498.

(9) For details, please see the Supporting Information (SI).

(10) For a recent review on transition-metal (typically noble metals)-catalyzed intramolecular hydroarylation of alkynes, see: (a) Yamamoto, Y. *Chem. Soc. Rev.* **2014**, *43*, 1575−1600. For recent selected examples on the gold-catalyzed intramolecular hydroarylation of alkynes, see: (b) Ding, D.; Mou, T.; Feng, M.; Jiang, X. *J. Am. Chem. Soc.* **2016**, *138*, 5218−5221. (c) Zhang, L.; Wang, Y.; Yao, Z.-J.; Wang, S.; Yu, Z.-X. *J. Am. Chem. Soc.* **2015**, *137*, 13290−13300. (d) Pflästerer, D.; Schumacher, S.; Rudolph, M.; Hashmi, A. S. K. *Chem.-Eur. J.* **2015**, *21*, 11585−11589. (e) Pflästerer, D.; Rettenmeier, E.; Schneider, S.; de Las Heras Ruiz, E.; Rudolph, M.; Hashmi, A. S. K. *Chem.-Eur. J.* **2014**, *20*, 6752−6755. (f) Qiu, Y.; Ma, D.; Kong, W.; Fu, C.; Ma, S. *Org. Chem. Front.* **2014**, *1*, 62−67. (g) Dong, Z.; Liu, C.-H.; Wang, Y.; Lin, M.; Yu, Z.-X. *Angew. Chem., Int. Ed.* **2013**, *52*, 14157−14161. (h) Qiu, Y.; Kong, W.; Fu, C.; Ma, S. *Org. Lett.* **2012**, *14*, 6198−6201. (i) Gronnier, C.; Odabachian, Y.; Gagosz, F. *Chem. Commun.* **2011**, *47*, 218−220. (j) Loh, C. C. J.; Badorrek, J.; Raabe, G.; Enders, D. *Chem.-Eur. J.* **2011**, *17*, 13409−13414. (k) Hashmi, A. S. K.; Hamzic, M.; Rominger, F.; Bats, J. W. *Chem.-Eur. J.* **2009**, *15*, 13318−13322. (l) England, D. B.; Padwa, A. *Org. Lett.* **2008**, *10*, 3631−3634. (m) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.-Eur. J.* **2007**, *13*, 1358−1373. (n) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105−1109. (o) Nevado, C.; Echavarren, A. M. *Chem.-Eur. J.* **2005**, *11*, 3155−3164.

(11) CCDC-1469674 (**2a**) and CCDC-1501786 (**2ta**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) (a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600−3740. (b) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39−46. (c) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995.

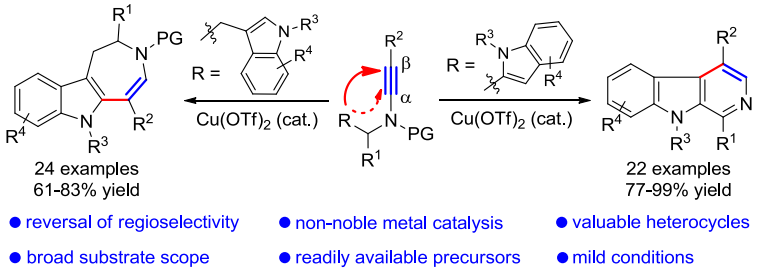
(13) (a) Decker, M.; Lehmann, J. *Arch. Pharm. Med. Chem.* **2003**, *336*, 466−476. (b) Elliott, A. J.; Gold, E. H.; Guzik, H. *J. Med. Chem.* **1980**, *23*, 1268−1269.

(14) Hargrave, K. D.; Miao, C. K.; Parks, T. P.; Potocki, I. F.; Snow, R. J. PCT Int. Appl. WO 9806719A1, **1998**.

(15) (a) Dantale, S. W.; Söderberg, B. C. G. *Tetrahedron* **2003**, *59*, 5507−5514. (b) Larsen, L. K.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1994**, *57*, 419−421.

(16) After the cyclization, the following intermediates/transition states all contain Cu(II) species and are not radicaloid at all. That is, the whole process does not follow a radical chain reaction mechanism, despite the precursor contains a radicaloid indolium group. For the relevant spin density distribution for some of the key intermediates and transition states, please see the Supporting Information for details.

(17) For recent selected examples, see: (a) Zhao, Y.-Z.; Yang, H.-B.; Tang, X.-Y.; Shi, M. *Chem.-Eur. J.* **2015**, *21*, 3562−3566. (b) Yang, Q.; Xu, T.; Yu, Z. *Org. Lett.* **2014**, *16*, 6310−6313. (c) Yang, Q.-Q.; Xiao, C.; Lu, L.-Q.; An, J.; Tan, F.; Li, B.-J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9137−9140.



Insert Table of Contents artwork here