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PAPER

Regioselective synthesis of 1,4-disubstituted imidazoles†

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A short and efficient synthesis of 1,4-disubstituted imidazoles has been developed which provides the desired products with complete regioselectivity. This protocol allows preparation of compounds which are challenging to prepare by current literature methods in a regioselective fashion, a sterically and electronically diverse range of *N*-substituents being accessible. The sequence involves an unusual double aminomethylenation of a glycine derivative, to yield a 2-azabuta-1,3-diene, onto which addition of an amine nucleophile results in a transamination/cyclization to prepare the substituted imidazole. The cyclization event is surprisingly insensitive to steric and electronic variations on the amine component, enabling a diverse range of imidazoles to be prepared.

In the context of a recent project, we required a regiochemically pure 1-substituted-4-carboxyimidazole **1** (Scheme 1). A thorough literature search revealed a very limited number of methods to efficiently prepare imidazoles of this type with complete control over the regioselectivity of the process. The most common route to imidazoles with this substitution pattern utilizes a regioselective monodecarboxylation of an imidazoledicarboxylic acid **2** (Scheme 1),[1] which itself is prepared in three steps from diaminomaleonitrile. Heating to 175 °C is required to affect the regioselective monodecarboxylation along with additional functional group interconversion (FGI) to prepare the desired imidazole **1**. While the lengthy sequence and high temperature decarboxylation are significant disadvantages for this route, the reliance on alkylation (to install R^2) represents the most significant challenge, limiting the breadth of derivatives available through this procedure. A shorter alternative involves an alkylation[2] or arylation[3] of an unsubstituted 4-carboxy-imidazole (Scheme 1); while rapid and relatively mild, poor regioselectivities plague such an approach, which is again completely reliant on alkylation or arylation and is therefore limited by the availability of suitable electrophiles.

In considering other methods to these imidazoles, ring forming condensations (such as [4 + 1] cyclizations) stood out as a viable strategy.[4] For our desired analogs, the most relevant report was present in the patent literature and described a two-step method for the regioselective formation of *N*-aryl-1,4-disubstituted imidazoles, though this proved unreproducible in our hands.[5] Herein we describe the development of a practical, reliable and reproducible method to convert a simple glycine derivative, in two steps, to a diverse range of 1-substituted imidazoles.

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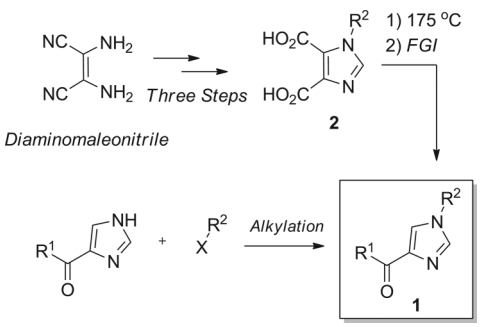
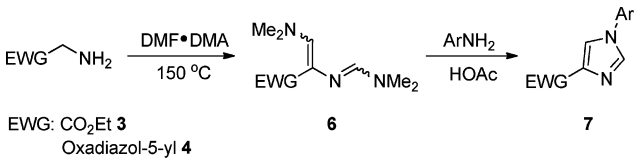
† Electronic supplementary information (ESI) available: Characterization data for all compounds are provided. See DOI: 10.1039/c1ob06690k

The previous report involved reaction of an electron-deficient amine derivative **3–5** (Scheme 2) and dimethylformamide dimethylacetal (DMF·DMA) at 150 °C, forming the corresponding 2-azabuta-1,3-diene (azadiene) **6**;[5] cyclization of **6** with anilines in acetic acid at 100 °C afforded the imidazoles **7**. While this process seemed to offer several advantages in terms of efficiency and regiochemical control, notable issues remained. Significantly, the first reaction is conducted at high temperatures (150 °C, approximately 40 °C above the boiling point of DMF·DMA) and the products **6** are purified by distillation at very low pressures (<0.05 torr). Additionally, only examples of anilines were reported as suitable nucleophilic partners in the condensation, limiting the method to the formation of *N*-aryl imidazoles **7**.



Scheme 1 Previously established routes.[1]



Scheme 2 Azadiene approach to imidazoles.[5]

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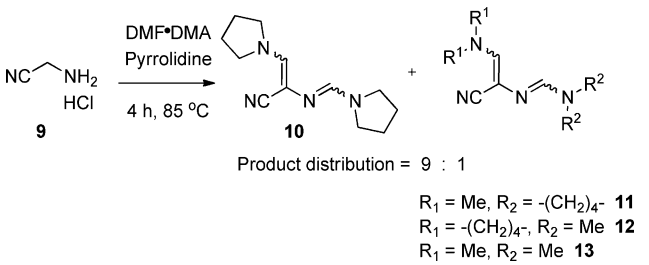
We started our investigation by examining the reactivity of the aminoacetonitrile (**5**) toward DMF·DMA under the reported conditions. Simply refluxing aminoacetonitrile in DMF·DMA yielded clean, albeit trace, conversion to the desired azadiene. We attributed the poor conversion to the low boiling point of DMF·DMA (102–103 °C) as we were unable to reproduce the reported results—even if the reaction was run at the reported bath temperature (150 °C). We hypothesized that higher temperatures may aid conversion; indeed carrying out the reaction in a sealed tube at 150 °C gave full conversion in ~6 h, more consistent with the original procedure but under significant pressure.[5] We focused on trying to eliminate the need for pressure equipment by exploring other reagents to effect the azadiene synthesis.

We thought that increasing the boiling point of the DMF–acetal would improve the conversion. Thus, dimethylformamide di*ethyl*acetal (bp = 130–133 °C), when heated to reflux, increased the rate of reaction compared to DMF·DMA, with complete conversion being observed in 4–6 days. Dimethylformamide di-n-propylacetal (bp = 183–185 °C) at 150 °C provided complete conversion, though still required 2 days (dimethylformamide di-*n*-propylacetal could be generated *in situ* by reacting DMF·DMA and 1-propanol, which yielded identical results).[6] While higher reaction temperatures provided increases in the reaction rate, further increases and lower temperatures were required to make this process practical. Screening additional aminomethylene sources revealed that Bredereck's reagent (*tert*-butoxy bis(dimethylamino)methane **8**, Fig. 1), was a much more effective reagent in this context, forming the azadiene **6** (EWG = CN) in *only ~4 h at 85 °C*;[7] a remarkable increase in reactivity compared to the DMF–acetals. We attempted to rationalize this finding to help drive our research forward. First, we considered that Bredereck's reagent could ionize (and thus react) at a lower temperature than a DMF–acetal based reagent (Fig. 1). Secondly, the greater concentration of amine bases in the system (Me_2NH in this case) could increase the concentration of the nucleophilic ionic-form of the substrate (*via* deprotonation), thus increasing the rate of condensation. However, as Bredereck's reagent is expensive, we sought methods to reproduce these two effects *in situ*.

It is known that heating DMF·DMA in the presence of secondary amines will result in an acetal exchange and generate an alkoxydiaminomethane of the Bredereck's type (**8**).[8] We elected to use pyrrolidine for this purpose due to its greater basicity over other common secondary amines, thus favoring both ionization and deprotonation. We therefore hoped that a mixture of DMF·DMA and pyrrolidine would mimic the two beneficial effects of Bredereck's reagent as stated above.

Gratifyingly, we observed clean conversion to the bispyrrolidino azadiene **10** derivative in only 4 h at a modest 85 °C (Scheme 3). In these early studies aminoacetonitrile (**5**), an unstable oil, had been employed. However, under these new conditions, the shelf-stable hydrochloride salt **9** could be utilized, simply by increasing the amounts of DMF·DMA and pyrrolidine (3.25 equivalents each). At complete conversion the product azadiene **10** (as a mixture of geometric isomers) is accompanied by small amounts (<10%) of the monopyrrolidino-monodimethyl **11–12** and bis-dimethylamino azadienes **13** (Scheme 3); the dimethylamine being derived from DMF·DMA. While additional pyrrolidine could be added to drive the azadienes completely to the bispyrrolidino-derivative **10**, this was not necessary as all the azadienes (**10–13**) undergo the subsequent cyclization (*vide infra*). After formation of the azadiene, dilution with dichloromethane and a simple aqueous extraction removed the pyrrolidinium salts and unreacted alkoxyaminomethane compounds. The solvent was then removed and the crude azadiene could then be used directly, without recourse to high vacuum distillation for purification. With an easy, mild and reliable method to prepare the azadiene in hand, the cyclization to the imidazole could be optimized.



Scheme 3 Formation of the azadienes **10–13**.

To study the formation of the desired imidazoles we investigated the cyclization using 4-bromoaniline (**21**) as our test nucleophile. Initial conditions were: 4-bromoaniline (1.25 equivalents relative to **9**) in acetic acid (5 mL g^{-1}) at 100 °C. Unfortunately, after a brief optimization study the yield only averaged around 30–38%. We hypothesized that the low yield was due to azadiene decomposition during the reaction, by way of cyano group elimination (Scheme 4).

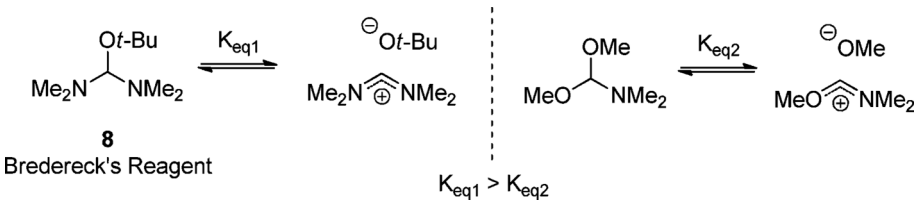
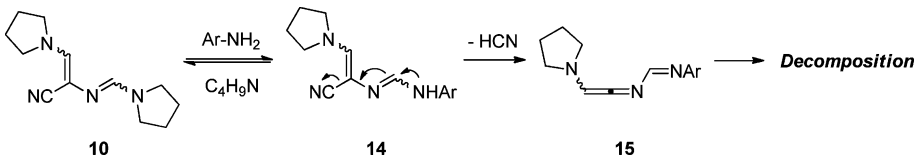


Fig. 1 Hypothesis on the greater reactivity of **8**.



Scheme 4 Potential decomposition pathway for azadiene **10**.

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In order to obviate this potential issue we decided to replace the cyano group with a tertiary morpholino amide **16** (Table 1), which should be a suitable substrate for the condensation and the subsequent cyclization, but be much less likely to undergo this potential decomposition pathway. The known amide **16** was easily prepared from *N*-Boc glycine morpholino amide.[9]

Gratifyingly, the amide **16** was converted to the mixture of azadienes (~90% **17**, ~10% **18–20**) under similar conditions as the aminoacetonitrile hydrochloride (Table 1). The amide **16** underwent only partial conversion to the corresponding azadienes, which necessitated an increase in the amount of DMF·DMA and pyrrolidine (7.5 molar excess each); under these slightly modified conditions, clean conversion to the azadienes **17–20** was obtained in only 4 h. Heating the crude azadienes in the presence of 4-bromoaniline (**21**, 1.5 equivalents) to 100 °C in acetic acid (5 mL g^{-1}) afforded the desired imidazole **22** in 73–75% yield over the two steps (Table 1), a significant increase over the original cyano substrate **10**.

With a high yielding method to selectively prepare the 4-bromophenyl imidazole **22** in hand, we examined electronic and steric effects on the aniline nucleophile. The efficiency of the cyclization was only weakly affected by the electronics of the aromatic system; both electron-rich and electron-deficient anilines (Table 1, entries 1–4) afforded the imidazoles in good yield. The more electron-deficient *p*-nitroaniline (**27**) required a longer reaction time (4 h), but still afforded the imidazole **28** in an acceptable 61% yield. Surprisingly the cyclization was remarkably tolerant to steric variation; examination of bulky anilines revealed that even the extremely sterically demanding 2,6-diisopropylaniline (**29**) gave a 56% yield of the corresponding imidazole **30** (Table 1, entry 5), a truly surprising result. Heterocyclic anilines also afforded the desired imidazoles (Table 1, entries 6,7). 3-Aminopyridine **31** formed the corresponding imidazole **32** in an acceptable 62% yield; however, 5-aminoindole (**33**) provided only 37% yield of **34**, presumably due to the acid sensitivity of the indole itself.

We were interested to try alkyl amines as they were not among the substrates noted in the original report.[5] We immediately determined that the more basic primary alkyl amines were far slower to cyclize to the corresponding imidazole (17–24 h). We were concerned about the stability of the azadiene in AcOH over these extended reaction times; indeed the azadienes were found to be moderately unstable at elevated temperatures in acetic acid. Thus it was clear that increasing the rate of the reaction with simple amines would be needed to achieve acceptable yield of the imidazole products.

We were excited to find that the addition of a catalytic amount (10 mol %) of a secondary aniline, *N*-methylaniline, greatly increased the rate of the addition/cyclization (full conversion with 1-butylamine **35** was obtained in only 2 h).[10] These modified conditions were successful for a range of primary amines (Table 1, entries 8–11). 1-Butylamine (**35**) afforded the imidazole **36** in excellent yield (82%). Alpha-branched systems such as (*S*)-(−)-α-methylbenzylamine (**(−)-37**, 99% e.e.) and (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol (**(+)-39**, 99% e.e.) formed the desired imidazoles without loss of stereochemical information (98.3% e.e. for **(+)-38** and 99.5% e.e. for **(+)-40**). The benzylamine **37** afforded the imidazole in 74% yield; however, the aminoindanol **39** formed the imidazole **40** with reduced efficiency (42%). Sterics again had little impact on the reactivity of the primary alkyl amines—*tert*-butylamine **41** produced the imidazole **42** in an exceptional 75% yield.

The cyclization was by far the most effective when carried out in acetic acid, other solvents giving significant reductions in yield (DMF, toluene, ethanol, acetonitrile and water were screened at a concentration of 5 mL g^{-1}). After completion of the reaction, the solvent is quenched with aqueous potassium carbonate and the imidazole extracted into dichloromethane to afford the crude product after concentration. The major side products, the *N*-acetylamino compounds, unreacted amine and small amounts of *N*-formyl pyrrolidine are conveniently removed by either crystallization or column chromatography.

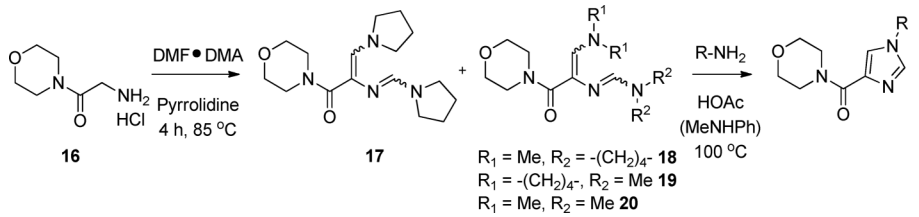
In summary, we have examined the regioselective formation of 1,4-disubstituted imidazoles from a simple glycine derivative *via* azadiene formation and subsequent condensation. By incorporating pyrrolidine in the condensation step with DMF·DMA, we have lowered the reaction temperature from 150 °C to 85 °C, and eliminated the purification of the intermediate azadienes. The combined use of DMF·DMA and pyrrolidine was utilized as an inexpensive replacement for Bredereck's reagent. We have broadened the scope of the cyclization to include a wide range of primary amines with varying steric requirements, where the cyclization can be catalyzed by small amounts of *N*-methylaniline.

Experimental section

(1-(4-Bromophenyl)-1*H*-imidazol-4-yl)(morpholino)methanone (22)

To a 25 mL round bottomed flask was added 2-amino-1-morpholinoethanone hydrochloride[9] (**16**, 1.00 g, 5.54 mmol, 1 equiv.). Pyrrolidine (3.45 mL, 41.52 mmol, 7.50 equiv.) was added slowly *via* syringe over 1 min, followed by dimethylformamide dimethylacetal (mild exotherm noted, 5.54 mL, 41.52 mmol, 7.50 equiv.). The clear solution was heated to 85 °C for 4 h before being cooled to room temperature. The yellow solution was diluted with dichloromethane (75 mL), washed with water (2 × 50 mL), and brine (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an orange oil (2.37 g). The orange oil was diluted with acetic acid (5.00 mL) and 4-bromoaniline (**21**, 1.45 g, 8.30 mmol, 1.5 equiv.) was added. The dark mixture was heated to 100 °C for 2 h, before being cooled to room temperature. The mixture was diluted with dichloromethane (50 mL) and added slowly to a beaker containing a 10% wt/wt aqueous solution of potassium carbonate (75 mL, gas evolution noted). The layers were separated and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a dark brown solid. The solid was slurried in 25% v/v THF in hexanes (20 mL) for 2 min then filtered through a Buchner filter. The cake was rinsed with hexanes (2 × 5 mL) yielding the imidazole **22** as a light brown powder (1.35 g, 73%). A duplicate reaction afforded 1.44 g (77%) of product. ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ 7.89 (d, J = 1.6 Hz, 1H, H_{Imid}), 7.75 (d, J = 1.3 Hz, 1H, H_{Imid}), 7.64 (app d, J = 8.5 Hz, 2H, ArH), 7.30, (app d, J = 8.8 Hz, 2H, ArH), 4.35 (br s, 2H, H_{morph}), 3.78 (br s, 6H, H_{morph}). ^{13}C NMR (125.8 MHz, $CDCl_3$, 23 °C): δ 162.2, 139.1, 135.6, 134.0, 133.2, 124.0, 123.1, 121.8, 67.0 (br s), 47.3 (br s), 43.0 (br s). FTIR (thin film) (cm^{-1}): 3121

Table 1 Regioselective synthesis of 1,4-disubstituted imidazoles



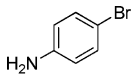
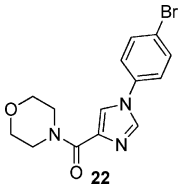
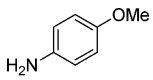
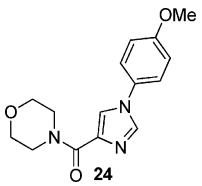
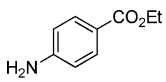
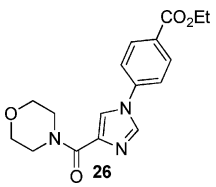
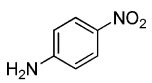
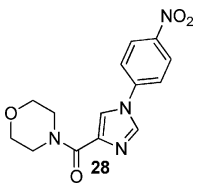
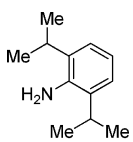
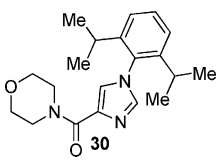
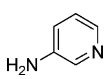
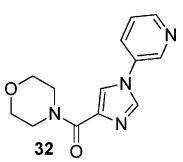
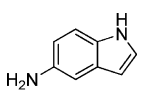
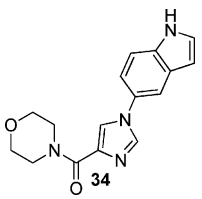
Entry	Amine	Imidazole	Yield[a]
1	 **21**	 **22**	75%
2	 **23**	 **24**	68%
3	 **25**	 **26**	65%
4	 **27**	 **28**	61%
5	 **29**	 **30**	56%
6	 **31**	 **32**	62%
7	 **33**	 **34**	37%

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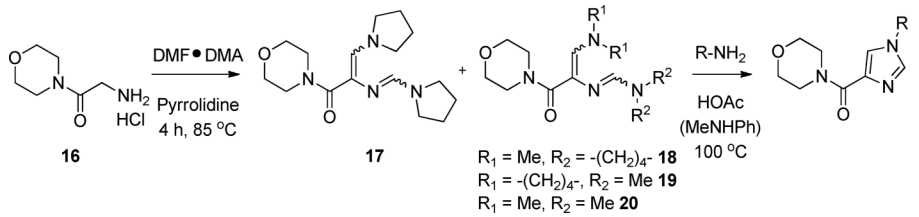
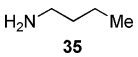
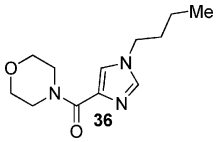
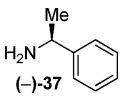
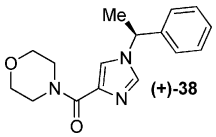
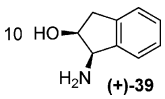
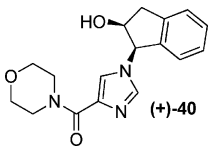
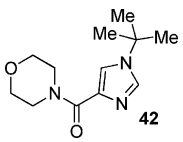
Table 1 (*Contd.*)



Entry	Amine	Imidazole	Yield[a]
8	 **35**	 **36**	82%[b]
9	 **(–)-37**	 **(+)-38**	74%[b]
10	 **(+)-39**	 **(+)-40**	42%[b]
11	 **41**	 **42**	75%[b]

[a] Yield is over two steps and is an average of two runs. [b] 10 mol % *N*-methylaniline was used.

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(w), 2957 (w), 1602 (m), 1505 (m), 1113 (m). HRMS (ESI) (*m*/*z*): Calc'd for $C_{14}H_{15}BrN_3O_2$ $[M + H]^+$: 336.03422, Found: 336.03409. Melting point: 219–221 °C.

(1-(4-Methoxyphenyl)-1*H*-imidazol-4-yl)(morpholino)methanone (24)

To a 25 mL round bottomed flask was added 2-amino-1-morpholinoethanone hydrochloride (**16**, 1.00 g, 5.54 mmol, 1 equiv.). Pyrrolidine (3.45 mL, 41.52 mmol, 7.50 equiv.) was added slowly *via* syringe slowly over 1 min, followed by dimethylformamide dimethylacetal (mild exotherm noted, 5.54 mL, 41.52 mmol, 7.50 equiv.). The clear solution was heated to 85 °C for 4 h before being cooled to room temperature. The yellow solution was diluted with dichloromethane (75 mL), washed with water (2 × 50 mL), and brine (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an orange oil (2.72 g). The orange oil was diluted with acetic acid (5.00 mL) and *p*-anisidine (**23**, 1.02 g, 8.30 mmol, 1.5 equiv.) was added. The dark mixture was heated to 100 °C for 2 h, before being cooled to room temperature. The mixture was diluted with dichloromethane (50 mL) and added slowly to a beaker containing a 10% wt/wt aqueous solution of potassium carbonate (75 mL, gas evolution noted). The layers were separated and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a dark brown solid. The solid was slurried in 25% v/v THF in hexanes (20 mL) for 2 min then filtered through a Buchner filter. The cake was rinsed with hexanes (2 × 5 mL) yielding the imidazole **24** as a light brown powder (1.09 g, 69%). A second reaction afforded 1.07 g (67%) of product. ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ 7.84 (d, J = 1.6 Hz, 1H, H_{Imid}), 7.67 (d, J = 1.3 Hz, 1H, H_{Imid}), 7.31 (app d, J = 8.8 Hz, 2H, ArH), 6.99, (app d, J = 8.8 Hz, 2H, ArH), 4.37 (br s, 2H, H_{morph}), 3.85 (s, 3H, CH_3), 3.77 (br s, 6H, H_{morph}). ^{13}C NMR (125.8 MHz, $CDCl_3$, 23 °C): δ 162.5, 159.3, 138.3, 134.4, 129.8, 124.6, 124.0, 123.2, 115.0, 67.1 (br s), 55.5, 47.2 (br s), 42.9 (br s). FTIR (thin film) (cm^{-1}): 3122 (w), 2959 (w), 1608 (m), 1456 (m), 1112 (m). HRMS (ESI) (*m*/*z*): Calc'd for $C_{15}H_{18}N_3O_3$ $[M + H]^+$: 288.13427, Found: 288.13389. Melting point: 174–175 °C.

Ethyl 4-(4-(morpholine-4-carbonyl)-1*H*-imidazol-1yl)benzoate (26)

To a 25 mL round bottomed flask was added 2-amino-1-morpholinoethanone hydrochloride (**16**, 1.00 g, 5.54 mmol, 1 equiv.). Pyrrolidine (3.45 mL, 41.52 mmol, 7.50 equiv.) was added slowly *via* syringe slowly over 1 min, followed by

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dimethylformamide dimethylacetal (mild exotherm noted, 5.54 mL, 41.52 mmol, 7.50 equiv.). The clear solution was heated to 85 °C for 4 h before being cooled to room temperature. The yellow solution was diluted with dichloromethane (75 mL), washed with water (2 × 50 mL), and brine (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an orange oil (2.63 g). The orange oil was diluted with acetic acid (5.00 mL) and benzocaine (**25**, 2.33 g, 13.84 mmol, 2.50 equiv.) was added. The dark mixture was heated to 100 °C for 2 h, before being cooled to room temperature. The mixture was diluted with dichloromethane (50 mL) and added slowly to a beaker containing a 10% wt/wt aqueous solution of potassium carbonate (75 mL, gas evolution noted). The layers were separated and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a brown solid. The solid was slurried in 25% v/v THF in hexanes (20 mL) for 5 min then filtered through a Buchner filter. The cake was rinsed with hexanes (2 × 20 mL). This process was repeated a second time to yield the imidazole **26** as a light yellow solid (1.18 g, 65%). A second reaction afforded 1.18 g (65%) of product. ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ 8.19 (d, J = 8.5 Hz, 2H, ArH), 7.98 (d, J = 1.6 Hz, 1H, H_{Imid}), 7.86 (d, J = 1.6 Hz, 1H, H_{Imid}), 7.50 (d, J = 8.8 Hz, 2H, ArH), 4.41 (q, J = 7.0 Hz, 2 H, CH_2), 4.35 (br s, 2H, H_{morph}), 3.78 (br s, 6H, H_{morph}), 1.42 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$, 23 °C): δ 165.3, 162.1, 139.8, 139.3, 133.9, 131.6, 130.1, 123.6, 120.8, 67.2 (br s), 67.1 (br s), 61.4, 47.3 (br s), 43.0 (br s), 14.3. FTIR (thin film) (cm^{-1}): 3137 (w), 1719 (m), 1610 (m), 1537 (m), 1116 (m). HRMS (ESI) (*m*/*z*): Calc'd for $C_{17}H_{20}N_3O_4$ [M + H]$^+$: 330.14483, Found: 330.14456. Melting Point: 192–194 °C.

(1-(4-Nitrophenyl)-1*H*-imidazol-4-yl)(morpholino)methanone (28)

To a 25 mL round bottomed flask was added 2-amino-1-morpholinoethanone hydrochloride (**16**, 1.00 g, 5.54 mmol, 1 equiv.). Pyrrolidine (3.45 mL, 41.52 mmol, 7.50 equiv.) was added slowly *via* syringe slowly over 1 min, followed by dimethylformamide dimethylacetal (mild exotherm noted, 5.54 mL, 41.52 mmol, 7.50 equiv.). The clear solution was heated to 85 °C for 4 h before being cooled to room temperature. The yellow solution was diluted with dichloromethane (75 mL), washed with water (2 × 50 mL), and brine (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an orange oil (2.85 g). The orange oil was diluted with acetic acid (10.00 mL) and *p*-nitroaniline (**27**, 1.15 g, 8.30 mmol, 1.5 equiv.) was added. The dark mixture was heated to 100 °C for 3 h, before being cooled to room temperature. The mixture added slowly to a beaker containing a 10% wt/wt aqueous solution of potassium carbonate (125 mL, Gas evolution noted). The precipitated solid was filtered and washed with water (2 × 20 mL) and dried. The solid was slurried in acetone (20 mL) for 5 min, then filtered. The cake was washed with acetone (2 × 20 mL) and dried to yield the imidazole **28** as a light yellow powder (1.03 g, 62%). A second reaction afforded 1.01 g (60%) of product. ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ 8.42 (d, J = 7.3 Hz, 2H, ArH), 8.02 (s, 1H, H_{Imid}), 7.90 (s, 1H, H_{Imid}), 7.62 (d, J = 7.3 Hz, 2H, ArH), 4.35 (br s, 2H, H_{morph}), 3.80 (br s, 6H, H_{morph}). ^{13}C NMR (125.8 MHz, $CDCl_3$, 23 °C): δ 161.8, 146.9, 141.2, 140.0, 133.9, 125.9, 123.5, 121.5, 67.3 (br s), 67.1 (br s), 47.3 (br s), 43.1 (br s). FTIR (thin film) (cm^{-1}): 3125 (w), 1616 (w), 1596 (m), 1342 (m), 1111 (m). HRMS (ESI) (*m*/*z*): Calc'd for $C_{14}H_{15}N_4O_4$ [M + H]$^+$: 303.10878, Found: 303.10864. Melting Point: 278 °C (decomposition).

(1-(2,6-Diisopropylphenyl)-1*H*-imidazol-4-yl)(morpholino)methanone (30)

To a 25 mL round bottomed flask was added 2-amino-1-morpholinoethanone hydrochloride (**16**, 1.00 g, 5.54 mmol, 1 equiv.). Pyrrolidine (3.45 mL, 41.52 mmol, 7.50 equiv.) was added slowly *via* syringe over 1 min, followed by dimethylformamide dimethylacetal (mild exotherm noted, 5.54 mL, 41.52 mmol, 7.50 equiv.). The clear solution was heated to 85 °C for 4 h before being cooled to room temperature. The yellow solution was diluted with dichloromethane (75 mL), washed with water (2 × 50 mL), and brine (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an orange oil (2.51 g). The orange oil was diluted with acetic acid (5.00 mL) and 2,6-diisopropylphenylaniline (**29**, 1.74 mL, 8.30 mmol, 1.50 equiv.) was added. The dark mixture was heated to 100 °C for 2 h, before being cooled to room temperature. The mixture was diluted with dichloromethane (50 mL) and added slowly to a beaker containing a 10% wt/wt aqueous solution of potassium carbonate (75 mL, gas evolution noted). The layers were separated and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a black oil. The crude mixture was purified by flash column chromatography over silica gel (120 g, 75 to 100% gradient of ethyl acetate in hexanes) to afford a yellow light solid. The solid was slurried in 10% v/v THF in hexanes (20 mL) for 2 min then filtered through a Buchner filter. The cake was rinsed with hexanes (2 × 5 mL) yielding the imidazole **30** as a white solid (1.06 g, 56%). A second reaction afforded 1.04 g (55%) of product. ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ 7.64 (d, J = 1.6 Hz, 1H, H_{Imid}), 7.45 (t, J = 7.8 Hz, 1H, ArH), 7.39 (d, J = 1.3 Hz, 1H, H_{Imid}), 7.26 (d, J = 7.0 Hz, 2H, ArH), 4.55 (br s, 2H, H_{morph}), 3.81 (br s, 6H, H_{morph}), 2.39 (septet, J = 6.8 Hz, 2H, CH), 1.14 (d, J = 6.0 Hz, 6H, CH_3), 1.12 (d, J = 5.7 Hz, 6H, CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$, 23 °C): δ 162.2, 146.2, 138.0. 137.2, 132.0, 130.2, 128.0, 123.9, 67.2 (br s), 47.2 (br s), 43.0 (br s), 28.2, 24.4, 24.2. FTIR (thin film) (cm^{-1}): 3105 (w), 2964 (s), 1616 (s), 1534 (s), 1116 (m). HRMS (ESI) (*m*/*z*): Calc'd for $C_{20}H_{28}N_3O_2$ [M + H]$^+$: 342.21760, Found: 342.21737. Melting Point: 165–166 °C.

(1-(Pyridin-3-yl)-1*H*-imidazol-4-yl)(morpholino)methanone (32)

To a 25 mL round bottomed flask was added 2-amino-1-morpholinoethanone hydrochloride (**16**, 1.00 g, 5.54 mmol, 1 equiv.). Pyrrolidine (3.45 mL, 41.52 mmol, 7.50 equiv.) was added slowly *via* syringe over 1 min, followed by dimethylformamide dimethylacetal (mild exotherm noted, 5.54 mL, 41.52 mmol, 7.50 equiv.). The clear solution was heated to 85 °C for 4 h before being cooled to room temperature. The yellow solution was diluted with dichloromethane (75 mL), washed with water (2 × 50 mL), and brine (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an orange oil (3.23 g). The orange oil was diluted with acetic acid

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(5.00 mL) and 3-aminopyridine (**31**, 782 mg, 8.30 mmol, 1.5 equiv.) was added. The dark mixture was heated to 100 °C for 3 h, before being cooled to room temperature. The mixture was diluted with dichloromethane (50 mL) and added slowly to a beaker containing a 10% wt/wt aqueous solution of potassium carbonate (75 mL), gas evolution noted). The layers were separated and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a light brown solid. The solid was slurried in MTBE (20 mL) for 5 min then filtered. The cake was washed with MTBE (2 × 20 mL) and dried to yield the imidazole **32** as a light brown solid (920 mg, 64%). A second reaction afforded 875 mg (61%) of product. ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ 8.78 (app d, J = 2.2 Hz, 1H, H_{Pyr}), 8.68 (app d, J = 3.8 Hz, 1H, H_{Pyr}), 7.94 (d, J = 1.3 Hz, 1H, H_{Imid}), 7.80 (d, J = 1.3 Hz, 1H, H_{Imid}), 7.76 (ddd, J = 8.2, 2.5, 1.3 Hz, 1H, H_{Pyr}), 7.48 (app dd, J = 7.6, 4.7 Hz, 1H, H_{Pyr}), 4.34 (br s, 2H, H_{morph}), 3.78 (br s, 6H, H_{morph}). ^{13}C NMR (125.8 MHz, $CDCl_3$, 23 °C): δ 162.0, 149.4, 142.9, 139.4, 134.0, 133.1, 129.0, 124.3, 123.8, 67.1 (br s), 66.9 (br s), 47.2 (br s), 42.9 (br s). FTIR (thin film) (cm^{-1}): 3113 (w), 2968 (w), 1608 (s), 1435 (m), 1107 (m). HRMS (ESI) (*m*/*z*): Calc'd for $C_{13}H_{15}N_4O_2$ [M + H]$^+$: 259.11895, Found: 259.11864. Melting Point: 173–174 °C.

(1-(1*H*-Indol-5-yl)-1*H*-imidazol-4-yl)(morpholino)methanone (34)

To a 25 mL round bottomed flask was added 2-amino-1-morpholinoethanone hydrochloride (**16**, 1.00 g, 5.54 mmol, 1 equiv.). Pyrrolidine (3.45 mL, 41.52 mmol, 7.50 equiv.) was added slowly *via* syringe over 1 min, followed by dimethylformamide dimethylacetal (mild exotherm noted, 5.54 mL, 41.52 mmol, 7.50 equiv.). The clear solution was heated to 85 °C for 4 h before being cooled to room temperature. The yellow solution was diluted with dichloromethane (75 mL), washed with water (2 × 50 mL), and brine (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an orange oil (2.49 g). The orange oil was diluted with acetic acid (5.00 mL) and 5-aminoindole (**33**, 1.14 g, 8.30 mmol, 1.50 equiv.) was added. The dark mixture was heated to 100 °C for 2 h, before being cooled to room temperature. The mixture was diluted with dichloromethane (50 mL) and added slowly to a beaker containing a 10% wt/wt aqueous solution of potassium carbonate (75 mL, gas evolution noted). The layers were separated and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a yellow solid. The solid was slurried in MTBE (20 mL) for 20 min then filtered through a Buchner filter. The cake was rinsed with MTBE (2 × 20 mL). This process was repeated a second time to yield the imidazole **34** as a light yellow solid (623 mg, 38%). A second reaction afforded 591 mg (36%) of product. ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ 8.71 (br s, 1H, NH), 7.92 (d, J = 1.3 Hz, 1H, H_{Imid}), 7.76 (d, J = 1.3 Hz, 1H, H_{Imid}), 7.63 (d, J = 1.9 Hz, 1H, H_{Indole}), 7.48 (d, J = 8.5 Hz, 1H, H_{Indole}), 7.35 (app t, J = 2.7 Hz, 1H, H_{Indole}), 7.18 (dd, J = 8.5, 2.2 Hz, 1H, H_{Indole}), 6.62 (app t, J = 2.2 Hz, 1H, H_{Indole}), 4.42 (br s, 2H, H_{morph}), 3.80 (br s, 6H, H_{morph}). ^{13}C NMR (125.8 MHz, $CDCl_3$, 23 °C): δ 162.9, 138.0, 135.2, 135.1, 129.7, 128.3, 126.5, 126.4, 125.4, 116.7, 114.4, 112.14, 112.09, 103.1, 103.0, 67.2 (br s, 47.4 (br s), 43.0 (br s). FTIR (KBr) (cm^{-1}): 3124 (w), 2918 (w), 1594 (s), 1549 (m), 1111 (s). HRMS (ESI) (*m*/*z*): Calc'd for $C_{16}H_{17}N_4O_2$ [M + H]$^+$: 297.13460, Found: 297.13425. Melting Point: 215–216 °C.

(1-Butyl-1*H*-imidazol-4-yl)(morpholino)methanone (36)

To a 25 mL round bottomed flask was added 2-amino-1-morpholinoethanone hydrochloride (**16**, 1.00 g, 5.54 mmol, 1 equiv.). Pyrrolidine (3.45 mL, 41.52 mmol, 7.50 equiv.) was added slowly *via* syringe over 1 min, followed by dimethylformamide dimethylacetal (mild exotherm noted, 5.54 mL, 41.52 mmol, 7.50 equiv.). The clear solution was heated to 85 °C for 4 h before being cooled to room temperature. The yellow solution was diluted with dichloromethane (75 mL), washed with water (2 × 50 mL), and brine (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an orange oil (2.71 g). The orange oil was diluted with acetic acid (5.00 mL) and *N*-methylaniline (60 µL, 0.55 mmol, 0.10 equiv.) was added. *n*-Butylamine (**35**, 1.37 mL, 13.84 mmol, 2.50 equiv.) was added slowly over 5 min (caution: exotherm). The dark mixture was heated to 100 °C for 3 h, before being cooled to room temperature. The mixture was diluted with dichloromethane (50 mL) and added slowly to a beaker containing a 10% wt/wt aqueous solution of potassium carbonate (75 mL, gas evolution noted). The layers were separated and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a dark brown residue. The crude mixture was purified by flash column chromatography over silica gel (120 g, 0 to 10% gradient of methanol in dichloromethane) to yield the imidazole **36** as a tan solid (1.08 g, 82%). A second reaction afforded 1.06 g (81%) of product. ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ 7.57 (s, 1H, H_{Imid}), 7.38 (s, 1H, H_{Imid}), 4.36 (br s, 2H, H_{morph}), 3.94 (t, J = 7.1 Hz, 2H, CH_2), 3.74 (br s, 6H, H_{morph}), 1.78 (pentet, J = 7.3 Hz, 2H, CH_2), 1.33 (sextet, J = 7.4 Hz, 2H, CH_2), 0.94 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$, 23 °C): δ 162.7, 137.8, 135.7, 125.2, 67.2 (br s), 47.2 (br s), 47.1, 42.9 (br s), 32.8, 19.6, 13.4. FTIR (thin film) (cm^{-1}): 3107 (w), 2959 (s), 1616 (s), 1541 (s), 1115 (m). HRMS (ESI) (*m*/*z*): Calc'd for $C_{12}H_{20}N_3O_2$ [M + H]$^+$: 238.15500, Found: 238.15488. Melting point: 64–65 °C.

(*S*)-(±)-(1-(1-Phenylethyl)-1*H*-imidazol-4-yl)(morpholino)methanone (38)

To a 25 mL round bottomed flask was added 2-amino-1-morpholinoethanone hydrochloride (**16**, 1.00 g, 5.54 mmol, 1 equiv.). Pyrrolidine (3.45 mL, 41.52 mmol, 7.50 equiv.) was added slowly *via* syringe over 1 min, followed by dimethylformamide dimethylacetal (mild exotherm noted, 5.54 mL, 41.52 mmol, 7.50 equiv.). The clear solution was heated to 85 °C for 4 h before being cooled to room temperature. The yellow solution was diluted with dichloromethane (75 mL), washed with water (2 × 50 mL), and brine (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an orange oil (2.66 g). The orange oil was diluted with acetic acid (5.00 mL) and *N*-methylaniline (60 µL, 0.55 mmol, 0.10 equiv.) was added. (*S*)-α-Methylbenzylamine (**37**, 1.78 mL, 13.84 mmol, 2.5 equiv.) was added slowly over 5 min (caution: exotherm).

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The dark mixture was heated to 100 °C for 3 h, before being cooled to room temperature. The mixture was diluted with dichloromethane (50 mL) and added slowly to a beaker containing a 10% wt/wt aqueous solution of potassium carbonate (75 mL, gas evolution noted). The layers were separated and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a dark brown residue. The crude mixture was purified by flash column chromatography over silica gel (120 g, 0 to 9% gradient of methanol in dichloromethane) to yield the imidazole **38** as a thick oil that slowly solidifies (1.19 g, 75%). The product was found to be 98.3% ee by chiral HPLC (Chiralpak AD-H, 60% heptanes, 40% methanol–ethanol (1 : 1 v/v), 1.0 mL min^{-1}, 220 nm, t_R (minor) = 8.22 min, t_R (major) = 11.53 min). A second reaction using (*R*)-α-methylbenzylamine afforded 1.15 g (73%, 99.2% ee, $[\alpha]_D^{23}$ −22.2 (*c* 0.01, CH_2Cl_2)) of product. ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ 7.65 (d, *J* = 1.6 Hz, 1H, H_{Imid}), 7.47 (d, *J* = 1.3 Hz, 1H, H_{Imid}), 7.31–7.38 (m, 3 H, ArH), 7.18 (app d, *J* = 6.6 Hz, 2H, ArH), 5.34 (q, *J* = 7.0 Hz, 1H, CH), 4.38 (br s, 2H, H_{morph}), 3.74 (br s, 6H, H_{morph}), 1.87 (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$, 23 °C): δ 162.6, 140.4, 137.7, 134.8, 129.0, 128.4, 126.1, 124.3, 67.2 (br s), 57.1, 47.2 (br s), 42.9 (br s), 21.9. FTIR (thin film) (cm^{-1}): 3113 (w), 2855 (s), 1610 (s), 1538 (m), 1114 (m). HRMS (ESI) (*m*/*z*): Calc'd for $C_{16}H_{20}N_3O_2$ [M + H]$^+$: 286.15500, Found: 286.15488. $[\alpha]_D^{23}$ = +22.0 (*c* = 0.01, CH_2Cl_2). Melting point: 96–97 °C.

(±)-(1-((1*R*,2*S*)-2-Hydroxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-imidazol-4-yl)(morpholino)methanone (40)

To a 25 mL round bottomed flask was added 2-amino-1-morpholinoethanone hydrochloride (**16**, 1.00 g, 5.54 mmol, 1 equiv.). Pyrrolidine (3.45 mL, 41.52 mmol, 7.50 equiv.) was added slowly *via* syringe over 1 min, followed by dimethylformamide dimethylacetal (mild exotherm noted, 5.54 mL, 41.52 mmol, 7.50 equiv.). The clear solution was heated to 85 °C for 4 h before being cooled to room temperature. The yellow solution was diluted with dichloromethane (75 mL), washed with water (2 × 50 mL), and brine (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an orange oil (2.70 g). The orange oil was diluted with acetic acid (5.00 mL) and *N*-methylaniline (60 μL, 0.55 mmol, 0.10 equiv.) and (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol (**39**, 1.24 g, 8.30 mmol, 1.50 equiv.) were added. The dark mixture was heated to 100 °C for 2 h, before being cooled to room temperature. The mixture was diluted with dichloromethane (50 mL) and added slowly to a beaker containing a 10% wt/wt aqueous solution of potassium carbonate (75 mL, gas evolution noted). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a black oil. The crude mixture was purified by flash column chromatography over silica gel (120 g, 0 to 10% gradient of methanol in dichloromethane) to yield the imidazole **40** as a light brown gel that quickly solidified (713 mg, 41%). The product was found to be 99.5% ee by chiral HPLC (Chiralpak IA, 60% heptanes, 40% methanol-ethanol (1 : 1 v/v), 1.0 mL min^{-1}, 220 nm, t_R (minor) = 6.14 min, t_R (major) = 9.92 min). A second reaction using (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol afforded 738 mg (43%, 99.7% ee, $[\alpha]_D^{23}$ −59.3 (*c* 0.01, CH_2Cl_2)) of product. ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ 7.42 (s, 1H, H_{Imid}), 7.32–7.36 (m, 2H, H_{Imid}, ArH), 7.27–7.28 (m, 1H, ArH), 7.23 (app td, *J* = 6.5, 1.9 Hz, 1H, ArH), 7.15 (d, *J* = 7.6 Hz, 1H, ArH), 5.48 (d, *J* = 5.0 Hz, 1H, CH), 4.70 (m, 1H, CH), 4.40 (br s, 1H, OH), 4.30 (br s, 2H, H_{morph}), 3.70 (br s, 6H, H_{morph}), 3.23 (dd, *J* = 16.2, 5.8 Hz, 1H, CH_2), 3.02 (dd, *J* = 16.2, 4.6 Hz, 1H, CH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$, 23 °C): δ 162.7, 141.1, 137.4, 136.4, 136.1, 129.5, 127.6, 126.1, 125.6, 125.3, 73.4, 67.0 (br s), 65.2, 47.3 (br s), 42.9 (br s), 38.8. FTIR (thin film) (cm^{-1}): 3312 (br s), 2920 (w), 1597 (s), 1456 (m), 1113 (m). HRMS (ESI) (*m*/*z*): Calc'd for $C_{17}H_{20}N_3O_3$ [M + H]$^+$: 314.14992, Found: 314.14969. $[\alpha]_D^{23}$ = +58.5 (*c* = 0.01, CH_2Cl_2). Melting point: 165–166 °C.

(1-(*tert*-Butyl)-1*H*-imidazol-4-yl)(morpholino)methanone (42)

To a 25 mL round bottomed flask was added 2-amino-1-morpholinoethanone hydrochloride (**16**, 1.00 g, 5.54 mmol, 1 equiv.). Pyrrolidine (3.45 mL, 41.52 mmol, 7.50 equiv.) was added slowly *via* syringe slowly over 1 min, followed by dimethylformamide dimethylacetal (mild exotherm noted, 5.54 mL, 41.52 mmol, 7.50 equiv.). The clear solution was heated to 85 °C for 4 h before being cooled to room temperature. The yellow solution was diluted with dichloromethane (75 mL), washed with water (2 × 50 mL), and brine (50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an orange oil (2.48 g). The orange oil was diluted with acetic acid (5.00 mL) and *N*-methylaniline (60 μL, 0.55 mmol, 0.10 equiv.) was added. The mixture was cooled in an ice water bath and *t*-butylamine (**41**, 1.49 mL, 13.84 mmol, 2.5 equiv.) was added slowly over 5 min (caution: large exotherm). The dark mixture was heated to 100 °C for 3 h, before being cooled to room temperature. The mixture was diluted with dichloromethane (50 mL) and added slowly to a beaker containing a 10% wt/wt aqueous solution of potassium carbonate (75 mL, gas evolution noted). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a brown solid. The crude mixture was purified by flash column chromatography over silica gel (120 g, 0 to 8% gradient of methanol in dichloromethane) to yield the imidazole **42** as an off white solid (985 mg, 75%). A second reaction afforded 979 mg (75%) of product. ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ 7.74 (d, *J* = 1.6 Hz, 1H, H_{Imid}), 7.54 (d, *J* = 1.6 Hz, 1H, H_{Imid}), 4.39 (br s, 2H, H_{morph}), 3.76 (br s, 6H, H_{morph}), 1.58 (s, 9H, CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$, 23 °C): δ 162.8, 137.3, 133.0, 123.1, 67.1 (br s), 55.5, 47.2 (br s), 42.9 (br s), 30.5. FTIR (thin film) (cm^{-1}): 3131 (w), 2965 (w), 1610 (m), 1534 (m), 1116 (m). HRMS (ESI) (*m*/*z*): Calc'd for $C_{12}H_{20}N_3O_2$ [M + H]$^+$: 238.15500, Found: 238.15497. Melting point: 164–166 °C.

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References

1 J. F. O'Connell, J. Parquette, W. E. Yelle, W. Wang and H. Rapoport, *Synthesis*, 1988, **10**, 767.

2 (*a*) M. A. Dumpis, E. M. Alekseeva, V. Litasova and L. B. Piotrovskii, *Russ. J. Gen. Chem.*, 2003, **73**, 126; (*b*) J. Bhaumik, Z. Yao, K. Eszter Borbas, M. Taniguchi and J. S. Lindsey, *J. Org. Chem.*, 2006, **71**, 8807; (*c*) L. Oresmaa, H. Taberman,M. Haukka, P. Vainiotalo and P. Aulaskari, *J. Heterocycl. Chem.*, 2007, **44**, 1445; (*d*) Q. Hu and G. M. Ksander, 2008, WO 2008/076860 A1; (*e*) M. Y. Berezin, J. Kao and S. Achilefu, *Chem.–Eur. J.*, 2009, **15**, 3560; (*f*) V. J. Cee, M. J. Frohn, S. C. Niera, B. A. Lanman, A. B. Reed and K. C. Sham, 2009, WO 2009/154775 A1; (*g*) P. O. Miranda and L.-I. Gundersen, *Arch. Pharm. Chem. Life Sci.*, 2010, **343**, 40; (*h*) A. Ciupa, N. J. Griffiths, S. K. Light, P. J. Wood and L. Caggiano, *Med. Chem. Commun.*, 2011, **2**, 1011.

3 (*a*) B. Zhu, S. M. Bauer, Z. J. Jia, Y. Song, G. D. Probst, Y. Zhang and C. Scarborough, 2008, WO 2008/086188 A2; (*b*) J. H. M. Lange, M. A. W. van der Neut, H. C. Wals, G. D. Kuil, A. J. M. Borst, A. Mulder, A. P. den Hartog, H. Zilaout, W. Goutier, H. H. van Stuivenberg and B. J. van Vliet, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1084.

4 (*a*) M. J. Alves, B. L. Booth, O. K. Al-Duaij, P. Eastwood, L. Nezhat, M. Fernanda, J. R. P. Proença and A. S. Ramos, *J. Chem. Research (S)*, 1993, 402; (*b*) K. Nunami, M. Yamada, T. Fukui and K. Matsumoto, *J. Org. Chem.*, 1994, **59**, 7635; (*c*) C. J. Helal and J. C. Lucas, *Org. Lett.*, 2002, **4**, 4133; (*d*) S. A. Barros, S. T. Gonçalves, A. M. F. Oliveira-Campos and F. R. P. Proença, *J. Heterocycl. Chem.*, 2007, **44**, 13; (*e*) A. Yahyazadeh and M. Haghi, *Asian, J. Chem.*, 2007, **19**, 4963; (*f*) T. Kuroita, Y. Imaeda, N. Taya, T. Oda, K. Iwanaga and Y. Asano, 2010, US patent 2010/0121048.

5 (*a*) H. Biere, A. Huth, D. Rahtz, R. Schmiechen, D. Seidelmann, H. H. Schneider and D. N. Stephens, 1988, German patent 3627155A1; (*b*) H. Biere, R. Rohde, H. H. Schneider and L. Turski, 1989, German patent 3742716A1.

6 D. Kurbanov, A. Taganliev, E. V. Pastushenko and Y. Khekimov, *Izv. An. Turk. SSR*, 1984, **3**, 100.

7 W. Kantlehner, F. Wagner and H. Bredereck, *Liebigs Ann. Chem.*, 1980, 344.

8 H. E. Winberg, 1966, US patent 3239519. While pyrrolidine was used in the azadiene synthesis in ref. 5, the beneficial rate enhancement was not mentioned.

9 M. C. Venuti, R. Alvarez, J. J. Bruno, A. M. Strosberg, L. Gu, H.-S. Chiang, I. J. Massey, N. Chu and J. H. Fried, *J. Med. Chem.*, 1988, **31**, 2145. The free base of **16** also could be used; however, for ease of preparation and handling we chose the hydrochloride salt.

10 The use of anilines to catalyze transamination is known: (*a*) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, 1962, **84**, 826; (*b*) A. Dirksen, S. Dirksen, T. M. Hackeng and P. E. Dawson, *J. Am. Chem. Soc.*, 2006, **128**, 15602; (*c*) A. Dirksen and P. E. Dawson, *Bioconjugate Chem.*, 2008, **19**, 2543; (*d*) Z. Rodriguez-Docampo and S. Otto, *Chem. Commun.*, 2008, 5301; (*e*) V. T. Bhat, A. M. Caniard, T. Luksch, R. Brenk, D. J. Campopiano and M. F. Greaney, *Nat. Chem.*, 2010, **2**, 490.

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