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Synthesis of Substituted Pyrazoles via Tandem Cross-Coupling/Electrocyclization of Enol Triflates and Diazoacetates

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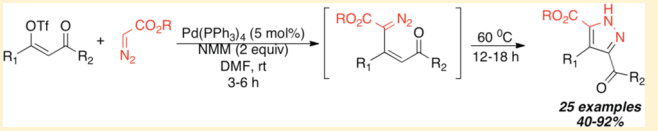
Supporting Information

ABSTRACT: The synthesis of 3,4,5-trisubstituted pyrazoles via a tandem catalytic cross-coupling/electrocyclization of enol triflates and diazoacetates is presented. The initial scope of this methodology is demonstrated on a range of differentially substituted acyclic and cyclic enol triflates as well as an elaborated set of diazoacetates to provide the corresponding pyrazoles with a high degree of structural complexity.



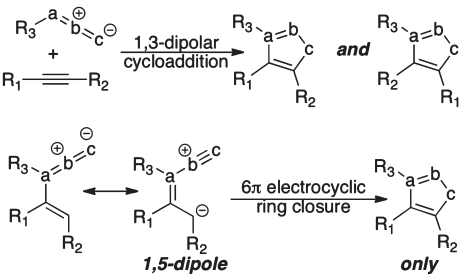
INTRODUCTION

Pericyclic reactions are powerful strategies for the construction of heterocyclic compounds. For example, 1,3-dipolar cycloadditions are rapidly becoming the method of choice for the construction of several classes of azoles including isoxazoles, triazoles, and pyrazoles.[1] However, while dipolar cycloadditions have enjoyed recent success in this arena, the corresponding electrocyclizations toward these heterocycles are much less utilized. A simple excuse for this divergence in utility between these related pericyclic reactions is the relative accessibility of the starting materials for each approach. While methods have been established to access various 1,3-dipoles with relative ease, synthetic approaches to the corresponding 1,5-dipoles are far from comparable. Nonetheless, electrocyclizations offer the promise of absolute regiocontrol in the synthesis of highly substituted azoles presenting an advantage over their pericyclic cousins that is quite obvious in unbiased systems (Scheme 1).[2,3] Thus, methodologies that are able to access 1,5-dipole precursors capable of electrocyclic ring-closure to polysubstituted azoles would provide a complementary approach to these valuable heterocycles.

Pyrazoles have been the recent target of numerous methodologies mostly due to their prevalence as scaffolds in drug discovery programs.[4,5] They have also found use as bifunctional ligands for metal catalysis,[6] as model systems to study excited-state intramolecular proton transfers,[7] as artificial receptors,[8] and as the backbone to numerous scorpionate ligands.[9] Classical approaches to substituted pyrazoles have involved simple condensations of hydrazines with 1,3-dicarbonyls[10] or the aforementioned dipolar cycloadditions.[1,11] Alternative methodologies have evolved that rely on sequential metalations around the pyrazole core,[12] direct C−H bond arylation,[13] or hydrohydrazinations of alkynes.[14] While these methods provide the synthetic chemist with a multitude of choices to construct substituted pyrazoles, almost all of them suffer from either regiochemical infidelity or multistep sequences.

Despite the discovery over 75 years ago that vinyldiazomethane readily undergoes electrocyclic ring closure to form pyrazole,[15] the exploitation of this pericyclic reaction to the synthesis of poly substituted pyrazoles has largely been ignored.[16] In our view, difficulty in acquiring the requisite substituted 3-diazoalkenes (i.e., 1,5-dipoles) has been the overriding limitation with this approach. Given our ability to readily access fully substituted, stereodefined enol triflates from acetoacetate derivatives,[17] we set out to develop a tandem approach involving cross-coupling diazoacetates with enol triflates that would provide substituted diazoalkenes

Scheme 1. Pericyclic Approaches to Azoles



Scheme 2. Electrocyclization Strategies toward Pyrazoles

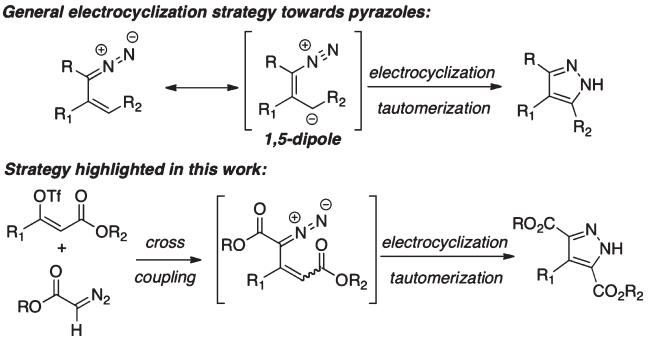


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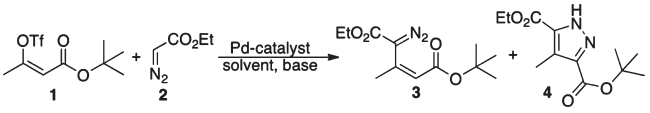
Table 1. Optimization of Cross-Coupling Reaction[a]



entry	catalyst[b]	solvent	base[c]	1[d] (%)	3 (%)	4 (%)
1	$Pd(PCy_3)_2$	CH_3CN	NMM	15		1
2	$Pd(P^tBu_3)_2$			15		1
3	$PdCl_2(dppf)$			22		
4	$Pd(PPh_3)_4$				53	27
5			Et_3N		16	9
6			DBU		2	1
7			Hünig's		56	5
8			K_2CO_3	31	31	7
9		toluene	NMM	33	68	9
10		THF		31	60	10
11		acetone		25	47	7
12	$Pd(PPh_3)_4$	DMF	NMM		70	29
13[e]						84

[a] Reactions performed at ambient temperature for 24 h at 0.2 M using 1.0 equiv of **1**, 1.5 equiv of **2**, and 8 equiv of base. [b] 5 mol %. [c] NMM = *N*-methylmorpholine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [d] HPLC assay yields and percent conversions determined using an analytical

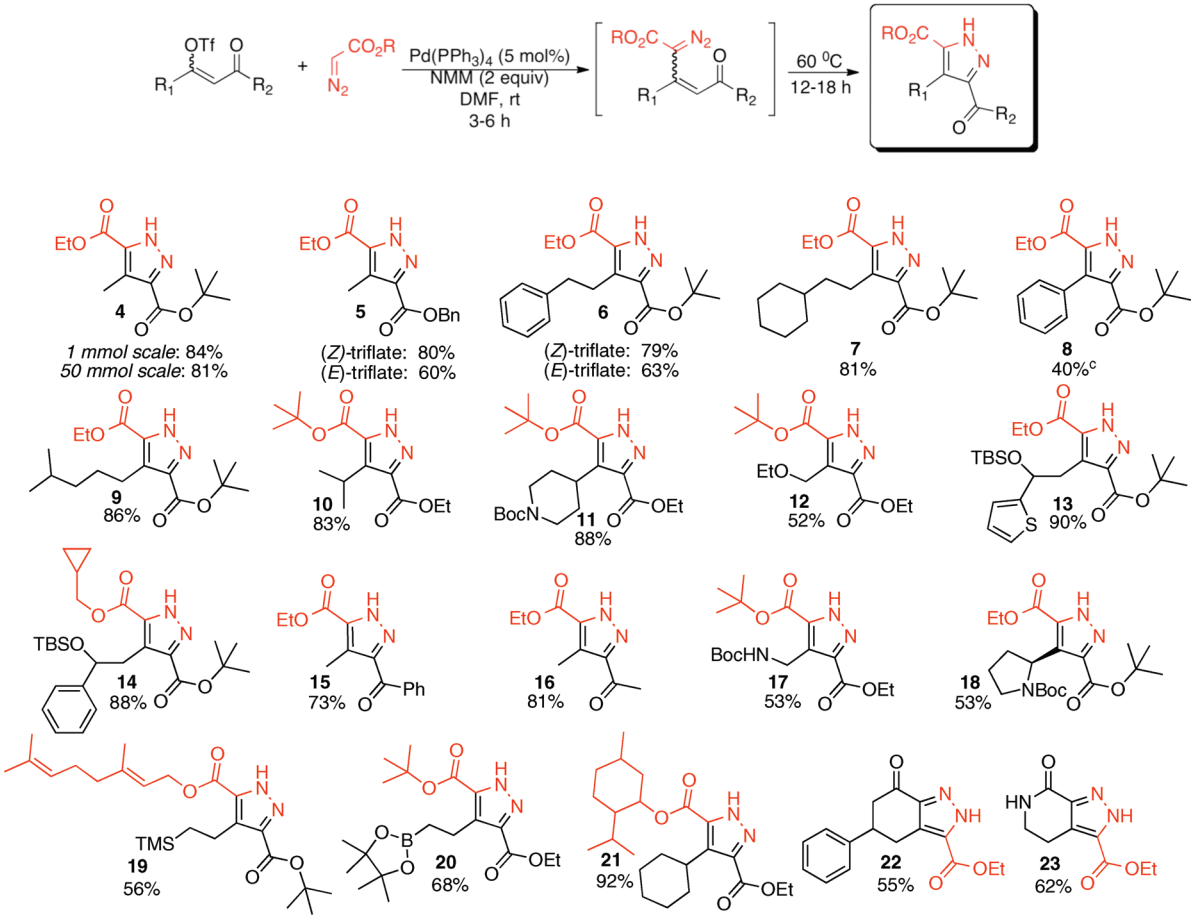
capable of facile electrocyclic ring-closure to 3,4,5-trisubstituted pyrazoles (Scheme 2).

RESULTS AND DISCUSSION

Our first experiments were designed to identify conditions to effectively cross-couple (*Z*)-enol triflate **1** and ethyl diazoacetate **2** and were based on the recent success with activated vinyl iodides.[18] We initially screened several commercially available Pd-catalysts, solvents and bases utilizing a rapid HPLC assay capable of quantifying unreacted **1**, the cross-coupled product **3**, and the corresponding pyrazole **4**. Selected results of this screen are presented in Table 1.[19]

While several catalysts were able to consume the starting triflate (entries 1−3), only $Pd(PPh_3)_4$ proved productive providing the vinyl diazoacetate and corresponding pyrazole in a combined 80% assay yield (entry 4). Further optimization identified DMF as the preferred solvent and *N*-methylmorpholine (NMM) as the ideal base, giving **3** and **4** in essentially quantitative yield (entry 12). We were further pleased to realize that by simply heating these reactions to 60 °C upon completion of the cross-coupling event, the thermal electrocyclization proceeded smoothly to provide pyrazole **4** as the sole product in 84% yield (entry 13).

Table 2. Synthesis of Substituted Pyrazoles via a Tandem Cross-Coupling/Electrocyclization of Enol Triflates and Diazoacetates[a,b]



[a] All reactions were performed at a 1 mmol scale using 1 equiv of (*Z*)-enol triflate, 1.5 equiv of diazoacetate, 2 equiv of *N*-methylmorpholine, and 5 mol % of catalyst at 0.2 M in DMF unless otherwise noted. [b] All yields are an average of two runs except for the 50 mmol scale reaction and **8**. [c] 10 mol % of $Pd(PPh_3)_4$ was used.

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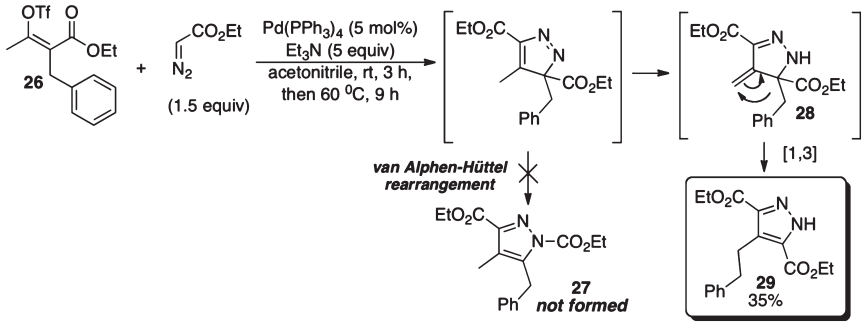
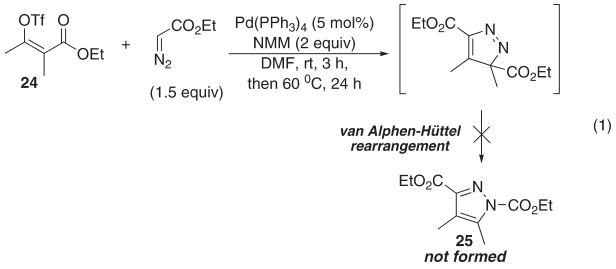
Scheme 3. Unprecedented Rearrangement of 3*H*-Pyrazoles



With these optimized conditions in hand, we turned our attention to more elaborate substrates in an effort to challenge this methodology to rapidly build complexity into our products. In addition, we were interested in the potential reactivity differences between stereoisomeric enol triflates (*Z* vs *E*) since the intramolecular chelation environments after the initial oxidative addition could impart dramatic influences on the catalytic pathway during the cross-coupling event. Furthermore, we wanted to extend the scope of the reaction to enol triflates derived from other 1,3-dicarbonyl derivatives. The culmination of our efforts thus far is highlighted in Table 2.

A broad range of substituted enol triflates and elaborated diazoacetates have been successfully employed in our approach. For example, acyclic enol triflates derived from 1,3-diketones can be utilized with a high degree of success (i.e., **15** and **16**). More importantly, cyclic enol triflates can be engaged to provide fused-bicyclic pyrazoles (**22** and **23**) in a single step that previously required multistep sequences.[20] Furthermore, diversified diazoacetates derived from geraniol and (±)-menthol proved capable in this tandem approach (**19** and **21**). Even boronate esters remain intact under these Pd-mediated conditions to provide pyrazoles capable of further cross-coupling sequences (i.e., **20**). The practicality and simplicity of the reaction is readily apparent by its scalability. In this regard, we have successfully carried out a 50 mmol scale reaction to produce pyrazole **4** in 81% yield. As we expected, we found distinct reactivity differences with respect to the stereochemistry of the starting enol triflate. Although only two examples are presented here (**5** and **6**), we have found that (*E*)-enol triflates provide the pyrazoles in consistently lower yields than their stereoisomeric (*Z*)-enol triflate counterparts. Closer inspection of these reaction via LC/MS analysis reveals that the (*E*)-enol triflates generate a number of olefinic side products during the initial cross-coupling step that are not evident with the (*Z*)-isomers. While we have yet to fully characterize these byproduct, we are intrigued by the potential divergent pathways accessible with stereodefined enol triflates (*E* vs *Z*) that are dictated by the inherent chelation environments of the intermediate cationic vinyl Pd(II) complexes.

In an attempt to generate complete substitution around the pyrazole core, we subjected tetrasubstituted (*Z*)-enol triflate **24** to the reaction conditions with the anticipation of taking advantage of the well-known van Alphen−Hüttel rearrangement[21] to access tetrasubstituted pyrazole **25** (eq 1). However despite our best efforts, we were never able to identify or isolate **25** from the complex product mixture that formed (over four different products were evident by LC/MS). Although discouraged by this initial result, we surveyed several other tetrasubstituted enol triflates including benzyl-substituted (*Z*)-enol triflate **26**. We were surprised to realize that instead of the anticipated acyl-migration to nitrogen via the van Alphen−Hüttel rearrangement, a 1,3-sigmatropic shift of the benzyl group via the presumed enamine intermediate **28** occurred to yield pyrazole **29** in 35% yield (Scheme 3). Similar rearrangements have been observed for 4,4-disubstituted pyrazolines,[22] but as far as we are aware, this is an unprecedented rearrangement of 3*H*-pyrazoles that has peaked our interest. Although the yield in this specific case is less than desirable, the mechanistic implications led us to explore additional substrates that could also participate in this novel rearrangement.



(1)

Thus, based on these results, we explored the tandem cross-coupling/electrocyclization reaction with propargyl-substituted enol triflates **30**−**32** anticipating that the 1,3-alkyl shift may be more facile in these cases.[23] Unexpectedly, the major products isolated from these reactions were allenyl pyrazoles **33**−**35** derived from a surprisingly facile [3,3]-Cope rearrangement (Scheme 4). For enol triflates **30** and **31**, the 1,3-alkyl shift product was formed as the minor product providing an inseparable mixture of the two isomeric pyrazoles in good overall yields. In contrast, enol triflate **32** converted almost exclusively to the allenyl pyrazole (<2% of the 1,3-alkyl shift product was observed in crude reaction mixtures) providing **35** as the sole isolated product in excellent yield (85%). While we have yet to fully exploit this reaction manifold, it appears given our limited set of substrates that the Cope rearrangement is favored when electron-deficient alkynes are incorporated in the starting enol triflate (as in **32**), while the [1,3]-alkyl shift is competitive with the Cope rearrangement when electron-rich acetylenes are used (as in **30**). We are actively looking into the dynamics of these diverging sigmatropic pathways through both experimental and theoretical studies that will shed additional light on the electronic preferences inherent in each.

Finally, we were intrigued by previous reports from Larock on the propensity of acyl migration from carbon to nitrogen en route to substituted indazoles.[24] During the course of their work on the

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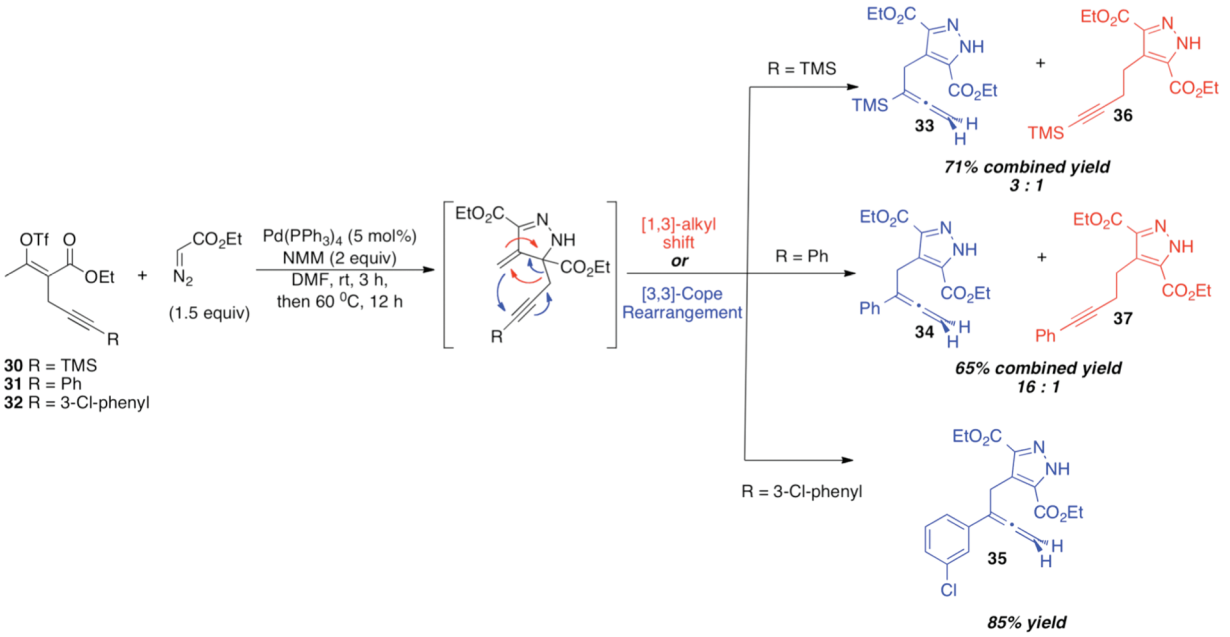
Scheme 4. Diverging Sigmatropic Rearrangements of Propargyl-Substituted 3*H*-Pyrazoles



cycloaddition between benzyne derivatives and diazo carbonyl compounds, they were able to demonstrate that ketone carbonyls migrate from carbon to nitrogen during the rearomatization process much more readily than ester carbonyls. We have observed the same phenomenon in our methodology as well. For example, we synthesized several fully substituted (*Z*)-enol triflates derived from 2,4-pentanedione and subjected them to our reaction conditions. We were pleased to observe clean acyl migration from carbon to nitrogen to provide the corresponding trisubstituted pyrazoles after a simple basic workup to drive the deacylation to completion (Table 3).

CONCLUSION

In summary, we believe this practical approach to substituted pyrazoles via a tandem cross-coupling/electrocyclization will prove useful in the development of new scaffolds for compound libraries and ligand design for metal catalysis. Efforts are underway to expand this approach to other 1,5-dipoles as well as delineating the mechanistic dichotomy between the divergent sigmatropic pathways presented in Scheme 4.

EXPERIMENTAL SECTION

General Information. The enol triflate starting materials were prepared according to either method A or method B as described below. Ethyl diazoacetate and $Pd(PPh_3)_4$ were obtained from commercial sources and were used without further purification. All other diazoacetates were prepared according to known literature procedures.[25,26] The cross-coupling reactions described here were performed under a nitrogen atmosphere using solvents and amine bases that were dried over 4 Å molecular sieves (typical water content by Karl Fischer titration <500 ppm). TLC analysis was performed on silica gel 60, aluminum backed TLC plates. The pyrazole products were purified via silica gel (230−400 mesh) column chromatography. Final products were characterized by LC/MS (low resolution mass spectroscopy, ESI ionization), and ^1H and ^{13}C NMR for structural assignment. LC/MS data was acquired on an HPLC equipped with a diode array detector and a single-quad mass spectrometer with a multimode ion source capable of both low-resolution ESI and APCI (positive and negative ionization). NMR spectra were obtained on either a 300 MHz or a 500 MHz spectrometer.

Procedures for the Synthesis of (*Z*)-Enol Triflates. Method A (Based on Our Previously Published Method).[17] To a round-bottom flask were added β-ketoester (1 equiv) and toluene to generate a 0.2 M solution. The solution was cooled in an ice bath (~10 °C), and aqueous LiOH (5 M solution in water, 7.5 equiv) was added in one portion. After the solution was stirred for 5 min, Tf_2O (2 equiv) was slowly added to maintain the reaction temperature <25 °C. Upon completion (as judged by TLC), the reaction was diluted with water, and the layers were separated. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. Purification, if needed, was performed using silica gel column chromatography to give the desired (*Z*)-enol triflate.

Method B. To a round-bottom flask was added sodium hydride (1.1 equiv) followed by a purge with nitrogen for ~15 min. To the flask was added dichloromethane (0.2 M with respect to β-ketoester) and the mixture cooled to 0 °C. The desired β-ketoester (1 equiv) was added, dropwise, and the mixture stirred for 15 min. Tf_2O (1.5 equiv) was added dropwise, and the reaction was allowed to warm to room temperature. Upon completion (as judged by TLC), the reaction was diluted with water and the organic layer separated, washed with brine, dried, and concentrated. Purification via silica gel column chromatography gave the desired (*Z*)-enol triflate. In general, this method gives mixtures of both (*Z*)- and (*E*)-enol triflates but was found to be suitable for substrates that fail using method A.

General Procedure for the Synthesis of 3,4,5-Trisubstituted Pyrazoles. To a round-bottom flask was added $Pd(PPh_3)_4$ (58 mg, 0.05 mmol, 5 mol %), capped with a rubber septum, and purged with nitrogen. DMF (5 mL) was added, followed by (*Z*)-enol triflate (1.0 mmol), *N*-methylmorpholine (0.22 mL, 2.0 mmol), and diazoacetate (1.5 mmol) via syringe. The reaction was stirred at room temperature and monitored for consumption of the enol triflate. Upon completion of the cross-coupling (as judged by TLC and LC/MS analysis), the reaction was heated to 60 °C until the intermediate vinyl diazoacetate was consumed. (For the deacylation procedure for the pyrazoles presented in Table 3, a 2.5 M solution of aqueous K_2CO_3 (5 equiv) was added directly to the reaction mixture and stirred at room temperature until complete prior to

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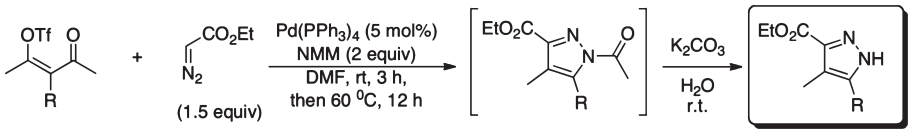
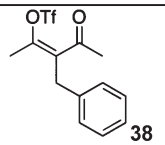
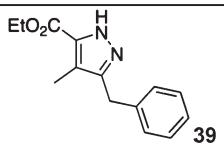
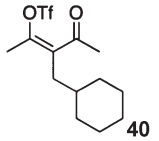
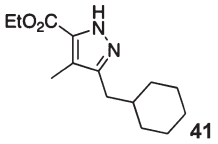
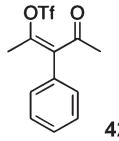
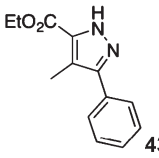
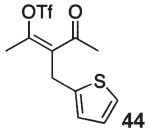
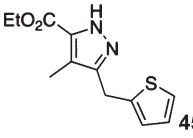
Table 3. Reactions with Tetrasubstituted Enol Triflates Derived from 2,4-Pentanedione[a]



entry	enol triflate	product[b]	yield[c]
1	 **38**	 **39**	74%
2	 **40**	 **41**	72%
3	 **42**	 **43**	87%
4	 **44**	 **45**	83%

[a] All reactions were performed at a 1 mmol scale using 1 equiv of (*Z*)-enol triflate, 1.5 equiv of diazoacetate, 2 equiv of *N*-methylmorpholine, and 5 mol % of catalyst at 0.2 M in DMF unless otherwise noted. [b] In each case, ~20−40% deacylation occurred during the course of the reaction. Thus, at the end of each reaction, 2.5 M K_2CO_3 (5 equiv) was added and the mixture stirred at room temperature to drive the deacylation to completion. [c] All yields reported are an average of two runs.

purification). The reaction was cooled to room temperature, transferred directly to a silica gel column, and eluted with EtOAc/hexanes. For large-scale reactions, DMF was removed via distillation, and the resultant crude oil was purified on a silica gel column.

Spectroscopic Analysis. Because of the dynamic tautomeric forms that NH-pyrazoles can adopt, their absolute spectroscopic analysis is convoluted and they often exhibit concentration-dependent NMR spectra.[27] The biggest effect can be seen in the ^{13}C NMR, in which the C-3 and C-5 carbons appear as very broad signals that are unresolved from the baseline. To circumvent this issue, salt forms (either via protonation or deprotonation) can be generated to provide spectra where all carbons can be accounted for. For example, compound **5** was treated with KO^{t}Bu to generate the corresponding potassium salt as a crystalline compound. This salt was analyzed by ^{13}C NMR to give a ^{13}C spectrum that provides much sharper singlets for both C-3 and C-5 as compared to the parent pyrazole. This example is provided as additional support for characterization of the pyrazole products via ^{13}C NMR. In some cases, trifluoroacetic acid was also added to help resolve the tautomeric issues by generating a salt in situ (i.e., pyrazole **23**). All other compounds are reported as the parent pyrazole.

*3-tert-Butyl 5-Ethyl 4-Methyl-1H-pyrazole-3,5-dicarboxylate (**4**).* Prepared from (*Z*)-*tert*-butyl 3-(trifluoromethylsulfonyloxy)but-2-enoate (synthesized using method A above) and ethyl diazoacetate to yield 84% of the title compound as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 10.81 (bs, 1H), 4.41 (q, J = 7.3 Hz, 2H), 2.54 (s, 3H), 1.63 (s, 9H), 1.43 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.6, 159.9, 124.3, 83.0, 61.2, 28.5, 14.5, 9.8. LC/MS: pos-MS = 277.1 (M + Na), neg-MS = 253.1 (M − H). Mp = 121−124 °C. HRMS-ESI (m/z): calcd for $C_{12}H_{18}N_2O_4$ (M + H) 255.1345, found 255.1360.

*3-Benzyl 5-Ethyl 4-Methyl-1H-pyrazole-3,5-dicarboxylate (**5**).* Prepared from (*Z*)-benzyl 3-(trifluoromethylsulfonyloxy)but-2-enoate (synthesized using method A above) and ethyl diazoacetate to yield 80% of the title compound as a yellow solid. Prepared from (*E*)-benzyl 3-(trifluoromethylsulfonyloxy)but-2-enoate and ethyl diazoacetate to yield 60% of the title compound as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 10.87 (bs, 1H), 7.47−7.34 (m, 5H), 5.40 (s, 2H), 4.41 (q, J = 7.3 Hz, 2H), 2.58 (s, 3H), 1.43 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.9, 135.3, 128.5, 128.5, 128.4, 125.0, 66.8, 61.2, 14.2, 9.5. LC/MS: pos-MS = 289.1 (M + H), 311.1 (M + Na), neg-MS = 287.1 (M − H). Mp = 84−87 °C. HRMS-ESI (m/z): calcd for $C_{15}H_{16}N_2O_4$ (M + H) 289.1188, found 289.1222.

Potassium 3-(Benzyloxycarbonyl)-5-(ethoxycarbonyl)-4-methylpyrazol-1-ide. Compound **5** (0.173 mmol) was added to a 20 mL scintillation vial and dissolved in THF (1 mL). The solution was stirred, and KO^{t}Bu (1 M in THF) was added dropwise at room temperature. The reaction was stirred for 45 min then concentrated under reduced pressure to yield a white crystalline solid. ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ = 164.5, 164.2, 140.6, 140.2, 137.5, 128.3, 127.7, 127.6, 124.0, 63.9, 58.2, 14.5, 10.8.

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*5-tert-Butyl 3-Ethyl 4-Phenethyl-1H-pyrazole-3,5-dicarboxylate (**6**).* Prepared from (*Z*)-*tert*-butyl 5-phenyl-3-(((trifluoromethyl)sulfonyl)-oxy)pent-2-enoate (synthesized using method A above) and ethyl diazoacetate to yield 79% of the title compound as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.37 (bs, 1H), 7.26−7.30 (m, 2H), 7.17−7.23 (m, 3H), 4.41 (q, *J* = 7.2 Hz, 2H), 3.34 (t, *J* = 8.0 Hz, 2H), 2.87 (t, *J* = 8.0 Hz, 2H), 1.61 (s, 9H), 1.42 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.7, 156.0, 141.9, 139.2, 136.7, 128.8, 128.5, 128.1, 126.1, 83.0, 61.3, 37.3, 28.5, 26.0, 14.5. LC/MS: pos-MS = 367.1 (M + Na), neg-MS = 343.2 (M-H). mp =100−103 °C. HRMS-ESI (*m*/*z*): calcd for $C_{19}H_{24}N_2O_4$ (M + H) 345.1814, found 345.1818.

*3-tert-Butyl 5-Ethyl 4-(2-Cyclohexylethyl)-1H-pyrazole-3,5-dicarboxylate (**7**).* Prepared from (*Z*)-*tert*-butyl 5-cyclohexyl-3-trifluoromethanesulfonyloxy-2-pentenoate (synthesized using method A above) and ethyl diazoacetate to yield 81% of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.39 (q, *J* = 7.1 Hz, 2H), 2.97−3.00 (m, 2H), 1.77 (bd, *J* = 13.0 Hz, 2H), 1.66−1.69 (m, 2H), 1.60−1.63 (m, 1H), 1.57 (s, 9H), 1.37−1.41 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.08−1.31 (m, 4H), 0.95 (bq, *J* = 12.0, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.6, 160.0, 138.9, 136.2, 129.6, 82.8, 61.1, 38.8, 38.3, 33.3, 28.3, 26.7, 26.5, 21.5, 14.3. LC/MS: pos-MS = 373.2 (M + Na), neg-MS = 349.3 (M − H). HRMS-ESI (*m*/*z*): calcd for $C_{19}H_{30}N_2O_4$ (M + H) 351.2284, found 351.2289.

*3-tert-Butyl 5-Ethyl 4-Phenyl-1H-pyrazole-3,5-dicarboxylate (**8**).* Prepared from (*Z*)-*tert*-butyl 3-phenyl-3-(((trifluoromethyl)sulfonyl)oxy)-acrylate (synthesized using method A above) and ethyl diazoacetate to yield 40% of the title compound as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.43 (bs, 1H), 7.34−7.39 (m, 3H), 7.29−7.30 (m, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.34 (s, 9H), 1.19 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.0, 159.4, 131.3, 130.2, 127.7, 127.5, 127.4, 82.9, 61.2, 27.9, 14.0. LC/MS: pos-MS = 339.1 (M + Na), neg-MS = 315.2 (M − H). HRMS-ESI (*m*/*z*): calcd for $C_{17}H_{20}N_2O_4$ (M + H) 317.1501, found 317.1493.

*3-tert-Butyl 5-Ethyl 4-(4-Methylpentyl)-1H-pyrazole-3,5-dicarboxylate (**9**).* Prepared from (*Z*)-*tert*-butyl-7-methyl-3-trifluoromethanesulfonyloxy-2-octenoate (synthesized using method A above) and ethyl diazoacetate to yield 86% of the title compound as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.78 (bs, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 2.97−3.02 (m, 2H), 1.63 (s, 9H), 1.56 (m, 3H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.23−1.31 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.6, 159.8, 129.1, 82.9, 61.2, 39.2, 29.1, 28.4, 28.2, 24.1, 22.8, 14.5. LC/MS: pos-MS = 347.2 (M + Na), neg-MS = 323.2 (M − H). HRMS-ESI (*m*/*z*): calcd for $C_{17}H_{28}N_2O_4$ (M + H) 325.2127, found 325.2141.

*5-tert-Butyl 3-Ethyl 4-Isopropyl-1H-pyrazole-3,5-dicarboxylate (**10**).* Prepared from ((*Z*)-ethyl 4-methyl-3-(trifluoromethylsulfonyloxy)pent-2-enoate (synthesized using method A above) and *tert*-butyl diazoacetate to yield 83% of the title compound as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.77 (bs, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.93 (septet, *J* = 7.2 Hz, 1H), 1.58 (s, 9H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.32 (d, *J* = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.6, 159.8, 134.2, 83.1, 61.3, 28.4, 23.6, 21.3, 14.4. LC/MS: pos-MS = 305.1 (M + Na), neg-MS = 281.2 (M − H). mp =88−91 °C. HRMS-ESI (*m*/*z*): calcd for $C_{14}H_{22}N_2O_4$ (M + H) 283.1658, found 283.1657.

*5-tert-Butyl 3-Ethyl 4-(1-(tert-Butoxycarbonyl)piperidin-4-yl)-1H-pyrazole-3,5-dicarboxylate (**11**).* Prepared from (*Z*)-*tert*-butyl 4-(3-ethoxy-3-oxo-1-(((trifluoromethyl)sulfonyl)oxy)prop-1-en-1-yl)piperidine-1-carboxylate (synthesized using method A above) and *tert*-butyl diazoacetate to yield 88% of the title compound as a light orange foam. ^{1}H NMR (300 MHz, CD_3OD): δ = 4.37 (q, *J* = 7.0 Hz, 2H), 4.14−4.24 (m, 2H), 3.82 (tt, *J* = 3.6 Hz, 12.6 Hz, 1H), 2.81 (bs, 2H), 2.27 (dq, *J* = 4.3 Hz, 12.6 Hz, 2H), 1.61 (s, 9H), 1.52−1.58 (m, 2H), 1.49 (s, 9H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.8, 159.9, 154.9, 130.8, 83.4, 79.4, 61.4, 45.2, 44.4, 32.3, 29.8, 28.7, 28.4, 14.3. LC/MS: pos-MS = 446.2 (M + Na), neg-MS = 422.3 (M − H). Mp = 65−70 °C. HRMS-ESI (*m*/*z*): calcd for $C_{21}H_{33}N_3O_6$ (M + H) 424.2448, found 424.2462.

*5-tert-Butyl 3-Ethyl 4-(Ethoxymethyl)-1H-pyrazole-3,5-dicarboxylate (**12**).* Prepared from (*Z*)-ethyl 4-ethoxy-3-(((trifluoromethyl)sulfonyl)-oxy)but-2-enoate (synthesized using method A above) and *tert*-butyl diazoacetate to yield 52% of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.87 (bs, 1H), 4.86 (s, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.60 (q, *J* = 7.0 Hz, 2H), 1.62 (s, 9H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.1, 159.4, 123.0, 83.1, 65.9, 61.2, 60.4, 28.1, 15.2, 14.1. LC/MS: pos-MS = 321.2 (M + Na), neg-MS = 297.2 (M − H). HRMS-ESI (*m*/*z*): calcd for $C_{14}H_{22}N_2O_5$ (M + H) 299.1607, found 299.1614.

*3-tert-Butyl 5-Ethyl 4-(2-((tert-Butyldimethylsilyl)oxy)-2-(thiophene-2-yl)ethyl)-1H-pyrazole-3,5-dicarboxylate (**13**).* Prepared from (±)-(*Z*)-*tert*-butyl 5-((*tert*-butyldimethylsilyl)oxy)-5-(thiophene-2-yl)-3-(((trifluoromethyl)sulfonyl)oxy)pent-2-enoate (synthesized using method A above) and ethyl diazoacetate to give 90% of the title compound as a low melting, light orange foam. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.92 (bs, 1H), 7.18 (d, *J* = 5.1 Hz, 1H), 6.91 (dd, *J* = 3.5 Hz, 5.1 Hz, 1H), 6.85 (d, *J* = 3.5 Hz, 1H), 5.28 (dd, *J* = 4.2 Hz, 9.7 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 3.69 (dd, *J* = 9.7 Hz, 13.14 Hz, 1H), 3.29 (dd, *J* = 4.2 Hz, 13.14 Hz, 1H), 1.64 (s, 9H), 1.46 (t, *J* = 7.1 Hz, 3H), 0.74 (s, 9H), −0.20 (s, 3H), −0.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.8, 159.9, 150.1, 126.2, 124.5, 123.7, 122.7, 83.1, 71.0, 61.3, 35.4, 28.4, 25.7, 18.0, 14.5, −5.2, −5.4. LC/MS: pos-MS = 503.2 (M + Na), neg-MS = 479.2 (M − H). HRMS-ESI (*m*/*z*): calcd for $C_{23}H_{36}N_2O_5SSi$ (M + H) 481.2192, found 481.2189.

*3-tert-Butyl 5-(Cyclopropylmethyl) 4-(2-((tert-Butyldimethylsilyl)oxy)-2-phenylethyl)-1H-pyrazole-3,5-dicarboxylate (**14**).* Prepared from (±)-(*Z*)-*tert*-butyl 5-((*tert*-butyldimethylsilyl)oxy)-5-phenyl-3-(((trifluoromethyl)-sulfonyl)oxy)pent-2-enoate (synthesized using method A above) and cyclopropylmethyl diazoacetate to yield 88% of the title compound as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.92 (bs, 1H), 7.39−7.42 (m, 2H), 7.29−7.32 (m, 2H), 7.20−7.25 (m, 1H), 5.00 (dd, *J* = 4.0 Hz, 9.8 Hz, 1H), 4.21 (d, *J* = 7.4 Hz, 2H), 3.57 (dd, *J* = 9.8 Hz, 13.3 Hz, 1H), 3.22 (dd, *J* = 4.0 Hz, 13.3 Hz, 1H), 1.62 (s, 9H), 1.28−1.35 (m, 1H), 0.70 (s, 9H), 0.63−0.67 (m, 2H), 0.39−0.42 (m, 2H), −0.32 (s, 3H), −0.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.8, 159.9, 145.7, 128.1, 127.0, 125.9, 125.5, 82.9, 74.8, 70.1, 35.0, 28.4, 25.8, 18.0, 10.1, 3.7, −5.0, −5.3. LC/MS: pos-MS = 523.3 (M + Na), neg-MS = 499.3 (M − H). HRMS-ESI (*m*/*z*): calcd for $C_{27}H_{40}N_2O_5Si$ (M + H) 501.2785, found 501.2786.

*Ethyl 3-Benzoyl-4-methyl-1H-pyrazole-5-carboxylate (**15**).*[28]. Prepared from (*Z*)-4-oxo-4-phenylbut-2-en-2-yl trifluoromethanesulfonate (synthesized using method A above) and ethyl diazoacetate to yield 73% of the title compound as a tan solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 4.47 (q, *J* = 7.1 Hz, 2H), 2.60 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$,): δ = 189.0, 160.1, 137.6, 132.8, 130.3, 128.3, 125.2, 61.7, 14.5, 10.2. LC/MS: pos-MS = 259.1 (M + H), 281.0 (M + Na), neg-MS = 257.1 (M − H). Mp =118−120 °C. HRMS-ESI (*m*/*z*): calcd for $C_{14}H_{14}N_2O_3$ (M + H) 259.1083, found 259.1095.

*Ethyl 3-Acetyl-4-methyl-1H-pyrazole-5-carboxylate (**16**)*[29]. Prepared from (*Z*)-4-oxopent-2-en-2-yl trifluoromethanesulfonate (synthesized using method A above) and ethyl diazoacetate to yield 81% of the title compound as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.83 (bs, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 2.62 (s, 3H), 2.59 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.0, 160.6, 148.9, 133.5, 123.8, 61.8, 27.9, 14.4, 9.9. LC/MS: pos-MS = 197.1 (M + H), 219.1 (M + Na), neg-MS = 195.1 (M − H). Mp = 118−122 °C.

*5-tert-Butyl 3-Ethyl 4-((tert-Butoxycarbonylamino)methyl)-1H-pyrazole-3,5-dicarboxylate (**17**).* Prepared from (*Z*)-ethyl 4-(*tert*-

butoxycarbonylamino)-3-(trifluoromethylsulfonyloxy)but-2-enoate (synthesized using method A above) and *tert*-butyl diazoacetate to yield 53% of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.49 (t, J = 6.1 Hz, 1H), 4.68 (d, J = 6.1 Hz, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.61 (s, 9H), 1.38−1.41 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$,): δ =161.5, 159.7, 155.5, 139.4, 137.44, 124.4, 83.9, 79.2, 61.7, 33.4, 28.5, 28.3, 14.3. LC/MS: pos-MS = 392.2 (M + Na), neg-MS = 368.2 (M − H). HRMS-ESI (m/z): calcd for $C_{17}H_{27}N_3O_6$ (M + H) 370.1978, found 370.1977.

*(S)-3-tert-Butyl 5-Ethyl 4-(1-(tert-Butoxycarbonyl)pyrrolidin-2-yl)-1H-pyrazole-3,5-dicarboxylate (**18**).* Prepared from (*S*,*Z*)-*tert*-butyl 2-(3-(*tert*-butoxy)-3-oxo-1-(((trifluoromethyl)sulfonyl)oxy)prop-1-en-1-yl)pyrrolidine-1-carboxylate (synthesized using method A above) and ethyl diazoacetate to yield 53% of the title compound as a yellow foam. ^{1}H NMR (300 MHz, CD_3OD): δ = 5.48 (t, J = 8.4 Hz, 1H), 4.29−4.42 (m, 2H), 3.50−3.70 (m, 2H), 2.16−2.37 (m, 1H), 1.77−2.14 (m, 2H), 1.59 (s, 9H), 1.34−1.40 (m, 3H), 1.12 (s, 9H). LC/MS: pos-MS = 410.2 (M + H), 432.2 (M + Na), neg-MS = 408.2 (M − H). Mp = 58−64 °C. HRMS-ESI (m/z): calcd for $C_{20}H_{31}N_3O_6$ (M + H) 410.2291, found 410.2293. The ^{13}C spectrum for this compound was complicated by the existence of multiple rotamers. However, the removal of the Boc-protecting group and *tert*-butyl ester to provide the amino acid provided much cleaner NMR spectra. Thus, compound **18** (0.05 mmol) taken up in CH_2Cl_2 (0.5 mL), TFA (∼15 drops) was added, and the mixture was stirred overnight. Removal of the solvent and azeotrope with toluene gave the corresponding amino acid as a white solid. ^{1}H NMR (300 MHz, CD_3OD): δ = 5.45−5.55 (m, 1H), 4.43 (q, J = 7.1 Hz, 2H), 3.61−3.73 (m, 1H), 3.41−3.52 (m, 1H), 2.03−2.23 (m, 2H), 2.24−2.35 (m, 1H), 2.36−2.50 (m, 1H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ = 164.1, 162.6, 121.7, 62.9, 55.2, 46.8, 33.01, 25.6, 14.5. LC/MS: pos-MS = 254.4 (M + H), 276.1 (M + Na), neg-MS = 252.1 (M-H).

*(E)-3-tert-Butyl 5-(3,7-Dimethylocta-2,6-dienyl) 4-(2-(trimethylsilyl)-ethyl)-1H-pyrazole-3,5-dicarboxylate (**19**).* Prepared from (*Z*)-*tert*-butyl 3-(trifluoromethylsulfonyloxy)-5-(trimethylsilyl)pent-2-enoate (synthesized using method A above) and (*E*)-3,7-dimethylocta-2,6-dienyl 2-diazoacetate to yield 56% of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ =10.75 (bs, 1H), 5.48 (bt, J = 6.1 Hz, 1H), 5.10 (t, J = 6.1 Hz, 1H), 4.89 (d, J = 6.9 Hz, 2H), 2.98−3.02 (m, 2H), 2.05−2.14 (m, 4H), 1.76 (s, 3H), 1.68 (s, 3H), 1.62 (s, 9H), 1.61 (s, 3H), 0.79−0.83 (m, 2H), 0.07 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.5, 160.0, 142.7, 132.0, 131.9, 123.9, 118.3, 82.7, 62.1, 39.7, 28.5, 26.5, 25.7, 18.9, 18.2, 17.8, 16.7, −1.6. LC/MS: pos-MS = 471.2 (M + Na), neg-MS = 447.3 (M − H). HRMS-ESI (m/z): calcd for $C_{24}H_{40}N_2O_4Si$ (M + H) 449.2836, found 449.2839.

*5-tert-Butyl 3-Ethyl 4-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)-1H-pyrazole-3,5-dicarboxylate (**20**).* Prepared from (*Z*)-ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(((trifluoromethyl)-sulfonyl)oxy)pent-2-enoate (synthesized using method B above) and *tert*-butyl diazoacetate to yield 68% of the title compound as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.00 (bs, 1H), 4.40 (q, J = 7.1 Hz, 2H), 3.07−3.12 (t, J = 8.4 Hz, 2H), 1.61 (s, 9H), 1.41 (t, J = 7.1 Hz, 3H), 1.21 (s, 12H), 1.06−1.11 (t, J = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$,): δ = 161.5, 159.8, 138.7, 136.2, 130.8, 83.0, 82.7, 61., 28.3, 25.0, 18.2, 14.3, 13.1. LC/MS: pos-MS = 417.2 (M + Na), neg-MS = 393.2 (M − H). HRMS-ESI (m/z): calcd for $C_{19}H_{31}BN_2O_6$ (M + H) 395.2353, found 395.2349.

*3-Ethyl 5-(2-Isopropyl-5-methylcyclohexyl) 4-Cyclohexyl-1H-pyrazole-3,5-dicarboxylate (**21**).* Prepared from (*Z*)-ethyl 3-cyclohexyl-3-(trifluoromethylsulfonyloxy)acrylate (synthesized using method A above) and 2-isopropyl-5-methylcyclohexyl 2-diazoacetate to yield 92% of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.82 (bs, 1H), 4.98 (bt, J = 10.9 Hz, 1H), 4.41 (q, J = 7.4 Hz, 2H), 3.59 (bt, J = 11.9 Hz, 1H), 2.12−2.17 (m, 1H), 1.91−2.07 (m, 3H), 1.78−1.85 (bs, 2H), 1.69−1.77 (m, 3H), 1.50−1.64 (m, 5H), 1.43 (t, J = 7.4 Hz, 3H), 1.31−1.38 (m, 3H), 1.14 (pentet, J = 11.8 Hz, 2H), 0.90−0.95 (m, 8H), 0.79 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 161.4, 160.6, 133.8, 128.7, 127.1, 75.8, 61.4, 47.2, 41.1, 34.3, 34.1, 31.6, 30.7, 27.2, 27.1, 26.4, 25.9, 23.5, 22.1, 20.9, 16.3, 14.4. LC/MS: pos-MS = 427.3 (M + Na), neg-MS = 403.3 (M − H). mp =72−75 °C. HRMS-ESI (m/z): calcd for $C_{23}H_{36}N_2O_4$ (M + H) 405.2753, found 405.2746.

*Ethyl 7-Oxo-5-phenyl-2H-indazole-3-carboxylate (**22**).* Prepared from (±)-5-phenyl-1-trifluoromethanesulfonyloxy-3-oxo-cyclohexene (synthesized using method B above) and ethyl diazoacetate to yield 52% of the title compound as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.63 (bs, 1H), 7.35−7.40 (m, 2H), 7.29−7.32 (m, 3H), 4.42 (q, J = 7.2 Hz, 2H), 3.48−3.57 (m, 2H), 3.05−3.13 (m, 1H), 2.86−2.94 (m, 2H), 1.40 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.4, 161.5, 142.7, 130.8, 128.9, 127.3, 126.9, 61.5, 45,7, 43.0, 29.3, 14.4. LC/MS: pos-MS = 285.1 (M + H), 307.1 (M + Na), neg-MS = 283.1 (M − H). Mp =132−136 °C. HRMS-ESI (m/z): calcd for $C_{16}H_{17}N_2O_3$ (M + H) 285.1239, found 285.1273.

*Ethyl 7-Oxo-4,5,6,7-tetrahydro-2H-pyrazolo[3,4-c]pyridine-3-carboxylate (**23**).* Prepared from 6-oxo-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (synthesized using method A above) and ethyl diazoacetate to yield 62% of the title compound as an orange solid. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ = 14.31 (bs, 1H), 7.81 (bs, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.37−3.45 (m, 2H), 2.90 (t, J = 6.8 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $(CD_3)_2SO$ with excess TFA): δ = 161.4, 160.5, 138.7, 135.9, 124.6, 61.0, 41.4, 21.1, 14.6. TFA resonances: 159.1 (q, J = 38.6), 115.6 (q, J = 287.8). LC/MS: pos-MS = 210.1 (M + H), 232.1 (M + Na), neg-MS = 207.9 (M − H). Mp = 288−291 °C. HRMS-ESI (m/z): calcd for $C_9H_{11}N_3O_3$ (M_2 + Na) 441.1499, found 441.1504.

*Diethyl 4-Phenethyl-1H-pyrazole-3,5-dicarboxylate (**29**).* Prepared from (*Z*)-ethyl 2-benzyl-3-(((trifluoromethyl)sulfonyl)oxy)but-2-enoate (**26**) (synthesized using method A above) and ethyl diazoacetate using triethylamine instead of *N*-methylmorpholine and acetonitrile instead of DMF. Obtained 35% of the title compound as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29−7.25 (m, 2H), 7.23−7.17 (m, 3H), 4.41 (q, J = 7.2 Hz, 4H), 3.35 (t, J = 8.0 Hz, 2H), 2.86 (t, J = 8.0 Hz, 2H), 1.42 (t, J = 7.2 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.9, 141.8, 137.6, 128.7, 128.4, 126.1, 61.7, 37.2, 26.3, 14.7. LC/MS: pos-MS = 317.2 (M + H), 339.1 (M + Na), neg-MS = 315.1 (M − H). Mp = 110−113 °C. HRMS-ESI (m/z): calcd for $C_{17}H_{20}N_2O_4$ (M + H) 317.1501, found 317.1520.

*Diethyl 4-(2-(Trimethylsilyl)buta-2,3-dien-1-yl)-1H-pyrazole-3,5-dicarboxylate (**33**).* Prepared from (*Z*)-ethyl 2-(1-(((trifluoromethyl)-sulfonyl)oxy)ethylidene)-5-(trimethylsilyl)pent-4-ynoate (**30**) (synthesized using method A above) and ethyl diazoacetate to yield 71% of a 3:1 mixture of the title compound and TMS-acetylene **36**. Data for **33**. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.33−4.41 (q, J = 7.1 Hz, 4H), 4.07 (t, J = 4.0 Hz, 2H), 3.72 (t, J = 4.0 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H), 0.16 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.9, 161.0, 137.8, 127.3, 126.4, 106.2, 94.8, 71.1, 61.5, 23.1, 14.6, −1.4. LC/MS: pos-MS = 337.1 (M + H), 359.1 (M + Na), neg-MS = 335.1 (M − H). HRMS-ESI (m/z): calcd for $C_{16}H_{24}N_2O_4Si$ (M + H) 337.1584, found 337.1585.

*Diethyl 4-(2-Phenylbuta-2,3-dien-1-yl)-1H-pyrazole-3,5-dicarboxylate (**34**).* Prepared from (*Z*)-ethyl 5-phenyl-2-(1-(((trifluoromethyl)sulfonyl)-oxy)ethylidene)pent-4-ynoate (**31**) (synthesized using method A above) and ethyl diazoacetate to yield 65% of a 16:1 mixture of the title compound and phenyl-acetylene **37**. Data for **34**. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.02 (bs, 1H), 7.50 (bd, J = 7.8 Hz, 2H), 7.36 (t, J = 7.7 Hz, 2H), 7.25 (t, J = 7.3 Hz, 1H), 4.80 (t, J = 4.1 Hz, 2H), 4.38 (q, J = 7.1 Hz, 4H), 4.23 (t, J = 4.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.9, 160.8, 136.3, 128.3, 126.8, 125.9, 79.9, 61.5, 14.3. LC/MS: pos-MS = 341.1 (M + H), 363.1 (M + Na), neg-MS = 339.1 (M − H). HRMS-ESI (m/z): calcd for $C_{19}H_{20}N_2O_4$ (M + H) 341.1501, found 341.1545.

*Diethyl 4-(2-(3-Chlorophenyl)buta-2,3-dien-1-yl)-1H-pyrazole-3,5-dicarboxylate (**35**).* Prepared from (*Z*)-ethyl 5-(3-chlorophenyl)-

2-(1-(((trifluoromethyl)sulfonyl)oxy)ethylidene)pent-4-ynoate (**32**) (synthesized using method A above) and ethyl diazoacetate to yield 85% of the title compound as a light yellow amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.28 (bs, 1H), 7.46 (t, J = 1.7 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.22−7.18 (m, 1H), 4.82 (t, J = 4.1 Hz, 2H), 4.37 (q, J = 7.1 Hz, 4H), 4.18 (t, J = 4.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.9, 160.7, 138.2, 137.8, 134.2, 129.4, 126.7, 125.9, 124.9, 123.9, 104.3, 80.4, 61.4, 24.0, 14.2. LC/MS: pos-MS = 375.1 (M + H), 397.0 (M + Na), neg-MS = 373.1 (M − H). HRMS-ESI (m/z): calcd for $C_{19}H_{19}ClN_2O_4$ (M + H) 375.1112, found 375.1117.

*Ethyl 3-Benzyl-4-methyl-1H-pyrazole-5-carboxylate (**39**).* Prepared from (*Z*)-3-benzyl-4-oxopent-2-en-2-yl trifluoromethanesulfonate (**38**) (synthesized using method A above) and ethyl diazoacetate to yield 74% of the title compound as a tan solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28−7.24 (m, 2H), 7.22−7.15 (m, 2H), 4.35 (q, J = 7.1 Hz, 2H), 4.01 (s, 2H), 2.19 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.6, 146.6, 138.3, 135.8, 128.4, 128.3, 126.3, 117.9, 60.8, 31.7, 14.4, 9.0. LC/MS: pos-MS = 245.1 (M + H), 267.1 (M + Na). Mp = 84−85 °C. HRMS-ESI (m/z): calcd for $C_{14}H_{16}N_2O_2$ (M + H) 245.1290, found 245.1299.

*Ethyl 3-(Cyclohexylmethyl)-4-methyl-1H-pyrazole-5-carboxylate (**41**).* Prepared from (*Z*)-3-(cyclohexylmethyl)-4-oxopent-2-en-2-yl trifluoromethanesulfonate (**40**) (synthesized using method A above) and ethyl diazoacetate to yield 72% of the title compound as a tan solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.38 (q, J = 7.1 Hz, 2H), 2.49 (d, J = 7.2 Hz, 2H), 2.22 (s, 3H), 1.73−1.61 (m, 5H), 1.60−1.52 (m, 1H), 1.39 (t, J = 7.1 Hz, 3H), 1.26−1.08 (m, 3H), 1.01−0.91 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.1, 146.0, 117.7, 60.7, 38.4, 33.2, 32.8, 26.5, 26.3, 14.5, 9.2. LC/MS: pos-MS = 251.2 (M + H), 273.2 (M + Na). Mp =120−122 °C. HRMS-ESI (m/z): calcd for $C_{14}H_{22}N_2O_2$ (M + H) 251.1760, found 251.1766.

*Ethyl 4-Methyl-3-phenyl-1H-pyrazole-5-carboxylate (**43**).*[30] Prepared from (*Z*)-4-oxo-3-phenylpent-2-en-2-yl trifluoromethanesulfonate (**42**) (synthesized using method A above) and ethyl diazoacetate to yield 87% of the title compound as a tan solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.50 (bs, 1H), 7.59 (d, J = 7.6 Hz, 2H), 7.49−7.44 (m, 2H), 7.42−7.38 (m, 1H), 4.43 (q, J = 7.2 Hz, 2H), 2.45 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.6, 145.8, 10.9, 128.6, 127.6, 117.2, 60.7, 14.2, 9.9. LC/MS: pos-MS = 231.1 (M + H), 253.1 (M + Na). Mp = 98−99 °C. HRMS-ESI (m/z): calcd for $C_{13}H_{14}N_2O_2$ (M + H) 231.1134, found 231.1140.

*Ethyl 4-Methyl-3-(thiophene-2-ylmethyl)-1H-pyrazole-5-carboxylate (**45**).* Prepared from (*Z*)-4-oxo-3-(thiophene-2-ylmethyl)pent-2-en-2-yl trifluoromethanesulfonate (**44**) (synthesized using method A above) and ethyl diazoacetate to yield 83% of the title compund as a tan solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (d, 5.2 Hz, 1H), 6.94−6.9 (m, 1H), 6.83−6.80 (m, 1H), 4.38 (q, J = 7.1 Hz, 2H), 4.19 (d, J = 1.0 Hz, 2H), 2.25 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.1, 147.7, 141.2, 134.4, 126.8, 125.1, 124.0, 118.3, 61.0, 26.6, 14.5, 9.0. LC/MS: pos-MS = 251.1 (M + H), 273.1 (M + Na), neg-MS = 249.0 (M − H). mp =84−85 °C. HRMS-ESI (m/z): calcd for $C_{12}H_{14}N_2O_2S$ (M + H) 251.0854, found 251.0861.

■ ASSOCIATED CONTENT

Supporting Information. A full account of the optimization screen and ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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