Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Direct Synthesis of 3-Acylindoles through Rhodium(III)-Catalyzed Annulation of *N*-Phenylamidines with α-Cl Ketones

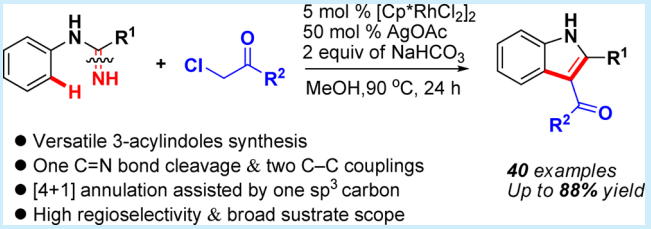
Jianhui Zhou,[†] Jian Li,[‡] Yazhou Li,[‡] Chenglin Wu,[‡] Guoxue He,[‡] Qiaolan Yang,[‡] Yu Zhou,*[,‡] and Hong Liu*[,‡]

[†]School of Pharmacy, Nanchang University, 461 Bayi Road, Nanchang 330006, China

[‡]State Key Laboratory of Drug Research and Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai 201203, China

Supporting Information

ABSTRACT: In the present study, a novel synthetic strategy to directly produce versatile 3-acylindoles through Rh(III)-catalyzed C−H activation and annulation cascade of *N*-phenylamidines with α-Cl ketones was developed, in which α-Cl ketones serve as unusual one-carbon (sp^3) synthons. This strategy features high regioselectivity, efficiency, wide substrate tolerance, and mild reaction conditions, which further underscore its synthetic utility in drug molecule synthesis.



Substituted indoles represent a class of privileged structures capable of binding to multiple receptors with high affinity in medicinal chemistry.[1] In particular, 3-acylindoles are frequently reported as important lead compounds with diverse pharmacological effects, such as anti-inflammatory, analgesic, immunomodulatory, antiemetic, antivirus, anticancer, and hypocholesterolemic activities (Figure 1).[2] However, their traditional synthetic approaches mostly originated from Friedel−Crafts-type reactions mediated by certain Lewis acids,[3] which generally suffered from harsh reaction conditions and multistep synthetic operations. Therefore, it is desirable to develop more convenient and efficient methods to directly access 3-acylindoles.

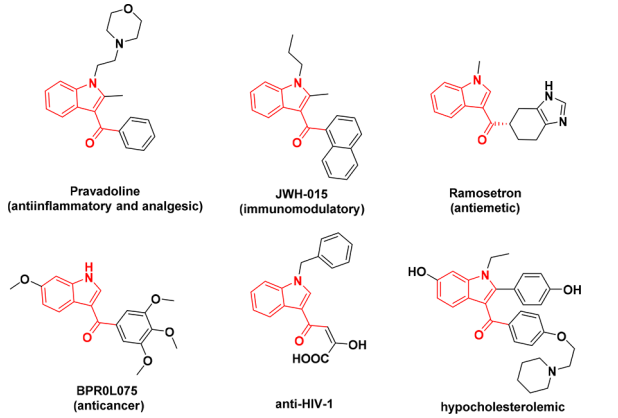
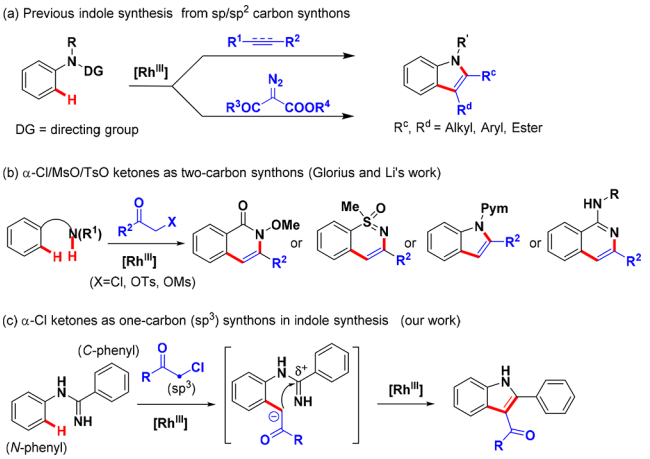


Figure 1. Selected examples of bioactive 3-acylindoles.

Recently, the transition-metal rhodium(III)-catalyzed C−H activation/annulation cascade has played a prominent role in the construction of indole scaffolds with alkyl, aryl, and ester substituents.[4−6] Among them, alkynes,[4] alkenes,[5] and diazo[6] compounds were usually used as the key synthons (Scheme 1a), in which sp- or sp^2-carbons were critical for these annulation reactions. However, sp^3-carbon synthons have been rarely reported in the construction of indole derivatives. In 2014, Glorius' group[7] reported a pioneering Rh(III)-catalyzed annulation to generate diverse *N*-heterocycles using C(sp^3)-based electrophiles α-Cl/MsO/TsO substituted ketones as

Scheme 1. Indoles and Other *N*-Heterocycles Synthesis *via* Rh(III)-Catalyzed C−H Activation/Annulation



Received: October 23, 2018

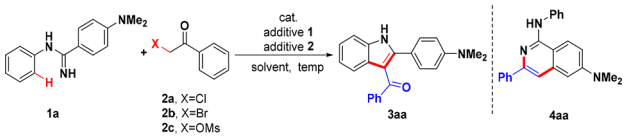
DOI: 10.1021/acs.orglett.8b03383
Org. Lett. XXXX, XXX, XXX−XXX

oxidized alkyne equivalents (Scheme 1b). Thereafter, Li and co-workers[8] reported a similar synthetic strategy for isoquinolines via Rh(III)-catalyzed C−H/N−H functionalization with α-Cl/MsO/TsO ketones. However, these α-halo or pseudo-haloketones only functioned as two-carbon reaction partners to construct these privileged scaffolds.[7−9] Unexpectedly, our recent study demonstrated that the easily accessible α-halogenated ketones[10] could be used as one-carbon reaction partners for direct construction of 3-acylindoles via rhodium-(III)-catalyzed annulation of *N*-phenylamidines with α-Cl substituted ketones. This transformation represents a highly effective synthetic strategy to prepare 3-acylindoles with mild reaction conditions and wide substrate tolerance; in particular, the C−H activation and subsequent annulation take place selectively at the *N*-phenyl ring (Scheme 1c).

Initially, 4-(dimethylamino)-*N*-phenylbenzimidamide (**1a**, 0.1 mmol) and α-Cl acetophenone (**2a**, 0.14 mmol) were treated with $[Cp^*RhCl_2]_2$ (5 mol %), AgOAc (100 mol %), and NaOAc (100 mol %) as the catalytic system in 1, 2-dichloroethane (DCE) at 90 °C for 24 h, and the results showed that the desired 3-acylindole product **3aa** could be obtained with 44% yield. Meanwhile, a isoquinoline byproduct **4aa** which was derived from a C−H activation and annulation cascade on the *C*-phenyl ring of **1a** could also be afforded in 15% yield, in which α-Cl acetophenone is used as a two-carbon reaction partner (Table 1, entry 1). Further exploration using different α-substituted acetophenones, such as α-Br and α-OMs acetophenones (**2b−2c**), indicated that these new groups were detrimental to the formation of the 3-acylindole scaffold (entries 2−3). Therefore, we chose α-Cl acetophenone (**2a**) as the key one-carbon synthon for further explorations. First, several typical additives, including $Zn(OAc)_2$, $Cu(OAc)_2$, and HOAc, were screened. However, the results showed that AgOAc remained the best additive for this transformation (entries 4−7). Other transition-metal (ruthenium and iridium) catalysts were also tested; however, the desired conversion was not observed (entries 8−9). Based on these results, we further replaced NaOAc with other bases, including Na_2CO_3, $NaHCO_3$, and $KHCO_3$ (entries 10−13). Surprisingly, a better yield and regioselectivity for this transformation were achieved in the presence of $NaHCO_3$. In particular, we obtained the indole products at 53% yield and realized better regioselectivity (**3aa**:**4aa** = 53:8). Subsequent solvent screening revealed that MeOH was the most efficient medium for this reaction, and only a trace amount of isoquinoline **4aa** could be detected (entries 14−16). Encouraged by these results, we further screened the optimum amount of additives and reaction temperatures (entries 17−21) and found that the optimum results could be achieved when *N*-phenylamidine (**1a**, 0.1 mmol) and α-Cl ketones (**2a**, 0.14 mmol) were treated with the catalytic system of $[Cp^*RhCl_2]_2$ (5 mol %), AgOAc (50 mol %), and $NaHCO_3$ (200 mol %) in MeOH at 90 °C for 24 h under an argon atmosphere.

With the optimized reaction conditions in hand, we explored the generality and scope of *N*-phenylamidines (**1a−1y**) with α-Cl ketone **2a** (Scheme 2). *N*-Phenylamidines bearing various electron-donating, electron-withdrawing, or halogen substituents could react smoothly with **2a** to produce the corresponding 2-substituted-3-acylindoles in 41−88% yields (**3aa−3ya**), in which the structure of product **3da** was unambiguously confirmed by X-ray crystallography (CCDC 1873346). In these explorations, we found that electron-donating substituents, such as Me, OMe, and NMe_2, on the *C*-

Table 1. Optimization of Reaction Conditions[a]



entry	additive **1**	additive **2**	solvent	yield (%) **3aa** (**4aa**)[b]
1	AgOAc	NaOAc	DCE	44 (15)
2[c]	AgOAc	NaOAc	DCE	25 (17)
3[d]	AgOAc	NaOAc	DCE	trace (22)
4	$Zn(OAc)_2$	NaOAc	DCE	33 (10)
5	$Cu(OAc)_2$	NaOAc	DCE	trace (21)
6	HOAc	NaOAc	DCE	0 (26)
7	–	NaOAc	DCE	trace (13)
8[e]	AgOAc	NaOAc	DCE	N.R.
9[f]	AgOAc	NaOAc	DCE	N.R.
10	AgOAc	Na_2CO_3	DCE	48 (17)
11	AgOAc	$NaHCO_3$	DCE	53 (8)
12	AgOAc	$KHCO_3$	DCE	50 (7)
13	AgOAc	–	DCE	22 (5)
14	AgOAc	$NaHCO_3$	THF	56 (14)
15	AgOAc	$NaHCO_3$	TFE	67 (12)
16	AgOAc	$NaHCO_3$	MeOH	77 (trace)
17[g]	AgOAc	$NaHCO_3$	MeOH	81 (trace)
18[g,h]	**AgOAc**	**$NaHCO_3$**	**MeOH**	**85 (trace)**
19[g,h,i]	AgOAc	$NaHCO_3$	MeOH	80 (trace)
20[g,h,j]	AgOAc	$NaHCO_3$	MeOH	83 (trace)
21[g,h,k]	AgOAc	$NaHCO_3$	MeOH	78 (trace)

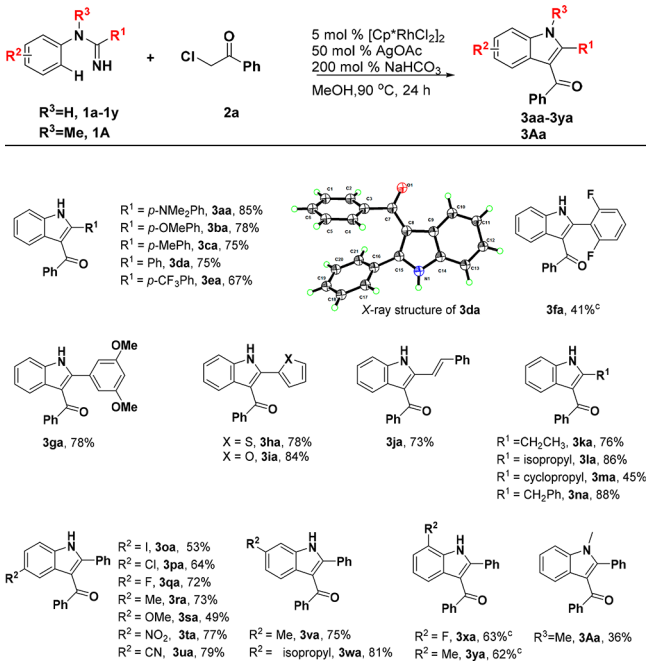
[a]General reaction conditions: **1a** (0.1 mmol), **2a** (0.14 mmol), X = Cl, $[Cp^*RhCl_2]_2$ (5 mol %), additive **1** (0.1 mmol), additive **2** (0.1 mmol), in solvent (2 mL) at 90 °C, under argon, 24 h. DCE = 1,2-dichloroethane. THF = tetrahydrofuran, TFE = trifluoroethanol. [b]Determined by crude ^{1}H NMR spectroscopy. [c]X = Br. [d]X = OMs. [e]$[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %). [f]$[Cp^*IrCl_2]_2$ (5 mol %). [g]$NaHCO_3$ (0.2 mmol). [h]AgOAc (0.05 mmol). [i]At 80 °C. [j]At 100 °C. [k]Under air. N.R. = no reaction.

phenyl ring of benzamidine were more favorable for this transformation than those of the electron-withdrawing groups including 2,6-difuoro, CF_3 (**3aa−3ga**). Subsequently, 2-heteroaryl-3-acylindoles (**3ha−3ia**) and 2-alkenyl-3-acylindoles (**3ja**) were also investigated and good yields were obtained (73−84% yield). Notably, *C*-alkyl imidamides were also successfully employed with considerable yields (**3ka−3na**), especially when a benzyl and an isopropyl group was introduced. In addition, certain electron-donating groups (Me, ^{i}Pr, and OMe), electron-withdrawing groups (NO_2 and CN), and halogen groups (I, Cl, and F) were introduced into the *p*-, *m*-, and *o*-positions of the *N*-phenyl ring of **1d**, respectively; all of them (**3oa−3ya**) were tolerated for this transformation and formed the desired products with moderate to good yields (49−81%) and regioselectivities. It is also worth noting that when testing *N*-methyl-*N*-phenylbenzimidamide (**1A**) with **2a**, we could directly obtain *N*-methylindole product (**3Aa**) with a 36% yield.

To further explore the scope of this transformation, more α-Cl ketones were investigated under the optimized conditions (Scheme 3). First, diverse monosubstituted α-Cl acetophenones (**2d−2h**) and disubstituted α-Cl acetophenones (**2i−2j**) were selected as the substrates for this reaction, furnishing the desired products **3dd−3dj** in moderate to high yields, in which strong electron-withdrawing groups (**3df**, **3di**, and **3dj**) did not appear to benefit this transformation. The reaction also showed

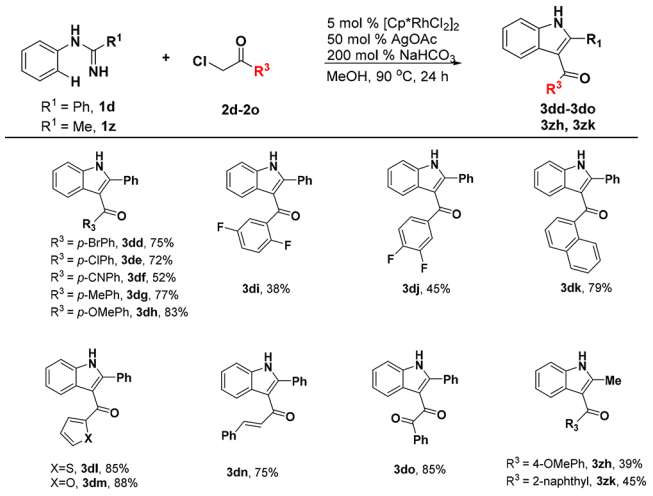
DOI: 10.1021/acs.orglett.8b03383
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Scope of *N*-Phenylamidines[a,b]



[a]Reaction conditions: **1** (0.5 mmol) and **2a** (0.70 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), AgOAc (0.25 mmol), $NaHCO_3$ (1.0 mmol) in MeOH (5 mL) at 90 °C, under Ar, 24 h. [b]Isolated yields are reported. [c]For 48 h

Scheme 3. Scope of α-Cl Ketones[a,b]

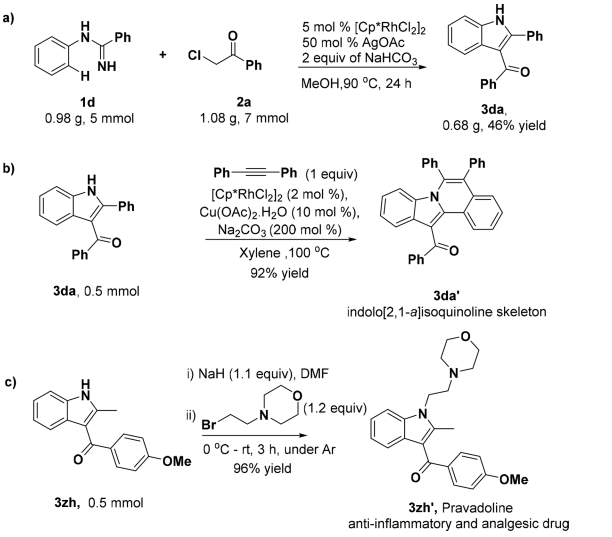


[a]Reaction conditions: **1** (0.5 mmol) and **2** (0.70 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), AgOAc (0.25 mmol), $NaHCO_3$ (1.0 mmol) in MeOH (5 mL) at 90 °C, under Ar, 24 h. [b]Isolated yields are reported.

good tolerance toward other ketones containing a naphthyl, heteroaryl, or alkenyl group (**3dk**–**3dn**), with good yields. Surprisingly, 3-diketoindole (**3do**) could also be synthesized successfully with considerable yields (85%) *via* this C–H activation strategy, although few methods have been reported for the dicarbonylation of indoles.[11] Finally, *N*-phenylacetamidine (**1z**) was examined with two types of α-Cl arylketones (**2h** and **2k**) and was smoothly transformed into 2-methyl-3-acylindole scaffold (**3zh** and **3zk**), which represents an essential structure unit in certain drug molecules.[2a,c]

To evaluate the synthetic utility of 3-acylindoles, a gram-scale preparation of product **3da** was carried out with a 46% yield (Scheme 4a). Delightfully, when employing another

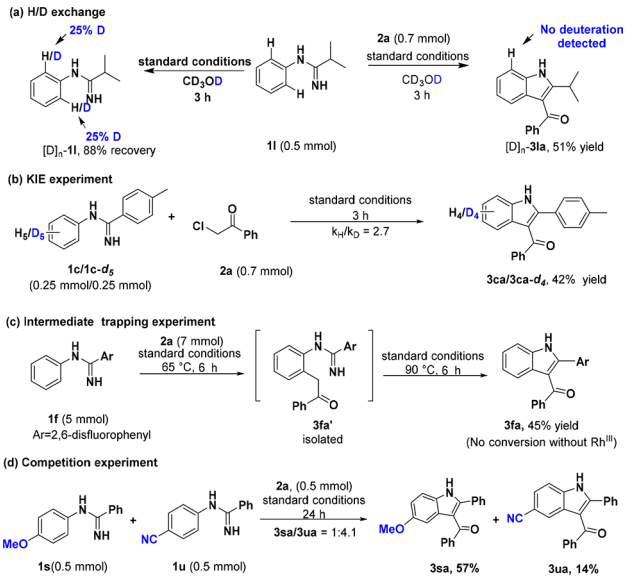
Scheme 4. Gram-scale Preparation and Conversion of the Product



Rh(III) catalyzed oxidative coupling of product **3da** with diphenylacetylene,[12] we obtained indolo[2,1-*a*]isoquinoline skeleton **3da′** (Scheme 4b), which not only shows a broad range of intriguing biological activities in various natural products[13] but also exhibits intense solid-state fluorescence in certain 5,6-diarylindolo[2,1-*a*]isoquinoline derivatives.[12] More significantly, this methodology could provide a short synthesis route for Pravadoline (**3zh′**), a potent anti-inflammatory and analgesic drug (IC_{50} = 4.9 μM against CB_1 receptor).[2a,b] Its synthetic protocol was provided in Scheme 4c.

To gain insight into the mechanism of the reaction, a series of experiments were performed. First, the reaction of **1l** in CD_3OD suggested that the C–H activation was reversible in the absence or presence of **2a** (Scheme 5a; see SI).

Scheme 5. Mechanism Studies

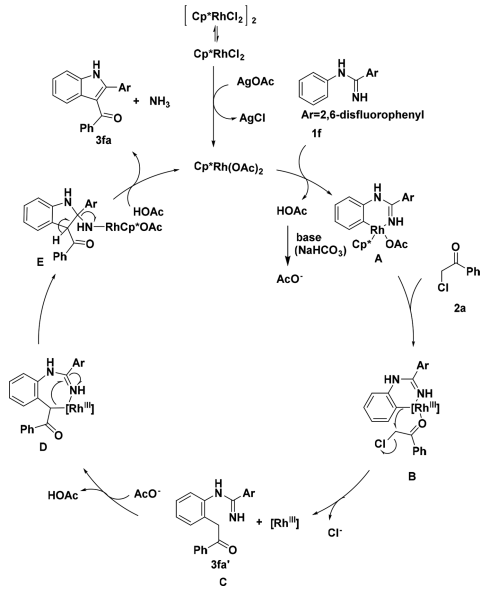


DOI: 10.1021/acs.orglett.8b03383
Org. Lett. XXXX, XXX, XXX–XXX

Additionally, the kinetic isotope effect (KIE) was determined by performing intermolecular competition experiments using an equimolar mixture of **1c** and **1c-d_5** in the couplings with **2a** (Scheme 5b). The k_H/k_D value of 2.7 was observed on the basis of the ^{1}H NMR analysis (see SI), indicating that the C−H bond cleavage was likely involved in the turnover-limiting step. Moreover, an intermediate trapping experiment was carried out at a relatively lower temperature (65 °C) with the standard catalyst systems (Scheme 5c), and the intermediate **3fa′** was isolated and characterized (see SI), suggesting that C−H alkylation took place before C═N bond cleavage. The key intermediate could be further converted into the desired product **3fa** under standard conditions (no conversion without Rh catalyst). Furthermore, a competition experiment was conducted with an equimolar amount of **1s** and **1u** with different electronic properties, respectively. The results showed that products **3sa** and **3ua** were afforded at a ratio of 1:4.1 (see ^{1}H NMR analysis in SI), thus displaying that the electron-deficient *N*-phenyl reacted faster (Scheme 5d), indicating the C−H activation might proceed through a concerted metalation−deprotonation (CMD) mechanism.[14]

According to these mechanistic investigations and the results of previous studies,[6c,7] a plausible reaction mechanism for the formation of 3-acyl indoles was hypothesized (Scheme 6).

Scheme 6. Preliminary Mechanistic



Initially, cyclometalation of the *N*-phenylamidine (**1f**) affords a six-membered cyclo-rhodium species **A** *via* CMD. Then, the oxygen atom of α-Cl ketone (**2a**) coordinates with species **A** to produce an intermediate **B**, in which the nucleophilic C(aryl)−Rh species further attacks the methylenes of α-Cl ketones to produce α-aryl-ketones species **C**. The resulting species **C** further chelates with the Rh^{III} catalyst to generate a seven-membered rhodacyclic intermediate **D**, under the assistance of an acetate ion. Intermediate **E** is then formed from unstable intermediate **D** by Rh−C(alkyl) migratory insertion into the C═N bond. Eventually, the final product **3fa** is released from **E** by elimination of the active Rh(III) catalyst and one molecule of ammonia from **E** upon protonolysis and intramolecular protonolysis.

In conclusion, we developed an unprecedented synthetic strategy to directly access practical 3-acylindoles *via* Rh(III)-catalyzed C−H activation and [4 + 1] annulation[15] of *N*-phenylamidines with readily accessible α-Cl ketones. High regioselectivity, mild reaction conditions, and wide substrate tolerance make this protocol efficient to prepare various 3-acylindole derivatives. The mechanism of α-Cl ketones acting as one-carbon synthons in the Rh(III)-catalyzed synthesis of indoles was proposed, which may provide wider application in constructing more acylated heterocyclic compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03383.

Experimental procedure, characterization of the products, and copies of ^{1}H, ^{19}F, and ^{13}C NMR spectra of products (PDF)

Accession Codes

CCDC 1873346 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: hliu@simm.ac.cn (H.L.).
*E-mail: zhouyu@simm.ac.cn (Y.Z.).

ORCID

Yu Zhou: 0000-0002-7684-2939
Hong Liu: 0000-0002-0863-7853

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (Nos. 21672232, 21632008, 81620108027) and the Strategic Priority Research Program of the Chinese Academy of Sciences (XDA12040217) for financial support.

■ REFERENCES

(1) For relevant books and reviews, see: (a) Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K. *Comprehensive Heterocyclic Chemistry III*; d'lschia, M., Napolitano, A., Pezzella, A., Eds.; Elsevier: Oxford, 2008; pp 353−383. (b) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761. (c) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489.

(2) For selected examples of bioactive 3-acylindoles, see: (a) D'Ambra, T. E.; Estep, K. G.; Bell, M. R.; Eissenstat, M. A.; Josef, K. A.; Ward, S. J.; Haycock, D. A.; Baizman, E. R.; Casiano, F. M. *J. Med. Chem.* **1992**, *35*, 124. (b) Haubrich, D. R.; Ward, S. J.; Baizman, E.; Bell, M. R.; Bradford, J.; Ferrari, R.; Miller, M.; Perrone, M.; Pierson, A. K.; Saelens, J. K. *J. Pharmacol. Exp. Ther.* **1990**, *255*, 511. (c) Huffman, J. W.; Zengin, G.; Wu, M.-J.; Lu, J.; Hynd, G.; Bushell, K.; Thompson, A. L. S.; Bushell, S.; Tartal, C.; Hurst, D. P.; Reggio, P. H.; Selley, D. E.; Cassidy, M. P.; Wiley, J. L.; Martin, B. R. *Bioorg. Med. Chem.* **2005**, *13*, 89. (d) Rabasseda, X. *Drug. Today* **2002**, *38*, 75. (e) Liou, J.; Chang, Y.; Kuo, F.; Chang, C.; Tseng, H.; Wang,

DOI: 10.1021/acs.orglett.8b03383
Org. Lett. XXXX, XXX, XXX−XXX

C.; Yang, Y.; Chang, J.; Lee, S.; Hsieh, H. *J. Med. Chem.* **2004**, *47*, 4247. (f) Barreca, M. L.; Ferro, S.; Rao, A.; De Luca, L.; Zappalà, M.; Monforte, A.-M.; Debyser, Z.; Witvrouw, M.; Chimirri, A. *J. Med. Chem.* **2005**, *48*, 7084. (g) Kauffman, R. F.; Bensch, W. R.; Roudebush, R. E.; Cole, H. W.; Bean, J. S.; Phillips, D. L.; Monroe, A.; Cullinan, G. J.; Glasebrook, A. L.; Bryant, H. U. *J. Pharmacol. Exp. Ther.* **1997**, *280*, 146.

(3) For 3-acylindole synthesis via Lewis acids mediated Friedel−Crafts-type reactions, see: (a) Ottoni, O.; Neder, A. d. V. F.; Dias, A. K. B.; Cruz, R. P. A.; Aquino, L. B. *Org. Lett.* **2001**, *3*, 1005. (b) Wynne, J. H.; Lloyd, C. T.; Jensen, S. D.; Boson, S.; Stalick, W. M. *Synthesis* **2004**, *2004*, 2277. (c) Katritzky, A. R.; Suzuki, K.; Singh, S. K.; He, H.-Y. *J. Org. Chem.* **2003**, *68*, 5720. (d) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451. (e) Guchhait, S. K.; Kashyap, M.; Kamble, H. *J. Org. Chem.* **2011**, *76*, 4753.

(4) For selected examples of indole synthesis via Rh(III)-catalyzed intermolecular C−H activation/annulation with alkynes, see: (a) Chen, J.; Song, G.; Pan, C.; Li, X. *Org. Lett.* **2010**, *12*, 5426. (b) Wang, C.; Sun, H.; Fang, Y.; Huang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 5795. (c) Yan, H.; Wang, H.; Li, X.; Xin, X.; Wang, C.; Wan, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 10613. (d) Liu, B.; Song, C.; Sun, C.; Zhou, S.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 16625. (e) Zheng, Li.; Hua, R. *Chem. - Eur. J.* **2014**, *20*, 2352. (f) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326. (g) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474. (h) Zhou, Z.; Liu, G.; Chen, Y.; Lu, X. *Adv. Synth. Catal.* **2015**, *357*, 2944. (i) Wang, C.; Huang, Y. *Org. Lett.* **2013**, *15*, 5294. (j) Huestis, M. P.; Chan, L. R.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338.

(5) For selected examples of indole synthesis via Rh(III)-catalyzed intermolecular C−H activation/annulation with alkenes, see: (a) Zhao, D.; Vasquez-Cespedes, S.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 1657. (b) Kim, M.; Park, J.; Sharma, S.; Han, S.; Han, S. H.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Org. Biomol. Chem.* **2013**, *11*, 7427.

(6) For selected examples of indole synthesis via Rh(III)-catalyzed intermolecular C−H activation/annulation with diazo compounds, see: (a) Liang, Y.; Yu, K.; Li, B.; Xu, S.; Song, H.; Wang, B. *Chem. Commun.* **2014**, *50*, 6130. (b) Mishra, N. K.; Choi, M.; Jo, H.; Oh, Y.; Sharma, S.; Han, S. H.; Jeong, T.; Han, S.; Lee, S.-Y.; Kim, I. S. *Chem. Commun.* **2015**, *51*, 17229. (c) Qi, Z.; Yu, S.; Li, X. *Org. Lett.* **2016**, *18*, 700.

(7) Yu, D. G.; de Azambuja, F.; Glorius, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 2754.

(8) Li, J.; Zhang, Z.; Tang, M.; Zhang, X.; Jin, J. *Org. Lett.* **2016**, *18*, 3898.

(9) Xie, C.; Dai, Z.; Niu, Y.; Ma, C. *J. Org. Chem.* **2018**, *83*, 2317.

(10) For general overviews on the synthesis, reactivity, and synthetic application of α-haloketones, see: (a) De Kimpe, N.; Verhé, R. In *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1988; pp 1−489. (b) Erian, W. A.; Sherif, M. S.; Gaber, M. H. *Molecules* **2003**, *8*, 793.

(11) For reported methods of 3-diketoindole synthesis, see: (a) Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H. *Org. Lett.* **2000**, *2*, 1485. (b) Merkul, E.; Dohe, J.; Gers, C.; Rominger, F.; Muller, T. J. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2966. (c) Tang, R.; Guo, X.; Xiang, J.; Li, J. *J. Org. Chem.* **2013**, *78*, 11163. (d) Wu, J.; Song, R.; Wang, Z.; Huang, X.; Xie, Y.; Li, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 3453. (e) Gao, Q.; Zhang, J.; Wu, X.; Liu, S.; Wu, A. *Org. Lett.* **2015**, *17*, 134.

(12) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2068.

(13) (a) Ambros, R.; Schneider, M. R.; Von Angerer, S. *J. Med. Chem.* **1990**, *33*, 153. (b) Ewing, J.; Hughes, G. K.; Ritchie, E.; Taylor, W. C. *Nature* **1952**, *169*, 618. (c) Mamane, V.; Hannen, P.; Fürstner, A. *Chem. - Eur. J.* **2004**, *10*, 4556. (d) Orito, K.; Harada, R.; Uchiito, S.; Tokuda, M. *Org. Lett.* **2000**, *2*, 1799.

(14) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118.

(15) For a recent review of [4 + 1] annulation, see: Chen, J.; Hu, X.; Lu, L.; Xiao, W. *Chem. Rev.* **2015**, *115*, 5301.

DOI: 10.1021/acs.orglett.8b03383
Org. Lett. XXXX, XXX, XXX−XXX