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Effect of Bronsted Acids and Bases, and Lewis Acid (Sn^{2+}) on the Regiochemistry of the Reaction of Amines with Trifluoromethyl-β-diketones: Reaction of 3-Aminopyrrole to Selectively Produce Regioisomeric 1*H*-Pyrrolo[3,2-*b*]pyridines

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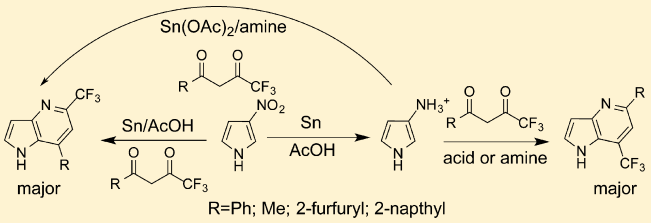
Supporting Information

ABSTRACT: Reaction of 3-aminopyrrole (as its salt) with trifluoromethyl-β-diketones gave γ-1*H*-pyrrolo[3,2-*b*]pyridines via reaction at the less reactive carbonyl group. The trifluoromethyl group increased the electrophilicity of the adjacent carbonyl group and decreased the basicity of the hydroxyl group of the CF_3 amino alcohol formed. This amino alcohol was formed faster, but its subsequent dehydration to the β-enaminone was slow resulting in the preferential formation of the γ-regioisomer. Reaction of 4,4,4-trifluoro-1-phenyl-1,3-butadione with 3-aminopyrrole was carried out using a series of 6 amine buffers. Yields of the α-1*H*-pyrrolo[3,2-*b*]pyridine increased as the pK_a of the amine buffer decreased. Surprisingly the yield went down at higher pK_as. There was a change in mechanism as the reaction mixture became more basic. With strong amines trifluoromethyl-β-diketones were present mainly or completely as the enolate. Under reductive conditions (3-nitropyrrole/Sn/AcOH/trifluoromethyl-β-diketone) the α-1*H*-pyrrolo[3,2-*b*]pyridine was the major product as a result of Lewis acid catalysis by Sn^{2+}. Similar α-regiochemistry was observed when the reaction of the 3-aminopyrrole salt with trifluoromethyl-β-diketones was carried out in the presence of base and tin(II) acetate.

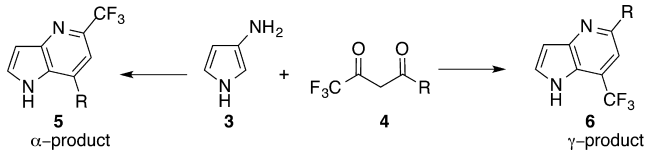


INTRODUCTION

Reactions of amines[1−4] with fluoro-substituted 1,3-diketones to give enamines,[5] imines,[5−7] heterocycles[8−15] and ligands[16−21] have been studied. Much of this work has been driven by the effect of fluorine atoms on the steric, electronic, and lipophilic properties of biologically active molecules.[22] Recently we reported the first isolation of 3-aminopyrrole as a stable salt **2**. Addition of base, to its salt, can be used to generate the 3-aminopyrrole in situ.[23] The reaction of 3-aminopyrrole with fluoro-substituted 1,3-diketones would give 1*H*-pyrrolo[3,2-*b*]pyridines—4-azaindoles that are of interest because of their potential biological activity.[24] An analogous reaction with 2-aminopyrroles to give 1*H*-pyrrolo[2,3-*b*]pyridines has been reported.[25] An intriguing aspect of the reaction of unsymmetrical fluoro-substituted 1,3-diketones with amines, is the regiochemistry of the reaction.

Pashkevich carried out the first systematic study of the reaction of amines with fluoro-substituted 1,3-diketones.[5] In general, the major product was an enamine (β-enaminone) from the reaction of the amino group with the less reactive (electrophilic) carbonyl group. When an alkyl amine was used, it was the only product.[4,5] Results depended on temperature, solvent, substituents, and the basicity of the amine. Similar results have been reported for the formation of pyridine rings from heterocyclic amines, where the γ-regioisomer is generally favored.[3−9] Exceptions to this regiochemistry have been reported and will be discussed below. Scheme 1 illustrates the possible regiochemistry of the reaction of 3-aminopyrrole

Scheme 1. Formation of Regioisomeric 1*H*-Pyrrolo[3,2-*b*]pyridines



with unsymmetrical fluoro-substituted 1,3-diketones to give regioisomeric 1*H*-pyrrolo[3,2-*b*]pyridine isomers.

Recently the reaction of 3-aminopyrrole with 1,3,5-triazines was carried out under two sets of conditions: in a one-step reaction 3-nitropyrrole (**1**) was reduced with Sn/AcOH to 3-aminopyrrole in the presence of the 1,3,5-triazine, and in a two step process in which the salt of the aminopyrrole was treated with a base in the presence of the 1,3,5-triazine.[26] Analogously, the reaction of 3-aminopyrrole with trifluoromethyl-β-diketones was carried out under both sets of conditions. In our initial studies the reaction of the tetraphenylborate salt of 3-

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aminopyrrole (**2**) with 4,4,4-trifluoro-1-phenyl-1,3-butadione (**4a**) in the presence of a buffering amine (two-step reaction), gave the expected γ-regioisomer as the predominate product. Surprisingly, the one-step reaction gave predominately the α-regioisomer. Given the great interest in this reaction for the synthesis of heterocyclic ring systems and other derivatives, a systematic study of these two reactions was carried out in order to optimize the formation of the two regioisomers. On the basis of the results of this study, mechanisms are proposed to explain the change in regiochemistry of the reaction of amines with trifluoromethyl-β-diketones under different reaction conditions.

RESULTS

Reactions of 3-aminopyrrole with trifluoromethyl-β-diketones **4a**−**e** and symmetrical 1,3-diketones **4f**−**j** were studied. Figure 1 illustrates the products obtained. Initial reaction of the model

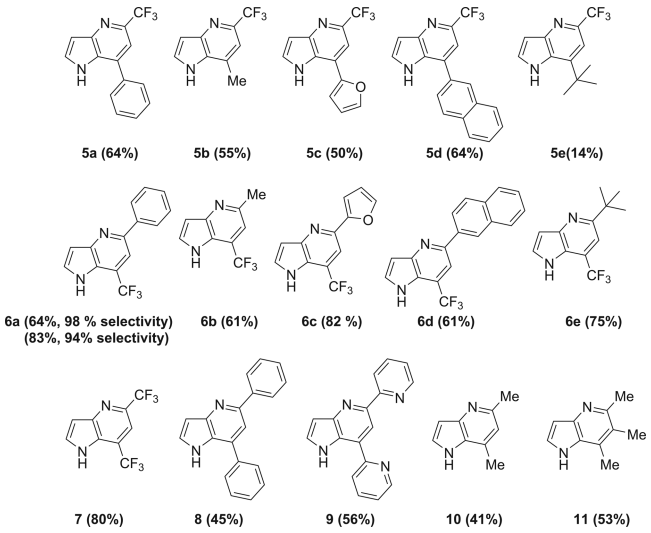

Figure 1. 1*H*-Pyrrolo[3,2-*b*]pyridine optimized products.

compound 4,4,4-trifluoro-1-phenyl-1,3-butadione (**4a**) with the tetraphenylborate salt of 3-aminopyrrole (**2**) was carried out in dichloromethane (DCM) containing three equivalents of diisopropylethylamine (DIPEA) and the γ-regioisomer was isolated in 64% yield and the α-regioisomer in 4% yield by flash chromatography (Table 1, entry 13).

The structure of the γ-regioisomer was determined by single crystal X-ray crystallography.[27] During the course of this study it became clear that the formation of the γ-regioisomer, 1*H*-pyrrolo[3,2-*b*]pyridine, was acid catalyzed (see Table 1). Different amine buffers were therefore used to change the acidity of the reaction. Table 1 summarizes the results obtained from the reaction of the tetraphenylborate salt of 3-aminopyrrole (**2**) with 1,3-diketones **4a**−**e**.

Formation of a 1*H*-pyrrolo[3,2-*b*]pyridine from the one-step reaction under reductive conditions (3-nitropyrrole/AcOH/Sn/trifluoromethyl-β-diketone) would be expected to be a shorter and possibly higher yielding route to the final product. When the reaction was carried out with 4,4,4-trifluoro-1-phenyl-1,3-butadione (**4a**), the ^{1}H NMR indicated that the major product was not the expected γ-regioisomer. This product was isolated and identified by single crystal X-ray crystallography as the α-regioisomer **5a**. The α-regioisomer was isolated in 54% yield and the γ-regioisomer in 11% yield (Table 2, entry 1) to give a γ/α ratio of 0.20 compared to a γ/α ratio of 16 when the two-step reaction was used (Table 1). The carbon attached to the CF_3 of the α-regioisomers had a signal (quartet, J = 33−34 Hz) at 141−143 ppm in the ^{13}C NMR spectrum that was diagnostic for this regioisomer. Table 2 summarizes the results obtained in the one-step reaction under reductive conditions.

Reduction of 3-nitropyrrole with Sn/AcOH would also form Sn^{2+}—a potential Lewis acid catalyst. The two-step reaction (3-aminopyrrole salt/trifluoromethyl-β-diketone/buffering amine) was carried out in the presence of Sn(II) acetate. The results in Table 3 clearly showed the results: the regiochemistry switched from predominant γ-regioisomer to the α-regioisomer when Sn^{2+} was present. In the reaction of 4,4,4-trifluoro-1-phenyl-1,3-butadione (**4a**), in the presence of Sn^{2+}, the α-regioisomer was isolated in 51% yield and the γ-regioisomer in 19% yield to give a γ/α ratio of 0.27 compared to a γ/α ratio of 16 in the absence of Sn^{2+} (Table 1). Regiochemistry was affected by the presence of a Lewis acid and also the nature of buffering amine. Reduction of 3-nitropyrrole also produced water. The effect of this generated water, on regiochemistry, will be discussed in the section below that treats the effect of Sn^{2+} on the reaction. Examination of Tables 1−3 clearly showed a steric effect. When the *tert*-butyl derivative **4e** was used, the γ-regioisomer **6e** was favored under all reaction conditions studied.

Reactions were also carried out with 3-nitropyrrole (**1**), tin acetate, acetic acid, and symmetrical 1,3-diketones **4f**−**j**. Table 4 summarizes the optimized yields obtained.

When the reaction was carried out between the symmetrical 1,3-diketones **4f** and **4g** and the aminopyrrole salt **2**, a new major product **12** was obtained with **4g** (Table 5). The ^{1}H NMR of **12** showed the presence of four phenyl groups—two sets in a ratio of 1:1. Single crystal X-ray crystallography demonstrated that it was the boron complex **12**. When the CF_3 group was present it did not form because the oxygen was not basic enough to bond to boron. The complex was strong enough that even acetic/H_2O was not strong enough to break it apart.

A solvent effect has been reported on the selectivity of the reaction of amines with trifluoromethyl-β-diketones.[1] The effect of adding methanol to the reaction mixture can be seen by comparing entries 15 and 16 in Table 1. When methanol was present the total yield went up, but selectivity decreased. The presence of molecular sieve also affected selectivity. This can be seen by comparing entries 7 and 8 in Table 1. When molecular sieve was present there was a small increase in selectivity. As a result reactions were optimized for maximum selectivity in DCM with molecular sieve present.

DISCUSSION

A. Effect of the Trifluoromethyl Group. The role of the trifluoromethyl group can be seen by examining the regiochemistry of reactions of amines with 1,3-ketones to give β-enaminones: when no fluoro substituents are present, as expected, the more reactive carbonyl group reacts preferentially.[28] This can be contrasted to when fluoro-substituents are present where the reaction takes place at the least reactive carbonyl.[2] At least three explanations have been proposed to explain the regiochemistry of the reaction of amines with fluoro-substituted 1,3-diketones: (1) regiochemistry is controlled by hard and soft acid and base (HSAB) interactions;[8] (2) reaction occurred via the enol;[2,6,29,30] (3) in protic solvents the initially formed amino alcohol (from the more electrophilic carbonyl) was stable and did not react further with the amine.[11]

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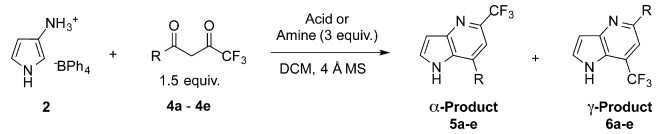
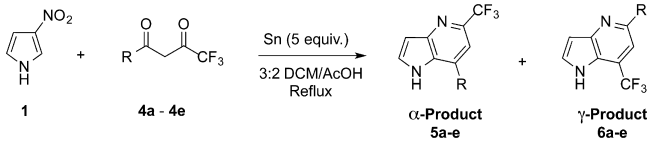
Table 1. Reaction of 2 with 1,3-Diketones 4a−e under Acidic and Buffered Conditions



entry	diketone: R	acid/amine (pK_a)	temp. (°C)	time (h)	yield 5α[a]	yield 6γ[a]	yield α+γ	% 6γ[j]
1	Ph (**4a**)	X	20	4d	14% (**5a**)	55% (**6a**)	69%	80%
2	Ph (**4a**)	25% TFA[b] (0.23)	20	24	5% (**5a**)	30% (**6a**)	35%	86%
3	Me (**4b**)	Pyrazine (0.40)	20	24	Trace[c] (**5b**)	Trace[c] (**6b**)	ND[d]	ND[d]
4	Ph (**4a**)	Pyrazine (0.40)	20	24	5% (**5a**)	83% (**6a**)	88%	94%
5	2-Furyl (**4c**)	Pyrazine (0.40)	20	24	7% (**5c**)	82% (**6c**)	89%	92%
6	2-Naphthyl[e] (**4d**)	Pyrazine (0.40)	20	24	ND[d] (**5d**)	46% (**6d**)	ND[d]	ND[d]
7	Ph[f] (**4a**)	Phthalazine (3.4)	20	22	19% (**5a**)	66% (**6a**)	85%	78%
8	Ph (**4a**)	Phthalazine (3.4)	20	24	14% (**5a**)	64% (**6a**)	78%	82%
9	Ph (**4a**)	Benzimidazole (5.6)	20	23	12% (**5a**)	61% (**6a**)	73%	84%
10	Ph (**4a**)	2-Methylimidazole (7.9)	20	24	10% (**5a**)	59% (**6a**)	69%	86%
11	Me (**4b**)	DIPEA[g] (11.0)	20	70	3% (**5b**)	35% (**6b**)	38%	92%
12	Me (**4b**)	DIPEA[g] (11.0)	reflux	38	7% (**5b**)	61% (**6b**)	68%	90%
13	Ph (**4a**)	DIPEA[g] (11.0)	20	21	4% (**5a**)	64% (**6a**)	68%	94%
14	*t*-Butyl (**4e**)	DIPEA[g] (11.0)	20	48	<5%[h] (**5e**)	72% (**6e**)	>72%	ND[d]
15	Ph[i] (**4a**)	Proton Sponge (12.0)	20	24	19% (**5a**)	57% (**6a**)	76%	75%
16	Ph (**4a**)	Proton Sponge (12.0)	20	24	1% (**5a**)	64% (**6a**)	65%	98%
17	Me (**4b**)	Proton Sponge (12.0)	reflux	40	7% (**5b**)	61% (**6b**)	68%	90%
18	2-Furyl (**4c**)	Proton Sponge (12.0)	20	24	7% (**5c**)	63% (**6c**)	70%	90%
19	2-Naphthyl (**4d**)	Proton Sponge (12.0)	20	24	6% (**5d**)	61% (**6d**)	67%	91%
20	*t*-Butyl (**4e**)	Proton Sponge (12.0)	20	46	1% (**5e**)	75% (**6e**)	76%	99%

[a]Isolated yield of purified products. [b]Trifluoroacetic acid. [c]As analyzed by TLC. [d]Not determined. [e]Reaction mixture contaminated with an inseparable byproduct. [f]No Molecular Sieves (MS) were added. [g]Diisopropylethylamine. [h]Not detected by ^{1}H NMR of product mixture. [i]The reaction was run in a 1:1 DCM/MeOH solvent system. [j]%6γ = (6γ/α+γ) × 100%

Table 2. Reaction of 3-Nitropyrrole with 1,3-Diketones under Reductive Conditions



entry	diketone: R	time (h)	yield 5α[a]	yield 6γ[a]	yield α+γ	% α[d]
1	Ph (**4a**, 1 equiv)	24	54% (**5a**)	11% (**6a**)	65%	83%
2	Ph (**4a**, 1 equiv)[b]	22	29% (**5a**)	29% (**6a**)	58%	50%
3	Ph (**4a**, 1 equiv)[c]	28	34% (**5a**)	12% (**6a**)	46%	74%
4	Me (**4b**, 1.5 equiv)	21	55% (**5b**)	8% (**6b**)	63%	87%
5	2-Furyl (**4c**, 1 equiv)	38	50% (**5c**)	11% (**6c**)	61%	82%
6	2-Naphthyl (**4d**, 1 equiv)	24	56% (**5d**)	20% (**6d**)	76%	74%
7	*t*-Butyl (**4e**, 1.5 equiv)	44	14% (**5e**)	52% (**6e**)	66%	21%

[a]Isolated yield of purified products. [b]4 Å Molecular sieves were added to the reaction mixture. [c]100 equiv of H_2O was added—the reaction mixture was biphasic. [d]%α = (α/α+γ) × 100%

In acid, enamine and heterocyclic-ring formation exhibit the same regiochemistry; therefore they should share the same first step—formation of an amino alcohol. The mechanistic scheme proposed in this work is based on the electronic effect[22] of the trifluoromethyl group, and also by analogy to the accepted mechanisms of the reaction of amino derivatives with aldehydes and ketones to give imines, oximes, and semicarbazones.[31,32]

Enamine formation is a two-stage process in which the initially formed amino alcohol (tetrahedral intermediate), in the presence of a catalyzing acid, undergoes dehydration to give the enamine (Scheme 2).[33,34] A trifluoromethyl group increases the electrophilicity of the adjacent carbonyl group and therefore the rate of formation of amino alcohol **16**; it also decreases the basicity of the hydroxyl group of amino alcohol **6**.[22] The net effect is that the CF_3 amino alcohol **16** is formed faster, but it subsequent dehydration, via protonation of the hydroxyl group, is slow. A consequence of this is that amino alcohols analogous to **16**, can, in some cases, be detected or isolated.[35−40] In contrast, while the reaction with the unactivated carbonyl is slower, the subsequent dehydration of the amino alcohol to the enamine is faster. The equilibrium is therefore driven in the γ-direction. It has been reported that in the reaction of 1,3-diketones with hydrazines to give pyrazoles, regiochemistry is the result of differing rates of dehydration of the respective intermediates.[37]

An interesting question is why the enamine and not the imine was formed when a primary amine was reacted with the trifluoromethyl-β-diketone or fluorosubstituted-β-diketone.[2] It has been observed that in enamines, when the β-carbon of the double bond had an electron-withdrawing group such as a CH_3CO, nitro or ester group, the enamine was more stable than the imine.[41] It would be expected that the strong electron-withdrawing $CF_3C{=}O$ group would help to stabilize the enamine product.

Another example of how stability controlled the nature of the final product was the formation of imines when an acid stronger

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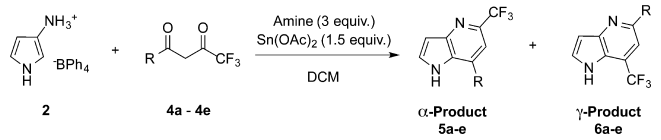
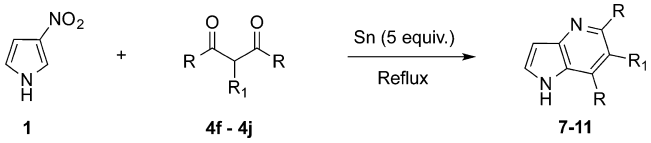
Table 3. Reaction of 2 with 1,3-Diketones 4a−e in the Presence of Tin(II) Acetate



entry	diketone: R_1	amine	temp (°C)	time (h)	yield α[a]	yield γ[a]	yield $\alpha+\gamma$	% 5α[c]
1	Phenyl (**4a**) 1.1 equiv	DIPEA[b]	Reflux	24	51% (**5a**)	19% (**6a**)	70%	73%
2	Phenyl (**4a**) 1 equiv	Phthalazine	20	24	64% (**5a**)	9% (**6a**)	73%	88%
3	Me (**4b**) 1 equiv	Phthalazine	20	48	21% (**5b**)	7% (**6b**)	28%	75%
4	Me (**4b**) 1 equiv	Phthalazine	Reflux	24	44% (**5b**)	8% (**6b**)	52%	85%
5	2-Furyl (**4c**) 1 equiv	Phthalazine	20	26	39% (**5c**)	8% (**6c**)	47%	83%
6	2-Furyl (**4c**) 1 equiv	Phthalazine	Reflux	24	50% (**5c**)	12% (**6c**)	62%	81%
7	2-Naphthyl (**4d**) 1 equiv	Phthalazine	20	24	64% (**5d**)	8% (**6d**)	72%	89%
8	*t*-Butyl (**4e**) 1 equiv	Phthalazine	20	48	7% (**5e**)	53% (**6e**)	60%	13%

[a]Isolated yield of purified products. [b]Diisopropylethylamine. [c]%α = (α/α+γ) × 100%

Table 4. Reaction of 3-Nitropyrrole with Symmetrical 1,3-Diketones



entry	diketone: R/R_1	solvent	time (h)	yield[a]
1	CF_3/H (**4f**) 1.5 equiv	3:2 DCM/AcOH	21	80% (**7**)
2	Ph/H (**4g**) 1 equiv	3:2 DCM/AcOH	44	45% (**8**)
3	2-Pyridyl/H (**4h**) 1 equiv	5:3 DCM/AcOH	24	56% (**9**)
4	Me/H (**4i**) 5 equiv	AcOH	30	41% (**10**)
5	Me/Me (**4j**) 3 equiv	AcOH	40	53% (**11**)

[a]Isolated yield of purified products.

Table 5. Reaction of 2 with Symmetrical 1,3-Diketones 4f and 4g

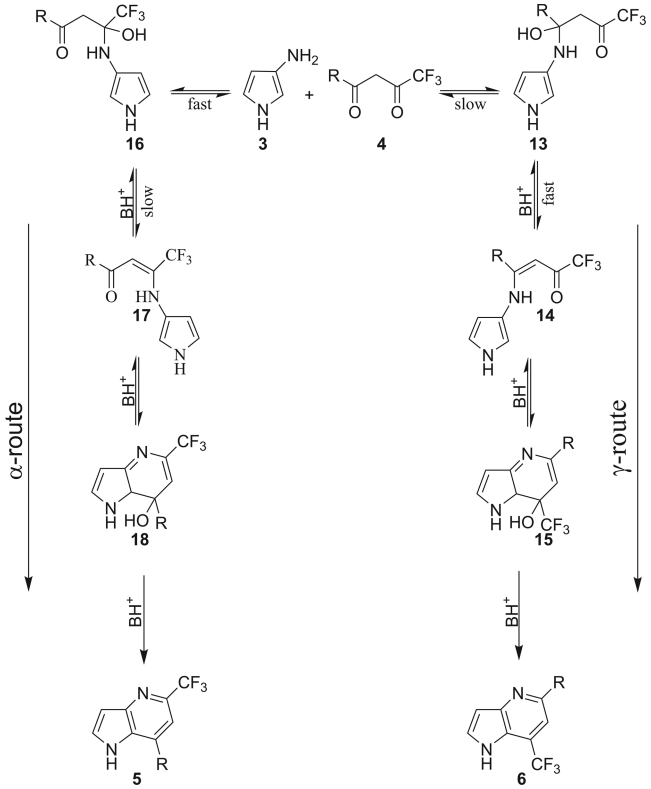
entry	diketone: R	acid/ additive	temp. (°C)	time (h)	yield 7 or 8[a]	yield 12[a]
1	CF_3 (**4f**)	X	20	18	54% (**7**)	0% (**12**)[b]
2	CF_3 (**4f**)	AcOH[c]	reflux	20	70% (**7**)	0% (**12**)[b]
3	Ph (**4g**)	AcOH[d]/ H_2O[d]	reflux	53	11% (**8**)	79% (**12**)[e]

[a]Isolated yield of purified products. [b]Not detected in the reaction mixture. [c]The reaction was run in a 5:3 DCM/AcOH solvent system. [d]One equivalent. [e]Structure determined by X-ray crystallography.

than acetic acid was used. Under these conditions an imine was generally observed from the reaction of the CF_3CO side with the amino group of an aromatic amine.[6,7,21−23,26] This product appeared to be stabilized by hydrogen bonding with the enol tautomer of the remaining carbonyl group.

B. Effect of Acidity and Amine Basicity. It can seen from the above discussion that the dehydration of the amino alcohol **16** leading to the α-product is slow because of the lower basicity of the hydroxyl group. A possible solution is to increase the acidity of the reaction mixture. Similar amino alcohols are

Scheme 2. Acid Catalyzed Reaction of 3-Aminopyrrole with Trifluoromethyl-β-diketones



formed in the reactions of aldehydes and ketones to give imines, oximes, and hydrazones. In these cases general acid catalysis is observed where the pK_a of the catalyzing acid is the determining factor and not the hydrogen ion concentration as in specific acid catalysis.[31,32] The situation with regard to enamine formation is not as clear. Kinetic studies have been carried out on the hydrolysis of enamines, but not of their formation.[42] On the basis of the principle of microscopic reversibility, where the forward and reverse mechanisms must be the same, the mechanism of enamine formation could, in principle, be elucidated from the hydrolysis mechanism.[43] This is complicated by complex specific and general acid catalysis where the rate-determining step changed with pH.[25]

Almost all the reported heterocyclic-ring formation reactions of heterocyclic amines and fluoro-substituted-β-diketones were

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carried out in acetic acid and gave mostly or only the γ-regioisomer.[4−9] The synthesis of 1*H*-pyrazolo[3,4-*b*]pyridines was first reported to give the 4-isomer (α-regioisomer).[9] Subsequently it was found to be the 6-isomer (γ-regioisomer).[10] Recently it was reported that in EtOH/acetic acid the 6-isomer (γ-regioisomer) was formed, but in the absence of solvent with *para*-toluenesulfonic acid, the 4-isomer (α-regioisomer) was the only product.[13] It has been reported that the reaction of trifluoromethyl-β-diketones with phenylhydrazines and hydroxylamine to give pyrazoles[38,44] and isoxazoles[44] respectively, gave the equivalent of the α-regisomer as the major product when strong acids such as H_2SO_4 or PPA were used.

Preparation of β-enaminoketonato ligands, in the absence of steric effects, went preferentially via the α-route when acids stronger than acetic were used such as formic acid[6,16,17] or *para*-toluenesulfonic acid.[18,21,7] These results would seem to indicate that acids stronger than acetic acid, favored the α-route.

In order to test the possibility of general acid catalysis, the reaction of 4,4,4-trifluoro-1-phenyl-1,3-butadione (**4a**) with 3-aminopyrrole (**3**) was carried out using a series of 6 amine buffers from pK_a = 0.4 (pyrazine) to pK_a = 12.0 (1,8-bis(dimethylamino)naphthalene (Proton-sponge)).[45] Buffers were generated by adding 3 equiv of the amine to the reaction mixture containing the aminopyrrole salt. Results are in Table 1 and Figures 2 and 3. These results clearly showed that changing

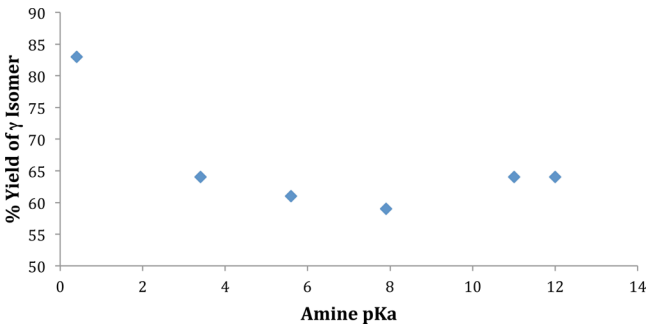

Figure 2. Amine pK_a vs yield of γ-isomer.

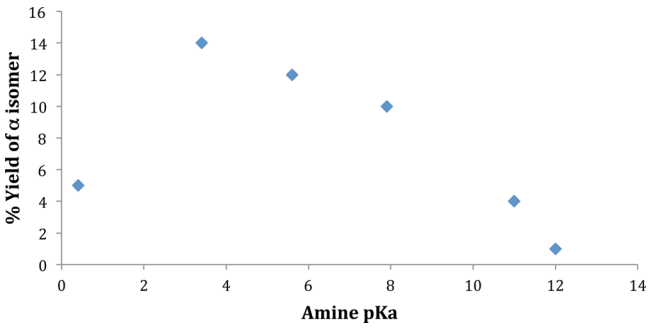

Figure 3. Amine pK_a vs yield of α-isomer.

the pK_a of the amine used affected both selectivity and the total yield (sum of both regioisomers). Yields of the α-regioisomer did increase as the pK_a of the amine buffer decreased, but surprisingly the yield went down at higher pK_as. It was also found that the yields of the γ-regioisomer were highest in the presence of pyrazine. This was attributed to an increase in the rates of dehydration of both amino alcohols **16** and **13**. Increased acidity might also increase the rate of formation of amino alcohol **13**.

The change in the slopes of the graphs in Figures 2 and 3 clearly showed a change in mechanism as the reaction mixture became more basic.

It does not appear to have been previously noted that in the reaction of strong amines with trifluoromethyl-β-diketones such as 4,4,4-trifluoro-1-phenyl-1,3-butadione (pK_a = 6.3)[46] and 1,1,1-trifluoro-2,4-pentadione (pK_a = 6.4)[46] the reactive species might be the enolate rather than the 1,3-diketone or its enol.[4,47] When DIPEA (pK_a = 11.0) or 1,8-bis(dimethylamino)-naphthalene (pK_a = 12.0) were used, the trifluoromethyl-β-diketone would be essentially completely converted to its enolate. Scheme 3 illustrates the proposed mechanism for the reaction of trifluoromethyl-β-diketones with very basic amines. In this mechanism proton transfer to the enolate and attack at the CF3 side are concerted. Regiochemistry (formation of the γ-product) is the result the steric interaction between the phenyl group and the pyrrole-ring N−H. This mechanism would explain the results previously reported with strongly basic amines that did not need an acid catalysis for formation.[5] It can also be used to reinterpret results obtained in a study on regiochemistry of the reaction of hydrazines with fluorosubstituted-β-diketones to give pyrazoles.[38] It was observed that the α-route was preferred in H_2SO_4 but under neutral conditions (absence of an added acid catalysis), it depended on the basicity of the hydrazine. The results of the buffer study not only showed the effect of acidity on regiochemistry, but also indicated that reactions carried out in the presence of a non-nucleophilic strong base, such as DIPEA or 1,8-bis-(dimethylamino)naphthalene, should give optimal γ-regioisomer regioselectivity.

C. Effect of Sn^{2+}. The one-step reaction gave primarily the α-regioisomer (Table 2). As noted above one-step reactions (using Sn/AcOH) differ from the two-step process in that in the course of the reaction Sn^{2+} and 2 equiv of water were produced. This suggested that the presence of Sn^{2+} and/or water changed the reaction mechanism. To test this reactions were run with added tin(II) acetate. Comparison of Tables 1 and 3 clearly demonstrated the effect on regiochemistry of adding Sn^{2+} as tin(II) acetate. Base was added to help form the enolate of the 1,3-diketone. In the reaction of 3-aminopyrrole salt with 4,4,4-trifluoro-1-phenyl-1,3-butadione and added DIPEA and tin(II) acetate, the α/γ ratio was 2.68 compared to 0.06 without added tin(II) acetate. Scheme 4 illustrates the proposed mechanism for the formation of β-enaminone **17**. A variety of Lewis acids[48−54] have been reported to catalyze the formation of β-enaminones analogous to **17**. Catalysis[51] by Sn^{4+} has been reported, but not to our best knowledge by Sn^{2+}.[55] When the reaction was carried out in the presence of 4A molecular sieve, equal amounts of both regioisomers were formed—there did not appear to be any preference. It is proposed that the water formed during the reaction helped to solubilize the tin salt and increase the catalytic concentration of Sn^{2+} in the reaction mixture and the regioselectivity. When additional water was added to the reaction mixture, a second layer was formed.

■ CONCLUSIONS

The results of this study suggested the reaction conditions needed to maximize the yield of the desired regioisomer from the reaction of an amine with a trifluoromethyl-β-diketone. It should be noted that reaction of an amino group with a

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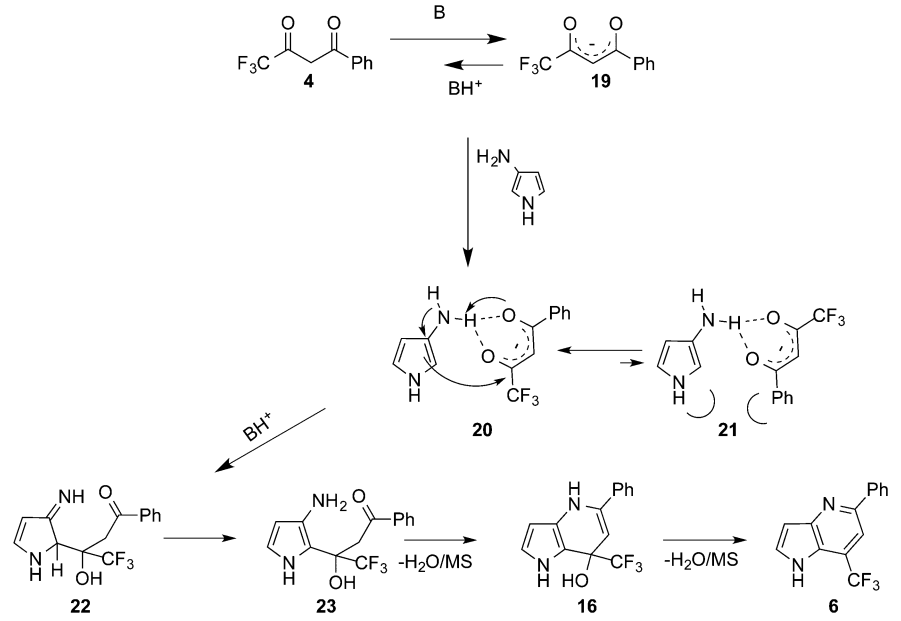
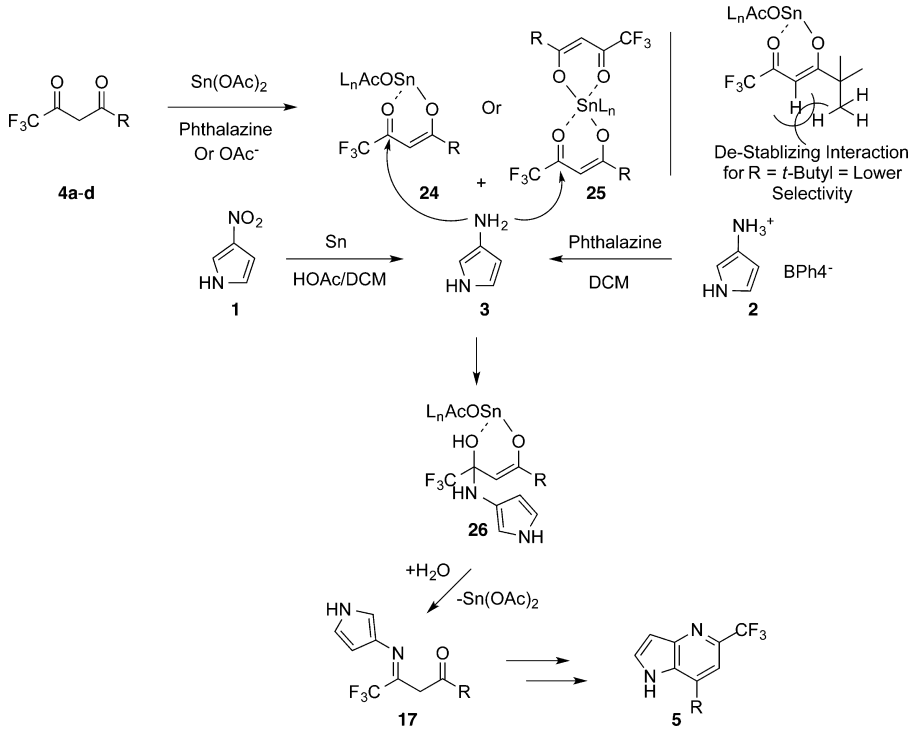
Scheme 3. Reaction of 4,4,4-Trifluoro-1-phenyl-1,3-butadione with Very Basic Amines (B)



Scheme 4. Sn^{2+} Catalyzed Reaction of 3-Aminopyrrole with Trifluoromethyl-β-diketones



trifluoromethyl-β-diketone (or any unsymmetrical β-diketone) is complicated by the fact that the β-diketone has two electrophilic centers and can exist in three tautomeric forms.[37] Further under what are considered neutral conditions (absence of an acid catalysis), the trifluoromethyl-β-diketone is sufficiently acidic[46] that it can be deprotonated to some extent by the amine or amino containing compound with which it is reacting. As a result there are eight potential reaction pathways leading to two different amino alcohols that dehydrate at different rates. The presence of a steric effect can reduce the number of possible routes to four. Most of the steps are equilibria. Only enamine or imine formation (if water is removed) and cyclization are irreversible. The stability of the enamine or imine intermediate is a consideration. Therefore, the variability of the regiochemistry reported in the literature is not surprising. The mechanisms proposed in this study should help to clarify past results and inform future studies.

EXPERIMENTAL SECTION

All reactions were performed under an atmosphere of nitrogen gas. Reactions were monitored by TLC analysis and visualization was accomplished with a 254 nm UV light. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ or acetone-d_6. Chemical shifts were reported in parts per million with the residual

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solvent peak or TMS used as an internal standard. ^{1}H NMR spectra were recorded at 400 MHz and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), number of protons, and coupling constants. ^{13}C NMR were recorded at 100 MHz using a proton-decoupled pulse sequence with a d_1 of 5 s, and are tabulated by observed peak. The 3-nitropyrrole (**1**) used in this study was commercially available. The 1*H*-pyrrol-3(2*H*)-iminium tetraphenylborate salt (**2**) was synthesized according to a newly published procedure and further purified by recrystallization as reported below.[23] All of the diketones (**4a**−**j**) used in this study were commercially available.

Further Purification of the 1*H*-Pyrrol-3(2*H*)-iminium Tetraphenylborate Salt (2). A gray suspension of tin (2.382 g, 20.07 mmol) and 3-nitropyrrole (0.450 g, 4.014 mmol) in AcOH (25 mL) was stirred at room temperature for 2.5 h. The thick reaction mixture was diluted with distilled water (3.0 mL) and the resulting thin suspension was pressure filtered through a plug of Celite (∼1″, preflushed with water) into a stirred solution of $NaBPh_4$ (5.49 g, 16.1 mmol) in distilled water (25 mL). The plug of Celite was flushed with distilled water until no longer yellow in color. The resulting yellow precipitate was isolated by vacuum filtration, washed with distilled water (50 mL) and dried in vacuo over P_2O_5. The dry yellow solids were suspended in DCM (50 mL) to which MeOH (7 mL) was then added with stirring. The cloudy green/brown mixture was vacuum filtered and the filtrate was slowly diluted with hexane (250 mL) with stirring. After 15 min, the green suspension was vacuum filtered. The isolated solids were washed with hexane (50 mL) and dried in vacuo over P_2O_5 to afford **2** as a light green solid (1.40 g, 87%).

One Pot Reactions of Trifluoromethyl-*β*-Diketones with 3-Nitropyrrole under Reductive Tin Conditions: Synthesis of Compounds 5a−d as the Major Reaction Products. *7-Phenyl-5-(trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**5a**, Table 2: Entry 1).* A gray suspension of **1** (0.0350 g, 0.312 mmol), **4a** (0.0674 g, 0.312 mmol, 1 equiv) and tin (0.185 g, 1.56 mmol, 5 equiv) in a 5:3 DCM/glacial AcOH (4.0 mL) mixture was heated to reflux for 24 h. The heterogeneous orange reaction mixture was cooled to room temperature and concentrated by rotary evaporation (55 °C, vacuum pump) in the presence of SiO_2 (0.500 g). The dry dark orange solids were flash column chromatographed (SiO_2; DCM → 1:1 DCM/EtOAc gradient). Products **5a** and **6a** were isolated together and concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.250 g). The dry light yellow solids were flash column chromatographed a second time (SiO_2; 2:1 hexane/EtOAc). Products **5a** and **6a** were isolated and the column fractions were concentrated separately by rotary evaporation (45 °C). *Minor Product*: Product **6a** was transferred to a preweighed vial with DCM (2.0 mL), concentrated by a stream of N_2 (g) and dried in vacuo over P_2O_5 affording **6a** as a pale yellow crystalline solid (0.0086 g, 11%). The spectral properties of **6a** are identical to those reported herein (R_f = 0.37 (2:1 hexane/EtOAc)). *Major Product*: Product **5a** was recrystallized from a boiling 10:1 hexane/DCM mixture (5 mL) which was slowly cooled to room temperature and then to 0 °C for 1 h. The precipitate was isolated by vacuum filtration, washed with hexane (5 mL) and dried in vacuo over P_2O_5 to afford **5a** as white crystalline needles (0.441 g, 54%): R_f = 0.24 (SiO_2; 2:1 hexane/EtOAc); mp 191.7−192.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (br-s, 1H), 7.67−7.65 (m, 2H), 7.59 (t, 1H, J = 3.2 Hz), 7.56 (s, 1H), 7.54−7.46 (m, 3H), 6.86 (dd, 1H, J = 3.2, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 142.4 (q, J_{CF} = 34 Hz), 135.7, 133.3, 130.4, 129.6 (2C), 129.4, 128.0 (2C), 127.7, 122.6 (q, J_{CF} = 272 Hz), 112.8 (q, J_{CF} = 3.0 Hz), 104.7; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{10}N_2F_3$ 263.0796, found 263.0789.

Note 1*: The reactions of **4a with **1** run in the presence of 4 Å Molecular Sieves or H_2O (Table 2, entries 2−3) were run according to the parameters listed in Table 2 and were worked up according to the above procedure.

*7-Methyl-5-(trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**5b**, Table 2: Entry 4).* A gray suspension of **1** (0.0350 g, 0.312 mmol), **4b** (56.3 μL, 0.468 mmol, 1.5 equiv) and tin (0.185 g, 1.56 mmol, 5 equiv) in a 5:3 DCM/glacial AcOH (4.0 mL) mixture was heated to reflux for 21 h. The reaction mixture was cooled to room temperature and concentrated by rotary evaporation (50 °C, vacuum pump) in the presence of SiO_2 (0.500 g). The dry solids were flash column chromatographed (SiO_2; 1:1 DCM/EtOAc). Two products **5b** and **6b** were isolated and the column fractions were concentrated separately by rotary evaporation (45 °C). *Major product*: The residue of product **5b** was recrystallized from a boiling 15:1 hexane/DCM mixture (5 mL) which was slowly cooled to room temperature and then to 0 °C for 1 h. The precipitate was isolated by vacuum filtration, washed with hexane (7 mL) and dried in vacuo over P_2O_5 to afford **5b** as a light yellow/green crystalline solid (0.0344 g, 55%): R_f = 0.60 (SiO_2; 1:1 DCM/EtOAc); mp 138.8−139.9 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (br-s, 1H), 7.57 (t, 1H, J = 3.2 Hz), 7.36 (s, 1H), 6.78 (dd, 1H, J = 3.2, 1.2 Hz), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 141.8 (q, J_{CF} = 34 Hz), 130.2 (d, J_{CF} = 1.0 Hz), 130.1, 129.9, 122.6 (q, J_{CF} = 272 Hz), 114.5 (q, J_{CF} = 3.0 Hz), 104.1, 16.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_9H_8F_3N_2$ 201.0640, found 201.0634. *Minor product*: The residue of product **6b** was transferred to a small test tube with DCM (1 mL), concentrated to dryness via. stream of N_2 (g) and the partially crystalline solid was triturated with hexane (1 mL) at 0 °C for 30 min. The resulting precipitate was isolated by vacuum filtration, washed with hexane (3 mL) and dried in vacuo over P_2O_5 to afford **6b** as a light yellow/green solid (0.0048 g, 8%). The spectral properties of **6b** are identical to those reported herein (R_f = 0.38 (1:1 DCM/EtOAc)).

*7-(Furan-2-yl)-5-(trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**5c**, Table 2: Entry 5).* A gray suspension of **1** (0.0350 g, 0.312 mmol), **4c** (46.2 μL, 0.312 mmol, 1 equiv) and tin (0.185 g, 1.56 mmol, 5 equiv) in a 5:3 DCM/glacial AcOH (4.0 mL) mixture was heated to reflux for 38 h. The thick heterogeneous dark red/orange reaction mixture was cooled to room temperature and then distilled water (1.5 mL) was added. After stirring for 4 h at room temperature the resulting thin orange mixture was concentrated by rotary evaporation (60 °C, vacuum pump) in the presence of SiO_2 (0.500 g). The dry dark orange solids were flash column chromatographed (SiO_2; 2:1 hexane/EtOAc). Products **5c** and **6c** were isolated and the column fractions were concentrated separately by rotary evaporation (50 °C). Both **5c** and **6c** were recrystallized from boiling solutions of 10:1 hexane/DCM (**5c** − 4.0 mL, **6c** − 2.0 mL) which were slowly cooled to room temperature and then to −20 °C for 24 h. The precipitates were isolated by vacuum filtration, washed with ice cold hexane (3 mL) and dried in vacuo over P_2O_5. *Minor Product*: Product **6c** was isolated as a light green powder (0.0088 g, 11%). The spectral properties of **6c** are identical to those reported herein (R_f = 0.38 (2:1 hexane/EtOAc)). *Major Product*: Product **5c** was isolated as light pink crystalline needles (0.0397 g, 50%): R_f = 0.25 (SiO_2; 2:1 hexane/EtOAc); mp 143.1−143.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (br-s, 1H), 7.69 (dd, 1H, J = 2.0, 0.80 Hz), 7.66 (s, 1H), 7.64 (t, 1H, J = 3.2 Hz), 7.09 (dd, 1H, J = 3.2, 0.80 Hz), 6.88 (dd, 1H, J = 3.6, 2.0 Hz), 6.65 (dd, 1H, J = 3.6, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 147.7, 144.0, 142.0 (q, J_{CF} = 33 Hz), 130.6, 124.4, 122.5 (q, J_{CF} = 273), 121.2, 112.5, 109.9, 107.6 (d, J_{CF} = 2.0 Hz), 104.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_8N_2F_3O$ 253.0589, found 253.0585.

*7-(Naphthalen-2-yl)-5-(trifluoromethyl)-1H-pyrrolo[3,2-b]-pyridine (**5d**, Table 2, Entry 6).* A gray suspension of **1** (0.0350 g, 0.312 mmol), **4d** (0.0831 g, 0.312 mmol, 1 equiv) and tin (0.185 g, 1.56 mmol, 5 equiv) in a 5:3 DCM/glacial AcOH (4.0 mL) mixture was heated to reflux for 24 h. The heterogeneous light brown reaction mixture was cooled to room temperature and distilled water (1.0 mL) was added. After stirring for 3 h, the cloudy brown mixture was concentrated by rotary evaporation (65 °C, vacuum pump) in the presence of SiO_2 (0.500 g). The dry brown/orange solids were flash column chromatographed (SiO_2; 3:1 hexane/EtOAc). Products **5d** and **6d** were isolated and the column fractions were concentrated separately by rotary evaporation (45 °C). *Minor Product*: Product **6d** was transferred to a preweighed vial with DCM (2.0 mL) and concentrated by a stream of N_2 (g). The resulting solids were triturated with hexane (0.2 mL) and the orange hexane solution was removed. The solids were dried in vacuo over P_2O_5 to afford **6d** as a pale yellow solid (0.0198 g, 20%). The spectral properties of **6d** are

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identical to those reported herein (R_f = 0.38 (SiO_2; 3:1 hexane/EtOAc). *Major Product*: Product **5d** was recrystallized from boiling hexane (5 mL) which was slowly cooled to room temperature and then to 0 °C for 1 h. The precipitate was isolated by vacuum filtration, washed with hexane (2 mL) and dried in vacuo over P_2O_5 to afford **5d** as a fluffy white crystalline solid (0.0545 g, 56%): R_f = 0.30 (SiO_2; 3:1 hexane/EtOAc); mp 210.6−212.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (br-s, 1H), 8.13 (d, 1H, J = 1.2 Hz), 8.03 (d, 1H, J = 8.4 Hz), 7.95−7.89 (m, 2H), 7.74 (dd, 1H, J = 8.4, 1.6 Hz), 7.66 (s, 1H), 7.61 (t, 1H, J = 3.2 Hz), 7.60−7.56 (m, 2H), 6.91 (dd, 1H, J = 3.6, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 142.1 (q, J_{CF} = 34 Hz), 133.5, 133.4, 133.2, 133.0, 130.4, 129.6, 128.2, 127.9 (2C), 127.5, 127.2, 127.1, 125.3, 122.6 (q, J_{CF} = 272 Hz), 113.0, 104.8; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{12}N_2F_3$ 313.0953, found 313.0939.

*7-tert-Butyl-5-(trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**5e**, Table 2: Entry 7).* A gray suspension of **1** (0.0350 g, 0.312 mmol), **4e** (81.2 μL, 0.468 mmol, 1.5 equiv) and tin (0.185 g, 1.56 mmol, 5 equiv) in a 5:3 DCM/glacial AcOH (4.0 mL) mixture was heated to reflux for 44 h. The heterogeneous light brown reaction mixture was cooled to room temperature and distilled water (100 μL) was added. After stirring for 1 h, the homogeneous mixture was concentrated by rotary evaporation (60 °C, vacuum pump) in the presence of SiO_2 (0.500 g). The dry solids were flash column chromatographed (SiO_2; 5:1 → 2:1 hexane/EtOAc gradient). Two products **5e** and **6e** were isolated and the column fractions were concentrated separately by rotary evaporation (45 °C). The resulting oils were transferred to preweighed vials with DCM (2.0 mL) and were concentrated by a stream of N_2 (g). *Major Product*: Product **6e** was crystallized by trituration with hexane (0.5 mL) which was removed by a stream of N_2 (g). The resulting solids were dried in vacuo over P_2O_5 to afford **6e** as an off-white solid (0.0392 g, 52%). The spectral properties of **6e** are identical to those reported herein (R_f = 0.39 (SiO_2; 5:1 hexane/EtOAc). *Minor Product*: Product **5e** was dried and crystallized in vacuo over P_2O_5. Product **5e** was isolated as a pale yellow crystalline solid (0.0106 g, 14%): R_f = 0.08 (SiO_2; 5:1 hexane/EtOAc); mp 118.6−120.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (br-s, 1H), 7.55 (t, 1H, J = 3.2 Hz), 7.43 (s, 1H), 6.87 (dd, 1H, J = 3.6, 2.0 Hz), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 142.7, 142.1 (q, J_{CF} = 33 Hz), 129.0, 127.8, 122.7 (q, J_{CF} = 273 Hz), 110.6, 104.4, 35.0, 30.0 (3C); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_{14}N_2F_3$ 243.1109, found 243.1111.

Optimized Reactions of 3-Aminopyrrole and Trifluoro-β-Diketones in the Presence of Tin(II) Acetate: Synthesis of Compounds 5a−d as the Major Reaction Products. *7-Phenyl-5-(trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**5a**, Table 3: Entry 2).* A cloudy lemon yellow mixture of **4a** (0.0538 g, 0.249 mmol), tin(II) acetate (0.0884 g, 0.374 mmol, 1.5 equiv) and phthalazine (0.0972 g, 0.747 mmol, 3 equiv) in DCM (5.0 mL) was stirred at room temperature for 1 h and then **2** (0.100 g, 0.249 mmol) was added. The green suspension was stirred at room temperature for 24 h, turned brown and was concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.500 g). The solids were flash column chromatographed (SiO_2; 2:1 hexane/EtOAc). Products **5a** and **6a** were isolated and the column fractions were concentrated by rotary evaporation (45 °C). *Minor Product*: Product **6a** was isolated as a cloudy yellow oil which was dissolved in DCM (3.5 mL), dried (Na_2SO_4) and filtered through a tightly packed plug of cotton (packed in a 6" pasture pipet) with DCM (5 mL) into a preweighed vial. The filtrate was concentrated by a stream of N_2 (g) and the residue was triturated with hexane (2×, 2 drops) which was then removed. The remaining solids were dried in vacuo over P_2O_5 to afford **6a** as an off white solid (0.0060 g, 9%). *Major Product*: Product **6a** was recrystallized from a boiling 10:1 hexane/DCM (3 mL) mixture which was slowly cooled to room temperature for 30 min. The precipitate was isolated by vacuum filtration, washed with hexane (3 mL) and dried in vacuo over P_2O_5 to afford **5a** as a fluffy white solid (0.0420 g, 64%). The spectral properties of **5a** and **6a** are identical to those reported herein.

Note 2*: The reaction of **4a with **2** run in the presence of DIPEA (Table 3, entry 1) was run according to the parameters listed in Table 3 and was worked up according to the above procedure.

*7-Methyl-5-(trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**5b**, Table 3: Entry 4).* A pale yellow suspension of **4b** (30.0 μL, 0.249 mmol), tin(II) acetate (0.0884 g, 0.374 mmol, 1.5 equiv) and phthalazine (0.0972 g, 0.747 mmol, 3 equiv) in DCM (5.0 mL) was stirred at room temperature for 1 h and then **2** (0.100 g, 0.249 mmol) was added. The resulting olive green reaction mixture was heated to reflux for 24 h, turned light brown and was cooled to room temperature. The mixture was then suspended in a boiling 7:1 hexane/DCM (10 mL) mixture which was cooled to room temperature for 30 min. The light brown precipitate was removed by vacuum filtration and was washed with hexane (10 mL). It is suspected that this precipitate is a tin(II) tetraphenylborate salt based on ^{1}H NMR (400 MHz, acetone-d_6, see Supporting Information p.36). The yellow filtrate was concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.500 g). The dry solids were flash column chromatographed (SiO_2; 2:1 DCM/EtOAc). Products **5b** and **6b** were isolated and the column fractions were concentrated by rotary evaporation (55 °C). *Major Product*: Product **5b** was isolated as a slightly impure oil which was filtered through a plug of SiO_2 (packed in a 6" pasture pipet) with DCM (~20 mL). The filtrate was concentrated in a preweighed vial via. a stream of N_2 (g) and the resulting solids were further dried in vacuo over P_2O_5 to afford **5b** as a pale yellow solid (0.0218 g, 44%). *Minor Product*: Product **6b** was transferred to a preweighed vial with DCM (2.0 mL), was reconcentrated by a stream of N_2 (g) and was dried in vacuo over P_2O_5. Product **6b** was isolated as a pale yellow solid (0.0039 g, 8%). The spectral properties of **5b** and **6b** are identical to those reported herein.

Note 3*: The reaction of **4b with **2** run at room temperature (Table 3, entry 3) was run according to the parameters listed in Table 3 and was worked up according to the above procedure.

*7-(Furan-2-yl)-5-(trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**5c**, Table 3: Entry 6).* A lemon yellow suspension of **4c** (36.9 μL, 0.249 mmol), tin(II) acetate (0.0884 g, 0.374 mmol, 1.5 equiv) and phthalazine (0.0972 g, 0.747 mmol, 3 equiv) in DCM (5.0 mL) was stirred at room temperature for 1 h and then **2** (0.100 g, 0.249 mmol) was added. The resulting blue/green reaction mixture was heated to reflux for 24 h, was cooled to room temperature and the now black mixture was concentrated by rotary evaporation (50 °C) in the presence of SiO_2 (0.500 g). The dry dark brown solids were flash column chromatographed (SiO_2; 2:1 hexane/EtOAc). Two products **5c** and **6c** were isolated and the column fractions were concentrated by rotary evaporation (55 °C). The residues of **5c** and **6c** were recrystallized separately from boiling hexane (**5c**-4 mL, **6c**-2 mL) which upon turbidity was slowly cooled to room temperature and then to 0 °C for 1h (**5c**) or −20 °C for 18 h (**6c**). The resulting precipitates were isolated by vacuum filtration, washed with ice cold hexane (4 mL) and dried in vacuo over P_2O_5. *Minor Product*: Product **6c** was isolated as a light brown crystalline solid (0.0077 g, 12%). *Major Product*: Product **5c** was isolated as a light brown crystalline solid (0.0317 g, 50%). The spectral properties of **5c** and **6c** were identical to those reported herein.

Note 4*: The reaction of **4c with **2** run at room temperature (Table 3, entry 5) was run according to the parameters listed in Table 3 and was worked up according to the above procedure.

*7-(Naphthalen-2-yl)-5-(trifluoromethyl)-1H-pyrrolo[3,2-b]-pyridine (**5d**, Table 3: Entry 7).* A cloudy yellow/green mixture of **4d** (0.0663 g, 0.249 mmol), tin(II) acetate (0.0884 g, 0.374 mmol, 1.5 equiv) and phthalazine (0.0972 g, 0.747 mmol, 3 equiv) in DCM (5.0 mL) was stirred at room temperature for 1 h and then **2** (0.100 g, 0.249 mmol) was added. The reaction mixture was stirred at room temperature for 24 h, turned brown and was concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.500 g). The dry solids were flash column chromatographed (SiO_2; 3:1 hexane/EtOAc). Products **5d** and **6d** were isolated and the column fractions were concentrated by rotary evaporation (60 °C). *Minor Product*: Product **6d** was transferred to a preweighed vial with DCM (1.5 mL), concentrated by a stream of N_2 (g) and was triturated with hexane (3

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drops) which was then removed. The solids were dried in vacuo over P_2O_5 to afford **6d** as a pale yellow solid (0.0061 g, 8%). *Major Product*: Product **5d** was recrystallized from a boiling 20:1 hexane/DCM (7 mL) mixture which was slowly cooled to room temperature and then to 0 °C for 30 min. The precipitate was isolated by vacuum filtration, washed with hexane (5 mL) and dried in vacuo over P_2O_5 to afford **5d** as a white crystalline solid (0.0495 g, 64%). The spectral properties of **5d** and **6d** are identical to those reported herein.

*7-tert-Butyl-5-(trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**5e**, Table 3: Entry 8).* A cloudy pale yellow mixture of **4e** (43.2, 0.249 mmol), tin(II) acetate (0.0884 g, 0.374 mmol, 1.5 equiv) and phthalazine (0.0972 g, 0.747 mmol, 3 equiv) in DCM (5.0 mL) was stirred at room temperature for 1 h and then **2** (0.100 g, 0.249 mmol) was added. The heterogeneous green reaction mixture was stirred at room temperature for 48 h and was concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.500 g). The dry solids were flash column chromatographed (SiO_2; 5:1 → 1:1 hexane/EtOAc gradient). Products **5e** and **6e** were isolated and the column fractions were concentrated by rotary evaporation (50 °C). *Major Product*: Product **6e** was transferred to a preweighed vial with DCM (1.5 mL), reconcentrated by a stream of N_2 (g), triturated with hexane (2 drops), reconcentrated by a stream of N_2 (g) and dried in vacuo over P_2O_5 to afford **6e** as a pale yellow crystalline solid (0.0318 g, 53%). *Minor Product*: Product **5e** was isolated impure, was dissolved in DCM (10 mL) and concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.200 g). The solids were flash column chromatographed a second time (SiO_2; 5:1 → 1:1 hexane/EtOAc gradient). Product **5e** was isolated and the column fractions were concentrated by rotary evaporation (50 °C). The isolated oil was transferred to a preweighed vial with DCM (1.5 mL), concentrated by a stream of N_2 (g), the residue was triturated with hexane (1.0 mL) which was removed by a stream of N_2 (g) and the solids were dried in vacuo over P_2O_5 to afford **5e** as a pale yellow crystalline solid (0.0043 g, 7%). The spectral properties of **5e** and **6e** are identical to those reported herein.

Reaction of 3-Aminopyrrole with Trifluoromethyl-β-Diketones under Acidic or Buffered Conditions: Synthesis of Compounds 6a−e as the Major Reaction Products. *5-Phenyl-7-(trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**6a**, Table 1: Entry 16).* A dark green suspension of **2** (0.100 g, 0.249 mmol), proton sponge (0.1601 g, 0.747 mmol, 3 equiv) and 4 Å molecular sieves (0.100 g) in DCM (5.0 mL) was stirred at room temperature for 1 h and then **4a** (0.0807 g, 0.374 mmol, 1.5 equiv) was added. The reaction mixture was stirred at room temperature for 24 h, turned black and was concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.500 g). The dry brown solids were flash column chromatographed (SiO_2; 2:1 hexane/EtOAc). Two products **5a** and **6a** were isolated and the column fractions were concentrated by rotary evaporation (45 °C). *Major Product*: Product **6a** was isolated as a pale yellow oil and was recrystallized from boiling hexane (3 mL) which was slowly cooled to room temperature and then to −20 °C for 10 h. The precipitate was isolated by vacuum filtration, washed with ice cold hexane (5 mL) and dried in vacuo over P_2O_5 to afford **6a** as a clear crystalline solid (0.0417 g, 64%): mp 131.9−132.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (br-s, 1H), 8.05−8.02 (m, 2H), 7.71 (s, 1H), 7.54 (t, 1H, J = 3.2 Hz), 7.53−7.47 (m, 2H), 7.43−7.39 (m, 1H), 6.90 (dd, 1H, J = 3.2, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 148.8, 139.6, 130.0, 128.9 (2C), 128.7, 127.2 (2C), 123.9 (q, J_{CF} = 271 Hz), 122.3 (q, J_{CF} = 2.0 Hz), 121.0 (q, J_{CF} = 34 Hz), 110.8 (q, J_{CF} = 4.0 Hz), 104.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{10}N_2F_3$ 263.0796, found 263.0788. *Minor Product*: Product **5a** was isolated as a pale yellow oil and was recrystallized from boiling hexane (2 mL) which was cooled to room temperature for 10 h. The precipitate was isolated by vacuum filtration, washed with hexane (2 mL) and dried in vacuo over P_2O_5 to afford **5a** as a fluffy white solid (0.0070 g, 1%). The spectral properties of **5a** are identical to those reported herein.

*5-Phenyl-7-(trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**6a**, Table 1: Entry 4).* A dark green suspension of **2** (0.100 g, 0.249 mmol), pyrazine (0.0598 g, 0.747 mmol, 3 equiv) and 4 Å molecular sieves (0.100 g) in DCM (5.0 mL) was stirred at room temperature for 15 min and then **4a** (0.0807 g, 0.374 mmol, 1.5 equiv) was added. The reaction mixture was stirred at room temperature for 24 h, turned black and was concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.500 g). The dry solids were flash column chromatographed (SiO_2; 10:1 DCM/EtOAc). Two products **5a** and **6a** were isolated together and the column fractions were concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.500 g). The dry solids were flash column chromatographed a second time (SiO_2; 2:1 hexane/EtOAc). Products **5a** and **6a** were isolated, the column fractions were concentrated by rotary evaporation (45 °C), the resulting oils were transferred to preweighed vials with DCM (2.0 mL), were concentrated by a stream of N_2 (g) and dried in vacuo over P_2O_5. *Major Product*: Product **6a** was isolated as a white crystalline solid (0.0540 g, 83%). *Minor Product*: Product **5a** was isolated as a white crystalline solid (0.0030 g, 5%). The spectral properties of **5a** and **6a** are identical to those reported herein.

Note 5*: The reactions of **4a with **2** run in the presence of no acid, 25% TFA, phthalazine, benzimidazole, 2-methylimidazole, DIPEA and in the 1:1 DCM/MeOH solvent system (Table 1, entries 1, 2, 7−10, 13, 15) were run according to the parameters listed in Table 1 and were worked up according to the above procedure.

*5-Methyl-7-(trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**6b**, Table 1: Entry 17).* A dark green suspension of **2** (0.100 g, 0.249 mmol), proton sponge (0.1601 g, 0.747 mmol, 3 equiv) and 4 Å molecular sieves (0.100 g) in DCM (5.0 mL) was stirred at room temperature for 1 h and then **4b** (45.0 μL, 0.374 mmol, 1.5 equiv) was added. The reaction mixture was heated to reflux for 40 h, turned brown, was cooled to room temperature and was concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.500 g). The dry solids were flash column chromatographed (SiO_2; 1:1 DCM/EtOAc). Products **5b** and **6b** were isolated and the column fractions were concentrated separately by rotary evaporation (45 °C). Both products **5b** and **6b** were found to be contaminated with proton sponge by TLC, were individually dissolved in DCM (0.25 mL) and were individually filtered through SiO_2 (packed in a 6" pasture pipet) with DCM (∼30 mL). The isolated products were concentrated by rotary evaporation (45 °C), dissolved in DCM (2.0 mL), transferred to preweighed vials, reconcentrated by a stream of N_2 (g) and dried in vacuo over P_2O_5. *Minor Product*: Product **5b** was isolated as a pale yellow solid (0.0034 g, 7%). The spectral properties of **5b** are identical to those reported herein. *Major Product*: Product **6b** was isolated as a white crystalline solid (0.0305 g, 61%): mp 113.0−113.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (br-s, 1H), 7.52 (t, 1H, J = 3.2 Hz), 7.21 (s, 1H), 6.77 (dd, 1H, J = 3.2, 2.0 Hz), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 148.2, 129.3, 123.8 (q, J_{CF} = 271 Hz), 121.6 (q, J_{CF} = 2.0 Hz), 120.7 (q, J_{CF} = 33 Hz), 112.7 (q, J_{CF} = 4.0 Hz), 103.7, 24.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_8N_2F_3$ 201.0640, found 201.0624.

Note 6:* The reactions of **4b and **2** run in the presence of pyrazine and DIPEA (Table 1, entries 3, 11 and 12) were run according to the parameters listed in Table 1 and were worked up according to the above procedure.

*5-(Furan-2-yl)-7-(trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**6c**, Table 1: Entry 5).* A light green suspension of **2** (0.100 g, 0.249 mmol), pyrazine (0.0598 g, 0.747 mmol, 3 equiv) and 4 Å molecular sieves (0.100 g) in DCM (5.0 mL) was stirred at room temperature for 20 min and then **4c** (55.4 μL, 0.374 mmol, 1.5 equiv) was added. The reaction mixture was stirred at room temperature for 24 h, turned brown and was concentrated by rotary evaporation (60 °C) in the presence of SiO_2 (0.500 g). The dry solids were flash column chromatographed (SiO_2; 2:1 hexane/EtOAc). Two products **5c** and **6c** were isolated and the column fractions were concentrated by rotary evaporation (60 °C). *Major Product*: Product **6c** was isolated as a yellow oil and was recrystallized from boiling hexane (5 mL) which was slowly cooled to room temperature and then to 0 °C for 30 min. The resulting precipitate was isolated by vacuum filtration, washed with ice cold hexane (5 mL) and dried in vacuo over P_2O_5 to afford **6c** as a light brown crystalline solid (0.0514 g, 82%): mp 180.1−181.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (br-s, 1H), 7.79 (s, 1H), 7.56−7.55 (m, 2H), 7.08 (dd, 1H, J = 3.6, 0.80 Hz), 6.87 (dd, 1H, J = 3.2,

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2.0 Hz), 6.55 (dd, 1H, J = 3.2, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 148.4, 144.0, 143.2, 130.1, 123.7 (q, J_{CF} = 271 Hz), 122.2, 121.1 (q, J_{CF} = 34 Hz), 112.1, 109.2 (q, J_{CF} = 3.0 Hz), 107.9, 104.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_8N_2F_3O$ 253.0589, found 253.0581. *Minor Product*: Product **5c** was isolated as a pale yellow oil and was transferred to a preweighed vial with DCM (2.0 mL). The DCM was removed by a stream of N_2 (g) and the product was further dried in vacuo over P_2O_5 to afford **5c** as a pale yellow/orange solid (0.0041 g, 7%). The spectral properties of **5c** are identical to those reported herein.

*5-(Furan-2-yl)-7-(trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**6c**, Table 1: Entry 18).* A dark green suspension of **2** (0.100 g, 0.249 mmol), proton sponge (0.1601 g, 0.747 mmol, 3 equiv) and 4 Å molecular sieves (0.100 g) in DCM (5.0 mL) was stirred at room temperature for 1 h and then **4c** (55.3 μL, 0.374 mmol, 1.5 equiv) was added. The reaction mixture was stirred at room temperature for 24 h, turned black and was concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.500 g). The dry SiO_2 was let to sit overnight which seems to help prevent the streaking of proton sponge through the column during chromatography. The dry solids were then flash column chromatographed (SiO_2; 2:1 hexane/EtOAc). Two products **5c** and **6c** were isolated and the column fractions were concentrated by rotary evaporation (50 °C). The resulting pale yellow oils were transferred to preweighed vials with DCM (2.0 mL), reconcentrated by a stream of N_2 (g) and were dried in vacuo over P_2O_5. *Major Product*: Product **6c** was isolated as a light brown crystalline solid (0.0393 g, 63%). *Minor Product*: Product **5c** was isolated as a pale yellow crystalline solid (0.0044 g, 7%). The spectral properties of **5c** and **6c** are identical to those reported herein.

*5-(Naphthalen-2-yl)-7-(trifluoromethyl)-1H-pyrrolo[3,2-b]-pyridine (**6d**, Table 1: Entry 19).* A dark green suspension of **2** (0.100 g, 0.249 mmol), proton sponge (0.1601 g, 0.747 mmol, 3 equiv) and 4 Å molecular sieves (0.100 g) in DCM (5.0 mL) was stirred at room temperature for 1 h and then **4d** (0.0996 g, 0.374 mmol, 1.5 equiv) was added. The reaction mixture was stirred at room temperature for 24 h, turned black and was concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.500 g). The dry SiO_2 was let to sit overnight which seems to help prevent the streaking of proton sponge through the column during chromatography. The solids were flash column chromatographed two times (SiO_2; 3:1 hexane/EtOAc). Products **5d** and **6d** were isolated, the column fractions were concentrated by rotary evaporation (45 °C), the resulting oils were transferred to preweighed vials with DCM (2 mL) and were concentrated by a stream of N_2 (g). *Major Product*: Product **6d** was isolated and triturated with hexane (0.25 mL). The hexane was removed and the remaining solids were dried in vacuo over P_2O_5 to afford **6d** as a white crystalline solid (0.0476 g, 61%): mp 191.7−193.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (br-s, 1H), 8.51 (m, 1H), 8.24 (dd, 1H, J = 8.8, 2.0 Hz), 7.97 (m, 2H), 7.93 (s, 1H), 7.90−7.87 (m, 1H), 7.59 (t, 1H, J = 2.8 Hz), 7.53−7.49 (m, 2H), 6.96 (dd, 1H, J = 3.2, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 148.9, 136.9, 133.6, 133.5, 130.0, 128.7, 128.6, 127.7, 126.4 (3C), 124.9, 123.9 (q, J_{CF} = 271 Hz), 122.3, 121.1 (q, J_{CF} = 34 Hz), 110.9 (q, J_{CF} = 4.0 Hz), 104.8; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{12}N_2F_3$ 313.0953, found 313.0962. *Minor Product*: Isolated product **5d** was dried in vacuo over P_2O_5 and was isolated as a white solid (0.0044 g, 6%). The spectral properties of **5d** are identical to those reported herein.

Note 7*: The reaction of **4d and **2** run in the presence of pyrazine (Table 1, entry 6) was run according to the parameters listed in Table 1 and was worked up according to the above procedure. A reaction side product complicated the purification of **6d** and inhibited the isolation of **5d** affording low isolated yields.

*5-tert-Butyl-7-(trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**6e**, Table 1: Entry 20).* A dark green suspension of **2** (0.100 g, 0.249 mmol), proton sponge (0.1601 g, 0.747 mmol, 3 equiv) and 4 Å molecular sieves (0.100 g) in DCM (5.0 mL) was stirred at room temperature for 1 h and then **4e** (64.9 μL, 0.374 mmol, 1.5 equiv) was added. The reaction mixture was stirred at room temperature for 46 h, turned black and was concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.500 g). The dry solids were flash column chromatographed (SiO_2; 5:1 DCM/EtOAc). A mixture of products **5e** and **6e** and proton sponge were isolated and the column fractions were concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.250 g). The dry solids were flash column chromatographed a second time (SiO_2; 5:1 → 2:1 → 1:1 hexane/EtOAc gradient). Products **5e** and **6e** were isolated, the column fractions were concentrated by rotary evaporation (45 °C), the residues were transferred to preweighed vials with DCM (1.5 mL), reconcentrated by a stream of N_2 (g), triturated with hexane (1.5 mL), reconcentrated by a stream of N_2 (g) and dried in vacuo over P_2O_5. *Major Product*: Product **6e** was isolated as a clear crystalline solid (0.0454 g, 75%): mp 126.1−127.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (br-s, 1H), 7.52 (t, 1H, J = 3.2 Hz), 7.40 (d, 1H, J = 0.40 Hz), 6.84 (dd, 1H, J = 3.6, 2.0 Hz), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 147.7, 129.1, 124.1 (q, J_{CF} = 270 Hz), 121.4 (q, J_{CF} = 2.0 Hz), 120.3 (q, J_{CF} = 33 Hz), 108.9 (q, J_{CF} = 4.0 Hz), 104.1, 37.7, 30.7 (3C); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_{14}N_2F_3$ 243.1109, found 243.1110. *Minor Product*: Product **5e** was isolated as a pale yellow crystalline solid (0.0020 g, 1%). The spectral properties of **5e** are identical to those reported herein.

Note 8*: The reaction of **2 and **4e** run in the presence of DIPEA (Table 1, entry 14) was run according to the parameters listed in Table 1 and was worked up according to the above procedure.

Reaction of 2-Aminopyrrole with Symetrical-β-Diketones to Afford 1*H*-Pyrrolo[3,2-*b*]pyridines 7 and 8 and Boron Complex 12. *5,7-Bis(trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**7**, Table 5: Entry 2).* To a dark green suspension of **2** (0.100 g, 0.249 mmol) in a 5:3 DCM/glacial AcOH mixture was added **4f** (52.9 μL, 0.374 mmol, 1.5 equiv) at room temperature. The reaction mixture was heated to reflux for 20 h, cooled to room temperature and the resulting brown homogeneous mixture was concentrated by rotary evaporation (50 °C, vacuum pump) in the presence of SiO_2 (0.500 g). The dry solids were flash column chromatographed (SiO_2; DCM). The isolated product was concentrated by rotary evaporation (45 °C). The resulting solids were recrystallized from a boiling 15:1 hexane/DCM (5 mL) mixture which was slowly cooled to room temperature and then to 0 °C for 1 h. The precipitate was isolated by vacuum filtration, washed with hexane (5 mL) and dried in vacuo over P_2O_5 to afford **7** as a clear crystalline solid (44.5 mg, 70%). The spectral properties of **7** are identical to those reported herein.

Note 9*: The reaction of **2 with **4f** at room temperature (Table 5, entry 1) was run according to the parameters listed in Table 2 and was worked up according to the above procedure.

*5,7-Diphenyl-1H-pyrrolo[3,2-b]pyridine and (Z)-3-(Diphenylboryloxy)-1,3-diphenylprop-2-en-1-one (**8** and **12**, Table 5: Entry 3).* To a green suspension of **2** (0.100 g, 0.249 mmol) and **4g** (0.0839 g, 0.374 mmol, 1.5 equiv) in DCM (5.0 mL) was added AcOH (14.3 μL, 0.249 mmol) followed by H_2O (4.5 μL, 0.249 mmol) at room temperature. After 5 h, the reaction mixture was heated to reflux for 53 h and was then concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.500 g). The dark green solids were flash column chromatographed (SiO_2; gradient elution DCM → 1:1 DCM/EtOAc). Products **8** and **12** were isolated and the column fractions were concentrated by rotary evaporation (45 °C). Product **8** was isolated as a yellow/green oil which was recrystallized from a boiling 5:1 DCM/hexane mixture (2.5 mL) and slowly cooled to room temperature and then to 0 °C for 30 min. The resulting precipitate was isolated by vacuum filtration, washed with hexane (5 mL) and dried in vacuo over P_2O_5 to afford **8** as a pale brown crystalline solid (0.0072 g, 11%). The spectral properties of **8** are identical to those reported herein. Product **12** was transferred to a preweighed vial with DCM and the DCM was removed by a stream of N_2 (g). This sample was further dried in vacuo over P_2O_5 to afford **12** as a bright yellow solid (0.0746 g, 79%): R_f = 0.85 (SiO_2; 1:1 DCM/EtOAc); ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.47−8.44 (m, 4H), 7.82−7.78 (m, 2H), 7.70−7.67 (m, 4H), 7.62−7.60 (m, 4H), 7.57 (m, 1H), 7.23−7.19 (m, 4H), 7.15−7.11 (m, 2H). ^{13}C NMR (100 MHz, Acetone-d_6) δ 184.2 (2C), 149.0 (2C, br), 135.7 (2C), 134.1 (2C), 132.0 (4C), 130.1 (4C), 129.7 (4C), 127.9 (4C), 127.0 (2C), 95.6. A sample of **12** (0.0050 g) was dissolved in DCM

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(0.3 mL) and crystallized via. slow vapor diffusion method with pentane. These crystals of **12** were of X-ray quality and allowed for the determination of the structure of this compound.

Optimized One Pot Reactions of Symmetrical-β-Diketones with 3-Nitropyrrole under Reductive Tin Conditions: Synthesis of Compounds 7−11. *5,7-Bis(trifluoromethyl)-1H-pyrrolo[3,2-b]-pyridine (**7**, Table 4: Entry 1).* A gray suspension of **1** (0.0350 g, 0.312 mmol), **4f** (66.2 μL, 0.468 mmol, 1.5 equiv) and tin (0.185 g, 1.56 mmol, 5 equiv) in a 5:3 DCM/glacial AcOH (4.0 mL) mixture was heated to reflux for 21 h. The pale orange reaction mixture was cooled to room temperature and concentrated by rotary evaporation (50 °C, vacuum pump) in the presence of SiO_2 (0.500 g). The dry solids were flash column chromatographed (SiO_2; DCM). The product fractions were concentrated by rotary evaporation (45 °C). The white solids were recrystallized from a boiling 15:1 hexane/DCM mixture (5 mL) which was slowly cooled to room temperature and then to 0 °C for 1 h. The precipitate was isolated by vacuum filtration, washed with hexane (5 mL) and dried in vacuo over P_2O_5 to afford **7** as clear crystalline needles (0.0633 g, 80%): R_f = 0.38 (SiO_2; DCM); mp 144.5−145.8 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (br-s, 1H), 7.74 (m, 2H), 7.00 (dd, 1H, J = 3.6, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 142.0 (q, J_{CF} = 35 Hz), 132.1, 124.5, 123.2 (q, J_{CF} = 271 Hz), 121.9 (q, J_{CF} = 272 Hz), 121.0 (q, J_{CF} = 35 Hz), 109.8 (m, 2C, J_{CF} = 3.0 Hz), 105.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_5F_6N_2$ 255.0357, found 255.0350.

*5,7-Diphenyl-1H-pyrrolo[3,2-b]pyridine (**8**, Table 4: Entry 2).* A gray suspension of **1** (0.0250 g, 0.223 mmol), **4g** (0.0500 g, 0.223 mmol, 1 equiv) and tin (0.133 g, 1.12 mmol, 5 equiv) in a 3:2 DCM/glacial AcOH (2.5 mL) mixture was heated to reflux for 44 h. The dark brown heterogeneous reaction mixture was cooled to room temperature, concentrated by rotary evaporation (60 °C, vacuum pump) in the presence of SiO_2 (0.500 g) and further dried in vacuo over P_2O_5. The dry solids were flash column chromatographed (SiO_2; 1:1 DCM/EtOAc). The product fractions were concentrated by rotary evaporation (40 °C). The resulting yellow oil was recrystallized from a boiling 5:1 hexane/DCM (10 mL) mixture which was cooled to room temperature and then to 0 °C for 30 min. The precipitate was isolated by vacuum filtration, washed with hexane (5 mL) and dried in vacuo over P_2O_5 to afford **8** as a white crystalline solid (0.0271 g, 45%): R_f = 0.39 (SiO_2; 1:1 DCM/EtOAc); mp 186.6−187.0 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (br-s, 1H), 8.07−8.04 (m, 2H), 7.70−7.68 (m, 2H), 7.61 (s, 1H), 7.56−7.52 (m, 2H), 7.49−7.44 (m, 4H), 7.40−7.36 (m, 1H), 6.85 (dd, 1H, J = 3.2, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 147.1, 140.9, 137.0, 133.1, 129.4 (2C), 128.8, 128.6 (2C), 128.5, 128.0 (3C), 127.3 (2C), 125.9, 114.4, 104.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{15}N_2$ 271.1235, found 271.1208.

*5,7-Di(pyridin-2-yl)-1H-pyrrolo[3,2-b]pyridine (**9**, Table 4: Entry 3).* A gray/brown suspension of **1** (0.0350 g, 0.312 mmol), **4h** (0.0706 g, 0.312 mmol, 1 equiv) and tin (0.185 g, 1.56 mmol, 5 equiv) in a 5:3 DCM/glacial AcOH (4.0 mL) mixture was heated to reflux for 24 h. The dark gray/brown reaction mixture was cooled to room temperature and concentrated by rotary evaporation (55 °C, vacuum pump). The residue was triturated with a saturated $NaHCO_3$ solution (15 mL) at room temperature for 1 h. The resulting gray/brown precipitate was isolated by vacuum filtration, washed with distilled water (2 × 15 mL), dried in vacuo over P_2O_5, suspended in EtOAc (40 mL) and concentrated by rotary evaporation (50 °C) in the presence of SiO_2 (0.500 g). The dry solids were flash column chromatographed (SiO_2; EtOAc). The product fractions were concentrated by rotary evaporation (50 °C). The pale yellow oil was recrystallized from a boiling 3:1 hexane/DCM mixture (5 mL) which upon turbidity was cooled to room temperature and then to 0 °C for 30 min. The precipitate was isolated by vacuum filtration, washed with hexane (5 mL) and dried in vacuo over P_2O_5 to afford **9** as a pale yellow crystalline solid (0.0478 g, 56%): R_f = 0.25 (SiO_2; EtOAc); mp 172.6−173.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.06 (br-s, 1H), 8.86 (s, 1H), 8.78 (dq, 1H, J = 4.0, 0.8 Hz), 8.71 (dq, 1H, J = 4.0, 0.80 Hz), 8.59 (dt, 1H, J = 6.8, 1.2 Hz), 8.36 (dt, 1H, J = 7.2, 0.80 Hz), 7.88−7.82 (m, 2H), 7.62 (dd, 1H, J = 3.2, 0.40 Hz), 7.35−7.28 (m, 2H), 6.87 (dd, 1H, J = 3.2, 0.80 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 155.9, 150.4, 149.0, 148.9, 148.4, 137.0, 136.9, 129.2, 127.7, 127.1, 123.1, 122.9, 121.1, 121.0, 110.81, 103.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}N_4$ 273.1140, found 273.1131.

*5,7-Dimethyl-1H-pyrrolo[3,2-b]pyridine (**10**, Table 4: Entry 4).* A gray suspension of **1** (0.0350 g, 0.312 mmol), **4i** (161 μL, 1.56 mmol, 5 equiv) and tin (0.185 g, 1.56 mmol, 5 equiv) in glacial AcOH (4.0 mL) was heated to reflux for 30 h. The homogeneous red/orange mixture was cooled to room temperature and a solid precipitated. Distilled water (1.5 mL) was added to the heavy suspension and after stirring for 1 h at room temp, a cloudy solution resulted. This solution was slowly added to a stirred mixture of DCM (25 mL) and a saturated $NaHCO_3$ (75 mL) solution. Following the addition, the mixture was stirred for 30 min, emulsified and was vacuum filtered. A brown solid was removed which contained no product by TLC (SiO_2, EtOAc). The DCM layer was then removed from the filtrate and the aqueous layer was extracted with DCM (2 × 25 mL). The combined DCM layers were dried (Na_2SO_4) and concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.500 g). The dry brown/orange solids were flash column chromatographed (SiO_2; EtOAc → EtOAc (1% MeOH) gradient). The product fractions were combined and concentrated by rotary evaporation (50 °C). The resulting yellow/orange oil was recrystallized from a boiling 7:1 hexane/DCM mixture (5 mL) which upon turbidity was cooled to room temp and then to 0 °C for 1 h. The precipitate was isolated by vacuum filtration, washed with hexane (5 mL) and dried in vacuo over P_2O_5 to afford **10** as a pale yellow crystalline solid (0.0186 g, 41%): R_f = 0.17 (SiO_2, EtOAc); mp 178.5−179.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (br-s, 1H), 7.37 (t, 1H, J = 2.8 Hz), 6.83 (s, 1H), 6.64 (dd, 1H, J = 2.8, J = 1.2 Hz), 2.62 (s, 3H), 2.47 (d, 3H, J = 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 145.4, 129.5, 127.3, 127.0, 118.1, 103.1, 24.2, 16.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{11}N_2$ 147.0922, found 147.0933.

*5,6,7-Trimethyl-1H-pyrrolo[3,2-b]pyridine (**11**, Table 4: Entry 5).* A gray suspension of **1** (0.0350 g, 0.312 mmol), **4j** (109 μL, 0.936 mmol, 3 equiv) and tin (0.185 g, 1.56 mmol, 5 equiv) in glacial AcOH (4.0 mL) was heated to reflux for 40 h. The dark black homogeneous reaction mixture was cooled to room temperature and distilled water (1.5 mL) was added. After 15 min of stirring, the solution was added slowly to a stirred mixture of DCM (50 mL) and a saturated $NaHCO_3$ (75 mL) solution. This mixture was stirred for 30 min, the DCM layer was removed and the aqueous layer was extracted with DCM (3 × 35 mL). The combined DCM layers were dried (Na_2SO_4) and concentrated by rotary evaporation (45 °C) in the presence of SiO_2 (0.500 g). The dry yellow/orange solids were flash column chromatographed (SiO_2; EtOAc → EtOAc (5% MeOH) → EtOAc (10% MeOH) gradient). The product fractions were concentrated by rotary evaporation (50 °C). The resulting pale yellow solids were recrystallized from a boiling 5:1 hexane/DCM mixture (4 mL) which was slowly cooled to room temperature and then to 0 °C for 30 min. The precipitate was isolated by vacuum filtration, washed with hexane (5 mL) and dried in vacuo to afford **11** as a pale yellow crystalline solid (0.0265 g, 53%): R_f = 0.11 (SiO_2; EtOAc); mp 202.8−204.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (br-s, 1H), 7.30 (t, 1H, J = 2.8 Hz), 6.60 (d, 1H, J = 3.2 Hz), 2.62 (s, 3H), 2.43 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 142.7, 128.3, 127.3, 126.3, 123.2, 102.9, 23.8, 14.9, 13.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{13}N_2$ 161.1079, found 161.1084.

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic data (excluding structure factors) for structure **5a** (CCDC 1421293), **6a** (CCDC 1421221) and **12** (CCDC1421500) in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). The Supporting

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NMR spectra (H^1 and C^{13}) of products and X-ray structures of **5a**, **6a** and **12** are presented. (PDF)

Crystal data. (CIF)

Crystal data. (CIF)

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Notes

The authors declare no competing financial interest.

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