A three-component synthesis of β-alkoxy-β-keto-enamides—flexible precursors for 4-hydroxypyridine derivatives and their palladium-catalysed reactions†

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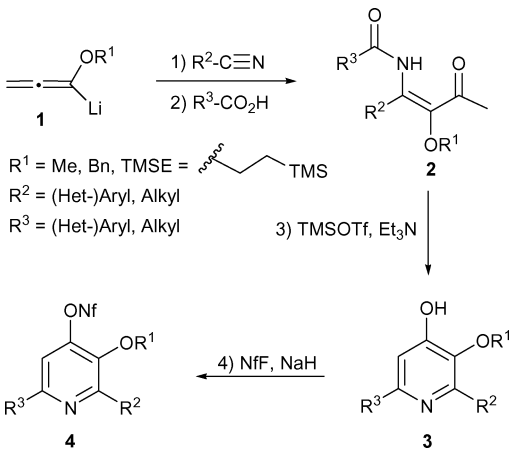
The flexible three-component reaction of lithiated alkoxyallenes with nitriles and carboxylic acids provided a series of highly functionalised β-alkoxy-β-ketoenamide derivatives. Upon base induced cyclisation and conversion to 4-pyridyl nonaflates various palladium-catalysed coupling reactions could be employed. The efficacy of this approach to functionalised pyridine derivatives was demonstrated by a fairly short route to a key intermediate suitable for a Glenvastatin synthesis. After Sonogashira couplings of alkynes with 4-pyridyl nonaflates subsequent cyclisations led to highly fluorescent [2,3*c*]furopyridine derivatives, whereas Suzuki reactions afforded 4-pyridyl stilbenes and by photocyclisation a highly substituted benzoisoquinoline derivative.

Introduction

Lithiated alkoxyallenes **1** have proved to be remarkably versatile C3-building blocks in the synthesis of a broad range of heterocycles.[1] The addition of **1** to nitriles, followed by quenching with carboxylic acids led to a novel three-component reaction which provides highly substituted β-alkoxy-β-ketoenamides **2** (Scheme 1). The mechanism of this reaction has been previously described in more detail.[2] The enamide moieties can be found as substructures in natural products[3] and they have been used for the asymmetric synthesis of amides and amino acids.[3,4] In particular, the specifically substituted β-alkoxy-β-ketoenamides **2** were found to be ideal precursors for the cyclisation to heteroaromatic compounds such as pyrimidines,[5a,5b] oxazoles,[5c] or 4-hydroxypyridine derivatives like **3**.[2] In addition, we reported on the high utility of nonafluorobutanesulfonyl fluoride (NfF)[6,7] for the conversion of 4-hydroxypyridines into 4-pyridyl nonaflates **4** and their subsequent application in diverse palladium-catalysed coupling reactions.[2,3]

Owing to their incontestable importance in material science, and their diverse applications such as agrochemicals and pharmaceuticals,[8] we devoted considerable attention to the synthesis of highly substituted pyridine derivatives.[9,10] Recently, we described the scope of this intriguing three-component reaction for the synthesis of perfluorinated pyridines *via* the corresponding carboxylic acids in full detail.[2g] In this article we want to disclose the scope and limitation of the synthesis of the crucial β-alkoxy-β-ketoenamide intermediates using different alkoxyallenes, a broad range of mono carboxylic acids and of nitriles. Moreover, their subsequent transformation into 4-pyridyl nonaflates and further conversion to annulated pyridine derivatives *via* palladium-catalysed coupling reactions are presented.



Scheme 1 Approach to 4-pyridinyl nonaflates **4** *via* **3** by cyclisation of β-alkoxy-β-ketoenamides **2** starting from lithiated alkoxyallenes **1**.

Results and discussion

Synthesis of β-alkoxy-β-ketoenamides

In general, enamides **2a–q** were prepared by following the reported procedure[2] using 2.7 equivalents of lithiated alkoxyallene **1**, which is generated *in situ* by deprotonation of the alkoxyallene with *n*-butyllithium, 1.0 equivalent of the corresponding nitrile and an excess of the carboxylic acid (method A, Table 1). A slightly modified procedure (method B, Table 1) differs from method A in the stoichiometry of the reagents: lithiated alkoxyallene (1.0 equiv.) is the limiting component and the nitrile (1.5–3.0 equiv.)

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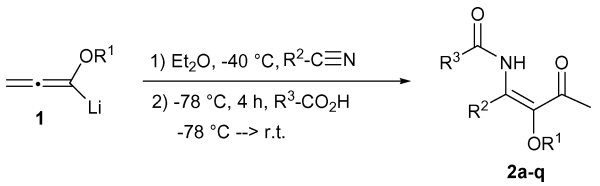
‡ Responsible for X-ray crystal structure analyses.

Table 1 Synthesis of β-alkoxy-β-ketoenamides **2** using method A or B



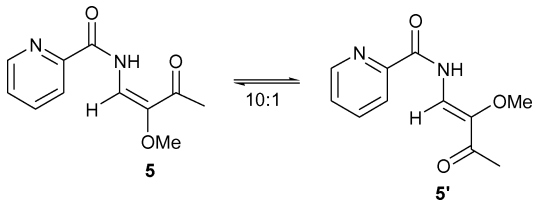
Entry	R^1	R^2	R^3	**2**, Yield (%), (method[a])
1	Me	Me	Ph[b]	**2a**, 13 (A)
2	Me	Me	2-Py[c]	**2b**, 22 (A)[d]
3	Me	CH_2OMe	2-Py[c]	**2c**, 33 (A)[e]
4	Me	*i*-Pr	Ph[b]	**2d**, 53 (B)
5	Me	*c*-Pr	*c*-Pr	**2e**, 79 (A)
6	Me	*t*-Bu	CH_2OPh	**2f**, 63 (A)
7	Me	*t*-Bu	Ph	**2g**, 76 (A)
8	Me	*t*-Bu	C≡CH	**2h**, 72 (B)
9	Me	Ph	Ph[b]	**2i**, 45 (B)
10	Me	Ph	2-Thienyl[b]	**2j**, 43 (A)
11	Me	2-Thienyl	Me	**2k**, 72 (A)
12	Me	2-Thienyl	CH_2OMe	**2l**, 47 (A)
13	Bn	*c*-Pr	*c*-Pr	**2m**, 56 (A)
14	Bn	Ph	Ph[b]	**2n**, 54 (A)
15	Bn	Ph	2-Py[c]	**2o**, 27 (B)
16	Bn	2-Thienyl	2-Thienyl[b]	**2p**, 32 (B)
17	TMSE	2-Thienyl	Ph[b]	**2q**, 71 (A)

[a] Method A: 2.7 equiv. lithiated alkoxyallene, 1.0 equiv. nitrile, 5.4 equiv. carboxylic acid; method B: 1.0 equiv. lithiated alkoxyallene, 1.5–3.0 equiv. nitrile, 6.0 equiv. carboxylic acid. [b] Dissolved in Et_2O or THF. [c] Dissolved in DMF. [d] 5% of enamide **5** (R^2 = H) was isolated. [e] 10% of enamide **5** (R^2 = H) was isolated.

and the carboxylic acid (*ca.* 5.0 equiv.) are used in excess. Table 1 reveals that poor to good yields (13–79%) were obtained. Aliphatic, aromatic and heteroaromatic substituents could successfully be introduced into the desired enamides **2**. Functional groups such as ether or alkynyl units were tolerated without problems (Table 1, entries 3, 8, 12). The synthesis of enamides **2** is not restricted to methoxyallene as precursor. Benzyloxyallene or (2-trimethylsilyl)ethoxyallene are also feasible, which allow subsequent reactions under modified conditions.

In the case of solid (hetero)aromatic carboxylic acids, these precursors were dissolved in suitable solvents *prior* addition to the reaction mixture at −78 °C. Whereas benzoic acid and thiophene carboxylic acid are soluble in diethyl ether or THF, picolinic acid has to be dissolved in DMF. A partial precipitation could not be avoided, which might be the reason for lower yields in these cases (Table 1, entries 2, 3, 15) demonstrating a limitation of the current protocol. The relatively high α-acidity of the corresponding nitriles employed in entries 1–3 might also lead to an additional decrease of efficacy due to side-product formation.[2g] Thus, we obtained the best yields with aliphatic carboxylic acids such as cyclopropyl carboxylic acid, propiolic or acetic acid and nitriles without acidic α-protons (entries 5, 8, 11).

The reactions of α-acidic nitriles with picolinic acid dissolved in DMF (entries 2, 3) afforded an unexpected side product in 5% and 10% yield, which could be identified as enamide **5**. Upon storage **5** provided a 10 : 1 mixture with its stereoisomer **5′** (Scheme 2). This behaviour was only observed for **5**/**5′**, whereas for other enamides **2** substituents R^2 = aryl or alkyl apparently strongly stabilise the *E*-configuration.



Scheme 2 Equilibrium of enamide **5** with **5′**.

Constitution and *E*-configuration of enamide **5** were unambiguously proved by NOESY-spectra and an X-ray crystal structure analysis (Fig. 1). Currently, no definite explanation for the formation of **5** can be offered. Formally, hydrogen cyanide has served as electrophile, which seems fairly unlikely. A control experiment with lithiated methoxyallene, DMF and picolinic acid did not give defined products.

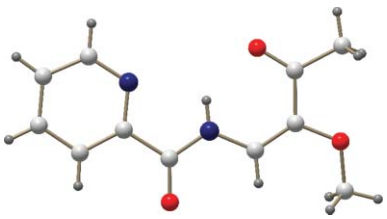
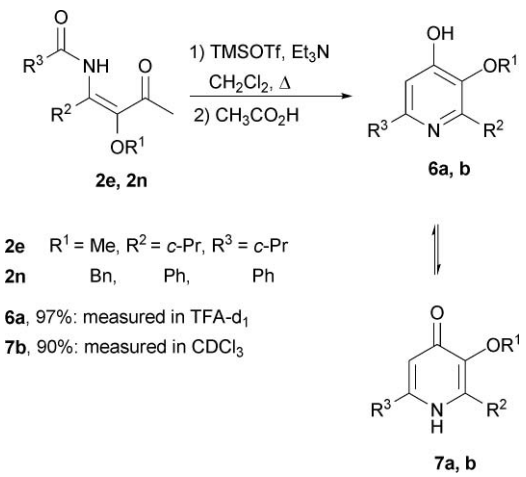


Fig. 1 X-Ray crystal structure of enamide **5**.[11]

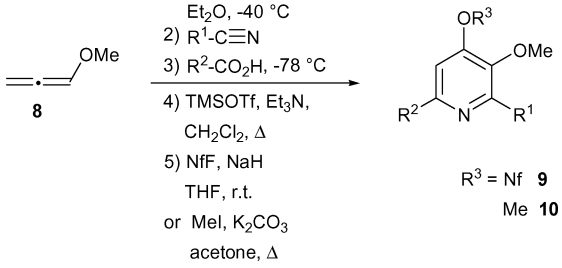
Cyclisation to 4-hydroxypyridine derivatives

Enamides **2e** and **2n** have been cyclised under standard conditions[2] employing an excess of trimethylsilyltrifluoromethane sulfonate in the presence of triethylamine. After acidic workup the desired pyridine derivatives **6a** and **7b** were obtained in very good yields (90–97%) (Scheme 3). The NMR spectra recorded in $CDCl_3$ show the corresponding 4-hydroxypyridines **6**, which are generally in equilibrium with their tautomeric pyridinones **7**. The ratio of tautomers strongly depends on the substitution pattern at C-2 and C-6. In the case of R^2 = R^3 = Ph only pyridinone **7b** was observed. In polar protic solvents such as TFA-d_1 or CD_3OD the NMR spectra show only one set of signals that has been assigned



Scheme 3 Cyclisation of enamides **2e** and **2n** to pyridine derivatives **6a**, **6b** and **7a**, **7b**.

Table 2 Three-step/one-pot procedure to 4-pyridyl nonaflates **9** and 4-methoxypyridines **10**



Entry	R^1	R^2	**9** or **10**, Yield (%)[a]
1	*i*-Pr	Ph	**9a**, 52[b]
2	*c*-Pr	*c*-Pr	**9b**, 42
3	*t*-Bu	Me	**9c**, 57
4	*t*-Bu	Ph	**9d**, 38
5	*t*-Bu	C≡C-TMS[c]	**9e**, 22
6	Ph	2-Py	**9f**, 55
7	Ph	2-Thienyl	**9g**, 23
8	Me	2-Py	**10a**, 53[b]
9	2-Thienyl	Me	**10b**, 58[b]

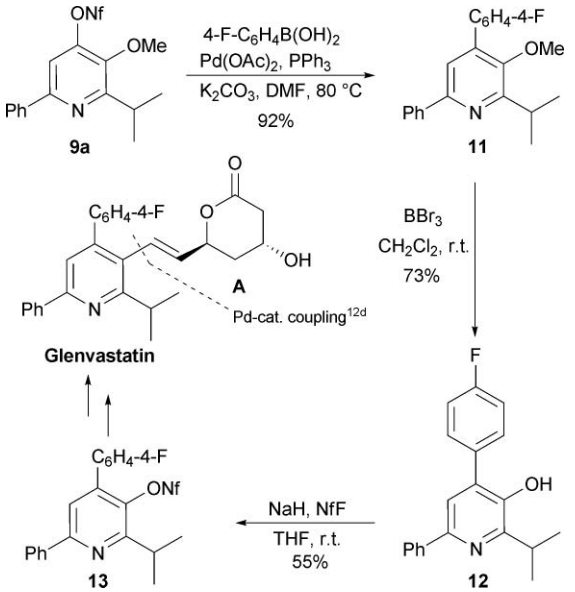
[a] Overall yields for three steps. [b] Overall yield for two steps starting from the corresponding enamide **2**. [c] Starting material propiolic acid.

to the 4-hydroxypyridine structure **6** (*e.g.* compound **6a** with $R^2 = R^3 = c$-Pr, measured in TFA-d_1).

Owing to the problematic purification and characterisation of 4-hydroxypyridines at this stage, we developed a three-step/one-pot procedure starting from methoxyallene **8** (Table 2). After lithiated methoxyallene was subjected to the standard conditions, the crude enamides were cyclised without purification and the resulting pyridine derivatives were either directly converted into 4-pyridyl nonaflates **9** or into *O*-methylated compounds **10**. The yields mainly depend on the first step (enamide formation, see above) and vary between 22% and 57% (entries 1–7) after three steps. Since an excess of trimethylsilyltrifluoromethane sulfonate has been used the alkynyl-substituted derivative **9e** was exclusively obtained as TMS-protected compound (entry 5). Although the procedures have not been optimised in these cases, and therefore several transformations occur only in fairly moderate overall yields, the simplicity and flexibility of this synthesis of highly functionalised pyridine derivatives compensates for these disadvantages. There is certainly room for improvement in individual experiments.

Access to a Glenvastatin building block

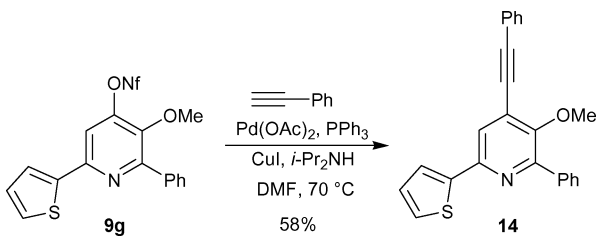
Pyridyl nonaflates have already been proven as useful precursors in palladium-catalysed reactions.[2] In this report, nonaflate **9a** has been employed as starting material for a rapid access to Glenvastatin building block **13**[12a] using standard Suzuki conditions (Scheme 4). Coupling of **9a** with *p*-fluorophenylboronic acid to intermediate **11** was achieved in 92% yield. Cleavage of the methyl ether moiety with BBr_3 led to 3-hydroxypyridine derivative **12** which could easily be transformed into 3-pyridyl nonaflate **13**. The overall yield after six steps starting from methoxyallene **8** is 19%. For a completion of the synthesis of the potent HMG-CoA inhibitor Glenvastatin **13** has to be coupled to literature known[12b–d] lactone **A** building blocks.



Scheme 4 Approach to Glenvastatin building block **13** starting from **9a**.

Cyclisation of 4-hydroxypyridines to furo[2,3*c*]pyridines and investigation of their photophysical properties

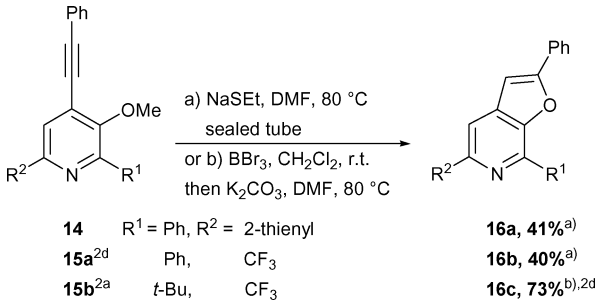
Smooth coupling reactions of pyridyl nonaflates with alkynes proceeded under Sonogashira conditions. In contrast to earlier results with similar 4-pyridyl nonaflates,[2d] the coupling of **9g** with phenylacetylene gave a relatively low yield of 58%, even under optimised conditions (Scheme 5). Possibly, the 6-thienylpyridine moiety is a competing ligand for the palladium making the desired coupling less efficient in this specific case.



Scheme 5 Sonogashira coupling of **9g** with phenylacetylene to **14**.

The previously developed cyclisation[2d] of compounds such as **14** and **15a–b** to furo[2,3*c*]pyridines[13] **16a–c** as depicted in Scheme 6 occurred after cleavage of the methoxy group with either sodium ethanethiolate (method a) or BBr_3 (method b). In the case of method a the furan ring was immediately generated after cleavage, whereas in method b a base had to be added to achieve ring closure.[14] In most cases method a was only applied when method b did not succeed in complete deprotection. Method b generally gives higher yields than method a.

Furopyridines such as **16** have interesting photophysical properties[2d] that might be attractive for material science *e.g.* organic electronics and optoelectronic devices.[15] Due to their similar substitution pattern, compounds **16a–c** were suitable candidates to start a systematic investigation. In Fig. 2 the absorption and emission data of compounds **16a–c** have been displayed. While



Scheme 6 Cyclisation to furo[2,3*c*]pyridines **16a–c**.

the maxima of absorption are all in the same range of 290–310 nm, the Stokes shifts increase parallel to the extension of the corresponding π-system. The largest value was determined for **16a** with a maximum of emission at 410 nm and a Stokes shift of 110 nm. Investigation of other derivatives is required for understanding these effects.

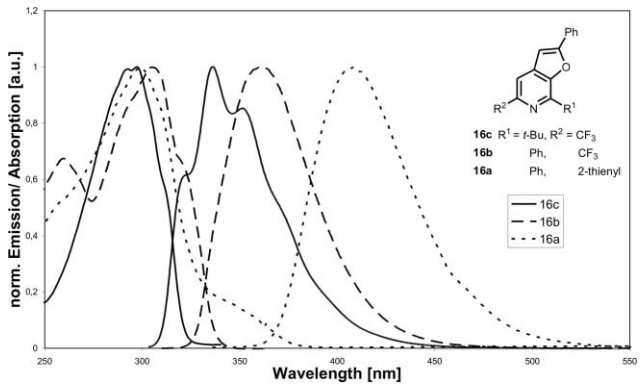
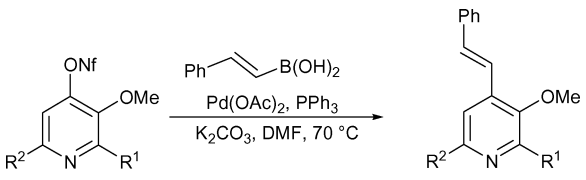


Fig. 2 UV and fluorescence spectra of furo[2,3*c*]pyridine derivatives **16a–c**.

Photocyclisation of pyridyl styrenes to benzoisoquinoline derivatives

The photocyclisation of stilbenes leading to phenanthrenes is a common reaction. However, there are limited literature reports on their aza analogues[16] and particularly the photocyclisation of pyridyl styrenes are less explored. The Suzuki coupling reactions of nonaflates **9c** and **9f** with *trans*-2-styryl boronic acid was carried out using optimised conditions to afford 92% of 4-pyridyl styrene derivative **17a** and 89% of **17b**, respectively (Scheme 7). Constitution and configuration of compound **17a** were confirmed by an X-ray crystal structure analysis (Fig. 3).



Scheme 7 Suzuki couplings of nonaflates **9c** and **9f** with *trans*-2-styryl boronic acid to 4-pyridyl stilbene derivatives **17a–b**.

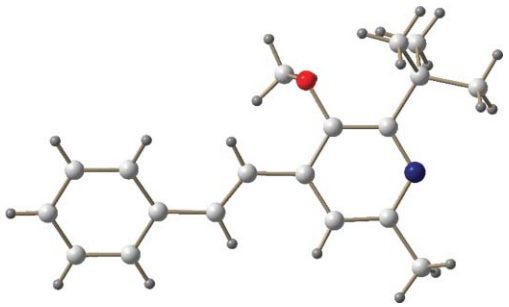
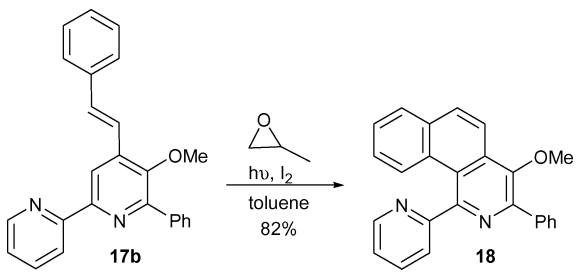


Fig. 3 X-Ray crystal structure of 4-pyridyl stilbene derivative **17a**.[11]

The photoirradiation of 4-styryl pyridine derivative **17b** in the presence of I_2 and an excess of propylene oxide[16b] in toluene as solvent using a 150 W medium pressure lamp (λ = 254 nm) furnished benzoisoquinoline **18** in good yield of 82% (Scheme 8) demonstrating the synthetic potential of 4-pyridyl nonaflates such as **9f** for further elaboration to more complex heterocyclic compounds.



Scheme 8 Photocyclisation of 4-pyridyl styrene derivative **17b** to benzoisoquinoline **18**.

Conclusions

In conclusion, we demonstrated that the three-component reaction of lithiated alkoxyallenes with different nitriles and carboxylic acids constitutes a simple and very flexible synthesis of highly substituted β-alkoxy-β-ketoenamides **2**. These enamides have been proven to be suitable precursors for the preparation of 4-hydroxypyridine derivatives **6**. The corresponding nonaflates **9** derived thereof allow a variety of palladium-catalysed coupling reactions leading to specifically substituted pyridine derivatives. As an example a short and fairly efficient route to the pyridine core of Glenvastatin has been developed. Whereas Sonogashira reactions can be combined with a subsequent cyclisation to provide highly fluorescent furo[2,3*c*]pyridine derivatives **16**, an alternative reaction sequence *via* 4-pyridyl stilbenes **17** allows the preparation of other complex heterocycles such as benzoisoquinoline **18**. All these transformations impressively show the high versatility and synthetic value of alkoxyallene-based β-alkoxy-β-ketoenamides as crucial intermediates.

Experimental

General

Reactions were generally performed under argon in flame-dried flasks. Solvents and reagents were added by syringes. Solvents were

dried using standard procedures. Reagents were purchased and were used as received without further purification unless otherwise stated. Unless otherwise stated, products were purified by flash chromatography on silica gel (230–400 mesh, Merck or Fluka) or HPLC (Nucleosil 50-5). Unless otherwise stated, yields refer to analytical pure samples. NMR spectra were recorded on Bruker (AC 500) and JOEL (Eclipse 500 and ECX 400) instruments. Chemical shifts are reported relative to TMS (^{1}H: $\delta = 0.00$ ppm), $CDCl_3$ (^{1}H: $\delta = 7.25$ ppm, ^{13}C: $\delta = 77.0$ ppm) or CF_3CO_2D ($\delta = 11.50$ ppm, ^{13}C: $\delta = 116.6$ ppm). Integrals are in accordance with assignments; coupling constants are given in Hz. All ^{13}C NMR spectra are proton-decoupled. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), m_c (centered multiplet), dd (doublet of doublet), s_{br} (broad singlet). For detailed peak assignments 2D spectra were measured (COSY, HMBC and HMQC). IR spectra were measured with an FT-IRD spectrometer Nicolet 5 SXC. UV/Vis spectra were measured with a UV-Vis spectrophotometer Scinco S-3150 PDA. Fluorescence spectra were measured with a spectrofluorometer Jasco FP-6500. For both techniques a concentration of 10^{-6} M in degassed CH_3CN (1 cm cuvette) at 25 °C was used. MS and HRMS analyses were performed with Finnigan MAT 711 (EI, 80 eV, 8 kV), MAT CH7A (EI, 80 eV, 3 kV), CH5DF (FAB, 3 kV), Varian Ionspec QFT-7 (ESI-FT ICRMS) and Agilent 6210 (ESI-TOF) instruments. Elemental analyses were carried out with Perkin Elmer CHN-Analyzer 2400 and Vario EL Elemental Analyzer. Melting points were measured with a Reichert apparatus Thermovar and are uncorrected. Single-crystal X-ray data were collected on a Bruker-XPS diffractometer (CCD area detector, Mo-Kα radiation, $l = 0.71073$ Å, graphite monochromator), empirical absorption correction using symmetry-equivalent reflections (SADABS), structure solution and refinement by SHELXS-97 and SHELXL-97 in the WINGX System.[17] The hydrogen atoms were located by difference Fourier syntheses. The pyridine derivatives **15a**[2d] and **15b**[2b] were prepared using our previously reported procedure.

Representative experimental procedures

Preparation of (*E*)-*N*-(1-cyclopropyl-2-methoxy-3-oxobut-1-enyl)cyclopropanecarboxamide (2e). Methoxyallene **8** (1.00 g, 14.3 mmol) was dissolved in diethyl ether (28 mL) and *n*-butyllithium (5.15 mL, 12.8 mmol, 2.5 M in hexanes) was added at –40 °C. After 25 min at –50 to –40 °C the solution was cooled to –78 °C and cyclopropylnitrile (0.35 mL, 4.77 mmol) was added. After stirring for 4 h at this temperature cyclopropane carboxylic acid (2.26 mL, 28.6 mmol) was added and the mixture was warmed up over night to room temperature. Then the reaction mixture was quenched with satd. aq. $NaHCO_3$ solution (25 mL) and extracted with diethyl ether (3 × 25 mL). The combined organic phases were dried with Na_2SO_4 and then evaporated. The residue was purified by chromatography on silica gel (hexane–ethyl acetate, 10 : 1) to afford 844 mg (79%) of **2e** as a colourless solid. Mp: 71 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 0.79$–0.85, 0.96–1.02 (2 m, 4 H, 4 H, *c*-Pr), 1.54 (m_c, 1 H, 1′-H), 2.14 (m_c, 1 H, 1″-H), 3.65 (s, 3 H, OMe), 11.76 (s_{br}, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): $\delta = 8.4$, 8.8, 11.6, 16.6, 27.1, 61.6, 140.3, 146.8, 172.7, 201.1 ppm. IR (KBr): $\nu = 3380$–3250 (N–H), 3095–2835 (C–H), 1700–1570 (C=O, C=C) cm^{-1}. Calcd. for $C_{12}H_{17}NO_3$ (223.3): C 64.55, H 7.67, N 6.27%; found: C 64.79, H 7.52, N 5.94%.

Preparation of 3-(benzyloxy)-2,6-diphenylpyridin-4(1*H*)-one (7b). Enamide **2n** (338 mg, 0.910 mmol) was dissolved in dichloromethane (5 mL) and treated at 0 °C with triethylamine (0.38 mL, 2.73 mmol) and trimethylsilyl triflate (0.53 mL, 2.73 mmol). The mixture was heated under reflux for 3 d and then quenched at room temperature with satd. aq. NH_4Cl solution (8 mL), extracted with dichloromethane (3 × 10 mL) and the combined organic phases were dried with Na_2SO_4 and evaporated to provide the crude product. The resulting crude product was dissolved again in dichloromethane (8 mL) and treated first with acetic acid (1 mL) and then with water (10 mL). It was extracted with dichloromethane (3 × 8 mL) and the combined organic extracts were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane–ethyl acetate, 4 : 1) to afford 289 mg (90%) of **7b** as a light yellow solid. Mp: 47–50 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 4.80$ (s, 2 H, CH_2Ph), 6.77 (s, 1 H, 5-H), 6.97–7.68, 8.08–8.10 (2 m, 15 H, Ph), 10.43 (s_{br}, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): $\delta = 73.3$, 113.2, 127.1, 128.1, 128.32, 128.34, 128.6, 129.0, 129.28, 129.35, 129.8, 130.2, 131.0, 132.9, 136.9, 142.5, 148.9, 170.3 ppm. IR (KBr): $\nu = 3250$ (N–H), 3060–2865 (=C–H, C–H), 1700–1570 (C=O, C=C) cm^{-1}. HRMS (ESI-TOF): calcd for $C_{24}H_{20}NO_2$ $[M+H]^+$: 534.0239; found: 534.0248.

Preparation of 2-*tert*-butyl-3-methoxy-6-methyl-4-pyridinyl nonaflate (9c). Methoxyallene **8** (1.65 mL, 19.8 mmol) was dissolved in diethyl ether (40 mL) and *n*-butyllithium (6.60 mL, 16.5 mmol, 2.5 M in hexanes), was added at –40 °C. After 25 min at –50 to –40 °C the solution was cooled to –78 °C and pivalonitrile (0.66 mL, 5.97 mmol) was added. After stirring for 4 h at this temperature acetic acid (2.23 mL, 39.0 mmol) was added and the mixture was warmed up over night to room temperature. The reaction mixture was then quenched with satd. aq. $NaHCO_3$ solution (40 mL) and extracted with diethyl ether (3 × 35 mL). The combined organic phases were dried with Na_2SO_4 and then evaporated. The residue was dissolved in dichloromethane (35 mL) and treated at 0 °C with triethylamine (2.51 mL, 17.9 mmol) and trimethylsilyl triflate (3.46 mL, 17.9 mmol). The mixture was heated under reflux for 3 d and then quenched at room temperature with satd. aq. NH_4Cl solution (40 mL), extracted with dichloromethane (3 × 35 mL), dried with Na_2SO_4 and evaporated to provide the crude product. The resulting crude product was dissolved in THF (35 mL) and NaH (1.44 g, 60% in mineral oil, 36.0 mmol) was added under an argon atmosphere. Nonafluorobutanesulfonyl fluoride (6.48 mL, 36.0 mmol) was added dropwise at room temperature. The mixture was stirred at room temperature over night and quenched by slow addition of methanol and water. It was extracted with ethyl acetate (3 × 35 mL), dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane–ethyl acetate, 40 : 1) to afford 1.62 g (57%) of **9c** as a light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.40$ (s, 9 H, *t*-Bu), 2.50 (s, 3 H, CH_3), 3.88 (s, 3 H, OMe), 6.92 (s, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): $\delta = 24.2$, 29.3, 38.5, 61.7, 114.1, 144.9, 149.8, 153.1, 163.8 ppm. IR (film): $\nu = 2960$–2930 (=C–H), 2870 (C–H), 1590 (C=C) cm^{-1}. MS (EI): m/z (%) = 477 (18) $[M]^+$, 462 (13),

194 (100), 69 (25). HRMS (EI): Calcd. for $C_{15}H_{16}F_9NO_4S$ $[M]^+$: 477.06564; found: 477.06638.

Preparation of 3,4-dimethoxy-6-methyl-2-thiophen-2-yl-pyridine (10b). Enamide **2k** (478 mg, 2.00 mmol) was dissolved in 1,2-dichloroethane (10 mL) followed by the addition of triethylamine (1.12 mL, 8.00 mmol) and trimethylsilyl triflate (1.82 mL, 10.0 mmol). The reaction mixture was heated under reflux for 3 d and then quenched with satd. aq. NH_4Cl solution (10 mL). After extraction with dichloromethane (3 × 10 mL) the combined organic phases were dried with Na_2SO_4 and evaporated. The crude product was dissolved in acetone (15 mL) and K_2CO_3 (405 mg, 3.00 mmol) and methyl iodide (0.25 mL, 4.00 mmol) were added under an argon atmosphere. The mixture was refluxed for 7 h, monitored by tlc, and diluted with water (15 mL). It was extracted with ethyl acetate (3 × 10 mL), dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane–ethyl acetate, 1 : 1) to afford 273 mg (58%) of **10b** as a brown solid. Mp 64–65 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.50 (s, 3 H, CH_3), 3.84 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 6.57 (s, 1 H, 5-H), 7.09 (dd, 1 H, J = 5.1, 3.7 Hz, 2′-H), 7.35 (dd, 1 H, J = 5.1, 1.2 Hz, 3′-H), 7.95 (dd, 1 H, J = 3.7, 1.2 Hz, 5′-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 24.8, 55.7, 60.0, 105.6, 127.53, 127.56, 127.59, 139.9, 141.2, 144.8, 154.7, 159.4 ppm. IR (KBr): ν = 3100–3070 (=C–H), 2950–2850 (C–H), 1570–1520 (C=C) cm^{-1}. MS (EI): m/z (%) = 235 (100) $[M]^+$, 220 (82), 83 (27). HRMS (EI): Calcd. for $C_{12}H_{13}NO_2S$ $[M]^+$: 235.06670; found: 235.06722.

Sonogashira coupling reaction of 9e to 3-methoxy-2-phenyl-4-(phenylethynyl)-6-(thiophen-2-yl)pyridine (14). A mixture of pyridyl nonaflate **9e** (350 mg, 0.991 mmol), $Pd(OAc)_2$ (11 mg, 0.050 mmol), PPh_3 (52 mg, 0.198 mmol), CuI (9.4 mg, 0.050 mmol), phenylacetylene (122 mg, 1.19 mmol) in DMF (4.6 mL) and diisopropylamine (2.3 mL) was heated to 70 °C for 3 h under an argon atmosphere. The mixture was allowed to cool to room temperature, diluted with brine (8 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel (hexane–ethyl acetate, 40 : 1) to afford 211 mg (58%) of **14** as a colourless solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.83 (s, 3 H, OMe), 7.11 (dd, 1 H, J = 5.0, 3.7 Hz, 4′-H), 7.38 (dd, 1 H, J = 5.0, 1.1 Hz, 3′-H), 7.39–7.51, 7.60–7.63, 8.08–8.12 (3 m, 6 H, 2 H, 2 H, Ph), 7.58 (dd, 1 H, J = 3.7, 1.1 Hz, 5′-H), 7.71 (s, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 61.0, 83.8, 97.5, 120.8, 122.3, 124.3, 126.7, 127.4, 128.0, 128.2, 128.5, 128.8, 129.2, 129.3, 131.8, 137.1, 144.3, 147.6, 151.1, 153.3 ppm. IR (KBr): ν = 3105–3030 (=C–H), 3005–2850 (C–H), 2215 (C≡C), 1600–1570 (C=C) cm^{-1}. HRMS (ESI-TOF): Calcd. for $C_{24}H_{18}NOS$ $[M+H]^+$: 368.1104; found: 368.1108. Calcd. for $C_{24}H_{17}NOS$ (367.5): C 78.45, H 4.66, N 3.81%; found: C 78.15, H 4.21, N 3.87%.

Preparation of 2,7-diphenyl-5-(thiophen-2-yl)furo[2,3-*c*]pyridine (16a) (method a). A mixture of pyridine **14** (118 mg, 0.321 mmol), sodium thioethanolate (216 mg, 2.57 mmol) in DMF (2 mL) was heated in an ACE-sealed tube to 80 °C for 1 h. The reaction mixture was allowed to cool to room temperature, quenched with brine (4 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. Column chromatography on silica gel (hexane–ethyl acetate, 10 : 1) afforded 46 mg (41%) of **16a** as a colourless solid. Mp 181–183 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.07 (s, 1 H, 3-H), 7.13 (dd, 1 H, J = 5.0, 3.7 Hz, 4′-H), 7.37 (dd, 1 H, J = 5.0, 1.1 Hz, 3′-H), 7.43–7.61, 7.93–7.96, 8.57–8.59 (3 m, 6 H, 2 H, 2 H, Ph), 7.62 (dd, 1 H, J = 3.7, 1.1 Hz, 5′-H), 7.80 (s, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 100.7, 109.4, 123.3, 125.7, 126.6, 127.9, 128.60, 128.63, 129.0, 129.35, 129.39, 129.9, 136.0, 137.9, 140.5, 145.9, 146.1, 148.8, 159.2 ppm. IR (KBr): ν = 3105–2855 (=C–H, C–H), 1620–1575 (C=C) cm^{-1}. HRMS (ESI-TOF): Calcd. for $C_{23}H_{15}NOS$ $[M+H]^+$: 354.0947; found 354.0940.

Preparation of 7-*tert*-butyl-2-phenyl-5-(trifluoromethyl)furo[2,3-c]pyridine (16c) (method b). To a solution of pyridine **15b** (200 mg, 0.60 mmol) in dichloromethane (6 mL) under argon atmosphere was added BBr_3 (0.90 mL, 1 M in CH_2Cl_2, 0.90 mmol) dropwise at 0 °C and warmed up to room temperature. The reaction mixture was monitored by tlc; upon completion, ice water was added and the mixture was extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with water and brine, dried with Na_2SO_4 and evaporated under reduced pressure. The residue was dissolved in DMF (5 mL) and K_2CO_3 (243 mg, 1.80 mmol) and water (1 mL) were added. After stirring at 80 °C for 12 h, the mixture was diluted with water (12 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. Column chromatography on silica gel (hexane–ethyl acetate, 10 : 1) afforded 139 mg (73%) of **16c** as a colourless solid.

Characterisation of **16c** has been previously reported.[2d]

Suzuki coupling reaction of 9f to 5-methoxy-6-phenyl-4-styryl-[2,2′]bipyridinyl (17b). A mixture of 4-pyridyl nonaflate **9f** (530 mg, 1.00 mmol), *trans*-2-phenyl vinyl boronic acid (178 mg, 1.20 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PPh_3 (52 mg, 0.20 mmol) and K_2CO_3 (135 mg, 1.00 mmol) in DMF (5 mL) was heated to 70 °C for 7 h under an argon atmosphere. The mixture was allowed to cool to room temperature and diluted with water (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic phase was dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane–ethyl acetate, 7 : 1) to give 324 mg (89%) of **17b** as a colourless solid. Mp 121–122 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.59 (s, 3 H, OMe), 7.29 (ddd, 1 H, J = 7.4, 4.7, 1.2 Hz, 5′-H), 7.33–7.36 (m, 1 H, Ph), 7.41–7.44 (m, 2 H, Ph), 7.45–7.48 (m, 1 H, Ph), 7.51–7.54 (m, 2 H, Ph), 7.54 (d, 1 H, J = 16.4 Hz, HC=C), 7.60 (d, 1 H, J = 16.5 Hz, HC=C), 7.64–7.66 (m, 2 H, Ph), 7.81 (td, 1 H, J = 7.4, 1.6 Hz, 4′-H), 8.14–8.16 (m, 2 H, Ph), 8.58 (dt, 1 H, J = 7.9, 1.0 Hz, 3′-H), 8.70 (s, 1 H, 3-H), 8.74 (ddd, 1 H, J = 4.7, 1.8, 0.8 Hz, 6′-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 61.3, 116.3, 121.0, 121.3, 123.5, 127.3, 128.4, 128.71, 128.74, 128.9, 129.3, 134.1, 136.92, 136.95, 138.2, 139.8, 149.0, 151.2, 151.6, 152.5, 156.2 ppm. IR (KBr): ν = 3080–3000 (=C–H), 2950–2830 (C–H), 1630, 1540–1500 (C=C) cm^{-1}. MS (EI): m/z (%) = 364 (100) $[M]^+$, 349 (82), 287 (24). HRMS (EI): Calcd. for $C_{25}H_{20}N_2O$ $[M]^+$: 364.15756; found 364.15756.

Photocyclisation to 4-methoxy-3-phenyl-1-pyridin-2-yl-benzo-[h]isoquinoline (18). A solution of pyridyl styrene derivative **17b** (50 mg, 0.137 mmol) in toluene (60 mL) in the presence of I_2 (42 mg, 0.165 mmol) and propylene oxide (1.9 mL, 27.4 mmol)

in a double-walled Pyrex tube cooled by water was irradiated (λ = 254 nm) with a 150 W medium pressure lamp for 10 h. The photoirradiation was monitored by tlc. The reaction mixture was washed with aqueous sodium thiosulfate solution and brine, dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane–ethyl acetate, 5 : 1) to afford 41 mg (82%) of **18** as a colourless solid. Mp 73–74 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.74 (s, 3 H, OMe), 7.21 (td, 1 H, J = 8.6, 1.4 Hz, 8-H), 7.31 (dd, 1 H, J = 8.6, 0.8 Hz, 7-H), 7.40 (td, 1 H, J = 7.4, 2.0 Hz, Ph), 7.42 (ddd, 1 H, J = 7.7, 4.9, 1.1 Hz, 4′-H), 7.49 (dt, 1 H, J = 8.0, 1.2 Hz, 9-H), 7.47–7.50 (m, 2 H, Ph), 7.88 (dd, 1 H, J = 8.0, 1.4 Hz, 10-H), 7.91 (td, 1 H, J = 7.7, 1.0 Hz, 5′-H), 7.95 (dt, 1 H, J = 7.7, 1.7 Hz, 6′-H), 7.98 (d, 1 H, J = 9.2 Hz, 6-H), 8.19 (d, 1 H, J = 9.2 Hz, 5-H), 8.20–8.21 (m, 2 H, Ph), 8.67 (ddd, 1 H, J = 4.8, 1.8, 0.9 Hz, 3′-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 61.5, 119.4, 123.2, 124.4, 126.3, 127.0, 127.5, 128.5, 128.8, 129.3, 129.4, 132.1, 133.4, 133.7, 137.6, 137.8, 143.6, 149.1, 149.5, 152.5, 161.6 ppm. IR (KBr): ν = 3050 (=C–H), 2930–2850 (C–H), 1620–1580, 1550–1475 (C=C) cm^{-1}. MS (EI): m/z (%) = 362 (65) [M]$^+$, 346 (31), 43 (100). HRMS (EI): Calcd. for $C_{25}H_{18}N_2O$ [M]$^+$: 362.14191; found 362.14277.

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