ChemInform Abstract: Synthesis of Highly Functionalized Biaryls by Condensation of 2-Fluoro-1,3-bis(silyloxy) 1,3-Dienes with 3-Cyanochromones and Subsequent Domino "Retro-Michael/...

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · NOVEMBER 2010

Impact Factor: 4.72 · DOI: 10.1021/jo1018443 · Source: PubMed

JOC Note

pubs.acs.org/joc

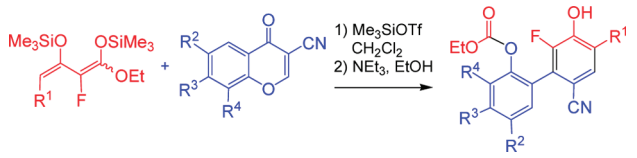
Synthesis of Highly Functionalized Biaryls by Condensation of 2-Fluoro-1,3-bis(silyloxy) 1,3-Dienes with 3-Cyanochromones and Subsequent Domino "Retro-Michael/Aldol/Fragmentation"

Muhammad Farooq Ibad,[†] Obaid-ur-Rahman Abid,[†] Muhammad Adeel,[†,‡] Muhammad Nawaz,[†] Verena Wolf,[†] Alexander Villinger,[†] and Peter Langer*[,†,§]

[†]*Institut für Chemie der Universität Rostock, Albert-Einstein-Strasse 3a, D-18059 Rostock, Germany,* [‡]*Department of Chemistry, Gomal University, Dera Ismail Khan, K.P.K., Pakistan, and* [§]*Leibniz Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Strasse 29a, D-18059 Rostock, Germany*

peter.langer@uni-rostock.de

Received September 17, 2010



The Me_3SiOTf-mediated condensation of 1-ethoxy-2-fluoro-1,3-bis(trimethylsilyloxy) 1,3-dienes with 3-cyanochromones afforded 3-cyano-2-(4-ethoxy-3-fluoro-2,4-dioxobutyl)-chroman-4-ones. Their reaction with triethylamine afforded fluorinated azaxanthones or biaryls. The product distribution depends on the structure of the diene. The formation of the biaryls can be explained by an unprecedented domino "retro-Michael/aldol/fragmentation" reaction.

Organofluorine compounds are of considerable importance in medicinal chemistry.[1] The fluorine atom combines a high electronegativity with a small size which often results in an improvement of drug-receptor interactions. Undesired metabolic transformations are rare because of the chemical and biological stability of the carbon−fluorine bond. The transport of the drug is facilitated by the high lipophilicity of organofluorine compounds. Fluorinated arenes and heteroarenes are also versatile building blocks in transition-metal-catalyzed cross-coupling reactions.[2] Last but not least, organofluorine compounds are used as ligands[3] in catalytic reactions and as organocatalysts.[4]

Aryl fluorides are available by reaction of arenes with fluorine, xenon fluorides, or related strong electrophilic reagents.[5] However, these methods are often not practical because the reagents are difficult to handle, dangerous, or expensive. Selectfluor represents a very useful, commercially available electrophilic fluorination agent.[6] However, direct fluorinations of arenes using Selectfluor suffer from low o/p regioselectivity.[6,7] In addition, only highly reactive (electron-rich) arenes can be successfully used as substrates.[7] The synthesis of heavily substituted fluorinated arenes is particularly difficult because of the low reactivity of sterically hindered starting materials which are not readily available.

An alternative approach to aryl fluorides relies on a building block strategy.[8] In recent years, we studied the chemistry of 1,3-bis(silyloxy)-1,3-butadienes[9] and their application to organofluorine chemistry.[10] We have also studied the reaction of 1,3-bis(silyloxy)-1,3-butadienes with chromone derivatives.[11] In this context, we developed a new synthesis of azaxanthones by condensation of 1,3-bis(silyloxy)-1,3-butadienes with 3-cyanochromones and the subsequent base-mediated domino[12] "retro-Michael/nitrile-addition/heterocyclization" reaction.[13] We have also reported a synthetic approach to biaryl lactones

(1) (a) *Fluorine in Bioorganic Chemistry*; Filler, R., Kobayasi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993. (b) Filler, R. *Fluorine Containing Drugs in Organofluorine Chemicals and Their Industrial Application*; Pergamon: New York, 1979; Chapter 6. (c) Hudlicky, M. *Chemistry of Organic Compounds*; Ellis Horwood: Chichester, 1992. (d) Kirsch, P. *Modern Fluoroorganic Chemistry*; VCH: Weinheim, 2004. (e) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell Publishing CRC Press: Boca Raton, 2004.

(2) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004.

(3) (a) Schmidbaur, H.; Kumberger, O. *Chem. Ber.* **1993**, *126*, 3. (b) Dinger, M. B.; Henderson, W. *J. Organomet. Chem.* **1998**, *560*, 233. (c) Liedtke, J.; Loss, S.; Widauer, C.; Grützmacher, H. *Tetrahedron* **2000**, *56*, 143. (d) Schneider, S.; Tzschucke, C. C.; Bannwarth, W. In *Multiphase Homogeneous Catalysis*; Cornils, B., Herrmann, W. A., Horvath, I. T., Leitner, W., Mecking, S., Olivier-Booubigou, H., Vogt, D., Eds.; Wiley-VCH: New York, 2005; Chapter 4, p 346. (e) Clarke, D.; Ali, M. A.; Clifford, A. A.; Parratt, A.; Rose, P.; Schwinn, D.; Bannwarth, W.; Rayner, C. M. *Curr. Top. Med. Chem.* **2004**, *7*, 729.

(4) Reviews: (a) Wittkopp, A.; Schreiner, P. R. *The Chemistry of Dienes and Polyenes*; John Wiley & Sons Ltd.: New York, 2000; Vol. 2. (b) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. See also: (c) Wittkopp, A.; Schreiner, P. R. *Chem.—Eur. J.* **2003**, *9*, 407. (d) Kleiner, C. M.; Schreiner, P. R. *Chem. Commun.* **2006**, 4315. (e) Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, *5*, 779. Review: Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.

(5) Reviews: (a) Tredwell, M.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 26. (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (c) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, *17*, 2561. (d) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431. (e) Purrington, S. T.; Kagen, B. S.; Patrick, T. B. *Chem. Rev.* **1986**, *86*, 997.

(6) Reviews: (a) Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem.* **2005**, *117*, 196. *Angew. Chem., Int. Ed.* **2005**, *44*, 192. (b) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31. Banks, R. E.; Besheesh, M. K.; Mohialdin-Khaffaf, S. N.; Sharif, I. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2069.

(7) Stavber, S.; Jereb, M.; Zupan, M. *Synlett* **1999**, *9*, 1375. For a recent example of a Fries rearrangement of 4-fluorophenol, see: Sebille, S.; de Tullio, P.; Becker, B.; Antoine, M.-H.; Boverie, S.; Pirotte, B.; Lebrun, P, P. *J. Med. Chem.* **2005**, *48*, 614.

(8) For examples, see: (a) Shi, G.-q.; Cottens, S.; Shiba, S. A.; Schlosser, M. A. *Tetrahedron* **1992**, *48*, 10569. (b) Shi, G.-q.; Schlosser, M. *Tetrahedron* **1993**, *49*, 1445. (c) Patrick, T. B.; Rogers, J.; Gorrell, K. *Org. Lett.* **2002**, *4*, 3155. Lefebvre, O.; Brigaud, T.; Portella, C. *Tetrahedron* **1998**, *54*, 5939.

(9) For a review of 1,3-bis(silyloxy)-1,3-butadienes in general, see: Langer, P. *Synthesis* **2002**, 441.

(10) For a review of applications of 1,3-bis(silyloxy)-1,3-butadienes in fluorine chemistry, see: Langer, P. *Synlett* **2009**, 2205.

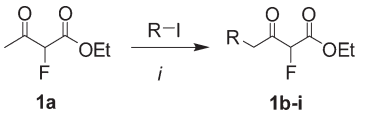
(11) For a review of reactions of chromones with 1,3-bis(silyloxy)-1,3-butadienes, see: Langer, P. *Synlett* **2007**, 1016.

(12) For reviews of domino reactions, see: (a) Tietze, L. F.; Beifuss, U. *Angew. Chem.* **1993**, *105*, 137; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(13) (a) Langer, P.; Appel, B. *Tetrahedron Lett.* **2003**, 5133. (b) Rashid, M. A.; Rasool, N.; Appel, B.; Adeel, M.; Karapetyan, V.; Mkrtchyan, S.; Reinke, H.; Fischer, C.; Langer, P. *Tetrahedron* **2008**, *64*, 5416.

DOI: 10.1021/jo1018443 Published on Web 11/09/2010

SCHEME 1. Synthesis of 1b−i[a]



[a]Conditions: (i) 1) LDA (2.3 equiv), THF, −78 °C, 1 h; (2) BnBr or R-I, −78 → +20 °C, 14 h; (3) HCl (10%).

TABLE 1. Synthesis of 1b−i

1	R	% yield[a]
b	Bn	60
c	Me	59
d	*n*-Pr	59
e	*n*-Bu	63
f	*n*-Pent	74
g	*n*-Hex	64
h	*n*-Oct	62
i	*n*-Dec	61

[a]Yields of isolated products.

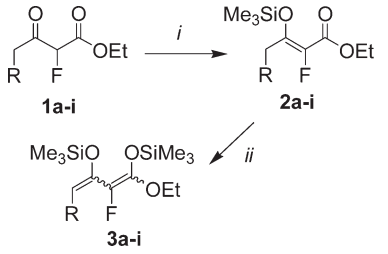
by condensation of 1,3-bis(silyloxy)-1,3-butadienes with chromones and subsequent base-mediated domino "retro-Michael/aldol/lactonization" reaction.[14] Herein, we report, for the first time, the reaction of 3-cyanochromones with 2-fluoro-1,3-bis(silyloxy) 1,3-dienes which give rise to the unexpected formation of highly functionalized fluorinated biaryls. The formation of the products can be explained by an hitherto unprecedented domino "retro-Michael/aldol/fragmentation" reaction. These reactions are preparatively useful as they provide a convenient approach to highly substituted fluorinated biaryls which are not readily available by other methods.

For our studies, there was the need to develop a new and general method for the synthesis of various 2-fluoro-3-oxoesters. The reaction of 1,3-dicarbonyl dianions with alkyl halides has been widely used for the synthesis of β-ketoesters.[15] The application of this methodology to the synthesis of fluorinated derivatives has, to the best of our knowledge, not been reported to date. We were pleased to find that the reaction of the dianion of commercially available ethyl 2-fluoroacetoacetate (**1a**) with benzyl bromide and various alkyl iodides afforded the 2-fluoro-3-oxo esters **1b−i** (Scheme 1, Table 1). The yields (59−74%) are typical for dianion reactions, and the experiments thus show that the fluorine substituent is compatible with the reaction conditions.

The silylation of **1a−i** afforded silyl enol ethers **2a−i**. The latter were transformed, by deprotonation (LDA) at −78 °C and subsequent addition of trimethylchlorosilane, into the 1-ethoxy-2-fluoro-1,3-bis(trimethylsilyloxy) 1,3-dienes **3a−i** (Scheme 2, Table 2). The fluorine substituent again proved to be compatible with the reaction conditions. The synthesis of **3a** has been previously reported.[16] Dienes **3a−i** can be stored at −20 °C under inert atmosphere for several weeks.

The Me_3SiOTf-mediated reaction of **3a** with 3-cyanochromone (**4a**) afforded 3-cyano-2-(4-ethoxy-3-fluoro-2,4-dioxobutyl)chroman-4-one **7a**. The reaction of an ethanol solution of the crude product of **7a** with triethylamine afforded the fluorinated azaxanthone **5a** in 56% yield (Scheme 3). Its formation can be explained by a domino "retro-Michael/nitrile-addition/heterocyclization" reaction (path A). The retro-Michael

SCHEME 2. Synthesis of 3a−i[a]



[a]Conditions: (i) Me_3SiCl, NEt_3, benzene, 20 °C, 48 h; (ii) (1) LDA, THF, −78 °C, 1 h, (2) Me_3SiCl, −78 → +20 °C, 14 h.

TABLE 2. Synthesis of 3a−f

2, 3	R	2[a] (%)	3[a] (%)
a	H	81	94
b	Bn	83	91
c	Me	67	88
d	*n*-Pr	82	90
e	*n*-Bu	80	93
f	*n*-Pent	65	89
g	*n*-Hex	77	87
h	*n*-Oct	84	94
i	*n*-Dec	81	92

[a]Yields of isolated products.

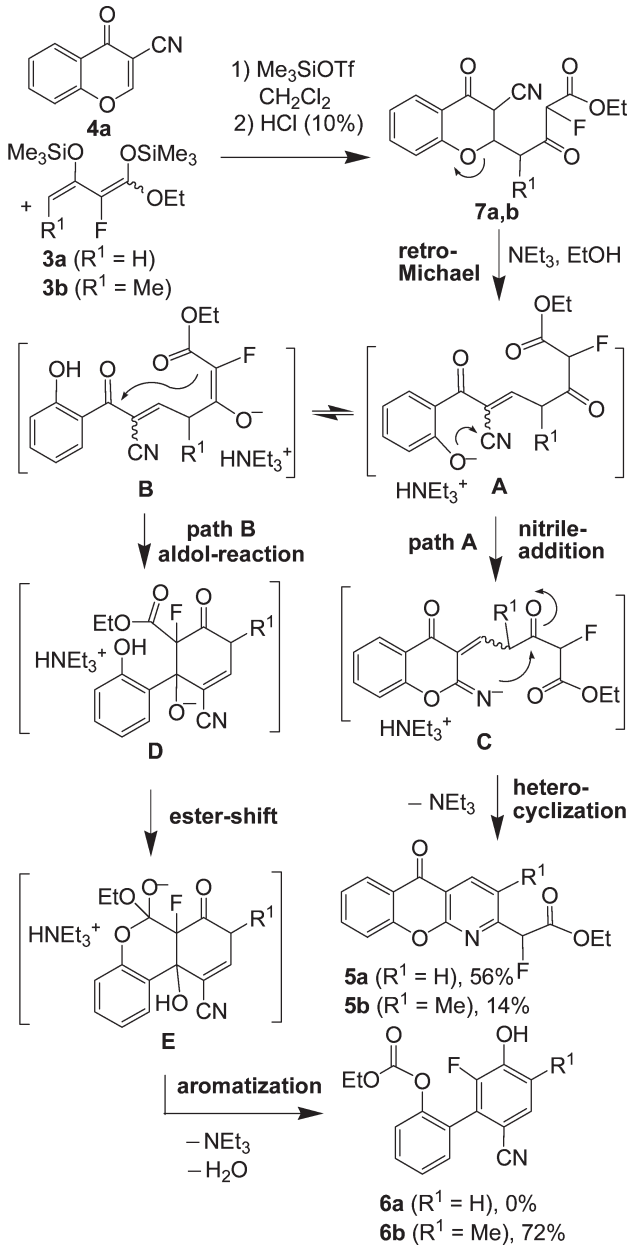
reaction gave intermediate **A**, which underwent a nitrile addition to give intermediate **C**. Heterocyclization of the latter afforded **5a**. A completely different product, fluorinated biaryl **6b** (72% yield), was obtained when **4a** was reacted with diene **3b** (Scheme 3). The isomeric azaxanthone **5b** was isolated in only 14% yield. The formation of **6b** can be explained by a domino "retro-Michael/aldol/1,5-ester-shift" reaction (path B). A proton shift of intermediate **A** afforded **B**, which underwent an intramolecular aldol reaction to give **D**. An intramolecular ester shift (intermediate **E**) and subsequent aromatization gave rise to the formation of **6b**. This process is related to the formation of biaryl lactones by condensation of 1,3-bis(silyloxy)-1,3-butadienes with simple chromones and subsequent base-mediated domino "retro-Michael/aldol/lactonization" reaction.[14] In contrast to this process, a direct aromatization during the intramolecular aldol reaction is not possible in the present reaction because a quaternary carbon atom is involved. However, the aromatization can take place because of the fragmentation.

The experiments described above suggest that the product distribution depends on the chain length of the diene. To prove this assumption, the substituents of the diene and of the chromone were systematically varied (Scheme 4, Table 3). The reaction of parent 3-cyanochromone (**4a**) with substituted dienes **3c−i** mainly afforded the biaryls **6b−h**. Azaxanthones were isolated as side products or not at all. The reaction of unsubstituted diene **3a** with 3-cyanochromone **4c**, containing two electron-donating methyl groups, exclusively afforded azaxanthone **5j**. In contrast, biaryls **6k**,**l** were the main products in the reaction of **4c** with substituted dienes **3d**,**g**.

The reaction of **3a** with 3-cyanochromones **4f** and **4g**, containing electron-withdrawing halogen substituents, exclusively afforded the azaxanthones **5w** and **5ab**. In contrast, fluorinated biaryls were formed in the reaction of **4e−g** with substituted dienes. The structures of **5ab** and **6d** were independently confirmed by X-ray crystal structure analyses (see the Supporting Information).

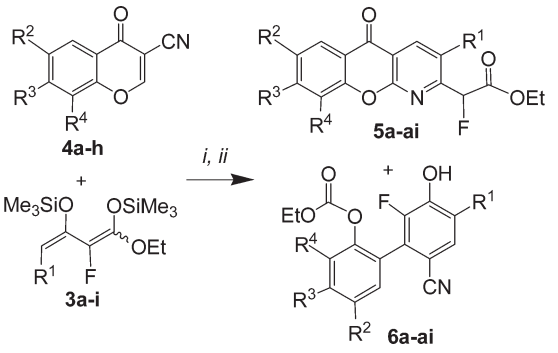
(14) Appel, B.; Saleh, N. N. R.; Langer, P. *Chem.—Eur. J.* **2006**, *12*, 1221.
(15) Weiler, L. *J. Am. Chem. Soc.* **1970**, *92*, 6702.
(16) Adeel, M.; Reim, S.; Wolf, V.; Yawer, M. A.; Hussain, I.; Villinger, A.; Langer, P. *Synlett* **2008**, 2629.

SCHEME 3. Possible Mechanisms of the Formation of 5a and 6b



In conclusion, we have reported the Me_3SiOTf-mediated condensation of 1-ethoxy-2-fluoro-1,3-bis(trimethylsilyloxy) 1,3-dienes with 3-cyanochromones to give 3-cyano-2-(4-ethoxy-3-fluoro-2,4-dioxobutyl)chroman-4-ones. Their reaction with triethylamine afforded fluorinated azaxanthones or biaryls. The use of unsubstituted 2-fluoro-1,3-bis(trimethylsilyloxy)-1,3-butadiene **3a** generally resulted in exclusive formation of fluorinated azaxanthones **5** by a domino "retro-Michael/nitrile-addition/heterocyclization" reaction. In contrast, the employment of substituted homologues gave rise to the formation of fluorinated biaryls as the main products. Their formation can be explained by an unprecedented domino "retro-Michael/aldol/fragmentation" reaction. In some reactions, the corresponding azaxanthones were isolated as side products. Thus, the product distribution is influenced by the chain length of the diene. An influence of the structure of the diene on the product distribution has been previously

SCHEME 4. Synthesis of 5a–ai and 6a–ai[a]



[a]Key: (i) (1) Me_3SiOTf, 1 h, 20 °C, (2) CH_2Cl_2, 0 → 20 °C, 12 h, (3) HCl (10%); (ii) (1) NEt_3, EtOH, 20 °C, 12 h, (2) HCl (10%).

TABLE 3. Synthesis of 5a–ai and 6a–ai

3	4	5, 6	R^1	R^2	R^3	R^4	5[a] (%)	6[a] (%)
a	**a**	**a**	H	H	H	H	56	0
c	**a**	**b**	Me	H	H	H	14	72
d	**a**	**c**	*n*-Pr	H	H	H	17	71
e	**a**	**d**	*n*-Bu	H	H	H	0	71
f	**a**	**e**	*n*-Pent	H	H	H	13	72
g	**a**	**f**	*n*-Hex	H	H	H	11	69
h	**a**	**g**	*n*-Oct	H	H	H	20	63
i	**a**	**h**	*n*-Dec	H	H	H	13	76
g	**b**	**i**	*n*-Hex	Me	H	H	13	70
a	**c**	**j**	H	Me	Me	H	46	0
d	**c**	**k**	*n*-Pr	Me	Me	H	14	71
g	**c**	**l**	*n*-Hex	Me	Me	H	9	73
f	**d**	**m**	*n*-Pent	Me	H	Me	12	70
g	**d**	**n**	*n*-Hex	Me	H	Me	10	66
i	**d**	**o**	*n*-Dec	Me	H	Me	18	63
b	**e**	**p**	Bn	Cl	H	H	0	68
c	**e**	**q**	Me	Cl	H	H	14	77
d	**e**	**r**	*n*-Pr	Cl	H	H	13	73
e	**e**	**s**	*n*-Bu	Cl	H	H	0	72
f	**e**	**t**	*n*-Pen	Cl	H	H	12	70
g	**e**	**u**	*n*-Hex	Cl	H	H	10	70
h	**e**	**v**	*n*-Oct	Cl	H	H	0	77
a	**f**	**w**	H	Cl	H	Cl	35	0
c	**f**	**x**	Me	Cl	H	Cl	9	79
d	**f**	**y**	*n*-Pr	Cl	H	Cl	13	73
h	**f**	**z**	*n*-Oct	Cl	H	Cl	21	63
i	**f**	**aa**	*n*-Dec	Cl	H	Cl	0	76
a	**g**	**ab**	H	F	H	H	33	0
c	**g**	**ac**	Me	F	H	H	11	73
d	**g**	**ad**	*n*-Pr	F	H	H	16	75
f	**g**	**ae**	*n*-Pent	F	H	H	11	77
g	**g**	**af**	*n*-Hex	F	H	H	7	73
i	**g**	**ag**	*n*-Dec	F	H	H	0	77
c	**h**	**ah**	Me	Et	H	H	10	72
g	**h**	**ai**	*n*-Hex	Et	H	H	12	70

[a]Yields of isolated products.

observed in our study related to the reaction of 1,3-bis(silyloxy) 1,3-dienes with 3-cyanochromones.[13] For specific dienes, containing a substituent located at carbon atom C-4 but no substituent at C-2, the formation of biaryl lactones by domino "retro-Michael/aldol/lactonization" reactions was observed. But this transformation was not general, and in most cases, azaxanthones were formed. Therefore, the fluorine atom attached to carbon atom C-2 of dienes **3** must have an important influence on the mechanism and biaryl formation. The steric influence of the fluorine atom and of the substituent R^1 may result in a conformation which facilitates the intramolecular aldol reaction at the expense of the nitrile addition. Preliminary

results suggest that reactions of dienes containing a chlorine instead of a fluorine atom exclusively afford azaxanthones and not chlorinated biaryls.

From a preparative viewpoint, the reactions reported are useful as they allow for a convenient approach to highly substituted fluorinated biaryls which are not readily available by other methods.

Experimental Section

General Procedure for the Synthesis of Azaxanthones 5 and Biaryls 6. To neat 3-cyanochromone **4** (1.0 equiv) were added Me_3SiOTf (1.3 equiv) and CH_2Cl_2 (1 mL) at 20 °C. After the mixture was stirred for 1 h, CH_2Cl_2 (10 mL) and 1,3-bis(trimethylsilyloxy)-1,3-butadiene **3** (1.3 equiv) were added at 0 °C. The mixture was stirred for 12 h at 20 °C and subsequently poured into hydrochloric acid (10%). The organic and the aqueous layer were separated, and the latter was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water, dried (Na_2SO_4), and filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in ethanol (10 mL), NEt_3 (2.0 equiv) was added, and the solution was stirred for 12 h at 20 °C. To the solution were subsequently added an aqueous solution of hydrochloric acid (1 M) and ether (50 mL). The organic and the aqueous layer were separated, and the latter was extracted with ether (3 × 100 mL). The combined organic layers were washed with water, dried (Na_2SO_4), and filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc/hexane).

Ethyl 2-Fluoro-2-(5-oxo-3-propyl-5*H*-chromeno[2,3-*b*]pyridine-2-yl)acetate (5c) and 6-Cyano-2-fluoro-3-hydroxy-4-propyl-2′-ethoxycarbonyloxybiphenyl (6c). Starting with 3-cyanochromone **4a** (171 mg, 1.0 mmol), Me_3SiOTf (288 mg, 0.23 mL, 1.3 mmol), **3d** (435 mg, 1.3 mmol), CH_2Cl_2 (9.0 mL), EtOH (10 mL), and triethylamine (202 mg, 0.28 mL, 2.0 mmol), **5c** (244 mg, 17%) and **6c** (58 mg, 71%) were isolated as slightly yellow solids. **5c**: mp 97−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.97 (t, ^3J = 7.3 Hz, 3H), 1.23 (t, ^3J = 6.9 Hz, 3H), 1.60−1.77 (m, 2H), 2.70−2.86 (m, 2H), 4.19−4.35 (m, ^3J = 6.9 Hz, 2H), 6.07 (d, $^2J_{FH}$ = 47.7 Hz), 7.36 (t, J = 7.5 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.72 (dt, J = 7.8 Hz, 1.7 Hz, 1H), 8.24 (d, J = 8.1 Hz, 1H), 8.53 (s, 1H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ = 13.2, 14.1, 24.6, 32.5, 62.3, 87.9 (d, $^1J_{FC}$ = 188 Hz), 117.0 (d, ^4J = 1.8 Hz), 118.5, 121.5, 124.7, 126.7, 135.1, 135.8, 138.9, 155.6 (d, $^2J_{F,C}$ = 18.8 Hz), 155.8, 157.8, 167.0 (d, $^2J_{F,C}$ = 25.6 Hz), 177.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ = −182.15; IR (ATR, cm^{-1}) ν = 3359 (w), 3054 (w), 3071 (w), 2964 (w), 2920 (w), 2850 (w), 1762 (s), 1663 (s), 1601 (s), 1562 (w), 1469 (m), 1438 (m), 1423 (s), 1374 (m), 1312 (m), 1201 (m), 1099 (m), 1054 (s), 1014 (m), 754 (s), 665 (m), 595 (w); MS (GC, 70 eV) m/z 345 (M^+ + 2, 2), 344 (M^+ + 1), 343 (M^+, 75), 328 (100), 315 (15), 294 (7), 270 (17), 254 (39), 210 (7), 139 (3), 121 (3), 76 (4), 51 (1); HRMS (EI) calcd for $C_{19}H_{18}FNO_4$ [M^+] 343.12144, found 343.121662. **6c**: mp 110−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.90 (t, ^3J = 7.5 Hz, 3H), 1.13 (t, ^3J = 7.0 Hz, 3H), 1.52−1.64 (m, 2H), 2.57 (dt, $^3J_{HH}$ = 7.5 Hz, $^4J_{FH}$ = 1.5 Hz, 2H), 4.08 (q, ^3J = 7.1 Hz, 2H), 7.25 (s, 1H), 7.27−7.35 (m, 3H), 7.41 (dt, ^3J = 7.2 Hz, ^4J = 2.1 Hz, 1H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ = 13.8, 13.9, 22.8, 31.4 (d, $^4J_{FC}$ = 2.3 Hz), 65.0, 104.2 (d, $^3J_{F,C}$ = 4.6 Hz), 117.4 (d, $^4J_{C,F}$ = 3.7 Hz), 122.3, 124.0, 126.0 (d, $^2J_{F,C}$ = 18 Hz), 126.3, 130.3 (d, $^4J_{F,C}$ = 3.0), 130.7, 131.4, 132.2 (d, $^4J_{F,C}$ = 2.7 Hz), 146.1 (d, $^2J_{F,C}$ = 15.8 Hz), 149.8, 150.7 (d, $^1J_{C,F}$ = 260 Hz); IR (ATR, cm^{-1}) ν = 3305 (b), 2962 (w), 2932 (w), 2872 (w), 2225 (w), 1762 (m), 1617 (m), 1480 (s), 1433 (m), 1369 (m), 1242 (s), 1203 (s), 1152 (m), 1094 (m), 996 (m), 900 (w), 767 (m), 665 (w), 579 (w); MS (GC, 70 eV) m/z 343 (M^+, 2), 326 (1), 299 (5), 284 (35), 271 (35), 254 (7), 243 (26), 242 (100), 228 (7), 207 (6), 177 (3), 158 (3), 139 (3), 94 (1), 44 (7), 32 (32); HRMS (EI) calcd for $C_{19}H_{18}FNO_4$ [M^+] 343.12144, found 343.12230.

Acknowledgment. Financial support by the DAAD (stipends for M.F.I., O.-u.-R.A., and M.N.) and by the State of Pakistan (HEC scholarships for M.N. and O.-u.-R.A.) is gratefully acknowledged.

Supporting Information Available: Synthetic procedures, compound characterization, copies of NMR spectra, and X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.