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Synthesis of α-Arylated Cycloalkanones from Congested Trisubstituted Spiro-Epoxides: Application of the House-Meinwald Rearrangement for Ring Expansion.

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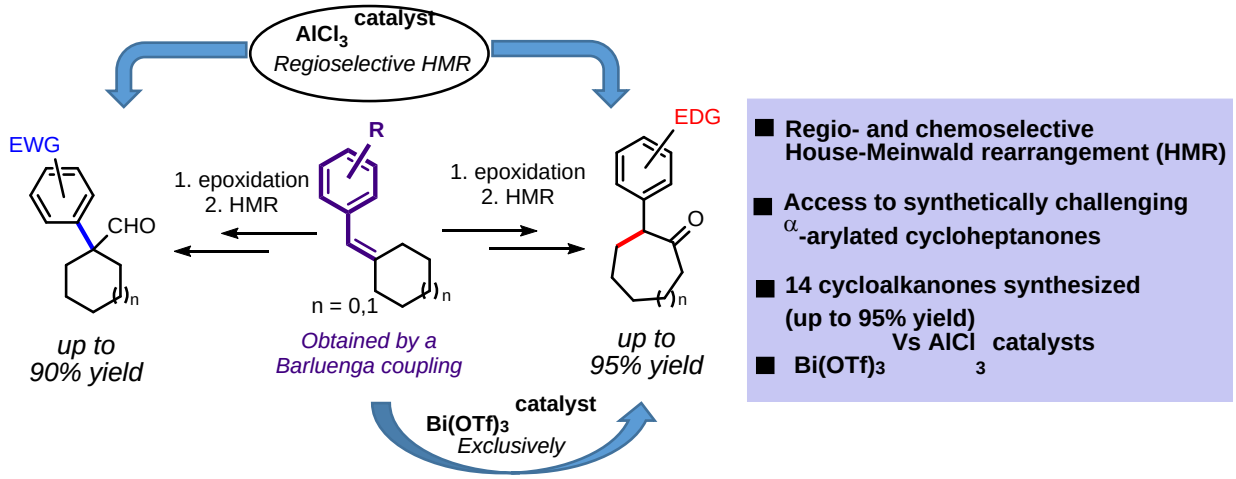
Dedicated to the memory of Professor Jerrold Meinwald (1927-2018), 2014 winner of the National Medal of Science (USA)

TOC/Abstract Graphic



ABSTRACT:

A three-step sequence for the synthesis of α-arylated cyclohexanones and the most challenging cycloheptanones is reported. First, an efficient one-pot synthesis of *β,β'*-disubstituted benzylidene

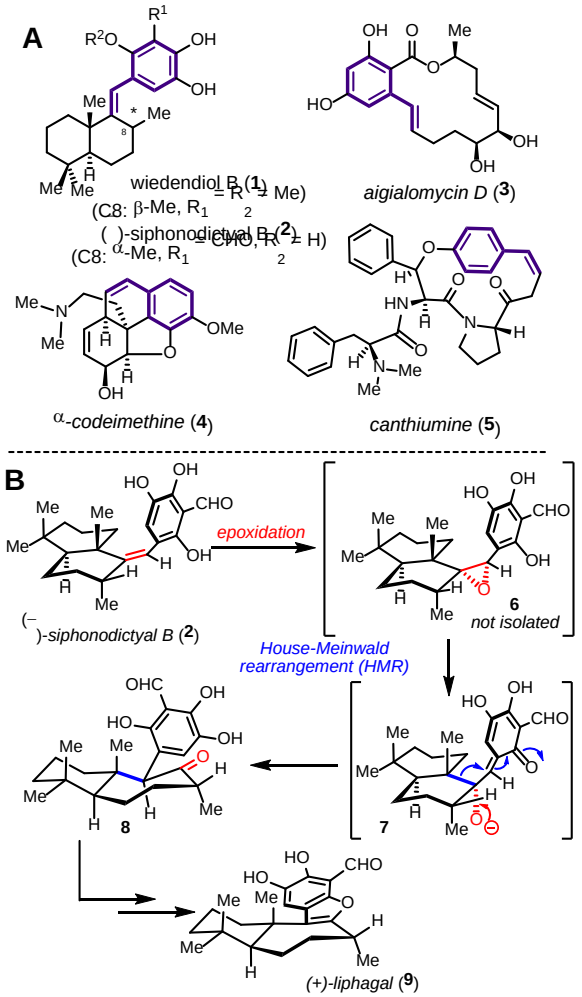
cycloalkanes (styrenes) using the palladium-catalyzed Barluenga reaction from readily available feedstock chemicals is described. Furthermore an epoxidation followed by the House-Meinwald rearrangement (HMR) of spiro-epoxides is reported to produce a number of α-arylated cycloalkanones upon ring expansion. Reactions catalyzed by bismuth triflate underwent quasi-exclusively ring expansion for all substrates (electronically poor and rich), with yields ranging from 15% to 95% thus demonstrating the difficulty to achieve the ring enlargement for electron deficient spiro-epoxides. On the other hand, by means of catalysis with aluminium trichloride, the rearrangement of spiro-epoxides proceeded typically in high yields and with remarkable regioselectivity on a broader substrate scope. In this case, a switch of regioselectivity was achieved for spiro-epoxides with electron-withdrawing substituents which enable the method to be successfully extended to some chemospecific arene shifts and the synthesis of aldehydes bearing a α-quaternary carbon. While the HMR has been extensively studied for smaller ring enlargement, we are pleased to report herein that larger cyclohexanones and cycloheptanones can be obtained efficiently from more sterically demanding trisubstituted spiro-epoxides bearing electron-releasing and electron-neutral arene substituents.

Keywords: Aryl halides; Barluenga cross-coupling; β,β'-Disubstituted styrenes; Spiro-epoxide rearrangement; House–Meinwald rearrangement (HMR); Lewis acid catalysis; α-arylated cycloalkanones, ring enlargement.

1. Introduction

Styrenes are ubiquitous building blocks for the synthesis of polymers and also pertain to several architecturally complex natural products (*e.g.* **1-5**, Figure 1A).

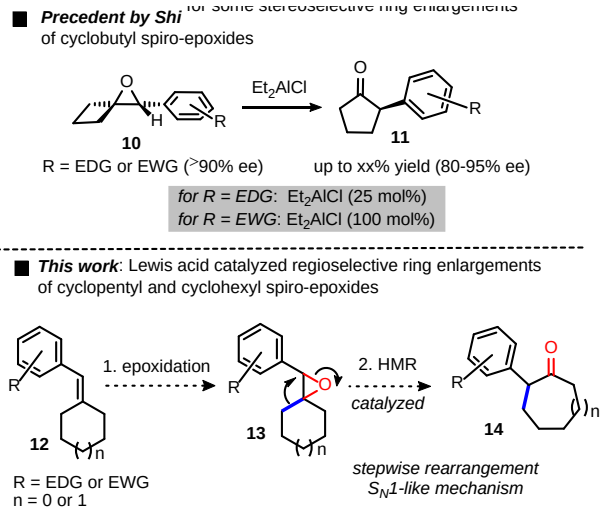
Figure 1. Styrenes functionality embedded in natural products



Given their inherent reactivity as π-nucleophiles, styrenes are not only unique functionalities in natural products, but are also important building blocks for the construction of more elaborated molecules and macromolecules such as polymers.[1] Recently, an interesting biosynthetic proposal for the transformation of the natural product (–)-siphonodictyal B (**2**) to (+)-liphagal (**9**) through a sequence of epoxidation and skeletal rearrangement (ring expansion),[2] caught the attention of several research groups (Figure 1B).[3] This straightforward approach to a highly functionalized medium-sized ring has been proposed to occur *via* the regio- and stereoselective rearrangement of a styrenyl epoxide intermediate **6**. Indeed, spiro-epoxide **6** was proposed to rearrange via a non-trivial ring enlargement reaction known as the House–Meinwald rearrangement (HMR) to deliver the α-arylated cycloheptanone skeleton **8**.[4] While the George group reported their elegant stereoselective total synthesis of (+)-liphagal (**9**) by the intermediacy of a biomimetic diastereoselective HMR and the stereochemical revision of **2**,[3b] our group was already engaged in similar biomimetic studies

and decided to focus on studying the pivotal HMR reaction to better understand the stereoelectronic factors governing the HMR reaction of spiro-epoxides.

Scheme 1. Possible access to six and seven-membered cyclic ketones by means of a catalyzed HMR.

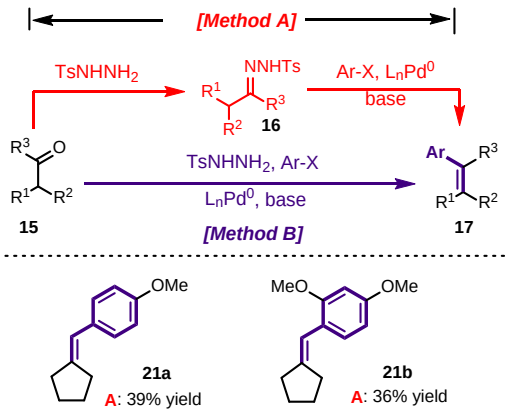


Even though the HMR reaction of acyclic epoxides has been extensively studied,[5] the rearrangement of carbocyclic fused[6] and spirocyclic epoxides[7,8] remains largely unexplored. Given the high propensity of strained cyclopropanes and cyclobutanes to rearrange to larger four and five-membered rings respectively, it is not surprising that only few examples of HMR ring expansion of larger spiro-epoxides have been reported.[8] Certainly one of the most impressive example of HMR ring-enlargement was reported by Shi with the highly regio- and stereoselective rearrangement of cyclobutenyl spiro-epoxides **10** into the corresponding cyclopentanones **11** (Scheme 1).[7c] In this report, the most challenging rearrangement reactions of spiro-epoxides bearing electron-deficient benzene appendages ($\sigma+ < 0.15$) were outlined by the need of spending stoichiometric amounts of Lewis acid (*e.g.* Et_2AlCl). Collectively, these previous reports on the HMR support that the rearrangement of sterically-demanding trisubstituted (spiro)epoxides **13** remains a synthetic challenge.[7,8] Herein, we report results for some unprecedented catalyzed HMRs of larger cyclopentyl and cyclohexyl spiro-epoxides **13** that further expand the initial reaction scope reported by Shi to prepare the corresponding α-arylated cyclopentanones and cycloheptanones **14**. This study also reveals the importance of both stereo- and electronic effects on the innate reactivity of the spiro-epoxides and on the regioselectivity path taken during the rearrangement.

2. Results and Discussion

2.1. High Yielding Access to β,β'-Disubstituted Styrenyl Substrates.

In order to develop a useful methodology toward several ring size of α-arylated cyclic ketones, we intuitively decided to mimic the HMR reaction highlighted in the synthesis of liphagal (**9**) from the styrenyl precursor **2** (Figure 1B). Therefore, a straightforward and potentially high yielding sequence of three steps was planned with 1) the synthesis of β,β'-disubstituted styrenes, followed by 2) epoxidation and concluded by 3) a catalyzed HMR.

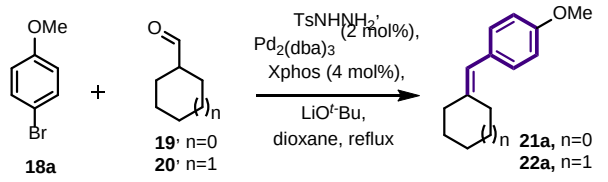


Scheme 2. Comparison of a two-step (Method A) vs one-pot (Method B) palladium-catalyzed styrene synthesis [a]

Styrenes are most commonly produced synthetically by metathesis,[9] Wittig[10] and palladium cross-coupling reactions.[11] In 2007, Barluenga reported a new type of palladium-catalyzed cross-coupling reaction, a versatile and efficient transformation for the synthesis of mono- and polysubstituted styrenes as well as β,β'-disubstituted styrenes **17** from a carbonyl functional group **15** via the intermediacy of tosylhydrazone **16** (Scheme 2; Method A).[12] Soon thereafter, the same research group reported the direct coupling of an aldehyde or a ketone with aryl halides in a multicomponent fashion[13] through the *in situ* transient formation of a diazonium intermediate from a tosylhydrazone (Scheme 1 Method B).[14]

Unfortunately, the Barluenga coupling of electron-rich electrophilic arene partners is a delicate reaction due to the difficult oxidative addition of the palladium(0) catalyst. Indeed, the syntheses of the electron-rich cyclopentyl-derived styrenes in two steps (Method A) were hampered by the lack of reactivity of the corresponding hydrazones leading to the isolation of **21a** and **21b** in the modest yields of 39% and 36% yields respectively.

Table 1. One-pot Barluenga cross-coupling reaction (Method B)[a-c]

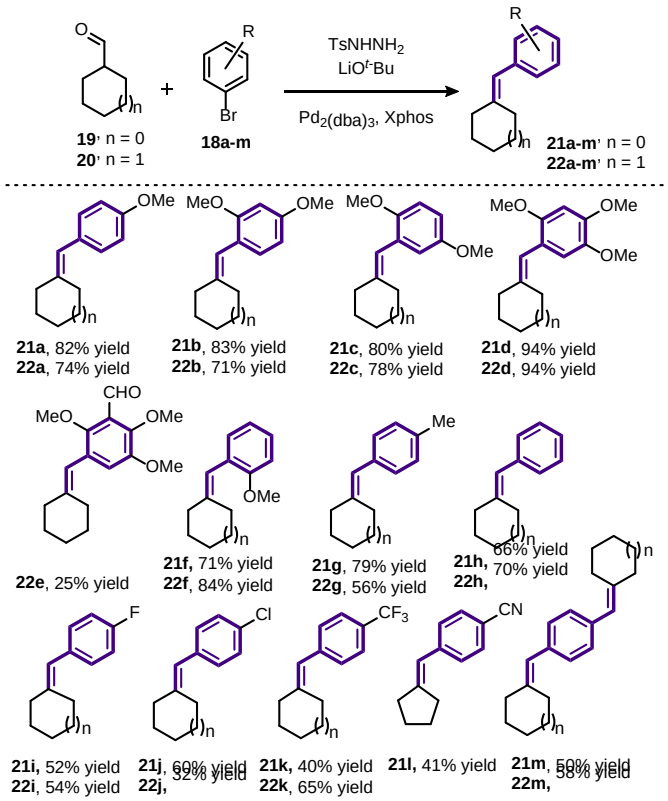


Entry	19/20 (eq.)[a]	LiO^t-Bu (eq.)	Reaction Time (hours)	Conv. (%)[b]	Yield (%)[c]
1	**20** (1.0)	3.5	28	50	**22a** (45)
2	**20** (1.7)	2.3	28	< 55	**22a** (38)
3	**20** (1.7)	4.0	2.5	80	**22a** (62)
4	**20** (2.0)	4.0	2.5	100	**22a** (74)
5	**19** (2.0)	4.0	2.5	100	**21a** (82)

[a] Aldehyde and $TsNHNH_2$ are used in 1:1 ratio; [b] Conversions were determined by ^1H NMR of the crude reaction mixture; [c] Isolated yields are reported.

Not only the formation of the tosylhydrazone from the cyclopentane carboxaldehyde proved to be difficult (< 47% yield), but the efficiency of the cross-coupling under the typical conditions reported by Barluenga was moderate (50% conversion, see Supporting Information).

Scheme 3. Scope for the synthesis of β,β'-disubstituted styrenes **21-22**[a]



[a] Reactions carried on a 0.5 mmol scale of aryl bromides **18a-m** (1 eq.) with aldehyes **19** or **20** (2 eq.), $TsNHNH_2$ (2 eq.), LiO*t*Bu (4 eq.), $Pd_2(dba)_3$ (2 mol%), and Xphos (4 mol%) in dioxane [0.1 M] for 2-5 hours. Isolated yields are reported.

In this context, a one-pot Barluenga multicomponent reaction strategy (Method B) was evaluated to achieve a quick access to electron rich β,β'-disubstituted styrenes. Reaction conditions were screened to optimize the Pd(0)-catalyzed cross-coupling reaction in a multicomponent fashion for an electron-rich aryl bromide **18a** with both cyclopentane and cyclohexane carboxaldehyde **19-20** (Table 1).

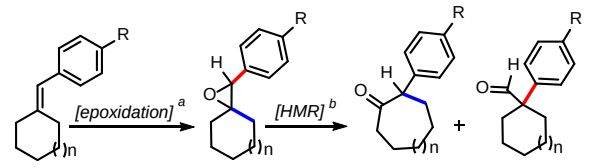
Upon the typical reaction conditions reported by Barluenga (Entries 1-2), conversions to the desired styrene **22a** remained low (< 55%). Forcing reaction conditions with an excess of aldehyde **20** to facilitate the *in situ* hydrazone formation and a larger excess of base to promote the decomposition towards the reactive carbene led to drastic improvements in conversion and isolated yields 62% and 74%

yields respectively (Entries 3-4). As shown in entry 5, the cyclopentyl styrene **21a** was synthesized in 82% yields through the optimized protocol. With this optimized protocol in hand, 24 styrenes **21**/**22** with five and six membered rings bearing electron–donating and electron–withdrawing groups have been synthesized (Scheme 3) in one-step with moderate to good yields (25-94% yields). The styrenes were freshly prepared and purified on silica gel to avoid polymerization and decomposition (most styrenes were stored and found stable for only up to two weeks at -78 °C).

2.2. Optimization of the catalyzed House–Meinwald Rearrangement (HMR) of spirocyclic epoxides.

Having established some optimized reaction conditions for the palladocatalyzed Barluenga cross-coupling and the synthesis of styrenes **21**/**22**, we turned our attention to evaluate the scope of the pivotal HMR step.

Table 2. Derivatization of styrenes through the epoxidation and House–Meinwald rearrangement sequence.[a-d]



21a, n=0, R= OMe
21h, n=0, R= H
22a, n=1, R= OMe
22h, n=1, R= H

23a (99% yield)
23h (80% yield)
24a (87% yield)
24h (75% yield)

25a
25h
26a
26h

27a
27h
28a
28h

Entry	Epoxide	Catalyst (10 mol%)	Time (min)	ketone:aldehyde ratio[c]	Isolated yield (%)
1[d]	**23a**	Et_2AlCl	2	1:0	**25a** (98)
2[d]	**23a**	Me_3Al	2 days	1:0	**25a** (75)
3	**23a**	MABR	60	1:0	**25a** (85)
4	**23a**	$AlCl_3$	< 2	1:0	**25a** (92)
5	**23a**	$Bi(OTf)_3$	< 10	1:0	**25a** (79)
6	**24a**	Et_2AlCl	< 2	1:0	**26a** (85)
7	**24a**	$AlCl_3$	< 2	1:0	**26a** (90)
8	**24a**	$Bi(OTf)_3$	60	1:0	**26a** (75)
9	**23h**	Et_2AlCl	300	-	NR
10	**23h**	$Bi(OTf)_3$	10	1:0	**25h** (15)
11	**23h**	$AlCl_3$	5	0:1	**27h** (90)
12	**24h**	$Bi(OTf)_3$	15	25:1	**26h** (20)
13	**24h**	$AlCl_3$	5	1:8	**28h** (78)

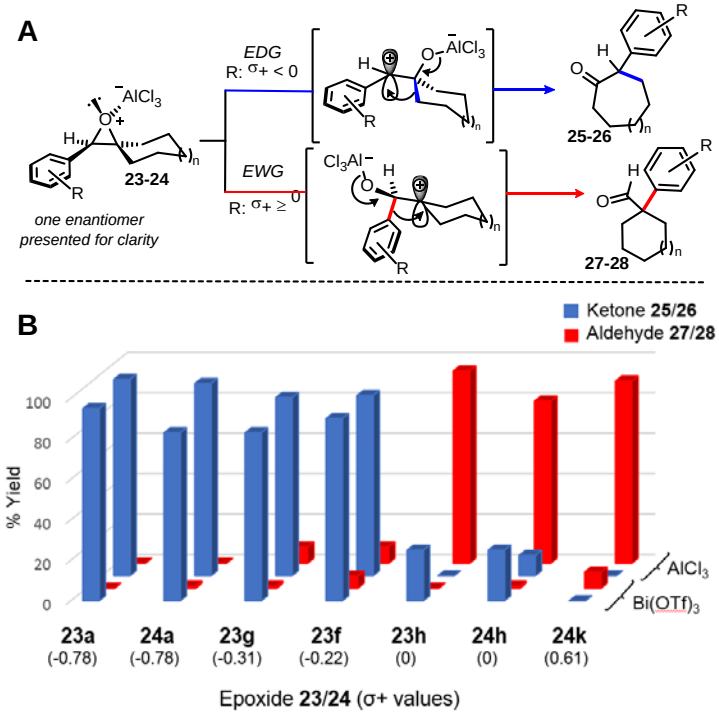
[a] Reaction conditions: styrene (1.0 mmol), oxone (1.0 eq.), acetone [0.03 M], sat. $NaHCO_3$ [0.05 M] in H_2O [0.09 M]. [b] Reaction conditions: catalyst (10 mol%) in DCE [0.05 M] at -20 °C unless otherwise stated. [c] Ratios of structural isomers and yields were determined by ^1H NMR of the crude reaction mixture with mesitylene as internal standard. [d] Reactions carried at -78 °C (entry 1) and at 60 °C (entry 2).

To this aim, we were pleased to see that typical conditions for the epoxidation of trisubstituted alkenes with oxone can be utilized in a general manner to efficiently obtain the spirocyclic epoxides.[15] Under the optimized conditions for styrene epoxidation, spiro-epoxides **23a**/**24a** and **23h**/**24h** were prepared in 75-90% yields. Higher loadings of oxone and longer reaction times were required in case of electron poor styrene to achieve full conversions and high yielding epoxidations. Importantly, we noticed that epoxides can be purified on neutralized alumina, kept for months in a freezer, and

were more stable than their styrene counterparts. These epoxides were therefore engaged in the rearrangement reaction to evaluate the scope of the HMR reaction and optimize conditions for the catalysis.[16] Numerous catalysts have been previously reported to efficiently promote the HMR of acyclic epoxides.[5] From an extensive screening of solvents and over twenty catalysts encompassing Lewis and Brønsted acids,[16] the aluminium–based catalysts and bismuth triflate $Bi(OTf)_3$ were identified to promote efficient rearrangement in dichloroethane (DCE) as shown by the best results reported in Table 2. From this initial screening, two stereoelectronic trends have also emerged. Firstly, although $Bi(OTf)_3$ was found to be an efficient catalysts for the HMR, aluminium-based catalysts appeared to be more suitable to promote catalysis and enable epoxide opening and ring enlargement via a carbon–carbon bond 1,2-shift (Entries 1-5). Our current explanation lays on the fact that a cohesive catalyst for the HMR reaction must trigger both ring-opening (Lewis acid nature) which might operate from both epoxide lone pairs and also release electron density from the zwitterionic intermediate to promote the σ-bond 1,2-shift (Figure 2). Therefore a fine tune between Lewis acidity and the oxophilic nature of the catalyst must be consider to optimize the HMR reaction. Indeed the five-to-six membered ring enlargement of the electronically rich spiro-epoxide **23a** (EDG, R = *p*-methoxy; σ+ value of -0.78)[17] was efficiently catalyzed by Et_2AlCl and $AlCl_3$ leading to the corresponding α-aryl cyclohexanone **25a** in 98% and 92% yields respectively (Entries 1 & 4). We were also pleased that similar conditions enabled the six-to-seven membered ring expansion to proceed smoothly and delivered the α-aryl cycloheptanone **26a** in 85% and 90% yields respectively (Entries 6-7). In this case, $Bi(OTf)_3$ was found to similarly catalyze the HMR and produce **26a** in 75% yield. The second trend in the HMR reaction unraveled upon evaluating the rearrangement of several electronically deficient spiro-epoxides.[16] As shown in Table 2 (Entries 9-13) and on the proposed mechanism schematic for the HMR regioselectivity (Figure 2), electron deficient spiro-epoxide underwent a different bond-breaking reaction. In the case of spiro-epoxides **23h** and **24h** (R = H; σ+ value of 0),[17] the reaction

did not proceed with the Et_2AlCl catalyst at lower temperature (Table 2, entry 9) and resulted in decomposition under forced conditions while reactions catalyzed by $Bi(OTf)_3$ afforded the desired enlarged cycloalkanones **25h** and **26h** in only 15% and 20% yields respectively.

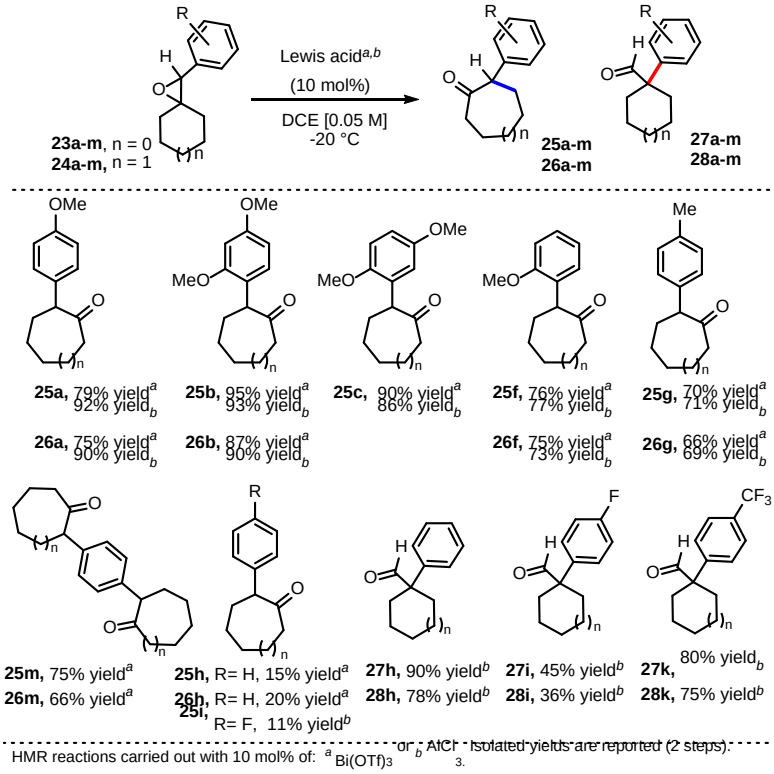
Figure 2. Regioselectivity outcome for the HMR reaction of spiro-epoxides **23/24** catalyzed by $Bi(OTf)_3$ versus $AlCl_3$



These modest yields for electron poor substrates (EWG, σ+ value > 0) might be explained by considering that the rate determining carbocation formation could not be enhanced by the Lewis acidity of the bismuth catalyst. On the other hand, catalyzed rearrangements of the same epoxides **23h** and **24h** proceeded efficiently and rapidly with $AlCl_3$ to afford the corresponding α-arylated aldehydes **27h** and **28h** in 90% and 78% yields respectively. These results suggest that not only the stereoelectronic nature of the catalysts is crucial for the rearrangement to proceed, but more importantly that the regioselectivity originates mainly from the substrate. An overview of the HMR regioselectivity outcome is presented in Figure 2A. Regio-isomeric ratios and NMR yields reported were obtained from crude reaction mixtures (integrations average from 2-3 peaks/compound) using mesitylene as internal standard (Figure 2B). In the case of aluminium trichloride, the catalyst demonstrated high efficiency presumably by facilitating the formation of carbocations either at the benzylic position (*e.g.* rearrangement of **23a**, **24a**, **23f** and **23g**) or at the tertiary position in the case of **23h**, **24h** and **24k**. As previously suggested by Yamamoto, the Lewis acid catalyst might well discriminate the two lone pairs of epoxides to chelate preferentially on the less hindered side

(Figure 2A).[7g] After ring opening, the carbocation may endure a σ-bond shift concomitant to the π-bond formation of the carbonyl, therefore forcing the group antiperiplanar to the Lewis acid to specifically migrate. Given the number of precedents that support a highly chemoselective shift in the HMR,[5b] our observation of a specific arene shift suggest that the migratory aptitude is less relevant than the Lewis acid positioning on the spiro-epoxide substrates. Even in this case of an electron deficient arene in epoxide **24k** (EWG, R = *p*-CF_3; σ+ value of 0.61), the hydride migration is not observed, instead the unexpected trifluoromethylbenzene migration occurred to deliver the cyclohexyl carboxaldehyde **28k** bearing a α-quaternary center with high yield and in a chemospecific manner. Having in hand two efficient catalysts for the ring expansion reaction or the regioisomeric hydride shift, the reaction scope was evaluated (Scheme 4).

Scheme 4. Scope of the ring enlargement strategy for the synthesis of α-arylated cycloalkanones **25**/**26** and cycloalkyl carboxaldehydes **27**/**28**. [a,b]



Overall, eleven electronically rich or neutral substrates (σ+ ≤ 0, **25a-c**, **25f-g**, **25m**, **26a-b**, **26f-g** and **26m**) have been synthesized and rearranged with ring-expansion in good to high yield and with excellent chemoselectivity without observing any major differences in efficiency between the reactions carried with either the bismuth or the aluminium catalysts. To our delight, six α-aryl cycloheptanones have been synthesized in moderate to good yields (up to 95% yield) and some dimeric structures **25m**/**26m** have been also obtained in high yields through two rearrangements occurring in the same pot. On the other end, **25h**/**27h, 26h**/**28h**, **27i**, **28i**, **27k**

and **28k** with electron neutral or deficient substituents ($\sigma+ > 0$) have been synthesized and were only obtained through the aluminium trichloride catalysis. Overall these results from this study tend to demonstrate that aluminium trichloride is the most general catalyst amenable to efficiently rearrange a broad range of substrates with high chemoselectivity.

3. Conclusion

In summary, we reported a general strategy for a three-step sequence that enable a rapid access to α-arylated cyclohexanones and cycloheptanones from commercially inexpensive starting materials. The sequence comprised of a Barluenga cross-coupling and epoxidation enabled a rapid and straightforward access to spiro-epoxides in high yields. The targeted α-arylated cycloalkanones which are challenging building blocks to synthesize by previous methods[7], have been readily obtained from a Lewis acid-catalyzed House-Meinwald rearrangement (HMR). The reactions presented have been optimized to deliver a series of six and seven-membered ring α-arylated cycloalkanones in good yields. Bismuth triflate and aluminium trichloride have emerged from this study to be the most efficient and complementary catalysts to promote the HMR on a broad substrate scope (20 compounds with up to 95% yield and high regioselectivity). This study demonstrates that the rearrangement' regioselectivity is essentially governed by electronic factors inherent to the spiro-epoxides. The scope for the ring expansion reaction catalyzed by aluminium trichloride encompasses spiropentyl- and spirohexyl-epoxides with electron-releasing and electron-neutral substituents. A regioselectivity switch was observed for spiro-epoxides with electron withdrawing substituents which enable the method to be successfully applied to a chemospecific 1,2-shift of arenes for the synthesis of aldehydes bearing a α-quaternary carbon. Finally, this study revealed that the innate regioselectivity in spiro-epoxide opening could not be overcome by any of the Brønsted and Lewis acid catalysts evaluated, yet aluminium trichloride was found a be the most efficient and suitable catalyst to achieve this rearrangement. Given the

significance of ring enlargements in complex natural products,[2,3] we anticipate that the efficiency of HMR catalyzed by aluminium trichloride will be applicable by others in the context of challenging medium-sized ring enlargement. Ongoing studies are aimed at developing an asymmetric variant of this ring enlargement transformation from enantioenriched spiro-epoxides.

4. Experimental Section

Reactions were performed in flame-dried glassware under a positive pressure of argon. Yields refer to spectroscopically pure compounds. Analytical TLC was performed on 0.25 mm glass backed 60Å F-254 TLC plates (Silicycle, Inc.). The plates were visualized by exposure to UV light (254 nm) and developed by a solution of vanillin in ethanol/sulfuric acid or cerium-ammonium-molybdate in water/sulfuric acid and heat. Flash chromatography was performed using 200-400 mesh silica gels (Silicycle, Inc.). Infrared spectra were recorded on a Nicolet IS5 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on Varian Mercury400 and Bruker biospinGmbH (400 MHz) spectrometers and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm or CD_3CN at 1.96 ppm). NMR spectra were performed using standard parameter and data are reported as: (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded on Varian Mercury400 (100 MHz) spectrometer. Chemical shifts are reported in ppm, with solvent resonance employed as the internal standard ($CDCl_3$ at 77.2 ppm or CD_3CN at 1.3 and 118.3 ppm). Melting points were determined using Digimelt digital melting point apparatus. The GC-MS (gas chromatography –mass spectroscopy) analysis was performed using Perkin Elmer auto system XL with Turbo mass. Electron ionization (EI) source was used and Restek (Rtx®-5) capillary column with 30 m length, 1.25 mm internal diameter and 0.1µm film thickness. Accurate mass (High resolution HRMS) was obtained from University of Florida using Agilent 6220 TOF and Bruker Daltonics, Impact II QTOF instrument.

General Procedure A *for the Barluenga coupling reaction using preformed tosylhydrazone and an electron-rich aryl bromide.*

A two neck round bottom flask under argon equipped with a condenser was charged with N'-(cyclopentylmethylene)-4-methylbenzenesulfonohydrazide (200 mg, 0.75 mmol, 1.5 equiv.) or N'-(cyclohexylmethylene)-4-methylbenzenesulfonohydrazide (210 mg, 0.75 mmol, 1.5 equiv.), tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] (9 mg, 0.01 mmol, 2 mol %),

dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos) (9 mg, 0.02 mmol, 4 mol %), followed by LiO*t*-Bu (140 mg, 1.75 mmol, 3.5 equiv.), 1,4-dioxane (5.0 mL, [0.1 M]) and the desired aryl bromide **18a-m** (0.5 mmol, 1.0 equiv.). The heterogeneous solution was then stirred at reflux for 24 hours. After completion of the reaction (judged by TLC), the reaction mixture was directly filtered through a pad of celite and washed with *n*-hexanes (10 x 5 mL). Solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel using an isocratic solvent system of 100% n-hexanes.

General Procedure B *for the one-pot Barluenga coupling reaction of cyclohexanecarboxaldehyde and aryl bromide.*

A two-neck round bottom flask equipped with a condenser was charged under argon with Xphos (9 mg, 0.02 mmol, 4 mol %), $[Pd_2(dba)_3]$ (9 mg, 0.01 mmol, 2 mol %), LiO*t*-Bu (160 mg, 2 mmol, 4 equiv.), cyclopentanecarboxaldehyde **19** (98 mg, 1 mmol, 2 equiv.) or cyclohexanecarboxaldehyde **20** (112 mg, 1 mmol, 2 equiv.), tosylhydrazine (186 mg, 1 mmol, 2 equiv.) and 1,4-dioxane (5.0 mL, [0.1 M]). After 1 minute, the desired aryl halide **18a-m** (0.5 mmol, 1.0 equiv.) was added. The reaction mixture was stirred under reflux and monitored by TLC until completion (x hours). When the reaction was completed the crude reaction mixture was allowed to cool down to room temperature, taken up into *n*-hexanes (5 mL) and filtered through a pad of celite. The celite pad was further washed with *n*-hexanes (10 x 5 mL). Solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel using *n*-hexanes as solvent.

General Procedure C *for the epoxidation of styrenes*.

A one neck round bottom flask under argon was charged with styrene **21a-m** or **22a-m** (1.0 mmol, 1.0 equiv.) which was dissolved in acetone (33 mL, [0.03 M]) and cooled down to 0 ˚C. A saturated sodium bicarbonate solution (20 mL, [0.05 M]) was added to the solution at 0 ˚C. A solution of oxone (x mmol) in water (10 mL, [0.1 M]) was then added dropwise for 5 min. The reaction was stirred until the completion while carefully maintaining the reaction temperature at 0 ˚C. The reaction progress was monitored using neutralized TLC plate (platepretreated with 5% Et_3N). The reaction mixture was diluted with n-hexanes (10 mL) and water (10 mL) to facilitate phase separation. The two layers were separated and the aqueous phase was extracted at least 7 times using *n*-hexanes (7 X 10 mL). Combined organic layers were washed with a saturated brine solution (5 mL) and then dried over Na_2SO_4. The solvent was evaporated under vacuum and the product was purified by flash chromatography on neutralized silica gel (silica gel pretreated with

5% Et_3N). ***Caution:*** The epoxides described below are sensitive to long exposure to non-neutralized silica gel leading to decomposition and some epoxide rearrangement.

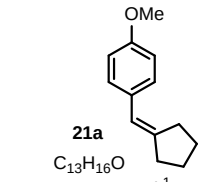
General Procedure D *for the catalyzed House-Meinwald rearrangement reaction*.

A flame dried one neck round bottom flask under argon was charged with the desired spiro-epoxides **23a-m** or **24a-m** (0.1 mmol, 1.0 equiv.) in dichloroethane (DCE) (2.0 mL, [0.05 M]) at -20 °C. Lewis acids such as $Bi(OTf)_3$ (7 mg, 10 mol %) or $AlCl_3$ (1 mg, 10 mol %), were added and the reaction mixture was stirred at -20 °C until the reaction completion. The reaction mixture was diluted with dichloromethane (DCM) (2 mL) and allowed to room temperature. The reaction is quenched with water (5 mL) under a strong agitation. The two layers were separated and product was extracted from the aqueous layer using DCM (3 x 2 mL). Combined organic layers were washed with a saturated brine solution (2 mL) and then dried over Na_2SO_4. The solvent was evaporated under vacuum and the product was purified by flash chromatography using an isocratic eluent of ethyl acetate in n-hexanes (5:95).

Compounds Characterization

The syntheses and characterizations of compounds **21a**,[18a] **21f-g**,[18b] **21h**,[18a] **21i-j**,[18c] **21k**,[18a] **22a**,[18a] **22g-h**,[18d] **22j**,[18e] **23h**,[19] **24h**,[19] **25a-b**,[20a] **25c**,[20b] **25f**,[20c] **25g**,[20d] **25h**,[20e] **25i**,[20f] **26a**,[20g] **26b**,[20h] **26f**,[20i] **26g-h**,[20j] **27h**,[21a] **27i**,[21b] **27k**,[21c] **28h**,[21d] **28i**,[21e] **28k**,[21f] were previously reported.

1-(cyclopentylidenemethyl)-4-methoxybenzene **21a**:

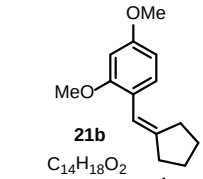


21a
$C_{13}H_{16}O$
MW: 188.27 g.mol^{-1}

Compound **21a** was synthesized and purified accordingly to *general procedure A* from 1-bromo-4-methoxybenzene **18a** (94 mg, 0.5 mmol, 1.0 equiv.) and obtained in pure form as a yellow oil **21a** (73 mg, 0.39 mmol, 77% yield).

Compound **21a** was also synthesized from aryl bromide **18a** (94 mg, 0.5 mmol, 1.0 equiv.) under reflux for 2.5 hours and purified accordingly *to general procedure B* to obtain pure material **21a** (77 mg, 0.41 mmol, 82% yield). $\mathbf{R_f}$ = 0.47 (Et_2O/*n*-hexanes 1:9). **IR**νmax (neat): 2938, 1599, 1500, 1185, 830 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.32-6.28 (m, 1H), 3.81 (s, 3H), 2.54 – 2.45 (m, 4H), 1.80 – 1.75 (m, 2H), 1.69 – 1.55 (m, 2H). **^{13}C NMR** (100 MHz, CD_3CN) δ (ppm) 158.6, 145.5, 132.6, 130.0 (2C), 120.9, 114.5 (2C), 55.8, 36.5, 31.6, 27.9, 26.4. Spectral data for compound **21a** were consistent with the data previously reported in the literature.[18a] **SMILES**: COC1=CC=C(/C=C2CCCC/2)C=C1

1-(cyclopentylidenemethyl)-2,4-dimethoxybenzene **21b**:



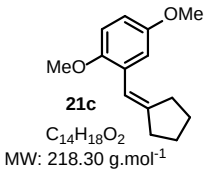
21b
$C_{14}H_{18}O_2$
MW: 218.30 g.mol^{-1}

Compound **21b** was synthesized and purified accordingly to *general procedure A* using 1-bromo-2,4-dimethoxybenzene **18b** (109 mg, 0.5 mmol, 1.0 equiv.) and obtained in pure form as a yellow oil (89 mg, 0.41 mmol, 82% yield).

Compound **21b** was also synthesized from aryl bromide **18b** (109 mg, 0.5 mmol, 1.0 equiv.) under reflux for 3 hours and purified accordingly to *general procedure B* to obtain pure material **21b** (92 mg, 0.42 mmol, 83% yield). $\mathbf{R_f}$ = 0.28 (Et_2O/*n*-hexanes 1:99). **IR**νmax (neat): 2950, 1606, 1500, 1205, 1153, 1035, 832 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.33 – 7.23 (m, 1H), 6.60 – 6.40 (m, 3H), 3.81 (s, 6H), 2.48 (dd, *J* = 16.9, 8.0 Hz, 4H), 1.74 (dt, *J* = 13.7, 6.8 Hz, 2H), 1.66 (dt, *J* = 13.8, 6.8 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 159.0, 157.5, 145.2, 129.1, 120.9, 114.3, 103.9, 98.3, 55.4, 55.3, 35.3, 31.0, 27.0, 25.6. **GCMS** (EI) m/z: [$M^{+\cdot}$] Calcd for $C_{14}H_{18}O_2$ 218; Found 218.

SMILES: COC1=CC=C(/C=C2CCCC/2)C(OC)=C1

2-(cyclopentylidenemethyl)-1,4-dimethoxybenzene **21c**:

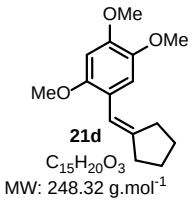


21c
$C_{14}H_{18}O_2$
MW: 218.30 g.mol^{-1}

Compound **21c** was synthesized from 2-bromo-1,4-dimethoxybenzene **18c** (109 mg, 0.5 mmol, 1.0 equiv.) under reflux for 3 hours and purified accordingly *to general procedure B* to obtain pure material as a yellow oil (87 mg, 0.40 mmol, 80% yield). $\mathbf{R_f}$ = 0.28 (Et_2O/*n*-hexanes 1:99). **IR**νmax (neat): 2950, 1606, 1500, 1205, 1153, 1035, 832 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 6.95 (d, *J* = 3.0 Hz, 1H), 6.78 (d, *J* = 8.9 Hz, 1H), 6.70 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.57 – 6.55 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 2.55 – 2.48 (m, 4H), 1.79 – 1.71 (m, 2H), 1.71 – 1.65 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm). 153.4, 151.1, 147.8, 129.0, 115.1, 114.9, 111.5, 111.4, 56.3, 55.9, 35.6, 31.3, 27.1, 25.7. **GCMS** (EI) m/z: [$M^{+\cdot}$] Calcd for $C_{14}H_{18}O_2$ 218; Found 218.

SMILES: COC1=CC=C(OC)C=C1/C=C2CCCC/2

1-(cyclopentylidenemethyl)-2,4,5-trimethoxybenzene **21d**:

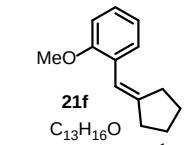


21d
$C_{15}H_{20}O_3$
MW: 248.32 g.mol^{-1}

Compound **21d** was synthesized from 1-bromo-2,4,5-trimethoxybenzene **18d** (124 mg, 0.5 mmol, 1.0 equiv.) under reflux for 12 hours and purified accordingly *to general procedure B* to obtain pure material as a yellow oil (117 mg, 0.47 mmol, 94% yield). $\mathbf{R_f}$ = 0.41 (EtOAc/*n*-hexanes 5:95). **IR**νmax (neat): 2950, 1606, 1500, 1205, 1153, 1035, 832 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 6.96 (s, 1H), 6.51 (s, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 2.50 (td, *J* = 7.2, 2.0 Hz, 4H), 1.77 – 1.72 (m, 2H), 1.68 (d, *J* = 7.3 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 151.2, 148.0,

145.5, 142.8, 120.1, 114.6, 113.0, 97.8, 56.7(2C), 56.3, 35.6, 31.2, 27.2, 25.8. **GCMS** (EI) m/z: [$M^{+\cdot}$] Calcd for $C_{15}H_{20}O_3$ 248, Found 248. **SMILES**: COC1=CC(OC)=C(OC)C=C1/C=C2CCCCC/2

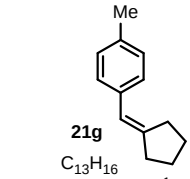
1-(cyclopentylidenemethyl)-2-methoxybenzene **21f**:



21f
$C_{13}H_{16}O$
MW: 188.27 g.mol^{-1}

Compound **21f** was synthesized from 1-bromo-2-methoxybenzene **18f** (94 mg, 0.5 mmol, 1.0 equiv.) under reflux for 4 hours and purified accordingly to *general procedure B* to obtain pure material as a clear oil (67 mg, 0.36 mmol, 71% yield). $\mathbf{R_f}$ = 0.30 (*n*-hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.35 (d, *J* = 7.7 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.58 (s, 1H), 3.84 (s, 3H), 2.50 (dd, *J* = 14.5, 7.3 Hz, 4H), 1.74 (dd, *J* = 13.9, 7.0 Hz, 2H), 1.70 – 1.63 (m, 2H). Spectral data for compound **21f** were consistent with the data previously reported in the literature.[18b] **SMILES**: COC1=CC=CC=C1/C=C2CCCC/2

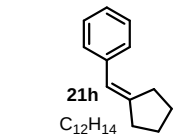
1-(cyclopentylidenemethyl)-4-methylbenzene **21g**:



21g
$C_{13}H_{16}$
MW: 172.27 g.mol^{-1}

Compound **21g** was synthesized from 1-bromo-4-methylbenzene **18g** (86 mg, 0.5 mmol, 1.0 equiv.) under reflux for 4 hours and purified accordingly to *general procedure B* to obtain pure material as a clear oil (68 mg, 0.40 mmol, 79% yield). $\mathbf{R_f}$ = 0.64 (*n*-hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.21 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.35-6.31 (m, 1H), 2.54 56-2.50 (t, *J* = 7.0 Hz, 2H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.34 (s, 3H), 1.81 – 1.75 (m, 2H), 1.70 – 1.63 (m, 2H). Spectral data for compound **21g** were consistent with the data previously reported in the literature.[18b] **SMILES**: CC1=CC=C(/C=C2CCCC/2)C=C1

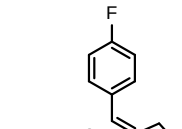
Cyclopentylidenemethyl benzene **21h**:



21h
$C_{12}H_{14}$
MW: 158.24 g.mol^{-1}

Compound **21h** was synthesized from bromobenzene **18h** (79 mg, 0.5 mmol, 1.0 equiv.) under reflux for 5 hours and purified accordingly to *general procedure B* to obtain pure material as a clear oil (52 mg, 0.33 mmol, 66% yield). $\mathbf{R_f}$ = 0.50 (*n*-hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.33-7.14 (m, 5H), 6.38 – 6.34 (m, 1H), 2.59 – 2.53 (m, 2H), 2.52 – 2.46 (m, 2H), 1.82-1.75 (m, 2H), 1.70-1.63 (m, 2H). Spectral data for compound **21h** were consistent with the data previously reported in the literature.[18a] **SMILES**: [H]C1=CC=C(/C=C2CCCC/2)C=C1

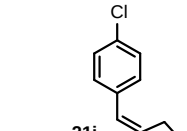
1-(cyclopentylidenemethyl)-4-fluorobenzene **21i**:



21i
$C_{12}H_{13}F$
MW: 176.23 g.mol^{-1}

Compound **21i** was synthesized from 1-bromo-4-fluorobenzene **18i** (88 mg, 0.5 mmol, 1.0 equiv.) under reflux for 4 hours and purified accordingly to *general procedure B* to obtain pure material as a clear oil (46 mg, 0.26 mmol, 52% yield). $\mathbf{R_f}$ = 0.77 (*n*-hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.26 – 7.08 (m, 2H), 7.00 (t, *J* = 8.9 Hz, 2H), 6.34-6.30 (m, 1H), 2.49 (dt, *J* = 10.9, 7.2 Hz, 4H), 1.79 (p, *J* = 7.0 Hz, 2H), 1.67 (p, *J* = 7.3 Hz, 2H). Spectral data for compound **21i** were consistent with the data previously reported in the literature.[18c] **SMILES**: FC1=CC=C(/C=C2CCCC/2)C=C1

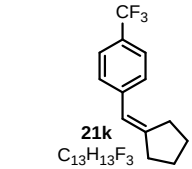
1-chloro-4-(cyclopentylidenemethyl)benzene **21j**:



21j
$C_{12}H_{13}Cl$
MW: 192.69 g.mol^{-1}

Compound **21j** was synthesized from 1-bromo-4-chlorobenzene **18j** (96 mg, 0.5 mmol, 1.0 equiv.) at 90 °C for 3 hours and purified accordingly to *general procedure B* to obtain pure material white needles (46 mg, 0.26 mmol, 52% yield). $\mathbf{R_f}$ = 0.50 (*n*-hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.28 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.32-6.30 (m, 1H), 2.53-2.47 (m, 4H), 1.86 – 1.73 (m, 2H), 1.73 – 1.59 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 148.2, 137.4, 131.2, 129.2 (2C), 128.4 (2C), 119.8, 36.1, 31.3, 27.3, 25.8. Spectral data for compound **21j** were consistent with the data previously reported in the literature.[18c] **SMILES**: ClC1=CC=C(/C=C2CCCC/2)C=C1

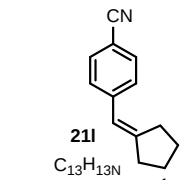
1-(cyclopentylidenemethyl)-4-(trifluoromethyl)benzene **21k**:



21k
$C_{13}H_{13}F_3$
MW: 226.24 g.mol^{-1}

Compound **21k** was synthesized from 1-bromo-4-(trifluoromethyl)benzene **18k** (113 mg, 0.5 mmol, 1.0 equiv.) under reflux for 7 hours and purified accordingly to *general procedure B* to obtain pure material as a clear oil (45 mg, 0.2 mmol, 40% yield). $\mathbf{R_f}$ = 0.48 (EtOAc/*n*-hexanes 4:96). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.56 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 6.40 – 6.37 (m, 1H), 2.58-2.51 (m, 4H), 1.85 – 1.78 (m, 2H), 1.73 – 1.64 (m, 2H). Spectral data for compound **21k** were consistent with the data previously reported in the literature.[18a] **SMILES**: FC(C1=CC=C(/C=C2CCCC/2)C=C1)(F)F

4-(cyclopentylidenemethyl)benzonitrile **21l**:

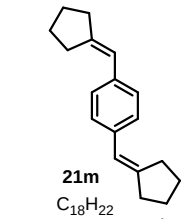


21l
$C_{13}H_{13N}$
MW: 183.25 g.mol^{-1}

Compound **21l** was synthesized from 4-bromobenzonitrile **18l** (91 mg, 0.5 mmol, 1.0 equiv.) under reflux for 5 hours and purified accordingly to *general procedure B* to obtain pure material as white needles (38 mg, 0.21 mmol, 41% yield). $\mathbf{R_f}$ = 0.59 (*n*-hexanes). **IR**νmax (neat): 2955, 2228, 1705, 1272, 831 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.56 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 6.40

– 6.37 (m, 1H), 2.55-2.50 (m, 4H), 1.84-1.77 (m, 2H), 1.72– 1.65 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 152.3, 143.4, 132.1 (2C), 128.3 (2C), 119.9, 119.4, 108.7, 36.5, 31.7, 27.3, 25.6. **SMILES**: N#CC1=CC=C(/C=C2CCCC/2)C=C1

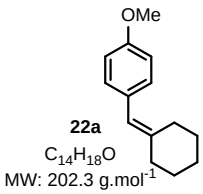
1,4-bis(cyclopentylidenemethyl)benzene **21m**:



Compound **21m** was synthesized from 1,4-dibromo benzene **18m** (118 mg, 0.5 mmol, 1.0 equiv.) under reflux for 10 hours and purified accordingly to the protocol adopted from *general procedure B* to obtain pure material as white crystals (60 mg, 0.3 mmol, 50% yield). The optimized reaction condition for this adopted *general procedure B* includes cyclopentane-carboxaldehyde **19** (246 mg, 2.5 mmol, 5 equiv.), tosylhydrazine (466 mg, 2.5 mmol, 5 equiv.), $Pd_2(dba)_3$ (18 mg, 0.02 mmol, 4 mol %), XPhos (18 mg, 0.04 mmol, 8 mol %), Li*O*t-Bu (319 mg, 3.5 mmol, 7 equiv.), 1,4-dioxane (5.0 mL, [0.1 M]). **R_f** = 0.59 (*n*-hexanes). **IR**νmax (neat): 2923, 2850, 1650, 933, 760 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.26 (d, J = 1.1 Hz, 2H), 6.36 – 6.29 (m, 1H), 2.58-2.53 (m, 2H), 2.50-2.46 (m, 2H), 1.84 – 1.73 (m, 2H), 1.71 – 1.61 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 146.8 (2C), 136.4 (2C), 127.9 (4C), 120.8 (2C), 36.2 (2C), 31.4 (2C), 27.4 (2C), 25.8 (2C). **GCMS** (EI) m/z: [$M^{+\cdot}$] Calcd for $C_{18}H_{22}$ 238; Found 238.

SMILES: C1(/CCCC1)=C/C2=CC=C(/C=C3CCCC/3)C=C2

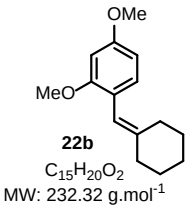
1-(cyclohexylidenemethyl)-4-methoxybenzene **22a**:



Compound **22a** was synthesized from 1-bromo-4-methoxybenzene **18a** (94 mg, 0.5 mmol, 1.0 equiv.) under reflux for 2.5 hours and purified accordingly to *general procedure B* to obtain pure material as clear oil (75 mg, 0.37 mmol, 74% yield). **R_f** = 0.47 (Et_2O/*n*-hexanes 1:9). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.13 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.17 (s, 1H), 3.76 (s, 3H), 2.36 – 2.32 (m, 2H), 2.25 – 2.21 (m, 2H), 1.64-1.57 (m, 4H), 1.56-1.50 (m, 2H). **^{13}C NMR** (100 MHz, CD_3CN) δ (ppm) 158.8, 143.0, 131.6, 130.8 (2C), 122.1, 114.4 (2C), 55.8, 38.2, 30.0, 29.5, 28.6, 27.4. Spectral data for compound **22a** were consistent with the data previously reported in the literature.[18a] **SMILES**: COC1=CC=C(/C=C2CCCCC/2)C=C1

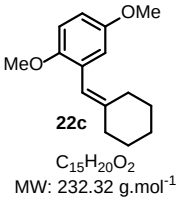
1-(cyclohexylidenemethyl)-2,4-dimethoxybenzene **22b**:

Compound **22b** was synthesized from 1-bromo-2,4-dimethoxybenzene **18b** (109 mg, 0.5 mmol, 1.0 equiv.) under reflux for 5 hours and purified accordingly to *general procedure B* to obtain pure



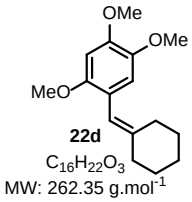
material as clear oil (95 mg, 0.41 mmol, 82% yield). $\mathbf{R_f}$ = 0.47 (Et_2O/*n*-hexanes 1:9). **IR**νmax (neat): 2923, 2850, 1606, 1500, 1205, 1035, 832 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.05 (d, *J* = 8.3 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 6.45 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.14 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.30-2.26 (m, 4H), 1.64 – 1.56 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 159.5, 158.3, 142.5, 131.0, 120.1, 117.0, 103.9, 98.5, 55.6, 55.5, 37.7, 30.0, 28.8, 28.1, 26.9. **HRMS** (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{21}O_2$ 233.1536; Found 233.1536 (0 ppm). **SMILES**: COC1=CC=C(/C=C2CCCCC/2)C(OC)=C1

2-(cyclohexylidenemethyl)-1,4-dimethoxybenzene **22c**:



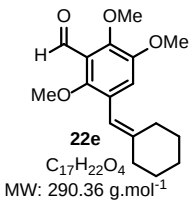
Compound **22c** was synthesized from 2-bromo-1,4-dimethoxybenzene **18c** (109 mg, 0.5 mmol, 1.0 equiv.) under reflux for 5 hours and purified accordingly to *general procedure B* to obtain pure material as a yellow oil (91 mg, 0.39 mmol, 78% yield). $\mathbf{R_f}$ = 0.23 (*n*-hexanes). **IR**νmax (neat): 2924, 2851, 1582, 1490, 1216, 1047, 799 cm^{-1}. **^{1}H NMR** (400 MHz, CD_3CN) δ (ppm) 6.85 (d, *J* = 8.9, 1H), 6.75 (dd, *J* = 8.9, 3.1 Hz, 1H), 6.68 (d, *J* = 3.1 Hz, 1H), 6.15 (s, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 2.30 – 2.24 (m, 4H), 1.63 – 1.58 (m, 4H), 1.56 – 1.51 (m, 2H). **^{13}C NMR** (100 MHz, CD_3CN) δ (ppm) 154.0, 152.4, 144.1, 128.6, 118.5, 117.3, 112.6, 112.4, 56.4, 56.1, 38.1, 30.4, 29.4, 28.6, 27.3. **HRMS** (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{21}O_2$ 233.1536; Found 233.1536 (0 ppm). **SMILES**: COC1=CC=C(OC)C=C1/C=C2CCCCC/2

1-(cyclohexylidenemethyl)-2,4,5-trimethoxybenzene **22d**:



Compound **22d** was synthesized from 1-bromo-2,4,5-trimethoxybenzene **18d** (124 mg, 0.5 mmol, 1.0 equiv.) under reflux for 12 hours and purified accordingly to *general procedure B* to obtain pure material as a yellow oil (123 mg, 0.47 mmol, 94% yield). $\mathbf{R_f}$ = 0.41 (EtOAc/*n*-hexanes 5:95). **IR**νmax (neat): 2950, 1606, 1500, 1205, 1153, 1035, 832 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 6.71 (s, 1H), 6.52 (s, 1H), 6.16 (s, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 2.31-2.27 (m, 5H), 1.66-1.63 (s, 2H), 1.58-1.56 (s, 3H). **^{13}C NMR** (100 MHz, CD_3CN) δ (ppm) 152.7, 149.7, 143.5, 142.9, 119.3, 116.2 (2C), 99.1, 57.2, 56.8, 56.6, 38.1, 30.5, 29.5, 28.6, 27.4. **HRMS** (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{23}O_3$ 263.1642; Found 263.1644 (0.8 ppm). **SMILES**: COC1=CC(OC)=C(OC)C=C1/C=C2CCCCC/2

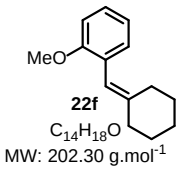
3-(cyclohexylidenemethyl)-2,5,6-trimethoxybenzaldehyde **22e**:



Compound **22e** was synthesized from 3-bromo-2,5,6-trimethoxybenzaldehyde **18e** (34 mg, 0.13 mmol, 1.0 equiv.) under reflux for 12 hours and purified accordingly to *general procedure B* to obtain pure material as a clear oil (9 mg, 0.03 mmol, 25% yield). $\mathbf{R_f}$ = 0.49 (EtOAc/*n*-hexanes 5:95). **IR**νmax (neat): 2929, 1696, 1477, 1230, 1128, 1008 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 10.41 (s, 1H), 6.92 (s, 1H), 6.18 (s, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.73 (s, 3H), 2.28 25 (dt, *J* = 11.8, 5.7 Hz, 4H), 1.66-1.62 (m, 3H), 1.59-1.57 (m, 1H), 1.55-1.51 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 190.2, 152.9, 149.9, 148.8, 145.1, 128.3, 124.0, 120.6, 116.6, 62.3, 62.2, 56.6, 37.5, 30.2, 28.7, 27.9, 26.7. **HRMS** (ESI/TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{23}O_4$ 291.1591; Found 291.1594 (1.0 ppm).

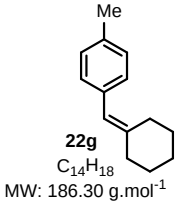
SMILES: [H]C(C1=C(OC)C(/C=C2CCCCC/2)=CC(OC)=C1OC)=O.

1-(cyclohexylidenemethyl)-2-methoxybenzene **22f**:



Compound **22f** was synthesized from 1-bromo-2-methoxybenzene **18f** (94 mg, 0.5 mmol, 1.0 equiv.) under reflux for 7 hours and purified accordingly to *general procedure B* to obtain pure material as a clear oil (85 mg, 0.42 mmol, 84% yield). $\mathbf{R_f}$ = 0.30 (*n*-hexanes). **IR**νmax (neat): 2945, 1609, 1504, 1201, 1037, 820 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.36 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.17 (td, *J* = 7.5, 1.5 Hz, 1H), 6.93 (t, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.61-6.57 (m, 1H), 3.83 (s, 3H), 2.32 – 2.29 (m, 4H), 1.68-1.62 (m, 2H), 1.61-1.55 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 157.3, 143.5, 130.7, 127.5, 127.3, 120.1, 117.5, 110.5, 55.6, 37.8, 30.0, 28.8, 28.1, 26.9. **GCMS** (EI) m/z: $[M^{+\cdot}]$ Calcd for $C_{14}H_{18}O$ 202; Found 202. **SMILES**: COC1=CC=CC=C1/C=C2CCCCC/2

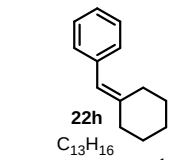
1-(cyclohexylidenemethyl)-4-methylbenzene **22g**:



Compound **22g** was synthesized from 1-bromo-4-methylbenzene **18g** (86 mg, 0.5 mmol, 1.0 equiv.) under reflux for 6 hours and purified accordingly to *general procedure B* to obtain pure material as a clear oil (52 mg, 0.28 mmol, 56% yield). $\mathbf{R_f}$ = 0.72 (*n*-hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.12 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.19 (s, 1H), 2.40 – 2.34 (m, 2H), 2.33 (s, 3H), 2.27 – 2.21 (m, 2H), 1.68 – 1.57 (m, 4H), 1.55 (t, *J* = 6.4 Hz, 2H). Spectral data for compound **22g** were consistent with the data previously reported in the literature.[18d] **SMILES**: CC1=CC=C(/C=C2CCCCC/2)C=C1

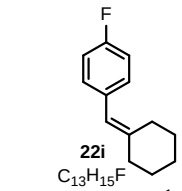
(cyclohexylidenemethyl)benzene **22h**:

Compound **22h** was synthesized from bromobenzene **18h** (79 mg, 0.5 mmol, 1.0 equiv.) under reflux for 6 hours and purified accordingly to *general procedure B* to obtain pure material as a


22h
$C_{13}H_{16}$
MW: 172.27 g.mol^{-1}

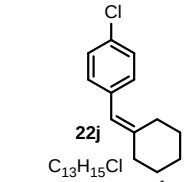
clear oil (60 mg, 0.35 mmol, 70% yield). $\mathbf{R_f}$ = 0.70 (*n*-hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.41 – 7.27 (m, 5H), 3.87 (s, 1H), 1.87-1.81 (m, 1H), 1.77 – 1.59 (m, 3H), 1.54 – 1.39 (m, 4H), 1.33 – 1.24 (m, 2H). Spectral data for compound **22h** were consistent with the data previously reported in the literature.[18d] **SMILES**: C1(/C=C2CCCCC/2)=CC=CC=C1.

1-(cyclohexylidenemethyl)-4-fluorobenzene **22i**:


22i
$C_{13}H_{15}F$
MW: 190.26 g.mol^{-1}

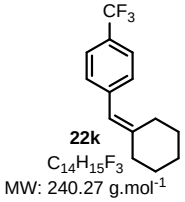
Compound **22i** was synthesized from 1-bromo-4-fluorobenzene **18i** (88 mg, 0.5 mmol, 1.0 equiv.) under reflux for 5 hours and purified accordingly to *general procedure B* to obtain pure material as a clear oil (51 mg, 0.27 mmol, 54% yield). $\mathbf{R_f}$ = 0.77 (*n*-hexanes). **IR**νmax (neat): 2925, 2853, 1505, 1219, 1156, 864, 849, 762 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.16-7.12 (m, 2H), 7.01-6.96 (m, 2H), 6.17 (s, 1H), 2.34-2.31 (m, 2H), 2.26 – 2.23 (m, 2H), 1.64-1.62 (m, 4H), 1.57-1.51 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 161.3 (d, *J* = 244.7 Hz), 143.6, 134.5 (d, *J* = 3.1 Hz), 130.5 (d, *J* = 7.6 Hz, 2C), 121.0, 114.94 (d, *J* = 21.2 Hz, 2C), 37.7, 29.5, 28.7, 28.0, 26.8. **GCMS** (EI) m/z: [$M^{+\cdot}$] Calcd for $C_{13}H_{15}F$ 190; Found 190. **SMILES**: FC1=CC=C(/C=C2CCCCC/2)C=C1.

1-chloro-4-(cyclohexylidenemethyl)benzene **22j**:


22j
$C_{13}H_{15}Cl$
MW: 206.71 g.mol^{-1}

Compound **22j** was synthesized from 1-bromo-4-chlorobenzene **18j** (96 mg, 0.5 mmol, 1.0 equiv.) under stirred at 90 °C for 3 hours and purified accordingly to *general procedure B* to obtain pure material as white needles (33 mg, 0.16 mmol, 32% yield). $\mathbf{R_f}$ = 0.81 (*n*-hexanes). **^{1}H NMR** (400 MHz, CD_3CN) δ (ppm) 7.34 – 7.29 (m, 2H), 7.19 (dd, *J* = 6.4, 4.2 Hz, 2H), 6.20 (s, 1H), 2.37 – 2.31 (m, 2H), 2.26-2.24 (m, 2H), 1.66 – 1.59 (m, 4H), 1.56-1.53 (m, 2H). Spectral data for compound **22j** were consistent with the data previously reported in the literature.[18e] **SMILES**: ClC1=CC=C(/C=C2CCCCC/2)C=C1.

1-(cyclohexylidenemethyl)-4-(trifluoromethyl)benzene **22k**:

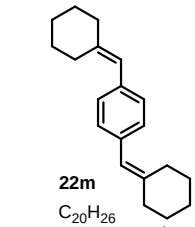

22k
$C_{14}H_{15}F_3$
MW: 240.27 g.mol^{-1}

Compound **22k** was synthesized from 1-bromo-4-(trifluoromethyl)benzene **18k** (113 mg, 0.5 mmol, 1.0 equiv.) under reflux for 7 hours and purified accordingly to *general procedure B* to obtain pure material as white needles (78 mg, 0.33 mmol, 65% yield). $\mathbf{R_f}$ = 0.81 (*n*-hexanes). **IR**νmax (neat): 2929, 2855, 1321, 1120, 851 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.55 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 6.24 (s, 1H), 2.47 – 2.32 (m, 2H), 2.32 – 2.24 (m, 2H), 1.71 – 1.59 (m, 4H), 1.59-1.56 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 146.2, 142.6, 129.6 (3C), 124.9 (q, *J* = 272.0 Hz), 125.4

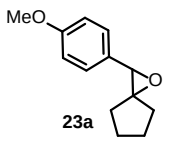
(q, *J* = 3.0 Hz, 2C), 121.4, 38.2, 30.0, 29.1, 28.3, 27.1. **GCMS** (EI) m/z: [$M^{+\cdot}$] Calcd for $C_{14}H_{15}F_3$ 240; Found 240. **SMILES**: FC(C1=CC=C(/C=C2CCCCC/2)C=C1)(F)F.

1,4-bis(cyclohexylidenemethyl)benzene **22m**:

Compound **22m** was synthesized from 1,4-dibromo benzene **18m** (118 mg, 0.5 mmol, 1.0 equiv.) under reflux for 10 hours and purified accordingly to the protocol adopted from *general procedure B* to obtain pure material as white crystals (77 mg, 0.29 mmol, 58% yield). The optimized reaction condition for this adopted *general procedure B* includes cyclohexanecarboxaldehyde **20** (224 mg, 2.0 mmol, 4.0 equiv.), tosylhydrazine (372 mg, 2.0 mmol, 5.0 equiv.), $Pd_2(dba)_3$ (18 mg, 0.02 mmol, 4 mol %), XPhos (18 mg, 0.04 mmol, 8 mol %), Li*O*t-Bu (319 mg, 3.5 mmol, 7.0 equiv.), 1,4-dioxane (5 mL, [0.1 M]). **R_f** = 0.83 (*n*-hexanes). **IR**νmax (neat): 2922, 2850, 1650, 933, 751 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.14 (s, 4H), 6.20 (s, 2H), 2.42 – 2.39 (m, 4H), 2.27 – 2.24 (m, 4H), 1.66 – 1.60 (m, 7H), 1.59 – 1.53 (m, 5H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 143.3 (2C), 136.1 (2C), 128.7 (4C), 122.0 (2C), 37.9 (2C), 29.7 (2C), 28.8 (2C), 28.0 (2C), 26.9 (2C). **GCMS** (EI) m/z: [$M^{+\cdot}$] Calcd for $C_{20}H_{26}$ 266; Found 266. **SMILES**: C1(/C=C2CCCCC/2)=CC=C(/C=C3CCCCC/3)C=C1

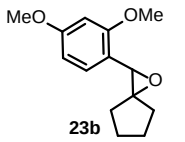

22m
$C_{20}H_{26}$
MW: 266.43 g.mol^{-1}

2-(4-methoxyphenyl)-1-oxaspiro[2.4]heptane **23a.**


23a
$C_{13}H_{16}O_2$
MW: 204.27 g.mol^{-1}

Compound **23a** was synthesized from styrene **21a** (188 mg, 1.0 mmol, 1.0 equiv.) and oxone (615 mg, 1.0 mmol, 1.0 equiv.) at 0 ˚C for 1 hour and purified accordingly to *general procedure C* to obtain pure material as a clear oil (192 mg, 0.94mmol, 94% yield). **R_f** = 0.54 (*n*-hexanes). **IR**νmax (neat): 2920, 1613, 1513, 1446, 1245, 1035 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.18(d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 3.96 (s, 1H), 3.81 (s, 3H), 2.02-1.97 (m, 1H), 1.85-1.76 (m, 4H), 1.68-1.43 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 159.2, 129.3, 127.5 (2C), 113.7 (2C), 72.6, 63.2, 55.4, 34.1, 28.5, 25.4, 25.3. **HRMS** (ESI/TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}O_2$ 205.1223; Found 205.1225 (1.0 ppm). **SMILES**: COC1=CC=C(C2C3(O2)CCCC3)C=C1

2-(2,4-dimethoxyphenyl)-1-oxaspiro[2.4]heptane **23b.**

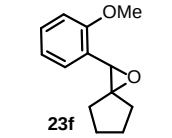


23b
$C_{14}H_{18}O_3$
MW: 234.30 g.mol^{-1}

Compound **23b** was synthesized from styrene **21b** (218 mg, 1.0 mmol, 1.0 equiv.) and oxone (615 mg, 1.0 mmol, 1.0 equiv.) at 0 ˚C for 1 hour and purified accordingly to *general procedure C* to obtain pure material as a clear oil (194 mg, 0.83 mmol, 83% yield). $\mathbf{R_f}$ = 0.48 (*n*-hexanes). **IR**νmax (neat): 2950, 1606, 1500, 1205, 1153, 1035, 832 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.06 (d, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 2.3 Hz, 1H), 6.48 (dd, *J* = 8.4 , 2.3 Hz, 1H), 4.13 (s, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 2.07-2.01 (m, 2H), 1.86-1.80 (m, 3H), 1.75 – 1.70 (m, 2H), 1.69-1.66 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 159.0, 127.2, 118.7, 118.5, 103.9, 98.3, 72.3, 59.8, 55.6, 55.5, 33.7, 28.7, 25.3, 25.2. **HRMS** (ESI/QTOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{18}O_3Na$ 257.1148; Found 257.1152 (1.5 ppm). **SMILES**: COC1=CC(OC)=C(C2C3(O2)CCCC3)C=C1

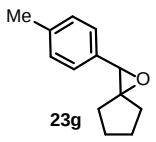
2-(2-methoxyphenyl)-1-oxaspiro[2.4]heptane **23f.**

Compound **23f** was prepared from styrene **21f** (188 mg, 1.0 mmol, 1.0 equiv.) and oxone (615 mg, 1.0 mmol, 1.0 equiv.) at 0 ˚C for 1.5 hour and purified accordingly to *general procedure C* to obtain pure material as a clear oil (168 mg, 0.82 mmol, 82% yield). $\mathbf{R_f}$ = 0.23 (*n*-hexanes). **IR**νmax (neat): 2957, 1493, 1241, 1026, 752cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.23 (td, *J* = 1.2, 7.9 Hz, 1H), 7.18 (dd, *J* = 7.5, 1.4 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 4.20 (s, 1H), 3.85 (s, 3H), 2.12-2.04 (m, 1H), 1.87-1.80 (m, 2H), 1.76 – 1.64 (m, 2H), 1.57 – 1.50 (m, 2H), 1.42 – 1.35 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 157.9, 128.3, 126.5, 125.9, 120.3, 110.0, 72.3, 59.9, 55.5, 33.7, 28.7, 25.3, 25.1. **SMILES**: COC1=C(C2C3(O2)CCCC3)C=CC=C1



23f
$C_{13}H_{16}O_2$
MW: 204.27 g.mol^{-1}

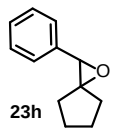
2-(p-tolyl)-1-oxaspiro[2.4]heptane **23g.**



23g
$C_{13}H_{16}O$
MW: 188.27 g.mol^{-1}

Compound **23g** was synthesized from styrene **21g** (172 mg, 1.0 mmol, 1.0 equiv.) and oxone (615 mg, 1.0 mmol, 1.0 equiv.) at 0 ˚C for 3 hour and purified accordingly to *general procedure C* to obtain pure material as a clear liquid at room temperature and white solid at 4-5 °C (168 mg, 0.89 mmol, 89% yield). $\mathbf{R_f}$ = 0.31 (*n*-hexanes). **IR**νmax (neat): 2957, 1515, 1193, 787, 755 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.15 (s, 4H), 3.98 (s, 1H), 2.35 (s, 3H), 2.03 – 1.98 (m, 1H), 1.88 – 1.78 (m, 3H), 1.68 – 1.60 (m, 2H), 1.57 – 1.44 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 137.2, 134.3, 128.9 (2C), 126.3 (2C), 72.6, 63.4, 34.1, 28.5, 25.4, 25.3, 21.3. **SMILES**: CC1=CC=C(C2C3(O2)CCCC3)C=C1

2-phenyl-1-oxaspiro[2.4]heptane **23h.**

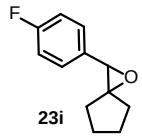


$C_{12}H_{14}O$
MW: 174.24 g.mol^{-1}

Compound **23h** was synthesized from styrene **21h** (158 mg, 1.0 mmol, 1.0 equiv.), acetone (66 mL, [0.02 M]), sat. $NaHCO_3$ solution (40 mL, [0.03 M]), oxone (1.84 g, 3.0 mmol, 3.0 equiv.) and water (20 mL, [0.05 M]) at 0 ˚C for 5 hour and purified accordingly to *general procedure C* to obtain pure material as a clear oil (152 mg, 0.87 mmol, 87% yield). $\mathbf{R_f}$ = 0.31 (EtOAc/*n*-hexanes 3:97). **IR**νmax (neat): 2957, 1496, 1454, 745, 698 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.37 – 7.25 (m, 5H), 4.01 (s, 1H), 2.09 – 1.99 (m, 1H), 1.85 – 1.79 (m, 3H), 1.71 – 1.57 (m, 2H), 1.50 – 1.43 (m, 2H). Spectral data for compound **23h** were consistent with the data previously reported in the literature.[19] **SMILES**: C1(C2C3(O2)CCCC3)=CC=CC=C1

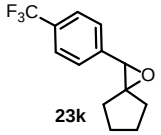
2-(4-fluorophenyl)-1-oxaspiro[2.4]heptane **23i.**

Compound **23i** was synthesized from styrene **21i** (176 mg, 1.0 mmol, 1.0 equiv.), acetone (66 mL, [0.02 M]), Sat. $NaHCO_3$ solution (40 mL, [0.03 M]), oxone (1.84 g, 3.0 mmol, 3.0 equiv.) and water (20 mL, [0.05 M]) at room temperature for 2 hours and purified accordingly to *general procedure C* to obtain pure material as a white solid (150 mg, 0.78 mmol, 78% yield). $\mathbf{R_f}$ = 0.11 (*n*-hexanes). **IR**νmax (neat): 2959, 1510, 1222, 840, 764 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.38 – 7.35 (m, 2H), 7.02 (t, *J* = 8.1 Hz, 2H), 4.58 (s, 1H), 1.81-1.73 (m, 4H), 1.62-1.58 (m, 3H), 1.30 – 1.25 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 162.5 (d, *J* = 246.5 Hz), 137.0, 129.1(d, *J* = 8.0 Hz, 2C), 115.1 (d, *J* = 21.2 Hz, 2C), 84.9, 79.1, 37.9, 36.1, 23.8, 23.7. **HRMS** (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{14}FO$ 193.1023; Found 193.1024 (0.5 ppm). **SMILES**: FC1=CC=C(C2C3(O2)CCCC3)C=C1



$C_{12}H_{13}FO$
MW: 192.23 g.mol^{-1}

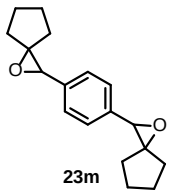
2-(4-(trifluoromethyl)phenyl)-1-oxaspiro[2.4]heptane **23k.**



$C_{13}H_{13}F_3O$
MW: 242.24 g.mol^{-1}

Compound **23k** was synthesized from styrene **21k** (226 mg, 1.0 mmol, 1.0 equiv.), acetone (66 mL, [0.02 M]), sat. $NaHCO_3$ solution (40 mL, [0.03 M]), oxone (1.84 g, 3.0 mmol, 3.0 equiv.) and water (20 mL, [0.05 M]) at room temperature for 2 hours and purified accordingly to *general procedure C* to obtain pure material as a white solid (189 mg, 0.78 mmol, 78% yield). $\mathbf{R_f}$ = 0.60 (Et_2O/*n*-hexanes 15:85). **IR**νmax (neat): 2959, 1510, 1222, 840, 764 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.62 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 4.08 (s, 1H), 2.15 – 1.99 (m, 1H), 1.94 – 1.52 (m, 5H), 1.47-1.43 (m, 1H), 1.31-1.29 (m, 1H). **SMILES**: FC(C1=CC=C(C2C3(O2)CCCC3)C=C1)(F)F

1,4-di(1-oxaspiro[2.4]heptan-2-yl)benzene **23m.**

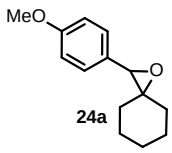


23m

$C_{18}H_{22}O_2$
MW: 270.37 g.mol^{-1}

Compound **23m** was synthesized from styrene **21m** (238 mg, 1.0 mmol, 1.0 equiv.), acetone (132 mL, [8 mM]), sat. $NaHCO_3$ solution (80 mL, [10 mM]), oxone (3.69 g, 6.0 mmol, 6.0 equiv.) and water (40 mL, [30 mM]) at room temperature for 4 hours and purified accordingly to *general procedure C* to obtain pure material as a white solid (200 mg, 0.74 mmol, 74% yield). $\mathbf{R_f}$ = 0.23 (*n*-hexanes). **IR**νmax (neat): 2926, 1451, 910, 773, 709 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.23 (s, 4H), 4.00 (d, *J* = 1.1 Hz, 2H), 2.05 – 1.96 (m, 2H), 1.87 – 1.74 (m, 7H), 1.71 – 1.60 (m, 5H), 1.59 – 1.52 (m, 2H), 1.50 – 1.42 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 136.6 (2C), 126.1 (4C), 72.7 (2C), 63.2 (2C), 31.4 (2C), 28.5 (2C), 25.4 (2C), 25.3 (2C). **HRMS** (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{23}O_2$ 271.1693; Found 271.1688 (1.8 ppm); m/z: $[M+NH_4]^+$ Calcd for $C_{18}H_{26}NO_2$ 288.1958; Found 288.1954 (1.4 ppm). **SMILES**: C1(C2C3(O2)CCCC3)=CC=C(C4C5(CCCC5)O4)C=C1

2-(4-methoxyphenyl)-1-oxaspiro[2.5]octane **24a.**

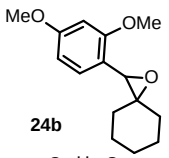


24a

$C_{14}H_{18}O_2$
MW: 218.13 g.mol^{-1}

Compound **24a** was synthesized from styrene **22a** (202 mg, 1.0 mmol, 1.0 equiv.) and oxone (615 mg, 1.0 mmol, 1.0 equiv.) at 0 ˚C for 2 hours and purified accordingly to *general procedure C* to obtain pure material as a clear oil (203 mg, 0.93mmol, 93% yield). $\mathbf{R_f}$ = 0.70 (EtOAc/*n*-hexanes 5:95). **IR**νmax (neat): 2931, 1512, 1243, 1169, 1063, 806 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.22 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 3.80 (s, 1H), 3.77 (s, 3H), 1.78-1.74 (m, 1H), 1.64-1.56 (m, 2H), 1.55-1.46 (m, 2H), 1.45-1.33 (m, 2H), 1.29-1.16 (m, 3 H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 159.0, 128.6, 127.6 (2C), 113.6 (2C), 65.6, 64.5, 55.4, 35.5, 28.5, 25.7, 25.5, 24.7. **HRMS** (ESI/TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{19}O_2$ 219.1380; Found 219.1384 (1.8 ppm). **SMILES**: COC1=CC=C(C2C3(CCCCC3)O2)C=C1

2-(2,4-dimethoxyphenyl)-1-oxaspiro[2.5]octane **24b.**



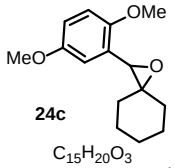
24b

$C_{15}H_{20}O_3$
MW: 248.32 g.mol^{-1}

Compound **24b** was synthesized from styrene **22b** (232 mg, 1.0 mmol, 1.0 equiv.) and oxone (615 mg, 1.0 mmol, 1.0 equiv.) at 0 ˚C for 3 hours and purified accordingly to *general procedure C* to obtain pure material as a clear oil (176 mg, 0.71 mmol, 71% yield). $\mathbf{R_f}$ = 0.35 (*n*-hexanes). **IR**νmax (neat): 2949, 1606, 1505, 1211, 1038, 836 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.12 (dd, *J* = 8.5, 0.8 Hz, 1H), 6.48 – 6.43 (m, 2H), 3.86 (s, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 1.77 – 1.71 (m, 2H), 1.66 – 1.60 (m, 4H), 1.55 – 1.51 (m, 2H), 1.40 – 1.35 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 160.2, 158.8, 128.1, 117.8, 103.6, 98.2, 65.4, 61.9, 55.5, 55.4, 35.5, 28.9, 25.8, 25.4, 24.8.

SMILES: COC1=C(C2C3(CCCCC3)O2)C=CC(OC)=C1

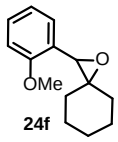
2-(2,5-dimethoxyphenyl)-1-oxaspiro[2.5]octane **24c.**



24c
$C_{15}H_{20}O_3$
MW: 248.32 g.mol^{-1}

Compound **24c** was synthesized from styrene **22c** (232 mg, 1.0 mmol, 1.0 equiv.) and oxone (615 mg, 1.0 mmol, 1.0 equiv.) at 0 ˚C for 3 hours and purified accordingly to *general procedure C* to obtain pure material as a clear oil (194 mg, 0.78 mmol, 78% yield). $\mathbf{R_f}$ = 0.35 (*n*-hexanes). **IR**νmax (neat): 2950, 1606, 1500, 1485, 1223, 1153, 1035, 832 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 6.83 (d, *J* = 2.0 Hz, 1H), 6.88 (d, *J* = 4.0 Hz, 1H), 6.70(d, *J* = 3.1 Hz, 1H), 3.91 (s, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 1.82-1.73 (m, 2H),1.71-1.63 (m, 2H), 1.53-1.50 (m, 2H), 1.39-1.37 (m, 2H), 1.29-1.21 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 153.4, 151.9, 126.3, 113.3, 112.9, 110.8, 65.5, 61.9, 55.9, 55.8, 35.5, 28.8, 25.7, 25.2, 24.7. **SMILES**: COC1=C(C2C3(CCCCC3)O2)C=C(OC)C=C1

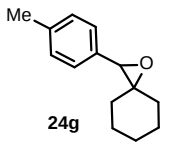
2-(2-methoxyphenyl)-1-oxaspiro[2.5]octane **24f.**



24f
$C_{14}H_{18}O_2$
MW: 218.30 g.mol^{-1}

Compound **24f** was synthesized from styrene **22f** (202 mg, 1.0 mmol, 1.0 equiv.) and oxone (615 mg, 1.0 mmol, 1.0 equiv.) at 0 ˚C for 2 hours and purified accordingly to *general procedure C* to obtain pure material as a white solid (153 mg, 0.70 mmol, 70% yield). $\mathbf{R_f}$ = 0.68 (EtOAc/*n*-hexanes 1:9). **IR**νmax (neat): 2929, 1494, 1241, 1026, 752 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.25 – 7.23 (m, 2H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 3.93 (s, 1H), 3.86 (s, 3H), 1.83-1.74 (m, 2H), 1.70 – 1.65 (m, 2H), 1.55 – 1.53 (m, 2H), 1.42 – 1.34 (m, 2H), 1.29 – 1.19 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 157.8, 128.3, 127.6, 125.3, 120.2, 109.8, 65.5, 62.1, 55.4, 35.6, 29.0, 25.8, 25.4, 24.8. **HRMS** (ESI/TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{19}O_2$ 219.1380; Found 219.1385 (2.3 ppm). **SMILES**: COC1=C(C2C3(CCCCC3)O2)C=CC=C1

2-(p-tolyl)-1-oxaspiro[2.5]octane **24g.**

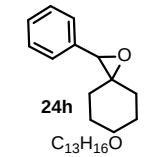


24g
$C_{14}H_{18}O$
MW: 202.30 g.mol^{-1}

Compound **24g** was synthesized from styrene **22g** (186 mg, 1.0 mmol, 1.0 equiv.) and oxone (615 mg, 1.0 mmol, 1.0 equiv.) at 0 ˚C for 3 hours and purified accordingly to *general procedure C* to obtain pure material as a clear oil (170 mg, 0.84 mmol, 84% yield). $\mathbf{R_f}$ = 0.81 (EtOAc/*n*-hexanes 1:9). **IR**νmax (neat): 2927, 1447, 915, 802, 794 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.19 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 3.83 (s, 1H), 2.35 (s, 3H), 1.85 – 1.80 (m, 1H), 1.77 – 1.68 (m, 1H), 1.68 – 1.56 (m, 3H), 1.51 – 1.36 (m, 3H), 1.32 – 1.25 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 137.2, 134.3, 128.9 (2C), 126.6 (2C), 72.5, 63.4 (2C), 34.1, 28.5, 25.4, 25.3, 21.3. **HRMS**

(ESI/TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{19}O$ 203.1430; Found 203.1434 (1.8 ppm). **SMILES**: CC1=CC=C(C2C3(CCCCC3)O2)C=C1

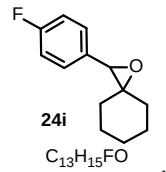
2-phenyl-1-oxaspiro[2. 5]octane **24h.**



$C_{13}H_{16}O$
MW: 188.27 g.mol^{-1}

Compound **24h** was synthesized from styrene **22h** (172 mg, 1.0 mmol, 1.0 equiv.) and oxone (615 mg, 1.0 mmol, 1.0 equiv.) at 0 ˚C for 5 hours and purified accordingly to *general procedure C* to obtain pure material as a white solid (151 mg, 0.80 mmol, 80% yield). $\mathbf{R_f}$ = 0.12 (*n*-hexanes). **IR**νmax (neat): 2930, 1452, 910, 751, 701 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.38 – 7.27 (m, 5H), 3.87 (s, 1H), 1.89 – 1.57 (m, 5H), 1.52 – 1.37 (m, 3H), 1.33 – 1.24 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 136.5, 128.1 (2C), 127.4, 126.5 (2C), 65.6, 64.7, 35.6, 28.5, 25.6, 25.5, 24.7. Spectral data for compound **24h** were consistent with the data previously reported in the literature.[19] **SMILES**: C1(C2C3(CCCCC3)O2)=CC=CC=C1

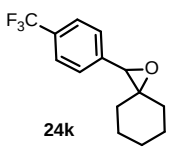
2-(4-fluorophenyl)-1-oxaspiro[2.5]octane **24i.**



$C_{13}H_{15}FO$
MW: 206.26 g.mol^{-1}

Compound **24i** was synthesized from styrene **22i** (190 mg, 1.0 mmol, 1.0 equiv.), acetone (66 mL, [0.02 M]), sat. $NaHCO_3$ solution (40 mL, [0.03 M]), oxone (1.84 g, 3.0 mmol, 3.0 equiv.) and water (20 mL, [0.05 M]) at room temperature for 3.5 hours and purified accordingly to *general procedure C* to obtain pure material as a white solid (153 mg, 0.74 mmol, 74% yield). $\mathbf{R_f}$ = 0.77 (*n*-hexanes). **IR**νmax (neat): 2931, 1510, 1215, 814, 767 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.30 – 7.24 (m, 2H), 7.02 (t, *J* = 8.7 Hz, 2H), 3.82 (s, 1H), 1.83-1.80 (m, 1H), 1.73 – 1.69 (m, 1H), 1.66 – 1.54 (m, 5H), 1.46 – 1.39 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 162.2 (d, *J* = 245.2 Hz), 132.2, 128.0 (d, *J* = 8.8 Hz, 2C), 115.0 (d, *J* = 22.1 Hz, 2C), 65.7, 64.1, 35.4, 28.4, 25.5, 25.4, 24.6. **HRMS** (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{16}FO$ 207.1181; Found 207.1176 (1.8 ppm). **SMILES**: FC1=CC=C(C2C3(CCCCC3)O2)C=C1

2-(4-(trifluoromethyl)phenyl)-1-oxaspiro[2.5]octane **24k.**

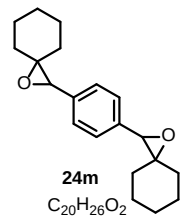


$C_{14}H_{15}F_3O$
MW: 256.27 g.mol^{-1}

Compound **24k** was synthesized from styrene **22k** (240 mg, 1.0 mmol, 1.0 equiv.), acetone (66 mL, [0.02 M]), sat. $NaHCO_3$ solution (40 mL, [0.03 M]), oxone (1.84 g, 3.0 mmol, 3.0 equiv.) and water (20 mL, [0.05 M]) at room temperature for 7 hours and purified accordingly to *general procedure C* to obtain pure material as a clear liquid (236 mg, 0.92 mmol, 92% yield). $\mathbf{R_f}$ = 0.17 (*n*-hexanes); **IR**νmax (neat): 2934, 1321, 1121, 1065 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.60 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 3.89 (s, 1H), 1.83 (s, 1H), 1.78 – 1.59 (m, 4H), 1.51 – 1.35 (m, 3H), 1.30

– 1.20 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 140.7, 129.6 (q, *J* = 32.3 Hz), 126.8 (2C), 125.1 (q, *J* = 3.7 Hz, 2C), 124.3 (q, *J* = 271.9 Hz, 1C), 66.1, 64.0, 35.5, 28.5, 25.5, 25.4, 24.6. **HRMS** (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{16}F_3O$ 257.1148; Found 257.1142 (2.3 ppm). **SMILES**: FC(C1=CC=C(C2C3(CCCCC3)O2)C=C1)(F)F

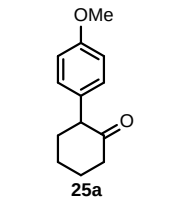
1,4-di(1-oxaspiro[2.5]octan-2-yl)benzene **24m.**



24m
$C_{20}H_{26}O_2$
MW: 298.43 g.mol^{-1}

Compound **24m** was synthesized from styrene **22m** (266 mg, 1.0 mmol, 1.0 equiv.), acetone (132 mL, [8 mM]), sat. $NaHCO_3$ solution (80 mL, [10 mM]), oxone (3.69 g, 6.0 mmol, 6.0 equiv.) and water (40 mL, [30 mM]) at room temperature for 5 hours and purified accordingly to *general procedure C* to obtain pure material as a white solid (269 mg, 0.9 mmol, 90% yield). $\mathbf{R_f}$ = 0.8 (EtOAc/*n*-hexanes 85:15). **IR**νmax (neat): 2922, 1455, 910, 773, 710 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.27 (s, 4H), 3.84 (s, 2H), 1.85 – 1.78 (m, 2H), 1.76 – 1.59 (m, 8H), 1.51 – 1.38 (m, 6H), 1.33 – 1.21 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 135.5 (2C), 126.1 (4C), 65.7 (2C), 64.6 (2C), 35.5 (2C), 28.5 (2C), 25.6 (2C), 25.4 (2C), 24.6 (2C). **HRMS** (ESI/QTOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{27}O_2$ 299.2006; Found 299.2002 (1.3 ppm).
SMILES: C1(C2C3(CCCCC3)O2)=CC=C(C4C5(CCCCC5)O4)C=C1

2-(4-methoxyphenyl)cyclohexan-1-one **25a.**

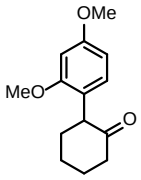


25a
$C_{13}H_{16}O_2$
MW: 204.27 g.mol^{-1}

Compound **25a** was synthesized from styrene oxide **23a** (20 mg, 0.1 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a white powder (16 mg, 0.079mmol, 79% yield) using $Bi(OTf)_3$ and (18 mg, 0.09mmol, 92 % yield) using $AlCl_3$. $\boldsymbol{R_f}$ = 0.40 (Et_2O/*n*-hexanes 2:8). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.06 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 3.80 (s, 3H), 3.57 (dd, *J* = 12.2, 5.5 Hz 1H), 2.55 – 2.41 (m, 2H), 2.28 – 2.24 (m, 1H), 2.18 – 2.11 (m, 1H), 2.05 – 1.95 (m, 2H), 1.88 – 1.77 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 210.9, 158.5, 130.9, 129.5 (2C), 113.9 (2C), 56.7, 55.3, 42.3, 35.4, 27.9, 25.5. Spectral data for compound **25a** were consistent with the data previously reported in the literature.[20a] **SMILES**: O=C1CCCCC1C2=CC=C(OC)C=C2

2-(2,4-dimethoxyphenyl)cyclohexan-1-one **25b.**

Compound **25b** was synthesized from styrene oxide **23b** (30 mg, 0.13 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a white powder (29 mg, 0.12 mmol, 95% yield) using $Bi(OTf)_3$ and (28 mg, 0.12 mmol, 93% yield) using $AlCl_3$. R_f = 0.35 (Et_2O/*n*-hexanes 2:8). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.01 (d, *J* = 8.2 Hz, 1H), 6.49 (d, *J* = 2.5 Hz, 1H), 6.47 (dd, *J* = 8.2, 2.5 Hz, 1H), 3.85 (dd, *J* = 12.8, 5.7 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 2.53 – 2.43 (m, 1H), 2.35 – 2.32 (m, 1H), 2.14 – 2.08 (m, 3H), 1.86 – 1.67 (m, 3H). Spectral data for compound **25b** were consistent with the data previously reported in the literature.[20a]

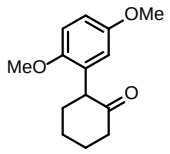


25b
$C_{14}H_{18}O_3$
MW: 234.30 g.mol^{-1}

SMILES: O=C1CCCCC1C2=C(OC)C=C(OC)C=C2

2-(2,5-dimethoxyphenyl)cyclohexan-1-one **25c.**

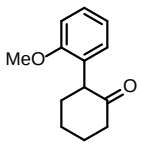
Compound **25c** was synthesized from styrene oxide **23c** (20 mg, 0.1 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a white powder (18 mg, 0.08 mmol, 90% yield) using $Bi(OTf)_3$ and (17 mg, 0.07 mmol, 86% yield) using $AlCl_3$. R_f = 0.40 (Et_2O/*n*-hexanes 2:8). **IR**νmax (neat): 2937, 1713, 1452, 1050, 803 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 6.86-6.75 (m, 3H), 3.93 (dd, *J* = 10.3, 5.3 Hz 1H), 3.77 (s, 3H), 3.73 (s, 3H), 2.89 – 2.85 (m, 2H), 2.07 – 1.96 (m, 4H), 1.72 – 1.69 (m, 1H), 1.56 – 1.44 (m, 2H). Spectral data for compound **25c** were consistent with the data previously reported in the literature.[20b] **SMILES**: O=C1CCCCC1C2=CC(OC)=CC=C2OC



25c
$C_{14}H_{18}O_3$
MW: 234.30 g.mol^{-1}

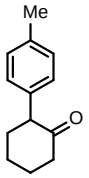
2-(2-methoxyphenyl)cyclohexan-1-one **25f.**

Compound **25f** was synthesized from styrene oxide **23f** (50 mg, 0.25 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a white powder (38 mg, 0.19 mmol, 76% yield) using $Bi(OTf)_3$ and (39 mg, 0.07 mmol, 77% yield) using $AlCl_3$. R_f = 0.35 (EtOAc/*n*-hexanes 2:8). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.23 (dd, *J* = 7.0, 1.2 Hz, 1H), 7.11 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.95 (td, *J* = 7.5, 1.1 Hz, 1H), 6.88 (dd, *J* = 8.2, 0.9 Hz, 1H), 3.93 (dd, *J* = 12.7, 5.4 Hz, 1H), 3.77 (s, 3H), 2.57 – 2.44 (m, 2H), 2.24 – 2.13 (m, 2H), 2.09 – 1.97 (m, 2H), 1.89 – 1.74 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 209.9, 157.1, 128.9, 128.1, 120.7 (2C), 110.8, 55.6, 51.2, 42.4, 33.6, 27.7, 25.8. Spectral data for compound **25f** were consistent with the data previously reported in the literature.[20c] **SMILES**: O=C1CCCCC1C2=C(OC)C=CC=C2



25f
$C_{13}H_{16}O_2$
MW: 204.27 g.mol^{-1}

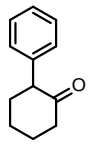
2-(p-tolyl)cyclohexan-1-one **25g.**



25g
$C_{13}H_{16}O$
MW: 188.27 g.mol^{-1}

Compound **25g** was synthesized from styrene oxide **23g** (50 mg, 0.27 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a white powder (35 mg, 0.19 mmol, 70% yield) using $Bi(OTf)_3$ and (36 mg, 0.19 mmol, 71% yield) using $AlCl_3$. R_f = 0.53 (EtOAc/*n*-hexanes 2:8). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.16 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 3.58 (dd, *J* = 12.0, 5.4 Hz, 1H), 2.57 – 2.41 (m, 2H), 2.34 (s, 3H), 2.31 – 2.23 (m, 1H), 2.21 – 2.11 (m, 1H), 2.04 – 1.98 (m, 2H), 1.91 – 1.79 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 210.6, 136.6, 135.9, 129.2 (2C), 128.5 (2C), 57.1, 42.3, 35.2, 27.9, 25.4, 21.2. Spectral data for compound **25g** were consistent with the data previously reported in the literature.[20d] **SMILES**: O=C1CCCCC1C2=CC=C(C)C=C2

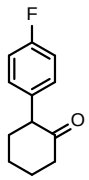
2-phenylcyclohexan-1-one **25h.**



25h
$C_{12}H_{14}O$
MW: 174.24 g.mol^{-1}

Compound **25h** was synthesized from styrene oxide **23h** (20 mg, 0.1 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a white powder (3 mg, 0.015 mmol, 15% yield) using $Bi(OTf)_3$. R_f = 0.55 (Et_2O/*n*-hexanes 2:8). **IR**νmax (neat): 2937, 2855, 1710, 1452 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.32 (d, *J* = 6.9 Hz, 2H), 7.24 (m, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 3.57 (dd, *J* = 12.8, 5.7 Hz, 1H), 2.50 – 2.41 (m, 2H), 2.36 – 2.33 (m, 2H), 2.14 – 2.08 (m, 3H), 1.86 – 1.75 (m, 1H). Spectral data for compound **25h** were consistent with the data previously reported in the literature. [20e] **SMILES**: O=C1CCCCC1C2=CC=CC=C2

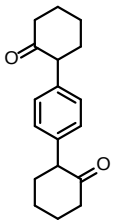
2-(4-fluorophenyl)cyclohexan-1-one **25i.**



25i
$C_{12}H_{13}OF$
MW: 192.23 g.mol^{-1}

Compound **25i** was synthesized from styrene oxide **23i** (20 mg, 0.1 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a clear oil (2 mg, 0.01 mmol, 11% yield) using $AlCl_3$. R_f = 0.6 (EtOAc/*n*-hexanes 2:8). **IR**νmax (neat): 2937, 2855, 1710, 1452 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.15 – 7.07 (m, 2H), 7.06 – 6.97 (m, 2H), 3.60 (dd, *J* = 12.2, 5.3 Hz, 1H), 2.58 – 2.41 (m, 2H), 2.31 – 2.22 (m, 1H), 2.19-2.15 (m, 1H), 2.02-1.92 (m, 2H), 1.87 – 1.78 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 210.1, 162.0 (d, *J* = 244.8 Hz), 134.6, 130.2 (d, *J* = 8.0 Hz, 2C), 115.3 (d, *J* = 21.5 Hz, 2C), 56.8, 42.3, 35.6, 27.9, 25.5. Spectral data for compound **25i** were consistent with the data previously reported in the literature.[20f] **SMILES**: O=C1CCCCC1C2=CC=C(F)C=C2

2,2'-(1,4-phenylene)bis(cyclohexan-1-one) **25m.**

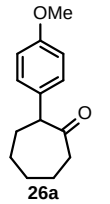


25m
$C_{18}H_{22}O_2$
MW: 270.37 g.mol^{-1}

Compound **25m** was synthesized from styrene oxide **23m** (14 mg, 0.05 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a white powder (10 mg, 0.038 mmol, 75% yield) using $Bi(OTf)_3$ (7 mg, 0.01 mmol, 20 mol %). R_f = 0.35 (Et_2O/*n*-hexanes 2:8). **IR**νmax (neat): 2927, 2854, 1702, 1452 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.11 (s, 4H), 3.60 (dd, *J* = 11.9, 3.3 Hz, 2H), 2.55 – 2.41 (m, 4H), 2.31-2.25 (m, 2H), 2.17-2.12 (m, 2H), 2.07 – 1.96 (m, 4H), 1.87-1.78 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 210.6 (2C), 137.2 (2C), 128.6 (4C), 57.1 (2C), 42.3 (2C), 35.1 (2C), 28.0 (2C), 25.4 (2C). **HRMS** (ESI/TOF) m/z: $[M+NH_4]^+$ Calcd for $C_{18}H_{26}NO_2$ 288.1958; Found 288.1954 (1.4 ppm); $[M+H]^+$ Calcd for $C_{18}H_{23}O_2$ 271.1693; Found 271.1688 (1.8 ppm). **SMILES**: O=C1CCCCC1C2=CC=C(C3CCCCC3=O)C=C2

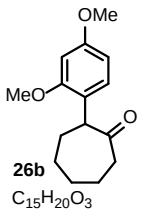
2-(4-methoxyphenyl)cycloheptan-1-one **26a.**

Compound **26a** was synthesized from styrene oxide **24a** (20 mg, 0.1 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a white powder (16 mg, 0.075 mmol, 75% yield) using $Bi(OTf)_3$ and (20 mg, 0.09 mmol, 90 % yield) using $AlCl_3$. R_f = 0.3 (EtOAc/*n*-hexanes 2:8).**^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.15 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 3H), 3.67 (dd, *J* = 11.4, 4.2 Hz, 1H), 2.73 – 2.62 (m, 1H), 2.54 – 2.45 (m, 1H), 2.18 – 2.08 (m, 1H), 2.05 – 1.87 (m, 4H), 1.69 – 1.58 (m, 1H), 1.49 – 1.40 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 213.8, 158.7, 132.6, 128.9 (2C), 114.1 (2C), 58.1, 55.4, 42.6, 32.2, 30.2, 28.6, 25.5. Spectral data for compound **26a** were consistent with the data previously reported in the literature.[20g] **SMILES**: O=C1CCCCCC1C2=CC=C(OC)C=C2



26a
$C_{14}H_{18}O_2$
MW: 218.30 g.mol^{-1}

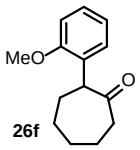
2-(2,4-dimethoxyphenyl)cycloheptan-1-one **26b.**



26b
$C_{15}H_{20}O_3$
MW: 248.32 g.mol^{-1}

Compound **26b** was synthesized from styrene oxide **24b** (40 mg, 0.2 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a white powder (35 mg, 0.14 mmol, 87% yield) using $Bi(OTf)_3$ and (36 mg, 0.14 mmol, 90% yield) using $AlCl_3$. R_f = 0.35 (Et_2O/*n*-hexanes 2:8). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.01(d, *J* = 8.2 Hz, 1H), 6.50 (d, *J* = 2.5 Hz, 1H), 6.48 (dd, *J* = 8.2 Hz, *J* = 2.5 Hz, 1H), 3.86 (dd, *J* = 12.8, 5.7 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 2.53 – 2.43 (m, 2H), 2.35 – 2.32 (m, 2H), 2.14 – 2.08 (m, 2H), 1.86 – 1.54 (m, 3H), 0.75 – 0.54 (m, 3H). Spectral data for compound **26b** were consistent with the data previously reported in the literature.[20g] **SMILES**: O=C1CCCCCC1C2=C(OC)C=C(OC)C=C2

2-(2-methoxyphenyl)cyclohexan-1-one **26f.**

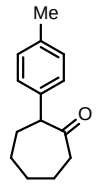


26f
$C_{14}H_{18}O_2$
MW: 218.30 g.mol^{-1}

Compound **26f** was synthesized from styrene oxide **24f** (50 mg, 0.25 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a white powder (38 mg, 0.17 mmol, 75% yield) using $Bi(OTf)_3$ and (37 mg, 0.17 mmol, 73% yield) using $AlCl_3$. R_f = 0.35 (EtOAc/*n*-hexanes 2:8). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.24 – 7.14 (m, 2H), 6.93 (dd, *J* = 7.5, 6.5 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 3.97 (dd, *J* = 11.1, 3.0 Hz, 1H), 3.77 (s, 3H), 2.73 – 2.70 (m, 2H), 2.03 – 1.91 (m, 4H), 1.79 – 1.65 (m, 2H), 1.53 – 1.42 (m, 2H). Spectral data for compound **26f** were consistent with the data previously reported in the literature.[20i]

SMILES: O=C1CCCCCC1C2=CC=CC=C2OC

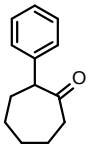
2-phenylcycloheptan-1-one **26g.**



26g
$C_{14}H_{18}O$
MW: 202.30 g.mol^{-1}

Compound **26g** was synthesized from styrene oxide **24g** (20 mg, 0.1 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a white solid (13 mg, 0.066 mmol, 66% yield) using $Bi(OTf)_3$ and (14 mg, 0.069 mmol, 69% yield) using $AlCl_3$. R_f = 0.35 (Et_2O/*n*-hexanes 8:2). **IR**νmax (neat): 2925, 2854, 1702, 1448, 820 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.14 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 3.69 (dd, *J* = 11.4, 4.2 Hz, 1H), 2.73 – 2.66 (m, 1H), 2.55 – 2.48 (m, 1H), 2.37 – 2.31 (m, 3H), 2.15 – 2.10 (m, 1H), 2.08 – 1.91 (m, 4H), 1.71 – 1.58 (m, 2H), 1.53 – 1.41 (m, 2H). Spectral data for compound **26g** were consistent with the data previously reported in the literature.[20j] **SMILES**: O=C1CCCCCC1C2=CC=CC=C2

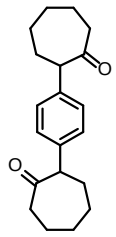
2-phenylcyclohexan-1-one **26h.**



26h
$C_{13}H_{16}O$
MW: 188.27 g.mol^{-1}

Compound **26h** was synthesized from styrene oxide **24h** (19 mg, 0.1 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a white solid (4 mg, 0.02 mmol, 20% yield) using $Bi(OTf)_3$. R_f = 0.22 (EtOAc/*n*-hexanes 3:97). **IR**νmax (neat): 2925, 2854, 1703, 1448, 840 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.33-7.21 (m, 5H), 3.72 (dd, *J* = 11.3, 4.3 Hz, 1H), 2.73 – 2.66 (m, 1H), 2.55 – 2.50 (m, 1H), 2.18 – 2.11 (m, 1H), 2.06 – 1.92 (m, 4H), 1.69 – 1.59 (m, 1H), 1.51-1.44 (m, 2H). Spectral data for compound **26h** were consistent with the data previously reported in the literature.[20j] **SMILES**: O=C1CCCCCC1C2=CC=CC=C2

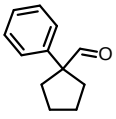
2,2'-(1,4-phenylene)bis(cyclohexan-1-one) **26m.**



26m
$C_{20}H_{26}O_2$
MW: 298.43 g.mol^{-1}

Compound **26m** was synthesized from styrene oxide **24m** (15 mg, 0.05 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a white powder (10 mg, 0.033 mmol, 66% yield) using $Bi(OTf)_3$ (7 mg, 0.01 mmol, 20 mol %). R_f = 0.31 (EtOAc/hexanes 2:8). **IR**νmax (neat): 2930, 2855, 1700, 1455 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.17 (s, 4H), 3.69 (dd, *J* = 11.4, 4.2 Hz, 2H), 2.72 – 2.61 (m, 2H), 2.53 – 2.47 (m, 2H), 2.17 – 2.09 (m, 2H), 2.02 – 1.92 (m, 5H), 1.65 – 1.51 (m, 5H), 1.48 – 1.37 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm) 213.6 (2C), 139.0 (2C), 128.1 (4C), 58.6 (2C), 42.8 (2C), 32.01 (2C), 30.1 (2C), 28.6 (2C), 25.5 (2C). **HRMS** (ESI/TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{27}O_2$ 299.2006; Found 299.2002 (1.3 ppm). **SMILES**: O=C1CCCCC1C2=CC=C(C3CCCCC3=O)C=C2

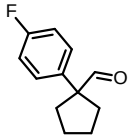
1-phenylcyclopentane-1-carbaldehyde **27h.**



27h
$C_{12}H_{14}O$
MW: 174.24 g.mol^{-1}

Compound **27h** was synthesized from styrene oxide **23h** (17 mg, 0.1 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a clear oil (~16 mg, 0.09 mmol, 90% yield) using $AlCl_3$. R_f = 0.77 (*n*-hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 9.37 (s, 1H), 7.43 – 7.24 (m, 5H), 2.32 – 2.28 (m, 1H), 2.02 (s, 1H), 1.89 – 1.78 (m, 1H), 1.75 – 1.63 (m, 2H), 1.54 – 1.45 (m, 2H), 1.35 – 1.26 (m, 1H). Spectral data for compound **27h** were consistent with the data previously reported in the literature.[21a] **SMILES**: O=CC1(CCCC1)C2=CC=CC=C2

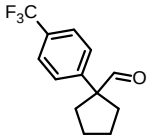
1-(4-fluorophenyl)cyclopentane-1-carbaldehyde **27i.**



27i
$C_{12}H_{13}FO$
MW: 192.23 g.mol^{-1}

Compound **27i** was synthesized from styrene oxide **23i** (20 mg, 0.1 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a clear oil (7 mg, 0.045 mmol, 45% yield) using $AlCl_3$. R_f = 0.91 (EtOAc/*n*-hexanes 2:8). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 9.37 (s, 1H), 7.23 – 7.20 (m, 2H), 7.06 – 7.02 (m, 3H), 2.53 – 2.49 (m, 2H), 1.89 – 1.81 (m, 2H), 1.78 – 1.72 (m, 2H), 1.69 – 1.65 (m, 2H). Spectral data for compound **27i** were consistent with the data previously reported in the literature.[21b] **SMILES**: O=CC1(CCCC1)C2=CC=C(F)C=C2

1-(4-(trifluoromethyl)phenyl)cyclopentane-1-carbaldehyde **27k.**

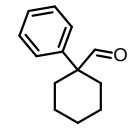


27k
$C_{13}H_{13}F_3O$
MW: 242.24 g.mol^{-1}

Compound **27k** was synthesized from styrene oxide **23k** (20 mg, 0.08 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a clear oil (16 mg, 0.045 mmol, 80% yield) using $AlCl_3$. R_f = 0.75 (EtOAc/*n*-hexanes 15:85). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 9.41 (s, 1H), 7.61 (d, *J* = 8.2

Hz, 2H), 7.38 (d, *J* = 8.2 Hz), 3.82 (dd, *J* = 12.8, 5.7 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 2.53 – 2.43 (m, 1H), 2.35 – 2.32 (m, 2H), 1.86 – 1.67 (m, 4H). Spectral data for compound **27k** were consistent with the data previously reported in the literature.[21c] **SMILES**: O=CC1(CCCC1)C2=CC=C(C(F)(F)F)C=C2

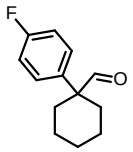
1-phenylcyclohexane-1-carbaldehyde **28h.**



28h
$C_{13}H_{16}O$
MW: 188.27 g.mol^{-1}

Compound **28h** was synthesized from styrene oxide **24h** (19 mg, 0.1 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a pale yellow oil (16 mg, 0.078 mmol, 78% yield) using $AlCl_3$. R_f = 0.35 (Et_2O/*n*-hexanes 2:8). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 9.37 (s, 1H), 7.40 – 7.26 (m, 5H), 2.32 – 2.28 (m, 2H), 1.88 – 1.82 (m, 2H), 1.69 – 1.64 (m, 3H), 1.54 – 1.43 (m, 2H), 1.35 – 1.27 (m, 1H). **HRMS** (ESI/TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}O$ 189.1274; Found 189.1283 (4.8 ppm). Spectral data for compound **28h** were consistent with the data previously reported in the literature.[21d] **SMILES**: O=CC1(CCCCC1)C2=CC=CC=C2

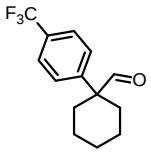
1-(4-fluorophenyl)cyclohexane-1-carbaldehyde **28i.**



28i
$C_{13}H_{15}FO$
MW: 206.26 g.mol^{-1}

Compound **28i** was synthesized from styrene oxide **24i** (21 mg, 0.1 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a clear oil (7 mg, 0.036 mmol, 36% yield) using $AlCl_3$. R_f = 0.27 (EtOAc/*n*-hexanes 0.2:9.8). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 9.35 (s, 1H), 7.35-7.22 (m, 2H), 7.13 – 6.98 (m, 2H), 2.33 – 2.20 (m, 2H), 1.87 – 1.73 (m, 2H), 1.73 – 1.58 (m, 4H), 1.58 – 1.32 (m, 2H). Spectral data for compound **28i** were consistent with the data previously reported in the literature.[21e] **SMILES**: O=CC1(CCCCC1)C2=CC=C(F)C=C2

1-(4-(trifluoromethyl)phenyl)cyclohexane-1-carbaldehyde **28k.**



28k
$C_{14}H_{15}F_3O$
MW: 256.27 g.mol^{-1}

Compound **28k** was synthesized from styrene oxide **24k** (26 mg, 0.1 mmol, 1 equiv.) and purified accordingly to *general procedure D* to obtain pure material as a clear oil (19 mg, 0.075 mmol, 75% yield) using $AlCl_3$. R_f = 0.35 (EtOAc/*n*-hexanes 0.1:9.9). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 9.40 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 2.34 – 2.28 (m, 2H), 1.90 – 1.84 (m, 2H), 1.67 – 1.61 (m, 3H), 1.57 – 1.47 (m, 2H), 1.35 – 1.32 (m, 1H). Spectral data for compound **28k** were consistent with the data previously reported in the literature.[21f] **SMILES**: O=CC1(CCCCC1)C2=CC=C(C(F)(F)F)C=C2

▪ ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxxxxx

Tables for Barluenga cross-coupling condition optimizations and for screening of Lewis and Brønsted acids to catalyze the House–Meinwald rearrangement, as well as the copies of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF).

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Notes
The authors declare no competing financial interest.

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