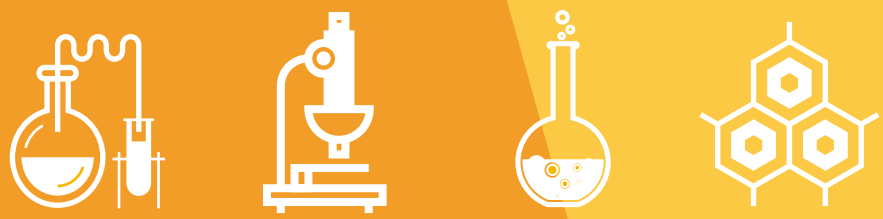
APOLLO LABS

Your Manufacturing Partner



APOLLO SCIENTIFIC
Supporting Discovery

Our Mission Statement:

To be the socially responsible partner of choice in the manufacture and supply of high quality research chemicals, supporting discovery across the global market.

Supporting You

We're specialists in the manufacture and supply of aromatic, heterocyclic and aliphatic compounds, fluorochemicals and life sciences reagents.

With unrivalled service and expertise in the sourcing and manufacture of available and novel products, we offer the support you need to take your project from concept to completion.

- We can free up your time and be an extension of your labs, where you can source novel building blocks, or outsource synthesis of raw materials and key intermediates.
- We can make the compounds you need for the research phase, and can develop within our group companies as the project and scale progresses.
- We can manufacture sets of compounds based around a particular series or product class.
- We can save your time allowing you to focus your resources on other areas of research or projects.
- Virtual pharma - allow us to be your labs.
- FTE or bespoke pricing / quotes - we can work to your business model.

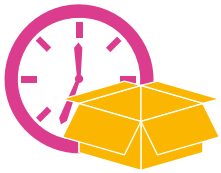
Send your enquiries through to sales@apolloscientific.co.uk

Apollo Labs

We are specialists in manufacturing small multifunctional and unusually substituted arenes and heterocycles. Currently we carry out reactions between -78 °C & +250 °C in conventional 50 mL to 20 L glass vessels under inert reaction conditions if required. As well as conventional batch synthesis, we operate a flow reactor system to assist with new reaction development and simple scale up of optimised reactions.

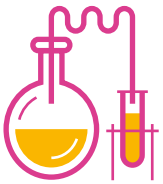
At Apollo, we are committed to delivering the best service as well as the highest quality products. We guarantee the quoted price, independent of the success of the initially planned synthetic route and regardless of whether more work is required to complete the synthesis successfully. Additionally, we explore alternative synthetic methods and purification procedures and can provide detailed options for scale-up synthesis in customer-tailored reports.

Key Benefits of Using Apollo Labs



Quick lead times, due to the large number of precursors we hold in stock, with a high on-time delivery rate

High % success rate on unproven chemistry



Small but subsequently very responsive and flexible team with experienced management

R&D/route development is a main focus of production, so we are well equipped to supply products not available on the market

Large background of experience from over 3,500 compounds previously made in-house

Full written reports / conferencing updates provided as required

Modern, well equipped labs, with GC, LCMS and NMR on site

Facility to utilise flow technology as well as batch production

Scale up can be done within parent group (process transfer)

Full confidentiality as required

Competitive quotes

Large number stock precursors

"We have an excellent track record of 93% on time delivery (100% within an additional week); combined with a 94% completion rate on all back orders over the last five years."

Environmental and Social Responsibility

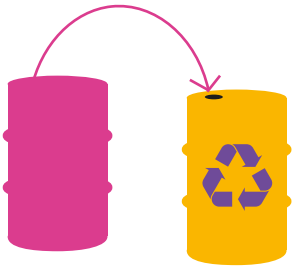
Apollo labs is committed to our social responsibility policy and actively seeks to minimise our environmental impact through:

Minimising solid waste, especially silica, by using prepacked cartridges with high concentration packing capacity

Using water coolers on reactions only for low boiling solvents <100 °C contributing to our lower water usage

Recycling solvents from re-crystallisations and flash column chromatography whenever possible

Reusing solvent / reagent mixtures on large repetitive projects when possible



Considering the use of Flow reactor on all projects to improve process safety, quicker reaction optimisation and more facile scale up which, in turn, results in reduced solvent and reagent usage

Changing reaction conditions to more environmentally benign reagents, e.g., heavy metal oxidants like $KMnO_4$ to Oxone®, or switching from stoichiometric to catalysed systems whenever possible

Recycling all heavy metal waste through dedicated, licenced company

A “water off” policy for rotary evaporators not in use, reducing our water consumption by 40% from the previous year.

Ratings and Accreditations

We have held ISO14001 accreditation since 2012 and in 2022 recieved our second EcoVadis platinum rating, putting us in the top 1% of companies assessed within the industry, for our sustainability practices. We’re also committed to becoming a net zero company by 2040 and have been net zero against our scope 1&2 emissions since 2021.

As your socially responsible partner of choice we are committed to ensuring sustainable growth through promoting environmentally sound practices giving you the reassurance that when you outsource through us we will maintain your green supply chain.

ECOVADIS PLATINUM STATUS

PLATINUM Top 1% 2022 ecovadis Sustainability Rating

UN GLOBAL COMPACT

WE SUPPORT UN GLOBAL COMPACT

ISO 14001: 2015

ISO 9001 ISOQAR REGISTERED alcumus.com

Certificate number:
6422-EMS-001
ISO 9001

ISO 9001: 2015

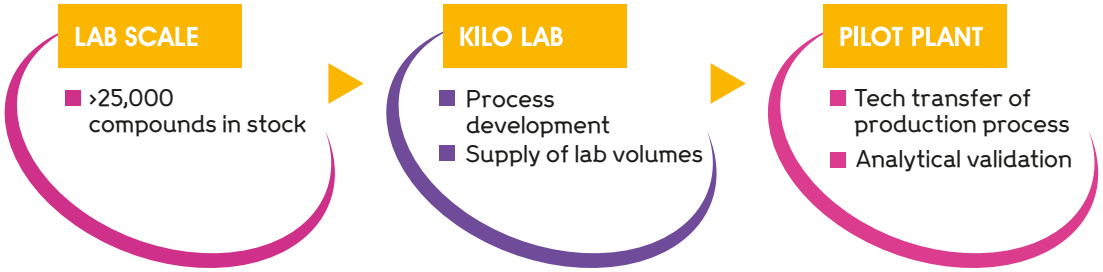
ISO 14001 ISOQAR REGISTERED alcumus.com

Certificate Number:
6422-EMS-001
ISO 14001

Learn more in our latest CSR report.

Supporting Your Business

HOW WE CAN SUPPORT YOUR PROJECT
FROM CONCEPT TO REALITY



- Located in Manchester, UK
- 17 fume hoods, including 4 walk-ins
- Team of 10 chemists
- Up to 20 L glass vessels
- 20 L rotary evaporator
- Flow reactor
- Biotage ® Isolera ™
- 2x LCMS, 1x GC
- Benchtop NMR
- Dedicated, independent QC facilities

Example Reaction Types

Classic Reactions:
- Halogenation
- Nitration
- Oxidation
- Reduction
- Sandmeyer
- S_NAr
- Heterocycle formation
- Hoffman rearrangement
- Amide coupling

Metallations:
- Halogen exchange (Grignard)
- Ortho-lithiation

Coupling Reactions:
- Suzuki
- Sonogashira
- Ullman
- Buchwald-Hartwig
- Chan-Lam

Fluorination:
- Halex-exchange
- Deoxyfluorination
- Trifluoromethylation
- Balz Schiemann
- Difluoromethylation

Reactions are carried out in glass vessels ranging from 50 ml to 20 L with a variety of heating mantles and Drysyn heating blocks, including multi-reaction blocks for rapid reaction screening. The scale of the reactions ranges from 25 g to 1 kg of starting material per batch, with an emphasis of 100 g - 500 g product. Larger orders will be combined to a homogenous mixture and sampled and tested by QC after blending.

We are specialists in manufacturing small, multifunctional and unusually substituted aromatic and heteroaromatic compounds, with over 70% of these containing fluorine. Typical reactions carried out within our labs to aid this goal are ortho-lithiations and metal / halogen exchange reactions with *n*BuLi or *i* PrMgCl, sandmeyer reactions, halogenation, nitration and a variety of functional group interconversion and substitution reactions (oxidation, reduction, F-displacement amongst others).

Palladium catalysed reactions (e.g. Sonogashira, Suzuki) and aminations (e.g. Chan - Lam and Buchwald - Hartwig aminations) also feature on a regular basis.

[1] Available from Asynt

Flow Technology

At Apollo we are always keen to invest in new technology and develop more efficient and economical processes within our manufacturing where possible. With this in mind, we have been quick to adopt bringing flow technology into the lab environment to further enhance our custom synthesis and catalogue compound offerings therefore complementing our strong track record of batch production.

Most recently we have expanded our range of equipment with a Vapourtec R4 Flow reactor system. In addition to the standard dual HPLC R2S pump module (for precise and steady addition of solutions) we also have included the R2C peristaltic pump module (to allow pumping of gasses and slurries) for maximum flexibility.

Our range of reactors currently comprises 5 different types:

- A standard 10 mm tube reactor
- A fixed solid bed reactor
- Two cooled tube reactors with split 2/8 mm and 5/5 mm inlets
- The UV-150 photochemistry kit with various filters.
- V-3 gas connection kit

To complete our current set-up, we have installed a Zaiput Flow Technologies™ BPR-10 precise backpressure regulator, and have the capability to extend the normal tube reactor manually with a selection of connectors and tubing to accommodate variable residence times.

Advantages of flow

- Faster reactions
- Easy scale-up

Economical:
- Reduced energy consumption
- Solvent reduction
- Higher yields/lower impurity levels

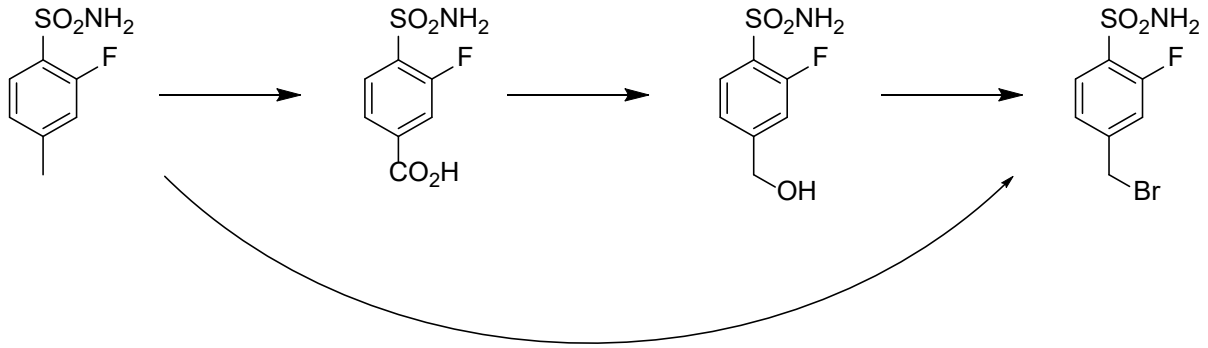
Safety:
- Efficient heat transfer of exothermic reactions
- Energetic intermediates are generated in small quantities in-situ

Reaction types:

- Photo-induced chemistry
- Low / medium pressure carbonylations and hydrogenations
- The use of highly reactive intermediates such as organic azides or in situ generated diazomethane

Case study: 4-(bromomethyl)-2-fluoro benzenesulphonamide:

Initial attempts to make the compound in a single-step bromination on a batch process only gave a very low conversion, so the following route was developed over three steps, with an overall yield of 18%, and used a heavy metal in the first step:



To meet a customer's requirement for kg quantities, we developed a light-induced bromination method on the flow reactor, resulting in a reduction of over 50% in the labour cost, an improvement in the yield to 81%, and we used this process to make over 5 kg of material. This route also had the added benefit of generating no heavy metal waste.

Quality Control

Apollo's QC lab is covered within the scope of our ISO 9001:2015 certification, with calibration records, and fully documented procedures, and provides assurance on quality for the entire range of chemicals in Apollo's inventory, as well as independent analysis and batch release of the materials made in-house. Impurity quantification and validated methods can be undertaken upon request.

Mettler Toledo MP80 melting point system

Nexis GC-2030 with FID detector

Shimadzu NexeraXR

Agilent Cary 630 FTIR

Metrohm 915 KF Ti Touch titrator

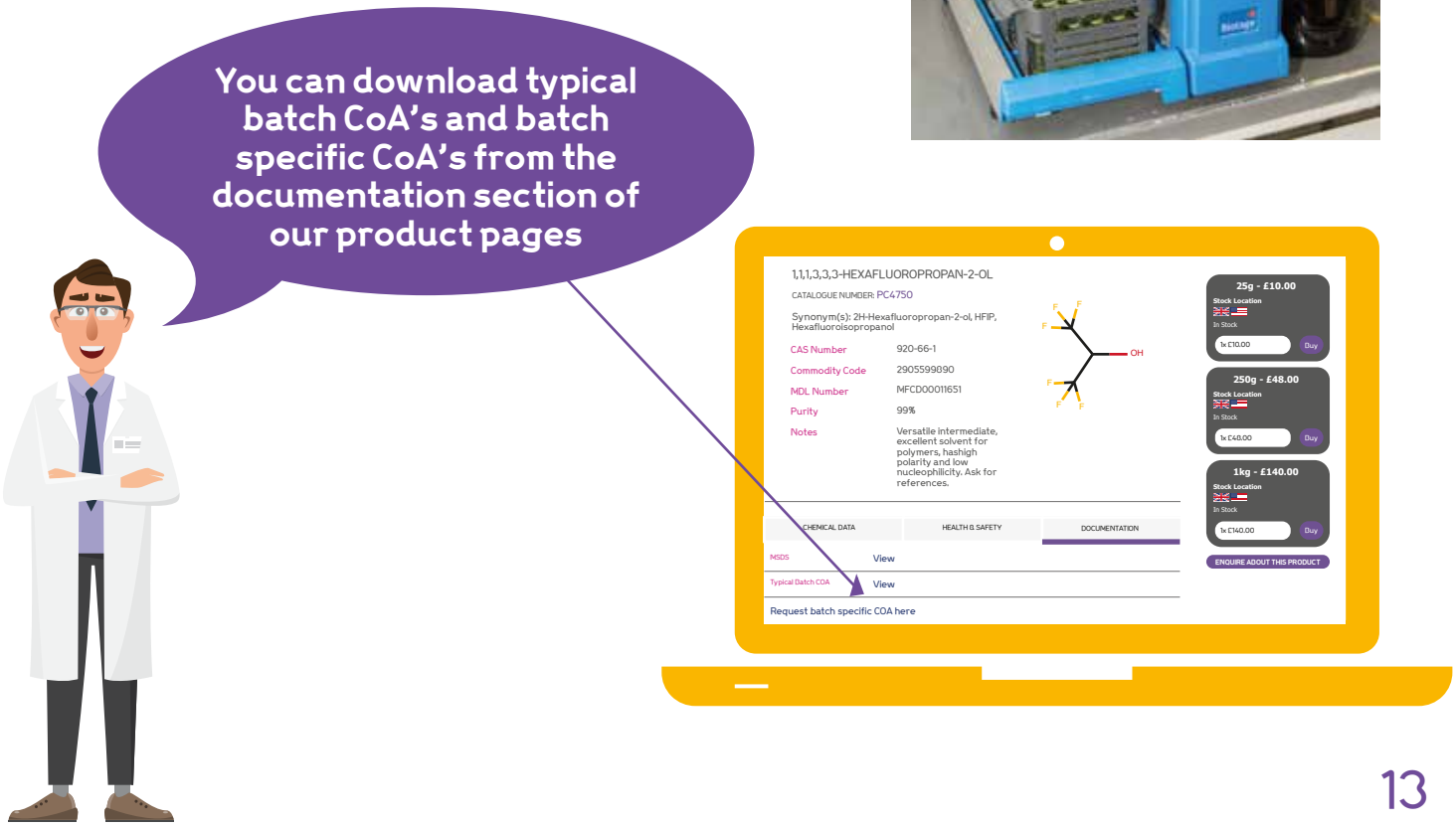
We have contracts in place for third-party analysis, such as NMR, ICP, XRF, CHN analysis and optical rotation, under full confidentiality.

In-Process Analytical Equipment

Reaction control is undertaken with an Agilent 1260 Infinity II Quadrupole 6120 HPLC-MS system, a Waters ACQUITY Arc/QDa HPLC-MS and a Shimadzu Nexis GC-2030 GC. We also use a Magritek Spinsolve™ benchtop NMR (60 MHz) for internal analysis. NMR's (400 MHz) for our customers are carried out externally on demand.

Purification Equipment

Further equipment to facilitate reaction work-up and purification are a high pressure filtration system and a Biotage® Isolera for small scale purification or isolation of analytical samples for structure determination; alongside a large variety of distillation (Oldershaw, Vigreux and packed columns, up to 3 foot) and chromatography columns (up to 4 kg of normal and reverse - phase silica).



Scale up opportunities within the Central Glass group

Apollo Labs currently synthesise in reaction vessels up to 20 L in volume. By utilising multiple batch synthesis or optimising processes for production in our flow reactor we are able to manufacture compounds within our labs in low multi kg quantities. Further scale up opportunities are available through our parent company (Central Glass) facilities into which Apollo processes can be transferred and optimised further to 100 kg's and even MT level.

SYNQUEST LABORATORIES

Within the US, at our sister company Synquest Laboratories facility, we have access to a 30 gallon (approx 113 L) Hastelloy and glass vessels up to 75 gallon (approx. 283 L). This facility also provides us with access to high pressure reactors up to 10 L volume and specialised distillation equipment, including spinning band and wiped film evaporator.

The US site also has capability for continuous production, including two continuous UV chlorinators, multiple hot tube reactors in which we can carry out catalytic hydrogenations and dechlorinations (Pd catalyst) as well as fluorinations (Cr_2O_3 catalysed) utilizing HF for chlorine / fluorine exchange. In addition, there are two 1 foot (30 cm) tube furnaces for some select thermal decompositon reactions, such as eliminating HF or HCl to create a double bond

CENTRAL GLASS

We have an office located in Shanghai to assist project management, building on long standing established links and developing an increasing portfolio of trusted third party manufacturers. This office performs manufacturing site audits and arranges customer visits to our third party manufacturers, as well as being available at the manufacturing site as needed when projects are in production. We ensure that we are working with trusted partners, when sharing our developed methods, who have a proven track record for quality and confidentiality. Non-disclosure agreements can be arranged with manufacturers as required.

SUPPORTING

DISCOVERY

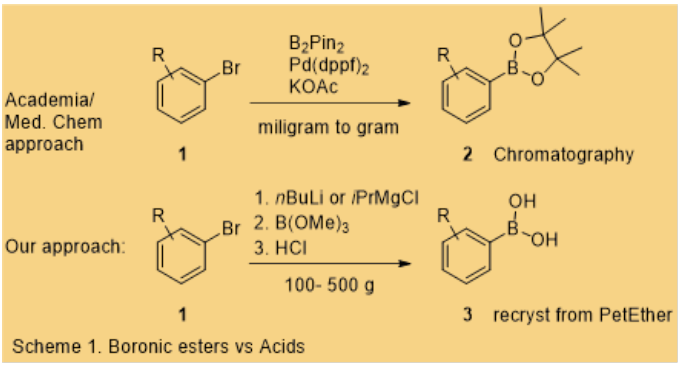
100 g to 1 kg - The Forgotten Scale

Excerpt from 100 g to 1 kg - The Forgotten Scale poster presented by Apollo Scientific at ESOC-19, July 2019.

Abstract: Nowadays, reactions performed on milligram scale are dominating the primary literature including patents. Reactions on scale larger than 5 g are rarely reported. Can these milligram procedures be used to make 100 g of a compound or more? What factors need to be considered to convert a small scale reaction to a multigram procedure? Here we take a look at some key parameters and the challenges we face on a daily basis making synthetic building blocks. In the end the questions are: Have we forgotten about making larger amounts and are we training the skills to synthesise 100 g to the new generation of chemists?

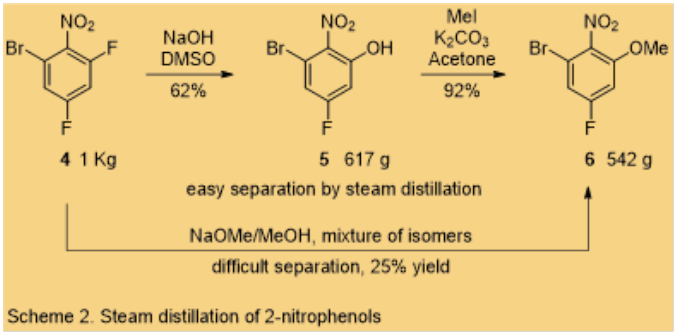
Purification: Purification and the available purification techniques (re-crystallisation, distillation, trituration, dry flash chromatography) have a much bigger impact on the reaction procedures. Expected by-products and excess reagents have to be taken into consideration and will influence the choice of reagent or even the route to a desired compound.

For example pinacol esters **2** typically don't crystallise very well and require column chromatography to remove excess B_2Pin_2, pinacol and dppf. In contrast the boronic acids crystallise from pet ether and the expected by-products are either soluble in pet ether or volatile liquids and can be removed easily.

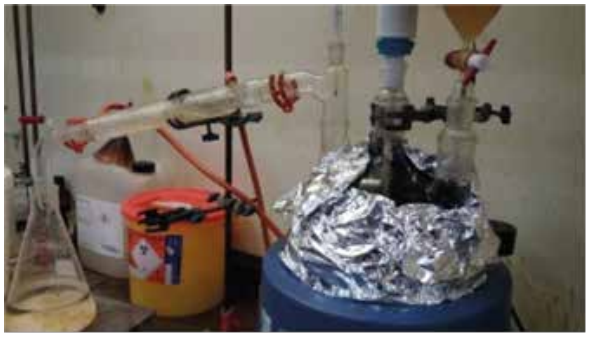


Scheme 1. Boronic esters vs Acids

The reaction of **4** with NaOMe gives a mixture of ortho- and para-methoxy derivatives which is impossible to purify by distillation or crystallisation. However, the two step process gives phenol **5** as intermediate which can be steam distilled out of the reaction mixture and a much improved yield is obtained. Because of the easy purifications the two step procedure is also quicker (time-space-yield) (**Scheme 2**).



Scheme 2. Steam distillation of 2-nitrophenols

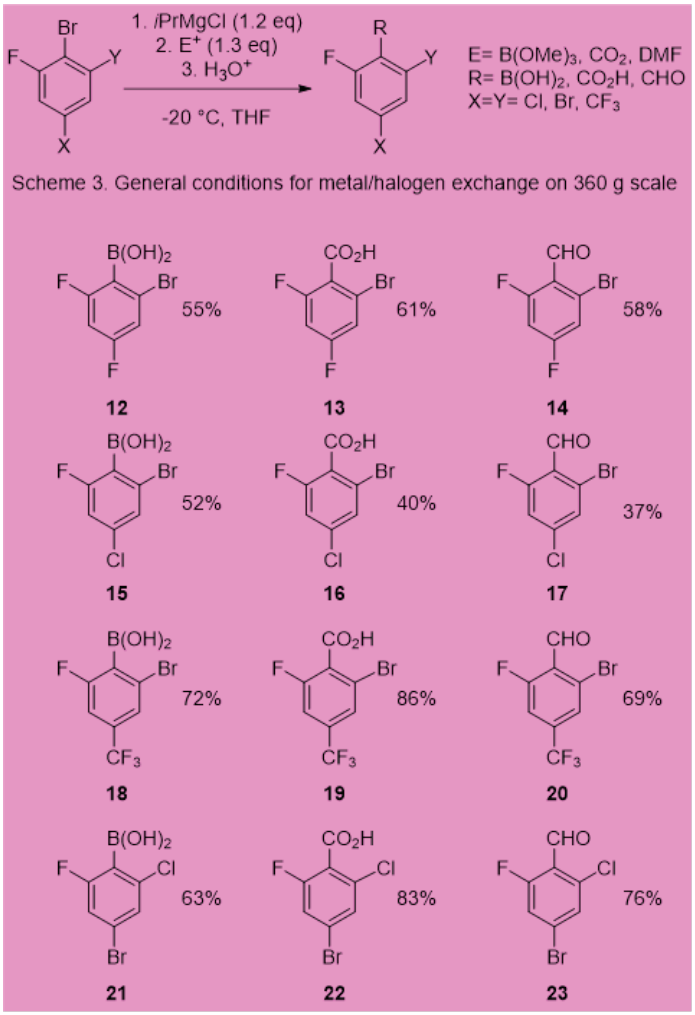


Cooling / Heating and Mixing : Controlling delayed exotherms is a major challenge for large scale reactions. There are several methods available (e.g. dropwise addition of reagent e.g. nBuLi, adding to an already refluxing solvent e.g. $KMnO_4$ into water). In all cases the build up of reagents has to be prevented to avoid the reaction "running away". Cooling a nBuLi reaction to -70 °C is unhelpful if the deprotonation only takes place at -40 °C. Additionally efficient mixing is crucial to avoid the emergence of dead zones and hot spots. Using the right type of stirrer in the right sized flask is therefore an important factor for scale-up reactions. Accurate temperature monitoring will have to take place inside the reaction vessel not in the surrounding Drysyn, oil or ice bath.

Dilution: Small scale reactions are often carried out at 0.1 - 0.2 M. This concentration can usually not be applied to larger scale reactions, e.g. a 200 g reaction of a normal sized aromatic compound would require 10 - 20 L of solvent which is costly and the handling (aqueous work-up and extractions) would take a lot of time. Instead concentrations of 0.7 - 1.5 M are more commonly used. But this has consequences for repeating literature procedures. Yields and especially regio or stereoselectivities are usually difficult to reproduce.

Waste: Excess reagents, high dilution, high catalyst loadings and column chromatography generate a lot of waste which is environmentally undesirable and also has cost implications. In general, reactions with more than 1% catalyst loading are not suitable for scale-up if the catalyst cannot be recovered easily.

The Chemistry: The scale of the reactions is largely determined by the amount ofreagent and solvent not by the amount of starting material. The regioselective halogen / metal exchange reactions with iPrMgCl, described in **Scheme 3**, are carried out using 2 bottles of commercially available Grignard solution (2 M) in 10 L flasks. On this scale the temperature is easy to control and the amount of solvent (6 L total) is also manageable. Remarkably there are a lot of "easy" looking building blocks that have not been synthesised previously (e.g. **12 - 23**, in **Scheme 3**).



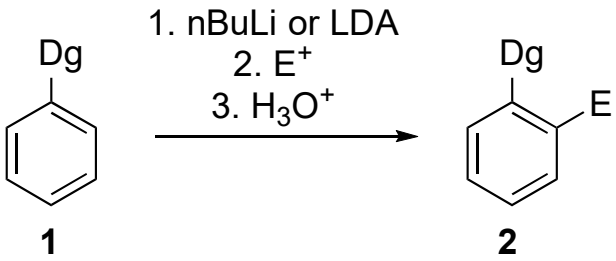
Scheme 3. General conditions for metal/halogen exchange on 360 g scale

Flow Chemistry: One of the advantages of flow chemistry is the theoretically easy scalability. An optimised reaction will only be required to run for a prolonged time to increase the amount of product. However, due to concentration, residence time, reactor size, tubing and mixing reproducibility is again an issue that needs to be addressed in future

Conclusions: Literature procedures on milligram scale are difficult to adapt for multigram scale. In general extensive optimisation work is required. Commonly it is easier to fall back onto known working reactions and design an alternative route to described compounds. Carrying out reactions on these two different scales require different mind-sets and different skills, to balance safety, environmental impact, and efficiency / cost effectiveness .

Chemistry

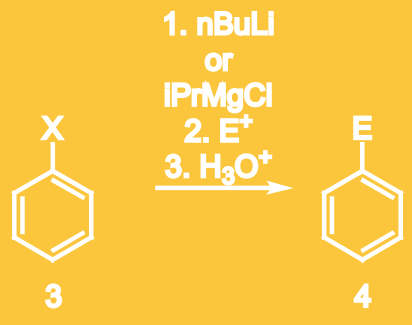
One of the most versatile reactions for the Apollo Labs is the ortho- lithiation of compounds with a suitable directing group such as F, Cl, OMe, NBoc or CF_3[1]. The lithiated intermediate can then be trapped with an electrophile to obtain a variety of compounds such as aldehydes, benzoic acids and boronic acids. We typically carry out this chemistry on 50 g to 500 g scale.



Dg= F, Cl, OMe, NBoc, CF_3
E= CHO, CO_2, I, $B(OH)_2$

Scheme 1. Ortho-lithiation[1]

In some cases, *ortho*-lithiation can be difficult to control e.g. if two or more acidic protons are available or if the compound can form a more stable lithium species via Li / H-shift or the "halogen dance". In these cases, metal / halogen exchange can be a powerful tool to circumvent the problems and is used on 50 g to 500 g scale at Apollo labs to synthesis a range of new diversely substituted benzoic acids, aldehydes and boronic acids.

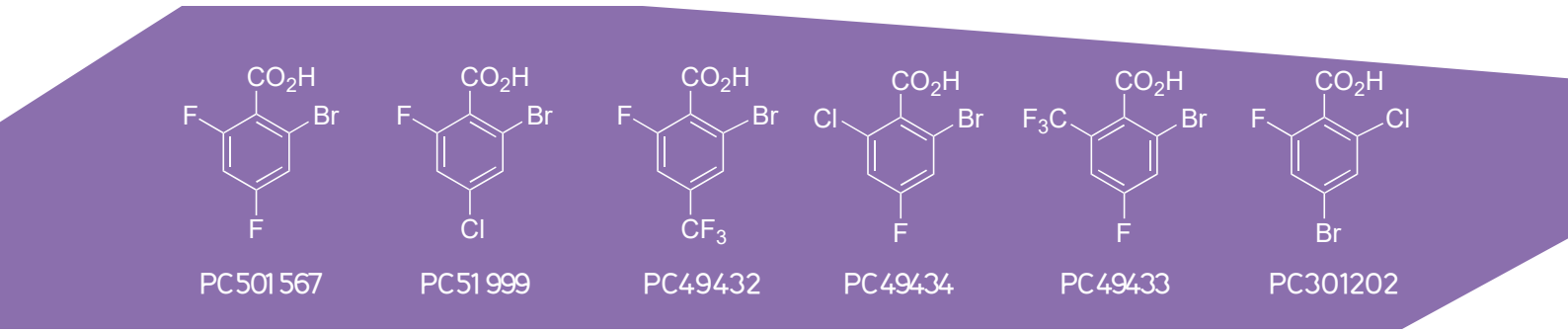


X= Br, I
E= CHO, CO_2, Br, I, $B(OH)_2$

Scheme 2. Metal/halogen exchange[2]

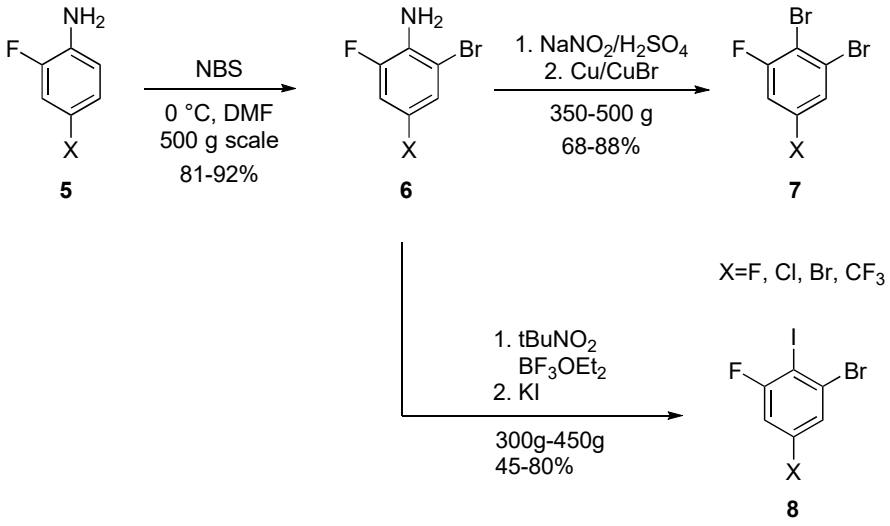
1. Review: El-Hiti, G. A. et al. *Arkivoc* **2015**, *(vi)*, 19–47
2. Reviews: Ziegler, D.S. et al. *Chem. Eur. J.* **2019**, *25*, 2695-2703; Cahiez, G. et al. Chem. *Rev.* **2009**, 109, 1434-1476; El Sheikh, S. et al. *Current opinion in drug discovery & development* **2004**, *7*, 882-95

We recently have developed a method using metal / halogen exchange to make a range of uniquely substituted compounds, along with their Apollo codes.



Classic aromatic chemistry

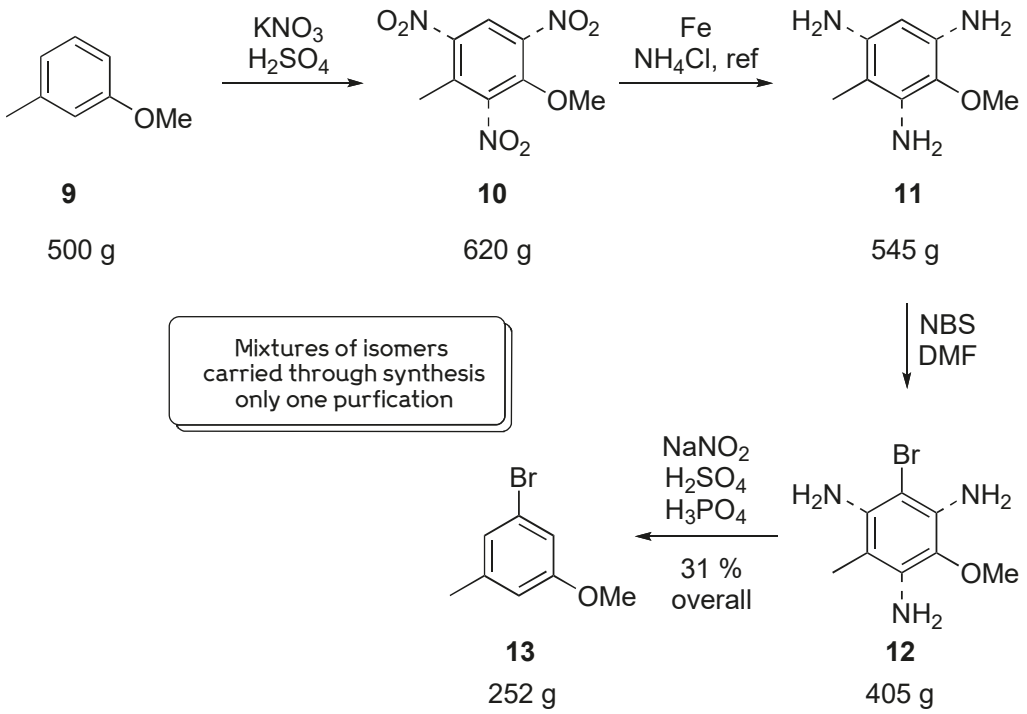
The synthesis of multi functionalised building blocks often starts with simple arenes. They can be quickly transformed into usable intermediates for new compounds, e.g. via nitration and subsequent reduction to anilines. The latter can be rapidly further derivatised by brominations or iodinations with NBS, Br_2, NIS, ICl_3, I_2 and others[3]. Another very adaptable reaction in this context is the Sandmeyer-reaction to functionalise anilines to give e.g. oligo-halide derivatives with a wide substrate scope. All of these transformations are building a set of core reactions to make versatile intermediates on large scale to synthesise more complex building blocks at Apollo Labs. This also includes the Balz - Schiemann reaction as a special case of the Sandmeyer chemistry to introduce fluorine by thermal degradation of the tetrafluoroborate diazonium salts.



Scheme 3. Synthesis of diverse multi-halogenated aromatic compounds

3. Sandmeyer, T.; *Berichte der deutschen chemischen Gesellschaft* **1884**, *17*, 1633-1635. doi:10.1002/cber.18840170219.; Wang, Z. in *"Comprehensive Organic Name Reactions and Reagents."* John Wiley & Sons, **2010,** 2471-2475, ISBN 9780470638859.

A set of well established classic aromatic reactions can also be used in a similar manner to synthesise, otherwise very difficult to achieve electronically rich 1,3,5-trisubstituted benzenes. In the example below the nitro and aniline moieties are used as a directing group, and despite the intermediate being a mixture of isomers, only one product is obtained after removal of the amino groups in a good overall yield.

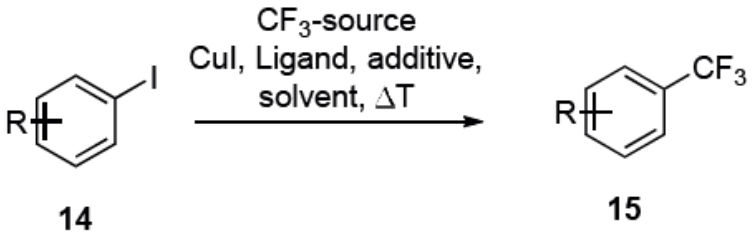


Scheme 4. Synthetic strategy for the synthesis of electronic rich 1,3,5-disubstituted benzenes

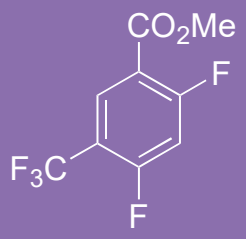
Introduction of Fluorine containing moieties

The following examples show a range of reactions routinely performed in our UK Labs to introduce CF_3 or CF_2H groups.

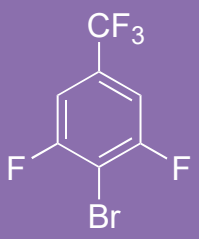
Trifluoromethylations of aryl iodides (aryl bromides and benzeneboronic acids have also been reported) is the most common reaction to introduce a CF_3-group into organic compounds. It usually involves a CF_3 source e.g. $TMSCF_3$ (PC7779), CF_3CO_2Na (PC6570), ClF_2CO_2Et (PC3170), ICF_3 (PC7680), $FO_2SCF_2CO_2Me$ (PC5097), a ligand and CuI to generate the active "$CuCF_3$"species *in situ*.[4]



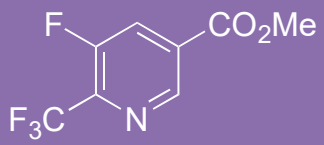
Scheme 5. Trifluoromethylation



PC53039



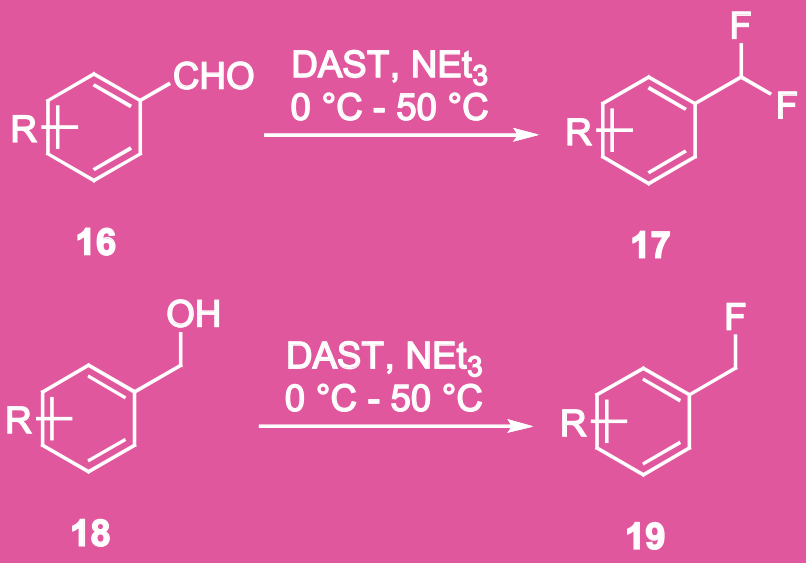
PC0321



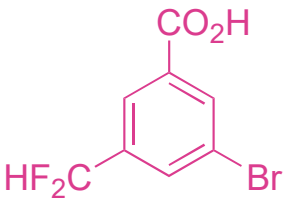
PC56122

Handling of explosive reagents and intermediates provide a safety challenge to industry. One specific reaction is the synthesis of difluoromethylbenzenes from the corresponding benzaldehydes with DAST. We have recently introduced this transformation safely to our labs on up to 100 g scale. The same approach is used to make benzyl fluorides from benzyl alcohols.

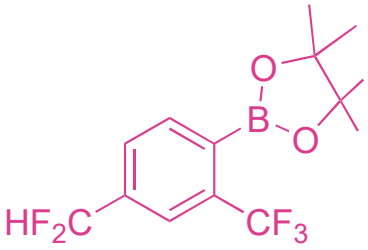
4. a) Beckers, H. et al. *J. Organomet. Chem.* **1986**, *316*, 41-50 b) Prakash, G. K. S. et al. *J. Am. Chem. Soc.* **1989**, *111*, 393-395 c) Tomashenko O. A. et al.; *Chem. Rev.* **2011,** *111*, 4475–4521.



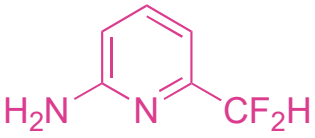
Scheme 6. Using DAST safely to synthesise Difluoromethylbenzenes and Benzyl fluorides[5]



PC57725



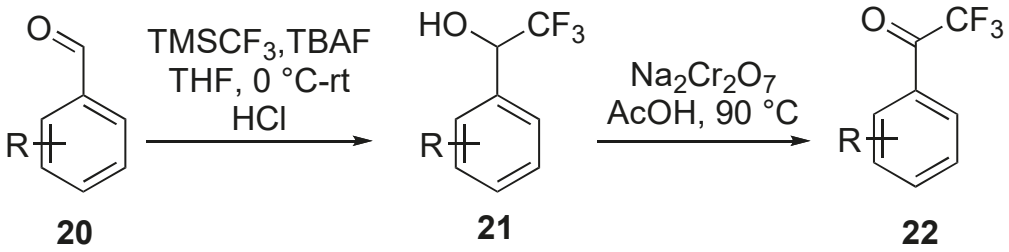
PC10486



PC56952

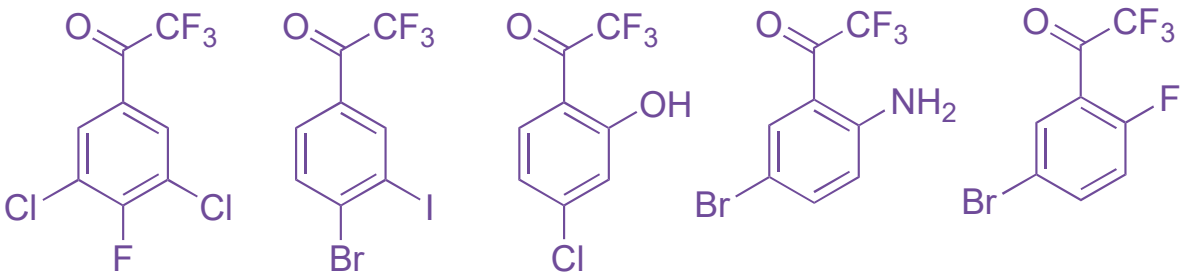
2,2,2-Trifluoroacetophenones are a versatile functional group of increasing popularity especially within the pharmaceutical industry. Several approaches for the synthesis of 2,2,2-trifluoroacetophenones have been developed, e.g. Friedel-Crafts acetylations with trifluoroacetic anhydride (PC7170) or the addition of organometallic reagents to ethyl trifluoroacetate (PC3270). However, the broadest substrate spectrum is utilised in a two step procedure from widely available benzaldehydes. The first step is a TBAF induced nucleophilic addition of $TMSCF_3$ (Ruppert-Prakash reagent, PC7779) to the aldehyde with a subsequent hydrolysis of the TMS ethers to obtain 2,2,2,-trifluoro-1-ethanol derivatives **21**, followed by an oxidation to the acetophenones **22** (Scheme 7).

5. Review: Al-Maharik, N. et al. *Aldrichim. Acta* **2011**, *44*, 65-75. Singh, R. P. et al. *Adv. Org. Synth.* **2006**, *2*, 291-326. Fuchigami, T. et al. in *"Organic Electrochemistry (5th Edition)"* **2016**, 807-826.



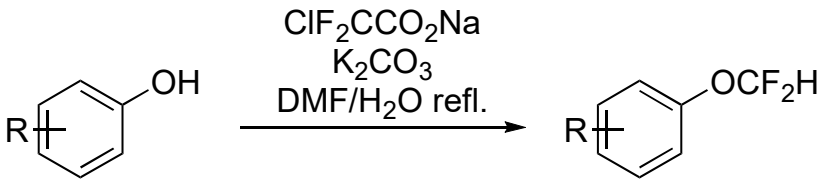
20 **21** **22**

Scheme 7. Trifluoroacetophenones from benzaldehydes



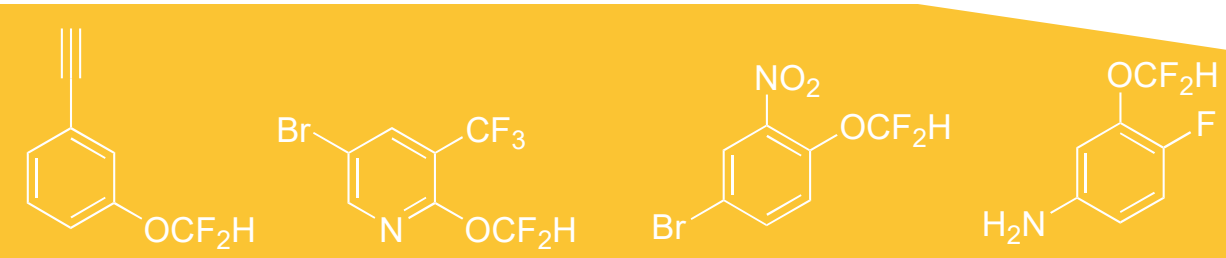
PC49287 PC501269 PC57071 PC49164 PC51159

Difluoromethoxylations of phenols are described as early as 1979[6], with chlorodifluormethane (Freon 22) initially being the electrophile of choice. Today, sodium chlorodifluoroacetate (PC6460)[7] and bromodifluoromethyl diethylphosphonate (PC1393D)[8] are more commonly used for environmental reasons. Other reagents include ethyl chlorodifluoroacetate (PC3170), methyl chlorodifluoroacetate (PC5070) and CF_2HTMS (PC408038).



23 **24**

Scheme 8. Standard conditions for difluoromethylations



PC5953 PC502205 PC501880 PC501941

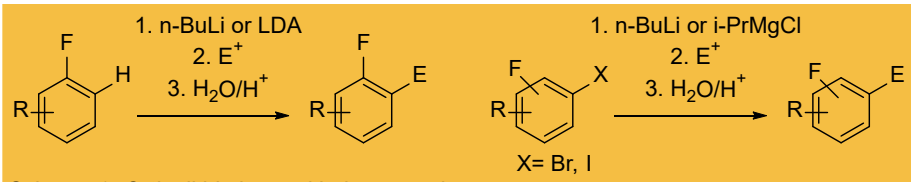
6. American Cyanamid Co. Patent US4178460 A1, **1979.**
7. ACTELION PHARMACEUTICALS LTD WO2009/156951 A2, **2009.**
8. Zafrani, Y. et al. *Tetrahedron* **2009,** 65, 5278 – 5283.

Study on the Selective Synthesis of Highly Substituted Benzoic Acids and Benzeneboronic Acids from Asymmetric Benzenedibromides on Multigram Laboratory Scale.

Excerpt from poster presented by Apollo Scientific at 26th International symposium: Synthesis in organic chemistry at Cambridge, UK, July 2019.

Abstract: Highly functionalized benzoic acids, benzaldehydes and phenylboronic acids, which are amongst the most commonly used building blocks in all fields of synthetic chemistry, can be synthesised from easily accessible asymmetric dibromobenzenes via selective metal / halogen exchange with i-PrMgCl and reacting the intermediates with suitable electrophiles in good to very good yields on 50 - 360 g scale.

Background: One fundamental strategy to synthesise these compounds is by ortho-lithiation or metal halogen exchange **(Scheme 1).**



Scheme 1. *Ortho*-lithiation and halogen exchange

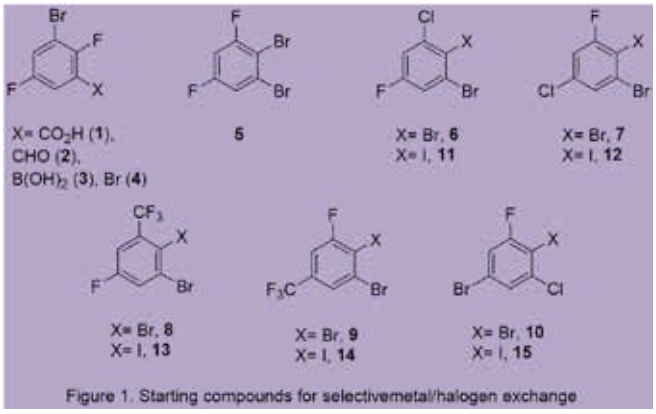
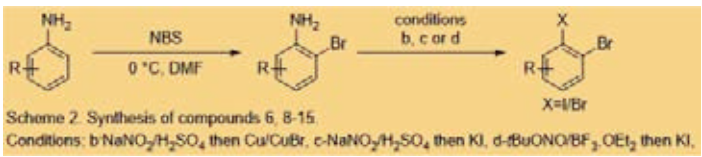


Figure 1. Starting compounds for selectivemetal/halogen exchange

However, ortho-lithiation can be complex if there is more than one acidic proton available or if the compound can form a more stable lithium species via Li / H-shift or the "halogen dance". In these cases metal / halogen exchange can very often be the only way forward. In our ongoing efforts to make new building blocks for our extensive catalogue we recently developed a facile reaction protocol to synthesise benzoic acids **1**, benzaldehydes **2** and phenylboronic acids **3** from symmetric dibromodifluorobenzenes **4** (only 1 example shown) in good to very good yields on 50-360g scale. We have now extended this protocol to asymmetric dibromobenzenes **5 - 10** and iodobromobenzenes **11 - 15** (Figure 1).

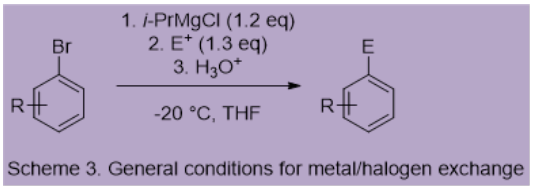
Results: Compounds **6-15** were synthesised following the route in **Scheme 2** in good to excellent yields on 500 g scale. Only 11 gave lower yields suggesting that the intermediate diazonium salt is decomposing more rapidly.



Scheme 2. Synthesis of compounds 6, 8-15.
Conditions: b-$NaNO_2/H_2SO_4$ then Cu/CuBr, c-$NaNO_2/H_2SO_4$ then KI, d-tBuONO/$BF_3.OEt_2$ then KI.

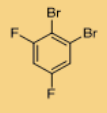
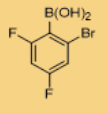
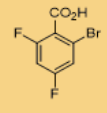
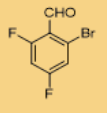
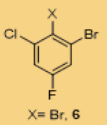
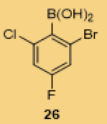
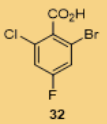
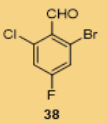
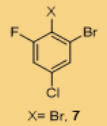
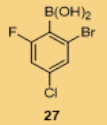
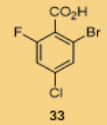
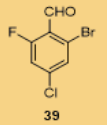
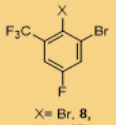
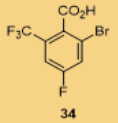
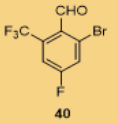
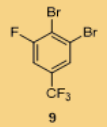
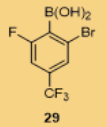
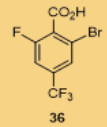
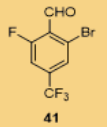
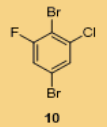
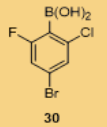
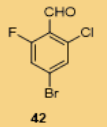
Non aqueous conditions for the Sandmeyer reaction to obtain compounds **11 - 15** resulted in cleaner reaction profiles and better yields for all compounds.

The directing abilities of the ortho-group is largely dependent on the electronegativity. High selectivities (typically 16:1) and good to very good yields were achieved for ortho-fluoro compounds (**5, 7, 9, 10**).



Scheme 3. General conditions for metal/halogen exchange

Table 1. Reaction of arylhalogens with *i*-PrMgCl on 50 g scale

Aryl halide	E= $B(OMe)_3$ HCl	Selectivity[a] Yield[b]	E= CO_2	Selectivity[a] Yield[b]	E= DMF HCl	Selectivity[a] Yield[b]
 **5**	 **25**	55%	 **31**	61%	 **37**	47%
 X= Br, **6** X= I, **11**	 **26**	X= Br 2.5:1 yield n.d. X= I 56%	 **32**	X= Br 2.3:1 yield n.d. X= I 64%	 **38**	X= Br 2.4:1 yield n.d. X= I 57%
 X= Br, **7** X= I, **12**	 **27**	X= Br 15:1 yield 52%	 **33**	X= Br 15:1 yield 40%	 **39**	X= Br 15:1 yield 37% X= I 99:1 yield 85%
 X= Br, **8**, X= I, **13**	 **28**	X= Br 3:1 yield n.d. X= I 0%[c]	 **34**	X= Br 3:1 yield n.d. X= I 48%	 **40**	X= Br 2.9:1 yield n.d. X= I 46%
 **9**	 **29**	72%	 **36**	86%	 **41**	69%
 **10**	 **30**	63%	 **36**	83%	 **42**	76%

[a] selectivities were determined by quenching a reaction sample into MeOH and compared the resulting mixtures to the corresponding monobromobenzenes by GC, all monobromobenzenes are verified by comparing the data with authentic samples [b] isolated yields, [c] quenching the lithiated species into DMF showed a single aldehyde (91%), after adding $B(OMe)_3$ 3 different isomers were found by HPLC analysis

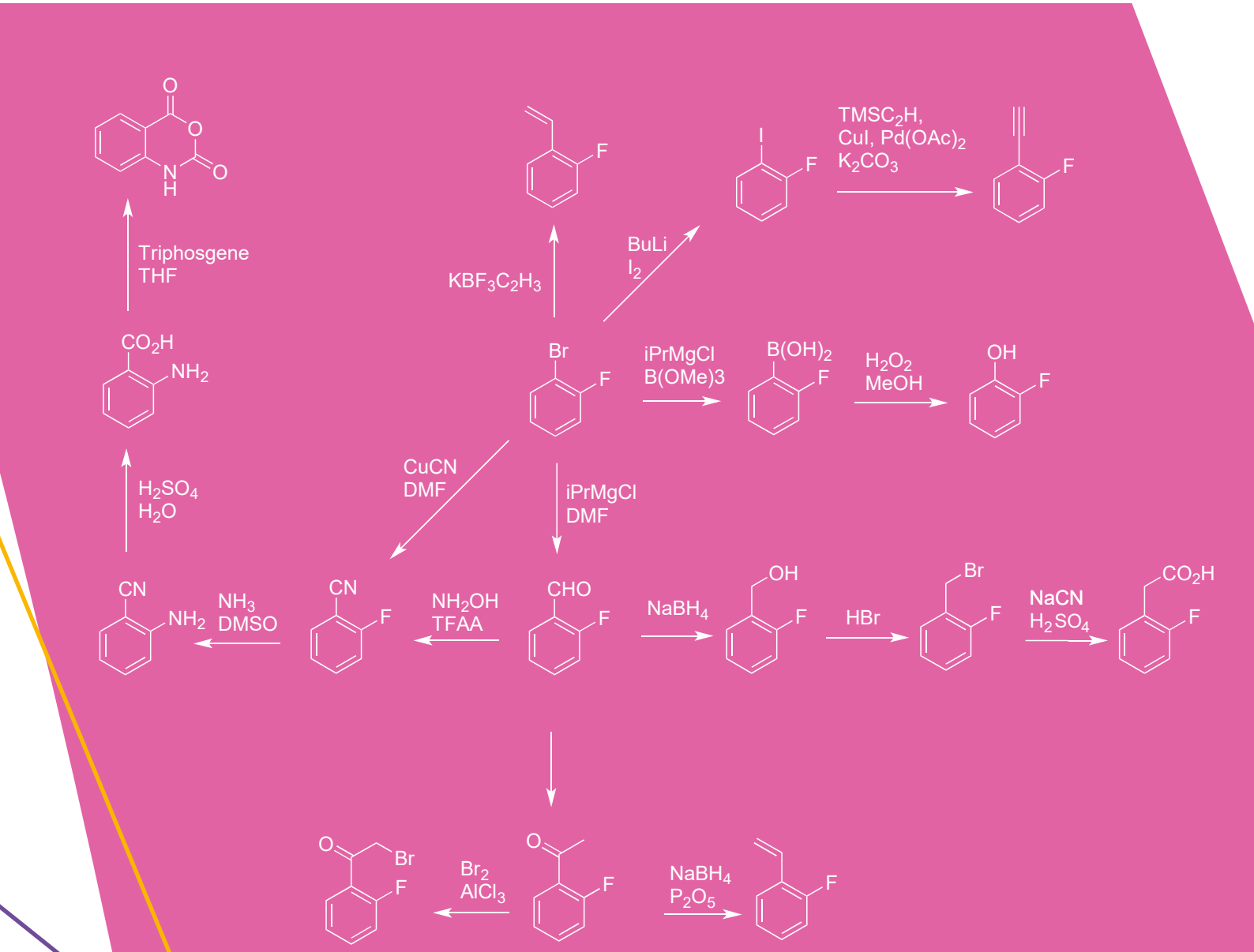
In the case of **7** the small amount of isomer that was formed was very difficult to remove which resulted in low yields, but when we made **39** via the corresponding Iodo compound **12** then high yields of 85% were obtained. Purification of benzoic and boronic acids is easily achieved by re-crystallisation from petroleum ether. Aldehydes were purified by distillation or re-crystallisation. The lower selectivites of ~3:1 for Cl (**6**) and CF_3 (**8**) containing directing groups were predicted but are lower than expected and proved not to be useful on multigram scale. To overcome this difficulty the corresponding iodo-derivatives (**11-15**) were synthesised for comparison and very good selectivities (>60:1) and good to very good yields were obtained. To the best of our knowledge only 3 of the 18 synthesised compounds **25** to **42** have been previously reported (**31**,[1] **37**,[2,3] **39**,[4,5]).

Conclusions: In summary, we have established a mild and efficient protocol to synthesise different multi-functional building blocks from the same starting material on 50 – 360 g scale using the same methodology and without the need for chromatography in good to very good yields. Selectivity of the halogen / metal exchange on dibromoarenes are synthetically useful for ortho-fluoroderivatives. The lower selectivities with other directing groups were overcome by synthesising the corresponding iodo-derivatives.

1. Schlosser, M.; et al. *Eur. J. Org. Chem.* **2003**, 23, 4618-4624.
2. Swahn, B.-M.; et al. *J. Med. Chem.* **2012,** 55, 9346-9361.
3. Chen, X.-Y.; et al. *J. Am. Chem. Soc.* **2018**, 140, 2789-2792.
4. Menzel, K.; et al. *Org. Process Res. Dev.* **2009**, 13, 519-524 and literature therein.
5. Kumiai Chemical Industry co., ltd.; Ihara Chemical Industry co., ltd. WO2007/34755, **2007**.

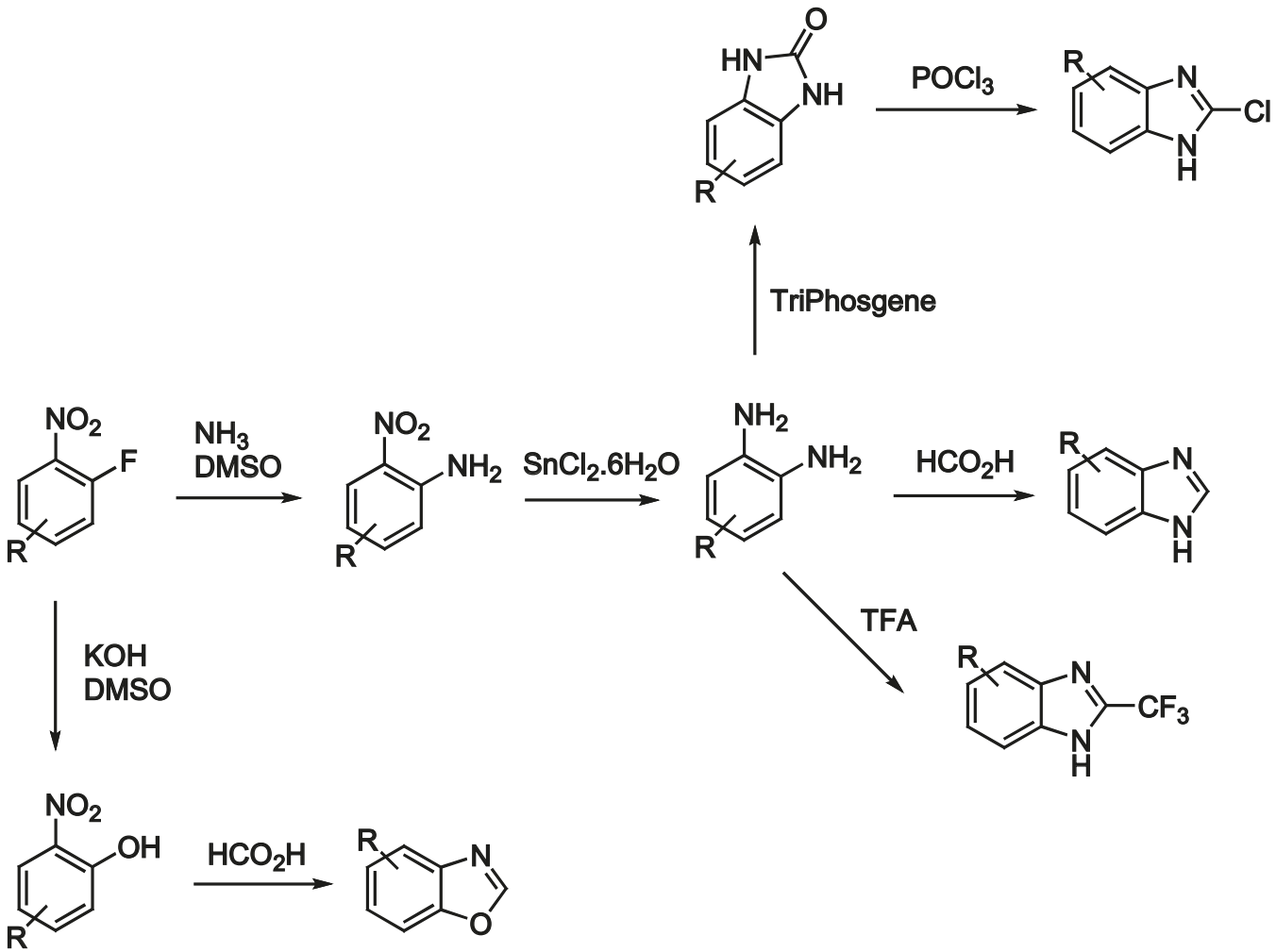
Other Reactions and Products

In addition to the highlighted chemical transformations we routinely perform a whole range of reactions including oxidation to phenols, benzonitrile formation (either by cyanation of aryl halides with Cu(I)CN or from benzaldehydes), activated F-displacements with ammonia or hydroxide e.g. to synthesise salicylic acids / aldehydes , reductions of benzaldehydes or benzoic acids, phenacyl bromide formation, Sonogashira reaction to form acetylenes, Suzuki couplings and the synthesis of styrenes, phenylacetic acids and isatoic anhydrides. The following general scheme gives an overview on these transformations:



Scheme 9. Schematic overview on typical transformations at Apollo Labs

Another range of versatile intermediates such as 1,2-benzenediamines, and 2-aminophenols, are versatile building blocks and are routinely synthesised from 2-fluoronitrobenzenes. They can be easily converted into small heterocycles such as benzimidazoles, benzoxazoles and other related structures as shown in Scheme 10.



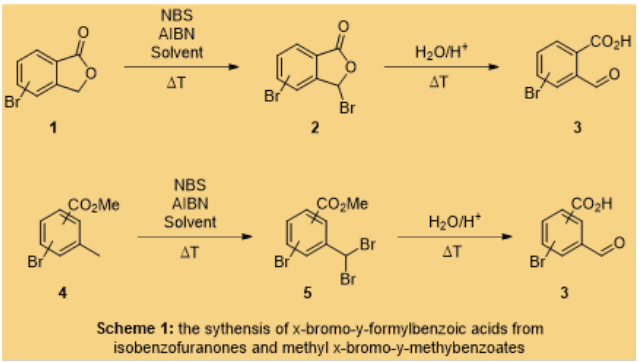
Synthesis of X-Bromo-2-formylbenzoic Acids and other X-bromo-Y-formylbenz -oic Acids using Flow Chemistry.

Exerpt from poster, presented by Apollo Scientific at 34th Postgraduate Symposium: Heterocyclic & Synthesis Group in Macclesfield, UK. September 2019.

Abstract: In our ongoing efforts to expand our catalogue of building blocks, we have synthesised a range of x-bromo-y-formylbenzoic acids via bromination of the readily and cheaply available toluenes under flow photochemical conditions, followed by a simple hydrolysis step. A total of nine x-bromo-y-formylbenzoic acids were synthesised in moderate to good yields. The challenges, limitations and solutions are presented below.

Background: x-Bromo-2-formylbenzoic acids are important building blocks and commonly made from isobenzofuran-1(3H)-ones / phthalides **1** but the approach is limited by the availability of the phthalides and the use of toxic and environmentally dangerous solvents such as 1,2-dichloroethane or CCl_4.

A general protocol for light-induced benzylic brominations in continuous flow conditions has been established[1] giving benzyl bromides in good selectivity. Small amounts of benzal bromides were observed as side products. Building on the results and our own R&D into continuous flow photochemical benzylic brominations, we envisaged a procedure from the readily and cheaply available toluenes **4** via the benzal bromides **5**; which also should give access to the other isomers (**Scheme 1**).



Scheme 1: the sythensis of x-bromo-y-formylbenzoic acids from isobenzofuranones and methyl x-bromo-y-methybenzoates

Results: Initially the bromination of 5-bromophthalide using a Vapourtec R series flow reactor fitted with a UV150 photochemical reactor (10ml), medium pressure mercury lamp and a silver type 1 filter (**Image 1**) was investigated. Based on the literature and our own previous work, stock solutions of 5-bromophthalide and NBS were made up in acetonitrile and passed through a static mixing element before reaction in the 10 mL reactor (schematic, **Image 2**). Several trial reactions were performed, and using the optimised conditions gave a product stream containing 87% of the brominated phthalide intermediate.

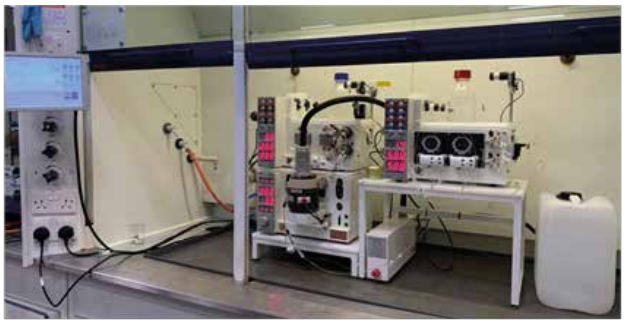


Image 1: Vapourtec R series at Apollo labs.

The product stream was reduced in vacuo and the resulting solids were boiled in water for several hours and worked up to give 80.4 g (80%) of 4-bromo-2-formylbenzoic acid (**Table 1**, entry 1).

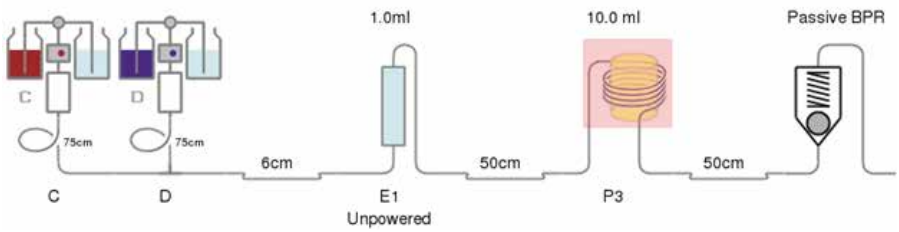
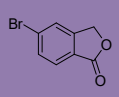
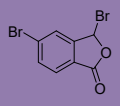
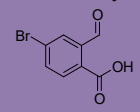
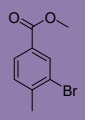
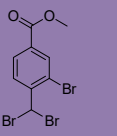
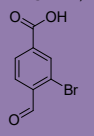
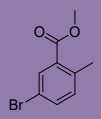
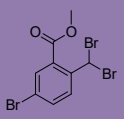
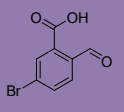
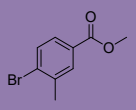
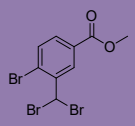
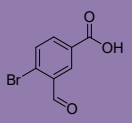
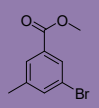
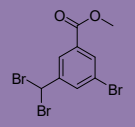
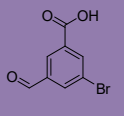
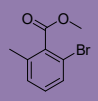
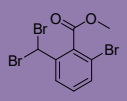
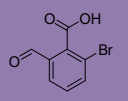
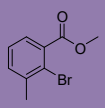
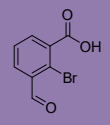
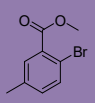
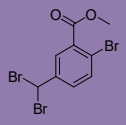
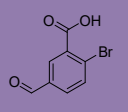
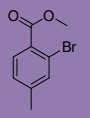
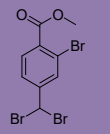
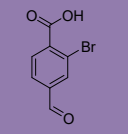
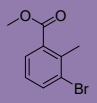
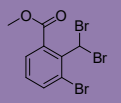
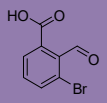


Image 2: schematics of the flow reactor set up for photochemical brominations

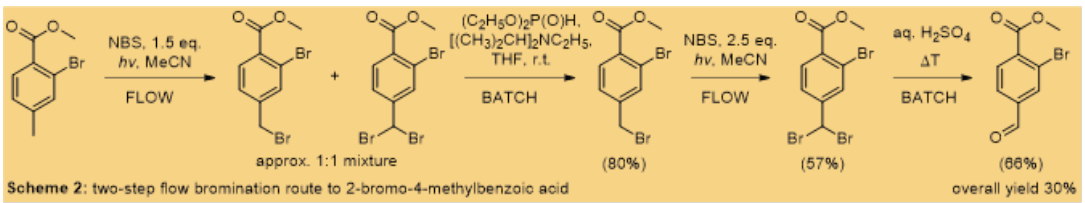
A total of nine methyl benzoates (**Table 1**, entries **2-9**) were used in the flow step. All reactions required optimisation with regards to concentration, residence time, reagent ratio and lamp intensity. Entry **9** (**Table 1**) could not be pushed to acceptable levels of benzal bromide. Instead, the tribrominated derivative was formed in significant amounts alongside the product. To solve the problem, it was necessary to establish a four-step procedure (**Scheme 2**).
Hydrolysis was achieved by heating in aq. sulphuric acid (50%-90%). Crude yields for the benzoic acids were usually significantly better than the isolated yields. Even small impurities proved difficult to remove, despite the purity of the crudes being above 90%.

Table 1. Synthesis of x-Bromo-y-Formylbenzoic acid (Scheme 2.)

Entry	Starting Material	Intermediate compound (residence time, total run time, mass, yield)	Product (crude LC/MS purity, isolated mass & yield)
1		 (3.3 min, 29.3 h, 87%*)	 (92.5% by LC/MS **80.4 g, 80%**)
2		 (15.0 min, 48 h, 33.4 g 96%)	 (98% by LC/MS, **14.3 g, 83%**)
3		 (9.4 min, 60 h, 122.4 g, 87%)	 (96.3% by LC/MS, **58.6 g, 80%**)
4		 (7.5 min, 36.1 h, 93.9 g, 90%)	 (91.3% by LC/MS, **37.3 g, 67%**)
5		 (3.8 min, 29.7 h, 150.2 g, 86%)	 (100% by LC/MS, **20.0 g, 64%**)

Entry	Starting Material	Intermediate compound (residence time, total run time, mass, yield)	Product (crude LC/MS purity, isolated mass & yield)
6		 (9.4 min, 48.2 h, 103.9 g, 93%)	 (93.3% by LC/MS, **40.6 g, 66%**)
7		 (18.8 min, 82.8 h, 29.3 g, 51%)	 (92.7% by LC/MS, **14 g, 80%**)
8		 (4.2 min, 30 h, 71 g, 46%)	 (94.2% by LC/MS, **37.9 g, 90%**)
9		 (6.5 min, 20.4 h 41 g, 46%)	 (94.2% by LC/MS, **15.8 g, 65%**)
10		 (14%**)	 n/a

*not isolated, yield determined by LC/MS and GC
**benzal bromide 14% *in situ* by LC/MS. 111.7 g (83%) of methyl 3-bromo-2-(bromomethyl)benzoate isolated, 3.76 min residence time, total run time 29 h.



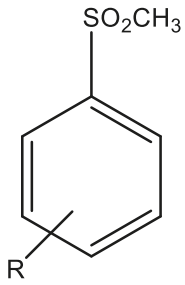
Scheme 2: two-step flow bromination route to 2-bromo-4-methylbenzoic acid

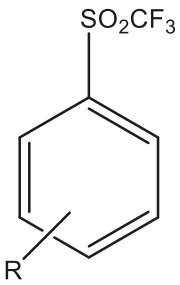
Conclusions: Robust methods for nine x-bromo-y-formyl benzoic acids were developed and the final products synthesised in moderate to good yields on 10-80 g scale from cheap commercially available methyl x-bromo-y-methylbenzoates. The corresponding acid could not be used due to solubility issues. We are currently expanding the concept to other diversly substituted methyl benzoates.

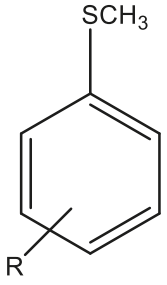
1. David Cantillo, et al, *J. Org. Chem.*, **2014**, 79, 1, 223–229.

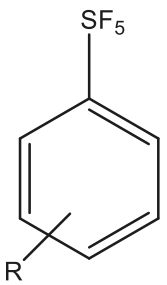
Typical aromatic and heterocyclic building blocks

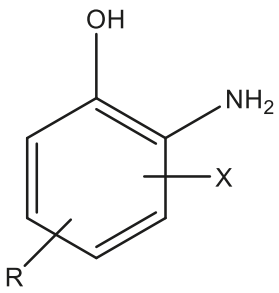
The following are examples of common product group functionalities and substitutions we synthesize in-house:

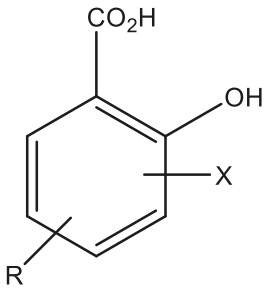


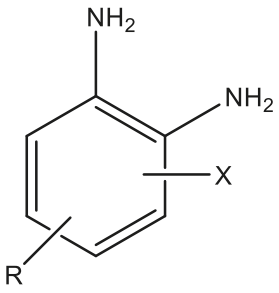


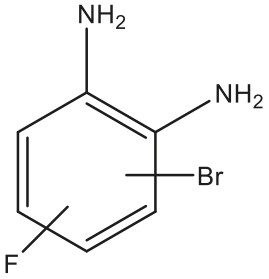


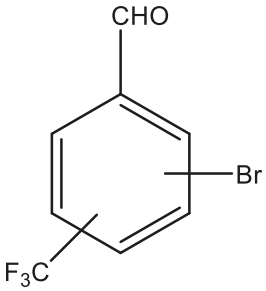


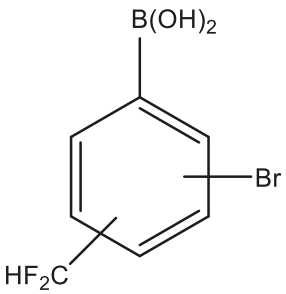


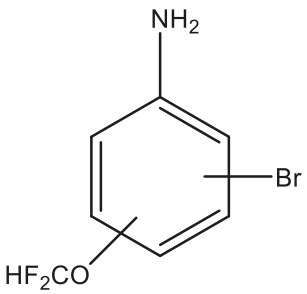


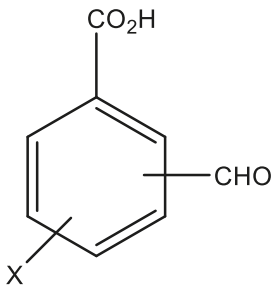


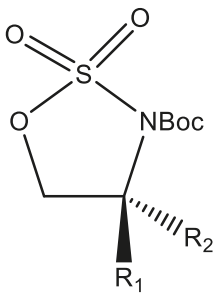


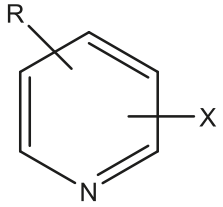


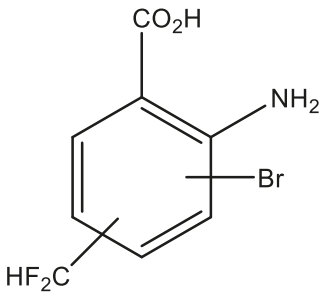


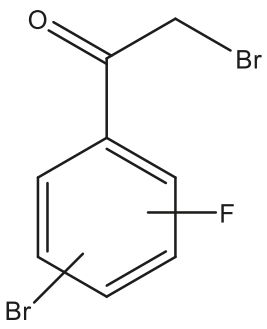


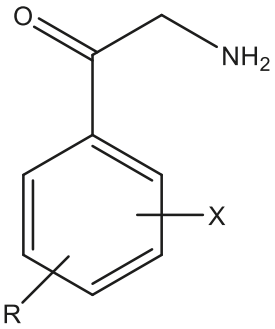


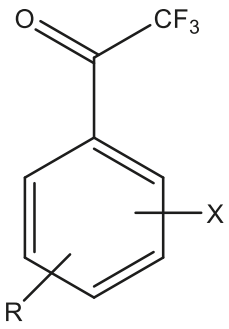


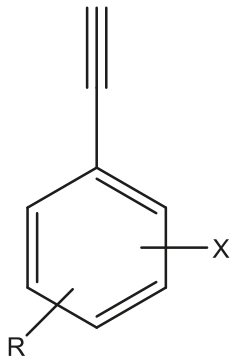


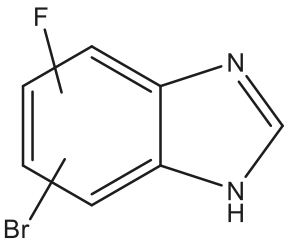


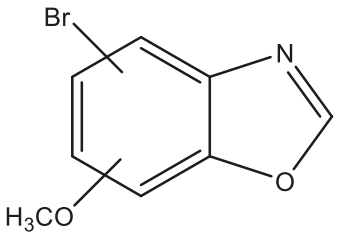

O
Br
F
Br

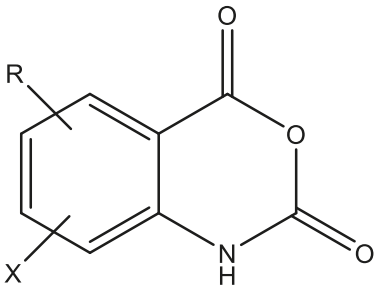

O
NH2
X
R

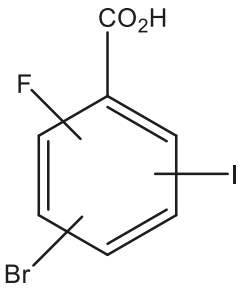

O
CF3
X
R

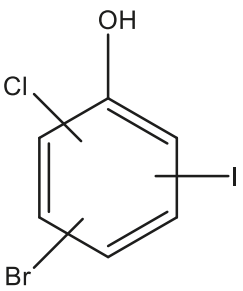

X
R

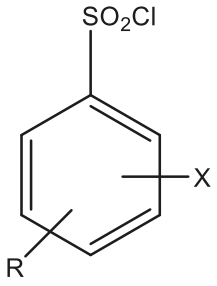

F
N
N
H
Br

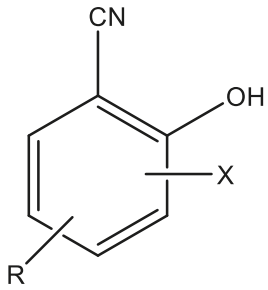

Br
N
O
H3CO

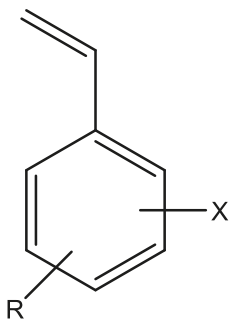

O
R
O
N
H
O
X

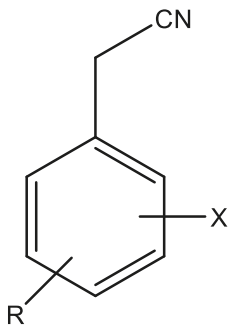

CO2H
F
I
Br

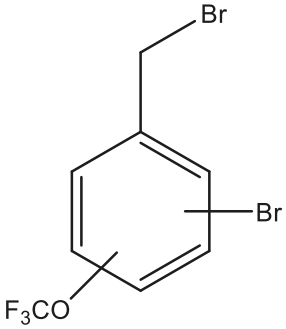

OH
Cl
I
Br

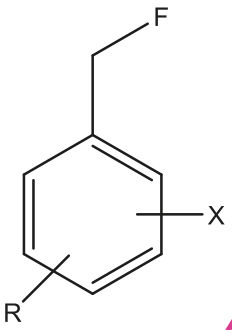

SO2Cl
X
R


CN
OH
X
R


X
R

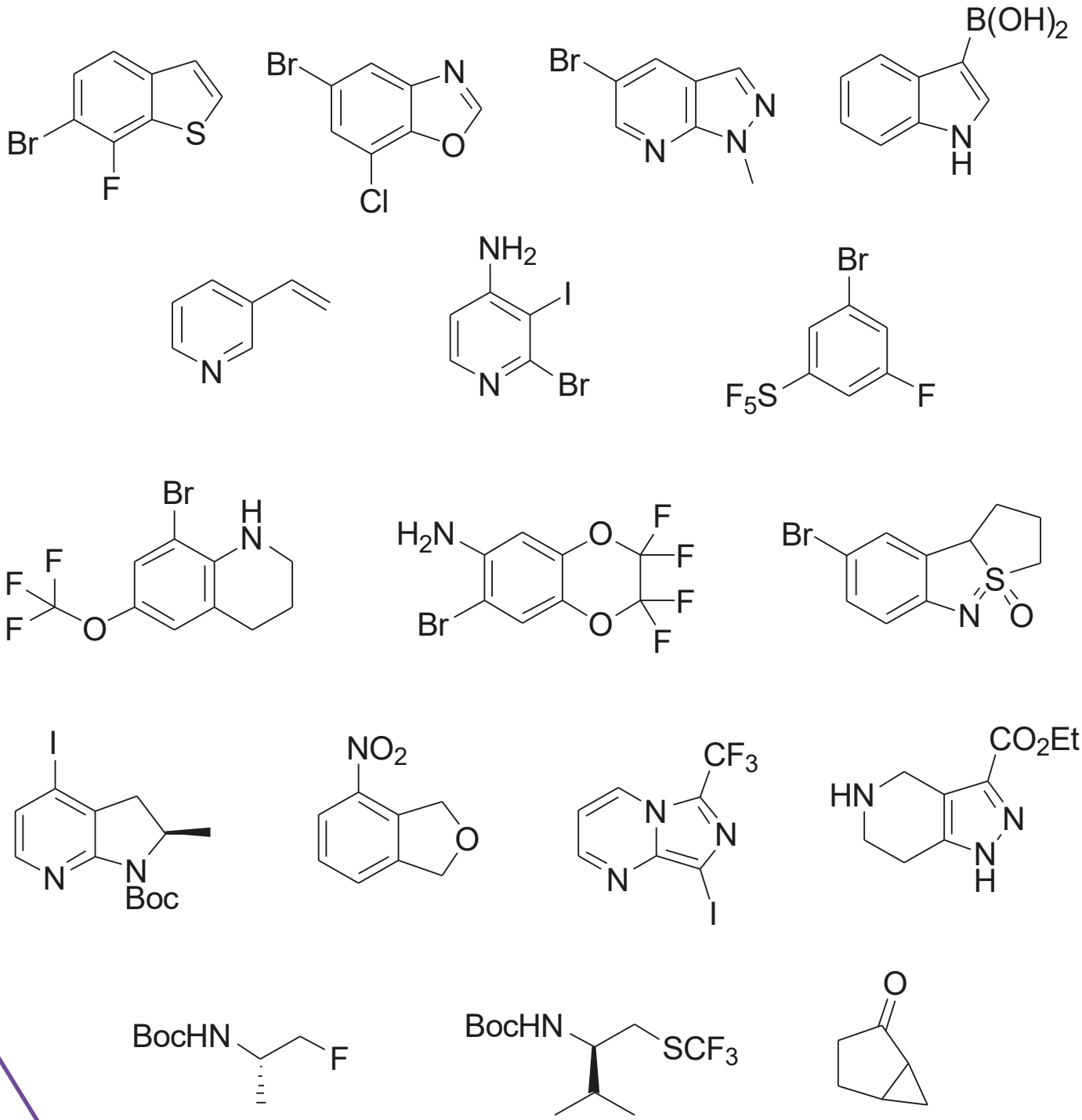

CN
X
R

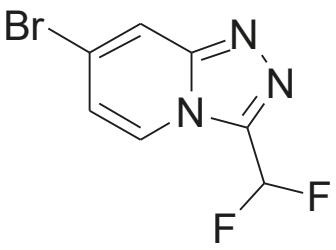

Br
Br
F3CO

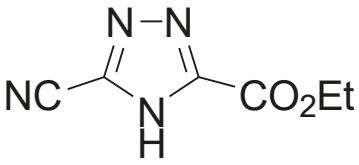

F
X
R

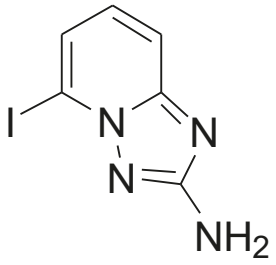
In-house manufacturing

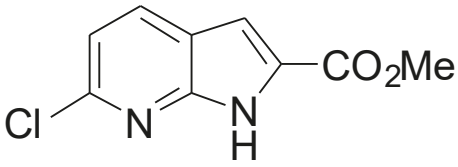
The following are a selection of compounds made in our lab, which demonstrate some of the diversity of products we can make:

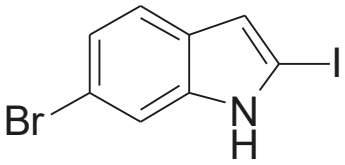


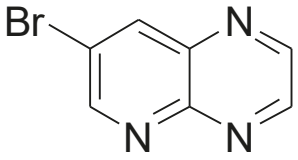

Br
N
N
N
F
F

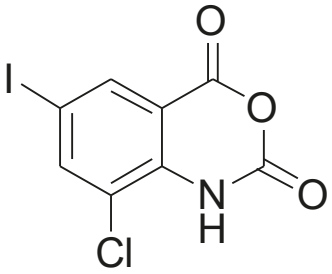

N–N
NC
CO2Et
N
H

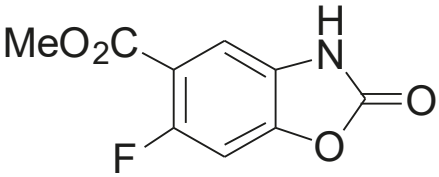

I
N
N
N
NH2

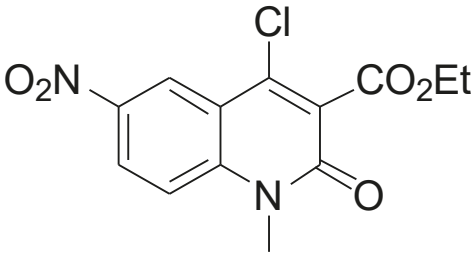

CO2Me
Cl
N
N
H

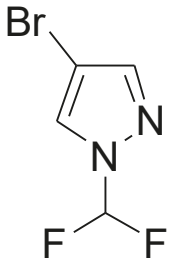

I
Br
N
H

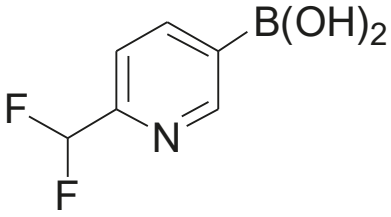

Br
N
N
N

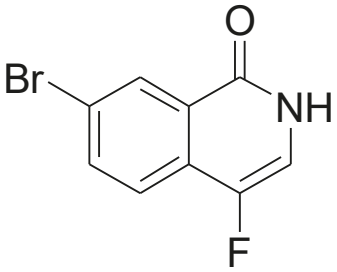

O
I
O
N
H
O
Cl

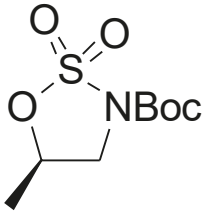

MeO2C
H
N
O
F
O

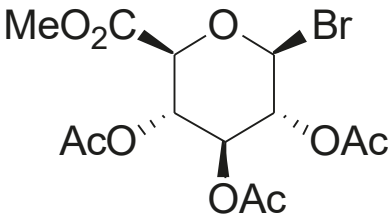

Cl
O2N
CO2Et
N
O

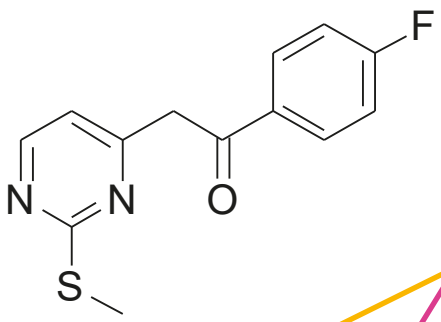

Br
N
N
F
F


B(OH)2
F
N
F


O
Br
NH
F


O
O
S
O
NBoc


MeO2C
O
Br
AcO
OAc
OAc


F
N
N
O
S

CENTRAL GLASS

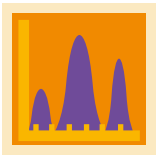
APOLLO SCIENTIFIC
Supporting Discovery

SYNQUEST LABORATORIES

CENTRAL GLASS GROUP AT A GLANCE

Locations & Accreditations

- USA
- Japan ISO9001, ISO14001, OHSAS18001)
- Ecovadis rating Apollo Scientific - Platinum
  Central Glass Ube Plant - Gold.
- UK (ISO9001, ISO14001, AEO & Known Consignor Status)



Production Facilities

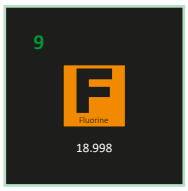
- Reactors from lab scale to 7 kL (Inc. SUS, GL, PFA & Hastelloy)
- High pressure reactors up to 10 L
- Flow reactors for R&D/Medium scale production
- Distillation equipment includes spinning band & wiped film evaporator
- Operational temp ranges from -80 deg C to +280 deg C
- Full analytical suites (inc. GC, HPLC, GC-MS, LC-MS, (U)HPLC with UV-, RI-, Fluorescence-, ELSD- and CAD detection, NMR, IR, KF, GPC, UV, XRD, ICP-MS, ICP-AES, Ion Chromatography, DSC)

Core Technology Competencies

- Continuous reaction
- Batch reaction
- High pressure reaction
- Cryogenic reaction
- Distillation expertise
- High volume fluorination
- Pyrogenic reaction
- Gas Handling
- Phosgenation

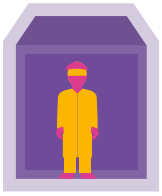
Business Models

- Catalogue compounds (over 25k in stock)
- Custom Synthesis on an FFSA / fixed cost basis R&D on a FTE basis
- Small scale manufacturing/clinical phase I - III supplies
- Large scale manufacturingin batch or continuous production
- Contract Research & Development on a
- Contract/ toll manufacturing
- Sourcing of chemicals from al b commercial scale



Fluorination Expertise

- Selective halex reaction by HF
- Electrochemical fluorination
- Direct fluorination by F_2 Gas
- Triflic acid & derivatives
- Deoxyfluorination (SF^4/DAST etc).
- Trifluoromethylation
- Difluoromethylation
- Balz-Schiemann
- KF exchange



Product Group Strengths

- Substituted aromatic & heterocyclic building blocks/intermediates
- Aliphatic compounds
- Gases
- Fluorinated chiral compounds
- Fluorinating reagents
- API production under GMP
- Key fluorination technology allows us to offer many unique fluorinated compounds, alongside a vast number of non-fluorinated compounds

Find the right chemistry. Speak to us today.

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