ORGANIC LETTERS

2012
Vol. 14, No. 11
2790–2793

# Silver Triflate and Palladium Acetate Co-catalyzed Reaction of *N*′-(2-Alkynylbenzylidene)hydrazide with *N*-Allyl Ynamide

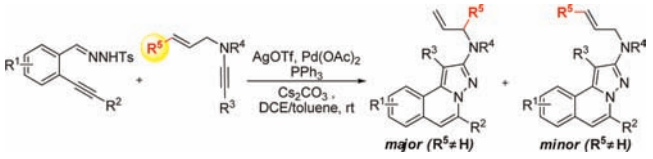
**Ping Huang,[†] Zhiyuan Chen,*[,†] Qin Yang,[‡] and Yiyuan Peng*[,†,‡]**

*Key Laboratory of Functional Small Organic Molecules, Ministry of Education and College of Chemistry & Chemical Engineering, and Jiangxi's Key Laboratory of Green Chemistry and College of Life Science, Jiangxi Normal University, 99 Ziyang Road, Nanchang, Jiangxi 330022, China*

*yiyuanpeng@yahoo.com; zchenjx@yahoo.cn*

**Received April 19, 2012**

## ABSTRACT




**A silver triflate and palladium acetate co-catalyzed reaction of *N*′-(2-alkynylbenzylidene)hydrazide with *N*-allyl ynamide is described, which generates 2-amino-*H*-pyrazolo[5,1-*a*]isoquinolines in good to excellent yield. The transformation proceeds with high efficiency through 6-*endo* cyclization, [3 + 2] cycloaddition, 3,3-sigmatropic rearrangement, and aromatization.**

The isoquinoline skeleton has been widely known as a privileged framework in naturally occurring alkaloids and biologically active molecules.[1] Moreover, as an important member of the family, fused isoquinoline has attracted much attention because of its remarkable biological activities.[2] For example, lamellarin D, containing a highly substituted pyrroloisoquinoline core, is found to be a potent inhibitor of human topoisomerase I[2c] and was recently realized to act on mitochondria to induce apoptosis.[2d] Therefore, there has been considerable interest concerning the synthesis of these compounds.[3,4] Recently, Wu and co-workers have developed a small library of *H*-pyrazolo[5,1-*a*]-isoquinolines via tandem reactions starting from *N*′-(2-alkynylbenzylidene)hydrazide with various nucleophiles.[4] Some hits were discovered with promising inhibitory activities versus targets such as CDC25B, TC-PTP, or PTP1B.[4a]

[†] Key Laboratory of Functional Small Organic Molecules.

[‡] Jiangxi's Key Laboratory of Green Chemistry and College of Life Science.

(1) For selected examples, see: (a) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic: Sydney, 1998; Vol. 1. (b) Trotter, B. W.; Nanda, K. K.; Kett, N. R.; Regan, C. P.; Lynch, J. J.; Stump, G. L.; Kiss, L.; Wang, J.; Spencer, R. H.; Kane, S. A.; White, R. B.; Zhang, R.; Anderson, K. D.; Liverton, N. J.; McIntyre, C. J.; Beshore, D. C.; Hartman, G. D.; Dinsmore, C. J. *J. Med. Chem.* **2006**, *49*, 6954. (c) Ikedou, K. Takeuchi, M. Ogino, Y. Banno, H. Tawada Yamane, T. PCT Int. Appl. WO 2002062764 A1, 2002, 600 pp. (d) Kaneda, T.; Takeuchi, Y.; Matsui, H.; Shimizu, K.; Urakawa, N.; Nakajyo, S. *J. Pharmacol. Sci.* **2005**, *98*, 275. (e) Marchand, C.; Antony, S.; Kohn, K. W.; Cushman, M.; Ioanoviciu, A.; Staker, B. L.; Burgin, A. B.; Stewart, L.; Pommier, Y. *Mol. Cancer Ther.* **2006**, *5*, 287.

(2) (a) Su, S.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744. (b) Bailly, C. *Curr. Med. Chem. Anti-Cancer Agents* **2004**, *4*, 363. (c) Marco, E.; Laine, W.; Tardy, C.; Lansiaux, A.; Iwao, M.; Ishibashi, F.; Bailly, C.; Gago, F. *J. Med. Chem.* **2005**, *48*, 3796. (d) Kluza, J.; Gallego, M.-A.; Loyens, A.; Beauvillain, J. -C.; Fernandez; Sousa-Faro, J.-M.; Cuevas, C.; Marchetti, P.; Bailly, C. *Cancer Res.* **2006**, *66*, 3177.

(3) For selected examples, see: (a) Roy, S.; Roy, S.; Neuenswander, B.; Hill, D.; Larock, R. C. *J. Comb. Chem.* **2009**, *11*, 1061. (b) Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 4462. (c) Yanada, S.; Obika, S.; Kono, H.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3822. (d) Asao, N.; Iso, K.; Yudha, S. S. *Org. Lett.* **2006**, *8*, 4149. (e) Asao, N.; Yudha, S. S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526.

(4) (a) Chen, Z.; Wu, J. *Org. Lett.* **2010**, *12*, 4856. (b) Chen, Z.; Yu, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 6356. (c) Chen, Z.; Pan, X.; Wu, J. *Synlett* **2011**, 964. (d) Li, S.; Wu, J. *Org. Lett.* **2011**, *13*, 712. (e) Ye, S.; Yang, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 5238. (f) Yu, X.; Ye, S.; Wu, J. *Adv. Synth. Catal.* **2010**, *352*, 2050. (g) Yu, X.; Chen, Z.; Yang, X.; Wu, J. *J. Comb. Chem.* **2010**, *12*, 374. (h) Chen, Z.; Yang, X.; Wu, J. *Chem. Commun.* **2009**, 3469. (i) Chen, Z.; Ding, Q.; Yu, X.; Wu, J. *Adv. Synth. Catal.* **2009**, *351*, 1692. (j) Chen, Z.; Su, M.; Yu, X.; Wu, J. *Org. Biomol. Chem.* **2009**, *7*, 4641.

10.1021/ol301023m 
**Published on Web 05/22/2012**

With a goal of finding better lead antitumor compounds by biological evaluations of analogous structures, the development of efficient and novel methods for rapid syntheses of *H*-pyrazolo-[5,1-*a*]isoquinolines is still of urgent importance.

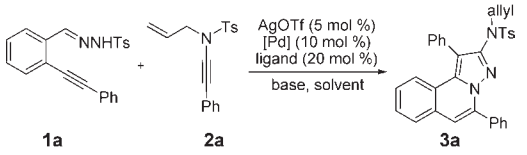
As versatile and useful building blocks, ynamides have been widely applied in synthetic organic chemistry.[5] For example, Witulski[6] and Tanaka[7] independently reported expedient synthesis of functionalized conjugated arenes through a transition-metal catalyzed [2 + 2 + 2] cycloaddition of conjugated ynamides with diynes. Hsung reported a palladium-catalyzed transformation of *N*-allyl-*N*-sulfonyl ynamides to amidines.[8] The reaction was featured as a palladium-catalyzed *N*-to-*C* allyl transfer to form a key intermediate ketenimine via ynamido−palladium−$\pi$-allyl complexes.

Recently, ketenimine chemistry, which involves a copper-(I)-catalyzed azide−alkyne cycloaddition for the generation of various heterocycles, has been an attractive area.[9] We have disclosed two efficient approaches for the rapid access of polysubstituted indoles and 1,2-dihydroisoquinolin-3(4*H*)-imines, based on the ketenimine chemistry.[10] Additionally, the ketenimine species could also be applied in the reaction of *N*′-(2-alkynylbenzylidene)hydrazide.[4d] Prompted by the advancement mentioned above, we conceived that ynamides, which could be regarded as a potential ketenimine species, would be involved in the reaction of *N*′-(2-alkynylbenzylidene)hydrazide to form *H*-pyrazolo[5,1-*a*]isoquinoline derivatives. Herein, we disclose our recent efforts for this transformation.

Since a palladium catalyst is crucial for the generation of the ketenimine intermediate and silver triflate has been demonstrated to be an effective catalyst for the cyclization of *N*′-(2-alkynylbenzylidene)hydrazide,[4] a multicatalytic process is proposed. To identify the practicability of the protocol, initial experiments focused on the reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a** and *N*-allyl-*N*-tosyl ynamide **2a** in the presence of silver triflate (5 mol %) and a palladium catalyst in dichloroethane.

At first, $Pd(PPh_3)_4$ was used as the catalyst and $K_2CO_3$ was employed as the base. To our delight, the desired product **3a** was isolated in 49% yield after 12 h at room temperature under $N_2$ atmosphere (Table 1, entry 1). The structure of **3a** was confirmed by X-ray diffraction analysis

**Table 1.** Optimization of Reaction Conditions




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

| entry | [Pd] | ligand | base | solvent | yield[a] (%) |
|---|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | | $K_2CO_3$ | DCE | 49 |
| 2 | $Pd_2(dba)_3$ | | $Cs_2CO_3$ | DCE | 37 |
| 3 | $Pd(OAc)_2$ | $PPh_3$ | $K_2CO_3$ | DCE | 45 |
| 4 | $Pd(PPh_3)_2Cl_2$ | $PPh_3$ | $K_2CO_3$ | DCE | 46 |
| 5 | $Pd(OAc)_2$ | $PPh_3$ | $K_2CO_3$ | THF | 63 |
| 6 | $Pd(OAc)_2$ | $PPh_3$ | $K_2CO_3$ | THF | 53[b] |
| 7 | $Pd(OAc)_2$ | X-Phos | $K_2CO_3$ | THF | 36 |
| 8 | $Pd(OAc)_2$ | $PCy_3$ | $K_2CO_3$ | THF | trace |
| 9 | $Pd(OAc)_2$ | S-Phos | $K_2CO_3$ | THF | trace |
| 10 | $Pd(OAc)_2$ | $PPh_3$ | $Cs_2CO_3$ | THF | 81 |
| 11 | $Pd(OAc)_2$ | $PPh_3$ | $Na_2CO_3$ | THF | 45 |
| 12 | $Pd(OAc)_2$ | $PPh_3$ | NaOAc | THF | 50 |
| 13 | $Pd(OAc)_2$ | $PPh_3$ | $Et_3N$ | THF | 13 |
| 14 | $Pd(OAc)_2$ | $PPh_3$ | $K_3PO_4$ | THF | 66 |
| 15 | $Pd(OAc)_2$ | $PPh_3$ | $Cs_2CO_3$ | DCE/Toluene | 90 |
| 16 | $Pd(OAc)_2$ | $PPh_3$ | $Cs_2CO_3$ | DCE/1,4-dioxane | 82 |
| 17 | $Pd(OAc)_2$ | $PPh_3$ | $Cs_2CO_3$ | DCE/DCM | 76 |
| 18 | $Pd(OAc)_2$ | $PPh_3$ | $Cs_2CO_3$ | DCE/$CH_3CN$ | 50 |
| 19 | $Pd(OAc)_2$ | $PPh_3$ | $Cs_2CO_3$ | DCE/DMF | 73 |
| 20 | $Pd(OAc)_2$ | $PPh_3$ | $Cs_2CO_3$ | DCE/$CHCl_3$ | 76 |
| 21 | $Pd(OAc)_2$ | $PPh_3$ | $Cs_2CO_3$ | DCE/Toluene | 81[c] |
| 22 | $Pd(OAc)_2$ | $PPh_3$ | $Cs_2CO_3$ | DCE/Toluene | 72[d] |
| 24 | $Pd(OAc)_2$ | $PPh_3$ | $Cs_2CO_3$ | DCE/Toluene | 53[e] |

[a] Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide **1a**. [b] 4 Å MS as additive. [c] $Pd(OAc)_2$ (5 mol %). [d] The reaction was carried out at 60 °C. [e] The reaction was carried out at 90 °C.

(see the Supporting Information). A palladium(II) catalyst, such as $Pd(OAc)_2$ or $Pd(PPh_3)_2Cl_2$, could also be used as the cocatalyst. Considering the catalyst's stability and the ease of controlment, we chose the easily handled $Pd(OAc)_2$ and $PPh_3$ system as a replacement of $Pd(PPh_3)_4$ in the subsequent investigation (Table 1, entries 2−4). The product yield of **3a** could be improved to 63% when the reaction was carried out in THF (Table 1, entry 5).

Interestingly, the ligand effect was found to be crucial for product generation, and $PPh_3$ was proven to be most suitable toward the other phosphine ligands such as X-Phos, $PCy_3$, and S-Phos (Table 1, entries 7−9). The reaction was tested with various bases as well, which showed the best result (81% yield) was generated in $Cs_2CO_3$ (Table 1, entry 10). Other inorganic bases, including $Na_2CO_3$, NaOAc, $K_3PO_4$, and $K_2CO_3$, were proven to be reactive while the organic base was inefficient (Table 1, entries 10−14). The reaction was explored in various solvents as well. Good result was obtained when DCE/toluene was used as the reaction medium, the desired product **3a** could be isolated in 90% yield, while no obvious improvement was achieved in other solvents (Table 1, entries 15−20). Further screening revealed that attempts to reduce the amount of palladium

(5) For reviews on ynamides, see: (a) Zificsak, C.; Mulder, J.; Hsung, R.; Rameshkumar, C.; Wei, L. *Tetrahedron* **2001**, *57*, 7575. (b) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455. (c) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. (d) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (e) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064.

(6) (a) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2426. (b) Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281.

(7) (a) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586. (b) Tanaka, K.; Takeishi, K. *Synthesis* **2007**, 2920.

(8) (a) Zhang, Y.; DeKorver, K. A.; Lohse, A. G.; Zhang, Y. S.; Huang, J.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 899. (b) DeKorver, K. A.; Hsung, R. P.; Lohse, A. G.; Zhang, Y. *Org. Lett.* **2010**, *12*, 1840.

(9) For reviews on ketenimines, see: (a) Kim, S. H; Park, S. H.; Choi, J. H.; Chang, S. *Chem. Asian J.* **2011**, *6*, 2618. (b) Lu, P.; Wang, Y. G. *Synlett*. **2010**, 165. (c) Yoo, E. J.; Chang, S. *Curr. Org. Chem.* **2009**, *13*, 1766.

(10) (a) Chen, Z.; Zheng, D.; Wu, J. *Org. Lett.* **2011**, *13*, 848. (b) Chen, Z.; Ye, C.; Gao, L.; Wu, J. *Chem. Commun.* **2011**, *47*, 5623.

catalyst loading or increasing the reaction temperature were ineffective and led to a lower yield (Table 1, entries 21−24).

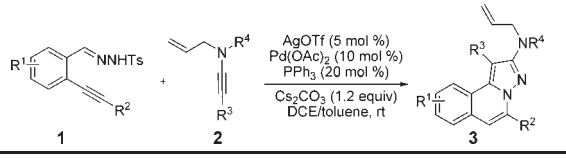
With the optimized conditions in hand, we next investigated the reaction scope with various *N*′-(2-alkynylbenzylidene)hydrazides **1** and *N*-allyl-*N*-sulfonyl ynamides **2**, and the results are summarized in Table 2. To assess the impact of the structural and functional motifs on the reaction of *N*-allyl-*N*-tosylsulfonyl ynamide **2a**, we tested a range of *N*′-(2-alkynylbenzylidene)hydrazide **1**. For all cases, compounds **1** reacted with ynamide **2a** leading to the corresponding 2-amino-*H*-pyrazolo[5,1-*a*]isoquinolines **3** in moderate to excellent yields. Moreover, it was found that substrates with electron-donating groups on the $R^1$ position were less reactive to some extent than those with the electron-withdrawing groups when the $R^2$ group was phenyl. For example, reaction of 5-methyl- or 4,5-dimethoxy-substituted *N*′-(2-phenylbenzylidene)hydrazide with compound **2a** gave rise to the desired product **3** in 66% or 63% yield, respectively (Table 2, entries 2 and 3). While for the 5-Cl- or 4-F-substituted substrate **1d** or **1e** the corresponding yield was 80% or 85%, respectively (Table 2, entries 4 and 5). It is noteworthy that the heterocyclic substrate **1f** could also be well tolerated in the reaction, leading to the desired product **3f** in 85% yield (Table 2, entry 6).

However, when the $R^2$ group attached on the triple bond was an alkyl group, the corresproding product could be isolated only in moderate yield. This might be due to the lower stability of the substrates under the reaction conditions (Table 2, entries 7−10). We next examined the reactivity of *N*-allyl-*N*-sulfonyl ynamide **2** with substituents on the triple bond moiety. As expected, the corresponding products were obtained in good yields whenever the *N*-allyl-*N*-sulfonyl ynamides **2** were attached with an electron-donating or electron-withdrawn group (Table 2, entries 10−20). Interestingly, the terminal alkyne **2e** could also be reactive under the standard reaction conditions, leading to the corresponding product **3q** in an acceptable yield (Table 2, entry 20). A good yield (74%) was obtained when *N*-allyl-*N*-4-bromobenzenesulfonyl ynamide **2f** was employed in the transformation (Table 2, entry 21).

Next, we devoted our efforts to the reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1** with *N*-3′-methyl allyl ynamide **2** under the standard reaction conditions (Table 3). Good results were obtained as well, and two isomers ranging from a ratio of 5:3 to 3:1 were isolated. For example, the reaction proceeded smoothly when *N*-3′-methyl allyl-*N*-tosyl ynamide **2g**, **2c**, or **2d** was used in the reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a**, giving rising to a total yield of 82%, 85%, or 80%, respectively, while for the reaction of *N*′-(2-alkynylbenzylidene) hydrazide **1e** with *N*-3′-methyl allyl-*N*-tosyl ynamide **2g** the corresponding product yield was 88%, with a molecular ration of 2:1. The structure of the two isomers **4** and **4′** were confirmed by X-ray diffraction analysis as well (also see the Supporting Information).

Surprisingly, for the reaction of *N*-methyl-*N*-tosyl ynamide **2j** or *N*-benzyl-*N*-tosyl ynamide **2k** with compound **1a**, no reaction was detected under the standard reaction conditions (Scheme 1). Prolonging the reaction time or elevating the temperature only resulted in decomposion of the starting materials. These results strongly indicated the crucial importance of the allyl group in the starting ynamide.

**Table 2.** Generation of 2-Amino-*H*-pyrazolo[5,1-*a*]-isoquinolines **3** via Silver Triflate and Palladium Acetate Co-catalyzed Reaction of *N*′-(2-Alkynylbenzylidene)hydrazide **1** with *N*-Allyl Ynamide **2**

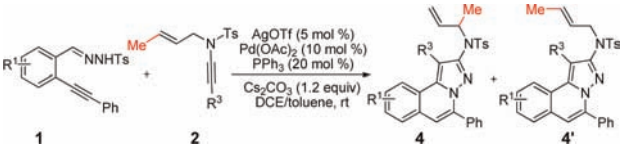



1 2 3

| entry | $R^1$, $R^2$ (**1**) | $R^3$, $R^4$ (**2**) | yield[a] (%) |
|---|---|---|---|
| 1 | H, Ph (**1a**) | Ph, Ts (**2a**) | 90 (**3a**) |
| 2 | 5-Me, Ph (**1b**) | (**2a**) | 66 (**3b**) |
| 3 | 4,5-dimethoxy, Ph (**1c**) | (**2a**) | 63 (**3c**) |
| 4 | 5-Cl, Ph (**1d**) | (**2a**) | 80 (**3d**) |
| 5 | 4-F, Ph (**1e**) | (**2a**) | 88 (**3e**) |
| 6 | 4,5-benzothio, Ph(**1f**) | (**2a**) | 85 (**3f**) |
| 7 | H, Bu (**1g**) | (**2a**) | 51 (**3g**) |
| 8 | 5-Me, Bu (**1h**) | (**2a**) | 40 (**3h**) |
| 9 | 4-F, Bu (**1i**) | (**2a**) | 64 (**3i**) |
| 10 | 4-F, cyclopropyl (**1j**) | (**2a**) | 46 (**3j**) |
| 11 | (**1a**) | Bu, Ts (**2b**) | 84 (**3k**) |
| 12 | (**1a**) | PMP, Ts (**2c**) | 85 (**3l**) |
| 13 | (**1a**) | 4-Cl-Ph, Ts(**2d**) | 88 (**3m**) |
| 14 | (**1b**) | (**2b**) | 74 (**3n**) |
| 15 | (**1b**) | (**2c**) | 68 (**3o**) |
| 16 | (**1b**) | (**2d**) | 71 (**3p**) |
| 17 | (**1e**) | (**2b**) | 85 (**3q**) |
| 18 | (**1e**) | (**2c**) | 87 (**3r**) |
| 19 | (**1e**) | (**2d**) | 92 (**3s**) |
| 20 | (**1e**) | H, Ts (**2e**) | 61 (**3t**) |
| 21 | (**1a**) | 4-Cl-Ph, 4-Br-PhSO$_2$(**2f**) | 74 (**3u**) |

[a] Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide **1**. PMP = 4-MeO-Ph.

**Table 3.** Generation of 2-Amino-*H*-pyrazolo[5,1-*a*]-isoquinolines **4** via Silver Triflate and Palladium Acetate Co-catalyzed Reaction of *N*′-(2-Alkynylbenzylidene) Hydrazide **1** with *N*-Substituted Allyl Ynamide **2**

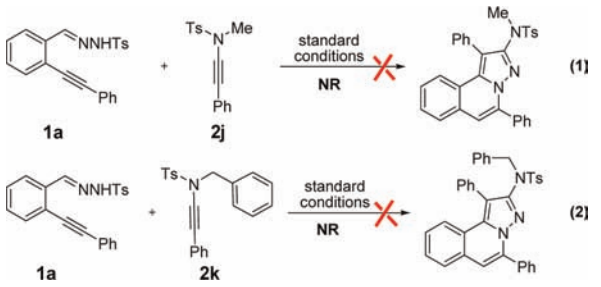



1 2 4 4'

| entry | $R^1$ (**1**) | $R^3$ (**2**) | yield of **4** (%)[a] | ratio (**4**/**4′**)[a] |
|---|---|---|---|---|
| 1 | H (**1a**) | Ph (**2g**) | 82 (**4a** + **4a′**) | 2:1 |
| 2 | (**1a**) | PMP (**2c**) | 85 (**4b** + **4b′**) | 5:3 |
| 3 | (**1a**) | 4-Cl-Ph (**2d**) | 80 (**4c** + **4c′**) | 3:1 |
| 4 | 4-F, Ph (**1e**) | Ph (**2g**) | 88 (**4d** + **4d′**) | 2:1 |

[a] Isolated yield based on *N*′-(2-alkynylbenzylidene) hydrazide **1**. PMP = 4-MeO-Ph.

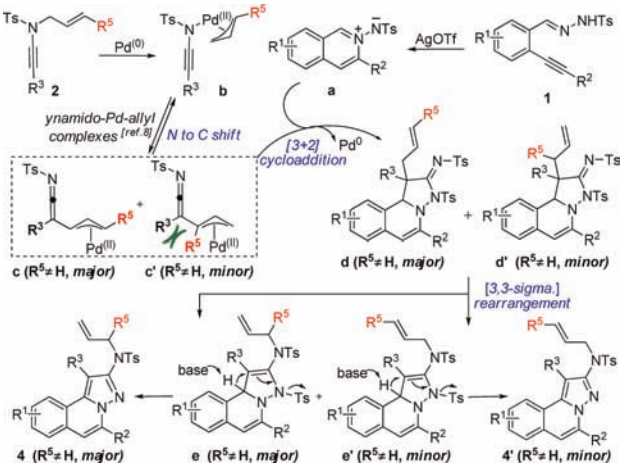
**Scheme 1.** Mechanistic Investigation for the Silver(I) and Palladium(II) Co-catalyzed Reaction of *N*′-(2-Alkynylbenzylidene) hydrazide **1** with Ynamide **2**




On the basis of the above observation, and prompted by the advancement of the ynamide chemistry,[5,8] we proposed a plausible mechanism for this cascade cyclization (Scheme 2). We envisioned that in the presence of a Pd(0) catalyst, the reactive ketenimine **c** would be derived from *N*-allyl-*N*-tosyl ynamide **2** via a ynamido-Pd-$\pi$-allyl complex **b** and the subsequent allyl migration from N to C atom. Meanwhile, isoquinolinium-2-yl amide **a** would be formed via silver-catalyzed 6-*endo*-cyclization of *N*′-(2-alkynylbenzylidene)hydrazide **1**.[4] The intermolecular [3 + 2] cyclization reaction would occur to generate the key intermediate **d**. Subsequently, an intramolecular [3,3]-sigmatropic rearrangement would be involved in the reaction to produce the intermediate **e**, which would then undergo the release of tosyl group and subsequent aromatization to furnish the 2-amino-*H*-pyrazolo[5,1-*a*]isoquinoline **3** or **4**. It is noticeable that for the alkyl substituted allyl ynamide ($R^5$ = Me), the chemoselective of the two isomers **c** and **c**′ could be easily formed due to the substitutent hindrance in the reactive ketenimine complex during the process of the allyl migration from N to C atom. The key intermediate **c**, in which had less substitutent hindrance between $R^3$ and $R^5$ groups, would be formed in a major portion as compared with another intermediate **c**′.

In conclusion, we have developed an efficient reaction of *N*′-(2-alkynylbenzylidene)hydrazide with *N*-allyl ynamide

**Scheme 2.** Plausible Mechanism for the Reaction of *N*′-(2-Alkynylbenzylidene)hydrazide **1** with *N*-Allyl Ynamide **2**




co-catalyzed by silver triflate and palladium acetate, affording 2-amino-*H*-pyrazolo[5,1-*a*]isoquinolines in good yields. The transformation proceeds with high efficiency through 6-*endo* cyclization, [3 + 2] cycloaddition, 3,3-sigmatropic rearrangement, and aromatization. Additionally, the reaction condition is mild, which is attractive for further library construction.

**Acknowledgment.** Financial support from National Natural Science Foudation of China (No. 20962010 and 21162012), Jiangxi Educational Committee (GJJ10386), and Foundation for Young People (Yang Qin) of Jiangxi Normal University is gratefully acknowledged. Z.C. acknowledges financial support from the Jiangxi Provincial Education Department (GJJ12192).

**Supporting Information Available.** Experimental procedure, characterization data, $^1$H and $^{13}$C NMR spectra of compounds **3** and **4**, X-ray data for compounds **3a**, **4a**′, and **4c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.