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## Palladium-catalyzed enolate arylation as a key C–C bond-forming reaction for the synthesis of isoquinolines†

Ben S. Pilgrim,<sup>‡a</sup> Alice E. Gatland,<sup>a</sup> Carlos H. A. Esteves,<sup>a</sup> Charlie T. McTernan,<sup>a</sup> Geraint R. Jones,<sup>a</sup> Matthew R. Tatton,<sup>a</sup> Panayiotis A. Procopiou<sup>b</sup> and Timothy J. Donohoe<sup>\*a</sup>

The palladium-catalyzed coupling of an enolate with an *ortho*-functionalized aryl halide (an  $\alpha$ -arylation) furnishes a protected 1,5-dicarbonyl moiety that can be cyclized to an isoquinoline with a source of ammonia. This fully regioselective synthetic route tolerates a wide range of substituents, including those that give rise to the traditionally difficult to access electron-deficient isoquinoline skeletons. These two synthetic operations can be combined to give a three-component, one-pot isoquinoline synthesis. Alternatively, cyclization of the intermediates with hydroxylamine hydrochloride engenders direct access to isoquinoline *N*-oxides; and cyclization with methylamine, gives isoquinolinium salts. Significant diversity is available in the substituents at the C4 position in four-component, one-pot couplings, by either trapping the *in situ* intermediate after  $\alpha$ -arylation with carbon or heteroatom-based electrophiles, or by performing an  $\alpha,\alpha$ -heterodiarylation to install aryl groups at this position. The  $\alpha$ -arylation of nitrile and ester enolates gives access to 3-amino and 3-hydroxyisoquinolines and the  $\alpha$ -arylation of *tert*-butyl cyanoacetate followed by electrophile trapping, decarboxylation and cyclization, C4-functionalized 3-aminoisoquinolines. An oxime directing group can be used to direct a C–H functionalization/bromination, which allows monofunctionalized rather than difunctionalized aryl precursors to be brought through this synthetic route.

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## Introduction

It has been over a century since the first synthetic routes to isoquinolines were published. The Bischler–Napieralski,<sup>1</sup> Pictet–Spengler<sup>2</sup> and Pomeranz–Fritsch reactions,<sup>3</sup> all based around the lynchpin of electrophilic aromatic substitution, were the mainstay of the synthetic chemist's toolkit for much of the intervening period. However, the ubiquity of the isoquinoline motif in biologically-active natural products,<sup>4</sup> alongside its applications in pharmaceuticals,<sup>5</sup> functional organic materials<sup>6</sup> and ligands for catalysis<sup>7</sup> has recently inspired a resurgence in synthetic efforts towards this template.<sup>8</sup>

A number of notable recent contributions have exploited the versatility provided by modern synthetic methodology to access this motif, in particular the scope afforded by transition metal catalysis,<sup>9</sup> and in so doing have vastly expanded the synthetically-accessible isoquinoline motifs, particularly those containing electron-deficient core structures which were unobtainable *via* the traditional methods.

Our contribution to this area began when we embarked on a research program employing the palladium-catalyzed cross-coupling of a ketone enolate with an aryl halide to construct the C4–C4' bond *en route* to the isoquinoline nucleus.<sup>10</sup> This  $\alpha$ -arylation reaction has become a powerful addition to the arsenal of the synthetic chemist<sup>11</sup> since its discovery in 1997<sup>12</sup> and is now a well-established, albeit underutilized, palladium-catalyzed coupling procedure. It had previously been utilized in the synthesis of various five-membered heterocyclic frameworks, including indoles,<sup>13</sup> benzofurans<sup>14</sup> and benzothiophenes,<sup>14b</sup> where together the aryl halide and enolate provided all required skeletal carbon atoms. In our work we discovered that aryl halides that were *ortho*-functionalized with a protected aldehyde or ketone moiety, could be efficiently coupled furnishing a protected 1,5-dicarbonyl, which possessed all

<sup>a</sup>Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, UK. E-mail: timothy.donohoe@chem.ox.ac.uk

<sup>b</sup>GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, UK

† Electronic supplementary information (ESI) available: Copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra for all novel compounds; crystallographic details for compound **4n**, **4z**, **5a**, **5b** and **15f**. CCDC 1422535–1422539. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob02320c

‡ Current Address: Department of Chemistry, The University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, United Kingdom



necessary carbon atoms to cyclize to an isoquinoline upon subjection to a mildly acidic source of ammonia, forming the C1–N and N–C3 bonds in the process. Later we disclosed how the greater acidity imparted on the  $\alpha$ -carbon by the addition of the aryl group meant that the  $\alpha$ -arylated intermediate (which sat deprotonated as the anion *in situ*) could be treated with a reactive electrophile to install additional functionality at the C4 position.<sup>15</sup> This resulted in an efficient multi-component coupling procedure which could be applied to the synthesis of a series of highly-substituted isoquinolines. The  $\alpha$ -arylation and electrophile trapping of the enolate of *tert*-butyl cyanoacetate gave an intermediate which could be decarboxylated and cyclized to furnish 3-aminoisoquinolines. We have recently applied this methodology to the synthesis of a number of natural products.<sup>16</sup>

Herein we present significant extensions of this earlier work, revealing for the first time how this protocol can be applied to the  $\alpha$ -arylation of enolates derived from the less acidic nitriles and esters, allowing swift access to 3-amino and 3-hydroxyisoquinolines. We also report the first direct access to an isoquinolinium salt. Furthermore, we disclose here how exchanging the acetal protecting group for an oxime directing group, allows the procedure to be extended to unfunctionalized benzaldehydes and phenyl ketones *via* the application of C–H functionalization/bromination chemistry. In addition to these previously unexplored areas, we include a number of additional novel examples and single crystal X-ray structures of some of our earlier methods. We have presented these together with our previous results to provide proper context and allow the full scope (and limitations) of this research program to be discussed in detail.

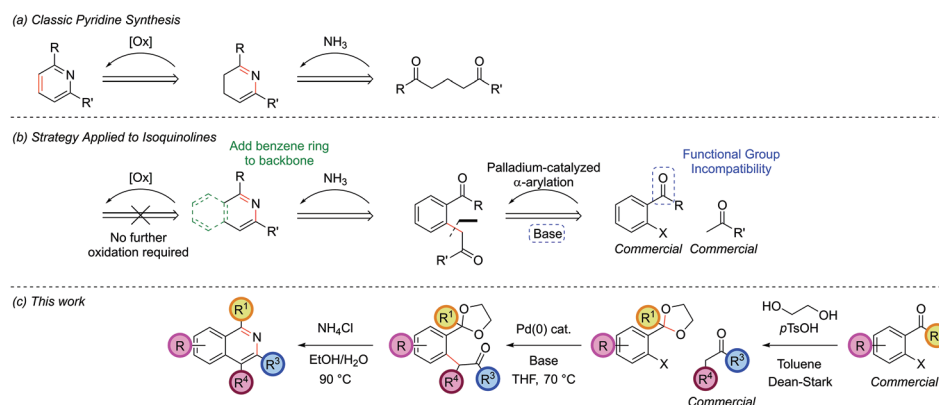
## Results and discussion

A classic retrosynthetic disconnection of a pyridine ring involves the condensation of a 1,5-dicarbonyl with a source of ammonia to form a dihydropyridine followed by an oxidation to a pyridine (Scheme 1, part (a)). The addition of a fused

benzene ring to the backbone of the 1,5-dicarbonyl engenders the intermediate suitable for isoquinoline synthesis and formally increases the oxidation level, hence removing the need for a separate oxidation step in the synthesis (part (b)).

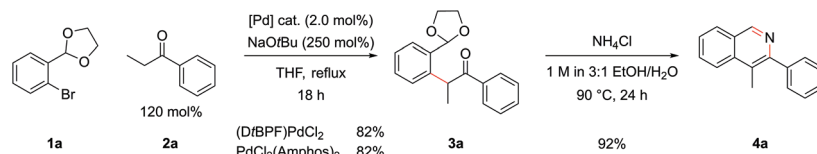
Disconnection of the 1,5-dicarbonyl at the carbon–aryl bond indicated leads to two simple commercially available building blocks, an enolizable ketone and an aryl halide possessing a formyl group or similar at the *ortho*-position. Benzaldehydes are vulnerable to aldol condensations in the presence of enolizable ketones under the basic reaction conditions of the  $\alpha$ -arylation reaction and so a cyclic acetal protecting group was chosen for this moiety (part (c)). While protecting groups in chemical synthesis are always undesirable, the use of an acetal is notable in requiring only inexpensive reagents to both install and remove, the latter of which is able to occur *in situ* in the final step of our procedure. The prototype acetal **1a** is commercially available, however, when the requisite acetals were not they could be synthesized in near quantitative yield by refluxing the benzaldehyde with ethylene glycol and catalytic *para*-toluenesulfonic acid in toluene in a Dean–Stark apparatus.<sup>10,15,16</sup> Dioxolane acetals had been previously shown to be compatible with  $\alpha$ -arylation in the *meta* position,<sup>12a</sup> but their tolerance in the sterically more encumbering *ortho*-position, where there was also a possibility of chelation, was unknown at the outset of this project.

A model reaction was chosen, using commercially available aryl bromide **1a** and ketone **2a**, and a range of palladium catalyst/ligand combinations were screened in addition to various bases and solvents. NaOtBu proved to be the best base and THF the best solvent of a variety screened. It was found that an excess of base (250 mol%) increased product yield, as had been noted in previous studies.<sup>17</sup> The most successful ligand/catalyst systems were the air stable Pd(II) precursors (DtBPF) PdCl<sub>2</sub><sup>18</sup> and PdCl<sub>2</sub>(Amphos)<sub>2</sub>.<sup>19</sup> Employing (DtBPF)PdCl<sub>2</sub> (2.0 mol%) in this system gave a yield of **3a** of 82%; PdCl<sub>2</sub>(Amphos)<sub>2</sub> (2.0 mol%) was equally as proficient, also giving a yield of 82% (Scheme 2). These two preformed catalysts both contain electron-rich bulky phosphines bearing two *tert*-butyl groups and one electron-rich arene, giving an indication of the



Scheme 1 Retrosynthetic strategy for isoquinolines.





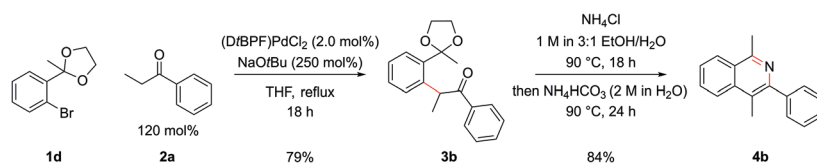
**Scheme 2** Optimized  $\alpha$ -arylation and cyclization conditions for  $R_1 = H$ .

optimal ligand for the reaction. The air stable nature of these catalysts greatly increased the practicality of the synthetic procedure.

In order to concurrently promote acetal hydrolysis and the cyclization to form the isoquinoline in one synthetic procedure, both a source of acid and a source of ammonia were needed. Both were provided by a solution of  $\text{NH}_4\text{Cl}$  in  $\text{EtOH}/\text{H}_2\text{O}$  ( $\text{pH} \approx 5$ ), which enabled the smooth conversion of intermediate **3a** to isoquinoline **4a**. Further acidifying the  $\text{NH}_4\text{Cl}$  solution did not result in increased yields. This procedure could also be extended to employ aryl chlorides and iodides in place of bromides, which greatly increased the scope of commercially available substrates that could be channelled into the reaction (Table 1). Under the optimized  $\alpha$ -arylation reaction conditions, aryl iodide **1b** gave comparable yields to that of the aryl bromide (entry 10). The chloride **1c** was understandably less reactive, but with higher catalyst loadings and longer reaction times improved yields could be obtained with  $\text{PdCl}_2(\text{Amphos})_2$  as the catalyst (entry 3).

**Table 1**  $\alpha$ -Arylation of chlorides, bromides and iodides

	X	Catalyst	Loading	Ketone	Time	Yield
1	Cl	(DtBPF)PdCl <sub>2</sub>	5.0 mol%	200 mol%	18 h	30%
2	Cl	PdCl <sub>2</sub> (Amphos) <sub>2</sub>	5.0 mol%	200 mol%	18 h	45%
3	Cl	PdCl <sub>2</sub> (Amphos) <sub>2</sub>	5.0 mol% × 2	200 mol%	96 h	74%
4	Br	(DtBPF)PdCl <sub>2</sub>	0.5 mol%	120 mol%	18 h	71%
5	Br	(DtBPF)PdCl <sub>2</sub>	0.5 mol%	200 mol%	18 h	74%
6	Br	(DtBPF)PdCl <sub>2</sub>	2.0 mol%	120 mol%	18 h	82%
7	Br	(DtBPF)PdCl <sub>2</sub>	2.0 mol%	200 mol%	18 h	83%
8	Br	(DtBPF)PdCl <sub>2</sub>	5.0 mol%	200 mol%	18 h	89%
9	Br	PdCl <sub>2</sub> (Amphos) <sub>2</sub>	2.0 mol%	120 mol%	18 h	82%
10	I	(DtBPF)PdCl <sub>2</sub>	2.0 mol%	120 mol%	18 h	79%



**Scheme 3** Optimized  $\alpha$ -arylation and cyclization conditions for  $R_1 \neq H$ .

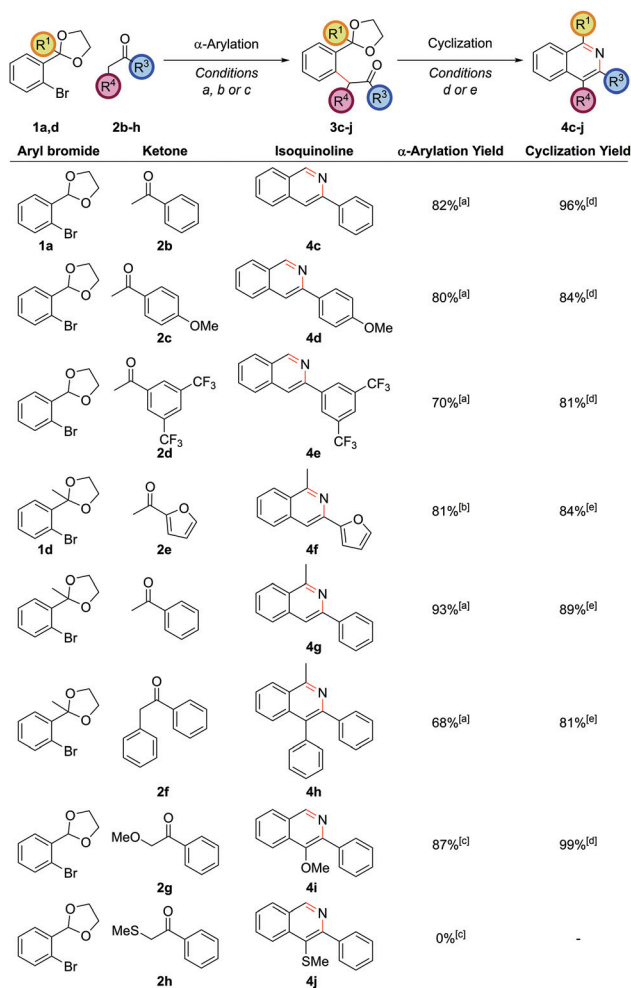
Employing protected 2'-bromophenyl ketones as the aryl bromide partner allowed access to isoquinolines bearing substitution at the C1 position, where the extra steric hindrance induced by the additional methyl group in **1d** did not detrimentally affect the  $\alpha$ -arylation reaction of **1d** with propiophenone (Scheme 3). In contrast to the benzaldehyde case, where cyclization ensued rapidly after deprotection of the intermediate acetal at pH 5, here cyclization and aromatization at pH 5 was sluggish. The optimum pH for cyclization of these substrates was approximately pH 9. To effect this sequence efficiently, aqueous 2 M  $\text{NH}_4\text{HCO}_3$  was added to increase the pH after acetal hydrolysis was complete and then the reaction was heated for a further 24 h at 90 °C.

Exploring the scope of substitution revealed that the C3 substituent could include electron-rich benzene rings **4d**, electron-deficient benzene rings **4e**, and heteroaryl rings **4f** (Fig. 1). It should be noted that cross-couplings between two heteroarenes in the *ortho*-position to both heteroatoms are often difficult to carry out and so this is an important strength of this route.<sup>20</sup> Deoxybenzoin **2f** could also be employed as the ketone partner allowing a phenyl substituent to be installed at the C4 position in **4h**. The successful coupling of deoxybenzoin prompted investigation as to whether more acidic carbonyl derivatives could be employed with heteroatom functionality attached to the carbonyl  $\alpha$ -position. 2-Methoxyacetophenone could be successfully coupled to give **4i** providing a mild base such as  $\text{K}_3\text{PO}_4$  was employed in the  $\alpha$ -arylation step. However, other heteroatom-functionalized enolates (such as that from 2-(methylthio)acetophenone, **2h**), decomposed under the action of base or failed to couple.

The  $\alpha$ -arylation of cyclic ketones and subsequent cyclization furnished tricyclic isoquinoline moieties (*i.e.* with alkyl substitution at both the C3 and C4 positions) – these are difficult substituent patterns to access by most modern methods. Cycloheptanone was successfully arylated to give isoquinolines **4k** and **4l** (Fig. 2).

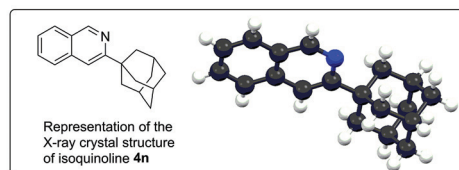
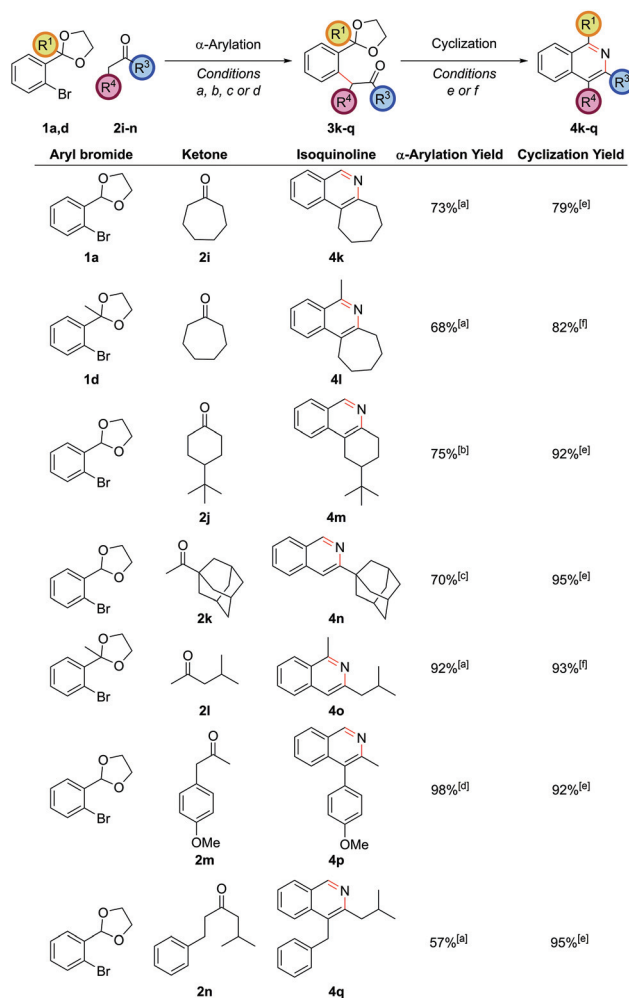
Cyclic ketones with smaller rings than cycloheptanone proved more troublesome with  $\text{NaOtBu}$ , as had been noted in





**Fig. 1** Exploring the scope with aryl ketones. [a] (DtBPF)PdCl<sub>2</sub> (2.0 mol%), NaOtBu (250 mol%), ketone (120 mol%), THF, reflux, 18 h; [b] (DtBPF)PdCl<sub>2</sub> (5.0 mol%), NaOtBu (250 mol%), ketone (200 mol%), THF, reflux, 18 h; [c] (DtBPF)PdCl<sub>2</sub> (5.0 mol%), K<sub>3</sub>PO<sub>4</sub> (250 mol%), ketone (120 mol%), THF, reflux, 18 h; [d] NH<sub>4</sub>Cl (1 M in 3 : 1 EtOH/H<sub>2</sub>O), 90 °C, 24 h; [e] NH<sub>4</sub>Cl (1 M in 3 : 1 EtOH/H<sub>2</sub>O), 90 °C, 18 h, then NH<sub>4</sub>HCO<sub>3</sub> (2 M in H<sub>2</sub>O), 90 °C, 24 h.

previous studies,<sup>21</sup> due to increased likelihood for aldol condensations. With cyclohexanone-based ketones such as **2j**, an α-arylation yield of 75% could be obtained by using the strong base lithium tetramethylpiperidide to fully deprotonate the ketone and form the enolate at −78 °C, before adding the aryl bromide and heating at reflux as before. The propensity for aldol condensations is also a problem for linear dialkyl ketones, making successful α-arylation of these substrates a challenging problem.<sup>22</sup> Superior partners are usually ketones bearing a bulky group on one side of the carbonyl so as to ensure a regioselective arylation reaction. The α-arylation of adamantyl methyl ketone, **2k**, enabled synthesis of isoquinoline **4n** where the bulky adamantyl group is directly attached to the ring, as evidenced in the crystal structure. Attaching an adamantyl group on a preformed arene ring is very difficult, confirming the power of installing substituents pre-cyclization.



**Fig. 2** Exploring the scope with alkyl ketones. [a] (DtBPF)PdCl<sub>2</sub> (5.0 mol%), NaOtBu (250 mol%), ketone (200 mol%), THF, reflux, 18 h; [b] (DtBPF)PdCl<sub>2</sub> (5.0 mol%), nBuLi (250 mol%), TMP (270 mol%), ketone (200 mol%), THF, −78 °C to reflux, 18 h; [c] (DtBPF)PdCl<sub>2</sub> (2.0 mol%), NaOtBu (250 mol%), ketone (120 mol%), THF, reflux, 18 h; [d] (DtBPF)PdCl<sub>2</sub> (5.0 mol%), Cs<sub>2</sub>CO<sub>3</sub> (250 mol%), ketone (200 mol%), THF, reflux, 18 h; [e] NH<sub>4</sub>Cl (1 M in 3 : 1 EtOH/H<sub>2</sub>O), 90 °C, 24 h; [f] NH<sub>4</sub>Cl (1 M in 3 : 1 EtOH/H<sub>2</sub>O), 90 °C, 18 h, then NH<sub>4</sub>HCO<sub>3</sub> (2 M in H<sub>2</sub>O), 90 °C, 24 h.

Where the two alkyl groups differed substantially, such as in isobutyl methyl ketone, **2l**, α-arylation could be accomplished exclusively on the methyl as opposed to the methylene position *en route* to isoquinoline **4o**. In cases where the methylene carbon was more acidic, such as 4'-methoxyphenyl acetone, **2m**, the strength of base became important in determining the outcome of the reaction. Utilizing NaOtBu as the base gave a 1 : 5 mixture of arylation at the methylene to methyl positions respectively. However, with the weaker base Cs<sub>2</sub>CO<sub>3</sub> complete





regioselectivity for arylation at the methylene position could be obtained. The use of stronger bases to achieve arylation exclusively at the methyl position led solely to decomposition of starting material in this case. On the more similarly substituted isobutyl 2-phenylethyl ketone, **2n**, selectivity could even be achieved for  $\alpha$ -arylation at the less hindered and slightly more activated methylene position on the side of the phenyl group, highlighting how subtle steric and electronic factors can give rise to useful regioselectivity.

On the aryl bromide partner, a variety of substitution could be tolerated. Methoxy-substituted partners worked well, allowing access to isoquinolines **4r**, **4s** and **4t** (Fig. 3). The successful coupling to synthesize **4t** is particularly noteworthy, as this  $\alpha$ -arylation reaction features a bromide flanked by two *ortho*-substituents, both of which contain oxygen atoms that could possibly chelate to palladium. The electron-rich bromides could also include heteroaryl moieties such as a thiophene, leading to thienopyridine **4u**.

Of the electron-neutral aryl bromides, alkyl and aryl substituents could be readily incorporated to give isoquinolines **4v** and **4w**. Fluorinated aryl bromides were also competent substrates giving fluorinated isoquinolines **4x**, **4y** and **4z** (of which a crystal structure of isoquinoline **4z** was obtained) – the ability to install fluorinated motifs being a desirable property in medicinal chemistry to protect against metabolic instability. The trifluoromethyl group is also prevalent in medicinal chemistry and could be successfully installed at the C7 position in isoquinoline **4aa**, giving the first truly electron-deficient isoquinoline accessed *via* this methodology. Other electron-poor systems could be accessed too. Nitro groups could be incorporated (**4ab** with the use of the weaker base  $\text{Cs}_2\text{CO}_3$  and  $\text{PdCl}_2(\text{Amphos})_2$ ), and methyl esters could also be incorporated (**4ac** with the use of  $\text{K}_3\text{PO}_4$  and  $\text{PdCl}_2(\text{Amphos})_2$ ); both of these are important functional groups for further synthetic manipulation post-heterocycle construction. The ready access to electron-deficient heterocyclic frameworks is a strength of this route over traditional methods. As well as demonstrating the success of the procedure with electron-rich through to electron-deficient aryl bromide partners, we had now shown that substitution could be incorporated at all positions on the carbocyclic ring of the isoquinolines, with no problems over regiocontrol.

This synthetic procedure enabled the synthesis of a range of substituted isoquinolines in two or three steps from commercial chemicals. However, in order to increase the synthetic practicality of the procedure it was thought that a one-pot procedure could be developed. This would be aided by the fact that the THF solvent for the  $\alpha$ -arylation reaction and the EtOH/ $\text{H}_2\text{O}$  solvent for the cyclization were miscible, allowing both reactions to be performed sequentially in one vessel. Therefore, after TLC analysis indicated that the  $\alpha$ -arylation was complete, the reaction mixture was adjusted to pH 5 by the dropwise addition of aqueous 1 M HCl, an  $\text{NH}_4\text{Cl}$  solution was added and the mixture heated to ensure cyclization. This procedural change eliminated one step and purification from the reaction sequence. Seven isoquinolines were synthesized *via* this one-pot protocol (Fig. 4) and the one-pot yield was only

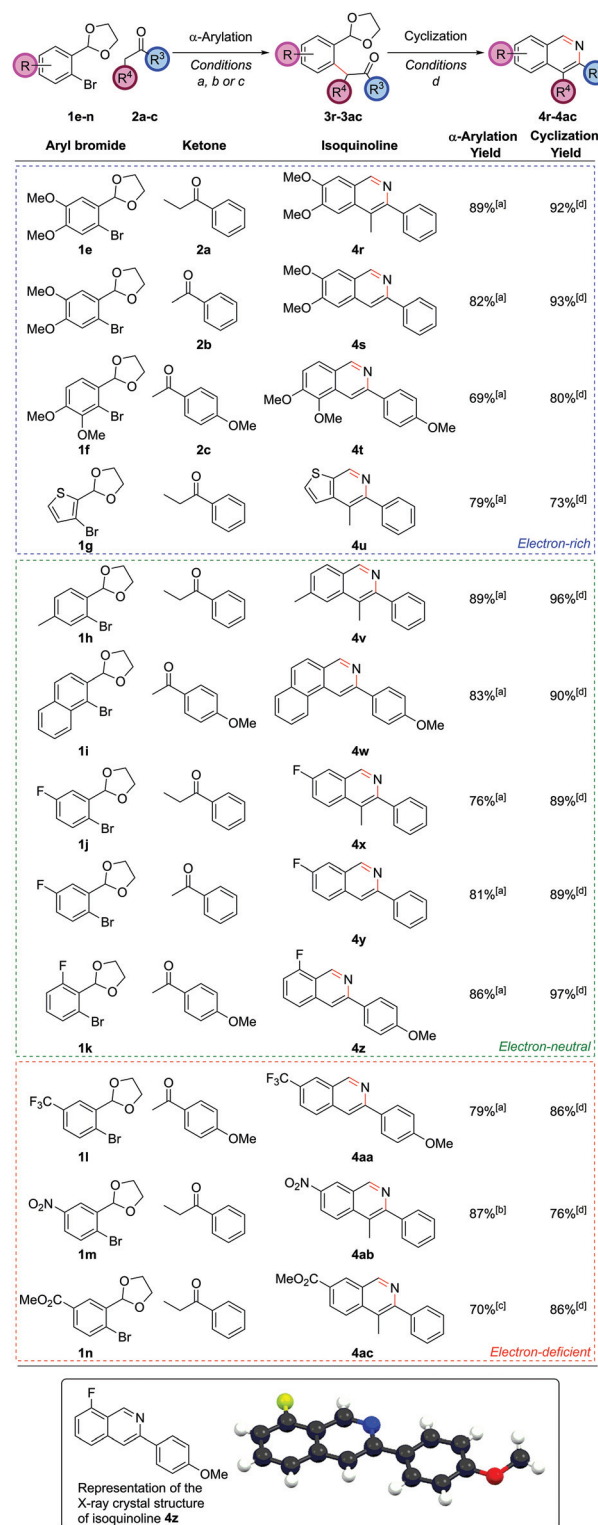
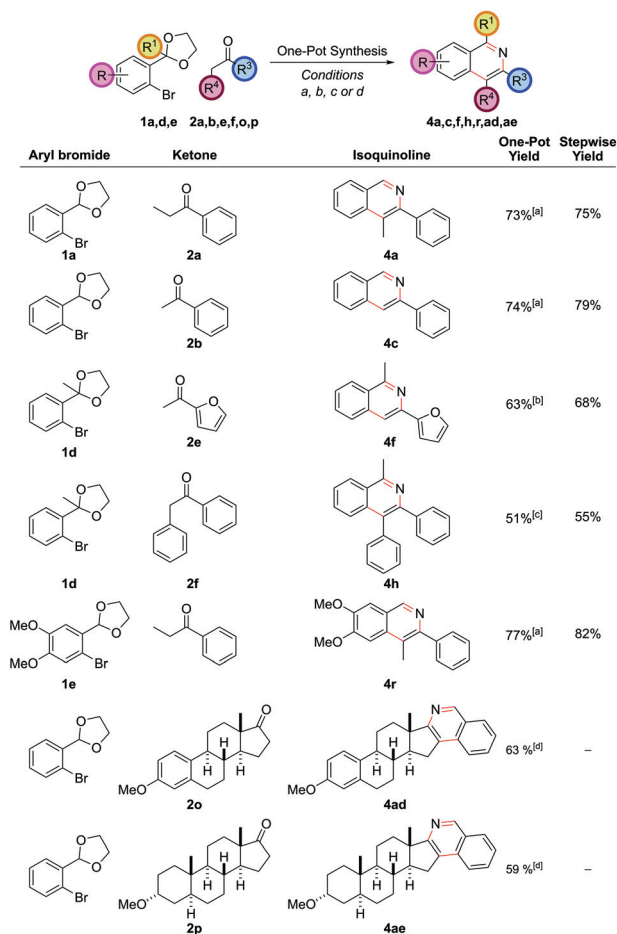


Fig. 3 Exploring the scope of the aryl bromide partner. [a] (DtBPF) $\text{PdCl}_2$  (2.0 mol%), NaOtBu (250 mol%), ketone (120 mol%), THF, reflux, 18 h; [b]  $\text{PdCl}_2(\text{Amphos})_2$  (5.0 mol%),  $\text{Cs}_2\text{CO}_3$  (250 mol%), ketone (200 mol%), THF, reflux 18 h; [c]  $\text{PdCl}_2(\text{Amphos})_2$  (5.0 mol%),  $\text{K}_3\text{PO}_4$  (250 mol%), ketone (120 mol%), THF, reflux, 18 h; [d]  $\text{NH}_4\text{Cl}$  (1 M in 3 : 1 EtOH/ $\text{H}_2\text{O}$ ), 90 °C, 24 h.



**Fig. 4** One-pot synthesis of isoquinolines. [a] (DtBPF)PdCl<sub>2</sub> (2.0 mol%), NaOtBu (250 mol%), ketone (120 mol%), THF, reflux, 18 h, then HCl<sub>(aq)</sub>, NH<sub>4</sub>Cl (1 M in 3 : 1 EtOH/H<sub>2</sub>O), 90 °C, 24 h; [b] (DtBPF)PdCl<sub>2</sub> (5.0 mol%), NaOtBu (250 mol%), ketone (200 mol%), THF, reflux, 18 h, then HCl<sub>(aq)</sub>, NH<sub>4</sub>Cl (1 M in 3 : 1 EtOH/H<sub>2</sub>O), 90 °C, 18 h, then NH<sub>4</sub>HCO<sub>3</sub> (2 M in H<sub>2</sub>O), 90 °C, 24 h; [c] (DtBPF)PdCl<sub>2</sub> (2.0 mol%), NaOtBu (250 mol%), ketone (120 mol%), THF, reflux, 18 h, then HCl<sub>(aq)</sub>, NH<sub>4</sub>Cl (1 M in 3 : 1 EtOH/H<sub>2</sub>O), 90 °C, 18 h, then NH<sub>4</sub>HCO<sub>3</sub> (2 M in H<sub>2</sub>O), 90 °C, 24 h; [d] (DtBPF)PdCl<sub>2</sub> (5.0 mol%), NaOtBu (250 mol%), aryl bromide (150 mol%), THF, reflux, 18 h, then HCl<sub>(aq)</sub>, NH<sub>4</sub>Cl (1 M in 3 : 1 EtOH/H<sub>2</sub>O), 90 °C, 24 h.

marginally less than the overall yield of the stepwise procedure. This more practical synthetic procedure represents a three-component (aryl bromide, ketone, ammonia source), one-pot coupling, where three of the six heteroarene ring bonds were made in a single synthetic operation.

Included in the one-pot examples were two ketones derived from steroidal hormones which could be converted into hexacyclic isoquinoline skeletons (with the steroidal ketone, now the expensive coupling partner, used as the limiting reagent). A large number of pharmaceutical drugs are constructed upon a steroid core, often significantly modified on the five-membered D-ring with the addition of extra heteroatom or heterocyclic functionality. The one-pot protocol hence allows expedient access to an array of modified steroids by variation in the aryl bromide partner which may be of value in target screening.

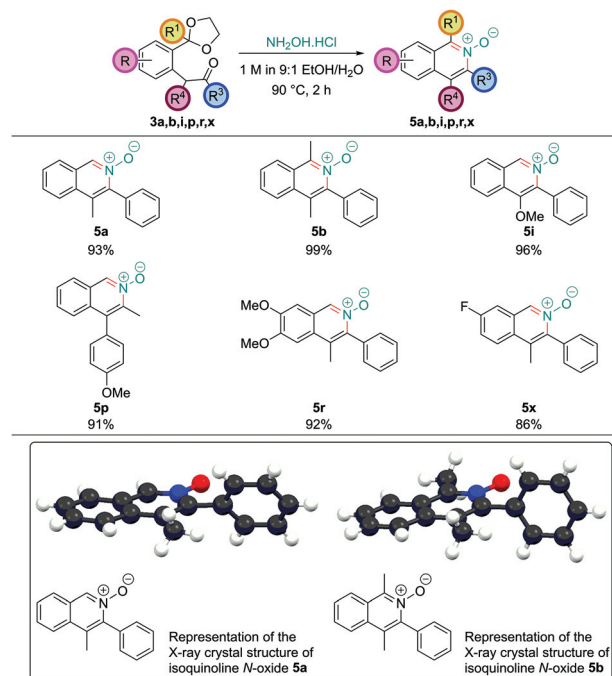
## Change of nitrogen oxidation state: isoquinoline *N*-oxides

Isoquinoline *N*-oxides are also high value targets, and are particularly useful if further substitution on the arene ring is desired after the ring construction. As they are more electron-rich than the corresponding isoquinoline they undergo electrophilic aromatic substitution with much greater ease and they also show propensity for C–H functionalization reactions.<sup>23</sup> Direct access to isoquinoline *N*-oxides avoids the need for oxidation of the parent isoquinoline – a reaction which often requires conditions that do not tolerate sensitive functionality. Limited literature precedent revealed that analogous 1,5-dicarbonyls had been converted into isoquinoline *N*-oxides directly by treatment with hydroxylamine, however, no systematic study had been undertaken.<sup>24</sup> A number of intermediates obtained in this work were treated with a solution of hydroxylamine hydrochloride (which had a pH of around 4.5). This leads to rapid and clean deprotection, and cyclization to the corresponding isoquinoline *N*-oxide (Fig. 5). Single crystal X-ray structures were also obtained of isoquinoline *N*-oxides **5a** and **5b**.

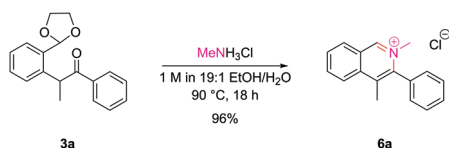
Isoquinoline *N*-oxides bearing C1 substitution, such as **5b**, unlike their parent isoquinolines, could be synthesized without needing to basify the reaction conditions after acetal hydrolysis; this is likely due to the increased nucleophilicity of the hydroxylamine nitrogen atom.

## Isoquinolinium salts

The successful cyclization to synthesize *N*-oxides raised the possibility as to whether the dicarbonyl intermediates could be treated with primary amines to also allow access to isoquinoli-



**Fig. 5** Synthesis of isoquinoline *N*-oxides.



Scheme 4 Synthesis of isoquinolinium salt 6a.

nium salts directly. Pleasingly, intermediate 3a underwent clean conversion to isoquinolinium salt 6a upon treatment with methylamine hydrochloride (Scheme 4).

With bulkier primary amines, higher temperatures were required to encourage cyclization, and significant amounts of the dealkylated isoquinoline were observed, which unfortunately limited this approach to sterically-unhindered primary amines. However, the inherent nucleophilicity of the isoquinoline nitrogen atom can be used to alkylate post-cyclization with a tethered electrophile which we employed *en route* to several natural products within our laboratory.<sup>16</sup>

### Change of carbon oxidation state: 3-amino and 3-hydroxyisoquinolines

By employing hydroxylamine hydrochloride instead of ammonium chloride in the cyclization step, the resulting heterocycle was formed one oxidation level higher. Alternatively, we can utilize a higher oxidation level reagent in the  $\alpha$ -arylation step, leading to the synthesis of 3-aminoisoquinolines or 3-hydroxyisoquinolines, derivatives of which are known to display significant biological activity.<sup>25</sup> This tactic would require the arylation of the enolate of a nitrile, ester or similar compound rather than a ketone. The  $\alpha$ -arylation of nitriles is significantly more challenging than ketones for a variety of reasons; for example, the proton to be removed is less acidic, meaning stronger bases are often required and there are problems of diarylation due to the less sterically-hindered nature of the nitrile product. However, recently some advances have been made in this area.<sup>26</sup> Applying the  $\alpha$ -arylation conditions that we had used successfully with ketones to nitriles such as propionitrile were unsuccessful, but as we desired an operationally simple procedure that could directly employ commercially available nitriles, we examined nitriles bearing an additional acidifying substituent such that their  $pK_a$  was similar to the ketones that had been successfully coupled (2-phenylacetonitrile has a  $pK_a$  of 21.9 in DMSO,<sup>27</sup> compared to 24.4 for propiophenone<sup>28</sup> for example). It was found that 2-phenylacetonitrile, 7a, could be successfully coupled with aryl bromide 1a with 5.0 mol%  $\text{PdCl}_2(\text{Amphos})_2$  and  $\text{Cs}_2\text{CO}_3$  as the base (Fig. 6). Cyclization of intermediate 8a required basification and furnished the 3-aminoisoquinoline 9a (as opposed to the 3-hydroxyisoquinoline or its isoquinolone tautomer), clearly evidenced by the broad singlet at 4.42 ppm (relative integral 2H) from the  $\text{NH}_2$  group in the  $^1\text{H}$  NMR spectrum. This matched the literature data for this compound<sup>29</sup> and was expected as isoquinolines substituted in the 3-position are

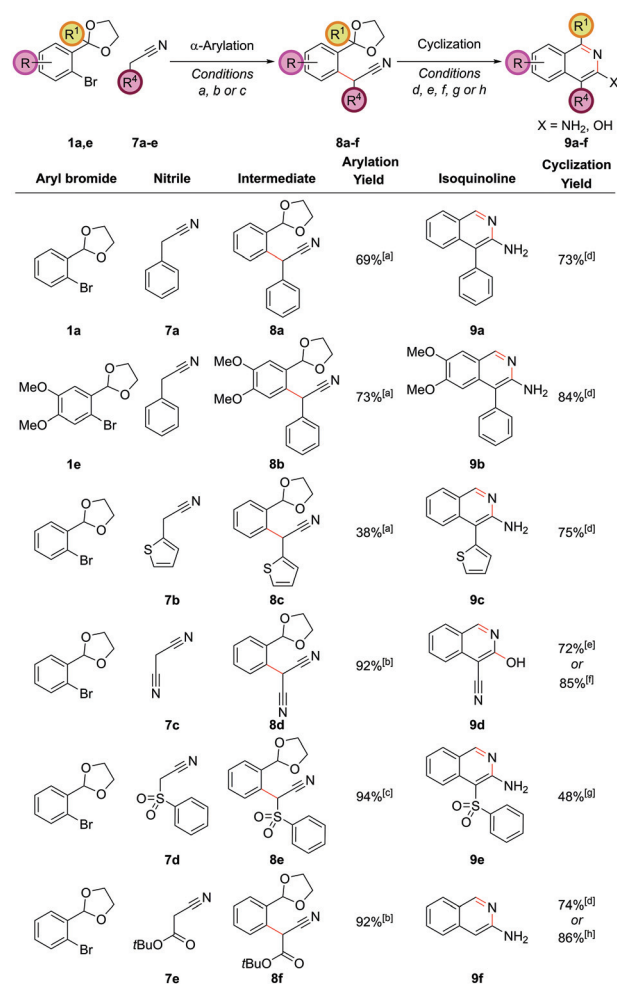


Fig. 6 Access to 3-amino and 3-hydroxyisoquinolines. [a]  $\text{PdCl}_2(\text{Amphos})_2$  (5.0 mol%),  $\text{Cs}_2\text{CO}_3$  (250 mol%), nitrile (200 mol%), THF, reflux, 18 h; [b]  $(\text{DPPF})\text{PdCl}_2$  (2.0 mol%),  $\text{NaOtBu}$  (250 mol%), nitrile (100 mol%), aryl bromide (120 mol%), 1,4-dioxane, 70 °C, 4 h; [c]  $(\text{DPPF})\text{PdCl}_2$  (2.0 mol%),  $\text{NaOtBu}$  (250 mol%), nitrile (100 mol%), aryl bromide (120 mol%), 1,4-dioxane, 70 °C, 18 h; [d]  $\text{NH}_4\text{Cl}$  (1 M in 3 : 1 EtOH/ $\text{H}_2\text{O}$ ), 90 °C, 18 h, then  $\text{NH}_4\text{HCO}_3$  (2 M in  $\text{H}_2\text{O}$ ), 90 °C, 24 h; [e]  $\text{NH}_4\text{Cl}$  (1 M in 3 : 1 EtOH/ $\text{H}_2\text{O}$ ), 90 °C, 18 h; [f]  $p\text{TsOH}$  (10 mol%), THF/ $\text{H}_2\text{O}$  (1 : 1), 50 °C, 18 h; [g]  $\text{NH}_4\text{Cl}$  (1 M in 3 : 1 EtOH/ $\text{H}_2\text{O}$ ), 90 °C, 4 h, then  $\text{NH}_4\text{HCO}_3$  (2 M in  $\text{H}_2\text{O}$ ), 65 °C, 1 h; [h] EtOH/ $\text{H}_2\text{O}$  (3 : 2), 90 °C, 18 h, then  $\text{NH}_4\text{Cl}$  (1000 mol%), 90 °C, 3 h, then  $\text{NH}_4\text{HCO}_3$  (2 M in  $\text{H}_2\text{O}$ ), 90 °C, 3 h.

known to favour the amino/hydroxy forms over the imine/oxo forms.

Other classes of acidifying substituents could also be employed, but here again a slight change in the  $\alpha$ -arylation conditions was required in order to get optimal yields. Utilizing  $(\text{DPPF})\text{PdCl}_2$  as the catalyst<sup>30</sup> in dioxane solvent led to a 92% yield in the coupling of malononitrile, 7c, with aryl bromide 1a. Interestingly, this intermediate showed a preference to cyclize to the 3-hydroxyisoquinoline 9d under the  $\text{NH}_4\text{Cl}$  cyclization conditions, confirmed by high resolution mass spectrometry, the OH stretch in the IR, and by inference from the fact that this same cyclization could also be effected in higher yield in the absence of an external nitrogen source





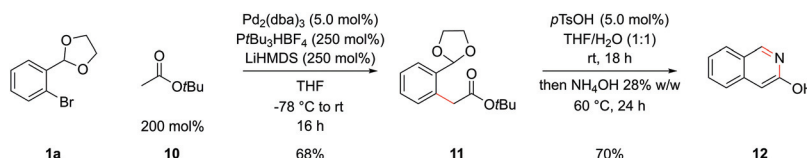
by the action of *para*-toluenesulfonic acid on intermediate **8d**. (Phenylsulfonyl)acetonitrile, **7d**, functioned well as the nitrile substrate, and gave intermediate **8e** which could be cyclized to 3-aminoisoquinoline **9e**. *tert*-Butyl cyanoacetate, **7e**, was also proficient in the  $\alpha$ -arylation reaction, but surprisingly after treatment with the cyclization conditions the unsubstituted 3-aminoisoquinoline, **9f**, was produced, due to an ester hydrolysis and decarboxylation under the reaction conditions prior to cyclization. This meant the protocol had achieved the equivalent of  $\alpha$ -arylation of acetonitrile directly;<sup>31</sup> this is an extremely challenging substrate in  $\alpha$ -arylation methodology. This *in situ* decarboxylation also gave opportunities for further diversification which we sought to use to our advantage (*vide infra*).

Esters are also significantly less acidic than the corresponding ketones and have the potential to undergo Claisen condensations under basic conditions, complicating an attempted  $\alpha$ -arylation.<sup>32</sup> Again hoping to design a general procedure that didn't rely on specialized reagents, we proceeded with *tert*-butyl acetate, **10**, LiHMDS as a base and  $\text{PtBu}_3$  (formed *in situ* from deprotonation of the air stable tetrafluoroborate salt) similar to conditions initially developed by Hartwig and coworkers.<sup>32b</sup> This delivered intermediate **11** in 68% yield, which could be cyclized to 3-hydroxyisoquinoline **12** in 70% yield, by hydrolysis of the acetal with *p*TsOH and then basification with  $\text{NH}_4\text{OH}$  (Scheme 5); the data of this compound matched that from commercial suppliers. Unfortunately, the coupling of methyl and ethyl esters in this system was unsuccessful and *tert*-butyl esters of more sophisticated carboxylic acids coupled only in poor yields.

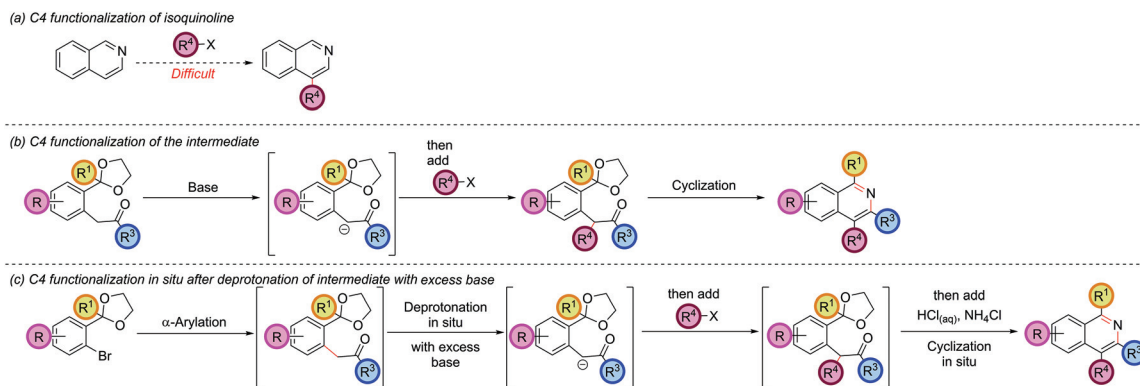
## Functionalization at the C4 position

The isoquinoline C4 position is typically unreactive and difficult to selectively manipulate in preformed isoquinolines, since nucleophiles usually add to C1 or C3, and electrophiles to C5 or C8 (Scheme 6, part (a)).

Functionalization at C4 typically requires reduction or addition across the C1–N bond to form a 1,2-dihydroisoquinoline, followed by reaction of the resulting enamine with an electrophile at C4, and a final elimination or reoxidation of the C1–N bond.<sup>33</sup> Our strategy had thus far required the C4 substituent to be pre-installed on the ketone coupling partner and was limited by the accessibility of the requisite ketones and the compatibility of such ketones with the basic  $\alpha$ -arylation conditions (such as the failure of **2h**, Fig. 1). The regioselectivity of the  $\alpha$ -arylation reaction for functionalization at the most acidic/least sterically-hindered position also imparted fundamental restrictions on the relative orientation of the groups present at C3 and C4 (*vide supra* Fig. 2). However, it was thought that the enolate intermediate in our synthetic route was a prime candidate for further functionalization at the  $\alpha$ -position *via* deprotonation and reaction with an electrophile. Subsequent cyclization would then install this group at the isoquinoline C4 position (Scheme 6, part (b)). In our earlier optimization, excess base was included in the  $\alpha$ -arylation reaction to ensure complete reaction of the starting ketone, especially as the intermediate was preferentially deprotonated under the reaction conditions. Intercepting this intermediate *in situ* with an electrophile opened up the possibility of doing the  $\alpha$ -arylation and C4-functionalization in one-pot (Scheme 6, part (c)). Combining this protocol with an *in situ*



Scheme 5  $\alpha$ -Arylation and cyclization of ester enolates.



Scheme 6 Functionalization of the C4 position.



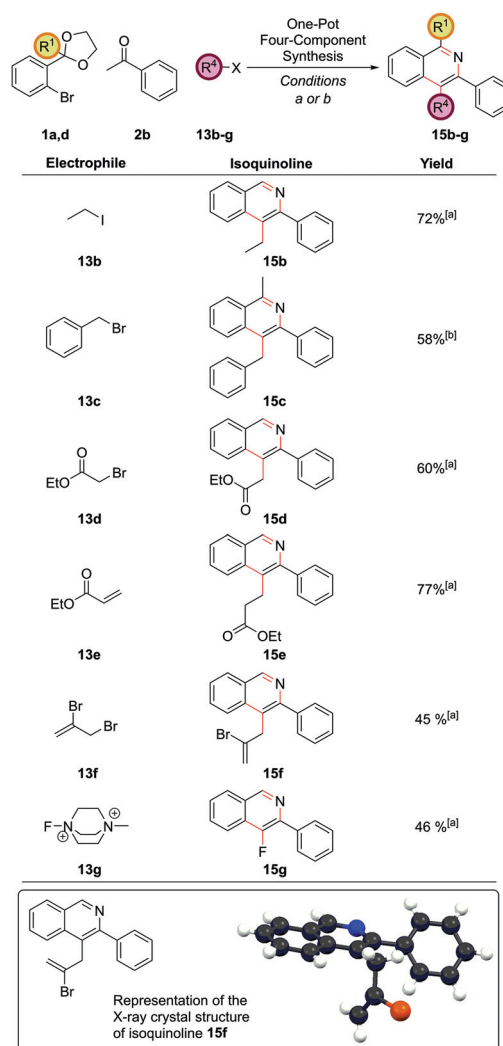


cyclization would transform the isoquinoline synthesis from a one-pot, three-component coupling (aryl bromide, ketone, and ammonia source) to a one-pot, four-component coupling protocol (aryl bromide, ketone, electrophile and ammonia source). Hartwig had previously employed iodomethane to trap the arylated enolate of diethylmalonate,<sup>34</sup> and Wang also trapped the arylated enolate of *tert*-butylcyanoacetate,<sup>30</sup> hinting at the possibility of a more general enolate trapping strategy being successful. Our envisaged approach also bore resemblance to Myers's trapping of eneamido anions with electrophiles *en route* to substituted isoquinolines.<sup>35</sup>

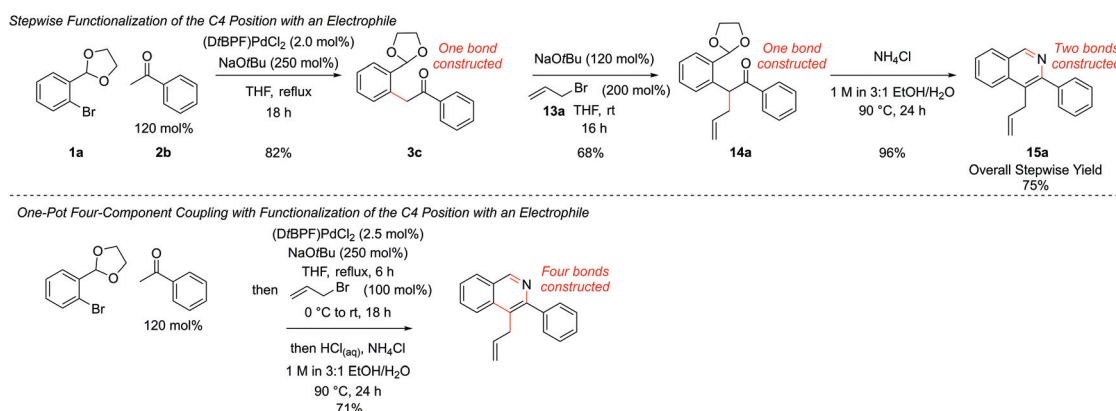
Resubjection of intermediate **3c** to NaOtBu, followed by the addition of allyl bromide, **13a**, furnished functionalized intermediate **14a** in 68% yield. This could be cyclized to produce C4-functionalized isoquinoline **15a** in 96% yield (Scheme 7). In order to combine all three steps in one-pot, the  $\alpha$ -arylation was performed as previously, but the reaction was quenched first by addition of the electrophile. After stirring for a further period the reaction was acidified with HCl, the NH<sub>4</sub>Cl solution added, and cyclization ensued. This protocol gave isoquinoline **15a** in 71% yield, compared to 75% overall yield for the isolated stepwise procedure. Hence a multi-component protocol had been developed which comprised three distinct chemical transformations, constructed four important skeletal bonds and coupled four different components in one-pot.

The method was broadly applicable to a range of carbon-based electrophiles (Fig. 7). Alkyl **15b** and benzyl **15c** groups could be readily installed.  $\alpha$ -Bromoesters **13d** and acrylates **13e** were also reactive electrophiles and the cyclization conditions were sufficiently mild for the ester moieties to survive to furnish **15d** and **15e**. Vinyl bromides could also be introduced to form **15f**, with no protodebromination observed, giving possibility for further synthetic modification *via* coupling reactions after isoquinoline formation. A single crystal X-ray structure was obtained for isoquinoline **15f**. The use of Selectfluor® II, **13g**, to give 4-fluoroisoquinoline **15g** was also notable.

Exploring the variation accessible with different aryl bromide and ketone partners illustrated that both electron-deficient **11**



**Fig. 7** One-pot four-component coupling procedure. [a] (DtBPF)PdCl<sub>2</sub> (2.5 mol%), NaOtBu (250 mol%), THF, reflux, 18 h, then electrophile, rt, 8 h, then HCl<sub>(aq)</sub>, NH<sub>4</sub>Cl (1 M in 3 : 1 EtOH/H<sub>2</sub>O), 90 °C, 24 h; [b] (DtBPF)-PdCl<sub>2</sub> (5.0 mol%), NaOtBu (250 mol%), THF, reflux 18 h, then electrophile, rt, 8 h, then HCl<sub>(aq)</sub>, NH<sub>4</sub>Cl (1 M in 3 : 1 EtOH/H<sub>2</sub>O), 90 °C, 24 h.



**Scheme 7** Development of four-component one-pot coupling.

and electron-rich **1o** aryl bromides could be employed as before to give **15h** and **15i** (Fig. 8). Trifunctionalized isoquinolines **15j** and **15k** could be accessed by the use of the sterically more hindered acetophenone-derived *ortho*-acetal **1d**. Diphenyldisulfide, **13j**, could also be employed as the electrophile, providing 4-thioether substituted isoquinoline **15l**. Note that the direct arylation of a ketone bearing thioether functionality in the  $\alpha$ -position to synthesize 4-thioether substituted isoquinolines could not be accomplished under our reaction conditions as the requisite ketone decomposed (*vide supra* ketone **2h** Fig. 1), highlighting a strength of this route. Isobutyl methyl ketone could also be employed to give a range of differently substituted dialkyl isoquinolines **15m**, **15n** and **4q** (iso-

quinoline **4q** also having been a target under our first generation approach *vide supra* Fig. 2), which had required a more specialized ketone partner **2n**, which had to be synthesized.

The incorporation of an aryl group at C4 was also challenging under the first generation route due to the limited commercial availability of benzyl ketones. It was envisaged that C4-aryl isoquinolines could be accessed by *in situ* functionalization as well, *via* the  $\alpha,\alpha$ -heterodiarylation of a methyl ketone, followed by acetal cleavage and cyclization. Although the palladium-catalyzed diarylation of methyl ketones had been previously reported, to the best of our knowledge this was limited to homodiarylation, achieved using an excess of one unhindered aryl halide<sup>36</sup> or observed as an undesired over-reaction.<sup>12a,18e,37</sup> Achieving an  $\alpha,\alpha$ -heterodiarylation is challenging. If two aryl bromides with similar reactivity were added simultaneously then a statistical mixture of homodiarylated and heterodiarylated products would be formed. If two aryl bromides with differing reactivity were added simultaneously then homodiarylation with the more reactive partner would occur first, followed by homodiarylation of the remaining ketone with the less reactive partner. There is little precedent for selective  $\alpha,\alpha$ -heterodiarylation in the literature, but it was thought this could be achieved by stepwise addition of the two aryl bromides, as long as the less reactive one was added first under conditions that did not induce diarylation before the more reactive one was added afterwards.

In our first generation isoquinoline synthesis,<sup>16</sup> diarylation of the ketone enolates was not observed even when the aryl bromide was in excess, presumably due to the steric hindrance inhibiting the second coupling. Therefore, it was decided to attempt a second  $\alpha$ -arylation *in situ* with a sufficiently unhindered aryl bromide, which would only be added after the first arylation was complete. Following the monoarylation of ketone **2b** with aryl bromide **1a** closely by TLC analysis indicated it was largely complete after 6 h, (Scheme 8) and so the second aryl bromide **16a** was added at this point. This enabled the same palladium catalyst to promote both couplings; leaving the first reaction for longer times led to the need to add more palladium catalyst. The second arylation reaction was then run for 18 h to ensure complete conversion to intermediate **17a**. No triarylated product was observed, presumably due to the now very high steric hindrance at this position. To the best of our knowledge, this transformation is the first reported one-pot palladium-catalyzed  $\alpha,\alpha$ -heterodiarylation reaction of a ketone, enabled by exploiting the steric dependence of the two aryl halides on the reaction. To fully generalise the procedure, increasing the temperature to 100 °C for the second  $\alpha$ -arylation ensured it could always be driven to completion. This heterodiarylation could be incorporated seamlessly into the one-pot protocol to afford C4-aryl isoquinolines directly. In the case of isoquinoline **18a**, the one-pot yield of 77% was comparable to the overall stepwise yield of 81%.

The reaction worked well with both electron-rich **16b** and electron-deficient aryl bromides **16g** (Fig. 9). Aryl bromides with significant steric hindrance such as *ortho*-methyl **16c** and

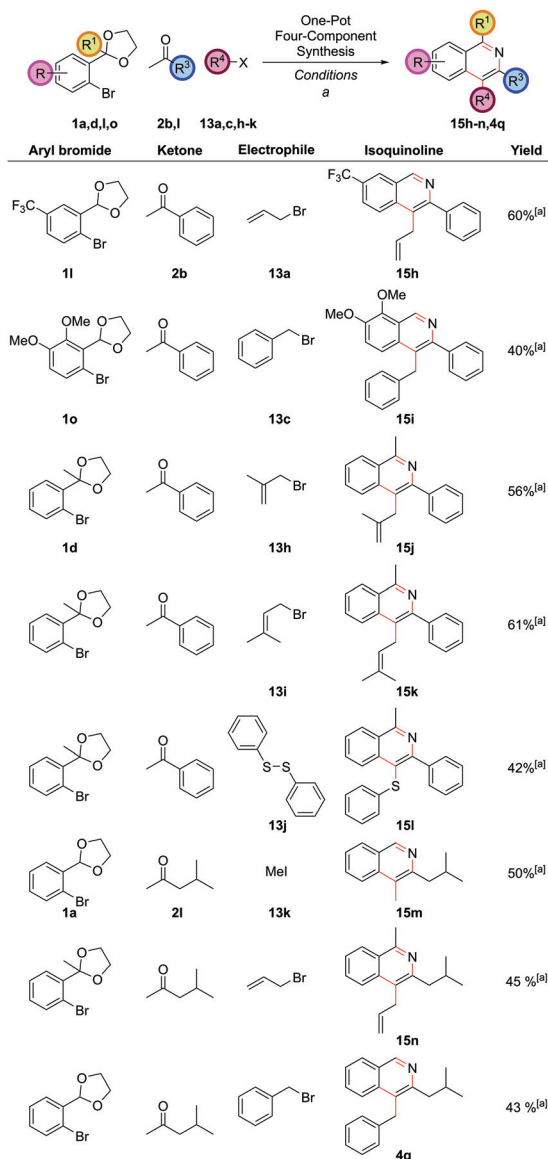
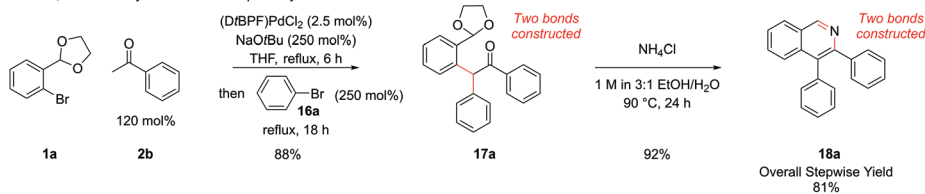
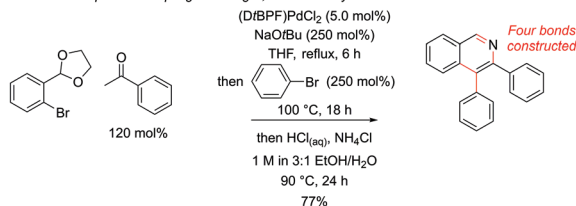
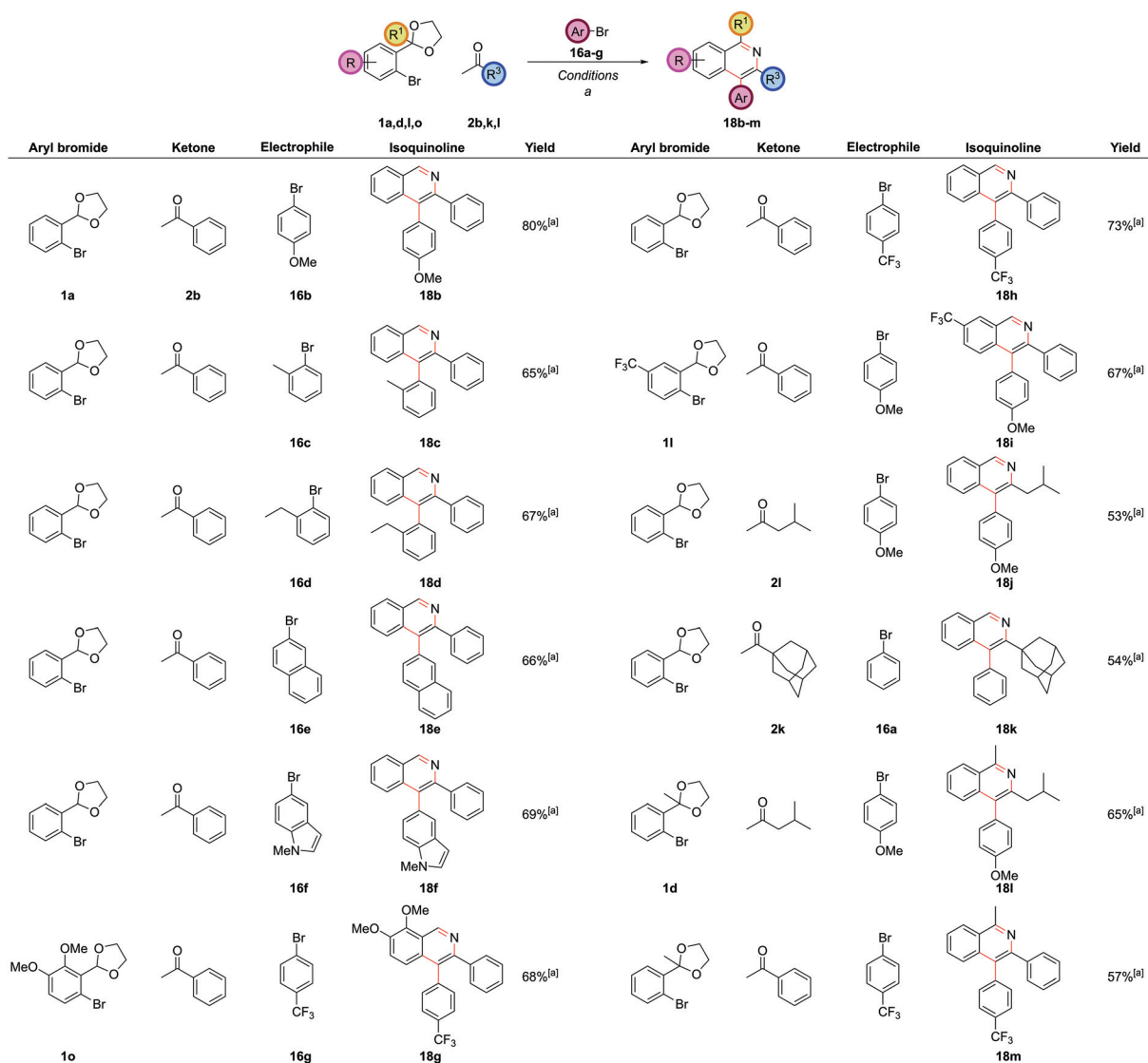


Fig. 8 Further exemplification of the one-pot four-component coupling procedure. [a] (DtBPF)PdCl<sub>2</sub> (2.5 mol%), NaOtBu (250 mol%), THF, reflux, 18 h, then electrophile, rt, 8 h, then HCl<sub>(aq)</sub>, NH<sub>4</sub>Cl (1 M in 3 : 1 EtOH/H<sub>2</sub>O), 90 °C, 24 h.



A One-Pot  $\alpha$ , $\alpha$ -Heterodiarylation and Subsequent CyclizationOne-Pot Four-Component Coupling including  $\alpha$ , $\alpha$ -Heterodiarylation

Scheme 8 Development of one-pot diarylation.

Fig. 9 Scope of four-component coupling procedure with two aryl bromides. [a] (DtBPF)PdCl<sub>2</sub> (5.0 mol%), NaOtBu (250 mol%), THF, reflux, 6 h, then aryl bromide, reflux, 18 h, then HCl(aq), NH<sub>4</sub>Cl (1 M in 3 : 1 EtOH/H<sub>2</sub>O), 90 °C, 24 h.

*ortho*-ethyl **16d** groups could be employed, as could larger aromatic groups such as naphthalenes **16e** and *N*-methyl indoles **16f**. As before, a wide range of substitution was possible with the other reaction partners, including electron-rich **10** and electron-deficient **11** carbocyclic rings, C1-substitution **1d**, and bulky alkyl substituents at C3 **2k**.

### Electrophile trapping and decarboxylation of *tert*-butyl cyanoacetate

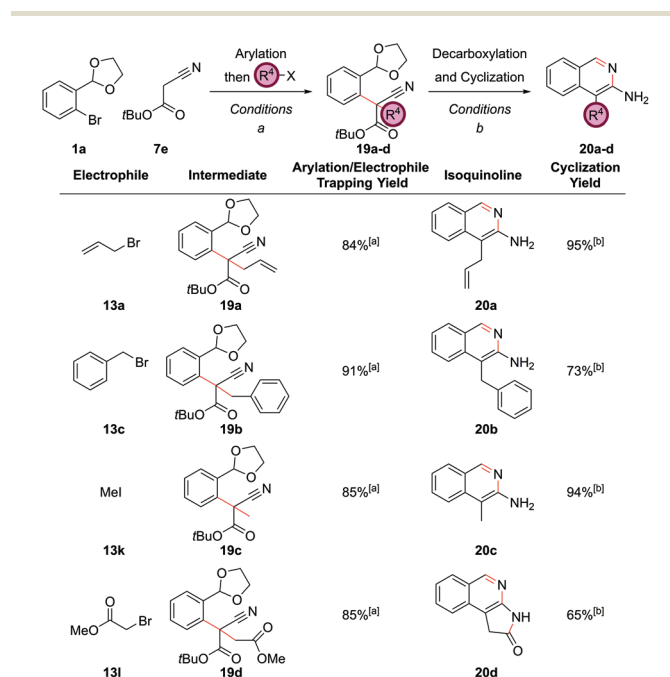
Extending the four-component coupling procedure to nitriles would allow a greater variety of 3-amino isoquinolines to be synthesized, however this would require acetonitrile as one of the coupling partners, a difficult substrate to  $\alpha$ -arylate. Our previous studies had shown that *tert*-butyl cyanoacetate could behave as a synthetic equivalent for acetonitrile due to the decarboxylation that could be encouraged after the  $\alpha$ -arylation (*vide supra* Fig. 6). Literature precedent also illustrated that ethyl cyanoacetate could be  $\alpha$ -arylated and then alkylated *in situ* in a one-pot procedure,<sup>30</sup> and so we investigated *in situ* trapping in this system. Addition of allyl bromide, **13a**, and heating to 70 °C could be employed to trap the product of the  $\alpha$ -arylation of *tert*-butyl cyanoacetate, **7e**, to give intermediate **19a** in 84% yield (Fig. 10). Attempted decarboxylation of **19a** under mildly acidic conditions (NH<sub>4</sub>Cl) led to partial hydration of the nitrile and formation of a mixture of the 3-hydroxy and 3-aminoisoquinoline. The optimal procedure involved decarboxylation under neutral conditions, which occurred when intermediate **19a** was heated in aqueous ethanol. Hence, the prime set of cyclization conditions involved first heating in a

mixture of ethanol and water to effect decarboxylation, adding ammonium chloride to cleave the acetal (the prior removal of the ester stopped the hydration of the nitrile at this stage) and then basification with ammonium bicarbonate to cyclize to 3-aminoisoquinoline **20a**. This occurred in a yield of 95%, and was also a better set of conditions for the cyclization of the unalkylated intermediate (86% *vs.* 74%, *vide supra* Fig. 6). With such *tert*-butyl cyanoacetate couplings, the one-pot procedure gave lower yields, presumably due to the free amino group in the product reacting with an excess of one of the starting reagents. Hence, exemplification of this protocol was performed over two steps. Benzyl bromide, **13c**, and iodo-methane, **13k**, could be employed as electrophiles to give isoquinolines **20b** and **20c** respectively, the presence of the amino group always characterized by the broad singlet (relative integral 2H) between 4.3 and 4.5 ppm in the <sup>1</sup>H NMR spectra. With methyl bromoacetate, **13l**, the 3-amino group underwent further cyclization onto the tethered ester furnishing lactam-fused isoquinoline **20d** in 65% yield.

### A C–H functionalization approach to isoquinolines

During the past two decades, chelation-assisted direct C–H functionalization has emerged as a powerful synthetic strategy due to its ability to bypass prefunctionalized starting materials. Imines,<sup>38</sup> amines,<sup>39</sup> oximes,<sup>40</sup> amides<sup>41</sup> and other nitrogen-centred directing groups<sup>42</sup> have all been utilized for C–H functionalization *en route* to isoquinolines using transition metal-catalyzed annulation of alkynes or alkenes or allenes. However, these methods often suffer from regioselectivity issues when using unsymmetrical substrates and are limited by the commercial availability of the requisite starting materials. Our  $\alpha$ -arylation methodology offered broad functional group tolerance and reliable regioselectivity but required the difunctionalized *ortho*-halobenzaldehydes or *ortho*-halo phenyl ketones as precursors. We therefore set out to adapt this methodology to incorporate a C–H functionalization reaction, thus allowing the inexpensive and commercially more abundant benzaldehydes to be integrated into this route. At the outset of this project, the direct arylation of nucleophilic carbonyl derivatives *via* an intermolecular C–H functionalization was a mode of reactivity with little precedent. Recently, some groups have made efforts towards this, however, a general procedure remains elusive.<sup>9b,43</sup> Whilst studies towards this endeavour are still underway in our laboratories, an alternative strategy was envisaged whereby known C–H halogenation chemistry could pave the way for the economical benzaldehydes to enter our synthetic route to isoquinolines.

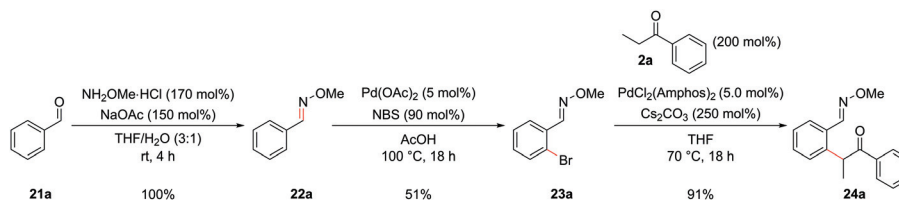
*O*-Methyl oximes have recently been reported as proficient directing groups for palladium-catalyzed C–H functionalization and it was thought that these could not only serve to direct the C–H halogenation but also to protect the aldehyde/ketone in the subsequent  $\alpha$ -arylation reaction from aldol reactions with the enolate. The *O*-methyl oxime of benzaldehyde, **22a** could be synthesized from benzaldehyde, **21a**, in quantitative yield by treatment of **21a** with methoxylamine



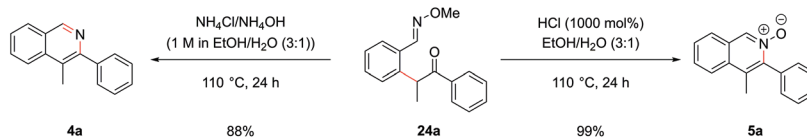
**Fig. 10**  $\alpha$ -Arylation and functionalization of *tert*-butyl cyanoacetate. [a] (DPPF)PdCl<sub>2</sub> (2.0 mol%), NaOtBu (250 mol%), 1,4-dioxane, 70 °C, 4 h, then R<sup>4</sup>-X, 70 °C, 8 h; [b] EtOH/H<sub>2</sub>O (3 : 2), 90 °C, 18 h, then NH<sub>4</sub>Cl (1000 mol%), 90 °C, 3 h, then NH<sub>4</sub>HCO<sub>3</sub> (2 M in H<sub>2</sub>O), 90 °C, 3 h.







**Scheme 9** C–H functionalization allowing benzaldehyde derivatives to be incorporated into the synthetic route.



**Scheme 10** Cyclization of oxime **24a** to both isoquinoline **4a** and isoquinoline *N*-oxide **5a**.

hydrochloride under basic conditions (Scheme 9). The desired *ortho*-bromide **23a** was obtained by using the conditions reported by Sanford and coworkers.<sup>44</sup> NBS was used as the limiting reagent to minimise the formation of polybrominated products. The  $\alpha$ -arylation reaction could be performed in a 91% yield to furnish intermediate **24a** with 5.0 mol%  $\text{PdCl}_2(\text{Amphos})_2$  catalyst. Pleasingly, the *O*-methyl oxime survived the  $\alpha$ -arylation reaction conditions when the weaker base  $\text{Cs}_2\text{CO}_3$  was employed but was destroyed if  $\text{NaOtBu}$  was used.

Cyclization of oxime intermediate **24a** under the conditions developed for the acetal-protected carbonyls gave a mixture of starting material, the desired isoquinoline **4a** and the isoquinoline *N*-oxide **5a**, the latter presumably formed by solvent-mediated demethylation of the oxygen from the *O*-methyl oxime after cyclization to the isoquinoline. The ratio between these was highly pH dependant. Full conversion to the isoquinoline could be achieved by cyclization with a mixture of ammonium chloride and ammonium hydroxide (at pH 10) at an elevated temperature of 110 °C in a yield of 88% (Scheme 10). It was also possible to exploit this pH dependence of the cyclization to selectively synthesize isoquinoline *N*-oxide **5a** in quantitative yield by treating intermediate **24a** with 1 M HCl. It is worth highlighting the atom-efficiency of this protocol since, in contrast to some C–H functionalization reactions, the directing group is incorporated into the desired product, acting as the N–O source, and is not cleaved in a subsequent step.

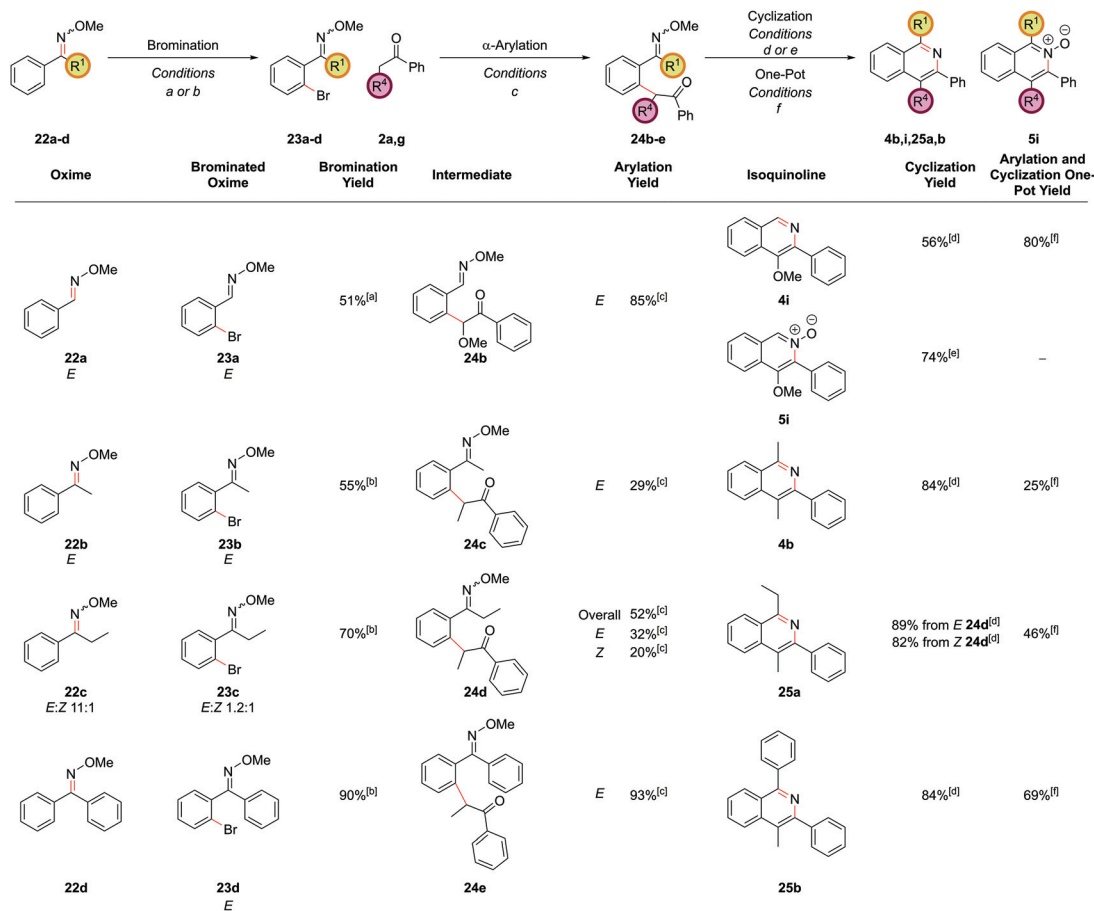
The  $\alpha$ -arylation and cyclization reactions could again be combined into a one-pot protocol, furnishing isoquinoline **4a** from bromo oxime **24a** in 83% yield, or *N*-oxide **5a** in 64% yield. This modified protocol sufficiently enhanced the scope available at the C1 position of the resulting isoquinoline, which was previously limited by the low commercial availability of *ortho*-bromophenyl ketones and the difficulty of forming cyclic acetals on such moieties. With *O*-methyl oximes of ketones there is the possibility of *E/Z* isomerism, with the *E* isomer generally predominating unless the R group is sterically

bulky. It was envisaged that *E* geometry, where the lone pair on nitrogen is oriented *syn* to the aromatic ring, is required to direct in the palladium for C–H functionalization, as has been previously noted for rhodium-catalyzed alkyne annulation.<sup>40f</sup> The geometric isomers of ethyl oxime **22c** could be separated *via* column chromatography but equilibrated back to the thermodynamic ratio after standing in  $\text{CDCl}_3$  and hence it was postulated that the unreactive *Z* oximes could isomerize under the acidic bromination conditions and thus also be reacted. Methyl oxime **22b** and ethyl oxime **22c** were both converted through to the corresponding isoquinolines **4b** and **25a** respectively (Fig. 11), with only the  $\alpha$ -arylation step occurring in lower yields than the benzaldehyde case. Significant unreacted starting material was recovered from these reactions and it was thought that deprotonation  $\alpha$  to the oxime under the basic reaction conditions might be retarding the reaction. This notion was supported by the failure of the benzyl-substituted variant to undergo arylation. In the case of the ethyl variant, both *E* and *Z* isomers of intermediate **24d** could be separately carried through the sequence successfully. Phenyl oxime **22d** was a particularly efficient substrate and this was attributed to the conformational rigidity of the intermediates, placing the nitrogen lone pair close to the C–H bond to be functionalized, hence increasing the scope of substitution available at the C1 position (isoquinoline **25b**).

## Conclusions

The advent of innovative transition metal-catalyzed reactions enables aromatic heterocycles to be constructed in ever more adventurous ways – the palladium-catalyzed  $\alpha$ -arylation of enolates in the synthesis of isoquinolines being a prime example of this retrosynthetic strategy. Throughout this project we sought to keep the ideals of modularity and practicality at the forefront. The three-component or four-component coupling procedures herein developed, involving multiple bond





**Fig. 11** C–H bromination route to isoquinolines. [a] Pd(OAc)<sub>2</sub> (5.0 mol%), NBS (90 mol%), AcOH, 100 °C, 18 h; [b] Pd(OAc)<sub>2</sub> (5.0 mol%), NBS (110 mol%), AcOH, 100 °C, 18 h; [c] (PdCl<sub>2</sub>(Amphos))<sub>2</sub> (5.0 mol%), Cs<sub>2</sub>CO<sub>3</sub> (250 mol%), ketone (200 mol%), THF, 70 °C, 18 h; [d] NH<sub>4</sub>Cl/NH<sub>4</sub>OH (1 M in 3 : 1 EtOH/H<sub>2</sub>O), 110 °C, 24 h; [e] HCl (1000 mol%), EtOH/H<sub>2</sub>O (3 : 1), 110 °C, 24 h; [f] (PdCl<sub>2</sub>(Amphos))<sub>2</sub> (5.0 mol%), Cs<sub>2</sub>CO<sub>3</sub> (250 mol%), THF, 70 °C, 18 h, then NH<sub>4</sub>Cl/NH<sub>4</sub>OH (1 M in 3 : 1 EtOH/H<sub>2</sub>O), 110 °C, 24 h.

construction processes, provide access to highly complex isoquinoline frameworks in one-pot from largely commercially available starting materials, with only one work up and purification procedure required. Versatility of a synthetic route is also highly prized and demonstrated here by the utilization of ketone, ester or nitrile enolates, electron-rich, electron-deficient or sterically-hindered aryl halides, the direct access to 3-aminoisoquinolines, 3-hydroxyisoquinolines, isoquinoline *N*-oxides and isoquinolinium salts and the *in situ* functionalization of intermediates. The robustness of the process has been successfully proven in the arena of natural product synthesis,<sup>45</sup> and also in the creation of a library of novel compounds charting new areas of chemical space giving chemists much greater flexibility when constructing their desired isoquinoline skeleton.

## Experimental

### General experimental details

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a 300 MHz or 400 MHz spectrometer in CDCl<sub>3</sub>, CD<sub>2</sub>Cl<sub>2</sub>, CD<sub>3</sub>OD or acetone-*d*<sub>6</sub>

and referenced to residual solvent peaks. Chemical shifts are quoted in ppm (parts per million) to the nearest 0.01 ppm with signal splitting recorded as singlet (s), doublet (d), triplet (t), quartet (q), septet (sept.), multiplet (m) and broad singlet (br. s). Coupling constants, *J*, are measured in Hz to the nearest 0.1 Hz. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at room temperature. Infrared spectra were recorded as thin films of neat samples on a Bruker Tensor 27 FT-IR spectrometer equipped with Attenuated Total Reflectance sampling accessories. High resolution mass spectra are given to four decimal places and were recorded on a Bruker MicroTof (resolution = 10 000 FWHM) under conditions of electrospray ionization (ESI). Melting points (m.p.) were obtained from recrystallized samples using a Lecia VMTG heated-stage microscope and are uncorrected. The solvent systems used for recrystallization are quoted in parentheses. Flash column chromatography was performed using silica gel (60 Å, 0.033–0.070 mm, BDH) or using basic alumina (pH 9.5, 58 Å, 150 mesh, Sigma-Aldrich). TLC analyses were performed on Merck Kiesegel 60 F<sub>254</sub> 0.25 mm precoated silica plates or Macherey-Nagel Alugram Alox N/UV<sub>254</sub> 0.20 mm precoated alumina plates. Reagents obtained



from Sigma-Aldrich, Alfa, Fluorochem and TCI suppliers were used directly as supplied other than alkyl bromides which were first purified by being passed through a short plug of  $\text{K}_2\text{CO}_3$ . All palladium catalysts were obtained from Johnson Matthey. The palladium catalysts and bases were stored in a desiccator. Compounds that contained acetals of electron-rich benzaldehydes were found to undergo slow hydrolysis (over a period of weeks) due to atmospheric moisture and hence were also stored in a desiccator. This increased their lifetime to many months. All anhydrous reactions were carried out in flame dried glassware and under an inert atmosphere of argon provided by a balloon. All reactions were stirred with magnetic followers. Petrol refers to petroleum ether in the boiling range 40–60 °C. THF, toluene and  $\text{CH}_2\text{Cl}_2$  were dried by purification through two activated alumina purification columns. Brine refers to a saturated aqueous solution of NaCl. Crystal structure determination was carried out using X-ray diffraction data measured on an Enraf-Nonius Kappa CCD diffractometer. Intensity data were processed using the DENZO SMN package and further processing was carried out using the Crystals, Cameron and Mercury software. Experimental procedures and characterization data for new compounds or compounds made by a new method are listed below; for the experimental procedures and characterization data of the remaining compounds, see ref. 10, 15 and 16.

#### General procedure A

A resealable reaction tube, containing a magnetic follower, was sealed with a rubber septum and flame dried under a flow of argon.  $(\text{D}t\text{BPF})\text{PdCl}_2$  (2.0 mol%) and  $\text{NaOtBu}$  (250 mol%) were added to the tube. The aryl bromide (100 mol%) was dissolved in dry THF (5 mL  $\text{mmol}^{-1}$ ) and the resulting solution was added *via* syringe to the tube. The ketone (120 mol%) was then added to the tube. The rubber septum was replaced with a screw cap and the tube was heated at 70 °C for 18 h. The reaction was then cooled to room temperature and quenched by the addition of  $\text{H}_2\text{O}$  (25 mL). The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 × 25 mL) and the combined organics were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent removed *in vacuo*.

#### General procedure B

A solution of  $\text{NH}_4\text{Cl}$  (1000 mol%, 1.0 M in 3 : 1  $\text{EtOH}/\text{H}_2\text{O}$ ) was added to the cyclization substrate (100 mol%) in a resealable reaction tube containing a magnetic follower. The tube was sealed with a screw cap and heated at 90 °C for 24 h. The reaction was then cooled to room temperature and quenched by the addition of saturated aqueous  $\text{NaHCO}_3$  (25 mL). The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 × 25 mL) and the combined organics were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent removed *in vacuo*.

#### General procedure C

A solution of  $\text{NH}_4\text{Cl}$  (1000 mol%, 1.0 M in 3 : 1  $\text{EtOH}/\text{H}_2\text{O}$ ) was added to the cyclization substrate (100 mol%) in a resealable reaction tube containing a magnetic follower. The tube was sealed with a screw cap and heated at 90 °C for 18 h. A solu-

tion of  $\text{NH}_4\text{HCO}_3$  (2.0 M in  $\text{H}_2\text{O}$ ) was then added until the pH of the reaction mixture had been adjusted to approximately pH 9. The tube was resealed and heated for a further 24 h at 90 °C. The reaction was then cooled to room temperature and quenched by the addition of  $\text{H}_2\text{O}$  (25 mL). The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 × 25 mL) and the combined organics were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent removed *in vacuo*.

#### General procedure D

A solution of hydroxylamine hydrochloride (1000 mol%, 1.0 M in 9 : 1  $\text{EtOH}/\text{H}_2\text{O}$ ) was added to the cyclization substrate (100 mol%) in a resealable reaction tube containing a magnetic follower. The tube was sealed with a screw cap and heated at 90 °C for 2 h. The reaction was then cooled to room temperature and the solvent removed *in vacuo* using a toluene azeotrope.

#### General procedure E

A resealable reaction tube, containing a magnetic follower, was sealed with a rubber septum and flame dried under a flow of argon.  $\text{PdCl}_2(\text{Amphos})_2$  (5.0 mol%) and  $\text{Cs}_2\text{CO}_3$  (250 mol%) were added to the tube. The aryl bromide (100 mol%) was dissolved in dry THF (5 mL  $\text{mmol}^{-1}$ ) and the resulting solution was added *via* syringe to the tube. The nitrile (200 mol%) was then added to the tube. The rubber septum was replaced with a screw cap and the tube was heated at 70 °C for 18 h. The reaction was then cooled to room temperature and quenched by the addition of  $\text{H}_2\text{O}$  (25 mL). The aqueous layer was extracted with  $\text{EtOAc}$  (3 × 25 mL) and the combined organics were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent removed *in vacuo*.

#### General procedure F

A microwave vial, containing a magnetic follower, was sealed with a rubber septum and flame dried under vacuum.  $(\text{DPPF})\text{PdCl}_2$  (5.0 mol%),  $\text{NaOtBu}$  (250 mol%) and the nitrile (100 mol%) were added to the vial. The septum was replaced with a microwave cap and the vial was evacuated and backfilled with argon before a solution of the aryl bromide (120 mol%) in anhydrous 1,4-dioxane (4 mL  $\text{mmol}^{-1}$ ) was added *via* syringe to the vial and the reaction was heated at 70 °C for a specified time. The reaction was then cooled to room temperature and quenched by the addition of saturated aqueous  $\text{NH}_4\text{Cl}$  (25 mL). The aqueous layer was extracted with  $\text{EtOAc}$  (3 × 25 mL) and the combined organics were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent removed *in vacuo*.

#### General procedure G

Methoxylamine hydrochloride (160 mol%) was added to a solution of the ketone (100 mol%) and pyridine (1.2 mL  $\text{mmol}^{-1}$ ) in  $\text{EtOH}$  (10 mL  $\text{mmol}^{-1}$ ) and the reaction was stirred at a specified temperature for a specified time. The solvent was removed *in vacuo* and then the remaining residue redissolved in  $\text{EtOAc}$  (10 mL  $\text{mmol}^{-1}$ ), washed with  $\text{H}_2\text{O}$  (50 mL) and brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent removed *in vacuo*.



### General procedure H<sup>44</sup>

Palladium(II) acetate (5.0 mol%) was added to a solution of the *O*-alkyl oxime (100 mol%) and *N*-bromosuccinimide (110 mol%) in acetic acid (8.0 mL mmol<sup>-1</sup>) in a resealable reaction tube containing a magnetic follower. The reaction was heated at 100 °C for a specified time then cooled to room temperature and the solvent removed *in vacuo*.

### General procedure I

A resealable reaction tube, containing a magnetic follower, was sealed with a rubber septum and flame dried under a flow of argon. PdCl<sub>2</sub>(Amphos)<sub>2</sub> (5.0 mol%) and Cs<sub>2</sub>CO<sub>3</sub> (250 mol%) were added to the tube. A solution of the aryl bromide (100 mol%) in anhydrous THF (5.0 mL mmol<sup>-1</sup>) and the ketone (200 mol%) were then added *via* syringe. The septum was replaced with a screw cap and the reaction was heated at 70 °C for 18 h. The reaction was cooled to room temperature, quenched with H<sub>2</sub>O (25 mL), the aqueous layer extracted with Et<sub>2</sub>O (3 × 25 mL) and the combined organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent removed *in vacuo*.

### General procedure J

A solution of NH<sub>4</sub>Cl (1000 mol%, 1.0 M in 3:1 EtOH/H<sub>2</sub>O) which had been basified to ~pH 9 by the dropwise addition of 25% aqueous NH<sub>4</sub>OH was added to the cyclization substrate (100 mol%) in a resealable reaction tube containing a magnetic follower. The tube was sealed with a screw cap and heated at 110 °C for 24 h. The reaction was then cooled to room temperature and quenched by the addition of saturated aqueous NH<sub>4</sub>Cl (25 mL). The aqueous layer was extracted with Et<sub>2</sub>O (3 × 25 mL) and the combined organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent removed *in vacuo*.

### General procedure K

A resealable reaction tube, containing a magnetic follower, was sealed with a rubber septum and flame dried under a flow of argon. PdCl<sub>2</sub>(Amphos)<sub>2</sub> (5.0 mol%) and Cs<sub>2</sub>CO<sub>3</sub> (250 mol%) were added to the tube. A solution of the aryl bromide (100 mol%) in anhydrous THF (5.0 mL mmol<sup>-1</sup>) and the ketone (200 mol%) were then added *via* syringe. The septum was replaced with a screw cap and the reaction was heated at 70 °C for 18 h. The reaction was cooled to room temperature, then a solution of NH<sub>4</sub>Cl (1000 mol%, 1.0 M in 3:1 EtOH/H<sub>2</sub>O) which had been basified to ~pH 9 by the dropwise addition of 25% aqueous NH<sub>4</sub>OH was added, the tube resealed with a screw cap and then heated at 110 °C for 24 h. The reaction was cooled to room temperature, quenched with saturated aqueous NH<sub>4</sub>Cl (25 mL), the aqueous layer extracted with Et<sub>2</sub>O (3 × 25 mL) and the combined organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent removed *in vacuo*.

### General procedure L

A solution of HCl (1000 mol%, 1.0 M in 9:1 EtOH/H<sub>2</sub>O) was added to the cyclization substrate (100 mol%) in a resealable reaction tube containing a magnetic follower. The tube was

sealed with a screw cap and heated at 110 °C for 24 h. The reaction was then cooled to room temperature and the solvent removed *in vacuo* using a toluene azeotrope.

**2-(2-(1,3-Dioxolan-2-yl)phenyl)-1-(4-methoxyphenyl)ethanone 3d.** Aryl bromide **1a** (51.8 mg, 0.226 mmol) was subjected to General procedure A with 4'-methoxyacetophenone, **2g**. Purification by flash column chromatography [petrol/EtOAc 19:1 grading to 9:1] furnished ketone **3d** (53.8 mg, 0.180 mmol, 80%) as rods. **M.p.** 131–133 °C (petrol/CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 8.04 (2H, d, *J* 8.9), 7.59 (1H, dd, *J* 7.1, 1.8), 7.34–7.28 (2H, m), 7.18 (1H, dd, *J* 6.6, 2.0), 6.95 (2H, d, *J* 8.9), 5.90 (1H, s), 4.45 (2H, s), 4.06–3.94 (4H, m), 3.87 (3H, s); <sup>13</sup>C[<sup>1</sup>H] NMR (100 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 196.2, 163.4, 135.5, 134.0, 131.3, 130.7, 130.0, 129.2, 126.9, 126.9, 113.8, 102.7, 65.0, 55.5, 42.3; IR ν<sub>max</sub> (thin film)/cm<sup>-1</sup> 2894, 2839, 1679, 1600, 1575, 1510, 1420, 1329, 1258, 1220, 1170, 1112, 1074, 1027, 992, 963, 833; HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>18</sub>H<sub>18</sub>NaO<sub>4</sub> 321.1097; Found 321.1097.

**2-(2-(1,3-Dioxolan-2-yl)phenyl)-1-(3,5-bis(trifluoromethyl)phenyl)ethanone 3e.** Aryl bromide **1a** (165 mg, 0.677 mmol) was subjected to General procedure A with 3',5'-bis(trifluoromethyl)acetophenone, **2d**. Purification by flash column chromatography [petrol/EtOAc 49:1 grading to 19:1] furnished ketone **3e** (191 mg, 0.472 mmol, 70%) as prisms. **M.p.** 88–90 °C (petrol/CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 8.51 (2H, s), 8.06 (1H, s), 7.61–7.59 (1H, m), 7.38–7.31 (2H, m), 7.21–7.18 (1H, m), 5.91 (1H, s), 4.52 (2H, s), 4.04–4.01 (2H, m), 3.99–3.96 (2H, m); <sup>13</sup>C NMR[<sup>1</sup>H] (100 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 195.1, 138.4, 135.4, 132.3 (q, <sup>2</sup>*J* 33.9), 132.1, 131.1, 129.4, 128.6 (q, <sup>3</sup>*J* 3.2), 127.5, 127.5, 126.1 (sept., <sup>3</sup>*J* 3.6), 122.9 (q, <sup>1</sup>*J* 272.9), 102.9, 64.9, 42.9; <sup>19</sup>F[<sup>1</sup>H] NMR (377 MHz, CDCl<sub>3</sub>) δ<sub>F</sub>: –62.9; IR ν<sub>max</sub> (thin film)/cm<sup>-1</sup> 2895, 1699, 1617, 1381, 1322, 1277, 1249, 1173, 1129, 1077, 1046, 968, 943, 914, 842; HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>14</sub>F<sub>6</sub>NaO<sub>3</sub> 427.0739; Found 427.0732.

**2-(2-(2-Methyl-1,3-dioxolan-2-yl)phenyl)-1-phenylethanone 3g.** Aryl bromide **1d** (174 mg, 0.717 mmol) was subjected to General procedure A with acetophenone, **2b**. Purification by flash column chromatography [petrol/EtOAc 49:1 grading to 24:1] furnished ketone **3g** (189 mg, 0.670 mmol, 93%) as plates. **M.p.** 55–57 °C (petrol/CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 8.08 (2H, dd, *J* 6.9, 1.5), 7.65–7.63 (1H, m), 7.61–7.58 (1H, m), 7.51 (2H, t, *J* 7.5), 7.35–7.28 (2H, m), 7.18–7.16 (1H, m), 4.55 (2H, s), 3.89–3.85 (2H, m), 3.66–3.63 (2H, m), 1.69 (3H, s); <sup>13</sup>C NMR[<sup>1</sup>H] (100 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 197.8, 141.2, 137.4, 133.0, 132.8, 132.3, 128.6, 128.1, 128.1, 127.1, 126.4, 109.0, 64.2, 43.8, 27.7; IR ν<sub>max</sub> (thin film)/cm<sup>-1</sup> 2988, 2892, 1690, 1484, 1447, 1374, 1331, 1238, 1214, 1193, 1124, 1066, 1034, 995, 951, 868; HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>18</sub>H<sub>18</sub>NaO<sub>3</sub> 305.1148; Found 305.1140.

**2-(2-(1,3-Dioxolan-2-yl)phenyl)-4-(tert-butyl)cyclohexan-1-one 3m.** 2,2,6,6-Tetramethylpiperidine (214 mg, 1.52 mmol, freshly distilled) was added to a resealable reaction tube containing a magnetic follower and sealed with a rubber septum and cooled to –78 °C. *n*BuLi (0.56 mL, 2.5 M in hexanes) was added dropwise and the reaction stirred for 10 min at –78 °C





then for 10 min at 0 °C. After recooling to −78 °C, 4-*tert*-butylcyclohexanone, **2j**, (173 mg, 1.12 mmol) was added dropwise. The reaction was stirred for 10 min at −78 °C, before being warmed to 0 °C. A solution of aryl bromide **1a** (129 mg, 0.562 mmol) in dry THF (2.2 mL) was added *via* syringe followed by (D*t*BPF)PdCl<sub>2</sub> (18.3 mg, 0.0281 mmol). The rubber septum was replaced with a screw cap and the tube heated at 70 °C for 18 h. The reaction was then cooled to room temperature and quenched by the addition of H<sub>2</sub>O (25 mL). The aqueous layer was extracted with Et<sub>2</sub>O (3 × 25 mL) and the combined organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography [petrol/EtOAc 50:1 grading to 5:1] furnished ketone **3m** (59.3 mg, 0.241 mmol, 75%) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 7.48 (1H, d, *J* 7.6), 7.29 (1H, m), 7.19 (1H, m), 7.14 (1H, d, *J* 7.8), 5.79 (1H, s), 4.06 (1H, m), 4.00–3.95 (2H, m), 3.93–3.88 (2H, m), 2.49–2.39 (2H, m), 2.26–2.20 (1H, m), 2.14–2.08 (1H, m), 1.77–1.64 (2H, m), 1.60–1.47 (1H, m), 0.86 (9H, s); <sup>13</sup>C NMR [<sup>1</sup>H] (100 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 210.5, 138.0, 135.3, 129.0, 128.8, 126.7, 126.3, 102.4, 65.1, 65.0, 52.2, 47.7, 41.8, 36.6, 32.6, 28.6, 27.7; IR ν<sub>max</sub> (thin film)/cm<sup>−1</sup> 2954, 2869, 2360, 1715, 1477, 1366, 1227; HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>26</sub>NaO<sub>3</sub> 325.1762; Found 325.1774.

**1-(2-(1,3-Dioxolan-2-yl)phenyl)-1-(4-methoxyphenyl)propan-2-one 3p.** A resealable reaction tube, containing a magnetic follower, was sealed with a rubber septum and flame dried under a flow of argon. (D*t*BPF)PdCl<sub>2</sub> (32.0 mg, 0.0492 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (801 mg, 2.46 mmol) were added to the tube. Aryl bromide **1a** (225 mg, 0.983 mmol) was dissolved in dry THF (4.9 mL) and the resulting solution was added *via* syringe to the tube. 4-Methoxyphenylacetone, **2m**, (323 mg, 1.97 mmol) was then added to the tube. The rubber septum was replaced with a screw cap and the tube was heated at 70 °C for 18 h. The reaction was then cooled to room temperature and quenched by the addition of H<sub>2</sub>O (25 mL). The aqueous layer was extracted with Et<sub>2</sub>O (3 × 25 mL) and the combined organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography [petrol/EtOAc 24:1 grading to 14:1] furnished ketone **3p** (301 mg, 0.965 mmol, 98%) as an oil. <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>) δ<sub>H</sub>: 7.57 (1H, d, *J* 7.3), 7.33 (1H, t, *J* 7.4), 7.28 (1H, t, *J* 7.3), 7.18 (2H, d, *J* 8.6), 7.15 (1H, d, *J* 7.8), 6.90 (2H, d, *J* 8.6), 5.98 (1H, s), 5.79 (1H, s), 4.19–4.03 (4H, m), 3.78 (3H, s), 2.18 (3H, s); <sup>13</sup>C NMR [<sup>1</sup>H] (100 MHz, acetone-*d*<sub>6</sub>) δ<sub>C</sub>: 206.0, 159.6, 139.0, 136.5, 131.5, 131.2, 130.6, 129.6, 127.8, 127.4, 114.7, 103.3, 65.8, 65.6, 59.3, 55.5, 30.0; IR ν<sub>max</sub> (thin film)/cm<sup>−1</sup> 2956, 2891, 2837, 1714, 1609, 1582, 1510, 1456, 1408, 1353, 1303, 1250, 1181, 1155, 1109, 1071, 1031, 970, 945; HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>20</sub>NaO<sub>4</sub> 335.1254; Found 335.1238.

**5-Methyl-1-phenylhexan-3-ol S1.** Isobutylmagnesium bromide (8.95 mL, 2 M in THF) was added dropwise over 40 min to a solution of phenylpropionaldehyde (2.00g, 14.9 mmol) in THF (74 mL) at 0 °C in a flame dried flask containing a magnetic follower. The reaction was warmed to room temperature and then stirred for a further 2 h. The reaction was quenched by

the addition of saturated aqueous NH<sub>4</sub>Cl (100 mL), the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 25 mL) and the combined organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography [pentane/EtOAc 4:1] furnished alcohol **S1** (1.35 g, 7.02 mmol, 47%) as an oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 7.32–7.26 (2H, m), 7.25–7.16 (3H, m), 3.71 (1H, tt, *J* 8.6, 4.4), 2.82 (1H, ddd, *J* 13.7, 9.9, 5.9), 2.68 (1H, ddd, *J* 13.7, 9.9, 6.5), 2.12 (1H, s), 1.86–1.67 (3H, m), 1.44 (1H, ddd, *J* 14.1, 8.8, 5.4), 1.29 (1H, ddd, *J* 13.7, 8.8, 4.4), 0.93 (6H, t, *J* 6.1); <sup>13</sup>C NMR [<sup>1</sup>H] (100 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 142.3, 128.4 (2 signals), 125.7, 69.3, 46.8, 39.7, 32.1, 24.6, 23.9, 22.2. Data were consistent with those previously reported.<sup>46</sup>

**5-Methyl-1-phenylhexan-3-one 2n.** A solution of alcohol **S1** (720 mg, 3.74 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (37 mL) was added to a flame dried flask containing a magnetic follower. The reaction was cooled to 0 °C and Dess–Martin periodinane (4.76 g, 11.2 mmol) was added. The reaction was warmed to room temperature, stirred for 14 h and then quenched by the addition of H<sub>2</sub>O (40 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 25 mL) and the combined organics were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography [pentane/EtOAc 19:1] furnished ketone **2n** (680 mg, 3.57 mmol, 95%) as an oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 7.31–7.25 (2H, m), 7.22–7.16 (3H, m), 2.89 (2H, t, *J* 8.0), 2.71 (2H, t, *J* 8.0), 2.27 (2H, d, *J* 6.9), 2.20–2.07 (1H, m), 0.89 (6H, d, *J* 6.6); <sup>13</sup>C NMR [<sup>1</sup>H] (100 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 210.1, 141.3, 128.6, 128.5, 126.2, 52.2, 44.9, 29.8, 24.7, 22.7; IR ν<sub>max</sub> (thin film)/cm<sup>−1</sup> 3028, 2871, 2360, 2341, 1711; HRMS (ESI-TOF) *m/z*: [M + H]<sup>+</sup> Calcd for C<sub>13</sub>H<sub>19</sub>O 191.14325; Found 191.14304.

**2-(2-(1,3-Dioxolan-2-yl)phenyl)-5-methyl-1-phenylhexan-3-one 3q.** Aryl bromide **1a** (100 mg, 0.436 mmol) was subjected to a modified General procedure A with ketone **2n** (200 mol%) and (D*t*BPF)PdCl<sub>2</sub> (5.0 mol%). Purification by flash column chromatography [pentane/EtOAc 19:1] furnished ketone **3q** (84.2 mg, 0.249 mmol, 57%) as an oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 7.50–7.44 (1H, m), 7.30–7.00 (8H, m), 5.62 (1H, s), 4.38 (1H, dd, *J* 8.4, 5.8), 4.06–3.91 (4H, m), 3.33 (1H, dd, *J* 13.5, 8.4), 2.75 (1H, dd, *J* 13.5, 5.8), 2.15–2.00 (2H, m), 1.99–1.87 (1H, m), 0.68 (3H, d, *J* 6.1), 0.57 (3H, d, *J* 6.1); <sup>13</sup>C NMR [<sup>1</sup>H] (100 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 209.7, 140.3, 137.6, 135.4, 129.5, 129.1, 128.2, 128.0, 127.1, 126.9, 126.1, 102.4, 65.1, 65.0, 55.6, 51.2, 39.1, 24.4, 22.6, 22.1; IR ν<sub>max</sub> (thin film)/cm<sup>−1</sup> 3028, 2872, 2360, 2341, 1709; HRMS (ESI-TOF) *m/z*: [M + H]<sup>+</sup> Calcd for C<sub>22</sub>H<sub>27</sub>O<sub>3</sub> 339.19562; Found 339.19547.

**2-(2-(1,3-Dioxolan-2-yl)-4,5-dimethoxyphenyl)-1-phenylethanone 3s.** Aryl bromide **1e** (86.2 mg, 0.298 mmol) (synthesis<sup>10</sup>) was subjected to General procedure A with acetophenone, **2b**. Purification by flash column chromatography [petrol/EtOAc 19:1 grading to 4:1] furnished ketone **3s** (79.9 mg, 0.243 mmol, 82%) as prisms. **M.p.** 97–99 °C (petrol/CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 8.05 (2H, d, *J* 7.4), 7.58 (1H, t, *J* 7.3), 7.48 (2H, t, *J* 7.6), 7.14 (1H, s), 6.68 (1H, s), 5.82 (1H, s), 4.43 (2H, s), 4.06–3.93 (4H, m), 3.90 (3H, s), 3.84 (3H, s); <sup>13</sup>C NMR [<sup>1</sup>H] (100 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 197.8, 149.2, 147.7, 136.9,



133.1, 128.6, 128.4, 127.7, 125.9, 114.3, 110.1, 102.4, 65.0, 55.9, 55.9, 42.1; **IR**  $\nu_{\max}$  (thin film)/cm<sup>-1</sup> 2944, 1684, 1596, 1573, 1525, 1466, 1447, 1349, 1331, 1273, 1242, 1215, 1199, 1115, 1002, 887, 861; **HRMS** (ESI-TOF)  $m/z$ : [M + Na]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>20</sub>NaO<sub>5</sub> predicted 351.1203, Found 351.1198.

**2-(2-(1,3-Dioxolan-2-yl)-4-fluorophenyl)-1-phenylethanone 3y.** Aryl bromide **1j** (102 mg, 0.412 mmol) (synthesis<sup>10</sup>) was subjected to General procedure A with acetophenone, **2b**. Purification by flash column chromatography [petrol/EtOAc 24:1 grading to 14:1] furnished ketone **3y** (95.0 mg, 0.332 mmol, 81%) as prisms. **M.p.** 63–65 °C (petrol/CH<sub>2</sub>Cl<sub>2</sub>); **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 8.05 (2H, dd, *J* 8.0, 1.3), 7.60 (1H, t, *J* 7.5), 7.50 (2H, t, *J* 7.6), 7.34 (1H, dd, *J* 9.7, 2.7), 7.15 (1H, dd, *J* 7.9, 5.6), 7.03 (1H, td, *J* 8.3, 2.8), 5.86 (1H, s), 4.46 (2H, s), 4.03–3.98 (2H, m), 3.97–3.93 (2H, m); **<sup>13</sup>C[<sup>1</sup>H] NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 197.3, 161.8 (d, <sup>1</sup>*J* 245.2), 138.4 (d, <sup>3</sup>*J* 7.2), 136.8, 133.2, 133.0 (d, <sup>3</sup>*J* 8.0), 129.0 (d, <sup>4</sup>*J* 3.2), 128.7, 128.3, 115.7 (d, <sup>2</sup>*J* 20.7), 113.8 (d, <sup>2</sup>*J* 23.1), 101.6 (d, <sup>4</sup>*J* 1.6), 65.0, 41.8; **<sup>19</sup>F[<sup>1</sup>H] NMR** (377 MHz, CDCl<sub>3</sub>)  $\delta_{\text{F}}$ : -115.2; **IR**  $\nu_{\max}$  (thin film)/cm<sup>-1</sup> 3064, 2929, 1689, 1639, 1597, 1499, 1448, 1382, 1333, 1257, 1215, 1159, 1113, 1066, 1036, 1014, 962, 907, 873, 834, 812; **HRMS** (ESI-TOF)  $m/z$ : [M + Na]<sup>+</sup> Calcd for C<sub>17</sub>H<sub>15</sub>FNao<sub>3</sub> 309.0897; Found 309.0897.

**4-Methyl-3-phenylisoquinoline 4a. Method A:** Ketone **24a** (63.9 mg, 0.239 mmol) was subjected to General procedure J. Purification by flash column chromatography [petrol/EtOAc 17:3] furnished isoquinoline **4a** (46.3 mg, 0.211 mmol, 88%) as a solid. **Method B:** Oxime **23a** (67.0 mg, 0.313 mmol) was subjected to General procedure K with propiophenone, **2a**. Purification by flash column chromatography [petrol/EtOAc 17:3] furnished isoquinoline **4a** (56.7 mg, 0.258 mmol, 83%) as a solid. **M.p.** 97–99 °C; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 9.22 (1H, s), 8.07 (1H, d, *J* 8.3), 8.01 (1H, d, *J* 8.1), 7.77 (1H, ddd, *J* 8.4, 7.0, 1.3), 7.66–7.58 (3H, m), 7.54–7.46 (2H, m), 7.46–7.38 (1H, m), 2.67 (3H, s); **<sup>13</sup>C[<sup>1</sup>H] NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 151.8, 150.2, 141.3, 136.2, 130.4, 129.9, 128.1, 128.1, 127.6, 127.3, 126.6, 124.0, 123.6, 15.5. Data were consistent with those previously reported.<sup>10</sup>

**1,4-Dimethyl-3-phenylisoquinoline 4b. Method A:** Ketone **24c** (57.2 mg, 0.203 mmol) was subjected to General procedure J. Purification by flash column chromatography [petrol/EtOAc 97:3] furnished isoquinoline **4b** (39.8 mg, 0.171 mmol, 84%) as a solid. **Method B:** Aryl bromide **23b** (240 mg, 1.05 mmol) was subjected to General procedure K with propiophenone, **2a**. Purification by flash column chromatography [CH<sub>2</sub>Cl<sub>2</sub>] furnished isoquinoline **4b** (61.2 mg, 0.263 mmol, 25%) as a solid. **M.p.** 96–98 °C; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 8.18 (1H, d, *J* 8.3), 8.07 (1H, d, *J* 8.3), 7.76 (1H, t, *J* 7.7), 7.67–7.55 (3H, m), 7.49 (2H, t, *J* 7.5), 7.44–7.36 (1H, m), 3.01 (3H, s), 2.62 (3H, s); **<sup>13</sup>C[<sup>1</sup>H] NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 155.9, 150.6, 141.5, 136.3, 129.9, 129.9, 128.1, 127.5, 126.3, 126.2, 126.1, 124.2, 122.3, 22.5, 15.4. Data were consistent with those previously reported.<sup>10</sup>

**3-(4-Methoxyphenyl)isoquinoline 4d.** Ketone **3d** (121 mg, 0.406 mmol) was subjected to General procedure B. Purification by flash column chromatography [petrol/EtOAc

14:1 grading to 9:1] furnished isoquinoline **4d** (79.8 mg, 0.339 mmol, 84%) as prisms. **M.p.** 99–101 °C (petrol/CH<sub>2</sub>Cl<sub>2</sub>); **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 9.31 (1H, s), 8.10 (2H, dt, *J* 8.9, 2.4), 7.99 (1H, s), 7.96 (1H, d, *J* 8.3), 7.83 (1H, d, *J* 8.1), 7.67 (1H, td, *J* 7.6, 1.1), 7.55 (1H, td, *J* 7.5, 0.9), 7.05 (2H, dt, *J* 8.9, 2.5), 3.88 (3H, s); **<sup>13</sup>C[<sup>1</sup>H] NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 160.1, 152.3, 151.0, 136.8, 132.2, 130.4, 128.2, 127.5, 127.4, 126.7, 126.7, 115.4, 114.2, 55.4. Data were consistent with those previously reported.<sup>47</sup>

**3-(3,5-Bis(trifluoromethyl)phenyl)isoquinoline 4e.** Ketone **3e** (39.2 mg, 0.0969 mmol) was subjected to General procedure B. Purification by flash column chromatography [petrol/EtOAc 24:1 grading to 19:1] furnished isoquinoline **4e** (26.9 mg, 0.0788 mmol, 81%) as needles. **M.p.** 121–122 °C (petrol/CH<sub>2</sub>Cl<sub>2</sub>); **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 9.36 (1H, s), 8.62 (2H, s), 8.16 (1H, s), 8.04 (1H, d, *J* 8.1), 7.95–7.92 (2H, m), 7.77 (1H, ddd, *J* 8.2, 6.9, 1.3), 7.68 (1H, ddd, *J* 8.1, 7.0, 1.1); **<sup>13</sup>C NMR[<sup>1</sup>H]** (100 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 152.9, 147.8, 141.6, 136.4, 132.1 (q, <sup>2</sup>*J* 33.1), 131.1, 128.3, 128.2, 127.7, 127.1, 126.9 (q, <sup>3</sup>*J* 3.1), 123.5 (q, <sup>1</sup>*J* 272.6), 121.9 (sept., <sup>3</sup>*J* 3.8), 117.3; **<sup>19</sup>F[<sup>1</sup>H] NMR** (377 MHz, CDCl<sub>3</sub>)  $\delta_{\text{F}}$ : -62.8; **IR**  $\nu_{\max}$  (thin film)/cm<sup>-1</sup> 2925, 1628, 1495, 1391, 1383, 1336, 1288, 1212, 1167, 1125, 1058, 895, 882, 845; **HRMS** (ESI-TOF)  $m/z$ : [M + Na]<sup>+</sup> Calcd for C<sub>17</sub>H<sub>9</sub>F<sub>6</sub>NNa 364.0531; Found 364.0523.

**1-Methyl-3-phenylisoquinoline 4g.** Ketone **3g** (61.2 mg, 0.217 mmol) was subjected to General procedure C. Purification by flash column chromatography [petrol/EtOAc 24:1 grading to 19:1] furnished isoquinoline **4g** (42.3 mg, 0.193 mmol, 89%) as an oil. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 8.17–8.13 (3H, m), 7.94 (1H, s), 7.87 (1H, d, *J* 8.3), 7.68 (1H, ddd, *J* 8.1, 7.1, 1.2), 7.58 (1H, ddd, *J* 7.9, 6.9, 1.3), 7.52 (2H, t, *J* 7.6), 7.41 (1H, tt, *J* 7.4, 1.2), 3.06 (3H, s); **<sup>13</sup>C NMR[<sup>1</sup>H]** (100 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 158.6, 150.0, 139.9, 136.8, 130.0, 128.7, 128.3, 127.6, 127.0, 126.8, 126.6, 125.7, 115.2, 22.7. Data were consistent with those previously reported.<sup>48</sup>

**4-Methoxy-3-phenylisoquinoline 4i.** **Method A:** Ketone **24b** (54.0 mg, 0.191 mmol) was subjected to General procedure J. Purification by flash column chromatography [petrol/EtOAc 49:1] furnished isoquinoline **4i** (25.3 mg, 0.108 mmol, 56%) as an oil. **Method B:** Oxime **23a** (102 mg, 0.477 mmol) was subjected to General procedure K with 2-methoxyacetophenone, **2g**. Purification by flash column chromatography [petrol/EtOAc 97:3] furnished isoquinoline **4i** (89.6 mg, 0.381 mmol, 80%) as an oil. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 9.16 (1H, s), 8.23 (1H, d, *J* 8.3), 8.10 (2H, d, *J* 7.6), 8.02 (1H, d, *J* 8.3), 7.76 (1H, t, *J* 7.6), 7.63 (1H, t, *J* 7.8), 7.52 (2H, t, *J* 7.7), 7.42 (1H, t, *J* 7.3), 3.70 (3H, s); **<sup>13</sup>C[<sup>1</sup>H] NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 149.0, 147.8, 143.1, 138.0, 132.0, 130.4, 129.3, 129.2, 128.4, 128.1, 127.4, 127.3, 121.6, 61.2. Data were consistent with those previously reported.<sup>10</sup>

**2-(tert-Butyl)-1,2,3,4-tetrahydrophenanthridine 4m.** Ketone **3m** (50.5 mg, 0.174 mmol) was subjected to General procedure B. Purification by flash column chromatography [petrol/EtOAc 50:1 grading to 3:1] furnished isoquinoline **4m** (38.4 mg, 0.160 mmol, 92%) as yellow prisms. **M.p.** 300 °C (decomp.) (petrol/CH<sub>2</sub>Cl<sub>2</sub>); **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 9.03 (1H, s),



7.92–7.90 (1H, m), 7.90–7.87 (1H, m), 7.67 (1H, dd,  $J$  7.1, 1.5), 7.50 (1H, t,  $J$  7.3), 3.23–3.13 (2H, m), 3.11–3.01 (1H, m), 2.75–2.65 (1H, m), 2.18–2.11 (1H, m), 1.62–1.53 (2H, m), 1.04 (9H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 150.0, 135.6, 130.2, 128.2, 126.8, 125.8, 125.8, 124.6, 121.9, 44.2, 33.8, 32.6, 27.4, 26.5, 24.3; IR  $\nu_{\text{max}}$  (thin film)/ $\text{cm}^{-1}$  2959, 2361, 2342, 1623, 1584, 1454, 1366, 1226; HRMS (ESI-TOF)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd for  $\text{C}_{17}\text{H}_{22}\text{N}$  240.1747, Found 240.1754.

**4-(4-Methoxyphenyl)-3-methylisoquinoline 4p.** Ketone **3p** (41.1 mg, 0.132 mmol) was subjected to General procedure B. Purification by flash column chromatography [petrol/EtOAc 19:1 grading to 14:1] furnished isoquinoline **4p** (30.4 mg, 0.122 mmol, 92%) as prisms. **M.p.** 96–98 °C (petrol/ $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 9.21 (1H, s), 7.97 (1H, d,  $J$  7.3), 7.58–7.50 (2H, m), 7.46 (1H, d,  $J$  8.6), 7.22 (2H, d,  $J$  8.6), 7.06 (2H, d,  $J$  8.5), 3.91 (3H, s), 2.51 (3H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 159.0, 150.9, 149.2, 136.2, 131.1, 130.6, 129.7, 130.3, 126.0, 127.5, 126.8, 125.0, 114.0, 55.3, 23.0; IR  $\nu_{\text{max}}$  (thin film)/ $\text{cm}^{-1}$  3000, 2956, 2929, 2836, 1779, 1723, 1611, 1573, 1513, 1456, 1441, 1379, 1286, 1242, 1175, 1106, 1029, 964, 922, 830; HRMS (ESI-TOF)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd for  $\text{C}_{17}\text{H}_{16}\text{NO}$  250.1226; Found 250.1220.

**4-Benzyl-3-isobutylisoquinoline 4q.** Ketone **3q** (40.0 mg, 0.118 mmol) was subjected to General procedure B. Purification by flash column chromatography [4:1 pentane/EtOAc] furnished isoquinoline **4q** (31.1 mg, 0.113 mmol, 95%) as a solid. **M.p.** 63–64 °C (petrol/ $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 9.10 (1H, s), 7.85 (1H, d,  $J$  7.9), 7.76 (1H, d,  $J$  8.5), 7.49 (1H, t,  $J$  8.5), 7.40 (1H, t,  $J$  7.9), 7.21–7.04 (3H, m), 6.97 (2H, d,  $J$  7.3), 4.39 (2H, s), 2.80 (2H, d,  $J$  7.2), 2.24–2.10 (1H, m), 0.86 (6H, d,  $J$  6.6);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 153.6, 150.9, 140.0, 135.9, 130.3, 128.5, 128.1, 128.1, 127.3, 126.1, 125.9, 125.9, 123.7, 44.3, 33.4, 29.5, 22.6. Data were consistent with those previously reported.<sup>15</sup>

**6,7-Dimethoxy-3-phenylisoquinoline 4s.** Ketone **3s** (52.6 mg, 0.160 mmol) was subjected to General procedure B. Purification by flash column chromatography [petrol/EtOAc 9:1 grading to 4:1] furnished isoquinoline **4s** (39.3 mg, 0.148 mmol, 93%) as prisms. **M.p.** 126–127 °C (petrol/ $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 9.11 (1H, s), 8.08 (2H, dt,  $J$  7.4, 1.6), 7.91 (1H, s), 7.49 (2H, t,  $J$  7.6), 7.39 (1H, tt,  $J$  7.4, 1.3), 7.19 (1H, s), 7.09 (1H, s), 4.02 (3H, s), 4.02 (3H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 153.2, 150.3, 150.2, 149.8, 139.9, 133.3, 128.8, 128.2, 126.8, 123.8, 115.5, 105.2, 105.0, 56.1, 56.1. Data were consistent with those previously reported.<sup>49</sup>

**7-Fluoro-3-phenylisoquinoline 4y.** Ketone **3y** (58.2 mg, 0.203 mmol) was subjected to General procedure B. Purification by flash column chromatography [petrol/EtOAc 19:1 grading to 14:1] furnished isoquinoline **4y** (40.4 mg, 0.181 mmol, 89%) as prisms. **M.p.** 132–134 °C (petrol/ $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 9.30 (1H, s), 8.12 (2H, dd,  $J$  8.0, 1.6), 8.06 (1H, s), 7.89 (1H, dd,  $J$  9.0, 5.2), 7.60 (1H, dd,  $J$  8.5, 2.3), 7.54–7.41 (4H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 160.8 (d,  $^1J$  249.3), 151.6 (d,  $^4J$  5.6), 151.0 (d,  $^6J$  3.2), 139.3, 133.7, 129.6 (d,  $^3J$  8.8), 128.8, 128.6, 128.2 (d,  $^3J$  8.0), 126.9, 121.2 (d,  $^2J$  25.6), 116.2 (d,  $^5J$  1.6), 110.6 (d,  $^2J$  20.7);  $^{19}\text{F}$  NMR

(377 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{F}}$ : –111.3. Data were consistent with those previously reported.<sup>47</sup>

**4-Methyl-3-phenylisoquinoline N-oxide 5a.** **Method A:** Ketone **24a** (25.6 mg, 0.0958 mmol) was subjected to General procedure L. Purification by flash column chromatography on alumina [EtOAc/MeOH 4:1] furnished isoquinoline *N*-oxide **5a** (22.2 mg, 0.0943 mmol, 99%) as a solid. **Method B:** A resealable reaction tube, containing a magnetic follower, was sealed with a rubber septum and flame dried under a flow of argon.  $\text{PdCl}_2(\text{Amphos})_2$  (22.8 mg, 0.0322 mmol) and  $\text{Cs}_2\text{CO}_3$  (525 mg, 1.61 mmol) were added to the tube. A solution of the aryl bromide **23a** (138 mg, 0.645 mmol) in anhydrous THF (3.2 mL) and propiophenone, **2a**, (174 mg, 1.29 mmol) were then added *via* syringe. The septum was replaced with a screw cap and the reaction was heated at 70 °C for 18 h. The reaction was cooled to room temperature, then a solution of HCl (12.9 mL, 1.0 M in 9:1 EtOH/ $\text{H}_2\text{O}$ ) was added, the tube resealed with a screw cap and then heated at 110 °C for 24 h. The reaction was cooled to room temperature and the solvent removed *in vacuo* using a toluene azeotrope. Purification by flash column chromatography on alumina [EtOAc/MeOH 19:1] furnished isoquinoline *N*-oxide **5a** (97.4 mg, 0.413 mmol, 64%) as a solid. **M.p.** 180–181 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 8.87 (1H, s), 8.02–7.89 (1H, m), 7.79–7.70 (1H, m), 7.69–7.58 (2H, m), 7.57–7.45 (3H, m), 7.44–7.36 (2H, m), 2.42 (3H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 146.1, 135.1, 132.9, 130.9, 130.0, 129.5, 128.9, 128.9, 128.6, 128.5, 128.5, 125.4, 124.0, 16.1. Data were consistent with those previously reported.<sup>10</sup>

**4-Methoxy-3-phenylisoquinoline N-oxide 5i.** **Method A:** Ketone **3i** (17.1 mg, 0.0573 mmol) (synthesis<sup>10</sup>) was subjected to General procedure D. Purification by flash column chromatography on alumina [EtOAc/MeOH 49:1 grading to 3:1] furnished isoquinoline *N*-oxide **5i** (13.8 mg, 0.0549 mmol, 96%) as a solid. **Method B:** Ketone **24b** (104 mg, 0.367 mmol) was subjected to General procedure L. Purification by flash column chromatography on alumina [EtOAc] furnished isoquinoline *N*-oxide **5i** (67.9 mg, 0.270 mmol, 74%) as a solid. **M.p.** 175–178 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 8.81 (1H, s), 8.10–8.01 (1H, m), 7.78–7.69 (1H, m), 7.67–7.58 (4H, m), 7.57–7.45 (3H, m), 3.55 (3H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 152.1, 140.3, 133.4, 130.6, 129.5, 129.2 (2 signals), 128.7, 128.5, 128.3, 125.8, 124.7, 122.0, 61.6; IR  $\nu_{\text{max}}$  (thin film)/ $\text{cm}^{-1}$  3062, 2941, 2852, 1733, 1659, 1624, 1588, 1490, 1465, 1445, 1427, 1365, 1312, 1223, 1179, 1098, 1045, 1025, 962, 909, 894, 862; HRMS (ESI-TOF)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd for  $\text{C}_{16}\text{H}_{14}\text{NO}_2$  252.1019; Found 252.1024.

**4-(4-Methoxyphenyl)-3-methylisoquinoline N-oxide 5p.** Ketone **3p** (48.7 mg, 0.156 mmol) was subjected to General procedure D. Purification by flash column chromatography on alumina [ $\text{CH}_2\text{Cl}_2$ /MeOH 99:1 grading to 39:1] furnished isoquinoline *N*-oxide **5p** (37.7 mg, 0.142 mmol, 91%) as prisms. **M.p.** 237–238 °C (MeOH/EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta_{\text{H}}$ : 8.88 (1H, s), 7.75 (1H, d,  $J$  7.6), 7.55 (1H, t,  $J$  7.5), 7.45 (1H, t,  $J$  7.6), 7.35 (1H, d,  $J$  8.6), 7.24 (2H, d,  $J$  8.6), 7.10 (2H, d,  $J$  8.6), 3.92 (3H, s), 2.40 (3H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta_{\text{C}}$ :





160.0, 145.1, 135.7, 135.4, 131.1, 129.7, 128.6, 128.6, 128.4, 128.3, 126.0, 124.8, 114.6, 55.8, 15.7; **IR**  $\nu_{\max}$  (thin film)/ $\text{cm}^{-1}$  2992, 2955, 2930, 2832, 1607, 1593, 1513, 1490, 1462, 1423, 1384, 1315, 1288, 1243, 1203, 1164, 1146, 1107, 1029, 1002, 970, 943, 894, 872, 850; **HRMS** (ESI-TOF)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd for  $\text{C}_{17}\text{H}_{16}\text{NO}_2$  266.1176; Found 266.1166.

**6,7-Dimethoxy-4-methyl-3-phenylisoquinoline-N-oxide 5r.** Ketone **3r** (57.8 mg, 0.205 mmol) (synthesis<sup>10</sup>) was subjected to General procedure D. Purification by flash column chromatography on alumina [EtOAc/MeOH 19:1 grading to 3:1] furnished isoquinoline-N-oxide **5r** (41.3 mg, 0.188 mmol, 92%) as prisms. **M.p.** 193–195 °C (petrol/ $\text{CH}_2\text{Cl}_2$ ); **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 8.72 (1H, s), 7.54–7.50 (2H, m), 7.48–7.44 (1H, m), 7.40–7.38 (2H, m), 7.11 (1H, s), 6.98 (1H, s), 4.04 (3H, s), 4.03 (3H, s), 2.35 (3H, s); **<sup>13</sup>C[<sup>1</sup>H] NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 151.8, 151.6, 144.5, 133.8, 133.3, 130.1, 129.1, 128.7, 128.6, 125.7, 124.6, 103.5, 102.8, 56.2, 56.1, 16.3; **IR**  $\nu_{\max}$  (thin film)/ $\text{cm}^{-1}$  2926, 1622, 1506, 1465, 1423, 1388, 1364, 1312, 1254, 1208, 1167, 1072, 1030, 990; **HRMS** (ESI-TOF)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{18}\text{H}_{17}\text{NNaO}_3$  318.1101; Found 318.1101.

**2,4-Dimethyl-3-phenylisoquinolin-2-ium chloride 6a.** A solution of  $\text{MeNH}_3\text{Cl}$  (2.47 mL, 1.0 M in 19:1 EtOH/ $\text{H}_2\text{O}$ ) was added to ketone **3a** (69.7 mg, 0.247 mmol) (synthesis<sup>10</sup>) in a resealable reaction tube containing a magnetic follower. The tube was sealed with a screw cap and heated at 90 °C for 18 h. The reaction was then cooled to room temperature and quenched by the addition of saturated aqueous  $\text{NaHCO}_3$  (25 mL). The aqueous layer was extracted with EtOAc (3  $\times$  25 mL) and the combined organics were dried over  $\text{Na}_2\text{SO}_4$ , filtered and the solvent removed *in vacuo*. Purification by flash column chromatography on alumina [EtOAc/MeOH 4:1 grading to MeOH] furnished isoquinolinium salt **6a** (63.6 mg, 0.237 mmol, 96%) as prisms. **M.p.** 280 °C (decomposed) (MeOH/EtOAc); **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 11.49 (1H, s), 8.81 (1H, d,  $J$  8.3), 8.18–8.12 (2H, m), 7.90 (1H, td,  $J$  7.3, 1.7), 7.63–7.61 (3H, m), 7.35 (2H, dd,  $J$  6.5, 3.0), 4.31 (3H, s), 2.46 (3H, s); **<sup>13</sup>C[<sup>1</sup>H] NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 151.9, 143.5, 137.4, 137.1, 133.1, 132.6, 131.4, 130.9, 130.7, 130.0, 129.1, 126.9, 123.9, 48.2, 16.1; **IR**  $\nu_{\max}$  (thin film)/ $\text{cm}^{-1}$  1633, 1597, 1500, 1481, 1445, 1376, 1343, 1269, 1189, 1077, 1007, 811; **HRMS** (ESI-TOF)  $m/z$ :  $\text{M}^+$  Calcd for  $\text{C}_{17}\text{H}_{16}\text{N}$  234.1278, Found 234.1281.

**2-(2-(1,3-Dioxolan-2-yl)phenyl)-2-phenylacetonitrile 8a.** Aryl bromide **1a** (82.2 mg, 0.359 mmol) was subjected to General procedure E with 2-phenylacetonitrile, **7a**. Purification by flash column chromatography [petrol/EtOAc 39:1 grading to 9:1] furnished nitrile **8a** (65.6 mg, 0.247 mmol, 69%) as an oil. **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.62 (1H, d,  $J$  7.7), 7.45 (1H, d,  $J$  8.2), 7.42–7.32 (7H, m), 5.95 (1H, s), 5.90 (1H, s), 4.16–4.03 (4H, m); **<sup>13</sup>C NMR[<sup>1</sup>H]** (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 135.8, 134.9, 134.7, 130.0, 129.7, 129.1, 128.3, 128.1, 127.9, 127.6, 120.0, 102.3, 65.2, 65.1, 37.8; **IR**  $\nu_{\max}$  (thin film)/ $\text{cm}^{-1}$  2892, 2244, 1601, 1494, 1452, 1406, 1217, 1112, 1075, 1043, 970, 943, 894; **HRMS** (ESI-TOF)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{17}\text{H}_{15}\text{NNaO}_2$  288.0995; Found 288.0992.

**2-(2-(1,3-Dioxolan-2-yl)-4,5-dimethoxyphenyl)-2-phenylacetonitrile 8b.** Aryl bromide **1e** (87.8 mg, 0.304 mmol) (synthesis<sup>10</sup>)

was subjected to General procedure E with 2-phenylacetonitrile, **7a**. Purification by flash column chromatography [petrol/ $\text{Et}_2\text{O}$  19:1 grading to 1:1] furnished nitrile **8b** (72.6 mg, 0.223 mmol, 73%) as prisms. **M.p.** 57–59 °C (petrol/ $\text{CH}_2\text{Cl}_2$ ); **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.37–7.36 (4H, m), 7.34–7.31 (1H, m), 7.11 (1H, s), 6.84 (1H, s), 5.82 (1H, s), 5.82 (1H, s), 4.17–4.02 (4H, m), 3.91 (3H, s), 3.81 (3H, s); **<sup>13</sup>C[<sup>1</sup>H] NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 149.9, 148.6, 135.9, 129.0, 128.0, 127.6, 127.4, 126.7, 120.0, 112.2, 110.1, 101.8, 65.1, 65.0, 56.0, 56.0, 37.4; **IR**  $\nu_{\max}$  (thin film)/ $\text{cm}^{-1}$  2960, 2893, 2243, 1609, 1518, 1494, 1453, 1402, 1351, 1290, 1268, 1201, 1180, 1114, 1066, 1030, 1003, 959, 940, 913, 868; **HRMS** (ESI-TOF)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{19}\text{H}_{19}\text{NNaO}_4$  348.1206; Found 348.1203.

**2-(2-(1,3-Dioxolan-2-yl)phenyl)-2-(thiophen-2-yl)acetonitrile 8c.** Aryl bromide **1a** (107 mg, 0.467 mmol) was subjected to General procedure E with 2-thiopheneacetonitrile, **7b**. Purification (twice) by flash column chromatography [petrol/EtOAc 9:1 then petrol/ $\text{CH}_2\text{Cl}_2$  1:1] furnished nitrile **8c** (48.1 mg, 0.177 mmol, 38%) as an oil. **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.59 (2H, m), 7.45 (1H, td,  $J$  7.5, 1.6), 7.39 (1H, td,  $J$  7.5, 1.3), 7.27 (1H, dd,  $J$  5.2, 1.2), 7.11 (1H, dt,  $J$  3.5, 1.1), 6.97 (1H, dd,  $J$  5.1, 3.6), 6.09 (1H, s), 5.90 (1H, s), 4.20–4.05 (4H, m); **<sup>13</sup>C[<sup>1</sup>H] NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 138.5, 134.5, 134.2, 130.0, 129.2, 128.6, 127.6, 126.9, 126.8, 126.4, 119.3, 102.2, 65.1, 65.0, 33.6; **IR**  $\nu_{\max}$  (thin film)/ $\text{cm}^{-1}$  2959, 2925, 2891, 2855, 1738, 1601, 1470, 1389, 1259, 1216, 1074, 1043, 1023, 969, 942, 910; **HRMS** (ESI-TOF)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{15}\text{H}_{13}\text{NNaO}_2\text{S}$  294.0559; Found 294.0554.

**2-(2-(1,3-Dioxolan-2-yl)phenyl)malononitrile 8d.** Malononitrile, **7c**, (26.4 mg, 0.400 mmol) and aryl bromide **1a** (110 mg, 0.480 mmol) were subjected to General procedure F for 4 h. Purification by flash column chromatography [petrol/ $\text{CH}_2\text{Cl}_2$  1:3] furnished nitrile **8d** (72.5 mg, 0.338 mmol, 85%) as an oil. **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.75 (1H, dd,  $J$  7.5, 1.3), 7.60–7.48 (3H, m), 5.89 (1H, s), 5.87 (1H, s), 4.21–4.14 (2H, m), 4.14–4.07 (2H, m); **<sup>13</sup>C[<sup>1</sup>H] NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 134.6, 130.7, 130.3, 129.3, 129.2, 125.5, 112.3, 102.8, 65.0, 24.9; **IR**  $\nu_{\max}$  (thin film)/ $\text{cm}^{-1}$  2899, 2257, 1459, 1405, 1289, 1228, 1114, 1075, 1043; **HRMS** (ESI-TOF)  $m/z$ :  $[\text{M} - \text{H}]^-$  Calcd for  $\text{C}_{12}\text{H}_9\text{N}_2\text{O}_2$  213.0670; Found 213.0662.

**2-(2-(1,3-Dioxolan-2-yl)phenyl)-2-(phenylsulfonyl)acetonitrile 8e.** (Phenylsulfonyl)acetonitrile, **7d**, (92.2 mg, 0.509 mmol) and aryl bromide **1a** (140 mg, 0.611 mmol) were subjected to General procedure F for 18 h. Purification by flash column chromatography [petrol/EtOAc 7:3] furnished nitrile **8e** (158 mg, 0.480 mmol, 94%) as a solid. **M.p.** 99–101 °C; **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.83 (2H, dd,  $J$  8.3, 1.2), 7.75 (1H, td,  $J$  7.5, 1.1), 7.68 (1H, d,  $J$  7.6), 7.60–7.56 (2H, m), 7.47 (1H, ddd,  $J$  7.9, 6.3, 2.5), 7.37–7.31 (2H, m), 6.38 (1H, s), 6.18 (1H, s), 4.10–3.94 (4H, m); **<sup>13</sup>C[<sup>1</sup>H] NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 138.1, 135.2, 135.0, 130.6, 130.4, 129.9, 129.2, 129.1, 127.0, 123.7, 114.1, 101.4, 65.0, 64.9, 58.9; **IR**  $\nu_{\max}$  (powder)/ $\text{cm}^{-1}$  2936, 2891, 1691, 1582, 1447, 1391, 1327, 1310, 1154, 1104, 1064, 1027; **HRMS** (ESI-TOF)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{17}\text{H}_{15}\text{NNaO}_4\text{S}$  352.0614; Found 352.0605.





**tert-Butyl 2-(2-(1,3-dioxolan-2-yl)phenyl)-2-cyanoacetate**  
**8f.** *tert*-Butyl cyanoacetate, **7e**, (74.4 mg, 0.527 mmol) and aryl bromide **1a** (145 mg, 0.633 mmol) were subjected to General procedure F for 4 h. Purification by flash column chromatography [petrol/EtOAc 17:3] furnished nitrile **8f** (140 mg, 0.484 mmol, 92%) as an oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.61 (1H, dd,  $J$  7.6, 1.3), 7.55 (1H, dd,  $J$  7.5, 1.5), 7.50–7.36 (2H, m), 5.93 (1H, s), 5.34 (1H, s), 4.17–4.00 (4H, m), 1.46 (9H, s);  $^{13}\text{C}$  [ $^1\text{H}$ ] NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 164.0, 135.0, 129.9, 129.7, 129.5, 128.9, 128.0, 116.6, 102.7, 84.2, 65.1, 64.9, 41.0, 27.7; IR  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  2980, 1739, 1456, 1395, 1370, 1259, 1145, 1109, 1076, 1045; HRMS (ESI-TOF)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{16}\text{H}_{19}\text{NNaO}_4$  312.1206; Found 312.1193.

**4-Phenylisoquinolin-3-amine 9a.** Nitrile **8a** (52.6 mg, 0.198 mmol) was subjected to General procedure C. Purification by flash column chromatography [petrol/EtOAc 19:1 grading to 2:1] furnished isoquinoline **9a** (32.1 mg, 0.146 mmol, 73%) as prisms. **M.p.** 145–147 °C ( $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 8.91 (1H, s), 7.83 (1H, d,  $J$  8.1), 7.56 (2H, t,  $J$  7.3), 7.47 (1H, t,  $J$  7.5), 7.42–7.40 (3H, m), 7.29 (1H, d,  $J$  9.7), 7.25 (1H, d,  $J$  7.1), 4.42 (2H, br. s);  $^{13}\text{C}$  NMR [ $^1\text{H}$ ] (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 151.7, 151.2, 137.3, 135.7, 130.6, 130.5, 129.4, 127.9, 127.9, 123.8, 123.0, 122.7, 111.6. Data were consistent with those previously reported.<sup>29</sup>

**6,7-Dimethoxy-4-phenylisoquinolin-3-amine 9b.** Nitrile **8b** (40.6 mg, 0.125 mmol) was subjected to General procedure C. Purification by flash column chromatography [petrol/EtOAc 4:1 grading to EtOAc/MeOH 39:1] furnished isoquinoline **9b** (29.5 mg, 0.105 mmol, 84%) as an oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta_{\text{H}}$ : 8.59 (1H, s), 7.58 (2H, t,  $J$  7.5), 7.48 (1H, t,  $J$  7.1), 7.37 (2H, d,  $J$  7.3), 7.23 (1H, s), 6.49 (1H, s), 3.91 (3H, s), 3.65 (3H, s);  $^{13}\text{C}$  [ $^1\text{H}$ ] NMR (100 MHz,  $\text{CD}_3\text{OD}$ )  $\delta_{\text{C}}$ : 154.3, 151.2, 148.0, 147.5, 136.2, 134.9, 130.6, 129.6, 128.1, 119.9, 112.3, 105.9, 101.2, 55.3, 54.9; IR  $\nu_{\text{max}}$  (thin film)/ $\text{cm}^{-1}$  3476, 3375, 3176, 3001, 2934, 2830, 2360, 1627, 1598, 1579, 1495, 1452, 1425, 1401, 1354, 1246, 1197, 1160, 1092, 1031, 1011, 927, 844; HRMS (ESI-TOF)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd for  $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_2$  281.1285; Found 281.1292.

**4-(Thiophen-2-yl)isoquinolin-3-amine 9c.** Nitrile **8c** (51.6 mg, 0.190 mmol) was subjected to General procedure C. Purification by flash column chromatography [EtOAc/MeOH 99:1] furnished isoquinoline **9c** (43.1 mg, 0.143 mmol, 75%) as an oil.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 8.82 (1H, s), 7.72 (1H, dd,  $J$  8.1, 0.7), 7.45 (1H, dt,  $J$  5.2, 0.9), 7.38 (2H, d,  $J$  3.6), 7.22–7.14 (2H, m), 7.03 (1H, dd,  $J$  3.4, 0.9), 4.55 (2H, br. s);  $^{13}\text{C}$  [ $^1\text{H}$ ] NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 153.2, 152.3, 138.5, 136.0, 130.9, 128.8, 127.9, 127.8, 127.2, 123.6, 122.9, 122.9, 103.4; IR  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3301, 3170, 1620, 1578, 1492, 1455, 1426, 1373, 1346, 1264, 1217, 1147, 956, 925, 853, 816; HRMS (ESI-TOF)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd for  $\text{C}_{13}\text{H}_{11}\text{N}_2\text{S}$  227.0638; Found 227.0633.

**3-Hydroxyisoquinoline-4-carbonitrile 9d.** **Method A:** Nitrile **8d** (84.5 mg, 0.394 mmol) was subjected to General procedure B, extracting with 4:1 EtOAc/*n*BuOH (5 × 10 mL). Purification by flash column chromatography [C18 reversed phase  $\text{SiO}_2$ ,  $\text{H}_2\text{O}$ ] furnished isoquinoline **9d** (48.3 mg, 0.284 mmol, 72%) as a bright yellow solid. **Method B:** *para*-Toluenesulfonic acid

monohydrate (9.5 mg, 0.050 mmol) was added to a solution of nitrile **8d** (97.1 mg, 0.453 mmol) in 1:1 THF/ $\text{H}_2\text{O}$  (2.5 mL) in a resealable reaction tube containing a magnetic follower. The tube was sealed with a screw cap and heated at 50 °C for 18 h. The reaction was then cooled to room temperature and quenched by the addition of saturated aqueous  $\text{NaHCO}_3$  (25 mL). The aqueous layer was extracted with 4:1 EtOAc/*n*BuOH (5 × 10 mL) and the combined organics were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography [C18 reversed phase  $\text{SiO}_2$ ,  $\text{H}_2\text{O}$ ] furnished isoquinoline **9d** (65.4 mg, 0.384 mmol, 85%) as a bright yellow solid. **M.p.** >320 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta_{\text{H}}$ : 8.83 (1H, s), 7.75 (1H, d,  $J$  8.1), 7.59–7.52 (2H, m), 7.12 (1H, ddd,  $J$  8.1, 6.4, 1.5);  $^{13}\text{C}$  [ $^1\text{H}$ ] NMR (100 MHz,  $\text{CD}_3\text{OD}$ )  $\delta_{\text{C}}$ : 173.0, 158.1, 141.9, 133.0, 130.0, 122.4, 121.8, 121.7, 120.7, 83.2; IR  $\nu_{\text{max}}$  (powder)/ $\text{cm}^{-1}$  3263, 2581, 2214, 1622, 1580, 1555, 1467, 1438, 1221, 1179, 1047, 1014; HRMS (ESI-TOF)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{10}\text{H}_6\text{N}_2\text{NaO}$  193.0372; Found 193.0369.

**4-(Phenylsulfonyl)isoquinolin-3-amine 9e.** A solution of  $\text{NH}_4\text{Cl}$  (1.63 mL, 1.0 M in 3:1 EtOH/ $\text{H}_2\text{O}$ ) was added to nitrile **8e** (53.8 mg, 0.163 mmol) in a resealable reaction tube containing a magnetic follower. The tube was sealed with a screw cap and heated at 90 °C for 4 h. A solution of  $\text{NH}_4\text{HCO}_3$  (3.26 mL, 2.0 M in  $\text{H}_2\text{O}$ ) was then added. The tube was resealed and heated for a further 1 h at 65 °C. The reaction was then cooled to room temperature and quenched by the addition of  $\text{H}_2\text{O}$  (25 mL). The aqueous layer was extracted with 4:1 EtOAc/*n*BuOH (3 × 10 mL) and the combined organics were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography [petrol/EtOAc 4:1] furnished isoquinoline **9e** (22.2 mg, 0.0781 mmol, 48%) as a solid. **M.p.** 191–193 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 8.91 (1H, s), 8.44 (1H, dd,  $J$  8.8, 0.7), 8.01–7.98 (2H, m), 7.74 (1H, dd,  $J$  8.1, 0.8), 7.62–7.51 (2H, m), 7.49–7.45 (2H, m), 7.28 (1H, dd,  $J$  7.0, 0.9), 6.66 (2H, br. s);  $^{13}\text{C}$  [ $^1\text{H}$ ] NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 159.1, 155.3, 143.0, 134.6, 133.1, 133.0, 129.2, 129.0, 126.0, 123.6, 123.5, 122.0, 103.1; IR  $\nu_{\text{max}}$  (powder)/ $\text{cm}^{-1}$  3441, 3293, 3170, 1633, 1557, 1478, 1437, 1291, 1136, 1083; HRMS (ESI-TOF)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{15}\text{H}_{12}\text{N}_2\text{NaO}_2\text{S}$  307.0512; Found 307.0503.

**Isoquinolin-3-amine 9f.** **Method A:** Nitrile **8f** (70.2 mg, 0.242 mmol) was subjected to General procedure C. Purification by flash column chromatography [petrol/EtOAc 4:1] furnished isoquinoline **9f** (25.8 mg, 0.179 mmol, 74%) as an oil. **Method B:** A solution of nitrile **8f** (53.6 mg, 0.185 mmol) in 3:2 EtOH/ $\text{H}_2\text{O}$  (1.85 mL) was added to a resealable reaction tube containing a magnetic follower. The tube was sealed with a screw cap and heated at 90 °C for 18 h. The reaction was cooled to room temperature,  $\text{NH}_4\text{Cl}$  (99.0 mg, 1.85 mmol) was added and then the reaction was reheated at 90 °C for 3 h. The reaction was cooled to room temperature and basified by the addition of 2 M aqueous  $\text{NH}_4\text{HCO}_3$  (1.85 mL). The reaction mixture was heated at 90 °C for 3 h and then cooled to room temperature. The aqueous layer was extracted with 4:1 EtOAc/*n*BuOH (3 × 10 mL) and the



combined organics were dried over  $\text{Na}_2\text{SO}_4$ , filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [petrol/EtOAc 4 : 1] furnished isoquinoline **9f** as a yellow solid (22.8 mg, 0.158 mmol, 86%). **M.p.** 175–180 °C  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 8.87 (1H, s), 7.78 (1H, dd,  $J$  8.2, 0.5), 7.58–7.46 (2H, m), 7.28–7.21 (1H, m), 6.74 (1H, s), 4.19 (2H, br. s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 154.5, 151.6, 138.9, 130.4, 127.8, 124.6, 123.8, 123.0, 99.4. Data were consistent with those previously reported.<sup>50</sup>

**tert-Butyl 2-(2-(1,3-dioxolan-2-yl)phenyl)acetate 11.** A resealable reaction tube, containing a magnetic follower, was sealed with a rubber septum and flame dried under a flow of argon.  $t\text{Bu}_3\text{P}\cdot\text{HBF}_4$  (10.9 mg, 0.0377 mmol) and  $\text{Pd}_2(\text{dba})_3$  (17.3 mg, 0.0189 mmol) were added to the tube. Aryl bromide **1a** (83.6 mg, 0.377 mmol) was dissolved in dry toluene (0.9 mL) and the resulting solution was added *via* syringe to the tube. *tert*-Butyl acetate, **10**, (87.6 mg, 0.754 mmol) was then added to the tube. The reaction mixture was cooled to –78 °C and degassed with argon for 15 min. A degassed solution of  $\text{LiHDSM}$  (0.942 mL, 1 M in toluene) was then added *via* syringe. The reaction was degassed for a further 15 min, the rubber septum replaced with a screw cap and the reaction stirred at room temperature for 16 h. The reaction was then quenched by the addition of saturated aqueous  $\text{NaHCO}_3$  (25 mL). The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 × 25 mL) and the combined organics were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography [petrol/EtOAc 50 : 1 grading to 5 : 1] furnished ester **11** (67.8 mg, 0.256 mmol, 68%) as a pale yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.46 (1H, dd,  $J$  7.5, 1.7), 7.28–7.15 (3H, m), 5.89 (1H, s), 4.10–4.01 (2H, m), 4.00–3.93 (2H, m), 3.63 (2H, s), 1.37 (9H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 170.9, 135.6, 133.6, 131.4, 129.2, 127.0, 126.8, 102.6, 80.7, 65.1, 39.6, 28.0; IR  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  2360, 1731, 1455, 1393, 1368, 1334, 1147; HRMS (ESI-TOF)  $m/z$ :  $[\text{M} + \text{Na}]^+$  Calcd for  $\text{C}_{15}\text{H}_{20}\text{NaO}_4$  287.1254; Found 287.1260.

**Isoquinolin-3-ol 12.** *para*-Toluenesulfonic acid monohydrate (3.7 mg, 0.0197 mmol) was added to a solution of ester **11** (104 mg, 0.393 mmol) in 1 : 1 THF/ $\text{H}_2\text{O}$  (1.6 mL) in a resealable reaction tube containing a magnetic follower. The tube was sealed with a screw cap and stirred at room temperature for 18 h. Aqueous  $\text{NH}_4\text{OH}$  (28% w/w, 1.6 mL) was added and the reaction was heated at 60 °C for 24 h. The reaction was then cooled to room temperature, diluted with brine (25 mL) and extracted with EtOAc (2 × 25 mL). The aqueous layer was then neutralised to pH 7 by the addition of 2 M HCl and again extracted with EtOAc (2 × 25 mL). The combined organics were then washed with 2 M HCl (3 × 25 mL) and the organic phase discarded. The aqueous phase was then neutralised to pH 7 by the addition of 2 M NaOH and then extracted with EtOAc (3 × 25 mL). The combined organics were then dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography [EtOAc/MeOH 100 : 1 grading to 3 : 1] furnished isoquinoline **12** (40.2 mg, 0.275 mmol, 70%) as bright yellow prisms.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta_{\text{H}}$ : 8.66 (1H, s), 7.81 (1H, dd,  $J$  8.6, 1.0), 7.59–7.49 (2H, m), 7.23 (1H, dd,

$J$  6.4, 1.2), 6.87 (1H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ )  $\delta_{\text{C}}$ : 161.0, 144.1, 142.2, 131.7, 127.8, 124.7, 123.3, 121.3, 104.9. Data were consistent with a commercially available sample from Sigma Aldrich.

**3-Phenyl-4-(*o*-tolyl)isoquinoline 18c.** A microwave vial, containing a magnetic follower, was sealed with a rubber septum and flame dried under vacuum. (DPPF) $\text{PdCl}_2$  (19.2 mg, 0.0262 mmol) and  $\text{NaOtBu}$  (249 mg, 1.31 mmol) were added to the vial. The septum was replaced with a microwave cap and the vial was evacuated and backfilled with argon before a solution of aryl bromide **1a** (120 mg, 0.524 mmol) in anhydrous THF (2.1 mL) and acetophenone, **2b**, (75.6 mg, 0.629 mmol) were added *via* syringe to the vial. The reaction was heated at 70 °C for 6 h. The reaction was then cooled to room temperature and 2-bromotoluene, **16c**, (225 mg, 1.31 mmol) was added *via* syringe and the reaction was heated at 100 °C for 18 h. The reaction was cooled to room temperature, acidified to pH 5 by the addition of 1 M HCl, then a 1 M solution of  $\text{NH}_4\text{Cl}$  in 3 : 1 EtOH/ $\text{H}_2\text{O}$  (5.24 mL) was added and the reaction was heated at 90 °C for 24 h. The reaction was cooled to room temperature and quenched by the addition of saturated aqueous  $\text{NaHCO}_3$  (25 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL) and the combined organics were then dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent removed *in vacuo*. Purification by flash column chromatography [ $\text{CH}_2\text{Cl}_2$ ] furnished isoquinoline **18c** (100 mg, 0.339 mmol, 65%) as a solid. **M.p.** 125–130 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 9.42 (1H, d,  $J$  0.7), 8.10–8.04 (1H, m), 7.64–7.58 (2H, m), 7.47–7.39 (3H, m), 7.33–7.28 (1H, m), 7.26–7.16 (6H, m), 1.90 (3H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 151.8, 150.3, 140.6, 137.0, 136.5, 135.8, 131.3, 130.5, 130.1, 129.7, 129.8, 129.7, 127.8, 127.6, 127.2, 127.2, 126.8, 125.7, 125.5, 19.9; IR  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3058, 1617, 1558, 1498, 1449, 1370, 1247, 1029; HRMS (ESI-TOF)  $m/z$ :  $[\text{M} + \text{H}]^+$  Calcd for  $\text{C}_{22}\text{H}_{18}\text{N}$  296.1434; Found 296.1434.

**(*E*)-Benzaldehyde *O*-methyl oxime 22a.** Methoxylamine hydrochloride (1.34 g, 16.0 mmol) was added to a solution of benzaldehyde, **21a**, (1.00 g, 9.43 mmol) and sodium acetate trihydrate (1.92 g, 14.1 mmol) in 3 : 1  $\text{H}_2\text{O}$ /THF (18.9 mL). The reaction was stirred at room temperature for 4 h and then diluted with  $\text{Et}_2\text{O}$  (50 mL), washed with brine (100 mL), then dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent removed *in vacuo* to furnish (*E*)-*O*-methyl oxime **22a** (1.23 g, 9.41 mmol, 100%) as a colourless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 8.10 (1H, s), 7.67–7.55 (2H, m), 7.43–7.35 (3H, m), 4.01 (3H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 148.6, 132.2, 129.8, 128.7, 127.0, 62.0. Data were consistent with those previously reported.<sup>51</sup>

**(*E*)-Acetophenone *O*-methyl oxime 22b.** Acetophenone, **2b**, (1.55 g, 12.9 mmol) was subjected to General procedure G, stirring at room temperature for 3 h, furnishing (*E*)-*O*-methyl oxime **22b** (1.56 g, 10.4 mmol, 81%) as a colourless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.72–7.62 (2H, m), 7.47–7.33 (3H, m), 4.03 (3H, s), 2.26 (3H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 154.6, 136.7, 129.0, 128.4, 126.0, 61.9, 12.6. Data were consistent with those previously reported.<sup>52</sup>



**Propiophenone *O*-methyl oxime 22c.** Propiophenone, **2a**, (1.29 g, 9.58 mmol) was subjected to General procedure G, stirring at room temperature for 4 h, furnishing an 11 : 1 mixture of (*E*)- and (*Z*)-*O*-methyl oxime **22c** (1.42 g, 8.70 mmol, 91%) as a colourless oil. (*E*)-**22c**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.72–7.62 (2H, m), 7.46–7.33 (3H, m), 4.01 (3H, s), 2.78 (2H, q, *J* 7.6), 1.16 (3H, t, *J* 7.6);  $^{13}\text{C}$ [ $^1\text{H}$ ] NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 159.8, 135.6, 129.0, 128.5, 126.3, 61.9, 20.1, 11.2. (*Z*)-**22c**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.74–7.61 (2H, m), 7.46–7.32 (3H, m), 3.86 (3H, s), 2.58 (2H, q, *J* 7.6), 1.09 (3H, t, *J* 7.5);  $^{13}\text{C}$ [ $^1\text{H}$ ] NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 159.0, 133.9, 128.6, 128.1, 127.8, 61.6, 28.9, 11.6. Data were consistent with those previously reported.<sup>53</sup>

**Benzophenone *O*-methyl oxime 22d.** Benzophenone (1.30 g, 7.14 mmol) was subjected to General procedure G, heating at 50 °C for 24 h, furnishing *O*-methyl oxime **22d** (1.43 g, 6.77 mmol, 95%) as a colourless solid. **M.p.** 58–60 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.58–7.31 (10H, m), 4.02 (3H, s);  $^{13}\text{C}$ [ $^1\text{H}$ ] NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 156.7, 136.4, 133.3, 129.3, 129.2, 128.9, 128.3, 128.1, 127.9, 62.4; IR  $\nu_{\text{max}}$  (thin film)/ $\text{cm}^{-1}$  2935, 1494, 1444, 1326, 1164, 1051, 1030; **HRMS** (ESI-TOF) *m/z*: [ $\text{M} + \text{H}$ ] $^+$  Calcd for  $\text{C}_{14}\text{H}_{14}\text{NO}$  212.1070; Found 212.1079.

**(*E*)-2-Bromobenzaldehyde *O*-methyl oxime 23a.** Oxime **22a** (55.0 mg, 0.407 mmol) was subjected to a modified General procedure H, with 90 mol% of *N*-bromosuccinimide, for 18 h. Purification by flash column chromatography [petrol/ $\text{CH}_2\text{Cl}_2$  4 : 1] furnished (*E*)-oxime **23a** (44.4 mg, 0.208 mmol, 51%) as a colourless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 8.46 (1H, s), 7.88 (1H, d, *J* 7.8), 7.57 (1H, d, *J* 8.1), 7.35–7.18 (2H, m), 4.01 (3H, s);  $^{13}\text{C}$ [ $^1\text{H}$ ] NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 147.9, 133.1, 131.5, 131.0, 127.5, 127.5, 123.8, 62.3. Data were consistent with those previously reported.<sup>51</sup>

**(*E*)-1-(2-Bromophenyl)ethanone *O*-methyl oxime 23b.** Oxime **22b** (800 mg, 5.36 mmol) was subjected to General procedure H for 18 h. Purification by flash column chromatography [petrol/ $\text{CH}_2\text{Cl}_2$  4 : 1] furnished (*E*)-oxime **23b** (669 mg, 2.93 mmol, 55%) as a colourless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.64–7.53 (1H, m), 7.37–7.17 (3H, m), 4.00 (3H, s), 2.22 (3H, s);  $^{13}\text{C}$ [ $^1\text{H}$ ] NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 157.0, 138.9, 133.1, 130.3, 130.0, 127.4, 121.8, 61.9, 16.5; IR  $\nu_{\text{max}}$  (thin film)/ $\text{cm}^{-1}$  2937, 1471, 1427, 1100, 1048; **HRMS** (ESI-TOF) *m/z*: [ $\text{M} + \text{H}$ ] $^+$  Calcd for  $\text{C}_9\text{H}_{11}^{79}\text{BrNO}$  228.0019; Found 228.0023.

**1-(2-Bromophenyl)propan-1-one *O*-methyl oxime 23c.** Oxime **22c** (497 mg, 3.05 mmol) was subjected to General procedure H for 18 h. Purification by flash column chromatography [petrol/ $\text{CH}_2\text{Cl}_2$  4 : 1] furnished a 1.2 : 1 mixture of stereoisomers of oxime **23c** (517 mg, 2.14 mmol, 70%) as a colourless oil. **Major isomer**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.65–7.54 (1H, m), 7.39–7.30 (1H, m), 7.29–7.16 (2H, m), 3.97 (3H, s), 2.75 (2H, q, *J* 7.7), 1.00 (3H, t, *J* 7.6);  $^{13}\text{C}$ [ $^1\text{H}$ ] NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 161.9, 137.5, 132.9, 130.8, 129.9, 127.3, 122.3, 61.9, 22.7, 10.0. **Minor isomer**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.64–7.54 (1H, m), 7.39–7.29 (1H, m), 7.29–7.17 (1H, m), 7.07 (1H, dd, *J* 7.6, 1.3), 3.83 (3H, s), 2.54 (2H, q, *J* 7.4), 1.12 (3H, t, *J* 7.5);  $^{13}\text{C}$ [ $^1\text{H}$ ] NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 158.4, 136.9, 132.6, 129.5, 128.5, 127.1, 120.5, 61.8, 28.4, 10.8; IR  $\nu_{\text{max}}$  (thin film)/

$\text{cm}^{-1}$  2972, 2937, 1463, 1432, 1048, 1026; **HRMS** (ESI-TOF) *m/z*: [ $\text{M} + \text{H}$ ] $^+$  Calcd for  $\text{C}_{10}\text{H}_{13}^{79}\text{BrNO}$  242.0175; Found 242.0176.

**(*E*)-(2-Bromophenyl)(phenyl)methanone *O*-methyl oxime 23d.** Oxime **22d** (1.00 g, 4.74 mmol) was subjected to General procedure H for 2 h. Purification by flash column chromatography [petrol/ $\text{CH}_2\text{Cl}_2$  4 : 1] furnished (*E*)-oxime **23d** (1.24 g, 4.27 mmol, 90%) as an oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 7.65–7.53 (3H, m), 7.49 (1H, dd, *J* 7.6, 1.8), 7.44–7.34 (4H, m), 7.32–7.23 (1H, m), 4.07 (3H, s);  $^{13}\text{C}$ [ $^1\text{H}$ ] NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 155.8, 138.0, 133.4, 132.4, 131.9, 130.3, 130.1, 129.5, 128.0, 127.4, 123.5, 62.6; IR  $\nu_{\text{max}}$  (thin film)/ $\text{cm}^{-1}$  2936, 1468, 1445, 1328, 1059, 1036; **HRMS** (ESI-TOF) *m/z*: [ $\text{M} + \text{H}$ ] $^+$  Calcd for  $\text{C}_{14}\text{H}_{13}^{79}\text{BrNO}$  290.0175; Found 290.0176.

**(*E*)-2-(1-Oxo-1-phenylpropan-2-yl)benzaldehyde *O*-methyl oxime 24a.** Oxime **23a** (200 mg, 0.934 mmol) was subjected to General procedure I with propiophenone, **2a**. Purification by flash column chromatography [petrol/EtOAc 99 : 1] furnished (*E*)-ketone **24a** (227 mg, 0.850 mmol, 91%) as an oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 8.45 (1H, s), 7.93–7.86 (2H, m), 7.62–7.55 (1H, m), 7.50–7.43 (1H, m), 7.40–7.32 (2H, m), 7.30–7.20 (2H, m), 7.18–7.11 (1H, m), 5.34 (1H, q, *J* 6.8), 3.96 (3H, s), 1.52 (3H, d, *J* 6.8);  $^{13}\text{C}$ [ $^1\text{H}$ ] NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 200.5, 148.1, 140.3, 136.3, 132.8, 130.2, 129.7, 129.1, 128.7, 128.5, 128.1, 127.1, 62.1, 44.2, 18.6; IR  $\nu_{\text{max}}$  (thin film)/ $\text{cm}^{-1}$  2953, 1684, 1597, 1448, 1222, 1048; **HRMS** (ESI-TOF) *m/z*: [ $\text{M} + \text{Na}$ ] $^+$  Calcd for  $\text{C}_{17}\text{H}_{17}\text{NNaO}_2$  290.1151; Found 290.1151.

**(*E*)-2-(1-Methoxy-2-oxo-2-phenylethyl)benzaldehyde *O*-methyl oxime 24b.** Oxime **23a** (105 mg, 0.490 mmol) was subjected to General procedure I with 2-methoxyacetophenone, **2g**. Purification by flash column chromatography [petrol/EtOAc 49 : 1 petrol] furnished (*E*)-ketone **24b** (118 mg, 0.417 mmol, 85%) as an oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 8.36 (1H, s), 7.99 (2H, d, *J* 7.3), 7.59 (1H, d, *J* 7.1), 7.55–7.48 (2H, m), 7.47–7.31 (4H, m), 6.23 (1H, s), 3.76 (3H, s), 3.51 (3H, s);  $^{13}\text{C}$ [ $^1\text{H}$ ] NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 195.8, 148.3, 135.6, 134.8, 133.2, 130.7, 129.8, 129.8, 128.8, 128.6, 128.5, 82.5, 61.9, 58.0; IR  $\nu_{\text{max}}$  (thin film)/ $\text{cm}^{-1}$  2936, 1693, 1597, 1448, 1210, 1088, 1043, 1003; **HRMS** (ESI-TOF) *m/z*: [ $\text{M} + \text{Na}$ ] $^+$  Calcd for  $\text{C}_{17}\text{H}_{17}\text{NNaO}_3$  306.1101; Found 306.1097.

**(*E*)-2-(2-(1-(Methoxyimino)ethyl)phenyl)-1-phenylpropan-1-one 24c.** Oxime **23b** (194 mg, 0.851 mmol) was subjected to General procedure I with propiophenone, **2a**. Purification by flash column chromatography [petrol/EtOAc 99 : 1] furnished (*E*)-ketone **24c** (69.5 mg, 0.247 mmol, 29%) as an oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 8.06–7.98 (2H, m), 7.51–7.43 (1H, m), 7.42–7.34 (2H, m), 7.32–7.18 (4H, m), 5.17 (1H, q, *J* 6.8), 3.94 (3H, s), 2.27 (3H, s), 1.53 (3H, d, *J* 6.8);  $^{13}\text{C}$ [ $^1\text{H}$ ] NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 200.9, 155.8, 139.2, 136.3, 132.7, 129.0, 128.9, 128.8, 128.4, 127.9, 126.9, 61.8, 44.1, 19.4, 16.6; IR  $\nu_{\text{max}}$  (thin film)/ $\text{cm}^{-1}$  2935, 1684, 1448, 1220, 1048; **HRMS** (ESI-TOF) *m/z*: [ $\text{M} + \text{Na}$ ] $^+$  Calcd for  $\text{C}_{18}\text{H}_{19}\text{NNaO}_2$  304.1308; Found 304.1300.

**(*E*)-2-(2-(1-(Methoxyimino)propyl)phenyl)-1-phenylpropan-1-one (*E*)-24d.** Oxime **23c** (142 mg, 0.587 mmol) was subjected to General procedure I with propiophenone, **2a**. Purification by flash column chromatography [petrol/EtOAc 99 : 1] furnished (*E*)-ketone (*E*)-**24d** (54.9 mg, 0.186 mmol, 32%) as an oil.





**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 8.11–8.00 (2H, m), 7.51–7.43 (1H, m), 7.42–7.33 (2H, m), 7.31–7.18 (4H, m) 5.13 (1H, q, *J* 6.8), 3.91 (3H, s), 2.87–2.66 (2H, m), 1.52 (3H, d, *J* 7.1), 1.13 (3H, t, *J* 7.6); **<sup>13</sup>C[<sup>1</sup>H] NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 201.0, 160.8, 139.6, 136.4, 135.1, 132.7, 129.0, 128.9, 128.9, 128.3, 128.0, 126.7, 61.7, 44.0, 23.4, 19.6, 10.6; **IR**  $\nu_{\text{max}}$  (thin film)/cm<sup>−1</sup> 2965, 1683, 1449, 1260, 1221, 1046; **HRMS** (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>21</sub>NNaO<sub>2</sub> 318.1465; Found 318.1460.

**(Z)-2-(2-(1-(Methoxyimino)propyl)phenyl)-1-phenylpropan-1-one (Z)-24d**. Oxime 23c (142 mg, 0.587 mmol) was subjected to General procedure I with propiophenone, 2a, (155 mg, 1.17 mmol). Purification by flash column chromatography [petrol/EtOAc 97:3] furnished (Z)-ketone (Z)-24d (34.7 mg, 0.115 mmol, 20%) as an oil. **Major rotamer**: **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 8.01 (2H, d, *J* 7.6), 7.59–7.23 (6H, m), 7.11–6.96 (1H, m), 4.74–4.59 (1H, m), 3.44 (3H, s), 2.70–2.51 (2H, m), 1.51 (3H, d, *J* 7.1), 1.18 (3H, t, *J* 7.5); **<sup>13</sup>C[<sup>1</sup>H] NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 200.5, 159.4, 138.0, 136.3, 134.6, 132.7, 128.8, 128.6, 128.5, 126.9, 126.7, 61.2, 43.7, 29.8, 20.1, 11.4. **Minor rotamer**: **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 7.90 (2H, d, *J* 7.6), 7.58–7.23 (6H, m), 7.11–6.96 (1H, m), 4.75–4.57 (1H, m), 3.90 (3H, s), 2.46–2.21 (2H, m), 1.57 (3H, d, *J* 6.8), 1.01 (3H, t, *J* 7.5); **<sup>13</sup>C[<sup>1</sup>H] NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 201.8, 159.2, 137.2, 137.1, 135.1, 132.9, 128.7, 128.5 (2 carbons), 128.4, 128.4, 128.2, 126.3, 61.6, 43.7, 29.7, 19.2, 10.6; **IR**  $\nu_{\text{max}}$  (thin film)/cm<sup>−1</sup> 2935, 1684, 1449, 1252, 1221, 1057, 1030; **HRMS** (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>21</sub>NNaO<sub>2</sub> 318.1465; Found 318.1458.

**(E)-2-(2-(Methoxyimino)(phenyl)methyl)phenyl)-1-phenylpropan-1-one 24e**. Oxime 23d (100 mg, 0.345 mmol) was subjected to General procedure I with propiophenone, 2a. Purification by flash column chromatography [petrol/EtOAc 97:3] furnished (E)-ketone 24e (110 mg, 0.320 mmol, 93%) as a solid. **M.p.** 84–86 °C; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 7.88 (2H, d, *J* 7.3), 7.65–7.55 (2H, m), 7.49–7.37 (4H, m), 7.36–7.20 (6H, m), 5.02 (1H, q, *J* 6.7), 4.04 (3H, s), 1.35 (3H, d, *J* 6.8); **<sup>13</sup>C[<sup>1</sup>H] NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 200.8, 155.8, 140.4, 136.3, 135.7, 133.4, 132.7, 131.1, 130.1, 129.7, 129.5, 128.8, 128.4, 128.2, 128.0, 126.8, 62.5, 44.3, 18.9; **IR**  $\nu_{\text{max}}$  (powder)/cm<sup>−1</sup> 2934, 1683, 1447, 1220, 1042; **HRMS** (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> Calcd for C<sub>23</sub>H<sub>21</sub>NNaO<sub>2</sub> 366.1465; Found 366.1453.

**1-Ethyl-4-methyl-3-phenylisoquinoline 25a. Method A**: Ketone (E)-24d (49.9 mg, 0.169 mmol) was subjected to General procedure J. Purification by flash column chromatography [petrol/EtOAc 49:1] furnished isoquinoline 25a (37.2 mg, 0.150 mmol, 89%) as a solid. **Method B**: Ketone (Z)-24d (45.0 mg, 0.152 mmol) was subjected to General procedure J. Purification by flash column chromatography [petrol/EtOAc 49:1] furnished isoquinoline 25a (30.8 mg, 0.125 mmol, 82%) as a solid. **Method C**: Oxime 23c (73.1 mg, 0.302 mmol) was subjected to General procedure K with propiophenone, 2a. Purification by flash column chromatography [petrol/EtOAc 49:1] furnished isoquinoline 25a (34.7 mg, 0.140 mmol, 46%) as a solid. **M.p.** 58–61 °C; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 8.23 (1H, d, *J* 8.3), 8.08 (1H, d, *J* 8.6), 7.75 (1H, td, *J* 7.6, 1.1), 7.67–7.57 (3H, m), 7.50 (2H, t, *J* 7.5), 7.45–7.36 (1H, m), 3.39

(2H, q, *J* 7.6), 2.63 (3H, s), 1.48 (3H, t, *J* 7.6); **<sup>13</sup>C[<sup>1</sup>H] NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 160.7, 150.6, 141.7, 136.6, 130.0, 129.7, 128.1, 127.4, 126.2, 125.8, 125.3, 124.3, 122.1, 28.7, 15.5, 14.3. Data were consistent with those previously reported.<sup>54</sup>

**4-Methyl-1,3-diphenylisoquinoline 25b. Method A**: Ketone 24e (50.3 mg, 0.146 mmol) was subjected to General procedure J. Purification by flash column chromatography [petrol/EtOAc 99:1] furnished isoquinoline 25b (36.4 mg, 0.123 mmol, 84%) as a solid. **Method B**: Oxime 23d (105 mg, 0.362 mmol) was subjected to General procedure K with propiophenone, 2a, (95.4 mg, 0.724 mmol). Purification by flash column chromatography [petrol/EtOAc 99:1] furnished isoquinoline 25b (74.0 mg, 0.251 mmol, 69%) as a solid. **M.p.** 78–83 °C; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$ : 8.15 (2H, dd, *J* 8.5, 3.9), 7.84–7.71 (3H, m), 7.67 (2H, d, *J* 7.3), 7.62–7.38 (7H, m), 2.73 (3H, s); **<sup>13</sup>C[<sup>1</sup>H] NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$ : 158.3, 151.0, 141.4, 139.8, 137.1, 130.2, 130.1, 130.0, 128.3, 128.2, 128.1, 128.1, 127.5, 126.4, 125.4, 123.9, 123.2, 15.7. Data were consistent with those previously reported.<sup>38c</sup>

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