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Silver(I)-Catalyzed Annulation for the Regioselective Synthesis of N-Imino-γ-Carbolinium Ylides from Hydrazones of Indole-3-Carbonyl Derivatives and Propargylic Alcohols

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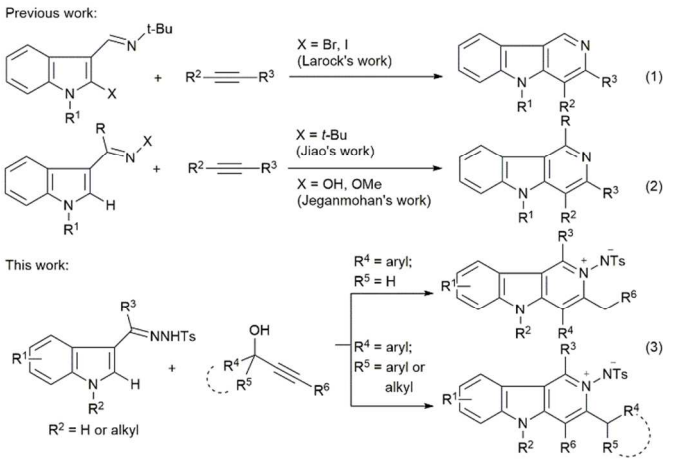
A regioselective efficient synthetic approach to N-imino-γ-carbolinium ylides via AgOTf-catalyzed iminoannulation has been developed. This transformation proceeds via a silver(I) triflate-catalyzed consecutive Friedel-Crafts reaction/N-C bond formation sequence between readily available indole derivatives and propargylic alcohols.

Pyrido[4,3-b]-5H-indoles, commonly known as γ-carbolines, which rarely documented in natural products.[1] However, a number of reports have shown that γ-carboline motifs are important substructures in pharmaceutical research.[2-5] Several γ-carboline derivatives have been synthesized and examined in a series of biological activity tests and have demonstrated antibiotic,[2] antitumor,[3] antipsychotic,[4] and other related activities.[5] Therefore, substantial efforts for the development of efficient synthetic strategies towards these targets have been undertaken.[6-10] Indole-3-carbonyl derivatives have emerged as a powerful precursor to construct γ-carboline skeletons by adopting multistep reactions.[7] Recently, some straightforward synthetic studies of γ-carboline derivatives have been disclosed. Larock et al. developed a palladium-catalyzed annulation between alkynes and 2-haloindole derivatives (Scheme 1, eq. 1).[8] Jiao et al. reported the synthesis of γ-carbolines via direct C-H bond cleavage from internal alkynes and indole derivatives (Scheme 1, eq. 2).[9] A practical route to synthesize γ-carboline *via* ruthenium-catalyzed highly regioselective cyclization of ketoxime derivatives with alkynes by C-H bond activation has been disclosed by Jeganmohan and coworkers (Scheme 1, eq. 2).[10]

Propargylic alcohols have proven to be very useful in organic synthesis due to the ease with which a wide variety of complicated heterocarbocycles can be rapidly constructed.[11] Recently, we have developed a general synthesis of pyrrolo[1,2-α]indole derivatives by the silver(I)-catalyzed consecutive Friedel-Crafts reaction/annulation sequence between propargyl alcohols and 3-substituted indoles.[12] The N-C bond formed from the 5-*endo* addition of indole-NH to an alkyne or allene moiety.



Scheme 1.γ-Carboline Synthesis from Indole-3-Carbonyl Derivatives.

Here, we report the successful synthesis of various N-imino-γ-carbolinium ylides by silver(I)-catalyzed Friedel-Crafts reaction/N-C bond formation sequence from indole derivatives and propargylic alcohols (Scheme 1, eq. 3). The regioselectivity of the reaction was sensitive to the nature of the propargylic alcohols.

Alternatively, this is the first example of γ-carbolines synthesis, which contained N-ylide group. Conveniences may be achieved in the further transformations due to the 1,3-dipolar character of the compounds bearing N-ylide groups, that allows cycloaddition processes to take place efficiently.[13]

We began our study by treating propargylic alcohol **1a** and hydrazone **2a** with catalytic amounts of AgOTf at 70 °C in THF. **3aa** was formed after 24 hours in 60% yield (Table 1, entry 1). Different solvents were then tested, but no improvement was achieved. The desired product **3aa** was not observed due to indissolvable character of **2a** in PhMe and PhCl (Table 1, entries 2 and 3). Using CH_3CN or

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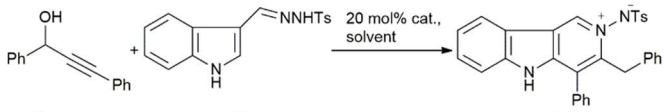
DCE as the solvent at reflux, no product was formed after 24 hours (Table 1, entries 4 and 5). The reaction also took place in a less effective manner, using solvents, such as DMF (10%), CH_3NO_2 (50%), and dioxane (58%) (Table 1, entries 6-8). By raising the temperature to 100 °C in THF, the desired target compound **3aa** was obtained in a higher yield of 78%, accompanied by decreasing of the reaction time to 12 hours (Table 1, entry 9). We then examined different catalysts (Table 1, entries 10-17). When several lewis acids were utilized in THF, the reaction proceeded to afford **3aa** in 37-65% yields (Table 1, entries 10-14). $FeCl_3$ also gave **3aa** but in a lower yield of 5% (Table 1, entry 15), whereas $Ph_3PAuNTf_2$ led to decomposition of **2a** (Table 1, entry 16). Addition of p-toluenesulfonic acid (PTSA) failed to catalyze this annulation (Table 1, entry 17). Furthermore, the reaction was sluggish when catalyst loading was decreased to 10 mol% (Table 1, entry 18).

Table 1. Screening for the reaction conditions[a]



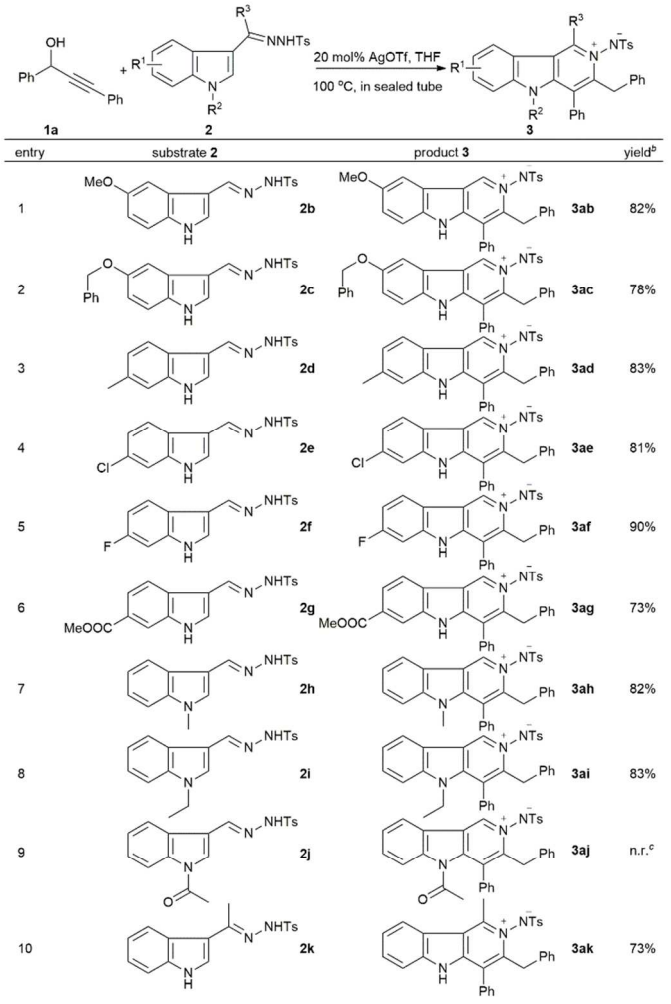
1a 2a 3aa

entry	catalyst	solvent	temp.	time	yield[b]
1	AgOTf	THF	70 °C	24 h	60%
2	AgOTf	PhMe	110 °C	24 h	n.r.[c]
3	AgOTf	PhCl	130 °C	24 h	n.r.[c]
4	AgOTf	MeCN	80 °C	24 h	n.r.[c]
5	AgOTf	DCE	80 °C	24 h	n.r.[c]
6	AgOTf	DMF	120 °C	24 h	10%
7	AgOTf	$MeNO_2$	100 °C	24 h	50%
8	AgOTf	dioxane	100 °C	24 h	58%
9[d]	AgOTf	THF	100 °C	12 h	78%
10[d]	$Cu(OTf)_2$	THF	100 °C	12 h	65%
11[d]	$In(OTf)_3$	THF	100 °C	12 h	60%
12[d]	$Bi(OTf)_3$	THF	100 °C	12 h	55%
13[d]	$Sm(OTf)_3$	THF	100 °C	12 h	37%
14[d]	$Zn(OTf)_2$	THF	100 °C	12 h	45%
15[d]	$FeCl_3$	THF	100 °C	12 h	5%
16[d]	$Ph_3PAuNTf_2$	THF	100 °C	12 h	0
17[d]	PTSA	THF	100 °C	24 h	n.r.[c]
18[d]	AgOTf	THF	100 °C	24 h	68%[e]

[a]Reaction conditions: **1a** (0.45 mmol), **2a** (0.3 mmol), catalyst (0.06 mmol), solvent (3 mL). [b]Isolated yield. [c]n.r. = no reaction. [d]The reaction performed in sealed tube. [e]10 mol% AgOTf was used.

With the optimized conditions in hand, we next shifted our focus to the substrate scope of **2** (Table 2). As shown in Table 2, hydrazones of indole-3-carbonyl derivatives **2** bearing different substituents at the C5 position, such as 5-MeO or 5-BnO, gave the desired products **3ab** and **3ac** in good yields (Table 2, entries 1 and 2). Substrates with either an electron-donating group (R^1 = 6-Me) or an electron-withdrawing group (R^1 = 6-Cl, 6-F, or 6-COOMe) at the C6 position were suitable to afford N-imino-γ-carbolinium ylides **3ad-ag** in satisfactory yields (73-90% yield, Table 2, entries 3-6). Next, the substituents at the nitrogen atom of indole ring were varied. Indole derivatives **2** containing aliphatic groups (R^2 = Me or Et) gave the expected products **3ah** and **3ai** in 82% (Table 2, entry 7) and 83% yield (Table 2, entry 8), respectively, whereas with acetyl group (R^2 = acetyl) only led to the recovery of the starting material **2j** (Table 2, entry 9). This method was also applicable to the hydrazone **2k** (R^3 = Me). The corresponding product **3ak** was obtained in 73% yield (Table 2, entry 10).

Table 2. Exploring the Scope of Various Hydrazones of Indole-3-Carbonyl Derivatives 2.[a]



[a]Reaction conditions: **1a** (0.45 mmol), **2** (0.3 mmol), AgOTf (0.06 mmol), THF (3 mL). [b]Isolated yield. [c]n.r. = no reaction.

The substrate scope was further explored with various propargylic alcohols **1**. Replacing the phenyl ring with substituted phenyl ring or naphthaline ring, the products **3ba-fa** were isolated in

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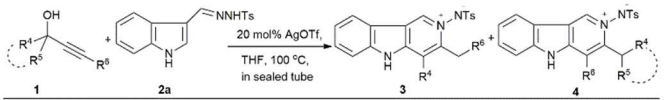
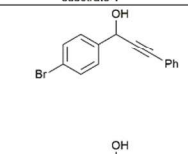
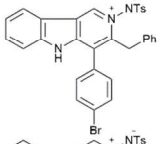
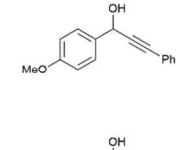
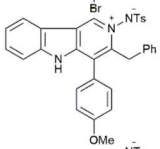
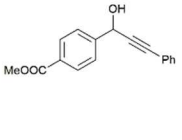
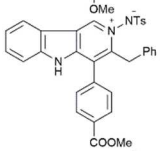
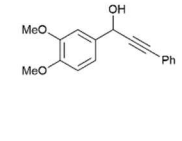
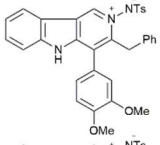
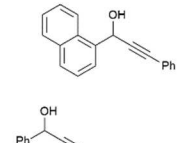
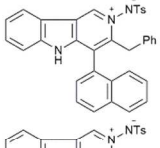
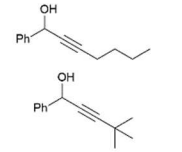
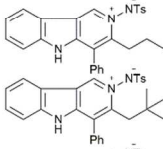
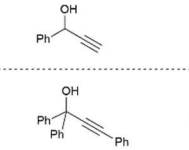
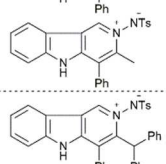
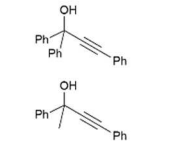
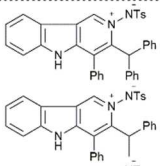
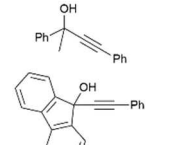
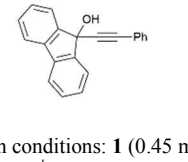
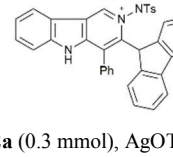
moderate to good yields (Table 3, entry 1-5). Changing the terminal aromatic ring of the alkyne to n-butyl led to a low yield of **3ga** (Table 3, entry 6). When the propargylic alcohol **1h** substituted by t-butyl reacted with **2a**, the N-imino-γ-carbolinium ylide **3ha** was obtained in 75% yield (Table 3, entry 7). However, treatment of the propargylic alcohols **1i** bearing terminal alkyne group with **2a** under the standard conditions led to recovery of a majority of the starting materials (Table 3, entry 8). To further define the generality of this cyclization, attention was turned to the reactions of tertiary propargylic alcohols. Intriguingly, the substitution patterns were opposite to those of secondary propargylic alcohols. On the basis of literature reports, we reasoned these products may be afforded via allenyl cation intermediates. The reactions of **1j** and **1k** proceeded very well affording the desired products **4ja** and **4ka** in 67% and 70% yields, respectively (Table 3, entries 9 and 10). The substrate 1l was also smoothly converted into the product **4la** in 40% yield (Table 3, entry 11). The structure of **3aa** and **3fa** were confirmed by an X-ray diffraction crystal-structure analysis (Figure 1).[14]

Table 3. Exploring the Scope of Propargylic Alcohols **1**.[a]



entry	substrate **1**		product **3** or **4**		yield[b]
1		**1b**		**3ba**	81%
2		**1c**		**3ca**	85%
3		**1d**		**3da**	67%
4		**1e**		**3ea**	88%
5		**1f**		**3fa**	88%
6		**1g**		**3ga**	40%
7		**1h**		**3ha**	75%
8		**1i**		**3ia**	n.r.[c]
9		**1j**		**4ja**	67%
10		**1k**		**4ka**	70%
11		**1l**		**4la**	40%

[a]Reaction conditions: **1** (0.45 mmol), **2a** (0.3 mmol), AgOTf (0.06 mmol), THF (3 mL). [b]Isolated yield. [c]n.r. = no reaction.

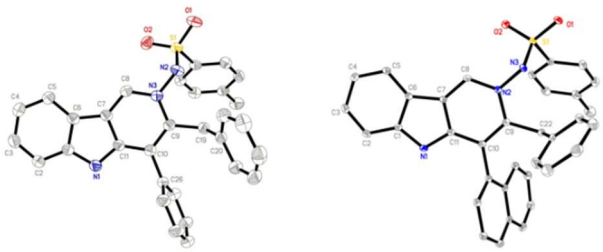
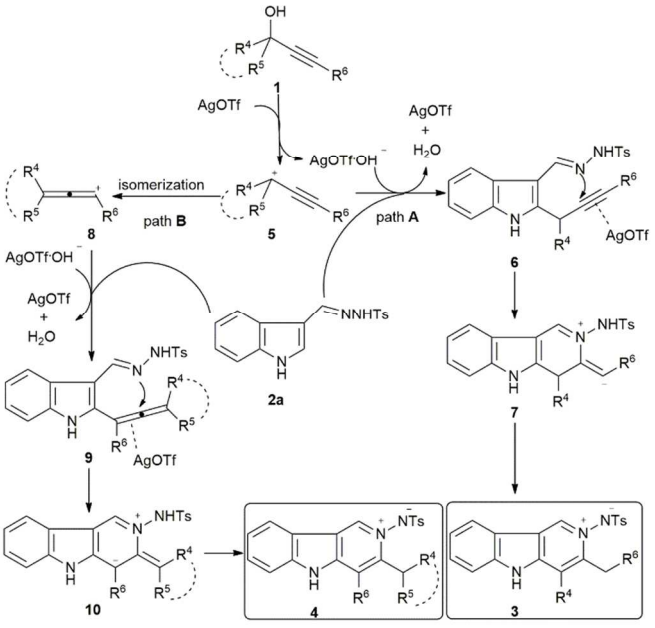


Figure 1. X-Ray crystal structures of **3aa** and **3fa**.

On the basis of the experiments and our previous report, a plausible mechanism is outlined in Scheme 2. The secondary propargylic alcohols **1** (R^4 = aryl; R^5 = H) follow path **A**. In path **A**, the Lewis acid mediated ionization of **1** deliver propargylic cation species **5**, which reacts with **2a** affording a substitution product **6**. Through Ag(I)-mediated π-activation, a 6-exo-dig cyclization occurs



Scheme 2. Possible Reaction Mechanism.

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to generate the intermediate **7**, which then undergoes isomerization to the product **3**. In path **B** (R^4 = aryl; R^5 = aryl or alkyl), the propargylic cation species **5** isomerize to the allenyl cation **8**. The nucleophilic substitution of **2a** with **8** gives a species **9**. The subsequent Ag(I) catalyzed intramolecular 6-endo-trig cyclization of the intermediate **9** gives an intermediate **10**, which easily isomerizes to the N-imino-γ-carbolinium ylide **4**.

Conclusions

In summary, we have reported a simple and efficient procedure for the silver(I)-catalyzed regioselective formation of N-imino-γ-carbolinium ylides using commercially or readily available hydrazones of indole-3-carbonyl derivatives and propargylic alcohols as starting materials. The synthetic method tolerates a broad range of functional groups that allows for the efficient and atom-economical assembly of a variety of N-imino-γ-carbolinium ylides.

Acknowledgements

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14 CCDC 1000558 and 1004332 contains 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.

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