Trimethylsilyl Trifluoromethanesulfonate-Promoted Cyclocondensation of β-Ketoenamides and Subsequent Nonaflation to Pyrid-2-yl and Pyrid-4-yl Nonaflates as Flexible Precursors for Polysubstituted Pyridines

Paul Hommes, Sarah Berlin, Hans-Ulrich Reissig*

Institut für Chemie und Biochemie, Freie Universität Berlin, Takustr. 3, 14195 Berlin, Germany
Fax +49(30)83855367; E-mail: hans.reissig@chemie.fu-berlin.de

Received: 07.08.2013; Accepted after revision: 16.09.2013

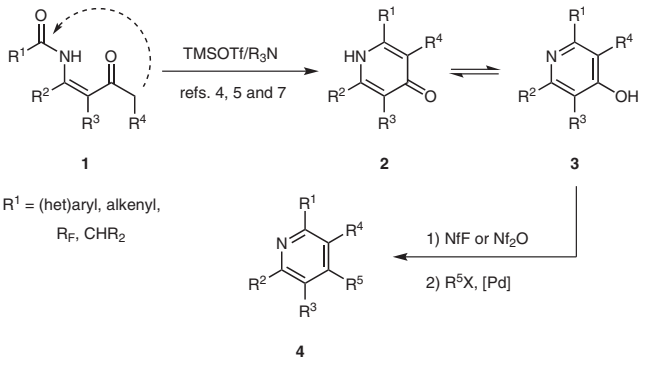
Dedicated to Professor Ernst Schaumann on the occasion of his 70th birthday

Abstract: The intramolecular condensation of β-ketoenamides to 2- and/or 4-pyridone derivatives using either KO*t*-Bu or trimethylsilyl trifluoromethanesulfonate/Hünig's base was investigated. Subsequent nonaflation of the cyclization products allowed a facile purification and further functionalization through Suzuki–Miyaura couplings leading to new highly substituted pyridine derivatives. The dependence of the regioselectivity of cyclocondensation on the structure of the β-ketoenamides is discussed.

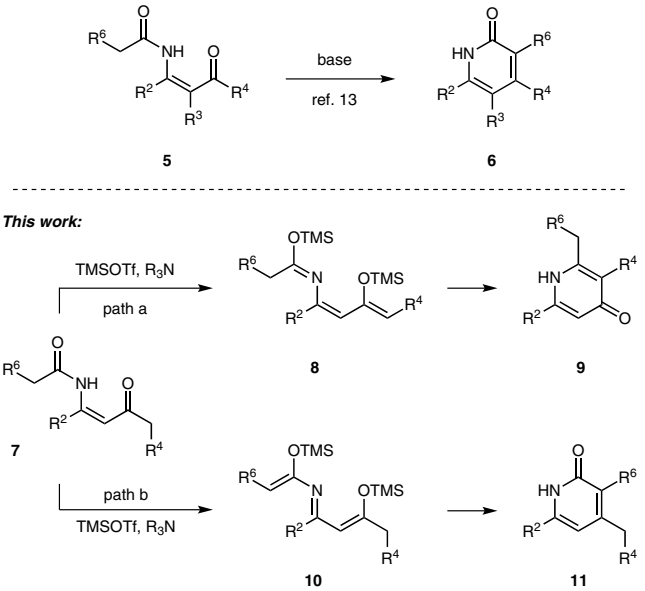
Key words: enamides, pyridines, cyclocondensation, nonaflates, cross couplings

With its ubiquitous structural motif in biologically active compounds and functional materials pyridines belong without doubt to the most important heterocycles.[1] Since the early days of organic chemistry this has been motivating chemists to search for efficient methods to synthesize functionalized pyridine derivatives.[2,3] In recent years our group developed a remarkably flexible approach for the preparation of highly functionalized pyrid-4-ones **2** by a trimethylsilyl trifluoromethanesulfonate (TMSOTf)/base-promoted intramolecular condensation of β-ketoenamides **1** (Scheme 1). A mechanistic proposal for the TMSOTf-promoted cyclocondensation has previously been presented suggesting an aldol-type step of an enolate or its equivalent with the amide carbonyl group.[4] Suitable cyclization precursors can be synthesized by a three-component reaction of lithiated alkoxyallenes, nitriles, and carboxylic acids,[5] or by N-acylation of β-ketoenamines. Suitable enamines are easily accessible via amination of 1,3-diketones,[6] or by trapping the Blaise intermediate with acetic acid anhydride.[7,8] Conversion of 4-hydroxypyridines **3** (the tautomers of **2**) into the corresponding nonafluorobutanesulfonates (nonaflates)[9] allows for versatile subsequent transformations through Pd-catalyzed cross-coupling reactions.[10,11]

It is known that β-ketoenamides of type **5** bearing fairly acidic protons in α-position to the amide carbonyl moiety [R^6 = (het)aryl or electron-withdrawing substituents] cyclize under basic conditions to provide pyrid-2-one derivatives **6** (Scheme 2).[12,13] We were therefore interested, if this kind of transformation would also be possible via a TMSOTf/base-promoted condensation. Furthermore, we wanted to explore the reactivity of β-ketoenamides **7** bearing two enolizable methylene groups. We envisioned that upon treatment with TMSOTf these compounds may cyclize via intermediate **8** to give pyrid-4-ones **9** (path a) as well as via **10** to give pyrid-2-ones **11** (path b).



Scheme 1 Synthesis of highly functionalized pyridine derivatives via TMSOTf-promoted cyclocondensation of β-ketoenamides **1** (Nf = nonafluorobutanesulfonyl)

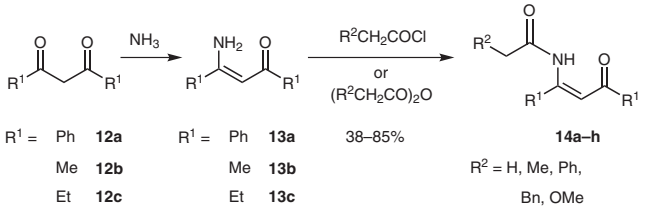


Scheme 2 Cyclocondensation of β-ketoenamides to pyrid-2-ones **11** and/or pyrid-4-ones **9**

SYNTHESIS 2013, 45, 3288–3294
Advanced online publication: 10.10.2013
DOI: 10.1055/s-0033-1338548; Art ID: SS-2013-T0555-OP

An analogous regiounselective reactivity is well known from the Camps cyclization[14] – the base-promoted cyclocondensation of *o*-(amido)acetophenones. The use of substrates with two α-acidic carbonyl moieties in the Camps cyclization employing alkali hydroxides or alkoxides as base usually provides mixtures of 2- and 4-quinolones as products. In contrast, as recently reported, treatment of such *o*-(acetamido)acetophenone derivatives with TMSOTf in presence of triethylamine exclusively provides 4-quinolones.[15]

In order to explore the reactivity of β-ketoenamides of type **5** and **7**, we prepared a series of cyclization precursors as depicted in Scheme 3: amination of simple 1,3-diketones **12a**–**c** to enamines **13a**–**c** followed by acylation with acyl chlorides or the corresponding anhydrides provided the β-ketoenamides **14a**–**h** in moderate to good yields (see Supporting Information for details).

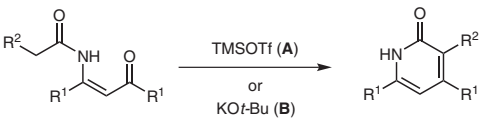


Scheme 3 Preparation of β-ketoenamides **14a**–**h**

Next, the cyclizations of β-ketoenamides **14a**–**h** were investigated (Tables 1 and 2). We first conducted the intramolecular condensation of the dibenzoylmethane (**12a**)-derived enamides **14a** and **14b** using TMSOTf and diisopropylethylamine (DIPEA; Hünig's base) (Table 1, entries 1 and 3). Due to the lack of a methyl ketone moiety as in **7** these substrates cannot cyclize to pyrid-4-ones. We were pleased to find that they were converted into the expected pyrid-2-ones **15a** and **15b** in good yields upon treatment with TMSOTf. For the cyclization of compound **14a** the traditional conditions using KO*t*-Bu[16] allowed a shorter reaction time and provided a slightly higher yield (entry 2). For compound **14b**, however, the TMSOTf-promoted condensation proved to be the superior method since the KO*t*-Bu protocol failed in this case (entry 4). Using the latter protocol the acetylacetone (**12b**)- and heptan-3,5-dione (**12c**)-derived enamides **14c** and **14d** smoothly cyclized to the pyrid-2-ones **15c**[16] and **15d** (entries 5 and 6). In both cases a competing deacylation leading to the formation of the corresponding enamines **13b** and **13c** was observed. For enamide **14e** the KO*t*-Bu protocol resulted in complete deacylation to **13b**, the expected pyrid-2-one **15e** was not detected, indicating that this method – as also concluded by Fisyuk et al. for related compounds[17] – requires substituents that are able to stabilize a negative charge next to R^2.

The TMSOTf/DIPEA promoted intramolecular condensations of β-ketoenamides **14c**–**h** are summarized in Table 2. In these cases isolation and purification of the cyclization products was rather difficult.[18] Therefore, we chose to

Table 1 Cyclocondensation of β-Ketoenamides **14a**–**d** to Pyrid-2-ones **15a**–**d**



14 **15**

Entry		R^1	R^2	Method[a]		Yield (%)
1	**14a**	Ph	Ph	A	**15a**	79
2		Ph	Ph	B		87
3	**14b**	Ph	Me	A	**15b**	93
4		Ph	Me	B		–[b]
5	**14c**	Me	Ph	B	**15c**	62[c]
6	**14d**	Et	Ph	B	**15d**	81[d]
7	**14e**	Me	H	B	**15e**	–[e]

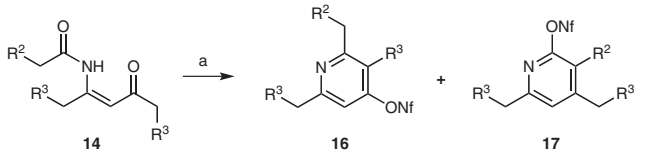
[a] Method A: TMSOTf (5.0 equiv), DIPEA (4.0 equiv), DCE, sealed tube, 90 °C, 3 d; Method B: KO*t*-Bu (1.5 equiv), THF, 0 °C to r.t., 20 h.
[b] No conversion.
[c] Enamine **13b** detected in traces.
[d] Enamine **13c** isolated in 11% yield.
[e] Enamine **13b** isolated in 90% yield.

directly convert the crude product mixture into the corresponding nonaflates whose dramatically decreased polarity allows a facile chromatographic purification. As anticipated, enamides **14c**–**h** can cyclize via two different pathways. After subsequent nonaflation of the unpurified intermediates the pyrid-4-yl nonaflates **16** and in some cases small amounts of the pyrid-2-yl nonaflates **17** were obtained.[19] Except for pyrid-4-yl nonaflate **16g** (76%, Table 2, entry 5), the yields were only moderate, nevertheless the experiments clearly reveal that upon treatment with TMSOTf there is a strong preference of the β-ketoenamides **14c**–**h** to cyclize via intermediates of type **8** to deliver pyrid-4-ones. Unless being enforced in precursors such as **14a**,**b** ($R^1 \neq CH_2R$, Table 1), the TMSOTf-promoted cyclocondensation via intermediates of type **10** apparently plays only a minor role. This competing cyclization to pyrid-2-ones was only observed for enamides **14c**, **14d**, and **14h** bearing substituents R^2 that facilitate enolization[20] of the amide methylene moiety (R^2 = Ph or OMe).

Pyrid-2-ones **15c** and **15d** obtained by the KO*t*-Bu-promoted cyclization could also successfully be nonaflated. The corresponding pyrid-2-yl nonaflates **17c** and **17d** were obtained in good yields (Scheme 4).

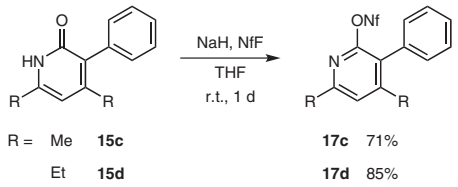
As already mentioned in the introduction, the nonafloxy group allows a large number of subsequent transformations. Exemplarily, we subjected the pyridyl nonaflates **16c** and **17d** to Suzuki–Miyaura reactions[10,21] (Scheme 5). The excellent yields of the cross-coupled products **18** and

Table 2 TMSOTf-Promoted Cyclocondensation of β-Ketoenamides **14c–h** and Subsequent Nonaflation[a]



Entry		R^2	R^3		Yield (%)[b]		Yield (%)[b]
1	**14c**	Ph	H	**16c**	15–20	**17c**	3–9
2	**14d**	Ph	Me	**16d**	30	**17d**	6
3	**14e**	H	H	**16e**	33	**17e**	–
4	**14f**	Me	H	**16f**	52	**17f**	–
5	**14g**	Bn	H	**16g**	76	**17g**	–
6	**14h**	OMe	H	**16h**	12	**17h**	6

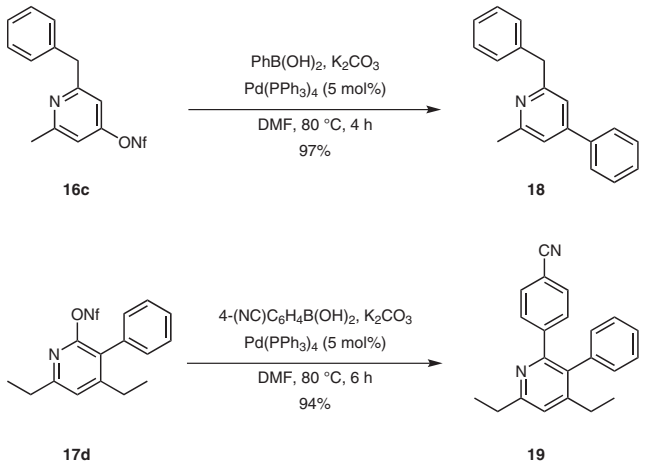
[a] Reaction conditions: 1. TMSOTf (5.0 equiv), DIPEA (4.0 equiv), DCE, sealed tube, 90 °C, 3 d; 2. NaH (5.0–7.0 equiv), NfF (2.5–3.0 equiv), THF, r.t., overnight.
[b] Yields over two steps.



Scheme 4 Nonaflation of pyrid-2-ones **15c** and **15d**

19 once again demonstrate that pyridyl nonaflates are ideal substrates for Pd-catalyzed reactions.

In conclusion, we could demonstrate in this report that it is indeed possible to cyclize suitably substituted β-ketoenamides to pyrid-2-ones via the TMSOTf-promoted intramolecular condensation and that the presented method adds a new version to established protocols. β-Ketoenamides bearing two enolizable methylene groups showed a strong preference to cyclize to pyrid-4-one derivatives. Although the yields are often only moderate the simplicity and versatility of this approach should be useful. The cyclization products could successfully be transformed to the corresponding nonaflates that could be used as components of Pd-catalyzed couplings to highly substituted pyridine derivatives.



Scheme 5 Suzuki–Miyaura couplings of pyrid-4-yl and pyrid-2-yl nonaflates **16c** and **17d** leading to highly substituted pyridine derivatives

Reactions were generally performed under argon in flame-dried flasks or sealed tubes; liquid components were added by syringe. Products were purified by flash column chromatography on silica gel (230–400 mesh, Merck and Macherey & Nagel). Unless stated otherwise, yields refer to analytically pure samples. ^{1}H NMR [$CHCl_3$ (δ = 7.26), TMS (δ = 0.00) as internal standard], ^{13}C NMR [$CDCl_3$ (δ = 77.0) as internal standard], and ^{19}F NMR spectra were recorded with Bruker AC 500, Jeol ECX 400, or Jeol Eclipse 500 instruments in $CDCl_3$ solutions. Integrals are in accordance with assignments; coupling constants are given in Hz. All ^{13}C NMR spectra are proton-decoupled. For detailed peak assignments 2D spectra were measured (COSY, HMQC, HMBC). ^{13}C NMR signals of Nf group [$CF_3(CF_2)_3$] are not given since unambiguous assignment was not possible due to strong splitting by coupling with the ^{19}F nuclei. IR spectra were recorded on a Jasco FT/IR-4100 spectrometer. HRMS analyses were performed with Varian Ionspec QFT-7 (ESI-FT ICRMS) and Agilent 6210 ESI-TOF instruments. The elemental analyses were recorded with PerkinElmer CHN-Analyzer 2400, Vario EL, or Vario EL III instruments. Melting points were measured with a Reichert apparatus and are uncorrected. CH_2Cl_2 and THF were purified with a MB SPS-800 dry solvent system. Unless stated otherwise all other solvents and reagents were purchased from commercial suppliers and were used without further purification. Compounds **13a**,[22] **13b**,[23] **13c**,[6] **14e**,[24] and **15c**[16] were prepared according to literature procedures.

TMSOTf-Promoted Cyclization of β-Ketoenamides; General Procedure 1 (Method A)

TMSOTf (5 equiv) was added dropwise to a stirred solution of the β-ketoenamide (1 equiv) and DIPEA (4 equiv) in DCE (25 mL/mmol) under an atmosphere of argon. The mixture was stirred at 90 °C in a sealed tube for 3 d (large scale reactions may be performed using a Schlenk flask equipped with a reflux condenser). After cooling to r.t., sat. aq NH_4Cl solution was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 or EtOAc (3 ×) and the combined organic layers were dried with Na_2SO_4, filtered, and evaporated to dryness. The obtained crude product was purified by flash column chromatography on silica gel.

KO*t*-Bu-Promoted Cyclization of β-Ketoenamides; General Procedure 2 (Method B)

Following a procedure by Fisyuk et al.,[15] KO*t*-Bu (1.5 equiv) was added to a stirred solution of the β-ketoenamide (1 equiv) in THF (~10 mL/mmol) at 0 °C. The mixture was stirred overnight while being allowed to warm up to r.t. The solvent was evaporated under reduced pressure and the remaining residue was stirred for 5 min with H_2O (~5 mL/mmol). The precipitate was collected by filtration and dried under reduced pressure to provide the product.

In case of no or only little precipitation, CH_2Cl_2 was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 ×) and the combined organic layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. If required, the obtained product was purified by flash column chromatography on silica gel.

3,4,6-Triphenylpyridin-2(1*H*)-one (15a)

Method A: According to general procedure 1, β-ketoenamide **14a** (175 mg, 0.51 mmol) was treated with DIPEA (0.34 mL, 2.00 mmol) and TMSOTf (0.47 mL, 2.59 mmol) in DCE (13 mL). The workup was performed by diluting the reaction mixture with EtOAc (40 mL). After washing with H_2O–brine (1:1, 3 × 40 mL), drying (Na_2SO_4), and filtration the organic layer was evaporated under reduced pressure. The obtained crude product was purified by flash column chromatography on silica gel (hexanes–EtOAc = 5:1 → 2:1) and washed with Et_2O (10 mL) to provide pyrid-2-one **15a** (130 mg, 79%) as a colorless solid.

Method B: According to general procedure 2, β-ketoenamide **14a** (143 mg, 0.42 mmol) was treated with KO*t*-Bu (70 mg, 0.62 mmol) in THF (5 mL). Precipitation provided pyrid-2-one **15a** (118 mg, 87%) as a colorless solid; mp >230 °C (sublimation).

IR (ATR): 3120–2860 (N–H, =C–H), 1620, 1595, 1575, 1500 (C=C, C=N), 1440, 1355, 1255 cm^{-1}.

^1H NMR [$CDCl_3$–CF_3CO_2D (7:1), 500 MHz]: δ = 7.17–7.20, 7.29–7.37 (2 m, 4 H, 6 H, C_6H_5), 7.41 (s, 1 H, 5-H), 7.59–7.63, 7.76–7.77 (2 m, 3 H, 2 H, C_6H_5).

^{13}C NMR [$CDCl_3$–CF_3CO_2D (7:1), 126 MHz]: δ = 116.4 (d, C-5), 125.6 (s, C-3), 127.2, 128.68, 128.71, 128.9*, 129.7, 129.9, 130.6, 130.8, 130.9, 132.1, 136.8 (7 d, 2 s, d, s, C_6H_5), 146.8 (s, C-4), 159.3, 160.7 (2 s, C-2, C-6), * the signal corresponds to two carbon atoms.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{23}H_{18}NO$ $[M + H]^+$: 324.1383; found: 324.1374.

Anal. Calcd for $C_{23}H_{17}NO$ (323.4): C, 85.42; H, 5.30; N, 4.33. Found: C, 85.45; H, 5.34; N, 4.35.

3-Methyl-4,6-diphenylpyridin-2(1*H*)-one (15b)

According to general procedure 1, β-ketoenamide **14b** (252 mg, 0.90 mmol) was treated with DIPEA (0.61 mL, 3.59 mmol) and TMSOTf (0.82 mL, 4.52 mmol) in DCE (23 mL). Workup was performed with sat. aq NH_4Cl solution (30 mL) and CH_2Cl_2 (3 × 30 mL). The obtained crude product was purified by flash column chromatography on silica gel (hexanes–EtOAc = 1:1) to provide pyrid-2-one **15b** (218 mg, 93%) as a pale brownish solid; mp 243–245 °C.

IR (ATR): 3120–2800 (N–H), 3030 (=C–H), 2980–2850 (C–H), 1625–1500 (C=C, C=N), 1450, 1375–1265, 1180, 1150 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 2.14 (s, 3 H, CH_3), 6.50 (s, 1 H, 5-H), 7.37–7.49, 7.79–7.81 (2 m, 8 H, 2 H, C_6H_5), 12.07 (s br, 1 H, NH).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 13.6 (q, CH_3), 107.2 (d, C-5), 124.4 (s, C-3), 126.4, 128.0, 128.2, 128.4, 129.0, 129.6, 133.5, 139.8 (6 d, 2 s, C_6H_5), 142.3 (s, C-6), 151.4 (s, C-4), 165.3 (s, C-2).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{18}H_{16}NO$ $[M + H]^+$: 262.1234; found: 262.1226.

Anal. Calcd for $C_{18}H_{15}NO$ (261.3): C, 82.73; H, 5.79; N, 5.36. Found: C, 82.83; H, 5.68; N, 5.31.

4,6-Diethyl-3-phenylpyridin-2(1*H*)-one (15d)

According to general procedure 2, β-ketoenamide **14d** (273 mg, 1.11 mmol) was treated with KO*t*-Bu (187 mg, 1.67 mmol) in THF (9 mL). Workup was performed with H_2O–brine (1:1, 60 mL) and CH_2Cl_2 (4 × 60 mL). The obtained crude product was purified by flash column chromatography on silica gel (hexanes–EtOAc = 3:1 → 1:1) to provide β-ketoenamine **13c** (16 mg, 11%) as a yellow oil and pyrid-2-one **15d** (203 mg, 81%) as a colorless solid; melting range 65–70 °C.

IR (ATR): 3130 (N–H), 3075–3025 (=C–H), 2970, 2935, 2870 (C–H), 1625–1600, 1555 (C=C, C=N), 1495–1440 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.04, 1.22 (2 t, *J* = 7.6 Hz, 3 H each, CH_3), 2.32, 2.51 (2 q, *J* = 7.6 Hz, 2 H each, CH_2), 5.99 (s, 1 H, 5-H), 7.23–7.26, 7.29–7.32, 7.37–7.40 (3 m, 2 H, 1 H, 2 H, C_6H_5), 12.15 (s br, 1 H, NH).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 12.6, 14.3 (2 q, CH_3), 26.2, 26.7 (2 t, CH_2), 105.4 (d, C-5), 126.9 (d, C_6H_5), 127.1 (s, C-3), 128.0, 130.2, 135.9 (2 d, s, C_6H_5), 148.8, 155.0 (2 s, C-4, C-6), 164.4 (s, C-2).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{15}H_{18}NO$ $[M + H]^+$: 228.1383; found: 228.1369.

Anal. Calcd for $C_{15}H_{17}NO$ (227.3): C, 79.26; H, 7.54; N, 6.16. Found: C, 79.19; H, 7.52; N, 6.17.

TMSOTf-Promoted Cyclization of β-Ketoenamides Followed by Nonaflation of the Crude Product; General Procedure 3

The reaction was set up according to the general procedure 1. After performance of the cyclization step and cooling to r.t., the solvent was carefully evaporated under reduced pressure. The remaining residue was dissolved in THF (10–20 mL/mmol) under an atmosphere of argon. NaH (5–7 equiv, 60% in mineral oil) was washed with hexanes (2 ×) under an atmosphere of argon and was suspended in a small amount of THF. This suspension was slowly transferred (*slow addition was crucial because of vigorous hydrogen evolution*) to the solution of the crude cyclization product. NfF (2.5–3.0 equiv) was added and the mixture stirred at r.t. overnight. Sat. aq NH_4Cl solution was slowly added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 ×) and the combined organic layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The obtained crude product was purified by flash column chromatography on silica gel.

Nonaflation of Pyrid-2-ones; General Procedure 4

NaH (3–4 equiv, 60% in mineral oil) was washed twice with hexanes (2 ×) under an atmosphere of argon and was suspended in a small amount of THF. This suspension was slowly transferred (*slow addition is crucial because of vigorous hydrogen evolution*) to a mixture of the pyrid-2-one and THF (10–20 mL/mmol) under an atmosphere of argon. NfF (2.5– 3.0 equiv) was added and the mixture stirred at r.t. for 1 d. The mixture was diluted with CH_2Cl_2 (or Et_2O) and sat. aq NH_4Cl solution was slowly added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (or Et_2O) (2–3 ×). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The obtained crude product was purified by flash column chromatography on silica gel.

2-Benzyl-6-methylpyridin-4-yl Nonaflate (16c) and 4,6-Dimethyl-3-phenylpyridin-2-yl Nonaflate (17c)

According to general procedure 3, β-ketoenamide **14c** (217 mg, 1.00 mmol) was treated with DIPEA (0.68 mL, 4.00 mmol) and TMSOTf (0.91 mL, 5.02 mmol) in DCE (25 mL) using a sealed tube, followed by nonaflation of the crude product using NaH (300 mg, 7.50 mmol) and NfF (0.54 mL, 3.00 mmol) in THF (15 mL). Workup was performed with sat. aq NH_4Cl solution (20 mL) and CH_2Cl_2 (2 × 20 mL). The obtained crude product was purified by flash column chromatography on silica gel (hexanes–EtOAc = 30:1) to provide pyridyl nonaflates **17c** (15 mg, 3%) and **16c** (98 mg, 20%) as yellow oils.

16c

IR (ATR): 3085–3030 (=C–H), 2965–2925 (C–H), 1600–1580 (C=N, C=C), 1425, 1235–1195, 1145 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 2.61 (s, 3 H, CH_3), 4.17 (s, 2 H, CH_2), 6.77 (d, *J* = 2.0 Hz, 1 H, 5-H), 6.92 (d, *J* = 2.0 Hz, 1 H, 3-H), 7.24–7.32 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 24.7 (q, CH_3), 44.6 (t, CH_2), 112.4 (d, C-5), 112.9 (d, C-3), 126.8, 128.8, 129.1, 138.1 (3 d, s, C_6H_5), 157.2, 161.4, 164.0 (3 s, C-2, C-4, C-6).

^{19}F NMR ($CDCl_3$, 471 MHz): δ = –125.7, –120.8 (2 m_c, 2 F each, CF_2), –108.6 (t, *J* = 13.6 Hz, 2 F, CF_2), –80.5 (t, *J* = 9.6 Hz, 3 F, CF_3).

HRMS (ESI-TOF): *m/z* calcd for $C_{17}H_{13}F_9NO_3S$ [M + H]$^+$: 482.0467; found: 482.0506.

Anal. Calcd for $C_{17}H_{12}F_9NO_3S$ (481.3): C, 42.42; H, 2.51; N, 2.91; S, 6.66. Found: C, 42.40; H, 2.40; N, 2.79; S, 6.53.

4,6-Dimethyl-3-phenylpyridin-2-yl Nonaflate (17c)

According to general procedure 4, pyrid-2-one **15c** (110 mg, 0.55 mmol) was treated with NaH (100 mg, 2.50 mmol) and NfF (0.30 mL, 1.67 mmol) in THF (5 mL). Workup was performed with sat. aq NH_4Cl solution (20 mL) and CH_2Cl_2 (4 × 20 mL). The obtained crude product was purified by flash column chromatography on silica gel (hexanes–EtOAc = 50:1) to provide pyridyl nonaflate **17c** (188 mg, 71%) as a colorless oil.

IR (ATR): 3070–3035 (=C–H), 2930–2855 (C–H), 1620 (C=N, C=C), 1420, 1350, 1235–1200, 1140 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.17 (s, 3 H, 4-CH_3), 2.54 (s, 3 H, 6-CH_3), 7.13 (s, 1 H, 5-H), 7.20–7.23, 7.40–7.47 (2 m, 2 H, 3 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 20.0 (q, 4-CH_3), 23.5 (q, 6-CH_3), 125.2 (d, C-5), 125.7 (s, C-3), 128.4, 128.5, 129.5, 132.5 (3 d, s, C_6H_5), 151.3, 153.1, 156.4 (3 s, C-2, C-4, C-6).

^{19}F NMR ($CDCl_3$, 471 MHz): δ = –125.9, –121.0 (2 m_c, 2 F each, CF_2), –109.3 (t, *J* = 13.7 Hz, 2 F, CF_2), –80.6 (t, *J* = 9.6 Hz, 3 F, CF_3).

HRMS (ESI-TOF): *m/z* calcd for $C_{17}H_{13}F_9NO_3S$ [M + H]$^+$: 482.0467; found: 482.0486.

Anal. Calcd for $C_{17}H_{12}F_9NO_3S$ (481.3): C, 42.42; H, 2.51; N, 2.91; S, 6.66. Found: C, 42.56; H, 2.31; N, 2.61; S, 6.59.

2-Benzyl-6-ethyl-3-methylpyridin-4-yl Nonaflate (16d) and 4,6-Diethyl-3-phenylpyridin-2-yl Nonaflate (17d)

According to general procedure 3, β-ketoenamide **14d** (320 mg, 1.30 mmol) was treated with DIPEA (0.85 mL, 5.00 mmol) and TMSOTf (1.18 mL, 6.50 mmol) in DCE (33 mL) using a sealed tube, followed by nonaflation of the crude product using NaH (364 mg, 9.10 mmol) and NfF (0.70 mL, 3.90 mmol) in THF (16 mL). After evaporation of THF under reduced pressure, the remaining residue was dissolved in CH_2Cl_2 (40 mL) and washed with H_2O (3 × 40 mL). The organic layer was dried with Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The obtained crude product was purified by flash column chromatography on silica gel (hexanes–EtOAc = 50:1 → 20:1) to provide pyridyl nonaflates **17d** (41 mg, 6%) and **16d** (200 mg, 30%) as pale yellow oils.

16d

IR (ATR): 3090–3030 (=C–H), 2970, 2925, 2875–2850 (C–H), 1605, 1560, 1545 (C=C, C=N), 1430, 1235–1145 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.32 (t, *J* = 7.7 Hz, 3 H, CH_2CH_3), 2.20 (s, 3 H, 3-CH_3), 2.85 (q, *J* = 7.7 Hz, 2 H, CH_2CH_3), 4.24 (s, 2 H, CH_2Ph), 6.98 (s, 1 H, 5-H), 7.16–7.21, 7.25–7.28 (2 m, 3 H, 2 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 11.7 (q, 3-CH_3), 13.7 (q, CH_2CH_3), 31.2 (t, OCH_2), 42.6 (t, CH_2Ph), 112.2 (d, C-5), 121.6 (s, C-3), 126.5, 128.6*, 138.1 (2 d, s, C_6H_5), 156.0 (s, C-4), 161.9 (s, C-2), 162.9 (s, C-6), * the signal corresponds to two carbon atoms.

^{19}F NMR ($CDCl_3$, 376 MHz): δ = –125.7, –120.7 (2 m_c, 2 F each, CF_2), –109.3 (t, *J* = 12.6 Hz, 2 F, CF_2), –80.5 (t, *J* = 9.2 Hz, 3 F, CF_3).

HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{17}F_9NO_3S$ [M + H]$^+$: 510.0780; found: 510.0767.

Anal. Calcd for $C_{19}H_{16}F_9NO_3S$ (509.4): C, 44.80; H, 3.17; N, 2.75; S, 6.29. Found: C, 44.76; H, 3.09; N, 2.84; S, 6.32.

4,6-Diethyl-3-phenylpyridin-2-yl Nonaflate (17d)

According to general procedure 4, pyrid-2-one **15d** (169 mg, 0.74 mmol) was treated with NaH (90 mg, 2.25 mmol) and NfF (0.32 mL, 1.78 mmol) in THF (5 mL). Workup was performed with sat. aq NH_4Cl solution (30 mL) and Et_2O (3 × 30 mL). The obtained crude product was purified by flash column chromatography on silica gel (hexanes–EtOAc = 30:1) to provide pyridyl nonaflate **17d** (320 mg, 85%) as a colorless oil.

IR (ATR): 3085–3030 (=C–H), 2980, 2940–2855 (C–H), 1615, 1545 (C=C, C=N), 1475, 1415, 1245–1200, 1150 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.09, 1.34 (2 t, *J* = 7.6 Hz, 3 H each, CH_2CH_3), 2.49, 2.83 (q, *J* = 7.6 Hz, 2 H each, CH_2CH_3), 7.15 (s, 1 H, 5-H), 7.21–7.24, 7.40–7.47 (2 m, 2 H, 3 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 13.0 (q, 6-CH_2CH_3), 14.4 (q, 4-CH_2CH_3), 26.2 (t, 4-CH_2), 30.3 (t, 6-CH_2), 122.2 (d, C-5), 125.3 (s, C-3), 128.3, 128.5, 129.6, 132.4 (3 d, s, C_6H_5), 153.3 (s, C-2), 157.1 (s, C-4), 161.8 (s, C-6).

^{19}F NMR ($CDCl_3$, 376 MHz): δ = –125.8, –121.1 (2 m_c, 2 F each, CF_2), –109.1 (t, *J* = 13.8 Hz, 2 F, CF_2), –80.6 (t, *J* = 9.2 Hz, 3 F, CF_3).

HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{17}F_9NO_3S$ [M + H]$^+$: 510.0780; found: 510.0770.

Anal. Calcd for $C_{19}H_{16}F_9NO_3S$ (509.4): C, 44.80; H, 3.17; N, 2.75; S, 6.29. Found: C, 44.93; H, 3.15; N, 2.89; S, 6.39.

2,6-Dimethylpyridin-4-yl Nonaflate (16e)

According to general procedure 3, β-ketoenamide **14e** (300 mg, 2.13 mmol) was treated with DIPEA (1.45 mL, 8.50 mmol) and TMSOTf (1.93 mL, 10.1 mmol) in DCE (53 mL) using a reflux condenser, followed by nonaflation of the crude product using NaH (425 mg, 10.6 mmol) and NfF (0.95 mL, 5.31 mmol) in THF (20 mL). Workup was performed with sat. aq NH_4Cl solution (30 mL) and CH_2Cl_2 (3 × 30 mL). The obtained crude product was purified by flash column chromatography on silica gel (hexanes–EtOAc = 20:1 → 5:1) to provide pyridyl nonaflate **16e** (282 mg, 33%) as a pale yellow oil.

IR (ATR): 3080 (=C–H), 2970–2855 (C–H), 1600, 1585 (C=C, C=N), 1430, 1350, 1235–1115 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.58 (s, 6 H, CH_3), 6.90 (s, 2 H, 3-H, 5-H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 24.7 (q, CH_3), 112.5 (d, C-3, C-5), 157.0 (s, C-4), 161.2 (s, C-2, C-6).

^{19}F NMR ($CDCl_3$, 376 MHz): δ = –125.8, –120.8 (2 m_c, 2 F each, CF_2), –108.7 (t, *J* = 13.7 Hz, 2 F, CF_2), –80.6 (t, *J* = 9.6 Hz, 3 F, CF_3).

HRMS (ESI-TOF): *m/z* calcd for $C_{11}H_9F_9NO_3S$ [M + H]$^+$: 406.0154; found: 406.0203.

Anal. Calcd for $C_{11}H_8F_9NO_3S$ (405.2): C, 32.60; H, 1.99; N, 3.46; S, 7.91. Found: C, 32.64; H, 1.93; N, 3.50; S, 8.21.

2-Ethyl-6-methylpyridin-4-yl Nonaflate (16f)

According to general procedure 3, β-ketoenamide **14f** (155 mg, 1.00 mmol) was treated with DIPEA (0.68 mL, 4.00 mmol) and TMSOTf (0.91 mL, 5.02 mmol) in DCE (25 mL) using a sealed tube, followed by nonaflation of the crude product using NaH (300 mg, 7.50 mmol) and NfF (0.54 mL, 3.00 mmol) in THF (15 mL). Workup was performed with sat. aq NH_4Cl solution (20 mL) and CH_2Cl_2 (3 × 20 mL). The obtained crude product was purified by flash column chromatography on silica gel (hexanes–EtOAc = 30:1) to provide pyridyl nonaflate **16f** (217 mg, 52%) as a pale yellow oil.

IR (ATR): 2975, 2940–2885 (C–H), 1600–1575 (C=C, N=C), 1430, 1350, 1235–1200, 1140–1120 cm^{-1}. Due to their weak intensity an unambiguous assignment of the =C–H signals was not possible.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.30 (t, *J* = 7.6 Hz, 3 H, CH_2CH_3), 2.58 (s, 3 H, CH_3), 2.84 (q, *J* = 7.6 Hz, 2 H, CH_2), 6.89, 6.90 (2 d, $J_{AB} \approx$ 1.9 Hz, 1 H each, 3-H, 5-H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 13.6 (q, CH_2CH_3), 24.7 (q, CH_3), 31.5 (t, CH_2), 111.2 (d, C-3), 112.6 (d, C-5), 157.1 (s, C-6), 161.2 (s, C-2), 166.6 (s, C-4).

^{19}F NMR ($CDCl_3$, 376 MHz): δ = –125.7, –120.8 (2 m_c, 2 F each, CF_2), –108.7 (t, *J* = 13.9 Hz, 2 F, CF_2), –80.6 (t, *J* = 9.6 Hz, 3 F, CF_3).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{12}H_{11}F_9NO_3S$ [M + H]$^+$: 420.0310; found: 420.0323.

Anal. Calcd for $C_{12}H_{10}F_9NO_3S$ (419.3): C, 34.38; H, 2.40; N, 3.34; S, 7.65. Found: C, 34.46; H, 2.25; N, 3.29; S, 7.64.

2-Methyl-6-(2-phenylethyl)pyridin-4-yl Nonaflate (16g)

According to general procedure 3, β-ketoenamide **14g** (231 mg, 1.00 mmol) was treated with DIPEA (0.68 mL, 4.00 mmol) and TMSOTf (0.91 mL, 5.02 mmol) in DCE (25 mL) using a sealed tube, followed by nonaflation of the crude product using NaH (300 mg, 7.50 mmol) and NfF (0.54 mL, 3.00 mmol) in THF (15 mL). Workup was performed with sat. aq NH_4Cl solution (20 mL) and CH_2Cl_2 (3 × 20 mL). The obtained crude product was purified by flash column chromatography on silica gel (hexanes–EtOAc = 30:1) to provide pyridyl nonaflate **16g** (374 mg, 76%) as a pale yellow oil.

IR (ATR): 3085–3030 (=C–H), 2965–2865 (C–H), 1600–1580 (C=C, C=N), 1425, 1240–1200, 1140 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.61 (s, 3 H, CH_3), 3.05, 3.10 (2 m_c, 2 H each, CH_2CH_2), 6.78 (d, *J* = 1.9 Hz, 1 H, 5-H), 6.91 (d, *J* = 1.9 Hz, 1 H, 3-H), 7.16–7.20, 7.25–7.28 (2 m, 3 H, 2 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 24.7 (q, CH_3), 35.6, 40.1 (2 t, CH_2CH_2), 112.2 (d, C-5), 112.8 (d, C-3), 126.2, 128.3, 128.4, 140.7 (3 d, s, C_6H_5), 156.9 (s, C-4), 161.4 (s, C-2), 164.2 (s, C-6).

^{19}F NMR ($CDCl_3$, 471 MHz): δ = –125.7, –120.7 (2 m_c, 2 F each, CF_2), –108.6 (t, *J* = 13.6 Hz, 2 F, CF_2), –80.5 (t, *J* = 9.6 Hz, 3 F, CF_3).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{18}H_{15}F_9NO_3S$ [M + H]$^+$: 496.0631; found: 496.0616.

Anal. Calcd for $C_{18}H_{14}F_9NO_3S$ (495.4): C, 43.64; H, 2.85; N, 2.83; S, 6.47. Found: C, 43.73; H, 2.64; N, 2.72; S, 6.23.

2-(Methoxymethyl)-6-methylpyridin-4-yl Nonaflate (16h) and 3-Methoxy-4,6-dimethylpyridin-2-yl Nonaflate (17h)

According to general procedure 3, β-ketoenamide **14h** (171 mg, 1.00 mmol) was treated with DIPEA (0.68 mL, 4.00 mmol) and TMSOTf (0.91 mL, 5.02 mmol) in DCE (25 mL) using a sealed tube, followed by nonaflation of the crude product using NaH (300 mg, 7.50 mmol) and NfF (0.54 mL, 3.00 mmol) in THF (15 mL). Workup was performed with sat. aq NH_4Cl solution (20 mL) and CH_2Cl_2 (3 × 25 mL). The obtained crude product was purified by flash column chromatography on silica gel (hexanes–EtOAc = 20:1 → 10:1) to provide pyridyl nonaflates **17h** (28 mg, 6%) and **16h** (51 mg, 12%) as brownish oils.

16h

IR (ATR): 3085 (=C–H), 2990–2825 (C–H), 1620–1585 (C=C), 1430, 1235–1200, 1140–1120 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.60 (s, 3 H, CH_3), 3.49 (s, 3 H, OCH_3), 4.58 (s, 2 H, OCH_2), 6.98 (d, *J* = 1.9 Hz, 1 H, 3-H), 7.20 (d, *J* = 1.9 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 24.5 (q, CH_3), 58.9 (q, OCH_3), 74.7 (t, OCH_2), 110.4 (d, C-5), 113.9 (d, C-3), 157.5 (s, C-2), 161.3 (s, C-6), 161.9 (s, C-4).

^{19}F NMR ($CDCl_3$, 471 MHz): δ = –125.7, –120.7 (2 m_c, 2 F each, CF_2), –108.6 (t, *J* = 13.7 Hz, 2 F, CF_2), –80.5 (t, *J* = 9.6 Hz, 3 F, CF_3).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{12}H_{11}F_9NO_4S$ [M + H]$^+$: 436.0267; found: 436.0265.

Anal. Calcd for $C_{12}H_{10}F_9NO_4S$ (435.3): C, 33.11; H, 2.32; N, 3.22; S, 7.37. Found: C, 33.09; H, 2.16; N, 3.29; S, 7.24.

17h

IR (ATR): 3010 (=C–H), 2940–2845 (C–H), 1615 (C=N, C=C), 1485, 1415, 1320, 1235–1195, 1145 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.33 (s, 3 H, 4-CH_3), 2.43 (s, 3 H, 6-CH_3), 3.84 (s, 3 H, OCH_3), 7.02 (s, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 15.7 (q, 4-CH_3), 23.1 (q, 6-CH_3), 61.2 (q, OCH_3), 126.6 (d, C-5), 142.9 (s, C-3), 144.9 (s, C-4), 148.1 (s, C-2), 151.8 (s, C-6).

^{19}F NMR ($CDCl_3$, 471 MHz): δ = –125.7, –120.8 (2 m_c, 2 F each, CF_2), –109.1 (t, *J* = 13.7 Hz, 2 F, CF_2), –80.5 (t, *J* = 9.7 Hz, 3 F, CF_3).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{12}H_{10}F_9NNaO_4S$ [M + Na]$^+$: 458.0085; found: 458.0075.

Pd-Catalyzed Coupling of Pyridyl Nonaflates with Boronic Acids; General Procedure 5

DMF (~5 mL/mmol) was purged with argon for 30 min. The solvent was then transferred to a Schlenk-tube that was charged with the pyridyl nonaflate (1 equiv), $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (1 equiv) and the boronic acid (1.1 equiv) under an atmosphere of argon. The mixture was stirred at 80 °C for the indicated time. After cooling to r.t., the mixture was diluted with EtOAc and washed with an equal volume of a mixture of H_2O and brine (1:1, 3 ×). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The obtained crude product was purified by flash column chromatography.

2-Benzyl-6-methyl-4-phenylpyridine (18)

According to general procedure 5, pyridyl nonaflate **16c** (350 mg, 0.73 mmol) was treated with phenylboronic acid (97 mg, 0.80 mmol), $Pd(PPh_3)_4$ (40 mg, 0.04 mmol), and K_2CO_3 (100 mg, 0.73 mmol) in DMF (3.5 mL) for 4 h. Workup was performed with EtOAc (40 mL) and H_2O–brine (1:1, 3 × 40 mL). The obtained crude product was purified by flash column chromatography on silica gel (hexanes–EtOAc = 10:1) to provide pyridine **18** (183 mg, 97%) as a yellow oil.

IR (ATR): 3055–3025 (=C–H), 2920–2845 (C–H), 1600–1550 (C=C, C=N), 1495–1450, 1400, 1075 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.63 (s, 3 H, CH_3), 4.21 (s, 2 H, CH_2), 7.10, 7.21 (2 d, *J* = 1.1 Hz, 1 H each, 3-H, 5-H), 7.22–7.24, 7.31–7.32, 7.39–7.45, 7.54–7.55 (4 m, 1 H, 4 H, 3 H, 2 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 24.6 (q, CH_3), 44.8 (t, CH_2), 118.2 (d, C-3), 118.9 (d, C-5), 126.3, 127.0, 128.5, 128.7, 128.9, 129.1, 138.7, 139.6 (6 d, 2 s, C_6H_5), 149.2 (s, C-4), 158.3 (s, C-6), 160.9 (s, C-2).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{19}H_{18}N$ [M + H]$^+$: 260.1441; found: 260.1451.

4-(4,6-Diethyl-3-phenylpyridin-2-yl)benzonitrile (19)

According to the general procedure 5, pyridyl nonaflate **17d** (272 mg, 0.53 mmol) was treated with 4-cyanophenylboronic acid (86 mg, 0.59 mmol), $Pd(PPh_3)_4$ (31 mg, 0.03 mmol), and K_2CO_3 (74 mg, 0.54 mmol) in DMF (3 mL) for 6 h. Workup was performed with EtOAc (40 mL) and H_2O–brine (1:1, 3 × 40 mL). The obtained crude product was purified by flash column chromatography on silica gel (hexanes–EtOAc = 10:1) to provide pyridine **19** (156 mg, 94%) as a colorless solid; mp 90–92 °C.

IR (ATR): 3060, 3030 (=C–H), 2970, 2935, 2875 (C–H), 2230 (C≡N), 1605, 1590, 1545 (C=C, C=N), 1465, 1440, 1385 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.09, 1.39 (2 t, *J* = 7.6 Hz, 3 H each, CH_2CH_3), 2.49, 2.90 (2 q, *J* = 7.6 Hz, 2 H each, CH_2CH_3), 7.02–7.06 (m, 2 H, C_6H_5), 7.17 (s, 1 H, 5'-H), 7.26–7.29 (m, 3 H, C_6H_5), 7.33–7.36, 7.41–7.44 (2 m, 2 H each, 2-H, 3-H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.0 (q, 6′-CH_2CH_3), 14.5 (q, 4′-CH_2CH_3), 26.2 (t, 4′-CH_2), 31.2 (t, 6′-CH_2), 110.6 (s, C-1), 119.0 (s, CN), 121.1 (d, C-5′), 127.3, 128.3 (2 d, C_6H_5), 130.3, 130.5, 131.3 (3 d, C_6H_5, C-2, C-3), 133.2 (s, C_6H_5), 137.5 (s, C-3′), 145.8 (s, C-4), 152.6 (s, C-4′), 154.8 (s, C-2′), 162.5 (s, C-6′).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{22}H_{20}N_2Na$ $[M + Na]^+$: 335.1519; found: 335.1525.

Anal. Calcd for $C_{22}H_{20}N_2$ (312.4): C, 84.58; H, 6.45; N, 8.97. Found: C, 84.67; H, 6.47; N, 8.90.

Acknowledgment

Generous support of this work by the Deutsche Forschungsgemeinschaft (GK 1582 and RE 514/14) and Bayer HealthCare is most gratefully acknowledged.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are experimental procedures for the synthesis of compounds **14a**–**d** and **14f**–**h** as well as copies of ^{1}H and ^{13}C NMR spectra for all new compounds.

References

(1) (a) Kleemann, A.; Engel, J.; Kutscher, B. *Pharmaceutical Substances*; Thieme: Stuttgart, **2000**, 4th ed. (b) McAteer, C. H.; Balasubramanian, M.; Murugan, R. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; Elsevier: Oxford, **2008**, 309.

(2) (a) Spitzner, D. In *Science of Synthesis*; Vol. 15; Black, D. S. C., Ed.; Thieme: Stuttgart, **2004**, 11. (b) Keller, P. A. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; Elsevier: Oxford, **2008**, 217.

(3) (a) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043. (b) Hill, M. D. *Chem. Eur. J.* **2010**, *16*, 12052.

(4) Eidamshaus, C.; Reissig, H.-U. *Eur. J. Org. Chem.* **2011**, 6056.

(5) (a) For a review, see: Lechel, T.; Reissig, H.-U. *Pure Appl. Chem.* **2010**, *82*, 1835. (b) Flögel, O.; Dash, J.; Brüdgam, I.; Hartl, H.; Reissig, H.-U. *Chem. Eur. J.* **2004**, *10*, 4283. (c) Dash, J.; Lechel, T.; Reissig, H.-U. *Org. Lett.* **2007**, *9*, 5541. (d) Lechel, T.; Dash, J.; Brüdgam, I.; Reissig, H.-U. *Eur. J. Org. Chem.* **2008**, 3647. (e) Eidamshaus, C.; Reissig, H.-U. *Adv. Synth. Catal.* **2009**, *351*, 1162. (f) Lechel, T.; Dash, J.; Hommes, P.; Lentz, D.; Reissig, H.-U. *J. Org. Chem.* **2010**, *75*, 726. (g) Lechel, T.; Dash, J.; Eidamshaus, C.; Brüdgam, I.; Lentz, D.; Reissig, H.-U. *Org. Biomol. Chem.* **2010**, *8*, 3007. (h) Bera, M. K.; Reissig, H.-U. *Synthesis* **2010**, 2129. (i) Eidamshaus, C.; Kumar, R.; Bera, M. K.; Reissig, H.-U. *Beilstein J. Org. Chem.* **2011**, *7*, 962. (j) Lechel, T.; Gerhard, M.; Trawny, D.; Brusilowskij, B.; Schefzig, L.; Zimmer, R.; Rabe, J. P.; Lentz, D.; Schalley, C. A.; Reissig, H.-U. *Chem. Eur. J.* **2011**, *17*, 7480.

(6) Dash, J.; Reissig, H.-U. *Chem. Eur. J.* **2009**, *15*, 6811.

(7) Acylation of the Blaise intermediate: (a) Chun, Y. S.; Lee, K. K.; Ko, Y. O.; Shin, H.; Lee, S.-g. *Chem. Commun.* **2008**, 5098. (b) Kim, J. H.; Chun, Y. S.; Shin, H.; Lee, S.-g. *Synthesis* **2012**, *44*, 1809. For reactions of the Blaise intermediate with propiolates leading to pyrid-2-ones, see: (c) Chun, Y. S.; Ryu, K. Y.; Ko, Y. O.; Hong, J. Y.; Hong, J.; Shin, H.; Lee, S.-g. *J. Org. Chem.* **2009**, *74*, 7556. For reactions with isocyanates leading to pyrimidin-2,4-diones, see: (d) Chun, Y. S.; Xuan, Z.; Kim, J. H.; Lee, S.-g. *Org. Lett.* **2013**, *15*, 3162.

(8) Hommes, P.; Jungk, P.; Reissig, H.-U. *Synlett* **2011**, 2311.

(9) For a review summarizing the advantages of alkenyl and aryl nonaflates in transition-metal-catalyzed reactions, see: Högermeier, J.; Reissig, H.-U. *Adv. Synth. Catal.* **2009**, *351*, 2747.

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

(11) For recent examples utilizing pyrid-4-yl nonaflates, see: (a) Bera, M. K.; Hommes, P.; Reissig, H.-U. *Chem. Eur. J.* **2011**, *17*, 11838. (b) Eidamshaus, C.; Hommes, P.; Reissig, H.-U. *Synlett* **2012**, *23*, 1670. (c) Gholap, S. L.; Hommes, P.; Neuthe, K.; Reissig, H.-U. *Org. Lett.* **2013**, *15*, 318. (d) Bera, M. K.; Gholap, S. L.; Hommes, P.; Neuthe, K.; Trawny, D.; Rabe, J. P.; Lentz, D.; Zimmer, R.; Reissig, H.-U. *Adv. Synth. Catal.* **2013**, *355*, in press; DOI 10.1002/adsc.201306613.

(12) (a) Gewald, K.; Rehwald, M.; Müller, H.; Bellmann, P. *Liebigs Ann. Chem.* **1995**, 787. (b) Fisyuk, A. S.; Bogza, Y. P.; Poendaev, N. V.; Goncharov, D. S. *Chem. Heterocycl. Compd.* **2010**, *46*, 844; and references cited therein.

(13) An analogous reaction leading to 2-quinolones are known for structurally related *o*-acyl(aminoacyl)benzenes: (a) Blackburn, T. P.; Cox, B.; Guildford, A. J.; Le Count, D. J.; Middlemiss, D. N.; Pearce, R. J.; Thornber, C. W. *J. Med. Chem.* **1987**, *30*, 2252. (b) Mochalov, S. S.; Chasanov, M. I. *Chem. Heterocycl. Compd.* **2008**, *44*, 628. (c) Mochalov, S. S.; Chasanov, M. I.; Fedotov, A. N.; Zefirov, N. S. *Chem. Heterocycl. Compd.* **2011**, *47*, 1105.

(14) (a) Camps, R. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3228. (b) Camps, R. *Arch. Pharm. (Weinheim, Ger.)* **1899**, *237*, 659. (c) Camps, R. *Arch. Pharm. (Weinheim, Ger.)* **1901**, *239*, 591. (d) Pflum, D. A. In *Name Reactions in Heterocyclic Chemistry*; Li, J. J.; Corey, E. J., Eds.; Wiley-Interscience: Hoboken, **2005**. (e) Jones, C. P.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 7968.

(15) Eidamshaus, C.; Triemer, T.; Reissig, H.-U. *Synthesis* **2011**, 3261.

(16) Goncharov, D. S.; Kostuchenko, A. S.; Fisyuk, A. S. *Chem. Heterocycl. Compd.* **2009**, *45*, 793.

(17) Fisyuk, A. S.; Poendaev, N. V.; Bundel, Y. G. *Mendeleev Commun.* **1998**, *8*, 12.

(18) Due to their high polarity, separation of the pyridones from the salt of trifluoromethanesulfonic acid and DIPEA formed after aqueous workup is very tedious and requires multiple runs of chromatography.

(19) Repeated experiments to cyclize **14c** and subsequent nonaflation resulted in slightly varying ratios of **16c** and **17c**.

(20) Toullec, J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, **1990**, 323.

(21) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83. (c) Suzuki, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i.; de Meijere, A., Eds.; Wiley: New York, **2002**, 249.

(22) Sugiura, M.; Kumahara, M.; Nakajima, M. *Chem. Commun.* **2009**, 3585.

(23) Gao, Y.; Zhang, Q.; Xu, J. *Synth. Commun.* **2004**, *34*, 909.

(24) Guin, J.; Mueck-Lichtenfeld, C.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2007**, *129*, 4498.

