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Synthesis of *meta*-substituted anilines *via* a three-component reaction of acetone, amines, and 1,3-diketones†

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A facile method for the synthesis of *meta*-substituted arylamines from acyclic precursors was developed. This method is based on three-component cyclo-condensation/aromatization of *in situ* generated imines of acetone with 1,3-diketones either under conventional heating or under microwave irradiation. The utility of this methodology is illustrated by the possibility of a gram scale synthesis of various anilines from readily available reagents.

Introduction

It is hard to overstate the importance of aniline derivatives which are commonly used for manufacturing commodity chemicals,[1] such as plastics, dyes, agrochemicals, pharmaceuticals, and catalysts.[2–6] They are also employed as convenient building blocks in target-oriented organic synthesis, pharmaceutical chemistry, and drug discovery.[7–11] Among other privileged pharmacophoric scaffolds, the *m*-trifluoromethylaniline motif is extensively used in medicinal chemistry due to the fact that typically the introduction of fluorine (in particular, the trifluoromethyl group) into biologically active scaffolds may lead to dramatic changes in their physicochemical properties, increased metabolic stability, and improved pharmacokinetic properties, and oftentimes could enhance the desired biological effect.[12–14] Furthermore, anilines with carbonyl substituents at the *meta*-position are also widely employed in medicinal chemistry,[15–18] serving as pharmacophoric moieties of biologically active agents or structural cores for their chemical modification and diversification in drug discovery. For example, there is a handful of successfully marketed medicinal agents (Fig. 1) containing the *m*-trifluoromethylaniline or *m*-carbonylaniline moiety including important anticancer drugs Casodex® (Bicalutamide),[19,20] Nexavar® (Sorafenib),[21,22] Tasigna® (Nilotinib),[23,24] Avodart® (Dutasteride),[25,26] and Tazemetostat.[27,28] Other important examples are the topical anesthetic Alcaine® (Proxymetacaine),[29,30] the anti-inflamma-

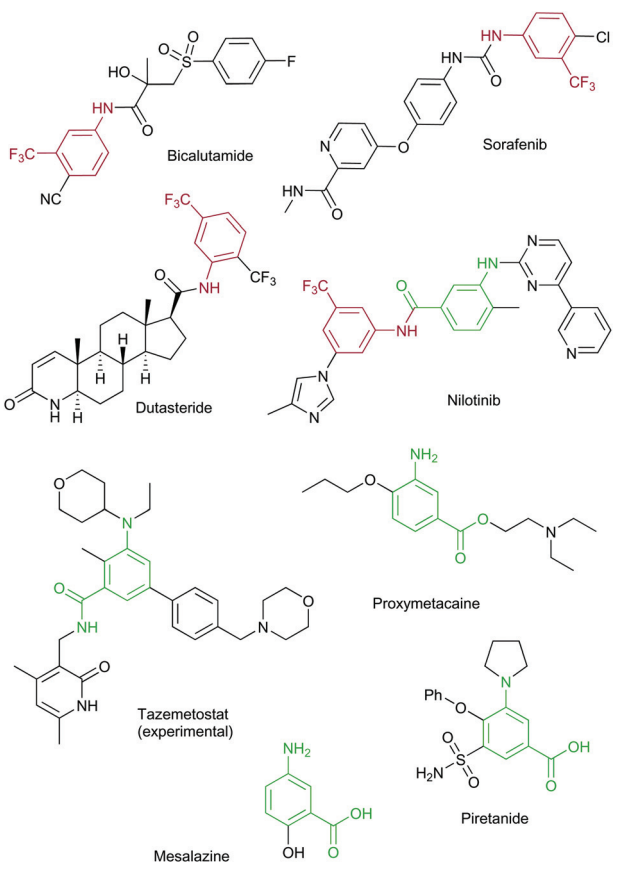

Fig. 1 *m*-Substituted anilines in medicinal chemistry.

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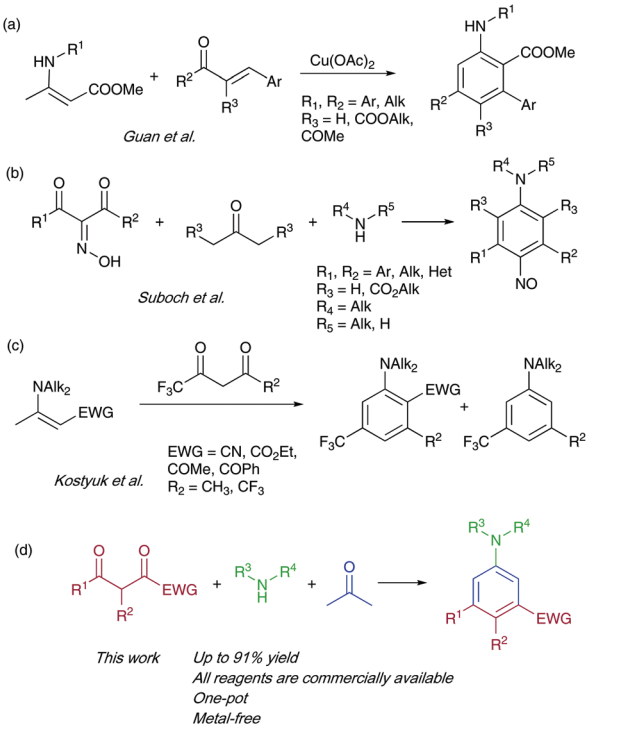
tory agent Asacol® (Mesalazine),[31,32] and the loop diuretic Arelix® (Piretanide).[33,34] From this perspective, it is not surprising that synthetic efforts towards the *m*-substituted aniline core continue to be the focus of attention of many research groups. Typically, molecules of this class are accessed *via* transition metal-catalyzed C–N bond forming reactions, such as the Ullmann reaction and Buchwald–Hartwig and Chan–Lam aminations.[35–37] Another commonly used approach involves the modification of an existing arylamine moiety *via* a sequence of steps, involving electrophilic aromatic substitution (S_EAr), directed metalation, C–H activation or metal-catalyzed cross-coupling reactions. Most of these reactions, however, allow for direct and selective functionalization of the *ortho*-position only. Functionalizations of the *meta*- and *para*-positions of the arylamine core are much less straightforward, and typically require the installation and subsequent removal of temporary directing groups.[38–41] In general, *meta*-functionalization of arylamines is rather problematic for both electrophilic substitution methods and transition-metal-catalyzed reactions.[40,41] Alternative approaches, involving the *de novo* assembly of the arylamine core from non-aromatic precursors still remain insufficiently explored. There are several different synthetic strategies known that employ formal [4 + 2] cycloaddition reactions.[42–46] Another method is based on the dehydrogenative aromatization of cyclohexenones or their derivatives.[47–51] The synthesis of arylamines from 1,5-dicarbonyl compounds and alkyl or dialkylamines has also been reported.[52–55] An example was reported, describing the synthetic efforts focused on the synthesis of nitroanilines from dinitropyridone.[56] Arguably, the greatest potential for the *de novo* assembly of *m*-substituted anilines could be achieved *via* synthetic approaches based on formal [3 + 3] cycloaddition–aromatization reactions (Scheme 1a–c). Thus, recently, Guan's[57] and Yaragorla's[58] groups accessed biarylamines *via* cyclocondensation of push–pull enamines with enones followed by oxidation promoted by $Cu(OAc)_2$ or chloranil (Scheme 1a). The synthesis of *p*-nitrosoanilines by the condensation of amines, ketones and 2-hydroxyimino-1,3-diketones has been developed (Scheme 1b).[59–61] However, the reaction requires a long time (up to several months), often giving low yields. Kostyuk *et al.* reported the reaction of enamines with 1,3-dicarbonyl compounds or their surrogates, which is limited to only activated push–pull enamines and a two-component strategy (Scheme 1c).[62–64] We envisioned that these cyclization methods could be potentially employed for the highly efficient assembly of *m*-substituted anilines. Potentially, a three-component one-pot and metal-free cyclocondensation protocol could be designed (Scheme 1d). Herein we wish to report on our progress towards this goal.

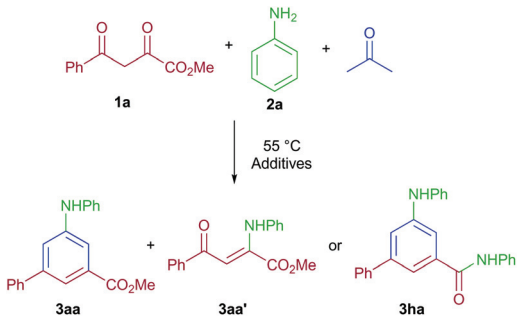


Scheme 1

Results and discussion

Initially, we decided to test our design of the three-component cascade transformation by employing benzoylpyruvate **1a** as the 1,3-dicarbonyl component. To this end, **1a** was stirred with equimolar amounts of aniline (**2a**) in acetone at 55 °C for 24 h. However, the target aniline structure **3aa** was formed in a disappointingly low yield (Table 1, entry 1) along with enamine **3aa′** resulting from the concurrent attack of aniline on the highly electrophilic carbonyl group at C2 of pyruvate **1a**.[65] Taking into account that the formation of enamines is reversible, and that the formation of the aromatic ring should be thermodynamically favored, we wondered if the addition of catalytic amounts of acids might help drive the reaction to completion. Indeed, the addition of a weak protic acid (AcOH, 30 mol%) improved the yield of **3aa** (entry 2). Addition of formic acid, however, led to the predominant formation of enamine **3aa′**, while benzoic acid improved the formation of both **3aa** and **3aa′** compounds. Strong acids (TFA and TsOH, entries 5 and 6) drastically shifted the distribution of the products, resulting in the predominant formation of the side product **3aa′** and only trace amounts of the desired aniline **3aa**. It should be pointed out that the use of aniline hydrochloride also led to the formation of enamine **3aa′** as a major product. Next, we tested the possibility of promoting the cyclization process by employing Lewis acids. To this end, the reaction was carried out in the presence of $ZnCl_2$ (entry 7), $Cu(OAc)_2$ or $FeCl_3$ (not shown in Table 1), all of which provided equally poor results. Our next attempt to improve the cyclization outcome involved the use of basic catalysts. For this purpose, the reaction between **1a**, aniline (**2a**), and acetone was carried out in the presence of 30 mol% of triethylamine (entry 8). Unfortunately, this approach also proved to be unsuccessful and resulted in the predominant formation of arylamine **3ha**. This molecule, in which the ester function was con-

Table 1 Optimization of the three-component reaction by employing pyruvate **1a**



Entry	Additive	Yield[b], % 3aa	3aa′
1	None	14	16
2	30 mol% AcOH	32	16
3	30 mol% HCO_2H	17	55
4	30 mol% $PhCO_2H$	34	38
5	30 mol% TFA	9	42
6	10 mol% $TsOH{\cdot}H_2O$	11	53
7	10 mol% $ZnCl_2$	16	42
8	30 mol% Et_3N	11	9
9[c]	30 mol% AcOH, 125 mg MS 4Å	63	5
10[c]	30 mol% AcOH, 250 mg MS 4Å	69	3
11[c,d]	30 mol% AcOH, 250 mg MS 4Å	73 (60[e])	3

[a] Reagents and conditions: **1a** (0.50 mmol), aniline (0.50 mmol), and acetone (0.5 mL) in a capped vial for 1 d. [b] NMR yields using 1,4-dimethoxybenzene as an internal standard. [c] 2 d. [d] Aniline (0.55 mmol) was used. [e] Isolated yield.

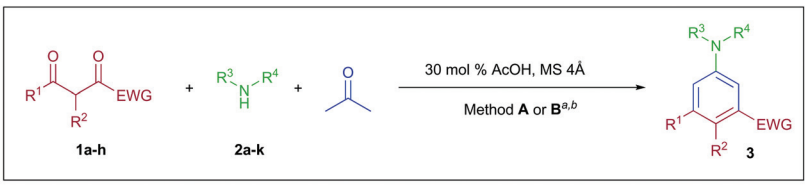
verted into the *N*-phenylamide group, was produced in 25% NMR yield, while ester **3aa** and enamine **3aa′** were formed in insignificant amounts (entry 8). Much better results were obtained in experiments carried out in the presence of 4 Å molecular sieves (MS) added to the reaction mixture in order to remove the water produced as a by-product.[66,67] To our delight, the combination of MS and acetic acid increased the regioselectivity towards the formation of the arylamine **3aa** (entries 9 and 10). A small excess of amine **2** also slightly improved the yield, although this reaction required a longer time to reach completion (entry 11, optimal conditions).

With the optimized conditions in hand, we began to explore the scope of the method. We tested the reaction of series of different acylpyruvates **1** with acetone and a variety of amines **2** (Scheme 2). It should be pointed out that the efficiency of the cyclocondensation process and reaction rates were directly dependent on the amine nucleophilicity employed. Thus, aniline required 2 days to achieve full conversion (**3aa**, 60% yield), while the more reactive *o*-aminophenol achieved full conversion in just 30 min (**3ab**, 91% yield). It should be pointed out that sterically hindered mesithylamine was also successfully involved in this reaction (**3ad**, 73% yield). In order to reduce the reaction time, the effect of microwave irradiation was examined, but it was found that increasing the reaction temperature up to 150 °C increased the amount of side products including enamines and carboxamides derived from acylpyruvic acids. We also tested the reactions with alkylamines and dialkylamines, which afforded the desired products **3ae**, **3bf** in good yields (Scheme 2).

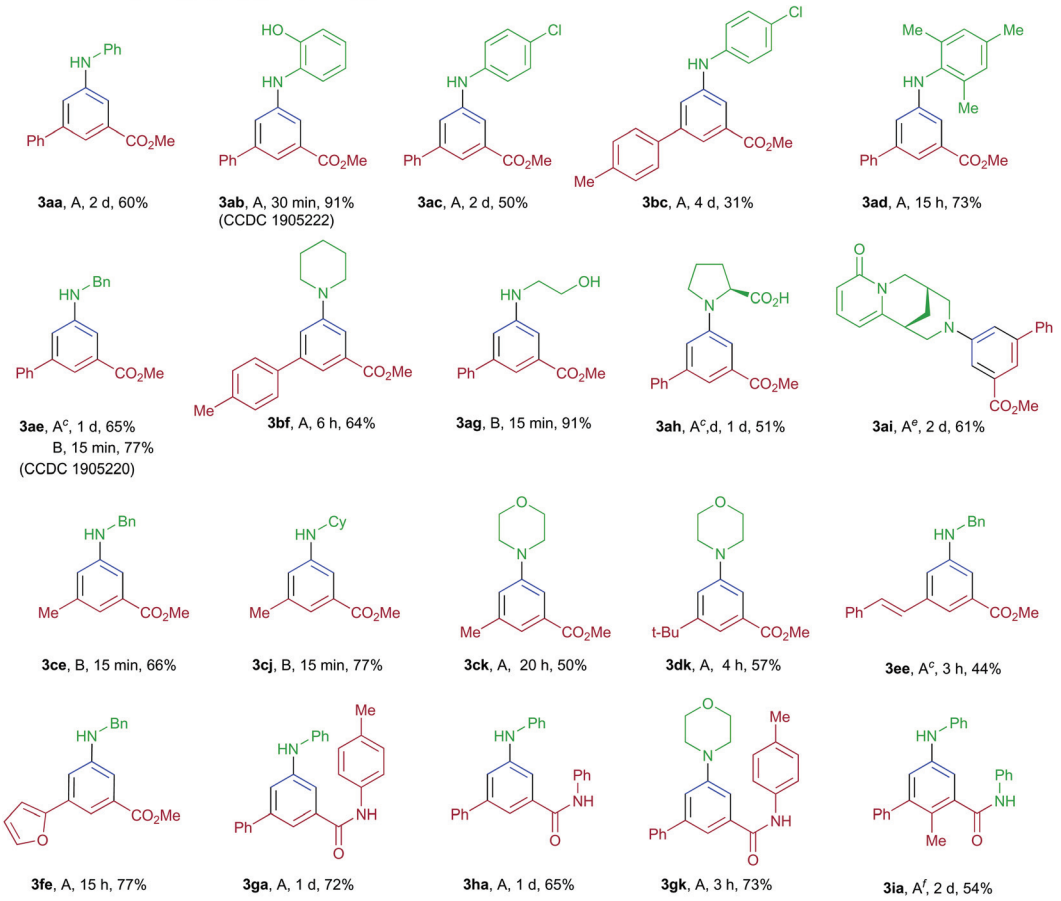
In these cases, the utilization of microwave irradiation was successful and allowed for notable increase of reaction rates without detrimental effect on chemoselectivity. Products **3ae**, **3ag**, **3ce**, **3cj** were obtained according to this modified protocol in 15 min at 150 °C in high yields. It should be stressed that the developed reaction conditions were compatible with unprotected amino alcohols and amino acids (**3ag**, **3ah**). The utility of this method for the modification of more complex amines was also demonstrated by the example of the formation of *N*-aryl substituted cytisine **3ai**. Encouraged by these initial results, we planned on extension of the method to synthesize derivatives of other acylpyruvates (**1c–f**): acetyl, pivaloyl, cinnamoyl, and furoyl. In most cases, the reactions proceeded smoothly to provide the desired products in good yields. It was also demonstrated that the carbonyl group at the C2 of the 1,3-dicarbonyl substrate could also be activated by a carboxamide functionality (**3ga**, **3ha**, **3gk**). It is should be stressed that an EWG group adjacent to one of the carbonyls in the 1,3-diketone is a requisite for the successful implementation of this reaction, as was confirmed by the inefficient reaction with dibenzoylmethane or benzoylacetone, in which trace amounts of the desired products (under the optimized conditions) were detected.

To examine the compatibility of this method with the substitution at the α-position of 1,3-diketones, the reaction with α-methyl substituted benzoylpyruvate (**1i**) was performed. Unexpectedly, the only isolable product formed in this reaction was identified as *m*-carbamoylaniline **3ia**. Most likely, this product was formed *via* the reaction of amines with α-substituted aroylpyruvates affording dihydroxypyrrolones (**3ia′**, Scheme 3) first,[68] which underwent ring cleavage to produce the corresponding amides of aroylpyruvic acids. Subsequent transformation of these amides provides products such as **3ia**. We also tested the reaction of 1,3-diketones bearing a halogen atom at the α-position targeting further functionalization of the would-be product *via* transition metal-catalyzed cross-coupling reactions. Unfortunately, under various conditions these experiments (see the ESI† for details) did not afford *p*-halo-substituted anilines, providing only dehalogenated analogs instead.

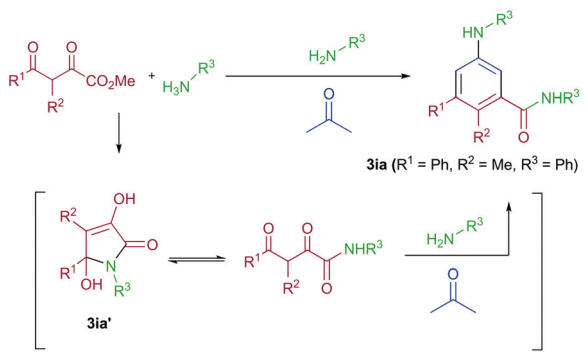
At the next stage of our investigation, in order to access *m*-trifluoromethylated anilines, the reaction of 1,3-diketones **4a–d** bearing the trifluoromethyl group with various amines was examined (Scheme 4). It should be pointed out that the interaction of trifluoromethyl 1,3-diketones with arylamines required prolonged heating. For example, product **5al** was isolated in a yield of 17% after 4 days at 55 °C. Heating at higher temperatures under microwave irradiation accelerated the reaction drastically, and more importantly, reduced the amount of side products (see the discussion on the mechanistic rationale below). The yield of products **5** also depended on the nucleophilicity of arylamines. Thus, the reaction of the least nucleophilic (among the tested arylamines) *p*-trifluoromethylaniline (**2n**) proceeded to completion in 1 h at 150 °C, affording product **5an** in 54% yield. Both alkyl-



1: R^1 = Ph, R^2 = H, EWG = CO_2Me (a); R^1 = *p*-Tol, R^2 = H, EWG = CO_2Me (b); R^1 = Me, R^2 = H, EWG = CO_2Me (c); R^1 = *t*-Bu, R^2 = H, EWG = CO_2Me (d); R^1 = PhCH=CH, R^2 = H, EWG = CO_2Me (e); R^1 = furan-2-yl, R^2 = H, EWG = CO_2Me (f); R^1 = Ph, R^2 = H, EWG = CONH(*p*-Tol) (g); R^1 = Ph, R^2 = h, R^3 = CONHPh; R^1 = Ph, R^2 = Me, EWG = CO_2Me (i);
2: H_2NPh (a); *o*-aminophenol (b); *p*-$ClC_6H_4NH_2$ (c); H_2NMes (d); H_2NBn (e); piperidine (f); $H_2N(CH_2)_2OH$ (g); L-proline (h); cytisine (i); H_2NCy (j); morpholine (k);

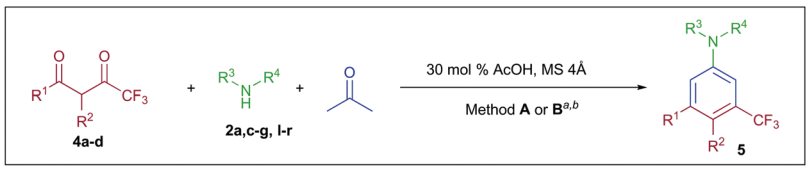


Scheme 2 [a] Method A: **1** (0.50 mmol), **2** (0.55 mmol), AcOH (0.15 mmol), MS 4Å (250 mg) and acetone (0.5 mL) in a capped vial at 55 °C. Method B: **1** (0.5 mmol), **2** (0.55 mmol), AcOH (0.15 mmol), MS 4Å (250 mg) and acetone (2 mL) in a vial under microwave irradiation at 150 °C. [b] Isolated yields are provided. [c] 2.0 mmol scale. [d] At RT. [e] 0.2 mmol scale. [f] 0.25 mmol scale (2 equiv. of aniline were used).

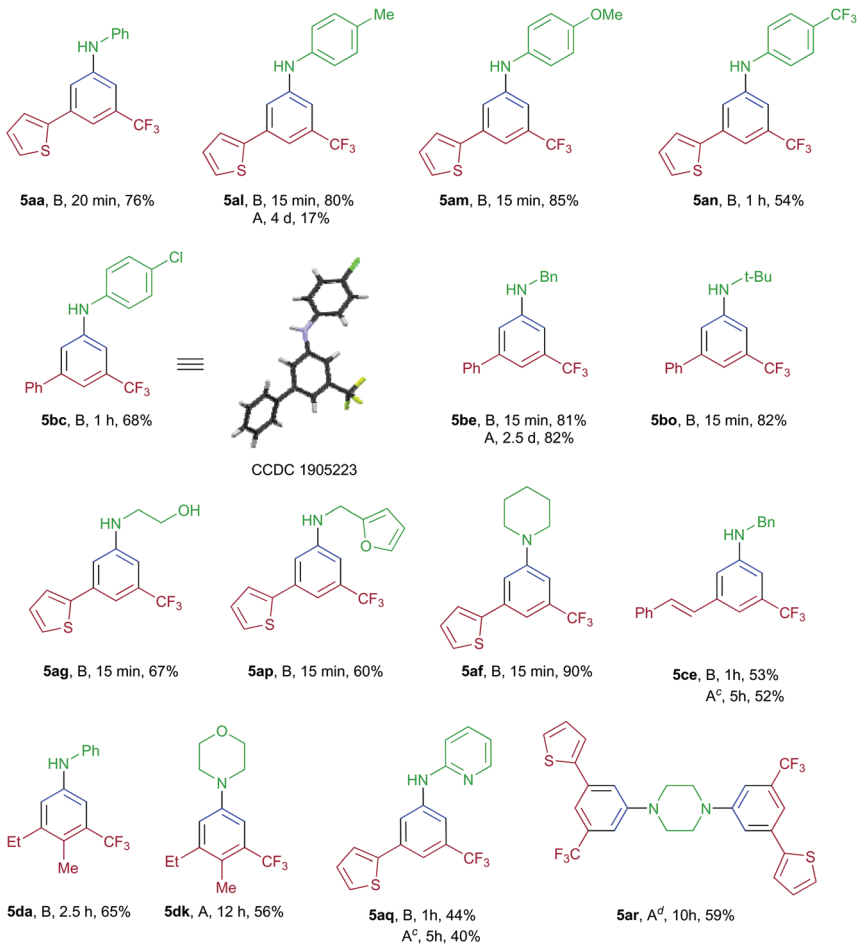


Scheme 3

and dialkylamines were successfully utilized in the synthesis of the corresponding anilines which were obtained in good to excellent yields under either conventional heating or microwave irradiation. The possibility of employing α-methylsubstituted diketones in this method was demonstrated by the preparation of adducts **5da** and **5dk**. Unfortunately, the application of weakly nucleophilic nitrogen-based heterocycles in the reaction with 1,3-diketones did not result in the desired products (see the ESI† for the tested heterocycles). Nevertheless, we were able to obtain product **5aq** from 2-aminopyridine (**2q**) under microwave irradiation (for 1 h at 150 °C) or under heating in a steel bomb (for 5 h at 150 °C). By employing this method, we also managed to



4: R^1= thiophen-2-yl, R^2 = H (a); R^1= Ph, R^2 = H (b); R^1= PhCH=CH, R^2 = H (c);R^1= Et, R^2 = Me (d);
2: H_2NPh (a); $H_2N(p\text{-}ClC_6H_4)$ (c); H_2NBn (e); piperidine (f); $H_2N(CH_2)_2OH$ (g): $H_2N(p\text{-Tol})$ (l); $H_2N(p\text{-}OMeC_6H_4)$ (m); $H_2N(p\text{-}CF_3C_6H_4)$ (n); $H_2N(t\text{-Bu})$ (o); furfurylamine (p); 2-aminopyridine (q); piperazine (r);

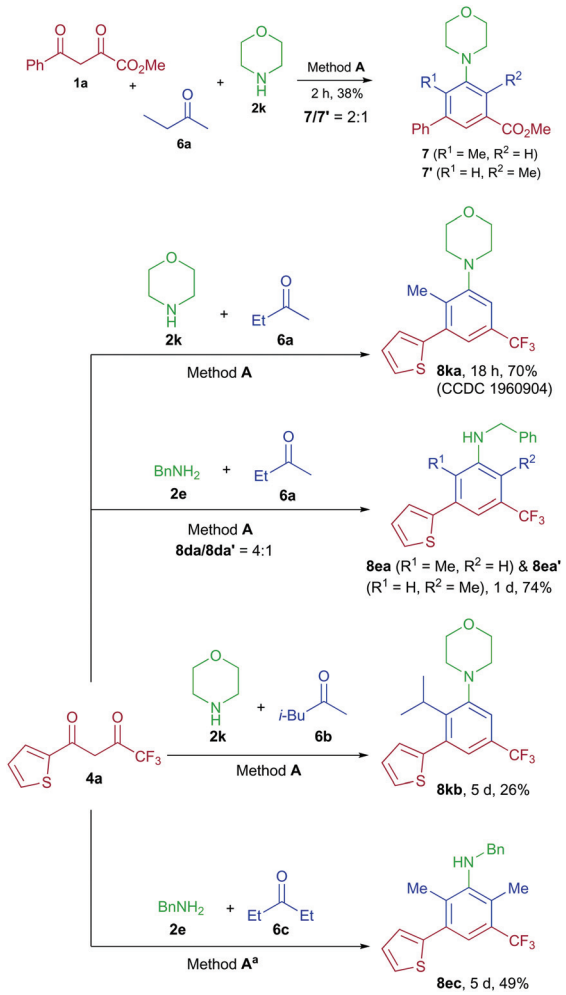


Scheme 4 [a] Method A: **4** (0.50 mmol), **2** (0.55 mmol), AcOH (0.15 mmol), MS 4Å (250 mg) and acetone (0.5 mL) in a capped vial at 55 °C. Method B: **4** (0.5 mmol), **2** (0.55 mmol), AcOH (0.15 mmol), MS 4Å (250 mg) and acetone (2 mL) in a vial under microwave irradiation at 150 °C. [b] Isolated yields are provided. [c] In a steel bomb at 150 °C. [d] 1.00 mmol scale.

access the symmetric product **5ar** by the double-fold interaction of **4a** and acetone with piperazine (**2r**); however, it was not possible to carry out the reaction selectively in a ratio of 1 : 1 to obtain the corresponding mono-adduct.

Although we synthesized anilines with some readily removable protecting groups (*N*-Bn and *N*-*t*-Bu), the assembly of anilines with an unprotected primary amino group proved unsuccessful. To this end, we tested two different NH_3 sources (aqueous NH_3 and NH_4OAc); however, none of them provided satisfactory results. Typically, complex mixtures of products were obtained with the predominant formation of pyridine, resulting from Hantzsch-type cyclization (see the ESI† for details).

During the next stage of our investigation, we tested the reaction of higher homologs of acetone. Interaction of benzoyl pyruvate **1a** with butan-2-one (MEK, **6a**) and morpholine (**2k**), carried out at 55 °C, led to the formation of a mixture of regioisomeric products **7** and **7′** in a ratio of 2 : 1. The predominant formation of regiomer **7** suggests the initial formation of less sterically hindered (kinetic) enamines. According to LC-MS analysis, the test reactions of more sterically hindered ketones (such as isobutyl methyl ketone and diethyl ketone), carried out at 55 °C or at reflux, led to the formation of aroylpyruvic amides as the main products (Scheme 5).



Scheme 5 Method A: **1** or **4** (0.50 mmol), **2** (0.55 mmol), AcOH (0.15 mmol), MS 4A (250 mg) and ketone **6** (0.5 mL) in a capped vial at 55 °C. [a] TSA·H2O (10 mol %) used as a catalyst instead of AcOH.

The reaction of diketone **4a** with MEK (**6a**) and morpholine (**2k**) takes place in a regioselective manner, providing product **8ka** in 70% yield. A similar reaction with benzylamine (**2e**) affords the mixture of regioisomeric products **8ea** and **8ea′** in a ratio of 4 : 1 (Scheme 5). An attempt to employ the more sterically hindered isobutyl methyl ketone (**6b**) resulted in a very sluggish reaction, in which full conversion of diketone (**4a**) was not achieved even after 5 days, but aniline derivative **8kb** was isolated as the sole product in a poor yield. The reaction of diketone **4a** with diethyl ketone **6c** and morpholine (**2k**), carried out at 55 °C, as confirmed using LC-MS analysis, led to the formation of a mixture of stable intermediates that did not transform into final products even after prolonged heating. To implement the dehydration step (see the discussion on the mechanistic rationale below) we attempted to employ a stronger tosic acid as a catalyst, which allowed the isolation of 49% of the target product **8kc** after 5 days of heating (Scheme 5).

It should be pointed out that the developed synthetic protocol can be easily scaled up. For example, products **3jk**, **3ee**

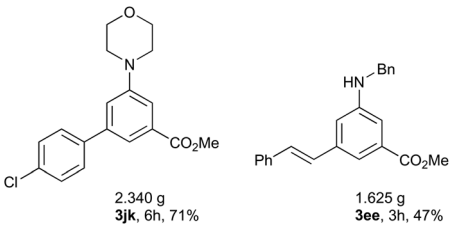
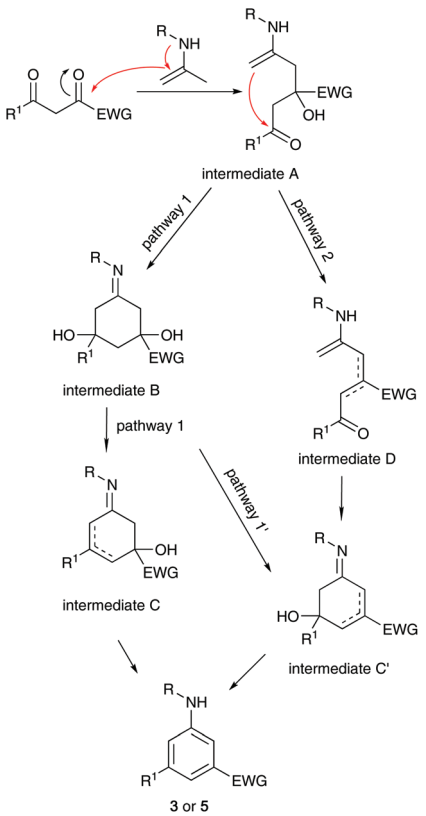


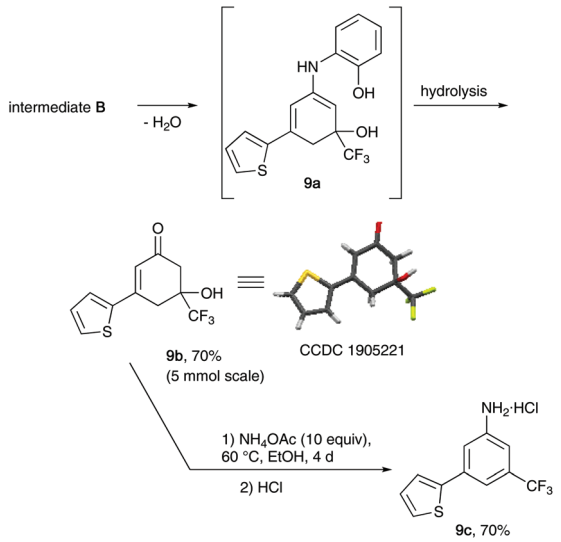
Fig. 2 Scale-up experiments on formal (3 + 3)-cyclocondensation. Reaction conditions: **1** (10 mmol), **2** (11 mmol), AcOH (3.0 mmol), MS 4 Å (2.5 g) and acetone (10 mL) were stirred at 55 °C. Isolated yields of the purified compounds are shown.

were isolated on a gram scale without reducing the yields after simple crystallization (Fig. 2).

A plausible mechanistic rationale for the studied transformation is shown in Scheme 6. It is reasonable to propose the aldol addition of the *in situ* generated imine of acetone[66] to the more electrophilic activated carbonyl group at the C2 of the 1,3-diketone as the initial stage. Next, the newly formed enamine (intermediate **A**) could undergo 6-enolendo-*exo*-*trig* cyclization (pathway 1) to form *exo*-cyclic imine (intermediate **B**). Acid-assisted dehydration should provide intermediate **C** or **C′** (*via* pathway 1 or 1′), and subsequent elimination of a second molecule of water would lead to its aromatization into aniline (**3** or **5**). Alternatively, elimination of the first equivalent of water could take place in the molecule of intermedi-



Scheme 6



Scheme 7

ate **A** to afford intermediate **D** (pathway 2). The latter could undergo 6-enolendo-*exo-trig* cyclization to form intermediate **C′**; however, an alternative mechanism involving isomerization and 6π-electrocyclization is also possible.[40]

When trifluoromethyl-substituted 1,3-diketones, in particular, **4a**, reacted with *o*-aminophenol (or other aromatic amines) at 55 °C, the formation of sufficiently stable intermediates with a molecular mass of 353 a.m.u. (**9a**), which is 18 a.m.u. higher than that of the target product, was observed by LC-MS. This mass could correspond to the structures of intermediates **C**, **C′ or D** (in reactions of acylpyruvates, such intermediates were not detected). Prolonged heating resulted in an increase in the proportion of the side product with a mass of 262 a.m.u. (*via* hydrolysis of the aminophenol moiety), which did not ultimately convert into the target product. Since the structure of this side product (**9b**) could provide valuable information on the mechanism, we isolated this material and established its structure by single crystal X-ray diffraction. A trifluoromethyl alcohol moiety stable to oxidation[41,69,70] or dehydration was revealed, which explains the predominant formation of this material. From the reaction performed at −10 °C, we also isolated the type **C** intermediate **9a** (Scheme 7). Unfortunately, due to its high lability, it was difficult to obtain this material in a sufficiently pure form. Overall, our observations indicated that most likely pathway 1 is operational, at least for the reactions of trifluoromethyl 1,3-diketones. It should be pointed out that cyclohexanone **9b** proved to be suitable for the straightforward synthesis of unprotected anilines (**9c**, Scheme 7) without the formation of unwanted pyridines compared to the direct reaction of 1,3-diketones with NH_4OAc (*vide supra*).

Conclusion

In conclusion, we have developed a convenient synthetic method to access *meta*-substituted anilines *via* a metal-free three-component (3 + 3)-cyclocondensation cascade reaction by employing readily available reagents: acetone (or MEK), amines, and 1,3-diketones. The reaction can be carried out under conventional heating as well as under microwave irradiation and scaled up easily, allowing the synthesis of a wide range of arylamines containing electron-withdrawing substituents in the *meta*-position, including a trifluoromethyl group or synthetically useful functionalities such as an ester or an amide group.

Experimental

General information

^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance III HD spectrometer (at 400, 101, or 377 MHz, respectively) at 40 °C in $CDCl_3$ or DMSO-d_6 using the residual solvent peak ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; DMSO-d_6: δ_H = 2.50 ppm; δ_C = 39.5 ppm) and $PhCF_3$ ($CDCl_3$: δ_F = −62.6 ppm; DMSO-d_6: δ_F = −60.9 ppm)[71] or C_6F_6 ($CDCl_3$: δ_F = −161.64 ppm; DMSO-d_6: δ_F = −162.45 ppm)[71] as internal standards. Splitting patterns of apparent multiplets were designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broadened), *etc*. FT-IR spectra were recorded as mulls or neat samples in mineral oil by employing a PerkinElmer Spectrum Two spectrometer. Melting points were measured with Mettler Toledo MP70 Melting Point apparatus. Reaction progress was monitored by LC-MS on a Waters Acquity UPLC I-Class instrument equipped with a PDA eλ detector and a Xevo TQD detector in ESI + ionization mode. High-resolution mass spectra were measured using a Bruker microTOF-QTM ESI-TOF mass spectrometer. X-ray structural analyses of compounds **3ab**, **3ae**, **5bc**, **8ka** and **9b** were performed on an Xcalibur Ruby diffractometer using a Mo X-ray source (MoK^{α} 0.71073 Å), by scanning at 295(2) K. Microwave-assisted reactions were performed in standard reaction vessels, sealed with silicone septa, in a Monowave 300 (Anton Paar) instrument equipped with an internal IR probe. Column chromatography was performed on silica gel (Acros Organics, 35–70 μm or 60–200 μm). TLC was performed on silica gel 60 F254 plates (Merck); spots were visualized with UV light (254 nm) and iodine vapors. 4 Å MS were activated prior to use by heating in a vacuum. β-Diketones (**1** and **4**) were purchased from commercial vendors or were synthesized according to the known procedures.[72,73]

General procedure A (conventional heating). A microreactor vessel of an appropriate volume was charged with 4 Å molecular sieves (250 mg), AcOH (9 μL, 30 mol%), amine **2** (0.55 mmol, 1.1 equiv.), and a solution of β-diketone **1** or **4** (0.5 mmol, 1 equiv.) in an appropriate amount of ketone (acetone or **6**, 0.5 mL). The vessel was sealed with a silicone septum and heated at 55 °C (in a preheated aluminium block) for a specified time, as shown in Schemes 2 and 4. The reaction progress was monitored by LC-MS. When the reaction was completed, the molecular sieves were filtered off and washed several times with warm acetone. The combined organic solu-

tions were evaporated, and the residue was purified by preparative column chromatography or re-crystallization.

Scale-up procedure. A 50 mL round bottomed flask equipped with a reflux condenser and a drying tube was charged with a solution of β-diketone **1** (10 mmol, 1.0 equiv.) in acetone (10 mL), 4 Å molecular sieves (2.5 g), AcOH (180 μL), and an appropriate amount of amine **2** (11 mmol, 1.1 equiv.). The mixture was placed in a preheated oil bath and stirred at 55 °C for a specified time, as shown in Fig. 2. After the reaction was completed, the molecular sieves were filtered off, the solution was concentrated in a vacuum and the residual material was purified by re-crystallization.

Reaction in a bomb. A stainless steel bomb charged with β-diketone **4** (0.5 mmol, 1.0 equiv.), acetone (2 mL), 4 Å molecular sieves (250 mg), AcOH (9 μL, 30 mol%), and amine (0.55 mmol, 1.1 equiv.) was heated at 150 °C (preheated oven) for 5 h. After the reaction was completed, the molecular sieves were filtered off, the solution was concentrated in a vacuum and the residual material was purified by column chromatography.

General procedure B (microwave activation). A vessel charged with β-diketone **1** or **4** (0.5 mmol, 1.0 equiv.), acetone (2 mL), 4 Å molecular sieves (250 mg), AcOH (9 μL, 30 mol%), and amine **2** (0.55 mmol, 1.1 equiv.) was placed in a microwave oven and heated at 150 °C for an appropriate time (Schemes 2 and 4). When the reaction was completed, the molecular sieves were filtered off and washed several times with warm acetone. The solution was evaporated, and the residue was purified by column chromatography.

Methyl 5-(phenylamino)-[1,1′-biphenyl]-3-carboxylate (3aa)

Method A (0.5 mmol scale), purified by column chromatography (toluene, R_f 0.42), beige solid (91 mg, 0.30 mmol, 60%), mp 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (t, J = 1.5 Hz, 1H), 7.72 (dd, J = 2.3, 1.5 Hz, 1H), 7.65–7.57 (m, 2H), 7.48 (dd, J = 2.3, 1.6 Hz, 1H), 7.47–7.42 (m, 2H), 7.40–7.30 (m, 3H), 7.19–7.13 (m, 2H), 7.06–6.98 (m, 1H), 5.78 (br. s, 1H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 144.2, 142.9, 142.5, 140.4, 132.0, 129.7 (2C), 129.0 (2C), 127.9, 127.3 (2C), 122.2, 121.0, 120.2, 118.9 (2C), 117.3, 52.3. IR (mineral oil), cm^{-1}: 3374, 1730, 1699, 1591. HRMS (ESI) m/z calcd for $C_{20}H_{18}NO_2^+$ $(M + H)^+$: 304.1332, found: 304.1335.

Methyl 5-((2-hydroxyphenyl)amino)-[1,1′-biphenyl]-3-carboxylate (3ab)

Method A (0.5 mmol scale) (should be isolated as soon as possible, due to the high tendency of the *o*-aminophenol moiety to undergo oxidation) purified by column chromatography (toluene–acetone = 10 : 1, R_f 0.34), yellow-orange solid (145 mg, 91%), mp 130–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (t, J = 1.5 Hz, 1H), 7.59–7.53 (m, 2H), 7.51 (dd, J = 2.3, 1.4 Hz, 1H), 7.46–7.39 (m, 2H), 7.39–7.29 (m, 1H), 7.28–7.23 (m, 1H), 7.22–7.19 (m, 1H), 7.13–7.05 (m, 1H), 7.01 (dd, J = 8.0, 1.6 Hz, 1H), 6.92 (td, J = 7.6, 1.6 Hz, 1H), 6.08 (s, 1H), 5.65 (s, 1H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 150.4, 146.0, 142.9, 140.3, 131.9, 129.0, 128.9 (2C), 127.9, 127.2 (2C), 125.9, 123.7, 121.3, 120.4, 118.9, 115.9, 115.9, 52.4. IR (mineral oil), cm^{-1}: 3396, 3250, 1684, 1595. HRMS (ESI) m/z calcd for $C_{20}H_{18}NO_3^+$ $(M + H)^+$: 320.1281, found: 320.1288.

Methyl 5-((4-chlorophenyl)amino)-[1,1′-biphenyl]-3-carboxylate (3ac)

Method A (0.5 mmol scale), purified by crystallization from EtOH, peach solid (85 mg, 50%), mp 139–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (t, J = 1.6 Hz, 1H), 7.66 (dd, J = 2.3, 1.4 Hz, 1H), 7.61–7.54 (m, 2H), 7.48–7.40 (m, 3H), 7.40–7.32 (m, 1H), 7.30–7.17 (m, 2H), 7.13–6.98 (m, 2H), 5.74 (br. s, 1H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 143.9, 143.0, 141.3, 140.2, 132.2, 129.7 (2C), 129.0 (2C), 128.0, 127.3 (2C), 126.8, 121.4, 120.4, 120.0 (2C), 117.4, 52.4. IR (mineral oil), cm^{-1}: 3386, 1707, 1590, 1540. HRMS (ESI) m/z calcd for $C_{20}H_{17}ClNO_2^+$ $(M + H)^+$: 338.0942, found: 338.0951.

Methyl 5-((4-chlorophenyl)amino)-4′-methyl-[1,1′-biphenyl]-3-carboxylate (3bc)

Method A (0.5 mmol scale), purified by crystallization from EtOH–H_2O, pale yellow solid (54 mg, 31%), mp 140–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (t, J = 1.5 Hz, 1H), 7.65 (dd, J = 2.3, 1.4 Hz, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.45–7.39 (m, 1H), 7.31–7.19 (m, 4H), 7.06 (d, J = 8.8 Hz, 2H), 4.94 (br. s, 1H), 3.93 (s, 3H), 2.40 (s, 3H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 143.8, 143.0, 141.4, 137.9, 137.3, 132.1, 129.7 (2C), 129.7 (2C), 127.1 (2C), 126.7, 121.2, 120.3, 119.9 (2C), 117.2, 52.3, 21.3. IR (mineral oil), cm^{-1}: 3362, 1711, 1607, 1584, 1525. HRMS (ESI) m/z calcd for $C_{21}H_{19}ClNO_2^+$ $(M + H)^+$: 352.1099, found: 352.1099.

Methyl 5-(mesitylamino)-[1,1′-biphenyl]-3-carboxylate (3ad)

Method A (0.5 mmol scale), purified by column chromatography (toluene–hexane = 2 : 1, R_f 0.26), colorless oil (125 mg, 73%, solidifies on standing (semisolid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (t, J = 1.5 Hz, 1H), 7.59–7.49 (m, 2H), 7.44–7.38 (m, 2H), 7.38–7.29 (m, 1H), 7.21 (dd, J = 2.4, 1.5 Hz, 1H), 6.97 (dq, J = 1.3, 0.7 Hz, 2H), 6.84 (dd, J = 2.4, 1.7 Hz, 1H), 5.15 (br. S, 1H), 3.91 (s, 3H), 2.33 (d, J = 0.7 Hz, 3H), 2.22 (d, J = 0.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 147.4, 142.7, 140.9, 136.1, 136.0, 134.9, 131.9, 129.6 (2C), 128.8 (2C), 127.7 (2C), 127.3 (2C), 118.2, 115.8, 113.3, 52.1, 21.0, 18.4 (2C). IR ($CHCl_3$), cm^{-1}: 3420, 3200, 1714, 1597. HRMS (ESI) m/z calcd for $C_{23}H_{24}NO_2^+$ $(M + H)^+$: 346.1802, found: 346.1808.

Methyl 5-(benzylamino)-[1,1′-biphenyl]-3-carboxylate (3ae)

Method B (0.5 mmol scale), purified by column chromatography (toluene–acetone = 20 : 1; R_f 0.69), off-white/white solid (122 mg, 77%), mp 114–116 °C. Method A (2 mmol scale), purified by crystallization from EtOH (414 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (t, J = 1.5 Hz, 1H), 7.51–7.41 (m, 2H), 7.38–7.14 (m, 9H), 6.94 (dd, J = 2.4, 1.6 Hz, 1H), 4.50 (br. s, 1H), 4.33 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 148.4, 142.7, 140.9, 138.9, 131.8, 128.9 (2C), 128.9 (2C), 127.8 (2C), 127.7, 127.6, 127.3 (2C), 118.3, 116.3, 113.0, 52.2, 48.7. IR (mineral oil), cm^{-1}: 3388, 1709, 1605, 1526. HRMS

(ESI) *m*/*z* calcd for $C_{21}H_{20}NO_2^+$ (M + H)$^+$: 318.1489, found: 318.1497.

Methyl 4′-methyl-5-(piperidin-1-yl)-[1,1′-biphenyl]-3-carboxylate (3bf)

Method A (0.5 mmol scale), purified by column chromatography (toluene–acetone = 50 : 1, R_f 0.59), red-orange solid (99 mg, 64%), mp 49–51 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, *J* = 1.5 Hz, 1H), 7.60 (dd, *J* = 2.5, 1.4 Hz, 1H), 7.55–7.50 (m, 2H), 7.33 (dd, *J* = 2.5, 1.6 Hz, 1H), 7.29–7.21 (m, 2H), 3.94 (s, 3H), 3.33–3.20 (m, 4H), 2.41 (s, 3H), 1.82–1.71 (m, 4H), 1.70–1.57 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 152.6, 142.3, 138.3, 137.4, 131.4, 129.5 (2C), 127.2 (2C), 119.5, 119.1, 115.9, 52.1, 50.6 (2C), 25.9 (2C), 24.4, 21.2. IR (mineral oil), cm^{-1}: 1728, 1596, 1570, 1516. HRMS (ESI) *m*/*z* calcd for $C_{20}H_{24}NO_2^+$ (M + H)$^+$: 310.1802, found: 310.1809.

Methyl 5-((2-hydroxyethyl)amino)-[1,1′-biphenyl]-3-carboxylate (3ag)

Method B (0.5 mmol scale), purified by column chromatography (toluene–acetone = 2 : 1, R_f 0.52), light-yellow solid (123 mg, 91%), mp 83–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (t, *J* = 1.5 Hz, 1H), 7.60–7.55 (m, 2H), 7.47–7.39 (m, 2H), 7.39–7.32 (m, 1H), 7.30 (dd, *J* = 2.4, 1.4 Hz, 1H), 7.03 (dd, *J* = 2.4, 1.6 Hz, 1H), 3.91 (s, 3H), 3.90–3.84 (m, 2H), 3.39 (dd, *J* = 5.7, 4.8 Hz, 2H), 3.00 (br. s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 148.8, 142.7, 140.9, 131.8, 128.9 (2C), 127.7, 127.3 (2C), 118.2, 116.5, 112.8, 61.4, 52.2, 46.3. IR (mineral oil), cm^{-1}: 3380, 1710, 1595, 1525. HRMS (ESI) *m*/*z* calcd for $C_{16}H_{18}NO_3^+$ (M + H)$^+$: 272.1281, found: 272.1288.

(5-(Methoxycarbonyl)-[1,1′-biphenyl]-3-yl)-L-proline (3ah)

Method A (2 mmol scale). The solvent was evaporated and the residue was poured into $NaHCO_3$ (sat; 5 mL) and extracted with Et_2O (3 × 5 mL), the water layer was acidified (with conc. HCl, pH *ca.* 2–3), and the formed precipitate was filtered off, affording a peach solid (333 mg, 51%), mp 69–72 °C. An additional portion of **3ah** could be isolated by the extraction of the acidified supernatant with ethyl acetate (3 × 5 mL), affording 105 mg (16%) with purity *ca.* 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (br. s, 1H), 7.64 (d, *J* = 1.3 Hz, 1H), 7.57 (d, *J* = 7.1 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.36–7.30 (m, 1H), 7.25 (d, *J* = 1.8 Hz, 1H), 6.95 (t, *J* = 1.9 Hz, 1H), 4.38 (dd, *J* = 8.3, 2.6 Hz, 1H), 3.90 (s, 3H), 3.66 (td, *J* = 8.4, 3.1 Hz, 1H), 3.44 (q, *J* = 8.0 Hz, 1H), 2.45–2.23 (m, 2H), 2.22–1.91 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 167.7, 147.2, 142.7, 141.1, 131.7, 128.9 (2C), 127.7, 127.4 (2C), 117.5, 115.3, 112.2, 61.0, 52.2, 48.9, 31.1, 23.9. IR (mineral oil), cm^{-1}: 1717, 1598. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{20}NO_4^+$ (M + H)$^+$: 326.1387, found: 326.1389.

Methyl 5-((1*R*,5*S*)-8-oxo-1,5,6,8-tetrahydro-2*H*-1,5-methanopyrido[1,2-*a*][1,5]diazo1(4*H*)-yl)-[1,1′-biphenyl]-3-carboxylate (3ai)

Method A (0.2 mmol scale). Procedure: 125 mg of 4 Å molecular sieves, 3.6 μL of AcOH and cytisine (**2i**; 38 mg, 0.20 mmol, 1.0 equiv.) were added to a solution of **1a** (41 mg, 0.20 mmol, 1.0 equiv.) in acetone (0.5 mL). The resultant solution was stirred at 55 °C for 2 d; after the reaction was completed, the solution was evaporated, and purified by column chromatography (toluene–MeOH = 10 : 1, R_f 0.19), affording a light-orange oil (49 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, *J* = 1.5 Hz, 1H), 7.56–7.48 (m, 2H), 7.45–7.37 (m, 3H), 7.37–7.28 (m, 2H), 7.13 (dd, *J* = 2.5, 1.6 Hz, 1H), 6.55 (dd, *J* = 9.0, 1.3 Hz, 1H), 6.14 (dd, *J* = 6.9, 1.4 Hz, 1H), 4.19 (d, *J* = 15.6 Hz, 1H), 4.01 (ddd, *J* = 15.6, 6.7, 1.1 Hz, 1H), 3.90 (s, 3H), 3.85–3.78 (m, 1H), 3.73 (ddt, *J* = 11.4, 3.3, 1.6 Hz, 1H), 3.23–3.00 (m, 3H), 2.77–2.56 (m, 1H), 2.09–2.01 (m, 1H), 1.99–1.85 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 163.5, 151.8, 150.5, 142.6, 140.7, 139.2, 131.5, 128.9 (2C), 127.8, 127.3 (2C), 120.7, 120.4, 117.1, 116.5, 105.8, 57.2, 57.0, 52.2, 50.1, 35.4, 28.0, 25.6. IR ($CHCl_3$), cm^{-1}: 1718, 1651, 1595, 1548. HRMS (ESI) *m*/*z* calcd for $C_{25}H_{25}N_2O_3^+$ (M + H)$^+$: 401.1860, found: 401.1852.

Methyl 3-(benzylamino)-5-methylbenzoate (3ce)

Method B (0.5 mmol scale), purified by column chromatography (toluene–acetone = 10 : 1, R_f 0.73), off-white solid (84 mg, 66%), mp 64–66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5H), 7.24 (tt, *J* = 1.4, 0.7 Hz, 1H), 7.16 (ddd, *J* = 2.3, 1.5, 0.6 Hz, 1H), 6.65 (ddd, *J* = 2.3, 1.5, 0.7 Hz, 1H), 4.35 (s, 2H), 4.31 (br. s, 1H), 3.88 (s, 3H), 2.30 (dd, *J* = 0.7, 0.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 148.2, 139.3, 139.1, 131.2, 128.8 (2C), 127.7 (2C), 127.5, 120.0, 118.3, 111.2, 52.0, 48.6, 21.6. IR (mineral oil), cm^{-1}: 3384, 1708, 1605, 1526. HRMS (ESI) *m*/*z* calcd for $C_{16}H_{18}NO_2^+$ (M + H)$^+$: 256.1332, found: 256.1336.

Methyl 3-(cyclohexylamino)-5-methylbenzoate (3cj)

Method B (0.5 mmol scale), purified by column chromatography (toluene–acetone = 50 : 1, R_f 0.39), light-yellow solid (95 mg, 77%), mp 70–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (tt, *J* = 1.4, 0.7 Hz, 1H), 7.06 (ddd, *J* = 2.3, 1.5, 0.6 Hz, 1H), 6.57 (tt, *J* = 1.6, 0.8 Hz, 1H), 3.88 (s, 3H), 3.58 (br. s, 1H), 3.30 (tt, *J* = 10.1, 3.8 Hz, 1H), 2.30 (dd, *J* = 0.7, 0.6 Hz, 3H), 2.12–1.98 (m, 2H), 1.85–1.72 (m, 2H), 1.71–1.57 (m, 1H), 1.49–1.33 (m, 2H), 1.31–1.07 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 147.6, 139.1, 131.2, 119.0, 118.5, 111.3, 51.9, 51.7, 33.5 (2C), 26.0, 25.1 (2C), 21.5. IR (mineral oil), cm^{-1}: 3369, 1726, 1707, 1603, 1530. HRMS (ESI) *m*/*z* calcd for $C_{15}H_{22}NO_2^+$ (M + H)$^+$: 248.1645, found: 248.1645.

Methyl 3-methyl-5-morpholinobenzoate (3ck)

Method A (0.5 mmol scale), purified by column chromatography (toluene–EtOAc = 10 : 1, R_f 0.33), pale yellow oil (59 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 2H), 6.95 (d, *J* = 2.2 Hz, 1H), 3.89 (s, 3H), 3.89–3.85 (m, 4H), 3.25–3.11 (m, 4H), 2.36 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 151.2, 139.3, 131.2, 122.4, 121.2, 114.1, 66.9 (2C), 52.2, 49.7 (2C), 21.7. IR ($CHCl_3$), cm^{-1}: 1716, 1599. HRMS (ESI) *m*/*z* calcd for $C_{13}H_{18}NO_3^+$ (M + H)$^+$: 236.1281, found: 236.1284.

Methyl 3-(*tert*-butyl)-5-morpholinobenzoate (3dk)

Method A (0.5 mmol scale), purified by column chromatography (toluene–acetone = 10 : 1, R_f 0.47), light-yellow oil (solidifies in a fridge; 79 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (t, J = 1.6 Hz, 1H), 7.41 (dd, J = 2.5, 1.4 Hz, 1H), 7.19–7.07 (m, 1H), 3.90 (s, 3H), 3.90–3.84 (m, 4H), 3.38–3.12 (m, 4H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 152.6, 151.3, 130.9, 119.0, 118.1, 114.1, 67.0 (2C), 52.1, 49.8 (2C), 35.2, 31.5 (3C). IR ($CHCl_3$), cm^{-1}: 1716, 1598. HRMS (ESI) m/z calcd for $C_{16}H_{24}NO_3^+$ $(M + H)^+$: 278.1751, found: 278.1750.

Methyl (*E*)-3-(benzylamino)-5-styrylbenzoate (3ee)

Method A (2 mmol scale). The reaction mixture was filtered through a short column of silica gel, and purified by crystallization from EtOH, light-yellow solid (299 mg, 44%), mp 129–131 °C. Method A (10 mmol scale), purified by crystallization from EtOH (1.625 g, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (td, J = 1.5, 0.5 Hz, 1H), 7.50 (dtd, J = 7.7, 1.7, 1.0 Hz, 2H), 7.46–7.19 (m, 9H), 7.11 (d, J = 16.3 Hz, 1H), 7.03 (d, J = 16.3 Hz, 1H), 6.95–6.91 (m, 1H), 4.50 (br. s, 1H), 4.41 (s, 2H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 148.3, 138.9, 138.8, 137.3, 131.7, 129.8, 128.9 (2C), 128.8 (2C), 128.4, 127.9, 127.8 (2C), 127.7, 126.8 (2C), 117.6, 115.4, 113.4, 52.2, 48.7. IR (mineral oil), cm^{-1}: 3373, 1708, 1595, 1520. HRMS (ESI) m/z calcd for $C_{23}H_{22}NO_2^+$ $(M + H)^+$: 344.1645, found: 344.1633.

Methyl 3-(benzylamino)-5-(furan-2-yl)benzoate (3fe)

Method A (0.5 mmol scale), purified by column chromatography (toluene, R_f 0.36), light-yellow solid (119 mg, 77%), mp 104–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (t, J = 1.5 Hz, 1H), 7.45 (dd, J = 1.8, 0.8 Hz, 1H), 7.42–7.26 (m, 5H), 7.25 (dd, J = 2.4, 1.4 Hz, 1H), 7.14 (dd, J = 2.4, 1.5 Hz, 1H), 6.66 (dd, J = 3.4, 0.8 Hz, 1H), 6.46 (dd, J = 3.4, 1.8 Hz, 1H), 4.40 (s, 2H), 4.24 (br. s, 1H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 153.6, 148.6, 142.3, 139.0, 132.1, 131.8, 128.8 (2C), 127.7 (2C), 127.5, 114.8, 112.7, 112.2, 111.8, 105.8, 52.2, 48.4. IR (mineral oil), cm^{-1}: 3398, 1728, 1707, 1604, 1525. HRMS (ESI) m/z calcd for $C_{19}H_{18}NO_3^+$ $(M + H)^+$: 308.1281, found: 308.1284.

5-(Phenylamino)-*N*-(*p*-tolyl)-[1,1′-biphenyl]-3-carboxamide (3ga)

Method A (0.5 mmol scale), purified by column chromatography (toluene–acetone = 30 : 1, R_f 0.24), light-yellow solid (136 mg, 72%), mp 76–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.60–7.52 (m, 2H), 7.55–7.48 (m, 4H), 7.48–7.38 (m, 3H), 7.41–7.32 (m, 1H), 7.35–7.26 (m, 2H), 7.21–7.12 (m, 4H), 7.02 (tt, J = 7.5, 1.1 Hz, 1H), 4.67 (br. s, 1H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 144.5, 143.3, 142.1, 140.4, 137.3, 135.5, 134.4, 129.7 (2C), 129.7 (2C), 129.0 (2C), 128.0, 127.3 (2C), 122.6, 120.5 (2C), 119.4 (2C), 118.9, 118.1, 115.1, 21.0. IR (mineral oil), cm^{-1}: 3344, 1652, 1590. HRMS (ESI) m/z calcd for $C_{26}H_{23}N_2O^+$ $(M + H)^+$: 379.1805, found: 379.1810.

***N*-Phenyl-5-(phenylamino)-[1,1′-biphenyl]-3-carboxamide (3ha)**

Method A (0.5 mmol scale), isolated by trituration with EtOH (toluene–EtOAc = 10 : 1, R_f 0.45), beige solid (119 mg, 65%), mp = 148–149 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.68–7.61 (m, 2H), 7.59–7.55 (m, 2H), 7.52 (p, J = 1.6 Hz, 2H), 7.47–7.40 (m, 3H), 7.40–7.28 (m, 5H), 7.19–7.11 (m, 3H), 7.02 (tt, J = 7.3, 1.1 Hz, 1H), 4.92 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 144.7, 143.4, 142.1, 140.4, 138.1, 137.2, 129.7 (2C), 129.2 (2C), 129.0 (2C), 128.1, 127.3 (2C), 124.8, 122.6, 120.5 (2C), 119.4 (2C), 118.9, 117.9, 115.0. HRMS (ESI) m/z calcd for $C_{25}H_{21}N_2O^+$ $(M + H)^+$: 365.1648, found: 365.1642.

5-Morpholino-*N*-(*p*-tolyl)-[1,1′-biphenyl]-3-carboxamide (3gk)

Method A (0.5 mmol scale), purified by crystallization from EtOH, off-white solid (135 mg, 73%), mp 182–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.66–7.56 (m, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.49–7.41 (m, 4H), 7.40–7.34 (m, 1H), 7.23 (dd, J = 2.5, 1.5 Hz, 1H), 7.16 (d, J = 8.2 Hz, 2H), 4.12–3.60 (m, 4H), 3.39–3.17 (m, 4H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 152.1, 143.1, 141.0, 137.0, 135.6, 134.4, 129.7 (2C), 129.0 (2C), 128.0, 127.4 (2C), 120.5 (2C), 117.7, 116.9, 113.7, 66.9 (2C), 49.3 (2C), 21.0. IR (mineral oil), cm^{-1}: 1640, 1590, 1525. HRMS (ESI) m/z calcd for $C_{24}H_{25}N_2O_2^+$ $(M + H)^+$: 373.1911, found: 373.1914.

2-Methyl-*N*-phenyl-5-(phenylamino)-[1,1′-biphenyl]-3-carboxamide (3ia)

Method A (0.25 mmol scale). Procedure: 125 mg of 4 Å molecular sieves, 4 μL of AcOH (30 mol%) and aniline (**2a**; 24 μL, 0.286 mmol, 1.1 equiv.) were added to a solution of ethyl 3-methyl-2,4-dioxo-4-phenylbutanoate (**1i**; 61 mg, 0.26 mmol, 1 equiv.) in acetone (0.5 mL). The resultant solution was heated at 55 °C. When the reaction was completed, the molecular sieves were filtered off and washed several times with warm acetone. The solution was evaporated, and the residue was purified by column chromatography (toluene–EtOAc = 25 : 1, R_f 0.28), affording a grey solid (26 mg, 54%), mp 122–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.55 (m, 3H), 7.45–7.32 (m, 5H), 7.31–7.22 (m, 4H), 7.21–7.03 (m, 5H), 6.96 (t, J = 7.4 Hz, 1H), 5.10 (br. s, 1H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 144.9, 142.5, 141.4, 140.9, 139.0, 138.1, 129.7 (2C), 129.2 (4C), 128.3 (2C), 127.4, 125.9, 124.8, 122.1, 121.1, 120.1 (2C), 118.7 (2C), 115.2, 17.0. IR (CCl_4), cm^{-1}: 3401, 3289, 1652, 1594. HRMS (ESI) m/z calcd for $C_{26}H_{23}N_2O^+$ $(M + H)^+$: 379.1805, found: 379.1811.

Methyl 4′-chloro-5-morpholino-[1,1′-biphenyl]-3-carboxylate (3jk)

Method A (10 mmol scale), purified by crystallization from EtOH, off-white solid (2.34 g, 71%), mp 97–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (t, J = 1.5 Hz, 1H), 7.58 (dd, J = 2.5, 1.4 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 7.22 (dd, J = 2.5, 1.6 Hz, 1H), 3.93 (s, 3H), 3.91–3.87 (m, 4H), 3.31–3.20 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 152.0, 141.5, 139.4, 134.0, 131.9, 129.1 (2C), 128.6 (2C), 119.9, 118.6, 115.8, 66.9 (2C), 52.3, 49.4 (2C). IR (mineral oil), cm^{-1}: 1727, 1602. HRMS (ESI) m/z calcd for $C_{18}H_{19}ClNO_3^+$ $(M + H)^+$: 332.1048, found: 332.1052.

***N*-Phenyl-3-(thiophen-2-yl)-5-(trifluoromethyl)aniline (5aa)**

Method B (0.5 mmol scale), purified by column chromatography (toluene, R_f 0.87), grey solid (121 mg, 76%), mp

47–49 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.30 (m, 6H), 7.19 (ddd, J = 2.3, 1.5, 0.7 Hz, 1H), 7.18–7.14 (m, 2H), 7.13–7.05 (m, 2H), 5.85 (br. s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 143.0, 141.7, 136.6, 132.6 (q, J = 32.2 Hz), 129.8 (2C), 128.3, 125.8, 124.3, 124.1 (q, J = 272.7 Hz), 122.8, 119.6 (2C), 116.9, 114.7 (q, J = 4.0 Hz), 112.1 (q, J = 3.9 Hz). ^{19}F NMR (377 MHz, $CDCl_3$, $PhCF_3$) δ −62.9. IR (mineral oil), cm^{-1}: 3390, 1609, 1594, 1538. HRMS (ESI) m/z calcd for $C_{17}H_{13}F_3NS^+$ $(M + H)^+$: 320.0715, found: 320.0706.

3-(Thiophen-2-yl)-*N*-(*p*-tolyl)-5-(trifluoromethyl)aniline (5al)

Method B (0.5 mmol scale), purified by column chromatography (toluene, R_f 0.88), apricot solid (134 mg, 80%), mp 102–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.32 (m, 3H), 7.31 (q, J = 1.2 Hz, 1H), 7.21–7.13 (m, 2H), 7.13–7.01 (m, 4H), 5.78 (br. s, 1H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7, 143.2, 138.9, 136.5, 132.9, 132.6 (q, J = 32.0 Hz), 130.3 (2C), 128.2, 125.7, 124.2, 124.2 (q, J = 272.7 Hz), 120.7 (2C), 116.2, 114.1 (q, J = 4.0 Hz), 111.3 (t, J = 3.9 Hz), 20.9. ^{19}F NMR (377 MHz, $CDCl_3$, C_6F_6) δ −62.9. IR (mineral oil), cm^{-1}: 3404, 1599, 1515. HRMS (ESI) m/z calcd for $C_{18}H_{15}F_3NS^+$ $(M + H)^+$: 334.0872, found: 334.0863.

N-(4-Methoxyphenyl)-3-(thiophen-2-yl)-5-(trifluoromethyl) aniline (5am)

Method B (0.5 mmol scale), purified by column chromatography (toluene, R_f 0.67), apricot solid (148 mg, 85%), mp 80–82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.28 (m, 3H), 7.25–7.20 (m, 1H), 7.18–7.11 (m, 2H), 7.11–7.07 (m, 1H), 7.00 (ddd, J = 2.2, 1.5, 0.7 Hz, 1H), 6.98–6.91 (m, 2H), 5.67 (br. s, 1H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6, 146.8, 143.3, 136.4, 134.2, 132.5 (q, J = 32.0 Hz), 128.2, 125.6, 124.2 (q, J = 272.6 Hz), 124.1, 123.9 (2C), 115.1 (3C), 113.5 (q, J = 3.9 Hz), 110.3 (q, J = 3.9 Hz), 55.7. ^{19}F NMR (377 MHz, $CDCl_3$, $PhCF_3$) δ −62.9. IR (mineral oil), cm^{-1}: 3397, 1599, 1513. HRMS (ESI) m/z calcd for $C_{18}H_{15}F_3NOS^+$ $(M + H)^+$: 350.0821, found: 350.0809.

3-(Thiophen-2-yl)-5-(trifluoromethyl)-*N*-(4-(trifluoromethyl) phenyl)aniline (5an)

Method B (0.5 mmol scale), purified by column chromatography (toluene, R_f 0.86), off-white solid (104 mg, 54%), mp 59–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.54 (m, 2H), 7.51–7.45 (m, 2H), 7.40–7.32 (m, 2H), 7.31–7.23 (m, 1H), 7.17–7.08 (m, 3H), 6.04 (br. s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5, 143.0, 142.5, 137.0, 133.0 (q, J = 32.4 Hz), 128.4, 127.2 (q, J = 3.7 Hz, 2C), 126.2, 124.5 (q, J = 271.0 Hz), 123.9 (q, J = 272.7 Hz), 123.6 (q, J = 32.8 Hz), 119.1, 117.0 (2C), 116.6 (q, J = 3.9 Hz), 114.2 (q, J = 3.9 Hz). ^{19}F NMR (377 MHz, $CDCl_3$, $PhCF_3$) δ −61.6, −62.9. IR (neat), cm^{-1}: 3437, 3405, 1600, 1526. HRMS (ESI) m/z calcd for $C_{18}H_{10}F_6NS^-$ $(M - H)^-$: 386.0444, found: 386.0442.

N-(4-Chlorophenyl)-5-(trifluoromethyl)-[1,1′-biphenyl]-3-amine (5bc)

Method B (0.5 mmol scale), purified by column chromatography (toluene, R_f 0.88), apricot solid (118 mg, 68%), mp 82–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.54 (m, 2H), 7.50–7.44 (m, 2H), 7.44–7.38 (m, 2H), 7.38–7.35 (m, 1H), 7.32–7.28 (m, 2H), 7.21 (ddd, J = 2.3, 1.5, 0.7 Hz, 1H), 7.12–7.04 (m, 2H), 5.84 (br. s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4, 143.7, 140.7, 139.9, 132.6 (q, J = 32.0 Hz), 129.8 (2C), 129.1 (2C), 128.3, 127.5, 127.3 (2C), 124.2 (q, J = 272.6 Hz), 120.6 (2C), 118.7, 116.6 (q, J = 3.9 Hz), 112.5 (q, J = 3.8 Hz). ^{19}F NMR (377 MHz, $CDCl_3$, $PhCF_3$) δ −62.7. IR (mineral oil), cm^{-1}: 3397, 1612, 1589, 1520. HRMS (ESI) m/z calcd for $C_{19}H_{14}ClF_3N^+$ $(M + H)^+$: 348.0761, found: 348.0750.

N-Benzyl-5-(trifluoromethyl)-[1,1′-biphenyl]-3-amine (5be)

Method B (0.5 mmol scale), purified by column chromatography (toluene, R_f 0.82), light-orange oil (132 mg, 80%). Method A (0.5 mmol scale) yielded 135 mg (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.54 (m, 2H), 7.55–7.32 (m, 8H), 7.26 (td, J = 1.6, 0.8 Hz, 1H), 7.01 (t, J = 1.9 Hz, 1H), 6.90 (ddd, J = 2.2, 1.5, 0.7 1H), 4.43 (s, 2H), 4.30 (br. s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8, 143.3, 140.6, 138.7, 132.2 (q, J = 31.7 Hz), 128.9(4C), 128.0, 127.7, 127.7 (2C), 127.3 (2C), 124.5 (q, J = 272.6 Hz), 114.6, 113.3 (q, J = 3.9 Hz), 108.2 (q, J = 3.9 Hz), 48.4. ^{19}F NMR (377 MHz, $CDCl_3$, $PhCF_3$) δ −62.6. IR ($CHCl_3$), cm^{-1}: 3423, 1611, 1521. HRMS (ESI) m/z calcd for $C_{20}H_{17}F_3N^+$ $(M + H)^+$: 328.1308, found: 328.1311.

N-(*tert*-Butyl)-5-(trifluoromethyl)-[1,1′-biphenyl]-3-amine (5bo)

Method B (0.5 mmol scale), purified by column chromatography (toluene, R_f 0.52), light-orange oil (121 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.52 (m, 2H), 7.50–7.42 (m, 2H), 7.41–7.30 (m, 1H), 7.20 (td, J = 1.6, 0.8 Hz, 1H), 7.11 (d, J = 2.0 Hz, 1H), 6.97 (d, J = 1.9 Hz, 1H), 4.07 (br. s, 1H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8, 143.0, 140.8, 132.0 (q, J = 31.6 Hz), 129.0 (2C), 127.9, 127.3 (2C), 124.6 (q, J = 272.5 Hz), 118.0, 113.3 (q, J = 3.9 Hz), 111.5 (q, J = 3.9 Hz), 51.7, 30.1 (3C). ^{19}F NMR (377 MHz, $CDCl_3$, $PhCF_3$) δ −62.6. IR ($CHCl_3$), cm^{-1}: 3428, 1606, 1578, 1526. HRMS (ESI) m/z calcd for $C_{17}H_{19}F_3N^+$ $(M + H)^+$: 294.1464, found: 294.1461.

2-((3-(Thiophen-2-yl)-5-(trifluoromethyl)phenyl)amino)ethan-1-ol (5ag)

Method B (0.5 mmol scale), purified by column chromatography (toluene–acetone, 4 : 1, R_f 0.32), off-white solid (96 mg, 67%), mp 77–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (m, 2H), 7.20 (tt, J = 1.6, 0.8 Hz, 1H), 7.08 (dd, J = 5.1, 3.6 Hz, 1H), 7.02–6.96 (m, 1H), 6.77 (ddd, J = 2.3, 1.5, 0.7 Hz, 1H), 4.19 (br. s, 1H), 3.89 (dd, J = 5.7, 4.8 Hz, 2H), 3.37 (dd, J = 5.7, 4.8 Hz, 2H), 1.73 (br. s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 143.4, 136.3, 132.4 (q, J = 31.9 Hz), 128.2, 125.5, 124.3 (q, J = 272.7 Hz), 124.0, 113.5, 112.2 (q, J = 4.0 Hz), 108.4 (q, J = 3.9 Hz), 61.2, 45.9. ^{19}F NMR (377 MHz, $CDCl_3$, $PhCF_3$) δ −62.9. IR (mineral oil), cm^{-1}: 3289, 1609, 1531, 1512. HRMS (ESI) m/z calcd for $C_{13}H_{13}F_3NOS^+$ $(M + H)^+$: 288.0664, found: 288.0667.

N-(Furan-2-ylmethyl)-3-(thiophen-2-yl)-5-(trifluoromethyl) aniline (5ap)

Method B (0.5 mmol scale), purified by column chromatography (toluene, R_f 0.73), pale yellow solid (97 mg, 60%), mp

36–39 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 1.9, 0.8 Hz, 1H), 7.35–7.30 (m, 2H), 7.24 (td, J = 1.6, 0.8 Hz, 1H), 7.09 (dd, J = 5.1, 3.6 Hz, 1H), 7.03 (t, J = 1.9 Hz, 1H), 6.82 (ddd, J = 2.3, 1.5, 0.7 Hz, 1H), 6.36 (dd, J = 3.2, 1.9 Hz, 1H), 6.30 (dq, J = 3.3, 0.8 Hz, 1H), 4.39 (s, 2H), 4.33 (br. s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9, 148.3, 143.5, 142.4, 136.2, 132.4 (q, J = 31.9 Hz), 128.2, 125.5, 124.3 (q, J = 272.7 Hz), 124.0, 113.5, 112.4 (q, J = 4.0 Hz), 110.6, 108.6 (q, J = 3.9 Hz), 107.6, 41.3. ^{19}F NMR (377 MHz, $CDCl_3$, $PhCF_3$) δ −62.84. IR (mineral oil), cm^{-1}: 3393, 1609, 1514, 1504. HRMS (ESI) m/z calcd for $C_{16}H_{13}F_3NOS^+$ $(M + H)^+$: 324.0664, found: 324.0663.

1-(3-(Thiophen-2-yl)-5-(trifluoromethyl)phenyl)piperidine (5af)

Method B (0.5 mmol scale), purified by column chromatography (toluene, R_f 0.82), orange oil (140 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 3.6, 1.2 Hz, 1H), 7.33–7.26 (m, 3H), 7.10 (dd, J = 5.1, 3.6 Hz, 1H), 7.09–7.06 (m, 1H), 3.37–3.23 (m, 4H), 1.84–1.70 (m, 4H), 1.68–1.58 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7, 143.9, 136.1, 132.2 (q, J = 31.7 Hz), 128.1, 125.4, 124.5 (q, J = 272.7 Hz), 124.0, 116.6, 113.2 (d, J = 4.3 Hz), 111.6 (q, J = 3.9 Hz), 50.2 (2C), 25.8 (2C), 24.3. ^{19}F NMR (377 MHz, $CDCl_3$, $PhCF_3$) δ −62.7. IR (neat), cm^{-1}: 1687, 1602, 1531. HRMS (ESI) m/z calcd for $C_{16}H_{17}F_3NS^+$ $(M + H)^+$: 312.1028, found: 312.1032.

(*E*)-*N*-Benzyl-3-styryl-5-(trifluoromethyl)aniline (5ce)

Method A (0.5 mmol scale; steel bomb, 150 °C), purified by column chromatography (toluene–hexane, 1 : 2.5, R_f 0.30), off-white solid (92 mg, 52%), mp 75–77 °C. Method B (0.5 mmol scale), purified by column chromatography, off-white solid (94 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.48 (m, 2H), 7.44–7.27 (m, 8H), 7.18 (tt, J = 1.3, 0.6 Hz, 1H), 7.10 (d, J = 16.3 Hz, 1H), 7.02 (d, J = 16.3 Hz, 1H), 6.93 (t, J = 1.7 Hz, 1H), 6.81 (ddd, J = 2.2, 1.5, 0.7 Hz, 1H), 5.08 (br. s, 1H), 4.40 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0, 139.4, 138.2, 137.0, 132.2 (q, J = 31.8 Hz), 130.4, 129.0 (2C), 128.9 (2C), 128.2, 127.9 (2C), 127.9, 127.9, 126.8 (2C), 124.4 (q, J = 272.4 Hz), 114.3, 113.2 (q, J = 4.0 Hz), 109.2 (q, J = 4.0 Hz), 48.9. ^{19}F NMR (376 MHz, $CDCl_3$, $PhCF_3$) δ −62.8. IR (mineral oil), cm^{-1}: 3419, 1715, 1636, 1604, 1517. HRMS (ESI) m/z calcd for $C_{22}H_{19}F_3N^+$ $(M + H)^+$: 354.1464, found: 354.1467.

3-Ethyl-4-methyl-*N*-phenyl-5-(trifluoromethyl)aniline (5da)

Method B (0.5 mmol scale), purified by column chromatography (toluene–hexane = 1 : 4, R_f 0.42), colorless oil (91 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 2H), 7.23 (d, J = 2.5 Hz, 1H), 7.12–7.02 (m, 3H), 7.01–6.88 (m, 1H), 5.76 (s, 1H), 2.67 (q, J = 7.5 Hz, 2H), 2.36 (q, J = 1.7 Hz, 3H), 1.23 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 145.8, 142.9, 140.8, 130.3 (q, J = 28.9 Hz), 129.7 (2C), 127.1, 124.8 (q, J = 274.2 Hz), 121.8, 121.3, 118.2 (2C), 113.6 (q, J = 6.1 Hz), 26.9, 14.6, 14.1 (q, J = 2.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, C_6F_6) δ −60.34. HRMS (ESI) m/z calcd for $C_{16}H_{17}F_3N^+$ $(M + H)^+$: 280.1308, found: 280.1311.

4-(3-Ethyl-4-methyl-5-(trifluoromethyl)phenyl)morpholine (5dk)

Method A (0.5 mmol scale), purified by column chromatography (toluene, R_f 0.27), colorless oil (76 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 2.7 Hz, 1H), 6.91 (d, J = 2.6 Hz, 1H), 4.02–3.67 (m, 4H), 3.35–2.96 (m, 4H), 2.68 (q, J = 7.5 Hz, 2H), 2.33 (q, J = 1.7 Hz, 3H), 1.23 (t, J = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.1, 145.5, 130.0 (q, J = 28.3 Hz), 125.7, 125.0 (q, J = 274.2 Hz), 119.3, 111.3 (q, J = 6.2 Hz), 66.9 (2C), 49.6 (2C), 27.2, 14.7, 13.9 (q, J = 2.6 Hz). ^{19}F NMR (377 MHz, $CDCl_3$, C_6F_6) δ −60.12. IR ($CHCl_3$), cm^{-1}: 1615. HRMS (ESI) m/z calcd for $C_{14}H_{19}F_3NO^+$ $(M + H)^+$: 274.1413, found: 274.1418.

N-(3-(Thiophen-2-yl)-5-(trifluoromethyl)phenyl)pyridin-2-amine (5aq)

Method A (0.5 mmol scale; steel bomb, 150 °C), purified by column chromatography (toluene–EtOAc, 25 : 1, R_f 0.28), light yellow solid (65 mg, 40%), mp 71–73 °C. Method B (0.5 mmol scale), purified by column chromatography, light yellow solid (70 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (ddd, J = 5.1, 2.0, 0.9 Hz, 1H), 7.81 (t, J = 1.9 Hz, 1H), 7.67–7.62 (m, 1H), 7.57 (ddd, J = 8.4, 7.2, 1.9 Hz, 1H), 7.48 (td, J = 1.6, 0.8 Hz, 1H), 7.36 (dd, J = 3.6, 1.2 Hz, 1H), 7.33 (dd, J = 5.1, 1.2 Hz, 1H), 7.21 (br. s, 1H), 7.10 (dd, J = 5.1, 3.6 Hz, 1H), 6.88 (dd, J = 8.4, 1.0 Hz, 1H), 6.83 (ddd, J = 7.3, 5.1, 0.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1, 147.9, 142.8, 141.8, 138.4, 136.5, 132.4 (q, J = 32.3 Hz), 128.3, 126.0, 124.4, 124.1 (q, J = 272.7 Hz), 119.9, 116.6 (q, J = 4.1 Hz), 116.1, 115.0 (q, J = 3.9 Hz), 109.7. ^{19}F NMR (377 MHz, $CDCl_3$, C_6F_6) δ −62.7. IR (mineral oil), cm^{-1}: 1611, 1598, 1547. HRMS (ESI) m/z calcd for $C_{16}H_{12}F_3N_2S^+$ $(M + H)^+$: 321.0668, found: 321.0668.

1,4-Bis(3-(thiophen-2-yl)-5-(trifluoromethyl)phenyl)piperazine (5ar)

Method A (1 mmol scale), after completion, water was added, and the formed precipitate filtered off and washed with EtOH, off-white solid (316 mg, 59%), mp 211–213 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.28 (m, 8H), 7.15–7.05 (m, 4H), 3.48 (s, 8H). ^{13}C NMR (101 MHz, $CDCl_3$, all signals are 2C) δ 151.8, 143.4, 136.5, 132.5 (q, J = 31.8 Hz), 128.3, 125.8, 124.3, 124.3 (q, J = 272.7 Hz), 116.7, 114.5 (d, J = 4.2 Hz), 111.7 (t, J = 4.1 Hz), 49.0. ^{19}F NMR (377 MHz, $CDCl_3$, C_6F_6) δ −62.7. IR (mineral oil), cm^{-1}: 1601. HRMS (ESI) m/z calcd for $C_{26}H_{21}F_6N_2S_2^+$ $(M + H)^+$: 539.1045, found: 539.1065.

Methyl 6-methyl-5-morpholino-[1,1′-biphenyl]-3-carboxylate (7) and methyl 4-methyl-5-morpholino-[1,1′-biphenyl]-3-carboxylate (7′)

Method A (0.5 mmol scale), isolated as a mixture of isomers (ratio 2 : 1, NMR) *via* column chromatography (toluene–EtOAc = 50 : 1, R_f 0.12 and 0.13), colorless oil (60 mg, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (7, major) 7.74 (d, J = 1.7 Hz, 1H), 7.70 (d, J = 1.7 Hz, 1H), 7.47–7.33 (overlapped m, 3H), 7.34–7.26 (m, 2H), 3.91 (s, 3H), 3.91–3.88 (overlapped m, 4H), 3.07–3.00 (m, 4H), 2.27 (s, 3H); (7′, minor) 7.81 (d, J = 1.9 Hz, 1H), 7.62–7.56 (m, 2H), 7.49–7.33 (overlapped m, 4H), 3.92 (s, 3H), 3.91–3.88

(overlapped m, 4H), 3.00–2.94 (m, 4H), 2.57 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (7, major) 167.2, 152.0, 144.1, 141.7, 136.3, 129.3 (2C), 128.3 (2C), 128.3, 127.3, 126.4, 119.1, 67.4 (2C), 52.7 (2C), 52.1, 16.4; (7′, minor) 168.7, 152.8, 140.5, 139.4, 133.3, 132.7, 128.9 (2C), 127.6, 127.1 (2C), 123.9, 121.4, 67.4 (2C), 52.7 (2C), 52.0, 15.3. IR ($CHCl_3$), cm^{-1}: 1717, 1602, 1572. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{22}NO_3^+$ $(M + H)^+$: 312.1594, found: 312.1605.

4-(2-Methyl-3-(thiophen-2-yl)-5-(trifluoromethyl)phenyl) morpholine (8ka)

Method A (0.5 mmol scale), purified by column chromatography (toluene, R_f 0.35), white solid (114 mg, 70%), mp 100–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 1.8 Hz, 1H), 7.39 (dd, J = 5.1, 1.2 Hz, 1H), 7.28 (d, J = 1.8 Hz, 1H), 7.12 (dd, J = 5.0, 3.5 Hz, 1H), 7.08 (dd, J = 3.5, 1.2 Hz, 1H), 3.96–3.88 (m, 4H), 3.14–2.91 (m, 4H), 2.42 (d, J = 1.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6, 142.2, 136.9, 135.6, 128.8 (q, J = 32.2 Hz), 127.4, 127.3, 126.0, 124.3 (q, J = 272.1 Hz), 122.5 (q, J = 3.9 Hz), 115.3 (q, J = 3.8 Hz), 67.3 (2C), 52.5 (2C). ^{19}F NMR (377 MHz, $CDCl_3$, C_6F_6) δ −62.19. IR ($CHCl_3$), cm^{-1}: 1582. HRMS (ESI) *m*/*z* calcd for $C_{16}H_{17}F_3NOS^+$ $(M + H)^+$: 328.0977, found: 328.0969.

N-Benzyl-2-methyl-3-(thiophen-2-yl)-5-(trifluoromethyl)aniline (8ea) and *N*-benzyl-2-methyl-5-(thiophen-2-yl)-3-(trifluoromethyl)aniline (8ea′)

Method A (0.5 mmol scale), isolated as a mixture of isomers (ratio 4 : 1, NMR) *via* column chromatography (toluene–hexane = 1 : 3, R_f 0.35), colorless oil (128 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (**8ea**, major) 7.53–7.33 (m, 6H), 7.16–7.12 (m, 2H), 7.06 (dd, J = 3.5, 1.2 Hz, 1H), 6.94 (s, 1H), 4.46 (s, 2H), 4.28 (s, 1H), 2.25 (s, 3H); (**8ea′**, minor) 7.53–7.33 (m, 6H), 7.30–7.27 (m, 2H), 7.11–7.07 (m, 2H), 4.49 (s, 2H), 4.28 (s, 1H), 2.31 (d, J = 1.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (**8ea**, major) 146.8, 142.5, 138.5, 135.4, 129.0 (2C), 128.9 (q, J = 31.9 Hz), 127.9 (2C), 127.8, 127.3, 127.2, 125.8, 124.6 (q, J = 272.2 Hz), 124.5, 116.9, 106.1, 48.8, 14.6; (**8ea′**, minor) 147.3, 144.1, 138.5, 133.2, 130.1 (q, J = 29.3 Hz), 129.0 (2C), 128.1, 127.8 (3C), 125.0, 124.8 (q, J = 274.1 Hz), 123.5, 119.8, 112.7, 111.2, 48.8, 12.9 (q, J = 2.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, C_6F_6) δ −59.66 (minor), −62.38 (major). IR ($CHCl_3$), cm^{-1}: 3470, 3440, 1588. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{17}F_3NS^+$ $(M + H)^+$: 348.1028, found: 348.1031.

4-(2-Isopropyl-3-(thiophen-2-yl)-5-(trifluoromethyl)phenyl) morpholine (8kb)

Method A (0.5 mmol scale), purified by column chromatography (toluene–hexane = 1 : 1, R_f 0.30), colorless liquid (47 mg, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.56 (m, 1H), 7.43 (dq, J = 2.1, 0.7 Hz, 1H), 7.36 (ddd, J = 5.2, 1.2, 0.5 Hz, 1H), 7.07 (ddd, J = 5.2, 3.5, 0.5 Hz, 1H), 6.97 (ddd, J = 3.5, 1.2, 0.5 Hz, 1H), 3.88 (s, 4H), 3.43 (p, J = 7.0 Hz, 1H), 2.90 (s, 4H), 1.35 (d, J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 149.6, 142.4, 136.7, 128.7 (q, J = 32.5 Hz), 127.4, 127.0, 126.5 (q, J = 3.8 Hz), 125.9, 124.0 (q, J = 272.1 Hz), 121.9 (q, J = 3.5 Hz), 67.3 (2C), 54.7 (2C), 30.6, 22.4 (2C). ^{19}F NMR (377 MHz, $CDCl_3$, C_6F_6) δ −62.28. IR ($CHCl_3$), cm^{-1}: 1579, 1522. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{21}F_3NOS^+$ $(M + H)^+$: 356.1290, found: 356.1302.

N-Benzyl-2,6-dimethyl-3-(thiophen-2-yl)-5-(trifluoromethyl) aniline (8ec)

Method A (0.5 mmol scale), 0.1 equiv. of TSA·H_2O was used as the catalyst instead of AcOH. Before column chromatography, 0.3 equiv. of triethylamine was added to neutralize TSA and the mixture was purified by column chromatography (hexane–toluene = 4 : 1, R_f 0.29), colorless oil (89 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.43–7.30 (m, 6H), 7.11 (dd, J = 5.2, 3.5 Hz, 1H), 7.04 (dd, J = 3.5, 1.2 Hz, 1H), 4.16 (s, 2H), 3.59 (s, 1H), 2.47 (q, J = 1.5 Hz, 3H), 2.37 (d, J = 0.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8, 142.5, 139.5, 133.6, 133.4, 128.9 (3C), 128.2 (2C), 127.8, 127.7 (q, J = 29.2 Hz), 127.2, 127.2, 125.7, 124.7 (q, J = 273.7 Hz), 122.9 (q, J = 6.2 Hz), 53.4, 16.7, 14.3 (q, J = 2.5 Hz). ^{19}F NMR (377 MHz, $CDCl_3$, C_6F_6) δ −60.30. IR ($CHCl_3$), cm^{-1}: 3381, 1567. HRMS (ESI) *m*/*z* calcd for $C_{20}H_{19}F_3NS^+$ $(M + H)^+$: 362.1185, found: 362.1179.

2-((3-Hydroxy-5-(thiophen-2-yl)-3-(trifluoromethyl)cyclohexa-1,5-dien-1-yl)amino)phenol (9a)

A solution of 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione (**4a**; 666 mg, 3.00 mmol, 1.00 equiv.) and *o*-aminophenol (**2b**; 338 mg, 3.10 mmol, 1.03 equiv.) in acetone (5 mL) was placed in a fridge (−10 °C, overnight). The reaction mixture was evaporated, and *ca.* 10 mL of $CHCl_3$ was added. The formed precipitate was filtered off, affording 428 mg of an yellow-orange solid, which contained the title product **9a** (*ca.* 85%), **9b**, *o*-aminophenol, and 2-((3-(thiophen-2-yl)-5-(trifluoromethyl) phenyl)amino)phenol, as shown by LC-MS. NMR analysis resulted in complicated spectra, due to significant decomposition of **9a**. HRMS (ESI) *m*/*z* calcd for $C_{17}H_{15}F_3NO_2S^+$ $(M + H)^+$: 354.0770, found: 354.0775.

5-Hydroxy-3-(thiophen-2-yl)-5-(trifluoromethyl)cyclohex-2-en-1-one (9b)

A solution of 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione (**4a**; 1.11 g, 5.00 mmol, 1.00 equiv.) and *o*-aminophenol (**2b**; 109 mg, 1.00 mmol, 0.20 equiv.) in acetone (3 mL) was heated at 55 °C for 1 day. Water was added to the reaction mixture, and the formed precipitate was filtered off and washed with warm hexane, affording a peach-yellow solid (922 mg, 70%), mp 152–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, J = 5.0, 1.1 Hz, 1H), 7.43 (dd, J = 3.8, 1.1 Hz, 1H), 7.12 (dd, J = 5.2, 3.8 Hz, 1H), 6.52 (d, J = 1.5 Hz, 1H), 2.86 (br. s, 1H), 3.13 (s, 2H), 2.83–2.73 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 146.8, 141.8, 129.9, 128.7, 128.3, 125.1 (q, J = 284.3 Hz), 121.6, 74.4 (q, J = 29.8 Hz), 42.4, 33.6. ^{19}F NMR (377 MHz, $CDCl_3$, C_6F_6) δ −83.6. IR (mineral oil), cm^{-1}: 3307, 1645, 1594. HRMS (ESI) *m*/*z* calcd for $C_{11}H_{10}F_3O_2S^+$ $(M + H)^+$: 263.0348, found: 263.0349.

3-(Thiophen-2-yl)-5-(trifluoromethyl)aniline hydrochloride (9c)

Procedure: NH_4OAc (5 mmol, 385 mg, 10 equiv.) was added to a solution of **9b** (0.50 mmol, 131 mg, 1.00 equiv.) in EtOH

(2 mL), and the formed mixture was heated at 60 °C for 4 days. After completion, the mixture was diluted with water (10 mL) and extracted with dichloromethane (2 × 10 mL). The organic phase was evaporated, and $CHCl_3$ was added to the residue, followed by 1.20 equiv. of conc. HCl. The formed precipitate was filtered off, affording an apricot solid (98 mg, 70%), mp 225–228 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (dd, J = 5.1, 1.2 Hz, 1H), 7.59 (dd, J = 3.7, 1.2 Hz, 1H), 7.53–7.44 (m, 2H), 7.20 (t, J = 1.6 Hz, 1H), 7.16 (dd, J = 5.1, 3.7 Hz, 1H), 5.65 (s, 3H + H_2O). ^{13}C NMR (101 MHz, DMSO-d_6) δ 142.2, 141.3, 135.8, 130.8 (q, J = 32.0 Hz), 128.6, 126.9, 125.2, 123.8 (q, J = 272.8 Hz), 118.8, 114.7, 113.6. ^{19}F NMR (377 MHz, DMSO-d_6, C_6F_6) δ −61.4. IR (mineral oil), cm^{-1}: 1608, 1561. HRMS (ESI) m/z calcd for $C_{11}H_9F_3NS^+$ $(M + H - HCl)^+$: 244.0402, found: 244.0403.

Conflicts of interest

There are no conflicts to declare.

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