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Enantioselective desymmetrization of *cis*-3,5-*O*-arylidenecyclohexanones catalyzed by *Cinchona* derived quaternary ammonium salts.

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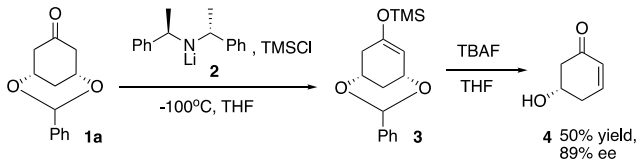
KEYWORDS. Phase Transfer Catalysis, Desymmetrization, Active Pharmaceutical Ingredients

ABSTRACT: An enantioselective protocol for the desymmetrization of *cis*-3,5-*O*-arylidenecyclohexanones has been developed that proceeded under the catalysis of readily available and inexpensive *Cinchona*-derived quaternary ammonium salts. The synthetic relevance of the methodology was exemplified by the synthesis of a key intermediate that could be used in the preparation of the active pharmaceutical ingredient, paricalcitol (Zemplar®).

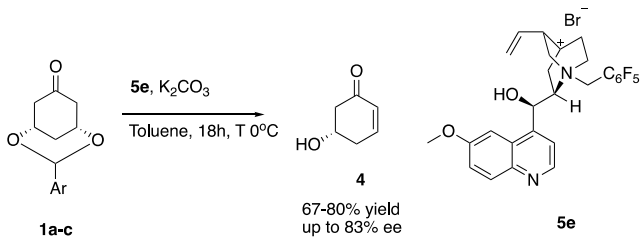
INTRODUCTION

Enantioenriched 5-hydroxycyclohex-2-enone **4** (Scheme 1) is a useful synthetic building block, which has been used in the synthesis of drugs[1a] and natural products.[1b] Many synthetic routes to prepare **4**, or their 5-hydroxy protected analogues, have been reported; including chemoenzymatic protocols,[1c] organocatalytic procedures,[1d] or desymmetrization of prochiral cyclohexanones.[1e] Nicolau reported a seven step sequence to prepare **4** as an intermediate *en route* to the synthesis of natural product Regulosin,[1f] while Sato reported the synthesis of **4** *via* Kulinkovich cyclopropanation.[1g]

Previous Work:

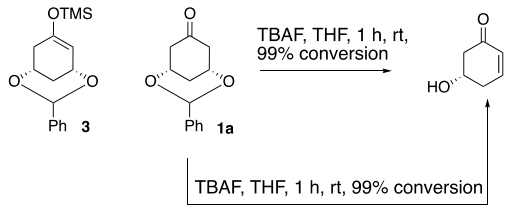


This Work:



Scheme 1. Desymmetrization of *meso*-ketones using chiral lithium amide **2**[1e] and this work.

The preparation of compound **4**, *via* desymmetrization of prochiral **1a**, has been reported by Honda (Scheme 1).[1e] Compound **1a** (Scheme 1) was reacted with a stoichiometric amount of chiral lithium amide **2** to selectively provide, after quenching, trimethylsilyl enolate **3**. Crucial to obtain high levels of enantioselectivity was the temperature of exercise that was optimal at -100 ˚C. Treatment of **3** with 0.3 equivalents of tetrabutylammonium fluoride (TBAF) gave **4** in moderate (50%) yield and in 89% ee. During our studies on the preparation of compound **4**, we discovered a faster protocol to convert ketones **1a-c** to correspondent cyclohexenones **4**. This new procedure made use of enantiopure quaternary ammonium salts[2]

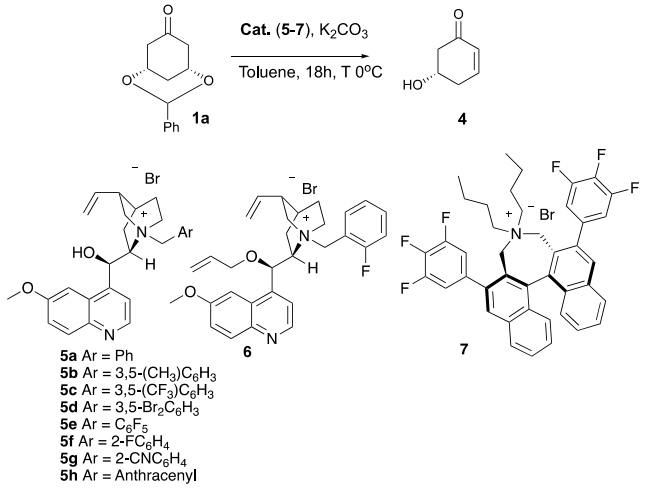


Scheme 2. TBAF catalyzed eliminative rearrangement on *meso*-ketone **1a** and silyl enol ether **3.**

and inexpensive inorganic bases, providing compound **4** (Scheme 1) in higher yields (up to 80%) and similar enantiopurity. The new synthesis could be performed at room temperature to 0 °C and without exclusion of air or moisture. Hence, the methodology herein reported provides significant advantages over literature precedents, could be easily scaled up and employed in the manufacture of paricalcitol (Zemplar®).[3] Asymmetric

phase transfer catalysis (PTC) has been a popular area of research in the past decades and many groups[4,5] have shown its applicability to the industrial manufacture of pharmaceutical ingredients (APIs).

Table 1. Representative results of the screening of *Cinchona*-derived quinidinium salts **5a-h**, **6**, **7**.[a]



Entry[a]	Cat.	Temp [°C]	T [*h*]	Conv. [%][c]	er[*S*/*R*][d]	Major isomer
1	**5a**[b]	20	120	≥95	65.6/34.5	(*S*)
2	**5b**	20	18	≥95	71.5/28.5	(*S*)
3	**5c**	20	18	≥95	78/22	(*S*)
4	**5d**	20	18	≥95	76/24	(*S*)
5	***5e***	***20***	***18***	**≥95**	***81/19***	***(S)***
6	**5f**	20	18	≥95	37/63	(*R*)
7	**5g**	20	18	≥95	24.5/75.5	(*R*)
8	**5h**	20	48	≥95	43/57	(*R*)
9	**6**	20	18	≥95	47/53	(*R*)
10	**7**	20	18	≥95	50/50	-
11	**5e**	0	48	≥95	78/22	(*S*)
12	**5g**	0	48	≥95	23/77	(*R*)
13	**5b**	-20	96	≥95	71.5/28.5	(*S*)
14[e]	**5e**	-20	96	≥95	79/21	(*S*)
15[f]	**5e**	0	18	≥95	83.5/16.5	(*S*)
16[g]	**5e**	**0**	**18**	**≥95**	**87.5/12.5**	**(*S*)**

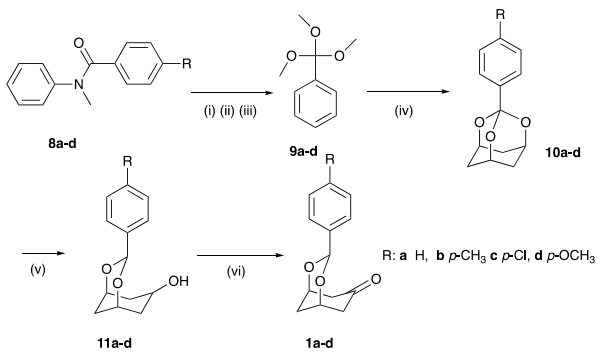
[a] Reaction Conditions: [a] *cis*-3,5-O-benzylidenecyclohexanones **1a** (0.1 mmol), toluene (1.0 mL), cat. **5a-h**, **6**, **7** (10 mol%), K_2CO_3 (0.1 mmol). [b] **5a** Used as fluoride salt. [c] Conversion was determined by ^{1}H NMR analysis *vs* an internal standard [d] The ee of **4** was determined by chiral stationary phase HPLC. [e] Reaction carried out using 5 mL of toluene. [f] Reaction carried out using cat. **5e** (30 mol%). [g] Reaction carried out at 0 °C using 2.0 mL of toluene, K_2CO_3 (0.2 mmol) and a stoichiometric amount of **5e** (1 equiv.).

However, the use of PTC for the desymmetrization of prochiral ketones has been scarcely studied, with the reports of Levacher,[6] Shiori[7] and Maruoka[8] being notable examples. In particular, Levacher reported the desymmetrization of 4-substituted cyclohexanones using quaternary ammonium salts, that provided the corresponding trapped enolates in good yields but only in modest enantioselectivity.[6] Arai and Shiori reported a Horner–Wadsworth–Emmons desymmetrization of 4-substitued cyclohexanones[7] and Maruoka reported the desymmetrization of *meso*-epoxyketones.[8]

RESULTS AND DISCUSSION

Herein we report the discovery of a new phase transfer catalyzed desymmetrization of compounds **1a-c** and its optimization using *Cinchona*-derived quaternary ammonium salts to provide enantioenriched 5-hydroxy enone **4** (Scheme 1). During our studies on the preparation of racemic **4** (Scheme 2),[1e] we reacted a batch containing 50% of silyl enol ether **3** and 50% of ketone **1a** with 0.1 eq. of tetrabutylammonium fluoride (TBAF) in THF. This experiment provided desired **4** in almost quantitative yield, demonstrating that basic TBAF converted equally **3** and **1a** to compound **4**. A control experiment was then run in which *meso*-ketone **1a** was reacted with 0.1 eq. of TBAF in THF at room temperature (Scheme 2). This test confirmed that a quaternary ammonium salt and a base formed an excellent reagent mixture for the conversion of **1a** to **4**. In addition, it was demonstrated that trapping of TMS enolate intermediate **3,** and its subsequent reaction at low temperature, was not necessary—essentially cutting one step and simplifying the execution of the synthesis. Encouraged by this result, we posed the question of whether an enantiopure quaternary ammonium salt, used in place of TBAF, could carry out a desymmetrising deprotonation of **1a**. If this question could be answered positively, then the resulting chiral enolate would have undergone a subsequent elimination to provide enantiomerically enriched enone **4** (See Scheme 4). In a preliminary test, compound **1a** was reacted with catalyst **5a** as a fluoride salt, providing target compound **4** quantitatively but in a low, yet promising, 31% ee (Table 1, entry 1). This reaction proved to be quite slow and required up to 5 days to achieve full conversion. In an effort to enhance the enantioselectivity and the rate of reaction, we undertook an investigation by variation of key reaction parameters, such as: solvent, temperature, dilution, and base. This study identified K_2CO_3 and toluene as the most suitable media, providing complete conversion of **1a** in 18 h at 20 °C. With optimal conditions in hand, we evaluated several quaternary ammonium salts, derived from *Cinchona* alkaloids, as catalysts (Table 1). Hence, compound **1a** was subjected to reaction with *Cinchona*-derived quinidinium catalysts **5a-h**, **6** and quaternary ammonium salt **7** (Table 1). Catalyst **5e** (Table 1, entry 5) produced the best results and was chosen to be carried forward for the final optimization phase, providing desired **4** in up to 62% ee and with the (*S*)- absolute configuration, required for the preparation of paricalcitol.[1] It was also noted that the presence of a hydrogen bond acceptor in the *ortho* position, *i.e.* CN or F as in compounds **5f-g** (Table 1, entries 7-8) provided product **4** with opposite (*R*)- absolute stereochemistry.

Optimization studies carried out for the preparation of **4** under the catalysis of **5e** revealed that only a small improvement of enantioselectivity could be achieved by: (*i*) decrease of the temperature (Table 1, compare entries 5, 14 and 15); (*ii*) increase of the catalyst loading (Table 1, compare entries 5, 15 and 16); and (*iii*) dilution of the reaction media (Table 1, compare entries 5 and 16). Importantly, chiral PTCs lacking a free alcohol functional group, such as **6** or **7**, gave product **4** as a racemate—suggesting the involvement of a free alcohol functionality in the stereoselective reaction mechanism (Table 1, compare entries 5, 9 and 10).[9] With the aim of increasing the enantioselectivity of compound **4**, we decided to synthesize novel analogues of **1a**, namely *cis*-3,5-*O*-arylidenecyclohexanones **1b-c** possessing different *para*-substituents (Scheme 3). It was hoped that inclusion of bulkier groups on acetals **1** might have impacted on the enantioselectivity of the reaction leading to **4**. Hence, starting from compounds **8b-d**, orthobenzoates **9b-d** where obtained in three steps following previously reported procedures.[10] Thus, reaction of compounds **9b-d** with *cis*,*cis*-1,3,5-cyclohexanetriol, under catalysis of $BF_3{\cdot}Et_2O$, provided orthoesters **10b-d**. These latter were selectively reduced to acetals **11b-d** by reaction with BH_3 in THF. Compounds **11b-d** were then oxidised with Dess–Martin[11] periodinane to afford ketones **1b-c**. While compounds **1b-c** were successfully obtained in moderate yields, we were unable to identify a set of suitable conditions to transform **11d** to ketone **1d** (Scheme 3, R = OCH_3). Compound **1a** was synthesised according to the procedure reported by Honda.[1e]



Scheme 3. *Reagents:* (*i*) $CF_3SO_3CH_3$ (1.2 eq.), DCM, rt, 20 h, (*ii*) CH_3ONa, MeOH, rt, 10 min, (*iii*) CH_3COOH CH_3OH, rt, 15min, Yield: H 86%, *p*-CH_3 30%, *p*-Cl 70%, *p*-OCH_3 67%; (*iv*) cis,cis-1,3,5-cyclohexanetriol (0.6 eq.), $BF_3{\cdot}Et_2O$ (1.1 eq.) , DCM, rt, 20h, Yield: H 98%, *p*-CH_3 76%, *p*-Cl 97% *p*-OCH_3 58%; (*v*) HMPA-THF, $BH_3{\cdot}THF$ (2 eq.), THF, 0 °C, 18 h Yield: H 43%, *p*-CH_3 48%, *p*-OCH_3 6%; $BH_3{\cdot}THF$ (4 eq.), THF, 0 °C, 18 h, Yield: *p*-Cl 85%; (*vi*) Dess–Martin periodinane (2.99 eq.), DCM 0 °C, 15 min, Yield: H 75%, *p*-CH_3 90%, *p*-Cl 85%, *p*-OCH_3 0%.

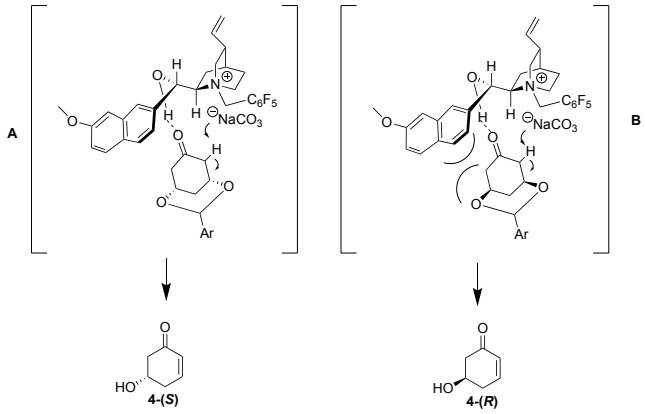
Oxidation of **11d** to provide **1d** was also attempted using milder oxidants, including Swern oxidation and TEMPO hypochlorite.[12] These experiments did not provide desired **1d**, but a complex mixture of decomposed or over-oxidized products. Compounds **1b-c** were therefore reacted under best conditions identified (Table 1, entry 5) that involved carrying out the conversion of **1** to **4** in the presence of 0.1 molar equivalents of **5e**. This set of experiment revealed that a methyl group in the *para* position reduced enantioselectivity when the reaction was carried out at room temperature (Table 2, entries 1 and 3). However, when carried at 0 °C, the results obtained with **1a** and **1b** were comparable. (Table 2, entries 2 and 4).

Table 2. Desymmetrization of *meso* ketones **1a-c** using phase transfer catalyst **5e**.[a]

Entry	R	ketone	Yield (%)[c]	er (*S*/*R*)	ee (%)
1	H	**1a**[a]	67	81/19	62
2	H	**1a**[b]	80	87.5/12.5	75
3	CH_3	**1b**[a]	78	75.5/24.5	51
4	CH_3	**1b**[b]	76	86.5/13.5	73
5	Cl	**1c**[a]	76	85.5/14.5	71
6	Cl	**1c**[b]	80	91.5/8.5	83

[a] Reaction Conditions: [a] *cis*-3,5-O-arylidenecyclohexanones **1a-c** (0.1 mmol), toluene (1.0 mL), cat. **5e** (10 mol%), K_2CO_3 (0.1 mmol), T = 20 °C [b] *cis*-3,5-O-arylidenecyclohexanones **1a-c** (0.1 mmol), cat. **5e** (10 mol%), toluene (2.0 mL), K_2CO_3 (0.2 mmol), T = 0 °C. [c] Isolated yields after flash column chromatography [d] The enantioselectivity of the product was determined by chiral stationary phase HPLC.

The introduction of chloride as an aryl-substituent was beneficial for enantioselectivity, with compound **1c** providing **4** in higher ee than **1a**, both at room temperature and at 0 °C (Table 2, entries 1 and 5; entries 2 and 6). Based on the experimental observations discussed below, we propose the following model for the stereoselection process of catalyst **5e** in the desymmetrization of *meso*-ketones **1a-c** (Scheme 4).



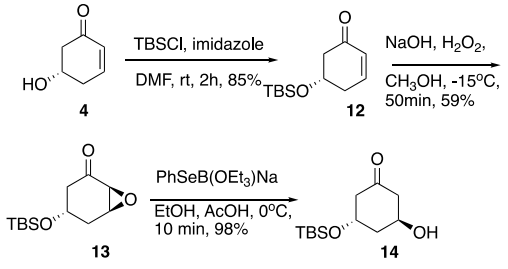
Scheme 4. Proposed mechanism for the operation of catalyst **5e** in the desymmetrization of *meso*-ketones **1a-c**.

It is well known that *Cinchona*-derived quaternary ammonium species bearing a free hydroxyl motif can participate in H-bonding with suitable H-bond acceptors such as ketones (Scheme 4).[9] The relevance of the -OH

moiety of **5e** to the reaction mechanism was confirmed by the data obtained with catalysts **6** and **7** (Table 1, entries 9 and 10)—which is also supported by literature data.[13] Interaction between the base charged ammonium salt **5e** and substrates **1**, *via* H-bonding at the C_9-OH position, generates two transition states (Scheme 4, A and B). Transition state A is preferred over B, due to lack of steric hindrance between the quinoline of the catalyst and the acetal moeity of the substrate. Hence, the steric interaction between the catalyst and substrate orients the prochiral methylene to facilitate selective deprotonation of less hindered alpha-proton by the base, producing only one enolate. Subsequent elimination leads to product **4** in (*S*)-configuration. On the other hand, the (*R*)-configuration obtained through reacting **1a** with 2-substituted ammonium species **5g** and **5f**, could be explained by the preferential formation of a [catalyst- catalyst-N^+CH--O=C] hydrogen bonding interaction[14] forming between the catalyst and **1a**, which would invert the facial selectivity of the deprotonation step. This latter stereoselection mechanism cannot be excluded, mostly in consideration of the presence of multiple fluorine aryl-substituents of **5e**, which would enhance H-bond donating character of the benzylic protons.

We have shown that optically active enone **4** could be readily converted to paricalcitol key intermediate **14** (Scheme 5). Treatment of **4** with TBDMS-Cl and imidazole in DMF provided the silylated enone **12**,[15] which was then converted to compound **13** as a 9 : 1 mixture of diastereoisomers by reaction with $NaOH/H_2O_2$. Although this step was reported to only provide one diastereoisomer,[1e] in our hands this reaction provided a mixture of diastereoisomers. We have therefore complemented this step by implementing a re-crystallization step. Hence, by dissolving the 9 : 1 mixture of diastereoisomers in heptane and allowing crystallization to occur at –20 °C, product **13** was obtained as a single diastereoisomer in 59% isolated yield. Successive reductive ring opening of compound **13** using sodium phenylseleno(triethyl)borate complex ($PhSe^-B(OEt)_3Na^+$),[16] provided target compound **14**.

In conclusion, we have reported a novel synthetic procedure which employs a desymmetrising elimination of prochiral ketones to provide synthetically useful cyclohexanol derivatives in high ees (up to 91.5 : 8.5 *S*/*R*, 83% ee). The reaction proceeds under mild conditions and under the stereoselective control of a cheap, readily available, and recoverable[2,4] phase transfer catalyst.



Scheme 5. Preparation of synthon **14**.

The synthetic relevance of this method has been exemplified by the conversion of enone (*S*)-**4** into compound **14**, a synthon that could be used for the preparation of paricalcitol and seveal natural products.[1] Future work will include extension of the substrate scope to other pharmaceutically relevant cycloalkanols and theoretical and experimental studies on the key interaction formed by the catalyst and the substrate that governs the enantioselectivity of this transformation.

EXPERIMENTAL SECTION

Materials and Methods: NMR experiments were performed on a Bruker Avance 400 instrument and samples were obtained in $CDCl_3$ (referenced to 7.26 ppm for ^{1}H and 77.0 for ^{13}C) and in DMSO-d_6 (referenced to 2.52 and 3.35 ppm for ^{1}H and 40.0 for ^{13}C). Coupling constants (*J*) are in Hz. Multiplicities are reported as follows: s, singlet; d, doublet; dd, doublets of doublets; t, triplet, q; quartet, m, multiplet; c, complex; and br, broad. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD, Chiralcel OD), using a UV detector operating at 254 nm. Tetrahydrofuran was freshly distilled over sodium benzophenone prior to use according to standard procedure. All other reagents and solvents were used as purchased from Aldrich. Reactions were monitored for completion by TLC (EM Science, silica gel 60 F254). Flash chromatography was performed using silica gel 60 (0.040-0.063 mm, 230-400 mesh). Retention factors (R_f) are reported to ± 0.05. Mass spectra and HRMS were recorded using a EI mass spectrometer.

Synthesis of *N*-4-dimethyl-*N*-phenylbenzamide **8b**

To a stirred solution of Ph_2PCl (10.9 g, 49.6 mmol, 0.75 eq.) and imidazole (10.1 g, 148.7 mmol, 2.25 eq.) in CH_2Cl_2 (165 mL), iodine (12.6 g, 49.6 mmol, 0.75 eq.) and *p*-toluic acid (9.0 g, 66.1 mmol, 1 eq.) were sequentially added. *N*-methyl aniline (7.1 g, 66.1 mmol, 1 eq.) was then added and the mixture was left stirring for 5 h. The reaction mixture was washed with a saturated aqueous sol. of $NaHCO_3$ (3 × 150 mL), 10% w/v aqueous sodium thiosulfate sol. (2 × 150 mL), brine, dried over Na_2SO_4, and the solvent removed *in vacuo*. The yellow residue was purified by column chromatography (1:1 PE:EtOAc, v/v) to afford the anilide **8b** as a white solid (R_f: 0.56, PE:AcOEt, 1:1), (12.6 g, 85%): mp 61-63 °C; IR (KBr) 3464, 2960, 2928, 2361, 2329, 1632, 1585, 1364, 1286 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.21 (m, 4H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 7.4 Hz, 2H), 6.99 (d, *J* = 8.1 Hz, 2H), 3.52 (s, 3H), 2.28 (s, 3H);[17] ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.2, 145.6, 140.3, 133.3, 129.6, 129.3, 128.8, 127.3, 126.8, 39.0, 21.8; HRMS (EI$^+$) *m/z*: [M]+ Calculated for $C_{15}H_{15}NO$ 225.1154; Found 225.1151.

Synthesis of 4-chloro-*N*-methyl-*N*-phenylbenzamide **8c**

Starting from *p*-chloro benzoic acid (37 g, 236.6 mmol), the synthesis occurred as per compound **8d**. The crude anilide **8c**, obtained as a pale yellow solid, was used for

next step without further purification (57.2 g, 99%): mp 41-43 °C;[18] IR (KBr) 3452, 3263, 3058, 3030, 2931, 2364, 2328, 1642, 1591, 1287, 1275, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29- 7.17 (m, 5H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 3.51 (s, 3H); $^{113}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.6, 144.8, 135.8, 134.4, 130.4, 129.5, 128.1, 127.00, 126.9, 38.6. HRMS (EI^+) *m/z*: $[M]^+$ Calculated for $C_{14}H_{12}ClNO$ 245.0603; Found 245.0607.

Synthesis of 4-methoxy-*N*-methyl-*N*-phenylbenzamide **8d**

Oxalyl chloride (26 mL, 39 g, 307.6 mmol) was added dropwise to a dispersion of *p*-methoxy benzoic acid (36 g, 236 mmol) in CH_2Cl_2 (520 mL), followed by 16 drops of DMF. The resulting mixture was stirred at room temperature for 3 h and then solvent was removed *in vacuo*. A solution of *N*-Methyl aniline (3.18 mL, 2.74 g, 38.5 mmol, 1.30 eq), TEA (49.6 mL, 354.9 mmol) and CH_2Cl_2 (400 mL), was cooled at -10 °C. The crude acid chloride, dissolved in CH_2Cl_2 (45 mL), was added dropwise to the stirred *N*-methyl aniline solution at such a rate that the internal temperature was maintained <5 °C. Upon completion of the addition, the mixture was stirred at room temperature for further 30 min. The mixture was then threated with 2N HCl (60 mL), washed with brine (500 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude amide **8d**, obtained as a white-yellow solid, was used for next step without further purification (57 g, 98%): mp 68-70 °C; IR (KBr) 3263, 3031, 2932, 2838, 1632, 1596, 1487, 1361, 1246, 1361 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (m, 4H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 2H), 6.48 (d, *J* = 8.6 Hz, 2H), 3.55 (s, 3H), 3.30 (s, 3H);[17] $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.4, 160.7, 145.6, 131.0, 129.3, 127.0, 126.4, 113.1, 55.2, 38.7; HRMS (EI^+) m/z: $[M]^+$ Calculated for $C_{15}H_{15}NO_2$ 241.1103; Found 241.1108.

Synthesis 1-methyl-4-(trimethoxymethyl)benzene **9b**

N-4-dimethyl-*N*-phenylbenzamide **8b** (10 g, 44.3 mmol) and methyl trifluoromethanesulfonate (8.61 g, 5.93 mL, 52.5 mmol) were dissolved in dry methylene chloride (20 mL) and the solution was stirred 18 h. Dry diethyl ether (70 mL) was added, resulting in separation of the benzimidatoniumtrifluoromethanesulfonate salt as a white solid. The salt was separated by decantation, washed with dry ether (10 mL) and re-dissolved in methylene chloride (20 mL). The mixture was cooled at 0 °C and then threated with a sodium methoxide solution [sodium (2.5 g) dissolved in dry methanol (35 mL)]. The mixture was stirred 10 min at rt. Evaporation of the solvent gave the crude anilide acetal mixed with the trifluoromethane sulfonate salt. The mixture was dissolved in hexane (150-200 mL), filtered (to remove the salt), and the solvent removed *in vacuo*. The acetal, dissolved in dry methanol (35 mL), was treated with glacial acetic acid (3.4 mL) and the mixture was stirred at rt for 15 minutes. The mixture was threated K_2CO_3 (3g), solvent evaporated and then diethyl ether and water were added. The organic layer was separated and the solvent removed *in vacuo* to yield the crude orthoester as a white-yellow oil that was purified by fractional distillation at 0.1 mmHg to produce *N*-methylaniline at 25-30 °C followed at 90-100 °C by orthoester **9b** (2.5 g, 30%): IR (KBr) 2959, 2929, 2848, 1638, 1590, 1366, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 3.12 (s, 9H), 2.36 (s, 3H);[10] $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 138.7, 133.7, 129.3, 128.8, 127.7, 49.8, 21.3; HRMS (EI^+) *m/z*: $[M]^+$ Calculated for $C_{11}H_{16}O_3$ 196.1099; Found 196.1097.

Synthesis 1-chloro-4-(trimethoxymethyl)benzene **9c**

Following the procedure for compound **9b** and starting from 4-chloro-*N*-methyl-*N*-phenylbenzamide **8c** (16.5 g, 66 mmol). Fractional distillation at 0.1 mmHg produced *N*-methylaniline at 25-30 °C followed at 90-100 °C by the orthoester **9c**[19] (8.2 g, 57%): IR (KBr) 3097, 3061, 3012, 2907, 2032, 1632, 1594, 1488, 1361, 1287, 1263, 1184, 1078, 849, 821 cm-1; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 3.12 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 135.4, 134.9, 129.1, 128.4, 116.0, 49.9; HRMS (EI^+) *m/z*: $[M]^+$ Calculated for $C_{10}H_{13}ClO_3$ 216.0553; Found 216.0558.

Synthesis 1-methoxy-4-(trimethoxymethyl)benzene **9d**

Following the procedure for **9b** and starting from methyl 4-methoxy-*N*-methyl-*N*-phenylbenzamide amide **8d** (16 g, 66 mmol). Fractional distillation at 0.1 mmHg produced *N*-methylaniline at 25-30 °C followed at 90-100 °C by orthoester **9d**[19] (4.35 g, 31%): IR (KBr) 3073, 3002, 2959, 2915, 2828, 2040, 1906, 1606, 1578, 1507, 1460, 1916, 1243, 1172, 1078, 1034, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 3.82 (s, 3H), 3.12 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.0, 129.1, 128.9, 115.2, 113.4, 55.4, 49.8; HRMS (EI^+) *m/z*: $[M]^+$ Calculated for $C_{11}H_{16}O_4$ 212.1049; Found 212.1046.

Preparation 3-phenyl-2,4,10-trioxaadamantane **10a**

In a 10L reactor, trimethylorthobenzoate (500 g, 2.75 mol, 1.73 eq.) and boron trifluoride diethyl etherate (21 mL, 24.1 g, 0.170 mol, 0.11 eq.) were sequentially added to a dispersion of *cis,cis*-1,3,5-cyclohexanetriol (210 g, 1.59 mol, 1.00 eq.) in dry DCM (4.3 L) under N_2 atmosphere and at 20°C (cryostat was used to control the temperature). The mixture was left stirring for 16h. After this time, the reaction mixture became homogeneous and yellow pale yellow colored. At this point, a saturated solution of $NaHCO_3$ (1.2 L) was added. The organic layer was washed with brine and then dried over Na_2SO_4. Evaporation of the solvent gave a white crystalline solid dispersed in a colourless oil. The solid was suspended in methanol (800 mL). The mixture was stirred at 50-55 °C for 30 min, kept at room temperature for 30 min and then stirred for further 30 min at 0°C. The crystals obtained were filtered and washed with water (2 × 200 mL). The solid collected was

kept in a rotavapor at 60-65 °C and at 30 psi for 2h and then dried under high vacuum overnight. Compound **10a** was obtained as white solid (339 g, 98%) (R_f: 0.42, PE:AcOEt:DCM 8:2:1): mp 182-184 °C;[20] IR (KBr) 2966, 2927, 2852, 1948, 1452,1362, 1310, 1121, 995, 979 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 2H), 7.40 – 7.33 (m, 3H), 4.64 – 4.53 (m, 3H), 2.81 – 2.72 (m, 3H), 1.82 (d, *J* = 12.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 139.4, 128.9, 127.8, 124.8, 108.7, 68.7, 32.7; HRMS (EI^+) *m/z*: $[M+H]^+$ Calculated for $C_{13}H_{15}O_3$ 219.1021; Found 219.1014.

Preparation of 3-(*p*-tolyl)-2,4,10-trioxaadamantane **10b**

Following the procedure for compound **10a** and starting from 1-methyl-4-(trimethoxymethyl)benzene (900 mg, 6.8 mmol, 1 eq.), compound **10b** was obtained pure after flash column chromatography (4:1 PE:EtOAc, v/v) as a white crystals (1.2 g, 76 %) (R_f: 0.39, PE:EtOAc 8:2): mp 177-179 °C;[21] IR (KBr) 3034, 2943, 2845, 1914, 1622, 1453,1366, 1331, 1311, 1129, 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.55 (s, 3H), 2.75 (d, *J* = 13.3 Hz, 3H), 2.33 (s, 3H), 1.80 (d, *J* = 12.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 138.9, 136.9, 128.8, 125.0, 109.1, 68.9, 33.1, 21.4; HRMS (ES^+) *m/z*: $[M + H]^+$ Calculated for $C_{14}H_{16}O_3$ 232.1099; Found 232.1091.

Preparation of 3-(4-chlorophenyl)-2,4,10-trioxaadamantane **10c**

Following the procedure for compound **10a** and starting from 1-chloro-4-(trimethoxymethyl)benzene **9c** (800 mg, 6.05 mmol, 1 eq.), compound **10c** was obtained pure after flash column chromatography (4:1 PE:EtOAc, v/v) as a white solid (1.48 g, 97%) (R_f: 0.43, PE:AcOEt 8:2): mp 146-148 °C;[6] IR (KBr) 2960, 2925, 2850, 1941, 1605, 1357,1325, 1309, 1128, 1010, 974, 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.58 (s, 3H), 2.76 (d, *J* = 8 Hz, 3H), 2.33 (s, 3H), 1.83 (d, *J* = 16 Hz, 3H); $^{113}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 138.3, 134.9, 128.2, 126.7, 108.6, 68.9, 32.9; HRMS (ES^+) *m/z*: $[M + H]^+$ Calculated for $C_{13}H_{14}O_3Cl$ 253.0631; Found 253.0633.

Preparation of 3-(4-methoxyphenyl)-2,4,10-trioxaadamantane **10d**

Following the procedure for compound **10a** and starting from 1-methoxy-4-(trimethoxymethyl)benzene **9d** (480 mg, 3.6 mmol, 1 eq.) compound **10d** was obtained pure after flash column chromatography (4:1 PE:EtOAc, v/v) as white crystals (510 mg, 58 %) (R_f: 0.35, PE:EtOAc 8:2): mp 106-108 °C; IR (KBr) 2943, 2841, 1614, 1520,1354, 1318, 1263, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.56 (s, 3H), 2.74 (d, *J* = 14.0 Hz, 3H), 1.80 (d, *J* = 12.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.2, 132.4, 126.6, 113.4, 109.1, 69.0, 55.4, 33.1. HRMS (ES^+) *m/z*: $[M]^+$ Calculated for $C_{14}H_{17}O_4$ 249.1119; Found 249.1127.

Preparation *cis*-3,5-*O*-benzylidenecyclohexanol **11a**

In a 2L reactor, HMPA (54 mL) was added to a dispersion of 3-phenyl-2,4,10-trioxaadamantane **10a** (60 g, 275 mmol, 1.00 eq.) in dry THF (600 mL) and kept under a N_2 atmosphere at 0°C. A BH_3·THF solution (1M in THF, 630 mmol, 630 mL, 2.29 eq.) was then added dropwise over a period of 1h and the mixture left stirring for the next 21 h. At this point, TBME (1.5 L) was added and the mixture was cooled at -10 °C by an ice-ethanol bath. After this time, H_2O (600 mL) was added dropwise and then the temperature was allowed reaching room temperature (20°C). The organic layer was separated and the water phase extracted with additional TBME (600 mL). The combined organic layers were washed with brine (1 L), dried over Na_2SO_4 and the solvent removed under reduced pressure until reached a volume of 60-70 mL. This crude mixture was then charged into a silica gel column (600 g silica, 9 cm diameter column). Elution using a mixture 4:1 PE:EtOAc, v/v (4L) gave the orthoester contaminated by benzaldehyde; Elution using a mixture 2:3 PE:EtOAc, v/v (2.5L) gave product **11a** as a white solid (25.9 g, 43%) (R_f: 0.43, PE:AcOEt 1:1): mp 185-187 °C;[5] IR (KBr) 3566, 2924, 2853, 1470, 1384, 1301, 1210, 1124, 1076, 742, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.44 - 7.31 (m, 3H), 6.20 (s, 1H), 4.72 (br s, 2H), 4.09 (dt, *J* = 10.4, 4.9 Hz, 1H), 3.80 (d, *J* = 11.1 Hz, 1H), 3.02 (dtt, *J* = 14.7, 4.9, 2.4 Hz, 1H), 2.51 (d, *J* = 15.4 Hz, 2H), 1.78 (dd, *J* = 15.0, 5.0 Hz, 2H), 1.57 (d, *J* = 14.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 138.2, 128.8, 128.3, 126,3, 91.8, 69.2, 65.9, 39.2, 26.9; HRMS (ES^+) *m/z*: $[M + H]^+$ Calculated for $C_{13}H_{17}O_3$ 221.1178; Found 221.1162.

Preparation of 3-(*p*-tolyl)-2,4-dioxabicyclo[3.3.1]nonan-7-ol **11b**

Following the procedure for compound **11a** and starting from 1-methyl-4-(trimethoxymethyl)benzene **10b** (300 mg, 1.29 mmol) compound **11b** was obtained pure after flash column chromatography (1:1 PE:EtOAc, v/v) as a white solid (145 mg, 48%): mp 176-178 °C; IR (KBr) 3549, 2842, 1466, 1343, 1305, 1217, 1124, 1213, 725, 701 cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 7.37 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.21 (s, 1H), 4.64 (bs, 2H), 4.06 (bs, 1H), 3.04 (dtt, *J* = 14.7, 4.9, 2.3 Hz, 1H), 2.37 (bs, 2H), 2.35 (s, 2H), 1.87 (dd, *J* = 15.0, 4.9 Hz, 2H), 1.66 (d, *J* = 14.7 Hz, 1H).; $^{113}C\{^1H\}$ NMR (101 MHz, MeOD) δ 139.8, 137.7, 129.9, 127.4, 93.2, 70.8, 67.8, 40.0, 27.6, 21.2; HRMS (ES^+) *m/z*: $[M + Na]^+$ Calculated for $C_{14}H_{18}O_3Na$ 257.1154; Found 257.1143.

Preparation of 3-(*p*-chlorophenyl)-2,4-dioxabicyclo[3.3.1]nonan-7-ol **11c**

Following the procedure for compound **11a** and starting from 1-methyl-4-(trimethoxymethyl)benzene **10c** (1 g, 3.96 mmol, 1 eq.) and using 4 eq. of BH_3·THF complex solution (1M in THF, 15.84 mmol, 15.84 mL). Purification by flash column chromatography (1:1 PE:EtOAc, v/v) gave pure **11c** as a white solid (854 mg, 85%): mp 130-132; IR (KBr) 3557, 2962, 2856, 1572, 1358, 1312, 1125, 1012, 726 cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 7.50 (d, *J* = 8.4 Hz, 2H),

7.36 (d, J = 8.4 Hz, 2H), 6.22 (s, 1H), 4.63 (bs, 2H), 4.06 (bs, 1H), 3.02 (dtt, J = 14.7, 4.9, 2.3 Hz, 1H), 2.34 (bd, J = 15.5 Hz, 2H), 1.86 (dd, J = 14.9, 5.0 Hz, 2H), 1.66 (d, J = 14.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, MeOD) δ 139.2, 135.6, 129.4, 129.3, 92.5, 70.8, 67.5, 49.0, 40.0, 27.6; HRMS (ES^+) *m/z*: $[M + Na]^+$ Calculated for $C_{13}H_{15}O_3NaCl$ $C_{13}H_{17}NO_3$ 277.0600; Found 277.0607.

Preparation of 3-(*p*-methoxyphenyl)-2,4-dioxabicyclo[3.3.1]nonan-7-ol **11d**

Following the procedure for compound **11a** and starting from 1-methyl-4-(trimethoxymethyl)benzene **10d** (185 mg, 0.75 mmol) compound **11d** was obtained after purification by flash column chromatography (1:1 PE:EtOAc, v/v) as a white solid (11.3 mg, 6%): mp 133-135 °C; IR (KBr) 3572, 2962, 1364, 1312, 1137,1042, 746, 723, 698 cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 7.41 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 6.19 (s, 1H), 4.62 (bs, 2H), 4.06 (bs, 1H), 3.78 (s, 3H), 3.03 (dtt, J = 14.7, 4.8, 2.4 Hz, 1H), 2.35 (bd, J = 14.1 Hz, 2H), 1.86 (dd, J = 15.1, 4.0 Hz, 2H), 1.65 (d, J = 14.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, MeOD) δ 139.8, 137.3, 129.9, 127.4, 93.2, 70.8, 67.8, 40.0, 27.6, 21.2; HRMS (ES^+) *m/z*: $[M + Na]^+$ Calculated for $C_{14}H_{18}O_4Na$ C13H17NO3Na 273.1107; Found 273.1103.

Preparation of *Cis*-3,5-*O*-Benzylidenecyclohexanone **1a** (Procedure A)[20]

Dess Martin Periodinane (9.40 g, 22.16 mmol, 2.99 eq.) was added portionwise over 3-5 minutes to a solution of *cis*-3,5-*O*-benzylidenecyclohexanol **11a** (1.64 g, 7.40 mmol, 1.00 eq.) in DCM (12.7 mL) under Argon and at 0°C. The mixture was left stirring for further 15-20 minutes at the same temperature. Diethyl Ether was then added and the mixture was quenched with solid $NaHCO_3$. The organic layer is separated and washed several times with $NaHCO_3$ and brine. The aqueous layers were collected and extracted with a further amount of Et_2O. The collected organic layer were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford product **1a** as a white solid (1.48 g, 92%). The product can be crystalized over methanol to obtain white crystals (1,2 g, 75%) (R_f = 0.46, EP/AcOEt 1/1).

Preparation of *Cis*-3,5-*O*-Benzylidenecyclohexanone **1a** (Procedure B)

To a solution of *cis*-3,5-O-benzylidenecyclohexanol **11a** (1.1 g, 4.98 mmol, 1.00 eq.) in dichloromethane (15 mL) was added a solution of KBr (42.6 mg) and $NaHCO_3$ (642 mg) in water (15 mL). TEMPO (180 mg, 0.19 mmol, 0.23 eq.) was added and the mixture was cooled at 0°C. The biphasic mixture was then vigorously stirred, then NaOCl (10% v/v, 19.9 mL, 19.92 mmol, 4.00 eq.) was added over 15 minutes. The mixture was left stirring for further 45 min, then the organic layer was separated. The aqueous layer was extracted three times with dichloromethane (3×15 mL). The collected organic layer were washed with brine, dried over $MgSO_4$ and concentrated to give product **11a** as a white solid (650 mg, 60%).

Preparation of *Cis*-3,5-*O*-Benzylidenecyclohexanone **1a** (Procedure C)

Cis-3,5-O-Benzylidenecyclohexanol **11a** (10.5 g, 47.7 mmol, 1.00 eq.) was dissolved in DCM (60 mL). DMSO (180 mL) was added, the mixture cooled at 0 °C followed by addition of triethylamine (27.5 mL, 192 mmol, 4.00 eq.). A solution of SO_3·Pyridine (31 g, 192mmol, 4 eq.) in DMSO (120 mL) was added to the reaction mixture dropwise over 3-5 minutes. The mixture was left stirring for further 3.5 hours leaving the temperature rising gradually to room temperature (20°C). TBME (100 mL), H_2O (100 mL) and NaH_2PO_4 buffer (100 mL) were sequentially added and the mixture stirred for 10 minutes. The organic layer was separated and the aqueous phase extracted with further TBME (3 x 500 mL). The collected organic layers were washed with brine (300 mL), dried over Na_2SO_4 and evaporated to give product **1a** as a white solid (8.6g, 83%). The yield were increased to 96% by carrying out a second extraction with EtOAc (500 mL) (1.34 g) (R_f: 0.46, TBME): mp 117-119 °C;[20] IR 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.29 (m, 5H), 5.99 (s, 1H), 4.85 (m, 2H), 3.10 (dtt, J = 14.8, 4.9, 2.5 Hz, 1H), 2.99 - 2.89 (m, 2H), 2.49 (ddd, J = 16.1, 2.4, 1.3 Hz, 2H), 1.96 (dt, J = 14.9, 1.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 26.3, 49.7, 69.7, 91.9, 126.6, 128.3, 129.3, 138, 207.2; HRMS (ES^+) *m/z*: $[M]^+$ Calculated for $C_{13}H_{14}O_3$ 218.0943; Found 218.0938.

Preparation of 3-(*p*-tolyl)-2,4-dioxabicyclo[3.3.1]nonan-7-one **1b**

Following the procedure for compound **1a** (procedure A) and starting from 3-(*p*-tolyl)-2,4-dioxabicyclo [3.3.1]nonan-7-one **11b** (100 mg, 0.42 mmol) compound **1b** was obtained pure by flash column chromatography (1:1 PE:EtOAc, v/v) as a white solid (88 mg, 88 %): IR (KBr) 2954, 2972, 2813, 1737, 1482, 1497, 1409, 1090, 1062, 924 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3) δ 7.24 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 6.01 (s, 1H), 4.78 (bs, 2H), 3.11 (dt, J = 14.8, 4.8 Hz, 1H), 2.83 (bd, J = 11.9 Hz, 2H), 2.63 (d, J = 1.7 Hz, 2H), 2.30 (s, 3H), 2.15 (d, J = 14.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, CD_3COCD_3) δ 207.2, 138.9, 137.3, 129.1, 127.3, 91.9, 70.7, 50.2, 26.3, 21.0; HRMS (ES^+) *m/z*: $[M]^+$ Calculated for $C_{14}H_{16}O_3$ 232.1099; Found 232.1097.

Preparation of 3-(p-Chlorophenyl)-2,4-dioxabicyclo[3.3.1]nonan-7-one **1c**

Following the procedure for compound **1a** (procedure A) and starting from 3-(*p*-chlorophenyl)-2,4-dioxabicyclo[3.3.1]nonan-7-ol **11c** (100 mg, 0.39) compound **1c** was obtained after purification by flash column chromatography (1:1 PE:EtOAc, v/v) as a white solid (81 mg, 84%): IR (KBr) 2959, 2927, 2852, 1716, 1496, 1494, 1409, 1121, 1090, 1003, cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.33 (s, 4H), 5.97 (s, 1H), 5.32 (s, 1H), 4.83 (bs, 2H), 3.07 (dtt, J = 14.6, 4.7, 2.4 Hz, 1H), 2.85 (d, J = 16.6 Hz, 2H), 2.51 (d, J = 15.6 Hz, 2H), 1.98 (d, J = 14.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 206.8, 136.7, 134.2, 128.3, 128.0, 90.9, 69.9, 49.5, 26.2; HRMS ((ES^+) *m/z*: $[M]^+$ Calculated for $C_{13}H_{13}O_3Cl$ 252.0553; Found 252.0574.

Procedure for the screening of catalysts **5a-h**, **6**, **7** (Table 1)

Catalyst **5a-h**, **6** or **7** (0.1-1mmol, 0.1 eq.) and K_2CO_3 (138mg 1.0 mmol, 1.00 eq.) were sequentially added to a stirred solution of *cis*-3,5-*O*-arylidenecyclohexanones **1a** (218 mg, 1.0 mmol, 1 eq.) in Toluene. The mixture was left stirring at 0°C for 18 h. The mixture was filtered over a small silica pad and the solvent removed *in vacuo*. The crude material was then taken up in $CDCl_3$ (5 mL), freshly recrystallised 1,3,5-tribromobenzene (133 mg, 0.33 equiv.) added to obtain a solution and ^{1}H-NMR recorded. Calculation of conversion was obtained by relative integration of 1,3,5-tribromobenzene at δ 7.61 (s) and integration of starter **1a** at δ 5.99. The ee of **4** was determined by chiral stationary phase HPLC, Chiralcel AD column [hexane/i-PrOH (95:5)]; flow rate 0.75 mL/min; major = 16.69 min, minor = 19.34 min.

Procedure for the preparation of (5*S*)-5-Hydroxycyclohex-2-enone **4** (Table 2)

Catalyst **5e** (56 mg, 0.1mmol, 0.1 eq.) and K_2CO_3 (1.58 g, 1.15 mmol, 1.00 eq.) were sequentially added to a stirred solution of *cis*-3,5-*O*-arylidenecyclohexanones **1a-c** (1.15 mmol, 1 eq.) in toluene (11 or 22 mL). The mixture was left stirring at 0°C for 18 h. The mixture was filtered over a small silica pad and the solvent removed *in vacuo*. The product was purified by silica gel chromatography (4:1 to 1:1 PE:EtOAc, v/v) to afford the product as a viscous colourless oil (103 mg, 80%) (R_f: 0.1, PE:EtOAc 1:1): $[\alpha]^{25}_D$ = -31.0° (c 0.3, $CHCl_3$);[5] IR (KBr) 3412, 1670, 1381, 1252, 1070, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (ddd, *J* = 10.1, 4.8, 3.6 Hz, 1H), 6.09 (dt, *J* = 10.1, 2.0 Hz, 1H), 4.34 (ddt, *J* = 8.8, 7.2, 4.3 Hz, 1H), 2.76 (dd, 1H), 2.73 – 2.65 (m, 1H), 2.54 (dd, *J* = 16.2, 9.0 Hz, 1H), 2.49 – 2.40 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 198.3, 146.7, 129.8, 66.6, 46.9, 34.3; HRMS (ES$^+$) *m/z*: $[M+Na]^+$ Calculated for $C_6H_8O_2Na$ 135.0422; Found 135.0427. The ee was determined by HPLC using a Chiralcel AD column [hexane/i-PrOH (95:5)]; flow rate 0.75 mL/min; major = 16.69 min, minor = 19.34 min.

Preparation of (5*S*)-5-(*tert*-butyldimethylsiloxy)cyclohex-2-enone **12**[22]

Imidazole (119.14 mg, 1.75 mmol, 1.95 eq.) and TBSCl (263.70 mg, 1.75 mmol, 1.95 eq.) were sequentially added to a solution of *(5S)*-5-Hydroxycyclohex-2-enone **4** (101 mg, 0.90 mmol, 1 eq.) in DMF (4.5 mL). The mixture was left stirring at room temperature for 1.5 h. The reaction mixture was quenched with MeOH (0.13 mL) and then extracted with Et_2O. The organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed *in vacuo*. The residue was purified by flash chromatography (99:1 to 9:1 PE: Et_2O, v/v) (R_f = 0.30, PE:Et_2O 9:1) to afford product **12** as a colourless oil (165 mg, 82%): IR (neat) 1684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (ddd, *J* = 10.1, 5.1, 3.2 Hz, 1H), 6.05 (dt, *J* = 10.1, 1.9 Hz, 1H), 4.29 – 4.14 (m, 1H), 2.72 – 2.54 (m, 2H), 2.48 (dd, *J* = 16.0, 9.7 Hz, 1H), 2.42 – 2.32 (m, 1H), 0.87 (s, 9H), 0.06 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 199.3, 147.4, 130.3, 67.9, 48.3, 35.9, 25.9, 18.1, -4.5, -4.6; HRMS (ES$^+$) *m/z*: $[M + H]^+$ Calculated for $C_{12}H_{23}O_2Si$ 227.1467; Found 227.1478.

Preparation of (2*S*,3*S*,5*S*)-5-(tert-Butyldimethylsiloxy)-2,3-epoxycyclohexanone **13**[1e]

NaOH (73.66 µl of a 0.1 M solution, 0.00736 mmol, 0.02 eq.) and H_2O_2 (163.20 mg, 1.42 mmol, 2.80 eq.) were sequentially added at to a stirred solution of (5*S*)-5-(*tert*-butyldimethylsiloxy)cyclohex-2-enone (115 mg,0.51 mmol, 1 eq.) in MeOH (3.94 mL) at -15 °C. The mixture was left stirring 50 min at the same temperature. The reaction mixture was quenched with a saturated NH_4Cl solution. MeOH was removed *in vacuo* and the mixture extracted with Et_2O (3×10 mL). Collected organic layer were washed with brine, dried over Na_2SO_4 and solvent removed by rotatory evaporation. The residue was purified by column chromatography (4:1 PE:Et_2O, v/v) to afford the product as colourless viscous oil and as mixture of diasteroisomers (93/7) (95 mg, 78%). Crystallization over heptane at -20°C (95 mg / 0.2-0.3 mL) afforded product **13** as white crystals and a single enantiomer (73 mg, 60%) (R_f=0.2, EP:Et_2O, 95:5): IR (neat) 2929, 2888, 2857, 1726, 1472, 1406, 1361, 1331, 1255, 1075, 1031, 985, 935,871, 837, 778, 715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 – 4.16 (m, 1H), 3.52 (t, *J* = 3.5 Hz, 1H), 3.23 (d, *J* = 3.8 Hz, 1H), 2.74 (dd, *J* = 15.3, 3.2 Hz, 1H), 2.36 (dd, *J* = 15.2, 4.0 Hz, 1H), 2.16 (dd, *J* = 15.5, 6.3 Hz, 1H), 2.03 – 1.90 (br d, *J* = 15.3 Hz, 1H), 0.82 (s, 9H), 0.02 (s, 6H); ^{13}C{^{1}H} NMR 204.8, 67.3, 55.4, 54.7, 44.9, 32.9, 25.5, 17.8, -5.0, -5.1; HRMS (ES$^+$) *m/z*: $[M+Na]^+$ Calculated for $C_{12}H_{22}O_3SiNa$ 2651236; Found 265.1242.

Preparation of (3*S*,5*S*)-3-(*tert*-butyldimethylsilyloxy)-5 hydroxycyclohexanone **14**

$NaBH_4$ (29.16 mg, 0.78 mmol, 3 eq.) was added to a solution of diphenyldiselenide (121.73 mg, 0.39 mmol, 1.5 eq.) in dry ethanol (1.56 mL) under argon and at room temperature. The mixture was left stirring for 2 minutes followed by addition of acetic acid (7.8 µl). The resulting orange solution was added at once to a cold solution (0°C) of (2*S*,3*S*,5*S*)-5-(*tert*-butyldimethylsiloxy)-2,3-epoxycyclohexanone **13** (63 mg, 0.26 mmol, 1 eq.) in dry ethanol (1.04 mL) and the mixture was stirred for further 13 minutes. The resulting mixture was diluted with ethyl acetate and washed with brine. The mixture was left stirring 10 min open to air. The organic layer was separated while the aqueous one was extracted with ethyl acetate (5 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed by rotatory evaporation to afford a residue that was purified by flash chromatography. Elution with petroleum ether gave $(PhSe)_2$. Further elution with AcOEt provided **14** as a colourless oil (60 mg, 94%) (R_f :0.20, 1:1 PE:EtOAc): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 – 4.31 (m, 2H), 2.68 (s, 1Hx, 2.70 – 2.60 (m, 1H), 2.50 (dd, *J* = 14.2, 3.9 Hz, 1H), 2.35 (dd, *J* = 14.2, 7.3 Hz, 2H), 2.11 – 2.00 (m, 1H), 1.91 (ddd, *J* = 13.7, 8.2, 2.9 Hz, 1H), 0.83 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C{^{1}H} NMR 208.5, 66.9, 66.2, 50.4, 50.2, 49.9, 41.2, 18.0, -3.5, -4.9;

HRMS (ES+) *m/z*: $[M+H]^+$ Calculated for $C_{12}H_{25}O_3Si$ 245.1573; Found 245.1547.

ASSOCIATED CONTENT

Supporting Information: copies of the ^1H- and ^{13}C- NMR of compounds **1**, **3**, **4** and **8**-**14**; and copies of chiral HPLC traces for experiments listed in Table 2. The Supporting Information is available free of charge on the ACS Publications website.

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SYNOPSIS TOC