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Vinylogous Reactivity of Enoldiazoacetates with Donor-Acceptor Substituted Hydrazones. Synthesis of Substituted Pyrazole Derivatives

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Abstract

A regiospecific synthesis of multi-functional pyrazoles has been developed from a cascade process triggered by Rh(II)-catalyzed dinitrogen extrusion from enoldiazoacetates 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 nitriles[3] as well as catalytic processes have provided effective methodologies for the synthesis of heterocyclic compounds.[4] Catalytic generation of metal carbenes for heterocyclic syntheses have been performed with diazocarbonyl compounds ranging from diazoacetates[4e, 4g] and diazomalonates[3e] to diazo ketones[4a, 4f] and diazoacetoacetates[4d], although vinyldiazoacetates have also been employed.[1a] A key element in the uses of these diazo compounds is the change of polarity in the carbon alpha to the carbonyl group in the catalytic transformation to an electrophilic metal carbene (Scheme 1).

Increased attention has recently been given to enoldiazoacetates where the generated metal enolcarbene 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 Rh_2(*R*-PTL)$_4$ catalyzed highly enantioselective vinylogous N-H insertion; subsequent Sc(OTf)$_3$-catalyzed Mannich addition generated the corresponding tetrahydropyridazine derivatives **3** in high yield and diastereoselectivity (eq 1).[7] Shortly thereafter Vicario[8] and Lassaletta[9] independently reported using donor-acceptor substituted hydrazones as acyl anion equivalents that undergo addition reactions with α,β-unsaturated aldehydes or ketoesters, respectively, at the hydrazone carbon instead of at the conjugated hydrazone nitrogen. These successful examples of umpolung transformations suggested that

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Supporting Information Available: NMR spectra of new compounds and X-ray diffraction analysis data of **8c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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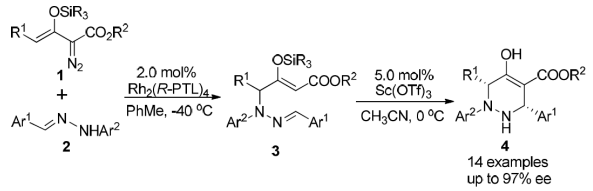
reactions of metal enolcarbenes with donor-acceptor disubstituted hydrazones could have a different outcome than was found with **2** in eq 1, forming **6** or **7** instead of **3** in dirhodium(II) catalyzed reactions (Scheme 2). This transformation and the subsequent outcome from Lewis acid catalysis have been explored.



(1)

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 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 $Sc(OTf)_3$ offered the best results with 89% isolated yield (Scheme 3). The structure of the pyrazole product **8** was confirmed by single-crystal X-ray diffraction analysis of its chloro-derivative **8c** (Figure 1).[11] To increase reaction efficiency we carried out the two-step process in one-pot since both of the two reactions are carried out in dichloromethane. By adding $Sc(OTf)_3$ 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 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-diketoesters 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 multi-functionalized 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 (entries 1~6). In addition, changing the ester alkyl group of the enoldiazoacetate (R^2) 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 (R^1) lowered product yield by about 10% in 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 R^1 = 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 enodiazoacetate **1a**. Deuterium was found to reside exclusively on the carbon alpha to the carboxylate ester in the pyrazole product **8a** formed between **1a** and **5a**. However, with vinyl-substituted enoldiazoacetate **1d** (R^1 = Me) in this reaction, only 65% of the deuterium was found in the final pyrazole product **8i** (Scheme 4). These diverse results 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 pyrrazole product **8i** was rationalized as due to proton shifts in reaction intermediates as shown in Scheme 5, although alternative hydrazone N-H 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 deuteron-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 enolcarbene-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 reported with $Sc(OTf)_3$ 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 synthsis via the Knorr condensation reaction in which a hydrazine 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 a reaction of a hydazone derivative **15** that was formed as a byproduct from the $Sc(OTf)_3$-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 $Sc(OTf)_3$ (Table 1) even after treatment for 24 hours, 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 multi-functional pyrazoles starting from enoldiazoacetates and donor-acceptor substituted hydrazones in good to high overall yields. The sequence of reactions is triggered by Rh(II)-catalyzed dinitrogen extrusion from enoldiazoacetates to form the substrate-dependent intermediates with 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 position 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 enoldiazoacetates 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). ^{1}H 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: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and 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. Enoldiazoacetates **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 minutes 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) then washed with HCl 1M (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** that 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), $Rh_2(OAc)_4$ (2.0 mol %) and hydrazone **5** (0.50 mmol) in dichloromethane (2.0 mL), was added enoldiazoacetate **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**.

(2*Z*,5*E*)-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. ^{1}H 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) calculated for $C_{22}H_{35}N_2O_6Si$ $[M+H]^+$: 451.2259; found: 451.2231.

(*Z*)-6-Ethyl 1-Methyl 3-[(*tert*-Butyldimethylsilyl)oxy]-5-[(*E*)-(4-methoxyphenyl)diazenyl]-4-methylhex-2-enedioate (7i)

Yellow oil. 100% conversion, 193 mg (0.42 mmol), 83% yield. ^{1}H 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) calculated for $C_{23}H_{37}N_2O_6Si$ $[M+H]^+$: 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, Rf (material) ≈ 0.8, Rf (product) ≈ 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)

To an oven-dried flask containing a magnetic stirring bar, 4 Å molecular sieves (100 mg), $Rh_2(OAc)_4$ (2.0 mol %) and hydrazone **5** (0.50 mmol) in dichloromethane (2.0 mL), was added enoldiazoacetate **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 $Sc(OTf)_3$ (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)-1*H*-pyrazole-3-carboxylate (8a)

Yellow oil. 138 mg (0.44 mmol), 87% yield. ^{1}H 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) calculated for $C_{16}H_{19}N_2O_5$ $[M+H]^+$: 319.1288; found: 319.1278.

Ethyl 5-(2-Methoxy-2-oxoethyl)-1-(*p*-tolyl)-1*H*-pyrazole-3-carboxylate (8b)

Yellow oil. 137 mg (0.46 mmol), 91% yield. ^{1}H 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) calculated for $C_{16}H_{19}N_2O_4$ $[M+H]^+$: 303.1339; found: 303.1348.

Ethyl 1-(4-Chlorophenyl)-5-(2-methoxy-2-oxoethyl)-1*H*-pyrazole-3-carboxylate (8c)

White solid, mp = 109–110 °C. 145 mg (0.45 mmol), 90% yield. ^{1}H 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) calculated for $C_{15}H_{16}ClN_2O_4$ $[M+H]^+$ $_{15}H_{16}ClN_2O_4$ $[M+H]^+$: 323.0793; found: 323.0799.

Ethyl 5-(2-Methoxy-2-oxoethyl)-1-phenyl-1*H*-pyrazole-3-carboxylate (8d)

Yellow oil. 128 mg (0.45 mmol), 89% yield. ^{1}H 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) calculated for $C_{15}H_{17}N_2O_4$ $[M+H]^+$: 289.1183; found: 289.1172.

Ethyl 5-(2-Methoxy-2-oxoethyl)-1-(4-nitrophenyl)-1*H*-pyrazole-3-carboxylate (8e)

Yellow solid, mp = 124–126 °C. 118 mg (0.36 mmol), 71% yield. ^{1}H 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) calculated for $C_{15}H_{16}N_3O_6$ $[M+H]^+$: 334.1034; found: 334.1031.

Ethyl 1-(2,4-Dichlorophenyl)-5-(2-methoxy-2-oxoethyl)-1*H*-pyrazole-3-carboxylate (8f)

White solid, mp = 81–82 °C. 128 mg (0.36 mmol), 72% yield. ^{1}H 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) calculated for $C_{15}H_{15}$ $Cl_2N_2O_4$ $[M+H]^+$: 357.0403; found: 357.0433.

Ethyl 5-[2-(*tert*-Butoxy)-2-oxoethyl]-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (8g)

Yellow oil. 160 mg (0.45 mmol), 89% yield. ^{1}H 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) calculated for $C_{19}H_{25}N_2O_5$ $[M+H]^+$: 361.1758; found: 361.1779.

Ethyl 5-[2-(Benzyloxy)-2-oxoethyl]-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (8h)

Yellow oil. 173 mg (0.44 mmol), 88% yield. ^{1}H 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) calculated 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-1*H*-pyrazole-3-carboxylate (8i)

Yellow solid, mp =107–108 °C. 123 mg (0.37 mmol), 74% yield. ^{1}H 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) calculated 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-1*H*-pyrazole-3-carboxylate (8j)

Yellow solid, mp = 106–108 °C. 111 mg (0.33 mmol), 66% yield. ^{1}H 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) calculated 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-1*H*-pyrazole-3-carboxylate (8k)

White solid, mp = 111–112 °C. 141 mg (0.34 mmol), 69% yield. ^{1}H 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) calculated 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)-1*H*-pyrazole-3-carboxylate (8l)

Yellow solid, mp = 78–79 °C. 101 mg (0.24 mmol), 48% yield. ^{1}H 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) calculated for $C_{24}H_{27}N_2O_5$ $[M+H]^+$: 423.1914; found: 423.1911.

General Procedure for the Deuteration Reactions (Scheme 4)

To 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 ^{1}H NMR (about 10 mins, **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. ^{1}H 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

To 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 enoldiazoacetate **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 eq) was added. This solution was stirred overnight under 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-1*H*-pyrazole-3-carboxylate (14)

Yellow solid, mp = 67–68 °C. 137 mg (0.30 mmol), 59% yield. ^{1}H 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) calculated 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 byproduct in 16 % yield from the reaction of **1d** with **5c** under the condition of **Method B.** To an oven-dried flask containing a magnetic stirring bar, **15** (28.0 mg, 0.08 mmol) in dichloromethane (2.0 mL), was added trifluoroacetic acid(TFA, 1d) at room temperature. The reaction turned out 100% convert to the corresponding pyrazole **8j** in 96% isolated yield after stirred overnight under this condition.

(*E*)-1-Ethyl 6-Methyl 2-[2-(4-Chlorophenyl)hydrazono]-3-methyl-4-oxohexanedioate (15)

Yellow solid, mp = 92–93 °C. 28 mg, 16% yield. ^{1}H 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) calculated for $C_{16}H_{20}ClN_2O_5$ $[M+H]^+$: 355.1055; found: 355.1058.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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REFERENCES

(1). (a) Doyle, MP.; McKervey, MA.; Ye, T. Modern CatalyticMethods for Organic Synthesis with Diazo Compounds. John Wiley & Sins; New York: 1998. (b) Davies HML, Beckwith REJ. Chem. Rev. 2003; 103:2861. [PubMed: 12914484] (c) Padwa A, Weingarten MD. Chem. Rev. 1996; 96:223. [PubMed: 11848752] (d) Doyle MP, Duffy R, Ratnikov M, Zhou L. Chem. Rev. 2010; 110:704. [PubMed: 19785457] (e) Davies HML, Morton D. Chem. Soc. Rev. 2011; 40:1857. [PubMed: 21359404] For reviews, see:

(2). (a) Selander JN, Fokin VV. J. Am. Chem. Soc. 2012; 134:2477. [PubMed: 22233190] (b) Nadeau E, Ventura DL, Brekan JA, Davies HML. J. Org. Chem. 2010; 75:1927. [PubMed: 20170115] (c) Xu X, Hu W, Doyle MP. Angew. Chem. Int. Ed. 2011; 50:6392.(d) Cui X, Xu X, Lu H, Zhu S, Wojtas L, Zhang XP. J. Am. Chem. Soc. 2011; 133:3304. [PubMed: 21332140] (e) Zhang Z, Liu Y, Ling L, Li Y, Dong Y, Gong M, Zhao X, Zhang Y, Wang J. J. Am. Chem. Soc. 2011; 133:4330. [PubMed: 21370919] (f) Takeda K, Oohara T, Shimada N, Nambu H, Hashimoto S. Chem. Eur. J. 2011; 17:13992. [PubMed: 22095784] (g) Xu X, Qian Y, Yang L, Hu W. Chem. Commun. 2011; 47:797.Selected recent examples:

(3). (a) Doyle MP, Dorow RL, Tamblyn WH. J. Org. Chem. 1982; 47:4059.(b) Gao D, Zhai H, Parvez M, Back TG. J. Org. Chem. 2008; 73:8057. [PubMed: 18798677] (c) Wu L, Shi M. J. Org. Chem. 2010; 75:2296. [PubMed: 20205439] (d) González-Bobes F, Fenster MDB, Kiau S, Kolla L, Kolotuchin S, Soumeillant M. Adv. Synth. Catal. 2008; 350:813.(e) Lu L, Lu P, Ma S. Eur. J. Org. Chem. 2007:676.

(4). (a) Padwa A. J. Org. Chem. 2009; 74:6421. [PubMed: 19663447] (b) Padwa A. Pure Appl. Chem. 2004; 76:1933.c) Padwa A, Brodney MA, Marino JP, Osterhout MH, Price AT. J. Org. Chem. 1997; 62:67. [PubMed: 11671365] (d) Honey MA, Pasceri R, Lewis W, Moody CJ. J. Org. Chem. 2012; 77:1396. [PubMed: 22264218] (e) Zhao L, Guan Z, Han Y, Xie Y, He S, Liang Y. J. Org. Chem. 2007; 72:10276. [PubMed: 18041850] (f) Seki H, Georg GI. J. Am. Chem. Soc. 2010; 132:15512. [PubMed: 20958040] (g) Li Y, Shi Y, Huang Z, Wu X, Xu P, Wang J, Zhang Y. Org. Lett. 2011; 13:1210. [PubMed: 21306152]

(5). (a) Xu X, Hu W, Zavalij PY, Doyle MP. Angew. Chem. Int. Ed. 2011; 50:11152.(b) Wang X, Xu X, Zavalij PY, Doyle MP. J. Am. Chem. Soc. 2011; 133:16402. [PubMed: 21932856] (c) Xu X, Zavalij PJ, Hu W, Doyle MP. Chem. Commun. 2012; 48:11522.(d) Xu X, Shabashov D, Zavalij PY, Doyle MP. Org. Lett. 2012; 14:800. [PubMed: 22272728] (e) Xu X, Ratnikov MO, Zavalij PY, Doyle MP. Org. Lett. 2011; 13:6122. [PubMed: 22032199] (f) Wang X, Abrahams QM, Zavalij PY, Doyle MP. Angew. Chem. Int. Ed. 2012; 51:5907.(g) Qian Y, Xu X, Wang X, Zavalij PJ, Hu W, Doyle MP. Angew. Chem. Int. Ed. 2012; 51:5900.(h) Xu X, Shabashov D, Zavalij PY, Doyle MP. J. Org. Chem. 2012; 77:5313. [PubMed: 22621315]

(6). (a) Lian Y, Davies HML. J. Am. Chem. Soc. 2011; 133:11940. [PubMed: 21739977] (b) Lian Y, Hardcastle KI, Davies HML. Angew. Chem. Int. Ed. 2011; 50:9370.(c) Valette D, Lian Y, Haydek JP, Hardcastle KI, Davies HML. Angew. Chem. Int. Ed. 2012; 51:8636.(d) Smith AG,

Davies HML. J. Am. Chem. Soc. 2012; 134:18241. [PubMed: 23098215] (e) Hansen JH, Davies HML. Chem. Sci. 2011; 2:457.Davies and coworkers have reported analogous vinylogous reactivity with metal carbenes derived from vinyldiazoacetates, especially styryldiazoacetate:

(7). Xu X, Zavalij PJ, Doyle MP. Angew. Chem. Int. Ed. 2012; 51:9829.

(8). Fernández M, Uria U, Vicario JL, Reyes E, Carrillo L. J. Am. Chem. Soc. 2012; 134:11872. [PubMed: 22780683]

(9). Crespo-Peña A, Monge D, Martín-Zamora E, Álvarez E, Fernández R, Lassaletta JM. J. Am. Chem. Soc. 2012; 134:12912.

(10). The structure of the product **6a** was confirmed by deuterium exchange and 2D HSQC NMR analysis, see Supporting Information for details.

(11). CCDC 909103 contains the supplementary crystallographic data of **8c** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12). (a) Pargellis C, Tong L, Churchill L, Cirillo PF, Gilmore T, Graham AG, Grob PM, Hickey ER, Moss N, Pav S, Regan J. Nat. Struct. Biol. 2002; 9:268. [PubMed: 11896401] (b) Honma T, Yoshizumi T, Hashimoto N, Hayashi K, Kawanishi N, Fukasawa K, Takaki T, Ikeura C, Ikuta M, Suzuki-Takahashi I, Hayama T, Nishimura S, Morishima H. J. Med. Chem. 2001; 44:4628. [PubMed: 11741480] (c) Ashton WT, Sisco RM, Dong H, Lyons KA, He H, Doss GA, Leiting B, Patel RA, Wu JK, Marsilio F, Thornberry NA, Weber AE. Bioorg. Med. Chem. Lett. 2005; 15:2253. [PubMed: 15837304] (d) Genin MJ, Biles C, Keiser BJ, Poppe SM, Swaney SM, Tarpley WG, Yagi Y, Romero DL. J. Med. Chem. 2000; 43:1034. [PubMed: 10715167]

(13). (a) Herk T, Brussee J, Nieuwendijk AMCH, Klein PAM, Ijzerman AP, Stannek C, Burmeister A, Lorenzen A. J. Med. Chem. 2003; 46:3945. [PubMed: 12930155] (b) Katoch-Rouse R, Pavlova OA, Caulder T, Hoffman AF, Mukhin AG, Horti AG. J. Med. Chem. 2003; 46:642. [PubMed: 12570386] (c) Despotopoulou C, Klier L, Knochel P. Org. Lett. 2009; 11:3326. [PubMed: 19580307] (d) McLaughlin M, Marcantonio C, Chen C-Y, Davies IW. J. Org. Chem. 2008; 73:4309. [PubMed: 18444682] (e) Goikhman R, Jacques TL, Sames D. J. Am. Chem. Soc. 2009; 131:3042. [PubMed: 19206533] (f) Padwa, A.; Pearson, WH. Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products. John Wiley & Sons; New York: 2002. (g) Schroeder G. M.; Wei D, Banfi P, Cai ZW, Lippy J, Menichincheri M, Modugno M, Naglich J, Penhallow B, Perez HL, Sack J, Schmidt RJ, Tebben A, Yan C, Zhang L, Galvani A, Lombardo LJ, Borzilleri RM. Bioorg. Med. Chem. Lett. 2012; 22:3951. [PubMed: 22608393]

(14). (a) Padwa A, Kulkarni YS, Zhang Z. J. Org. Chem. 1990; 55:4144.(b) Weiss R, Bess M, Huber SM, Heinemann FW. J. Am. Chem. Soc. 2008; 130:4610. [PubMed: 18341332] (c) Fuchibe K, Takahashi M, Ichikawa J. Angew. Chem. Int. Ed. 2012; 51:12059.(d) Ponti A, Molteni G. J. Org. Chem. 2001; 66:5252. [PubMed: 11463282] (e) Deng X, Mani NS. Org. Lett. 2008; 10:1307. [PubMed: 18302402] (f) Delaunay T, Genix P, Es-Sayed M, Vors J, Monteiro N, Balme G. Org. Lett. 2010; 12:3328. [PubMed: 20597542] (g) Persson T, Nielsen J. Org. Lett. 2006; 8:3219. [PubMed: 16836370] (h) Hu J, Chen S, Sun Y, Yang J, Rao Y. Org. Lett. 2012; 14:5030. [PubMed: 22988906] (i) Kumar R, Varma D, Mobin SM, Namboothiri. Org. Lett. 2012; 14:4070. [PubMed: 22856331] (j) Li P, Wu C, Zhao J, Rogness DC, Shi F. J. Org. Chem. 2012; 77:3149. [PubMed: 22414117]

(15). (a) Knorr L, Blank A. Ber. 1885; 18:311.(b) Robertson J, Hatley RJD, Watkin DJ. J. Chem. Soc. Perkin. Trans. 2000; 1:3389.(c) Wurtz NR, Turner JM, Baird EE, Dervan PB. Org. Lett. 2001; 3:1201. [PubMed: 11348194] (d) Ballini R, Bosica G, Fiorini G, Giarlo G. Synthesis. 2001:2003. (e) Braun RU, Zeitler K, Müller TJJ. Org. Lett. 2001; 3:3297. [PubMed: 11594818] (f) Arrowsmith J, Jennings SA, Clark AS, Stevens MFG. J. Med. Chem. 2002; 45:5458. [PubMed: 12459014] (g) Minetto G, Raveglia LF, Taddei M. Org. Lett. 2004; 6:389. [PubMed: 14748600] For some recent applications of Knorr syntheses see:

(16). (a) Schmidt A, Habeck T, Kindermann MK, Nieger M. J. Org. Chem. 2003; 68:5977. [PubMed: 12868936] (b) Martins MAP, Freitag RA, de Rosa A, Flores AFC, Zanatta N, Bonacorso HG. J. Heterocycl. Chem. 1999; 36:217.(c) Wang Z, Qin H. Green. Chem. 2004; 6:90.(d) Fustero S, Román R, Sanz-Cervera JF, Simón-Fuentes A, Cuñat AC, Villanova S, Murguía M. J. Org. Chem. 2008; 73:3523. [PubMed: 18399658]

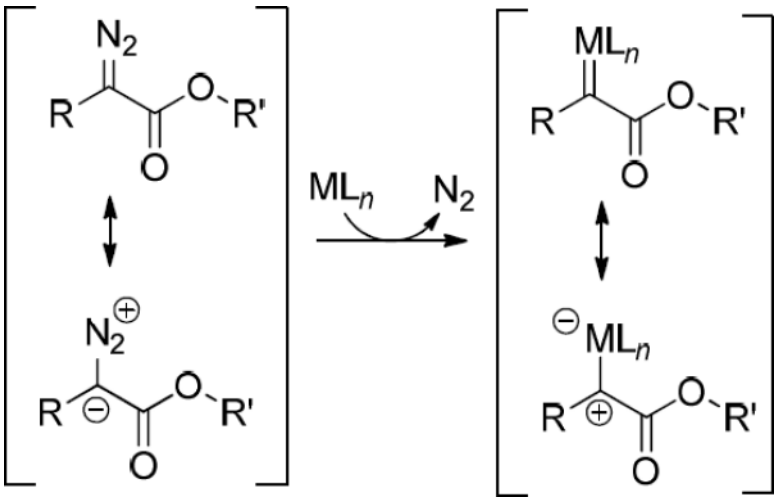
(17). The structure of the product **7i** was confirmed by deuterium exchange and 2D HSQC NMR analysis, see Supporting Information for details

(18). (a) Bach RD, Canepa C, Glukhovtsev MN. J. Am. Chem. Soc. 1999; 121:6542.(b) Liang Y, Liu S, Yu Z. Synlett. 2009; 6:905.(c) Maercker A, Daub VEE. Tetrahedron. 1994; 50:2439.For 1,4-H shift see:For 1,6-H shift see:

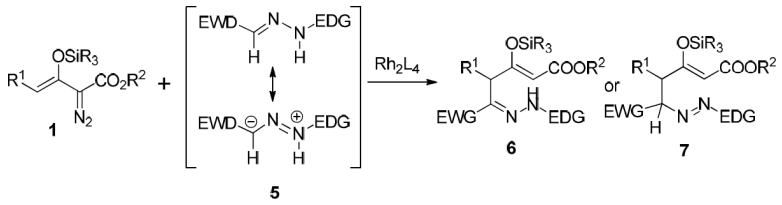
(19). The structures of **14** was confirmed by 1D-NOE and 2D-SHQC NMR analysis, see Supporting Information for details.

(20). The pyrazole synthesis via Knorr reaction occurs by the nucleophilic nitrogen attacking the carbonyl carbon, see ref 15 and 16.

(21). (a) Davies HML, Peng Z-Q, Houser JH. Tetrahedron Lett. 1994; 35:8939.(b) Ueda Y, Roberge G, Vinet V. Can. J. Chem. 1984; 62:2936.(c) Davies HML, Ahmed G, Churchill MR. J. Am. Chem. Soc. 1996; 118:10774.(d) Schwartz BD, Denton JR, Lian Y, Davies HML, Williams CM. J. Am. Chem. Soc. 2009; 131:8329. [PubMed: 19445507]

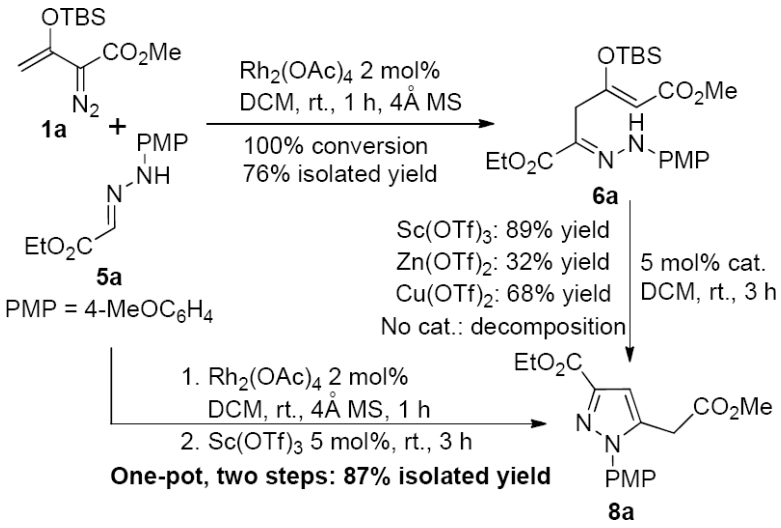


Scheme 1.
Change in polarity from diazocarbonyl compounds to the correspong metal carbenes



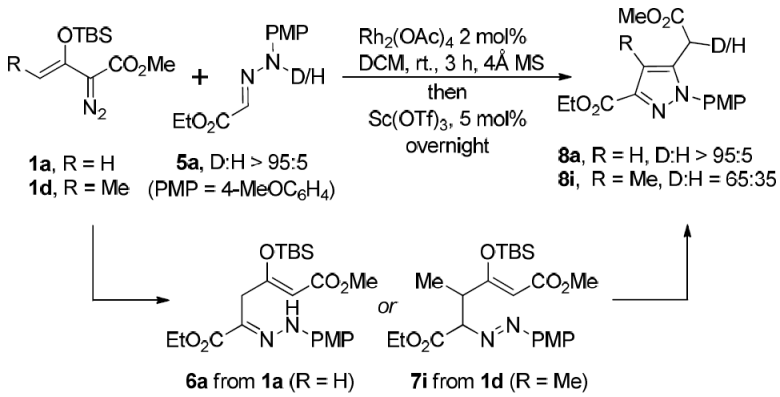
Scheme 2.

Umpolung with donor-acceptor substituted hydrazones in dirhodium(II) catalyzed reactions of **1**



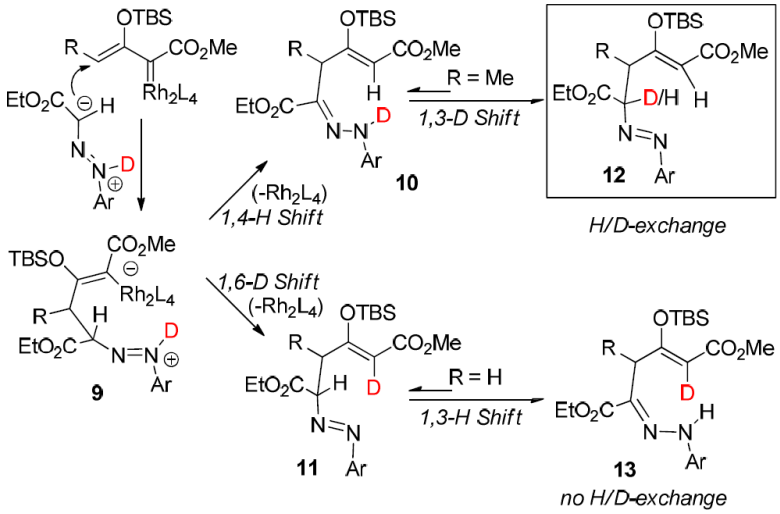
Scheme 3.

Two-step conversion compared to one-pot two-step process

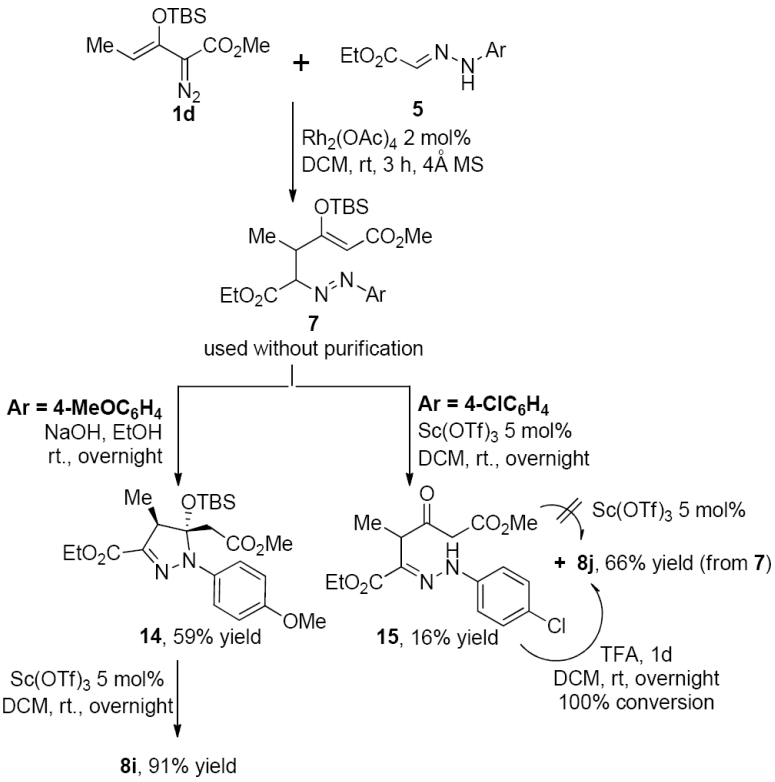


Scheme 4.

Labeling experiments define outcome of vinylogous addition step



Scheme 5.
Possible pathways for deuterium retention/loss



Scheme 6.

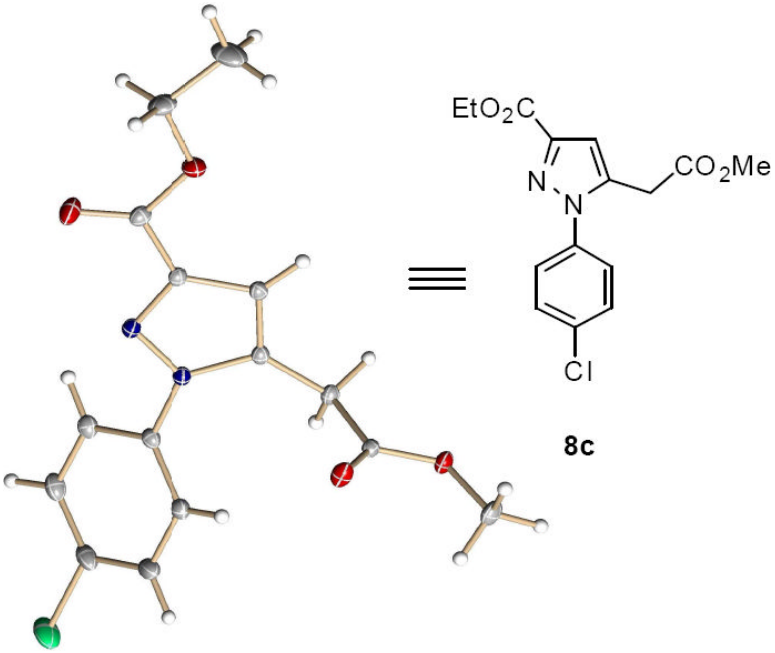
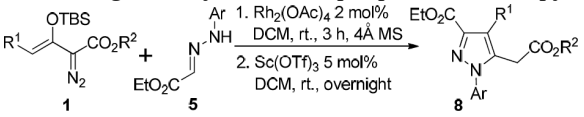


Figure 1.
Crystal structure of **8c**

Table 1

Substrate generality in the one-pot production the pyrazoles



entry	R^1/R^2 (1)	Ar in 5	8	yield 8(%)[b]
1	H/Me (**1a**)	4-$MeOC_6H_4$ (**5a**)	**8a**	87
2	H/Me (**1a**)	4-MeC_6H_4 (**5b**)	**8b**	91
3	H/Me (**1a**)	4-ClC_6H_4 (**5c**)	**8c**	90
4	H/Me (**1a**)	Ph (**5d**)	**8d**	89
5	H/Me (**1a**)	4-$NO_2C_6H_4$ (**5e**)	**8e**	71
6	H/Me (**1a**)	2,4-$2ClC_6H_3$ (**5f**)	**8f**	72
7	H/^{t}Bu (**1b**)	4-$MeOC_6H_4$ (**5a**)	**8g**	89
8	H/Bn (**1c**)	4-$MeOC_6H_4$ (**5a**)	**8h**	88
9	Me/Me (**1d**)	4-$MeOC_6H_4$ (**5a**)	**8i**	74
10	Me/Me (**1d**)	4-ClC_6H_4 (**5c**)	**8j**	66
11	Me/Bn (**1e**)	4-$MeOC_6H_4$ (**5a**)	**8k**	69
12	Et/Bn (**1f**)	4-$MeOC_6H_4$ (**5a**)	**8l**	48

[a] Reactions 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 DCM with $Rh_2(OAc)_4$ (2.0 mol%) at room temperature; then $Sc(OTf)_3$ (5.0 mol%) was added and stirred at room temperature overnight.

[b] Isolated yield of **8** based on limiting reagent **5**.