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N−O Tethered Carbenoid Cyclopropanation Facilitates the Synthesis of a Functionalized Cyclopropyl-Fused Pyrrolidine

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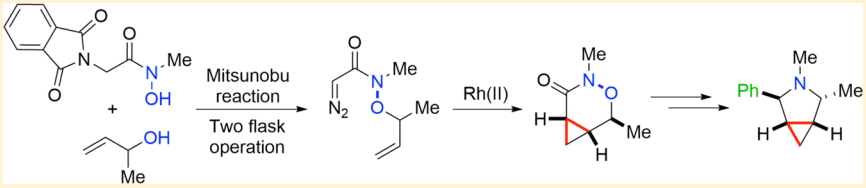
Supporting Information



ABSTRACT: We report a facile approach to a cyclopropyl-fused pyrrolidine, which contains four stereogenic centers, by employing the N−O tethered carbenoid methodology. The synthesis was facilitated by the development of a direct Mitsunobu reaction of alcohols with *N*-alkyl-*N*-hydroxyl amides to give diazo precursors, which upon intramolecular cyclopropanation yielded a library of N−O containing cyclopropyl-fused bicyclic intermediates. Elaboration of the N−O moiety of one member of this library resulted in the formation of the desired pyrrolidine ring demonstrating the potential of this methodology for making cyclopropyl-fused heterocycles.

INTRODUCTION

Small molecules that contain polyfunctionalized pyrrolidine structural units have interesting biological properties and have found diverse applications in medicine.[1−4] Cyclopropyl-fused pyrrolidines are of particular interest as these structural motifs have been shown to possess an extensive range of pharmacological properties. For example, these compounds have been shown to be inhibitors of dipeptidyl peptidase IV and have the potential to be used as antidiabetic drugs.[5] Another example of a biologically active cyclopropyl-fused pyrrolidine is the antibiotic indolizomycin[6] (more examples of such compounds can be found in ref 7). Because of their useful biological activities and promise for medicinal applications, there has been interest in the development of general strategies for the synthesis of polysubstituted pyrrolidines.

As a part of our research program that focuses on remote C−H bond functionalization, we recently reported a method utilizing *N*-alkoxy-*N*-alkyl amides as atom-economical tethers for performing regioselective C−H insertion reactions[8] that employed diazo-containing substrates.[8−22] Motivated by this success, we reasoned that if we could extend this idea and utilize N−O tethers for cyclopropanation and then elaborate the N−O moiety to generate the pyrrolidine ring, we would have a new approach for the synthesis of functionalized pyrrolidines. To achieve this goal, we first developed three new and improved approaches for making *N*-alkoxy-*N*-alkyl diazo precursors and proceeded to perform N−O tether-directed cyclopropanation to generate a library of cyclopropyl-fused heterocycles. Cleavage of the N−O bond followed by cyclization of the resulting amino alcohol gave the desired cyclopropyl-fused substituted pyrrolidine (**A** in Scheme 1a).

RESULTS AND DISCUSSION

For the synthesis of **A**, two traditional carbenoid cyclopropanation strategies[23−30] could be envisaged using 2,5-dihydro-1*H*-pyrrole **1** (strategy (a) in Scheme 1a) or diazoamide **2** (strategy (b) in Scheme 1a) as substrates, followed by further elaboration. However, we decided against these two approaches because of potential drawbacks with each of them. For strategy (a), the two faces of **1** are both sterically encumbered with either an aryl or alkyl group, so achieving diastereoselective cyclopropanation would be nontrivial. Strategy (b) was also not deemed to be ideal because the C−H insertion side-reactions of **2** to give 4-membered rings[31] or cyclopropanation of *N*-benzyl group to afford the Buchner ring-expanded product[32,33] (blue dotted arrow in Scheme 1a) could compete with the desired cyclopropanation of the olefin (blue dotted lines in Scheme 1a). In light of the limitations in these two approaches, we designed a third approach to prepare **A** (strategy (c), Scheme 1a), using the N−O tethered diazoamide **4.** We hypothesized that this approach could yield the desired cyclopropanation product **5** because the conformational preference of the *N*-alkoxy amide places the alkene group closer to the carbenoid than the *N*-alkyl group in **4** (see Scheme 1b,c and refs 8, 34−38 for the basis of this hypothesis). Rotation about the C−N bond in diazoamides (cis-to-trans isomerization) is known to be slow; hence, we expected that the conformational preference of the N−O tethered diazoamide would influence product distribution.[8] A computational

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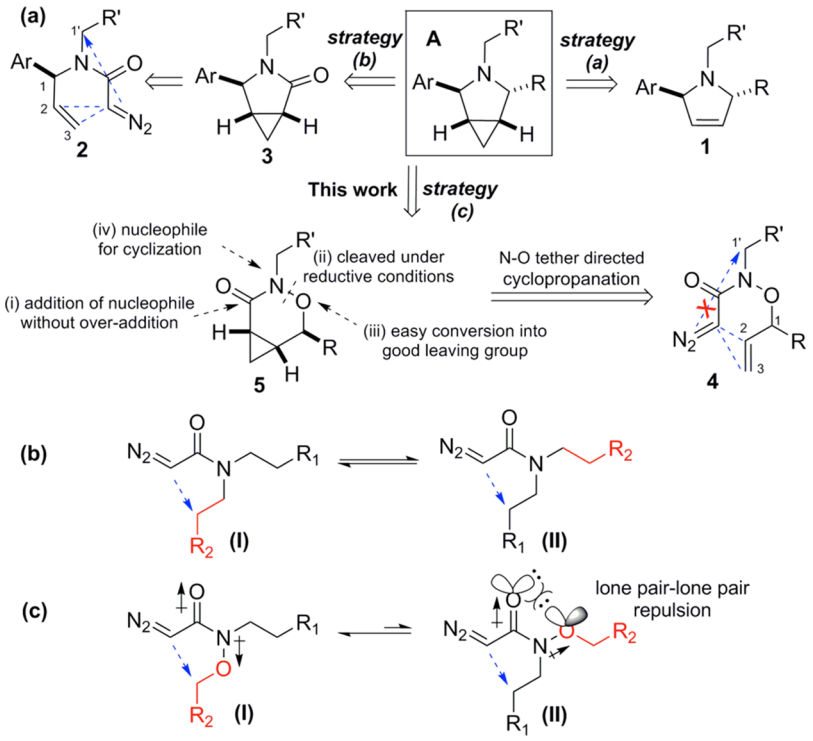
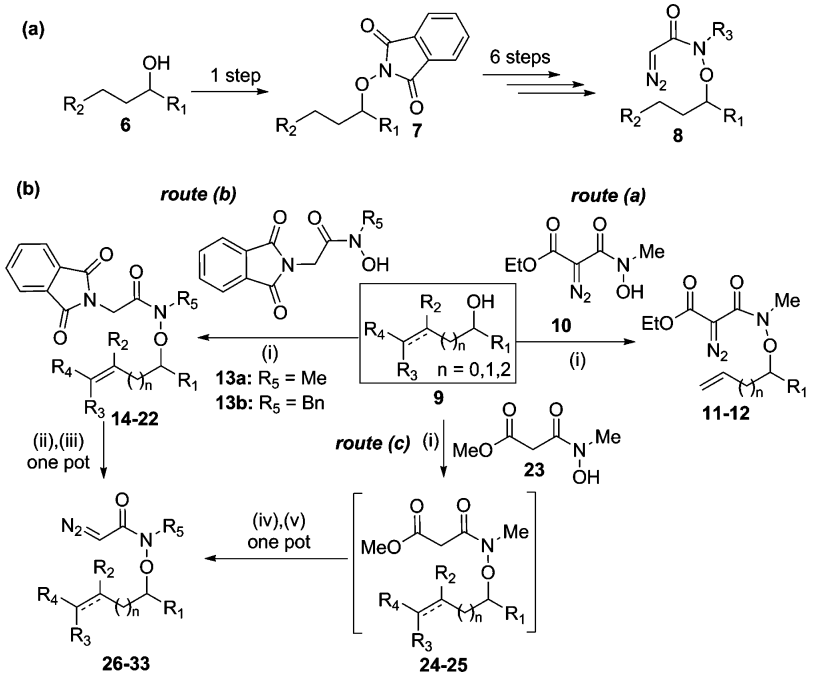
Scheme 1. (a) Reterosynthetic Analysis of Cyclopropyl-Fused Pyrrolidine (A); (b) Carbenoid Reactivity in Amide Systems Is Not Regioselective Because of Equal Populations of Conformers (I) and (II); (c) For *N*-Alkoxy-*N*-alkyl Diazoamides, However, The Major Conformer Is (I), Which Is Predicted to Be about 5.0 kcal mol^{-1} More Stable than Conformer II in Some Systems[8,39] [a]



[a]Dotted line denotes cyclopropanation, and dotted arrow denotes C−H insertion or aromatic cyclopropanation if R′ = phenyl.

Scheme 2. (a) Previously Used Strategy for the Synthesis of N−O Tethered Diazo Substrates;[8] (b) New Routes Developed in This Study for the Synthesis of N−O Tethered Diazo Substrates[a]



[a]Reaction conditions: (i) di-*tert*-butyl azodicarboxylate, PPh_3, CH_2Cl_2; (ii) NH_2NH_2, CH_2Cl_2/EtOH, 40 °C; (iii) $NaNO_2$, AcOH, H_2O, CH_2Cl_2; (iv) MsN_3, DBU, CH_2Cl_2; (v) KOH, THF/H_2O (1:1).

analysis of conformational preferences of *N*-alkoxy carbenoids can be found in ref 8.

Our first challenge was to develop a facile route for the synthesis of the requisite diazo precursors (compounds of

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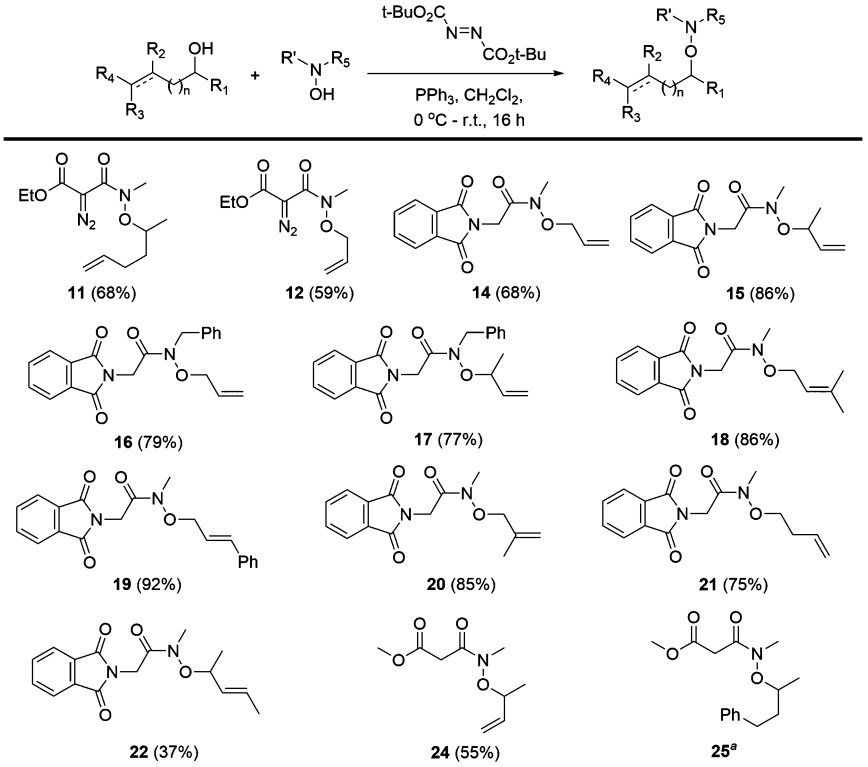
Scheme 3. Substrates Made via Mitsunobu Reaction



[a]Compound **25** was not purified but converted directly into diazo precursor **S8** in 57% over 3 steps (see Supporting Information).

prototype **4** in Scheme 1a). In previous work, we had developed a methodology for the synthesis of N−O tethered diazo substrates that relied on a Mitsunobu reaction[40−48] between *N*-hydroxy phthalimide and a precursor alcohol **6** to give substrate **7** (Scheme 2a).[8] Although successful in yielding the desired products **8** in acceptable overall yields, this protocol entailed a long 7-step synthesis, which involved several chromatographic separations. Therefore, we decided to investigate other more facile approaches for synthesizing our diazo precursors.

We were successful in developing three new methods (Scheme 2b) for the synthesis of various N−O tethered diazo substrates via either a single flask operation (route (a)) or two flasks operations (routes (b) and (c)). This is a remarkable improvement over our previous method (Scheme 2a).[8] Whereas our previous approach utilized *N*-hydroxy phthalimide for the Mitsunobu reaction, our new methods employ *N*-alkyl-*N*-hydroxy amides (compounds **10**, **13**, and **23**).[49,50] We were initially apprehensive about using these amides for the Mitsunobu reaction because of two reasons: (i) the lower acidity of the OH group in *N*-alkyl-*N*-hydroxy amides ($pK_a \sim 8.8$),[51] compared to that of the commonly used Mitsunobu substrate, *N*-hydroxy phthalimide ($pK_a \sim 6.1$),[52] would render them less reactive than *N*-hydroxy phthalimide, and (ii) the possibility that the diazo moiety of **10** may undergo an undesirable side reaction with the phosphine reagent to form phosphonium ylides, after the extrusion of nitrogen.[53−55] These initial apprehensions were however found to be premature because treatment of *N*-methyl-*N*-hydroxy diazoamide **10** with olefinic alcohols under Mitsunobu reaction conditions afforded products **11** and **12** (Scheme 3) in variable yields. Also, *N*-hydroxy-*N*-phthalyl amides **13** reacted with alcohols to give products **14**−**22**, and *N*-hydroxy-*N*-methyl malonyl amide **23** gave products **24** and **25** in good to moderate yields (Scheme 3). The Mitsunobu reaction was sensitive to the nature of phosphines, azodicarboxylates, and solvent. For example, triphenylphosphine (TPP) was superior to a variety of phosphines tested. Replacement of one of the phenyl groups in TPP by a pyridyl group resulted in reduction of product yield.

When 4-(dimethylamino)phenyldiphenylphosphine, 2-[2-(diphenylphosphino)ethyl] pyridine or tributylphosphine were used, no product was obtained. Di-*tert*-butylazodicarboxylate was superior to a variety of azodicarboxylates and azodiamides that were tested (diisopropyl azodicarboxylate, 1,1′- (azodicarbonyl)dipiperidine, di-*tert*-butyl azodicarboxylate, diethyl azodicarboxylate solution (40 wt % in toluene), di-(4-chlorobenzyl)azodicarboxylate). Solvent also played a key role in the reaction. Dichloromethane (CH_2Cl_2) and benzene were superior solvents to tetrahydrofuran (we preferred CH_2Cl_2 over benzene because of safety considerations). The Mitsunobu reaction of *N*-alkyl-*N*-hydroxy amides and alcohols is general and works for primary and secondary alcohols and also for both unsaturated and saturated alcohols (see Scheme 3 and Supporting Information, Table S1).

The simple conversion of olefinic alcohols into *N*-alkoxy-*N*-alkyl products (compounds **14**−**21**, Scheme 3) was interesting to us because we anticipated that we could convert these products into diazo substrates, which would be amenable to intramolecular cyclopropanation to afford cyclopropyl-fused bicycles. The diazo substrates **26**−**33** were readily prepared in one flask by deprotection of the phthalamide moiety in **14**−**21** with hydrazine followed by treating the resulting primary amine with sodium nitrite and acetic acid (Table 1). Next, we investigated N−O tethered intramolecular cyclopropanation of **26**−**33** with dirhodium tetraacetate. The reactivity of *N*-alkoxy-

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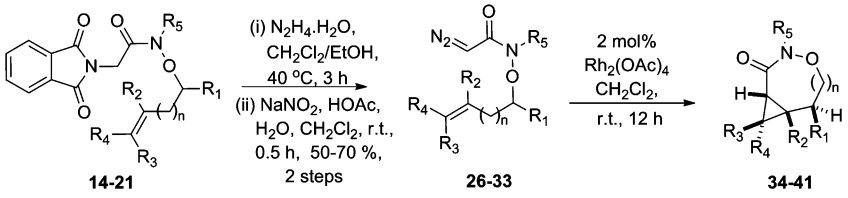
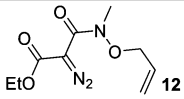
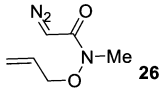
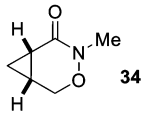
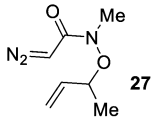
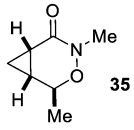
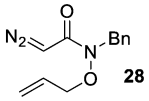
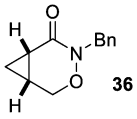
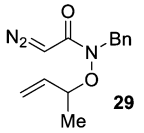
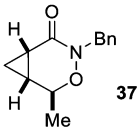
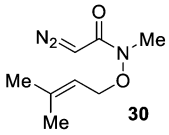
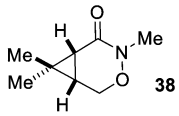
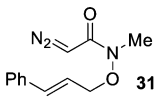
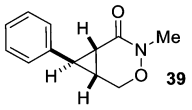
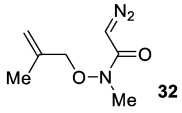
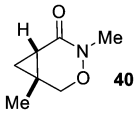
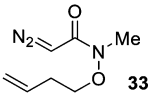
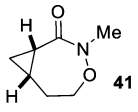
Table 1. Synthesis of N−O Tethered Cyclopropyl Amides 34−41



Entry	Substrate	Product	Yield[a] (%)
1	 **12**	No reaction	-
2	 **26**	 **34**	55
3	 **27**	 **35**	67
4	 **28**	 **36**	89
5	 **29**	 **37**	64
6	 **30**	 **38**	71
7	 **31**	 **39**	77
8	 **32**	 **40**	51
9	 **33**	 **41**	66

[a]Yields were obtained after purification of products by chromatography on silica.

N-alkyl diazoamides is influenced by the substituent that is alpha to diazo moiety. Whereas a hydrogen substituent permitted cyclopropanation (entries 2−9 in Table 1), an *α*-carbonyl substituent suppressed cyclopropanation (entry 1 in Table 1). For this compound (**12**), 2 mol % of three different catalysts, $Rh_2(OAc)_4$, $RuCl_3$, and $Rh_2(cap)_4$ (cap = caprolactamate), were screened, but none catalyzed product formation. Encouragingly, however, the intramolecular cyclopropanations of compounds **26**−**33** were successful and afforded products **34**−**41** in 51−89% yields (Table 1). For entries 3, 5, and 7 (Table 1), only one diastereomer (shown in Table 1) was obtained after column chromatography (assignment of each

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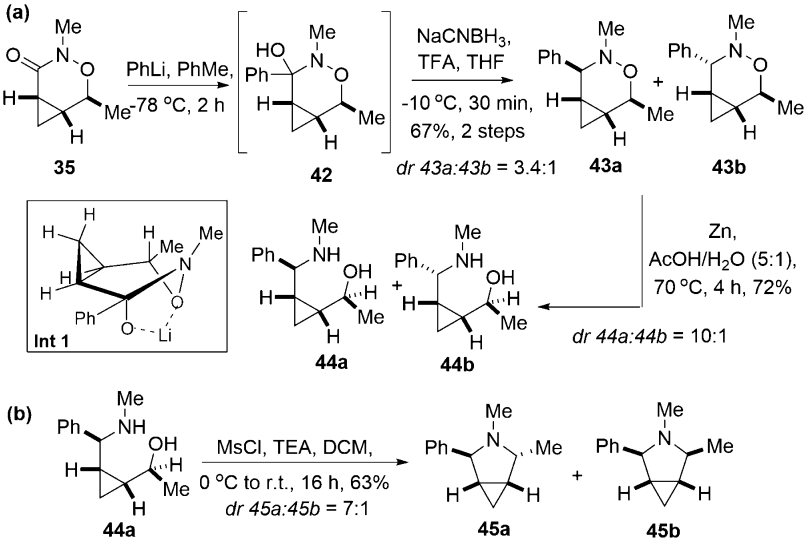
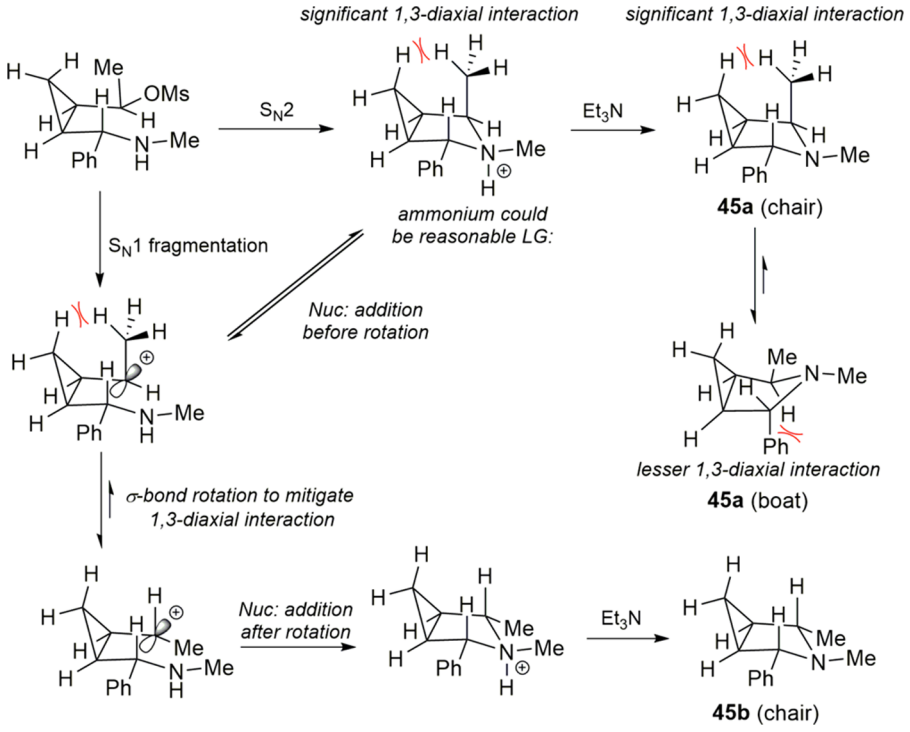
Scheme 4. (a) Synthesis of Cyclopropyl-Amino Alcohol 44 from N−O-Containing Bicycle 35; (b) Elaboration of 44a into Cyclopropyl-Fused Pyrrolidine 45



Scheme 5. Plausible Mechanism to Account for the Formation of Compound 45b from the *O*-Mesylate of 44a



diastereomer was based on a NOESY experiment, see Supporting Information).

N−O tether is a value-added[56,57] moiety because it can be converted into different functional groups found in biologically active molecules. For example, it is possible to add nucleophiles to *N*-alkoxy amides without overaddition, which is usually seen with esters.[58] Pleasingly, in line with our expectation, a phenyl group was successfully added to substrate **35** to give **42**. Overaddition is presumably prevented by the formation of stable chelate between the lithium and the two oxygens leading to the formation of **Int 1** (Scheme 4a). Compound **42** was then reduced with $NaCNBH_3$ to give compound **43** (*dr* of **43a**:**43b** = 3.4:1). A similar pattern of diastereoselectivity was observed at 10 and 23 °C. Cleavage of the N−O bond of **43** (**43a**:**43b** = 3.4:1), using zinc in acetic acid−water mixture, resulted in diastereoselective reduction to give amino alcohol **44** (**44a**:**44b** = 10:1). The enhancement of *de* from 3.4:1 in starting material to 10:1 in product was unexpected, and a hypothesis to account for this is provided in the Supporting Information. Next, we sought to convert the hydroxyl group into a better leaving group so that an intramolecular displacement of this leaving group by nitrogen would afford a nitrogen-containing bicycle.[59,60] Because nitrogen is also nucleophilic and would also react with the sulfonyl chlorides, this strategy is suitable for the substrates in which the nitrogen is more sterically encumbered than the hydroxyl group. Treating compound **44a** with

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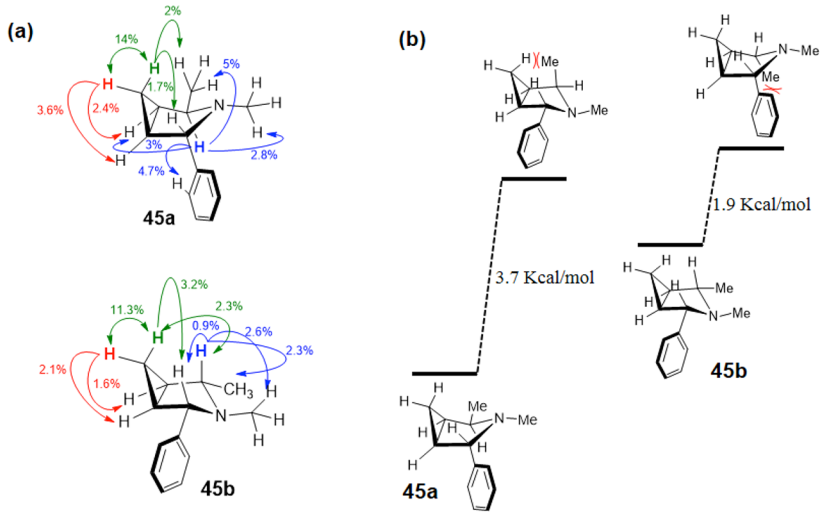

Figure 1. (a) NOE 1D experiments on compounds **45a** and **45b**. (b) Calculation of the conformation energy of **45a** and **45b** in $CHCl_3$.

tosylchloride (TsCl) resulted in a compound whereby the sulfonyl group reacted with the nitrogen and not the hydroxyl group (compound **S9** in Supporting Information). On the other hand, using mesyl chloride (MsCl) resulted in oxygen but not nitrogen mesylation. The active electrophile generated from TsCl is probably a sulfonyl ammonium intermediate, which may be less reactive than the sulfene intermediate, generated from MsCl. In constrast to the less reactive sulfonyl ammonium, which selects for the more nucleophilic amine nucleophile, the sulfene intermediate may have a high enough reactivity to react with either the 2° amine or alcohol, and so steric differences between these two functionalities could underpin the observed selectivity.[61] Upon mesylation of the hydroxyl group in **44a**, a subsequent intramolecular displacement of the mesylate by the amine resulted in the formation of bicycle **45a** (Scheme 4b). A minor compound, **45b** was also obtained presumably because of a double displacement (the chloride anion from the mesyl chloride displaces the mesylate in an intermolecular fashion before an intramolecular displacement by the amine). An alternative hypothesis to account for the formation of the minor product **45b** from the *O*-mesylate of **44a**, suggested by an anonymous reviewer (and which we like), is shown in Scheme 5.

Attempts to suppress the presumed double displacement by using mesylating agents with less nucleophilic leaving groups, such as mesyl triflate or mesyl anhydride, did not work. In these cases, a complex reaction mixture was obtained. Compounds **45a** and **45b** are however separable, using silica gel so the production of the minor product **45b** is not too much of a detriment.

We determined the conformational preferences of **45a** and **45b** via NMR (NOE) and computational methods by calculating the relative energies of the different conformers. NOE data suggests that **45a** exists as a boat conformer, whereas **45b** exists as a chair conformer (Figure 1a). The assignment, based on NOE, was corroborated by calculations (see Supporting Information for computational details). The boat conformer of **45a** is 3.7 kcal/mol more stable than its chair conformer. In contrast, the chair conformer of **45b** is 1.9 kcal/mol more stable than its boat conformer. These results are consistent with a hypothesis, which posits that chair conformation in **45a** would have an unfavorable steric clash between the methyl group and the cyclopropane hydrogens, whereas a boat conformation in **45b** would result in an unfavorable diaxial interaction between the methyl and phenyl groups (see Figure 1b).

In addition to enabling the synthesis of cyclopropyl-fused pyrrolidine compound **45**, N−O containing intermediates (such as compounds **34**−**41**) have several other potential applications. For example, such intermediates can be utilized to make other medically useful cyclopropyl-fused pyrrolidine compounds such as indolizomycin (an antibiotic)[6] and DOV21947 (a potential antidepressant drug).[62] Moreover, 7-membered N−O containing cyclopropyl-fused heterocycles (similar to compound **41**) can be elaborated to generate cyclopropyl-fused piperidines such as GSK1360707 (an antidepressant drug).[63]

CONCLUSION

N−O-containing intermediates have a rich history of being used for the synthesis of nitrogen-containing molecules. A traditional way to make these intermediates involves the cycloaddition of nitrones and π systems.[64−67] In this paper, we have demonstrated a complementary route for making N−O containing heterocycles. We have demonstrated that *N*-alkoxy-*N*-alkyl diazoamides are useful intermediates for the synthesis of interesting and functionalized nitrogen-containing compounds, including amino alcohols and nitrogen-containing bicyclic compounds. Of note, we demonstrate that *N*-hydroxy-*N*-alkyl amides are suitable substrates for Mitsunobu reaction. Bicyclic compound **45** was synthesized in only six-flask operations, staring from 3-buten-2-ol. The stereochemistries in the final products are controlled by the stereochemistry of the starting alcohol. Also, this strategy has allowed functionalization of four contiguous centers on pyrrolidine ring. The use of N−O tethered diazo substrates for the synthesis of functionalized nitrogen-containing compounds adds to the toolbox of complex molecule synthesis using diazo substrates.[9−22]

EXPERIMENTAL SECTION

General Methods. All reactions were performed using oven-dried glassware (120 °C) under inert atmosphere of argon (Ar). Dichloromethane (CH_2Cl_2) and triethylamine (Et_3N) were distilled over calcium hydride (CaH_2) and toluene (PhMe) over sodium (Na) prior to use, while other solvents and reagents were used as received

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from the supplier. Reactions were monitored by thin-layer chromatography (TLC). Visualization of TLC plates was accomplished by UV light or by staining with iodine (I_2), potassium permanganate ($KMnO_4$), phosphomolybdic acid (PMA), and ninhydrin solution. The purification of reaction mixtures were performed using flash column chromatography on silica gel (230–400 mesh). Low temperatures were obtained by ice bath or by mixing dry ice with acetone, whereas thermostat controlled silicone oil baths were employed to attain elevated temperatures. The chemical structures of the isolated compounds were characterized by nuclear magnetic resonance spectroscopy (^{1}H and ^{13}C) and high-resolution mass spectra (HRMS) using a TOF instrument with ESI as the ionization method. ^{1}H NMR chemical shifts are reported as (δ) in ppm and are calibrated according to residual solvent peaks or indicated external standards. ^{1}H NMR coupling constants (J values) are reported in hertz (Hz), and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentaplet), dd (doublet of doublets), td (triplet of doublets), dq (doublet of quartets), ddd (doublet of doublet of doublets), tdd (triplet of doublet of doublets), dddd (doublet of doublet of doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), m (multiplet), bs (broad singlet), app (apparent). ^{13}C NMR chemical shifts are reported as ppm relative to residual solvent peak. Ethyl 2-diazomalonyl chloride was prepared as reported in literature,[68] and all the alcohols were purchased from commercial supplier.

General Procedure for the Synthesis of *N*-Hydroxy Amides. *Ethyl 2-diazo-3-(hydroxy(methyl)amino)-3-oxopropanoate (**10**).* To a cooled (0 °C) solution of *N*-methylhydroxylamine hydrochloride (79 mg, 0.95 mmol) and Et_3N (0.3 mL, 2.26 mmol) in CH_2Cl_2 (25 mL) under Ar was added dropwise a solution of ethyl 2-diazomalonyl chloride[68] (160 mg, 0.91 mmol) in CH_2Cl_2 (5 mL). The mixture was slowly warmed to room temperature and stirred for 2 h. 1% HCl (15 mL) was then added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexanes 1:9 to 2:3) on silica gel to give hydroxy amide **10** (102 mg, 60%) as a yellowish oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.96 (s, 1H), 4.32 (q, J = 7.1 Hz, 2H), 3.27 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.0, 162.1, 62.7, 36.9, 14.5; HRMS (ESI-TOF) m/z calcd. for $C_6H_{10}N_3O_4$ $[M + H]^+$ 188.0671, found 188.0662.

*2-(1,3-Dioxoisoindolin-2-yl)-N-hydroxy-N-methylacetamide (**13a**).* Following the described general procedure above, phthalylglycyl chloride (0.75 g, 3.35 mmol) and *N*-methylhydroxylamine hydrochloride (0.3 g, 3.52 mmol) afforded hydroxylamide **13a** (0.7 g, 89%), as a white solid, after flash chromatography (EtOAc/CH_2Cl_2 1:1) on silica gel column: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91–7.88 (m, 2H), 7.7–7.75 (m, 2H), 4.71 (s, 2H), 3.26 (s, 3H), 1.69 (brs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.6, 167.3, 134.5, 132.3, 132.2, 123.8, 39.2, 36.6; HRMS (ESI-TOF) m/z calcd. for $C_{11}H_{11}N_2O_4$ $[M + H]^+$ 235.0719, found 235.0723.

*N-Benzyl-2-(1,3-dioxoisoindolin-2-yl)-N-hydroxyacetamide (**13b**).* Following the described general procedure above, phthalylglycyl chloride (0.65 g, 2.90 mmol) and *N*-benzylhydroxylamine hydrochloride (0.44 g, 3.05g) afforded hydroxy amide **13b** (0.83 g, 92%), as an off-white solid, after flash chromatography (EtOAc/hexanes 1:4) on silica gel column: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84–7.83 (m, 2H), 7.75–7.73 (m, 2H), 7.30–7.27 (m, 4H), 6.85–6.83 (m, 1H), 4.81 (s, 2H), 4.73 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.8, 168.6, 166.9, 135.4, 134.4, 132.3, 129.0, 128.9, 128.1, 123.8, 52.7, 39.3 ppm; HRMS (ESI-TOF) m/z calcd. for $C_{17}H_{15}N_2O_4$ $[M + H]^+$ 311.1032, found 311.1029.

*Methyl 3-(hydroxy(methyl)amino)-3-oxopropanoate (**23**).* To a suspension of *N*-methylhydroxylamine hydrochloride (334 mg, 4.00 mmol) in CH_2Cl_2 (30 mL) was added dry DBU (0.89 mL, 6.00 mmol) at room temperature. The mixture was cooled to −40 °C and a solution of methyl malonyl chloride (0.2 mL, 2.00 mmol) in CH_2Cl_2 (5 mL) was added slowly via syringe pump over a period of 1 h. The mixture was slowly warmed to room temperature and stirred for 18 h before being concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH/CH_2Cl_2 1:20) to afford product **23** (268 mg, 92%) as maroon color oil: ^{1}H NMR (CD_3OD, 400 MHz) δ 3.73 (s, 3H), 3.53 (s, 2H), 3.24 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 168.4, 167.4, 51.4, 39.4, 34.9; HRMS (ESI-TOF) m/z calcd. for $C_5H_{10}NO_4$ $[M + H]^+$ 148.0610, found 148.0607.

General Procedure for the Synthesis of Mitsunobu Adducts. To a cooled (0 °C) solution of hydroxylamide (1.0 mmol), PPh_3 (1.2 mmol) and alcohol (1.2 mmol) in CH_2Cl_2 (50 mL) was added a solution of di-*tert*-butyl azodicarboxylate (1.2 mmol) in CH_2Cl_2 (10 mL) slowly via syringe pump over a period of 1 h. The reaction was slowly warmed to room temperature and stirred for 16 h. The solvent was concentrated in vacuo, and the residue was purified by flash chromatography (EtOAc/hexanes) on silica gel to give the desired Mitsunobu product.

*Ethyl 2-diazo-3-[(hex-5-en-2-yloxy)(methyl)amino]-3-oxopropanoate (**11**).* Following the procedure described above for the Mitsunobu reaction, diazo amide **10** (78 mg, 0.42 mmol) and 5-hexen-2-ol (60 μL, 0.50 mmol) afforded **11** (76 mg, 68%), as yellow oil, after flash chromatography (EtOAc/hexanes 1:6) on silica gel column: IR (neat) ν 3098, 2978, 2120, 1727, 1642, 1367, 1284 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.81–5.71 (m, 1H), 5.05–4.97 (m, 2H), 4.28 (q, J = 7.1 Hz, 2H), 4.07–4.01 (m, 1H), 3.23 (s, 3H), 2.15–2.10 (m, 2H), 1.76–1.72 (m, 1H), 1.57–1.53 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.22 (d, J = 6.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.0, 161.1, 137.6, 115.5, 79.2, 61.8, 36.0, 33.6, 29.7, 18.1, 14.5; HRMS (ESI-TOF) m/z calcd. for $C_{12}H_{20}N_3O_4$ $[M + H]^+$ 270.1454, found 270.1427.

*Ethyl 3-[(allyloxy)(methyl)amino]-2-diazo-3-oxopropanoate (**12**).* Following the procedure described above for the Mitsunobu reaction, diazo amide **10** (55 mg, 0.29 mmol) and allyl alcohol (24 μL, 0.35 mmol) afforded **12** (39 mg, 59%), as yellow oil, after flash chromatography (EtOAc/hexanes 1:6) on silica gel column: IR (neat) ν 3078, 2982, 2119, 1727, 1645, 1369, 1282 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.96–5.90 (m, 1H), 5.42–5.37 (m, 2H), 4.36 (d, J = 6.4 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.26 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.7, 161.3, 130.8, 121.6, 75.3, 61.8, 35.0, 14.5; HRMS (ESI-TOF) m/z calcd. for $C_9H_{14}N_3O_4$ $[M + H]^+$ 228.0984, found 228.0977.

*N-(Allyloxy)-2-(1,3-dioxoisoindolin-2-yl)-N-methylacetamide (**14**).* Following the procedure described above for the Mitsunobu reaction, amide **13a** (87 mg, 0.37 mmol) and allyl alcohol (30 μL, 0.44 mmol) afforded **14** (69 mg, 68%), as a white solid, after flash chromatography (EtOAc/hexanes 1:6 to 1:5) on silica gel column: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86–7.84 (m, 2H), 7.72–7.70 (m, 2H), 6.07–5.98 (m, 1H), 5.48–5.39 (m, 2H), 4.62 (s, 1H), 4.48 (d, J = 6.5 Hz, 2H), 3.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.1, 167.7, 134.2, 132.4, 131.1, 123.6, 121.5, 75.4, 39.1, 33.9; HRMS (ESI-TOF) m/z calcd. for $C_{14}H_{15}N_2O_4$ $[M + H]^+$ 275.1032 found 275.1035.

*N-(But-3-en-2-yloxy)-2-(1,3-dioxoisoindolin-2-yl)-N-methylacetamide (**15**).* Following the procedure described above for the Mitsunobu reaction, amide **13a** (100 mg, 0.43 mmol) and 3-buten-2-ol (44 μL, 0.51 mmol) afforded **15** (106 mg, 86%), as a white solid, after flash chromatography (EtOAc/hexanes 1:3) on silica gel column: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84–7.81 (m, 2H), 7.71–7.68 (m, 2H), 5.97–5.88 (m, 1H), 5.37–5.32 (m, 2H), 4.66–4.53 (m, 2H), 4.51–4.45 (m, 1H), 3.19 (s, 3H), 1.38 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.4, 168.1, 137.1, 134.1, 132.4, 123.5, 120.0, 81.8 39.4, 35.3, 19.3; HRMS (ESI-TOF) m/z calcd. for $C_{15}H_{17}N_2O_4$ $[M + H]^+$ 289.1188, found 289.1178.

*N-(Allyloxy)-N-benzyl-2-(1,3-dioxoisoindolin-2-yl)acetamide (**16**).* Following the procedure described above for the Mitsunobu reaction, amide **13b** (350 mg, 1.12 mmol) and allyl alcohol (92 μL, 1.35 mmol) afforded **16** (298 mg, 79%), as a white solid, after flash chromatography (EtOAc/hexanes 1:6 to 1:5) on silica gel column: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91–7.88 (m, 2H), 7.76–7.72 (m, 2H), 7.38–7.30 (m, 5H), 5.99–5.91 (m, 1H), 5.38–5.34 (m, 2H), 4.84 (s, 2H), 4.68 (m, 2H), 4.39 (d, J = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.8, 168.2, 135.9, 134.2, 132.5, 131.0, 128.9,

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128.7, 128.1, 123.7, 121.4, 76.5, 51.1, 39.4; HRMS (ESI-TOF) m/z calcd. for $C_{20}H_{19}N_2O_4$ $[M + H]^+$ 351.1345, found 351.1336.

*N-Benzyl-N-(but-3-en-2-yloxy)-2-(1,3-dioxoisoindolin-2-yl)-acetamide (**17**).* Following the procedure described above for the Mitsunobu reaction, amide **13b** (145 mg, 0.47 mmol) and 3-buten-2-ol (49 μL, 0.56 mmol) afforded **17** (131 mg, 77%), as a white solid, after flash chromatography (EtOAc/hexanes 1:6) on silica gel column: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (dd, J = 5.6, 3.2 Hz, 2H), 7.73 (dd, J = 5.6, 3.2 Hz, 2H), 7.37−7.30 (m, 5H), 5.98−5.89 (m, 1H), 5.37−5.26 (m, 2H), 4.92−4.79 (m, 2H), 4.73−4.62 (m, 2H), 4.84−4.45 (m, 1H), 1.35 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.8 168.2, 136.9, 136.0, 134.2, 132.5, 128.8, 128.6, 127.9, 123.7, 120.3, 82.0, 51.6, 39.7, 19.3 ppm; HRMS (ESI-TOF) m/z calcd. for $C_{21}H_{21}N_2O_4$ $[M + H]^+$ 365.1501, found 365.1498.

*2-(1,3-Dioxoisoindolin-2-yl)-N-methyl-N-(3-methylbut-2-enyloxy)acetamide (**18**).* Following the procedure described above for the Mitsunobu reaction, amide **13a** (170 mg, 6.98 mmol) and 3-methyl-2-buten-1-ol (85 μL, 8.38 mmol) afforded **18** (182 mg, 86%), as a white solid, after flash chromatography (EtOAc/hexanes 1:4) on silica gel column: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (dd, J = 5.4, 3.0 Hz, 2H), 7.69 (dd, J = 5.5, 3.0 Hz, 2H), 5.44 (tdt, J = 7.6, 3.0, 1.5 Hz, 1H), 4.60 (s, 2H), 4.44 (d, J = 7.5 Hz, 2H), 3.21 (s, 3H), 1.82 (s, 3H), 1.75 (d, J = 1.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 167.3, 142.0, 133.8, 132.2, 123.2, 117.1, 70.2, 38.9, 33.5, 25.7, 18.0; HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{19}N_2O_4$ $[M + H]^+$ 303.1345, found 303.1320.

*(E)-N-(Cinnamyloxy)-2-(1,3-dioxoisoindolin-2-yl)-N-methylacetamide (**19**).* Following the procedure described above for the Mitsunobu reaction, amide **13a** (0.86 g, 3.53 mmol) and cinnamyl alcohol (0.56 g, 4.24 mmol) afforded **19** (1.13 g, 92%), as a white solid, after flash chromatography (EtOAc/hexanes 1:4) on silica gel column: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (dd, J = 5.5, 3.0 Hz, 2H), 7.71 (dd, J = 5.5, 3.0 Hz, 2H), 7.47−7.42 (m, 2H), 7.41−7.36 (m, 2H), 7.35−7.30 (m, 1H), 6.77 (d, J = 15.9 Hz, 1H), 6.39 (dt, J = 15.9, 6.7 Hz, 1H), 4.69 (s, 2H), 4.65 (dd, J = 6.7, 1.3 Hz, 2H), 3.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 168.0, 136.9, 136.1, 134.4, 132.6, 129.1, 128.9, 127.2, 123.8, 122.0, 75.6, 39.4, 34.4; HRMS (ESI-TOF) m/z calcd. for $C_{20}H_{19}N_2O_4$ $[M + H]^+$ 351.1345, found 351.1346.

*2-(1,3-Dioxoisoindolin-2-yl)-N-methyl-N-(2-methylallyloxy)-acetamide (**20**).* Following the procedure described above for the Mitsunobu reaction, amide **13a** (150 mg, 0.61 mmol) and 2-methyl-2-propen-1-ol (62 μL, 0.74 mmol) afforded **20** (150 mg, 85%), as a white solid, after flash chromatography (EtOAc/hexanes 1:4) on silica gel column: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (dd, J = 5.5, 3.1 Hz, 2H), 7.68 (dd, J = 5.5, 3.0 Hz, 2H), 5.09 (s, 1H), 5.03 (s, 1H), 4.60 (s, 2H), 4.36 (s, 2H), 3.21 (s, 3H), 1.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 167.8, 139.3, 134.4, 132.6, 123.8, 116.3, 78.9, 39.2, 34.1, 20.3; HRMS (ESI-TOF) m/z calcd. for $C_{15}H_{17}N_2O_4$ $[M + H]^+$ 289.1188, found 289.1182.

*N-(But-3-en-1-yloxy)-2-(1,3-dioxoisoindolin-2-yl)-N-methylacetamide (**21**).* Following the procedure described above for the Mitsunobu reaction, amide **13a** (135 mg, 0.57 mmol) and 3-buten-1-ol (60 μL, 0.69 mmol) afforded **21** (125 mg, 75%), as a white solid, after flash chromatography (EtOAc/hexanes 2:3) on silica gel column: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92−7.88 (m, 2H), 7.77−7.73 (m, 2H), 5.93−5.84 (m, 1H), 5.25−5.16 (m, 2H), 4.64 (s, 2H), 4.07 (t, J = 6.5 Hz, 2H), 3.25 (s, 3H), 2.49 (q, J = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.0, 167.4, 134.0, 133.5, 132.2, 123.4, 118.0, 73.4, 38.9, 33.4, 32.4; HRMS (ESI-TOF) m/z calcd. for $C_{15}H_{17}N_2O_4$ $[M + H]^+$ 289.1188, found 289.1154.

*(E)-2-(1,3-Dioxoisoindolin-2-yl)-N-methyl-N-(pent-3-en-2-yloxy)-acetamide (**22**).* Following the procedure described above for the Mitsunobu reaction, amide **13a** (0.154 mg, 0.63 mmol) and 3-penten-2-ol (77 μL, 0.75 mmol) afforded **22** (70 mg, 37%), as a white solid, after flash chromatography (EtOAc/hexanes 1:4) on silica gel column: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (dd, J = 5.5, 3.1 Hz, 2H), 7.70 (dd, J = 5.5, 3.0 Hz, 1H), 5.81 (dq, J = 15.3, 6.4 Hz, 1H), 5.55 (ddd, J = 15.3, 8.5, 1.7 Hz, 1H), 4.64−4.51 (m, 2H), 4.43 (dq, J = 8.5, 6.4 Hz, 1H), 3.18 (s, 3H), 1.79 (dd, J = 6.5, 1.7 Hz, 3H), 1.35 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.4, 168.3, 134.3, 132.9, 132.7, 130.3, 123.8, 81.5, 39.7, 35.3, 19.8, 18.2; HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{19}N_2O_4$ $[M + H]^+$ 303.1345, found 303.1345.

*Methyl 3-((but-3-en-2-yloxy)(methyl)amino)-3-oxopropanoate (**24**).* Following the procedure described above for the Mitsunobu reaction, amide **23** (250 mg, 1.70 mmol) and 3-buten-2-ol (0.2 mL, 2.03 mmol) afforded **24** (189 mg, 55%), as clear oil, after flash chromatography (EtOAc/hexanes 1:6) on silica gel column: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.89−5.80 (m, 1H), 5.32−5.27 (m, 2H), 4.41−4.34 (m, 1H), 3.75 (s, 3H), 3.56−3.44 (m, 2H), 3.23 (s, 3H), 1.33 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.9, 168.3, 137.4, 120.2, 82.2, 52.7, 41.0, 35.5, 19.5; HRMS (ESI-TOF) m/z calcd. for $C_9H_{16}NO_4$ $[M + H]^+$ 202.1079, found 202.1080.

*Ethyl 2-diazo-3-{methyl[(4-phenylbutan-2-yl)oxy]amino}-3-oxopropanoate (**S1**).* Following the procedure described above for the Mitsunobu reaction, diazo amide **10** (94 mg, 0.50 mmol) and 4-phenyl-2-butanol (94 μL, 0.60 mmol) afforded **S1** (115 mg, 72%), as dark yellow oil, after flash chromatography (EtOAc/hexanes 1:6 to 1:3) on silica gel column: IR (neat) ν 2979, 2123, 1692, 1641, 1286 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (t, J = 7.3 Hz Hz, 2H), 7.22−7.17 (m, 3H), 4.29 (q, J = 7.1 Hz, 2H), 4.09−4.01 (m, 1H), 3.22 (s, 3H), 2.74−2.68 (m, 2H), 2.01−1.97 (m, 1H), 1.83−1.79 (m. 1H), 1.31 (t, J = 7.1 Hz Hz, 3H), 1.27 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz,) δ 163.0, 161.2, 141.2, 128.7, 128.5, 126.3, 61.8, 36.2, 31.7, 28.4, 18.3, 14.6; HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{22}N_3O_4$ $[M + H]^+$ 320.1610, found 320.1618.

*Ethyl 2-[(2-diazo-3-ethoxy-N-methyl-3-oxopropanamido)oxy]-4-phenylbutanoate (**S2**).* Following the procedure described above for the Mitsunobu reaction, diazo amide **10** (87 mg, 0.46 mmol) and ethyl 2-hydroxy-4-phenylbutanoate (0.1 mL, 0.55 mmol) afforded **S2** (110 mg, 63%), as yellow oil, after flash chromatography (EtOAc/hexanes 1:6) on silica gel column: IR (neat) ν 2982, 2130, 1727, 1643, 1287 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (t, J = 7.4 Hz, 2 H), 7.23−7.19 (m, 3H), 4.43 (t, J = 6.6 Hz, 1 H), 4.31−4.26 (m, 2H), 4.19 (q, J = 7.1 Hz, 2H), 3.25 (s, 3H), 2.83−2.70 (m, 2H), 2.35−2.09 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.5, 162.6, 162.3, 140.3, 128.7, 128.5, 126.5, 81.4, 61.8, 61.7, 37.2, 32.7, 31.2, 28.3, 14.5, 14.2; HRMS (ESI-TOF) m/z calcd. for $C_{18}H_{24}N_3O_6$ $[M + H]^+$ 378.1665, found 378.1649.

*Ethyl 3-[(but-3-yn-1-yloxy)(methyl)amino]-2-diazo-3-oxopropanoate (**S3**).* Following the procedure described above for the Mitsunobu reaction, diazo amide **10** (64 mg, 0.34 mmol) and 3-butyn-1-ol (31 μL, 0.41 mmol) afforded **S3** (20 mg, 24%), as a yellowish oil, after flash chromatography (EtOAc/hexanes 1:6) on silica gel column: IR (neat) ν 3243, 2982, 2120, 1723, 1641, 1368, 1282 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.30 (q, J = 7.1 Hz, 2H), 4.01 (t, J = 6.6 Hz, 2H) 3.27 (s, 3H), 2.53 (td, J = 6.6, 2.6 Hz, 2H), 2.04 (t, J = 2.6 Hz, 1H), 1.32 (t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.6, 161.6, 79.7, 72.0, 70.4, 61.8, 35.2, 18.4, 14.6; HRMS (ESI-TOF) m/z calcd. for $C_{10}H_{14}N_3O_4$ $[M + H]^+$ 240.0984, found 240.0974.

*Ethyl 2-diazo-3-[methyl(prop-2-yn-1-yloxy)amino]-3-oxopropanoate (**S4**).* Following the procedure described above for the Mitsunobu reaction, diazo amide **10** (70 mg, 0.37 mmol) and propargyl alcohol (30 μL, 0.45 mmol) afforded **S4** (41 mg, 49%), as a yellowish oil, after flash chromatography (EtOAc/hexanes 1:6) on silica gel column: IR (neat) ν 3245, 2982, 2121, 1723, 1641, 1369, 1283 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.54 (d, J = 2.4 Hz, 2H), 4.29 (q, J = 7.1 Hz, 2H), 3.29 (s, 3H), 2.60 (t, J = 2.4 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.5, 162.0, 77.7, 76.7, 62.0, 61.8, 35.5, 28.3, 14.5 ppm; HRMS (ESI-TOF) m/z calcd. for $C_9H_{12}N_3O_4$ $[M + H]^+$ 226.0828, found 226.0842.

*2-(1,3-Dioxoisoindolin-2-yl)-N-methyl-N-(prop-2-yn-1-yloxy)-acetamide (**S5**).* Following the procedure described above for the Mitsunobu reaction, amide **13a** (120 mg, 0.51 mmol) and propargyl alcohol (36 μL, 0.61 mmol) afforded **S5** (110 mg, 79%), as a white solid, after flash chromatography (EtOAc/hexanes 1:6) on silica gel column: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86−7.84 (m, 2H), 7.73−7.70 (m, 2H), 4.75 (s, 2H), 4.60 (s, 2H), 3.26 (s, 3H), 2.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.6, 168.1, 134.2, 132.5, 123.6,

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78.24, 76.9, 39.6, 34.0; HRMS (ESI-TOF) m/z calcd. for calculated for $C_{14}H_{13}N_2O_4$ $[M + H]^+$ 273.0875, found 273.0869.

*N-(But-3-yn-1-yloxy)-2-(1,3-dioxoisoindolin-2-yl)-N-methylacetamide (**S6**).* Following the procedure described above for the Mitsunobu reaction, amide **13a** (105 mg, 0.45 mmol) and 3-butyn-1-ol (41 μL, 0.54 mmol) afforded **S6** (63 mg, 49%), as a white solid, after flash chromatography (EtOAc/hexanes 1:6) on silica gel column: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85−7.82 (m, 2H), 7.72−7.69 (m, 2H), 4.68 (s, 2H), 4.09 (t, J = 6.0 Hz, 2H), 3.22 (s, 3H), 2.59 (m, 2H), 2.07 (t, J = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.0, 134.1, 132.4, 123.6, 80.1, 72.2, 70.6, 39.1, 33.8, 18.5; HRMS (ESI-TOF) m/z calcd. for $C_{15}H_{15}N_2O_4$ $[M + H]^+$ 287.1032, found 287.1039.

General Procedure for the Synthesis of Diazo Compounds. *N-(But-3-en-2-yloxy)-2-diazo-N-methylacetamide (**27**).* To a solution of **15** (540 mg, 1.87 mmol) in CH_2Cl_2/EtOH (15:0.3 mL) was added hydrazine hydrate (65% aq solution (0.2 mL, 2.8 mmol)), and the mixture was heated to 40 °C. After stirring for 1 h, white suspension appeared in the reaction, and the mixture was stirred vigorously at 40 °C for another 3 h before cooling down to room temperature. The solvent was concentrated in vacuo, and the resultant residue was suspended in $CHCl_3$ (75 mL) and then filtered. The filtrate was concentrated in vacuo to give primary amine product as colorless oil, which was pure enough to proceed to the next stage of the reaction. To a solution of crude amine in CH_2Cl_2 (15 mL) was added acetic acid (0.5 mL, 9.36 mmol) followed by addition of solution of $NaNO_2$ (155 mg, 2.25 mmol) in water (3 mL). The reaction was stirred vigorously for 0.5 h at room temperature and neutralized with saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL × 2). The combined organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo to afford crude product, which was chromatographed on silica gel (EtOAc/hexanes 1:6) to give diazo compound **27** (223 mg, 70%, 2 steps) as yellow oil: IR (neat) ν 2101, 1619 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.88−5.80 (m, 1H), 5.32−5.24 (m, 3H), 4.35−4.31 (m, 1H), 3.19 (s, 3H), 1.32 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 137.3, 118.9, 81.4, 46.9, 36.0, 19.1

*N-(Allyloxy)-2-diazo-N-methylacetamide (**26**).* Compound **14** (220 mg, 0.80 mmol) afforded **26** (69 mg, 55%, 2 steps), as a yellow oil, after flash chromatography (EtOAc/hexanes 1:6) on silica gel column: IR (neat) ν 2108, 1645, 1382 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.99−5.91 (m, 1H), 5.41−5.33 (m, 3H), 4.32 (d, J = 6.3 Hz, 2H), 3.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.4, 131.9, 121.1, 75.7, 47.0, 35.0.

*N-(Allyloxy)-N-benzyl-2-diazoacetamide (**28**).* Compound **16** (196 mg, 0.56 mmol) afforded **28** (68 mg, 53%, 2 steps) as yellow oil, after flash chromatography (EtOAc/hexanes 1:5) on silica gel column: IR (neat) ν 2106, 1639 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.28 (m, 5H), 5.92−5.83 (m, 1H), 5.39 (s, 1H), 5.31−5.27 (m, 2H), 4.81 (s, 2H), 4.23−4.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 136.4, 131.4, 128.7, 128.5, 127.7, 120.5, 76.2, 51.5, 47.0.

*N-Benzyl-N-(but-3-en-2-yloxy)-2-diazoacetamide (**29**).* Compound **17** (318 mg, 0.87 mmol) afforded **29** (133 mg, 62%, 2 steps), as yellow oil, after flash chromatography (EtOAc/hexanes 1:6) on silica gel column: IR (neat) ν 2102, 1616 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.28 (m, 5H), 5.87−5.78 (m, 1H), 5.36 (s, 1H), 5.24−5.17 (m, 2H), 4.89−4.72 (m, 2H), 4.31−4.27 (m, 1H), 1.27 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 137.2, 136.5, 128.7, 128.4, 127.6, 119.0, 81.6, 52.1, 47.4, 19.1.

*2-Diazo-N-methyl-N-(3-methylbut-2-enyloxy)acetamide (**30**).* Compound **18** (1.07 g, 3.53 mmol) afforded **30** (0.36 g, 56%, 2 steps), as yellow oil, after flash chromatography (EtOAc/hexanes 1:6) on silica gel column: IR (neat) ν 2101, 1621 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.37−5.32 (m, 2H), 4.29 (d, J = 7.5 Hz, 2H), 3.19 (s, 3H), 1.78 (d, J = 1.4 Hz, 3H), 1.72 (d, J = 1.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 141.7, 117.8, 70.8, 46.8, 34.7, 26.2, 18.5.

*(E)-N-(Cinnamyloxy)-2-diazo-N-methylacetamide (**31**).* Compound **19** (498 mg, 1.42 mmol) afforded **31** (165 mg, 50%, 2 steps), as yellow oil, after flash chromatography (EtOAc/hexanes 1:4) on silica gel column: IR (neat) ν 2106, 1626, 1381 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44−7.32 (m, 5H), 6.71 (d, J = 15.9 Hz, 1H), 6.32 (dt, J = 15.8, 6.8 Hz, 1H), 5.41 (s, 1H), 4.49 (dd, J = 6.8, 1.2 Hz, 2H), 3.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 168.5, 135.5, 135.3, 128.2, 127.9, 126.2, 121.6, 74.5, 46.1, 34.3.

*2-Diazo-N-methyl-N-(2-methylallyloxy)acetamide (**32**).* Compound **20** (0.7 g, 2.42 mmol) afforded **32** (0.28 g, 68%, 2 steps), as yellow oil, after flash chromatography (EtOAc/hexanes 1:5) on silica gel column: IR (neat) ν 2107, 1629, 1381 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.36 (s, 1H), 5.07−5.02 (m, 2H), 4.23 (s, 2H), 3.22 (s, 3H), 1.84−1.83 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.1, 139.7, 115.9, 78.9, 34.8, 28.5, 20.3.

*N-(But-3-enyloxy)-2-diazo-N-methylacetamide (**33**).* Compound **21** (0.4 g, 1.38 mmol) afforded **33** (163 mg, 70%, 2 steps), as yellow oil, after flash chromatography (EtOAc/hexanes 1:6) on silica gel column: IR (neat) ν 2106, 1630, 1381 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.84 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H), 5.37 (s, 1H), 5.24−5.11 (m, 2H), 3.89 (t, J = 6.5 Hz, 2H), 3.22 (s, 3H), 2.41 (qt, J = 6.6, 1.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.6, 134.6, 118.4, 74.0, 47.1, 35.0, 33.1.

*2-Diazo-N-methyl-N-(4-phenylbutan-2-yloxy)acetamide (**S8**).* Amide **23** (150 mg, 1.01 mmol) was reacted with 4-phenyl-2-butanol, PPh_3 and di-*tert*-butyl azodicarboxylate (Mitsunobu reaction condition) as described above to afford crude **25** as pale yellow residue. The residue was quickly passed through short silica gel column (EtOAc/hexanes 1:6) to remove $Ph_3P{=}O$, and the crude product **25** (yield 50%) was used immediately for the next step. To a solution of intermediate **25** in CH_2Cl_2 (15 mL) was added mesyl azide (148 mg, 1.22 mmol) followed by DBU (0.2 mL, 1.42 mmol) at room temperature and stirred for 18 h. The solvent was concentrated in vacuo to afford crude intermediate **S7** as light yellow oil, which was employed for the next step without further purification in the same flask. For characterization purposes, small sample of reaction mixture was purified by flash chromatography (EtOAc/hexanes 1:3) on silica gel to afford pure **S7** as yellowish oil: IR (neat) ν 2125, 1741, 1666, 1369 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.28 (m, 2H), 7.25−7.19 (m, 3H), 4.09−4.04 (m, 1H), 3.86 (s, 3H), 3.25 (s, 3H), 2.78−2.63 (m, 2H), 2.09−1.94 (m, 1H), 1.89−1.75 (m, 1H), 1.29 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.8, 161.2, 141.4, 128.9, 128.7, 126.6, 79.3, 53.0, 36.4, 36.0, 32.0, 18.5. Crude **S7** was dissolved in THF/water (5:5 mL), to which was added a concentrate solution of KOH (571 mg, 10.2 mmol) in water (2 mL) and stirred for 3 h. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to afford light yellow oil, which was chromatographed on silica gel (EtOAc/hexanes 1:4) to give product **S8** as clear oil (144 mg, 57%, 3 steps). Detailed characterization of **S8** is reported in ref 8.

General Procedure for the Synthesis of Cyclopropane-Fused N−O Containing Bicyclics. *(±)-2,4-Dimethyl-3-oxa-4-azabicyclo[4.1.0]heptan-5-one (**35**).* A solution of **27** (164 mg, 0.97 mmol) in dry CH_2Cl_2 (10 mL) was degassed by bubbling Ar for 30 min in one flask (solution A). Likewise, a solution of catalyst $Rh_2(OAc)_4$ (8.6 mg, 2 mol %) in dry CH_2Cl_2 (30 mL) was degassed for 30 min in another flask (solution B). After degassing, solution A was transferred to the injector and was injected to solution B via syringe pump over a period of 1 h under Ar atmosphere. The reaction mixture was stirred for 18 h at room temperature and concentrated in vacuo. The resultant green residue was purified by flash column chromatography (EtOAc/Hexane 1:6) on silica gel to give **35** (91 mg, 67%) as clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.31 (q, J = 6.4 Hz, 1H), 3.17 (s, 3H), 1.85−1.80 (m, 1H), 1.60−1.58 (m, 1H), 1.49−1.46 (m, 1H), 1.34 (d, J = 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 168.3, 71.7, 34.9, 22.1, 17.4, 15.6, 8.6; HRMS (ESI-TOF) m/z calcd. for $C_7H_{12}NO_2$ $[M + H]^+$ 142.0868, found 142.0863.

*4-Methyl-3-oxa-4-azabicyclo[4.1.0]heptan-5-one (**34**).* Compound **26** (87 mg, 0.56 mmol) afforded **34** (63 mg, 55%), as a clear oil, after flash chromatography (EtOAc/hexanes 1:1) on silica gel column, by employing the general procedure described above for compound **35**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.14−4.11 (m, 1H), 3.98−3.96 (m, 1H), 3.17 (s, 3H), 1.87−1.82 (m, 1H), 1.77−1.72 (m,

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1H), 1.55−1.51 (m, 1H), 1.08−1.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.1, 66.6, 33.8, 16.8, 16.2, 7.1; HRMS (ESI-TOF) m/z calcd. for $C_6H_{10}NO_2$ $[M + H]^+$ 128.0712, found 128.0714.

*4-Benzyl-3-oxa-4-azabicyclo[4.1.0]heptan-5-one (**36**).* Compound **28** (63 mg, 0.27 mmol) afforded **36** (49 mg, 89%) as clear oil, after flash chromatography (EtOAc/hexanes 1:4) on silica gel column, by employing the general procedure described above for compound **35**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.28 (m, 5H), 4.90−4.86 (m, 1H), 4.64−4.60 (m, 1H), 4.10−4.07 (m, 1H), 3.81−3.78 (m, 1H), 1.94−1.89 (m, 1H), 1.76−1.73 (m, 1H), 1.58−1.54 (m, 1H), 1.10−1.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.7, 136.2, 128.5, 128.2, 127.6, 67.1, 50.1, 17.0, 16.3, 7.2; HRMS (ESI-TOF) m/z calcd. for $C_{12}H_{14}NO_2$ $[M + H]^+$ 204.1025, found 204.1032.

*(±)-4-Benzyl-2-methyl-3-oxa-4-azabicyclo[4.1.0]heptan-5-one (**37**).* Compound **29** (93 mg, 0.38 mmol) afforded **37** (53 mg, 64%), as a clear oil, after flash chromatography (EtOAc/hexanes 1:2) on silica gel column, by employing the general procedure described above for compound **35**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.28 (m, 5H), 4.71 (s, 2H), 4.23 (q, J = 6.4 Hz, 1H), 1.89−1.84 (m, 1H), 1.58−1.53 (m, 1H), 1.50−1.46 (m, 1H), 1.09−1.04 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.4, 136.5, 129.2, 128.8, 128.0, 72.0, 51.0, 22.7, 17.9, 16.0, 9.1; HRMS (ESI-TOF) m/z calcd. for $C_{13}H_{16}NO_2$ $[M + H]^+$ 218.1181, found 218.1183.

*(±)-4,7,7-Trimethyl-3-oxa-4-azabicyclo[4.1.0]heptan-5-one (**38**).* Compound **30** (200 mg, 1.09 mmol) afforded **38** (120 mg, 71%), as a clear oil, after flash chromatography (EtOAc/hexanes 1:2) on silica gel column, by employing the general procedure described above for compound **35**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.16 (qd, J = 11.9, 3.5 Hz, 2H), 3.14 (s, 3H), 1.64 (d, J = 8.5 Hz, 1H), 1.48 (ddd, J = 8.6, 4.3, 2.8 Hz, 1H), 1.28 (s, 3H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 66.6, 33.9, 28.6, 27.7, 27.2, 26.0, 16.6; HRMS (ESI-TOF) m/z calcd. for $C_8H_{14}NO_2$ $[M + H]^+$ 156.1025, found 156.1052.

*(±)-4-Methyl-7-phenyl-3-oxa-4-azabicyclo[4.1.0]heptan-5-one (**39**).* Compound **31** (75 mg, 0.32 mmol) afforded **39** (50 mg, 77%), as a clear oil, after flash chromatography (EtOAc/hexanes 2:3) on silica gel column, by employing the general procedure described above for compound **35**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.25 (m, 2H), 7.25−7.21 (m, 1H), 7.21−7.11 (m, 1H), 4.27 (dt, J = 11.2, 0.8 Hz, 1H), 4.04 (dt, J = 11.1, 1.0 Hz, 1H), 3.23 (s, 3H), 3.03 (t, J = 4.6 Hz, 1H), 2.21−2.18 (m, 1H), 2.08 (ddt, J = 8.3, 4.9, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.8, 139.0, 129.0, 127.1, 126.6, 66.6, 34.3, 27.2, 26.1, 24.5; HRMS (ESI-TOF) m/z calcd. for $C_{12}H_{14}NO_2$ $[M + H]^+$ 204.1025, found 204.1055.

*(±)-1,4-Dimethyl-3-oxa-4-azabicyclo[4.1.0]heptan-5-one (**40**).* Compound **32** (192 mg, 1.13 mmol) afforded **40** (82 mg, 51%), as a clear oil, after flash chromatography (EtOAc/hexanes 2:3) on silica gel column, by employing the general procedure described above for compound **35**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.94 (dd, J = 10.8, 0.9 Hz, 1H), 3.75 (d, J = 10.9 Hz, 1H), 3.13 (s, 3H), 1.66 (t, J = 4.7 Hz, 1H), 1.61−1.58 (m, 1H), 1.19 (s, 3H), 0.91−0.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.4, 71.0, 34.1, 24.5, 23.9, 18.0, 15.2; HRMS (ESI-TOF) m/z calcd. for $C_7H_{12}NO_2$ $[M + H]^+$ 142.0868, found 142.0862.

*(±)-3-Methyl-4-oxa-3-azabicyclo[5.1.0]octan-2-one (**41**).* Compound **33** (110 mg, 0.65 mmol) afforded **41** (60 mg, 66%), as a clear oil, after flash chromatography (EtOAc/hexanes 1:1) on silica gel column, by employing the general procedure described above for compound **35**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.07 (ddd, J = 11.3, 6.6, 1.3 Hz, 1H), 3.83 (td, J = 11.4, 5.1 Hz, 1H), 3.15 (s, 3H), 2.33−2.27 (m, 1H), 1.79 (td, J = 9.0, 5.4 Hz, 1H), 1.23−1.10 (m, 1H), 1.09−0.98 (m, 2H), 0.58 (q, J = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0, 69.4, 33.6, 29.0, 18.5, 11.0, 10.1; HRMS (ESI-TOF) m/z calcd. for $C_7H_{12}NO_2$ $[M + H]^+$ 142.0868, found 142.1064.

*(±)-2,4-Dimethyl-5-phenyl-3-oxa-4-azabicyclo[4.1.0]heptane (**43**).* To a cooled (−78 °C) solution of **35** (155 mg, 1.10 mmol) in anhydrous toluene (9 mL) was added PhLi (1.8 M solution in dibutyl ether (1.3 mL, 2.30 mmol)) dropwise under argon atmosphere and stirred for 2 h. The red/orange reaction was slowly warmed to −10 °C, during which time the color changed to pale yellow. The reaction was quenched by the addition of 1 M HCl (5 mL). The resultant colorless solution was diluted with saturated aqueous $NaHCO_3$ (50 mL), and the aqueous layer was extracted with $CHCl_3$ (2 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo to yield crude product **42** as a mixture of two inseparable diastereomers that were used in the subsequent transformation without separation. Small sample of crude was purified for characterization of major isomer from the mixture of diastereomers: clear oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97−7.94 (m, 2H), 7.47−7.43 (m, 1H), 7.40−7.35 (m, 2H), 3.42 (dq, J = 9.5, 6.2 Hz, 1H), 2.77−2.71 (m, 1H), 2.16 (s, 3H), 1.54−1.46 (m, 1H), 1.33−1.29 (m, 1H), 1.22 (d, J = 6.2 Hz, 3H), 1.03 (ddd, J = 8.8, 7.3, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.1, 132.3, 128.3, 128.2, 128.1, 126.1, 74.8, 39.0, 29.5, 23.2, 19.4, 10.9; HRMS (ESI-TOF) m/z calcd. for $C_{13}H_{18}NO_2$ $[M + H]^+$ 220.1338, found 220.1284.

To a stirred solution of crude **42** in THF (5 mL) was added $NaCNBH_3$ (103 mg, 1.64 mmol) portionwise at −10 °C, followed by trifluoroacetic acid (5−6 drops). The reaction mixture was stirred for 30 min and then concentrated in vacuo. To the residue was added saturated aqueous $NaHCO_3$ (20 mL), and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), and concentrated in vacuo to yield crude **43** as a mixture of 2 inseparable diastereomers (*dr* **43a**:**43b** = 3.4:1). Purification by flash column chromatography (EtOAc/hexanes 5:95) on silica gel afforded **43a**/**43b** (144 mg, 67%, 2 steps) as clear oil in a ratio of 4:1, respectively. Data for compound **43a** (major): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 −7.32 (m, 2H), 7.30−7.23 (m, 2H), 7.23−7.18 (m, 1H), 4.08 (qd, J = 6.5, 1.5 Hz, 1H), 3.53 (bs, 1H), 2.15 (s, 3H), 1.44 (d, J = 6.4 Hz, 3H), 1.16−1.10 (m, 1H), 0.94−0.88 (m, 1H), 0.71−0.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.6, 129.1, 128.2, 127.5, 75.6, 68.3, 43.2, 21.3, 17.4, 15.3, 10.9. Data for compound **43b** (minor): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.18−7.29 (m, 5H), 4.05−3.99 (m, 1H), 3.65 (d, J = 3.6 Hz, 1H), 2.29 (s, 3H),1.27 (d, J = 6.5 Hz, 3H), 1.22−1.20 (m, 1H), 1.02−0.96 (m, 2H), 0.60−0.54 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.0, 128.5, 127.9, 127.5, 73.4, 44.0, 21.3, 19.7, 18.5, 10.2; HRMS (ESI-TOF) m/z calcd. for $C_{13}H_{18}NO$ $[M + H]^+$ 204.1388, found 204.1391.

*Amino alcohol (±)-**44**.* A solution of mixture **43a**/**43b** (3.4:1, 140 mg, 0.67 mmol) in AcOH/H_2O (10:2 mL) was degassed for 10 min by bubbling Ar. After degassing, Zn dust (0.9 g, 13.8 mmol) was added to the mixture, which was heated at 70 °C with vigorous stirring for 4 h. The reaction was quenched to pH 9 by the addition of aqueous Na_2CO_3 solution (1 M). The resultant precipitate was filtered, and the aqueous layer was extracted with $CHCl_3$ (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to yield **44** (*dr* **44a**/**44b** 10:1). Purification by flash chromatography (CH_2Cl_2/MeOH/NH_4OH 1:9:0.1) afforded **44a** (102 mg, 72%) as off-white semisolid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.28 (m, 2H), 7.24−7.15 (m, 3H), 4.15 (bs, 1H), 3.53−3.43 (m, 1H), 3.09−3.04 (m, 1H), 2.10 (s, 3H), 1.28 (d, J = 6.2 Hz, 3H), 1.13−1.03 (m, 2H), 0.65 (td, J = 8.3, 5.1 Hz, 1H), 0.23 (q, J = 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.2, 128.8, 127.4, 126.6, 69.8, 65.1, 32.8, 25.7, 23.4, 22.5, 10.3; HRMS (ESI-TOF) m/z calcd. for $C_{13}H_{20}NO$ $[M + H]^+$ 206.1545, found 206.1568.

*(±)-2,3-Dimethyl-4-phenyl-3-azabicyclo[3.1.0]hexane (**45**).* To a cooled (0 °C) solution of amino alcohol **44a** (43 mg, 0.21 mmol) and Et_3N (87 μL, 0.63 mg) in anhydrous CH_2Cl_2 (3 mL) was added mesyl chloride (25 μL, 0.25 mmol) under argon atmosphere, and the mixture was stirred for 1 h. The mixture was slowly warmed to room temperature for 16 h before being concentrated in vacuo. To the residue was added 1 M HCl (1 mL) and EtOAc (5 mL). The aqueous layer was separated, basified with 1 M NaOH (pH 8−9) and extracted with $CHCl_3$ (2 × 10 mL). The organic layers were combined, washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo to yield crude **45** as a mixture of 2 diastereomers (*dr* **45a**:**45b** = 7:1) and unreacted **44a**. Purification by flash column chromatography (3:7 EtOAc/hexanes) afforded **45a** (25 mg, 63%) as clear oil. **45a** (5 mg) was converted to its hydrochloride salt. Data for compound **45a** (major): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.30 (m, 2H), 7.28−7.22 (m, 3H), 4.03 (s, 1H), 2.94 (qd, J = 5.8, 3.6 Hz, 1H), 1.88 (s,

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3H), 1.67 (ddd, J = 10.4, 7.7, 3.7 Hz, 1H), 1.48−1.43 (m, 1H), 1.08 (d, J = 5.9 Hz, 3H), 0.83−0.79 (m, 1H), 0.48 (td, J = 7.8, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.8, 128.8, 128.1, 127.1, 69.5, 57.3, 34.6, 23.4, 20.4, 16.5, 6.0. Data for compound **45b** (minor): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46−7.43 (m, 2H), 7.35−7.31 (m, 2H), 7.28−7.22 (m, 1H), 3.30 (d, J = 1.8 Hz, 1H), 2.51 (qd, J = 6.3, 1.8 Hz, 1H), 2.12 (s, 3H), 1.48−1.43 (m, 1H), 1.37 (tdd, J = 7.7, 4.0, 1.8 Hz, 1H), 1.30 (d, J = 6.3 Hz, 1H), 0.92 (td, J = 8.0, 4.6 Hz, 1H), 0.37−0.34 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.9, 128.3, 127.6, 126.9, 75.9, 66.7, 38.5, 27.0, 26.2, 20.9, 19.3.

Data for (±)-**45a** (Hydrochloride salt): Clear gum, ^{1}H NMR (CD_3OD, 400 MHz) δ 7.44 (d, J = 1.0 Hz, 5H), 4.65 (s, 1H), 3.73 (qd, J = 6.4, 3.7 Hz, 1H), 2.21−2.15 (m, 4H), 1.85 (td, J = 7.0, 4.8 Hz, 1H), 1.39 (d, J = 6.4 Hz, 3H), 0.92−0.86 (m, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 133.7, 131.6, 131.2, 130.6, 72.4, 64.1, 35.6, 23.5, 20.4, 13.7, 5.6; HRMS (ESI-TOF) m/z calcd. for $C_{13}H_{18}N$ $[M + H]^+$ 188.1439, found 188.1434.

*(±)-N-((2-(1-Hydroxyethyl)cyclopropyl)(phenyl)methyl)-N,4-dimethylbenzenesulfonamide (**S9**).* Following the procedure described for **45**, amino alcohol **44a** (13 mg, 0.063 mmol) and tosyl chloride (14 mg, 0.075 mmol) afforded compound **S9** (14 mg, 62%), as a clear oil, after flash column chromatography ($EtOAc/CH_2Cl_2$ 7:93) on silica gel: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47−7.45 (m, 2H), 7.16−7.14 (m, 3H), 7.13−7.09 (m, 4H), 4.78 (d, J = 10.5 Hz, 1H), 3.74−3.66 (m, 1H), 3.42 (d, J = 2.8 Hz, 1H), 2.73 (s, 3H), 2.30 (s, 3H), 1.48 (ddt, J = 10.5, 8.3, 4.1 Hz, 1H), 1.30 (d, J = 6.2 Hz, 3H), 1.26−1.18 (m, 1H), 0.86 (td, J = 8.7, 5.1 Hz, 1H), 0.05 (q, J = 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.5, 139.2, 135.9, 129.5, 128.4, 128.1, 127.8, 67.4, 60.8, 30.2, 27.0, 23.0, 21.6, 19.9, 9.9; HRMS (ESI-TOF) m/z calcd. for $C_{20}H_{26}NO_3S$ $[M + H]^+$ 360.1633, found 360.1625.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectra, ^{13}C NMR spectra, NOESY spectra, computational data, and an explanation for the conversion of compound **43** (*dr* 3.4:1) into **44** (*dr* 10:1). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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