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Regiospecific synthesis of 1,5-disubstituted-1*H*-pyrazoles containing differentiated 3,4-dicarboxylic acid esters via Suzuki coupling of the corresponding 5-trifluoromethane sulfonates

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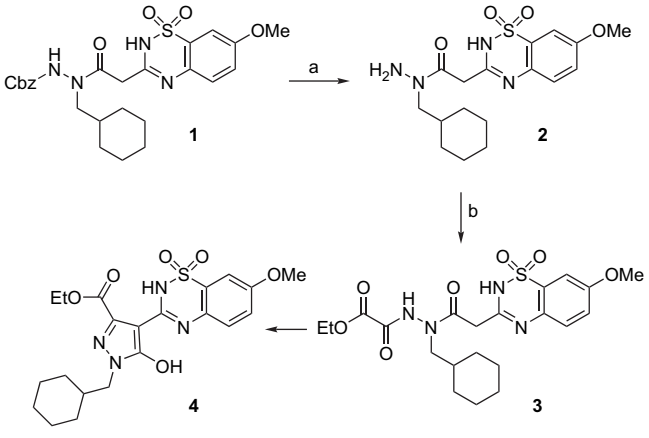
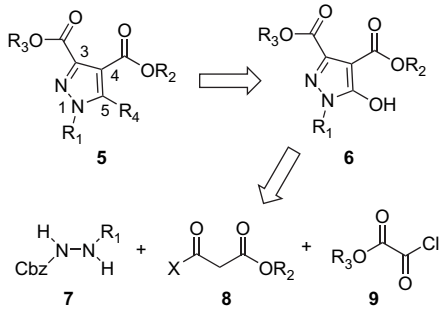
Abstract—A general procedure is described for the regiospecific preparation of 1-substituted-5-hydroxy-1*H*-pyrazoles containing differentiated ester moieties at the 3- and 4-positions. This process involves the coupling of monosubstituted benzyl carbazates with various malonyl chlorides or acids, deprotection of the coupling products via catalytic hydrogenation, and subsequent derivatization of the resulting hydrazides with monoalkyl oxalyl chlorides. The 5-hydroxy-1*H*-pyrazoles are readily transformed to the corresponding trifluoromethane sulfonates, which undergo palladium-mediated Suzuki coupling with a variety of boronic acids (aryl, heteroaryl, and alkenyl) in moderate to excellent yields (24–92%). The ester groups present in one of the resulting 1,5-disubstituted-1*H*-pyrazoles are further modified by selective hydrolysis or conversion to the corresponding dicarboxylic acid derivative followed by selective mono-esterification.

1. Introduction

During the course of our recent efforts to develop novel antiviral agents, we attempted to transform compound **1** to the corresponding diacyl derivative **3** via removal of the Cbz protecting group and treatment of the resulting hydrazide (**2**) with monoethyl oxalyl chloride (Scheme 1). Instead, this sequence afforded a 47% isolated yield of the 5-hydroxy-1*H*-pyrazole[1] **4**, which apparently arose from intramolecular cyclization of **3** and subsequent dehydration. This result suggested a novel approach to the regiospecific construction of 1-substituted-3,4-diester-containing-5-hydroxy-1*H*-pyrazoles (**6**, Scheme 2) via the coupling of monosubstituted benzyl carbazates (**7**) with malonyl chlorides or acids (**8**) followed by Cbz removal and derivatization of the resulting hydrazides with monoalkyl oxalyl chlorides (**9**).[2] Subsequent Suzuki coupling of the corresponding 5-trifluoromethanesulfonyloxy-1*H*-pyrazoles[3] would provide a general method for the regiospecific synthesis of highly functionalized 1,5-disubstituted-1*H*-pyrazoles bearing carboxylic acids or esters at the 3- and 4-positions (**5**, Scheme 2) that would complement the existing preparations of such



Scheme 1. Reagents and conditions: (a) H_2, Pd on C, EtOAc, 23 °C; (b) $ClC(O)CO_2Et$, *i*-Pr_2NEt, CH_2Cl_2, 0→23 °C, 47% from **1**.



Scheme 2. X=OH, Cl.

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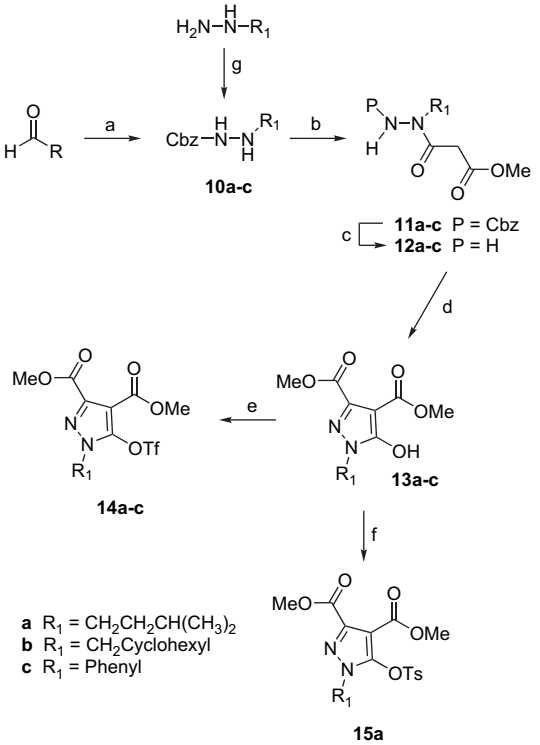
heterocycles.[4] Herein, we report our development of this new approach to pyrazole synthesis including (1) the efficient preparation of 1-substituted-5-hydroxy-1*H*-pyrazoles from monosubstituted carbazates, (2) the optimization of reaction conditions to effect Suzuki couplings with the corresponding 1-substituted-5-trifluoromethanesulfonyloxy-1*H*-pyrazoles, and (3) the selective derivatization of the carboxylic acid ester moieties present in one of the 1*H*-pyrazole Suzuki coupling products.

2. Results and discussion

The optimized syntheses of several dimethyl-1-substituted-3,4-dicarboxylate-1*H*-pyrazoles using our new methodology are depicted in Scheme 3 along with their conversion to several substrates suitable for use in Suzuki coupling reactions. In one example, reductive coupling of benzyl carbazate and isovaleraldehyde afforded monosubstituted carbazate **10a** [R_1=$CH_2CH_2CH(CH_3)_2$] in good yield. Acylation of **10a** with methyl malonyl chloride at elevated temperature then provided intermediate **11a** in excellent yield after basic work-up and silica gel chromatography. The Cbz moiety present in **11a** was removed by hydrogenation and the crude hydrazide thus obtained (**12a**) was treated with excess monomethyl oxalyl chloride in the presence of *N*,*N*-diisopropylethylamine to give pyrazole **13a**. Due to its polar nature, it was difficult to completely separate this material from minor impurities using flash chromatography. However, treatment of slightly impure **13a** with excess trifluoromethanesulfonic anhydride in pyridine provided triflate **14a**

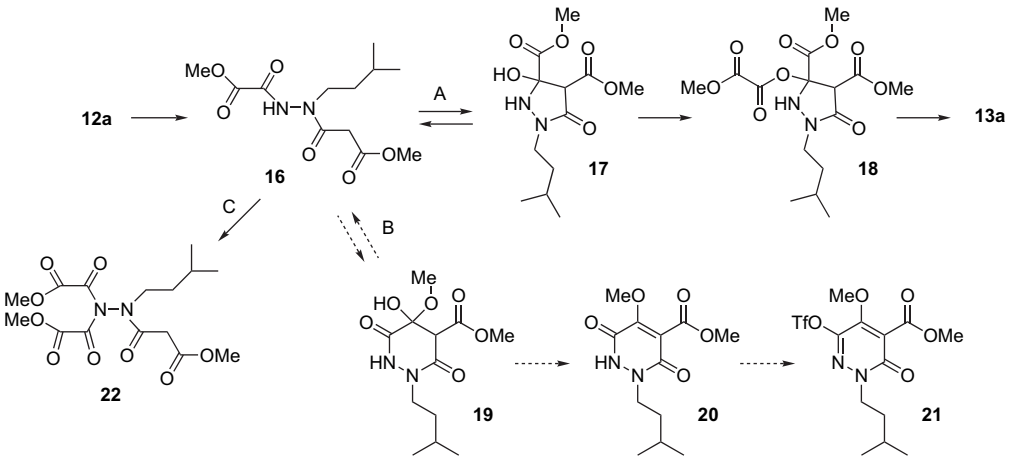


Scheme 3. Reagents and conditions: (a) $CbzNHNH_2$, $NaBH_3CN$, HOAc, CH_3OH, 0→23 °C, 44–77%; (b) $ClC(O)CH_2CO_2Me$, 1,4-dioxane, 100 °C, 89–98%; (c) H_2, Pd on C, EtOAc, 23 °C; (d) $ClC(O)CO_2Me$, *i*-Pr_2NEt, CH_2Cl_2, 0→23 °C, 95% (**13a** from **11a**); (e) Tf_2O, pyridine, 0 °C, 86% (**14a**), 68% (**14b** from **11b**), 77% (**14c** from **11c**); (f) TsCl, Et_3N, DMAP, CH_2Cl_2, 23 °C, 81% from **11a**; (g) Ref. 17.

in good yield and purity after chromatography on silica gel.[5] Similar derivatization of crude **13a** with *p*-toluenesulfonyl chloride and triethylamine in the presence of catalytic 4-dimethylaminopyridine provided tosylate **15a** in excellent overall yield. Attempts to convert **13a** to 5-chloro or 5-bromopyrazoles via treatment with the corresponding phosphoryl halide or phosphorous trihalide (POX_3 or PX_3, respectively) were unsuccessful and afforded numerous unidentified decomposition products. Both triflate **14a** and tosylate **15a** exhibited minimal decomposition by ^1H NMR after long-term (e.g., three months) storage as neat materials at −20 °C. However, **14a** slowly decomposed to pyrazole **13a** when left for extended periods of time on untreated (dry) silica gel (approximately 10% conversion per day). As detailed below, pyrazole triflates such as **14a** that are repeatedly exposed to atmospheric moisture during long-term use and storage should be dried prior to utilizing them in Suzuki coupling reactions.

As part of the above activities, considerable effort was spent optimizing the transformation of hydrazide **12a** to pyrazole **13a**. A mechanism summarizing our current understanding of this process is depicted in Scheme 4. Thus, hydrazide **12a** reacts with one equivalent of monomethyl oxalyl chloride to afford acylated derivative **16**. This intermediate then undergoes rapid (and likely reversible) intramolecular closure to give **17** (path A), which subsequently reacts with a second equivalent of monomethyl oxalyl chloride to provide intermediate **18**. Elimination of monomethyl oxalic acid ester from **18** then affords the observed pyrazole **13a**. This sequence is consistent with the observation that attempted conversion of **12a** to **13a** using fewer than 2 equiv of monomethyl oxalyl chloride consistently resulted in incomplete consumption of the starting hydrazide.[6] Intermediate **16** may conceivably undergo an alternate intramolecular closure to afford hemiketal **19** (path B) followed by dehydration to provide pyridazinone **20** (a structural isomer of **13a**). However, the formation of significant amounts of cyclization products via this alternate pathway was discounted by the independent synthesis of a Suzuki coupling product expected to arise from the corresponding pyridazinone triflate **21** (see Scheme 5).[7] In addition to undergoing the intramolecular closure described above, intermediate **16** may instead react directly with a second equivalent of monomethyl oxalyl chloride (Scheme 4, path C). The resulting bis-acylated adduct (**22**) could, in fact, be detected in minor amounts by LCMS and TLC analysis of the reaction mixture. However, addition of pyridine or 4-dimethylaminopyridine to the reaction medium greatly increased the amount of **22** formed relative to **13a**. These results suggest that such additives accelerate the acylation of **16** more than the corresponding transformation of **17**, and indicate that their use should be avoided in the preparation of pyrazoles such as **13a**.[8]

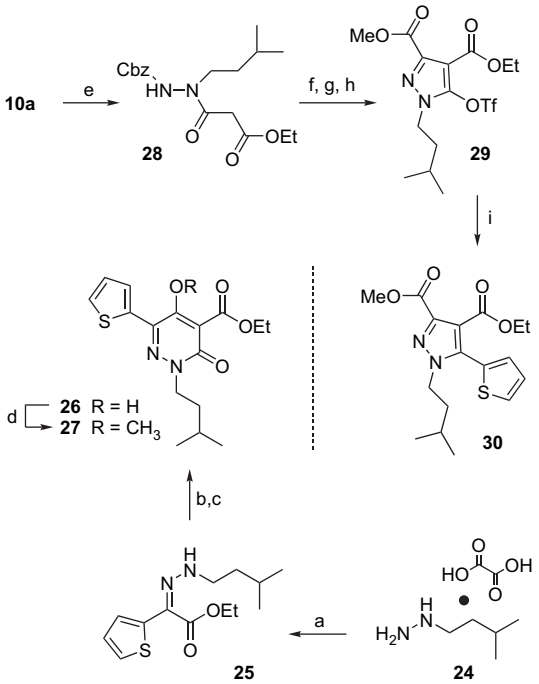
Having successfully prepared pyrazole triflate **14a**, we then examined its ability to participate in a Suzuki coupling reaction with phenylboronic acid.[9] We initially studied a literature protocol that had been successfully employed for the Suzuki coupling of related pyrazole triflates (Table 1, entry 1).[3] Somewhat surprisingly, we obtained only a modest yield of the desired coupling product (**23a**) utilizing these reaction conditions. We then surveyed several other literature procedures that are reported to couple organotriflates and boronic



Scheme 4.

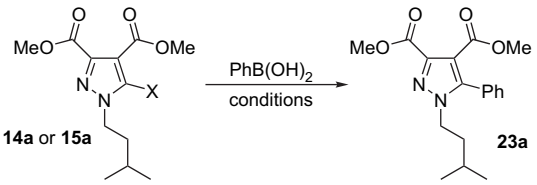
acids or esters in good yield (Table 1, entries 2–4).[10] Unfortunately, these procedures either completely failed to provide the desired coupling product (entry 2) or did so in relatively poor yield (entries 3 and 4).[11] In all cases, we observed significant amounts of pyrazole **13a** by TLC and LCMS analysis of the reaction mixtures suggesting that triflate **14a** underwent facile hydrolysis instead of the desired coupling. A control experiment confirmed that **14a** was rapidly converted to pyrazole **13a** when heated at 75 °C in DME/H_2O (95:5) containing 2 equiv of Na_2CO_3 (100% conversion after 4 h). This transformation proceeded more slowly when conducted at the same temperature in anhydrous DME in the presence of 2 equiv of Na_2CO_3 (60% conversion after 20 h)[12] and did not occur at all in the absence of both added water and Na_2CO_3 (0% conversion after 48 h at 75 °C). Accordingly, we examined anhydrous variants of several Suzuki coupling conditions [$Pd(PPh_3)_4$+ Na_2CO_3/K_2CO_3] and observed dramatically increased yields of the desired product **23a** (Table 1, entries 5 and 6). These improved yields were somewhat dependent on the nature of the carbonate base employed, as we obtained lower isolated quantities of **23a** using Cs_2CO_3 in place of Na_2CO_3 or K_2CO_3 (entry 7). Hoping to reduce the water sensitivity of the coupling reaction, we also examined coupling of tosylate **15a** with phenylboronic acid using several conditions reported in the literature (Table 1, entries 8–10).[13] Unfortunately, these experiments afforded none of the desired product **23a** either due to tosylate hydrolysis (entries 8 and 10) or its complete lack of reactivity (entry 9). Since water has a deleterious effect on the coupling reaction, we were not surprised to observe a reduction in the coupling yield when employing triflate **14a** that had been repeatedly exposed to the atmosphere during long-term use and storage (especially when the compound was kept below 0 °C).[14] These variations could be easily avoided by azeotropically drying the triflate (via concentration from toluene) prior to conducting the coupling reactions.

We next examined whether the anhydrous reaction conditions described above could be utilized to couple triflate **14a** with boronic acids and esters other than phenylboronic acid. Good yields of the desired products were obtained with phenylboronic acids bearing both electron-donating and withdrawing substituents at the 4-position (Table 2, entries 1–4). Use of *ortho*- and *meta*-substituted phenylboronic acids also afforded the desired coupling products in good yields (Table 2, entries 5 and 6). Several heterocyclic boronic acids underwent the desired coupling as well, albeit in lower yields than those observed for the phenylboronic acid derivatives described above (Table 2, entries 7 and 8). Certain heterocyclic boronic acids, however, failed to provide the desired coupling products when subjected to the anhydrous reaction conditions (e.g., 3-pyridyl, 4-pyridyl, 2-furyl, and 3-furylboronic acids). All of these unreactive substrates were highly insoluble in DME, even at elevated temperatures. The addition of water as a co-solvent to increase the solubility of these reagents was not examined



Scheme 5. Reagents and conditions: (a) ethyl thiophene-2-glyoxylate, NaOAc, EtOH, 80 °C, 65%; (b) $ClC(O)CH_2CO_2Et$, 1,4-dioxane, 75 °C; (c) NaOEt, EtOH, 23 °C, 64% from **25**; (d) NaH, MeI, DMF, 23→45 °C, 50%; (e) $ClC(O)CH_2CO_2Et$, 1,4-dioxane, 100 °C, 91%; (f) H_2, Pd on C, EtOAc, 23 °C; (g) $ClC(O)CO_2Me$, *i*-Pr_2NEt, CH_2Cl_2, 0→23 °C; (h) Tf_2O, pyridine, 0 °C, 25% from **28**; (i) 2-thienylboronic acid, Na_2CO_3, $Pd(PPh_3)_4$, DME, 75 °C, 27%.

Table 1. Optimization of coupling reaction conditions



Entry[a]	X	$PhB(OH)_2$ equiv	Catalyst	Additive	Base (equiv)	Solvent	T (°C)	Time[b] (h)	Yield[c] (%)	Ref.
1	OTf	3.0	8% $PdCl_2(dppf)$[d]	4% dppf	K_3PO_4 (3.0)	1,4-Dioxane	100	16	37	3
2	OTf	1.1	1% $Pd(OAc_2)$	1% PCy_3	KF (3.3)	THF	25	4	0	10a
3[e]	OTf	1.2	5% $Pd(PPh_3)_4$	None	Na_2CO_3 (2.0)	8:1 DME/H_2O	75	1.5	28	10b,c
4	OTf	1.1	2.4% $Pd(PPh_3)_4$	None	K_2CO_3 (2.1)	5:1 DME/H_2O	65	0.75	13	10d
5	OTf	1.5	5% $Pd(PPh_3)_4$	None	Na_2CO_3 (2.0)	DME	75	18	84	—
6	OTf	1.5	5% $Pd(PPh_3)_4$	None	K_2CO_3 (2.0)	DME	75	16	70	—
7	OTf	1.5	5% $Pd(PPh_3)_4$	None	Cs_2CO_3 (2.0)	DME	75	16	49	—
8	OTs	1.5	3% $Pd(OAc)_2$	7% DCPTB[f]	$K_3PO_4 \cdot H_2O$ (3.0)	*t*-BuOH	80	2	0	13a
9	OTs	1.5	3% $Ni(COD)_2$	12% PCy_3	K_3PO_4 (3.0)	THF	25	18[g]	0	13b
10	OTs	1.2	5% $PdCl_2(PPh_3)_2$	None	KF (8.0)	1:1 THF/H_2O	60	22	0	13c

[a] Reactions performed using approximately 0.50 mmol of starting OTf/OTs compound at 0.1 M concentration.
[b] Time required for complete disappearance of starting OTf/OTs compound by TLC.
[c] Isolated yield of purified coupling product after silica gel chromatography.
[d] 1:1 Complex with CH_2Cl_2.
[e] OTf compound employed at 0.03 M concentration.
[f] 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.
[g] Starting OTs compound remained unchanged by TLC after 18 h.

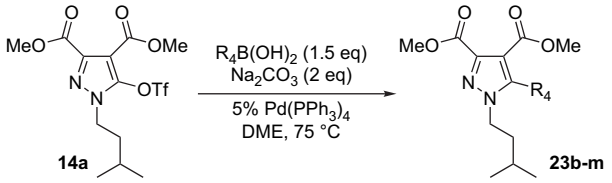
due to the incompatibility of triflate **14a** with basic, aqueous environments (see above).[15] Instead, the pinacol ester of one unreactive heterocyclic boronic acid (4-pyridyl) was successfully coupled with **14a** in moderate yield using the anhydrous reaction conditions (Table 2, entry 9). An unrelated heterocyclic pinacol boronic ester was also coupled with **14a** in similar yield using the identical reaction conditions (Table 2, entry 10). The use of boronic esters may therefore improve the yields of the desired coupling products in cases where the coupling reaction is limited by poor solubility of the corresponding boronic acids. Alkenyl boronic acids participated in the coupling reaction with **14a** and afforded the corresponding products in yields that were somewhat lower than those obtained with phenylboronic acids (Table 2, entries 11 and 12). Several alkyl boronic acid derivatives were also examined in the coupling reaction with **14a** (e.g., isobutyl, cyclobutyl, and cyclohexyl), but these failed to provide any of the desired products. Collectively, the experiments described above demonstrate that various 1,5-disubstituted-1*H*-pyrazoles can be prepared from triflate **14a** in good to moderate yields and also detail some of the limitations associated with our methodology.[16]

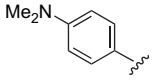
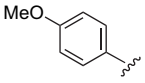
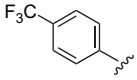
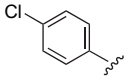
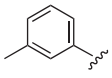
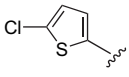
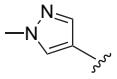
Having determined that a variety of boronic acid derivatives could be successfully coupled to triflate **14a** under anhydrous conditions, we then explored whether other related pyrazole triflates could be prepared using our new methodology and subsequently utilized as Suzuki reaction substrates. The synthesis of two such examples (**14b** and **14c**) is illustrated in Scheme 3. Triflate **14b** was prepared in a manner analogous to that utilized to synthesize **14a**, beginning with the reductive coupling of cyclohexanecarboxaldehyde and benzyl carbazate to produce **10b** (R_1=CH_2cyclohexyl). In contrast, the monosubstituted benzyl carbazate required for the preparation of triflate **14c** (**10c**, R_1=phenyl) was obtained via condensation of commercially available phenylhydrazine and benzyl chloroformate.[17] Intermediates **10b** and **10c** were transformed to the corresponding pyrazole triflates (**14b** and **14c**, respectively) in good yields using a reaction sequence analogous to that employed in the conversion of **10a** to **14a**.[18] As with the latter compound, both **14b** and **14c** were purified by silica gel chromatography and were stable for extended periods of time when stored as neat materials at −20 °C. As illustrated in Table 3, triflates **14b** and **14c** readily participated in Suzuki coupling reactions with substituted phenylboronic acids using the anhydrous conditions described above to similarly transform **14a**. Collectively, these results demonstrate the ability of our methodology to regioselectively prepare a variety of 1-substituted-3,4-diester-containing-5-hydroxy-1*H*-pyrazoles and to transform them via the corresponding triflates to their 1,5-disubstituted analogs.

As depicted in Scheme 4, treatment of hydrazide **12a** with monomethyl oxalyl chloride may conceivably produce pyridazinone **20** instead of pyrazole **13a**. The former entity would likely be converted to the pyridazinone triflate **21** by the reaction conditions utilized to transform 5-hydroxy-1*H*-pyrazoles such as **13a** to their corresponding triflates (cf. Scheme 3). In addition, the Suzuki coupling products derived from **21** would be structural isomers of compounds **23a–m** with identical molecular weights and potentially very similar ^1H and/or ^{13}C NMR characteristics. Although the ^{13}C NMR spectra of the Suzuki products described in this work are consistent with their assignment as 1,5-disubstituted-3,4-diester-containing-1*H*-pyrazoles,[19] we wished to obtain additional evidence that our methodology did not afford pyridazinone products.

Accordingly, we completed an independent synthesis of an appropriately substituted 5-methoxy-3(2*H*)-pyridazinone derivative and compared this entity with the corresponding isomeric 1,5-disubstituted-1*H*-pyrazole (Scheme 5). Thus, hydrazine **24** (oxalic acid salt) was converted to hydrazone

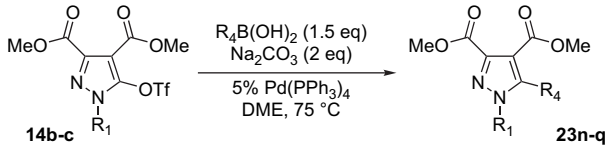
Table 2. Suzuki coupling of triflate **14a**

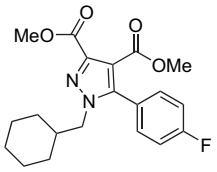
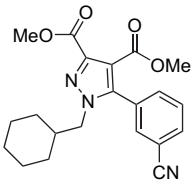
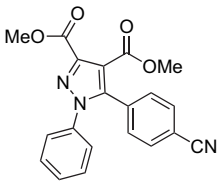
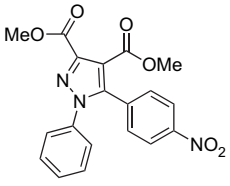


Entry[a]	R_4	Product #	Yield[b] (%)
1		**23b**	79
2		**23c**	78
3		**23d**	76
4		**23e**	72
5		**23f**	77
6		**23g**	89
7		**23h**	34
8		**23i**	33
9[c,d]		**23j**	26
10[c]		**23k**	24
11		**23l**	40
12		**23m**	30

[a] Reactions performed using approximately 0.50 mmol of **14a** at 0.1 M concentration.
[b] Isolated yield after purification on silica gel.
[c] The appropriate pinacol boronic ester was employed in lieu of the corresponding boronic acid.
[d] Use of 4-pyridylboronic acid did not afford any of the desired coupling product.

Table 3. Suzuki coupling of triflates **14b** and **14c**

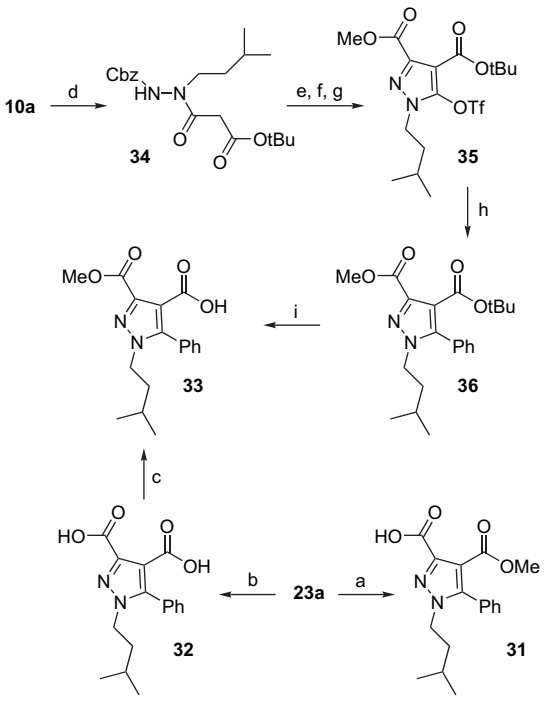


Entry[a]	OTf	Product	#	Yield[b] (%)
1	**14b**		**23n**	88
2	**14b**		**23o**	56
3	**14c**		**23p**	65
4	**14c**		**23q**	66

[a] Reactions performed using approximately 1.0 mmol of starting OTf at 0.1 M concentration.
[b] Isolated yield after purification on silica gel.

25 (mixture of isomers) by thermal condensation with commercially available ethyl thiophene-2-glyoxylate. A minor amount of the corresponding amide condensation product was also formed during this reaction and this material was separated from the desired hydrazone via chromatography. Intermediate **25** was then acylated at elevated temperature with ethyl malonyl chloride and the resulting crude acylhydrazone (mixture of isomers, not shown) was cyclized to pyridazinone **26** by exposure to sodium ethoxide. Methylation of the enol moiety present in **26** then provided methyl ether **27** in good yield.[20] Separately, pyrazole triflate **29** was synthesized from monosubstituted carbazate **10a** by condensation with ethyl malonyl chloride followed by removal of the Cbz moiety, treatment with excess monomethyl oxalyl chloride, and reaction of the resulting 5-hydroxy-1*H*-pyrazole (not shown) with trifluoromethanesulfonic anhydride (cf. Scheme 3). Triflate **29** was subsequently converted to pyrazole **30** in 27% yield via Suzuki coupling with 2-thienylboronic acid using the anhydrous reaction conditions described above. Compounds **27** and **30** exhibit distinct TLC R_f values, LC retention times, and ^{1}H and ^{13}C NMR spectral characteristics, clearly indicating that the major products derived from the methodology described in this work are not 6-substituted-3(2*H*)-pyridazinones.

The preparation of pyrazole **30** described in Scheme 5 illustrates one example of the use of our methodology to regiospecifically prepare 1,5-disubstituted-1*H*-pyrazoles containing differentiated ester moieties at the 3- and 4-positions. Several additional syntheses of such differentiated 1,5-disubstituted-1*H*-pyrazoles are depicted in Scheme 6. In one instance, careful hydrolysis of the Suzuki coupling product **23a** with aqueous LiOH gave monoacid **31** in good yield



Scheme 6. Reagents and conditions: (a) LiOH, CH_3OH, 23 °C, 55%; (b) BBr_3, CH_2Cl_2, 0→23 °C, 78%; (c) BBr_3, CH_2Cl_2/CH_3OH, 23 °C, 54% from **23a**; (d) $HO_2CCH_2CO_2t$-Bu, HATU, *i*-Pr_2NEt, DMF, 23 °C, 74%; (e) H_2, Pd on C, EtOAc, 23 °C; (f) $ClC(O)CO_2Me$, *i*-Pr_2NEt, CH_2Cl_2, 0→23 °C; (g) Tf_2O, pyridine, 0 °C, 73% from **34**; (h) phenylboronic acid, Na_2CO_3, $Pd(PPh_3)_4$, DME, 75 °C, 92%; (i) TFA/CH_2Cl_2, 23 °C, 92%.

after a simple work-up procedure. Alternatively, treatment of **23a** with BBr_3 afforded the diacid **32** in good yield following an equally simple aqueous work-up. Adding methanol to the crude hydrolysis reaction mixture obtained by exposing **23a** to BBr_3 provided monoacid **33** in good yield and suggested that diacid **32** could be selectively mono-esterified without isolation.[21] Although preparative HPLC methods were utilized to obtain analytical samples of compounds **31**–**33**, the crude reaction products were relatively pure and could likely be utilized directly in subsequent transformations (e.g., amide formation).

The locations of the ester and acid moieties present in compounds **31** and **33** were confirmed by an independent synthesis of the latter molecule (Scheme 6). Thus, monosubstituted carbazate **10a** (Scheme 3) was coupled with commercially available mono-*tert*-butyl malonate to afford intermediate **34** in good yield. This material was converted to triflate **35** in excellent yield by a reaction sequence analogous to that used to transform intermediate **11a** to triflate **14a** (cf. Scheme 3). Suzuki coupling of triflate **35** with phenylboronic acid using the anhydrous reaction conditions described above proceeded uneventfully and provided compound **36** in 92% yield after purification by flash chromatography. Selective cleavage of the *tert*-butyl ester present in **36** by exposure to trifluoroacetic acid afforded a material whose crude ^1H NMR spectrum was identical to that of monoacid **33** (prepared from **23a** as described above) and clearly distinct from that of monoacid **31**. These results confirm the structural assignments for compounds **31** and **33** and also illustrate the use of malonate and oxalyl chloride derivatives containing orthogonally protected ester moieties in our new methodology.

3. Experimental section

3.1. General

All reactions were performed in septum-sealed vials or flasks under a slight positive pressure of dry nitrogen. All commercial reagents were used as received from their respective suppliers. 1,2-Dimethoxyethane (DME, >99%) was purchased from Sigma–Aldrich and was used without additional purification. All other solvents were purchased from EMD in anhydrous form and were used without additional purification. All employed solutions of reagents, acids, and bases were aqueous in nature unless otherwise indicated. Flash chromatography was performed on silica gel using either self-packed glass columns (Merck silica gel 60, 40–63 μM, manual elution) or commercially available cartridges (Analogix Superflash) and automated elution systems. Preparative HPLC was performed using a Thomson C18 ODSA column (5 micron, 50×21.2 mm ID). ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (δ) using internal solvent signals as references and coupling constants (when given) are reported in hertz (Hz).

3.1.1. *N′*-(3-Methylbutyl)hydrazinecarboxylic acid benzyl ester (10a). Benzyl carbazate (19.1 g, 115 mmol) was added to a solution of isovaleraldehyde (9.56 g, 115 mmol) in CH_3OH (300 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 30 min, then was cooled to 0 °C. Glacial acetic acid (12.5 mL) and sodium cyanoborohydride (18.0 g, 286 mmol) were added sequentially and the mixture was allowed to warm to 23 °C. After stirring at 23 °C for 17 h, the reaction mixture was concentrated under reduced pressure to approximately 100 mL volume and was then partitioned between half-saturated $NaHCO_3$ and a 1:1 mixture of EtOAc and hexanes. The organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by chromatography (Superflash cartridge, gradient elution, 5→50% EtOAc in hexanes) afforded **10a** (10.3 g, 77%) as a white, waxy solid: mp=45–46 °C; R_f=0.64 (50% EtOAc in hexanes); ^1H NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7.1), 1.36 (2H, q, J=7.2), 1.58–1.68 (1H, m), 2.88 (2H, t, J=7.2), 5.13 (2H, s), 7.28–7.34 (5H, m); ^{13}C NMR ($CDCl_3$) δ: 22.6, 25.9, 36.5, 50.1, 66.9, 127.9, 128.0, 128.3, 135.9, 157.0; HRMS (ESI-TOF) calcd for $C_{13}H_{21}N_2O_2$ $[M+H]^+$: 237.1597; found: 237.1596.

3.1.2. *N′*-Cyclohexylmethylhydrazinecarboxylic acid benzyl ester (10b). Benzyl carbazate (8.41 g, 50.6 mmol) was added to a solution of cyclohexylcarboxaldehyde (5.68 g, 50.6 mmol) in CH_3OH (80 mL) at 0 °C. The reaction mixture was warmed to 23 °C and stirred at that temperature for 30 min, then was cooled back to 0 °C. Glacial acetic acid (8.0 mL) and sodium cyanoborohydride (7.95 g, 127 mmol) were added sequentially and the mixture was allowed to warm to 23 °C. After stirring at 23 °C for 16 h, the reaction mixture was partitioned between half-saturated $NaHCO_3$ and a 1:1 mixture of EtOAc and hexanes. The organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by chromatography (gradient elution, 15→40% EtOAc in hexanes) afforded **10b** (12.0 g, 44%) as a white solid: mp=48–49 °C; R_f=0.69 (50% EtOAc in hexanes); ^1H NMR ($CDCl_3$) δ: 0.94 (2H, q, J=11.3),

1.12–1.28 (3H, m), 1.45–1.53 (1H, m), 1.66–1.78 (5H, m), 2.73 (2H, d, J=5.9), 5.13 (2H, s), 7.31–7.38 (5H, m); ^{13}C NMR ($CDCl_3$) δ: 26.0, 26.6, 31.3, 36.2, 58.5, 67.1, 128.0, 128.1, 128.3, 135.9, 156.9; HRMS (ESI-TOF) calcd for $C_{15}H_{23}N_2O_2$ $[M+H]^+$: 263.1754; found: 263.1751.

3.1.3. 3-[*N*′-Benzyloxycarbonyl-*N*-(3-methylbutyl)-hydrazino]-3-oxopropionic acid methyl ester (11a). Compound **10a** (12.0 g, 50.78 mmol) was dissolved in anhydrous 1,4-dioxane (300 mL), and methyl malonyl chloride (7.63 g, 55.86 mmol) was slowly added via syringe at 23 °C. The resulting solution was heated to 100 °C for 1 h after which time TLC analysis indicated completion of the reaction. The mixture was allowed to cool to 23 °C and then was poured into half-saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with a 1:1 mixture of EtOAc in hexanes. The organic layers were dried over Na_2SO_4 and concentrated to afford a yellow oil. This residue was purified by chromatography (gradient elution, 10→70% EtOAc in hexanes) to provide **11a** (7.76 g, 91%) as a pale yellow oil, which subsequently solidified to a white, waxy solid; mp=49–50 °C; R_f=0.56 (50% EtOAc in hexanes); ^{1}H NMR (DMSO-d_6) δ: 0.84 (6H, d, J=6.1), 1.31–1.33 (2H, m), 1.49–1.56 (1H, m), 3.00–3.85 (7H, m), 5.13 (2H, s), 7.31–7.36 (5H, m), 9.97 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 22.5, 25.8, 35.2, 40.7, 46.2, 52.5, 68.1, 128.1, 128.4, 128.5, 135.0, 154.6, 167.9; Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.73; H, 7.19; N, 8.70.

3.1.4. 3-(*N*′-Benzyloxycarbonyl-*N*-cyclohexylmethyl-hydrazino)-3-oxopropionic acid methyl ester (11b). Compound **10b** (7.00 g, 26.70 mmol) was dissolved in anhydrous 1,4-dioxane (175 mL) and methyl malonyl chloride (4.01 g, 29.37 mmol) was slowly added via syringe at 23 °C. The resulting solution was heated to 100 °C for 1 h after which time TLC analysis indicated completion of the reaction. The mixture was allowed to cool to 23 °C and then was poured into half-saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with a 1:1 mixture of EtOAc in hexanes. The organic layers were dried over Na_2SO_4 and were concentrated to afford a yellow oil. This residue was purified by chromatography (Superflash cartridge, gradient elution, 2→50% EtOAc in hexanes) to provide **11b** (8.56 g, 89%) as a white, waxy solid: mp=96–98 °C; R_f=0.33 (30% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.97–0.99 (2H, m), 1.17–1.23 (3H, m), 1.58–1.73 (6H, m), 3.34–3.89 (7H, m), 5.20 (2H, s), 7.36–7.38 (5H, m); ^{13}C NMR ($CDCl_3$) δ: 26.0, 26.6, 30.8, 35.7, 41.0, 52.7, 53.9, 68.4, 128.4, 128.6, 128.8, 135.3, 154.7, 168.4; Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73. Found: C, 62.98; H, 6.96; N, 7.97.

3.1.5. 3-(*N*′-Benzyloxycarbonyl-*N*-phenylhydrazino)-3-oxopropionic acid methyl ester (11c). Methyl malonyl chloride (1.85 mL, 17.25 mmol) was added to a solution of *N*′-phenylhydrazinecarboxylic acid benzyl ester[17] (**10c**, 3.80 g, 15.68 mmol) in 1,4-dioxane (90 mL) at 23 °C. The mixture was refluxed for 1 h, then was cooled to 23 °C and was partitioned between saturated $NaHCO_3$ and a 1:1 mixture of EtOAc and hexanes. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (Superflash cartridge, gradient elution, 0→70% EtOAc in hexanes) to provide **11c** (5.25 g, 98%) as a pale yellow oil: R_f=0.28 (30% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, mixture of rotational isomers) δ: 3.41 (br s, 2H), 3.71 (br s, 3H), 5.19 (s, 2H), 7.33–7.41 (m, 10H); ^{13}C NMR ($CDCl_3$, mixture of rotational isomers) δ: 40.5, 41.3, 41.9, 52.9, 68.3, 68.6, 127.8–129.2 (peaks are broadened due to dynamic processes), 129.4, 129.9, 135.6, 140.8, 141.3, 155.1, 156.2, 165.8, 167.2, 167.8, 168.3; Anal. Calcd for $C_{18}H_{18}N_2O_5\cdot 0.10H_2O$: C, 62.82; H, 5.33; N, 8.14. Found: C, 62.49; H, 5.68; N, 8.18.

3.1.6. 1-(3-Methylbutyl)-5-trifluoromethanesulfonyloxy-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (14a). Palladium on carbon (0.67 g, 5%) was added to a solution of **11a** (2.51 g, 7.46 mmol) in EtOAc (30 mL) at 23 °C. The resulting suspension was stirred under an atmosphere of hydrogen (balloon) for 19 h, then was filtered through Celite. The Celite was washed with EtOAc and the combined washings and filtrate were concentrated under reduced pressure to afford a yellow oil (crude **12a**). This material was dissolved in CH_2Cl_2 (80 mL) and was cooled to 0 °C. *N*, *N*-Diisopropylethylamine (5.7 mL, 32.76 mmol) and monomethyl oxalyl chloride (1.43 mL, 15.6 mmol) were then added sequentially. The resulting dark brown solution was stirred for 20 min at 0 °C then was warmed to 23 °C for 3 h and partitioned between 1.0 M HCl and CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and were concentrated. The residue was purified by chromatography (Superflash cartridge, gradient elution, 5% CH_3OH in CH_2Cl_2) to afford **13a** (2.00 g, 95%) as a pale yellow liquid: R_f=0.22 (5% CH_3OH in CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ: 0.87 (6H, d, J=6.2), 1.42–1.53 (3H, m), 3.50 (3H, s), 3.60–3.63 (2H, m), 3.67 (3H, s). This material (1.4 g, 5.18 mmol) was dissolved in pyridine (15 mL) at 0 °C and trifluoromethanesulfonic anhydride (1.3 mL, 7.8 mmol) was added dropwise via syringe. The mixture was allowed to stir for 2 h at 0 °C then was partitioned between 1.0 M HCl and a 1:1 mixture of EtOAc and hexanes. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (Superflash cartridge, gradient elution, 0→100% EtOAc in hexanes) to provide **14a** (1.79 g, 86%) as a pale yellow oil: R_f=0.46 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.97 (6H, d, J=7.0), 1.61 (1H, septet, J=6.7), 1.79–1.84 (2H, m), 3.88 (3H, s), 3.96 (3H, s), 4.14 (2H, t, J=8.1); ^{13}C NMR ($CDCl_3$) δ: 22.4, 26.0, 37.9, 48.4, 52.5, 53.0, 105.2, 118.5 (q, J=320), 140.8, 142.4, 159.8, 161.0; Anal. Calcd for $C_{13}H_{17}F_3N_2O_7S$: C, 38.81; H, 4.26; N, 6.96. Found: C, 39.1; H, 4.17; N, 7.20.

3.1.7. 1-Cyclohexylmethyl-5-trifluoromethanesulfonyl-oxy-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (14b). Palladium on carbon (1.07 g, 5%) was added to a solution of **11b** (4.00 g, 11.0 mmol) in EtOAc (75 mL) at 23 °C. The resulting suspension was stirred under an atmosphere of hydrogen (balloon) for 2 h, and then was filtered through Celite. The Celite was washed with EtOAc and the combined washings and filtrate were concentrated under reduced pressure to afford a clear oil. This material was dissolved in CH_2Cl_2 (120 mL) and was cooled to 0 °C. *N*,*N*-Diisopropylethylamine (8.0 mL, 46.2 mmol) and monomethyl oxalyl chloride (2.0 mL, 22 mmol) were then added sequentially. The resulting dark brown solution was stirred for 30 min at 0 °C then was warmed to 23 °C for 4 h and partitioned between 1.0 M HCl and EtOAc. The combined

organic layers were dried over Na_2SO_4 and were concentrated. The residue was purified by chromatography (Superflash cartridge, gradient elution, 5% CH_3OH in CH_2Cl_2) to afford **13b** as a pale yellow solid. This material was dissolved in pyridine (20 mL) at 0 °C and trifluoromethanesulfonic anhydride (1.7 mL, 10.13 mmol) was added dropwise via syringe. The mixture was allowed to stir for 2 h at 0 °C then was partitioned between 1.0 M HCl and a 1:1 mixture of EtOAc and hexanes. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (Superflash cartridge, gradient elution, 0→100% EtOAc in hexanes) to provide **14b** (2.33 g, 68% from **11b**) as a pale yellow oil: R_f=0.54 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.92–1.01 (2H, m), 1.11–1.27 (3H, m), 1.56 (2H, d, J=11.0), 1.66–1.74 (3H, m), 1.94–2.04 (1H, m), 3.87 (3H, s), 3.94–3.95 (5H, m); ^{13}C NMR ($CDCl_3$) δ: 25.7, 26.1, 30.6, 38.1, 52.5, 53.0, 55.8, 105.1, 118.5 (q, J=320), 141.3, 142.3, 159.9, 161.1; Anal. Calcd for $C_{15}H_{19}F_3N_2O_7S$: C, 42.06; H, 4.47; N, 6.54. Found: C, 42.29; H, 4.53; N, 6.82.

3.1.8. 1-Phenyl-5-trifluoromethanesulfonyloxy-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (14c). Palladium on carbon (0.70 g, 10%) was added to a solution of **11c** (5.17 g, 15.10 mmol) in EtOAc (100 mL) at 23 °C. The resulting suspension was stirred under an atmosphere of hydrogen (balloon) for 8 h, and then was filtered through Celite. The Celite was washed with EtOAc and the combined washings and filtrate were concentrated under reduced pressure to afford a pale yellow oil. This material was dissolved in CH_2Cl_2 (120 mL) and was cooled to 0 °C. *N*,*N*-Diisopropylethylamine (11.05 mL, 63.42 mmol) and monomethyl oxalyl chloride (2.78 mL, 30.20 mmol) were then added sequentially. The resulting dark brown solution was stirred for 20 min at 0 °C then was warmed to 23 °C for 2 h and partitioned between 1.0 M HCl and CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and were concentrated to afford crude **13c** as a pale yellow solid. This material was dissolved in pyridine (5.5 mL) at 0 °C and trifluoromethanesulfonic anhydride (0.547 mL, 3.26 mmol) was added dropwise via syringe. The mixture was allowed to stir for 1 h at 0 °C then was partitioned between 1.0 M HCl and a 1:1 mixture of EtOAc and hexanes. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (Superflash cartridge, gradient elution, 0→40% EtOAc in hexanes) to provide **14c** (0.68 g, 77% from **11c**) as a white solid: mp=105–106 °C; R_f=0.55 (30% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 3.94 (s, 3H), 4.00 (s, 3H), 7.54 (br s, 5H); ^{13}C NMR ($CDCl_3$) δ: 52.7, 53.3, 106.5, 117.8 (q, J=321), 124.8, 129.8, 130.4, 135.5, 141.4, 143.5, 159.8, 161.1; Anal. Calcd for $C_{14}H_{11}F_3N_2O_7S$: C, 41.18; H, 2.72; N, 6.86. Found: C, 41.28; H, 3.01; N, 6.92.

3.1.9. 1-(3-Methylbutyl)-5-(toluene-4-sulfonyloxy)-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (15a). Palladium on carbon (0.35 g, 5%) was added to a solution of **11a** (1.21 g, 3.60 mmol) in EtOAc (25 mL) at 23 °C. The resulting suspension was stirred under an atmosphere of hydrogen (balloon) for 1.5 h, then was filtered through Celite. The Celite was washed with EtOAc and the combined washings and filtrate were concentrated under reduced pressure to afford crude **12a** as a colorless oil. This material was dissolved in CH_2Cl_2 (40 mL) and was cooled to 0 °C. *N*,*N*-Diisopropylethylamine (2.63 mL, 15.1 mmol) and monomethyl oxalyl chloride (0.622 mL, 7.20 mmol) were then added sequentially. The resulting orange-red solution was stirred for 20 min at 0 °C then was warmed to 23 °C for 2 h and partitioned between 1.0 M HCl and EtOAc. The combined organic layers were dried over Na_2SO_4 and were concentrated to afford crude **13a** as a brown oil. This material was dissolved in CH_2Cl_2 (40 mL) at 23 °C and 4-dimethylaminopyridine (0.045 g, 0.37 mmol), *p*-toluenesulfonyl chloride (1.03 g, 5.40 mmol), and triethylamine (0.802 mL, 5.75 mmol) were added sequentially. The reaction mixture was stirred at 23 °C for 1.75 h, then was partitioned between half-saturated $NaHCO_3$ and a 1:1 mixture of EtOAc and hexanes. The combined organic layers were dried over Na_2SO_4 and were concentrated. The residue was purified by chromatography (Superflash cartridge, gradient elution, 0→65% EtOAc in hexanes) to provide **15a** (1.24 g, 81% from **11a**) as a pale yellow oil: R_f=0.53 (50% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.92 (d, 6H, J=6.6), 1.48–1.56 (m, 1H), 1.69–1.75 (m, 2H), 2.50 (s, 3H), 3.57 (s, 3H), 3.93 (s, 3H), 3.97–4.02 (m, 2H), 7.40 (d, 2H, J=8.3), 7.80 (d, 2H, J=8.3); ^{13}C NMR ($CDCl_3$) δ: 22.2, 22.6, 26.1, 38.0, 48.1, 52.2, 52.9, 105.4, 129.1, 130.4, 131.5, 141.6, 142.9, 147.1, 160.8, 161.5; Anal. Calcd for $C_{19}H_{24}N_2O_7S$: C, 53.76; H, 5.70; N, 6.60. Found: C, 53.77; H, 5.70; N, 6.72.

3.2. General procedure for Suzuki coupling of triflates 14a–c

The triflate (1 mmol) was dissolved in 10 mL anhydrous DME and the desired boronic acid or ester (1.5 mmol), Na_2CO_3, (2.0 mmol), and $Pd(PPh_3)_4$ (0.05 mmol) were added sequentially. The resulting orange suspension was purged with nitrogen for 3 min and then was heated at 75 °C for 20 h. After cooling to 23 °C, the reaction mixture was filtered, concentrated in vacuo, and chromatographed on silica gel (eluting with EtOAc in hexanes) to afford the desired coupling products.[22]

3.2.1. 1-(3-Methylbutyl)-5-phenyl-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (23a). Oil; R_f=0.37 (30% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.78 (6H, d, J=6.2), 1.40–1.50 (1H, m), 1.63–1.69 (2H, m), 3.69 (3H, s), 3.97 (3H, s), 4.02–4.06 (2H, m), 7.34–7.38 (2H, m), 7.46–7.50 (3H, m); ^{13}C NMR ($CDCl_3$) δ: 22.5, 25.9, 39.3, 49.1, 52.2, 52.8, 114.4, 128.3, 128.7, 129.9, 142.3, 145.6, 162.5, 163.3; Anal. Calcd for $C_{18}H_{22}N_2O_4 \cdot 0.10H_2O$: C, 65.08; H, 6.73; N, 8.43. Found: C, 64.95; H, 6.36; N, 8.38.

3.2.2. 5-(4-Dimethylaminophenyl)-1-(3-methylbutyl)-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (23b). Oil; R_f=0.13 (33% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.81 (6H, d, J=6.6), 1.44–1.52 (1H, m), 1.64–1.73 (2H, m), 3.06 (s, 6H), 3.72 (3H, s), 3.96 (3H, s), 4.03–4.09 (2H, m), 6.91 (br s, 2H), 7.26 (2H, d, J=8.8); ^{13}C NMR ($CDCl_3$) δ: 22.5, 26.0, 30.0, 39.2, 40.6, 48.9, 52.1, 52.6, 112.0, 113.9, 130.7, 142.0, 146.1, 150.7, 162.6, 163.7; HRMS (ESI-TOF) calcd for $C_{20}H_{28}N_3O_4$ $[M+H]^+$: 374.2074; found: 374.2070.

3.2.3. 5-(4-Methoxyphenyl)-1-(3-methylbutyl)-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (23c). Oil;

R_f=0.45 (33% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.80 (6H, d, J=6.6), 1.44–1.50 (1H, m), 1.64–1.70 (2H, m), 3.71 (3H, s), 3.88 (3H, s), 3.97 (3H, s), 4.03–4.07 (2H, m), 6.99–7.01 (2H, dt, J=8.8, 2.2), 7.28–7.30 (2H, dt, J=8.8, 2.2); ^{13}C NMR ($CDCl_3$) δ: 22.4, 25.9, 39.2, 48.9, 52.1, 52.7, 55.5, 114.1, 116.1, 120.1, 131.2, 142.1, 145.4, 160.5, 162.5, 163.4; Anal. Calcd for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71; N, 7.77. Found: C, 63.17; H, 6.91; N, 7.82.

3.2.4. 1-(3-Methylbutyl)-5-(4-trifluoromethylphenyl)-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (23d). Oil; R_f=0.22 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.78 (6H, d, J=6.2), 1.40–1.50 (1H, m), 1.63–1.69 (2H, m), 3.69 (3H, s), 3.97 (3H, s), 4.02–4.06 (2H, m), 7.34–7.38 (2H, m), 7.46–7.50 (3H, m); ^{13}C NMR ($CDCl_3$) δ: 22.4, 25.9, 39.1, 49.2, 52.2, 52.8, 114.5, 123.7 (q, J=271.7), 125.6 (q, J=3.8), 130.4, 131.9, 131.9 (q, J=33.0), 142.6, 144.1, 162.2, 162.8; Anal. Calcd for $C_{19}H_{21}F_3N_2O_4$: C, 57.28; H, 5.31; N, 7.03. Found: C, 57.22; H, 5.49; N, 7.21.

3.2.5. 5-(4-Chlorophenyl)-1-(3-methylbutyl)-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (23e). Oil; R_f=0.27 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.79 (6H, d, J=6.6), 1.46 (1H, septet, J=6.6), 1.66 (2H, q, J=7.0), 3.69 (3H, s), 3.96 (3H, s), 4.00–4.04 (2H, m), 7.30 (2H, dt, J=8.6, 2.3), 7.46 (2H, dt, J=8.2, 1.6); ^{13}C NMR ($CDCl_3$) δ: 22.4, 25.8, 39.1, 49.1, 52.1, 52.7, 114.3, 126.5, 128.9, 131.1, 136.1, 142.4, 144.3, 162.3, 163.0; Anal. Calcd for $C_{18}H_{21}ClN_2O_4$: C, 59.26; H, 5.80; N, 7.68. Found: C, 59.39; H, 6.04; N, 7.92.

3.2.6. 1-(3-Methylbutyl)-5-*o*-tolyl-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (23f). Oil; R_f=0.37 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.77 (6H, d, J=6.5), 1.44 (1H, septet, J=6.6), 1.57–1.68 (2H, m), 2.13 (3H, s), 3.65 (3H, s), 3.77–3.84 (1H, m), 3.92–3.95 (1H, m), 3.98 (3H, s), 7.16 (1H, d, J=7.7), 7.28–7.33 (2H, m), 7.37–7.41 (1H, m); ^{13}C NMR ($CDCl_3$) δ: 19.7, 22.1, 25.5, 38.7, 48.5, 51.7, 52.5, 113.8, 125.6, 127.7, 129.7, 129.8, 130.0, 137.5, 142.3, 145.2, 162.3, 162.6; Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.06; H, 7.16; N, 8.22.

3.2.7. 1-(3-Methylbutyl)-5-*m*-tolyl-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (23g). Oil; R_f=0.37 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.79 (6H, d, J=6.9), 1.46 (1H, septet, J=6.6), 1.65–1.70 (2H, m), 2.42 (3H, s), 3.70 (3H, s), 3.96 (3H, s), 4.03 (2H, t, J=7.8), 7.15 (2H, d, J=7.2), 7.28 (1H, d, J=8.0), 7.36 (1H, t, J=7.7); ^{13}C NMR ($CDCl_3$) δ: 21.5, 22.2, 25.7, 39.0, 48.8, 51.9, 52.5, 114.1, 126.7, 127.9, 128.3, 130.0, 130.3, 138.1, 141.8, 145.5, 162.2, 163.1; Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.43; H, 6.78; N, 8.48.

3.2.8. 1-(3-Methylbutyl)-5-(4-methylthiophen-3-yl)-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (23h). Oil; R_f=0.20 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.81 (6H, d, J=6.6), 1.46 (1H, septet, J=6.6), 1.64 (2H, q, J=7.0), 2.07 (3H, s), 3.82–4.10 (2H, br s), 3.70 (3H, s), 3.98 (3H, s), 7.09 (1H, m), 7.30 (1H, d, J=3.1); ^{13}C NMR ($CDCl_3$) δ: 14.7, 22.4, 25.8, 39.1, 48.9, 52.0, 52.7, 114.3, 122.2, 127.1, 128.7, 137.4, 141.1, 142.6, 162.4, 162.8; Anal. Calcd for $C_{17}H_{22}N_2O_4S$: C, 58.27; H, 6.33; N, 7.99. Found: C, 58.60; H, 6.26; N, 8.08.

3.2.9. 5-(5-Chlorothiophen-2-yl)-1-(3-methylbutyl)-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (23i). Oil; R_f=0.30 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.83 (6H, d, J=6.6), 1.50 (1H, septet, J=6.6), 1.69 (2H, q, J=8.2), 3.75 (3H, s), 3.96 (3H, s), 4.09–4.13 (2H, m), 6.99 (2H, d, J=4.3), 7.16 (1H, dd, J=6.1, 1.2), 7.45–7.50 (2H, m); ^{13}C NMR ($CDCl_3$) δ: 22.4, 26.0, 39.3, 49.3, 52.3, 52.7, 116.2, 125.4, 126.5, 130.1, 133.8, 136.9, 141.9, 161.8, 162.8; HRMS (ESI-TOF) calcd for $C_{16}H_{20}ClN_2O_4S$ [M+H]$^+$: 371.0827; found: 371.0821.

3.2.10. 1-(3-Methylbutyl)-5-pyridin-4-yl-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (23j). Oil; R_f=0.56 (5% CH_3OH in CH_2Cl_2); ^{1}H NMR (CD_3OD) δ: 0.83 (6H, d, J=6.3), 1.46 (1H, septet, J=6.6), 1.66 (2H, q, J=7.3), 3.69 (3H, s), 3.95 (3H, s), 4.14 (2H, t, J=7.3), 7.55 (2H, d, J=5.3), 8.75 (2H, br s); ^{13}C NMR (CD_3OD) δ: 22.6, 26.8, 39.9, 50.3, 52.6, 53.2, 115.2, 126.3, 138.6, 144.0, 150.6, 163.8, 163.9; HRMS (ESI-TOF) calcd for $C_{17}H_{21}N_3O_4$ [M+H]$^+$: 332.1605; found: 332.1601.

3.2.11. 1′-Methyl-2-(3-methylbutyl)-2*H*,1′*H*-[3,4′]bipyrazolyl-4,5-dicarboxylic acid dimethyl ester (23k). Oil; R_f=0.13 (33% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.85 (6H, d, J=6.6), 1.49 (1H, septet, J=6.6), 1.67 (2H, dt, J=7.8, 6.6), 3.72 (3H, s), 3.89 (3H, s), 3.97 (3H, s), 4.15–4.19 (2H, m), 7.67 (1H, s), 7.94 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 22.6, 26.1, 30.0, 39.2, 49.2, 52.3, 52.7, 114.2, 131.6, 137.5, 142.2, 162.3, 163.7; HRMS (ESI-TOF) calcd for $C_{16}H_{23}N_4O_4$ [M+H]$^+$: 335.1714; found: 335.1709.

3.2.12. 1-(3-Methylbutyl)-5-propenyl-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (23l). Oil; R_f=0.19 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.96 (6H, d, J=6.6), 1.57–1.66 (1H, m), 1.74 (2H, q, J=7.0), 1.96 (3H, d, J=5.0), 3.86 (3H, s), 3.93 (3H, s), 4.16 (2H, t, J=7.8), 6.26–6.36 (2H, m); ^{13}C NMR ($CDCl_3$) δ: 19.6, 22.6, 26.1, 30.0, 39.0, 49.3, 52.3, 52.6, 113.0, 116.5, 136.3, 141.7, 142.0, 162.4, 164.3; Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found: C, 61.29; H, 7.41; N, 9.55.

3.2.13. 5-Cyclopent-1-enyl-1-(3-methylbutyl)-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (23m). Oil; R_f=0.22 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.94 (6H, d, J=6.6), 1.59 (1H, septet, J=6.6), 1.70–1.76 (2H, m), 2.07 (2H, quintet, J=7.4), 3.83 (3H, s), 3.94 (3H, s), 4.09–4.13 (2H, m), 2.56–2.61 (2H, m), 2.62–2.67 (2H, m), 5.98 (1H, quintet, J=1.9); ^{13}C NMR ($CDCl_3$) δ: 22.6, 24.0, 26.1, 31.1, 33.8, 36.2, 49.2, 52.1, 52.6, 113.6, 131.3, 136.0, 142.0, 142.9, 162.4, 163.5; Anal. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.56; H, 7.86; N, 9.05.

3.2.14. 1-Cyclohexylmethyl-5-(4-fluorophenyl)-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (23n). Oil; R_f=0.66 (30% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.69–0.78 (2H, m), 1.00–1.20 (3H, m), 1.45 (2H, d, J=10.8), 1.61–1.63 (3H, m), 1.87–1.93 (1H, m), 3.67 (3H, s), 3.83 (2H, d, J=7.0), 3.95 (3H, s), 7.14–7.18 (2H, m),

7.30–7.34 (2H, m); ^{13}C NMR ($CDCl_3$) δ: 25.7, 26.3, 30.6, 38.5, 52.1, 52.8, 56.3, 114.3, 115.9 (d, J=20), 124.2, 132.2, 142.4, 145.3, 162.4, 163.1, 163.4 (d, J=250); Anal. Calcd for $C_{20}H_{23}FN_2O_4$: C, 64.16; H, 6.19; N, 7.48. Found: C, 64.06; H, 6.54; N, 7.51.

3.2.15. 5-(3-Cyanophenyl)-1-cyclohexylmethyl-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (23o). Oil; R_f=0.44 (30% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.66–0.78 (2H, m), 1.01–1.20 (3H, m), 1.45 (2H, d, J=10.8), 1.61–1.63 (3H, m), 1.87–1.94 (1H, m), 3.69 (3H, s), 3.82 (2H, d, J=7.2), 3.94 (3H, s), 7.58–7.64 (3H, m), 7.78–7.79 (1H, m); ^{13}C NMR ($CDCl_3$) δ: 25.7, 26.3, 30.6, 38.6, 52.3, 52.9, 56.5, 113.2, 114.4, 117.9, 129.6, 129.8, 133.3, 133.6, 134.6, 142.8, 143.9, 162.2, 162.6; HRMS (ESI-TOF) calcd for $C_{21}H_{23}N_3O_4$ $[M+H]^+$: 382.1761; found: 382.1756.

3.2.16. 5-(4-Cyanophenyl)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (23p). Purified by reverse phase HPLC (20–100% CH_3CN in H_2O; 22 mL/min); oil; R_f=0.25 (30% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 3.78 (s, 3H), 3.99 (s, 3H), 7.19 (d, 2H, J=7.9), 7.33–7.35 (m, 3H), 7.38 (d, 2H, J=8.0), 7.61 (d, 2H, J=8.1); ^{13}C NMR ($CDCl_3$) δ: 52.7, 53.1, 113.6, 116.0, 118.1, 125.8, 129.3, 129.5, 131.0, 132.2, 132.5, 138.1, 143.0, 143.9, 162.0, 162.9; HRMS (ESI-TOF) calcd for $C_{20}H_{15}N_3O_4$ $[M+H]^+$: 362.1135; found: 362.1130.

3.2.17. 5-(4-Nitrophenyl)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylic acid dimethyl ester (23q). Yellow solid; mp=138–139 °C; R_f=0.30 (30% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 3.76 (s, 3H), 3.97 (s, 3H), 7.19 (d, 2H, J=7.7), 7.29–7.34 (m, 3H), 7.44 (d, 2H, J=8.6), 8.15 (d, 2H, J=8.6); ^{13}C NMR ($CDCl_3$) δ: 52.7, 53.1, 115.8, 116.1, 123.6, 125.7, 129.4, 131.4, 134.3, 138.1, 142.7, 143.9, 148.3, 162.0, 162.8; Anal. Calcd for $C_{19}H_{15}N_3O_6$: C, 59.84; H, 3.96; N, 11.02. Found: C, 59.65; H, 4.31; N, 10.99.

3.2.18. (3-Methylbutyl)hydrazine, oxalic acid salt (24). This compound was prepared following the method of Anderson et al.[23] A solution of ethyl carbazate (22.0 g, 211 mmol) and isovaleraldehyde (18.2 g, 211 mmol) in *i*-PrOH (120 mL) was refluxed for 2 h, then cooled to 23 °C and let stand overnight. The volatiles were removed under reduced pressure and the residue was dissolved in EtOH (100 mL). Platinum on carbon (4.0 g, 5%) was added and the resulting suspension was stirred at 23 °C under an atmosphere of hydrogen (balloon) for 55 h. The reaction mixture was filtered through Celite and then concentrated under reduced pressure. The residue was suspended in aqueous NaOH (140 mL of a 30 wt %/wt solution) and heated at 100 °C for 2 h. The reaction mixture was cooled to 23 °C, then was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, then were transferred to a large beaker. Solid oxalic acid (18.2 g, 202 mmol) was added at 23 °C and the mixture was vigorously stirred for 30 min. The resulting precipitate was collected by filtration and was washed with CH_2Cl_2 and Et_2O to afford (after drying in the air) 28.7 g (74%) of **24** as a white solid: ^{1}H NMR (DMSO-d_6) δ: 0.86 (6H, d, J=6.8), 1.41 (2H, m), 1.60 (1H, m), 2.88 (2H, m), 8.07 (3H, br s); ^{13}C NMR (DMSO-d_6) δ: 22.3, 25.3, 33.3, 48.9, 164.6.

3.2.19. [(3-Methylbutyl)hydrazono]thiophen-2-yl-acetic acid ethyl ester (25). A suspension of hydrazine oxalate **24** (6.91 g, 36 mmol), ethyl thiophene-2-glyoxylate (5.53 g, 30 mmol), and sodium acetate (3.69 g, 45 mmol) in absolute ethanol (100 mL) was stirred at 80 °C under a nitrogen atmosphere for 40 h. The mixture was cooled to 23 °C, then was diluted with water and EtOAc and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed in vacuo and the residue was purified by chromatography (Superflash cartridge, gradient elution, 0→100% EtOAc in hexanes) to afford **25** as a mixture of two isomers (oil; 5.23 g, 65%): (major isomer) R_f=0.75 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.97 (6H, d, J=6.8), 1.43 (3H, t, J=7.2), 1.57 (2H, m), 1.72 (1H, m), 3.56 (2H, m), 4.35 (2H, q, J=7.2), 6.96 (1H, dd, J=5.2, 4.0), 7.11 (1H, dd, J=5.2, 1.2), 7.34 (1H, dd, J=4.0, 1.2); LCMS (ESI$^+$): *m/e* 269.2 $[M+1]^+$, 537.4 $[2M+1]^+$, 559.0 $[2M+Na]^+$ (exact MS: 268.12).

3.2.20. 5-Hydroxy-2-(3-methylbutyl)-3-oxo-6-thiophen-2-yl-2,3-dihydropyridazine-4-carboxylic acid ethyl ester (26). Compound **25** (2.08 g, 7.76 mmol) was dissolved in anhydrous 1,4-dioxane (20 mL), and ethyl malonyl chloride (1.32 mL, 9.31 mmol) was slowly added via syringe at 23 °C. The reaction mixture was stirred at 100 °C for 20 min, then was cooled to 23 °C. The mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvents were removed in vacuo to give the crude acylhydrazone intermediate. This residue was dissolved in EtOH (25 mL) at 23 °C, and sodium ethoxide solution (3.50 mL of a 21 wt % solution in EtOH, 9.31 mmol) was added. The reaction mixture was stirred for 30 min at 23 °C, then aqueous HCl (5%, 6.3 mL) was added slowly, and the resulting suspension was extracted with EtOAc. The combined organic layers were washed with brine and were dried over Na_2SO_4. The solvents were removed in vacuo and the residue was purified by chromatography (Superflash cartridge, gradient elution, 0→100% EtOAc in hexanes) to afford **26** (1.67 g, 64%) as yellow solid: R_f=0.3 (50% EtOAc in hexanes); ^{1}H NMR (DMSO-d_6) δ: 0.91 (6H, d, J=6.0), 1.27 (3H, t, J=6.8), 1.51–1.61 (3H, m), 4.03 (2H, t, J=7.2), 4.26 (2H, q, J=7.2), 7.11 (1H, dd, J=5.2, 3.6), 7.59 (1H, dd, J=4.8, 1.2), 7.78 (1H, dd, J=3.6, 1.2); ^{13}C NMR ($CDCl_3$) δ: 14.4, 22.7, 26.0, 37.4, 50.9, 63.3, 103.3, 127.4, 127.8, 128.3, 134.9, 135.9, 156.7, 163.8, 171.5; Anal. Calcd for $C_{16}H_{20}N_2O_4S$: C, 57.12; H, 5.99; N, 8.33. Found: C, 56.75; H, 6.29; N, 8.36.

3.2.21. 5-Methoxy-2-(3-methylbutyl)-3-oxo-6-thiophen-2-yl-2,3-dihydropyridazine-4-carboxylic acid ethyl ester (27). Compound **26** (0.726 g, 2.16 mmol) was dissolved in anhydrous DMF (8 mL), and NaH (60% in mineral oil, 0.259 g, 6.48 mmol) was added in three portions at 23 °C under a nitrogen atmosphere. The reaction mixture was stirred at 23 °C for 15 min, then was heated to 45 °C and stirred for 15 min. Methyl iodide (1.34 mL, 21.6 mmol) was added and stirring was continued at 45 °C for 24 h. The mixture was cooled to 23 °C, quenched with water (10 mL), and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by chromatography (Superflash cartridge, gradient elution,

0→100% EtOAc in hexanes) to afford **27** (0.38 g, 50%) as a colorless oil: R_f=0.45 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.99 (6H, d, J=6.0), 1.45 (3H, t, J=7.2), 1.64–1.78 (3H, m), 4.07 (3H, s), 4.19 (2H, m), 4.47 (2H, q, J=7.2), 7.08 (1H, dd, J=5.2, 3.6), 7.39 (1H, dd, J=4.8, 0.8), 7.68 (1H, dd, J=3.6, 1.2); ^{13}C NMR ($CDCl_3$) δ: 14.4, 22.7, 26.1, 37.3, 50.5, 58.6, 62.9, 115.3, 127.5, 127.8, 128.2, 136.1, 136.8, 153.6, 158.7, 164.6; Anal. Calcd for $C_{17}H_{22}N_2O_4S$: C, 58.27, H, 6.33; N, 7.99. Found: C, 58.02; H, 6.67; N, 8.12.

3.2.22. 3-[*N*′-Benzyloxycarbonyl-*N*-(3-methylbutyl)-hydrazino]-3-oxopropionic acid ethyl ester (28). Compound **10a** (12.5 g, 53 mmol) and ethyl malonyl chloride (8.1 mL, 64 mmol) were dissolved in anhydrous 1,4-dioxane (100 mL) and heated to 100 °C for 30 min. The reaction was cooled to room temperature, quenched with saturated aqueous $NaHCO_3$, and diluted with water until clear. This aqueous solution was extracted twice with EtOAc and the combined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuo, and chromatographed (Superflash cartridge, gradient elution, 0→50% EtOAc in hexanes) to give **28** (16.9 g, 91%) as a clear yellow oil: R_f=0.24 (30% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.91 (6H, d, J=6.2), 1.27 (3H, t, J=7.0), 1.43 (2H, q, J=6.6), 1.55–1.62 (1H, m), 3.2–3.6 (4H, br s), 4.16 (2H, q, J=7.0), 5.20 (2H, s), 7.09 (1H, br s), 7.36–7.38 (5H, m); ^{13}C NMR ($CDCl_3$) δ: 14.4, 22.7, 26.0, 35.4, 41.2, 46.3, 61.8, 68.3, 128.4, 128.3, 128.7, 168.1; Anal. Calcd for $C_{18}H_{26}N_2O_5$: C, 61.70; H, 7.48; N, 7.99. Found: C, 61.74; H, 7.56; N, 8.09.

3.2.23. 1-(3-Methylbutyl)-5-trifluoromethanesulfonyl-oxy-1*H*-pyrazole-3,4-dicarboxylic acid 4-ethyl ester 3-methyl ester (29). Compound **28** (16.9 g, 48.2 mmol) was dissolved in EtOH (200 mL) and to this solution was added palladium on carbon (3.5 g, 5%). The atmosphere in the flask was removed under reduced pressure and back-filled with H_2; this process was repeated twice. The resulting slurry was stirred under a slight positive pressure of H_2 for 12 h, upon which it was filtered through Celite and concentrated in vacuo to give 10.4 g of a clear yellow oil. This material was dissolved in CH_2Cl_2 (160 mL) and cooled to 0 °C. To this solution was added sequentially *N*,*N*-diisopropylethylamine (20.1 mL, 120.5 mmol) and monomethyl oxalyl chloride (5.8 mL, 62.7 mmol). After 1 h at 0 °C, the reaction was warmed to 23 °C and stirred an additional 2 h, whereupon it was partitioned between 1.0 M HCl and EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was filtered through a plug of silica gel that was rinsed well with 10% CH_3OH in CH_2Cl_2. The filtrate was concentrated under reduced pressure to give a colorless liquid. This material was dissolved in anhydrous pyridine (10 mL) and cooled to 0 °C. To this solution was added dropwise trifluoromethanesulfonic anhydride (10 mL). After stirring 30 min at 0 °C and 30 min at 23 °C, the reaction was partitioned between 1.0 M HCl and EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography (Superflash cartridge, gradient elution, 0→100% EtOAc in hexanes) to give **29** (5.1 g, 25% from **28**) as a clear yellow oil: R_f=0.4 (25% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.96 (6H, d, J=6.6), 1.36 (3H, t, J=7.0), 1.60 (1H, septet, J=6.6), 1.77–1.83 (2H, m), 3.94 (3H, s), 4.10–4.14 (2H, m), 4.35 (2H, q, J=7.0); ^{13}C NMR ($CDCl_3$) δ: 14.2, 22.3, 26.0, 37.9, 48.2, 52.9, 61.8, 105.5, 118.4 (q, J=321), 140.6, 142.3, 159.5, 161.1; Anal. Calcd for $C_{14}H_{19}F_3N_2O_7S$: C, 40.38; H, 4.60; N, 6.73. Found: C, 40.60; H, 4.75; N, 7.00.

3.2.24. 1-(3-Methylbutyl)-5-thiophen-2-yl-1*H*-pyrazole-3,4-dicarboxylic acid 4-ethyl ester 3-methyl ester (30). This compound was prepared in 27% isolated yield after chromatography by coupling triflate **29** with 2-thienylboronic acid using the anhydrous reaction conditions described above: oil; R_f=0.50 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.86 (6H, d, J=6.8), 1.21 (3H, t, J=7.2), 1.56 (1H, m), 1.73 (2H, m), 3.97 (3H, s), 4.16 (1H, m), 4.22 (2H, q, J=7.2), 7.16 (1H, dd, J=4.8, 3.6), 7.22 (1H, dd, J=3.6, 0.8), 7.55 (1H, dd, J=5.2, 1.2); ^{13}C NMR ($CDCl_3$) δ: 14.2, 22.5, 26.1, 39.4, 49.5, 52.7, 61.3, 116.5, 127.0, 127.4, 128.9, 130.7, 138.1, 141.9, 162.1, 162.7; Anal. Calcd for $C_{17}H_{22}N_2O_4S$: C, 58.27; H, 6.33; N, 7.99. Found: C, 58.65; H, 6.73; N, 8.21.

3.2.25. 1-(3-Methylbutyl)-5-phenyl-1*H*-pyrazole-3,4-dicarboxylic acid 4-methyl ester (31). Compound **23a** (0.11 g, 0.333 mmol) was dissolved in CH_3OH (8 mL) at 23 °C. A 2.0 M, aqueous solution of LiOH (2 mL) was added and the mixture was stirred at 23 °C for 30 min. The mixture was then partitioned between 1.0 M HCl and EtOAc. The organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo to a faintly yellow oil. Purification by reverse phase HPLC (20–100% CH_3CN in H_2O; 22 mL/min) followed by lyophilization from a mixture of 1:5 1,4-dioxane and H_2O (5 mL) afforded **31** (0.057 g, 55%) as a white solid: mp=74–75 °C; R_f=0.2–0.3 (100% EtOAc); ^{1}H NMR ($CDCl_3$) δ: 0.76 (6H, d, J=6.1), 1.45 (1H, septet, J=6.7), 1.68 (2H, q, J=7.5), 3.63 (3H, s), 3.99–4.03 (2H, m), 7.28–7.30 (2H, m), 7.49–7.55 (3H, m); ^{13}C NMR ($CDCl_3$) δ: 22.3, 25.9, 39.0, 49.6, 53.2, 110.5, 128.6, 129.4, 130.0, 143.6, 148.2, 160.3, 167.5; HRMS (ESI-TOF) calcd for $C_{17}H_{20}N_2O_4$ $[M+H]^+$: 317.1496; found: 317.1489.

3.2.26. 1-(3-Methylbutyl)-5-phenyl-1*H*-pyrazole-3,4-dicarboxylic acid (32). Compound **23a** (0.064 g, 0.194 mmol) was dissolved in CH_2Cl_2 (1.16 mL) at 23 °C. The mixture was chilled to 0 °C and boron tribromide (1.16 mL of a 1.0 M solution in CH_2Cl_2, 1.16 mmol) was added dropwise. The ice bath was removed and the mixture stirred at 23 °C for 5 h. Water (5 mL) was added dropwise and the mixture was stirred at 23 °C for 5 min then was partitioned between EtOAc and H_2O. The organic layer was washed with brine, then was dried over $MgSO_4$, filtered, and concentrated in vacuo to a brown oil. Purification by reverse phase HPLC (20–100% CH_3CN in H_2O; 22 mL/min) followed by lyophilization from a mixture of 1:5 1,4-dioxane and H_2O (5 mL) afforded **32** (0.046 g, 78%) as a white solid: mp=91–94 °C; R_f=0.05 (100% EtOAc); ^{1}H NMR ($CDCl_3$) δ: 0.76 (6H, d, J=6.4), 1.44 (1H, septet, J=6.5), 1.64 (2H, q, J=7.3), 4.02 (2H, t, J=8.0), 7.30–7.36 (2H, m), 7.46–7.55 (3H, m); ^{13}C NMR ($CDCl_3$) δ: 22.3, 25.8, 38.0, 49.5, 112.6, 128.0, 128.7, 129.6, 130.1, 141.2, 150.0, 164.3, 165.0; HRMS (ESI-TOF) calcd for $C_{16}H_{18}N_2O_4$ $[M+H]^+$: 303.1339; found: 303.1332.

3.2.27. 1-(3-Methylbutyl)-5-phenyl-1*H*-pyrazole-3,4-dicarboxylic acid 3-methyl ester (33). Compound **23a** (0.1 g, 0.303 mmol) was dissolved in CH_2Cl_2 (1.82 mL) at 23 °C. The mixture was chilled to 0 °C and boron tribromide (1.82 mL of a 1.0 M solution in CH_2Cl_2, 1.82 mmol) was added dropwise. The ice bath was removed and the mixture was stirred at 23 °C for 4 h. TLC analysis indicated complete hydrolysis to produce intermediate **32**. CH_3OH (5 mL) was then added dropwise to the reaction mixture and the solution was stirred at 23 °C for 2.5 h. The mixture was diluted with EtOAc and washed sequentially with H_2O and brine. The organic phase was dried over $MgSO_4$, filtered, and was concentrated in vacuo to a brown oil. Purification by reverse phase HPLC (20–100% CH_3CN in H_2O; 22 mL/min) followed by lyophilization from a mixture of 1:5 1,4-dioxane and H_2O (5 mL) afforded **33** (0.052 g, 54%) as a white, waxy, solid: mp=93–95 °C; R_f=0.65 (100% EtOAc); ^{1}H NMR ($CDCl_3$) δ: 0.78 (6H, d, J=6.2), 1.45 (1H, septet, J=6.6), 1.62–1.68 (2H, m), 4.02–4.06 (2H, m), 4.13 (3H, s), 7.30–7.33 (2H, m), 7.49–7.53 (3H, m); ^{13}C NMR ($CDCl_3$) δ: 22.3, 25.8, 39.1, 49.5, 54.2, 115.1, 128.3, 128.6, 129.6, 129.9, 138.5, 150.4, 160.5, 166.6; HRMS (ESI-TOF) calcd for $C_{17}H_{20}N_2O_4$ $[M+H]^+$: 317.1496; found: 317.1493.

3.2.28. 1-(3-Methylbutyl)-5-phenyl-1*H*-pyrazole-3,4-dicarboxylic acid 3-methyl ester (33) (alternate preparation). Compound **36** (0.037 g, 0.099 mmol) was dissolved in CH_2Cl_2 (4 mL) at 23 °C. Trifluoroacetic acid (3 mL) was added and the reaction mixture was stirred at 23 °C for 20 min. Toluene (8 mL) was added and the volatiles were removed under reduced pressure. Toluene (8 mL) was added to the residue and the volatiles were again removed under reduced pressure to afford crude **33** (0.029 g, 92%) as a colorless oil: ^{1}H NMR data in $CDCl_3$ identical to those described above.

3.2.29. 3-[*N*′-Benzyloxycarbonyl-*N*-(3-methylbutyl)-hydrazino]-3-oxopropionic acid *tert*-butyl ester (34). Compound **10a** (2.57 g, 10.9 mmol) was dissolved in DMF (60 mL) at 23 °C and mono-*tert*-butyl malonate (1.67 mL, 10.8 mmol), HATU (4.13 g, 10.9 mmol), and *N*,*N*-diisopropylethylamine (4.17 mL, 23.9 mmol) were added sequentially. The reaction mixture was stirred at 23 °C for 1 h, then the volatiles were removed under reduced pressure. The residue was partitioned between 0.5 M HCl and a 1:1 mixture of EtOAc and hexanes. The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by chromatography (Superflash cartridge, gradient elution, 0→60% EtOAc in hexanes) provided **34** (3.06 g, 74%) as a light pink solid: mp=111–112 °C; R_f=0.49 (30% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) (mixture of isomers) δ: 0.90–0.92 (m), 1.45 (br s), 1.58 (br s), 3.25–3.52 (m), 5.20 (br s), 7.11 (br s), 7.34–7.39 (m); ^{13}C NMR ($CDCl_3$) δ: 22.9, 26.2, 28.4, 35.6, 42.6, 46.4, 68.3, 82.5, 128.4, 128.8, 128.9, 135.5, 154.9, 167.3, 168.7; Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.68; H, 8.23; N, 7.61.

3.2.30. 1-(3-Methylbutyl)-5-trifluoromethanesulfonyloxy-1*H*-pyrazole-3,4-dicarboxylic acid 4-*tert*-butyl ester 3-methyl ester (35). Palladium on carbon (0.70 g, 5%) was added to a solution of **34** (2.78 g, 7.34 mmol) in EtOAc (50 mL) at 23 °C. The resulting suspension was stirred under an atmosphere of hydrogen (balloon) for 1.5 h then was filtered through Celite. The Celite was washed with EtOAc and the combined washings and filtrate were concentrated under reduced pressure to afford a clear oil. This material was dissolved in CH_2Cl_2 (75 mL) and was cooled to 0 °C. *N*,*N*-Diisopropylethylamine (5.63 mL, 32.3 mmol) and monomethyl oxalyl chloride (1.42 mL, 15.4 mmol) were then added sequentially. The resulting dark brown solution was stirred for 20 min at 0 °C then was warmed to 23 °C for 2.5 h and partitioned between 1.0 M HCl and CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and were concentrated. The red/brown residue was dissolved in pyridine (50 mL) at 0 °C and trifluoromethanesulfonic anhydride (1.37 mL, 8.10 mmol) was added dropwise via syringe. The mixture was allowed to stir for 1.5 h at 0 °C then was partitioned between 1.0 M HCl and a 1:1 mixture of EtOAc and hexanes. The combined organic layers were washed with saturated $NaHCO_3$, then dried over Na_2SO_4, and concentrated. The residue was purified by chromatography (Superflash cartridge, gradient elution, 0→50% EtOAc in hexanes) to provide **35** (2.38 g, 73% from **34**) as a pale yellow oil: R_f=0.61 (30% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.96 (6H, d, J=6.5), 1.56 (9H, s), 1.58–1.63 (1H, m), 1.77–1.82 (2H, m), 3.94 (3H, s), 4.09–4.13 (2H, m); ^{13}C NMR ($CDCl_3$) δ: 22.4, 26.1, 28.2, 38.1, 48.2, 52.9, 83.4, 107.3, 118.6 (q, J=320.5), 140.2, 142.1, 159.1, 161.4; Anal. Calcd for $C_{16}H_{23}F_3N_2O_7S$: C, 43.24; H, 5.22; N, 6.30. Found: C, 43.29; H, 5.37; N, 6.40.

3.2.31. 1-(3-Methylbutyl)-5-phenyl-1*H*-pyrazole-3,4-dicarboxylic acid 4-*tert*-butyl ester 3-methyl ester (36). Compound **35** (0.439 g, 0.998 mmol) was dissolved in 10 mL anhydrous DME and phenylboronic acid (0.181 g, 1.48 mmol), Na_2CO_3 (0.209 g, 1.97 mmol), and $Pd(PPh_3)_4$ (0.057 g, 0.049 mmol) were added sequentially. The resulting orange suspension was purged with nitrogen for 3 min and then was heated at 75 °C for 18 h. The reaction mixture was filtered through Celite and the Celite was washed with EtOAc. The combined filtrate and washings were concentrated in vacuo and purified by chromatography (Superflash cartridge, gradient elution, 0→40% EtOAc in hexanes) to provide **36** (0.338 g, 92%) as a colorless oil: R_f=0.58 (30% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ: 0.78 (6H, d, J=6.7), 1.33 (9H, s), 1.44–1.47 (1H, m), 1.62–1.68 (2H, m), 3.96 (3H, s), 3.99–4.03 (2H, m), 7.33–7.35 (2H, m), 7.46–7.48 (3H, m); ^{13}C NMR ($CDCl_3$) δ: 22.5, 25.9, 28.2, 39.3, 49.0, 52.6, 81.4, 116.2, 128.6, 128.8, 129.7, 129.9, 142.2, 145.1, 161.8, 162.6; Anal. Calcd for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58; N, 7.52. Found: C, 67.87; H, 7.83; N, 7.75.

Acknowledgements

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References and notes

1. Where applicable, the pyrazole compounds described in this work are arbitrarily drawn as their 5-hydroxy tautomers.
2. For other preparations of 1-substituted-5-hydroxy-1*H*-pyrazoles containing carboxylic esters or acids at the 3- and

4-positions, see: (a) Ruhemann, S. *J. Chem. Soc.* **1907**, *91*, 1359; (b) Ruhemann, S. *Proc. Chem. Soc., London* **1908**, *23*, 195.
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4. For other syntheses of 1,5-disubstituted-1*H*-pyrazoles containing carboxylic esters or acids at the 3- and 4-positions, see: (a) Vicentini, C. B.; Mazzanti, M.; Morelli, C. F.; Manfrini, M. *J. Heterocycl. Chem.* **2000**, *37*, 175; (b) Washizuka, K.-I.; Nagai, K.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1999**, *40*, 8849; (c) Veronese, A. C.; Callegari, R.; Morelli, C. F.; Vicentini, C. B. *Tetrahedron* **1997**, *42*, 14497; (d) Kano, K.; Scarpetti, D.; Warner, J. C.; Anselme, J.-P.; Springer, J. P.; Arison, B. H. *Can. J. Chem.* **1986**, *64*, 2211; (e) Schultz, A. G.; Ravichandran, R. *Tetrahedron Lett.* **1981**, *22*, 1771.
5. O-Triflation is inferred by the subsequent transformation of **14a** to the corresponding Suzuki coupling products **23a**–**m**. No attempt was made to quantitate any minor amounts of the corresponding N-triflation product that may also have been formed during the conversion of **13a** to **14a**.
6. This observation also suggests that the acylation of **17** is not dramatically slower than that of **12a**.
7. No attempt was made to quantitate minor amounts of any pyridazinone cyclization products that may have been produced during the conversion of **12a** to **13a**.
8. Adduct **22** was not isolated and rigorously characterized. However, the assignment depicted in Scheme 4 is consistent with: (a) the molecular weight observed by LCMS, (b) the belief that structure **22** is more likely to be detected by TLC analysis than other reaction intermediates or side products which share the same chemical formula (e.g., **18**), and (c) the inability to convert **22** to **13a** by its prolonged exposure to the pyrazole-forming reaction conditions.
9. For reviews of the Suzuki reaction, see: (a) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147; (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
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12. The hydrolysis observed in this example is most likely due to trace amounts of water present in the Na_2CO_3 and the small scale of the experiment.
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14. For example, the yield of **23a** was reduced to 38% when using coupling conditions identical to those listed in Table 1, entry 5 but employing **14a** that had been stored at −20 °C and exposed to the atmosphere five times.
15. The use of DMF as solvent was also examined to improve the coupling of insoluble heterocyclic boronic acids with **14a**. However, this modification did not afford any of the desired products.
16. Initial attempts to couple amines to triflate **14a** using known literature conditions did not afford any of the desired products: (a) Åhman, J.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6363; (b) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268; (c) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264.
17. Pirkle, W. H.; Gravel, P. L. *J. Org. Chem.* **1976**, *23*, 3763.
18. Intermediate **13c** was not purified by chromatography prior to its conversion to triflate **14c**.
19. For example, compound **23a** exhibits the following ^{13}C resonances in $CDCl_3$: 114.4, 142.3, 145.6 (pyrazole carbon atoms), 162.5, and 163.3 (ester carbonyl carbon atoms) ppm. The related 1,5-dimethyl-1*H*-pyrazole-3,4-dicarboxylic acid 3-ethyl ester 4-methyl ester[4c] exhibits corresponding resonances at 112.0, 143.1, 143.6, 162.5, and 163.5 ppm in the same solvent.
20. Methylation of the enol oxygen atom present in **26** is inferred by the close similarity of this molecule's ^1H and ^{13}C NMR spectra with those of **27**. It is expected that other possible methylation products (e.g., methylation of the ester or amide oxygen atoms or the enol carbon atom) would exhibit greater spectral differences when compared with **26**.
21. The formation of an anhydride intermediate following treatment of **23a** with BBr_3 cannot be excluded.
22. The coupling procedure has also been successfully performed in parallel using a Bodan mini-block XT under a nitrogen atmosphere.
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