DOI: 10.1002/adsc.201000525

# Chemoselective Cascade Synthesis of N-Fused Heterocycles *via* Silver(I) Triflate-Catalyzed Friedel–Crafts/N-C Bond Formation Sequence

Lu Hao,[a] Yingming Pan,[a] Tao Wang,[a] Min Lin,[a] Li Chen,[a] and Zhuang-ping Zhan[a,*]

[a] Department of Chemistry, College of Chemistry and Chemical Engineering, and State Key Laboratory for Physical Chemistry of Solid Surfaces, Xiamen University, Xiamen 361005, Fujian, People's Republic of China
Fax: (+86)-592-218-0318; phone: (+86)-592-218-0318; e-mail: zpzhan@xmu.edu.cn

Received: July 5, 2010; Revised: September 6, 2010; Published online: December 5, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000525.

**Abstract:** An efficient cascade methodology toward chemoselective synthesis of N-fused heterocycles including 9*H*-pyrrolo[1,2-*a*]indole, 3*H*-pyrrolo[1,2-*a*]indole and 1*H*-pyrrolo[1,2-*a*]indole derivatives has been developed. This transformation proceeds *via* a silver(I) triflate-catalyzed consecutive Friedel–Crafts reaction/N−C bond formation sequence between readily available propargyl alcohols and 3-substituted 1*H*-indoles. Not only is excellent chemoselectivity observed according to the substitution patterns of propargyl alcohols, but also the Lewis acid-catalyzed N−C bond formation process can be carried out under base- and ligand-free conditions.

**Keywords:** cascade reaction; Friedel-Crafts reaction; indoles; N-fused heterocycles; propargyl alcohol; silver

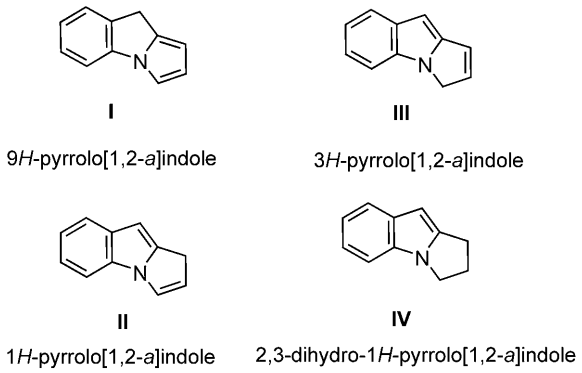


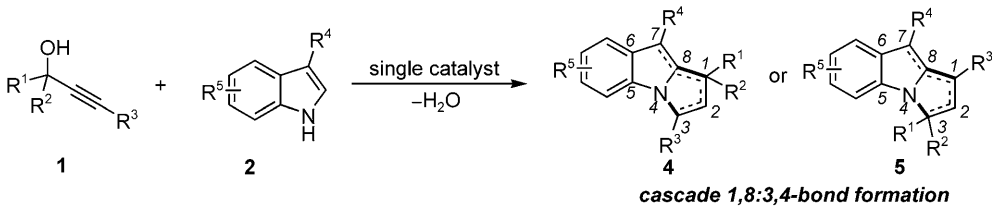

**Figure 1.** Several key N-fused heterocyclic skeletons.

Nitrogen-containing heterocyclic scaffolds are prevalent in naturally occurring and pharmaceutically active molecules, and therefore play a key role in medicinal chemistry and organic synthesis. Molecules containing bicyclic 9*H*-pyrrolo[1,2-*a*]indoles (**I**), 1*H*-pyrrol[1,2-*a*]indoles (**II**), 3*H*-pyrrolo[1,2-*a*]indoles (**III**) and other closely related cores such as reduced analogues (**IV**) have increasingly been of paramount interest in recent years due to their latent biological activity[1] (Figure 1). For instance, it was shown that these molecules exhibited strong anti-tumor,[2] anti-S1P1-associated disorder[3] and anti-diabetes[1b,4h] activities. Although several synthetic routes to those N-fused heterocycles have existed in recent years,[4] these methods have some limitations such as multi-step procedures, harsh conditions and poor selectivity. Accordingly, new approaches allowing for the selective assembly of different N-fused heterocyclic skeletons with diverse substitution patterns catalyzed by single catalyst are in high demand.

Over the past several years, our group has developed effective methods for the construction of O- and N-containing heterocycles *via* consecutive propargyl substitution and cycloisomerization, both of which were catalyzed by the same metallic catalyst.[5] It seemed plausible that this strategy could be extended to prepare the above-mentioned N-fused heterocycles from readily available propargyl alcohols and 3-substituted 1*H*-indoles. Thus, we envisioned a direct C-C/N−C bond-formation pathway for the synthesis of **4** or **5** (Scheme 1). Overall, this atom-economical transformation would provide a new avenue to access N-fused heterocyclic cores through consecutive formation of C−C and N−C bonds using a single catalyst from simple substrates.

Although this cascade sequence could have considerable utility, to achieve our desired transformation, we would need to overcome a significant obstacle: the initial C−C bond-formatin process, which could be achieved by a Friedel–Crafts reaction and was gener-

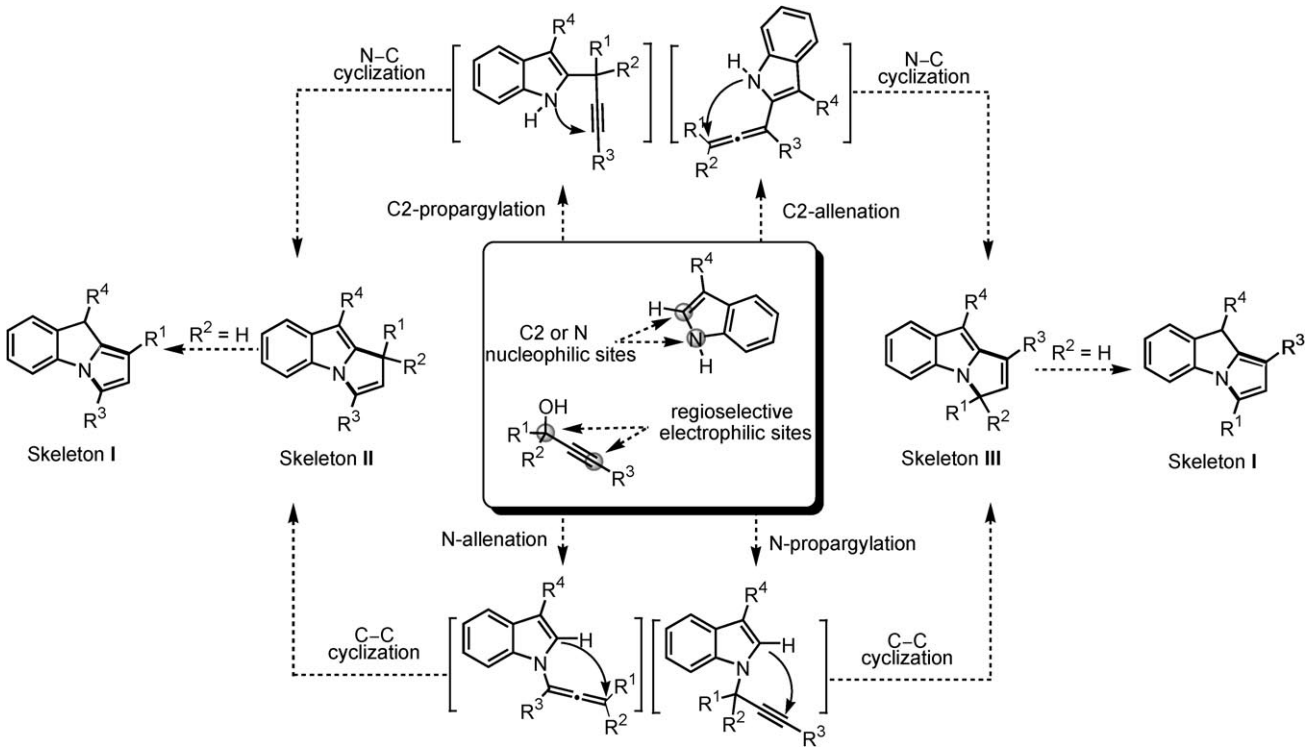
  




**Scheme 1.** Proposed cascade reaction for the synthesis of N-fused heterocycles.

ally catalyzed by Brønsted or Lewis acids,[6,7] whereas the addition of 1*H*-indole-NH to an alkyne moiety was always performed under basic conditions.[8] Therefore, it was necessary to search for a catalyst which must not only favor the Friedel–Crafts reaction but also facilitate the nucleophilic attack of 1*H*-indole-NH on alkyne-C. On the other hand, a challenge was posed for us: 3-substituted 1*H*-indoles possess two nucleophilic centers,[9] and similarly, propargyl alcohols have two electrophilic sites,[10] which make both the mechanism and final products complicated (Scheme 2). Also, in the case of $R^2 = H$, the two double bonds in the bicyclic skeleton are probably prone to isomerization by virtue of relative thermodynamic stability of the products, making the reaction result much more uncertain. With these in mind and after exhaustive exploration, we were pleased to discover that the novel cascade reaction could be successfully carried out in the presence of 5 mol% AgOTf.[11,12] Importantly, excellent chemoselectivity was observed, generating the three different skeletons **I**, **II** and **III** according to the substitution pattern of the substrates.

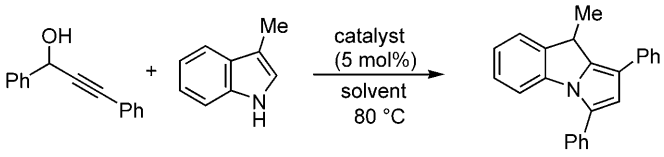
Our investigation began with the catalyst optimization. On the basis of our previous success in Fe(III)-catalyzed propargyl substitution reactions,[13,14] we initially treated propargyl alcohol **1a** with 3-methyl-1*H*-indole **2a** in toluene at 80 °C using 5 mol% $FeCl_3$ as the catalyst. Unfortunately, only a small amount of desired product **3aa** was formed under these reaction conditions (Table 1, entry 1). We reasoned that the poor yield of **3aa** was probably due to the weak ability of $FeCl_3$ to activate the alkyne moiety. Thus, Lewis acids such as $BiCl_3$, $InCl_3$, $Sc(OTf)_3$, $Bi(OTf)_3$, $Cu(OTf)_2$ and AgOTf, which are generally considered to possess both strong Lewis acidity and good alkynophilicity, were adopted as the catalysts (Table 2, entries 2–7). To our delight, it was found that, in the presence of 5 mol% AgOTf, the reaction result was drastically improved and the target product **3aa** was




**Scheme 2.** Plausible routes of formation and products in the synthesis of N-fused heterocycles.

**Table 1.** Optimization of catalysts and solvents.[a]




**1a** **2a** **3aa**

| Entry | Catalyst | Solvent[b] | Time [h] | Yield[c] [%] |
|---|---|---|---|---|
| 1 | $FeCl_3$ | toluene | 24 | 10 |
| 2 | $BiCl_3$ | toluene | 24 | 26 |
| 3 | $InCl_3$ | toluene | 24 | 13 |
| 4 | $Sc(OTf)_3$ | toluene | 0.5 | 63 |
| 5 | $Bi(OTf)_3$ | toluene | 8 | 16 |
| 6 | $Cu(OTf)_2$ | toluene | 24 | 49 |
| 7 | AgOTf | toluene | 0.5 | 82 |
| 8 | $Zn(OTf)_2$ | toluene | 12 | 31 |
| 9 | $ZnCl_2$ | toluene | 24 | 0 |
| 10 | *p*-TSA | toluene | 24 | 0 |
| 11 | TfOH | toluene | 3 | 25 |
| 12[d] | AgOTf | toluene | 0.5 | 84 |
| 13 | $AgBF_4$ | toluene | 3 | 59 |
| 14 | $AgSbF_6$ | toluene | 3 | 35 |
| 15 | AgOAc | toluene | 12 | 0 |
| 16 | $AgNO_3$ | toluene | 12 | traces |
| 17 | AgOTf | $CH_3CN$ | 24 | 16 |
| 18 | AgOTf | 1,2-DCE | 1 | 61 |
| 19 | AgOTf | $CH_3NO_2$ | 1 | 55 |
| 20 | AgOTf | $CH_2Cl_2$ | 24 | 0 |
| 21 | AgOTf | THF | 24 | 8 |
| 22 | AgOTf | Acetone | 24 | 11 |

[a] All reactions were performed with **1a** (0.5 mmol, 1.0 equiv.) and **2a** (0.55 mmol, 1.1 equiv.) in toluene (2 mL) at 80 °C for an appropriate time.
[b] 1,2-DCE = 1,2-dichloroethane; THF = tetrahydrofuran.
[c] Isolated yields based on propargyl alcohol **1a**.
[d] 10 mol% AgOTf.

furnished in 82% yield (Table 1, entry 7). In contrast, the reactions catalyzed by other Lewis acids proceeded with either more sluggish conversion or lower yields (Table 1, entries 2–6, 8 and 9), among which $Sc(OTf)_3$ displayed an acceptable catalytic efficacy albeit inferior to that of AgOTf (Table 1, entry 4, 63% yield). The catalytic efficacy of Brønsted acids was also explored. *p*-TSA gave no product (Table 1, entry 10), while TfOH afforded the product in 25% yield (Table 1, entry 11). Increasing the catalyst loading of AgOTf from 5% to 10% made an unremarkable influence on the reaction, in which the expected product was formed in 84% yield (Table 1, entry 12). Plainly, 5 mol% AgOTf was adequate for complete conversion of the substrates into the final products. Subsequently, the effect of counterions of silver salts on this cascade transformation was investigated (Table 1, entries 13–16). It was found when adopting $AgBF_4$ and $AgSbF_6$ as the catalysts the desired product could be obtained, but longer reaction time was required and lower yields were given (Table 2, entries 13 and 14). In the case of AgOAc and $AgNO_3$, no or only a trace of product was produced accompanied by the recovery of the starting materials (Table 2, entries 15 and 16). Such results showed that the nature of the counterions markedly affected the catalytic activity of silver(I) salts: the trifluoromethanesulfonate anion may be the best counterion to facilitate this cascade reaction. Next, solvent screening demonstrated that toluene was still the preferential solvent (Table 1, entries 17–22).

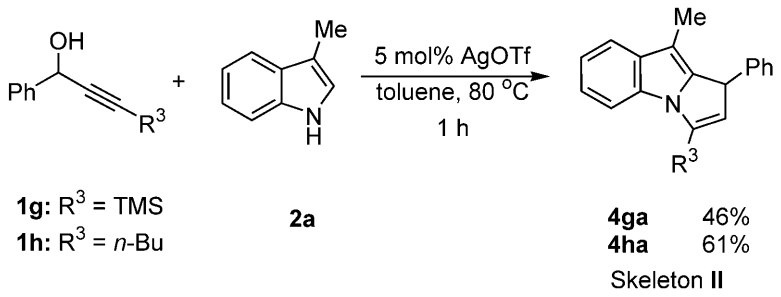
This preliminary study confirmed the efficacy of 5 mol% AgOTf in toluene to catalyze both the Friedel–Crafts reaction and the nucleophilic addition of the 1*H*-indole-NH to alkyne-C. Importantly, the latter process was for the first time accomplished under Lewis acid-catalyzed, and base- and ligand-free conditions. It was noteworthy that in this case ($R^1$, $R^3$ = phenyl, $R^2$ = H), the N-fused heterocyclic skeleton **I** (Figure 1) was chemoselectively constructed.

Next, the scope of this reaction was investigated under the optimized conditions (Table 2). We were pleased to find that aryl-substituted secondary propargyl alcohols ($R^1$ = aryl, $R^2$ = H) proceeded very well in this transformation, offering an easy access to N-fused heterocyclic skeleton **I** with various substitution patterns. A wide range of functionalities such as chloro, bromo, methoxy and methoxycarbonyl could be well tolerated, leading to the products in moderate to good yields (Table 2). An electron-donating substituent ($R^1$ = *p*-$MeOC_6H_4$; Table 2, entry 2) increased the rate of this reaction and gave a good yield, whereas an electron-withdrawing substituent ($R^1$ = Br; Table 2, entry 3) slowed the transformation down and provided a moderate yield. In particular, the presence of a strong electron-withdrawing ($R^1$ = *p*-$MeOOCC_6H_4$) group on the propargyl alcohol had an apparent adverse impact on the conversion (Table 2, entry 4, 48% yield). This result could be attributed to the instability of the propargyl cation intermediate. In addition, the presence of α-thiophenyl group did not retard this reaction leading to a moderate yield (Table 2, entry 6). We also tested the reactivity of alkyl-substituted secondary propargyl alcohol ($R^1$ = pentyl, $R^2$ = H), but we found that no expected product was obtained (Table 2, entry 7).

Encouraged by these results, we next examined the reactivity of aryl-substituted secondary propargyl alcohols bearing trimethylsilyl and alkyl groups on the alkyne moiety (Scheme 3). Interestingly, products **4ga** and **4ha** with the skeleton pattern **II** were exclusively generated in 46% and 61% yields, respectively.

To further define the generality of the present procedure, attention was turned to the reactions of tertiary propargyl alcohols. Intriguingly, it was found not only were the N-fused heterocyclic skeletons **III** exclusively obtained but also the substitution patterns

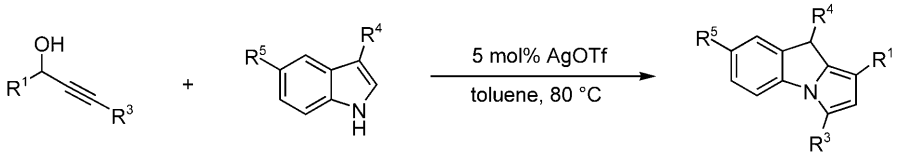
  



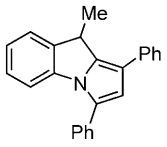
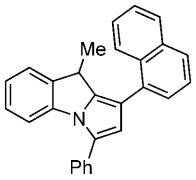
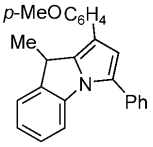
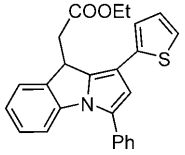
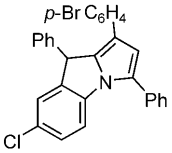
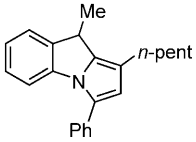
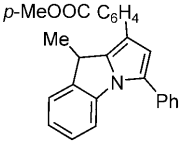

**Scheme 3.** Cascade reactions of TMS- and alkyl-substituted propargyl alcohols with 3-methyl-1*H*-indole.

were opposite to those of secondary propargyl alcohols (Table 3). On the basis of literature reports and our previous observations, we reasoned these N-fused products may be afforded *via* a C2-allenation/N–C cyclization route[15] as shown in Scheme 2. The substrate investgation revealed that substrates possessing a variety of functionalities exhibited very good reactivity and moderate to excellent yields were obtained. The reaction of triaryl-substituted propargyl alcohols ($R^1$, $R^2$, $R^3$ = aryl) proceeded very well affording the desired products in 84–96% yields (Table 3, entries 1, 5–14). On the other hand, the substrate with a substitution pattern of $R^1$ = aryl, $R^2$ = methyl and $R^3$ = aryl was also smoothly converted into the N-fused heterocycle in good yield (Table 3, entry 2). However, in the case of $R^3$ = alkyl or TMS, only moderate yields were

**Table 2.** Cascade synthesis of N-fused heterocycles (skeleton **I**) from secondary propargyl alcohols.[a]




**1** **2** **3**

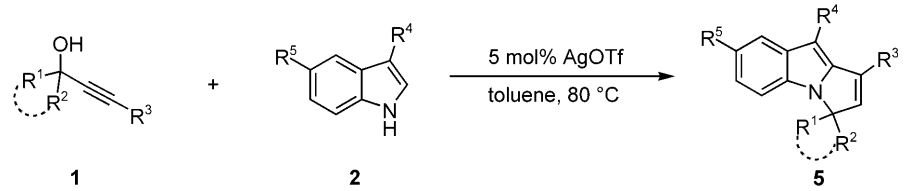
| Entry | **1**: $R^1$, $R^3$<br>**2**: $R^4$, $R^5$ | Product | Time [h] | Yield[b] [%] | Entry | **1**: $R^1$, $R^3$<br>**2**: $R^4$, $R^5$ | Product | Time [h] | Yield[b] [%] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a**: Ph; Ph<br>**2a**: Me; H | **3aa**  | 0.5 | 82 | 5 | **1e**: 1-naphthyl; Ph<br>**2a**: Me; H | **3ea**  | 0.5 | 83 |
| 2 | **1b**: *p*-$MeOC_6H_4$; Ph<br>**2a**: Me; H | **3ba**  | 0.4 | 85 | 6 | **1f**: 2-thienyl; Ph<br>**2c**: $CH_2COOEt$; H | **3fc**  | 2 | 68 |
| 3 | **1c**: *p*-$BrC_6H_4$; Ph<br>**2b**: Ph; Cl | **3cb**  | 0.7 | 79 | 7 | **1g**: *n*-pent; Ph<br>**2a**: Me; H | **3ga**  | 12 | 0 |
| 4 | **1d**: *p*-$MeOOCC_6H_4$; Ph<br>**2a**: Me; H | **3da**  | 3 | 48 | | | | | |

[a] All reactions were performed with propargyl alcohols **1** (0.5 mmol, 1.0 equiv.), 3-substituted indoles **2** (0.55 mmol, 1.1 equiv.) and 5 mol% AgOTf (0.025 mmol) in toluene (2 mL) at 80 °C for an appropriate time.

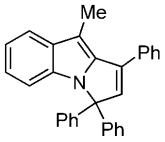
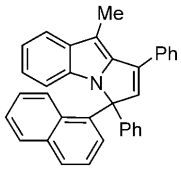
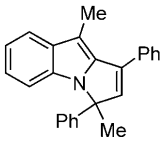
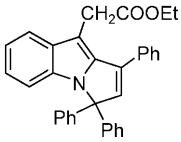
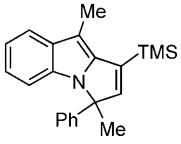
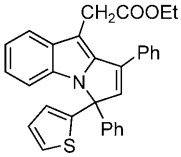
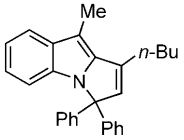
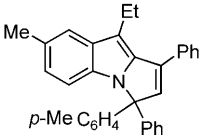
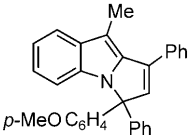
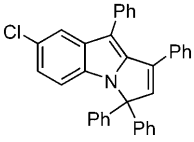
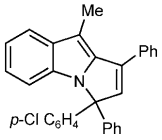
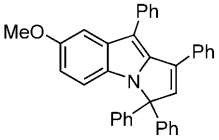
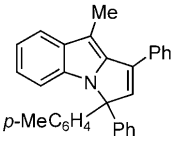
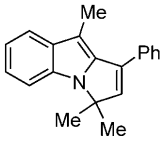
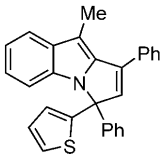
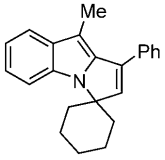
[b] Isolated yields based on propargyl alcohols **1**.

**Table 3.** Cascade synthesis of N-fused heterocycles (skeleton **III**) from tertiary propargyl alcohols.[a]




**1** **2** **5**

| Entry | **1**: $R^1$; $R^2$; $R^3$<br>**2**: $R^4$; $R^5$ | Product | Time [h] | Yield[b] [%] | Entry | **1**: $R^1$; $R^2$; $R^3$<br>**2**: $R^4$; $R^5$ | Product | Time [h] | Yield[b] [%] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1i**: Ph; Ph; Ph<br>**2a**: Me; H | **5ia**  | 0.4 | 92 | 9 | **1q**: 1-naphthyl; Ph; Ph<br>**2a**: Me; H | **5qa**  | 0.4 | 94 |
| 2 | **1j**: Ph; Me; Ph<br>**2a**: Me; H | **5ja**  | 0.4 | 89 | 10 | **1i**: Ph; Ph; Ph<br>**2c**: $CH_2COOEt$; H | **5ic**  | 0.7 | 90 |
| 3 | **1k**: Ph; Me; TMS<br>**2a**: Me; H | **5ka**  | 0.8 | 65 | 11 | **1p**: 2-thienyl; Ph; Ph<br>**2c**: $CH_2COOEt$; H | **5pc**  | 0.7 | 84 |
| 4 | **1l**: Ph; Ph; *n*-Bu<br>**2a**: Me; H | **5la**  | 0.7 | 71 | 12 | **1o**: *p*-$MeC_6H_4$; Ph; Ph<br>**2d**: Et; Me | **5od**  | 0.4 | 93 |
| 5 | **1m**: *p*-$MeOC_6H_4$; Ph; Ph<br>**2a**: Me; H | **5ma**  | 0.3 | 96 | 13 | **1i**: Ph; Ph; Ph<br>2b: Ph; Cl | **5ib**  | 0.4 | 91 |
| 6 | **1n**: *p*-$ClC_6H_4$; Ph; Ph<br>**2a**: Me; H | **5na**  | 0.4 | 90 | 14 | **1i**: Ph; Ph; Ph<br>**2e**: Ph; MeO | **5ie**  | 0.3 | 95 |
| 7 | **1o**: *p*-$MeC_6H_4$; Ph; Ph<br>**2a**: Me; H | **5oa**  | 0.4 | 93 | 15[c] | **1r**: Me; Me; Ph<br>**2a**: Me; H | **5ra**  | 12 | 35 |
| 8 | **1p**: 2-thienyl; Ph; Ph<br>**2a**: Me; H | 5pa  | 0.4 | 88 | 16[c] | **1s**: -$(CH_2)_5$-; Ph<br>**2a**: Me; H | **5sa**  | 12 | 32 |

[a] All reactions were performed with propargyl alcohols **1** (0.5 mmol, 1.0 equiv.), 3-substituted indoles **2** (0.55 mmol, 1.1 equiv.) and 5 mol% AgOTf (0.025 mmol) in toluene (2 mL) at 80 °C for an appropriate time.

[b] Isolated yields based on propargyl alcohols **1**.

[c] The reactions were performed in nitromethane ($CH_3NO_2$) instead of toluene.

obtained (Table 3, entries 3 and 4). In addition, 3-substituted 1*H*-indoles with either electron-withdrawing groups ($R^4 = CH_2COOEt$ or $R^5 = Cl$) or electron-donating groups ($R^5 = Me$ or OMe) on the 3- or 5- position all showed excellent reactivity, generating the products in 84–95% yields (Table 3, entries 10–14). It was noteworthy that in contrast with secondary propargyl alcohols, the electronic effect of $R^1$ did not have any obvious influence on the reactivity of the tertiary propargyl alcohols. The reactions of tertiary propargyl alcohols with electron-withdrawing and electron-donating groups both provided the desired products in good yields (Table 3, entries 5–7). We also carried out this transformation using dialkyl-substituted tertiary propargyl alcohols as the substrates. Unfortunately, we found that no desired products were obtained. We replaced toluene with nitromethane as the solvent.[16] To our delight, the corresponding N-fused heterocycles were formed albeit with prolonged reaction times and in low yields (Table 3, entries 15 and 16). The example of entry 16 offered a new access to N-containing spirocyclic compounds, which may possess potential biological activity.

To validate the formation mechanism of the three different N-fused heterocyclic skeletons **I**, **II** and **III**, attempts were made to capture the possible corresponding intermediates. Thus, three reactions were performed at room temperature to 50 °C, and three key intermediates **6**, **7** and **8** were successfully isolated and fully characterized by $^1H$ and $^{13}C$ NMR methods and high resolution mass spectroscopic (HR-MS) data (Figure 2).[17] It was further discovered that without isolation and after being heated to 80 °C for an appropriate time, the three intermediates **6**, **7** and **8** smoothly converted into the corresponding heterocyclic products **3aa**, **4ha** and **5ja**.

The above work demonstrated that the formation of the three N-fused heterocyclic skeletons proceeded in two ways: one was the C2-propargylation/N−C cyclization (5-*endo-dig*) route, and the other was the C2-allenation/N−C cyclization (5-*endo-trig*) route. Thus, we proposed the following mechanism for this substitution/cyclization sequence (Scheme 4). First, the activation of propargyl alcohol through coordination of the metal catalyst with the hydroxy group and the triple bond delivered intermediate **A**, which underwent elimination to give the alkynyl cation species **B** and its allenic resonance form **C**.[10] The following Friedel–Crafts reaction occurred by C2-nucleophilic attack of 3-substituted 1*H*-indoles on **B** and **C**, leading to the substitution products **D** and **E**, respectively. Through Ag(I)-mediated π-activation, **D** would experience a *5-endo-dig* cyclizaiton to generate two different N-fused skeletons **I** (**F**) and **II** (**G**) according to the $R^3$ substitution pattern, whereas **E** would undergo a *5-endo-trig* cyclization to furnish the skeleton **III** (**H**). Finally, the released Ag(I) catalyst entered into the next catalytic cycle. Notably, excellent chemoselectivity was obtained between skeleton **I** and skeleton **II**, which was presumably due to the relative stability of the two types of N-fused heterocycles. When the $R^1$ and $R^3$ were both aryl groups, the total conjugation effect of $R^1$ and $R^3$ with the pyrrole ring of the N-fused heterocycle made skeleton **I** more stable than skeleton **II**. Hence, skeleton **I** would be formed preferentially through double bond isomerization. When the $R^1$ = aryl and $R^3$ = alkyl or TMS, such a conjugation effect of $R^3$ disappeared, resulting in the skeleton **II** which was more stable than skeleton **I** in this case as well as being the initial product of the cyclization process of compound **D**.

In summary, we have developed an efficient cascade Friedel–Crafts reaction/N−C bond formation protocol for the chemoselective assembly of N-fused heterocyclic compounds starting from readily available propargyl alcohols and 3-substituted 1*H*-indoles. Three useful N-fused heterocyclic cores can be easily obtained in the presence of 5 mol% AgOTf under mild conditions and a broad range of functional groups are well tolerated. Importantly, this is the first example of a single metallic Lewis acid-catalyzed nucleophilic addition of 1*H*-indole-NH to alkyne-C and allene-C under base- and ligand-free conditions. Through the isolation and characterization of key intermediates, we confirmed two distinct routes to the three skeletons: C2-propargylation/N-C *5-endo-dig*-cyclization and C2-allenation/N-C *5-endo-trig*-cyclization. Further study to expand the scope of synthetic utilities of this novel reaction is in progress in our laboratory.

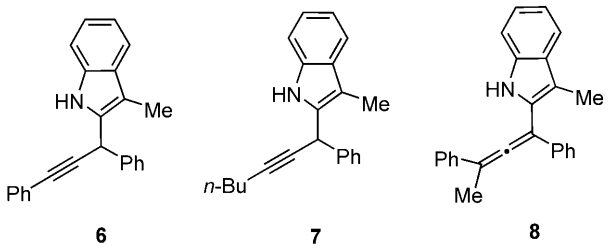


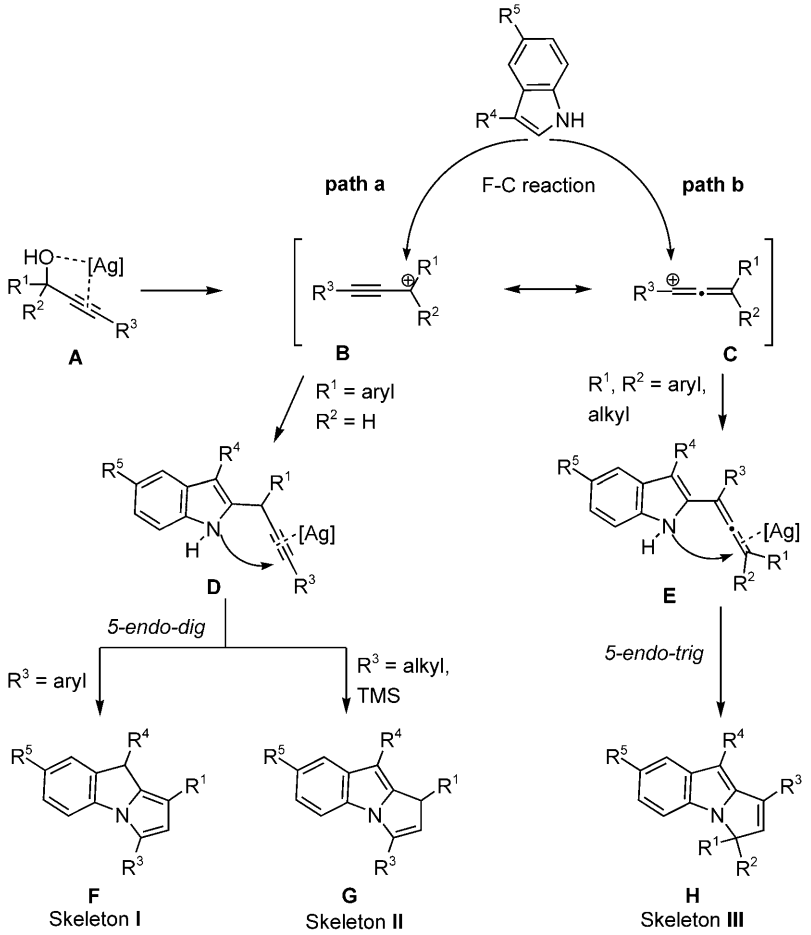

**Figure 2.** Isolated intermediates formed by Friedel–Crafts reaction of propargyl alcohols and 3-methyl-1*H*-indole.

## Experimental Section

### Typical Procedure

To a dry 10-mL flask equipped with a magnetic bar, propargyl alcohol **1** (0.5 mmol, 1.0 equiv.), 3-substituted indole **2** (0.55 mmol, 1.1 equiv.), toluene (2 mL) and 5 mol% AgOTf (0.025 mmol) were successively added. The reaction mixture was stirred at 80 °C and monitored periodically by thin layer chromatography (TLC). Upon completion, the solvent was removed under reduced pressure, and the residue was puri-




**Scheme 4.** Proposed mechanism for the formation of the three N-fused heterocycles.

fied by column chromatography on silica gel to afford the N-fused heterocyclic compounds.

## Acknowledgements

*We gratefully acknowledge the financial support of the National Natural Science Foundation of China (Nos. 20772098 and 21072159).*

## References

[1] For studies on the biological activity and reactivity of these N-fused heterocycles, see: a) R. Kakadiya, H. Dong, P. Lee, N. Kapuriya, X. Zhang, T. Chou, T. Lee, K. Kapuriya, A. Shan, T. Su, *Bioorg. Med. Chem.* **2009**, *17*, 5614–5626; b) M. Tanaka, S. Sagawa, J. Hoshi, F. Shimoma, K. Yasue, M. Ubukata, T. Ikemoto, Y. Hase, M. Takahashi, T. Sasase, N. Ueda, M. Matsushita, T. Inaba, *Bioorg. Med. Chem.* **2006**, *14*, 5781–5794; c) R. W. Franck, K. F. Bernady, *J. Org. Chem.* **1968**, *33*, 3050–3055.

[2] T. Su, T. Chou, US Patent 0117125, **2009**.

[3] R. M. Jones, D. J. Buzard, A. M. Kawasaki, H. S. Kim, L. Thoresen, J. Lehmann, X. Zhu, WO Patent 027431, **2010**.

[4] For recent reviews and selected examples, see: a) A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor, in: *Comprehensive Heterocyclic Chemistry III*, Vol. 11, (Ed.: J. Cossy), Elsevier, Oxford, **2008**, pp 1–40; b) D. M. Schultz, J. P. Wolfe, *Org. Lett.* **2010**, *12*, 1028–1031; c) W. He, K. Yip, N. Zhu, D. Yang, *Org. Lett.* **2009**, *11*, 5626–5628; d) X. Huang, S. Zhu, R. Shen, *Adv. Synth. Catal.* **2009**, *351*, 3118–3122; e) K. S. Feldman, D. K. Hester, M. R. Iyer, P. J. Munson, C. S. Lopez, O. N. Faza, *J. Org. Chem.* **2009**, *74*, 4958–4974; f) C. S. Bryan, M. Lautens, *Org. Lett.* **2008**, *10*, 4633–4636; g) K. S. Feldman, D. K. Hester, C. S. Lopez, O. N. Faza, *Org. Lett.* **2008**, *10*, 1665–1668; h) M. Tanaka, M. Ubukata, T. Matsuo, K. Yasue, K. Matsumoto, Y. Kajimoto, T. Ogo, T. Inaba, *Org. Lett.* **2007**, *9*, 3331–3334; i) K. S. Feldman, M. R. Iyer, D. K. Hester, *Org. Lett.* **2006**, *8*, 3113–3116; j) W. H. Pearson, W. Fang, *J. Org. Chem.* **2000**, *65*, 7158–7174; k) N. Matsumura, Y. Yagyu, M. Ito, T. Adachi, K. Mizuno, *J. Org. Chem.* **2000**, *65*, 3341–3345; l) A. R. Katritzky, C. N. Fali, J. Li, *J. Org. Chem.* **1997**, *62*, 4148–4154.

[5] For our previous research on heterocyclic synthesis catalyzed by a single catalyst *via* the consecutive propargyl

substitution and cycloisomerization strategy, see: a) X. Liu, L. Huang, F. Zheng, Z. Zhan, *Adv. Synth. Catal.* **2008**, *350*, 2778–2788; b) Y. Pan, S. Zhao, W. Ji, Z. Zhan, *J. Comb. Chem.* **2009**, *11*, 103–109.

[6] For recent reviews of Friedel–Crafts reaction, see: a) S. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190–2201; b) M. Rueping, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2010**, *6*, No. 6; c) M. Badini, M. Tragni, *Org. Biomol. Chem.* **2009**, *7*, 1501–1507.

[7] For selected examples of the Friedel–Crafts reaction of propargyl alcohols, see: a) Y. Nishibayashi, M. Yoshikawa, Y. Inada, M. Hidai, S. Uemura, *J. Am. Chem. Soc.* **2002**, *124*, 11846–11847; b) Y. Nishibayashi, Y. Inada, M. Yoshikawa, M. Hidai, S. Uemura, *Angew. Chem.* **2003**, *115*, 1533–1536; *Angew. Chem. Int. Ed.* **2003**, *42*, 1495–1498; c) Y. Inada, M. Yoshikawa, M. D. Milton, Y. Nishibayashi, S. Uemura, *Eur. J. Org. Chem.* **2006**, 881–890; d) H. Matsuzawa, Y. Miyake, Y. Nishibayashi, *Angew. Chem.* **2007**, *119*, 6608–6611; *Angew. Chem. Int. Ed.* **2007**, *46*, 6488–6491; e) H. Matsuzawa, K. Kanao, Y. Miyake, Y. Nishibayashi, *Org. Lett.* **2007**, *9*, 5561–5564; f) M. Yoshimatsu, T. Otani, S. Matsuda, T. Yamamoto, A. Sawa, *Org. Lett.* **2008**, *10*, 4251–4254; g) C. Li, J. Wang, *J. Org. Chem.* **2007**, *72*, 7431–7434; h) ref.[16a]

[8] To the best of our knowledge, the N–C bond formation between 1*H*-indole-NH and alkyne-C is exclusively achieved in the presence of base or ligand, and the single metallic Lewis acid-catalyzed addition has not been reported previously. For a recent example of Cu(I)-catalyzed tandem synthesis of N-fused heterocycles in the presence of strong base and ligand, see: A. K. Verma, T. Kesharwani, J. Singh, V. Tandon, R. C. Larock, *Angew. Chem.* **2009**, *121*, 1158–1163; *Angew. Chem. Int. Ed.* **2009**, *48*, 1138–1143.

[9] Although the normal electrophilic site of 3-substituted 1*H*-indoles is known to be at C2, two recent examples revealed that direct transition metal-catalyzed N–C formation between the free N-H of 3-subsituted 1*H*-indoles and multi-bonds could occur, see: a) ref.[8]; b) M. R. Luzung, C. A. Lewis, P. S. Baran, *Angew. Chem.* **2009**, *121*, 7159–7163; *Angew. Chem. Int. Ed.* **2009**, *48*, 7025–7029.

[10] For research on the resonance of alkynyl cation and allenic cation, see: a) J. Andres, R. Cardenas, E. Silla, O. Tapia, *J. Am. Chem. Soc.* **1988**, *110*, 666–674; b) G. A. Olah, R. J. Spear, P. W. Westerman, J. Denis, *J. Am. Chem. Soc.* **1974**, *96*, 5855–5859; c) H. G. Richey, J. C. Philips, L. E. Rennick, *J. Am. Chem. Soc.* **1965**, *87*, 1381–1382.

[11] For recent reviews of Ag(I)-catalyzed synthesis of heterocycles and related mechanistic rationale, see: a) M. Alvarez-Corral, M. Munoz-Dorado, I. Rodriguez-Garcia, *Chem. Rev.* **2008**, *108*, 3174–3198; b) J. Weibel, A. Blanc, P. Pale, *Chem. Rev.* **2008**, *108*, 3149–3173; c) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395–3442; d) Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3199–3222; e) M. Naodovic, H. Yamamoto, *Chem. Rev.* **2008**. *108*. 3132–3148.

[12] For selected examples of Ag(I)-catalyzed synthesis of N-containing heterocycles, see: a) K. Ji, X. Shu, S. Zhao, H. Zhu, Y. Niu, X. Liu, Y. Liang, *Org. Lett.* **2009**, *11*, 3206–3209; b) Y. Niu, Z. Yan, G. Gao, H. Wang, X. Shu, K. Ji, Y. Liang, *J. Org. Chem.* **2009**, *74*, 2893–2896; c) I. V. Seregin, A. W. Schammel, V. Gevorgyan, *Org. Lett.* **2007**, *9*, 3433–3436; d) J. T. Binder, S. F. Kirsch, *Org. Lett.* **2006**, *8*, 2151–2153.

[13] For other groups' and our research on Fe(III)-catalyzed propargyl substitution, see: a) P. Li, Y. Zhang, L. Wang, *Chem. Eur. J.* **2009**, *15*, 2045–2049; b) Z. Zhan, J. Yu, H. Liu, Y. Cui, R. Yang, W. Yang, J. Li, *J. Org. Chem.* **2006**, *71*, 8298–8301; c) Z. Zhan, X. Cai, S. Wang, J. Yu, H. Liu, Y. Cui, *J. Org. Chem.* **2007**, *72*, 9838–9841; d) W. Ji, Y. Pan, S. Zhao, Z. Zhan, *Synlett* **2008**, 3046–3052.

[14] For recent reviews of the metal-catalyzed propargyl substitution, see: a) N. Ljungdahl, N. Kann, *Angew. Chem.* **2009**, *121*, 652–654; *Angew. Chem. Int. Ed.* **2009**, *48*, 642–644; b) R. J. Detz, H. Hiemstra, J. H. Maarseveen, *Eur. J. Org. Chem.* **2009**, 6263–6276.

[15] For recent selected examples of C-allenation reactions of propargyl compounds, see: a) R. Sanz, D. Miguel, A. Martinez, J. M. Alvarez-Gutierrez, F. Rodriguez, *Org. Lett.* **2007**, *9*, 727–730; b) ref.[16b]

[16] The work of Bach and Yoshimatsu directed us to the use of $CH_3NO_2$ as the solvent, which was considered a good medium to stabilize the propargyl cation intermediate. For the successful use of nitromethane in propargyl substitution reactions, see: a) P. Rubenbauer, E. Herdtweck, T. Strassner, T. Bach, *Angew. Chem.* **2008**, *120*, 10260–10263; *Angew. Chem. Int. Ed.* **2008**, *47*, 10106–10109; b) M. Yoshimatsu, T. Yamamoto, A. Sawa, T. Kato, G. Tanabe, O. Muraoka, *Org. Lett.* **2009**, *11*, 2952–2955; c) M. Yoshimatsu, T. Otani, S. Matsuda, T. Yamamoto, A. Sawa, *Org. Lett.* **2008**, *10*, 4251–4254.

[17] The experiments on capturing the three key intermediates are performed with propargyl alcohols **1** (0.5 mmol, 1.0 equiv.), 3-substituted indoles **2** (0.55 mmol, 1.1 equiv.) and 5 mol% AgOTf (0.025 mmol) in toluene (2 mL), which are shown below. In the course of forming **6**, **7** and **8**, certain amounts of the corresponding final N-fused heterocycles (**3aa**, **4ha** and **5ja**) were also furnished. Without isolation and after being heated for an appropriate time, these intermediates would be converted completely into corresponding N-fused heterocyclic products.