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Transition-Metal-Free Decarboxylative Photoredox Coupling of Carboxylic Acids and Alcohols with Aromatic Nitriles

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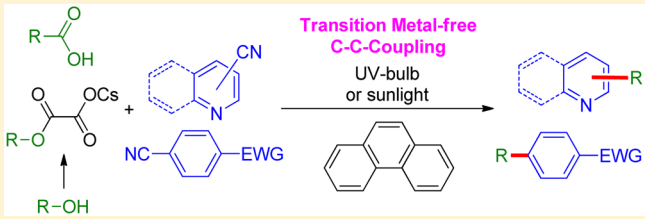
Supporting Information

ABSTRACT: A transition-metal-free protocol for the redox-neutral light-induced decarboxylative coupling of carboxylic acids with (hetero)aromatic nitriles at ambient temperature is presented. A broad scope of acids and nitriles is accepted, and alcohols can be coupled in a similar fashion through their oxalate half esters. Various inexpensive sources of UV light and even sunlight can be used to achieve this C−C bond formation proceeding through a free radical mechanism.



The homolytic substitution of heteroaromatic bases, mostly in their protonated form, by nucleophilic carbon-centered radicals is commonly referred to as the Minisci reaction.[1−4] A range of radical precursors has been used, including alcohols, ethers, alkyl halides, aldehydes, olefins, and carboxylic acids.[2] In particular the latter substrates are inexpensive and readily available sources of C-centered radicals.[5−7] The desire to use light as a sustainable energy source for C−C bond forming reactions has led to the emergence of photoredox catalysis, which is currently in the focus of interest of a steadily growing research community.[5,8−12] Recent work has combined photoredox catalysis with the traditional Minisci reaction and used radical additions to aromatic heterocycles as a synthetically appealing way of trapping the radicals generated in the course of photoredox-catalyzed transformations.[13−16] A particular advantage of photoredox catalysis is the feasibility to perform net redox-neutral reactions;[8] by incorporation of an anionic leaving group into electron-deficient aromatics, Minisci-type reactions with carboxylic acids can proceed without stoichiometric oxidants.[17] MacMillan et al. reported the photoredox-catalyzed coupling of various α-amino and α-oxy acids with a variety of aromatic nitriles at ambient temperature.[18] However, an expensive, tailored iridium complex served as the photocatalyst. The search for metal-free, cheaper alternatives such as eosin Y,[19] rose bengal,[20] or Fukuzumi-acridinium[21] is particularly challenging in this case, since the catalyst has to be both a strong reductant and a strong oxidant to reduce the (hetero)arene and to oxidize the carboxylate.[18]

Phenanthrene proved to have suitable characteristics, as its excited state offers remarkable redox properties (vide infra). Therefore, it has been used since the late 1970s as a catalyst in photochemical electron transfer reactions, most notably by Sakurai et al.[22−26] The decarboxylative coupling of carboxylic acids with 1,4-dicyanobenzene was occasionally observed when this nitrile was used as an oxidative quencher or electron shuttle in combination with phenanthrene as photocatalyst.[27−30] The alkylated cyanobenzenes were obtained in very low to moderate yields as undesired side products or in the absence of a suitable radical trap.[27−30] In 2009, Yoshimi et al. reported the phenanthrene-catalyzed substitution of a nitrile group in 1,2-, 1,3-, and 1,4-dicyanobenzene by radicals generated from oxidative decarboxylation of carboxylic acids.[17] However, moderate yields were mostly obtained using exclusively unfunctionalized, aliphatic carboxylic acids and the scope of aromatic nitriles was limited to dicyanobenzenes.[17]

Herein, we report a detailed study of the coupling of carboxylic acids with various aromatic and heteroaromatic nitriles at ambient temperature using phenanthrene as a cheap and recyclable photoredox catalyst. An extensive reaction optimization was conducted including base, solvent, and concentration screens as well as studies concerning the catalyst loading (see the Supporting Information). In addition, the first transition-metal-free deoxygenative photoredox coupling of alcohols with aromatic nitriles could be achieved through their readily accessible oxalate half-esters. Finally, the range of suitable light sources for this coupling reaction was extended to energy-saving CFL bulbs and even to sunlight.

We first investigated the phenanthrene-catalyzed coupling of Boc-L-valine with 4-cyanopyridine in the presence of various bases in mixtures of acetonitrile and water (Tables S1−S3 in the Supporting Information). Even though a loading of 5 mol % of phenanthrene was found to be sufficient (up to 27% yield within 24 h), the best results were obtained with a catalyst loading of 75 mol % (up to 77% yield within 24 h; Table S4 in the Supporting Information). Since phenanthrene is inexpensive (<1 USD/g), is readily available, and can be recovered almost quantitatively (90−96% recovery in seven randomly chosen experiments from Scheme 1), the use of stoichiometric amounts of this catalyst appears justified and is common practice.[17,27−30] Using the optimized conditions, the scope of this transition-metal-free coupling was investigated (Scheme 1).

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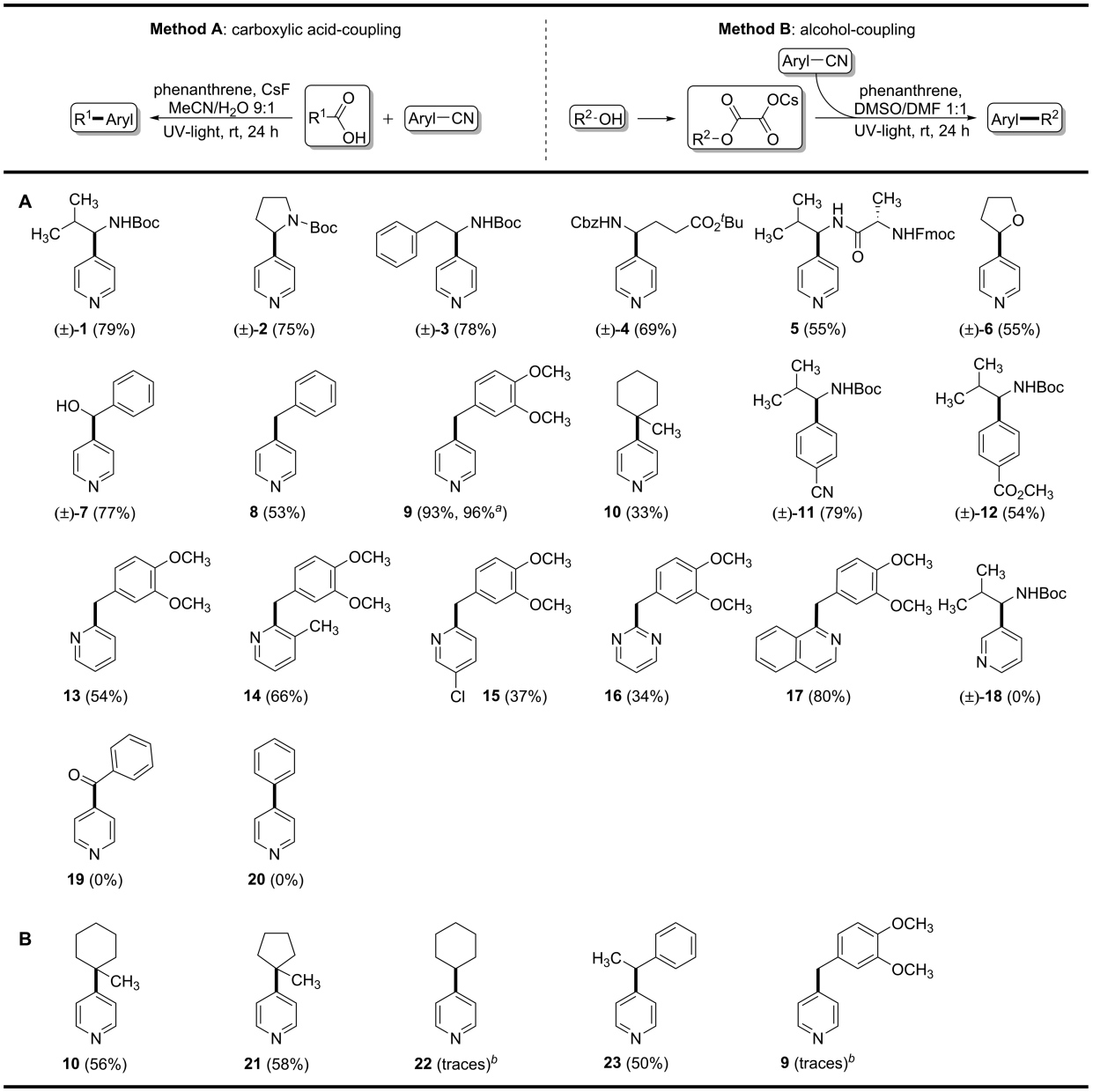
Scheme 1. Scope of the Phenanthrene-Catalyzed Coupling of Carboxylic Acids and Alcohols with Aromatic Nitriles[c]



[a]Performed on a multigram scale using 26 mmol of 4-cyanopyridine. [b]Product not isolated. [c]Method A: a solution of the aromatic nitrile (1.20 mmol, 1.00 equiv), the carboxylic acid (3.60 mmol, 3.00 equiv), CsF (3.60 mmol, 3.00 equiv), and phenanthrene (0.90 mmol, 0.75 equiv) in acetonitrile (54 mL) and water (6 mL) was irradiated according to General Procedure A. Method B: a solution of the aromatic nitrile (0.90 mmol, 1.00 equiv), the cesium oxalate (2.70 mmol, 3.00 equiv), and phenanthrene (1.13 mmol, 1.25 equiv) in a mixture of DMF (34 mL) and DMSO (34 mL) was irradiated according to General Procedure B. Unless stated otherwise, all yields are those of isolated products.

Gratifyingly, a set of proteinogenic α-amino acids furnished the desired products **1**–**5** in high yields and the usual carbamate protecting groups (Boc, Cbz, and Fmoc) were well tolerated.[31] Since esters are not attacked under the reaction conditions, the coupling of amino acids bearing carboxylate side chains is feasible (compound **4**). The first photoredox-catalyzed coupling of a dipeptide with an aromatic nitrile could be effected in 55% yield (compound **5**). The reaction protocol could be successfully applied to α-oxy acids, and even the presence of an unprotected α-hydroxy group was tolerated (compounds **6** and **7**). Arylacetic acids afforded the desired products **7**–**9** in good to excellent yields, while an α-quaternary aliphatic acid gave a yield of only 33% (compound **10**). The presented coupling reaction proved to be scalable, and a 5 g batch of compound **9** could be prepared in 96% yield. 1,4-Dicyanobenzene afforded coupling product **11** in a yield of 79%, and the second nitrile function could be replaced by a methoxycarbonyl moiety (compound **12**). At this point, we questioned how photoredox catalysis may be used to overcome difficulties associated with the traditional Minisci reaction. The regioselectivity of the latter is determined by the LUMO coefficient, which is largest at the γ-position of the pyridine core.[3] Thus, the alkylation of pyridine under traditional Minisci conditions affords mixtures in which the 2-alkylpyridine isomer usually is the minor product.[2,32] When the nitrile group was introduced at the 2-position, the desired 2-alkylated pyridines

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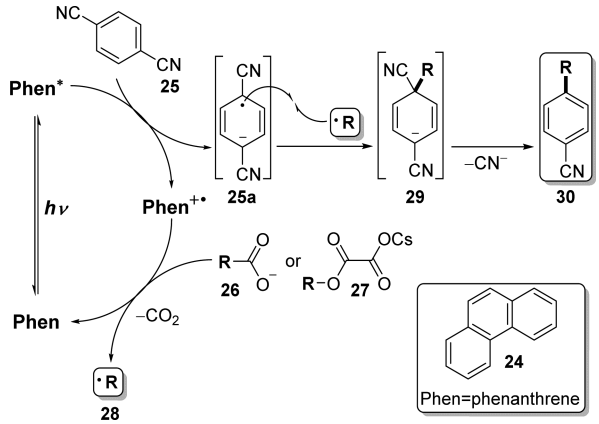
13–**15** could be isolated in 54%, 66%, and 37% yields, respectively, and no 4-substitution product could be found. In contrast to the traditional Minisci reaction, no polyalkylation was observed even when 1,4-dicyanobenzene was used as the coupling component.[2,32,33] It is noteworthy that halides do not represent suitable leaving groups for the coupling reported herein (Scheme S1 in the Supporting Information) and, thus, the selective substitution of a nitrile group in the presence of a halide is feasible (compound **15**, no double-alkylated product could be found). This opens up the possibility of combining this transition-metal-free decarboxylative photoredox coupling with traditional cross-coupling reactions for the construction of complex molecules. To test the suitability of the C–C coupling reported herein for the synthesis of alkaloid-like structures, homoveratric acid was coupled to 1-cyanoisoquinoline to furnish compound **17** in 80% yield. The alkylation of 3-cyanopyridine was unsuccessful (compound **18**), as were attempts to use sp^2-centered radicals for the acylation or arylation of aromatic nitriles (compounds **19** and **20**).

Finally, the scope of radical precursors for this coupling reaction should be extended to alcohols which are another readily available source for structurally diverse carbon-centered radicals.[2,34,35] Recently, the groups of MacMillan and Overman have shown that cesium oxalates of secondary and tertiary alcohols can be used as easily accessible and bench-stable precursors of alkyl radicals in photoredox reactions.[34] Thus, coupling of such oxalate salts with 4-cyanopyridine was investigated. Again, a detailed optimization study was conducted (Tables S6–S10 in the Supporting Information) and the scope of this unprecedented coupling reaction was investigated (Scheme 1). The cesium oxalates were obtained in high yields and without chromatographic workup by treating the corresponding alcohols with either methyl 2-chloro-2-oxoacetate or oxalyl chloride, followed by hydrolysis of the resulting oxalic esters or chlorides.[34] Oxalates of tertiary alcohols could be coupled with 4-cyanopyridine in yields of 56–58% (compounds **10** and **21**). Thus, they appear to be better suited as precursors of sterically demanding tertiary radicals for the coupling with aromatic nitriles than the corresponding carboxylic acids (compare yields of **10** in Scheme 1). However, except for tertiary alcohols, only secondary benzylic alcohols appear to undergo the coupling reported herein (compound **23**), as the oxalates of cyclohexanol and veratryl alcohol both afforded only traces of the desired products **22** and **9**.

A plausible mechanism for the transition-metal-free coupling reported herein is presented in Scheme 2.

Irradiation with UV light produces an excited state of phenanthrene (**24**) (for absorption spectra see Figure S1 in the Supporting Information). Fluorescence quenching experiments strongly indicate that an oxidative quenching cycle is operating, starting with an electron transfer from excited phenanthrene to the nitrile ($E_{1/2}(\text{Phen}^{\bullet+}/^1[\text{Phen}]^*) = -2.1$ V vs SCE;[36] for 1,4-dicyanobenzene $E_{1/2}(\text{DCB}/\text{DCB}^{\bullet-}) = -1.61$ V vs SCE[18]).[17,25] The resulting radical cation of phenanthrene is a strong oxidant ($E_{1/2}(\text{Phen}^{\bullet+}/\text{Phen}) = +1.50$ V vs SCE),[37] and it is well established that this species causes decarboxylation of carboxylates **26** (for Boc-Pro-OCs $E_{1/2}^{\text{red}} = +0.95$ V vs SCE)[18] by single-electron oxidation.[17,27−30,38,39] Decarboxylation of cesium oxalates of type **27** (for ^{t}BuOCOCO$_2$Cs $E_{1/2}^{\text{red}} = +1.28$ V vs SCE)[34] should also be feasible. Combination of the nitrile's radical anion **25a** with the alkyl radical **28** formed by decarboxylation affords anion **29**, which is stabilized by the elimination of cyanide.[18] The absence of noteworthy amounts of homocoupled products could be explained by the so-called persistent radical effect.[40] The radical anions **25a** do not combine and have a much longer lifetime than the alkyl radicals **28** obtained from decarboxylation. This causes a significant excess of the radical anions **25a** after short reaction times, strongly favoring the desired cross-coupling reaction.[40] The mechanistic proposal is in accordance with literature reports[17,18] and is supported by control experiments (Tables S5 and S11 in the Supporting Information). Regardless of the radical source, the coupling reaction afforded the unchanged starting materials when performed in the dark and only traces of the desired product were obtained upon irradiation of the samples in the absence of phenanthrene.

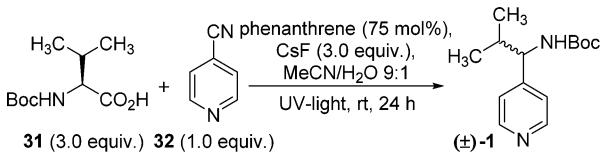
Scheme 2. Plausible Reaction Mechanism for the Phenanthrene-Catalyzed Coupling of Carboxylic Acids and Oxalates with Aromatic Nitriles



A drawback of phenanthrene is the necessity for using UV light, which represents only about 3% of the solar spectrum, for its excitation.[41] Since it appeared questionable whether this justifies the use of very expensive iridium complexes as visible-light-absorbing catalysts (especially on a preparative scale), we examined various readily available sources of UV light for the exemplary coupling of Boc-L-valine (**31**) with 4-cyanopyridine (**32**) (Table 1).

Detailed information about all lamps and the reaction setups for the irradiations are included in the Supporting Information.

Table 1. Screening for Light Sources[a]



31 (3.0 equiv.) **32** (1.0 equiv.) (±)-**1**

entry	light source	yield (%)
1	400 W medium-pressure metal halide lamp	79[b]
2	25 W energy-saving UV/vis CFL bulb	82[b]
3	sunlight[c]	61[b]
4	400 W UV-A spotlight	27[d]
5	25 W energy-saving UV-A lamp	26[d]
6	25 W energy-saving UV-A lamp[e]	70[d]

[a]Unless stated otherwise, all reactions were performed according to General Procedure A. [b]Isolated yields. [c]30 h irradiation time. [d]Yields determined by ^{1}H NMR spectroscopy using 1,4-bis(trimethylsilyl)-benzene as internal standard. [e]Reaction performed in an NMR tube.

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We were delighted to find that the strong mercury lamps typically used for phenanthrene-catalyzed photoreactions[17,27−30,38,39] could be replaced by an inexpensive and widely available 25 W energy-saving UV/vis CFL bulb for application in terrariums (82% yield within 24 h, entries 1 and 2). Even more remarkable is the finding that sunlight is well suited to promote the coupling reported herein (61% yield within 30 h of discontinuous irradiation, April, 50° N, entry 3). Since the glassware used shows no significant transmission of light with wavelengths of less than about 300 nm and given the absorption spectra of phenanthrene in both solvents used (Figure S1 in the Supporting Information), excitation of this arene in the course of the coupling reactions should mainly be attributed to 300−350 nm light (see the Supporting Information for a more detailed discussion). Thus, black light (UV-A) sources whose emission maximum lies above 350 nm afford significantly reduced yields (entries 4 and 5), while much better results can be obtained when the reaction is performed in an NMR tube (entry 6). This is probably due to the larger surface-to-volume-ratio and improved penetration by light.

In summary, the phenanthrene-catalyzed, net redox-neutral coupling of carboxylic acids with aromatic nitriles reported by Yoshimi et al. in 2009[17] was substantially optimized and the scope of acids as well as nitriles was significantly extended. For the first time, the photochemical, deoxygenative coupling of alcohols, activated as oxalates, with aromatic nitriles is reported. Studies concerning suitable light sources revealed that these coupling reactions are not only devoid of any expensive reagents or catalysts but also can be performed with natural sunlight, the most sustainable energy source imaginable.

EXPERIMENTAL SECTION

Unless stated otherwise, all solvents and reagents were obtained from commercial suppliers and used without prior purification. Phenanthrene had a purity of >96% (HPLC). Reaction solvents were degassed in an ultrasonic bath by argon sparging for 20 min. Anhydrous tetrahydrofuran and diethyl ether were distilled from potassium or sodium and benzophenone. Reactions requiring anhydrous conditions were performed in dried glassware under an atmosphere of argon. Chromatographic purification of products was performed with flash column chromatography on silica gel (35−70 μm, Acros Organics) according to the procedure of Still.[42] NMR spectra were recorded on a 300 MHz (300 MHz ^{1}H NMR, 75.5 MHz ^{13}C NMR) or a 400 MHz (400 MHz ^{1}H NMR, 100.6 MHz ^{13}C NMR) spectrometer. All ^{13}C NMR spectra were broad-band ^{1}H-decoupled. Chemical shifts are referenced to residual solvent signals ($CDCl_3$ 7.26 and 77.16 ppm and DMSO-d_6 2.50 and 39.52 ppm for ^{1}H NMR and ^{13}C NMR, respectively) and reported in parts per million (ppm) relative to tetramethylsilane (TMS). Coupling constants (J) are given in Hz using the conventional abbreviations (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and combinations thereof). Infrared (IR) spectra were recorded on a FTIR spectrometer equipped with a diamond ATR unit and are reported in terms of frequency of absorption ν (cm^{-1}). Melting points were determined in open capillary tubes using a digital electrothermal apparatus. Electron spray ionization (ESI) mass spectra were recorded on an HPLC system with binary pump and integrated diode array detector coupled to an ion trap mass spectrometer or a on an ESI/QTOF instrument. High-resolution masses were recorded on an ESI/QTOF instrument with a suitable external calibrant.

General Procedure A: Coupling of Carboxylic Acids with Aromatic Nitriles (Scheme 1). A 100 mL round-bottom flask equipped with a stir bar and a septum was flushed with argon and charged with acetonitrile (54 mL) and deionized water (6 mL). Both solvents were previously degassed by ultrasonication (see above). The aromatic nitrile (1.20 mmol, 1.00 equiv), the carboxylic acid (3.60 mmol, 3.00 equiv), CsF (3.60 mmol, 3.00 equiv), and phenanthrene (0.90 mmol, 0.75 equiv) were added, followed by argon sparging for 1 min. The mixture was irradiated with a 400 W medium-pressure Hg-metal halide lamp from a distance of 50 cm for 24 h. A saturated aqueous $NaHCO_3$ solution (30 mL) was added, followed by extraction with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Phenanthrene was recovered by filtration through a short pad of silica using cyclohexane. The remaining components of the reaction mixture were collected by washing with methanol, and the solvent was removed in vacuo. Flash column chromatography afforded the desired product.

General Procedure B: Coupling of Oxalates with Aromatic Nitriles (Scheme 1). The procedure was similar to the carboxylic acid coupling, but a mixture of DMF and DMSO (34 mL each, both degassed) was used as the solvent. The aromatic nitrile (0.90 mmol, 1.00 equiv), the cesium oxalate (2.70 mmol, 3.00 equiv), and phenanthrene (1.13 mmol, 1.25 equiv) were irradiated under identical conditions. The combined organic layers were washed with water (50 mL), dried over Na_2SO_4, and concentrated in vacuo. Phenanthrene was recovered, and the products were isolated as described for the use of carboxylic acids. The required cesium oxalates were prepared according to a one-pot procedure by Overman et al.[34] Briefly, the alcohol was reacted with methyl chlorooxoacetate in the presence of DMAP and triethylamine in dry THF followed by hydrolysis of the mixed oxalate ester with CsOH, extractive workup, and lyophilization.

*tert-Butyl (2-Methyl-1-(pyridin-4-yl)propyl)carbamate (**1**).* This compound was prepared according to General Procedure A using 4-cyanopyridine (125 mg, 1.20 mmol, 1.00 equiv) and Boc-L-Val-OH (782 mg, 3.60 mmol, 3.00 equiv). Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc/NEt_3 40/10/1) afforded the title compound (236 mg, 943 μmol, 79%) as a slightly yellow foam. R_f = 0.13 (SiO_2, ^{c}Hex/EtOAc/NEt_3 40/10/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 3243, 2972, 2875, 1695, 1601, 1525, 1456, 1390, 1365, 1246. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.55−8.52 (m, 2H, H-2′,6′), 7.15−7.13 (m, 2H, H-3′,5′), 5.01 (d, J = 8.2 Hz, 1H, NH), 4.44/4.22 (s, 1H, H-1), 2.05−1.89 (m, 1H, H-2), 1.41 (s, 9H, $C(CH_3)_3$), 0.88 (app t, J = 7.0 Hz, 6H, $CH(CH_3)_2$). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 155.5 (CO), 151.3 (C-4′), 149.9 (2C, C-2′,6′), 122.1 (2C, C-3′,5′), 79.9 ($OC(CH_3)_3$), 59.6 (C-1), 33.2 (C-2), 28.5 ($C(CH_3)_3$), 19.7 ($CH(CH_3)$ (CH_3)), 18.1 ($CH(CH_3)(CH_3)$). ESI-MS (pos): m/z 251.1 (100%, $[M + H]^+$), 195.2 (8%, $[M - {}^t\mathrm{Bu} + H]^+$). ESI-HRMS (pos): calculated for $[C_{14}H_{23}N_2O_2]^+$ m/z 251.1754, found 251.1752. Hydrogen H-1 gives two signals in the ^{1}H NMR spectrum, due to the hindered rotation around the CO−N bond.

*tert-Butyl 2-(Pyridin-4-yl)pyrrolidine-1-carboxylate (**2**).* This compound was prepared according to General Procedure A using 4-cyanopyridine (125 mg, 1.20 mmol, 1.00 equiv) and Boc-L-Pro-OH (775 mg, 3.60 mmol, 3.00 equiv). Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 1/1) afforded the title compound (224 mg, 902 μmol, 75%) as a colorless solid. R_f = 0.14 (SiO_2, ^{c}Hex/EtOAc 1/1). Mp: 71.5−72.3 °C. IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2975, 2932, 2879, 1693, 1599, 1391, 1161, 1115, 993, 904. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): **A**, δ/ppm 8.51 (d, J = 5.5 Hz, 2H, H-2′,6′), 7.09−7.07 (m, 2H, H-3′,5′), 4.91−4.86 (m, 1H, H-2), 3.66−3.46 (m, 2H, H-5), 2.40−2.25 (m, 1H, H-3a), 1.90−1.83 (m, 2H, H-4), 1.82−1.73 (m, 1H, H-3b), 1.44 (s, 9H, $C(CH_3)_3$); **B**, δ/ppm 8.51 (d, J = 5.5 Hz, 2H, H-2′,6′), 7.09−7.07 (m, 2H, H-3′,5′), 4.74−4.69 (m, 1H, H-2), 3.66−3.46 (m, 2H, H-5), 2.40−2.25 (m, 1H, H-3a), 1.90−1.83 (m, 2H, H-4), 1.82−1.73 (m, 1H, H-3b), 1.18 (s, 9H, $C(CH_3)_3$). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): **A**, δ/ppm 154.3 (C_q), 154.2 (C_q), 149.8 (2C, C-2′,6′), 120.8 (2C, C-3′,5′), 79.9 ($C(CH_3)_3$), 60.0 (C-2), 47.4 (C-5), 34.4 (C-3), 28.6 ($C(CH_3)_3$), 23.7 (C-4); **B**, δ/ppm 154.3 (C_q), 154.2 (C_q), 149.8 (2C, C-2′,6′), 120.8 (2C, C-3′,5′), 79.9 ($C(CH_3)_3$), 60.6 (C-2), 47.2 (C-5), 35.6 (C-3), 28.2 ($C(CH_3)_3$), 23.3 (C-4). ESI-MS (pos): m/z 249.1 (100%, $[M + H]^+$), 193.1 (6%, $[M - {}^t\mathrm{Bu} + H]^+$). ESI-HRMS (pos): calculated for $[C_{14}H_{21}N_2O_2]^+$ m/z 249.1603, found 249.1608. The product gives two sets of NMR signals, due to the presence of rotamers (A/B = 0.36/

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0.64). The spectral data are consistent with those reported in the literature.[18]

*tert-Butyl (2-Phenyl-1-(pyridin-4-yl)ethyl)carbamate (**3**).* This compound was prepared according to General Procedure A using 4-cyanopyridine (125 mg, 1.20 mmol, 1.00 equiv) and Boc-L-Phe-OH (955 mg, 3.60 mmol, 3.00 equiv). Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 2/1) afforded the title compound (281 mg, 942 μmol, 78%) as a colorless solid. R_f = 0.10 (SiO_2, ^{c}Hex/EtOAc 2/1). Mp: 117.2−118.4 °C. IR (ATR): $\tilde{\nu}$ (cm^{-1}) 3236, 3029, 2977, 1707, 1601, 1525, 1497, 1366, 1251, 1169. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.55 (br s, 2H, H-2″,6″), 7.28−7.19 (m, 3H, H-3′,4′,5′), 7.12 (br s, 2H, H-3″,5″), 7.03−7.01 (m, 2H, H-2′,6′), 4.95 (br s, 2H, NH, H-1), 3.05−2.98 (m, 2H, H-2), 1.37 (s, 9H, $C(CH_3)_3$).^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 155.1 (CO), 150.0 (2C, C-2″,6″), 149.9 (C-4″), 136.3 (C-1′), 129.4 (C-3′,5′), 128.7 (C-2′,6′), 127.1 (C-4′), 121.7 (2C, C-3″,5″), 80.2 ($C(CH_3)_3$), 55.1 (C-1), 42.7 (C-2), 28.4 ($C(CH_3)_3$). ESI-MS (pos): *m*/*z* 299.2 (100%, $[M + H]^+$), 243.1 (4%, $[M - {}^t\text{Bu} + H]^+$). ESI-HRMS (pos): calculated for $[C_{18}H_{23}N_2O_2]^+$ *m*/*z* 299.1760, found 299.1757.

*tert-Butyl 4-((((Benzyloxy)carbonyl)amino)-4-(pyridin-4-yl)-butanoate (**4**).* This compound was prepared according to General Procedure A using 4-cyanopyridine (125 mg, 1.20 mmol, 1.00 equiv) and Cbz-L-Glu(O-^{t}Bu)-OH (1.22 g, 3.60 mmol, 3.00 equiv). Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 1/1) afforded the title compound (305 mg, 823 μmol, 69%) as a colorless oil. R_f = 0.19 (SiO_2, ^{c}Hex/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 3324, 3032, 2978, 1720, 1601, 1530, 1454, 1367, 1251, 1150. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.55 (d, *J* ≈ 5.4 Hz, 2H, H-2′,6′), 7.33 (br s, 5H, Ph-*H*), 7.20 (d, *J* ≈ 5.4 Hz, 2H, H-3′,5′), 5.61 (d, *J* = 7.7 Hz, 1H, NH), 5.12−5.00 (m, 2H, Ph−CH_2O), 4.70 (app q, *J* = 7.1 Hz, 2H, H-4), 2.30 (t, *J* = 7.0 Hz, 2H, H-2), 2.01 (app q, *J* = 7.0 Hz, 2H, H-3), 1.43 (s, 9H, $OC(CH_3)_3$). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 172.6 (C-1), 155.9 (NCO), 151.4 (C-4′), 150.1 (2C, C-2′,6′), 136.3 (C-1″), 128.6/128.3 (5C, CH of phenyl group), 121.4 (2C, C-3′,5′), 81.2 ($OC(CH_3)_3$), 67.1 (CH_2O), 54.6 (C-4), 32.2 (C-2), 30.8 (C-3), 28.2 ($OC(CH_3)_3$). ESI-MS (pos): *m*/*z* 393.2 (6%, $[M + Na]^+$), 371.2 (100%, $[M + H]^+$). ESI-HRMS (pos): calculated for $[C_{21}H_{27}N_2O_4]^+$ *m*/*z* 371.1971, found 371.1967.

*tert-Butyl ((((9H-Fluoren-9-yl)methoxy)carbonyl)-L-alanyl)(2-methyl-1-(pyridin-4-yl)propyl)carbamate (**5**).* This compound was prepared according to General Procedure A using 4-cyanopyridine (125 mg, 1.20 mmol, 1.00 equiv) and Fmoc-L-Ala-L-Val-OH (1.45 g, 3.60 mmol, 3.00 equiv). Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 1/3) afforded the title compound (291 mg, 656 μmol, 55%) as a colorless solid. R_f = 0.14 (SiO_2, ^{c}Hex/EtOAc 1/3). Mp: 84.6−85.2 °C. IR (ATR): $\tilde{\nu}$ (cm^{-1}) 3305, 3040, 2965, 2935, 1662, 1601, 1537, 1450, 1255, 737. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.52−8.50/8.44−8.42 (m, 1H/m, 1H, H-2″,6″), 7.76 (d, *J* = 7.5 Hz, 2H, H-4′,5′), 7.55 (app t, *J* = 7.3 Hz, 2H, H-1′,8′), 7.39 (app t, *J* = 7.5 Hz, 2H, H-3′,6′), 7.31−7.26 (m, 2H, H-2′,7′), 7.12/7.08−7.06 (d, *J* = 5.5 Hz, 1H/m, 1H, H-3″,5″), 6.99−6.93 (m, 1H, N*H*CH(pyridin-4-yl)), 5.56 (s, 1H, N*H*CH(CH_3)), 4.73−4.66 (m, 1H, C*H*(pyridin-4-yl)), 4.43−4.37 (m, 2H, CH_2O), 4.37−4.26 (m, 1H, NHC*H*(CH_3)), 4.23−4.16 (m, 1H, H-9′), 2.05−1.90 (m, 1H, C*H*(CH_3)$_2$), 1.40/1.35 (d, *J* = 6.8 Hz, 1H/d, *J* = 6.8 Hz, 2H, NHCH(CH_3)), 0.84 (td, *J* = 15.7, 6.8 Hz, 6H, CH(CH_3)$_2$). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 172.0 (N(CO)-C), 156.6 (N(CO)O), 150.4 (C-4″), 150.0/149.9 (2C, C-2″,6″), 143.7 (2C, C-8′a,9′a), 141.4 (2C, C-4′a,4′b), 128.0 (2C, C-3′,6′), 127.2 (2C, C-2′,7′), 125.0 (2C, C-1′,8′), 122.1 (2C, C-3″,5″), 120.2 (2C, C-4′,5′), 67.4 (CH_2O), 58.4 (*C*H(pyridin-4-yl)), 50.6 (NH*C*H(CH_3)), 47.1 (C-9′), 33.0 (*C*H(CH_3)$_2$), 19.8/19.7 (1C, CH(CH_3)$_2$), 18.4/18.2/18.1 (2C, CH(CH_3)$_2$, NHCH(CH_3)). ESI-MS (pos): *m*/*z* 466.2 (5%, $[M + Na]^+$), 444.3 (100%, $[M + H]^+$). ESI-HRMS (pos): calculated for $[C_{27}H_{30}N_3O_3]^+$ *m*/*z* 444.2287, found 444.2296.

*4-(Tetrahydrofuran-2-yl)pyridine (**6**).* This compound was prepared according to General Procedure A using 4-cyanopyridine (125 mg, 1.20 mmol, 1.00 equiv) and tetrahydrofuran-2-carboxylic acid (418 mg, 3.60 mmol, 3.00 equiv). Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 1/1) afforded the title compound (98 mg, 657 μmol, 55%) as a colorless liquid. R_f = 0.17 (SiO_2, ^{c}Hex/EtOAc 1/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 3027, 2976, 2871, 1600, 1559, 1412, 1364, 1320, 1062, 924. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.54−8.52 (m, 2H, H-2,6), 7.23−7.21 (m, 2H, H-3,5), 4.88 (t, *J* = 7.1 Hz, 1H, H-2′), 4.10−4.04 (m, 1H, H-5′a), 3.97−3.91 (m, 1H, H-5′b), 2.41−2.32 (m, 1H, H-3′a), 2.03−1.92 (m, 2H, H-4′), 1.79−1.70 (m, 1H, H-3′b). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 152.9 (C-4), 149.9 (C-2,6), 120.6 (C-3,5), 79.2 (C-2′), 69.1 (C-5′), 34.4 (C-3′), 26.0 (C-4′). ESI-MS (pos): *m*/*z* 150.1 (100%, $[M + H]^+$). ESI-HRMS (pos): calculated for $[C_9H_{12}NO]^+$ *m*/*z* 150.0919, found 150.0916.

*Phenyl(pyridin-4-yl)methanol (**7**).* This compound was prepared according to General Procedure A using 4-cyanopyridine (125 mg, 1.20 mmol, 1.00 equiv) and (*S*)-(+)-mandelic acid (548 mg, 3.60 mmol, 3.00 equiv). Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 1/2) afforded the title compound (171 mg, 923 μmol, 77%) as a colorless solid. R_f = 0.19 (SiO_2, ^{c}Hex/EtOAc 1:2). Mp: 122.1−123.8 °C, lit.[43] mp 120−122 °C. IR (ATR): $\tilde{\nu}$ (cm^{-1}) 3358, 3192, 2986, 1600, 1494, 1453, 1415, 1189, 1051, 1004. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.29−8.26 (m, 2H, H-2′,6′), 7.32−7.27 (m, 7H, Ph-H, H-3′,5′), 5.72 (s, 1H, H-1), 5.43 (br s, 1H, OH). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 153.7 (C-4′), 149.1 (2C, C-2′,6′), 143.2 (C-1″), 128.8 (2C, CH of phenyl group), 128.1 (CH of phenyl group), 126.9 (2C, CH of phenyl group), 121.5 (2C, C-3′,5′), 74.7 (C-1). ESI-MS (pos): *m*/*z* 186.0 (100%, $[M + H]^+$). ESI-HRMS (pos): calculated for $[C_{12}H_{12}NO]^+$ *m*/*z* 186.0919, found 186.0948. The spectral data are consistent with those reported in the literature.[43]

*4-Benzylpyridine (**8**).* This compound was prepared according to General Procedure A using 4-cyanopyridine (125 mg, 1.20 mmol, 1.00 equiv) and phenylacetic acid (490 mg, 3.60 mmol, 3.00 equiv). Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 2/1) afforded the title compound (107 mg, 632 μmol, 53%) as a yellow oil. R_f = 0.24 (SiO_2, ^{c}Hex/EtOAc 2/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 3065, 3027, 2921, 1596, 1559, 1495, 1415, 1219, 1071, 994. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.49 (d, *J* = 5.7 Hz, 2H, H-2,6), 7.34−7.29 (m, 2H, H-3′,5′), 7.27−7.22 (m, 1H, H-4′), 7.19−7.16 (m, 2H, H-2′,6′), 7.11−7.08 (m, 2H, H-3,5), 3.96 (s, 2H, CH_2). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 150.0 (C-4), 149.9 (2C, C-2,6), 138.9 (C-1′), 129.1 (2C, C-2′,6′), 128.8 (2C, C-3′,5′), 126.8 (C-4′), 124.3 (2C, C-3,5), 41.3 (CH_2). ESI-MS (pos): *m*/*z* 170.0 (100%, $[M + H]^+$). The spectral data are consistent with those reported in the literature.[44]

*4-(3,4-Dimethoxybenzyl)pyridine (**9**).* This compound was prepared according to General Procedure A using 4-cyanopyridine (125 mg, 1.20 mmol, 1.00 equiv) and homoveratric acid (706 mg, 3.60 mmol, 3.00 equiv). Since no nonvolatile byproducts are formed, the title compound (254 mg, 1.11 mmol, 93%) can be isolated without column chromatography as a yellow oil by a second extraction procedure using dilute hydrochloric acid, neutralization with solid NaOH and extraction with ethyl acetate: R_f = 0.20 (SiO_2, ^{c}Hex/EtOAc 1/2). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 2998, 2935, 2835, 1597, 1513, 1463, 1415, 1260, 1237, 1139. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.46 (br s, 2H, H-2,6), 7.07 (d, *J* = 5.0 Hz, 2H, H-3,5), 6.79 (d, *J* = 8.2 Hz, 1H, H-5′), 6.69 (dd, *J* = 8.2, 1.8 Hz, 1H, H-6′), 6.64 (d, *J* = 1.8 Hz, 1H, H-2′), 3.88 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 150.4 (C-4), 149.8 (C-2,6), 149.1 (C-3′), 147.8 (C-4′), 131.3 (C-1′), 124.1 (2C, C-3,5), 121.1 (C-6′), 112.2 (C-2′), 111.3 (C-5′), 55.9/55.8 (2C, OCH_3), 40.8 (CH_2). ESI-MS (pos): *m*/*z* 230.1 (100%, $[M + H]^+$). ESI-HRMS (pos): calculated for $[C_{14}H_{16}NO_2]^+$ *m*/*z* 230.1181, found 230.1180.

*4-(1-Methylcyclohexyl)pyridine (**10**).* This compound was prepared according to General Procedure A using 4-cyanopyridine (125 mg, 1.20 mmol, 1.00 equiv) and 1-methylcyclohexane-1-carboxylic acid (512 mg, 3.60 mmol, 3.00 equiv). Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 3/1) afforded the title compound (69 mg, 394 μmol, 33%) as a slightly yellow oil. R_f =

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0.15 (SiO_2, ^{c}Hex/EtOAc 3/1). IR (ATR): $\bar{\nu}$ (cm^{-1}) 2928, 2858, 1595, 1549, 1454, 1409, 1303, 1225, 996, 818. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.52−8.50 (m, 2H, H-2,6), 7.27−7.25 (m, 2H, H-3,5), 2.02−1.93 (m, 2H), 1.60−1.52 (m, 4H), 1.48−1.32 (m, 4H), 1.17 (s, 3H, CH_3). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 159.2 (C-4), 149.9 (2C, C-2,6), 121.6 (2C, C-3,5), 38.2 (C-1′), 37.3 (2C, CH_2), 30.1 (CH_3), 26.3 (CH_2), 22.6 (2C, CH_2). ESI-MS (pos): m/z 176.1 (100%, $[M + H]^+$). ESI-HRMS (pos): calculated for $[C_{12}H_{18}N]^+$ m/z 176.1439, found 176.1443.

This compound was also obtained from 1-methylcyclohexan-1-ol, which was first converted to cesium 2-((1-methylcyclohexyl)oxy)-2-oxoacetate according to a procedure by Overman et al.[34] This oxalate (859 mg, 2.70 mmol, 3.00 equiv) was then reacted with 4-cyanopyridine (94.0 mg, 900 μmol, 1.00 equiv) according to the General Procedure B. Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 5/1) afforded the title compound (88.0 mg, 502 μmol, 56%) as a slightly yellow oil. Analytical data are as reported above.

*tert-Butyl (1-(4-Cyanophenyl)-2-methylpropyl)carbamate (**11**).* This compound was prepared according to General Procedure A using 1,4-dicyanobenzene (154 mg, 1.20 mmol, 1.00 equiv) and Boc-L-Val-OH (782 mg, 3.60 mmol, 3.00 equiv). Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 10/1) afforded the title compound (261 mg, 951 μmol, 79%) as a colorless solid. R_f = 0.17 (SiO_2, ^{c}Hex/EtOAc 10/1). Mp: 132.3−133.5 °C, lit.[27] mp 135−136 °C. IR (ATR): $\bar{\nu}$ (cm^{-1}) 3356, 2972, 2933, 2875, 2229, 1696, 1609, 1505, 1390, 1366. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 7.62−7.59 (m, 2H, H-2′,6′), 7.32 (d, J = 8.2 Hz, 2H, H-3′,5′), 4.96 (s, 1H, NH), 4.46/4.25 (s, 1H, H-1), 2.01−1.90 (m, 1H, H-2), 1.40 (s, 9H, $C(CH_3)_3$), 0.91 (d, J = 6.7 Hz, 3H, $CH(CH_3)$ (CH_3)), 0.84 (d, J = 6.7 Hz, 3H, $CH(CH_3)(CH_3)$). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 155.5 (CO), 148.0 (C-1′), 132.3 (2C, C-2′,6′), 127.6 (2C, C-3′,5′), 119.0 (CN), 110.9 (C-4′), 80.0 ($C(CH_3)_3$), 60.5 (C-1), 33.6 (C-2), 28.4 ($C(CH_3)_3$), 19.7 (($CH(CH_3)$ (CH_3)), 18.3 (($CH(CH_3)(CH_3)$). ESI-MS (pos): m/z 297.1 (13%, $[M + Na]^+$), 275.1 (9%, $[M + H]^+$), 219.1 (100%, $[M - {}^t\mathrm{Bu} + H]^+$). ESI-HRMS (pos): calculated for $[C_{16}H_{22}N_2O_2Na]^+$ m/z 297.1579, found 297.1591. H-1 gives two resonances in the ^{1}H NMR spectrum due to the hindered rotation around the CO−N bond. The spectral data are consistent with those reported in the literature.[18]

*Methyl 4-(1-((tert-Butoxycarbonyl)amino)-2-methylpropyl)-benzoate (**12**).* This compound was prepared according to General Procedure A using methyl 4-cyanobenzoate (193 mg, 1.20 mmol, 1.00 equiv) and Boc-L-Val-OH (782 mg, 3.60 mmol, 3.00 equiv). Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 7/1) afforded the title compound (199 mg, 647 μmol, 54%) as a colorless foam. R_f = 0.21 (SiO_2, ^{c}Hex/EtOAc 7/1). IR (ATR): $\bar{\nu}$ (cm^{-1}) 3370, 2965, 2932, 2874, 1700, 1518, 1366, 1280, 1170, 1113. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.01−7.97 (m, 2H, H-2,6), 7.28 (d, J = 8.3 Hz, 2H, H-3,5), 4.91 (br s, 1H, NH), 4.48/4.31 (br s, 1H, H-1′), 3.90 (s, 3H, CO_2CH_3), 2.05−1.88 (m, 1H, H-2′), 1.40 (br s, 9H, $C(CH_3)_3$), 0.92 (d, J = 6.7 Hz, 3H, $CH(CH_3)$ (CH_3)), 0.84 (d, J = 6.7 Hz, 3H, $CH(CH_3)(CH_3)$). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 167.1 (CO_2CH_3), 155.6 ($COC(CH_3)_3$), 147.7 (C-4), 129.8 (2C, C-2,6), 129.0 (C-1), 126.9 (2C, C-3,5), 79.8 ($C(CH_3)_3$), 60.5 (C-1′), 52.2 (CO_2CH_3), 33.8 (C-2′), 28.5 (3C, $C(CH_3)_3$), 19.8/18.5 (2C, $CH(CH_3)_2$). ESI-MS (pos): m/z 330.2 (33%, $[M + Na]^+$), 252.1 (100%, $[M - {}^t\mathrm{Bu} + H]^+$). ESI-HRMS (pos): calculated for $[C_{17}H_{25}NO_4Na]^+$ m/z 330.1681, found 330.1678. H-1 gives two resonances in the ^{1}H NMR spectrum due to the hindered rotation around the CO−N bond.

*2-(3,4-Dimethoxybenzyl)pyridine (**13**).* This compound was prepared according to General Procedure A using 2-cyanopyridine (125 mg, 1.20 mmol, 1.00 equiv) and homoveratric acid (706 mg, 3.60 mmol, 3.00 equiv). Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 1/1) afforded the title compound (149 mg, 650 μmol, 54%), as a slightly yellow oil. R_f = 0.21 (SiO_2, ^{c}Hex/EtOAc 1/1). IR (ATR): $\bar{\nu}$ (cm^{-1}) 3062, 3003, 2935, 2834, 1590, 1512, 1464, 1259, 1236, 1139. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.55−8.53 (m, 1H, H-6), 7.57 (app td, J = 7.7, 1.9 Hz, 1H, H-4), 7.12−7.09 (m, 2H, H-3,5), 6.81−6.79 (m, 3H, H-2′,5′,6′), 4.09 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 161.4 (C-2), 149.4 (C-6), 149.1/147.7 (2C, C-3′,4′), 136.7 (C-4), 132.2 (C-1′), 123.1/121.3 (2C, C-3,5), 121.2/112.4/111.4 (3C, C-2′,5′6′), 56.0/55.9 (2C, OCH_3), 44.4 (CH_2). ESI-MS (pos): m/z 230.1 (100%, $[M + H]^+$). ESI-HRMS (pos): calculated for $[C_{14}H_{16}NO_2]^+$ m/z 230.1181, found 230.1190.

*2-(3,4-Dimethoxybenzyl)-3-methylpyridine (**14**).* This compound was prepared according to General Procedure A using 2-cyano-3-methylpyridine (142 mg, 1.20 mmol, 1.00 equiv) and homoveratric acid (706 mg, 3.60 mmol, 3.00 equiv). Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 1/1) afforded the title compound (194 mg, 797 μmol, 66%) as a slightly yellow oil. R_f = 0.19 (SiO_2, ^{c}Hex/EtOAc 1/1). IR (ATR): $\bar{\nu}$ (cm^{-1}) 2998, 2953, 2834, 1589, 1514, 1464, 1448, 1260, 1140, 1028. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.42−8.40 (m, 1H, H-6), 7.42−7.39 (m, 1H, H-4), 7.07 (dd, J = 7.6, 4.9 Hz, 1H, H-5), 6.76−6.73 (m, 2H, Ph-H), 6.70−6.68 (m, 1H, Ph-H), 4.11 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 159.1 (C-2), 148.9/147.5 (2C, C-3′,4′), 146.8 (C-6), 138.1 (C-4), 131.8/131.6 (2C, C-3,1′), 121.8 (C-5), 120.7 (CH of phenyl group), 112.1/111.1 (2C, CH of phenyl group), 55.9 (2C, OCH_3), 41.9 (CH_2), 19.1 (CH_3). ESI-MS (pos): m/z 244.1 (100%, $[M + H]^+$). ESI-HRMS (pos): calculated for $[C_{15}H_{18}NO_2]^+$ m/z 244.1338, found 244.1337.

*5-Chloro-2-(3,4-dimethoxybenzyl)pyridine (**15**).* This compound was prepared according to General Procedure A using 5-chloro-2-picolinonitrile (166 mg, 1.20 mmol, 1.00 equiv) and homoveratric acid (706 mg, 3.60 mmol, 3.00 equiv). Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 5/1) afforded the title compound (116 mg, 440 μmol, 37%) as a colorless oil. R_f = 0.15 (SiO_2, ^{c}Hex/EtOAc 5/1). IR (ATR): $\bar{\nu}$ (cm^{-1}) 3000, 2934, 2835, 1514, 1466, 1261, 1238, 1139, 1029, 804. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.46 (d, J = 2.5 Hz, 1H, H-6), 7.50 (dd, J = 8.3, 2.5 Hz, 1H, H-4), 7.02 (d, J = 8.3 Hz, 1H, H-3), 6.81−6.72 (m, 3H, Ph-H), 4.03 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 159.5 (C-2), 149.0 (C3′ or C-4′), 148.0 (C-6), 147.7 (C3′ or C-4′), 136.2 (C-4), 131.5 (C-1′), 129.6 (C-5), 123.7 (C-3), 121.0 (CH of phenyl group), 112.2 (CH of phenyl group), 111.3 (CH of phenyl group), 55.9/55.8 (2C, OCH_3), 43.6 (CH_2). ESI-MS (pos): m/z 264.1 (100%, $[M + H]^+$). ESI-HRMS (pos): calculated for $[C_{14}H_{15}NO_2Cl]^+$ m/z 264.0791, found 264.0788.

*2-(3,4-Dimethoxybenzyl)pyrimidine (**16**).* This compound was prepared according to General Procedure A using 2-cyanopyrimidine (126 mg, 1.20 mmol, 1.0 equiv) and homoveratric acid (706 mg, 3.60 mmol, 3.0 equiv). Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 1/4) afforded the title compound (93 mg, 404 μmol, 34%) as a colorless foam. R_f = 0.19 (SiO_2, ^{c}Hex/EtOAc 1/4). IR (ATR): $\bar{\nu}$ (cm^{-1}) 2999, 2936, 2834, 1561, 1515, 1417, 1261, 1234, 1140, 1028. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.66 (d, J = 4.9 Hz, 2H, H-4,6), 7.10 (t, J = 4.9 Hz, 1H, H-5), 6.90−6.87 (m, 2H, Ph-H), 6.81−6.77 (m, 1H, Ph-H), 4.21 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 170.3 (C-2), 157.4 (2C, C-4,6), 148.9/147.8 (2C, C-3′,4′), 130.8 (C-1′), 121.2 (CH of phenyl group), 118.7 (C-5), 112.3 (CH of phenyl group), 111.3 (CH of phenyl group), 55.9 (2C, OCH_3), 45.7 (CH_2). ESI-MS (pos): m/z 253.0 (2%, $[M + Na]^+$), 231.1 (100%, $[M + H]^+$). ESI-HRMS (pos): calculated for $[C_{13}H_{15}N_2O_2]^+$ m/z 231.1134, found 231.1136.

*1-(3,4-Dimethoxybenzyl)isoquinoline (**17**).* This compound was prepared according to General Procedure A using 1-cyanoisoquinoline (185 mg, 1.20 mmol, 1.00 equiv) and homoveratric acid (706 mg, 3.60 mmol, 3.00 equiv). Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 2/1) afforded the title compound (263 mg, 962 μmol, 80%) as a brown foam. R_f = 0.12 (SiO_2, ^{c}Hex/EtOAc 2/1). IR (ATR): $\bar{\nu}$ (cm^{-1}) 3052, 2999, 2934, 2834, 1514, 1463, 1259, 1234, 1141, 1028. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.50 (d, J = 5.8 Hz, 1H, H-3), 8.19−8.16 (m, 1H, H-8), 7.81 (d, J = 8.2

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Hz, H-5), 7.63 (ddd, J = 8.2, 6.9, 1.1 Hz, 1H, H-6), 7.57−7.51 (m, 2H, H-4,7), 6.84 (d, J = 1.9 Hz, 1H, H-2′), 6.80 (dd, J = 8.2, 1.9 Hz, 1H, H-6′), 6.75 (d, J = 8.2 Hz, 1H, H-5′), 4.61 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 160.4 (C-1), 149.0 (C-4′), 147.6 (C-3′), 142.1 (C-3), 136.7 (2C, C-4a,8a), 132.1 (C-1′), 130.0 (C-6), 127.5 (C-5), 127.3 (C-7), 125.9 (C-8), 120.7 (C-6′), 119.9 (C-4), 112.0 (C-2′), 111.3 (C-5′), 55.9 (2C, OCH_3), 41.8 (CH_2). ESI-MS (pos): m/z 302.1 (2%, $[M + Na]^+$), 280.1 (100%, $[M + H]^+$). ESI-HRMS (pos): calculated for $[C_{18}H_{18}NO_2]^+$ m/z 280.1338, found 280.1345. The spectral data are consistent with those reported in the literature.[45]

*4-(1-Methylcyclopentyl)pyridine (**21**).* 1-Methylcyclopentan-1-ol was first converted to cesium 2-((1-methylcyclopentyl)oxy)-2-oxoacetate according to a procedure by Overman et al.[34] This oxalate (821 mg, 2.70 mmol, 3.00 equiv) was then reacted with 4-cyanopyridine (94.0 mg, 900 μmol, 1.00 equiv) according to General Procedure B. Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 5/1) afforded the title compound (84.0 mg, 521 μmol, 58%) as a slightly yellow oil. R_f = 0.16 (SiO_2, ^{c}Hex/EtOAc 5/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 3023, 2958, 2872, 1597, 1550, 1450, 1410, 1330, 1223, 821. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.49−8.46 (m, 2H, H-2,6), 7.22−7.19 (m, 2H, H-3,5), 1.90−1.68 (m, 8H), 1.23 (s, 3H, CH_3). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 160.2 (C-4), 149.7 (2C, C-2,6), 121.6 (2C, C-3,5), 47.0 (C-1′), 39.3 (2C, CH_2), 28.8 (CH_3), 23.8 (2C, CH_2). ESI-MS (pos): m/z 162.1 (100%, $[M + H]^+$). ESI-HRMS (pos): calculated for $[C_{11}H_{16}N]^+$ m/z 162.1283, found 162.1281.

*4-(1-Phenylethyl)pyridine (**23**).* 1-Phenylethanol was first converted to cesium 2-oxo-2-(1-phenylethoxy)acetate according to a procedure by Overman et al.[34] This oxalate (880 mg, 2.70 mmol, 3.00 equiv) was then reacted with 4-cyanopyridine (94.0 mg, 900 μmol, 1.00 equiv) according to General Procedure B. Purification of the crude product by flash column chromatography (SiO_2, ^{c}Hex/EtOAc 3/1) afforded the title compound (82.0 mg, 447 μmol, 50%) as a yellow oil. R_f = 0.19 (SiO_2, ^{c}Hex/EtOAc 3/1). IR (ATR): $\tilde{\nu}$ (cm^{-1}) 3062, 3027, 2971, 2933, 2876, 1595, 1494, 1452, 1413, 1220. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm 8.51−8.48 (m, 2H, H-2,6), 7.34−7.28 (m, 2H, Ph-H), 7.26−7.17 (m, 3H, Ph-H), 7.14−7.12 (m, 2H, H-3,5), 4.11 (q, J = 7.2 Hz, 1H, $HC(CH_3)$), 1.64 (d, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$): δ/ppm 155.1 (C-4), 149.9 (2C, C-2,6), 144.5 (C-1′), 128.7 (2C, CH of phenyl group), 127.7 (2C, CH of phenyl group), 126.7 (CH of phenyl group), 123.1 (2, C-3,5), 44.3 ($HC(CH_3)$), 21.2 (CH_3). ESI-MS (pos): m/z 184.1 (100%, $[M + H]^+$). ESI-HRMS (pos): calculated for $[C_{13}H_{14}N]^+$ m/z 184.1126, found 184.1124. The spectral data are consistent with those reported in the literature.[46]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01215.

Detailed optimization studies for the coupling reactions reported herein, precise descriptions of the used light sources, absorption spectra of phenanthrene in both reaction solvents, experiments concerning halides as potential leaving groups and the recovery of excess radical precursor, and NMR spectra of all compounds, including the cesium oxalates (PDF)

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Notes

The authors declare no competing financial interest.

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