DOI: 10.1002/ejoc.201403355

Ir^{III}-Catalyzed Direct C-7 Amidation of Indolines with Sulfonyl, Acyl, and Aryl Azides at Room Temperature

Wei Hou,[a] Yaxi Yang,[a] Wen Ai,[b] Yunxiang Wu,[a] Xuan Wang,[a] Bing Zhou,*[a] and Yuanchao Li*[a]

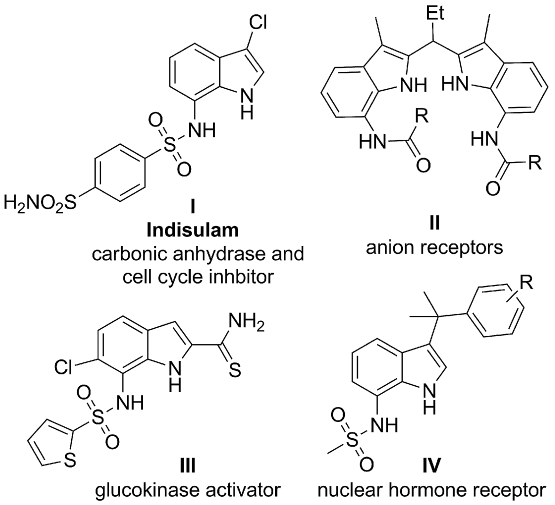
Keywords: Nitrogen heterocycles / C–H activation / Iridium / Regioselectivity / Amidation

A general procedure for an Ir^{III}-catalyzed C-7 selective C–H amidation and amination of indolines is reported. The reaction exhibits good functional group tolerance, requires no external oxidants, and releases N_2 as the single byproduct, thus providing an environmentally benign, readily scalable method for the synthesis of 7-aminoindolines. More importantly, acyl, sulfonyl, and aryl azides can be employed as the amino source in this C–H amidation reaction under very mild and pH-neutral reaction conditions (i.e., room temperature) to afford *N*-(7-indolinyl)amides, *N*-(7indolinyl)-sulfonamides, and *N*-(7-indolinyl)arylamines in good to excellent yields. In addition, a one-pot synthesis for 7-aminoindoles was developed. Overall, this procedure is robust, reliable, and compatible in air.

Introduction

Indoles are of great interest in organic synthesis because of their presence in numerous natural products, pharmaceuticals, and agrochemicals.[1] Among them, 7-substituted indoles are particularly important as a result of their ubiquitous presence in numerous biologically active compounds (see Figure 1).[2] Therefore, a method for a general, rapid, and regioselective preparation of 7-substituted indoles would be highly desirable.

Recently, transition-metal-catalyzed C–H bond activations have become an increasingly viable tool for direct C–H bond functionalizations, as this process removes the need for the tedious prefunctionalization of the substrate, thus enhancing the overall scope and efficiency.[3] Given the significance of 7-substituted indoles, it would be highly desirable and attractive if we could directly functionalize the C–H bond at the C-7 position of an indole by using a transition-metal-catalyzed C–H activation pathway. Although considerable studies of transition-metal-catalyzed C–H bond functionalizations at the C-2 and C-3 positions of indole have been carried out over the past decades,[4] there are few reports of a C-7 selective C–H bond functionalization of indole.[5,6] Moreover, these approaches are generally limited to C–C bond formation,[5] and only one example that involves the construction of a C–N bond has been reported, thus proving it to be a formidable challenge (see Scheme 1, a).[6] Despite this great breakthrough, this approach still has some constraints, such as a limited substrate scope, a high reaction temperature, and the need for 0.5 equiv. of AgOAc. Therefore, it is of utmost importance to develop a new method for the efficient construction of biologically important 7-aminoindoles.[1,2]



I **Indisulam** carbonic anhydrase and cell cycle inhbitor

II anion receptors

III glucokinase activator

IV nuclear hormone receptor

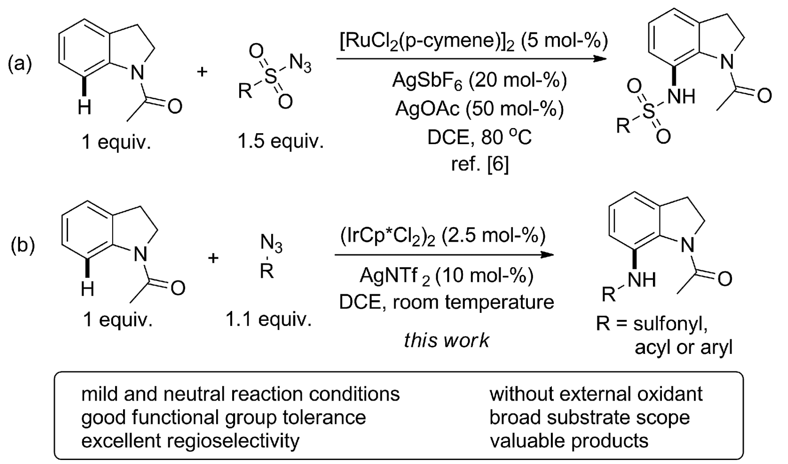
Figure 1. Representative biologically active compounds that contain the 7-aminoindole structural motif.

Along with our continuous efforts towards the regioselective C–H functionalization of indoles[4l,4o] and transition-metal-catalyzed C–H amidation reactions,[7b,7e] we herein report a general approach under air for the amidation of

---

[a] Department of Medicinal Chemistry, Shanghai Institute of Materia Medica, Chinese Academy of Sciences,
555 Zu Chong Zhi Road, Shanghai 201203, P. R. China
E-mail: zhoubing2012@hotmail.com
ycli@mail.shcnc.ac.cn
http://english.simm.cas.cn/
[b] Key Lab for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology,
130 Meilong Road, Shanghai 200237, P. R. China

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403355.



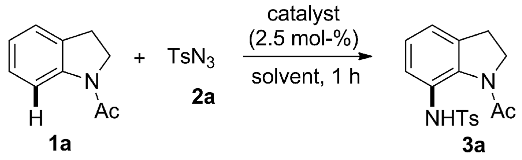
Scheme 1. C-7 amidation of indolines (DCE = 1,2-dichloroethane, Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl, Tf = trifluoromethylsulfonyl).

the C–H bond at the C-7 position of indoline by employing an iridium-catalyzed C–H bond activation (see Scheme 1, b). This reaction tolerates various synthetically important functional groups, requires no external oxidants, and releases benign N_2 as the only byproduct. Significantly, acyl, sulfonyl, and aryl azides can be employed as the amino source in this C–H amidation reaction to afford *N*-(7-indolinyl)amides, *N*-(7-indolinyl)sulfonamides, and *N*-(7-indolinyl)arylamines, respectively, in good to excellent yields under very mild and neutral reaction conditions (i.e., at room temperature).

Results and Discussion

N-Acetylindoline (**1a**) and tosyl azide (**2a**) were chosen as the model substrates (see Table 1). First, the reaction was catalyzed by using known reaction conditions {prepared Rh^{III} precursor $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (2.5 mol-%) in DCE at 80 °C; see Table 1, Entry 1).[7] Unfortunately, no conversion occurred. The employment of a cationic Rh^{III} species, which was generated in situ by treating $(RhCp^*Cl_2)_2$ with $AgSbF_6$, was also an ineffective catalyst for this C–H amidation reaction (see Table 1, Entry 2). Next, other catalysts were screened. $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol-%), with $AgSbF_6$ (10 mol-%) gave the desired product **3a** in 13% yield (see Table 1, Entry 3). Surprisingly, when the reaction was treated with $(IrCp^*Cl_2)_2$ (2.5 mol-%) and $AgSbF_6$ (10 mol-%), a dramatic increase in the reaction yield (80%) was observed (see Table 1, Entry 4). Moreover, using $AgNTf_2$, a different halide abstractor, further improved the yield (see Table 1, Entry 5). When other organic solvents were used, the yield decreased, and thus DCE proved to be the optimal solvent for the reaction (see Table 1, Entries 5–7). Notably, this reaction could be carried out at room temperature without a decrease in the yield (see Table 1, Entry 8).

Table 1. Optimization of direct C–H amidation at C-7 of indolines.[a]

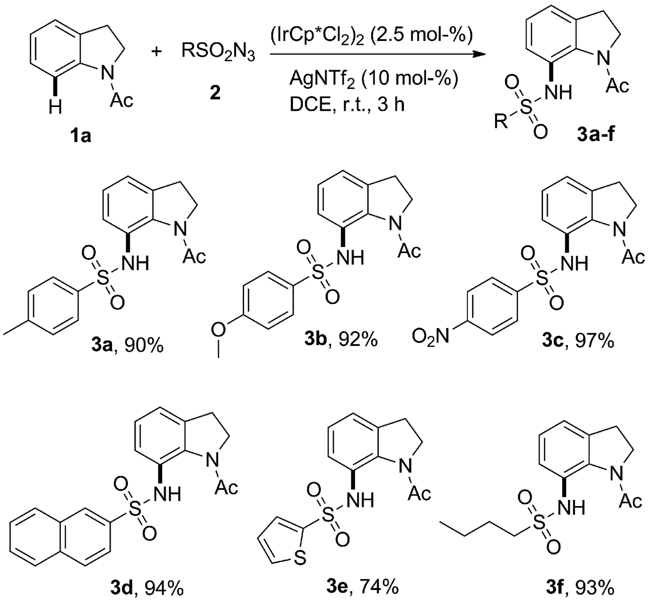


Entry	Catalyst	Solvent	Yield [%][b]
1	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	DCE	0
2	$(RhCp^*Cl_2)_2/AgSbF_6$	DCE	0
3	$[RuCl_2(p\text{-cymene})]_2/AgSbF_6$	DCE	13
4	$(IrCp^*Cl_2)_2/AgSbF_6$	DCE	80
5	$(IrCp^*Cl_2)_2/AgNTf_2$	DCE	90
6	$(IrCp^*Cl_2)_2/AgNTf_2$	THF[c]	30
7	$(IrCp^*Cl_2)_2/AgNTf_2$	PhMe	40
8[d]	$(IrCp^*Cl_2)_2/AgNTf_2$	DCE	90

[a] Reagents and conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), catalyst (0.005 mmol, 2.5 mol-%), and solvent (1 mL) at 80 °C for 1 h. [b] Yield of isolated product. [c] THF = tetrahydrofuran. [d] The reaction was carried out at room temperature for 3 h.

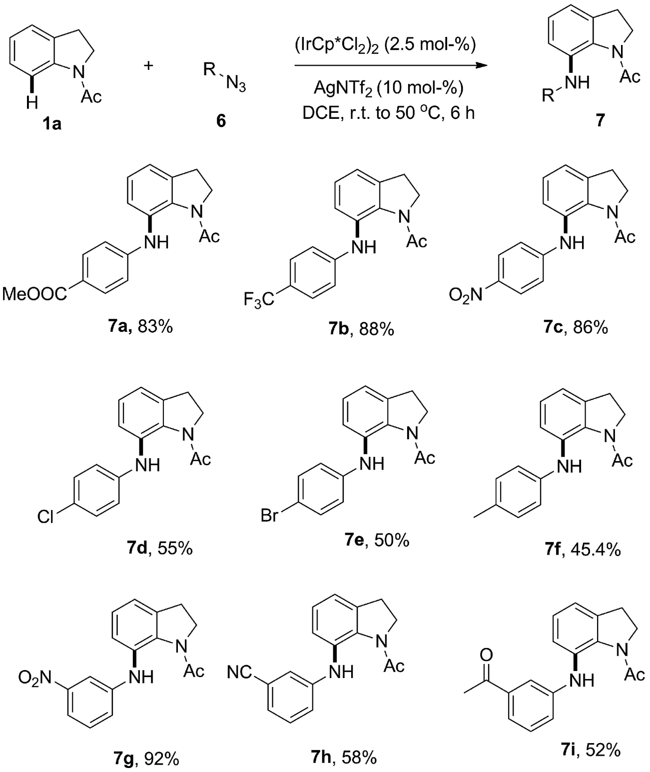
With an optimized catalytic system in hand, we examined the scope of the sulfonyl azides (see Scheme 2). To our delight, the arenesulfonyl azides that contained either electron-donating (i.e., **3a** and **3b**) or electron-withdrawing groups (i.e., **3c**) were well tolerated and gave the corresponding products in >90% yield. The large naphthalene-2-sulfonyl azide also readily participated in the amidation reaction to provide product **3d** in 94% yield. Furthermore, good yields were obtained when heteroaromatic (i.e., **3e**) and alkylsulfonyl azides (i.e., **3f**) were used in the reaction, which demonstrated the generality of this method.

Encouraged by the successful results of the amidation with sulfonyl azides, we turned our attention to acyl azides (see Scheme 3). In contrast to previous results,[8] we were pleased to find that acyl azides also worked well to facilitate

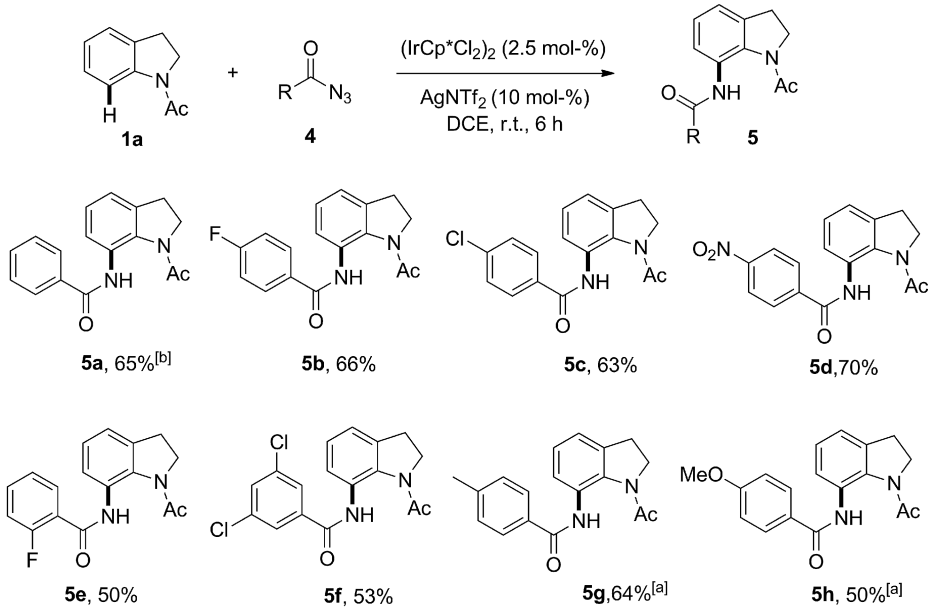


Scheme 2. Ir-catalyzed C-7 amidation of indolines with sulfonyl azides. Reagents and conditions: **1a** (0.2 mmol), **2** (0.22 mmol), $(IrCp^*Cl_2)_2$ (2.5 mol-%), $AgNTf_2$ (10 mol-%), and DCE (1 mL) at room temperature for 3 h. The yield of the isolated product is provided.

the direct amidation of indolines at room temperature. Benzoyl azides that contained electron-withdrawing (i.e., **5b**–**5f**), electron-neutral (i.e., **5a**), or electron-donating substituents (i.e., **5g** and **5h**) at the *para* (i.e., **5b**–**5d, 5g**, and **5h**), *ortho* (i.e., **5e**), or *meta* (i.e., **5f**) position were tolerated in this amidation reaction to give the corresponding products in good yields.



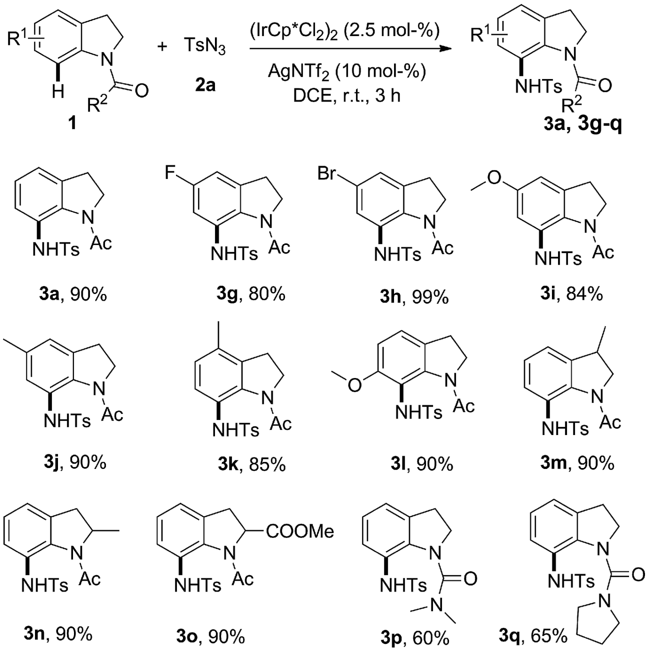
Scheme 4. Substrate scope for aryl azides. Reagents and conditions: **1** (0.2 mmol), **6** (0.24 mmol), $(IrCp^*Cl_2)_2$ (2.5 mol-%), $AgNTf_2$ (10 mol-%), and DCE (1 mL) at room temperature for 6 h. The yield of the isolated product is provided.



Scheme 3. Ir-catalyzed C-7 amidation of indolines with acyl azides. Reagents and conditions: **1a** (0.2 mmol), **4** (0.22 mmol), $(IrCp^*Cl_2)_2$ (2.5 mol-%), $AgNTf_2$ (10 mol-%), and DCE (1 mL) at room temperature for 6 h. The yield of isolated product is provided. [a] The reaction was carried out at 50 °C for 6 h.

In addition to sulfonyl and acyl azides, the scope of the reaction with aryl azide substrates was also explored (see Scheme 4). To our delight, aryl azides that contained electron-withdrawing (i.e., **7a**–**7e** and **7g**–**7i**) or electron-donating substituents (i.e., **7f**) at the *para* (i.e., **7a**–**7f**) or *meta* (i.e., **7g**–**7i**) position were tolerated in this amidation reaction to afford the corresponding products in moderate to excellent yields.

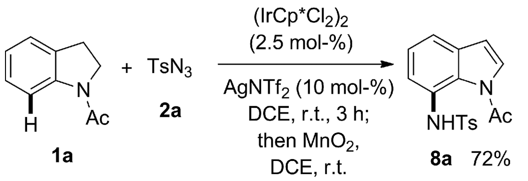
Next, we surveyed the substrate scope of the reaction of various indolines with sulfonyl azides (see Scheme 5). To our delight, indolines that contained electron-withdrawing (i.e., **3g**, **3h**, and **3o**) or electron-donating groups (i.e., **3i**–**3m**) at the C-2, C-3, C-4, C-5, or C-6 position of the indoline ring were tolerated in this reaction to afford the corresponding amidation product in 80–99% yield. Notably, halo and ester substituents, which can provide opportunities for further transformations, were tolerated. In addition, *N*,*N*-disubstituted carbamoylindolines were also successfully employed in this reaction to yield product **3p** and **3q** in 60 and 65% yield, respectively.



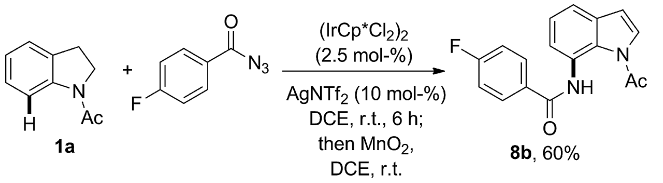
Scheme 5. Substrate scope for indolines. Reagents and conditions: **1** (0.2 mmol), **2a** (0.22 mmol), $(IrCp^*Cl_2)_2$ (2.5 mol-%), $AgNTf_2$ (10 mol-%), and DCE (1 mL) at room temperature for 3 h. The yield of the isolated product is provided.

The usefulness of this method was further demonstrated by the development of the one-pot synthesis for 7-aminoindoles **8a** and **8b**. The amidation of **1a** with a sulfonyl and acyl azide under the optimized conditions and subsequent oxidation with MnO_2 in one pot yielded 7-aminoindoles **8a** and **8b**, respectively, see Equations (1) and (2). More significantly, *N*-(7-indolinyl)arylamine **7c**, which was accessible by the present direct C–H amination reaction, enabled the subsequent oxidative C–C coupling reaction to allow for the preparation of pyrrolo[2,3-*a*]carbazole **8c**, see Equation (3).

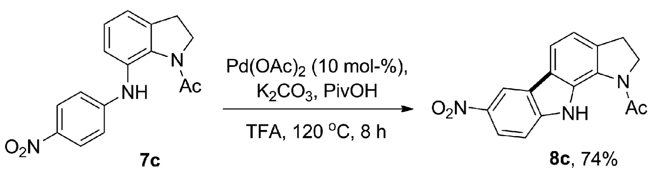
Finally, we were pleased to find that this reaction was successfully scalable, and gram amounts of substrate could be used without a decrease to the yield. Moreover, the amidated product was easily isolated by a simple recrystallization process, see Equation (4).



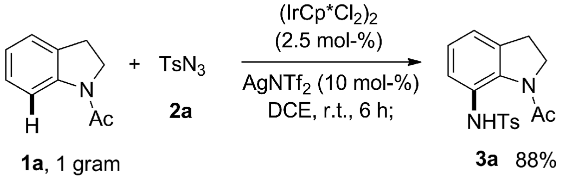
(1)



(2)

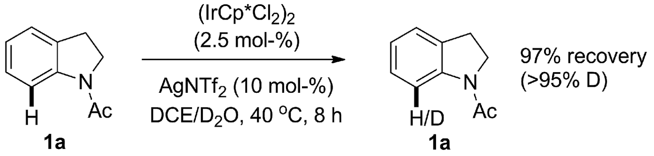


(3)



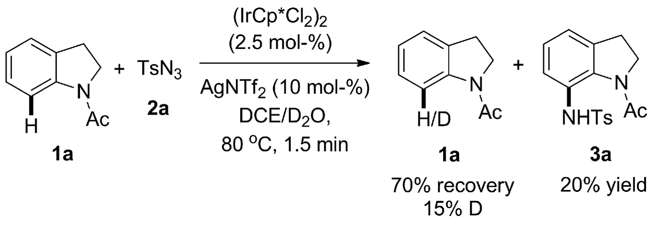
(4)

To gain insight into the mechanism, the following experiments were performed. When **1a** was treated with a catalytic amount of $(IrCp^*Cl_2)_2$ and $AgNTf_2$ in DCE and D_2O, a significant H/D scrambling was observed at the C-7 position of indoline **1a**, see Equation (5). When the reaction was performed in the presence of a sulfonyl azide in DCE/D_2O for 1.5 min, the incorporation of deuterium was also observed in unreacted **1a**, which indicates that the cleavage of the C–H bond at the C-7 position is a reversible process, see Equation (6).



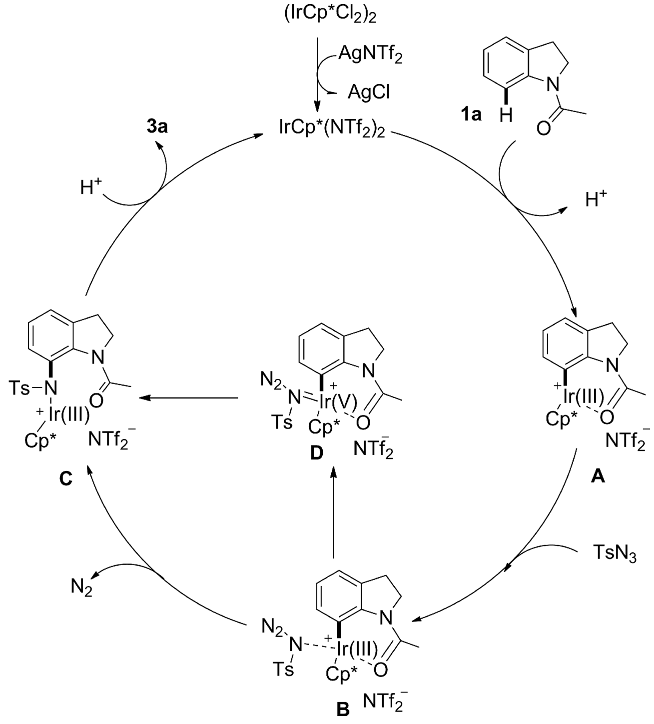
(5)

On the basis of these mechanistic studies and previous literature,[7] a plausible mechanistic pathway is proposed (see Scheme 6). First, the treatment of a dimeric iridium species with $AgNTf_2$ affords monomeric $IrCp^*(NTf_2)_2$, which then induces the C–H cleavage of indoline **1a** to produce cyclometalated Ir^{III} complex **A**.[9] The azide then inter-



(6)

acts with the cationic metal center of **A** to give **B**, which can be converted into Ir^{III} amido species **C** through a concerted migratory insertion or through high valent iridium(V) nitrenoid species **D** in an oxidative manner. In each path, a molecule of N_2 is released. Finally, protonolysis of **C** affords product **3a**.



Scheme 6. Proposed mechanism.

Conclusions

In summary, we have developed a general method for the Ir^{III}-catalyzed C-7 selective C–H bond amidation of indolines by using sulfonyl, acyl, and aryl azides as the amine source. Mild and pH-neutral reaction conditions, low catalyst loadings without external oxidants, good functional group tolerance, and a broad substrate scope characterize this transformation. In addition, a one-pot synthesis of 7-aminoindoles was developed.

Experimental Section

General Methods: Mass spectrometry and high resolution mass spectrometry were performed on a Finnigan MAT-95 mass spectrometer. The ^1H and ^{13}C NMR spectroscopic data were recorded with Bruker AM-300, Bruker AM-400, and Bruker AM-500 instruments. Tetramethylsilane was used as the internal reference. The NMR data are reported as chemical shift, multiplicity [s (singlet), br. s (broad singlet), d (doublet), br. d (broad doublet), t (triplet), or m (multiplet)], and coupling constant [*J* in Hertz (Hz)]. Silica gel 60H (200–300 mesh), manufactured by Qingdao Haiyang Chemical Group Co. (China), was used for general chromatography. All reagents were purchased from commercial sources and used without further purification, unless otherwise indicated. $[Cp^*RhCl_2]_2$, $[Cp^*Rh(MeCN)_3][SbF_6]_2$, the substituted indolines, the benzenesulfonyl azides, the acyl azides, and the aryl azides were synthesized according to published procedures.

General Procedure for Direct C–H Amidation at the C-7 Position of Indolines: $(IrCp^*Cl_2)_2$ (2.5 mol-%), $AgNTf_2$ (10 mol-%), indolines **1** (0.2 mmol), azides **2** or **4** (0.22 mmol, 1.1 equiv.), and DCE (1 mL) were added to a test tube. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was purified by chromatography on a silica gel column to give product **3** or **5**.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization of products, and copies of ^1H and ^{13}C NMR spectra.

Acknowledgments

Support of this work by the National Natural Science Foundation of China (NSFC) (grant number 21302200) is gratefully acknowledged.

---

[1] a) R. J. Sundberg, *Indoles*, Academic Press, San Diego, **1996**; b) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2005**, *22*, 73; c) T. Kawasaki, K. Higuchi, *Nat. Prod. Rep.* **2005**, *22*, 761; d) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489.

[2] a) Y. Ozawa, K. Kusano, T. Owa, A. Yokoi, M. Asada, K. Yoshimatsu, *Cancer Chemother. Pharmacol.* **2012**, *69*, 1353; b) T. Owa, A. Yokoi, K. Yamazaki, K. T. Yoshimatsu, T. Yamori, T. Nagasu, *J. Med. Chem.* **2002**, *45*, 4913; c) T. Owa, H. Yoshino, T. Okauchi, K. Yoshimatsu, Y. Ozawa, N. H. Sugi, T. Nagasu, N. Koyanagi, K. Kitoh, *J. Med. Chem.* **1999**, *42*, 3789; d) P. Dydio, T. Zielinski, J. Jurczak, *Chem. Commun.* **2009**, 4560; e) T. Yasuma, O. Ujikawa, M. Itoh, K. Aoki, U.S. Patent 2008/0096877 Al, **2008**; f) L. C. Eli, M. G. Bell, K. Gavardinas, D. L. Gernert, T. A. Grese, P. K. Jadhav, P. A. Lander, M. I. Steinberg, WO 2004067529 A1, **2004**.

[3] For selected reviews on C–H activation, see: a) J. Q. Yu, Z. J. Shi (Eds.), *C–H Activation*, vol. 292: *Topics in Current Chemistry*, Springer, Heidelberg, Germany, **2010**; b) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; c) J. Wencel-Delord, T. Drçge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; d) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315; e) K. M. Engle, T. S. Mei, M. Wasa, J. Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; f) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; *Angew. Chem.* **2012**, *124*, 10382; g) N. Kuhl, N. Schroder, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 1443.

[4] For selected reviews, see: a) I. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173; b) L. Joucla, L. Djakovitch, *Adv. Synth. Catal.* **2009**, *351*, 673; c) G. Broggini, E. M. Beccalli, A. Fasana, S. Gazzola, *Beilstein J. Org. Chem.* **2012**, *8*, 1730; for selected examples, see: d) B. S. Lane, D. Sames, *Org. Lett.* **2004**, *6*, 2897; e) X. Wang, B. S. Lane, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 4996; f) B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050; g) N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972; h)

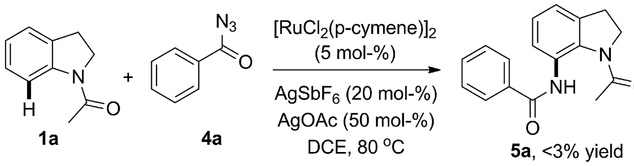
B. B. Toure, B. S. Lane, D. Sames, *Org. Lett.* **2006**, *8*, 1979; i) D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 12072; j) S.-D. Yang, C.-L. Sun, Z. Fang, B.-J. Li, Y.-Z. Li, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2008**, *47*, 1473; *Angew. Chem.* **2008**, *120*, 1495; k) L. Jiao, T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 12990; l) B. Zhou, Y. Yang, Y. Li, *Chem. Commun.* **2012**, *48*, 5163; m) S. Pan, N. Ryu, T. Shibata, *J. Am. Chem. Soc.* **2012**, *134*, 17474; n) L. Jiao, E. Herdtweck, T. Bach, *J. Am. Chem. Soc.* **2012**, *134*, 14563; o) B. Zhou, Y. Yang, S. Lin, Y. Li, *Adv. Synth. Catal.* **2013**, *355*, 360; p) Z. Ding, N. Yoshikai, *Angew. Chem. Int. Ed.* **2012**, *51*, 4698; *Angew. Chem.* **2012**, *124*, 4776; q) K. S. Kanyiva, Y. Nakao, T. Hiyama, *Heterocycles* **2007**, *72*, 677; r) D. J. Schipper, M. Hutchinson, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6910; s) L. Yang, G. Zhang, H. Huang, *Adv. Synth. Catal.* **2014**, *356*, 1509; t) B. Gong, J. Shi, X. Wang, Y. Yan, Q. Li, Y. Meng, H. E. Xu, W. Yi, *Adv. Synth. Catal.* **2014**, *356*, 137; u) H. Zhang, D. Liu, C. Chen, C. Liu, A. Lei, *Chem. Eur. J.* **2011**, *17*, 9581.

[5] For C–C bond formations, see: a) N. Chatani, S. Yorimitsu, T. Asaumi, F. Kakiuchi, S. Murai, *J. Org. Chem.* **2002**, *67*, 7557; b) Z. Shi, B. Li, X. Wan, J. Cheng, Z. Fang, B. Cao, C. Qin, Y. Wang, *Angew. Chem. Int. Ed.* **2007**, *46*, 5554; *Angew. Chem.* **2007**, *119*, 5650; c) T. Nishikata, A. R. Abela, S. Huang, B. H. Lipshutz, *J. Am. Chem. Soc.* **2010**, *132*, 4978; d) L. Jiao, M. Oestreich, *Chem. Eur. J.* **2013**, *19*, 10845; e) S. R. Neufeldt, C. K. Seigerman, M. Sanford, *Org. Lett.* **2013**, *15*, 2302; f) B. Urones, R. G. Arrays, J. C. Carretero, *Org. Lett.* **2013**, *15*, 1120; g) L. Jiao, M. Oestreich, *Org. Lett.* **2013**, *15*, 5374; h) Z. Song, R. Samanta, A. P. Antonchick, *Org. Lett.* **2013**, *15*, 5662; i) S. Pan, T. Wakaki, N. Ryu, T. Shibata, *Chem. Asian J.* **2014**, *9*, 1257; j) S. Pan, N. Ryu, T. Shibata, *Adv. Synth. Catal.* **2014**, *356*, 929.

[6] For a C–N bond formation, see: C. Pan, A. Abdukader, J. Han, Y. Cheng, C. Zhu, *Chem. Eur. J.* **2014**, *20*, 3606.

[7] For Rh-catalyzed arene C–H amidations, see: a) J. Y. Kim, S. H. Park, J. Ryu, S. H. Cho, S. H. Kim, S. Chang, *J. Am. Chem. Soc.* **2012**, *134*, 9110; b) J. Shi, B. Zhou, Y. Yang, Y. Li, *Org. Biomol. Chem.* **2012**, *10*, 8953; c) J. Ryu, K. Shin, S. H. Park, J. Y. Kim, S. Chang, *Angew. Chem. Int. Ed.* **2012**, *51*, 9904; *Angew. Chem.* **2012**, *124*, 10042; d) D. G. Yu, M. Suri, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 8802; e) B. Zhou, Y. Yang, J. Shi, H. Feng, Y. Li, *Chem. Eur. J.* **2013**, *19*, 10511; f) S. H. Park, J. Kwak, K. Shin, J. Ryu, Y. Park, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 2492; for Ru-catalyzed C–H amidations, see: g) V. S. Thirunavukkarasu, K. Raghuvanshi, L. Ackermann, *Org. Lett.* **2013**, *15*, 3286; h) J. Kim, S. Chang, *Chem. Eur. J.* **2013**, *19*, 7328; i) M. R. Yadav, R. K. Rit, A. K. Sahoo, *Org. Lett.* **2013**, *15*, 1638; j) Q.-Z. Zheng, Y.-F. Liang, C. Qin, N. Jiao, *Chem. Commun.* **2013**, *49*, 5654; for Ir-catalyzed amidations, see: k) J. Ryu, J. Kwak, K. Shin, D. Lee, S. Chang, *J. Am. Chem. Soc.* **2013**, *135*, 12861; l) J. Kim, S. Chang, *Angew. Chem. Int. Ed.* **2014**, *53*, 2203. During the preparation of this manuscript, Chang's group reported the same transformation by using a similar catalytic system. For details, see: K. Shin, S. Chang, *J. Org. Chem.* **2014**, DOI: 10.1021/jo5018475.

[8] No desired amidated product was observed by using Zhu's conditions. For details, see ref.[6]



[9] a) D. L. Davies, S. M. A. Donald, O. Al-Duaij, S. A. Macgregor, M. Pölleth, *J. Am. Chem. Soc.* **2006**, *128*, 4210; b) L. Li, W. W. Brennessel, W. D. Jones, *J. Am. Chem. Soc.* **2008**, *130*, 12414; c) L. Li, W. W. Brennessel, W. D. Jones, *Organometallics* **2009**, *28*, 3492.

Received: October 15, 2014
Published Online: November 27, 2014