Tetrahedron 66 (2010) 2570–2581

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of a versatile 2 (1*H*)-pyrazinone core for the preparation of Tissue Factor-Factor VIIa inhibitors

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ARTICLE INFO

Article history:
Received 24 November 2009
Received in revised form
28 January 2010
Accepted 2 February 2010
Available online 8 February 2010

ABSTRACT

A new, general synthetic route to 2(1*H*)-pyrazinones **11** is described. The four-step synthesis is accomplished utilizing a regioselective hydrolysis and N-alkylation. These compounds efficiently undergo metal-catalyzed cross-coupling reactions to install P2 diversity groups in the 6-position, which can be used to refine the SAR of the S2 pocket of the Tissue Factor/Factor VIIa (TF/VIIa) complex.

1. Introduction

Cardiovascular disease, which is characterized by acute coronary syndromes (ACS) such as unstable angina and myocardial infarction, is the leading cause of death in the western world.[1,2] A common cause for ACS is the occlusion of coronary arteries by a thrombus. This thrombus formation is triggered by vascular injury when the plasma serine protease Factor VIIa (VIIa) comes in contact with its cofactor Tissue Factor (TF), which is an integral membrane protein not normally in contact with blood. Formation of the TF/VIIa complex is the first step in an enzymatic cascade that ultimately leads to the formation of a potentially life threatening fibrin clot.[3] The development of safe and efficacious antithrombotics is needed to combat these diseases. Most research has centered on inhibition of enzymes found down stream in the coagulation cascade such Factor Xa and thrombin.[4] However there is growing evidence, including from our own laboratories, that small molecule inhibitors of the TF/VIIa complex may provide effective anticoagulation while minimizing the risk of bleeding side effects.[4] As a result there has been increased interest in the development of a small molecule inhibitor of TF/VIIa.[5] We therefore believed TF/VIIa to be an attractive target to address this large unmet medical need for safe and efficacious orally available antithrombotics.[6]

Our group recently reported the design, synthesis and structure–activity relationship (SAR) of a series of pyrazinone antithrombotics of the general structure shown in Figure 1.[7] These compounds had nanomolar potency against TF/VIIa and exhibited excellent selectivity over other serine proteases such as thrombin and Factor Xa. Importantly, the pyrazinone core orients the constituents in the correct spatial arrangement to probe the S1, S2, and S3 pockets of the TF/VIIa complex. The pyrazinone cores for this study were prepared according to literature procedures to provide templates for library synthesis. The approach involved a modified Strecker reaction between glycine benzyl ester, trimethylsilylcyanide, and an aldehyde to give the α-cyanoamine. This intermediate was then cyclized to the pyrazinone core with oxalyl chloride (Scheme 1).[8] Most notably this approach installs the P2 diversity element at the 6-position from the aldehyde very early in the synthesis. This P2 moiety was found to be crucial for both potency and selectivity.[7b] Unfortunately, many aldehydes completely failed this reaction sequence or gave low yields of pyrazinone. In many cases the aldehyde failed to form the iminium ion intermediate of the Strecker reaction. Other times the

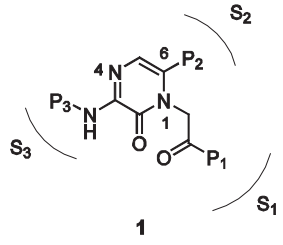

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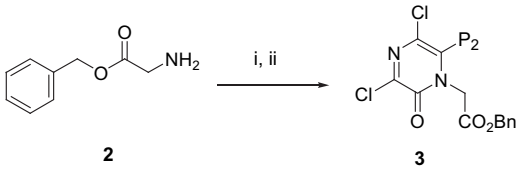
Figure 1. Pyrazinone core structure.



2 3

Scheme 1. Pyrazinone Synthesis. Reagents: (i) TMSCN, P_2CHO; (ii) $(ClCO)_2$.

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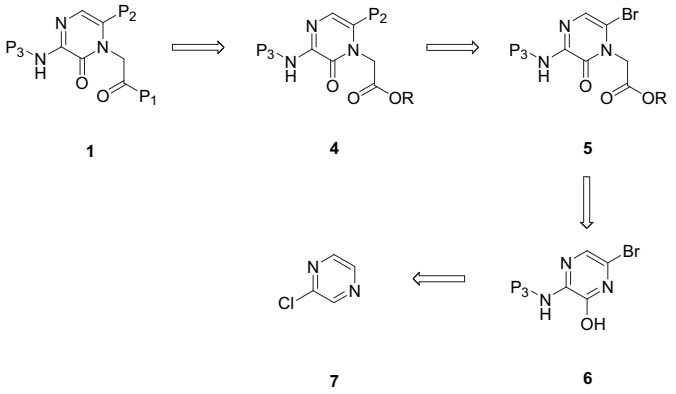
doi:10.1016/j.tet.2010.02.026

α-cyanoamine intermediate was unstable to the harsh conditions of cyclization to the pyrazinone core. In order to further refine the SAR in this pyrazinone series we set out to develop a new scalable route to a pyrazinone core that will be more amenable to the introduction of a P2 diversity element.

2. Results and discussion

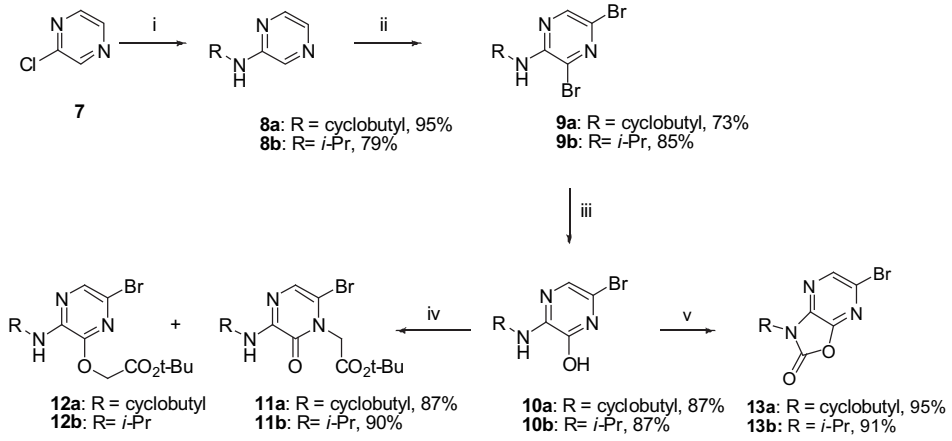
The strategy to a more versatile pyrazinone intermediate is outlined in Scheme 2. We believed that installation of the P2 moiety via a metal-catalyzed process from compound **5** would be mild, efficient and easily scalable. This would allow the installation of diverse and complex moieties required to fully explore the S2 pocket of the enzyme. This intermediate could also serve to explore diversity in the S1 and S3 pockets as well. Intermediate **5** can be derived from selective alkylation of hydroxypyrazine **6**. There are many reports in the literature for the preparation of hydroxypyrazines.[9] Most involve the condensation of an α-aminoacid amide and a 1,2-dicarbonyl compound or the cyclization of a dipeptide. Regiochemical issues plague the latter route when unsymmetrical 1,2-dicarbonyl compounds are used. Conversely, the dipeptide route does not offer the required diversity. We surmised that preparing intermediate **6** from an intact pyrazine ring would avoid the harsh conditions of forming the heterocyclic nucleus and potential regiochemical problems, while maintain the versatility we require. So we envisioned the general structure **5** being ultimately derived from commercially available chloropyrazine **7**. Therefore, we set out to prepare compound **5**.



Scheme 2. Retrosynthetic plan.

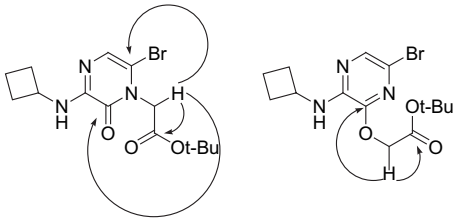
The synthesis of the pyrazinone core is shown in Scheme 3. The P3 inputs were restricted to small aliphatic amines, isopropylamine, and cyclobutylamine, based on the reported SAR.[7b] There are many reports of nucleophilic substitution of chloropyrazine **7** with amines.[10] Most of these methods require long reaction times and give low to moderate yields of the desired product. The initial attempt to perform this substitution reaction was also disappointing employing these methods. Refluxing a solution of **7** and 5 equiv of amine in acetonitrile, toluene or 2-propanol gave only meager yields of **8** (2–18%). It appeared that the poor yields of **8** were related to the volatility of the amines, which may have been lost during heating. We found that heating a neat solution of chloropyrazine **7** in the presence of 2 equiv of amine in a sealed tube resulted in good to excellent yields of *N*-alkylaminopyrazine **8**. With **8** in hand, aminopyrazine **8** and *N*-bromosuccinimde were stirred in an aqueous solution of DMSO to give the dibromopyrazine **9**.[11] Regioselective hydrolysis of **9** was readily accomplished by refluxing in aqueous KOH to give hydroxypyrazine **10**.[11b,e,12] In order to confirm the regiochemistry of hydrolysis, a solution of **10** was heated in the presence of carbonyldiimidazole (CDI) in tetrahydrofuran, which resulted in the formation of benzoxazolinone **13**.[13] This product can only be formed from regioisomer **10**.

The alkylation of hydroxypyrazines, such as **10**, reported in the literature tend to be non-selective as both the N- and O- alkylated products are formed.[14] The alkylation of intermediate **10** to the targeted molecule **11** was also problematic. Heating a solution of **10a** with *tert*-butyl bromoacetate in the presence of potassium carbonate gave a 1:4.5 ratio of isomers **11a** and **12a** respectively, in a combined yield of 91%. The structures of the isomers were determined by 1-D and 2-D NMR experiments since the ^{1}H NMR spectra of the isomers were indistinguishable. Structural assignment of these compounds was accomplished with 2-D HMBC and 1-D APT experiments. The assignment of the methylene carbon of the acetate group in both isomers was accomplished by 1-D APT experiments, which in turn ultimately lead to the structural assignment of the isomers. In compound **12a**, this appeared at δ 63.7, which is characteristic of an oxygen bearing carbon.[15] Conversely, the methylene group in **11a** appeared at δ 49.7, which is common for nitrogen bearing carbons.[15] Long-range carbon–hydrogen couplings observed in the 2-D HMBC further confirmed these assignments (Scheme 4). For example, the methylene singlet at δ 4.74 for **12a** exhibited a cross peak to the ester carbonyl carbon at δ 167.2 and the oxygen bearing carbon of the pyrazine ring found at δ 135.7. For compound **11a**, cross peaks were observed between the methylene singlet found at δ 4.79 and



Scheme 3. Synthesis of 2(1*H*)-pyrazinones. Reagents and conditions: (i) 2 equiv of RNH_2; (ii) 2 equiv NBS, DMSO/H_2O; (iii) KOH, H_2O, reflux; (iv) 1.1 equiv *tert*-butyl bromoacetate, 2 equiv CaH_2, THF, reflux; (v) CDI, THF.

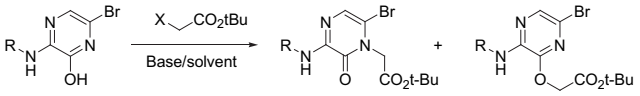
the ester carbonyl carbon at δ 165.8, the oxygen bearing carbon of the pyrazine found at δ 152.5, and the bromine bearing carbon found at δ 105.1. By analogy, similar shifts were observed for **11b** and **12b**. This allowed structural assignment of the isomers **11** and **12**.



Scheme 4. 2D-HMBC long-range carbon–hydrogen couplings observed for **11a** and **12a**.

Since the O-alkylation product **12a** was formed as the major product, we decided to perform a small alkylation study in hope of reversing the regiochemisty. The results are summarized in Table 1. The use of bromoacetate decreased the ratio of **12a**:**11a** relative to chloroacetate (entries 1 and 2). Carbonate bases all gave the O-alkylation product **12a** as the major product (entries 1–4). However, increasing the equivalence of base did slightly decrease the ratio (entries 3 and 4). The use of a strong kinetic base, lithium hexamethyldisilylazide, resulted in nearly the exclusive formation of **12a** in the ratio of approximately 25:1 (entry 6). The use of a stronger thermodynamic base, 1 equiv of calcium hydride resulted in a 3:1 ratio of **11a** to **12a** (entry 7). We found that refluxing a solution of **10a** and *tert*-butyl bromoacetate in the presence of 2 equiv of calcium hydride gave the desired N-alkylation product **11a** in a ratio of 12:1 in an isolated yield of 87% (entry 8). Application of these conditions to the alkylation of **10b** resulted in a 10:1 ratio also favoring the desired product **11b** in an isolated yield of 90% (entry 9). It is important to note, this route allows the introduction of base labile acetates, such as methyl acetate, which can be utilized for orthogonal protecting group strategies.

Table 1
Alkylation study of **10**



10a: R = cyclobutyl
10b: R= *i*-pr

11a: R = cyclobutyl
11b: R= *i*-pr

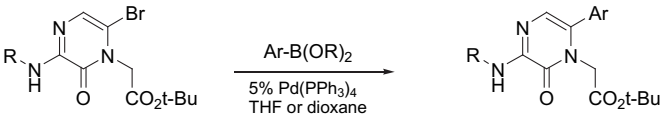
12a: R = cyclobutyl
12b: R= *i*-pr

Entry	Pyrazine	Base/Solvent	X	Time (h)	Ratio 11:12[a]
1	**10a**	K_2CO_3 (1 equiv)/DMSO	Br	3	1:4.5
2	**10a**	K_2CO_3 (1 equiv)/DMSO	Cl	3	1:6
3	**10a**	K_2CO_3 (2 equiv)/DMSO	Br	1	1:2.8
4	**10a**	Cs_2CO_3 (2 equiv)/DMSO	Br	1.5	1:2.9
5	**10a**	DBU (2 equiv)/THF	Br	14	1:4.7
6	**10a**	LHMDS (1 equiv)/THF	Br	3	1:24.7
7	**10a**	CaH_2 (1 equiv)/THF	Br	24	3:1
8	**10a**	CaH_2 (2 equiv)/THF	Br	24	12:1
9	**10b**	CaH_2 (2 equiv)/THF	Br	24	10:1

[a] Ratios were determined by LC-MS on crude reaction mixtures.

Pyrazines have been extensively utilized in various metal-catalyzed cross-coupling reactions.[10b,11d,16–19] However, there are only a limited number of reports involving 2(1*H*)-pyrazinones in such processes. Nearly all of these reports involve metal-catalyzed cross-coupling at the C3 or C5-position of 2(1*H*)-pyrazinones.[14h,20] Now with the targeted pyrazinone in hand, we set out to examine the use of various metal-catalyzed reactions to introduce P2 diversity groups at the C6-position. As shown in Table 2, compounds

Table 2
Suzuki Cross-coupling of **11**[a]



11a: R = cyclobutyl
11b: R= *i*-pr

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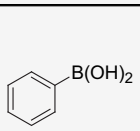
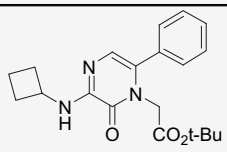
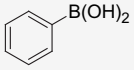
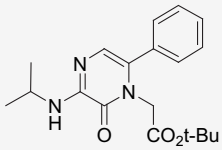
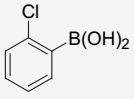
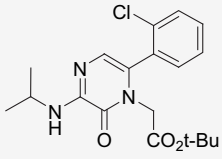
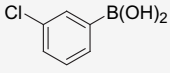
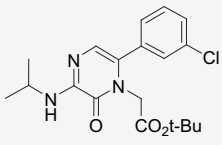
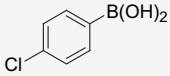
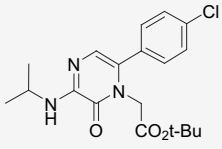
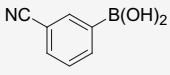
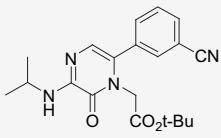
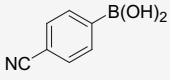
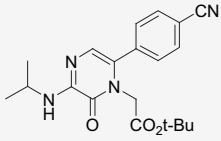
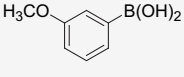
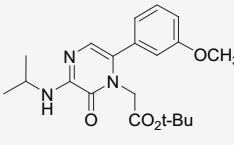
Entry	Bromide	Ar-B(OR)$_2$	Product	Yield (%)
1	**11a**		 **14a**	82
2	**11b**		 **14b**	80
3	**11b**		 **14c**	59
4	**11b**		 **14d**	74
5	**11b**		 **14e**	86
6	**11b**		 **14f**	73
7	**11b**		 **14g**	57
8	**11b**		 **14h**	70

(*continued on next page*)

Table 2 (*continued*)

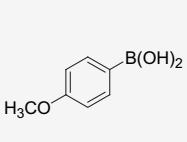
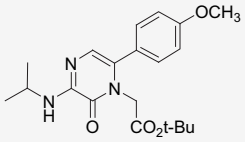
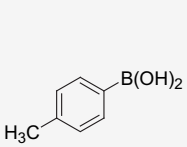
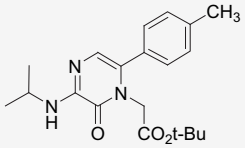
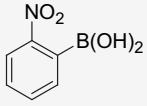
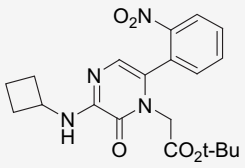
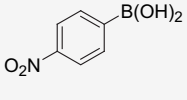
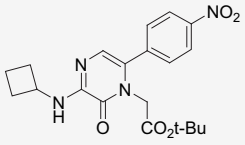
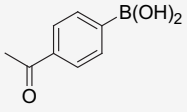
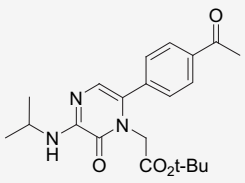
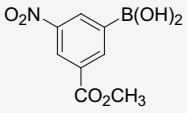
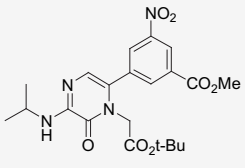
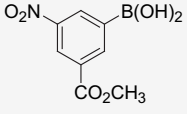
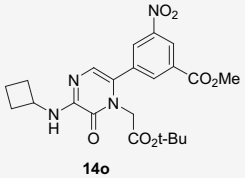
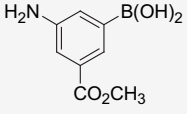
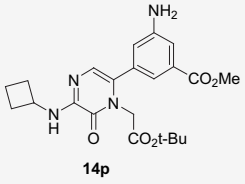
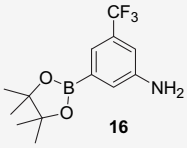
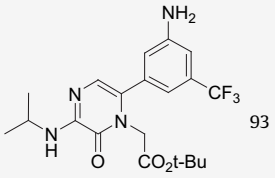
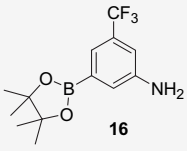
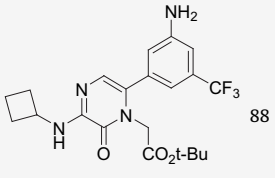
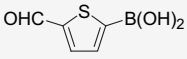
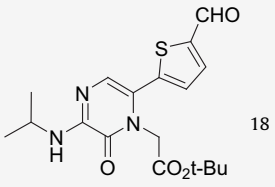
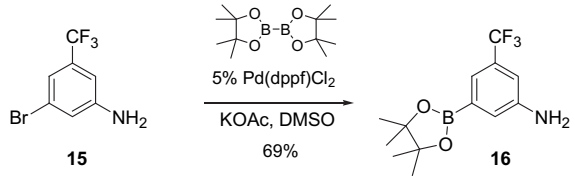
Entry	Bromide	Ar-B(OR)$_2$	Product	Yield (%)
9	**11b**		 **14i**	85
10	**11b**		 **14j**	75
11	**11a**		 **14k**	71
12	**11a**		 **14l**	53
13	**11b**		 **14m**	55
14	**11b**		 **14n**	59
15	**11a**		 **14o**	62
16	**11a**		 **14p**	52

Table 2 (*continued*)

Entry	Bromide	Ar-B(OR)$_2$	Product	Yield (%)
17	**11b**	 **16**	 **14q**	93
18	**11a**	 **16**	 **14r**	88
19	**11b**		 **14s**	18

[a] Reagents and conditions: 1.1 equiv Aryl boronate, 2.0 equiv Na_2CO_3 (aq), 5 mol % $Pd(PPh_3)_4$.

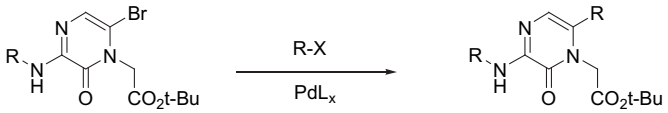
11 readily undergo the Suzuki Cross-Coupling reaction in moderate to good yield (entries 1–18).[21] Due to the established SAR, which suggests that aryl groups at P2 are optimal, only arylboronic acids and esters were used.[7b] This reaction is not optimized, and the conditions used were typical for the Suzuki Cross-Coupling reaction.[21] Diminished yields are due to typical cross-coupling by-products such as homo-coupling of the bromide and the arylboronic acid, reductive debromination, and protolytic deborolation.[21] As shown in Table 2, substitution on the aryl boronate can be tolerated in the *othro*, *meta*, and *para* positions with a minimal impact on yield (entries 3–5). The *othro* substituted boronic acid gave the lowest yield of product as expected (entry 3).[21] Compounds **11** also readily undergo cross-coupling with boronic esters in good yield (entries 17 and18). The boronic ester **16** was prepared from the corresponding bromide **15** as shown in Scheme 5.[22] Importantly, many compounds were prepared in good to moderate yield that were previously not accessible via the Strecker route (entries 6,7,11,12).[23]



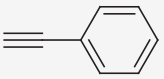
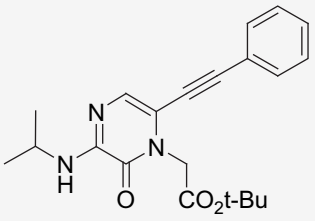
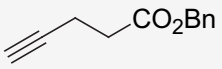
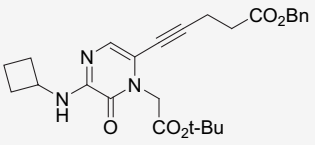
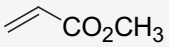
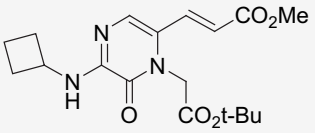
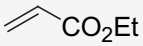
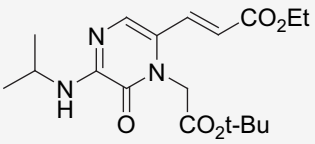
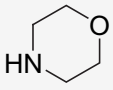
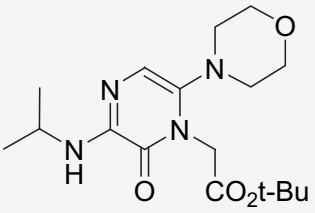
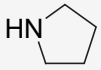
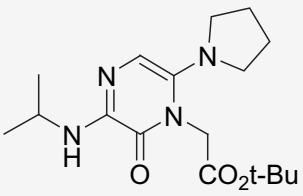
Scheme 5. Preparation of boronate **16**.

We also decided to examine the use of **11** in other metal-catalyzed processes in order to assess the versatility of this intermediate. These results are summarized in Table 3. These intermediates do serve as substrates in Sonogashira[24] (entries 1 and 2), Heck[25] (entries 3 and 4) and Buchwald–Hartwig cross-coupling

Table 3
Metal-catalyzed cross-coupling reactions of **11**[a]



11a: R = cyclobutyl
11b: R= *i*-pr

Entry	Bromide	R-X	Product	Yield (%)
1	**11b**		 **17a**	59
2	**11a**		 **17b**	47
3	**11a**		 **17c**	42
4	**11b**		 **17d**	39
5	**11b**		 **17e**	28
6	**11b**		 **17f**	32

[a] Reagents and conditions: 1.1 equiv Aryl boronate, 2.0 equiv Na_2CO_3 (aq), 5 mol% $Pd(PPh_3)_4$.

reactions[26] (entries 5 and 6). While the yields of these reactions are moderate at best, these reactions were not optimized. More importantly, these products would not be easily obtainable, if at all, via the Strecker route.

3. Conclusion

A new route to 2(1*H*)-pyrazinones, designed for the preparation of novel antithrombotics, has been developed. The route is very scalable and has been performed on a kilogram scale. To the best of our knowledge, this work represents the first metal-catalyzed cross-coupling reactions at the C6-position of 2(1*H*)-pyrazinones. These processes provide a mild and efficient method for the introduction of a P2 input on the core **11**. Most notably, compounds that were not assessable via the Strecker route are now obtainable in moderate to excellent yield. Utilization of the chemistry developed by Miyaura and others for the preparation of arylboronic esters and the extremely large number of commercially available aryl bromides and aryl chlorides results in a large pool of potential P2 diversity elements.[22] This can be used to fully develop the SAR around the S2 pocket of the TF/VIIa complex. Just as importantly, this methodology can also be used to explore the SAR of the S1 and S3 pockets of the enzyme by simple substitution of amines at P3 and P1. The application of this chemistry to the preparation of TF/VIIa antithrombotic inhibitors will be reported in due course.

4. Experimental section

4.1. General

Solvents and chemicals were reagent grade or better and were obtained from commercial sources. Air and moisture sensitive reactions were carried out in oven dried (at 120 °C) glassware. ^{1}H, ^{13}C, ^{19}F NMR spectra were recorded using a 300 or 400 MHz NMR spectrometer. Sample purities were determined by HPLC analysis equipped with a mass spectrometric detector using a C18 3.5 um, 30×2.1 mm column, eluting with a gradient system of 5:95 to 95:5 acetonitrile/water with a buffer consisting of 0.1% TFA over 4.5 min at 1 mL/min and detected by DAD. Analytical Thin Layer Chromatography (TLC) was performed on Merck silica gel plates (Merck Kieselgel 60, 0.25 mm thickness) with F254 indicator. Compounds were visualized under UV lamp or by developing in iodine. Medium pressure liquid chromatography (MPLC) separations were carried out using commercially available columns using technical grade solvents. Compound **8b** has been reported in the literature, but with limited spectroscopic data.[11a,c]

*4.1.1. N-Cyclobutylpyrazin-2-amine (**8a**).* A solution of 26.12 g (228.0 mmol) chloropyrazine **7** and 40.00 mL (468.5 mmol) cyclobutylamine was heated in a pressure reaction flask with stirring to 110 °C for 16 h. The brown reaction mixture was allowed to cool to room temperature and was diluted with water (750 mL). The aqueous solution was extracted with ethyl acetate (2×250 mL). The combined organic solutions were washed with water (1×250 mL), saturated sodium hydrogen carbonate (1×250 mL), and brine (2×250 mL). The organic solution was dried ($MgSO_4$), filtered, and solvents removed under reduced pressure. The crude product was purified by MPLC (20% ethyl acetate in hexanes to 40% ethyl acetate in hexanes) to afford **8a** in 95% yield as a light yellow solid: ^{1}H NMR (300 MHz, DMSO) δ 7.97–7.96 (m, 1H), 7.82–7.79 (m, 2H), 5.12 (br s, 1H), 4.30–4.18 (m, 1H), 2.51–2.39 (m, 2H), 1.97–1.73 (m, 4H); ^{13}C NMR (75 MHz, DMSO) δ 149.3, 137.6, 128.3, 126.9, 42.2, 26.7, 10.7; HRMS (ES) calcd for $C_8H_{12}N_3$ ($M+H^+$) 150.1031, found 150.0992.

*4.1.2. N-Isopropylpyrazin-2-amine (**8b**)[10a].* A 50-mL stainless steel stirred Parr autoclave equipped with a glass liner, was charged with 7.50 g (65.5 mmol) chloropyrazine **7** and 14.0 g (238 mmol) isopropylamine. The autoclave was sealed, purged with nitrogen (2×3 bar), and pressurized with nitrogen to about 7.7 bar (100 psig). The reactor was stirred and heated to 130 °C for 24 h. The maximum pressure reached during the reaction was about 13 bar (180 psig). After cooling to room temperature, the mixture was diluted with 150 mL of water and extracted with ethyl acetate (3×75 mL). The combined organic solutions were washed with saturated sodium hydrogen carbonate (1×100 mL) and brine (1×100 mL). The organic solution was then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was then filtered through a silica gel plug (ethyl acetate). Removal of solvents under reduced pressure afforded a yellow oil. Addition of about 30 mL of pentane to the oil and cooling to 0 °C afforded, after washing with cold pentane and drying, 79% of **8b** as light tan crystals. Mp 48–49 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J=1.3, 2.8 Hz, 1H), 7.85 (d, J=1.3 Hz, 1H), 7.75 (d, J=2.8 Hz, 1H), 4.96 (br d, J=5.1 Hz, 1H), 4.09–3.97 (m, 1H), 1.25 (d, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 141.8, 132.02, 131.86, 42.4, 22.6; HRMS (ES) calcd for $C_7H_{12}N_3$ ($M+H^+$) 138.1031, found 138.0990.

*4.1.3. 3,5-Dibromo-N-cyclobutylpyrazin-2-amine (**9a**).* To a solution of 30.36 g (203.5 mmol) **8a** in 407.0 mL dimethyl sulfoxide (0.5 M) and 10.0 mL (20 M) water was added 79.17 g (444.8 mmol) *N*-bromosuccinimide over a 30 min period with the temperature being kept below 15 °C with an ice water bath. After the addition was completed the ice bath was removed and the reaction mixture was allowed to warm to room temperature and stirred for 5 h. The reaction mixture was then poured into 1.0 L of ice water and the aqueous solution was extracted with ethyl acetate (5×250 mL). The combined organic solutions were washed with 5% sodium carbonate (2×250 mL), water (1×250 mL), and brine (1×250 mL). The organic solution was dried ($MgSO_4$), filtered, and concentrated to a yellow solid. Purification of the crude product by MPLC (20% ethyl acetate in hexanes) gave pure **9a** in 73% yield as a light yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 5.31 (br d, J=4.8 Hz, 1H), 4.39–4.30 (m, 1H), 2.44–2.37 (m, 2H), 1.95–1.85 (m, 2H), 1.83–1.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 143.0, 125.0, 121.6, 47.2, 31.4, 15.4; HRMS (ES) calcd for $C_8H_{10}Br_2N_3$ ($M+H^+$) 307.9221, found 307.9214.

*4.1.4. 3,5-Dibromo-N-isopropylpyrazin-2-amine (**9b**).* To a solution of 22.95 g (167.3 mmol) **8b** in 330.0 mL dimethyl sulfoxide (0.5 M) and 8.0 mL water (20 M) was added 75.24 g (422.7 mmol) *N*-bromosuccinimide over a 30 min period with the temperature being kept below 15 °C with an ice water bath. After the addition was completed the ice bath was removed and the reaction mixture was allowed to warm to room temperature and stirred for approximately 18 h. The reaction was protected from light as a precautionary measure. The reaction mixture was then poured into 1.0 L of ice water and the aqueous solution was extracted with ethyl acetate (4×250 mL). The combined organic solutions were washed with 1 N NaOH (1×250 mL), water, and brine (2×250 mL). The organic solution was dried ($MgSO_4$), filtered, and concentrated to a yellow solid. Purification of the crude product by MPLC (20% ethyl acetate in hexanes) gave pure **9b** in 85% yield as a light yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 6.50 (br s, 1H), 4.12–4.04 (m, 1H), 1.23 (d, J=6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 142.7, 125.0, 120.9, 43.6, 22.5; HRMS (ES) calcd for $C_9H_{10}Br_2N_3$ ($M+H^+$) 295.9221, found 295.9186.

*4.1.5. 6-Bromo-3-(cyclobutylamino)pyrazin-2-ol (**10a**).* To a suspension of 25.03 g (81.53 mmol) **9a** in 500.0 mL water (0.16 M) was added 22.90 g (408.1 mmol) potassium hydroxide in 480.0 mL water (0.85 M). The resulting suspension was heated to reflux for approximately 18 h. The reaction mixture was then added charcoal and

refluxed for an additional 15 min. The mixture was then allowed to cool for 5 min and was filtered through Celite 545®. The filtrate was cooled in an ice bath and was acidified with concentrated hydrochloric acid to a pH of approximately 5 (litmus paper) upon which a white precipitate forms. The precipitate was collected by filtration, washed twice with water and dried under vacuum to afford pure **10a** in 87% yield: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.43 (s, 1H), 7.18 (br d, J=5.1 Hz, 1H), 6.87 (s, 1H), 4.29–4.19 (m, 1H), 2.16–2.09 (m, 2H), 2.03–1.93 (m, 2H), 1.63–1.51 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.0, 144.2, 119.9, 41.3, 26.0, 10.8; HRMS (EI) calcd for $C_8H_{11}BrN_3O$ (M+H$^+$) 244.0085, found 244.0086.

*4.1.6. 6-Bromo-3-(isopropylamino)pyrazin-2-ol (**10b**).* To a suspension of 38.58 g (130.79 mmol) **9b** in 820.0 mL water (0.16 M) was added 36.74 g (654.79 mmol) potassium hydroxide in 750.0 mL water (0.87 M). The resulting suspension was heated to reflux for approximately 20 h. The clear, yellow, homogeneous reaction mixture was then added charcoal and refluxed for an additional 15 min. The mixture was then allowed to cool for 5 min and was filtered through Celite 545®. The filtrate was cooled in an ice bath and was acidified with concentrated hydrochloric acid to a pH of approximately 4 (litmus paper) upon which a white precipitate forms. The precipitate was collected by filtration, washed twice with water and dried under vacuum to afford pure **10b** in 87% yield: ^{1}H NMR (400 MHz, DMF-d_7) δ 12.49 (br s, 1H), 6.96 (s, 1H), 6.57 (br d, J=7.5 Hz, 1H), 4.14–4.02 (m, 1H), 1.21 (d, J=6.5 Hz, 6H); ^{13}C NMR (100 MHz, DMF-d_7) δ 152.1, 149.6, 124.6, 103.7, 42.6, 22.2; HRMS (EI) calcd for $C_7H_{11}BrN_3O$ (M+H$^+$) 232.0080, found 232.0078.

*4.1.7. tert-Butyl [6-bromo-3-(cyclobutylamino)-2-oxopyrazin-1(2H)-yl]acetate (**11a**).* To a suspension of 1.7246 g (40.96 mmol) calcium hydride in 80.0 mL tetrahydrofuran (0.50 M) was added 5.0477 g (20.68 mmol) **10a** in 50.0 mL tetrahydrofuran (0.41 M) drop wise via an addition funnel. The resulting suspension was heated to reflux for 30 min. To this mixture was then added a solution of 3.40 mL (23.03 mmol) *tert*-butyl bromoacetate in tetrahydrofuran (2.3 M). Refluxing of the mixture was continued for 18 h. The reaction mixture was allowed to cool to room temperature, and then cautiously poured in to a stirred ice water mixture (600.0 mL). The aqueous layer was extracted with ethyl acetate (4×250 mL). The combined organic solutions were washed with saturated sodium hydrogen carbonate (1×250 mL) and brine (2×250 mL). The organic solution was dried ($MgSO_4$), filtered, and solvents removed under reduced pressure. Purification of the crude product by MPLC (20% ethyl acetate in hexanes) afforded pure **11a** in 87% yield as an off white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.18 (br d, J=7.5 Hz, 1H), 4.79 (s, 2H), 4.39–4.29 (m, 1H), 2.41–2.34 (m, 2H), 1.96–1.86 (m, 2H), 1.79–1.68 (m, 2H) 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 152.5, 149.0, 124.6, 105.1, 83.3, 49.7, 46.3, 31.3, 28.2, 15.6; HRMS (ES) calcd for $C_{14}H_{21}N_3O_3$ (M+H$^+$) 358.0766, found 358.0746.

*4.1.8. tert-Butyl [6-bromo-3-(isopropylamino)-2-oxopyrazin-1(2H)-yl]acetate (**11b**).* To a suspension of 8.92 g (211.9 mmol) calcium hydride in 350 mL tetrahydrofuran (0.60 M) was added 20.21 g (87.08 mmol) **10b** in one portion as a solid. The resulting suspension was heated to reflux for 30 min. The mixture was then added a solution of 15.40 mL (104.3 mmol) *tert*-butyl bromoacetate in 85.0 mL tetrahydrofuran (1.2 M) drop wise over a 30 min period via an addition funnel. Refluxing of the mixture was continued for 18 h. The reaction mixture was allowed to cool to room temperature, and then cautiously poured in to a stirred ice water mixture. The aqueous layer was extracted with ethyl acetate (5×250 mL). The combined organic solutions were washed with 1 N HCl (2×500 mL) and brine (2×500 mL). The organic solution was dried ($MgSO_4$), filtered, and solvents removed under reduced pressure. Purification of the crude product by MPLC (20% ethyl acetate in hexanes) afforded pure **11b** in 90% yield as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 1H), 5.97 (br d, J=7.5 Hz, 1H), 4.84 (s, 2H), 4.12–4.03 (m, 1H), 1.49 (s, 9H), 1.24 (d, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 152.3, 148.9, 124.2, 104.3, 82.9, 49.3, 42.4, 27.8, 22.1; HRMS (ES) calcd for $C_{13}H_{20}BrN_3O_3$ (M+H$^+$) 346.0766, found 346.0753.

*4.1.9. tert-Butyl {[6-bromo-3-(cyclobutylamino)pyrazin-2-yl]oxy} acetate (**12a**).* To a solution of 2.0668 g (8.467 mmol) of **10a** in 30.0 mL dimethyl sulfoxide (0.2 M) was added 1.4017 g (10.14 mmol) potassium carbonate and heated to 45 °C. The resulting suspension was stirred for approximately 15 min. The mixture was then added 1.40 mL (9.481 mmol) *tert*-butyl bromoacetate in 13.0 mL in dimethyl sulfoxide (0.73 M) drop wise over a 10 min period. After stirring for approximately 3 h, the reaction was quenched by the addition of water (250 mL). The aqueous solution was extracted with ethyl acetate (4×50 mL). The combined organic solutions were washed with brine (2×50 mL), dried ($MgSO_4$), filtered, and solvents removed under reduced pressure. The crude reaction mixture was purified by MPLC (10% ethyl ether in hexanes to 25% ethyl ether in hexanes) afforded pure **12a** in 75% yield and pure **11a** in 16% yield. Data for **12a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 5.22 (br d, J=7.3 Hz, 1H), 4.74 (s, 2H), 4.44–4.35 (m, 1H), 2.43–2.36 (m, 2H), 1.91–1.83 (m, 2H), 1.78–1.69 (m, 2H) 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 145.6, 143.3, 135.7, 118.5, 82.8, 63.7, 46.4, 31.5, 28.2, 15.5; HRMS (ES) calcd for $C_{14}H_{21}N_3O_3$ (M+H$^+$) 358.0766, found 358.0754.

*4.1.10. tert-Butyl {[6-bromo-3-(isopropylamino)pyrazin-2-yl]oxy} acetate (**12b**).* Following the procedure for the preparation of **12a**, pure **12b** was obtained in 77% yield and pure **11b** in 12% yield after purification by MPLC (hexanes to 16% ethyl acetate in hexanes). Data for **12b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 4.94 (br d, J=7.4 Hz, 1H), 4.77 (s, 2H), 4.20–4.08 (m, 1H), 1.49 (s, 9H), 1.25 (d, J=6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 145.4, 143.3, 135.3, 117.8, 82.4, 63.4, 42.4, 28.0, 22.6; HRMS (ES) calcd for $C_{13}H_{21}BrN_3O_3$ (M+H$^+$) 346.0761, found 346.0756.

*4.1.11. 6-Bromo-3-cyclobutyl[1,3]oxazolo[4,5-b]pyrazin-2(3H)-one (**13a**).* A solution of 6.0129 g (24.63 mmol) of **10a** in 125.0 mL dry tetrahydrofuran (0.2 M) was added 6.0221 g (37.14 mmol) 1,1′-carbonyldiimidazole in one portion. The resulting solution was then heated to reflux over night. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (500 mL). The organic solution was washed with 1 N HCl (2×150 mL), saturated sodium hydrogen carbonate (1×150 mL), and brine (1×150 mL). The organic solution is then dried ($MgSO_4$), filtered, and solvents removed under reduced pressure. Purification by MPLC (20% ethyl acetate in hexanes) afforded pure **13** in 95% yield as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 4.90–4.81 (m, 1H), 3.05–2.94 (m, 2H), 2.41–2.33 (m, 2H), 2.04–1.96 (m, 2H), 1.92–1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 145.6, 139.5, 129.1, 47.9, 27.1, 15.2; HRMS (ES) calcd for $C_9H_8BrN_3O_2$ (M+NH$_4^+$) 269.9878, found 269.9825.

*4.1.12. 6-Bromo-3-isopropyl[1,3]oxazolo[4,5-b]pyrazin-2(3H)-one (**13b**).* Following the procedure for the preparation of **13a**, pure **13b** was obtained in 91% yield after MPLC purification (15% ethyl ether in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 4.72–4.62 (m, 1H), 1.61 (d, J=6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 145.7, 139.4, 139.2, 128.9, 47.4, 19.5; HRMS (ES) calcd for $C_8H_8BrN_3O_2$ (M+NH$_4^+$) 275.0144, found 275.0119.

4.2. General procedure for the Suzuki Cross-coupling reaction of 11 with boronates

To a two-neck flask equipped with stirring bar, septum, and argon line was charged with **11** and boronate (1.1 equiv), was

purged with argon for approximately 10 min. The flask was then added tetrahydrofuran to give a 0.15 M solution followed by aqueous sodium carbonate (2.0 equiv of 2.0 M solution) and 5 mol % of tetrakis(triphenylphosphine) palladium (0). The resulting mixture was allowed to reflux for approximately 18 h. The crude reaction mixture was allowed to cool to room temperature and was diluted with ethyl acetate. The organic solution was washed with saturated sodium hydrogen carbonate (1×), and brine (2×), dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. Hereafter this is designated as method A.

*4.2.1. tert-Butyl [3-(cyclobutylamino)-2-oxo-6-phenylpyrazin-1(2H)-yl]acetate (**14a**).* Method A, from **11a**. The crude product was purified by MPLC (20% ethyl acetate in hexanes) to give an 82% yield of pure **14a** as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.30 (m, 5H), 6.79 (s, 1H), 6.31 (d, J=7.7 Hz, 1H), 4.54–4.31 (m, 1H), 4.39 (s, 2H), 2.49–2.40 (m, 2H), 2.04–1.91 (m, 2H), 1.85–1.73 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 152.0, 149.5, 132.9, 130.0, 129.2, 128.90, 128.55, 122.7, 82.7, 48.0, 46.2, 31.5, 28.1, 15.6; HRMS (ES) calcd for $C_{20}H_{26}N_3O_3$ ($M+H^+$) 356.1974, found 356.1992.

*4.2.2. tert-Butyl [3-(isopropylamino)-2-oxo-6-phenylpyrazin-1(2H)-yl]acetate (**14b**).* Method A, from **11b**. The crude product was purified by MPLC (hexanes to 16% ethyl acetate in hexanes) to give an 80% yield of pure **14b** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.33 (m, 5H), 6.81 (s, 1H), 6.04 (br d, J=7.7 Hz, 1H), 4.40 (s, 2H), 4.21–4.12 (m, 1H), 1.42 (s, 9H), 1.28 (d, J=6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 151.8, 149.3, 132.06, 129.7, 128.79, 128.54, 127.8, 122.4, 82.3, 47.6, 42.3, 27.8, 22.4; HRMS (ES) calcd for $C_{19}H_{26}N_3O_3$ ($M+H^+$) 344.1969, found 344.1996.

*4.2.3. tert-Butyl [6-(2-chlorophenyl)-3-(isopropylamino)-2-oxo pyrazin-1(2H)-yl]acetate (**14c**).* Method A, from **11b**. The crude product was purified by MPLC (hexanes to 25% ethyl acetate in hexanes) to give a 59% yield of pure **14c** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.47 (m, 1H), 7.41–7.37 (m, 2H), 7.32–7.28 (m, 1H), 6.76 (s, 1H), 6.09 (br d, J=7.5 Hz, 1H), 4.38 (ABq, $\Delta\nu$=454.8 Hz, J_{AB}=16.9 Hz, 2H), 4.22–4.13 (m, 1H), 1.34–1.28 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 151.7, 149.7, 135.2, 133.3, 131.2, 130.7, 129.5, 126.8, 124.5, 122.9, 82.3, 46.7, 42.4, 27.8, 22.4; HRMS (ES) calcd for $C_{19}H_{25}ClN_3O_3$ ($M+H^+$) 378.1579, found 378.1585.

*4.2.4. tert-Butyl [6-(3-chlorophenyl)-3-(isopropylamino)-2-oxo pyrazin-1(2H)-yl]acetate (**14d**).* Method A, from **11b**. The crude product was purified by MPLC (hexanes to 16% ethyl acetate in hexanes) to give a 74% yield of pure **14d** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.33 (m, 3H), 7.25–7.22 (m, 3H), 6.79 (s, 1H), 6.08 (br d, J=7.7 Hz, 1H), 4.39 (s, 2H), 4.20–4.11 (m, 1H), 1.45 (s, 9H), 1.28 (d, J=6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 151.7, 149.5, 134.49, 134.35, 129.87, 129.71, 129.01, 127.8, 126.4, 122.8, 82.7, 47.7, 42.4, 27.8, 22.4; HRMS (ES) calcd for $C_{19}H_{25}ClN_3O_3$ ($M+H^+$) 378.1579, found 378.1591.

*4.2.5. tert-Butyl [6-(4-chlorophenyl)-3-(isopropylamino)-2-oxo pyrazin-1(2H)-yl]acetate (**14e**).* Method A, from **11b**. The crude product was purified by MPLC (hexanes to 16% ethyl acetate in hexanes) to give a 86% yield of pure **14e** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 1H), 6.97–6.89 (m, 3H), 6.82 (s, 1H), 6.03 (br d, J=7.8 Hz, 1H), 4.40 (s, 2H), 4.20–4.12 (m, 1H), 3.80 (s, 3H), 1.44 (s, 9H), 1.28 (d, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 159.5, 151.8, 149.3, 133.8, 127.7, 122.3, 121.9, 115.1, 114.6, 82.4, 55.2, 47.8, 42.3, 27.8, 22.4; HRMS (ES) calcd for $C_{20}H_{28}N_3O_4$ ($M+H^+$) 374.2074, found 374.2062.

*4.2.6. tert-Butyl [6-(3-cyanophenyl)-3-(isopropylamino)-2-oxo pyrazin-1(2H)-yl]acetate (**14f**).* Method A, from **11b**. The crude product was purified by MPLC (hexanes to 33% ethyl acetate in hexanes) to give a 73% yield of pure **14f** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.54 (m, 4H), 6.79 (s, 1H), 6.14 (br d, J=7.8 Hz, 1H), 4.37 (s, 2H), 4.21–4.11 (m, 1H), 1.45 (s, 9H), 1.29 (d, J=6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 151.6, 149.7, 134.01, 133.89, 132.95, 132.21, 129.6, 125.4, 123.2, 117.8, 113.0, 82.9, 47.6, 42.4, 27.8, 22.3; HRMS (ES) calcd for $C_{20}H_{25}N_4O_3$ ($M+H^+$) 369.1921, found 369.1909.

*4.2.7. tert-Butyl [6-(4-cyanophenyl)-3-(isopropylamino)-2-oxo pyrazin-1(2H)-yl]acetate (**14g**).* Method A, from **11b**. The crude product was purified by MPLC (hexanes to 33% ethyl acetate in hexanes) to give a 57% yield of pure **14g** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J=8.2 Hz, 2H), 7.50 (d, J=8.2 Hz, 2H), 6.81 (s, 1H), 6.15 (br d, J=7.7 Hz, 1H), 4.38 (s, 2H), 4.21–4.12 (m, 1H), 1.44 (s, 9H), 1.28 (d, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 151.7, 149.7, 137.2, 132.3, 130.0, 126.1, 123.4, 118.1, 112.5, 82.8, 47.8, 42.4, 27.8, 22.3; HRMS (ES) calcd for $C_{20}H_{25}N_4O_3$ ($M+H^+$) 369.1921, found 369.1945.

*4.2.8. tert-Butyl [3-(isopropylamino)-6-(3-methoxyphenyl)-2-oxo-pyrazin-1(2H)-yl]acetate (**14h**).* Method A, from **11b**. The crude product was purified by MPLC (hexanes to 16% ethyl acetate in hexanes) to give a 70% yield of pure **14h** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 1H), 6.97–6.89 (m, 3H), 6.82 (s, 1H), 6.03 (br d, J=7.8 Hz, 1H), 4.40 (s, 2H), 4.20–4.12 (m, 1H), 3.80 (s, 3H), 1.44 (s, 9H), 1.28 (d, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 159.5, 151.8, 149.3, 133.8, 127.7, 122.3, 121.9, 115.1, 114.6, 82.4, 55.2, 47.8, 42.3, 27.8, 22.4; HRMS (ES) calcd for $C_{20}H_{28}N_3O_4$ ($M+H^+$) 374.2074, found 374.2062.

*4.2.9. tert-Butyl [3-(isopropylamino)-6-(4-methoxyphenyl)-2-oxo-pyrazin-1(2H)-yl]acetate (**14i**).* Method A, from **11b**. The crude product was purified by MPLC (hexanes to 16% ethyl acetate in hexanes) to give a 85% yield of pure **14i** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J=8.7 Hz, 2H), 6.92 (d, J=8.8 Hz, 2H), 6.78 (s, 1H), 6.00 (br d, J=7.6 Hz, 1H), 4.39 (s, 2H), 4.19–4.11 (m, 1H), 3.84 (s, 3H), 1.43 (s, 9H), 1.28 (d, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 160.0, 151.9, 149.2, 131.1, 127.5, 124.9, 122.4, 113.9, 82.3, 55.2, 47.6, 42.3, 27.8, 22.4; HRMS (ES) calcd for $C_{20}H_{28}N_3O_4$ ($M+H^+$) 374.2074, found 374.2048.

*4.2.10. tert-Butyl [3-(isopropylamino)-6-(4-methylphenyl)-2-oxo-pyrazin-1(2H)-yl]acetate (**14j**).* Method A, from **11b**. The crude product was purified by MPLC (hexanes to 16% ethyl acetate in hexanes) to give a 75% yield of pure **14j** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (m, 4H), 6.79 (s, 1H), 6.02 (br d, J=7.5 Hz, 1H), 4.39 (s, 2H), 4.20–4.11 (m, 1H), 1.43 (s, 9H), 1.28 (d, J=6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 151.9, 149.2, 138.8, 129.71, 129.58, 129.22, 127.8, 122.3, 82.3, 47.7, 42.3, 27.8, 22.4, 21.2; HRMS (ES) calcd for $C_{20}H_{28}N_3O_3$ ($M+H^+$) 358.2125, found 358.2139.

*4.2.11. tert-Butyl [3-(cyclobutylamino)-6-(2-nitrophenyl)-2-oxo pyrazin-1(2H)-yl]acetate (**14k**).* Method A, from **11a**. The crude product was purified by MPLC (20% ethyl acetate in hexanes to 40% ethyl acetate in hexanes) to give a 71% yield of pure **14k** as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.99 (m, 1H), 7.60–7.58 (m, 2H), 7.48–7.46 (m, 1H), 6.54 (s, 1H), 6.34 (d, J=7.8 Hz, 1H), 4.45–4.35 (m, 1H), 4.30 (ABq, $\Delta\nu$=503.0 Hz, J_{AB}=17.2 Hz, 2H), 2.42–2.34 (m, 2H), 1.99–1.89 (m, 2H), 1.78–1.66 (m, 2H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 151.7, 150.0, 134.5, 133.2, 131.0, 126.9, 124.6, 123.3, 121.9, 82.9, 48.0, 46.2, 31.4, 28.1, 15.5; HRMS (ES) calcd for $C_{20}H_{25}N_4O_5$ ($M+H^+$) 401.1825, found 401.1834.

*4.2.12. tert-Butyl [3-(cyclobutylamino)-6-(4-nitrophenyl)-2-oxo pyrazin-1(2H)-yl]acetate (**14l**).* Method A, from **11a**. Purification

by crystallization (ethyl acetate and hexanes) afforded a 53% yield of pure **14l** as a yellow solid. ^{1}H NMR (400 MHz, DMF-d_7) δ 8.50 (dd, J=1.9, 7.0 Hz, 2H), 7.87 (dd, J=1.9, 7.0 Hz, 2H), 7.64 (d, J=8.1 Hz, 1H), 4.74–4.64 (m, 3H), 2.49–2.29 (m, 4H), 1.91–1.83 (m, 2H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, DMF-d_7) δ 167.4, 151.7, 150.2, 148.1, 139.9, 131.1, 127.2, 124.3, 123.6, 82.5, 48.2, 46.3, 30.8, 27.6, 15.3; HRMS (ES) calcd for $C_{20}H_{25}N_4O_5$ (M+H$^+$) 401.1825, found 401.1846.

*4.2.13. tert-Butyl [6-(4-acetylphenyl)-3-(isopropylamino)-2-oxo pyrazin-1(2H)-yl]acetate (**14m**).* Method A, from **11b**. The crude product was purified by MPLC (hexanes to 25% ethyl acetate in hexanes) to give a 55% yield of pure **14m** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J=8.2 Hz, 2H), 7.47 (d, J=8.3 Hz, 2H), 6.83 (s, 1H), 6.11 (br d, J=7.8 Hz, 1H), 4.40 (s, 2H), 4.21–4.11 (m, 1H), 2.64 (s, 3H), 1.44 (s, 9H), 1.29 (d, J=6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 166.4, 151.8, 149.6, 137.21, 136.96, 129.6, 128.5, 126.8, 123.0, 82.6, 47.9, 42.4, 27.8, 26.6, 22.3; HRMS (ES) calcd for $C_{21}H_{28}N_3O_4$ (M+H$^+$) 386.2074, found 386.2056.

*4.2.14. Methyl 3-[1-(2-tert-butoxy-2-oxoethyl)-5-(isopropylamino)-6-oxo-1,6-dihydropyrazin-2-yl]-5-nitrobenzoate (**14n**).* Method A, from **11b**. The crude product was purified by MPLC (hexanes to 30% diethyl ether in hexanes) to give a 59% yield of pure **14n** as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89–8.88 (m, 1H), 8.45–8.44 (m, 1H), 8.38–8.37 (m, 1H), 6.85 (s, 1H), 6.18 (d, J=7.9 Hz, 1H), 4.38 (s, 2H), 4.23–4.14 (m, 1H), 4.00 (s, 3H), 1.45 (s, 9H), 1.30 (d, J=6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 164.2, 151.6, 149.9, 148.4, 135.9, 134.9, 132.4, 128.0, 124.62, 124.46, 123.91, 83.3, 52.9, 47.9, 42.6, 27.8, 22.3; HRMS (ES) calcd for $C_{21}H_{27}N_4O_7$ (M+H$^+$) 447.1880, found 447.1885.

*4.2.15. Methyl 3-[1-(2-tert-butoxy-2-oxoethyl)-5-(cyclobutylamino)-6-oxo-1,6-dihydropyrazin-2-yl]-5-nitrobenzoate (**14o**).* Method A, from **11a**. The crude product was purified by MPLC (hexanes to 20% diethyl ether in hexanes) to give a 62% yield of pure **14o** as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83–8.82 (m, 1H), 8.37–8.36 (m, 1H), 8.31–8.30 (m, 1H), 6.77 (s, 1H), 6.39 (d, J=7.5 Hz, 1H), 4.48–4.38 (m, 1H), 4.31 (s, 2H), 3.93 (s, 3H), 2.44–2.36 (m, 2H), 2.00–1.90 (m, 2H), 1.80–1.71 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 164.5, 151.7, 150.0, 148.7, 136.1, 135.1, 132.7, 128.3, 125.3, 124.8, 124.1, 83.6, 53.2, 48.1, 46.3, 31.3, 28.1, 15.6; HRMS (ES) calcd for $C_{22}H_{27}N_4O_7$ (M+H$^+$) 459.1880, found 459.1907.

*4.2.16. Methyl 3-amino-5-[1-(2-tert-butoxy-2-oxoethyl)-5-(cyclobutylamino)-6-oxo-1,6-dihydropyrazin-2-yl]benzoate (**14p**).* Method A, from **11a**. The crude product was purified by MPLC (15% ethyl acetate in hexanes to 30% ethyl acetate in hexanes) to give a 52% yield of pure **14p**. ^{1}H NMR (400 MHz, DMF-d_7) δ 7.38–7.37 (m, 1H), 7.19 (d, J=8.0 Hz, 1H), 7.13–7.12 (m, 1H), 6.88–6.87 (m, 1H), 6.71 (s, 1H), 5.69 (s, 2H), 4.54–4.44 (m, 1H), 4.41 (s, 2H), 3.81 (s, 3H), 2.32–2.25 (m, 2H), 2.19–2.09 (m, 2H), 1.73–1.65 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, DMF-d_7) δ 167.1, 166.8, 151.5, 150.1, 149.6, 134.0, 131.4, 128.8, 121.7, 119.5, 117.9, 115.0, 82.2, 51.9, 47.8, 46.1, 30.7, 27.5, 15.1; HRMS (ES) calcd for $C_{22}H_{29}N_4O_5$ (M+H$^+$) 429.2138, found 429.2138.

*4.2.17. tert-Butyl [6-[3-amino-5-(trifluoromethyl)phenyl]-3-(isopropylamino)-2-oxopyrazin-1(2H)-yl]acetate (**14q**).* Method A, from **11b**. The crude product was purified by MPLC (hexanes to 30% ethyl acetate in hexanes) to give a 93% yield of pure **14q** as a white solid. ^{1}H NMR (300 MHz, DMF-d_7) δ 7.26 (s, 1H), 7.11 (s, 1H), 7.02 (s, 1H), 6.97–6.96 (m, 1H), 6.11 (s, 2H), 4.65 (s, 2H), 4.65 (s, 2H), 4.43–4.31 (m, 1H), 1.59 (s, 9H), 1.45 (d, J=6.5 Hz, 6H); ^{13}C NMR (75 MHz, DMF-d_7) δ 167.5, 151.8, 150.9, 150.1, 135.0, 131.81, 131.39, 131.00, 130.56, 128.1, 126.8, 123.2, 122.2, 118.8, 113.1, 110.5, 82.4, 42.6, 27.7, 22.1; ^{19}F NMR (282 MHz, DMF-d_7) δ −63.1; HRMS (ES) calcd for $C_{20}H_{26}F_3N_4O_3$ (M+H$^+$) 427.1957, found 427.1966.

*4.2.18. tert-Butyl [6-[3-amino-5-(trifluoromethyl)phenyl]-3-(cyclobutylamino)-2-oxopyrazin-1(2H)-yl]acetate (**14r**).* Method A, from **11a**. The crude product was purified by MPLC (10% ethyl acetate in hexanes to 40% ethyl acetate in hexanes) to give an 88% yield of pure **14r** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89–6.88 (m, 2H), 6.73 (s, 1H), 6.72 (s, 1H), 6.30 (d, J=7.8 Hz, 1H), 4.46–4.36 (m, 1H), 4.33 (s, 2H), 4.05 (br s, 1H), 2.43–2.35 (m, 2H), 1.97–1.87 (m, 2H), 1.79–1.67 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 151.6, 149.3, 147.3, 134.2, 132.57, 132.25, 131.93, 131.61, 127.3, 125.0, 122.41, 122.28, 118.6, 115.72, 115.69, 115.65, 111.58, 111.54, 111.50, 82.8, 47.8, 46.0, 31.1, 27.8, 15.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.4; HRMS (ES) calcd for $C_{21}H_{26}F_3N_4O_3$ (M+H$^+$) 439.1957, found 439.1980.

*4.2.19. tert-Butyl [6-(5-formylthien-2-yl)-3-(isopropylamino)-2-oxopyrazin-1(2H)-yl]acetate (**14s**).* Method A, from **11b**. The crude product was purified by MPLC (20% ethyl acetate in hexanes to 60% ethyl acetate in hexanes) to give an 18% yield of pure **14s** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.72 (d, J=3.8 Hz, 1H), 7.14 (d, J=4.0 Hz, 1H), 6.22 (br d, J=7.9 Hz, 1H), 4.56 (s, 2H), 4.23–4.11 (m, 1H), 1.47 (s, 9H), 1.28 (d, J=6.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.6, 166.4, 151.5, 150.2, 144.5, 143.0, 135.9, 129.6, 125.4, 119.6, 83.1, 47.6, 42.6, 27.9, 22.3; HRMS (ES) calcd for $C_{18}H_{24}N_3O_4$ (M+H$^+$) 378.1488, found 378.1484.

*4.2.20. 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)aniline (**16**).* To a two-neck, oven dried flask equipped with stirring bar, septum and argon line was charged with 15.00 g (62.5 mmol) of 3-bromo-5-(trifluoromethyl)aniline, 19.53 g (76.92 mmol) bis(pinacolato)diboron, and 18.40 g (187.5 mmol) potassium acetate was purged with argon for approximately 10 min. The flask was then added 375.0 mL dimethyl sulfoxide (0.16 M) and 1.54 g (3 mol %) dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct. The resulting mixture was heated to 80 °C and stirred for approximately 18 h. The crude reaction mixture was allowed to cool to room temperature and was diluted with brine (1 L). The aqueous solution was extracted with ethyl acetate (3×500 mL). The combined organic solutions were washed with water (1×250 mL), brine (2×250 mL) dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. Purification by Kugelrohr distillation to gave 69% yield of pure **16**. Bp 144–146 °C/0.7 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.25 (m, 1H), 6.97 (s, 1H), 3.99 (s, 2H), 1.32 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) 145.8, 131.0, 124.3, 122.8, 121.34, 121.31, 114.02, 113.98, 84.2, 24.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.2.

4.3. General procedure for the Sonogashira coupling of 11 with acetylenes

To a two-neck flask equipped with stirring bar, septum and argon line was charged with **11** and was purged with argon for approximately 10 min. The flask was then charged with 1,4-dioxane to give a 0.2 M solution followed by the acetylene (1.1 equiv) and triethylamine (5.0 equiv) The resulting mixture was then added *trans*-dichlorobis(triphenylphosphine) palladium (II) (5 mol %), copper (I) iodide (1 mol %) and the resulting mixture was heated to 80 °C and stirred for approximately 18 h. The crude reaction mixture was allowed to cool to room temperature and filtered through a pad of Celite 545®. The filtrate was diluted with ethyl acetate. The organic solution was washed with saturated sodium hydrogen carbonate (1×), and brine (2×), dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. Hereafter this is designated as method B.

*4.3.1. tert-Butyl [3-(isopropylamino)-2-oxo-6-(phenylethynyl)pyrazin-1(2H)-yl]acetate (**17a**).* Method B, from **11b**. The crude product was purified by MPLC (hexanes to 25% ethyl acetate in hexanes) to give a 84% yield of pure **17a** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2H), 7.35–7.34 (m, 3H), 7.26 (s, 1H), 6.30 (br d, J=7.7 Hz, 1H), 4.86 (s, 2H), 4.21–4.11 (m, 1H), 1.44 (s, 9H), 1.27 (d, J=6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 151.1, 149.9, 131.1, 128.87, 128.69, 128.36, 122.0, 111.4, 95.7, 82.7, 80.7, 47.2, 42.6, 27.9, 22.2; HRMS (ES) calcd for $C_{21}H_{26}N_3O_3$ ($M+H^+$) 368.1969, found 368.1983.

*4.3.2. Benzyl 5-[1-(2-tert-butoxy-2-oxoethyl)-5-(cyclobutylamino)-6-oxo-1,6-dihydropyrazin-2-yl]pent-4-ynoate (**17b**).* Method B, from **11a**. The crude product was purified by MPLC (hexanes to 25% ethyl acetate in hexanes) to give a 47% yield of pure **17b** as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 5H), 7.02 (s, 1H), 6.43 (br d, J=7.8 Hz, 1H), 5.12 (s, 2H), 4.65 (s, 2H), 4.45–4.35 (m, 1H), 2.73–2.69 (m, 2H), 2.62–2.59 (m, 2H), 2.42–2.34 (m, 2H), 1.97–1.87 (m, 2H), 1.79–1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 166.0, 151.0, 149.5, 135.5, 128.51, 128.28, 128.21, 128.13, 111.8, 94.7, 82.6, 72.9, 66.6, 47.2, 45.9, 33.0, 31.0, 27.9, 15.46, 15.26; HRMS (ES) calcd for $C_{26}H_{31}N_3O_5$ ($M+H^+$) 466.2342, found 466.2326.

4.4. General procedure for Heck Reaction of 11 with acrylates

To a two-neck flask equipped with stirring bar, septum and argon line was charged with **11** and tri-*o*-tolylphosphine (5 mol %), was purged with argon for approximately 10 min. The flask was then charged with acetonitrile to give a 1.0 M solution followed by acrylate (1.5 equiv) and triethylamine (2.0 equiv) The resulting suspension was then added palladium (II) acetate (1.5 mol %) and then heated to 80 °C and stirred for approximately 18 h. The crude reaction mixture was allowed to cool to room temperature and filtered through a pad of Celite 545®. The filtrate was diluted with ethyl acetate. The organic solution was washed with saturated sodium hydrogen carbonate (1×), and brine (2×), dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. Hereafter this is designated as method C.

*4.4.1. Methyl (2E)-3-[1-(2-tert-butoxy-2-oxoethyl)-5-(cyclobutylamino)-6-oxo-1,6-dihydropyrazin-2-yl]acrylate (**17c**).* Method C, from **11a**. The crude product was purified by MPLC (hexanes to 20% ethyl acetate in hexanes) to give a 42% yield of pure **17c** as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.24 (m, 2H), 6.59 (d, J=7.8 Hz, 1H) 6.18 (d, J=15.3 Hz, 1H), 4.71 (s, 2H), 4.50–4.40 (m, 1H), 3.75 (s, 1H), 2.44–2.37 (m, 2H), 2.02–1.91 (m, 2H), 1.82–1.71 (m, 2H) 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 165.9, 151.1, 150.1, 134.2, 124.9, 123.2, 117.6, 83.3, 51.8, 46.0, 45.9, 31.0, 27.9, 15.3; HRMS (ES) calcd for $C_{18}H_{26}N_3O_5$ ($M+H^+$) 364.1872, found 364.1883.

*4.4.2. Ethyl (2E)-3-[1-(2-tert-butoxy-2-oxoethyl)-5-(isopropylamino)-6-oxo-1,6-dihydropyrazin-2-yl]acrylate (**17d**).* Method C, from **11b**. The crude product was purified by MPLC (hexanes to 25% ethyl acetate in hexanes) to give a 39% yield of pure **17a** as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.25 (m, 2H), 6.35 (br d, J=7.9 Hz, 1H), 6.20 (br d, J=15.6 Hz, 1H), 4.75 (s, 2H), 4.26–4.14 (m, 1H), 1.50 (s, 9H), 1.31–1.26 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.9, 151.2, 150.2, 133.9, 125.0, 122.8, 117.7, 83.2, 60.5, 45.8, 42.6, 27.8, 22.2, 14.1; HRMS (ES) calcd for $C_{18}H_{28}N_3O_5$ ($M+H^+$) 366.2023, found 366.2030.

4.5. General procedure for Buchwald–Hartwig coupling of 11b with amines

To a two-neck flask equipped with stirring bar, septum and argon line was charged with **11**, 2-(di-*tert*-butylphosphino)biphenyl (20 mol %), and tris(dibenzylideneacetone)dipalladium (0) (10 mol %), was purged with argon for approximately 10 min. The flask was then charged with dimethoxyethane to give a 0.5 M solution followed by sodium *tert*-butoxide (1.4 equiv), and amine (1.2 equiv). The resulting solution was then heated to 80 °C and stirred for approximately 18 h. The crude reaction mixture was allowed to cool to room temperature and filtered through a pad of Celite 545®. The filtrate was diluted with ethyl acetate. The organic solution was washed with saturated sodium hydrogen carbonate (1×), and brine (2×), dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Hereafter this is designated as method D.

*4.5.1. tert-Butyl [3-(isopropylamino)-6-morpholin-4-yl-2-oxopyrazin-1(2H)-yl]acetate (**17e**).* Method D, from **11b**. The crude product was purified by MPLC (28% ethyl acetate in hexanes to 80% ethyl acetate in hexanes) to give a 28% yield of pure **17e** as a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (s, 1H), 5.87 (d, J=7.8 Hz, 1H), 4.73 (s, 2H), 4.13–4.05 (m, 1H), 3.89–3.86 (m, 2H), 3.63–3.58 (m, 2H), 2.94–2.83 (m, 4H), 1.49 (s, 9H), 1.24 (d, J=6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 152.0, 148.4, 135.3, 115.4, 82.2, 67.0, 53.2, 43.7, 42.2, 27.9, 22.4; HRMS (ES) calcd for $C_{17}H_{29}N_4O_4$ ($M+H^+$) 353.2183, found 353.2215.

*4.5.2. tert-Butyl [3-(isopropylamino)-2-oxo-6-pyrrolidin-1-ylpyrazin-1(2H)-yl]acetate (**17f**).* Method D, from **11b**. The crude product was purified by MPLC (16% diethyl ether in hexanes to 60% diethyl ether in hexanes) to give a 32% yield of pure **17f** as a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (s, 1H), 5.77 (d, J=7.7 Hz, 1H), 4.69 (s, 2H), 4.13–4.02 (m, 1H), 2.99–2.96 (m, 4H), 1.90–1.87 (m, 4H), 1.48 (s, 9H), 1.23 (d, J=6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 152.1, 147.6, 134.8, 114.0, 81.9, 53.6, 44.3, 42.1, 27.9, 24.6, 22.5; HRMS (ES) calcd for $C_{17}H_{29}N_4O_3$ ($M+H^+$) 337.2234, found 337.2248.

Acknowledgements

We wish to thank James P. Doom, David Masters-Moore, and Ralph C. Scheibel for HRMS analysis, Dr. Thaddeus Franczyk for experiments performed in an autoclave, and Dr. Claude R. Jones for thoughtful discussions and help performing 2-D NMR experiments.

Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2010.02.026.

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