JOC Article

Highly Regioselective Friedländer Annulations with Unmodified Ketones Employing Novel Amine Catalysts: Syntheses of 2-Substituted Quinolines, 1,8-Naphthyridines, and Related Heterocycles

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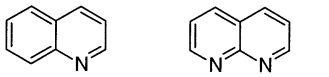
Catalysts were evaluated on the preparation of 2-substituted quinolines, 1,8-naphthyridines, and chromone derivatives from unmodified methyl ketones and *o*-aminoaromatic aldehydes. While oxide catalysts yielded the 2,3-dialkyl substituted products, cyclic secondary amines provided the 2-alkylsubstutited products regioselectively. In particular, pyrrolidine derivatives provided the highest regioselectivity favoring the 2-substituted products. The most reactive and regioselective catalyst was the bicyclic pyrrolidine derivative, TABO (1,3,3-trimethyl-6-azabicyclo[3.2.1]octane), yielding 1,8-naphthyridines with as high as 96:4 regioselectivity. Regioselectivity increased with slow addition of the methyl ketone substrate to the reaction mixture, and was positively related to temperature. Isolated yields of single regioisomers were typically 65−84%, while observed regioselectivities were ≥90:10 for 1,8-naphthyridines and ≥84:16 for quinolines.

Introduction

Quinolines and 1,8-naphthyridines share the common structural motif of an aromatic ring fused to a pyridine ring. What sets the two classes apart is the presence of an additional nitrogen atom in the second aromatic ring of 1,8-naphthyridines. Although an additional nitrogen atom can result in profound differences in chemical behavior, analogous applications and modes of preparation highlight the similarities shared by both classes of compounds. Both classes of compounds display a broad range of biological activity. Quinolines have long been developed as anti-malarial agents since the discovery of the Cincona alkaloids,[1] and the 1,8-naphthyridine core has been the focus of studies and practical applications as antibacterial agents.[2] Recent parallels in biological activity of the two classes of compounds have been found in the form of antibacterial,[3] antiinflammatory,[4] antihypertensive,[5] and antiplatelet activity.[6] In addition to medicinal applications, both classes of compounds have been employed in the study of bioorganic and bioorganometallic processes.[7] Although the Cincona alkaloid dihydroxylation process is well-established in the field of organometallic chemistry,[8] quinolines and 1,8-naphthyridines have been the basis for a variety of other organometallic applications as well.[9]



Quinoline 1,8-Naphthyridine

The Friedländer quinoline synthesis is arguably the best known method for preparing quinolines and related azaheterocycles.[10] Although discovered nearly 120 years

(1) (a) Chauhan, P. M. S.; Srivastava, S. K. *Curr. Med. Chem.* **2001**, *8*, 1535. (b) Yates, F. S. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon Press: New York, 1984; Vol. 2, Chapter 2.09.

(2) (a) Stanforth, S. P. In *Comprehensive Heterocyclic Chemistry II*; Ramsden, C. A., Ed.; Pergamon Press: Tarrytown, 1996; Vol. 7, Chapter 7.15. For recent examples, see: (b) Mogilaiah, K.; Chowdary, D. S.; Rao, R. B. *Ind. J. Chem.* **2001**, *40B*, 43. (c) *Drugs Future* **2000**, *25*, 1194. (d) *Drugs Future* **2000**, *25*, 542.

(3) For recent examples, see: ref 2b and Chen, Y.-L.; Fang, K.-C.; Sheu, J.-Y.; Hsu, S.-L.; Tzeng, C.-C. *J. Med. Chem.* **2001**, *44*, 2374.

(4) For recent examples, see: (a) Roma, G.; Braccio, M. D.; Grossi, G.; Mattioli, F.; Ghia, M. *Eur. J. Med. Chem.* **2000**, *35*, 1021. (b) Kalluraya, B.; Sreenizasa, S. *Farmaco* **1998**, *53*, 399.

(5) For recent examples, see: (a) Morizawa, Y.; Okazoe, T.; Wang, S.-Z.; Sasaki, J.; Ebisu, H.; Nishikawa, M.; Shinyama, H. *J. Fluorine Chem.* **2001**, *109*, 83. (b) Ferrarini, P. L.; Mori, C.; Badawneh, M.; Calderone, V.; Greco, R.; Manera, C.; Martinelli, A.; Nieri, P.; Saccomanni, G. *Eur. J. Chem.* **2000**, *35*, 815.

(6) For recent examples, see: (a) Ko, T.-C.; Hour, M.-J.; Lien, J.-C.; Teng, C.-M.; Lee, K.-H.; Kuo, S.-C.; Huang, L.-J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 279. (b) Ferrarini, P. L.; Mori, C.; Badawneh, M.; Manera, C.; Martinelli, A.; Miceli, M.; Ramagnoli, F.; Saccomanni, G. *J. Heterocycl. Chem.* **1997**, *34*, 1501.

(7) For recent example, see: (a) Saito, I.; Sando, S.; Nakatani, K. *Bioorg. Med. Chem.* **2001**, *9*, 2381. (b) He, C.; Lippard, S. J. *J. Am. Chem. Soc.* **2001**, *40*, 1414. (c) Nakatani, K.; Sando, S.; Saito, I. *J. Am. Chem. Soc.* **2000**, *122*, 2172. (d) Nguyen, C. H.; Marchand, C.; Delage, S.; Sun, J.-S.; Garestier, H.; Bisagni, E. *J. Am. Chem. Soc.* **1998**, *120*, 2501.

(8) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem Rev.* **1994**, *94*, 2483.

(9) For recent examples, see: ref 2b and (a) Gunnlaugsson, T.; MacDónaill, D. A.; Parker, D. *J. Am. Chem. Soc.* **2001**, *123*, 12866. (b) He, C.; DuBois, J. L.; Hedman, B.; Hodgson, K. O.; Lippard, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1484. (c) Che, C.-M.; Wan, C.-W.; Ho, K.-Y.; Zhou, Z.-Y. *New. J. Chem.* **2001**, *25*, 63. (d) Ziessel, R.; Harriman, A.; El-ghayoury, A.; Douce, L.; Leize, E.; Nierengarten, H.; Dorsselaer, A. V. *New J. Chem.* **2000**, *24*, 729.

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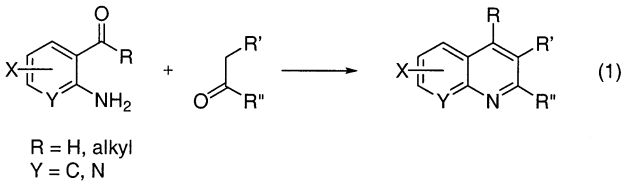
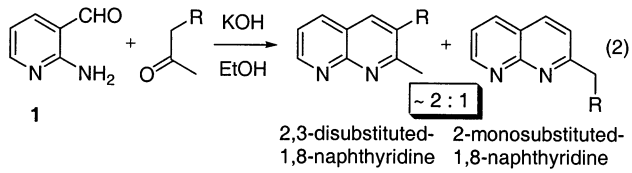
ago, the Friedländer reaction is still considered one of the most useful methods of preparing quinolines and related bicyclic azaaromatic compounds. In its original form, the Friedländer quinoline synthesis consisted of the reaction between an aromatic ortho-aminoaldehyde and an aldehyde or ketone bearing an alpha-methylene functionality (eq 1). Since Friedländer's initial discovery, the reaction has been extended to include a wide range of substrates, including aromatic ortho-aminoketones and nitrogen heterocycles for the synthesis of 1,8-naphthyridines and related polycyclic heterocycles.



(1)

The longevity of the Friedländer reaction is due in large part to the observed broad range of functional group compatibility. With regard to the aromatic ortho-aminoaldehyde component, a wide range of functional groups is tolerated on the aromatic ring. With regard to ketone component, the literature is replete with examples of symmetrical ketones, or ketones with additional activating functionality alpha to the carbonyl group. The Friedländer reaction is, however, not without its limitations. This is exemplified by the dearth of examples wherein unactivated, unsymmetrical ketones, such as 2-alkanones, have been employed in the Friedländer reaction. Presumably, this is due to a perception that there is an inherent lack of regiocontrol in the formation of the reactive species derived from the ketone component. The examples reported thus far indicate that the major isomer formed in Friedländer reactions employing 2-alkanones is the 2,3-disubstituted product, although usually with poor regioselectivity. For example, we (vide infra) and others have found that the standard hydroxide-catalyzed Friedländer reaction conditions provide roughly a 2:1 ratio of 2,3-disubstituted to 2-monosubstituted 1,8-naphthyridines when applied to the reaction of 2-alkanones with 2-aminonicotinaldehyde (**1**) (eq 2).[11] To date, we are aware of only one cited example in which a 2-alkanone had yielded the 2-substituted product as the major isomer in a Friedländer reaction. In this isolated example, regioselectivity appears to be largely a function of the unique properties of the substrate examined.[12,13] Herein lies an apparent limitation of the Friedländer annulation in its current state. One solution to this problem is to employ methyl ketone surrogates that are activated toward regioselective attack at the terminal position.[14] Due to our need for regioselective control in the preparation of 2-alkyl-substituted naphthyridines in the most efficient and economical manner possible, we chose to pursue a general solution to the problem of preparing these compounds directly from 2-alkanones. Herein we disclose the successful outcome of this endeavor, in which pyrrolidine and pyrrolidine derivatives provide very high yields of annulation products with good to excellent regioselectivity in favor of the 2-monosubstituted derivatives.



(2)

Results and Discussion

Our study began with a screen of the types of catalysts typically employed in the Friedländer reaction. Both acids and bases have been used, with NaOH or NaOEt usually the reagents of choice. Typical acids employed in the Friedländer reaction include pTsOH and H_2SO_4. Although the detailed mechanism of the Friedländer reaction is still a matter of speculation, one would suspect that enamine, enolate, and/or enol forms of the ketone component would be requisite intermediates in most plausible mechanistic proposals. Enols and Enolates could be invoked for any reaction employing acids and bases, respectively. Enamines, on the other hand, could only be implicated if one proposes that the aminoaldehyde forms an enamine with the ketone component, or in reactions in which an external amine is added as a catalyst. Considering the prominence of enamines in the nucleophilic chemistry of ketones, invoking an enamine intermediate would appear to be an attractive proposal. To our surprise, however, very little precedent existed for the use of amines as catalysts in the Friedländer reaction. To our knowledge, only piperidine has been used extensively in the Friedländer reaction.[15] Therefore, along with the standard conditions typically employed for the Friedländer reaction, we included a diverse structural variety of amines as part of our initial survey.

(10) (a) Cheng, C.-C.; Yan, S.-J. In *Organic Reactions*; Dauben, W. G., Ed.; John Wiley & Sons: New York, 1982; Vol. 28, Chapter 2. (b) Friedländer, P. *Berichte* **1882**, *15*, 2572. For reviews of quinoline and naphthyridine syntheses, see: (c) Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Ramsden, C. A., Ed.; Pergamon Press: Tarrytown, 1996; Vol. 5., Chapter 5.05. (d) Reference 2a. (e) Jones, G. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon Press: New York, 1984; Vol. 2, Chapter 2.08. (f) Lowe, P. A. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon Press: New York, 1984; Vol. 2, Chapter 2.11.

(11) Hsiao, Y.; Rivera, N. R.; Yasuda, N.; Hughes, D. L.; Reider, P. J. *Org. Lett.* **2001**, *3*, 1102. The authors have noted that in the original publication the observed regioselectivity in the NaOH-catalyzed Friedländer reactions were inadvertently transposed in the table. The correction has been published. See: Hsiao, Y.; Rivera, N. R.; Yasuda, N.; Hughes, D. L.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1242.

(12) (a) Fehnel, E. A. *J. Org. Chem.* **1966**, *31*, 2899. The potassium hydroxide-catalyzed reaction between methyl ethyl ketone and 2-aminobenzophenone was reported to provide a mixture of isomers, from which the 2-substituted product was isolated as the major component in 71% yield. This result contrasts with all other published results to date wherein similar conditions are used with a variety of other aminoaldehydes and methyl ketones. For examples, see those presented herein, as well as from ref 11 and those cited in ref 10a.

(13) A recent report describes the reaction of methyl ketones with 2-aminobenzyl alcohol in the presence of KOH and a ruthenium catalyst, providing the 2-substituted quinolines as products. Two examples of aliphatic methyl ketones are reported to yield the 2-substituted quinolines in excess of the 2,3-disubstituted quinolines (ratios ranged from 70:30 to 80:20). The mechanism has not been discerned as yet, but is believed to proceed by way of oxidation of the 2-aminobenzyl alcohol to 2-aminobenzaldehyde, followed by a Friedländer reaction sequence. Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2001**, 2576.

(14) For a highly regioselective process employing β-ketophosphonates as methyl ketone surrogates, see ref 11.

(15) (a) Mogilaiah, K.; Reddy, N. V. *Indian J. Chem., Sec. B* **2002**, *41*, 215. (b) Reference 10a.

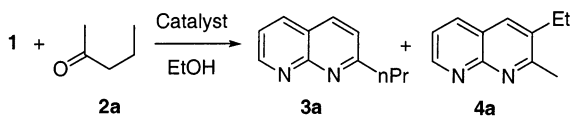
TABLE 1. Screen of Catalysts for the Friedländer Reaction between 2-Aminonicotinaldehyde and 2-Pentanone

$$\mathbf{1} + \mathbf{2a} \xrightarrow[H_2SO_4,\ EtOH]{\text{catalyst}} \mathbf{3a} + \mathbf{4a}$$

catalyst	conversion[a]	ratio[b]
sodium hydroxide	>99	37:63
sodium ethoxide	87	49:51
ammonium acetate	44 (89)	42:58 (40:60)
ammonia	18 (28)	44:56 (43:57)
octylamine	92	55:45
diethylamine	1 (7)	(74:26)
piperidine	11 (39)	89:11 (88:12)
morpholine	8 (26)	78:22 (77:23)
proline	5 (64)	83:17 (70:30)
pyrrolidine	**97**	**86:14**
azetidine[c]	98	54:46
2-methylaziridine	1 (9)	(41:59)
DBU	69 (98)	24:76 (27:73)
Et_3N	0	N/A
H_2SO_4[d]	0	N/A

[a] Mole percent conversion to **3a** + **4a** after 23 h at 23 °C, determined by HPLC. Values in parentheses are after an additional 23 h at 70 °C. [b] Ratio of **3a**:**4a** after 23 h at 23 °C, determined by GC. Values in parentheses are after an additional 23 h at 70 °C. [c] Reaction run with 1.1 equiv of azetidine hydrochloride and 1.0 equiv of DIPEA. [d] Reaction with 0.05 equiv of H_2SO_4.

The screening of potential catalysts required a standard reaction and set of reaction conditions with which to use as a gauge of success. The Friedländer reaction between **1** and 2-pentanone (**2a**) was chosen as our model reaction (eq 3). This reaction would produce the desired 2-propylnaphthyridine (**3a**), as well as 2-methyl-3-ethylnaphthyridine (**4a**). The aminoaldehyde component **1** was easy to prepare and is a stable crystalline solid.[16] Furthermore, the reactivity of **1** under Friedländer conditions had already been demonstrated to give a mixture of isomers with poor regioselectivity.[11] Thus, **1** appeared to be a good substrate for initial screening experiments. Scouting experiments with piperidine as a catalyst indicated the reaction was very slow when substoichiometric quantities were employed, and that a small amount of added HCl or H_2SO_4 provided an observable rate acceleration.[17] Therefore, in screening runs employing an amine catalyst, a 10% excess of the amine in combination with 5% H_2SO_4 was used. As a means of accelerating our discovery process, we employed the Anachem SK-233 Workstation automated system for running the survey reactions.[18]



(3)

The results of our initial screen are shown in Table 1. Not unexpectedly, catalysis with hydroxide or alkoxide resulted in high conversion, but poor regioselectivity in favor of the undesired 2,3-dialkylnaphthyridine **4a**. Ammonia and ammonium acetate also behaved similarly to oxide bases with regard to regioselectivity, although the conversions were lower. Octylamine provided good conversion to product, but with poor regioselectivity.[19] The secondary amine, diethylamine, did not catalyze the reaction to any significant extent. With the six-membered cyclic amines, piperidine and morpholine, we began to observe good regioselectivity in favor of **3a**. However, conversions with these catalysts were only modest, even after prolonged aging at elevated temperature. The self-catalyzing, five-membered cyclic amine, proline, also provided an outcome similar to the six-membered cyclic amines, albeit with somewhat better conversion and lower regioselectivity. In contrast to the other cyclic amines, pyrrolidine not only provided good regioselectivity in favor of **3a**, but also very high conversion at ambient temperature. Consistent with the literature reports regarding the high reactivity of azetidine-derived enamines, the reaction between **1** and **2a** in the presence of azetidine provided the Friedländer products in high conversion, albeit with essentially no regioselectivity.[20] The aziridine derivative was neither reactive, nor regioselective. While DBU displayed catalytic activity with poor regioselectivity in favor of the undesired isomer, other trialkylamines examined were unreactive.[21] The reaction with sulfuric acid alone provided no significant amounts of product.

Among the initial catalysts screened, pyrrolidine appeared to couple the optimal properties of all the catalysts studied, providing for both high conversion with good regioselectivity. To our knowledge, this is the first example in which pyrrolidine has been used as a catalyst in the Friedländer reaction. *Furthermore, this appears to be the highest regioselectivity ever observed favoring the 2-substutituted product in a Friedländer reaction between a simple ketone and an aromatic aminoaldehyde.*

Our next iteration of screening experiments surveyed a series of pyrrolidine and related derivatives (Table 2). All the pyrrolidine derivatives except 3-pyrroline provided good regioselectivity in favor of the 2-substituted naphthyridine.[22] With regard to reactivity, substitution at the 2-position in the monocyclic pyrrolidines clearly slowed the rate of reaction. In contrast, the 2-substituted bicyclic derivative, TABO, appeared to display high reactivity as well as regioselectivity.[23] Clearly the data in Table 2 indicates that pyrrolidines have a general

(16) (a) Rivera, N. R.; Hsiao, Y.; Cowen, J. A.; McWilliams, J. C.; Armstrong, J. D.; Yasuda, N. Hughes, D. L. *Synth. Commun.* **2001**, *31*, 1573. (b) Turner, J. A. *J. Org. Chem.* **1983**, *48*, 3401.

(17) The small rate acceleration observed is presumed to be acid catalysis involved in the formation of imine and enamine intermediates: Cervinka, O. In *The Chemistry of the Enamines*; Rappaport, Z., Ed.; John Wiley & Sons: New York, 1994; Part 1, Chapter 9.

(18) A description of the automated discovery procedure can be found in the Experimental Section.

(19) Adamantylamine and *tert*-butylamine were also evaluated in a screening run. At 23 °C, less than 0.5 mol % product was observed. After 24 h at 70 °C, the major products were the corresponding imines. A small amount (<5mol %) of Friedländer products was observed after aging at 70 °C, with regioselectivity of 40:60 and 33:66 in favor of **4a** for adamantylamine and *t*-butylamine, respectively.

(20) An independent examination of the reaction with catalytic amounts of azetidine (5%) indicated that this was the most reactive of the amine catalysts. The regioselectivity remained essentially the same as with 1.1 equivalents of catalyst. The substituted azetidine, L-azetidine 2-carboxylic acid, did not catalyze the Friedländer reaction at room temperature, but provided an 87 mol % conversion after 23 h at 70 °C, albeit with only a 67:33 ratio of **3a**:**4a**, respectively.

(21) Quinuclidine and DABCO also displayed similar lack of catalytic activity, yielding ≤1 mol % of the Friedländer products after 24 h at 70 h.

(22) One must also bear in mind that commercially available 3-pyrroline contains small amounts of pyrrolidine as an impurity, and this is likely to account for some of the product formed.

(23) TABO = 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane.

TABLE 2. Screen of Pyrrolidine Catalysts for the Friedländer Reaction between 2-Aminonicotinaldehyde with 2-Pentanone

$$\mathbf{1} + \mathbf{2a} \xrightarrow[H_2SO_4,\ EtOH]{\text{catalyst}} \mathbf{3a} + \mathbf{4a}$$

catalyst	conversion[a]	ratio[b]
pyrrolidine	99	86:14
3-pyrroline	97	79:21
3-pyrrolidinol	75 (82)	84:16 (84:16)
(*S*)-2-pyrrolidinemethanol	40 (73)	86:14 (86:14)
2-methylpyrrolidine	66 (89)	87:13 (87:13)
TABO[c]	>99	87:13

[a] Mole percent conversion to **3a** + **4a** after 23 h at 23 °C, determined by HPLC. Values in parentheses are after an additional 23 h at 70 °C. [b] Ratio of **3a**:**4a** after 23 h at 23 °C, determined by GC. Values in parentheses are after an additional 23 h at 70 °C. [c] TABO = 1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane.

TABLE 3. Survey of Pyrrolidine Catalysts in the Friedländer Reaction of 2-Aminonicotinaldehyde with 2-Pentanone Employing 5% Catalyst

$$\mathbf{1} + \mathbf{2a} \xrightarrow[H_2SO_4,\ EtOH]{\text{5\% catalyst}} \mathbf{3a} + \mathbf{4a}$$

catalyst	conversion[a]	ratio[b]
2-methylpyrrolidine	7 (21)	83:17 (85:15)
2-methylpyrrolidine + H_2SO_4	11 (29)	85:15 (84:16)
3-pyrroline	60 (80)	72:28 (68:32)
3-pyrroline + H_2SO_4	60 (77)	63:37 (62:38)
pyrrolidine	46 (72)	88:12 (88:12)
pyrrolidine + H_2SO_4	54 (78)	87:13 (87:13)
TABO	51 (80)	83:17 (83:17)
TABO + H_2SO_4	76 (92)	83:17 (82:18)

[a] Mole percent conversion to **3a** + **4a** after 23 h at 23 °C, determined by HPLC. Values in parentheses are after an additional 23 h at 70 °C. [b] Ratio of **3a**:**4a** after 23 h at 23 °C, determined by GC. Values in parentheses are after an additional 23 h at 70 °C.

propensity to select for the 2-substituted naphthyridines, and any of the saturated derivatives could be employed to access 2-substituted naphthyridines. However, from the data generated thus far, it was not yet clear which would be the optimal catalyst for the Friedländer reaction.

In a screening experiment designed to identify the most reactive catalyst among the pyrrolidine derivatives, we obtained results from a series of experiments employing only 5% loading of some of the pyrrolidine derivatives (Table 3).[24] At ambient temperature, 5% catalyst loading was insufficient to drive the reaction to completion within 96 h. In general, acid catalysis appeared to accelerate the reaction, although this was not observed for 3-pyrroline. Not surprisingly, catalytic quantities of 2-methylpyrrolidine displayed insufficient reactivity at ambient temperature to be of practical value. Under these conditions, the bicyclic amine, TABO, stands out as the most reactive catalyst, while pyrrolidine as the most regioselective.

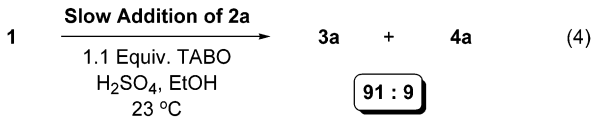
Interestingly, with all the catalysts except pyrrolidine, we observed a consistent decrease in regioselectivity when comparing substoichiometric (Table 3) with stoichiometric charges of catalysts (Table 2). From this, we surmised that a high concentration of catalyst relative to substrate may have a positive effect on the regioselectivity of the reaction. Therefore, we examined the reaction of the most reactive catalyst, TABO, under conditions in which the concentration of TABO would remain high relative to that of **2a**. Accordingly, **2a** was added slowly to a solution of **1**, 1.1 equivalents of TABO, and 5% H_2SO_4 (eq 4). We were pleased to observe a reproducible increase in the regioselectivity of the reaction under these conditions, providing **3a** and **4a** in a 91:9 ratio, respectively. Not surprisingly, the same conditions applied to the reaction with pyrrolidine gave no enhancement in regioselectivity.

TABLE 4. Effect of Temperature on the Friedländer Reaction of 2-Aminonicotinaldehyde with 2-Pentanone Employing Pyrrolidine or TABO as Catalysts

$$\mathbf{1} + \mathbf{2a} \xrightarrow[H_2SO_4,\ EtOH]{\text{catalyst}} \mathbf{3a} + \mathbf{4a}$$

catalyst[a]	temp (°C)	ratio[b]
pyrrolidine	23	87:13
pyrrolidine	75	88:12
TABO	−20	74:26
TABO	10	90:10
TABO	23	91:09
TABO	45	94:06
TABO	75	96:04

[a] 1.1 equivalents of catalyst was employed. All reactions proceeded to >98% converision by HPLC analysis. [b] Ratio of **3a**:**4a** determined by GC.



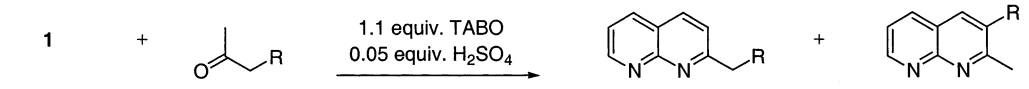
In the next series of experiments, we explored the effect of temperature on the regioselective outcome of the reaction using either pyrrolidine or TABO as catalyst (Table 4). Unexpectedly, the regioselectivity was positively related to increasing temperature. The effect was most pronounced when TABO was used as the catalyst. With TABO as the catalyst, the Friedländer reaction between **1** and **2a** yielded the desired 2-substituted naphthyridine **3a** with 96% regioselectivity at 75 °C!

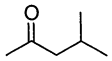
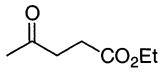
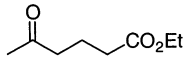
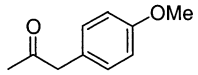
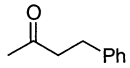
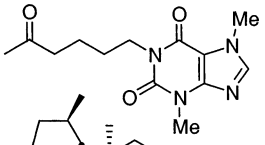
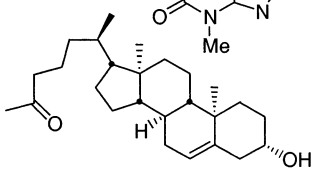
It now appeared that we had a set of conditions that gave excellent regioselectivity in the reaction of **1** with **2a**. Therefore, we set out to delineate the scope of the reaction. The results of the TABO-catalyzed Friedländer reaction of **1** and a range of ketone substrates were compared to that of NaOH catalysis (Table 5). In all cases but one, that of 2-butanone, the 2-alkylnaphthyridine derivative made up at least 90% of the product distribution.[25] When compared to the results obtained under typical Friedländer reaction conditions (i.e., NaOH), a complete reversal in regioselectivity was observed for all but one of the substrates examined (entry 4). One clear trend that stands out from the data in Table 5 is that substitution at the beta position of the carbonyl group has a marked effect on the regiochemical outcome of the

(24) 2-Methylpyrroldine was also included because it displayed high regioselectivity.

(25) In general, we observed a roughly 2−3% variation in regioselectivity from run to run. For example, several runs between **1** and **2a** provided **3a** within a range of 93−96% regioselectivity.

TABLE 5. TABO-Catalyzed Friedländer Reaction between 2-Aminonicotinamide and Various Methyl Ketones



Entry	Ketone (R)		Yield[a]	Ratio (**3**:**4**)[b]	Ratio with NaOH[c]
1		n = 1 (**2b**)	>99 (74)	78:22	12:88
2		n = 2 (**2a**)	96 (84)	93:07	35:65
3		n = 3 (**2c**)	94 (85)	94:06	30:70
4		**2d**	99 (86)	99.6:0.4	95:05[d]
5		**2e**	96 (77)	90:10	15:85[e,f,g]
6		**2f**	94 (71)	94:06	28:72[e,f]
7		**2g**	88 (66)	93:07	38:62
8		**2h**	97 (71)	92:08	32:68
9		**2i**	98 (65)[h]	96:04	19:81[h]
10		**2j**	82 (77)[h]	96:04	32:68[h]

[a] Assay yield of naphthyridine products (**3a**−**j** + **4a**−**j**) determined by HPLC using isolated standards. Yields in parentheses are isolated yields for the major isomer **3a**−**j**. [b] Ratio of **3a**−**j**/**4a**−**j** determined by GC and/or NMR. [c] Ratio of **3a**−**j**/**4a**−**j** produced in the reaction with 1.1 equiv of NaOH in EtOH. [d] 70 mol % conversion under otherwise identical conditions. [e] Reaction run with 1.1 equiv of EtONa. [f] Products were the carboxylate sodium salts. [g] The mixture also contained 28% of **5**. [h] Reaction run in MeOH.

reaction. No substitution at the beta position leads to a drop in regioselectivity (entry 1). Simple alkyl substitution yields high regioselectivity (entries 2, 3, 9, and 10). While dialkyl substitution at the beta position provides excellent regioselectivity with either Friedländer reaction protocol, we still observed a significant increase in regioselectivity (>99%) with the new procedure employing TABO as a catalyst (entry 4).

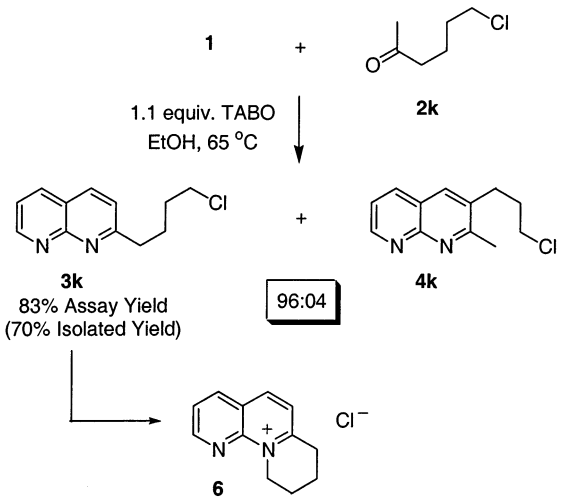
Substitution of an electron-withdrawing ester functionality at the beta or gamma positions resulted in a marked increase in the 2,3-dialkylnaphthyridine isomer under the standard Friedländer reaction conditions (entries 5 and 6). The observed deviation on the regioselective outcome for the ester-substituted substrates is likely a consequence of a decrease in the pK_a of the alpha-hydrogens situated on the ester side of the carbonyl group stemming from subtle inductive effects imparted by the ester functionality. It is interesting to note that the effect was less pronounced under the TABO-catalyzed conditions. Under TABO-catalyzed conditions, a small decrease was observed when an ester functionality is located at the beta position, whereas no decrease is seen for the substrate with an ester functionality at the gamma position.

The keto-ester substrates (**2e** and **2f**) exemplify the functional group compatibility of this protocol relative to alternative Friedländer conditions. These substrates would be inaccessible to approaches that require the formation of β-ketophosphonates from esters, or those requiring other Group I or II organometallic protocols, due to the sensitivity of the ester group toward these reagents. Furthermore, the strongly basic conditions typically employed in the Friedländer reaction are unacceptable for simple keto-ester substrates such as **2e** and **2f** for saponification of the ester functionality would occur under these conditions.[26]

Aryl substitution at the alpha or beta position of the ketone resulted in only very small changes in regioselectivity (entries 7 and 8). Aryl substitution alpha to the carbonyl group appeared to have essentially no effect on the TABO-catalyzed reaction, while affecting a slight decrease in the regioselectivity of the hydroxide-catalyzed reaction (entry 7). Phenyl substitution beta to the carbonyl group resulted in a very subtle decrease in the regioselectivity of the TABO-catalyzed reaction, while also increasing the regioselectivity of the NaOH-catalyzed reaction in favor of the 2,3-disubstituted naphthyridine (entry 8).

The last two examples in Table 5 (entries 9 and 10) highlight the application of more complex structures with potential biological applications. Both Trental **2i** and steroid derivative **2j** provided the desired Friedländer

SCHEME 1



isomers in high yield and with regioselectivity typical of this protocol. In both of these examples it was possible to isolate the products by direct crystallization from the reaction mixture.

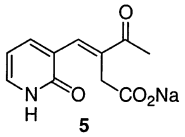
We also examined the reaction of the sensitive chloroketone **2k** (Scheme 1).[27] We were pleased to find that the TABO-catalyzed Friedländer reaction between **1** and **2k** provided **3k** and **4k** in a 96:4 ratio, respectively.[28] Although the product could be isolated in 70% yield, it underwent gradual intramolecular cyclization to the quaternary ammonium salt **6** if allowed to stand at 23 °C.

Chain-linked diketones offer a platform for the rapid synthesis of linked naphthyridines. For example, the diketone **2l** could provide entry to the ethylene-linked, bis(naphthyridine) **7**. Structures such as **7** have interesting potential applications as chelating ligands in organometallic chemistry. However, double Friedländer annulation of **2l** can lead to three different products (**7**, **8**, and **9**), only one of which (**7**) would be applicable for chelating to a single metal center. Under the typical Friedländer conditions, little or none of **7** is observed, with the isomers **8** and **9** forming in a 70:30 ratio, respectively. In contrast, the TABO-catalyzed Friedländer provides **7** as the predominant product. A somewhat lower yield than usual may be a consequence of competing intramolecular reactions of **2l**. However, when one considers the yield corresponds to 82% for each naphthyridine-forming reaction, the overall yield is quite reasonable. Furthermore, the product was easily isolated by direct crystallization from the reaction mixture.

We next turned our attention to further delineating the scope of the reaction by applying the new Friedländer reaction conditions to the synthesis of heterocycles other than 1,8-naphthyridines. Table 6 summarizes our results with the TABO-catalyzed Friedländer reaction applied to the preparation of quinolines and chromone **16**, and comparing these reactions to the traditional hydroxide or alkoxide-catalyzed Friedländer conditions. In all cases the major product was the 2-substituted derivative, in contrast to the hydroxide or alkoxide-catalyzed Friedländer conditions. Good yields of the 2-substituted quinolines were readily obtained by this procedure. The dibromo-substituted aminoaldehyde **10** provided high yields and regioselectivity only slightly lower than that with **1** (entries 1 and 2). The chloro-derivative **13** also provided the 2-substituted chloroquinoline **14** as the major isomer, albeit with somewhat lower regioselectivity than was observed for **10**. Last, the Friedländer reaction between the chromone derivative **15** and **2c** exhibited the lowest regioselectivity of all the aminoaldehyde substrates (entry 4). Nevertheless, the 2-substituted isomer **16** is still obtained as the major isomer and isolated in good yield. Interestingly, under the standard NaOH conditions used as a control for all of the substrates examined, no Friedländer products were observed between **15** and **2c**.[29]

In another set of experiments, intended to outline the scope of the new Friedländer protocol, we examined the reaction of sterically congested ketones in which reactivity rather than regioselectivity was the key concern. Toward that end, we examined the reaction of cyclic, α-methyl-substituted ketones (Scheme 3). Methylcyclopentanone **17** smoothly underwent Friedländer reaction with **1** at room temperature using pyrrolidine as catalyst, providing the desired naphthyridine in 92% assay yield.[30] Ketone **19** was much less reactive than the methyl ketones **2a**−**k**, and required a larger excess of reagent and prolonged aging at elevated temperature to drive the reaction to completion.[31] Nevertheless, the desired Friedländer product **20** was obtained in 68% assay yield (58% isolated yield). The enantiomerically enriched, α-methyl acyclic ketone **21** was prepared according to the literature and evaluated as a substrate in the Friedländer reaction with **1**.[32] Like ketone **19**, **21** also required a longer age time to consume **1**. After 67 h, the product **22** was produced in 67% assay yield (61% isolated yield). While catalysis with TABO resulted in product **22** of 75% enantiomeric excess, **22** was obtained in 82% enantiomeric excess when pyrrolidine was used as the catalyst. Although some loss in enantiopurity is indicated, the new Friedländer conditions still provide a potential route to

(26) NaOH would always be present whether employing hydroxide or alkoxide bases because two equivalents of water are liberated for each molecule of product formed. Nevertheless, when NaOH was used in the reaction between **1** and **2e**, a complex mixture was obtained. In the reaction of **1** with **2e** employing NaOEt, we also observed the product **5**, which comprised 28% of the mixture.



5

(27) For examples of reactions between 5-chloroalkylalkanones and amines or alcohols, see: (a) Fujimoto, K.; Maekawa, H.; Matsubara, Y. *Chem. Lett.* **1996**, 143. (b) Rybar, A.; Turcani, P.; Alfoeldi, J. *Collect. Czech. Chem. Commun* **1993**, *58*, 1169. (c) Soti, F.; Incze, M.; Dardos-Balogh, Z. *J. Chem. Res., Synop.* **1991**, *8*, 198.

(28) The corresponding reaction with NaOH provided a 29:71 ratio of **3k** and **4k**, respectively.

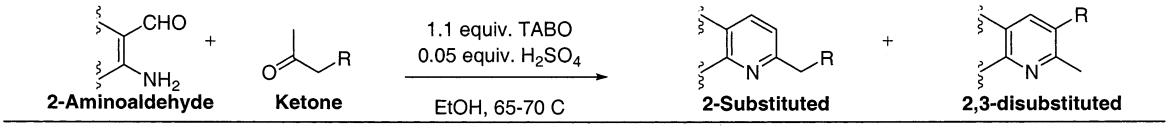
(29) HPLC and NMR analysis of the crude reaction mixture indicated **16** remained in tack, while **2a** had reacted to form other products.

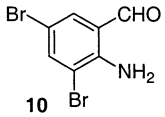
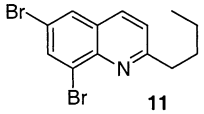
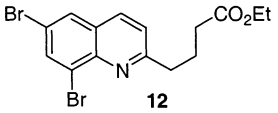
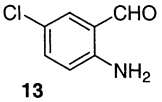
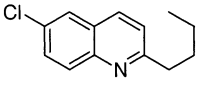
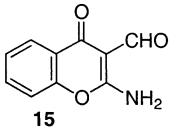
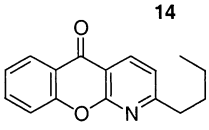
(30) The reaction between **1** and **17** also proceeded when only 5% pyrrolidine was employed, but higher yields were obtained with stoichiometric quantities of pyrrolidine.

(31) Pyrrolidine also catalyzed the reaction between **19** and **1**, but conversions were lower and the reaction mixture contained several side products.

(32) Djerassi, C., Geller, L. E. *J. Am. Chem. Soc.* **1959**, *81*, 2789−2794.

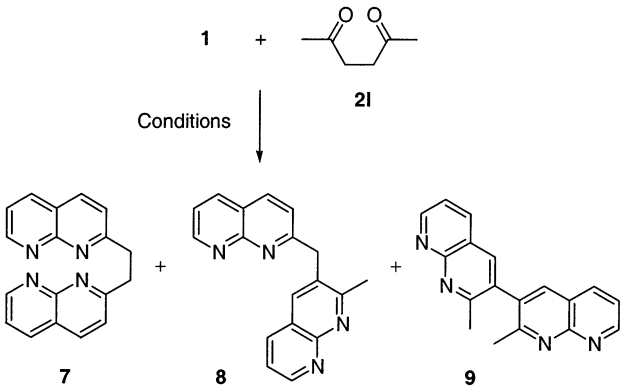
TABLE 6. TABO-Catalyzed Friedländer Reaction In the Preparation of 2-Substituted Quinolines and Chromeno[2,3-b]-pyridines



Entry	2-Aminoaldehyde	Ketone (R)	Major Isomer	Yield[a]	Ratio[b]	Ratio with NaOH[c]
1	 **10**	**2c**	 **11**	90 (78)	88:12	30:70
2	**10**	**2f**	 **12**	93 (84)[d]	89:11	24:76[e]
3	 **13**	**2c**	 **14**	99 (77)[f]	84:16	30:70
4	 **15**	**2c**	 **16**	99 (70)[f]	80:20	NP[g]

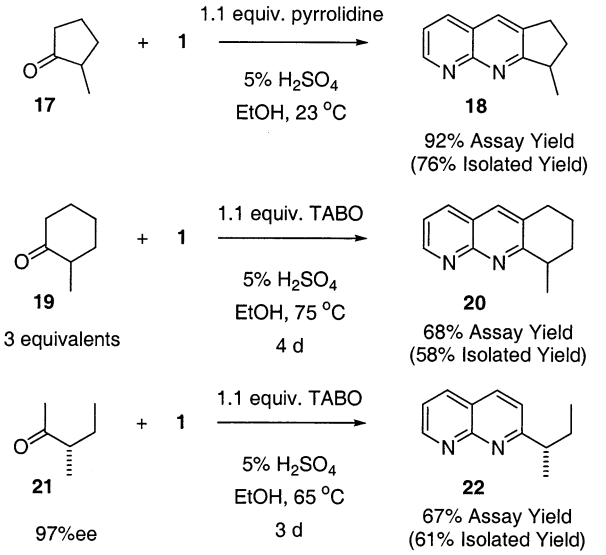
[a] Assay yield of both naphthyridine regioisomers determined by HPLC using isolated standards. Yields in parentheses are isolated yields for the major isomers **11**−**12**, **14**, and **16**. [b] Ratio of 2-substituted/2,3-disubstituted regioisomers determined by GC and/or NMR. [c] Ratio of 2-substituted/2,3-disubstituted regioisomers produced in the reaction with 1.1 equivalents of NaOH in EtOH. [d] Product was isolated as a 89:11 mixture of isomers. [e] Products were the carboxylate sodium salts. [f] The reaction was conducted by slow addition of the aminoaldehyde to a heated solutin of **2a**, TABO, and H_2SO_4 in EtOH. [g] No Friedländer products.

SCHEME 2



Conditions	Ratio (**7**:**8**:**9**)	
NaOH, EtOH	<1:70:30	
1.1 Equiv. TABO 0.05 equiv. H_2SO_4 EtOH, 65 °C	95:05:00	68% Assay Yield 46% Isolated Yield (direct crystallization)

SCHEME 3



Catalyst	%ee (**22**)
TABO	75
pyrrolidine	82

enantiomerically enriched, α-substituted-1,8-naphthyridines.

The mechanism of the Friedländer reaction has not been determined, and is likely to vary depending upon substrate structure and reaction conditions. Numerous intermediates can be implicated in the steps leading from starting aminoaldehyde and ketone to final aromatized product. The role of an amine catalyst could be implicated in almost any of these steps. The simplest role an amine could play would be solely that of a Brønsted base. Clearly the amine catalysts provide a source of a base significantly stronger than that of **1** or the aminobenzaldehyde substrates. However, there does not appear to be a clear correlation between base strength and either reactivity or regioselectivity (Table 1). For example, while

triethylamine, quinuclidine, diethylamine, piperidine, and pyrrolidine are reported to have pK_a values between 10.8 and 11.3, only pyrrolidine and piperidine display significant catalytic activity.[33] Further, morpholine and piperidine appear similar in catalytic activity, yet they differ by nearly 3 pK_a units. With regard to regioselectivity, similar observations can be made. For example, pyrrolidine and azetidine display similar catalytic activity and are reported to be of similar base strength, yet the regioselectivity of azetidine more closely matches that of ammonia, which is reported to have a pK_a >2 units lower than that of azetidine.

The Friedländer reaction with amine or oxide catalysis is a complex sequence of events, and competing mechanistic pathways are likely to be occurring to varying degrees depending upon the structure of the substrates and catalyst. Further studies are needed to understand these processes with precision.

Conclusion

In this report we have presented novel conditions for conducting the Friedländer reaction that allow for the use of unactivated, methyl ketones in the synthesis of 2-substituted azaheterocycles, including 1,8-naphthyridines, quinolines, and chromeno[2,3-b]pyridines. The conditions described appear to be general with regard to both ketone and aminoaldehyde component, providing the 2-substituted product as the major regioisomer in each case. The conditions are mild enough to tolerate additional sensitive functionality, such as esters and alkyl chlorides, and have been demonstrated in the preparation of complex molecules. This appears to be the first example of a Friedländer reaction employing pyrrolidines as catalysts. Further investigations into the mechanism of this reaction and the interesting reactivity of the bicyclic amine, TABO, are underway.

Experimental Section

General Considerations. All reactions were preformed under a nitrogen atmosphere. Slow additions of liquids were performed using a syringe pump. Unless otherwise noted, all reagents and solvents were purchased from commercial sources and used without further purification. 2-Amino-3,5-dibromobenzaldehyde was purchased from a commercial source and purified by chromatography on silica gel (2:1 → 1:1 Hexanes/DCM) prior to use. 2-Aminonicotinaldehyde was prepared according to literature procedures.[34] HPLC analysis was performed with a Zorbax Extend-C18 column (4.6 × 75 mm, 3.5 μm particle size). Assay yields were obtained by HPLC analysis from crude reaction mixtures, or by analysis of the mother liquor and crystalline products for those examples in which the product was crystallized directly from the reaction mixture. All assays were calculated using the purified products as standards. Isomeric ratios were determined by gas chromatographic analysis employing a Restek Rtx-1 (60 m × 0.32 mm ID × 1.5 μm df) column and/or NMR analysis. Enantiopurity of **22** was determined by supercritical fluid chromatography (SFC) using a Chiralcel OJ column (4.6 mm × 25 cm) with a mobile phase of 4% methanol in carbon dioxide, outlet pressure of 200 bar, flow rate of 1.5 mL/min, and column temperature of 35 °C. Retention times of **R-22** and **S-22** were 5.49 and 5.76 min, respectively. Melting points were determined on an open air apparatus and are uncorrected. The purity of new compounds reported herein was established by combustion analysis. In cases where microanalysis was not available, purity is estimated to be >95% on the basis of ^{1}H and ^{13}C NMR analysis.

General Procedure for Automated Catalyst Survey Reactions (Tables 1−3). 2-Aminonicotinaldehyde (183 mg, 1.5 mmol) was manually charged to reaction vessels. All other reagent and substrate additions, except that of the solid catalysts proline and ammonium acetate, were charged to the vessels by the automated robotic arm. A 2.5 M solution of 2-pentanone in EtOH (0.66 mL, 1.65 mmol), containing H_2SO_4 (4.2 μL, 0.076 mmol) for those runs in which employed H_2SO_4 catalysis, was charged to the reaction vessel. The basic catalysts and additional ethanol (sufficient to bring the total reaction volume to 3.0 mL) were added to the reaction vessels. The reactions were stirred at 23 °C for 23 h, whereupon samples were withdrawn by the robotic arm and diluted appropriately for HPLC and GC analysis. The reactions were then heated to 70 °C and stirred an additional 23 h, whereupon samples were withdrawn for HPLC and GC analysis.

General Procedure. 2-Ethyl-1,8-naphthyridine (3b). Under nitrogen, a solution of 2-aminonicitinaldehyde (2.50 g, 20.5 mmol), 95% 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (4.0 mL, 22 mmol), and H_2SO_4 (57 μL, 1.0 mmol) in ethanol (12.5 mL) was heated to 65 °C. To this solution was added a 2.82 M solution of 2-butanone in ethanol (8.00 mL, 22.5 mmol) over 90 min. The solution was aged at 65 °C for an additional 60 min, whereupon it was concentrated. Gas chromatography and ^{1}H NMR indicated a 78:22 ratio of naphthyridine isomers. Chromatography on silica gel (EtOAc) yielded the title compound as an oil. The oil was dissolved in MTBE and solvent-switched to *n*-heptane, whereupon the resultant crystals were filtered and washed with *n*-heptane, yielding the title compound as a white solid (2.18 g, 74%): mp = 77.8−79.4 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.98 (dd, J = 4.3, 1.9, 1H), 8.36 (dd, J = 8.3, 1H), 7.56−7.52 (m, 2H), 3.03 (q, J = 7.6, 2H), 1.39 (t, J = 7.6, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 168.1, 155.0, 152.8, 137.8, 137.6, 122.2, 121.6, 121.4, 31.6, 12.6; FTIR (CH_2Cl_2) 1610, 1559, 1498, 1455 cm^{-1}. Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.72; H, 6.34; N, 17.46.

2-Propyl-1,8-naphthyridine (3a). The general procedure was followed with the use of 2-aminonicitinaldehyde (2.50 g, 20.5 mmol), 95% 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (4.0 mL, 22 mmol), H_2SO_4 (57 μL, 1.0 mmol), ethanol (11 mL), and a 2.8 M solution of 2-pentanone in ethanol (8.00 mL, 22.5 mmol). Gas chromatography and ^{1}H NMR indicated a 93:7 ratio of naphthyridine isomers. Chromatography on silica gel (MTBE → 50:50 MTBE/EtOAc) yielded the title compound as an oil, which crystallized upon solvent-switching to *n*-heptane. The resultant crystals were filtered and washed with *n*-heptane, yielding the title compound as a white solid (2.74 g, 78%): mp = 79.9−80.9 °C;^{1}H NMR (CD_3OD, 400 MHz) δ 9.00 (dd, J = 4.4, 1.9, 1H), 8.39 (dd, J = 8.1, 1.9, 1H), 8.33 (d, J = 8.4, 1H), 7.58 (dd, J = 8.1, 4.4, 1H), 7.55 (d, J = 8.3, 1H), 3.00 (t, J = 7.6, 2H), 1.94−1.84 (m, 2H), 1.02 (t, J = 7.3, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 166.9, 155.0, 152.8, 137.7, 137.5, 122.7, 121.6, 121.3, 40.4, 22.5, 12.8; FTIR (CH_2Cl_2) 1610, 1556, 1501, 1451 cm^{-1}. Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.58; H, 7.06; N, 16.17.

2-Butyl-1,8-naphthyridine (3c). The general procedure was followed with the use of 2-aminonicotinaldehyde (2.50 g, 20.5 mmol), 95% 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (4.0 mL, 22 mmol), H_2SO_4 (57 μL, 1.0 mmol), EtOH (11 mL), and a 2.8 M solution of 2-hexanone in ethanol (8.00 mL, 22.5 mmol). Gas chromatography and ^{1}H NMR indicated a 94:6 ratio of naphthyridine isomers. Concentration and chromatography on silica gel (10:90 EtOAc/CH_2Cl_2 → 40:60 EtOAc/CH_2Cl_2) yielded the title compound as an oil (3.23 g, 85%): ^{1}H NMR (CD_3OD, 400 MHz) δ 9.02 (dd, J = 4.3, 1.9, 1H), 8.09 (dd, J = 8.1, 1.9, 1H), 8.03 (d, J = 8.3, 1H), 7.37 (dd, J = 8.1,

(33) Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution: Supplement 1972*; Buttersworth: London, 1972.
(34) Reference 16.

4.3, 1H), 7.34 (d, J = 8.3, 1H), 3.00 (t, J = 7.8, 2H), 1.87−1.80 (m, 2H), 1.43−1.37 (m, 2H), 0.92 (t, J = 7.3, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 167.0, 156.1, 153.2, 136.8, 136.7, 122.5, 121.3, 121.0, 39.1, 31.5, 22.6, 14.0; FTIR (CH_2Cl_2) 1610, 1556, 1498, 1451 cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.58; H, 7.51; N, 15.15.

2-Isobutyl-1,8-naphthyridine (3d). To a solution of 2-aminonicotinaldehyde (9.8 g, 80.3 mmol), pyrrolidine (7.4 mL, 88 mmol), and H_2SO_4 (130 μL, 2.4 mmol) in ethanol (50 mL) was added MIBK (11 mL, 88.3 mmol). The solution was stirred at 23 °C for 24 h. Gas chromatography and ^{1}H NMR indicated a 99.4:0.6 ratio of naphthyridine isomers. Concentration provided the title compound as an oil, which crystallized upon solvent-switching to *n*-heptane. The resultant crystals were filtered and washed with *n*-heptane, yielding the title compound as a white solid (12.8 g, 86%): mp = 56.2−57.5 °C; (^{1}H NMR (CD_3OD, 400 MHz) δ 8.99 (dd, J = 4.4, 2.3, 1H), 8.38 (dd, J = 8.1, J = 1.9, 1H), 8.30 (d, J = 8.4, 1H), 7.59−7.55 (m, 2H), 4.10 (q, J = 7.1, 2H), 3.33 (t, J = 7.1, 2H), 2.98 (t, J = 7.2, 2H), 1.19 (t, J = 7.1, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.1, 156.0, 153.2, 136.6 (2 carbons), 123.0, 121.3, 120.9, 48.4, 29.1, 22.5; FTIR (CH_2Cl_2) 1610, 1552, 1501 cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04; Found: C, 77.19; H, 7.62; N, 14.95.

Ethyl 3-(1,8-Naphthyridin-2-yl)propionate (3e). The general procedure was followed with the use of 2-aminonicotinaldehyde (2.50 g, 20.5 mmol), 95% 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (4.0 mL, 22 mmol), H_2SO_4 (57 μL, 1.0 mmol), EtOH (12.5 mL), and a 2.77 M solution of ethyl levulinate (8.2 mL, 22.7 mmol) in ethanol. Gas chromatography and ^{1}H NMR indicated a 90:10 ratio of naphthyridine isomers. Concentration and chromatography on silica gel (80:20 MTBE/EtOAc) provided the title compound as an oil, which crystallized upon solvent-switching to *n*-heptane. The resultant crystals were filtered and washed with *n*-heptane, yielding the title compound as a white solid (1.83 g, 77%):[11] mp = 61.1−63.2 °C; (^{1}H NMR (CD_3OD, 400 MHz) δ 8.99 (dd, J = 4.4, 2.3, 1H), 8.38 (dd, J = 8.1, J = 1.9, 1H), 8.30 (d, J = 8.4, 1H), 7.59−7.55 (m, 2H), 4.10 (q, J = 7.1, 2H), 3.33 (t, J = 7.1, 2H), 2.98 (t, J = 7.2, 2H), 1.19 (t, J = 7.1, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.0, 164.9, 154.9, 152.7, 137.7, 137.5, 122.9, 121.7, 121.5, 60.2, 32.9, 32.0, 13.1; FTIR (CH_2Cl_2) 1729, 1610, 1556, 1501, 1451 cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.79; H, 6.11; N, 12.15.

Ethyl 4-(1,8-Naphthyridin-2-yl)butanoate (3f). The general procedure was followed with the use of 2-aminonicitinaldehyde (2.50 g, 20.5 mmol), 95% 1,3,3-trimethyl-6-azabicyclo-[3.2.1]octane (4.0 mL, 22 mmol), H_2SO_4 (57 μL, 1.0 mmol), ethanol (11 mL) and a 2.8 M solution of acetylbutyrate in ethanol (8.00 mL, 22.5 mmol). Gas chromatography and ^{1}H NMR indicated a 94:6 ratio of naphthyridine isomers. Chromatography on silica gel (EtOAc) yielded the title compound as an oil, which crystallized upon solvent-switching to *n*-heptane. The resultant crystals were filtered and washed with *n*-heptane, yielding the title compound as a white solid (3.5 g, 71%): mp = 45.5−47.0 °C;^{1}H NMR (CD_3OD, 400 MHz) δ 9.00 (dd, J = 4.4, 1.9, 1H), 8.39 (dd, J = 8.1, 1.9, 1H), 8.33 (d, J = 8.4, 1H), 7.58 (dd, J = 8.1, 4.4, 1H), 7.55 (d, J = 8.3, 1H), 3.00 (t, J = 7.6, 2H), 1.94−1.84 (m, 2H), 1.02 (t, J = 7.3, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.5, 166.0, 154.9, 152.8, 137.8, 137.6, 122.7, 121.7, 121.4, 60.0, 37.4, 33.1, 24.1, 13.1; FTIR (CH_2Cl_2) 1729, 1610, 1556, 1502, 1451 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.63; H, 6.57; N, 11.41.

2-(4-Methoxyphenyl)methyl-1,8-naphthyridine (3g). The general procedure was followed with the use of 2-aminonicotinaldehyde (2.50 g, 20.5 mmol), 95% 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (4.0 mL, 22 mmol), H_2SO_4 (57 μL, 1.0 mmol), EtOH (12.5 mL), and a 2.68 M solution of 4-methoxyphenylacetone in ethanol (8.40 mL, 22.5 mmol). Gas chromatography and ^{1}H NMR indicated a 93:7 ratio of naphthyridine isomers. Concentration and chromatography on silica gel (CH_2Cl_2 → 10:90 EtOAc/CH_2Cl_2) yielded the title compound as an oil. The oil was dissolved in MTBE and solvent-switched to *n*-heptane. The resultant crystals were filtered and washed with *n*-heptane, yielding the title compound as a white solid (3.23 g. 63%):[11] mp = 78.0−80.1 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 9.08 (dd, J = 4.3, 2.0, 1H), 8.11 (dd, J = 8.1, 2.0, 1H), 8.03 (d, J = 8.4, 1H), 7.43 (dd, J = 8.1, 4.3, 1 H), 7.32−7.27 (m, 3H), 6.84 (d, J = 8.7, 2H), 4.35 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 165.6, 158.5, 155.9, 153.4, 137.2, 136.7, 131.0, 130.4, 122.5, 121.6, 121.1, 114.2, 55.3, 45.0; FTIR (CH_2Cl_2) 1610, 1556, 1513 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 77.01; H, 5.73; N, 11.14.

2-(2-Phenylethyl)-1,8-naphthyridine (3h). The general procedure was followed with the use of 2-aminonicitinaldehyde (2.50 g, 20.5 mmol), 95% 1,3,3-trimethyl-6-azabicyclo[3.2.1]-octane (4.0 mL, 22 mmol), H_2SO_4 (57 μL, 1.0 mmol), ethanol (12.5 mL), and a 2.82 M solution of benzylacetone in ethanol (8.00 mL, 22.5 mmol). Gas chromatography and ^{1}H NMR indicated a 92:8 ratio of naphthyridine isomers. Chromatography on silica gel (MTBE) yielded the title compound as an oil. The oil was dissolved in MTBE and solvent-switched to *n*-heptane, whereupon the resultant crystals were filtered and washed with *n*-heptane, yielding the title compound as a white solid (3.5 g, 71%): mp = 83.0−84.2 °C;^{1}H NMR (CD_3OD, 400 MHz) δ 8.95 (dd, J = 4.3, 1.9, 1H), 8.26 (dd, J = 1.9, 8.1, 1H), 8.16 (d, J = 8.3, 1H), 7.50−7.46 (m, 1H), 7.37 (d, J = 8.3, 1H), 7.21−7.08 (m, 5H), 3.25 (t, J = 8.0, 2H), 3.11 (t, J = 8.0, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ165.9, 155.0, 152.8, 141.0, 137.6, 137.5, 128.1, 128.0, 125.7, 122.9, 121.6, 121.4, 40.2, 35.1; FTIR (CH_2Cl_2) 1610, 1552, 1498, 1451 cm^{-1}. Anal. Calcd for $C_{10}H_{10}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.94; H, 6.01; N, 11.98.

3,7-Dimethyl-1-[4-(1,8-naphthyridin-2-yl)butyl]-3,7-dihydro-1*H*-purine-2,6-dione (3i). Under nitrogen, a solution of pentoxifylline (2.0 g, 7.2 mmol), 1,3,3-trimethyl-6-azabicyclo-[3.2.1]octane (1.34 mL, 7.9 mmol), and H_2SO_4 (400 μL of a 0.88 M solution in ethanol, 0.35 mmol) in methanol (10 mL) was heated to 60 °C. To this solution was added 2-aminonicitinaldehyde (0.92 g, 7.2 mmol) in methanol (15 mL) over 45 min. The solution was aged at 60 °C for an additional 2 h, whereupon it was cooled to room temperature. ^{1}H NMR indicated a 96:4 ratio of naphthyridine isomers. The product was filtered and washed with cold methanol (20 mL) yielding the title compound as a tan solid (1.79 g, 65%): mp = 196.8−199.0 °C;[351]H NMR ($CDCl_3$, 400 MHz) δ 9.05 (dd, J = 4.3, 2.0, 1H), 8.18 (dd, J = 8.1, 2.0, 1H), 8.08 (d, J = 8.3, 1H), 7.49 (s, 1H), 7.43 (dd, J = 8.1, 4.3, 1H), 7.39 (d, J = 8.3, 1H), 4.10 (t, J = 7.3, 2H), 3.95 (s, 3H), 3.53 (s, 3H), 3.10 (t, J = 7.7, 2H), 1.96 (m, 2H), 1.79 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 155.9, 155.3, 153.2, 151.5, 148.7, 141.4, 137.0, 136.7, 122.6, 121.4, 121.0, 107.6, 41.1, 38.9, 33.5, 32.3, 29.6, 27.8, 26.7; FTIR (CH_2Cl_2) 1706, 1660, 1610, 1552, 1498, 1445 cm^{-1}.

(3*β*)-24-(1,8-Naphthyridin-2-yl)chol-5-en-3-ol (3j). Under nitrogen, a solution of 27-Nor-5-cholesten-3β-ol-25-one (1.7 g, 4.2 mmol), 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (83 mL, 4.6 mmol), and H_2SO_4 (240 μL of a 0.88 M solution in ethanol, 0.21 mmol) in methanol (20 mL) was heated to 60 °C. To this solution was added 2-aminonicitinaldehyde (54 g, 4.4 mmol) in methanol (8.00 mL) over 45 min. The solution was aged at 60 °C for an additional 2 h, whereupon it was cooled to room temperature. ^{1}H NMR indicated a 96:4 ratio of naphthyridine isomers. The product was filtered and washed with cold methanol (20 mL) yielding the title compound as a tan solid (1.61 g, 77%): mp = 253.5−255.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.05 (dd, J = 4.2, 1.9, 1H), 8.18 (dd, J = 8.0, 1.8, 1H), 8.08 (d, J = 8.1, 1H), 7.43 (dd, J = 8.1, 4.3, 1H), 7.39 (d, J = 8.5, 1H), 5.33 (m, 1H), 3.53 (m, 1H), 3.0 (m, 2H), 2.3−0.7 (m, 34 H); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 167.1, 156.0, 153.2, 140.8, 136.8, 136.7, 122.5, 121.6, 121.3, 71.7, 56.7,

(35) Differential scanning calorimetry also identified an early transition at 168.2 °C.

55.8, 50.1, 42.3, 39.9, 39.7, 37.2, 36.5, 35.9, 35.6, 31.9, 31.6, 28.2, 26.0, 24.2, 21.0, 19.4, 18.7, 11.8; FTIR (CH_2Cl_2) 1610, 1552, 1521, 1502 cm^{-1}.

2-(4-Chlorobutyl)-1,8-naphthyridine (3k). The general procedure was followed with the use of 2-aminonicotinaldehyde (2.50 g, 20.5 mmol), 95% 1,3,3-trimethyl-6-azabicyclo[3.2.1]-octane (4.0 mL, 22 mmol), H_2SO_4 (57 μL, 1.0 mmol), EtOH (12.5 mL), and a 2.72 M solution of 6-chloro-2-hexanone in ethanol (8.3 mL, 22.6 mmol). Gas chromatography and ^{1}H NMR indicated a 93:7 ratio of naphthyridine isomers. Concentration and chromatography on silica gel (CH_2Cl_2 → 10:90 EtOAc/ CH_2Cl_2) yielded the title compound as an oil (3.15 g, 70%): ^{1}H NMR (CD_3OD, 400 MHz) δ 9.03 (dd, J = 4.3, 1.9, 1H), 8.11 (dd, J = 8.1, 1.9, 1H), 8.06 (d, J = 8.2, 1H), 7.39 (dd, J = 8.1, 4.3, 1H), 7.35 (d, J = 8.3, 1H), 3.55 (t, J = 6.7, 2H), 3.04 (t, J = 7.6, 2H), 2.07−2.01 (m, 2H), 1.99−1.82 (m, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ 165.9, 156.0, 153.4, 137.1, 136.8, 122.5, 121.5, 121.1, 44.8, 38.3, 32.2, 26.4.

2-[2-(1,8-Naphthyridin-2-yl)ethyl]-1,8-naphthryidine (7). The general procedure was followed with the use of 2-aminonicotinaldehyde (2.50 g, 20.5 mmol), 95% 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (4.0 mL, 22 mmol), H_2SO_4 (57 μL, 1.0 mmol), EtOH (12.5 mL), and a 1.36 M solution of 2,5-hexadione (6.37 mL, 8.66 mmol) in ethanol. HPLC indicated a 95:05:0 ratio of **7**, **8**, and **9**, respectively. After aging at 65 °C for 60 min, the reaction was cooled to 0 °C and *n*-heptane (10 mL) was added over 10 min. The slurry was aged an additional 40 min at 0 °C, whereupon the crystals were filtered and washed with *n*-heptane, yielding the title compound as a tan solid (1.15 g, 48%): mp = 256.5−258.5 °C; (^{1}H NMR (CD_3OD, 400 MHz) δ 8.97 (dd, J = 4.3, 1.9, 2H), 8.36 (dd, J = 8.2, 1.9, 2H), 8.3 (d, J = 8.4, 2H), 7.6 (d, J = 8.3, 2H), 7.56 (dd, J = 8.2, 4.3, 2H), 3.62 (s, 4H); ^{13}C NMR (CD_3OD, 100 MHz) δ 165.6, 154.6, 153.1, 138.2, 138.0, 123.2, 122.0, 121.6, 37.4; FTIR (CH_2Cl_2) 1606, 1552, 1498 cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_2$: C, 75.50; H, 4.93; N, 19.57. Found: C, 75.09; H, 4.78; N, 19.39.

2-Butyl-6,8-dibromoquinoline (11). The general procedure was followed with the use of 2-amino-3,5-dibromobenzaldehyde (2.70 g, 9.68 mmol), 95% 1,3,3-trimethyl-6-azabicyclo-[3.2.1]octane (1.9 mL, 10.6 mmol), H_2SO_4 (27 μL, 0.49 mmol), EtOH (9.2 mL), and a 2.72 M solution of 2-hexanone in ethanol (3.9 mL, 10.6 mmol). ^{1}H NMR indicated an 88:12 ratio of naphthyridine isomers. Concentration and chromatography on silica gel (90:10 hexanes/CH_2Cl_2 → 80:20 hexanes/CH_2Cl_2) yielded the title compound as an oil (2.59 g, 78%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, J = 2.1, 1H), 7.95 (d, J = 8.4, 1H), 7.90 (d, J = 2.1, 1H), 7.36 (d, J = 8.4, 1H), 3.03 (t, J = 7.8, 2H), 1.90−1.82 (m, 2H), 1.50−1.44 (m, 2H), 0.99 (t, J = 7.3, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.7, 143.8, 135.5, 135.4, 129.4, 128.6, 125.8, 123.1, 118.6, 38.9, 31.4, 22.6, 14.0; FTIR (CH_2Cl_2) 1605, 1590, 1544, 1482,1444 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2$: C, 45.51; H, 3.82; N, 4.08. Found: C, 45.33; H, 3.65; N, 4.03.

Ethyl 3-(6,8-Dibromoquinolin-2-yl)butanoate (12). The general procedure was followed with the use of 2-amino-3,5-dibromobenzaldehyde (2.39 g, 8.58 mmol), 95% 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (2.1 mL, 11.7 mmol), H_2SO_4 (29 μL, 0.52 mmol), EtOH (10.0 mL), and a 2.78 M solution of ethyl 4-acetylbutyrate in ethanol (4.2 mL, 11.7 mmol). ^{1}H NMR indicated an 89:11 ratio of naphthyridine isomers. Concentration and chromatography on silica gel (90:10 *n*-heptane/MTBE) yielded an 89:11 mixture of **12** and the corresponding regioisomer, respectively, as an oil (2.90 g, 75% yield of **12**): ^{1}H NMR (Major isomer, $CDCl_3$, 400 MHz) 8.14 (d, J = 2.0, 1H), 7.95 (d, J = 8.4, 1H), 7.89 (d, J = 2.0, 1H), 7.35 (d, J = 8.4, 1H), 4.13 (q, J = 7.1, 2H), 3.07 (t, J = 7.4, 2H), 2.49 (t, J = 7.4, 2H), 2.23 (t, J = 7.4, 2H), 1.26 (t, J = 7.1, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4, 163.1, 143.6, 135.6, 129.3, 128.5, 125.8, 123.0, 118.7, 60.3, 37.9, 33.6, 23.9, 14.3; FTIR (CH_2Cl_2) 1729, 1605, 1590, 1544, 1482, 1444 cm^{-1}.

2-Butyl-6-chloroquinoline (14). To a solution of 98% 2-hexanone (1.9 mL, 15.4 mmol), 95% 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (2.8 mL, 15.4 mmol), H_2SO_4 (38 μL, 0.68 mmol) and methanol (8.0 mL) in a bath at 65 °C was added a 0.848 M solution 2-amino-5-chlorobenzaldehyde in methanol (16.5 mL, 14.0 mmol) over 60 min. The solution was aged for an additional 60 min, whereupon it was concentrated. ^{1}H NMR indicated an 84:16 ratio of naphthyridine isomers. Chromatography on silica gel (50:50 cyclohexane/CH_2Cl_2 → 20:80 cyclohexane/CH_2Cl_2), yielded the title compound as an oil (2.37 g, 77%): ^{1}H NMR (CD_3OD, 400 MHz) δ 8.19 (d, J = 8.5, 1H), 7.94 (d, J = 9.0, 1H), 7.90 (d, J = 2.3, 1H), 7.68 (dd, J = 9.0, 2.3, 1H), 7.46 (d, J, = 8.5, 1H), 2.95 (t, J = 7.8, 1H), 1.79−1.74 (m, 2H), 1.46−1.40 (m, 2H), 0.9733 (t, J = 7.4, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 163.6, 145.5, 136.1, 131.2, 130.1, 129.0, 127.5, 126.1, 122.3; FTIR (CH_2Cl_2) 1602, 1556, 1490 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2$: C, 71.07; H, 6.42; N, 6.38. Found: C, 70.88; H, 6.35; N, 6.32.

2-Butyl-5*H*-chromeno[2,3-*b*]pyridin-5-one (16). To a solution of 98% 2-hexanone (1.24 mL, 9.85 mmol), 95% 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (1.8 mL, 10.0 mmol), H_2SO_4 (25 μL, 0.45 mmol) and ethanol (10.0 mL) in a bath at 65 °C was added a slurry of 97% 2-amino-3-formylchromone (1.75 g, 8.97 mmol) in ethanol (16.5 mL) over 80 min. The solution was aged an additional 60 min, whereupon it was concentrated. ^{1}H NMR indicated an 80:20 ratio of regioisomers. Chromatography on silica gel (10:90 hexanes/CH_2Cl_2 → 100% CH_2Cl_2), yielded the title compound, which crystallized upon solvent-switching to *n*-heptane. The resultant crystals were filtered and washed with *n*-heptane, yielding the title compound as a white solid (1.59 g, 70%): mp = 58.0−59.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.61 (d, J = 8.0, 1H), 8.32 (dd, J = 8.0, 1.7, 1H), 7.79−7.75 (m, 1H), 7.62 (broad d, J = 7.9, 1H), 7.45−7.41 (m, 1H), 7.30 (d, J = 8.0, 1H), 2.94 (t, J = 7.7, 2H), 1.84−1.78 (m, 2H), 1.49−1.39 (m, 2H), 0.97 (t, J = 7.3, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 177.5, 169.2, 160.1, 155.7, 137.3, 135.3, 126.6, 124.5, 121.7, 120.6, 118.4, 114.4, 38.5, 31.5, 22.5, 13.8; FTIR (CH_2Cl_2) 1664, 1617, 1606, 1587, 1559, 1463 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.92; H, 5.93; N, 5.39.

8-Methyl-7,8-dihydro-6*H*-cyclopenta[*b*]-1,8-naphthyridine (18). Under nitrogen, a solution of 2-aminonicitinaldehyde (2.50 g, 20.5 mmol), pyrrolidine (1.9 mL, 22.8 mmol) and H_2SO_4 (57 μL, 1.0 mmol) in ethanol (18 mL) was stirred at 24 °C. To this solution was added 2-methylcyclopentanone (2.42 mL, 22.5 mmol) over 35 min. The solution was aged at 24 °C for an additional 18 h, whereupon it was concentrated. Chromatography on silica gel (CH_2Cl_2 → 30:70 EtOAc/CH_2Cl_2) yielded the title compound, which crystallized upon solvent switching to *n*-heptane. The resultant crystals were filtered and washed with *n*-heptane, yielding the title compound as a white solid (2.88 g, 76%): mp = 94.1−95.6 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.96 (dd, J = 4.2, 1.9, 1H), 8.06 (dd, J = 8.1, 1.9, 1H), 7.84 (s, 1H), 7.36 (dd, J = 8.1, 4.2, 1H), 3.36−3.30 (m, 1H), 3.05−2.94 (m, 2H), 2.50−2.41 (m, 1H), 1.79−1.72 (m, 1H), 1.49 (d, J = 6.9, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 174.8, 156.3, 151.8, 136.7, 136.6, 130.7, 121.7, 121.1, 40.9, 33.1, 28.7, 18.1; FTIR (CH_2Cl_2) 1629, 1602, 1563, 1486, 1455 cm^{-1}.

9-Methyl-6,7,8,9-tetrahydrobenzo[*b*]-1,8-naphthyridine (20). Under nitrogen, a solution of 2-aminonicitinaldehyde (1.31 g, 10.7 mmol), 99% 2-methylcyclohexanone (2.6 mL, 21,2 mmol), TABO (2.1 mL, 11.8 mmol) and H_2SO_4 (30 μL, 0.54 mmol) in ethanol (5 mL) was heated to 70 °C for 40 h, whereupon additional 2-methylcylcohexanone (1.3 mL, 10.6 mmol) was added. The solution was aged at 70 °C for an additional 48 h, whereupon it was concentrated. Chromatography on silica gel (50:50 CH_2Cl_2/EtOAc) yielded the title compound, which crystallized upon solvent-switching to *n*-heptane. The resultant crystals were filtered and washed with *n*-heptane, yielding the title compound as a white solid (1.15 g, 58%): mp = 99.8−102.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.97 (dd, J = 4.2, 1.9, 1H), 8.02 (dd, J = 8.1, 1.9, 1H), 7.76 (s, 1H), 7.33 (dd, J = 8.1, 4.2, 1H), 3.26−3.15 (m, 1H), 2.96 (t, J

= 6.7, 2H), 2.17−2.08 (m, 2H), 2.00−1.90 (m, 2H), 1.87−1.76 (m, 2H), 1.73−1.62 (m, 2H), 1.53 (d, J = 7.0, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.0, 154.9, 152.4, 136.0, 135.4, 132.1, 121.3, 121.2, 37.1, 31.3, 29.7, 21.1, 20.6; FTIR (CH_2Cl_2) 1613, 1601, 1552, 1478, 1447 cm^{-1}.

2-[(1*S*)-1-Methylpropyl]-1,8-naphthyridine (22). Under nitrogen, a solution of 2-aminonicitinaldehyde (5.0 g, 41 mmol), 95% 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (7.7 mL, 45 mmol), H_2SO_4 (437 μL, 8 mmol), and (*S*)-3-methyl-2-pentanone[36] in ethanol (50 mL) was heated to 65 °C. The solution was aged at 65 °C for 67 h, whereupon it was concentrated. Chromatography on silica gel (20:80 DCM/EtOAc) yielded the title compound as an oil (4.7 g, 61%). SFC analysis indicated the enantiomeric excess of **22** was 75%: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.00 (dd, J = 4.4, 1.9, 1H), 8.08 (dd, J = 8.1, 2.0, 1H), 8.05 (dd, J = 8.4, 2.4, 1H), 7.36 (dd, J = 8.0, 4.3, 1H), 7.33 (d, J = 8.4, 1H), 3.03 (dq, J = 13.8, 6.9, 1H), 1.90 (m, 1H), 1.70 (m, 1H), 1.34 (d, J = 6.9, 3H), 0.83 (t, J = 7.4, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 70.8, 155.9, 153.1, 136.9, 136.6, 121.4, 121.3, 121.1, 44.5, 29.7, 20.1, 12.1; FTIR (CH_2Cl_2) 1610, 1552, 1498, 1451 cm^{-1}.

(36) Djerassi, C.; Geller, L. E. *J. Am. Chem. Soc.* **1959**, *81*, 2789.

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Supporting Information Available: ^{1}H and ^{13}C NMR data for compounds **3i**, **3j**, **3k**, **12**, **18**, **20**, and **22.** This material is available free of charge via the Internet at http://pubs.acs.org.

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