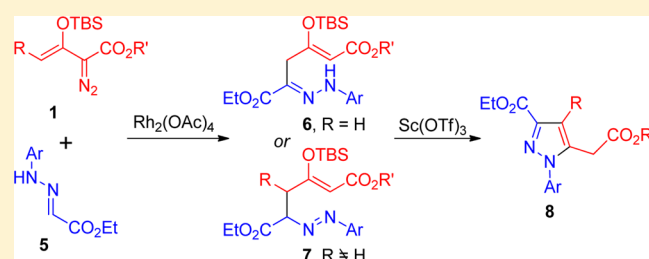


Vinylogous Reactivity of Enol Diazoacetates with Donor–Acceptor Substituted Hydrazones. Synthesis of Substituted Pyrazole Derivatives

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S Supporting Information

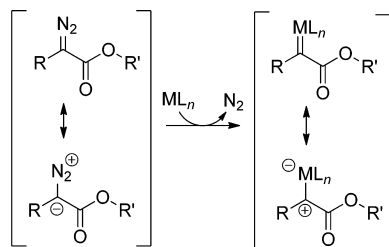
ABSTRACT: A regiospecific synthesis of multifunctional pyrazoles has been developed from a cascade process triggered by Rh(II)-catalyzed dinitrogen extrusion from enol diazoacetates with vinylogous nucleophilic addition followed by Lewis acid catalyzed cyclization and aromatization.



INTRODUCTION

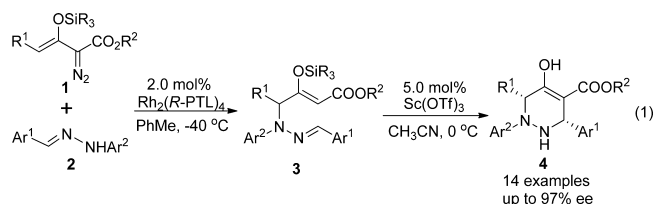
Diazo compounds have been extensively studied during the last few decades, and their value in organic synthesis is well-known.^{1,2} Direct dipolar cycloaddition to α,β -unsaturated carbonyl compounds and nitriles³ as well as catalytic processes have provided effective methodologies for the synthesis of heterocyclic compounds.⁴ Catalytic generation of metal carbenes for heterocyclic syntheses has been performed with diazocarbonyl compounds ranging from diazoacetates^{4e,g} and diazomalones^{3c} to diazo ketones^{4a,f} and diazoacetoacetates,^{4d} although vinyl diazoacetates have also been employed.^{1a} A key element in the uses of these diazo compounds is the change of polarity in the carbon α to the carbonyl group in the catalytic transformation to an electrophilic metal carbene (Scheme 1).

Scheme 1. Change in Polarity from Diazocarbonyl Compounds to the Corresponding Metal Carbenes



Increased attention has recently been given to enol diazoacetates, where the generated metal enol carbene shows electrophilic character at both the carbene and vinylogous positions and preferential reaction occurs at the vinylogous position.^{5,6} In one example of a vinylogous reaction we reported a stepwise [3 + 3]-cycloaddition of enoldiazoacetates **1** with diarylhydrazones **2** in

which Rh₂((R)-PTL)₄ catalyzed highly enantioselective vinylogous N–H insertion; a subsequent Sc(OTf)₃-catalyzed Mannich addition generated the corresponding tetrahydropyridazine derivatives **3** in high yield and diastereoselectivity (eq 1).⁷



Shortly thereafter Vicario⁸ and Lassaletta⁹ independently reported using donor–acceptor substituted hydrazones as acyl anion equivalents that undergo addition reactions with α,β -unsaturated aldehydes or keto esters, respectively, at the hydrazone carbon instead of at the conjugated hydrazone nitrogen. These successful examples of umpolung transformations suggested that reactions of metal enol carbenes with donor–acceptor disubstituted hydrazones could have a different outcome than was found with **2** in eq 1, forming **6** or **7** instead of **3** in dirhodium(II)-catalyzed reactions (Scheme 2). This transformation and the subsequent outcome from Lewis acid catalysis have been explored.

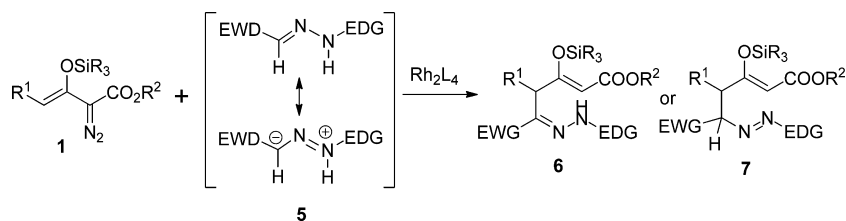
RESULTS AND DISCUSSION

At the onset we enlisted methyl enoldiazoacetate **1a** and donor–acceptor substituted hydrazone **5a** as substrates, and their rhodium acetate catalyzed reaction rapidly underwent complete conversion

Received: December 11, 2012

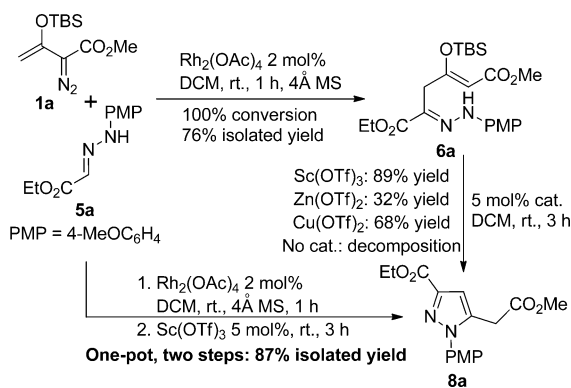
Published: January 9, 2013

Scheme 2. Umpolung with Donor–acceptor Substituted Hydrazones in Dirhodium(II)-Catalyzed Reactions of 1



to give **6a** in 76% isolated yield.¹⁰ Although **6a** was unstable and decomposed slowly in dichloromethane, this product was converted to pyrazole **8a** efficiently when catalyzed by a Lewis acid, and $\text{Sc}(\text{OTf})_3$ offered the best results with 89% isolated yield (Scheme 3). The structure of the pyrazole product **8** was

Scheme 3. Two-Step Conversion Compared to One-Pot Two-Step Process



confirmed by single-crystal X-ray diffraction analysis of its chloro derivative **8c** (Figure 1).¹¹ To increase reaction efficiency, we

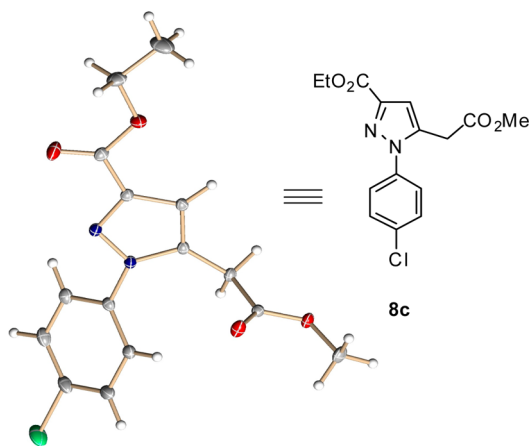


Figure 1. Crystal structure of **8c**.

carried out the two-step process in one pot since both of the reactions are carried out in dichloromethane. By adding $\text{Sc}(\text{OTf})_3$ directly into the reaction mixture at room temperature immediately after complete conversion to **6a**, pyrazole product **8a** was smoothly generated in high yield (87% isolated yield from **5a**), which avoided unnecessary losses from isolation of intermediate **6**.

The pyrazole scaffold is well-represented in bioactive structures.¹² Pyrazoles having a functionality installed at the C-3 or C-5 position have attracted a significant amount of attention.¹³

Numerous methodologies have been reported for pyrazole syntheses,¹⁴ and the Knorr condensation reaction of dicarbonyl compounds is the most prevalent approach for pyrazole synthesis.¹⁵ However, this classic condensation between α,γ -diketo esters and hydrazines is hampered by low regioselectivity,¹⁶ and general synthetic processes for functionalized pyrazoles having structural diversity and complexity continue to be needed. With the process that is described in Scheme 3 we present a versatile cascade reaction to produce multifunctionalized pyrazoles by a dirhodium(II)-catalyzed vinylogous umpolung reaction followed by Lewis acid catalyzed cyclization and aromatization.

To test the generality of this cascade reaction, a series of donor–acceptor substituted hydrazones was employed under the same conditions. In all cases, the isolated yield of the pyrazoles exceeded 70%, regardless of the electronic properties and different substituents at the aryl group (Table 1, entries 1–6).

Table 1. Substrate Generality in the One-Pot Production of the Pyrazoles^a

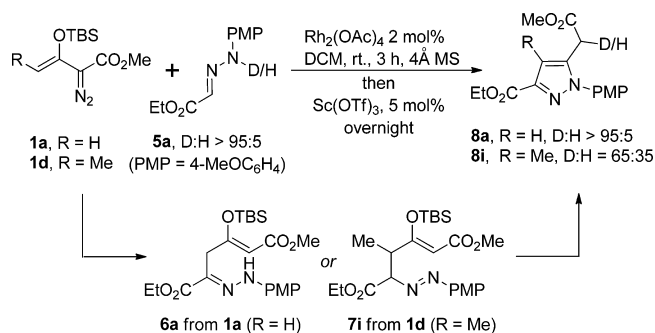
entry	R ¹ /R ² (1)	Ar in 5	8	yield of 8 (%) ^b
1	H/Me (1a)	4-MeOC ₆ H ₄ (5a)	8a	87
2	H/Me (1a)	4-MeC ₆ H ₄ (5b)	8b	91
3	H/Me (1a)	4-ClC ₆ H ₄ (5c)	8c	90
4	H/Me (1a)	Ph (5d)	8d	89
5	H/Me (1a)	4-NO ₂ C ₆ H ₄ (5e)	8e	71
6	H/Me (1a)	2,4-Cl ₂ C ₆ H ₃ (5f)	8f	72
7	H/ ^t Bu (1b)	4-MeOC ₆ H ₄ (5a)	8g	89
8	H/Bn (1c)	4-MeOC ₆ H ₄ (5a)	8h	88
9	Me/Me (1d)	4-MeOC ₆ H ₄ (5a)	8i	74
10	Me/Me (1d)	4-ClC ₆ H ₄ (5c)	8j	66
11	Me/Bn (1e)	4-MeOC ₆ H ₄ (5a)	8k	69
12	Et/Bn (1f)	4-MeOC ₆ H ₄ (5a)	8l	48

^aReactions were carried out on a 0.5 mmol scale: **1** (0.6 mmol), **5** (0.5 mmol), 4 Å MS (100 mg), in 3.0 mL of DCM with $\text{Rh}_2(\text{OAc})_4$ (2.0 mol %) at room temperature; then $\text{Sc}(\text{OTf})_3$ (5.0 mol %) was added and stirred at room temperature overnight. ^bIsolated yield of **8** based on limiting reagent **5**.

In addition, changing the ester alkyl group of the enoldiazoacetate (R²) from methyl to *tert*-butyl and benzyl gave the same product yields (entries 1, 7, and 8), but substituents other than hydrogen at the vinylogous position (R¹) lowered the product yield by about 10% on going from hydrogen to methyl and an additional 20% by changing from methyl to ethyl (entries 9, 11, and 12). Reactions with more sterically bulky substrates (e.g., enoldiazoacetate with R¹ = Ph or the donor–acceptor substituted hydrazone derived from ethyl 2-oxopropanoate) showed only decomposition of the diazo compound.

The proton transfer step of the hydrazone carbon-centered vinylogous addition was further studied by using deuterium-labeled hydrazone **5a** in reactions with enol diazoacetate **1a**. Deuterium was found to reside exclusively on the carbon α to the carboxylate ester in the pyrazole product **8a** formed between **1a** and **5a**. However, with vinyl-substituted enoldiazoacetate **1d** ($R^1 = \text{Me}$) in this reaction, only 65% of the deuterium was found in the final pyrazole product **8i** (Scheme 4). These diverse results

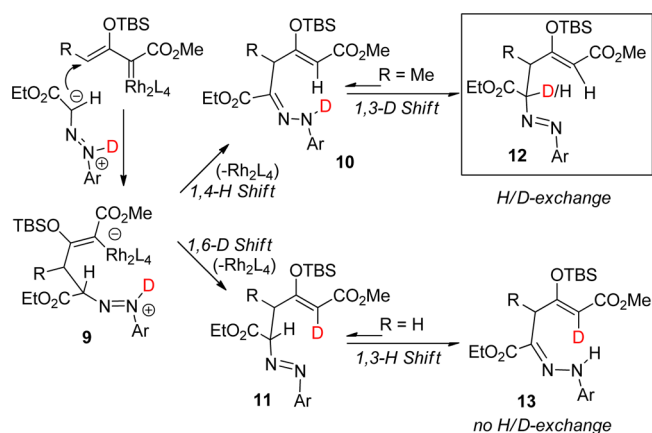
Scheme 4. Labeling Experiments Define Outcome of Vinylogous Addition Step



prompted us to look at the intermediates of the vinylogous addition step (**6a** and **7i**), and 2D-SHQC NMR analysis showed that these two isolated compounds possessed different structures: **6a** had a C–N double bond, while **7i** had a N–N double bond.¹⁷

The loss of deuterium in forming pyrazole product **8i** was rationalized as due to proton shifts in reaction intermediates as shown in Scheme 5, although alternative hydrazone N–H

Scheme 5. Possible Pathways for Deuterium Retention/Loss

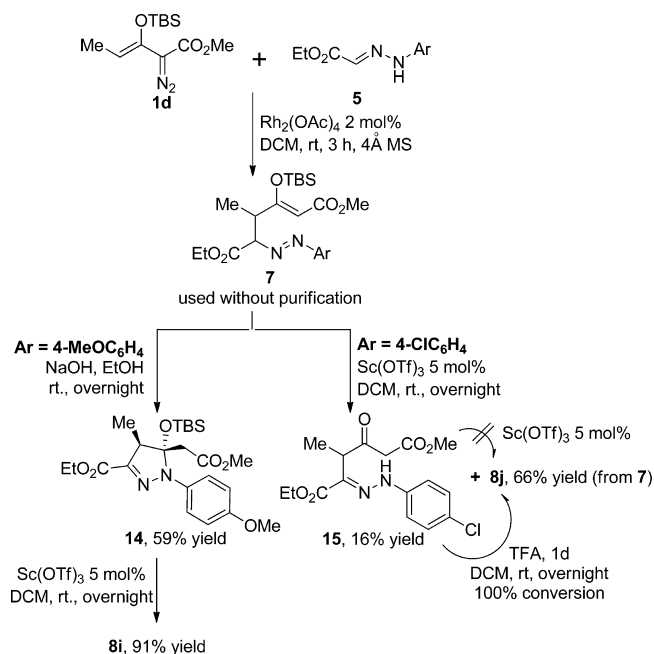


insertion at the metal carbene center followed by an aza-[3,3]-sigmatropic rearrangement cannot be ruled out. Kinetically controlled 1,4-H and 1,6-D shifts of the vinylogous addition intermediate **9**,¹⁸ dependent on the acidity of the proton adjacent to the carboxylate group, give **10** and **11**, respectively, and **10** is prone to deuterium–proton exchange (from **10** to **12**) with further loss occurring during cyclization and aromatization.

Further investigation of the cyclization step using base instead of Lewis acid with the reaction mixture from **1d** and **5** that contained azo compound **7** demonstrated that the enol carbene generated vinylogous addition product can be converted to the ring-closed product through catalysis by sodium hydroxide in ethanol at room temperature. The cyclized pyrazole precursor **14** was formed in 59% isolated yield as only one

diastereoisomer (Scheme 6)¹⁹ and was smoothly converted to pyrazole **8i** in high yield under the same conditions as was

Scheme 6



reported with $\text{Sc}(\text{OTf})_3$ in Table 1. The base-promoted reaction is consistent with a mechanism through which the hydrazone anion undergoes intramolecular Michael addition, and this pathway differs from that of the conventional pyrazole synthesis via the Knorr condensation reaction, in which a hydrazone anion directly attacks the carbonyl carbon.²⁰ Support for this proposal—that of Michael addition instead of attack on the carbonyl group formed by hydrolysis of the vinyl silyl ether—comes from the reaction of the hydrazone derivative **15**, which was formed as a byproduct from the $\text{Sc}(\text{OTf})_3$ -catalyzed reaction of **7**; compound **15** has the same structural framework as the intermediate of the Knorr reaction.^{16d} This byproduct (**15**) did not form the pyrazole product under standard Lewis acid conditions with $\text{Sc}(\text{OTf})_3$ (Table 1) even after treatment for 24 h, and only with trifluoroacetic acid did conversion to **8j** occur.

In conclusion, we have developed a regiospecific cascade transformation that enables the efficient preparation of multifunctional pyrazoles starting from enol diazoacetates and donor–acceptor substituted hydrazones in good to high overall yields. The sequence of reactions is triggered by Rh(II)-catalyzed dinitrogen extrusion from enol diazoacetates to form the substrate-dependent intermediates with a C–N (**6**) or N–N (**7**) double bond followed by Lewis acid promoted direct addition and aromatization. Although many nucleophilic addition reactions to vinylogous positions have been reported, this is the rare example using the hydrazone’s “C” instead of “N” for vinylogous reactivity. Further expansions of vinylogous reactions with enol diazoacetates are being pursued.

EXPERIMENTAL SECTION

General Information. Reactions were performed in oven-dried (140 °C) glassware under an atmosphere of dry N_2 . Dichloromethane (DCM) was passed through a solvent column prior to use and was kept over 3 Å molecular sieves. Thin-layer chromatography (TLC) was

carried out using silica gel plates. The developed chromatogram was analyzed by a UV lamp (254 nm). Liquid chromatography was performed using flash chromatography of the indicated system on silica gel (230–400 mesh). ^1H NMR and ^{13}C NMR spectra were recorded in CDCl_3 on a 400 MHz spectrometer; chemical shifts are reported in ppm with the solvent signals as reference, and coupling constants (J) are given in Hertz. The peak information is described as follows: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = composite. High-resolution mass spectra (HRMS) were performed on a TOF-CS mass spectrometer using CsI as the standard. Dirhodium tetraacetate, scandium(III) triflate, and other Lewis acids were obtained commercially and used as received. Enol diazoacetates **1**²¹ were synthesized according to literature procedures. Hydrazones **5** were synthesized as described.⁸

General Procedure for the Preparation of Hydrazones 5. A suspension of aryl hydrazine hydrochloride (14.0 mmol) in anhydrous THF (20.0 mL) was treated with triethylamine (2.0 mL, 14.0 mmol) before a solution of ethyl glyoxylate (50% solution in toluene, 2.9 mL, 14.5 mmol) was added dropwise into the reaction mixture at 0 °C. The mixture was stirred at this temperature for 30 min and then for 12 h at room temperature. The reaction mixture was then filtered under vacuum to collect the triethylamine hydrochloride salt. The filtrates were concentrated under reduced pressure, and the resulting solid was dissolved in dichloromethane (30 mL) and then washed with 1 M HCl (20 mL) and water (2×20 mL). The resulting organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to produce the desired hydrazone **5**, which was further purified by recrystallization from ether before use.

General Procedure for the Dirhodium-Catalyzed Reactions. To an oven-dried flask containing a magnetic stirring bar, 4 Å molecular sieves (100 mg), $\text{Rh}_2(\text{OAc})_4$ (2.0 mol %), and hydrazone **5** (0.50 mmol) in dichloromethane (2.0 mL) was added enol diazoacetate **1** (0.60 mmol) in dichloromethane (1.0 mL) over 1 h via a syringe pump at 0 °C. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent hexanes/EtOAc 50/1 to 30/1) to give the pure product **6** or **7**.

(2Z,5E)-6-Ethyl 1-Methyl 3-[(tert-Butyldimethylsilyl)oxy]-5-[2-(4-methoxyphenyl)hydrazono]hex-2-enedioate (6a). Yellow oil. 100% conversion, 170 mg (0.38 mmol), 76% yield. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.18 (bs, 1H), 7.15 (d, $J = 9.0$ Hz, 2H), 6.85 (d, $J = 9.0$ Hz, 2H), 5.03 (s, 1H), 4.31 (q, $J = 7.1$ Hz, 2H), 3.77 (s, 3H), 3.60 (s, 3H), 3.49 (s, 2H), 1.38 (t, $J = 7.1$ Hz, 3H), 1.01 (s, 9H), 0.31 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): 165.5, 165.0, 160.5, 155.6, 136.9, 128.6, 115.7, 114.8, 99.1, 61.5, 55.7, 50.8, 33.9, 25.9, 18.7, 14.5, -3.9. HRMS (ESI): m/z calcd for $\text{C}_{22}\text{H}_{35}\text{N}_2\text{O}_6\text{Si}$ [$\text{M} + \text{H}$]⁺ 451.2259, found 451.2231.

(Z)-6-Ethyl 1-Methyl 3-[(tert-Butyldimethylsilyl)oxy]-5-[(E)-(4-methoxyphenyl)diazonyl]-4-methylhex-2-enedioate (7i). Yellow oil. 100% conversion, 193 mg (0.42 mmol), 83% yield. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.74 (d, $J = 9.0$ Hz, 2H), 6.96 (d, $J = 9.0$ Hz, 2H), 5.12 (s, 1H), 5.52 (d, $J = 7.3$ Hz, 1H), 4.62–4.21 (comp, 2H), 3.87 (s, 3H), 3.63 (s, 3H), 3.34–3.27 (m, 1H), 1.29–1.26 (comp, 6H), 1.03 (s, 9H), 0.31 (s, 3H), 0.29 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): 169.6, 168.0, 165.9, 162.4, 146.3, 124.9, 114.2, 98.9, 81.3, 61.6, 55.8, 50.8, 44.0, 26.2, 18.9, 15.4, 14.4, -3.6, -3.7. HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{37}\text{N}_2\text{O}_6\text{Si}$ [$\text{M} + \text{H}$]⁺ 465.2415, found 465.2443.

General Procedure for the Lewis Acid Catalyzed Pyrazole Synthesis (Method A). To an oven-dried flask containing a magnetic stirring bar, Lewis acid (5.0 mol %) and **6** or **7** (0.30 mmol) in dichloromethane (2.0 mL) were stirred for 3 h (or as indicated) at room temperature. Once the diazo compound was consumed (determined by TLC, eluent hexanes/EtOAc 2/1, R_f (material) $\approx$ 0.8, R_f (product) $\approx$ 0.1), the reaction mixture was purified by column chromatography on silica gel (eluent hexanes/EtOAc 3/1 to 1/1) to give the pure pyrazole **8** in high yield.

General Procedure for Pyrazole Synthesis in One Pot (Method B, Table 1). In an oven-dried flask containing a magnetic stirring bar, 4 Å molecular sieves (100 mg), $\text{Rh}_2(\text{OAc})_4$ (2.0 mol %),

and hydrazone **5** (0.50 mmol) in dichloromethane (2.0 mL) was added enol diazoacetate **1** (0.60 mmol) in dichloromethane (1.0 mL) over 1 h via a syringe pump at 0 °C. The reaction solution was stirred for another 2 h at room temperature followed by adding solid $\text{Sc}(\text{OTf})_3$ (5.0 mol %) directly into the reaction mixture and was stirred overnight under the same conditions. The crude reaction mixture was purified by column chromatography on silica gel (eluent hexanes/EtOAc 3/1 to 1/1) to give the pure pyrazole **8** in good to high yield.

Ethyl 5-(2-Methoxy-2-oxoethyl)-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (8a). Yellow oil. 138 mg (0.44 mmol), 87% yield. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.33 (d, $J = 9.0$ Hz, 2H), 6.96 (d, $J = 9.0$ Hz, 2H), 6.90 (s, 1H), 4.40 (q, $J = 7.1$ Hz, 2H), 3.84 (s, 3H), 3.66–3.65 (comp, 5H), 1.38 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): 169.3, 162.4, 160.2, 144.0, 137.5, 131.6, 127.6, 114.4, 109.9, 61.1, 55.7, 52.6, 32.0, 14.5. HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_5$ [$\text{M} + \text{H}$]⁺ 319.1288, found 319.1278.

Ethyl 5-(2-Methoxy-2-oxoethyl)-1-(p-tolyl)-1H-pyrazole-3-carboxylate (8b). Yellow oil. 137 mg (0.46 mmol), 91% yield. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.30 (d, $J = 8.2$ Hz, 2H), 7.25 (d, $J = 8.2$ Hz, 2H), 6.91 (s, 1H), 4.40 (q, $J = 7.1$ Hz, 2H), 3.68 (s, 2H), 3.65 (s, 3H), 2.40 (s, 3H), 1.38 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): 169.3, 162.4, 144.1, 139.4, 137.4, 136.2, 129.9, 126.0, 110.1, 61.1, 52.6, 32.0, 21.3, 14.5. HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_4$ [$\text{M} + \text{H}$]⁺ 303.1339, found 303.1348.

Ethyl 1-(4-Chlorophenyl)-5-(2-methoxy-2-oxoethyl)-1H-pyrazole-3-carboxylate (8c). White solid, mp 109–110 °C. 145 mg (0.45 mmol), 90% yield. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.44 (d, $J = 9.0$ Hz, 2H), 7.39 (d, $J = 9.0$ Hz, 2H), 6.90 (s, 1H), 4.38 (q, $J = 7.1$ Hz, 2H), 3.68 (s, 2H), 3.65 (s, 3H), 1.37 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): 169.1, 162.2, 144.5, 137.4, 137.2, 135.2, 129.6, 127.3, 110.5, 61.2, 52.6, 31.9, 14.4. HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{16}\text{ClN}_2\text{O}_4$ [$\text{M} + \text{H}$]⁺ 323.0793, found 323.0799.

Ethyl 5-(2-Methoxy-2-oxoethyl)-1-phenyl-1H-pyrazole-3-carboxylate (8d). Yellow oil. 128 mg (0.45 mmol), 89% yield. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.48–7.42 (comp, 5H), 6.93 (s, 1H), 4.41 (q, $J = 7.1$ Hz, 2H), 3.70 (s, 2H), 3.65 (s, 3H), 1.39 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): 169.2, 162.4, 144.3, 138.7, 137.4, 129.4, 129.3, 126.1, 110.2, 61.2, 52.6, 32.0, 14.5. HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_4$ [$\text{M} + \text{H}$]⁺ 289.1183, found 289.1172.

Ethyl 5-(2-Methoxy-2-oxoethyl)-1-(4-nitrophenyl)-1H-pyrazole-3-carboxylate (8e). Yellow solid, mp 124–126 °C. 118 mg (0.36 mmol), 71% yield. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.39 (d, $J = 9.1$ Hz, 2H), 7.75 (d, $J = 9.1$ Hz, 2H), 6.99 (s, 1H), 4.45 (q, $J = 7.1$ Hz, 2H), 3.81 (s, 2H), 3.72 (s, 3H), 1.42 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): 169.0, 162.0, 147.7, 145.6, 134.8, 137.6, 126.4, 125.0, 111.7, 61.6, 53.0, 32.2, 14.6. HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{16}\text{N}_3\text{O}_6$ [$\text{M} + \text{H}$]⁺ 334.1034, found 334.1031.

Ethyl 1-(2,4-Dichlorophenyl)-5-(2-methoxy-2-oxoethyl)-1H-pyrazole-3-carboxylate (8f). White solid, mp 81–82 °C. 128 mg (0.36 mmol), 72% yield. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.54 (s, 1H), 7.43–7.37 (m, 2H), 6.94 (s, 1H), 4.40 (q, $J = 7.1$ Hz, 2H), 3.70–3.44 (comp, 5H), 1.38 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): 168.7, 162.1, 145.2, 138.8, 136.9, 134.9, 133.3, 131.2, 130.2, 128.2, 109.8, 61.3, 52.6, 31.6, 14.5. HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{15}\text{Cl}_2\text{N}_2\text{O}_4$ [$\text{M} + \text{H}$]⁺ 357.0403, found 357.0433.

Ethyl 5-[2-(tert-Butoxy)-2-oxoethyl]-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (8g). Yellow oil. 160 mg (0.45 mmol), 89% yield. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.36 (d, $J = 9.0$ Hz, 2H), 6.96 (d, $J = 9.0$ Hz, 2H), 6.89 (s, 1H), 4.41 (q, $J = 7.1$ Hz, 2H), 3.84 (s, 3H), 3.57 (s, 2H), 1.40–1.33 (comp, 12H). ^{13}C NMR (100 MHz, CDCl_3): 168.1, 162.0, 160.1, 143.9, 138.2, 131.9, 127.6, 114.4, 109.8, 82.2, 61.1, 55.8, 32.5, 28.0, 14.6. HRMS (ESI): m/z calcd for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_5$ [$\text{M} + \text{H}$]⁺ 361.1758, found 361.1779.

Ethyl 5-[2-(Benzyloxy)-2-oxoethyl]-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (8h). Yellow oil. 173 mg (0.44 mmol), 88% yield. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.37–7.29 (comp, 7H), 6.94 (s, 1H), 6.91 (d, $J = 9.0$ Hz, 2H), 5.12 (s, 2H), 4.43 (q, $J = 7.1$ Hz, 2H), 3.85 (s, 3H), 3.72 (s, 2H), 1.42 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): 168.8, 162.5, 160.2, 144.0, 137.5, 135.3, 131.7, 128.8, 128.7, 128.6, 127.7, 114.5, 110.1, 67.4, 61.2, 55.8, 32.3, 14.6.

HRMS (ESI): m/z calcd for $C_{22}H_{23}N_2O_5$ $[M + H]^+$ 395.1601, found 395.1617.

Ethyl 5-(2-Methoxy-2-oxoethyl)-1-(4-methoxyphenyl)-4-methyl-1H-pyrazole-3-carboxylate (8i). Yellow solid, mp 107–108 °C. 123 mg (0.37 mmol), 74% yield. 1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (d, $J = 9.0$ Hz, 2H), 6.96 (d, $J = 9.0$ Hz, 2H), 4.42 (q, $J = 7.1$ Hz, 2H), 3.85 (s, 3H), 3.67 (s, 3H), 3.61 (s, 2H), 2.31 (s, 3H), 1.41 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 169.5, 163.3, 160.2, 141.6, 135.4, 132.0, 127.7, 120.0, 114.4, 60.8, 55.8, 52.6, 30.6, 14.6, 9.5. HRMS (ESI): m/z calcd for $C_{17}H_{21}N_2O_5$ $[M + H]^+$ 333.1445, found 333.1425.

Ethyl 1-(4-Chlorophenyl)-5-(2-methoxy-2-oxoethyl)-4-methyl-1H-pyrazole-3-carboxylate (8j). Yellow solid, mp 106–108 °C. 111 mg (0.33 mmol), 66% yield. 1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.48 (d, $J = 9.0$ Hz, 2H), 7.42 (d, $J = 9.0$ Hz, 2H), 4.45 (q, $J = 7.1$ Hz, 2H), 3.71 (s, 3H), 3.66 (s, 2H), 2.34 (s, 3H), 1.43 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 169.3, 163.1, 142.4, 137.7, 135.24, 135.18, 129.7, 127.6, 120.6, 61.1, 52.8, 30.7, 14.7, 9.5. HRMS (ESI): m/z calcd for $C_{16}H_{18}ClN_2O_4$ $[M + H]^+$ 337.0950, found 337.0977.

Ethyl 5-[2-(Benzyloxy)-2-oxoethyl]-1-(4-methoxyphenyl)-4-methyl-1H-pyrazole-3-carboxylate (8k). White solid, mp 111–112 °C. 141 mg (0.34 mmol), 69% yield. 1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 (comp, 7H), 6.89 (d, $J = 9.0$ Hz, 2H), 5.12 (s, 2H), 4.44 (q, $J = 7.1$ Hz, 2H), 3.85 (s, 3H), 3.65 (s, 2H), 2.31 (s, 3H), 1.42 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 168.9, 163.2, 160.1, 141.6, 135.5, 135.4, 132.0, 128.8, 128.7, 128.6, 127.8, 120.1, 114.4, 67.4, 60.9, 55.8, 30.9, 14.7, 9.5. HRMS (ESI): m/z calcd for $C_{23}H_{25}N_2O_5$ $[M + H]^+$ 409.1758, found 409.1772.

Ethyl 5-(2-(Benzyloxy)-2-oxoethyl)-4-ethyl-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (8l). Yellow solid, mp 78–79 °C. 101 mg (0.24 mmol), 48% yield. 1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39–7.29 (comp, 7H), 6.88 (d, $J = 9.0$ Hz, 2H), 5.11 (s, 2H), 4.44 (q, $J = 7.1$ Hz, 2H), 3.84 (s, 3H), 3.65 (s, 2H), 2.76 (q, $J = 7.5$ Hz, 2H), 1.42 (t, $J = 7.1$ Hz, 3H), 1.17 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 169.1, 163.0, 160.1, 141.1, 135.4, 134.9, 132.0, 128.8, 128.72, 128.68, 127.8, 126.5, 114.4, 67.4, 60.9, 55.7, 32.7, 17.6, 15.3, 14.6. HRMS (ESI): m/z calcd for $C_{24}H_{27}N_2O_5$ $[M + H]^+$ 423.1914, found 423.1911.

General Procedure for the Deuteration Reactions (Scheme 4). In an oven-dried flask containing a magnetic stirring bar and hydrazone **5a** (0.50 mmol) in DCM (2.0 mL) was added D_2O (0.10 mL) at room temperature, and the deuteration experiment of **5a** was monitored by 1H NMR (about 10 min, $5a(H)/5a(D) < 5/95$). This mixture was used directly for the deuterium tracing study by following the condition of method B to give deuterated **8a(D)** in 81% yield. 1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 (d, $J = 9.0$ Hz, 2H), 6.98 (d, $J = 9.0$ Hz, 2H), 6.93 (s, 1H), 4.43 (q, $J = 7.1$ Hz, 2H), 3.88 (s, 3H), 3.69–3.67 (comp, 4H), 1.41 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 169.4, 162.5, 160.3, 144.1, 137.6, 131.7, 127.7, 114.5, 110.0, 61.2, 55.8, 52.7, 32.1, 14.6.

General Procedure for the Synthesis of 14. In an oven-dried flask containing a magnetic stirring bar, 4 Å molecular sieves (100 mg), $Rh_2(OAc)_4$ (2.0 mol %), and hydrazone **5a** (0.5 mmol) in dichloromethane (2.0 mL) was added enol diazoacetate **1d** (0.6 mmol) in dichloromethane (1.0 mL) over 1 h via a syringe pump at 0 °C. After addition was complete, the reaction solution was stirred for another 2 h at room temperature, and after removal of the solvent under reduced pressure, anhydrous ethanol (2.0 mL) and NaOH (1.0 equiv) were added. This solution was stirred overnight under the same conditions, and the crude reaction mixture was purified by column chromatography on silica gel (eluent hexanes/EtOAc 50/1 to 30/1) to give pure **14** in 59% isolated yield, which was smoothly converted to **8i** in 91% yield according to the conditions of method A.

Ethyl 5-[(tert-Butyldimethylsilyl)oxy]-5-(2-methoxy-2-oxoethyl)-1-(4-methoxyphenyl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxylate (14). Yellow solid, mp 67–68 °C. 137 mg (0.30 mmol), 59% yield. 1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (d, $J = 9.1$ Hz, 2H), 6.88 (d, $J = 9.1$ Hz, 2H), 4.40 (q, $J = 7.1$ Hz, 2H), 3.82 (s, 3H), 3.72 (s, 3H), 3.66 (s, 2H), 3.54 (q, $J = 7.2$ Hz, 1H), 3.37 (d, $J = 15.7$ Hz, 1H), 2.77 (d, $J = 15.7$ Hz, 1H), 1.39 (t, $J = 7.1$ Hz, 3H), 1.28

(d, $J = 7.2$ Hz, 3H), 0.84 (s, 9H), 0.10 (s, 3H), –0.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 169.7, 162.4, 157.0, 144.3, 134.2, 123.4, 114.1, 98.1, 61.2, 55.7, 52.0, 50.4, 39.3, 25.8, 15.3, 14.6, –2.9, –3.9. HRMS (ESI): m/z calcd for $C_{23}H_{37}N_2O_6Si$ $[M + H]^+$ 465.2415, found 465.2442.

General Procedure for the Synthesis of Pyrazole **8j** from **15**.

This ketone precursor **15** was isolated as a byproduct in 16% yield from the reaction of **1d** with **5c** under the conditions of method B. In an oven-dried flask containing a magnetic stirring bar and **15** (28.0 mg, 0.08 mmol) in dichloromethane (2.0 mL) was added trifluoroacetic acid (TFA, 1 drop) at room temperature. The reaction gave 100% conversion to the corresponding pyrazole **8j** in 96% isolated yield after stirring overnight under these conditions.

(E)-1-Ethyl 6-Methyl 2-[2-(4-Chlorophenyl)hydrazone]-3-methyl-4-oxohexanedioate (15). Yellow solid, mp 92–93 °C. 28 mg, 16% yield. 1H NMR (400 MHz, $CDCl_3$): δ (ppm) 12.24 (bs, 1H), 7.27 (d, $J = 9.0$ Hz, 2H), 7.12 (d, $J = 9.0$ Hz, 2H), 4.31 (q, $J = 7.2$ Hz, 2H), 3.96 (q, $J = 7.0$ Hz, 1H), 3.57 (s, 3H), 3.56–3.52 (comp, 2H), 1.42–1.35 (comp, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 200.0, 167.8, 163.0, 141.8, 129.5, 127.6, 127.1, 115.3, 61.6, 52.5, 50.2, 47.5, 14.6, 14.2. HRMS (ESI): m/z calcd for $C_{16}H_{20}ClN_2O_5$ $[M + H]^+$ 355.1055, found 355.1058.

■ ASSOCIATED CONTENT

Supporting Information

Text, figures, and CIF files giving NMR spectra of new compounds and X-ray diffraction analysis data for **8c**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the support for this research from the National Institutes of Health (GM 46503).

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