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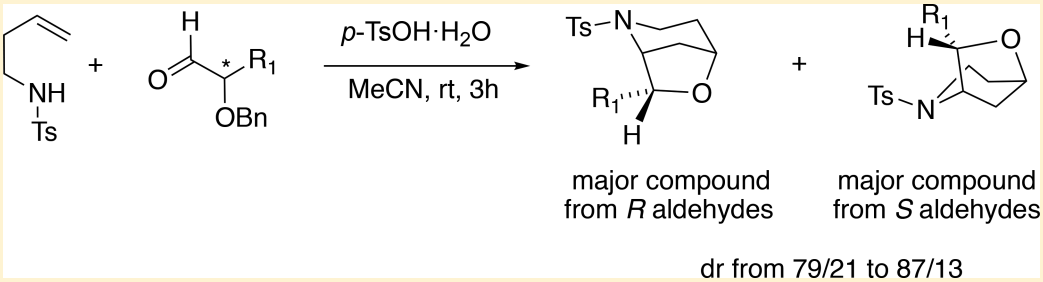
Diastereoselective Construction of the 6-Oxa-2-azabicyclo[3.2.1]octane Scaffold from Chiral α-Hydroxyaldehyde Derivatives by the Aza-Prins Reaction

Alejandro Mahía,[†,‡] Ramón Badorrey,[†] José A. Gálvez,[*,†] and María D. Díaz-de-Villegas[*,†]

[†]Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), CSIC—Universidad de Zaragoza, Departamento de Química Orgánica, Pedro Cerbuna 12, 50009 Zaragoza, Spain

Supporting Information



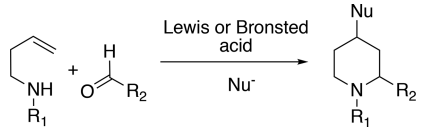
ABSTRACT: (*R*)-2,3-Di-*O*-benzylglyceraldehyde and *N*-tosyl homoallylamine undergo aza-Prins cyclization to afford (1*R*,5*S*,7*S*)-7-[(benzyloxy)methyl]-2-tosyl-6-oxa-2-azabicyclo[3.2.1]octane in a highly diastereoselective manner through an unexpected intramolecular nucleophilic attack. Our work has opened a new route toward the asymmetric synthesis of 7-(alkyl or aryl)-6-oxa-2-azabicyclo[3.2.1]octane derivatives from chiral α-hydroxyaldehyde derivatives in one step.

INTRODUCTION

Among the different routes that are available to prepare piperidines, the aza-Prins cyclization, together with its alkyne, silyl, and acyliminium variants, provides straightforward access to this heterocyclic system,[1−3] and this method has been successfully applied to the synthesis of several natural products and analogues.[4]

The classical aza-Prins reaction is a three-component coupling of an aldehyde, a homoallylic amine, and a nucleophile that is usually promoted by a Lewis[5−9] or Brønsted[10−13] acid and takes place through the formation of an iminium intermediate, which is trapped by the nucleophile. Different 2,4-disubstituted piperidines have been obtained depending on the reaction conditions (Scheme 1).

Scheme 1. Aza-Prins Reaction



There are examples in the literature concerning the use of different acidic catalysts, nucleophiles, N-homoallylamines, and carbonyl compounds, but to the best of our knowledge, a study on the use of chiral aldehydes for the synthesis of chiral 2,4-disubstitued piperidines in a diastereoselective manner has not been performed to date. In recent years, we have been interested in the development of versatile synthetic methodologies for the synthesis of chiral nitrogen-containing heterocycles using chiral imines that are readily available from renewable sources as starting materials. In this context, imines derived from conveniently protected (*R*)-glyceraldehyde, obtained from inexpensive D-mannitol, have proven to be excellent precursors for the construction of the piperidine heterocyclic ring.[14−16] As a consequence, we decided to study the behavior of conveniently protected glyceraldehyde as the carbonyl compound in the aza-Prins cyclization directed at the asymmetric synthesis of 2,4-disubstituted piperidines. The first reaction was carried out between *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide[17] **1a** (1 equiv) and (*R*)-2,3-di-*O*-benzylglyceraldehyde **2a** (1 equiv) in benzene at room temperature using $BF_3{\cdot}OEt_2$ (1.1 equiv) as the Lewis acid as a means to obtain chiral 4-arylpiperines **3** through an aza-Prins−Friedel−Crafts reaction[18] (Scheme 2). However, trapping by the arene was not observed, and a 74/24 mixture of diastereomeric 6-oxa-2-azabicyclo[3.2.1]octanes **4a** and **5a**, formed by intramolecular quenching, was obtained in 77% yield.

Both diastereoisomers were isolated by silica gel chromatography, and their corresponding structures and stereochemistries were determined by ^{1}H NMR spectroscopy and NOE experiments, as detailed below.

The 6-oxa-2-azabicyclo[3.2.1]octane scaffold is present in biologically relevant molecules and natural products such as

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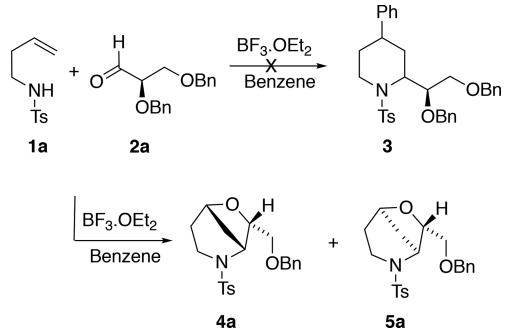
Scheme 2. Aza-Prins Reaction of (*R*)-2,3-Di-*O*-Benzylglyceraldehyde 2a



stemona alkaloids[19] or scopoline[20] (Figure 1), and it has served as an intermediate in the synthesis of azasugars.[21]

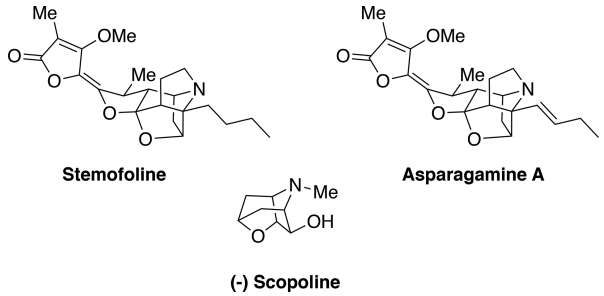


Figure 1. Structures of some natural products based on a 6-oxa-2-azabicyclo[3.2.1]octane scaffold.

The reported procedures for the construction of the 6-oxa-2-azabicyclo[3.2.1]octane skeleton are based on the intramolecular nucleophilic displacement of a leaving group at C-6 by an amino group at C-2 on an aminomannofuranoside[21] and the reaction of tetrahydropyridines with formaldehyde in the presence of manganese dioxide[22] or Pd-catalyzed N,O-bicyclization of an aminoalkenitol.[23] In all cases, the reported procedure led to a defined compound, usually as a racemic mixture, and the methodology was not extended to different substrates. Due to the lack of a versatile methodology for the preparation of 6-oxa-2-azabicyclo[3.2.1]octane derivatives, and given the potential of the observed cyclization for the asymmetric synthesis of 7-substituted derivatives from chiral α-hydroxyaldehydes in only one step, we decided to study this reaction in more detail in order to optimize the formation of the bicyclic ring and to explore the scope of this transformation.

RESULTS AND DISCUSSION

We began our study by testing the effect of the solvent on the formation of the 6-oxa-2-azabicyclo[3.2.1]octane skeleton (Table 1). The reaction did not work efficiently when it was conducted in ethereal solvents (entries 2,3). The use of other polar aprotic solvents gave yields in the range 69−77%, and the best result as far as yield and diastereoselectivity are concerned was obtained when the reaction was performed in acetonitrile (entry 5).

To identify the best catalyst for the reaction, a series of Lewis acids and Brønsted acids were screened in both dry acetonitrile and dry toluene (Table 2). When using Lewis acids, the reaction did not work with Zn^{2+} salts, which are considered borderline acids according to the HBSA theory[24] (entries 1−3).

Table 1. Solvent Screening of the Aza-Prins Reaction of 1a and 2a[a]

entry	solvent	yield[b] (%)	4a/5a[b]
1	benzene	77	74/26
2	Et_2O	35	60/40
3	THF	0	
4	CH_2Cl_2	69	70/30
5	MeCN	79	86/14
6	toluene	70	79/21

[a]All reactions were carried out under the following conditions: aldehyde (0.33 mmol), tosylamine (0.3 mmol), $BF_3{\cdot}OEt_2$ (0.33 mol), dry solvent (5 mL), room temperature, 20 h, under Ar. [b]Determined from the crude reaction mixture by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard.

Table 2. Catalyst Screening for the Aza-Prins Reaction of 1a and 2a in Acetonitrile (A) and Toluene (B)[a]

entry	acid	yield A[b] (%)	yield B[b] (%)	4a/5a A[b]	4a/5a B[b]
1	$ZnCl_2$	0	0		
2	ZnI_2	0	0		
3	$Zn(OTf)_2$	0	0		
4	$BiCl_3$	28	12	82/18	67/33
5	$Bi(OTf)_3$	80	48	85/15	77/23
6	$Yb(OTf)_3$	24	36	79/21	69/31
7	$In(OTf)_3$	78	52	87/13	71/29
8	$Sc(OTf)_3$	91	0[c]	85/15	
9	$FeCl_3{\cdot}6H_2O$	69	57	83/17	74/26
10	$FeBr_3$	16	61	81/19	75/25
11	$AlCl_3$	51	74	80/20	70/30
12	BBr_3	49	0	82/28	
13	$TiCl_4$	54	74	83/17	74/26
14	HOAc	0	0		
15	TFA	27	0	78/22	
16	MsOH	83	66	81/19	73/27
17	*p*-TsOH	86	0[c]	86/14	

[a]All reactions were carried out under the following conditions: aldehyde (0.33 mmol), tosylamine (0.3 mmol), catalyst (0.33 mol), dry solvent (5 mL), room temperature, 20 h, under Ar. [b]Determined from the crude reaction mixture by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c]The catalyst was not soluble in toluene.

When using Lewis acids with a higher hardness, the reaction worked to a greater or lesser extent and the diastereoselectivity was in the range 67/33−87/13 (diastereomeric ratio). In many cases, the diastereoselectivity and yield were higher in acetonitrile than in toluene. Scandium triflate was found to give the best results, and this gave an 85/15 diastereomeric mixture of 6-oxa-2-azabicyclo[3.2.1]octanes **4a** and **5a** in 91% yield in dry acetonitrile (entry 8). When using Brønsted acids, the reactivity depended on the acidity, with stronger acids giving higher yields. The best results were obtained by using *p*-toluensulfonic acid in dry acetonitrile, i.e., 86% yield and an 86/14 diastereomeric ratio (entry 17).

The results obtained with scandium triflate in dry acetonitrile at room temperature were taken as a reference, and the reaction conditions were reinvestigated in an effort to improve the diastereoselectivity (Table 3). The use of a lower reaction temperature did not improve the reaction efficiency (cf. entries 2 and 3 vs 1). We proceeded to test the evolution of the reaction, and after only 3 h, similar results were obtained (entry

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Table 3. Optimization of the Aza-Prins Reaction Conditions for 1a and 2a[a]

entry	T (°C)	t (h)	solvent	acid	yield[b] (%)	4a/5a[b]
1	rt	20	dry MeCN	$Sc(OTf)_3$	91	85/15
2	0	20	dry MeCN	$Sc(OTf)_3$	80	85/15
3	−40	20	dry MeCN	$Sc(OTf)_3$	85	85/15
4	rt	3	dry MeCN	$Sc(OTf)_3$	81	85/15
5	rt	20	MeCN	$Sc(OTf)_3$	88	85/15
6	rt	20	MeCN/H_2O (9/1)	$Sc(OTf)_3$	57	82/18
7[c]	rt	20	dry MeCN	$Sc(OTf)_3$	48	83/17
8[c]	rt	72	dry MeCN	$Sc(OTf)_3$	37	84/16
9[d]	rt	3	MeCN	$Sc(OTf)_3$	85	86/14
10[d]	rt	3	MeCN	*p*-TsOH·H_2O	83	84/16
11[d,e]	rt	3	MeCN	*p*-TsOH·H_2O	92	84/16
12[d,f]	rt	3	MeCN	*p*-TsOH·H_2O	92	84/16

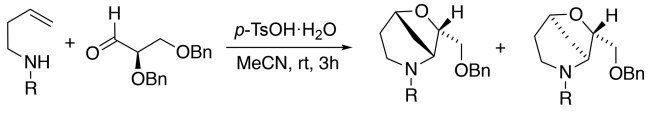
[a]The model reaction was carried out under the following conditions: aldehyde (0.33 mmol), tosylamine (0.3 mmol), acid (0.33 mol), solvent (5 mL), under Ar. [b]Determined from the crude reaction mixture by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c]20 mol % of $Sc(OTf)_3$. [d]Without an argon atmosphere. [e]1.3 equiv of *p*-TsOH·H_2O. [f]1.5 equiv of *p*-TsOH·H_2O.

4). Rigorously anhydrous conditions were not required (entry 5), but the presence of water as a cosolvent[25] led to a decrease in the yield to 57% (entry 6). Finally, the use of a substoichiometric amount of scandium triflate was investigated. It was observed that a reaction occurred, albeit to a lesser extent (entry 7), even when prolonging the reaction time (entry 8). From this study, a ratio of 1.1/1/1 aldehyde/amine/scandium triflate in acetonitrile at room temperature for 3 h without an argon atmosphere was selected as the optimal reaction condition. In this way, an 86/14 diastereomeric mixture of 6-oxa-2-azabicyclo[3.2.1]octanes **4a** and **5a** was obtained in 85% yield (entry 9). Under these new conditions, the replacement of scandium triflate by the cheaper *p*-toluensulfonic acid monohydrate led to similar results, i.e., 83% yield and an 84/16 diastereomeric ratio (entry 10). The yield could be improved to 92% by slightly increasing the excess of *p*-toluensulfonic acid monohydrate (entry 11).

The scope and limitation of this reaction were investigated next. Although both the reaction yield and diastereoselectivity were worse than with *N*-tosylhomoallylamine **1a**, the reaction also worked with other N-protecting groups that are capable of increasing the electrophilicity of the iminium intermediate, such as the benzyloxycarbonyl or diphenylphosphoryl groups (Table 4). The reaction of benzyl but-3-en-1-ylcarbamate **1b** (1 equiv) with (*R*)-2,3-di-*O*-benzylglyceraldehyde **2a** (1.1 equiv) in acetonitrile at room temperature using *p*-toluensulfonic acid monohydrate (1.3 equiv) as the Brønsted acid provided a 70/30 diastereomeric mixture of 6-oxa-2-azabicyclo[3.2.1]octanes **4b** and **5b** in 50% yield. Similarly, the reaction of diphenyl but-3-en-1-ylphosphoramidate **1c** (1 equiv) with (*R*)-2,3-di-*O*-benzylglyceraldehyde **2a** (1.1 equiv) in acetonitrile at room temperature using *p*-toluensulfonic acid monohydrate (1.3 equiv) as the Brønsted acid provided an 80/20 diastereomeric mixture of 6-oxa-2-azabicyclo[3.2.1]octanes **4c** and **5c** in 44% yield.

The reaction of more highly substituted alkenyl homoallylic tosylamines **1d**−**f** with (*R*)-2,3-di-*O*-benzylglyceraldehyde **2a** was also investigated. As a general trend, the presence of additional substituents on the C═C moiety led to complex

Table 4. Scope of the Aza-Prins Reaction, Homoallylamine Derivative Screening[a]



entry	R	tosylamine	products	yield[b] (%)	4/5[b]
1	Ts	**1a**	**4a**, **5a**	92	84/16
2	Cbz	**1b**	**4b**, **5b**	50	70/30
3	$P(O)(OPh)_2$	**1c**	**4c**, **5c**	44	80/20

[a]All reactions were carried out under the following conditions: aldehyde (0.33 mmol), tosylamide (0.3 mmol), *p*-TsOH (0.39 mol %), acetonitrile (5 mL), room temperature, 3 h. [b]Determined from the crude reaction mixture by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard.

mixtures of compounds with a markedly reduced yield in the formation of the 6-oxa-2-azabicyclo[3.2.1]octane ring.

When homoallylic tosylamine **1d** was used as the substrate, in addition to a 87/13 mixture of diastereomeric 6-oxa-2-azabicyclo[3.2.1]octanes **4d** and **5d** (43% isolated yield), octahydroisoquinolines **6** and **7** were isolated from the reaction mixture (Scheme 3).

When homoallylic tosylamine **1e** was used as the substrate, the formation of 6-oxa-2-azabicyclo[3.2.1]octanes **4e** and **5e** was significantly reduced (28% combined yield). Furthermore, an 87/13 mixture of two diastereomeric (piperidin-4-yl)-acetamides **8** was also isolated from the reaction mixture in around 36% yield (Scheme 4).

The use of homoallylic tosylamine **1f** in the reaction led to the formation a 60/40 mixture of two diastereomeric pyrrolidines **9** in 55% combined yield, and the formation of 6-oxa-2-azabicyclo[3.2.1]octanes was not detected (Scheme 5).

The absolute configurations of compounds **6**, **7**, **8**, and **9** were not determined. The use of other substituted alkenyl homoallylic tosylamines was ruled out due to the disappointing results in the formation of the desired 6-oxa-2-azabicyclo[3.2.1]octanes observed with tosylamines **1d**,**e**.

The use of other α-hydroxyaldehyde derivatives was subsequently explored (Table 5). 2-Benzyloxyaldehydes **2b**−**d**, with alkyl and aryl substituents at C_2, were successfully employed as substrates in the aza-Prins reaction promoted by *p*-toluensulfonic acid monohydrate to give the corresponding mixture of 6-oxa-2-azabicyclo[3.2.1]octanes in reasonable yields and diastereoselectivities. When aldehydes **2c**,**d** of opposite configuration were used, 6-oxa-2-azabicyclo[3.2.1]octanes with opposite configurations at C_1 and C_5 were obtained preferentially.

Finally, the use of a different protecting group on the hydroxy moiety was investigated. Although the reactions showed complete consumption of the starting aldehyde, low yields of 6-oxa-2-azabicyclo[3.2.1]octanes were observed with *O*-*tert*-butyldimethylsilyl α-hydroxyaldehyde **2e** (25% yield, entry 5, Table 5) and 2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **2f** (59% yield, entry 6, Table 5) bearing more labile protecting groups in acidic media. The use of aldehyde **2f** led to a diastereoselectivity that gave only a 66/34 diastereometic ratio.

The structures and stereochemistries of compounds **4** and **5** were established on the basis of their ^1H NMR spectra[26] and NOESY experiments (Figure 2). In the ^1H NMR spectra of all

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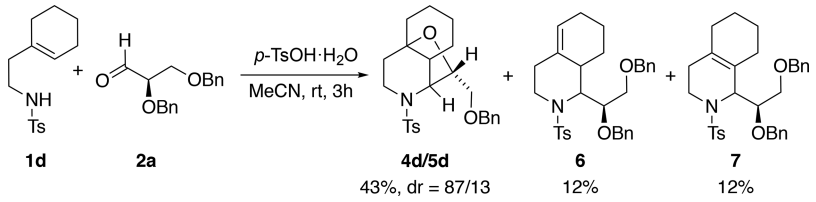
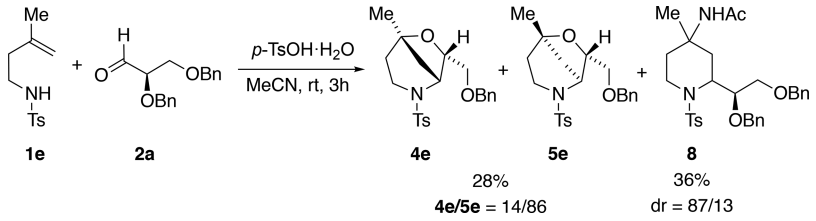
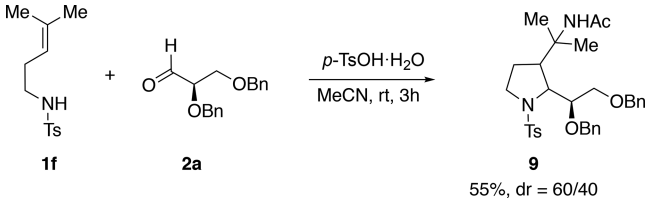
Scheme 3. Aza-Prins Reaction of (*R*)-2,3-Di-*O*-benzylglyceraldehyde 2a with Alkene 1d



Scheme 4. Aza-Prins Reaction of (*R*)-2,3-Di-*O*-benzylglyceraldehyde 2a with Alkene 1e



Scheme 5. Aza-Prins Reaction of (*R*)-2,3-Di-*O*-benzylglyceraldehyde 2a with Alkene 1f



compounds, it was possible to assign unambiguously the H_{3a} signal due to the presence of two large coupling constants, which is indicative of the axial disposition of this proton. Clear cross-peaks were observed between H_{3a} and the corresponding resonance of the vicinal nuclei of the substituent at C_7 in the spectra of compounds **4a−f,i**, which were obtained from aldehydes with an *R*-configuration. These cross-peaks clearly indicate a close spatial disposition, which is only possible for the (1*R*,5*S*) stereoisomers. In the ^{1}H NMR spectra of compounds **5a−f,i**, obtained from aldehydes with an *R*-configuration, the presence of clear cross-peaks between H_{3a} and H_7 resonances clearly indicates the close spatial disposition of these two nuclei, which is only possible for the (1*S*,5*R*) stereoisomers. For compounds **4g,h** and **5g,h**, which were obtained from aldehydes with an *S*-configuration, NOESY cross-peaks were observed between the H_{3a} and H_7 resonances or those for H_{3a} and the group at C_7, respectively, thus confirming the absolute configuration. Furthermore, the structure of **4a** was confirmed by X-ray crystallography.

Mechanistically, it has been proposed[17,27,28] that the aza-Prins reaction proceeds through the formation of an *N*-sulfonyl iminium ion. Theoretical calculations have demonstrated that *E*-imimiun cations are more stable than *Z*-imimiun cations.[17,29]

The iminium ion undergoes cyclization with an olefin to afford an intermediate carbocation, which is trapped by a nucleophile present in the reaction medium to afford 4-substituted piperidines. If aldehyde **2a** was used, intramolecular trapping of the resulting carbocation by the oxygen of the secondary benzyloxy moiety would result in the formation of the observed 6-oxa-2-azabicyclo[3.2.1]octanes. Depending on the absolute configuration of the chiral aldehyde, 6-*endo-trig* cyclization occurs with the preferential iminium top-face approach of the alkene (a) or the iminium bottom-face approach of the alkene (b) to produce 6-oxa-2-azabicyclo[3.2.1]octane **4a** or **5a** in excess (Scheme 6).

This model can be used to rationalize the results obtained. The presence of internal substituents on the olefin moiety would make intramolecular quenching of the intermediate carbocation difficult, and this could evolve in a different way.[17] An elimination reaction would explain the formation of alkenes **6** and **7** when homoallylic tosylamine **1d** was used as the substrate. The intermolecular trapping with acetonitrile through a Ritter sequence[7,30] would explain the formation of acetamide **8** when homoallylic tosylamine **1e** was used as the substrate. Dobbs et al. observed the exclusive formation of pyrrolidines when trisubstituted homoallylic amine **1f** was used in the aza-Prins reaction with aliphatic aldehydes due to the preferential formation of a tertiary carbocation upon cyclization to a five-membered ring.[17] In our case, the Ritter reaction of the tertiary carbocation with acetonitrile used as solvent would explain the formation of compound **9**.

Cleavage of the *N*-tosyl group was performed by heating compound **4a** under reflux with an excess of magnesium turnings (20 equiv) in methanol for 4 h.[31] Under these conditions, compound **10** was obtained in 83% yield. Alternatively, tosyl cleavage by reduction with magnesium turnings in anhydrous methanol under ultrasound conditions at room temperature was tested.[32] When 5 equiv of magnesium was used, the tosyl group in **4a** remained unaltered after sonication for 20 h. Efficient deprotection under ultrasound conditions required a larger excess of magnesium (20 equiv) and sonication under reflux. In this way, compound **10** was obtained in 92% yield after 4 h (Scheme 7).

In summary, we have shown that the aza-Prins reaction of *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide (**1a**) with chiral α-hydroxyaldehyde derivatives takes place by an intramolecular nucleophilic attack to form compounds with a 6-oxa-2-azabicyclo[3.2.1]octane moiety. This structural motif is present in compounds with interesting biological properties. Optimization of the reaction conditions allowed the development of a new and efficient procedure for the asymmetric synthesis of 6-oxa-2-azabicyclo[3.2.1]octanes with different substituents at C_7 in one step using *p*-toluenesulfonic acid monohydrate as a promoter and without the need to employ strictly anhydrous conditions.

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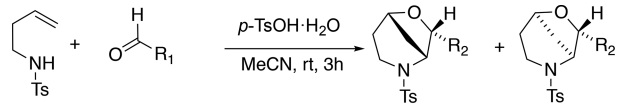
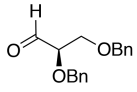
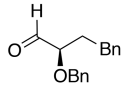
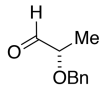
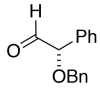
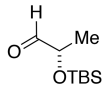
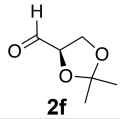
Table 5. Scope of the Aza-Prins Reaction, Aldehyde Screening[a]



1a 2a-f 4a,f-g 5a,f-g

entry	Aldehyde	Products	R_2	yield (%)[b,c]	4/5[b]
1	 2a	4a, 5a	CH_2OBn	92 (77)	84/16
2	 2b	4f, 5f	CH_2Bn	69 (52)	86/14
3	 2c	4g, 5g	Me	76 (42)	21/79
4	 2d	4h, 5h	Ph	69 (40)	13/87
5	 2e	4g, 5g	Me	25	24/76
6	 2f	4i, 5i	CH_2OH	59	66/44

[a]All reactions were carried out under the following conditions: aldehyde (0.33 mmol), tosylamide (0.3 mmol), *p*-TsOH (0.39 mol %), acetonitrile (5 mL), room temperature, 3 h. [b]Determined from the crude reaction mixture by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c]The yield of the major isolated compound is in brackets.

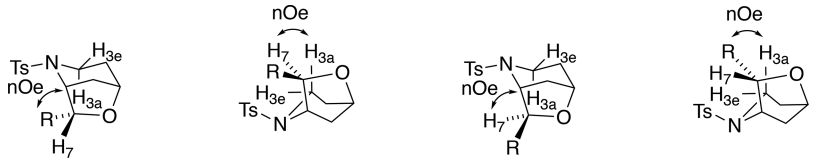
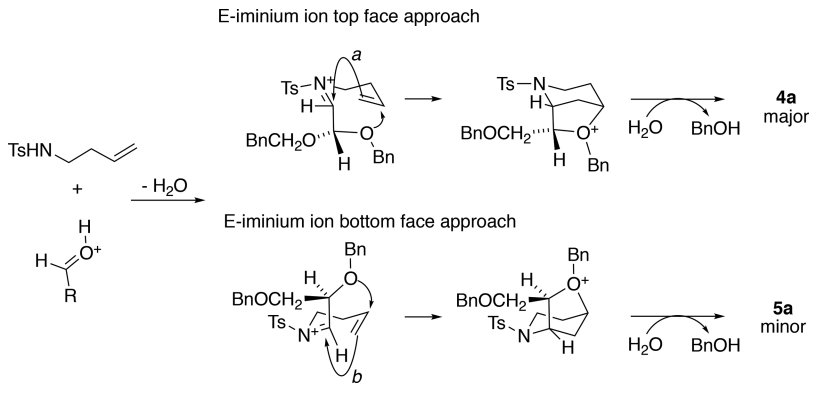


Figure 2. Diagnostic NOE cross-peaks for the unambiguous determination of the configurations of compounds **4** and **5**.

Scheme 6. Possible Model for the Aza-Prins Reaction of 2a



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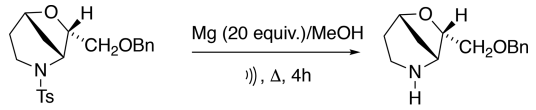
Scheme 7. Cleavage of the Tosyl Group



4a 10 92%

EXPERIMENTAL SECTION

General Details. Unless otherwise specified, all reagents were obtained from commercial suppliers and were used without purification. For anhydrous conditions, reactions were carried out under Ar in solvents dried using a solvent purification system (SPS). TLC was performed on precoated silica gel polyester plates, and products were visualized using UV light (254 nm) and ninhydrin, anisaldehyde, or potassium permanganate solutions followed by heating. Column chromatography was performed on silica gel (60, 40−63 μm) with air pressure. The sonication treatment was performed in an ultrasonic cleaner (ultrasonic frequency 45 Hz, HF effective power 80 W) with an integrated heater, up to 80 °C.

Melting points were determined in open capillary tubes and were not corrected. FT-IR spectra were recorded as thin films on NaCl plates; ν_{max} values expressed in cm^{-1} are given for the main absorption bands. Optical rotations were measured on a digital polarimeter at λ 589 nm and 25 °C in cells with 1 or 10 cm path length, and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Concentrations are given in g/100 mL. ^1H NMR and ^{13}C NMR spectra were acquired in deuterated solvent at room temperature unless otherwise stated at 400 and 100 MHz, respectively, using a 5 mm probe. All chemical shifts (δ) are reported in parts per million (ppm) with the solvent resonance as the internal standard,[33] and coupling constants are reported (J) in hertz (Hz). NOESY spectra were acquired in the phase sensitive mode with gradient pulses in the mixing time as 2048 × 256 hipercomplex files with 8 transients for 256 time increments. A mixing time of 900 ms was used, and processing was carried out using a sine-bell-squared function shifted by $\pi/2$ and a states-TPPI method. Special precautions such as degassing of the sample were not taken. High-resolution mass spectra were recorded from methanolic solutions on a MICROTOF-Q (quadrupole time-of-flight) microscale instrument using the positive electrospray ionization mode (ESI+). The X-ray diffraction data were collected at room temperature on a four-circle diffractometer, using graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å). The following N-protected alkenyl homoallylic amines were synthesized according to previously published procedures: **1a**,[34] **1b**,[35] **1d**,[36] **1e**,[17] and **1f**.[17] The following α-hydroxyaldehyde derivatives were synthesized according to previously published procedures: **2c**,[37,38] **2d**,[39] **2e**,[40] and **2f**.[41]

*Diphenyl But-3-en-1-ylphosphoramidate (**1c**).*[42] To an ice-cold solution of phenol (376 mg, 4.0 mmol) in CH_2Cl_2 (60 mL) were added sequentially $POCl_3$ (307 mg, 2.0 mmol) and Et_3N (1.4 mL, 10.0 mmol). After stirring for 0.5 h at 0 °C, but-3-en-1-amine (142 mg, 2.0 mmol) was added and stirring was continued first for 1 h at 0 °C and then for 16 h at room temperature. The solvent was evaporated in vacuo, and CH_2Cl_2 (30 mL) and water (30 mL) were added. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (Et_2O/hexanes, 1/1) afforded 455 mg (75% yield) of compound **1c** as a yellowish oil: IR (Nujol) 3223, 1591, 1491; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.15 (m, 10H), 5.69 (ddt, J = 17.2, 10.4, 6.8 Hz, 1H), 5.11−5.01 (m, 2H), 3.22−3.11 (m, 3H), 2.27−2.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8 (d, J = 6.7 Hz), 134.6, 129.7, 124.9 (d, J = 0.9 Hz), 120.2 (d, J = 5.0 Hz), 117.9, 40.7 (d, J = 0.4 Hz), 35.5 (d, J = 6.4 Hz).

*(R)-2,3-Bis(benzyloxy)propanal (**2a**).* To a solution of 1,2,5,6-tetra-*O*-benzyl-D-mannitol[43] (1.90 g, 3.5 mmol) in dry THF (18 mL) was added solid $NaIO_4$ (1.50 g, 7.0 mmol). Then water (1.8 mL) was added dropwise with stirring to dissolve the $NaIO_4$, and the solution was vigorously stirred at 35 °C for 1 h. The solvents were evaporated in vacuo, and the solid residue was washed with Et_2O (3 × 15 mL). The combined filtrates were concentrated in vacuo, and the residue was purified by silica gel column chromatography (hexanes/Et_2O, 1/1) to afford 1.77 g (94% yield) of compound **2a** as a colorless oil. Spectroscopic and physical data are in good agreement with those reported in the literature.[44]

*(R)-2-(Benzyloxy)-4-phenylbutanal (**2b**).* To a solution of ethyl (*R*)-2-hydroxy-4-phenylbutanoate (208 mg, 1.0 mmol) and *O*-benzyl-2,2,2-trichloroacetimidate (505 mg, 2.0 mmol) in dry hexane/CH_2Cl_2 7/1 v/v (5 mL) at room temperature under an argon atmosphere was added dropwise trifluoromethanesulfonic acid (15 mg, 0.1 mmol). After stirring for 72 h at room temperature, the reaction mixture was filtered to remove the white precipitate, which was washed with hexane. The combined organic filtrates were washed with a saturated aqueous solution of $NaHCO_3$ (15 mL). The aqueous layer was extracted with hexane (15 mL). Combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The purification of the residue by silica gel column chromatography (hexanes/Et_2O, 9/1) afforded 210 mg (70% yield) of ethyl (*R*)-2-benzyloxy-4-phenylbutanoate as a yellowish oil. **2b**: $[\alpha]_D^{25}$ = 55.0 (*c* 1.02, $CHCl_3$); IR (neat) 1745; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.23 (m, 7H), 7.21−7.12 (m, 3H), 4.72 (d, J = 11.6 Hz, 1H), 4.40 (d, J = 11.6 Hz, 1H), 4.26−4.14 (m, 2H), 3.92 (dd, J = 7.6, 5.2 Hz, 1H), 2.81 (ddd, J = 13.6, 8.8, 6.4 Hz, 1H), 2.75−2.65 (m, 1H), 2.16−2.00 (m, 2H), 1.28 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 141.1, 137.5, 128.5, 128.4, 128.4, 128.1, 127.9, 126.0, 77.3, 72.3, 60.8, 34.6, 31.4, 14.3.

To a solution of the obtained ethyl (*R*)-2-benzyloxy-4-phenylbutanoate (151 mg, 0.51 mmol) in dry Et_2O (5 mL) at −78 °C under an argon atmosphere was added dropwise, while stirring, a 1 M solution of DIBAL-H in hexane (0.77 mL, 0.77 mmol), and stirring continued for 1.5 h at the same temperature. Upon complete consumption of the ester, a 4 M aqueous solution of HCl (5 mL) was added and the reaction mixture was left to reach room temperature. The aqueous layer was separated and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford 120 mg (93% yield) of compound **2b** as a yellowish oil. Spectroscopic and physical data are in good agreement with those reported in the literature for **ent-2b**.[45]

General Procedure A: Optimization of the Aza-Prins Reaction of (*R*)-2,3-Di-*O*-benzylglyceraldehyde with *N*-Tosyl-homoallylamine. To a solution of *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **1a** (67.5 mg, 0.30 mmol) and (*R*)-2,3-di-*O*-benzylglyceraldehyde **2a** (89 mg, 0.33 mmol) in the selected dry solvent (5 mL) at room temperature under an argon atmosphere was added the corresponding Lewis or Brønsted acid (0.33 mmol). The resulting solution was stirred for the required time at room temperature. The crude product was concentrated under reduced pressure, then diluted in CH_2Cl_2 (20 mL), and washed with a saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The reaction was concentrated in vacuo, and the residue was analyzed by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard[46] to determine the reaction yield and diastereoselectivity. The purification of the residue was performed by column chromatography.

General Procedure B: The Aza-Prins Reaction of Hydroxyaldehyde Derivatives with *N*-Tosyl-homoallylamine. To a solution of *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **1a** (67.5 mg, 0.30 mmol) and an α-hydroxyaldehyde derivative (0.33 mmol) in acetonitrile (5 mL) at room temperature was added *p*-toluensulfonic acid monohydrate (74.2 mg, 0.39 mmol). The resulting solution was stirred for 3 h at room temperature. The crude product was concentrated under reduced pressure, then diluted in CH_2Cl_2 (20 mL), and washed with a saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography to give 6-oxa-2-azabicyclo[3.2.1]octanes.

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*(1R,5S,7S)-7-[(Benzyloxy)methyl]-2-tosyl-6-oxa-2-azabicyclo-[3.2.1]octane (**4a**) and (1S,5R,7S)-7-[(Benzyloxy)methyl]-2-tosyl-6-oxa-2-azabicyclo[3.2.1]octane (**5a**).* By following General Procedure B with *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **1a** (67.5 mg, 0.30 mmol), (*R*)-2,3-di-*O*-benzylglyceraldehyde **2a** (89 mg, 0.33 mmol), and *p*-toluensulfonic acid monohydrate (74.2 mg, 0.39 mmol), the purification by column chromatography (Et_2O/hexanes, 3/2) afforded 89 mg (77% yield) of compound **4a** as a white solid and 17 mg (15% yield) of compound **5a** as a yellowish oil. **4a**: mp 101−102 °C; $[\alpha]_D^{25}$ = 7.44 (*c* 1.00, $CHCl_3$); IR (Nujol) 1159; ^{1}H NMR (400 MHz, C_6D_6) δ 7.70−7.65 (m, 2H), 7.39−7.34 (m, 2H), 7.24−7.18 (m, 2H), 7.14−7.07 (m, 1H), 6.83−6.78 (m, 2H), 4.50−4.47 (m, 1H), 4.40 (d, *J* = 12.1 Hz, 1H), 4.36 (d, *J* = 12.1 Hz, 1H), 4.06 (ddd, *J* = 8.7, 5.7, 3.0 Hz, 1H), 4.01 (ddd, *J* = 6.2, 4.6, 1.3 Hz, 1H), 3.75−3.65 (m, 2H), 3.51 (ddd, *J* = 13.4, 7.4, 1.8 Hz, 1H), 3.20 (ddd, *J* = 13.4, 10.5, 5.9 Hz, 1H), 1.93 (s, 3H), 1.39−1.30 (m, 1H), 1.30−1.19 (m, 1H), 1.09−1.02 (m, 1H), 0.95−0.84 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 142.7, 139.2, 138.9, 129.7, 128.5, 127.6, 127.3, 81.6, 73.7, 73.3, 69.3, 56.2, 40.2, 36.6, 305, 21.1; HRMS (ESI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{25}NO_4SNa$ 410.1397, found 410.1413. **5a**: $[\alpha]_D^{25}$ = 49.8 (*c* 0.92, $CHCl_3$); IR (neat) 1164; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.53 (m, 2H), 7.34−7.00 (m, 7H), 4.48−4.32 (m, 4H), 3.68−3.60 (m, 1H), 3.44 (dd, *J* = 6.6, 5.1 Hz, 1H), 3.19 (dd, *J* = 9.8, 5.1 Hz, 1H), 3.09 (dd, *J* = 9.8, 6.6 Hz, 1H), 2.82−2.73 (m, 1H), 2.31 (s, 3H), 1.94−1.85 (m, 1H), 1.71 (d, *J* = 11.7 Hz, 1H), 1.67−1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 137.8, 135.1, 129.6, 128.4, 127.7, 127.7, 127.6, 78.1, 74.5, 73.4, 71.0, 57.9, 40.2, 36.0, 30.7, 21.5; HRMS (ESI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{25}NO_4SNa$ 410.1397, found 410.1385.

*Benzyl (1R,5S,7S)-7-[(Benzyloxy)methyl]-6-oxa-2-azabicyclo-[3.2.1]octane-2-carboxylate (**4b**) and Benzyl (1S,5R,7S)-7-[(Benzyloxy)methyl]-6-oxa-2-azabicyclo[3.2.1]octane-2-carboxylate (**5b**).* By following General Procedure B with benzyl but-3-en-1-ylcarbamate **1b** (61.5 mg, 0.30 mmol), (*R*)-2,3-di-*O*-benzylglyceraldehyde **2a** (89 mg, 0.33 mmol), and *p*-toluensulfonic acid monohydrate (74.2 mg, 0.39 mmol), the purification by column chromatography (Et_2O/hexanes, 3/2) afforded 35 mg (32% yield) of compound **4b** as a yellowish oil and 15 mg (14% yield) of compound **5b** as a yellowish oil. **4b**: $[\alpha]_D^{25}$ = 10.6 (*c* 1.42, $CHCl_3$); IR (neat) 1699; ^{1}H NMR (400 MHz, C_7D_8, 383 K) δ 7.26−7.00 (m, 10H), 5.09 (d, *J* = 12.4 Hz, 1H), 5.04 (d, *J* = 12.4 Hz, 1H), 4.78−4.63 (m, 1H), 4.37 (d, *J* = 13.0 Hz, 1H), 4.33 (d, *J* = 13.0 Hz, 1H), 4.16−4.10 (m, 1H), 3.98 (ddd, *J* = 5.6, 5.6, 2.8 Hz, 1H), 3.70−3.55 (m, 3H), 3.17 (ddd, *J* = 13.2, 9.6, 7.0 Hz, 1H), 1.64−1.55 (m, 1H), 1.50−1.42 (m, 1H), 1.31 (d, *J* = 12.0 Hz, 1H), 1.23−1.12 (m, 1H); ^{13}C NMR (100 MHz, C_7D_8, 383 K) δ 155.7, 139.6, 138.1, 128.6, 128.5, 128.2, 128.0, 127.6, 82.2, 74.2, 73.9, 69.8, 67.5, 55.1, 39.3, 37.3, 31.2; HRMS (ESI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{25}NO_4Na$ 390.1676, found 390.1675. **5b**: $[\alpha]_D^{25}$ = 25.4 (*c* 0.42, $CHCl_3$); IR (neat) 1700; ^{1}H NMR (400 MHz, $CDCl_3$, 333 K) δ 7.37−7.27 (m, 10H), 5.17 (d, *J* = 12.6 Hz, 1H), 5.14 (d, *J* = 12.6 Hz, 1H), 4.81−4.73 (m, 1H), 4.59−4.48 (m, 3H), 4.23 (dd, *J* = 5.4, 5.4 Hz, 1H), 4.02−3.93 (m, 1H), 3.48 (dd, *J* = 10.0, 5.4 Hz, 1H), 3.41−3.35 (m, 1H), 3.31 (ddd, *J* = 13.6, 11.2, 5.6 Hz, 1H), 2.01−1.91 (m, 1H), 1.81−1.72 (m, 1H), 1.68−1.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 333 K) δ 154.7, 138.2, 137.0, 128.5, 128.4, 128.0, 127.8, 127.6, 81.2, 74.9, 73.6, 71.7, 67.2, 56.0, 38.6, 35.7, 31.3; HRMS (ESI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{25}NO_4Na$ 390.1676, found 390.1675.

*Diphenyl [(1R,5S,7S)-7-[(Benzyloxy)methyl]-6-oxa-2-azabicyclo-[3.2.1]octan-2-yl]phosphonate (**4c**) and Diphenyl [(1S,5R,7S)-7-[(Benzyloxy)methyl]-6-oxa-2-azabicyclo[3.2.1]octan-2-yl]-phosphonate (**5c**).* By following General Procedure B with diphenyl but-3-en-1-ylphosphoramidate **1c** (90.9 mg, 0.30 mmol), (*R*)-2,3-di-*O*-benzylglyceraldehyde **2a** (89 mg, 0.33 mmol), and *p*-toluensulfonic acid monohydrate (74.2 mg, 0.39 mmol), the purification by column chromatography (Et_2O/hexanes, 2/1) afforded 42 mg (30% yield) of compound **4c** as a yellowish oil and 6 mg (4% yield) of compound **5c** as a yellowish oil. **4c**: $[\alpha]_D^{25}$ = 1.31 (*c* 0.80, $CHCl_3$); IR (neat) 1590, 1488, 1192; ^{1}H NMR (400 MHz, C_6D_6) δ 7.42−7.32 (m, 6H), 7.21−7.16 (m, 2H), 7.12−7.06 (m, 1H), 7.05−6.96 (m, 4H), 6.88−6.80 (m, 2H), 4.43−4.36 (m, 1H), 4.34 (d, *J* = 12.1 Hz, 1H), 4.27 (d, *J* = 12.1 Hz, 1H), 4.14−4.08 (m, 2H), 3.71 (dd, *J* = 10.1, 6.0 Hz, 1H), 3.62 (dd, *J* = 10.1, 5.4 Hz, 1H), 3.52−3.43 (m, 1H), 3.29−3.18 (m, 1H), 1.49−1.38 (m, 1H), 1.38−1.29 (m, 1H), 1.14−1.08 (m, 1H), 1.07−0.97 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 151.7 (d, *J* = 3.3 Hz), 151.6 (d, *J* = 3.1 Hz), 139.2, 129.9, 129.8, 128.5, 127.7, 127.5, 125.0 (d, *J* = 0.9 Hz), 124.9 (d, *J* = 0.9 Hz), 120.8 (d, *J* = 5.0 Hz), 120.7 (d, *J* = 5.1 Hz), 82.0 (d, *J* = 5.0 Hz), 74.1 (d, *J* = 0.4 Hz), 73.2, 69.1, 55.6 (d, *J* = 4.1 Hz), 39.6 (d, *J* = 1.4 Hz), 38.4 (d, *J* = 2.0 Hz), 31.0 (d, *J* = 5.3 Hz); HRMS (ESI$^+$) *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{29}NO_5P$ 466.1778, found 466.1789. **5c**: $[\alpha]_D^{25}$ = 12.4 (*c* 0.27, $CHCl_3$); IR (neat) 1590, 1488, 1192; ^{1}H NMR (400 MHz, C_6D_6) δ 7.45−7.39 (m, 4H), 7.27−7.22 (m, 2H), 7.17−7.12 (m, 2H), 7.11−7.06 (m, 1H), 7.04−6.96 (m, 4H), 6.87−6.80 (m, 2H), 4.56 (dd, *J* = 7.8, 3.9 Hz, 1H), 4.22−4.16 (m, 3H), 4.10 (dd, *J* = 5.4, 5.4 Hz, 1H), 3.62−3.53 (m, 1H), 3.28 (dd, *J* = 9.9, 4.3 Hz, 1H), 3.24−3.14 (m, 1H), 3.06 (dd, *J* = 9.9, 7.0 Hz, 1H), 1.68−1.56 (m, 1H), 1.39−1.30 (m, 1H), 1.28−1.23 (m, 1H), 1.11−0.98 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 151.7 (d, *J* = 4.8 Hz), 151.5 (d, *J* = 5.1 Hz), 138.8, 129.9, 129.8, 128.6, 128.3, 127.5, 124.9 (d, *J* = 0.9 Hz), 124.8 (d, *J* = 0.8 Hz), 120.8 (d, *J* = 5.1 Hz), 120.6 (d, *J* = 5.3 Hz), 81.2 (d, *J* = 4.0 Hz), 74.8 (d, *J* = 0.6 Hz), 73.3, 71.7, 57.0 (d, *J* = 3.2 Hz), 39.4 (d, *J* = 2.2 Hz), 36.3 (d, *J* = 2.9 Hz), 31.5 (d, *J* = 5.8 Hz); HRMS (ESI$^+$) *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{29}NO_5P$ 466.1778, found 466.1766.

*(1R,4aS,8aR,10S)-10-[(Benzyloxy)methyl-2-tosyloctahydro-2H-4a,1-(epoxymethano)isoquinoline (**4d**), (1S,4aR,8aS,10S)-10-[(Benzyloxy)methyl-2-tosyloctahydro-2H-4a,1-(epoxymethano)-isoquinoline (**5d**), 1-[(S)-1,2-Bis(benzyloxy)ethyl]-2-tosyl-1,2,3,4,6,7,8,8a-octahydroisoquinoline (**6**), and 1-[(S)-1,2-Bis-(benzyloxy)ethyl]-2-tosyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (**7**).* By following General Procedure B with *N*-(2-(cyclohex-1-en-1-yl)ethyl)-4-methylbenzenesulfonamide **1d** (83.8 mg, 0.30 mmol), (*R*)-2,3-di-*O*-benzylglyceraldehyde **2a** (89 mg, 0.33 mmol), and *p*-toluensulfonic acid monohydrate (74.2 mg, 0.39 mmol), the purification by column chromatography (hexanes/Et_2O, 4/1) afforded 19 mg (ca. 12% yield) of slightly unpurified compound **6** as a brown solid and 19 mg (ca. 12% yield) of slightly unpurified compound **7** as a yellowish oil. A further elution (Et_2O/hexanes, 2/1) provided 57 mg (43% yield) of a 87/13 diastereomeric mixture of compounds **4d**/**5d** as a yellowish oil. **4d** (from the 87/13 diastereomeric mixture): IR (neat) 1346; ^{1}H NMR (400 MHz, C_6D_6) δ 7.73−7.69 (m, 2H), 7.36−7.32 (m, 2H), 7.21−7.14 (m, 2H), 7.12−7.05 (m, 1H), 6.81−6.76 (m, 2H), 4.55−4.52 (m, 1H), 4.40−4.30 (m, 4H), 3.74 (dd, *J* = 10.0, 5.8 Hz, 1H), 3.68 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.61 (ddd, *J* = 13.4, 7.6, 1.6 Hz, 1H), 3.21 (ddd, *J* = 13.4, 10.5, 6.0 Hz, 1H), 1.89 (s, 3H), 1.78−1.71 (m, 1H), 1.40−1.28 (m, 3H), 1.27−1.15 (m, 3H), 1.12−1.01 (m, 1H), 0.89−0.62 (m, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 142.7, 139.1, 139.1, 129.7, 128.5, 127.8, 127.6, 127.3, 80.4, 79.8, 73.4, 70.2, 61.9, 47.5, 40.9, 37.5, 33.4, 25.5, 24.1, 21.3, 21.1; HRMS (ESI$^+$) *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{32}NO_4S$ 442.2047, found 442.2052. **6** (from the mixture): IR (Nujol) 1340, 1165, 1114; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.70 (m, 2H), 7.40−7.18 (m, 12H), 5.26 (bs, 1H), 4.81 (d, *J* = 11.6 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.20 (dd, *J* = 6.8, 2.8 Hz, 1H), 4.06−4.01 (m, 1H), 3.80 (dd, *J* = 10.2, 12.0 Hz, 1H), 3.74 (dd, *J* = 10.2, 6.4 Hz, 1H), 3.75−3.68 (m, 2H), 2.41 (s, 3H), 2.35−2.24 (m, 1H), 2.08−2.01 (m, 1H), 1.97−1.89 (m, 2H), 1.89−1.79 (m, 2H), 1.76−1.40 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 138.9, 138.9, 138.3, 134.3, 129.7, 128.4, 127.9, 127.8, 127.6, 127.1, 127.0, 127.0, 120.7, 79.6, 73.5, 73.3, 73.1, 58.2, 43.7, 38.1, 31.9, 26.0, 25.2, 22.2, 21.5; HRMS (ESI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_{32}H_{37}NNaO_4S$ 554.2336, found 554.2341. 7 (from the mixture): IR (neat) 1335, 1158, 1089; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.62 (m, 2H), 7.42−7.17 (m, 12H), 4.72 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.14−4.09 (bs, 1H), 3.97−3.74 (m, 5H), 2.40 (s, 3H), 1.97−1.83 (m, 1H), 1.76−1.32; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 138.9, 138.6, 138.0, 129.6, 129.1, 128.3, 128.1, 127.8, 127.5, 127.4, 127.4, 127.1, 124.5, 79.0, 73.8, 73.6, 72.8, 58.5, 41.0, 30.0, 27.8, 27.0, 22.8, 22.5, 21.4; HRMS (ESI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_{32}H_{37}NNaO_4S$ 554.2336, found 554.2354.

*(1R,5S,7S)-7-[(Benzyloxy)methyl]-5-methyl-2-tosyl-6-oxa-2-azabicyclo[3.2.1]octane (**4e**), (1S,5R,7S)-7-[(Benzyloxy)methyl]-5-methyl-2-tosyl-6-oxa-2-azabicyclo[3.2.1]octane (**5e**), and N-{2-[(S)-1,2-Bis(benzyloxy)ethyl]-4-methyl-1-tosylpiperidin-4-yl}-*

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*acetamide (**8**).* By following General Procedure B with 4-methyl-*N*-(3-methylbut-3-en-1-yl)benzenesulfonamide **1e** (71.8 mg, 0.30 mmol), (*R*)-2,3-di-*O*-benzylglyceraldehyde **2a** (89 mg, 0.33 mmol), and *p*-toluensulfonic acid monohydrate (74.2 mg, 0.39 mmol), the partial purification by column chromatography (hexanes/Et_2O, 3/2) afforded 16 mg of compound **5e** slightly unpurified with unreacted **1e** and **2a** (**5e**/**2a**/**1e** = 79/14/7) and 7 mg of compound **4e** unpurified with **5e** and unreacted **2a** (**4e**/**5e**/**2a** = 72/25/3). A further elution (EtOAc) provided 59 mg (36% yield) of compound **8** as a 83/17 mixture of diastereoisomers as a yellowish oil. **4e** (from the mixture): IR (neat) 1349; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.66 (m, 2H), 7.41−7.23 (m, 7H), 4.58−4.53 (m, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 4.24 (ddd, J = 7.0, 4.4, 3.2 Hz, 1H), 3.71 (dd, J = 13.6, 7.2 Hz, 1H), 3.58 (dd, J = 10.0, 7.0 Hz, 1H), 3.50 (dd, J = 10.0, 4.4 Hz, 1H), 3.37−3.23 (m, 1H), 2.42 (s, 3H), 1.82−1.69 (m, 2H), 1.62−1.52 (m, 1H), 1.48−1.42 (m, 1H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 138.0, 137.6, 129.8, 128.3, 127.7, 127.6, 126.9, 81.4, 80.3, 73.4, 68.9, 57.6, 42.6, 40.9, 35.8, 25.6, 21.5; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{22}H_{27}NNaO_4S$ 424.1553, found 424.1559. **5e** (from the mixture): IR (neat) 1342; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.61 (m, 2H), 7.41−7.28 (m, 5H), 7.18−7.12 (m, 2H), 4.57−4.53 (m, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 3.76−3.69 (m, 1H), 3.48 (dd, J = 6.8, 4.8 Hz, 1H), 3.26 (dd, J = 9.6, 4.8 Hz, 1H), 3.16 (dd, J = 9.6, 6.8 Hz, 1H), 2.86 (ddd, J = 11.6, 11.6, 5.2 Hz, 1H), 2.39 (s, 3H), 1.83−1.65 (m, 2H), 1.63−1.55 (m, 2H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 138.0, 135.2, 129.6, 128.4, 127.7, 127.6, 127.6, 80.6, 78.6, 73.3, 71.3, 59.5, 41.4, 40.7, 36.4, 25.0, 21.5; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{22}H_{27}NNaO_4S$ 424.1553, found 424.1547. **8** (major compound from the 83/17 diastereomeric mixture): IR (neat) 3370, 1676; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.60 (m, 2H), 7.30−7.14 (m, 12H), 6.47 (bs, 1H), 4.67 (d, J = 11.2 Hz, 1H), 4.51 (d, J = 11.8 Hz, 1H), 4.40 (d, J = 11.8 Hz, 1H), 4.36 (d, J = 11.2 Hz, 1H), 4.16 (dd, J = 6.8, 6.8 Hz, 1H), 3.87 (ddd, J = 6.8, 4.0, 3.6 Hz, 1H), 3.71 (dd, J = 10.8, 3.6 Hz, 1H), 3.71−3.62 (m, 1H), 3.56 (dd, J = 10.8, 4.0 Hz, 1H), 3.24−3.13 (m, 1H), 2.40−2.39 (m, 1H), 2.32 (s, 3H), 1.91−1.84 (m, 1H), 1.27 (s, 3H), 1.10−1.01 (m, 1H), 1.06 (s, 3H), 0.77 (ddd, J = 13.6, 13.6, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 143.4, 138.1, 137.7, 137.4, 129.8, 128.6, 128.4, 128.0, 127.9, 127.8, 127.6, 126.9, 79.1, 73.5, 71.9, 68.8, 51.9, 49.5, 39.3, 35.3, 31.0, 27.5, 23.8. 21.4; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{31}H_{39}N_2O_5S$ 551.2574, found 551.2592.

*N-{2-[2-[(S)-1,2-Bis(benzyloxy)ethyl]-1-tosylpyrrolidin-3-yl]-propan-2-yl} Acetamide (**9**).* By following General Procedure B with 4-methyl-*N*-(4-methylpent-3-en-1-yl)benzenesulfonamide **1f** (76 mg, 0.30 mmol), (*R*)-2,3-di-*O*-benzylglyceraldehyde **2a** (89 mg, 0.33 mmol), and *p*-toluensulfonic acid monohydrate (74.2 mg, 0.39 mmol), the purification by column chromatography (first eluent Et_2O/hexanes, 3/2; second eluent EtOAc) afforded 93 mg (55% yield) of compound **9** as a 60/40 mixture of diastereoisomers as a yellowish oil. Major compound (from the 60/40 diastereomeric mixture): IR (neat) 3331, 1160; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.63 (m, 2H), 7.39−7.21 (m, 12H), 6.62 (bs, 1H), 4.87 (d, J = 11.6 Hz, 1H), 4.65 (d, J = 11.6 Hz, 1H), 4.61−4.42 (m, 2H), 4.23−4.17 (m, 1H), 3.83−3.65 (m, 3H), 3.38−3.23 (m, 2H), 2.61−2.53 (m, 1H), 2.40 (s, 3H), 1.89−1.76 (m, 1H), 1.58−1.47 (m, 1H), 1.44 (s, 3H), 1.22 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 144.0, 138.0, 137.7, 134.2, 129.7, 128.5, 128.3, 128.3, 128.1, 127.6, 127.6, 127.5, 79.3, 73.4, 72.9, 69.0, 60.9, 54.9, 50.4, 49.5, 26.1, 25.3, 23.7, 21.5, 19.5. Minor compound (from the 60/40 diastereomeric mixture): IR (neat) 3331, 1160; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.68 (m, 2H), 7.39−7.21 (m, 12H), 6.49 (bs, 1H), 4.72 (d, J = 11.2 Hz, 1H), 4.64−4.42 (m, 3H), 4.00−3.90 (m, 2H), 3.83−3.65 (m, 2H), 3.50−3.39 (m, 1H), 3.38−3.23 (m, 1H), 2.65 (ddd, J = 8.8, 4.8, 2.4 Hz, 1H), 2.39 (s, 3H), 2.07−1.95 (m, 1H), 1.69−1.59 (m, 1H), 1.53 (s, 3H), 1.14 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 143.6, 137.8, 137.8, 136.1, 129.6, 128.4, 128.3, 128.1, 127.9, 127.7, 127.4, 80.5, 73.9, 73.4, 70.5, 61.3, 55.5, 49.5, 48.3, 27.0, 25.1, 23.8, 21.4, 20.7. HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{32}H_{41}N_2O_5S$ 565.2731, found 565.2741.

*(1R,5S,7R)-7-Phenethyl-2-tosyl-6-oxa-2-azabicyclo[3.2.1]octane (**4f**).* By following General Procedure B with *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **1a** (67.5 mg, 0.30 mmol), (*R*)-2-(benzyloxy)-4-phenylbutanal **2b** (84 mg, 0.33 mmol), and *p*-toluensulfonic acid monohydrate (74.2 mg, 0.39 mmol), the purification by column chromatography (Et_2O/hexanes, 1/1) afforded 58 mg (52% yield) of compound **4f** as a yellowish solid. **4f**: mp = 80.0−81.2 °C; $[\alpha]_D^{25}$ = 5.64 (c 0.98, $CHCl_3$); IR (Nujol) 1347, 1164; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75−7.68 (m, 2H), 7.32−7.23 (m, 4H), 7.22−7.14 (m, 3H), 4.48−4.39 (m, 2H), 3.90 (ddd, J = 7.6, 6.4, 2.8 Hz, 1H), 3.68 (dd, J = 13.6, 7.4 Hz, 1H), 3.44 (ddd, J = 13.6, 10.8, 6.0 Hz, 1H), 2.80−2.65 (m, 2H), 2.38 (s, 3H), 1.98−1.76 (m, 3H), 1.75−1.63 (m, 1H), 1.46 (dd, J = 11.6, 0.8 Hz, 1H), 1.41 (dddd, J = 13.2, 10.8, 7.4, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 141.5, 137.6, 129.7, 128.3, 128.2, 126.7, 125.8, 81.3, 73.4, 56.4, 40.1, 36.9, 32.4, 30.9, 30.3, 21.4; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{21}H_{26}NO_3S$ 372.1628, found 372.1635.

*(1R,5S,7S)-7-Methyl-2-tosyl-6-oxa-2-azabicyclo[3.2.1]octane (**4g**) and (1S,5R,7S)-7-Methyl-2-tosyl-6-oxa-2-azabicyclo[3.2.1]octane (**5g**).* By following General Procedure B with *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **1a** (67.5 mg, 0.30 mmol), (*S*)-2-(benzyloxy)propanal **2c** (54 mg, 0.33 mmol), and *p*-toluensulfonic acid monohydrate (74.2 mg, 0.39 mmol), the purification by column chromatography (Et_2O/hexanes, 3/2) afforded 11 mg (13% yield) of compound **4g** as a white solid and 35 mg (42% yield) of compound **5g** as a white solid. **4g**: mp = 86.8−87.3 °C; $[\alpha]_D^{25}$ = −12.2 (c 0.50, $CHCl_3$); IR (Nujol) 1343, 1166; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.63 (m, 2H), 7.36−7.30 (m, 2H), 4.43 (ddd, J = 5.6, 4.8, 0.8 Hz, 1H), 4.19 (bd, J = 4.4 Hz, 1H), 3.73−3.66 (m, 1H), 3.47 (q, J = 6.4 Hz, 1H), 2.90 (ddd, J = 11.6, 10.8, 5.8 Hz, 1H), 2.44 (s, 3H), 2.00−1.92 (m, 1H), 1.74 (dd, J = 11.6, 0.8 Hz, 1H), 1.71−1.61 (m, 2H), 0.96 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 135.4, 129.8, 127.3, 75.6, 74.4, 60.5, 40.3, 35.1, 30.8, 21.5, 21.0; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{14}H_{20}NO_3S$ 282.1158, found 282.1171. **5g**: mp = 102.1−103.0 °C; $[\alpha]_D^{25}$ = 3.08 (c 1.02, $CHCl_3$); IR (Nujol) 1333, 1160; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.68 (m, 2H), 7.32−7.27 (m, 2H), 4.44−4.38 (m, 1H), 4.33 (dd, J = 3.2, 2.8 Hz, 1H), 4.06 (qd, J = 6.6, 2.8 Hz, 1H), 3.66−3.58 (m, 1H), 3.39 (ddd, J = 13.2, 10.4, 5.6 Hz, 1H), 2.41 (s, 3H), 1.95 (dddd, J = 11.6, 6.4, 3.2, 1.6 Hz, 1H), 1.73−1.62 (m, 1H), 1.49 (dd, J = 11.6, 1.2 Hz, 1H), 1.42 (dddd, J = 13.2, 10.8, 7.2, 1.2 Hz, 1H), 1.19 (d, J = 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 137.7, 129.7, 126.8, 77.7, 73.6, 57.5, 39.9, 37.2, 30.3, 21.5, 14.8; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{14}H_{20}NO_3S$ 282.1158, found 282.1165.

*(1R,5S,7S)-7-Phenyl-2-tosyl-6-oxa-2-azabicyclo[3.2.1]octane (**4h**) and (1S,5R,7S)-7-Phenyl-2-tosyl-6-oxa-2-azabicyclo[3.2.1]octane (**5h**).* By following General Procedure B with *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **1a** (67.5 mg, 0.30 mmol), (*S*)-2-(benzyloxy)-2-phenylacetaldehyde **2d** (74.6 mg, 0.33 mmol), and *p*-toluensulfonic acid monohydrate (74.2 mg, 0.39 mmol), the purification by column chromatography (CH_2Cl_2) afforded mixtures, which were enriched in one or the other diastereoisomer **4h** and **5h**. A further purification by recrystallization (MeOH) of fractions enriched in **5h** provided 45 mg (40% yield) of compound **5h** as a white solid. **4h** [from the mixture of **4h** unpurified with **5h** and unreacted **1a** (**4h**/**5h**/**1a** = 76/14/10)]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75−7.70 (m, 2H), 7.33−7.20 (m, 5H), 7.10−7.05 (m, 2H), 4.67−4.62 (m, 1H), 4.60−4.58 (m, 1H), 4.37 (bd, J = 4.2 Hz, 1H), 3.82−3.75 (m, 1H), 3.13 (ddd, J = 11.6, 11.6, 5.4 Hz, 1H), 2.37 (s, 3H), 1.90−1.77 (m, 1H), 1.73−1.62 (m, 2H), 1.59−1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 140.9, 135.9, 129.9, 128.3, 127.5, 127.3, 125.2, 81.4, 75.0, 62.3, 40.7, 33.9, 30.9, 21.6; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{19}H_{21}NNaO_3S$ 366.1134, found 366.1144. **5h**: mp = 142−143 °C; $[\alpha]_D^{25}$ = −5.23 (c 1.02, $CHCl_3$); IR (Nujol) 1594; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.44 (m, 2H), 7.43−7.38 (m, 2H), 7.31−7.20 (m, 3H), 7.20−7.14 (m, 2H), 5.13 (bd, J = 3.7 Hz, 1H), 4.92−4.88 (m, 1H), 4.68−4.62 (m, 1H), 3.40−3.33 (m, 1H), 2.95 (ddd, J = 14.0, 11.4, 5.4 Hz, 1H), 2.37 (s, 3H), 2.10−2.05 (m, 1H), 1.71−1.62 (m, 2H), 1.47−1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 137.8, 137.5, 129.6, 128.1, 127.0, 126.9, 125.7, 82.1, 74.8, 57.1, 39.8,

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37.3, 30.3, 21.5; HRMS (ESI$^+$) m/z [M + Na]$^+$ calcd for $C_{19}H_{21}NNaO_3S$ 366.1134, found 366.1152.

*[(1R,5S,7S)-2-Tosyl-6-oxa-2-azabicyclo[3.2.1]octan-7-yl]-methanol (**4i**) and [(1S,5R,7S)-2-Tosyl-6-oxa-2-azabicyclo[3.2.1]-octan-7-yl]methanol (**5i**).* By following General Procedure B with *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **1a** (67.5 mg, 0.30 mmol), (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **2f** (43 mg, 0.33 mmol), and *p*-toluensulfonic acid monohydrate (74.2 mg, 0.39 mmol), the purification by column chromatography (Et_2O/EtOAc, 1/1) afforded 35 mg (39% yield) of compound **4i** as a yellowish oil and 18 mg (20% yield) of compound **5i** as a yellowish oil. **4i**: $[\alpha]_D^{25}$ = −6.74 (*c* 0.36, $CHCl_3$); IR (neat) 3402, 1348, 1160; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.69 (m, 2H), 7.36−7.30 (m, 2H), 4.46 (ddd, *J* = 6.0, 3.6, 3.2 Hz, 1H), 4.42−4.38 (m, 1H), 3.98 (ddd, *J* = 7.6, 6.4, 2.8 Hz, 1H), 3.85−3.70 (m, 2H), 3.45 (ddd, *J* = 12.6, 7.6, 6.8 Hz, 1H), 3.33 (ddd, *J* = 12.6, 7.2, 4.4 Hz, 1H), 2.44 (s, 3H), 1.92 (dddd, *J* = 12.0, 6.4, 3.6, 2.0 Hz, 1H), 1.87−1.76 (m, 1H), 1.69−1.57 (m, 1H), 1.52 (dd, *J* = 12.0, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 136.1, 129.9, 126.9, 81.9, 73.3, 60.6, 55.2, 39.0, 34.7, 31.1, 21.6; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{14}H_{20}NO_4S$ 298.1108, found 298.1118. **5i**: IR (neat) 3459, 1347, 1163; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.65 (m, 2H), 7.36−7.29 (m, 2H), 4.51−4.45 (m, 1H), 4.41 (bd, *J* = 4.4 Hz, 1H), 3.77−3.70 (m, 1H), 3.44 (dd, *J* = 6.4, 5.2 Hz, 1H), 3.40−3.30 (m, 2H), 2.91 (ddd, *J* = 11.2, 10.8, 5.6 Hz, 1H), 2.44 (s, 3H), 1.98−1.90 (m, 1H), 1.80 (dd, *J* = 12.0, 0.6 Hz, 1H), 1.77−1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 129.9, 127.4, 79.5, 74.8, 64.0, 57.5, 40.3, 36.4, 30.8, 21.6; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{14}H_{20}NO_4S$ 298.1108, found 298.1101.

*(1R,5S,7S)-7-[(Benzyloxy)methyl]-6-oxa-2-azabicyclo[3.2.1]-octane (**10**).* To a solution of compound **4a** (116 mg, 0.30 mmol) in anhydrous MeOH (6 mL) under an argon atmosphere were added magnesium turnings (146 mg, 6.0 mmol), and the mixture was sonicated at 70 °C until all the magnesium turnings dissolved (∼4 h). The solvent was evaporated in vacuo, and CH_2Cl_2 (10 mL) and aqueous saturated NH_4Cl (10 mL) were added. The aqueous layer was separated and extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The purification of the residue by filtration through a silica gel path (first eluent Et_2O, second eluent MeOH) afforded 64 mg (93% yield) of compound **10** as a yellowish oil. **10**: $[\alpha]_D^{25}$ = −59.3 (*c* 0.95, $CHCl_3$); IR (neat) 3331; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.24 (m, 5H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.54−4.49 (m, 1H), 4.12 (ddd, *J* = 6.4, 6.0, 2.4 Hz, 1H), 3.87 (dd, *J* = 9.8, 6.4 Hz, 1H), 3.78 (dd, *J* = 9.8, 6.0 Hz, 1H), 3.42 (bs, 1H), 3.13 (ddd, J = 12.2, 12.0, 6.0 Hz, 1H), 2.84 (dd, *J* = 12.2, 6.8 Hz, 1H), 2.12 (bs, 1H), 2.04−1.96 (m, 1H), 1.76 (bd, *J* = 11.2 Hz, 1H), 1.75−1.65 (m, 1H), 1.63−1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 128.3, 127.7, 127.6, 81.5, 75.0, 73.3, 68.3, 54.6, 39.5, 39.4, 31.7; HRMS (ESI$^+$) m/z [M + H]$^+$ calcd for $C_{14}H_{20}NO_2$ 234.1487, found 234.1497.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01291.

X-ray crystallographic data for compound **4a** (CIF)

^{1}H NMR and ^{13}C NMR spectra of starting materials products and X-ray crystallographic data (ORTEP) for compound **4a** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: jagl@unizar.es.

*E-mail: loladiaz@unizar.es.

ORCID

María D. Díaz-de-Villegas: 0000-0001-9033-8459

Present Address

‡Instituto de Biocomputación y Física de Sistemas Complejos (BIFI), Mariano Esquillor, Edificio I + D Campus Río Ebro, Universidad de Zaragoza, 50018 Zaragoza, Spain.

Notes

The authors declare no competing financial interest.

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