Indium-Mediated Reformatsky-Type Reaction of β-Aminovinyl Chlorodifluoromethyl Ketones with Heteroaryl Aldehydes

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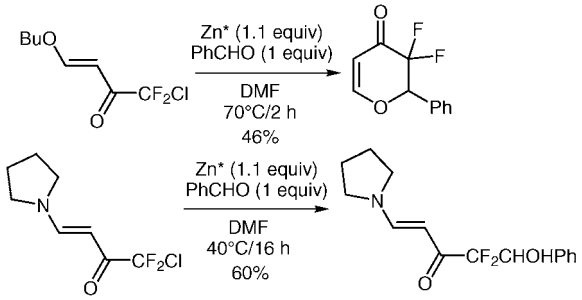
Abstract: Indium can efficiently mediate the Reformatsky-type reaction between some β-aminovinyl chlorodifluoromethyl ketones and a series of heteroaryl aldehydes, to afford the corresponding difluoromethylene compounds in good to high yields.

Key words: indium, Reformatsky, fluorine, β-aminovinyl ketones, nucleophilic additions

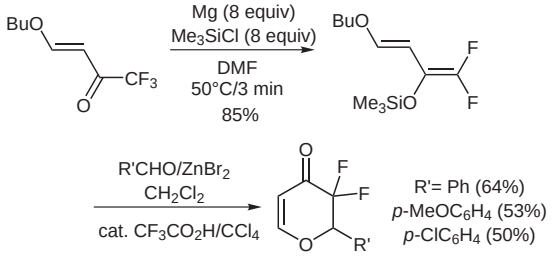
There is still interest in new approaches for the synthesis of new *gem*-difluoromethylene compounds because of their synthetic and biological importance.[1] For some years, we have been interested in the search of new methodologies to prepare fluorinated organic molecules;[2] among the recent studies developed in our laboratories, we have shown that a series of aromatic and heterocyclic-CF_2X (X: Br, Cl) substrates could be successfully engaged in anionic[3] and radical coupling reactions.[4] Some of the compounds were found to exhibit some interesting biological activities such as anti-HIV-1 agents.[5]

In a project devoted to the synthesis of new therapeutic agents, we needed a mild and quick approach for the synthesis of functionalized difluoromethylene β-aminovinyl ketones, as useful starting materials for further chemical elaboration. Mostly trifluoromethylated β-aminovinyl ketones are known, and are frequently used as building blocks for heterocyclic synthesis;[6,7] however, as far as we know, the reactivity of the C–Cl bond of the chlorodifluoromethylated aminovinyl ketones has been rarely investigated. Lang et al.[8] reported a Reformatsky reaction of 4-butoxy-1-chloro-1,1-difluorobut-3-en-2-one and benzaldehyde with activated zinc in DMF (70 °C, 2 h); the final product, a *gem*-difluoromethylene dihydropyrone was isolated in 46% yield and resulted from a spontaneous cyclization. However in the same solvent, with less vigorous conditions (40 °C, 16 h) a vinylogous amide and benzaldehyde gave a simple addition product in 60% yield (Scheme 1).



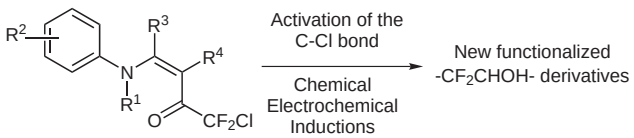
Scheme 1

It is noteworthy that Uneyama et al.[9] recently presented an elegant electron-transfer based methodology to prepare the difluorinated analog of Danishefsky's diene starting from 4-butoxy-1,1,1-trifluorobut-3-en-2-one; this approach was applied to the synthesis of *gem*-difluoromethylene dihydropyrone (and dihydropyridone) derivatives via hetero Diels–Alder reaction (Scheme 2).



Scheme 2

This paper describes our recent investigations in the chemical and electrochemical activation of the C–Cl bond of a series of chlorodifluoromethylated β-aminovinyl ketones in order to prepare, under very mild conditions, new $–CF_2CHOH–$ derivatives for our target-oriented program (Equation 1).



Equation 1

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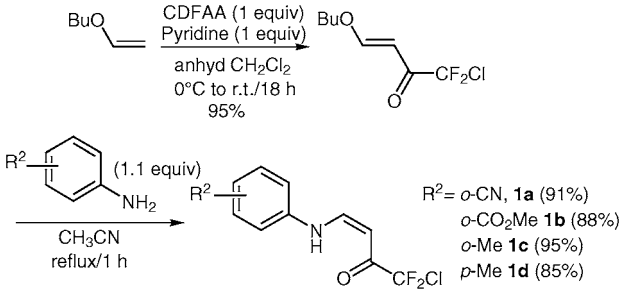
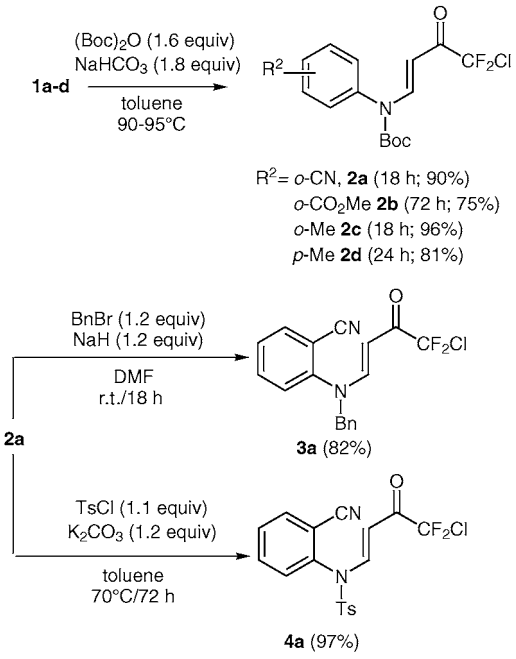
Starting materials of general structure **1**, were prepared in good yields in two steps, chlorodifluoroacetylation of commercially available butyl vinyl ether [chlorodifluoroacetic anhydride (CDFAA)/pyridine in anhyd CH_2Cl_2], followed by an O–N exchange reaction of the resulting crude 4-butoxy-1-chloro-1,1-difluorobut-3-en-2-one, with the corresponding aromatic amine in refluxing CH_3CN. Compounds **1a**–**d** were obtained as *Z* isomers as determined by ^1H NMR (Scheme 3).



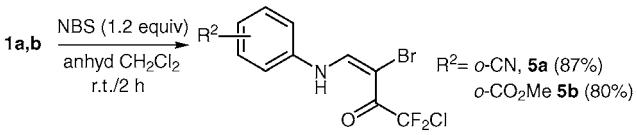
Scheme 3

Protection of the free NH of substrates **1** was achieved with $(Boc)_2O$ in good to excellent yields; benzylation and tosylation of substrate **1a** gave the corresponding protected substrates **3a** and **4a** in 82% and 97% isolated yields (Scheme 4).



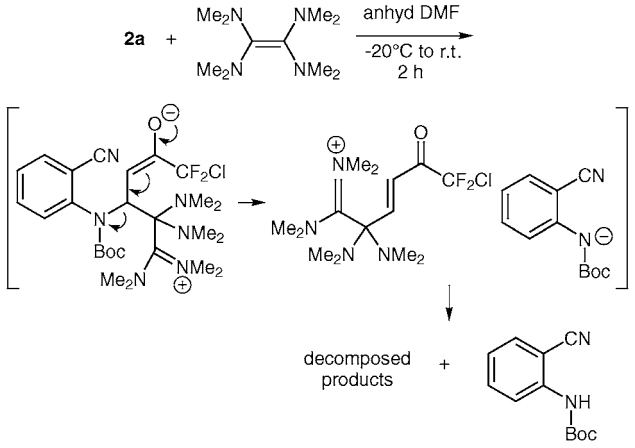
Scheme 4

To introduce further functionality at the olefinic site of starting materials **1**, bromination of compounds **1a** and **1b** was carried out. The corresponding mono-brominated materials **5a** and **5b** were obtained in good yields with 1.2 equivalent of NBS in anhydrous dichloromethane (Scheme 5).



Scheme 5

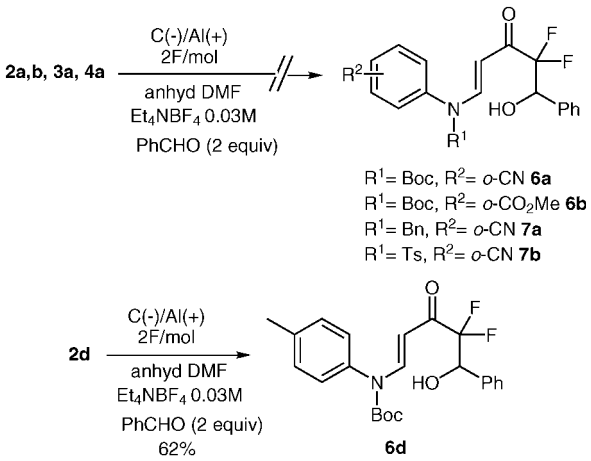
Since we have already developed some useful carbon-carbon bond forming reactions between aromatic and heterocyclic chlorodifluoromethylated ketones and unsaturated compounds, by utilizing tetrakis(dimethylamino)ethylene (TDAE)[3] as a synthetic electron-transfer reagent or electrochemical reduction, we intended to apply these electron-transfer induced approaches to the coupling reaction between **2a** and benzaldehyde. Careful examination, by cyclic voltammetry, of the reduction potential of starting materials **1a**–**d**, **2a**–**d**, **3a**, **4a** and **5a**, **5b** shown that these compounds were reduced at relatively low potentials close to –1.25 to –1.60 V vs SCE (first peaks potentials measured in DMF/NBu_4PF_6 0.1 M), with **5b** being the most difficult to reduce. These reduction steps correspond to the cleavage of the C–Cl bond and to the formation of the corresponding reduction product –$COCF_2H$– (by comparison with authentic samples). As substrate **2a** is a good electron-acceptor, we thought of using the TDAE as a mild and efficient organic reductant for the in situ generation and trapping of corresponding α,α-difluoroacetyl anion with benzaldehyde. However, TDAE did not afford any coupling product **6a** with benzaldehyde, but gave the corresponding Boc-protected anthranilonitrile through a plausible retro-Michael addition (Scheme 6).[10]



Scheme 6

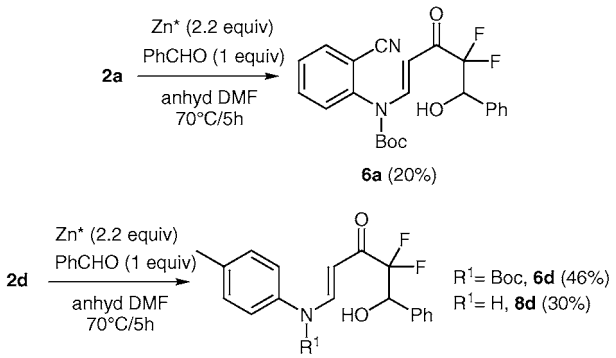
Electrochemical activation of substrates **2a**, **2b**, **3a**, and **4a** using an undivided cell (carbon felt cathode/aluminum anode)[11] at controlled potential electrolysis corresponding to the first peak potential measured by cyclic voltammetry (–1.25 V vs SCE for **2a**, –1.43 V vs SCE for **2b**, –1.26 V vs SCE for **3a**, –1.60 V vs SCE for **3b**) surprisingly didn't afford coupling product with benzaldehyde, and most of unreacted starting materials with some minor amount of reduction products were recovered, with a consumption of electricity close to 2F/mol. However substrate **2d** gave

under the same conditions (electrolysis potential of –1.42 V vs SCE corresponding to the first peak potential; 2F/mol) coupling product **6d** in 62% yield (Scheme 7).[11]



Scheme 7

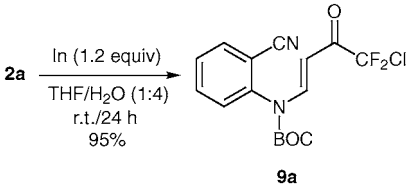
The Reformatsky reaction of halogenodifluoromethyl ketones with carbonyl compounds mediated by zinc[1] is one of the well-known synthetic methodologies to obtain the corresponding carbon-carbon bond coupling products. Using the conditions described by Lang et al.[8] with benzaldehyde as electrophile, starting material **2d** gave the corresponding coupling product **6d** and its deprotected form **8d** in the ratio of 3:2 (combined yield 76%). However with starting material **2a**, coupling product **6a** was only obtained in 20% yield (Scheme 8). In addition we found it difficult to get reproducible results, which may came from the purity of zinc as well as its mode of activation.



Scheme 8

In order to find an alternative and general approach for the formation of coupling products from the β-aminovinyl chlorodifluoromethyl ketones, we became aware of a recent publication by Welch et al.[12] who described the efficient coupling reactions of heteroaryl chlorodifluoromethylated ketones, mediated by indium, with various aldehydes. Indium closely resembles zinc in several aspects, and its first ionization potential (5.8 eV) is the lowest relative to other metal elements near it in the periodic table.[13] Its synthetic use in organo-fluorine chemistry is recent[14] and most of the work reported in the literature is related to allylation reactions of fluorinated compounds or indium-mediated cross-coupling reactions of a *gem*-difluoropropargyl starting material that generates a stable difluoroallenyl indium species.

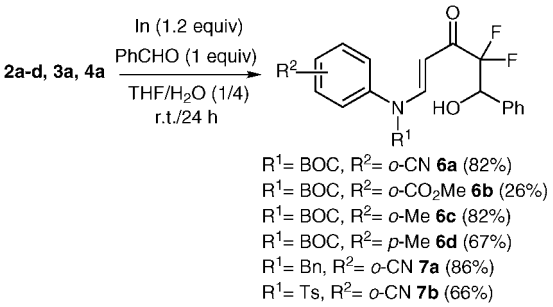
We first examined the possibility of reducing the C–Cl bond of starting material **2a** into the corresponding reduction product **9a**; as observed by Welch et al.,[12] we found that THF containing 80% water by volume resulted in clean reduction of **2a**, after 24 h of vigorous stirring (Scheme 9). In DMF containing water or anhydrous DMF, starting material was recovered.



Scheme 9

This result may indicate that indium has the characteristics as a suitable reagent for SET (single electron transfer) processes.

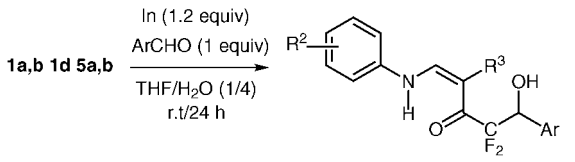
We therefore examined the coupling reaction of **2a** with benzaldehyde and found that the corresponding alcohol **6a** could be obtained in 82% yield after silica gel chromatography. Similarly protected compounds **3a** and **4a** gave the corresponding alcohols **7a** and **7b** in 86% and 66% yields, respectively. The Boc protected alcohol **6b**, with an *o*-CO_2Me substituent, was only obtained in 26% yield, because of the low solubility of starting material **2b** (73% recovered) in water. The reaction seems to be independent of substituents on the aromatic ring, as starting materials **2c** and **2d**, with methyl substituents at the *ortho* or *para* position afforded corresponding alcohols adducts **6c** and **6d** in 82% and 67% isolated yields. All the protected alcohols were obtained as *E* isomers (Scheme 10).



Scheme 10

More practically we also found that the unprotected free NH starting materials **1a**–**d** as well as **5a**, **5b** could also react successfully with benzaldehyde and other heteroaldehydes such as 2-furaldehyde, 3,4-dimethoxybenzaldehyde and *p*-dimethylamino *trans*-cinnamaldehyde to

give the corresponding alcohols **8** in 54–84% yields (Scheme 11). So far the reaction failed with other aldehydes such as 2- and 4-pyridine carboxaldehydes probably due to competitive binding of nitrogen atoms at the indium center, 5-nitrofurfuraldehyde because of competitive reduction of the nitro group into the corresponding amino group and *p*-trifluoromethylbenzaldehyde because of pinacol coupling product formation.



R^2= *o*-CN, R^3= H, Ar= Ph **8a$_1$** (80%)
R^2= *o*-CN, R^3= H, Ar= 2-furyl **8a$_2$** (84%)
R^2= *o*-CN, R^3= H, Ar= 3,4-dimethoxyphenyl **8a$_3$** (71%)
R^2= *o*-CN, R^3= H, Ar= *p*-$Me_2NC_6H_4CH$=CH **8a$_4$** (55%)
R^2= *o*-CO_2Me, R^3= H, Ar= Ph **8b$_1$** (86%)
R^2= *p*-Me, R^3= H, Ar= Ph **8d** (57%)
28% of **1d** was recovered
R^2= *o*-CN, R^3= Br, Ar= Ph **8a$_5$** (54%)
29% of **8a$_1$** was also obtained
R^2= *o*-CO_2Me, R^3= Br, Ar= Ph **8b$_2$** (76%)
24% of **8b$_1$** was also obtained

Scheme 11

In conclusion, we have demonstrated that indium was an efficient reagent for the coupling reactions of β-aminovinyl chlorodifluoromethylated ketones with a series of heteroaryl aldehydes. Although the mechanism of the reaction still remains to be elucidated, indium species (In, In^+ and/or In^{2+}) may act as an electron-transfer reagent to generate a reactive difluorinated enolate. This mild approach seems to be applicable to whatever substituent and its position on the aromatic ring; this is in sharp contrast with the electrochemical approach, which only worked with a substituent at the *para* position of the aromatic ring. We have still not yet clarified why the electrochemical approach did not work with substrates **6a,b** and **7a,b**. Is it a steric, or an electronic effect? We are currently working on the electrochemical coupling reaction of **2c** so as to compare it with the electrochemical/indium activation of protected **2a**–**d**. From a synthetic point of view we are currently extending the indium methodology to other substrates and electrophiles. The compounds described in this report are now utilized for further chemical elaboration to achieve the synthesis of a series of novel *gem*-difluoromethylene heterocycles of biological importance; these results will be presented in our forthcoming papers.

Solvents were distilled before use. Reagents were obtained commercially and used without further purification except for 3,4-dimethoxybenzaldehyde, which was recrystallized from petroleum ether (bp 45–60 °C). ^{1}H and ^{19}F NMR spectra were recorded in $CDCl_3$ at 300 MHz and 282 MHz, respectively. Chemical shifts are given in ppm relative to TMS (^{1}H) or $CFCl_3$ (^{19}F) as internal references. Coupling constants are given in hertz. Flash chromatography was performed on Merck Silica gel 60M (0.04–0.063 mm). Melting points (uncorrected) were determined in capillary tubes on a Büchi apparatus.

1a–d; General Procedure

To a stirred soln of butyl vinyl ether (2.0 g, 20 mmol) and pyridine (1.58 g, 20 mmol) in anhyd CH_2Cl_2 (20 mL) was added dropwise chlorodifluoroacetic anhydride (4.86 g, 20 mmol) with cooling (0 °C). When the addition was finished, the soln was stirred at 0 °C for 30 min and slowly warmed-up to r.t. and stirred at this temperature for 18 h. The yellowish solution was quenched with H_2O (20 mL), the organic phase separated and washed with an aq soln of 1 N HCl (20 mL) and dried over $MgSO_4$. Evaporation of the solvent left a viscous yellow oil, 4-butoxy-1-chloro-1,1-difluorobut-3-en-2-one (4.03 g, 19 mmol, 95%), which was used for the next step.

To a stirred soln of 4-butoxy-1-chloro-1,1-difluorobut-3-en-2-one (3.54 g, 16.6 mmol) in CH_3CN (20 mL) was added the appropriate substituted aniline (18.2 mmol) and the solution heated at reflux for 1 h (TLC monitoring). The solvent was removed under reduced pressure and the residue purified by recrystallization or flash chromatography to give pure compounds.

1a

Yield: 91%; recrystallized (petroleum ether–EtOAc, 1:2); pale yellow needles; mp 113–114 °C .

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.81 (d, *J* = 7.7 Hz, 1 H), 7.23 (dd, *J* = 7.6, 1.0 Hz, 1 H), 7.25–7.27 (m, 1 H), 7.31 (d, *J* = 8.1 Hz, 1 H), 7.60–7.73 (m, 3 H), 11.88 (br d, *J* = 10.2 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –66.18 (s, 2 F)

HRMS (CI): *m*/*z* calcd for $C_{11}H_8ClF_2N_2O$: 257.0293 (MH^+); found: 257.0298.

1b

Yield: 88%; recrystallized (petroleum ether–EtOAc, 1:10); yellow crystals; mp 83–84 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.03 (s, 3 H), 5.71 (d, *J* = 7.9 Hz, 1 H), 7.17 (td, *J* = 7.6, 1.0 Hz, 1 H), 7.35 (d, *J* = 8.5 Hz, 1 H), 7.57 (td, *J* = 7.9, 1.6 Hz, 1 H), 7.70 (dd, *J* = 13.0, 8.1 Hz, 1 H), 8.10 (dd, *J* = 7.9, 1.6 Hz, 1 H), 13.20 (br d, *J* = 11.3Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –65.73 (s, 2 F).

HRMS (CI): *m*/*z* calcd for $C_{12}H_{11}ClF_2NO_3$: 290.0395 (MH^+); found: 290.0390.

1c

Yield: 95%; recrystallized (petroleum ether–EtOAc, 1:10); brown crystals; mp 45–46 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 5.70 (d, *J* = 7.3Hz, 1 H), 7.09–7.29 (m, 4 H), 7.69–7.75 (dd, *J* = 12.8, 7.3 Hz, 1 H), 11.87 (br s, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –65.13 (s, 2 F).

HRMS (CI): *m*/*z* calcd for $C_{11}H_{11}ClF_2NO$: 246.0497 (MH^+); found: 246.0498.

1d

Yield: 85%; flash chromatography (petroleum ether–EtOAc, 1:10); yellow crystals; mp 70–71 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 5.62 (d, *J* = 7.5 Hz, 1 H), 7.03 (d, *J* = 8.5 Hz, 2 H), 7.19 (d, *J* = 8.3 Hz, 2 H), 7.63 (dd, *J* = 13.2, 7.5 Hz, 1 H), 11.72 (br d, *J* = 7.9 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –65.28 (s, 2 F).

HRMS (CI): *m*/*z* calcd for $C_{11}H_{11}ClF_2NO$: 246.0497 (MH^+); found: 246.0497.

2a–d; General Procedure

To a stirred soln of **1a**–**d** (4 mmol) in toluene (15 mL) containing $NaHCO_3$ (0.60 g, 7.2 mmol) was added $(Boc)_2O$ (1.40 g, 6.4 mmol)

and the soln heated at reflux until the starting material had been completely consumed (**1a**, 18 h; **1b**, 72 h; **1c**, 18 h; **1d**, 24 h). The solvent was removed under reduced pressure and the residue purified by recrystallization or flash chromatography to give pure compounds **2a**–**d**.

2a

Yield: 90%; recrystallized (petroleum ether–Et_2O, 1:1); pale yellow needles; mp 78–79 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 9 H), 5.20(d, *J* = 14.0 Hz, 1 H), 7.36 (d, *J* = 7.9 Hz, 1 H), 7.61 (t, *J* = 7.7 Hz, 1 H), 7.77 (d, *J* = 7.7 Hz, 1 H), 7.84 (t, *J* = 7.7 Hz, 1 H), 8.74 (d, *J* = 14.0 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = 67.39 (s, 2 F).

HRMS (CI): *m*/*z* calcd for $C_{16}H_{16}ClF_2N_2O_3$: 357.0818 (MH^+); found: 357.0817.

2b

Yield: 75%; flash chromatography (petroleum ether–EtOAc, 10:1); pale yellow crystals; mp 62–63 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 3.84 (s, 3 H), 5.13 (d, *J* = 13.7 Hz, 1 H), 7.22 (dd, *J* = 7.8, 0.8 Hz, 1 H), 7.56 (td, *J* = 7.5, 1.1 Hz, 1 H), 7.68 (td, *J* = 7.7, 1.6 Hz, 1 H), 8.15 (dd, *J* = 7.9, 1.5 Hz, 1 H), 8.76 (d, *J* = 13.7 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –67.00 (s, 2 F).

HRMS (CI): *m*/*z* calcd for $C_{17}H_{19}ClF_2NO_5$: 390.0920 (MH^+), found 390.0917.

2c

Yield: 96%; flash chromatography (petroleum ether–EtOAc, 25:1); oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 2.12 (s, 3 H), 5.15 (dd, *J* = 13.5, 1.1 Hz, 1 H), 7.05 (d, *J* = 7.1 Hz, 1 H), 7.32–7.37 (m, 3 H), 8.76 (d, *J* = 13.6 Hz, 1 H).

^{19}F NMR (282MHz, $CDCl_3$): δ = –67.13 (s, 2 F).

HRMS (CI): *m*/*z* calcd for $C_{16}H_{18}ClF_2NO_3$: 346.1022 (MH^+); found: 346.1020.

2d

Yield: 81%; flash chromatography (petroleum ether–EtOAc, 25:1); pale yellow solid; mp 80–81 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (s, 9 H), 2.43 (s, 3 H), 5.32 (d, *J* = 13.8 Hz, 1 H), 7.04 (d, *J* = 8.1 Hz, 2 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 8.77 (d, *J* = 13.7 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –67.12 (s, 2 F).

HRMS (CI): *m*/*z* calcd for $C_{16}H_{19}ClF_2NO_3$: 346.1022 (MH^+), found. 346.1023.

3a

To a stirred soln of **1a** (0.72 g, 2.8 mmol) in DMF (5 mL) was added 60% NaH (0.13 g, 3.37 mmol) with cooling (0 °C). The solution was further stirred at 0 °C for 30 min and then benzyl bromide (0.40 g, 3.37 mmol) was added dropwise. After complete addition, the solution was warmed up to r.t. and stirred at this temperature for 18 h. Solution was quenched with ice-water, extracted with EtOAc (2 × 15 mL), the combined organic phases washed with water (4 × 15 mL) and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure left a red-wine oil (1.40 g) as crude product, which crystallized on standing to gave **3a** as a mixture of 2 rotamers (0.80 g, 2.3 mmol, 82%); colorless pellets; mp 97–98 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.02 (br s, 2 H), 4.90 and 5.83 (2 br s, 1 H), 7.08 (br s, 1 H), 7.19–7.25 (m, 2 H), 7.32 and 7.34 (2 s, 3 H), 7.48 (br s, 1 H), 7.62 (td, *J* = 7.8, 1.6 Hz, 1 H), 7.77 (br s, 1 H), 8.05 and 8.19 (2 br s, 1 H).

^{19}F NMR (282MHz, $CDCl_3$): δ = –66.48 and –66.29 (2 s, 2 F).

HRMS (CI): *m*/*z* calcd for $C_{18}H_{14}ClF_2N_2O$: 347.0763 (MH^+); found: 347.0771.

4a

To a stirred soln of **1a** (1.28 g, 5 mmol) and TsCl (1.05 g, 5.5 mmol) in toluene (10 mL) was added K_2CO_3 (0.83 g, 6 mmol) and the mixture heated at 70 °C for 72 h until **1a** had been completely consumed. The soln was quenched with water, extracted with EtOAc (2 × 15 mL), the combined organic phases washed with water (4 × 15 mL) and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure left a brown oil (2.51 g) as crude product, which was purified by flash chromatography (petroleum ether–EtOAc, 2:1) **4a** (2.0 g, 4.86 mmol, 97%); yellow crystals; mp 103–105 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3 H), 5.09 (d, *J* = 13.6 Hz, 1 H), 7.31 (d, *J* = 7.9 Hz, 1 H), 7.36 (d, *J* = 8.3 Hz, 2 H), 7.60 (d, *J* = 8.5 Hz, 2 H), 7.67 (d, *J* = 7.7 Hz, 1 H), 7.76 (d, *J* = 7.5 Hz, 2 H), 8.66 (d, *J* = 13.6 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –64.60 (s, 2 F).

HRMS (CI): *m*/*z* calcd for $C_{18}H_{14}ClF_2N_2O_3S$: 411.0382 (MH^+); found: 411.0384.

5a, 5b; General Procedure

To a stirred soln of **1a** or **1b** (3 mmol) in CH_2Cl_2 (15 mL) was added *N*-bromosuccinimide (0.65 g, 3.6 mmol) and the mixture stirred at r.t. until the starting material had been completely consumed. The solution was quenched with an aq soln of $Na_2S_2O_3$ (15 mL), the organic layer separated and washed with water (3 × 15 mL) and dried over Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure left a yellow solid (1.05 g) as crude product, which was recrystallized to give pure product.

5a

Yield: 87%; recrystallized (petroleum ether–EtOAc, 4:1); pale yellow crystals; mp 117–118 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (t, *J* = 7.5 Hz, 2 H), 7.64–7.72 (m, 2 H), 7.98 (br d, *J* = 12.8 Hz, 1 H), 8.42 (d, *J* = 12.8 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –57.67 (s, 2 F).

HRMS (CI): *m*/*z* calcd for $C_{11}H_7BrClF_2N_2O$: 334.9398 (MH^+); found: 334.9397.

5b

Yield 80%; recrystallized (petroleum ether–EtOAc, 10:1); pale yellow crystals; mp 84–85 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.00 (s, 3 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 7.28 (d, *J* = 7.6 Hz, 1 H), 7.62 (td, *J* = 7.9 Hz, 1 H), 8.11 (dd, *J* = 8.0, 1.4 Hz, 1 H), 8.58 (d, *J* = 13.2 Hz, 1 H), 11.41 (br d, *J* = 12.5 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –56.95 (s, 2 F).

HRMS (CI): *m*/*z* calcd for $C_{12}H_{10}BrClF_2NO_3$: 367.9501 (MH^+); found: 367.9502.

Electrolysis Coupling Reactions; General Procedure

The reaction was conducted in an undivided cylindrical Pyrex cell, fitted with a carbon felt cathode (S = 15 cm^2) and an aluminium rod as anode under nitrogen. Starting material (0.5 mmol) was added to a soln of anhyd DMF (40 mL) containing Et_4NBF_4 (0.26 g, 1.12 mmol). The electrolysis was performed under a constant current (I = 0.01–0.018 A) until 2F/mol of electricity had passed. The solution was hydrolyzed with a sat. aq soln of NaCl (60 mL) and the or-

ganic portion was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with a sat. aq. soln of NaCl (3 × 60 mL), water (3 × 60 mL) and dried over anhyd Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure left a residue, which was purified by flash chromatography (petroleum ether–EtOAc) to give the pure product.

Indium Coupling Reactions; General Procedure

Under a nitrogen atmosphere, indium powder (1.2 mmol, 100 mesh) was added to a suspension of starting material (1 mmol) and aldehyde (1 mmol) in THF (1 mL) and H_2O (4 mL), and the mixture was vigorously stirred. After 24 h, the reaction was quenched with a soln of sat. aq NH_4Cl (20 mL). The organic portion was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhyd Na_2SO_4. Filtration and evaporation of the solvent under reduced pressure left a residue, which was purified by flash chromatography (petroleum ether–EtOAc) to give the pure product.

6a

Yield: 82%; oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 9 H), 2.91 (s, 1 H), 5.05–5.21 (m, 2 H), 7.13–7.38 (m, 7 H), 7.55 (td, *J* = 7.7, 1.1 Hz, 1 H), 7.70 (t, *J* = 7.3 Hz, 1 H), 7.89 (d, *J* = 7.5 Hz, 1 H), 8.61 (d, *J* = 14.0 Hz, 1 H).

^{19}F NMR (282MHz, $CDCl_3$): δ = –121.95 (dd, *J* = 269.2, 14.9 Hz, 1 F), –114.15 and –113.57 (2 dd, *J* = 270.7, 6.9 Hz, 1 F)

HRMS (CI): *m*/*z* calcd for $C_{23}H_{23}F_2N_2O_4$: 429.1626 (MH^+); found: 429.1624.

6b

Yield: 26%; oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 2.99 (br d, *J* = 17.7 Hz, 1 H), 3.82 (2 s, 3 H), 5.06–5.14 (m, 2 H), 7.09 (t, *J* = 4.7 Hz, 1 H), 7.30–7.40 (m, 5 H), 7.50 (t, *J* = 7.7 Hz, 1 H), 7.56–7.65 (m, 1 H), 8.11 (d, *J* = 7.7 Hz, 1 H), 8.67 (d, *J* = 13.7 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –122.14 and –121.70 (2 dd, *J* = 271.9, 15.2Hz, 1 F), –112.56 (d, *J* = 269.6 Hz, 1 F).

HRMS (CI): *m*/*z* calcd for $C_{23}H_{23}F_2N_2O_6$: 462. 1728 (MH^+); found: 462.1730.

6c

Yield 82%; oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 9 H), 2.01 and 2.04 (2 s, 3 H), 3.12 (d, *J* = 4.4 Hz, 1 H), 5.07–5.20 (m, 1 H), 5.13 (d, *J* = 13.8 Hz, 1 H), 6.94 (t, *J* = 7.7 Hz, 1 H), 7.21–7.40 (m, 8 H), 8.63 (d, *J* = 13.7 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –121.61 and –121.44 (2 dd, *J* = 270.7, 16.1 Hz, 1 F), –113.52 and –113.33 (2d, *J* = 270.7 Hz, 1 F).

HRMS (CI): *m*/*z* calcd for $C_{23}H_{26}F_2NO_4$: 418.1830 (MH^+); found: 418.1829.

6d

Yield: 67%; oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 2.39 (s, 3 H), 3.05 (br s, 1 H), 5.15 (ddd, *J* = 16.6, 7.2, 3.2 Hz, 1 H), 5.32 (d, *J* = 13.7 Hz, 1 H), 6.94 (d, *J* = 8.3 Hz, 2 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 7.33–7.43 (m, 5 H), 8.65 (d, *J* = 13.7 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –121.99 (dd, *J* = 271.9, 16.0 Hz, 1 F), –112.96 (dd, *J* = 271.9, 6.9 Hz, 1 F).

HRMS (CI): *m*/*z* calcd for $C_{23}H_{26}F_2NO_4$: 418.1830 (MH^+); found: 418.1825.

7a

Yield: 86%; pale yellow crystals; mp 128–129 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.89 (br s, 1 H), 4.86 (br s, 2 H), 5.10 and 5.83 (2 br s, 1 H), 5.16 (dd, *J* = 17.6, 7.4 Hz, 1 H), 6.90–7.45 (m, 12 H), 7.52 (td, *J* = 8.1, 1.3 Hz, 1 H), 7.67 (d, *J* = 7.5 Hz, 1 H), 8.06 (br s, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –121.63 (d, *J* = 268.4 Hz, 1 F), –113.07 (d, *J* = 265.0 Hz, 1 F).

HRMS (CI): *m*/*z* calcd for $C_{25}H_{21}F_2N_2O_2$: 419.1571 (MH^+); found: 419.1572.

7b

Yield: 66%; recrystallized (Et_2O); white crystals; mp 73–74 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.48 (s, 3 H), 2.93 (br s, 1 H), 5.09 (d, *J* = 13.7 Hz, 1 H), 5.12 (br dd, *J* = 16.0, 6.0 Hz, 1 H), 7.18 (br t, *J* = 1.1 Hz, 1 H), 7.28–7.41 (m, 7 H), 7.61 (d, *J* = 8.3 Hz, 2 H), 7.63–7.75 (m, 3 H), 8.55 (d, *J* = 13.7 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –122.64 and –122.51 (2 dd, *J* = 268.4, 16.1 Hz, 1 F), –113.39 and –113.03 (2 dd, *J* = 267.3, 5.7 Hz, 1 F).

HRMS (CI): *m*/*z* calcd for $C_{25}H_{21}F_2N_2O_4S$: 483.1190 (MH^+), found: 483.1189.

8a$_1$

Yield: 80%; recrystallized (petroleum ether–EtOAc, 2:1); pale yellow crystals; mp 152–153 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.08 (d, *J* = 4.7 Hz, 1 H), 5.31 (ddd, *J* = 17.8, 6.3, 4.7 Hz, 1 H), 5.83 (dd, *J* = 7.9, 1.1 Hz, 1 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.28 (d, *J* = 8.5 Hz, 2 H), 7.35–7.42 (m, 3 H), 7.45–7.51 (m, 2 H), 7.52 (dd, *J* = 12.0 and 4.1 Hz, 1 H), 7.59 (d, *J* = 9.2 Hz, 1 H), 7.65 (dd, *J* = 7.7, 1.3 Hz, 1 H), 12.15 (br d, *J* = 11.7 Hz, 1 H).

^{19}F NMR (282MHz, $CDCl_3$): δ = –122.58 (dd, *J* = 269.6, 17.8 Hz, 1 F), –111.96 (dd, *J* = 269.6, 6.3 Hz, 1 F).

HRMS (CI): *m*/*z* calcd for $C_{18}H_{15}F_2N_2O_2$: 329.1101 (MH^+); found: 329.1110.

8a$_2$

Yield 84%; white solid; mp 113–114 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.13 (s, 1 H), 5.33 (dd, *J* = 15.8, 7.1 Hz, 1 H), 5.90 (dd, *J* = 7.9, 2.1 Hz, 1 H), 6.40–6.44 (m, 1 H), 6.49 (d, *J* = 3.2 Hz, 1 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.30 (d, *J* = 8.4 Hz, 1 H), 7.44–7.46 (m, 1 H), 7.55–7.69 (m, 3 H), 12.13 (br d, *J* = 12.0 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –121.40 (dd, *J* = 270.7, 16.6 Hz, 1 F), –112.32 (dd, *J* = 269.6, 7.5 Hz, 1 F).

HRMS (CI): *m*/*z* calcd for $C_{16}H_{13}F_2N_2O_3$: 319.0894 (MH^+); found: 319.0895.

8a$_3$

Yield: 71%; yellow solid; mp 157–158 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.03 (br s, 1 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 5.25 (dd, *J* = 16.4, 7.8 Hz, 1 H), 5.82 (d, *J* = 7.5 Hz, 1 H), 6.86 (d, *J* = 8.1 Hz, 1 H), 6.98–7.03 (m, 2 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 7.48–7.68 (m, 3 H), 12.16 (br d, *J* = 12.0 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –122.06 (dd, *J* = 266.1, 16.6 Hz, 1 F), –113.24 (dd, *J* = 266.1, 6.9 Hz, 1 F).

HRMS (CI): *m*/*z* calcd for $C_{20}H_{19}F_2N_2O_4$: 389.1313 (MH^+); found: 389.1313.

$8a_4$
Yield: 55%; brown solid; mp 150–152 °C.

^{1}H NMR (300MHz, $CDCl_3$): δ = 2.90 (br s, 1 H), 2.96 (s, 6 H), 4.76–4.86 (m, 1 H), 5.93 (d, *J* = 7.1 Hz, 1 H), 6.05 (dd, *J* = 15.9, 7.0 Hz, 1 H), 6.65–6.75 (m, 3 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 7.26–7.35 (m, 3 H), 7.55–7.67 (m, 3 H), 12.10 (br d, *J* = 12.0 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –121.75 (dd, *J* = 265.6, 14.3 Hz, 1 F), –113.92 (dd, *J* = 265.0, 8.0 Hz, 1 F).

HRMS (CI): *m*/*z* calcd for $C_{22}H_{22}F_2N_3O_2$: 398.1680 (MH^+); found: 398.1683.

$8a_5$
Yield: 54%; oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.44 (br s, 1 H), 5.32 (dd, *J* = 18.5, 4.7 Hz, 1 H), 7.13 (d, *J* = 8.3 Hz, 2 H), 7.22 (td, *J* = 7.7, 0.8 Hz, 1 H), 7.34–7.52 (m, 5 H), 7.56–7.66 (m, 2 H), 7.92 (br d, *J* = 12.8 Hz, 1 H), 8.37 (d, *J* = 13.0 Hz, 1 H).

^{19}F NMR (282MHz, $CDCl_3$): δ = –113.36 (dd, *J* = 278.8, 18.4 Hz, 1 F), –101.26 (dd, *J* = 278.8, 5.7 Hz, 1 F).

HRMS (CI): *m*/*z* calcd for $C_{18}H_{14}BrF_2N_2O_2$: 407.0207 (MH^+); found: 407.0204.

$8b_1$
Yield: 86%; yellow crystals; mp 151–152 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, *J* = 7.0 Hz, 3 H), 3.61 (s, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 5.30 (dd, *J* = 17.4, 4.1 Hz, 1 H), 5.35 (s, 1 H), 7.20–7.30 (m, 1 H), 7.33–7.41 (m, 3 H), 7.48–7.51 (m, 2 H), 7.56–7.59 (m, 2 H), 7.67 (d, *J* = 7.7 Hz, 1 H), 12.71 (s, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –121.60 (dd, *J* = 261.5, 16.1 Hz, 1 F), –111.93 (dd, *J* = 262.7, 6.9 Hz, 1 F).

HRMS (CI): *m*/*z* calcd for $C_{19}H_{18}F_2NO_4$: 373.1364 (MH^+); found: 373.1361.

$8b_2$
Yield: 76%; white solid; mp 160–162 °C.

^{1}H NMR (300MHz, $CDCl_3$): δ = 3.49 (d, *J* = 3.8 Hz, 1 H), 3.99 (s, 3 H), 5.36 (dt, *J* = 20.0 and 4.1 Hz, 1 H), 7.12 (td, *J* = 7.5, 0.8 Hz, 2 H), 7.33–7.48 (m, 4 H), 7.49–7.57 (m, 3 H), 8.08 (dd, *J* = 7.9,1.3 Hz, 1 H), 8.56 (d, *J* = 13.2 Hz, 1 H), 11.33 (br d, *J* = 13.0 Hz, 1 H).
^{19}F NMR (282 MHz, $CDCl_3$): δ = –113.23 (dd, *J* = 282.8, 20.0 Hz, 1 F), –100.00 (dd, *J* = 282.8 and 4.0 Hz, 1 F).

HRMS (CI): *m*/*z* calcd for $C_{19}H_{17}BrF_2NO_4$: 440.0309 (MH^+); found: 440.0316.

8d
Yield: yellow solid; mp 157–158 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 3.38 (d, *J* = 4.7 Hz, 1 H), 5.15 (ddd, *J* = 16.1, 7.3, 4.7 Hz, 1 H), 5.62 (d, *J* = 7.5 Hz, 1 H), 7.01 (d, *J* = 8.3 Hz, 2 H), 7.18 (d, *J* = 8.3 Hz, 2 H), 7.32–7.40 (m, 3 H), 7.45–7.55 (m, 3 H), 11.92 (br d, *J* = 12.0 Hz, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –121.54 (dd, *J* = 265.0, 16.1 Hz, 1 F), –112.94 (dd, *J* = 263.9, 7.5 Hz, 1 F).

HRMS (CI): *m*/*z* calcd for $C_{18}H_{18}F_2NO_2$: 318.1306 (MH^+); found: 318.1309.

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