

N-Heterocyclic Carbene-Catalyzed Intramolecular Aldehyde–Nitrile Cross Coupling: An Easy Access to 3-Aminochromones[†]

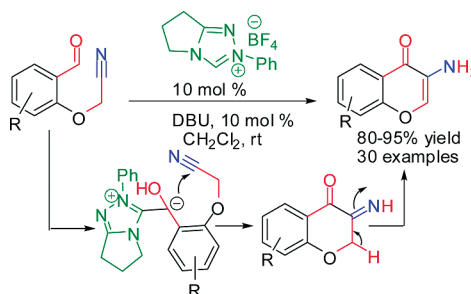
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ABSTRACT



An immense effort has been made to develop an efficient strategy for the carbon–carbon bond formation between aldehyde and nitrile intramolecularly using an N-heterocyclic carbene catalyst to derive 3-aminochromone derivatives in good to excellent yields (80–95%).

Chromone is one of the most common heterocyclic motifs found in pharmaceutically active compounds.¹ One of the most important subfamilies of chromone is 3-aminochromone, whose derivatives show interesting therapeutic effects.² From

previous research efforts, a wide variety of functionalized 3-aminochromone derivatives have been identified to possess anti-inflammatory (**T-614**) (**I**),³ antirheumatic (**I**),⁴ leukemic B-cells apoptosis (**II**),⁵ and antimutagenic (**III**) activities.⁶ They were found to be effective in the selective inhibition

[†] Dedicated to Professor Charles E. McKenna on the occasion of his 65th birthday.

(1) (a) Gobbi, S.; Cavalli, A.; Rampa, A.; Belluti, F.; Piazzi, L.; Paluszczak, A.; Hartmann, R. W.; Recanatini, M.; Bisi, A. *J. Med. Chem.* **2006**, *49*, 4777–4780. (b) Nutley, B. P.; Smith, N. F.; Hayes, A.; Kelland, L. R.; Brunton, L.; Golding, B. T.; Smith, G. C. M.; Martin, N. M. B.; Workman, P.; Raynaud, F. I. *Br. J. Cancer*. **2005**, *93*, 1011–1018. (c) Boumendjel, A.; Nicolle, E.; Moraux, T.; Gerby, B.; Blanc, M.; Ronot, X.; Boutonnat, J. *J. Med. Chem.* **2005**, *48*, 7275–7281. (d) Ahmed-Belkacem, A.; Pozza, A.; Muñoz-Martínez, F.; Bates, S. E.; Castanys, S.; Gamarro, F.; Di Pietro, A.; Pérez-Victoria, J. M. *Cancer Res.* **2005**, *65*, 4852–4860. (e) Morris, J.; Wishka, D. G.; Lin, A. H.; Humphrey, W. R.; Wiltse, A. L.; Gammill, R. B.; Judge, T. M.; Bisaha, S. N.; Olds, N. L.; Jacob, C. S.; Bergh, C. L.; Cudahy, M. M.; Williams, D. J.; Nishizawa, E. E.; Thomas, E. W.; Gorman, R. R.; Benjamin, C. W.; Shebusk, R. J. *J. Med. Chem.* **1993**, *36*, 2026–2032. (f) Horie, T.; Tominaga, H.; Kawamura, Y.; Hada, T.; Ueda, N.; Amano, Y.; Yamamoto, S. *J. Med. Chem.* **1991**, *34*, 2169–2176.

(2) Dauzonne, D.; Folléas, B.; Martinez, L.; Chabot, G. G. *Eur. J. Med. Chem.* **1997**, *32*, 71–82.

(3) (a) Sawada, T.; Hashimoto, S.; Tohma, S.; Nishioka, Y.; Nagai, T.; Sato, T.; Ito, K.; Inoue, T.; Iwata, M.; Yamamoto, K. *Immunopharmacol.* **2000**, *49*, 285–294. (b) Inaba, T.; Tanaka, K.; Takeno, R.; Nagaki, H.; Yoshida, C.; Takano, S. *Chem. Pharm. Bull.* **2000**, *48*, 131–139.

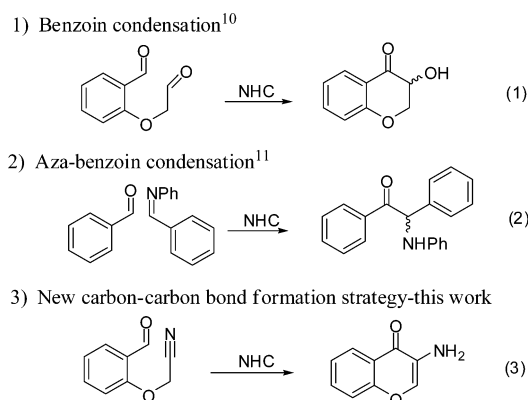
(4) (a) Tanaka, K.; Yamamoto, T.; Aikawa, Y.; Kizawa, K.; Muramoto, K.; Matsuno, H.; Muraguchi, A. *Rheumatology* **2003**, *42*, 1365–1371. (b) Kuriyama, K.; Higuchi, C.; Tanaka, K.; Yoshikawa, H.; Itoh, K. *Biochem. Biophys. Res. Commun.* **2002**, *299*, 903–909. (c) Aikawa, Y.; Yamamoto, M.; Yamamoto, T.; Morimoto, K.; Tanaka, K. *Inflammation Res.* **2002**, *51*, 188–194. (d) Kawakami, A.; Tsuboi, M.; Urayama, S.; Matsuoka, N.; Yamasaki, S.; Hida, A.; Aoyagi, T.; Furuichi, I.; Nakashima, T.; Migita, K.; Kawabe, Y.; Nakashima, M.; Origuchi, T.; Eguchi, K. *J. Lab. Clin. Med.* **1999**, *133*, 566–574. (e) Aikawa, Y.; Tanuma, N.; Shin, T.; Makino, S.; Tanaka, K.; Matsumoto, Y. *J. Neuroimmunol.* **1998**, *89*, 35–42.

of v-*abl* tyrosine protein kinase (III).⁷ Thus, facile preparation of chromone derivatives remains an essential research topic in organic synthesis.

It is evident from prior research that the synthesis of the chromone scaffold often suffers lengthy steps, harsh reaction conditions, and absence of diversified substrate scope. The potential utility of 3-aminochromones has prompted organic chemists to look for alternatives to replace conventional chromone syntheses.⁸ In this context, the N-heterocyclic carbene (NHC) catalyzed carbon–carbon bond formation strategy is, in our opinion, a more attractive and innovative approach.⁹ This approach generally facilitates the reactions such as benzoin condensation,¹⁰ aza-benzoin condensation,¹¹ Stetter reaction,¹² addition reactions to homoenoate intermediate,¹³ intramolecular nucleophilic addition of carbonyl anion,¹⁴ etc. These reactions involve an alternating acceptor and donor reactivity pattern called umpolung,⁹ which develops a new carbon–carbon bond and shortens the conventional synthetic routes in organic synthesis. Thus we felt that this umpolung derived strategy would allow the synthesis of 3-aminochromones in an expeditious manner.

Our synthetic strategy was acquired from the observation of two NHC-catalyzed reactions (Scheme 1): the reaction

Scheme 1. Blueprint for NHC-Catalyzed C–C Bond Formation Strategy



between two aldehydes (Benzoin condensation, eq 1) and between an aldehyde and an imine (aza-benzoin condensation, eq 2). The central core of both the reactions is trivial variation of polarity of the carbonyl and imine bonds which is effortlessly attacked by the Breslow intermediate¹⁵ to form a carbon–carbon bond. We envisioned that this umpolung derived reactivity could be applied to the intramolecular carbon–carbon bond formation reaction between aldehyde and nitrile, which would significantly simplify traditional synthetic routes and allow an easy access to diversity-oriented 3-aminochromones (eq 3).

Our initial efforts were focused on the systematic evaluation of various catalysts and reaction conditions to optimize

(5) Quiney, C.; Dauzonne, D.; Kern, C.; Fourneron, J.-D.; Izard, J.-C.; Mohammad, R. M.; Kolb, J.-P.; Billard, C. *Leukemia Res.* **2004**, *28*, 851–861.

(6) Beudot, C.; De Méo, M. P.; Dauzonne, D.; Elias, R.; Laget, M.; Guiraud, H.; Balansard, G.; Duménil, G. *Mutat. Res.* **1998**, *417*, 141–153.

(7) Geissler, J. F.; Roesel, J. L.; Meyer, T.; Trinks, U. P.; Traxler, P.; Lydon, N. B. *Cancer Res.* **1992**, *52*, 4492–4498.

(8) (a) Fridén-Saxin, M.; Pemberton, N.; da Silva Andersson, K.; Dyrager, C.; Friberg, A.; Gröthli, M.; Luthman, K. *J. Org. Chem.* **2009**, *74*, 2755–2759. (b) Bauvois, B.; Puiffe, M.-L.; Bongui, J.-B.; Paillat, S.; Monneret, C.; Dauzonne, D. *J. Med. Chem.* **2003**, *46*, 3900–3913. (c) DeWald, H. A.; Heffner, T. G.; Jaen, J. C.; Lustgarten, D. M.; McPhail, A. T.; Meltzer, L. T.; Pugsley, T. A.; Wise, L. D. *J. Med. Chem.* **1990**, *33*, 445–450.

(9) (a) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691–2698. (b) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000. (c) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655. (d) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724. (e) Vijay, N.; Santhamma, B.; Vellalath, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130–5135. (f) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175. (g) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534–541. (h) Grasa, G. A.; Singh, R.; Nolan, S. P. *Synthesis* **2004**, 971–985. (i) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239–258.

(10) (a) Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2009**, *74*, 9214–9217. (b) Enders, D.; Niemeier, O.; Raabe, G. *Synlett* **2006**, 2431–2434. (c) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1463–1467. (d) Hachisu, Y.; Bode, J. W.; Suzuki, K. *Adv. Synth. Catal.* **2004**, *346*, 1097–1100. (e) Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125*, 8432–8433. (f) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743–1745. (g) White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124–5131. (h) Heck, R.; Henderson, A. P.; Köhler, B.; Rétey, J.; Golding, B. T. *Eur. J. Org. Chem.* **2001**, 2623–2627. (i) Iding, H.; Dünnwald, T.; Greiner, L.; Liese, A.; Müller, M.; Siegert, P.; Grötzinger, J.; Demir, A. S.; Pohl, M. *Chem.—Eur. J.* **2000**, *6*, 1483–1495. (j) López-Calahorra, F.; Rubires, R. *Tetrahedron* **1995**, *51*, 9713–9728. (k) Chen, Y. T.; Barletta, G. L.; Haghighi, K.; Cheng, J. T.; Jordan, F. *J. Org. Chem.* **1994**, *59*, 7714–7722. (l) Diederich, F.; Lutter, H. D. *J. Am. Chem. Soc.* **1989**, *111*, 8438–8446. (m) Castells, J.; López Calahorra, F.; Domingo, L. *J. Org. Chem.* **1988**, *53*, 4433–4436. (n) Matsumoto, T.; Ohishi, M.; Inoue, S. *J. Org. Chem.* **1985**, *50*, 603–606. (o) Lapworth, A. *J. Chem. Soc.* **1903**, 83, 995–996. (p) Wöhler, F.; Liébig, J. *Ann. Pharm.* **1832**, *3*, 249–282.

(11) (a) Li, G.-Q.; Dai, L.-X.; You, S.-L. *Chem. Commun.* **2007**, 852–854. (b) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 1654–1655. (c) Li, W.; Lam, Y. *J. Comb. Chem.* **2005**, *7*, 644–647. (d) Mattson, A. E.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 4363–4366. (e) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696–9697. (f) Castells, J.; López-Calahorra, F.; Bassedas, M.; Urrios, P. *Synthesis* **1988**, 314–315.

(12) (a) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872–10874. (b) Rovis, T. *Chem. Lett.* **2008**, *37*, 2–7. (c) de Alaniz, J. R.; Kerr, M. S.; Moore, J. L.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 2033–2040. (d) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552–2553. (e) Reynolds, N. T.; Rovis, T. *Tetrahedron* **2005**, *61*, 6368–6378. (f) Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195–197. (g) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314–2315. (h) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876–8877. (i) Barrett, A. G. M.; Love, A. C.; Tedeschi, L. *Org. Lett.* **2004**, *6*, 3377–3380. (j) Raghavan, S.; Anuradha, K. *Synlett* **2003**, 711–713. (k) Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934–1936. (l) Raghavan, S.; Anuradha, K. *Tetrahedron Lett.* **2002**, *43*, 5181–5183. (m) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298–10299. (n) Braun, R. U.; Zeitler, K.; Müller, T. J. *J. Org. Lett.* **2001**, *3*, 3297–3300. (o) Ciganek, E. *Synthesis* **1995**, 1311–1314. (p) Stetter, H. *Angew. Chem., Int. Ed.* **1976**, *15*, 639–647. (q) Stetter, H.; Kuhlmann, H. *Synthesis* **1975**, 379–380. (r) Stetter, H.; Schreckenberger, M. *Angew. Chem., Int. Ed.* **1973**, *12*, 81.

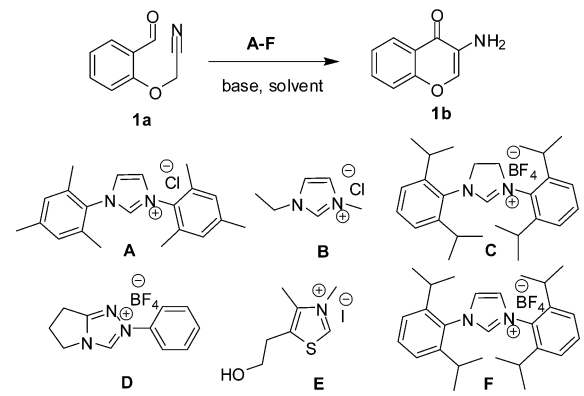
(13) (a) Chiang, P.-C.; Rommel, M.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 8714–8718. (b) Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2416–2417. (c) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2740–2741. (d) Chiang, P. C.; Kaobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520–3521. (e) He, M.; Ue Gerson, J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088–15089. (f) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736–8737. (g) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131–3134. (h) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205–6208.

(14) (a) Hirano, K.; Biju, A. T.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 14190–14191. (b) He, J.; Tang, S.; Liu, J.; Su, Y.; Pan, X.; She, X. *Tetrahedron* **2008**, *64*, 8797–8800.

(15) (a) Breslow, R.; Schmuck, C. *Tetrahedron Lett.* **1996**, *37*, 8241–8242. (b) Breslow, R.; Kim, R. *Tetrahedron Lett.* **1994**, *35*, 699–702. (c) Breslow, R.; Kool, E. *Tetrahedron Lett.* **1988**, *29*, 1635–1638. (d) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.

the reaction. To gauge the performance of the reaction, a simple phenyl (**1a**) was used as a model substrate. The scope of this transformation was examined using the NHC catalyst precursors (**A–F**) (Table 1, entries 1–6). Among the tested

Table 1. Optimization of Intramolecular Aldehyde–Nitrile Cross Coupling



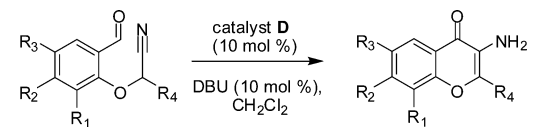
entry ^a	catalyst (equiv)	base ^b	solvent (0.1 M)	yield ^c (%)
1	A (0.10)	DBU	CH ₂ Cl ₂	53
2	B (0.10)	DBU	CH ₂ Cl ₂	trace
3	C (0.10)	DBU	CH ₂ Cl ₂	65
4	D (0.10)	DBU	CH₂Cl₂	83
5	E (0.10)	DBU	CH ₂ Cl ₂	77
6	F (0.10)	DBU	CH ₂ Cl ₂	67
7	D (0.15)	DBU	CH₂Cl₂	84
8	D (0.05)	DBU	CH ₂ Cl ₂	70
9	D (0.10)	DBU	THF	59
10	D (0.10)	DBU	CH ₃ CN	63
11	D (0.10)	DBU	Toluene	54
12	D (0.10)	DBU	DMF	72
13	D (0.10)	DBACO	CH ₂ Cl ₂	43
14	D (0.10)	Cs ₂ CO ₃ ^d	CH ₂ Cl ₂	69
15	D (0.10)	LiHMDS	CH ₂ Cl ₂	53

^a Unless otherwise specified, all of the reactions were carried out with freshly distilled dry solvents at room temperature for 24 h. ^b Equal mol % with respect to catalyst. ^c Isolated yields. ^d 3 equiv of base was used with respect to catalyst.

catalysts, catalyst **D** was found to be efficient (entry 4). Use of solvent other than dichloromethane gave diminished yields (entries 9–12). DBU was found to be the best among the bases tested (entries 13–15). With this optimized condition, we ensued to scrutinize the scope and generality of the method using a variety of substrates.

Our results show that cross coupling could be adapted for various salicylaldehyde derivatives ranging from electron-poor to electron-rich aromatic rings (Table 2). The alkyl-substituted aldehydes (entries 1–6) and employment of the fused ring aromatic system (entry 4) exhibited prominently good yields. A variety of methoxy (entries 7–10) and hydroxy substituents (entry 11) also provided excellent yields. Notably, halo (entries 12–18) and nitro (entries 19 and 20) substituents were observed to give excellent yields. Thus, the scope of the reaction is wide, allowing the facile generation of a variety of 3-aminochromones. The high yields

Table 2. Reaction Scope for 3-Aminochromone Derivatives



entry ^a	substrate	R ₁	R ₂	R ₃	R ₄	product	yield ^b (%)
1	1a	H	H	H	H	1b	83
2	2a	Me	H	H	H	2b	81
3	3a	^t Bu	H	^t Bu	H	3b	88
4	4a	H	H	–Ph–	H	4b	83
5	5a	H	H	Me	H	5b	85
6 ^c	6a	Allyl	H	H	H	6b	81
7	7a	OMe	H	H	H	7b	92
8	8a	H	OMe	H	H	8b	95
9	9a	H	H	OTBS	H	9b	91
10	10a	H	H	OMe	H	10b	89
11	11a	H	H	OH	H	11b	86
12	12a	H	H	Cl	H	12b	95
13	13a	Cl	H	Cl	H	13b	93
14	14a	H	H	Br	H	14b	86
15	15a	Br	H	Br	H	15b	91
16	16a	I	H	I	H	16b	82
17	17a	OMe	H	I	H	17b	89
18	18a	Br	H	Cl	H	18b	93
19	19a	OMe	H	NO ₂	H	19b	90
20	20a	H	H	NO ₂	H	20b	83
21	21a	F	H	H	H	21b	83
22	22a	H	F	H	H	22b	87
23	23a	F	H	F	H	23b	81
24	24a	H	H	OCF ₃	H	24b	88
25	25a	H	H	F	H	25b	85
26	26a	H	F	H	Me	26b	90
27	27a	F	H	H	Me	27b	81
28	28a	H	H	F	Me	28b	80
29	29a	OMe	H	H	Me	29b	83
30	30a	OMe	H	H	Ph	30b	85

^a See Supporting Information for a detailed experimental procedure. ^b Isolated yield. ^c Isolated as an acetamide derivative due to the unstable nature of amine upon column purification.

of the halo-substituted derivatives prompted us to study the biologically viable⁷ fluoro derivatives (entries 21–28). For the fluoro-substituted substrate study, results were equally good. Further hearten implementation was the inclusion of methyl phenyl substituents at the R₄ position which produced the desired products in good to excellent yields (entries 26–30). The structure of the 3-amino-chromone motif was further confirmed by X-ray crystallography (Figure 2, **7b**).

On the basis of the results, we propose the reaction mechanism as illustrated below (Scheme 2). Presumably, the

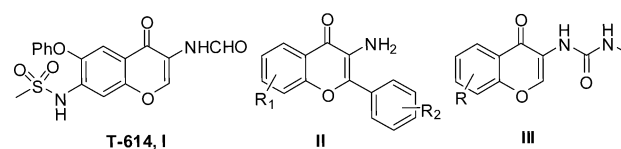


Figure 1. 3-Aminochromone scaffold.

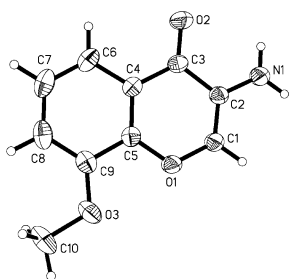
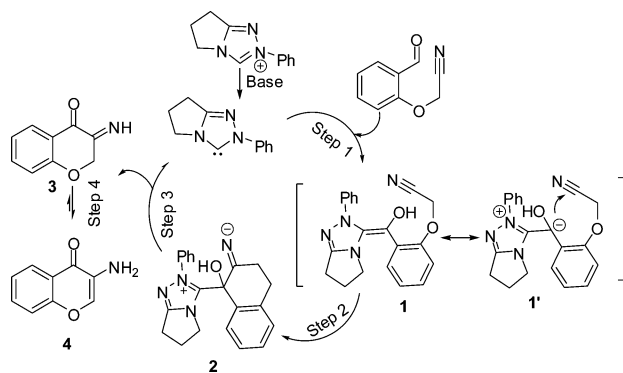


Figure 2. X-ray structure of 3-amino-8-methoxy-4*H*-chromen-4-one (**7b**).

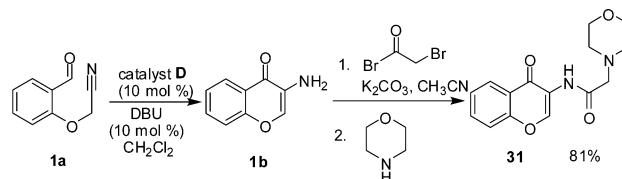
reaction proceeds through the Breslow intermediate **1** (step 1), which reacts intramolecularly with the nitrile to give imine **3** (steps 2 and 3) which subsequently tautomerizes to form 3-aminochromone **4** (step 4). The second step of the mechanism is crucial since an imine anion intermediate **2** (step 2) has been formed when the mesomeric carbanion **1'** from Breslow intermediate **1** attacked the sp carbon of the nitrile. Subsequent proton exchange and NHC elimination results in imine **3**, which further tautomerizes to form

Scheme 2. Plausible Reaction Mechanism



3-aminochromone. Compound **1b** served as a model to straightforwardly illustrate this synthetic potential of amine functionalization (Scheme 3). Delightfully, similar morpho-

Scheme 3. Amine Functionalization



line attached chromones are being synthesized and actively investigated in our laboratory to evaluate the potent anti-cancer activity.¹

In conclusion, we have developed a novel method for carbon–carbon bond formation between sp^2 carbon (aldehyde) and sp carbon (nitrile). This method allows the usage of salicylaldehyde derivatives to assemble a variety of heterocycles at room temperature, and good to excellent yields were obtained. The results herein disclose considerable extension of the substrate scope for the synthesis of a wide pool of 3-aminochromones in an expeditious, straightforward, and efficient manner. This methodology is likely to find immediate synthetic applications, given that it is the first example of a carbon–carbon bond formation between aldehyde and nitrile.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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