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Diversity in the Synthesis of Functionalized Cyclohexene Oxide Derivatives by a Cycloaddition−Fragmentation Sequence from Benzene Oxide

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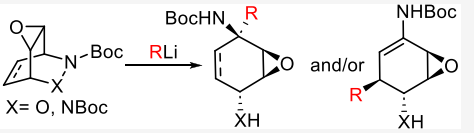
ABSTRACT: A cycloaddition−fragmentation sequence from benzene oxide and a nitroso- or azo-dienophile was investigated as a tool for access to highly substituted cyclohexene oxide derivatives. Alkyl lithium-promoted fragmentation of the cycloadducts led to the cyclic derivatives after 1,4- or 1,2-addition of a second equivalent of the lithium reagent. New fragmentation processes were observed when using non-nucleophilic bases of highly hindered alkyl lithium reagents. All reactions proceeded with complete stereocontrol.



INTRODUCTION

Synthetic sequences including cycloaddition and fragmentation reactions have been widely used in the synthesis of natural products, as they benefit from the high level of stereocontrol in the cycloaddition step.[1−3] Diels−Alder/fragmentation sequences often use cyclic dienes as starting materials, with fragmentation reactions involving retro-Diels−Alder reactions,[4] reductive cleavage of a heteroatom−heteroatom bond,[5] or anionic elimination[6] (Figure 1).

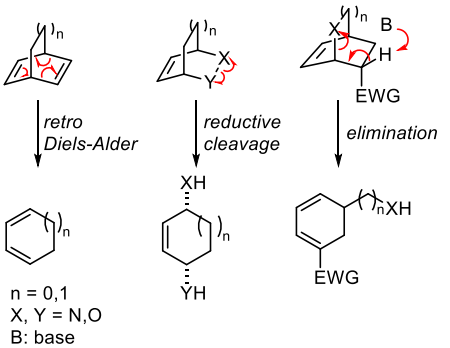


Figure 1. Typical fragmentation reactions of Diels−Alder cycloadducts.

We have disclosed a new fragmentation reaction of cycloadducts obtained from acylnitroso dienophiles and benzene oxide **1** as the diene.[7] This fragmentation involves C−H activation by carbonyl-assisted deprotonation and a subsequent elimination reaction, cleaving the N−O bond and leading to highly functionalized cyclohexene oxide derivatives that could undergo the further addition of organolithium reagents (Figure 2). Therefore, this synthetic sequence could lead to a high level of molecular diversity.

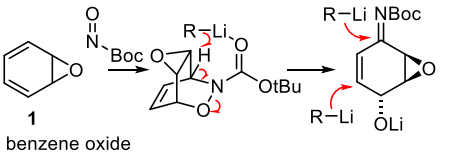


Figure 2. New cycloaddition/fragmentation sequence from benzene oxide **1**.

We have in previous studies discussed the role of the epoxide functionality. In this present report, we would describe further insights into the reactivity of benzene oxide toward cycloaddition, further examples of fragmentation reactions, and new accesses to molecular diversity.

RESULTS AND DISCUSSION

The chemistry of benzene oxide **1** started in 1991 when Burnell and co-workers synthesized it in three steps from 1,4-cyclohexadiene and assessed its reactivity as a diene in Diels−Alder reactions with simple dienophiles.[8] Further studies have confirmed not only the synthetic potential of **1** but also its low reactivity in cycloadditions.[9] Concomitant to our work, Johnson and co-workers have explored the reactivity of **1** toward cyclic all-carbon and heterodienophiles, especially azo dienophiles.[10] These series of experiments could assess not only the reactivity of **1** but also the stability of the epoxide functionality; although it is rather stable in cycloadducts, we observed the rapid decomposition of **1** to phenol in the

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presence of Lewis acids, thus reducing the scope of dienophiles compatible with **1** in thermal cycloadditions.[11]

Benzene oxide **1** was prepared from 1,4-cyclohexadiene according to the described procedure[8] (a, Br_2 and DCM; b, mCPBA and DCM; c, DBU and THF) and stored as a crude solution due to its volatility. It should be pointed out that careful removal of DBU is necessary, as prolonged exposure to this base results in the degradation of **1** by the formation of the byproduct **2**, which could be isolated in the crude products of cycloadditions (Figure 3).

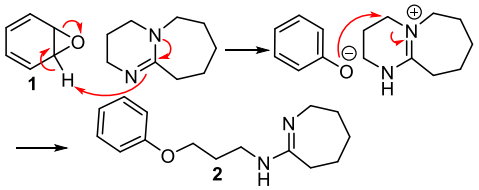


Figure 3. Decomposition of **1** with DBU.

The reactivity of **1** toward heterodienophiles was next investigated. We previously reported that **1** reacted with acylnitroso reagents with good yields and complete stereoselectivity.[7] We investigated the reactivity toward other nitroso reagents such as pyridylnitroso, since the latter has been successfully used in catalytic asymmetric nitroso Diels–Alder reactions.[12] Unfortunately, no cycloaddition was observed with a series of aromatic nitroso derivatives (Figure 4). Addition of copper complexes to pyridylnitroso derivatives did not trigger the reaction.

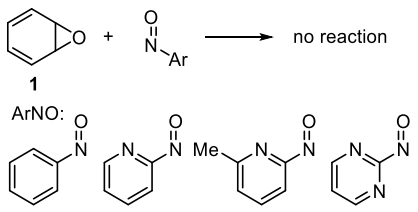


Figure 4. Cycloaddition of benzene oxide **1** with aryl nitroso derivatives.

The reactivity of **1** seems to be limited to highly activated dienophiles; however, phosphinoylnitroso derivatives,[13] although less reactive than their acyl counterparts, gave high yields of cycloadducts such as **3**, which was obtained as a single diastereomer (Figure 5).

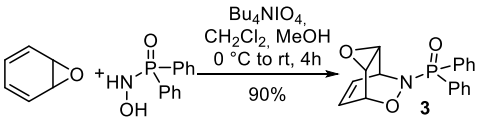


Figure 5. Cycloaddition between benzene oxide **1** and a phosphinoyl nitroso derivative.

The reactivity of azo dienophiles in cycloadditions was next investigated. On the basis of the results obtained by Johnson and co-workers,[10] a series of acyclic azo derivatives were prepared and reacted with **1** (Scheme 1 and Table 1).

As expected, azo dienophiles proved to be less reactive than nitroso derivatives, as only those possessing two carbamate substituents gave the cycloadducts (entries 1 and 2). No

Scheme 1. Cycloadditions between Benzene Oxide 1 and Azo Derivatives 4a–e

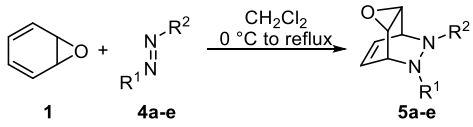


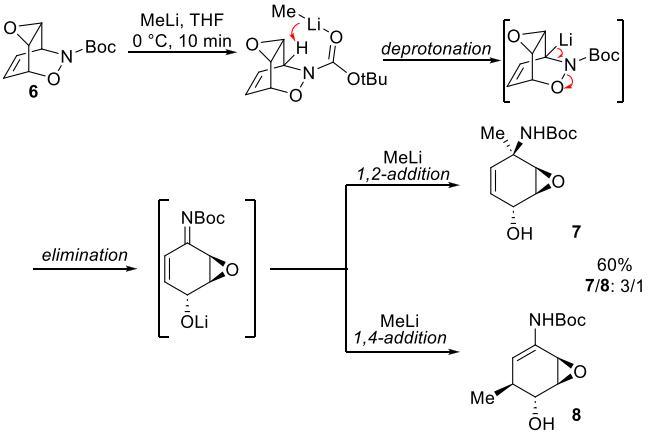
Table 1. Cycloadditions between Benzene Oxide 1 and Azo Dienophiles 4a–e

entry	dienophile	R^1	R^2	product	yield (%)
1	**4a**	Boc	Boc	**5a**	99
2	**4b**	CO_2iPr	CO_2iPr	**5b**	99
3	**4c**	2-Py	Boc	**5c**	0
4	**4d**	2-Py	Troc	**5d**	0
5	**4e**	2-Py	Cbz	**5e**	0

reaction was observed with 2-pyridyl derivatives[14] (entries 3–5), even when the reaction was performed at a higher temperature. Cycloadducts **5a** and **5b** were obtained as single diastereomers.

The fragmentation reaction of the benzene oxide cycloadduct was next studied using the Boc-protected cycloadduct **5a** and the nitroso cycloadduct **6**. In the preliminary studies, we observed the formation of two compounds **7** and **8** in a 3:1 ratio upon treatment with excess methyllithium. The suggested reaction pathway involves carbamate-assisted deprotonation at the bridgehead position followed by *β*-elimination, resulting in the cleavage of the N–O bond and giving an intermediate-conjugated imine that could undergo the further addition of methyllithium. 1,2-Addition of MeLi gave **7** or conjugate addition gave **8**, which was isolated as an enamine (Scheme 2).

Scheme 2. Fragmentation of Cycloadduct 6 in the Presence of Methyllithium



The reaction was fast, with complete conversion being obtained after 10 min at 0 °C. All products were obtained as single diastereomers, with an addition of MeLi *anti* to the epoxide in the case of 1,2-addition and *anti* to the neighboring group in the case of the 1,4-addition. The stereochemistry was previously confirmed by X-ray crystallography.[7]

The scope and selectivity of this sequence were further investigated. In particular, the selectivity between 1,2- and 1,4-addition in the second addition of the organolithium reagent was studied using different nucleophiles and temperatures from cycloadduct **6** (Scheme 3 and Table 2).

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Scheme 3. Fragmentation Reactions of Cycloadducts 6 in the Presence of Various Organolithium Reagents

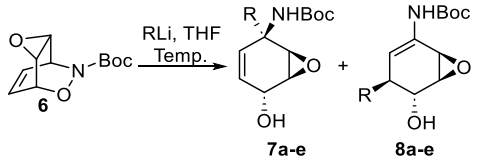


Table 2. Scope and Selectivity of Fragmentation Reaction of Cycloadduct 6 in the Presence of Organolithium Reagents

entry	R	temperature	time	yield (%)	7/8 ratio[a]
1	Me	0 °C	10 min	60	**7a/8a** 3:1
2	Me	−78 °C	30 min	67	**7a/8a** 1:1
3	*n*Bu	0 °C	30 min	50	**7b/8b** 2:3
4	*n*Bu	−78 °C	30 min	75	**7b/8b** 1:5
5	$TMSCH_2$	0 °C	30 min	10[b]	**7c/8c** 2:1
6	$TMSCH_2$	−78 °C	5 h	50[b]	**7c/8c** 1:2
7	Ph	0 °C	30 min	47	**7d/8d** 0:1
8	Ph	−78 °C	30 min	81	**7d/8d** 0:1
9	$pMeOC_6H_4$	0 °C	-	-	-
10	$pMeOC_6H_4$	−78 °C	5 h	47	**7e/8e** 0:1
11	$pClC_6H_4$	−78 °C	5 h	39	**7f/8f** 0:1

[a]Ratio determined with the isolated products. [b]Incomplete conversion.

The reaction was studied at both 0 and −78 °C. Yields were higher at low temperature, indicating the probable degradation of products at the higher temperature. It is possible that the enamine function in products **8a−f** is responsible for this partial degradation. This feature may also account for the reversal of 1,2- vs 1,4-selectivity: at low temperature, higher selectivity for conjugate products **8a−f** is observed (entries 2, 4, end 6). The use of aromatic lithium reagents leads to complete 1,4-selectivity regardless of the temperature (entries 7−10). In all cases, the products were obtained as single diastereomers.

Although the temperature and choice of reagents may affect yields and selectivity, the choice of solvent proved to also be crucial. Initial studies were carried out in THF. Switching to other solvents proved to be deleterious, as the reaction in diethyl ether was slower with reduced yields and selectivity, whereas the reaction in toluene gave only traces of products (Figure 6). This difference in reactivity could be explained by the aggregation state of the organolithium reagents, which are known to deaggregate into more reactive solvated dimers in neat THF.[15]

In addition to these studies, we also investigated the possibility of using less basic organometallic reagents or even non-nucleophilic bases such as LDA, which would ensure

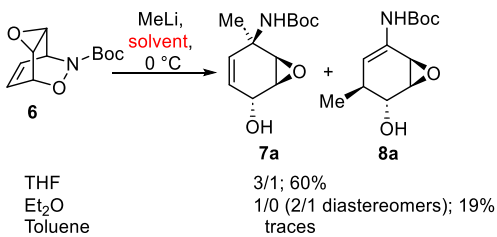
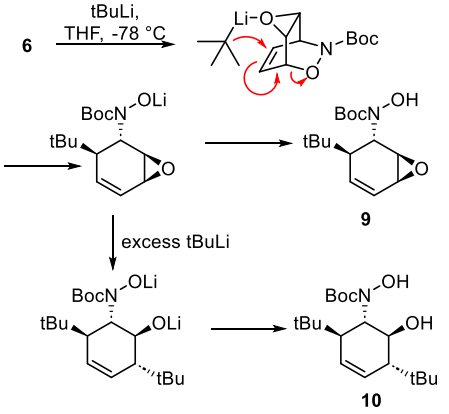


Figure 6. Role of solvent in the fragmentation reaction of cycloadduct **6**..

deprotonation and elimination but exclude a second addition to the intermediate. Unfortunately, no reaction occurred when Grignard reagents, cuprates, or LDA was used, with the starting material being recovered.

The use of hindered organometallic reagents such as *tert*-butyllithium gave completely different results from those obtained with other lithium derivatives. No deprotonation occurred at the bridgehead position, probably for steric reasons. Instead, coordination of the oxygen atom in the epoxide by lithium allows a SN_2' fragmentation in which the *tert*-butyl group adds to the double bond, thus triggering the cleavage of the carbon−oxygen bond and leading to the cyclohexyl hydroxylamine **9**. The use of excess *tert*-butyllithium results in the opening of the epoxide to give the crystalline compound **10**, the structure of which could be assigned by X-ray (Scheme 4, Figure 7). Both **9** and **10** were obtained as

Scheme 4. A New Fragmentation Reaction in the Presence of *tert*-Butyllithium



single diastereomers. This new fragmentation reaction is remarkable because it uses the nucleophilic character of *tert*-butyllithium rather than its basic character, which is quite rare.

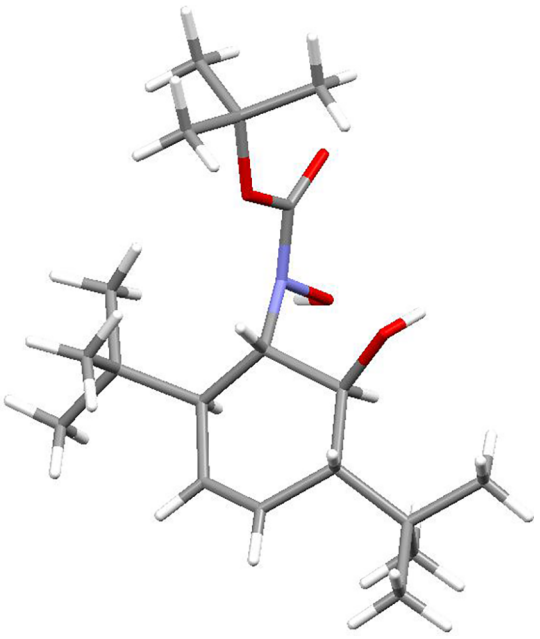


Figure 7. Crystallographic structure of compound **10.**

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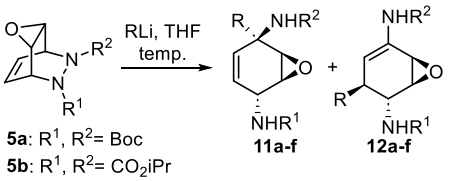
It also increases the degree of diversity by allowing the formation of a different structure using a different nucleophile.[16]

The fragmentation reaction was also studied with cycloadducts **5a** and **5b**, which arise from cycloaddition between benzene oxide and azo dienophiles. The same conditions as with cycloadduct **6** were applied (Scheme 5 and Table 3).

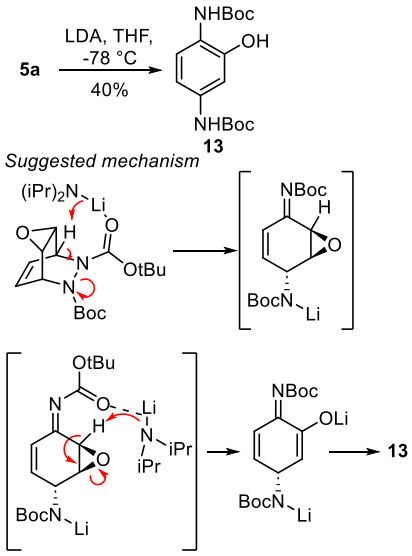
Scheme 5. Fragmentation Reactions of Cycloadducts 5a and 5b



Azo cycloadducts **5a** and **5b** undergo the fragmentation sequence the same way as nitroso cycloadduct **6**. Identical products and selectivities were obtained starting from both compounds, although yields were higher starting from the Boc-protected adduct **5a** (entries 1 and 2). Therefore, the scope of the reaction was studied solely with this starting material. As for the previous series, yields and 1,4-selectivity were higher at low temperature despite an important increase in the reaction times compared to the nitroso cycloadduct. This indicates that the nitrogen−nitrogen bond-containing derivatives were less reactive than their nitrogen−oxygen bond-containing counterparts. The 1,2-selectivity is generally higher in these series than with the nitroso derivative **6**, as illustrated by exclusive formation of product **11a** with methyllithium and by the lower selectivity for the conjugate addition product **12e** with phenyllithium. As before, single diastereomers were obtained for all compounds.

As for the previous series, the possibility to perform the fragmentation sequence with other organometallic reagents or with non-nucleophilic bases was investigated with the same negative outcome. However, an interesting insight into the reactivity of intermediates was brought when the reaction was performed with cycloadduct **5a** in the presence of LDA. Cleavage of the nitrogen−nitrogen bond was observed, but the aromatic compound **13** was isolated instead of the expected compounds **11a** and **12a**. A possible mechanism for this transformation would involve further deprotonation of the epoxide and ring-opening as described in the rearrangements of cyclohexene oxides to cyclohexenols,[17] with the coordination of the imine Boc protecting group facilitating proton abstraction[18,19] (Scheme 6).

Scheme 6. Fragmentation of Cycloadduct 5a with Non-Nucleophilic Base LDA



In the reaction study, an important parameter is the deprotonation, which is the early step of the fragmentation sequence. It was important to assess the influence of the neighboring double bond in cycloadducts **5a** and **6** on the acidity of the bridgehead position. Therefore, cycloadducts **5a** and **6** were hydrogenated under standard conditions and the resulting saturated derivatives **14** and **15** were submitted to the fragmentation conditions (Scheme 7). At low temperature, the fragmentation occurs, leading to enamines **16** and **17**. With the oxygen-bearing substrate **15**, partial addition of the organometallic reagent to the imine was observed, as well as an epoxide shift of the enamine product.

These experiments first prove that the double bond is not necessary for deprotonation. Therefore, it corresponds to an carbonyl-assisted C−H activation rather than an allylic metalation. Moreover, the fragmentation leads to a different set of products, mainly those devoid of second organometallic reagents. The key feature in this sequence is the intermediate

Table 3. Scope of the Fragmentation Reaction of Cycloadducts 5a and 5b in the Presence of Organolithium Reagents

entry	cycloadduct	R	temperature	time	yield (%)	11/12[a]
1	**5a**	Me	0 °C	15 min	57	**11a/12a** 1:0
2	**5b**	Me	0 °C	15 min	42	**11b/12b** 1:0
3	**5a**	Me[b]	−78 °C	6 h	80	**11a/12a** 1:0
4	**5a**	*n*-Bu	0 °C	30 min	21	**11c/12c** 2:3
5	**5a**	*n*-Bu	−78 °C	30 min	53	**11c/12c** 1:3
6	**5a**	$TMSCH_2$	0 °C	30 min	22	**11d/12d** 2:3
7	**5a**	$TMSCH_2$	−78 °C	1 h	22[c]	**11d/12d** 1:1
8	**5a**	Ph	0 °C	30 min	26	**11e/12e** 1:4
9	**5a**	Ph	−78 °C	48 h	39	**11e/12e** 1:3
10	**5a**	$pMeOC_6H_4$	0 °C	-	-	-
11	**5a**	$pMeOC_6H_4$	−78 °C	6 h[c]	39	**11f/12f** 1:3
12	**5a**	$pClC_6H_4$	−78 °C	-	-	-

[a]Ratio determined with the isolated products. [b]The reaction was performed with 5 equiv of methyllithium. [c]Incomplete conversion.

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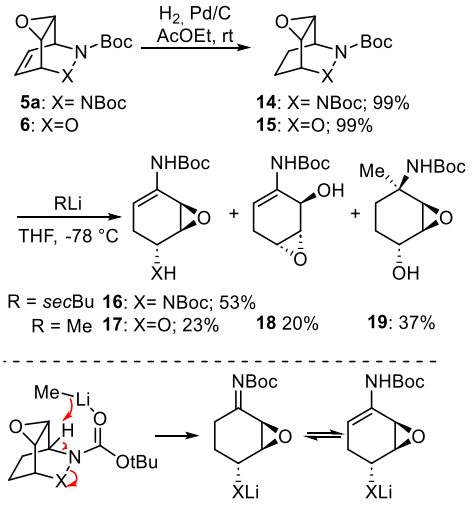
Scheme 7. Fragmentation of Saturated Substrates 14 and 15



imine, which is not conjugated and therefore less prone to aromatization. Furthermore, the imine−enamine equilibrium partially prevents nucleophilic addition. Exploiting the enamine reactivity would allow the new introduction of substituents in a different position.

CONCLUSION

We have developed an original fragmentation sequence from benzene oxide cycloadducts, which can lead to a great variety of products via organometallic reactions. Benzene oxide cycloadducts are efficient scaffolds for the generation of diversity in the stereoselective synthesis of functionalized cyclohexane and cyclohexene oxide derivatives, where every component (epoxide, double bond, and heteroatom) plays a crucial role in the divergent synthesis. The high level of stereocontrol illustrates the efficiency of strategy using rigid bicyclic compounds for the generation of stereodefined monocyclic products. A further level of diversity may be obtained by taking advantage of residual functional group reactivity (enamine and epoxide). These aspects as well as the development of enantioselective methods are under investigation in our laboratory.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all reactions were performed under an argon atmosphere with anhydrous solvents. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone; dichloromethane (DCM) and toluene were distilled from calcium hydride. *n*-BuLi solutions were titrated with 2,2-diphenylacetic acid prior to use. *meta*-Chloroperoxybenzoic acid was purified prior to use by washing it with a buffer solution of NaOH and KH_2PO_4 according to the literature.[16] All other chemicals and solvents were purchased from their commercial sources and used as it received. For reactions that required heating, a heating block adapted to the flask size was used. Reactions were monitored with analytical thin-layer chromatography (TLC) on silica gel 60 F254 plates and visualized under UV (254 nm) and/or by staining with a $KMnO_4$ solution or a phosphomolybdic acid hydrate solution (6%) in EtOH, followed by heating. Purifications were performed by column chromatography using silica gel. ^{1}H NMR spectra were recorded on 400, 360, or 300 MHz instruments at 295 K. Chemical shifts (δ) are given in parts per million with respect to the residual protonated solvent (δ 7.26 ppm for chloroform-*d*, δ 3.31 ppm for methanol-d_4, δ 2.05 ppm for acetone-d_6, and δ 2.50 ppm for dimethyl sulfoxide-d_6), which served as an internal standard. ^{13}C NMR spectra were recorded at 100, 90, or 75 MHz. Chemical shifts are expressed with respect to the residual deuterated solvent (δ 77.16 ppm for chloroform-*d*, δ 49.00 ppm for methanol-d_4, δ 29.84 ppm for acetone-d_6, and δ 39.52 ppm for dimethyl sulfoxide-d_6), which served as an internal standard. ^{31}P NMR spectra were recorded at 120 MHz on a 360 MHz apparatus. Coupling constants (J) in hertz (Hz) were measured from one-dimensional spectra, and multiplicities were abbreviated as follows: br (broad), s (singlet), d (doublet), t (triplet), q (quadruplet), and m (multiplet). High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) or atmospheric-pressure chemical ionization (APCI).

*N-(3-Phenoxypropyl)-3,4,5,6-tetrahydro-2H-azepin-7-amine (**2**).* This compound is a byproduct in the synthesis of **1** that could be observed in cycloaddition crude products. Brown oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.14−7.19 (m, 2H), 6.65−6.70 (m, 3H), 3.48 (t, J = 6.6 Hz, 2H), 3.32−3.34 (m, 2H), 3.14 (t, J = 6.5 Hz, 2H), 2.52−2.55 (m, 2H), 1.63−1.82 (m, 8H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.5, 148.1, 129.4, 117.4, 113.3, 49.7, 45.6, 40.7, 37.4, 30.1, 28.7, 27.0, 23.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd. for $C_{15}H_{23}N_2O$ 247.1805, found 247.1798; R_f = 0.55 (EtOAc/MeOH 95:5)

*Diphenyl((1S,2R,4R,5R)-3,6-dioxa-7-azatricyclo[3.2.2.0^{2,4}]non-8-en-7-yl)phosphine Oxide (**3**).* A solution of *N*-hydroxy-*P*,*P*-diphenylphosphinic amide **SI-7** (150 mg, 0.64 mmol, 1.0 equiv) in methanol (12 mL) was added dropwise to a stirred mixture of tetrabutylammonium periodate (303 mg, 0.70 mmol, 1.1 equiv) and crude benzene oxide **1** (3.20 mmol, 5.0 equiv) in DCM (6 mL) at 0 °C under argon. After stirring at 0 °C for 6 h, the reaction mixture was quenched with a 0.1 M aqueous $Na_2S_2O_3$ solution (10 mL) and the two layers were separated. The organic layer was extracted with DCM (4 × 10 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (EtOAc/PE 70:30) to yield the desired phosphinoylnitroso cycloadduct **3** (188 mg, 0.58 mmol, 90% yield over two steps) as a light yellow powder. ^{1}H NMR (360 MHz, acetone-d_6) δ 7.83−7.94 (m, 4H), 7.59−7.48 (m, 6H), 6.03 (t, J = 7.3 Hz, 1H), 5.89 (t, J = 7.3 Hz, 1H), 4.95−4.99 (m, 1H), 4.52−4.57 (m, 1H), 3.65 (t, J = 4.6 Hz, 1H), 3.58 (t, J = 4.5 Hz, 1H); ^{13}C{^{1}H} NMR (90 MHz, acetone-d_6) δ 133.4 (d, J = 9.2 Hz), 133.1 (d, J = 9.2 Hz), 133.0 (d, J = 2.5 Hz), 132.7 (d, J = 2.5 Hz), 132.1, 131.9, 129.3 (d, J = 12.5 Hz), 129.1 (d, J = 12.5 Hz), 127.8 (d, J = 5.3 Hz), 126.5, 75.0, 53.3, 42.6, 41.5 (d, J = 12.6 Hz); ^{31}P NMR (121 MHz, acetone-d_6) δ 27.7; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd. for $C_{18}H_{17}NO_3P$ 326.0940, found 326.0933; R_f = 0.27 (PE/EtOAc 80:20).

General Procedure for Azo Cycloadditions. Crude benzene oxide **1** (5.0 equiv) was added dropwise to a solution of the corresponding azodicarboxylate (1.0 equiv) in DCM (0.1 M) under argon at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and warmed to rt for 20 h (for cycloadduct **5b**) or for 72 h (for cycloadduct **5a**). The solvent was then concentrated *in vacuo*. The crude residue was purified by column chromatography (PE/EtOAc 80:20) to yield the corresponding azo cycloadduct **5a** or **5b**.

*Di-tert-butyl (1R,2S,4R,5S)-3-Oxa-6,7-diazatricyclo[3.2.2.0^{2,4}]-non-8-ene-6,7-dicarboxylate (**5a**).* The reaction of di-*tert*-butyl azodicarboxylate (1.0 g, 4.34 mmol, 1.0 equiv) with crude benzene oxide **1** (21.7 mmol, 5.0 equiv) according to the general procedure afforded the corresponding cycloadduct **5a** (1.4 g, 99% yield over two steps) as a white powder. ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.24 (t, J = 6.8 Hz, 1H), 6.01 (t, J = 7.3 Hz, 1H), 5.16−5.23 (m, 2H), 3.61 (brs, 1H), 3.46 (brs, 1H), 1.47 (s, 9H), 1.41 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 323 K) δ 157.3, 156.5, 130.7, 124.7, 81.7, 54.4, 53.7, 42.6, 41.5, 28.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd. for $C_{16}H_{25}N_2O_5$ 325.1758, found 325.1747; R_f = 0.50 (PE/EtOAc 80:20).

*Diisopropyl (1R,2S,4R,5S)-3-Oxa-6,7-diazatricyclo[3.2.2.0^{2,4}]non-8-ene-6,7-dicarboxylate (**5b**).* The reaction of diisopropyl azodicarboxylate (0.48 mL, 2.47 mmol, 1.0 equiv) with crude benzene oxide **1** (12.4 mmol, 5.0 equiv) according to the general procedure afforded the corresponding cycloadduct **5b** (648 mg, 89% yield over two steps) as a white powder. ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.17 (t, J = 6.3 Hz, 1H), 5.94 (t, J = 7.4 Hz, 1H), 5.14−5.21 (m, 2H), 4.81−4.92 (m,

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2H), 3.55 (brs, 1H), 3.39 (brs, 1H), 1.13−1.18 (m, 12H); $^{13}C\{^1H\}$ NMR (90 MHz, $CDCl_3$) δ 157.9, 157.1, 130.7, 124.5, 70.4, 70.3, 54.3, 53.6, 42.4, 41.2, 21.7, 21.6; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd. for $C_{14}H_{20}N_2NaO_5$ 319.1264, found 319.1264; R_f = 0.27 (PE/EtOAc 80:20).

General Procedures for Acylnitroso Cycloadduct Fragmentations. *Procedure for the Synthesis of Compounds **7a−d** and **8a−d**.* A solution of acylnitroso cycloadduct **6** (1 equiv) in THF (0.1 M) was cooled to −78 or 0 °C before the dropwise addition of the organolithium compound (2.5 equiv, titrated prior to use). The reaction mixture was stirred at −78 or 0 °C for the corresponding time. Water (10 mL) was then added to the mixture before it was warmed to rt and the organic phase was separated. The aqueous phase was extracted with DCM (3 × 5 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography afforded the desired 1,2- and 1,4-addition products.

*Compounds **7a** and **8a**.* The reaction of acylnitroso cycloadduct **6** (200 mg, 0.89 mmol, 1.0 equiv) with methyllithium (1.50 mL, 2.23 mmol, 2.5 equiv, 1.50 M in Et_2O) for 10 min at 0 °C according to the general procedure afforded the two addition products **7a** and **8a** (129 mg, 60% yield) as a yellow oil.

The reaction of acylnitroso cycloadduct **6** (200 mg, 0.89 mmol, 1.0 equiv) with methyllithium (1.53 mL, 2.23 mmol, 2.5 equiv, 1.45 M in Et_2O) for 30 min at −78 °C according to the general procedure afforded the two addition products **7a** and **8a** (141 mg, 67% yield) as a yellow oil. Purification conditions are as follows: PE/EtOAc (60:40). These products were obtained as an inseparable mixture of 1,2-addition and 1,4-addition products in a 3:1 ratio.

*tert-Butyl ((1S,2S,5S,6R)-5-Hydroxy-2-methyl-7-oxabicyclo-[4.1.0]hept-3-en-2-yl)carbamate (**7a**).* ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (d, J = 10.2 Hz, 1H), 5.57 (dd, J = 3.8, 10.4 Hz, 1H), 4.86 (s, 1H), 4.38 (brs, 1H), 3.43 (brs, 1H), 3.35 (brs, 1H), 2.98 (d, J = 5.8 Hz), 1.56 (s, 3H), 1.39 (s, 9H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 154.7, 130.9, 123.5, 79.8, 62.2, 57.0, 55.0, 51.8, 28.4, 24.7.

*tert-Butyl ((1S,5S,6R)-5-Hydroxy-4-methyl-7-oxabicyclo[4.1.0]-hept-2-en-2-yl)carbamate (**8a**).* ^1H NMR (300 MHz, $CDCl_3$) δ 6.36 (s, 1H), 5.63 (s, 1H), 3.86 (brs, 1H), 3.51−3.53 (m, 1H), 3.37−3.39 (m, 1H), 2.46 (brs, 1H), 2.14 (s, 1H), 1.43 (s, 9H), 1.05 (d, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$) δ 154.0, 130.0, 118.5, 81.0, 69.2, 58.0, 49.5, 36.9, 28.4, 20.6; R_f = 0.21 (PE/EtOAc 70:30). Recorded data are consistent with previously recorded values.[7]

*Compounds **7b** and **8b**.* The reaction of acylnitroso cycloadduct **6** (200 mg, 0.89 mmol, 1.0 equiv) with *n*-butyllithium (1.45 mL, 2.23 mmol, 2.5 equiv, 1.52 M in hexane) for 30 min at 0 °C according to the general procedure afforded the two addition products **7b** and **8b** (125 mg, 50% yield) as a light yellow oil.

The reaction of acylnitroso cycloadduct **6** (200 mg, 0.89 mmol, 1.0 equiv) with *n*-butyllithium (1.53 mL, 2.23 mmol, 2.5 equiv, 1.44 M in hexane) for 30 min at −78 °C according to the general procedure afforded the two addition products **7b** (29 mg, 12% yield) and **8b** (158 mg, 63% yield) as light yellow oils. Purification conditions are as follows: PE/EtOAc (70:30).[7]

*tert-Butyl ((1S,2S,5S,6R)-2-Butyl-5-hydroxy-7-oxabicyclo[4.1.0]-hept-3-en-2-yl)carbamate (**7b**).* ^1H NMR (360 MHz, $CDCl_3$) δ 5.73 (ddd, J = 1.9, 4.4, 10.4 Hz, 1H), 5.66 (dd, J = 1.5, 10.6 Hz, 1H), 4.71 (brs, 1H), 4.44 (brs, 1H), 3.51 (brs, 1H), 3.38−3.40 (m, 1H), 2.04−2.14 (m, 1H), 1.92−2.01 (m, 1H), 1.76 (brs, 1H), 1.43 (s, 9H), 1.23−1.35 (m, 4H), 0.90 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (90 MHz, $CDCl_3$) δ 154.5, 129.8, 124.8, 79.8, 62.6, 56.4, 55.2, 54.9, 36.3, 28.5, 26.3, 23.0, 14.1; R_f = 0.46 (PE/EtOAc 70:30). Recorded data are consistent with previously recorded values.[7]

*tert-Butyl ((1S,4R,5S,6R)-4-Butyl-5-hydroxy-7-oxabicyclo[4.1.0]-hept-2-en-2-yl)carbamate (**8b**).* ^1H NMR (360 MHz, $CDCl_3$) δ 6.29 (brs, 1H), 5.69 (brs, 1H), 3.98 (brs, 1H), 3.51−3.53 (m, 1H), 3.40−3.42 (m, 1H), 3.12 (brs, 1H), 2.33−2.35 (m, 1H), 1.45 (s, 9H), 1.23−1.32 (m, 6H), 0.88 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (90 MHz, $CDCl_3$) δ 153.7, 130.1, 116.5, 80.8, 67.7, 57.8, 49.4, 42.3, 35.4, 29.7, 28.4, 22.8, 14.1; R_f = 0.36 (PE/EtOAc 80:20). Recorded data are consistent with previously recorded values.[7]

*Compounds **7c** and **8c**.* The reaction of acylnitroso cycloadduct **6** (100 mg, 0.44 mmol, 1.0 equiv) with trimethylsilylmethyllithium (1.16 mL, 1.10 mmol, 2.5 equiv, 0.95 M in pentane) for 30 min at 0 °C according to the general procedure afforded the two addition products **7c** (11 mg, 8% yield) and **8c** (4 mg, 2% yield) as light yellow oils.

The reaction of acylnitroso cycloadduct **6** (100 mg, 0.44 mmol, 1.0 equiv) with trimethylsilylmethyllithium (1.26 mL, 1.10 mmol, 2.5 equiv, 0.87 M in pentane) for 5 h at −78 °C according to the general procedure afforded the two addition products **7c** (23 mg, 17% yield) and **8c** (46 mg, 33% yield) as light yellow oils. Purification conditions are as follows: PE/EtOAc (80:20).

*tert-Butyl ((1S,2S,5S,6R)-5-Hydroxy-2-((trimethylsilyl)methyl)-7-oxabicyclo[4.1.0]hept-3-en-2-yl)carbamate (**7c**).* ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (dd, J = 1.5, 10.6 Hz, 1H), 5.61 (ddd, J = 2.1, 4.7, 10.5 Hz, 1H), 4.71 (s, 1H), 4.46 (d, J = 4.4 Hz, 1H), 3.65 (brs, 1H), 3.39−3.41 (m, 1H), 1.77 (d, J = 14.6 Hz, 1H), 1.70 (brs, 1H), 1.43 (s, 9H), 1.26 (d, J = 14.6 Hz, 1H), 0.08 (s, 9H); $^{13}C\{^1H\}$ NMR (90 MHz, $CDCl_3$) δ 154.6, 131.8, 123.2, 79.8, 62.7, 57.4, 55.5, 54.2, 28.5, 27.3, 0.5; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd. for $C_{15}H_{27}NNaO_4Si$ 336.1602, found 336.1599; R_f = 0.17 (PE/EtOAc 80:20).

*tert-Butyl ((1S,2S,5S,6R)-5-Hydroxy-2-((trimethylsilyl)methyl)-7-oxabicyclo[4.1.0]hept-3-en-2-yl)carbamate (**8c**).* ^1H NMR (360 MHz, $CDCl_3$) δ 6.25 (s, 1H), 5.67 (brs, 1H), 3.92 (brs, 1H), 3.53−3.56 (m, 1H), 3.42−3.44 (m, 1H), 3.08 (brs, 1H), 2.42−2.48 (m, 1H), 1.45 (s, 9H), 0.65−0.80 (m, 2H), −0.01 (s, 9H); $^{13}C\{^1H\}$ NMR (90 MHz, $CDCl_3$) δ 153.7, 129.7, 118.2, 80.8, 70.1, 57.9, 49.3, 38.4, 28.4, 24.2, −0.7; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd. for $C_{15}H_{27}NNaO_4Si$ 336.1602, found 336.1605; R_f = 0.11 (PE/EtOAc 80:20).

*Compound **8d**.* The reaction of acylnitroso cycloadduct **6** (100 mg, 0.44 mmol, 1.0 equiv) with phenyllithium (0.65 mL, 1.10 mmol, 2.5 equiv, 1.69 M in dibutyl ether) for 30 min at 0 °C according to the general procedure afforded the 1,4-addition product **8d** (62 mg, 47% yield) as a yellow oil.

The reaction of acylnitroso cycloadduct **6** (100 mg, 0.44 mmol, 1.0 equiv) with phenyllithium (0.65 mL, 1.10 mmol, 2.5 equiv, 1.69 M in dibutyl ether) for 30 min at −78 °C according to the general procedure afforded the 1,4-addition product **8d** (108 mg, 81% yield) as a yellow oil. Purification conditions are as follows: PE/EtOAc (70:30).

*tert-Butyl ((1S,4S,5S,6R)-5-Hydroxy-4-phenyl-7-oxabicyclo-[4.1.0]hept-2-en-2-yl)carbamate (**8d**).* ^1H NMR (360 MHz, $CDCl_3$) δ 7.22−7.32 (m, 5H), 6.64 (brs, 1H), 5.74 (brs, 1H), 4.07 (brs, 1H), 3.71 (t, J = 5.0 Hz, 1H), 3.51−3.54 (m, 1H), 3.44−3.46 (m, 1H), 3.30 (brs, 1H), 1.49 (s, 9H); $^{13}C\{^1H\}$ NMR (90 MHz, $CDCl_3$) δ 153.4, 141.8, 131.8, 128.7, 128.5, 126.9, 114.1, 80.9, 71.2, 57.9, 49.0, 48.5, 28.3; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd. for $C_{17}H_{21}NNaO_4$ 326.1363, found 326.1353; R_f = 0.15 (PE/EtOAc 80:20).

*Procedure for the Synthesis of Compounds **7e, 7f, 8e, and 8f**.* A solution of the aryl bromide precursor (1.10 mmol, 2.5 equiv) in THF (2 mL) was cooled to −78 °C before the dropwise addition of the organolithium compound (2.5 or 5 equiv, titrated prior to use). After 30 min, a solution of acylnitroso cycloadduct **6** (100 mg, 0.44 mmol, 1.0 equiv) in THF (2 mL) was added to the reaction mixture, and the resultant mixture was stirred for the corresponding time at −78 or 0 °C. Water (10 mL) was then added to the mixture before it was warmed to rt and the organic phase was separated. The aqueous phase was extracted with DCM (3 × 5 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude mixture. Purification by silica gel column chromatography afforded the desired 1,4-addition products.

*Compound **8e**.* The reaction of acylnitroso cycloadduct **6** (100 mg, 0.44 mmol, 1.0 equiv) with 4-bromoanisole (0.14 mL, 1.10 mmol, 2.5 equiv) and *tert*-butyllithium (1.38 mL, 2.20 mmol, 5 equiv, 1.60 M in

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pentane) for 5 h at −78 °C according to the general procedure afforded the 1,4-addition product **8e** (69 mg, 47% yield) as a colorless oil. Purification conditions are as follows: PE/acetone (80:20).

*tert-Butyl ((1S,4S,5S,6R)-5-Hydroxy-4-(4-methoxyphenyl)-7-oxabicyclo[4.1.0]hept-2-en-2-yl)carbamate (**8e**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 6.54 (brs, 1H), 5.70 (brs, 1H), 4.00 (brs, 1H), 3.76 (s, 3H), 3.64 (t, J = 5.0 Hz, 1H), 3.51 (brs, 1H), 3.46 (brs, 1H), 3.14 (brs, 1H), 1.46 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.6, 153.3, 133.7, 131.7, 129.7, 114.4, 114.0, 80.9, 71.5, 58.0, 55.3, 49.0, 47.8, 28.4; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd. for $C_{18}H_{23}NNaO_5$ 356.1468, found 356.1452; R_f = 0.12 (PE/acetone 80:20).

*Compound **8f**.* The reaction of acylnitroso cycloadduct **6** (100 mg, 0.44 mmol, 1.0 equiv) with 1-bromo-4-chlorobenzene (211 mg, 1.10 mmol, 2.5 equiv) and *n*-butyllithium (0.83 mL, 1.10 mmol, 2.5 equiv, 1.33 M in hexane) for 5 h at −78 °C according to the general procedure afforded the 1,4-addition product **8f** (57 mg, 39% yield) as a colorless oil. Purification conditions are as follows: PE/acetone (90:10).

*tert-Butyl ((1S,4S,5S,6R)-4-(4-Chlorophenyl)-5-hydroxy-7-oxabicyclo[4.1.0]hept-2-en-2-yl)carbamate (**8f**).* ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.25 (brs, 1H), 5.75 (brs, 1H), 4.07 (dd, J = 1.9, 5.4 Hz, 1H), 3.71 (t, J = 5.0 Hz, 1H), 3.56 (d, J = 3.5 Hz, 1H), 3.45 (dd, J = 1.5, 4.2 Hz, 1H), 1.49 (s, 9H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) δ 153.1, 140.3, 132.3, 130.1, 128.8, 127.7, 112.6, 81.2, 71.4, 57.8, 49.0, 48.2, 28.4; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd. for $C_{17}H_{20}ClNNaO_4$ 360.0973, found 360.0962; R_f = 0.10 (PE/acetone 85:15).

*Large-Scale Procedure for the Fragmentation of an Acylnitroso Cycloadduct (Synthesis of Compound **8d**).* A solution of acylnitroso cycloadduct **6** (300 mg, 1.33 mmol, 1 equiv) in THF (10 mL, 0.1 M) was cooled to −78 °C before the dropwise addition of phenyllithium (1.85 mL, 3.33 mmol, 2.5 equiv, 1.80 M in dibutyl ether). The reaction mixture was stirred at −78 °C for 45 min. Water (20 mL) was then added to the mixture before it was warned to rt and the organic phase was separated. The aqueous phase was extracted with DCM (3 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography (PE/acetone 80:20) afforded the desired 1,4-addition product **8d** (296 mg, 73% yield) as a yellow oil.

*Compounds **9** and **10**.* A 0.1 M solution of acylnitroso cycloadduct **6** (100 mg, 0.44 mmol, 1.0 equiv) in THF was cooled to −78 °C before the dropwise addition of *tert*-butyllithium (0.69 mL, 1.10 mmol, 2.5 equiv, 1.60 M in pentane). The reaction mixture was stirred at −78 °C for 15 min. Water (10 mL) was then added to the mixture before it was warmed to rt and the organic phase was separated. The aqueous phase was extracted with DCM (3 × 5 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude mixture. Purification by silica gel column chromatography (PE/acetone 90:10 with 1% Et_3N) afforded a mixture of **9** and **10** (56 mg, 45% yield).

*tert-Butyl ((1S,2R,3R,6R)-3-(tert-Butyl)-7-oxabicyclo[4.1.0]hept-4-en-2-yl)(hydroxy)carbamate (**9**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (brs, 1H), 6.04 (d, J = 10.6 Hz, 1H), 5.92 (d, J = 4.6, 10.6 Hz, 1H), 4.65 (s, 1H), 3.34 (brs, 1H), 3.23 (m, 1H), 2.32 (brs, 1H), 1.49 (s, 9H), 0.92 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 155.9, 133.7, 122.6, 82.8, 56.1, 52.4, 49.4, 46.1, 34.0, 28.5, 28.4; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd. for $C_{15}H_{25}NNaO_4$ 306.1676, found 306.1669; R_f = 0.26 (PE/acetone 90:10).

*tert-Butyl ((1R,2R,5R,6R)-2,5-Di-tert-butyl-6-hydroxycyclohex-3-en-1-yl)(hydroxy)carbamate (**10**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (brs, 1H), 5.63 (q, J = 10.8 Hz, 2H), 3.87−3.94 (m, 2H), 2.99 (d, J = 2.9 Hz, 1H), 2.36 (d, J = 7.8 Hz, 1H), 2.04 (brs, 1H), 1.47 (s, 9H), 0.99 (s, 9H), 0.97 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.1, 128.5, 128.2, 82.4, 68.3, 64.0, 52.0, 45.2, 33.8, 33.5, 28.6, 28.0; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd. for $C_{19}H_{35}NNaO_4$ 364.2458, found 364.2443; R_f = 0.32 (PE/acetone 90:10). Crystallization: slow evaporation of methanol

General Procedures for Azo Cycloadduct Fragmentations. *Synthesis of compounds **11a**, **11c−e**, **12a**, and **12c−e**.* A 0.1 M solution of azo cycloadduct **5a** (1 equiv) in THF was cooled to −78 or 0 °C before the dropwise addition of the organolithium compound (2.5 equiv, titrated prior to use). The reaction mixture was stirred at −78 or 0 °C for corresponding time. Water (10 mL) was then added to the mixture before it was warmed to rt and the organic phase was separated. The aqueous phase was extracted with DCM (3 × 5 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude mixture. Purification by silica gel column chromatography afforded the desired 1,2- and 1,4-addition products.

*Compound **11a**.* The reaction of azo cycloadduct **5a** (200 mg, 0.62 mmol, 1.0 equiv) with methyllithium (1.00 mL, 1.55 mmol, 2.5 equiv, 1.50 M in Et_2O) for 15 min at 0 °C according to the general procedure afforded the 1,2-addition product **11a** (121 mg, 57% yield) as a colorless powder.

The reaction of azo cycloadduct **5a** (100 mg, 0.31 mmol, 1.0 equiv) with methyllithium (1.03 mL, 1.55 mmol, 5.0 equiv, 1.50 M in Et_2O) for 6 h at −78 °C according to the general procedure afforded the 1,2-addition product **11a** (84 mg, 80% yield) as a colorless powder. Purification conditions are as follows: PE/EtOAc (85:15).

*Di-tert-butyl ((1S,2S,5S,6R)-2-Methyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-diyl)dicarbamate (**11a**).* ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.74 (d, J = 10.1 Hz, 1H), 5.42−5.45 (m, 1H), 4.83 (s, 1H), 4.49 (brs, 2H), 3.41 (brs, 1H), 3.35 (brs, 1H), 1.57 (s, 3H), 1.43 (s, 9H), 1.40 (s, 9H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) δ 155.1, 154.6, 131.2, 121.5, 80.3, 79.7, 56.9, 54.3, 51.7, 44.2, 28.4, 28.2, 24.7; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd. for $C_{17}H_{28}N_2NaO_5$ 363.1890, found 363.1884; R_f = 0.38 (PE/EtOAc 80:20).

*Compounds **11c** and **12c**.* The reaction of azo cycloadduct **5a** (200 mg, 0.62 mmol, 1.0 equiv) with *n*-butyllithium (1.02 mL, 1.55 mmol, 2.5 equiv, 1.52 M in hexane) for 30 min at 0 °C according to the general procedure afforded the two addition products **11c** (20 mg, 8% yield) and **12c** (30 mg, 13% yield) as colorless oils.

The reaction of azo cycloadduct **5a** (200 mg, 0.62 mmol, 1.0 equiv) with *n*-butyllithium (1.08 mL, 1.55 mmol, 2.5 equiv, 1.44 M in hexane) for 30 min at −78 °C according to the general procedure afforded the two addition products **11c** (30 mg, 13% yield) and **12c** (95 mg, 40% yield) as colorless oils. Purification conditions are as follows: PE/EtOAc (85:15).

*Di-tert-butyl ((1S,2S,5S,6R)-2-Butyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-diyl)dicarbamate (**11c**).* ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.65 (d, J = 10.4 Hz, 1H), 5.54 (ddd, J = 1.9, 4.7, 10.4 Hz, 1H), 4.72 (brs, 1H), 4.55 (brs, 1H), 4.35 (d, J = 8.2 Hz, 1H), 3.46 (brs, 1H), 3.34 (brs, 1H), 2.05−2.16 (m, 1H), 1.86−1.95 (m, 1H), 1.45 (s, 9H), 1.42 (s, 9H), 1.28−1.37 (m, 2H), 1.20−1.26 (m, 2H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) δ 155.1, 154.5, 129.7, 123.0, 80.4, 79.7, 56.3, 54.7, 54.7, 44.1, 36.2, 28.4, 26.3, 22.9, 14.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd. for $C_{20}H_{35}N_2O_5$ 383.2540, found 383.2531; R_f = 0.30 (PE/EtOAc 85:15).

*Di-tert-butyl ((1S,4R,5S,6R)-4-Butyl-7-oxabicyclo[4.1.0]hept-2-ene-2,5-diyl)dicarbamate (**12c**).* ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.18 (brs, 1H), 5.77 (brs, 1H), 4.70 (d, J = 9.0 Hz, 1H), 4.16 (d, J = 9.0 Hz, 1H), 3.52 (brs, 1H), 3.38 (brs, 1H), 2.21 (q, J = 6.9 Hz, 1H), 1.46 (s, 9H), 1.42 (s, 9H), 1.24−1.34 (m, 6H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) δ 155.1, 153.3, 130.4, 115.2, 80.8, 79.9, 57.1, 48.8, 47.1, 41.0, 37.3, 29.9, 28.5, 28.4, 22.8, 14.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd. for $C_{20}H_{35}N_2O_5$ 383.2540, found 383.2530; R_f = 0.24 (PE/EtOAc 85:15).

*Compounds **11d** and **12d**.* The reaction of azo cycloadduct **5a** (200 mg, 0.62 mmol, 1.0 equiv) with trimethylsilylmethyllithium (1.78 mL, 1.55 mmol, 2.5 equiv, 0.87 M in pentane) for 30 min at 0 °C according to the general procedure afforded the two addition products **11d** (35 mg, 13% yield) and **12d** (22 mg, 9% yield) as light yellow oils.

The reaction of azo cycloadduct **5a** (200 mg, 0.62 mmol, 1.0 equiv) with trimethylsilylmethyllithium (1.63 mL, 1.55 mmol, 2.5 equiv, 0.95 M in pentane) for 1 h at −78 °C according to the general procedure afforded the two addition products **11d** (28 mg, 11% yield) and **12d**

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(29 mg, 11% yield) as colorless oils. Purification conditions are as follows: PE/EtOAc (80:20).

*Di-tert-butyl ((1S,2S,5S,6R)-2-((Trimethylsilyl)methyl)-7-oxabicyclo[4.1.0]hept-3-ene-2,5-diyl)dicarbamate (**11d**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (d, J = 10.1 Hz, 1H), 5.45 (ddd, J = 1.7, 5.0, 10.3 Hz, 1H), 4.69 (brs, 1H), 4.55 (brs, 1H), 4.34 (d, J = 8.2 Hz, 1H), 3.63 (brs, 1H), 3.34−3.36 (m, 1H), 1.75 (d, J = 14.5 Hz, 1H), 1.46 (s, 9H), 1.42 (s, 9H), 1.10 (d, J = 14.6 Hz, 1H), 0.08 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.1, 154.6, 132.0, 121.3, 80.5, 79.8, 57.3, 54.7, 54.2, 44.3, 28.5, 28.4, 27.3, 0.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd. for $C_{20}H_{36}N_2NaO_5Si$ 435.2286, found 435.2265; R_f = 0.31 (PE/EtOAc 85:15).

*Di-tert-butyl ((1S,5S,6R)-4-((Trimethylsilyl)methyl)-7-oxabicyclo-[4.1.0]hept-2-ene-2,5-diyl)dicarbamate (**12d**).* ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.05 (s, 1H), 5.75 (brs, 1H), 4.67 (d, J = 9.2 Hz, 1H), 4.13 (d, J = 9.6 Hz, 1H), 3.55 (brs, 1H), 3.40 (brs, 1H), 2.35 (q, J = 7.1 Hz, 1H), 1.47 (s, 9H), 1.43 (s, 9H), 0.84−0.88 (m, 2H), 0.00 (s, 9H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) δ 155.1, 153.3, 130.0, 116.8, 80.8, 79.8, 57.3, 49.6, 48.8, 37.0, 28.5, 28.4, 26.3, −0.7; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd. for $C_{20}H_{36}N_2NaO_5Si$ 435.2286, found 435.2271; R_f = 0.23 (PE/EtOAc 85:15).

*Compounds **11e** and **12e**.* The reaction of azo cycloadduct **5a** (100 mg, 0.31 mmol, 1.0 equiv) with phenyllithium (0.46 mL, 0.78 mmol, 2.5 equiv, 1.69 M in dibutyl ether) for 30 min at 0 °C according to the general procedure afforded the two addition products **11e** and **12e** (32 mg, 26% yield) as light yellow oils.

The reaction of azo cycloadduct **5a** (100 mg, 0.31 mmol, 1.0 equiv) with phenyllithium (0.55 mL, 0.78 mmol, 2.5 equiv, 1.69 M in dibutyl ether) for 48 h at −78 °C according to the general procedure afforded the two addition products **11e** (13 mg, 10% yield) and **12e** (36 mg, 29% yield) as yellow oils. Purification conditions are as follows: PE/acetone (85:15).

*Di-tert-butyl ((1S,2R,5S,6R)-2-Phenyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-diyl)dicarbamate (**11e**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.41 (m, 4H), 7.28−7.33 (m, 1H), 5.91 (d, J = 10.1 Hz, 1H), 5.70 (ddd, J = 1.7, 5.1, 10.2 Hz, 1H), 5.27 (brs, 1H), 4.66 (brs, 1H), 4.39 (d, J = 8.0 Hz, 1H), 3.62 (brs, 1H), 3.43−3.44 (m, 1H), 1.46 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.1, 154.0, 141.7, 129.1, 127.7, 125.6, 122.9, 81.6, 80.6, 57.7, 57.3, 54.7, 44.1, 28.5, 28.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd. for $C_{22}H_{30}N_2NaO_5$ 425.2047, found 425.2029; R_f = 0.18 (PE/acetone 90:10)

*Di-tert-butyl ((1S,4R,5S,6R)-4-Phenyl-7-oxabicyclo[4.1.0]hept-2-ene-2,5-diyl)dicarbamate (**12e**).* ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.26−7.29 (m, 4H), 7.18−7.21 (m, 1H), 6.30 (s, 1H), 5.83 (brs, 1H), 4.87 (d, J = 7.8 Hz, 1H), 4.37 (d, J = 7.8 Hz, 1H), 3.74 (brs, 1H), 3.53 (brs, 1H), 3.47 (brs, 1H), 1.50 (s, 9H), 1.46 (s, 9H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) δ 155.2, 153.2, 142.4, 132.1, 128.7, 128.3, 126.7, 112.0, 81.0, 80.1, 57.1, 50.9, 48.4, 46.2, 28.5, 28.4; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd. for $C_{22}H_{30}N_2NaO_5$ 425.2047, found 425.2035; R_f = 0.12 (PE/acetone 90:10).

*Synthesis of Compounds **11f** and **12f**.* A solution of 4-bromoanisole (58 mg, 0.31 mmol, 1.0 equiv) in THF (1.5 mL) was cooled to −78 °C before the dropwise addition of *n*-butyllithium (0.55 mL, 0.93 mmol, 3 equiv, 1.50 M in hexane). After 30 min, a solution of azo cycloadduct **5a** (100 mg, 0.31 mmol,) in THF (1.5 mL) was added, and the mixture stirred for 6 h at −78 °C. Water (10 mL) was then added to the mixture before it was warmed to rt and the organic phase was separated. The aqueous phase was extracted with DCM (3 × 5 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude mixture. Purification by silica gel column chromatography afforded the two addition products **11f** (12 mg, 9% yield) and **12f** (40 mg, 30% yield) as colorless oils. Purification conditions are as follows: PE/acetone (90:10).

*Di-tert-butyl ((1S,2R,5S,6R)-2-(4-Methoxyphenyl)-7-oxabicyclo-[4.1.0]hept-3-ene-2,5-diyl)dicarbamate (**11f**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 5.93 (d, J = 10.1 Hz, 1H), 5.68 (ddd, J = 1.9, 5.0, 10.2 Hz, 1H), 5.24 (brs, 1H), 4.62−4.68 (m, 1H), 4.37 (d, J = 8.4 Hz, 1H), 3.81 (s, 3H), 3.57 (brs, 1H), 3.40−3.43 (m, 1H), 1.46 (s, 9H), 1.34 (brs, 9H); ^{13}C{^{1}H} NMR (100 MHz, CDCl3) δ 159.1, 155.1, 154.0, 135.5, 129.3, 126.7, 122.6, 114.5, 81.6, 80.1, 57.4, 55.4, 54.7, 51.0, 44.1, 28.5, 28.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd. for $C_{23}H_{32}N_2NaO_6$ 455.2153, found 455.2140; R_f = 0.22 (PE/acetone 85:15).

*Di-tert-butyl ((1S,4S,5S,6R)-4-(4-Methoxyphenyl)-7-oxabicyclo-[4.1.0]hept-2-ene-2,5-diyl)dicarbamate (**12f**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, J = 8.3 Hz, 2H), 6.80 (d, J = 8.4 Hz, 2H), 6.39 (brs, 1H), 5.80 (brs, 1H), 4.90 (d, J = 8.5 Hz, 1H), 4.31 (d, J = 8.5 Hz, 1H), 3.76 (s, 3H), 3.67 (brs, 1H), 3.51 (brs, 1H), 3.45−3.47 (m, 1H), 1.49 (s, 9H), 1.45 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, CDCl3) δ 158.4, 155. 2, 153.2, 134.5, 131.9, 129.7, 113.6, 112.5, 81.0, 80.1, 57.1, 55.4, 50.9, 48.4, 45.4, 28.5, 28.; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd. for $C_{23}H_{32}N_2NaO_6$ 455.2153, found 455.2139; R_f = 0.16 (PE/acetone 85:15).

*Diisopropyl ((1S,2S,5S,6R)-2-Methyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-diyl)dicarbamate (**11b**).* A solution of the azo cycloadduct **5b** (200 mg, 0.62 mmol, 1.0 equiv) in THF (6 mL) was cooled to 0 °C before the dropwise addition of methyllithium (1.00 mL, 1.55 mmol, 2.5 equiv, 1.50 M in Et_2O). The reaction mixture was stirred at 0 °C for 15 min. Water (10 mL) was then added to the mixture before it was warmed to rt and the organic phase was separated. The aqueous phase was extracted with DCM (3 × 5 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude mixture. Purification of the residue by silica gel column chromatography (PE/EtOAc, 80:20) afforded the 1,2-addition product **11b** (87 mg, 42% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (dt, J = 1.6, 10.3 Hz, 1H), 5.48 (ddd, J = 1.8, 4.8, 10.3 Hz, 1H), 4.82−5.00 (m, 3H), 4.56 (brs, 1H), 4.49 (brs, 1H), 3.45−3.47 (m, 1H), 3.40 (brs, 1H), 1.62 (s, 3H), 1.20−1.27 (m, 12H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 155.6, 154.9, 131.3, 121.6, 69.0, 68.2, 56.9, 54.3, 51.9, 44.6, 24.7, 22.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd. for $C_{15}H_{24}N_2NaO_5$ 335.1577, found 335.1566; R_f = 0.20 (PE/EtOAc 80:20).

*Di-tert-butyl (2-Hydroxy-1,4-phenylene)dicarbamate (**13**).* A solution of freshly distilled diisopropylamine (0.26 mL, 1.86 mmol, 3.0 equiv) in THF (3 mL) was cooled to −78 °C before dropwise addition of *n*-butyllithium (1.03 mL, 1.55 mmol, 2.5 equiv, 1.51 M in hexane). After 30 min, a solution of azo cycloadduct **5a** (200 mg, 0.62 mmol, 1.0 equiv) with THF (3 mL) was added and the mixture stirred for 1 h at −78 °C. Water (10 mL) was then added to the mixture before it was warmed to rt and the organic phase was separated. The aqueous phase was extracted with DCM (3 × 5 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude mixture. Purification of the residue by silica gel column chromatography (DCM/MeOH 99:1) afforded **13** (80 mg, 40% yield). ^{1}H NMR (360 MHz, DMSO) δ 9.61 (brs, 1H), 9.12 (s, 1H), 7.66 (s, 1H), 7.35 (d, J = 8.5 Hz, 1H), 7.13 (d, J = 1.9 Hz, 1H), 6.79 (dd, J = 2.0, 8.6 Hz, 1H), 1.46 (s, 9H), 1.44 (s, 9H); ^{13}C{^{1}H} NMR (90 MHz, DMSO) δ 153.2, 152.7, 147.9, 135.7, 121.5, 120.7, 108.9, 105.8, 78.9, 78.7, 28.1, 28.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd. for $C_{16}H_{24}N_2NaO_5$ 347.1577, found 347.1568; R_f = 0.34 (PE/EtOAc 80:20).

General Procedure for The Hydrogenation of Cycloadducts. Palladium on carbon (0.08 equiv) was added to a solution of the corresponding cycloadduct (1.0 equiv) in EtOAc (0.1 M). The flask was evacuated and flushed with hydrogen, and the mixture was stirred for 30 min at rt with continuous hydrogen bubbling. Filtration through a path of Celite followed by concentration *in vacuo* gave the pure corresponding reduced product.

*Di-tert-butyl (1R,2S,4R,5S)-3-Oxa-6,7-diazatricyclo[3.2.2.0^{2,4}]-nonane-6,7-dicarboxylate (**14**).* The reaction of cycloadduct **5a** (200 mg, 0.89 mmol, 1.0 equiv) with palladium on carbon (80 mg, 0.071 mmol, 0.08 equiv) according to the general procedure afforded the corresponding reduced cycloadduct **14** (202 mg, quant.) as a white powder. ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.53 (brs, 1H), 4.43 (brs, 1H), 3.50 (brs, 1H), 3.40 (brs, 1H), 1.56−1.74 (m, 4H), 1.38 (brs, 18H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) δ 156.3, 155.7, 81.4, 81.2, 53.0, 51.7, 50.6, 48.9, 28.0, 21.7, 20.7; HRMS (ESI-TOF) m/z

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$[M + Na]^+$ calcd. for $C_{16}H_{26}N_2NaO_5$ 349.1734, found 349.1723; R_f = 0.52 (PE/EtOAc 80:20).

*tert-butyl (1S,2R,4R,5R)-3,6-Dioxa-7-azatricyclo[3.2.2.0^{2,4}]-nonane-7-carboxylate (**15**).* The reaction of cycloadduct **6** (200 mg, 0.62 mmol, 1.0 equiv) with palladium on carbon (53 mg, 0.050 mmol, 0.08 equiv) according to the general procedure afforded the corresponding reduced cycloadduct **15** (202 mg, quant.) as a white powder. ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.39 (brs, 2H), 3.51 (t, J = 4.8 Hz, 1H), 3.48 (t, J = 4.8 Hz, 1H), 1.59−1.78 (m, 4H), 1.36 (s, 9H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) δ 155.9, 81.8, 74.4, 51.6, 48.9, 48.7, 28.1, 22.9, 21.5; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd. for $C_{11}H_{17}NNaO_4$ 250.1050, found 250.1042; R_f = 0.33 (PE/EtOAc 80:20).

*Di-tert-butyl ((1S,5S,6R)-7-Oxabicyclo[4.1.0]hept-2-ene-2,5-diyl)-dicarbamate (**16**).* A solution of compound **14** (100 mg, 0.44 mmol, 1.0 equiv) in THF (5 mL) was cooled to −78 °C before the dropwise addition of *sec*-butyllithium (0.71 mL, 0.78 mmol, 2.5 equiv, 1.10 M in cyclohexane). The reaction mixture was stirred at −78 °C for 45 min. Water (10 mL) was added to the mixture before it was warmed to rt and the organic phase was separated. The aqueous phase was extracted with DCM (3 × 5 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude mixture. Purification of the residue by silica gel column chromatography (PE/acetone 90:10) afforded the Boc-protected enamine **16** (53 mg, 53% yield, colorless oil). ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.25 (s, 1H), 5.62 (m, 1H), 4.77 (d, J = 8.5 Hz, 1H), 4.39 (t, J = 7.3 Hz, 1H), 3.50 (m, 1H), 3.39 (m, 1H), 2.33 (ddd, J = 2.1, 6.1, 17.0 Hz, 1H), 2.09 (ddd, J = 2.0, 7.2, 17.0 Hz, 1H), 1.45 (s, 9H), 1.42 (s, 9H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) δ 155.3, 153.3, 130.7, 109.0, 80.8, 79.9, 55.4, 49.2, 43.1, 28.5, 28.4, 26.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{16}H_{27}N_2O_5$ 327.1914, found 327.1911; R_f = 0.21 (PE/EtOAc 85:15).

*Compounds **17**−**19**.* A solution of **15** (100 mg, 0.44 mmol, 1.0 equiv) in THF (5 mL) was cooled to −78 °C before the dropwise addition of methyllithium (1.46 mL, 2.20 mmol, 5.0 equiv, 1.50 M in Et_2O). The reaction mixture was stirred at −78 °C for 2 h. Water (10 mL) was then added to the mixture before it was warmed to rt and the organic phase was separated. The aqueous phase was extracted with DCM (3 × 5 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum to afford the crude mixture. Purification of the residue by silica gel column chromatography (PE/acetone 85:15) afforded **17** (23 mg, 23% yield), **18** (20 mg, 20% yield), and **19** (40 mg, 37% yield) as three separated fractions.

*tert-Butyl ((1S,5S,6R)-5-Hydroxy-7-oxabicyclo[4.1.0]hept-2-en-2-yl)carbamate (**17**).* Colorless oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.09 (s, 1H), 5.61 (m, 1H), 4.35 (m, 1H), 3.53−3.55 (m, 1H), 3.45−3.46 (m, 1H), 2.29−2.34 (m, 2H), 1.76 (brs, 1H), 1.47 (s, 9H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) δ 153.5, 130.5, 109.5, 81.0, 63.8, 55.9, 49.6, 28.8, 28.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{11}H_{18}NO_4$ 228.1230, found 228.1228; R_f = 0.29 (PE/acetone 75:25).

*tert-Butyl ((1R,2S,6S)-2-Hydroxy-7-oxabicyclo[4.1.0]hept-3-en-3-yl)carbamate (**18**).* Colorless oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.21 (brs, 1H), 5.07 (s, 1H), 4.92 (brs, 1H), 4.66 (s, 1H), 3.42 (s, 1H), 3.31 (s, 1H), 2.64 (s, 2H), 1.45 (s, 9H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) δ 154.6, 132.5, 107.3, 81.3, 64.7, 54.7, 49.9, 28.4, 24.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd. for $C_{11}H_{18}NO_4$ 228.1230, found 228.1228; R_f = 0.40 (PE/acetone 75:25).

*tert-Butyl ((1S,2S,5S,6R)-5-Hydroxy-2-methyl-7-oxabicyclo-[4.1.0]heptan-2-yl)carbamate (**19**).* Colorless oil; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.95 (s, 1H), 4.29 (d, J = 7.9 Hz, 1H), 4.15 (d, J = 7.9 Hz, 1H), 3.31 (t, J = 3.1 Hz, 1H), 2.97−2.98 (m, 1H), 2.12 (dt, J = 4.5, 14.1 Hz, 1H), 2.12 (dt, J = 3.2, 14.1 Hz, 1H), 1.44−1.51 (m, 2H), 1.42 (s, 9H), 1.29 (s, 3H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) δ 155.5, 80.5, 64.6, 59.5, 54.5, 48.9, 28.4, 27.3, 25.4, 23.3; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd. for $C_{12}H_{21}NNaO_4$ 266.1363, found 266.1359; R_f = 0.57 (PE/acetone 75:25).

■ ASSOCIATED CONTENT

Data Availability Statement

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

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c00398.

Copies of NMR and X-ray data (PDF)

FAIR data, including the primary NMR FID files, for compounds **2**, **3**, **5a**, **5b**, **7c**, **8c**, **8d**, **9**, **10**, **11a−f**, **12c−f**, and **13−19** (ZIP)

Accession Codes

CCDC 2242037 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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