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Microwave-Assisted and Continuous Flow Multistep Synthesis of 4-(Pyrazol-1-yl)carboxanilides

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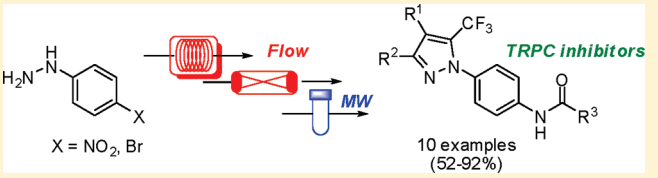
Supporting Information

ABSTRACT: A series of 4-(pyrazol-1-yl)carboxanilides active as inhibitors of canonical transient receptor potential channels were synthesized in an efficient three-step protocol using controlled microwave heating. The general synthetic strategy involves condensation of 4-nitrophenylhydrazine with appropriate 1,3-dicarbonyl building blocks, followed by reduction of the nitro group to the amine, which is then amidated with carboxylic acids. Compared to the conventional protocol a dramatic reduction in overall processing time from ~2 days to a few minutes was achieved, accompanied by significantly improved product yields. In addition, the first two steps in the synthetic pathway were also performed under continuous flow conditions providing similar isolated product yields. As an alternative to the three-step protocol, a novel two-step route to the desired 4-(pyrazol-1-yl)carboxanilides was devised involving condensation of 4-bromophenylhydrazine with appropriate 1,3-dicarbonyl building blocks, followed by Pd-catalyzed Buchwald−Hartwig amidation with carboxylic acid amides.



INTRODUCTION

The pyrazole ring is an important heterocyclic core structure in a large number of biologically active compounds. The spectrum of pharmaceutical action of pyrazole derivatives encompasses, for example, substances acting on the central nervous system, pharmacodynamic agents, drugs aimed at metabolic diseases, and chemotherapeutics.[1] Recent examples are the CB_1 cannabinoid receptor antagonist Rimonabant (Sanofi-Aventis)[2] and analogous molecules active as protein kinase inhibitors, in addition to anti-estrogens acting as potential antitumor therapeutics.[3] The past decade brought the discovery of a new class of drugs targeting the Na^+/Ca^{2+} signaling pathways, which play a key role in many pathogenic processes including systemic diseases, inflammation, and cancer.[1,4] One important topic in this rapidly growing field are drugs which are tuning the activity of canonical transient receptor potential channels (TRPC), controlling the influx of intracellular Ca^{2+} into a plethora of mammalian cell types.[5] Mori and co-workers recently described a number of 4-(pyrazol-1-yl)carboxanilides (Figure 1) acting as both selective TRPC inhibitors and transcription factor regulators of the nuclear factor of activated T-cells (NFAT).[6] One of these compounds, the trichloroacryl derivative of pyrazole scaffold **1** ("Pyr 3"), specifically attenuates activation of NFAT and hypertrophic growth in rat neonatal cardiomyocytes and in vivo pressure overload-induced cardiac hypertrophy in mice and therefore may also lead to the development of useful drugs for the safer therapeutic treatment of pathological cardiac hypertrophy and heart failure.[6,7] In addition, the related 4-(pyrazol-1-yl)carboxanilide structural skeleton **2** has been implemented by pharmaceutical companies such as

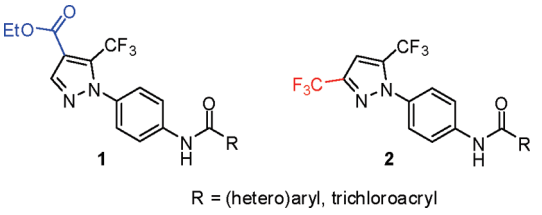


Figure 1. Pyrazole-based family of TRPC inhibitors/NFAT transcription factor regulators.[6−10]

Abbott,[8] Astellas,[9] and Boehringer-Ingelheim[10] into the development of discovery libraries in the search for potential lead compounds in these areas.[7]

Today, performing organic synthesis under continuous flow conditions is getting widely accepted in both industry and academia, while at the same time the available technology is getting more mature.[11,12] One of the important features of flow reactors is the ability of the used capillaries or channels (~50−1000 μm) to withstand high internal pressures, allowing flow processing to be performed in a high-temperature/high-pressure regime, superheating solvents far above their boiling point, sometimes reaching supercritical conditions.[13] This feature can be used to realize a central process intensification philosophy:[14] the drastic acceleration of chemical processes at high temperatures, where a reduction of reaction times from days to hours (or hours to minutes) is often possible, a feature shared with

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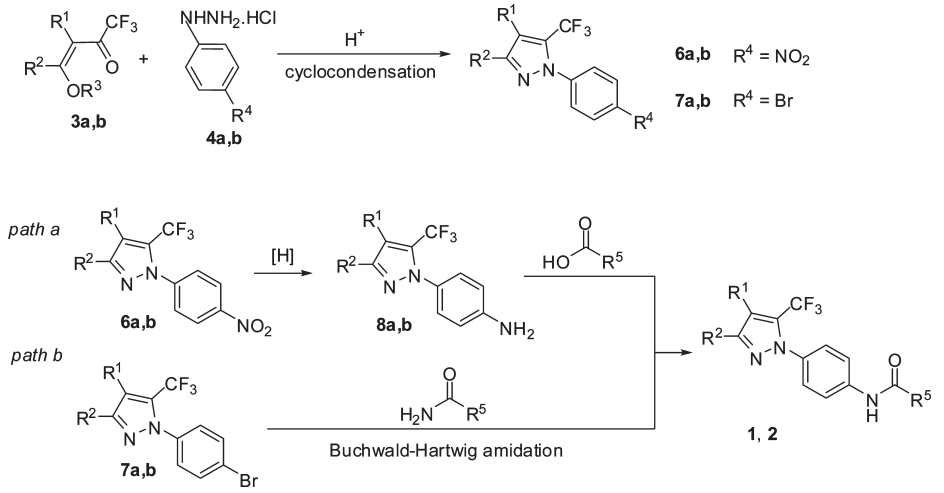
Scheme 1. Bifurcated Synthesis Path to 4-(Pyrazol-1-yl)carboxanilides of Type 1 or 2 (Figure *1*) Incorporating Hydrogenation/Peptide Coupling (Path a) or Buchwald−Hartwig Amidation (Path b)



microwave chemistry in sealed vessels.[15,16] Importantly, the process window of microwave batch reactors (up to 300 °C and 30 bar) employing sealed glass vessels is overlapping to a great extent with the temperature/pressure regime of most commercially available continuous flow reactors (200−350 °C and up to 180 bar).[13] As a consequence, microwave batch reactors are ideal tools to initially optimize a chemical reaction before moving to a high-temperature/high-pressure continuous flow process (microwave-to-flow paradigm).[17] As compared to solely relying on flow equipment for the optimization step,[18] using batch microwave technology allows a quick evaluation of a large matrix of reaction conditions (different solvents, reagents, etc.) in a very short time frame. In addition, problematic reaction conditions (e.g., precipitation) are recognized at an early stage before moving to flow conditions.

Herein we describe improved (process intensified) synthetic protocols that allow the rapid multistep synthesis of 4-[trifluoromethyl-(pyrazol-1-yl-)]carboxanilides of type **1** and **2** (Figure 1).[6,8−10] These procedures are based on the use of microwave batch or continuous flow chemistry as enabling technologies to allow the reduction of reaction times from a few days down to minutes.[19]

RESULTS AND DISCUSSION

The known synthetic strategies for the preparation of 4-(pyrazol-1-yl)carboxanilides generally pursue a pragmatic three-step approach relying on standard procedures (Scheme 1, path a), to generate small amounts of the target compounds for biological screenings.[6−10] Starting with a cyclocondensation reaction between 4-nitrophenylhydrazine and an enone or 1,3-dicarbonyl compound under acidic conditions, the resulting 1-(4-nitrophenyl)-1*H*-pyrazoles **6** are further reduced to the corresponding anilines **8** in a catalytic hydrogenation (Pd/C) step.[6−10] For diversity generation, a large number of different amides have been synthesized from the aniline and various carboxylic acids using EDC/DMAP (or BOP/DIPEA; HBTU/TEA)-based peptide coupling protocols.[6−10] In a similar fashion, acid chloride couplings have also been used in the final amidation step.[6−10] These methods are based on conventional round-bottomed flask chemistry, and the overall reaction time for the three steps is generally in the order of 2 days or more, while the obtained overall yields range from 20% to 30% at best.[6−10] As a considerable additional improvement, we have considered a Buchwald−Hartwig direct amidation starting from a 1-(4-bromophenyl)-1*H*-pyrazole **7** as an attractive alternative to the reduction/peptide coupling sequence (Scheme 1, path b).

It was therefore one of our objectives to provide a simplified, less time-consuming, and high-yielding procedure using a combination of specifically tailored microwave-[15,16] and microreaction techniques[11−13] for process intensification. All reactions performed under flow conditions were optimized and adapted to flow equipment by a series of preceding microwave batch experiments.[17]

The use of multiple flow reaction devices in series, the synthesis of complex molecules in "automated" fashion, is an interesting approach whereby the product solutions generated by individual flow reactors are not collected for isolation of intermediates but directly fed to other flow reactors downstream of the process.[20] Key to this method is a very careful process design, which has to ensure the compatibility of every individual flow reaction with all other downstream steps.

Pyrazole Formation. For the generation of *N*-substituted functionalized pyrazoles, a large number of synthetic procedures is available.[21] These methods are most commonly based on the cyclocondensation of hydrazines with various bifunctional molecules such as 1,3-dicarbonyl compounds, α,β-unsaturated ketones, and β-aminoenones, as well as 1,3-dipolar cycloaddition reactions.[21] Recently published approaches include, for example, the cyclocondensation of *N*-arylhydrazones with nitroolefins in ethylene glycol in the presence of air[22] or the Pd-catalyzed four-component reaction of a terminal alkyne, hydrazine (hydroxylamine), CO, and an aryl iodide.[23] Mori and co-workers have used a well established protocol to prepare the starting nitro-substituted pyrazoles **6a,b** in the three-step synthesis of 4-[5-trifluormethyl-(pyrazol-1-yl-)]carboxanilides **1** and **2** (Figure 1), employing enone **3a** or 1,3-dicarbonyl compound **3b** and 4-nitrophenylhydrazine as starting materials.[6] Using controlled microwave heating in sealed vessels as enabling technology,

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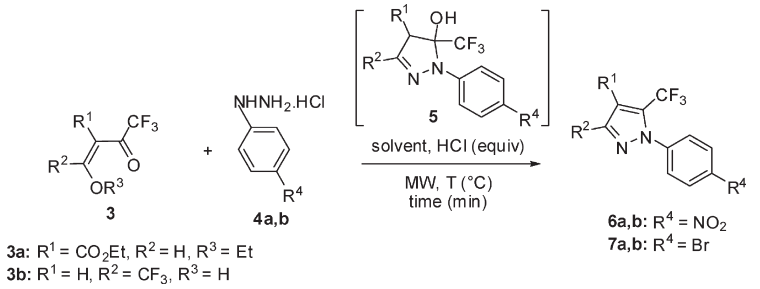
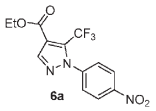
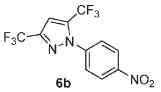
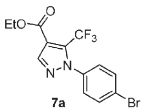
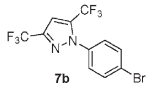
Table 1. Optimized Conditions for the Microwave Batch Synthesis of 1*H*-Pyrazoles 6a,b and 7a,b[a]



entry	product	T (°C)	time(min)	solvent/conc (mol/L)	HCl (equiv)	yield (%)
1	 **6a**	160	2	EtOH/0.45	-	81
2		175	1.5	MeOH/0.1	-	82
3	 **6b**	160	5	EtOH/0.45	4	89
4		205	15	*n*-PrOH:H_2O 3:1/0.75[b]	-	87
5	 **7a**	100	5	DMF/0.5	-	92
6	 **7b**	150	5	MeOH:H_2O 2:1/1	10	98

[a] All reactions were performed in a single-mode microwave reactor (Monowave 300) using 10 mL Pyrex vials and magnetic stirring from the hydrazinium salts on a ~1−2.5 mmol scale except for **7a** (30 mL vial, 10 mmol scale) with 1.05 equiv of **3** in 2 mL (20 mL) of solvent. [b] A switch from ethanol to the 1-propanol/water 3:1 (v/v) mixture displaying a slightly lower vapor pressure was necessary in order to stay below the pressure limit of around 30 bar of the used microwave reactor.

we sought to drastically accelerate and simplify the published protocols, which often require an overnight reflux to reach full conversion.[6−10]

With access to microwave reactors capable of superheating organic solvents under carefully controlled internal temperature monitoring conditions, this goal was easily achievable.[24] An initial modification of the original protocol[6−10] was the replacement of the typically employed combination of 4-nitrophenylhydrazine base with H_2SO_4 or HCl acid with the more stable and commercially available phenylhydrazinium chloride salts **4**, thus eliminating the addition of an acid catalyst. The cyclocondensation of both the enone **3a** or 1,3-dicarbonyl compound **3b** and arylhydrazinium chloride salts **4** to the corresponding pyrazoles is governed by the dehydration of the intermediate 4,5-dihydro-5-hydroxypyrazole **5** (Table 1) as important kinetic bottleneck.[25] Depending on the substrate, the dehydration generally required relatively high temperatures and strongly acidic conditions to reach full conversion within the intended time scale of a few minutes. For both the 5-trifluoromethyl-1*H*-pyrazole as well as the 3,5-bis(trifluoromethyl)-1*H*-pyrazole scaffolds (**1** and **2**, Figure 1), we synthesized the corresponding 4-nitroaryl- and 4-bromoaryl-substituted derivatives **6** and **7** (Table 1). This provided us with the possibility to pursue two different amidation routes (Scheme 1), allowing diversity introduction in the last step of the synthesis. Initial experiments involved microwave heating of a 0.45 M suspension of 4-nitrophenylhydrazinium chloride (**4a**) and enone **3a** (1.05 equiv) in ethanol at 160 °C for 2 min to afford pyrazole **6a** in 82% yield. For the envisaged flow implementation we switched to a more dilute, homogeneous protocol (0.1 M) in methanol after minor adjustments on temperature and time, obtaining a similar yield. While the dehydration of intermediate **5** (R^2 = CO_2Et) to the aromatic 4-ethoxycarbonyl-5-trifluormethyl-substituted pyrazole ring in **6a** worked sufficiently well under self-catalysis by the liberated HCl, the replacement of the ester group by an additional strongly electron-withdrawing CF_3 group results in the formation of a much more stable 4,5-dihydro-5-hydroxypyrazole intermediate **5** (R^2 = CF_3).[25] Addition of conc HCl (3 equiv) was necessary to reach full conversion at 160 °C toward pyrazole **6b** (Table 1, entry 3). During our optimization runs, we observed that for example the 4,5-dihydro-5-hydroxypyrazole intermediate **5** is almost the exclusively formed product (HPLC/GC−MS), when performing the reaction at lower temperature (100 °C, 5 min in DMF). However, complete dehydration of the formed intermediate **5** into 3,5-bis(trifluoromethyl)-1*H*-pyrazole **6b** could be achieved within 15 min by raising the reaction temperature to 205 °C (entry 4).

In a similar manner, the arylbromides **7a,b** were prepared in excellent yields (92−98%) using 4-bromophenylhydrazinium chloride (**4b**) as starting material. DMF as solvent was found

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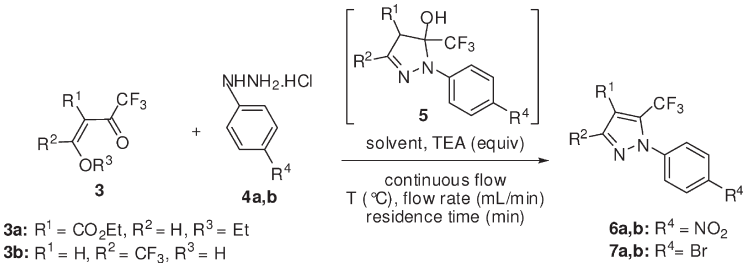
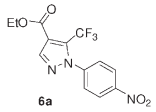
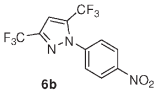
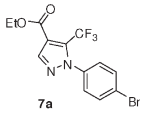
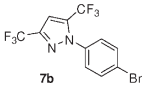
Table 2. Optimized Conditions for the Continuous Flow Synthesis of 1*H*-Pyrazoles 6a,6b and 7a,7b[a]



product	flow rate (mL/min)	*T* (°C)	residence time (min)	solvent/conc (mol/L)	TEA (equiv)	yield[b] (%)
 **6a**	2.6	175	1.5	AcOH/0.1 M	1.05	91
 **6b**	4	265	1	AcOH/0.1 M	1.05	-[c]
 **7a**	1.6	100	5	DMF/0.5 M	-	81
 **7b**	1.6	230	5	AcOH:H_2O 40:3/0.5 M	2	69

[a] All reactions were performed in a stainless steel flow reactor (X-Cube Flash, Thales Nanotechnology Inc.) utilizing either a 4 mL (**6a,b**) or 8 mL (**7a,b**) stainless steel coil (i.d. 1 mm) and a flow rate of 1.6−2.6 mL/min. For further details, see Experimental Section. [b] Isolated yields after flash chromatography. [c] No isolated yield for compound **6b**, instead the corresponding aniline **8b** was obtained in 57% yield.

to solubilize both starting materials and product much better as compared to ethanol and was therefore considered as the solvent of choice in the preparation of pyrazole **7a** (entry 5). Not unexpectedly, the preparation of the respective electron-deficient 3,5-bis(trifluoromethyl)-1*H*-pyrazole **7b** did again require significantly higher temperatures (150 vs 100 °C for 5 min) and HCl addition (10 equiv) to reach full conversion (entry 6). Arylbromide **7b** is a relatively volatile liquid and was thus prepared using a solution of the starting materials in low boiling MeOH/H_2O 2:1 (v/v) to facilitate isolation. After careful evaporation of the solvent, **7b** was obtained in excellent yield (98%).

The application of microreactor technology for the generation of heterocyclic compounds was recently reviewed.[26] In this context, it is worth mentioning that Seeberger and co-workers have reported a three-step synthesis for the antiobesity drug Rimonabant as an example for the continuous flow synthesis of a prominent pyrazole drug.[27] The set of conditions obtained in the microwave experiments (Table 1) served as a good starting point for the implementation into a flow regime, by and large fulfilling the basic requirements for a continuous flow process of being homogeneous and reaching completion within the envisaged reaction time of less than 5 min. Bearing in mind the wide operating window of the chosen stainless steel flow equipment (up to 350 °C/180 bar),[28] the generated protocols in batch were clearly aimed at exploiting the merits of the exceptionally rapid kinetics at high temperatures, resulting in reaction times of only 1−5 min, depending on the substrate.

All continuous flow experiments for the cyclocondensation to pyrazoles were done in a stainless steel capillary microreactor (1 mm i.d., X-Cube Flash, Thales Nanotechnology Inc.),[28] to which the premixed reaction mixture (0.1 M) was fed by an HPLC pump while a constant inner pressure of 120−140 bar was maintained. The stainless steel coil was protected from the corrosive action of HCl by the addition of 1.05−2.0 equiv of triethylamine and, where possible, by further minimization of residence times.[29] In contrast to the corresponding microwave protocols (Table 1, entries 1 and 2), we switched from ethanol/methanol to acetic acid as solvent, resulting in a significantly higher yield for **6a** as compared to the procedure using ethanol relying solely on self-catalysis by the hydrazinium chloride salt (91% vs 81%) (Table 2).

An important side reaction that can occur in microreactors made of stainless steel is the reduction of nitro groups to the corresponding amines (Bechamp reduction).[29] Accordingly, our initial experiments involving the reaction of enone **3a** with 4-nitrophenylhydrazinium chloride (**4a**) in ethanol at 160 °C and 5 min residence time showed 10% (HPLC-UV at 215 nm or GC−MS) of the nitro compound being reduced to the corresponding aniline derivative **8a**. Further dilution of the reaction mixture (0.1 → 0.02 M) and conducting the reaction at lower temperatures (100−140 °C) were improper means to alleviate the reducing effect of the stainless steel coil. We found that at the used temperature of 160−175 °C a reduction of residence time was the most effective measure in order to suppress the reduction

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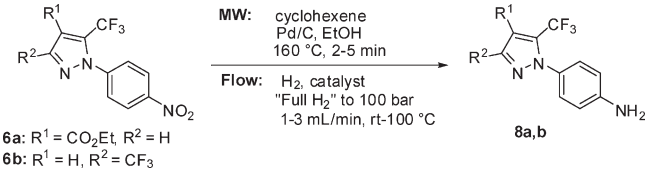
to the aniline (**8a**) (14% after 5 min vs. 2% after 1.5 min). Thus, we were able to synthesize the nitro-substituted pyrazole derivative **6a** at 175 °C and 1.5 min residence time in 91% yield after flash chromatography (Table 2).

However, the requirement of adding an acid scavenger such as triethylamine and working with extremely short residence times has its limits: for pyrazole **6b** bearing an additional CF_3 group, no combination of temperature/residence time preventing the reduction to the aniline could be found. At the chosen conditions, a temperature of >200 °C turned out to be essential to achieve dehydration of the relatively electron-poor and thus quite stable 5-hydroxy-intermediate **5**. We suspect that at these elevated temperatures diffusion to the coil and reaction kinetics of the reduction are very rapid and cannot be avoided any more by reducing residence time. This assumption is supported by the fact that in this case nitro compound **6b** could not be isolated, and instead only the corresponding aniline **8b** was obtained in 57% yield (Table 2).

Bromide **7a** was synthesized in 81% yield at 100 °C at a residence time of 5 min employing DMF as solvent; this solvent switch allows raising the substrate concentration to 0.5 M. The analogous bromide **7b** differing from **7a** in having an additional CF_3 group did again require a higher reaction temperature (230 °C) and acetic acid as solvent in order to achieve full dehydration to the aromatic pyrazole ring. At the chosen concentration of 0.5 M, the addition of water in combination with an increased amount of triethylamine (2 equiv) was needed to fully homogenize the reaction mixture. Bromide **7b** was obtained in 69% yield after flash chromatography (Table 2).

Scheme 2. Hydrogenation of 1-(4-Nitrophenyl)-1*H*-pyrazoles 6a,b under Microwave and Continuous Flow Conditions



6a: $R^1 = CO_2Et$, $R^2 = H$
6b: $R^1 = H$, $R^2 = CF_3$

Nitro Group Reduction. The reduction of aliphatic and aromatic nitro compounds to the corresponding amines is one of the most frequently used synthetic processes in organic chemistry, for which a plethora of methods is available.[30] However, many well-known methods for the reduction of nitro groups, such as catalytic hydrogenations, are difficult to implement into a microwave approach. The use of molecular hydrogen in a catalytic hydrogenation is impeded by the difficulty of introducing hydrogen into the sealed reaction vessels of most currently available microwave reactors.[31] Although recently a microwave accessory that allows performing catalytic hydrogenations with externally supplied hydrogen gas was commercialized,[31,32] we favored a catalytic transfer hydrogenation because of the simplified overall procedure.[33] Recent examples include the reduction of nitroarenes to anilines using a hydrazine hydrate/$FeCl_3$ mixture[34] or $Mo(CO)_6$/DBU in ethanol[35] and the reduction of aliphatic nitro groups using ammonium formate and catalytic amounts of Pd/C in MeOH.[36]

Our first optimization attempts were closely related to literature reports by groups from AMRI and GSK employing 1,4-cyclohexadiene or 1-methyl-1-cyclohexene as hydrogen donor for microwave-assisted catalytic transfer hydrogenations.[33] However, these more reactive reagents can be replaced by less expensive cyclohexene,[33] which does not negatively affect the transformation of the chosen substrates in terms of conversion or selectivity. In an attempt to reduce the amount of catalyst and hydrogen donor, we moved our initial protocol operating at 100 °C in ethanol toward a high-temperature regime at 160 °C. We were pleased to see that this measure not only led to a reduction in time from 10 to 2 min for substrate **6a** but also allowed a reduction in the amount of added Pd/C from 5% to 1% while using 2 equiv of cyclohexene instead of 5 equiv. This protocol furnished the corresponding anilines **8a** (92%) and **8b** (96%) in high yield after isolation by flash chromatography.

In contrast to our preliminary batch microwave experiments, the use of molecular hydrogen in the inherently safe process environment of a flow hydrogenator was considered a particularly attractive approach.[37] The hydrogenation experiments in continuous flow were done in a benchtop flow-hydrogenator

Table 3. Screening of Reaction Conditions for the Continuous Flow Hydrogenation of 1-(4-Nitrophenyl)-1*H*-pyrazole 6a (Scheme 2)

entry	catalyst (w/w%)	*T* (°C)	solvent/concn (mol/L)	flow rate (mL/min)	H_2 pressure[a] (bar)	conversion[b] (%)
1	10% Pd/C	25	EtOH/0.02	1	atm	0
2	10% Pd/C	40	EtOH/0.02	1	atm	31
3	10% Pd/C	60	EtOH/0.02	1	atm	71
4	10% Pd/C	70	EtOH/0.02	1	atm	89
5	10% Pt/C	25	EtOH/0.02	1	atm	59 + 20[c]
6	10% Pd/Al_2O_3	25	EtOH/0.02	1	atm	0
7	10% Pd/Al_2O_3	50	EtOH/0.02	1	atm	89
8	10% Pd/Al_2O_3	70	EtOH/0.02	1	atm	>99
9	10% Pd/Al_2O_3	70	DMF/0.1	3	100	>99
10	RaNi	70	DMF/0.1	1	100	>99
11	RaNi	100	EtOH/0.03	3	90	>99
12	RaNi	100	EtOH/0.03	2.5	70	>99[d]
13	10% Pd/Al_2O_3	25	AcOH/0.03	2	atm	>99
14	10% Pd/Al_2O_3	40	AcOH/0.03	2	atm	>99[e]
15	10% Pd/Al_2O_3	100	AcOH/0.03	2	atm	86

[a] atm = H-Cube in "full H_2" mode at atmospheric pressure; 70−100 bar = H-Cube in "controlled" mode. [b] Purity as measured by HPLC at 215 nm. [c] Total percentage of byproducts. [d] 93% yield after isolation. [e] Free of impurity traces in HPLC at 215 nm.

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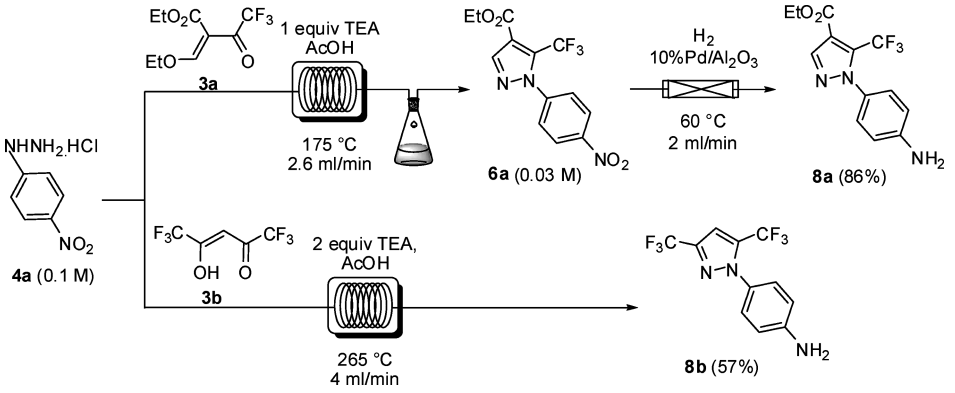
Scheme 3. Process Scheme and Reaction Conditions for the Synthesis of 1-(4-Aminophenyl)-1*H*-pyrazoles 8a,b under Continuous Flow Conditions[a]



(H-Cube, Thales Nanotechnology Inc.).[38] The use of heterogeneous catalysts on a fixed catalyst bed has the advantage of circumventing the need for filtering off the catalyst, a feature of general importance in the production of pharmaceuticals. Initially, a thorough screening of different catalysts and reaction conditions was performed in order to indicate a range of suitable conditions for the reduction of nitro-compound **6a** as substrate (Table 3).

Starting with 10% Pd/C, a 0.02 M substrate solution at 1 mL/min, and temperatures up to 70 °C led to partial conversion into the corresponding aniline (Table 3, entries 1−4), whereas 10% Pt/C seemed to be more active but even at ambient temperatures was too unselective (Table 3, entry 5). On the other hand, the application of 10% Pd/Al_2O_3 as well as RaNi led to complete and selective reduction of the nitro functionality under a variety of temperatures and flow rates, employing either ethanol, DMF, or acetic acid as solvents (Table 3, entries 6−15). Despite the lower price of RaNi, 10% Pd/Al_2O_3 became our catalyst of choice in combination with AcOH as a solvent, due to the incompatibility of AcOH with RaNi. New reaction conditions were developed, ranging from ambient to 80 °C (0.03 M), under which the nitro group was fully converted, with temperatures in the range of 40−60 °C being most preferable for a clean process. At a flow rate of 2 mL/min, this corresponds to a molar throughput of 3.6 mmol/h.

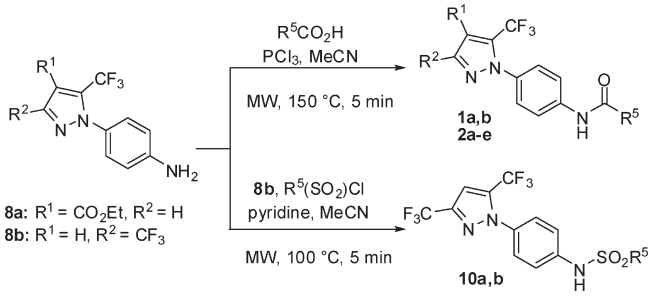
Two-Step Continuous Flow Synthesis of Amines 8a and 8b. Equipped with a set of optimized conditions, carefully designed to ensure the compatibility of the initial pyrazole formation in continuous flow with the subsequent flow hydrogenation as downstream reaction, our next goal was to join the two individual flow steps to generate the amine precursors **8a** and **8b** without isolation and purification of the corresponding nitro-substituted pyrazoles **6a,b** (Scheme 3). Using both the X-Cube Flash coil reactor and H-Cube hydrogenator under the previously optimized conditions for the two individual steps of the cyclocondensation−hydrogenation sequence (Table 2, Table 3), nitro compound **6a** was generated at a reaction temperature of 175 °C and 1.5 min residence time in acetic acid (0.1 M) as solvent (Table 1). The obtained crude product solution was directly reduced in the flow hydrogenator at 60 °C on 10% Pd/Al_2O_3 (Table 3), providing aniline **8a** in 86% yield after flash chromatography. As already mentioned, an alternative synthesis path toward amine **8b** arose from the inadvertent reduction of the formed nitro functionalized pyrazole **6b** by the stainless steel capillary material (Bechamp reduction).[29] At the preferred reaction temperature of 265 °C and a residence time of 1 min, the corresponding amine **8b** was immediately generated after in situ formation of **8b** inside the stainless steel capillary and was isolated in acceptable yield after flash chromatography (57%) (Table 2).

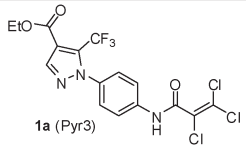
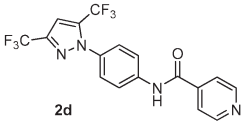
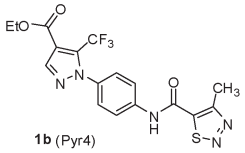
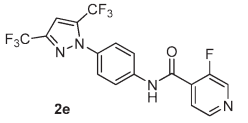
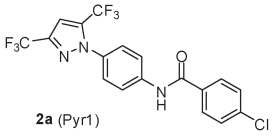
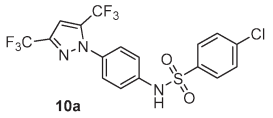
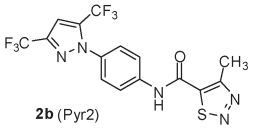
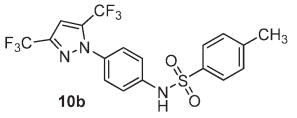
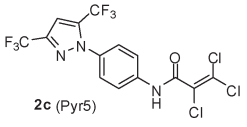
Amidation. The amide function on the two pyrazole scaffolds (Figure 1) is introduced in the last step of the synthesis and thus is very well suited to diversify the molecule. In today's chemical literature there is a large variety of different amidation techniques, of which carbodiimide-based peptide coupling protocols are particularly attractive owing to the broad range of applicable substrates and its high chemoselectivity.[39] Ley and co-workers have established a very versatile and clean continuous flow method for the generation of di- and tripeptides using immobilized peptide coupling reagents (PyBroP/HOBt) in combination with catch and release strategies in a flow environment, with the resulting benefit of greatly simplifying or even obviating workup.[40] Along similar lines, the Cosford group successfully synthesized a range of imidazo[1,2-*a*]pyridine-2-carboxamides in a glass-chip reactor using a homogeneous peptide protocol based on EDC/HOBt in DMF and DIPEA as base.[41]

In the case of the desired 4-(pyrazol-1-yl)carboxanilides of type **1** and **2**, we have evaluated a variety of peptide coupling conditions using both room temperature and microwave protocols.[42] Disappointingly, for all tested conditions the yields of the anticipated coupling products were unsatisfactory (<30%). Apparently, amine **8a** and acids such as trichloroacrylic acid were particularly unreactive substrates under these coupling conditions (see structure **1a**, Table 4). These findings are in agreement with the low yield (35%) obtained by Mori and co-workers for the final amidation step in the synthesis of the TRPC 3 channel inhibitor **1a** ("Pyr 3") using a room temperature peptide coupling protocol (BOP/DIPEA in DMF).[6]

At this stage we considered a 2009 protocol by Nikem Research that allows experimentally very straightforward microwave-assisted amidations that simply involve heating aromatic amines and carboxylic acids (aromatic, heteroaromatic, aliphatic) in acetonitrile in the presence of 1 equiv of phosphorus trichloride.[43] Applying 150 °C reaction temperature for 5 min high isolated yields for a large variety of amide motifs were obtained.[43] The fact that this amidation protocol forms a suspension makes an implementation into a flow process not feasible with currently available flow equipment.

Table 4. Isolated Yields for Carboxanilides 1a,b, 2a−e and Sulfonamides 10a,b Under Microwave Batch Conditions[a]



product	yield[b] (%)	product	yield[b] (%)
 **1a** (Pyr3)	76	 **2d**	89
 **1b** (Pyr4)	62	 **2e**	52
 **2a** (Pyr1)	86	 **10a**	90
 **2b** (Pyr2)	63	 **10b**	92
 **2c** (Pyr5)	85		

[a] All reactions were performed in a single-mode microwave reactor (Monowave 300) using 10 mL Pyrex vials and magnetic stirring. Experiments were made using anilines **8a,b** on a 0.5 mmol scale with 1.1−1.5 equiv of carboxylic acid and 1.1−1.5 equiv of PCl_3 in 2 mL of MeCN at 150 °C and 5 min reaction time. Sulfonamides **10a,b** were prepared on a 0.5 mmol scale using 1.5 equiv of the acid chloride and 100 μL of pyridine at 100 °C and 5 min reaction time. [b] Isolated yields after flash chromatography.

In any event, using this simplified acid chloride coupling method, the amidation of anilines **8a,b** with a selection of both electron-poor and electron-rich carboxylic acids was achieved in a very convenient and straightforward manner. At a reaction temperature of 150 °C, 5 min reaction time and acetonitrile as solvent in a microwave batch experiment, we obtained a variety of different amides in moderate to good yields (52−89%). Two sulfonamides **10a,b** were prepared in high yields (>90%) by analogous sulfonyl chloride couplings under microwave conditions at 100 °C and 5 min in acetonitrile/pyridine.

Buchwald−Hartwig Amidation. In order to further simplify the synthesis not only by reducing reaction time but also by an alternative two-step approach instead of the more traditional three-step synthetic pathway, we briefly evaluated a cyclocondesation step involving a 4-bromophenylhydrazine species followed by a Pd-catalyzed Buchwald−Hartwig amidation protocol to deliver the desired carboxanilides (Scheme 1, path b). Having the cyclocondensation step already optimized under microwave as well as under continuous flow conditions (see above), we focused our efforts on the optimization of the C−N cross-coupling process. Pd-catalyzed C−N bond-forming reactions between aryl halides and amides as nucleophiles have received broad interest in the past two decades.[44] The versatility of the substrates and tolerated functionalities has turned this coupling into one of the most important reactions currently under development. The Buchwald−Hartwig amidation process is implemented into a wide range of fine chemical and natural product syntheses as well as into drug discovery processes. Furthermore, a plethora of transition-metal-catalyzed coupling reactions have been successfully translated into high-speed microwave processes, including Buchwald−Hartwig couplings.[16] Notably, in a previous project, we were able to successfully perform Pd-catalyzed *N*-amidations on the somewhat related 4-(bromophenyl)-dihydropyrimidine scaffold under microwave conditions.[45]

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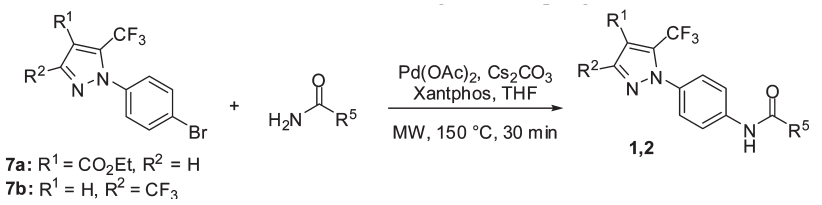
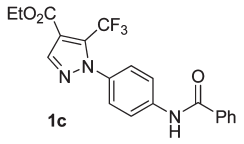
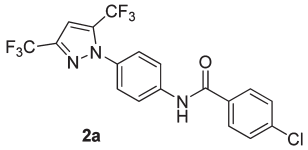
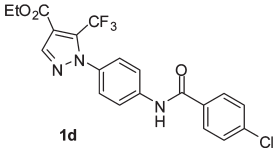
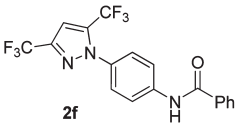
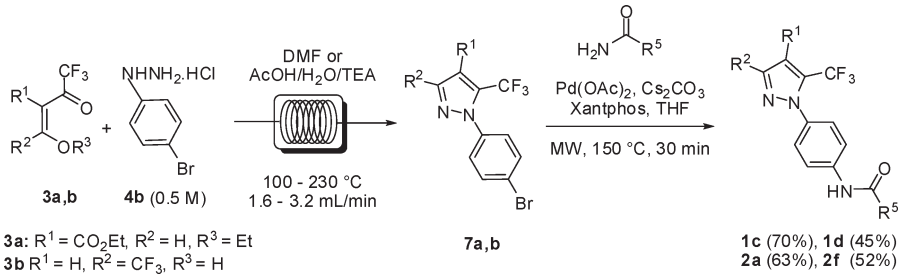
Table 5. Microwave-Assisted Buchwald−Hartwig C−N Coupling Reactions[a]



product	yield[b] (%)	product	yield[b] (%)
 **1c**	87	 **2a**	92
 **1d**	56	 **2f**	75

[a] All reactions were performed in a single-mode microwave reactor (Monowave 300) using 10 mL Pyrex vials and magnetic stirring. [b] Isolated yields after flash chromatography.

Scheme 4. Process Scheme and Reaction Conditions for the Combined Continuous Flow/Microwave Batch Synthesis of Amides 1c,d and 2a,f



We thus decided to explore the scope of the Pd-catalyzed version of the amide *N*-arylation reaction. Applying our previously optimized[45] microwave conditions to the current substrates [5 mol % $Pd(OAc)_2$ as precatalyst, Xantphos as the ligand, and Cs_2CO_3/THF as base/solvent combination at 150 °C and 15 min reaction time], a promising conversion of nearly 87% was achieved. A successful microwave protocol was developed by only slightly modifying this procedure in extending the reaction time to 30 min, otherwise keeping the remaining reaction parameters unchanged. Further trials to change the base, ligand, or solvent to additionally optimize the process remained unsuccessful, delivering only partial conversion of the 1-(4-bromophenyl)-1*H*-pyrazoles **7a,b**. These aryl bromides were effectively converted into the corresponding carboxanilides **1c,d** and **2a,f** in 56−92% yield after flash chromatography (Table 5), therefore expanding the structural diversity of the desired 4-(pyrazol-1-yl)carboxanilides scaffolds.

Very recently, continuous flow Buchwald−Hartwig reactions have been demonstrated.[46] To overcome solid bridging and constriction disturbing the flow regime, the reactor coil was sonicated during the process. An attempt to translate our optimized microwave conditions into a continuous flow protocol failed as a result of the restrictions of the available flow equipment, as well as to the inhomogeneity of the reaction mixture when using the optimized reaction conditions. Ultimately, the two individually optimized steps (continuous flow cyclocondensation and microwave batch Buchwald−Hartwig amidation) were merged into one process, directly using the product stream obtained in the initial flow cyclocondensation step (Scheme 4). Applying the already optimized microwave batch conditions allowed the isolation of the carboxamides **1c,d** and **2a,f** in 45−70% overall yield after purification by flash chromatography.

■ CONCLUSION

In conclusion, we have presented improved synthetic protocols for the generation of pyrazole-derived inhibitors of TRPC3 of type **1** and **2** that can be easily scaled to multigram quantities for pharmacological research purposes.[47] Our methods rely on the initial optimization of reaction conditions using sealed vessel

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microwave synthesis as a process intensification technique. The use of high-temperature/pressure conditions not only resulted in a dramatic reduction of the required reaction and overall processing times but also provided consistently better product yields than the conventional methods. This new method will be very useful for generating compound libraries of these (and related) scaffolds, in particular considering the translation of the method disclosed herein to a parallel microwave synthesis approach. In addition, we have demonstrated that for strictly homogeneous transformations the high-temperature microwave conditions were readily transferable to a conventionally heated continuous flow regime, which would in principle allow a simple scale-up option to prepare larger quantities of compounds. As an alternative to the original three-step method, a two-step microwave-assisted protocol for the synthesis of 4-(pyrazol-1-yl)carboxanilides that relies on a Pd-catalyzed Buchwald−Hartwig amidation chemistry was also developed.

EXPERIMENTAL SECTION

General Remarks. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz instrument. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet, respectively. Low resolution mass spectra were either obtained on a LC−MS instrument using atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI) in positive or negative mode. GC−MS monitoring was based on electron impact ionization (70 eV) using a HP/5MS column (30 m × 0.250 mm × 0.025 mm). After 1 min at 50 °C the temperature was increased in 25 °C/min steps up to 300 °C and kept at 300 °C for 4 min. The carrier gas was helium, and the flow rate was 1.0 mL/min in constant-flow mode. High-resolution mass spectra were recorded on a FT-ICR-MS instrument using electrospray ionization (ESI) in positive mode. Analytical HPLC analysis was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 μm) at 25 °C using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.0 mL/min. The following gradient was applied: linear increase from solution 30% B to 100% B in 9 min, hold at 100% solution B for 1 min. All chemicals, solvents, catalysts, and ligands were obtained from known commercial suppliers and were used without any further purification. Microwave irradiation experiments were carried out in a single-mode microwave instrument in Pyrex vials using standard procedures.[24] Reaction times refer to hold times at the temperature indicated, not to total irradiation times. The temperature was measured using the IR temperature sensor of the instrument. The flow chemistry examples described herein were performed using a stainless steel capillary microreactor and a flow hydrogenation reactor according to established principles.[28,38] The synthesized compounds were purified using an automated chromatography system on cartridges packed with KP-SIL, 60 Å (40−63 mm particle size) and ethyl acetate (or ethyl acetate containing 1% triethylamine for the purification of anilines **8a**, **8b**)/petroleum ether mixtures as eluent. The purity of all synthesized compounds (>98%) was either established by HPLC at 215 nm and/or ^{1}H NMR spectroscopy. Melting points were determined on a standard melting point apparatus and are uncorrected.

Ethyl 1-(4-Nitrophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (6a). *Microwave Batch Preparation, Method A (entry 1, Table 1).* To a stirred mixture of 4-nitrophenylhydrazine hydrochloride (**4a**) (171 mg, 0.9 mmol) and ethanol (2 mL) in a 10 mL Pyrex microwave vial was added ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutyrate (**3a**) (228 mg, 1.05 equiv). The reaction vial was sealed with a snap-on cap, and the suspension was subjected to microwave heating for 2 min (hold time) at 160 °C after which the reaction mixture was cooled to 50 °C. After evaporation of the solvent, the residue was put on a silica column and purified by flash chromatography to afford ethyl 1-(4-nitrophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**6a**) as a yellowish solid (240 mg, 81%), mp 106−108 °C.[6] ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.31 (t, J = 7.1 Hz, 3H), 4.44 (q, J = 9.0 Hz, 2H), 7.89 (d, J = 8.9 Hz, 2H), 8.39 (s, 1H), 8.43 (d, J = 9.0 Hz, 2H). MS (neg APCI): m/z (%) 330 (100) [M − 1].

Method B (entry 2, Table 1). To a solution of 4-nitrophenylhydrazine hydrochloride (**4a**) (189.6 mg, 1 mmol) in methanol (10 mL) in a 30 mL Pyrex microwave vial was added ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutyrate (**3a**) (247.4 mg, 1.03 equiv). The mixture was stirred/sonicated for 1 min and sealed with a snap-on cap. The reaction mixture was subjected to microwave heating for 1.5 min (hold time) at 175 °C and then cooled to 50 °C. After evaporation of the solvent, the residue was purified by flash chromatography to afford ethyl 1-(4-nitrophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**6a**) as a yellowish solid (271 mg, 82%).

Continuous Flow Preparation. To a stirred solution of 4-nitrophenylhydrazine hydrochloride (**4a**) (189.6 mg, 1 mmol, 0.1 M) in acetic acid (10 mL) in a cylindrical glass vessel were added ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutyrate (**3a**) (252.2 mg, 1.05 equiv) and triethylamine (106.3 mg, 1.05 equiv). After stirring/sonication for 2 min, the homogeneous reaction mixture was subjected to flow processing in the X-Cube Flash. A 4 mL stainless-steel coil was mounted, and the instrument flushed with acetic acid at a constant flow rate of 2.6 mL/min (1.5 min residence time) and a backpressure of 140 bar. After reaching the temperature set point of 175 °C, the inlet tubing was quickly changed from the solvent reservoir to the sample vessel and, after collection of the main fraction of the product mixture on the outlet, placed back into the solvent reservoir for flushing the instrument (~5 min). The collected product solution (~25 mL) was reduced under vacuum, and the residue was purified by flash chromatography to afford ethyl 1-(4-nitrophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**6a**) as yellowish crystals (299 mg, 91%).

1-(4-Nitrophenyl)-3,5-bis(trifluoromethyl)-1*H*-pyrazole (6b). *Microwave Batch Preparation, Method A (entry 4, Table 1).* To a stirred mixture of 4-nitrophenylhydrazine hydrochloride (**4a**) (171 mg, 0.9 mmol) and ethanol (2 mL) in a 10 mL Pyrex microwave vial was added 1,1,1,5,5,5-hexafluoroacetylacetone (**3b**) (197 mg, 1.05 equiv) was added, followed by dropwise addition of conc HCl (300 μL, 4 equiv). The reaction vial was sealed with a snap-on cap, and the suspension was subjected to microwave heating for 5 min (hold time) at 160 °C and subsequently cooled to 50 °C. The so-formed yellow reaction mixture was concentrated under reduced pressure, and the residue purified by flash chromatography (petrol ether/ethyl acetate 6:1) to afford 1-(4-nitrophenyl)-3,5-bis(trifluoromethyl)-1*H*-pyrazole (**6b**) as a yellow oil (260 mg, 89%).[8a] ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.94−7.98 (m, 3H), 8.45−8.49 (m, 2H). MS (pos APCI): m/z (%) 326 (100) [M + 1].

Method B (entry 5, Table 1). To a stirred solution of 4-nitrophenylhydrazine hydrochloride (**4a**) (462.4 mg, 2.44 mmol) in *n*-propanol/water 3:1 (v/v) (4 mL) in a 10 mL Pyrex microwave vial was added 1,1,1,5,5,5-hexafluoroacetylacetone (**3b**) (532.8 mg, 1.05 equiv). The mixture was stirred/sonicated for 1 min, and the reaction vial was sealed with a snap-on cap. The homogeneous reaction mixture was subjected to microwave heating for 15 min (hold time) at 205 °C and then cooled to 50 °C. The reaction mixture was carefully reduced in vacuum (40 °C, 10 mbar), and the oil residue was taken up in 25 mL of diethyl ether, washed with satd sodium bicarbonate (3 × 10 mL) and brine, and dried over $MgSO_4$. After evaporation of the diethylether, nitrophenyl-3,5-bis(trifluoromethyl)-1*H*-pyrazole (**6b**) was obtained as a yellow oil (688 mg, 87%).

Ethyl 1-(4-Bromophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (7a). *Microwave Batch Preparation (entry 5, Table 1).* To a stirred solution of 4-bromophenylhydrazine hydrochloride (**4b**)

(1.88 g, 10 mmol) in DMF (20 mL) in a 30 mL Pyrex microwave vial was added ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutyrate (**3a**) (2.52 g, 1.05 equiv). The mixture was stirred/sonicated for 1 min, and the reaction vial sealed with a snap-on cap. The homogeneous reaction mixture was subjected to microwave heating for 5 min (hold time) at 100 °C and then cooled to 50 °C. The reaction mixture was reduced in vacuum (60 °C, 2 mbar), and DMF traces were removed azeotropically (toluene) to afford ethyl 1-(4-bromophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**7a**) as a pale yellow residue (3.33 g, 92%) or as yellow needles after recrystallization in methanol/water 2:1 (v/v): mp 69−72 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 (t, J = 7.2 Hz, 3H), 4.32 (q, J = 7.2 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 7.80 (d, J = 8.7, 2H), 8.31 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 61.5, 116.82, 116.83, 119.3 (q, J_{CF} = 269.4 Hz), 123.9, 128.7, 132.1 (q, J_{CF} = 39.4 Hz), 138.6, 142.8, 160.7 ppm. HRMS (ESI) calcd for $C_{13}H_{11}BrF_3N_2O_2$ 362.9956 $[M + H]^+$, found 362.9954

Continuous Flow Preparation. To a stirred solution of 4-bromophenylhydrazine hydrochloride (**4b**) (0.752 g, 4 mmol, 0.5 M) in DMF (8 mL) in a cylindrical glass vessel was added ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutyrate (**3a**) (1.01 g, 1.05 equiv) was added. After stirring/sonication for 2 min, the homogeneous reaction mixture was subjected to flow processing in the X-Cube Flash. A 8 mL stainless-steel coil was mounted, and the instrument was flushed with DMF at a constant flow rate of 1.6 mL/min (5 min residence time) and a backpressure of 100 bar. After reaching the temperature set point of 100 °C, the inlet tubing was quickly changed from the solvent reservoir to the sample vessel and, after collection of the main fraction of the product mixture on the outlet, put back into the solvent reservoir for flushing the instrument (∼10 min). The product solution (∼25 mL) was reduced under vacuum, and DMF traces were removed azeotropically (toluene), taken up in 30 mL of ethyl acetate, washed with water (3 × 10 mL) and brine (3 × 10 mL), dried over $MgSO_4$, and evaporated to afford ethyl 1-(4-bromophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**7a**) as a pale yellow residue (1.174 g, 81%).

1-(4-Bromophenyl)-3,5-bis(trifluoromethyl)-1*H*-pyrazole (7b). *Microwave Batch Preparation (entry 6, Table 1).* To a stirred solution of 4-bromophenylhydrazine hydrochloride (**4b**) (564.1 mg, 2.52 mmol) in methanol/water 2:1 (v/v) (3 mL) in a 10 mL Pyrex microwave vial were added 1,1,1,5,5,5-hexafluoroacetylacetone (**3b**) (655.4 mg, 1.05 equiv) and conc HCl (1 mL, ∼10 equiv). The mixture was stirred/sonicated for 1 min, and the reaction vial sealed with a snap-on cap. The homogeneous reaction mixture was subjected to microwave heating for 5 min (hold time) at 150 °C and then cooled to 50 °C. The solvent was carefully evaporated (40 °C, 2 mbar), and 1-(4-bromophenyl)-3,5-bis(trifluoromethyl)-1*H*-pyrazole (**7b**) was either directly obtained as a dark oil (895 mg, 99%) or further purified by flash chromatography and obtained as a pale yellow oil (832 mg, 92%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.61 (d, J = 8.4, 2H) 7.82−7.85 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 108.9, 119.2 (q, J_{CF} = 268.0 Hz), 120.9 (q, J_{CF} = 267.4 Hz), 124.5, 128.8, 133.0, 134.2 (q, J_{CF} = 39.8 Hz), 137.3, 142.1 (q, J_{CF} = 38.7 Hz) ppm; HRMS (ESI) calcd for $C_{11}H_6N_2F_6Br$ 358.9619 $[M + H]^+$, found 358.9615

Continuous Flow Preparation. To a stirred solution of 4-bromophenylhydrazine hydrochloride (**4b**) (0.752 mg, 4 mmol, 0.5 M) in acetic acid/water 40:3 (8 mL of acetic acid + 0.6 mL of water) in a cylindrical glass vessel were added 1,1,1,5,5,5-hexafluoroacetylacetone (**3b**) (873.8 mg, 1.05 equiv) and triethylamine (809.5 mg, 2 equiv). After stirring/sonication for 2 min, the homogeneous reaction mixture was subjected to flow processing in the X-Cube Flash. An 8 mL stainless steel coil was mounted, and the instrument was flushed with acetic acid at a constant flow rate of 1.6 mL/min (5 min residence time) and a backpressure of 140 bar. After reaching the temperature set point of 230 °C, the inlet tubing was quickly changed from the solvent reservoir to the sample vessel and, after collection of the main fraction of the product mixture on the outlet, put back into the solvent reservoir for flushing the instrument (∼10 min). The product solution (∼25 mL) was diluted with 10 mL of brine and extracted with ethyl acetate (3 × 10 mL). After successive washings with satd sodium bicarbonate (10 mL), water (3 × 10 mL) and brine, the organic phase was dried over $MgSO_4$ and evaporated carefully (40 °C, 2−5 mbar) to afford 1-(4-bromophenyl)-3,5-bis(trifluoromethyl)-1*H*-pyrazole (**7b**) as a yellow-brown oil (988 mg, 69%).

Catalyst Screening for the Continuous Flow Hydrogenation of Nitro-Compound 6a (Table 3). All screenings were done in the H-Cube continuous flow hydrogenator (Thales Nanotechnology Inc.). Stock solutions of ethyl 1-(4-nitrophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**7a**) in various polar solvents were prepared (0.02−0.1 M in ethanol, DMF, acetic acid, as appropriate; see Table 3 for more details). Prior to every screening series, the instrument was equipped with a fresh catalyst cartridge (10% Pd/C, 10% Pt/C, 10% Pd/Al_2O_3, or RaNi). The desired values for the flow rate (1−3 mL/min), H_2 pressure ("Full H_2" atmospheric pressure up to 100 bar H_2 overpressure), and cartridge temperature (rt−100 °C) were set on the input panel of the instrument, and a constant flow of pure solvent was pumped through the instrument until the system had stabilized at the chosen set points. At that moment the inlet filter frit of the H-Cube was switched from the solvent reservoir into the stock solution and the nitro-compound was pumped into the H-Cube; simultaneously, the outlet was changed to a fresh 1 mL HPLC vial. After processing ∼1 mL of stock solution, the inlet was again changed to the solvent reservoir, a new set point (temperature, time, flow rate) was programmed, the instrument was flushed with solvent until the set points were reached, the inlet changed to the stock solution, and so forth. The collected product solutions were subjected to HPLC analysis at 215 nm to determine conversions/purities (see Table 3).

Ethyl 1-(4-Aminophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (8a). *Microwave Batch Preparation.* To a stirred mixture of ethyl 1-(4-nitrophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**6a**) (200 mg, 0.61 mmol) and ethanol (2 mL) in a 10 mL Pyrex microwave vial was added cyclohexene (100 mg, 1.21 mmol, 125 μL), immediately followed by 10% (w/w) Pd/C (6.5 mg, 0.0061 mmol, 1 mol %). The reaction vial was sealed with a snap-on cap, and the suspension was subjected to microwave heating for 2 min (hold time) at 160 °C and then cooled to 50 °C. After evaporation of the solvent, the residue was subjected to flash chromatography to afford ethyl 1-(4-aminophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**8a**) as a white solid (167 mg, 92%), mp 107−109 °C.[6] ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.28 (t, J = 7.1 Hz, 3H), 4.28 (q, J = 7.1 Hz, 2H), 5.61 (s, 2H), 6.63 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 8.6 Hz, 2H), 8.17 (s, 1H). MS (pos APCI): m/z (%) 300 (100) $[M + 1]$.

Continuous Flow Hydrogenation (entry 15, Table 3). A 0.03 M solution of ethyl 1-(4-nitrophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**6a**) (148.2 mg, 0.45 mmol) in ethanol (15 mL) was prepared. Using a fresh RaNi cartridge, the H-Cube was first flushed with pure ethanol, while ramping to the desired set point (H_2 "Controlled" mode, 70 bar hydrogen overpressure, a flow rate of 2.5 mL/min and a cartridge temperature of 100 °C). Next, the inlet of the H-Cube was quickly changed from the solvent reservoir to the substrate solution, and the outlet was simultaneously changed to a collection flask. After processing the whole volume of starting material, the inlet was changed back to the solvent reservoir, and the instrument was flushed with a further 15−20 mL. After evaporation of the solvent, ethyl 1-(4-aminophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**8a**) was obtained as yellowish residue (125 mg, 93%).

4-(3,5-Bis(trifluoromethyl)-1*H*-pyrazol-1-yl)aniline (8b). *Microwave Batch Preparation.* To a stirred mixture of 1-(4-nitrophenyl)-3,5-bis(trifluoromethyl)-1*H*-pyrazole (**6b**) (355 mg, 1.1 mmol) and ethanol (2 mL) in a 10 mL Pyrex microwave vial was added cyclohexene (448 mg, 5.5 mmol, 554 μL), immediately followed by 10% (w/w)

Pd/C (35 mg, 0.0033 mmol, 3 mol %). The reaction vial was sealed with a snap-on cap, and the reaction mixture was subjected to microwave heating for 5 min (hold time) at 150 °C and subsequently cooled to 50 °C. After evaporation of the solvent, the residue was subjected to flash chromatography (petrol ether/ethyl acetate + 1% triethylamine 3:1) to afford 4-(3,5-bis(trifluoromethyl)-1*H*-pyrazol-1-yl)aniline (**8b**) as a white solid (312 mg, 96%), mp 140−142 °C; lit.[48] 130−133 °C.[8a] ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.68 (s, 2H), 6.64 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H), 7.67 (s, 1H). MS (pos APCI): m/z (%) 296 (100) [M+1].

Two-Step Continuous Flow Synthesis of Amines 8a,b (Cyclocondensation−Reduction Sequence). Ethyl 1-(4-Aminophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (8a). The optimized continuous flow-procedures for the individual single-step preparations of **6a** (X-Cube Flash, procedure as disclosed in the single-step protocol) and **8a** (H-Cube, procedure as disclosed in the single-step protocol) were used to assemble a continuous two-step flow protocol (1 mmol scale) without isolation of the intermediate. According to the single-step procedure, **6a** was prepared at 175 °C and a flow rate of 2.6 mL/min in a 4 mL stainless steel coil (1.5 min residence time) in acetic acid (0.1 M) with addition of 1.05 equiv of triethylamine. The crude product solution exiting the X-Cube Flash containing **6a** was collected, diluted to 0.03 M concentration, and directly pumped into the H-Cube. After hydrogenation of the crude product solution in "Full H_2" mode at 60 °C and a flow rate of 2 mL/min using Pd/Al_2O_3 as catalyst, the collected product solution was reduced under vacuum, brought onto a sample holder, and subjected to flash chromatography (petrol ether/ethyl acetate + 1% triethylamine 3:1) to afford ethyl 1-(4-aminophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**8a**) as yellow crystals (259 mg, 86%).[6]

4-(3,5-Bis(trifluoromethyl)-1*H*-pyrazol-1-yl)aniline (8b). To a stirred solution of 4-nitrophenylhydrazine hydrochloride (**4a**) (189.6 mg, 1 mmol, 0.1 M) in acetic acid (10 mL) in a cylindrical glass vessel were added 1,1,1,5,5,5-hexafluoroacetylacetone (**3b**) (214.3 mg, 1.03 equiv) and triethylamine (106.3 mg, 1.05 equiv). After stirring/sonication for 2 min, the homogeneous reaction mixture was subjected to flow processing in the X-Cube Flash. A 4 mL stainless-steel coil was mounted, and the instrument was flushed with acetic acid at a constant flow rate of 4 mL/min (1 min residence time) and a backpressure of 140 bar. After reaching the temperature set point of 265 °C, the inlet tubing was quickly changed from the solvent reservoir to the sample vessel and, after collection of the main fraction of the product mixture on the outlet, put back into the solvent reservoir for flushing the instrument (∼5 min). The collected product solution (∼25 mL) was reduced under vacuum and subjected to flash chromatography (petrol ether/ethyl acetate + 1% triethylamine 3:1) to afford 4-(3,5-bis(trifluoromethyl)-1*H*-pyrazol-1-yl)-aniline (**8b**) as an off-white solid (186 mg, 57%).[8a]

General Procedure for the Amidation of 4-(Pyrazol-1-yl)anilines 8a,b to Carboxamides (1a,b; 2a−e) and Sulfonamides (10a,b) (Table 4). Carboxamides (1a,b; 2a−e). To a stirred mixture of either ethyl 1-(4-aminophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**8a**) (150 mg, 0.5 mmol) or 4-(3,5-bis-(trifluoromethyl)-1*H*-pyrazol-1-yl)aniline (**8b**) (200 mg, 0.5 mmol) and acetonitrile (2 mL) in a 10 mL Pyrex microwave vial was added the selected carboxylic acid (0.55 mmol for **1b**, **2c** and 0.75 mmol for **1a**, **2a**, **2b**, **2d**) was added, followed by dropwise addition of phosphorus trichloride (103 mg, 0.75 mmol, 66 μL). The reaction vial was sealed with a snap-on cap, and the suspension subjected to microwave heating for 5 min (hold time) at 150 °C and then cooled to a temperature of 50 °C. The solvent was evaporated, and the residue was subjected to flash chromatography to obtain the pure products.

Ethyl 1-(4-(2,3,3-Trichloroacrylamido)phenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (1a)[6]. White solid (175 mg, 76%), mp 151−153 °C (toluene). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.29 (t, J = 7.1 Hz, 3H), 4.31 (q, J = 7.1 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 8.8 Hz, 2H), 8.28 (s, 1H), 11.33 (s, 1H). MS (pos APCI): m/z (%) 458 (100) [M + 1].

Ethyl 1-(4-(4-Methyl-1,2,3-thiadiazole-5-carboxamido)-phenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (1b)[6,10c]. White solid (180 mg, 78%), mp 119−120 °C; lit.[10c] mp 118−120 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ1.31 (t, J = 7.2, 3H), 2.83 (s, 3H), 4.32 (q, J = 7.2, 2H), 7.57 (d, J = 8.7, 2H), 7.88 (d, J = 8.7, 2H), 8.30 (s, 1H), 11.03 (s, 1H). MS (neg ESI): 424 (100) [M − 1].

***N*-(4-(3,5-Bis(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-4-chlorobenzamide (2a)[9c].** Off-white powder (215 mg, 86%), mp 195−197 °C (toluene); lit.[9c] mp 196−197 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.61−7.66 (m, 4H), 7.83 (s, 1H), 7.99−8.04 (m, 4H), 10.66 (s, 1H). MS (neg APCI): m/z (%) 432 (100) [M − 1].

***N*-(4-(3,5-Bis(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide (2b)[9c].** Brownish solid (179 mg, 63%), mp 165−167 °C; lit.[9c] mp 164−166 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3H), 7.64 (d, J = 8.7 Hz, 2H), 7.82 (s, 1H), 7.91 (d, J = 8.8 Hz, 2H), 11.06 (s, 1H). MS (neg APCI): m/z (%) 420 (100) [M − 1].

***N*-(4-(3,5-Bis(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-2,3,3-trichloroacrylamide (2c)[6].** White solid (192 mg, 85%), mp 147−149 °C (toluene). ^{1}H NMR (300 MHz, DMSO-d_6) δ7.64 (d, J = 8.7, 2H), 7.82−7.85 (m, 3H), 11.35 (s, 1H). MS (neg ESI): 450 (100) [M − 1].

***N*-(4-(3,5-Bis(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)isonicotinamide (2d)[8a].** White solid (101 mg, 89%), mp 170−172 °C; lit.[8a] mp 156−157 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ7.64 (d, J = 8.7 Hz, 2H), 7.82 (s, 1H), 7.87−7.89 (m, 2H), 7.97−8.01 (m, 2H), 8.80−8.82 (m, 2H), 10.84 (s, 1H). MS (pos APCI): m/z (%) 401 (100) [M + 1].

***N*-(4-(3,5-Bis(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide (2e)[9c].** White solid (147 mg, 52%), mp 162−163 °C; lit.[9c] mp152−153 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.64 (d, J = 8.7 Hz, 2H), 7.77 (t, J = 5.3 Hz, 1H), 7.84 (s, 1H), 7.92 (d, J = 8.7 Hz, 2H), 8.62 (d, J = 4.7, 1H), 8.79 (s, 1H), 11.06 (s, 1H). MS (neg APCI): m/z (%) 417 (100) [M − 1].

Sulfonamides (10a,b). To a stirred mixture of 4-(3,5-bis-(trifluoromethyl)-1*H*-pyrazol-1-yl)aniline (**8b**) (200 mg, 0.5 mmol) and acetonitrile (2 mL) 10 mL Pyrex vial was added either 4-chlorobenzenesulfonyl chloride (158 mg, 0.75 mmol) or 4-methylbenzenesulfonyl chloride (142 mg, 0.75 mmol), followed by dropwise addition of pyridine (100 μL). The reaction vial was sealed with a snap-on cap, and the suspension was subjected to microwave heating for 5 min (hold time) at 100 °C and then cooled to a temperature of 50 °C. The solvent was evaporated, and the residue was subjected to flash chromatography to obtain the pure products.

***N*-(4-(3,5-Bis(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-4-chlorobenzenesulfonamide (10a).** White powder (211 mg, 90%), mp 126−128 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.29 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 9 Hz, 2H), 7.68 (d, J = 8.7 Hz, 2H), 7.79 (s, 1H), 7.84 (d, J = 8.7 Hz, 2H) 10.91 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 108.4, 119.1 (q, J_{CF} = 267.9 Hz), 120.3, 120.9 (q, J_{CF} = 270.0 Hz), 127.8, 129.1, 130.0, 133.7, 134.1 (q, J_{CF} = 39.6 Hz), 138.5, 138.7, 140.0, 141.9 (q, J_{CF} = 38.6 Hz) ppm; HRMS (ESI) calcd for $C_{17}H_{11}O_2N_3F_6SCl$ 470.0165 $[M + H]^+$, found 470.0165.

***N*-(4-(3,5-Bis(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-4-methylbenzenesulfonamide (10b).** White powder (225 mg, 92%), mp 105−107 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ2.34 (s, 3H), 7.24−7.29 (m, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.71 (d, J = 8.1 Hz, 2H), 7.77 (s, 1H), 10.73 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.4, 108.4, 119.2 (q, J_{CF} = 268.0 Hz), 119.8, 120.9 (q, J_{CF} = 267.4 Hz), 127.2, 127.8, 130.3, 133.3, 134.1 (q, J_{CF} =

39.5 Hz), 136.8, 140.5, 141.8 (q, J_{CF} = 38.6 Hz), 144.2 ppm; HRMS (ESI) calcd for $C_{18}H_{14}O_2N_3F_6S$ 450.0711 $[M + H]^+$, found 450.0706.

General Procedure for the Direct Amidation via Buchwald−Hartwig Pd-Cross-Coupling Reaction (Table 5). To a stirred mixture of either ethyl 1-(4-bromophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**7a**) (54.5 mg, 0.15 mmol) or 1-(4-bromophenyl)-3,5-bis(trifluoromethyl)-1*H*-pyrazole (**7b**) (53.9 mg, 0.15 mmol) and THF (2 mL) in a 10 mL Pyrex microwave vial was added benzamide (36.3 mg, 2 equiv) or 4-chlorobenzamide (46.7 mg, 2 equiv), followed by addition of Xantphos (8.71 mg, 10 mol %), cesium carbonate (97.8 mg, 2 equiv), and palladium acetate (1.7 mg, 5 mol %). The reaction vial was sealed with a snap-on cap, and the suspension was subjected to microwave heating for 30 min (hold time) at 150 °C and then cooled to a temperature of 50 °C. The solvent was evaporated, and the residue was subjected to flash chromatography to obtain the pure products.

Ethyl 1-(4-Benzamidophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (1c). White powder (52 mg, 86%), mp 212−214 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.01 (t, J = 6.9 Hz, 3H), 4.33 (q, J = 7.2 Hz, 2H), 7.52−7.63 (m, 5H), 7.97−8.00 (m, 4H), 8.29 (s, 1H) 10.57 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.4, 61.5, 116.5, 119.5 (J_{CF} = 269.4 Hz), 120.8, 127.0, 128.2, 128.9, 131.9 (J_{CF} = 39.2 Hz), 132.3, 134.5, 135.1, 141.2, 142.5, 160.8, 166.4 ppm; HRMS (ESI) calcd for $C_{20}H_{17}O_3N_3F_3$ 404.1222 $[M + H]^+$, found 404.1218.

Ethyl 1-(4-(4-Chlorobenzamido)phenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (1d)[9d]. White powder (37 mg, 56%), mp 189−191 °C; lit.[9d] mp 201−202 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.31 (t, J = 7.2 Hz, 3H), 4.32 (q, J = 7.2 Hz, 2H), 7.52−7.66 (m, 4H), 7.95−8.00 (m, 4H), 8.29 (s, 1H) 10.62 (s, 1H). MS (neg APCI): m/z (%) 436 (100) $[M - 1]$.

***N*-(4-(3,5-Bis(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-4-chlorobenzamide (2a)[9c].** White powder (60 mg, 92%), mp 195−197 °C (toluene); lit.[9c] mp 196−197 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.60−7.65 (m, 4H), 7.83 (s, 1H), 7.99−8.03 (m, 4H), 10.65 (s, 1H). MS (neg APCI): m/z (%) 432 (100) $[M - 1]$.

***N*-(4-(3,5-Bis(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-benzamide (2f).** White powder (55 mg, 92%),[10c] mp 238−240 °C; lit.[10c] mp 243−245 °C. ^{1}H NMR (300 MHz, DMSO-d_6): 7.53−7.68 (m, 5H), 7.81 (s, 1H), 7.97−8.03 (m, 4H), 10.60 (s, 1H). MS (neg ESI): 398 (100) $[M - 1]$.

■ ASSOCIATED CONTENT

Supporting Information. Copies of NMR spectra and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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