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Modular Construction of Fluoroarenes from a New Difluorinated Building Block by Cross-Coupling/Electrocyclisation/ Dehydrofluorination Reactions

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Abstract: Palladium-catalysed coupling reactions based on a novel and easy-to-synthesise difluorinated organotrifluoroborate were used to assemble precursors to 6π-electrocyclisations of three different types. Electrocyclisations took place at temperatures between 90 and 240 °C, depending on the central component of the π-system; nonaromatic trienes were most reactive, but even systems that required the temporary dearomatisation of two arenyl subunits underwent electrocyclisation, albeit at elevated temperatures. Photochemical conditions were effective for these more demanding reactions. The package of methods delivered a structurally diverse set of fluorinated arenes, spanning a 20 kcal mol^{-1} range of reactivity, by a flexible route.

Introduction

Fluoroarenes are of considerable interest and utility in the fields of agrochemical and pharmaceutical discovery and development chemistry;[1] advances in positron emission tomography (PET)[2] have added to this level of interest. While traditional methods like direct fluorination, the Balz–Schiemann reaction, and the Halex reaction have been used extensively,[3] and new functional-group transformations have been developed,[4] metal-catalysed transformations are gaining in impact and popularity.[5] Copper-,[6] iron-,[7] nickel-,[8] palladium-[9] and silver-based[10] methods are all known. These novel metal-based and catalytic methods complement the older (and usually harsher) methods well; all involve assembly of the arene or heteroarene scaffold, complete with the appropriate precursor functionality, before fluorination takes place. For simple arenes, these novel methods are hard to beat; however, not all precursor types are readily available. A strategically different approach to fluoroarene synthesis could start from nonfluorinated species like indanones by carbene transfer and rearrangement,[11] or from readily available fluorinated building blocks like fluoroenynes,[12] fluorinated dienophiles[13] or most recently, and very effectively, from difluoroalkenes[14] by electrophilic cyclisation or Ni-catalysed [2+2+2]-cycloaddition. Acetal **1** and carbamate **2** (Figure 1), which are readily-prepared from trifluoroethanol,[15] can be converted to organozinc halides **3** and **4**, which can be deployed in Negishi coupling reactions[16] with aryl halides. Iodides **5** and **6** underwent Suzuki–Miyaura couplings with a wide range of Molander borates,[17] while Katz and co-workers[18] have shown how acetal **1** can be converted to Molander borate **7**.

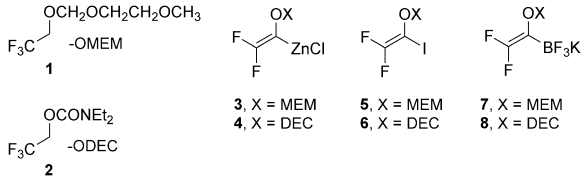

Figure 1. Fluorinated building blocks derived from trifluoroethanol from the literature (**1**–**7**) and proposed in this work (**8**).

It follows that a range of methods that allow sp^2–sp^2 couplings involving difluoroalkenol units are available. While the preparation of building block **7** requires a low-temperature reaction, it can be stored and deployed under conditions that are less expensive to achieve and maintain, which would make unknown **8** an attractive species.

The route proposed in this manuscript (Scheme 1) sought to exploit the 6π-disrotatory thermal electrocyclic interconversion between hexatriene **9** and cyclohexadiene **10**. Dehydrofluorination of the difluorinated cyclohexadiene product would be assisted by the development of aromaticity in **11**, and would therefore be expected to be facile.[19] Tandem electrocyclisa-

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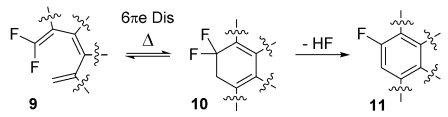
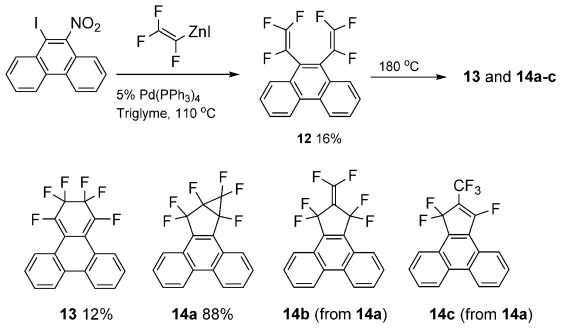


Scheme 1. The relationship between 1,1-difluorinated hexa-1,3Z,5-triene **9** and fluorobenzene **11** through tandem electrocyclisation/dehydrofluorination.

tion/oxidation strategies are well known and effective.[20] However, while sigmatropic rearrangements have been used extensively for the synthesis of selectively fluorinated molecules,[21] the hexatriene/cyclohexadiene electrocyclisation reaction has been used very lightly.[22] Dolbier and co-workers[23] reported an interesting attempted electrocyclisation of **12** (Scheme 2); free radical chemistry intervened and fluorinated cyclopentene products **14a–c** predominated, rather than the anticipated **13**. Dolbier also showed that terminal difluorination diverted the related Cope rearrangement through a boat transition state;[24] the electrocyclisation transition state has a similar geometry, in which two hydrogen atoms approach quite closely at opposite ends of the ring-closing bond (vide infra).



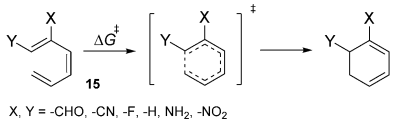
Scheme 2. Negishi coupling affords an electrocyclisation precursor but free radical chemistry accounts for the bulk of the reaction mixture.

When the atoms at one of the termini are fluorines, additional steric repulsion will arise, raising the reaction barrier. However, an sp^2 carbon bearing two fluorine atoms is rehybridising to sp^3 during the course of the reaction, which will help to lower the barrier; the effect is well-known in rearrangement chemistry, having been observed in Claisen[25] and oxy-Cope[26] rearrangements inter alia. If the two effects are at or close to balance, the electrocyclisations of the fluorinated systems should not be significantly disadvantaged relative to their desfluoro counterparts, and dehydrofluorination to a fluoroarene will provide a strong overall driving force. We therefore sought to develop a route to fluoroarenes based on as short a sequence of reactions as possible and using electronic structure calculations to guide us towards successful transformations and avoid nugatory synthetic effort.

Results and Discussion

Computational triage

Before carrying out any synthetic chemistry, we surveyed the range of methods used to study the hexatriene/cyclohexadiene electrocyclisation reaction through electronic structure calculations. While the early work by Houk and co-workers used the MP2/6-31G*//RHF/3-21G* level of theory,[27] Rodriguez–Otero recommended the energies obtained using the B3LYP functional and the 6-31G** basis as reasonably accurate[28] when compared to more computationally expensive methods.[29] More recently, Fu, Liu, and co-workers used a two-layer ONIOM method ((QCISD-(T)/6-31 + G(d,p))/B3LYP/6-311 + G(2df,2p))) to study captodative effects on the electrocyclisation of **15** (Scheme 3) and predict accurate free energies of activation.[30] We wished to anticipate the feasibility of the electrocyclisation of larger systems so the cost of the calculations needed to be kept to a minimum. The level of accuracy sought was only around ± 2 kcal mol^{-1}; we were interested in a level of accuracy that would predict rate changes of approximately tenfold (we are considering a default $\Delta G^{\ddagger}$ of 30 kcal mol^{-1} at 100 °C). We investigated the level of agreement between Rodriguez-Otero's low-cost method and the ONIOM method by optimising transition structures and hexatriene ground states for a set of 1-substituted, 2-substituted, and 1,2-disubstituted hexatrienes using Spartan'08.[31]



Scheme 3. Electrocyclisation systems studied using the ONIOM ((QCISD-(T)/6-31 + G(d,p))/ B3LYP/6-311 + G(2df,2p)) and B3LYP/6-31G** methods.

Figure 2 plots the data and shows an acceptable level of agreement between the two sets of values with the largest differences around 1.5 kcal mol^{-1}, and most points falling within the ± 1 kcal mol^{-1} error bars of the line.

The prototypical electrocyclisation system is represented by the transition state from **16a** (**16aTS**, optimised at the B3LYP/6-31G** level of theory), the H···H interatomic distance measured from the transition structure is 1.86 Å, which is short compared to the sum of the van der Waals radii at 2.4 Å (Figure 3). In the fluorinated system **16bTS**, the H···F interatomic distance is 1.93 Å, which is proportionally shorter still compared to the sum of the van der Waals radii at 2.71 Å, but the calculated barrier heights ($\Delta G^{\ddagger}$) are very similar (31.0 and 31.7 kcal mol^{-1}, respectively), with the former comparing well with the experimental value ($E_a = 29.9$ kcal mol^{-1}).

We concluded that a single difluorinated terminus would have only a very small negative or possibly no effect on the rate of electrocyclisation, and that the electrocyclisation could probably be carried out at convenient temperatures.

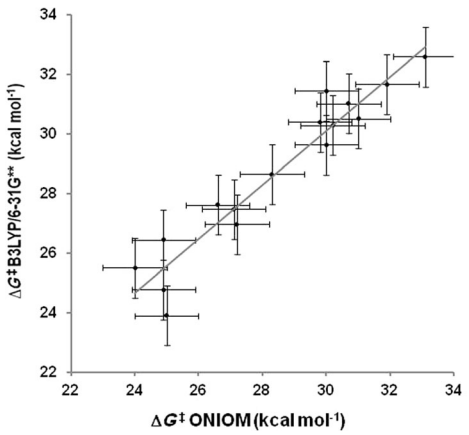


Figure 2. Correlation between $\Delta G^{\ddagger}$ calculated using the ONIOM method ((QCISD-(T)/6-31 + G(d,p))/B3LYP/6-311 + G(2df,2p)) and lower cost DFT method (B3LYP/6-31G** (298 K, gas phase)). Error bars are set at 1 kcal mol^{-1} (B3LYP values) and 1 kcal mol^{-1} (ONIOM values).

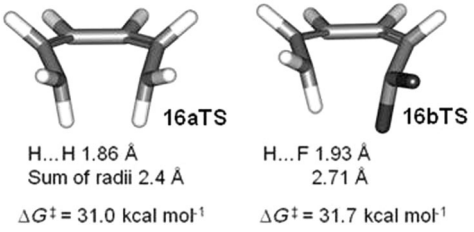


Figure 3. Optimised transition structures (B3LYP/6-31G**) for electrocyclisation from a) prototype hexa-1,3*Z*,5-triene **16a** and b) 1,1-difluoro-hexa-1,3*Z*,5-triene **16b**.

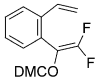
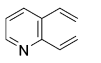
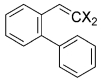
The system also accommodated the *N*,*N*-dimethylcarbamoyloxy group (–ODMC) without any energetic penalty. Table 1 lists the calculated free energies of activation for three prototypical electrocyclisation systems. Divinylbenzene system **17a** could be cyclised at slightly higher cost ($\Delta G^{\ddagger} = 37.7$ kcal mol^{-1}), with a similar barrier obtainined for the related pyridyl system **18** (38.6 kcal mol^{-1}). The barrier rose sharply (to 49.2 kcal mol^{-1}) for the biaryl system **19a** (lowered to 44.3 kcal mol^{-1} by the inclusion of two fluorine atoms in **19b**), while the inclusion of an heteroaryl ring in **20a** and **20b** instead of the phenyl, lowered the barrier by approximately 5 kcal mol^{-1}, consistent with the lower aromaticity of the thiophene and furan cores.[32] These findings suggested that quite a wide range of structures could be taken through the electrocyclisation, leading not only to substituted benzenes but also to fused-ring arenes and heteroarenes.[33] Synthetic chemistry was initiated to assemble precursors to electrocyclisation and to verify these predictions.

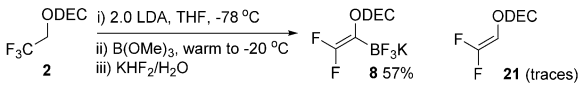
Synthetic chemistry

We sought to secure a proof-of-concept using precursors assembled from **8**. If successful, the reactions would produce HF, so we anticipated that enol acetal precursors made from **7** would not survive the electrocyclisation reaction conditions. Aryloxycarbamates are useful species in directed metallation reactions,[34] and as electrophilic partners in Ni-catalysed coupling[35] and amination[36] reactions, so products elaborated from **8** and containing the *N*,*N*-diethylcarbamoyloxy (–ODEC) group looked potentially valuable. We chose the Suzuki–Miyaura approach because our Negishi couplings were impaired by the presence of *ortho*-substituents on the aryl halide, whereas the couplings reported for **7** by Katz were tolerant of one or two methyl groups at the *ortho*-position. The ordering of the events was chosen so that the fluorinated material was taken through the smallest number of steps possible.

Borate **8** was prepared as a free-flowing crystalline solid in approximately 10 g quantities (57% yield) by intercepting the organolithium reagent derived from **2**[15b] with trimethylborate, followed by a fluoride workup, based on methodology described by Genêt and co-workers (Scheme 4).[37]

Table 1. Calculated (kcal mol^{-1}, B3LYP/6-31G**, 298 K) free energies of activation for electrocyclisation reactions of prototypical systems.

Substrate		$\Delta G^{\ddagger}$	Substrate		$\Delta G^{\ddagger}$
	**16a**	31.0		**17c**	34.4
	**16b**	31.7		**17d**	36.5
	**16c**	29.5		**18**	38.6
	**16d**	29.3		**19a** (X = H), **19b** (X = F)	49.2, 44.3
	**17a**	37.7		**20a**	46.3
	**17b**	35.7		**20b**	44.7



Scheme 4. Preparation of difluorinated building block **8** (showing side product **21**). LDA = lithium diisopropylamide.

Examination of crude reaction solutions revealed the presence of **8** alone, with only trace amounts of alkene **21** as the sole side product. Single crystals were grown for analysis by X-ray crystallography (Figure 4), revealing an interesting structure based on a corrugated 2D coordination polymer (see the Supporting Information for a fuller description).

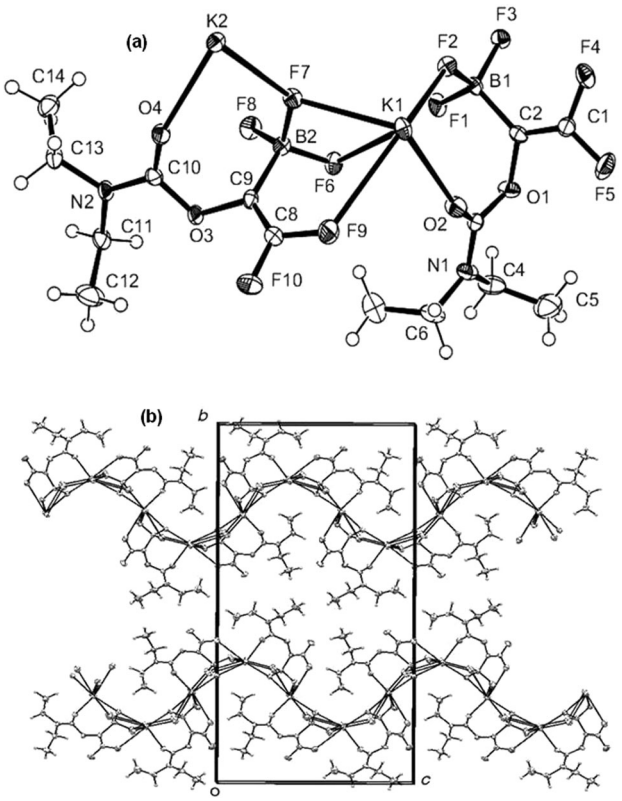
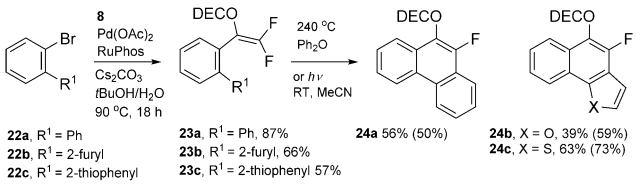


Figure 4. a) Contents of the asymmetric unit of **8** with non-H atoms drawn with 50% probability ellipsoids; b) packing diagram of **8** viewed along the crystallographic *a* direction.

Katz and co-workers used a combination of $PdCl_2$ pre-catalyst and the bulky and electron-rich RuPhos ligand (with triethylamine in n-propanol) to couple **7** to a range of aryl bromides. Molander and co-workers used a closely related set of conditions for cross-coupling between heteroaryl trifluoroborates, and aryl and heteroaryl halides.[38] The transmetallation step is usually thought to be rate-determining in Suzuki–Miyaura coupling, with trifluoroborate hydrolysis to $RBF_n(OH)_{3-n}$ an important determinant of the effectiveness of that part of the cycle.[39] While Katz found that Cs_2CO_3 was not an effective base, it performed much better in our hands in the *t*BuOH/water mixture that we had found effective for the Suzuki–Miyaura couplings of iodide **6**. In some of the reactions carried out in this work, the use of less hindered alcohol solvents lead to nucleophilic additions to the coupling products. We were able to use $Pd(OAc)_2$ as the precatalyst, a modest excess of **8**, a slightly lower loading of ligand than in the Katz procedure, short reaction times, and vessels open to air in some cases while achieving full conversion of starting halide. Couplings proceeded more slowly under the conditions we reported for iodide **6** ($(Ph_3P)_2PdCl_2$, Cs_2CO_3, *t*BuOH/water, 90 °C), returning alkene **21** as a significant side product. Use of the *mono*(RuPhos)Pd^0 complex in Suzuki–Miyaura reactions would usually be expected to result in faster reactions than when the bis(triphenylphosphino)Pd^0 catalyst was used, though recent rigorous examinations of the role of dispersive interactions have questioned this simple dictum.[40] Commercial 2-bromobiphenyl **22a** was used to prepare the first substrate **23a** which was isolated in 87% yield by this method. Furyl and thiophenyl bromides **22b** and **22c** were prepared by Mioskowski's method[41] and coupled to afford **23b** and **23c** in good yields (66 and 57%, respectively, Scheme 5).



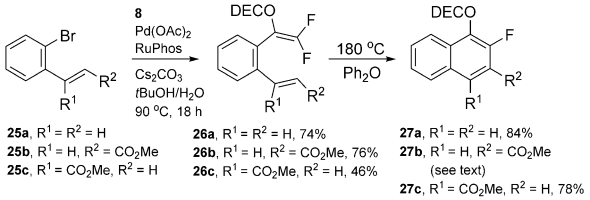
Scheme 5. Preparation and electrocyclisation/dehydrofluorination of first generation species; photochemical yields are shown in parentheses (%).

Slow reactions took place when the three species were heated at 240 °C in degassed Ph_2O; complete consumption of **23a** required 11 days and phenanthrene **24a** was isolated in moderate (56%) yield from a tarry mixture. Any reaction that produces HF clearly requires care; the electrocyclisation was carried out in a crimp-sealed microwave vial that was heated conventionally. At the end of the reaction, the vial cap was penetrated by a syringe needle fitted with a barrel containing KF and $CaCO_3$. Any volatile HF produced would then vent through a chemical scrub. The headspace was then blown out with nitrogen and aqueous KF solution was added to the vial before it was opened and worked up conventionally. We observed moderate levels of etching of the inside of reaction vessels; microwave vials used in this way were not reused for strongly heated reactions. With a calculated free energy of activation of nearly 50 kcal mol^{-1}, this reaction is the most demanding of those attempted in the manuscript; all of the systems prepared subsequently were significantly more reactive. Furyl species **23b** and thiophenyl analogue **23c** electrocyclised to **24b** (39%) and **24c** (63%) respectively, after shorter reaction times (6 days), consistent with the lower degrees of aromaticity in the heteroarenes (and the lower calculated barriers).

While we had secured a valuable proof-of-concept, the reaction times and conditions were far from attractive so we made a preliminary exploration of photochemical reaction conditions. Exposure of acetonitrile solutions of **23a–c** to a 254 nm/9 W source resulted in rapid (within 4 h) and full consumption

of the precursors, and conversion to **24a–c**, respectively. These reactions were carried out on small scales (0.06–0.08 mmole) in quartz NMR tubes or cuvettes placed close to the light source. The small-scale reactions (NMR tubes) afforded moderate to good yields of **24a** (50%), **24b** (59%) and **24c** (73%) after four hours. Photochemical electrocyclisations of 1,2-diarylethenes are known and are usually reversible;[42] the irreversible elimination of HF from our photoproducts commits the reactions. Seeberger and co-workers recently reported a (Mallory) photocycloaddition that was rendered irreversible by dehydrobromination of the photocycloadduct.[43]

Bromostyrenes **25a–c** were easy to make. The first system studied (**25a**) was prepared from *ortho*-bromobenzaldehyde by a Wittig methylenation following the method of Hibino.[44] The same aldehyde was taken through a Knoevenagel reaction,[45] then esterification[46] afforded alkenoate **25b**. The alkoxycarbonyl group was moved to the internal position in **25c**, prepared from the commercial phenylacetic acid that was esterified (99%)[47] and then condensed with formaldehyde (58%).[48] Suzuki–Miyaura couplings between **8** and **25a–c** using procedure A, delivered electrocyclisation precursors in moderate to good yields (Scheme 6).



Scheme 6. Preparation and electrocyclisation/dehydrofluorination of second-generation species.

For example, **26b** coupled reproducibly in good yield (76%) on 0.2–10 mmol scales; the coupling could even be carried out open to the air (though we routinely worked under nitrogen).

As the calculated free-energy barrier to electrocyclisation of **26a** was 26.5 kcal mol^{-1} and the effects of π-acceptor groups at the terminal (+1 kcal mol^{-1} for a cyano group) and internal position (−5 kcal mol^{-1} for a cyano group) of the parent hexatriene system were relatively small, we anticipated that all three substrates could be electrocyclised under roughly similar conditions. Precursor **26a** was not consumed completely after overnight heating at 130–170 °C; however, raising the temperature to 180 °C for 24 hours resulted in complete consumption of **26a** and the formation of naphthalene **27a** in 84% yield. Heating **26b** at 180 °C (in diphenyl ether) overnight resulted in full consumption of **26b** and the isolation of electrocyclisation product **27b** and indanone **28** (products that were only separable by preparative HPLC) in a 3:2 ratio (by ^{19}F NMR, ca. 40% overall). The indanone structure was established by correlation spectroscopy, by calculation of the NMR chemical shifts and by comparison of the measured ^{19}F NMR chemical shift with the limited number of related literature compounds.[49] We initially assumed that the structure of this product was tetralone **29** (Figure 5), which had failed to undergo dehydrofluorination.

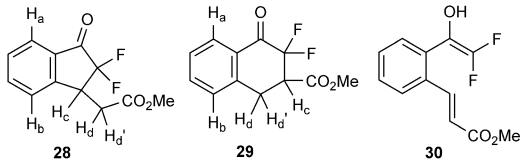


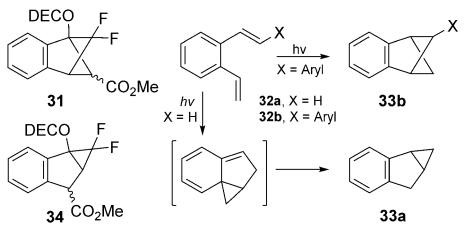
Figure 5. Indanone **28**, tetralone **29** and potential enol intermediate **30**.

Unambiguous assignment of protons H_a and H_b from the HMBC spectrum (the carbonyl carbon is a useful starting point) allows the assignment of critical cross peaks correlating C_b/H_b with the methine proton and carbon, and not with the methylene protons or carbon.

In **28**, a cross peak between H_b and C_c represents a $^3J_{C-H}$ coupling; in **29**, that cross peak would represent a $^4J_{C-H}$ coupling, which is much less likely. The HMBC spectrum recorded is therefore much more consistent with indanone **28** than with tetralone **29**. Further confidence in the structural assignment was built by calculation of the ^{13}C and ^{1}H NMR chemical shifts for **28** and **29** by using the EDF2/6-31G* method implemented in Spartan'08.[31] Much better correlations were obtained between calculated and experimental ^{13}C and ^{1}H NMR chemical shifts for **28** ($R^2 = 0.9963$ and 0.9940, respectively) than for **29** ($R^2 = 0.9873$ and 0.9393, respectively; see the Supporting Information for more details). Reactions at 200 and 220 °C resulted in complete consumption of **26b** and formed **27b** and **28** in a 1:1 ratio at both temperatures. The indanone could arise from direct 5-*exo* conjugate addition of an enol on the alkenoate. It is also possible that the enol carbamate could cleave to enol **30**, though this would require an equivalent of acid; however, HF becomes available once electrocyclisation has begun.

A most surprising outcome occurred when **26b** was exposed to the photochemical conditions. Neither **27b** nor **28** was the major product; instead, we isolated a novel difluorinated compound assigned bridged tricyclic structure **31** (35%; Scheme 7) on the basis of 2D NMR spectra, limited literature precedents[50] and calculated NMR chemical shifts (see the Supporting Information for full details of the assignment).

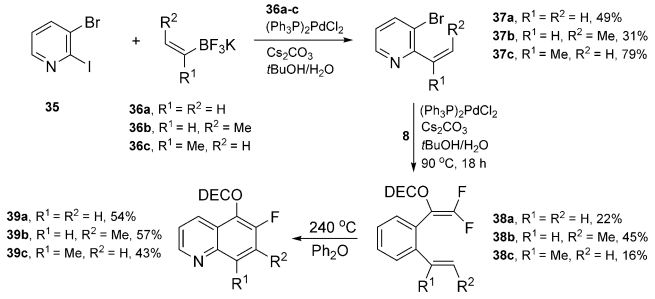
The benzobicyclo[2.1.1]hexane or methanoindene structure was first prepared by Pomerantz from the reaction of benzyne and bicyclobutane. Photolysis of divinylbenzene **32a**, studied independently by Pomerantz[51] and Meinwald and Mazzocchi[52] produces a different molecular core **33a** (after vinylcyclo-



Scheme 7. Novel photocycloadduct **31**, isomeric structure **34** and divinylbenzene photochemistry.

propane rearrangement of the initial photoadduct); the corresponding product from our system would be **34**. However, the inclusion of a phenyl[53] or heteroaryl[33b] group as in **32b** results in the formation of the bicyclo[2.1.1] skeleton **33b**. Given the unexpected complexity of these outcomes, and more positive results under thermal conditions, we pursued the latter exclusively for the rest of the study.

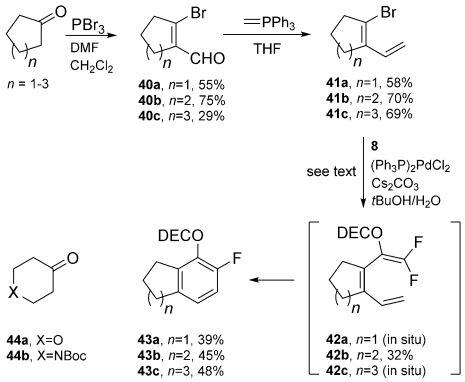
Suzuki–Miyaura reaction between **8** and **25c** afforded **26c** (45–60%); electrocyclisation/dehydrofluorination followed (180 °C, 24 h, Ph_2O) to afford **27c** in good (78%) yield. The competing conjugate addition in this case would be much less favourable than 5-*endo* cyclisation, so the electrocyclisation would be expected to win the competition. We had also attempted to prepare **25a** by selective monocoupling of *ortho*-iodobromobenzene with potassium vinyltrifluoroborate (**36a** from Scheme 8). While a good conversion of the aryl dihalide could be achieved, the reaction was capricious with significant run-to-run variation in the levels of inseparable side products. The Wittig-based methodology was significantly more reproducible and was therefore preferred (vide supra). Beaudry and co-workers[54] have recently reported on selective monocouplings of this type, suggesting that a vinyl group lowers the reactivity of an *ortho* C–Br bond towards oxidative addition by η^2-coordination to palladium, assisting selective monocoupling.



Scheme 8. Proof-of-concept quinoline construction through sequential Suzuki–Miyaura coupling.

However, the selective monocoupling approach was more successful from 2-iodo-3-bromopyridine **35**, which was prepared from commercial 2,3-dibromopyridine under literature conditions.[55] Selective couplings at C-2 of 2,3-disubstituted pyridines are known[56] and the preparation of the 2-iodo species was intended to accentuate the higher reactivity of this position. We used this approach to attempt to secure a proof-of-concept for quinoline construction. However, Langer and co-workers[57] had reported that two-fold Heck reaction/electrocyclisations based on 2,3-dihalopyridines were unsuccessful, so the precedent was discouraging. If our electrocyclisation/dehydrofluorination was successful, the possibility of dialing-in different alkenyl components through the Suzuki–Miyaura reaction made this an interesting system. The bis(triphenylphosphino)Pd^0 (procedure B) conditions were used to secure **37a–c** from **35** and the commercial trifluoroborates **36a–c** in poor to excellent (unoptimised) yields (Scheme 8). Couplings with **8** were carried out under the same conditions to afford **38a–c**. Though the yields for these reactions were disappointingly low, enough material was secured to test the key aromatisation step. We noted that while **37b** was isolated as a 10:1 mixture of alkene *Z* (major) and *E* (minor) diastereoisomers, **38b** was isolated as a 1:5 mixture of alkene *Z* (minor) and *E* (major) diastereoisomers on the basis of the (^3J) alkene proton couplings in the ^{1}H NMR spectrum. Because the yield for this step was 45%, *Z*/*E* isomerisation must have taken place during the coupling reaction. The electrocyclisations were carried out at 240 °C to afford the quinolines **39a–c**. While these represent relatively preliminary results (the couplings to **38a–c** clearly require optimisation), they do demonstrate proof-of-concept for the electrocyclisation/dehydrofluorination on the pyridine template, and the availability of monofluorinated quinolines by this route.

The electrocyclisations of all the substrates examined up to this point require temporary dearomatisation which adds to the activation energy; a triene without an aromatic core should react at significantly lower energetic cost (ca. 6 kcal mol^{-1} from the calculations) and therefore at much lower temperatures. Cyclohexanone was formylated under Vilsmeier conditions from the literature to afford enal **40b**,[58] followed by Wittig reaction to afford bromodiene **41b**, to test this idea.[59] Suzuki–Miyaura reaction (procedure B) with **8** at 50 °C afforded precursor **42b** (32%) and traces of arene **43b** (Scheme 9). The low yield arose from the isolation and purification of **42b**; a more efficient protocol was subsequently discovered.



Scheme 9. Fluoroarene construction from wholly nonaromatic precursors.

In these alkenyl halide cases, we found that the RuPhos ligand could be omitted without any reduction in reaction yields. Running the coupling of **41b** at 90 °C for a longer period (18 h) secured **43b** in one-pot in 45% yield (for the two steps). Lower and higher homologues **43a** (39%) and **43c** (48%) were also secured by this route directly from the dienyl bromides; the triene precursors were not isolated for the homologues, but cyclised in situ at 90 °C under coupling conditions to afford the arenes directly. The cycloalkene component is additionally beneficial because it locks the triene in a productive arrangement; without the ring, the triene would be expected to be prone to isomerisation into an unproductive *E*-linked species competitively with electrocyclisation. Unfortu-

nately, we were unable to take either pyranone **44a** or piperidone **44b** through the Vilsmeier chemistry successfully; formylated products could not be identified.

Conclusions

These sequences represent very concise proof-of-concept elaborations of commercial, or easy-to-synthesise and storable materials (**8**) into a structurally wide range of fluoroarenes. The overall yields over several steps are good in some cases and the temperatures required to carry out the key electrocyclisations are acceptable for laboratory applications. These findings show that this de novo strategy is practical, even when the precursor is a simple *ortho*-disubstituted benzene; rapid, clean and high-yielding photochemical conditions can be used to secure products in these cases. This methodology represents a significant expansion of the repertoire applicable to the synthesis of selectively fluorinated aromatic molecules, particularly fused-ring aromatic systems.

Experimental Section

General

NMR spectra were recorded on a Bruker DPX-400, AV-500 and Avance-II+ 600 spectrometers. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded using the deuterated solvent as the lock and the residual solvent as the internal reference. The multiplicities of the spectroscopic data are presented in the following manner: s = singlet, d = doublet, dd = double doublet, dt = doublet of triplets, dq = doublet of quartets, t = triplet, q = quartet, m = multiplet and br. = broad. Unless stated otherwise, all couplings refer to ^{3}J homocouplings. IR spectra were recorded on an ATR IR spectrometer. GCMS spectra were obtained on an instrument fitted with a DB5-type column (30 m × 0.25 μm) running a 40–320 °C temperature program, ramp rate 20 °C min^{-1} with helium carrier gas flow at 1 cm^{3} min^{-1}. Chemical ionisation (CI; methane) mass spectra were recorded on an Agilent Technologies 5975C mass spectrometer. HRMS measurements were obtained from a Waters GCT Premier MS (CI), Finnigan Mat 95 XP (EIMS and/or APCI-MS), or Thermo Scientific LTQ Orbitrap XL via Advion TriVersa NanoMate infusion (NSI-ES) spectrometers (EPSRC National Mass Spectrometry Service Centre, Swansea). Thin layer chromatography was performed on pre-coated aluminium-backed silica gel plates (E. Merck AG, Darmstadt, Germany. Silica gel 60 F254, thickness 0.2 mm). Visualisation was achieved using potassium permanganate or UV detection at 254 nm. Column chromatography was performed on silica gel (Zeochem, Zeoprep 60 HYD, 40–63 μm) using a Büchi Sepacore system. Hexane was distilled before chromatography. THF was dried using a PureSolv system from Innovative Technology, Inc. *tert*-Butanol/water (2.7:1 *v/v* mixture) and diphenyl ether were degassed by sparging with nitrogen through a finely drawn out pipette for 30 min before use. With the exception of **8**, potassium trifluoroborate salts were purchased from Sigma Aldrich and used as received. All other chemicals were purchased from Sigma Aldrich, Apollo Scientific, Alfa Aesar, or Fluorochem. 1-(*N*,*N*-Diethylcarbamoyloxy)-2,2,2-trifluoroethane was prepared according to the method of Howarth.[15b] Details of the electronic structure calculations are contained in the Supporting Information.

Potassium 2,2-difluoro-1-(*N*,*N*-diethylcarbamoyloxy)ethenyl trifluoroborate (8)

A solution of LDA (99 mL of a 1.91 M solution in THF/heptanes/ethyl benzene, 0.18 mol) was taken up in dry THF (75 mL) under N_2 and cooled to −78 °C. Carbamate **2** (16.85 mL, 95 mmol) was added dropwise over 20 min. The reaction mixture was stirred at −78 °C for 1.5 h. Trimethylborate (15.6 mL, 0.143 mol) was then added by syringe in one portion and stirring was continued at −78 °C for 1 h further. The colour of the reaction was light brown/dark orange over this time. The reaction mixture was allowed to warm to room temperature with stirring over 2 h, during which time the reaction colour continued to lighten to pale orange/dark yellow. The reaction mixture was then cooled to 0 °C and aqueous potassium hydrogen difluoride (44.3 g, 0.57 mol in water (164 mL)) was added in three roughly equal portions. The reaction mixture was stirred at room temperature overnight appearing as a lemon-coloured suspension the next morning. The solvent was removed as rigorously as possible under reduced pressure to reveal a mixture of fine white solid and viscous orange syrup. The syrup was then extracted with an acetone/methanol (4:1) mixture (3 × 100 mL). The extracts were then concentrated as rigorously as possible under reduced pressure until a small amount of precipitate was apparent; fuller precipitation was achieved by adding diethyl ether (30 mL), and swirling and scratching vigorously to afford free-flowing finely crystalline **8** (15.4 g, 57%). M.p. 152–154 °C (acetone); ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 3.23$ (q, $J = 7.1$ Hz, 4H), 1.05 ppm (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta =$ 157.7 (dd, $^{1}J_{C\text{-}F} = 298.3$, 277.0 Hz), 153.8, 115.8 (br s), 41.2, 13.4 ppm; ^{19}F NMR (376 MHz, [D$_6$]DMSO): $\delta = -91.6$ (d, $^{2}J = 63.8$ Hz, 1F), −109.2 (dq, $^{2}J = 63.8$, $^{4}J = 8.6$ Hz, 1F), −140.9–−141.7 ppm (m, 3F); IR (film): $\tilde{\nu} = 2978$, 1734, 1699, 1481, 1428, 1266, 1217, 1019, 983, 914 cm^{-1}; LRMS (EI): *m/z* (%): 246 [*M*−K]$^{-}$; HRMS (NSI): calcd for $C_7H_{10}BF_5NO_2$: 246.0725 [*M*−K]$^{-}$; found: 246.0724; Crystal data: $C_7H_{10}BF_5KNO_2$, crystal size = 0.30 × 0.22 × 0.02 mm^{3}, $M = 285.07$, monoclinic, $a = 4.9950(2)$, $b = 31.7122(15)$, $c = 14.7918(7)$ Å, $\alpha = 90$, $\beta = 91.740(4)$, $\gamma = 90°$, $U = 2341.98(18)$ Å^{3}, $T = 123(2)$ K, space group = $P21/c$, $Z = 8$, $\mu(Mo_{K\alpha}) = 0.507$ mm^{-1}, 11580 reflections measured, 5500 [R(int) = 0.0353], which were used in all calculations. Final R indices [$F^2 > \sigma(F^2)$] $R1 = 0.0498$, $wR2 = 0.0762$; R indices (all data) $R1 = 0.0819$, $wR2 = 0.0850$. Crystals were grown from acetone by slow evaporation.

2-(1′-*N*,*N*-Diethylcarbamoyloxy-2′-difluoroethenyl)biphenyl (23a); Suzuki–Miyaura coupling procedure A

A three-necked round-bottomed flask (50 mL) fitted with a reflux condenser and take-off head was charged with a mixture of trifluoroborate **8** (0.942 g, 3.3 mmol), caesium carbonate (2.94 g, 9 mmol), 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl (0.141 g, 0.3 mmol) and palladium acetate (33 mg, 0.15 mmol) through the wide centre neck. An oval-shaped stirrer bead (15 mm × 0.8 mm) was added and the necks were sealed with lightly-greased glass stoppers and the atmosphere was purged with nitrogen several times. A degassed mixture of *t*BuOH and water (17 mL of a 2.7:1 *v/v* mixture) was added by syringe, followed by 2-bromobiphenyl (0.52 mL, 3.0 mmol) against a positive pressure of nitrogen and heating and stirring were started immediately. The palladium salt dissolved at ca. 60 °C and the solution took on a warm golden colour which darkened to dark amber as it heated to 90 °C, reaching that temperature within 10 min of the start of heating. The mixture was heated overnight; TLC revealed the persistence of aryl bromide. Extending the time further and adding additional portions of **8** did not force the reaction to completion.

Cessation of the stirring revealed a colourless aqueous phase (which contained no chromophoric material) beneath a clear brown organic layer. The cooled mixture was diluted with water (30 mL) and dichloromethane (30 mL) and shaken vigorously. The layers were separated through an hydrophobic frit and the aqueous phase was re-extracted with dichloromethane (30 mL) and separated through an hydrophobic frit. The combined organic layers were concentrated under reduced pressure to afford a brown oil (1.4 g). The mixture was washed through a pad of silica gel (15 g) in a sinter funnel (40 mm diameter) with *n*-hexane (125 mL) to elute unreacted bromide, followed by diethyl ether/*n*-hexane (1:3; 125 mL) to elute **23 a** (0.862 g, 87%) as a clear oil; $R_f = 0.27$ diethyl ether/*n*-hexane (1:4); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.62–7.57$ (m, 1H), 7.49–7.31 (env., 8H), 3.19 (q, $J = 7.1$ Hz, 2H), 3.00 (q, $J = 7.1$ Hz, 2H), 1.61 (t, $J = 7.1$ Hz, 3H), 1.06 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 154.8$ (dd, $^1J_{C\text{-}F} = 291.0$, 284.1 Hz), 153.2, 141.7 (br. d, $^3J_{C\text{-}F} = 3.1$ Hz), 141.4, 130.10, 130.06, 129.7, 128.8, 128.4, 127.6, 127.4, 111.8 (dd, $^2J_{C\text{-}F} = 44.0$, 19.6 Hz), 41.6, 40.8, 13.3, 12.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -96.5$ (d, $^2J = 51.6$ Hz, 1F), -106.6 ppm (d, $^2J = 51.6$ Hz, 1F); (film): $\tilde{\nu} = 2978$, 1724, 1422, 1267, 1141, 983, 744, 703 cm^{-1}; UV/Vis (acetonitrile): λ_{max} (ε) = 206 (34 260), 229 nm (18 900 mol^{-1} dm^3 cm^{-1}); LRMS (CI): *m/z*: 360.1 (8) $[M+C_2H_5]^+$, 332.1 (30) $[M+H]^+$, 215.0 (75) $[M-OCONEt_2]^+$, 100.0 (100) $[CONEt_2]^+$; HRMS (NSI): *m/z*: calcd for $C_{19}H_{20}F_2NO_2^+$: 332.1457 $[M+H]^+$; found: 332.1456; GC (98%); $t_R = 14.70$ minutes.

2-(1′-*N*,*N*-Diethylcarbamoyloxy-2′-difluoroethenyl)biphenyl (23 a): Suzuki–Miyaura coupling procedure B

A mixture of trifluoroborate **8** (332 mg, 1.16 mmol), 2-bromobiphenyl **22 a** (232 mg, 1.0 mmol), caesium carbonate (978 mg, 3.0 mmol), and bis(triphenylphosphino)palladium dichloride (14 mg, 0.02 mmol) was taken up in a degassed mixture (6.5 mL) of *tert*-butanol and H_2O (2.7:1 *v/v*) in a Schlenk tube. The reaction mixture was stirred at 90 °C for 18 h, then cooled to room temperature and partitioned between dichloromethane (30 mL) and H_2O (30 mL). The organic phase was separated and dried by passing through a hydrophobic frit. The aqueous phase was extracted with dichloromethane (30 mL) and the extract was dried by passing through a hydrophobic frit. The organic phases were combined and the solvent was removed under reduced pressure. The ^{19}F NMR spectrum revealed a mixture of **21** and **23 a** (1:5) which was not purified further.

Phenanthrene 24 a; general electrocyclisation/dehydrofluorination procedure

Electrocyclisation precursor **23 a** (0.397 g, 1.2 mmol) was taken up in degassed diphenyl ether (12 mL); the solution was divided equally between four microwave vials. Each vial was sealed and heated with stirring for 264 h. The reaction solution was cooled to room temperature and each vial cap was pierced with a syringe needle attached to a syringe barrel containing a dry scrub (KF and $CaCO_3$). A stream of nitrogen was then passed through the headspace of each vial for 20 minutes, then KF (2 mL of a saturated aqueous solution) was added via syringe. The quenched reaction mixture was stirred for 10 min then each vial was opened and the solution extracted with dichloromethane (2×3 mL). The organic extracts were combined and passed through a hydrophobic frit and the solvent removed under reduced pressure to reveal a solution of crude product in diphenyl ether. The crude solution was purified by flash column chromatography on silica (100% *n*-hexane, then 20% diethyl ether in n-hexane) to afford fluoroarene **24 a** (0.209 g, 56%), which crystallised from pentane/dichloromethane) as blocks (m.p. 122–124 °C); $R_f = 0.27$ diethyl ether/*n*-hexane (1:4); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.71–8.68$ (m, 2H), 8.22–8.19 (m, 1H), 8.03–8.01 (m, 1H), 7.72–7.66 (m, 4H), 3.69 (q, $J = 7.0$ Hz, 2H), 3.52 (q, $J = 7.0$ Hz, 2H), 1.47 (t, $J = 7.0$ Hz, 3H), 1.32 ppm (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 153.2$, 148.0 (d, $^1J_{C\text{-}F} = 251.0$ Hz), 130.0 (d, $^2J_{C\text{-}F} = 12.0$ Hz), 129.5 (d, $J_{C\text{-}F} = 5.1$ Hz), 128.1 (d, $J_{C\text{-}F} = 4.3$ Hz), 127.4, 127.1, 126.2, 124.3 (d, $^2J_{C\text{-}F} = 16.4$ Hz), 122.9, 122.7 (d, $J_{C\text{-}F} = 2.9$ Hz), 121.8 (d, $J_{C\text{-}F} = 6.8$ Hz), 121.2 (d, $J_{C\text{-}F} = 6.5$ Hz), 42.7, 42.3, 14.4, 13.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -135.9$ ppm (s); IR (film): $\tilde{\nu} = 3070$-2860, 1716, 1651, 1454, 1424, 1340, 1247, 1256, 1152, 949, 770, 726, 754 cm^{-1}; UV/Vis (acetonitrile): λ_{max} (ε) = 250 (57 000), 295 nm (14 000 mol^{-1} dm^3 cm^{-1}); *m/z*: 340 (5%) $[M+C_2H_5]^+$, 312 (20) $[M+H]^+$, 100 (100) $[CONEt_2]^+$; GC (98%): t_R: 17.10 min; elemental analysis calcd (%) for $C_{19}H_{18}FNO_2$: C 73.30, H 5.83, N 4.50; found: C 73.02, H 5.63, N 4.33; Crystal data: $C_{19}H_{18}FNO_2$, crystal size = 0.35×0.32×0.20 mm^3, $M = 311.34$, monoclinic, $a = 9.1329(4)$, $b = 13.4075(5)$, $c = 12.8569(5)$ Å, $\alpha = 90$, $\beta = 91.015(4)$, $\gamma = 90°$, $U = 1574.07(11)$ Å^3, $T = 123(2)$ K, space group = $P21/n$, $Z = 4$, $\mu(Mo_{K\alpha}) = 0.093$ mm^{-1}, 6702 reflections measured, 3339 [R(int) = 0.0359] which were used in all calculations. Final R indices [$F^2 > \sigma(F^2)$] $R1 = 0.0481$, $wR2 = 0.1078$; R indices (all data): $R1 = 0.0795$, $wR2 = 0.1282$.

9-*N*,*N*-Diethylcarbamoyloxy-10-fluorophenanthrene 24 a; small scale photochemical procedure

Electrocyclisation precursor **23 a** (21 mg, 0.06 mmol) was taken up in [D3]acetonitrile (0.5 mL) and exposed to UV-C radiation (254 nm, 9W) in a quartz NMR tube for 4 h. Full conversion of **23 a** was confirmed by ^{19}F NMR. KF (2 mL of 1.0 M aqueous solution) was added to the tube via syringe and the tube contents were emptied. The organic solvent was removed from the quenched reaction mixture under reduced pressure, then the mixture was extracted with dichloromethane (3×5 mL). The organic extracts were combined and the phases were separated by passing through a hydrophobic frit. The solvent was removed under reduced pressure and the residue was taken up in methanol (3 mL). Silica (ca. 500 mg) was added and the solvent was removed under reduced pressure. The silica was loaded onto the top of a silica column and the purified product was obtained by flash column chromatography (10% diethyl ether in *n*-hexane) to afford phenanthrene **24 a** (10 mg, 0.03 mmol, 50%) as a colourless solid.

1-*N*,*N*-Diethylcarbamoyloxy-2-fluoro-5,6,7,8-tetrahydronaphthalene 43 b; one-pot bisphosphino coupling/electrocyclisation)

A mixture of trifluoroborate **8** (168 mg, 0.59 mmol), diene **41 b** (100 mg, 0.54 mmol), caesium carbonate (528 mg, 1.6 mmol) and bis(triphenylphosphino)palladium dichloride (8 mg, 0.01 mmol) was taken up in a degassed mixture (3.5 mL) of *tert*-butanol and H_2O (2.7:1 *v/v*) in a Schlenk tube. The reaction mixture was stirred at 90 °C for 18 h, then cooled to room temperature and partitioned between dichloromethane (15 mL) and H_2O (15 mL). The organic phase was separated and dried by passing through a hydrophobic frit. The aqueous phase was extracted with dichloromethane (15 mL) and the extract was dried by passing through a hydrophobic frit. The organic phases were combined and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (20% diethyl ether in *n*-hexane) to afford fluoroarene **43 b** (64 mg, 45%) as a colourless oil; $R_f = 0.10$ (20% diethyl ether in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.90–6.86$ (m, 2H), 3.51–3.35 (m, 4H), 2.78–2.62 (m, 4H), 1.82–1.73 (m, 4H), 1.34–1.18 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 152.7$ (d, $J_{C\text{-}F} =$

244.9 Hz), 153.0, 136.8 (d, $J_{C\text{-}F}=12.4$), 135.4 (d, $J_{C\text{-}F}=3.7$ Hz), 132.2, 126.2 (d, $J_{C\text{-}F}=7.1$ Hz), 112.9 (d, $J_{C\text{-}F}=18.6$ Hz), 42.4, 42.0, 28.8, 23.3 (d, $J_{C\text{-}F}=2.0$ Hz), 22.5, 22.1, 14.1, 13.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta=-134.5$ ppm (t, $J_{F\text{-}H}$, $^4J_{F\text{-}H}=7.5$ Hz); IR (film): $\tilde{\nu}=2933$, 2325, 1719, 1493, 1415, 1264, 1205, 1151, 1067, 937, 799, 755 cm^{-1}; LRMS (CI): *m/z*: 266 (100) $[M+H]^+$; HRMS (ESI): calcd for $C_{15}H_{21}FNO_2$ 266.1551 $[M+H]^+$; found: 266.1559; GC (97%) $t_R=14.62$ min.

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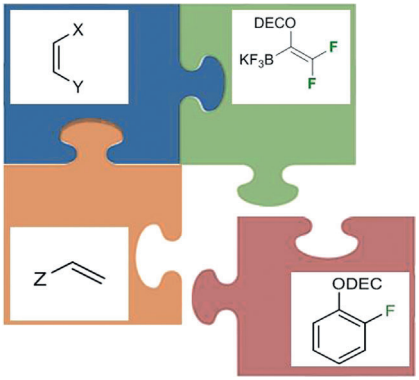
FULL PAPER

Electrocyclic reactions: Thermal and photochemical electrocyclisations combine with Suzuki–Miyaura couplings of a novel fluorinated building block to deliver a set of structurally diverse fluoroarenes, based on computational triage by a low-cost DFT method (see figure).



Palladium

J. M. Percy, H. Emerson, J. W. B. Fyfe, A. R. Kennedy, S. Maciuk, D. Orr, L. Rathouská, J. M. Redmond, P. G. Wilson*

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Modular Construction of Fluoroarenes from a New Difluorinated Building Block by Cross-Coupling/Electrocyclisation/Dehydrofluorination Reactions