NHC Catalysis

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

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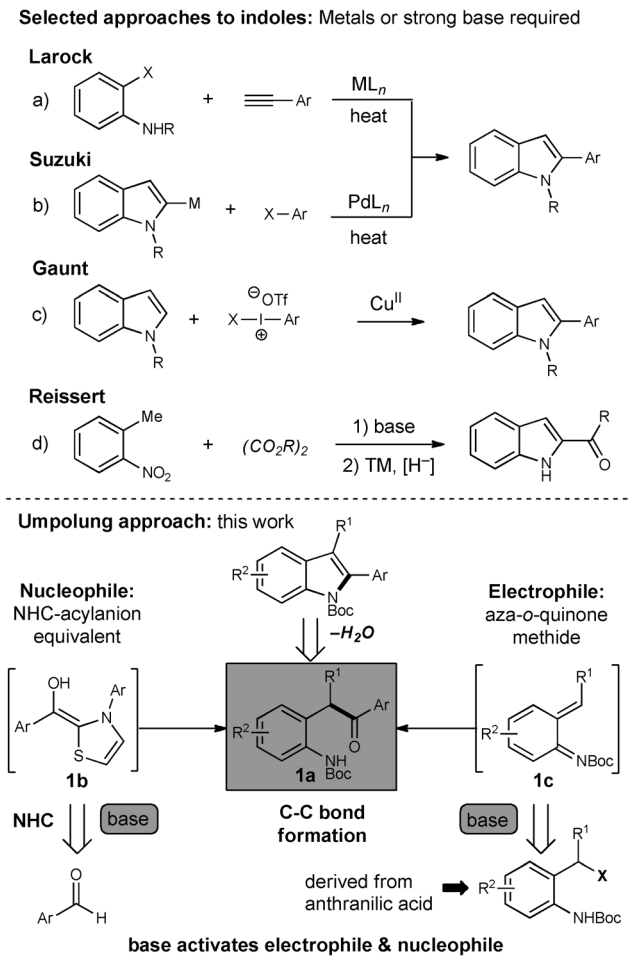
Abstract: *A convergent and efficient transition-metal-free catalytic synthesis of 2-aryl-indoles has been developed. The interception of a highly reactive and transient aza-ortho-quinone methide by an acyl anion equivalent generated through N-hetereocyclic carbene catalysis is central to this successful strategy. High yields and a wide scope as well as the streamlined synthesis of a kinase inhibitor are reported.*

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 develop 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, and more recent work describes the copper-catalyzed arylation of indoles.[8a,b] Although greatly expanding the access to diverse indole structures, these methods use metal catalysts, which can contaminate the desired products with toxic metal impurities, or require potentially expensive starting materials (such as alkynes and prefunctionalized indoles).[8c–e] Given these requirements, metal-free approaches with a 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]



Scheme 1. Strategies for the synthesis of 2-aryl-indoles.

A review of the relevant literature identified several indole syntheses that intercepted 2′-aminobenzylic ketone **1a** (Scheme 1).[12] The synthesis of this intermediate usually proceeds through the acylation of a benzylic anion, followed by 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 disconnection from acyl anion equivalent **1b** and transient aza-*ortho*-quinone methide (A*o*-QM) **1c**.[13,14] Several strategies to generate and intercept A*o*-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]

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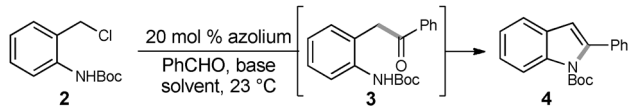
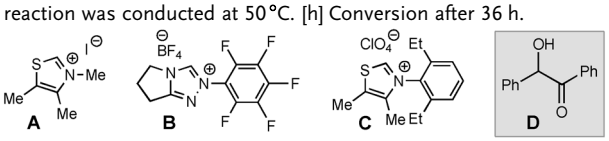
A base elimination strategy would allow for direct access from numerous commercially available, substituted anthranilic acid derivatives in 2–3 steps (see the Supporting Information for details). Ultimately, the success of our approach would rely on the concomitant generation of the A*o*-QM and the NHC catalyst using a single Brønsted base 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 (1,8-diazabicyclo[5.4.0]undec-7-ene) yielded the desired ketone **3** in moderate to low yield (Table 1, entries 1 and 2). Under

Table 1: Optimization of the 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_2CO_3 (2.5)	10	$CHCl_3$	60	–
4	**C**	Cs_2CO_3 (2.5)	1.5	THF	82	–
5	**C**	Cs_2CO_3 (2.5)	1.0[d]	THF	80	–
6	**C**	Cs_2CO_3 (2.5)	1.2	THF	86	–
7	**C**	**Cs_2CO_3 (1.2)**	**1.2**	**THF**	**88**	–
8[e]	**C**	**Cs_2CO_3 (1.2)**	**1.2**	**1,4-dioxane**	–	**82**
9[e,f]	**C**	Cs_2CO_3 (1.2)	1.2	1,4-dioxane	–	56
10[e,g]	**C**	Cs_2CO_3 (1.2)	1.2	1,4-dioxane	–	61
11	**C**	K_2CO_3 (3.0)	1.2	1,4-dioxane	31[h]	–

[a] Yield of the isolated product. [b] Determined by ^{1}H NMR spectroscopy (500 MHz) with 1,3,5-trimethoxybenzene as internal standard. [c] 30 mol% azolium. [d] Benzoin **D** used instead of benzaldehyde. [e] After 36 h, 6.5 equiv MsOH was added. [f] 10 mol% azolium. [g] The reaction was conducted at 50 °C. [h] Conversion after 36 h.



these reaction conditions, no other triazolium or imidazolium NHC precursor gave appreciable yield (>10%) of the desired ketone **3**. Thorough investigations revealed the formation of unproductive adducts between nucleophilic bases (e.g., DBU, Et_3N) and chloride **2**. In turn, an exhaustive screen of azolium precatalysts and solvents with non-nucleophilic cesium carbonate as base was undertaken. These experiments showed that 30 mol% of azolium **B** in chloroform afforded the highest yield of ketone **3**, however, 10 equiv of aldehyde was required (entry 3).

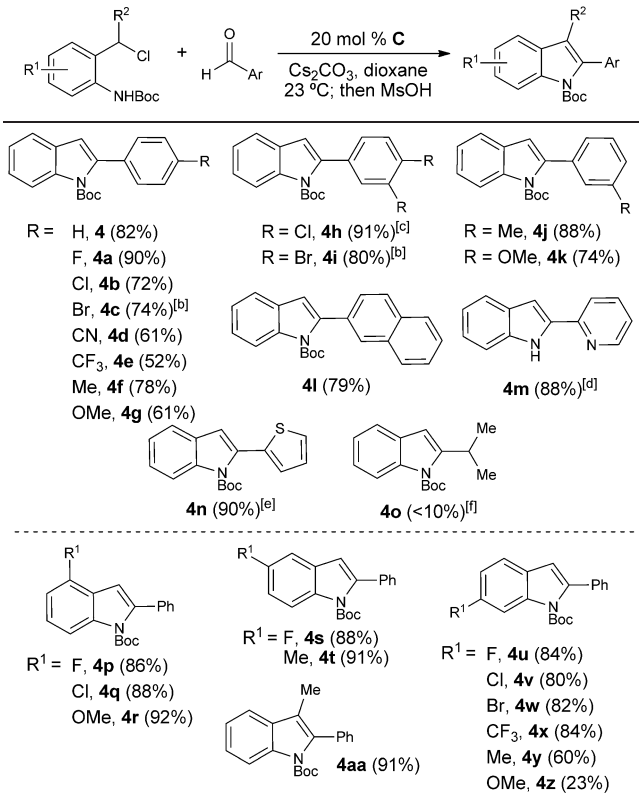
The promising yields obtained with azoliums **A** and **B** prompted us to explore several new *N*-aryl thiazoliums prepared with the 2,6-diethylphenyl moiety, which has been shown to increase catalyst performance.[20,21] Gratifyingly, thiazolium **C** in THF afforded the isolated ketone **3** in 82% yield (entry 4). Notably, the replacement of benzaldehyde with benzoin **D** furnished the ketone in a 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 (entries 6 and 7).

With optimized conditions for the NHC/A*o*-QM synthesis of ketone **3** in hand, the in situ dehydration for the preparation of 2-aryl-indole **4** was explored. The exposure of the 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. To streamline the indole synthesis to a single flask operation, many ethereal solvents and organic acids were evaluated. We found that 1,4-dioxane mediated the NHC-catalyzed ketone synthesis as well as the acid promoted dehydration. The addition of methanesulfonic acid promoted the in situ dehydration of ketone **3** to the desired indole **4** (entry 8). Attempts to further optimize the conditions by reducing the precatalyst loading or by increasing the reaction temperature were unsuccessful and rather reduced the overall yield (entries 9 and 10). The use of other bases, such as potassium carbonate, showed minimal conversion (entry 11).

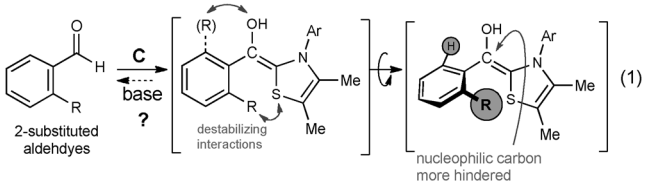
With efficient single-flask conditions identified for the synthesis of 2-aryl-indoles, we surveyed the scope of this transformation (Table 2). Aryl aldehydes with electron-withdrawing or -donating groups in the *para*-position were tolerated, giving rise to the corresponding indoles in good to excellent yield (**4a**–**4g**). Furthermore, *meta*-substituted aryl aldehydes with electron-withdrawing and -donating groups were also 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 performed at an elevated temperature (50 °C). The 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 higher when the amount of aryl aldehyde (2.2 equiv) was increased. At this time, reactions with *ortho*-substituted aryl aldehydes usually lead to the recovery of unreacted starting materials or low conversion to the intermediate ketone.[22] Either the production of the nucleophilic Breslow intermediate (**1b**) is slow and/or disfavored, because of destabilizing interactions, or, once formed, the engendered strain 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 with 2-naphthyl (**4l**), pyridyl (**4m**), and thiophenyl (**4n**) substituents at C-2. Aliphatic aldehydes (**4o**) showed only minimal activity with azolium **B** and no activity with **C**.

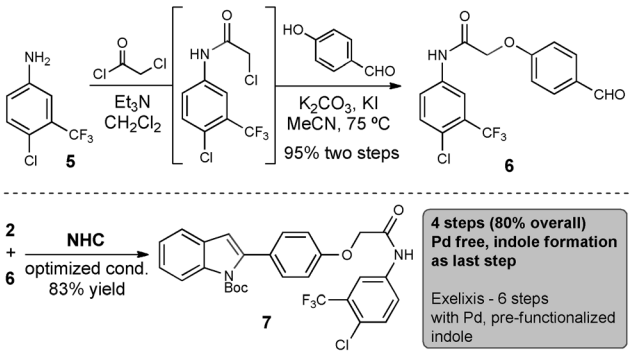
Table 2: Substrate scope.[a]



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



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, and C-6 position affording indoles **4p**–**4z** in moderate to high yields. The low yield observed for **4z** was due to the rapid decomposition of the starting material under the reactions conditions. Attempts to prepare indoles with substitution at C-7 proved unproductive, and only recovered starting material or decomposition at elevated reaction temperatures (50 °C) was observed. Initial data suggests that o*rtho* substitution of benzylic chlorides **2** impedes the deprotonation necessary for A*o*-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.



Scheme 2. Improved synthesis of c-Kit kinase inhibitor **7**. See the Supporting Information for details.

2-Aryl-indoles have gained increased attention for their potential in therapeutic development.[1c,d] 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 IC_{50} values 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 pre-functionalized 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 six 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 allows 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 C-2′ on the aryl group derived from the aldehyde reactant. To demonstrate the utility of this new approach, a known pharmaceutical intermediate was synthesized rapidly without applying transition metals, cryogenic temperature, 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.

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[1] a) T. Kawasaki, K. Higuchi, *Nat. Prod. Rep.* **2005**, *22*, 761 – 793; b) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489 – 4497; c) S. Lal, T. J. Snape, *Curr. Med. Chem.* **2012**, *19*, 4828 – 4837; d) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma, E. H. Choi, *Molecules* **2013**, *18*, 6620 – 6662.

[2] R. Möhlau, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 171 – 175.

[3] a) E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241 – 2245; b) E. Fischer, O. Hess, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559 – 568.

[4] a) T. L. Gilchrist, *J. Chem. Soc. Perkin Trans. 1* **2001**, 2491 – 2515; b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873 – 2920; c) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875 – 2911; d) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786 – 9824; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608 – 9644; e) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195 – 7210; f) M. Platon, R. Amardeil, L. Djakovitch, J.-C. Hierso, *Chem. Soc. Rev.* **2012**, *41*, 3929 – 3968; g) N. Lebrasseur, I. Larrosa, *Recent Advances in the C2 and C3 Regioselective Direct Arylation of Indoles*, *Vol. 105*, Elsevier, Amsterdam, **2012**; h) M. Inman, C. J. Moody, *Chem. Sci.* **2013**, *4*, 29 – 41.

[5] a) C.-y. Chen, C. H. Senanayake, T. J. Bill, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *J. Org. Chem.* **1994**, *59*, 3738 – 3741; b) B. A. Haag, Z.-G. Zhang, J.-S. Li, P. Knochel, *Angew. Chem.* **2010**, *122*, 9703 – 9706; *Angew. Chem. Int. Ed.* **2010**, *49*, 9513 – 9516; c) S. Müller, M. J. Webber, B. List, *J. Am. Chem. Soc.* **2011**, *133*, 18534 – 18537; d) M. Inman, A. Carbone, C. J. Moody, *J. Org. Chem.* **2012**, *77*, 1217 – 1232; e) A. Kuznetsov, A. Makarov, A. E. Rubtsov, A. V. Butin, V. Gevorgyan, *J. Org. Chem.* **2013**, *78*, 12144 – 12153.

[6] a) V. Sridharan, S. Perumal, C. Avendaño, J. C. Menéndez, *Synlett* **2006**, 91 – 95; b) Y. Vara, E. Aldaba, A. Arrieta, J. L. Pizarro, M. I. Arriortua, F. P. Cossío, *Org. Biomol. Chem.* **2008**, *6*, 1763 – 1772.

[7] For reviews see Ref. [4b,f,g]. For selected examples of transition-metal-catalyzed indole syntheses, see: a) S. Wagaw, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 10251 – 10263; b) A. Takeda, S. Kamijo, Y. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 5662 – 5663; c) J. Barluenga, M. Trincado, E. Rubio, J. M. González, *Angew. Chem.* **2003**, *115*, 2508 – 2511; *Angew. Chem. Int. Ed.* **2003**, *42*, 2406 – 2409; d) K. R. Campos, J. C. S. Woo, S. Lee, R. D. Tillyer, *Org. Lett.* **2003**, *6*, 79 – 82; e) A. Saito, A. Kanno, Y. Hanzawa, *Angew. Chem.* **2007**, *119*, 4005 – 4007; *Angew. Chem. Int. Ed.* **2007**, *46*, 3931 – 3933; f) B. M. Trost, A. McClory, *Angew. Chem.* **2007**, *119*, 2120 – 2123; *Angew. Chem. Int. Ed.* **2007**, *46*, 2074 – 2077; g) K. Cariou, B. Ronan, S. Mignani, L. Fensterbank, M. Malacria, *Angew. Chem.* **2007**, *119*, 1913 – 1916; *Angew. Chem. Int. Ed.* **2007**, *46*, 1881 – 1884; h) J. Barluenga, A. Jiménez-Aquino, C. Valdés, F. Aznar, *Angew. Chem.* **2007**, *119*, 1551 – 1554; *Angew. Chem. Int. Ed.* **2007**, *46*, 1529 – 1532; i) D. R. Stuart, M. g. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474 – 16475; j) S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge, F. Glorius, *Angew. Chem.* **2008**, *120*, 7340 – 7343; *Angew. Chem. Int. Ed.* **2008**, *47*, 7230 – 7233; k) M. Shen, B. E. Leslie, T. G. Driver, *Angew. Chem.* **2008**, *120*, 5134 – 5137; *Angew. Chem. Int. Ed.* **2008**, *47*, 5056 – 5059; l) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui, N. Jiao, *Angew. Chem.* **2009**, *121*, 4642 – 4646; *Angew. Chem. Int. Ed.* **2009**, *48*, 4572 – 4576; m) R. Bernini, G. Fabrizi, A. Sferrazza, S. Cacchi, *Angew. Chem.* **2009**, *121*, 8222 – 8225; *Angew. Chem. Int. Ed.* **2009**, *48*, 8078 – 8081; n) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326 – 18339; o) B. J. Stokes, S. Liu, T. G. Driver, *J. Am. Chem. Soc.* **2011**, *133*, 4702 – 4705; p) K. Sun, S. Liu, P. M. Bec, T. G. Driver, *Angew. Chem.* **2011**, *123*, 1740 – 1744; *Angew. Chem. Int. Ed.* **2011**, *50*, 1702 – 1706; q) S. Cacchi, G. Fabrizi, A. Goggiamani, C. Molinaro, R. Verdiglione, *J. Org. Chem.* **2014**, *79*, 401 – 407.

[8] a) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689 – 6690; b) R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172 – 8174; for a review on the removal of toxic metal impurity, see: c) C. E. Garrett, K. Prasad, *Adv. Synth. Catal.* **2004**, *346*, 889 – 900; for palladium contamination in Larock syntheses, see: d) V. W. Rosso, D. A. Lust, P. J. Bernot, J. A. Grosso, S. P. Modi, A. Rusowicz, T. C. Sedergran, J. H. Simpson, S. K. Srivastava, M. J. Humora, N. G. Anderson, *Org. Process Res. Dev.* **1997**, *1*, 311 – 314; for examples of non-commercially available alkynes in Larock indole syntheses, see Ref. [4c] and references therein.

[9] a) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719 – 724; b) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416 – 5470; c) R. P. Wurz, *Chem. Rev.* **2007**, *107*, 5570 – 5595; d) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471 – 5569; e) D. W. C. MacMillan, *Nature* **2008**, *455*, 304 – 308.

[10] a) V. Nair, S. Bindu, V. Sreekumar, *Angew. Chem.* **2004**, *116*, 5240 – 5245; *Angew. Chem. Int. Ed.* **2004**, *43*, 5130 – 5135; b) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606 – 5655; c) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046 – 3058; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988 – 3000; d) V. Nair, S. Vellalath, B. P. Babu, *Chem. Soc. Rev.* **2008**, *37*, 2691 – 2698; e) E. M. Phillips, A. Chan, K. A. Scheidt, *Aldrichimica Acta* **2009**, *42*, 55 – 66; f) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose, V. Sreekumar, *Chem. Soc. Rev.* **2011**, *40*, 5336 – 5346; g) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511 – 3522; h) J. Douglas, G. Churchill, A. Smith, *Synthesis* **2012**, 2295 – 2309; i) S. De Sarkar, A. Biswas, R. C. Samanta, A. Studer, *Chem. Eur. J.* **2013**, *19*, 4664 – 4678; j) S. J. Ryan, L. Candish, D. W. Lupton, *Chem. Soc. Rev.* **2013**, *42*, 4906 – 4917.

[11] List and coworkers reported an organo–phosphoric acid-catalyzed asymmetric Fischer indole synthesis in **2011**, see Ref. [5d].

[12] A. Reissert, *Ber. Dtsch. Chem. Ges.* **1897**, *30*, 1030 – 1053.

[13] a) H. Stetter, A. Landscheidt, *Chem. Ber.* **1979**, *112*, 2419 – 2422; b) H. Stetter, W. Basse, J. Nienhaus, *Chem. Ber.* **1980**, *113*, 690 – 698; c) A. E. Mattson, A. R. Bharadwaj, K. A. Scheidt, *J. Am. Chem. Soc.* **2004**, *126*, 2314 – 2315.

[14] Selected recent examples of NHC acyl anion equivalents reacting with unconventional electrophiles, see: a) Y. Li, F.-Q. Shi, Q.-L. He, S.-L. You, *Org. Lett.* **2009**, *11*, 3182 – 3185; b) Q. Y. Toh, A. McNally, S. Vera, N. Erdmann, M. J. Gaunt, *J. Am. Chem. Soc.* **2013**, *135*, 3772 – 3775; for a related, yet noncatalytic, NHC-mediated acyl anion addition to primary benzyl halides, see: c) L. Lin, Y. Li, W. Du, W.-P. Deng, *Tetrahedron Lett.* **2010**, *51*, 3571 – 3574; for the catalytic addition of NHC-mediated acyl anions to benzylic/activated alkyl halides, see: d) M. Padmanaban, A. T. Biju, F. Glorius, *Org. Lett.* **2011**, *13*, 98 – 101.

[15] a) E. M. Burgess, L. McCullagh, *J. Am. Chem. Soc.* **1966**, *88*, 1580 – 1581; b) M. Ikeda, S. Matsugashita, F. Tabusa, H. Ishibashi, Y. Tamura, *J. Chem. Soc. Chem. Commun.* **1975**, 575 – 576; c) M. Lancaster, D. J. H. Smith, *J. Chem. Soc. Chem. Commun.* **1980**, 471 – 472; d) K. Wojciechowski, *Tetrahedron* **1993**, *49*, 7277 – 7286.

[16] Y. Ito, S. Miyata, M. Nakatsuka, T. Saegusa, *J. Am. Chem. Soc.* **1981**, *103*, 5250 – 5251.

[17] a) R. D. Bowen, D. E. Davies, C. W. G. Fishwick, T. O. Glasbey, S. J. Noyce, R. C. Storr, *Tetrahedron Lett.* **1982**, *23*, 4501 – 4504; b) E. Foresti, P. Spagnolo, P. Zanirato, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1354 – 1356; c) C. K. Lau, L. Trimble, A. S. Caille, J. M. Wiebe, *Tetrahedron* **1996**, *52*, 11705 – 11724; d) K. Nish-

iyama, H. Kubo, T. Sato, K. Higashiyama, S. Ohmiya, *Heterocycles* **1998**, *48*, 1103 – 1106.
[18] a) H. Steinhagen, E. J. Corey, *Angew. Chem.* **1999**, *111*, 2054 – 2056; *Angew. Chem. Int. Ed.* **1999**, *38*, 1928 – 1931; b) F. Avemaria, S. Vanderheiden, S. Bräse, *Tetrahedron* **2003**, *59*, 6785 – 6796; c) Q.-Q. Yang, C. Xiao, L.-Q. Lu, J. An, F. Tan, B.-J. Li, W.-J. Xiao, *Angew. Chem.* **2012**, *124*, 9271 – 9274; *Angew. Chem. Int. Ed.* **2012**, *51*, 9137 – 9140; d) Q.-Q. Yang, Q. Wang, J. An, J.-R. Chen, L.-Q. Lu, W.-J. Xiao, *Chem. Eur. J.* **2013**, *19*, 8401 – 8404.
[19] a) A. E. Mattson, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 4508 – 4509; b) H. Lv, L. You, S. Ye, *Adv. Synth. Catal.* **2009**, *351*, 2822 – 2826; c) J. Izquierdo, A. Orue, K. A. Scheidt, *J. Am. Chem. Soc.* **2013**, *135*, 10634 – 10637; d) H. Lv, W.-Q. Jia, L.-H. Sun, S. Ye, *Angew. Chem.* **2013**, *125*, 8769 – 8772; *Angew. Chem. Int. Ed.* **2013**, *52*, 8607 – 8610.
[20] a) G. C. Vougioukalakis, R. H. Grubbs, *J. Am. Chem. Soc.* **2008**, *130*, 2234 – 2245; b) I. Piel, M. D. Pawelczyk, K. Hirano, R. Fröhlich, F. Glorius, *Eur. J. Org. Chem.* **2011**, 5475 – 5484.
[21] a) B. Cardinal-David, D. E. A. Raup, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 5345 – 5347; b) D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766 – 771.
[22] For recent examples documenting/discussing this effect, see: a) S. E. O'Toole, C. A. Rose, S. Gundala, K. Zeitler, S. J. Connon, *J. Org. Chem.* **2011**, *76*, 347 – 357; b) C. Rose, S. Gundala, S. Connon, K. Zeitler, *Synthesis* **2011**, 190 – 198; c) C. A. Rose, S. Gundala, C.-L. Fagan, J. F. Franz, S. J. Connon, K. Zeitler, *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. [14d].
[24] A Reaxys substructure search yielded no results for multiple iterations.
[25] "c-Kit Modulators and Methods of Use": W. Cheng, E. W. Co, M. H. Kim, R. R. Klein, D. T. Le, A. Lew, J. M. Nuss, W. Xu, W. Bajjalieh, WIPO. WO 2005/020921A2. March 10, **2005**.

