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Investigating Scale-Up and Further Applications of DABAL-Me_3 Promoted Amide Synthesis

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Supporting Information

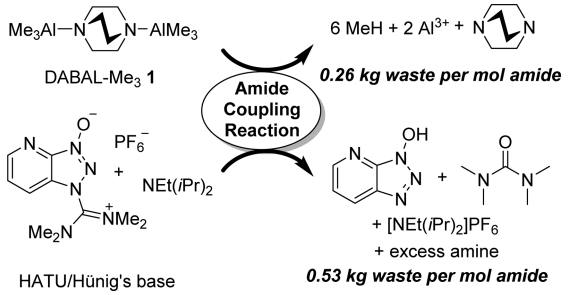
ABSTRACT: Methods for the batch scale up of DABAL-Me_3 promoted direct ester to amide synthesis have been demonstrated at 10−100 g scales using a *tert*-amide model compound. Procedures for 20 g scale couplings in standard laboratory glassware and up to 0.1 kg in industry-standard jacketed glass reactors in near quantitative yields are given. A derivative of the anticancer agent Imatinib (Gleevec) has been synthesized on a 26 g scale (98% yield, >98% purity) establishing DABAL-Me_3 as a potential alternative for the synthesis of amides in API scale preparations. Continuous flow methodology provides a method for larger scales (productivities of >50 g h^{-1}). In addition, nitriles were coupled to primary amines and hydrazines with DABAL-Me_3, resulting in the clean formation of free amidines (16 examples) and amidrazones.

INTRODUCTION

Amide formation is one of the most commonly used transformations in API synthesis today.[1] A large range of commercially available coupling reagents exist at present that can fulfill the needs of even the most demanding substrates. However, many of these are expensive and produce a considerable amounts of byproduct and environmental waste at the end of the reaction.[2] An ideal reagent that covers a broad coupling scope, is inexpensive, and produces little or no environmental burden is yet to be demonstrated, and the choice of "coupling reagent" is often a compromise of these factors. DABAL-Me_3 (bis(trimethylaluminum)-1,4-diazabicyclo[2.2.2]-octane)[3] **1** is a commercially available, air-stable adduct of $AlMe_3$ and DABCO (1,4-diazabicyclo[2.2.2]octane) which has been shown to quickly and cleanly facilitate the synthesis of a wide range of amides from esters and carboxylic acids.[4] DABAL-Me_3 **1** is a viable "mid-table" option in terms of cost ($9100 mol^{-1} vs HATU at $24 300 mol^{-1})[5] and can be a good compromise candidate in terms of environmental impact versus the latter (Scheme 1). Additionally, the aqueous waste stream from **1** provides only benign $Al^{3+}_{(aq)}$ and potentially recoverable DABCO.

Although DABAL-Me_3 **1** is a potentially attractive option for use in preclinical candidates at decagram and higher scales its use has only been demonstrated previously on ≤5 mmol couplings. Previous attempts at amide couplings promoted by **1** beyond 5 mmol have been met with inefficient reactivity and poor reaction rates.[6] Herein we report conditions for successful scale up of DABAL-Me_3 **1** promoted amide couplings utilizing batch and flow scale up methodologies applicable to reactions at, at least, 0.1 kg. Additionally, we report an expansion of the coupling scope of **1**, by utilizing nitriles and primary amines a clean and efficient synthesis of amidines and amidrazones is realized.

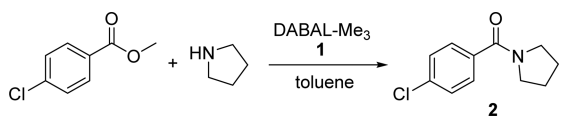
Scheme 1. DABAL-Me_3 1 vs HATU/Hünig's Base Waste Burdens at Molar Scales



RESULTS AND DISCUSSION

Previously it was found that formation of **2** (Scheme 2) was approximately 6 times slower at a 5 mmol vs a 1 mmol scale and that prolonged reflux (5 h) was required to overcome this.[6] One solution to this problem was use of microwave reactors (which reduced the conversion times to 8−16 min).[7] However, the use of microwave heating at large scales is expensive and requires specialist equipment. It was postulated that the small

Scheme 2. Model Amide Coupling System Used in Heating Effect Studies[a]



[a]A 1 M solution of ester and pyrrolidine was used.

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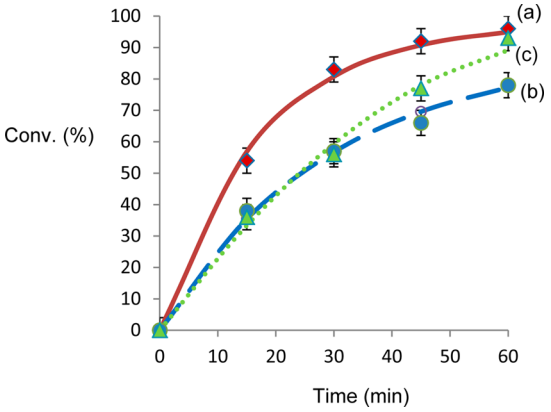
heaters used in the original preliminary reflux studies had insufficient power for effective heat management at larger scales. It was therefore logical to explore heating effects on reaction efficiency and whether "flash heating" protocols would be viable and safe.

To allow direct comparison with previous kinetic results,[6] a model coupling of methyl 4-chlorobenzoate and pyrrolidine to provide **2** was used. A premixed solution of the ester, amine, and DABAL-Me_3 **1** was prepared, at a 5 mmol scale, in a solution of toluene (1 M in ester) under argon. The reaction vessel was submerged into a large oil bath that had been thermally equilibrated to 120 °C (Chart 1a). Gratifyingly, as monitored by ^{1}H NMR spectroscopy, a 54% conversion was attained after just 15 min increasing to >95% after just 1 h (compared to 5 h in our original study).

Chart 1. Conversion over Time for Flash Heated Reaction at 5 mmol Scale, Conversion Determined by ^{1}H NMR Spectroscopy[a]

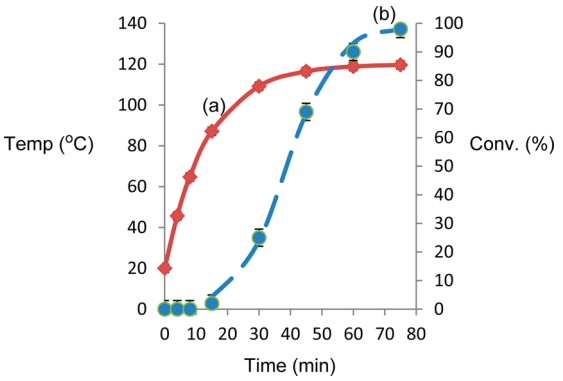


[a](a) direct heating of all pre-combined components to 120 °C (red ◆, solid line, rate constant 0.056(4) min^{-1}); (b) solid DABAL-Me_3 **1** added after ester and amine equilibrated at 120 °C (blue ●, dashed line, rate constant 0.034(4) min^{-1}); (c) toluene/pyridine solution of DABAL-Me_3 **1** (4.2 mL, 0.9 M) added over 20 min (green ▲, dotted line). Error bars on conversions are ±4%.

Heat transfer plays a crucial role in the efficiency of these reactions at a larger scale. For example, simply adding the DABAL-Me_3 **1** (1.03 g on a 5 mmol amide scale) directly into the refluxing mixture of ester/amine in toluene slows the reaction down by a factor of 1.6 (Chart 1b) due to the sudden increase in heat capacity in the system. Adding DABAL-Me_3 **1** as a solution in 3:1 toluene:pyridine[8] over a period of 20 min (Chart 1c) led to recovery of the reaction rate as the slower addition allows faster thermal re-equilibration of the reaction vessel. Run 1c showed complex kinetics and a best fit was attained to half order kinetics (k = 0.26(4) min^{-1} $\%^{1/2}$). This may be due to the fact that the reaction volume is changing with time and that, initially, the quantity of DABAL-Me_3 **1** in the reaction mixture is being restricted. Ultimately, all three methods (Chart 1a-c) provide similar yields after 2 h of reaction time, so there is a degree of flexibility in how this reaction can be implemented (or processed). The origin of the poor kinetic performance ($k \sim 0.005$ min^{-1}), of our preliminary study[6] was revealed to be inefficient heating and thermal lagging of overly large reactors on microscale heaters.

To further examine the effects of heating, a temperature-programmed reaction was run which was heated from 20 to 120 °C over 80 min (Chart 2). The conversion follows S-curve behavior, and it can be estimated that the onset of efficient

Chart 2. Temperature-Programmed Conversion to 2 (5 mmol, Pre-Mixed Reagents Identical Concentrations to Chart 1a)[a]



[a](a) Temperature (°C) vs time, error bars ±2, (red ◆, solid line); (b) conversion (error bars ±4%), the fit to $100/(1 + \exp\{k(t - t_{1/2})\}$, apparent k = 0.13(4) min^{-1} $t_{1/2}$ = 39 min, R^2 0.99 (blue ●, dashed line).

amide formation is ~90 °C and that the reaction only operates efficiently above this temperature. Complete conversion takes place in just over an hour after it reaches temperatures above 90 °C. Inspection of the individual rate constants for the temperature range 80−120 °C supports this assertion (see Supporting Information). Reassuringly none of the kinetic data collected provided indications of autocatalysis suggesting the behavior of large scale reactions would be entirely predictable. Using the simplest and most efficient method (premixing of all components), couplings to prepare **2** at 50 mmol (ca. 10 g) and 100 mmol (ca. 20 g) were successfully implemented. The methodology transferred particularly well to these larger scale reactions, providing >99% conversion (99% isolated yields) after just 1 h. The crude product was isolated in high analytical purity (>98% purity by ^{1}H NMR spectroscopy, at best traces of addition−elimination compounds resulting from pyrrolidine attack on the Ar−Cl of **2** could be detected). Longer heating of these reactions was not necessary and preliminary studies indicated this was deleterious to the overall isolated yields.

To validate use of DABAL-Me_3 **1** in a preclinical and kilo lab environment, the synthesis of **2** was additionally carried out in a jacketed reactor at a 0.5 mole (ca. 0.1 kg) scale in the development lab at Aesica Pharmaceuticals Ltd. The coupling was performed in a 5 L jacketed glass reactor (under nitrogen) connected to a Huber Unistat 340 oil circulator which was heated in steps of 40 °C at a time (up to 120 °C), to allow the reaction mixture temperature to equilibrate with the heating jacket. After 1 h at reflux the starting material was completely consumed, and the jacket was cooled down (temperature reduction in 40 °C steps to avoid thermal stress on the reactor). Once the reaction mixture was at 15 °C, the jacket was set up for the quench, which was carried out via the slow addition of 1 M HCl. In the smaller (<10 g) laboratory set-ups this is typically carried out relatively quickly (ca. 10 min) by cooling the reaction in an ice bath and adding HCl dropwise until any effervescence subsided. On the larger scale, the quench took significantly longer (ca. 100 min). This was primarily due to two reasons: (a) the jacketed reactor could only be cooled to

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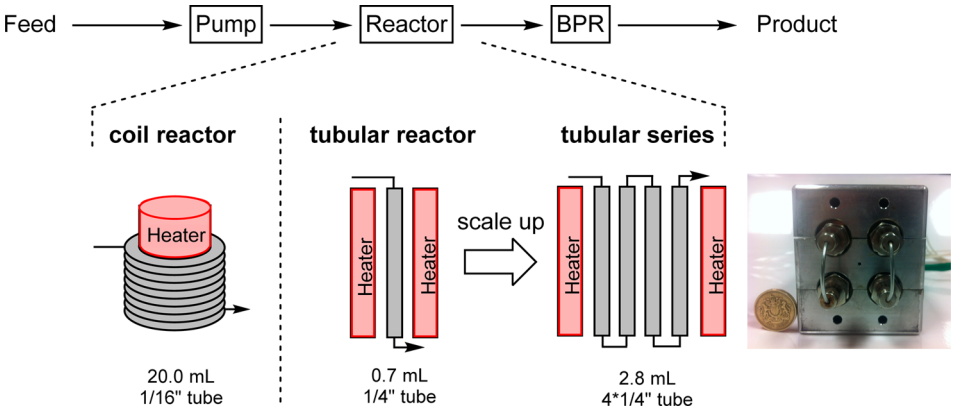
Scheme 3. Graphic Comparing the Commercial Coil Reactor to Simple Tubular Reactors



15 °C; (b) the internal reaction temperature was kept within 40 °C of the jacket temperature to prevent thermal shock on the glass reactor. The initial addition of aqueous HCl (5 mL, 1 M) quench led to a rapid increase in internal temperature, close to this 40 °C temperature difference limit, and therefore, the addition was stopped to allow the reactor contents to cool down. Incremental quenching was repeated over the course of the next 80 min until a total of 40 mL of 1 M HCl was added. After this point the exothermic events, caused by hydrolysis of the reactive residual Al-Me bonds present ceased. Once the quench was complete, the amide was isolated in the typical way, yielding (after trituration with pentane) the model amide **2** in 95% yield (100 g). While the chemistry is robust and reliable at this 0.1 kg batch scale, the highly exothermic quench is problematic. One solution to this issue is to use an off-line quench whereby the reaction mixture is pumped into the hydrolysis solution allowing for a safe and controllable process at scale. With this in mind, a flow process was considered advantageous whereby the reaction mixture would be flowed through a heated and pressurized reactor tube and subsequently quenched in a continuous manner.

■ CONTINUOUS FLOW PROCESSING

Given that DABAL-Me_3 **1** promoted amide couplings work cleanly in batch, are most effective above 90 °C, and are promoted by rapid heat transfer, it was hypothesized that heated pressurized continuous flow systems would be viable. An initial "proof of concept" was attained in a commercially available FlowSyn unit at ca. 5 g scales using sample loops loaded with the mixture needed for **2** (Scheme 2) into the FlowSyn reactor.[9] Sample loops were used to avoid potential aluminum oxide/hydroxide formation in the pumping system. However, such fixed volume sample loops rather limit operations to below 10 g. For larger scale work a simple continuous flow system was designed to specifically allow vacuum drying of the reactor, operations under argon, and "through pump" delivery of DABAL-Me_3 **1** as a THF solution (Scheme 3).

The design of the continuous flow rig (see Supporting Information) consisted of a tubular reactor packed with glass beads and heated by means of an external heating block. The entire rig was fitted with an in-line hi-vacuum and an argon inlet to allow the system to be evacuated before running the experiment. We elected to use a plunger HPLC pump (Jasco PU-2080i Plus) equipped with inert working parts (graphite, PTFE, and PEEK), which could easily be removed and dried in a glovebox prior to use to avoid/minimize pump blockage through any hydrolysis of **1**. It is worth noting, in the interest of replicating the system, that the rig consists of simple, readily available, commercial equipment and was constructed without any specialist knowledge within 2 weeks. While the reactors and heating cartridges were built in-house, commercially available equivalents are also readily available.

With the rig ready, the same test reaction (Scheme 2) was carried out. To eliminate moisture contamination several procedures were carried out before a reaction was run: (a) the rig was heated to 150 °C and put under hi-vacuum overnight, then backfilled with argon before use; (b) the BPR (back pressure regulator) set up was purged with argon as this is not under vacuum; (c) the pump head, inlet pipe, and priming valve of the pump were dried under vacuum in a glovebox antechamber prior to use (once refitted, they were purged with argon); (d) the crude reaction mixture (ester + amine + **1**) was Schlenk filtered through a pad of oven-baked Celite to remove any insoluble aluminum oxides that could cause any blockages (Figure 1).

Figure 1. Reaction mixture before (left) and after (right) Schlenk filtration.

Table 1 outlines the key points in optimizing the system for conversion of the ester to amide **2**. An initial unpressurized run (Table 1, entry 1) was carried out at 0.25 M and 130 °C provided erratic flow. Pressurizing the system (Table 1, entry 2) did little to the conversion but allowed for a more consistent flow of product from the outlet pipe. Without back pressure the flow of material leaving the rig was very sporadic (caused, we believe, by vaporized THF). An increase in reagent concentrations gave a positive result (Table 1, entry 3); however, higher pressures had little to no effect on conversion at 130 °C (Table 1, entries 4–5). It was confirmed that

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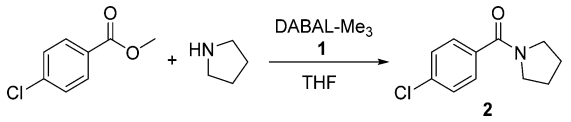
Table 1. Optimisation of Conditions in Larger Scale Continuous Flow[a]



entry	conc. (M)	flow rate (mL min^{-1})	temp. (°C)	pressure (bar)	conversion (%)
1	0.25	1	130	n/a	7
2	0.25	1	130	50	10
3	0.5	1	130	50	25
4	0.5	1	130	75	22
5	0.5	1	130	100	20
6	0.5	1	150	100	40
7	0.5	1	170	100	97
8	0.5	1	170	50	99
9	0.5	1	190	50	98
10	0.5	2	190	50	100
11	0.5	4	190	50	100
12	0.75	8	190	50	86

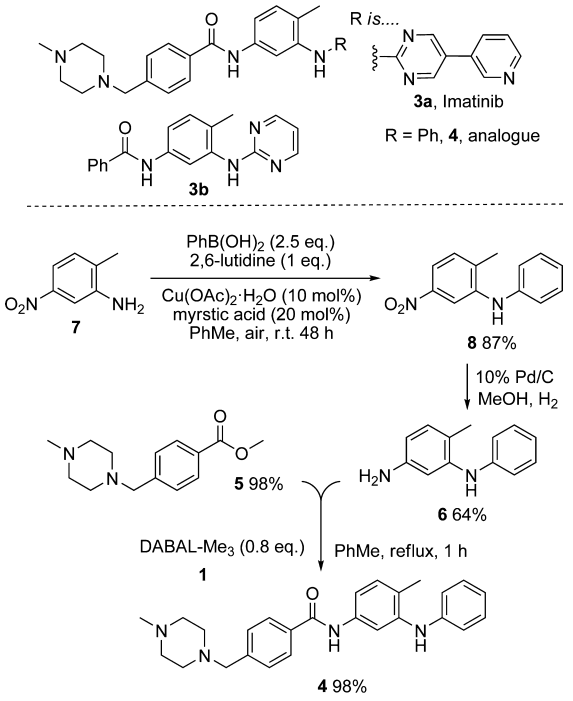
[a]Typical reaction mixtures: methyl 4-chlorobenzoate (1 equiv), pyrrolidine (1.2 equiv), and DABAL-Me$_3$ **1** (0.8 equiv), The amount of THF was adjusted to the deliver the appropriate concentration. Conversion was determined by ^{1}H NMR spectroscopy. Note: As we established that efficient heat transfer is vital for this chemistry, we opted for simply adjusting each of the parameters of the reaction rather than employing a lengthy DoE (Design of Experiments) protocol.

reaction temperature is the most important variable and at 170 °C the conversion was again found to be excellent (Table 1, entry 7). At 190 °C the system could handle flow rates of up to 4 mL min^{-1}, and it was not until the flow rate was at 8 mL min^{-1} that the conversion began to drop again. To improve space-time yields, we looked at maintaining an excellent heat-mass transfer with higher volumes and therefore comparable residence time. A multiple-pass reactor with a small footprint was designed instead of a larger and longer single tube reactor. For a large-scale demonstration, four reactors in series were assembled (Scheme 3, also see Supporting Information), and the starting materials were pumped through at 10 mL min^{-1} for 65 min. After brief extraction model amide **2** was isolated in 92% (54.8 g). In the academic laboratory, we have limited ourselves to a ca. 50 g scale demonstration; however, this productivity (>50 g h^{-1}) could easily provide >1 kg per day if needed.

After the success with the model system, the feasibility of DABAL-Me$_3$ **1** promoted amide couplings with a more functionalized API model were investigated. Imatinib **3a**, a classic potent anticancer agent,[10] was considered as a candidate. However, in the interest of safety in the academic lab, it was decided to moderate its biological activity by synthesizing an analogue **4** of Imatinib to minimize exposure risks to this highly bioactive compound (Scheme 4). Tolerance of the 2-amino-pyrimidine function was demonstrated in an independent trial coupling providing **3b** in >90%. DABAL-Me$_3$ **1** couplings are already known to tolerate the pyridine unit in **3a**.[6]

Ester fragment **5** is available through literature procedures in 98% yield.[11] Amine **6** was prepared in two steps from low cost 2-methyl-5-nitroaniline **7**. Initial Chan-Lam style coupling,[12] with phenylboronic acid, provided **8**. The coupling was carried out in four 3.8 g parallel reactions to ensure oxygen uptake was maximized. Typically reactions of these begin to suffer on larger

Scheme 4. Imatinib 3a and Synthesis of Analogue 4



scales due to poor dioxygen mass transfer.[13] Additionally, it was found that 10 mol % of Cu(OAc)$_2$·H$_2$O and an extra equivalent of PhB(OH)$_2$ were necessary drive the reaction to completion (24 h). Nitroaniline **8** was isolated in a combined yield of 87% and subsequently reduced using Pd/C and H$_2$ yielding the desired amine fragment **6** in 64% yield.[14] The ester **5** and amine **6** fragments were coupled successfully using the previous large-scale DABAL-Me$_3$ **1** batch conditions. After just 1 h at reflux complete consumption of the starting material was observed. The Imatinib analogue **4** was isolated in 98% (26.5 g) yield as an analytically pure solid. This could be converted to the corresponding salt **4**·3HCl allowing further purification by recrystallization from EtOH which provided analytically pure material (>97% by HPLC) with good recovery.

■ COUPLING OF NITRILES AND AMINES

The amidine motif is present in a range of biologically active compounds and features in a variety of patents.[15] The scope of DABAL-Me$_3$ **1** couplings has typically been limited to esters/carboxylic/amines combinations[4,6,7] and some limited use in heterocycle formation.[6,16] Use of nitriles with **1** is expected to allow easy access to amidines and related compounds as related AlMe$_3$ transformations are known.[17,24a] Brief optimization of conditions (Table 2) focused on our previous microwave reactions (used for amide formation).[7] Using benzonitrile and benzylamine as an initial trial yielded promising results (Table 2, entry 1). Increasing the reaction time to 15 min (Table 2, entry 2) typically led to poorer chemoselectivity as observed in the ^{1}H NMR spectra of the crude products. This was also observed when using 1 eq. of DABAL-Me$_3$ **1** (Table 2, entry 3). Increasing to 1.1 equiv of benzonitrile (Table 2, entry 4) ensured all of the amine is reacted as typically the amine and amidine are difficult to separate via chromatography.[18] It was found that 12 min was optimum to obtain a full clean conversion (Table 2, entry 5) with the desired amidine obtained cleanly in 98% yield. Any unreacted nitrile can then be

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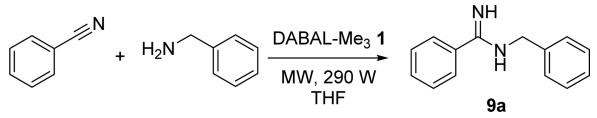
Table 2. Optimisation of Nitrile and Amine Coupling[a]



9a

entry	PhCN (equiv)	DABAL-Me_3 **1** (equiv)	temp. (°C)	time (min)	conversion (%)[b]
1	1	0.8	130	8	60
2	1	0.8	130	15	98[c]
3	1	1	130	8	83[c]
4	1.1	0.8	130	8	72
5	1.1	0.8	130	12	99[d]

[a]Typical reaction mixture: PhCN (1 mmol), benzylamine (1 equiv), and DABAL-Me_3 **1** (0.8 equiv) in THF (1 mL). [b]Conversion was determined by ^{1}H NMR spectroscopy. [c]Significant decomposition evident. [d]Isolated yield of 98%.

removed in work up by back extraction of the amidine in an acidic aqueous layer (2 M HCl), separating off the organic phase containing the nitrile, followed by liberation of the amidine with 2 M NaOH and extraction with dichloromethane. Further washing with water allowed removal of leftover DABCO from the reaction, leaving only the desired amidine. This workup procedure is attractive as chromatographic separations of amidines frequently prove challenging. With optimal conditions in hand, a study in to the substrate scope was carried out (Scheme 5).

The reaction tolerated a range of alkyl and aryl nitriles, giving the amidines in moderate to excellent yields (**9a**–**9f**). The amine scope also covers a wide range of primary amines in decent yields (**10a**–**10j**). For the coupling of aniline (**10b**), toluene was used as the solvent as a significant amount of unwanted byproducts **11** and **12** were isolated due to the ring opening of THF promoted by aluminum Lewis acids (Scheme 6a).[19] Secondary amines (**13a**–**b**), a pyridine containing amine (**13c**), and several nitriles (**14a**–**d**) were not tolerated under the conditions used, leading instead to complex mixtures (Scheme 6b). Hydrazines were also coupled to nitriles, under somewhat milder conditions. Simple heating in toluene to 80 °C under inert atmospheres yielded the desired free amidrazones (**10i** and **10j**), which were isolated after the applying the same work up as described for the amidine substrates.

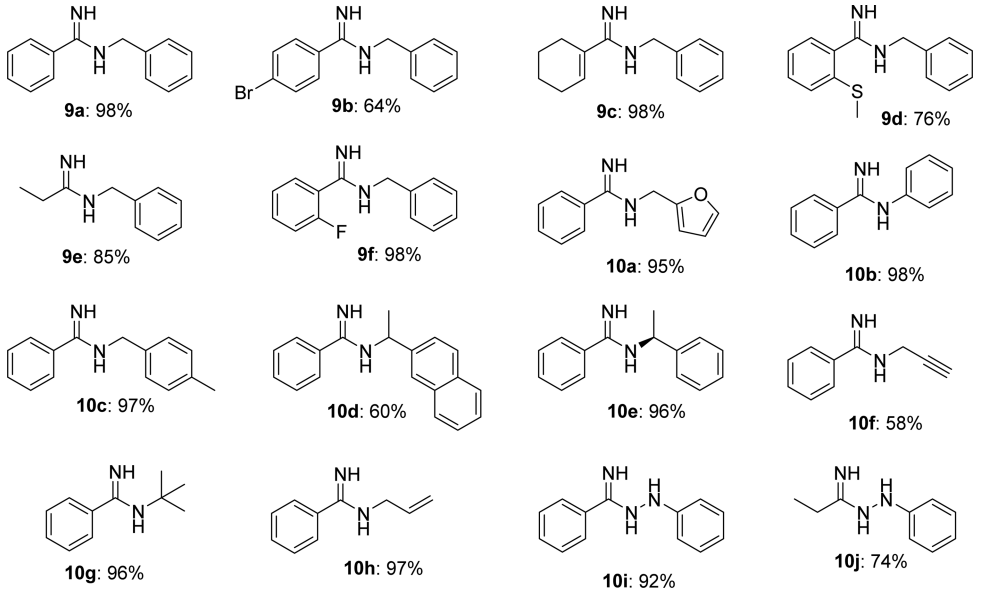
CONCLUSION

All previous investigations of the use of DABAL-Me_3 **1** in amide C–N formations have focused on small scale reactions (all <5 g and typically ~1 mmol). The applicability of these transformations, at least to preclinical applications at 10 g to 0.1 kg has been demonstrated in both batch and flow operations. All of these reactions are well-behaved, and synthesis at higher scales would appear readily viable. Simple methodology for the synthesis of amidines (and amidrazones) has also been introduced. Previously, such species have been problematic to synthesize easily due to unwanted dimerization and other side reactions.[20]

EXPERIMENTAL SECTION

General Experimental Section. The experimental set up has been described before.[21] Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Toluene was distilled from CaH_2 under argon prior to use. All liquid amines and nitriles were dried over activated 3 Å MS prior to use. Microwave reactions were conducted in a CEM Discover benchtop reactor. For batch optimization reactions Schlenk tubes of the following diameters were used: 38 mm external diameter × 220 mm length, internal volume = 130 mL. NMR spectra (^{1}H, ^{13}C) were recorded with Bruker AV400, DPX400, AV(III)400, AV(III)500, and JEOL EX 270 spectrometers at ambient temperatures unless otherwise specified. Chemical shift values are reported in ppm, and solvent resonances were used as internal standards ($CHCl_3$: δ = 7.26 ppm for ^{1}H, δ = 77.16 ppm for ^{13}C; DMSO-d_6: δ = 2.50 ppm for ^{1}H, δ = 39.52 ppm for ^{13}C; MeOD: δ = 3.31 ppm for ^{1}H, δ = 49.00 ppm). Coupling constants (J) are quoted in Hertz. Proton NMR multiplicities and connectivities were assigned by using COSY experiments. Carbon NMR multiplicities and connectivities were assigned by using DEPT, HMQC, and HMBC experi-

Scheme 5. Scope of Amidines and Amidrazones



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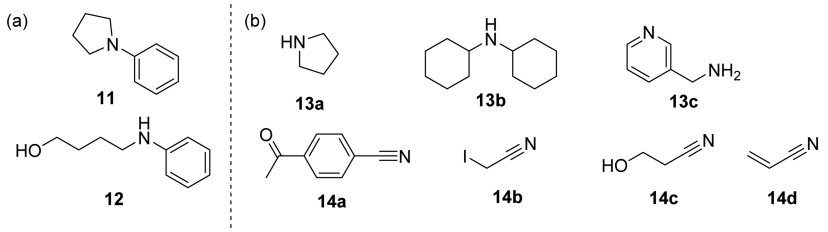
Scheme 6. (a) Byproducts from the Reaction with Aniline in THF and (b) Incompatible Amines and Nitriles



ments. The same instruments were used for ^{19}F NMR experiments. IR spectra were recorded as a thin film with a Perkin−Elmer 1600 FTIR spectrometer. HRMS were recorded with a Bruker Apex IV FT-ICRMS instrument (ESI). Melting points were determined with a Stuart Scientific SMP3 melting point apparatus. Ester **5** was prepared as reported in the literature.[11] DABAL-Me_3 **1** was prepared as reported in literature.[3c]

Medium Scale (20 g) DABAL-Me_3 1 Coupling in Batch. To a flame-dried Schlenk tube (60 mm external diameter × 300 mm length, internal volume = 550 mL) was added DABAL-Me_3 **1** (20.51 g, 80 mmol), methyl 4-chlorobenzoate (17.01 g, 100 mmol), and pyrrolidine (8.21 mL, 100 mmol). Toluene (100 mL) was added, and the flask was submerged in to a preheated oil bath (120 °C) with stirring. After 10 s effervescence began, usually subsiding after 30 min. After 1 h the reaction mixture was checked by TLC to ensure complete consumption of the starting materials. The flask was then removed from the oil bath, cooled to r.t., and then to 0 °C in an ice bath. The quenching solution (2 M aqueous HCl) was added slowly with care to the stirring mixture (a large amount of methane is given off). The quenched mixture was extracted three times with dichloromethane, the combined organic layers are dried over $MgSO_4$ and the solvent removed in vacuo. Amide **2** was isolated as a pale yellow solid (20.8 g, 99%) that could be recrystallized from *n*-hexane to give glinting colorless flakes in excellent recovery.

Large Scale (100 g) DABAL-Me_3 1 Coupling in Batch. The reaction was carried out in a glass jacketed reaction vessel (5 L) connected to an oil circulation unit (Huber Unistat 340 and Huber oil). The jacketed vessel was fitted with an overhead stirrer (PTFE 11 cm paddle), a reflux condenser, and a nitrogen bubbler. The bottom runoff (B.R.O.) outlet was connected to a 3-neck 2 L RBF that has an exhaust into the fume hood. The vessel was dried and purged with nitrogen through a top joint (10 min) and through the B.R.O. (10 min). Methyl 4-chlorobenzoate (85.06 g, 0.5 mol) and DABAL-Me_3 **1** (102.54 g, 0.4 mol) were added to the reactor via a funnel. Toluene (500 mL, anhydrous grade, max water. 0.00185% by Karl Fischer titration) was added washing down any residual solid into the vessel. Stirring was started, and pyrrolidine (41.1 mL, 0.5 mol) was added in one portion. The oil circulator was heated to 60 °C and left to equilibrate the jacket temperature with the internal temperature for 10 min. The temperature was further increased to 100 °C and left for a further 10 min to equilibrate. Finally, the oil circulation temperature was increased to 120 °C, and after 5 min at this temperature white foaming appeared on the surface of the reaction mixture. The reaction was left for 70 min and was checked for consumption of the starting ester by TLC (after 1 h at 120 °C). Once confirmed the reaction was complete, the oil circulation bath was set to cool down in stages, initially 80 °C then 40 °C and finally 15 °C, allowing 5 min between each adjustment to equilibrate the jacket temperature with the reaction mixture. The reaction vessel was fitted with an internal temperature probe and a graduated addition funnel that contained aqueous HCl (1 M). One of the stoppers was removed to allow surplus methane generated to escape. Quenching: 1 M hydrochloric acid was added dropwise and the internal temperature monitored for temperature rises (**CARE! The addition of HCl is initially very exothermicand therefore must be carried out with caution and temperature monitoring**). The external jacket and internal reaction temperatures were always maintained within 40 °C of each other to avoid any excessive stress on reactor glassware that could cause its failure. After the addition of ca. 5 mL of 1 M HCl dropwise the temperature increased from 15 to 37 °C in 5 min, the temperature rise was coupled with excessive gas evolution. Quench addition was stopped until this subsided and the temperature returned to 15 °C. The HCl addition was recommenced dropwise until the temperature began to increase more than 3 °C per min, whereupon the addition was then stopped and the mixture stirred until the exothermic event subsided and the internal temperature was back to ca. 15 °C. After repeating this procedure over the next 80 min (40 mL, 1 M aqueous HCl added), the exothermic behavior ceased, and the internal temperature did not increase again when further HCl was added. The rest of the HCl was then added more quickly but still with caution and temperature monitoring, until a total of 1.5 L had been added. The stirring was stopped and the layers separated out. The layers were separated out through the B.R.O. in to two separate three-necked 2 L RBFs. The aqueous layer was run back into the reaction vessel and extracted with CH_2Cl_2 (200 mL); the organic layer was then combined with the previous organic fraction and this procedure repeated another two times. The combined organic fractions were dried over $MgSO_4$, which was then filtered off. The solvent was removed on a rotary evaporator, to yield a viscous yellow/orange oil which crystallized upon standing. The solid was washed with pentane (40 mL), filtered off, and dried under vacuum for 2 h. Amide **2** was isolated as a yellow solid (100 g, 95%) in high purity.

*(4-Chlorophenyl)(pyrrolidin-1-yl)methanone (**2**).*[22] Pale yellow crystalline solid: mp 76−78 °C (lit. mp 74−76 °C[22]); ^1H NMR (270 MHz; DMSO-d_6, 90 °C) δ 1.74−1.91 (m, 4H), 3.35 (br t, J = 10.0 Hz, 2H), 3.45 (br t, J = 10.0 Hz, 2H), 7.46−7.56 (m, 4H); ^{13}C NMR (68 MHz, DMSO-d_6, 90 °C) δ 23.9 (CH_2), 26.0 (CH_2), 46.0 (CH_2), 48.8 (CH_2), 128.3 (CH × 2), 129.1 (CH × 2), 134.4 (C), 135.9 (C), 167.1 (CO); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{12}ClNONa$ 232.0500; found 232.0483 (^{35}Cl).

Synthesis of API Analogue. *2-Methyl-5-nitro-N-phenylaniline (**8**).*[23] To a 1 L round-bottom flask containing a large stirrer bar was added $Cu(OAc)_2 \cdot H_2O$ (0.5 g, 10 mol %),

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myristic acid (1.15 g, 20 mol %), and $PhB(OH)_2$ (4.57 g, 37.5 mmol), solids were washed down with toluene (25 mL). The mixture was then stirred, and 2,6-lutidine (2.93 mL, 25 mmol) was added followed by 2-methyl-5-nitroaniline **7** (3.8 g, 25 mmol) and another 25 mL of toluene. The mixture was stirred for 24 h while open to air, during which time it turned green. A second equivalent of $PhB(OH)_2$ (3.05 g, 25 mmol) was added, and the mixture stirred for a further 24 h. Neat EtOAc (100 mL) was added to the flask and the mixture filtered through a pad of Celite. The filtrate was then washed with aqueous 1 M HCl (2 × 75 mL), the organic layer dried over $MgSO_4$, and the solvent removed in vacuo. The resulting solid was stirred with activated charcoal in diethyl ether for 1 h, filtered through a pad of Celite, and the solvent removed in vacuo to yield the biaryl amine **8** as an orange solid which was used directly without further purification. This experiment was run as four parallel reactions as oxygen uptake was found to be rate-limiting. The combined yield of amine **8** obtained from the 4 runs was 19.96 g, 87%. For **8**: mp 91−93 °C (lit. mp 87−89 °C[23]); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.35 (s, 3H), 7.06−7.11 (m, 3H), 7.29 (br d, J = 8.0 Hz, 1H), 7.34−7.38 (m, 2H), 7.69 (dd, J = 8.0, 2.3 Hz, 1H), 8.01 (d, J = 2.3 Hz, 1H), NH signals not observed due to exchange; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (CH_3), 109.9 (CH), 115.3 (CH), 120.1 (CH × 2), 123.2 (CH), 129.9 (CH × 2), 131.3 (CH), 133.1 (C), 141.6 (C), 143.2 (C), 147.6 (C); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{12}N_2O_2Na$ 251.0791; Found 251.0781.

*6-Methyl-N-phenylbenzene-1,3-diamine (**6**).*[23] Solid 2-methyl-5-nitro-*N*-phenylaniline **8** (9.33 g, 41 mmol) was placed in a 1 L flame-dried Schlenk RBF; a stirrer bar was added followed by methanol (400 mL). Solid Pd/C (10%, 0.435 g) was added and the reaction vessel transferred to a hydrogenation frame. The frame and flask were evacuated and backfilled with hydrogen 3 times; on the third time a reservoirs was filled with hydrogen and the system sealed. Hydrogen uptake was monitored by displacement of the hydrogen in the reservoir by water. Uptake ceased after ca. 2.0−2.1 L of hydrogen indicating the reaction was complete. The system was evacuated and backfilled with air. The mixture was filtered through a pad of Celite and the solvent removed in vacuo. The resultant oily solid was dissolved in aqueous 5 M HCl and then washed with dichloromethane, the aqueous layer was then neutralized with aqueous 2 M NaOH and extracted three times with dichloromethane. The combined organic layers were dried over $MgSO_4$ and the solvent removed in vacuo. The desired aniline **6** was then isolated as a pale gray solid which was used without further purification (5.2 g, 64%). (The reaction was carried out three times to amass the desired quantity of material for route progression). For **6**: mp 91−93 °C (Lit. mp 92−93 °C[23]); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.19 (s, 3H), 6.32 (dd, J = 7.6, 2.2 Hz, 1H), 6.63 (d, J = 2.2 Hz, 1H), 6.94−6.99 (m, 1H), 7.00−7.05 (m, 3H), 7.28−7.33 (m, 2H), NH signals not observed due to exchange; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0 (CH_3), 105.9 (CH), 109.5 (CH), 117.9 (CH × 2), 118.6 (C), 120.5 (CH), 129.2 (CH × 2), 131.5 (CH), 142.0 (C), 143.7 (C), 144.0 (C); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{15}N_2$ 199.1230; Found 199.1213.

*N-(4-Methyl-3-(phenylamino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (**4**).* To a large flame-dried Schlenk tube (60 mm diameter × 300 mm length, internal volume = 550 mL) was added DABAL-Me_3 **1** (13.45 g, 52.5 mmol), amine **8** (13 g, 65.6 mmol), and ester **5** (16.3 g, 65.6 mmol). Toluene (100 mL) was added, and the flask was submerged in to a preheated oil bath (between 110 and 130 °C) with stirring. After 10 s effervescence began, usually subsiding after 30 min. After 1 h the reaction mixture was checked by TLC to ensure complete consumption of the starting materials. The flask was then removed from the oil bath, cooled to r.t., and then to 0 °C in an ice bath. Rochelle's salt was added slowly with care to the stirring mixture (**CARE! significant amounts of methane released**). The quenched mixture is then extracted three times with dichloromethane, the combined organic layers are dried over $MgSO_4$ and the solvent removed in vacuo. The title compound was isolated as a pale yellow solid (26.5 g, 98%). For **4**: mp 58−61 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.24 (s, 3H), 2.29 (s, 3H), 2.46 (br s, 8H), 3.55 (s, 2H), 5.43 (s, NH), 6.91−6.95 (m, 1H), 7.02 (br d, J = 8.0 Hz, 2H), 7.15−7.18 (m, 1H), 7.22−7.30 (m, 3H), 7.42 (br d, J = 8.0 Hz, 2H), 7.45 (br s, 1H), 7.69 (s, NH), 7.76−7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 19 °C) δ 15.6 (CH_3), 46.2 (CH_3), 53.3 (CH_2), 55.2 (CH_2), 62.7 (CH_2), 109.8 (CH), 113.6 (CH), 118.4 (CH), 121.2 (CH), 123.9 (C), 127.1 (CH), 129.5 (CH), 129.6 (CH), 131.4 (CH), 134.0 (C), 136.8 (C), 142.1 (C), 142.7 (C), 143.4 (C), 165.6 (CO); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{26}H_{31}N_4O$ 415.2492; Found 415.2506.

*N-(4-Methyl-3-(pyrimidin-2-ylamino)phenyl)benzamide (**3b**).* To a flame-dried microwave tube was added 6-methyl-N^1-(pyrimidin-2-yl)benzene-1,3-diamine (120 mg, 0.6 mmol), DABAL-Me_3 **1** (0.123 mg, 0.48 mmol) and methyl benzoate (76 μL, 0.6 mmol). THF (0.6 mL) was added, and the solution was heated in a microwave reactor for 8 min (130 °C, 290 W). The mixture was cooled to room temperature and quenched by dropwise addition of Rochelle's salt (2 mL). The mixture was then extracted three times with dichloromethane, dried over $MgSO_4$, and the solvent removed in vacuo. The title compound was isolated as a white solid (0.177 g, 97%). For **3b**: mp 198−202 °C; ^{1}H NMR (400 MHz, MeOD) δ 2.26 (s, 3H), 6.76 (t, J = 4.8 Hz, 1H), 7.24 (d, J = 8.3 Hz, 1H), 7.61−7.41 (m, 4H), 7.95−7.88 (m, 2H), 7.99 (t, J = 2.3 Hz, 1H), 8.36 (d, J = 4.8 Hz, 2H), NH signals not observed due to exchange; ^{13}C NMR (100 MHz, MeOD, 19 °C) δ 17.7 (CH_3), 113.0 (CH), 118.8 (CH), 119.1 (CH), 128.6 (CH × 2), 129.6 (CH × 2), 129.8 (C), 131.7 (CH), 132.8 (CH), 136.4 (C), 138.3 (C), 138.8 (C), 159.4 (CH × 2), 162.3 (C), 168.8 (C); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}N_4O$ 305.1397; Found 305.1403.

Large-Scale Flow Experiment. To a flame-dried 1 L Schlenk flask under argon was added methyl 4-chlorobenzoate (50 g, 294 mmol) and DABAL-Me_3 **1** (60.3 g, 235 mmol). The two solids were then dissolved in THF (590 mL) followed by the addition of pyrrolidine (29 mL, 353 mmol). The mixture was sonicated for 5 min to break up and aid final dissolution of DABAL-Me_3 **1**. The reaction mixture was then Schlenk filtered through baked Celite to remove any insoluble particles (Figure 1). The clear reaction mixture was collected in a second Schlenk flask and sealed with a suba seal and argon balloon.

The flow rig was dried overnight by applying a high vacuum to all parts (except the pump and BPR) and setting the reactor heating block to 150 °C. The pump inlet pipe, check valves, and pump heads were placed under vacuum (0.1 mbar) overnight. The reactor temperature was set to 190 °C. The vacuum was removed, and the system was flushed with argon through the BPR. The pump was reassembled and flushed with argon through the priming valve. The inlet valve was attached last and placed into the reaction flask but not in to the mixture. Argon from the reaction mixture vessel was drawn through the pump via the priming syringe, the pump was then primed with

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the reaction mixture. The argon flow to the system was shut off and the pressure set to 50 bar on the BPR. A 1.5 L conical flask containing aqueous HCl (2 M, 300 mL) was placed at the outlet pipe with an argon flow to keep the outlet pipe under argon. The pump was set to 10 mL min^{-1} and the reaction mixture flowed through the system. After 65 min the receiver flask was switched and the reactor washed through with anhydrous THF, until no more active reagent mixture remained in the reactor or pump. The collected amide product **2** was separated and the aqueous fraction extracted with dichloromethane (2 × 150 mL). The combined organic fractions were dried over $MgSO_4$, filtered and the solvent removed in vacuo. The solid was triturated with pentane to yield the model amide **2** was isolated as a yellow solid (54.8 g, 92% based on material collected after an initial 2 min equilibration).

General Procedure for the Coupling of Nitriles with Primary Amines. To a flame-dried 10 mL microwave tube under argon containing a small stirrer bar was added DABAL-Me_3 **1** (205 mg, 0.8 mmol), the desired nitrile (1 mmol), and the desired amine (1 mmol) followed by THF (1 mL). The flask was sealed with a microwave cap and placed in the microwave for 12 min (130 °C, 290 W). Once the microwave system had completed its cooling program to ambient temperature, the microwave tube was cooled further to 0 °C in an ice bath. The reaction was quenched with Rochelle's salt (5 mL) and then extracted three times with dichloromethane (5 mL). The organic fraction was washed three times with aqueous 2 M HCl (5 mL). The aqueous fractions are then combined and neutralized with aqueous 2 M NaOH (ca. 20 mL) and extracted three times with dichloromethane (10 mL). The combined organic fractions were washed with water, dried over $MgSO_4$ and the solvent removed in vacuo to yield the desired amidine without any need for further purification. In the case of coupling of benzonitrile to aniline (**10b**) the coupling was carried in toluene to prevent undesired side reactions (seen in THF).

*N-Benzylbenzimidamide (**9a**).*[24] Yellow oil (98%); ^{1}H NMR (500 MHz; DMSO-d_6) δ 4.35 (s, 2H), 6.59 (br s, 2 × NH), 7.19−7.22 (m, 1H), 7.30−7.33 (m, 2H), 7.37−7.43 (m, 5H), 7.83−7.84 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 49.3 (CH_2), 126.0 (CH), 126.5 (CH × 2), 127.5 (CH × 2), 127.9 (CH × 2), 128.0 (CH × 2), 129.3 (CH), 137.2 (C), 141.9 (C), 156.7 (C═N); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{15}N_2$ 211.1230; Found 211.1239.

*N-Benzyl-4-bromobenzimidamide (**9b**).*[25] Clear yellow oil (64%); ^{1}H NMR (400 MHz; MeOD) δ 4.44 (s, 2H), 7.21−7.27 (m, 1H), 7.30−7.35 (m, 2H), 7.36−7.40 (m, 2H), 7.50−7.66 (m, 4H), NH signals not apparent due to exchange; ^{13}C NMR (100 MHz, MeOD) δ 48.7 (CH_2), 125.3 (C), 127.9 (CH), 128.6 (CH × 2), 129.5 (CH × 2), 129.8 (CH × 2), 132.6 (CH × 2), 137.4 (C), 140.7 (C), 163.1 (C═N); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}BrN_2$ 289.0335; Found 289.0334 (^{79}Br).

*N-Benzylcyclohex-1-ene-1-carboximidamide (**9c**).* Orange oil (98%); ^{1}H NMR (400 MHz; MeOD) δ 1.60−1.74 (m, 4H), 2.14−2.19 (m, 2H), 2.26−2.30 (m, 2H), 4.37 (s, 2H), 6.32 (tt, J = 3.8, 1.7 Hz, 1H), 7.21−7.26 (m, 1H), 7.29−7.33 (m, 4H), NH signals not apparent due to exchange; ^{13}C NMR (100 MHz, MeOD) δ 22.8 (CH_2), 23.5 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 47.1 (CH_2), 128.0 (CH), 128.4 (CH × 2), 129.5 (CH × 2), 131.5 (CH), 135.2 (C), 140.1 (C), 166.6 (C═N); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{19}N_2$ 215.1543; Found 215.1546.

*N-Benzyl-2-(methylthio)benzimidamide (**9d**).* Clear pale yellow oil (76%); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.44 (s, 3H), 4.53 (br s, 2H), 7.12−7.16 (m, 1H), 7.22−7.34 (m, 7H), 7.39−7.41 (m, 1H), the NH signals at ca. δ_H 3.5 are very broadened; ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0 (CH_3), 46.6 (CH_2), 125.0 (CH), 126.0 (CH), 126.8 (CH), 127.1 (CH), 127.3 (CH), 127.8 (CH), 128.0 (CH), 128.6 (CH), 129.7 (CH), 136.2 (C), 139.0 (C), 143.4 (C), 163.4 (C═N), compound **9d** is conformationally locked; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{16}N_2SNa$ 279.0926; Found 279.0922.

*N-Benzylpropionimidamide (**9e**).*[26] Clear yellow oil (85%); ^{1}H NMR (400 MHz; MeOD) δ 1.20 (t, J = 7.6 Hz, 3H), 2.24 (q, J = 7.6 Hz, 2H), 4.28 (s, 2H), 5.13 (br s, NH × 2), 7.21−7.26 (m, 1H), 7.29−7.35 (m, 4H), NH signals apparent in concentrated samples; ^{13}C NMR (100 MHz, MeOD) δ 12.4 (CH_3), 30.4 (CH_2), 47.6 (CH_2), 127.9 (CH), 128.6 (CH × 2), 129.4 (CH × 2), 140.7 (C), 168.6 (C═N); HRMS (EI+) m/z: $[M]^+$ Calcd for $C_{10}H_{14}N_2$ 162.1157; Found 162.1155.

*N-Benzyl-2-fluorobenzimidamide (**9f**).* Clear yellow oil (98%); ^{1}H NMR (400 MHz; MeOD) δ 4.47 (s, 2H), 4.99 (br s, NH × 2), 7.15−7.26 (m, 3H), 7.31−7.35 (m, 2H), 7.39−7.47 (m, 3H), 7.51−7.55 (m, 1H), NH signals apparent in concentrated samples; ^{13}C NMR (100 MHz, MeOD) δ 48.0 (CH_2), 117.0 (d, $^2J_{C-F}$ = 22.0 Hz, CH), 125.4 (d, $^3J_{C-F}$ = 4.0 Hz, CH), 127.2 (d, $^2J_{C-F}$ = 24 Hz, C), 127.9 (CH), 128.6 (CH × 2), 129.4 (CH × 2), 130.8 (d, $^4J_{C-F}$ = 3.0 Hz, CH), 132.4 (d, $^3J_{C-F}$ = 8.0 Hz, CH), 140.5 (C), 159.8 (d, $^1J_{C-F}$ = 247.0 Hz, C), 160.7 (C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −155.61 (s); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}FN_2$ 229.1136; Found 229.1140. $[M + Na]^+$ Calcd for $C_{14}H_{13}FN_2Na$ 251.0955; Found 251.0967.

*N-(Furan-2-ylmethyl)benzimidamide (**10a**).* Orange oil (95%); ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.47 (s, 2H), 5.48 (br s, NH × 2), 6.24 (dd, J = 3.2, 0.8 Hz, 1H), 6.30 (dd, J = 3.2, 1.6 Hz, 1H), 7.31−7.39 (m, 4H), 7.52−7.54 (m, 2H), NH signals apparent in concentrated samples; ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.5 (CH_2), 107.0 (CH), 110.4 (CH), 126.2 (CH × 2), 128.6 (CH × 2), 130.1 (CH), 137.3 (C), 141.9 (CH), 152.5 (C), 162.8 (C═N); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{13}N_2O$ 201.1022; Found 201.1016.

*N-Phenylbenzimidamide (**10b**).*[24] pale yellow solid (98%); mp 115−118 °C (Lit. mp 117−118 °C[24a]); ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.92 (br s, NH × 2), 6.97−7.00 (m, 2H), 7.07 (tt, J = 7.6, 1.2 Hz, 1H), 7.33−7.37 (m, 2H), 7.42−7.51 (m, 3H), 7.84 (d, J = 6.8 Hz, 2H), NH signals apparent in concentrated samples; ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.9 (CH × 2), 123.3 (CH), 127.0 (CH × 2), 128.6 (CH × 2), 129.6 (CH × 2), 130.8 (CH), 135.5 (C), 149.0 (C), 155.6 (C═N); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{13}N_2$ 197.1073; Found 197.1082.

*N-(4-Methylbenzyl)benzimidamide (**10c**).*[25] pale green solid (97%); mp 65−68 °C (lit. mp. 65−66 °C[25]); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.35 (s, 3H), 4.51 (s, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.36−7.42 (m, 3H), 7.57−7.60 (m, 2H), NH signals not apparent due to exchange; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 (CH_3), 46.6 (CH_2), 126.1 (CH × 2), 127.8 (CH × 2), 128.7 (CH × 2), 129.4 (CH × 2), 130.1 (CH), 135.9 (C), 137.0 (C), 137.8 (C), 163.7 (C═N); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{17}N_2$ 225.1386; Found 225.1398.

*N-(1-(Naphthalen-2-yl)ethyl)benzimidamide (**10d**).* Yellow oil (60%); ^{1}H NMR (400 MHz; MeOD) δ 1.62 (d, J = 6.8 Hz,

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3H), 4.98 (q, J = 6.8 Hz, 1H), 5.02 (br s, NH × 2), 7.39−7.47 (m, 6H), 7.56 (dd, J = 8.4, 1.6 Hz, 1H), 7.67−7.69 (m 2H), 7.78−7.86 (m, 3H), NH signals apparent in concentrated samples; ^{13}C NMR (100 MHz, MeOD) δ 23.8 (CH_3), 53.7 (CH), 125.5 (CH), 125.7 (CH), 126.6 (CH), 127.1 (CH), 128.1 (CH × 2), 128.6 (CH), 128.8 (CH), 129.3 (CH), 129.5 (CH × 2), 131.4 (CH), 134.1 (C), 134.9 (C), 138.1 (C), 143.2 (C), 164.2 (C═N); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{19}N_2$ 275.1543; Found 275.1542.

*(S)-N-(1-Phenylethyl)benzimidamide (**10e**).* Yellow oil (96%): $[\alpha]_D^{21}$ +10.0 (c 1.0, $CHCl_3$) ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.44 (d, J = 8.0 Hz, 3H), 4.80−4.82 (m, 1H), 5.64 (vbr s, NH × 2), 7.11−7.30 (m, 8H), 7.45 (br d, J = 8.0 Hz, 2H), NH signals very exchanged broadened; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4 (CH_3), 51.9 (CH), 125.9 (CH × 2), 126.1 (CH × 2), 126.9 (CH), 128.5 (CH × 2), 128.6 (CH × 2), 130.0 (CH), 137.5 (C), 141.2 (C), 162.0 (C═N); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{17}N_2$ 225.1386; Found 225.1387.

*N-(Prop-2-yn-1-yl)benzimidamide (**10f**).*[27] Orange oil (58%); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.23 (t, J = 2.4 Hz, 1H), 4.07 (d, J = 2.4 Hz, 2H), 7.31−7.40 (m, 3H), 7.54−7.56 (m, 2H), NH signals not apparent due to exchange; ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.6 (CH_2), 71.3 (CH), 80.7 (C), 126.2 (CH × 2), 128.5 (CH × 2), 130.2 (CH), 136.7 (C), 161.9 (C═N); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{11}N_2$ 159.0917; Found 159.0918.

*N-(tert-Butyl)benzimidamide (**10g**).*[28] Yellow oil (96%); ^{1}H NMR (400 MHz; MeOD) δ 1.48 (s, 9H), 5.13 (s, NH × 2), 7.38−7.45 (m, 3H), 7.55−7.58 (m, 2H), NH signals apparent in concentrated samples; ^{13}C NMR (100 MHz, MeOD) δ 29.1 (CH_3 × 3), 52.0 (C), 127.6 (CH × 2), 129.5 (CH × 2), 130.9 (CH), 140.8 (C), 166.0 (C═N); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{16}N_2Na$ 199.1206; Found 199.1217.

*N-Allylbenzimidamide (**10h**).*[27] Yellow oil (97%); ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.06 (d, J = 5.2 Hz, 2H), 5.29 (dd, J = 10.4, 1.2 Hz, 1H), 5.40 (dd, J = 17.2, 1.6 Hz, 1H), 5.78 (br s, NH × 2) 6.11 (dtd, J = 17.2, 10.4, 5.2 Hz, 1H), 7.47−7.55 (m, 3H), 7.69−7.71 (d, J = 8.0 Hz, 2H), NH signals apparent in concentrated samples; ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.0 (CH_2), 115.4 (CH_2), 125.9 (CH × 2), 128.2 (CH × 2), 129.6 (CH), 134.7 (CH), 137.4 (C), 162.7 (C═N); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{13}N_2$ 161.1073; Found 161.1069.

General Procedure for the Coupling of Nitriles with Hydrazines. To a flame-dried Schlenk tube (10 mL) under argon was added DABAL-Me_3 **1** (0.8 mmol), benzonitrile (103 μL, 1 mmol), and the desired hydrazine (1 mmol). Toluene (1 mL) was added and the reaction flask submerged into an 80 °C oil bath for 20 min. The flask was removed and cooled to 0 °C in an ice bath. The reaction mixture was quenched with Rochelle's salt (ca. 5 mL) and extracted three times with dichloromethane (5 mL). The organic fraction is washed three times with aqueous 2 M HCl (5 mL); the aqueous fractions are then combined and neutralized with aqueous 2 M NaOH (ca. 20 mL) and extracted three times with dichloromethane (10 mL). The combined organic fractions were washed with water (20 mL), dried over $MgSO_4$, and the solvent removed in vacuo to yield the desired amidrazone **10** in good yield. Further purification was not necessary.

*N′-Phenylbenzimidohydrazide (**10i**).*[29] Orange oil (92%); ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.76 (br s, NH × 2), 5.99 (br s, NH), 6.89 (t, J = 7.8 Hz, 1H), 7.09 (d, J = 7.8 Hz, 2H), 7.27 (t, J = 7.8 Hz, 2H), 7.41−7.44 (m, 3H), 7.77−7.81 (m, 2H), NH signals apparent in concentrated samples; ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.6 (CH × 2), 120.3 (CH), 125.9 (CH × 2), 128.7 (CH × 2), 129.2 (CH × 2), 129.9 (CH), 130.0 (C), 147.9 (C), 163.1 (C═N); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{14}N_3$ 212.1182; Found 212.1182.

*N′-Phenylpropionimidohydrazide (**10j**).* Orange oil (74%); ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.20 (t, J = 7.6 Hz, 3H), 2.27 (q, J = 7.6 Hz, 2H), 4.73 (br s, NH × 2), 5.61 (vbr s, NH), 6.82 (tt, J = 7.2, 1.2 Hz, 1H), 6.87−6.90 (m, 2H), 7.18−7.23 (m, 2H), NH signals apparent in concentrated samples; ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (CH_3), 26.9 (CH_2), 114.3 (CH × 2), 119.7 (CH), 128.9 (CH × 2), 148.3 (C), 158.6 (C═N); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_9H_{14}N_3$ 164.1182; Found 164.1186.

■ ASSOCIATED CONTENT

Supporting Information

Detailed optimization of flow experiments, schematics for the large scale flow rig, external quench procedure, rate constant determination, and associated ^{1}H and ^{13}C spectra for compounds **2**, **4**, **9a**−**9f**, and **10a**−**10j**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00101.

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Notes

The authors declare no competing financial interest.

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