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Synthetic Route Design of AZD4635, an $A_{2A}R$ Antagonist

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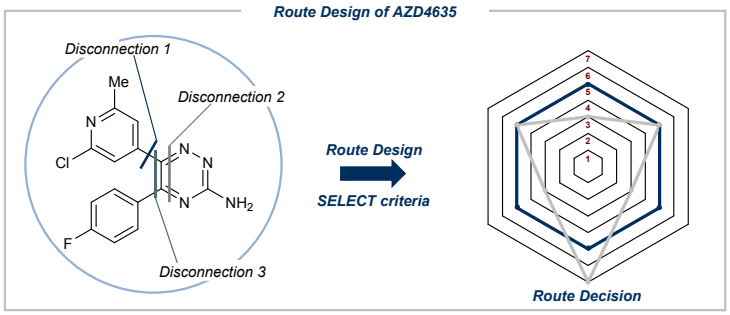
For Table of Contents only



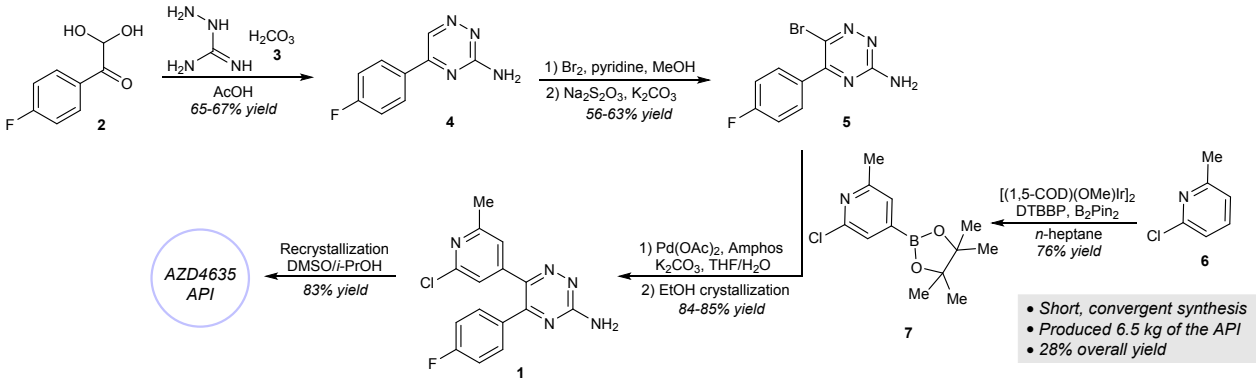
ABSTRACT: The AstraZeneca approach to synthetic Route Design is exemplified through our AZD4635 chemical development programme. The identification of possible new route concepts is presented, as well as their subsequent prioritization for practical exploration based on project objectives. Selected ideas were tested to demonstrate proof of concept for the bond formation strategy, and where successful, were fed into a decision tool based on key SELECTion principles.

KEYWORDS: *Route Design, Process Design, SELECT criteria, Route Decision*

INTRODUCTION

Within AstraZeneca, effective, ambitious Route Design is viewed as integral to the development process, enabling early identification of the best synthetic route for commercial supply. We define Route Design as the identification of our bond formation strategy. Further development of the overall delivery strategy, such as the selection of reagents and conditions (Process Design and Optimization), are a consideration but not a priority of the Route Design exercise. The culture within AstraZeneca promoting Route Design as the most value adding activity in the development process has led to tangible benefits, including savings in supply chain costs, waste reduction, focused application of resource, and reduced regulatory challenge.[1]

AZD4635 (**1**) is an $A_{2A}R$ antagonist currently in clinical trials for the treatment of solid tumours.[2] To date, the original discovery route has been used to meet clinical demands for AZD4635 following development to enable appropriate scale-up. This route is concise and operationally robust, affording **1** in ca. 30% yield over five steps, and has been used to produce 6.5 kg of the active pharmaceutical ingredient (API) (Scheme 1).[3,4,5]

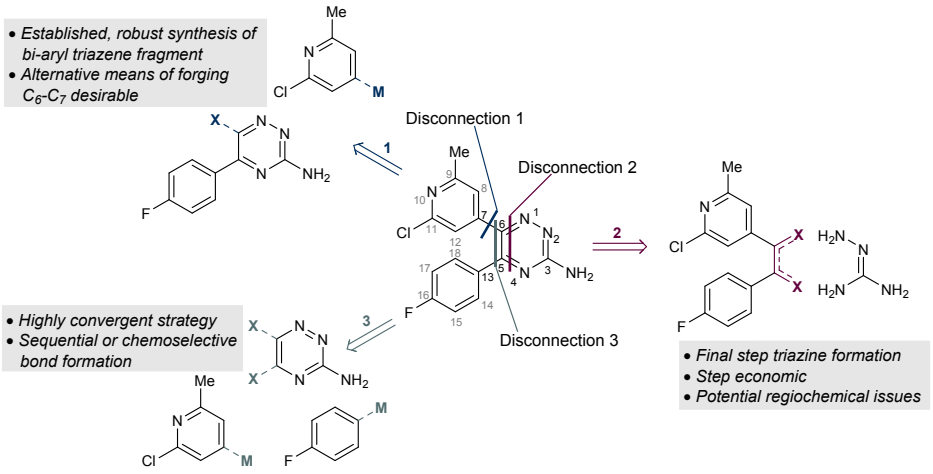


Scheme 1. Developed Route to AZD4635

The key feature of this route is the regioselective preparation of the 3-amino-1,2,4-triazine[6] core **4** through condensation of **2** and amino guanidine **3**. Subsequent bromination gave access to **5** with Suzuki-Miyaura coupling of BPin **7**, obtained through iridium catalyzed borylation of pyridine **6**, delivering AZD4635. The bromination step (**4** to **5**) afforded a moderate isolated of **5** (56-63%).[5] Furthermore, the bromination conditions were identified as being incompatible with tantalum reactor components,[5] and a previous manufacture of the API had to be halted due to reactor corrosion. Although manufacture could be carried out using vessels without metal components, to reduce risk, allow greater flexibility for manufacture, and potentially allow for improvements in overall yield, step count, etc., a second-generation synthesis was desirable for future API deliveries. This prompted a Route Design exercise assessing alternative strategies towards AZD4635, culminating in a Route Decision for future supply of API.

RESULTS AND DISCUSSION

Our Route Design approach begins with idea generation supported by literature searching and the use of retrosynthesis software.[7] We sought to be ambitious in our proposed disconnections and identified several synthetic strategies towards the API (Scheme 2).

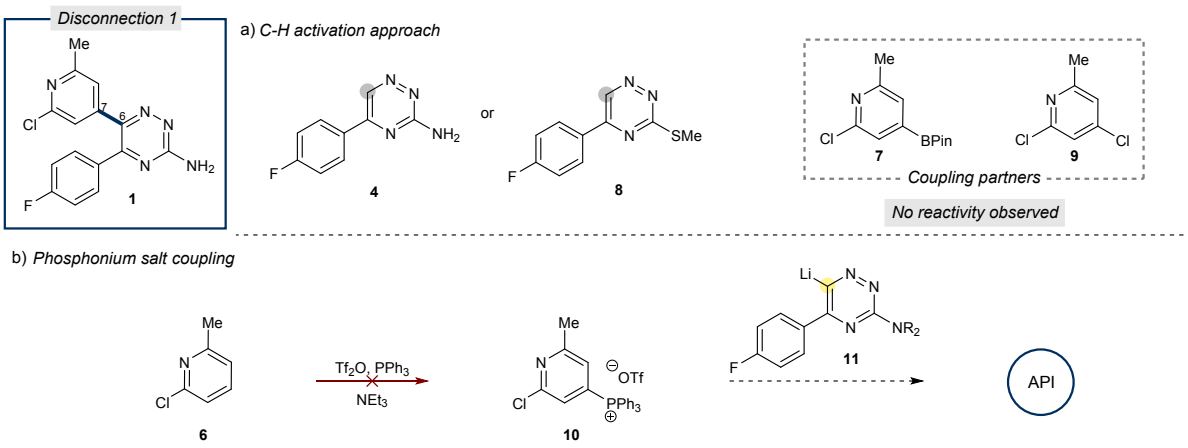


Scheme 2. Key disconnections identified

The synthetic strategies proposed were grouped by key bond disconnections: Disconnections 1 and 3 around the triazine ring, and disconnection 2 of the ring itself. These strategies were then prioritized taking into consideration which approaches were viewed as having a higher likelihood of success based on literature precedent and which were seen as the most value adding with respect to cost, manufacturability, and control (risk/reward). Step count was used as a surrogate for cost at the proof of concept stage, and strategies with a perceived high level of risk due to limited or the absence of literature precedent were prioritized where success would be highly beneficial to the project (high risk, high reward). Disconnections dissecting the amino guanidine unit were avoided as they were not perceived to offer improvement of the original route.[8]

Proof of Concept Work. This strategy could then allow the selection of the most promising routes for further investigation, with specific focus on establishing a proof of concept for key bond formations. In parallel to this, further Process Design activities were also commenced on the original route, with the aim of identifying milder bromination conditions for this stage.

Disconnection 1. The C_6-C_7 disconnection, which was used in the original synthesis,[5] merited further investigation. The robust, efficient synthesis of amino triazine **4** made this disconnection an attractive prospect and therefore alternative means of activating C_6 were investigated. (Scheme 3).

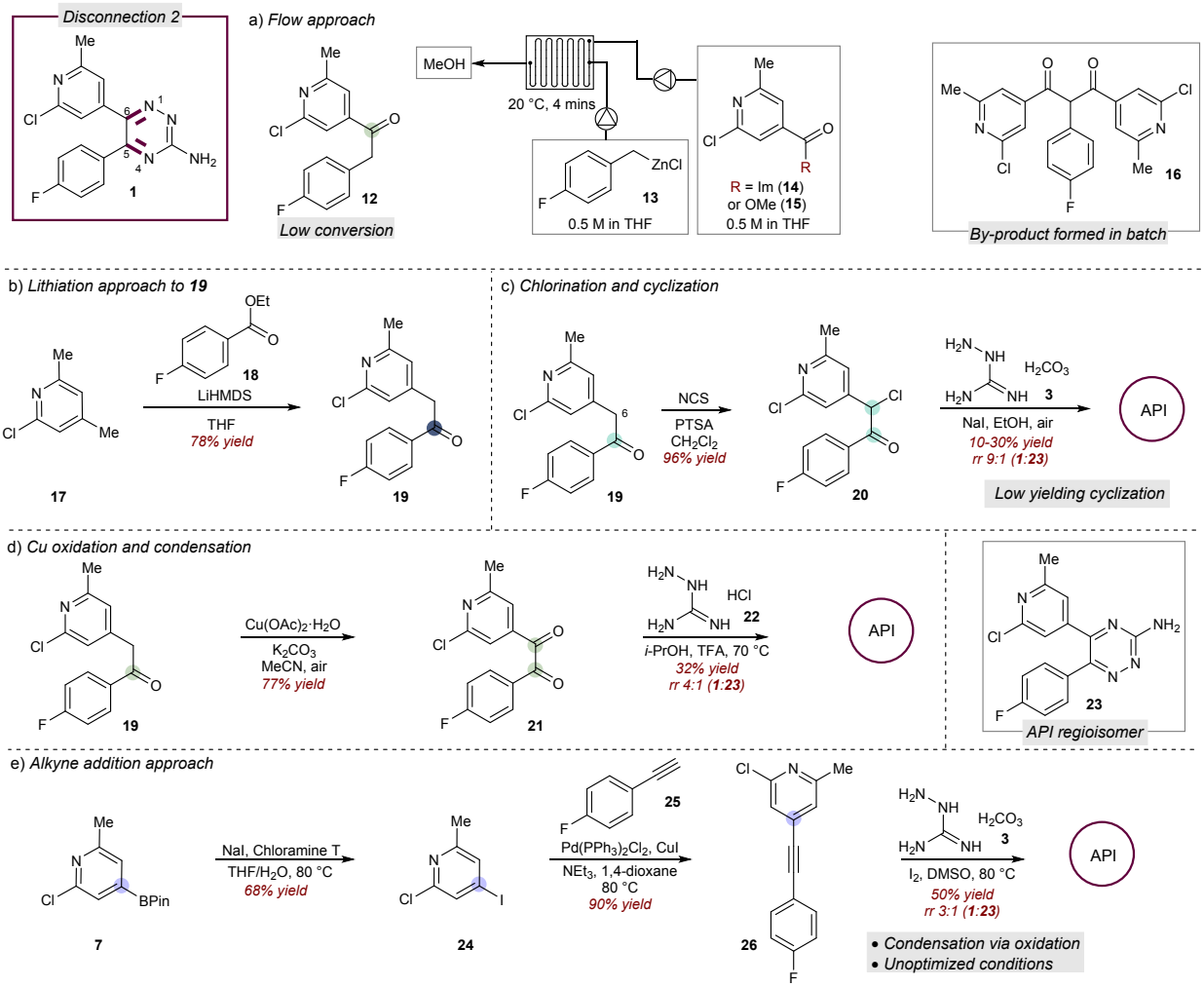


Scheme 3. C_6-C_7 disconnection proof of concept work

To avoid pre-functionalization of C_6, a C-H activation strategy could be a powerful and atom economic means of forging the C_6-C_7 bond, removing a step from the original route (Scheme 3a).[9] Although this was viewed as a higher risk route strategy, due to a lack of literature precedent for the transformation on these substrates, the opportunity to exploit high-throughput experimentation (HTE) techniques to rapidly assess this option made its investigation viable. Thiomethyl analogue **8** was prepared to alleviate concerns over the free NH_2 motif in the C-H activation. A range of conditions were assessed on both **4** and **8**, using aryl BPin **7** and aryl chloride **9** as coupling partners.[10] Disappointingly, no reactivity was observed in this screen, and as such this tactic of C_6-C_7 bond formation could be eliminated from further investigations.

Reports detailing the use of phosphonium salts as pseudo halogens for reaction with nucleophiles inspired us to target phosphonium salt **10** for subsequent reaction with lithiated species **11** (Scheme 3b).[11] This strategy also gave a reduced step count from the original route, and was hoped to be a successful, high yielding means of forging the C_6-C_7 bond. 2-Halo pyridines are known to be competent substrates for phosphonium salt formation,[11] however attempts to synthesise **10** from pyridine **6** did not afford the desired product, rather a mixture of unidentifiable by-products, and this approach was not taken further.[12]

Disconnection 2. The N_1-C_6, N_4-C_5 disconnection was proposed as an efficient means of assembling the fully substituted amino triazine core in a single step (Scheme 4).



Scheme 4. Disconnection 2 proof of concept work. rr = regioisomeric ratio (**1**:**23**)

We investigated the synthesis of a biaryl fragment comprising of the pyridyl and *p*-fluoro benzene rings, which could then be reacted with the amino guanidine **3** to deliver the API.

We targeted mono-ketone **12**, envisaging a step-wise condensation with amino guanidine **3**, activation of the methylene, and final cyclization to furnish the API. Although linear in nature, this approach would allow access to the API in one step less than the original route and was perceived to have a high likelihood of success. Attempts to synthesize mono-ketone **12** from reaction of acyl imidazole **14** and zinc species **13** had resulted in over reaction due to the basicity of the zinc species, forming an impurity consistent with di-ketone **16**. We saw an opportunity to utilize flow chemistry to circumvent this issue by avoiding high concentrations of the reactive species in the presence of the desired product (Scheme 4a). Disappointingly, under these conditions very low conversion to the desired product was observed, and the comparative reaction using methyl ester **15** also gave no conversion to **12**. Alternatively, mono-ketone **19** was targeted. Synthesis of **19** proved facile; ester **18** was reacted with the lithium anion of pyridine **17**, affording mono-ketone **19** in 78% yield (Scheme 4b).[13]

Initial attempts to access a cyclization precursor from **19** focused around the synthesis of α-chloro ketone **20** (Scheme 4c). Treatment of **19** with *N*-chlorosuccinimide (NCS) gave chlorinated compound **20** cleanly and selectively. Cyclization using catalytic NaI and air as oxidant typically afforded AZD4635 in yields of 10–30% and in 9:1 selectivity for the desired

regioisomer. The low yield was due to the formation of several by-products resulting from non-ring closed intermediates and competing dimerization. Attempts to improve the selectivity of this reaction were unsuccessful, and therefore alternative means of activating C_6 were investigated.

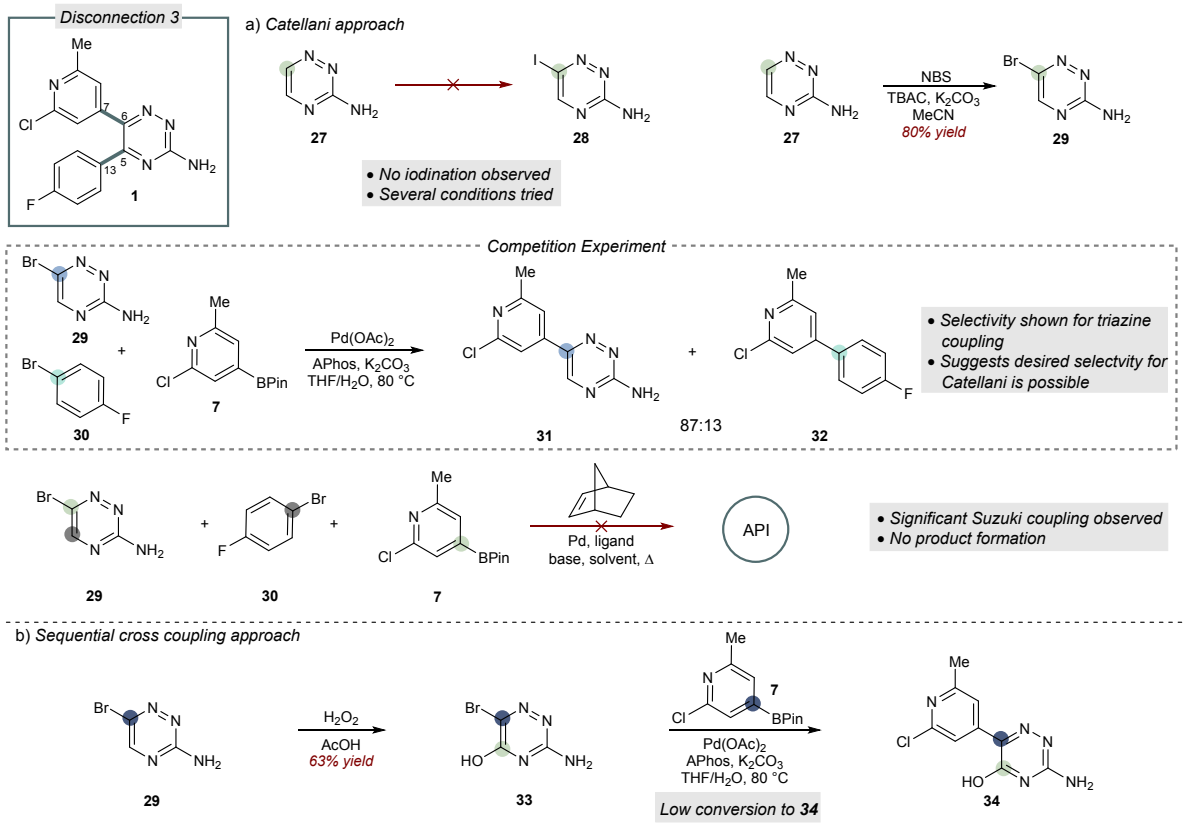
Di-ketone **21** was then targeted as a means of bringing C_5 and C_6 in at the correct oxidation state, despite initial concerns regarding the regioselectivity of the proposed condensation reaction (Scheme 4d).[8] Initial screening for the oxidation of mono-ketone **19** identified a hit using $Cu(OAc)_2 \cdot H_2O$ under air atmosphere. The di-ketone could then be condensed with the amino guanidine **22** to give the API in promising yield of 32% with 4:1 regioselectivity meriting further development *vide infra* and providing proof of concept for this route.

Alternatively, alkyne **26** was viewed as a potential API precursor, in a relatively high risk, but potentially extremely atom efficient strategy (Scheme 4e). Literature precedent for in situ oxidation of alkynes and subsequent condensation with diamine units,[14] as well as the promising results from the di-ketone route (Scheme 4d), gave us optimism for this approach.

Bi-aryl alkyne **26** proved a challenging intermediate to access efficiently. In principle, **26** could be formed through a Sonogashira reaction, disconnecting either the C_6-C_7 bond or C_5-C_{13} bond depending on the coupling partners chosen. As BPin **7** was available in-house, deborylative iodination using NaI and Chloramine T was carried out successfully,[15] affording iodo-pyridyl species **24** in 68% yield. Sonogashira coupling of **24** with aryl alkyne **25** proceeded in 90% yield, giving access to our desired alkyne **26**. Under non-optimized conditions, oxidation of the alkyne and subsequent condensation with amino guanidine **3** afforded the API in 50% yield and 3:1 regioisomeric ratio, in favour of the desired regioisomer **1**. Although this route delivered the API successfully, it was not viewed as favourably as the route from mono-ketone **19** due to the inefficient access to alkyne **26**, and the lack of any obvious way to improve its synthesis.

The most promising route strategy arising from this disconnection was therefore considered to be the formation of mono-ketone **19**, followed by oxidation to di-ketone **21**, and final condensation with amino guanidine **22** to form the API.

Disconnection 3. Bringing in the amino triazine unit intact was an attractive prospect regarding the convergency and efficiency of the synthesis. This strategy would rely on chemoselective bond formation between C_6 and C_7, and C_5 and C_{13} (Scheme 5).



Scheme 5. Disconnection 3 proof of concept work

The Catellani reaction was viewed as a challenging, yet potentially rewarding means of developing a highly convergent synthesis of the API (Scheme 5a).[16] Disconnection of the triaryl motif afforded three proposed fragments; iodo **28**, known BPin **7**, and aryl bromide **30**. Concerns were raised surrounding the use of the amino triazine core which cast doubt on the viability of this chemistry with respect to our API. It was unclear how the presence of the ortho-nitrogen of the desired iodo-triazine would affect the reaction, as the Catellani reaction typically requires a substituent ortho to the iodide, known as the ortho-effect.[17]

Disappointingly, we were unable to access the desired iodo **28** from iodination of unsubstituted amino triazine **27**. Catellani type reactions have largely been limited to aryl iodides, the "aryl iodide constraint",[18] however there are literature examples of aryl triflates[19] and bromides.[18] Bromination of **27** proceeded smoothly, and therefore we considered the use of bromo **29** in the Catellani reaction. To cleanly access our API, we required chemoselective oxidative addition to bromo **29** in the presence of **30**.[18] To give an indication of whether this approach would be viable, we carried out a competitive Suzuki-Miyaura reaction using **29** and **30**. Under the conditions utilized for the Suzuki-Miyaura coupling to prepare AZD4635 in the original route, the coupling was largely selective for the triazine bromide **29**, affording **31** and **32** in 60% and 9% conversion respectively (ratio ca. 6.5:1). Encouraged by this result, we investigated the desired Catellani reaction with bromo **29**, bromo **30**, and BPin **7**. Disappointingly, from a screen of typical Catellani conditions,[18] we observed no formation of the desired API.[10] At this juncture we considered the significant amount of screening likely to be required to develop conditions making the Catellani a competitive route with regard to the alternative strategies being developed, and therefore we chose not to progress with the Catellani based approach.

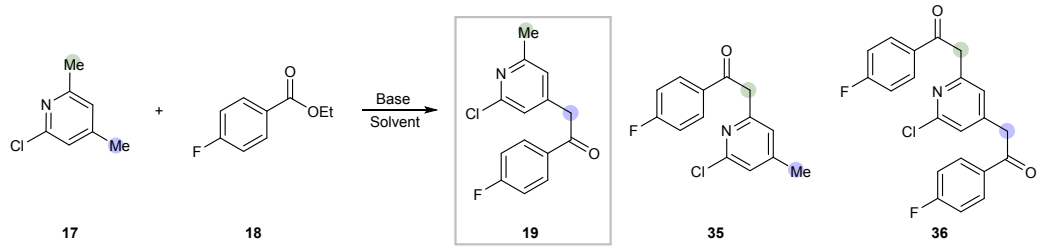
An analogous method was also envisaged where C_6-C_7 and C_5-C_{13} could be formed through sequential cross couplings (Scheme 5b). We proposed that access to bromo/hydroxy compound **33** could enable coupling with the required pyridyl nucleophile and, following conversion of the hydroxy moiety to a triflate, enable coupling with a *p*-fluoro aryl nucleophile.

Key precursor **33** was prepared by oxidation of bromo **29** with H_2O_2.[20] We then used the Suzuki-Miyaura conditions developed for the preparation of AZD4635 to carry out the coupling. Disappointingly, moderate conversion to product **34** was observed in this reaction, ca. 40%, with the formation of several unidentified by-products. Clean isolation of the Suzuki-Miyaura product was challenging and, due to time constraints, this approach was not investigated further.

Process Design and Optimization of Selected Route Strategies. Following these proof of concept studies, the most promising new strategy was identified as the di-ketone condensation route (Scheme 4d) and therefore Process Design activities were initiated to develop this route option.

The formation of mono-ketone **19** was further investigated. It was found that the regioselectivity of deprotonation was both base and solvent dependent (Table 1).

Table 1. Base and solvent dependence of mono-ketone **19** formation[a]



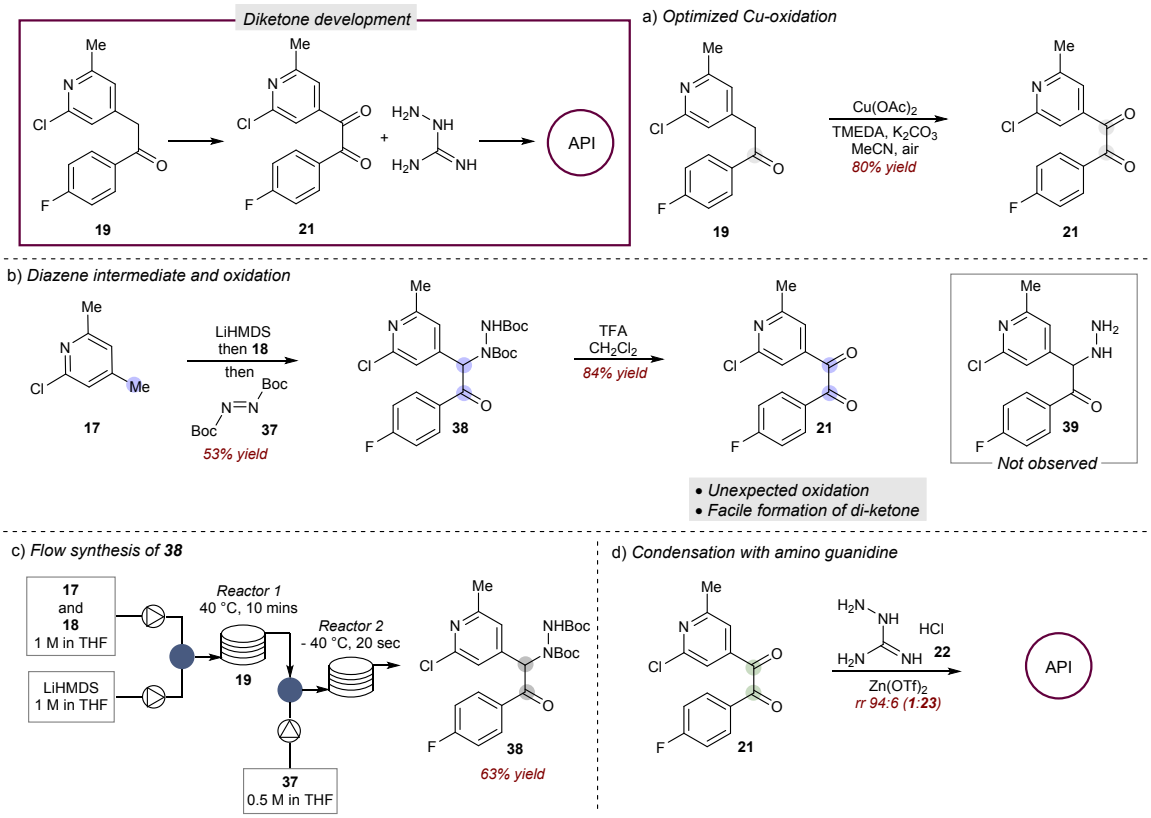
17 18 19 35 36

Entry	Base	Solvent	Time (h)	19[c]	35[c]	36[c]
1	LiHMDS	THF	4	89	1	5
2	LiHMDS	2-MeTHF[b]	4	33	34	25
3	LiHMDS	TBME	4	0	65	0
4	LiHMDS	Toluene[d]	4	0	41	0
5	LiHMDS	Hexane	4	0	43	0
6	NaHMDS	THF	4	31	58	3
7	KHMDS	THF	4	29	33	1
8	KHMDS	2-MeTHF	4	18	41	1
9	KHMDS	TBME	4	7	76	7

[a]Reactions were carried out using **17** (7.06 mmol, 1.00 equiv), **18** (7.08 mmol, 1.00 equiv), base (1.00 M, 16.0 mmol, 2.30 equiv) at 20 °C. [b]LiHMDS 0.50 M in 2-MeTHF. [c]Area% calculated by HPLC at 220 nm. [d]Area% of toluene subtracted from chromatograph.

The use of less polar solvents than THF led to a reversal of selectivity, affording regioisomer **35** rather than the desired product **19** (entries 3–5). 2-MeTHF gave equal amounts of **19** and **35**, and an increase in double addition product **36** (entry 2). Change of the HMDS counterion also gave a decrease in selectivity, with low conversion to the desired product (entries 6–9). These effects are consistent with an interaction between the pyridyl nitrogen and the counterion, facilitating the reaction at the less acidic 2–methyl group.[21] Therefore, we retained the original conditions of LiHMDS in THF.

Diketone **21** was originally accessed through Cu-mediated oxidation of **19** under air (Scheme 4d). We sought to improve reaction understanding and assess the overall sequence as a potential route for API manufacture (Scheme 6).



Scheme 6. Development of the di-ketone condensation route. rr = regisomeric ratio

We observed that the outcome of the oxidation was highly dependent on the agitation of the reaction mixture and concluded that this was a result of variable oxygen mass transfer. Optimized conditions of 5 mol% $Cu(OAc)_2$ in MeCN, with tetramethylethylenediamine (TMEDA), K_2CO_3 and bubbling air through the reaction gave full conversion of the starting material in 16 h, and **21** in 80% isolated yield (Scheme 6a).

Due to potential safety concerns regarding the atmospheric oxidation,[22] we assessed whether the reaction could run efficiently under an atmosphere of 5% oxygen. Disappointingly, it was found that the oxidation only progressed to ca. 20% conversion after 20 h under these conditions. Running the reaction under air in a water/MeCN (9:1 v/v) solvent mixture to reduce flammability did not give any conversion to the desired product. There are literature reports of using (NMP), a high flash point solvent (90 °C), to allow the safe use of air as an oxidant, however in this solvent conversion to the desired product was very low ca. 5%.[23]

Given these safety concerns, alternative routes from **19** were investigated. Quenching of the lithium enolate of **19** with diazene **37** afforded intermediate **38** (Scheme 6b). When deprotection of **38** was attempted under acidic conditions, with the hope of reacting the deprotected product **39** with urea equivalents such as cyanamide, the unexpected formation of di-ketone **21** was observed. This was not dependant on atmospheric oxygen as equivalent results were obtained when the reaction was carried out under inert conditions. Although the

specific mechanistic details of this transformation remain unclear, we assessed this route in flow as an alternative means of safely accessing di-ketone **21** on scale (Scheme 6c).

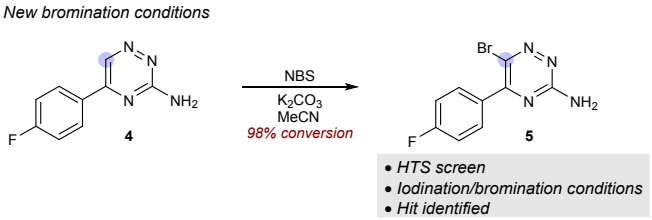
Assessment of flow conditions towards the mono-ketone (**19**) showed that although higher temperatures enabled shorter residence times, they also increased formation of a by-product resulting from dimerization. Therefore, a residence time of 10 minutes at 40 °C was selected. The quench with diazene **37** had been carried out successfully at –70 °C in batch, however this was not compatible with the flow process as the 0.5 M solution of **37** began to crystallize at temperatures lower than –50 °C. A residence time of 20 seconds at –40 °C was found to be optimal, and this process gave **38** in 63% yield after work-up and crystallization. Deprotection to di-ketone **21** could then be carried out in batch. With a means of accessing di-ketone **21** in hand, we focused on the key condensation with amino guanidine **22** (Scheme 6d).

In initial experiments, we screened a range of conditions to assess di-ketone conversion, by-product formation, and regioselectivity.[10] The best conditions identified at this point were 1.1 equiv **22** in H_2O/*i*-PrOH at reflux, affording AZD4635 in 50% isolated yield and 87:13 regioselectivity. Several by-products resulting from condensation of the di-ketone with two equivalents of amino guanidine, or incomplete condensation were identified, and further optimization sought to reduce these. We found that guanidine salts of stronger acids i.e. HCl gave improved regioisomeric ratios as did reduced water levels. Where acid additives were added ($MeSO_3H$ or H_3PO_4), higher charges of the additive also improved regioselectivity, however the higher acid charge resulted in reduced yields arising from degradation.[10]

This prompted us to assess Lewis acids as an alternative means of activating the reaction. A screen of Lewis acid mediators was carried out,[10] and the reactions showing promising (> 9:1) regioselectivity were considered for further development. $Zn(OTf)_2$ gave a regioisomeric ratio of 94:6 in favour of the desired regioisomer, however conversion to the API was incomplete. Due to time constraints, when the Route Decision was made, these conditions had not been progressed further, however we had obtained proof of concept and were confident the reaction could be optimized. Further studies showed that the unwanted regioisomer **23** could be purged to 0.04% by slurrying in hot toluene, which gave us further confidence in the potential of this route.

Overall, this three-step route (mono-ketone **19** formation, oxidation to **21**, and condensation with amino guanidine) delivered the API in 30% yield and high purity, and was therefore competitive with the current route, despite the limited optimization carried out. Although the oxidation of **19** to **21** gave concerns with regard to process safety on scale up, we were confident that safe, efficient conditions could be established. We considered running the oxidation in flow or the use of a chemical oxidant as safer alternatives to be investigated should the route be progressed, and the potential for these improvements was taken into account in the Route Decision.

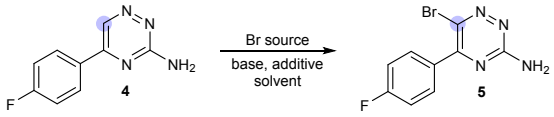
During the Route Design exercise, Process Design on the original bromination was carried out with the aim of identifying milder conditions for this transformation. Both bromination and iodination conditions for **4** were assessed via a HTE format.[10] A hit was identified from this screen and, following further optimization, new conditions were identified. *N*-bromosuccinimide (NBS) and K_2CO_3 in MeCN displayed 98% conversion of the starting material (Scheme 7).



Scheme 7. Bromination hit from HTE screening

As the initial bromination hit required stringent inertion and was capricious outside of a glovebox, a second round of HTE was carried out to develop these conditions. The screen was carried out in a 96-well plate format, looking at a wide range of bromination conditions (Table 2).

Table 2. Optimization of bromination hit[a]



Entry	Br source (equiv.)	Base (equiv.)	Additive (equiv.)	Solvent	5 (%)[b]
1	NBS (1.2)	DBU (2)	-	MeCN	71
2	NBS (1.2)	DBU (2)	-	EtOAc	82
3	DBH (0.6)	DBU (2)	-	EtOAc	74
4	NBS (1.2)	TBACl (2)	-	MeCN	67
5	NBS (1.2)	K_2CO_3 (2)	-	MeCN	78
6	NBS (1.2)	K_2CO_3 (2)	TBACl (1)	MeCN	quant. (64[c])
7	NBS (1.2)	K_2CO_3 (2)	TBACl (1)	PrCN	99
8	DBH (0.6)	K_2CO_3 (2)	TBACl (1)	MeCN	96
9	Br_2 (1.2)	K_2CO_3 (2)	TBACl (1)	MeCN	86

[a]Reactions were carried out using 0.1 mmol **4**, at 25 °C in a glovebox. [b]HPLC conversion at 20 h, *m*-terphenyl (0.04 M in PhMe) used as internal standard. [c]Reaction carried out on 1.05 mmol **4**, isolated yield.

The addition of tetrabutylammonium chloride (TBACl) was found to be beneficial (presumably generating BrCl as the active brominating agent in situ).[24] NBS was typically the best brominating agent, followed by 1,3-dibromo-5,5-dimethylhydantoin (DBH), with bromine the least effective. NBS in combination with K_2CO_3 and TBACl gave full conversion in MeCN and could reliably be performed outside a glovebox (Entry 6). At this point the work-up and isolation of **5** was unoptimized, affording an isolated yield of 64%. The cause of the low isolated yield was unclear however we were confident that with further development this could be improved. These milder bromination conditions did not display the corrosive properties of the previous reaction (Scheme 1),[5] and therefore rendered the original route significantly more attractive with respect to further campaigns.

Route Decision. At the time of the scheduled route decision, the new route work had not undergone significant development, however we undertook the decision process considering the potential for the improvement of the new routes through further process development. We defined our parameters for assessment using SELECT criteria; the Safety of the route, the

Environmental impact of the route, Legal considerations, Economic factors, the Control of the route, and the potential Throughput of the route.[25] These parameters were considered in turn for the routes assessed, and a benchmark set i.e. all parameters in the current route were scored 5.

When all potential new routes were assessed against each other, the di-ketone condensation route (Scheme 6), furthermore known as New Route One (NR1), was considered the most promising and lowest risk of the new approaches. Although the new bromination conditions had not undergone significant development, the bromination step was embedded in an otherwise reliable and well-developed route.[5] Therefore, a Pugh matrix[26] was used to compare NR1 and the original route, incorporating the newly developed bromination conditions, with the original route set as the benchmark (Figure 1).

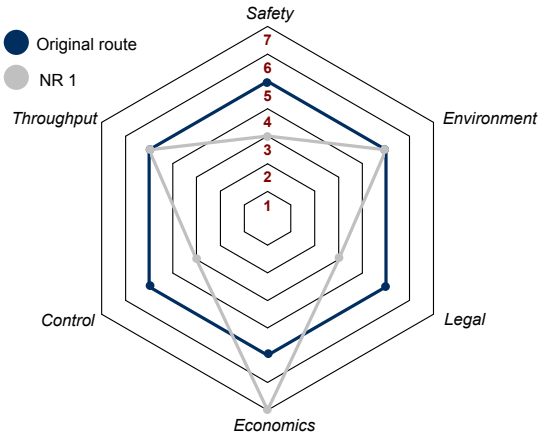


Figure 1. Pugh matrix scoring the original route (new bromination conditions) and NR1

Consideration of the SELECT criteria surrounding the original route identified risk regarding the inclusion of the new bromination process and therefore potentially new impurities, and possible problematic off-gassing from the borylation stage (H_2). The environmental impact of the Ir catalyst and the relatively low atom economy (halogenation/borylation stages) were considered. At the time of the route decision, we had limited understanding of the new bromination reaction, including its mechanism, inertion requirements, and concerns surrounding product isolation. However, the route historically delivered high quality material, in good overall yield (35% excluding final recrystallization), and therefore was seen as a robust means of API delivery.

As previously mentioned, NR1 had safety concerns surrounding the use of atmospheric oxygen and with respect to the purging of impurities which had undergone little development. Each stage required high dilution (≥ 30 L/kg limiting reactant), however NR1 had excellent atom economy, and was a step shorter than the original route. However, the formation of the API regioisomer in the final bond-forming step of the process, and limited purge data available represented a significant risk to the control strategy for this route going forward. The route supplied high quality material in good overall yield (30% excluding final recrystallization), however had not yet been assessed beyond gram scale.

A direct comparison of the key parameters is shown in Table 3.

Table 3. Direct Comparison of Key Parameters

Parameter	NR1	Original Route (New Bromination)
Step Count	3 linear	4 (3 linear)
Yield	Predicted 30%	Predicted 35%
Atom Economy	High	Bromination and Borylation

CONCLUSION

When all factors were considered, the decision was taken to progress the original route. Despite the fact that the new routes were not progressed, the Route Design exercise could still be considered a success. The strategic framework of an AZ Route Design programme was used to ensure the route decision taken was as informed as possible. The new routes investigated were identified and the prioritization of these routes was based on our ideal of ambitious Route Design, including strategies which were viewed as "high risk, high reward" such as the Catellani approach. Despite the short time frame available, the new route work was carried out to achieve proof of concept of novel bond disconnections and was successful in delivering new routes to contend with the original process. The information generated enabled structured decision making to confidently make the best informed Route Decision.

EXPERIMENTAL METHODS

General. All reactions were carried out in dry vessels under an atmosphere of dry nitrogen unless otherwise specified. All reagents and solvents were used as received without further purification unless specified. NMR spectra were recorded on a Bruker 500 MHz or 400 MHz spectrometer. Accurate mass spectra analyses were recorded on a Waters LC-MS ZQ 2000 system in positive electrospray ionization mode (ESI). Reactions carried out in microwave tubes were brought to the desired reaction temperature in a heating block.

HPLC Methods. *Flow synthesis of **12**.* Samples for HPLC analysis (conversion to product) were prepared through the addition of 1:1 (v/v) MeCN:H_2O (1 mL) to a sample of the reaction following quench with MeOH. HPLC was obtained on an Agilent 1100, using a Phenomenex Kinetex C18 column. Analysis was performed using a gradient method, eluting with 5% of a 1% (v/v) aqueous TFA solution, 5-90% MeCN in H_2O over 4.8 minutes at a flow rate of 1.2 mL/min and a wavelength of 220 nm.

Mono-ketone formation screening (Table 1). Samples for HPLC analysis (20 µL aliquot of crude reaction) were diluted into a 10% solution of citric acid in 1:1 (v/v) MeCN/H_2O (1.5 mL), injection volume 3 µL. HPLC was obtained on an Agilent 1100, using a Acquity BEH Phenyl column. Analysis was performed using a gradient method, eluting with 3% of a 1% (v/v) aqueous TFA in 5-90% MeCN in H_2O over 6.2 minutes at a flow rate of 2.0 mL/min and a wavelength of 220 nm.

AZD4635 regioisomer determination. Samples for HPLC analysis (20 µL aliquot of crude reaction) were diluted into 1:1 (v/v) MeCN/H_2O (1.5 mL), injection volume 3 µL. HPLC was obtained on an Agilent 1100, using a Acquity BEH C18 column (40°C). Analysis was performed using a gradient method, eluting with 0.003% (v/v) TFA in MeCN and 0.003% (v/v)

TFA in H_2O over 17.3 minutes (5%-90%), then held to 23.5 minutes at a flow rate of 2.0 mL/min and a wavelength of 271 nm.

Halogenation screening (Scheme 7). Samples for HPLC analysis were prepared by taking a 10 µL aliquot of the reaction mixture and diluting into 4:1 (v/v) MeCN/H_2O (1.5 mL), 1.0 µL injection volume. HPLC was obtained on an Agilent 1100, using a Phenomenex Kinetex C18 column. Analysis was performed using a gradient method, eluting with 5-95% of a 0.03% (v/v) TFA/MeCN solution in a 0.03% (v/v) aqueous TFA solution over 5 minutes at a flow rate of 1.2 mL/min and a wavelength of 220 nm.

Bromination screening (Table 2). Samples for HPLC analysis were prepared through the addition of DMSO (200 µL) to the reaction and stirring for 10 minutes. A 10 µL aliquot was then taken and diluted into 4:1 (v/v) MeCN/H_2O (1.5 mL), 0.7 µL injection volume. HPLC was obtained on an Agilent 1100, using a Phenomenex Kinetex C18 column. Analysis was performed using a gradient method, eluting with 5-95% of a 0.03% (v/v) TFA/MeCN solution in a 0.03% (v/v) aqueous TFA solution over 5 minutes at a flow rate of 1.2 mL/min and a wavelength of 220 nm.

*Characterization data of AZD4635 (**1**)*: ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.72 (br s, 2H), 7.51-7.46 (m, 2H), 7.30-7.24 (m, 3H), 7.15 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 163.3 (d, $^1J_{C\text{-}F}$ = 248.5 Hz), 161.9, 159.1, 155.9, 149.1, 147.9, 145.4, 131.9 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 131.9, 122.0, 120.6, 115.5 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 23.60; ^{19}F NMR (470 MHz, DMSO-d_6): δ -109.96; HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{12}N_5ClF$) requires *m/z* 316.0765, found *m/z* 316.0766.

*Synthesis of **8***. Aminothiourea (5.00 g, 54.9 mmol, 1.00 equiv) and EtOH (55 mL) were charged to a 100 mL flask and iodomethane (3.4 mL, 55 mmol, 1.00 equiv) added in one portion. The reaction was brought to 75 °C for 5 h. The reaction was allowed to cool to room temperature and the solvent removed in vacuo to afford a pale yellow solid. The material was washed with MTBE (30 mL) and filtered under vacuum until dry to afford 3-amino-2-methyl-isothiourea hydroiodide as an off-white solid (12.32 g, 52.86 mmol, 96%) which was used without further purification. 1-(4-Fluorophenyl)-2,2-dihydroxy-ethanone (1.00 g, 5.88 mmol, 1.00 equiv), 3-amino-2-methyl-isothiourea hydroiodide (1.51 g, 6.47 mmol, 1.10 equiv), and acetic acid (12 mL) were charged to a flask and the reaction brought to 75 °C for 3 h. The reaction was allowed to cool to room temperature, diluted with water (200 mL) and extracted with EtOAc (4 x 100 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a dark brown residue. The material was purified by flash silica column chromatography, eluent 20% EtOAc/*iso*-hexane, to afford a dark orange solid. The material was then dissolved in minimal CH_2Cl_2, and *iso*-hexane added until a precipitate formed. The solid was filtered and dried in vacuo to afford triazine **8** as a pale orange solid (708 mg, 3.20 mmol, 54%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.82 (s, 1H), 8.45-8.36 (m, 2H), 7.50-7.43 (m, 2H), 2.68 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 172.4, 165.0 (d, $^1J_{C\text{-}F}$ = 251.8 Hz), 153.1, 142.6, 130.6 (d, $^3J_{C\text{-}F}$ = 9.3 Hz), 129.3 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 116.5 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 13.2; ^{19}F NMR (470 MHz, DMSO-d_6): δ -106.56; HRMS: exact mass calculated for $[M+H]^+$ ($C_{10}H_9N_3FS$) requires *m/z* 222.0501, found *m/z* 222.0504.

*Flow synthesis of **12***. 2-Chloro-6-methyl-pyridine-4-carboxylic acid (2.57 g, 15.0 mmol, 1.00 equiv), 1,1'-carbonyldimidazole (2.55 g, 15.4 mmol, 1.03 equiv), and THF (24 mL) were charged to a 50 mL vessel in a glovebox. The reaction was stirred overnight and then concentrated in vacuo to afford **14** as a solid which was used without further purification. In a Uniqsis FlowSyn system, the lines and reactor plate were flushed with MeOH, and then feeds 1 and 2 were flushed with dry THF. Once the system was completely purged the lines were

filled with their respective feeds. 4-fluorobenzylzinc chloride (0.50 M in THF, 0.15 mL/min) and **14** (0.25 M in THF, 0.30 mL/min) were fed into a Uniqsis glass chip (1.8 mL) at 20 °C. The residence time was 4 minutes. The crude solution was then quenched into MeOH. Very low conversion to product observed ca. 5%.

*Synthesis of ketone **19***. LiHMDS (1.00 M in THF) (577 mL, 577 mmol, 2.05 equiv) was charged to a 1 L vessel which had been purged with nitrogen. The vessel was cooled to 10 °C and a mixture of 2-chloro-4,6-dimethyl-pyridine (**17**) (40.0 g, 283 mmol, 1.00 equiv) and ethyl-4-fluorobenzoate (**18**) (47.5 g, 283 mmol, 1.00 equiv) added dropwise using an addition funnel over 1 h. Once complete, the addition funnel was rinsed with THF (20 mL) and the reaction maintained at 10 °C overnight. The jacket temperature was set to -10 °C and the reaction quenched by dropwise addition of aq. H_2SO_4 (2.00 M, 300 mL) over 1 h and the phases separated. The aqueous phase was separated, and the batch was then distilled at 40 °C and 186 mbar over 1.5 h. Toluene (400 mL) was added and the mixture was distilled to ca. 400 mL at 55 °C and 160 mbar. Water (200 mL) was added and the layers separated. The aqueous was removed and the organics heated to 60 °C before being filtered. The filtrate was recharged to the jacketed vessel and distilled to ca. 200 mL at 60 °C and 100 mbar. The solution was maintained at 60 °C and heptane (200 mL) added dropwise over 1 h. The solution was seeded and stirring continued at 60 °C overnight. The slurry was cooled to 0 °C over 5 h and stirred overnight at 0 °C. The slurry was filtered and the cake washed with heptane (120 mL) followed by 2-propanol (120 mL). The cake was dried at 40 °C under vacuum to constant weight to give ketone **19** as an off-white solid (62.6 g, 221 mmol, 78%). Assay (QNMR) 93% w/w.
A portion of the material was further purified by recrystallization from 2-propanol for analytical data. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15-8.09 (m, 2H), 7.44-7.35 (m, 2H), 7.24 (s, 1H), 7.16 (s, 1H), 4.48 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 194.7, 165.2 (d, $^1J_{C\text{-}F}$ = 252.3 Hz), 158.6, 149.2, 148.3, 132.9 (d, $^4J_{C\text{-}F}$ = 2.8 Hz), 131.3 (d, $^3J_{C\text{-}F}$ = 9.6 Hz), 124.0, 122.6, 115.8 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 43.4, 23.4; ^{19}F NMR (376 MHz, DMSO-d_6): δ -105.43; HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{12}NOFCl$) requires *m/z* 264.0591, found *m/z* 264.0596.

*Synthesis of chloro **20***. Ketone **19** (200 mg, 0.758 mmol, 1.00 equiv), PTSA (mono-hydrate) (7 mg, 0.0368 mmol, 0.05 equiv), and CH_2Cl_2 (1.5 mL) were charged to a flask and NCS (104 mg, 0.779 mmol, 1.03 equiv) added portionwise and the reaction stirred for 2 h. The reaction was diluted with water (10 mL) and the organics extracted with CH_2Cl_2 (3 x 10 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a colourless oil. The crude material was purified by flash silica column chromatography, eluent 15% EtOAc/*iso*-hexane, to afford chloro **20** as a colourless oil (216 mg, 0.725 mmol, 96%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03-7.98 (m, 2H), 7.25 (s, 1H), 7.20-7.13 (m, 3H), 6.05 (s, 1H), 2.54 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 188.9, 166.5 (d, $^1J_{C\text{-}F}$ = 258.0 Hz), 160.4, 151.3, 147.3, 132.2 (d, $^3J_{C\text{-}F}$ = 9.7 Hz), 130.0 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 121.3, 120.6, 116.5 (d, $^2J_{C\text{-}F}$ = 22.1 Hz), 58.3, 24.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ -101.89; HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{11}NOFCl_2$) requires *m/z* 298.0202, found *m/z* 298.0204.

*Synthesis of AZD4635 (**1**) (Scheme 4c)*. Chloro **20** (100 mg, 0.34 mmol, 1.00 equiv) and EtOH (1 mL) were charged to a flask. 1-aminoguanidine bicarbonate (**3**) (46 mg, 0.34 mmol, 1.00 equiv) and NaI (10 mg, 0.07 mmol, 0.20 equiv) were added and the reaction stirred at room temperature overnight. Analysis showed incomplete oxidation to the desired product and therefore the reaction was heated to 75 °C for 2 h. The reaction was cooled to room temperature and water (0.5 mL) added. The reaction was stirred for 2 h before being filtered under vacuum until dry to afford AZD4635 (**1**) as a pale yellow solid (17 mg, 0.054 mmol, 16%, **1**:**23** = 9:1).

*Synthesis of di-ketone **21** (Scheme 4d).* Ketone **19** (100 mg, 0.379 mmol, 1.00 equiv), $Cu(OAc)_2 \cdot H_2O$ (4 mg, 0.0200 mmol, 5 mol%), K_2CO_3 (2 mg, 0.0145 mmol, 5 mol%) and CH_3CN (1 mL) were charged to a vial and the reaction stirred vigorously under air for 72 h. 77% ^{1}H NMR assay yield, benzylbenzoate as standard. See optimized procedure (Scheme 6a) for characterization data.

*Synthesis of AZD4635 (**1**) (Scheme 4d).* Diketone **21** (1.00g, 3.53 mmol, 1.00 equiv), 1-aminoguanidine hydrochloride (**22**) (507 mg, 4.59 mmol, 1.30 equiv), and *i*-PrOH (20 mL) were charged to a flask, TFA (1 mL, 13.1 mmol, 3.70 equiv) added and the reaction heated to 70 °C under air for 5 h. The reaction was allowed to cool to room temperature, quenched with NEt_3 (1.63 mL, 11.7 mmol, 3.32 equiv) and diluted with water (30 mL). The reaction was stirred for 16 h and filtered to afford AZD4635 (**1**) as an orange solid (403 mg, 1.28 mmol, **1**:**23** = 4:1, Assay (QNMR) 89.5%, 32% corrected yield).

*Synthesis of iodo **24**.* BPin **7** (200 mg, 0.625 mmol, 1.00 equiv) was charged to a 3-neck flask fitted with reflux condenser and the flask purged with nitrogen (x 3). THF (2 mL) and water (2 mL) were added and the flask wrapped in aluminium foil. NaI (468 mg, 3.12 mmol, 5.00 equiv) was added, followed by chloramine T (527 mg, 1.87 mmol, 3.00 equiv) and the reaction brought to 80 °C for 4 h. The reaction was allowed to cool to room temperature before being quenched by dropwise addition of $Na_2S_2O_3 \cdot 5(H_2O)$ (620 mg, 2.50 mmol, 4.00 equiv) in water (8 mL). The organics were extracted with EtOAc (3 x 20 mL), combined, dried over Na_2SO_4, filtered, and evaporated to afford a beige solid. The crude material was purified by flash silica column chromatography, eluent EtOAc/*iso*-hexane, to afford iodo **24** as a white solid (107 mg, 0.422 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (s, 1H), 7.47 (s, 1H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.0, 150.8, 131.1, 129.9, 106.9, 23.9; HRMS: exact mass calculated for $[M+H]^+$ (C_6H_6NClI) requires *m/z* 253.9233, found *m/z* 253.9235.

*Synthesis of alkyne **26**.* Iodo **24** (394 mg, 1.55 mmol, 1.00 equiv), 1-ethynyl-4-fluoro-benzene (**25**) (206 mg, 1.72 mmol, 1.10 equiv), $Pd(PPh_3)_2Cl_2$ (55 mg, 0.0784 mmol, 5 mol%), and CuI (20 mg, 0.105 mmol, 6 mol%) were charged to a flask and the flask purged with nitrogen (x 3). 1,4-dioxane (8 mL) was added, followed by NEt_3 (8 mL) and the reaction placed in a pre-heated block at 80 °C for 20 minutes. The reaction was allowed to cool to room temperature, diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a pale brown oil. The crude material was purified by flash silica column chromatography, eluent 0-5% EtOAc/*iso*-hexane, to afford alkyne **26** as a pale yellow solid (345 mg, 1.40 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.48 (m, 2H), 7.23 (s, 1H), 7.15 (s, 1H), 7.03-7.12 (m, 2H), 2.53 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.3 (d, $^1J_{C\text{-}F}$ = 251.6 Hz), 159.5, 150.9, 134.3, 134.1 (d, $^3J_{C\text{-}F}$ = 8.6 Hz), 123.7, 122.9, 118.0 (d, $^4J_{C\text{-}F}$ = 3.6 Hz), 116.1 (d, $^2J_{C\text{-}F}$ = 22.3 Hz), 93.7, 85.7 (d, $^5J_{C\text{-}F}$ = 1.4 Hz), 24.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ -108.69; HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{10}NClF$) requires *m/z* 246.0486, found *m/z* 246.0490.

*Synthesis of AZD4635 (**1**) (Scheme 4e).* Alkyne **26** (54 mg, 0.220 mmol, 1.00 equiv) and DMSO (2.2 mL) were charged to a microwave tube. I_2 (11 mg, 0.0433 mmol, 0.20 equiv) was added, the tube sealed with a suba seal, and the reaction brought to 130 °C in a heating block for 34 h. The reaction was allowed to cool to room temperature and 1-aminoguanidine bicarbonate (**3**) (30 mg, 0.220 mmol, 1.00 equiv) added. The reaction was stirred at room temperature for 2 h, then brought to 80 °C for a further 6 h. The reaction was allowed to cool to room temperature, diluted with water (30 mL) and the organics extracted with EtOAc (3 x 20 mL). The organics

were combined, dried over Na_2SO_4, filtered, and evaporated to afford an orange residue. The residue was taken up in *iso*-hexane (10 mL) and filtered. The residue was then taken up in toluene, heated gently with a heat gun and filtered. The filtrate was concentrated in vacuo to afford AZD4635 (**1**) as an orange gum (35 mg, 0.111 mmol, 50%, **1**:**23** = 3:1 by ^{1}H NMR).

*Synthesis of bromo **29**.* 1,2,4-triazin-3-amine (**27**) (150 mg, 1.56 mmol, 1.00 equiv), TBACl (434 mg, 1.56 mmol, 1.00 equiv), and K_2CO_3 (432 mg, 3.13 mmol, 2.00 equiv) were charged to a flask and the flask purged with nitrogen (x 4). MeCN (1.6 mL) was added, followed by dropwise addition of a solution of NBS (333 mg, 1.87 mmol, 1.20 equiv) in MeCN (3 mL). The reaction was stirred for 10 minutes before being quenched with a solution of $Na_2S_2O_3$ (155 mg, 0.625 mmol, 0.40 equiv) in water (1 mL) and stirred for 10 minutes. The reaction was diluted with water (10 mL) and EtOAc (20 mL). The layers were separated and the organics washed with 2 M HCl (2 x 10 mL). The acidic washes were combined and basified with 2 M NaOH before being extracted with EtOAc (3 x 20 mL). The organics were then combined, dried over Na_2SO_4, filtered, and evaporated to afford a pale purple solid. The crude material was purified by flash silica column chromatography, eluent 40% EtOAc/CH_2Cl_2, to afford bromo **29** as a beige solid (218 mg, 1.25 mmol, 80%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.40 (s, 1H), 7.47 (br s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 162.3, 152.6, 135.5; HRMS: exact mass calculated for $[M+H]^+$ ($C_3H_4N_4Br$) requires *m/z* 174.9619, found *m/z* 174.9618. The spectroscopic data are in agreement with the reported literature.[27]

Competitive Suzuki Miyaura experiment. Bromo **29** (38 mg, 0.217 mmol, 1.00 equiv), BPin **7** (70 mg, 0.219 mmol, 79% w/w, 1.00 equiv), $Pd(OAc)_2$ (2 mg, 0.00891 mmol, 4 mol%), APhos (6 mg, 0.0226 mmol, 10 mol%), and K_2CO_3 (45 mg, 0.326 mmol, 1.50 equiv) were charged to a microwave tube and the tube sealed with a suba seal and purged with nitrogen (x 3). 1,4-Dioxane (0.6 mL) was added, followed by 1-bromo-4-fluorobenzene **30** (24 µL, 0.220 mmol, 1.00 equiv), and water (0.2 mL). The reaction was placed in a pre-heated block at 80 °C for 4 h. The reaction was allowed to cool to room temperature, filtered through celite eluting with EtOAc, and concentrated in vacuo. Triazine coupling product **31**: 60%, 1-bromo-4-fluorobenzene coupling product **32**: 9%. Yield by QNMR (1,4-dinitrobenzene as internal standard).

Analytical samples obtained by silica column chromatography (eluent EtOAc/*iso*-hexane):

31: ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.92 (s, 1H), 7.90 (s, 1H), 7.87 (s, 1H), 2.51 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 162.8, 159.8, 150.3, 148.9, 145.4, 144.4, 117.4, 116.1, 23.7; HRMS: exact mass calculated for $[M+H]^+$ ($C_9H_9N_5Cl$) requires *m/z* 222.0546, found *m/z* 222.0539.

32: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94-7.86 (m, 2H), 7.63 (s, 1H), 7.62 (s, 1H), 7.39-7.32 (m, 2H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.1 (d, $^1J_{C\text{-}F}$ = 247.5 Hz), 159.6, 150.3, 149.8, 132.4 (d, $^4J_{C\text{-}F}$ = 3.1 Hz), 129.4 (d, $^3J_{C\text{-}F}$ = 8.6 Hz), 119.9, 118.3, 116.1 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 23.6; ^{19}F NMR (376 MHz, DMSO-d_6): δ -111.87; HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{10}NFCl$) requires *m/z* 222.0486, found *m/z* 222.0481.

*Synthesis of bromo **33**.* Bromo **29** (96 mg, 0.549 mmol, 1.00 equiv) and acetic acid (1.5 mL) were charged to a vial and H_2O_2 (33% w/w in H_2O) (0.1 mL, 1.10 mmol, 2.00 equiv) added dropwise. The reaction was stirred for 24 h, before being diluted with *iso*-hexane (10 mL) and filtered. The filtercake was washed with further *iso*-hexane (2 x 20 mL) before being taken up in MeOH (20 mL) and the solvent removed in vacuo to afford **33** as a white solid (66 mg, 0.346 mmol, 63%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.51 (s, 1H, O*H*), 7.07 (br s, 2H, NH_2); ^{13}C NMR (126 MHz, DMSO-d_6): δ 158.5, 155.9, 135.6; HRMS: exact mass calculated for $[M+H]^+$

($C_3H_4N_4OBr$) requires *m/z* 190.9568, found *m/z* 190.9572.

Procedure for mono-ketone screening (Table 1). Reactions were performed in oven dried tubes at 20 °C under nitrogen. Pyridine **17** (1.00 g, 7.06 mmol, 1.00 equiv), 4-fluorobenzoate (**18**) (1.19 g, 7.08 mmol, 1.00 equiv), and the required solvent (7 mL) were charged to a tube and the required base added over ca. 5 minutes at room temperature. The reactions were stirred for 4 h before being analysed by HPLC.

*Synthesis of di-ketone **21** (Scheme 6a).* Ketone **19** (200 mg, 0.758 mmol, 1.00 equiv), $Cu(OAc)_2$ (14 mg, 0.0771 mmol, 10 mol%), K_2CO_3 (4 mg, 0.0404 mmol, 5 mol%), and MeCN (2.5 mL) were charged to a vial. TMEDA (6 µL, 0.0400 mmol, 5 mol%) was added and air bubbled through the reaction for 20 h. The reaction was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a green oil which solidified on standing. The crude material was purified by flash silica column chromatography, eluent 15% EtOAc/*iso*-hexane, to afford diketone **21** as a pale yellow solid (168 mg, 0.605 mmol, 80%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.14-8.08 (m, 2H), 7.73 (s, 2H), 7.51-7.43 (m, 2H), 2.56 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) 190.8, 189.9, 166.3 (d, $^1J_{C\text{-}F}$ = 255.7 Hz), 161.2, 150.3, 142.2, 133.6 (d, $^3J_{C\text{-}F}$ = 10.2 Hz), 128.7 (d, $^4J_{C\text{-}F}$ = 2.6 Hz), 121.6, 120.3, 116.5 (d, $^2J_{C\text{-}F}$ = 22.4 Hz) , 23.62; ^{19}F NMR (470 MHz, DMSO-d_6): δ -101.50; HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{10}NO_2FCl$) requires *m/z* 278.0384, found *m/z* 278.0383.

*Synthesis of **38**.* 2-Chloro-4,6-dimethylpyridine (**17**) (200 mg, 1.41 mmol, 1.00 equiv) and ethyl 4-fluorobenzoate (**18**) (238 mg, 1.42 mmol, 1.00 equiv) were charged to a flask which had been flushed with nitrogen, cooled to 0 °C, and LiHMDS (1 M in THF) (3.2 mL, 3.20 mmol, 2.30 equiv) added dropwise. After 1 h a solution of **37** (358 mg, 1.55 mmol, 1.10 equiv) in THF (2.8 mL) was added dropwise. The reaction was stirred at room temperature for 15 h before being diluted with water (30 mL) and EtOAc (30 mL). The layers were separated and the aqueous extracted with further EtOAc (2 x 30 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a pale orange oil. The crude material was purified by flash silica column chromatography, eluent 20% EtOAc/*iso*-hexane to afford **38** as a white solid (367 mg, 0.743 mmol, 53%). ^{1}H NMR (500 MHz, DMSO-d_6, 90 °C): δ 8.90 (br s, 1H), 8.17-8.04 (m, 2H), 7.36-7.24 (m, 4H), 6.53 (s, 1H), 2.24 (s, 3H), 1.34 (s, 9H), 1.26 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6, 90 °C): δ 191.5, 164.8 (d, $^1J_{C\text{-}F}$ = 252.8 Hz), 158.2, 154.3 (br), 148.8, 131.2 (d, $^3J_{C\text{-}F}$ = 9.5 Hz), 123.0, 121.8, 115.2 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 81.2, 79.2, 65.3 (br), 27.3, 27.3, 23.1; ^{19}F NMR (470 MHz, DMSO-d_6, 90 °C): δ -105.46; HRMS: exact mass calculated for $[M+H]^+$ ($C_{24}H_{30}N_3O_5FCl$) requires *m/z* 494.1858, found *m/z* 494.1863.

*Synthesis of di-ketone **21** (Scheme 6b).* **38** (55 mg, 0.111 mmol, 1.00 equiv) and CH_2Cl_2 (1 mL) were charged to a flask and TFA (0.1 mL, 1.00 M) added dropwise. After 24 h the reaction was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organics were combined, dried over Na_2SO_4, filtered, and evaporated to afford a pale yellow residue. The crude material was purified by flash silica column chromatography, eluent 15% EtOAc/*iso*-hexane, to afford di-ketone **21** as an off-white solid (26 mg, 0.0936 mmol, 84%).

*Flow synthesis of **38**.* In a VAPOURTEC E-series, the lines were flushed with THF before a mixture of **17** (18 mL, 1.00 M in THF, 18.0 mmol) and **18** (18 mL, 1.00 M in THF, 18.0 mmol) (0.30 mL/min), and LiHMDS (42 mL, 1.00 M in THF, 42.0 mmol, 0.70 mL/min) were fed into a reactor 1 (standard coiled tubular reactor, 10 mL) at 40 °C. The residence time was 10 minutes. This solution and a solution of **37** (51 mL, 0.50 M in THF, 25.5 mmol, 0.85 mL/min)

were then fed into reactor 2 (glass microreactor, 0.6 mL) at – 40 °C and the residence time was 20 seconds. The crude solution was then quenched into AcOH. The solution was diluted with MTBE and water/brine and the layers separated. The organics were concentrated in vacuo and the crude material recrystallized from acetone/water to afford **38** as a white solid (7.66 g, 15.5 mmol, Assay (QNMR) 73% w/w, 63% corrected yield).

*Synthesis of AZD4635 (**1**) (Scheme 6d).* Di-ketone **21** (50 mg, 0.180 mmol, 1.00 equiv) and IPA (0.5 mL) were charged to a tube. $Zn(OTf)_2$ (5 mg, 0.0233 mmol, 13 mol%) was added, followed by aminoguanidine hydrochloride (**22**) (20 mg, 0.181 mmol, 1.00 equiv) and the reaction brought to 50 °C for 24 h. HPLC analysis showed regioisomeric ratio 94:6 (**1**:**23**) with ca. 50% conversion.

*Process for purging of regioisomer **23**.* AZD4635 (1.06 g, 3.36 mmol, **1**:**23** = 98:2) was slurried in PhMe (10 mL) at 100 °C, allowed to cool to room temperature and stirred for 10 minutes. The material was then filtered and the cake washed with PhMe (10 mL). The cake was slurried in further PhMe (10 mL), filtered, and the cake washed with PhMe (2 x 10 mL) and filtered under vacuum until dry to afford AZD4635 as an off-white solid (770 mg, 2.44 mmol, 73%, **1**:**23** = 99.96:0.04).

Procedure for halogenation screening (Scheme 7). Reactions were performed in 4 mL vials in a 24-well plate format, situated in an inerted glovebox (< 10 ppm O_2 and < 1 ppm H_2O). **4** (50 mg, 0. mmol, 1.00 equiv) and all other solid reagents were dispensed into all vials via a Quantos QX96 weighing robot (accuracy +/- 2%). Stir disks were added to all vials. Degassed solvent (1 mL) was added to each vial, followed by addition of liquid reagents. The reactions were sealed and heated to 25 °C for 2 h and then 65 °C for a further 18 h. Conversion by HPLC. See optimized procedure (Table 2) for characterization data.

Procedure for bromination screening (Table 2). Reactions were performed in 1 mL vials in a 96-well plate format, situated in an inerted glovebox (< 10 ppm O_2 and < 1 ppm H_2O). From a stock solution of *m*-terphenyl (0.04 M in toluene) a known volume was dispensed into all vials before evaporation of the solvent. **4** (20 mg, 0.105 mmol, 1.00 equiv) was dispensed into all vials via a Quantos QX96 weighing robot (accuracy +/- 0.5 mg), followed by TBACl and K_2CO_3. Stir disks were added to all vials. Degassed solvent (250 µL) was added to each vial, followed by addition of the desired base. The reactions were stirred for 10 minutes before addition of the desired brominating agent in a solution of MeCN (150 µL) via a multi-dispense pipette. The reactions were sealed and heated to 25 °C for 20 h.

*Synthesis of **5** (Scale-up of screening hit for isolation, Table 2).* Triazine **4** (200 mg, 1.05 mmol, 1.00 equiv) and K_2CO_3 (291 mg, 2.11 mmol, 2.00 equiv) were charged to a flask and the flask sealed with a suba seal and purged with nitrogen (x 3). MeCN (1 mL) was added, followed by dropwise addition of a solution of NBS (225 mg, 1.26 mmol, 1.20 equiv) in MeCN (2 mL) at room temperature and the reaction stirred for 0.5 h. The reaction was quenched with a solution of $Na_2S_2O_3 \cdot 5H_2O$ (261 mg, 1.05 mmol, 1.00 equiv) in water (4 mL) and stirring continued for 0.5 h. The reaction was diluted with EtOAc (10 mL) and the layers separated. The aqueous was further extracted with EtOAc (2 x 10 mL), the organics combined, dried over Na_2SO_4, filtered, and evaporated to afford a brown solid. The crude material was purified by flash silica column chromatography, eluent 10-30% EtOAc/*iso*-hexane to afford bromo **5** as a beige solid (180 mg, 0.669 mmol, 64%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.86-7.80 (m, 2H), 7.54 (br s, 2H), 7.40-7.34 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.4 (d, $^1J_{C\text{-}F}$ = 248.8 Hz), 162.3, 157.3, 134.5, 131.8 (d, $^3J_{C\text{-}F}$ = 8.9 Hz), 131.5 (d, $^4J_{C\text{-}F}$ = 3.1 Hz), 115.3 (d, $^2J_{C\text{-}F}$ = 22.0 Hz); ^{19}F NMR

(376 MHz, DMSO-d_6): δ -109.64; HRMS: exact mass calculated for $[M+H]^+$ ($C_9H_7N_4FBr$) requires *m/z* 268.9838, found *m/z* 268.9840.

Associated Content

Supporting Information

Tables of optimization data and NMR spectra of all compounds.

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