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Exploration of a Nitromethane-Carbonylation Strategy during Route Design of an Atropisomeric KRAS^{G12C} Inhibitor

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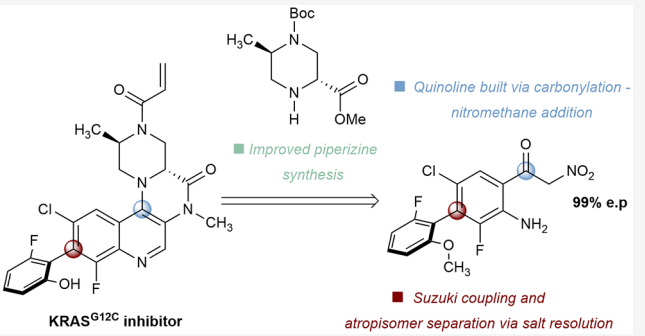
ABSTRACT: Route design and proof of concept synthesis was conducted on a synthetically challenging atropisomeric KRAS^{G12C} inhibitor to support clinical API manufacture. Improvements to the synthesis of a chiral piperazine fragment gave reduced step count and streamlined protecting group strategy via the formation and methanol ring opening of an *N*-carboxy-anhydride (NCA). The complex atropisomeric nitroquinoline was accessed via an early stage salt-resolution followed by a formal two-part nitromethane-carbonylation, avoiding a high temperature Gould–Jacobs cyclization that previously led to atropisomer racemization. The substrate scope of the formal nitromethane-carbonylation strategy was further explored for a range of *ortho*-substituted bromo/iodo unprotected anilines.



INTRODUCTION

Compound **1** is a small molecule inhibitor of the KRAS^{G12C} mutant GTPase, binding covalently to the cysteine residue creating an allosteric pocket on the GDP-bound protein and locking it in an inactive state.[1] The KRAS protein acts as a molecular switch and oncogenic mutations, such as the cysteine mutations at codon 12, lock it in the active, GTP-bound form causing aberrant activation of downstream effector pathways, driving tumor cell proliferation and survival.[2,3] Historically, attempts to drug KRAS have met with limited success; however, the atropisomeric, complex small molecule sotorasib, AMG 510, has recently been approved by the FDA for use in patients with non-small-cell lung cancer (NSCLC) whose tumors express a KRAS^{G12C} mutation.[4] Compound **1** (Figure 1) possesses similar structural complexity, containing a densely substituted quinoline ring and three stereogenic centers, one of which is an atropisomeric, tetrasubstituted biaryl. The initial medicinal chemistry route installed the atropisomer via an unselective Suzuki–Miyaura cross coupling in the final stages of the route, after coupling with the chiral piperazine **2**.

This inefficient sequence leads to a requirement for increased quantities of the synthetically challenging piperazine, as half is wasted during the subsequent atropisomer separation. A second generation route was identified during compound delivery to support preclinical studies[5] which generated the atropisomer at an earlier stage, prior to the introduction of piperazine **2**. While this reduced the synthetic burden of the piperazine, the route still required separation of the atropisomers by supercritical fluid chromatography (SFC) purification. Furthermore, the complex quinoline fragment **3** was formed via a route including a high temperature Gould–Jacobs cyclization operated at >200 °C (Figure 1). In order to support clinical development, a route was required that was capable of delivering multiple kilograms of compound **1**. The end game, including the late-stage introduction of the sensitive, covalently binding acrylamide, had been used in preclinical manufactures and was deemed suitable for the initial clinical manufactures. Given this, our initial scale up planning activities identified the synthesis of piperazine **2** and the single atropisomer of key quinoline fragment **3**, as the two most pressing areas for development. Herein, we report how these goals were ultimately addressed, first with an improved piperazine synthesis in reduced step count and with streamlined protecting group strategy, via the formation and methanol ring opening of an *N*-carboxy-anhydride (NCA), and second, the identification of a new route to quinoline **3** via an early stage salt-resolution of an atropisomeric biaryl, followed by a formal two-part nitromethane-carbonylation to give key nitro-acetophenone intermediate **5** (Figure 1).

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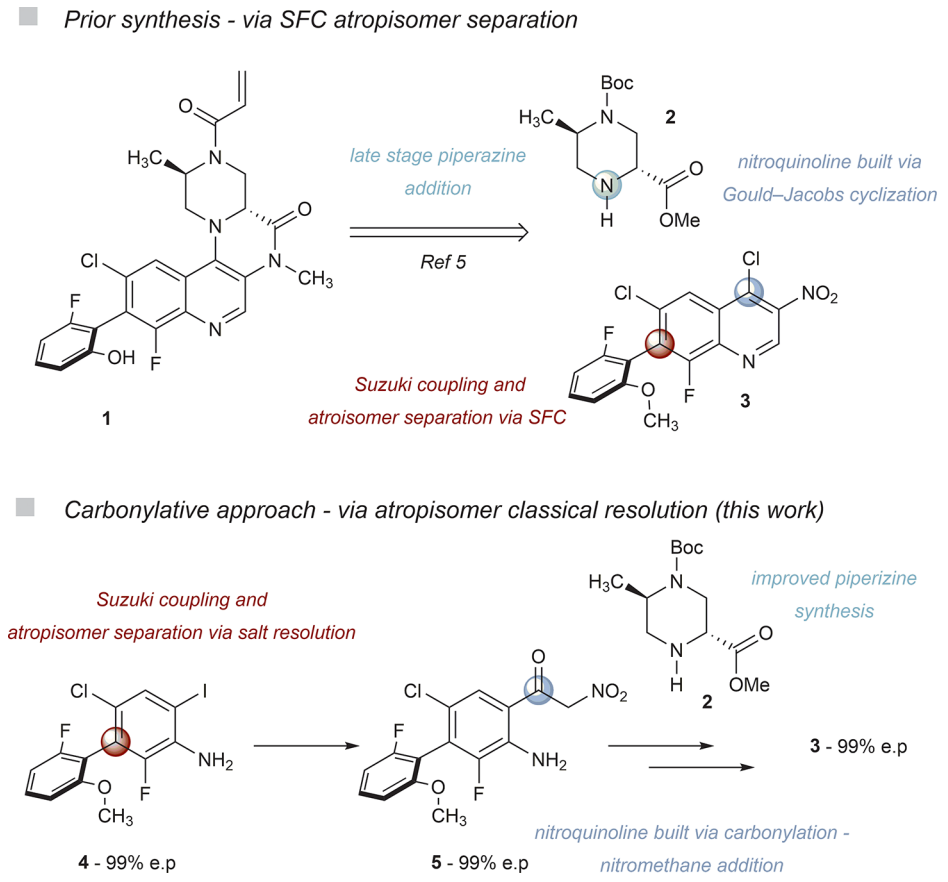
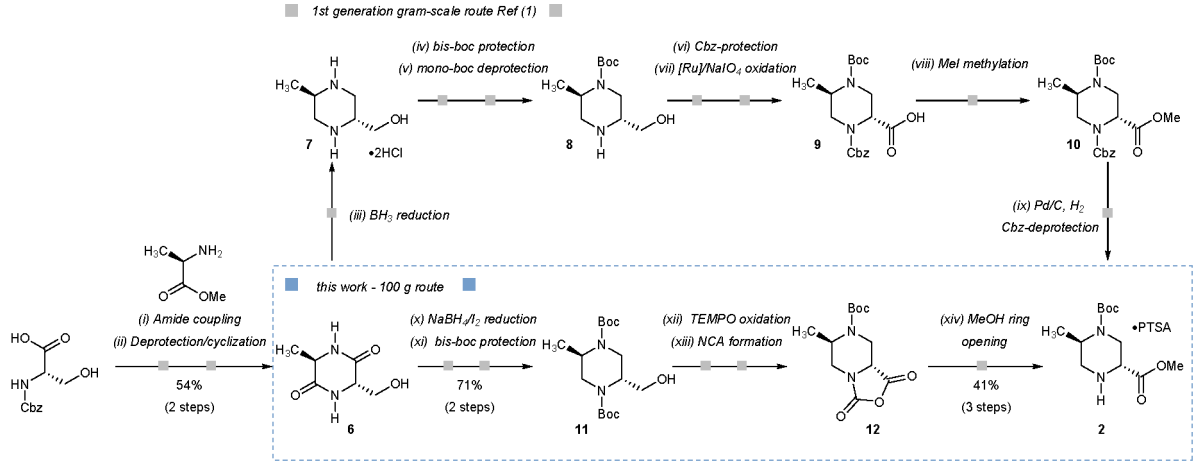


Figure 1. Previous strategy for the synthesis of compound **1** and the discussed carbonylative approach.

Scheme 1. Synthesis of Piperazine 2 via the First Generation Route and the New, Developed Route[a]



[a](i) EDCI (1.3 equiv), amine (1.2 equiv), *i*-Pr_2NEt (3.3 equiv), CH_2CI_2, 16 h, 15 °C; (ii) Pd/C (0.1 w/w), cyclohexene (1.5 equiv), MeOH, 18 h, 50 °C; (iii–ix) see ref 1; (x) $NaBH_4$ (6.0 equiv), I_2 (2.5 equiv), THF, 18 h, 60 °C; (xi) Boc_2O (2.5 equiv), Na_2CO_3 (11.0 equiv), 2-MeTHF, H_2O, 16 h, rt; (xii) TEMPO (0.02 equiv), trichloroisocyanuric acid (1.2 equiv), NaBr (0.2 equiv), $NaHCO_3$ (3.0 equiv), acetone, water, 2 h, 40 °C; (xiii) $SOCl_2$ (1.5 equiv), DMF (1.5 equiv), pyridine (2.0 equiv), MeCN, 5 °C, 1 h; (xiv) MeOH, 2 h, 40 °C then PTSA (1.0 equiv), 2-MeTHF, 12 h, 50 °C.

Development of the Synthesis of Piperazine 2. For early toxicology studies the key piperazine fragment **2** was accessed via Cbz-protected serine and alanine-methyl ester, using the synthesis reported by Tamanini et al. (Scheme 1).[6,7] Although the synthesis is derived from chiral pool starting materials and was suitable to provide gram quantities of the material, there were a number of challenges for further scale up. Overall the sequence operated in only 10–15% yield and required ten steps, of which eight were either protecting group manipulations or oxidation state changes. In particular, the mono Boc deprotection under basic conditions proved difficult to reproduce when scaled up, equally the free base product (**2**) was an oil and difficult to isolate in high purity. Furthermore, the redox stages were considered a challenge to run on

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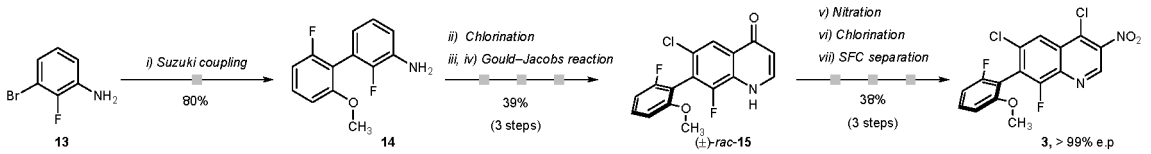
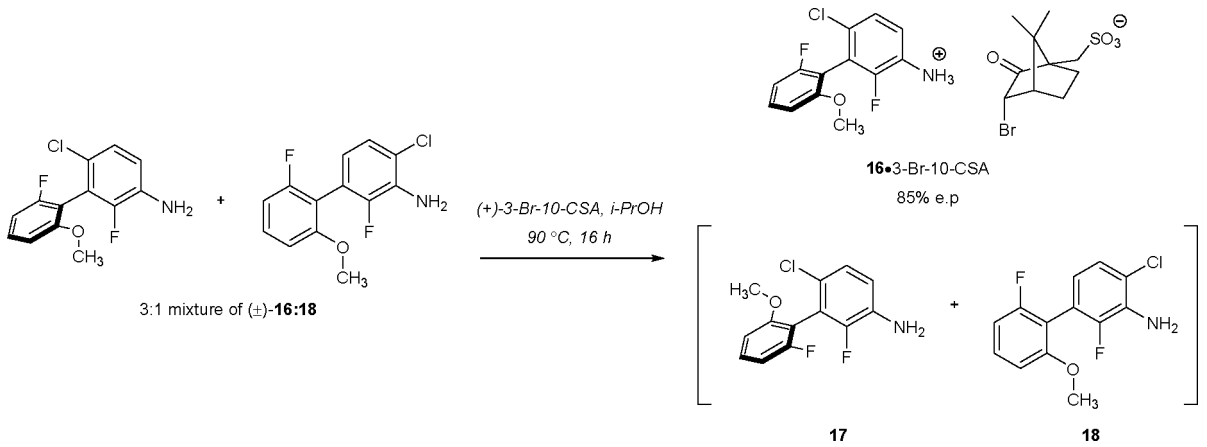
Scheme 2. Second Generation Synthesis of Isoquinolone 3[a]



[a](i) (2-fluoro-6-methoxyphenyl)boronic acid, (1.5 equiv), $PdCl_2$(dtbpf) (2 mol %), *i*-Pr_2NEt (3.0 equiv), 2-MeTHF/H_2O, 1 h, 80 °C; (ii) DCDMH (1.05 equiv), 2-MeTHF, 2 h, rt; (iii) 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione, 2-MeTHF, 1 h, rt; (iv) Dowtherm A, 230 °C, 30 min; (v) nitric acid (1.5 equiv), sulfolane, 2 h, 90 °C; (vi) $SOCl_2$ (3.0 equiv), DMF, 1 h, rt.

Scheme 3. Chiral Salt Resolution of Racemic Biaryl (±)-16



production scale and the formation of the methyl-ester via alkylation of carboxylic acid **9** with methyl iodide is atom inefficient. In order to meet requirements for later toxicology and clinical studies, we looked to optimize the synthesis to reduce the number of protecting group manipulations, improve the processes of the redox stages, and ensure the isolation of high quality material.

Looking to retain the chiral pool starting materials used in the current route we repeated the synthesis of bis-lactam **6**.[1] In our hands, the BH_3 reduction to give **7** was low yielding and gave moderate purity product, and was replaced with a $NaBH_4/I_2$ reduction which consistently gave high yield and high quality material. With efficient and scalable conditions to provide bis-Boc piperazine **11**, we considered an alternative sequence that would both streamline the protecting group strategy while concurrently providing the required methyl ester functionality. To this end, after conducting the bis Boc-protection we deviated from the original route, to perform the alcohol oxidation to the corresponding acid using a more scalable TEMPO oxidation[8] (71%, 2 steps). Boc-deprotection and methyl ester formation was carried out via the intermediacy of the NCA[9] **12**, with subsequent methanol ring-opening providing the desired piperazine **2** in 65% yield as an 82% w/w orange oil. The purity and handling could be improved by formation of the solid PTSA salt in 80% yield, giving 97% w/w strength and no unintentional deprotection of the Boc group. This new route (Scheme 1) shortens the original synthesis to seven steps, provides a stable solid product in high quality, and mitigates many of the problematic features of the original synthesis, and thus was deemed viable for intermediate-scale delivery.

Development of the Synthesis of Quinoline 3. The early medicinal chemistry synthesis had previously been developed[5] to provide a second generation route to quinoline **3**, capable of supporting the preclinical toxicology studies (Scheme 2). This progressed via Suzuki coupling of aniline **13** followed by unselective chlorination to generate a racemic atropisomeric biaryl. Subsequent Gould–Jacobs cyclization from a Meldrum's acid precursor gave the quinolone **15**, with nitration and chlorination providing racemic quinoline **3** prior to SFC atropisomer separation. While providing material to meet ongoing demand, a number of limitations were identified which merited further development work to provide a route suitable for further scale up. Namely, during investigation of the Gould–Jacobs cyclization with a single atropisomer, significant racemization was observed at the reaction temperature of 230 °C, which limited separation of the atropisomers by SFC until after the formation of quinolone **15**. The route also contained a nitration using nitric acid, which was operable but can be a general challenge to perform at scale due to safety concerns. Our route design efforts therefore focused on efficiently accessing the desired atropisomer at an early stage, then preserving its enantiopurity while exploring other options for introduction of the nitro group.

Compound **1** was designed as a stable, class 3 atropisomer with respect to biological conditions,[10] but no significant work had been done to determine the barrier to rotation under process relevant conditions. To characterize the torsion-rotation rate of the biaryl group within quinolone intermediate **15**, density functional theory (DFT) calculations were carried out to determine an accurate rotational barrier and the dependence of the racemization half-life on temperature. Full details of the calculations are provided in the SI, section 1. The computed free-energy barrier was determined as 36.4 kcal mol^{-1} at 25 °C, corresponding to a half-life of <1 h at 190 °C which was in line with the observed racemization in the previous Gould–Jacobs cyclization. Pleasingly, the calculations suggested a half-life at 150 °C of >5 days, suggesting an

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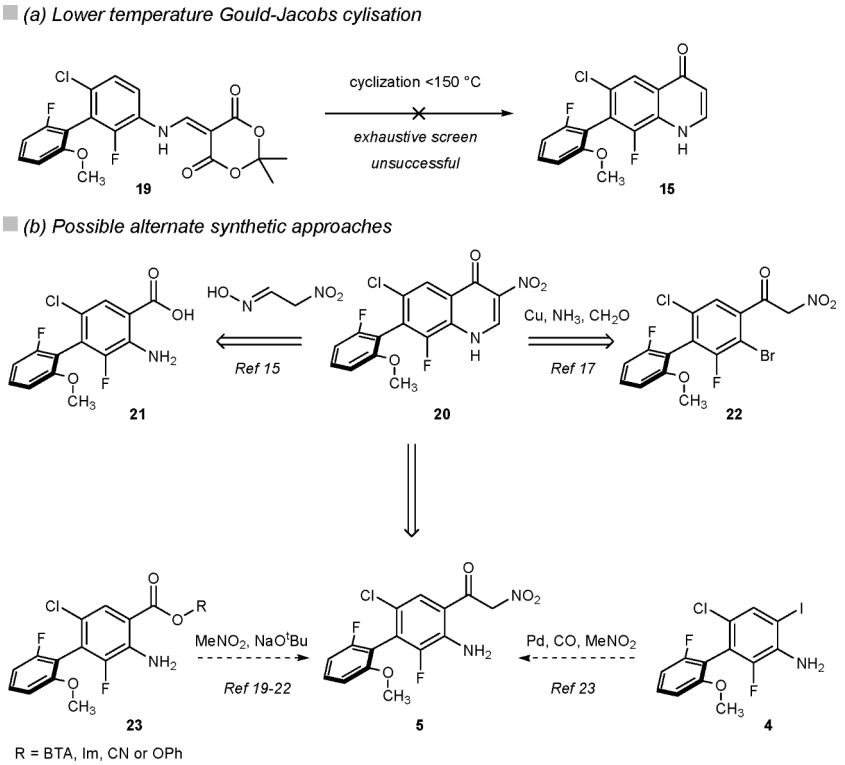

Figure 2. Alternative approaches to the synthesis of quinolone **20**.

alternative synthesis of **15**, proceeding at typical plant operating temperatures, could progress on a single atropisomer without risk of racemization.

With this information in hand, route design began with attempts toward an atroposelective Suzuki coupling to form the tetrasubstituted biaryl **16** (Scheme 3), but proved unsuccessful.[11] The likelihood of finding a suitable process capable of delivering was deemed low and not pursued further; however, atroposelective cross coupling remains an active area of research within AstraZeneca.[12] For the first clinical manufacture of **3** we instead focused our efforts on developing a classical salt resolution of biaryl **16**, in combination with a synthesis of isoquinolone **15**, which avoided high temperature (>150 °C) or racemizing conditions.

Conditions to synthesize biaryl **14** had previously been well developed,[5] with the subsequent chlorination generating racemic atropisomeric aniline **(±)-16**, which was considered a good candidate for classical resolution. Although the chlorination reaction proceeds with modest regioselectivity (3:1 in favor of the *para*-chloro product **16**), the undesired *ortho*-chloro isomer **18** could be easily purged during the first stage of the Gould–Jacobs reaction. Without this purge point, any new synthesis required a resolution that was capable of purging both the undesired atropisomer **17**, as well as the undesired chloro-regioisomer **18**.

An initial screen of chiral acids and solvents identified no suitable salt resolution conditions; however, a focused investigation into acids with a low pK_as identified several potential systems which gave varying levels of enantioenrichment.[11] Of these initial hits only [(1*S*)-*endo*]-(+)-3-bromo-10-camphorsulfonic acid (**(+)-3-Br-10-CSA**) showed robust enrichment for the desired atropisomer. Running the resolution in isopropyl alcohol (IPA) gave **16** with 74% enantiopurity (ep) and analysis of the filtrate showed 30% e.p (Scheme 3). We also found that **(−)-3-Br-8-CSA** gave 80% e.p for the undesired opposite atropisomer; the enantiomer of this resolving agent is commercially available on scale, potentially providing another option for resolution. Importantly, when we performed these resolutions with input material containing a 3:1 mixture of regioisomers, the undesired regioisomer **18** was completely rejected. With these promising results in hand, we then investigated alternative routes to isoquinolone **15** that avoided racemizing conditions.

We initially screened reaction conditions and additives for the classical Gould–Jacobs method in an effort to lower the reaction temperature to below 150 °C (Figure 2a). Limited literature precedent suggested the use of an ionic liquid as solvent[13] may allow reduced temperatures; however, these conditions, along with a thorough survey of both Lewis and Brønsted acids was unsuccessful.[11] The use of poly phosphoric-acid (PPA) at 80 °C could provide quinolone **15**; however, its use is challenging on scale due to its viscosity. Analogous reaction media, such as Eaton's reagent (7.7% w/w phosphorus pentoxide (P_2O_5) in methanesulfonic acid) gave greatly reduced conversion, as did the reported additive[14] $POCl_3$. As it became apparent the Gould–Jacobs cyclization would not be a viable strategy at low temperature, we focused on alternative routes, especially those that may allow direct access to the nitroquinolone core, eliminating the requirement for the nitration stage. The synthesis of nitroquinolones have been reported via anthranilic acids,[15] such as **21**, by treatment with methazonic acid; however, the significant safety concerns[16] with this reagent eliminated it from further consideration (Figure 2b). A recently reported Cu-mediated three-component coupling[17] of a 2-bromo-nitro-acetophenone analogue **22** was considered, but would have required a significant change to the synthesis of the biaryl (Figure 2b). Building upon the use of a nitro-acetophenone precursor, it has

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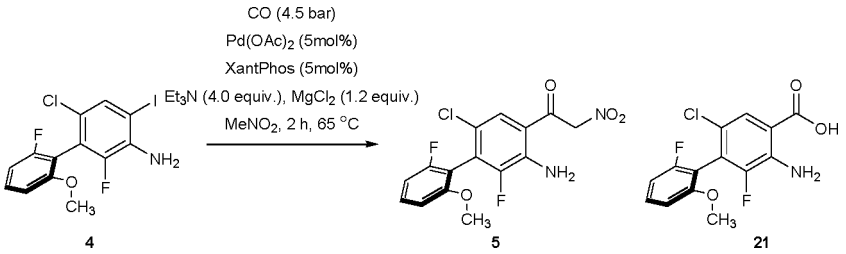
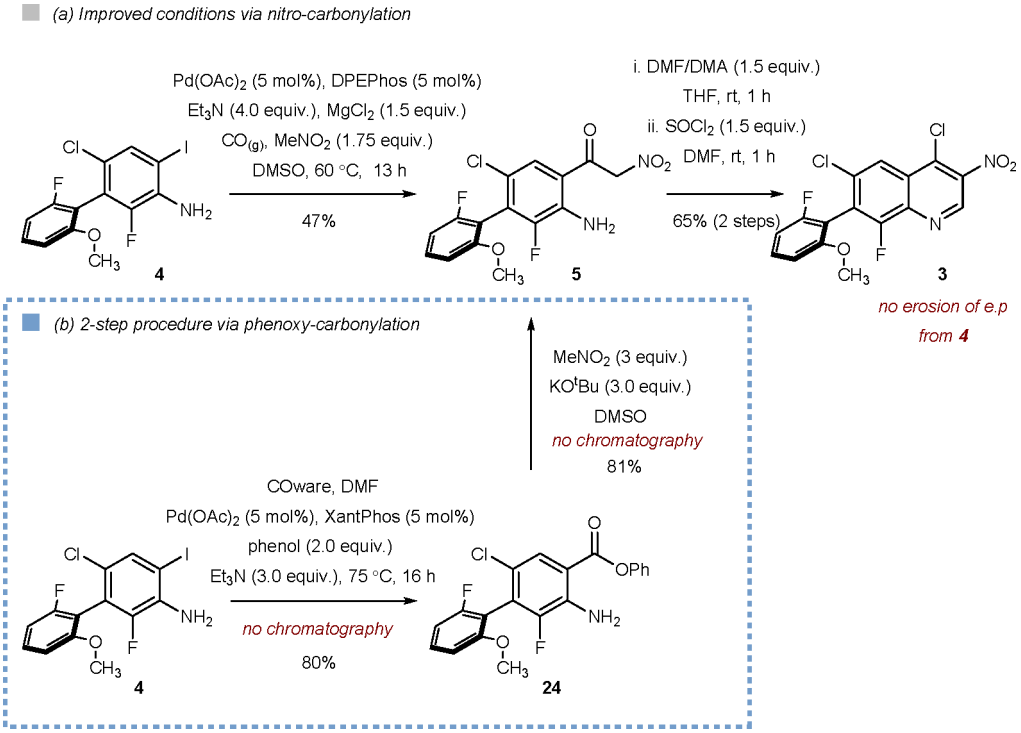
Table 1. Optimization of the of the Carbonylative Arylation of Nitromethane



entry	variation from shown	H_2O content (ppm)	5[a]	21[a]
1[b]	None	ND	67 (51)	3
2[c]	None	89	79	10
3[c]	mol sieves	39	76	12
4[c]	1.0 equiv of H_2O	779	81	11
5[c]	50 °C	ND	72	9
6[c]	70 °C	ND	65	13
7[c]	$MgBr_2$	ND	73	9
8[c]	$Mg(OTf)_2$	ND	74	8

[a]UHPLC area % (254 nm) of crude reaction mixture; value in brackets represents isolated yield. [b]Reaction conducted using COware apparatus at unknown CO pressure. [c]Reaction conducted in a BiotageEndeavor reactor.

Scheme 4. Nitrocarbonylative and Phenoxycarbonylative Approaches to 5



been previously shown that the analogous nitrile-acetophenone could be cyclized successfully[18] to the quinolone, suggesting a similar strategy from nitro-acetophenone **5** should be viable. We envisioned multiple ways to access the nitro-acetophenone group within **5**, most proceeded via acylation of nitromethane by an activated aryl acyl species such as the acyl benzotriazole (BTA),[19] acyl imidazole (Im),[20] acyl cyanide,[21] or phenoxy ester (OPh)[22] (Figure 2b). A recently reported one-step method by the group of Skrydstrup[23] operates via palladium catalyzed carbonylative arylation of nitromethane. Although this protocol uses nitromethane as solvent and was not demonstrated on free anilines such as **4**, the carbonylation of which can pose a significant challenge,[24] it was considered a viable strategy and was prioritized for detailed investigation.

The required aryl iodide starting material was readily prepared using *N*-iodosuccinimide (NIS)/AcOH conditions, providing **4** in 90% yield, on gram scale as a single regioisomer. Initial application of the reported carbonylation conditions using the COware system led to a promising 51% yield along with carboxylic acid **21** as a major side product, among others[11] (observed in 5−20% of the crude reaction mixture). The decomposition of nitro-acetophenones to arylcarboxylic acids has been reported;[25] however, **5** was stable to the reaction conditions[26] and did not appear to correlate with temperature or reaction time (Table 1). Furthermore, it

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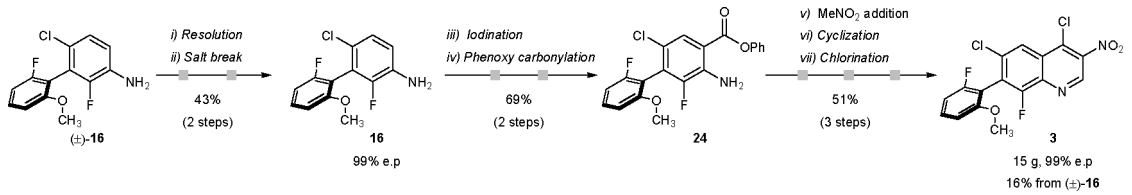
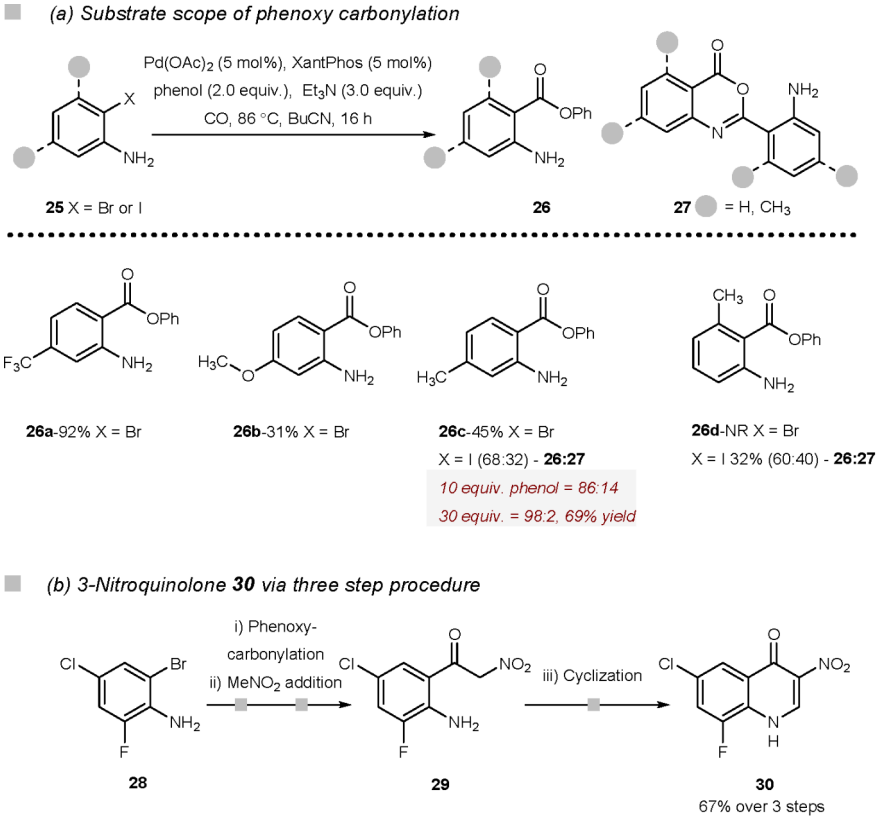
Scheme 5. Proof-of-Concept for the New Seven-Step Route to Quinoline 3 from Aniline (±)-16[a]



[a](i) Br-CSA (1.0 equiv), IPA, 1 h, 95 °C, then recrystallization from IPA; (ii) NaOH (2.0 equiv), 2-MeTHF, rt, 2 h; (iii) NIS (1.05 equiv), AcOH, rt, 2 h, chromatography; (iv) $Pd(OAc)_2$ (2 mol %), XantPhos (2 mol %), phenol (1.0 equiv), Et_3N (3.0 equiv), DMF, CO(g), 16 h, 80 °C, chromatography; (v) $MeNO_2$ (3.1 equiv) KO^{t}Bu (3.1 equiv), DMSO, 10 °C, 16 h; (vi) DMF/DMA (1.5 equiv), THF, 40 °C, 2 h; (vii) $SOCl_2$ (3.0 equiv), DMF, rt, 1 h.

Scheme 6. Substrate Scope of Phenoxy Carbonylation and Demonstration of Access to 3-Nitroquinolones[a]



[a](i) $Pd(OAc)_2$ (10 mol %), XantPhos (10 mol %), phenol (2.0 equiv), Et_3N (3.0 equiv), *n*-BuCN, CO(g), 86 °C, 16 h (99%); (ii) $MeNO_2$ (3 equiv) KO^{t}Bu (3.0 equiv), DMSO, rt, 2 h (92%); (iii) DMF/DMA (1.5 equiv), THF, 45 °C, 16 h, (80%).

appeared independent of reaction water content and Mg source (Table 1; Cl, Br, OTf). We postulate the carboxylic acid may be, at least in part, formed via competitive O-acylation,[27] vs the desired C-acylation of nitromethane, followed by further decomposition to yield nitrile oxide and the side product **21**.[28]

The modest 51% isolated yield was viewed as acceptable at this stage of investigation; however, the use of nitromethane as solvent posed a significant concern and was not viewed as a viable option on scale. Further screening of alternative reaction conditions successfully led to the reduction of nitromethane to stoichiometric quantities, with DMSO as the solvent.[11] However, these conditions appeared poorly reproducible across different carbonylation reaction platforms, and still resulted in significant formation of carboxylic side product **21**.[27] Although far from optimal, we sought to confirm the viability of the overall carbonylation/cyclization sequence, and furthermore ensure no racemization of the atropisomeric biaryl was occurring. Following the nitrocarbonylation in DMSO (47% yield), the crude product could be taken on directly to a cyclization using DMF/DMA, with subsequent chlorination leading to the target nitroquinoline **3** (Scheme 4a). We then progressed an enantioenriched development sample through the three-step process, confirming no loss of enantiopurity through the sequence.

Given the inability to control the aryl acid side product effectively, combined with the necessity for the iodo aniline, rather than a preferred bromo aniline, alternative carbonylative routes were considered. We returned to the two-step sequence of carbonylation to provide an activated aryl acyl species, followed by addition of nitromethane (Scheme 4b). The most applicable to carbonylation was considered the phenoxy group, since the phenoxy carbonylation of aryl halides is well documented. Carbonylation of iodoaniline **4** in the presence of phenol provided phenoxy ester **24** in 80% yield as the only

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observable product. In a single, unoptimized reaction, the target nitro-acetophenone **5** was isolated in 81% using previously reported[22] NaO*t*Bu/$MeNO_2$/DMSO conditions. Importantly, the nitro-acetophenone **5** was isolated directly as a solid in good purity, following precipitation during the reaction work up, in 65% yield over two steps, representing the potential for manufacturing advantages compared to the one-step procedure.

To further assess the potential long-term viability of the nitro-acetophenone route we conducted a proof-of-concept synthesis incorporating the full sequence, starting from resolution of an atropisomeric mixture of racemic aniline (±)-**16** (Scheme 5). Following the developed (+)-**3-Br-10-CSA** resolution, aniline **16** was isolated in 88% e.p. A second slurry of the salt in IPA improved this to 99% e.p and, following a salt break, gave aniline **16** in 43% yield. The iodination and phenoxy carbonylation performed well on decagram scale (71%, two steps); chromatography was used to purify **24** however small scale experiments showed that this can be replaced with a crystallization. Compound **24** was then taken through the unoptimized sequence of nitro-acetophenone formation, cyclization, and chlorination (51%, three steps), to give quinoline **3** in good purity and without erosion of enantiopurity. This new five-step route from aniline **16** compares favorably to the previous high temperature Gould–Jacobs cyclization, as it both avoids nitration chemistry and, crucially, does not lead to racemization of the biaryl, allowing an efficient early stage atropisomer separation.

At this point, the development of compound **1** for clinical trials was placed on hold; however, following our proof-of-concept route to access **20**, we continued to assess the three-step sequence to nitro-quinolones, aiming to showcase a general route applicable to both aryl bromides and iodides. We began with a re-evaluation of the reaction conditions using a simplified analogue **28** (Scheme 6b) without the atropisomeric biaryl. Validation of screening results on preparative scale using the COware system found butyronitrile at 85 °C to be optimal (85% yield), although requiring 10 mol % of $Pd(OAc)_2$ and Xantphos to operate efficiently on the aryl bromide. With optimized conditions in hand, we tested a range of substrates with varying electronic and steric properties using the BiotageEndeavor system (Scheme 6a). It was observed that the electron-deficient aryl system **25a** (4-CF_3) provided a good yield, while more electron-rich substrates gave only moderate conversions and yields (**25b** 4-MeO, **25c** 4-Me). As expected, sterics also had an influence on the phenoxy carbonylation with the 2,3-disubstituted aniline **26d** formed in only trace amounts. For the more electron-rich, low-yielding substrates, use of the aryl iodide led to full starting material consumption and moderate yields of **26c,d**. Isolated along with the desired phenoxyester, however, were significant quantities of the pseudodimeric side products **27**. Protection of the aniline as the *N*-Boc led to no conversion, consistent with the challenge of these substrates. We proposed that these dimers are formed via competing nucleophilic attack of the aniline on the acyl palladium species, as demonstrated by Kollár,[29] presumably due to the increased nucleophilicity of the more electron rich aniline.[30] Although not constituting a practical solution, acylation of phenol to give the desired product **26c** could outcompete the aniline if used in significant excess, with 10 equiv giving a 86:14 ratio, and 30 equiv leading to 98:2 (**26**:**27**) in a 69% isolated yield. Although limited in substrate scope, the utility of the method as a means to access nitro-acetophenones and the subsequent nitro-quinolones was demonstrated via the preparation of **30**, from a 2 mmol input of **28** in 67% overall yield through three steps (Scheme 6b). The first two stages could be telescoped without workup; however, this required extended reaction time for the formation of **29** and led to increased formation of the carboxylic acid side product (8%).

CONCLUSION

In summary, route design and proof-of-concept synthesis has been demonstrated for two key fragments of the synthetically challenging $KRAS^{G12C}$ inhibitor **1**. For piperazine **2**, the synthetic sequence was shortened by two steps incorporating a TEMPO-mediated oxidation and a carboxylic acid-assisted selective deprotection of an *N*-Boc group via the NCA. A PTSA salt of **2** was discovered, which gave an excellent isolation point, providing high purity and avoiding the use of chromatography.

For quinoline **3** an efficient resolution of biaryl aniline **16** was developed, providing an early stage separation of the atropisomers. A new route from the single atropisomer of aniline **16** was developed via a nitro-acetophenone intermediate. This was accessed most efficiently from a formal two-step nitromethane-carbonylation, incorporating a Pd-catalyzed phenoxy carbonylation followed by nitromethane addition. Importantly this method, unlike the previously used high temperature Gould–Jacobs cyclization, did not lead to racemization of the biaryl. The generality of this approach was tested on a limited range of *ortho*-substituted bromo/iodo unprotected anilines, resulting in moderate to good yields for electron poor substrates.

EXPERIMENTAL SECTION

General Methods. All reactions were performed under an atmosphere of nitrogen. All reagents were commercially available and were used without further purification. ^1H and ^{13}C NMR were measured in $CDCl_3$, DMSO-d_6, or CD_3OD and recorded on Bruker Avance-400 or Bruker Avance-500 spectrometers at 25 °C (unless otherwise stated), frequency stated in each experiment. The chemical shifts (δ) are reported in parts per million (ppm), with the residual solvent signal used as a reference. Coupling constants (J) are reported as Hz. NMR abbreviations are used as follows: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. NMR peaks were assigned using MestReNova 8.0.1 or ACD/Spectrus Processor 2020.2.0. Assays of intermediates and final products are given as weight/weight (w/w) and were determined by ^1H NMR measurements and using 1,2,3,4-tetrachloro-5-nitrobenzene as an internal standard.

Enantiomeric excess was determined by analytical SFC (UPC, Waters, Milford, MA, USA). For compound **16** a Lux Cellulose 3 150 × 4.6 mm, 3 μm column (Phenomenex) was used, the mobile phase was 5% 20 mmol NH_3 in isopropyl alcohol in CO_2 for 8 min then 50% 20 mmol NH_3 in isopropyl alcohol in CO_2 at 35 °C, 150 bar and a flow rate of 3.5 mL/min. For compound **3** a Chiralpak IC 150 × 4.6 mm, 3 μm column (Chiral Technologies, Illkirch, France) was used; the mobile phase was 5% ethanol (containing 0.05% diethylamine) in CO_2 for 5 min, then 40% ethanol (containing 0.05% diethylamine) in CO_2 for 1 min at 35 °C, 100 bar, and a flow rate of 2.5 mL/min. HRMS measurements were performed on a Waters Synapt G2-Si quadrupole-time-of-flight mass spectrometer using electrospray ionization (ESI) techniques.

*Di-tert-butyl (2R,5R)-2-(hydroxymethyl)-5-methylpiperazine-1,4-dicarboxylate (**11**).* To a solution of **6** (40 g, 0.25 mol), prepared following a published procedure,[1] in THF (600 mL) at 15–25 °C was added $NaBH_4$ (57 g, 1.5 mol, 6.0 equiv) portionwise. The reaction was then heated using a jacketed vessel to 50–60 °C and a solution of

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iodine (79 g, 0.63 mol, 2.5 equiv) in THF (600 mL) was added dropwise. The reaction was then heated to 60−70 °C for a further 18 h. The reaction mixture was cooled to 30 °C and MeOH (200 mL) added followed by 12 M aqueous HCl (200 mL). The mixture was then stirred at 40−50 °C for a further 5 h, cooled and filtered to give a white solid. The wet cake was dissolved in 2-MeTHF (1600 mL) and a solution of Na_2CO_3 (292 g, 2.75 mol, 11 equiv) in water (2000 mL) was added. To the reaction di-*tert*-butyl decarbonate (137 g, 0.63 mol, 2.5 equiv) was added and the reaction stirred for 18 h. The resulting mixture was filtered, the organic phase isolated and concentrated to 120 mL. Heptane was added to the solution and the resulting solid filtered and dried to give **11** as a white solid (59 g, 0.18 mol, 71%). ^{1}H NMR broad and split due to the presence of *N*-Boc rotamers not resolved at high temperature (500 MHz, CD_3OD) δ 4.43−4.04 (m, 2H), 4.02−3.87 (m, 1H), 3.75 (br d, J = 12.4 Hz, 1H), 3.66−3.48 (m, 2H), 3.27−3.06 (m, 2H), 1.58−1.42 (m, 18H), 1.16 (br d, J = 5.9 Hz, 3H). 13C{1H} NMR (126 MHz, CD3OD) δ 156.1, 155.5, 80.1, 80.2, 58.1, 52.7, 51.3, 45.6, 43.7, 42.2, 37.9, 36.8, 27.3, 14.2, 13.8, 156.1, 155.9, 156.3, 155.5, 80.1, 80.2, 58.1, 52.7, 51.3, 45.6, 43.7, 42.2, 37.9, 36.8, 27.3, 14.2, 13.8.

*1-(tert-Butyl) 3-methyl (3R,6R)-6-methylpiperazine-1,3-dicarboxylate (**2**).* To a solution of **11** (520 g, 1.57 mol, 1.0 equiv) in acetone (5.2 L) and water (2.6 L) was added $NaHCO_3$ (396 g, 4.71 mol, 3.0 equiv), NaBr (32 g, 0.31 mol, 0.2 equiv) and TEMPO (4.9 g, 0.03 mol, 0.02 equiv). The reaction mixture was heated in a jacketed vessel to 40−45 °C, trichloroisocyanuric acid (462 g, 1.98 mol, 1.2 equiv) was added and the reaction stirred for 2 h. The reaction mixture was cooled to 15−25 °C, diluted with isopropyl alcohol (1.7 L) and stirred for 2 h. The resulting slurry was filtered and the filtrate concentrated to dryness. The resulting residue was dissolved in ethyl acetate (6 L) and washed with water. The aqueous layer was extracted with ethyl acetate (6 L) and the organic layers combined and concentrated. The resulting solid was slurried in heptane (6 L), filtered and dried to give (2*R*,5*R*)-1,4-bis(*tert*-butoxycarbonyl)-5-methylpiperazine-2-carboxylic acid as a white solid (410 g, 1.19 mol, 76%) ^{1}H NMR broad and split due to the presence of *N*-Boc rotamers not resolved at high temperature (500 MHz, DMSO-d_6) δ 4.62−4.33 (m, 1H), 4.19 (br d, J = 12.9 Hz, 2H), 3.59−3.45 (m, 1H), 3.41−3.12 (m, 2H), 1.48−1.28 (m, 18H), 1.06 (br d, J = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 171.6, 171.3, 155.1, 155.0, 154.9, 154.8, 154.1, 154.0, 154.0, 153.4, 79.5, 79.5, 79.3, 79.2, 79.1, 54.4, 52.8, 46.9, 46.4, 45.3, 45.5, 44.6, 44.0, 44.0, 38.3, 27.9, 27.8, 15.6, 15.2, 15.0, 14.7.

(2*R*,5*R*)-1,4-Bis(*tert*-butoxycarbonyl)-5-methylpiperazine-2-carboxylic acid (400 g, 1.16 mol, 1.0 equiv) was dissolved in acetonitrile (4 L) and pyridine (183 g, 2.32 mol, 2.0 equiv) and this solution was added to a cooled solution of $SOCl_2$ (207 g, 1.74 mol, 1.5 equiv), DMF (127 g, 1.74 mol, 1.5 equiv) in acetonitrile (2 L) maintaining the internal temperature between 0 and 10 °C. The resulting mixture was added to water (4 L) cooled to 0 °C. The resulting mixture was extracted with ethyl acetate (4 L) and the organic layer washed with a saturated NaCl (aq) solution (3 L). The organic layer was concentrated to 500 mL and *n*-heptane (1.5 L) added. The mixture was stirred for 1 h then filtered and dried to give **12** (299 g, 1.11 mol, 90%) as white solid. **12** (200 g, 0.74 mol) was dissolved in methanol (4 L) and held at 35−40 °C for 2 h. The solution was then concentrated to give **2** (151 g, 82% w/w, 0.48 mol, 65%) as an orange oil matching previously reported characterization data.[1]

*1-(tert-Butyl) 3-methyl (3R,6R)-6-methylpiperazine-1,3-dicarboxylate (**2**).PTSA.* 1-(*tert*-Butyl) 3-methyl (3*R*,6*R*)-6-methylpiperazine-1,3-dicarboxylate (**2**) (10.0 g, 82% w/w, 31.8 mmol) was dissolved in 2-MeTHF (70 mL) at room temperature. *para*-Toluene sulfonic acid (0.80 g, 4.65 mmol, 0.15 equiv) was added followed by **2**.PTSA (0.7 mg, 0.16 mmol, 0.005 equiv) and the reaction stirred until a thin slurry had formed. The thin slurry was heated to 50 °C using a stirrer hot plate and a solution of *para*-toluene sulfonic acid (4.53 g, 26.4 mmol, 0.85 equiv) in 2-MeTHF (30 mL) was added via a syringe pump over 3 h. The slurry was cooled to room temperature, *tert*-butyl methyl ether (50 mL) added and the mixture stirred for 18 h. The resulting mixture was filtered using a split-buchner funnel under reduced pressure and the cake washed with *tert*-butyl methyl ether (2 × 25 mL). The solid was dried under reduced pressure at 40 °C to give **2**.PTSA as a white solid (13.5 g, 98% w/w, 26.1 mmol, 82%,). $[\alpha]_D^{20}$ −13.5 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.43 (br s, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 4.46 (br d, J = 3.1 Hz, 1H), 4.36−4.21 (m, 2H), 3.79 (s, 3H), 3.42 (dd, J = 4.4, 15.0 Hz, 1H), 3.30 (m, 1H), 3.06 (dd, J = 3.0, 13.3 Hz, 1H), 2.29 (s, 3H), 1.39 (s, 9H), 1.19 (d, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 167.7, 153.0, 145.6, 137.6, 128.0, 125.5, 80.0, 53.2, 52.8, 44.0, 43.2, 37.1, 27.8, 20.8, 14.9.

*6-Chloro-2,2′-difluoro-6′-methoxy-[1,1′-biphenyl]-3-amine ((±)-**16**).* 5-[(*E*)-[4-Chloro-2-fluoro-3-(2-fluoro-6-methoxy-phenyl)-phenyl]iminomethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**9**) (150.0 g, 0.35 mol), prepared following a published procedure,[5] was dissolved in ethanol (1500 mL). Ethane-1,2-diamine (84.9 g, 94.3 mL, 1.42 mol, 4.0 equiv) was added to the reaction which was stirred for hours at 20−25 °C. The resulting suspension was filtered and the liquors concentrated under a vacuum. The residue was dissolved in ethyl acetate (1000 mL) and washed with a 2 M aqueous solution of citric acid (1000 mL). The organic layer was concentrated under a vacuum to give (±)-**16** as a white solid matching previously reported characterization data.[5]

*(S)-6-Chloro-2,2′-difluoro-6′-methoxy-[1,1′-biphenyl]-3-amine (**16**).* 4-Chloro-2-fluoro-3-(2-fluoro-6-methoxy-phenyl) aniline ((±)-**16**) (83.0 g, 0.31 mol, 1.0 equiv) and [(1*S*)-*endo*]-(+)-3-bromo-10-camphorsulfonic acid monohydrate (102.0 g, 0.31 mol, 1.0 equiv) were mixed in isopropanol (1.7 L) and the mixture heated to 90−95 °C using a stirrer hot plate until all the solids dissolved. The mixture was cooled to 15−20 °C and stirred for 16 h. The slurry was filtered and washed with isopropanol (0.4 L), then dried. The solid was then slurried with isopropanol (0.6 L) and heated to 85 °C for 2 h. The resulting slurry was cooled to 20 °C, filtered and washed with isopropanol (0.2 L). The solid was then suspended in 2-MeTHF (500 mL) and NaOH (11.5 g, 0.29 mol, 0.95 equiv) and water (300 mL) were added. The reaction was stirred for 2 h at 20−25 °C, the organic layer isolated and concentrated to dryness to give **16** as an off-white powder (35.5 g, 43%, 99% e.p). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dt, J = 6.7, 8.4 Hz, 1H), 7.09 (dd, J = 1.6, 8.6 Hz, 1H), 6.88−6.79 (m, 2H), 6.79−6.74 (m, 1H), 3.81 (s, 3H), 3.78−3.68 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.5 (d, J = 246.6 Hz), 158.3 (d, J = 7.3 Hz), 149.3 (d, J = 241.1 Hz), 133.3 (d, J = 14.1 Hz), 130.4 (d, J = 10.4 Hz), 124.6 (d, J = 4.1 Hz), 123.6 (d, J = 3.6 Hz), 119.4 (d, J = 18.2 Hz), 116.8 (d, J = 4.5 Hz), 110.3 (d, J = 19.1 Hz), 107.9 (d, J = 22.3 Hz), 106.6 (d, J = 2.7 Hz), 56.2. ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ −117.4 (d, J = 3.0 Hz), −135.5 (d, J = 3.5 Hz). HRMS (ESI) m/z calculated for $C_{13}H_{11}ClF_2NO$ $[M + H]^+$, 270.0497, found 270.0497.

*(S)-6-Chloro-2,2′-difluoro-4-iodo-6′-methoxy-[1,1′-biphenyl]-3-amine (**4**).* To a solution of (*S*)-6-chloro-2,2′-difluoro-6′-methoxy-[1,1′-biphenyl]-3-amine (**16**) (35.0 g, 0.13 mol, 1.0 equiv) in acetic acid (400 mL) was added *N*-iodosuccinimide (12.3 g, 0.14 mol, 1.05 equiv) and the reaction stirred at 20−25 °C for 2 h. The reaction was diluted with ethyl acetate and water and the organic layer isolated and concentrated to dryness. The residue was purified by silica gel chromatography (SiO_2, 0 to 20% ethyl acetate:heptane) with fractions containing the desired product combined and concentrated to give **4** as a white solid (47.0 g, 0.12 mol, 92%). $[\alpha]_D^{20}$ −4.4 (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.62 (d, J = 1.8 Hz, 1H), 7.48 (dt, J = 7.1, 8.4 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.94 (t, J = 8.6 Hz, 1H), 5.37 (br s, 2H), 3.76 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 159.5 (d, J = 243.4 Hz), 157.8 (d, J = 6.8 Hz), 146.3 (d, J = 245.2 Hz), 136.8 (d, J = 15.0 Hz), 132.8 (d, J = 3.2 Hz), 131.3 (d, J = 10.9 Hz), 120.6 (d, J = 3.6 Hz), 118.7 (d, J = 18.6 Hz), 109.0 (d, J = 19.5 Hz), 107.6 (d, J = 20.0 Hz), 107.5, 83.0 (d, J = 3.6 Hz), 56.1. ^{19}F{^{1}H} NMR (470 MHz, DMSO-d_6) δ −113.6 (d, J = 2.2 Hz), −124.2 (d, J = 2.6 Hz). HRMS (ESI) m/z calculated for $C_{13}H_{10}ClF_2INO$ $[M + H]^+$, 395.9464, found 395.9466.

Scaled-up Two-Stage Synthesis of 5 from 4. *Phenyl (S)-3-amino-6-chloro-2,2′-difluoro-6′-methoxy-[1,1′-biphenyl]-4-carboxylate (**24**).* (*S*)-6-Chloro-2,2′-difluoro-4-iodo-6′-methoxy-[1,1′-

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biphenyl]-3-amine (**4**) (42.0 g, 0.11 mol, 1.0 equiv), phenol (10.5 g, 0.11 mol, 1.0 equiv), Xantphos (1.4 g, 2.5 mmol, 2.3 mol %), $Pd(OAc)_2$ (0.5 g, 2.3 mmol, 2.1 mol %), triethyl amine (33.0 g, 0.34 mol, 3 equiv) were dissolved in DMF (400 mL). The solution was purged with nitrogen then the atmosphere pressurized with carbon monoxide (50 psig) and heated to 75−80 °C. Once the reaction was complete by CO uptake it was cooled to 20−25 °C and ethyl acetate (600 mL) and water (1600 mL) were added. The aqueous layer was removed and the organic layer concentrated to dryness. The residue was purified by silica gel chromatography (SiO_2, 0 to 20% ethyl acetate:pet ether) with fractions containing the desired product combined and concentrated to give **24** as a white solid (32.0 g, 0.083 mol, 75%). $[\alpha]_D^{20}$ −3.0 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, DMSO-d_6) δ 7.93 (d, *J* = 1.6 Hz, 1H), 7.59−7.45 (m, 3H), 7.37−7.28 (m, 3H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.99 (t, *J* = 8.6 Hz, 1H), 6.83 (s, 2H), 3.80 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 164.4 (d, *J* = 3.6 Hz), 159.4 (d, *J* = 243.9 Hz), 157.7 (d, *J* = 6.8 Hz), 150.2, 148.6 (d, *J* = 243.4 Hz), 139.7 (d, *J* = 15.9 Hz), 131.7 (d, *J* = 10.9 Hz), 129.5, 126.1, 125.6 (d, *J* = 3.2 Hz), 123.2 (d, *J* = 17.3 Hz), 122.1, 118.1 (d, *J* = 3.6 Hz), 110.1 (d, *J* = 5.9 Hz), 108.5 (d, *J* = 19.1 Hz), 107.6 (dd, *J* = 9.8, 12.0 Hz), 56.3. $^{19}F\{^1H\}$ NMR (470 MHz, DMSO-d_6) δ −113.7 (d, *J* = 2.2 Hz), −127.6 (d, *J* = 2.6 Hz). HRMS (ESI) *m*/*z* calculated for $C_{20}H_{15}ClF_2NO_3$ [M + H]+, 390.0709, found 390.0708.

*(S)-1-(3-Amino-6-chloro-2,2′-difluoro-6′-methoxy-[1,1′-biphenyl]-4-yl)-2-nitroethan-1-one (**5**).* A solution of *t*BuOK (54.0 g, 0.23 mol, 3.1 equiv) and nitromethane (15.0 g, 0.23 mol, 3.1 equiv) in DMSO (80 mL) was cooled to 0−10 °C. To this solution was added a solution of **24** (30.0 g, 0.077 mol, 1.0 equiv) in DMSO (40 mL) over 10 min. After 16 h acetic acid (46.0 g, 0.77 mol, 10 equiv) and water (460 mL) were added and the reaction cooled to 0−5 °C and stirred for 1 h. The resulting solid was filtered, washed with water (200 mL) and dried to give **5** as a white solid (26.0 g, 0.073 mol, 95%). $[\alpha]_D^{20}$ +7.0 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, DMSO-d_6) δ 7.63 (d, *J* = 1.4 Hz, 1H), 7.53 (dt, *J* = 7.1, 8.4 Hz, 1H), 7.37 (s, 2H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.98 (t, *J* = 8.7 Hz, 1H), 6.52 (s, 2H), 3.78 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 188.0 (d, *J* = 2.3 Hz), 159.3 (d, *J* = 244.3 Hz), 157.6 (d, *J* = 6.8 Hz), 148.4 (d, *J* = 244.3 Hz), 139.4 (d, *J* = 15.0 Hz), 131.8 (d, *J* = 10.4 Hz), 125.8 (d, *J* = 3.6 Hz), 123.7 (d, *J* = 17.3 Hz), 117.9 (d, *J* = 3.2 Hz), 115.0 (d, *J* = 5.4 Hz), 108.3 (d, *J* = 19.1 Hz), 107.7 (d, *J* = 2.7 Hz), 107.7 (br d, *J* = 21.8 Hz), 83.0, 56.3. $^{19}F\{^1H\}$ NMR (470 MHz, DMSO-d_6) δ −113.7 (d, *J* = 2.2 Hz), −127.8 (d, *J* = 2.6 Hz). HRMS (ESI) *m*/*z* calculated for $C_{15}H_{12}ClF_2N_2O_4$ $[M + H]^+$, 357.0454, found 357.0451.

Direct Nitrocarbonylation Reaction for the Preparation of 5 from 4. *1-(3-Amino-6-chloro-2,2′-difluoro-6′-methoxy-[1,1′-biphenyl]-4-yl)-2-nitroethan-1-one ((±)-**5**).* To a 16 mL HP Chemscan reactor vessel within a glovebox was added palladium(II) acetate (11.4 mg, 0.05 mmol, 5 mol %), bis(2-diphenylphosphinophenyl)-ether (30.0 mg, 0.05 mmol, 5 mol %) magnesium chloride (144 mg, 1.5 mmol, 1.5 equiv), **4** (400 mg, 1.0 mmol), DMSO (4.0 mL, 10 mL/mmol) triethylamine (560 μL, 4.0 mmol, 4.0 equiv) and nitromethane (95.0 μL, 1.75 mmol, 1.75 equiv) The vessel was sealed within the glovebox and transferred to the HPChemScan reactor platform. The manifold and lines were purged with carbon monoxide and nitrogen to extrude any air and the vessel purged with carbon monoxide. The contents were warmed to 65 °C, pressurized with carbon monoxide up to 3.5 barg (4.5 bara) and stirred for 16 h at 1000 rpm. Recorded gas uptake data indicated reaction completion in 13 h. The reaction solution was added to 25 mL of 2 N H_3PO_4 forming a light brown solid precipitate, which was filtered, washed with water and dried to give (±)-**5** which was consistent with data reported in this paper (417 mg, 40% w/w by NMR, 47% yield).

*(S)-6-Chloro-8-fluoro-7-(2-fluoro-6-methoxyphenyl)-3-nitroquinolin-4(1H)-one (**20**).* A solution of (*S*)-1-(3-amino-6-chloro-2,2′-difluoro-6′-methoxy-[1,1′-biphenyl]-4-yl)-2-nitroethan-1-one (**5**) (26.0 g, 0.073 mol, 1.0 equiv) in THF (200 mL) was warmed to 40 °C with a stirrer hot plate. To this solution, DMF−DMA (13.0 g, 0.110 mol, 1.5 equiv) was added dropwise over 0.5 h. The reaction was stirred for 2 h at 40 °C. Ethyl acetate (500 mL), acetic acid (40.0 g, 0.73 mol, 10 equiv) and water (400 mL) were added to reaction. The aqueous layer was removed and organic layer washed with $NaHCO_3$ (8% in water) twice then saturated NaCl. The organic layer was concentrated under a vacuum then ethyl acetate (150 mL) was added to the residue. The resulting mixture was stirred for 2 h at 10−15 °C to give a slurry which was filtered, washed with ethyl acetate (50 mL) and dried to give **20** as a white powder (20.0 g, 0.055 mol, 75%). $[\alpha]_D^{20}$ −18.1 (*c* 1.0, $CHCl_3$/MeOH, 99:1). ^1H NMR (500 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.19 (d, *J* = 1.4 Hz, 1H), 7.60 (dt, *J* = 7.0, 8.4 Hz, 1H), 7.14−7.08 (m, 1H), 7.04 (t, *J* = 8.5 Hz, 1H), 3.79 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 165.7 (d, *J* = 2.3 Hz), 159.5 (d, *J* = 245.2 Hz), 157.8 (d, *J* = 6.4 Hz), 150.1 (d, *J* = 254.3 Hz), 142.8, 132.47, 131.8, 131.2 (d, *J* = 2.7 Hz), 130.0, 126.9 (d, *J* = 14.5 Hz), 122.3 (d, *J* = 16.8 Hz), 121.2 (d, *J* = 3.6 Hz), 107.9, 107.8 (d, *J* = 18.2 Hz), 107.4 (d, *J* = 19.1 Hz), 56.4. $^{19}F\{^1H\}$ NMR (470 MHz, DMSO-d_6) δ −113.3 (d, *J* = 2.6 Hz), −122.2 (d, *J* = 2.6 Hz). HRMS (ESI) *m*/*z* calculated for $C_{16}H_{10}ClF_2N_2O_4$ $[M + H]^+$, 367.0297, found 367.0297.

*(S)-4,6-Dichloro-8-fluoro-7-(2-fluoro-6-methoxyphenyl)-3-nitroquinoline (**3**).* (*S*)-6-Chloro-8-fluoro-7-(2-fluoro-6-methoxyphenyl)-3-nitroquinolin-4(1H)-one (**20**) (20.0 g, 0.055 mol, 1 equiv) was dissolved in DMF (60 mL) and the solution cooled to 0−5 °C. $SOCl_2$ (19.5 g, 0.164 mol, 3.0 equiv) was added dropwise and the reaction stirred for 1 h at 15−20 °C. The reaction was poured cautiously onto ice water (260 mL). The resulting solid was filtered and washed with water (100 mL). The solid was purified by silica gel chromatography (SiO_2, CH_2Cl_2) and fractions containing the desired product were combined and concentrated to dryness to give **3** as a yellow solid (15.0 g, 0.039 mol, 71%, 99% e.p). ^1H NMR (500 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.37 (d, *J* = 1.7 Hz, 1H), 7.48 (dt, *J* = 6.7, 8.4 Hz, 1H), 6.95−6.80 (m, 2H), 3.80 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 160.0 (d, *J* = 248.0 Hz), 157.8 (d, *J* = 6.4 Hz), 155.5 (d, *J* = 263.4 Hz), 144.3 (d, *J* = 1.4 Hz), 142.0, 137.8 (d, *J* = 13.6 Hz), 137.5 (d, *J* = 4.1 Hz), 135.2 (d, *J* = 3.6 Hz), 131.5 (d, *J* = 10.4 Hz), 126.4 (d, *J* = 1.8 Hz), 123.1 (d, *J* = 18.6 Hz), 120.5 (d, *J* = 5.0 Hz), 108.2 (d, *J* = 19.1 Hz), 107.9 (d, *J* = 21.8 Hz), 106.5 (d, *J* = 3.2 Hz), 55.9. $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ −112.0 (d, *J* = 3.9 Hz), −115.0 (d, *J* = 3.5 Hz). HRMS (ESI) *m*/*z* calculated for $C_{16}H_9Cl_2F_2N_2O_3$ $[M + H]^+$, 384.9958, found 384.9963.

General Procedure for the Carbonylation of Aniline Halides. A 5 mL test tube was charged with aryl halide (0.40 mmol), $Pd(OAc)_2$ (4.5 mg, 0.04 mmol), XantPhos (11.6 mg, 0.04 mmol), phenol (75.0 mg, 0.80 mmol), triethylamine (0.17 mL, 1.2 mmol) and butyronitrile (4 mL). The test tube was fitted in a Biotage Endeavor catalyst screening system, closed off and flushed with nitrogen three times. The vial was heated to 86 °C after which the vial was pressurized with carbon monoxide (20 psig) and overhead stirring was initiated (900 rpm). The reactions were monitored by measuring the carbon monoxide uptake. After completion of the reaction the contents of the vial was extracted with ethyl acetate (25 mL), washed with sat. aq. NH_4Cl (25 mL), K_2CO_3 (10% w/w, 25 mL), brine (25 mL) and dried over $MgSO_4$. The volatiles were removed in vacuo and the crude was subjected to silica gel chromatography to furnish the title compound.

*Phenyl 2-amino-4-(trifluoromethyl)benzoate (**26a**).* 2-Bromo-5-(trifluoromethyl)aniline (96 mg, 0.40 mmol) was used in general procedure. The crude product was purified by silica gel chromatography (SiO_2, 3:1, *n*-heptane:dichloromethane) to yield **26a** as a yellow solid (103 mg, 0.37 mmol, 92%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.4 Hz, 1H), 7.40−7.49 (m, 2H), 7.29 (t, *J* = 7.54 3 Hz, 1H), 7.16−7.22 (m, 2H), 6.89−6.97 (m, 2H), 5.96 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.1, 150.9, 150.5, 136.2 (q, *J* = 32.4 Hz), 132.6, 129.6, 126.1, 121.8, 123.4 (q, *J* = 272.9 Hz), 113.6 (q, *J* = 4.0 Hz), 112.4 (q, *J* = 3.4 Hz), 112.0. ^{19}F {1H} NMR (376 MHz, $CDCl_3$) δ −63.99. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{11}F_3NO_2$ $[M + H]^+$, 282.0742, found 282.0740.

*Phenyl 2-amino-4-methoxybenzoate (**26b**).* 2-Iodo-5-methoxyaniline (97 mg, 0.40 mol) was used in general procedure. The crude product was purified by silica gel chromatography (SiO_2, 1:9, ethyl acetate:*n*-heptane) to yield **26b** as an orange solid (30 mg, 0.12 mmol,

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31%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 9.0 Hz, 1H), 7.47−7.38 (m, 2H), 7.30−7.22 (m, 1H), 7.20−7.13 (m, 2H), 6.31 (dd, J = 9.0, 2.5 Hz, 1H), 6.14 (d, J = 2.4 Hz, 1H), 5.83 (br. s, 2H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.2, 164.6, 153.1, 150.6, 133.2, 129.1, 125.3, 121.8, 104.7, 103.0, 99.0, 55.0. HRMS (ESI) m/z calculated for $C_{14}H_{14}NO_3$ $[M + H]^+$, 244.0974, found 244.0972.

*Phenyl 2-amino-4-methylbenzoate (**26c**).* 2-Iodo-5-methylaniline (91 mg, 0.40 mmol) was used in general procedure. The crude product purified by silica gel chromatography (SiO_2, 85:15, *n*-heptane/ethyl acetate) to yield **26c** as a yellow solid (62 mg, 0.28 mmol, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 8.2 Hz, 1H), 7.38−7.47 (m, 2H), 7.21−7.25 (m, 1H), 7.17 (dt, J = 8.9, 1.8 Hz, 2H), 6.49−6.57 (m, 2H), 5.70 (s, 2H), 2.30 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.5, 151.0, 150.6, 145.5, 131.2, 129.1, 125.4, 121.8, 117.7, 116.5, 107.0, 21.5. HRMS (ESI) m/z calculated for $C_{14}H_{14}NO_2$ $[M + H]^+$, 228.1019, found 228.1016.

*Phenyl 2-amino-6-methylbenzoate (**26d**).* 2-Iodo-3-methylaniline (93 mg, 0.40 mmol) was used in the general procedure. The crude product purified by silica gel chromatography (SiO_2, 85:15, *n*-heptane:ethyl acetate) to yield **26d** as a yellow solid (32 mg, 0.13 mmol, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.36 (m, 2H), 7.32−7.08 (m, 4H), 6.58 (t, J = 7.5 Hz, 2H), 5.31 (br s, 2H), 2.61 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.9, 150.5, 150.4, 140.8, 132.9, 129.6, 125.9, 121.9, 120.6, 115.3, 114.8, 112.3, 23.6. HRMS (ESI) m/z calculated for $C_{14}H_{14}NO_2$ $[M + H]^+$, 228.1025, found 228.1024.

*1-(2-Amino-5-chloro-3-fluorophenyl)-2-nitroethan-1-one (**29**).* To COware[23] chamber 2 was charged 2-bromo-4-chloro-6-fluoroaniline (450 mg, 2.0 mmol, 1.0 equiv), $Pd(OAc)_2$ (45 mg, 0.2 mmol, 0.1 equiv), XantPhos (115 mg, 0.02 mmol, 0.1 equiv) and phenol (0.37 g, 4.0 mmol, 2.0 equiv). The chamber was sealed with a screwcap fitted with a Teflon-lined septum and a pressure disk. To COware chamber 1 was charged 9-methyluorene-9-carbonyl chloride (1.23 g, 5.0 mmol, 2.5 equiv), $Pd(dba)_2$ (144 mg, 0.25 mmol, 0.13 equiv), $HBF_4.P(t\text{Bu})_3$ (145 mg, 0.50 mmol, 0.25 equiv). Chamber 1 was sealed with a screwcap fitted with a Teflon-lined septum and a pressure disk. The chambers were evacuated and backfilled with N_2 three times. Chamber 2 was than charged with butyronitrile (20 mL) and triethylamine (0.61 g, 6.0 mmol, 3 equiv). Chamber 1 was charged with anisole (20 mL) and triethylamine (1.21 g, 12.0 mmol, 6 equiv). The closed COware system was then placed in a heating block set to 86 °C and stirred for 16 h after which the system was purged with air. The contents of chamber 2 was diluted with ethyl acetate (50 mL) and washed with sat. aq. NH_4Cl (50 mL) and the organic layer dried over $MgSO_4$. The volatiles were removed in vacuo to give an oil which was purified by silica gel chromatography (SiO_2, 3:1, *n*-heptane:CH_2Cl_2) to yield phenyl 2-amino-5-chloro-3-fluorobenzoate as an orange solid (454 mg, 1.9 mmol, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (t, J = 1.9 Hz, 1H), 7.45 (m, 2H) 7.29 (m, 1H), 7.15−7.23 (m, 3H), 5.86 (br. s, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 165.4 (d, J = 3.9 Hz), 151.3 (d, J = 244.6 Hz), 139.5 (d, J = 14.0 Hz), 132.0, 129.7, 126.3, 126.2 (d, J = 3.7 Hz), 121.9, 120.0 (d, J = 21.6 Hz), 119.3 (d, J = 9.9 Hz), 111.9 (d, J = 5.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −132.91 (dd, J = 9.5; 1.1 Hz). HRMS (ESI) calculated for $C_{13}H_{10}ClFNO_2$ $[M + H]^+$, 266.0384, found 266.0379.

To a solution of *t*-BuOK (130 mg, 1.2 mmol, 3 equiv) in DMSO (2 mL) at 18 °C was added nitromethane (65 μL, 1.2 mmol) and the reaction left stirring for 30 min. A solution of phenyl 2-amino-5-chloro-3-fluoro-benzoate (93 mg, 0.40 mmol, 1.0 equiv) in DMSO (0.9 mL) was then added in dropwise to the reaction. The reaction mixture was stirred for 2 h, then quenched with aq. acetic acid (10% v/v, 2 mL). The resulting solid was filtered and washed with cold water (3 × 1 mL). The residue was dissolved in ethyl acetate and concentrated to yield **29** (80 mg,, 0.37 mmol, 92%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) 7.22 (dd, J = 10.6, 2.2 Hz, 1H), 7.13 (t, J = 1.8 Hz, 1H), 6.43 (s, 2H), 5.82 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) 185.3 (d, J = 2.7 Hz), 151.0 (d, J = 247.2 Hz), 139.4 (d, J = 13.8 Hz), 123.6 (d, J = 3.9 Hz), 120.5 (d, J = 2.7 Hz), 119.0 (d, J = 9.6 Hz), 115.5 (d, J = 4.7 Hz), 81.2. ^{19}F NMR (470 MHz, $CDCl_3$) −131.68 (d, J = 10.6 Hz). HRMS (ESI) calculated for $C_8H_7ClFN_2O_3$ $[M + H]^+$, 233.0129, found 233.0125.

*6-Chloro-8-fluoro-3-nitroquinolin-4(1H)-one (**30**).* To a solution of 1-(2-amino-5-chloro-3-fluorophenyl)-2-nitroethan-1-one (**29**) (93 mg, 0.40 mmol, 1.0 equiv) in THF (4 mL) was added DMF−DMA (0.2 mL, 1.2 mmol) and the resulting solution was stirred for 16 h at 45 °C. After this period the product was extracted with ethyl acetate (25 mL) and washed sequentially with aq. acetic acid (10% v/v, 25 mL), water (25 mL) and brine (25 mL) and then dried over $MgSO_4$. The volatiles were removed in vacuo and the resulting solid was slurry washed in methanol to furnish **30** as a white solid (87 mg, 80%). ^{1}H NMR (500 MHz, DMSO-d_6) 13.40 (s, 1H), 8.95 (s, 1H), 7.97−8.03 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) 165.6, 152.3 (d, J = 255.5 Hz), 142.3, 131.7, 130.5, 130.0 (d, J = 9.4 Hz), 126.9 (d, J = 13.7 Hz), 120.9 (d, J = 3.7 Hz), 119.0 (d, J = 20.8 Hz). ^{19}F NMR (470 MHz, DMSO-d_6) −124.4 (d, J = 9.7 Hz). HRMS (ESI) calculated for $C_9H_5ClFN_2O_3$ $[M + H]^+$, 242.9973, found 242.9975.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01736.

Compound characterization data, including ^{1}H, ^{13}C NMR spectra, SFC chiral analysis, computational data for compound **15**; Selected data for asymmetric Suzuki coupling of **16**, salt resolution of **16**, low temperature Gould−Jacobs cyclization, and additional nitrocarbonylation results and optimization (PDF)

FAIR data, including the primary NMR FID files, for compounds **2**.PTSA, **3**, **4**, **5**, **11**, **16**, **20**, **24**, **26a**, **26b**, **26c**, **26d**, **29**, and **30** (ZIP)

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Notes

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