Published in final edited form as:

Angew Chem Int Ed Engl. 2014 September 1; 53(36): 9603–9607. doi:10.1002/anie.201405035.

N-Heterocyclic Carbene-Catalyzed Synthesis of 2-Aryl Indoles

M. Todd Hovey, Christopher T. Check, Alexandra F. Sipher, and Karl A. Scheidt*

Department of Chemistry Center for Molecular Innovation and Drug Discovery, Northwestern University, 2145 Sheridan Road, Evanston, IL 60208 (USA)

Keywords

cooperative catalysis; asymmetric synthesis; N-heterocyclic carbene

The indole nucleus is the most common heterocycle found in nature.^[1] Many indole-containing compounds possess potent biological activity, which has earned this structural core the description of “privileged” in therapeutic discovery. Beginning with Möhlau^[2] and Fischer,^[3] the indole has captured the attention of the chemical community since the late 19th century.^[4] Historically, the most common method is the Fischer indole synthesis, but this reaction can be limited in scope due to the stability of the hydrazine component, preparation of aryl hydrazines, and strong acidic conditions.^[3,5] The Bischler-Möhlau synthesis of 2-aryl indoles usually requires high temperatures that can lead to low yields and regiochemistry problems.^[6] To enable new strategies to access this key heterocycle, modern chemical research has focused on transition metal-catalyzed approaches (Scheme 1).^[7] For example, the Larock indole synthesis and Suzuki coupling strategies have enabled the synthesis of previously inaccessible indole scaffolds, with more recent work describing a copper-catalyzed arylation of indoles.^{[8]a,b} While greatly expanding access to diverse indole structures, these methods use metal catalysts which can contaminate the desired products with difficult to remove toxic-metal impurities or require potentially expensive starting materials (such as alkynes and prefunctionalized indoles).^{[8]c-e} Given these requirements, metal-free approaches with broad scope and easily accessible precursors could provide new and complimentary routes to indole structures. With this goal, we set out to develop an organocatalytic indole synthesis by harnessing *Umpolung* reactivity.^[9] In particular, N-heterocyclic carbenes (NHCs) have emerged as powerful Lewis base catalysts to construct a vast array of carbocyclic, heterocyclic, and polycyclic compounds.^[10] Herein, we report a convergent synthesis of 2-aryl indoles promoted by NHC catalysis under mild conditions.^[11]

Reaction Plan: A review of the relevant literature identified several indole syntheses that intercepted 2'-aminobenzyl ketone **1a** (Scheme 1).^[12] The synthesis of this intermediate usually arises from acylation of a benzylic anion with subsequent reduction of the nitro moiety to promote C–N bond formation. In contrast, we surmised that this strategic ketone (**1a**) could be accessed in a conceptually distinct manner through an *Umpolung*

[*] scheidt@northwestern.edu.

Supporting information for this article is available on the Web under <http://www.angewandte.org> or from the author.

disconnection from acyl-anion equivalent **1b** and transient aza-*ortho*-quinone methide (Ao-QM) **1c** reaction partners.^{[13],[14]} Several strategies to generate and intercept Ao-QMs have been reported, including photochemical fragmentation,^[15] fluoride induced elimination of ammonium salts,^[16] pyrolysis of *o*-hydroxymethyl anilines,^[17] and Brønsted base-induced elimination.^[18]

A base elimination strategy would allow for direct access from numerous commercially available, substituted anthranilic acids in 2-3 steps (see Supp. Info. for details). Ultimately, the success of our approach would rely on concomitant generation of the Ao-QM and the NHC catalyst using a single Brønsted base species along with balancing the concentrations of each reactive intermediate during the course of the reaction (i.e., **1b** and **1c**).^[19]

Additionally, it was undetermined if the Lewis basic NHC catalyst would directly trap a reactive electrophile **1c**. Initial experiments with benzyl chloride **2** and benzaldehyde in the presence of precatalysts **A** or **B** with DBU yielded the desired ketone **3** in moderate to low yield (Table 1, entry 1-2). Under these reaction conditions, no other triazolium or imidazolium NHC precursor gave appreciable yield (>10 %) of the desired ketone **3**. Thorough investigation revealed the formation of unproductive adducts between nucleophilic bases (e.g., DBU, Et₃N) and chloride **2**. In turn, an exhaustive screen of azolium precatalysts and solvents with non-nucleophilic cesium carbonate as base was undertaken. These experiments revealed that 30 mol % of azolium **B** in chloroform afforded the highest yield of ketone **3**, 10 equiv. of aldehyde was required (entry 3).

The promising yields obtained with azoliums **A** and **B** prompted us to explore several new *N*-aryl thiazoliums prepared with the 2,6-diethylphenyl moiety, which has been shown to increase catalyst performance.^{[20],[21]} Gratifyingly, thiazolium **C** afforded ketone **3** in 82% isolated yield in THF (entry 4). Notably, the replacement of benzaldehyde with benzoin **D** furnished the ketone in similar yield, providing evidence for the reversibility of the benzoin condensation under these conditions (entry 5). Importantly, the ability to cycle this undesired Umpolung product back into the desired reaction allows for less aldehyde substrate (i.e., 1.2 equiv) than typical intermolecular acyl anion reactions.^{[22],[23]} Further improvement in yield was achieved by reducing the equivalents of benzaldehyde and cesium carbonate (entry 6-7).

With optimized conditions for the NHC/Ao-QM synthesis of ketone **3** developed, the *in situ* dehydration to prepare 2-aryl indole **4** was explored. The exposure of isolated ketone **3** to TFA in dichloromethane delivered the desired *N*-Boc indole in nearly quantitative yield (5 min, 96%). Unfortunately, the direct addition of TFA or other organic acids to the reaction mixture did not produce the desired results. Based on the results with TFA, it was clear that the Lewis basicity of the solvent played a key role in the dehydration step. In order to streamline the indole synthesis to a single flask operation, many ethereal solvents and organic acids were evaluated. With gratification, 1,4-dioxane mediated the NHC-catalyzed ketone synthesis as well as the acid promoted dehydration. The addition of methanesulfonic acid promoted *in situ* dehydration of ketone **3** to the desired indole **4** (entry 8). Attempts to optimize further by reducing the precatalyst loading or by increasing reaction temperature reduced the overall yield (entry 9 & 10). The use of other bases, such as potassium carbonate, showed minimal conversion (entry 11).

With efficient single-flask conditions identified for the synthesis of 2-aryl indoles, we surveyed the scope of this transformation (Table 2). Aryl aldehydes with electron-withdrawing or donating groups in the *para*-position were tolerated, giving rise to the corresponding indoles in good to excellent yield (**4a-4g**). Furthermore, *meta*-substituted aryl aldehydes possessing electron-withdrawing and donating groups were accommodated under the reaction conditions, affording indoles **4h-4k** in high yield.

Indoles **4c** and **4i** were isolated in higher yield when the reaction was conducted at an elevated temperature (50 °C). Synthesis of indole **4i** is noteworthy because it has never been prepared to date (N-Boc or N-H) and transition metal catalyzed strategies should prove difficult due to competing insertion reactions.^[24] The yield of indole **4h** was significantly improved by increasing the amount of aryl aldehyde (2.2 equiv). At this time, reactions with *ortho*-substituted aryl aldehydes provide recovery of unreacted starting materials or low conversion to the intermediate ketone.^[22] Either production of the nucleophilic Breslow intermediate (**1b**) is slow and/or disfavored due to destabilizing interactions or once formed, the strain engendered promotes a conformational change placing the aryl ring orthogonal to the enol thiazolium system, thus sterically encumbering the nucleophilic acyl anion carbon (eq 1). Investigation of heteroaryl-aldehydes produced indoles containing 2-naphthyl (**4l**), pyridyl (**4m**), and thiophenyl (**4n**) C-2 substitutions. Aliphatic aldehydes (**4o**) showed only minimal activity with azolium **B** and no activity with **C**.

The tolerance of functionality and substitution on the amino-benzyl chloride **2**, was also investigated. Both electron-withdrawing and electron-donating groups were tolerated at the C-4, C-5, C-6 positions affording indoles **4p-4z** in moderate to high yield. The low yield observed for **4z** was due to rapid decomposition of the starting material under the reactions conditions. Attempts to prepare indoles with substitution at C-7 proved unproductive, with only recovered starting material or decomposition at elevated reaction temperatures (50 °C) observed. Initial data suggests that *ortho* substitution of benzylic chlorides (**2**) impedes the deprotonation necessary for *Ao*-QM formation and approaches to circumvent this are currently being investigated. Lastly, substitution at the C-3 position gave access to indole **4aa** in 91% isolated yield.

2-Aryl-indoles have gained increased attention for their potential in therapeutic development.^[1c,1d] To directly demonstrate the practicality of this new indole synthesis, we synthesized a reported pharmacologically active 2-aryl-indole. Recent work by Exelixis showed that several 2-aryl-indoles are potent c-Kit kinase inhibitors (N-H and N-Boc indoles reported with IC₅₀ of 0.5–5.0 μmol, Scheme 2).^[25] In their approach, the synthesis of **7** relied on the use of a palladium catalyzed cross-coupling with a prefunctionalized indole boronic acid to construct the target in six steps overall. Our approach began from commercially available aniline **5**. A two-step amide formation and phenol alkylation yielded

aldehyde **6** in 95% yield. Employing our optimized conditions to a mixture of aldehyde **6** and aniline **2** gave heterocycle **7** in 83% yield. The route is unique in that only one chromatographic purification is required from benzyl chloride **2**. In contrast, the reported proprietary synthesis required 6 steps and a Suzuki coupling involving 10 mol % Pd to furnish the C-2 arylated indole.

In conclusion, a highly efficient, Umpolung synthesis of 2-aryl indoles using organocatalysis has been developed. The synthesis of a 2,6-diethylphenyl substituted thiazolium-derived NHC and modulation of the Lewis basicity of the solvent are necessary to access the indoles in high yield in a single flask operation. To the best of our knowledge, this represents the first indole synthesis facilitated by NHC catalysis. This new approach to these privileged heterocycles is operationally straightforward and provides for the incorporation of a wide range of aryl groups at the indole 2-position in good to excellent yield. Substitution around the indole nucleus is also well tolerated with the exception of C2' on the aryl group derived from the aldehyde reactant. In order to demonstrate the utility of this new approach, a known pharmaceutical intermediate was synthesized rapidly without transition metals, cryogenic temperatures, or strong bases. The application of this transformation in therapeutic endeavors and the leveraging of the basic conditions used to access active carbene catalysts for the production of reactive electrophiles in new bond forming processes are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

[**] Financial support has been generously provided by the NIH (R01-GM073072). A.F.S. thanks Northwestern University for a Summer Undergraduate Research Grant. We thank Michael Wang (NU) for providing X-ray crystallography support (NU).

References

- [1]. a) Kawasaki T, Higuchi K. *Nat. Prod. Rep.* 2005; 22:761–793. [PubMed: 16311634] b) Kochanowska-Karamyan AJ, Hamann MT. *Chem. Rev.* 2010; 110:4489–4497. [PubMed: 20380420] c) Lal S, Snape TJ. *Curr. Med. Chem.* 2012; 19:4828–4837. [PubMed: 22830349] d) Kaushik NK, Kaushik N, Attri P, Kumar N, Kim CH, Verma AK, Choi EH. *Molecules.* 2013; 18:6620–6662. [PubMed: 23743888]
- [2]. Möhlau R. *Chem. Ber.* 1881; 14:171–175.
- [3]. a) Fischer E, Jourdan F. *Chem. Ber.* 1883; 16:2241–2245. b) Fischer E, Hess O. *Chem. Ber.* 1884; 17:559–568.
- [4]. a) Gilchrist TL. *J. Chem. Soc., Perkin Trans.* 2001; 1:2491–2515. b) Cacchi S, Fabrizi G. *Chem. Rev.* 2005; 105:2873–2920. [PubMed: 16011327] c) Humphrey GR, Kuethe JT. *Chem. Rev.* 2006; 106:2875–2911. [PubMed: 16836303] d) Bandini M, Eichholzer A. *Angew. Chem. Int. Ed.* 2009; 48:9608–9644. e) Taber DF, Tirunahari PK. *Tetrahedron.* 2011; 67:7195–7210. f) Platon M, Amardeil R, Djakovitch L, Hierso J-C. *Chem. Soc. Rev.* 2012; 41:3929–3968. [PubMed: 22447100] g) Lebrasseur, N.; Larrosa, I. *Recent Advances in the C2 and C3 Regioselective Direct Arylation of Indoles.* Vol. 105. Elsevier Inc.; 2012. h) Inman M, Moody CJ. *Chem. Sci.* 2013; 4:29–41.
- [5]. a) Chen, C.-y.; Senanayake, CH.; Bill, TJ.; Larsen, RD.; Verhoeven, TR.; Reider, PJ. *J. Org. Chem.* 1994; 59:3738–3741. b) Haag BA, Zhang Z-G, Li J-S, Knochel P. *Angew. Chem. Int. Ed.* 2010; 49:9513–9516. c) Müller S, Webber MJ, List B. *J. Am. Chem. Soc.* 2011; 133:18534–

18537. [PubMed: 22044311] d) Inman M, Carbone A, Moody CJ. *J. Org. Chem.* 2011; 77:1217–1232. [PubMed: 21977901] e) Kuznetsov A, Makarov A, Rubtsov AE, Butin AV, Gevorgyan V. *J. Org. Chem.* 2013; 78:12144–12153. [PubMed: 24255969]

- [6]. a) Sridharan V, Perumal S, Avendaño C, Menéndez JC. *Synlett.* 2006:91–95. b) Vara Y, Aldaba E, Arrieta A, Pizarro JL, Arriortua MI, Cossío FP. *Org. Biomol. Chem.* 2008; 6:1763–1772. [PubMed: 18452011]
- [7]. a) Wagaw S, Yang BH, Buchwald SL. *J. Am. Chem. Soc.* 1999; 121:10251–10263. For reviews see refs 4(b), 4(f), and 4(g). For selected examples of transition metal-catalyzed indole syntheses, see: b) Takeda A, Kamijo S, Yamamoto Y. *J. Am. Chem. Soc.* 2000; 122:5662–5663. c) Barluenga J, Trincado M, Rubio E, González JM. *Angew. Chem. Int. Ed.* 2003; 42:2406–2409. d) Campos KR, Woo JCS, Lee S, Tillyer RD. *Org. Lett.* 2003; 6:79–82. [PubMed: 14703355] e) Saito K, Kanno A, Hanzawa Y. *Angew. Chem. Int. Ed.* 2007; 46:3931–3933. f) Trost BM, McClory A. *Angew. Chem. Int. Ed.* 2007; 46:2074–2077. g) Cariou K, Ronan B, Mignani S, Fensterbank L, Malacria M. *Angew. Chem. Int. Ed.* 2007; 46:1881–1884. h) Barluenga J, Jiménez-Aquino A, Valdés C, Aznar F. *Angew. Chem. Int. Ed.* 2007; 46:1529–1532. i) Stuart DR, Bertrand-Laperle M. g. Burgess KMN, Fagnou K. *J. Am. Chem. Soc.* 2008; 130:16474–16475. [PubMed: 19554684] j) Würtz S, Rakshit S, Neumann JJ, Dröge T, Glorius F. *Angew. Chem. Int. Ed.* 2008; 47:7230–7233. k) Shen M, Leslie BE, Driver TG. *Angew. Chem. Int. Ed.* 2008; 47:5056–5059. l) Shi Z, Zhang C, Li S, Pan D, Ding S, Cui Y, Jiao N. *Angew. Chem. Int. Ed.* 2009; 48:4572–4576. m) Bernini R, Fabrizi G, Sferrazza A, Cacchi S. *Angew. Chem. Int. Ed.* 2009; 48:8078–8081. n) Stuart DR, Alsabeh P, Kuhn M, Fagnou K. *J. Am. Chem. Soc.* 2010; 132:18326–18339. [PubMed: 21133376] o) Stokes BJ, Liu S, Driver TG. *J. Am. Chem. Soc.* 2011; 133:4702–4705. [PubMed: 21401042] p) Sun K, Liu S, Bec PM, Driver TG. *Angew. Chem. Int. Ed.* 2011; 50:1702–1706. q) Cacchi S, Fabrizi G, Goggiani A, Molinaro C, Verdiglione R. *J. Org. Chem.* 2014:401–407. [PubMed: 24308283]
- [8]. a) Larock RC, Yum EK. *J. Am. Chem. Soc.* 1991; 113:6689–6690. b) Phipps RJ, Grimster NP, Gaunt MJ. *J. Am. Chem. Soc.* 2008; 130:8172–8174. [PubMed: 18543910] c) Garrett CE, Prasad K. *Adv. Synth. Catal.* 2004; 346:889–900. For a review on toxic-metal impurity removal, see: d) Rosso VW, Lust DA, Bernot PJ, Grosso JA, Modi SP, Rusowicz A, Sedergran TC, Simpson JH, Srivastava SK, Humora MJ, Anderson NG. *Org. Process Res. Dev.* 1997; 1:311–314. For palladium contamination in Larock syntheses, see: For examples of non-commercially available alkynes in Larock indole syntheses, see ref 4(c) and references therein.
- [9]. a) Seayad J, List B. *Org. Biomol. Chem.* 2005; 3:719–724. [PubMed: 15731852] b) Erkkilä A, Majander I, Pihko PM. *Chem. Rev.* 2007; 107:5416–5470. [PubMed: 18072802] c) Wurz RP. *Chem. Rev.* 2007; 107:5570–5595. [PubMed: 18072804] d) Mukherjee S, Yang JW, Hoffmann S, List B. *Chem. Rev.* 2007; 107:5471–5569. [PubMed: 18072803] e) MacMillan DWC. *Nature.* 2008; 455:304–308. [PubMed: 18800128]
- [10]. a) Nair V, Bindu S, Sreekumar V. *Angew. Chem. Int. Ed.* 2004; 43:5130–5135. b) Enders D, Niemeier O, Henseler A. *Chem. Rev.* 2007; 107:5606–5655. [PubMed: 17956132] c) Marion N, Díez-González S, Nolan SP. *Angew. Chem. Int. Ed.* 2007; 46:2988–3000. d) Nair V, Vellalath S, Babu BP. *Chem. Soc. Rev.* 2008; 37:2691–2698. [PubMed: 19020682] e) Phillips EM, Chan A, Scheidt KA. *Aldrichimica Acta.* 2009; 42:55–66. [PubMed: 21072130] f) Nair V, Menon RS, Biju AT, Sinu CR, Paul RR, Jose A, Sreekumar V. *Chem. Soc. Rev.* 2011; 40:5336–5346. [PubMed: 21776483] g) Bugaut X, Glorius F. *Chem. Soc. Rev.* 2012; 41:3511–3522. [PubMed: 22377957] h) Vora HU, Wheeler P, Rovis T. *Adv. Synth. Catal.* 2012:1617–1639. [PubMed: 23538785] i) Douglas J, Churchill G, Smith A. *Synthesis.* 2012; 44:2295–2309. j) De Sarkar S, Biswas A, Samanta RC, Studer A. *Chem.—Eur. J.* 2013; 19:4664–4678. [PubMed: 23436489] k) Ryan SJ, Candish L, Lupton DW. *Chem. Soc. Rev.* 2013; 42:4906–4917. [PubMed: 23403488]
- [11]. List and coworkers reported an organo-phosphoric acid catalyzed asymmetric Fischer indole synthesis in 2011, see ref 5(d)
- [12]. Reissert A. *Chem. Ber.* 1897; 30:1030–1053.
- [13]. a) Stetter H, Landscheidt A. *Chem. Ber.* 1979; 112:2419–2422. b) Stetter H, Basse W, Nienhaus J. *Chem. Ber.* 1980; 113:690–698. c) Mattson AE, Bharadwaj AR, Scheidt KA. *J. Am. Chem. Soc.* 2004; 126:2314–2315. [PubMed: 14982429]
- [14]. a) Li Y, Shi F-Q, He Q-L, You S-L. *Org. Lett.* 2009; 11:3182–3185. Selected recent examples of NHC acyl-anion equivalents reacting with unconventional electrophiles, see: [PubMed:

- 19580259] b) Toh QY, McNally A, Vera S, Erdmann N, Gaunt MJ. J. Am. Chem. Soc. 2013; 135:3772–3775. [PubMed: 23445238] c) Lin L, Li Y, Du W, Deng W-P. Tetrahedron Lett. 2010; 51:3571–3574. For a related, yet *non*-catalytic, NHC-mediated acyl anion addition to primary benzyl halides, see: d) Padmanaban M, Biju AT, Glorius F. Org. Lett. 2011; 13:98–101. For catalytic addition of NHC-mediated acyl anions to benzylic/activated alkyl halides, see: [PubMed: 21117622]
- [15]. a) Burgess EM, McCullagh L. J. Am. Chem. Soc. 1966; 88:1580–1581. [PubMed: 5914530] b) Ikeda M, Matsugashita S, Tabusa F, Ishibashi H, Tamura Y. J. Chem. Soc., Chem. Commun. 1975:575–576. c) Lancaster M, Smith DJH. J. Chem. Soc., Chem. Commun. 1980:471–472. d) Wojciechowski K. Tetrahedron. 1993; 49:7277–7286.
- [16]. Ito Y, Miyata S, Nakatsuka M, Saegusa T. J. Am. Chem. Soc. 1981; 103:5250–5251.
- [17]. a) Bowen RD, Davies DE, Fishwick CWG, Glasbey TO, Noyce SJ, Storr RC. Tetrahedron Lett. 1982; 23:4501–4504. b) Foresti E, Spagnolo P, Zanirato P. J. Chem. Soc., Perkin Trans. 1989; 1:1354–1356. c) Lau CK, Trimble L, Caille AS, Wiebe JM. Tetrahedron. 1996; 52:11705–11724. d) Nishiyama K, Kubo H, Sato T, Higashiyama K, Ohmiya S. Heterocycles. 1998; 48:1103–1106.
- [18]. a) Steinhagen H, Corey EJ. Angew. Chem. Int. Ed. 1999; 38:1928–1931. b) Avemaria F, Vanderheiden S, Bräse S. Tetrahedron. 2003; 59:6785–6796. c) Yang Q-Q, Xiao C, Lu L-Q, An J, Tan F, Li B-J, Xiao W-J. Angew. Chem. Int. Ed. 2012; 51:9137–9140. d) Yang Q-Q, Wang Q, An J, Chen J-R, Lu L-Q, Xiao W-J. Chem.—Eur. J. 2013; 19:8401–8404. [PubMed: 23670915]
- [19]. a) Mattson AE, Scheidt KA. J. Am. Chem. Soc. 2007; 129:4508–4509. [PubMed: 17378561] b) Lv H, You L, Ye S. Adv. Synth. Catal. 2009; 351:2822–2826. c) Izquierdo J, Orue A, Scheidt KA. J. Am. Chem. Soc. 2013; 135:10634–10637. [PubMed: 23829462] d) Lv H, Jia W-Q, Sun L-H, Ye S. Angew. Chem. Int. Ed. 2013; 52:8607–8610.
- [20]. a) Vougioukalakis GC, Grubbs RH. J. Am. Chem. Soc. 2008; 130:2234–2245. [PubMed: 18220390] b) Piel I, Pawelczyk MD, Hirano K, Fröhlich R, Glorius F. Eur. J. Org. Chem. 2011; 2011:5475–5484.
- [21]. a) Cardinal-David B, Raup DEA, Scheidt KA. J. Am. Chem. Soc. 2010; 132:5345–5347. [PubMed: 20345186] b) Raup DEA, Cardinal-David B, Holte D, Scheidt KA. Nat. Chem. 2010; 2:766–771. [PubMed: 20729898]
- [22]. a) O'Toole SE, Rose CA, Gundala S, Zeitler K, Connon SJ. J. Org. Chem. 2011; 76:347–357. For recent examples documenting/discussing this effect, see: [PubMed: 20977280] b) Rose C, Gundala S, Connon S, Zeitler K. Synthesis. 2011:190–198. c) Rose CA, Gundala S, Fagan C-L, Franz JF, Connon SJ, Zeitler K. Chem. Sci. 2012; 3:735–740.
- [23]. Decreased yields have been observed in NHC acyl anion chemistry with benzoin as the starting material, see ref 14(d)
- [24]. A Reaxys substructure search yielded no results for multiple iterations
- [25]. Cheng, W.; Co, EW.; Kim, MH.; Klein, RR.; Le, DT.; Lew, A.; Nuss, JM.; Xu, W.; Bajjalieh, W. c-Kit Modulators and Methods of Use. Mar 10. 2005 WIPO. WO 2005/020921 A2

Selected approaches to indoles: Metals or strong base required

Larock

Suzuki

Gaunt

Reissert

Umpolung approach: this work

Scheme 1.
2-Aryl indole strategies.

Scheme 2.
 Improved Synthesis of c-Kit Kinase Inhibitor **7** [a]
 [a] See Supporting Information for details.

Table 1

Optimization of Reaction Conditions.

entry	NHC	base (equiv)	PhCHO (equiv)	solvent	yield 3 ^[a]	yield 4 ^[a]
1	A	DBU (1.5)	1.5	THF	19 ^[b]	--
2	B	DBU (1.5)	1.5	THF	35 ^[b]	-
3 ^[c]	B	Cs ₂ CO ₃ (2.5)	10	CHCl ₃	60	--
4	C	Cs ₂ CO ₃ (2.5)	1.5	THF	82	--
5	C	Cs ₂ CO ₃ (2.5)	1.0 ^[d]	THF	80	--
6	C	Cs ₂ CO ₃ (2.5)	1.2	THF	86	--
7	C	Cs ₂ CO ₃ (1.2)	1.2	THF	88	--
8 ^[e]	C	Cs ₂ CO ₃ (1.2)	1.2	1,4-dioxane	--	82
9 ^{[e],[f]}	C	Cs ₂ CO ₃ (1.2)	1.2	1,4-dioxane	--	56
10 ^{[e],g}	C	Cs ₂ CO ₃ (1.2)	1.2	1,4-dioxane	--	61
11	C	K ₂ CO ₃ (3.0)	1.2	1,4-dioxane	31 ^[h]	--

A	B	C	D

^[a] Isolated yield.^[b] Determined by ¹H NMR spectroscopy (500 MHz) with 1,3,5-trimethoxybenzene as internal standard.^[c] 30 mol % azolium.^[d] Benzoin **D** used in place of benzaldehyde.^[e] After 36 h, 6.5 equiv MsOH was added.^[f] 10 mol % azolium.

^gReaction conducted at 50 °C.

^[h]Conversion after 36 h.

Table 2

Substrate Scope ^[a]

[b] Reaction conducted at 50 °C.

[c] 2.2 equiv of aryl aldehyde.

[d] Deacylation occurred prior to dehydration over 12 h.

[e] Isolated as a 5:4 mixture of *N*-Boc/*N*-H indole.[f] 20 mol % **B**.

[g] Starting material decomposes rapidly.

^[a] See Supporting Information for details. Reactions conducted on 0.32 mmol scale. Yields are of isolated product after column chromatography.