Organic LETTERS

Letter

pubs.acs.org/OrgLett

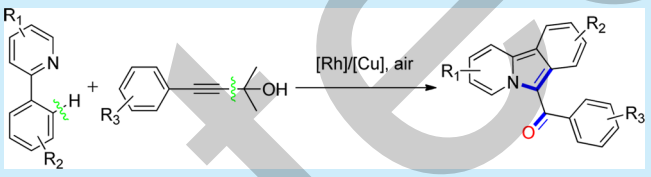
Facile Synthesis of 6-Acylated Pyrido[2,1-*a*]isoindoles from 2-Arylpyridines and γ-Substituted *tert*-Propargyl Alcohols via Rhodium-Catalyzed C−H Bond Activation and β-Carbon Elimination

Zhen Wang* and Ting Li

Department of Chemistry, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China

Supporting Information

ABSTRACT: A step- and atom-economic protocol for the synthesis of 6-acylated pyrido[2,1-*a*]isoindoles from 2-arylpyridines and γ-substituted *tert*-propargyl alcohols has been developed.

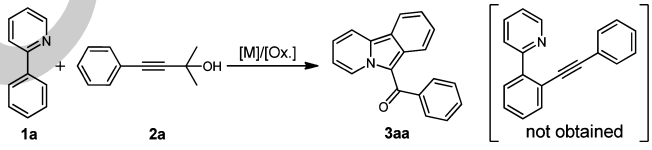


Alkynes are a recurring functional group in numerous natural products, bioactive compounds, and organic materials.[1] Transition-metal-mediated cross-coupling reactions play a prominent role among the methods for the incorporation of alkynyl functionality into organic molecules.[2] For $C_{SP}-C_{SP}$ coupling, one of the most valuable transformations in this context is the Glaser coupling[3] and related reaction involving terminal alkynes,[4] alkynyltrifluoroborates,[5] or alkynyltellurides,[6] etc. For $C_{SP}-C_{SP^2}$ coupling, arguably the most widely used methods are Sonogashira[7] and related alkynylation reactions[8] involving terminal alkynes reacting with aryl or vinyl halides. For $C_{SP}-C_{SP^3}$ coupling, a significant contribution in this field was made by Lei's group, as they succeeded in the palladium-catalyzed oxidative cross-coupling of alkylzinc halides with alkynylstannanes[9] or even terminal alkynes.[10] From a step- and atom-economic point of view, direct C−H alkynylation of polyfluoroarenes,[11] phenols,[12] anilines,[13] electron-rich arenes,[14] and heterocycles[15] was achieved by using the alkynyl source derived from terminal alkynes in recent years. Despite such progress, the direct catalytic *o*-phenyl C−H alkynylation of 2-arlypyridines remains a great challenge, although the introduction of various fuctional groups has emerged.[16]

On the other hand, the alkynyl coupling partner plays an important role for the direct *o*-phenyl C−H alkynylation of 2-arylpyridines. Because of polymerization under high temperature and insertion to the cyclcometaled C−M bond to afford the alkenyl products,[17] terminal alkynes could rarely be employed in this transformation. In 2005, Miura[18] reported a $[Rh(OH)(COD)]_2$ (COD: 1,5-cyclooctadiene) catalyzed regio- and stereoselective homocoupling of γ-arylated *tert*-propargyl alcohols via β-carbon elimination with liberation of a ketone. In such a coupling, an alkynylmetal intermediate generated in situ by selective cleavage of one of the three C−C bonds of the *tert*-propargyl alcohols, which offers possibility of utilizing *tert*-propargyl alcohols as alkyne-coupling partner. With our ongoing efforts on *o*-phenyl C−H functionalizations of 2-arlypyridines, we envision that under transition-metal catalysis, *tert*-propargyl alcohols might also be available for direct *o*-phenyl C−H alkynylation of 2-arylpyridines.

To test the viability of our hypothesis, 2-phenylpyridine **1a** and 2-methyl-4-phenyl-3-butyn-2-ol **2a** were chosen as model substrates. No desired alkynyl product was obtained after a series of transition-metal catalysts were screened (entries 1−4, Table 1). To our surprise, when $[Cp^*RhCl_2]_2$ (Cp*: pentamethylcyclopentadienyl) and excess $Cu(OAc)_2·H_2O$ (2.5 equiv) were employed as the catalytic system, **3aa** was isolated in 43% yield along with a small amount of 1,4-diphenylbuta-1,3-diyne (8%) instead of alkynyl product (entry 5, Table 1). To our knowledge, only a few examples for the construction of 6-acylated pyrido[2,1-*a*]isoindoles,[19] a recurring

Table 1. Screening of Reaction Conditions[a]



1a 2a 3aa

entry	[M]	solvent	yield (%)
1	$Pd(OAc)_2$	toluene	0
2	$[IrCl(COD)]_2$	toluene	0
3	$[Ru(p\text{-cymene})Cl_2]_2$	toluene	0
4	$[Os(p\text{-cymene})Cl_2]_2$	toluene	0
5	$[Cp^*RhCl_2]_2$	toluene	43[b]
6	$[RhCl(COD)]_2$	toluene	61
7	$[RhCl(COD)]_2$	toluene/*t*-AmOH(4:1)	72

[a]Conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), [M] (2.5 mol %), [Ox.]: $Cu(OAc)_2·H_2O$ (2.5 mmol) and solvent (10 mL) under air at 130 °C (bath temperature) for 24 h, *t*-AmOH: *tert*-amyl alcohol, yield of isolated products based on **1a**. [b]1,4-Diphenylbuta-1,3-diyne was also isolated as a minor byproduct.

Received: October 29, 2014
Published: December 5, 2014

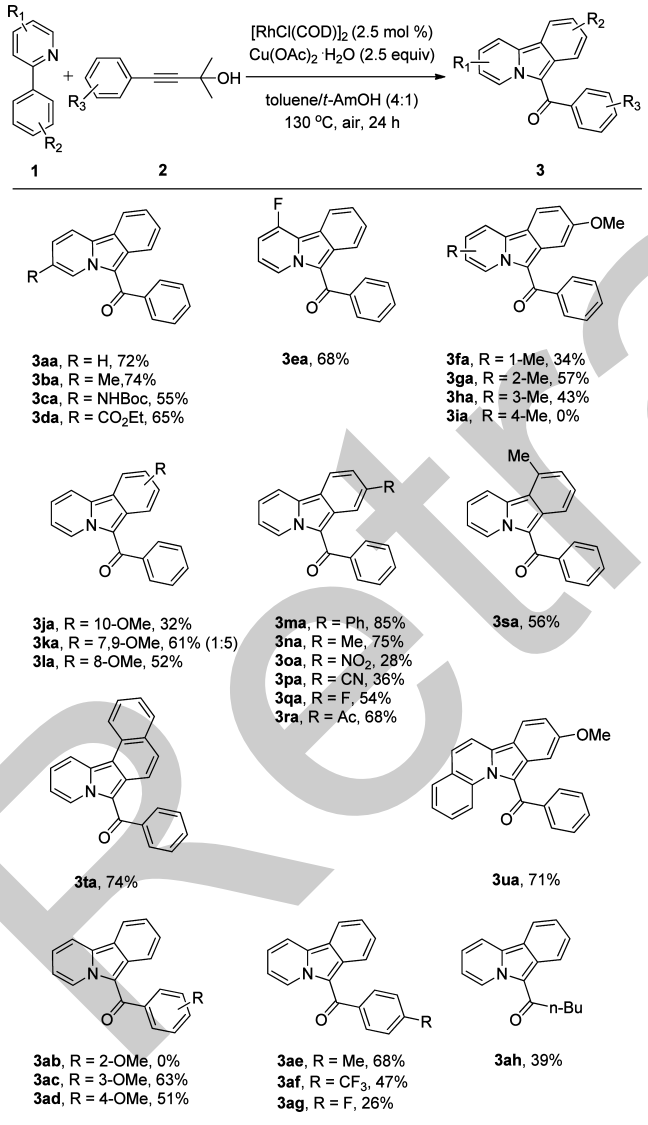
dx.doi.org/10.1021/ol503157k | *Org. Lett.* 2014, 16, 6366−6369

structural motif found in many pharmaceuticals[20] and functional materials,[21] have been reported up to now. Further studies showed that $[RhCl(COD)]_2/Cu(OAc)_2{\cdot}H_2O$ might be promising system for the transformation (entry 6, Table 1). In order to increase the solubility of $Cu(OAc)_2{\cdot}H_2O$, *t*-AmOH was added to the reaction mixture, and the satisfactory conditions came to light, that is, the reaction should be promoted by $[RhCl(COD)]_2/Cu(OAc)_2{\cdot}H_2O$ system in the mixed solvent of toluene/*t*-AmOH(4:1) at 130 °C under air (entry 7, Table 1).

With the optimized conditions in hand, a number of 2-arylpyridines as well as γ-substituted *tert*-propargyl alcohols were explored to examine the scope of this method (Scheme 1). First, with regard to the reaction of **1** and **2a**, 2-arlypyridines with various substitution patterns such as Me, NHBoc, and CO_2Et at the C-4 position of the pyridine ring all gave the expected products in moderate to good yields (**3ba**−**da**); notably, 3-fluoro-2-phenylpyridine also worked comparatively well (**3ea**). When the phenyl ring was fixed with OMe at the para position, substrates with Me at the C-3, C-4, or C-5 positions of the pyridine ring afforded the corresponding products in moderate yields (**3fa**−**ha**); however, when it came to the C-6 position, **3ia** was not obtained due to steric hindrance. 2-Arylpyridines with OMe at the ortho- and para-positions of the phenyl ring proceeded well together with regiomeric mixture of products at meta-position (**3ja**−**la**), then substrates bearing electron-donating substituents such as OMe and Ph and electron-withdrawing groups including CN, NO_2, F, and Ac at the para position of the phenyl ring were studied, and acceptable yields were achieved, respectively (**3la**, **3ma**−**ra**); 2-(*o*-tolyl)pyridine, 2-(naphthalen-1-yl)pyridine, and 2-(4-methoxyphenyl)quinoline were fairly effective (**3sa**−**ua**). Second, as for the reaction of 2-phenylpyridine **1a** and γ-substituted *tert*-propargyl alcohols, several γ-substituted *tert*-propargyl alcohols were investigated under the standard conditions, γ-arylated *tert*-propargyl alcohols with OMe at meta- and para-position of the phenyl ring were tolerated except for ortho-position owing to steric hindrance (**3ab**−**ad**), and substrates bearing Me, OMe, CF_3, and F at the para-position of the phenyl ring afforded the corresponding benzoylpyrido[2,1-*a*]isoindoles in reasonable yields (**3ad**−**ag**). What's more, 2-methyloct-3-yn-2-ol underwent this transformation smoothly (**3ah**). Finally, the structure of all the obtained products was unambiguously confirmed by single-crystal X-ray diffraction analysis of compound **3ma** (see the Supporting Information).

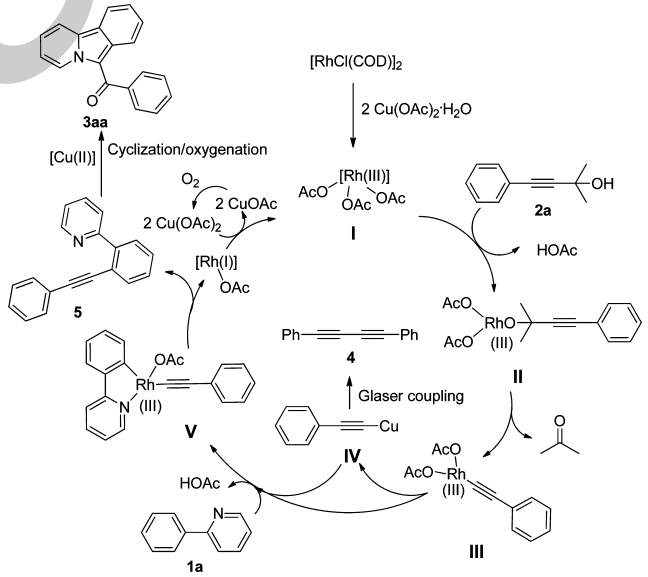
A plausible mechanism for this fascinating process is depicted in Scheme 2. Take the reaction of **1a** and **2a** ,for example.

Scheme 1. Substrate Scope[a]



[a]Conditions: **1** (1.0 mmol), **2** (1.5 mmol), $[RhCl(COD)]_2$ (2.5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (2.5 mmol) in toluene/*t*-AmOH (4:1, 10 mL) under air at 130 °C (bath temperature) for 24 h, yield of isolated products based on **1**.

Scheme 2. Proposed Mechanism

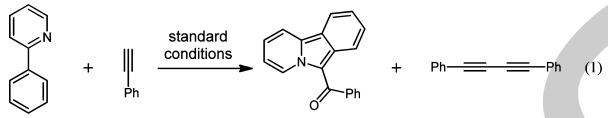


Initially, oxidiation of $[RhCl(COD)]_2$ by $Cu(OAc)_2{\cdot}H_2O$ occurs, generating the $[Rh(III)](OAc)_3$ precursor **I**.[22] Then, with the help of elimination of HOAc, the hydroxy group of *tert*-propargyl alcohol coordinates to the active species **I** to afford rhodium alcoholate **II**, which could easily undergo selective cleavage of one of the three C−C bonds with liberation of acetone to form an alkynylrhodium **III**. Transmetalation of the alkynl group from Rh to Cu generated the alkynylcopper **IV**, which could undergo Glaser coupling[2b] to

dx.doi.org/10.1021/ol503157k | Org. Lett. 2014, 16, 6366−6369

afford conjugate diyne **4** as a byproduct. The next step could involve electrophilic deprotonation of the *o*-phenyl C−H bond of **1a** with the help of elimination of HOAc and transmetalation of the alkynl group from Cu to Rh to form an intermediate **V**. Then, reductive elimination of **V** would afford an alkyne **5** and extrude [Rh(I)]OAc, which could be reoxidized by Cu(II) to the catalytically active species **I** to complete the catalytic cycle. Cu(II) might also regenerate from Cu(I) with O_2 in the air. The resulting alkyne **5** could undergo a radical annulation and oxygenation mediated by excess Cu(II) in the reaction system to yield the final product **3aa**. Recently, Zhu[23] described a new copper-catalyzed intramolecular dehydrogenative aminooxygenation of *N*-allyl-2-aminopyridines to imidazo[1,2-*a*]pyridine-3-carbaldehydes. Moreover, Chiba[24] demonstrated a copper-catalyzed aerobic intramolecular carbo- and amino-oxygenation of alkynes for the synthesis of azaheterocycles. In their process, peroxy-Cu(III) intermediate generated by single-electron transfer from Cu to O_2 makes a crucial rule. Although the detailed mechanism is not clear so far, we reason that annulation and oxygenation of alkyne **5** might also involve the similar pathway.

To gain insight into the above-mentioned mechanism, the reaction of **1a** with acetylene were performed under the standard conditions (eq 1). We found that **3aa** was obtained in 35% yield along with 38% of **1a** recovered. Of note, 1,4-diphenylbuta-1,3-diyne **4** was afforded in a relatively higher yield (24%).



1a, 38% recovered **3aa**, 35% **4**, 24%

In summary, we have developed a novel, highly efficient rhodium-catalyzed cascade protocol to afford 6-acylated pyrido[2,1-*a*]isoindoles from 2-arylpyridines and γ-substituted *tert*-propargyl alcohols. These reactions proceed in satisfactory to excellent yields with high regioselectivities. Further investigation on detailed mechanism and synthetic applications is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectral data for all products, and X-ray data in CIF of **3ma** (CCDC 927520). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: 896698921@qq.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Program for New Century Excellent Talents in University of China (NCET-08-0472).

■ REFERENCES

(1) *Acetylene Chemistry: Chemistry, Biology, and Material Science*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, 2005.

(2) For selected reviews on transition-metal-mediated alkynyl coupling, see: (a) Shi, W.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2011**, *40*, 2761. (b) Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165.

(3) For intial reports on Glaser coupling, see: (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422. (b) Glaser, C. *Ann. Chem. Pharm.* **1870**, *2*, 137.

(4) Yin, W.; He, C.; Chen, M.; Zhang, H.; Lei, A. *Org. Lett.* **2009**, *11*, 709.

(5) Paixão, M. W.; Weber, M.; Braga, A. L.; de Azeredo, J. B.; Deobald, A. M.; Stefani, H. A. *Tetrahedron Lett.* **2008**, *49*, 2366.

(6) Singh, F. V.; Amaral, M. F. Z. J.; Stefani, H. A. *Tetrahedron Lett.* **2009**, *50*, 2636.

(7) For recent review on Sonogashira coupling, see: (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874. (b) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084.

(8) For selected review of related alkynylation catalyzed by palladium, see: (a) Negishi, E.-i.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (b) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (c) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780.

(9) Zhao, Y.; Wang, H.; Hou, X.; Hu, Y.; Lei, A.; Zhang, H.; Zhu, L. *J. Am. Chem. Soc.* **2006**, *128*, 15048.

(10) Chen, M.; Zheng, X.; Li, W.; He, J.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 4101.

(11) Wei, Y.; Zhao, H.; Kan, J.; Su, W.; Hong, M. *J. Am. Chem. Soc.* **2010**, *132*, 2522.

(12) Kobayashi, K.; Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2002**, *124*, 8528.

(13) Amemiya, R.; Fujii, A.; Yamaguchi, M. *Tetrahedron Lett.* **2004**, *45*, 4333.

(14) Haro, T. d.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 1512.

(15) For selected examples for direct C−H alkynylation of heterocycles, see: (a) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742. (b) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250. (c) Brand, J. P.; Charpentier, J.; Waser, J. R. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346. (d) Besselièvre, F.; Piguel, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9553. (e) Jie, X.; Shang, Y.; Hu, P.; Su, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 3630.

(16) For selected examples for C−H functionalization of 2-arlypyridines, see: (a) Li, B.; Wu, Z.-H.; Gu, Y.-F.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1109. (b) Li, Y.; Li, B.-J.; Wang, W.-H.; Huang, W.-P.; Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2115. (c) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 1248. (d) Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7094. (e) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (f) Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249. (g) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523. (h) Kitahara, M.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2011**, *133*, 2160. (i) Shuai, Q.; Yang, L.; Guo, X.; Baslé, O.; Li, C.-J. *J. Am. Chem. Soc.* **2010**, *132*, 12212. (j) Kim, J.; Chang, S. *J. Am. Chem. Soc.* **2010**, *132*, 10272. (k) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518. (l) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (m) Chatani, N.; Tobisu, M.; Ano, Y. *Synlett* **2012**, *23*, 2763. For a recent example of Cu(II)-mediated ortho C−H alkynylation of (hetero)arenes with terminal alkynes, see: (n) Shang, M.; Wang, H.-L.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 11590.

(17) (a) Zhou, B.; Chen, H.; Wang, C. *J. Am. Chem. Soc.* **2013**, *135*, 1264. (b) Cheng, K.; Yao, B.; Zhao, J.; Zhang, Y. *Org. Lett.* **2008**, *10*, 5309.

(18) Funayama, A.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2005**, *127*, 15354.

(19) For examples on the synthesis of pyrido[2,1-*a*]isoindole, see: (a) Zhang, Y.; Xie, C.; Xu, P. *Synlett* **2008**, 3115. (b) Huang, X.; Zhang, T. *Tetrahedron Lett.* **2009**, *50*, 208. (c) Liu, S.; Hu, X.; Li, X.; Cheng, J. *Synlett* **2013**, *24*, 847.

(20) Diana, P.; Martorana, A.; Barraja, P.; Montalbano, A.; Dattolo, G.; Cirrincione, G.; Dall'Acqua, F.; Salvador, A.; Vedaldi, D.; Basso, G.; Viola, G. *J. Med. Chem.* **2008**, *51*, 2387.
(21) Mitsumori, T.; Bendikov, M.; Dautel, O.; Wudl, F.; Shioya, T.; Sato, H.; Sato, Y. *J. Am. Chem. Soc.* **2004**, *126*, 16793.
(22) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326.
(23) Wang, H.; Wang, Y.; Liang, D.; Liu, L.; Zhang, J.; Zhu, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 5678.
(24) Toh, K. K.; Sanjaya, S.; Sahnoun, S.; Chong, S. Y.; Chiba, S. *Org. Lett.* **2012**, *14*, 2290.

dx.doi.org/10.1021/ol503157k | *Org. Lett.* 2014, 16, 6366−6369