Efficient Syntheses of New Heteroarotinoids through Functional Pyridylzinc Reagents and Palladium-Catalyzed Cross-Coupling Reactions

Mouâd Alami,*[a] Jean-François Peyrat,[a] Larbi Belachmi,[b] and Jean-Daniel Brion[a]

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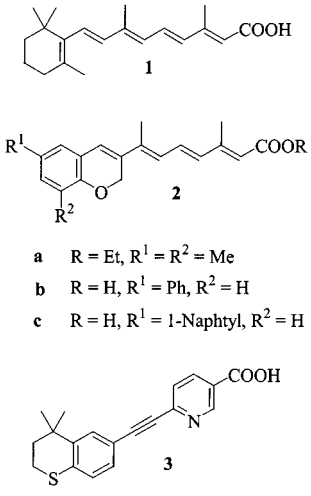
A convergent synthesis of heteroarotinoids **4**, **5a**, and **5b**, bearing chromene rings in association with pyridyl or ethynylpyridyl moieties, from 6-bromo-2-pyridylzinc chloride (**11**) is described. This new functional heteroarylzinc reagent, readily accessible from 2,6-dibromopyridine, may undergo a selective palladium-catalyzed carbon–carbon bond-forming reaction to yield the corresponding 6-substituted-2-bromopyridines **13**. Further manipulation of the remaining bromine atom in **13** to give the zinc derivative **14**, and subsequent coupling with ethyl 4-iodobenzoate under palladium catalysis conditions afforded heteroarotinoid **4**. Coupling of the substituted bromopyridines **13** or the triflate **22** with appropriate alkynes under Sonogashira conditions give the corresponding heteroarotinoids **5a**, **5b**, and **6**.

Introduction

The important roles of retinoids, including retinoic acid **1** and its analogues, in a large variety of biological processes (proliferation, differentiation, apoptosis, ...) have been demonstrated during last decade.[1] Their ability to restore regulation of differentiation and growth in certain premalignant and malignant cells in vitro and in vivo should particularly be emphasized.[2] Retinoids have demonstrated significant results in the treatment of dermatological disorders[3] (psoriasis, acne) and chemopreventable cancers[4] (renal cell carcinoma, acute promyelocytic leukemia, breast cancer). Additionally, recent results have demonstrated that retinoids may act as potent inhibitors of angiogenesis,[5] a phenomenon involving the formation of new blood vessels, required for the growth of solid tumors. All these biological properties have made retinoids an attractive target for therapeutic chemistry and have in recent years resulted in significant development of syntheses of new retinoid analogues.[1] When these compounds are used at pharmacological doses, however, they may display important undesirable side effects, including teratogenesis and bone toxicity, rendering them unfit for clinical application.[1] One of today's challenges in this field is to devise and develop compounds at least as efficacious as **1** and yet less toxic.

Recent studies from our laboratory[6] have shown that this toxicity may be considerably reduced [relative to that of retinoic acid (**1**)] if a heterocyclic ring is incorporated.[7] For instance, the presence of a substituted chromene moiety in the retinoic acid backbone, such as in the oxaretinoids **2**, considerably reduced the toxicity of the compounds. Moreover, **2c** exhibited an interesting bone anti-resorptive activity (Scheme 1).



Scheme 1

These results prompted us to synthesize new heteroarotinoids **4**–**6**, incorporating chromene rings associated with pyridyl or ethynylpyridyl moieties (Scheme 2), in the hope that the presence of pyridyl rings would increase hydrophilicity and stability. Moreover, further comparative biological studies would contribute to better understanding of the pharmacophore in such compounds (triple bond vs. heteroaryl ring, for example). Compounds **5**–**6** may be viewed as analogues of tazarotene (**3**; Zorac®), currently used for the treatment of psoriasis.[8] In this paper we describe our efforts towards the development of an efficient and flexible synthesis of heteroarotinoids **4**–**6**. Compounds **4** and **5a**–**b**, characterized by the presence of 2,6-disubstituted pyridine rings, may be obtained from readily available 2,6-dibromopyridine (**10**). This compound, thanks to the presence of two reactive functions, may act as a multi-coupling reagent and is synthetically equivalent to the synthons **7**–**9**[9] (Scheme 2).

[a] Laboratoire de Chimie Thérapeutique, associé au CNRS (BioCIS), Université Paris-Sud, Faculté de Pharmacie,
Rue Jean-Baptiste Clément, 92296 Châtenay-Malabry, France
Fax: (internat.) + 33-1/46835828
E-mail: mouad.alami@cep.u-psud.fr
[b] Université Cadi Ayyad, Faculté des Sciences et Techniques Guéliz,
40000 Marrakech, Morocco

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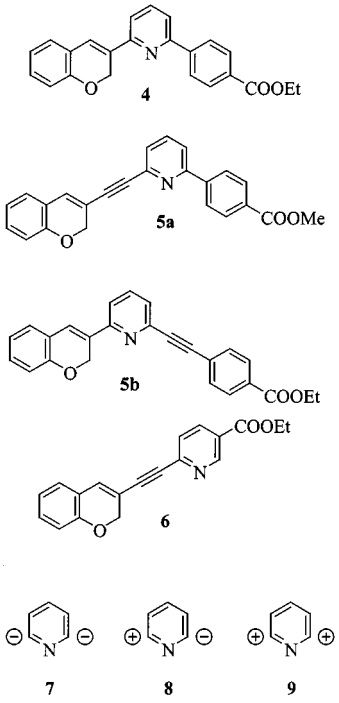
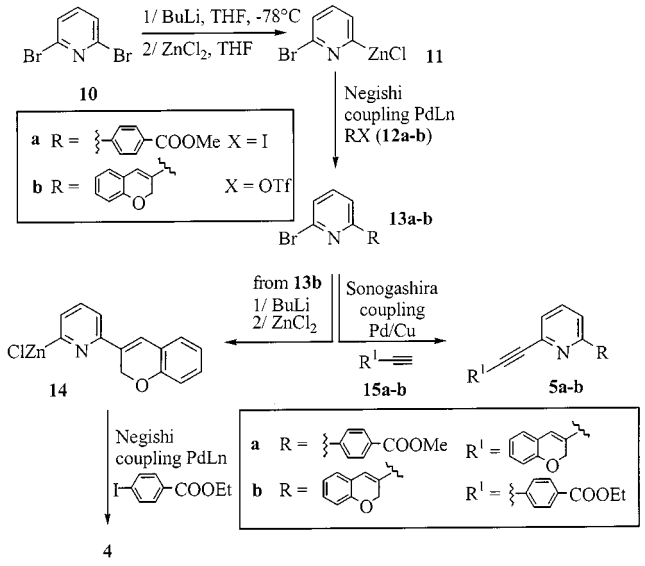


Scheme 2



Scheme 3

Results and Discussion

The devised synthetic approach to 2,6-disubstituted pyridine compounds **4** and **5a−b** involves as a key step the formation of 6-bromo-2-pyridylzinc chloride (**11**), which is synthetically equivalent to the synthons **7** and **8**. This new polyfunctional heteroarylzinc reagent may undergo two successive Negishi[10] cross-coupling reactions to give heteroarotinoid **4**, or two sequential cross-coupling reactions under palladium catalysis conditions to give **5a−b**, through Negishi and Sonogashira reactions, respectively (Scheme 3).

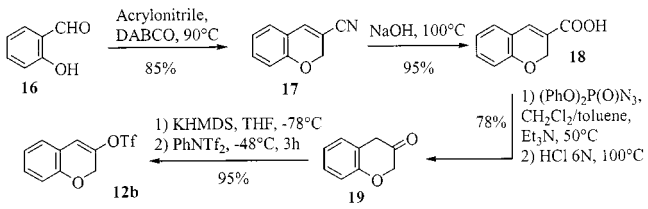
Our attention was first directed towards the preparation of substituted bromopyridine **13a**. Thus, the required functional heteroarylzinc reagent **11** was obtained by conversion of 2,6-dibromopyridine (**10**), in the presence of *n*BuLi at −78 °C, into the corresponding monolithium compound according to the method of Cai,[11] to avoid production of the 2,6-dilithiopyridine derivative. Subsequent transmetallation with anhydrous zinc chloride[12] furnished the expected zinc reagent **11**, characterized by a typical blue-green color. Coupling of **11** (1.1 equiv.) with methyl 4-iodobenzoate (**12a**) occurred smoothly at 60 °C in THF in the presence of $PdCl_2$(dppf)[13] (5%) to give the coupling product **13a** in 58% isolated yield in 12 h (Table 1, entry 3). Attempts to improve the chemical yield by the use of other palladium catalysts, including $PdCl_2$(dppp) and $Pd(PPh_3)_4$, gave either similar or lower yields (entries 1 and 2). The addition of a polar cosolvent (DME), however, as we have previously reported,[14] improved the chemical yield. The best result was finally obtained when the reaction was performed in the presence of $PdCl_2(PPh_3)_2$ in a medium consisting of 3:1 THF/DME, at 65 °C. Under these conditions, the desired coupling product **13a** was obtained in 80% isolated yield (entry 7). It should be noted that the yield of **13a** was lower in the absence of DME (entry 4, 32% instead of 80%).

Table 1. Palladium-catalyzed cross coupling reaction between organozinc derivative **11** and methyl 4-iodobenzoate (**12a**)

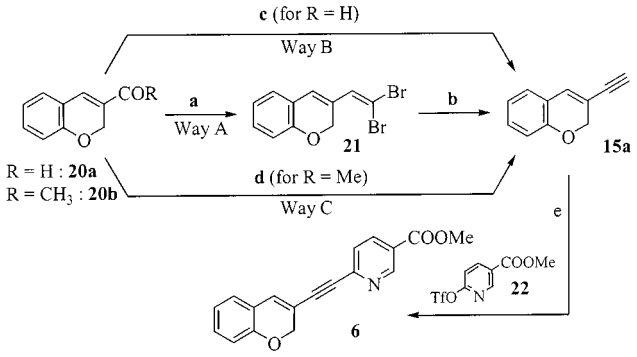
Entry[a]	PdLn[b]	Cosolvent[c]	Yield[d] of **13a** (%)
1	$Pd(PPh_3)_4$	−	42
2	$PdCl_2$(dppp)	−	53
3	$PdCl_2$(dppf)	−	58
4	$PdCl_2(PPh_3)_2$	−	32
5	$PdCl_2$(dppf)	DME	72
6	$Pd(PPh_3)_4$	DME	75
7	$PdCl_2(PPh_3)_2$	DME	80

[a] 1.2 equiv. of **11** was used. All reactions were performed in THF at 60 °C for 12 h. − [b] 5 mol % of palladium catalyst was used. − [c] 5 equiv. of DME was used. − [d] Isolated yields based on **12a**.

The selectivity of this coupling reaction must be particularly emphasized, since the remaining electrophilic C−Br bond in **13** does not react under these mild conditions. Similarly, no reaction occurred when **11** was treated with methyl 4-bromobenzoate. However, the palladium-catalyzed cross-coupling reaction of functional heteroarylzinc reagent **11** with chromene triflate **12b**[15] in the presence of tetrakis(triphenylphosphane)palladium (5 mol %) in THF/DME at 60 °C furnished the desired coupling product **13b** in 53% yield. The chromene triflate **12b** was prepared in a four-step sequence from salicylic aldehyde **16** using Corey's procedure[16] (60% overall yield, Scheme 4). Thus, sequential O-cyanoethylation, aldol cyclization, and hydrolysis gave the corresponding chromene acid **18**. Conversion of **18** into the acyl azide, Curtius rearrangement, and acid-catalyzed hydrolysis provided ketone **19**, which, when subjected to the



Scheme 4



Scheme 5. **a**: CBr_4 (2 equiv.), PPh_3 (2 equiv.), Zn (2 equiv.), CH_2Cl_2 (98%). − **b**: LDA or *n*BuLi (2.2 equiv.), −78 °C (61%). − **c**: *t*BuOK (1.9 equiv.), $[(Ph_3PCHBr_2)^+Br^-]$ (2.0 equiv.), THF then *t*BuOK (5.0 equiv.) (49%). − **d**: iPr_2NEt (4 equiv.), CH_2Cl_2, −78 °C, Tf_2O (1.2 equiv.), 0 °C (81%). e/ $Pd(PPh_3)_4$ (5%), CuI (10%), Et_3N, 60 °C (65%).

presence of Tf_2O and iPr_2NEt, afforded the enol triflate **12b**.

The prepared substituted bromopyridine compounds **13a** and **13b** were then converted into heteroarotinoids **4** and **5a−b** according to Scheme 3. Lithiation of **13b**, followed by formation of the heteroarylzinc reagent **14** and coupling with ethyl 4-iodobenzoate in the presence of palladium catalyst $Pd(PPh_3)_4$ in THF/DME, afforded polyfunctional heteroarotinoid **4** in 52% isolated yield.

For the synthesis of heteroarotinoids **5a−b** from **13a−b** we planned to introduce alkynyl moieties by means of the palladium-mediated Sonogashira coupling reaction.[17] In order to study the best approach to the required ethynyl chromene **15a**, three synthetic pathways were investigated (Scheme 5). The first (pathway A) involved the Corey−Fuchs homologation[18] of aldehyde **20a**[19] (98%) followed by an elimination reaction performed on the intermediate 1,1-dibromo derivative **21** in the presence of LDA or *n*BuLi (61%). Attempts to improve the chemical yield of the elimination step by the use of a variety of bases including MeLi, *i*PrMgCl, and *t*BuOK were unsuccessful. The second (pathway B), based on the Wittig-type condensation of the aldehyde **20a** with dibromomethyltriphenylphosphonium bromide in the presence of *t*BuOK, allowed ethynyl chromene **15a** (49%) to be obtained in a one-pot procedure.[20] Finally, the best yield of **15a** was obtained when the reaction was carried out starting from the chromene ketone **20b** (pathway C). Thus, treatment of **20b** with Tf_2O in the presence of an excess of Hünig base gave the terminal alkyne **15a** in 81% yield. It should be pointed out that the resulting vinyl triflate intermediate was not stable under these conditions and could not be isolated even by use of a stoichiometric amount of Hünig base.

Coupling of substituted bromopyridine **13a−b** with readily accessible terminal alkynes[21] **15a−b** in the presence of catalytic amounts of $Pd(PPh_3)_4$ and CuI in Et_3N afforded heteroarotinoids **5a−b** in 70% and 66% isolated yields, respectively. It should be noted that of all the palladium catalysts examined, $Pd(PPh_3)_4$ in Et_3N turned out to be the best suited for a rapid and selective transformation. Interestingly, the Sonogashira procedure could also successfully be applied to the synthesis of heteroarotinoid **6**. Thus, treatment of ethynyl chromene **15a** with pyridinyl triflate **22**[22] under conditions identical to those used for the preparation of **5a−b** afforded **6** in 65% isolated yield (Scheme 5).

In summary, we have succeeded in the development of a convergent and flexible synthetic route to four heteroarotinoids **4−6**, each containing a chromene ring associated with a pyridyl or an ethynylpyridyl core. The key step is the use of multicoupling reagent **11**, which allowed sequential and selective formation of carbon−carbon bonds to be performed under palladium catalysis conditions, resulting in various functionalized disubstituted pyridine compounds. Compounds **4−6** are currently being evaluated in vitro; the results emerging from these studies will be published elsewhere.

Experimental Section

All experiments were carried out in flame-dried glassware under an inert atmosphere. − All NMR spectra were recorded on Bruker AC 200 or ARX 400 MHz spectrometers in deuteriochloroform [$CDCl_3$, δ (ppm), *J* (Hz)]. − Mass spectra were recorded on Nermag R 10/10 or Esquire Bruker (electrospray) instruments. − IR spectra were measured on a Perkin−Elmer 841 (neat, cm^{-1}). − Analytical TLC was performed on 0.25 mm precoated silica gel plates (Merck). Products were purified by column chromatography (silica gel 60 230−400 mesh ASTM, 0.040−0.063 mm) purchased from E. Merck. − Satisfactory microanalyses were obtained for all new compounds. − Melting points are uncorrected. THF and DME were distilled from sodium and benzophenone. − Catalysts: $Pd(PPh_3)_4$,[23] $PdCl_2(PPh_3)_2$,[24] $PdCl_2$(dppp),[24] $PdCl_2$(dppf),[25] and alkyne **15b**[21] were prepared following literature procedures. 2,6-Dibromopyridine was obtained from Acros Chemical Company, Inc., its purity was 98% and was used without further purification. Acrolein, methyl vinyl ketone, and salicylaldehyde **16**, available from Aldrich Chemical Company, Inc., were distilled prior to use.

General Procedure for the Cross-Coupling Reaction of 6-Bromo-2-pyridylzinc Chloride (11): A solution of 2,6-dibromopyridine (2.24 mmol, 526 mg) in THF (4 mL) was added dropwise at −78 °C to a solution of *n*BuLi (1.6 mL, 1.6 M in hexanes, 2.48 mmol) in THF, and the resulting dark green mixture was stirred for 15 min at this temperature. A solution of anhydrous zinc chloride (2.50 mmol, 335 mg) in DME (1 mL, 9.8 mmol) was then added, and stirring was continued for 15 min at −78 °C. A solution of $PdCl_2(PPh_3)_2$ (0.098 mmol, 5 mol %, 70 mg) and compound **12a** or **12b** (1.95 mmol) in THF (5 mL) was then added dropwise, and the reaction mixture was slowly allowed to warm to room temperature and then heated at 60 °C for 12 h. After cooling, the reaction was

quenched with water. The mixture was extracted with ethyl acetate, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under vacuum. The crude products were purified by silica gel column chromatography.

Methyl 4-(6-Bromopyridin-2-yl)benzoate (13a): 454 mg (80%, beige solid) obtained from methyl 4-iodobenzoate (**12a**, 1.95 mmol, 511 mg). − R_f = 0.35 (cyclohexane/EtOAc 9:1). − M.p. 142−144 °C. − IR (KBr): $\tilde{\nu}$ = 1718, 1608, 1571, 1549, 1276, 1106, 766 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.95 (s, 3 H), 7.46 (dd, *J* = 7.6, 1.0 Hz, 1 H), 7.62 (t, *J* = 7.6 Hz, 1 H), 7.73 (dd, *J* = 7.6, 1.0 Hz, 1 H), 8.01−8.15 (AA′BB′, 4 H). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 52.3, 119.5, 126.9, 127.2, 130.1, 131.0, 139.2, 141.7, 142.4, 157.3, 166.7. − MS (GCMS, electrospray): *m*/*z* (rel. int.): 293 (82) [$M^{+\cdot}$], 292 (19), 291 (76) [$M^{+\cdot}$], 262 (100), 260 (96), 232 (25), 153 (41). − $C_{13}H_{10}BrNO_2$ (292.0): calcd. C 53.45, H 3.45; found C 52.89, H 3.57.

2-Bromo-6-(2*H*-chromen-3-yl)pyridine (13b): 297 mg (53%, yellow solid) obtained from the chromene triflate **12b** (1.95 mmol, 546 mg). − R_f = 0.40 (cyclohexane/EtOAc 9:1). − M.p. 163−165 °C. − IR (KBr): $\tilde{\nu}$ = 1610, 1560, 1490, 1460, 1110, 940 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 5.28 (s, 2 H), 6.85−7.22 (m, 5 H), 7.35−7.53 (m, 3 H). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 66.0, 88.4, 115.7, 121.8, 122.2, 127.1, 127.3, 128.6, 130.1, 134.9, 153.6. − MS (GCMS, electrospray): *m*/*z* (rel. int.): 289 (97) [$M^{+\cdot}$], 288 (58), 287 (100) [$M^{+\cdot}$], 260 (47), 258 (96), 208 (37), 180 (31), 131 (57). − $C_{14}H_{10}BrNO$ (288.0) calcd. C 85.36, H 3.50; found C 85.52, H 3.62.

Ethyl 4-[6-(2*H*-Chromen-3-yl)pyridin-2-yl]benzoate (4): *n*BuLi (0.26 mL, 1.6 M in hexanes, 0.40 mmol) was added dropwise at −78 °C to a solution of substituted bromopyridine **13b** (0.34 mmol, 98 mg) in THF (2 mL), and the resulting mixture was stirred for 20 min at this temperature. A solution of anhydrous zinc chloride (0.40 mmol, 54 mg) in THF (2 mL) was added, and stirring was continued for an additional 20 min. The mixture was treated with a solution of $Pd(PPh_3)_4$ (0.017 mmol, 5 mol %, 20 mg) and ethyl 4-iodobenzoate (**12a**, 0.40 mmol, 111 mg) in DME (2 mL), allowed to warm slowly to room temperature, and then heated at 60 °C for 12 h. After cooling, the reaction was quenched with water. The mixture was extracted with ethyl acetate, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under vacuum. Purification by silica gel column chromatography (cyclohexane/EtOAc 9:1) afforded retinoid **4** as a white solid in 52% yield (63 mg). − M.p. 170−172 °C. − IR (KBr): $\tilde{\nu}$ = 2972, 1714, 1588, 1453, 1272 cm^{-1}. − ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.45 (t, *J* = 7.1 Hz, 3 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 5.49 (s, 2 H), 6.91 (br. d, *J* = 8.0 Hz, 2 H), 6.95 (td, *J* = 7.4, 1.4Hz, 1 H), 7.17 (dd, *J* = 7.3, 1.4 Hz, 1 H), 7.18 (td, *J* = 7.4, 1.4 Hz, 1 H), 7.27 (s, 1 H), 7.58 (dd, *J* = 7.8, 0.6 Hz, 1 H), 7.69 (dd, *J* = 7.8, 0.6 Hz, 1 H), 7.79 (t, *J* = 7.8 Hz, 1 H), 8.15−8.16 (m, 4 H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3, 61.0, 66.2, 115.7, 117.9, 119.00, 121.5, 122.4, 123.0, 126.6 (2 C), 127.6, 129.9 (3 C), 130.8, 131.5, 137.1, 143.1, 154.3 (2 C), 155.0, 166.4. − MS (electrospray): *m*/*z* (rel. int.): 358 (100), 326 (81), 219 (8). − $C_{23}H_{19}NO_3$ (357.1) calcd. C 77.29, H 5.36; found C 77.02, H 5.49.

2*H*-Chromene-3-carbonitrile (17): Salicylaldehyde **16** (81.96 mmol, 10 g), acrylonitrile (409 mmol, 21.7 g), and 1,4-diazabicyclo[2.2.2]octane (18.3 mmol, 2.10 g) were stirred for 24 h at 90 °C. The reaction mixture was concentrated under vacuum and the crude residue was then dissolved in CH_2Cl_2 (150 mL) and washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layers were dried with Na_2SO_4 and concentrated under vacuum. Purification by silica gel column chromatography (R_f = 0.30, cyclohexane/CH_2Cl_2 70:30) afforded nitrile **17** as a yellow solid in 85% yield (10.94 g). − M.p. 42−43 °C (ref.[19,26] = 45 °C). − IR (KBr): $\tilde{\nu}$ = 2212, 1634, 1600, 1573, 1140, 1010, 750 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.82 (d, *J* = 1.2 Hz, 2 H), 6.85 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.98 (td, *J* = 8.0, 1.2 Hz, 1 H), 7.12 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.28 (dt, *J* = 8.0, 1.2 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 63.9, 103.0, 116.2, 119.7, 122.1, 128.2, 132.4, 132.9, 138.4, 153.9. − $C_{10}H_7NO$ (157.0) calcd. C 76.42, H 4.49; found C 75.89, H 4.61.

2*H*-Chromene-3-carboxylic Acid (18): Nitrile **17** (64.10 mmol, 10.1 g) was treated with a 10% aqueous solution of NaOH (180 mL) and heated at 100 °C for 6 h. After this had cooled, an aqueous solution of HCl (5 N) was added dropwise until pH = 3 was attained and the produced precipitate was filtered. The pure acid **18** was obtained by recrystallization (petroleum ether/Et_2O 25:75) as a yellow solid in 95% yield (10.72 g). − M.p. 192−194 °C. − IR (KBr): $\tilde{\nu}$ = 3300−2700, 1690, 1165 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.80 (d, *J* = 1.2 Hz, 2 H), 6.78 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.95 (td, *J* = 8.0, 1.2 Hz, 1 H), 7.25 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.30 (dt, *J* = 8.0, 1.2 Hz, 1 H), 12.04 (br. s, 1 H). − ^{13}C NMR (DMSO, 50 MHz): δ = 64.4, 115.8, 121.1, 121.9, 123.6, 129.3, 131.9, 132.5, 154.7, 165.7. − MS (GCMS, electrospray): *m*/*z* (rel. int.): 176 (42) [$M^{+\cdot}$], 175 (35), 131 (100), 77 (27). The spectral properties were in good agreement with the literature.[26]

Chroman-3-one (19): A solution of $(PhO)_2P(O)N_3$ (50 mmol, 13.75 g) in toluene (40 mL) was added dropwise at room temperature over a period of 25 min to a solution of acid **18** (45.41 mmol, 8.0 g) in triethylamine (8 mL) and CH_2Cl_2 (100 mL). The reaction mixture was warmed to 50 °C for 1 h, toluene (100 mL) was then added, and the reaction mixture was heated to 85 °C for 3 h. After this had cooled to room temperature, an aqueous solution of HCl (6 N, 80 mL) was added and the reaction mixture was then heated at reflux for an additional 3 h. The layers were separated, and the organic extracts were washed with a saturated solution of $NaHCO_3$ and with brine. The organic layers were dried with Na_2SO_4 and concentrated under vacuum. Purification by silica gel column chromatography (R_f = 0.26, cyclohexane/EtOAc 80:20) afforded ketone **19** as a yellow oil in 78% yield (5.25 g). − IR[27a] (KBr): $\tilde{\nu}$ = 2860, 1720, 1660, 1180 cm^{-1}. − ^1H NMR[27a] ($CDCl_3$, 200 MHz): δ = 3.61 (s, 2 H), 4.42 (s, 2 H), 7.02 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.05 (td, *J* = 8.0, 1.2 Hz, 1 H), 7.23 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.35 (td, *J* = 8.0, 1.2 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 40.9, 72.9, 117.7, 120.2, 123.3, 128.4, 128.9, 176.7, 207.5. − MS[27b] (GCMS, electrospray): *m*/*z* (rel. int.): 148 (78) [$M^{+\cdot}$], 119 (31), 91 (100), 89 (39).

2*H*-Chromen-3-yl Trifluoromethanesulfonate (12b): A solution of KHMDS (9.78 mmol, 1.95 g) in THF (10 mL) was slowly added to a solution of ketone **19** (6.75 mmol, 1.0 g) in THF (10 mL) at −78 °C and the resulting mixture was stirred for 25 min at this temperature. A solution of $PhNTf_2$ (9.8 mmol, 3.50 g) in THF (6 mL) was then added, and stirring was continued for 3 h at −48 °C. The reaction mixture was quenched with water and extracted with ethyl acetate, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under vacuum. Purification by silica gel column chromatography (R_f = 0.80, cyclohexane/EtOAc 80:20) afforded the triflate **12b** as a yellow oil in 95% yield (1.55 g). − IR (KBr): $\tilde{\nu}$ = 1610, 1185, 1060−1020 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.78 (d, *J* = 1.2 Hz, 2 H), 6.55 (br. s, 1 H), 6.80 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.92 (dt, *J* = 8.0, 1.2 Hz, 1 H), 7.08 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.21 (td, *J* = 8.0, 1.2 Hz, 1 H). − ^{13}C

NMR ($CDCl_3$, 50 MHz): δ = 64.8, 115.4, 116.1, 122.5, 127.8, 130.4 (2 C), 142.7, 155.4. − MS (GCMS, electrospray): *m*/*z* (rel. int.): 248 (80), 220 (21), 121 (87), 80 (100), 52 (50).

2*H*-Chromene-3-carbaldehyde (20a): K_2CO_3 (136 mmol, 18.80 g) was added to a solution of salicylaldehyde **16** (136 mmol, 16.6 g) and propenal (150 mmol, 8.40 g) in dioxane (100 mL), and the reaction mixture was then heated at reflux for 2 h before being treated with water (100 mL). The layers were separated and extracted with ether, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under vacuum. Purification by silica gel column chromatography (R_f = 0.53, cyclohexane/CH_2Cl_2 70:30) afforded the aldehyde **20a** as a yellow solid in 72% yield (15.67 g). − M.p. 42−43 °C (ref.[19] = 44 °C). − IR (KBr): ṽ = 2827, 1730, 1662, 1600, 754 cm^{-1}. − ^1H NMR[28] ($CDCl_3$, 200 MHz): δ = 5.02 (s, 2 H), 6.86−7.00 (m, 2 H), 7.20−7.34 (m, 3 H), 9.59 (s, 1 H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 62.6, 115.8, 119.9, 121.4, 128.9, 131.0, 132.6, 140.3, 155.4, 189.0. − MS (electrospray): *m*/*z* (rel. int.): 183 (8) [M + Na], 161 (100) [M + H^+], 175 (10).

1-(2*H*-Chromen-3-yl)ethanone (20b): K_2CO_3 (82 mmol, 11.33 g) was added to a solution of salicylaldehyde **16** (82 mmol, 10 g) and but-3-en-2-one (90.20 mmol, 6.31 g) in 2-butanone (100 mL), and the reaction mixture was then heated at reflux for 2 h before being treated with water (150 mL). The layers were separated and extracted with ether, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under vacuum. Purification by silica gel column chromatography (R_f = 0.54, cyclohexane/EtOAc, 80:20) afforded the ketone **20b** as a yellow solid, in 80% yield (11.43 g). − M.p. 48 °C (ref.[19] = 48 °C). − IR (KBr): ṽ = 2865, 1634, 1600, 1211, 754 cm^{-1}. − ^1H NMR[28] ($CDCl_3$, 200 MHz): δ = 2.41 (s, 3 H), 5.00 (s, 2 H), 6.83−6.97 (m, 2 H), 7.14−7.22 (m, 2 H), 7.30 (s, 1 H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.6, 63.9, 120.4, 130.4, 115.9, 121.5, 128.9, 132.1, 133.6, 155.2, 195.5. − MS (electrospray): *m*/*z* (rel. int.): 175 (100) [M + H^+], 141 (7).

3-(2,2-Dibromovinyl)-2*H*-chromene (21): Triphenylphosphane (10 mmol, 2.62 g), zinc powder (10 mmol, 654 mg), and carbon tetrabromide (10 mmol, 3.32 g) were successively added to a solution of aldehyde **20** (5 mmol, 800 mg) in CH_2Cl_2 (25 mL). After stirring at room temperature for 3 h, the reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under vacuum. Purification by silica gel column chromatography (R_f = 0.91, cyclohexane/CH_2Cl_2 70:30) afforded compound **21** as a yellow solid in 98% yield (1.54 g). − M.p. 131−133 °C. − IR (KBr): ṽ = 1605, 1560, 1485, 1455, 1109, 1038 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 5.11 (s, 2 H), 6.66 (br. s, 1 H), 6.83 (dd, *J* = 7.6, 1.2 Hz, 1 H), 6.88 (td, *J* = 7.3, 1.2 Hz, 1 H), 7.03 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.16 (td, *J* = 7.6, 1.2 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 66.1, 87.9, 115.7, 121.8, 122.3, 127.1, 127.3, 128.7, 130.1, 134.9, 153.6. − MS (GCMS, electrospray): *m*/*z* (rel. int.): 318 (47) [$M^{+\cdot}$], 317 (44), 316 (100) [$M^{+\cdot}$], 315 (71), 314 (52) [$M^{+\cdot}$], 238 (52), 235 (58),156 (78), 155 (91), 131 (56), 128 (90).

3-Ethynyl-2*H*-chromene (15a). − From 21: A solution of LDA (3.3 mL, 1.5 M in cyclohexane, 4.83 mmol) was slowly added at −78 °C to a solution of **21** (2.20 mmol, 691 mg) in THF (5 mL), and the resulting mixture was allowed to warm slowly to room temperature and stirred for 4 h. After addition of water (20 mL), the layers were separated and extracted with ethyl acetate, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under vacuum. Purification by silica gel column chromatography (R_f = 0.49, cyclohexane/CH_2Cl_2, 60:40) afforded terminal alkyne **15a** as a yellow oil, in 61% yield (210 mg).

From 20b: *i*Pr_2NEt (23.25 mmol, 3.0 g) and Tf_2O (6.88 mmol, 1.94 g) were successively added at −78 °C to a solution of **20b** (5.74 mmol, 1.0 g) in CH_2Cl_2 (30 mL). After stirring at −10 °C for 1 h, the reaction mixture was quenched with aqueous hydrochloric acid (1 M) and extracted with Et_2O. The combined organic layers were then dried with $MgSO_4$ and the solvent was removed in vacuo. Purification by silica gel column chromatography afforded terminal alkyne **15a** in 81% yield (726 mg). − IR (KBr): ṽ = 3284, 2090, 1603, 1484, 1203, 1035, 750 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.15 (s, 1 H), 4.75 (d, *J* = 1.2 Hz, 2 H), 6.78 (br. s, 1 H), 6.82 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.90 (td, *J* = 8.0, 1.2 Hz, 1 H), 7.02 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.15 (td, *J* = 8.0, 1.2 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 67.1, 80.9, 81.3, 114.3, 116.0, 121.9, 127.1, 128.3, 130.2, 131.2, 153.6. − MS (GCMS, electrospray): *m*/*z* (rel. int.): 156 (80) [$M^{+\cdot}$], 155 (100), 128 (30), 127 (26).

General Procedure for the Sonogashira Coupling Reaction: A solution of 1-alkyne (1.44 mmol) in triethylamine (2 mL) was slowly added at 60 °C to a degassed solution of $Pd(PPh_3)_4$ (0.06 mmol, 5 mol %, 70 mg), bromopyridine **13** or triflate **23** (1.2 mmol), and CuI (0.12 mmol, 23 mg) in triethylamine (3 mL). The reaction was stirred at 60 °C and monitored by TLC until complete consumption of starting materials. After evaporation of the solvent in vacuo, the crude material was purified by silica gel column chromatography.

Methyl 4-[6-[(2*H*-Chromen-3-yl)ethynyl]pyridin-2-yl]benzoate (5a): 308 mg (70%, beige solid) obtained from **13a** (1.20 mmol, 350 mg) and **15a** (1.44 mmol, 225 mg). − R_f = 0.30 (cyclohexane/EtOAc: 80:20). − IR (KBr): ṽ = 1710, 1600, 1450, 1270, 1210 cm^{-1}. − ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.86 (s, 3 H), 4.80 (d, *J* = 1.2 Hz, 2 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 6.83 (td, *J* = 7.5, 1.5 Hz, 1 H), 6.85 (1 H, br. s), 6.95 (dd, *J* = 7.5, 1.7 Hz, 1 H), 7.07 (td, *J* = 7.8, 1.7 Hz, 1 H), 7.37 (br. d, *J* = 7.8 Hz, 1 H), 7.62 (br. d, *J* = 7.4 Hz, 1 H), 7.68 (dd, *J* = 7.8, 7.4 Hz, 1 H), 8.03 (m, 4 H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 52.2, 67.0, 86.4, 92.7, 114.3, 115.9, 120.3, 121.9, 126.4, 127.1 (2 C), 127.2, 130.0 (2 C), 130.3, 130.7, 131.6, 137.0, 142.8, 143.2, 153.7, 156.8, 166.8. − MS (electrospray): *m*/*z* (rel. int.): 757 (100) [2 M + Na^+], 404 (33), 368 (63) [MH^+], 150 (38). − $C_{24}H_{17}NO_3$ (367.1): calcd. C 78.46, H 4.66; found C 78.63, H 4.78.

Ethyl 4-[[6-(2*H*-Chromen-3-yl)pyridin-2-yl]ethynyl]benzoate (5b): 302 mg (66%, beige solid) obtained from **13b** (1.20 mmol, 345 mg) and **15b** (1.44 mmol, 251 mg). − R_f = 0.30 (cyclohexane/EtOAc: 80:20). − IR (KBr): ṽ = 1712, 1603, 1453, 1272, 1214 cm^{-1}. − ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.39 (t, *J* = 7.0 Hz, 3 H), 4.38 (q, *J* = 7.0 Hz, 2 H), 5.36 (s, 2 H), 6.87 (br. d, *J* = 8.5 Hz, 1 H), 6.90 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.12 (br. d, *J* = 7.5 Hz, 1 H), 7.15 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.23 (s, 1 H), 7.40 (d, *J* = 7.6 Hz, 1 H), 7.48 (d, *J* = 7.6 Hz, 1 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 7.66 (d, *J* = 8.0 Hz, 2 H), 8.03 (d, *J* = 8.0 Hz, 2 H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3, 61.2, 66.1, 88.0, 91.3, 115.7, 118.5, 121.5, 122.3, 123.6, 125.9, 126.8, 127.7, 129.4 (2 C), 130.0, 130.5, 130.8, 131.9 (2 C), 136.4, 142.4, 154.3, 154.9, 165.9. − MS (electrospray): *m*/*z* (rel. int.): 404 (3) [M + Na^+], 382 (100) [MH^+], 279 (10). − $C_{25}H_{19}NO_3$ (381.1): calcd. C 78.72, H 5.02; found C 78.51, H 5.15.

Ethyl 6-[(2*H*-Chromen-3-yl)ethynyl]nicotinate (6): 227 mg (65%, yellow solid) obtained from **22** (1.20 mmol, 342 mg) and **15b** (1.44 mmol, 251 mg). − R_f = 0.40 (CH_2Cl_2). − M.p. 157−159 °C. − IR (KBr): ṽ = 2260, 1730, 1620, 1615, 1160 cm^{-1}. − ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.98 (s, 3 H), 4.89 (br. s, 2 H), 6.78

(br. d, J = 8.0 Hz, 1 H), 6.88 (dt, J = 8.0, 2.0 Hz, 1 H), 7.04 (br. s, 1 H), 7.15 (d, J = 8.0 Hz, 1 H), 7.16 (dt, J = 8.0, 2.0 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 1 H), 8.29 (dd, J = 8.0, 2.0 Hz, 1 H), 9.18 (d, J = 2.0 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 52.6, 66.2, 91.1, 104.7, 116.1, 121.9, 122.4, 126.8, 127.5, 129.3, 130.7, 132.7 (2 C), 137.3, 140.0, 147.5, 151.3, 166.1. − $C_{18}H_{13}NO_3$ (291.1): calcd. C 74.22, H 4.50; found C 75.03, H 4.71.

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