Origins of Diastereoselectivity in the Addition of Enoxysilanes to Vinyl Diazonium Salts

Avery Peck,[b] Manman Sun,[a,c] Evan Howard,[b] Xin Hong,*[a,d,e] and Matthias Brewer*[b]

[a]Center of Chemistry for Frontier Technologies, Department of Chemistry, State Key Laboratory of Clean Energy Utilization, Zhejiang University, Hangzhou 310027, China

[b]Department of Chemistry, University of Vermont, 82 University Place, Burlington, VT 05495, USA

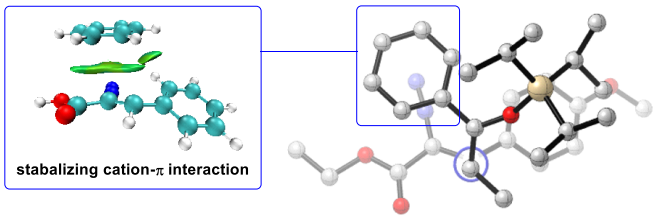
[c]Advanced Research Institute and School of Pharmaceutical Science, Taizhou University, Jiaojiang, Zhejiang 318000, China

[d]Beijing National Laboratory for Molecular Sciences, Zhongguancun North First Street NO. 2, Beijing 100190, China

[e]State Key Laboratory of Physical Chemistry of Solid Surfaces, Xiamen University, Xiamen 361005, China

E-mail: hxchem@zju.edu.cn, Matthias.brewer@uvm.edu

GRAPHICAL ABSTRACT



The high diastereoselectivity observed for some additions of enoxysilanes to vinyl diazonium salts is due to a cation-π interaction.

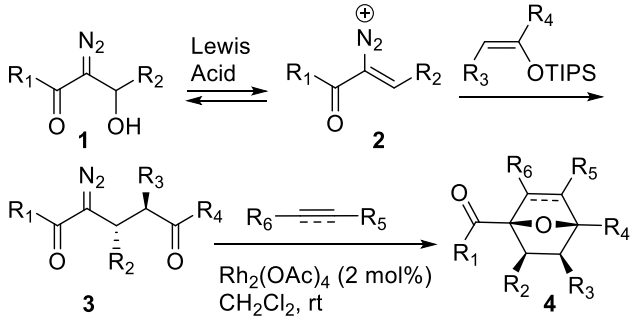
ABSTRACT

The addition of enoxysilanes to vinyl diazonium ions occurs with varying levels of diastereoselectivity. To understand the origins of the stereoselectivity, we studied these transformations using density functional theory (DFT) calculations. The selectivity stems from a stabilizing cation-π interaction that orients the nucleophile and the diazonium ion.

1,4-Conjugate addition reactions are one of the most effective strategies for bond formation in synthesis.[1-4] Mukaiyama-Michael addition reactions, wherein a Lewis acid activates an α,β-unsaturated carbonyl compound and facilitates the conjugate addition of an enoxysilane nucleophile, is a particularly mild and selective method to prepare 1,5-dicarbonyl compounds.[5-7] When the enoxysilane and α,β-unsaturated carbonyl compound are appropriately substituted, these reactions lead to the formation of two new stereocenters with varying levels of simple diastereoselectivity. The stereochemical course of Mukaiyama-Michael additions has been studied, albeit less thoroughly than that of aldol additions.[8-10] For example, Heathcock rationalized that enoxysilanes give anti stereochemistry in Mukaiyama-Michael additions because the reaction is under thermodynamic control and minimization of gauche interactions is the controlling factor.[11-12]

We recently showed that vinyl diazonium salts (**2**, Scheme 1) generated from readily available α-diazo-β-hydroxy carbonyls (**1**) under mild Lewis acid catalysis are strong electrophiles that will react productively at the β-position with a variety of nucleophiles.[13-15] Of these, the addition of silyl enol ethers is notable in that it is similar to a Mukaiyama-Michael addition but provides 2-diazo-1,5-diketone (**3**) products in high yields. These diazo products can be used to make a variety of structurally complex substituted furans (e.g. **4**).[16]

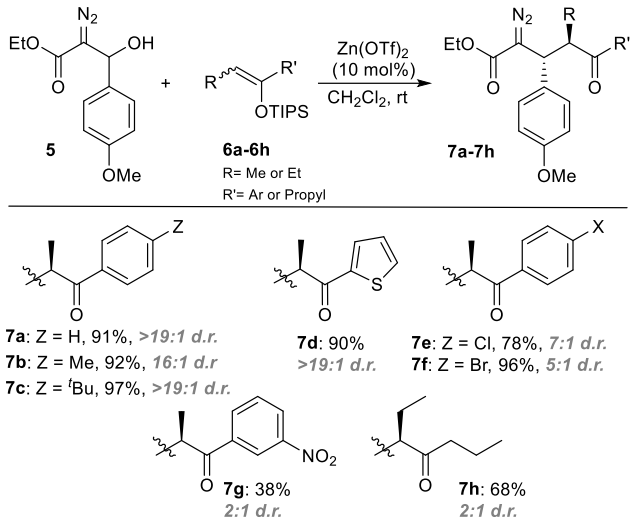
Scheme 1. Formation and Reaction of Vinyl Diazonium Ion



We noted that in many instances the addition of enoxysilanes to vinyl diazonium ions proceeded with high levels of diastereoselectivity favoring the anti-product (Table 1). The diastereoselectivity was greatest when the nucleophilic enoxysilane was derived from an alkyl aryl ketone that had an electron rich or electron neutral aryl or heteroaryl ring. For example, enoxysilanes **6a-d** added to the vinyl diazonium ion intermediate obtained from diazo alcohol **5** with high selectivity (typically >19:1). However, when the enoxysilane contained an electron poor aromatic ring (**6e-g**) or was derived from a dialkyl ketone (**6h**), the diastereoselectivity was greatly diminished. These

differing outcomes could not solely be explained by the argument put forward by Heathcock for Mukaiyama-Michael additions, and the origins of the diastereoselectivity in this case were not obvious to us. To understand these differing selectivity profiles, we studied these transformations with density functional theory (DFT) calculations and here we report a rational for the observed selectivity differences.

Table 1. Diastereoselectivity of Previously Reported Addition Reactions

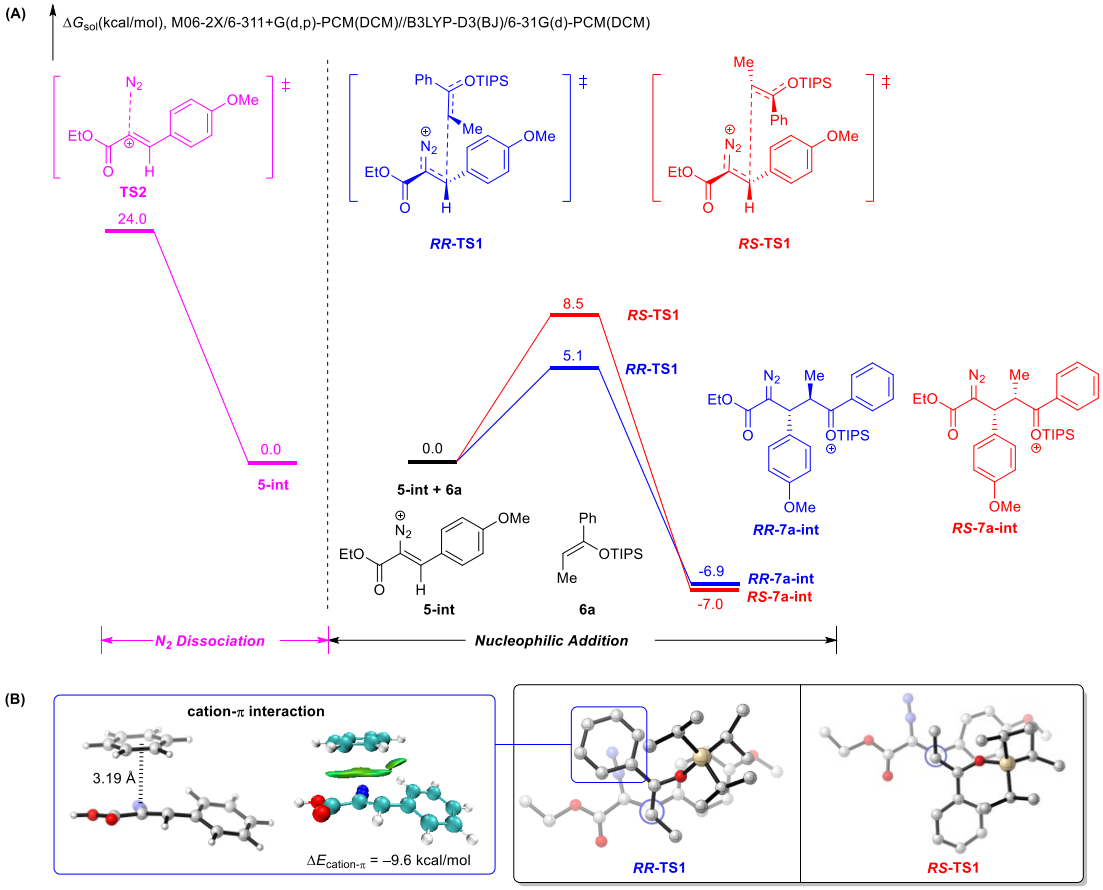


All density functional theory (DFT) calculations were performed using Gaussian 16 program.[17] Geometry optimizations of all intermediates and transition states were carried out using B3LYP functional[18-20] with 6-31G(d) basis set, including Grimme's D3 empirical dispersion corrections with BJ-damping.[21] The solvation effects in DCM were calculated with a self-consistent reaction field (SCRF) using the PCM implicit solvation model.[21-24] Frequency analysis was also performed at the same level of theory as geometry optimization to confirm whether optimized stationary points were either a local minimum or a transition state, as well as to evaluate zero-point vibrational energies and thermal corrections for enthalpies and free energies at 298.15 K. For critical transition states, intrinsic reaction coordinates (IRC) analysis was also performed at the same level of theory as geometry optimization to verify the proposed process. Single-point energies were evaluated with M062X functional[25] and 6-311+G(d,p) basis set with the inclusion of solvent correction at the PCM (DCM) level. Conformational searches for the intermediates and transition states have been conducted to ensure that the lowest energy conformers were located. The 3D diagrams of molecules were generated using CYLView.[26] Independent Gradient Model (IGM)[27] analysis was performed with Multiwfn[28] software package, using high quality grid option to generate files for further

plotting, and the visualization of IGM analysis results are presented with VMD[29] visualization software. Calculation of cation–π interaction energy between the interacting fragments was performed at M062X/6-311+G(d,p) level of theory in gas-phase with basis set superposition error (BSSE) correction using the counterpoise method.

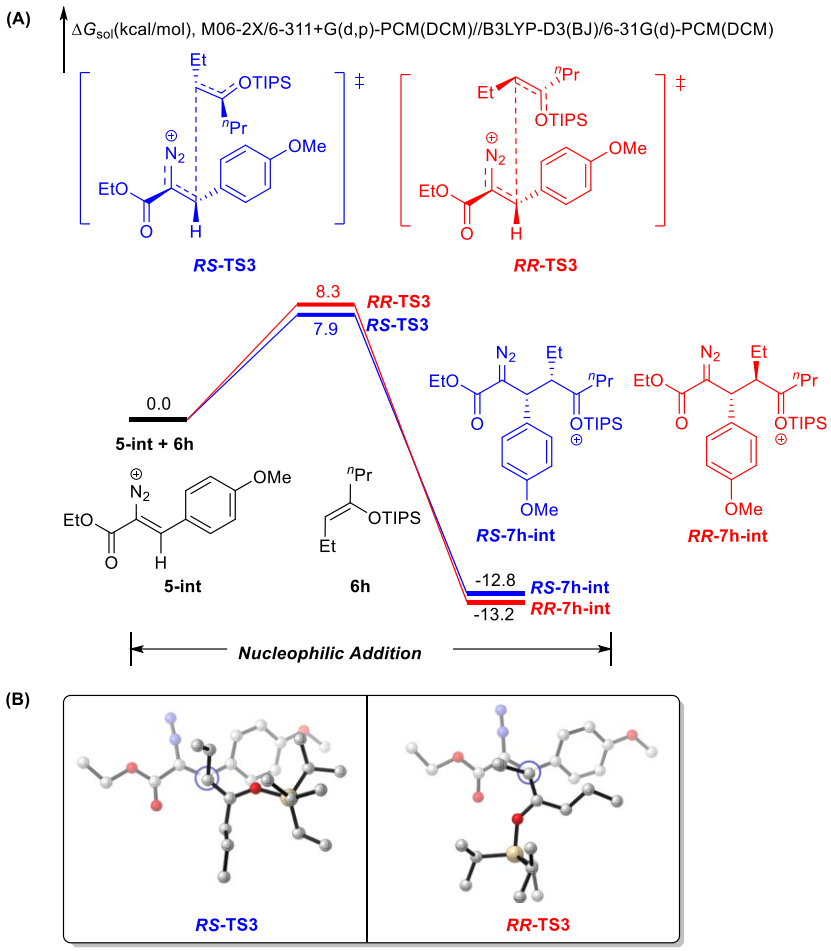
The addition of enoxysilane **6a** (Table 1, R=Me, R'= Ph) to the vinyl diazonium ion **5-int** generated from **5** gave high levels of diastereoselectivity and we chose this reaction to model using DFT. It should be mentioned that the used enoxysilanes were prepared as a mixture of *Z*/*E*-isomers. Due to the fast isomerization rate of *Z*/*E*-enoxysilanes in the presence of Lewis acidic metal catalyst, the isomerization of ***E*-6a** to ***Z*-6a** may occur prior to, or be concomitant with the addition reaction.[30,31] Hence, the reaction was modeled with ***Z*-6a**. The free energy profile for the two lowest energy conformers (***RR*-TS1** and ***RS*-TS1**) of the transition states leading to the *RR* and *RS* products are shown in Scheme 2A. These transition states are both significantly lower in energy than loss of nitrogen (24.0 kcal/mol),[32] which is a known alternative reaction pathway that leads to the formation of a vinyl cation. ***RR*-TS1** is 3.4 kcal/mol lower in energy than ***RS*-TS1**, which is consistent with the experimental observation that ***RR*-7a-int** forms as a single diastereomer. Closer inspection of ***RR*-TS1** reveals that the phenyl group on **6a** is oriented over the diazonium ion at a distance of 3.19 Å (Scheme 2B). This orientation provides a cation-π interaction that stabilizes RR-TS1 by 9.6 kcal/mol (Scheme 2B). No other conformers benefit from this stabilizing interaction which overcomes the unfavorable steric interactions shown in Scheme 2B. Other low energy conformations are provided in Fig. S1 (see SI). Benchmark studies on computational methods were also conducted to further support the calculated diastereoselectivities.[33] The calculated energy differences are summarized in Table S1 (see SI), which are consistent with the methods originally applied.

Scheme 2. DFT Calculations for the Addition of Enoxysilane 6a to 5-int. (A) Free Energy Profile. (B) Analysis of Diastereo-determining Transition States



We also computationally modeled the addition of enoxysilane **6h** to vinyl diazonium ion **5-int**, which gave low levels of diastereoselectivity. The free energy profile for the two lowest energy conformers (***RR*-TS3** and ***RS*-TS3**) of the transition states leading to the *RR* and *RS* products are shown in Scheme 3A. The optimized geometries and calculated energies for the conformations are provided in Fig. S3 (see SI).In this case, there is no possibility of a stabilizing cation-π interaction with the diazonium ion, and the difference in energy between ***RR*-TS3** and ***RS*-TS3** is computed to be only 0.4 kcal/mol (Scheme 3B).

Scheme 3. DFT Calculations for the Addition of Enoxysilane 6h to 5-int. (A) Free Energy Profile. (B) Structures of Diastereo-determining Transition States

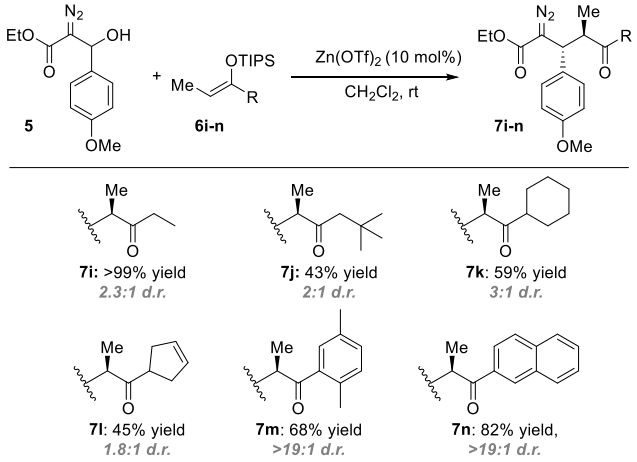


The addition of enoxysilanes **6e** and **6f** gave moderate diastereoselectivities (7:1 d.r. and 5:1 d.r), while the addition of **6g** gave low diastereoselectivity (2:1 d.r.). This trend is consistent with the computed stabilizing effect of the cation-π interaction and the relative strengths of the electron withdrawing group on the aryl ring of the enoxysilane.[34,35] When we examined the addition of **6g** to vinyl diazonium ion **5-int**, we noticed a much greater bond distance (3.24 Å) between the cation of the diazonium and the 3-nitrophenyl ring of the enoxysilane, which translates to a smaller energy difference (0.1 kcal/mol) between the ***RR*-TS4** and the ***RS*-TS4** resulting in low diastereoselectivity. The optimized geometries and calculated energies for the conformations are provided in Fig. S4 (see SI).

Working on the premise that a cation-π interaction is necessary to realize high levels of diastereoselectivity, we prepared several more enoxysilane nucleophiles and reacted them with the vinyl diazonium ion formed from diazo **5** (Table 2). Consistent with this model of stereoinduction,

enoxysilanes derived from aliphatic ketones (**6i–k**) added with low levels of diastereoselectivity while the two enoxysilanes derived from aromatic ketones that have sterically larger aromatic rings still gave excellent diastereoselectivity (**6m** and **6n**). We also tested enoxysilane **6l** to see if an alkene would be capable of producing sufficient cation-π interaction to impart diastereoselectivity. Cation-π interactions with alkenes tend to be less stabilizing than those with aryl rings,[36] and in this case the product formed with low levels of selectivity (1.8:1 d.r.).

Table 2. Diastereoselectivity of Alkyl and Aryl Enol Ether Addition Reactions



In conclusion, this work indicates that the origins of the observed diastereoselectivity for the addition of enoxysilanes to vinyl diazonium ions can be attributed to a stabilizing cation-π interaction between the cationic diazonium ion and an aryl ring that is present on the enoxysilane nucleophile. In cases where this interaction is not present, or when the cation-π interaction is weakened by incorporation of electron withdrawing groups on the aryl ring, diastereoselectivity is low.

EXPERIMENTAL SECTION

All reactions were performed under an atmosphere of nitrogen in glassware which was flame-dried under vacuum. Tetrahydrofuran (THF), toluene (PhMe), and dichloromethane (CH_2Cl_2) were dried by passing through activated alumina columns and dispensed from a solvent dispensing system under argon. Pyridine was freshly distilled from CaH_2 prior to use. $Zn(OTf)_2$ was dried in a vacuum oven (140 °C, 30 mmHg) for 4 hours prior to use. All other commercially available reagents were used as received unless otherwise indicated. Flash chromatography was performed on manually packed silica gel (230-400 mesh), or on a Teledyne ISCO CombiFlash® automated chromatography system using pre-packaged silica gel columns. NEt_3-deactivated silica was made by preparing a

silica gel slurry with 1% NEt_3 in hexanes and allowing the hexanes to evaporate. TLC analysis was carried out on glass-backed silica gel plates (250 μm thickness), and plates were visualized using ultraviolet light, I_2 vapor, or ceric ammonium molybdate (CAM) stain.

^1H and $^{13}C\{1H\}$ NMR data were collected at room temperature on a Bruker Avance NMR spectrometer at 500 MHz (^1H) and 125 MHz (^{13}C). Chemical shifts are reported in ppm (δ units) downfield from tetramethylsilane; ^1H NMR spectra are referenced to the TMS signal at 0.00 ppm, the internal $CDCl_3$ signal at 7.26 ppm, or the internal CD_3CN signal at 1.94 ppm. ^{13}C NMR spectra are referenced to the internal $CDCl_3$ signal at 77.16 ppm, or the internal CD_3CN signal at 1.32 ppm. Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, sept = septet, m = multiplet, app = apparent, br = broad. IR data were collected on a Shimadzu IR Affinity-1 FTIR and values are reported in wavenumbers. Exact mass analysis was performed using a Waters Xevo G2-XS QTof LCMS operated in positive ESI mode or an Agilent 6530 QToF LCMS operated in positive ESI mode.

General procedure for the $Zn(OTf)_2$-catalyzed addition of enoxysilanes to vinyl diazonium salts. A solution of the ethyl 2-diazo-3-hydroxy-3-(4-methoxyphenyl)propanoate (1.0 eq.) and enoxysilane (1.6-2.0 eq.) in 1 mL CH_2Cl_2 was rapidly added to a rapidly stirring suspension of $Zn(OTf)_2$ (0.1 eq.) suspended in CH_2Cl_2 (4 mL) at room temperature. The mixture was allowed to stir at room temperature until TLC analysis indicated complete consumption of the β-hydroxy-α-diazo carbonyl starting material. The reaction mixture was then passed directly through a plug of NEt_3-deactivated silica gel, and the plug was eluted thoroughly with CH_2Cl_2. The effluent was concentrated in vacuo and the residue purified by flash chromatography on NEt_3-deactivated silica gel to afford the conjugate addition products.

Ethyl 2-diazo-3-(4-methoxyphenyl)-4-methyl-5-oxoheptanoate (7i). Prepared from ethyl 2-diazo-3-hydroxy-3-(4-methoxyphenyl)propanoate (75 mg, 0.30 mmol) and (*E*/*Z*)-triisopropyl(pent-2-en-3-yloxy)silane (**6i**) (146 mg, 0.60 mmol) according to the general procedure. The resulting residue was purified by flash chromatography on Et_3N deactivated SiO_2 (gradient elution, 0-2% EtOAc in 99:1 hexanes:Et_3N) to give the title compound as a yellow oil (96 mg, 2.3:1 d.r., quantitative yield). R_f = 0.12 (10% EtOAc/hexanes); ^1H-NMR (500 MHz, $CDCl_3$) δ 7.18 (m 2H), 6.86, (m, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 3.74 (d, *J* = 11.2 Hz, 1H), 3.30-3.22 (m, 1H), 2.66-2.57 (m, 1H), 2.52-2.43 (m, 1H), 1.23-1.19 (3H), 1.07 (t, *J* = 7.2 Hz, 3H), 0.96 (d, *J* = 7.0 Hz,

3H); $^{13}C\{1H\}$-NMR (125 MHz, $CDCl_3$) δ 213.1, 166.6, 159.0, 132.3, 128.9, 114.4, 60.9, 55.4, 48.4, 42.2, 34.3, 16.5, 14.5, 7.9. IR (neat): 2979, 2937, 2908, 2877, 2838, 2077, 1702, 1684, 1610, 1584, 1513, 1456, 1370, 1303, 1248, 1179, 1101, 1080, 1034, 975, 956, 914, 880, 831. HRMS (ESI) m/z: [M + Na]+ Calcd for $C_{17}H_{22}N_2O_4Na$ 341.1477, found 341.1479.

Observable resonances for minor diastereomer: ^1H-NMR (500 MHz, $CDCl_3$) δ 7.13 (m, 2H), 6.81 (m, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.85 (d, *J* = 11.5 Hz, 1H), 3.77 (s, 3H), 2.41-2.31 (m, 1H), 2.12-2.02 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.81 (t, *J* = 7.2 Hz, 3H); $^{13}C\{1H\}$-NMR (125 MHz, $CDCl_3$) δ 213.7, 132.8, 128.6, 114.3, 61.1, 55.3, 48.7, 42.5, 35.9, 16.4, 14.6, 7.5.

(3S,4S)-ethyl 2-diazo-3-(4-methoxyphenyl)-4,7,7-trimethyl-5-oxooctanoate (7j). Prepared according to the general procedure from (*E*/*Z*)-((5,5-dimethylhex-2-en-3-yl)oxy)triisopropylsilane **(6j)** (170 mg, 0.6 mmol, 2.0 eq.) and ethyl 2-diazo-3-hydroxy-3-(4-ethoxyphenyl)propanoate (75 mg, 0.3 mmol, 1.0 eq.). Purification by flash chromatography on SiO_2 (gradient elution, 0 to 6% EtOAc in 99:1 hexanes:NEt_3) gave the title compound as a yellow oil (46 mg, 2:1 d.r., 43% yield). R_f = 0.40 (10% EtOAc/hexanes); ^1H-NMR (500 MHz, $CDCl_3$) δ 7.20-7.16 (m, 2H), 6.87-6.84 (m, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 3.68 (d, J = 11.3 Hz, 1H), 3.24-3.15 (m, 1H), 2.47 (d, J = 16.9 Hz, 1H), 2.40 (d, J = 16.9 Hz, 1H), 1.22 (t, J = 7.2 Hz, 3H), 1.02 (s, 9H), 0.93 (d, J = 7.0 Hz, 3H); $^{13}C\{1H\}$-NMR (125 MHz, $CDCl_3$) δ 211.9, 166.6, 159.0, 132.5, 129.0, 114.3, 60.9, 55.4, 49.5, 42.4, 30.7, 29.6, 16.2, 14.6.

Observable resonances for minor diastereomer: ^1H-NMR (500 MHz, $CDCl_3$) δ 7.16- 7.13 (m, 2H), 6.83-6.80 (m, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.77 (s, 3H), 3.13-3.06 (m, 1H), 2.21 (d, J = 16.7 Hz, 1H), 1.98 (d, J = 16.7 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.18 (d, J = 6.9 Hz, 3H), 0.80 (s, 9H); $^{13}C\{1H\}$-NMR (125 MHz, $CDCl_3$) δ 212.5, 158.9, 133.0, 128.8, 114.2, 61.1, 53.4, 49.9, 42.5, 30.5, 29.5, 16.1. HRMS (ESI) m/z: [M + Na]+ Calcd for $C_{20}H_{28}N_2O_4Na$ 383.1941, found 383.1936.

Ethyl 5-cyclohexyl-2-diazo-3-(4-methoxyphenyl)-4-methyl-5-oxopentanoate (7k). Prepared according to the general procedure from (*Z*)-((1-cyclohexylprop-1-en-1-yl)oxy)triisopropylsilane **(6k)** (178 mg, 0.6 mmol, 2.0 eq.) and ethyl 2-diazo-3-hydroxy-3-(4-methoxyphenyl)propanoate (75 mg, 0.3 mmol, 1.0 eq.). Purification by flash chromatography on SiO_2 (gradient elution, 0 to 3% EtOAc in 99:1 hexanes:NEt_3) gave the title compound as a yellow oil (66 mg, 3:1 d.r., 59% yield). R_f = 0.22 (10% EtOAc/hexanes); ^1H-NMR (500 MHz, CDCl3) δ 7.23-7.18 (m, 2H), 6.87-6.83 (m, 2H), 4.18-4.10 (m, 2H), 3.79 (s, 3H), 3.71 (d, J = 11.0 Hz, 1H), 3.49-3.39 (m, 1H), 2.52 (tt, J = 11.1,

3.1 Hz, 1H), 1.83-1.74 (m, 4H), 1.70-1.54 (m, 3H), 1.48-1.39 (m, 1H), 1.33-1.14 (m, 5H), 0.93 (d, J = 6.9 Hz, 3H); ^{13}C{1H}-NMR (125 MHz, CDCl3) δ 216.1, 166.6, 158.9, 132.5, 129.1, 114.3, 60.8, 55.4, 50.3, 46.7, 42.4, 28.9, 28.5, 25.9, 25.9, 25.7, 17.8, 16.7, 14.6.

Observable resonances for minor diastereomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.16- 7.12 (m, 2H), 6.08-6.77 (m, 2H), 4.20 (q, J = 7.0 Hz, 2H), 3.83 (d, J = 11.5 Hz, 1H), 3.76 (s, 3H), 3.37-3.27 (m, 1H), 2.16-2.09 (m, 1H); ^{13}C{1H}-NMR (125 MHz, CDCl3) δ 215.3, 158.85, 133.4, 128.9, 114.1, 61.0, 51.2, 47.6, 42.7, 28.3, 27.8, 25.8, 25.6, 16.8. HRMS (ESI) m/z: [M + Na]+ Calcd for $C_{21}H_{28}N_2O_4Na$ 395.1947, found 395.1948.

Ethyl 5-(cyclopent-3-en-1-yl)-2-diazo-3-(4-methoxyphenyl)-4-methyl-5-oxopentanoate (7l). Prepared according to the general procedure from (*Z*)-((1-(cyclopent-3-en-1-yl)prop-1-en-1-yl)oxy)triisopropylsilane **(6l)** (168 mg, 0.6 mmol, 2.0 eq.) and ethyl 2-diazo-3-hydroxy-3-(4-ethoxyphenyl)propanoate (75 mg, 0.3 mmol, 1.0 eq.). Purification by flash chromatography on SiO_2 (gradient elution, 0 to 1% EtOAc in 99:1 hexanes:NEt_3) gave the title compound as a yellow oil (48 mg, 1.8:1 d.r., 45% yield). R_f = 0.20 (10% EtOAc/hexanes); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.23-7.18 (m, 2H), 6.88-6.84 (m, 2H), 5.68-5.65 (m, 1H), 5.64-5.60 (m, 1H), 4.15 (app. qd, *J* = 7.1, 2.0 Hz, 2H), 3.79 (s, 3H), 3.48-3.37 (m, 2H), 2.72-2.31 (m, 5H), 1.27-1.19 (m, 3H), 0.99 (d, *J* = 7.1 Hz, 3H); ^{13}C{1H}-NMR (125 MHz, $CDCl_3$) δ 213.9, 166.6, 159.0, 132.3, 129.3, 129.0, 128.83, 128.81, 128.7, 128.5, 114.3, 60.9, 55.4, 48.8, 48.0, 42.3, 36.5, 35.5, 16.5, 14.6.

Observable resonances for minor diastereomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.17-7.13 (m, 2H), 6.63-6.78 (m, 2H), .54-5.50 (m, 1H), 5.47-5.43 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.87 (d, *J* = 11.5 Hz, 1H), 3.76 (s, 3H), 3.34-3.25 (m, 1H), 3.10-3.00 (m, 1H), 2.25-2.17 (m, 1H), 2.05-1.97 (m, 1H); ^{13}C{1H}-NMR (125 MHz, $CDCl_3$) δ 214.8, 166.9, 158.9, 133.1, 114.2, 61.1, 55.4, 48.9, 47.9, 42.7, 35.1, 35.0, 16.7. IR (neat): 3059, 2978, 2436, 2852, 2080, 1687, 1512, 1460, 1370, 1302, 1256, 1104, 1037 cm^{-1}. HRMS (ESI) m/z: [M + Na]+ Calcd for $C_{20}H_{24}N_2O_4Na$ 379.1628, found 379.1634.

Ethyl 2-diazo-5-(2,5-dimethylphenyl)-3-(4-methoxyphenyl)-4-methyl-5-oxopentanoate (7m). Prepared from ethyl 2-diazo-3-hydroxy-3-(4-methoxyphenyl)propanoate (75 mg, 0.30 mmol and (*E*/*Z*)-((1-(2,5-dimethylphenyl)prop-1-en-1-yl)oxy)triisopropylsilane **(6m)** (191 mg, 0.60 mmol) according to the general procedure . The resulting residue was purified by flash chromatography on Et_3N deactivated SiO_2 (gradient elution, 0-2% EtOAc in 99:1 hexanes/Et_3N) to give the title

compound as a yellow oil (80 mg, single d.r. ,68% yield). R_f = 0.15 (10% EtOAc/hexanes); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.21-7.16 (m, 3H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 7.8 Hz 1H), 6.79-6.75 (m, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.09 (d, *J* = 11.2 Hz, 1H), 4.00 (brs, 1H), 3.75 (s, 3H), 2.34 (s, 3H), 2.09 (s, 3H), 1.38 (d, *J* = 6.7 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C{1H}-NMR (125 MHz, $CDCl_3$) δ 206.2, 166.9, 158.8, 158.5, 135.1, 135.1, 133.0, 131.9, 131.6, 128.8, 128.1, 114.1, 55.3, 46.6, 21.1, 20.0, 17.8, 17.4, 14.6. IR (neat): 2975, 2930, 2870, 2837, 2077, 1684, 1611, 1584, 1512, 1496, 1456, 1370, 1303, 1345, 1216, 1179, 1124 ,1097, 1034, 1000, 969, 870, 820. HRMS (ESI) m/z: [M + Na]+ Calcd for [$C_{23}H_{26}N_2O_4$Na 417.1790, found 417.1799.

Ethyl 2-diazo-3-(4-methoxyphenyl)-4-methyl-5-(naphthalen-2-yl)-5-oxopentanoate (7n). Prepared from ethyl 2-diazo-3-hydroxy-3-(4-methoxyphenyl)propanoate (75 mg, 0.30 mmol and (*E*/*Z*)-triisopropyl((1-(naphthalen-2-yl)prop-1-en-1-yl)oxy)silane **(6n)** (204 mg, 0.60 mmol) according to the general procedure . The resulting residue was purified by flash chromatography on Et_3N deactivated SiO_2 (gradient elution, 0-2-4% EtOAc in 99:1 hexanes/Et_3N) to give the title compound as a yellow oil (101 mg, single d.r., 82% yield). R_f = 0.12 (10% EtOAc/hexanes); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.80 (m, 1H), 7.62 (dd, *J* = 7.23, 1,28 Hz, 1H), 7.48-7.44 (m, 1H), 7.44-7.40 (m, 2H), 7.24-7.18 (m, 2H), 6.72-6.67 (m, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.19-4.10 (m, 2H), 3.67 (s, 3H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C{1H}-NMR (125 MHz, $CDCl_3$) δ 205.8 167.0, 158.8, 136.8, 133.9, 133.0, 132.5, 130.3, 128.9, 128.3, 127.8, 126.5, 125.6, 124.3, 114.2, 61.1, 55.3, 47.7, 29.8, 17.4, 14.6. IR (neat): 3047, 2978, 2933, 2971, 2837, 2077, 1684, 1611, 1511, 1462, 1393, 1370, 1303, 1235, 1215, 1179, 1179, 1099, 1034, 940, 912, 829, 805. HRMS (ESI) m/z: [M + Na]+ Calcd for $C_{25}H_{24}N_2O_4$Na 439.1634, found 439.1636.

NOTE: This compound was sensitive to SiO_2.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information Statement

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org. Experimental details (including experimental procedures, copies of NMR spectra and computational details).

AUTHOR INFORMATION

Corresponding Authors

Matthias Brewer – Department of Chemistry, University of Vermont, 82 University Place, Burlington, VT 05495, USA; orcid.org/0000-0003-4250-7195; E-mail: Matthias.brewer@uvm.edu

Xin Hong - Center of Chemistry for Frontier Technologies, Department of Chemistry, State Key Laboratory of Clean Energy Utilization, Zhejiang University, Hangzhou 310027, China; Beijing National Laboratory for Molecular Sciences, Beijing 100190, China; State Key Laboratory of Physical Chemistry of Solid Surfaces, Xiamen University, Xiamen 361005, China; orcid.org/0000-0003-4717-2814; Email: hxchem@zju.edu.cn

Author:

Avery Peck - Department of Chemistry, University of Vermont, 82 University Place, Burlington, VT 05495, USA

Manman Sun - Center of Chemistry for Frontier Technologies, Department of Chemistry, State Key Laboratory of Clean Energy Utilization, Zhejiang University, Hangzhou 310027, China; Advanced Research Institute and School of Pharmaceutical Science, Taizhou University, Jiaojiang, Zhejiang 318000, China; orcid.org/0000-0003-1126-8777

Evan Howard- Department of Chemistry, University of Vermont, 82 University Place, Burlington, VT 05495, USA

Notes:

The authors declare no competing financial interest.

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