Regioselectivity Control of the Ring Opening of Epoxides With Sodium Azide in a Microreactor

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The reaction of different types of aromatic and aliphatic epoxides with sodium azide to give vicinal azido alcohols was studied in a microreactor with and without pillars in the channels. Dependent on the substrate, the regioselectivity of the ring opening is affected by the used solvent system, viz. acetonitrile–water (sometimes with 10% acetic acid to promote the reactivity of substrates) or *t*-butyl acetate–water containing Tween80 as a surfactant. For styrene oxide and α -methylstyrene oxide, the α/β regioselectivity changes from 4 to 10 and 1.7 to 6.2, respectively, going from acetonitrile–water to Tween80-containing *t*-butyl acetate–water. The addition of a surfactant (Tween80) stabilizes the interface in the biphasic *t*-butyl acetate–water. Pillar-containing microreactors gave better conversions than microreactors without pillars and lab scale reactions, probably due to better mixing.

Keywords: microreactors, epoxides, regioselectivity, 1,2-azido alcohols, surfactants

1. Introduction

Vicinal azido alcohols are versatile compounds in organic synthesis [1] because they not only constitute as components of biologically active natural products but also serve as important precursors in the synthesis of amino sugars [2], carboxylic nucleosides [3], lactams [4], oxazolines [5], and amino alcohols [6]. The method most employed to prepare 1,2-azido alcohols is azidolysis of the corresponding epoxides (Scheme 1) [7]. It uses aqueous solutions of sodium azide (NaN_3) and ammonium chloride (NH_4Cl) or organic media with trimethylsilyl azide as the azide source. However, it generally requires long reaction times (12–48 h), and the formation of an azidohydrin is often accompanied by diol formation, toxic HN_3 formation in strong acidic medium, and lack of regioselectivity. To overcome some of these hurdles, a number of improved methodologies have been developed for the azidolysis of epoxides using Lewis acids [8], controlling the pH of the reaction medium (pH 4.2 and 9.5 give rise to a different regioselectivity) [9], phase transfer catalysts [10], and transition and lanthanoid metal catalysts [11].

Though the above mentioned methods have their own advantages, many of these procedures suffer from one or more of the limitations such as longer reaction times, strongly acidic conditions, unsatisfactory yields, expensive catalysts, and lack of regioselectivity. Therefore, there is a need and challenge to develop alternative mild and effective methods for the synthesis of 1,2-azido alcohols.

The ring opening of epoxides with azides follows an $\text{S}_{\text{N}}2$ mechanism under neutral or basic conditions [12]. Generally, when there are no electronic effects induced by the substituents, the azide ion prefers to attack the less substituted carbon atom of the epoxide. However, in the presence of an aromatic ring as the substituent, electronic effects operate to direct the incoming azide group more to the benzylic position because the positive charge at the benzylic carbon is stabilized by resonance with the aromatic ring. Under acidic conditions, the oxygen of the epoxide is protonated [9], developing more positive charge on the epoxide carbon bearing more substituents, to which azide attack is enhanced. In general, the presence of a Lewis acid has the same effect enhancing the reaction.

Microreactors are evolving as a promising tool to perform organic reactions [13] [14] [15]. It provides numerous advantages

Scheme 1. Ring opening reaction of epoxides with azide

like, very large surface area-to-volume ratio, rapid heat and mass transfer, which in turn influence the reaction time and yield. The small dimensions of the microchannels result in a short radial diffusion time with better mixing than in the conventional system [16]. In addition, it is very safe to carry out reactions with toxic substances [17], and for multiphase reactions, the interfacial interaction can be controlled using different flow regimes.

Using a microreactor as a useful reaction platform, in the present work, we performed the ring opening reaction of epoxides using NaN_3 as an inexpensive azide source to form 1,2-azido alcohols, in a continuous flow glass microreactor with and without pillars under different conditions (homogeneous solvent mixture, biphasic solvent mixture with a surfactant, presence of acid, and varying temperature) to study the effect on the reaction time, the regioselectivity (α/β), and the formation of side product (diol).

2. Results and Discussion

Using styrene oxide as a model substrate (Scheme 2), optimization reactions were carried out to investigate the influence of the solvent system, a surfactant, Lewis acids, temperature, and the presence/absence of pillars in the microreactor. The classical protocol [18] for the ring opening of epoxides by azides described by Caron and Sharpless uses $\text{MeOH}/\text{H}_2\text{O}$ (8:1) as solvent medium, 5 equiv. of NaN_3 , and 2.2 equiv. of NH_4Cl , resulting in a heterogeneous reaction mixture. However,

Scheme 2. Ring opening of styrene oxide with sodium azide

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Figure 1. Ring opening of styrene oxide by NaN_3 using 1:1 ACN– H_2O . Reaction conditions: Syringe 1: A= NaN_3 , B= NH_4Cl in water. Syringe 2: styrene oxide (C) in ACN. Flow rates of aqueous and organic phases are equal. The lines in the figure corresponds to (---) 2.5 M (A), 1.1 M (B), and 0.5 M (C); (····) 1.25 M (A), 1.1 M (B), and 0.5 M (C); (—◆—) 0.625 M (A), 0.55 M (B), and 0.5 M (C)

in microreactors, in order to avoid clogging of the microchannels, a homogeneous reaction mixture is preferred.

2.1. Acetonitrile–Water Solvent Medium. A microreactor with pillars in the microchannels to induce very effective mixing was used to carry out the ring opening reaction of styrene oxide using sodium azide. Among different alcohol–water and acetonitrile–water (ACN– H_2O) solvent mixtures, the latter gave a homogeneous reaction mixture. Using 1:1 ACN– H_2O , the ring opening of styrene oxide gave conversions close to 90 % and a regioselectivity (α/β) of around 4 in 29 min. Figure 1 shows that using 0.625 M NaN_3 and 0.55 M NH_4Cl , conversions close to 75% ($\alpha/\beta=4$) were obtained for a reaction time of 29 min at 75 °C. Doubling the concentration of NaN_3 from 0.625 M to 1.25 M enhances the conversion (89%), but the regioselectivity ($\alpha/\beta=4$) remains the same. Increasing the concentration of NaN_3 from 1.25 M to 2.5 M, and the concentration of NH_4Cl from 0.55 M to 1.1 M, does not influence the conversion. However, there is a marginal increase in the regioselectivity, which is ascribed to the change in NH_4Cl concentration from 0.55 M to 1.1 M. NH_4Cl coordinates to the epoxide [19] and thereby favors the regioselective attack at the α -position of the styrene oxide. At high salt concentrations (2.5 M NaN_3 and 0.55 M NH_4Cl) over a period of 5 h, the salts deposit on the walls of the channels, clogging the microreactor.

Furthermore, upon addition of acetic acid (10%) to the water phase of 1:1 ACN– H_2O , the regioselectivity (α/β) increased to 6 with nearly the same conversions (86%). The increased regioselectivity is attributed to protonation of the epoxide, favoring the azide to preferentially attack the α -carbon of the styrene oxide. So far, the flow rates of aqueous and organic phases are equal. Applying differential flow rates of the aqueous and organic phases of ACN– H_2O showed that higher flow rates of aqueous to organic phase (5:1) resulted in a higher regioselectivity ($\alpha/\beta=7$) and fast conversions (94%) in around 4 min of residence time, compared to equal flow rates. The increase in the conversions may be ascribed to the availability of the huge excess (12.5 equivalents) of azide. The reason for the increase in the regioselectivity may be attributed to the change in the polarity of the reaction mixture. The conversions and regioselectivity gradually decrease upon decreasing the ratio of the flow rates of aqueous and organic phases.

2.2. Influence of Process Conditions in the ACN– H_2O System. In order to demonstrate the efficiency of the use of a microreactor over lab scale, the ring opening reaction of styrene oxide was carried out both in a microreactor and at lab scale in

ACN– H_2O under identical conditions (Figure S1, supporting information). The conversions in a microreactor (89%) are slightly better than those at lab scale (78%) in ACN– H_2O , owing to the homogeneous reaction mixture present at 75 °C, while the regioselectivity remained the same [20].

The temperature influence was investigated using ACN– H_2O (Figure S2, supporting information). Upon slowly decreasing the temperature from 75 °C to 40 °C, for a residence time of 29 min, the conversions gradually decreased from 89% to 21%, while the regioselectivity (α/β) steadily increased from 4 to 8.5.

Compared to a microreactor without pillars, the presence of pillars in a microreactor gave rise to higher conversions for ACN– H_2O (increase from 76% to 89% for 29-min residence time) under identical conditions (Figure S3, supporting information). Fluorescence images of the reaction mixture were taken using anthracene dye (5 μM) in the organic phase, to monitor the interaction of aqueous and organic phases in a microreactor with and without pillars (Figure 2). In case of a microreactor with pillars using ACN–water, a small slug is formed from time to time (Figure 2a). A microreactor without pillars using ACN– H_2O displays slug formation in the beginning of the channels. The slugs gradually decrease in size resulting in a homogeneous phase (Figure 2b). Because of the better mixing and a homogeneous reaction mixture obtained in a microreactor with pillars, it gives higher conversions than in one without pillars using ACN– H_2O .

2.3. *t*-Butyl Acetate–Water Solvent Medium. Using immiscible solvents as aqueous and organic phases in flow conditions mostly results in a segmented (slug) flow. Upon formation of slugs, an internal fluid vortex is generated, resulting in rapid mixing within a slug by continuously refreshing the diffusion interface [21]. In order to study the influence of these conditions

Figure 2. Fluorescence images of ACN– H_2O in microreactors with and without pillars. a) ACN– H_2O with pillars, b) ACN– H_2O without pillars. Flow rates of aqueous and organic phases are equal

Figure 3. Ring opening of styrene oxide by NaN_3 using 1:1 $t\text{-BuOAc-H}_2\text{O}$. Reaction conditions: Syringe 1: 1.25 M NaN_3 , 0.55 M NH_4Cl , Tween80 (v/v) in water. Syringe 2: 0.5 M styrene oxide in $t\text{-BuOAc}$. Flow rates of aqueous and organic phases are equal. The lines in the figure correspond to varying amounts of Tween80 in water (·····)—nil, (---□---)—12 $\mu\text{L/mL}$, (---◇---)—60 $\mu\text{L/mL}$, (---△---)—100 $\mu\text{L/mL}$, (····◇····)—150 $\mu\text{L/mL}$, and (····□····)—200 $\mu\text{L/mL}$.

on the regioselectivity and the conversion, $t\text{-butyl acetate-water}$ ($t\text{-BuOAc-H}_2\text{O}$) was used as the reaction medium. Although the conversions (27% in 29 min) are poor, the regioselectivity (α/β) has increased from 4 to 9.5, which is more than a two-fold rise in regioselectivity compared to $\text{ACN-H}_2\text{O}$ (Figure 3).

In order to enhance the interfacial interaction between the two phases, the influence of surfactants was studied. Using ionic surfactants like dodecyltrimethylammonium bromide (DTAB) and sodium dodecyl sulfate (SDS) in the aqueous phase containing NaN_3 and NH_4Cl resulted in the formation of a precipitate. However, Tween80 as a neutral surfactant in $t\text{-BuOAc-H}_2\text{O}$ gave rise to a higher conversion with good regioselectivity. Upon varying the Tween80 concentration from 12 to 200 $\mu\text{L/mL}$ of aqueous phase, the conversions increased until the concentration of Tween80 reached 100 $\mu\text{L/mL}$ beyond which it declined. The regioselectivity (α/β) showed slight variations (from 11 to 9) upon increasing the surfactant concentration from 12 to 200 $\mu\text{L/mL}$ of Tween80 (Figure 3). The small changes in the regioselectivity may be ascribed to a small change in the polarity at the interface of aqueous and organic phases [22]. Fluorescence images of the reaction mixture were taken using anthracene dye (5 μM) in the organic phase in order to monitor the interaction of aqueous and organic phases (Figure 4). A fine dispersion (a sort of micro-emulsion) of aqueous and organic phases was observed at 100 $\mu\text{L/mL}$ of Tween80, resulting in a maximum conversion of 49% and a regioselectivity (α/β) of 10 (Figure 4b). However, using Tween80, 12 (Figure 4a), 60, 150, and 200 (Figure 4c) $\mu\text{L/mL}$ of aqueous phase showed the formation of aqueous and organic phase slugs of different sizes.

2.4. Influence of Process Conditions in the $t\text{-BuOAc-H}_2\text{O}$ System. The ring opening reaction of styrene oxide was carried out both in a microreactor and at lab scale in $t\text{-BuOAc-H}_2\text{O}$ under identical conditions (Figure S1, supporting information). The conversions in a microreactor are better than those at lab scale in $t\text{-BuOAc-H}_2\text{O}$, while the regioselectivity remained the same. However, the conversions at lab scale depend on the stirring speed, with good conversions at higher rates on account of the better mixing of aqueous and organic phase. However, the conversions obtained in a microreactor (49%) are still better than at lab scale (40%) demonstrating the efficient mixing in a microreactor with pillars [23].

Compared to a microreactor without pillars, the presence of pillars in a microreactor gave rise to higher conversions for $t\text{-BuOAc-H}_2\text{O}$ with Tween80 (increase from 20% to 49% for 29-min residence time), and the regioselectivity remained the same (Figure S3, supporting information). Using $t\text{-BuOAc-H}_2\text{O}$ having 100 $\mu\text{L/mL}$ of Tween80 in the aqueous phase, a microreactor with pillars shows a fine dispersion as mentioned before. However, under the same conditions in a microreactor without pillars bilayer formation is observed in the beginning of the channels. The bilayers gradually transform into slugs and continue as slugs throughout the channels (Figure 4d). The interfacial interaction between the two immiscible phases of $t\text{-BuOAc-H}_2\text{O}$ having Tween80 in the aqueous phase is considerably enhanced by the presence of pillars, which eventually results in higher conversions than using a microreactor without pillars.

2.5. Substrate Scope. The optimized reaction conditions for styrene oxide as the model substrate, namely 0.5 M substrate in

Figure 4. Fluorescence images of $t\text{-BuOAc-H}_2\text{O}$ with Tween80 in the aqueous phase: a) 12 $\mu\text{L/mL}$, b) 100 $\mu\text{L/mL}$, c) 200 $\mu\text{L/mL}$ with pillars in a microreactor, d) 100 $\mu\text{L/mL}$ without pillars in a microreactor. Flow rates of aqueous and organic phases are equal. 5 μM anthracene was added to the organic phase

Table 1. Ring opening of styrene oxide derivatives by NaN_3 under different conditions

Entry	Epoxide ^a	Solvent system	Conversion (%)	Azido-alcohol (%)	Diol (%)	Regioselectivity
1[1]		ACN–H ₂ O ^b	89	89	–	4 (α/β)
		ACN–H ₂ O ^d (10% AcOH in water)	86	86	–	6 (α/β)
		<i>t</i> -BuOAc–H ₂ O ^c	49	49	–	10 (α/β)
2[24]		ACN–H ₂ O ^b	96	93	3	β Isomer traces
		ACN–H ₂ O ^d (10% AcOH in water)	95 ^e	43	41	12 (α/β)
		<i>t</i> -BuOAc–H ₂ O ^c	43	43	–	β Isomer traces
3[25]		ACN–H ₂ O ^b	70	61	9	1.7 (α/β)
		ACN–H ₂ O ^d (10% AcOH in water)	93	43	50	β Isomer traces
		<i>t</i> -BuOAc–H ₂ O ^c	17	16	–	6.5 (α/β)
4[26]		ACN–H ₂ O ^b	41	41	–	β Isomer traces
		ACN–H ₂ O ^d (10% AcOH in water)	41	38	3	β Isomer traces
		<i>t</i> -BuOAc–H ₂ O ^c	12	12	–	β Isomer traces

^a Reaction conditions: Syringe 1: ^b NaN_3 (1.25 M) and NH_4Cl (0.55 M) in H_2O ; ^c NaN_3 (1.25 M), NH_4Cl (0.55 M) and Tween80 (100 $\mu\text{L}/\text{mL}$) in H_2O ; ^d NaN_3 (1.25 M), NH_4Cl (0.55 M) and 10% acetic acid in H_2O . Syringe 2: ^{b,c,d} Substrate (0.5 M) in the respective solvent. ^e Residence time is around 4 min. Reactions were carried out in a microreactor with pillars. Residence time: 29 min. Flow rates of aqueous and organic phases are equal. Traces mean that the formation is <2%.

the organic phase and 1.25 M NaN_3 and 0.55 M NH_4Cl in H_2O for all solvent systems, while in the case of *t*-BuOAc– H_2O also 100 $\mu\text{L}/\text{mL}$ Tween80 in water was present, were used to study the substrate scope starting with related compounds (Table 1). Tetrahydronaphtho-oxirene (Table 1, entry 2) is more reactive than styrene oxide because of the presence of strain from the additional 6-membered ring. It showed 96% conversion in ACN– H_2O giving preferentially the α -isomer along with diol (3%). The reaction is faster in ACN– H_2O with 10% acetic acid (AcOH) in the aqueous phase giving 95% conversion in around 4 min of residence time. However, the formation of diol is increased from 3 to 41%, while the regioselectivity ($\alpha/\beta=12$) is decreased. In the presence of AcOH, the epoxide ring is protonated, resulting into a highly reactive intermediate that is prone to the attack of both azide ion and water. α -Methylstyrene oxide (Table 1, entry 3) gave 70% conversion and a regioselectivity (α/β) of 1.7 along with diol (9%) using ACN–water. The poor regioselectivity may be attributed to the steric hindrance caused by the methyl group at the α -position of the styrene oxide for the attack of the azide ion. Using ACN– H_2O with 10% AcOH in the aqueous phase enhances the conversion to 93% and affords preferentially the α -isomer; however, diol is formed in a very high percentage (50%). In the presence of

AcOH, protonation of α -methylstyrene oxide takes place, generating a considerably more positive charge on the tertiary α -carbon atom, which is prone to the nucleophilic attack of both water and azide ion, resulting in a high percentage of diol. β -Methylstyrene oxide (Table 1, entry 4) provided 41% conversion, and the α -isomer is formed preferentially without any traces of diol formation using ACN– H_2O . Using ACN– H_2O with 10% AcOH in the aqueous phase, the conversions remained the same as before; however, the formation of diol (3%) is detected.

In case of *t*-BuOAc– H_2O with Tween80, the α -isomer was formed preferentially in all cases (Table 1, entries 1–4), and no diols were detected with GC. The lower conversions ($\leq 49\%$) may be ascribed to the less polar solvent medium and the absence of a homogeneous reaction mixture.

The substrate scope was extended studying different types of epoxides, viz. phenyl glycidyl ether, glycidyl methacrylate, 1-methylcyclohexene oxide, 1,2-epoxydodecane, 1,2-epoxy-9-decene; the results are summarized in Table 2. Phenyl glycidyl ether (Table 2, entry 1) gave a good conversion (80%) with predominantly β -isomer formation in ACN– H_2O . Using ACN– H_2O with 10% AcOH in the aqueous phase, the conversion increased to 87%; however, formation of diol (7%) was detected. Glycidyl methacrylate (Table 2, entry 2) exhibited good

Table 2. Ring opening of aliphatic epoxides by NaN_3 under different conditions

Entry	Epoxide ^a	Solvent system	Conversion (%)	Azido-alcohol (%)	Diol (%)	Regioselectivity
1[1]		ACN–H ₂ O ^b	80	80	–	α Isomer traces
		ACN–H ₂ O ^d (10% AcOH in water)	87	80	7	α Isomer traces
		<i>t</i> -BuOAc–H ₂ O ^c	13	13	–	α Isomer traces
2[10d]		ACN–H ₂ O ^b	85	82	3	α Isomer traces
		ACN–H ₂ O ^d (10% AcOH in water)	89	81	8	16 (β/α)
		<i>t</i> -BuOAc–H ₂ O ^c	40	40	–	α Isomer traces
3[1]		ACN–H ₂ O ^b	30	29	<1	1.5 (β/α)
		ACN–H ₂ O ^d (10% AcOH in water)	78	62	16	2.3 (α/β)
		<i>t</i> -BuOAc–H ₂ O ^c	11	11	–	1.5 (β/α)
4[27]		ACN–H ₂ O ^b	7	7	–	13 (β/α)
		ACN–H ₂ O ^d (10% AcOH in water)	7	6.5	<1	5 (β/α)
		<i>t</i> -BuOAc–H ₂ O ^c		ND		
5		ACN–H ₂ O	16	16	–	15 (β/α)
		ACN–H ₂ O (10% AcOH in water)	14	13.5	<1	5 (β/α)
		<i>t</i> -BuOAc–H ₂ O		Traces		NA

^{a,b,c,d,e} The notes mentioning the reaction conditions are the same as in Table 1. ND=not detected, NA=not applicable.

conversions using ACN–H₂O (85%) and ACN–H₂O with 10% AcOH in the aqueous phase (89%); however, the formation of diol increased from 3% to 8%, respectively. In case of 1-methylcyclohexene oxide (Table 2, entry 3), the conversion (30%) and regioselectivity ($\beta/\alpha=1.5$) are modest using ACN–H₂O, while using ACN–H₂O with 10% AcOH in the aqueous phase, good conversions (78%) were achieved; however, 16% diol was formed. The regioselectivity ($\alpha/\beta=2.3$) not only increased, but also reversed, which is due to the formation of significantly more positive charge at the tertiary α -carbon atom upon protonation of 1-methylcyclohexene oxide, that is more susceptible to the attack of the azide ion. Both 1,2-epoxydodecane and 1,2-epoxy-9-decene showed poor conversions, 7% and 16%, respectively, but with good regioselectivities (β/α) of 13 and 15, respectively, using ACN–H₂O. Apparently, the presences of long carbon chains make the substrates less reactive [25]. The conversions did not improve using ACN–H₂O with 10% AcOH in the aqueous phase, and the regioselectivity decreased compared to ACN–H₂O, which is ascribed to the fact that, upon protonation of the substrates (Table 2, entries 4 and 5), the azide ion prefers to attack the α -carbon.

Using *t*-BuOAc–H₂O with Tween80, the conversions are not impressive ($\leq 13\%$) for all epoxides in Table 2, except for glycidyl methacrylate (Table 2, entry 2) showing 40% conversion. The β -isomers are formed preferentially for all substrates, and no diol formation is detected.

The reactivity of aliphatic epoxides is poor under the optimized reaction conditions used above. To increase the conversions, different Lewis acids (LiBF₄, GaCl₃, BF₃·Et₂O, and CeCl₃·7H₂O) were explored in case of 1-methylcyclohexene oxide, but they either precipitated while preparing the samples or clogged the channels while running the microreactor. By varying the solvent to toluene–water, isopropyl alcohol–water, dioxane–water, DMSO–water, and DMF–water and increasing the temperature from 75 to 90 °C, it turned out that DMF–water and DMSO–water gave excellent conversions, while the regioselectivity (β/α) was around 2 (Table 3).

3. Conclusions

In conclusion, we have shown that, in general, the regioselectivity of the ring opening of epoxides becomes higher by changing the solvent from ACN–H₂O to *t*-BuOAc–H₂O containing Tween80 although, in the latter case, the conversions are lower. The presence of a surfactant stabilizes the interface in the biphasic system. To our best knowledge, the latter conditions involve the first example of azidolysis under biphasic circumstances. Addition of 10% AcOH to the aqueous phase of ACN–H₂O accelerates the reaction and enhances the attack of the azide group at the carbon atom bearing more substituents although, in most cases, accompanied with diol formation. In the case of the ring opening of 1-methylcyclohexene oxide, the regioselectivity is even reversed from ($\beta/\alpha=1.5$) to ($\alpha/\beta=2.3$).

Compared to lab scale, in general, there is a slight improvement in the conversion of the ring opening of epoxides in a microreactor with pillars, while the regioselectivity remains the

same. This study clearly demonstrated that a microreactor with pillars is a very useful vehicle to study not only biphasic reactions but also homogeneous reactions due to their intrinsically effective mixing.

4. Experimental section

4.1. Materials. The chemicals and solvents were purchased from Sigma Aldrich unless otherwise stated and were used without purification unless specified. Styrene oxide (97%) was purified by vacuum distillation, NaN₃ (BioXtra), NH₄Cl (99+%, Acros organics), *t*-butyl acetate (>99%), Tween® 80 (pure, Acros organics), acetic acid (>99%), and 1-methylcyclohexene oxide (>95%, TCI Europe); α -methylstyrene oxide (95%, ABCR chemicals) was purified by vacuum distillation, 1,2-dihydronaphthalene (98%), phenyl glycidyl ether (99%), glycidyl methacrylate (>97%), 1,2-epoxy-9-decene (96%), trans-1-phenyl-1-propene (>98%), 2-methyl-1-phenyl-1-propene (99%), LiBF₄ (98%), BF₃OEt₂ (36%), GaCl₃ (99.99% trace metals basis), and CeCl₃·7H₂O (99.9% trace metals basis); and water was purified with the Milli-Q pulse (Millipore, $R=18.2$ M Ω cm) ultra pure water system and acetonitrile (for analysis EMSURE® ACS, Reag. Ph Eur, Merck). Tetrahydronaphthalene-1,2-epoxide [22] and β -methylstyrene oxide [28] were synthesized according to literature procedures.

4.2. Methods. Analytical TLC was performed using Merck-prepared plates (silica gel 60 F-254 on aluminium). Column chromatography was carried out on Merck silica gel 60 (230–400 mesh). ¹H NMR and ¹³C NMR spectra were recorded on a Varian Unity INOVA (300 MHz) spectrometer. ¹H NMR chemical shift values (300 MHz) are reported as δ using the residual solvent signal as an internal standard (CDCl₃, δ 7.257). ¹³C NMR chemical shift values (75 MHz) are reported as δ using the residual solvent signal as an internal standard (CDCl₃, δ 77.0). All NMR spectra were recorded in CDCl₃. The electrospray ionization (positive mode) high-resolution mass spectrum was recorded on a WATERS LCT mass spectrometer. Gas chromatography (GC) samples were prepared by collecting a 40- μ L reaction mixture sample (20 μ L organic and 20 μ L aqueous), which was diluted to 80 μ L in a glass insert, with ACN for ACN–water and with *t*-BuOAc for *t*-BuOAc–water containing Tween80. One microliter samples of the organic layer of the reaction mixtures were injected onto an Agilent DB-5MS UI column (30 m $\times$ 0.32 mm i.d., 25 μ m film thickness) with a constant pressure of 11.9 psi. The oven temperature was held at 65 °C for 1 min and increased linearly at a rate of 10 °C/min to 250 °C with a final hold of 5 min. GC conversions were determined from the area under the curve of the peaks corresponding to epoxide and products. The peaks were identified by injecting the products, which were separately synthesized by lab scale experiments following literature procedures. The error bars in Figures 1 and 3 represent the standard deviation calculated over two measurements for each point. Fluorescence microscopy images were taken using an Olympus inverted research microscope IX71 equipped with a mercury burner U-RFL-T as light source and a digital Olympus DR70 camera for image acquisition. Violet excitation

Table 3. Ring opening of 1-methylcyclohexene oxide by NaN₃ in different solvent mixtures

Reaction conditions ^a	Temperature (°C)	Conversion (%)	Yield (%)	Diol (%)	Regioselectivity (β/α)
Toluene–water	90	16.5	16	<1	1.2
Isopropyl alcohol–water	80	55	53	1.7	1.8
Dioxane–water	85	57	55	1.6	1.6
DMF–water	90	96	93	3	2.1
DMSO–water	90	97	93.5	3.5	2.0

^a Reaction conditions: Syringe 1: NaN₃ (1.25 M) and NH₄Cl (0.55 M) in H₂O. Syringe 2: 1-methylcyclohexene oxide (0.5 M) in the respective solvent. Reactions were carried out in a microreactor with pillars. Residence time: 29 min. Flow rates of aqueous and organic phases are equal.

(λ_{ex} =315–380 nm) and blue emission (λ_{em} =430–490 nm) was filtered using the U-MWB5 Olympus filter. The fluorescence microscopy images were acquired at 75 °C.

4.3. 1-Azido-2-Hydroxy-9-Decene. To a solution of 1,2-epoxy-9-decene (771 mg, 5 mmol) in a mixture of MeOH (8 mL) and H₂O (1 mL), NH₄Cl (588 mg, 11 mmol) and NaN₃ (1.625 g, 25 mmol) were added. The resulting reaction mixture was heated at reflux overnight. The solution was cooled to room temperature, and the product was extracted with dichloromethane (3 × 50 mL) and washed with brine (2 × 75 mL). The combined organic layers were dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography using 7:3 ethyl acetate/hexane as eluent to afford the target compound as a colorless oil (91 %). ¹H NMR: δ 5.72–5.86 (m, 1 H, =CH), 5.01–4.91 (m, 2 H, =CH₂), 3.73 (br s, 1 H, CHOH), 3.35 (dd, 1 H, J =3 and 12 Hz, CHHN₃), 3.23 (dd, 1 H, J =6 and 12 Hz, CHHN₃), 2.0–2.06 (m, 2 H, CH₂), 1.32–1.46 (m, 10 H, CH₂ and CH₃); ¹³C NMR: δ 139.3, 114.4, 71.1, 57.3, 34.5, 33.9, 29.6, 29.2, 29.1, 25.6; HRMS (ESI): m/z 198.1355 [M+H]⁺, calculated for C₁₀H₁₉N₃O: 198.1528.

4.4. Flow Apparatus. In all microreactor experiments, the sample solutions were mobilized by means of a PHD 22/2000 series syringe pump (Harvard Apparatus, United Kingdom) equipped with 250- μ L flat tip syringes (Hamilton). Syringes were connected to fused silica capillaries (100 μ m i.d., 362 μ m o.d., Polymicro Technologies) by means of Upchurch Nanoport™ assembly parts (i.e., Nano-Tight™ unions and fittings, Upchurch Scientific Inc. USA). During the experiments, the microreactor was placed in a home-built chip holder designed for fitting fused silica fibers into the inlet/outlet chip reservoirs by means of commercially available Upchurch Nanoport™ assembly parts. The temperature in the microreactor was controlled by interfacing a thermoelectric module with a heat sink to the microreactor. The temperature variation on the glass surface of the microreactor measured with a thermocouple was $\leq \pm 0.1$ °C. A glass microreactor with pillars inside the microfluidic channels with a residual volume of 7.25 μ L was purchased from Micronit Microfluidics. It has dimensions of 645.6-mm length, 52- μ m depth, 254- μ m channel top width, and 150- μ m channel bottom width. A glass microreactor without pillars with the same dimensions has a residual volume of 7.85 μ L.

4.5. Microreactor Experiments. Two 250- μ L syringes, one with the aqueous solution and the other with the organic solution containing a substrate (for concentrations of the reagents, see the notes under Figures 1, 3 and Tables 1–3), were loaded onto the syringe pump and connected to the fused silica capillaries through a Nanoport assembly (using peek needle port, nanotight union, capillary tubing, nanotight nut and ferrule). The ends of the capillaries were connected to the inlets of a microreactor with or without pillars through a Nanoport assembly (using nut, steel compression ring, and ferrule). The outlet of the microreactor was again connected to the capillaries through a Nanoport assembly (using nut, steel compression ring, capillary tubing, and ferrule) and directed to a glass vial, where the reaction product was collected and analyzed offline using GC. The flow rates were varied from 1, 0.5, 0.25, to 0.125 μ L/min, which resulted in residence times of 3.625, 7.25, 14.5, and 29 min, respectively, using a microreactor with pillars. In

order to obtain the same residence times using a microreactor without pillars, the flow rates were increased to 1.08, 0.54, 0.27, and 0.135 μ L/min, respectively.

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Supporting information

Figures of the azidolysis of styrene oxide in *t*-BuOAc–H₂O using different Tween80 concentrations, under comparable microreactor and lab scale conditions, and in 1:1 ACN–H₂O at different temperatures.

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