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A Survey of Enoldiazo Nucleophilicity in Selective C-C Bond Forming Reactions for the Synthesis of Natural Product-Like Frameworks

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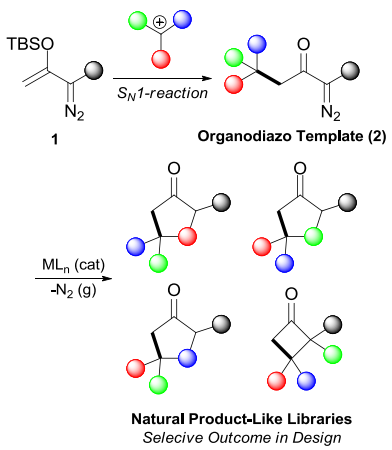
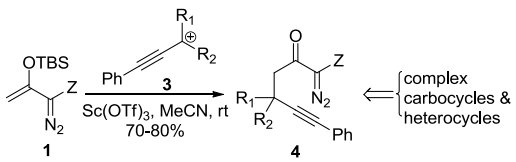
A survey of *in situ*, catalytically generated carbocations for coupling with enoldiazoacetate nucleophiles was performed. These couplings facilitate the rapid assembly of complex organodiazo compounds that provide a template for the synthesis of a variety of carbocyclic and heterocyclic ring systems.

Complex organodiazo templates **2** have shown great potential as platforms for syntheses (Scheme 1), but methods for their preparation have been limited. Recently our group,[1a-d] and others,[1e,f] have endeavoured to unlock the full synthetic potential of enoldiazo reagents **1** as a way to prepare these complex organodiazo templates. In addition to their dirhodium (II)-catalyzed dinitrogen extrusion reactions,[2] enoldiazo compounds **1** can serve as a general nucleophile in substitution,[1a] aldol,[1b] Michael,[1c] and Mannich[1d] reactions whereby the diazo functionality is retained. These nucleophilic transformations provide complex organodiazo templates **2** that have long been of interest in organic synthesis.



Scheme 1 General Coupling Strategy

Recent explorations of the couplings of enoldiazo compounds **1** (Z = COOR, SO_2Ar, COPh, and H) with propargylic carbocations **3** have revealed the great potential of S_N1-like couplings with **1** to construct complex alkynyl tethered diazoketones **4** via selective C-C bond formation (Scheme 2).[1a] Organodiazo compounds **4** were in turn shown to be versatile synthetic templates for constructing a diverse array of polyfunctionalized carbo- and heterocyclic products. From the perspective of Diversity Oriented Synthesis (DOS),[3] intermediates derived from carbocationic couplings of **1** provide organodiazo templates **2** that offer a range of possibilities for accessing diverse libraries of small molecules and makes enoldiazo chemistry a promising platform for drug discovery. S_N1-like couplings place substituents at the δ-position of diazoacetoacetates that is most advantageous for catalytic intramolecular reactions of the diazo ester. Herein we report a generalization of this electrophilic addition process exemplified by selective C-C bond forming reactions of methyl enoldiazoacetate **1a** (Z = COOMe) with a broad series of carbocation structures. In addition, we have explored the potential of complex organodiazo frameworks such as **4** to prepare unique carbocyclic and heterocyclic scaffolds bearing natural product-like features.



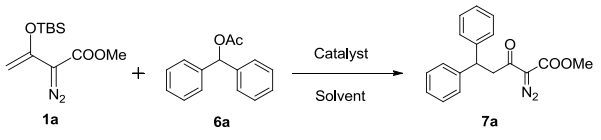
Scheme 2 Enoldiazoacetate Coupling with Propargyl Acetates (Z = COOR, SO_2Ar, COPh, and H)

The reactions of methyl enoldiazoacetate **1a** with *in situ* generated benzylic, allylic and oxonium carbocations were surveyed. Carbocation generation was designed to occur under mild conditions using a Lewis acid catalyst. In prior efforts[4] zinc triflate and scandium triflate had both been found to be optimal; and they were evaluated along with several other Lewis acids in this study. Optimization was performed with benzhydryl acetate **6a** which formed 2-diazo-3-oxo-5,5-diphenyl pentanoate **7a** when reactions were performed under anhydrous conditions for 16 h. The results reported in Table 1 describe the influence of catalyst, catalyst loading, solvent and temperature on the yield of the diazoacetoacetate product.

Initially we found that the reaction of **1a** with **6a** was sluggish when catalyzed by 2 mol % of anhydrous $Zn(OTf)_2$ (Table 1, entry 1), but the yield of **7a** was dramatically improved to a moderate yield of 53% when 1 mol % of anhydrous $Sc(OTf)_3$ was the catalyst (entry 2). An increase in yield of **7a** to 59% was observed when molecular sieve was used (entry 3). Further optimization by changing the Lewis acid catalyst (entry 4-6) did not result in any improvement over that provided by $Sc(OTf)_3$.

Although DCM was used in earlier investigations of electrophilic addition reactions with enoldiazoacetates,[1b-d] as found in reactions with propargyl acetates,[1a] dipolar aprotic acetonitrile was the optimum solvent for these reactions; lower yields of the desired product were found in reactions performed in THF and DCM (entry 7-8). Increasing the catalyst loading from 1% to 3 mol% improved product yield from 59% to 79% with little further change occurring with an increase in catalyst loading to 5 mol% $Sc(OTf)_3$ (entries 3,9 and 10) . However, although the effect of increasing catalyst loading often suggests a sluggish reaction, heating the reaction mixture at 40 ℃ did not increase the yield of **7a** (entry 11). The major operational concern with this reaction is hydrolysis of **1a** to methyl diazoacetoacetate and, because of this, a 20% excess of the enoldiazoacetate was employed.

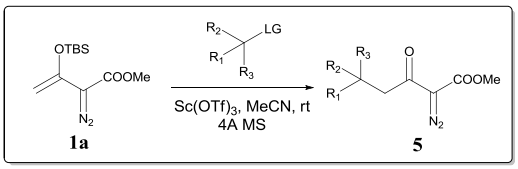
Table 1 Optimization of the reaction conditions [a]

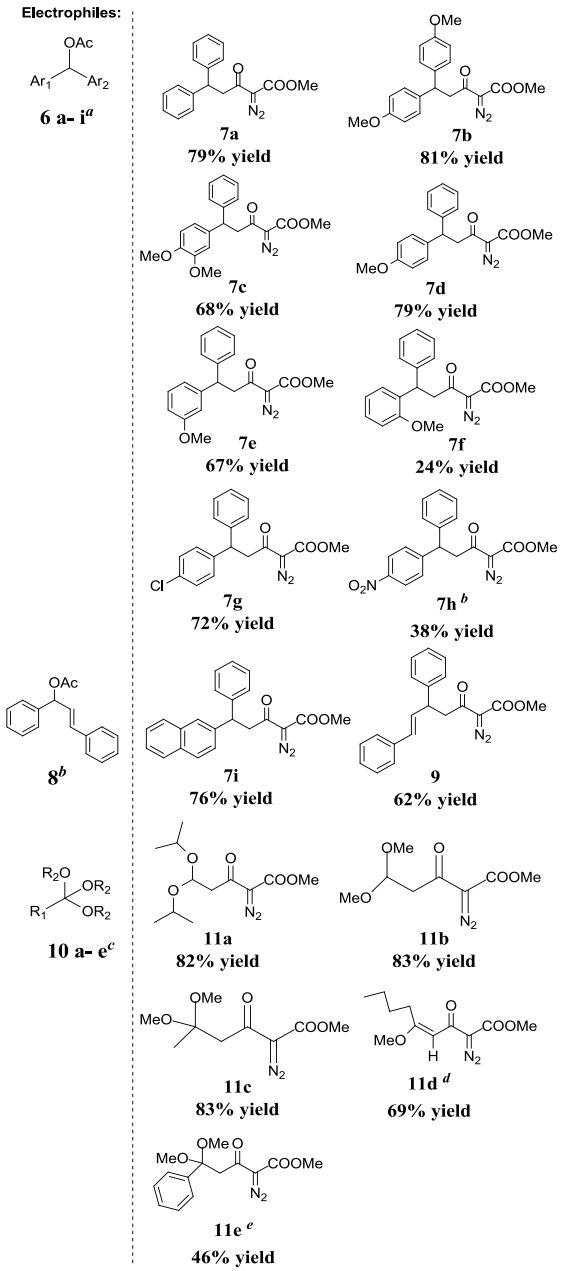


Entry	Catalyst (mol %)	Solvent	Temperature (℃)	Yield **7a** [b] (%)
1	$Zn(OTf)_2$ (2)	MeCN	r.t.	8
2 [c]	$Sc(OTf)_3$ (1)	MeCN	r.t.	53
3	$Sc(OTf)_3$ (1)	MeCN	r.t.	59
4	AgOTf (2)	MeCN	r.t.	trace
5	$In(OTf)_3$ (2)	MeCN	r.t.	trace
6	$Cu(OTf)_2$ (2)	MeCN	r.t.	38
7	$Sc(OTf)_3$ (1)	THF	r.t.	21
8	$Sc(OTf)_3$ (1)	DCM	r.t.	50
9	$Sc(OTf)_3$ (3)	MeCN	r.t.	79
10	$Sc(OTf)_3$ (5)	MeCN	r.t.	82
11	$Sc(OTf)_3$ (3)	MeCN	40	79

[a] Reaction conditions: A mixture of methyl enoldiazoacetate (1.2 equiv.), benzhydryl acetate (1.0 equiv.), molecular sieve (100 mg/mmol) and catalyst (1-5 mol %) in freshly distilled solvent (0.5M) was stirred at the specified temperature for 16 hours. [b] Isolated yields. [c] Reaction without molecular sieve.

With the optimized protocol in hand, we explored the scope and limitations of the reaction process with respect to various benzylic substrates. The results from these investigations are given in Scheme 3. Benzhydryl acetates **6a-i** reacted with enoldiazoacetate **1a** to give the corresponding coupling products in moderate to good yields. These reactions were limited only when the benzhydryl framework was substituted with the strongly electron-withdrawing nitro group. A methoxy substituted in the ortho position significantly decreased product yield, and *m*-methoxybenzhydryl acetate was less reactive than the para-isomer. However, a chloride substituent para on the benzene ring **6g** afforded **7g** in good yield. The reaction of enoldiazoacetate **1a** with 1,3-diphenylallyl acetate **8** occurred to form the corresponding coupling product methyl 2-diazo-3-oxo-5,7-diphenylhept-6-enoate **9** in moderate yield (62%). However, 1-phenyl-2-propenyl acetate, which would produce an unsymmetrical allyl cation intermediate, gave a mixture of regioisomers in reactions with methyl enoldiazoacetate **1a**. The sensitivity of the benzhydryl system to substituent effects was expected and suggests the limitation of this methodology – under the conditions employed in this study benzyl acetates and simple allyl acetates did not undergo coupling with methyl enoldiazoacetate **1a**, but we can anticipate that the use of more Lewis acidic catalysts and/or stronger leaving groups would broaden the scope of this transformation.





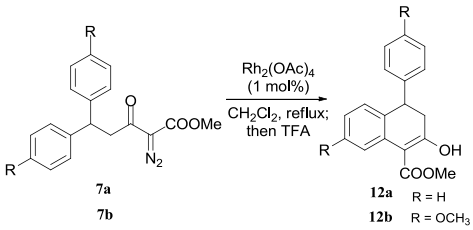
[a] Reaction conditions: A mixture of enoldiazoacetate (1.2 equiv.), substrate (1.0 equiv.), molecular sieve (100 mg/mmol) and anhydrous $Sc(OTf)_3$ (3.0 mol %) in freshly distilled acetonitrile (0.5M) was stirred at room temperature for 16 hours. [b] The reaction was catalyzed by 5.0 mol % anhydrous $Sc(OTf)_3$ under the same conditions. [c] The reaction was catalyzed by 0.50 mol %

anhydrous $Sc(OTf)_3$ under the same conditions. [d] **11d** was formed after treating the reaction mixture with 1.0 equivalent TFA, and its configuration was determined by ^{1}D NOE experiments. See SI for details. [e] The reaction was catalyzed by 1.5 mol % anhydrous $Sc(OTf)_3$.

Scheme 3 S_N1 Reactions of Enoldiazoacetates with Benzhydryl/Allyl Acetates and Orthoesters

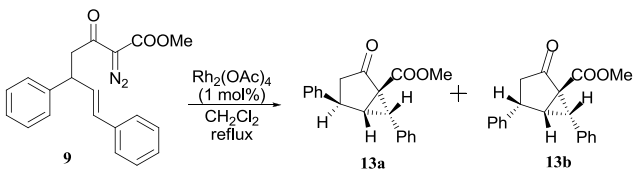
Orthoesters are a convenient source of relatively stable carbocations suitable for reactions with diazo compounds,[5] and with their use we have observed couplings with enoldiazoacetate **1a** that form acetal- and ketal-tethered diazoacetoacetates[5] in good to excellent yields (Scheme 3). Use of zinc triflate in DCM gave lower product yields (65% for R = Me; 62% for R = Et; 56% for R = *i*-Pr) than did scandium triflate in acetonitrile, but catalyst loadings for both zinc and scandium triflates at only 0.5 mol % were adequate (see the Supporting Information for details). Other Lewis acids, including $La(OTf)_3$, $Yb(OTf)_3$, $Sn(OTf)_2$, and copper(II) catalysts were also used, but without improvement. Changing the R_2 substituent of orthoformates from isopropyl **10a** to methyl **10b** had no effect on product yield (82% and 83%, respectively), and neither did increasing the number of equivalents of orthoformate. In addition to orthoformates (R_1 = H) this coupling reaction could be extended to orthoesters with R_1 = methyl, *n*-butyl and phenyl. However, with trimethyl orthovalerate **10d**, the initially formed ketal underwent elimination of methanol under even these mild catalytic conditions to form enonediazoacetate **11d** in only the (*E*)-configuration, as confirmed by NOE experiments; complete conversion to **11d** was facilitated by treatment with trifluoroacetic acid. Furthermore, trimethyl orthobenzoate **11e**, which does not undergo coupling with **1a** in DCM catalyzed by $Zn(OTf)_2$, formed **11e** in moderate yield (46%) from reactions in acetonitrile catalyzed by $Sc(OTf)_3$, albeit with higher catalyst loading. At long reaction times these couplings are sensitive to the presence of trace amounts of water that cause conversion of the orthoester to the corresponding ester and alcohol causing a subsequent cascade in loss of orthoester reactant.

To exemplify the utility of this general methodology we have investigated catalytic intramolecular reactions of these δ-substituted diazoacetoacetates. The products from condensation with benzhydryl acetates are suitably constructed for intramolecular cycloaddition or substitution of catalyst-generated metal carbenes into the aromatic ring.[6] Although, the vast array of intramolecular substitution reactions have been performed with aromatic rings at the γ-position [7] and, conversely, most intramolecular aromatic cycloaddition reactions have occurred with aromatic rings at the δ-position,[8] this system was examined with the potential that either or both processes could occur. The reaction of 7**a** with $Rh_2(OAc)_4$ in refluxing CH_2Cl_2 gave a mixture of substitution and aromatic cycloaddition products that, following treatment with TFA provided β-tetralone[9] **12** in 82% yield (Scheme 4), which bears resemblance to biologically active tetralin natural products, such as the calamenenes,[10] and synthetic intermediates used to prepare drug-like molecules.[11] The *p*-methoxy derivative **7b** afforded the corresponding derivative in 84% yield.



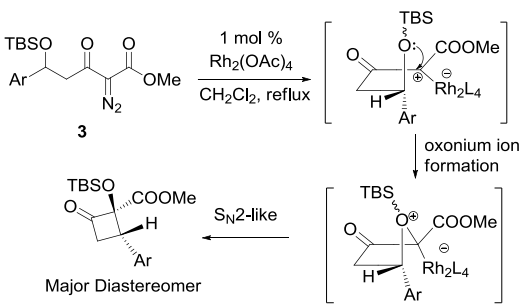
Scheme 4 Benzylation to Access β-Tetralone Derivatives

Diazoacetoacetate **9** provided an opportunity to assess chemoselectivity in catalytic dinitrogen extrusion reactions. A prior report from a dirhodium(II) catalysed reaction of a diazoketone showed cyclopropanation to be competitive with aromatic cycloaddition with rhodium acetate.[12] However, rhodium acetate catalysed reaction of **9** gave only the bicyclic cyclopentanone **13** through cyclopropanation (Scheme 5), and products from aromatic cycloaddition or substitution into the phenyl ring were not observed. In this event, cyclopentanone **13** was produced in 56% yield with 65:35 diastereoselectivity (**13a**:**13b**). Rhodium caprolactamate was also used in refluxing DCE, but without improvement of diastereoselectivity. Cyclopropanes such as **13** have proven to be versatile intermediates in the synthesis of more complex biologically active compounds.[13]



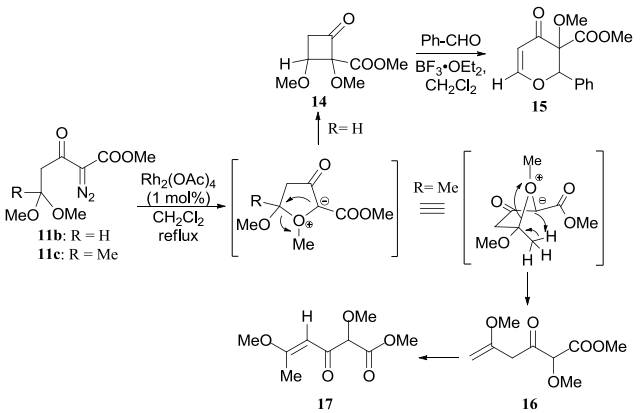
Scheme 5 Prenylation Products to Synthesize Cylcopentanones

δ,δ-dialkoxy-β-keto-α-diazoesters **11b,c** allowed divergent access to interesting compounds based solely on the R-group used in the couplings of **10b,c** with **1a**. The placement of an ether oxygen at the δ-position allows formation of oxonium ylide intermediates that can undergo skeletal rearrangements.[14] Previously, the coupling products formed catalytic Mukaiyama-aldol reactions of **1a** were shown to form cyclobutanone products with good diastereoselectivity (Scheme 6).[15] Transformation of the intermediate dirhodium carbene to the corresponding oxonium ylide formed with the siloxy oxygen was completed by an internal S_N2-type displacement that resulted in ring closure to the observed cyclobutanone products.



Scheme 6 Formation of Cyclobutanone Products from the Mukaiyama-aldol Condensation of **1a** with Aldehydes

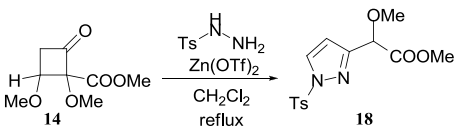
Reaction of **11b** with $Rh_2(OAc)_4$ (1 mol %) provided cyclobutanones **14** via ring contraction of an intermediate oxonium ylide in excellent yield (80%) and 75:25 diastereoselectivity (Scheme 7). Use of the more electrophilic rhodium perfluorobutyrate gave **14** in only 46% yield (dr = 58:42), but the sterically bulky rhodium triphenylacetate had little impact on diastereoselectivity (73% yield, dr = 70:30). Under the same conditions in refluxing DCM, rhodium caprolactamate did not cause dinitrogen extrusion from **11b**. While in refluxing DCE, rhodium caprolactamate gave **14** in only 28% yield (dr =70:30). As expected, varying the acetal alkyl groups of **11** had little effect on product yields, but did influence diastereoselection in cyclobutanone formation (R = Et, 75% yield, dr = 72:28; R = i-Pr, 72 % yield, dr = 53:47). On the other hand, the reaction of **11c** with $Rh_2(OAc)_4$ afforded β -ketoester **17** in 82% yield, and only the (*E*)-configuration for **17** was observed as established by NOE experiments. In this case, a terminal alkene **16** was formed after migration of the methoxy group, which then readily tautomerized to β -ketoester **17** by proton transfer. What is different in this latter case from the ylide mechanism depicted for the formation of cyclobutanone **14** is that the enolate anion of the ylide intermediate undergoes deprotonation at the terminal methyl group instead of undergoing nucleophilic attack.



Scheme 7 Acetal Products to Prepare Cyclobutanones, Pyranones and β -ketoester

Based on the known sensitivity of strained cyclobutanones to cleavage, [16] we considered that cleavage of the C-C bond between the quaternary carbon and tertiary carbon of **14** would be facile and could be applied to synthesis of other functionalized molecules. Lewis acid catalyzed cycloadditions of aldehydes and ketones, as well as of imines and allylsilanes,[17] with 3–alkoxy-2,2-dimethylcyclobutanones have been reported. Cyclobutanones **14** were investigated as latent 1,4-dipoles in dipolar cycloaddition reactions with benzaldehyde, which provided the pyranone compound **15** in 40% yield and 60:40 diastereoselectivity (Scheme 7). The final pyranone compound bears remarkable resemblance to the core structure of the chrolactomycin natural products.[18]

Another application of β-alkoxycyclobutanone compounds is the synthesis of pyrazoles by reacting for β-alkoxycyclobutanone with monosubstituted hydrazines. [19] In a one-pot process methyl 5,5-dimethoxy-3-oxo-2-diazo-pentanoate was sequentially treated with rhodium acetate and without isolation of methyl 1,2-dimethoxy-4-oxo-cyclobutanecarboxylate **14,** 1.0 equivalent of tosylhydrazine and 10 mol% zinc triflate were added to the reaction solution. The reaction was run at refluxing DCM for 6 h to yield the desired pyrazole product **18** in 55% isolated yield after purification (Scheme 8).



Scheme 8 Activated Cyclobutanones to Synthesize Pyrazoles

Conclusions

In summary, we have developed a general Lewis-acid catalyzed carbocationic coupling reaction of enoldiazo compounds, including coupling with benzhydryl, allylic and oxonium carbocations. This report has further demonstrated the utility of enoldiazo coupling reactions to prepare complex organodiazo templates, which are useful for the construction of natural product-like scaffolds. When combined with the array of coupling reactions that have been reported for enoldiazo compounds, the application these reagents presents a unique opportunity to apply DOS-type strategies to rapidly access large and diverse libraries of medicinally interesting compounds.

Experimental

General considerations

All reactions were carried out under an inert atmosphere of dry nitrogen with magnetic stirring. All solvents were dried and distilled according to standard procedures. Flash chromatography was performed with silica gel (32-63 μm) supplied by Dynamic Adsorbents and reactions were monitored by thin layer chromatography (TLC) using UV light to visualize the course of the reactions. ^{1}H NMR spectra were recorded on a Bruker DRX-400 (400 MHz) spectrometer and chemical shifts were reported in ppm. The peak information was described as: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = composite; coupling constant(s) is given in Hz. ^{13}C NMR spectra were recorded on a Bruker DRX-400 (100 MHz). High-resolution mass spectra (HRMS) were performed on JEOL AccuTOF-CS mass spectrometer using CsI as the standard.

General procedure for products 7a-i, 9, 11a-e

Molecular sieve (100 mg) was added to the Schlenk tube and flame dried under vacuum, then anhydrous $Sc(OTf)_3$ was added and heated (110 ℃) under vacuum for 1 h to dehydrate the catalyst. After cooling to room temperature the electrophile precursor (**6a-i**/**8**/**10a-e**: 1.0 mmol) in 3 mL of dry acetonitrile was added, and this mixture was stirred at room temperature for 5 min. Enoldiazoacetate **1a** (1.2 mmol, 1.2 equiv.) was added *via* syringe all at once. The bright yellow solution was stirred vigorously at room temperature. After 16 h the reaction mixture was concentrated under reduced pressure, and the resulting mixture was purified by silica gel chromatography, eluting with 1:10 EtOAc/hexane to give the corresponding product.

General procedure for product 12a-b

A solution of **7a/7b** (0.5 mmol) in 2 mL of anhydrous CH_2Cl_2 was added *via* syringe pump over 2 h to a refluxing solution of 2 mg $Rh_2(OAc)_4$ (0.005 mmol) in 1 mL of anhydrous CH_2Cl_2, followed by in situ treatment with TFA (0.5 mmol, 1.0 equiv.) for 1 hour. The catalyst was removed by passing the resulting solution through a short plug of silica, and the solvent was removed under reduced pressure to give the corresponding product.

General procedure for products 13, 14, 17

A solution of compound **9/ 11b/ 11c** (0.5 mmol) in 2 mL of anhydrous CH_2Cl_2 was added *via* syringe pump over 2 h to a refluxing solution of 2 mg $Rh_2(OAc)_4$ (0.005 mmol) in 1 mL of anhydrous CH_2Cl_2. The catalyst was removed by passing the resulting solution through a short plug of silica and the solvent was removed under reduced pressure to give the corresponding product.

General procedure for product 15

Compound **14** (0.5 mmol) was dissolved in 3 mL CH_2Cl_2, followed by addition of benzaldehyde (0.5 mmol, 1.0 equiv.). The stirred solution was cooled to -45℃ with an acetonitrile-dry ice bath. Boron trifluoride etherate (1.0 mmol, 2.0 equiv.) was then added to the reaction solution. The reaction mixture was stirred at -45℃ for 1 hour and then at room temperature for 1 hour. After the acetonitrile-dry ice bath was removed, the color of the reaction slowly turned from pale yellow to reddish brown. The reaction was quenched with saturated aqueous sodium bicarbonate solution and washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by flash column chromatography, eluting with 1:3 EtOAc/hexane to give a pale yellow liquid as product.

General procedure for product 18

Compound **14** (0.5 mmol) was dissolved in 3 mL CH_2Cl_2, followed by addition of *p*-toluenesulfonyl hydrazide (0.5 mmol, 1.0 equiv.) and zinc triflate (0.05 mmol, 0.1 equiv.). The color of the reaction turned from yellow to reddish brown upon addition of the aryl hydrazine. The reaction was allowed to reflux for 6 h. The catalyst was then removed by passing the resulting solution through a short plug of silica, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography, eluting with 1:2 EtOAc/hexanes to give a pale yellow crystalline as product.

Methyl 2-Diazo-3-oxo-5,5-diphenylpentanoate (7a). Yield: 79%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.29 (comp, 8H), 7.24 – 7.17 (comp, 2H), 4.74 (t, *J* = 7.6 Hz, 1H), 3.87 (s, 3H), 3.70 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 162.1, 144.1, 128.8, 128.2, 126.7, 52.5, 46.4, 45.8; HRMS (ESI) calcd for $C_{18}H_{19}N_2O_3$ $[M+H]^+$ calcd 309.1239; found 309.1228.

Methyl 2-Diazo-5,5-bis(4-methoxyphenyl)-3-oxopentanoate (7b) Yield: 81%; pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.06 (comp, 4H), 6.82 – 6.62 (comp, 4H), 4.56 (t, *J* = 7.7 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 6H), 3.56 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 159.7, 155.9, 134.2, 126.6, 111.8, 53.2, 50.2, 43.7, 42.5; HRMS (ESI) for $C_{20}H_{21}N_2O_5$ $[M+H]^+$ calcd 369.1451; found 369.1457.

Methyl 2-Diazo-5-(3,4-dimethoxyphenyl)-3-oxo-5-phenylpentanoate (7c) Yield: 68%; pale yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20 – 7.18 (comp, 4H), 7.11 – 7.07 (m, 1H), 6.79 – 6.65 (comp, 3H), 4.58 (t, *J* = 7.7 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 3.65 (dd, *J* = 16.7, 7.7 Hz, 1H), 3.48 (dd, *J* = 16.7, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 161.1, 148.2, 146.9, 143.4, 135.6, 127.9, 127.0, 125.7, 118.9, 110.8, 110.5, 55.2, 55.1, 51.6, 45.2, 44.7; HRMS (ESI) for $C_{20}H_{21}N_2O_5$ $[M+H]^+$ calcd 369.1451; found 369.1465.

Methyl 2-Diazo-5-(4-methoxyphenyl)-3-oxo-5-phenylpentanoate (7d) Yield: 79%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.13 (comp, 4H), 7.14 – 7.03 (comp, 3H), 6.78 – 6.67 (comp, 2H), 4.58 (t, *J* = 7.2 Hz, 1H), 3.74 (s, 3H), 3.66 (s, 3H), 3.58 (dd, *J* = 16.1, 7.2 Hz, 1H), 3.53 (dd, *J* = 16.1, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 161.1, 157.4, 143.5, 135.3, 128.1, 127.9, 127.1, 125.7, 113.2, 54.5, 51.6, 44.9, 44.7; HRMS (ESI) for $C_{19}H_{19}N_2O_4$ $[M+H]^+$ calcd 339.1345; found 339.1325.

Methyl 2-Diazo-5-(3-methoxyphenyl)-3-oxo-5-phenylpentanoate (7e) Yield: 67%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (comp, 4H), 7.24 – 7.20 (comp, 2H), 6.94 – 6.92 (m, 1H), 6.89 – 6.85 (m, 1H), 6.77 – 6.75 (m, 1H), 4.74 (t, *J* = 7.6 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.74 (dd, *J* = 17.0, 7.6 Hz, 1H), 3.68 (dd, *J* = 17.0, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 161.8, 159.7, 145.4, 143.7, 129.5, 128.6, 127.8, 126.5, 120.2, 113.9, 111.5, 55.2, 52.3, 46.2, 45.4; HRMS (ESI) for $C_{19}H_{19}N_2O_4$ $[M+H]^+$ calcd 339.1345; found 339.1325.

Methyl 2-Diazo-5-(2-methoxyphenyl)-3-oxo-5-phenylpentanoate (7f) Yield: 24%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.14 (comp, 4H), 7.13 – 7.04 (comp, 3H), 6.84 – 6.80 (m, 1H), 6.77-6.75 (m, 1H), 5.05 (t, *J* = 7.7 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.67 (dd, *J* = 17.3, 7.7 Hz, 1H), 3.49 (dd, *J* = 17.3, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 162.3, 157.3, 144.0, 132.6, 128.7, 128.5, 128.4, 127.9, 126.5, 120.9, 111.2, 55.9, 52.6, 45.0, 39.6; HRMS (ESI) for $C_{19}H_{19}N_2O_4$ $[M+H]^+$ calcd 339.1345; found 339.1326.

Methyl 5-(4-Chlorophenyl)-2-diazo-3-oxo-5-phenylpentanoate (7g) Yield: 72%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.19 (comp, 4H), 7.16 – 7.09 (comp, 5H), 4.61 (t, *J* = 7.6 Hz, 1H), 3.77 (s, 3H), 3.60 (dd, *J* = 17.0, 7.6 Hz, 1H), 3.53 (dd, *J* = 17.0, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 161.7, 143.3, 142.3, 132.2, 129.2, 128.7, 127.7, 126.6, 52.3, 45.5, 45.3; HRMS (ESI) for $C_{18}H_{16}ClN_2O_3$ $[M+H]^+$ calcd 343.0849; found 343.0843.

Methyl 2-Diazo-5-(4-nitrophenyl)-3-oxo-5-phenylpentanoate (7h) Yield: 38%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.02 (comp, 2H), 7.43 – 7.34 (comp, 2H), 7.28 – 7.26 (comp, 2H), 7.21 – 7.14 (comp, 3H), 4.77 (t, *J* = 7.6 Hz, 1H), 3.81 (s, 3H), 3.71 (dd, *J* = 17.3, 7.6 Hz, 1H), 3.60 (dd, *J* = 17.3, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 160.7, 150.4, 145.5, 141.1, 127.9, 127.7, 126.7, 126.1, 122.8, 51.3, 44.8, 43.9; HRMS (ESI) for $C_{18}H_{16}N_3O_5$ $[M+H]^+$ calcd 354.1090; found 354.1074.

Methyl 2-Diazo-5-(naphthalen-2-yl)-3-oxo-5-phenylpentanoate (7i) Yield: 76%; pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.65 (comp, 4H), 7.40 – 7.29 (comp, 3H), 7.27 – 7.20 (comp, 4H), 7.12 – 7.08 (m, 1H), 4.81 (t, *J* = 7.6 Hz, 1H),

3.77 (s, 3H),3.73 (dd, *J* = 16.9, 7.6 Hz, 1H), 3.66 (dd, *J* = 16.9, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 162.2, 144.1, 141.6, 133.9, 132.6, 129.0, 128.6, 128.4, 128.2, 128.0, 127.2, 126.9, 126.4, 126.2, 125.9, 52.7, 46.6, 45.7; HRMS (ESI) for $C_{22}H_{19}N_2O_3$ $[M+H]^+$ calcd 359.1396; found 359.1389.

Methyl 2-Diazo-3-oxo-5,7-diphenylhept-6-enoate (9) Yield: 62%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.21 (comp, 5H), 7.21 – 7.08 (comp, 5H), 6.36 – 6.26 (comp, 2H), 4.09 (dd, J = 13.8, 7.2 Hz, 1H), 3.75 (s, 3H), 3.38 – 3.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 162.2, 143.4, 137.6, 132.7, 130.4, 129.0, 128.9, 128.2, 127.7, 127.1, 126.7, 52.6, 45.8, 44.8; HRMS (ESI) for $C_{20}H_{19}N_2O_3$ $[M+H]^+$ calcd 335.1396; found 335.1376.

Methyl 5,5-Diisopropoxy-3-oxo-2-diazopentanoate (11a) Yield: 82%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (t, *J* = 5.6 Hz, 1H), 3.93 – 3.90 (comp, 2H), 3.86 (s, 3H), 3.20 (d, *J* = 5.6 Hz, 2H), 1.21 (d, *J* = 6.2 Hz, 6H), 1.17 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 189.4, 162.0, 97.2, 68.8, 52.7, 46.5, 31.3, 23.7, 22.8. HRMS (ESI) for $C_{12}H_{20}N_2O_5$ $[M+H]^+$ calcd 273.1450; found 273.1461.

Methyl 5,5-Dimethoxy-3-oxo-2-diazopentanoate (11b) Yield: 83%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (t, *J* = 5.7 Hz, 1H), 3.86 (s, 3H), 3.39 (s, 6H), 3.25 (d, *J* = 5.7 Hz, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 161.6, 101.0, 53.5, 52.3, 43.4; HRMS (ESI) for $C_8H_{13}N_2O_5$ $[M+H]^+$ calcd 217.0824; found 217.0836.

Methyl 5,5-Dimethoxy-3-oxo-2-diazohexanoate (11c) Yield: 83%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.29 (s, 2H), 3.23 (s, 6H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.2, 161.1, 100.0, 51.6, 47.9, 44.1, 21.4; HRMS (ESI) for $C_9H_{14}N_2O_5$ $[M+H]^+$ calcd 231.0981; found 231.0975.

Methyl (*E*)-2-Diazo-5-methoxy-3-oxonon-4-enoate (11d) Yield: 69%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (s, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 2.73 – 2.69 (t, *J* = 7.3 Hz, 2H), 1.51 – 1.43 (m, 2H), 1.34 – 1.24 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 167.3, 161.4, 78.7, 54.0, 50.9, 38.5, 30.3, 28.0, 21.4, 12.8; HRMS (ESI) for $C_{11}H_{18}N_2O_4$ $[M+H]^+$ calcd 241.1188; found 241.1197.

Methyl 2-Diazo-5,5-dimethoxy-3-oxo-5-phenylpentanoate (11e) Yield: 46%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.37 (comp, 2H), 7.27 – 7.19 (comp, 3H), 3.59 (s, 3H), 3.52 (s, 2H), 3.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.2, 161.6, 140.0, 128.4, 128.1, 127.6, 102.3, 52.4, 49.4, 45.7; HRMS (ESI) for $C_{13}H_{13}N_2O_4$ $[M+H\text{-}CH_3OH]^+$ calcd 261.0875; found 261.0856.

Methyl 2-Hydroxy-4-phenyl-3,4-dihydronaphthalene-1-carboxylate (12a) Yield: 82%; pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.18 (s, 1H), 7.70 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.29 – 7.18 (comp, 3H), 7.17 – 7.07 (comp, 3H), 6.99 – 6.98 (m, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 4.09 (t, *J* = 5.9 Hz, 1H), 3.86 (s, 3H), 2.85 (dd, *J* = 14.3, 5.9 Hz, 1H), 2.80 (dd, J = 14.3, 5.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 171.5, 141.0, 134.9, 130.6, 127.9, 127.4, 126.9, 126.1, 126.0, 125.4, 124.6, 99.3, 51.1, 42.5, 35.9; HRMS (ESI) for $C_{18}H_{19}O_3$ $[M+H]^+$ calcd 281.1177; found 281.1177.

Methyl 2-Hydroxy-7-methoxy-4-(4-methoxyphenyl)-3,4-dihydronaphthalene-1-carboxylate (12b) Yield: 84%; pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.11 (s, 1H), 7.73 (d, *J* = 8.7, 1H), 7.21 – 7.04 (comp, 2H), 6.92 – 6.84 (comp, 2H), 6.81 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.48 (d, *J* = 2.8 Hz, 1H), 4.10 (t, *J* = 7.4 Hz, 1H), 3.95 (s, 3H), 3.83 (s, 3H), 3.75 (s, 3H), 2.87 (d, *J* = 7.4 Hz, 1H), 2.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 172.6, 158.9, 157.6, 138.4, 134.0, 129.5, 127.6, 124.4, 114.4, 114.3, 111.7, 100.1, 55.7, 55.6, 52.2, 43.3, 37.2; HRMS (ESI) for $C_{20}H_{21}O_5$ $[M+H]^+$ calcd 341.1389; found 341.1374.

Methyl 2-Oxo-4,6-diphenylbicyclo[3.1.0]hexane-1-carboxylate (13a and b) Yield 56%;
13a: yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.20 (comp, 8H), 7.19 – 7.14 (comp, 2H), 3.57 (d, *J* = 8.3 Hz, 1H), 3.42 (s, 3H), 3.20 (d, *J* = 5.5 Hz, 1H), 2.99 (d, *J* = 5.5 Hz, 1H), 2.85 (dd, *J* = 19.0, 8.3 Hz, 1H), 2.32 (d, *J* = 19.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 164.4, 143.9, 132.6, 128.6, 127.8, 127.8, 127.3, 126.6, 125.7, 51.7, 47.8, 42.1, 38.7, 37.2, 37.1, 30.4; HRMS (ESI) for $C_{20}H_{19}O_3$ $[M+H]^+$ calcd 307.1334; found 307.1342. **13b:** pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.30 (comp, 2H), 7.29 – 7.23 (comp, 4H), 7.23 – 7.18 (comp, 4H), 4.08 – 3.92 (m, 1H), 3.46 (t, *J* = 5.4 Hz, 1H), 3.42 (s, 3H), 3.12 (d, *J* = 5.4 Hz, 1H), 2.76 (dd, *J* = 18.3, 10.0 Hz, 1H), 2.47 (dd, *J* = 18.3, 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 163.8, 139.5, 131.8, 127.6, 127.3, 127.2, 126.7, 125.9, 125.5, 51.0, 47.3, 38.7, 36.6, 35.4, 33.6; HRMS (ESI) for $C_{20}H_{19}O_3$ $[M+H]^+$ calcd 307.1334; found 307.1340.

1,2-Dimethoxy-4-oxocyclobutanecarboxylate (14) Yield: 80%; pale yellow liquid; **major isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (dd, *J* =8.0, 4.0 Hz, 1H), 3.76 (s, 3H), 3.61 (s, 3H), 3.38 – 3.46 (m, 1H), 3.42 (s, 3H), 3.06 (dd, *J* =18.0, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 168.3, 96.2, 73.3, 58.6, 56.7, 52.8, 52.5; **minor isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (t, *J* = 8.0 Hz, 1H), 3.79 (s, 3H), 3.53 (s, 3H), 3.37 (s, 3H), 3.21 (dd, *J* = 18.0, 8.0 Hz, 1H), 3.11 – 3.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 167.0, 99.6, 75.1, 58.5, 55.5, 52.6, 48.9; HRMS (ESI) for $C_8H_{13}O_5$ $[M+H]^+$ calcd 189.0762; found 189.0763.

Methyl 3,4-Dihydro-3-methoxy-4-oxo-2-phenyl-2H-pyran-3-carboxylate (15) Yield: 40%; pale yellow liquid; **major isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.44 (comp, 5H), 5.65 (s, 1H), 5.60 (d, *J* = 8.0 Hz, 1H), 3.70 (s, 3H), 3.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2, 168.4, 164.5, 133.0, 129.5, 128.7, 128.5, 105.1, 85.4, 83.9, 55.1, 52.8; **minor isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.44 (comp, 5H), 5.44 (s, 1H), 5.67 (d, *J* = 8.0 Hz, 1H), 3.67 (s, 3H), 3.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9,168.2, 163.8, 129.9, 129.0, 128.6,127.4, 107.5, 84.3, 82.7, 56.1, 52.8; HRMS (ESI) for $C_{14}H_{14}O_5$ $[M+H]^+$ calcd 263.0919; found 263.0931.

Methyl (*E*)-2,5-Dimethoxy-3-oxohex-4-enoate (17) Yield: 82%; pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (s, 1H), 4.22 (s, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 3.40 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 176.3, 167.4, 93.1, 86.4, 57.3, 55.1, 51.7, 19.6; HRMS (ESI) for $C_9H_{15}O_5$ $[M+H]^+$ calcd 203.0919; found 203.0932.

Methyl 2-Methoxy-2-(1-tosyl-1*H*-pyrazol-3-yl) acetate (18) Yield: 55%; pale yellow crystalline; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 4.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.48 (d, *J* = 4.0 Hz, 1H), 4.92 (s, 1H), 3.71 (s, 3H), 3.34 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 153.8, 146.0, 133.9, 132.5, 130.0, 128.1, 107.3, 76.8, 57.6, 52.5, 21.7; HRMS (ESI) for $C_{14}H_{16}N_2O_5S$ $[M+H]^+$ calcd 325.0858; found 325.0850.

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Notes and references

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‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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