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An efficient methodology for the C–C bond forming radical cyclization of hydrophobic substrates in water: effect of additive on radical reaction in water

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Abstract—The combination of the water-soluble radical initiator, 2,2′-azobis[2-(2-imidazolin-2-yl)propane] (VA-061), water-soluble chain carrier, 1-ethylpiperidine hypophosphite (EPHP) and surfactant, cetyltrimethylammonium bromide (CTAB), was found to be the most suitable condition for effective radical cyclization in water for a variety of hydrophobic substrates. The effect of additives and surfactant in the radical cyclization reaction in water was also investigated. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Water has many potential advantages as a solvent for organic reactions from the vantage point of its cost, safety and environmental concern. Therefore, the development of an efficient and convenient synthetic methodology to accomplish C–C bond formation in water is an important subject. Recently, various C–C bond formations in aqueous media have been reported.[1] For instance: (i) Diels–Alder reaction,[2] (ii) Claisen rearrangement,[3] (iii) Barbier-type allylation,[4] (iv) Mukaiyama aldol reaction,[5] and so on were successfully carried out in water.

Radical reaction[6] is one of the most useful methods for organic reaction in water, because most of the organic radical species are stable in water, and they do not react with water. In the last decade, some radical reactions in water have been reported. These reactions in water can be classified into two types. The first type utilizes a chain carrier to carry out the reaction. For example, the radical reductions in water have been reported using water-soluble Sn compounds by Breslow et al.,[7] and water-soluble Si compounds by Togo and Yokoyama et al.[8] In these successful reports, the substrates always had hydrophilic functional groups, which facilitated the solubility of substrates in water. The second type makes use of some radical reactions in water without any chain carrier. Thus, an intramolecular radical cyclization in water has been reported by Oshima et al.[9] using α-iodocarbonyl compounds as the substrate; however, increasing the hydrophobicity of the substrate tended to decrease the reactivity. Recently, the same group has achieved an intermolecular radical addition using α-bromocarbonyl compounds in water.[10] Naito et al. reported a radical addition reaction in water by the use of highly polar imine compounds, which can dissolve easily in water.[11] We tried to develop a general methodology for the C–C bond forming radical reaction with an efficient chain carrier in water.

Recently, some reports are available for the radical reactions of hydrophobic substrates in water.[12] We have developed an unprecedented C–C bond forming radical reaction of hydrophobic substrates in water using an efficient radical reaction system. Our strategy is based upon the use of a combination of a water-soluble radical initiator, water-soluble chain carrier and surfactant. Recently, we have reported the radical cyclization of hydrophobic substrates in water using the combination of 2,2′-azobis[2-(2-imidazolin-2-yl)propane] (VA-061), 1-ethylpiperidine hypophosphite (EPHP) and cetyltrimethylammonium bromide (CTAB).[13] Here, we wish to report the full account of the studies on the radical cyclization in water using the system we developed, together with the effect of additives in these reactions.

2. Results and discussion

Initially, we examined the radical cyclization of the hydrophobic substrate, 2-iodo-1-aryl-1-prop-2-enyloxy-ethane (**1a**) in water using conditions (i) and (ii) shown in Scheme 1. When the reaction was carried out using Et_3B in water in the absence of a chain carrier, the reaction did not proceed to completion. Consequently, we chose the hypophosphorous acid derivatives (H_3PO_2+$NaHCO_3$ and

Keywords: cetyltrimethylammonium bromide; C–C bond; radical reactions.

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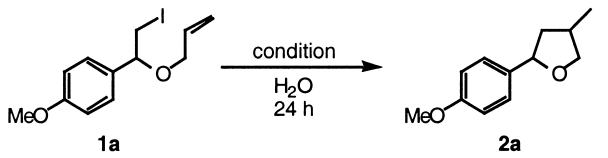


	conditions	yield
(i)	Et_3B, r. t.	0%
(ii)	initiator: AIBN, Et_3B, V–70L chain carrier: H_3PO_2 + $NaHCO_3$, EPHP temperature: r. t. ~ 80 °C	< 15%

Scheme 1. Radical cyclization reaction of **1a** in water.

EPHP)[14] as the chain carriers, and examined the reaction of **1a** using the water-insoluble radical initiators (AIBN, Et_3B and V-70L[15]). Under these conditions, we observed that the cyclization product (**2a**) was formed, albeit in low yields (<15%). From these results, it is realized that the cyclization of the hydrophobic substrate (**1a**) in water using the above conditions is difficult.

We presumed that a combination of water-soluble radical initiators and water-soluble chain carriers would be an effective system for radical reaction of **1a** in water. We used the water-soluble azo-type radical initiators for these studies, which are shown in Figure 1.[16] These water-soluble azo-type compounds, which are efficient initiators in the synthesis of polymers, are expected to generate radical species effectively in water. The 10-hour half-life decomposition temperatures of these initiators are included in Figure 1. We presumed that water-soluble initiators are more suitable for radical reactions in water since the decomposition products from these initiators are easily removable compared to those generated from water-insoluble initiators (AIBN, Et_3B and V-70L). We chose the hypophosphorous reagent[14] as a chain carrier, since this reagent is less toxic than the commonly used Sn compounds. In addition, Sn compounds have some disadvantages from the standpoint of the purification process. On the other hand, hypophosphorous reagent is water-soluble and is easily removable from the product. In this point of view, we investigated the optimum combination of the water-soluble

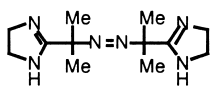
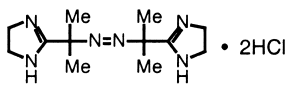
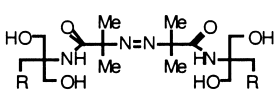
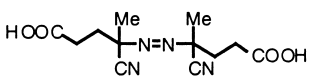
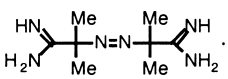
name	structure	10 hour half-life decomposition temperature
VA–061		61 °C in MeOH
VA–044		44 °C in H_2O
VA–080 R = OH VA–082 R = H		80 °C in H_2O 82 °C in H_2O
V–501		69 °C in H_2O
V–50		56 °C in H_2O

Figure 1. Various water-soluble azo-type radical initiators.

Table 1. Radical cyclization reaction of **1a** using water-soluble initiators and chain carriers at 80°C for 24 h

Entry	Initiator (1 equiv.)	Chain carrier (10 equiv.)	Yield (*trans*/*cis*)[a]
1	VA-061	EPHP	64% (74:26) [24%]
2	VA-061	H_3PO_2+$NaHCO_3$[b]	33% (52:48) [37%]
3	VA-061	NaH_2PO_2	41% (76:24) [43%]
4	V-501	EPHP	62% (51:49) [3%]
5	V-50	EPHP	63% (51:49) [13%]

[a] The ratios were determined by ^{1}H NMR. The recovered yield of starting material is shown in brackets.
[b] The ratio of the reagent: H_3PO_2/$NaHCO_3$=1:1.

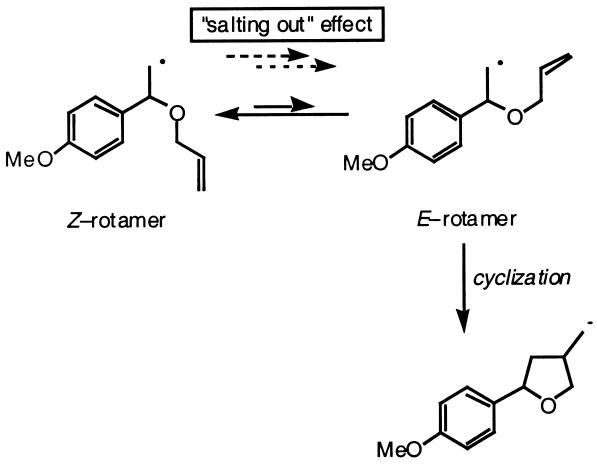
azo-type initiators and hypophosphorous reagents for the reaction of **1a** in water (Table 1). As a result, we found that the combinations of these water-soluble initiators (VA-061, V-501 and V-50) and EPHP were more effective for the radical cyclization of **1a** than the former cases (cf. Scheme 1).

To improve the yield of these radical reactions in water, we decided to add an additive to our reaction system comprising VA-061 and EPHP. Breslow et al. have already reported that Diels–Alder reactions in water were accelerated by the addition of the 'salting out' salt (e.g. LiCl) to the system, and the rate of the reaction decreased by the addition of the 'salting in' salt (e.g. guanidine hydrochloride).[2,17] A 'salting out' salt is a material that increases the hydrophobic effect of water and thereby decreases the solubility of hydrocarbons, and a 'salting in' salt is a material that decreases the association of hydrocarbon residues in water and thus increases the water solubility of hydrocarbons. With this background, we first examined the additive effect of NaCl as a 'salting out' salt (Table 2). When the cyclization was carried out in the presence of 1–10 equiv. of NaCl, the reaction of **1a** proceeded more effectively than that without any additive; however, the rate of the reaction decreased when more than 50 equiv. of the salt were added, and the starting material (**1a**) was recovered. The side-reaction scarcely occurred. We guess that this 'salting out' effect in the addition of the moderate amount of the salt functioned to change the conformation of the cyclization substrate. In other words, the addition of the salt to the water system helps to increase the internal pressure in water, thereby the cyclization substrate is transformed from the non-compact forming *Z*-rotamer into the compact forming *E*-rotamer, which is essential for the cyclization (Scheme 2).[1b,17] Therefore, the yield of the cyclization reaction was found to be higher than that observed without an additive. This kind of effect has

Table 2. Effect of the 'salting out' salt NaCl: radical cyclization reaction of **1a** using VA-061 (1 equiv.) and EPHP (10 equiv.) at 80°C for 24 h

Entry	Equivalent of NaCl	Concentration (M)	Yield (*trans*/*cis*)[a]
1	None	0	64% (74:26) [24%]
2	1	0.05	85% (60:40) [9%]
3	5	0.25	85% (58:42) [12%]
4	10	0.5	88% (60:40) [10%]
5	50	2.5	55% (67:33) [44%]
6	Saturation	> 6	26% (70:30) [74%]

[a] The ratios were determined by ^{1}H NMR. The recovered yield of starting material is shown in brackets.



Scheme 2. The effect of the 'salting out' salt.

Table 3. Effect of various 'salting out' salts: radical cyclization reaction of **1a** using VA-061 (1 equiv.) and EPHP (10 equiv.) at 80°C for 24 h

Entry	Additive (1 equiv., 0.05 M)	Yield (*trans*/*cis*)[a]
1	NaF	89% (65:35) [6%]
2	NaBr	84% (60:40) [10%]
3	NaI	92% (68:32) [8%]
4	$NaHCO_3$	85% (74:26) [12%]
5	Na_2CO_3	90% (58:42) [9%]
6	$NaNO_3$	89% (63:37) [10%]
7	$NaHSO_4$	89% (52:48) [10%]
8	Na_2SO_4	75% (64:36) [22%]
9	KBr	89% (57:43) [9%]
10	LiCl	88% (58:42) [8%]

[a] The ratios were determined by ^{1}H NMR. The recovered yield of starting material is shown in brackets.

previously been reported by Oshima et al.[9c] in the radical cyclization of allyl iodoacetate in water. In addition, when excess amount of the 'salting out' salt is added, the substrate **1a** is precipitated from the water system and the solubility of the water-soluble initiators decreased in water, resulting in a decrease in the rate of the reaction.

The characteristic effect of various 'salting out' salts in the radical cyclization of **1a** in water is apparent from Table 3. From these observations, we found that all salts have similar effect on the radical cyclization of **1a**. This effect is useful for the cyclization of **1a**, however, the reaction did not reach completion until 24 h.

Table 4. Effect of the 'salting in' salt guanidine hydrochloride: radical cyclization reaction of **1a** using VA-061 (1 equiv.) and EPHP (10 equiv.) at 80°C

Entry	Equivalent of guanidine·HCl	Concentration (M)	Time (h)	Yield (*trans*/*cis*)[a]
1	None	0	24	64% (74:26) [24%]
2	1	0.05	24	93% (62:38) [5%]
3	10	0.5	24	94% (59:41) [3%]
4	50	2.5	20	96% (55:45)
5	100	5	5	97% (54:46)
6[b]	Saturation	>20	1	97% (52:48)

[a] The ratios were determined by ^{1}H NMR. The recovered yield of starting material is shown in brackets.
[b] VA-061 (0.5 equiv.) was used.

We then investigated the additive effect of guanidine hydrochloride as a 'salting in' salt (Table 4). The reaction was accelerated by the addition of the salt, and it went to completion furnishing higher yields when more than 50 equiv. of the salt were added to the system.

The characteristic effect of various 'salting in' salts in the radical cyclization of **1a** in water is apparent from Table 5. Here also, we found that the rate of the reaction was increased by the addition of salts. It should be mentioned here that in the case of using 'salting in' salts, a large quantity of the salt was necessary to facilitate the cyclization reaction of **1a**. To circumvent this disadvantage, we searched for a more efficient additive for these reactions.

We planned the use of a surfactant[18] to solubilize the hydrophobic substrate in water. We examined the radical cyclization of **1a** using various surfactants in the presence of VA-061 and EPHP (Table 6). As a result, we found that surfactants functioned as the most efficient additive for the radical cyclization of **1a** from the viewpoint of its rate acceleration effect. The concentration of cetyltrimethylammonium bromide (CTAB)[18] used in our reactions is within the range of micelle formation and therefore the possibility of a micellar reaction cannot be ruled out. When catalytic amount of the surfactants was used in the reaction, the yield of the cyclization product (**2a**) was found to be higher than the case of using other salts ('salting in' and 'salting out' agent). Our method is quite efficient, since a highly toxic Sn compound is generally used as the chain carrier[19] despite the disadvantage from the environmental point of view.

Table 5. Effect of various 'salting in' salts: radical cyclization reaction of **1a** using VA-061 (1 equiv.) and EPHP (10 equiv.) at 80°C for 24 h

Entry	Additive (1 equiv., 0.05 M)	Yield (*trans*/*cis*)[a]
1	$Et_4N^+Br^-$	91% (56:44) [7%]
2	NH_4Cl	90% (60:40) [6%]
3	$LiClO_4$	88% (58:42) [9%]
4	$NaClO_4$	91% (58:42) [7%]
5	Urea	82% (64:36) [13%]

[a] The ratios were determined by ^{1}H NMR. The recovered yield of starting material is shown in brackets.

Table 6. Effect of various surfactants: radical cyclization reaction of **1a** using VA-061 (1 equiv.) and EPHP (10 equiv.) at 80°C

Entry	Surfactant (0.2 equiv.)	Time (h)	Yield (*trans*/*cis*)[a]
1	None	24	64% (74:26) [24%]
2	CTAB	2	98% (55:45)
3	CTAC[b]	2	98% (62:38)
4	SDS[c]	3.5	98% (51:49)
5	Triton X-100[d]	4	98% (62:38)
6	KBr	24	82% (72:28) [17%]
7	$Et_4N^+Br^-$	24	85% (65:35) [7%]

[a] The ratios were determined by ^{1}H NMR. The recovered yield of starting material is shown in brackets.
[b] CTAC: cetyl-trimethylammonium chloride.
[c] SDS: sodium dodecyl sulfate.
[d] Triton X-100: polyoxyethylene(10) isooctylphenyl ether.

Table 7. Study of various initiators: radical cyclization reaction of **1a** using EPHP (10 equiv.) and CTAB (0.2 equiv.) at 80°C

Entry	Initiator (1 equiv.)	Time (h)	Yield (*trans*/*cis*)[a]
1	VA-061	2	98% (55:45)
2	VA-044	2.5	95% (50:50)
3	VA-080	5	76% (50:50)
4	VA-082	24	71% (50:50)
5	V-501	24	72% (51:49)
6	V-50	4	92% (51:49)
7	AIBN	24	19% (57:43) [56%]
8[b]	Et_3B	24	50% (67:33) [46%]

[a] The ratios were determined by ^1H NMR. The recovered yield of starting material is shown in brackets.
[b] Room temperature.

We again examined the various initiators in the presence of EPHP and CTAB (Table 7). The reaction did not go to completion when the typical radical initiator AIBN was used (entry 7). While using Et_3B, a known radical initiator at low temperature, the yield of the desired product was found to be low (entry 8). On the other hand, water-soluble initiators were found to be quite effective in promoting the intramolecular cyclization of **1a**. Remarkably, VA-061 was found to be the most suitable initiator under these conditions (entry 1), and thus the use of VA-061 was explored further.

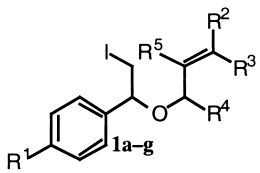
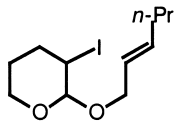
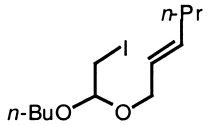
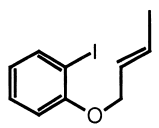
We next pursued for an expedient chain carrier for our system containing VA-061 and CTAB (Table 8). After screening a series of chain carriers such as hypophosphorous acid derivatives (EPHP, H_3PO_2+Et_3N, etc.)[14] and tris(trimethylsilyl)silane [$(TMS)_3SiH$],[20] we

Table 8. Study of various chain carriers: radical cyclization reaction of **1a** using VA-061 (1 equiv.) and CTAB (0.2 equiv.) at 80°C

Entry	Chain carrier	Time (h)	Yield (*trans*/*cis*)[a]
1	None	24	No reaction
2	EPHP (10 equiv.)	2	98% (55:45)
3	EPHP (5 equiv.)	4	87% (64:36)
4	H_3PO_2 (10 equiv.)+Et_3N (10 equiv.)	2	98% (52:48)
5	H_3PO_2 (10 equiv.)+$NaHCO_3$ (10 equiv.)	6	84% (78:22)
6	NaH_2PO_2 (10 equiv.)	24	58% (78:22) [8%]
7[b]	$(TMS)_3SiH$ (2 equiv.)	0.5	94% (67:33)

[a] The ratios were determined by ^1H NMR. The recovered yield of starting material is shown in brackets.
[b] VA-061 (0.5 equiv.) was used.

Table 9. Radical cyclization reaction of various hydrophobic substrates (**1a**–**j**) using the combination of VA-061 (1 equiv.), EPHP (10 equiv.) and CTAB (0.2 equiv.) at 80°C

Entry	Substrate		R^1	R^2	R^3	R^4	R^5	Time (h)	Product	Yield (*trans*/*cis*)[a]
1		**1a**	MeO	H	H	H	H	2	**2a**	98% (55:45) [64% (74:26)][b]
2		**1b**	MeO	Me	H	H	H	4	**2b**	88% (66:34) [53% (62:38)][b]
3		**1c**	MeO	Me	Me	H	H	3	**2c**	94% (61:39)
4		**1d**	MeO	H	H	H	Me	4	**2d**	86%
5		**1e**	MeO	H	$-(CH_2)_3-$		H	3	**2e**	94%[c]
6		**1f**	MeO	CO_2Et	H	H	H	2	**2f**	96% (75:25)
7		**1g**	H	H	H	H	H	2	**2g**	87% (78:22)
8[d]		**1h**						0.5	**2h**	98%[e] [21%][f]
9[g]		**1i**						2	**2i**	99% (74:26) [9% (67:33)][b]
10[h]		**1j**						18	**2j**	64% [22%][b]

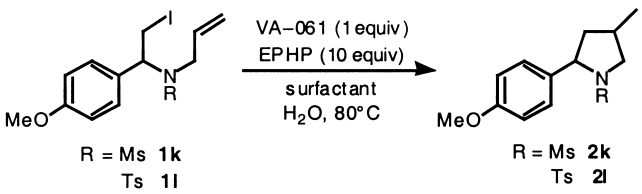
[a] The ratios were determined by ^1H NMR.
[b] When CTAB was not used; reaction time: 24 h.
[c] Obtained as a mixture of *endo* and *exo* (53:47).
[d] VA-061 (0.5 equiv.) was used.
[e] Obtained as a mixture of *endo* and *exo* (76:24).
[f] Obtained as a mixture of *endo* and *exo* (75:25) when CTAB was not used; reaction time: 0.5 h.
[g] $NaHCO_3$ (10 equiv.) was added.
[h] VA-061 (1.5 equiv.) was used.

found that EPHP and the combination of hypophosphorous acid and triethylamine are suitable for our system. The role of these reagents can be explained as follows. The organic bases (1-ethylpiperidine and triethylamine) used in the reaction are incorporated in the formation of micellar system, and the hypophosphorous reagent is efficiently incorporated in micellar system with the organic bases. The radical cyclization of **1a** using 5 equiv. of EPHP proceeded slowly and in lower yield than that using 10 equiv. of EPHP. When $(TMS)_3SiH$ was used as the chain carrier, the target product was obtained in good yield within a short period of time, however, it required a tedious procedure for the isolation of the desired product from the by-product derived from $(TMS)_3SiH$. Thus, we discovered that the combination of VA-061, EPHP and CTAB is the most appropriate condition for the radical reactions of the substrate **1a** in water.

The utility and generality of this method was confirmed by applying to a series of hydrophobic substrates (**1a–j**). In all cases, the intramolecular cyclization proceeded with high efficiency and yield (Table 9). Notable is the fact that the reaction showed low reactivity when the surfactant (CTAB) was not used. The present method using the iodides (**1a–j**) was tried to extend to bromides, and we found that bromides were unsuitable as the substrate. Thus, when the bromide of **1a** was used as the substrate, the cyclic compound (**2a**) was produced in only 4% yield and the starting material was recovered in 25% yield.

In order to test the scope and limitations of our methodology, we subsequently tried the radical cyclization strategy to yield pyrrolidines, which are often present in natural products. Thus, the allyl amine **1k** was subjected to the radical reaction conditions in water at 80°C to give the corresponding pyrrolidine **2k** in 90% yield. The results are obtained for other substrates and are summarized in Table 10. As a consequence, we found that our method is also effective for the radical cyclization in water to afford pyrrolidines (entry 2). As expected, in the absence of the surfactant, the reaction proceeded with decrease in reactivity (entries 1, 3). The following experimental results using a more hydrophobic substrate (**1l**) supported the apparent effectiveness of the surfactant CTAB (entries 4–6). By tuning the amount of CTAB, the reactivity can be greatly enhanced. The yield of the cyclization product (**2l**) was found to be lower when other surfactants (SDS or Triton X-100) were used. Thus, it is concluded that CTAB is the most effective surfactant for our system.

Table 10. Application to highly hydrophobic substrates



R = Ms **1k**, Ts **1l** → R = Ms **2k**, Ts **2l**

Entry	R	Surfactant	Time (h)	Yield (*trans*/*cis*)[a]
1	Ms	None	24	90% (72:28)
2	Ms	CTAB (0.2 equiv.)	8	99% (72:28)
3	Ts	None	24	8% (53:47) [23%]
4	Ts	CTAB (0.2 equiv.)	24	46% (75:25) [21%]
5	Ts	CTAB (1 equiv.)	24	65% (75:25) [14%]
6	Ts	CTAB (2 equiv.)	6	87% (75:25)
7	Ts	SDS (2 equiv.)	24	33% (75:25) [11%]
8	Ts	Triton X-100 (2 equiv.)	24	49% (75:25) [39%]

[a] The ratios were determined by ^1H NMR. The recovered yield of starting material is shown in brackets.

3. Conclusion

In summary, we have discovered that a combination of water-soluble azo-type radical initiator (VA-061), water-soluble chain carrier (hypophosphorous acid derivative, EPHP) and surfactant (CTAB) is an ideal reaction system to accomplish radical cyclization in water. This method is an elegant way to achieve C–C bond forming radical reactions in water for various hydrophobic substrates. In addition, we found that the yield of the radical cyclization reaction in water was increased by the addition of the 'salting out and salting in' salts. Therefore, we believe that the addition of additives (surfactant and other salts) would be applied to various other cyclization reactions in water.

4. Experimental

4.1. General

All melting points are uncorrected. Infrared (IR) absorption spectra were recorded on a Shimadzu FTIR-8100 spectrometer using KBr pellets. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ on VARIAN VXR-200, JEOL JNM-EX 270, JEOL JNM-AL 300 and JEOL JNM-LA 500 spectrometers with TMS or $CHCl_3$ as the internal standard. E. Merck silica gel 60 (70–230 mesh ASTM) and Fuji Silysia Chemical silica gel BW-300 were used for column chromatography and flash column chromatography. Anhydrous CH_2Cl_2 was distilled from P_2O_5. Anhydrous THF was distilled from sodium/benzophenone under nitrogen. The assignment of stereochemistry of the cyclization product was based on NOE difference. *cis–trans* (or *exo–endo*) ratios were determined from the integration in the ^1H NMR spectra of the diastereomeric mixture.

4.2. General procedure for the preparation of allyl ether 1a–i and allyl amine 1k–l

Under nitrogen atmosphere, the allyl alcohol or amine (7.52 mmol) was added to a solution of the olefin (3.76 mmol) in dry CH_2Cl_2 (25 ml) at room temperature. After 5 min, the reaction mixture was cooled to −78°C, added *N*-iodosuccinimide (5.64 mmol) and allowed to reach 0°C in about 1–6 h. To the reaction mixture, a saturated aqueous solution of $Na_2S_2O_3$ was added, and stirred vigorously for 5 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silicagel using hexane/Et_2O (20:1–1:1) to give the products **1a–i**, **k** and **l**.

4.2.1. 2-Iodo-1-(4-methoxyphenyl)-1-prop-2-enyloxy-ethane (1a). Obtained in 98% as colorless oil: ^1H NMR

($CDCl_3$) δ: 3.27–3.41 (m, 2H), 3.81 (s, 3H), 3.81 (dd, 1H, J=12.5, 5.0 Hz), 3.98 (dd, 1H, J=12.5, 5.0 Hz), 4.43 (dd, 1H, J=8.0, 5.0 Hz), 5.18 (dd, 1H, J=10.0, 1.0 Hz), 5.27 (dd, 1H, J=17.0, 1.0 Hz), 5.85–5.98 (m, 1H), 6.89 (d, 2H, J=9.0 Hz), 7.24 (d, 2H, J=9.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 10.9, 55.3, 69.9, 80.5, 114.0, 117.4, 127.8, 131.9, 134.4, 159.6. HRMS (EI) calcd for $C_{12}H_{15}O_2I$ (M^+): 318.0117. Found: 318.0113. Anal. calcd for $C_{12}H_{15}O_2I$: C, 45.30; H, 4.75; I, 39.89. Found: C, 45.50; H, 4.74; I, 39.73.

4.2.2. 1-But-2-enyloxy-2-iodo-1-(4-methoxyphenyl)-ethane (1b). Obtained in 86% as colorless oil: ^{1}H NMR ($CDCl_3$) δ: 1.70 (d, 3H, J=6.0 Hz), 3.26–3.40 (m, 2H), 3.82 (s, 3H), 3.72–3.98 (m, 2H), 4.41 (dd, 1H, J=8.0, 5.0 Hz), 5.53–5.71 (m, 2H), 6.85–6.92 (m, 2H), 7.22–7.25 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 11.1, 17.8, 55.2, 69.7, 80.3, 114.0, 127.2, 127.9, 129.9, 132.1, 159.5. HRMS (EI) calcd for $C_{13}H_{17}O_2I$ (M^+): 332.0273. Found: 332.0268.

4.2.3. 2-Iodo-1-(3-methylbut-2-enyloxy)1-(4-methoxyphenyl)ethane (1c). Obtained in 99% as colorless oil: ^{1}H NMR ($CDCl_3$) δ: 1.57 (s, 3H), 1.74 (s, 3H), 3.25–3.39 (m, 2H), 3.81 (s, 3H), 3.87 (t, 2H, J=8.5 Hz), 4.40 (dd, 1H, J=8.0, 5.0 Hz), 5.38 (t, 1H, J=6.0 Hz), 6.89 (d, 2H, J=8.0 Hz), 7.24 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 11.2, 18.1, 25.8, 55.3, 65.5, 80.5, 114.0, 120.6, 127.9, 132.3, 137.9, 159.6. HRMS (EI) calcd for $C_{14}H_{19}O_2I$ (M^+): 346.0430. Found: 346.0432.

4.2.4. 2-Iodo-1-(4-methoxyphenyl)-1-(2-methylprop-2-enyloxy)ethane (1d). Obtained in 70% as colorless oil: ^{1}H NMR ($CDCl_3$) δ: 1.79 (s, 3H), 3.27–3.42 (m, 2H), 3.69 (d, 1H, J=12.5 Hz), 3.82 (s, 3H), 3.86 (d, 1H, J=12.5 Hz), 4.40 (dd, 1H, J=8.5, 4.5 Hz), 4.90 (s, 1H), 4.95 (s, 1H), 6.90 (d, 2H, J=8.5 Hz), 7.24 (d, 2H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 10.8, 19.9, 55.3, 72.9, 80.3, 112.9, 114.0, 127.9, 132.0, 141.8, 159.6. HRMS (EI) calcd for $C_{13}H_{17}O_2I$ (M^+): 332.0273. Found: 332.0292.

4.2.5. 1-Cyclohex-2-enyloxy-2-iodo-1-(4-methoxyphenyl)-ethane (1e). Obtained in 75% as diastereomeric mixture. Further purification of the diastereomers using column chromatography was unsuccessful; colorless oil: ^{1}H NMR ($CDCl_3$) δ: 1.39–1.75 (m, 3H), 1.87–2.13 (m, 3H), 3.25–3.35 (m, 2H), 3.81 (s, 3H), 3.68–3.76, 3.82–3.93 (each m, total 1H), 4.52–4.57 (m, 1H), 5.56–5.59, 5.84–5.87 (each m, total 1H), 5.87–5.89 (m, 1H), 6.89 (d, 2H, J=8.5 Hz), 7.28 (d, 2H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 11.7. 12.0, 18.8, 19.3, 25.2, 27.2, 29.6, 55.3, 70.4, 72.5, 79.5, 79.9, 113.9, 114.0, 127.2, 127.6, 127.7, 127.8, 131.0, 131.5, 133.1, 133.4, 159.4. HRMS (EI) calcd for $C_{15}H_{19}O_2I$ (M^+): 358.0430. Found: 358.0436.

4.2.6. Ethyl 4-[2-iodo-1-(4-methoxyphenyl)ethoxy]but-2-enoate (1f). Obtained in 56% as colorless oil: IR (KBr) cm^{-1}: 1717. ^{1}H NMR ($CDCl_3$) δ: 1.30 (t, 3H, J=7.0 Hz), 3.31 (dd, 1H, J=10.0, 5.0 Hz), 3.39 (dd, 1H, J=10.0, 8.5 Hz), 3.82 (s, 3H), 3.96–4.12 (m, 2H), 4.21 (q, 2H, J=7.0 Hz), 4.43 (dd, 1H, J=8.5, 4.5 Hz), 6.19 (td, 1H, J=15.5, 2.0 Hz), 6.90 (d, 2H, J=8.5 Hz), 6.92 (td, 1H, J=15.5, 4.0 Hz), 7.23 (d, 2H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 10.3, 14.3, 55.3, 60.4, 67.5, 81.5, 114.2, 121.5, 127.8, 131.3, 143.8, 159.8, 166.3. HRMS (EI) calcd for $C_{15}H_{19}O_4I$ (M^+): 390.0328. Found: 390.0323.

4.2.7. 2-Iodo-1-phenyl-1-prop-2-enyloxyethane (1g).[21] Obtained in 14% as colorless oil: ^{1}H NMR ($CDCl_3$) δ: 3.30–3.42 (m, 2H), 3.85 (dd, 1H, J=12.5, 6.0 Hz), 3.99 (dd, 1H, J=12.5, 5.5 Hz), 4.48 (dd, 1H, J=8.0, 5.0 Hz), 5.20 (dd, 1H, J=10.0, 1.5 Hz), 5.29 (dd, 1H, J=17.0, 1.5 Hz), 5.88–5.94 (m, 1H), 7.30–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 10.6, 70.1, 80.9, 117.5, 126.6, 128.4, 128.7, 134.3, 140.0.

4.2.8. 6-Hex-2-enyloxy-5-iodooxane (1h). Obtained in 98% as colorless oil: ^{1}H NMR ($CDCl_3$) δ: 0.91 (t, 3H, J=7.0 Hz), 1.35–1.48 (m, 2H), 1.52–1.64 (m, 1H), 1.71–1.83 (m, 1H), 1.96–2.08 (m, 3H), 2.33–2.43 (m, 1H), 3.58 (ddd, 1H, J=11.0, 7.0, 3.5 Hz), 3.95–4.03 (m, 2H), 4.08–4.14 (m, 1H), 4.20 (dd, 1H, J=12.0, 5.5 Hz), 4.68 (d, 1H, J=5.5 Hz), 5.52–5.61 (m, 1H), 5.69–5.78 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 13.7, 22.1, 25.5, 29.5, 32.7, 34.3, 63.4, 68.9, 101.2, 125.4, 135.3. HRMS (FAB) calcd for $C_{11}H_{19}O_2NaI$ (M^++Na): 333.0327. Found: 333.0329.

4.2.9. 1-Butoxy-1-hex-2-enyloxy-2-iodoethane (1i). Obtained in 99% as colorless oil: ^{1}H NMR ($CDCl_3$) δ: 0.91 (t, 3H, J=7.5 Hz), 0.93 (t, 3H, J=7.5 Hz), 1.35–1.47 (m, 4H), 1.53–1.63 (m, 2H), 2.03 (td, 2H, J=7.0, 6.5 Hz), 3.23 (d, 2H, J=5.5 Hz), 3.48 (td, 1H, J=9.0, 6.5 Hz), 3.60 (td, 1H, J=9.0, 6.5 Hz), 4.00 (ddd, 1H, J=11.5, 6.5, 2.0 Hz), 4.10 (ddd, 1H, J=11.5, 6.5, 2.0 Hz), 4.64 (t, 1H, J=5.5 Hz), 5.53–5.60 (m, 1H), 5.68–5.75 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 5.5, 13.7, 13.9, 19.3, 22.2, 31.7, 34.3, 66.2, 67.4, 101.0, 125.7, 135.2. HRMS (FAB) calcd for $C_{12}H_{23}O_2NaI$ (M^++Na): 349.0640. Found: 349.0648.

4.2.10. *Z*-1-But-2-enyloxy-2-iodobenzene (1j).[22] Under nitrogen atmosphere, DEAD (40% solution in toluene, 2.16 ml, 4.77 mmol) was added to a mixture of 2-iodophenol (500 mg, 2.27 mmol), triphenylphosphine (1.25 g, 4.77 mmol) and crotyl alcohol (0.407 ml, 4.77 mmol) in dry THF (20 ml) and stirred at room temperature for 3 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silicagel using hexane/AcOEt (20:1) to give **1j** (615 mg, 99%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ: 1.76 (d, 3H, J=5.0 Hz), 4.52 (d, 2H, J=4.0 Hz), 5.70–5.94 (m, 2H), 6.71 (d, 1H, J=8.0 Hz), 6.87 (d, 1H, J=8.0 Hz), 7.24–7.30 (m, 1H), 7.77 (d, 1H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 17.9, 69.8, 86.8, 112.6, 122.5, 125.5, 129.3, 130.1, 139.5, 157.3. HRMS (EI) calcd for $C_{10}H_{11}OI$ (M^+): 273.9855. Found: 273.9830.

4.2.11. [2-Iodo-1-(4-methoxyphenyl)ethyl](methylsulfonyl)prop-2-enylamine (1k). Obtained in 34% as colorless oil: IR (KBr) cm^{-1}: 1329, 1150. ^{1}H NMR ($CDCl_3$) δ: 2.79 (s, 3H), 3.64 (dd, 1H, J=16.0, 7.0 Hz), 3.72–3.89 (m, 3H), 3.83 (s, 3H), 5.11 (t, 1H, J=8.0 Hz), 5.18–5.28 (m, 2H), 5.72–5.85 (m, 1H), 6.92 (d, 2H, J=8.5 Hz), 7.29 (d, 2H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 6.1, 41.1, 48.0, 55.3, 62.9, 114.1, 118.9, 127.8, 129.7, 134.7, 159.7. HRMS (EI) calcd for $C_{13}H_{18}NO_3SI$ (M^+): 395.0052. Found: 395.0066.

Anal. calcd for $C_{13}H_{18}NO_3SI$: C, 39.50; H, 4.59; N, 3.54. Found: C, 39.62; H, 4.54; N, 3.51.

4.2.12. [2-Iodo-1-(4-methoxyphenyl)ethyl][(4-methylphenyl)sulfonyl]prop-2-enylamine (1l). Obtained in 30% as colorless columnar crystals: mp 104–105°C: IR (KBr) cm^{-1}: 1336, 1159. ^1H NMR ($CDCl_3$) δ: 2.44 (s, 3H), 3.35 (dd, 1H, J=16.5, 8.0 Hz), 3.59–3.71 (m, 2H), 3.79 (s, 3H), 3.89 (dd, 1H, J=16.5, 4.0 Hz), 5.05 (d, 2H, J=12.0 Hz), 5.14 (dd, 1H, J=10.5, 5.5 Hz), 5.58–5.72 (m, 1H), 6.80 (d, 2H, J=8.5 Hz), 6.97 (d, 2H, J=8.5 Hz), 7.30 (d, 2H, J=8.0 Hz), 7.70 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 5.1, 21.6, 47.1, 55.2, 62.0, 113.8, 117.7, 126.8, 127.2, 129.7, 130.0, 135.8, 137.7, 143.5, 159.5. HRMS (EI) calcd for $C_{19}H_{22}NO_3SI$ (M^+): 471.0365. Found: 471.0377. Anal. calcd for $C_{19}H_{22}NO_3SI$: C, 48.41; H, 4.70; N, 2.97. Found: C, 48.32; H, 4.69; N, 2.95.

4.3. General procedure for the preparation of tetrahydrofuran 2a–g, j–l and pyrrolidine 2h, i using VA-061

VA-061 (37.6 mg, 0.15 mmol) was added to a solution of **1a–l** (0.30 mmol), CTAB (21.9 mg, 0.060 mmol) and aqueous EPHP (538 mg, 3.0 mmol; H_2O solution, 3 ml) in H_2O (3 ml) at room temperature. The reaction mixture was then stirred and heated to 80°C. The progress of the reaction was monitored by TLC. An additional amount of the initiator VA-061 (37.6 mg, 0.15 mmol) was added to the reaction mixture, when the reaction showed slow conversion. The reaction mixture was then extracted with AcOEt, and the organic layer was dried using Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silicagel using hexane/Et_2O (20:1–1:1) to give the products **2a–l** (64–99%).

4.3.1. 1-Methoxy-4-(4-methyl-2-oxolanyl)benzene (2a). Obtained in 98% as diastereomeric mixture. Further purification of the diastereomers using column chromatography was unsuccessful; colorless oil: ^1H NMR ($CDCl_3$) *trans*-**2a** δ: 1.09 (d, 3H, J=6.5 Hz), 1.86–2.01 (m, 2H), 2.37–2.54 (m, 1H), 3.44 (dd, 1H, J=8.0, 7.0 Hz), 3.79 (s, 3H), 4.20 (dd, 1H, J=8.0, 7.0 Hz), 4.97 (t, 1H, J=7.0 Hz), 6.86 (d, 2H, J=8.5 Hz), 7.24 (d, 2H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) *trans*-**2a** δ: 17.8, 33.3, 42.6, 55.3, 75.6, 79.8, 113.6, 126.8, 135.8, 158.7. ^1H NMR ($CDCl_3$) *cis*-**2a** δ: 1.10 (d, 3H, J=6.5 Hz), 1.38–1.49 (m, 1H), 2.37–2.54 (m, 2H), 3.56 (t, 1H, J=8.0 Hz), 3.79 (s, 3H), 4.06 (t, 1H, J=8.0 Hz), 4.85 (dd, 1H, J=10.0, 5.5 Hz), 6.86 (d, 2H, J=8.5 Hz), 7.24 (d, 2H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) *cis*-**2a** δ: 17.5, 34.9, 43.8, 55.3, 75.3, 81.4, 113.7, 127.0, 135.3, 158.8. HRMS (EI) calcd for $C_{12}H_{16}O_2$ (M^+): 192.1150. Found: 192.1166.

4.3.2. 4-(4-Ethyl-2-oxolanyl)-1-methoxybenzene (2b). Obtained in 88% as diastereomeric mixture. Further purification of the diastereomers using column chromatography was unsuccessful; colorless oil: ^1H NMR ($CDCl_3$) *trans*-**2b** δ: 0.93 (t, 3H, J=7.5 Hz), 1.40–1.50 (m, 2H), 1.93–1.99 (m, 2H), 2.19–2.47 (m, 1H), 3.50 (t, 1H, J=8.0 Hz), 3.79 (s, 3H), 4.21 (dd, 1H, J=8.0, 7.0 Hz), 4.93 (t, 1H, J=7.0 Hz), 6.86 (d, 2H, J=8.5 Hz), 7.27 (d, 2H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) *trans*-**2b** δ: 12.8, 26.4, 40.5, 40.8, 55.2, 73.9, 79.8, 113.6, 126.8, 135.9, 158.7. ^1H NMR ($CDCl_3$) *cis*-**2b** δ: 0.93 (t, 3H, J=7.5 Hz), 1.40–1.50 (m, 3H), 2.19–2.47 (m, 2H), 3.64 (t, 1H, J=7.5 Hz), 3.79 (s, 3H), 4.07 (t, 1H, J=8.0 Hz), 4.83 (dd, 1H, J=10.5, 5.5 Hz), 6.86 (d, 2H, J=8.5 Hz), 7.27 (d, 2H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) *cis*-**2b** δ: 12.9, 26.1, 41.7, 42.2, 55.2, 73.7, 81.2, 113.7, 127.0, 135.1, 158.8. HRMS (EI) calcd for $C_{13}H_{18}O_2$ (M^+): 206.1307. Found: 206.1309.

4.3.3. 1-Methoxy-4-[4-(methylethyl)-2-oxolanyl]benzene (2c). Obtained in 94% as diastereomeric mixture. Further purification of the diastereomers using column chromatography was unsuccessful; colorless oil: ^1H NMR ($CDCl_3$) *trans*-**2c** δ: 0.89–0.96 (m, 6H), 1.41–1.60 (m, 1H), 1.93–2.20 (m, 3H), 3.52 (t, 1H, J=8.5 Hz), 3.80 (s, 3H), 4.21 (t, 1H, J=7.0 Hz), 4.96 (t, 1H, J=6.0 Hz), 6.87 (d, 2H, J=8.5 Hz), 7.24 (d, 2H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) *trans*-**2c** δ: 21.6, 31.7, 39.1, 46.3, 55.2, 73.0, 80.2, 113.6, 126.7, 136.1, 158.6. ^1H NMR ($CDCl_3$) *cis*-**2c** δ: 0.89–0.96 (m, 6H), 1.41–1.60 (m, 2H), 1.93–2.20 (m, 1H), 2.31–2.40 (m, 1H), 3.71 (t, 1H, J=8.5 Hz), 3.80 (s, 3H), 4.08 (t, 1H, J=8.0 Hz), 4.84 (dd, 1H, J=10.5, 5.5 Hz), 6.87 (d, 2H, J=8.5 Hz), 7.24 (d, 2H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) *cis*-**2c** δ: 21.5, 32.1, 40.6, 48.1, 55.2, 72.7, 81.5, 113.7, 126.9, 135.1, 158.8. HRMS (EI) calcd for $C_{14}H_{20}O_2$ (M^+): 220.1463. Found: 220.1463.

4.3.4. 1-Methoxy-4-(4,4-dimethyl-2-oxolanyl)benzene (2d). Obtained in 86% as colorless oil: ^1H NMR ($CDCl_3$) δ: 1.14 (s, 3H), 1.19 (s, 3H), 1.67 (dd, 1H, J=12.5, 9.5 Hz), 2.07 (dd, 1H, J=12.5, 6.5 Hz), 3.63 (d, 1H, J=8.0 Hz), 3.74 (d, 1H, J=8.0 Hz), 3.79 (s, 3H), 4.98 (dd, 1H, J=9.5, 6.5 Hz), 6.87 (d, 2H, J=7.0 Hz), 7.27 (d, 2H, J=7.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 26.5, 26.7, 40.1, 49.7, 55.2, 80.5, 80.8, 113.7, 126.9, 135.6, 158.7. HRMS (EI) calcd for $C_{13}H_{18}O_2$ (M^+): 206.1307. Found: 206.1316.

4.3.5. 1-Methoxy-4-(7-oxabicyclo[4.3.0]non-8-yl)benzene (2e). Obtained in 94% as diastereomeric mixture. Further purification of the diastereomers using column chromatography was unsuccessful; colorless oil: ^1H NMR ($CDCl_3$) *endo*-**2e** δ: 1.22–1.79 (m, 7H), 1.86–2.30 (m, 4H), 3.80 (s, 3H), 4.23 (d, 1H, J=3.5 Hz), 5.13 (t, 1H, J=7.5 Hz), 6.84–6.89 (m, 2H), 7.24–7.33 (m, 2H). ^1H NMR ($CDCl_3$) *exo*-**2e** δ: 1.22–1.79 (m, 8H), 1.86–2.30 (m, 2H), 2.33–2.42 (m, 1H), 3.80 (s, 3H), 3.99 (d, 1H, J=5.0 Hz), 4.90 (t, 1H, J=7.5 Hz), 6.84–6.89 (m, 2H), 7.24–7.33 (m, 2H). ^{13}C NMR ($CDCl_3$) *endo*+*exo*-**2e** δ: 20.5, 21.5, 23.8, 24.1, 27.3, 28.5, 28.6, 28.9, 38.1, 38.7, 40.4, 41.9, 55.2, 77.8, 78.5, 79.3, 113.6, 113.7, 126.7, 126.9, 136.3, 137.3, 158.5, 158.6. HRMS (EI) calcd for $C_{15}H_{20}O_2$ (M^+): 232.1463. Found: 232.1465.

4.3.6. Ethyl 2-[4-(4-methoxyphenyl)-3-oxolanyl]acetate (2f). Obtained in 96% as diastereomeric mixture. Further purification of the diastereomers using column chromatography was unsuccessful; colorless oil: IR (KBr) cm^{-1}: 1732. ^1H NMR ($CDCl_3$) *trans*-**2f** δ: 1.26 (t, 3H, J=7.0 Hz), 1.97–2.12 (m, 2H), 2.45–2.56 (m, 2H), 2.72–2.85 (m, 1H), 3.55 (dd, 1H, J=8.5, 7.0 Hz), 3.79 (s, 3H), 4.14 (q, 2H, J=7.0 Hz), 4.28 (dd, 1H, J=8.5, 7.0 Hz), 4.94 (t, 1H, J=7.0 Hz), 6.87 (d, 2H, J=8.5 Hz), 7.24 (d, 2H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) *trans*-**2f** δ: 14.2, 35.4, 37.8, 40.2, 55.2,

60.5, 73.5, 79.6, 113.7, 126.8, 135.0, 158.8, 172.3. ^{1}H NMR ($CDCl_3$) *cis*-**2f** δ: 1.26 (t, 3H, J=7.0 Hz), 1.43–1.55 (m, 1H), 2.45–2.56 (m, 3H), 2.72–2.85 (m, 1H), 3.68–3.74 (m, 1H), 3.79 (s, 3H), 4.10–4.18 (m, 1H), 4.14 (q, 2H, J=7.0 Hz), 4.84 (dd, 1H, J=6.5, 6.0 Hz), 6.87 (d, 2H, J=8.5 Hz), 7.24 (d, 2H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) *cis*-**2f** δ: 14.2, 36.4, 38.1, 41.3, 55.2, 60.5, 73.1, 80.9, 113.7, 127.0, 135.0, 158.8, 172.3. HRMS (EI) calcd for $C_{15}H_{20}O_4$ (M^+): 264.1361. Found: 264.1368.

4.3.7. 3-Methyl-5-phenyloxolane (2g).[23] Obtained in 87% as diastereomeric mixture. Further purification of the diastereomers using column chromatography was unsuccessful; colorless oil: ^{1}H NMR ($CDCl_3$) *trans*-**2g** δ: 1.09 (d, 3H, J=7.0 Hz), 1.90–2.05 (m, 2H), 2.37–2.49 (m, 1H), 3.47 (dd, 1H, J=8.0, 7.0 Hz), 4.22 (dd, 1H, J=8.0, 7.0 Hz), 5.03 (t, 1H, J=7.0 Hz), 7.20–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) *trans*-**2g** δ: 17.7, 33.2, 42.6, 75.7, 80.0, 125.5, 127.0, 128.2, 154.1. ^{1}H NMR ($CDCl_3$) *cis*-**2g** δ: 1.09 (d, 3H, J=7.0 Hz), 1.45 (dd, 1H, J=9.5, 2.0 Hz), 2.40–2.55 (m, 2H), 3.58 (t, 1H, J=8.0 Hz), 4.09 (t, 1H, J=8.0 Hz), 4.92 (dd, 1H, J=9.5, 6.0 Hz), 7.20–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) *cis*-**2g** δ: 17.3, 35.0, 43.9, 75.4, 81.6, 125.9, 127.0, 128.3, 154.1.

4.3.8. 7-Butyl-2,9-dioxabicyclo[4.3.0]nonane (2h). Obtained in 98% as diastereomeric mixture. Further purification of the diastereomers using column chromatography was unsuccessful; colorless oil: ^{1}H NMR ($CDCl_3$) *endo*-**2h** δ: 0.90 (t, 3H, J=7.0 Hz), 1.10–1.50 (m, 6H), 1.50–1.99 (m, 5H), 2.20–2.39 (m, 1H), 3.38–3.56 (m, 1H), 3.57–3.79 (m, 2H), 3.94 (t, 1H, J=8.0 Hz), 5.28 (d, 1H, J=3.0 Hz). ^{13}C NMR ($CDCl_3$) *endo*-**2h** δ: 14.0, 19.2, 22.9, 23.3, 26.7, 30.5, 36.5, 41.0, 61.0, 70.2, 102.1. ^{1}H NMR ($CDCl_3$) *exo*-**2h** δ: 0.90 (t, 3H, J=7.0 Hz), 1.10–1.50 (m, 6H), 1.50–1.99 (m, 5H), 2.20–2.39 (m, 1H), 3.38–3.56 (m, 1H), 3.57–3.79 (m, 1H), 3.82–3.92 (m, 1H), 4.28 (t, 1H, J=8.0 Hz), 4.99 (d, 1H, J=3.0 Hz). ^{13}C NMR ($CDCl_3$) *exo*-**2h** δ: 14.0, 20.8, 22.4, 22.9, 30.8, 32.4, 37.8, 44.2, 64.5, 74.3, 102.2. HRMS (FAB) calcd for $C_{14}H_{20}O_2$ (M^++H): 185.1542. Found: 185.1525.

4.3.9. 3-Butyl-5-butoxyoxolane (2i).[24] Obtained in 99% as diastereomeric mixture. Further purification of the diastereomers using column chromatography was unsuccessful; colorless oil: ^{1}H NMR ($CDCl_3$) *trans*-**2i** δ: 0.89 (t, 3H, J=7.5 Hz), 0.92 (t, 3H, J=7.5 Hz), 1.21–1.60 (m, 11H), 1.98–2.45 (m, 2H), 3.31–3.47 (m, 2H), 3.62–3.71 (m, 1H), 3.94 (t, 1H, J=7.5 Hz), 5.10 (dd, 1H, J=5.5, 3.0 Hz). ^{13}C NMR ($CDCl_3$) *trans*-**2i** δ: 13.9, 14.0, 19.4, 22.8, 30.9, 31.9, 32.8, 38.6, 39.1, 67.5, 71.9, 104.5. ^{1}H NMR ($CDCl_3$) *cis*-**2i** δ: 0.89 (t, 3H, J=7.5 Hz), 0.92 (t, 3H, J=7.5 Hz), 1.21–1.60 (m, 11H), 1.98–2.45 (m, 2H), 3.31–3.47 (m, 2H), 3.62–3.71 (m, 1H), 4.04 (t, 1H, J=8.0 Hz), 5.10 (dd, 1H, J=5.5, 3.0 Hz). ^{13}C NMR ($CDCl_3$) *cis*-**2i** δ: 13.9, 14.0, 19.4, 22.8, 30.7, 31.8, 33.7, 37.0, 39.3, 67.0, 72.6, 104.1.

4.3.10. 3-Ethyloxaindane (2j).[22] Obtained in 64% as colorless oil: ^{1}H NMR ($CDCl_3$) δ: 0.99 (t, 3H, J=7.5 Hz), 1.56–1.69 (m, 1H), 1.75–1.86 (m, 1H), 3.33–3.43 (m, 1H), 4.23 (dd, 1H, J=9.0, 6.5 Hz), 4.64 (t, 1H, J=9.0 Hz), 6.78–6.89 (m, 2H), 7.10–7.19 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 11.4, 27.6, 43.3, 76.5, 109.4, 120.2, 124.3, 128.0, 130.9, 159.9.

4.3.11. 1-(Methylsulfonyl)-4-methyl-2-(4-methoxyphenyl)pyrrolidine (2k). Obtained in 98% as diastereomeric mixture. Further purification of the diastereomers using column chromatography was unsuccessful; colorless needles: mp 105–106°C: IR (KBr) cm^{-1}: 1337, 1149. ^{1}H NMR ($CDCl_3$) *cis*-**2k** δ: 1.08 (d, 3H, J=6.5 Hz), 1.55–1.67 (m, 1H), 2.24–2.38 (m, 1H), 2.44–2.58 (m, 1H), 2.54 (s, 3H), 3.04 (t, 1H, J=10.5 Hz), 3.80 (s, 3H), 3.97 (dd, 1H, J=10.5, 8.5 Hz), 4.77 (dd, 1H, J=10.0, 7.0 Hz), 6.88 (d, 2H, J=8.5 Hz), 7.28 (d, 2H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) *cis*-**2k** δ: 16.4, 33.8, 39.2, 45.7, 55.2, 55.8, 63.9, 114.0, 128.0, 134.2, 159.0. ^{1}H NMR ($CDCl_3$) *trans*-**2k** δ: 1.09 (d, 3H, J=6.5 Hz), 1.96–2.05 (m, 2H), 2.44–2.58 (m, 1H), 2.67 (s, 3H), 3.15 (t, 1H, J=9.0 Hz), 3.70 (dd, 1H, J=9.0, 6.5 Hz), 3.80 (s, 3H), 4.90 (dd, 1H, J=6.5, 4.5 Hz), 6.88 (d, 2H, J=8.5 Hz), 7.28 (d, 2H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$) *trans*-**2k** δ: 17.1, 31.7, 38.1, 43.8, 55.2, 55.5, 62.3, 113.9, 127.4, 134.9, 158.8. HRMS (EI) calcd for $C_{13}H_{19}NO_3S$ (M^+): 269.1085. Found: 269.1091. Anal. calcd for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20; S, 11.90. Found: C, 57.74; H, 6.96; N, 5.14; S, 11.80.

4.3.12. 4-Methyl-1-[(4-methylphenyl)sulfonyl]-2-(4-methoxyphenyl)pyrrolidine (2l). Obtained in 88% as diastereomeric mixture. Further purification of the diastereomers using column chromatography was unsuccessful; colorless needles: mp 103–104°C: IR (KBr) cm^{-1}: 1346, 1159. ^{1}H NMR ($CDCl_3$) *cis*-**2l** δ: 0.95 (d, 3H, J=6.5 Hz), 1.41–1.52 (m, 1H), 1.77–1.87 (m, 1H), 2.29–2.36 (m, 1H), 2.41 (s, 3H), 3.07 (t, 1H, J=11.0 Hz), 3.78–3.84 (m, 1H), 3.79 (s, 3H), 4.58 (dd, 1H, J=9.5, 7.0 Hz), 6.81 (d, 2H, J=8.0 Hz), 7.22 (d, 2H, J=8.0 Hz), 7.24 (d, 2H, J=8.0 Hz), 7.59 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) *cis*-**2l** δ: 16.5, 21.5, 33.2, 45.6, 55.3, 56.6, 64.2, 113.7, 127.4, 127.5, 129.5, 135.0, 135.7, 143.1, 158.7. ^{1}H NMR ($CDCl_3$) *trans*-**2l** δ: 0.87 (d, 3H, J=6.5 Hz), 1.48–1.60 (m, 1H), 1.77–1.87 (m, 1H), 2.29–2.36 (m, 1H), 2.42 (s, 3H), 2.85 (t, 1H, J=9.0 Hz), 3.72 (dd, 1H, J=9.0, 7.0 Hz), 3.79 (s, 3H), 4.79 (dd, 1H, J=8.0, 2.5 Hz), 6.83 (d, 2H, J=8.0 Hz), 7.22 (d, 2H, J=8.0 Hz), 7.28 (d, 2H, J=8.0 Hz), 7.66 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$) *trans*-**2l** δ: 16.9, 21.5, 31.3, 43.5, 55.3, 55.8, 62.7, 113.6, 127.2, 127.5, 129.5, 135.0, 135.5, 143.2, 158.6. HRMS (EI) calcd for $C_{19}H_{23}NO_3S$ (M^+): 345.1398. Found: 345.1396. Anal. calcd for $C_{19}H_{23}NO_3S$: C, 66.06; H, 6.71; N, 4.05; S, 9.28. Found: C, 66.06; H, 6.72; N, 4.00; S, 9.21.

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