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3-Aminoindole Synthesis from 2-Nitrochalcones and Ammonia or Primary Amines

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Abstract: A step-economic strategy for 3-aminoindoles synthesis with ammonia or primary amines as "N" source under transition-metal-free conditions was achieved. A series of 3-aminoindoles was obtained with abundant "N" source featuring high efficiency, mild conditions, environmental friendliness and scalability. Efficient syntheses of the intermediates of COX-2 inhibitor and tubulin polymerization inhibitor were successfully accomplished with this newly developed strategy.

Keywords: 3-aminoindole; 2-nitrochalcone; ammonia; primary amines; metal-free

3-Aminoindole frameworks are prevalent structural motifs in myriad synthetic intermediates[1] and biologically active molecules[2] (Figure 1A). Owing to the significance of 3-aminoindoles, the development of efficient synthetic approaches to access 3-aminoindoles has gained great attention. A few versatile and concise methods have been established in which "N" source on C3 position of 3-aminoindoles was mainly derived from cyano, [3] *O*-benzoyl hydroxylamines,[4] amide,[5] *N*-pivaloyloxylamides,[6] isonitrile[7] and so on. Despite the great advance, however, these known methods cannot avoid the transition-metal catalysts, multi-step syntheses are always required either in order to access the starting materials or to construct the key scaffold, and limited substrate ranges severely hamper the broad application of these methods in modern synthetic chemistry (Figure 1B). Therefore the development of mild and pragmatic method to access 3-aminoindoles is highly desirable. As one of the most abundant and inexpensive N-containing compounds, ammonia is indisputable the most accessible N source;[8] meanwhile, primary amines as one of the most valuable building blocks in organic synthesis,[9] they are abundant and readily available as well. Surprisingly, "N" source of C3 position from the above two abundant N-containing compounds for the construction of 3-aminoindoles has yet to be reported, probably due to the difficulty of construction of C_{Ar}-N bond with them. We present herein a step-economic strategy for 3-aminoindoles synthesis in one-step reaction with ammonia or primary amines as "N" source (Figure 1C).

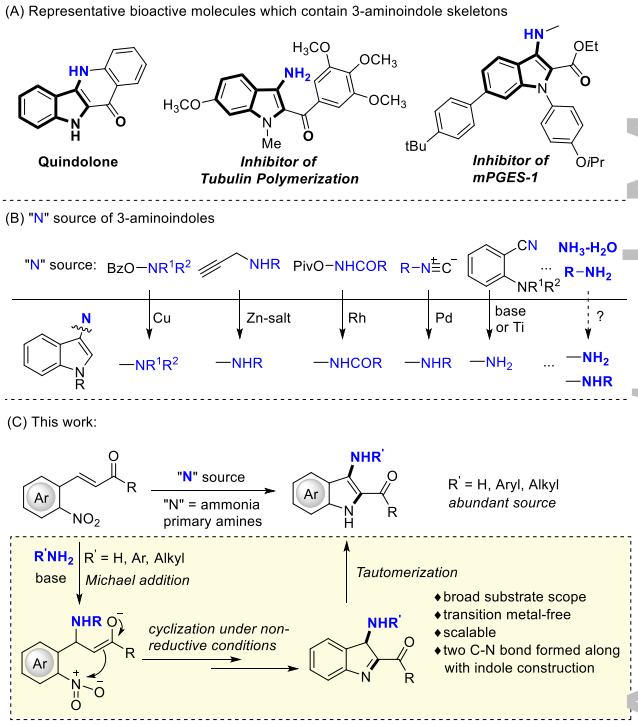

Figure 1. Motivation and 3-Aminoindoles Synthesis.

Recently, Lee reported carbazoles or 3-naphthylindoles synthesis through condensation of an enolate to a nitro group intramolecularly.[10] In terms of 3-aminoindoles, we envision that a process involving Michael addition between ammonia or primary amines as "N" source and 2-nitrochalcones[11] would occur first to render the enolate intermediate with a new C-N bond formed at *β*-position, later intramolecular cyclization between the enolate and nitro group will eventually deliver 3-

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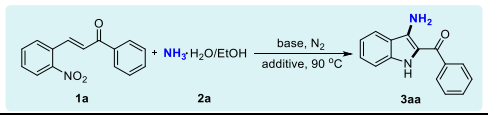
aminoindole derivatives. There are several advantages on this method: 1) "N" sources for this strategy are abundant and the starting materials are readily available, which makes the method easily operational and pragmatic; 2) a tandem reaction is generated in one-step synthesis with high efficiency and two C-N bonds formed along with the construction of indole rings; 3) this reaction proceeds under transition-metal free conditions, which features mildness, environmental benignness, scalability, good functional group tolerability as well as broad substrate scopes.

To validate our hypothesis, 2-nitrochalcone (**1a**) and ammonia (**2a**) in EtOH were chosen as the test substrates for the optimization study because of their ready availability (Table 1). To our delight, exposure of **1a** to NH_3-EtOH and Na_2CO_3 triggered both C-N bond construction as well as indole formation to afford product **3aa** in 51% yield (entry 1). Further base screening suggested that K_2CO_3 was the best one among Na_2CO_3, CsF and K_3PO_4 (entries 1−4). Next, reaction temperature was surveyed (entries 5–6). Interestingly, the temperature decreasing from 100 °C to 90 °C improved the yield of **3aa** (entry 5). Shortening the reaction time from 4 hours to 1 hour did not affect the efficiency of the reaction, and the desired product was obtained in 65% isolated yield (entry 8). A slightly lower yield was observed when the time was reduced to 0.5 hour (entry 9). The yield of **3aa** was further increased when the loading of K_2CO_3 was reduced to 0.5 equivalent (entry 10). Gratifyingly, changing the ammonia in EtOH to aqueous ammonia improved the 3-aminoindole product **3aa** to 75% (entry 11). There may be oxidant in the system that was detrimental to the 3-aminoindole product, so we used Hantzsch ester (diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate) as an additive and the yield has indeed increased to 85% (entries 11-12).

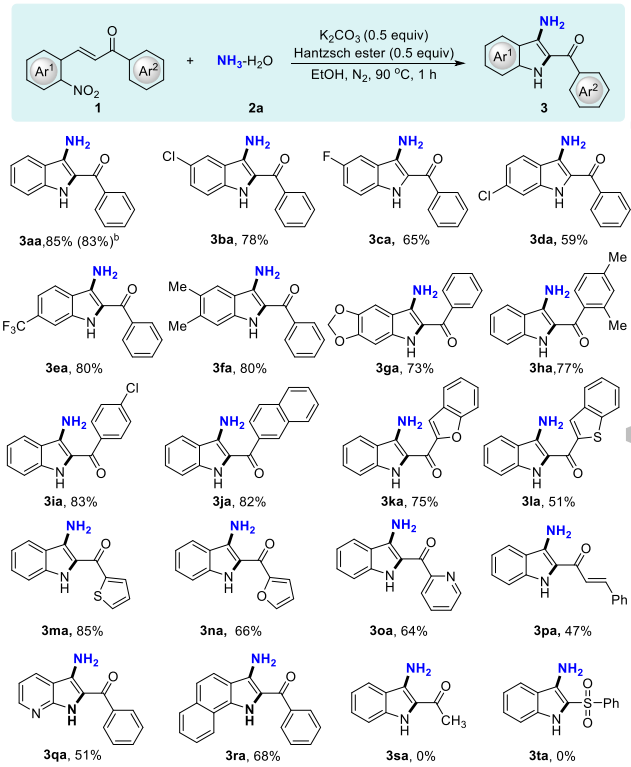
Table 1. Development of optimized conditions for 3-amioindole formation[a].



Entry	Base (equiv)	Temp (°C)	Ammonia /Solvent (mL)	Time (h)	Yield [b] (%)
1	Na_2CO_3 (2)	100	NH_3-EtOH (2)	4	51
2	CsF (2)	100	NH_3-EtOH (2)	4	48
3	K_3PO_4 (2)	100	NH_3-EtOH (2)	4	38
4	K_2CO_3 (2)	100	NH_3-EtOH (2)	4	55
5	K_2CO_3 (2)	90	NH_3-EtOH (2)	4	65
6	K_2CO_3 (2)	80	NH_3-EtOH (2)	4	63
7	K_2CO_3 (2)	90	NH_3-EtOH (2)	2	64
8	K_2CO_3 (2)	90	NH_3-EtOH (2)	1	65
9	K_2CO_3 (2)	90	NH_3-EtOH (2)	0.5	60
10	K_2CO_3 (0.5)	90	NH_3-EtOH (2)	1	70
11	**K_2CO_3 (0.5)**	**90**	**NH_3-H_2O(0.2)/EtOH (0.8)**	**1**	**75**
12[c]	K_2CO_3 (0.5)	90	NH_3-H_2O(0.2)/EtOH (0.8)	1	84
13[d]	**K_2CO_3 (0.5)**	**90**	**NH_3-H_2O(0.2)/EtOH (0.8)**	**1**	**85**

Reaction conditions: a) 2-nitrochalcone **1a** (0.2 mmol) under N_2 atomosphere unless otherwise specified; b) isolated yield; c) Hantzsch ester as additive (0.6 equiv); d) Hantzsch ester as additive (0.5 equiv)

With the optimized conditions available, the substrate scope of 2-nitrochalcones in this tandem transformation was investigated (Scheme 1). First, we demonstrated that our reaction could be scalable without significant reduction in yield. To probe the universality of the current reaction, a variety of halo-, alkyl-, alkoxy-, and heteroaryl-substituted 2-nitrochalcones **1** were tested as electrophile partners under standard reaction conditions with aqueous ammonia. In comparison with 2-nitrochalcone, similar yields were obtained with halogenated substituents on aromatic rings (Cl and F) (**3ba-3da, 3ia**). Different substituents on Ar^1 rings, such as trifluoromethyl, methyl, alkoxy as well as other ether did not impede under the standard conditions (**3ea-3ga**). When Ar^2 rings were replaced by naphthalene, benzofuran, benzothiophene, thiophene, furan and pyridine, the corresponding products **3ja**–**3oa** were obtained in moderate to good yields (51-85%). The structure of **3na** was unambiguously confirmed by X-ray crystallographic analysis.[12] 2-Nitrodibenzylideneacetone was a good substrate for this transformation as well with high regioselectivity, the corresponding 3-aminoindole product was obtained with moderate yield (**3pa**). Aza-indole and 1*H*-benzo[g]indole were important structural units of biologically active molecules, this method also can be applied for the preparation of 3-amino- aza-indole (**3qa**) and 3-amino-1*H*-benzo[g]indole (**3ra**) with moderate yields. Unfortunately, 2-acyl-3-amino indole (**3sa**) and 2-sulfonyl-3-amino indole (**3ta**) cannot be obtained under standard conditions.



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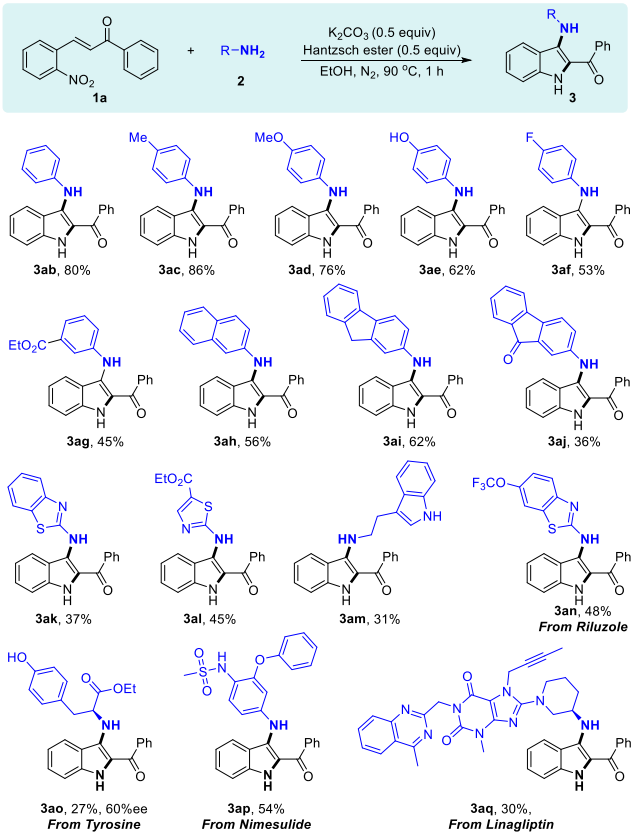
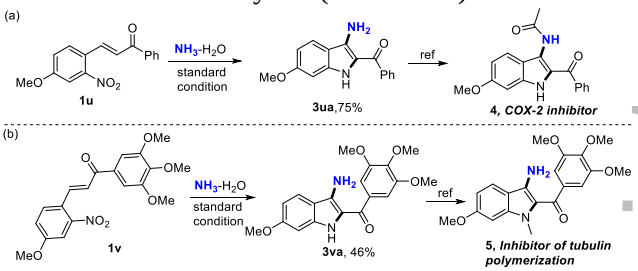
Scheme 1. Substrate scope of 2-Nitrochalcones.[a] Reaction conditions: a) 2-nitrochalcone **1** (0.2 mmol), NH_3-H_2O (0.2 mL), K_2CO_3 (0.1 mmol), Hantzsch ester (0.1 mmol), EtOH (0.8 mL), 90 °C, 1 h; b) Reaction performed on a 10 mmol scale.

Then we explored the scope of amines, both primary aromatic and alkyl amines worked well with 2-nitrochalcone (**1a**) under the standard conditions to afford the desired products **3ab**-**3aq** (Scheme 2). A range of aromatic amines were efficiently transformed into the corresponding 3-aminoindoles (**3ab**-**3al**), including those possessing free phenol (**3ae**), halide (**3af**), ester (**3ag**, **3al**), fluorene (**3ai**), fluorenone (**3aj**) and aromatic heterocyclic amines (**3ak**, **3al**). Notably, transformations with alkyl-substituted amines were equally efficient (**3am**). Owing to the extensive existence of primary amines in drugs and nature products, the importance of the tandem reaction can be further featured by modifying these active molecules. Riluzole, Tyrosine, Nimesulide and Linagliptin with **1a** could be smoothly converted into the corresponding 3-amioindole products (**3an**-**3aq**) with excellent functional group tolerance, partial racemization occurred in **3ao**.



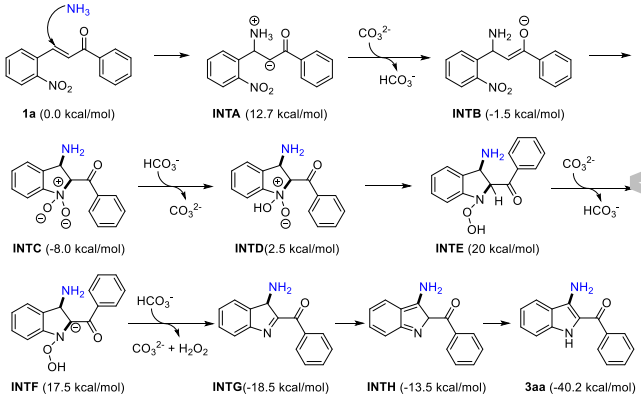
Scheme 2. Substrate scope of amines. Reaction conditions: 2-nitrochalcone **1a** (0.2 mmol), amine (0.4 mmol), K_2CO_3 (0.1 mmol), Hantzsch ester (0.1 mmol), EtOH (2 mL), 90 °C, 1 h.

With the development of C_{Ar}-N bond construction along with the indole formation reaction for the synthesis of 3-aminoindole derivatives, we decided to demonstrate the applicability towards the syntheses of some biologically active compounds. Compound **4**, a COX-2 inhibitor,[2b] was efficiently synthesized by using 2-nitro-4-methoxychalcone (**1u**) and ammonia under the standard conditions (Scheme 3a). Upon the treatment of 3',4',5'-trimethoxy-2-nitro-4-methoxy chalcone (**1v**) and ammonia under the standard condition, 3-aminoindole product **3va**, which is the intermediate of tubulin polymerization inhibitor **5**,[2h] was obtained in 46% yield (Scheme 3b).



Scheme 3. Synthetic applications.

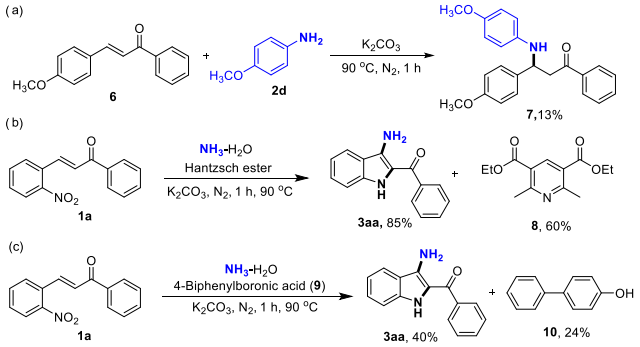
On the basis of the above results and previous reports, [10, 13] we proposed a mechanism for this transformation (Scheme 4), which was supported by density functional theory (DFT) calculations on a thermodynamic examination (see the Supplementary Information (SI) for details). 2-Nitrochalcone (**1a**) and ammonia (**2a**) undergo Michael addition to obtain the enolate intermediate **INTB** with -1.5 kcal/mol of exothermicity, then the nitro group in **INTB** is attacked by the in situ newly formed enolate to afford bicyclic intermediate **INTC** (-8.0 kcal/mol) via an intramolecular cyclization. Intermediate **INTC** undergoes protonation and rearrangement to give *N*-hydroperoxide **INTD** (20.0 kcal/mol), which further eliminate H_2O_2 under the induction of base (CO_3^{2-}) to render 3*H*-indole **INTG** with -18.5kcal/mol of exothermicity.[10] Finally, tautomerization to the desired 3-aminoindole product **3aa** is highly exothermic by -40.2 kcal/mol.



Scheme 4. Proposed mechanism.

In order to validate the mechanism of this reaction, the following experiments were implemented

(Scheme 5). 4-Methoxychalcone without 2-nitro was subjected to the similar reaction conditions and the Michael addition product was obtained in 13% yield, thus showing first undergoing Michael addition of this transformation (Scheme 5a). Hantzsch ester as additive was converted into pyridine product **8** and 4-phenylboronic acid (**9**) was oxidized to 4-phenylphenol (**10**) in our system, which indicated that an oxidant (H_2O_2)[14] was generated in our system (Scheme 5b and 5c).



Scheme 5. Control experiment.

We have developed a novel approach for 3-aminoindoles synthesis with ammonia or primary amines as "N" source under transition-metal-free conditions. By using this method, the intermediates of COX-2 inhibitor and tubulin polymerization inhibitor were successfully accomplished with high efficiency. Our future experiments are aimed at further optimizing product structure and investigating bioactivities of these compounds.

Experimental Section

General procedure A for the preparation of 3-aminoindole products from NH_3-H_2O and *o*-nitrochalcones. In air, a 25 mL schlenk tube was charged with *o*-Nitrochalcone (0.2 mmol, 0.0506 g, 1 equiv), Hantzsch ester (0.1 mmol, 0.0253 g, 0.5 equiv) and potassium carbonate (0.1 mmol, 0.0138 g, 0.5 equiv). The tube was evacuated and filled with nitrogen for three cycles. Then, NH_3-H_2O (0.20 mL) and Ethanol (0.8 mL) or amines (0.4 mmol, 2 equiv) and Ethanol (2 mL) were added to the tube at room temperature. The reaction was allowed to stir at 90 °C for 1 h. Upon completion, the reaction was cooled to room temperature and proper amount of silica gel was added. After removal of the solvent, the crude reaction mixture was purified on silica gel (petroleum ether: ethyl acetate = 5:1-3:1) to afford the desired product.

General procedure B for the preparation of 3-aminoindole products from amines and *o*-nitrochalcones. In air, a 25 mL schlenk tube was charged with o-Nitrochalcone (0.2 mmol, 0.0506 g, 1 equiv), amines (0.4 mmol, 2 equiv), Hantzsch ester (0.1 mmol, 0.0253 g, 0.5 equiv) and potassium carbonate (0.1 mmol, 0.0138 g, 0.5 equiv). The tube was evacuated and filled with nitrogen for three cycles. Then, ethanol (2 mL) was added at room temperature. The reaction was allowed to stir at 90 °C for 1 h. Upon completion, the reaction was cooled to room temperature and proper amount of silica gel was added. After removal of the solvent, the crude reaction mixture was purified on silica gel (petroleum ether: ethyl acetate = 5:1-3:1) to afford the desired product.

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References

[1] a) C. Papamicaël, G. Quéguiner, J. Bourguignon, G. Dupas, *Tetrahedron* **2001**, *57*, 5385-5391; b) Y. Liu, W. W. McWhorter, *J. Am. Chem. Soc.* **2003**, *125*, 4240-4252; c) R. Nakajima, T. Ogino, S. Yokoshima, T. Fukuyama, *J. Am. Chem. Soc.* **2010**, *132*, 1236-1237; d) G. Xu, L. Zheng, Q. Dang, X. Bai, *Synthesis* **2013**, *45*, 743-752.

[2] a) F. G. Salituro, B. M. Baron, 1992, EP 0483881; *b*) R. W. Stevens, K. Nakao, K. Kawamura, 1999, WO 9905104; c) E. Arzel, P. Rocca, P. Grellier, M. Labaeïd, F. Frappier, F. Guéritte, C. Gaspard, F. Marsais, A. Godard, G. Quéguiner, *J. Med. Chem.* **2001**, *44*, 949-960; d) A. Kumar, S. Sharma, A. K. Bajaj, S. Sharma, H. Panwar, T. Singh, V. K. Srivastava, *Bioorg. Med. Chem.* **2003**, *11*, 5293-5299; e) G. H. Ladouceur, B. Bear, C. Bi, D. R. Brittelli, M. J. Burke, G. Chen, J. Cook, J. Dumas, R. Sibley, M. R. Turner, 2004. WO 2004043950; f) K. Olofsson, E. Suna, B. Pelcman, V. Ozola, M. Katkevics, I. Kalvins, 2005, WO 2005005415; g) N. C. Ray, G. Hynd, R. Arienzo, H. Finch, 2007, WO 2007045867; h) R. Romagnoli, P. G. Baraldi, T. Sarkar, M. D. Carrion, C. L. Cara, O. Cruz-Lopez, D. Preti, M. A. Tabrizi, M. Tolomeo, S. Grimaudo, A. Di Cristina, N. Zonta, J. Balzarini, A. Brancale, H.-P. Hsieh, E. Hamel, *J. Med. Chem.* **2008**, *51*, 1464-1468; i) J. Lavrado, K. Gani, P. A. Nobre, S. A. Santos, P. Figueiredo, D. Lopes, V. d. Rosário, J. Gut, P. J. Rosenthal, R. Moreira, A. Paulo, *Bioorg. Med. Chem.* **2010**, *20*, 5634-5637.

[3] a) A. Couture, E. Deniau, Y. Gimbert, P. Grandclaudon, *Tetrahedron* **1993**, *49*, 1431-1444; b) C. M. Seong, C. M. Park, J. Choi, N. S. Park, *Tetrahedron Lett.* **2009**, *50*, 1029-1031; c) L. H. Leijendekker, J. Weweler, T. M. Leuther, J. Streuff, *Angew. Chem. Int.Ed.* **2017**, *56*, 6103-6106; d) P.-C. Diao, Q. Li, M.-J. Hu, Y.-F. Ma, W.-W. You, K. H. Hong, P.-L. Zhao, *Eur. J. Med. Chem.* **2017**, *134*, 110-118; e) X. Geng, X. Wu, C. Wang, P. Zhao, Y. Zhou, X. Sun, L.-J. Wang, W.-J. Guan, Y.-D. Wu, A.-X. Wu, *Chem. Commun.* **2018**, *54*, 12730-12733; f) P. Chen, Y.-X. Zhuang, P.-C. Diao, F.

Yang, S.-Y. Wu, L. Lv, W.-W. You, P.-L. Zhao, *Eur. J. Med. Chem.* **2019**, *162*, 525-533.

[4] N. Matsuda, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2012**, *77*, 617-625.

[5] Z. Hu, X. Tong, G. Liu, *Org. Lett.* **2016**, *18*, 2058-2061.

[6] G. C. Senadi, W.-P. Hu, S. S. K. Boominathan, J.-J. Wang, *Chem. Eur. J.* **2015**, *21*, 998-1003.

[7] a) A. Pews-Davtyan, A. Tillack, A.-C. Schmöle, S. Ortinau, M. J. Frech, A. Rolfs and M. Beller, *Org. Biomol. Chem.* **2010**, *8*, 1149-1153; b) A. Pews-Davtyan and M. Beller, *Org. Biomol. Chem.* **2011**, *9*, 6331-6334.

[8] a) J. Schranck, A. Tlili, *ACS Catal.* **2018**, *8*, 405-418; b) L. Zhang, J. Li, Z. Hu, J. Dong, X.-M. Zhang, X. Xu, *Adv. Synth. Catal.* **2018**, *360*, 1938.

[9] a) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564-12649; b) F. J. R. Klauck, M. J. James, F. Glorius, *Angew. Chem. Int. Ed.* **2017**, *56*, 12336-12339; (c) C. H. Basch, J. Liao, J. Xu, J. J. Piane, M. P. Watson, *J. Am. Chem. Soc.* **2017**, *139*, 5313-5316.

[10] a) T. N. Poudel, Y. R. Lee, *Chem. Sci.* **2015**, *6*, 7028-7033; b) T. N. Poudel and Y. R. Lee, *Adv. Synth. Catal.* **2017**, *359*, 1552-1562; c) T. N. Poudel, S. Karanjit, H. D. Khanal, R. J. I. Tamargo, Y. R. Lee, *Org. Lett.* **2018**, *20*, 5648-5652.

[11] Z. Lin, Z. Hu, X. Zhang, J. Dong, J.-B. Liu, D.-Z. Chen, X. Xu, *Org. Lett.* **2017**, *19*, 5284-5287.

[12] CCDC 1881042 (**3na**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[13] a) N. Moskalev, M. Makosza, *Chem. Commun.* **2001**, 1248-1249; b) M. Makosza, *Chem. Eur. J.* **2014**, *20*, 5536-5545.

[14] a) J. Simon, S. Salzbrunn, G. K. Surya Prakash, N. A. Petasis, G. A. Olah, *J. Org. Chem.* **2001**, *66*, 633-634; b) G. K. S. Prakash, S. Chacko, C. Panja, T. E. Thomas, L. Gurung, G. Rasul, T. Mathew, G. A. Olah, *Adv. Synth. Catal.* **2009**, *351*, 1567-1574.

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3-Aminoindole Synthesis from 2-Nitrochalcones and Ammonia or Primary Amines

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